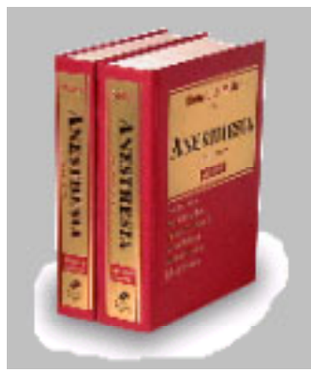

By OkDoKeY

CHURCHILL LIVINGSTONE
A division of Harcourt Brace & Company
The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data
Anesthesia / editor, Ronald D. Miller; atlas of regional anesthesia
procedures illustrated by Gwenn Afton-Bird.--5th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-443-07988-9 (set)
1. Anesthesia. I. Miller, Ronald D.
[DNLM: 1. Anesthesia. WO 200 A573 2000]
RD81.A54 2000
617.9
6--dc21
DNLM/DLC 99-19722

ANESTHESIA 0-443-07988-9(set)

0-443-07995-1(Vol. 1)

 0-443-07996-X(Vol. 2)

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

/das/book/view/29494766/875/1.html

ANESTHESIA

FIFTH EDITION

Volume 1

Edited by

Ronald D. Miller M.D.
Professor and Chairman of Anesthesia and Perioperative Care
Professor of Cellular and Molecular Pharmacology
Department of Anesthesia
University of California, San Francisco
School of Medicine
San Francisco, California
Atlas of Regional Anesthesia Procedures illustrated by Gwenn Afton-Bird, M.S.

A Division of Harcourt Brace & Company
Philadelphia London Toronto Montreal Sydney Tokyo Edinburgh

Contributors

Hugo van Aken M.D., Ph.D.

Chairman and Professor of Anesthesiology
Westfalische Wilhelms-Universitat,
Munster, Germany

David D. Alfery M.D.

Department of Anesthesiology,
Centennial Medical Center,
Nashville, Tennessee

J. Jeffrey Andrews M.D.

Professor and Vice-Chair for Clinical Development,
Department of Anesthesiology,
University of Alabama at Birmingham
School of Medicine,
Birmingham, Alabama;

Chief, Anesthesiology Service,
Veterans Administration,
Birmingham VA Medical Center,
Birmingham, Alabama

Joseph F. Antognini M.D.

Associate Professor, Department of Anesthesiology,
University of California, Davis,
School of Medicine,
Davis, California

William P. Arnold III M.D.

Associate Professor, Department of Anesthesiology,
University of Virginia Health System,
University of Virginia School of Medicine,
Charlottesville, Virginia

Solomon Aronson M.D.

Associate Professor and Director of Cardiothoracic Anesthesia,
Department of Anesthesia and Critical Care,
University of Chicago Hospitals,
Chicago, Illinois

Michael J. Avram Ph.D.

Associate Professor, Department of Anesthesiology,
Northwestern University Medical School,
Chicago, Illinois

Jeffrey M. Baden F.R.C.A., M.R.C.P. (UK)

Professor, Department of Anesthesia,
Stanford University School of Medicine,
Stanford, California;

Staff Anesthesiologist,
Veterans Affairs Health Care System,
Palo Alto, California

Peter Bailey M.D.

Professor and Director, Cardiothoracic Anesthesia,
Department of Anesthesia,

**University of Utah, Health Sciences Center,
Salt Lake City, Utah**

Michael J. Banner Ph.D.

**Associate Professor, Department of Anesthesiology,
University of Florida, Shands Teaching Hospital,
Gainesville, Florida**

Steven J. Barker M.D.

**Professor and Chair, Department of Anesthesiology,
University of Arizona,
Tucson, Arizona**

Nathan M. Bass M.D., Ph.D.

**Professor, Department of Medicine,
University of California, San Francisco,
School of Medicine,
San Francisco, California;**

**Attending Physician,
Division of Gastroenterology,
University of California, San Francisco Medical Center,
San Francisco, California**

Jonathan L. Benumof M.D.

**Professor, Department of Anesthesiology,
University of California, San Diego, School of Medicine
La Jolla, California**

Susan Black M.D.

**Associate Professor,
Department of Anesthesiology,
University of Florida College of Medicine,
Gainesville, Florida**

Thomas J.J. Blanck M.D., Ph.D.

**Professor, Departments of Anesthesiology and Physiology and Biophysics,
Joan and Sanford I. Weill Medical College of Cornell University,
New York, New York;**

**Director, Department of Anesthesiology,
Hospital for Special Surgery,
New York, New York**

David L. Brown M.D.

**Professor and Head,
Department of Anesthesia,
University of Iowa College of Medicine,
Iowa City, Iowa;**

**Head, Department of Anesthesia,
University of Iowa Hospital and Clinics,
Iowa City, Iowa**

Michael K. Cahalan M.D.

**Professor, Department of Anesthesia,
University of California, San Francisco, School of Medicine;**

**Director of Anesthesia for Cardiac Surgery,
Moffitt and Long Hospitals,
San Francisco, California**

James E. Caldwell M.D.

**Professor and Director of Perioperative Medicine,
Department of Anesthesia,
University of California, San Francisco, School of Medicine,
San Francisco, California**

Enrico M. Camporesi M.D.

**Professor and Chair,
Department of Anesthesiology;
Professor of Physiology,
State University of New York Health Science Center at Syracuse College of Medicine,
Syracuse, New York**

Donald Caton M.D.

**Professor, Departments of Anesthesiology and Obstetrics and Gynecology,
University of Florida College of Medicine,
Gainesville, Florida**

Charles J. Cote M.D.

**Professor, Department of Anesthesiology and Pediatrics,
Northwestern University Medical School,
Chicago, Illinois;**

**Vice Chairman, Director of Research,
Department of Pediatric Anesthesiology,
Children's Memorial Hospital,
Chicago, Illinois**

Roy F. Cucchiara M.D.

**Professor, Department of Anesthesiology,
University of Florida College of Medicine,
Gainesville, Florida**

Bernard J. Dalens M.D.

**Pediatric Anesthesiologist,
University Hospital Hotel-Dieu,
Pavillon Gosselin,
Clermont-Ferrand, France**

Sudhir Diwan M.D.

**Instructor in Anesthesiology,
Joan and Sanford I. Weill Medical College of Cornell University,
New York, New York;**

**Assistant Attending Anesthesiologist,
Associate Director, Pain Service,
Department of Anesthesiology,
New York Presbyterian Hospital,
New York, New York**

Barbara A. Dodson M.D.

**Professor, Department of Anesthesia,
University of California, San Francisco,
School of Medicine,
San Francisco, California**

John V. Donlon Jr. M.D.

**Associate Clinical Professor, Anaesthesia,
Harvard Medical School,
Cambridge, Massachusetts;**

**Chief, Anesthesia Department,
Massachusetts Eye and Ear Infirmary,
Boston, Massachusetts**

John C. Drummond M.D.

**Professor and Chair,
Department of Anesthesiology,
University of California, San Diego, School
of Medicine
La Jolla, California;**

**Staff Anesthesiologist,
Department of Anesthesiology,
Veterans Administration Medical Center,
San Diego, California**

Talmage D. Egan M.D.

**Assistant Professor, Department of Medicine,
University of Utah School of Medicine,
Salt Lake City, Utah**

Edmond I. Eger II M.D.

**Professor, Department of Anesthesia,
University of California, San Francisco, School of Medicine
San Francisco, California**

Neil E. Farber M.D., Ph.D.

Associate Professor, Department Anesthesiology,

**Pharmacology and Toxicology, and Pediatrics;
Director of Pediatric Anesthesiology Research,
Medical College of Wisconsin,
Milwaukee, Wisconsin**

Ronald J. Faust M.D.

**Professor, Department of Anesthesiology,
Mayo School of Medicine,
Rochester, Minnesota;**

**Consultant in Anesthesiology,
Mayo Clinic,
Rochester, Minnesota**

Thomas W. Feeley M.D.

**Charles M. McBride Professor and Chairman,
Departments of Anesthesiology and Critical Care,
University of Texas
M.D. Anderson Cancer Center,
Houston, Texas**

John Feiner M.D.

**Assistant Professor, Department of Anesthesia,
University of California, San Francisco,
School of Medicine,
San Francisco, California**

Leonard Firestone M.D.

**Professor and Chairman,
Department of Anesthesiology and Critical Care Medicine,
University of Pittsburgh School of Medicine,
Pittsburgh, Pennsylvania**

Steven P. Fischer M.D.

**Assistant Professor, Department of Anesthesia,
Stanford University School of Medicine,
Stanford, California**

Dennis M. Fisher M.D.

**Professor, Departments of Anesthesia and Pediatrics,
University of California, San Francisco,
School of Medicine,
San Francisco, California**

Lee A. Fleisher M.D.

**Associate Professor, Department of Anesthesiology and Critical Care Medicine,
Joint Appointments in Medicine and Health Policy & Management,
The Johns Hopkins Medical Institutions,
Baltimore, Maryland;**

**Attending Anesthesiologist,
The Johns Hopkins Hospital,
Baltimore, Maryland**

Joseph F. Foss M.D.

**Assistant Clinical Professor, Department of Anesthesia and Critical Care,
University of Chicago Pritzker School
of Medicine,
Chicago, Illinois**

Robert J. Fragen M.D.

**Professor, Department of Anesthesiology,
Northwestern University Medical School,
Chicago, Illinois;**

**Staff Anesthesiologist,
Northwestern Memorial Hospital,
Chicago, Illinois**

Steven M. Frank M.D.

**Associate Professor,
Department of Anesthesiology and Critical Care Medicine,
The Johns Hopkins Medical Institutions,
Baltimore, Maryland**

David M. Gaba M.D.

**Associate Professor, Department of Anesthesia,
Stanford University School of Medicine,**

Stanford, California;

Staff Anesthesiologist,
Veterans Affairs Health Care System,
Palo Alto, California

Thomas J. Gal M.D.

Professor, Department of Anesthesiology,
University of Virginia Health Sciences Center,
Charlottesville, Virginia

Simon Gelman M.D., Ph.D.

Leroy D. Vandam/Benjamin G. Covino Professor of Anaesthesia,
Harvard Medical School,
Boston, Massachusetts;

Chairman, Department of Anesthesia,
Brigham and Women's Hospital,
Boston, Massachusetts

Peter S.A. Glass M.D.

Associate Professor, Department of Anesthesiology,
Duke University Medical Center,
Durham, North Carolina

Beth Glosten M.D.

Anesthesiologist,
Redmond, Washington

Christopher M. Grande M.D., M.P.H.

Professor, Department of Anesthesiology,
West Virginia University School of Medicine;
Director of Trauma Anesthesia,
Jon Michael Moore Trauma Center,
Robert C. Byrd Health Sciences Center,
Morgantown, West Virginia

Executive Director,
International Trauma Anesthesia
and Critical Care Society,
Baltimore, Maryland

William J. Greeley M.D.

Professor, Departments of Anesthesia and Pediatrics,
University of Pennsylvania
School of Medicine,
Philadelphia, Pennsylvania;

Chair, Department of Anesthesia and Critical Care Medicine,
Children's Hospital of Philadelphia,
Philadelphia, Pennsylvania

George A. Gregory M.D.

Professor, Departments of Anesthesia and Pediatrics,
University of California, San Francisco,
School of Medicine,
San Francisco, California

Alan Grogono M.D.

Merryl & Sam Israel Professor and
Chairman Emeritus, Department of Anesthesiology,
Tulane University Medical Center,
New Orleans, Louisiana;

Past President of the Association of Anesthesiology Program Directors

Gerald A. Gronert M.D.

Professor, Department of Anesthesiology,
University of California, Davis, School of Medicine,
Davis, California

Zaharia Hillel M.D., Ph.D.

Associate Professor of Clinical Anesthesiology,
Columbia University College of Physicians and Surgeons;

Director of Cardiothoracic Anesthesia,

**St. Luke's Roosevelt Hospital Center,
New York, New York**

Steven K. Howard M.D.

**Assistant Professor, Department of
Anesthesia,
Stanford University School of Medicine,
Stanford, California**

Carl C. Hug Jr. M.D., Ph.D.

**Professor, Departments of Anesthesiology and Pharmacology,
Emory University School of Medicine,
Atlanta, Georgia;**

**Attending Anesthesiologist,
Division of Cardiothoracic Anesthesiology and Critical Care Medicine,
Emory University Hospital,
Atlanta, Georgia**

Jean L. Joris M.D., Ph.D.

**Associate Professor,
Department of Anesthesia and Intensive Care Medicine,
CHU de Liege, Domaine du Sart Tilman,
Liege, Belgium**

Alan D. Kaye M.D., Ph.D.

**Professor and Chairman,
Department of Anesthesiology,
Texas Tech. University Medical Center,
Lubbock, Texas;**

**Professor, Department of Pharmacology,
Texas Tech. University Health Sciences Center,
Lubbock, Texas**

Frank H. Kern M.D.

**Professor and Chief of Pediatric Anesthesia,
Departments of Anesthesiology and Pediatrics,
Duke University Medical Center,
Durham, North Carolina**

Robert R. Kirby M.D.

**Professor of Anesthesiology,
University of Florida College of Medicine,
Gainesville, Florida;**

**System Chief, Anesthesiology Service,
Veterans Affairs Medical Center,
Gainesville, Florida**

Donald D. Koblin M.D., Ph.D.

**Professor, Department of Anesthesia and Perioperative Care,
University of California, San Francisco,
School of Medicine,
San Francisco, California;**

**Staff Anesthesiologist,
Department of Veterans Affairs
Medical Center,
San Francisco, California**

W. Daniel Kovarik M.D.

**Director of Pediatric Anesthesia,
Spectrum Medical Group,
Maine Medical Center,
Portland, Maine**

A. Joseph Layon M.D.

**Professor, Departments of Anesthesiology, Surgery, and Medicine,
University of Florida College of Medicine,
Gainesville, Florida;**

**Associate Director of Burn Center,
Shands Teaching Hospital, University
of Florida,
Gainesville, Florida**

David L. Lee M.D.

Assistant Professor of Anesthesiology,
Cornell University Medical College,
New York, New York;

Attending Anesthesiologist,
Hospital for Special Surgery,
New York, New York

Cynthia A. Lein M.D.

Associate Professor, Department of Anesthesiology,
New York Presbyterian Hospital,
Joan and Sanford I. Weill Medical College of Cornell University,
New York, New York

Lawrence Litt M.D., Ph.D.

Professor, Departments of Anesthesia and Radiology,
University of California, San Francisco,
School of Medicine,
San Francisco, California;

Attending Physician in Anesthesia,
Moffitt and Long Hospitals,
UCSF-Stanford Medical Center,
San Francisco, California

David A. Lubarsky M.D.

Associate Professor and Vice Chairman, Department of Anesthesiology,
Duke University Medical Center,
Durham, North Carolina

Alex Macario M.D.

Assistant Professor, Department of
Anesthesia,
Stanford University School of Medicine,
Stanford, California

Ronald A. Mackenzie D.O.

Assistant Professor, Department of Anesthesiology,
Mayo School of Medicine,
Rochester, Minnesota;

Consultant, Department of Anesthesiology,
Mayo Clinic,
Rochester, Minnesota

Michael E. Mahla M.D.

Associate Professor, Departments of Anesthesiology and Neurosurgery,
Associate Chairman for Education,
University of Florida College of Medicine,
Gainesville, Florida

Vinod Malhotra M.D.

Professor, Department of Anesthesiology,
Joan and Sanford I. Weill Medical College of Cornell University,
New York, New York;

Clinical Director of the Operating Rooms,
Department of Anesthesiology,
New York Presbyterian Hospital,
New York, New York

Jonathan B. Mark M.D.

Associate Professor of Anesthesiology;
Assistant Professor in Medicine,
Duke University Medical Center,
Durham, North Carolina;

Chief, Anesthesiology Service,
Durham Veterans Affairs Medical Center,
Durham, North Carolina

Jeevendra Martyn M.D.

Professor of Anaesthesia;
Director, Clinical and Biochemical Pharmacology Laboratory,
Harvard Medical School,
Massachusetts General Hospital,
Boston, Massachusetts

Mervyn Maze M.D.

Magill Professor of Anaesthetics,
Magill Department of Anaesthesia, Intensive Care, and Pain Management,
Imperial College School of Medicine,
Chelsea and Westminster Hospital,
Chelsea, London, England

William J. Mazzei M.D.

Clinical Professor, Department of Anesthesiology,
UCSD Medical Center,
San Diego, California

Joseph M. Messick Jr.

Former Professor, Department of Anesthesiology,
Mayo School of Medicine,
Rochester, Minnesota

Edward D. Miller Jr. M.D.

Dean of the Medical Faculty, CEO, Johns Hopkins Medicine, Professor, Department of Anesthesiology and Critical Care Medicine,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland

Ronald D. Miller M.D.

Professor and Chairman of Anesthesia and Perioperative Care;
Professor of Cellular and Molecular Pharmacology,
Department of Anesthesia, University of California, San Francisco,
School of Medicine,
San Francisco, California

Charles S. Modell J.D.

Share Holder and Director,
Larkin, Hoffman, Daly and Lindgren,
Bloomington, Minnesota

Jerome H. Modell M.D.

Professor of Anesthesiology,
University of Florida College of Medicine,
Gainesville, Florida;

Associate Vice President for Health Affairs,
University of Florida,
Gainesville, Florida

Richard E. Moon M.D.

Professor, Department of Anesthesiology,
Associate Professor, Department of Pulmonary and Critical Care Medicine,
Duke University School of Medicine,
Durham, North Carolina;

Attending Anesthesiologist,
Attending Pulmonologist,
Duke University Medical Center,
Durham, North Carolina

Kenjiro Mori M.D.

Emeritus Professor, Department of Anesthesia,
Kyoto University Faculty of Medicine,
Kyoto, Japan;

Hospital Director,
Takamatsu Red Cross Hospital,
Takamatsu, Japan

Jonathan Moss M.D., Ph.D.

Professor, Department of Anesthesia and Critical Care;
Professor of the College;
Professor, Committee on Clinical Pharmacology,
Vice Chairman for Research,
University of Chicago
Pritzker School of Medicine,
Chicago, Illinois

Stanley Muravchick M.D., Ph.D.

Professor, Department of Anesthesia,
University of Pennsylvania School
of Medicine,

Philadelphia, Pennsylvania;

Staff Anesthesiologist,
Hospital of the University of Pennsylvania,
Philadelphia, Pennsylvania

Shin-ichi Nakao M.D., Ph.D.

Assistant Professor, Department of Anesthesiology,
Kansai Medical University, Moriguchi,
Osaka, Japan

Susan C. Nicolson M.D.

Professor of Anesthesia,
University of Pennsylvania School
of Medicine,
Philadelphia, Pennsylvania;

Director, Cardiac Anesthesiology,
The Children's Hospital of Philadelphia,
Philadelphia, Pennsylvania

Edward J. Norris M.D.

Assistant Professor, Department of Anesthesiology and Critical Care Medicine,
The Johns Hopkins University School of Medicine,
Baltimore, Maryland;

Attending Anesthesiologist,
Section Head, Vascular Anesthesia,
The Johns Hopkins Medical Institutions,
Baltimore, Maryland

Fredrick K. Orkin M.D.

Professor of Health Evaluation Sciences;
Professor, Department of Anesthesiology,
Pennsylvania State University College of Medicine,
Hershey, Pennsylvania;

Anesthesiologist,
The Milton S. Hershey Medical Center,
Penn State Geisinger Health System,
Hershey, Pennsylvania

P. Pearl O'Rourke M.D.

Director of Pediatric Intensive Care,
Children's Hospital Medical Center,
University of Washington School of Medicine,
Seattle, Washington

Paul S. Pagel M.D., Ph.D.

Associate Professor, Department of Anesthesiology,
Medical College of Wisconsin,
Milwaukee, Wisconsin

Dale A. Parks Ph.D.

Associate Professor, Department of Anesthesiology; Physiology and Biophysics; and Pediatrics; and Center for Free Radical Research,
University of Alabama at Birmingham School of Medicine,
Birmingham, Alabama

Piyush M. Patel M.D.

Associate Professor, Department of Anesthesiology,
University of California, San Diego, School of Medicine,
La Jolla, California;

Staff Anesthesiologist, Department of Anesthesiology,
Veterans Administration Medical Center,
San Diego, California

William T. Peruzzi M.D.

Associate Professor, Department of Anesthesiology,
Northwestern University Medical School,
Chicago, Illinois

Isaac N. Pessah Ph.D.

Professor, Department of Molecular Biosciences,
University of California, Davis, School
of Veterinary Medicine,

Davis, California

Ira J. Rampil M.D.

**Associate Professor, Department of Anesthesia and Perioperative Care,
University of California, San Francisco, School of Medicine,
San Francisco, California**

L. Brian Ready

**Professor, Department of Anesthesiology,
University of Washington School of Medicine,
Seattle, Washington;**

**Director, University of Washington Medical
Center Pain Service,
University of Washington Medical Center,
Seattle, Washington**

Cheryl Renz M.D.

**Fellow, Committee on Clinical Pharmacology,
Department of Anesthesia and Critical Care,
University of Chicago Pritzker School of Medicine,
Chicago, Illinois**

J. Gerald Reves M.D.

**Professor and Chairman, Department of Anesthesiology,
Duke University Medical Center,
Durham, North Carolina**

Susan A. Rice Ph.D.

**Department of Anesthesia,
Stanford University School of Medicine,
Stanford, California**

Michael F. Roizen M.D.

**Professor and Chairman, Department of Anesthesia and Critical Care;
Professor, Department of Medicine,
University of Chicago Pritzker School of Medicine,
Chicago, Illinois**

John C. Rowlingson M.D.

**Professor and Director, Pain Medicine Services,
Department of Anesthesiology,
University of Virginia Health System,
University of Virginia School of Medicine,
Charlottesville, Virginia**

Monica M. Sa Rego M.D.

**Resident in Anaesthesia,
Brigham and Women's Hospital,
Harvard Medical School,
Boston, Massachusetts**

John J. Savarese M.D.

**The Joseph F. Artusio Professor and Chairman,
Department of Anesthesiology,
New York Presbyterian Hospital,
Joan and Sanford I. Weill Medical College of Cornell University,
New York, New York**

Alan Jay Schwartz M.D.

**Professor and Chair, Department of Anesthesiology,
Professor of Pharmacology,
Hahnemann University School of Medicine,
Philadelphia, Pennsylvania;**

**Chair, Department of Anesthesiology,
City Avenue Hospital,
Hahnemann University Hospital,
Medical College of Pennsylvania Hospital,
Philadelphia, Pennsylvania**

Debra Schwinn M.D.

**Professor of Anesthesiology,
Department of Anesthesiology,
Duke University School of Medicine,
Durham, North Carolina**

Daniel I. Sessler M.D.

**Professor and Director, Outcomes Research,
Department of Anesthesia and Perioperative Care,
University of California, San Francisco,
School of Medicine,
San Francisco, California;**

**Professor, Ludwig Boltzmann Institute,
Vice-Chair, Department of Anesthesia,
University of Vienna,
Vienna, Austria**

Steven L. Shafer M.D.

**Associate Professor, Department of Anesthesia,
Stanford University School of Medicine,
Palo Alto, California**

**Staff Anesthesiologist,
Veterans Affairs Health Care System,
Palo Alto, California;**

Jack S. Shanewise M.D.

**Assistant Professor, Department of Anesthesiology,
Emory University School of Medicine,
Atlanta, Georgia;**

**Director, Intraoperative Echocardiography Service,
Emory University Hospital,
Atlanta, Georgia**

Robert E. Shangraw M.D., Ph.D.

**Associate Professor, Department of Anesthesiology,
Oregon Health Sciences University,
Portland, Oregon**

Barry A. Shapiro M.D.

**Professor and James E. Eckenhoff Chair, Department of Anesthesiology,
Northwestern University Medical School,
Chicago, Illinois**

Nigel E. Sharrock M.B.

**Assistant Clinical Professor, Department of Anesthesiology,
Joan and Sanford I. Weill Medical College of Cornell University,
New York, New York;**

**Senior Scientist and Attending Anesthesiologist,
The Hospital for Special Surgery,
New York, New York**

Koh Shingu M.D.

**Professor and Chairman, Department of Anesthesiology,
Kansai Medical University, Moriguchi,
Osaka, Japan**

Kelly A. Skinner Ph.D.

**Research Associate, Department of Physiology and Biophysics,
University of Alabama at Birmingham School of Medicine,
Birmingham, Alabama**

Robert N. Sladen M.B.

**Professor and Vice-Chair, Department of Anesthesiology,
College of Physicians and Surgeons of Columbia University,
New York, New York;**

**Medical Director, Cardiothoracic-Surgical Intensive Care Unit,
New York Presbyterian Hospital (Columbia Campus),
New York, New York**

Thomas F. Slaughter M.D.

**Assistant Professor, Department of Anesthesiology,
Duke University School of Medicine,
Durham, North Carolina;**

**Attending Physician,
Durham Veterans Affairs Medical Center,**

Durham, North Carolina

Peter Southorn M.D.

**Associate Professor, Department of Anesthesiology, Mayo School of Medicine,
Rochester, Minnesota;**

**Consultant, Mayo Clinic,
Rochester, Minnesota**

Theodore H. Stanley M.D.

**Professor, Department of Anesthesiology,
University of Utah School of Medicine,
University Hospital,
Salt Lake City, Utah**

Donald R. Stanski M.D.

**Professor, Departments of Anesthesia and Medicine,
Stanford University School of Medicine,
Stanford, California**

Linda Stehling M.D.

**Former Professor, Departments of Anesthesiology and Pediatrics,
State University of New York Health Sciences Center at Syracuse College of Medicine,
Syracuse, New York;**

**Medical Consultant,
Scottsdale, Arizona**

John K. Stene M.D., Ph.D.

**Associate Professor, Department of Anesthesiology,
Pennsylvania State University, College of Medicine,
Hershey, Pennsylvania;**

**Director of Trauma Anesthesia,
Co-Director of Surgical Intensive Care Unit,
Penn State Geisinger Health System,
Milton S. Hershey Medical Center,
Hershey, Pennsylvania**

Paul E. Stensrud M.D.

**Instructor in Anesthesiology,
Mayo School of Medicine,
Rochester, Minnesota;**

**Consultant in Anesthesiology,
Mayo Foundation,
Rochester, Minnesota**

James M. Steven M.D.

**Associate Professor, Departments of Anesthesia and Pediatrics,
University of Pennsylvania School of Medicine,
Philadelphia, Pennsylvania;**

**Associate Anesthesiologist-in-Chief,
The Children's Hospital of Philadelphia,
Philadelphia, Pennsylvania**

David J. Stone M.D.

**Professor, Departments of Anesthesiology and Neurological Surgery,
University of Virginia Health Sciences Center,
Charlottesville, Virginia**

Gary Strichartz M.D.

**Professor, Department of Anesthesia and Pharmacology,
Director, Pain Research Center,
Harvard Medical School,
Brigham and Women's Hospital,
Boston, Massachusetts**

Cheri A. Sulek M.D.

**Assistant Professor, Department of Anesthesiology,
University of Florida College of Medicine,
Gainesville, Florida;**

**Staff Anesthesiologist, Veterans Affairs Medical Center,
Gainesville, Florida;**

**Shands Teaching Hospital, University of Florida,
Gainesville, Florida**

James F. Szocik M.D.

**Assistant Professor, Department of Anesthesiology,
University of Michigan Medical Center,
Ann Arbor, Michigan**

Stephen J. Thomas M.D.

**Professor and Vice Chair, Department of Anesthesiology,
Joan and Sanford I. Weill Medical College of Cornell University,
New York, New York**

Daniel M. Thys M.D.

**Professor, Department of Anesthesiology,
Columbia University College of Physicians and Surgeons;
Director, Department of Anesthesiology,
St. Luke's Roosevelt Hospital Center,
New York, New York**

Kevin Tremper M.D., Ph.D.

**R.B. Suite Professor and Chair,
Department of Anesthesiology,
University of Michigan Medical School,
Ann Arbor, Michigan**

Leroy D. Vandam M.D.

**Professor Emeritus of Anesthesia,
Harvard Medical School,
Brigham and Women's Hospital,
Boston, Massachusetts**

Janet van Vlymen M.D.

**Associate Professor, Department of Anaesthesiology and Critical Care,
Queen's University Faculty of Medicine,
Kingston, Ontario, Canada**

Thomas C. Vary Ph.D.

**Professor, Department of Cellular and Molecular Physiology,
Pennsylvania State University,
College of Medicine,
Hershey, Pennsylvania**

Jorgen Viby-Mogensen M.D.

**Professor, Department of Anaesthesia,
Copenhagen University Hospital, Rigshospitalet,
Copenhagen, Denmark**

David C. Warltier M.D., Ph.D.

**Professor and Vice Chairman for Research,
Departments of Anesthesiology, Pharmacology and Toxicology, and Medicine (Division of Cardiovascular Diseases),
Medical College of Wisconsin,
Milwaukee, Wisconsin**

Denise J. Wedel M.D.

**Professor, Department of Anesthesiology,
Mayo Clinic,
Rochester, Minnesota**

Paul F. White M.D., Ph.D.

**Professor and Holder of the Margaret Milan McDermott Distinguished Chair in Anesthesiology,
Department of Anesthesiology and Pain Management,
University of Texas Southwestern Medical Center at Dallas,
Dallas, Texas**

Roger D. White M.D.

**Professor, Department of Anesthesiology,
Mayo School of Medicine,
Rochester, Minnesota;**

**Consultant in Anesthesiology,
Mayo Clinic,**

Preface to the Fifth Edition

The Fourth Edition of *Anesthesia* is widely recognized as the most complete and thorough analysis and presentation available on the specialty of anesthesiology. The consulting editors and I examined the Fourth Edition carefully to ensure that the entire specialty of anesthesiology in the Fifth Edition is adequately addressed in a scholarly, thorough, and contemporary manner. Each author was instructed to revise his or her chapter in a manner that ensured its being a contemporary treatment of the subject matter being described.

There are some modest changes in the subject matter and its reorganization in the Fifth Edition of *Anesthesia.* From a monitoring point of view, the use of transesophageal echocardiography is increasingly becoming a standard in anesthesia, not only for patients with cardiac surgery but also for many other patients with critical illnesses or procedures being performed. In that regard, we made the decision to have a separate chapter on transesophageal echocardiography (Chapter 31) written by Dr. Michael Cahalan, who is regarded as an international expert on this topic. We also recognized the increasing importance of information systems in the clinical setting in which we work. As a result, Dr. Ira Rampil added a chapter on "Finding Professional Information on the Internet" (Chapter 78). Also, recognizing the increasing requirement of assessing the effectiveness of clinical care, Dr. Dennis Fisher added a section on outcomes in his statistical analysis in Chapter 21.

As in previous editions, each chapter is written as a complete discussion of its topic and is fully referenced. As a result, there is some overlap from chapter to chapter. This overlap provides the reader with contrasting but equally valid views on many important areas in anesthesia. Also, there was an attempt to provide cross-referencing from one chapter to another on a particular topic.

With each new edition of *Anesthesia,* the number of pages and illustrations has progressively increased. This is a reflection of the increasing knowledge base that anesthesiologists need in order to have a complete understanding of the practice of anesthesiology. Therefore, a major emphasis in the Fifth Edition was to facilitate the overall understanding of the subject being discussed. In the Fourth Edition, color illustrations were inserted with regard to certain key illustrations. In the Fifth Edition, additional color was added, which should facilitate the ease of reading the text. Furthermore, a decision was made to develop a CD-ROM to provide a verbal and visual description of some of the more difficult technical procedures described in the text. It was our view that the addition of the CD-ROM would greatly enhance the understanding of some of the more technical aspects of our specialty. CD-ROM icons placed throughout both volumes indicate the related videos.

There is increasing recognition in health care delivery that standardization of health care not only increases quality but also tends to decrease cost. While one can debate this conclusion, there is no doubt that the practice of medicine is moving in a direction of standardization; anesthesiology is no exception. As a result, we are very grateful to the American Society of Anesthesiologists and Michael Todd, M.D., Editor-in-Chief of *Anesthesiology,* for allowing us to publish the ASA Practice Guidelines. The practice parameters described in these guidelines have been referenced to the appropriate chapters. This will allow the reader to compare leading experts' approaches to a particular topic with the standard recommendations of the American Society of Anesthesiologists.

As with the Fourth Edition, we believe that this text is truly peer-reviewed and that the review process by our consulting editors equals that of many excellent journals. I, therefore, especially thank Drs. Roy F. Cucchiara, Edward D. Miller, Jr., J. Gerald Reves, Michael F. Roizen, and John J. Savarese for their expertise and help in the development of the Fifth Edition of *Anesthesia.* Finally, I would like to acknowledge the support of Lewis Reines, President, and Allan Ross, Medical Editor, as well as the assistance of the editorial and production staff at W.B. Saunders Company, especially Ann Ruzycka, Senior Development Editor; Shelley Hampton, Production Editor; and Scott Filderman, Copy Editor.

INTRODUCTION

Anesthesia is considered an American invention, although innovations of such significance can hardly have arisen spontaneously. The individual's well-being was not genuinely considered until the need for surgical treatment of disease arose; attempts at relieving pain were previously sporadic. True, operations had been performed over the centuries but always for the superficial malady--a fracture, amputation, cataract extraction, trephination of the skull, or removal of bladder calculus. To these ends, the anesthetic properties of hypnosis and trance, pressure over peripheral nerves and blood vessels, application of cold, alcohol intoxication, or ingestion of herbal concoctions were used. A more influential approach to illness had been the galenic concept of disease, in which an imbalance among four cardinal body humors--blood, phlegm, and yellow and black bile--was said to exist; this concept survived well into the present century.

Section 1 - Introduction

Chapter 1 - History of Anesthetic Practice

Leroy D. Vandam

ANTECEDENTS OF MODERN ANESTHESIA

The gastrointestinal tract long remained the only avenue for medicinal therapy. The inhalation of vapors became an alternative approach. With techniques of anesthetic administration more or less divided into schools, the choice now lies between inhalational, intravenous, or regional techniques or combinations thereof. However, the seeds of all three methodologies were implanted during the Middle Ages. Although this chapter mainly considers subsequent developments and the birth of a new medical specialty, anesthesiology, it is worthwhile to look to the antecedents.

Inhalational Anesthesia

Around 1540, Paracelsus, a Swiss physician and alchemist, sweetened the feed of fowl with sweet oil of vitriol, a substance earlier prepared by Valerius Cordus, then named Aether by Frobenius--the familiar diethyl ether that would later be inhaled by most surgical patients over a span of 100 years or more. Paracelsus was led to exclaim, "... and besides, it has associated with it such sweetness that it is taken even by chickens and they fall asleep from it for a while but awaken later without harm."

Local Anesthesia

The coca leaf was believed to be a gift to the Incas from Manco Capac, son of the sun god, as a token of esteem and sympathy for their suffering. Initially used narrowly for religious and political purposes, the leaves achieved a more ominous significance with the destruction of the Incan civilization in the 16th century by Francisco Pizarro's conquistadores. The lower classes and slaves were paid off in coca leaves, an effective method of increasing and prolonging their productivity and ensuring low-cost, high-output labor. Customarily, coca leaves bound into a ball (cocada) with guano and cornstarch were chewed with lime or alkaline ash to release the active alkaloid. Anthropologic documentation of that era indicates that trephination was successful as the

---

Figure 1-1 (Figure Not Available) A wood engraving illustrating the intravenous injection of medicinals, employing a quill and bladder and two tourniquets. *(From Major DJ: Chirurgia Infusoria placidis CL: Virorium Dubiis impugnata, cum modesta, ad Eadem, Responsione. Kiloni, 1667.)*

operator permitted cocaine-drenched saliva to drip from the mouth onto the wound, thereby providing creditable local anesthesia.

Intravenous Anesthesia

One can construe that Harvey's studies of the circulation enabled both Percival Christopher Wren and Daniel Johann Major (Fig. 1-1) (Figure Not Available) to conceive the idea of injection of medicinals into the blood stream. Consequently, in 1665, Wren wrote that he could

> easily contrive a way to convey any liquid thing immediately into the circulating mass of blood; thus, in pretty big and lean dogs, by making ligatures on the veins and then opening them on the side of the ligature towards the heart; and by putting into them slender syringes or quills, fastened to bladders containing the matter to be injected ... whereof the success was that opium, being soon circulated into the brain did within a short time stupefy, though not kill the dog: but a large dose of the crocus metallorum, made another dog vomit up life and all.

The dried crocus or saffron was at the time employed as a stimulant, antispasmodic, and emmenagogue.

THE RISE OF INHALATIONAL ANESTHESIA

Primary observations on the physiology of the circulation and respiration eventually led to the discovery of gases and vapors and their experimental inhalation. In the mid-17th century, a Belgian, J. B. van Helmont, recognized a group of gases that were different from those of the atmosphere and attempted to classify them, and Harvey, during his studies on the circulation, noticed a difference in color, from dark to florid, when blood passed through the lungs. Robert Hooke opened the chest of a dog while sustaining lung inflation with a bellows, thereby proving that their rhythmic expansion is not immediately necessary for survival. A related conclusion was that some part of the atmosphere must enter the lungs, an essential ingredient named phlogiston by Stahl. Concurrently, Robert Boyle, in exhausting air from a bell jar containing a lighted taper and a living bird, extinguished the lives of both. In 1774, in the process of heating mercuric oxide, Joseph Priestley liberated oxygen, a gas with a "goodness" that sustained life, perhaps identical with the phlogiston of Becher and his pupil Stahl. Incidentally, Priestley also obtained nitrous oxide from nitric oxide. However, Antoine Lavoisier recognized phlogiston as the oxygen we breathe in the atmosphere. He concluded that only a smaller share of it was concerned in respiration, the larger share being irrespirable (nitrogen). He also observed that exhaled air precipitated lime water and concluded that it must also contain chalky air or carbon dioxide. Thus, the outlines of external respiration were delineated.

In the last decade of the 18th century, a center for the pneumatic treatment of disease was established in Birmingham, England. Joseph Priestley, James Watt, Josiah Wedgwood, Dr. Richard S. Pearson, and Thomas Beddoes were among the founders. Ether could be inhaled by a sufferer via a funnel to alleviate congestion and phlegm. Beddoes wrote that the medicinal use of these factitious airs was beneficial in the cure of bladder calculus, sea scurvy, and catarrhal fever. Realizing that more intensive experimentation was required, this group, with little knowledge of the causes of disease, established a Pneumatic Institute at Clifton, Bristol, and providentially appointed Humphry Davy, the youthful, brilliant chemist and physiologist, as superintendent. First, Davy disproved the theory proposed by the American Samuel Latham Mitchell that nitrous oxide was the contagium of disease. While breathing nitrous oxide for the relief of headache and the pain of an erupting third molar tooth, Davy experienced a "thrilling and an uneasiness swallowed up in pleasure." Thus originated his seminal pronouncement: "As nitrous oxide in its extensive operation appears capable of destroying pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place." Not a surgeon, Davy failed to pursue the idea, but Henry Hill Hickman of Shifnal in Shropshire did so. Hickman was a practitioner and surgeon who lamented that "something had not been thought of whereby the fears [of a patient] may be tranquilized and suffering relieved." Having partially asphyxiated several animal species to a state of insensibility with carbon dioxide, Hickman in 1824 addressed his famous message to the Royal Society: "Letter on Suspended Animation--with the View of Ascertaining its Probable Utility in Surgical Operations on Human Subjects." Unfortunately and sadly, Hickman came the closest of all to the concept of surgical anesthesia, but utilizing an unlikely agent.

Davy's subjective experiences were duplicated among friends and visitors to the Institute and were soon taken up by the adventurous public in the form of frolics. In the United States, Crawford W. Long, while a student at the

University of Pennsylvania in the late 1830s, could very well have observed and participated in such fantasies. Sometime after his return to Jefferson, Georgia, as a general practitioner, Long probably not only introduced such frolics but also surely persuaded a young man, James M. Venable, to inhale ether while a growth was excised from the nape of his neck on March 30, 1842. Even though this venture was repeated several times, the matter was kept secret until the first report appeared in 1848 in the *Southern Medical and Surgical Journal,* several years delayed by influential physicians who were using mesmerism for surgical operations. Later it became known that William E. Clarke, a student at the Vermont Medical College, had employed ether for a tooth extraction in January 1842.

Within 2 years of this first clandestine surgical anesthetic, on December 10, 1844, Gardner Quincy Colton took his itinerant medicine show to Hartford, Connecticut, where an audience could experience the exhilarating effects of nitrous oxide inhalation. So intoxicated, Samuel A. Cooley did not notice at first that he had injured a leg in the melee, but in the audience, Horace Wells, a dentist, was quick to pick up the significance of this suggestion of analgesia. The next day, Wells had one of his own carious teeth painlessly extracted by a fellow dentist, while Colton administered the anesthetic. The anguish of dental pain could now be assuaged, and Wells set about to tell the world of his discovery. Circumstantially, a one-time student of Wells, William Thomas Green Morton, then in practice in Boston and enrolled in a course of lectures at Harvard Medical School, arranged for a demonstration by Wells in January 1845 before a group of medical students. However, the nitrous oxide demonstration proved a failure because a student screamed out in pain as his tooth came out, even though he later admitted to no recollection of pain. No doubt the time of induction was too brief and the gas reservoir too small to provide a surgical plane of anesthesia.

W.T.G. Morton, probably a witness to this abortive demonstration, also yearned to relieve pain because a dental prosthesis of his invention could be applied only after the rotted roots of teeth were extirpated, an experience few patients would venture to endure. As a domiciliary student with Charles T. Jackson, eccentric geologist and chemist, Morton learned from him that pure ether applied to the gums would, through evaporation, yield a degree of cold anesthesia. After experiments with inhalation of the vapor of ether in several animal species, Morton went a step further, and on September 30, 1846, in his Boston office, he painlessly removed a tooth from the mouth of Eben H. Frost, a merchant of that city. When notice of the operation appeared in a newspaper the next day, Henry Jacob Bigelow, a surgeon at the Massachusetts General Hospital, arranged to observe several additional anesthetics of the kind given by Morton. Suitably impressed and convinced of its surgical utility, Bigelow arranged for a trial of anesthesia at the hospital with John Collins Warren, a renowned surgeon, one-time dean of Harvard Medical School, and founder of the hospital in 1821 with several others. Warren was also an originator of the *Boston Medical and Surgical Journal,* now the *New England Journal of Medicine.* On October 16, 1846, using a hastily devised glass reservoir incorporating the drawover principle of vaporization, Morton anesthetized Edward Gilbert Abbott, a young printer, while Warren deftly ligated a congenital venous malformation in the left cervical triangle. This feat culminated in J.C. Warren's memorable remark to the assembled gallery, "Gentlemen, this is no humbug" (Fig. 1-2) (Figure Not Available) .

The Massachusetts General Hospital has, to this day, designated the incident as the first public demonstration, rather than discovery, and Oliver Wendell Holmes, professor of anatomy and literateur extraordiniare, chose the Greekderived noun "anaesthesia" to characterize the process. He had also considered "neurolepsis," a term employed today to describe the drugs used in one variety of balanced anesthesia. With a medical discovery of universal significance, it was only natural that a prolonged period of controversy would ensue as to who might be given the credit. Fortunately, such an outcome did not impede further application of the method, enhanced by the prestige of the hospital and its

Figure 1-2 (Figure Not Available) William Thomas Green Morton giving the first public demonstration of etherization at the Massachusetts General Hospital, Boston, October 16, 1846. Physicians around Edward Gilbert Abbott, patient, are from left to right: H.J. Bigelow, A.A. Gould, J. Mason Warren, J. Collins Warren, Morton, Samuel Parkman, George Hayward, and S.D. Townsend. *(From a steel engraving in Rice NP: Trials of a Public Benefactor, 1859.)*

Harvard-affiliated physicians, who knowledgeably reported on the pharmacology and physiology of the phenomenon.

In a situation of multiple discoveries as recounted here, sociologists of science would assert that the concept of anesthesia was "in the air," merely awaiting the appropriately receptive mind and social circumstance. Perhaps the Americans succeeded because of their pioneering spirit and lack of authoritative medical institutions. In England, on the brink of the industrial revolution, a medical hierarchy had already existed, made up of hospitals and societies, with public health a new concern and the general practitioner the dominant figure--here, a revolutionary therapy might not be adopted so readily.

W. Stanley Sykes, in an essay on "The Seven Foundation Stones, in Order of Merit," ranked the contenders for recognition in descending order of importance. First was Hickman, who "above all others had the idea of anaesthesia most deeply and spontaneously engrained in him." Second was Horace Wells, who "given the stimulus and the sight of a man partly under the influence of gas failing to notice an injury ... saw the possibility of it at once, as no one else had done." Third was W.T.G. Morton "to whom belongs the undoubted credit of introducing successful anaesthesia with sufficient publicity to ensure that it immediately achieved world-wide acceptance." Fourth, "Humphry Davy discovered the analgesic properties of nitrous oxide by inhaling it and made his famous suggestion that it could be used for surgical operations." Fifth was Crawford W. Long, "another pioneer who could easily have held a much higher place and had only himself to blame." "Long's place in the ranking order is low simply because of his extraordinary reticence." "There was no originality about James Young Simpson," and Charles T. Jackson, the last of the pioneers, "really does not deserve to be in the list at all. He did not have the idea of anaesthesia in the first place. All he did was to try and cash in upon it when it proved to be successful."

PROFESSIONAL ANESTHESIA IN ENGLAND: APPLICATION TO OBSTETRICS

John Snow, general practitioner, clinical investigator, and epidemiologist (who halted a cholera epidemic in London), became the first of a long line of British physician anesthetists, in contrast to America, where that species was to blossom only around the turn of the century (Fig. 1-3) (Figure Not Available) . In 1847, Snow's text on *The Inhalation of the Vapour of Ether* appeared, containing case reports and an elaborate description of the traditional signs and stages of ether anesthesia. An earlier tract on ether written by Robinson, a dentist, had appeared, as well as an account by Plomley of the stages of anesthesia, but Snow's pronouncements were definitive. Likewise, in Great Britain toward the end of 1847, James Young Simpson, obstetrician, who had first used ether to relieve the pain of labor, adopted chloroform for the purpose, as suggested to him by David Waldie (Ch. 57) . The compound had been independently synthesized by Samuel Guthrie of Sackett's Harbor, New York; Eugene Soubeiran, of France, and Justus von Liebig, of Germany. Although the clergy as well as other physicians opposed the concept of relieving pain during

Figure 1-3 (Figure Not Available) John Snow (1813-1858). Physician, epidemiologist, and first specialist in anesthesia. *(Reproduced from the Asclepiad, 1887, vol 4.)*

childbirth, the method took hold and achieved lasting status after Queen Victoria gave birth to Prince Leopold while being given chloroform at the hands of John Snow; this method was dubbed "anesthesia a la reine." To further strengthen the principle of obstetric anesthesia, Walter Channing, professor of midwifery and medical jurisprudence at Harvard, in 1847 wrote a *Treatise on Etherization in Childbirth,* the results of a survey to settle the important issue of safety. Although the validity of the study is questioned, Channing cited the use of morphine during labor and also included cases in which chloroform had been employed. Because of its less objectionable properties, more pleasant odor, and rapid induction and emergence, chloroform superseded ether in Great Britain. In 1858, a second text by Snow was published, *On Chloroform and Other Anaesthetics,* completed posthumously, with a biography added by Benjamin Ward Richardson, Snow's successor.

DEVELOPMENTS IN SURGERY

Surprisingly, the initial use of both ether and chloroform led to little alteration in surgical practice, which remained largely of an external nature: trephining of the skull, tapping of the chest for fluid removal, relief of strangulated hernia, extraction of bladder calculus, reduction of fracture, and amputation of extremities. Surgical writings and lectures then pertained mostly to anatomy. Moreover, with an increase in the number of hospitals and their consequent use rather than the home to treat illness, a new problem arose, that of infection, which came to be known as hospitalism. The initial solution, listerism, or surgical antisepsis using

carbolic acid, was not widely practiced until 1879, when it was acclaimed at an international conference. Then arose steam sterilization and true antisepsis.

Siegrist observed that the introduction of anesthesia was not the first attempt to render patients insensible to pain. Why then did surgery not have its great development before the mid-19th century, coincident with, rather, than resulting from, anesthesia? The answer lies in studies of the development of concepts of disease, "for surgery is only one method of treatment and like any other method is largely determined by the concept of disease prevailing at the time." As noted in the introduction to this chapter, for more than 2,000 years disease was considered to be the result of a disturbed balance of the cardinal humors of the body, which enjoyed health when in balance but showed symptoms of disease when upset.

Then, in the 18th and 19th centuries, with Morgagni describing the results of large numbers of autopsies, it was learned that organic lesions were responsible for disease. It seemed, then, that if an organ were abnormal, its function would also be abnormal. Consequently, it became the purpose of diagnostics to perceive anatomic changes in the living patient by the use of percussion and auscultation and by the use of bulbs and mirrors to look into the body cavities. Roentgenology was the ultimate triumph in this direction. By draining an abscess or excising an ulcer or tumor the surgeon was removing the disease and correcting the organ. Undoubtedly, however, surgery could not develop freely before the two bonds that enslaved it had been removed--pain and infection.

LOCAL ANESTHESIA

Cocaine began to receive attention in Europe and America during the mid-19th century (Ch. 13) . Around 1860, Albert Niemann, a pupil of Friedrich Wohler, isolated the alkaloid in crystalline form. Twenty years later, von Anrep wrote an extensive review on the physiologic and pharmacologic properties of cocaine, clearly citing the locally numbing effect on the tongue and dilation of the pupil, the former leading him to suggest that some day cocaine might become of medical importance. Later, Sigmund Freud of Vienna began to study the properties of the drug when given samples for trial by the Merck Company. As a result of reviewing *The Index Catalogue* of the Library of the Surgeon General's Office of the United States Army, which referenced some 25 papers and 10 monographs under the heading "Erythroxylin Coca," Freud, in 1884, wrote his classic paper "Uber Coca." Believing coca to be a worthy substitute for morphine, Freud first attempted to eliminate the morphine addiction of a close friend, Ernst von Fleischl-Marxow, who had long suffered from a painful posttraumatic thenar neuroma. von Fleischl-Marxow developed a new addiction as a consequence, as would many a cocaine user later on, but Freud himself never seemed to go down that path.

Sigmund Freud and Karl Koller

Sigmund Freud and Karl Koller, an intern in the Department of Ophthalmology at the Allgemeinen Krankenhaus in Vienna, used a dynamometer to study the effect of coca on muscle strength. Both researchers noticed the numbing effect on the tongue as they swallowed the experimental drug. Koller had a burning desire to anesthetize the cornea and conjunctiva for ophthalmologic operations and had already tried morphine and chloral bromide. In Freud's absence, he and Joseph Gartner dissolved a trace of the white powder in distilled water and instilled the solution into the conjunctival sac of a frog. After a minute or so, "the frog allowed its cornea to be touched and it also bore injury to the cornea without a trace of reflex action or defense." Koller wrote, "one more step had yet to be taken. We trickled the solution under each other's lifted eyelids. Then we placed a mirror before us, took pins, and with the head tried to touch the cornea. Almost simultaneously we were able to state jubilantly: I can't feel anything." A communication describing this finding, dated early September 1884, was read and a practical demonstration given by Joseph Brettauer at the Ophthalmological Congress at Heidelberg on September 15 of that year. Koller did not have the means to travel there. Koller gave full credit to Freud for the inspiration. Despite the latter's disappointment at not being first with the discovery, Freud is considered by many to be the founder of psychopharmacology because of his initial use of cocaine, the forerunner of mescaline, lysergic acid diethylamide, and the amphetamines to modify behavior and subsequently to relieve mental illness.

James Leonard Corning

After Koller, James Leonard Corning deserves citation for his analytic approach to local anesthesia in humans on the basis of laboratory experimentation. Having learned of Koller's report, Corning recalled the experiment in which strychnine is injected subcutaneously in the frog, causing the animal to have violent spasms as a result of an effect on the spinal cord. Because a much smaller quantity of strychnine injected beneath the membranes is equally effective following laminectomy, he assumed that the poison must act via vascular absorption. Cognizant of the presence of the many small veins, venae spinosum, about the spinal column and cord, Corning reasoned that it might be possible to utilize cocaine therapeutically. Accordingly, in a young dog, about 20 minims of a 2 percent solution of cocaine was injected between the spinous processes of the dorsal vertebrae. After some minutes, incoordination of the posterior extremities developed, followed by insensibility. These results were almost immediately applied to a patient, a man suffering from spinal weakness and seminal incontinence. "To this end, I injected 30 minims of a 3 percent solution of the hydrochloride of cocaine into the space situated between the spinous processes of the 11th and 12th dorsal vertebrae." After a lapse of 6 to 8 minutes, when nothing happened, the injection was repeated. Finally, 10 minutes later, anesthesia began to appear in the lower extremities, and a sound could be passed through the urethra without pain. Corning concluded his report with the statement, "Whether the method will ever find application as a substitute for etherization in genitourinary or other branches of surgery, further experience alone can show." This conclusion follows the pattern of statements made by Wren, Davy, and von Anrep

---

in relation to intravenous, inhalational, and local anesthesia, respectively, thereby further confirming the evolutionary aspects of science. Corning's textbook on local anesthesia, published in 1886, was the first devoted to the subject.

Regional Anesthesia Techniques and Agents: Procaine and Epinephrine

In juxtaposition to inhalational anesthesia, and because of toxicologic problems with chloroform, high anesthetic mortality, and lack of trained personnel to give general anesthesia, local anesthesia became highly popular with surgeons, especially in France and Germany, and to some extent in the United States. After a trial on himself that resulted in the first-known development of a lumbar puncture headache, August Bier of Germany began to give spinal anesthesia in 1898, followed by Matas in America and Tuffier in France. Then, because of the evident toxicity and tendency toward addiction of cocaine, a number of ester substitutes were synthesized, procaine (Novocain) by Einhorn becoming the more lasting of the group. As a result of pharmacologist John J. Abel's efforts at Johns Hopkins Medical School, epinephrine was isolated from the capsule of the suprarenal gland in 1897 and was ultimately crystallized by Takamine. Heinrich Braun, a German surgeon, advocated the use of cocaine in conjunction with epinephrine when, in 1903, he reported on its practical importance in inducing anemia of the mucosa in rhinolaryngologic and urologic surgery, thereby permitting the concentration of cocaine to be lowered and diminishing the dangers of intoxication.

Most currently used techniques of regional anesthesia were devised during that first decade: brachial plexus block, axillary and supraclavicular approaches, intravenous regional anesthesia (Bier), celiac plexus block, caudal anesthesia, hyperbaric and hypobaric techniques of spinal anesthesia, and all the presently employed nerve blocks about the head and neck that are applied in dentistry and plastic surgery. Thereafter, aside from technical innovation and understanding of some of the physiologic and toxicologic responses to local anesthetics, the great impetus to regional anesthesia came from the synthesis of the amide local anesthetics and an understanding of their pharmacodynamic and especially pharmacokinetic properties.

INTRAVENOUS ANESTHESIA

We have cited the experiments of Wren and Major in introducing medicinals into the circulation, quick upon Harvey's description of the circulation (Chs. 8 and 11) . Around the 1850s, the hypodermic hollow needle and glass and metal syringes were introduced via the inventions of Scotsmen Francis Rynd (1845) and Alexander Wood (1855) and Charles Gabriel Pravaz (1853). Although these improvements over the quill and bladder were to herald both intravenous and regional anesthesia, Rynd and Wood were making injections into the vicinity of nerves for the relief of neuralgia, and Pravaz injected ferric chloride via trocar into arterial aneurysms in an attempt to induce thrombosis.

Pierre-Cyprien Ore

W. Stanley Sykes, in a posthumously published essay, cited Pierre-Cyprien Ore as the true pioneer of intravenous anesthesia. Employing chloral hydrate for the purpose, his first report on the method was addressed to the Surgical Society of Paris in 1872. Utilizing a modification of the Pravaz syringe and needle, because he had found the latter likely to transfix the vein and cause the solution to be injected perivenously, Ore claimed that chloral hydrate was the most powerful of all anesthetics. As usual, opposition arose as critics raised the possibility of development of phlebitis and clotting. In a monograph published with a detailed account of 36 cases, some 18 for cataract surgery and others for treating tetanus, Ore claimed not to have encountered a single instance of clotting or phlebitis. Cardiac arrest occurred in one patient, an otherwise healthy, middle-aged man undergoing cataract extraction.

Anociassociation

Early in the 1900s, an essential concept was proposed toward the development of balanced anesthesia in which intravenous anesthesia is a major component. This was the anociassociation theory of George W. Crile, who in 1901 stated, "In conscious individuals, all noxious stimuli reach the brain. During general anesthesia only the traumatic stimuli are perceived centrally while with complete anociassociation all stimuli are blocked." Enlarged on by Harvey Cushing in 1902, the idea of anociassociation became the basis for the use of opioids intravenously, so prominent in practice today. Incidentally, George Crile, at the Cleveland Clinic, and the Mayo brothers, of Rochester, were the first to employ nurse anesthetists in their surgical practices. Cushing had a number of "firsts" relative to the development of anesthesia: coining the term "regional anesthesia," keeping anesthesia records, being the first in the United States to employ the Riva-Rocci technique for measurement of blood pressure intraoperatively, using a precordial stethoscope during operation, and being a surgeon who first appointed a physician, Walter M. Boothby, in charge of anesthesia at his clinic in Boston.

The Barbiturates

The major impetus for the subsequent development of intravenous anesthesia lay in the synthesis of the short-acting, water-soluble barbiturates. In 1903, long after von Baeyer had synthesized barbituric acid, or malonylurea (1864), Fischer and von Mering prepared the first sedative barbiturate, diethyl barbiturate, or barbital, a long-lasting hypnotic soon to be succeeded by the sodium salt of phenobarbital. Then, as other soluble compounds were devised, a number of barbiturates of short, medium, and long duration became available. Pernoston, a shorter-acting agent, was first given intravenously in 1927, in a 10 percent aqueous solution, and in 1928, John S. Lundy began to supplement inhalational anesthesia with amytal, then pentobarbital, intravenously, a procedure he designated balanced anesthesia. Because by current standards both drugs provide only a relatively slow onset

of action, the advent of hexobarbital, or Evipal, in 1932 (Weese) resulted in the first rapidly acting intravenous anesthetic to receive wide use. Ultimately, a sulfur derivative of barbituric acid yielded the necessary qualities, with the result that thiopental, a derivative of pentobarbital, was adopted both by Lundy, at the Mayo Clinic, and by Waters, at Wisconsin. Dundee noted how remarkable it is that this drug has survived and withstood the challenge of so many others. As in every intravenously given compound, no matter what the therapeutic ends, the lasting effects of such drugs depend on specific pharmacodynamic and pharmacokinetic properties, as first shown by Brodie and colleagues around 1950.

THE EVOLUTION OF PROFESSIONALISM IN AMERICA

The British were indeed fortunate in having physicians, beginning with John Snow, who specialized in anesthesia, a circumstance that eventually led to the formation of societies and publication of articles in the 1890s in such journals as *Lancet, British Medical Journal,* then the *Proceedings of the Royal Society of Medicine,* in which the subject of anesthesia had its own section. By definition, professionalism is a calling in which one professes to have acquired some special knowledge used by way of instructing, guiding, or advising others or in serving them in some art.

The Milieu

In America at the time of the first public demonstration, medicine was in a period of frontier expansion, in contrast to Great Britain. The general practitioner did all the work, and although the easterners began to loom as specialists and leaders, a good deal of emphasis was placed on practice as a business, with medical education at a low level. The only medium for scientific publication in the first part of the 19th century was the *Transactions of the Royal Society.* At the turn of the century, a class of physicians emerged that was clearly identified with anesthesia. Interestingly, the primordial group was made up mostly of midwesterners and Canadians, who may have had as peculiar characteristics, "their pioneering traditions, their common purpose, devotion to equality and their struggle for success." Of the pioneers, Ralph Waters was to remark in a reflective mood that "the development of a specialty could be traced in terms of men, publications and organizations." Three figures stand out in this regard, Waters among them.

Francis Hoeffer McMechan

F.H. McMechan, born in Cincinnati and son of a physician, excelled in college in oratory and dramatics and became a newspaper reporter on graduation, before matriculating at the Cincinnati Medical School. There, as would be the custom for many a decade, he was required to administer anesthetics, for his father as well, so that he became a devotee of the method. Between 1903 and 1910, he combined anesthesia with general practice, but progressively crippling arthritis forced abandonment of practice and his subsequent preoccupation with the organization of anesthesia and medical editing.

In 1912, in conjunction with Bainbridge, a surgeon, Yandell Henderson, a physiologist, and James T. Gwathmey, an anesthetist, McMechan founded the American Association of Anesthetists. As a result of his persuasion, the *American Journal of Surgery* began to publish a *Quarterly Supplement of Anesthesia and Analgesia* in 1914 (Fig. 1-4) , which survived until 1926, with McMechan as editor; he also served as editor of a *Year Book on Anesthesia and Analgesia.* His formation of one group after another in the United States and Canada led ultimately to the National Anesthesia Research Society, then to the International Society, whose medium of reporting in 1922 became *Current Researches in Anesthesia and Analgesia,* the first publication devoted solely to those subjects. Assisted in these endeavors by his wife, McMechan, who died in 1939, would have been gratified to know that the International Society and its publication, *Anesthesia and Analgesia,* still exist.

Elmer I. McKesson

The second of the trio, E.I. McKesson, was an innovator, teacher, and inventor, born in 1881 in Walkerton, Indiana. A teacher at first, McKesson was graduated from Rush Medical School and while an intern in Toledo became attracted to anesthesia. Later, he would found the University of Toledo,

Figure 1-4 "Quarterly Supplement of Anesthesia and Analgesia," Introductory Number, October 1914, edited by F. Hoeffer McMechan, as it appeared in the *American Journal of Surgery.*

where he served as associate professor of physiology and physiologic chemistry. McKesson invented and developed many pieces of apparatus: gas-oxygen machines, suction apparatus, metabolism-measuring devices, intermittent and demand gas flow valves, oxygen tents, and other instruments, all manufactured by the Toledo Technical Appliance Company. The Nargraf apparatus and the McKesson gas machine remained standard equipment until well into the 1950s.

Ralph M. Waters

Third, we have R.M. Waters, who left his mark on several generations of anesthetists by way of far-reaching vision, combining in no small measure all the stellar attributes of the other early American anesthetists. Born in 1883 in Bloomfield, Ohio, he was graduated from Western Reserve University Medical School, served as an intern in Cleveland, and then practiced privately in Sioux City, Iowa, with obstetrics as a chief interest. He began to give anesthesia for operations performed by the other practitioners, although some of them employed nurses for that purpose. Self-trained and with only a few specialized writings at his disposal-- *Proceedings of the Royal Society, McMechan*' *s Quarterly,* and Gwathmey and Baskerville's *American Text Book of Anesthesia*-- Waters wrote an article, "Why The Professional Anesthetist" in 1919. Such was his growing reputation that by 1927, he was invited to a post on the faculty of the University of Wisconsin as assistant professor of surgery in charge of anesthesia and was one of a group of luminaries in surgery, physiology, and pharmacology. For the first time, he established a resident training program in anesthesia coupled with an investigative effort that entailed, among other things, the examination of hydrocarbon-epinephrine cardiac arrhythmias, the pharmacology of cyclopropane, and a reexamination of the toxicology of chloroform. Many an apparatus arose from this clinical-investigative milieu, some rediscovered, others new: cuffed endotracheal tubes, laryngoscopic blades and pharyngeal airways, carbon dioxide absorption canisters, and precision-controlled liquid anesthetic vaporizers.

There were other outstanding innovators in American anesthesia, among them Arthur A. Guedel, John Silas Lundy, and a later generation of university chairmen-professors, including E.A. Rovenstine (New York University), R.M. Tovell (Hartford Hospital), H.K. Beecher (Harvard), S.C. Cullen (Iowa and San Francisco), John Adriani (Tulane), R.D. Dripps (Pennsylvania), E.M. Papper (Columbia-Presbyterian Hospital), P.P. Volpitto (Georgia), and L.D. Vandam (Harvard).

/das/book/view/29494766/875/13.html

THE DEVELOPMENT OF MODERN ANESTHESIA

The American Society of Anesthesiologists

In 1905, a group of physicians, with Adolf F. Erdman as the catalyst, formed the Long Island Society of Anesthetists, "to promote the art and science of anesthesia." As the membership grew, the name of the organization was changed to the New York Society of Anesthetists in 1911, then augmented by out-of-state anesthetists so that by 1916, 60 members were enrolled. On the 25th anniversary (1930) of the founding of the Society, a 2-day scientific program was convened in New York City. In 1936, the name was once again changed to describe its breadth and character, The American Society of Anesthetists, Incorporated, with 484 adherents.

Over succeeding years, all the attributes of a specialty society were fulfilled, and the designation anesthesiologist replaced the nondescript term *anesthesia* to indicate that anesthesiologists are physicians who have received formal training in anesthesia. A certification committee was appointed that led to the acceptance of a section on anesthesiology into the hierarchy of the American Medical Association in 1940. That year marked the initial publication of its official journal, *Anesthesiology.* The stature of the Society was enhanced by incorporation of the Wood Library- Museum of Anesthesiology in 1950; to accommodate its multiple activities, a society headquarters was erected in Park Ridge, Illinois, in 1962, with an addition 2 years later to house the Library-Museum. The American Society of Anesthesiologists has dedicated itself to the following goals and endeavors: standards for equipment and patient care, education, repeated self-analysis via survey to crystallize the state and objectives of the Society, issues of manpower, affiliation with the World Federation of Societies of Anesthesiologists, and consideration of problems common to all kinds of medical practice. All these endeavors continue to progress with an eye toward discerning trends and future developments.

Progress Since 1940

After a gestational period of approximately 100 years, modern anesthesia began around the 1940s. At that time, as Lewis Thomas asserted, medicine was about to undergo a second revolution, from a mere art into a powerfully effective science. First, in the later 19th century, rebellion against the Galenical tradition had resulted in a practice in which the history, physical examination, and establishment of a diagnosis provided a basis for prognosis, not cure. This transition was succeeded in the late 1930s by the discovery of effective new drugs, initially the sulfonamides and then the antibiotics, for the treatment of infection. Inevitably, anesthesia would be caught up in the succeeding therapeutic and scientific ferment, as were all the specialties of medicine.

The first change in direction was the initial use during anesthesia of a curare product by Griffith and Johnson of Montreal in 1942. The muscle-paralyzing properties of the alkaloid derived from several preparations of South American plants had been known for centuries, and the site of action at the neuromuscular junction was graphically demonstrated by Claude Bernard. In the United States, crude extracts had been employed clinically to treat spasticity and to modify the convulsions induced during electroconvulsive therapy (ECT) for depression and other psychoses. Initially, when given the extract for experimental trial, S.C. Cullen, of Iowa City, and E.M. Papper, of New York, had independently deemed the paralytic effects to be too much a physiologic

trespass to be introduced to the anesthetic regimen. No one knows what subtle influence led Griffith to inject Intocostrin during the course of a cyclopropane anesthetic without prior experimentation. T.C. Gray of Liverpool, England, was reminded of John Hunter's advice to Edward Jenner in regard to vaccination: "Do not think--try." Perhaps Griffith was affected by the therapeutic revolution under way, even as Horace Wells in another era had perceived the concept of anesthesia while witnessing a demonstration of the mental effects of nitrous oxide.

The subsequent general use of curare had widespread repercussions. As a result of the muscle paralysis induced, tracheal intubation became necessary for manual control of pulmonary ventilation during anesthesia, followed rationally by the development of mechanical ventilators, obligatory studies on the physiology of central and peripheral respiration, and the invention of postanesthetic recovery rooms, where anesthesiologists would play a dominant role. In connection with this broadened participation in patient care, many physicians returning from World War II, during which they had had introductory experience with anesthesia, sought further training in this developing branch of medicine.

Anesthesiologists, as they now designated themselves, were soon impelled to scrutinize the safety of their performance, and the use of curare no doubt sharpened the focus. Thus, following the findings of several American anesthesia study commissions and reminiscent of the Hyderabad Chloroform Commissions of the late 19th century, H.K. Beecher, of Boston, initiated a prospective study of operating room deaths. This project incorporated the practice of some ten university-associated hospitals during the years 1948 to 1952. From a total of approximately 600,000 anesthetic administrations, the overall anesthetic-associated death rate was adjudged to be about 1:1560. In addition, many important epidemiologic data emerged. The most startling and controversial finding was a significantly higher mortality rate in patients given muscle relaxants, mainly curare, during anesthesia. Although Beecher ascribed this occurrence to an inherent drug toxicity, more likely the explanation was to be found in residual postanesthetic muscle paralysis and the associated respiratory insufficiency, which was inadequately treated or unrecognized in those days. One of the conclusions derived from this study suggests the state of anesthesia of that era: "Great changes in the use of anesthesia agents and techniques occurred within the five years of this study. This suggests that the practice of anesthesia is far as yet from achieving stability."

Also in the 1950s, following the admonition of W.T. Salter, a pharmacologist of Yale, that "without vision and research the professions die," research in anesthesia began, initially in conjunction with basic science departments in medical schools. Thus, S.S. Kety, of Philadelphia, and B.B. Brodie, of New York, inaugurated the science of pharmacokinetics in their respective studies on the uptake and distribution of inhaled anesthetics and the metabolism of thiopental. With this impetus, anesthesiologists enlarged on these basic concepts that today compose routine knowledge of the drugs we use. Soon thereafter, because of their unfavorable properties, most of the traditional inhaled anesthetics were replaced by the new anesthetics. Diethyl ether and cyclopropane were also abandoned, not only because of their flammability but also because of their poor pharmacodynamic and pharmacokinetic attributes. Only nitrous oxide maintained its place, and procaine was succeeded by local anesthetic agents of greater latitude.

The major inhaled anesthetic substitutions included the nonflammable, highly lipid-soluble and therefore potent, vapors; halogenated inhalants; more versatile neuromuscular blockers; and local anesthetics with the amide rather than ester structure. In some instances, there were unforeseen events, as when halothane was associated with development of postanesthetic fatal hepatic necrosis, a phenomenon previously well-documented for chloroform. A multiinstitutional cooperative endeavor supported by the National Institutes of Health led to the National Halothane Study. Although the conclusions of the survey were hotly debated, the data, derived from some 34 institutions based on approximately 850,000 anesthetic administrations, suggested an incidence of halothane-associated fatal hepatic necrosis approaching one in 10,000 anesthetics. Repeated administration of halogens for several anesthetics was an important contributing factor. Although an altered sensitivity to halothane was deemed responsible by some, a more convincing explanation implicated toxic metabolites induced by hypoxia as the cause. Only recently has evidence reappeared for an immunologic basis of the lesion (Ch. 6) .

Following these events, research on anesthesia began to reach its stride. First, the unsuspected fact emerged that inhaled anesthetics that were formerly considered

inert were indeed metabolized in various degrees; for example, halothane was 20 percent metabolized, and methoxyflurane was 50 percent metabolized. Not long after its introduction, methoxyflurane was discovered to induce a rare kind of renal failure with tubular necrosis, characterized by high urinary output that was unresponsive to vasopressin. Because of the pharmacokinetics and the production of a toxic metabolite, the free fluoride ion, a condition once described by the French as "diabetes insipidus fluorique," was found to occur after methoxyflurane anesthesia. Fluoroxene, another halogenated compound, was abandoned because of probable metabolite-induced hepatic necrosis. Investigations engendered by these events showed that the metabolism of halogenated anesthetics could be enhanced by hepatic enzymatic induction coincident with the use of barbiturates or phenytoin, with an actual proliferation of the endoplasmic reticulum and increase in cytochrome P-450. This discovery further emphasized the existing tenet that in their choice of anesthetics, anesthesiologists must remember the possibility of interactions with drugs of all kinds.

After the short-acting intravenous barbiturates were introduced, J.S. Lundy of Rochester coined the term "balanced anesthesia" to describe his use of these agents in conjunction with general or regional anesthesia. These practices were further advanced when, during the French-Indo-Chinese warfare of the late 1940s, Laborit and Huguenard of France used a "lytic cocktail" to prevent development of circulatory shock in the wounded. The resulting "artificial hibernation" induced by simultaneous injection of a barbiturate; an analgesic, meperidine; and the tranquilizer chloropromazine (L'Argactil), was typified by a state of stress-free suspended animation.

The tranquilizer was then succeeded by a butyrophenone, haloperidol, and meperidine was replaced by phenoperidine,

---

one of a new class of potent opioids. The concept was characterized as "neurolept-analgesia," a term Oliver Wendell Holmes had considered in 1846, before suggesting the term anaesthesia to describe the newly demonstrated phenomenon. In sequence, fentanyl (in combination with droperidol [Innovar]) was succeeded by the more potent opioids alfentanil and sufentanil. Purely intravenous anesthesia became possible, as practiced in clinics on the continent, and the potent analgesics were also given intraspinally (subarachnoid and epidural) to treat postoperative pain. This extra-anesthetic practice ushered in the era of anesthesiologists' concern with relief of acute postoperative pain, on the foundation of their previous pain treatment clinics that had mainly focused on chronic pain syndromes.

The profusion of unique agents and novel techniques introduced over the past 20 years naturally disclosed other unrecognized pharmacologic phenomena, some deleterious indeed. One category that pertains to all of drug therapy concerns pharmacogenetics, in which pharmacokinetic activity may be influenced by genetic factors. In this area, pharmacologists and anesthesiologists discovered that the metabolism of succinylcholine in plasma could be delayed or indeed prevented by the presence or absence of a variety of inherited pseudocholinesterases (Ch. 12) . Similarly, although elevations of body temperature and development of convulsions during ether anesthesia had long been noticed, a more malignant kind of hyperpyrexia came to be recognized. The malignant hyperthermia syndrome, often fatal, seemed to be triggered by a genetically determined response to agents such as succinylcholine and halothane (Ch. 27) .

Related to genetics is the fetal loss or development of fetal malformations that may occur when a pregnant woman is exposed to a variety of drugs, with some anesthetics suspect at least in animal experiments. One consequence of the putative adverse fetal effects was the initiation of epidemiologic studies that purported to show that the pregnant woman involved in operating room activities (nurses, anesthesiologists, and wives of anesthesiologists) could be exposed to trace anesthetic gases. A higher incidence of fetal loss was claimed, which led to the expensive installation of scavenging systems and the revival of closed-system anesthesia techniques with all of their complexities (Chs. 6 and 84) .

The development of contemporary anesthesia can be embellished by citing the improvement in anesthetic apparatus and monitoring systems toward greater safety or, on the pharmacologic side, continued search for the basis of narcosis at the molecular level. In this connection, a useful clinical yardstick was the concept of minimum alveolar concentration, which correlates closely with lipid solubility of anesthetics (Ch. 29) . Measurements of minimum alveolar concentration permitted comparison of studies on the physiologic effects of anesthetics in terms of their relative potencies. Parenthetically, there is the seemingly heretical suggestion that nitrous oxide should once and for all be abandoned because of the ever-present liability of hypoxemia, because of its effect on essential bone marrow metabolic enzymes, and last, because of its well-known nonpharmacologic properties in relation to air-containing body cavities.

The modern era of anesthesiology is reflected in the many respected scientific publications now devoted to that specialty the world over. Thus, the designation anesthesiologist may have been merited only after its adherents began to record their clinical experience and the results of laboratory investigations. We quote once more the lofty language of Salter's editorial, "The Leaven of the Profession," namely, "that professions do not live by service alone but rather by the words of wisdom which issue out of the mouths of those few demigods who in every generation lead and inspire the multitude of their professional associates."

We have suggested that modern anesthesia emerged about 100 years after the founding of clinical anesthesia. The events of the past decades have not been merely a parochial anesthetic excursion, but a manifestation of medicine's second revolution, which proceeds at an everquickening pace, anesthesiology included.

Suggested Readings
THE HISTORY

Bonner TN: The social and political attitudes of midwestern physicians, 1840-1940. J Hist Med 8:133, 1953.

Byck R (ed): Cocaine Papers. Sigmund Freud. New York, New American Library, 1974.

Cartwright FF: The English Pioneers of Anaesthesia. Bristol, John Wright & Sons, 1952.

Caws P: The structure of discovery: Scientific discovery is no less logical than deduction. Science 166:1375, 1969.

Channing W: A Treatise on Etherization in Childbirth. Boston, William D Ticknor, 1848.

Duncum B: The Development of Inhalation Anaesthesia. London, Oxford University Press, 1947.

Faulconer A, Keys TE: Foundations of Anesthesiology. Springfield, IL, Charles C Thomas, 1965.

Keys TE: The History of Surgical Anesthesia. New York, Schumans, 1945.

Laborit H, Huguenard P: Practique de l'hibernotherapie, en Chirurgie et en Medicine. Paris, Mason, 1954.

Merton RK: Singletons and multiples in scientific discovery: A chapter in the sociology of science. Proc Am Philos Soc 105:470, 1961.

Mortimer WG: History of Coca, "The Divine Plant" of the Incas. San Francisco, And/Or Press, 1974.

Ore PC: Etudes, cliniques sur l'anesthesie chirurgicale par la methode des injections de chloral dans les veines. Paris, JB Bailliere et Fils, 1875.

Siegrist HE: Surgery before anesthesia. Bull Sch Med U Md 31:116, 1947.

Smith WDA: Under the Influence. A History of Nitrous Oxide and Oxygen Anaesthesia. London, Macmillan, 1982.

Snow J: On the Inhalation of the Vapour of Ether. London, John Churchill, 1847.

Snow J: On Chloroform and Other Anaesthetics. London, John Churchill, 1858.

Sykes WS: Essays on the First Hundred Years of Anaesthesia, vols I and II. Edinburgh, Churchill Livingstone, 1960.

Sykes WS: Essays on the First Hundred Years of Anaesthesia, vol III. Edinburgh, Churchill Livingstone, 1982.

The Development of Modern Anesthesia

Beecher H, Todd DP: A study of the deaths associated with anesthesia and surgery. Ann Surg 140:2, 1954.

Brodie BB, Mark L, Papper EM et al: The fate of thiopental in man and a method for its estimation in biological material. J Pharmacol Exp Ther 98:85, 1950.

Bunker JP, Forrest WH, Mosteller F et al: The National Halothane Study: A study of the possible association between halothane anesthesia and postoperative hepatic necrosis. Bethesda, MD, U.S. Government Printing Office, 1969.

Cohen EN, Bellville JW, Brown BW: Anesthesia, pregnancy and miscarriage: A study of operating room nurses and anesthetists. Anesthesiology 35:343, 1971.

Crandall WB, Pappas SG, Macdonald A: Nephrotoxicity associated with methoxyflurane. Anesthesiology 27:591, 1966.

Griffith HR, Johnson GE: The use of curare in general anesthesia. Anesthesiology 3:418, 1942.

Kety SS: The theory and application of the exchange of inert gas at the lungs and tissues. Pharmacol Rev 3:1, 1953.

Mazze RI, Hitt BA, Cousins MJ: Effect of enzyme induction with phenobarbital on the in vivo and in vitro defluorination of isoflurane and methoxyflurane. J Pharmacol Exp Ther 190:523, 1974.

Nilsson E: Origin and rationale of neurolept analgesia. Anesthesiology 24:267, 1963.

Van Dyke RA, Chenoweth MB: Metabolism of volatile anesthetics. Anesthesiology 26:348, 1965.

Whittaker M: Plasma cholinesterase variants and the anaesthetist. Anaesthesia 35:174, 1980.

Section 2 - Scientific Principles

Chapter 2 - Basic Principles of Pharmacology Related to Anesthesia

Debra A. Schwinn
Steven L. Shafer

INTRODUCTION

Anesthesia involves administration of drugs to produce therapeutic effects while minimizing undesirable side effects or toxicity. Anesthesiologists give drugs to provide analgesia, amnesia, hypnosis, and muscle relaxation. They also administer drugs to manipulate major organ systems pharmacologically to maintain homeostasis and prevent injury. The therapeutic objective is to achieve adequate drug concentrations at specific sites of action to produce the desired effect. The anesthesiologist must select and administer appropriate drugs to provide tissue and receptor concentrations lower than those that produce unacceptable toxicity and higher than those that fail to provide effective therapy (i.e., within the therapeutic window).

The empiric approach to drug administration consists of selecting an initial dose and then titrating subsequent doses based on the clinical responses of the patient. The ability of the anesthesiologist to predict clinical response and hence to select optimal doses is, in part, the art of anesthesia. Continued research in the basic and clinical pharmacology of anesthetic drugs has produced guidelines by which the "science" of anesthesiology can enhance the art.

This chapter is divided into two sections: pharmacokinetic principles and pharmacodynamic principles. The pharmacokinetics section describes the relationship between drug administration and drug concentration at the site of action. Essential components of pharmacokinetics include volumes of distribution of drug within the tissues, binding of drugs to circulating plasma proteins, systemic clearance (usually hepatic metabolism for intravenous anesthetic drugs), biologic activity of metabolites, and transfer of drugs between plasma and tissues. Additionally, when drugs are administered by routes other than intravenous injection (e.g., transmucosal and transdermal fentanyl) the process of absorption is critical to the pharmacokinetic behavior of drugs. The first part of this chapter outlines how these processes determine the time course of drug concentration at the site of drug effect.

The pharmacodynamics section explores the relationship between drug concentration and pharmacologic effect. The broad areas of cellular mechanisms of drug action, clinical evaluation of drug effects, and variability in response are covered in this section.

An understanding of pharmacokinetic and pharmacodynamic principles provides the anesthesiologist with a scientific foundation for using drugs to achieve specific therapeutic objectives. These principles form the basis for the application of pharmacologic science to the practice of anesthesia.

PHARMACOKINETICS

Overview

Pharmacokinetics is the relationship between drug dose and plasma or effect-site drug concentration. The processes of absorption, distribution, and clearance govern this relationship. Absorption is not relevant to intravenously administered drugs, but it is highly relevant to all other routes of drug delivery. The pharmacokinetics of intravenously administered drugs is determined by distribution volumes and the processes of clearance. We first discuss the physiologic basis of pharmacokinetics, and then pharmacokinetic models that relate dose to plasma or tissue concentration.

Fundamental Pharmacokinetic Concepts

Volume of Distribution

The distribution of a drug throughout the plasma and tissues can be viewed as a process of dilution from the highly concentrated solution in the syringe to the dilute concentration in the plasma. This dilution follows the mixing of drug into a larger volume. The pharmacokinetic concept of volume is simply the apparent size of the tank required to explain the observed drug concentration. Figure 2-1 shows the dilution of administered drug into a tank of fluid. By definition, the concentration in the tank is the amount of drug administered divided by the volume of the tank. If we do not know the volume beforehand, but can measure the concentration, then we can rearrange the definition of concentration to tell us the volume of the tank:

Once the volume of the tank is known, the concentration following any bolus of drug can be calculated as the dose/volume. Just as the tank has a volume whether or not there is drug in it, the volume of distribution of a particular drug is an intrinsic property of the individual, whether or not any drug has been given. Unlike the tank in Figure 2-1 , the volume of distribution also depends on the properties of the drug.

Central Volume of Distribution

The central volume of distribution reflects the volume of the heart, great vessels, and the venous volume of the upper arm. It also reflects drug uptake by the lungs. For example, alfentanil is less lipophilic than fentanyl or sufentanil, resulting in less pulmonary uptake of alfentanil than of fentanyl or sufentanil. This results in a smaller central volume for alfentanil than for fentanyl or sufentanil. The central volume also reflects any metabolism that occurs between the venous injection site and the arterial sample.

Of the pharmacokinetic concepts that are introduced here, the central volume of distribution is the most problematic.

Figure 2-1 Volume represents the dilution of drug from the more concentrated form in the syringe to the dilute form in the blood.

The concept is based on an incorrect notion that the plasma concentration following bolus injection instantaneously mixes in this volume, resulting in an instantaneous peak at the moment of injection. Obviously, mixing is not instantaneous, and at the moment of intravenous injection, the arterial drug concentration is zero. The peak concentration is usually seen within 30 to 40 seconds of the injection. This 30- to 40-second delay is of no consequence for most therapeutics outside anesthesia, but within the field of anesthesia, the pharmacokinetic determinants of anesthetic induction are clinically important. The mathematics of the true time course including the time delay and recirculatory peaks have been worked out in detail by Krejcie et al, [1] as shown in Figure 2-2 .

Despite the assumption of instantaneous mixing, the concept of central volume of distribution is useful. The central volume represents the backward (and upward) extrapolation of the concentration versus time curve from its peak at about 30 seconds to the Y axis. It can be thought of as the initial concentration, had circulation been infinitely fast. Because of this backward extrapolation, estimates of the central volume are highly influenced by study design. A study with arterial samples has higher initial concentrations, and thus estimates a smaller central volume, than a study with venous samples. The timing of blood samples also influences the central volume of distribution. Over the first 2 or 3 minutes following bolus injection, the concentration of anesthetic drugs falls very rapidly. If the first sample is drawn at 30 seconds, the backward extrapolation of the concentration versus time curve to the Y axis predicts a high concentration at time 0, and thus a small central volume. If the first sample is drawn at 5 minutes, then the backward extrapolation of the concentration versus time curve to the Y axis predicts a much lower concentration and thus a larger central volume.

Total body water is decreased in elderly persons. One pharmacokinetic result is a reduced initial mixing volume. This smaller central volume of distribution leads to higher peak concentrations after a bolus or during the early part of an infusion. A decreased central volume of distribution partly accounts for the increased sensitivity of elderly patients to many anesthetic drugs.

Peripheral Volumes of Distribution

Anesthetic drugs distribute extensively into peripheral tissues. This distribution into the periphery is represented pharmacokinetically as additional volumes of distribution that are attached to the central volume. Peripheral volumes are linked to the central compartment (plasma) by blood flow, a process called "intercompartmental clearance." The linkage of peripheral volumes to a central volume is called a "mammillary" model. This name refers to the structure of the plumbing: peripheral piglets suckling off a central (mother) pig. At least, that is how the term was explained to us.

The size of the peripheral volumes of distribution reflects the drug's solubility in tissue relative to blood or plasma. The more soluble a drug is in peripheral tissues, relative to blood or plasma, the larger are the peripheral volumes of distribution. Because the tissue solubility of a drug depends on simple physiochemical constants, it would seem

Figure 2-2 A recirculatory model accounting for cardiac output (C.O.), transit delays and pulmonary uptake (Delay Elements--V_C), and nondistributive mixing pathways (V_{ND} and Cl_{ND}). All these components within the dashed circle are required to accurately model the central volume of distribution. In most situations, this complexity is not required, and the simpler approach of assuming instantaneous mixing within the central volume is an adequate approximation. Cl_{ND-F} and Cl_{ND-S}, fast and slow nondistributive clearances; Cl_{T-F} and Cl_{T-S}, fast and slow tissue clearances; V_{ND-F} and V_{ND-S}, fast and slow nondistributive volumes; V_{T-F} and V_{T-S}, fast and slow tissue volumes. *(From Krejcie TC, Auram MJ, Gentyw B et al: A recirculatory model of the pulmonary uptake and pharmacokinetics of lidocaine based on analysis of arterial and mixed venous data from dogs. J Pharmacokinet Biopharm 25:169, 1997)*

likely that peripheral volumes of distribution would be consistent from person to person. However, differences in body habitus and composition do occur, and these variations influence peripheral volumes of distribution. For example, aging is associated with decreased lean body mass, increased body fat, and decreased total body water. Because the lipid content of elderly patients is higher than that of young patients, elderly patients have more potential for lipophilic drugs to accumulate in peripheral volumes of distribution, leading to increased duration of effect for many anesthetic drugs.

Peripheral volumes of distribution explain the apparent dilution of the drug into all body tissues. We usually do not know the actual solubility of drugs in peripheral tissues. For the purpose of calculating drug dosage, a small true volume with high solubility is indistinguishable from a large true volume with low tissue solubility. The convention in pharmacokinetics is to assume that the solubility of the drug in tissue is the same as the solubility in plasma. This assumption does not compromise the role of peripheral compartments to characterize the dilution of drugs into tissues, but it does lead to very large volumes of distribution for highly soluble drugs (e.g., 5,000 L for propofol).

The volume of distribution at steady state (Vd_{ss}) is the volume that relates the plasma drug concentration at steady state (i.e., during a very long infusion) to the total amount of drug in the body. By rearranging the definition of concentration, we can calculate the Vd_{ss} as the total amount of drug in the body at steady state divided by the plasma drug concentration. The Vd_{ss} equals the central volume plus the peripheral volumes.

Clearance

Clearance is the process that removes drug from a volume. Systemic clearance permanently removes drug from the body, either by elimination or by transforming it into metabolites. Intercompartmental clearance moves drug from one compartment to another. Clearance is defined as the volume that is completely cleared of drug per unit of time. The units of clearance are therefore units of flow: volume per unit time (e.g., L/min). Clearance is most easily envisioned as flow to a clearing organ, as shown in Figure 2-3 (Figure Not Available) . [2] Clearance describes the body's capacity to remove drug. The actual rate of drug removal is the clearance times the concentration of the drug. If the clearance is 1 L/min, then the actual rate of drug elimination is zero if the concentration is zero, 1 mg/min if the concentration is 1 mg/L, 10 mg/min if the concentration is 10 mg/L, and so on.

Figure 2-3 (Figure Not Available) Clearance represents the flow of blood or plasma that is completely cleared of drug. If all the drug is extracted by the clearing organ (i.e., extraction ratio = 1), then clearance is simply the flow to the organ, as illustrated here. *(Modified from Shafer [2])*

Hepatic Clearance

Many drugs are cleared by hepatic biotransformation. The synthetic pathways for biotransformation are covered in detail in many biochemistry texts. Briefly, the liver metabolizes drugs through oxidation, reduction, hydrolysis, or conjugation. Oxidation and reduction occur in the cytochrome P-450 system. These enzymes can be induced by exposure to certain drugs, thus increasing the liver's intrinsic metabolic capacity. They can also be inhibited by drugs or hepatic disease. Routes of oxidative metabolism include hydroxylation, dealkylation, deamination, desulfuration, epoxidation, and dehalogenation. Conjugation and hydrolysis often occur outside the P-450 system, although glucuronidation involves the P-450 system as well. The effect of conjugation is to transform hydrophobic molecules into water-soluble molecules through addition of polar groups and thus to render the metabolites easier to excrete via the kidneys. The metabolites generated by the liver are generally inactive, although some drugs (e.g., morphine, midazolam) have metabolites that are as potent as the parent drug. Genetic polymorphism can occur in all these pathways, and this characteristic accounts for part of the variability in clearance in the population.

Systemic clearance of anesthetic drugs is generally via hepatic metabolism, although other mechanisms include plasma and tissue ester hydrolysis (remifentanil, succinylcholine, esmolol), renal elimination (pancuronium), and nonspecific "extrahepatic" metabolism for drugs whose clearance exceeds hepatic blood flow (propofol). The relationship between metabolism and clearance is complex, and although the following discussion assumes hepatic metabolism, the principles are valid for metabolism of drug in any tissue.

The rate of metabolism for most anesthetic drugs is proportional to the concentration of drug flowing into the liver. As shown later, this means that metabolic clearance is constant and independent of dose. This is such a common and fundamental assumption for anesthetic pharmacokinetics that we explore the conditions that must be satisfied for this to be valid. Of course, it cannot be true that metabolism is always proportional to concentration because the metabolic capacity of the liver is not infinite. At some rate of drug flow into the liver, the metabolic capacity becomes saturated, and the pharmacokinetics ceases to behave in a linear manner. To understand the rate of metabolism quantitatively, it is necessary to start with the simple observation that the rate at which drug flows *out* of the liver must be the rate at which drug flows *into* the liver less the rate of metabolism. The rate at which drug flows into the liver is liver blood flow (Q), times the concentration of drug flowing in (C_{inflow}). The rate at which drug flows out of the liver is Q times the concentration of drug flowing out ($C_{outflow}$). Putting this together, the rate of hepatic metabolism by the liver (R) is the difference between the C_{inflow} and $C_{outflow}$ times Q:

This relationship is illustrated in Figure 2-4 . Because hepatic metabolism does not have infinite capacity, the relationship between the rate of hepatic metabolism and concentration must be saturable. The saturation equation shows up repeatedly in pharmacokinetics and pharmacodynamics, so we inspect it carefully:

"Response" in this equation varies from 0 to 1, depending on the value of C. When C is 0, the response is 0. If C is greater than 0 but much less than C_{50}, then the response is nearly proportional to

. If C equals C_{50}, then the response is

, which is simply 0.5. That is where the term "C_{50}" comes from: it is the concentration associated with 50 percent response. As C becomes much greater than C_{50}, the equation approaches

, which is 1. The shape of this relationship is shown in Figure 2-5. . The relationship is linear at low concentrations, but at high concentrations, the response saturates

at 1.

We can model the relationship between hepatic metabolism and drug concentration using this equation for saturation. However, what concentration determines the rate of metabolism: the C_{inflow}, the average concentration within the liver, or $C_{outflow}$? All three have been used, but the most widely used model of metabolism views the rate of metabolism as a function of the $C_{outflow}$. This is discussed extensively by Wagner. [3]

Figure 2-4 The rate of metabolism can be computed as the rate of liver blood flow times the difference between the inflowing and outflowing drug concentrations. This is a common approach to analyzing metabolism or tissue uptake across an organ in mass-balance pharmacokinetic studies.

We can expand our equation of metabolism to include the observation that the rate of metabolism, R, approaches saturation at the maximum metabolic rate, V_m, as a function of $C_{outflow}$:

V_m is the maximum possible metabolic rate. The saturation part of this equation,

, determines fraction of the maximum metabolic rate. K_m, also called the Michaelis constant, is the concentration at which the metabolic rate is 50 percent of the maximum rate (V_m). This relationship is shown graphically in Figure 2-6 (Figure Not Available) . [2] The X axis is the outflow

Figure 2-5 The saturation equation,

. shows the decreasing incremental response as the system approaches saturation. Variations of this equation show up repeatedly in both pharmacokinetics and pharmacodynamics.

concentration, $C_{outflow}$, in units of K_m, the concentration that yields 50 percent of the maximum metabolic rate. The Y axis is the rate of drug metabolism, in units of V_m, the maximum rate of drug metabolism. By normalizing $C_{outflow}$ to K_m and the metabolic rate to V_m, the relationship in Figure 2-6 (Figure Not Available) is true for all values of V_m and K_m. Figure 2-6 (Figure Not Available) shows that as long as the $C_{outflow}$ is less than one-half of K_m, there is a nearly proportional change in metabolic rate with a proportional change in $C_{outflow}$. For most anesthetic drugs, the clinical concentrations do not exceed one-half of K_m, and so metabolism of anesthetic drugs is nearly proportional to concentration. We can also interpret Figure 2-6 (Figure Not Available) in terms of the metabolic rate (Y axis). As long as the metabolic rate is less than one-third of the maximum metabolic capacity, the rate of metabolism increases proportionally with concentration. The clinical message is that the metabolism is proportional to concentration, and thus pharmacokinetics remains linear, provided the rate of intravenous administration at steady state does not exceed one-third the maximum metabolic capacity.

So far, we have discussed the rate of metabolism and not hepatic clearance. If the liver could extract all the drug from the afferent flow, then clearance would equal Q. However, the liver cannot remove all the drug; there is always some drug in the effluent plasma. The fraction of inflowing drug extracted by the liver is

. This is called the extraction ratio. Clearance is the amount of blood completely cleared of drug per unit time. We can calculate clearance as Q times the extraction ratio:

With this basic understanding of clearance, let us divide each part of equation 4 by C_{inflow}:

Figure 2-6 (Figure Not Available) The relationship between concentration, expressed in units of K_m (Michaelis constant), and the rate of drug metabolism, in units of V_m (maximum rate). As long as the outflow concentration is less than half K_m, a change in concentration is matched by a proportional change in metabolic rate. This is true of nearly all anesthetic drugs. *(From Shafer [2])*

The third term is clearance: Q times the extraction ratio. Thus, each term must be equivalent to clearance. As such, each term brings insight into the process of clearance.

Consider the first term,

This indicates that clearance is a proportionality constant that relates arterial concentration to the rate of metabolism. If we want to maintain a given steady-state arterial drug concentration, we must infuse drug at the same rate that it is being metabolized. Thus, the infusion rate to maintain a given arterial concentration is the clearance times the desired arterial concentration.

What should we make of the third and fourth terms,

Taken together, these equations relate clearance to Q and the extraction ratio, as shown in Figure 2-7 (Figure Not Available) . [4] For drugs with an extraction ratio of nearly 1 (e.g., propofol), a change in Q produces a nearly proportional change in clearance. For drugs with a low extraction ratio (e.g., alfentanil), clearance is nearly independent of the rate of Q. This makes intuitive sense. If nearly 100 percent of the drug is extracted by the liver, this implies that the liver has tremendous metabolic capacity for the drug. In this case, the rate limiting step in metabolism is the flow of drug to the liver, and such drugs are said to be "flow limited." Any reduction in Q,

such as usually accompanies anesthesia, can be expected to reduce clearance. However, moderate changes in hepatic metabolic function per se have little impact on clearance, because hepatic metabolic capacity is overwhelmingly in excess of demand.

For many drugs (e.g., alfentanil), the extraction ratio is considerably less than 1. For these drugs, clearance is limited by the capacity of the liver to take up and metabolize the drug. These drugs are said to be "capacity dependent." Clearance changes in response to any change in the capacity of the liver to metabolize such drugs, such as could be caused by liver disease or enzymatic induction. However, changes in Q, as may be caused by the anesthetic state itself, usually have little influence on the clearance because the liver only handles a fraction of the drug it sees.

The last two components of equation 6 can also be used to show how the extraction ratio governs the response of clearance to changes in metabolic capacity (V_m). Figure 2-8 (Figure Not Available) shows the clearance for drugs with an extraction ratio ranging from 0.1 to 1, based on Q of 1.4 L/min. The extraction ratios were calculated for a $V_m = 1$. Changes in V_m, as could be caused by liver disease (reduced V_m) or enzymatic induction (increased V_m) have little effect on drugs with a high extraction ratio. However, drugs with a low extraction ratio have a nearly linear change in clearance with a change in intrinsic metabolic capacity (V_m).

So far, we have focused on linear pharmacokinetics, that is, the pharmacokinetics of drugs whose metabolic rate at clinical doses is less than $V_m/3$. The clearance of such drugs is generally expressed as a constant (e.g., propofol clearance = 1.6 L/min). Some drugs, such as phenytoin, exhibit saturable pharmacokinetics. The clearance of drugs with saturable metabolism is a function of drug concentration, rather than a constant.

Liver volume, Q, and hepatic metabolic capacity decrease with advancing age. These changes in hepatic physiology

Figure 2-7 (Figure Not Available) The relationship between liver blood flow (Q), clearance, and extraction ratio. For drugs with a high extraction ratio, clearance is nearly identical to liver blood flow. For drugs with a low extraction ratio, changes in liver blood flow have almost no effect on clearance. *(Modified from Wilkinson and Shand [4])*

Figure 2-8 (Figure Not Available) Corollary to Figure 2-7 (Figure Not Available) , showing the relationship between metabolic capacity, clearance, and extraction ratio (E.R.). Changes in maximum volume (V_m) have little effect on drugs with a high extraction ratio, but they cause a nearly proportional decrease in clearance for drugs with a low extraction ratio. *(From Shafer [2])*

account for the decreased clearance of opioids, hypnotics, benzodiazepines, and muscle relaxants and contribute to the increased sensitivity of elderly subjects to anesthetic drugs.

Renal Clearance

The kidneys clear drug from plasma by filtration at the glomerulus and direct transport into the tubules. Renal blood flow is inversely correlated with age, as is creatinine clearance, which can be predicted from age and weight [5] :

Men:

Women:
85% of the above

Equation 7 shows that age is an independent factor in predicting creatinine clearance. Thus, elderly people have decreased creatinine clearance, even in the presence of normal serum creatinine levels. Furthermore, inhalational anesthetics also decrease renal blood flow. Decreased renal clearance delays the offset of effect for renally excreted drugs. For instance, pancuronium is about 85 percent eliminated via renal clearance. The dose of pancuronium should be reduced in elderly patients on the basis of decreased clearance, even though they may have normal levels of creatinine.

Tissue Clearance

In some cases, anesthetic drugs are cleared in tissues, including blood, muscle, and lungs. For example, remifentanil is cleared by nonspecific esterases located primarily in muscle and intestines, whereas the lungs, liver, kidneys, and blood all contribute minimally to remifentanil clearance. Succinylcholine and mivacurium are all metabolized by plasma butyrylcholinesterases (formerly called pseudocholinesterase). The half-life ($t_{½}$) of succinylcholine and mivacurium in plasma is about 3 and 5 minutes, respectively. About half of atracurium's metabolism is hepatic, and the balance occurs in blood via nonspecific cholinesterases (but not by butyrylcholinesterases). Hofmann degradation is a spontaneous process in plasma at normal pH and temperature and does not depend on any circulating esterases. Hofmann degradation is a minor route of atracurium me-tabolism, but it is the major route of metabolism of cisatracurium, an isomer of atracurium. This is an important distinction: unlike atracurium and mivacurium, cisatracurium metabolism is unaffected by disease or genetic variants of cholinesterase metabolism.

Clearance by tissues other than blood can be analyzed using models similar to those for hepatic clearance. Tissue clearance can be flow limited, capacity limited, or both. Clearance within the blood itself cannot be flow limited and so is entirely dependent on intrinsic metabolic rate and capacity within the blood.

Distribution Clearance

Distribution clearance is the transfer of drug between the blood or plasma and the peripheral tissues. Unlike metabolic clearance, distribution clearance does not permanently remove drug from the body. Distribution clearance is a function of cardiac output, tissue blood flow, and the permeability of the capillary walls to the drug. For a drug that is avidly taken up in peripheral tissues, such as propofol, the sum of the metabolic clearance and the distribution clearance approaches cardiac output. For drugs that are metabolized directly in the plasma or in many peripheral tissues, such as succinylcholine and remifentanil, the sum of metabolic and distribution clearance can exceed cardiac output.

Tissue blood flow varies with cardiac output, which, in turn, changes with disease and in response to many drugs. Concurrently administered drugs can also raise or lower cardiac output or alter the distribution of cardiac output (i.e., redirect regional blood flow). Virtually all anesthetics decrease cardiac output, and so anesthesia likely decreases intercompartmental clearance.

Age, per se, only modestly reduces cardiac output in the absence of hypertension, coronary artery disease, valvular heart disease, or other cardiovascular disease. The net result is that advancing age modestly reduces intercompartmental clearance of anesthetic drugs.

The effect of decreased intercompartmental clearance is to increase initial plasma concentrations during drug administration. Following termination of drug administration, the role of decreased intercompartmental clearance is complex. In general, plasma concentrations decrease more rapidly following long infusions when intercompartmental clearance is decreased.

Protein Binding

Many drugs are bound to plasma proteins. The relationship between drugs and their binding proteins can be described as:

where [Free drug] is the free drug concentration, [Unbound protein binding sites] is the concentration of the available unbound protein binding sites, [Bound drug] is the concentration of drug bound to plasma proteins, k_{on} is the rate constant for binding of drug to plasma protein, and k_{off} is the rate constant for dissociation of bound drug from the plasma proteins. We can infer from this relationship that the rate of formation of bound drug is:

At equilibrium (which is nearly instantaneous), d[Bound drug]/dt = 0, permitting us to solve for k, the ratio of k_{on}/k_{off} , as:

Plasma proteins may have more than one binding site. Therefore, the total number of binding sites is the protein concentration, [Protein], times *n,* the average number of binding sites per protein molecule. For all the drugs used in anesthesia, the number of binding sites actually bound is only a trivial fraction of the total available binding sites, and so we can reasonably approximate [Unbound protein binding sites] by *n* [Protein]. Because *n,* the number of binding sites per molecule, is constant, we can just fold it into our rate constant, k, by defining the association constant, K_a , as:

Let us define f_u as the free fraction of drug:

When [Bound drug] = [Free drug], $f_u = 0.5$. Thus, we can think of a new term, $[\text{Free drug}]_{50}$, which is the free drug concentration associated with 50 percent binding. We could just as easily call it $[\text{Bound drug}]_{50}$, because [Bound drug] = [Free drug] when $f_u = 0.5$. Combining equations 10 and 11, we can solve for f_u in terms of the unbound drug concentration:

Two observations can be drawn from equation 12. First, the fraction bound to plasma protein solely depends only on the protein concentration, not on the drug concentration, within the approximation that [Bound drug] << *n*[Protein]. This approximation is always true for anesthetic drugs because of their potency. Even for thiopental, possibly the least potent drug used in contemporary anesthetic practice, [Bound drug] << *n*[Protein], and protein binding is independent of thiopental concentration.

Second, if we solve equation 12 for $f_u = 0.5$, we find that:

where $[\text{Protein}]_{50}$ is the concentration of protein at which the drug is half bound. Thus, another way of thinking about the K_a is that it is the inverse of the protein concentration associated with 50% binding. If we substitute

for K_a in equation 12, we have the relationship:

Figure 2-9 Relationship between plasma protein concentration as a fraction of the concentration associated with 50 percent binding and the fraction of drug that is unbound. This is another example of the saturation equation shown in Figure 2-5 .

This relationship is shown graphically in Figure 2-9 . On the left side of Figure 2-9 , [Protein] is much smaller than $[\text{Protein}]_{50}$. In this situation, the drug has little affinity for protein binding, so there is far less protein present than required to bind 50 percent of the drug. The drug is mostly free, and f_u is nearly 1. On the right side of Figure 2-9 , [Protein] is much greater than $[\text{Protein}]_{50}$. This means that there is far more protein present than would be required to bind 50 percent of the drug. The result is that drug is mostly bound to plasma proteins, and f_u is nearly 0.

K_a and its inverse, $[\text{Protein}]_{50}$, reflect the affinity of the drug for plasma proteins. They should not change in the presence of disease. However, [Protein] can change with disease, age, or concurrent drugs. Figure 2-10 (Figure Not Available) shows the relationship between changes in protein concentration and changes in the f_u of drug for drugs with different degrees of protein binding in normal clinical use. The lines on the graph correspond to different drugs whose f_u in normal plasma ranges from 1.0 (horizontal line) to
0.0 (straight diagonal line).

For drugs that are not bound ($f_u = 1.0$), there is no relationship between f_u and protein concentration, as indicated by the flat horizontal line. For drugs whose f_u is typically 90 percent, there is a small change in free drug concentration with changes in protein concentration. For drugs that are highly protein bound, the free drug concentration changes nearly in inverse with the change in protein concentration. As the percentage of binding approaches 100 percent (free drug
0.0), the relationship between change in protein concentration and change in fu becomes inversely proportional. Note that there is never a greater than proportional change in free drug concentration with change in plasma concentration. For example, the most that a 10 percent change in protein concentration would produce is a 10 percent

Figure 2-10 (Figure Not Available) The relationship between changes in protein concentration and changes in free fraction. The relationship depends on the free fraction in normal plasma with typical clinical doses. For a drug that is not bound (free fraction = 1), there is no change in free fraction with a change in protein concentration. For a highly bound drug with a free fraction that is nearly 0, any change in protein causes a nearly inversely proportional change in free fraction. *(From Shafer [z])*

change in free drug concentration, and that would only be the case if the drug were nearly 100 percent bound to plasma proteins.

The *in vitro* observation that changing protein concentration results in changing free drug concentration, as shown in Figure 2-10 (Figure Not Available) , does not necessarily apply to the *in vivo* situation. It is the free (e.g., unbound) drug that equilibrates between the plasma and the tissues. If protein binding is decreased, then the free drug concentration gradient between the plasma and peripheral tissues will increase. As a result, when protein binding decreases, equilibrium is achieved between the plasma and the tissue free drug concentrations at a lower total plasma drug concentration. This lower concentration gives the appearance that the drug has distributed into a larger total space. Thus, decreased protein binding causes an increase in the apparent volume of distribution when referenced to total, rather than free, drug concentration.

This explains why the increased Vd_{ss} seen with decreased plasma protein binding is mostly an illusion. Were only the unbound drug concentration measured, then for lipophilic drugs (such as most of those in anesthesia practice), there would be almost no change in the apparent volume of distribution because it is the partitioning of drug within peripheral tissues that primarily governs the free concentration of lipophilic drugs.

Changes in protein binding may affect the clearance of drugs. If a drug has a high extraction ratio, then the liver is going to remove nearly all the drug flowing to it, regardless of the extent of protein binding. However, if the drug has a low hepatic extraction ratio, then an increase in the f_u of drug will result in an increase in the driving gradient, with an associated increase in clearance. Protein binding also affects the apparent potency of a drug, when referenced to the total plasma drug concentration. An increase in f_u increases the driving pressure to the site of drug effect. Thus, a change in f_u increases the concentration at the effect site. Because of this change in apparent potency, decreased protein binding may decrease the dose required to produce a given drug effect even in the absence of pharmacokinetic changes.

Albumin and $alpha_1$ -acid glycoprotein are the primary sites of protein binding. Albumin concentration decreases with advancing age, hepatic disease, and malnutrition. In contrast, $alpha_1$ -acid glycoprotein concentration increases with advancing age and also with acute disease. Thus, the effects of age and disease on protein binding depend on which protein binds the drug. For example, because diazepam primarily binds to albumin, the f_u increases in elderly patients, and this may partly explain the increased sensitivity in elderly subjects. In contrast, lidocaine binds primarily to $alpha_1$ -acid glycoprotein, and in elderly patients increased $alpha_1$ -acid glycoprotein reduces the f_u , a factor that may contribute to the reduced clearance.

Stereochemistry

Typical pharmacokinetic analyses describe fictitious drugs. For example, the pharmacokinetics and pharmacodynamics of thiopental, fentanyl, and midazolam actually describe a drug that does not exist. The reason is that most

---

anesthetic drugs are chiral and are supplied as racemic mixtures. The body is a chiral environment, and drugs interact stereospecifically with enzymes, proteins, and receptors. The pharmacokinetics and pharmacodynamics of the enantiomers may differ. The enantiomers of bupivacaine and ketamine have been particularly well studied, in hopes of developing commercial products that lack the toxicity of the racemic mixtures. Although the importance of studying the pharmacokinetics and pharmacodynamics of individual stereoisomers is widely appreciated, the difficulty of doing such studies has precluded their wide-spread use.

Pharmacogenetics

Pharmacogenetics refers to the genetic diversity in the body's absorption, metabolism, and distribution of drugs (inborn pharmacokinetic variability) or to genetic diversity in the body's response to the drug, as may be caused by genetic differences in receptor structure (inborn pharmacodynamic variability). Most known pharmacogenetic variability refers to genetic diversity in drug metabolism. This may be because drug assays have been available for many years, whereas the molecular techniques to determine diversity in receptor populations have only recently been developed. Additionally, it is easy to understand how altered metabolism leads to higher or lower concentrations. It is much more difficult to understand how changes in receptor structure relate to differences in response to a drug.

However, there may be a biologic reason for pharmacogenetic variability in metabolism. It is probable that variability in drug metabolism is a natural adaptive response of animals to an environment that can present a huge variety of toxins. Enzymatic diversity is likely maintained through natural selection to ensure survival when species are confronted with novel environmental toxins.

In practical terms, this enzymatic diversity is rarely evident in the absence of drug therapy. In the presence of drug therapy, pharmacogenetic variation in metabolism is evident as unexpected toxicity, duration of action, or lack of efficacy to administered drugs. One of the best-studied pharmacogenetic variants is cytochrome P-450 2D6 (CYP2D6), also called debrisoquine hydroxylase. About 7 to 10 percent of whites are homozygous for an inactive variant of CYP2D6. This causes altered metabolism of at least 40 drugs. One of these drugs has potential interest to anesthesiologists: codeine. Codeine is a prodrug that is metabolized to morphine, the active drug, by CYP2D6. Patients who are homozygous for variant CYP2D6 do not have an analgesic response to codeine. Thus, the occasional patient who says that "codeine does nothing for me" is probably telling the truth--the patient is unable to convert codeine to morphine.

Anesthesiologists are familiar with the role of genetics in determining butyrylcholinesterase activity. Subjects with abnormal butyrylcholinesterase are at risk for prolonged paralysis from succinylcholine. Not surprisingly, there are ethnic differences in cholinesterase activity. For example, individuals of Middle Eastern descent are likely to have less butyrylcholinesterase activity than those of European descent. Molecular approaches have permitted extensive characterization of plasma cholines-terase variants. Many of these variants are not "all or none," but rather they reflect a spectrum of enzymatic activity.

Pharmacokinetic Models

Zero-Order and First-Order Processes

Zero-order processes and first-order processes are the basis of mathematical pharmacokinetic models. Processes such as the rotation of the earth or the flow of a river happen at a constant rate. These are called zero-order processes. The rate of change (dx/dt) for a zero-order process is:

Equation 15 simply states that the rate of change is constant. If x represents an amount of drug, and t represents time, then the units of k are amount/time. If we want to know the value of x at time t, x(t), we can compute it as the integral of the equation 15 from time 0 to time t:

where x_0 is the value of x at time 0. This is the equation of a straight line with a slope of k and an intercept of x_0.

Many other processes occur at a rate proportional to the amount. For example, the interest payment on a loan is proportional to the outstanding balance, and the rate at which water drains from a bathtub is proportional to amount of water in the tub. These are examples of first-order processes. The rate of change in a first-order process is only slightly more complex than for a zero-order process:

Here, the units of k are simply 1/time, because x on the right-hand side already includes the units for the amount. If we want to know the value of x at time t, x(t), again it can be computed as the integral from time 0 to time t:

where x_0 is the value of x at time 0. If k > 0, x(t) increases exponentially. If k < 0, x(t) decreases exponentially. In pharmacokinetics, k is negative because concentrations decrease over time. For clarity, the minus sign is usually explicit, so k is expressed as a positive number. Thus, the identical equation for pharmacokinetics, with the minus sign explicitly written, is:

Figure 2-11 shows the relationship between x and time, as described by equation 19. In Figure 2-11 , x continuously decreases over time, but the slope of the curve continuously increases (i.e., becomes less negative). Taking the natural logarithm of both sides of equation 19 gives:

Figure 2-11 Exponential decay curve, as given by $x(t) = x_0 e^{-kt}$, plotted on standard axes, with $x_0 = 10$ and $k = 0.5$.

This is the equation of a straight line, as shown in Figure 2-12 , where the vertical axis is ln(x(t)), the horizontal axis is t, the intercept is $\ln(x_0)$, and the slope of the line is -k.

How long will it take for x to go from some value, x_1 , to half that value, $x_1/2$? Because k is the slope of a straight line relating ln(x) to time:

where $t_{½}$ is the time required for a 50 percent decrease in x. We can simplify the numerator to:

This succinctly relates slope (or "rate constant"), k, to $t_{1/2}$:

Thus, if we measure the time it takes for x to fall by 50 percent, $t_{½}$, then we know the rate constant, k. If we know k from equation 23, we can easily deduce that the time it will take for x to fall by 50 percent is:

Physiologic Pharmacokinetic Models

It is possible to analyze volumes and clearances for each organ in the body and to construct models of pharmacokinetics by assembling the organ models into physiologically

Figure 2-12 The same exponential decay curve, $x(t) = x_0 e^{-kt}$, in Figure 2-11 , but now plotted on a log Y axis.

and anatomically accurate models of the entire animal. These models typically assume blood flows throughout the system as a zero-order process and drug transfers between the blood and tissues as a first-order process. Figure 2-13 (Figure Not Available) shows such a model for thiopental in rats. [6] Subsequent studies have shown that individual tissue volumes and blood flows can be scaled up from rats to humans, resulting in accurate models of human pharmacokinetics. This illustrates the potential utility of physiologically based pharmacokinetic models in developing human pharmacokinetic models from animal models.

Models that work with individual tissues are mathematically cumbersome and do not offer a better prediction of plasma drug concentration than models that lump the tissues into a few compartments. If the goal is to determine how to give drugs in order to obtain therapeutic plasma drug concentrations, then all that is needed is to relate dose to plasma concentration mathematically. For this purpose, conventional "compartmental" models are usually adequate.

Compartmental Pharmacokinetic Models

Compartmental models are built on the same basic concepts as physiologic models, but with gross simplifications. The "one-compartment model" seen in Figure 2-14 contains a single volume and a single clearance, as though we were built like buckets. For anesthetic drugs, we resemble several buckets connected by pipes. These are usually modeled using two- or three-compartment models, shown in Figure 2-14 . The volume to the right in the twocompartment model, and in the center of the three-compartment model, is the central volume. The other volumes are the peripheral volumes, and the sum of all the volumes is the Vd_{ss} . The clearance leaving the central compartment for the outside is the "central" or "metabolic" clearance. The clearances between the central compartment and the peripheral compartments are called "intercompartmental clearances."

Figure 2-13 (Figure Not Available) Physiologic model for thiopental in rats. The pharmacokinetics of distribution into each organ has been individually determined. The components of the model are linked by zero-order (flow) and first-order (diffusion) processes. *(From Ebling et al [6])*

One-Compartment Model

Bolus Pharmacokinetics

Think of the body as a bucket into which we pour drug. Let us call x_0 (x at time 0) the amount of drug that we pour into the bucket. The initial concentration, of course, is x_0 /V, where V is the volume of fluid in the bucket. Returning to equation 1, if we know the concentration we want to achieve, C_T (target concentration), and the volume in the bucket, we can calculate the dose to achieve C_T by rearranging the definition of concentration:

This is further discussed in Chapter 11 .

Let us assume that the fluid in the bucket is flowing out at a constant rate, which we call clearance, Cl. What is the rate, dx/dt, that drug is flowing out of the bucket? Because concentration is x/V, and Cl is the rate that the fluid in the bucket is flowing out, then the rate at which the drug is flowing out must be x/V times Cl. This rate is a first-order process if, and only if, it equals a constant, k, times the amount of drug in the bucket. Does it?

We stated earlier that the flow out of the bucket, Cl, was constant. The volume, V, is not a constant because it is shrinking as fluid flows from the bucket. So, let us open up a pipe at a rate that matches Cl to keep the V constant. Once V becomes a constant, the model looks like physiologic Cl

Figure 2-14 One-, two-, and three-compartment mammillary models.

(which does not require exsanguination). Because Cl and V are both constants,

is a constant. Referring back to equation 25, k, a constant by definition of first-order processes, equals

, a constant by the definition of Cl and V. This can be rearranged to yield the fundamental identity of linear pharmacokinetics:

What does this identity tell us about the relationship among $t_{½}$, V, and Cl? Rearranging the foregoing as

and remembering that

, we can conclude:

Figure 2-15 (Figure Not Available) shows a one-compartment model with an identical Cl but a bigger V than that seen in Figure 2-3 (Figure Not Available) It takes longer to clear drug from this bigger V, so the $t_{½}$ increases, as predicted by the foregoing equation. Figure 2-16 (Figure Not Available) shows a one-compartment model with an identical V but faster Cl than that seen in Figure 2-3 (Figure Not Available) . The concentrations fall more quickly (shorter $t_{½}$) with the larger Cl, as predicted by equation 27.

Because this is a first-order process, we know

, and the integral of this gives us the amount of drug at time t in terms of the amount at time 0, $x(t) = x_0 e^{-kt}$. If we divide both sides by V, and remember that x/V is the definition of concentration, we reach the equation that relates concentration following an intravenous bolus to time and initial concentration:

This equation defines the "concentration over time" curve for a one-compartment model, and it has the log-linear shape seen in Figure 2-12 . We can calculate Cl in one of two ways. First, we can calculate V by rearranging the definition of concentration, V = dose/initial concentration = dose/C_0 .

Figure 2-15 (Figure Not Available) A one-compartment model similar to Figure 2-3 (Figure Not Available) , but with an increased volume of distribution. Following drug administration, concentrations will fall more slowly in this model than in the model shown in Figure 2-3 (Figure Not Available) . *(Modified from Shafer [2])*

Referring back to equation 26, we can then calculate Cl as k × V. A more general solution is to consider the integral of the concentration over time curve, equation 28, known in pharmacokinetics as the area under the curve, or AUC:

We can rearrange equation 29 to solve for Cl:

Because x_0 is the dose of drug, Cl equals the dose divided by the AUC. This fundamental property of linear pharmacokinetic models applies to one-compartment models, multicompartment models, and to any type of intravenous drug

Figure 2-16 (Figure Not Available) A one-compartment model similar to Figure 2-3 (Figure Not Available) , but with increased clearance. Following drug administration, concentrations will fall faster in this model than in the model shown in Figure 2-3 (Figure Not Available) . *(Modified from Shafer [2])*

dosing (provided the *total* dose is used as the numerator). It directly follows that AUC is proportional to dose for linear models (i.e., models in which Cl is constant).

Infusion Pharmacokinetics

If you give an infusion at a rate of I (for input), the plasma concentration will rise as long as the rate of drug going in the body, I, exceeds the rate at which drug leaves the body, C × Cl, where C is the drug concentration. Once, I = C × Cl, drug is going in and coming out at the same rate, and the body is at steady state. We can calculate the concentration at steady state by observing that the rate of drug going in must equal the rate of drug coming out of the body. From equation 6, we know that rate of drug metabolism at steady state is:

where C
 is the arterial concentration at steady state. Because by definition at steady state the infusion rate must equal the metabolic rate, the infusion rate, I, at steady state must be I = C
Cl, where I is the rate of the drug infusion. Solving this for the concentration at steady state, C
gives

. Thus, the steady-state concentration during an infusion is the rate of drug input divided by Cl. It follows that if we want to calculate the infusion rate that will achieve a given C_T , at steady state, then the infusion rate must be C_T × Cl. This is discussed further in Chapter 11 .

is similar in form to the equation describing the concentration following a bolus injection:

. Thus, volume is a scalar relating bolus to initial concentration, and Cl is a scalar relating infusion rate to steady-state concentration. It follows that the initial concentration following a bolus is independent of Cl, and the steady-state concentration during a continuous infusion is independent of V.

During an infusion, the rate of change in the amount of drug, x, is rate of inflow, I, minus the rate of outflow, k times x.

We can calculate x at any time t as the integral from time 0 to time t. Assuming that $x_0 = 0$ (i.e., we are starting with no drug in the body), the result is:

As t

, e^{-kt}
 0, and equation 33 reduces to:

Let us say that we want to reach 50 percent of that amount, that is,

. From equation 34, we know that

. Substituting

for x(t) in equation 33, we have:

Solving equation 35 for t, we get:

. In equation 24, we found that the $t_{½}$ following a bolus injection was

. Here again, we have a parallel between boluses and infusions. With an infusion, the time to reach 50 percent of the steady-state concentration is one $t_{½}$. Similarly, it takes two $t_{½}$ to reach 75 percent, three $t_{½}$ to reach 88 percent, and five $t_{½}$ to reach 97 percent of the steady-state concentration. By four to five $t_{½}$, we typically consider the patient to be at steady state, although the concentrations only asymptotically approach the steady-state value.

Absorption Pharmacokinetics

In intravenous drug delivery, all the drug reaches the systemic circulation. When drugs are given by a different route, such as orally, transdermally, epidurally, or intramuscularly, the drug must first reach the systemic circulation. Oral drugs may be metabolized by first-pass hepatic metabolism before reaching the systemic circulation. Transdermally applied drugs may be sloughed off with the stratum corneum without being absorbed. We cannot assume that the dose given to the patient is the same as the dose that reaches the systemic circulation when working with alternative routes of drug delivery. The systemic dose is the administered dose times f, the fraction that is "bioavailable."

Alternative routes of drug delivery are often modeled by assuming that the drug is absorbed from a reservoir or depot, usually modeled as an additional compartment with a monoexponential rate of transfer to the systemic circulation:

where A(t) is the absorption rate at time t, f is the fraction bioavailable, D_{ora} is the dose taken orally (or intramuscularly or applied to the skin), and k_a is the absorption rate constant. Because the integral of $k_a e^{-k_a t}$ is 1, the total amount of drug absorbed is f times D_{ora}. To compute the concentrations over time, we first reduce the problem to differential equations, (e.g., equations 17 and 32) and then integrate. The differential equation for the amount, x, with oral absorption into a one-compartment disposition model is:

This is simply the rate of absorption at time t, A(t), minus the rate of exit, k x(t). To solve for the amount of drug, x, in the compartment at time t, we integrate this from 0, to time t, knowing that x(0) = 0:

Equation 38 describes the amount of drug in the systemic circulation when absorbed from some depot, such as the stomach, intramuscular injection, the skin, or even an epidural dose. To describe the concentrations, rather than amounts, of drug, it is necessary to divide both sides of equation 38 by Vd, the volume of distribution.

This covers the standard pharmacokinetic equations for one-compartment models. The one-compartment model introduces the concepts of rate constants and $t_{½}$ and relates them to the physiologic concepts of V and Cl. *Unfortunately, none of the drugs used in anesthesia can be accurately characterized by one-compartment models.* Distribution of anesthetic drugs into and out of peripheral tissues plays a crucial role in the time course of anesthetic drug effect. To describe intravenous anesthetics, we must extend the one-compartment model to account for distribution into tissues.

Multicompartment Models

The plasma concentrations over time following an intravenous bolus resemble the curve in Figure 2-17 . In contrast to Figure 2-12 , Figure 2-17 is not a straight line, even though it is plotted on a log Y axis. This curve has the characteristics

Figure 2-17 Concentration versus time relationship showing a very rapid initial decline after bolus injection. The terminal log-linear portion is only seen after most of the drug has left the plasma. This is characteristic of most anesthetic drugs. Different line types highlight the rapid, intermediate, and slow (log-linear) portions of the curve.

common to most drugs when given by intravenous bolus. First, the concentrations continuously decrease over time. Second, the rate of decline is initially steep, but it continuously becomes less steep, until we reach a portion that is "log-linear." During this log-linear phase, the slope continues to decrease over time. However, if we plot the log of concentration against time, the terminal part of the curve will appear linear.

For many drugs, three distinct phases can be distinguished, as suggested by Figure 2-17 . There is a rapid "distribution" phase (solid line in Fig. 2-17) that begins immediately after the bolus injection. Very rapid movement of the drug from the plasma to the rapidly equilibrating tissues characterizes this phase. Often, there is a slower second distribution phase (dashed line in Fig. 2-17) that is characterized by movement of drug into more slowly equilibrating tissues and return of drug to the plasma from the most rapidly equilibrating tissues (i.e., those that reached equilibrium with the plasma during phase 1). The terminal phase (dotted line in Fig. 2-17) is a straight line when plotted on a semilogarithmic graph. The terminal phase is often called the "elimination phase" because the primary mechanism for decreasing drug concentration during the terminal phase is drug elimination from the body. The distinguishing characteristic of the terminal elimination phase is that the relative proportion of drug in the plasma and peripheral volumes remains constant. During this "terminal phase," drug returns from the rapid and slow volumes to the plasma, and it is permanently removed from the plasma by metabolism or excretion.

The presence of three distinct phases following bolus injection is a defining characteristic of a mammillary model with three compartments. It is possible to develop hydraulic models, as shown in Figure 2-18 (Figure Not Available) , [7] for intravenous drugs. In this model, there are three tanks, corresponding (from left to right) with the slowly equilibrating peripheral compartment, the central compartment (the plasma, into which drug is injected), and the rapidly equilibrating peripheral compartment. The horizontal pipes represent intercompartmental clearance or (for the pipe draining onto the page) metabolic clearance. The volumes of each tank

correspond with the volumes of the compartments for fentanyl. The cross-sectional areas of the pipes correlate with fentanyl systemic and intercompartmental clearances. The height of water in each tank corresponds to drug concentration.

Figure 2-18 (Figure Not Available) A hydraulic model of fentanyl pharmacokinetics. Drug is administered into the central tank, from which it can distribute into two peripheral tanks, or it may be eliminated. The volume of the tanks is proportional to the volumes of distribution. The cross-sectional area of the pipes is proportional to the clearance. *(Modified from Youngs and Shafer [7])*

Using this hydraulic model, we can follow the processes that decrease drug concentration over time following bolus injection. Initially, drug flows from the central compartment to both peripheral compartments through intercompartmental clearance and completely out of the model through metabolic clearance. Because there are three places for drug to go, the central compartment concentration decreases very rapidly. At the transition between the solid line and the dashed line in Figure 2-18 (Figure Not Available) , there is a change in the role of the most rapidly equilibrating compartment. At this transition, the central compartment concentration falls to less than the concentration in the rapidly equilibrating compartment, and the direction of flow between them is reversed. After this transition (dashed line in Fig. 2-18) (Figure Not Available) , drug in the plasma only has two places to go: flow into the slowly equilibrating compartment and metabolic clearance. These processes are partly offset by the return of drug to the plasma from the rapidly equilibrating compartment. The net effect is that once the rapidly equilibrating compartment has come to equilibration, the central compartment concentration falls far more slowly than before.

Once the concentration in the central compartment falls to less than both the rapidly and slowly equilibrating compartments (dotted line in Fig. 2-18) (Figure Not Available) , then the only method of decreasing the plasma concentration is metabolic clearance. The return of drug from both peripheral compartments to the central compartment greatly slows the rate of decrease in plasma drug concentration.

Curves that continuously decrease over time, with a continuously increasing slope (i.e., curves that look like Figs. 2-17 and 2-18) (Figure Not Available) , can be described by a sum of exponentials. In pharmacokinetics, one way of denoting this sum of exponentials is to say that the plasma concentration over time is:

where t is the time since the bolus, C(t) is the drug concentration following a bolus dose, and A, alpha, B, beta, C, and gamma are parameters of a pharmacokinetic model. A, B, and C are called coefficients, whereas alpha, beta, and gamma are called exponents. Following a bolus injection, all six of the parameters in equation 39 are greater than zero.

The main reason that polyexponential equations are used is that they describe the concentrations observed after bolus injection (except for the misspecification in the first minute). Compartmental pharmacokinetics is strictly empiric: the models describe the data, not the processes by which the observations came to be. Fortunately, polyexponential equations permit us to use many of the one-compartment ideas just developed, with some generalization of the concepts. This involves translating equation 39 into a model of V and Cl that has an appealing, if not necessarily accurate, physiologic flavor.

Equation 39 states that the concentrations over time are the algebraic sum of three separate functions: $Ae^{-alpha\,t}$, $Be^{-beta\,t}$, and $Ce^{-gamma\,t}$. Typically, alpha > beta > gamma by about 1 order of magnitude. We can graph each of these functions separately, as well as their sum, as shown in Figure 2-19 . At time 0 (t = 0), equation 39 reduces to:

The sum of the coefficients A, B, and C, equals the concentration immediately following a bolus.

Special significance is often ascribed to the smallest exponent. This exponent determines the slope of the final log-linear portion of the curve. When the medical literature refers to the $t_{½}$ of a drug, unless otherwise stated, the $t_{½}$ is the terminal $t_{½}$ (i.e., 0.693/smallest exponent). However, the terminal $t_{½}$ for drugs with more than one exponential term is nearly uninterpretable. The terminal $t_{½}$ is merely

Figure 2-19 The disposition of a three-compartment model (i.e., triexponential model) consists of the sum of three monoexponential functions. See text for an explanation of the equations.

the upper limit on the time required for the concentrations to decrease by 50 percent after drug administration. Usually, the time for a 50 percent decrease is much faster than that upper limit. This is discussed further in Chapter 11 .

Constructing pharmacokinetic models represents a tradeoff among accurately describing the data, having confidence in the results, and mathematical tractability. Adding exponents to the model usually provides a better description of the observed concentrations. However, adding more exponent terms usually decreases our confidence in how well we know each coefficient and exponential and greatly increases the mathematical burden of the models. This is why most pharmacokinetic models are limited to two or three exponents.

Part of the continuing popularity of polyexponential models of pharmacokinetics is that they can be mathematically transformed from the admittedly unintuitive exponential form in equation 39 to a more easily intuited compartmental form, as shown in Figure 2-14 . Microrate constants, expressed as k_{ij} , define the rate of drug transfer from compartment i to compartment j. Compartment 0 is a compartment outside the model, so k_{10} is the microrate constant for those processes acting through biotransformation or elimination that irreversibly remove drug from the central compartment (analogous to k for a one-compartment model). The intercompartmental microrate constants (e.g., k_{12} , k_{21}) describe the exchange of drug between the central and peripheral compartments. Each compartment has at least two microrate constants, one for drug entry and one for drug exit. The microrate constants for the two- and three-compartment models can be seen in Figure 2-14 . The differential equations describing the rate of change for the amount of drugs in compartments 1, 2, and 3, follow directly from the microrate constants. For the two-compartment model, the differential equations for each compartment are:

For the three-compartmental model, the differential equations for each compartment are:

where I is the rate of drug input. An easy way to model pharmacokinetics is to convert the foregoing differential equations to difference equations, so that dx becomes Deltax, and dt becomes Deltat. With a Deltat of 1 second, the error from linearizing the differential equations is less than 1 percent. In this way, desktop computers

can simulate hours worth of pharmacokinetics in a matter of seconds using a spreadsheet.

For the one-compartment model, k was both the rate constant and the exponent. For multicompartment models, the relationships are more complex. The interconversion between the microrate constants and the exponents becomes exceedingly complex as more exponents are added, because every exponent is a function of every microrate constant and vice versa. Individuals interested in such interconversions can find them in the Excel spreadsheet "convert.xls," which can be downloaded over the World Wide Web at the following address: http://pkpd.icon.palo-alto.med.va.gov.

Time Course of Drug Effect

The plasma is not the site of drug effect for anesthetic drugs. There is a time lag between plasma drug concentration and effect-site drug concentration. For example, one significant difference between fentanyl and alfentanil is the more rapid onset of alfentanil drug effect. The black bar in the top graph of Figure 2-20 (Figure Not Available) shows the duration of a fentanyl infusion. [8] Rapid arterial samples document the rise in

Figure 2-20 (Figure Not Available) Fentanyl and alfentanil arterial concentrations (circles) and electroencephalographic (EEG) response (irregular line) to an intravenous infusion. With each drug, there is a time lag between the rise and fall in arterial concentration and the EEG response, but the time lag is much greater for fentanyl than for alfentanil. *(Modified from Scott et al [6])*

Figure 2-21 A three-compartment model with an added effect site to account for the equilibration delay between the rise and fall of arterial drug concentrations and the onset and offset of drug effect.

fentanyl concentration. The time course of electroencephalographic (EEG) effect lags about 2 minutes behind the rapid rise in arterial concentration. This lag is called hysteresis. The plasma concentration peaks at the moment the infusion is turned off. Following the peak plasma concentration, the fentanyl concentration rapidly decreases. However, the offset of fentanyl drug effect again lags well behind the decrease in concentration. The lower graph in Figure 2-20 (Figure Not Available) shows the same study in a patient receiving alfentanil. Because of alfentanil's rapid blood-brain equilibration, there is less hysteresis with alfentanil than with fentanyl.

Typically, the relationship between the plasma and the site of drug effect is modeled with an "effect-site" model, as shown in Figure 2-21 . The site of drug effect is connected to the plasma by a first-order process, as described earlier. The equation that relates effect-site concentration to plasma concentration is:

where Ce is the effect site concentration and Cp is the plasma drug concentration. k_{e0} is the rate constant for elimination of drug from the effect site. It is most easily understood in terms of its reciprocal, $0.693/k_{e0}$, the half-time for equilibration between the plasma and the site of drug effect.

The constant k_{e0} has a large influence on the rate of rise of drug effect, the rate of offset of drug effect, and the dose that is required to produce the desired drug effect. The mathematical basis of these relationships is explored in Chapter 11 .

Summary

Pharmacokinetics involves fundamental physiologic proc-esses, including metabolism, protein binding, tissue distri-bution, and drug transport into the site of drug effect. Pharmacokinetic models are mathematical relationships between dose and concentration, either in the plasma or at the site of drug effect. Such models can be used to determine how best to give drugs to achieve a therapeutic objective, but only when the relationship between drug concentration and drug effect is understood.

PHARMACODYNAMICS

Overview

Pharmacodynamics describes the relationship between plasma drug concentration and pharmacologic effect. Simply stated, pharmacodynamics attempts to explain what a drug does to the body. Although the study of clinically important drug effects is multifaceted, pharmacodynamics may be divided into three general areas. These areas are transduction of biologic signals, clinical evaluation of drug effects, and biologic variability. Each of these aspects of pharmacodynamics is explored in detail in the following sections.

Transduction of Biologic Signals

Receptor Theory

Definition

In the broadest sense, a receptor is a component of a cell that interacts selectively with an extracellular compound to initiate a biochemical change or a cascade of biochemical alterations that represent observed effects of the compound. Binding of drug to a receptor determines (1) the quantitative relationship between a given dose of a drug and the effect produced, (2) selectivity of a given drug's activity and effect,

---

and (3) an explanation of the pharmacologic activity of receptor agonists, antagonists, and inverse agonists. Receptors therefore serve to mediate or amplify the effect of a drug on the biologic system.

Historical Perspective

Although the overall concept of receptors is generally attributed to Paul Erhlich (1854-1915), earlier work performed by Claude Bernard (1813-1878) paved the way for receptor theory. This earlier work is of particular interest to anesthesiologists because it centered on elucidation of the mechanism of action of curare, an arrow poison. In his experiments, Claude Bernard ligated vessels leading to one hindlimb of a frog while leaving nerve input intact; he then administered intravenous curare. Pinching the paralyzed hindlimb produced reflex movements in the opposite unparalyzed vessel-ligated hindlimb. These experiments and others demonstrated for the first time the separation between sensory and motor nervous systems and also revealed that circulating "substances" produce selective effects on organ systems, a concept important in the development of receptor theory.

The concept of selectivity of effect eventually led Paul Erhlich to his conclusion that "agents cannot act unless they are bound," a cornerstone of receptor theory. Although Erhlich is attributed with discovering this concept, his contemporary J.N. Langley (1852-1926) coined the phrase "receptive substance" (or receptor). Langley extended Claude Bernard's work by showing that nicotine and curare have mutually antagonistic effects on the same receptive substance that is neither nerve nor muscle. Today, we recognize this "receptive substance" as the nicotinic acetylcholine receptor in the neuromuscular junction. Several decades of research have refined receptor theory to the point that receptors are now recognized as discrete excitable proteins.

Classic Receptor Theory

The binding of a ligand (drug molecule) to its receptor follows the laws of chemical reactions (analogous to Michaelis Menten enzyme kinetics) and can be summarized by the relationship:

where k_{on} is the rate constant for the ligand binding to the receptor, k_{off} is the rate constant for the ligand disassociating from the receptor, [L] is the concentration of the ligand, [R] is the concentration of the unbound receptor, and [LR] is the concentration of the bound receptor. Note that units for k_{or} are units of [L] multiplied by the units of [R] over time; typically, units of L are nanomoles per liter. The units for k_{off} are the units of [LR] over time. The term K_d, or dissociation constant, defines characteristics of ligand/receptor interactions at equilibrium. Mathematically,

The units of K_d are the units of [L], that is, units of concentration. When enough drug is administered to occupy exactly 50 percent of the receptors, the measured K_d is equal to the drug concentration. A low K_d indicates that less drug is required to occupy 50 percent of the receptors (because each molecule of drug is tightly associated with the receptor); a high K_d indicates that more drug is required to occupy 50 percent of receptors. The K_d has been determined for many of the drugs currently administered during anesthesia. The reciprocal of K_d is K_a, the association constant, which is exactly analogous to the K_a defined for protein binding. K_a is a measure of the affinity of the drug for the receptor. Hence, a drug with a low K_d constant has a high K_a and therefore high affinity for the receptor.

In practice, it is difficult to measure precise drug-receptor occupancy. It is often assumed that the drug-receptor complex represents an intermediate step in the production of a specific effect; therefore, many investigators apply pharmacodynamic theory to compare a given dose of a drug with a resulting effect. An effect can be any biochemical or physiologic variable that is measurable. A measured effect can be an alteration in a biochemical compound, an enzyme level, a physiologic variable such as heart rate or blood pressure, or a response to any graded input into the biologic system. For example, in evaluating the pharmacodynamics of muscle relaxants, the measured effect is not a direct measurement of drug-receptor complexes, but rather a response to a neuromuscular stimulus as delivered by a nerve stimulator.

From the discussion of pharmacokinetics, it is clear that the delivery of a drug to a given receptor is time- and dose-dependent. If the receptor is located within the

central compartment, there may be nearly instantaneous equilibration after an intravenous injection, and hence the peak effect may occur immediately. If drug must cross from the central compartment to the site of drug effect, this will cause a delay. The onset of drug effect can also be delayed by the time required for the body to respond to the drug. This delay may occur anywhere on the path between drug-receptor binding and clinical manifestation of drug effect. Examples of post-transduction time delays are drug-receptor complex- induced secondary messenger changes, increased enzyme synthesis, and the time required for physiologic change (e.g., reduced fluid content).

Receptor Agonists and Antagonists

Agonist drugs induce an effect that mimics endogenous hormones or neurotransmitters when bound to a receptor. This effect may be stimulatory or inhibitory. As described earlier, the term *affinity* as related to a given agonist is a measure of the attraction between the given drug and receptor. A drug with low affinity for a given receptor tends not to bind to the receptor, hence produces little or no effect. An agonist drug that binds avidly (or with high affinity) to a given receptor produces the receptor-determined effect at a lower given dose.

Full agonists completely activate a receptor, whereas partial agonists only partially activate a receptor (Fig. 2-22) . The difference between full and partial agonists results from differing intrinsic efficacy for each drug. Efficacy should not be confused with affinity. Two drugs can have

Figure 2-22 Effect of various types of ligands on receptor responses. Full agonist binding results in complete (100%) activation of a receptor, whereas partial agonist binding results in less than 100 percent activation. A neutral antagonist has no activity of its own, but it blocks agonist binding; hence, antagonists result in prevention of agonist responses. Inverse agonists can be thought of as "super antagonists" because binding of these compounds results in decreased responsiveness below the baseline response measured in the absence of drug. If the physiologic effect of the baseline levels of activated receptor (R*) is small, then the antagonists and inverse agonists may not be clinically distinguishable.

identical affinity for a receptor (and therefore bind to the same extent at a given drug concentration), yet they may produce different levels of activation of the receptor. Both are agonists, yet the drug that produces the maximal receptor activation is called a full agonist and has high efficacy, whereas the drug that produces less than a maximal receptor-mediated response is called a partial agonist with less intrinsic efficacy. The mechanisms underlying one drug's producing full versus partial agonist effects remain shrouded in mystery, but they may be related to the ability of the drug to stabilize the high-affinity state of the receptor (R*; see later).

Antagonist drugs inhibit or prevent receptor-mediated agonist effects by competing for receptor occupancy. A competitive antagonist can generally be displaced from the receptor complex by the administration of a large enough concentration of receptor agonist, thus permitting the agonist to produce the expected effect in spite of the presence of antagonist (see the clinical example later). However, a noncompetitive antagonist usually binds irreversibly to the receptor complex, producing loss of the expected effect that cannot be reproduced by concurrent administration of high-dose receptor agonist. Most antagonist drugs used in clinical medicine are competitive antagonists.

For example, vecuronium, a nondepolarizing muscle relaxant of moderate duration, is a competitive antagonist of acetylcholine. Acetylcholine mediates muscle contraction via the postsynaptic nicotinic acetylcholine receptor at the neuromuscular junction. When vecuronium binds to the post-synaptic acetylcholine receptor, acetylcholine agonism is blocked, and neuromuscular transmission is inhibited. The result is flaccid paralysis. Neuromuscular transmission may be reinstated by administering an acetylcholine esterase inhibitor. Acetylcholine esterase inhibitors prevent breakdown of acetylcholine, thus effectively raising the concentration of the agonist, acetylcholine, at the receptor, which then displaces vecuronium from the receptor complex. When enough vecuronium is displaced, muscle contraction is reinstated. This general principle is commonly used in anesthesia to reverse drug-induced muscle relaxation at the end of a surgical procedure.

Inverse agonists can be thought of as "superantagonists" because they decrease receptor responses to less than baseline (see Fig. 2-22). An example of concentration-response relationships for four different benzodiazepines and EEG response is shown in Figure 2-23 (Figure Not Available) . Note that in this example, EEG responses represent a surrogate clinical end point for binding of benzodiazepines to the $_{A}$ subunit of gamma-aminobutyric acid ($GABA_A$) ligand-gated ion channel complex with resultant modulations of ion fluxes in the central nervous system (CNS).

Receptor States

Classic receptor theory describes interaction between li-gand and receptor based on the laws of mass action. At a molecular level, this interaction has been interpreted over the years to suggest that binding of agonist to receptor initiates a change in receptor conformation, changing the receptor from an inactive (R) to an activated (R*) state (Fig. 2-24) . [2] [9] In this model, the change in receptor conformation facilitates activated receptor coupling to intermediary proteins (e.g., guanine nucleotide [G] proteins) or second messengers (effectors, E) which then initiate a rapid cascade of cellular responses.

Transgenic animal experiments have shed light on ligand and receptor interactions. In an elegant set of experiments in which beta $_{2}$ -adrenergic receptors were massively overexpressed in mouse myocardium, second messenger responses were increased *in the absence of ligand* when compared with normal mouse myocardium. In fact, adenylyl cyclase activity (the second messenger most commonly studied for $beta_2$ -adrenergic receptors) is identical at baseline in transgenic animals (in the absence of drug) compared with normal mice stimulated with isoproterenol (a beta $_{2}$ -adrenergic receptor agonist). Furthermore, isoproterenol stimulation of transgenic animals is unable to increase adenylyl cyclase activity higher than this elevated baseline. This finding suggests that, in these transgenic animals, a subpopulation of receptors is already fully activated. One way to analyze these findings is to consider that at baseline a small percentage (e.g., 1%) of receptors spontaneously exists in the activated (R*) state. Because this equilibration is the normal balance of the receptors in that tissue, the activity of these R* receptors is part of the baseline effect measured in the absence of drug. However, once massive overexpression of beta $_{2}$ -adrenergic receptors occurs (as in a transgenic animal), one percent of the total receptors becomes a very large number of activated receptors. This mimics

Figure 2-23 (Figure Not Available) The concentration-electroencephalographic (EEG) response relationship for four benzodiazepines: midazolam (full agonist), bretazenil (partial agonist), flumazenil (antagonist), and R0 19-4063 (an inverse agonist). The maximum effect seen in the EEG correlates with clinical action (full agonist > partial agonist > antagonist > inverse agonist). *(From Shafer, [2] based on Mandema et al [5])*

the effect of a maximal dose of drug, which would produce similar numbers of receptors in the R* state.

These findings have broad implications for understanding receptor states and drug-receptor interactions. Instead of ligand binding's causing a change from R to R* (as suggested by Fig. 2-24) , these data suggest spontaneous conversion from the R to the R* state (Fig. 2-25). In most tissues, the concentration of R* represents a small fraction of total overall receptor (hence the large arrow pointing toward R in Fig. 2-25). However, baseline receptor responses are known to differ among tissues, a finding suggesting that the absolute concentration of R* (and hence spontaneous conversion rates between R and R*) may be tissue-dependent. This finding is clinically important because inverse agonists, which drive receptors toward R and hence decrease responses to less than "baseline" to the true zero baseline, would be predicted to be most efficacious in tissues in which higher concentrations of spontaneous R* exist. Figure 2-23 (Figure Not Available) illustrates a tissue (CNS) in which enough activated $GABA_A$ ligand-gated ion channels (R*) are present to see EEG changes with an inverse agonist; this finding provides a rationale for the inverse agonist antiepileptic drugs currently being developed. Finally, it is important to note that the discussion thus far assumes only two receptor states, R (completely inactive) and R* (fully activated). More recent experimental evidence suggests the existence of intermediate transition states between R and R* (hence the use of curved lines in addition to straight lines in Fig. 2-25) . However, in the interest of simplicity, further discussion in this chapter utilizes only R and R*.

The discovery of spontaneous conversion between R and R* has implications for understanding the action of ligands (agonists, antagonists, inverse agonists). Instead of agonists' causing conversion from R to R*, it is now thought that li-gands stabilize a given receptor state. Specifically, as shown in Figure 2-26 , agonists stabilize (or energetically favor) R* and inverse agonists stabilize R, whereas neutral antagonists bind equally to R and R*. Binding of ligand to receptor removes the receptor from the equation because rapid coupling to second messengers occurs, thus driving (by mass action) the equation toward that specific state (Fig. 2-27) .

For example, once agonists bind to R*, the activated receptor-ligand complex is capable of activating second messenger pathways, so it is removed from the equation, driving the R
R* equation to the right to replace R*. Hence, the probability of being in the R* state increases in the presence of agonist. Conversely, inverse agonists drive the equation to the left, stabilizing the R configuration. Because baseline receptor

Figure 2-24 Schematic of classic receptor activation. For years, binding of ligand was thought to cause receptors to change from an inactive state (R) to an activated state (R*). The activated receptor then interacts with intermediary guanine nucleotide (G) proteins and/or directly with second messenger cascades (effectors, E). More recent information suggests a more complicated equilibrium between R and R*, as shown in Figure 2-27 .

responses represent a balance between R and R*, an inverse agonist often causes receptor response to fall to less than baseline to a true zero response level (see Fig. 2-22). Because antagonists are neutral (by definition), they bind equally to R and R*, thus preventing agonist responses but not changing the equilibrium between R and R*; hence, antagonists do not change the baseline response (see Fig. 2-22) . Many classic "antagonists" have now been tested and found to be inverse agonists rather than neutral antagonists. For example, "inverse efficacy" of common beta-adrenergic receptor antagonists has been determined as follows: timolol
propranolol > alprenolol
pindolol > labetalol > dichloroisoproterenol. Because inverse agonists may have theoretical advantages in treating certain diseases (e.g., seizures, congestive heart failure), clinicians should critically evaluate recent pharmacologic data prior to using an antagonist to distinguish whether the drug is an antagonist or an inverse agonist.

Figure 2-25 Spontaneous conversion of receptors from an inactive (R) to an active (R*) state. In most tissues, R* represents a small fraction of the total receptor population.

Figure 2-26 Ligand stabilization of receptor states. Agonists stabilize active receptors (R*), inverse agonists stabilize inactive receptors (R), and neutral antagonists bind equally to R and R* without affecting the equilibrium between the two receptor states.

Receptor Structure

General Principles

Receptors are located in many places in the cell--outer cell membrane, cytoplasm, intracellular organelle membranes, and nucleus. The overall physical structure of a receptor depends on the type of receptor considered as well as its location. For example, membrane receptors have structures different from those of cytoplasmic receptors. In general, cytoplasmic receptors (and/or nuclear receptors) bind ligands that readily traverse cell membrane lipid bilayers to reach the cytoplasm or nucleus. These ligands must therefore

Figure 2-27 Equilibrium between inactive receptors (R) and active receptors (R*) is tissue specific and depends on the type of ligand administered. By stabilizing R*, agonists drive the equilibrium to the right. In contrast, inverse agonists stabilize R, driving the equilibrium to the left. Because neutral antagonists bind equally to R and R*, they do not affect tissue specific equilibrium between R and R*.

Figure 2-28 Schematic of four types of membrane associated drug targets: membrane (G protein-coupled) receptor, ligand-gated ion channel, voltage-sensitive ion channel, and an enzyme. Potential sites of drug action are shown. betaAR, beta-adrenergic receptor; $GABA_A$, gamma-aminobutyric acid.

contain significant hydrophobic components. Examples of cytoplasmic and nuclear receptors include steroid and thyroid hormone receptors. In contrast, most receptors important to the anesthesiologist are excitable cell-membrane proteins, such as membrane receptors, ligand-gated ion channels, and voltage-gated ion channels (Fig. 2-28) . Many endogenous hormones and exogenous drugs are water soluble (hydrophilic and charged) and are unable to cross cell-membrane lipid bilayers. Therefore, a mechanism is required to transduce drug binding at the extracellular surface into changes in intracellular physiology. Membrane receptor structure depends on whether coupling to second messengers via intermediary proteins is required or whether the receptor is part of a larger ion channel complex (e.g., ligand-gated ion channels). Each of these types of membrane receptors has a role in mediating the action of various drugs important in anesthesiology. It is beyond the scope of this review to list all currently identified receptor proteins. However, prototypical examples are used to illustrate important pharmacodynamic principles.

Guanine Nucleotide (G) Protein-Coupled Receptors

One of the most common methods by which membrane receptors translate agonist occupancy into intracellular "action" is via intermediary G proteins. As a result, G protein-coupled receptors are the most abundant type of receptor known to date. The overall structure of G protein- coupled receptors is shown schematically in Figure 2-29 . Two-dimensional representation of G protein-coupled receptors reveals an extracellular amino terminus containing glycosylation sites, an intracellular carboxyl terminus, a fatty acid attachment (usually via palmitoylation or myristoylation) of a carboxyl terminal cysteine residue, three extracellular loops, and four intracellular loops. Major sites of G protein interactions with the receptor occur in the third and fourth (and to a lesser extent second) intracellular loops, whereas major sites of phosphorylation (important in desensitization, or dampening of receptor responses) generally occur in the third intracellular loop and carboxyl terminus.

Although a two-dimensional schematic is shown in Figure 2-29 , it is important to remember that G protein-coupled receptors are three-dimensional structures with transmembrane segments coalescing around a central binding pocket (Fig. 2-30) (Figure Not Available) . [10] Although transmembrane amino acids must be hydrophobic overall (in order to be energetically favored in the lipid membrane), side chains on individual amino acids may be charged. Specific amino acids therefore act as counterions to anchor charged (water-soluble) hormone or

Figure 2-29 Schematic of G protein-coupled receptors. A twodimensional version of receptor structure is shown with seven transmembrane domains, an extracellular amino (NH_2) terminus (with associated glycosylation sites [Y]), an intracellular carboxyl (COOH) terminus, palmitoylated cysteine residue (denoted by crooked line extending into membrane), three extracellular loops, and four intracellular loops. Major sites of G protein interactions with the receptor are speckled; potential sites of phosphorylation in the third intracellular loop and carboxyl terminus are enclosed in boxes.

Figure 2-30 (Figure Not Available) Schematic of the three dimensional structure of the beta $_2$ -adrenergic receptor (a prototypical G protein-coupled receptor), looking from the outside of the cell inward. Transmembrane domains (denoted by cylinders and numbered with Roman numerals) coalesce to form a binding pocket. The correct orientation of the agonist norepinephrine is shown. Note that agonist affinity is determined by specific amino acids located in transmembranes III, IV, and VII. These critical sites in transmembrane domains have been determined experimentally using chimeric receptor and mutagenesis approaches combined with sophisticated computer modeling techniques. Ultimate confirmation of these structures will require crystallographic data; this is currently being attempted by several laboratories. *(From Stapelfeldt [10])*

drug to the receptor. Therefore, structure-activity relationships between drug and the three-dimensional configuration of the receptor binding site are critically important. Although perhaps obvious, the chemical structure of a drug must match the three-dimensional configuration of the binding area of a receptor. Hence, subtle changes in drug structure may dramatically alter the ability of a drug to bind to a specific receptor population. In addition, two drugs with seemingly unrelated two-dimensional chemical structures may bind to the same receptor if their three-dimensional structures and charged areas are similar.

Ion Channels

In addition to membrane receptors, pharmacologic agents act on other excitable cell-membrane proteins, such as ion channels. These channels mediate neural signaling by modulating ion permeability in electrically excitable membranes. Because many drugs act directly or indirectly through ion channels, it is important for the anesthesiologist to understand their general function. Classic ion channels such as the sodium channel have charged regions that span the cell membrane. The formation of ion pairs between many positive and negative charges helps to stabilize the channel in the membrane. Voltage-dependent gating of the sodium channel is made possible by the presence of a voltage sensor--a collection of charges that moves under the influence of the cell-membrane electrical field, hence the name voltage-gated ion channels. During depolarization, these charges presumably move outward, causing conformational changes and rearrangement of ion pairs that result in sodium permeability. Blockade of sodium channels by local anesthetics is a major mechanism underlying pain insensibility. This concept is discussed in more detail in Chapter 13 .

In addition to classic voltage-gated ion channels, many drugs in anesthesiology act via ligand-gated ion channels. Both the nicotinic acetylcholine receptor and the $GABA_A$ receptor are receptor-ion channel complexes. The combination of a classic receptor protein plus an ion channel results in a ligand-gated ion channel, giving rise to the unique ability of certain drugs to alter membrane permeability to ions directly. This coupling is revealed in the physical structure of the receptor itself (Fig. 2-31) (Figure Not Available) . [11] [12] Whereas membrane receptors have hydrophobic transmembrane regions, and ion channels have a central charged transmembrane region, ligand-gated ion channels have both hydrophobic and central charged transmembrane regions. It is interesting to note that the binding of drugs to receptors in ligand-gated ion channel complexes usually enhances or dampens an already existing neurotransmitter ion flux. For example, the neurotransmitter GABA binds to its receptor within the $GABA_A$ ligand-gated ion channel complex and causes the movement of chloride ions intracellularly; this action results in lowered membrane potential, a hallmark of inhibitory neurotransmission. Drugs binding to other receptor sites in the GABA $_A$ ligand-gated ion channel (e.g., benzodiazepines, barbiturates, alcohols) facilitate the action of endogenous GABA. This process results in increased inhibitory chloride ion flux in the CNS (see Fig. 2-31) (Figure Not Available) .

Ion Pumps

Another type of excitable membrane protein is the ion pump. The sodium-potassium-adenosine triphosphatase (ATPase) pump is perhaps the most familiar ion pump to the anesthesiologist because it is inhibited by the drug digitalis. Extracellular fluid is high in sodium and low in potassium, whereas intracellular fluid is high in potassium and low in sodium. Action potentials activate sodium channels, allowing sodium to rush intracellularly. The sodium-potassium-ATPase pump then rapidly pumps sodium out of the cell in exchange for potassium, returning the cell to its original cation composition and electrical gradient. Drugs that act on ion pumps therefore alter intracellular/extracellular cation ratios, resulting in altered membrane electrical potential. This action accounts for some drug effects.

For example, the mechanism of action of digitalis is inhibition of sodium-potassium-ATPase pump function. This is of special importance in the myocardial cell, where sodium-potassium-ATPase exchange is replaced by slower sodium-calcium exchange, thereby increasing intracellular calcium concentrations. Because calcium increases myocardial contractility, improved myocardial pump function results. This is the basis of digitalis use in the treatment of congestive heart failure.

Second Messengers

The binding of a hormone or drug to its receptor does not instantly produce clinical effects. Instead, a series of rapid biochemical events couples receptor binding to ultimate clinical effects. These biochemical events are called second messengers. Because alterations in second messenger coupling can alter the effectiveness of a drug, it is important

Figure 2-31 (Figure Not Available) Schematic of the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex (a prototypical ligand-gated ion channel complex). Binding of benzodiazepine agonists to the $GABA_A$ ligand-gated ion channel facilitates the action of endogenous GABA. This results in increased inhibitory chloride ion flux in the central nervous system. (A) Schematic of the $GABA_A$ ligand-gated ion channel complex showing receptor sites for benzodiazepines and GABA, as well as distinct receptor sites for barbiturates and alcohol. *(From Berkowitz, [11] with permission)* (B) Model of the $GABA_A$ receptor-chloride ion channel protein complex composed of a heterooligomer of five subunits, including alpha, beta, and gamma, as well as delta or rho polypeptides. Each subunit has four putative membrane-spanning domains (numbered 1-4, represented by cylinders). *(From Firestone et al [12])*

that the anesthesiologist understand the general principles of second messenger action.

Many membrane receptors couple to their primary second messenger via G proteins, which are intermediate regulatory molecules. The coupling of G proteins to receptor-hormone complexes requires energy in the form of guanosine triphosphate (GTP). Once the receptor interacts with the G protein, the biochemical reaction in the effector cascade is triggered. There are stimulating (e.g., Gs, Gq) and inhibitory (e.g., Gi, Go) G proteins, and the physiologic effect is determined by the specific G protein and subsequent cellular response. G proteins are heterotrimeric, composed of three subunits--alpha, beta, and gamma. Receptor-G protein interactions result in dissociation of the G protein subunits into alpha and betagamma. The alpha subunit of most G proteins confers specificity between receptor and effectors. Although betagamma subunits were originally thought simply to anchor G proteins to the cell membrane, it is now clear that dissociated

betagamma subunits are capable of directly stimulating second messengers. In addition, betagamma subunits play a role in anchoring regulatory kinases to the cell membrane, leading to enhanced phosphorylation of membrane receptors.

Several receptor second messenger systems produce biologic effects in humans. One of the best understood second messenger systems is the adenylyl cyclase system. In this system, stimulatory G protein-receptor-hormone complexes increase activity of the enzyme adenylyl cyclase, resulting in increased levels of cyclic adenosine 3
,5
-monophosphate (cAMP) in the cell (Fig. 2-32) . Inhibitory G protein-receptor-hormone complexes decrease the activity of adenylyl cyclase, thus resulting in decreased levels of cellular cAMP. In general, increased levels of intracellular cAMP activate protein kinases that phosphorylate various proteins, ion channels, and second messenger enzymes. For example, beta-adrenergic receptor stimulation results in stimulation of adenylyl cyclase activity, increasing production of intracellular cAMP, which activates protein kinase A, which, in turn, phosphorylates the L-type calcium channel in myocardium to produce increases in intracellular calcium,

ultimately leading to increased inotropy. Examples of drugs or hormones that activate adenylyl cyclase include glucagon and histamine. In contrast, muscarinic (M_2, M_4) agonists, alpha$_2$-adrenergic agonists, and adenosine generally inhibit adenylyl cyclase.

Another example of a second messenger system is the phosphatidylinositol system. Here, hydrolysis of phospha-tidylinositol-4,5-bisphosphate (PIP_2) in the cell membrane, catalyzed by Gq activation of phospholipase C, generates two second messenger molecules, inositol-1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). IP_3 then mobilizes intracellular calcium from nonmitochondrial intracellular stores by interacting with distinct IP_3 receptors on the surface of these organelles. The resulting increase in intracellular calcium levels produces biologic effects such as smooth muscle contraction. Examples of drugs that mediate phosphatidylinositol hydrolysis include alpha$_1$-adrenergic, endothelin, and muscarinic (M_1, M_3, M_5) agonists.

Stimulation of receptors and second messengers ultimately leads to physiologic effects in a given tissue. The specific physiologic effects produced depend on the presence of specific receptor subtypes, G proteins, and second messen-gers within that tissue. An example of the wide-ranging cardiovascular

Figure 2-32 Schematic of the beta-adrenergic receptor signal transduction cascade. betaAR, beta-adrenergic receptor; Gsalpha, alpha subunit of the stimulatory G protein (Gs); betagamma, stimulatory G protein betagamma subunit; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate.

Figure 2-33 Adrenergic receptor subtype physiology. HR, heart rate; NE, norepinephrine.

effects produced by a single hormone-- norepinephrine, the predominant sympathetic neurotransmitter-- can be seen in Figure 2-33. Effects of sympathetic stimulation vary according to tissue. For example, acute effects of beta$_2$-adrenergic receptor-mediated vasodilation enhance skeletal muscle blood flow, beta-adrenergic receptor-mediated inotropic effects improve myocardial performance, and adrenergic effects in the CNS result in enhanced alertness; all these effects enable effective performance during stressful situations. Chronic stimulation of stress responses, however, leads to other adrenergically mediated effects, some maladaptive, such as alpha$_1$-adrenergic receptor-mediated hypertrophy, hypertension, and dampening of myocardial function.

Developments in Molecular Pharmacology

The field of molecular pharmacology is rapidly advancing understanding of excitable membrane proteins and their mechanisms of action. Prior to the advent of molecular biology, most pharmacology research utilized ligand binding and protein purification techniques to elucidate the structure and mechanism of action of various drugs and receptors. Although important, these studies were tedious because tissues contain more than one receptor subtype, and protein purification of receptors to homogeneity is a lengthy and complicated process. Molecular biology techniques provide a unique opportunity to study receptors and their structure at the DNA level. Many receptors and receptor subtypes have been discovered, paving the way for more receptor-specific pharmacologic agents. Future drugs for perioperative use will likely target receptor and receptor subtypes discovered using molecular approaches. For this reason, the general field of molecular pharmacology is briefly described.

Molecular pharmacology takes advantage of the finding that all proteins, including excitable membrane proteins, are encoded in the human genome as nucleic acids. Every amino acid present in a protein is encoded by a specific combination of three nucleotides in DNA. Therefore, if the DNA sequence that encodes a receptor protein can be determined, then the putative primary structure of the receptor can be deduced. In addition, these fragments of DNA (genes) can be inserted into special cells that will express (manufacture, assemble, and deliver to the appropriate location

in the cell) receptor protein in high quantity. This has several advantages.

First, studies on the receptor itself can be performed. By changing (mutating) nucleotide sequences, an abnormal (synthetic or "designer") receptor can be created. This abnormal receptor can then be compared with the original receptor to see whether the changes made affect binding of drug to the receptor or its coupling to second messengers. In this manner, precise portions of the receptor responsible for drug binding and/or second messenger coupling can be elucidated. This type of information is often called structure-activity relationships. G proteins and second messengers can be investigated in a similar manner.

The second advantage of using molecular techniques in pharmacology includes potential discovery of new receptors and receptor subtypes by searching for DNA sequences similar to those of known receptors. Once these new receptors are discovered, they can be easily characterized, because high expression in cells enables them to be screened by various pharmacologic agents.

Finally, and perhaps the most immediately clinically relevant, new investigational drugs can be rapidly screened for effects on various receptors. In this way, pharmacologic effects of individual receptors can be studied in a controlled manner, isolated from other receptors and receptor subtypes. Such studies have the potential to lead to development of new drugs for use in the perioperative period.

In addition to studying individual receptors expressed in cells, molecular pharmacology now includes creation and study of whole animals (usually mice) with altered physiologic features using transgenic and knock-out technology. In simplistic terms, transgenic animals overexpress a specific gene, whereas knock-out animals are missing a targeted gene. The physiologic consequence of such altered protein expression is then examined. Details of these technologies are beyond the scope of this chapter. The reading list at the end of this chapter includes several excellent reviews of the subject.

In order to interpret data from transgenic and knock-out animals correctly, it is important to consider several potential limitations of this technology. First, the genetic background of animals created should be carefully examined. If not carefully controlled, altered phenotypes may result from differences in animal "strain" (or genetic background), rather than from an overexpressed or knocked-out gene product. Second, elimination of specific receptors may be compensated for by alterations of other gene products. In this case, the final phenotype represents the net alteration of several genes; this is of particular concern when elimination of a gene is lethal because surviving progeny by definition have compensated in a way that enhances survival and therefore may not be representative of the results of a single gene knock-out. Finally, some receptors and proteins have different tissue localization in humans versus other animal species. Therefore, results from transgenic and knock-out animal studies should be interpreted cautiously in this circumstance lest incorrect conclusions be drawn regarding implications for human physiology.

In spite of these potential limitations, transgenic and knock-out animal models have proved very important in elucidating novel functions of receptors and proteins. Many unexpected physiologic roles for gene products have been discovered, and important physiologic questions have been answered and confirmed using these approaches. As an example, Table 2-1 lists conclusions drawn from transgenic and knock-out mice based on alterations of adrenergic receptors

TABLE 2-1 -- Summary of Results From Knockout and Transgenic Mice Illustrating Adrenergic Receptor Signaling Pathways

MODEL	TARGET	RESULT
Transgenic	beta$_2$ AR	basal AC, LV fn, atrial contractility, supraventricular premature beats, HR variability
Knock-out	beta$_1$ AR	70% prenatal death, survivors: nl AC, ISO-stim

Transgenic	GRK2	AC activity, fn betaARs, ISO-stim
Transgenic	GRK5	Enhanced betaAR desens, but not AngII desens
Transgenic	GRK2 inhib (net: GRK2)	Enhanced cardiac contractility with ISO
Knock-out	GRK2	Lethal phenotype, gestational hyperplasia LV, LVEF <70% in embryos
Transgenic	Gs	No Delta baseline EF, ISO-stim, myocardial fibrosis
Knock-out	phospholamban	betaAR-mediated contractile responses
Transgenic	$alpha_{1b}$ AR (*)	Myocardial hypertrophy
Transgenic	$alpha_{1b}$ AR (WT)	No myocardial hypertrophy
Transgenic	Gq	Myocardial hypertrophy 4-fold overexpression, higher expression gives heart failure
Transgenic	Gq inhib (net: Gq)	Prevention of myocardial hypertrophy
Knock-out	$alpha_{2a}$ AR	Presynaptic $alpha_2$ AR, mediates sedation/hypnosis, BP (central hypotension), analgesia, regulation of DA/5-HT, antiepileptogenic effects of NE
Knock-out	$alpha_{2b}$ AR	Mediates BP (peripheral vasoconstriction)
Knock-out	$alpha_{2c}$ AR	Mediates hypothermia, DA synthesis/metabolism

AC, adenylyl cyclase; AR, adrenergic receptor; angII, angiotensin II; BP, blood pressure; DA, dopamine; desens, desensitization; fn, functional; GRK, G protein-coupled receptor kinase (important in desensitization of receptors); HR, heart rate; inhib, inhibitor; ISO, isoproterenol; LV, left ventricle; LVEF, left ventricular ejection fraction; NE, norepinephrine; nl, normal; stim, stimulation; WT, wild type; 5-HT, serotonin;
, increase;
, decrease; Delta, change;*, constitutively active version of receptor.

and their signal transduction cascade. Novel functions for specific adrenergic receptor subtypes (e.g., the role of alpha $_{2c}$ -adrenergic receptors in temperature control, $alpha_{2b}$ -adrenergic receptors in mediating vasoconstriction, and alpha $_{2a}$ -adrenergic receptors in sedation and CNS-mediated hypotension) have been discovered. Furthermore, Table 2-1 illustrates that alterations in adrenergic receptor signal transduction pathways and modulating kinases have physiologic consequences in the whole animal.

Clinical Evaluation of Drug Effects

General Principles

Once pharmacologic agents have stimulated excitable cell-membrane proteins and have produced a physiologic effect, it is important to evaluate this effect clinically. This section focuses on methods of evaluating drug effects such as dose-response curves, efficacy, potency, the median effective dose (ED $_{50}$), the median lethal dose (LD_{50}), and the therapeutic index.

Concentration Versus Response Relationships

The standard comparison of a drug with its clinical effect is the concentration versus response curve, shown in Figure 2-34 . The relationship shown is the time-independent relationship between dose, concentration, or some other measure of exposure to the drug (X axis) and the measured effect

Figure 2-34 Dose-response relationships. A sigmoidal dose-response curve is generated when the log drug concentration is plotted against the clinical response or effect (curve A). The dose-response curve is shifted to the right in the presence of a competitive antagonist or when it is generated by another agonist with lower receptor affinity (K $_{a}$) and/or potency (curves B and C). Of note, desensitization also results in a shift of the doseresponse curve to the curve to the right.

(Y axis). The measured effect can be an absolute response (e.g., twitch height), a normalized response (e.g., percentage of twitch height depression), or a population response (e.g., fraction of subjects moving at incision). The standard equation for this relationship is the "Hill" equation, sometimes called the "sigmoid-E $_{max}$ relationship":

This is another example of the saturation equation shown in Figure 2-5 . In equation 44, E_0 is the baseline effect in the absence of drug, and E $_{max}$ is the maximum possible drug effect. C is typically concentration or dose, although other measures of drug exposure (e.g., AUC) can be used. C $_{50}$ is the concentration associated with 50 percent of peak drug effect and is a measure of drug potency. The exponent gamma relates to the sigmoidicity and steepness of the curve. If gamma = 1, and the curve is plotted on a standard X axis, then the curve appears hyperbolic (see Fig. 2-5). If gamma is greater than 1, then the curve appears sigmoidal, as in Figure 2-34 . If the X axis is plotted on a log scale, then the curve will always appear sigmoidal, regardless of the value of gamma.

Effect of Receptor Agonists and Antagonists on Dose-Response Relationships

Dose-response relationships can be modified by both agonists and antagonists. If two agonists have identical affinity (K $_{a}$) for a given receptor and identical effectiveness in coupling to second messengers, their resultant dose-response curves should be superimposable. However, if two agonists have different receptor affinities, in spite of identical effectiveness in coupling to second messengers, then their dose-response curves will be parallel (with the rightward shifted curve corresponding to the drug with lower receptor affinity; see Fig. 2-34 , curves B and C). When two agonists are administered simultaneously, one could predict that the

clinical effect would be dependent on the total amount of drug-receptor complexes generated; note that this implies a direct linear relationship between receptor-drug complex and measured effect. However, this is not always the case in biologic systems. For example, in neuromuscular transmission, measured change in effect on twitch height is not linear when receptor occupancy declines from 100 to 90 percent, as compared with the change from 80 to 70 percent occupancy. A further distinction between agonist effect is based on achievement of the maximum measured pharmacologic response or effect.

As stated earlier, full agonists produce maximal responses, whereas partial agonists produce less than maximal response at the same receptor occupancy. The precise molecular mechanism that explains this blunting of the maximal response by partial agonists is not known, but it may relate to the ability of full agonists to stabilize R* most effectively. Finally, the addition of a competitive antagonist shifts the dose-response curve to the right (higher agonist concentration is required to achieve effect; see Fig. 2-34 , curves B and C). The dose-response curve generated by the addition

of an agonist in the presence of a noncompetitive antagonist fails to demonstrate attainment of maximal response at any dose because blockade of effect (antagonism) cannot be reversed.

Effective Dose and Lethal Dose

The ED_{50} is the dose of a drug required to produce a specific effect in 50 percent of individuals to whom it is administered. The LD_{50} is the dose of a drug required to produce death in 50 percent of patients (or, more often, animals) to whom it is administered. The therapeutic index of a drug is the ratio between the LD_{50} and the ED_{50} (LD_{50}/ED_{50}). Hence, the higher the therapeutic index of a drug, the safer the drug is for clinical administration because the LD_{50} is far higher than the ED_{50}. The relationship among ED_{50}, LD_{50}, and therapeutic index is shown in Figure 2-35 .

Efficacy and Potency

Efficacy is a measure of the intrinsic ability of a drug to produce a given physiologic or clinical effect. Efficacy is influenced by receptor coupling to G proteins, activation of second messengers, and the ability to generate ultimate physiologic responses. The scale used to describe intrinsic efficacy at a given receptor ranges from 0 to 1. Efficacy for full agonists is 1.0, for neutral antagonists is 0, and for partial

Figure 2-35 Relationship between median effective dose (ED_{50}), median lethal dose (LD_{50}), and therapeutic index. These curves were generated from data in which animals were injected with varying doses of a sedative-hypnotic and clinical responses determined. ED_{50} is the dose of drug required to produce a specific effect (hypnosis) in 50 percent of animals to which it is administered (left curve). LD_{50} is the dose of drug required to produce death in 50 percent of animals to which drug is administered (right curve). The therapeutic index of the drug is the ratio between LD_{50} and ED_{50} (LD_{50}/ED_{50}).

agonists ranges between 0 and 1.0. In contrast, the term *potency* refers to the quantity of drug that must be administered to produce a specific effect. Two drugs may have the same efficacy, but if one drug produces the maximum effect at 1 mg while the second drug produces the maximum effect only at 100 mg, then the second drug is less potent. Figures 2-34 and 2-36 demonstrate the relationship among efficacy, potency, and the dose-response curve.

Desensitization

Desensitization is broadly defined as waning of physiologic responsiveness to a drug over time. In the perioperative period, acute desensitization of vasodilator responses to nitroprusside occurs; therefore, in order to achieve desired vasodilation, it is often necessary to increase the concentration of nitroprusside infusion over time. In general, stimulation of receptor pathways results in activation of kinases (e.g., protein kinase A, G protein-coupled receptor kinases, protein kinase C) that phosphorylate specific regions of the receptor, thus preventing further interaction of the receptor with G proteins and/or second messengers. Thus, desensitization provides a negative-feedback mechanism to receptor stimulation. Although desensitization was initially thought to occur only at the receptor level, it is now well recognized that alterations of G proteins and second messengers also occurs in response to agonist stimulation. Effectively, desensitization shifts the dose-response curve to the right (see Fig. 2-34 , curves B or C compared with curve A) and/or decreases maximal drug effect; hence, both efficacy and potency can be diminished by desensitization.

Desensitization of receptor responses is a feature of many diseases present in the aging population and therefore is relevant to consider during the perioperative period. Common diseases in which desensitization is important include

Figure 2-36 Relationship among efficacy, potency, and individual variability is shown as they relate to a typical sigmoidal dose-response curve.

congestive heart failure, hypertension, and diabetes; a hallmark of each of these diseases is elevation of hormone (agonist) concentrations. In the case of congestive heart failure, poor cardiac output induces compensatory sympathetic nervous system stimulation, resulting in a doubling of circulating catecholamine concentrations (specifically norepinephrine). On a long-term basis, this results in desensitization of the myocardial beta-adrenergic receptor signal transduc-tion pathway; specifically, $beta_1$-adrenergic receptor density and function decreases (
75%) with relative sparing of $beta_2$-adrenergic receptors (
25%). Gi levels also increase without change in Gs. Furthermore, G protein-coupled receptor kinase concentrations increase and modulation of adenylyl cyclase isoforms occurs. Physiologic effects of changes important in desensitization of myocardial beta- adrenergic receptors have been examined using transgenic and knock-out mice (see Table 2-1 and the earlier discussion of molecular pharmacology). In order to break the cycle of elevated agonist exposure and resultant desensitization, long-term low-dose beta-adrenergic receptor antagonists (
1/10 the usual dose for hypertension or myocardial ischemia) are now cautiously utilized by cardiologists in patients with congestive heart failure; this therapy has been shown to improve functional classification and longevity.

Increased Receptor Sensitivity

The opposite of desensitization is increased receptor sensitivity. Long-term exposure to a drug often results in compensatory responses by the receptor system. For example, when a receptor antagonist is administered on a long-term basis, receptor number (density) often increases. If the receptor antagonist is suddenly discontinued, exaggerated responsiveness to agonist may occur. This is the rationale for continuing long-term beta-adrenergic receptor antagonists during the perioperative period. Abrupt discontinuation of these drugs leaves the myocardium vulnerable to exaggerated heart rate and inotropic responses to routine procedures such as tracheal intubation, potentially leading to myocardial ischemia and infarction. Therefore, careful consideration should be given prior to discontinuing a long-term medication before surgery.

Biologic Variability

Individual variation in response to an identical dose of administered drug is a phenomenon observed daily by the anesthesiologist. Individual variation in response to a drug can occur as a result of differences in pharmacokinetic parameters such as absorption, distribution, metabolism, and excretion of a drug. Individual variation can also be due to differences in pharmacodynamic parameters. In this circumstance, an identical number of drug molecules present at an effector site produces different responses in different patients. The relationship between patient variability and a typical dose-response curve is shown in Figure 2-36 . In addition to

desensitization (discussed earlier), factors that affect pharmacodynamic responses include age, genetic variability, and concurrent diseases.

Age

Although important age-related pharmacokinetic differences have been investigated in detail, there is a paucity of data addressing pharmacodynamic differences among age groups. Overall, the presence or absence of age-related pharmacodynamic differences appears to depend on the drug. For example, both antiepileptic agents and digoxin have been examined in adults and children, and the effective plasma concentration is the same. This finding suggests that for these two types of drugs, no age-related differences in pharmacodynamic responses occur. However many drugs with CNS effects (e.g., benzodiazepines, opioids, propofol) appear to be intrinsically more potent in the elderly. In other words, the concentration associated with a given level of drug effect is reduced in elderly subjects. Pharmacodynamic models have quantified the influence of age on the potency of anesthetic drugs. Present research is now directed toward understanding the biologic basis of increased sensitivity in the elderly to anesthetic drugs.

Genetic Variability

Genetic variability also can affect pharmacodynamic parameters. If a receptor or second messenger is defective or hyperactive, then pharmacodynamic alterations in drug effect will be noted. The most striking example of genetic variability resulting in pharmacodynamic differences in anesthesia is the disease *malignant hyperthermia.* Malignant hyperthermia is manifested in approximately 1 in 20,000 anesthetic regimens. Various anesthetics, especially halothane, seem to trigger an abnormal hypermetabolic response that results in an uncontrolled rise in body temperature, muscle rigidity, metabolic acidosis, hyperkalemia, and hypercapnia. Although the exact cause of malignant hyperthermia is unknown, it appears to be related to abnormal calcium release and uptake by the sarcoplasmic reticulum within cells. Because the disease does not influence the uptake and distribution of drug, but is manifest once the drug interacts at the cellular level, it represents a classic genetic pharmacodynamic abnormality.

Disease States

Various diseases contribute to variation in drug response. Although diseases frequently result in pharmacokinetic variations (e.g., decreased perfusion in heart failure or decreased elimination in renal failure), pharmacodynamic variation is also observed. Diseases such as diabetes, thyroid disease, adrenal disease, myasthenia gravis, and hypertension alter receptor function and therefore represent pharmacodynamic effects. Alteration of receptor function resulting from elevated agonist concentration is described earlier in the desensitization section. In addition to desensitization, other changes can occur at receptors that result in diminished function. For example, in patients with myasthenia gravis, antibodies to the postsynaptic nicotinic acetylcholine receptor effectively decrease the number of receptors pres-ent. Muscle weakness characterizes the disease. As a result, these patients are exquisitely sensitive to muscle relaxants,

---

which act via the nicotinic acetylcholine receptor. Clinically, muscle relaxant dose must be decreased or these drugs must be eliminated in this patient population.

Summary

This chapter reviews general pharmacology by examining basic principles of pharmacokinetics and pharmacodynamics. Careful consideration of these principles should permit the anesthesiologist to understand drug movement from the site of administration through various body compartments to the site of action, and the mechanisms by which drugs act on receptors to bring about the desired clinical effect. Many factors may alter the pharmacokinetic and pharmacodynamic processes by which drugs exert their effects, including age, disease, and concurrent drug therapy. Understanding the basic pharmacologic processes, and how these may be altered in individual patients, should facilitate drug titration for each patient. There is a biologic basis for finding just the right drug, in just the right dose, to provide safe and effective patient care.

References

1. Krejcie TC, Avram MJ, Gentry WB et al: A recirculatory model of the pulmonary uptake and pharmacokinetics of lidocaine based on analysis of arterial and mixed venous data from dogs. J Pharmacokinet Biopharm 25:169, 1997.

2. Shafer S: Principles of pharmacokinetics and pharmacodynamics. In Longnecker DE, Tinker JH, Morgan GE (eds): Principles and Practice of Anesthesiology, 2nd ed. St. Louis, Mosby-Year Book, 1997, p 1159.

3. Wagner JG: Pharmacokinetics for the Pharmaceutical Scientist. Lancaster, Penna, Technomic Publishing, 1993.

4. Wilkinson GR, Shand DG: Commentary: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377, 1975.

5. Danziger RS, Tobin JD, Becker LC et al: The age-associated decline in glomerular filtration in healthy normotensive volunteers: Lack of relationship to cardiovascular performance. J Am Geriatr Soc 38:1127, 1990.

6. Ebling WF, Wada DR, Stanski DR: From piecewise to full physiologic pharmacokinetic modeling: Applied to thiopental disposition in the rat. J Pharmacokinet Biopharm 22:259, 1994.

7. Youngs EJ, Shafer SL: Basic pharmacokinetic and pharmacodynamic principles. In White PF (ed): Textbook of Intravenous Anesthesia. Baltimore, Williams & Wilkins, 1997, p 10.

8. Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234, 1985.

9. Mandema JW, Kuck MT, Danhof M: Differences in intrinsic efficacy of benzodiazepines are reflected in their concentration-EEG effect relationship. Br J Pharmacol 105:164, 1992.

10. Stapelfeldt WH: The autonomic nervous system. In Schwinn DA (ed): Scientific Principles of Anesthesia, vol 2. Philadelphia, Current Medicine, 1998.

11. Berkowitz DE: Cellular signal transduction. In Schwinn DA (ed): Scientific Principles of Anesthesia, vol 2. Philadelphia, Current Medicine, 1998.

12. Firestone L, Quinlan J, Gyulai F: Mechanisms of anesthetic action. In Schwinn DA (ed): Scientific Principles of Anesthesia, vol 2. Philadelphia, Current Medicine, 1998.

Suggested Readings

Alberts B, Bray D, Lewis J: Molecular Biology of the Cell, 3rd ed. New York, Garland Publishing, 1994.

Baldwin JM: Structure and function of receptors coupled to G proteins. Curr Opin Cell Biol 6:180, 1994.

Benet LZ, Kroetz DL, and Sheiner LB: Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In Hardman JG, Limbird LE (eds): The Pharmacological Basis of Therapeutics, 3rd ed. New York, McGraw-Hill, 1996, p 3.

Bjorkman S, Wada DR, Stanski DR et al: Comparative physiological pharmacokinetics of fentanyl and alfentanil in rats and humans based on parametric single-tissue models. J Pharmacokinet Biopharm 22:381, 1994.

Bond RA, Leff P, Johnson TD et al: Physiological effects of inverse agonists in transgenic mice with myocardial overexpression of the beta $_2$ -adrenoceptor. Nature 374:272, 1995.

Bowdle TA, Horita A, Kharasch ED: The Pharmacologic Basis of Anesthesiology. New York, Churchill Livingstone, 1994.

Clarke WP, Bond RA: The elusive nature of intrinsic efficacy. Trends Pharmacol Sci 19:270, 1998.

Conti-Tronconi BM, McLane KE, Raftery MA et al: The nicotinic acetylcholine receptor: structure and autoimmune pathology. Crit Rev Biochem Mol Biol 29:69, 1994.

Freedman NJ, Lefkowitz RJ: Desensitization of G protein-coupled receptors. Recent Prog Horm Res 51:319, 1996.

Hamm HE: The many faces of G protein signaling. J Biol Chem 273:669, 1998.

Jenkinson DH, Barnard EA, Hoyer D et al: International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. IX. Recommendations on terms and symbols in quantitative pharmacology. Pharmacol Rev 47:255, 1995.

Kalow W: Pharmacogenetics in biological perspective. Pharmacol Rev 49:369, 1997.

Kenakin T: The classification of seven transmembrane receptors in recombinant expression systems. Pharmacol Rev 48:413, 1996.

Krumins AM, Barber R: The stability of the agonist beta$_2$ -adrenergic receptor-Gs complex: Evidence for agonist-specific states. Mol Pharmacol 52:144, 1997.

Lambert JJ, Belelli D, Hill-Venning C et al: Neurosteroid modulation of native and recombinant GABA $_A$ receptors. Cell Mol Neurobiol 16:155, 1996.

Milano CA, Allen LF, Rockman HA, et al: Enhanced myocardial function in transgenic mice overexpressing the beta $_2$ -adrenergic receptor. Science 264:582, 1994.

Nies AS, Spielberg SP: Principles of therapeutics. In Hardman JG, Limbird LE (eds): The Pharmacological Basis of Therapeutics, 3rd ed. New York, McGraw-Hill, 1996.

Post SR, Hilal-Dandan R, Urasawa K et al: Quantification of signalling components and amplification in the beta-adrenergic-receptor- adenylate cyclase pathway in isolated adult rat ventricular myocytes. Biochem J 311:75, 1995.

Rockman HA, Koch WJ, Lefkowitz RJ: Cardiac function in genetically engineered mice with altered adrenergic receptor signaling. Am J Physiol 272:H1553, 1997.

Ross EM: Pharmacodynamics: Mechanisms of drug action and the relationship between drug concentration and effect. In Hardman JG, Limbird LE (eds): The Pharmacological Basis of Therapeutics, 3rd ed. New York, McGraw-Hill, 1996, p 29.

Rowland M, Tozer TN: Clinical Pharmacokinetics: Concepts and Applications, 3rd ed. Baltimore, Williams & Wilkins, 1995.

Schwinn DA (ed): Scientific Principles of Anesthesia, vol 2. Philadelphia, Current Medicine, 1997.

Schwinn DA, Watkins WD, Leslie JB: Basic principles of pharmacology related to anesthesia. In Miller RD (ed): Anesthesia, 4th ed. New York, Churchill Livingstone, 1994, p 43.

Shuldiner AR: Transgenic animals. N Engl J Med 334:653, 1996.

Skiba NP, Hamm HE: How Gsalpha activates adenylyl cyclase. Nat Struct Biol 5:88, 1998.

Smiley RM, Kwatra MM, Schwinn DA: New developments in cardiovascular adrenergic receptor pharmacology: Molecular mechanisms and clinical relevance. J Cardiothorac Vasc Anesth 12:80, 1998.

Tanelian DL, Kosek P, Mody I et al: The role of the GABA$_A$ receptor/ chloride channel complex in anesthesia. Anesthesiology 78:757, 1993.

Tang WJ, Hurley JH: Catalytic mechanism and regulation of mammalian adenylyl cyclases. Mol Pharmacol 54:231, 1998.

Vaughan M: Signaling by heterotrimeric G proteins minireview series. J Biol Chem 273:667, 1998.

Watson J, Gilman M, Witkowski J et al: Recombinant DNA, 2nd ed. New York, Scientific American, 1996.

/das/book/view/29494766/875/22.html

Chapter 3 - Mechanisms of Action

Donald D. Koblin

/das/book/view/29494766/875/23.html

INTRODUCTION

Although currently popular inhaled anesthetics include nitrous oxide, isoflurane, and sevoflurane, a far greater variety of inhaled agents can produce anesthesia (Fig. 3-1) . The properties of these anesthetics vary considerably. For example, cyclopropane and diethyl ether are no longer used because of their explosiveness and flammability. Halothane is nonflammable but possesses a permanent dipole moment, can form hydrogen bonds, and is metabolized by the liver. Xenon, an anesthetic more potent than nitrous oxide in humans, [1] is essentially inert and undergoes no known transformation in the body. The molecular size of inhaled anesthetics may differ by a factor of about 10.

The structural diversity of the inhaled anesthetics suggests that they all do not interact directly with a single specific receptor site. However, some correlations of the potencies of anesthetics with their physicochemical properties do suggest a common (unitary) mechanism of general anesthetic action. An example is the striking (albeit imperfect) relationship between anesthetic potency and lipid solubility (see *Physicochemical Nature of the Site of Anesthetic Action*). Although such correlations do not provide a detailed mechanism of anesthesia, they have been helpful in defining the environment in which anesthetics act.

Any molecular hypothesis of anesthesia must explain the effects of anesthetics on the whole organism. For instance, because anesthetic administration can rapidly induce unconsciousness, and awakening can quickly occur following the discontinuation of anesthesia, physical or biochemical changes important to the mechanism of anesthesia must occur within seconds. Similarly, physical or biochemical alterations

Figure 3-1 Chemical structures of various inhaled anesthetics. Anesthetics with asymmetric carbon atoms [indicated by (*)] are mixtures of the optical isomers.

caused by anesthetics are meaningful only at clinical doses and physiologic temperatures and not at high anesthetic levels. [2] High levels may produce toxic effects unrelated to the mechanism by which inhaled anesthetics act. Furthermore, anesthetic requirement does not change [3] (or only decreases slightly [4]) with increasing duration of anesthesia. Thus, any physical or biochemical change causally related to anesthesia should be stable for a period of hours or days.

Finally, the mechanism(s) by which inhaled anesthetics act may overlap the mechanism(s) of action of intravenous anesthetics (Chs. 8 - 10), local anesthetics (Ch. 13) , and even of alcohols. [5] This chapter considers only the inhaled agents.

MEASUREMENT OF ANESTHETIC POTENCIES

An exploration of the mechanism by which anesthetics act requires a knowledge of relative anesthetic potencies for each of the agents. The best estimate of anesthetic potency is the minimum alveolar concentration (MAC) (at 1 atm) of an agent that produces immobility in 50 percent of those subjects exposed to a noxious stimulus. [6] For determination of MAC in humans, the stimulus is a surgical skin incision. (Variations on the MAC concept may be used to estimate the potency of other anesthetic end points. For example, lack of response to verbal command [MAC awake] occurs at lower anesthetic concentrations, and lack of response to endotracheal intubation [MAC intubation] occurs at higher anesthetic concentrations than those needed to prevent movement to surgical skin incision [Ch. 29]). In animals, the noxious stimulus is usually produced by clamping the tail or by passing electrical current through subcutaneous electrodes. The advantage of measuring the alveolar concentration is that after a short period of equilibration, this concentration directly represents the partial pressure of anesthetic in the central nervous system (CNS) and is independent of the uptake and distribution of the agent to other tissues (Chs. 4 and 29) . Another advantage of MAC is its consistency for a given animal or species or between different species or classes of animals. [6] [7] This consistency makes it possible to discern small changes in anesthetic requirement, which may give a clue as to how anesthetics act.

The anesthetic concentration that abolishes the righting reflex in 50 percent of the animals is often used to measure anesthetic potencies in smaller animals, that is, it is an anesthetic 50 percent effective dose (ED_{50}). Because the inspired rather than the alveolar concentrations are measured, the method applies best to rapidly equilibrating (poorly blood-soluble) agents. Only with equilibration can it be assumed that the partial pressure of the inspired gas equals that at the site of action. The use of small animals and inspired concentrations facilitates work with agents at very high pressures (i.e., tens or hundreds of atmospheres). The anesthetic ED_{50} in the mouse, as determined by the rolling response (i.e., the righting reflex), correlates closely with MAC in humans over a 500-fold change in anesthetic requirements (Fig. 3-2) .

It must be noted, however, that the tail-clamp ED_{50} (MAC) and the righting-reflex ED_{50} are not identical. The

Figure 3-2 A close correlation exists between the MAC of various anesthetics, preventing a response to surgical incision in humans and the inspired dose of an anesthetic (ED_{50}) required to abolish the righting reflex in the mouse. *(Data from references [6] and [5])*

tail-clamp ED_{50} is higher than the righting-reflex ED_{50} , and the ratio of these measurements averages approximately 1.8 (Table 3-1) [8] [9] [10] . This ratio varies slightly with the anesthetic examined, implying that the righting reflex is depressed, at least in part, by a different mechanism from that which depresses the response to application of a tail clamp. [8] [9] [10] Thus, the absolute and relative potencies of inhaled anesthetics depend on the end point measured. [11]

ALTERATIONS IN ANESTHETIC REQUIREMENT PERTINENT TO THEORIES OF NARCOSIS

Effects of Temperature

In mammals, MAC decreases with decreasing body temperatures for all anesthetics, but the reduction (
2-5%) per degree decrease in body temperature varies slightly from agent to agent. [6] [12] Although the gas phase potencies of inhaled

TABLE 3-1 -- Ratios of Anesthetic Potencies

	TAIL-CLAMP ED_{50} /RIGHTING REFLEX ED_{50}	
ANESTHETIC	***MOUSE***	***RAT***
Halothane	1.67	1.74
Enflurane	1.91	--
Isoflurane	2.10	2.41
Chloroform	1.61	--
Cyclopropane	1.97	--
Nitrous oxide	>1.82	--
Methoxyflurane	1.63-2.08	--
Diethyl ether	--	1.25

Data from Deady et al, [8] Koblin et al, [9] and Kissin et al [10]

agents increase with decreasing temperature, there is an associated increase in anesthetic solubility with a decrease in temperature so that the aqueous phase potencies remain relatively constant with changes in temperature (Fig. 3-3) (Figure Not Available) . [13] For *in vitro* experiments involving clinical volatile anesthetics, aqueous concentrations equivalent to 1 MAC range from
200 to 600 mum. [13]

Effects of Pressure

The exposure of whole organisms to increasing hydrostatic pressures often increases the anesthetic dose required to bring about unresponsiveness, a phenomenon termed the *pressure reversal of anesthesia.* [14] In experiments with mammals, pressure is increased by the addition of helium because helium does not produce anesthesia and possesses little or no inherent anesthetic effect at high pressures. At a total pressure of 100 atm, a 30 to 60 percent increase in the partial pressure of inhaled anesthetics is required to abolish the righting reflex in the mouse. [15] However, not all species exhibit a pressure reversal of anesthesia. The reduction in swimming activity of freshwater shrimp induced by halothane, chloroform, and diethyl ether is not reversed by the application of high pressure. [16] It remains debatable whether pressure reversal represents a specific antagonism at the site of anesthetic action or is simply a generalized phenomenon that counteracts a global depression produced by anesthetics.

Effects of Age

In humans, MACs of volatile agents are maximal in infants at approximately 6 months of age (Fig. 3-4) . MAC gradually decreases with increasing age, and MAC in the octogenarian is approximately one-half that in the infant. The increase in potency (decrease in MAC) with increasing age is seen for all inhaled anesthetics and averages
6 percent change per decade of age. [17] Thus, the greater susceptibility of older patients to CNS depression by inhaled anesthetics is not related to the absolute potency of the agent. Animal models may be useful for studying the mechanisms of change in anesthetic potency with age because comparison of mice and humans over similar life-spans shows the decrease in anesthetic requirement of mice to parallel that clinically seen in humans (see Fig. 3-4) .

Effects of Ion Concentrations

Hypernatremia increases sodium proportionately in cerebrospinal fluid (CSF) and increases halothane MAC in dogs by as much as 43 percent. [6] Conversely, hyponatremia dilutes cerebrospinal fluid sodium and reduces halothane MAC. [6]

Hyperkalemia in dogs does not alter cerebrospinal fluid potassium or MAC. [6] Furthermore, intracerebroventricular injection of drugs (cromakalim, pinacidil) that enhance flow of ions through potassium channels does not change MAC in rats. [18]

Calcium infusions in dogs increase serum and CSF calcium by 2.6 and 1.3 times, respectively, without influencing halothane MAC. [19] However, calcium entry blockers (at relatively high concentrations) augment the potency of inhaled anesthetics. [20]

A 5-fold increase in serum magnesium is associated with a 12 percent increase in CSF magnesium in dogs and does not alter halothane MAC. [19] In rats, a 10-fold increase in plasma magnesium concentration above control levels decreases halothane MAC by approximately 60 percent. [21]

Alterations in anion concentrations via infusion of hydrochloric acid or sodium bicarbonate have little influence on MAC in spite of marked changes in arterial pH. [6] However, intrathecal or intracisternal administration of drugs that block chloride ion transport increases the MACs of isoflurane [22] and halothane [23] in rats.

Figure 3-3 (Figure Not Available) Plot of halothane MAC (in dogs) versus temperature. When measured as a function of the gas-phase partial pressure, MAC decreases with decreasing temperature. In contrast, when measured as a function of calculated aqueous concentrations, MAC remains relatively constant with changes in temperature from 28 to 43°C. *(From Franks and Lieb [15])*

Figure 3-4 Age-dependent alterations in halothane requirement (MAC) in humans and nitrous oxide requirement (righting-reflex ED_{50}) in mice over similar life spans. *(Data for halothane in humans are from Lerman et al [Anesthesiology 59: 421, 1983] and Gregory et al [Anesthesiology 30:488, 1969]. Data for nitrous oxide in mice are from Koblin et al [Anesthesiology 58:428, 1983].)*

These effects of temperature, pressure, aging, and ion concentrations may be used to test the various models of anesthetic action. Any valid theory of anesthetic action must account for the influence of these physical and physiologic parameters on anesthetic requirement.

ACTIONS OF INHALED ANESTHETICS IN THE CNS

Brain

Inhaled anesthetics may act by altering neuronal activity in selected regions of the CNS. Because the brain stem reticular formation plays a role in altering the state of consciousness and alertness and in regulating motor activity, it is often suggested that this structure is an important site of anesthetic action. Although the idea that anesthesia results from a decrease in "tone" in the ascending reticular system may be correct, it is most likely an oversimplification. [24] The effect of anesthesia on neuronal activity in the reticular formation is variable and can be increased, unchanged, or decreased, depending on the agent and the neuronal unit examined. [25]

General anesthetics interrupt transmission in the CNS at sites other than the reticular formation. Clinical concentrations of inhaled agents may alter spontaneous and evoked activity inthe mammalian cerebral cortex [26] and hippocampus. [27] Although inhaled anesthetics usually depress excitability of brain neurons, situations can be found in which anesthetics enhance excitability (Fig. 3-5) (Figure Not Available) . [27] In addition, inhibitory transmission may be influenced by volatile agents. For example, halothane prolongs gamma-aminobutyric acid (GABA)-induced inhibition in the hippocampus, [28] and volatile anesthetics may either enhance the amplitude and duration of inhibitory postsynaptic currents [29] or selectively depress inhibitory postsynaptic potentials. [30] Neuronal pathways between various brain regions and consisting of both excitatory and inhibitory components may also be influenced by inhaled agents. The transfer of sensory information from the thalamus to certain cortical regions is thought to be particularly sensitive to anesthetics. [31]

Spinal Cord

Both excitatory and inhibitory neurotransmission in mammalian spinal cord may be altered by inhaled anesthetics. [32] Anesthetic effects depend on the concentration of the agent and on the particular spinal cord pathway examined. Inhaled anesthetics alter responses of the spinal dorsal horn (sensory) to both noxious and nonnoxious stimuli. [32] Volatile anesthetics also depress spinal motor neurons. Clinical inhaled agents depress the F-wave amplitude (a measure of the excitability of spinal motor neurons) in rats [33] and humans. [34] Thus, both a reduction in the sensory processing and an inhibition of motor neuron excitation are likely to be involved in the anesthetic-induced lack of movement in response to a noxious stimulus. In addition to a direct action on the spinal cord, inhaled agents may indirectly influence activity of spinal neurons by altering the tonic input received from descending modulatory systems from the brain. [32] [35]

Sites of CNS Action and Anesthetic End Points

Traditionally, most investigators assumed that surgical anesthesia resulted from a supraspinal event. Although it remains probable that an interaction of inhaled anesthetics with various brain structures is required for the production

Figure 3-5 (Figure Not Available) The effects of halothane (left) and isoflurane (right) on three excitatory synaptic pathways in the rat hippocampal slice. The potential recordings were produced from stimulation of three discrete regions of the hippocampal slice: the stratum radiatum (RAD), the stratum oriens (OR), and perforant path (PP) fibers. Each superimposed series of records shows control (C) responses before (solid line) and after washout (light dotted line) together with two or three concentrations of anesthetic (numbers refer to volume percent). The horizontal calibration bar represents 20 ms and the vertical calibration bar represents 2.0 mV. These studies demonstrate that the ability of inhaled agents to depress or enhance neuronal excitability depends on the anesthetic, the anesthetic concentration, and the particular brain region examined. *(From MacIver and Roth [27])*

of amnesia, the ability of anesthetics to prevent a motor response to noxious stimulation likely results from a site of action in the spinal cord and not in the brain.

A focal cryogenic lesion that destroys much of the left parietal cortex in rats has no influence on halothane MAC in rats. [36] Moreover, isoflurane MAC in rats is not altered by bilateral decerebration (including removal of thalamus and hippocampus [37]) (Fig. 3-6) (Figure Not Available) nor by high thoracic spinal cord transection and functional separation of the rat brain from the spinal cord. [38] The cerebral blood supply of the goat allows for the preferential anesthetization of its forebrain, which results in an isoflurane MAC that is more than twice the value found when anesthetic is administered via the goat's native circulation. [39] This finding in a second species confirms the importance of extracranial structures in anesthesia as defined by MAC.

Thus, if anesthesia is defined as consisting of (at least) two components, amnesia and immobility in response to a noxious stimulus, there must be two separate anatomic sites of inhaled anesthetic action: a supraspinal site involved in the production of amnesia and a spinal site involved in the prevention of movement to noxious stimuli. [40] Given that the human CNS consists of billions of neurons, each having thousands of synapses, the discovery of the exact nature of these sites of anesthetic action presents a formidable challenge. Attempts to reduce this complexity have led to experiments on isolated neuronal preparations.

INTERRUPTION OF NEURONAL TRANSMISSION BY INHALED ANESTHETICS

Peripheral Receptors

The action of inhaled anesthetics cannot be explained by depression of peripheral receptors. Anesthetizing concentrations of clinical agents do not alter cutaneous receptor responses

Figure 3-6 (Figure Not Available) Decerebration does not alter anesthetic requirement, as measured by MAC. Removal of brain tissue rostral to the heavy black line does not alter isoflurane MAC in rats. Thl = thalamus; RN = red nucleus; PAG = periaqueductal gray; RF = reticular formation. *(From Rampil et al [37])*

to touch or movement of hair and can even sensitize and promote excitation of nociceptors in mammalian A and C fibers. [41] Moreover, a selective perfusion technique allowing for minimal (
0.2% atm) isoflurane concentration at the site of peripheral noxious stimulus in dogs while maintaining higher concentrations in the rest of the body results in no change in isoflurane MAC and demonstrates that the peripheral effects of isoflurane do not influence the response to a noxious stimulus. [42]

Highly Sensitive Neurons

From the previous discussion it is apparent that inhaled agents can alter excitability in many different anatomic regions of the brain or spinal cord. However, within each discrete area of the CNS there may exist a relatively small number of neurons that are exquisitely sensitive to anesthetics. The existence of such highly sensitive cells is demonstrated in molluscan ganglia having endogenous firing activity. [43] [44] The firing activity may be completely inhibited in selected neurons at halothane concentrations of
1 MAC (Fig. 3-7) (Figure Not Available) [43] [44] , with other neighboring neurons exhibiting little alteration in neuronal firing activity. There may even exist supersensitive sites in the CNS (i.e., sites that are maximally inhibited at anesthetic concentrations substantially less than MAC) that are related to the anesthetic-induced production of amnesia. [45]

Axonal Versus Synaptic Transmission

Concentrations of inhaled anesthetics that alter synaptic transmission typically have a smaller effect on axonal transmission, with synaptic events being
5-fold more sensitive to inhibition than impulse conduction. [46] Nevertheless, at near-clinical concentrations, inhaled anesthetics may alter transmission through axons, and even a partial decrease in action potential propagation could decrease the amount of neurotransmitter secreted and thereby influence synaptic transmission. That is, an apparent effect at the synapse may simply reflect depression of axonal transmission. Smalldiameter axons may exhibit enhanced susceptibility to inhaled anesthetics. In the rat hippocampus, isoflurane (1.4% atm) depresses the activity of thin (0.16 mum) unmyelinated fibers but has little influence on the larger-diameter (1 mum) myelinated fibers. [47]

The frequency at which axons transmit impulses may alter anesthetic potency. At low-impulse frequencies, volatile anesthetics produce a constant level of action potential block, whereas at relatively high frequencies, conduction block by volatile agents increases progressively. That is, the blockade is use-dependent. [48] The branch points of axons may be particularly sensitive to high-frequency conduction block.

Synapses

Anesthetics may disrupt normal synaptic transmission by interfering with the release of neurotransmitter from the presynaptic nerve terminals into the synaptic cleft by altering the reuptake of neurotransmitter following its release, by changing the binding of neurotransmitter to receptor sites on the postsynaptic membrane, or by influencing the ionic conductance change that follows activation of the postsynaptic receptor by neurotransmitter. [46]

Figure 3-7 (Figure Not Available) Certain molluscan neurons having endogenous firing activity are extremely sensitive to volatile agents. The figure shows a continuous intracellular recording of membrane potential before, during (bar), and after exposure of a sensitive cell to normal saline solution containing halothane at a partial pressure of 0.0080 atm. *(From Franks and Lieb [43])*

Presynaptic Action

A presynaptic site of inhaled anesthetic action may be implied from electrophysiologic recordings that compare postsynaptic potentials obtained via presynaptic stimulation versus those generated with direct application of neurotransmitter. For example, in mouse hippocampal slices, glutamatergic excitatory postsynaptic currents are reduced
50 percent by
1 MAC halothane, whereas halothane (even at concentrations of
5 MAC) has no effect on the currents induced by bath application of glutamatergic agonists. [49]

A presynaptic site of action is also implied from studies that demonstrate an influence of anesthetics on neurotransmitter release. [46] [50] Clinical concentrations of inhaled agents reduce depolarization-evoked release of norepinephrine but not acetylcholine from slices of rat cerebral cortex. [51] In the rat striatum, isoflurane and halothane increase spontaneous dopamine release [52] but decrease nicotine-evoked release of dopamine and have no effect on potassium-induced GABA release. [53] Inhaled agents do not alter basal glutamate release in guinea pig [54] or rat [55] cerebrocortical synaptosomes but are reported to either depress (in the guinea pig [54]) or have no effect on (in the rat [55]) potassium-evoked glutamate release from synaptosomes. Thus, the ability of anesthetics to alter neurotransmitter release depends on the biologic preparation examined, the method employed to evoke neurotransmitter release, the neurotransmitter, and the anesthetic and its concentration.

In addition to an effect on the presynaptic release of neurotransmitters, it is conceivable that inhaled anesthetics may alter the duration of neurotransmitter action by influencing the reuptake of neurotransmitter into the nerve terminal. Halothane and isoflurane inhibit the uptake of choline, [56] 5-hydroxytryptamine, [57] and dopamine [58] (but not GABA [59] [60]) by rat brain synaptosomes in a concentration-dependent manner. An anesthetic-induced increase in the uptake of glutamate [60] [61] has been

speculated to decrease excitatory transmission and contribute to the action of volatile agents.

Postsynaptic Action

Evidence is also available for postsynaptic effects of inhaled anesthetics on both excitatory and inhibitory neurons. Postsynaptic sites of anesthetic action may be studied by application of putative neurotransmitters thought to act directly on postsynaptic membrane receptors. [46] Depending upon the particular neuronal preparation and neurotransmitter examined, anesthetics may depress, have little influence on, or enhance the postsynaptic response. In the lamprey, halothane decreases synaptic response to bath-applied glutamate to the same extent that it decreases the excitatory postsynaptic potential, implying a postsynaptic site of action. [62] Halothane and isoflurane (0.5-2.5 MAC) reduce the depolarizing responses to iontophoretic applications of acetylcholine or glutamate to dendrites in guinea pig neocortical slices, with the acetylcholine response being depressed more than the glutamate response. [63] In contrast, halothane and isoflurane have little or no effect on the response induced by iontophoretic application of GABA to perikaryons in these neocortical slices. [63] In hippocampal neurons [64] and in neurons dissociated from the nucleus tractus solitarius of the rat, [65] volatile anesthetics enhance the currents produced by application of GABA (Fig. 3-8) (Figure Not Available) .

A postsynaptic action is also evident from the ability of clinical concentrations of inhaled agents to modulate current flow through a variety of ion channels found on postsynaptic membranes [66] (see *Membrane Proteins*). The enhancement of neuromuscular blockade by inhaled anesthetics observed in the clinical setting probably results from a reduced effectiveness of acetylcholine at the postsynaptic motor endplate. [67]

In summary, inhaled anesthetics act on synaptic regions, including afferent axons at the nerve terminal. Inhaled agents alter axonal and synaptic transmission in isolated mono- and polysynaptic neuronal systems and may have both pre- and postsynaptic effects. Clinical concentrations of inhaled agents can depress, leave unchanged, or enhance presynaptic neurotransmitter release and the postsynaptic response. The effect depends on the biologic preparation,

Figure 3-8 (Figure Not Available) (A) Effects of halothane (Hal), enflurane (Enf), and the convulsant hexafluorodiethyl ether [flurothyl] (HFE) on current responses evoked by GABA (3×10^{-6} M) application to dissociated CNS neurons of the rat. Responses are normalized to the peak current induced by 3×10^{-6} M GABA alone. (B) The GABA concentration-response curve is shifted to the left by halothane and to the right by HFE. Peak response was normalized to that evoked by 3×10^{-6} M GABA (*). *(From Wakamori et al [65])*

the frequency of neuronal transmission, the particular neurotransmitter, and the anesthetic examined.

ALTERATIONS IN NEUROREGULATORS ASSOCIATED WITH ANESTHESIA

The list of CNS transmitters is rapidly expanding. In addition to the "classic" transmitters(e.g., acetylcholine), endogenous amino acids and peptides may act as neurotransmitters or modulate the action of other neurotransmitters. Furthermore, the postsynaptic action of neurotransmitters may result in the formation of second messengers that mediate changes in neuronal transmission. Limited information is available concerning the relationship between the levels of neuroregulators in the CNS and the inhaled anesthetic requirement.

Acetylcholine

Inhaled anesthetics do not alter acetylcholine concentrations in macroscopic structures (e.g., cortex) of rat brain [66] but may increase [69] or decrease [70] acetylcholine content in specific brain nuclei. Inhaled agents decrease acetylcholine turnover rate, with the magnitude of the decrease varying with the brain region examined. [68] Synthesis of acetylcholine in brain is impaired by inhaled agents and is associated with an anesthetic-induced inhibition of choline uptake. [56] A hypothesis that depressed cholinergic neurotransmission plays a role in the mediation of the anesthetic state is supported by the finding that intracerebroventricular injection of hemicholinium-3 (which reduces synaptic levels of acetylcholine) decreases isoflurane MAC in rats. [71]

Catecholamines

Rats anesthetized with halothane or cyclopropane have unaltered norepinephrine concentrations in most brain regions but may have an elevated norepinephrine content in the nucleus accumbens, locus caeruleus, and central gray catecholamine areas. [72] Although anesthesia does not deplete brain norepinephrine, a change in norepinephrine availability significantly influences anesthetic requirement. Drugs that decrease central levels of norepinephrine result in a dose-related decrease in halothane MAC, whereas drugs that elevate central norepinephrine levels increase anesthetic requirement. [73] The ablation of certain norepinephrine-rich brainstem areas in rats lowers MAC by 16 to 35 percent compared with sham-operated littermate controls. [74]

In contrast to those of norepinephrine, central levels of dopamine appear to be inversely related to anesthetic requirement. Administration of levodopa to mice increases striatal dopamine content and decreases halothane MAC, [75] and an increase in striatal dopamine content is associated with halothane anesthesia. [76] Conversely, chemical destruction of dopaminergic neurons lowers dopamine content and increases halothane MAC. [75]

The administration of alpha$_2$ -adrenergic agonists markedly lowers inhaled anesthetic requirement in animals and humans. Dexmedetomidine, an agonist that is more selective for the alpha$_2$ -adrenoreceptor than clonidine, produces a remarkable decrease in halothane [77] MAC in dogs to less than 10 percent of the control value (Fig. 3-9) (Figure Not Available) . This effect appears to be highly specific for the alpha $_2$ -adrenoreceptor because the optical isomer L-medetomidine does not alter MAC (see Fig. 3-9) (Figure Not Available) . In isolated hippocampal neurons, dexmedetomidine exhibits only a small potentiation of the effects of isoflurane, [78] suggesting that hippocampal neurons are not representative of the CNS site(s) at which alpha $_2$ -adre-nergic agonists lessen anesthetic requirement *in vivo.*

Serotonin

Serotonin levels are unaltered in most brain regions of rats anesthetized with halothane orcyclopropane but may increase in specific brain structures (e.g., substantia nigra, nucleus raphedorsalis). [79] Destruction of the serotonin-rich nucleus raphe dorsalis in rats decreasesanesthetic requirement by as much as 25 percent. [74]

Adenosine

Administration of adenosine or an adenosine analogue to dogs [80] or rats [81] decreases halothane MAC by about 50 percent. The mechanism of this lowering in anesthetic requirement is probably related to an adenosine-induced decrease in CNS noradrenergic transmission. [80] [81] Although exogenous adenosine reduces anesthetic requirement, small alterations of endogenous adenosine concentrations do not substantially alter MAC. [80]

GABA

Although rats administered 1 to 4 percent atm halothane for 30 minutes exhibit no change in whole brain GABA content, [82] anesthesia may alter GABA levels in selected regions of brain. Treatment of rat cerebral cortex slices with 3 percent atm halothane inhibits the metabolism and increases the content of the inhibitory transmitter GABA but does not affect the uptake or release of GABA. [83] If the accumulation of GABA in inhibitory neurons is associated with an increase in inhibitory activity, the resulting decrease in synaptic transmission might contribute to the anesthetic state. [83] Findings consistent with this hypothesis include the production of anesthesia by a GABA analogue [84] and the ability of GABA antagonists to lessen the antinociceptive action of halothane [85] in rodents.

Excitatory Amino Acids

A role for excitatory amino acids in anesthesia is implied by the depression in glutamate-induced neurotransmission by inhaled anesthetics and the decreased requirements for volatile anesthetics after administering inhibitors of excitatory amino acid transmission. [86] Anesthesia does not result

---

Figure 3-9 (Figure Not Available) The D- stereoisomer (closed squares) of the alpha$_2$ -adrenergic agonist medetomidine causes a dose-dependent decrease in halothane MAC in dogs, whereas the L-stereoisomer (open squares) has little or no influence on halothane MAC. Asterisks indicate values that are significantly different from the controls. *(From Vickery et al [77])*

from a depletion of excitatory amino acids because rats anesthetized with halothane have an increased whole brain content of aspartate and glutamate. [82] It has been suggested that the ability of enflurane to enhance glutamate release from synaptosomes may provide an explanation for clinically observed enflurane-induced convulsions. [87]

Cyclic Nucleotides

The production of cyclic nucleotides may be influenced by neurotransmitters and anesthetics, and cyclic nucleotides may serve as second messengers in altering neurotransmission. The effect of anesthetics on cyclic adenosine monophosphate (cAMP) content varies with the species and tissues examined. [88] Most (but not all) studies demonstrate an increase in brain cAMP content of rodents during the administration of volatile anesthetics, with the magnitude of the increase varying among species and among brain regions. [88] In contrast, levels of cyclic guanosine monophosphate (cGMP) in brain are decreased by volatile agents. [89] Nitric oxide

activates adenyl cyclase to form cGMP and, in turn, nitric oxide production can be enhanced by excitatory neurotransmitters. It has been suggested that volatile anesthetics decrease brain cGMP by interfering with the neuronal nitric oxide-cGMP pathway. [89] Such alterations in brain cyclic nucleotide content may chemically alter (e.g., via phosphorylation) macromolecules that are important in neurotransmission.

Calcium

Calcium is mentioned as a neuroregulator because there is evidence that inhaled anesthetics alter intracellular concentrations of calcium and because changes in intracellular calcium may influence neuronal excitability [90] (e.g., via a calcium-dependent release of neurotransmitter). Inhaled anesthetics usually [90] (but not always [54]) increase resting cytoplasmic calcium concentration, and it has been proposed that the depressant action of halothane in rat hippocampal slices involves enhancement of GABA-mediated inhibition through release of intraneuronally stored calcium. [91] In contrast, increases in intraneuronal calcium evoked by various stimuli are often prevented by inhaled agents. [54] The mechanisms for the attenuation of the calcium rise by inhaled anesthetics may depend on the anesthetic and tissue examined and include impairment of calcium influx into cells [54] [90] and modulation of intracellular calcium release via action on inositoltriphosphate-dependent pathways. [92]

Endogenous Opiates

In the late 1970s, it was hypothesized that inhaled anesthetics may work through an action on the opiate receptor. [93] [94] Consistent with this hypothesis are the clinical observations and experimental findings that synthetic narcotics partially decrease the requirement for inhaled anesthetics. Furthermore, the administration of naloxone (a narcotic antagonist) partially reverses the action of inhaled anesthetics either when given intravenously [93] [94] or given into the cerebral ventricle. [94] [93] However, this antagonistic effect of naloxone can be explained by a minor shift in the anesthetic dose-response curve. Anesthetic requirement, as measured by lack of response to a noxious stimulus [96] or by the ability to abolish the righting reflex, [97] is altered no more than a small percentage by narcotic antagonists, even at doses of naloxone as high as 250 mg/kg. [96] The mild antagonism of inhalational

anesthesia by high doses of naloxone probably results from a general increase in CNS excitation and not by pharmacologic competition for opiate receptors. [97]

Another prediction of the opiate theory of anesthesia is that inhaled agents may release an endogenous opiate-like substance in the CNS. Data are available to support and refute this prediction. Nitrous oxide markedly increases proenkephalin-derived endogenous opioid peptides in canine third ventricle cerebrospinal fluid. [98] The lowering of halothane MAC in rats by transcranial electrical stimulation is reversed by naloxone, suggesting that release of endogenous opioids mediated the decrease in halothane requirement. [99] In patients anesthetized with a combination of halothane and nitrous oxide [100] or isoflurane, [101] there is no elevation in opioid peptides in cerebrospinal fluid. Thus, any contribution of the endogenous opiate system to the production of general anesthesia in humans does not appear to require the release of opioid peptides.

Nitric Oxide

Nitric oxide is now recognized as a neuromodulator and has been hypothesized to play a role in mediating consciousness. Although the short half-life (milliseconds to seconds) of nitric oxide makes it a difficult compound to study, administration of nitric oxide synthase inhibitors decreases (by 30-50%) MAC and righting-reflex ED_{50} s of halothane and isoflurane in rodents. [102] [103] However, sparing of anesthetic requirement by nitric oxide synthase inhibitors is not found in all experiments. [104] As noted before, [85] nitric oxide is involved in cellular communication processes via production of cGMP and various neurotransmitter pathways, processes that may be important to the anesthetic state.

In summary, the predominant effects of inhaled anesthetics cannot at present be explained by the depletion, production, or release of a single neuromodulator in the CNS. In all likelihood, the anesthetic state involves a balance between many different neuromodulator systems.

PHYSICOCHEMICAL NATURE OF THE SITE OF ANESTHETIC ACTION

The preceding sections suggest that anesthetics may act at several gross (e.g., spinal cord versus reticular activating system) or microscopic (e.g., presynaptic versus postsynaptic) sites. The varied nature of these sites, however, does not preclude a unique action at a molecular level. For instance, depression of presynaptic neurotransmitter release and blockade of current flow through the postsynaptic membrane may arise from an anesthetic perturbation at an identical molecular site, even though the geographic locations of these sites differ. The concept that all inhaled anesthetics have a common mode of action on a specific molecular structure is called the *unitary theory of narcosis.* The nature of this presumed common site has been explored by correlating the physical properties of anesthetics with their potencies. The rationale behind this approach is that the best correlation between anesthetic potency and a physical property will suggest the nature of the anesthetic site of action. For example, the correlation of MAC and lipid solubility (see below) implies that the site of action is hydrophobic. Note that the correlations that depend on forces exerted between anesthetic molecules (e.g., the boiling point of an anesthetic) are not important to the study of anesthetic mechanisms, as such intermolecular forces cannot be representative of a single site of action. That is, such correlations are defined by the interaction of each anesthetic with itself rather than with a common site.

Hydrophobic Site: The Meyer-Overton Rule

The physical property that correlates best with anesthetic potency is lipid solubility [105] [106] [107] [108] (Table 3-2 and Fig. 3-10) . This correlation is termed the *Meyer-Overton rule,* after its two discoverers. For the majority of inhaled agents, the product of the anesthetizing partial pressure and its olive oil/gas partition coefficient varies little over approximately a 100,000-fold range of anesthetizing partial pressures (see Table 3-2 and Fig. 3-10) . For the correlation to be perfect, this product would have to be the same for all anesthetics for a given animal. Within a given species, the product of anesthetizing partial pressure and oil/gas partition coefficient varies only slightly (see Table 3-2) . The closeness of this correlation implies a unitary molecular site of action and suggests that anesthesia results when a specific number of anesthetic molecules occupy a crucial hydrophobic region in the CNS. This finding has led many investigators to look for the molecular basis of anesthetic action in cellular hydrophobic regions.

Further Characterization of the Hydrophobic Site of Anesthetic Action

The correlation of potency to solubility in olive oil (see Fig. 3-10 and Table 3-2) suggests that olive oil closely mimics the anesthetic site of action and that anesthesia occurs when a critical anesthetic concentration is attained at that site. However, because olive oil is a mixture of oils and is not very well characterized from a physicochemical point of view, attempts have been made to examine anesthetic solubility in simpler solvents in order to better define the nature of the site of anesthetic action. A pure solvent may be characterized by a solubility parameter, which is a measure of the intermolecular forces in that solvent. [105] Anesthetic potency correlates best with solubility in solvents having solubility parameters of about 8 to 11 (calories/cm ^{3})^{½} [105] [109] . These values are representative of a solvent such as ben-zene and again imply a hydrophobic site of anesthetic action. However, even better correlations between anesthetic potency and solubility may be obtained when octanol [110] (having a solubility parameter of approximately 10 [calories/cm ^{3}]^{½}) or lecithin [111] (an amphipathic compound with hydrophobic and polar components) is used as the model solvent.

TABLE 3-2 -- Oil/Gas PartitionCoefficients and Potencies of Inhaled Anesthetics in Dogs, Humans, and Mice

ANESTHETIC	*OIL/GAS PARTITION COEFFICIENT (37° C)*	DOGS		HUMANS		MICE	
		MAC (ATM)	*MAC X OIL/GAS (ATM)*	*MAC (ATM)*	*MAC X OIL/GAS (ATM)*	*RIGHTING REFLEX ED_{50} (ATM)*	*RIGHTING REFLEX ED_{50} X OIL/GAS (ATM)*
Thiomethoxyflurane	7,230	0.00035	2.53				
Methoxyflurane	970	0.0023	2.23	0.0016	1.55	0.0023	2.23
Dioxychlorane	1,286	0.0011	1.41			0.0033	4.24
Chloroform	265	0.0077	2.08			0.00357	0.95
Halothane	224	0.0087	1.95	0.0074	1.66	0.00645	1.45
Enflurane	96.5	0.0267	2.58	0.0168	1.62	0.0123	1.19
Isoflurane	90.8	0.0141	1.28	0.0115	1.04	0.00663	0.60
Compound 485	25.8	0.125	3.23				
Desflurane	18.7	0.072	1.35	0.060	1.12		
$HFClCOCHFCF_3$	96.6	0.0224	2.16				
Iso-Indoklon	27.0	0.460	1.24			0.0265	0.72
Aliflurane	124	0.0184	2.28				
Synthane	95	0.012	1.14				
Diethyl ether	65	0.0304	1.98	0.0192	1.25	0.032	2.08
Fluroxene	47.7	0.0599	2.86	0.034	1.62	0.0345	1.65
Sevoflurane	47.2	0.0236	1.11	0.0205	0.97		
Cyclopropane	11.8	0.175	2.06	0.092	1.09	0.142	1.68
Xenon	1.9	1.19	2.26	0.71	1.35	0.95	1.80
Ethylene	1.26			0.67	0.84	1.30	1.64
Nitrous oxide	1.4	1.88	2.63	1.04	1.46	1.54	2.16
Krypton	0.5					4.5	2.25
Sulfur hexafluoride	0.293	4.9	1.44			5.4	1.58

Argon	0.15					15.2	2.28
Carbon tetrafluoride	0.073	26	1.90			18.7	1.36
Nitrogen	0.072					34.3	2.47
		43.5	3.13				
Mean ± S.E.			2.04 ± 0.14		1.30 ± 0.08		1.80 ± 0.19

Figure 3-10 Correlation of MAC in humans and dogs and the righting-reflex ED_{50} in mice with lipid solubility (i.e., the olive oil/gas partition coefficient.) Values are taken from Table 3-2 .

Additive Effects of Inhaled Anesthetics

The Meyer-Overton rule postulates that it is the number of molecules dissolved at the site of anesthetic action, and not the types of molecules present, that causes anesthesia. Thus, 0.5 MAC of one agent and 0.5 MAC of another agent should have the same effect as 1.0 MAC of either agent. In general, this prediction has been confirmed for clinically employed agents in animals and humans, [112] although slight antagonistic effects are also occasionally observed.

Apparent Exceptions to the Meyer-Overton Rule

Isomers

In spite of the close correlation between lipid solubility and anesthetic potency, deviations from this correlation do exist. For example, enflurane and isoflurane are structural isomers (see Fig.3-1) having approximately the same oil/gas partition coefficient, yet anesthetic requirement for enflurane is 45 to 90 percent greater than that for isoflurane (see Table 3-2) . These differences in anesthetic requirements for agents having similar oil/gas partition coefficients suggest that the potency of an agent depends on factors other than lipid solubility.

Several of the commonly used inhaled anesthetics (Fig. 3-1 A) exist as mixtures of two stereoisomers (nonsuperimposable compounds that are mirror images of each other, having identical physicochemical properties except for the direction in which they rotate polarized light). For isoflurane stereoisomers in rats, the (+)-isomer is 17 [113] to 53 percent [114] more potent than the (-)-isomer. Thus, the differential effects of the inhaled anesthetic stereoisomers are relatively modest.

Convulsant Gases

Another apparent exception to the Meyer-Overton rule is the ability of certain lipid-soluble compounds to produce convulsions. Indeed, complete halogenation (or full halogenation of the end-methyl groups) of alkanes and ethers tends to decrease the anesthetic potencies of these agents and to enhance convulsant activity. [115] Flurothyl ($CF_3 CH_2 OCH_2 CF_3$) produces convulsions at concentrations an order of magnitude less than those predicted to be anesthetic by the Meyer-Overton rule. [116] Although the loss of righting reflex in the mouse at very high flurothyl concentrations implies an anesthetic effect, 3 to 4 percent atm flurothyl only marginally decreases isoflurane MAC in dogs. [116]

Compound 485 (Fig. 3-1 C) possesses completely halogenated end-methyl groups and is a structural isomer of enflurane and isoflurane. It occasionally produced convulsions in dogs at concentrations near 6 percent atm. [117] As an isomer of enflurane and isoflurane, it was predicted to have similar potency and solubility characteristics; however, its MAC was found to be 12.5 percent atm. This high MAC value was balanced by an 4-fold lower oil/gas partition coefficient [117] (see Table 3-2) .

Convulsant halogenated ethers may have different physical properties from the anesthetic halogenated ethers because the convulsants are characterized by a low solubility parameter. [118] For example, flurothyl has a solubility parameter of 6.9, whereas the anesthetic halogenated ethers have values of approximately 8.0. [118] Furthermore, halogenated compounds that are anesthetics and convulsants may have different effects on synaptic transmission. Anesthetic agents block the excitatory glutamate response but not inhibitory transmission mediated by GABA at the crab neuromuscular junction, whereas convulsant agents block inhibitory but not excitatory transmission. [119] In dissociated rat brain neurons, halothane and enflurane enhance the response to GABA, whereas flurothyl decreases GABA response (see Fig. 3- 8) (Figure Not Available) . [65]

Cutoff Effect

There has been a long-standing impression that the highly lipid soluble paraffin hydrocarbon *n*-decane was nonanesthetic in animals, even though less soluble paraffin homologues such as *n*-pentane caused anesthesia. This decrease in anesthetic potency in the higher members of a homologous series is known as the *cutoff effect.* [120] However, detailed reexamination of this issue has revealed the cutoff for *n*-alkanes may be explained by limited delivery of the larger alkanes due to decreasing volatility. Although decane does not anesthetize rats when given alone at its saturated vapor pressure, anesthetic properties are demonstrated by an ability to decrease requirement for isoflurane. [121] In the fruitfly *Drosophila melanogaster,* anesthetic ED_{50} values (using lack of coordination and mobility as an end-point) can be measured for decane and undecane when given alone. [122] A surprising result of these studies was the finding that *n*-alkanes did not obey the Meyer-Overton rule, [122] [123] independent of the solvent used to measure alkane partitioning. [123]

A "true" cutoff exists for the perfluoroalkanes. [124] Perfluoromethane (CF_4) produces anesthesia in rats (MAC 60 atm), but perfluoroethane ($CF_3 CF_3$) and longer-chain perfluorinated derivatives are nonanesthetic despite being soluble in hydrophobic solvents and in tissues. [124]

Nonanesthetics (Nonimmobilizers)

In addition to the nonanesthetic perfluoroalkane gases noted previously, certain volatile polyhalogenated agents that are even more lipid-soluble yet lack anesthetic properties have also been discovered. [125] [126] Examples of such "nonanesthetics" are given in Figure 3-11 . These nonanesthetics do not produce anesthesia when administered alone (even when administered at partial pressures greater than those predicted to have an anesthetic effect by the Meyer-Overton hypothesis), and they do not lower MAC for conventional anesthetics. [125] [126]

These nonanesthetics are not inert. They quickly reach the brain, produce excitable behavior, and typically cause convulsions when administered at high enough partial pressures. [125] [126] [127] Because MAC is used as the end-point to

Figure 3-11 Examples of nonanesthetics (nonimmobilizers). Although these compounds have oil/gas partition coefficients (43.5 for 1,2-dichlorohexafluorocyclobutane; 25 for 2,3-dichlorooctafluorobutane) similar to those of conventional anesthetics (Table 3-2) , they completely lack anesthetic properties (as determined by MAC measurements). [125]

define a nonanesthetic, it may be more appropriate to call these compounds "nonimmobilizers" rather than nonanesthetics. It is possible that such nonanesthetics fail to produce immobility in response to a noxious stimulus but do cause amnesia. [40] [128]

The nonimmobilizers may be helpful in identifying anesthetic sites and mechanisms of action. Physiologic or biochemical/biophysical changes produced by conventional anesthetics in a model system thought to be important for the anesthetic state (as measured by MAC) should not be produced by the nonimmobilizers.

Hydrophilic Site

The suggestion of a possible nonhydrophobic anesthetic site of action is not new. For example, Pauling [129] suggested that anesthesia might be caused by the ability of anesthetics to precipitate the formation of hydrates. These hydrates are cage-like structures of water molecules surrounding a central anesthetic molecule, and it was speculated that hydrate microcrystals could alter the transmission of electrical charge through a neuron. [129] However, a unitary hydrate theory of anesthesia seems unlikely because there is a poor correlationbetween the ability of anesthetics to form hydrates and their anesthetic potency. [105]

Another hypothesis is that certain inhaled anesthetics act by disrupting hydrogen bonds. [130] (This cannot be a unitary hypothesis because compounds like xenon and argon are anesthetics but do not form hydrogen bonds.) One suggestion is that general anesthetic target sites have, in addition to an overall hydrophobicity, a polar component that is a relatively poor hydrogen bond donor but that accepts a hydrogen bond about as well as water. [130] If hydrogen bonds are important in anesthesia, then substitution of hydrogen for deuterium atoms in anesthetic molecules might alter the hydrogen bonding capabilities of a compound and change its anesthetic potency. However, the findings of identical anesthetic potencies of chloroform and deuterated chloroform [131] and of halothane and deuterated halothane [132] do not support this prediction.

Volume Expansion by Inhaled Anesthetics

Although the Meyer-Overton rule postulates that anesthesia occurs when a sufficient number of anesthetic molecules dissolve at a certain site, it does not explain why anesthesia results. Mullins [109] took the lipid solubility correlation one step further and hypothesized that anesthesia occurs when the absorption of anesthetic molecules expands the volume of a hydrophobic region beyond a critical amount *(critical volume hypothesis).* Such an expansion might produce anesthesia by obstructing ion channels or by altering the electrical properties of neurons.

One prediction of the volume expansion hypothesis was that anesthetizing partial pressures of inhaled agents should produce a consistent volume expansion in a model hydrophobic system. Indeed, anesthetizing doses of inhaled agents cause hydrophobic solvents to undergo a significant increase in volume. [133] The hypothesis also predicts that anesthesia should be reversed by compressing the volume of the expanded hydrophobic region, and high pressures do reverse many effects of anesthetics *in vivo.*[14] [15] However, the influence of body temperature on anesthetic requirement (see Fig. 3-3) (Figure Not Available) , a nonlinear pressure antagonism for certain anesthetics, and the fact that not all lipid-soluble compounds are anesthetics are findings that are difficult to explain. Thus, although the critical volume hypothesis is a useful model for estimating the interactions between pressure and inhaled anesthetics, it probably is an oversimplified view of the way in which anesthetics act.

THE MEMBRANE AS THE SITE OF ANESTHETIC ACTION

The electrical activity (i.e., transfer of ions) immediately underlying the transmission of nervous impulses occurs principally at the plasma membranes of nerves. Because inhaled agents disrupt this transmission, synaptic and/or axonal membranes are usually assumed to be the primary sites of anesthetic action. A membrane site of action is also consistent with the hydrophobic/amphipathic theories of anesthesia because plasma membranes consist largely of hydrophobic/amphipathic components.

Electrophysiologic studies reveal the effects of anesthetics on the flow of ions through excitable membranes. In isolated axons, the conduction of the nervous impulse requires the sequential flow of sodium and potassium ions through selective transmembrane channels. Excitation produces a rapid increase in sodium conductance to a peak (the activation process) followed by a slower decline in sodium conductance to zero (the inactivation process). Although channels in peripheral neurons tend to be relatively insensitive to anesthetics, [2] clinical concentrations of inhaled anesthetics may decrease the magnitude of both sodium [134] and potassium [135] currents in channels isolated from brain.

Electrophysiologic recordings of single membrane channels activated by neurotransmitter can be obtained by forming a seal between the tip of a glass micropipette and a membrane patch of a few square micrometers. Using this "patch clamp" technique, unitary acetylcholine receptor

channel currents have been measured in the absence and in the presence of inhaled anesthetics (Fig. 3-12). (Figure Not Available) [67] [136] [137] . Isoflurane decreases the average open duration of this membrane channel, and such an accelerated decay of the membrane current may decrease the net charge transferred across the membrane and impair transmission (see Fig. 3-12). (Figure Not Available) [67] [136] [137]

In contrast to the inhibitory effects of anesthetics on ion flow through membranes described earlier, other experiments suggest that anesthetics may act by enhancing the conductance of certain ions through membranes. Volatile anesthetics enhance the inhibitory current responses produced by GABA (see Fig. 3-8) (Figure Not Available) , [64] [64] [65] presumably by increasing the flow of chloride ions through GABA receptor-channel complexes in neuronal membranes. [138] Inhaled agents may also enhance potassium conductance, resulting in membrane hyperpolarization. [26] Molluscan neurons that are highly sensitive to volatile agents (see Fig. 3-7) (Figure Not Available) exhibit a halothane-induced activation of potassium current that is associated with a marked hyperpolarization of the cell membrane and an inability to initiate firing of action potentials. [43] [44] However, the finding that anesthetic effects on resting membrane potential are voltage-dependent and agent-specific [139] indicates that changes in membrane potential are not a universal feature of anesthetic action on CNS neurons.

The requirement of an intact plasma membrane for the transmission of nervous impulses and the abilities of anesthetics to disrupt the flow of ions through plasma membranes point to a membrane site of anesthetic action. Nevertheless, anesthetics could act indirectly at a cytoplasmic site. For example, anesthetics might alter the calcium-accumulating activity of cellular organelles (e.g., mitochondria [90]) and thereby alter the levels of intracellular free calcium. Such alterations in intracellular free calcium could in turn influence the conductance properties of excitable membranes and alter the presynaptic release of neurotransmitters. [90]

This discussion strongly suggests but does not prove that anesthesia results from an association of inhaled agents with plasma membranes of nerves. If so, which components of the plasma membrane are altered by the anesthetics? Biological membranes consist of a cholesterol-phospholipid bilayer matrix having a thickness of approximately 4 nm. Peripheral proteins are weakly bound to the exterior hydrophilic membrane, and integral proteins (such as ion channels) are deeply embedded in or pass through the lipid bilayer (Fig. 3-13) (Figure Not Available) . Synaptic plasma membranes are approximately half protein and half lipid by weight. If (as implied by the Meyer-Overton rule) inhaled agents bind to hydrophobic sites, anesthetics could act on the nonpolar interior of the lipid bilayer, at hydrophobic pockets in proteins extending outside or embedded into the lipid bilayer, or at the hydrophobic interface between intrinsic membrane proteins and the lipid matrix (see Fig. 3-13) (Figure Not Available) .

Attempts to better understand the penetration of inhaled agents into and their interaction with membrane sites have led to an examination of isolated membrane components.

Figure 3-12 (Figure Not Available) Examples of unitary acetylcholine receptor channel currents before, during, and after local microperfusion with 5 mM isoflurane. Channel openings are represented by downward directions of the current trace. When isoflurane is removed (bottom panel), the channels are indistinguishable from those observed under control conditions. *(From Brett et al [136])* Note that pre-equilibrated and 10-fold lower concentrations of isoflurane also decrease the average open duration of acetylcholine receptor channel currents. [67] [137]

Figure 3-13 (Figure Not Available) Four possible target sites for inhaled anesthetic molecules ( ) in a neuronal membrane include (a) the lipid bilayer as a whole, (b) lipids at a protein/lipid interface, (c) a protein site bounded by lipid, and (d) a protein site exposed to an aqueous environment. *(Modified from Franks and Lieb, [106] with permission of Elsevier Science.)*

These experiments were greatly aided by the discovery that phospholipids dispersed in an aqueous medium spontaneously form bilayers comprising the surface of spherical structures (liposomes). These phospholipid bilayers act as a permeability barrier to ions and are similar to those found in biomembranes. In contrast, membrane proteins are often difficult to isolate and purify, and membrane proteins typically exhibit an impaired function unless surrounded by a boundary layer of lipid. Nevertheless, recent advances have resulted in the biochemical characterization of several protein receptor/ionophores thought to permit the passage (tunneling) of ions through membranes during excitation. However, only limited information is available concerning the interaction of inhaled agents with these membrane protein ionophores, and many experiments that examine anesthetic-protein interactions employ soluble proteins as model systems. Such proteins are easy to prepare in reasonable quantities but may not mimic precisely the natural proteins responsible for ion translocation.

/das/book/view/29494766/875/31.html

INTERACTION OF INHALED ANESTHETICS WITH MEMBRANE LIPIDS

Binding of Anesthetics to Membrane Lipids

The solubilities of gaseous and volatile agents in membrane lipids tend to correlate with their anesthetic potencies. This correlation is as good [140] as or better [111] than that obtained when olive oil is the model solvent. The incorporation of cholesterol into phospholipid model membranes decreases the partitioning of inhaled agents but does not alter the good correlation between anesthetic potency and lipid membrane solubility. [140] The degree of saturation of lipid acyl chains [140] or the length of the acyl chains [141] has little effect on the partition coefficient. On the other hand, a decrease in temperature increases the partitioning of anesthetics into phospholipid membranes. [140] At anesthetic concentrations close to 1.0 MAC, lipid membranes may contain as many as 80 phospholipid molecules for every anesthetic molecule. [108]

The interaction of inhaled agents with membrane lipids is a dynamic process, and anesthetic molecules may rapidly exchange between the membrane and aqueous phases. Although anesthetics may penetrate to all depths of the lipid bilayer, current evidence indicates a preferential anesthetic distribution at the membrane interface [142] [143] [144] where regions of the lipid membrane contact the aqueous environment. In contrast, the "nonimmobilizers" 1,2-dichlorohexafluorocyclobutane and 2,3-dichlorooctafluorobutane (see Fig. 3-11) exhibit a preferential location in the lipid membrane hydrocarbon core. [143] [144] It has been speculated that the interfacial site may be associated with anesthetic-induced immobility in response to noxious stimuli and that the production of amnesia may be associated with anesthetic penetration into the nonpolar interior of a phospholipid bilayer. [40]

Effects on Membrane Permeability

Inhaled agents increase the cation permeability of liposomes in a dose-related manner. [105] [145] These anesthetic-induced increases in cation permeability occur both in the presence and absence of ionophores that facilitate the transport of ions through membranes. The magnitude of the increase depends on the composition of the liposome and on the anesthetic examined. [105]

Inhaled anesthetics also increase the flow of protons across lipid vesicles. [146] The rate of proton transfer across the membrane may depend on lipid composition. It has been suggested that anesthetics may act by increasing proton permeability across synaptic vesicles, collapsing the pH gradient required for retention of catecholamines in their charged form and thereby depressing neurotransmission by releasing catecholamines from synaptic storage vesicles. [147] However, this hypothesis seems unlikely because (1) marked depletion of brain catecholamines lowers MAC by a maximum of 40 percent (see *Alterations in Neuroregulators Associated with Anesthesia*), (2) clinical concentrations of

inhaled agents release only a small fraction of catecholamines trapped in vesicles, [146] and (3) not all anesthetics increase proton conduction across lipid vesicles.

Alterations in Membrane Dimension

Lipid monolayers adsorb inhaled agents, resulting in an increase in the lateral pressure of the monolayer that parallels the potency of the anesthetic. [148] This finding is consistent with the notion that anesthetics might expand membranes and exert pressure on the ionic channels needed for impulse transmission--a variation of the volume expansion theory of anesthesia--and thereby inhibit the opening or accelerate the closure of ionic channels.However, precise volume measurements show only a small (0.1%) expansion when suspensions of membranes in aqueous media are combined with inhaled agents at concentrations near 1.0 MAC. [149] Direct microscopic visualization of the erythrocyte surface shows an area of expansion ranging from 0.13 to 0.62 percent for clinical anesthetics at concentrations of one to four times MAC, [150] but long-chain alcohols that are not anesthetics also expand red cell surface area. This finding casts doubt on the role of membrane area expansion in anesthesia. [150] In addition, most studies indicate little or no effect of clinical concentrations of inhaled agents on membrane thickness. [140]

According to the critical volume hypothesis, an increase in pressure or a decrease in temperature should reverse anesthesia because these physical changes should compress membranes. However, a decrease in body temperature consistently decreases MAC (see Fig. 3-3) (Figure Not Available) . This apparent contradiction is partly resolved by the increased partitioning of anesthetics into membranes at lower temperatures. Moreover, the expansion of membranes by anesthetics and an increase in temperature may not be equivalent. For example, anesthetics might expand membranes without changing thickness. [140]

Alterations in Membrane Physical State

Further studies of the molecular changes occurring on the insertion of anesthetic molecules into lipid membranes led to the suggestion that anesthetics increase the mobility of membrane components (the *fluidization theory* of anesthesia). The ability of an anesthetic to *fluidize* a lipid bilayer depends on the agent examined and the composition of the lipid bilayer. [140] The incorporation of cholesterol [140] or gangliosides [151] into neutral phospholipid membranes enhances the membrane-disordering effects by a given partial pressure of inhaled anesthetic. At clinical concentrations, the increase in lipid fluidity by inhaled agents can be as small as 0.5 percent or as large as 31 percent, [152] depending on the lipid system examined and the method of fluidity measurement. Moreover, the anesthetic-induced changes in fluidity may even depend on membrane position. Inhaled agents can produce a small *decrease* in the fluidity of palmitoyloleoylphosphatidylcholine membranes near the headgroup region and increase fluidity in regions deep in the membrane bilayer. [144] [153] Of note are the findings that the nonimmobilizers 1,2-dichlorohexafluorocyclobutane and 2,3-dichlorooctafluorobutane (see Fig. 3-11) do not fluidize membrane lipids. [144] [153]

It has been suggested that even small changes in lipid fluidity may profoundly change membrane function. Some investigators have speculated that the increased decay rate of postsynaptic currents and accelerated decay rate of open membrane channels (see Fig. 3-12) (Figure Not Available) caused by inhaled agents may result from an increased fluidity of the postsynaptic membrane, allowing a more rapid relaxation (i.e., return to the closed configuration) of the proteins involved in the conductance change after activation. However, incompatible with this hypothesis is the fact that hypothermia (which lessens mobility of membrane lipids) potentiates anesthesia and that the raising of temperature does not mimic the pattern of accelerated channel closing rates produced by an inhaled agent. [136]

Liposomes composed of a single type of phospholipid undergo a *phase transition;* that is, a sudden conversion of the lipids from a solid or gel phase to a liquid or fluid phase as temperature increases past a critical point. Clinical concentrations of inhaled agents typically decrease this phase transition temperature by 0.5° C, although the composition and charge of the lipid bilayer determines the magnitude of the decrease in the phase transition temperature by anesthetics. [155] According to one hypothesis, lipids surrounding an excitable membrane channel are normally exclusively in the more rigid gel phase, thereby helping maintain patency of the channel. It has been speculated that adding anesthetic may fluidize these lipids, impair the surrounding structural support, and allow the channel to close. If a major phase transition is important in the production of anesthesia, one would predict a discontinuity in the relationship between temperature and anesthetic

potency. However, there is no such discontinuity (see Fig. 3-3) (Figure Not Available) .

An alternative hypothesis (the *lateral phase separation hypothesis*) proposes that neuronal membrane lipids coexist in both fluid and gel forms and that the expansion of a protein to allow passage of ions through channels requires conversion of lipids from a fluid to a gel phase. [156] Anesthetic molecules are thought to sustain lipids in their fluid phase, block the formation of the low volume gel phase, and thereby prevent the protein from changing its conformation to the open channel state. [156] However, both the fluidization and lateral phase separation theories are compromised by the fact that small increases (
1°C) in temperature increase membrane fluidity to approximately the same extent as clinical concentrations of inhaled anesthetics and therefore should but do not augment anesthesia.

Other theories of anesthetic action on lipids include anesthetic-induced alterations in membrane electrical properties or membrane pressures. Inhaled agents (at
1 MAC) can alter dipole potentials at a lipid membrane interface by
10 mV, and it has been suggested that such changes in membrane potential could modulate conformational transitions of membrane channel proteins. [157] Insertion of inhaled anesthetics into a lipid bilayer is predicted to increase lateral pressure at the membrane interface. [158] If ion channel opening increases the cross-sectional area of the protein channel more near the aqueous interface than in the middle of the bilayer, then the anesthetic-induced increase in lateral pressure

near the interface would tend to favor the closed state of the ion channel. [158]

INTERACTION OF INHALED AGENTS WITH PROTEINS

Most investigators agree that the ultimate action of inhaled anesthetics is on specific neuronal membrane proteins that permit the translocation of ions during membrane excitation. It remains a matter of debate, however, whether inhaled agents disrupt ion flow through membrane channels by an indirect action on the surrounding lipids or via a second messenger or by a direct and specific binding to channel proteins. Immobilized [159] and saturable binding sites for inhaled anesthetics in brain imply but do not prove a direct interaction of anesthetics with neuronal proteins. Because of the complexity involved in searching for specific anesthetic binding sites in whole brain or brain homogenate, attempts have been made to simplify this search by examining the interaction of anesthetics with isolated proteins.

Soluble Proteins

Distinct anesthetic binding sites have been identified in several soluble proteins, including hemoglobin, myoglobin, and albumin. [107] [160] [161] Anesthetics move rapidly between their binding sites in soluble proteins and the surrounding aqueous solvent and bind to albumin with an average lifetime of about 200 mus. [160] Discrete binding sites for halothane, involving aromatic amino acid residues, have been identified in albumin. [161]

The interaction of inhaled anesthetics with soluble enzymes may be reflected indirectly by changes in enzyme activity. Many enzymes, including several glycolytic enzymes and serum cholinesterase, are resistant to even saturated solutions of volatile agents. However, other soluble enzymes are highly sensitive to clinical anesthetic concentrations. The purified firefly luciferase enzyme combines with its substrate (luciferin) to produce a photon of light, and a variety of inhaled anesthetics (at
1.0 MAC) inhibit the activity (light intensity) of this enzyme by competing with luciferin. [162] However, it needs to be noted that these results apply only to firefly luciferase; studies with the bacterial form of the enzyme show poor agreement between the anesthetic concentrations required to inhibit bacterial luciferase and MAC. [163]

Membrane Proteins

Two major obstacles are encountered when one attempts to study the influence of inhaled anesthetics on the purified protein ionophores involved in the membrane translocation of ions. First, the biochemical purification of such protein ionophores in adequate quantities is a difficult and time- consuming process. Second, even when these membrane proteins can be isolated, they need to be reincorporated into lipids for measurement of their functional ability to translocate ions. This reincorporation of the purified ionophore into a lipid membrane makes it difficult to distinguish whether an anesthetic affects ion flow through a direct action on the membrane protein or via an indirect action on surrounding lipids.

Ligand-Gated Ion Channels

The binding of neurotransmitter alters membrane permeability of ligand-operated channels to specific ions. The muscle-type nicotinic acetylcholine receptor-ionophore complex is the best characterized of these membrane proteins with regard to interaction with inhaled anesthetics; it is the only channel complex that has been bichemically isolated in large enough quantities to be studied. This protein complex is composed of five containing four hydrophobic amino acid domains spanning the membrane) that form the wall of the membrane channel. Each subunit of the acetylcholine receptor binds halothane (as measured by a radioligand-binding assay following photoactivation of radioactive halothane). [164] Volatile agents stabilize the acetylcholine receptor in a conformational form that binds agonists with high affinity and may be associated with a desensitized and thus inactive (closed-channel) state. [165] Volatile anesthetics promote desensitization at clinically relevant concentrations, [165] [166] and desensitization is associated with (but probably not caused by) membrane lipid disordering. [167] Although the pharmacologies of inhaled anesthetic-induced acetylcholine receptor desensitization and general anesthesia are similar, it is unlikely that anesthesia results from desensitization of acetylcholine receptors. [167]

Additional information concerning anesthetic action on the nicotinic acetylcholine receptor-ionophore may be made by examining ion flow through channels of defined subunit composition incorporated (via cDNA or mRNA injection) into cellular systems. Such studies have revealed a markedly enhanced sensitivity of neuronal (as compared with muscular) nicotinic acetylcholine receptors to inhaled anesthetics [168] [169] (Fig. 3-14) (Figure Not Available) . Because neuronal nicotinic acetylcholine receptors can be inhibited at inhaled anesthetic concentrations as low as 0.1 MAC (see Fig. 3-14) (Figure Not Available) , these receptors may play some role in the behavioral and physiologic effects observed at subanesthetic concentrations. [45] [168] [169] The ability of specific amino acid mutations in the pore-forming domain of the acetylcholine receptor to enhance sensitivity to inhaled agents (with increased sensitivity associated with increased hydrophobicity of amino acid substitution) is consistent with a mechanism by which anesthetics bind within the pore of the nicotinic acetylcholine receptor. [170]

Other neurotransmitter-gated ion channels including the $GABA_A$, glycine, ionotropic glutamate, and $5\text{-}HT_3$ serotonin receptors have considerable overlap with the nicotinic acetylcholine receptor in amino acid sequence and have similar subunit structures. Interactions of anesthetics with particular subunits of these ligand-gated ion channels can be studied by molecular cloning and expression in cells that do not endogenously contain these receptors. [66] The dependence of GABA receptor subunit composition on the ability of inhaled anesthetics to alter ligand binding [171] or potentiate GABA-activated chloride currents [154] [172] implies specific GABA subunit binding sites for anesthetics. Interaction of

Figure 3-14 (Figure Not Available) The figure on the left shows the current from an oocyte that expresses the predominant nicotinic acetylcholine receptor subtype (alpha4beta2) found in the central nervous system. Isoflurane (320 muM) reduces the peak current obtained in response to 1 muM acetylcholine from 2.4 muA to 1.1 muA (46% of control). The graph on the right shows the dose-response curve of the inhibition of alpha4beta2 receptor subtype current by isoflurane. Note that some inhibition of receptor function occurs even at isoflurane concentration of 0.1 MAC. *(From Flood et al [168])*

anesthetics with the GABA receptor is also indicated by a direct (but small) activation by halothane in receptors of particular subunit composition, an effect that is reversed by GABA antagonists. [173] Inhaled anesthetics enhance the function of glycine [174] [175] and $5\text{-}HT_3$ [176] [177] serotonin receptors, but the degree of enhancement is not related to anesthetic potency. Inhaled anesthetics produce subunit-selective actions on excitatory glutamate receptors, with GluR3 (AMPA subtype) receptors being inhibited or unaffected by anesthetics, whereas GluR6 (kainate subtype) receptor function is enhanced by volatile agents. [178]

The nonimmobilizers 1,2-dichlorohexafluorocyclobutane and 2,3-dichlorooctafluorobutane (see Fig. 3-11) have little or no effect on GABA, [154] glycine, [175] $5\text{-}HT_3$, [176] and glutamate [178] receptor function and are minimally effective in producing desensitization of nicotinic acetylcholine receptors. [166] However, these nonimmobilizing agents are highly effective in blocking currents through the nicotinic acetylcholine receptor pore, [179] consistent with the concept that anesthetic action on nicotinic acetylcholine receptors might be important for anesthetic-induced behavioral changes (e.g., amnesia) but not important for preventing response to surgical

stimulation.

Voltage-Gated Ion Channels

The flux of ions through voltage-gated ion channels is controlled by the electric field across the membrane. These channels share structural similarities and include sodium and potassium channels involved in the propagation of neuronal action potentials and calcium channels that control entry of calcium through presynaptic membranes and eventual neurotransmitter release. Although voltage-gated ion channels are often found to be insensitive to even high anesthetic concentrations, [2] [180] it is recognized that pharmacologic effects on a particular channel may vary from tissue to tissue or among channel subtypes. Thus, 2 percent atm isoflurane inhibits voltage-gated calcium currents in rat hippocampal pyrimidal neurons [181] ; clinical concentrations of volatile anesthetics suppress sodium current through rat brain sodium channels expressed in a cell line [134] ; and 1 to 4 percent atm halothane inhibits potassium currents through rat brain potassium channels. [135] A protein site of anesthetic action is suggested by the lesser ability of halothane to block currents through potassium channels that have had 318 amino acids removed from their cytoplasmic C-terminus. [135]

Metabotropic Receptors and G Proteins

In contrast to the ionotropic multiple subunit ligand-gated ion channels where membrane ion permeabilities change within a few milliseconds of agonist binding, metabotropic receptors consist of a single subunit, are coupled to G proteins, and evoke changes in neuronal excitability over hundreds of milliseconds. The ability of halothane but not isoflurane to inhibit muscarinic signaling activated by acetylcholine indicates a variable effect of anesthetics and suggests that muscarinic inhibition might be more relevant to side effects of anesthetics than to anesthetic action per se. [182] The 5-hydroxytryptamine type 2A receptor is coupled to G proteins and is inhibited by both inhaled anesthetics and the nonimmobilizer 1,2-dichlorohexafluorocyclobutane (see Fig.3-11) , implying that this receptor is not important for the immobility component of anesthesia but may relate to anesthetic-induced behavioral changes. [183]

G proteins are potential membrane sites where anesthetics exert their functional effects. G proteins are guanine nucleotide-binding neuronal membrane proteins that couple many neurotransmitter receptors to ion channels in the brain. That is, the binding of a neurotransmitter to its receptor

can influence the activation state of a G protein, which in turn can control the opening or closing of an ion channel. Evidence for an anesthetic target site on G proteins is supported (but not proved) by the abilities of clinical concentrations of volatile anesthetics to alter interactions of G proteins with some (but not all) receptors and impair the ability of guanine nucleotides to depress the high affinity binding of agonists to receptors. [184]

Membrane Enzymes and Transporters

Photoaffinity labeling of radioactive halothane demonstrates a direct binding of halothane to Ca^{2+}-ATPase, [185] an enzyme found in synaptic membranes that is 20 to 30 percent inhibited by inhaled anesthetics at 1 MAC. [186] A direct anesthetic-protein interaction may also be inferred by the ability of inhaled agents to compete with ligands known to have specific binding sites on proteins. The Na^{+}-K^{+}-Cl^{-} cotransporter (a plasma membrane protein that simultaneously transports sodium, potassium, and chloride ions into the cell) is inhibited by halothane but not by other clinical anesthetics, possibly because this membrane protein contains a hydrophobic pocket of circumscribed dimensions that allows binding of halothane but not other inhaled agents. [187]

Protein kinase C is an enzyme involved in the phosphorylation of proteins and may modulate neurotransmission through effects on transmitter release and conductance of ions through membrane channels. Alteration protein kinase C activity by volatile anesthetics and the lowering of anesthetic requirement by a protein kinase C inhibitor (staurosporine) raises the possibility that protein kinase C inhibition may play a role in the production of general anesthesia. [188] However, protein kinase C exists in several isoforms, and anesthetic effects on this enzyme are complicated, with enzyme activity depending on the isoform and tissue examined, the presence of endogenous enzyme activators, and the particular anesthetic and its duration of treatment. [189]

USE OF ANIMAL MODELS: ATTEMPTS TO RELATE SUSTAINED ALTERATIONS IN ANESTHETIC POTENCY WITH NEUROCHEMICAL COMPOSITION

One approach to the mechanism of anesthetic action is to relate alterations in anesthetic requirement with biochemical and biophysical changes occurring in the CNS. A correlation between changes in anesthetic requirement and a structural change in the nervous system might indicate the critical properties of the anesthetic site of action and how anesthetics affect that site.

Dietary Studies

Mice fed diets of different fatty acid composition (saturated versus unsaturated) from birth have large alterations in certain synaptic membrane fatty acid components. [190] The most notable changes occur in the synaptic membrane phosphatidylethanolamine and phosphatidylserine fractions in mice fed the saturated fat diet; these mice exhibit a relative decrease in docosahexaenoic (22:6omega3) and increase in eicosatrienoic (20:3omega9) fatty acids. However, these alterations in synaptic membrane fatty acid composition have little or no influence on the righting-reflex ED_{50} for N_2O and isoflurane. [190] In contrast, diet-induced alterations in rat brain fatty acid composition can be correlated with alterations in anesthetic potency. [191] Compared with rats on a control diet, rats maintained on a fat-free diet exhibit lower levels of whole brain arachidonic acid (20:4omega6) and docosahexaenoic acid and an increase in eicosatrienoic acid. The fat-deprived animals exhibited a 10 to 33 percent decrease in MAC for methoxyflurane, halothane, isoflurane, and cyclopropane as compared with control rats. [191] Furthermore, the enhanced sensitivity of the fat-deprived rats to inhaled agents could be reversed by supplementing the fat-deprived animals with linoleic acid (18:2omega6). [191] The alterations in anesthetic potency are correlated with changes in brain arachidonyl-phosphatidylinositol content, and one speculation is that such changes in arachidonyl-phosphatidylinositol content might alter the ability of neurotransmitters to synthesize chemical second messengers, thus altering neuronal excitability and anesthetic requirement. [192]

Tolerance Studies

Chronic Tolerance

Inhaled anesthetic requirement can be increased by the chronic exposure of mice to subanesthetic levels of N_2O. [193] [194] [195] [196] The maximal increase in the N_2O righting-reflex ED_{50} for mice placed under 40 to 70 percent N_2O is approximately 0.25 atm and occurs after 2 weeks of continuous exposure. Tolerance disappears within 6 days of removing the mice from the subanesthetic N_2O environment. [193] [194] Mice tolerant to N_2O are also more tolerant to cyclopropane, [195] isoflurane, [195] and nitrogen. [196]

One possible mechanism for the tolerance that develops is that the continuous exposure to anesthetic alters the physical state of neuronal membranes and that the animals might adapt to this perturbation by adjusting the neuronal membrane lipid composition so that the physical state of the membrane is returned to that prior to anesthetic exposure. However, no significant differences in membrane order or in the composition of purified synaptic membrane fatty acid, phospholipid, or cholesterol occur in mice tolerant to N_2O. [193] [194] [197] Nevertheless, preliminary evidence indicates a lesser anesthetic-induced perturbation of membranes isolated from tolerant than from nontolerant animals. [197] Other possible mechanisms behind tolerance development include alterations in neurotransmitter levels or their receptors. Prolonged exposure of rats to N_2O decreases brain-stem opiate receptor density by approximately 20 percent and may in part account for the tolerance to the analgesic action of N_2O. [198]

Acute Tolerance

In humans, a tolerance to the analgesic effect of N_2O is seen in some but not all patients within 10 to 60 minutes of

administration. [199] A rapidly developing tolerance to the anesthetic effects of gaseous agents is also seen in mice, [200] and this is associated with a withdrawal syndrome that occurs when animals are removed from the anesthetic environment. [201] This syndrome may be related to the emergence delirium occasionally seen in patients after general anesthesia. Although an involvement of calcium channels is suggested by the ability of a calcium entry blocker to prevent N_2O tolerance and withdrawal seizures, [201] the mechanistic bases of the acute tolerance and the withdrawal syndrome remain to be determined.

Genetic Studies

Genetic approaches to anesthetic mechanisms involve the development of lines of animals or the discovery of mutants that are markedly sensitive or resistant to anesthetics and examination of the physiologic (cellular) and molecular changes in these selected animals that explain their altered anesthetic sensitivities. Most genetic studies have involved three different types of organisms: nematodes *(C. elegans),* fruit flies *(Drosophila),* and mice. Nematodes and fruit flies are advantageous in genetic studies because of their well-mapped genomes, defined nervous systems, short life cycles, and relatively low cost. However, the behavioral assays used to assess anesthetic potencies in these simpler organisms may be difficult to relate to the anesthetic-induced immobility and amnesia in patients during surgical anesthesia.

C. elegans

The potencies of inhaled agents in wild-type *C. elegans* parallel those found in higher animals. [202] [203] Although certain behavioral end points (e.g., mating, chemotaxis, coordinated movement) are disrupted at clinical anesthetic concentrations, [203] anesthetic-induced immobility of nematodes requires anesthetic concentrations of
10 MAC. [202] [203] Mutants of *C. elegans* have been developed that are hypersensitive to clinical anesthetics, and additional mutations were discovered that could suppress this hypersensitivity to some but not all anesthetics. [202] A genetic pathway was described that controls the sensitivity to volatile anesthetics in *C. elegans,* and it was suggested that at least three different sites of anesthetic action exist in this organism. [202] The molecular bases of these sites remain to be determined.

Drosophila

Potencies of inhaled anesthetics in wild-type *Drosophila*(measured by either response to mechanical [204] or heat [205] stimuli or disruption of coordinated movement [122]) approximate those required for surgical anesthesia. Mutant have been obtained that are resistant and sensitive to various anesthetics, [204] [205] with anesthetic sensitivity depending on the agent examined and end point measured. [205] Mutations that affect ion channels change the sensitivity of *Drosophila* to volatile

anesthetics in a manner suggesting an agentspecific action through different neuronal pathways. [206]

Mice

With selective breeding, use is made of the fact that anesthetic requirement varies slightly among animals of a given species and that members resistant and vulnerable to anesthesia may be found in a normal population. Mice can be selected from a normal population with consistently high and consistently low N_2O righting-reflex ED_{50}. [207] Repeating the process of selection, breeding, and testing for N_2O requirement through 15 generations produced two lines of mice with N_2O requirements separated by as much as 1 atm (Fig. 3-15). [9] [207] Mice resistant to N_2O also have a higher requirement for other inhaled anesthetics, but the separation in righting-reflex ED_{50} values between the two lines is inversely related to the lipid solubility of the anesthetic. [9] N_2O ED_{50} values of offspring produced by cross-mating animals of the resistant and vulnerable lines approximate the average value of the parents, implying that the genetic control of resistance or susceptibility probably involves many genes. [208] The differences in N_2O requirement between these lines of mice could not be explained by an alteration in synaptic membrane fatty acid, phospholipid, or cholesterol composition [207] but may be explained, at least in part, by a higher

Figure 3-15 Nitrous oxide righting-reflex ED_{50} values for male (closed symbols) and female (open symbols) offspring of mice selectively bred for resistance (HI group, circles) or susceptibility (LO group, triangles) to nitrous oxide anesthesia. The nitrous oxide requirements for HI and LO mice became progressively more separated over 15 generations of selective breeding. Standard errors about most points are less than 0.03 atm. Values for generations 1 through 10 are taken from references [9] and [207].

TABLE 3-3 -- Possible Sites of Anesthetic Action

ANATOMIC LEVEL	SITE OF ACTION	COMMENTS
Macroscopic	Central Nervous System	
	Brain vs. Spinal Cord	Anesthetics disrupt transmission throughout the CNS; decerebration does not alter MAC.
Microscopic	Axons vs. Synapses	Higher concentrations of inhaled anesthetic are typically required to disrupt axonal synaptic than transmission.
	Excitatory vs. Inhibitory Synapses	Anesthetics may block excitatory and enhance inhibitory transmission.
	Presynaptic vs. Postsynaptic	Anesthetics may alter presynaptic release of neuro-transmitter (perhaps via changes in intracellular Ca^{++}) and modify flow of ions through postsynaptic channels.
Molecular		*Meyer-Overton Rule* implies a hydrophobic site of action.
	Membrane	*Critical volume hypothesis* purports anesthetic action through membrane expansion. Possible importance of membrane/aqueous interface.
	Lipid vs. Protein	Lipid *fluidization* theories cannot account for the production of the anesthetic state. Evidence accumulating for direct binding of anesthetics to "excitable" membrane proteins.

brain norepinephrine content in resistant as compared with susceptible mice. [209]

An alternative genetic approach is to "knock out" a gene in embryonic stem cells thought to be important for the anesthetic state and examine anesthetic sensitivity in mice that lack functional genes. Targeted disruption of the neuronal nitrous oxide synthase gene has no influence on isoflurane MAC or isoflurane righting-reflex ED_{50} in knock-out compared to wild-type mice. [102] Unlike wild-type mice, acute administration of nitrous oxide synthase inhibitors does not decrease anesthetic

requirement in these knock-out mice, suggesting that other non-nitrous oxide mechanisms exist in the knock-out mice to compensate for the mutation. [102] Gene knock-out of the a6 subunit of the GABA receptor does not alter MAC or righting-reflex ED_{50} for enflurane or halothane, implying that this particular subunit of the GABA receptor is not important in the behavioral responses to volatile anesthetics. [210]

SUMMARY

We remain uncertain of the site of anesthetic action at the macroscopic, microscopic, and molecular levels (Table 3-3) . We do know that inhaled anesthetics disrupt neuronal transmission in many areas of the CNS. They may either enhance or depress excitatory or inhibitory transmission through axons or synaptic regions. Both pre- and postsynaptic effects have been found. Regardless of the macroscopic site of action, the ultimate action of inhaled agents is on neuronal membranes. Although a direct neuronal plasma membrane interaction seems likely, the possibility remains that inhaled anesthetics act indirectly via production of a second messenger. The correlation between lipid solubility and anesthetic potency suggests that anesthetics have a hydrophobic or amphipathic site of action. The discovery of "nonimmobilizers," lipid-soluble compounds that do not alter MAC, implies the site of action is different for different anesthetic end points. Anesthetics bind to and perturb both membrane lipids and proteins, but it is presently uncertain which of these components is most important and how such perturbations might lead to the anesthetic state. Future advances in anesthetic mechanisms will go hand in hand with the development of molecular biology techniques used to clone and characterize excitable membrane channels and biophysical and biochemical advances used to study neuronal interactions. The development of animal models with sustained alterations in anesthetic potency will allow for the testing of hypotheses that specific molecular changes in selected regions of the CNS are important in the production of anesthesia.

References

1. Goto T, Saito H, Shinkai M et al: Xenon provides faster emergence from anesthesia than does nitrous oxide-sevoflurane or nitrous oxide-isoflurane. Anesthesiology 86:1273, 1997.

2. Franks NP, Lieb WR: Molecular and cellular mechanisms of general anaesthesia. Nature 367:607, 1994.

3. Eger EI II, Johnson BH: MAC of I-653 in rats, including a test of the effect of body temperature and anesthetic duration. Anesth Analg 66:974, 1987.

4. Petersen-Felix S, Zbinden AM, Fischer M et al: Isoflurane minimum alveolar concentration decreases during anesthesia and surgery. Anesthesiology 79:959, 1993.

5. Fang Z, Ionescu P, Chortkoff BS et al: Anesthetic potencies of n-alkanols: results of additivity and solubility studies suggest a mechanism of action similar to that for conventional inhaled anesthetics. Anesth Analg 84:1042, 1997.

6. Quasha AL, Eger EI II, Tinker JH: Determination and applications of MAC. Anesthesiology 53:315, 1980.

7. Travis CC, Bowers JC: Interspecies scaling of anesthetic potency. Toxicol Ind Health 7:249, 1991.

8. Deady JE, Koblin DD, Eger EI II et al: Anesthetic potencies and the unitary theory of narcosis. Anesth Analg 60:380, 1981.

9. Koblin DD, Deady JE, Eger EI II: Potencies of inhaled anesthetics and alcohol in mice selectively bred for resistance and susceptibility to nitrous oxide anesthesia. Anesthesiology 56:18, 1982.

10. Kissin I, Morgan PL, Smith LR: Anesthetic potencies of isoflurane, halothane, and diethyl ether for various end points of anesthesia. Anesthesiology 58:88, 1983.

11. Kissin I: A concept for assessing interactions of general anesthetics. Anesth Analg 85:204, 1997.

12. Antognini JF, Lewis BK, Reitan JA: Hypothermia minimally decreases nitrous oxide anesthetic requirements. Anesth Analg 79:980, 1994.

13. Franks NP, Lieb WR: Temperature dependence of the potency of volatile general anesthetics. Anesthesiology 84:716, 1996.

14. Wann KT, MacDonald AG: Actions and interactions of high pressure and general anaesthetics. Prog Neurobiol 30:271, 1987.

15. Smith RA, Dodson BA, Miller KW: The interactions between pressure and anaesthetics. Phil Trans R Soc Lond B 304:69, 1984.

16. Smith EB, Bowser-Riley F, Daniels S et al: Species variation and the mechanism of pressure-anaesthetic interactions. Nature 311:56, 1984.

17. Mapleson WW: Effect of age on MAC in humans: A meta-analysis. Br J Anaesth 76:179, 1996.

18. Zucker JR: ATP-sensitive potassium channel agonists do not alter MAC for isoflurane in rats. Anesthesiology 76:560, 1992.

19. Tanifuji Y, Nezu T, Kobayashi K et al: Effect of brain calcium and magnesium on anesthetic requirement (MAC) in dogs. Jpn J Anesthesiol 29:741, 1980.

20. Schwartz AE, Maneksha FR, Backus WW et al: Nimodipine decreases the minimum alveolar concentration of isoflurane in dogs. Can J Anaesth 38:239, 1991.

21. Thompson SW, Moscicki JC, DiFazio CA: The anesthetic contribution of magnesium sulfate and ritodrine hydrochloride in rats. Anesth Analg 67:31, 1988.

22. Matsumara JS, Cole DJ, Schell RM et al: L-644,711, a novel anion transport inhibitor, increases isoflurane MAC in rats. Anesth Analg 73:199, 1991.

23. Rich GF, Sullivan MP, Adams JM: Effect of chloride transport blockade on the MAC of halothane in the rat. Anesth Analg 75:103, 1992.

24. Angel A: Processing of sensory information. Prog Neurobiol 9:1, 1977.

25. Ogawa T, Shingu K, Shibata M et al: The divergent actions of volatile anaesthetics on background neuronal activity and reactive capability in the central nervous system in cats. Can J Anaesth 39:862, 1992.

26. Berg-Johnsen J, Langmoen IA: Mechanisms concerned in the direct effect of isoflurane on rat hippocampal and human neocortical neurons. Brain Res 507:28, 1990.

27. MacIver MB, Roth SH: Inhalation anaesthetics exhibit pathway-specific and differential actions on hippocampal synaptic responses *in vitro.* Br J Anaesth 60:680, 1988.

28. Pearce RA: Volatile anaesthetic enhancement of paired-pulse depression investigated in the rat hippocampus *in vitro.* J Physiol (Lond) 492:823, 1996

29. Jones MV, Brooks PA, Harrison NL: Enhancement of gamma-aminobutyric acid-activated Cl^- currents in cultured rat hippocampal neurones by three volatile anaesthetics. J Physiol (Lond) 449:279, 1992.

30. Fujiwara N, Higashi H, Nishi S et al: Changes in spontaneous firing patterns of rat hippocampal neurones by volatile anesthetics. J Physiol (Lond) 402:155, 1988.

31. Angel A: Central neuronal pathways and the process of anaesthesia. Br J Anaesth 71:148, 1993.

32. Collins JG, Kendig JJ, Mason P: Anesthetic actions within the spinal cord: Contributions to the state of general anesthesia. Trends Neurosci 18:549, 1995.

33. Rampil IJ, King BS: Volatile anesthetics depress spinal motor neurons. Anesthesiology 85:129, 1996.

34. Zhou HH, Mehta M, Leis AA: Spinal cord motoneuron excitability during isoflurane and nitrous oxide anesthesia. Anesthesiology 86:302, 1997.

35. Borges M, Antognini JF: Does the brain influence somatic responses to noxious stimuli during isoflurane anesthesia? Anesthesiology 81:1511, 1994.

36. Todd MM, Weeks JB, Warner DS: A focal cryogenic brain lesion does not reduce the minimum alveolar concentration for halothane in rats. Anesthesiology 79:139, 1993.

37. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. Anesthesiology 78:707, 1993.

38. Rampil IJ, Mason P, Singh H: Anesthetic potency is not altered after hypothermic spinal cord transection in rats. Anesthesiology 80:606, 1994.

39. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. Anesthesiology 79:1244, 1993.

40. Eger EI II, Koblin DD, Harris RA et al: Hypothesis: Inhaled anesthetics produce immobility and amnesia by different mechanisms at different sites. Anesth Analg 84:915, 1997.

41. MacIver MB, Tanelian DL: Volatile anesthetics excite mammalian nociceptor afferents recorded *in vitro.* Anesthesiology 72:1022, 1990.

42. Antognini JF, Kien ND: Potency (minimum alveolar anesthetic concentration) of isoflurane is independent of peripheral anesthetic effects. Anesth Analg 81:69, 1995.

43. Franks NP, Lieb WR: Volatile general anaesthetics activate a novel neuronal K^+ current. Nature 333:662, 1988.

44. Winegar BD, Owen DF, Yost CS et al: Volatile general anesthetics produce hyperpolarization of *Aplysia* neurons by activation of a discrete population of baseline potassium channels. Anesthesiology 85:889, 1996.

45. Evers AS, Steinbach JH: Supersensitive sites in the central nervous system: Anesthetics block brain nicotinic receptors. Anesthesiology 86:760, 1997.

46. Pocock G, Richards CD: Excitatory and inhibitory synaptic mechanisms in anaesthesia. Br J Anaesth 71:134, 1993.

47. Berg-Johnsen J, Langmoen IA: The effect of isoflurane on unmyelinated and myelinated fibers in the rat brain. Acta Physiol Scand 127:87, 1986.

48. Strichartz G: Use-dependent conduction block produced by volatile anesthetic agents. Acta Anaesthesiol Scand 24:402, 1980.

49. Perouansky M, Baranov D, Salman M et al: Effects of halothane on glutamate receptor-mediated excitatory postsynaptic currents. Anesthesiology 83:109, 1995.

50. Griffiths R, Norman RI: Effects of anaesthetics on uptake, synthesis and release of transmitters. Br J Anaesth 71:96, 1993.

51. Bazil CW, Minneman KP: Clinical concentrations of volatile anesthetics reduce depolarization-evoked release of [^{3}H]norepinephrine, but not [^{3}H]acetylcholine, from rat cerebral cortex. J Neurochem 53:962, 1989.

52. Mantz J, Varlet C, Lecharny JB et al: Effects of volatile anesthetics, thiopental, and ketamine on spontaneous and depolarization-evoked dopamine release from striatal synaptosomes in the rat. Anesthesiology 80:352, 1994.

53. Salord F, Keita H, Lecharny JB et al: Halothane and isoflurane differentially affect the regulation of dopamine and gamma-aminobutyric acid release mediated by presynaptic acetylcholine receptors in the rat striatum. Anesthesiology 86:632, 1997.

54. Miao N, Frazer MJ, Lynch C III: Volatile anesthetics depress Ca^{2+} transients and glutamate release in isolated cerebral synaptosomes. Anesthesiology 83:593, 1995.

55. Schlame M, Hemmings HC: Inhibition by volatile anesthetics of endogenous glutamate release from synaptosomes by a presynaptic mechanism. Anesthesiology 82:1406, 1995

56. Griffiths R, Greiff JMC, Boyle E et al: Volatile anesthetics inhibit choline uptake into rat synaptosomes. Anesthesiology 81:953, 1994.

57. Martin DC, Adams RJ, Introna RPS: Halothane inhibits 5-hydroxytryptamine uptake by synaptosomes from rat brain. Neuropharmacology 29:9, 1990.

58. El-Maghrabi EA, Eckenhoff RG: Inhibition of dopamine transport in rat brain synaptosomes by volatile anesthetics. Anesthesiology 78:750, 1993.

59. Mantz J, Lecharny JB, Laudenbach V et al: Anesthetics affect the uptake but not the depolarization-evoked release of GABA in rat striatal synaptosomes. Anesthesiology 82:502, 1995.

60. Miyazaki H, Nakamura Y, Arai T et al: Increase of glutamate uptake in astrocytes: A possible mechanism of action of volatile anesthetics. Anesthesiology 86:1359, 1997.

61. Larsen M, Hegstad E, Berg-Johnsen J et al: Isoflurane increases the uptake of glutamate in synaptosomes from rat cerebral cortex. Br J Anaesth 78:55, 1997.

62. Yamamura T, Stevens WC, Okamura A et al: Correlative study of behavior and synaptic events during halothane anesthesia in the lamprey. Anesth Analg 76:342, 1993.

63. Puil E, El-Beheiry H: Anaesthetic suppression of transmitter actions in neocortex. Br J Pharmacol 101:61, 1990.

64. Zimmerman SA, Jones MV, Harrison NL: Potentiation of gamma-aminobutyric acid $_A$ receptor Cl^- current correlates with in vivo anesthetic potency. J Pharmacol Exp Ther 270:987, 1994.

65. Wakamori M, Ikemoto Y, Akaike N: Effects of two volatile anesthetics on the excitatory and inhibitory amino acid responses in dissociated CNS neurons of the rat. J Neurophysiol 66:2014, 1991.

66. Harris RA, Mihic J, Dildy-Mayfield JE et al: Actions of anesthetics on ligand-gated ion channels: role of receptor subunit composition. FASEB J 9:1454, 1995.

67. Wachtel RE: Relative potencies of volatile anesthetics in altering the kinetics of ion channels in BC $_3$H1 cells. J Pharmacol Exp Ther 274:1355, 1995.

68. Ngai SH, Cheney DL, Finck AD: Acetylcholine concentrations and turnover in rat brain structures during anesthesia with halothane, enflurane, and ketamine. Anesthesiology 48:4, 1978.

69. Taguchi K, Andresen MJ, Hentall ID: Acetylcholine release from the midbrain interpeduncular nucleus during anesthesia. Neuroreport 2:789, 1991.

70. Keifer JC, Baghdoyan HA, Lydic R: Pontine cholinergic mechanisms modulate the cortical electroencephalographic spindles of halothane anesthesia. Anesthesiology 84:945, 1996.

71. Zucker J: Central cholinergic depression reduces MAC for isoflurane in rats. Anesth Analg 72:790, 1991.

72. Roizen MF, Kopin KJ, Thoa NB et al: The effect of two anesthetic agents on norepinephrine and dopamine in discrete brain nuclei, fiber tracts, and terminal regions of the rat. Brain Res 110:515, 1976.

73. Muldoon SM, Cress L, Freas W: Presynaptic adrenergic effects of anesthetics. Int Anesth Clin 27:259, 1989.

74. Roizen MF, White PF, Eger EI II et al: Effects of ablation of serotonin or norepinephrine brainstem areas on halothane and cyclopropane MACs in rats. Anesthesiology 49:252, 1978.

75. Segal IS, Walton JK, Irwin I et al: Modulating role of dopamine on anesthetic requirements. Eur J Pharmacol 186:9, 1990.

76. Miyano K, Tanifuji Y, Eger EI II: The effect of halothane dose on striatal dopamine: An in vivo microdialysis study. Brain Res 605:342, 1993.

77. Vickery RG, Sheridan BC, Segal IS et al: Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha $_2$ -adrenergic agonist, in halothane-anesthetized dogs. Anesth Analg 67:611, 1988.

78. Savola MKT, MacIver MB, Doze VA et al: The alpha $_2$ -adrenoreceptor agonist dexmedetomidine increases the apparent potency of the volatile anesthetic isoflurane in rats in vivo and in hippocampal slice in vitro. Brain Res 548:23, 1991.

79. Roizen MF, Kopin IJ, Palkovits M et al: The effect of two diverse inhalation anesthetic agents on serotonin in discrete regions of the rat brain. Exp Brain Res 24:203, 1975.

80. Seitz PA, Riet MT, Rush W et al: Adenosine decreases the minimum alveolar concentration of halothane in dogs. Anesthesiology 73:990, 1990.

81. Birch BD, Louie GL, Vickery RG et al: L-phenylisopropyladenosine (L-PIA) diminishes halothane anesthetic requirements and decreases noradrenergic neurotransmission in rats. Life Sci 42:1355, 1988.

82. Arai T, Aoki M, Murakawa M et al: The effects of halothane on the contents of putative transmitter amino acids in whole rat brain. Neurosci Lett 117:353, 1990.

83. Cheng SC, Brunner EA: Inhibition of GABA metaabolism in rat brain slices by halothane. Anesthesiology 55:26, 1981.

84. Cheng SC, Brunner EA: Inducing anesthesia with a GABA analog, THIP. Anesthesiology 63:147, 1985.

85. Mason P, Owens CA, Hammond DL: Antagonism of the antinocifensive action of halothane by intrathecal administration of GABA $_A$ receptor antagonists. Anesthesiology 84:1205, 1996.

86. Hudspith MJ: Glutamate: A role in normal brain function, anaesthesia, analgesia and CNS injury. Br J Anaesth 78:731, 1997.

87. Hirose T, Inoue M, Uchida M et al: Enflurane-induced release of an excitatory amino acid, glutamate, from mouse brain synaptosomes. Anesthesiology 77:109, 1992.

88. Towler SC, Evers AS: Anesthesia and chemical second messenger generation in the adrenergic nervous system. Int Anesth Clin 27:234, 1989.

89. Rengasamy A, Pajewski TN, Johns RA: Inhalational anesthetic effects on rat cerebellar nitric oxide and cyclic guanosine monophosphate production. Anesthesiology 86:689, 1997.

90. Kress HG, Tas WL: Effects of volatile anaesthetics on second messenger Ca^{+2} in neurones and non-muscular cells. Br J Anaesth 71:47, 1993.

91. Mody I, Tanelian DL, MacIver MB: Halothane enhances tonic neuronal inhibition by elevating intracellular calcium. Brain Res 538:319, 1991.

92. Hossain MD, Evers AS: Volatile-anesthetic-induced efflux of calcium from IP_3 -gated stores in clonal (GH_3) pituitary cells. Anesthesiology 80:1379, 1994.

93. Finck AD, Ngai SH, Berkowitz BA: Antagonism of general anesthesia by naloxone in the rat. Anesthesiology 46:241, 1977.

94. Guo TZ, Poree L, Golden W et al: Antinociceptive response to nitrous oxide is mediated by supraspinal opiate and spinal alpha $_2$ -adrenergic receptors in the rat. Anesthesiology 85:846, 1996.

95. Arndt JO, Freye E: Perfusion of naloxone through the fourth cerebral ventricle reverses the circulatory and hypnotic effect of halothane in dogs. Anesthesiology 51:58, 1979.

96. Harper MH, Winter PM, Johnson BH et al: Naloxone does not antagonize general anesthesia in the rat. Anesthesiology 49:3, 1978.

97. Kraynack BJ, Gintautas JG: Naloxone: Analeptic action unrelated to opiate receptor antagonism? Anesthesiology 56:251, 1982.

98. Finck AD, Samaniego E, Ngai SH: Nitrous oxide selectively releases Met^5 -enkephalin and met^5 -enkephalin-Arg^6 -Phe^7 into canine third ventricle cerebral spinal fluid. Anesth Analg 80:664, 1995.

99. Mantz J, Azerad J, Limoge A et al: Transcranial electrical stimulation with Limoge's currents decreases halothane requirements in rats: Evidence for the involvement of endogenous opioids. Anesthesiology 76:253, 1992.

100. Way WL, Hosobuchi Y, Johnson BH et al: Anesthesia does not increase opioid peptides in cerebrospinal fluid of humans. Anesthesiology 60:43, 1984.

101. Sjostrom S, Tamsen A, Hartvig P et al: Cerebrospinal fluid concentrations of substance P and metenkephalin- ARG ^{6} -PHE^7 during surgery and patient-controlled analgesia. Anesth Analg 67:976, 1988.

102. Ichinose F, Huang PL, Zapol WM: Effects of targeted neuronal nitric oxide synthase gene disruption and nitro ^{G} - L-arginine methylester on the threshold for isoflurane anesthesia. Anesthesiology 83:101, 1995.

103. Pajewski TN, DiFazio CA, Moscicki JC et al: Nitric oxide synthase inhibitors, 7- nitro indazole and nitro ^{G} - L-arginine methyl ester, dose-dependently reduce the threshold for isoflurane anesthesia. Anesthesiology 85:1111, 1996.

104. Adachi T, Shinomura T, Nakao S et al: Chronic treatment with nitric oxide synthase (NOS) inhibitor profoundly reduces cerebellar NOS activity and cyclic guanosine monophosphate but does not modify minimum alveolar anesthetic concentration. Anesth Analg 81:862, 1995.

105. Miller KW, Paton WDM, Smith EB et al: Physicochemical approaches to the mode of action of general anesthetics. Anesthesiology 36:339, 1972.

106. Seeman P: The membrane actions of anesthetics and tranquilizers. Pharmacol Rev 24:583, 1972.

107. Miller KW: The nature of the site of general anaesthesia. Int Rev Neurobiol 27:1, 1985.

108. Franks NP, Lieb WR: What is the molecular nature of general anesthetic target sites? Trends Pharmacol Sci 8:169, 1987.

109. Mullins LJ: Some physical mechanisms in narcosis. Chem Rev 54:289, 1954.

110. Franks NP, Lieb WR: Where do general anaesthetics act? Nature 274:339, 1978.

111. Taheri S, Halsey MJ, Liu J et al: What solvent best represents the site of action of inhaled anesthetics in humans, rats, and dogs? Anesth Analg 72:627, 1991.

112. Eger EI II: Does 1 + 1 = 2? Anesth Analg 68:551, 1989.

113. Eger EI II, Koblin DD, Laster MJ et al: Minimum alveolar anesthetic concentration values for the enantiomers of isoflurane differ minimally. Anesth Analg 85:188, 1997.

114. Lysko GS, Robinson JL, Casto R et al: The stereospecific effects of isoflurane isomers in vivo. Eur J Pharmacol 263:25, 1994.

115. Rudo FG, Krantz JC: Anaesthetic molecules. Br J Anaesth 46:181, 1974.

116. Koblin DD, Eger EI II, Johnson BH et al: Are convulsant gases also anesthetics? Anesth Analg 60:464, 1981.

117. Koblin DD, Eger EI II, Johnson BH et al: Minimum alveolar concentrations and oil/gas partition coefficients of four anesthetic isomers. Anesthesiology 54:314, 1981.

118. Cohen S, Goldschmid A, Shtacher G et al: The inhalation convulsants: A pharmacodynamic approach. Mol Pharmacol 11:379, 1975.

119. Richter J, Landau EM, Cohen S: Anaesthetic and convulsant ethers act on different sites at the crab neuromuscular junction *in vitro.* Nature 266:70, 1977.

120. Raines DE, Miller KW: On the importance of volatile agents devoid of anesthetic action. Anesth Analg 79:1031, 1994.

121. Liu J, Laster MJ, Taheri S et al: Is there a cutoff in anesthetic potency for the normal alkanes? Anesth Analg 77:12, 1993.

122. Allada R, Nash HA: *Drosophila melanogaster* as a model for study of general anesthesia: The quantitative response to clinical anesthetics and alkanes. Anesth Analg 77:19, 1993.

123. Taheri S, Laster MJ, Liu J et al: Anesthesia by n-alkanes not consistent with the Meyer-Overton hypothesis: Determinations of the solubilities of alkanes in saline and various lipids. Anesth Analg 77:7, 1993.

124. Liu J, Laster MJ, Koblin DD et al: A cutoff in anesthetic potency exists in the perfluoroalkanes. Anesth Analg 79:238, 1994.

125. Koblin DD, Chortkoff BS, Laster MJ et al: Polyhalogenated and perfluorinated compounds that disobey the Meyer-Overton hypothesis. Anesth Analg 79:1043, 1994.

126. Fang Z, Sonner J, Laster MJ et al: Anesthetic and convulsant properties of aromatic compounds and cycloalkanes: Implications for mechanisms of narcosis. Anesth Analg 83:1097, 1996.

127. Fang Z, Laster MJ, Gong D et al: Convulsant activity of nonanesthetic gas combinations. Anesth Analg 84:634, 1997.

128. Kandel L, Chortkoff BS, Sonner J et al: Nonanesthetics can suppress learning. Anesth Analg 82:321, 1996.

129. Pauling L: A molecular theory of general anesthesia. Science 134:15, 1961.

130. Abraham MH, Lieb WR, Franks NP: Role of hydrogen bonding in general anesthesia. J Pharm Sci 80:719, 1991.

131. Wood S, Wardley-Smith B, Halsey MJ et al: Hydrogen bonding in mechanisms of anaesthesia tested with chloroform and deuterated chloroform. Br J Anaesth 54:387, 1982.

132. Vulliemoz Y, Triner L, Verosky M et al: Deuterated halothane: Anesthetic potency, anticonvulsant activity, and effect on cerebellar cyclic guanosine 3 ,5,-monophosphate. Anesth Analg 63:495, 1984.

133. Miller KW: Inert gas narcosis, the high pressure neurological syndrome, and the critical volume hypothesis. Science 185:867, 1974.

134. Rehberg B, Xiao YH, Duch DS: Central nervous system sodium channels are significantly suppressed at clinical concentrations of volatile anesthetics. Anesthesiology 84:1223, 1996.

135. Kulkarni RS, Zorn LJ, Anantharam V et al: Inhibitory effects of ketamine and halothane on recombinant potassium channels from mammalian brain. Anesthesiology 84:900, 1996.

136. Brett RS, Dilger JP, Yland KF: Isoflurane causes "flickering" of the acetylcholine receptor channel: Observations using the patch clamp. Anesthesiology 69:161, 1988.

137. Dilger JP, Vidal AM, Mody HI: Evidence for direct actions of general anesthetics on an ion channel protein. Anesthesiology 81:431, 1994.

138. Tanelian DL, Kosek P, Mody I, MacIver MB: The role of the GABA $_A$ receptor/chloride channel complex in anesthesia. Anesthesiology 78:757, 1993.

139. MacIver MB, Kendig JJ: Anesthetic effects on membrane resting potential are voltage-dependent and agent-specific. Anesthesiology 74:83, 1991.

140. Janoff AS, Miller KW: A critical assessment of the lipid theories of general anesthetic action. In Chapman D (ed): Biological Membranes. London, Academic Press, 1982, pp

417. -476.

141. Kamaya H, Kaneshina S, Ueda I: Partition equilibrium of inhalation anesthetics and alcohols between water and membranes of phospholipids with varying acyl chain-lengths. Biochim Biophys Acta 646:135, 1981.

142. Pohorille A, Cieplak P, Wilson MA: Interactions of anesthetics with the membrane- water interface. Chem Phys 204:337, 1996.

143. Tang P, Yan B, Xu Y: Different distribution of fluorinated anesthetics and nonanesthetics in model membrane: A ^{19} F NMR study. Biophys J 72:1676, 1997.

144. North C, Cafiso DS: Contrasting membrane localization and behavior of halogenated cyclobutanes that follow or violate the Meyer-Overton hypothesis of general anesthetic potency. Biophys J 72:1754, 1997.

145. Andoh T, Blanck TJJ, Nikonorov I, Recio-Pinto E: Volatile anaesthetic effects on calcium conductance of planar lipid bilayers formed with synthetic lipids or extracted lipids from sarcoplasmic reticulum. Br J Anaesth 78:66, 1997.

146. Akeson MA, Deamer DW: Steady-state catecholamine distribution in chromaffin granule preparations: A test of the pump-leak hypothesis of general anesthesia. Biochemistry 28:5120, 1989.

147. Bangham AD, Hill MW: The proton pump/leak mechanism of unconsciousness. Chem Phys Lipids 40:189, 1986.

148. Suezaki Y, Shibata A, Kamaya H et al: Atypical Langmuir adsorption of inhalation anesthetics on phospholipid monolayer at various compressional states: difference between alkane- type and ether-type anesthetics. Biochim Biophys Acta 817:139, 1985.

149. Franks NP, Lieb WR: Is membrane expansion relevant to anaesthesia? Nature 292:248, 1981.

150. Bull MH, Brailsford JD, Bull BS: Erythrocyte membrane expansion due to the volatile anesthetics, the 1-alkanols, and benzyl alcohol. Anesthesiology 57:399, 1982.

151. Harris RA, Groh GI: Membrane disordering effects of anesthetics are enhanced by gangliosides. Anesthesiology 62:115, 1985.

152. Ueda I, Hirakawa M, Arakawa K et al: Do anesthetics fluidize membranes? Anesthesiology 64:67, 1986.

153. Baber J, Ellena JF, Cafiso DS: Distribution of general anesthetics in phospholipid bilayers determined using ^{2} H NMR and ^{1} H-^{1} H NOE spectroscopy. Biochemistry 34:6533, 1995.

154. Mihic J, McQuilkin SJ, Eger EI II et al: Potentiation of gamma-aminobutyric acid type A receptor-mediated chloride currents by novel halogenated compounds correlates with their abilities to induce general anesthesia. Mol Pharmacol 46:851, 1994.

155. Galla HJ, Trudell JR: Asymmetric antagonistic effects of an inhalation anesthetic and high pressure on the phase transition temperature of dipalmitoyl phosphatidic acid bilayers. Biochim Biophys Acta 599:336, 1980.

156. Trudell JR: A unitary theory of anesthesia based on lateral phase separations in nerve membranes. Anesthesiology 46:5, 1977.

157. Qin Z, Szabo G, Cafiso DS: Anesthetics reduce the magnitude of the membrane dipole potential: Measurements in lipid vesicles using voltage-sensitive spin probes. Biochemistry 34 :5536, 1995.

158. Cantor RS: The lateral pressure profile in membranes: A physical mechanism of general anesthesia. Biochemistry 36:2339, 1997.

159. Xu Y, Tang P, Zhang W et al: Fluorine-19 nuclear magnetic resonance imaging and spectroscopy of sevoflurane uptake, distribution, and elimination in rat brain. Anesthesiology 83:766, 1995.

160. Xu Y, Tang P, Firestone L et al: ^{19} F Nuclear magnetic resonance investigation of stereoselective binding of isoflurane to bovine serum albumin. Biophys J 70:532, 1996.

161. Eckenhoff RG: Amino acid resolution of halothane binding sites in serum albumin. J Biol Chem 271:15521, 1996.

162. Dickinson R, Franks NP, Lieb WR: Thermodynamics of anesthetic/ protein interactions: Temperature studies on firefly luciferase. Biophys J 64:1264, 1993.

163. Curry S, Franks NP, Lieb WR: Effects of general anesthetics on the bacterial luciferase enzyme from *Vibrio harveyi:* An anesthetic target site with differential sensitivity. Biochemistry 29:4641, 1990.

164. Eckenhoff RG: An inhalational anesthetic binding domain in the nicotinic acetylcholine receptor. Proc Natl Acad Sci U S A 93:2807, 1996.

165. Raines DE, Rankin SE, Miller KW: General anesthetics modify the kinetics of nicotinic acetylcholine receptor desensitization at clinically relevant concentrations. Anesthesiology 82:276, 1995.

166. Raines DE: Anesthetic and nonanesthetic halogenated volatile compounds have dissimilar activities on nicotinic acetylcholine receptor desensitization kinetics. Anesthesiology 84:663, 1996.

167. Firestone LL, Alifimoff JK, Miller KW: Does general anesthetic-desensitization of the *Torpedo* acetylcholine receptor correlate with lipid disordering? Mol Pharmacol 46:508, 1994.

168. Flood P, Ramirez-Latorre J, Role L: alpha4beta2 neuronal nicotinic acetylcholine receptors in the central nervous system are inhibited by isoflurane and propofol, but alpha7-type nicotinic acetylcholine receptors are unaffected. Anesthesiology 86:859, 1997.

169. Violet JM, Downie DL, Nakisa RC et al: Differential sensitivities of mammalian neuronal and muscle nicotinic acetylcholine receptors to general anesthetics. Anesthesiology 86:866, 1997.

170. Foreman SA, Miller KW, Yellen G: A discrete site for general anesthetics on a postsynaptic receptor. Mol Pharmacol 48:574, 1995.

171. Harris BD, Wong G, Moody EJ et al: Different subunit requirements for volatile and nonvolatile anesthetics at gamma-aminobutyric acid type A receptors. Mol Pharmacol 47:363, 1995.

172. Harrison NL, Kugler JL, Jones MV et al: Positive modulation of human gamma-aminobutyric acid type A and glycine receptors by the inhalation anesthetic isoflurane. Mol Pharmacol 44:628, 1993.

173. Sincoff R, Tanguy J, Hamilton B et al: Halothane acts as a partial agonist of the alpha6beta2gamma2S GABA $_A$ receptor. FASEB J 10:1539, 1996.

174. Downie DL, Hall AC, Lieb WR et al: Effects of inhalational general anaesthetics on native glycine receptors in rat medullary neurones and recombinent glycine receptors in *Xenopus* oocytes. Br J Pharmacol 118:493, 1996.

175. Mascia MP, Machu TK, Harris RA: Enhancement of homomeric glycine receptor function by long-chain alcohols and anaesthetics. Br J Pharmacol 119:1331, 1996.

176. Machu TK, Harris RA: Alcohols and anesthetics enhance the function of 5- hydroxytryptamine $_3$ receptors expressed in *Xenopus laevis*oocytes. J Pharm Exp Ther 271:898, 1994.

177. Jenkins A, Franks NP, Lieb WR: Actions of general anaesthetics on 5-HT $_3$ receptors in N1E-115 neuroblastoma cells. Br J Pharmacol 117:1507, 1996.

178. Dildy-Mayfield JE, Eger EI II, Harris RA: Anesthetics produce subunit-selective actions on glutamate receptors. J Pharm Exp Ther 276:1058, 1996.

179. Forman SA: Non-anesthetic volatiles obey the Meyer-Overton correlation at the hydrophobic channel site in the nicotinic ACH receptor. Anesthesiology 87:A706, 1997.

180. Hall AC, Lieb WR, Franks NP: Insensitivity of P-type calcium channels to inhalational and intravenous general anesthetics. Anesthesiology 81:117, 1994.

181. Study RE: Isoflurane inhibits multiple voltage-gated calcium currents in hippocampal pyramidal neurons. Anesthesiology 81:104, 1994.

182. Durieux ME: Muscarinic signaling in the central nervous system: Recent developments and anesthetic implications. Anesthesiology 84:173, 1996.

183. Minami K, Minami M, Harris RA: Inhibition of 5-hydroxytryptamine type 2A receptor-induced currents by n-alcohols and anesthetics. J Pharm Exp Ther 281:1136, 1997.

184. Martin DC, Dennison RL, Introna RPS et al: Influence of halothane on the interactions of serotonin $_{1A}$ and adenosine A_1 receptors with G proteins in rat brain membranes. Biochem Pharmacol 42:1313, 1991.

185. Kosk-Kosicka D, Fomitcheva I, Lopez MM et al: Heterogeneous halothane binding in the SR Ca^{2+}-ATPase. FEBS Lett 402:189, 1997.

186. Franks JJ, Horn JL, Janicki PK et al: Halothane, isoflurane xenon and nitrous oxide inhibit calcium ATPase pump activity in rat brain synaptic plasma membranes. Anesthesiology 82 :108, 1995.

187. Tas PWL, Kress HG, Koschel K: General anesthetics can competitively interfere with sensitive membrane proteins. Proc Natl Acad Sci U S A 84:5972, 1987.

188. Firestone S, Firestone LL, Ferguson C, Blanck D: Staurosporine, a protein kinase C inhibitor, decreases the general anesthetic requirement in *Ranapipiens* tadpoles. Anesth Analg 77:1026, 1993.

189. Hemmings HC, Adamo AIB: Effect of halothane on conventional protein kinase C translocation and down-regulation in rat cerebrocortical synaptosomes. Br J Anaesth 78:189, 1997.

190. Koblin DD, Dong DE, Deady JE et al: Alteration of synaptic membrane fatty acid composition and anesthetic requirement. J Pharmacol Exp Ther 212:546, 1980.

191. Evers AS, Elliott WJ, Lefkowith JB et al: Manipulation of rat brain fatty acid composition alters volatile anesthetic potency. J Clin Invest 77:1028, 1986.

192. Haycock JC, Evers AS: Altered phosphoinositide fatty acid composition, mass and etabolism in brain essential fatty acid deficiency. Biochim Biophys Acta 960:54, 1988.

193. Koblin DD, Dong DE, Eger EI II: Tolerance of mice to nitrous oxide. J Pharmacol Exp Ther 211:317, 1979.

194. Koblin DD, Eger EI II, Smith RA et al: Chronic exposure of mice to subanesthetic doses of nitrous oxide. In Fink BR (ed): Progress in Anesthesiology, vol 2: Molecular Mechanisms of Anesthesia. New York, Raven Press, 1980, pp 157-164.

195. Smith RA, Winter PM, Smith M et al: Tolerance to and dependence on inhalational anesthetics. Anesthesiology 50:505, 1979.

196. Brauer RW, Dutcher JA, Hinson W et al: Effect of habituation to subanesthetic N_2 or N_2O levels on pressure and anesthesia tolerance. J Appl Physiol 62:421, 1987.

197. Frank ED, Honet J, Torjman M et al: Effects of chronic exposure to nitrous oxide on membrane fluidity in rats. Ann NY Acad Sci 625:545, 1991.

198. Ngai SH, Finck AD: Prolonged exposure to nitrous oxide decreases opiate receptor density in rat brainstem. Anesthesiology 57:26, 1982.

199. Ramsay DS, Brown AC, Woods SC: Acute tolerance to nitrous oxide in humans. Pain 51:367, 1992.

200. Smith RA, Winter PM, Smith M et al: Rapidly developing tolerance to acute exposures to anesthetic agents. Anesthesiology 50:496, 1979.

201. Dolin SJ, Little HJ: Effects of "nitrendipine" on nitrous oxide anesthesia, tolerance, and physical dependence. Anesthesiology 70:91, 1989.

202. Morgan PG, Sedensky MM: Mutations conferring new patterns of sensitivity to volatile anesthetics in *Caenorhabditis elegans.* Anesthesiology 81:888, 1994.

203. Crowder CM, Shebester LD, Schedl T: Behavioral effects of volatile anesthetics in *Caenorhabditis elegans.* Anesthesiology 85:901, 1996.

204. Gamo S, Ogaki M, Nakashima-Tanaka E: Strain differences in minimum anesthetic concentrations in *Drosophila melanogaster.* Anesthesiology 54:289, 1981.

205. Campbell DB, Nash HA: Use of *Drosophila* mutants to distinguish among volatile anesthetics. Proc Natl Acad Sci U S A 91:2135, 1994.

206. Leibovitch BA, Campbell DB, Krishnan KS et al: Mutations that affect ion channels change the sensitivity of *Drosophila melanogaster* to volatile anesthetics. J Neurogenet 10:1, 1995.

207. Koblin DD, Dong DE, Deady JE et al: Selective breeding alters murine resistance to nitrous oxide without alteration in synaptic membrane lipid composition. Anesthesiology 52:401, 1980.

208. Koblin DD, Eger EI II: Cross-mating of mice selectively bred for resistance and susceptibility to nitrous oxide anesthesia: Potencies of nitrous oxide in the offspring. Anesth Analg 60:646, 1981.

209. Roizen MF, Koblin DD, Johnson BH et al: Mechanism of age-related and nitrous oxide-associated anesthetic sensitivity: The role of brain catecholamines. Anesthesiology 69:716, 1988.

210. Homanics GE, Ferguson C, Quinlan JJ et al: Gene knockout of the a6 subunit of the gamma-aminobutyric acid type A receptor: Lack of effect on responses to ethanol, pentobarbital, and general anesthetics. Molec Pharmacol 51:588, 1997.

Chapter 4 - Uptake and Distribution

Edmond I. Eger II

INTRODUCTION

The modern anesthetist expeditiously develops and then sustains a brain anesthetic concentration sufficient for surgery, doing so with agents and techniques that usually permit a rapid recovery from anesthesia. Producing an adequate brain anesthetic concentration for surgery requires sufficient anesthetic delivery to the patient that does not impose excessive depression. Knowledge of the factors that govern the relationship between the delivered and brain (or heart or muscle) concentrations is indispensable to the optimum conduction of anesthesia.

THE INSPIRED TO ALVEOLAR ANESTHETIC RELATIONSHIP

Of the steps between delivered and brain anesthetic partial pressures, none is more pivotal than that between the inspired and alveolar gases. The alveolar partial pressure governs the partial pressures of anesthetic in all body tissues: all must approach and ultimately equal the alveolar partial pressure. By use of high inflow rates (and hence conversion to a nonrebreathing system), the anesthetist can precisely control the partial pressure of anesthetic that is inspired.

The Effect of Ventilation

Two factors determine the rate at which the alveolar concentration of anesthetic (F_A) rises toward the concentration being inspired (F_I): the inspired concentration (see The Concentration Effect) and alveolar ventilation. Ventilation exerts a powerful effect. On induction, the unopposed effect of ventilation rapidly increases the alveolar concentration (i.e., F_A/F_I quickly approaches 1). This occurs with preoxygenation to achieve high alveolar concentrations of oxygen. Normally, a 95 percent or greater washin of oxygen occurs in 2 minutes or less when a nonrebreathing (or high inflow rate) system is used (Fig. 4-1) (Figure Not Available) .

However, inhaled anesthetics do not mimic the rapid washin of oxygen. The solubility of anesthetics is far higher than that of oxygen (or nitrogen), and the higher solubility causes the transfer of substantial quantities of anesthetic to

Figure 4-1 (Figure Not Available) The washin of oxygen was determined in two patients breathing from a mask. Note that a 63% change is obtained in about a half minute, an 86% change in about a minute, and a 95- 98% change in 2 minutes. *(From Eger [unpublished data])*

the blood passing through the lung. This uptake opposes the effect of ventilation to increase the alveolar anesthetic concentration. At low inspired concentrations, the F_A/F_I ratio is ultimately determined by the balance between the delivery of anesthetic by ventilation and its removal by uptake. The relationship is a simple one. For example, if uptake removes one-third of the inspired anesthetic molecules, F_A/F_I equals two-thirds; if uptake removes two-thirds of the inspired molecules, F_A/F_I equals one-third.

Anesthetic Uptake Factors

Anesthetic uptake itself is the product of three factors: solubility (lambda), cardiac output (Q), and alveolar to venous partial pressure difference (P_A-P_V). [1] That is:

Uptake = (lambda) × (Q) × (P_A-P_V) divided by barometric pressure

The fact that uptake is a product of the three factors rather than a sum means that if any factor approaches zero, uptake must approach zero, and ventilation is free to rapidly drive the alveolar concentrations upward. Thus, if solubility is small (as in the case of oxygen), if cardiac output approaches zero (as in profound myocardial depression or death), or if the alveolar to venous difference becomes inconsequential (as might occur after an extraordinarily long anesthetic), uptake would be minimal, and F_A/F_I would quickly equal 1.

Solubility

The blood/gas partition coefficient (lambda, or "blood solubility") describes the relative affinity of an anesthetic for two phases and hence how that anesthetic partitions itself between the two phases when equilibrium has been achieved. For example, isoflurane has a blood/gas partition coefficient of 1.4, indicating that at equilibrium, isoflurane's concentration in blood is 1.4 times its concentration in the gas (alveolar) phase. "Equilibrium" means that no difference in partial pressure exists (i.e., a blood/gas partition coefficient of 1.4 does not indicate that the partial pressure in blood is 1.4 times that in the gas phase). The partition coefficient may be thought of in another way--it indicates the relative capacity of the two phases. Thus, a value of 1.4 means that each milliliter of blood holds 1.4 times as much isoflurane as a milliliter of alveolar gas.

A larger blood/gas partition coefficient produces a greater uptake and hence a lower F_A/F_I ratio. Because the anesthetic partial pressure in the alveoli is transmitted to the arterial blood and thence to all tissues (especially the brain), the development of an adequate brain anesthetic partial pressure may be delayed in the case of highly blood-soluble agents, such as ether and methoxyflurane (Table 4-1) [1] . Indeed, the delay in development of an anesthetizing cerebral partial pressure contributed to the elimination of such highly blood-soluble agents from anesthetic practice. Even the moderate solubility of enflurane, isoflurane, or halothane would slow induction of anesthesia with these agents were it not for the use of anesthetic overpressure--that is, we compensate for the uptake of anesthetic by delivering a higher concentration than we hope to achieve in the alveoli. For example, on induction of anesthesia, we may use 4 to 5 percent halothane to produce an alveolar concentration of 1 percent. The use of overpressure can eliminate differences among anesthetics that otherwise would result as a consequence of differences in solubility. For example, induction of anesthesia with 5 percent halothane is essentially as rapid as induction with 8 percent sevoflurane, despite a nearly fourfold greater solubility of halothane. [2]

TABLE 4-1 -- Partition Coefficients at 37°C

ANESTHETIC	BLOOD/GAS	BRAIN/BLOOD	LIVER/BLOOD	KIDNEY/BLOOD	MUSCLE/BLOOD	FAT/BLOOD
Desflurane	0.45	1.3	1.4	1.0	2.0	27
Nitrous oxide	0.47	1.1	0.8	--	1.2	2.3
Sevoflurane	0.65	1.7	1.8	1.2	3.1	48
Isoflurane	1.4	1.6	1.8	1.2	2.9	45
Enflurane	1.8	1.4	2.1	--	1.7	36
Halothane	2.5	1.9	2.1	1.2	3.4	51
Diethyl ether	12	2.0	1.9	0.9	1.3	5
Methoxyflurane	15	1.4	2.0	0.9	1.6	38

Data from Eger et al, [1] [81] [83] [86] [87] Cromwell and Eger, [82] Yasuda et al, [84] and Lerman et al [85]

Cardiac Output

The effect of altering cardiac output is intuitively obvious. A greater passage of blood through the lungs removes more anesthetic and thereby lowers the alveolar anesthetic concentration. To the beginning student of uptake and distribution, this may appear to produce a conflict. It would seem that if more agent were taken up and delivered more rapidly to the tissues, the tissue anesthetic partial pressure should rise more rapidly. In one sense this is true: an increase in cardiac output does hasten the equilibration of tissue anesthetic partial pressure with the partial pressure in arterial blood. [3] What this reasoning ignores is the fact that the anesthetic partial pressure in arterial blood is lower than it would be if cardiac output were normal.

The effect of a change in cardiac output is analogous to the effect of a change in solubility. As already noted, doubling solubility doubles the capacity of the same volume of blood to hold anesthetic. Doubling cardiac output also would double capacity, but in this case by increasing the volume of blood exposed to anesthetic.

The Alveolar to Venous Anesthetic Gradient

The alveolar to venous anesthetic partial pressure difference results from tissue uptake of anesthetic. Were there no tissue uptake, the venous blood returning to the lungs would contain as much anesthetic as it had when it left the lungs as arterial blood. That is, the alveolar (which equals arterial) to venous partial pressure difference would be zero. The presumption that alveolar and arterial anesthetic partial pressures are equal is reasonable in normal patients who have no barrier to diffusion of anesthetic from alveoli to pulmonary capillary blood and who do not have ventilation/perfusion ratio abnormalities. Later, we shall consider the effect of ventilation/perfusion ratio abnormalities on anesthetic uptake.

The factors that determine the fraction of anesthetic removed from blood traversing a given tissue parallel the factors that govern uptake at the lungs: tissue solubility, tissue blood flow, and arterial to tissue anesthetic partial pressure difference. Again, uptake is the product of these three factors. If any one factor approaches zero, uptake by that tissue becomes inconsequential. The succeeding paragraphs discuss the characteristics of each of these factors and then how uptake by individual tissues can be summed to give the venous component of the alveolar to venous anesthetic partial pressure difference.

Blood/gas partition coefficients span a range of values extending from 0.45 for desflurane to 15 for methoxyflurane (see Table 4-1) . In contrast, tissue/blood partition coefficients (i.e., tissue solubility) for lean tissues are close to 1, ranging from slightly less than 1 to a maximum of 3.4 (see Table 4-1) --that is, different lean tissues do not have greatly different capacities per milliliter of tissue. Put another way, a given anesthetic has roughly the same affinity for lean tissues and blood. As with blood/gas partition coefficients, tissue/blood partition coefficients define the concentration ratio of anesthetic at equilibrium. For example, a halothane brain/blood partition coefficient of 1.9 means that 1 mL of brain can hold 1.9 times as much halothane as 1 mL of blood having the same halothane partial pressure.

Lean tissues differ in the volume of tissue relative to the volume of blood passing that tissue. A larger volume of tissue relative to flow has two implications. First, the large tissue capacity increases the transfer of anesthetic from blood to tissue. Second, it takes longer to fill up a tissue with a large capacity (i.e., it takes longer for the tissue to equilibrate with the anesthetic partial pressure being delivered in arterial blood). That is, a large tissue volume relative to blood flow sustains the arterial to tissue anesthetic partial pressure difference (and hence uptake) for a longer time. With its high perfusion per gram, brain equilibrates rapidly with the anesthetic partial pressure brought to it in arterial blood. Per milliliter of tissue, muscle has about one-twentieth the perfusion of brain, and thus muscle takes about 20 times as long as brain to equilibrate. Uptake of anesthetic by muscle continues long after uptake by brain has ceased.

Fat has a tissue/blood coefficient that is significantly greater than 1, particularly for more potent anesthetics (see Table 4-1) . Fat/blood coefficients range from 2.3 (nitrous oxide) to 51 (halothane) to 61 (methoxyflurane). That is, each milliliter of fat tissue contains 2.3 times more nitrous oxide or 51 times as much halothane than a milliliter of blood having the same nitrous oxide or halothane partial pressure. This enormous capacity of fat for anesthetic means that most of the anesthetic contained in the blood perfusing fat is transferred to the fat. Although most of the anesthetic moves from the blood that perfuses fat into the fat, the anesthetic partial pressure in that tissue rises very slowly. Both the large capacity of fat and the low perfusion per milliliter of tissue prolong the time required to narrow the anesthetic partial pressure difference between arterial blood and fat.

Tissue Groups

The algebraic sum of uptake by individual tissues determines the alveolar to venous partial pressure difference and hence the uptake at the lungs. However, we do not need to analyze the effect of individual tissues to arrive at the algebraic sum; instead, we can group tissues in terms of their perfusion and solubility characteristics (i.e., in terms of those features that define the duration of a substantial arterial to tissue anesthetic partial pressure difference). Four tissue groups result from such an analysis (Table 4-2) . [1]

The vessel-rich group (VRG) is composed of the brain, heart, splanchnic bed (including liver), kidney, and endocrine glands. These organs make up less than 10 percent of the body weight but receive 75 percent of the cardiac output. This high perfusion confers several features. Access to a large flow of blood permits the VRG to take up a relatively large volume of anesthetic in the earliest moments of induction. However, the small volume of tissue relative to perfusion produces a rapid equilibration of this tissue group with the anesthetic delivered in arterial blood. The time to half equilibration (i.e., the time at which the VRG anesthetic partial pressure equals half that in arterial blood) varies from about 1 minute for nitrous oxide to 2 minutes for halothane. The longer time to equilibration with halothane results from its higher tissue/blood partition coefficients (see Table 4-1) . Equilibration of the VRG with the anesthetic partial pressure in arterial blood is over 90 percent complete in 4 to 8

TABLE 4-2 -- Tissue Group Characteristics

	VESSEL-RICH	GROUP		*VESSEL-POOR*
		MUSCLE	*FAT*	
Percentage of body mass	10	50	20	20
Perfusion as percentage of cardiac output	75	19	6	0

Adapted from Eger [1]

minutes. Thus, after 8 minutes, uptake by the VRG is too small (i.e., the arterial to VRG anesthetic partial pressure difference is too small) to significantly influence the alveolar concentration. For a substantial period after 8 minutes, uptake is principally determined by the muscle group.

Muscle and skin, which make up the muscle group, have similar blood flow and solubility (lean tissue) characteristics. The lower perfusion (about 3 mL of blood per 100 mL of tissue per minute) sets this group apart from the VRG (70 mL per 100 mL per minute). Although about half of the body bulk is muscle and skin, this volume receives only 1 L/min blood flow at rest. That is, this tissue group receives one-quarter the amount of anesthetic delivered to the VRG and initially takes up only approximately one-quarter as much anesthetic. The large bulk relative to perfusion means two things: (1) during induction, most of the anesthetic delivered to the muscle group is removed from the muscle group blood flow, and (2) the muscle group continues to remove anesthetic from its blood supply for a long time. The time to half equilibration ranges from 20 to 25 minutes (nitrous oxide) to 70 to 80 minutes (sevoflurane or halothane). Thus, long after equilibration of the VRG has taken place, muscle continues to take up substantial amounts of anesthetic. This tissue approaches equilibration in 2 to 4 hours.

Once equilibration of muscle is complete, only fat (i.e., the fat group) continues to serve as an effective depot for uptake. In a normal lean patient, fat occupies one-fifth of the body bulk and receives a blood flow of about 400 mL/min (i.e., the perfusion per 100 mL of fat nearly equals the perfusion per 100 mL of resting muscle). Thus, during the initial delivery of anesthetic to tissues, fat has access to only 40 percent of the anesthetic that is delivered to the muscle group (i.e., blood blow to the fat group is 40 percent of that to the muscle group). Fat also differs from muscle in its higher affinity for anesthetic, a property that greatly lengthens the

time over which it absorbs anesthetic. The half-time to equilibration of fat ranges from 70 to 80 minutes for nitrous oxide to 30 hours for sevoflurane and halothane. Equilibration with fat does not occur in the course of an ordinary halothane or enflurane anesthetic.

One tissue group, the vessel-poor group, remains to be defined. This group consists of ligaments, tendons, bone, and cartilage (i.e., those lean tissues that have little or no perfusion). The absence of a significant blood flow means that this group does not participate in the uptake process despite the fact that it makes up one-fifth of the body mass.

Synthesis of the Factors Governing the Rise of the F_A/F_I Ratio

We may now consider the combined impact of ventilation, solubility, and distribution of blood flow on the development of the alveolar anesthetic partial pressure. The initial rate of rise of F_A/F_I is rapid for all agents, regardless of their solubility (Fig. 4-2) [4] [5] . The rapidity of this upswing results from the absence of an alveolar to venous anesthetic partial pressure difference (there is no anesthetic present in the lung to create a gradient) and hence the absence of uptake in the first moment of induction. Thus, the effect of ventilation to generate a sudden rise in F_A/F_I is unopposed. Obviously, delivery of more and more anesthetic to the alveoli by ventilation produces a progressively greater alveolar to venous partial pressure difference. The resulting increase in uptake increasingly opposes the effect of ventilation to drive the alveolar concentration upwards. Ultimately, a rough balance is struck between the input by ventilation and the removal by uptake. The height of the F_A/F_I ratio at which the balance is struck depends on the solubility factor in the uptake equation (see equation for anesthetic uptake, earlier). A higher solubility produces a greater uptake for a given alveolar to venous partial pressure difference. Hence, the initial rapid rise in F_A/F_I is halted at a lower level with a more soluble agent. This results in the first "knee" in the curve--higher for desflurane than for sevoflurane, higher for sevoflurane than for isoflurane, and higher for isoflurane than for halothane. The position of nitrous oxide is discussed later (see The Concentration Effect).

The balance struck between ventilation and uptake does not remain constant. F_A/F_I continues to rise, albeit at a slower rate than seen in the first minute. This rise results from the progressive decrease in uptake by the VRG, a decrease to an inconsequential amount after 8 minutes. Thus, by about 8 minutes, three-quarters of the cardiac output returning to the lungs (i.e., the blood from the VRG) contains

Figure 4-2 The rise in alveolar (F_A) anesthetic concentration toward the inspired (F_I) concentration is most rapid with the least soluble anesthetics, nitrous oxide and desflurane, and slowest with the most soluble anesthetic, halothane. All data are from human studies. *(Data from Yasuda et al [1] [2])*

nearly as much anesthetic as it had when it left the lungs. The consequent rise in venous anesthetic partial pressure decreases the alveolar to venous partial pressure difference and hence the uptake, allowing ventilation to drive the alveolar concentration upward to the second knee at roughly 8 minutes.

With the termination of effective uptake by the VRG, muscle and fat become the principal determinants of tissue uptake. The slow rate of change of the anesthetic partial pressure difference between arterial blood and muscle or fat produces the relatively stable terminal portion of each curve in Figure 4-1 (Figure Not Available) . In fact, this terminal portion gradually ascends as muscle and, to a lesser extent, fat progressively equilibrate with the arterial anesthetic partial pressure. If the graphs were extended for several hours, a third knee would be found that indicates equilibration of the muscle group. Uptake after that time would principally depend on the partial pressure gradient between arterial blood and fat.

The Concentration Effect

The aforementioned analysis ignores the impact of the concentration effect on F_A/F_I. The inspired anesthetic concentration influences both the alveolar concentration that may be attained and the rate at which that concentration may be attained. [6] [7] Increasing the inspired concentration accelerates the rate of rise. At an inspired concentration of 100 percent, the rate of rise is extremely rapid because it is dictated solely by the rate at which ventilation washes gas into the lung; that is, at 100 percent inspired concentration, uptake no longer limits the level to which F_A/F_I may rise. The cause of this extreme effect is readily perceived. At 100 percent inspired concentration, the uptake of anesthetic creates a void, which draws gas down the trachea. This additional inspiration replaces the gas taken up. Because the concentration of the replacement gas is 100 percent, uptake cannot modify the alveolar concentration. This explains why the rise of nitrous oxide shown in Figure 4-2 is more rapid than the rise of desflurane, despite the identity of their blood/gas partition coefficients.

The concentration effect results from two factors, a concentrating effect and an augmentation of inspired ventilation. [8] Both are illustrated in Figure 4-3 (Figure Not Available) . The first rectangle represents a lung containing 80 percent nitrous oxide. If half of this gas is taken up, the residual 40 volumes of nitrous oxide exist in a total of 60 volumes, yielding a concentration of 67 percent Figure 4-3 (Figure Not Available) A. That is, uptake of half the nitrous oxide does not halve the concentration, because the remaining gases are "concentrated" in a smaller volume. If the void created by uptake is filled by drawing more gas into the lungs (an augmentation of inspired ventilation), the final concentration equals 72 Figure 4-3 (Figure Not Available) B.

This explanation has been criticized as overly simplistic, as ignoring the realities of some aspects of ventilation. [9] For example, if ventilation is controlled with a volume-limited respirator, an augmentation in inspired ventilation is limited to the period of the expiratory pause. If ventilation is spontaneous, this limitation is minimized. In any event, the reader needs to be aware that although Figure 4-3 (Figure Not Available) describes the basic factors governing the concentration (and second gas effects--see later), the actual situation is more complex.

The impact of the concentration effect on F_A/F_I may be thought of as identical to the impact of a change in solubility [10] ; as the inspired concentration increases, the effective solubility decreases. Thus, at 50 percent inspired nitrous oxide, the F_A/F_I rises as rapidly as the F_A/F_I of an anesthetic that has half the solubility of nitrous oxide and is given at 1 percent inspired concentration, and 75 percent inspired nitrous oxide acts as does an anesthetic given at 1 percent that has one-quarter the solubility of nitrous oxide.

The Second Gas Effect

The factors that govern the concentration effect also influence the concentration of any gas given concomitantly. [8] [11] This second gas effect applies to halothane or enflurane when it is administered with nitrous oxide. The loss of volume associated with the uptake of nitrous oxide concentrates the halothane or enflurane (see Fig. 4-3 (Figure Not Available) A). Replacement of the gas taken up by an increase in inspired ventilation augments the amount of halothane or enflurane present in the lung (see Fig. 4-3 (Figure Not Available) B).

Both the concentration effect and the second gas effect were demonstrated by the following experiments. [11] Dogs were given 0.5 percent halothane in either 10 percent nitrous oxide or 70 percent nitrous oxide. The F_A/F_I for nitrous oxide rose more rapidly when 70 percent nitrous oxide was inspired than when 10 percent was inspired (the concentration effect) (Fig. 4-4) (Figure Not Available) . Similarly, the F_A/F_I ratio for halothane rose more rapidly when 70 percent nitrous oxide

Figure 4-3 (Figure Not Available) The rectangle to the left represents a lung filled with 80% nitrous oxide plus 1% of a second gas. (A) Uptake of half the nitrous oxide does not halve the concentration of nitrous oxide, and the reduction in volume thereby increases the concentration of the second gas. (B) Restoration of the lung volume by addition of gas at the same concentration as that contained in the left-most rectangle will increase the nitrous oxide concentration and add to the amount of the second gas present in the lung. *(Modified from Stoelting and Eger [6])*

Figure 4-4 (Figure Not Available) In dogs, administration of 70% nitrous oxide produces a more rapid rise in the F_A/F_I ratio of nitrous oxide than administration of 10% (concentration effect, upper two curves). The F_A/F_I ratio for 0.5% halothane rises more rapidly when given with 70% nitrous oxide than when given with 10% (second gas effect, lower two curves). *(Modified from Epstein et al [11])*

was inspired than when 10 percent was inspired (second gas effect).

Percutaneous Anesthetic Loss

I have ignored three possible avenues by which anesthetics may be lost: (1) transcutaneous movement, (2) transvisceral movement, and (3) metabolism. Although transcutaneous movement occurs, the movement is small. [12] [13] [14] [15] The greatest loss per alveolar anesthetic percent occurs with nitrous oxide. Loss of nitrous oxide might equal 5 to 10 mL/min with an alveolar concentration of 70 percent. The movement of anesthetic across visceral or pleural surfaces during abdominal or pulmonary surgery is larger than the movement across skin, but such visceral losses are usually small relative to total uptake. [16]

Metabolism of Anesthetic

Although percutaneous loss of anesthetic may not appreciably affect anesthetic uptake, loss of anesthetic by biodegradation can produce significant changes, particularly with agents that undergo extensive biodegradation. Berman et al [17] found that phenobarbital pretreatment in rats decreased the arterial level of methoxyflurane. Carpenter et al [18] found biodegradation of as much as half of the halothane and three-quarters of the methoxyflurane that was taken up. They speculated that this biodegradation could explain the finding that the alveolar concentration of halothane decays more rapidly on recovery from anesthesia than the alveolar concentration of isoflurane, an anesthetic that is significantly less soluble in blood. [19] [20] Two reasons suggest that agents such as isoflurane and desflurane are less likely to be affected: first, they are not metabolized as readily as halothane or methoxyflurane, [21] [22] and second, anesthetizing concentrations appear to saturate the enzymes responsible for anesthetic metabolism. [23] Saturation of enzymes particularly may limit the impact of metabolism during the washin as opposed to the washout of anesthetic. The combined effect of these factors remains to be determined, but it appears that metabolism is not a significant determinant of F_A/F_I during anesthesia with isoflurane or desflurane. [4] [5] A small influence on the kinetics of sevoflurane may exist, explaining why there is a more substantial difference between the F_A/F_I for desflurane versus sevoflurane during induction and maintenance of anesthesia than for the parallel washout curves (F_A/F_{AO}) during recovery. [24]

Intertissue Diffusion

Carpenter et al [19] [20] examined the washin and washout of isoflurane, enflurane, halothane, and methoxyflurane given simultaneously for fixed periods of time to healthy young patients. Washout was examined for several days after discontinuation of anesthetic administration. Analysis suggested that a model with five compartments best explained the resulting data for all the anesthetics (i.e., the model was independent of solubility and anesthetic metabolism). The half-times of four of these compartments were consistent with the model used earlier in this chapter. Thus, these compartments could be related to washin and washout of the lungs, the VRG, the muscle group, and the fat group.

However, an additional important compartment was more difficult to explain. This compartment had a half-time of roughly 300 minutes, which is between those for muscle and for fat. This additional compartment, which was important because it accounted for almost one-third of the anesthetic taken up, could in part be explained by uptake by highly perfused fat, such as that found in bone marrow. However, the perfusion of such tissue is not sufficient to account for the major portion of uptake by this compartment. Carpenter et al [19] [20] speculated that this uptake resulted from diffusion of anesthetic from lean tissue to an adjacent thin layer of fat tissue. Such diffusion could be from the heart to pericardial fat, from the kidney to perirenal fat, from the intestine to mesenteric and omental fat, and from the dermis to subcutaneous fat. Yasuda et al [4] [5] confirmed these findings, extending them to desflurane and sevoflurane.

FACTORS MODIFYING THE RATE OF RISE OF F_A/F_I

Alteration of those factors that govern the rate of delivery of anesthetic to the lungs or its removal from the lungs alters the alveolar concentration of anesthetic. We have seen the importance of differences in solubility (see Fig. 4-2) . The succeeding sections examine the impact of differences in ventilation and circulation and the interaction of these differences with factors such as solubility.

The Effect of Ventilatory Changes

By augmenting delivery of anesthetic to the lungs, an increased ventilation accelerates the rate of rise of F_A/F_I [1] [25]

Figure 4-5 (Figure Not Available) The F_A/F_I ratio rises more rapidly if ventilation is increased. Solubility modifies this impact of ventilation: the effect on the anesthetizing partial pressure is greatest with the most soluble anesthetic (ether) and least with the least soluble anesthetic (nitrous oxide). *(Modified from Eger [9])*

(Fig. 4-5) (Figure Not Available) . A change in ventilation produces a greater relative change in F_A/F_I with a more soluble anesthetic. In Figure 4-5 (Figure Not Available) , an increase in ventilation from 2 to 8 L/min triples the ether concentration at 10 minutes, only doubles the halothane concentration, and scarcely affects the nitrous oxide concentration.

The impact of solubility may be explained as follows. With a poorly soluble agent, such as nitrous oxide, the rate of rise of F_A/F_I is rapid, even with hypoventilation. Because F_A normally cannot exceed F_I, there is little room for an augmentation of ventilation to increase F_A/F_I. With a highly soluble agent, such as ether and methoxyflurane, most of the anesthetic delivered to the lungs is taken up, so that if the uptake at 2 L/min ventilation equaled X, the uptake at 4 L/min would approach 2X. Thus, if cardiac output is held constant, ventilation of 4 L/min produces an arterial ether concentration that is nearly twice the concentration produced by a ventilation of 2 L/min. Because arterial and alveolar concentrations are in equilibrium, our example suggests that doubling ventilation must nearly double the concentration of a highly soluble anesthetic in lung or blood.

These observations imply that imposed alterations in ventilation (e.g., an increase produced by conversion from spontaneous to controlled ventilation) produce greater changes in anesthetic effect with more soluble agents. Because such effects include both anesthetic depth and depression of circulation, greater caution must be exercised when ventilation is augmented during anesthesia produced with a highly soluble agent.

Anesthetics themselves may alter ventilation and thereby alter their own uptake. [3] [26] Modern potent agents (desflurane, enflurane, halothane, isoflurane, sevoflurane) are profound respiratory depressants, whose depression of ventilation is inversely related to anesthetic dose. [27] [28] [29] [30] [31] At some dose, all inhaled anesthetics probably produce apnea, a feature that must limit the maximum alveolar concentration that can be obtained if ventilation is spontaneous.

Thus, administration of an anesthetic concentration that produces significant respiratory depression progressively decreases delivery of anesthetic to the alveoli. [3] [32] As a result, doubling the inspired concentration does not double the alveolar concentration attained at a given point in time. At high inspired concentrations, further increases in inspired concentration produce little absolute change in the alveolar concentration (Fig. 4-6) (Figure Not Available) . Anesthetics can thereby

Figure 4-6 (Figure Not Available) An increase in inspired halothane concentration does not produce a proportional increase in the alveolar concentration because of the progressively greater depression of ventilation which occurs as alveolar halothane is increased. The initial "overshoot" seen with 10 to 20% inspired halothane results from the delay in the transfer of alveolar halothane partial pressure to the brain. *(From Munson et al [5])*

exert a negative feedback effect on their own alveolar concentration, an effect that increases the safety of spontaneous ventilation by limiting the maximum concentration that is attained in the alveoli.

The Effect of Changes in Cardiac Output

The discussion in the previous section assumed a constant cardiac output and examined the effect of changes in ventilation. In this section, the reverse process is discussed. An increase in cardiac output augments uptake and thereby hinders the rise in F_A/F_I. [1] [33] As with a change in ventilation, a change in cardiac output scarcely affects the alveolar concentration of a poorly soluble agent; the alveolar concentration of a highly soluble agent is much more influenced (Fig. 4-7) (Figure Not Available) . The reason for the impact of a change in solubility is similar to the reason explaining the effect of a change in ventilation. A decrease in cardiac output can do little to increase the F_A/F_I ratio of a poorly soluble agent because the rate of rise is rapid at any cardiac output. In contrast, nearly all of a highly soluble agent is taken up, and a halving of blood flow through the lungs must concentrate the arterial (equals alveolar) anesthetic, nearly doubling its partial pressure in the case of an extremely soluble agent.

This effect of solubility suggests that conditions that lower cardiac output (e.g., shock) may produce unexpectedly high alveolar anesthetic concentrations if highly soluble agents are used. The higher F_A/F_I ratio should be anticipated and

Figure 4-7 (Figure Not Available) If unopposed by a concomitant increase in ventilation, an increase in cardiac output will decrease alveolar anesthetic concentration by augmenting uptake. The resulting alveolar anesthetic change is greatest with the most soluble anesthetic. *(Modified from Eger [9])*

the inspired anesthetic concentration lowered accordingly to avoid further depression of circulation. Shock presents a two-pronged problem: (1) an increase in ventilation usually accompanies the circulatory depression, and (2) both an increase in ventilation and a decrease in cardiac output accelerate the rise in F_A/F_I. Perhaps this is why such heavy reliance is placed on the use of nitrous oxide in patients in shock. In contrast to more soluble anesthetics (e.g., halothane), the alveolar concentration of nitrous oxide would be little influenced by the associated cardiorespiratory changes.

Anesthetics also affect circulation. Usually, they depress cardiac output, [34] [35] although stimulation may occur with some agents (e.g., nitrous oxide). In contrast to the negative feedback that results from respiratory depression, circulatory depression produces a positive feedback: depression decreases uptake, and this increases the alveolar concentration, which in turn further decreases uptake. A potentially lethal acceleration of the rise in F_A/F_I results from the depression of cardiac output (Fig. 4-8) (Figure Not Available) [3] [26] [32] . The impact of this acceleration increases in importance with increasing anesthetic solubility. High inspired concentrations of

agents such as enflurane and halothane should be administered with considerable caution, particularly if ventilation is controlled.

The Effect of Concomitant Changes in Ventilation and Perfusion

The preceding considerations of the effects of ventilatory and circulatory alterations presume that only one of these variables was changed while the other was held constant. In fact, both may change concomitantly. If both ventilation and cardiac output increase proportionately, an intuitive expectation

Figure 4-8 (Figure Not Available) Dogs given a constant ventilation demonstrate different rates of rise of F_A/F_I. The rates of rise depend on the inspired halothane concentration. The two higher concentrations accelerated the rate of rise by depressing cardiac output and thereby decreasing uptake. *(Modified from Gibbons et al [32])*

Figure 4-9 (Figure Not Available) Proportional increases in alveolar ventilation (VA) and cardiac output (Q) will increase the rate at which F_A/F_I rises. As indicated in the illustration, the effect is relatively small if the increase in cardiac output is distributed proportionately to all tissues (i.e., if cardiac output is doubled, all tissue blood flows are doubled). The greatest effect occurs with the most soluble anesthetic. *(From Eger et al [36])*

might be that F_A/F_I would be little altered. After all, uptake equals the product of solubility, the cardiac output, and the alveolar to venous anesthetic partial pressure difference (see anesthetic uptake equation, earlier). In the absence of other changes, doubling cardiac output doubles uptake, and this should exactly balance the influence of doubling of ventilation on F_A/F_I. That is, a doubling of both delivery of anesthetic to the lungs and removal of anesthetic from the lungs should produce no net change in the alveolar concentration.

This reasoning ignores one other factor in the equation that defines uptake. By accelerating the rate at which tissue equilibration occurs, an increase in cardiac output accelerates the narrowing of the alveolar to venous partial pressure difference [36] and thereby reduces the impact of the increase in cardiac output on uptake. Thus, a proportional increase in ventilation and cardiac output increases the rate of rise of F_A/F_I.

The magnitude of the acceleration of rise in F_A/F_I depends in part on distribution of the increase in cardiac output. If the increase is distributed proportionately to all tissues (e.g., if a doubling of output doubles flow to all tissues), the increase is fairly small (Fig. 4-9) (Figure Not Available) [36] [37] . Thus, conditions such as hyperthermia and thyrotoxicosis would only slightly influence the development of an anesthetizing anesthetic concentration through their influence on F_A/F_I. However, if the increase in cardiac output is diverted to the VRG, a greater effect is seen. Perfusion of the VRG is normally high and results in rapid equilibration. Further increases in perfusion only hasten the rate of equilibration. Because blood returning from the VRG soon has the same partial pressure as it had when it left the lungs, it cannot remove more anesthetic from the lungs. Thus, after a few seconds or minutes, the increase in ventilation is not matched, even in part, by an increase in uptake. The result is a considerable acceleration in the rise in F_A/F_I. This effect may be seen in a comparison of the F_A/F_I curves for children and adults (Fig. 4-10) (Figure Not Available) . Children (especially infants) have a relatively greater perfusion of the VRG and consequently show a significantly faster rise in F_A/F_I (Ch. 59) . [38] A clinical result of this accelerated rise is a more rapid development of anesthesia in young patients. The higher perfusion of the brain further accelerates the development of anesthesia.

Ventilation/Perfusion Ratio Abnormalities

Up to this point, I have assumed that alveolar and arterial anesthetic partial pressures are equal (i.e., that the alveolar gases completely equilibrate with the blood passing through the lungs). For normal patients, this assumption is approximately

Figure 4-10 (Figure Not Available) The alveolar rate of rise of halothane is more rapid in children (upper curve) than in adults (lower curve.) The difference probably results from the greater ventilation and perfusion per kilogram of tissue in children and the fact that a disproportionate amount of the increased perfusion is devoted to the vessel-rich group. *(Modified from Salanitre and Rackow [38])*

correct, but diseases such as emphysema and atelectasis, as well as congenital cardiac defects, produce substantial deviations from equilibration. The associated ventilation/perfusion ratio abnormality does two things: (1) increases the alveolar (end-tidal) anesthetic partial pressure and (2) decreases the arterial anesthetic partial pressure (i.e., a partial pressure difference appears between alveolar gas and arterial blood). The relative change depends on the solubility of the anesthetic. With a poorly soluble agent, the end-tidal concentration is slightly increased, but the arterial partial pressure is significantly reduced. The opposite occurs with a highly soluble anesthetic. [39]

The considerable decrease in the arterial anesthetic partial pressure that occurs with poorly soluble agents may be explained as follows. Ventilation/perfusion ratio abnormalities increase ventilation relative to perfusion of some alveoli, whereas in other alveoli, the reverse occurs. With a poorly soluble anesthetic, an increase in ventilation relative to perfusion does not appreciably increase alveolar or arterial anesthetic partial pressure issuing from those alveoli (see effect for nitrous oxide in Fig. 4-5) (Figure Not Available) . However, when ventilation decreases relative to perfusion, a significant effect can occur, particularly when ventilation is absent, as in a segment of atelectatic lung. Blood emerges from that segment with no additional anesthetic. Such anesthetic-deficient blood then mixes with the blood from the ventilated segments containing a normal complement of anesthetic. The mixture produces an arterial anesthetic partial pressure that is considerably below normal.

With highly soluble agents, a different situation results from similar ventilation/perfusion ratio abnormalities. In alveoli receiving more ventilation relative to perfusion, the anesthetic partial pressure rises to a higher level than usual (see Fig. 4-5 (Figure Not Available) for effect with diethyl ether). That is, blood issuing from these alveoli has an increased anesthetic content, the increase being nearly proportional to the increased ventilation. Assuming that overall (total) ventilation remains normal, this increase in the anesthetic contained by blood from the relatively hyperventilated alveoli compensates for the lack of anesthetic uptake in unventilated alveoli.

These effects are illustrated in Figure 4-11 (Figure Not Available) for a condition that may be iatrogenically produced, endobronchial intubation. Because all ventilation now is directed to the intubated lung, this lung is hyperventilated relative to perfusion. F_A/F_I for this lung is slightly increased (above that obtained in the absence of endobronchial intubation) with the poorly soluble cyclopropane and greatly increased with the highly soluble ether. As indicated earlier, the increase with ether compensates for the absence of uptake from the unventilated lung, a compensatory mechanism that is not available with cyclopropane. The result is that the cyclopropane arterial partial pressure is well below normal, whereas the ether arterial partial pressure is scarcely changed.

These concepts have been confirmed experimentally by comparing the rate of arterial anesthetic rise with and without endobronchial intubation in dogs. [40] Endobronchial intubation significantly slowed the arterial rate of rise of cyclopropane but did not influence the rise with methoxyflurane. An intermediate result was obtained with halothane (Fig. 4-12) (Figure Not Available) . These data suggest that in the presence of ventilation

Figure 4-11 (Figure Not Available) When no ventilation/perfusion abnormalities exist, the alveolar (P_A or P_{ET}) and arterial (Pa) anesthetic partial pressures rise together (continuous lines) toward the inspired partial pressure (P_I). When 50% of the cardiac output is shunted through the lungs, the rate of rise of the end-tidal partial pressure (dashed lines) is accelerated while the rate of rise of the arterial partial pressure (dot-dashed lines) is retarded. The greatest retardation is found with the least soluble anesthetic, cyclopropane. *(From Eger and Severinghaus [39])*

/perfusion ratio abnormalities, the anesthetic effect of agents such as nitrous oxide, desflurane, and sevoflurane may be delayed more than the anesthetic effect of isoflurane or halothane.

Figure 4-12 (Figure Not Available) In dogs, when only the right lung was ventilated, the rise of the very soluble anesthetic methoxyflurane in arterial blood was normal (i.e., did not deviate from control), while the rise for the poorly soluble anesthetic cyclopropane was significantly slowed. *(From Stoelting and Longnecker [40])*

/das/book/view/29494766/875/40.html

THE EFFECT OF NITROUS OXIDE ON CLOSED GAS SPACES

Volume Changes in Highly Compliant Spaces

During the course of anesthetic administration, appreciable volumes of nitrous oxide can move into closed gas spaces. Although this transfer does not influence F_A/F_I, it may have important functional consequences. There are two types of closed gas spaces in the body, those enclosed by compliant walls and those enclosed by noncompliant walls. The former (bowel gas, pneumothorax, or pneumoperitoneum) are subject to changes in volume secondary to the transfer of nitrous oxide into these spaces. [41] These spaces normally contain nitrogen (from air), a gas whose low solubility (blood/gas partition coefficient, 0.015) limits its removal by blood. Thus, the entrance of nitrous oxide (whose solubility permits it to be carried by blood in substantial quantities) is not countered by an equal loss, and the result is an increase in volume. The theoretical limit to the increase in volume is a function of the alveolar nitrous oxide concentration, because it is this concentration that is ultimately achieved in the closed gas space. That is, at equilibrium, the partial pressure of nitrous oxide in the closed gas space must equal its partial pressure in the alveoli. An alveolar concentration of 50 percent might double the gas space volume, and a 75 percent concentration might produce a fourfold increase.

These theoretic limits may be approached if equilibrium is rapidly achieved, as with pneumothorax or gas emboli. Administration of 75 percent nitrous oxide in the presence of a pneumothorax may double the pneumothorax volume by 10 minutes and may triple it by 30 minutes (Fig. 4-13) (Figure Not Available) [41] . This increase in volume may seriously impair

Figure 4-13 (Figure Not Available) The volume of a pneumothorax created by air injection is little affected when oxygen subsequently is breathed (filled triangle and circles). However, if 75% nitrous oxide is breathed, the volume doubles in 10 minutes and triples in a half-hour (open circles, squares, and triangles). *(From Eger and Saidman [41])*

cardiorespiratory function, [42] and the use of nitrous oxide is contraindicated in the presence of a significant pneumothorax.

A still more rapid expansion of volume occurs if air is inadvertently allowed to enter the blood stream in a patient anesthetized with nitrous oxide. Expansion may be complete in seconds rather than minutes. Munson and Merrick [43] demonstrated that the lethal volume of an air embolus was decreased in animals breathing nitrous oxide as opposed to air (Fig. 4-14) (Figure Not Available) . The difference could be entirely explained by expansion of the embolus in the animals breathing nitrous oxide (i.e., the predicted total volume of air plus nitrous oxide in the embolus equaled the volume of air needed to produce death in animals breathing only air). These studies suggest caution in the use of nitrous oxide for procedures in which air embolization is a risk (e.g., posterior fossa craniotomies, laparoscopy). They also suggest that if air embolization is suspected, nitrous oxide administration should be immediately discontinued. Conversely, a nitrous oxide "challenge" may be used to test whether air embolization has occurred. [44]

The endotracheal tube cuff normally is filled with air. It, too, is susceptible to expansion by nitrous oxide [45] ; the presence of 75 percent nitrous oxide surrounding such a cuff can double or triple the volume of the cuff. The result may be an unwanted increase in pressure exerted on the tracheal mucosa. Similarly, nitrous oxide may expand the cuffs of balloon-tipped (e.g., Swan-Ganz) catheters [46] [47] when the balloons are inflated with air. The expansion is rapid, and a doubling of volume may occur within 10 minutes.

Figure 4-14 (Figure Not Available) An air embolus equaling 0.55 mL/kg killed 50% of rabbits breathing oxygen. If the inspired gas mixture contained 75% nitrous oxide, only 0.16 mL/kg was required to kill half the animals. *(Modified from Munson and Merrick [43])*

Pressure Changes in Poorly Compliant Spaces

Pressure can be produced by the entrance of nitrous oxide into gas cavities surrounded by poorly compliant walls. Unwanted increases in intraocular pressure may be imposed by nitrous oxide administration after intravitreal sulfur hexafluoride injection. [48] Other examples include the gas space created by pneumoencephalography (now rare as a deliberate procedure) and the natural gas space in the middle ear. Pressures in the head or middle ear may rise by 20 to 50 mm Hg owing to the ingress of nitrous oxide at a faster rate than air can be removed. [49] [50] Recognition of this problem has decreased the use of nitrous oxide for tympanoplasty because the increased pressure may displace the graft. Increase in middle ear pressure may cause adverse postoperative effects on hearing. [51] The capacity of nitrous oxide to expand the gas in the middle ear has also been used to elevate an adherent atelectatic tympanic membrane off the promontory and the ossicles. [52]

ANESTHETIC CIRCUITRY

The previous discussions generally considered that the alveolar anesthetic concentration (F_A) was moving toward a constant inspired anesthetic concentration (F_I). In practice, the inspired concentration is usually not constant, because a nonrebreathing system is not used. The rebreathing that results from the use of an anesthetic circuit causes the inspired concentration to be less than that in the gas delivered from the anesthetic machine. The inspired concentration thus is influenced by the delivered concentration, by the need to "wash in" the circuit and by the depletion of anesthetic in rebreathed gases produced by uptake of anesthetic.

Washin of the Circuit

To begin anesthesia, anesthetic must be washed into the volume of the circuit. At inflow rates of 1 to 5 L/min and a circuit volume of 7 L (3-L bag, 2-L carbon dioxide absorber, and 2 L of corrugated hoses and fittings), the washin of the circuit is 75 to 100 percent complete in 10 minutes (Fig. 4-15) (Figure Not Available) . Higher inflow rates produce a more rapid rise in the inspired concentration, which suggests that induction can be accelerated and made more predictable by use of high inflow rates.

Figure 4-15 (Figure Not Available) The rate at which the inspired anesthetic concentration (F_{INS}) rises toward the inflowing concentration (F_{INF}) is determined by the inflow rate and circuit volume. In the case illustrated here, the circuit volume is 7 L. *(From Eger [91])*

Anesthetic Loss to Plastic and Soda Lime

Uptake of anesthetic by several depots also constitutes a hindrance to the development of an adequate inspired anesthetic concentration. The rubber or plastic components of the circuit may remove agent [53] [54] this was a significant problem with the obsolete anesthetic methoxyflurane, which has a high solubility in rubber and plastic (Table 4-3) . A minor problem exists for halothane and isoflurane, and no problem results from the solution of nitrous oxide, desflurane, or sevoflurane. [55]

Normal (moist) carbon dioxide absorbents containing 13 to 15 percent water can slightly increase the sevoflurane, and, to a lesser extent, the halothane requirement by degrading each of these anesthetics. [56] Degradation results in the removal of hydrogen fluoride and the production of unsaturated compounds. Nitrous oxide, desflurane, and isoflurane are not materially degraded. For sevoflurane and halothane, degradation is of concern because the unsaturated compounds produced are toxic (e.g., compound A from sevoflurane is nephrotoxic). [57]

TABLE 4-3 -- Rubber/Gas and Plastic/Gas Partition Coefficients

ANESTHETIC	POLYETHYLENE (CIRCUIT TUBE)	RUBBER (BAG)	POLYVINYL CHLORIDE (ENDOTRACHEAL TUBE)	
Nitrous oxide	--	1.2	--	
Desflurane	16	19		35
Sevoflurane	31	29		68
Isoflurane	58	49		114
Enflurane	--	74	--	
Halothane	128	190		233
Methoxyflurane	118	742	--	

Data from Titel and Lowe, [53] Eger et al, [54] [89] Targ et al, [55] and Munson and Eger. [88]

In contrast to normal (moist) carbon dioxide absorbents, desiccated absorbents materially degrade all potent inhaled anesthetics. [58] Degradation of sevoflurane materially increases anesthetic requirement. [59] In addition, dehydration of Baralyme increases compound A production from sevoflurane, but dehydration of soda lime does the opposite. [59] Desiccated absorbents degrade all anesthetics containing the CHF2-O- moiety (i.e., desflurane, enflurane, and isoflurane), the degradation product of concern being carbon monoxide. [58] Degradation by soda lime is minimal at hydrations approximately one-tenth those found in normal soda lime.

The Effect of Rebreathing

Inspired gas actually consists of two gases: that delivered from the anesthetic machine and that previously exhaled by the patient and subsequently rebreathed. Because the patient has removed (taken up) anesthetic from the rebreathed gas, the amount taken up and the amount rebreathed influence the inspired anesthetic concentration. An increase in uptake or rebreathing lowers the inspired concentration of a highly soluble gas more than the inspired concentration of a poorly soluble gas. This effect of uptake can be diminished by decreasing rebreathing, which is accomplished by increasing the inflow rate. With a ventilation of 5 L/min, rebreathing can be essentially abolished by use of a 5-L/min inflow rate. [60]

High inflow rates (i.e., 5 L/min or greater) have the advantage of increasing the predictability of the inspired anesthetic concentration, but they have the disadvantages of being wasteful and of increasing atmospheric pollution. High inflow rates may be unacceptably costly because of the attendant greater consumption of expensive volatile anesthetics. High inflow rates also may result in drier inspired gas and greater difficulty in estimating ventilation from excursions of the rebreathing bag. These several disadvantages lead us to consider techniques that avoid the use of high inflow rates.

/das/book/view/29494766/875/42.html

THE LOW-FLOW OR CLOSED-CIRCUIT TECHNIQUE

Much of the previous discussion assumed the use of a nonrebreathing system and a fixed inspired concentration of anesthetic. Although this approach does not invalidate the principles described earlier, it also does not reflect the variety of approaches applied in practice. Practice often deviates in two ways: (1) most anesthetists use lower inflow (fresh gas flow) rates in order to provide a more economical delivery of anesthesia, and (2) most anesthetists apply a constant alveolar, rather than a constant inspired, concentration because a constant alveolar concentration more closely reflects a constant level of anesthesia.

A low inflow rate results in several advantages and a few disadvantages, the latter particularly applying to kinetics. The advantages of low inflow administration (defined as fresh gas flows of less than half the minute volume, usually less than 3 L/min) or closed-circuit anesthesia (defined as delivery of gases in amounts sufficient to replace the gases--oxygen and anesthetic--removed by the patient) include lower cost, increased humidification, reduced heat loss, decreased release of anesthetic to the environment, and better capacity to assess physiologic variables, such as ventilation. On the debit side, one must be more concerned about oxygen levels (especially if nitrous oxide is used, but the patient also contributes nitrogen from stores in the body, and such nitrogen can slightly decrease the inspired concentration of oxygen), about increasing concentrations of carbon monoxide, and about rebreathing of toxic products from the breakdown of volatile anesthetics. Regarding this last point, carbon dioxide absorbents can degrade both halothane and sevoflurane to toxic unsaturated compounds. [61] [62] However, the debit of most immediate concern is the lack of control that low flows and, especially, closed circuits offer.

Closed-Circuit Anesthesia

The use of a closed circuit represents an extreme of anesthetic administration, one that is infrequently accomplished because few systems completely eliminate leakage of gas from the circuit. Indeed, anesthetists often apply a deliberate leak of approximately 200 mL/min by sampling gases for oxygen, carbon dioxide, and anesthetic analyses.

Usually, closed-circuit anesthesia requires replacement of three gases: (1) oxygen, (2) nitrous oxide, and (3) a potent volatile anesthetic. Each replacement implies somewhat different considerations. Oxygen replacement remains constant unless metabolism changes as a consequence of sympathetic response to stimulation, alteration in body temperature, or shivering. Replacement of nitrous oxide follows a fairly predictable course, in part because the concentration applied does not usually vary. Furthermore, it is the least soluble of anesthetics, especially in fat, and is the most prone to percutaneous loss (a constant value). Of most interest and potential variability are the uptakes of the potent inhaled anesthetics.

Uptake of potent anesthetics may be estimated from the values (constants) obtained by Yasuda et al [4] [5] in human volunteers. These values may be applied to obtain uptake at a constant alveolar concentration. To provide an appropriate level for comparison, I have assumed an alveolar concentration equal to the minimum alveolar concentration (MAC). The resulting figure (Fig. 4-16) reveals parallel shapes for each anesthetic, shapes dictated by the perfusion and solvent characteristics of the three major tissue compartments (plus intertissue diffusion). Thus, a large initial uptake rapidly decreases to a much lower level in 5 to 10 minutes, reflecting the high initial uptake of the VRG (high because of its large perfusion) and the rapid decrease in uptake imposed by a short time constant. The subsequent slower decrease primarily results from the longer time constant of the muscle group, which dominates this period until its uptake declines below that provided by fourth compartment and fat groups.

Although the curves for each anesthetic do not differ in shape, they differ in position. The height of each curve (i.e., uptake) is directly proportional to two factors: (1) solubility and (2) MAC. This relationship tends to minimize differences among anesthetics because solubility and MAC tend

Figure 4-16 The uptake (in milliliters per minute), as illustrated in this graph, resulted from the application of the constants calculated by Yasuda et al [4] [5] from their measurements in human volunteers. The application also assumes that the alveolar concentration equals maximum alveolar concentration (MAC). Uptake is a function of both MAC and solubility of the anesthetic in blood and tissues. Thus, the fivefold higher MAC for desflurane versus isoflurane is offset by a threefold lower solubility, producing less than a twofold difference in uptake at any point in time. Uptake for all anesthetics initially declines rapidly as a function of the rate at which the vessel-rich group equilibrates. The further decline after 5 to 10 minutes is a function of the approach to equilibration of the muscle group. *(Data from Yasuda et al [4] [5]*

to move inversely. For example, although the MAC for desflurane is five times that for isoflurane, its uptake is less than twice that of isoflurane because of its lower solubility in both blood and tissues.

Uptake may be estimated from the "square-root-of-time rule," first proposed by Severinghaus [63] and expanded greatly by Lowe and associates [64] [65] in their classic descriptions of closed-circuit anesthesia. This rule states that uptake at any point in time may be estimated as uptake during the first minute of anesthesia divided by the square root of time in minutes. Making certain assumptions permits an estimate of uptake during the first minute. In general, uptake equals the product of blood solubility, cardiac output, and alveolar to venous anesthetic partial pressure difference. Several sources supply standard values for solubility and cardiac output, and alveolar to venous anesthetic partial pressure difference may be estimated if we determine what alveolar partial pressure we wish and assume that venous anesthetic partial pressure is inconsequential. An inconsequential venous partial pressure is reasonable because no anesthetic can appear in venous blood before recirculation (about a half a minute) and even the anesthetic that appears is small because tissue uptake is maximal during the first minute. Thus, we might estimate isoflurane uptake in a normal adult as 1.4 times 5,400 times 0.0115, or 87 mL, where 1.4 is the blood/gas partition coefficient; 5,400 is a reasonable cardiac output, and 0.0115 is MAC as a fraction of one atmosphere (1 atm). By 4 minutes, uptake would equal 87 mL/2; by 9 minutes 87 mL/3; and by 64 minutes 87 mL/8.

Hendrickx et al [66] questioned the accuracy of the square root of time rule, suggesting that the rule overestimates the decrease in uptake with the passage of time. Eger [67] considered whether the evidence provided by Hendrickx overturns the square root of time rule, and the matter continues to be debated.

Replacement of anesthetic taken up may be accomplished by infusion of liquid anesthetic directly into the anesthetic circuit, either continuously or as boluses. A continuous infusion requires a pump of some sort, and an elegant solution uses a computer to direct a progressive decrease in infusion rate as a function of time. Bolus injection from a syringe has an elegant simplicity but has two disadvantages: (1) the circuit concentration modestly oscillates, and (2) the anesthetist is required to remember when and how much to inject. A further disadvantage accrues to the injection of desflurane by either pump or syringe. The high vapor pressure of desflurane (about 1 atm at room temperature) results in the unpredictable formation of bubbles of desflurane gas and a potential for a marked variability in the rate of infusion or injection, especially when smaller volumes of liquid are to be injected.

An alternative solution to injection of liquid applies a variable bypass (Tec-type) vaporizer, one capable of accurate delivery of a range of concentrations at low inflow rates (e.g., 200 mL/min). This solution may not be applicable in the initial delivery of anesthesia, because the demand for vapor may exceed the capability of presently

available vaporizers. For example, the maximum output of a conventional isoflurane vaporizer is 5 percent, and at a 200 mL/min flow of oxygen, only approximately 10 mL of isoflurane vapor can be produced per minute, far less than the 87 mL estimated earlier. Even after 1 hour of anesthesia, an isoflurane vaporizer is barely capable of meeting the demand for anesthetic (Fig. 4-17 A). This difficulty may be overcome in several ways. If a concentration less than MAC is acceptable, a lesser delivery of vapor is required. Thus, the concurrent use of nitrous oxide decreases the demand on the vaporizer. In addition, the use of nitrous oxide also increases the total fresh gas flow to compensate for the considerable uptake of nitrous oxide. If the fresh gas flow increases to 1,500 mL/min, 79 mL of isoflurane vapor can be produced. Another solution is to select an anesthetic having a vaporizer capability closer to demand. Such a solution tends to be available for less soluble anesthetics. For example, we calculate the uptake for desflurane in the first minute of anesthesia to be 0.45 × 5,400 × 0.06, or 146 mL. At a 200-mL/min flow of oxygen, the 18 percent maximum output of a desflurane vaporizer permits delivery of 44 mL. Although still inadequate to meet demand in the first minute, this figure is 2.6 times closer to meeting that demand than the isoflurane vaporizer, and within 10 minutes, the desflurane vaporizer can supply the required volume (see Fig.4-17 A).

Figure 4-17 A suggests one of the major difficulties associated with the closed-circuit approach, namely, control. Clearly, there is an enormous difference between delivered (i.e., vaporizer dial) and alveolar concentrations. The differences decrease with less soluble anesthetics, but even with an anesthetic such as desflurane and even after the initial high-uptake period is passed, the dialed concentration markedly exceeds the alveolar concentration that it sustains. This means that changes in uptake (e.g., secondary to the increase in cardiac output that may result from surgical stimulation) can cause considerable alterations in alveolar concentration unless the delivered concentration is altered. The alveolar concentration changes for two reasons: (1) assuming

Figure 4-17 (A-D) The ratio of delivered to alveolar concentrations (F_D/F_A) required to sustain the alveolar concentration constant at, for example, MAC, is a function of several factors. First, it is determined by uptake (see Fig. 4-16) . Second, it is determined by rebreathing. Thus, the ratio decreases with increasing inflow rates. Although these graphs have the same shape, notice the progressive decrease in the scale on the ordinate as inflow rate increases. The lowest values for any anesthetic result from a nonrebreathing system (i.e., when the inflow rate equals minute ventilation).

a constant ventilation, the difference between the alveolar and inspired concentrations varies directly with uptake (e.g., a greater uptake increases the difference), and (2) because of the rebreathing, the inspired concentration varies inversely with the uptake (e.g., an increased uptake lowers the inspired concentration). Thus, the sum of these effects either decreases or increases the alveolar concentration. A closed circuit has an inherent element of instability not present in an open circuit.

Low-Flow Anesthetic Delivery

The instability of the closed circuit may be greatly mitigated by the use of low-flow (less than half the minute ventilation) anesthetic delivery. Low-flow delivery may provide most of the advantages of closed systems without the attendant instability while retaining considerable advantages over open systems in economy, maintenance of humidification and temperature, and limited atmospheric pollution. Low-flow delivery also diminishes the disadvantages of the closed circuit in the areas of constancy of oxygen and anesthetic levels and elimination of carbon monoxide and toxic anesthetic breakdown products.

In a low-flow delivery system, two factors control the relationship between the concentration delivered from a vaporizer (F_D) and that in the alveoli (F_A), a relationship that may best be described as the ratio (F_D/F_A) of the two variables. First, we have already seen that uptake governs this ratio in a closed system (see Fig. 4-17 A). Thus, F_D/F_A is higher for more soluble anesthetics, and regardless of solubility, the ratio is highest early in anesthetic administration and decreases rapidly in the first 5 to 10 minutes of anesthesia (as uptake by the VRG of tissues decreases to the point of near-equilibration)

and more slowly thereafter (as uptake by tissue groups with longer time constants, such as muscle, the fourth compartment, and fat decreases).

Second, inflow rate also governs F_D/F_A. The relationship is inverse: the higher the inflow rate, the lower the ratio (compare Figs. 4-17 B-D with Fig. 4-17 A). An increase in inflow rate decreases F_D/F_A by decreasing rebreathing. Rebreathing is important because uptake of anesthetic depletes the anesthetic concentration in rebreathed gases, and the concentration in the delivered gases (F_D) must be sufficient to compensate for this depletion. The higher the inflow rate, the less the compensation required because rebreathing is less.

However, increases in inflow rate do not produce proportional decreases in F_D/F_A (compare Figs. 4-17 A-D). The greatest reduction in F_D/F_A comes with but modest increases in inflow rate. Thus, a large decrease occurs when the inflow rate is changed from that needed for a closed circuit to a 1-L/min inflow rate, whereas only a small decrease occurs when the inflow rate is increased from 2 to 4 L/min. Once the inflow rate exceeds minute ventilation (i.e., a nonrebreathing system exists), further increases in inflow rate have no effect on F_D/F_A, and F_D/F_A is the same as the ratio of inspired (F_I) to alveolar concentrations (i.e., $F_D/F_A = F_I/F_A$).

I have used the term anesthetic tether as a metaphor for the F_D/F_A ratio. [68] A large ratio equates to a long tether, one permitting considerable freedom or variability in the alveolar concentration. With a long tether, changes in uptake secondary to changes in physiologic variables (e.g., an increase in cardiac output consequent to surgical stimulation) can appreciably alter the alveolar concentration and thus the level of anesthesia. In the example just cited, there is positive feedback because by increasing uptake, surgical stimulation decreases the alveolar concentration and thereby increases the perception of that stimulation. Most anesthetists prefer a short anesthetic tether because a short tether provides a tighter control over the level of anesthesia. A shorter tether is produced by the use of less soluble anesthetics and higher inflow rates.

Another benefit to a short tether accrues to the anesthetist who does not have access to an agent-specific analyzer. In the absence of such an analyzer, some anesthetists would rely on the dial setting of the vaporizer to indicate the concentration of anesthetic in the patient's lungs (i.e., would assume that F_D equaled F_A). Although the vaporizer setting may correlate with the concentration in the lungs, the correlation may be a distant one. The correlation is poor: (1) early in anesthesia for all agents, (2) later in anesthesia for closed circuits or very low inflow rates, and (3) later in anesthesia for more soluble agents, such as isoflurane, even at higher inflow rates. Note that with poorly soluble anesthetics, such as sevoflurane and desflurane, by 30 to 60 minutes after the inception of anesthetic administration, the delivered concentration from the vaporizer may be less than 20 percent greater than that in the alveoli (i.e., the F_D/F_A ratio is 1.2), even at inflow rates of 1 to 2 L/min (Figs. 4-17 B and C).

Economic concerns increasingly dictate the practice of anesthesia. The reader may wish to appreciate the differences in anesthetic consumption as a function of the choice of inflow rate, the duration of anesthesia, and the choice of anesthetic. The reports by Yasuda et al [4] [5] provide constants that may be used to estimate the uptake of commonly available potent inhaled anesthetics. By using the gas laws and published values for specific gravities, the values for uptake of vapor may be converted to milliliters of liquid taken up. Combining this information with a knowledge of the function of circuit rebreathing systems [60] allows an estimate of the amounts of liquid in milliliters that must be delivered at various inflow rates to provide a constant alveolar concentration equal to MAC (Table 4-4) (Table Not Available) . [69] The relative costs of anesthesia may be estimated by applying the price of the anesthetic of interest to the number of milliliters needed to sustain anesthesia.

If both economy and a low F_D/F_A ratio are desirable, the aforementioned considerations suggest that a good compromise is the use of a low-flow delivery system after an initial period of higher flows. Higher flows (4 to 6 L/min) might be applied early in anesthesia (i.e., at the times of highest uptake) and then decreased progressively as uptake decreases. Flows of 2 to 4 L/min might be given for the period from 5 to 15 minutes after inducing anesthesia, and flows of 1 to 2 L/min may be given thereafter. If the average inflow rate were 2 L/min, 1 hour of anesthesia with the four potent anesthetics listed in Table 4-4 (Table Not Available) would require administration of 9.0 to 46.0 mL of liquid. This fivefold range of values is smaller than the eightfold range of potency (MAC) values because the amount of anesthetic delivered must account for more than potency. The amount delivered also must compensate for uptake and losses of anesthetic through the overflow valve. The relatively smaller uptake and losses of

TABLE 4-4 -- Milliliters of Liquid Anesthetic at Various Inflow Rates Needed to Sustain an Alveolar Concentration Equal to Minimum Alveolar Concentration

(Not Available)

Modified from Weiskopf and Eger [65]

the less soluble desflurane and sevoflurane are what account for the reduction from eightfold to fivefold. An even smaller range is found at lower inflow rates, decreasing to about twofold for a closed circuit. However, such flows should not be used with sevoflurane because of the greater concentrations of compound A that result.

RECOVERY FROM ANESTHESIA

General Principles

Nearly all the factors that govern the rate at which the alveolar anesthetic concentration rises on induction apply to recovery. Thus, the immediate decline is extremely rapid because the washout of the functional residual capacity by ventilation is as rapid as the washin. Only 2 minutes is required to eliminate 95 to 98 percent of nitrogen from the lungs when pure oxygen is breathed.

Nitrogen, however, is a poorly soluble gas relative to the inhaled anesthetics. As ventilation sweeps anesthetic from the alveoli, an anesthetic partial pressure gradient develops between that partial pressure in the returning venous blood and the partial pressure in the alveoli. This gradient drives anesthetic into the alveoli, thereby opposing the tendency of ventilation to lower the alveolar concentration. The effectiveness of the venous to alveolar gradient in opposing the tendency of ventilation to decrease the alveolar anesthetic partial pressure is in part determined by the solubility of the anesthetic. A highly soluble agent, such as methoxyflurane, opposes the elimination produced by ventilation more effectively than does a poorly soluble agent, such as nitrous oxide, because a greater reserve exists in blood for the highly soluble agent--that is, far more methoxyflurane is available at a given partial pressure for transfer to the alveoli. Thus, the fall in the alveolar partial pressure of methoxyflurane is slower than the fall with halothane, and the latter, in turn, is less rapid than the fall with nitrous oxide. The rate at which recovery occurs is similarly affected: it is rapid with nitrous oxide and may be slow with methoxyflurane. The rapidity of recovery thus largely depends on the solubility of the anesthetic. [70]

Differences Between Induction and Recovery

Recovery differs from induction in two crucial ways. First, on induction, the effect of solubility to hinder the rise in alveolar anesthetic concentration could be overcome by increasing the inspired anesthetic concentration (i.e., by applying overpressure). No such luxury is available during recovery; the inspired concentration cannot be reduced below zero. Second, on induction, all the tissues initially have the same anesthetic partial pressure--zero. On recovery, the tissue partial pressures are variable. The VRG has a pressure that usually equals that required for anesthesia; that is, the VRG has come to equilibrium with the alveolar anesthetic partial pressure. The muscle group may or may not have the same partial pressure as that found in the alveoli. A longer anesthetic (2 to 4 hours) might permit equilibrium to be approached, but a shorter case would not. The high capacity of fat for all anesthetics except nitrous oxide precludes equilibration of the fat group with the alveolar anesthetic partial pressure with hours or even days of anesthesia.

The failure of muscle and fat to equilibrate with the alveolar anesthetic partial pressure means that these tissues initially cannot contribute to the transfer of anesthetic back to the lungs. In fact, as long as an anesthetic partial pressure gradient exists between arterial blood and tissue blood, that tissue will continue to take up anesthetic. Thus, for the first several hours of recovery from halothane anesthesia, fat continues to take up halothane and by so doing accelerates the rate of recovery. Only after the alveolar (equals arterial) anesthetic partial pressure falls below that in a tissue can the tissue contribute anesthetic to the alveoli.

The failure of several tissues to reach equilibration with the alveolar anesthetic partial pressure means that the rate of decrease of alveolar anesthetic on recovery is more rapid than its rate of increase on induction, and that recovery depends in part on the duration of anesthesia (Fig. 4-18) (Figure Not Available) . [71] [72] A longer anesthetic puts more anesthetic into the slowly filling muscle and fat depots. Obviously, these reservoirs can supply more anesthetic to the blood returning to the lungs

Figure 4-18 (Figure Not Available) Both solubility and duration of anesthesia affect the fall of the alveolar concentration (F_E) from its value immediately preceding the cessation of anesthetic administration (F_{EO}). A longer anesthetic slows the fall, as does a greater solubility. *(From Stoelting and Eger [72])*

Figure 4-19 (Figure Not Available) The time to decrease the partial pressure in the alveoli or vessel-rich group by a certain fraction directly depends on several factors, primary among which are the solubility of the anesthetic and the duration of anesthesia. If between 80% of the anesthetic must be elimination to permit awakening, awakening from isoflurane will be delayed for progressively longer times as the duration of anesthesia is increased, but awakening from desflurane or sevoflurane will be minimally affected. If 90% of the anesthetic must be eliminated, awakening from both sevoflurane and isoflurane will be delayed more and more as the duration of anesthesia increases (isoflurane more than sevoflurane), but awakening from desflurane will be minimally affected. *(Modified from Bailey [73])*

when they are filled than when they are empty and thereby can prolong the time to recovery. [70]

Solubility influences the effect of duration of anesthesia on the rate at which the alveolar anesthetic partial pressure declines. [72] The decline of the partial pressure of a poorly soluble agent such as nitrous oxide is rapid in any case, and thus the acceleration imparted by a less than complete tissue equilibration cannot significantly alter the rate of recovery. The approach to equilibration becomes important with halothane and becomes even more important with methoxyflurane (see Fig. 4-18) (Figure Not Available) . Recovery may be rapid after a short methoxyflurane anesthetic but may be slow after a prolonged anesthetic. This is one of the reasons why nitrous oxide is usually a component of an inhaled (or for that matter, an injected) anesthetic regimen. The rapid elimination of this component permits at least a portion of recovery to be rapid. The recovery from anesthesia with desflurane and sevoflurane is more rapid than with more soluble agents, such as isoflurane and halothane. [70]

The importance of solubility and duration of anesthesia to the rate of recovery may be appreciated by the use of context-dependent times to reach particular levels of washout. [73] Regardless of duration of anesthesia, the alveolar concentrations of poorly soluble anesthetics (nitrous oxide, desflurane, sevoflurane) and moderately soluble anesthetics (isoflurane, halothane) decrease by 50 percent in roughly the same period of time. If recovery were reached at a 50 percent decrease, the choice of anesthetic would matter little to the time to recovery from anesthesia. The impact of solubility and anesthetic duration becomes evident if greater levels of washout are required to achieve recovery. If 80 percent washout is required, then increasing duration of anesthesia markedly affects recovery from isoflurane, but little affects recovery from desflurane and sevoflurane (Fig. 4-19) (Figure Not Available) . If 90 percent washout is required, then increasing duration of anesthesia affects both isoflurane and sevoflurane but not the less soluble desflurane (see Fig. 4-19) (Figure Not Available) . Indeed, the 90 percent washout may be of importance if anesthesia is maintained primarily with the potent inhaled anesthetic. After 2, 4, or 8 hours of anesthesia with 1.25 MAC sevoflurane versus desflurane, initial (Fig. 4-20) (Figure Not Available) and later (Fig. 4-21) (Figure Not Available) recovery is nearly twice as rapid with desflurane, and the difference between the recovery times appears to increase with increasing duration of anesthesia. [24]

Can I Have My Cake and Eat It Too?

The less soluble new inhaled anesthetics desflurane and sevoflurane offer a more rapid recovery from anesthesia than the more soluble older agents, such as isoflurane. However, this rapid recovery comes at a price: the new anesthetics are more expensive. Might it be possible to have the best of both worlds by using

isoflurane for the major portion of anesthesia, reserving desflurane (or sevoflurane) for the final

Figure 4-20 (Figure Not Available) The possibility of a differential time to awakening suggested by the analysis in Figure 4-19 (Figure Not Available) is shown to occur after 2, 4, or 8 hours of anesthesia at 1.25 MAC for desflurane versus sevoflurane. Awakening to response to command or to orientation is nearly twice as rapid after anesthesia with the less soluble desflurane. *(From Eger et al [24])*

Figure 4-21 (Figure Not Available) The differential suggested by Figure 4-19 (Figure Not Available) extends to measures of more subtle degrees of awakening such as the digit symbol substitution test (DSST), a measure of judgment and cognition. Note that there appears to be a greater spread between the results after 2 versus 8 hours of anesthesia. *(From Eger et al [24])*

minutes? The premise would be that such an approach would provide the economy of isoflurane and the rapid recovery of desflurane. Neumann et al [74] tested this premise. Volunteers were anesthetized for 2 hours on three occasions: once with 1.25 MAC of isoflurane; once with 1.25 MAC of desflurane; and once with 1.5 hours of 1.25 MAC of isoflurane followed by 0.5 hours of a combination of desflurane and isoflurane ("crossover"). The combination provided a total of 1.25 MAC (i.e., desflurane was added as the isoflurane was eliminated, the addition being sufficient to sustain a total of 1.25 MAC). To ensure economy, all anesthetics were delivered at a 2 L/min inflow rate.

The premise was not realized. Recovery after the crossover was no faster than recovery after isoflurane alone (Fig. 4-22) . Recovery after desflurane alone was considerably faster than recovery after either isoflurane or the crossover from isoflurane to desflurane.

Impact of Metabolism

Saturation of the enzymes responsible for the metabolism of anesthetics may limit the ability of metabolism to significantly alter the rate at which the alveolar anesthetic partial pressure rises. This limitation does not exist on recovery, and metabolism may be an important determinant of the rate at which the alveolar anesthetic partial pressure declines. The importance of metabolism to recovery is implied by results from Munson et al, [75] who showed that contrary to what might be predicted from their respective solubilities, the alveolar washout of halothane is more rapid than that of enflurane, a result later confirmed by Carpenter et al. [18] [19] This agrees with the relative ease with which these two agents are metabolized: 15 to 20 percent of the halothane taken up during the course of an ordinary anesthetic can be recovered as urinary metabolites, [76] whereas only 2 to 3 percent of enflurane can similarly be recovered. [77] Thus, there are two major routes by which halothane can be eliminated, the lung and the liver. With enflurane, elimination via the liver is relatively minor, which explains why Munson et al [75] found a more rapid fall in alveolar halothane. These results also apply to desflurane, isoflurane, and sevoflurane. Metabolism of desflurane and isoflurane is too small to accelerate their elimination, but metabolism of sevoflurane is sufficient to narrow the difference between its washout and that of desflurane. [24]

Diffusion Hypoxia

The uptake of large volumes of nitrous oxide on induction of anesthesia gives rise to the concentration and the second gas effects. On recovery from anesthesia, the outpouring of large volumes of nitrous oxide can produce what Fink [78] called diffusion anoxia. These volumes may cause hypoxia (Fig. 4-23) (Figure Not Available) in two ways. First, they may directly affect oxygenation by displacing oxygen. [78] [79] [80] Second, by diluting alveolar

Figure 4-22 Volunteers were anesthetized for 2 hours on three occasions: once with 1.25 MAC isoflurane; once with 1.25 MAC desflurane; and once with 1.5 hours of 1.25 MAC isoflurane followed by 0.5 hours of a combination of desflurane and isoflurane ("crossover"). The combination provided a total of 1.25 MAC (i.e., desflurane was added as the isoflurane was eliminated, the addition being sufficient to sustain a total of 1.25 MAC). All anesthetics were delivered at a 2-L/min inflow rate. At the end of 2 hours, anesthetic administration was discontinued and a nonrebreathing system applied. The digit symbol substitution test (DSST) was applied at 15-minute intervals, and the results are displayed as a percentage of the control (preanesthesia) results. Recovery of judgment and cognition as defined by the DSST was more rapid at 15, 30, and 45 minutes with desflurane given alone (asterisks indicate significant differences from isoflurane or crossover results). *(Data from Neumann et al [74])*

Figure 4-23 (Figure Not Available) At time zero, the inspired gas was changed from 21% oxygen/79% nitrous oxide to 21% oxygen/79% nitrogen. Arterial oxygen subsequently fell in association with the outpouring of nitrous oxide. *(Modified from Sheffer et al [79])*

carbon dioxide, they may decrease respiratory drive and hence ventilation. [80] Both of these effects require that large volumes of nitrous oxide be released into the alveoli. Because large volumes of nitrous oxide are released only during the first 5 to 10 minutes of recovery, this is the period of greatest concern. This concern is enhanced by the fact that the first 5 to 10 minutes of recovery also may be the time of greatest respiratory depression. For these reasons, many anesthetists administer 100 percent oxygen for the first 5 to 10 minutes of recovery. This procedure may be particularly indicated in patients with preexisting lung disease or in those in whom postoperative respiratory depression is anticipated (e.g., after a nitrous oxide-narcotic anesthetic).

Impact of the Anesthetic Circuit

The anesthetic circuit may limit the rate of recovery just as it limits induction. If the patient is not disconnected from the circuit on cessation of anesthetic delivery, the patient may continue to inspire anesthetic. To reduce the inspired level to zero or near-zero, several factors must be taken into account. The anesthetic within the circuit must be washed out. In addition, the rubber or plastic components of the circuit and the soda lime within the circuit will have absorbed anesthetic (see Table 4-3) that can be released back into the gas phase, [54] and this, too, must be washed out. Finally, the patient's exhaled air contains anesthetic that cannot be rebreathed if the inspired anesthetic concentration is to approach zero. The effect of each of these factors to raise the inspired anesthetic concentration can be overcome by the use of high inflow rates of oxygen (i.e., 5 L/min or greater).

References

1. Eger EI II: Uptake of inhaled anesthetics: The alveolar to inspired anesthetic difference. In Eger EI II (ed): Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 77-96.

2. Bacher A, Burton AW, Uchida T et al: Sevoflurane or halothane anesthesia: Can we tell the difference? Anesth Analg 85:1203-1206, 1997.

3. Munson ES, Eger EI II, Bowers DL: Effects of anesthetic-depressed ventilation and cardiac output on anesthetic uptake. Anesthesiology 38:251-259, 1973.

4. Yasuda N, Lockhart SH, Eger EI II et al: Kinetics of desflurane, isoflurane, and halothane in humans. Anesthesiology 74:489-498, 1991.

5. Yasuda N, Lockhart SH, Eger EI II et al: Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 72:316-324, 1991.

6. Eger EI II: The effect of inspired concentration on the rate of rise of alveolar concentration. Anesthesiology 24:153-157, 1963.

7. Eger EI II: Application of a mathematical model of gas uptake. In Papper EM, Kitz RJ (eds): Uptake and Distribution of Anesthetic Agents. New York, McGraw-Hill, 1963, pp 88-103.

8. Stoelting RK, Eger EI II: An additional explanation for the second gas effect: A concentrating effect. Anesthesiology 30:273-277, 1969.

9. Korman B, Mapleson WW: Concentration and second gas effects: Can the accepted explanation be improved? Br J Anaesth 78:618-625, 1997.

10. Eger EI II, Smith RA, Koblin DD: The concentration effect can be mimicked by a decrease in blood solubility. Anesthesiology 49:282-284, 1978.

11. Epstein RM, Rackow H, Salanitre E et al: Influence of the concentration effect on the uptake of anesthetic mixtures: The second gas effect. Anesthesiology 25:364-371, 1964.

12. Fassoulaki A, Lockhart S, Freire BA et al: Percutaneous loss of desflurane, isoflurane and halothane in humans. Anesthesiology 74:479-483, 1991.

13. Lockhart SH, Yasuda Y, Peterson N et al: Comparison of percutaneous losses of sevoflurane and isoflurane in humans. Anesth Analg 72:212- 215, 1991.

14. Cullen BF, Eger EI II: Diffusion of nitrous oxide, cyclopropane, and halothane through human skin and amniotic membrane. Anesthesiology 36:168-173, 1972.

15. Stoelting RK, Eger EI II: Percutaneous loss of nitrous oxide, cyclopropane, ether and halothane in man. Anesthesiology 30:278-283, 1969.

16. Laster MJ, Tahari S, Eger EI II et al: Visceral losses of desflurane, isoflurane, and halothane in swine. Anesth Analg 73:209-212, 1991.

17. Berman ML, Lowe HJ, Hagler KT et al: Uptake and elimination of methoxyflurane as influenced by enzyme induction in the rat. Anesthesiology 38:352-357, 1973.

18. Carpenter RL, Eger EI II, Johnson BH et al: The extent of metabolism of inhaled anesthetics in humans. Anesthesiology 65:201-205, 1986.

19. Carpenter RL, Eger EI II, Johnson BH et al: Does the duration of anesthetic administration affect the pharmacokinetics or metabolism of inhaled anesthetics in humans. Anesth Analg 66:1-8, 1987.

20. Carpenter RL, Eger EI II, Johnson BH et al: Pharmacokinetics of inhaled anesthetics in humans: Measurements during and after the

simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. Anesth Analg 65:575-582, 1986.

21. Sutton TS, Koblin DD, Gruenke LD et al: Fluoride metabolites following prolonged exposure of volunteers and patients to desflurane. Anesth Analg 73:180-185, 1991.

22. Halsey MJ, Sawyer DC, Eger EI II et al: Hepatic metabolism of halothane, methoxyflurane, cyclopropane, Ethrane and Forane in miniature swine. Anesthesiology 35:43-47, 1971.

23. Sawyer DC, Eger EI II, Bahlman SH et al: Concentration dependence of hepatic halothane metabolism. Anesthesiology 34:230-234, 1971.

24. Eger EI II, Gong D, Koblin DD et al: Effect of anesthetic duration on kinetic and recovery characteristics of desflurane vs. sevoflurane (plus compound A) in volunteers. Anesth Analg 86:414-421, 1998.

25. Yamamura H, Wakasugi B, Okuma Y et al: The effects of ventilation on the absorption and elimination of inhalation anaesthetics. Anaesthesia 18:427-438, 1963.

26. Fukui Y, Smith NT: Interactions among ventilation, the circulation, and the uptake and distribution of halothane--Use of a hybrid computer multiple model: I. The basic model. Anesthesiology 54:107-118, 1981.

27. Calverley RK, Smith NT, Jones CW et al: Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man. Anesth Analg 57:610-618, 1978.

28. Doi M, Ikeda K: Respiratory effects of sevoflurane. Anesth Analg 66:241-244, 1987.

29. Fourcade HE, Stevens WC, Larson CP Jr et al: The ventilatory effects of Forane, a new inhaled anesthetic. Anesthesiology 35:26-31, 1971.

30. Munson ES, Larson CP Jr, Babad AA et al: The effects of halothane, fluroxene and cyclopropane on ventilation: A comparative study in man. Anesthesiology 27:716-728, 1966.

31. Lockhart S, Rampil IJ, Yasuda N et al: Depression of ventilation by desflurane in humans. Anesthesiology 74:484-488, 1991.

32. Gibbons RT, Steffey EP, Eger EI II: The effect of spontaneous versus controlled ventilation on the rate of rise of alveolar halothane concentration in dogs. Anesth Analg 56:32-34, 1977.

33. Yamamura H: The effect of ventilation and blood volume on the uptake and elimination of inhalation anesthetic agents. In Progress in Anaesthesiology. Proceedings of the Fourth World Congress of Anesthesiologists. Amsterdam, Excerpta Medica, International Congress Series 200, 1968, pp 394-399.

34. Calverley RK, Smith NT, Eger EI II: Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg 57:619-628, 1978.

35. Eger EI II, Smith NT, Stoelting RK et al: Cardiovascular effects of halothane in man. Anesthesiology 32:396-409, 1970.

36. Eger EI II, Bahlman SH, Munson ES: Effect of age on the rate of increase of alveolar anesthetic concentration. Anesthesiology 35:365- 372, 1971.

37. Wahrenbrock EA, Eger EI II, Laravuso RB et al: Anesthetic uptake: Of mice and men (and whales). Anesthesiology 40:19-23, 1974.

38. Salanitre E, Rackow H: The pulmonary exchange of nitrous oxide and halothane in infants and children. Anesthesiology 30:388-394, 1969.

39. Eger EII, Severinghaus JW: Effect of uneven pulmonary distribution of blood and gas on induction with inhalation anesthetics. Anesthesiology 25:620-626, 1964.

40. Stoelting RK, Longnecker DE: Effect of right-to-left shunt on rate of increase in arterial anesthetic concentration. Anesthesiology 36:352- 356, 1972.

41. Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 26:61-66, 1965.

42. Hunter AR: Problems of anaesthesia in artificial pneumothorax. Proc R Soc Med 48:765, 1955.

43. Munson ES, Merrick HC: Effect of nitrous oxide on venous air embolism. Anesthesiology 27:783-787, 1966.

44. Shapiro HM, Yoachim J, Marshall LF: Nitrous oxide challenge for detection of residual intravascular pulmonary gas following venous air embolism. Anesth Analg 61:304-306, 1982.

45. Stanley TH, Kawamura R, Graves C: Effects of nitrous oxide on volume and pressure of endotracheal tube cuffs. Anesthesiology 41:256-262, 1974.

46. Eisenkraft JB, Eger EI II: Nitrous oxide anesthesia may double the balloon gas volume of Swan-Ganz catheters. Mt Sinai J Med 49:430-433, 1982.

47. Kaplan R, Abramowitz MD, Epstein BS: Nitrous oxide and air-filled balloon-tipped catheters. Anesthesiology 55:71-73, 1981.

48. Wolf GL, Capuano C, Hartung J: Nitrous oxide increases intraocular pressure after intravitreal sulfur hexafluoride injection. Anesthesiology 59:547-548, 1983.

49. Saidman LJ, Eger EI II: Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. Anesthesiology 26:67-72, 1965.

50. Thomsen KA, Terkildsen K, Arnfred J: Middle ear pressure variations during anesthesia. Arch Otolaryngol 82:609-611, 1985.

51. Waun JE, Sweitzer RS, Hamilton WK: Effect of nitrous oxide on middle ear mechanics and hearing acuity. Anesthesiology 28:846-850, 1987.

52. Graham MD, Knight PR: Atelectative tympanic membrane reversal by nitrous oxide supplemented general anesthesia and polyethylene ventilation tube insertion: A preliminary report. Laryngoscope 41:1469, 1981.

53. Titel JH, Lowe HJ: Rubber-gas partition coefficients. Anesthesiology 29:1215-1216, 1968.

54. Eger EI II, Larson CP Jr, Severinghaus JW: The solubility of halothane in rubber, soda lime and various plastics. Anesthesiology 23:356-359, 1962.

55. Targ AG, Yasuda N, Eger EI II: Solubility of I-653, sevoflurane, isoflurane, and halothane in plastics and rubber composing a conventional anesthetic circuit. Anesth Analg 68:218-225, 1989.

56. Eger EI II, Ionescu P, Gong D: Circuit absorption of halothane, isoflurane and sevoflurane. Anesth Analg (Submitted for publication), 1998.

57. Eger EI II, Koblin DD, Bowland T et al: Nephrotoxicity of sevoflurane vs. desflurane anesthesia in volunteers. Anesth Analg 84:160-168, 1997.

58. Fang ZX, Eger EI II, Laster MJ et al: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth Analg 80:1187-1193, 1995.

59. Eger EI II, Ionescu P, Laster MJ et al: Baralyme dehydration increases and soda lime dehydration decreases the concentration of compound A resulting from sevoflurane degradation in a standard anesthetic circuit. Anesth Analg 85:892-898, 1997.

60. Harper M, Eger EI II: A comparison of the efficiency of three anesthesia circle systems. Anesth Analg 55:724-729, 1976.

61. Sharp JH, Trudell JR, Cohen EN: Volatile metabolites and decomposition products of halothane in man. Anesthesiology 50:2- 8, 1979.

62. Morio M, Fujii K, Satoh N et al: Reaction of sevoflurane and its degradation products with soda lime: Toxicity of the byproducts. Anesthesiology 77:1155-1164, 1992.

63. Severinghaus JW: The rate of uptake of nitrous oxide in man. J Clin Invest 33:1183-1189, 1954.

64. Lowe HJ, Ernst EA: The Quantitative Practice of Anesthesia: Use of Closed Circuit. Baltimore, Williams & Wilkins, 1981.

65. Titel JH, Lowe HJ, Elam JO et al: Quantitative closed-circuit halothane anesthesia. Anesth Analg 47:560-569, 1968.

66. Hendrickx JFA, Soetens M, VanderDonck A et al: Uptake of desflurane and isoflurane during closed-circuit anesthesia with spontaneous and controlled mechanical ventilation. Anesth Analg 84:413-418, 1997.

67. Eger EI II: Complexities overlooked: Things may not be what they seem. Anesth Analg 84:239-240, 1997.

68. Eger EI II: Desflurane (Suprane): A Compendium and Reference. Rutherford, NJ, Healthpress Publishing Group, 1993.

69. Weiskopf RB, Eger EI II: Comparing the costs of inhaled anesthetics. Anesthesiology 79:1413-1418, 1993.

70. Eger EI II, Johnson BH: Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: A test of the effect of anesthetic concentration and duration in rats. Anesth Analg 66:977-982, 1987.

71. Mapleson WW: Quantitative prediction of anesthetic concentrations. In Papper EM, Kitz RJ (eds): Uptake and Distribution of Anesthetic Agents. New York, McGraw-Hill, 1963, pp 104-119.

72. Stoelting RK, Eger EI II: The effects of ventilation and anesthetic solubility on recovery from anesthesia: An in vivo and analog analysis before and after equilibration. Anesthesiology 30:290-296, 1969.

73. Bailey JM: Context-sensitive half-times and other decrement times of inhaled anesthetics. Anesth Analg 85:681-686, 1997.

74. Neumann MA, Weiskopf RB, Gong DH et al: Changing from isoflurane to desflurane towards the end of anesthesia does not accelerate recovery in humans. Anesthesiology 88:914-921, 1998.

75. Munson ES, Eger EI II, Tham MK et al: Increase in anesthetic uptake, excretion and blood solubility in man after eating. Anesth Analg 57:224-231, 1978.

76. Rehder K, Forbes J, Alter H et al: Halothane biotransformation in man: A quantitative study. Anesthesiology 28:711-715, 1967.

77. Chase RE, Holaday DA, Fiserova-Bergerova V et al: The biotransformation of Ethrane in man. Anesthesiology 35:262-267, 1971.

78. Fink BR: Diffusion anoxia. Anesthesiology 16:511-519, 1955.

79. Sheffer L, Steffenson JL, Birch AA: Nitrous-oxide-induced diffusion hypoxia in patients breathing spontaneously. Anesthesiology 37:436- 439, 1972.

80. Rackow H, Salanitre E, Frumin MH: Dilution of alveolar gases during nitrous oxide excretion in man. J Appl Physiol 16:723-728, 1961.

81. Eger EI II: Partition coefficients of I-653 in human blood, saline, and olive oil. Anesth Analg 66:971-973, 1987.

82. Cromwell TH, Eger EI II, Stevens WC et al: Forane uptake excretion and blood solubility in man. Anesthesiology 35:401-408, 1971.

83. Eger RR, Eger EI II: Effect of temperature and age on the solubility of enflurane, halothane, isoflurane and methoxyflurane in human blood. Anesth Analg 64:640-642, 1985.

84. Yasuda N, Targ AG, Eger EI II: Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 69:370-373, 1989.

85. Lerman J, Schmitt-Bantel BI, Gregory GA et al: Effect of age on the solubility of volatile anesthetics in human tissues. Anesthesiology 65:307-311, 1986.

86. Eger EI II, Shargel RO, Merkel G: Solubility of diethyl ether in water, blood and oil. Anesthesiology 24:676-678, 1963.

87. Eger EI II, Shargel R: The solubility of methoxyflurane in human blood and tissue homogenates. Anesthesiology 24:625-627, 1963.

88. Munson ES, Eger EI II: Methoxyflurane solubility in plastics. Anesthesiology 26:828, 1965.

89. Eger EI II, Brandstater B: Solubility of methoxyflurane in rubber. Anesthesiology 24:679-683, 1963.

90. Eger EI II: Ventilation, circulation and uptake. In Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 122-145.

91. Eger EI II: Effect of anesthetic circuit on alveolar rate of rise. In Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, pp 192-205.

Chapter 5A - Cardiovascular Pharmacology

Paul S. Pagel
Neil E. Farber
David C. Warltier

INTRODUCTION

This chapter will comprehensively describe the cardiovascular pharmacology of modern volatile anesthetics, nitrous oxide, and xenon. The actions of inhaled anesthetics on cardiovascular function, cardiac electrophysiology, the coronary circulation, and autonomic nervous system control of the circulation will be examined in detail.

VOLATILE ANESTHETICS AND CARDIOVASCULAR FUNCTION

Myocardial Contractility

All modern volatile anesthetics, including desflurane and sevoflurane, depress contractile function in normal myocardium *in vitro* and *in vivo.*[1] Investigations conducted in the 1960s demonstrated that halothane causes dose-related depression of force-velocity relations and Frank-Starling curves in isolated cardiac muscle preparations [2] [3] and in intact, closed-chest dogs, [4] respectively. These findings supported clinical observations of circulatory depression during halothane anesthesia in humans. [5] [6] [7] [8] Enflurane [9] and isoflurane [10] have also been shown to produce direct negative inotropic effects as indicated by decreases in maximal velocity of shortening, peak developed force, and maximal rate of force development during isotonic contraction in isolated feline papillary muscles. These reductions in intrinsic myocardial contractility by enflurane and isoflurane contribute to the cardiovascular depression observed with these agents in humans. [11] [12]

The relative degree of myocardial depression produced by different volatile anesthetics *in vivo* has been more difficult to establish because simultaneous alterations in systemic and pulmonary hemodynamics and autonomic nervous system activity often complicate assessment of left ventricular (LV) systolic function. Early studies using isovol-umic and ejection phase measures of myocardial contractility demonstrated that enflurane and halothane caused very similar negative inotropic effects in dogs [13] [14] [15] [16] and humans. [11] These findings were subsequently confirmed using the slope (E_{es}) of the LV end-systolic pressure-mid-axis diameter relation

as a relatively heart rate- and load-independent index of inotropic state in chronically instrumented dogs. [17] Equianesthetic concentrations of enflurane and halothane depress myocardial contractility to similar degrees *in vivo.*[17] In contrast, studies in experimental animals have repeatedly demonstrated that isoflurane produces less myocardial depression than does halothane or enflurane. Halothane caused greater reductions in LV peak-positive dP/dt than isoflurane when equianesthetic concentrations were directly compared in the presence and absence of autonomic nervous system function, [16] [18] [19] suggesting that differences in myocardial depression caused by these agents occurred independently of autonomic nervous system activity. [16] Differences in the negative inotropic effects of halothane and isoflurane have been quantified using the slope (M_w) of the regional preload recruitable stroke work relation derived from a differentially loaded series of LV pressure-segment length diagrams. [20] [21] In these studies conducted in chronically instrumented dogs, isoflurane maintained contractility an average of 20% greater as compared with an equi-MAC (minimum alveolar concentration) of halothane. [20] [21] Differences in the relative degree of myocardial depression produced by halothane and isoflurane have also been inferred in humans, using isovolumic and ejection phase measures of contractile function. [12] [22] [23] The negative inotropic actions of isoflurane (Fig. 5-1) (Figure Not Available) and halothane are exacerbated by hypocalcemia, [24] calcium (Ca^{2+}) channel blockers, [25] [26] [27] and $beta_1$-adrenoceptor antagonists [25] and can be reversed by administration of exogenous Ca^{2+} [24] [28] [29] [30] cardiac phosphodiesterase fraction III inhibitors, [31] [32] $beta_1$-adrenoceptor agonists, [1] Ca^{2+} channel agonists, [27] and myofilament Ca^{2+} sensitizers. [33] Importantly, the differential effects of halothane and isoflurane on myocardial contractility in dogs are maintained during depression or augmentation of inotropic state produced by these vasoactive drugs. [1]

Desflurane causes systemic and coronary hemodynamic effects that are remarkably similar to those produced by isoflurane. [34] Desflurane and isoflurane have been shown to depress myocardial function to equivalent degrees, using isovolumic and ejection phase measures of contractility in dogs, [16] [35] pigs, [36] and humans. [37] [38] These observations have been verified using both end-systolic pressure-volume relations and regional and global preload recruitable stroke work (Fig. 5-2) (Figure Not Available) in the presence and absence of autonomic nervous system activity *in vivo.*[9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] However, the unique cardiovascular stimulation associated with rapid increases in inspired desflurane concentration in humans [42] may lead to transient increases in myocardial contractility resulting from augmentation of sympathetic nervous system tone. [43] [44] [45]

The effects of sevoflurane on myocardial contractility have been shown to be also virtually indistinguishable from those produced by isoflurane in dogs. [46] [47] Another study conducted in pigs suggested that sevoflurane may produce less myocardial depression than an equi-MAC concentration of halothane. [48] Sevoflurane produces less myocardial depression than enflurane in volunteers as assessed by the heart rate-corrected velocity of circumferential fiber shortening versus left ventricular end-systolic wall stress relation derived from echocardiography. [49] Sevoflurane decreased contractile function to approximately 40 to 45 percent of control values at 1.75 MAC in the presence and absence of autonomic nervous system tone, using regional preload recruitable

Figure 5A-1 (Figure Not Available) End-systolic pressure-volume (top panel) and stroke work-end-diastolic volume relations (bottom panel) before (control 1; C_1), during 0.6, 0.9, and 1.2 MAC, and after isoflurane (control 2; C_2) in an experiment in an open-chest dog. *(From Hettrick et al [41])*

stroke work in dogs. [47] This magnitude of myocardial depression agrees with previous data for isoflurane and desflurane, using an identical experimental model. [39] [40] Thus, volatile anesthetics appear to depress contractile state in normal ventricular myocardium in the following order: Halothane = enflurane > isoflurane = desflurane = sevoflurane.

The effects of volatile anesthetics on LV systolic function in animal models of or patients with LV dysfunction have not been comprehensively studied. Early *in vitro* studies demonstrated that isoflurane [10] and enflurane [50] cause greater reductions in maximum shortening velocity and the peak rate of force development in feline papillary muscles from failing hearts subjected to chronic pressure overload than in those from normal hearts. Halothane also produced more pronounced myocardial depression in ischemic as compared with normal myocardium. [51] [52] More recently, isoflurane and halothane were shown to cause greater negative inotropic effects in ventricular myocardium obtained from cardiomyopathic as compared with normal hamsters (Fig. 5-3) (Figure Not Available) [53] These findings suggested that myocardial depression caused by volatile anesthetics in failing myocardium were accentuated; they provided indirect evidence that patients with underlying contractile dysfunction

Figure 5A-2 (Figure Not Available) Preload recruitable stroke work (PRSW) slope for chronically instrumented dogs during control and at 1.0 and 1.5 end-tidal MAC of desflurane (top) and isoflurane (bottom). Insets depict percent changes from control. *Significantly ($P < 0.05$) different from control; significantly ($P < 0.05$) different from 1.0 MAC. *(From Pagel et al [39])*

may be more sensitive to the negative inotropic effects of volatile agents. This hypothesis has not been extensively examined *in vivo,* however.

In experimental models of myocardial ischemia [51] or infarction, [54] volatile anesthetic-induced declines in contractile function were well tolerated and did not precipitate frank systolic dysfunction. In fact, volatile anesthetics exert important beneficial effects on mechanical function during myocardial ischemia and reperfusion injury. Volatile anesthetics reduce experimental myocardial infarct size, [55] [56] preserve metabolic and structural integrity during regional ischemia and reperfusion, [57]

[58] [59] enhance the functional recovery of postischemic-reperfused ("stunned") myocardium, [60] and improve indices of LV diastolic performance during brief coronary artery occlusion. [61] Halothane and isoflurane also produce beneficial decreases in LV preload and afterload in patients with heart failure and coronary artery disease, respectively. [62] [63] [64] These improvements in loading conditions in patients with compromised LV function may serve to partially offset the direct negative inotropic effects of anesthetics [62] and contribute to relative maintenance of cardiac performance by optimizing the operating range of the heart on the Starling curve or by improving LV diastolic function. Isoflurane and halothane have recently been demonstrated to produce dose-related depression of myocardial contractility in a canine model of

Figure 5A-3 (Figure Not Available) Comparison of the effects of halothane (left) and isoflurane (right) on isometric active force (AF) of papillary muscles from healthy hamsters (solid circles) and those with cardiomyopathy (open circles). Probability values refer to between-group differences. *Significantly ($P < 0.05$) different from control values. *(From Vivien et al [53])*

moderate LV dysfunction induced by chronic rapid LV pacing (Fig. 5-4) (Figure Not Available) [65] Nevertheless, isoflurane or halothane anesthesia was relatively well tolerated and did not precipitate frank LV failure in dogs with pacing-induced cardiomyopathy. These findings were attributed to simultaneous improvements in LV loading conditions and filling dynamics that contributed to relative maintenance of cardiac output in the setting of moderate LV dysfunction despite concomitant reductions in contractility. [65] The influence of volatile anesthetics on LV systolic function in the presence of overt heart failure remains to be defined, however. Halothane caused greater depression of contractile function than isoflurane in cardiomyopathic dogs, [66] [65] observations that are similar to those described in normal myocardium in experimental animals and humans. These results contrast with those in isolated ventricular myocardium obtained from cardiomyopathic hamsters, demonstrating that isoflurane and halothane produce similar negative inotropic effects. [53] Differential actions on autonomic nervous system tone caused by the volatile anesthetics may be responsible for the discrepancy in these findings *in vivo* and *in vitro.*

Cellular Mechanisms of Myocardial Depression

Volatile anesthetics depress myocardial contractility via alterations of intracellular Ca^{2+} homeostasis at several subcellular targets in the normal cardiac myocyte. [67] [68] Volatile agents cause dose-related inhibition of the transsarcolemmal

Figure 5A-4 (Figure Not Available) Histograms depicting the slope (M_w ; top panel) and length intercept (L_w ; middle panel) of the regional preload recruitable stroke work relation and the time constant of isovolumic relaxation (tau bottom panel) in the conscious state before (C; open bar) and after pacing (P) and during 1.1, 1.4, and 1.7 MAC (end-tidal concentration) isoflurane (hatched bars) and halothane (solid bars). [a] Significantly ($P < 0.05$) different from P; [b] significantly ($P < 0.05$) different from 1.1 MAC; [c] significantly ($P < 0.05$) different from corresponding isoflurane value. *(From Pagel et al [65])*

Ca^{2+} transient [69] [70] by affecting both L- and T-type Ca^{2+} channels. [69] [71] [72] [73] Isoflurane appears to cause less pronounced reductions in the intracellular Ca^{2+} transient than does halothane or enflurane, [69] although this contention remains somewhat controversial when equianesthetic concentrations of these agents are considered. [74] [75] The structural conformation and functional integrity of the voltage-dependent Ca^{2+} channel are directly altered by volatile anesthetics as indicated by attenuated binding of the dihydropyridine and phenylalkylamine Ca^{2+} channel blockers nitrendipine [76] [77] and galopamil, [78] respectively. The partial inhibition of Ca^{2+} influx via sarcolemmal Ca^{2+} channels has several important consequences, including declines in the availability of Ca^{2+} for contractile activation, depression of Ca^{2+} -dependent Ca^{2+} release from the sarcoplasmic reticulum (SR), and reduction of the amount of Ca^{2+} that can be subsequently stored in the SR. [75] [79] [80] [81] [82] Halothane and enflurane, [80] [82] but not isoflurane, [82] [83] [84] also stimulate Ca^{2+} release from the SR, a caffeine-like action that may cause transient, modest increases that precede subsequent, more profound reductions in contractility. [80] [85] [86] Unlike isoflurane, halothane and enflurane directly activate ryanodine-sensitive SR Ca^{2+} release channels, [87] [88] thereby reducing SR Ca^{2+} storage. Volatile anesthetics also provoke a nonspecific leak of Ca^{2+} from the SR, [89] [90] contributing to further decreases in accumulation of Ca^{2+} available for release during contraction. When combined with decreases in transsarcolemmal Ca^{2+} flux, these alterations in SR function represent important mechanisms by which halothane and enflurane depress the intracellular Ca^{2+} transient and reduce myocardial contractility to a greater extent than equianesthetic concentrations of isoflurane. [69] The partial preservation of the myocardial positive frequency staircase effect observed with isoflurane at physiologic excitation rates *in vitro*[75] [91] may also be attributed to the relative maintenance of SR function by this volatile agent, in contrast to halothane and enflurane.

Recent evidence indicates that volatile anesthetics may also depress contractile function by inhibiting sodium (Na^+)-Ca^{2+} exchange and reducing intracellular Ca^{2+} concentration independent of the voltage-dependent Ca^{2+} channel *in vitro.*[92] [93] [94] This effect may be particularly important in neonatal myocardium [92] because this tissue has been shown to be more sensitive to the negative inotropic actions of volatile anesthetics than adult myocardium. [95] However, the relative contribution of Na^+ -Ca^{2+} exchanger inhibition to anesthetic-induced depression of myocardial contractility in the intact heart has yet to be defined. Halothane, enflurane, and isoflurane may also exert direct effects on the contractile apparatus and the sensitivity of the myofilaments to activator Ca^{2+} . Volatile anesthetics decrease tension development of skinned cardiac myofibrils [96] [97] [98] and directly reduce myofibrillar ATPase activity, [95] [100] actions that may contribute to declines in actin-myosin cross-bridge kinetics during contraction. [101] In addition, volatile anesthetics either do not affect [102] or may decrease [103] the troponin C (TnC) affinity for Ca^{2+} , suggesting that myofilament Ca^{2+} sensitivity is not altered [104] or modestly reduced, [69] respectively, by these agents. Nevertheless, although volatile anesthetic-induced reductions in myofilament Ca^{2+} sensitivity have been implicated in some studies, this mechanism probably plays a relatively minor role in the negative inotropic effects of these agents at clinically relevant concentrations *in vivo.*[68]

The cellular mechanisms responsible for volatile anesthetic-induced depression of myocardial contractility in failing myocardium have not been extensively studied. It is very likely that alterations of intracellular Ca^{2+} regulation produced by volatile anesthetics in normal myocardium will also occur at similar subcellular targets in failing myocardium. Profound abnormalities in intracellular Ca^{2+} homeostasis are characteristic features of failing myocardium, [105] and it is likely that volatile anesthetics will cause further reductions in contractile function by producing additive or synergistic effects on Ca^{2+} metabolism.

Diastolic Function

Definitions of heart failure based solely on contractile dysfunction have been rendered inadequate by the recognition that LV function during diastole significantly influences overall cardiac performance. The heart serves dual roles,

Figure 5A-5 (Figure Not Available) Effects of desflurane, isoflurane, and halothane on the time constant of isovolumic relaxation (T_0). *Significantly ($P < 0.05$) different from control; significantly ($P < 0.05$) different from 1.0 MAC. *(From Pagel et al [114])*

propelling blood into the high-pressure arterial vasculature during systole and collecting blood from the low-pressure venous circulation during diastole. Thus, heart failure may occur not only from impaired contractility but also from altered LV diastolic function. The timing, rate, and extent of LV filling are determined by several major factors including the rate and degree of myocardial relaxation, the intrinsic mechanical properties of the LV itself and those imposed by external constraints, and the structure and function of the left atrium, the pulmonary venous circulation, and the mitral valve. [106] Although abnormalities in LV diastolic function may be linked to decreases in myocardial contractility, heart failure may result from primary diastolic dysfunction in the absence of or before the appearance of alterations in LV systolic function [107] [108] [109] in a variety of pathologic conditions including ischemic heart disease, pressure- or volume-overload hypertrophy, hypertrophic obstructive cardiomyopathy, and restrictive disease processes. [110] [111]

The effects of volatile anesthetics on diastolic function in the normal and diseased heart have been incompletely studied. Volatile anesthetics produce dose-related prolongation of isovolumic relaxation *in vivo* (Fig. 5-5) (Figure Not Available) [47] [112] [113] [114] This delay of isovolumic relaxation may be associated with declines in early LV filling [27] [30] [32] [47] but is probably not of sufficient magnitude to affect LV chamber stiffness. The significance of anesthetic-induced delays in isovolumic relaxation to early coronary blood flow has not been thoroughly investigated; however, coronary blood flow is highest during this phase of diastole, and delays in relaxation lead to impairment of flow during halothane anesthesia. [112] Prolongation of LV relaxation probably occurs as a result of simultaneous depression of myocardial contractility and not because of a direct negative lusitropic effect. [115] In fact, isoflurane, enflurane, and halothane have been shown to modestly enhance isotonic relaxation of isolated ferret myocardium *in vitro.*[116]

Volatile anesthetics cause concentration-related decreases in the rate and extent of early LV filling concomitant with negative inotropic effects. Isoflurane and halothane also reduce LV filling associated with atrial systole. [30] Isoflurane, desflurane, and sevoflurane do not alter invasively derived indices of regional myocardial or chamber stiffness, indicating that LV distensibility is unaffected by these volatile agents (Fig. 5-6) (Figure Not Available) [47] [114] Although some indirect evidence suggests that halothane affects LV compliance, [117] [118] [119] more recent studies [17] [114] [120] using invasively derived measures of LV passive elasticity and myocardial stiffness have indicated that this is not the case. Halothane increases LV enddiastolic pressure, indicating that the LV operates on a steeper, less compliant region of the LV end-diastolic

Figure 5A-6 (Figure Not Available) Left ventricular (LV) diastolic transmural pressure-Lagrangian strain relations in a conscious (squares) and halothane-anesthetized (triangles) dog. The pressure-strain relation was not altered by halothane anesthesia, indicating that this volatile anesthetic does not affect intrinsic myocardial stiffness. alpha = gain; beta = modulus of myocardial stiffness. *(From Van Trigt et al [17])*

pressure-volume relation; however, this volatile agent does not directly alter the intrinsic viscoelastic properties of the myocardium. [1]

The effects of isoflurane and halothane on LV diastolic function in a canine model of dilated cardiomyopathy have recently been described. [65] In contrast to the findings in dogs with normal LV function, isoflurane improved several indices of LV relaxation and filling in cardiomyopathic dogs despite producing simultaneous negative inotropic effects. In addition, halothane did not exacerbate preexisting dia-stolic dysfunction inherent to this experimental model. The findings with isoflurane and halothane were most likely related to favorable reductions in LV preload produced by these volatile agents and not because of direct positive lusitropic effects. [65] These data further suggest that isoflurane-induced improvements of LV isovolumic relaxation and filling dynamics may contribute to relative maintenance of cardiac output in the presence of LV dysfunction despite simultaneous reductions in contractility. [65] The findings in cardiomyopathic dogs supported earlier clinical observations [62] [64] reporting that patients with severe ischemic heart disease or congestive heart failure tolerated isoflurane or halothane anesthesia without acute hemodynamic decompensation.

Recent investigations have demonstrated that the afterload dependence of LV relaxation is markedly enhanced in failing myocardium. [121] [122] This observation has important clinical consequences because afterload reduction may not only increase LV systolic performance by decreasing impedance to LV ejection but may also increase the rate of LV relaxation and contribute to improvements in LV diastolic filling and compliance. [123] The effects of isoflurane and halothane on the afterload dependence of LV relaxation have recently been explored in dogs before and after the development of rapid LV pacing-induced cardiomyopathy. [66] The afterload dependence of LV relaxation was unaffected by isoflurane and halothane anesthesia in dogs with dilated cardiomyopathy (Fig. 5-7) (Figure Not Available) , further indicating that these volatile agents do not exert direct actions on LV isovolumic relaxation in failing myocardium.

Left Ventricular - Arterial Coupling and Mechanical Efficiency

Optimum transfer of stroke volume from the LV to the arterial circulation requires appropriate matching of these mechanical systems. Left ventricular-arterial coupling has most often been described using a series elastic chamber model of the cardiovascular system (Fig. 5-8) (Figure Not Available) [124] The elastances of the contracting LV (E_{es}) and the arterial vasculature (E_a) are determined from LV end-systolic pressure-volume and end-systolic arterial pressure-stroke volume relations, respectively. [124] [125] [126] The ratio of E_{es} to E_a defines coupling between the LV and the arterial circulation [124] [125] and provides a useful technique for assessment of the actions of drugs, including volatile anesthetics, on LV-arterial matching *in vivo.* [127] [128] Analysis of the pressure-volume relation also creates a framework for the study of LV mechanical efficiency defined by the ratio of stroke work (SW) to pressure-volume area (PVA). [129]

Figure 5A-7 (Figure Not Available) Linear relationship between the time constant of isovolumic relaxation (tau) and left ventricular end-systolic pressure (P_{es}) during inferior vena caval occlusion (left panels) in a typical dog before (open squares) and after (solid squares) the development of pacing-induced cardiomyopathy in the conscious state and during isoflurane and halothane anesthesia. The histograms on the right illustrate the slope (R) of the tau-versus P_{es} -relationship in the conscious state (top right panel) and during isoflurane (middle right panel) and halothane (bottom right panel) anesthesia before (open bars) and after (solid bars) pacing. [a] Significantly ($P < 0.05$) different from normal myocardium. *(From Pagel et al [66])*

The influence of volatile anesthetics on LV-arterial coupling and mechanical efficiency have been studied in the normal canine cardiovascular system but have yet to be described in models of heart failure. LV-arterial coupling may theoretically be maintained during anesthesia because declines in LV afterload may balance simultaneous reductions in myocardial contractility. Low concentrations of halothane (1 MAC), but not isoflurane, reduced E_{es}/E_a in barbiturate-anesthetized, acutely instrumented dogs, consistent with depression of mechanical coupling between the LV and arterial circulation. [130] However, isoflurane also decreased E_{es}/E_a at 2 MAC, suggesting that the vasodilating effects of this anesthetic were unable to compensate for the relatively greater declines in contractility. More recently, desflurane, sevoflurane, and isoflurane were shown to maintain optimum LV-arterial coupling and mechanical efficiency as evaluated by E_{es}/E_a and SW/PVA at low anesthetic concentrations (
0.9 MAC) by producing simultaneous declines in myocardial contractility and LV afterload (Fig. 5-9) (Figure Not Available) [41] However,

Figure 5A-8 (Figure Not Available) Left ventricular (LV) pressure-volume diagrams during inferior vena caval occlusion and the definition of LV-arterial coupling. The LV maximal elastances of each pressure-volume diagram are used to calculate the slope (E_{es}) of the end-systolic pressure-volume relation. Effective arterial elastance (E_a) is determined as the ratio of end-systolic arterial pressure and stroke volume during steady-state hemodynamic conditions. In the pressure-volume plane, E_a represents the magnitude of the slope connecting end-systole to end-diastole. *(From Hettrick et al [44])*

mechanical matching between the LV and the arterial vasculature and efficiency of total LV energy transfer to external stroke work degenerates at higher anesthetic concentrations, indicating that anesthetic-induced reductions in contractility are not appropriately balanced by declines in afterload. Halothane (<1.0 MAC) has also been shown to reduce the ratio of oscillatory to mean hydraulic power *in vivo,* indicating that this agent decreases LV mechanical efficiency as well. [131] Detrimental alterations in LV-arterial coupling produced by volatile anesthetics contribute to reductions in overall cardiac performance observed with these agents *in vivo.*

Left Ventricular Afterload

Although a definition of LV afterload that describes the mechanical properties of the arterial vasculature opposing LV ejection is intuitively clear, [132] quantitative evaluation of afterload *in vivo* remains difficult. Systemic vascular resistance, calculated as the ratio of mean arterial pressure to cardiac output, is the most commonly used estimate of LV afterload. However, systemic vascular resistance inadequately describes LV afterload [133] because this index ignores the mechanical characteristics of the blood and arterial walls, fails to account for the frequency-dependent, phasic nature of arterial blood pressure and blood flow, and does not consider the potential effects of arterial wave reflection. As a result, systemic vascular resistance cannot be reliably used to quantify changes in LV afterload produced by drugs,

Figure 5A-9 (Figure Not Available) Histograms depicting left ventricular-arterial coupling (E_{es}/E_a ; top panel) and mechanical efficiency (SW/PVA; bottom panel) before (control 1; C_1), during 0.6, 0.9, and 1.2 MAC, and after sevoflurane (control 2; C_2). [a] Significantly ($P < 0.05$) different from C_1 ; [b] significantly ($P < 0.05$) different from 0.9 MAC sevoflurane; [c] significantly ($P < 0.05$) different from 1.2 MAC sevoflurane. *(Adapted from Hettrick et al [41])*

including volatile anesthetics, or cardiovascular disease. [134] Aortic input impedance [Z_{in} (omega)] obtained from power spectral or Fourier series analysis of aortic pressure and blood flow waveforms provides a comprehensive description of LV afterload because Z_{in} (omega) incorporates arterial viscoelasticity, frequency dependence, and wave reflection. However, because analysis of Z_{in} (omega) is conducted in the frequency domain and not as a function of time, Z_{in} (omega) is most often interpreted using an electrical three-element Windkessel model of the arterial circulation that describes characteristic aortic impedance (Z_c), total arterial compliance (C), and total arterial resistance (R). Z_c represents aortic resistance to LV ejection; C is determined primarily by the compliance of the aorta and represents the energy storage component of the arterial circulation; and R equals the combined resistances of the remaining arterial vasculature (Fig. 5-10) (Figure Not Available) . The three-element Windkessel model has been shown to closely approximate Z_{in} (omega) in a variety of physiologic conditions. [135] [136]

Volatile anesthetics alter Z_{in} (omega) by affecting the mechanical properties of the arterial vascular tree. [137] [138] [139] [140] Isoflurane produced dose-related decreases in R in chronically instrumented

Figure 5A-10 (Figure Not Available) Schematic diagram depicting the three-element Windkessel model of the arterial circulation. Diode A represents the aortic valve. Time-dependent blood flow [F(t)] and blood pressure [P(t)] entering the arterial system first encounters the resistance of the ascending aorta (characteristic aortic impedance; Z_c). Further flow is dictated by total arterial resistance (R) and total arterial compliance (C), the energy storage component of the arterial vasculature. *(From Hettrick et al [139])*

dogs consistent with the known effects of this drug on systemic vascular resistance, in contrast to the results obtained with halothane. [139] Isoflurane and halothane also caused similar increases in C and Z_c concomitant with reductions in mean arterial pressure. Thus, the major difference between the effects of isoflurane and halothane on LV afterload derived from the Windkessel model of Z_{in} (omega) was related to R, a property of arteriolar resistance vessels, and not to C or Z_c, the mechanical characteristics of the aorta (Fig. 5-11) (Figure Not Available) . A subsequent investigation demonstrated that desflurane, but not sevoflurane, also reduces R in dogs. [140] In contrast to the findings with isoflurane, however, desflurane did not affect C and Z_c, suggesting that this agent does not alter the mechanical properties of the aorta. Importantly, the inverse relationship between C and mean arterial pressure remains unchanged by volatile anesthetics, [139] [140] unlike the findings with the arterial vasodilator sodium nitroprusside [139] [141] or the intravenous anesthetic propofol. [142]

Isoflurane and halothane produce alterations in Z_{in} (omega) in cardiomyopathic dogs that are substantially different than those observed in normal dogs. [143] These volatile anesthetics decreased arterial pressure but did not affect C and Z_c in the presence of LV dysfunction. Halothane increased R and isoflurane did not reduce R in dogs with dilated cardiomyopathy. Thus, neither isoflurane nor halothane reduces arterial hydraulic resistance or favorably improves the rectifying properties of the aorta in dogs with pacing-induced cardiomyopathy (Fig. 5-12) (Figure Not Available) . The findings suggest that volatile agents do not exert beneficial actions on LV afterload in the presence of failing myocardium.

Right Ventricular Function

The crescent-shaped right ventricle (RV) is composed of embryologically distinct inflow and outflow tracts [144] [145] that differ in their structure and response to those of autonomic nervous system activity. [146] The sequential contraction of the RV inflow and outflow tracts establish regional pressure gradients within the RV during systole [147] [148] [149] and account for the peristaltic mechanical action of this pump. True isovolumic relaxation does not occur in the RV. [150] Instead, ejection

Figure 5A-11 (Figure Not Available) Histograms depicting the effects of sodium nitroprusside (SNP), halothane, and isoflurane on total arterial compliance (C; top), total arterial resistance (R; middle), and characteristic aortic impedance (Z_c; bottom). The low, medium, and high doses of volatile anesthetics are 1.25, 1.5, and 1.75 MAC, respectively. SNP doses produce comparable changes in mean arterial pressure. *Significantly ($P < 0.05$) different from control;
significantly ($P < 0.05$) different from low dose; § significantly ($P < 0.05$) different from middle dose;
significantly ($P < 0.05$) different from halothane. *(From Hettrick et al [139])*

of blood from the outflow tract into the pulmonary artery continues after the inflow tract has begun to relax. [148] [150]

The effects of volatile anesthetics on the function and contraction sequence of the RV inflow and outflow tracts have been studied incompletely. By using a uniform definition of end-systole and end-diastole for both regions of the RV, [151] halothane was shown to produce similar depression of contractile function in RV inflow and outflow tracts in dogs. More recently, another investigation conducted in anesthetized pigs [152] demonstrated that halothane caused dose-related decreases in RV contractility evaluated using regional preload recruitable stroke work derived from RV pressure-segment length diagrams in the RV inflow and outflow tracts in the presence and absence of autonomic nervous system reflexes. Importantly, halothane also abolished the normal RV sequential contraction pattern without exerting differential negative inotropic effects in different regions of the RV. [152] These data suggest that volatile anesthetics

Figure 5A-12 (Figure Not Available) Histograms illustrating total arterial compliance (C; top panel), total arterial resistance (R; middle panel), and characteristic aortic impedance (Z_c; bottom panel) in the conscious state and during 1.1 and 1.5 MAC isoflurane in dogs before (normal; hatched bars) and after (cardiomyopathy; solid bars) the development of pacing-induced cardiomyopathy. [a] Significantly ($P < 0.05$) different from normal myocardium. *(From Hettrick et al [143])*

may alter RV contraction dynamics by adversely affecting cardiac autonomic nervous system activity.

Systemic Hemodynamics

Volatile anesthetics cause direct negative chronotropic actions *in vitro* by depressing sinoatrial node activity. [153] However, alterations in heart rate *in vivo* are primarily determined by the interaction of volatile agents and baroreceptor reflex activity. [154] [155] Halothane does not appreciably change heart rate in humans [6] because this agent attenuates baroreceptor reflex responses. [156] [157] [158] Heart rate increases to variable degrees with enflurane; however, these increases in heart rate may be insufficient to preserve cardiac output. [11] [159] Isoflurane increases heart rate in response to simultaneous decreases in arterial pressure. [12] These findings occur with this volatile agent because baroreceptor reflexes are relatively preserved when compared with those of equi-MAC concentrations of halothane and enflurane. [155] Desflurane also causes dose-related increases in heart rate in humans. [37] [38] [160] Desflurane- and isoflurane-induced tachycardia may be more ronounced in pediatric patients or in the presence of vagolytic agents and, conversely, may be attenuated in neonates [161] and geriatric patients or by the concomitant administration of opioids. [62] [163] Rapid increases in the inspired desflurane concentration above 1 MAC may be associated with further transient increases in heart rate and arterial pressure resulting from sympathetic nervous system activation. [42] [44] fsInterestingly, similar increases in heart rate are also observed when the inspired isoflurane concentration is rapidly increased. [44] The cardiovascular stimulation induced by rapid increases in desflurane or isoflurane concentration in humans results from activation of tracheopulmonary and systemic receptors [45] and is attenuated by pretreatment with $beta_1$ -adrenoceptor antagonists, $alpha_2$ -adrenoceptor agonists, or opioids. [43] In contrast to the findings with isoflurane and desflurane, sevoflurane neither alters heart rate [164] [165] [166] [167] nor causes cardiovascular stimulation during rapid increases in anesthetic concentration in humans. [168]

All modern volatile anesthetics cause concentration-related decreases in arterial pressure. [6] [11] [12] [37] [160] [164] fsfsThe mechanism by which these agents reduce arterial pressure differs among anesthetics. Decreases in arterial pressure produced by halothane and enflurane can be primarily attributed to reductions in myocardial contractility and cardiac output. [1] In contrast, decreases in arterial pressure associated with isoflurane, desflurane, and sevoflurane anesthesia occur as a result of reductions in LV afterload, [139] [140] whereas myocardial contractility is relatively preserved. [1] Thus, isoflurane, desflurane, and sevoflurane maintain cardiac output because these agents produce less pronounced reductions in myocardial contractility and greater decreases in systemic vascular resistance than does halothane or enflurane in humans. [34] [166] [169] Isoflurane and desflurane may also preserve autonomic nervous system regulation of the circulation to a greater degree than do other volatile anesthetics. [42] [155] [168] The baroreceptor reflex-mediated tachycardia that occurs during isoflurane and desflurane anesthesia serves to maintain cardiac output despite simultaneous declines in myocardial contractility and stroke volume. Declines in arterial pressure produced by volatile anesthetics may be attenuated by surgical stimulation or concomitant administration of nitrous oxide. [38] [170] Volatile anesthetics also cause modest, dose-related increases in right atrial pressure in humans. [34] [169] These effects probably occur as a result of direct negative inotropic actions. The vasodilating effects of isoflurane, desflurane, and sevoflurane cause less pronounced increases in right atrial pressure than those observed during halothane or enflurane anesthesia.

The cardiovascular effects of volatile anesthetics are altered by the duration of anesthesia. Increases in myocardial contractility and cardiac output and decreases in LV preload and afterload occur after several hours of constant MAC anesthesia. [6] [12] [37] [159] [171] Heart rate may also increase during prolonged halothane [6] [171] or enflurane [159] anesthesia; however, arterial pressure remains constant. Recovery from circulatory depression is greatest during halothane anesthesia [171] and less pronounced during prolonged administration of isoflurane [12] and desflurane. [37] The time-dependent improvements in hemodynamics observed with volatile anesthetics are antagonized by propranolol and may result from enhanced sympathetic nervous system activity. [172]

The systemic hemodynamic effects of volatile agents in the presence of LV dysfunction are similar but not identical to those observed in the normal heart. Volatile

anesthetics, including isoflurane, modestly increase or do not affect heart rate in experimental animals with pacing- or doxorubicin-induced dilated cardiomyopathy [65] [173] and in patients

with coronary artery disease and LV dysfunction. [62] [64] [174] [175] These findings may be attributed to altered baroreceptor reflex activity, beta $_1$ -adrenoceptor down regulation, and increases in central sympathetic and withdrawal of parasympathetic nervous system tone associated with heart failure. [176] Isoflurane and halothane cause pronounced reductions in LV end-diastolic pressure and chamber dimension in cardiomyopathic dogs concomitant with decreases in mean arterial pressure. [65] These findings support previously observed declines in pulmonary artery pressures during isoflurane, enflurane, and halothane anesthesia in patients with coronary artery disease and heart failure [62] [64] [174] [175] and indicate that venodilation represents a major hemodynamic consequence of these anesthetics in experimental and clinical heart failure. In contrast to the findings in normal dogs, isoflurane did not beneficially influence, and halothane detrimentally affected, the determinants of LV afterload in cardiomyopathic dogs. [143] As a result of these actions and the simultaneous declines in LV preload and myocardial contractility, cardiac output may be more profoundly reduced during isoflurane or halothane anesthesia in the presence of preexisting LV dysfunction. [143]

VOLATILE ANESTHETICS AND CARDIAC ELECTROPHYSIOLOGY

Cardiac Conduction

Volatile anesthetics slow the rate of sinoatrial node discharge by direct and indirect effects on sinoatrial node automaticity. [153] [177] These actions may be altered *in vivo* by vasoactive drugs or autonomic nervous system activity. [178] Halothane, enflurane and, to some extent, isoflurane shorten cardiac action potential and effective refractory period duration in normal Purkinje fibers [177] [179] [180] however, these agents prolong His-Purkinje and ventricular conduction times. [177] [180] [181] Halothane, enflurane, and isoflurane also prolong atrioventricular conduction time and refractoriness. [180] [182] [183] When combined with the direct actions of volatile anesthetics on sinoatrial node discharge, these data suggest that volatile anesthetics have the potential to produce bradycardia and atrioventricular conduction abnormalities. However, primary disturbances in atrioventricular conduction leading to second or third degree atrioventricular block in humans probably do not occur with volatile anesthetics in the absence of conduction disease or drugs that directly prolong the atrioventricular conduction time. [184] [185]

Volatile agents may have pro- or antiarrhythmogenic actions against abnormal cardiac electrophysiologic mechanisms produced by myocardial ischemia or infarction. Halothane, enflurane, and isoflurane have been shown to be cardioprotective against ventricular fibrillation produced by coronary artery occlusion [186] [187] and reperfusion. [188] Protective effects against ouabain-induced arrhythmias have also been demonstrated during halothane anesthesia. [189] Volatile anesthetics may also exert antiarrhythmic effects by opposing subsidiary pacemaker activity in infarcted myocardium. [179] Conversely, halothane and, to a lesser extent, isoflurane may be arrhythmogenic in Purkinje fibers in experimental myocardial infarction by facilitating reentrant activity or by increasing temporal dispersion of refractory-period recovery. [179] [190] These actions may be related to inhibition of slow Na^+ current in false tendon fibers and induction of reentry of premature impulses into more refractory Purkinje fibers in the border zone of an ischemic area. [191] Halothane, enflurane, and isoflurane have been shown to prolong the QT_c interval in humans. [192] These data suggest that patients with idiopathic or acquired long QT syndrome may be at greater risk of developing *torsades de pointes* tachycardia [193] during anesthesia with these drugs.

Epinephrine-Induced Arrhythmias

Halothane and, to a lesser extent, other volatile anesthetics sensitize myocardium to the arrhythmogenic effects of epinephrine. [194] [195] [196] Sensitization is the interaction between volatile anesthetics and catecholamines that leads to reductions in the threshold for both atrial and ventricular arrhythmias. Sequentially escalating doses of epinephrine produce premature ventricular contractions and sustained ventricular tachyarrhythmias during halothane anesthesia. [194] Halothane-epinephrine-induced arrhythmias are attenuated by pretreatment with thiopental, [194] presumably via effects on the atrioventricular node or the upper His bundle. [197] A synergistic interaction between $alpha_1$ - and beta-adrenoceptors has been strongly implicated in the pathogenesis of halothane-epinephrine-induced ventricular arrhythmias. [198] Stimulation of the $alpha_{1A}$ -adrenoceptor in the His-Purkinje system by epinephrine during halothane anesthesia transiently slows Purkinje fiber conduction. [199] [200] This proarrhythmogenic effect is mediated by phospholipase C and the intracellular second messenger, inositol triphosphate. [200] Recent evidence indicates that enhanced conduction in the Purkinje-ventricular muscle junction accompanied by simultaneous $alpha_1$ -adrenoceptor-mediated depression of Purkinje conduction also plays an important role in halothane-epinephrine-induced arrhythmias. [201] The doses of epinephrine required to produce ventricular arrhythmias during desflurane or sevoflurane anesthesia [198] [202] fsare similar to but significantly less than those observed during administration of isoflurane and halothane, respectively. Halothane-catecholamine sensitization also promotes abnormal automaticity of dominant and latent atrial pacemakers. [203] [204] [205] [206] These effects may produce premature ventricular contractions and arrhythmias originating from the His bundle. [203] Intact sinoatrial node function reduces the incidence of epinephrine-induced ventricular escape during halothane anesthesia and is protective against His bundle arrhythmias. [206]

VOLATILE ANESTHETICS AND THE CORONARY CIRCULATION

Coronary Vascular Effects In Vitro

Volatile anesthetics have been shown to cause direct coronary artery vasodilation *in vitro*; however, simultaneous reductions in the determinants of myocardial oxygen consumption (MVO_2), including heart rate, preload, afterload,

and inotropic state, produced by these agents cause coronary vasoconstriction *in vivo* via metabolic autoregulation. Volatile anesthetic-induced alterations in coronary blood flow are also affected by reductions in coronary perfusion pressure produced by these agents. Thus, the combination of direct and indirect actions ultimately determines the net effect of volatile anesthetics on coronary vascular tone. Halothane, isoflurane, and enflurane cause vasodilation of isolated coronary arteries. [207] [208] [209] [210] [211] [212] [213] [214] Halothane produces greater coronary artery dilation than does isoflurane at equivalent MAC [208] [209] [210] [212] [213] in isolated coronary arteries larger than 2000 mum. [208] [210] [211] [212] [213] In contrast, isoflurane causes vasodilation of predominantly small (<900 mum) canine epicardial coronary arteries. [211] Halothane may produce greater vasodilator effects in large coronary arteries than does isoflurane because halothane causes more pronounced suppression of voltage-dependent Ca^{2+} current. [215]

The direct negative inotropic effects of volatile anesthetics cause a reduction in coronary blood flow in isolated, contracting hearts during precise control of ventricular loading conditions via flow-metabolism coupling. [216] In these conditions, a decrease in myocardial O_2 demand is accompanied by an increase in coronary vascular resistance, findings that may be incorrectly interpreted suggesting that volatile agents produce coronary vasoconstriction. However, examination of the actions of volatile anesthetics on myocardial O_2 extraction and the ratio of myocardial O_2 delivery to MVO_2 reveals that inhalational anesthetics are coronary vasodilators. Halothane and isoflurane decrease myocardial O_2 extraction and increase the ratio of O_2 delivery to consumption in isolated, beating hearts. [217] [218] [219] [220] These findings indicate that volatile anesthetics produce direct coronary vasodilation in isolated hearts because myocardial O_2 delivery exceeds MVO_2 and coronary sinus O_2 tension increases. Halothane, isoflurane, and sevoflurane also cause similar reductions in adenosine-induced coronary flow reserve [221] in tetrodotoxin-arrested, isolated hearts. Because mechanical work is not performed in this preparation, these findings support the hypothesis that volatile agents cause direct coronary vasodilation of similar magnitude.

Coronary Vascular Effects In Vivo

Halothane has variable effects on coronary blood flow and coronary vascular resistance *in vivo* that occur concomitant with changes in MVO_2. [222] [223] [224] [225] Decreases in MVO_2 cause declines in coronary blood flow with relative maintenance or modest increases in coronary vascular resistance during halothane anesthesia. [14] [226] [227] Despite the decreases in coronary blood flow, halothane increases coronary sinus O_2 tension and decreases O_2 extraction, [223] [225] indicating that halothane is a relatively weak coronary vasodilator. Like halothane, isoflurane variably alters coronary blood flow *in vivo*. [19] [228] [229] [230] [231] Isoflurane reduces MVO_2 and simultaneously decreases O_2 extraction, indicating direct coronary vasodilation. [229] Isoflurane has also been shown to produce mild and transient increases in blood flow independent of changes in MVO_2 and autonomic nervous system activity during inhalational induction of anesthesia. [232] Perfusion of the left anterior descending coronary artery with blood previously equilibrated with isoflurane dramatically increases coronary blood flow [233]; however, only mild coronary vasodilation occurs after a period of anesthetic equilibration in a similar experimental model. [230] Isoflurane-induced increases in coronary blood flow are not accompanied by epicardial coronary artery dilation, indicating that isoflurane dilates predominantly small coronary arteries. [234] However, adenosine, a potent coronary vasodilator, causes considerably greater vasodilation in coronary microvessels than does isoflurane. [235] The effects of enflurane on the coronary circulation *in vivo* are somewhat controversial. [212] [218] [219] [220] Enflurane produces greater reductions in MVO_2 than does isoflurane, concomitant with metabolically determined declines in coronary blood flow. [236] [237] However, isoflurane produces more profound decreases in myocardial O_2 extraction than does enflurane, indicating that isoflurane is a more potent coronary vasodilator than its structural isomer. [237]

The influence of the new volatile anesthetics on coronary blood flow in the intact cardiovascular system has been examined incompletely. Desflurane and isoflurane caused similar increases in the ratio of O_2 delivery to consumption and decreases in O_2 extraction, consistent with those of coronary vasodilation. [238] However, the increases in coronary blood flow produced by desflurane, but not isoflurane, are attenuated by pharmacologic blockade of the autonomic nervous system, suggesting that isoflurane causes greater direct coronary vasodilation *in vivo* than does desflurane. [16] Sevoflurane does not appear to produce any significant degree of coronary vasodilation, [46] [221] [239] [240] [241] in contrast to the findings with other volatile agents.

Coronary Vasodilator Reserve and Autoregulation

Coronary vasodilator reserve, defined as the ratio of peak coronary blood flow after brief coronary artery occlusion (e.g., reactive hyperemia) and baseline flow, has been shown to be affected by halothane and isoflurane. [242] Coronary vasodilator reserve is greater during isoflurane as compared with halothane anesthesia. [242] This observation suggested that halothane may be a more potent coronary vasodilator than isoflurane because greater baseline coronary vasodilation should be accompanied by a reduced ability to further increase coronary blood flow in response to a brief ischemic episode. However, halothane also reduces the determinants of MVO_2 to a greater degree than does isoflurane *in vivo*. Peak coronary blood flow during reactive hyperemia and percent flow debt repayment are directly related to the intensity of the ischemic stimulus and the magnitude of O_2 debt accrued during coronary artery occlusion. Thus, differences in coronary vasodilator reserve produced by isoflurane and halothane may reflect differences in the intensity of ischemia during coronary occlusion and not the relative vasodilator efficacy of these volatile anesthetics. [216]

Dilation of coronary arteriolar resistance vessels by volatile anesthetics alters pressure autoregulation in the coronary vasculature. [243] Changes in autoregulation produced by vasoactive drugs, including volatile agents, are typically determined by the slope of the pressure-flow curve generated by progressive constriction of a coronary artery.

Figure 5A-13 (Figure Not Available) A qualitative description of the effects of volatile anesthetics on the coronary blood flow (CBF)-pressure relationship demonstrating the effect of adenosine-induced maximal coronary vasodilation in awake and anesthetized dogs. Solid lines are drawn from mean slopes determined by linear regression analysis. Dashed lines represent the nonlinear portion of the curve and are estimates. When compared with the findings obtained in awake dogs, the anesthetics affect absolute CBF variably but do not increase the slope of the

CBF-pressure plots. *(From Hickey et al [235])*

Changes in these pressure-flow curves demonstrate that autoregulation is disrupted during anesthesia when compared with that of the conscious state (Fig. 5-13) (Figure Not Available) . Isoflurane produces more profound alterations in autoregulation than does halothane or enflurane as indicated by greater increases in the slope of the pressure-flow relation. Coronary perfusion pressure also plays a more important role in the determination of coronary blood flow during anesthesia. Although volatile anesthetics impair coronary autoregulation to some degree, these agents do not produce the profound degree of coronary vasodilation and inhibition of autoregulation caused by adenosine or dipyridamole. [230] [237] [243] In contrast to volatile agents, these drugs cause maximal coronary vasodilation and inhibit pressure autoregulation to such a degree that coronary blood flow becomes directly dependent on coronary perfusion pressure. Volatile anesthetics are only weak coronary vasodilators.

Mechanisms of Volatile Anesthetic - *Induced Coronary Vasodilation*

Volatile anesthetics produce direct coronary artery relaxation by affecting intracellular Ca^{2+} regulation at several locations in the vascular smooth muscle cell. [216] Volatile agents inhibit Ca^{2+} influx through voltage- [215] and receptoroperated [207] [208] [212] [213] [244] Ca^{2+} channels in coronary vascular smooth muscle. Volatile anesthetics also reduce Ca^{2+} accumulation in and release by the coronary vascular smooth muscle sarcoplasmic reticulum (SR), [245] inhibit G proteins linked to phospholipase C, [244] and decrease formation of the second messenger inositol triphosphate. [246]

The coronary vasodilating actions of volatile agents are probably not related to the production or release of nitric oxide (endothelium-dependent relaxing factor). Investigations conducted in isolated coronary [214] and aortic [245] [247] [248] [249] vascular preparations and in the intact canine coronary circulation [233] demonstrated that volatile anesthetic-induced coronary vasodilation occurs independently of nitric oxide. However, some experimental evidence suggests that the direct coronary vasodilator effects of isoflurane may be mediated by the vascular endothelium. [207] [250] Conversely, other data indicate that halothane, enflurane, and isoflurane may adversely affect the release or action of nitric oxide. [247] [248] [249] [251] [252] Although nitric oxide-induced formation of cyclic guanosine monophosphate (cGMP) may be attenuated to some degree by halothane, [253] several studies indicate that volatile anesthetics do not affect vasodilation produced by the nitric oxide donors sodium nitroprusside and nitroglycerin. [248] [252] [254] [255] Volatile anesthetics may also reduce the stability of nitric oxide by generating oxygen-derived free radicals [255] while leaving nitric oxide release and its action on vascular smooth muscle unaffected. [251] Whether the results of these later studies conducted in isolated aortic preparations are applicable to the coronary circulation requires further evaluation, but these investigations provide important information about the potential effects of volatile agents on the coronary vasculature.

Halothane and isoflurane have recently been shown to cause coronary vasodilation by activation of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels. [256] [257] Increases in coronary blood flow in response to halothane and isoflurane were attenuated by the K_{ATP} channel antagonist glyburide in isolated rat hearts and anesthetized pigs, respectively. [256] [257] Glyburide also partially blocked increases in coronary blood flow during intracoronary administration of volatile anesthetic-equilibrated blood in canine hearts *in situ.*[258] Isoflurane-induced reductions in coronary vascular resistance were attenuated by the selective adenosine $_1$ (A_1) receptor antagonist 8-cyclopentyl-1,3,dipropylxanthine (DPCPX). [259] These data suggest that coronary vasodilation produced by isoflurane may partially occur as a result of stimulation of A_1 receptors coupled to K_{ATP} channels. [259] [260]

Volatile Anesthetics and Ischemic Myocardium

Halothane and isoflurane decrease subendocardial blood flow and myocardial lactate extraction, produce contractile dysfunction, and cause electrocardiographic changes in the presence of a coronary stenosis concomitant with declines in coronary perfusion pressure. [51] [261] [262] Regional ischemia during isoflurane- or halothane-induced reductions in perfusion pressure is functionally indicated by the appearance of paradoxical systolic lengthening and postsystolic shortening. [51] [263] Contractile dysfunction in the region distal to a critical coronary stenosis is more severe during isoflurane as compared with halothane anesthesia coincident with higher flows in the normal zone and lower flows in the ischemic zone. [262] [264] These findings suggest that coronary vasodilation produced by isoflurane may cause a detrimental redistribution

of coronary blood flow away from ischemic myocardium if hypotension is allowed to occur.

The adverse effects of volatile anesthetics on ischemic myocardium are avoided if coronary perfusion pressure is restored. Subendocardial blood flow in the perfusion bed distal to a critical coronary stenosis is reduced during isoflurane-induced declines in arterial pressure; however, treatment of hypotension with phenylephrine restores subendocardial blood flow to values observed before administration of isoflurane. [265] [266] The transmural distribution of coronary blood flow between the subendocardium and subepicardium (endo/epi ratio) decreases during isoflurane anesthesia despite control of arterial pressure. Administration of phenylephrine to maintain arterial pressure constant increases subepicardial blood flow more than subendocardial flow. This increase in subepicardial perfusion accounts for the decline in the endo/epi ratio in the absence of an absolute reduction in subendocardial flow. Restoration of coronary perfusion pressure to baseline levels during isoflurane anesthesia also increases coronary collateral blood flow and normalizes myocardial O_2 tension in the ischemic zone. [236]

Investigations in dogs with steal-prone anatomy (complete occlusion of a coronary artery with collateral flow from an adjacent vessel having a critical stenosis) have repeatedly demonstrated that isoflurane and halothane do not alter collateral-dependent or ischemic zone myocardial blood flow, [267] [268] [269] [270] [271] endo/epi distribution, [267] [268] or electrocardiogram [267] when diastolic arterial pressure is held constant. Coronary collateral perfusion is unchanged during isoflurane or halothane anesthesia in dogs at a mean arterial pressure of 50 mm Hg. [272] Coronary steal does not occur in a chronically instrumented canine model of coronary artery disease with isoflurane, [269] [271] halothane, [270] desflurane, [273] or sevoflurane [274] independent of coronary stenosis severity or coronary collateral development. [268] [269] [270] [271] The findings also refute earlier evidence in dogs with ameroid constrictor- induced augmentation of the coronary collateral circulation, suggesting that isoflurane reduces collateral blood flow and causes coronary steal *in vivo*. [275] These effects of volatile anesthetics are in marked contrast to those obtained with adenosine, a potent coronary vasodilator that produces coronary steal when arterial pressure is maintained at control levels in models of multivessel coronary artery disease (Fig. 5-14) (Figure Not Available) . [269] [271] [276]

Volatile Anesthetic - *Induced Myocardial Protection*

The relatively academic controversy about volatile anesthetic-induced coronary vasodilation and coronary steal has detracted from substantial experimental evidence indicating that volatile agents exert important cardioprotective effects during myocardial ischemia and reperfusion injury. Halothane attenuates ST segment changes caused by brief coronary artery occlusion [277] [278] and decreases ST segment elevation to a greater extent than do propranolol and sodium nitroprusside despite producing similar hemodynamic effects. [278] Halothane and isoflurane reduce myocardial infarct

Figure 5A-14 (Figure Not Available) Occluded-to-normal- and occluded-to-stenotic-zone myocardial blood flow in dogs with steal-prone coronary artery anatomy in the conscious state (C), during 1.1 and 1.9 MAC isoflurane (I) anesthesia, during adenosine (A) infusions (0.54 and 1.08 mg/min), and during maintenance of heart rate and arterial pressure at conscious values during the highest doses (BP). Isoflurane does not cause coronary steal, in contrast to significant (* $P < 0.05$) reductions in blood flow to collateral-dependent myocardium produced by adenosine. *(From Hartman et al [271])*

size after coronary artery ligation. [55] [56] [279] [280] [281] Enflurane decreases cardiac lactate production in the presence of a critical coronary artery stenosis during artificial control of perfusion pressure. [57] Isoflurane and desflurane have been shown to produce beneficial actions on LV diastolic mechanics during acute regional myocardial ischemia. [61] Halothane, enflurane, and isoflurane decrease myocardial reperfusion injury and improve functional recovery after global ischemia in isolated hearts. [282] [283] [284] [285] Volatile agents also enhance systolic functional recovery of stunned myocardium when these agents are administered before and during, [58] [60] but not after, [286] [287] brief periods of myocardial ischemia *in vivo* (Fig. 5-15) (Figure Not Available) . These effects are accompanied by preservation of high-energy phosphate levels. [58] Volatile anesthetics have been shown to attenuate the effect of oxygen-derived free radicals on LV pressure development in isolated hearts. [288] Halothane also preserves contractile function and ultrastructural integrity during reperfusion after normothermic cardioplegic arrest. [59]

Volatile anesthetics may also produce beneficial effects on blood flow to ischemic myocardium. Decreases in collateral blood flow after coronary artery occlusion have

been shown to be less pronounced than declines in flow to normal myocardium in the presence of halothane. [289] The ratio of myocardial O_2 delivery to MVO_2 is also increased in collateral-dependent myocardium during halothane anesthesia. [289] Recent evidence indicates that sevoflurane actually increases blood flow to collateral-dependent myocardium when arterial pressure is maintained at conscious values. [274] Halothane may inhibit platelet thrombi formation via increases in platelet cyclic adenosine monophosphate concentration and decrease cyclical variations in coronary blood flow associated with a critical coronary artery stenosis. [290] Most recently, volatile anesthetics have been shown to attenuate adhesion of neutrophils and platelets in the coronary vasculature after ischemia and reperfusion. [291]

The mechanisms responsible for volatile anesthetic-induced cardioprotection during myocardial ischemia and reperfusion are understood incompletely. The beneficial effects of volatile anesthetics may be attributed to a favorable reduction in myocardial oxygen demand required for active contraction with concomitant preservation of energy-dependent vital cellular processes because these agents cause direct negative inotropic, lusitropic, and chronotropic effects and decrease LV afterload. However, halothane also exerts protective effects during complete functional arrest induced by cardioplegia, [59] indicating that preferential alterations in myocardial oxygen supply-demand relations are not solely responsible for the antiischemic actions of this anesthetic. Halothane, enflurane, and isoflurane may significantly lower excessive intracellular Ca^{2+} during reperfusion via a direct decline in the net transsarcolemmal Ca^{2+} transient resulting from partially inhibited Ca^{2+} channel activity [69] [71] [72] [73] or an indirect reduction of oxygen-derived free radical formation. [288]

Recent evidence indicates that the cardioprotective effects of isoflurane during postischemic, reperfusion injury are partially mediated by activation of K_{ATP} channels. [260] The K_{ATP} channel antagonist glyburide completely abolished the protective effects of isoflurane in stunned myocardium but did not alter the time course of recovery of contractile function when administered alone (Fig. 5-16) (Figure Not Available) [259] [292] These results *in vivo* suggest that isoflurane activates K_{ATP} channels. This hypothesis is supported by preliminary data using patch clamp techniques demonstrating that isoflurane stimulates outward K^+ current through K_{ATP} channels in isolated ventricular myocytes. [293] Isoflurane may also reduce the sensitivity of K_{ATP} channels to inhibition by ATP, thereby increasing the open state probability of the channel. [294] The role of the A_1 receptor in the enhanced functional recovery of stunned myocardium produced by isoflurane has been recently examined. [295] The selective A_1 receptor antagonist DPCPX partially attenuated but did not completely abolish the beneficial effects of isoflurane in stunned myocardium produced by multiple brief episodes of ischemia and reperfusion. [295] However, isoflurane eliminated increases in interstitial adenosine measured with a myocardial microdialysis technique during repetitive periods of coronary artery occlusion and reperfusion in this study. The attenuation of ATP breakdown and subsequent reduction in interstitial adenosine observed during isoflurane anesthesia were similar to those observed after ischemic preconditioning [296] or

Figure 5A-15 (Figure Not Available) Segment-shortening data (expressed as a percent of control) during a 15-minute coronary artery occlusion (O) and at various times after reperfusion in the conscious (C) and halothane-anesthetized (H) states. Comparisons are made at various times with those animals anesthetized with halothane for 2.25 hours and allowed to emerge from anesthesia over a 5-hour period but not undergoing coronary artery occlusion and reperfusion. *(From Warltier et al [60])*

Figure 5A-16 (Figure Not Available) Percent segment shortening (%SS) in the intermittently ischemic and reperfused left anterior descending (LAD) coronary artery region. %SS decreases significantly ($P < 0.05$) from baseline during each 5-minute LAD occlusion and reperfusion in all groups. Significant decreases in %SS during each 5-minute reperfusion and throughout 180 minutes of final reperfusion are observed in dogs pretreated with glyburide, a K_{ATP} channel antagonist, in the presence or absence of isoflurane. %SS recovers to baseline values after reperfusion in dogs receiving isoflurane alone.
Significantly ($P < 0.05$) different from dogs pretreated with drug vehicle; § significantly ($P < 0.05$) different from dogs pretreated with glyburide;
significantly ($F < 0.05$) different from dogs receiving glyburide and isoflurane. *(From Kersten et al [255])*

administration of the K_{ATP} channel agonist bimakalim. [297] These findings suggest that isoflurane either directly activates A_1 receptors or indirectly enhances sensitivity of A_1 receptors to reduced quantities of endogenously released adenosine. [295] These results also support the hypothesis that K_{ATP} channel activation represents the end effector of the cardioprotective signal transduction pathway activated during isoflurane anesthesia. [260]

Experimental evidence suggests that isoflurane reduces myocardial infarct size *in vivo* by activating K_{ATP} channels in a manner that bears striking similarity to those observed during ischemic preconditioning. Isoflurane has been previously shown to decrease the extent of myocardial infarction [279] ; however, the mechanisms responsible for this beneficial action have only recently been elucidated. Halothane, enflurane, and isoflurane decreased infarct size in isolated and *in situ* rabbit hearts to an extent similar to that of ischemic preconditioning. [280] The protective effects of halothane were completely abolished by pretreatment with selective antagonists to either the A_1 receptor or protein kinase C. Isoflurane also markedly reduced the extent of myocardial infarction in barbiturate-anesthetized, acutely instrumented dogs. [56] The protective effect of isoflurane was equivalent to that caused by ischemic preconditioning, occurred despite discontinuation of isoflurane 30 minutes before prolonged coronary artery occlusion, could not be explained by beneficial alterations in hemodynamics, and was abolished by pretreatment with glyburide (Fig. 5-17) (Figure Not Available) [56] This "anesthetic-induced preconditioning" has also been described in rabbits. [281] These data indicate that isoflurane-induced reductions in myocardial infarct size are characterized by a short-term memory phase similar to that of ischemic preconditioning and are consistent with previous findings that pharmacologic stimulation of both A_1 receptors and K_{ATP} channels mimics the conditions present during ischemic preconditioning. [298]

Coronary Vascular Effects of Volatile Anesthetics in Humans

Evaluation of the actions of volatile anesthetics on the human coronary circulation is difficult not only because the methods used to determine coronary blood flow in humans are limited but also because the interpretation of clinical findings during anesthesia is complicated by the changes in hemodynamics, the impact of surgery, and the use of adjuvant anesthetics or vasoactive drugs. Halothane decreases MVO_2 [62] [299] and variably alters coronary blood flow in patients with coronary artery disease; however, metabolic or electrocardiographic evidence of ischemia has not been observed during halothane anesthesia. [62] [299] [300] [301] Coronary blood flow may be reduced by halothane or enflurane [302] in

Figure 5A-17 (Figure Not Available) Schematic illustration of canine myocardium subjected to a 60-minute coronary artery occlusion and reperfusion and then stained to identify the region of myocardial infarction (black area) within the area of myocardium at risk for infarction (light-gray area). Isoflurane decreased the extent of myocardial infarction. The protective effect of isoflurane was equivalent to that produced by ischemic preconditioning and was abolished by pretreatment with glyburide. *Significantly ($P < 0.05$) different from control. *(Modified from Kersten et al [56])*

some patients concomitant with decreases in MVO_2 , but simultaneous declines in O_2 extraction [62] [302] reflect relative coronary vasodilation.

A report published in 1983 by Reiz et al [63] described the occurrence of myocardial ischemia as indicated by new electrocardiographic changes and abnormal myocardial lactate extraction in 10 of 21 patients anesthetized with isoflurane undergoing major vascular surgery. Five patients were treated with phenylephrine and pacing to return arterial pressure and heart rate to control values, and after these interventions, electrocardiographic and metabolic derangements resolved in 2 of 5 patients. Despite the apparent dependence of these new episodes of myocardial ischemia on alterations in systemic hemodynamics, the authors [63] proposed that isoflurane had caused coronary steal in these patients, even though no specific evidence of blood flow redistribution between normal and collateral-dependent zones was presented. The data of Reiz et al [63] have not been uniformly supported by subsequent studies. Coronary blood flow has been shown to remain unchanged during isoflurane anesthesia in patients undergoing coronary artery bypass graft surgery; however, coronary sinus O_2 content increases consistent with modest coronary vasodilation. [303] [304] [305] Isoflurane alone does not produce electrocardiographic or metabolic evidence of ischemia. [304] Instead, myocardial ischemia occurring during isoflurane anesthesia is most often associated with tachycardia or hypotension. [64] [300] [303] [305] In addition, isoflurane actually increases the tolerance to pacing-induced ischemia in patients with coronary artery disease. [306] Comparisons of studies examining the effects of isoflurane on the incidence of intraoperative myocardial ischemia are also complicated by differences in patient age, surgical procedure, operative time, and preoperative LV ejection fraction. [307] [308] Importantly, compelling evidence demonstrating redistribution of coronary blood flow away from ischemic to normal myocardium in humans anesthetized with isoflurane has yet to appear.

The incidence of intraoperative myocardial ischemia in susceptible patients has been difficult to define. Less than 50 percent of intraoperative ischemic episodes have been linked to alterations in systemic hemodynamics. [309] [310] [311] [312] The strongest predictor of intraoperative ischemia remains preexisting ischemia on arrival to the operating room and not anesthetic technique. [309] [311] The only hemodynamic event definitively related to intraoperative ischemia in patients undergoing coronary artery bypass graft surgery is tachycardia. [311] Recent evidence [313] [314] advocating the perioperative use of beta $_1$ -adrenoceptor antagonists to prevent myocardial ischemia strongly supports this contention. Sternotomy causes greater increases in calculated indices of MVO_2 , [315] myocardial lactate production, [316] and the

incidence of hypertension requiring treatment with vasoactive drugs [316] during morphine as compared with halothane anesthesia. In contrast, induction of anesthesia with desflurane in patients undergoing coronary artery bypass surgery may be associated with tachycardia, hypertension, and a greater incidence of ischemia than that occurring during induction with sufentanil. [317] Steal-prone anatomy has been identified in 23 percent of patients with coronary artery disease enrolled in the Coronary Artery Surgery Study. [318] However, patients with steal-prone coronary anatomy do not have a greater incidence of ischemia during desflurane anesthesia as compared with other forms of coronary artery disease. [317] The incidence of myocardial ischemia and adverse cardiac outcomes has been shown to be similar in cardiac patients undergoing noncardiac surgery during sevoflurane as compared with isoflurane anesthesia. [319] New electrocardiographic changes, incidence of postoperative myocardial infarction, and mortality are similar in patients undergoing coronary artery bypass graft surgery independent of anesthetic technique [310] [311] [312] [315] [316] [317] [320] [321] [322] or the presence of steal-prone anatomy. [322] In summary, despite the findings that volatile anesthetics are mild coronary vasodilators, these agents do not cause abnormal redistribution of myocardial perfusion resulting in ischemia when tachycardia and hypotension are avoided.

VOLATILE ANESTHETICS AND NEURAL CONTROL OF THE CIRCULATION

Volatile anesthetics have been shown to depress baroreceptor reflex control of arterial pressure in experimental animals to varying degrees. [178] [323] [324] [325] [326] [327] [328] [329] [330] This inhibition of baroreceptor reflex activity occurs as a result of depression of central nervous system integration of afferent baroreceptor input, attenuation of efferent autonomic nervous system activity,

and reductions in ganglionic transmission and endorgan response. [178] [326] [331] [332] Volatile anesthetics increase resting afferent nerve traffic and enhance the sensitivity of arterial baroreceptors by a Ca^{2+}-dependent mechanism. [326] [331] [333] These anesthetic-induced increases in baroreceptor sensitivity and discharge frequency tonically reduce overall sympathetic nervous system activity and attenuate sympathetic responses to declines in arterial pressure. [334]

Halothane, enflurane, and isoflurane (Fig. 5-18) (Figure Not Available) inhibit preganglionic sympathetic efferent activity at clinically relevant concentrations *in vivo*. [326] [328] [329] [330] [331] Volatile agents reduce postganglionic sympathetic nerve activity. [326] [331] Postsynaptic nicotinic receptors in the stellate ganglion are also blocked by halothane. [335] [336] These findings indicate that attenuation of ganglionic transmission represents a major mechanism by which volatile agents depress sympathetic nerve traffic. [337] Depression of sympathetic outflow caused by volatile anesthetics has also been suggested by examination of endogenous plasma norepinephrine kinetics. [338] [339] Halothane, isoflurane, and enflurane decrease plasma concentrations of norepinephrine to varying degrees by causing a more pronounced reduction in norepinephrine spillover than in clearance. [338] [339] In fact, halothane-induced reductions in norepinephrine release from postganglionic sympathetic nerves [340] may also contribute to depression of reflex vasoconstriction in peripheral blood vessels observed with this agent. [341] Volatile anesthetics attenuate parasympathetic nervous system function as well. Halothane has been shown to depress vagal nerve efferent activity by direct measurement of parasympathetic nerve activity. [330] These findings are supported by the results of several other studies demonstrating that volatile anesthetics inhibit reflex bradycardia in response to increases in arterial pressure. [323] [326] [331] [342] Parasympathetic and sympathetic nervous system outflows appear to be depressed to equivalent degrees during halothane [331] [342] [343] or isoflurane anesthesia. [326]

The effects of volatile anesthetics on neural control of the cardiovascular system have been examined incompletely in healthy humans and have not been described in patients with autonomic nervous system dysfunction. Halothane [154] and enflurane [344] produce greater attenuation of baroreceptor reflex regulation of heart rate than do equi-MAC concentrations of isoflurane. [155] Depression of baroreceptor function by these volatile agents may be more profound when compared with that of fentanyl, diazepam, and nitrous oxide anesthesia. [345] Baroreceptor-mediated control of peripheral vascular resistance is also attenuated in young volunteers during halothane anesthesia. [158] Steady-state anesthetic concentrations of sevoflurane have recently been shown to cause greater depression of sympathetic nerve activity measured directly with microneurography than desflurane at equivalent levels of hypotension. [168] These findings parallel results demonstrating pronounced sympathetic hyperactivity during rapid increases in inspired desflurane concentration in humans (Fig. 5-19) (Figure Not Available) [42] [44] Importantly, the actions of volatile anesthetics on baroreceptor reflex control of the circulation may be profoundly altered during autonomic dysfunction in elderly patients [346] or those with essential hypertension, diabetes mellitus, or heart failure. [347] Further investigation will be required to test these hypotheses, however.

NITROUS OXIDE AND CARDIOVASCULAR FUNCTION

Myocardial Contractility and Left Ventricular Diastolic Function

Experiments in papillary muscle [348] [349] [350] and isolated heart preparations [220] have consistently demonstrated that nitrous oxide produces a direct negative inotropic effect. Conflicting results about the influence of nitrous oxide on contractility have been observed in experimental animals and healthy volunteers. Several problems have contributed to apparently contradictory results *in vivo*. Observed changes in contractile

Figure 5A-18 (Figure Not Available) Baseline renal sympathetic efferent nerve activity (NA) and arterial blood pressure (BP) recorded in a conscious and isoflurane (I)-anesthetized dog (1.5 and 2.5% inspired concentration). Nerve activity was depressed at 2.5% inspired isoflurane. *(From Seagard et al [326])*

Figure 5A-19 (Figure Not Available) Effects of desflurane (open squares) and isoflurane (open diamonds) on sympathetic nerve activity (top), heart rate (middle), and mean arterial pressure (bottom) in healthy volunteers. Desflurane or isoflurane administration began 2 minutes after anesthetic induction with sodium thiopental (STP). Sympathetic nerve excitation, tachycardia, and hypertension were observed in subjects receiving desflurane. *Different ($P < 0.05$) group response;
desflurane response different ($P < 0.05$) from STP value;
isoflurane response different ($P < 0.05$) from STP value. *(From Ebert and Muzi [42])*

function may be influenced by the actions of nitrous oxide on the systemic circulation or by autonomic nervous system reflex effects [351] [352] because nitrous oxide may increase sympathetic nervous system tone. [353] [354] [355] Studies using nitrous oxide alone are difficult to perform and interpret because this gas does not produce total anesthesia at partial pressures less than 1 atm. [356] [357] [358] [359] [360] [361] The effects of nitrous oxide on contractile function may be influenced by different baseline anesthetics. [362] [363] [364] [365] [366] [367] [368] Lastly, lack of use of load-insensitive measures of myocardial contractility has allowed only qualitative assessment of the effects of nitrous oxide on intrinsic inotropic state in the intact heart.

The regional preload recruitable stroke work relationship demonstrated that nitrous oxide depresses myocardial contractility in dogs anesthetized with isoflurane or sufentanil in the absence of autonomic nervous system activity (Fig. 5-20) (Figure Not Available) [369] Seventy percent nitrous oxide decreased M_w by 28 percent and 41 percent during sufentanil and isoflurane anesthesia, respectively. These results indicate that 70 percent nitrous oxide decreased contractility to approximately the same extent as 1 MAC isoflurane. Similar findings have been reported using LV end-systolic pressure-dimension relations in acutely instrumented dogs. [368] These nitrous oxide-induced myocardial depressant effects may be offset by concomitant increases in sympathetic nervous system tone. [354] The negative inotropic actions of nitrous oxide may be more pronounced in the presence of preexisting LV dysfunction. [370] In addition, nitrous oxide-induced depression of contractile function appears to overcome the mild sympathomimetic effect of this anesthetic gas in patients with coronary artery [360] [365] [366] [371] [372] [373] or valvular heart disease [360] [374] because increases in baseline sympathetic nervous system activity cannot be further augmented by nitrous oxide in these clinical conditions.

The actions of nitrous oxide on LV diastolic function have been studied incompletely. Modest increases in maximal

Figure 5A-20 (Figure Not Available) Effects of nitrous oxide on preload recruitable stroke work (PRSW) slope in the presence of isoflurane (top panel) and sufentanil (bottom panel) as presented as a percent of control (I or S only, respectively). *Significantly ($P < 0.05$) different from I or S only;
significantly ($P < 0.05$) different from I or S plus 30 percent nitrous oxide. *(From Pagel et al [369])*

lengthening velocity and maximal rate of decline of force have been observed in ferret papillary muscle concomitant with decreases in contractile state. [350] No changes in the rate of isometric or isotonic relaxation were observed, indicating that nitrous oxide does not substantially modify myocardial relaxation. [350] Nitrous oxide has recently been shown to modestly increase segmental indices of LV chamber compliance and reduce early LV filling in acutely instrumented dogs. [375] These findings are supported by evidence indicating that nitrous oxide may produce LV diastolic dysfunction after cardiopulmonary bypass in patients undergoing coronary artery bypass graft surgery. [373]

Nitrous oxide causes dose-related reductions in the intracellular Ca^{2+} transient *in vitro*. [350] [376] This finding indicates that nitrous oxide-induced depression of myocardial contractility is related to decreases in Ca^{2+} availability for contractile activation. Nitrous oxide does not affect myofibrillar sensitivity to Ca^{2+} [350] [377] or Ca^{2+} uptake and release from the SR. [377] In addition, the diastolic Ca^{2+} transient is unaffected by nitrous oxide, suggesting that this anesthetic gas does not alter myocardial relaxation kinetics. [376]

Hemodynamics

Assessment of the hemodynamic effects of nitrous oxide in humans is often complicated by concomitant administration of volatile anesthetics, opioids, or other anesthetic adjuvants in the presence or absence of cardiovascular disease. Typical clinical concentrations of nitrous oxide (e.g., 40-70%) cause modest increases in heart rate in healthy volunteers. [356] [378] Small increases in heart rate also occur when hyperbaric concentrations of nitrous oxide are administered [379] or when this anesthetic gas is added to volatile anesthetics. [380] Declines in heart rate have been observed with nitrous oxide in patients with coronary artery disease anesthetized with isoflurane [174] or halothane. [381] Modest reductions in heart rate have been also reported in patients anesthetized with morphine or fentanyl undergoing cardiac surgery. [360] [365] [366] Sixty percent nitrous oxide causes small increases in arterial pressure in humans. [378] Increases in arterial pressure also occur in hyperbaric conditions [379] or during halothane anesthesia in volunteers, [352] [362] consistent with a mild sympathomimetic effect. Other studies have also indicated that partial substitution of nitrous oxide for a volatile anesthetic either does not affect or modestly increases arterial pressure during enflurane, [367] isoflurane, [364] or desflurane [160] anesthesia in experiments conducted at constant MAC. In contrast, reductions in arterial pressure have been observed in patients with coronary artery disease receiving nitrous oxide in the presence and absence of opioids. [365] [371] [382]

Small increases in cardiac output and stroke volume have been observed during administration of 60 percent nitrous oxide in oxygen in volunteers. [378] Cardiac output remains unchanged in the presence of hyperbaric nitrous oxide, [379] however. Cardiac output has been shown to be greater in volunteers anesthetized with halothane and nitrous oxide than in those receiving halothane alone, [362] concomitant with increases in sympathetic nervous system tone. The addition of nitrous oxide to enflurane, isoflurane, or desflurane anesthesia also modestly increased cardiac output. [37] [38] [364] [367] In contrast, nitrous oxide reduces cardiac output and stroke volume in healthy volunteers [383] and patients with cardiac disease receiving opioids [360] [365] [366] [381] [382] Hyperbaric nitrous oxide (1.5 MAC) caused a modest reduction in systemic vascular resistance. [379] In contrast, systemic vascular resistance is higher during volatile anesthesia in the presence of as compared with the absence of

nitrous oxide. [37] [38] [362] [364] [376] Pretreatment with the ganglionic blocker hexamethonium attenuated the relative increase in systemic vascular resistance observed during administration of halothane and nitrous oxide, [352] findings that may be consistent with a reduction in sympathetic nervous system tone. Nitrous oxide-induced increases in systemic vascular resistance have also been reported in volunteers and patients with cardiac disease anesthetized with opioids. [360] [383] [384]

Nitrous oxide increases venous tone and decreases venous capacitance in conscious volunteers. [356] This anesthetic gas has also been shown to modestly increase pulmonary artery pressures and pulmonary vascular resistance in patients with coronary artery disease anesthetized with morphine and diazepam [365] or halothane. [385] Thus, the combined effects of enhanced venous return, elevated pulmonary vascular

resistance, and depressed contractile function probably contribute to the increases in central venous pressure observed with nitrous oxide in humans. Hyperbaric nitrous oxide also enhances central venous pressure in association with increases in pulmonary vascular resistance. [379] Nitrous oxide inhibits norepinephrine uptake by the lung, and subsequent increases in plasma norepinephrine levels detected in the pulmonary vasculature may be partially responsible for the characteristic increases in pulmonary vascular resistance observed during administration of this agent. [386] Nitrous oxide-induced increases in pulmonary vascular resistance may be more pronounced in adults with pulmonary hypertension [385] [387] and in children with increased pulmonary blood flow. [388] Elevations in pulmonary artery pressures and vascular resistance have also been described during administration of nitrous oxide in neonatal lambs. [389] Such increases in pulmonary vascular resistance may adversely enhance right-to-left atrial or ventricular shunts and compromise arterial oxygenation in patients with congenital heart disease. [390]

NITROUS OXIDE AND CARDIAC ELECTROPHYSIOLOGY

Reversible atrioventricular dissociation has been reported in humans anesthetized with nitrous oxide and volatile or opioid-based anesthetics. [391] Addition of nitrous oxide to halothane anesthesia lowers the threshold at which arrhythmias occur. [392] This observation may result from a combination of sympathetic nervous system stimulation by nitrous oxide and myocardial sensitization by halothane. [393] The incidence of arrhythmias has been shown to be reduced during combined nitrous oxide-opioid anesthesia when compared with halothane anesthesia alone. [394]

NITROUS OXIDE AND THE CORONARY CIRCULATION

Nitrous oxide does not produce direct effects on the coronary vasculature *in vitro*. [291] [395] [396] FSThis anesthetic gas alters coronary blood flow concomitant with changes in MVO_2 in dogs. [397] [398] Nitrous oxide decreases myocardial segment shortening, [399] [400] increases postsystolic shortening, [401] and redistributes transmural coronary blood flow preferentially to the subepicardium (decreased endo/epi ratio) [400] in experimental models of coronary artery disease. Nitrous oxide also decreases the recovery of contractile function of stunned myocardium. [402] Nitrous oxide-induced sympathetic nervous system activation and imbalances of myocardial O_2 supply and MVO_2 represent potential mechanisms by which this anesthetic gas further delays contractile recovery of stunned myocardium. [403] In the presence of a volatile anesthetic, nitrous oxide decreases MVO_2 and myocardial O_2 extraction [175] [381] and may exacerbate myocardial ischemia during concomitant reductions in arterial pressure in patients with coronary artery disease. [174] However, more recent studies demonstrate that the addition of nitrous oxide to volatile or opioid anesthetics does not increase the incidence of new regional wall motion abnormalities as assessed by transesophageal echocardiography. [175] [404]

NITROUS OXIDE AND NEURAL CONTROL OF THE CIRCULATION

Nitrous oxide causes pupillary dilation, diaphoresis, and increases in systemic vascular resistance, central blood volume, and forearm vascular resistance in volunteers during halothane anesthesia, [352] suggesting that nitrous oxide activates the sympathetic nervous system. A subsequent study demonstrated that nitrous oxide does indeed increase sympathetic nerve traffic measured using sympathetic microneurography in human volunteers, [354] especially during the first 15 to 30 minutes of exposure to this anesthetic gas. Although baroreceptor reflex-mediated control of heart rate is impaired during administration of nitrous oxide, regulation of sympathetic outflow to peripheral blood vessels is preserved. [353] This finding suggests nitrous oxide does not alter sympathetic vasoconstrictor-induced maintenance of arterial pressure and may be partially responsible for the relative stability of hemodynamics during nitrous oxide anesthesia.

XENON

The anesthetic properties of the noble gas xenon were first described more than 50 years ago. [405] Xenon has a blood gas partition coefficient less than that of nitrous oxide, [406] does not undergo biotransformation, [407] provides rapid induction and emergence from anesthesia, [408] [409] [410] and exerts analgesic effects [411] independent of alpha$_2$ -adrenergic and opioid receptors. [412] Despite these advantageous properties, xenon has not been routinely used for clinical anesthesia in the United States because it is more expensive than nitrous oxide and volatile anesthetics. In recent years, more efficient manufacturing techniques and development of low-flow administration and recycling systems have reduced the cost of xenon and rekindled interest in its clinical use. [409] [413] [414]

Xenon has been shown to cause minimal systemic and pulmonary hemodynamic effects *in vivo*, [408] [409] [415] [416] [417] preserve myocardial contractility in humans, [408] and attenuate increases in plasma epinephrine and cortisol concentrations associated with surgical stimulation. [415] The effects of xenon on systemic hemodynamics, LV systolic and diastolic function, and the determinants of LV afterload have recently been examined in chronically instrumented dogs before and after the development of rapid LV pacing-induced cardiomyopathy. [418] Xenon was remarkably devoid of hemodynamic effects in normal and cardiomyopathic dogs anesthetized with isoflurane. Xenon did not alter isofluraneinduced reductions in preload recruitable stroke work slope (M $_w$) in the presence and absence of pacing-induced LV dysfunction (Fig. 5-21) (Figure Not Available) . Xenon caused greater increases in tau in isoflurane-anesthetized, cardiomyopathic dogs as compared with normal dogs; however, indices of early LV filling and chamber compliance remained unchanged, suggesting that xenon does not appreciably influence LV diastolic function

Figure 5A-21 (Figure Not Available) Histograms illustrating the effects of isoflurane (ISO) and xenon on preload recruitable stroke work slope (M $_w$; top panel), the peak rate of increase of left ventricular pressure (+dP/dt$_{max}$; middle panel), and percent segment shortening (%SS; bottom panel) in normal (hatched bars) and cardiomyopathic dogs (solid bars) receiving 1.5 MAC isoflurane in the presence and absence of 30, 50, and 65% xenon. *Significantly ($P < 0.05$) different from conscious;
significantly ($P < 0.05$) different from ISO alone;
significantly ($P < 0.05$) different from ISO and 30 percent xenon; ¶ significantly ($P < 0.05$) different from corresponding value in normal dogs. *(From Hettrick et al [418])*

during isoflurane anesthesia. Xenon also produced relatively minor alterations in the determinants of LV afterload in dogs before and after pacing. Taken together, these recent data indicate that xenon produces very subtle cardiovascular effects during isoflurane anesthesia in dogs with and without experimental dilated cardiomyopathy. [418]

SUMMARY

Volatile anesthetics exert profound effects on the cardiovascular system by altering the inotropic, chronotropic, dromotropic, and lusitropic state of the heart. These agents also have significant actions on both the preload and afterload systems. These pharmacologic effects cause dramatic changes in hemodynamics that may be accentuated in patients with underlying cardiovascular disease. Less profound but equally important effects are observed with nitrous oxide and xenon. Recently, some of the volatile anesthetics have been shown to be cardioprotective, directly reducing the sequelae of ischemia and reperfusion injury. The use of inhaled anesthetics requires clear understanding of their complex cardiovascular pharmacology.

References

1. Pagel PS, Warltier DC: Anesthetics and left ventricular function. In: Warltier DC (ed): Ventricular Function. Baltimore, Williams and Wilkins, 1995, pp 213-52.

2. Goldberg AH, Ullrick WC: Effects of halothane on isometric contractions of isolated heart muscle. Anesthesiology 28:838, 1967.

3. Sugai N, Shimosato S, Etsten BE: Effect of halothane on force-velocity relations and dynamic stiffness of isolated heart muscle. Anesthesiology 29:267, 1968.

4. Shimosato S, Li TH, Etsten B: Ventricular function during halothane anesthesia in closed chest dog. Circ Res 12:63, 1963.

5. Deutsch S, Linde HW, Dripps RD et al: Circulatory and respiratory actions of halothane in normal man. Anesthesiology 23:631, 1962.

6. Eger II EI, Smith NT, Stoelting RK et al: Cardiovascular effects of halothane in man. Anesthesiology 32:396, 1970.

7. Severinghaus JW, Cullen SC: Depression of myocardium and body oxygen consumption with Fluothane. Anesthesiology 19:165, 1958.

8. Sonntag H, Donath U, Hillebrand W et al: Left ventricular function in conscious man and during halothane anesthesia. Anesthesiology 48:320, 1978.

9. Shimosato S, Sugai N, Iwatsuki N et al: The effect of Ethrane on cardiac muscle mechanics. Anesthesiology 30:513, 1969.

10. Kemmotsu O, Hashimoto Y, Shimosato S: Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. Anesthesiology 39:470, 1973.

11. Calverley RK, Smith NT, Prys-Roberts C et al: Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg 57:619, 1978.

12. Stevens WC, Cromwell TH, Halsey MJ et al: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 35:8, 1971.

13. Horan BF, Prys-Roberts C, Hamilton WK et al: Haemodynamic responses to enflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol. Br J Anaesth 49:1189, 1977.

14. Merin RG, Kumazawa T, Luka NL: Myocardial function and metabolism in the conscious dog and during halothane anesthesia. Anesthesiology 44:402, 1976.

15. Merin RG, Kumazawa T, Luka NL: Enflurane depresses myocardial function, perfusion, and metabolism in the dog. Anesthesiology 45:501, 1976.

16. Pagel PS, Kampine JP, Schmeling WT et al: Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. Anesthesiology 74:539, 1991.

17. Van Trigt P, Christian CC, Fagraeus L et al: The mechanism of halothane-induced myocardial depression: Altered diastolic mechanics versus impaired contractility. J Thorac Cardiovasc Surg 85:832, 1983.

18. Horan BF, Prys-Roberts C, Roberts JG et al: Haemodynamic responses to isoflurane anesthesia and hypovolaemia in the dog, and their modification by propranolol. Br J Anaesth 49:1179, 1977.

19. Merin RG: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? Anesthesiology 55:398, 1981.

20. Pagel PS, Kampine JP, Schmeling WT et al: Comparison of end-systolic pressure-length relations and preload recruitable stroke work as indices of myocardial contractility in the conscious and anesthetized, chronically instrumented dog. Anesthesiology 73:278, 1990.

21. Pagel PS, Nijhawan N, Warltier DC: Quantitation of volatile anesthetic-induced depression of myocardial contractility using a single beat index derived from maximal ventricular power. J Cardiothorac Vasc Anesth 7:688, 1993.

22. Graves CL, McDermott RW, Bidwai A: Cardiovascular effects of isoflurane in surgical patients. Anesthesiology 41:486, 1974.

23. Tarnow J, Bruckner JB, Eberlein HJ et al: Haemodynamics and myocardial oxygen consumption during isoflurane (Forane) anaesthesia in geriatric patients. Br J Anaesth 48:669, 1976.

24. Hysing ES, Chelly JE, Jacobson L et al: Cardiovascular effects of acute changes in extracellular ionized calcium concentration induced by citrate and $CaCl_2$ infusions in chronically instrumented dogs, conscious and during enflurane, halothane, and isoflurane anesthesia. Anesthesiology 72:100, 1990.

25. Makela VHM, Kapur PA: Amrinone and verapamil-propranolol induced cardiac depression during isoflurane anesthesia in dogs. Anesthesiology 66:792, 1987.

26. Merin RG, Chelly JE, Hysing ES et al: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. IV: Chronically administered oral verapamil and halothane, enflurane, and isoflurane. Anesthesiology 66:140, 1987.

27. Pagel PS, Hettrick DA, Warltier DC: Left ventricular mechanical consequences of dihydropyridine calcium channel modulation in conscious and anesthetized chronically instrumented dogs. Anesthesiology 81:190, 1994.

28. Denlinger JK, Kaplan JA, Lecky JH et al: Cardiovascular responses to calcium administered intravenously to man during halothane anesthesia. Anesthesiology 42:390, 1975.

29. Price HL: Calcium reverses myocardial depression caused by halothane: Site of action. Anesthesiology 41:576, 1974.

30. Pagel PS, Kampine JP, Schmeling WT et al: Reversal of volatile anesthetic-induced depression of myocardial contractility by extracellular calcium also enhances left ventricular diastolic function. Anesthesiology 78:141, 1993.

31. Makela VHM, Kapur PA: Amrinone blunts cardiac depression caused by enflurane or isoflurane anesthesia in the dog. Anesth Analg 66:215, 1987.

32. Pagel PS, Hettrick DA, Warltier DC: Amrinone enhances myocardial contractility and improves left ventricular diastolic function in conscious and anesthetized chronically instrumented dogs. Anesthesiology 79:753, 1993.

33. Pagel PS, Harkin CP, Hettrick DA et al: Levosimendan (OR-1259), a myofilament calcium sensitizer, enhances myocardial contractility but does not alter isovolumic relaxation in conscious and anesthetized dogs. Anesthesiology 81:974, 1994.

34. Eger II EI: New inhaled anesthetics. Anesthesiology 80:906, 1994.

35. Merin RG, Bernard JM, Doursout MF et al: Comparison of the effects of isoflurane and desflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. Anesthesiology 74:568, 1991.

36. Weiskopf RB, Holmes MA, Eger II EI et al: Cardiovascular effects of I653 in swine. Anesthesiology 69:303, 1988.

37. Weiskopf RB, Cahalan MK, Eger II EI et al: Cardiovascular actions of desflurane in normocarbic volunteers. Anesth Analg 73:143, 1991.

38. Cahalan MK, Weiskopf RB, Eger II EI et al: Hemodynamic effects of desflurane/nitrous oxide anesthesia in volunteers. Anesth Analg 73:157, 1991.

39. Pagel PS, Kampine JP, Schmeling WT et al: Influence of volatile anesthetics on myocardial contractility *in vivo*: Desflurane versus isoflurane. Anesthesiology 74:900, 1991.

40. Pagel PS, Kampine JP, Schmeling WT et al: Evaluation of myocardial contractility in the chronically instrumented dog with intact autonomic nervous system function: Effects of desflurane and isoflurane. Acta Anaesthesiol Scand 37:203, 1993.

41. Hettrick DA, Pagel PS, Warltier DC: Desflurane, sevoflurane, and isoflurane impair canine left ventricular-arterial coupling and mechanical efficiency. Anesthesiology 85:403, 1996.

42. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane. Anesthesiology 79:444, 1993.

43. Weiskopf RB, Eger II EI, Noorani M et al: Fentanyl, esmolol, and clonidine blunt the transient cardiovascular stimulation induced by desflurane in humans. Anesthesiology 81:1350, 1994.

44. Weiskopf RB, Moore MA, Eger II EI et al: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than rapid increase in isoflurane concentration in humans. Anesthesiology 80:1035, 1994.

45. Weiskopf RB, Eger II EI, Daniel M: Cardiovascular stimulation induced by rapid increases in desflurane concentration in humans results from activation of tracheopulmonary and systemic receptors. Anesthesiology 83:1173, 1995.

46. Bernard JM, Wouters PF, Doursout M-F et al: Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology 72:659, 1990.

47. Harkin CP, Pagel PS, Kersten JR et al: Direct negative inotropic and lusitropic effects of sevoflurane. Anesthesiology 81:156, 1994.

48. Lerman J, Oyston JP, Gallagher TM et al: The minimum alveolar concentration (MAC) and hemodynamic effects of halothane, isoflurane, and sevoflurane in newborn swine. Anesthesiology 73:717, 1990.

49. Kikura M, Ikeda K: Comparison of effects of sevoflurane-nitrous oxide and enflurane-nitrous oxide on myocardial contractility in humans: Load-independent and noninvasive assessment with transesophageal echocardiography. Anesthesiology 79:235, 1993.

50. Kemmotsu O, Hashimoto Y, Shimosato S: The effects of fluroxene and enflurane on contractile performance of isolated papillary muscles from failing hearts. Anesthesiology 40:252, 1974.

51. Lowenstein E, Foex P, Francis CM et al: Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in the dog. Anesthesiology 55:349, 1981.

52. Kissin I, Thomson CT, Smith LR: Effects of halothane on contractile function of ischemic myocardium. J Cardiovasc Pharmacol 5:438, 1983.

53. Vivien B, Hanouz J-L, Gueugniaud P-Y et al: Myocardial effects of halothane and isoflurane in hamsters with hypertrophic cardiomyopathy. Anesthesiology 87:1406, 1997.

54. Prys-Roberts C, Roberts JG, Foex P et al: Interaction of anesthesia, beta-receptor blockade, and blood loss in dogs with induced myocardial infarction. Anesthesiology 45:326, 1976.

55. Davis RF, DeBoer LW, Rude RE et al: The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. Anesthesiology 59:402, 1983.

56. Kersten JR, Schmeling TJ, Pagel PS et al: Isoflurane mimics ischemic preconditioning via activation of K_{ATP} channels: Reduction of myocardial infarct size with an acute memory phase. Anesthesiology 87:361, 1997.

57. Van Ackern K, Vetter HO, Bruckner UB et al: Effects of enflurane on myocardial ischaemia in the dog. Br J Anaesth 57:497, 1985.

58. Kanaya N, Fujita S: The effects of isoflurane on regional myocardial contractility and metabolism in "stunned" myocardium in acutely instrumented dogs. Anesth Analg 79:447, 1994.

59. Lochner A, Harper IS, Salie R et al: Halothane protects the isolated rat myocardium against excessive total intracellular calcium and structural damage during ischemia and reperfusion. Anesth Analg 79:226, 1994.

60. Warltier DC, Al-Wathiqui MH, Kampine JP et al: Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. Anesthesiology 69:552, 1988.

61. Pagel PS, Hettrick DA, Lowe D et al: Desflurane and isoflurane exert modest beneficial actions on left ventricular diastolic function during myocardial ischemia in dogs. Anesthesiology 83:1021, 1995.

62. Reiz S, Balfors E, Gustavsson B et al: Effects of halothane on coro-nary haemodynamics and myocardial metabolism in patients with ischaemic heart disease and heart failure. Acta Anaesthesiol Scand 26:133, 1982.

63. Reiz S, Balfors E, Sorensen MB et al: Isoflurane: A powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 59:91, 1983.

64. Reiz S, Ostman M: Regional coronary hemodynamics during isoflurane-nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg 64:570, 1985.

65. Pagel PS, Lowe D, Hettrick DA et al: Isoflurane, but not halothane, improves indices of diastolic performance in dogs with rapid ventricular, pacing-induced cardiomyopathy. Anesthesiology 85:644, 1996.

66. Pagel PS, Hettrick DA, Kersten JR et al: Isoflurane and halothane do not alter the enhanced afterload sensitivity of left ventricular relaxation in dogs with pacing-induced cardiomyopathy. Anesthesiology 87:952, 1997.

67. Rusy BF, Komai H: Anesthetic depression of myocardial contractility: A review of possible mechanisms. Anesthesiology 67:745, 1987.

68. Lynch III C: Myocardial excitation-contraction coupling. In: Yaksh TL, Lynch III C, Zapol WM et al (eds): Anesthesia: Biologic Foundations. Philadelphia, Lippincott-Raven, 1997, pp 1041-1079.

69. Bosnjak ZJ, Aggarwal A, Turner LA et al: Differential effects of halothane, enflurane, and isoflurane on Ca $^{2+}$ transients and papillary muscle tension in guinea pigs. Anesthesiology 76:123, 1992.

70. Bosnjak ZJ, Kampine JP: Effects of halothane on transmembrane potentials, Ca $^{2+}$ transients, and papillary muscle tension in the cat. Am J Physiol 251:H374, 1986.

71. Eskinder H, Rusch NJ, Supan FD et al: The effects of volatile anesthetics on L- and T-type calcium channel currents in canine cardiac Purkinje cells. Anesthesiology 74:919, 1991.

72. Lynch III C: Effects of halothane and isoflurane on isolated human ventricular myocardium. Anesthesiology 68:429, 1988.

73. Hatakeyama N, Momose Y, Ito Y: Effects of sevoflurane on contractile responses and electrophysiologic properties in canine single cardiac myocytes. Anesthesiology 82:559, 1995.

74. Bosnjak ZJ, Supan FD, Rusch NJ: The effects of halothane, enflurane, and isoflurane on calcium current in isolated canine ventricular cells. Anesthesiology 74:340, 1991.

75. Lynch III C: Differential depression of myocardial contractility by halothane and isoflurane *in vitro*. Anesthesiology 64:620, 1986.

76. Blanck TJJ, Runge S, Stevenson RL: Halothane decreases calcium channel antagonist binding to cardiac membranes. Anesth Analg 67:1032, 1988.

77. Drenger B, Quigg M, Blanck TJJ: Volatile anesthetics depress calcium channel blocker binding to bovine cardiac sarcolemma. Anesthesiology 74:155, 1991.

78. Hoehner PJ, Quigg MC, Blanck TJJ: Halothane depresses D600 binding to bovine heart sarcolemma. Anesthesiology 75:1019, 1991.

79. Katsuoka M, Kobayashi K, Ohnishi ST: Volatile anesthetics decrease calcium content of isolated myocytes. Anesthesiology 70:954, 1989.

80. Katsuoka M, Ohnishi ST: Inhalation anesthetics decrease calcium content of cardiac sarcoplasmic reticulum. Br J Anaesth 62:669, 1989.

81. Komai H, Rusy BF: Direct effect of halothane and isoflurane on the function of the sarcoplasmic reticulum in intact rabbit atria. Anesthesiology 72:694, 1990.

82. Wheeler DM, Katz A, Rice RT et al: Volatile anesthetic effects on sarcoplasmic reticulum Ca content and sarcolemmal Ca flux in isolated rat cardiac cell suspensions. Anesthesiology 80:372, 1994.

83. Wilde DW, Davidson BA, Smith MD et al: Effects of isoflurane and enflurane on intracellular Ca $^{2+}$ mobilization in isolated cardiac myocytes. Anesthesiology 79:73, 1993.

84. Luk HN, Lin CI, Chang CL et al: Differential inotropic effects of halothane and isoflurane in dog ventricular tissues. Eur J Pharmacol 136:409, 1987.

85. Lynch III C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. Anesthesiology 55:360, 1981.

86. Wheeler DM, Rice RT, Lakatta EG: The action of halothane on spontaneous contractile waves and stimulated contractions in isolated rat and dog heart cells. Anesthesiology 72:911, 1990.

87. Lynch III C, Frazer MJ: Anesthetic alteration of ryanodine binding by cardiac calcium release channels. Biochim Biophys Acta 1194:109, 1994.

88. Connelly TJ, Coronado R: Activation of the Ca^{2+} release channel of cardiac sarcoplasmic reticulum by volatile anesthetics. Anesthesiology 81:459, 1994.

89. Casella ES, Suite ND, Fisher YI et al: The effect of volatile anesthetics on the pH dependence of calcium uptake by cardiac sarcoplasmic reticulum. Anesthesiology 67:386, 1987.

90. Frazer MJ, Lynch III C: Halothane and isoflurane effects on Ca^{2+} fluxes of isolated myocardial sarcoplasmic reticulum. Anesthesiology 77:316, 1992.

91. Miao N, Lynch III C: Effect of temperature on volatile anesthetic depression of myocardial contractions. Anesth Analg 76:366, 1993.

92. Baum VC, Wetzel GT: Sodium-calcium exchange in neonatal myocardium: Reversible inhibition by halothane. Anesth Analg 78:1105, 1994.

93. Haworth RA, Goknur AB, Berkoff HA: Inhibition of Na-Ca exchange by general anesthetics. Circ Res 65:1021, 1989.

94. Haworth RA, Goknur AB: Inhibition of sodium/calcium exchange and calcium channels of heart cells by volatile anesthetics. Anesthesiology 82:1255, 1995.

95. Baum VC, Klitzner TS: Excitation-contraction coupling in neonatal myocardium: Effects of halothane and isoflurane. Dev Pharmacol Ther 16:99, 1991.

96. Su JY, Kerrick WG: Effects of halothane on Ca $^{2+}$ -activated tension development in mechanically disrupted rabbit myocardial fibers. Pflugers Arch 375:111, 1978.

97. Murat I, Ventura-Clapier R, Vassort G: Halothane, enflurane, and isoflurane decrease calcium sensitivity and maximal force in detergent-treated rat cardiac fibers. Anesthesiology 69:892, 1988.

98. Tavernier BM, Adnet PJ, Imbenotte M et al: Halothane and isoflurane decrease calcium sensitivity and maximal force in human-skinned cardiac fibers. Anesthesiology 80:625, 1994.

99. Merin RG, Kumazawa T, Honig CR: Reversible interaction between halothane and Ca^{2+} on cardiac actomyosin adenosine triphosphatase: Mechanism and significance. J Pharmacol Exp Ther 190:1, 1974.

100. Pask HT, England PJ, Prys-Roberts C: Effects of volatile inhalational anesthetic agents on isolated bovine cardiac myofibrillar ATPase. J Mol Cell Cardiol 13:293, 1981.

101. Murat I, Lechene P, Ventura-Clapier R: Effects of volatile anesthetics on mechanical properties of rat cardiac skinned fibers. Anesthesiology 73:73, 1990.

102. Blanck TJJ, Chiancone E, Salviati G et al: Halothane does not alter Ca $^{2+}$ affinity of troponin C. Anesthesiology 76:100, 1992.

103. Housmans PR: Negative inotropy of halogenated anesthetics in ferret ventricular myocardium. Am J Physiol 259:H827, 1990.

104. Baele P, Housmans PR: The effects of halothane, enflurane, and isoflurane on the length-tension relation of the isolated papillary muscle of the ferret. Anesthesiology 74:281, 1991.

105. Morgan JP: Abnormal intracellular modulation of calcium as a major cause of cardiac contractile dysfunction. N Engl J Med 325:625, 1991.

106. Pagel PS, Warltier DC: Mechanical function of the left ventricle. In: Yaksh TL, Lynch III C, Zapol W et al (eds): Anesthesia: Biologic Foundations. Philadelphia, Lippincott-Raven, 1997, pp 1081-1133.

107. Dougherty AH, Naccarelli GV, Gray EL et al: Congestive heart failure with normal systolic function. Am J Cardiol 54:778, 1984.

108. Katz AM, Smith VE: Regulation of myocardial function in the normal and diseased heart: Modification by inotropic drugs. Eur Heart J 3 (Suppl D):11, 1982.

109. Soufer R, Wohlgelernter D, Vita NA et al: Intact systolic left ventricular function in clinical congestive heart failure. Am J Cardiol 55:1032, 1985.

110. Pagel PS, Grossman W, Haering JM et al: Left ventricular diastolic function in the normal and diseased heart: Perspectives for the anesthesiologist. Anesthesiology 79:836, 1993.

111. Pagel PS, Grossman W, Haering JM et al: Left ventricular diastolic function in the normal and diseased heart: Perspectives for the anesthesiologist. Anesthesiology 79:1104, 1993.

112. Doyle RL, Foex P, Ryder WA et al: Effects of halothane on left ventricular relaxation and early diastolic coronary blood flow in the dog. Anesthesiology 70:660, 1989.

113. Humphrey LS, Stinson DC, Humphrey MJ et al: Volatile anesthetic effects on left ventricular relaxation in swine. Anesthesiology 73:731, 1990.

114. Pagel PS, Kampine JP, Schmeling WT et al: Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. Anesthesiology 74:1103, 1991.

115. Ihara T, Shannon RP, Komamura K et al: Effects of anaesthesia and recent surgery on diastolic function. Cardiovasc Res 28:325, 1994.

116. Housmans PR, Murat I: Comparative effects of halothane, enflurane, and isoflurane at equipotent anesthetic concentrations on isolated ventricular myocardium of the ferret. II: Relaxation. Anesthesiology 69:464, 1988.

117. Goldberg AH, Phear WPC: Halothane and paired stimulation: Effects on myocardial compliance and contractility. J Appl Physiol 28:391, 1970.

118. Rusy BF, Moran JE, Vongvises P et al: The effects of halothane and cyclopropane on left ventricular volume determined by high-speed biplane cineradiography in dogs. Anesthesiology 36:369, 1972.

119. Moores WY, Weiskopf RB, Baysinger M et al: Effects of halothane and morphine sulfate on myocardial compliance following total cardiopulmonary bypass. J Thorac Cardiovasc Surg 81:163, 1981.

120. Greene ES, Gerson JI: One versus two MAC halothane anesthesia does not alter the left ventricular diastolic pressure-volume relationship. Anesthesiology 64:230, 1986.

121. Ishizaka S, Asanoi H, Wada O et al: Loading sequence plays an important role in enhanced load sensitivity of left ventricular relaxation in conscious dogs with tachycardia-induced cardiomyopathy. Circulation 92:3560, 1995.

122. Eichhorn EJ, Willard JE, Alvarez L et al: Are contraction and relaxation coupled in patients with and without congestive heart failure? Circulation 85:2132, 1992.

123. Little WC: Enhanced load dependence of relaxation in heart failure: Clinical implications. Circulation 85:2326, 1992.

124. Sunagawa K, Maughan WL, Burkhoff D et al: Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 245:H773, 1983.

125. Sunagawa K, Maughan WL, Sagawa K: Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 56:586, 1985.

126. Burkhoff D, Sagawa K: Ventricular efficiency predicted by an analytical model. Am J Physiol 250:R1021, 1986.

127. Little WC, Cheng C-P: Left ventricular-arterial coupling in conscious dogs. Am J Physiol 261:H70, 1991.

128. Starling MR: Left ventricular-arterial coupling relations in the normal human heart. Am Heart J 125:1659, 1993.

129. Suga H: Ventricular energetics. Physiol Rev 70:247, 1990.

130. Kawasaki T, Hoka S, Okamoto H et al: The difference of isoflurane and halothane in ventriculoarterial coupling in dogs. Anesth Analg 79:681, 1994.

131. Hettrick DA, Pagel PS, Warltier DC: Isoflurane and halothane produce similar alterations in aortic distensibility and characteristic aortic impedance. Anesth Analg 83:1166, 1996.

132. Milnor WR: Hemodynamics, 2nd ed. Baltimore, Williams and Wilkins, 1989.

133. Lang RM, Borow KM, Neumann A et al: Systemic vascular resistance: An unreliable index of left ventricular afterload. Circulation 74:1114, 1986.

134. Milnor WR: Arterial impedance as ventricular afterload. Circ Res 36:565, 1975.

135. Burkhoff D, Alexander Jr J, Schipke J: Assessment of Windkessel as a model of aortic input impedance. Am J Physiol 255:H742, 1988.

136. Wesseling KH, Jansen JRC, Settels JJ et al: Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 74:2566, 1993.

137. Gersh BJ, Prys-Roberts C, Reuben SR et al: The effects of halothane on the interactions between myocardial contractility, aortic input impedance, and left ventricular performance. II: Aortic input impedance and the distribution of energy during ventricular ejection. Br J Anaesth 44:767, 1972.

138. Prys-Roberts C, Gersh BJ, Baker AB et al: The effects of halothane on the interactions between myocardial contractility, aortic impedance, and left ventricular performance. I: Theoretical considerations and results. Br J Anaesth 44:634, 1972.

139. Hettrick DA, Pagel PS, Warltier DC: Differential effects of isoflurane and halothane on aortic input impedance quantified using a three-element Windkessel model. Anesthesiology 83:361, 1995.

140. Lowe D, Hettrick DA, Pagel PS et al: Influence of volatile anesthetics on left ventricular afterload *in vivo:* Differences between desflurane and sevoflurane. Anesthesiology 85:112, 1996.

141. Pepine CJ, Nichols WW, Curry Jr RC et al: Aortic input impedance during nitroprusside infusion: A reconsideration of afterload reduction and beneficial action. J Clin Invest 64:643, 1979.

142. Lowe D, Hettrick DA, Pagel PS et al: Propofol alters left ventricular afterload as evaluated by aortic input impedance in dogs. Anesthesiology 84:368, 1996.

143. Hettrick DA, Pagel PS, Kersten JR et al: The effects of isoflurane and halothane on left ventricular afterload in dogs with dilated cardiomyopathy. Anesth Analg 85:979, 1997.

144. March HW, Ross JK, Lower RR: Observations on the behavior of the right ventricular outflow tract, with reference to its developmental origins. Am J Med 32:835, 1962.

145. Armour JA, Pace JB, Randall WC: Interrelationship of architecture and function of the right ventricle. Am J Physiol 218:174, 1970.

146. Pace JB, Keefe WF, Armour JA et al: Influence of sympathetic nerve stimulation on the right ventricular outflow tract pressure in anesthetized dogs. Circ Res 24:397, 1969.

147. Meier GD, Bove AA, Santamore WP et al: Contractile function in canine right ventricle. Am J Physiol 239:H794, 1980.

148. Pouleur H, Lefevre J, van Mechelen H et al: Free-wall shortening and relaxation during ejection in the canine right ventricle. Am J Physiol 239:H601, 1980.

149. Tobin Jr JR, Blundell PE, Goodrich RG et al: Induced pressure gradients across infundibular zone of right ventricle in normal dogs. Circ Res 16:162, 1965.

150. Myhre ESP, Slinker BK, LeWinter MM: Absence of right ventricular isovolumic relaxation in open-chest anesthetized dogs. Am J Physiol 263:H1587, 1992.

151. Priebe H-J: Effects of halothane on global and regional biventricular performances and on coronary hemodynamics before and during right coronary artery stenosis in the dog. Anesthesiology 78:541, 1993.

152. Heerdt PM, Pleimann BE: The dose-dependent effects of halothane on right ventricular contraction pattern and regional inotropy in swine. Anesth Analg 82:1152, 1996.

153. Bosnjak ZJ, Kampine JP: Effects of halothane, enflurane, and isoflurane in the SA node. Anesthesiology 58:314, 1983.

154. Bristow JD, Prys-Roberts C, Fisher A et al: Effects of anesthesia on baroreflex control of heart rate in man. Anesthesiology 31:422, 1969.

155. Kotrly KJ, Ebert TJ, Vucins E et al: Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 60:173, 1984.

156. Bagshaw RJ, Cox RH: Baroreceptor control of systemic haemodynamics at incremental halothane levels in the dog. Acta Anaesthesiol Scand 25:416, 1981.

157. Duke PC, Fownes D, Wade JG: Halothane depresses baroreflex control of heart rate in man. Anesthesiology 46:184, 1977.

158. Ebert TJ, Kotrly KJ, Vucins EJ et al: Halothane attenuates cardiopulmonary baroreflex control of peripheral resistance in humans. Anesthesiology 63:668, 1985.

159. Calverley RK, Smith NT, Jones CW et al: Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man. Anesth Analg 57:610, 1978.

160. Weiskopf RB, Cahalan MK, Ionescu P et al: Cardiovascular actions of desflurane with and without nitrous oxide during spontaneous ventilation in humans. Anesth Analg 73:165, 1991.

161. Murat I, Lapeyre G, Saint-Maurice C: Isoflurane attenuates baroreflex control of heart rate in human neonates. Anesthesiology 70:395, 1989.

162. Cahalan MK, Lurz FW, Eger II EI et al: Narcotics decrease heart rate during inhalational anesthesia. Anesth Analg 66:166, 1987.

163. Mallow JE, White RD, Cucchiara RF et al: Hemodynamic effects of isoflurane and halothane in patients with coronary artery disease. Anesth Analg 55:135, 1976.

164. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 54:100, 1981.

165. Kasuda H, Akazawa S, Shimizu R: The echocardiographic assessment of left ventricular performance during sevoflurane and halothane anesthesia. J Anesth 4:295, 1990.

166. Ebert TJ, Harkin CP, Muzi M: Cardiovascular responses to sevoflurane: A review. Anesth Analg 81:S11, 1995.

167. Frink Jr EJ, Malan TP, Atlas M et al: Clinical comparison of sevoflurane and isoflurane in healthy patients. Anesth Analg 74:241, 1992.

168. Ebert TJ, Muzi M, Lopatka CW: Neurocirculatory responses to sevoflurane in humans: A comparison to desflurane. Anesthesiology 83:88, 1995.

169. Eger II EI: The pharmacology of isoflurane. Br J Anaesth 56:71S, 1984.

170. Eger II EI: Nitrous Oxide/N_2 O. New York, Elsevier, 1985.

171. Bahlman SH, Eger II EI, Halsey MJ et al: The cardiovascular effects of halothane in man during spontaneous ventilation. Anesthesiology 36:494, 1972.

172. Price HL, Skovsted P, Pauca AL et al: Evidence for beta-receptor activation produced by halothane in normal man. Anesthesiology 32:389, 1970.

173. Blake DW, Way D, Trigg L et al: Cardiovascular effects of volatile anesthesia in rabbits: Influence of chronic heart failure and enalaprilat treatment. Anesth Analg 73:441, 1991.

174. Reiz S: Nitrous oxide augments the systemic and coronary haemodynamic effects of isoflurane in patients with ischaemic heart disease. Acta Anaesthesiol Scand 27:464, 1983.

175. Rydvall A, Haggmark S, Nyhman H et al: Effects of enflurane on coronary haemodynamics in patients with ischaemic heart disease. Acta Anaesthesiol Scand 28:690, 1984.

176. Braunwald E: Pathophysiology of heart failure. In: Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, 4th ed. Philadelphia, W.B. Saunders, 1992, pp 393-418.

177. Atlee III JL, Brownlee SW, Burstrom RE: Conscious-state comparisons of the effects of inhalational anesthetics on specialized atrioventricular conduction times in dogs. Anesthesiology 64:703, 1986.

178. Seagard JL, Bosnjak ZJ, Hopp Jr FA et al: Cardiovascular effects of anesthesia. In: Covino BG, Fozzard HA, Rehder K et al (eds): Effects of Anesthesia. Bethesda, Maryland, American Physiological Society, 1985, pp 149-177.

179. Turner LA, Bosnjak ZJ, Kampine JP: Actions of halothane on the electrical activity of Purkinje fibers derived from normal and infarcted canine hearts. Anesthesiology 67:619, 1987.

180. Atlee III JL, Rusy BF: Atrioventricular conduction times and atrioventricular nodal conductivity during enflurane anesthesia in dogs. Anesthesiology 47:498, 1977.

181. Hauswirth O: Effects of halothane on single atrial, ventricular and Purkinje fibers. Circ Res 24:745, 1969.

182. Atlee III JL, Rusy BF, Kreul JF et al: Supraventricular excitability in dogs during anesthesia with halothane and enflurane. Anesthesiology 49:407, 1978.

183. Atlee III JL, Yeager TS: Electrophysiologic assessment of the effects of enflurane, halothane, and isoflurane on properties affecting supraventricular re-entry in chronically instrumented dogs. Anesthesiology 71:941, 1989.

184. Atlee III JL, Bosnjak Z: Mechanisms for cardiac dysrhythmias during anesthesia. Anesthesiology 72:347, 1990.

185. Atlee III JL, Bosnjak ZJ, Yeager TS: Effects of diltiazem, verapamil, and inhalation anesthetics on electrophysiologic properties affecting reentrant supraventricular tachycardia in chronically instrumented dogs. Anesthesiology 72:889, 1990.

186. MacLeod BA, Augereau P, Walker MJA: Effects of halothane anesthesia compared with fentanyl anesthesia and no anesthesia during coronary ligation in rats. Anesthesiology 58:44, 1983.

187. Jang JL, MacLeod BA, Walker MJA: Effects of halogenated hydrocarbon anesthetics on responses to ligation of a coronary artery in chronically prepared rats. Anesthesiology 59:309, 1983.

188. Kroll DA, Knight PR: Antifibrillatory effects of volatile anesthetics in acute occlusion/reperfusion arrhythmias. Anesthesiology 61:657, 1984.

189. Morrow DH, Townley NT: Anesthesia and digitalis toxicity: An experimental study. Anesth Analg 43:510, 1964.

190. Turner LA, Polic S, Hoffmann RG et al: Actions of halothane and isoflurane on Purkinje fibers in the infarcted canine heart: Conduction, regional refractoriness, and reentry. Anesth Analg 76:718, 1993.

191. Turner LA, Polic S, Hoffmann RG et al: Actions of volatile anesthetics on ischemic and nonischemic Purkinje fibers in the canine heart: Regional action potential characteristics. Anesth Analg 76:726, 1993.

192. Schmeling WT, Warltier DC, McDonald DJ et al: Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. Anesth Analg 72:137, 1991.

193. Hanich RF, Levine JH, Spear JF et al: Autonomic modulation of ventricular arrhythmia in cesium chloride-induced long QT syndrome. Circulation 77:1149, 1988.

194. Atlee III JL, Malkinson CE: Potentiation by thiopental of halothane-epinephrine-induced arrhythmias in dogs. Anesthesiology 57:285, 1982.

195. Joas TA, Stevens WC: Comparison of the arrhythmic doses of epinephrine during Forane, halothane, and fluroxene anesthesia in dogs. Anesthesiology 35:48, 1971.

196. Sumikawa K, Ishizaka N, Suzaki M: Arrhythmogenic plasma levels of epinephrine during halothane, enflurane, and pentobarbital anesthesia in the dog. Anesthesiology 58:322, 1983.

197. MacCannell KL, Dresel PE: Potentiation by thiopental of cyclopropane-adrenaline cardiac arrhythmias. Can J Physiol Pharmacol 42:627, 1964.

198. Hayashi Y, Sumikawa K, Tashiro C et al: Arrhythmogenic threshold of epinephrine during sevoflurane, enflurane, and isoflurane anesthesia in dogs. Anesthesiology 69:145, 1988.

199. Turner LA, Marijic J, Kampine JP et al: A comparison of the effects of halothane and tetrodotoxin on regional repolarization characteristics of canine Purkinje fibers. Anesthesiology 73:1158, 1990.

200. Turner LA, Vodanovic S, Hoffmann RG et al: A subtype of alpha $_1$ -adrenoceptor mediates depression of conduction in Purkinje fibers exposed to halothane. Anesthesiology 82:1438, 1995.

201. Vodanovic S, Turner LA, Hoffmann RG et al: Actions of phenyl-ephrine, isoproterenol, and epinephrine with halothane on endocardial conduction and activation in canine left ventricular papillary muscles. Anesthesiology 87:117, 1997.

202. Weiskopf RB, Eger II EI, Holmes MA et al: Epinephrine-induced premature ventricular contractions and changes in arterial blood pressure and heart rate during I-653, isoflurane, and halothane anesthesia in swine. Anesthesiology 70:293, 1989.

203. Woehlck HJ, Vicenzi MN, Bosnjak ZJ et al: Anesthetics and automaticity of dominant and latent pacemakers in chronically instrumented dogs. I: Methodology, conscious state, and halothane anesthesia: Comparison with and without muscarinic blockade during exposure to epinephrine. Anesthesiology 79:1304, 1993.

204. Vicenzi MN, Woehlck HJ, Bosnjak ZJ et al: Anesthetics and automaticity of dominant and latent pacemakers in chronically instrumented dogs. II: Effects of enflurane and isoflurane during epinephrine with and without muscarinic blockade. Anesthesiology 79:1316, 1993.

205. Vicenzi MN, Woehlck HJ, Bajic J et al: Anesthetics and automaticity of dominant and latent pacemakers in chronically instrumented dogs. III: Automaticity after sinoatrial node excision. Anesthesiology 82:469, 1995.

206. Woehlck HJ, Vicenzi MN, Bajic J et al: Anesthetics and automaticity of dominant and latent pacemakers in chronically instrumented dogs. IV: Dysrhythmias after sinoatrial node excision. Anesthesiology 82:1447, 1995.

207. Blaise G, Sill JC, Nugent M et al: Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 67:513, 1987.

208. Bollen BA, Tinker JH, Hermsmeyer K: Halothane relaxes previously constricted isolated porcine coronary artery segments more than isoflurane. Anesthesiology 66:748, 1987.

209. Bollen BA, McKlveen RE, Stevenson JA: Halothane relaxes preconstricted small and medium isolated porcine coronary artery segments more than isoflurane. Anesth Analg 75:9, 1992.

210. Bollen BA, McKlveen RE, Stevenson JA: Halothane relaxes previously constricted human epicardial coronary artery segments more than isoflurane. Anesth Analg 75:4, 1992.

211. Hatano Y, Nakamura K, Yakushiji T et al: Comparison of the direct effects of halothane and isoflurane on large and small coronary arteries isolated from dogs. Anesthesiology 73:513, 1990.

212. Marijic J, Buljubasic N, Coughlan G et al: Effect of K^+ channel blockade with tetraethylammonium on anesthetic-induced relaxation in canine cerebral and coronary arteries. Anesthesiology 77:948, 1992.

213. Villeneuve E, Blaise G, Sill JC et al: Halothane 1.5 MAC, isoflurane 1.5 MAC, and the contractile responses of coronary arteries obtained from human hearts. Anesth Analg 72:454, 1991.

214. Witzeling TM, Sill JC, Hughes JM et al: Isoflurane and halothane attenuate coronary artery constriction evoked by serotonin in isolated porcine vessels and in intact pigs. Anesthesiology 73:100, 1990.

215. Buljubasic N, Rusch NJ, Marijic J et al: Effects of halothane and isoflurane on calcium and potassium channel currents in canine coronary arterial cells. Anesthesiology 76:990, 1992.

216. Kersten JR, Warltier DC: The coronary circulation. In: Yaksh TL, Lynch III C, Zapol WM et al (eds): Anesthesia: Biologic Foundations. Philadelphia, Lippincott-Raven, 1997, pp 1169-92.

217. Larach DR, Schuler HG, Skeehan TM et al: Direct effects of myocardial depressant drugs on coronary vascular tone: Anesthetic vasodilation by halothane and isoflurane. J Pharmacol Exp Ther 254:58, 1990.

218. Sahlman L, Henriksson B-A, Martner J et al: Effects of halothane, enflurane, and isoflurane on coronary vascular tone, myocardial performance, and oxygen consumption during controlled changes in aortic and left atrial pressure: Studies on isolated working rat hearts *in vitro.* Anesthesiology 69:1, 1988.

219. Stowe DF, Marijic J, Bosnjak ZJ et al: Direct comparative effects of halothane, enflurane, and isoflurane on oxygen supply and demand in isolated hearts. Anesthesiology 74:1087, 1991.

220. Stowe DF, Monroe SM, Marijic J et al: Comparison of halothane, enflurane, and isoflurane with nitrous oxide on contractility and oxygen supply and demand in isolated hearts. Anesthesiology 75:1062, 1991.

221. Larach DR, Schuler HG: Direct vasodilation by sevoflurane, isoflurane, and halothane alters coronary flow reserve in the isolated rat heart. Anesthesiology 75:268, 1991.

222. Smith G, Vance JP, Brown DM et al: Changes in myocardial blood flow and oxygen consumption in response to halothane. Br J Anaesth 46:821, 1974.

223. Domenech RJ, Macho P, Valdes J et al: Coronary vascular resistance during halothane anesthesia. Anesthesiology 46:236, 1977.

224. Weaver PC, Bailey JS, Preston TD: Coronary artery blood flow in the halothane-depressed canine heart. Br J Anaesth 42:678, 1970.

225. Wolff G, Claudi B, Rist M et al: Regulation of coronary blood flow during ether and halothane anaesthesia. Br J Anaesth 44:1139, 1972.

226. Amory DW, Steffenson JL, Forsyth RP: Systemic and regional blood flow changes during halothane anesthesia in the rhesus monkey. Anesthesiology 35:81, 1971.

227. Vatner SF, Smith NT: Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. Circ Res 34:155, 1974.

228. Brett CM, Teitel DF, Heymann MA et al: The cardiovascular effects of isoflurane in lambs. Anesthesiology 67:60, 1987.

229. Crystal GJ, Kim S-J, Czinn EA et al: Intracoronary isoflurane causes marked vasodilation in canine hearts. Anesthesiology 74:757, 1991.

230. Hickey RF, Cason BA, Shubayev I: Regional vasodilating properties of isoflurane in normal swine myocardium. Anesthesiology 80:574, 1994.

231. Priebe H-J: Differential effects of isoflurane on regional right and left ventricular performances and on coronary, systemic, and pulmonary hemodynamics in the dog. Anesthesiology 66:262, 1987.

232. Kenny D, Proctor LT, Schmeling WT et al: Isoflurane causes only minimal increases in coronary blood flow independent of oxygen demand. Anesthesiology 75:640, 1991.

233. Crystal GJ, Kim S-J, Salem MR et al: Nitric oxide does not mediate coronary vasodilation by isoflurane. Anesthesiology 81:209, 1994.

234. Sill JC, Bove AA, Nugent M et al: Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. Anesthesiology 66:273, 1987.

235. Hickey RF, Sybert PE, Verrier ED et al: Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. Anesthesiology 68:21, 1988.

236. Conzen PF, Hobbhahn J, Goetz AE et al: Regional blood flow and tissue oxygen pressures of the collateral-dependent myocardium during isoflurane anesthesia in dogs. Anesthesiology 70:442, 1989.

237. Habazettl H, Conzen PF, Hobbhahn J et al: Left ventricular oxygen tensions in dogs during coronary vasodilation by enflurane, isoflurane and dipyridamole. Anesth Analg 68:286, 1989.

238. Boban M, Stowe DF, Buljubasic N et al: Direct comparative effects of isoflurane and desflurane in isolated guinea pig hearts. Anesthesiology 76:775, 1992.

239. Conzen PF, Vollmar B, Habazettl H et al: Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. Anesth Analg 74:79, 1992.

240. Crawford MW, Lerman J, Saldivia V et al: Hemodynamic and organ blood flow responses to halothane and sevoflurane anesthesia during spontaneous ventilation. Anesth Analg 75:1000, 1992.

241. Manohar M, Parks CM: Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. J Pharmacol Exp Ther 231:640, 1984.

242. Gilbert M, Roberts SL, Mori M et al: Comparative coronary vascular reactivity and hemodynamics during halothane and isoflurane anesthesia in swine. Anesthesiology 68:243, 1988.

243. Conzen PF, Habazettl H, Vollmar B et al: Coronary microcirculation during halothane, enflurane, isoflurane, and adenosine in dogs. Anesthesiology 76:261, 1992.

244. Ozhan M, Sill JC, Atagunduz P et al: Volatile anesthetics and agonist-induced contractions in porcine coronary artery smooth muscle and Ca^{2+} mobilization in cultured immortalized vascular smooth muscle cells. Anesthesiology 80:1102, 1994.

245. Su JY, Zhang CC: Intracellular mechanisms of halothane's effect on isolated aortic strips of the rabbit. Anesthesiology 71:409, 1989.

246. Sill JC, Eskuri S, Nelson R et al: The volatile anesthetic isoflurane attenuates Ca^{2+} mobilization in cultured vascular smooth muscle cells. J Pharmacol Exp Ther 265:74, 1993.

247. Brendel JK, Johns RA: Isoflurane does not dilate isolated rat thoracic aortic rings by endothelium-derived relaxing factor or other cyclic GMP-mediated mechanisms. Anesthesiology 77:126, 1992.

248. Muldoon SM, Hart JL, Bowen KA et al: Attenuation of endothelium-mediated vasodilation by halothane. Anesthesiology 68:31, 1988.

249. Stone DJ, Johns RA: Endothelium-dependent effects of halothane, enflurane, and isoflurane on isolated rat aortic vascular rings. Anesthesiology 71:126, 1989.

250. Greenblatt EP, Loeb AL, Longnecker DE: Endothelium-dependent circulatory control--a mechanism for the differing peripheral vascular effects of isoflurane versus halothane. Anesthesiology 77:1178, 1992.

251. Blaise G, To Q, Parent M et al: Does halothane interfere with the release, action, or stability of endothelium-derived relaxing factor/nitric oxide? Anesthesiology 80:417, 1994.

252. Uggeri MJ, Proctor GJ, Johns RA: Halothane, enflurane, and isoflurane attenuate both receptor- and nonreceptor-mediated EDRF production in rat thoracic aorta. Anesthesiology 76:1012, 1992.

253. Hart JL, Jing M, Bina S et al: Effects of halothane on EDRF/cGMP-mediated vascular smooth muscle relaxations. Anesthesiology 79:323, 1993.

254. Toda H, Nakamura K, Hatano Y et al: Halothane and isoflurane inhibit endothelium-dependent relaxation elicited by acetylcholine. Anesth Analg 75:198, 1992.

255. Yoshida K-I, Okabe E: Selective impairment of endothelium-dependent relaxation by sevoflurane: Oxygen-free radicals participation. Anesthesiology 76:440, 1992.

256. Larach DR, Schuler HG: Potassium channel blockade and halothane vasodilation in conducting and resistance coronary arteries. J Pharmacol Exp Ther 267:72, 1993.

257. Cason BA, Shubayev I, Hickey RF: Blockade of adenosine triphosphate-sensitive potassium channels eliminates isoflurane-induced coronary artery vasodilation. Anesthesiology 81:1245, 1994.

258. Crystal GJ, Gurevicius J, Salem MR et al: Role of adenosine triphosphate-sensitive potassium channels in coronary vasodilation by halothane, isoflurane, and enflurane. Anesthesiology 86:448, 1997.

259. Kersten JR, Schmeling TJ, Hettrick DA et al: Mechanism of cardioprotection by isoflurane: Role of adenosine triphosphate-regulated potassium (K_{ATP}) channels. Anesthesiology 85:794, 1996.

260. Kersten JR, Gross GJ, Pagel PS et al: Activation of adenosine triphosphate-regulated potassium channels: Mediation of cellular and organ protection. Anesthesiology 88:495, 1998.

261. Hickey RF, Verrier ED, Baer RW et al: A canine model of acute coronary stenosis: Effects of deliberate hypotension. Anesthesiology 59:226, 1983.

262. Priebe H-J, Foex P: Isoflurane causes regional myocardial dysfunction in dogs with critical coronary artery stenoses. Anesthesiology 66:293, 1987.

263. Foex P, Francis CM, Cutfield GR et al: The pressure-length loop. Br J Anaesth 60 (8 Suppl 1):65S, 1988.

264. Priebe H-J: Isoflurane causes more severe myocardial dysfunction than halothane in dogs with a critical coronary stenosis. Anesthesiology 69:72, 1988.

265. Tatekawa S, Traber KB, Hantler CB et al: Effects of isoflurane on myocardial blood flow, function, and oxygen consumption in the presence of critical coronary stenosis in dogs. Anesth Analg 66:1073, 1987.

266. Wilton NCT, Knight PR, Ullrich K et al: Transmural redistribution of myocardial blood flow during isoflurane anesthesia and its effects on regional myocardial function in a canine model of fixed coronary stenosis. Anesthesiology 78:510, 1993.

267. Cason BA, Verrier ED, London MJ et al: Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: Their capacity to induce coronary steal. Anesthesiology 67:665, 1987.

268. Hartman JC, Kampine JP, Schmeling WT et al: Actions of isoflurane on myocardial perfusion in chronically instrumented dogs with poor, moderate, or well-developed coronary collaterals. J Cardiothorac Anesth 4:715, 1990.

269. Hartman JC, Kampine JP, Schmeling WT et al: Alterations in collateral blood flow produced by isoflurane in a chronically instrumented canine model of multivessel coronary artery disease. Anesthesiology 74:120, 1991.

270. Hartman JC, Kampine JP, Schmeling WT et al: Volatile anesthetics and regional myocardial perfusion in chronically instrumented dogs: Halothane versus isoflurane in a single-vessel disease model with enhanced collateral development. J Cardiothorac Anesth 4:588, 1990.

271. Hartman JC, Kampine JP, Schmeling WT et al: Steal-prone coronary circulation in chronically instrumented dogs: Isoflurane versus adenosine. Anesthesiology 74:744, 1991.

272. Moore PG, Kien ND, Reitan JA et al: No evidence for blood flow redistribution with isoflurane or halothane during acute coronary artery occlusion in fentanyl-anesthetized dogs. Anesthesiology 75:854, 1991.

273. Hartman JC, Pagel PS, Kampine JP et al: Influence of desflurane on the regional distribution of coronary blood flow in a chronically instrumented canine model of multivessel coronary artery obstruction. Anesth Analg 72:289, 1991.

274. Kersten JR, Brayer AP, Pagel PS et al: Perfusion of ischemic myocardium during anesthesia with sevoflurane. Anesthesiology 81:995, 1994.

275. Buffington CW, Romson JL, Levine A et al: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 66:280, 1987.

276. Cheng DCH, Moyers JR, Knutson RM et al: Dose-response relationship of isoflurane and halothane versus coronary perfusion pressures: Effects on flow redistribution in a collateralized chronic swine model. Anesthesiology 76:113, 1992.

277. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 45:287, 1976.

278. Gerson JI, Hickey RF, Bainton CR: Treatment of myocardial ischemia with halothane or nitroprusside-propranolol. Anesth Analg 61:10, 1982.

279. Davis RF, Sidi A: Effect of isoflurane on the extent of myocardial necrosis and on systemic hemodynamics, regional myocardial blood flow, and regional myocardial metabolism in dogs after coronary artery occlusion. Anesth Analg 69:575, 1989.

280. Cope DK, Impastato WK, Cohen MV et al: Volatile anesthetics protect the ischemic rabbit myocardium from infarction. Anesthesiology 86:699, 1997.

281. Cason BA, Gamperl AK, Slocum RE et al: Anesthetic-induced preconditioning: Previous administration of isoflurane decreases myocardial infarct size in rabbits. Anesthesiology 87:1182, 1997.

282. Buljubasic N, Stowe DF, Marijic J et al: Halothane reduces release of adenosine, inosine, and lactate with ischemia and reperfusion in isolated hearts. Anesth Analg 76:54, 1993.

283. Coetzee A, Brits W, Genade S et al: Halothane does have protective properties in the isolated ischemic rat heart. Anesth Analg 73:711, 1991.

284. Freedman BM, Hamm DP, Everson CT et al: Enflurane enhances postischemic functional recovery in the isolated rat heart. Anesthesiology 62:29, 1985.

285. Marijic J, Stowe DF, Turner LA et al: Differential protective effects of halothane and isoflurane against hypoxic and reoxygenation injury in the isolated guinea pig heart. Anesthesiology 73:976, 1990.

286. Mattheussen M, Rusy BF, Van Aken H et al: Recovery of function and adenosine triphosphate metabolism following myocardial ischemia induced in the presence of volatile anesthetics. Anesth Analg 76:69, 1993.

287. Belo SE, Mazer CD: Effect of halothane and isoflurane on post-ischemic "stunned" myocardium in the dog. Anesthesiology 73:1243, 1990.

288. Tanguay M, Blaise G, Dumont L et al: Beneficial effects of volatile anesthetics on decrease in coronary flow and myocardial contractility induced by oxygen-derived free radicals in isolated rabbit hearts. J Cardiovasc Pharmacol 18:863, 1991.

289. Smith G, Rogers K, Thornburn J: Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischaemia. Br J Anaesth 52:577, 1980.

290. Bertha BG, Folts JD, Nugent M et al: Halothane, but not isoflurane or enflurane, protects against spontaneous and epinephrine-exacerbated acute thrombus formation in stenosed dog coronary arteries. Anesthesiology 71:96, 1989.

291. Kowalski C, Zahler S, Becker BF et al: Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in the coronary system. Anesthesiology 86:188, 1997.

292. Kersten JR, Lowe D, Hettrick DA et al: Glyburide, a K_{ATP} channel antagonist, attenuates the cardioprotective effects of isoflurane in stunned myocardium. Anesth Analg 83:27, 1996.

293. Kwok W-M, Martinelli AT, Standnicka A et al: Differential effects of volatile anesthetics on the cardiac ATP-sensitive K^+ channel. Anesthesiology 85:A515, 1996.

294. Han J, Kim E, Ho WK et al: Effects of volatile anesthetic isoflurane on ATP-sensitive K^+ channels in rabbit ventricular myocytes. Biochem Biophys Res Commun 229:852, 1996.

295. Kersten JR, Orth KG, Pagel PS et al: Role of adenosine in isoflurane-induced cardioprotection. Anesthesiology 86:1128, 1997.

296. Van Wylen DGL: Effect of ischemic preconditioning on interstitial purine metabolite and lactate accumulation during myocardial ischemia. Circulation 89:2283, 1994.

297. Mizumura T, Nithipatikom K, Gross GJ: Bimakalim, an ATP-sensitive potassium channel opener, mimics the effects of ischemic preconditioning to reduce infarct size, adenosine release, and neutrophil function in dogs. Circulation 92:1236, 1995.

298. Yao Z, Mizumura T, Mei DA et al: K_{ATP} channels and memory of ischemic preconditioning in dogs: Synergism between adenosine and K_{ATP} channels. Am J Physiol 272:H334, 1997.

299. Hilfiker O, Larsen R, Sonntag H: Myocardial blood flow and oxygen consumption during halothane-nitrous oxide anaesthesia for coronary revascularization. Br J Anaesth 55:927, 1983.

300. Khambatta HJ, Sonntag H, Larsen R et al: Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 67:936, 1988.

301. Sahlman L, Milocco I, Ricksten S-E: Myocardial circulatory and metabolic effects of halothane when used to control intraoperative hypertension in patients with coronary artery disease. Acta Anaesthesiol Scand 36:283, 1992.

302. Moffitt EA, Imrie DD, Scovil JE et al: Myocardial metabolism and haemodynamic responses with enflurane anesthesia for coronary artery surgery. Can Anaesth Soc J 31:604, 1984.

303. Moffitt EA, Barker RA, Glen JJ et al: Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary arterial surgery. Anesth Analg 65:53, 1986.

304. O'Young J, Mastrocostopoulos G, Hilgenberg A et al: Myocardial circulatory and metabolic effects of isoflurane and sufentanil during coronary artery surgery. Anesthesiology 66:653, 1987.

305. Sahlman L, Milocco I, Appelgren L et al: Control of intraoperative hypertension with isoflurane in patients with coronary artery disease: Effects on regional myocardial blood flow and metabolism. Anesth Analg 68:105, 1989.

306. Tarnow J, Markschies-Hornung A, Schulte-Sasse U: Isoflurane improves the tolerance to pacing-induced myocardial ischemia. Anesthesiology 64:147, 1986.

307. Diana P, Tullock WC, Gorcsan III J et al: Myocardial ischemia: A comparison between isoflurane and enflurane in coronary artery bypass patients. Anesth Analg 77:221, 1993.

308. Inoue K, Reichelt W, El-Banayosy A et al: Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery?: A clinical study of 1178 patients. Anesth Analg 71:469, 1990.

309. Knight AA, Hollenberg M, London MJ et al: Perioperative myocardial ischemia: Importance of the preoperative ischemia pattern. Anesthesiology 68:681, 1988.

310. Pulley DD, Kirvassilis GV, Kelermenos N et al: Regional and global myocardial circulatory and metabolic effects of isoflurane and halothane in patients with steal-prone coronary anatomy. Anesthesiology 75:756, 1991.

311. Slogoff S, Keats AS: Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 70:179, 1989.

312. Tuman KJ, McCarthy RJ, Spiess BD et al: Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 70:189, 1989.

313. Wallace A, Layug B, Tateo I et al: Prophylactic atenolol reduces postoperative myocardial ischemia. Anesthesiology 88:7, 1998.

314. Mangano DT, Layug EL, Wallace A et al: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery: Multicenter Study of Perioperative Ischemia Group. N Engl J Med 335:1713, 1996.

315. Wilkinson PL, Hamilton WK, Moyers JR et al: Halothane and morphine-nitrous oxide anesthesia in patients undergoing coronary artery bypass operation: Patterns of intraoperative ischemia. J Thorac Cardiovasc Surg 82:372, 1981.

316. Moffitt EA, Sethna DH, Bussell JA et al: Myocardial metabolism and hemodynamic responses to halothane or morphine anesthesia for coronary artery surgery. Anesth Analg 61:979, 1982.

317. Helman JD, Leung JM, Bellows WH et al: The risk of myocardial ischemia in patients receiving desflurane versus sufentanil anesthesia for coronary artery bypass graft surgery: The SPI Research Group. Anesthesiology 77:47, 1992.

318. Buffington CW, Davis KB, Gillispie S et al: The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: An analysis of the Coronary Artery Surgery Study Registry. Anesthesiology 69:721, 1988.

319. Ebert TJ, Kharasch ED, Rooke GA et al: Myocardial ischemia and adverse cardiac outcomes in cardiac patients undergoing noncardiac surgery with sevoflurane and isoflurane: Sevoflurane Ischemia Study Group. Anesth Analg 85:993, 1997.

320. Heikkila H, Jalonen J, Arola M et al: Haemodynamics and myocardial oxygenation during anaesthesia for coronary artery surgery: Comparison between enflurane and high-dose fentanyl anaesthesia. Acta Anaesthesiol Scand 29:457, 1985.

321. Leung JM, Goehner P, O'Kelly BF et al: Isoflurane anesthesia and myocardial ischemia: Comparative risk versus sufentanil anesthesia in patients undergoing coronary artery bypass graft surgery. The SPI (Study of Perioperative Ischemia) Research Group. Anesthesiology 74:838, 1991.

322. Slogoff S, Keats AS, Dear WE et al: Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. Anesth Analg 72:22, 1991.

323. Biscoe TJ, Millar RA: The effects of cyclopropane, halothane and ether on central baroreceptor pathways. J Physiol (Lond) 184:535, 1966.

324. Cox RH, Bagshaw RJ: Influence of anesthesia on the response to carotid hypotension in dogs. Am J Physiol 237:H424, 1979.

325. Epstein RA, Wang H-H, Bartelstone HJ: The effects of halothane on circulatory reflexes of the dog. Anesthesiology 29:867, 1968.

326. Seagard JL, Elegbe EO, Hopp FA et al: Effects of isoflurane on baroreceptor reflex. Anesthesiology 59:511, 1983.

327. Sellgren J, Biber B, Henriksson B-A et al: The effects of propofol, methohexitone and isoflurane on the baroreceptor reflex in the cat. Acta Anaesthesiol Scand 36:784, 1992.

328. Skovsted P, Price HL: The effects of Ethrane on arterial pressure, preganglionic sympathetic activity, and barostatic reflexes. Anesthesiology 36:257, 1972.

329. Skovsted P, Price ML, Price HL: The effects of halothane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 31:507, 1969.

330. Skovsted P, Sapthavichaikul S: The effects of isoflurane on arterial pressure, pulse rate, autonomic nervous activity, and barostatic reflexes. Can Anaesth Soc J 24:304, 1977.

331. Seagard JL, Hopp FA, Donegan JH et al: Halothane and the carotid sinus reflex: Evidence for multiple sites of action. Anesthesiology 57:191, 1982.

332. Seagard JL, Hopp FA, Bosnjak ZJ et al: Sympathetic efferent nerve activity in conscious and isoflurane-anesthetized dogs. Anesthesiology 61:266, 1984.

333. Seagard JL, Hopp FA, Bosnjak ZJ et al: Extent and mechanism of halothane sensitization of the carotid sinus baroreceptors. Anesthesiology 58:432, 1983.

334. Ebert TJ, Seagard JL, Hopp Jr FA: Autonomic nervous system: Measurement and response under anesthesia. In: Yaksh TL, Lynch III C, Zapol WM et al (eds): Anesthesia: Biologic Foundations. Philadelphia, Lippincott-Raven, 1997, pp 1233-1255.

335. Alper MH, Fleisch JH, Flacke W: The effects of halothane on the responses of cardiac sympathetic ganglia to various stimulants. Anesthesiology 31:429, 1969.

336. Christ D: Effects of halothane on ganglionic discharges. J Pharmacol Exp Ther 200:336, 1977.

337. Bosnjak ZJ, Seagard JL, Wu A et al: The effects of halothane on sympathetic ganglionic transmission. Anesthesiology 57:473, 1982.

338. Deegan R, He HB, Wood AJJ et al: Effects of anesthesia on norepinephrine kinetics: Comparison of propofol and halothane anesthesia in dogs. Anesthesiology 75:481, 1991.

339. Deegan R, He HB, Wood AJJ et al: Effect of enflurane and isoflurane on norepinephrine kinetics: A new approach to assessment of sympathetic function during anesthesia. Anesth Analg 77:49, 1993.

340. Rorie DK, Tyce GM, Mackenzie RA: Evidence that halothane inhibits norepinephrine release from sympathetic nerve endings in dog saphenous vein by stimulation of presynaptic inhibitory muscarinic receptors. Anesth Analg 63:1059, 1984.

341. Cristoforo MF, Brody MJ: The effects of halothane and cyclopropane on skeletal muscle vessels and baroreceptor reflexes. Anesthesiology 29:36, 1968.

342. Price HL, Price ML, Morse HT: Effects of cyclopropane, halothane and procaine on the vasomotor "center" of the dog. Anesthesiology 26:55, 1965.

343. Price HL, Linde HW, Morse HT: Central nervous actions of halothane affecting the systemic circulation. Anesthesiology 24:770, 1963.

344. Morton M, Duke PC, Ong B: Baroreflex control of heart rate in man awake and during enflurane and enflurane-nitrous oxide anesthesia. Anesthesiology 52:221, 1980.

345. Kotrly KJ, Ebert TJ, Vucins EJ et al: Effects of fentanyl-diazepam-nitrous oxide anaesthesia on arterial baroreflex control of heart rate in man. Br J Anaesth 58:406, 1986.

346. Gribbin B, Pickering TG, Sleight P et al: Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 29:424, 1971.

347. Olshan AR, O'Connor DT, Cohen IM et al: Baroreflex dysfunction in patients with adult-onset diabetes and hypertension. Am J Med 74:233, 1983.

348. Goldberg AH, Sohn YZ, Phear WP: Direct myocardial effects of nitrous oxide. Anesthesiology 37:373, 1972.

349. Price HL: Myocardial depression by nitrous oxide and its reversal by Ca^{++}. Anesthesiology 44:211, 1976.

350. Carton EG, Wanek LA, Housmans PR: Effects of nitrous oxide on contractility, relaxation and the intracellular calcium transient of isolated mammalian ventricular myocardium. J Pharmacol Exp Ther 257:843, 1991.

351. Craythorne NW, Darby TD: The cardiovascular effects of nitrous oxide in the dog. Br J Anaesth 37:560, 1965.

352. Smith NT, Eger II EI, Stoelting RK et al: The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 32:410, 1970.

353. Ebert TJ: Differential effects of nitrous oxide on baroreflex control of heart rate and peripheral sympathetic nerve activity in humans. Anesthesiology 72:16, 1990.

354. Ebert TJ, Kampine JP: Nitrous oxide augments sympathetic outflow: Direct evidence from human peroneal nerve recordings. Anesth Analg 69:444, 1989.

355. Sellgren J, Ponten J, Wallin BG: Percutaneous recording of muscle nerve sympathetic activity during propofol, nitrous oxide, and isoflurane anesthesia in humans. Anesthesiology 73:20, 1990.

356. Eisele JH, Smith NT: Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 51:956, 1972.

357. Eriksen S, Johannsen G, Frost N: Effects of nitrous oxide on systolic time intervals. Acta Anaesthesiol Scand 24:74, 1980.

358. Falk Jr RB, Denlinger JK, Nahrwold ML et al: Acute vasodilation following induction of anesthesia with intravenous diazepam and nitrous oxide. Anesthesiology 49:149, 1978.

359. Lichtenthal P, Philip J, Sloss LJ et al: Administration of nitrous oxide in normal subjects: Evaluation of systems of gas delivery for their clinical use and hemodynamic effects. Chest 72:316, 1977.

360. Stoelting RK, Gibbs PS: Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary-artery disease. Anesthesiology 38:45, 1973.

361. Thornton JA, Fleming JS, Goldberg AD et al: Cardiovascular effects of 50 percent nitrous oxide and 50 percent oxygen mixture. Anaesthesia 28:484, 1973.

362. Bahlman SH, Eger II EI, Smith NT et al: The cardiovascular effects of nitrous oxide-halothane anesthesia in man. Anesthesiology 35:274, 1971.

363. Coetzee A, Fourie P, Bolliger C et al: Effect of N_2O on segmental left ventricular function and effective arterial elastance in pigs when added to a halothane-fentanyl-pancuronium anesthetic technique. Anesth Analg 69:313, 1989.

364. Dolan WM, Stevens WC, Eger II EI et al: The cardiovascular and respiratory effects of isoflurane-nitrous oxide anaesthesia. Can Anaesth Soc J 21:557, 1974.

365. Lappas DG, Buckley MJ, Laver MB et al: Left ventricular performance and pulmonary circulation following addition of nitrous oxide to morphine during coronary-artery surgery. Anesthesiology 43:61, 1975.

366. Lunn JK, Stanley TH, Eisele J et al: High-dose fentanyl anesthesia for coronary artery surgery: Plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 58:390, 1979.

367. Smith NT, Calverley RK, Prys-Roberts C et al: Impact of nitrous oxide on the circulation during enflurane anesthesia in man. Anesthesiology 48:345, 1978.

368. Van Trigt P, Christian CC, Fagraeus L et al: Myocardial depression by anesthetic agents (halothane, enflurane and nitrous oxide): Quantitation based on end-systolic pressure-dimension relations. Am J Cardiol 53:243, 1984.

369. Pagel PS, Kampine JP, Schmeling WT et al: Effects of nitrous oxide on myocardial contractility as evaluated by the preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology 73:1148, 1990.

370. Messina AG, Yao F-S, Canning H et al: The effect of nitrous oxide on left ventricular pump performance and contractility in patients with coronary artery disease: Effect of preoperative ejection fraction. Anesth Analg 77:954, 1993.

371. Eisele JH, Reitan JA, Massumi RA et al: Myocardial performance and N_2O analgesia in coronary-artery disease. Anesthesiology 44:16-20, 1976.

372. Hohner P, Backman C, Diamond G et al: Anaesthesia for abdominal aortic surgery in patients with coronary artery disease. II: Effects of nitrous oxide on systemic and coronary haemodynamics, regional ventricular function and incidence of myocardial ischaemia. Acta Anaesthesiol Scand 38:793, 1994.

373. Houltz E, Caidahl K, Hellstrom A et al: The effects of nitrous oxide on left ventricular systolic and diastolic performance before and after cardiopulmonary bypass: Evaluation by computer-assisted two-dimensional and Doppler echocardiography in patients undergoing coronary artery surgery. Anesth Analg 81:243, 1995.

374. Tempe D, Mohan JC, Cooper A et al: Myocardial depressant effect of nitrous oxide after valve surgery. Eur J Anaesthesiol 11:353, 1994.

375. Marsch SCU, Dalmas S, Philbin DM et al: Effects and interactions of nitrous oxide, myocardial ischemia, and reperfusion on left ventricular diastolic function. Anesth Analg 84:39, 1997.

376. Carton EG, Housmans PR: Role of transsarcolemmal Ca^{2+} entry in the negative inotropic effects of nitrous oxide in isolated ferret myocardium. Anesth Analg 74:575, 1992.

377. Su JY, Kerrick WGL, Hill SA: Effects of diethyl ether and nitrous oxide on functionally skinned myocardial cells of rabbits. Anesth Analg 63:451, 1984.

378. Kawamura R, Stanley TH, English JB et al: Cardiovascular responses to nitrous oxide exposure for two hours in man. Anesth Analg 59:93, 1980.

379. Winter PM, Hornbein TF, Smith G et al: Hyperbaric nitrous oxide anesthesia in man: Determination of anesthetic potency (MAC) and cardiorespiratory effects (abstract). Boston, American Society of Anesthesiologists Annual Meeting, 1972:103.

380. Hornbein TF, Martin WE, Bonica JJ et al: Nitrous oxide effects on the circulatory and ventilatory responses to halothane. Anesthesiology 31:250, 1969.

381. Moffitt EA, Sethna DH, Gary RJ et al: Nitrous oxide added to halothane reduces coronary flow and myocardial oxygen consumption in patients with coronary disease. Can Anaesth Soc J 30:5, 1983.

382. McDermott RW, Stanley TH: The cardiovascular effects of low concentrations of nitrous oxide during morphine anesthesia. Anesthesiology 41:89, 1974.

383. Wong KC, Martin WE, Hornbein TF et al: The cardiovascular effects of morphine sulfate with oxygen and with nitrous oxide in man. Anesthesiology 38:542, 1973.

384. Stoelting RK, Reis RR, Longnecker DE: Hemodynamic responses to nitrous oxide-halothane and halothane in patients with valvular heart disease. Anesthesiology 37:430, 1972.

385. Schulte-Sasse U, Hess W, Tarnow J: Pulmonary vascular responses to nitrous oxide in patients with normal and high pulmonary vascular resistance. Anesthesiology 57:9, 1982.

386. Rorie DK, Tyce GM, Sill JC: Increased norepinephrine release from dog pulmonary artery caused by nitrous oxide. Anesth Analg 65:560, 1986.

387. Hilgenberg JC, McCammon RL, Stoelting RK: Pulmonary and systemic vascular responses to nitrous oxide in patients with mitral stenosis and pulmonary hypertension. Anesth Analg 59:323, 1980.

388. Landry LD, Emerson CW, Philbin DM et al: The effect of nitrous oxide on pulmonary vascular resistance in children. Anesth Analg 59:548, 1980.

389. Eisele Jr JH, Milstein JM, Goetzman BW: Pulmonary vascular responses to nitrous oxide in newborn lambs. Anesth Analg 65:62, 1986.

390. Davidson JR, Chinyanga HM: Cardiovascular collapse associated with nitrous oxide anaesthetic: A case report. Can Anaesth Soc J 29:484, 1982.

391. Roizen MF, Plummer GO, Lichtor JL: Nitrous oxide and dysrhythmias. Anesthesiology 66:427, 1987.

392. Liu WS, Wong KC, Port JD et al: Epinephrine-induced arrhythmias during halothane anesthesia with the addition of nitrous oxide, nitrogen, or helium in dogs. Anesth Analg 61:414, 1982.

393. Eisele Jr JH: Cardiovascular effects of nitrous oxide. In: Eger II EI (ed): Nitrous Oxide/N_2O. New York, Elsevier, 1985, pp 125-56.

394. Puerto BA, Wong KC, Puerto AX et al: Epinephrine-induced dysrhythmias: Comparison during anaesthesia with narcotics and with halogenated inhalational agents in dogs. Can Anaesth Soc J 26:263, 1979.

395. Hughes JM, Sill JC, Pettis M, Rorie DK: Nitrous oxide constricts epicardial coronary arteries in pigs: Evidence suggesting inhibitory effects of endothelium. Anesth Analg 77:232, 1993.

396. Stowe DF, Monroe SM, Marijic J et al: Effects of nitrous oxide on contractile function and metabolism of the isolated heart. Anesthesiology 73:1220, 1990.

397. Dottori O, Haggendal E, Linder E et al: The haemodynamic effects of nitrous oxide anaesthesia on myocardial blood flow in dogs. Acta Anaesthesiol Scand 20:421, 1976.

398. Wilkowski DAW, Sill JC, Bonta W et al: Nitrous oxide constricts epicardial coronary arteries without effect on coronary arterioles. Anesthesiology 66:659, 1987.

399. Cason BA, Demas KA, Mazer CD et al: Effects of nitrous oxide on coronary pressure and regional contractile function in experimental myocardial ischemia. Anesth Analg 72:604, 1991.

400. Nathan HJ: Nitrous oxide worsens myocardial ischemia in isoflurane-anesthetized dogs. Anesthesiology 68:407, 1988.

401. Philbin DM, Foex P, Drummond G et al: Postsystolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. Anesthesiology 62:166, 1985.

402. Siker D, Pagel PS, Pelc LR et al: Nitrous oxide impairs functional recovery of stunned myocardium in barbiturate-anesthetized, acutely instrumented dogs. Anesth Analg 75:539, 1992.

403. Nathan HJ: Control of hemodynamics prevents worsening of myocardial ischemia when nitrous oxide is administered to isoflurane-anesthetized dogs. Anesthesiology 71:686, 1989.

404. Kozmary SV, Lampe GH, Benefiel D et al: No finding of increased myocardial ischemia during or after carotid endarterectomy under anesthesia with nitrous oxide. Anesth Analg 71:591, 1990.

405. Lawrence JH, Loomis WF, Tobias CA et al: Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils. J Physiol (Lond) 105:197, 1946.

406. Steward A, Allott PR, Cowles AL et al: Solubility coefficients for inhaled anaesthetics in water, oil and biological media. Br J Anaesth 45:282, 1973.

407. Kennedy RR, Stokes JW, Downing P: Anaesthesia and the "inert" gases with special reference to xenon. Anaesth Intensive Care 20:66, 1992.

408. Luttropp HH, Romner B, Perhag L et al: Left ventricular performance and cerebral haemodynamics during xenon anaesthesia: A transesophageal echocardiography and transcranial Doppler sonography study. Anaesthesia 48:1045, 1993.

409. Luttropp HH, Thomasson R, Dahm S et al: Clinical experience with minimal flow xenon anesthesia. Acta Anaesthesiol Scand 38:121, 1994.

410. Goto T, Saito H, Shinkai M et al: Xenon provides faster emergence from anesthesia than does nitrous oxide-sevoflurane or nitrous oxide-isoflurane. Anesthesiology 86:1273, 1997.

411. Yagi M, Mashimo T, Kawaguchi T et al: Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: Comparison with nitrous oxide. Br J Anaesth 74:670, 1995.

412. Ohara A, Mashimo M, Zhang P et al: A comparative study of the antinociceptive action of xenon and nitrous oxide. Anesth Analg 85:931, 1997.

413. Saito H, Saito M, Goto T et al: Priming of anesthesia circuit with xenon for closed circuit anesthesia. Artif Organs 21:70, 1997.

414. Luttropp HH, Rydgren G, Thomasson R et al: A minimal-flow system for xenon anesthesia. Anesthesiology 75:896, 1991.

415. Boomsma F, Rupreht J, Man In't Veld AJ et al: Haemodynamic and neurohumoral effects of xenon anaesthesia: A comparison with nitrous oxide. Anaesthesia 45:273, 1990.

416. Marx T, Froeba G, Wagner D et al: Effects on haemodynamics and catecholamine release of xenon anaesthesia compared to total IV anaesthesia in the pig. Br J Anaesth 78:326, 1997.

417. Zhang P, Ohara A, Mashimo T et al: Pulmonary resistance in dogs: A comparison of xenon with nitrous oxide. Can J Anaesth 42:547, 1995.

418. Hettrick DA, Pagel PS, Kersten JR et al: Cardiovascular effects of xenon in isoflurane-anesthetized dogs with dilated cardiomyopathy. Anesthesiology 89: (In press), 1998.

Chapter 5B - Pulmonary Pharmacology

Neil E. Farber
Paul S. Pagel
David C. Warltier

INTRODUCTION

This chapter describes the physiologic control mechanisms involved in modulating various anatomic components of the pulmonary system and the direct effects of inhaled anesthetics on this system. Specific sections of the chapter focus on airway and pulmonary vascular resistance, mucociliary function, and ventilatory control.

EFFECTS OF INHALED ANESTHETICS ON BRONCHOMOTOR TONE

Transient increases in airway resistance may be caused in part by an increase in bronchiolar smooth muscle tone. A retrospective review [1] found that patients without recent symptoms of asthma had a very low frequency of perioperative respiratory complications, but other retrospective studies [2] [3] have reported that intraoperative bronchospasm developed in approximately 6 percent of patients with asthma. Prospective studies have demonstrated that 1.7 percent of patients with asthma experienced a severe respiratory outcome [4] and that 25 percent wheezed after the induction of anesthesia. [5] Of 40 cases of bronchospasm resulting in settled malpractice claims (from the American Society of Anesthesiologists Closed Claims Project), 88 percent involved brain damage or death, and only half of these 40 patients had a history of asthma or chronic obstructive pulmonary disease. Significant bronchospasm can occur in normal subjects with no underlying lung disease secondary to a noxious stimulus, and the bronchial smooth muscle pharmacology of inhaled agents is of great clinical importance.

Pharmacology of Bronchial Smooth Muscle

Mougdil [6] and Pinto-Pereira [7] have summarized the mechanisms by which increases in airway resistance may occur. Airway smooth muscle, which extends as far distally as the terminal bronchioles, is under the influence of both parasympathetic and sympathetic nerves as well as non-adrenergic noncholinergic mechanisms. The parasympathetic nerves located in the vagi mediate baseline airway tone and reflex bronchoconstriction. Changes in intracellular calcium (Ca^{2+}) levels and Ca^{2+} influx can be caused by alterations in cyclic nucleotides. Agonist-induced contraction may be mediated by an increase in myosin light chain kinase activity, a phosphorylation of the 20-kd regulatory myosin light chain, and an increase in calcium sensitivity. Acetylcholine, or stimulation of the vagus nerve, is believed to provide an increase in the amounts of cyclic guanosine

---

monophosphate (cGMP) relative to cyclic adenosine monophosphate (cAMP), resulting in smooth muscle contraction. Release of histamine in the airway or various forms of mechanical or chemical stimulation can result in an increase in afferent vagal activity, with subsequent reflex bronchoconstriction. This increase in bronchomotor tone can be attenuated by atropine. In addition to M3 muscarinic receptors on airway smooth muscle that mediate bronchoconstriction, presynaptic M2 muscarinic receptors inhibit acetylcholine release, causing bronchodilation. Thus, low doses of pharmacologic agents such as ipratropium, which preferentially inhibit M2 receptors, may paradoxically result in bronchoconstriction. [8]

Adrenergic receptors in bronchial smooth muscle are classified into alpha and beta $_2$ types. alpha-Receptors are found in the bronchial tree in humans, but their activity seems to be low and clinically of undefined significance. beta $_2$ -Receptor subtypes play an important role in bronchiolar muscle responsiveness. Stimulation of $beta_2$ -receptors in bronchial smooth muscle causes relaxation, which is mediated by a relative increase in the intracellular concentration of cAMP.

The respiratory epithelium releases substances that can modulate bronchial smooth muscle tone. Removal of epithelium enhances contractile responses to acetylcholine, histamine, or serotonin in large airways and decreases relaxation responses to isoproterenol in small airways, [9] [10] analogous to the effect of damage of endothelium on vascular smooth muscle tone. Endogenous epithelial factors have not yet been identified, but the endothelial-derived relaxing factor, nitric oxide, may play a similar role in respiratory epithelium.

Inhaled Anesthetics

Volatile anesthetics have classically been considered to be potent bronchodilators, and there exists an overwhelming body of evidence in support of this contention. In a retrospective study, Shnider and Papper [2] found that in 49 patients with preanesthetic symptoms of bronchospasm, halothane was superior to ether, cyclopropane, and ethylene in decreasing wheezing. Colgan [11] noted an increase in "bronchial distensibility" in dogs anesthetized with halothane, ether, or methoxyflurane, with halothane having the most pronounced effect. Increasing concentrations of halothane caused a dose-dependent decrease in resting airway resistance in spontaneously breathing dogs. [12] However, the possibility of bronchodilation secondary to an increased resting arterial carbon dioxide tension ($PaCO_2$) with deeper planes of anesthesia was not excluded in either study. Halothane and diethyl ether caused relaxation of resting tone in isolated guinea pig tracheal strips. [13] These anesthetics also attenuated tracheal muscle constriction produced by acetylcholine, but only halothane accomplished this in clinically relevant doses.

Hickey et al [14] demonstrated the importance of controlled levels of $PaCO_2$ in evaluating the effects of drugs on bronchial smooth muscle tone. Halothane and cyclopropane produced no change in resistance of the resting unstimulated airway in anesthetized, mechanically ventilated, normocapnic dogs. When either administration of histamine or vagal stimulation induced a state of increased bronchial tone, 1.5 minimum alveolar concentration (MAC) halothane produced significant dilation compared with cyclopropane. Halothane, enflurane, and methoxyflurane were found to reverse the bronchoconstricting effects of hypocapnia *in vivo* in the isolated left lower lobe of the dog, [15] with halothane being most efficacious. Halothane also was shown to attenuate the bronchoconstricting effects of hypocarbia without significant actions on the resistive work of breathing in the unstimulated state in humans undergoing cardiopulmonary bypass. [16]

A series of studies using dogs sensitized to aerosolized ascaris antigen, a bronchospasm model developed by Hirshman and Bergman [17] has greatly contributed to our understanding of the effect of anesthetics on airway smooth muscle. Halothane and enflurane (1 MAC) similarly attenuate antigen-induced bronchospasm. However, unlike an asthmatic attack during anesthesia, the stimulus to incite bronchospasm was not continued throughout the study. Isoflurane and halothane (1.5 MAC) were found to produce a similar decrease in airway resistance using the same experimental preparation. [18] Similar results were obtained with methacholine-induced (direct-acting stimulus) airway constriction. These data suggest that isoflurane and halothane act both by depressing airway reflexes and by direct bronchodilation. Furthermore, whereas isoflurane appears to share significant bronchodilating properties with halothane and enflurane, halothane more effectively increased dynamic compliance (a measure of small airway resistance) than did isoflurane. This finding is made more interesting in light of data that showed that, *in vitro,* isoflurane preferentially relaxes the bronchiole in comparison with the bronchus. [19] The structure of the respiratory epithelium changes from pseudostratified columnar cells of the large airways to thinner, cuboidal cells of the bronchioles, and therefore it is not surprising that topographic heterogeneity exists. Park and colleagues have demonstrated that isoflurane and halothane equipotently dilate fourth-order bronchi at equivalent MAC multiples. [20]

Ascaris antigen-induced asthma was associated with increased plasma histamine levels, which were not prevented by halothane anesthesia. [21] In another study of histamine-induced bronchospasm, halothane and topical atropine both decreased bronchoconstriction, but halothane did not add to the bronchodilating effects of atropine. [22]

Brown and colleagues, [23] using computed tomography (CT), have shown that, at low concentrations, halothane is a better bronchodilator than is isoflurane (Fig. 5-22) (Figure Not Available) . Halothane has also been demonstrated to have a greater relaxing effect than isoflurane at similar MAC in intact airway smooth muscle as measured by high resolution CT. [24] All volatile anesthetic agents including the newer anesthetics sevoflurane [25] [26] and desflurane [27] have been shown to relax airway smooth muscle. Both halothane and desflurane, as with isoflurane and the intravenous anesthetics ketamine, midazolam, and propofol, [28] appear to relax

distal airways (bronchioles) more than they do proximal airways (bronchi). The relative potency of sevoflurane on relaxing distal versus proximal airways is unknown. Also, the efficacy of desflurane on methacholine or histamine-induced bronchoconstriction has not been investigated. Neither halothane, enflurane, sevoflurane, nor isoflurane (1 or 2 MAC) altered baseline pulmonary resistance and dynamic pulmonary compliance.

Figure 5B-22 (Figure Not Available) High-resolution computed tomography scan from one dog. Upper left = control; upper right = during 0.5 percent halothane; lower left = during 1.0 percent halothane; lower right = during 1.5 percent halothane. Note the progressive dilation of the airways as indicated by the arrows. *(From Brown et al [37])*

However, these four anesthetics significantly attenuated increases in pulmonary resistance and decreases in dynamic pulmonary compliance due to intravenous histamine. Halothane was most effective in altering indices of bronchodilation, whereas responses to isoflurane, enflurane, and sevoflurane were similar. [26] In contrast, halothane, enflurane, and sevoflurane were found to be equipotent at dilating third- or fourth-generation bronchi as measured directly *in vivo* with a fiberoptic bronchoscope. [29]

Mechanisms of Action

Volatile anesthetics relax airway smooth muscle by directly depressing smooth muscle contractility and affecting bronchial epithelium and indirectly by inhibiting reflex neural pathways.

The mechanism of the direct depression is unclear. Halothane was initially believed to have beta-agonist activity in airway smooth muscle as the reduction of airway resistance produced by halothane in dogs was blocked by the beta-adre-nergic receptor antagonist sotalol. [12] These effects may have been drug-specific rather than attributable to the drug class, or sotalol may have had smooth muscle contracting properties because propranolol does not antagonize the relaxing properties of halothane on acetylcholine-mediated bronchoconstriction. [13] The concentration of intracellular $Ca^{2+}{}_i$ is an important regulator of smooth muscle reactivity. There are several intracellular mediators responsible for Ca^{2+} mobilization, which are potential sites of action for volatile anesthetics. Halothane causes small increases in cAMP concentrations, which can lead to decreases in intracellular Ca^{2+} in airway smooth muscle. [30]

Halothane also suppressed the contraction of dog tracheal smooth muscle initiated by both direct and indirect electrical stimulation. [31] Halothane may inactivate or reduce free Ca^{2+} in the cytoplasm and/or suppress influx of Ca^{2+} across the cell membrane. Volatile anesthetics affect the function of G proteins (membrane-bound proteins that couple receptors to cellular effectors) in a variety of tissues. However, halothane does not depress airway contractility by an effect on pertussis toxin-sensitive inhibitory G proteins that attenuate beta -adrenoceptor-induced relaxation. [32] Halothane decreases the intracellular concentration of Ca^{2+} and Ca^{2+} influx during submaximal, but not maximal, muscarinic stimulation. [33] This anesthetic also decreases Ca^{2+} sensitivity, resulting in reduced force of contraction even in the presence of constant Ca^{2+} concentrations. [33] Recently, Warner and coworkers [34] demonstrated that halothane attenuates ACh-induced Ca^{2+} sensitization in canine tracheal smooth muscle to a greater extent than does isoflurane or sevoflurane (analogous to the differential effects of volatile anesthetics on relaxing airway smooth muscle). Warner also suggested that whereas halothane depletes sarcoplasmic reticular Ca^{2+} stores, this is not the mechanism by which a reduction in airway contractility occurs. [35]

The bronchoconstricting effects of low inhaled CO_2 mixtures were attenuated by inhaled but not by intravenous halothane. [16] This finding suggests that halothane acts directly on the airway musculature and/or local reflex arcs rather than via centrally controlled reflex pathways. Both halothane- and isoflurane-induced bronchodilation partially depend on the presence of bronchial epithelium. [20] A prostanoid (such as prostaglandin E_2 or I_2) and/or nitric oxide may mediate the bronchodilatory effects of the volatile anesthetics. Isoflurane-mediated bronchodilation is more dependent on nitric oxide than on prostanoids whereas the opposite is true for halothane. Focal epithelial damage or inflammation may occur in distal/small airways in those with asthma or allergen exposure, and as a consequence, the bronchodilatory response to volatile anesthetics may be reduced. [6] Thus, the greatest bronchodilatory action of the anesthetics in patients with chronic reactive airway disease may occur in the proximal airways.

Neural stimulation of intrinsic airway nerves *in vitro* produces a cholinergic contractile response that is inhibited by atropine. Volatile anesthetics bronchodilate, at least in part by modulating cholinergic neural transmission in the airways. [31] [36] The combination of atropine and halothane together did not increase airway caliber over that attained with each treatment alone, suggesting that halothane dilates baseline airways by blocking vagal tone. [37] There also exists a bronchodilatory neural reflex that is nonadrenergic and noncholinergic in nature and believed to be mediated by nitric oxide. [38] Halothane, at concentrations <1%, does not significantly affect the activity of the nonadrenergic, noncholinergic neural system or the formation or release of nitric oxide by this neural system. [39] Finally, the direct antagonism of histamine is not the mechanism of volatile anesthetic-induced bronchodilation. Antigen-induced increases in plasma histamine concentrations are not prevented by previously anesthetizing animals with halothane. [21]

Clinical Effects

Appropriate anesthetic management of the patient with reactive airways disease has been reviewed. [6] [7] [40] Volatile anesthetics may be an effective method of treating status asthmaticus when other more conventional treatments have failed. Gold and Helrich [41] evaluated the effect of halothane and tracheal intubation on six patients treated unsuccessfully for status asthmaticus for at least 72 hours with bronchodilators, steroids, and antibiotics. No significant change in airway resistance was recorded in either the anesthetic or immediate postanesthetic period. Patients improved within 3 days after treatment, but the lack of a control group precludes interpretation. Several studies, however, have demonstrated that in refractory patients with status asthmaticus, the use of inhalational anesthetics may be beneficial. [42] [43] [44] [45] [46] [47] Halothane treatment may be associated with an increased risk of cardiac arrhythmias and cardiovascular depression such that isoflurane has been suggested to be the inhaled anesthetic of choice in status asthmaticus. [47] However, use of 1 percent halothane in 12 patients in status asthmaticus who required mechanical ventilation was associated with a rapid reduction in bronchospasm and barotrauma injury, improvement in arterial blood gas tensions, and a lack of adverse hemodynamic effects, including cardiac arrhythmias. [46]

Rooke et al [48] recently compared the bronchodilating effects of halothane, isoflurane, sevoflurane, and thiopental/ nitrous oxide in 66 nonasthmatic patients undergoing induction of anesthesia and tracheal intubation (Fig. 5-23) (Figure Not Available) . All volatile anesthetics significantly reduced respiratory system resistance (thiopental/nitrous oxide did not change resistance), and equi-MAC sevoflurane decreased resistance as much as halothane and more so than isoflurane. Thus, the previously described animal studies demonstrating equipotency of sevoflurane and isoflurane and greater potency of halothane for bronchodilation must be extrapolated with caution to humans as ascaris- or histamine-mediated experimental bronchospasm may not precisely mimic tracheal intubation-induced bronchospasm in humans.

The effect of the addition of albuterol to halothane anesthesia on airway reactivity was examined in dogs. [49] Halothane attenuated histamine-induced bronchoconstriction,

Figure 5B-23 (Figure Not Available) The percentage change in respiratory system resistance in patients after 5 and 10 minutes of maintenance anesthesia with either 0.25 mg/kg/min thiopental + 50% nitrous oxide; or 1.1 MAC sevoflurane, halothane, or isoflurane. All volatile anesthetics decreased resistance. Sevoflurane decreased resistance more than did isoflurane. *(From Rooke et al [46])*

and the beta-adrenoceptor agonist albuterol further dilated the airways, indicating an additive or synergistic effect. There was also no negative interaction between the dilatory effects of halothane and isoproterenol on canine tracheal smooth muscle. [32] Neither halothane nor isoproterenol affected the ability of the alternative treatment to relax acetylcholine-contracted tracheal strips. These findings support the use of beta-adrenoceptor agonists in the treatment of bronchospasm in patients already receiving halothane. Results may differ somewhat with other volatile anesthetics or beta agonists. An example is the beta $_2$ -adrenergic agonist fenoterol: while lowering respiratory system resistance following endotracheal intubation, it did not further decrease resistance as that observed with 1.3 percent isoflurane alone. [50] The results of the latter study may be due in part to the methodology of measurement of respiratory system resistance, which also reflected alterations in lung and chest-wall resistance as well as tissue viscosity.

The actions of volatile anesthetics on bronchomotor tone, at least *in vitro,* are dependent on the agent eliciting contraction. [24] Relaxation of tracheal smooth muscle by halothane and isoflurane is greatest in the presence of the endogenous mediator serotonin (potentially representing anaphylactoid or immunologic reactions) in comparison to the contraction produced by acetylcholine (representing the neurally derived mediator of reflex bronchospasm). In contrast to the relaxing effects of isoproterenol, the absolute amount of airway smooth muscle relaxation by halothane is not dependent on the degree of contraction, suggesting that volatile anesthetics remain effective even during severe bronchospasm.

The actions of volatile anesthetics in decreasing bronchomotor tone and neurally mediated airway reflexes may be opposed in the anesthetized patient in part by a decrease in functional residual capacity, which results in increasing airway resistance. [51] Patients with asthma are at increased risk for morbidity and mortality in the perioperative period. Future investigations in humans with newer volatile anesthetics will benefit from advances in knowledge of mechanisms of anesthetic action on airway smooth muscle and contractile responses to pathophysiologic alterations.

Clinical Implications

Bronchospasm may occur in diseases other than asthma, and indeed even normal, healthy patients undergoing surgical stimulation of pulmonary parenchyma or airways are known to be at risk of developing bronchospasm. [52] Clinically discernible bronchospasm is not an unusual event following stimulation or irritation of the trachea by an endotracheal tube in lightly anesthetized patients. In anticipating such events in patients with known reactive airway disease, the choices of preoperative medication, induction agent, muscle relaxant, and type of inhalational anesthetic drug are important factors in minimizing clinical symptoms.

Halothane may be a more potent bronchodilator than other inhaled anesthetics. Studies in humans have not closely examined the effects of desflurane on airway resistance. However, the often-profound upper airway effects of desflurane as a respiratory irritant (coughing, respiratory secretions, breath-holding, and laryngospasm, especially in the pediatric population) may outweigh the benefit of any

direct bronchodilatory actions. Differences in bronchodilating effects between volatile anesthetics may exist, but of greater clinical importance is avoiding or minimizing airway irritation and maintaining adequate depth of anesthesia with the agent that is chosen.

EFFECTS OF INHALED ANESTHETICS ON MUCOCILIARY FUNCTION

Normal Mucociliary Function

Foreign particulate matter, microorganisms, and dead cells are removed by the upward clearance of mucus from the tracheobronchial tree as a primary pulmonary defense mechanism. Ciliated respiratory epithelium extends throughout the respiratory tract as far as the terminal bronchioles and decreases in density (as do mucus-producing goblet cells and submucous glands) from trachea to alveoli. [53] Ciliary motion consists of a rapid stroke in a cephalad direction, followed by a slower recovery stroke in the opposite direction. Movements of proximal cilia are coordinated to closely follow movements of cilia that are immediately distal. The resulting wave of motion is referred to as metachronism. The bending of individual cilia appears to be the result of an adenosine triphosphate (ATP)-dependent sliding of two parallel fibers within the ciliary filament and does not appear to involve the autonomic nervous system in mammals.

Mucus represents a mixture of water, electrolytes, and macromolecules (lipids, mucins, and enzymes) secreted by goblet cells and mucosal glands. The rheologic properties of mucus influence the rate and efficiency of ciliary function in that thicker layers of mucus appear to slow the removal of surface particles from the airway whereas high elasticity and low viscosity appear to promote the most rapid ciliary transport. The presence and characteristics of the mucus layer may also promote the coordination of ciliary beats. The physical and chemical characteristics of mucus in expectorated specimens have been studied extensively by Reid. [54] Characteristics may differ from those present *in vivo* because of contamination by salivary secretions and desiccation of expectorated secretions. [55]

Mucociliary function in single cilia or respiratory epithelial tissue cultures may be assessed by use of high-speed videomicroscopy to examine the ciliary beat frequency. *In vivo* techniques in animals have made use of a tracheal window, whereas in humans the velocity of mucus movement has been measured with radioactive markers or with a fiberoptic bronchoscope. The deposition of radiopaque or radioactive particles throughout the lung fields followed by radiographic examinations of clearance of these inhaled particles allows examination of mucociliary function in both peripheral and central airways.

Specific Effects of Anesthetics

Postoperative hypoxemia and atelectasis are common causes of perioperative morbidity. Many factors other than anesthesia may affect and diminish mucociliary function, particularly in the mechanically ventilated patient. Poorly humidified inspired gases may decrease ciliary movement and dry out mucus. In dogs, mucus flow rates were normally maintained for a 40-minute period if inspired air temperature was higher than 32°C and included an inspired water vapor content of 33 mg/L. [56] However, 3 hours of inhalation of dry air results in a complete cessation of tracheal mucus flow, which may be restored by use of inspired gases with 100 percent relative humidity at 38 C. [57] Other factors diminishing the rate of mucus movement are high inspired oxygen concentration, inflation of the endotracheal tube cuff, and positive-pressure ventilation. [58]

The effect of various anesthetic agents on mucociliary flow has been determined with scintillation counters measuring radioactive droplet progression in the trachea of dogs (Fig. 5-24) (Figure Not Available) . [58] [59] [60] Halothane, enflurane, nitrous oxide with halothane, and nitrous oxide with morphine--all dose-dependently and in a similar fashion--decreased mucociliary movement. [59] [60] Clearance of mucus from both central (trachea and mainstem bronchi) and peripheral airways following 6 hours of halothane (1.2 MAC) was delayed by at least 3 hours. [61]

Inhaled anesthetics may diminish rates of mucus clearance by decreasing ciliary beat frequency or disrupting metachronism or by altering the characteristics or quantity of mucus produced. Exposure to any of six inhaled anesthetics caused dose-related decreases in ciliary activity and cellular mobility of the ciliated protozoan *Tetrahymena pyriformis.*[62] The dose that effectively terminated organism and ciliary movement in 50 percent of the protozoans closely corresponded to MAC values of the various anesthetics. The mechanism by which cilia were affected was not delineated, but the rapidity and reversibility of the depression suggested that metabolic depression of ATP stores was not involved. Extrapolation from the protozoan to mammalian airway epithelia must be performed with caution, however; the results suggest a direct inhibitory effect on mucus clearance. Halothane (at doses greater than 3%) depressed ciliary movement in cultures of canine ciliated epithelium. [63] The sensitivity of cilia to halothane was less than that found in *T. pyriformis.* The effects of anesthetics on ciliary beat frequency in humans have yet to be elucidated.

Pulmonary surfactant decreases the work of breathing by reducing surface tension at the fluid-gas interface; like mucus, it plays a role in removing foreign particles from airways and enhances the bactericidal capacity of alveolar macrophages. The effects of halothane on cultured alveolar type II cells, which secrete surfactant, and on the metabolism of phosphatidylcholine, the main lipid component of surfactant, have been investigated. [64] Halothane dose-dependently reduced phosphatidylcholine synthesis (but not secretion) by alveolar cells during a 4-hour exposure (Fig. 5-25). (Figure Not Available) The reduction in phosphatidylcholine was progressive with longer durations of halothane exposure and reversible within 2 hours following termination of halothane. Also, high concentrations of halothane disrupted the energy metabolism of cultured alveolar cells, decreasing ATP content and increasing glycolytic metabolism (measured as lactate production).

Clinical Effects

Gamsu et al [65] compared the rate of tantalum clearance from the lungs of postoperative patients who had received general anesthesia for either intra-abdominal or lower extremity

Figure 5B-24 (Figure Not Available) Mucociliary clearance measured as tantalum clearance in patients undergoing surgery with either general or local anesthesia (awake). Note the decrease in mucociliary clearance in both peripheral and central airways during halothane and thiopental anesthesia. *(Modified from Forbes and Gamsu [61])*

orthopedic procedures. Patients who underwent orthopedic procedures showed no significant differences from a control group undergoing tracheography. These patients also did not develop atelectasis. In contrast, retention of tantalum was demonstrated for as long as 6 days following intra-abdominal surgery, with an average retention time three times that of the control group. Retention of tantalum was gravity-dependent and correlated with the retention of mucus demonstrated in areas of atelectasis. Disappearance of tantalum from these atelectatic areas occurred only after reexpansion of collapsed lung segments. In a study of tracheal mucus velocity, Teflon discs were placed on the tracheal mucosa and observed through a fiberoptic bronchoscope in young anesthetized women undergoing gynecologic surgery. [66] Control values of mucus velocity in awake volunteers were 20 mm/min. Anesthesia with 1 to 2 percent halothane and 60 percent nitrous oxide rapidly decreased the rate of mucus travel to 7.7 mm/min, with little or no motion observed after 90 minutes of anesthesia. Inspired gases were humidified, but the use of high inspired concentrations of oxygen, a cuffed endotracheal tube, and positive pressure ventilation were confounding factors. Thus, assessment of the direct effects of halothane is difficult. Bronchial mucosal transport velocity was also determined using radiolabeled albumin microspheres deposited distally in the mainstem bronchi by a fiberoptic bronchoscope in patients without lung disease undergoing general anesthesia. [67] There were no significant changes in mucus velocity following administration of isoflurane (1.5 MAC). Whether the lack of effect of isoflurane on mucus transport was related to the use of isoflurane rather than halothane or

species, i.e., the use of humans rather than animals, is unknown. Mucus pooling in animals occurs during and after anesthesia, suggesting a need in the immediate postoperative period for vigorous pulmonary therapy directed at enhancing clearance of secretions from the airways.

Konrad and coworkers [68] have shown in patients undergoing abdominal or thoracic surgery that smokers have significantly slower bronchial mucus transport velocities than do nonsmokers and postulated that this may be related to an increased incidence of postoperative pulmonary complications in smokers. Some evidence exists that patients with chronic obstructive pulmonary disease anesthetized by regional techniques show a lower incidence of respiratory failure than those having general anesthesia, [69] but other studies have failed to confirm this advantage. Possibly of greater importance

Figure 5B-25 (Figure Not Available) Effect of halothane on phosphatidylcholine (PC) synthesis by alveolar type II cells. PC synthesis measured as the incorporation of [^{3} H-methyl]-choline into PC and expressed as disintegrations per minute per microgram intracellular protein. * $P < 0.05$, ** $P < 0.01$ versus respective control. (A) Effect of increasing halothane concentration with 4-hour exposure. (B) Effect of increasing exposure time to 2 percent halothane. *(Modified from Molliex et al [64])*

are the consequences of the specific procedure, with intrathoracic and intra-abdominal surgery having greater morbidity related to compromised respiratory function as compared with peripheral procedures.

Clinical Implications

Many factors contribute to postoperative pulmonary complications. The specific roles of depressed mucociliary function and alterations in type II alveolar cells in such complications are unknown. Prolonged anesthesia may lead to pooling of mucus and changes in alveolar cell surfactant metabolism, resulting in deleterious effects on pulmonary function such as atelectasis and respiratory infections. Those at greatest risk would include patients with excessive or abnormal mucus or surfactant production (chronic bronchitis, asthma, respiratory tract infection, cystic fibrosis, and chronic mechanical ventilation).

Controlled studies of the effects of inhaled anesthetics on mucociliary function and surfactant metabolism in patients with pulmonary compromise have not been performed, nor has the precise effect of volatile anesthetics on the rate of pulmonary complications been clearly delineated. The actions of the newer volatile anesthetics desflurane and sevoflurane on mucociliary function have not been adequately studied, although there are no compelling reasons to suspect a clinically significant difference should exist among various anesthetics.

EFFECTS OF INHALED ANESTHETICS ON PULMONARY VASCULAR RESISTANCE

Determinants of Pulmonary Vascular Resistance

Determining the actions of pharmacologic agents on pulmonary vascular pressures and pulmonary vascular resistance (PVR) is a complicated task because many vasoactive

agents have direct effects on the pulmonary circulation as well as indirect effects mediated via alterations of cardiac output, preload, and afterload. Increased vascular distending pressure may cause an increase in cross-sectional diameter of the pulmonary vascular bed and a compensatory reduction in PVR. Similarly, changes in lung volume may alter the dimensions of the vasculature and, hence, affect resistance. Both increases in lung volume above functional residual capacity caused by increased airway pressure and decreases in lung volumes below normal functional residual capacity are associated with passive increases in PVR. High lung volumes compress pulmonary vessels; at low lung volumes, vessels are shorter, narrower, and more tortuous, apparently because of loss of supportive tethering of surrounding lung tissue. Resistance in the pulmonary circuit appears to be lowest at a lung volume equivalent to the functional residual capacity. Changes in PVR and pressure may have significant effects on gas or fluid exchange in the lung. Increased PVR gives rise to an increase in pulmonary artery pressure if cardiac output is maintained constant and thereby promotes increased transudation of fluid into the interstitium of the lung. PVR may be increased by alterations in positive end-expiratory pressure, lung volume, alveolar hypoxia and hypercarbia, and critical closing pressure (parallel shift in pressure-flow curves). Many anesthetic drugs tend to reduce lung volume and therefore may have indirect effects on PVR through this mechanism.

Direct changes in pulmonary vascular tone alter PVR (changes in slope of pressure-flow relationship). Such direct changes may be induced by alterations in sympathetic tone, by local changes in PO_2 and PCO_2, or by changes in concentrations of catecholamines and other vasoactive substances released locally or in blood perfusing the lung. Regional changes in PVR are particularly important in that they may alter the relative distribution of blood flow within the lung, leading to altered ventilation-perfusion relationships and accompanying changes in gas exchange. Thus, an increase in PVR in an area of atelectasis and localized tissue hypoxia optimizes gas exchange, including a decreased alveolar-arterial oxygen tension gradient [$P(A\text{-}a)O_2$], by shifting blood flow away from the atelectatic segment to better ventilated regions of the lung. This phenomenon, termed hypoxic pulmonary vasoconstriction (HPV), is unique to the pulmonary circulation as other vascular beds (e.g., coronary and cerebral) dilate in response to hypoxia. Hypoxic vasoconstriction appears to have protective value, and drugs that interfere with this protective mechanism may adversely affect gas exchange. Infusion of a pulmonary vasodilator such as nitroprusside attenuates HPV, decreases PaO_2, and increases pulmonary shunting in dogs with oleic acid-induced pulmonary edema. [70]

The pulmonary vasodilator action of inhaled anesthetics including halothane, isoflurane, enflurane, sevoflurane, and desflurane in normal lungs is minimal. [71] [72] [73] Mild decreases in PVR by volatile anesthetics are offset *in vivo* by a concurrent decrease in cardiac output. The net effect is usually little or no change in pulmonary artery pressure and a small decrease in pulmonary blood flow. Nitrous oxide has little effect on cardiac output and pulmonary blood flow. Overall, changes in PVR are small, tending to increase slightly during administration of nitrous oxide.

Hypoxic Pulmonary Vasoconstriction

HPV (Ch. 15) . is locally mediated; it occurs in isolated perfused lungs, and a similar response may be elicited in animals following autonomic nervous system blockade or catecholamine depletion. The sympathetic nervous system may, however, play a role in augmenting the response in certain circumstances, particularly in the presence of systemic hypoxemia. HPV in normal lungs appears when alveolar PO_2 is less than 100 mm Hg and is maximal when PO_2 is approximately 30 mm Hg. [74] [75] Recently, HPV has been investigated in humans with healthy lungs. [76] Unilateral graded hypoxia and unilateral single-step hypoxia produced similar reductions in the perfusion of the hypoxic lung to approximately 30 percent (at an inspired O_2 concentration of 0.05). Mixed venous PO_2 (PvO_2) may influence HPV in the atelectatic lung because PO_2 in the collapsed segment approaches that of PvO_2. [77] [78] Acidosis is also a pulmonary vasoconstrictor both in intact animals and in isolated perfused lungs. Changes in PVR in response to acidosis are small at normal alveolar oxygen tensions, but in the presence of alveolar hypoxia they are dramatically enhanced. Thus, elevations in arterial hydrogen ion concentration, alveolar PCO_2, or both may augment pulmonary vasoconstriction.

Inhaled Anesthetics and Hypoxic Pulmonary Vasoconstriction

Many mechanisms exist, such as pulmonary atelectasis and diminished functional residual capacity relative to closing capacity of the lung, that cause a decrease in oxygenation and an increase in $P(A\text{-}a)O_2$ during anesthesia. The effects of numerous inhaled anesthetics on HPV have been examined in a variety of animal and experimental models, with conflicting results. Experiments and results are summarized in Table 5-1 .

The effect of inhalational anesthetics on HPV is multifactorial, involving direct pulmonary vascular actions and indirect cardiovascular, autonomic, and humoral actions. In general, most *in vitro* studies have demonstrated some degree of attenuation of HPV with all inhalational anesthetics (Fig. 5-26) (Figure Not Available) . Inhibition of HPV has been demonstrated with halothane, [71] [79] [80] [81] [82] [83] isoflurane [71] [72] enflurane, [71] [84] sevoflurane, [72] desflurane, [73] and nitrous oxide, using isolated perfused lungs or an in situ preparation with constant perfusion. [85] [86] [87] Marshall et al [71] examined the effects of halothane, enflurane, and isoflurane on the HPV response to global hypoxia. All three drugs dose-dependently depressed HPV, and similar MAC values (approximately 0.6 MAC) depressed HPV by 50 percent in an *in vitro* preparation allowing for control of lung perfusion and eliminating any effect of the sympathetic nervous system. A more recent study in isolated rat lungs confirmed depression of HPV by both isoflurane and halothane, but the addition of verapamil reduced HPV by an additional 35 to 40 percent, implying an additive effect and different sites of action. [88] Furthermore, halothane reduced the resistance of the middle vascular segment in atelectatic and hypoxic lung, suggesting a direct action on small vessels and capillaries. [82] [89]

TABLE 5B-1 -- Effects of Inhaled Anesthetic on Airway Resistance

ANESTHETIC	REFERENCE	MODEL	MEASUREMENT	EFFECT
Halothane	Shnider & Papper [2]	Human: (retrospective)	Wheezing	++
	Hickey et al [14]	Dog: bronchospasm (vagus, histamine)	Raw	++

	Coon & Kampine [15]	Dog: LL lobe bronchoconstriction (CO_2)		Raw++
	Klide & Aviado [12]	Dog: normal	Raw	++
	Fletcher et al [13]	Guinea Pig: isolated tracheal muscle	Length	++
	Gold & Helrich [41]	Human: status asthmaticus	Raw	0
	Colgan [11]	Dog: normal	"Bronchial distensibility"	0
	Hirshman & Bergman [17]	Dog: bronchospasm *(Ascaris)*	Raw	++
Diethyl ether	Shnider & Papper [2]	Human: (retrospective)	Wheezing	+
Cyclopropane	Hickey et al [14]	Dog: bronchospasm (histamine, vagus)	Raw	+
	Colgan [11]	Dog: normal	"Bronchial distensibility"	0
Enflurane	Coon & Kampine [15]	Dog: LL Lobe bronchoconstriction (CO_2)	Raw	+
	Hirshman & Bergman [17]	Dog: bronchospasm *(Ascaris)*	Raw	++
Methoxyflurane	Coon & Kampine [15]	Dog: LL Lobe bronchoconstriction (CO_2)	Raw	+
Isoflurane	Hirshman et al [18]	Dog: Bronchospasm *(Ascaris)*	Raw	++

Abbreviations and symbols: LL, left lower; Raw, airway resistance; ++, pronounced bronchodilation; +, bronchodilation; 0, no effect.

Modified from Pavlin EG, Yu JY: Cardiopulmonary pharmacology. In Miller RD (ed): Anesthesia, Churchill Livingstone, New York, 1994.

With the left lower lobe of a dog lung selectively ventilated with an hypoxic gas mixture and the remainder of the lung ventilated with 100 percent oxygen, the effect of hypoxia on PVR was assessed by measuring blood flow to the isolated lobe and comparing it with total pulmonary blood flow. [90] [91] A significant decrease in flow to the isolated lobe occurred in the presence of localized alveolar hypoxia during constant pulmonary blood flow (cardiac output), pulmonary artery pressure, and left atrial pressure. Neither halothane nor nitrous oxide administered to the isolated lobe diminished the magnitude of HPV, although a dose-related inhibition could be demonstrated in the presence of isoflurane. These experiments were also performed with the anesthetic agent administered to the whole animal and to the isolated lung segment. Whereas halothane, isoflurane, and enflurane diminished cardiac output, the effects on blood flow to the isolated segment were almost identical to those obtained when administration of anesthetic gas was confined to the isolated lobe alone.

The mechanism of the direct inhibitory action of volatile anesthetics on HPV is unclear but may be related to enhancement of arachidonic acid metabolism [83] [92] or other endothelial-derived vasodilating factors. [93] However, volatile anesthetic-induced inhibition of HPV is not dependent on the presence of pulmonary vascular endothelium, nitric oxide, or guanylate cyclase. [94] [95] [96] Volatile anesthetics may also disrupt Ca^{2+} homeostasis, which is intimately involved in pulmonary vasoconstriction. Interestingly, halothane and isoflurane, in isolated canine pulmonary artery rings, attenuated endothelium-dependent vasodilation by inhibiting accumulation of cGMP [96] and an ATP-sensitive potassium channel-mediated interaction between nitric oxide and prostacyclin. [97] Halothane and enflurane also attenuate ATP-sensitive potassium channel-mediated pulmonary vasodilation in chronically instrumented dogs. [98] In contrast, isoflurane enhanced isoproterenol-mediated vasodilation. [99]

Findings from *in vitro* studies suggest that volatile anesthetics exert inhibitory actions on HPV, but results from *in vivo* investigations have been surprisingly inconclusive. Sykes et al [100] examined the effects of one-lung hypoxia on relative pulmonary blood flow distribution in dogs, as measured using xenon. [133] One lung was ventilated with nitrogen,

Figure 5B-26 (Figure Not Available) Concentration-dependent inhibition of hypoxic pulmonary vasoconstriction (HPV) in rabbit lungs by desflurane (closed circles) and halothane (open circles). Values are mean ± SEM and expressed as a percentage of control. * $P < 0.05$ versus control HPV. The half-maximum inhibiting effect (ED_{50}) values were within the range of 1 and 2 MAC (for rabbits) for both agents. *(From Loer et al [73])*

and the other was ventilated with 100 percent oxygen. A redistribution of flow to the well-oxygenated lung was found, indicating active HPV, which was preserved in the presence of halothane at inspired concentrations of up to 3 percent. In contrast, using the same experimental preparation, ether and nitrous oxide profoundly affected the redistribution of pulmonary blood flow in response to hypoxia. [101] [102] Other *in vivo* investigations have also determined that nitrous oxide markedly attenuates HPV. [90] [91] [103] Halothane, isoflurane, and enflurane may have minimal or no effects on HPV *in vivo*.[90] [91] [104] [105] [106] [107] Recently, Lennon and Murray [92] have shown that isoflurane anesthesia attenuates HPV in chronically instrumented dogs as compared with the response measured in the same animal in the conscious state. Pulmonary vascular pressure (pulmonary arterial pressure-left atrial pressure) versus pulmonary blood flow relationships were generated in the absence of baseline anesthesia and acute surgical trauma to demonstrate flow dependency of the HPV. Unlike the case of isoflurane, inhibition of HPV was not observed using the same preparation in the presence of sevoflurane or desflurane. [108]

Clinical Effects

One obvious explanation for differences in results between *in vitro* and *in vivo* studies is the influence of cardiac output. The effect of anesthetics on HPV versus the effect on cardiac output was compared using data from a variety of studies. [109] The efficacy of HPV varies inversely with cardiac output (as pulmonary blood flow), and a direct inhibition of HPV by anesthetics might be opposed by a decreased cardiac output such that HPV may appear to be unaffected. The net HPV response is unchanged when the cardiac output is reduced by potent inhalational anesthetics and attenuated when cardiac output is maintained (e.g., during nitrous oxide). Thus, whereas the HPV response may be directly inhibited by the volatile anesthetic, the effectiveness of the HPV response is indirectly enhanced by the depression of cardiac output.

Isoflurane does not affect pulmonary shunt in patients without pulmonary disease, even at concentrations that cause systemic hypotension. [110] The effects of diethyl ether and halothane on pulmonary blood flow distribution during nitrogen ventilation of one lung in humans were examined. [104] HPV occurred in the nitrogen-ventilated lung during intravenous anesthesia with barbiturates but disappeared with the inhalation of either halothane or diethyl ether in the ventilated lung. Abolition of HPV was accompanied in most patients by a decrease in PaO_2. In contrast to this study, clinical observations in patients undergoing one-lung ventilation during thoracic surgery have failed to demonstrate changes consistent with attenuation of HPV by halothane. No significant differences in shunt fraction or PaO_2 were found when pulmonary gas exchange during intravenous anesthesia (ketamine) was compared with that during enflurane anesthesia. [111] Ketamine does not inhibit HPV, and this suggests that enflurane also does not affect HPV. In clinical practice, thoracic surgery is typically carried out in patients in the lateral position with an open chest, altering relative distribution of perfusion pressures. The diseased nondependent lung would alter pulmonary vascular responsiveness to hypoxia, as might surgical manipulation of the lung. [112]

Benumof et al [113] have provided convincing evidence that inhalational anesthetics are safe to use in patients undergoing thoracotomy with one-lung ventilation and that halothane and isoflurane only minimally impair arterial oxygenation (Fig. 5-27) (Figure Not Available) . The increase in shunt and decrease in oxygenation caused by halothane or isoflurane was consistent with approximately a 20 percent inhibition of HPV at 1 MAC. Instead of a single lung being able to decrease its blood flow by 50 percent, 1 MAC halothane or isoflurane would result in a hypoxic lung being able to decrease its blood flow by 40 percent. This change in flow corresponds to an increase in the pulmonary shunt by 4 percent of the cardiac output. Isoflurane appears to preserve HPV to a greater extent than does halothane, which may be related to a greater maintenance of cardiac output. [113] Recently, minimal and similar changes were shown to occur with isoflurane and desflurane in patients undergoing thoracotomy and single lung ventilation. [114] Increases in shunt fraction and the alveolar-to-arterial oxygen tension gradient were attributed to the onset of one-lung ventilation rather than to a specific action of the volatile anesthetics.

An important factor involved in modulating the effects of HPV may be the overall effect of pulmonary artery pressure.

Figure 5B-27 (Figure Not Available) Arterial oxygenation (PaO_2) and intrapulmonary shunt (Qs/Qt) in patients ventilated with both lungs (2-LV) or with one lung (1-LV). Patients received either an inhalational (IH) agent halothane or isoflurane or an intravenous (IV) anesthetic thiopental. Note the minimal effect on PaO_2 and shunt that occurs in changing from a volatile anesthetic to an IV agent. *(Modified from Benumof et al [113])*

High pulmonary artery pressures may tend to cause passive distension of constricted vascular beds and thereby reverse HPV. Alternatively, reflex pulmonary and systemic vasoconstriction in response to stimuli such as hypotension may increase PVR in healthy lung segments, leading to a shift of blood flow to the diseased (hypoxic) areas of lung.

Remarkable and reversible increases in pulmonary shunting have been demonstrated by administration of pulmonary vasodilators such as nitroprusside and nitroglycerin in dogs with oleic acid-induced pulmonary edema. [70] Some anesthetics probably produce a similar response in patients with adult respiratory distress syndrome or with other types of pulmonary pathology associated with large right-to-left intrapulmonary shunts. Finally, although Lennon and Murray have demonstrated an inhibitory effect of isoflurane on HPV in chronically instrumented dogs, [92] these investigators have also shown that isoflurane did not influence pulmonary vascular tone in the presence of increased pulmonary vascular resistance following single-lung transplantation in chronically instrumented dogs. [115]

Clinical Implications

The precise effects of various anesthetics in patients with preexisting pulmonary disease remain to be defined; however, the action of anesthetic gases on the pulmonary vasculature must be taken into account as one possible factor when considering the causes of hypoxemia during general anesthesia. Additional investigations need to be performed, particularly in humans, before the actions of a particular anesthetic can be predicted.

The clinical findings appear to indicate that potent inhalational anesthetics exert only mild inhibitory effects on HPV and subsequent oxygenation. Furthermore, given the efficacy of nondependent lung continuous positive pressure in improving oxygenation, the inhibition of HPV by volatile anesthetics should not significantly influence clinical decisions. The net effect of anesthetics on HPV is multifactorial, depending on a number of other factors that commonly occur intraoperatively.

EFFECTS OF INHALED ANESTHETICS ON CONTROL OF VENTILATION

Alterations of minute ventilation are the most obvious effects of anesthetics. Many different stimuli interact in a complex manner to determine the level of ventilation in humans. The traditional approach to studying effects of anesthetics on ventilation has been to measure ventilatory responsiveness (expired minute volume, respiratory frequency, or $PaCO_2$) before and after drug administration. A complete description of ventilatory control is beyond the scope of this chapter; excellent reviews of this subject already exist. [116] [117] However, an understanding of normal ventilatory responses and control mechanisms is necessary to appreciate the actions of anesthetics and the methods by which these effects are measured.

Control of Breathing

A control system that modulates ventilation is necessary to maintain stability of blood gas tensions and acid-base status and to integrate frequency and tidal volume in such a manner as to minimize the work of breathing in response to variations in the total ventilatory requirements (Fig. 5-28) . The system responsible for receiving and integrating the many input signals and ultimately producing movement of air in and out of the lungs is composed of the following:

Sensors, which may be chemical (peripheral and central chemoreceptors) or mechanical (distortion receptors located in airways, alveoli, and respiratory muscles).

Respiratory control system, which integrates the signal inputs from the receptor sites, centers of consciousness, and

Figure 5B-28 Some aspects of the reflex control of ventilation. Sensors include central and peripheral chemoreceptors as well as a variety of mechanoreceptors. Inputs from these many sources interact to alter ventilatory controller output from pontomedullary sites to muscles of respiration, thus altering ventilation and ultimately gas exchange.

other influences (e.g., pain) and culminates in a level and pattern of nerve traffic to the muscles of respiration.

Motor system, composed of the chest wall and intercostal, diaphragmatic, and abdominal muscles, all of which respond to signals from the control center via the phrenic and spinal nerves.

The respiratory rhythm generator resides within the brain stem, where two main groups of respiratory neurons are found: the dorsal respiratory group, composed of cells active during inspiration; and the ventral respiratory group, containing both inspiratory and expiratory neurons. The isolated medulla oblongata is capable of generating a rhythmic, although abnormal, respiratory pattern. [118] However, the precise mechanism of rhythm generation is still unknown. An exciting *in vitro* neonatal brain slice model was developed by Smith [119] that demonstrates that at least in the immature animal, a group of pacemaker (self-oscillating) respiratory neurons in the rostral ventral respiratory group exists that might be the elusive rhythm generator. No analogous group of cells has been demonstrated to date in adult animal models. The rostral pons contains the pneumotaxic center, which involves inspiratory and expiratory neurons and plays a modulating role, integrating vagal and chemoreceptive inputs. The inspiratory controller output, independent of mechanical factors, may be measured in the human as the pressure developed in the first 0.1 second of inspiration at functional residual capacity by acute airway occlusion. [120]

General Ventilatory Effects of Anesthetics

In general, all volatile anesthetics decrease tidal volume. However, the resultant depression of minute ventilation may be partially offset by a concomitant increase in respiratory rate (Fig. 5-29) . [121] [122] Early studies demonstrated that isoflurane produced more profound respiratory depression than did halothane. In contrast to halothane, isoflurane did not progressively increase respiratory frequency (Fig. 5-30) (Figure Not Available) . [123] [124] Enflurane, like halothane, dosedependently reduces tidal volume and minute ventilation with a dose-related tachypnea. [125] The degree of respiratory depression, as shown by increased resting $PaCO_2$, lessened with prolonged administration (3-7 hours) of halothane or enflurane. [125] [126]

Figure 5B-29 Comparison of mean changes in resting $PaCO_2$, tidal volume, respiratory rate, and minute ventilation in patients anesthetized with either halothane (H), isoflurane (I), enflurane (E), sevoflurane (S), desflurane (D), or nitrous oxide (N). Anesthetic-induced tachypnea compensates in part for the ventilatory depression caused by all volatile anesthetics (decrease minute ventilation and tidal volume and concomitant increase in $PaCO_2$). Desflurane results in the greatest increase in $PaCO_2$ with corresponding reductions in tidal volume and minute ventilation. Isoflurane, like all other inhaled agents, increases respiratory rate; however, isoflurane does not result in dose-dependent tachypnea. *(Data from Eger [124] ; Hickey [122] ; Lockhart [127] ; Doi [126] ; Fourcade [123] ; Caverley [125])*

Figure 5B-30 (Figure Not Available) The effect of surgical stimulation on the ventilatory depression of inhaled anesthesia with isoflurane in the presence and absence of nitrous oxide. Surgical stimulation increased alveolar ventilation and decreased $PaCO_2$ at all depths of anesthesia examined. *(Modified from Eger et al [131])*

The newer inhalational anesthetics--desflurane and sevoflurane--also exhibit dose-related ventilatory depression, primarily by reducing tidal volume. [127] [128] [129] [130] Unlike isoflurane, sevoflurane and desflurane both cause dose-related increases in respiratory frequency. Thus, desflurane does not significantly reduce minute ventilation until concentrations greater than 1.6 MAC have been achieved. However, at higher concentrations, the reduction of respiratory rate was less than that which occurred with halothane. The relative increases in $PaCO_2$ as an index of respiratory depression with volatile anesthetics (<1.24 MAC) are:

Enflurane > desflurane = isoflurane > sevoflurane = halothane

At higher concentrations, the ventilatory depression produced by desflurane is similar to enflurane, and sevoflurane is similar to isoflurane. [122] [123] [127] [128] [129] [130] Eger et al [131] have demonstrated that isoflurane-induced respiratory depression is reduced by surgical stimulation (see Fig. 5-30) (Figure Not Available) . In addition, the resting $PaCO_2$ during desflurane or sevoflurane anesthesia is significantly decreased in the presence of nitrous oxide at equi-MAC.

Mechanoreceptors and Breathing

Central respiratory control mechanisms regulate tidal volume and inspiratory and expiratory times to achieve adequate ventilation and gas exchange. Input signals emanate not only from chemoreceptors but also from mechanoreceptors in the upper airways, lungs, and chest wall, mediated by the vagus nerve and spinal nerves. Respiratory muscle function may be assessed via measurements of neural activation or directly by an electromyogram and by mechanical responses (tidal volume, minute ventilation, and analysis of motion and pressures generated by specific muscles). It should be recognized that upper airway musculature, including pharyngeal, laryngeal, and those of the soft palate, may also be affected by inhaled anesthetics.

Lung and Airway Receptors

Airway receptors (Ch. 15) . that may have some relevance to the effect of anesthetics include laryngeal and pulmonary irritant receptors and pulmonary stretch receptors. These receptors play an important role in the regulation of breathing patterns, laryngeal and pulmonary defense mechanisms, and bronchomotor tone. Irritant receptors are situated between airway epithelial cells and may mediate rapid reflex responses such as coughing, laryngospasm, bronchoconstriction, and mucus secretion following the induction of general anesthesia, abrupt increases in the inspired concentration of volatile anesthetics, and sudden mechanical deformation of the laryngotracheobronchial system.

Slow-adapting pulmonary stretch receptors, located within small airway smooth muscle (high concentration near the carina), respond to stretching or changes in lung volume. Increases in lung volume increase afferent nerve traffic via the vagus nerve to the respiratory control center, thereby inhibiting further inspiration (the Hering-Breuer reflex). This limitation of inspiration elicited by pulmonary stretch receptors may determine the relationship between tidal volume and respiratory frequency, but unlike in animals, the Hering-Breuer reflex cannot be demonstrated in the awake resting human during normal tidal volume breathing. The alteration in ventilatory pattern by anesthetics has been attributed to sensitization of pulmonary stretch receptors, leading to lower tidal volumes and tachypnea. The presence of volatile anesthetics increased vagal afferent discharge at varying lung volumes in decerebrate cats (i.e., sensitization of pulmonary stretch receptors), [132] but little evidence exists of such a mechanism in humans. [133] There is evidence in the cat that halothane-induced tachypnea is primarily a suprapontine effect, but the mechanism of production of tachypnea with decreased tidal volume in anesthetized humans remains unclear.

The direct effects of halothane, isoflurane, and enflurane on pulmonary and laryngeal irritant receptors and on tracheobronchial slow-adapting stretch receptors have been investigated in spontaneously breathing and vagotomized, paralyzed dogs. [134] [135] All three volatile anesthetics increase the activity of laryngeal irritant receptors [134] and inhibit pulmonary irritant receptors. [135] In addition, the volatile anesthetics elevate the excitation threshold and increase the sensitivity of low-threshold stretch receptors. The inspiratory activity was augmented while the end-expiratory activity was greatly attenuated. [135] The clinical implications of these findings have yet to be determined, but these anesthetic-induced changes may in part relate to effects on reducing bronchomotor tone.

It has been suggested that general anesthesia may result in posterior tongue displacement, producing upper airway obstruction; however, several recent studies do not confirm this. [136] [137] Anteroposterior displacement of upper airway structures occurs with changes in head position that are in

---

Figure 5B-31 (Figure Not Available) Decrease in phasic inspiratory muscle activity, expressed as peak height of moving time average (MTA), in percent change from control (1% halothane), during halothane anesthesia in adult cats. Values are mean ± SEM. IC = intercostal muscle. * $P < 0.05$ compared with the diaphragm (DI); ** $P < 0.05$ compared with the genioglossus (GG) muscle. Note the differential sensitivities of these respiratory muscles. *(Modified from Ochiai et al [136])*

the same direction as that of the mandible. In addition, general anesthesia and paralysis may widen the dimensions of the larynx, [136] but the nasopharyngeal airway decreases in size. Volatile anesthetics produce a greater depression of the upper airway electromyogram [138] or nerve activity [139] as compared to that of the diaphragm in intact anesthetized, spontaneously breathing cats [138] (Fig. 5-31) (Figure Not Available) and in paralyzed, ventilated, vagotomized cats. [139] The extent to which this depression of upper airway motoneuron activity is a result of an anesthetic-induced inhibition of the reticular activating system is unknown.

Ventilatory Mechanics and Mechanoreceptors in the Chest Wall

Induction of general anesthesia reduces the functional residual capacity. Possible mechanisms involve a loss of tonic parasternal intercostal muscle activity [140] [141] [142] and development of phasic expiratory activity of respiratory muscles (Fig. 5-32) (Figure Not Available) , [142] alteration in diaphragm position, [141] or changes in thoracic blood volume. [142] There is a sparing of diaphragmatic activity relative to that of intercostal muscle function during halothane anesthesia. [140] [141] A change in diaphragmatic shape occurs whereby dependent regions shift cephalad, and non-dependent regions tend to shift caudad during anesthesia (Fig. 5-33) . [143] [144] Anesthesia-enhanced expiratory muscle activity results in inward displacement of the rib cage, thereby contributing to the reduction in functional residual capacity. In contrast, despite attenuation of parasternal intercostal muscle activity, inspiratory rib cage expansion may remain relatively well preserved due to phasic

Figure 5B-32 (Figure Not Available) Representative record from one subject while awake and during halothane anesthesia. Upper three tracings are electromyograms. Lower tracings represent rib cage and abdominal dimensions measured by respiratory impedance plethysmography. Open and closed circles denote the beginning and end of inspiration, respectively. Note that the amplitude of rib cage and abdominal excursions diminish during halothane, but the relationship between their amplitudes is preserved. *(From Warner et al [142])*

inspiratory activity of scalene muscles. [141] There is no direct correlation between changes in functional residual capacity and anesthesia-induced atelectasis. Areas of atelectasis in dependent lung regions frequently occur in anesthetized, spontaneously ventilating humans. Atelectatic densities may be related to alterations in respiratory muscle tone and not specifically to any single chest-wall structure. [143] They may be decreased by the application of positive end-expiratory pressure or by phrenic nerve stimulation of the diaphragm. [145]

The reason(s) for the differential anesthetic effects on inspiratory and expiratory respiratory muscles is unknown but may be related to direct actions on brain-stem control mechanisms or differential sensitivities of premotor neurons and motoneurons. Stuth et al [146] [147] have shown in vagotomized dogs that bulbospinal respiratory neurons are more resistant to the depressant effects of volatile anesthetics than is phrenic nerve activity. Increases in CO_2 drive can

Figure 5B-33 Diagram of a midsagittal section of the thorax while awake (solid lines) and while anesthetized (dashed lines) with 1.2 MAC halothane. Chest-wall configuration was determined using images of the thorax obtained by three-dimensional fast computed tomography. *(From Warner et al [143])*

---

only partially compensate for the anesthetic-induced depressant actions. There also exists a trend toward lesser depression of expiratory versus inspiratory bulbospinal premotor neurons to halothane. These findings suggest that the effects of inhalational agents on respiratory muscle func-tion may be a result of a more profound influence on the motor efferent pathways, including spinal respiratory motoneurons, rather than brain-stem mechanisms (Fig. 5-34) (Figure Not Available) . [147] Volatile anesthetics also depress neuromuscular transmission and skeletal muscle contractility. Isoflurane, enflurane, and sevoflurane depress the tension of the diaphragm in response to phrenic nerve stimulation. [148] [149] Note that whereas these results may help explain clinically observed phenomena in humans, species differences do exist. For example, volatile anesthetics decrease expiratory muscle activity in dogs and maintain parasternal intercostal activity, effects that are opposite of those in observed humans. [141] [142] [143]

Alterations in chest-wall positions change efferent impulses from stretch receptors in intercostal muscle spindles to maintain tidal volume during variations in inspiratory resistance. Increases in spindle discharge enhance motor activity to muscle fibers until muscle shortening relieves tension in the spindles. With increased inspiratory resistance, the muscle spindles detect a failure of shortening by the appropriate amount, and afferent signals are subsequently increased to the motor neuron pool. Accessory muscles of inspiration may be brought into use as well. This reflex increase in inspiratory effort results in sustained tidal volume and minute ventilation with increasing inspiratory resistive loads. These and other forces explain the ability of the body to maintain normal ventilation with different body positions

and inspiratory resistances and changes in compliance.

During halothane anesthesia, ventilation is maintained in spite of increases in resistance, such as during partial occlusion of an endotracheal tube or decrease in lung compliance, until a threshold is reached. [150] At that point, minute ventilation is diminished, with retention of CO_2. Minute ventilation is maintained by increasing the work of breathing, even during 2 MAC halothane anesthesia at modest inspiratory resistances as caused by small-diameter endotracheal tubes or humidifiers. [151]

Expiration is passively affected by the recoil characteristics of the lung during normal quiet breathing. In anesthetized patients, the ventilatory response to expiratory resistance is diminished more than that to inspiratory resistance. Both conscious and anesthetized humans exhibit decreases in respiratory rate during expiratory resistive loads, but only anesthetized subjects have rib cage-abdominal wall motion asynchrony. [152] Anesthetized subjects also have increased but less effective ventilation. This may have clinical relevance for spontaneously breathing anesthetized patients who have obstruction to exhalation either extrinsically such as in a breathing circuit or intrinsically as by asthma or emphysema. Consistent with this finding, patients with chronic obstructive pulmonary disease not retaining CO_2 while awake hypoventilated to a greater degree than did normal patients during halothane anesthesia (Fig. 5-35) (Figure Not Available) . [153]

Figure 5B-34 (Figure Not Available) Effect of increasing halothane on phrenic nerve and neuron activity. With increasing anesthetic depth, both peak phrenic nerve (PPA) and peak neuron activities are depressed. PPA shows the greatest sensitivity to halothane. (A) Phrenic nerve activity and the discharge frequency of an inspiratory bulbospinal neuron. Inspiratory (phrenic burst) duration decreases with increasing anesthetic depth. (B) Peak expiratory neuron (E), peak inspiratory neuron (I) activity, and PPA. Expiratory neuronal activity was most resistant to the effects of halothane. Bars = normalized mean ± SEM, numbers within bars = numbers of neurons studied for each condition. *(Modified from Stuth et al [147])*

Figure 5B-35 (Figure Not Available) Comparison of $PaCO_2$ in anesthetized, spontaneously breathing patients, relative to preoperative forced expiratory volume in 1 second (FEV_1). Patients with chronic obstructive pulmonary disease (COPD) did not exhibit CO_2 retention prior to anesthesia, yet the degree of alveolar hypoventilation is much greater in the more severely obstructed patients. *(From Pietak et al [153])*

EFFECTS OF ANESTHETICS ON VENTILATORY RESPONSE TO CHEMICAL STIMULI

Effects of anesthetics on respiratory drive are typically characterized by the ventilatory responsiveness to alterations in $PaCO_2$ or to a hypoxic insult. A complete discussion of chemical ventilatory control may be found in other reviews. [116] [117] In brief, chemoreceptors are both central and peripheral. Central chemoreceptors, located near the ventrolateral medulla and possibly more widespread in the brain stem, respond to changes in hydrogen ion concentration in the adjacent cerebrospinal fluid rather than to alterations in arterial PCO_2 or pH. Carbon dioxide, unlike the hydrogen ion, rapidly diffuses through the blood-brain barrier, and, thus, central chemoreceptors are more affected by respiratory than by metabolic alterations in blood gases. In contrast, peripheral chemoreceptors, located in the carotid bodies, are sensitive to changes in arterial $PaCO_2$, pH, and most importantly PaO_2. The mechanisms by which peripheral chemoreceptive cells respond to hypoxia and hypercapnia appear to be separate and synergistic in that hypoxemia potentiates the chemical drive to a CO_2 challenge. The peripheral chemoreceptors contribute about one-third to resting minute ventilation at normocapnia and normoxia. This contribution diminishes to about 15 percent during hyperoxic normocapnia, suggesting that the 85 percent of the CO_2 drive under hyperoxia is under central chemoreceptor control. Both stimuli cause membrane depolarization and activation of afferent nerve transmission. [154]

Responses to Carbon Dioxide

As described earlier, changes in ventilation secondary to alterations in $PaCO_2$ are mediated principally at the level of the medulla. Patients whose peripheral chemoreceptors have been denervated by bilateral carotid endarterectomy demonstrate approximately 85 percent of the increase in ventilation observed prior to denervation secondary to inhaled CO_2.

Apneic Thresholds

Apneic threshold is defined as the highest $PaCO_2$ at which a subject will remain apneic. The apneic threshold is approximately 4 or 5 mm Hg below resting $PaCO_2$ achieved during spontaneous ventilation. In humans, there are no significant agent-specific or depth-related effects of ether, halothane, or isoflurane on the relationship between apneic thresholds and resting $PaCO_2$ (Fig. 5-36) (Figure Not Available) . [155] The difference between resting $PaCO_2$ and apneic threshold is not related to the slope of the CO_2 response curves or to the level of resting $PaCO_2$. This suggests that assisted ventilation to lower $PaCO_2$ below the apneic threshold during anesthesia would ultimately become controlled ventilation.

Another clinically important aspect of this observation relates to reestablishment of spontaneous ventilation in the mechanically hyperventilated patient. Carbon dioxide stores in the body must accumulate to return the $PaCO_2$ level toward the apneic threshold on cessation of mechanical ventilation. The deeper the level of anesthesia, the longer the period of apnea necessary before the patient will commence spontaneous ventilation. Alternative methods of management might be to continue mechanical ventilation with the anesthetic gases progressively decreased or to maintain higher $PaCO_2$ during mechanical ventilation. These maneuvers will either decrease the apneic threshold or increase the resting $PaCO_2$, diminishing the time of apnea required to initiate spontaneous ventilation.

Carbon Dioxide Response Curves

Inspiration of CO_2 in normal subjects increases minute ventilation by approximately 3 L/min per mm Hg of $PaCO_2$, demonstrating a high gain from a central chemoreceptor in response to variations in $PaCO_2$. The slope of the plot of minute ventilation versus $PaCO_2$ is an index of ventilatory drive. Hypoxic conditions should be avoided to minimize peripheral chemoreceptor stimulation during such experiments. All inhaled anesthetics, including the newer agents desflurane and sevoflurane, dose-dependently depress the ventilatory response to hypercarbia. [122] [123] [124] [127] [128] [156] High concentrations of volatile anesthetics may virtually obliterate the hypercarbia-induced increase in ventilatory drive. Even nitrous oxide at 1.5 MAC under hyperbaric conditions lowers the response slope to 15 percent of control. [156] The slope of the ventilatory response curve during halothane

Figure 5B-36 (Figure Not Available) Ventilatory responses to increased CO_2 and apneic thresholds during ether, isoflurane, and halothane anesthesia in patients. The apneic threshold had a relatively fixed relationship to the resting $PaCO_2$. With an increase in ventilatory depression at increasing depth of anesthesia, resting $PaCO_2$ and apneic threshold increase by approximately the same amount. *(Modified from Hickey et al [155])*

anesthesia (like the resting $PaCO_2$) returns toward normal after 6 hours of anesthesia, although ventilatory responsiveness to CO_2 is still profoundly depressed. Studies by Hornbein et al [157] showed that addition of nitrous oxide to halothane depressed ventilation less than an equi-MAC dose of halothane alone. This does not appear, however, to alter the CO_2 ventilatory response slope of desflurane. [127] In contrast to the controversial effects of subanesthetic concentrations of inhalational agents on the hypoxic response (discussed below), low doses of volatile anesthetics (except enflurane [158]) do not significantly attenuate the ventilatory response to hypercarbia. [159]

Depression of ventilatory responsiveness to inhaled CO_2 has considerable clinical relevance. Carbon dioxide accumulation and concomitant acidemia may cause dysfunction in several organs, including the heart, where this condition may produce potentially dangerous arrhythmias. The attenuation of the normal ventilatory responses to elevated $PaCO_2$ makes clinical diagnosis of hypercarbia difficult and necessitates measurement of either arterial or end-tidal CO_2 tensions. During anesthesia, the ventilatory system will be less likely to compensate for CO_2 elevations secondary to rebreathing of CO_2 from malfunctioning anesthetic circuits or to increased metabolic production of CO_2. Pietak et al [153] have demonstrated the decreased ability of patients with chronic obstructive pulmonary disease to respond to increased $PaCO_2$ during anesthesia.

Experimental studies have shown that CO_2 rebreathing activates expiratory respiratory muscles such as the internal intercostals but does not reverse the profound depression of parasternal intercostal muscle activity produced by halothane. [160] There is a prolongation of expiration that leads to a decrease in breathing frequency during the course of rebreathing. That control of individual respiratory muscles is different in the halothane-anesthetized dog and human during rebreathing [161] does not necessarily indicate that other systems are dissimilar between species. Halothane dose-dependently depressed the peripheral chemoreceptor transduction (phrenic nerve response) to an acute, severe CO_2 stimulation of the peripheral chemoreceptors in paralyzed, vagotomized dogs. [162] The CO_2 sensitivity was diminished, but it was not abolished by surgical doses of halothane. It appears that halothane similarly depresses peripheral and central CO_2 sensitivities, [163] although the peripheral chemoreceptors only contribute to approximately 15 percent of the total CO_2 sensitivity. The response of peripheral chemoreceptors may not seem to be of great clinical import. However, if the peripheral chemoreceptor response to hypoxia is abolished at low doses of inhalational anesthetics, this may

contribute to a ventilatory impairment during concomitant episodes of hypercarbia and hypoxia, as may occur perioperatively.

Ventilatory Responses to Hypoxemia

Inhaled anesthetics, including nitrous oxide, dose-dependently attenuate the ventilatory response to hypoxia in both animals and humans. [158] [159] [164] [165] [166] The peripheral chemoreceptors appear to be the major site of the inhibitory action of anesthetics. This is evidenced by the rapidity of inhibition of the hypoxic response (30 seconds) [167] and that 0.5 to 1.0 percent halothane administered to decerebrate cats reduced carotid sinus nerve discharge when the peripheral chemoreceptors were stimulated by a variety of methods. [168] Alternatively, Stuth et al [169] demonstrated that in vagotomized dogs the phrenic nerve response to hypoxia is dose-dependently attenuated but not abolished by surgical doses of halothane. The results also did not indicate a selective depression of peripheral versus central effects of chemoreflexes. The etiology for these differences may be attributed to the profound degree of hypoxia induced in the animal studies (PO_2 <40 mm Hg), a more potent respiratory stimulus compared with that used in human studies (PO_2 approximately 50 mm Hg).

Figure 5B-37 (Figure Not Available) The ventilatory responses to acute isocapnic hypoxia (to approximately 44 mm Hg) in one subject during control (awake) and at 0.1 and 0.2 MAC isoflurane. Solid bars = period A (2-minute period before induction of hypoxia) and period B (minutes 3 and 4 of hypoxia); V_E = minute ventilation. *(From van den Elsen et al [177])*

A significant depression of hypoxia-induced ventilatory responsiveness was observed at 1 MAC halothane, and the usual synergistic effect of hypoxia and hypercarbia on ventilation was profoundly attenuated.

There is a biphasic response to hypoxia. Both adults and neonates display a similar initial hypoxia-induced increase in ventilation, but newborn animals and humans exhibit a more pronounced ventilatory decline to the prehypoxic level or less. This biphasic reaction may represent a balance between active inhibition of brain-stem neuronal activities and augmentation of peripheral chemoreceptor function. [170] Interestingly, halothane induces a biphasic ventilatory response (similar to that in the newborn) in kittens that have previously attained an adult-like hyperventilatory hypoxic response. [171] Whether the cause of this altered response is mediated solely via peripheral chemoreceptors or also at the level of the brainstem is unknown.

Knill and Gelb [159] demonstrated that peripheral chemoreceptor function was more sensitive to the effects of anesthetic agents in humans than in dogs, with significant attenuation of the response at 0.1 MAC halothane. The hypoxic ventilatory response was proposed to be more sensitive to the effects of inhaled anesthetics versus the response to hypercapnia. [158] [159] [172] Recently, there has been considerable controversy about subanesthetic concentrations of inhalational agents on hypoxic ventilatory drive. Temp and coworkers [173] [174] showed no effect of 0.1 MAC isoflurane on hypoxic drive in humans, whereas Dahan and coworkers [175] [176] [177] and others [178] have confirmed the original findings of Knill and Gelb (Fig. 5-37) (Figure Not Available) . The reason(s) for these discrepancies may be related to differences in techniques and study conditions, including differences in the state of arousal achieved in each study and the variability that may occur by studying subjects on different days. [174] Subanesthetic concentrations of most volatile anesthetics depress the ventilatory response to hypoxia in normocapnic, quiet, resting subjects, but desflurane does appear to be an exception (Fig. 5-38) (Figure Not Available) . However, subanesthetic concentrations of desflurane do decrease hypoxic sensitivity during concomitant hypercapnia, suggesting an effect at the peripheral chemoreceptors. [179] Robotham [180] has suggested, as discussed below, that the discrepant results of these hypoxia studies reinforce the clinical importance of volatile anesthetic effects on postoperative responses to hypoxia.

Clinical Implications

The profound depression of hypoxic responsiveness suggests that patients will manifest a diminished ventilatory response to hypoxemia for some time after cessation of an anesthetic and at concentrations of halothane that one would expect in a patient in the recovery room. The postoperative patient with residual anesthetic is at greater risk of hypoventilation in the absence of any significant stimuli such as pain or stimulation from recovery room personnel. Auxiliary modalities of stimulation that at least prevent eye-closing may, in part, attenuate the effects of low levels of anesthetics on hypoxic drive. Whereas surgical stimulation

Figure 5B-38 (Figure Not Available) Influence of 0.1 MAC of five volatile anesthetic agents on the ventilatory response to a step decrease in end-tidal oxygen concentration. Values are mean ± SD. Subanesthetic concentrations of the volatile anesthetics, except desflurane, profoundly depress the response to hypoxia. *(From Sarton et al [181])*

intraoperatively somewhat decreases anesthetic-induced ventilatory depression, this same amount of stimulation will not prevent impairment of chemoreflexes, including those of hypoxia and hypercarbia. [181] [182]

The importance of this depressive phenomenon may be more profound in patients who depend to some degree on a hypoxic drive to set their level of ventilation (such as those with chronic respiratory failure). Thus, the ability of these patients to maintain adequate ventilation while spontaneously breathing an inhaled anesthetic may be severely impaired. There are few clinical differences between the currently available volatile anesthetics, in terms of the hypoxia-induced ventilatory response. An exception appears to be the lack of effect of sedative doses of desflurane in normocapnic patients.

SUMMARY

Inhalational anesthetics have potent and clinically significant effects on respiratory function. Anesthetics reduce the tone of bronchial smooth muscle, mucociliary function, and pulmonary vasculature. In addition, they alter the activity of respiratory sensors, the central nervous system, and respiratory muscles. These actions are mediated via a variety of mechanisms including indirect actions on afferent, central, and efferent neural pathways and direct actions on peripheral end-organs and tissues. The depressant effects of these drugs are further enhanced in patients with pulmonary disorders. An understanding of the multifactorial actions of inhalational anesthetics on the respiratory system is critical to the safe delivery of anesthesia.

References

1. Warner DO, Warner MA, Barnes RD et al: Perioperative respiratory complications in patients with asthma [see comments]. Anesthesiology 85:460, 1996.

2. Shnider SM, Papper EM: Anesthesia for the asthmatic patient. Anesthesiology 22:886, 1961.

3. Gold MI, Helrich M: A study of the complications related to anesthesia in asthmatic patients. Anesth Analg 42:283, 1963.

4. Forrest JB, Rehder K, Cahalan MK et al: Multicenter study of general anesthesia. III: Predictors of severe perioperative adverse outcomes.Anesthesiology 76:3, 1992.

5. Pizov R, Brown RH, Weiss YS et al: Wheezing during induction of general anesthesia in patients with and without asthma: A randomized, blinded trial. Anesthesiology 82:1111, 1995.

6. Moudgil GC: The patient with reactive airways disease. Can J Anaesth 44:R77, 1997.

7. Pinto-Pereira LM, Orrett FA, Balbirsingh M: Physiological perspectives of therapy in bronchial hyperreactivity. Can J Anaesth 43:700, 1996.

8. Groeben H, Brown RH: Ipratropium decreases airway size in dogs by preferential M2 muscarinic receptor blockade in vivo. Anesthesiology 85:867, 1996.

9. Flavahan NA, Aarhus LL, Rimele TJ et al: Respiratory epithelium inhibits bronchial smooth muscle tone. J Appl Physiol 65:721, 1985.

10. Stuart-Smith K, Vanhoutte PM: Heterogeneity in the effects of epithelium-removal in the canine bronchial tree. J Appl Physiol 63:2510, 1987.

11. Colgan FJ: Performance of lungs and bronchi during inhalation anesthesia. Anesthesiology 26:778, 1965.

12. Klide AM, Aviado DM: Mechanism for the reduction in pulmonary resistance induced by halothane. J Pharmacol Exp Ther 158:28, 1967.

13. Fletcher SW, Flacke W, Alper MH: The actions of general anesthetic agents on tracheal smooth muscle. Anesthesiology 29:517, 1968.

14. Hickey RF, Graf PD, Nadel JA et al: The effects of halothane and cyclopropane on total pulmonary resistance in the dog. Anesthesiology 31:334, 1969.

15. Coon RL, Kampine JP: Hypocapnic bronchoconstriction and inhalation anesthetics. Anesthesiology 43:635, 1975.

16. Patterson RW, Sullivan SF, Malm JR et al: The effect of halothane on human airway mechanics. Anesthesiology 29:900, 1968.

17. Hirshman CA, Bergman NA: Halothane and enflurane protect against bronchospasm in an asthma dog model. Anesth Analg 57:629, 1978.

18. Hirshman CA, Edelstein G, Peetz S et al: Mechanism of action of inhalational anesthesia on airways. Anesthesiology 56:107, 1982.

19. Mazzeo AJ, Cheng EY, Stadnicka A et al: Topographical differences in the direct effects of isoflurane on airway smooth muscle. Anesth Analg 78:948, 1994.

20. Park KW, Dai HB, Lowenstein E et al: Isoflurane- and halothane-mediated dilation of distal bronchi in the rat depends on the epithelium. Anesthesiology 86:1078, 1997.

21. Hermens JM, Edelstein G, Hanifin JM et al: Inhalational anesthesia and histamine release during bronchospasm. Anesthesiology 61:69, 1984.

22. Shah MV, Hirshman CA: Mode of action of halothane on histamine-induced airway constriction in dogs with reactive airways. Anesthesiology 65:170, 1986.

23. Brown RH, Zerhouni EA, Hirshman CA: Comparison of low concentrations of halothane and isoflurane as bronchodilators. Anesthesiology 78:1097, 1993.

24. Yamamoto K, Morimoto N, Warner DO et al: Factors influencing the direct actions of volatile anesthetics on airway smooth muscle. Anesthesiology 78:1102, 1993.

25. Mitsuhata H, Saitoh J, Shimizu R et al: Sevoflurane and isoflurane protect against bronchospasm in dogs. Anesthesiology 81:1230, 1994.

26. Katoh T, Ikeda K: A comparison of sevoflurane with halothane, enflurane, and isoflurane on bronchoconstriction caused by histamine. Can J Anaesth 41:1214, 1994.

27. Mazzeo AJ, Cheng EY, Bosnjak ZJ et al: Differential effects of desflurane and halothane on peripheral airway smooth muscle. Br J Anaesth 76:841, 1996.

28. Cheng EY, Mazzeo AJ, Bosnjak ZJ et al: Direct relaxant effects of intravenous anesthetics on airway smooth muscle. Anesth Analg 83:162, 1996.

29. Hashimoto Y, Hirota K, Ohtomo N et al: In vivo direct measurement of the bronchodilating effect of sevoflurane using a superfine fiberoptic bronchoscope: Comparison with enflurane and halothane. J Cardiothorac Vasc Anesth 10:213, 1996.

30. Yamakage M: Direct inhibitory mechanisms of halothane on canine tracheal smooth muscle contraction. Anesthesiology 77:546, 1992.

31. Korenaga S, Takeda K, Ito Y: Differential effects of halothane on airway nerves and muscle. Anesthesiology 60:309, 1984.

32. Morimoto N, Yamamoto K, Jones KA et al: Halothane and pertussis toxin-sensitive G proteins in airway smooth muscle. Anesth Analg 78:328, 1994.

33. Jones KA, Wong GY, Lorenz RR et al: Effects of halothane on the relationship between cytosolic calcium and force in airway smooth muscle. Am J Physiol 266:L199, 1994.

34. Kai T, Bremerich DH, Jones KA et al: Agent-specific effects of volatile anesthetics on Ca^{2+} sensitization in airway smooth muscle. Anesthesiology 87:A1112, 1997.

35. Warner DO, Jones KA, Lorenz RR: The effects of halothane pretreatment on manganese influx induced by muscarinic stimulation of airway smooth muscle. Anesth Analg 84:1366, 1997.

36. Warner DO, Vettermann J, Brichant J-F et al: Direct and neurally mediated effects of halothane on pulmonary resistance in vivo. Anesthesiology 72:1057, 1990.

37. Brown RH, Mitzner W, Zerhouni E et al: Direct in vivo visualization of bronchodilation induced by inhalational anesthesia using high-resolution computed tomography. Anesthesiology 78:295, 1993.

38. Kannan MS, Johnson DE: Nitric oxide mediates the neural nonadrenergic, noncholinergic relaxation in pig tracheal smooth muscle. Am J Physiol 262:L511, 1992.

39. Lindeman KS, Baker SG, Hirshman CA: Interaction between halothane and the nonadrenergic, noncholinergic inhibitory system in porcine trachealis muscle. Anesthesiology 81:641, 1994.

40. Kingston HGG, Hirshman CA: Perioperative management of the patient with asthma. Anesth Analg 63:844, 1984.

41. Gold MI, Helrich M: Pulmonary mechanics during general anesthesia. V: Status asthmaticus. Anesthesiology 32:422, 1970.

42. Schwartz SH: Treatment of status asthmaticus with halothane. JAMA 251:2688, 1984.

43. Johnston RG, Noseworthy TW, Friesen EG et al: Isoflurane therapy for status asthmaticus in children and adults. Chest 97:698, 1990.

44. Parnass SM, Feld JM, Chamberlin WH et al: Status asthmaticus treated with isoflurane and enflurane. Anesth Analg 66:1193, 1987.

45. Echeverria M, Gelb AW, Wexler HR et al: Enflurane and halothane in status asthmaticus. Chest 89:152, 1986.

46. Saulnier FF, Durocher AV, Deturck RA et al: Respiratory and hemodynamic effects of halothane in status asthmaticus. Int Care Med 16:104, 1990.

47. Maltais F, Sovilj M, Goldberg P et al: Respiratory mechanics in status asthmaticus: Effects of inhalational anesthesia. Chest 106:1401, 1994.

48. Rooke GA, Choi J-H, Bishop MJ: The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. Anesthesiology 86:1294, 1997.

49. Tobias JD, Hirshman CA: Attenuation of histamine-induced airway constriction by albuterol during halothane anesthesia. Anesthesiology 72:105, 1990.

50. Wu RSC, Wu KC, Wong TKM et al: Isoflurane anesthesia does not add to the bronchodilating effect of a beta 2-adrenergic agonist after tracheal intubation. Anesth Analg 83:238, 1996.

51. Lehane JR, Jordan C, Jones JG: Influence of halothane and enflurane on respiratory airflow resistance and specific conductance in anaesthetized man. Br J Anaesth 52:773, 1980.

52. Bennett DJ, Torda TA, Horton DA et al: Severe bronchospasm complicating thoracotomy. Arch Surg 101:555, 1970.

53. Leeson TS, Leeson CR: A light and electron microscope study of developing respiratory tissue in the rat. J Anat 98:183, 1964.

54. Reid L: Natural history of mucous in the bronchial tree. Arch Environ Health 10:265, 1965.

55. Wanner A: Clinical aspects of mucociliary transport. Am Rev Respir Dis 116:73, 1977.

56. Forbes AR: Humidification and mucous flow in the intubated trachea. Br J Anaesth 45:874, 1973.

57. Hirsch JA, Tokayer JL, Robinson MJ et al: Effects of dry air and subsequent humidification on tracheal mucous velocity in dogs. J Appl Physiol 39:242, 1975.

58. Forbes AR, Gamsu G: Lung mucociliary clearance after anesthesia with spontaneous and controlled ventilation. Am Rev Respir Dis 120:857, 1979.

59. Forbes AR: Halothane depresses mucociliary flow in the trachea. Anesthesiology 45:59, 1976.

60. Forbes AR, Horrigan RW: Mucociliary flow in the trachea during anesthesia with enflurane, ether, nitrous oxide, and morphine. Anesthesiology 46:319, 1977.

61. Forbes AR, Gamsu G: Mucociliary clearance in the canine lung during and after general anesthesia. Anesthesiology 50:26, 1979.

62. Nunn JF, Sturrock JE, Wills EJ et al: The effect of inhalational anaesthetics on the swimming velocity of *Tetrahymena pyriformis.* J Cell Sci 15:537, 1974.

63. Manawadu BR, Mostow SR, LaForce FM: Impairment of tracheal ring ciliary activity by halothane. Anesth Analg 58:500, 1979.

64. Molliex S, Crestani B, Dureuil B et al: Effects of halothane on surfactant biosynthesis by rat alveolar type II cells in primary culture. Anesthesiology 81:668, 1994.

65. Gamsu G, Singer MM, Vincent HH et al: Postoperative impairment of mucous transport in the lung. Am Rev Respir Dis 114:673, 1976.

66. Lichtiger M, Landa JF, Hirsch JA: Velocity of tracheal mucus in anesthetized women undergoing gynecologic surgery. Anesthesiology 42:753, 1975.

67. Konrad F, Marx T, Schraag M, Kilian J: Combination anesthesia and bronchial transport velocity: Effects of anesthesia with isoflurane, fentanyl, vecuronium and oxygen-nitrous oxide breathing on bronchial mucus transport. Anaesthesist 46:403, 1997.

68. Konrad FX, Schreiber T, Brecht-Kraus D et al: Bronchial mucus transport in chronic smokers and nonsmokers during general anesthesia. J Clin Anesth 5:375, 1993.

69. Tarhan S, Moffitt EA, Sessler AD et al: Risk of anesthesia and surgery in patients with chronic bronchitis and chronic obstructive pulmonary disease. Surgery 74:720, 1973.

70. Colley PS, Cheney Jr FW, Hlastala MP: Ventilation-perfusion and gas exchange effects of sodium nitroprusside in dogs with normal and edematous lungs. Anesthesiology 50:489, 1979.

71. Marshall C, Lindgren L, Marshall BE: Effects of halothane, enflurane, and isoflurane on hypoxic pulmonary vasoconstriction in rat lungs *in vitro.* Anesthesiology 60:304, 1984.

72. Ishibe Y, Gui X, Uno H et al: Effect of sevoflurane on hypoxic pulmonary vasoconstriction in the perfused rabbit lung. Anesthesiology 79:1348, 1993.

73. Loer SA, Scheeren TWL, Tarnow J: Desflurane inhibits hypoxic pulmonary vasoconstriction in isolated rabbit lungs. Anesthesiology 83:552, 1995.

74. Marshall BE, Clarke WR, Costarino AT et al: The dose-response relationship for hypoxic pulmonary vasoconstriction. Respir Physiol 96:231, 1994.

75. Marshall BE, Marshall C, Benumof J et al: Hypoxic pulmonary vasoconstriction in dogs: Effect of lung segment size and oxygen-tension. J Appl Physiol 51:1543, 1981.

76. Hambraeus-Jonzon K, Bindslev L, Mellgard AJ et al: Hypoxic pulmonary vasoconstriction in human lungs: A stimulus-response study. Anesthesiology 86:308, 1997.

77. Benumof JL, Pirlo AF, Johanson I et al: Interaction of PvO_2 with PaO_2 on hypoxic pulmonary vasoconstriction. J Appl Physiol 51:871, 1981.

78. Domino KB, Wetstein L, Glasser SA et al: Influence of mixed venous oxygen tension (PvO_2) on blood flow to atelectatic lung. Anesthesiology 59:428, 1983.

79. Sykes MK, Davies DM, Chakrabarti MK et al: The effects of halothane, trichloroethylene and ether on the hypoxic pressor response and pulmonary vascular resistance in the isolated, perfused cat

lung. Br J Anaesth 45:655, 1973.

80. Loh L, Sykes MK, Chakrabarti MK: The effects of halothane and ether on the pulmonary circulation in the innervated perfused cat lung. Br J Anaesth 49:309, 1977.

81. Johnson D, Mayers I, Hurst T: Halothane inhibits hypoxic pulmonary vasoconstriction in the presence of cyclooxygenase blockade. Can J Anaesth 37:287, 1990.

82. Johnson D, Mayers I, To T: The effects of halothane in hypoxic pulmonary vasoconstriction. Anesthesiology 72:125, 1990.

83. Marshall C, Kim SD, Marshall BE: The actions of halothane, ibuprofen and BW755C on hypoxic pulmonary vasoconstriction. Anesthesiology 66:537, 1987.

84. Bjertnaes LJ, Mundal R: The pulmonary vasoconstrictor response to hypoxia during enflurane anesthesia. Acta Anaesthesiol Scand 24:252, 1980.

85. Hurtig JB, Tait AR, Loh L et al: Reduction of hypoxic pulmonary vasoconstriction by nitrous oxide administration in the isolated perfused cat lung. Can Anaesth Soc J 24:540, 1977.

86. Bindlsev L, Cannon D, Sykes MK: Effect of lignocaine and nitrous oxide on hypoxic pulmonary vasoconstriction in the dog constant-flow perfused left lower lobe preparation. Br J Anaesth 58:315, 1986.

87. Bindlsev L, Cannon D, Sykes MK: Reversal of nitrous oxide-induced depression of hypoxic pulmonary vasoconstriction by lignocaine hydrochloride during collapse and ventilation hypoxia of the left lower lobe. Br J Anaesth 58:451, 1986.

88. Kjaeve J, Bjertnaes LJ: Interaction of verapamil and halogenated inhalation anesthetics on hypoxic pulmonary vasoconstriction. Acta Anaesthesiol Scand 33:193, 1989.

89. Johnson DH, Hurst TS, Mayers I: Effects of halothane on hypoxic pulmonary vasoconstriction in canine atelectasis. Anesth Analg 72:440, 1991.

90. Benumof JL, Wahrenbrock EA: Local effects of anesthetics on regional hypoxic pulmonary vasoconstriction. Anesthesiology 43:525, 1975.

91. Mathers J, Benumof JL, Wahrenbrock EA: General anesthetics and regional hypoxic pulmonary vasoconstriction. Anesthesiology 46:111, 1977.

92. Lennon PF, Murray PA: Attenuated hypoxic pulmonary vasoconstriction during isoflurane anesthesia is abolished by cyclooxygenase inhibition in chronically instrumented dogs. Anesthesiology 84:404, 1996.

93. Johns RA: Endothelium, anesthetics, and vascular control. Anesthesiology 79:1381, 1993.

94. Marshall C, Marshall BE: Endothelium-derived relaxing factor is not responsible for inhibition of hypoxic pulmonary vasoconstriction by inhalational anesthetics. Anesthesiology 73:441, 1990.

95. Marshall C, Marshall BE: Inhalational anesthetics directly inhibit hypoxic pulmonary vasoconstriction. Anesthesiology 79:A1238, 1993.

96. Yoshida K, Tewari S, Kirby T et al: Halothane attenuates acetylcholine-induced vasorelaxation and cyclic GMP accumulation in human pulmonary artery. Anesthesiology 87:A1104, 1997.

97. Gambone LM, Murray PA, Flavahan NA: Isoflurane anesthesia attenuates endothelium-dependent pulmonary vasorelaxation by inhibiting the synergistic interaction between nitric oxide and prostacyclin. Anesthesiology 86:936, 1997.

98. Seki S, Sato K, Nakayama M et al: Halothane and enflurane attenuate pulmonary vasodilation mediated by adenosine triphosphate-sensitive potassium channels compared to the conscious state. Anesthesiology 86:923, 1997.

99. Lennon PF, Murray PA: Isoflurane and the pulmonary vascular pressure-flow relation at baseline and during sympathetic alpha- and beta-adrenoceptor activation in chronically instrumented dogs. Anesthesiology 82:723, 1995.

100. Sykes MK, Giggs JM, Loh L et al: Preservation of the pulmonary vasoconstrictor response to alveolar hypoxia during the administration of halothane to dogs. Br J Anaesth 50:1185, 1978.

101. Sykes MK, Hurtig JB, Tait AR et al: Reduction of hypoxic pulmonary vasoconstriction during diethyl ether anaesthesia in the dog. Br J Anaesth 49:293, 1977.

102. Sykes MK, Hurtig JB, Tait AR et al: Reduction of hypoxic pulmonary vasoconstriction in the dog during administration of nitrous oxide. Br J Anaesth 49:301, 1977.

103. Lejeune P, Deloof T, Leeman M et al: Multipoint pulmonary vascular pressure/flow relationships in hypoxic and in normoxic dogs: Effects of nitrous oxide with and without cyclooxygenase inhibition. Anesthesiology 68:92, 1988.

104. Bjertnaes LJ: Hypoxia-induced pulmonary vasoconstriction in man: Inhibition due to diethyl ether and halothane anesthesia. Acta Anaesthesiol Scand 22:570, 1978.

105. Fargas-Babjak A, Forrest JB: Effect of halothane on the pulmonary vascular response to hypoxia in dogs. Can Anaesth Soc J 26:6, 1979.

106. Naeije R, Lejeune P, Leeman M et al: Pulmonary arterial pressure-flow plots in dogs: Effects of isoflurane and nitroprusside. J Appl Physiol 63:969, 1987.

107. Domino KB, Borowec L, Alexander CM et al: Influence of isoflurane on hypoxic pulmonary vasoconstriction in dogs. Anesthesiology 64:423, 1986.

108. Lesitsky MA, Davis S, Murray PA: Preservation of hypoxic pulmonary vasoconstriction during sevoflurane and desflurane anesthesia in chronically-instrumented dogs. Anesthesiology 87:A1105, 1997.

109. Marshall BE, Marshall C: Anesthesia and the pulmonary circulation. In: Covino BG, Fozzard HA, Rehder K et al (eds): Effects of Anesthesia. Bethesda, Maryland, American Physiological Society, 1985, p 121.

110. Nishiwaki K, Nyhan DP, Rock P et al: N-omega-nitro-L-arginine and pulmonary vascular pressure-flow relationship in conscious dogs. Am J Physiol 262:H1331, 1992.

111. Rees DI, Gaines III GY: One lung anesthesia--a comparison of pulmonary gas exchange during anesthesia with ketamine or enflurane. Anesth Analg 63:521, 1984.

112. Anderson MW, Benumof JL: Intrapulmonary shunting during one-lung ventilation and surgical manipulation. Anesthesiology 55:A377, 1981.

113. Benumof JL, Augustine SD, Gibbons JA: Halothane and isoflurane only slightly impair arterial oxygenation during one-lung ventilation in patients undergoing thoracotomy. Anesthesiology 67:910, 1987.

114. Pagel P, Fu FL, Damask MC et al: Comparison of the effects of desflurane and isoflurane on systemic and pulmonary hemodynamics and arterial oxygenation in patients undergoing one-lung ventilation during thoracotomy. Anesth Analg 87 (In press), 1998.

115. Lennon PF, Murray PA: Pulmonary vascular effects of isoflurane anesthesia after left lung autotransplantation in chronically instrumented dogs. Anesthesiology 85:592, 1996.

116. Berger AJ, Mitchell RA, Severinghaus JW: Regulation of respiration. N Engl J Med 297:92, 1977.

117. Ward DS, Temp JA: Neuropharmacology of the control of ventilation. In: Yaksh TL, Lynch III C, Zapol WM et al (eds): Anesthesia: Biologic Foundations. Philadelphia, Lippincott-Raven, 1997.

118. Von Euler C: Neural organization and rhythm generation. In: Crystal RG, West JB, Barnes PJ et al (eds): The Lung: Scientific Foundations. New York, Raven Press, 1991, p 1307.

119. Smith JC, Ellenberger HH, Ballanyi K et al: Pre-Botzinger complex: A brainstem region that may generate respiratory rhythm in mammals. Science 254:726, 1991.

120. Whitelaw WA, Derenne JP, Milic-Emili J: Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 23:181, 1975.

121. Larson CP Jr, Eger EI II, Muallem M et al: The effects of diethyl ether and methoxyflurane on ventilation. II: A comparative study in man. Anesthesiology 30:174, 1969.

122. Hickey RF, Severinghaus JW: Regulation of breathing: Drug effects. In: Hornbein TF (ed): Regulation of Breathing. New York, Marcel Dekker, 1981, p 1251.

123. Fourcade HE, Stevens WC, Larson Jr CP et al: The ventilatory effects of Forane, a new inhaled anesthetic. Anesthesiology 35:26, 1971.

124. Eger EI II: Isoflurane: A review. Anesthesiology 55:559, 1981.

125. Calverley RK, Smith NT, Jones CW et al: Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man. Anesth Analg 57:610, 1978.

126. Fourcade HE, Larson Jr CP, Hickey RF et al: Effects of time on ventilation during halothane and cyclopropane anesthesia. Anesthesiology 36:83, 1972.

127. Lockhart SH, Rampil IJ, Yasuda N et al: Depression of ventilation by desflurane in humans. Anesthesiology 74:484, 1991.

128. Doi M, Ikeda K: Respiratory effects of sevoflurane. Anesth Analg 66:241, 1987.

129. Green Jr WB: The ventilatory effects of sevoflurane. Anesth Analg 81:s23, 1995.

130. Warltier DC, Pagel PS: Cardiovascular and respiratory actions of desflurane: Is desflurane different from isoflurane? Anesth Analg 75:S17, 1992.

131. Eger EI II, Dolan WM, Stevens WC et al: Surgical stimulation antagonizes the respiratory depression produced by Forane. Anesthesiology 36:544, 1972.

132. Whitteridge D, Bulbring E: Changes in activity of pulmonary receptors in anaesthesia and their influence on respiratory behavior. J Pharmacol Exp Ther 81:340, 1944.

133. Paskin S, Skovsted P, Smith TC: Failure of the Hering-Breuer reflex to account for tachypnea in anesthetized man: A survey of halothane, fluroxene, methoxyflurane and cyclopropane. Anesthesiology 29:550, 1968.

134. Nishino T, Anderson JW, Sant'Ambrogio G: Effects of halothane, enflurane, and isoflurane on laryngeal receptors in dogs. Respir Physiol 91:247, 1993.

135. Nishino T, Anderson JW, Sant'Ambrogio G: Responses of tracheobronchial receptors to halothane, enflurane, and isoflurane in anesthetized dogs. Respir Physiol 95:281, 1994.

136. Sivarajan M, Joy JV: Effects of general anesthesia and paralysis on upper airway changes due to head position in humans. Anesthesiology 85:787, 1996.

137. Nandi PR, Charlesworth CH, Taylor SJ et al: Effect of general anaesthesia on the pharynx. Br J Anaesth 66:157, 1991.

138. Ochiai R, Guthrie RD, Motoyama EK: Effects of varying concentrations of halothane on the activity of the genioglossus, intercostals, and diaphragm in cats: An electromyographic study. Anesthesiology 70:812, 1989.

139. Nishino T, Kohchi T, Yonezawa T et al: Responses of recurrent laryngeal, hypoglossal, and phrenic nerves to increasing depths of anesthesia with halothane or enflurane in vagotomized cats. Anesthesiology 63:404, 1985.

140. Tusiewicz K, Bryan AC, Froese AB: Contributions of changing rib cage-diaphragm interactions to the ventilatory depression of halothane anesthesia. Anesthesiology 47: 327, 1977.

141. Warner DO, Warner MA, Ritman EL: Mechanical significance of respiratory muscle activity in humans during halothane anesthesia. Anesthesiology 84:309, 1996.

142. Warner DO, Warner MA, Ritman EL: Human chest wall function while awake and during halothane anesthesia. I: Quiet breathing. Anesthesiology 82:6, 1995.

143. Warner DO, Warner MA, Ritman EL: Atelectasis and chest wall shape during halothane anesthesia. Anesthesiology 85:49, 1996.

144. Krayer S, Rehder K, Vettermann J et al: Position and motion of the human diaphragm during anesthesia-paralysis. Anesthesiology 70:891, 1989.

145. Hedenstierna G, Tokics L, Lundquist H et al: Phrenic nerve stimulation during halothane anesthesia: Effects on atelectasis. Anesthesiology 80:751, 1994.

146. Stuth EAE, Tonkovic-Capin M, Kampine JP, Zuperku EJ: Dose-dependent effects of isoflurane on the CO_2 responses of expiratory medullary neurons and the phrenic nerve activities in dogs. Anesthesiology 76:763, 1992.

147. Stuth EAE, Tonkovic-Capin M, Kampine JP et al: Dose-dependent effects of halothane on the carbon dioxide responses of expiratory and inspiratory bulbospinal neurons and the phrenic nerve activities in dogs. Anesthesiology 81:1470, 1994.

148. Ide T, Kochi T, Isono S et al: Effects of sevoflurane on diaphragmatic contractility in dogs. Anesth Analg 74:739, 1992.

149. Kochi T, Ide T, Isono S, Mizuguchi T et al: Differential effects of halothane and enflurane on diaphragmatic contractility in vivo. Anesth Analg 70:362, 1990.

150. Moote CA, Knill RL, Clement J: Ventilatory compensation for continuous inspiratory resistive and elastic loads during halothane anesthesia in humans. Anesthesiology 64:582, 1986.

151. Slee TA, Sharar SR, Pavlin EG et al: The effects of airway impedance on work of breathing during halothane anesthesia. Anesth Analg 69:374, 1989.

152. Isono S, Nishino T, Sugimori K et al: Respiratory effects of expiratory flow-resistive loading in conscious and anesthetized humans. Anesth Analg 70:594, 1990.

153. Pietak S, Weenig CS, Hickey R et al: Anesthetic effects on ventilation in patients with chronic obstructive pulmonary disease. Anesthesiology 42:160, 1975.

154. Gonzalez C, Almaraz L, Obeso A et al: Carotid body chemoreceptors from natural stimuli to sensory discharges. Physiol Rev 74:829, 1994.

155. Hickey RF, Fourcade HE, Eger EI II et al: The effects of ether, halothane and Forane on apneic thresholds in man. Anesthesiology 35:32, 1971.

156. Winter PM, Hornbein TF, Smith G et al: Hyperbaric nitrous oxide anesthesia in man. Abstracts of Scientific Papers, American Society of Anesthesiologists Meeting, 103:1972.

157. Hornbein TF, Martin WE, Bonica JJ et al: Nitrous oxide effects on the circulatory and ventilatory responses to halothane. Anesthesiology 31:250, 1969.

158. Knill RL, Manninen PH, Clement JL: Ventilation and chemoreflexes during enflurane sedation and anaesthesia in man. Can Anaesth Soc J 26:353, 1979.

159. Knill RL, Gelb AW: Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. Anesthesiology 49:244, 1978.

160. Warner DO, Warner MA: Human chest wall function while awake and during halothane anesthesia. II: Carbon dioxide rebreathing. Anesthesiology 82:20, 1995.

161. Warner DO, Joyner MJ, Ritman EL: Chest wall responses to rebreathing in halothane-anesthetized dogs. Anesthesiology 83:835, 1995.

162. Stuth EAE, Dogas Z, Krolo M et al: Effects of halothane on the phrenic nerve responses to carbon dioxide mediated by the carotid body chemoreceptors in vagotomized dogs. Anesthesiology 87:1440, 1997.

163. van Dissel JT, Berkenbosch A, Olievier CN et al: Effects of halothane on the ventilatory response to hypoxia and hypercapnia in cats. Anesthesiology 62:448, 1985.

164. Weiskopf RB, Raymond LW, Severinghaus JW: Effects of halothane on canine respiratory responses to hypoxia with and without hypercarbia. Anesthesiology 41:350, 1974.

165. Hirshman CA, McCullough RE, Cohen PJ et al: Depression of hypoxic ventilatory response by halothane, enflurane and isoflurane in dogs. Br J Anaesth 43:957, 1977.

166. Yacoub O, Doell D, Kryger MH et al: Depression of hypoxic ventilatory response by nitrous oxide. Anesthesiology 45:385, 1976.

167. Knill RL, Clement JL: Site of selective action of halothane on the peripheral chemoreflex pathway in humans. Anesthesiology 61:121, 1984.

168. Davies RO, Edwards Jr MW, Lahiri S: Halothane depresses the response of carotid body chemoreceptors to hypoxia and hypercapnia in the cat. Anesthesiology 57:153, 1982.

169. Stuth EAE, Dogas Z, Krolo M et al: Dose-dependent effects of halothane on the phrenic nerve responses to acute hypoxia in vagotomized dogs. Anesthesiology 87:1428, 1997.

170. Fung M-L, Wang W, Darnall RA et al: Characterization of ventilatory responses to hypoxia in neonatal rats. Respir Physiol 103:57, 1996.

171. Morray JP, Nobel R, Bennet L et al: The effect of halothane on phrenic and chemoreceptor responses to hypoxia in anesthetized kittens. Anesth Analg 83:329, 1996.

172. Knill RL, Kieraszewicz HT, Dodgson BG et al: Chemical regulation of ventilation during isoflurane sedation and anaesthesia in humans. Can Anaesth Soc J 30:607, 1983.

173. Temp JA, Henson LC, Ward DS: Does a subanesthetic concentration of isoflurane blunt the ventilatory response to hypoxia? Anesthesiology 77:1116, 1992.

174. Temp JA, Henson LC, Ward DS: Effect of a subanesthetic minimum alveolar concentration of isoflurane on two tests of the hypoxic ventilatory response. Anesthesiology 80:739, 1994.

175. Dahan A, van den Elsen MJLJ, Berkenbosch A et al: Effects of subanesthetic halothane on the ventilatory responses to hypercapnia and acute hypoxia in healthy volunteers. Anesthesiology 80:727, 1994.

176. van den Elsen MJLJ, Dahan A, Berkenbosch A et al: Does subanesthetic isoflurane affect the ventilatory responses to acute isocapnic hypoxia in healthy volunteers? Anesthesiology 81:860, 1994.

177. van den Elsen MJLJ, Dahan A, DeGoede J et al: Influences of subanesthetic isoflurane on ventilatory control in humans. Anesthesiology 83:478, 1995.

178. Nagyova B, Dorrington KL, Robbins PA: Effect of low-dose enflurane on the ventilatory response to hypoxia in humans. Br J Anaesth 72:509, 1994.

179. Dahan A, Sarton E, van den Elsen M et al: Ventilatory response to hypoxia in humans: Influences of subanesthetic desflurane. Anesthesiology 85:60, 1996.

180. Robotham JL: Do low-dose inhalational anesthetic agents alter ventilatory control? Anesthesiology 80:723, 1994.

181. Sarton E, Dahan A, Teppema L et al: Acute pain and central nervous system arousal do not restore impaired hypoxic ventilatory response during sevoflurane sedation. Anesthesiology 85:295, 1996.

182. Lam AM, Clement JL, Knill RL: Surgical stimulation does not enhance ventilatory chemoreflexes during enflurane anaesthesia in man. Can Anaesth Soc J 27:22, 1980.

Chapter 6 - Metabolism and Toxicity of Inhaled Anesthetics

Jeffrey M. Baden
Susan A. Rice

INTRODUCTION

The inhaled anesthetics are not biochemically inert. They are metabolized *in vivo*, and their metabolites can cause both acute and chronic toxicities. In this chapter, we present the metabolism and toxicity of the inhaled anesthetics and discuss their known and hypothesized associations.

METABOLISM

Biotransformation may produce profound effects on the actions of a drug. Metabolism may result in pharmacologic and toxicologic actions that may be equal to, greater than, or less than anticipated. Furthermore, the actions of a drug metabolite may be entirely different from those of its parent. Many factors, such as the extent of drug absorption, excretion, secretion, and metabolism, affect drug efficacy and toxicity. These factors themselves are affected by chemical and physical properties of the drug. In the following sections, we discuss the properties of drugs and cellular membranes that influence drug availability at the cellular sites of metabolism.

PHYSICOCHEMICAL CONSIDERATIONS

Properties of Drug Molecules

Three physicochemical properties primarily determine the distribution of a drug molecule and its availability for metabolism: ionization, lipid solubility, and molecular size and shape. The degree to which a drug is ionized depends on the negative log of the acid ionization constant (pK_a) of the drug and the pH of the solution in which it is dissolved. Most drugs are weak bases or weak acids and have one or more functional groups that can be ionized. The pK_a for weak acids is high, whereas that for weak bases is low. The relationships among the degree of ionization, the pK_a, and the pH of a drug is described by the Henderson-Hasselbach equation:

Lipid solubility of a drug is determined by the presence or absence of lipophilic (hydrophobic) or nonpolar groups. Alkyl groups (C_nH_{2n+1}), such as the methyl group (CH_3), are nonpolar. The lipophilic properties of a molecule increase as the length of the alkyl group increases. For example, the presence of an *n*-propyl group ($CH_3CH_2CH_2$) makes the compound more lipophilic than the presence of a methyl group. Lipophilic properties of molecules increase when an alkyl group is inserted, whether the substitution occurs on a carbon, nitrogen, oxygen, or sulfur atom. Substitution of oxygen by sulfur often markedly increases the lipophilic properties of a drug. The hydrophilic or polar properties are increased, and simultaneously the lipophilic properties are decreased, when a molecule contains structural elements that allow hydrogen bonding of water (e.g.,
OH,
O
,
CHO,
COOH,
COOR,
Cl, and
Br). The presence of unsaturated bonds (e.g.,
CH=CH
) further promotes the hydrophilic properties of a molecule. Molecular size and shape also determine drug distribution. Various types of

membranes have different pore sizes that allow the passage of different sized molecules. For example, molecules larger than 4 A in radius are excluded from the erythrocyte, and molecules up to about the size of albumin (molecular weight 69,000; major axis 150 A; minor axis 35 A) can appear in the glomerular filtrate. All three physicochemical factors
ionization, lipid solubility, and molecular size and shape
influence the distribution of a drug and its ability to penetrate cellular membranes.

Properties of Cellular Membranes

Cellular and subcellular membranes are lipid in nature. They contain large quantities of phospholipids, cholesterol, and neutral lipids in association with proteins. Membrane phospholipids have distinct polar and nonpolar regions. They form a bilayer in which nonpolar hydrocarbon chains are directed toward the center, whereas polar head groups remain in contact with the aqueous phase on the bilayer surface. This lipid structure is either completely or partially penetrated by membrane proteins that bind to interior and exterior surfaces of the bilayer. The proteins are necessary both for the maintenance of membrane integrity and for the specialized transport of endogenous and exogenous molecules. In concert with drug properties, membrane properties determine the ability of a drug to enter cells.

Very small molecules and ions (e.g., Cl^-) apparently diffuse through aqueous membrane channels, whereas lipid-soluble molecules may diffuse freely through the membrane. Water-soluble molecules and ions of moderate size, including the ionic form of most drugs, cannot passively diffuse through the membrane but enter the cell by specialized transport. The overall lipid solubility (i.e., the relative lipophilic and hydrophilic properties) of a drug molecule determines whether the drug will readily cross biologic membranes by a passive process. Membranes are generally permeable to the nonionized forms of lipid-soluble drugs. Ionized groups on a molecule (e.g.,
COO^- from
COOH, which is almost completely ionized at pH 7.4) interact strongly with water dipoles and, as a result, penetrate the lipoidal cell membrane poorly, if at all. The diffusion rate of a drug roughly parallels the concentration gradient for the nonionized drug form. In general, the greater the lipid solubility, the greater the rate at which a drug moves through membranes.

Function of the Liver in Drug Metabolism

Inhaled anesthetics are primarily metabolized by the liver and, to a lesser extent, by other tissues (e.g., gastrointestinal tract, kidneys, lungs, skin). The following discussion of drug metabolism is limited to the liver because most anesthetic biotransformation occurs in this organ, and the principles of drug metabolism are similar from tissue to tissue.

Hepatic physiology is fully discussed in Chapter 17 ; however, a brief description is included in this discussion to aid in understanding the relationship between drug metabolism and toxicity. The liver is the largest organ in the body and weighs about 1,500 g in adult humans. It is unique from the standpoint that it has a double blood supply: 70 percent of the flow from the portal vein and 30 percent from the hepatic artery. Blood in the portal vein comes from the alimentary canal, pancreas, and spleen. Thus, any toxic material absorbed from the alimentary canal is processed by the liver before it enters the systemic circulation. Blood flows through the hepatic sinusoids from the periphery of the hepatic lobule, fed by portal veins and hepatic arteries, to the centrally located hepatic venule (central vein).

The hepatocyte contains several structures that are involved in intermediary and drug metabolism, most notably the endoplasmic reticulum. This membranous matrix of lipoprotein is the major site of protein synthesis, electron transfer, lipid metabolism, and hormone and drug metabolism. It is also the main site for the synthesis of

the lipoid and protein structural components for the cell and its organelles. The rough endoplasmic reticulum (RER) is the site of protein synthesis and is identified by the presence of adjacent ribosomes. The RER is extensively developed in protein-secreting cells. The smooth endoplasmic reticulum (SER) is identified by its lack of ribosomes. It is the site of drug metabolism, bilirubin conjugation, steroid synthesis, and some enzyme synthesis. The SER is extensively developed in steroid-secreting cells. In hepatocytes, both RER and SER participate in drug metabolism. Many *in vitro* studies of the liver and its drug-metabolizing capability are performed with hepatocytes and microsomes. The latter organelles are not naturally occurring, but they are formed from the breakage and reformation of the RER and SER during cell fractionation.

DRUG METABOLISM

Discussion of xenobiotic metabolism for the purposes of this chapter is limited to the reactions that are most relevant to the inhaled anesthetics. Metabolism requires the interaction of drug (substrate) with an enzyme. These enzyme-catalyzed reactions proceed at a rate approximately 10^9 times faster than that of a noncatalyzed reaction. Enzymes enable the clearance of drugs at rates much faster than would otherwise occur. Under appropriate conditions, the enzyme and the parent drug molecule form a complex resulting from intermolecular forces (e.g., ionic, Van der Waals). The complex then decomposes, by one of many mechanisms, and the enzyme is regenerated and a product (metabolite), different from the parent drug, is liberated. The simple equation that follows serves to emphasize the point that metabolism is a multistep process.

Enzyme + drug
enzyme-drug complex
enzyme + metabolite (2)

Metabolism can be an important determinant of the therapeutic activity and the toxicity of a drug. Unlike most drugs, the inhaled anesthetics are administered in great excess of the amount metabolized. Biotransformation therefore has little effect on the pharmacologic activity of anesthetics,

but it may have a significant effect on the toxicity of anesthetics.

The major enzymatic reactions of drug metabolism are oxidation, reduction, hydrolysis, and conjugation. These reactions are biotransformation reactions. Conjugation is a synthesis reaction. A drug may have a chemical structure suitable for biotransformation via one or more of these reactions. When several reactions are possible, the result may be "competition" of several enzymes for the drug. Each enzymatic reaction results in a metabolite that itself may be further metabolized. The ratios of various metabolites depend on enzymatic reaction rates, drug concentration near the enzymes, physicochemical reactions between metabolites and enzymes, competition of multiple drugs or endogenous substrates for the same enzyme, and many other factors.

The pattern of drug metabolism is common to all animal species; it is biphasic and consists of stepwise biotransformation and synthesis reactions. Figure 6-1 shows the general scheme of drug metabolism. Phase 1 (biotransformation) consists of the oxidation (hydroxylation), hydrolysis, or reduction of a lipid-soluble or nonpolar drug. Phase 2 (synthesis) consists of the conjugation of a drug or its metabolite with an endogenous compound (predominantly glycine, sulfate, or glucuronic acid). The result of either phase of metabolism is the production of metabolites that are generally more polar than the parent drug and are more readily excreted in the bile or urine. Both phases of biotransformation are the result of drug interaction with enzymes present in plasma, cytoplasm, mitochondria, and endoplasmic reticulum. The quantitative and qualitative differences in metabolism that are seen among species reside mainly in the nature and the occurrence of these enzymes.

Phase 1 metabolism occurs primarily in the environment of the endoplasmic reticulum, whereas phase 2 metabolism occurs primarily in the more aqueous environment of the cytoplasm. Substrates of phase 1 reactions are seldom substrates of phase 2 reactions, but products of phase 1 metabolism are often substrates of phase 2 metabolism.

Phase 1 Reactions

Microsomal Drug-Metabolizing Enzymes

The phase 1 enzymes most relevant to metabolism of the inhaled anesthetics are the mixed-function oxidases. This large collection of phase 1 enzymes is also known as the cytochrome P-450. The cytochrome P-450-mediated reactions, along with other phase 1 enzyme reactions, provide important pathways whereby the cell makes xenobiotics into more polar and thus more easily eliminated compounds. These enzymes are capable of participating in several different types of reactions, but the oxidation reactions are the most common. Monooxygenase is another name that is descriptive of metabolism during which one atom of molecular oxygen (O_2) is inserted at the carbon-hydrogen bond of a substrate, while the other atom of oxygen is incorporated into cellular water (H_2O). The key enzymes of this membrane-bound multicomponent system are the hemoproteins, the cytochrome P-450 isozymes, and the flavoprotein, reduced nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome P-450 reductase. The cytochrome P-450 superfamily includes many isozymes, more than 150 of which have thus far been characterized in animals. [1] Thirty of an estimated 50 to 200 cytochrome P-450s have been characterized in humans. [2]

This system requires O_2 and NADPH for the overall hydroxylation reaction, which is represented as follows:

$RH + O_2 + NADPH + H^+$
$ROH + NADP^+ + H_2O$ (3)

RH is the substrate, ROH is the oxidized (i.e., hydroxylated) product, and NADPH is the reduced form of nicotinamide adenine dinucleotide phosphate. Electrons flow from NADPH to the flavoprotein, NADPH-cytochrome P-450 reductase, to the heme group of cytochrome P-450, and ultimately

Figure 6-1 Two phases of drug metabolism, biotransformation and synthesis, generally result in the formation of more water-soluble metabolites, which are readily excreted in the urine and bile.

to molecular oxygen. Under some circumstances, the reduced form of nicotinamide adenine dinucleotide (NADH) can contribute an electron instead of NADPH. The intermediate electron carrier for NADH is another microsomal hemoprotein, cytochrome b_5.

A scheme of cytochrome P-450-mediated drug hydroxylation is shown in Figure 6-2. In the figure, the heme iron of cytochrome P-450 is shown in its ferric (Fe^{3+}) state in the endoplasmic reticulum. The first step in biotransformation is the reaction of substrate (RH) with oxidized cytochrome P-450 (Fe^{3+}) to form a complex [$(RH)Fe^{3+}$]. This complex rapidly accepts one electron (e^-) from NADPH- cytochrome P-450 reductase that reduces the heme iron to its ferrous state [$(RH)Fe^{2+}$]. The

relative absence of oxygen at this point determines whether compounds that are capable of reductive metabolism will be reductively metabolized. One such anesthetic, halothane, is discussed later in the chapter. In the presence of O_2, the oxidative reaction occurs, and the reduced complex rapidly combines with O_2 to yield an oxygenated complex [$(RH)Fe^{2+}(O_2)$]. A second electron from NADPH-cytochrome P-450 reductase, or in some cases from NADH-cytochrome b_5 reductase, reduces the oxyferrous complex [$(RH)Fe^{3+}(O_2-)$]. Subsequently, the oxygen-oxygen bond is ruptured, and one atom of oxygen remains associated with the heme iron to produce an activated complex $(RH)(FeO)^{3+}$. This complex abstracts a hydrogen from the substrate, thus producing a free radical (R·). An internal electronic rearrangement occurs, resulting in the addition of a hydroxyl group to the substrate. The resultant complex [$(ROH)Fe^{3+}$] dissociates and liberates the hydroxylated substrate (ROH) and regenerates the oxidized form of cytochrome P-450 (Fe^{3+}).

As previously mentioned, cytochrome P-450 is not a single entity, but rather it is what is referred to as a superfamily of many isozymes having different substrate specificities.

Figure 6-2 A drug (RH), which is a substrate for the hepatic mixed-function oxidase system, interacts with cytochrome P-450 and is biotransformed to a hydroxylated product (ROH).

Along with differences in the hepatic content of cytochrome P-450 among mammalian species and individuals, the differences in cytochrome isozymes may be responsible for the variations in rates and pathways of anesthetic metabolism *in vivo* and *in vitro* that are observed between humans and laboratory animals. [3] [4] [5] Such variation has been observed for cytochrome P-450-mediated dehalogenation and dealkylation of the inhaled anesthetics. [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] Differences in metabolism must be carefully considered when estimating human risk for drug toxicity from animal data.

The older literature is very confusing, but recently, a uniform nomenclature was adopted to identify the cytochrome P-450. The following brief discussion should clear up any confusion about the various enzymes known to metabolize the inhaled anesthetics. The cytochrome P-450 nomenclature makes use of a combination of Arabic numerals and letters following P-450. The first numeral identifies the cytochrome P-450 family. The following letter designates the subfamily, and the subsequent number represents the gene within the subfamily. Cytochrome P-450 2E1, for example, is a member of the cytochrome P-450 2 family, which is a large family of isozymes that metabolizes many diverse drugs and endogenous compounds. [18] The isozymes of the cytochrome P-450 2E subfamily metabolize small, rather polar molecules, which include many inhaled anesthetics (e.g., halothane, enflurane, sevoflurane, and methoxyflurane) and halogenated hydrocarbons (e.g., chloroform, vinyl chloride, and trichloroethylene). Other cytochromes P-450 may also metabolize these molecules, but cytochrome P-450 2E is the predominant subfamily across animal species. The isozyme cytochrome P-450 2E1 is particularly important with regard to anesthetic metabolism. The highest concentration of cytochrome P-450 2E1 is found in the liver in perivenular hepatocytes of both humans and animals. This isozyme is also known to be present in extrahepatic tissues of rat (e.g., kidney, lung, and epithelial cells of the colon).

Globular molecules (e.g., phenobarbital) are the primary substrates of the cytochrome P-450 2B subfamily, but these isozymes also specifically metabolize methoxyflurane and halothane. Phenobarbital induces many members of the 2B subfamily in animals, but not in humans. The concentration of the 2B subfamily in human liver is very low and is not known to be induced. In human liver, the cytochrome P-450 3A subfamily may account for as much as 60 percent of the total cytochrome P-450 present. Large, nonplanar substrates (e.g., alfentanil, lidocaine, and midazolam) are preferred by these isozymes. Cytochrome P-450 3A metabolizes isoflurane in rats, but it is unclear whether this same isozyme is responsible for metabolism in humans. These cytochromes are induced by phenytoin, phenobarbital, and rifampin, to name a few agents.

Reactions Relevant to Inhaled Anesthetic Biotransformation

The most common drug biotransformation reactions are oxidation, reduction, and hydrolysis. Reactions within these categories are numerous and varied and are catalyzed by two classes of enzymes. The first primarily metabolizes endogenous (naturally occurring) substrates, but it can also

metabolize exogenous (foreign) substrates. The second class consists of the so-called drug-metabolizing enzymes, which reside in the endoplasmic reticulum of the hepatocyte and other cells throughout the body. The drug-metabolizing enzymes include the cytochrome P-450-mediated reactions, which are the primary means for xenobiotic biotransformation. The inhaled anesthetics are metabolized by these enzymes predominantly by oxidation reactions. Dehalogenation and O-dealkylation oxidation reactions are responsible for most anesthetic metabolism. Although an additional oxidation reaction, epoxidation, accounts for the biotransformation of only a few anesthetics, it is important because of the toxic potential of epoxides. Reductive reactions result in substrate reduction by transferring electrons to the substrate rather than to O_2. Examples of the biotransformation reactions relevant to the inhaled anesthetics are shown in the following sections.

O-Dealkylation

O-Dealkylation results from hydroxylation of an alkyl group (
CH_2R
) adjacent to the oxygen of an ether bond. The hemiacetal thus formed is a relatively unstable intermediate that rapidly decomposes to an alcohol (ROH) and an aldehyde (R
CHO). The aldehyde may then either be reduced by alcohol dehydrogenase to an alcohol or oxidized by aldehyde oxidase to form a carboxylic acid. The rate of the O-dealkylation reaction decreases as the length of the alkyl chain increases.

Dehalogenation

Dehalogenation is the result of hydroxylation of the halogen-containing carbon (
CHX_2). The resultant alcohol is chemically unstable and decomposes to a carboxylic acid and thus liberates halogen. Two halogens on the terminal carbon represent the optimal condition for dehalogenation, whereas a terminal carbon with three halogens is oxidized to a very limited extent.

Epoxidation

An epoxide is formed when oxygen is attached to adjacent unsaturated carbons of an olefin (
CH = CH
). Most epoxides are highly strained molecules and are extremely reactive because of the ease with which the epoxide ring can be opened. Some epoxides may be hydrated by the microsomal enzyme, epoxide hydrase.

Reduction

The reductively catalyzed reactions by cytochrome P-450 are very different from the oxidatively catalyzed reactions. Because oxygen inhibits the reductive reaction, at least one electron is presumably accepted directly by the substrate from cytochrome P-450. The reductive reactions relevant to the inhaled anesthetics are those in which a halogen (X) is replaced by a hydrogen. Reductive metabolism via cytochrome P-450 has been confirmed for only one anesthetic, halothane.

Phase 2 Reactions

Phase 2 reactions are conjugations. They occur when the drug contains a group suitable for combination with an endogenous compound (e.g., glycine, sulfate, glucuronic acid). The chemical groups on the drug molecule usually associated with these reactions are
OH,
COOH,
NH_2 , and
SH. The product is generally a polar, water-soluble metabolite that is readily excreted. A typical conjugation reaction is illustrated in the following equation:

Conjugation of a drug containing a hydroxyl (
OH) group with UDPGA (uridine diphosphate glucuronic acid; D-glucuronic acid in its "active" form) is catalyzed by glucuronyl

transferase, which is located in the hepatic RER. The resulting glucuronide is more water soluble than the parent drug because of the polar sugar moiety. The free carboxyl (
COOH) group of the glucuronide, which is almost completely ionized at body pH, further enhances water solubility. Although a drug initially may not contain a chemical group suitable for a conjugation reaction, one may be attained through a phase 1 reaction (i.e., by oxidation, reduction, or hydrolysis). Urochloralic acid is an example of an anesthetic metabolite that results from multiple consecutive biotransformations. [19] It is the glucuronic acid conjugate of trichloroethanol, a metabolite from the phase 1 metabolism of trichloroethylene.

Influences on Drug Metabolism

Although cytochrome P-450 is most often thought of as being responsible for the deactivation of toxic compounds, they are in fact also responsible for the activation of drugs and chemicals to toxic forms. Any factor that can influence metabolism has the potential to affect toxicity. Biotransformation is affected by many factors, including route of administration, species, strain, sex, age, diet, season, temperature, time of day, frequency of administration, and the previous or concurrent administration of other drugs or exposure to chemicals. Species generally has the greatest influence on both the therapeutic activity and the toxicity of a drug. The basis for species differences in drug action is ultimately genetic. Genetics ultimately determines absorption, distribution, metabolism, and excretion of all xenobiotics.

In humans, genetic factors that are otherwise undetected may be revealed in the expression of therapeutic activity or toxicity of a drug. For example, physiologic disposition of a drug may be unusual if there is structural variation in the serum protein that binds the drug. Even small changes in binding proteins may greatly affect a drug's disposition and, ultimately, its biologic activity. Genetic factors appear to be more important than environmental factors (e.g., diet and pollutant exposure) in determining the overall rate of drug metabolism and elimination in humans, although enzyme induction and inhibition may account for some unusual responses to drugs. Studies of halothane metabolism and elimination in twins lend support to the importance of genetic factors in metabolism. These studies demonstrated far less variation in identical twins than in fraternal twins or in the general population, even when environmental factors were quite dissimilar. [20]

Genetic differences also contribute to both qualitative and quantitative differences in drug metabolism among species. Differences may be observed in the ratios or types of metabolites that are formed. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative differences result from variations in the amount and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates. The amount of enzyme present in organs of different species can have a great effect on therapeutic activity and toxicity. Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. For example, rat liver contains approximately 30 to 50 nmol/g of liver, whereas human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent. These differences explain in part why humans metabolize drugs *in vivo* at rates that may be 10 to 20 times slower than the rate in rats. [2] [3] [4] [5]

Numerous genetic factors and environmental factors (including chemicals, drugs, and diet) affect the drug-metabolizing enzymes. The phenomena of enzyme induction and inhibition are the most obvious examples. Treatment of humans and animals with certain agents results in enzyme induction, the enhanced metabolism of a variety of drugs and chemicals. This phenomenon is due to an increased *de novo* rate of enzyme synthesis and, in some instances, a decreased rate of enzyme degradation. Cytochrome P-450 is the system best studied in this regard. It is known to be induced by numerous agents in humans and by literally hundreds of agents in experimental animals. [5] [21] [22] [23] Generally, enzyme inducers are highly lipophilic drugs and chemicals that are metabolized by the cytochrome P-450 isozymes they induce. Induction is thought to be determined largely by the extent and duration of the interaction of the inducing agent with the enzyme concerned. The inducing properties of a drug are unrelated to the nature of its pharmacologic or toxicologic activity and may differ markedly from those of other drugs in the same class.

Induction by drugs such as phenobarbital results in proliferation of the SER and an increase in liver weight. With this type of inducer, NADPH-cytochrome P-450 reductase and specific cytochrome P-450 isozymes are preferentially increased. Although other inducers increase the synthesis of specific cytochrome P-450 isozymes, they do not affect cytochrome P-450 reductase or liver weight. Many chemical and drug classes, including anesthetics, anticonvulsants, insecticides, sedatives, steroids, and tranquilizers, contain one or more compounds considered to be enzyme inducers. [5] [22] [23] Even the inhaled anesthetics can induce drug-metabolizing enzymes in experimental animals [7] [24] [25] and in humans [26] if exposure is sufficiently prolonged. In many case reports of drug toxicity, enzyme induction has been suggested to be a causative factor, although the claims are not often supported by good evidence. If the parent compound is toxic, enhanced metabolism decreases toxicity. If the metabolites are more toxic than the parent compound, metabolism increases toxicity. Enzyme-inducing agents have the potential to modify both acute and chronic toxicities of anesthetics. In view of the current practice of polypharmacy, enzyme induction may be common in patients undergoing surgery. Enzyme induction does not necessarily increase the metabolism of all drugs from the same class. For example, unlike methoxyflurane metabolism, enflurane metabolism is not significantly increased *in vivo* following phenobarbital or phenytoin treatment in humans [9] and in animals [8] [27] [28] or *in vitro* following treatment in animals. [8] [28] Even when anesthetics that are metabolized to toxic metabolites are administered to surgical patients taking enzyme-inducing drugs, significant amounts of toxic metabolites are not necessarily produced. [9] [13] [29]

The consequences of enzyme inhibition for therapeutic activity and toxicity can be just as great as those of enzyme induction. Many compounds inhibit the activity of the drug-metabolizing enzymes and thereby alter the duration and intensity of pharmacologic action and the severity of toxic effects.

There are several mechanisms of inhibition. [30] Protein synthesis inhibitors such as cycloheximide decrease enzyme synthesis and thus reduce enzyme concentrations. Other agents are reversible inhibitors that compete for the active site of the same enzyme responsible for metabolism of the drug of interest. Still others are irreversible inhibitors that degrade the heme in cytochrome P-450. It has been recognized for many years that millimolar concentrations of methoxyflurane (5.8 mmol/L), enflurane (13.3 mmol/L), and halothane (18.8 mmol/L) destroy cytochrome P-450 in microsomal preparations. [31]

/das/book/view/29494766/875/72.html

METABOLISM OF SPECIFIC ANESTHETICS

Nonhalogenated Inhaled Anesthetics

Nonhalogenated agents have been used as anesthetics, but only nitrous oxide (N_2O) is currently in use. The metabolism of several of these previously used agents was discussed in an earlier edition of this book. The interested reader will find information on diethyl ether and ethylene. [32] There is still no evidence to suggest mammalian metabolism of cyclopropane.

Nitrous Oxide

Nitrous oxide (N_2O) is not metabolized by enzymatic action in human tissue. There is, however, a physicochemical reaction of N_2O with vitamin B_{12} [33] in which N_2O is reductively metabolized by rat and human intestinal bacteria to molecular nitrogen (N_2). [34] N_2O reduction in bacteria may occur via a single electron transfer process that results in the formation of nitrogen gas (N_2) and free radicals. The reaction between vitamin B_{12} and N_2O was first reported in 1968, [33] but its clinical relevance was not realized for 10 years. [35] The clinical effects are discussed in the section on toxicity. The *in vivo* physicochemical reaction between N_2O and the cob(I)alamin [Cob(I)] of vitamin B_{12} and the mechanism of methionine synthase inactivation is not known. Experimental evidence in *Escherichia coli* implicates cob(I)alamin as the reactive intermediate that reductively degrades N_2O with the concomitant oxidation of the cobalamin. [36] Methionine synthase is inactivated when the highly reduced cob(I)alamin is oxidized by N_2O. N_2 and an oxidant are thus produced via a single-electron transfer. This concomitant formation of a damaging oxidant species implies that cobalamin is not the primary site of damage in the short term, but rather that the protein structure proximal to cobalamin is initially modified.

Evidence for induction of drug metabolism by N_2O is contradictory. Hepatic enzyme induction in experimental animals has been reported following prolonged exposure to unspecified concentrations of N_2O. [37] Conversely, rats continuously exposed to 20 percent N_2O for 14 to 35 days exhibited inhibition of hepatic drug metabolism and induction of pulmonary and testicular metabolism. [38] Mice exposed to as much as 50 percent N_2O for 4 hours per day for 14 weeks exhibited no increase in hepatic content of cytochrome P-450 or in defluorination of enflurane or methoxyflurane. [39] In another study, hexobarbital sleeping time in rats, used as an indicator of drug metabolism, was unchanged following exposure to 50 percent N_2O for 7 hours per day for 5 days. [24]

Halogenated Inhaled Anesthetics

This section addresses the metabolism of the halogenated inhaled anesthetics in use in the United States. Three older anesthetics that are not currently in use, chloroform, trichloroethylene, and fluroxene, have been extensively studied and have greatly contributed to our current understanding of halogenated hydrocarbon metabolism. These three anesthetics are discussed in a previous edition of this chapter. [32]

Halothane

Halothane (CF_3
$CHBrCl$) is extensively metabolized (i.e.,
25-45% of the absorbed halothane). Its major metabolite in humans and animals is trifluoroacetic acid, which is formed from oxidative metabolism via the cytochrome P-450 system. The end products of the oxidative pathways that are detected in the urine are the sodium salt

of trifluoroacetic acid, chloride (Cl^-), and bromide (Br^-). Two cytochrome P-450 isozymes (i.e., 2E1 and 2B4) are primarily responsible for oxidative metabolism of halothane to trifluoroacetic acid. [17] [18] [40] The rate-limiting step in oxidative metabolism is breakage of the carbon-hydrogen bond. [41] The first metabolite formed is 1,1,1-trifluoro-2-chloro-2-bromoethanol (not shown in Eq. 6-11), which rapidly decomposes to produce hydrogen Br^- and a reactive trifluoro-acetylchloride. This latter metabolite is also a reactive compound; it decomposes in the presence of water to produce trifluoroacetic acid. The trifluoroacetylchloride intermediate is also known to react with phosphatidyl ethanalomine, a membrane lipid [42] ; *N*-trifluoroacetyl-2-aminoethanol has been identified in urine. [43] Other potential reactions and products related to this intermediate are discussed in the section on hepatotoxicity. Although significant amounts of trifluoroethanol have been identified in the urine of experimental animals, neither trifluoroethanol nor its glucuronide conjugate has been found in human urine. Likewise, trifluoroacetaldehyde, another possible metabolite, has not been isolated from human urine.

An alternative and minor route of halothane metabolism (i.e., <1% of absorbed halothane) is via a reductive pathway that requires the relative absence of oxygen and the presence of an electron donor. Both Br^- and F^- are end products of this pathway. [44] [45] [46] Two volatile metabolites (1,1-difluoro-2-chloroethylene [CDE] and 1,1,1-trifluoro-2-chloroethane [CTE]) and a volatile metabolite-decomposition product (1,1-difluoro-2-bromo-2-chloroethylene [DBE]) were first identified in the exhaled gases of patients anesthetized with halothane. [47] The formation of CDE and the release of F^- probably results from a cytochrome P-450-mediated two-electron reduction of halothane, whereas CTE formation and the production of free radicals result from a cytochrome P-450-mediated one-electron reduction. [18] [48] [49] The suicidal inactivation of cytochrome P-450 observed under hypoxic conditions (<40 torr O_2) [50] is presumably the result of cytochrome P-450 binding covalently to a reactive intermediate of CTE metabolism. The release of F^-, CDE, and DBE from halothane under anaerobic conditions can be catalyzed by reduced cytochrome P-450, hemoglobin, or hemin. [45] This finding suggests that the reaction is nonenzymatic and may only require reduced heme. DBE can also be produced nonenzymatically through the base-catalyzed decomposition of halothane as a result of interaction with soda lime. [47]

The human cytochrome P-450 responsible for halothane metabolism has not been isolated, but in rabbits, cytochromes P-450 2B4 and P-450 2E1, the phenobarbital-and ethanol-inducible forms, respectively, metabolize halothane. [40] Cytochrome P-450 2E1 metabolized halothane more than twice as rapidly as did cytochrome P-450 2B4. The human equivalent of P-450 2E1 is inducible by both ethanol and isoniazid. In experimental animals, increased halothane metabolism

follows administration of inducing agents such as phenobarbital, [50] [51] [52] Aroclor 1254, [46] and isoniazid. [53] Prolonged exposure to subanesthetic concentrations of halothane results in increased drug metabolism in experimental animals [7] [24] and humans. [26]

Methoxyflurane

Metabolism of methoxyflurane (CH_3
O
CF_2
$CHCl_2$) has been studied extensively, both *in vivo* and *in vitro.* It is estimated that as much as 75 percent of absorbed methoxyflurane is metabolized by humans. The molecule can be oxygenated either at the methyl carbon or at the dichloroethyl carbon. [54] [55] The major metabolites are methoxydifluoroacetic acid, F^-, and dichloroacetic acid. [37] [54] [56] It is not known whether methoxydifluoroacetic acid is further metabolized in humans, although it would be expected to decompose in the acid environment of the kidneys and consequently to release oxalic acid and additional F^-. Cytochrome P-450 2B4 and 2E1 are the principal isozymes responsible for the hepatic metabolism of methoxyflurane. [57] Defluorination of methoxyflurane occurs more rapidly than its *O*-demethylation. [10] [54] [58] The carbon-hydrogen bond at the dichloroethyl carbon of methoxyflurane is broken approximately seven times more rapidly by

rabbit hepatic cytochrome P-450 2B4 than is the bond at the methyl carbon. [17] [57] Both these reactions require cytochrome b_5 to provide the second electron. [17] [58] [59] In the kidneys, cytochrome P-450 2E1 is also the primary isozyme for metabolism, followed by 2A6 and 3A4. [60] Metabolism of methoxyflurane is increased *in vivo* and *in vitro* following treatment with enzyme-inducing drugs such as phenobarbital, [6] phenytoin, [8] ethanol, [14] [15] diazepam, [16] and isoniazid. [11] [12] Its metabolism is subject to inhibition *in vivo* and *in vitro* by SKF-525A and *in vitro* by metyrapone. [10]

In addition to cytochrome P-450-dependent metabolism, methoxyflurane can be defluorinated by both an enzymatic, non-cytochrome P-450-dependent reaction [61] and a nonenzymatic [62] reaction. The enzymatic defluorination was confirmed and was suggested to be catalyzed by glutathione-S-transferase. [63] The nonenzymatic defluorination of meth-oxyflurane may not be significant *in vivo;* the reaction requires both glutathione and coenzyme B_{12} and shows an *in vitro* pH optimum of 10. [62]

Enflurane

Enflurane (CHF_2
O
CF_2
CHClF) is essentially no longer used in the United States, but examination of its metabolism serves to illustrate how relatively minor changes in chemical structure can dramatically affect the extent of metabolism. Enflurane is slowly metabolized (i.e.,
2-8% of absorbed enflurane). This low rate of reaction made metabolism studies difficult because of the limits of detection released by oxidative dehalogenation. Initial oxidation and breaking of the carbon-hydrogen bond may occur at either the chlorofluoromethyl carbon or at the difluoromethyl carbon. Studies of the metabolism of enflurane with rat [64] and human hepatic microsomes, [65] and the isolation of difluoro-methoxy-difluoroacetic acid from rat liver, [66] human urine, [66] [67] human hepatic microsomes, and c2 DNA-expressed P-450 2E1 [65] suggest that primary metabolism occurs at the chlorofluoromethyl carbon. Detection of insignificant amounts of chlorofluoroacetic acid further suggests that there is very little metabolism at the difluoromethyl carbon. [66] The reactive intermediate formed from oxidation at the chlorofluoromethyl carbon can either hydrolyze to produce difluoromethoxydifluoroacetic acid or acetylate tissue protein to produce an adduct with immunogenic potential. [68]

Surgical patients treated on a long-term basis with phenobarbital, phenytoin, or diazepam or who consumed ethanol prior to anesthesia did not have elevated serum F^- concentrations compared with untreated patients. [9] In contrast, about 50 percent of surgical patients on chronic isoniazid therapy demonstrated significantly elevated serum F^- concentrations. [13] It is unclear why 50 percent of patients did not significantly defluorinate enflurane. Purified cytochrome P-450 2E1 from rabbits [69] and humans [65] [70] demonstrates that this cytochrome is predominantly, if not exclusively, responsible for enflurane defluorination in human liver. Isoniazid alone seems to significantly enhance *in vitro* enflurane metabolism in rats, [11] [12] rabbits, [65] and humans. [71] Treatment of rats with phenobarbital, [8] [10] [28] phenytoin, [8] or ethanol [14] [15] only slightly increases enflurane metabolism. As with methoxyflurane, defluorination of enflurane in rats decreases following treatment with either SKF-525A or metyrapone. [10] Continuous exposure of rats to subanesthetic concentrations of enflurane significantly decreases hexobarbital sleeping time, an indication of enhanced metabolism, which, in turn, indicates enzyme induction. [24] Exposure of mice to 0.5 percent enflurane for 5 days per week up to 73 days did not alter hepatic microsomal cytochrome P-450 concentrations or defluorination rates of methoxyflurane, enflurane, or isoflurane. [72] Sevoflurane defluorination, however, was increased.

Isoflurane

Isoflurane (CHF_2
O
CHCl
CF_3), an isomer of enflurane, was the most slowly metabolized of the fluorinated inhaled anesthetics [3] [73] [74] [75] until the introduction of desflurane. The lipid and blood solubilities of isoflurane are limited (blood/gas partition coefficient of 1.41). [76] The metabolism of isoflurane, estimated to be approximately 0.2 percent of the absorbed anesthetic, results from oxidation of the alpha-carbon, presumably by hepatic cytochrome P-450 2E1. [77] As with enflurane, the difluoromethyl carbon of isoflurane is resistant to, but not without, oxidation [66] [78] as evidenced by traces of trifluoroacetic acid recovered from the urine of rats and humans. Trifluoroacetaldehyde and trifluoroacetylchloride, expected intermediates between isoflurane and trifluoroacetic acid, may also be produced. Cytochrome P-450 2E1 and 3A are thought to be responsible for the majority of isoflurane metabolism. [17] [77] [79]

Although phenobarbital, [6] [73] phenytoin, [8] ethanol, [14] and isoniazid [11] [12] pretreatments increase the defluorination of isoflurane, enzyme induction has not produced serum F^-

concentrations of clinical significance. [73] [75] Prolonged exposure to subanesthetic concentrations of isoflurane enhances the hexobarbital sleeping time of rats. [24] Mice exposed to as much as 0.5 percent isoflurane for 4 hours per day, 5 days per week for 9 weeks did not result in significant changes in hepatic microsomal cytochromes P-450 or b_5 or in defluorination rates of methoxyflurane, enflurane, or isoflurane. [80]

Desflurane

Desflurane (CHF_2
O
CHF
CF_3), previously known as I-653, is the newest volatile anesthetic. It is expected to be metabolized in a manner similar to isoflurane. It has low solubility in lipid and blood (blood/gas partition coefficient of 0.42). [76] [78] The substitution of a F in desflurane for the chlorine at the alpha-carbon in isoflurane decreases the metabolism at this site, such that there is significantly less metabolism of desflurane to F^- and nonvolatile organic F^- compounds compared with isoflurane. Peak serum F^- concentrations in rats are seen immediately after exposure to desflurane. No increases in serum F^- above baseline concentrations were measured after volunteers received 7.4 minimum alveolar concentration (MAC)-hours of desflurane. [81] Significant increases in serum trifluoroacetic acid concentrations, however, were measured; peak concentrations were attained 24 hours postexposure. Urinary trifluoroacetic acid excretion was also significantly increased. The same cytochrome P-450 that metabolizes isoflurane is expected to metabolize desflurane. Pretreatment of rats with phenobarbital or ethanol only slightly enhances serum F^- concentrations for a brief period. [78] [82]

Sevoflurane

Sevoflurane (CH_2 F
O
CH
$(CF_3)_2$) was investigated experimentally for over a decade before the first clinical trials were initiated in the United States. It is currently used in Japan. The *in vitro* rate of sevoflurane defluorination is approximately the same as that of methoxyflurane. [83] [84] *In vivo,* however, serum F^- concentrations following sevoflurane administration are significantly less than those following methoxyflurane, [83] [84] [85] presumably the result of great differences in blood/gas partition coefficients of the two agents (0.69 versus 10.2). [76] Approximately 1 to 5 percent of absorbed sevoflurane is biotransformed. [85] [86] The alpha-carbon is the most likely site of oxidation of sevoflurane rather than the trifluoromethyl carbons. Experiments using cytochrome P-450 2E1 purified from rabbits [69] and humans [77] [78] confirm the results of *in vitro* studies with liver microsomes and show that this isozyme is the predominant, if not the only, enzyme participating in sevoflurane defluorination. As with methoxyflurane, the addition of cytochrome b_5 to the reaction mixture significantly enhances metabolism.

In a study of human volunteers, nonvolatile organic fluoride, 80 percent of which was in the form of hexafluoroisopropanol, was detected in the blood and urine of volunteers

anesthetized with sevoflurane. [85] Hexafluoroisopropanol is not subject to further degradation, but it is conjugated to glucuronide. [85] [88] Studies in patients and volunteers have shown that much of the metabolism of sevoflurane to F^- occurs during anesthetic exposure, presumably because of the low tissue solubility of sevoflurane and the stability of its metabolites. [85] [88] [89] Peak serum F^- concentrations are reached within a few hours of the end of anesthesia. *In vivo* studies show increased sevoflurane defluorination in rats following phenobarbital treatment. [84] *In vitro,* sevoflurane defluorination is increased in rat hepatic microsomes by pretreatment with phenytoin, [8] isoniazid, [11] [12] ethanol, [15] and phenobarbital. [8] [84]

Several decomposition products are formed during the *in* vitro interaction of sevoflurane with soda lime. [90] Two products are found in the closed anesthesia circuit. Pentafluoroisopropenyl fluoromethyl ether [CF_2 =C(CF_3)OCH_2 F; compound A] is the major degradation product detected. A proton presumably is abstracted from hydrogen on the isopropyl group of sevoflurane by soda lime in a manner that is similar to the base-catalyzed deprotonation of halothane by soda lime to yield difluorobromochloroethylene (CF_2 =CClBr). [47] Compound B [CH_3 OCF_2 CH(CF_3)OCH_2 F] is the minor degradation product detected in the anesthesia circuit and presumably results from the addition of methoxide ion (CH_3 O^-) produced from the interaction of methanol with soda lime to compound A.

TOXICITY

Mechanisms of Toxicity

Expression of drug toxicity is influenced by many factors. In this section, we focus on mechanisms of tissue injury that are most relevant to the inhaled anesthetics. Toxicity is a dose-dependent response, and there is a threshold that must be surpassed before toxicity is produced. Toxicity may be induced by any of a number of mechanisms, including the intracellular accumulation of metabolites in toxic amounts, the formation of haptens that can initiate systemic hypersensitivity or immune responses, the production of reactive intermediates that either adduct (form covalent bonds) to tissue macromolecules or initiate destructive free radical chain reactions, and the depletion of endogenous compounds that act as intracellular and extracellular antioxidants.

The threshold dose for toxicity may change, but what can be called the molecular threshold dose generally would be constant. Thus, it is the molecular dose at the target site that determines toxicity. This dose may be achieved because of increased metabolite production, altered tissue sequestration, or decreased excretion. Other drugs or chemicals, altered physiologic states, or pathologic states may also have an effect. When the concentration of a metabolite surpasses the intracellular threshold for toxicity (i.e., molecular threshold dose), tissue injury results from the direct or indirect actions of the metabolite. Direct toxicity may result from the inhibition or modification of enzymatic and structural systems necessary for maintaining cellular integrity (e.g., membrane transport systems). Indirect toxicity may result from interaction with an endogenous compound that elicits an immune response.

Possibly the most important drug-mediated mechanism of toxicity is the production of reactive intermediates during metabolism. [91] Reactive intermediates may initiate toxicity by covalently binding with tissue macromolecules to form adducts or by initiating free radical chain reactions. Although few drugs themselves are sufficiently reactive to form covalent bonds with cell macromolecules (e.g., intracellular proteins, enzymes, nucleic acids), some drugs, including several inhaled anesthetics, produce reactive intermediates during phase 1 metabolism. Binding of a reactive intermediate with tissue protein to produce a hapten-protein conjugate is one example of a potentially toxic covalent interaction. The conjugate may, in turn, induce the synthesis of drug-or metabolite-specific antibodies and may initiate hypersensitivity or immune responses. [92] The binding of reactive intermediates to tissue macromolecules may adversely affect cellular metabolism, protein synthesis, replication, or transport mechanisms by covalently binding to proteins, nucleic acids, and other cellular components. The chemically stable adducts formed may produce a variety of injuries such as necrosis, mutagenesis, teratogenesis, carcinogenesis, and drug allergies.

In addition to producing nucleophilic intermediates, metabolism may produce intermediates with single unpaired electrons in their outer molecular orbital shells, known as free radicals. These are short-lived but highly reactive intermediates that can initiate chain reactions and produce pathologic damage. [93] Once generated, free radicals react with cellular components producing polymerization or cross-linking of enzymes and proteins, auto-oxidation of lipids within the membranes, and damage to nucleic acids (e.g., main chain breaks in the nucleic acid strands or degradation of purine and pyrimidine rings). [94] Free radicals are generated during the normal course of cell metabolism (e.g., cytochrome P-450-mediated reactions, which continue to function in the absence of intracellular substrate by transferring electrons to cell lipids). The concentration of these radicals is stringently maintained, however, at less than 10^{-9} mol/L. [93] Tissue injury ensues in the presence of free radical reactions when the endogenous antioxidants responsible for scavenging free radicals are depleted. Thus, the depletion of glutathione and other sulfhydryl-containing compounds promotes tissue injury that may progress to cell death.

Reactions of free radical intermediates are generally assumed to be so rapid that no radicals escape the tissue in

which they are formed. Because inhaled anesthetics are strongly lipophilic, damage from their reactive intermediates would occur mainly in lipid membranes that are especially rich in unsaturated fatty acids. These unsaturated compounds are highly susceptible to damage because the presence of a double bond weakens the carbon-hydrogen bond of the alpha-methylene carbon atom (i.e., the carbon atom adjacent to the carbon with an unsaturated bond). Free radicals initiate peroxidation by abstracting hydrogen from the alpha-methylene carbon. [94] This results in rearrangement of double bonds and subsequent attack by oxygen. Unless terminated, oxidative damage will be transferred to adjacent fatty acids. Halothane and chloroform at anesthetizing concentrations *in vivo* stimulate lipoperoxidation in phenobarbital-pretreated rats and may initiate tissue damage by this mechanism. [95]

The detrimental effects of reactive intermediates on cellular integrity depend on the extent of free radical reactions, subsequent covalent binding, and the cellular functions that are impaired. The precise mechanism by which specific reactive intermediates initiate cellular injury is seldom clear because total binding of a reactive intermediate does not correlate well with the degree of toxicity. For example, although the metabolites of certain chemical carcinogens bind covalently to liver microsomes, there is no strict correlation between total adduction and cell damage. New investigative tools have helped to determine experimentally which specific cellular macromolecule is adducted. The difficulty still lies in determining which interaction is responsible for which tissue damage.

Organs and Organ Systems

Effects on the Liver

Drug-mediated hepatotoxicity ranges in severity from slight dysfunction to massive hepatic necrosis. The cause may be hepatocellular damage, cholestasis, interference with bilirubin metabolism, or immunologically mediated [91] tissue injury. Direct hepatotoxins, such as carbon tetrachloride and chloroform, cause dose-related, consistent, and reproducible hepatic cellular damage. Indirect hepatotoxins, such as erythromycin and cloxacillin, cause dose-independent and inconsistent hepatic injury resulting from hypersensitivity and humoral or cellular immunoreactions. [92]

The incidence and extent of hepatotoxicity directly attributable to inhaled anesthetics are difficult to determine. All anesthetic techniques reduce liver blood flow to some degree and may contribute to postoperative liver dysfunction. [96] Although studies of healthy volunteers find no evidence of hypoxia or anaerobic metabolism in the liver, this may not be the case for patients with preexisting liver damage or other illnesses. In general, surgical manipulation and the surgical site appear to be more important factors in decreasing liver blood flow than is the anesthetic agent or technique. [96] The liver may be predisposed to postoperative dysfunction and necrosis by chronic liver disease, viral infection (e.g., viral hepatitis and cytomegalovirus), septicemia, severe burns, nutritional deficiency, and previous or concomitant drug treatment. Traditional measures of liver function, serum enzymes, proteins, and bilirubin, and the alkaline phosphatase and the aminotransferases (i.e., aspartate aminotransferase and alanine aminotransferase) have stood the test of time for characterizing hepatic damage. Unfortunately, clinical tests available to assess liver function are for the most part crude, not tissue specific, and only reflect abnormalities in the presence of severe disorders.

The inhaled anesthetics may act as both direct and indirect hepatotoxins. Chloroform and fluroxene have direct hepatotoxic effects, and both have been discontinued for clinical use because of their hepatotoxicity. The hepatotoxic effects of these anesthetics, along with those of diethyl ether and cyclopropane, are discussed in an earlier edition of this chapter. Halothane was introduced into clinical practice in 1956, but it was not until 1963 that several clinical reports of postoperative jaundice

and liver necrosis were published. [97] [98] [99] The clinical and pathologic findings resembled those of the classic hepatotoxin, chloroform. These reports prompted a number of retrospective studies from which it was generally concluded that halothane was associated with the same incidence of postoperative hepatic damage as other anesthetics. Because some fault could be found in all the retrospective studies (e.g., lack of proper control groups or inadequate numbers), the National Halothane Study was conducted. [100] A committee reviewed retrospectively the incidence of fatal massive hepatic necrosis occurring in approximately 850,000 surgical patients. The incidence of massive hepatic necrosis associated with halothane was 7 of 250,000 halothane anesthetics or about 1 in 35,000, and not 1 in 10,000, as is sometimes reported. The committee concluded that "unexplained fever and jaundice in a specific patient following halothane might reasonably be considered a contraindication to subsequent use." Dykes and Bunker [101] commented that massive or intermediate hepatic necrosis was not documented for any patient in the study who was jaundiced after halothane administration and who died following subsequent halothane administration.

It is now clear that halothane is associated occasionally with liver damage in adults, especially after repeated administration. [102] [103] [104] Even children, once thought immune to "halothane hepatitis," are now known to be susceptible. [105] [106] The lack of a suitable animal model hampered early efforts to elucidate the mechanism of halothanemediated hepatotoxicity. Unlike chloroform and fluroxene, which produce fatty infiltration, centrilobular necrosis, and elevated transaminase values in experimental animals, halothane did not produce hepatotoxicity in early animal models. Even prolonged exposure to halothane did not consistently result in hepatic lesions. Animal models of halothane-mediated hepatotoxicity eventually were developed that proved useful in determining the role of biotransformation in hepatic injury. Centrilobular necrosis following halothane exposure under various conditions occurs in rats pretreated with Aroclor 1254 (a mixture of polychlorinated biphenyls), [46] isoniazid, [53] phenobarbital, [52] and triiodothyronine. [107] These early models are discussed in a previous edition of this chapter [32] and in a published review. [108] Localized hypoxia, disturbed calcium homeostasis, altered cellular metabolism and depletion of energy stores, and immune-mediated injury are all mechanisms that have been proposed to explain halothane hepatotoxicity.

Because halothane hepatitis is both rare and unpredictable, it was speculated that some patients are predisposed to the condition because they produce unusual

amounts of hepatotoxic metabolites or they experience an immunologic response that initiates hepatotoxicity. The latter mechanism was proposed to explain the increased frequency and the overall reduced latency of hepatitis following repeated halothane exposure. The clinical features often associated with halothane hepatitis, such as fever, rash, peripheral eosinophilia, and increased incidence and severity with multiple administrations, are also observed with allergic reactions. It now appears that there are two separate clinical entities: one is a mild hepatotoxicity occurring shortly following halothane exposure, and the other is a rare, severe, often fatal hepatotoxicity with delayed onset. The mild form of hepatotoxicity that may be experienced by as many as 20 percent of anesthetized patients is possibly the result of some form of direct toxicity that has been demonstrated by one or more of the animal models. The fulminant form, halothane hepatitis, currently is thought to be an immune-mediated toxicity.

Halothane is oxidatively metabolized by cytochrome P-450 to trifluoroacetyl chloride (CF_3COCl), an unstable and reactive intermediate that can covalently trifluoroacetylate several proteins of the endoplasmic reticulum. The trifluoroacetylated hepatic proteins are believed to be involved in the immune response leading to halothane hepatitis. The immunologic basis for halothane hepatitis has been discussed in several articles. [92] [108] [109] [110] The first human data suggestive of an immune-mediated mechanism came in 1980 when an antibody from the sera from 7 of 11 patients with fulminant hepatic necrosis following halothane exposure reacted with the surface of hepatocytes isolated from halothane-exposed rabbits. [111] Patients had circulating antibodies that recognize halothane-altered hepatic microsomal proteins (neoantigens). Some of these neoantigens have since been identified as trifluoroacetylated endoplasmic reticulum proteins. At least 8 halothane-induced hepatic antigens have been identified in halothane-exposed rabbits, rats, and humans. [109] [110] [111] [112] [113] [114] [115]

Trifluoroacetylated proteins (i.e., antigens) are expressed in all halothane-exposed patients, but only a small portion of this population mounts an immune response to the antigens leading to hepatotoxicity. In patients who develop halothane hepatitis, antibody responses are elicited to a variety of trifluoroacetylated and normal liver antigens. [115] The antigens can become translocated from the endoplasmic reticulum to the surface membrane. One intriguing possibility is that the trifluoroacetylated epitope can be mimicked by an endogenous substance. Two such proteins have been identified that cross-react with antibodies from halothane-exposed animals and patients. [109] It is suggested that altered self-tolerance may be related to halothane hepatitis.

Enflurane was first used in North America in 1966. Of the millions of enflurane anesthetics administered since that time, there are relatively few case reports of liver damage that have been associated with its use. In 1986, Eger et al [116] published reviews of ten published reports and several unpublished reports of liver damage after enflurane. Many of the cases were missing critical information on the duration of anesthetic exposure, histologic confirmation of hepatic lesions, and previous exposure to hepatic disease and hepatotoxic agents. In addition, several patients were hypotensive and in shock and underwent operations with known potential for hepatic dysfunction. These investigators concluded that the evidence did not support the existence of enflurane-induced hepatic dysfunction similar to that seen with halothane.

Several case reports suggested that enflurane anesthesia of halothane-sensitized patients resulted in hepatotoxicity. [117] [118] Covalently bound, acetylated protein adducts from halothane and enflurane-exposed rats were recognized by specific anti-trifluoroacetylated protein antibodies isolated from the sera of patients with halothane hepatitis. [119] This cross-reactivity suggests that enflurane has the potential to produce an immune-mediated hepatotoxic response. The protein adducts formed from enflurane would be similar to those of halothane and thus could act as antigens and cross-react with halothane antibodies, or vice versa. Because the metabolism of enflurane is significantly less than that of halothane, presumably fewer antigenic tissue adducts are formed with enflurane, with a correspondingly smaller likelihood of toxicity.

Stoelting et al [120] reported the assessment of the contribution of isoflurane to 45 cases of hepatic dysfunction following anesthesia that had been reported to the Food and Drug Administration of the United States. They concluded that current evidence did not support an association between isoflurane and postoperative hepatic dysfunction. In 1993, a case was reported in which a patient with an uneventful initial exposure to isoflurane anesthetic for cecopexy had repeated episodes of hepatitis after subsequent exposures to isoflurane. [121] The second isoflurane anesthetic for pyloroplasty was for a 2-hour period, and the third anesthetic for gastrojejunostomy was 30 minutes of isoflurane, followed by 150 minutes of enflurane. This patient had a far greater serum transaminase and alkaline phosphatase concentration after the second anesthetic than after the third. Unfortunately, as with many other cases, the evidence is suggestive but insufficient to draw firm conclusions.

The potential for hepatotoxicity caused by halothane, enflurane, and isoflurane is directly related to their relative degree of oxidative metabolism to acetylated protein adducts. Twenty percent of absorbed halothane is oxidatively metabolized *in vivo* to a reactive acetylated halide metabolite, whereas only 2 percent of enflurane and 0.2 percent of isoflurane are metabolized to reactive metabolites.

Methoxyflurane was introduced into clinical practice in the United States in 1960. Although none of the metabolites of methoxyflurane is known to be hepatotoxic, there have been a number of reports of hepatic dysfunction and death from hepatic coma following methoxyflurane exposure. In a review of 24 cases of methoxyflurane-associated hepatitis, Joshi and Conn [122] presented evidence for a syndrome similar to that described earlier for unexplained hepatitis following halothane administration. They concluded that a rare and indirect immunologic hepatic injury may occur that may have a direct effect on the liver by interfering with splanchnic circulation. In humans, the adverse minor changes in liver function appear to be reversible and may be related to dose. It is still unclear whether hepatic dysfunction, as measured by bromsulphalein retention and serum hepatic enzyme elevation, was the result of the depth and duration of the anesthetic exposure, the type of operation, the extent of preexisting hepatic disease, or methoxyflurane itself.

Studies of patients and volunteers do not suggest that desflurane is associated with hepatic toxicity in humans. [123] [124]

There is, however, one report of a patient who developed fulminant hepatitis 12 days after receiving a desflurane anesthetic. [125] This patient had been exposed to halothane, 10 and 18 years previously, for periods of less than an hour. There is a suggestion that this patient experienced desflurane-induced fulminant hepatitis, because desflurane is metabolized to a trifluoroacetyl chloride metabolite, as is halothane, and the serum antibodies from this patient reacted with trifluoroacetylated liver microsomal proteins. Not unexpectedly, because of the limited metabolism of desflurane, animal studies have produced little evidence for hepatotoxicity with desflurane under the same conditions that produce hepatotoxicity in 20 percent of isoflurane-exposed and 100 percent of halothane-exposed rats. [82]

There are no reports of sevoflurane and hepatic dysfunction. A clinical study of 50 surgical patients showed no significant changes in transaminases and hepatic function following 1 to 7 MAC-hours of sevoflurane anesthesia. [89] Sevoflurane exposure of untreated, phenobarbital-treated, and Aroclor 1254-treated rats likewise showed no significant changes in serum transaminases, liver triglycerides, or glutathione concentrations. [126] There are no case reports of hepatic necrosis following N_2O administration when hypoxia has been ruled out as a possible contributing factor. Several cases of hepatic necrosis have been reported, however, when N_2O was combined with intravenous barbiturate administration. [127] [128] Evidence suggests that N_2O has little potential for producing hepatotoxicity. Continuous exposure of rats to 20 percent N_2O for as long as 35 days produced no significant changes in liver serum enzymes or in glutathione content. [38]

Effects on the Kidney

Inhaled anesthetics depress renal function; they decrease urine flow, glomerular filtration rate, renal blood flow, and electrolyte excretion. These changes are usually secondary to effects on the cardiovascular, sympathetic, and endocrine systems and almost always return to normal shortly after anesthesia and surgery. If they persist for any length of time into the postanesthetic period, the cause is often a combination of factors such as prior existence of renal or cardiovascular disease, severe fluid and electrolyte imbalance, and the administration of mismatched blood; the choice of anesthetic is seldom an important factor. Such physiochemical responses should be recognized, but they are not true toxic reactions and are not considered further. Occasionally, however, the inorganic F^- that is released during metabolism of fluorinated anesthetics may be directly nephrotoxic. Methoxyflurane is the classic example, and although this agent is seldom used in clinical practice, its nephrotoxicity is discussed briefly as a basis for understanding the nephrotoxic potential of all current and future fluorinated anesthetics.

Methoxyflurane

Vasopressin-resistant polyuric renal insufficiency was first reported in 1966 in patients receiving prolonged methoxyflurane anesthesia for abdominal surgery. [129] Subsequently, evidence indicated that the causative agent was F^-. The evidence was based on three observations. First, serum F^- concentrations following methoxyflurane administration in humans show positive correlation with the degree of renal dysfunction. [130] Second, vasopressin-resistant polyuric renal insufficiency similar to that seen in humans after prolonged methoxyflurane anesthesia can be consistently elicited in male Fischer 344 rats injected with sodium F^-. [131] Finally, F^- is a potent inhibitor of many enzyme systems including those involving antidiuretic hormone. [132] Fischer 344 rats are excellent models for studying F^--induced nephropathy because they demonstrate renal changes following F^- administration similar to those seen in humans, including polyuria, hypernatremia, serum hyperosmolality, increased blood urea nitrogen and creatinine, and decreased blood urea nitrogen and creatinine clearances. Furthermore, they have about the same serum F^- threshold for renal dysfunction as do humans.

The extent of nephrotoxicity in general surgical patients has been correlated with peak serum F^- concentrations and methoxyflurane dose (in MAC-hours, that is, end-tidal concentration as a fraction of MAC times the duration of anesthesia, in hours). [133] After 2.5 to 3.0 MAC-hours of methoxyflurane, which corresponds to peak serum F^- concentrations of 50 to 80 mumol/L, patients had subclinical toxicity characterized by a delayed return to maximum preoperative urinary osmolality, elevated serum urate concentration, and decreased urate clearance. If a test of vasopressin resistance had been performed on these surgical patients, the threshold methoxyflurane dose and serum F^- concentration to produce subclinical toxicity undoubtedly would have been lower. After 5 MAC-hours of methoxyflurane, serum F^- concentrations were 90 to 120 mumol/L, and patients had well-established but mild nephrotoxicity manifested by serum hyperosmolality, hypernatremia, polyuria, and urinary hypo-osmolality. Seven to 9 MAC-hours of methoxyflurane led to serum F^- concentrations up to 175 mumol/L and marked nephrotoxicity.

Despite the overall correlation between nephrotoxicity and peak serum F^- concentrations, individual patients given the same methoxyflurane dose vary in their nephrotoxic susceptibility. Genetic heterogeneity, drug interaction, preexisting renal disease, and a host of other factors could account for differences observed among patients. For example, enzyme induction is clearly important; both Fischer 344 rats [134] and human volunteers [133] pretreated on a long-term basis with the classic enzyme inducer phenobarbital, show increased defluorination and nephrotoxicity. Other enzyme inducers such as phenytoin, [8] ethanol, [14] [15] and diazepam [16] also increase methoxyflurane defluorination in rats. One example of a drug interaction is the additive nephrotoxic effect seen in patients receiving both methoxyflurane and the aminoglycoside antibiotic, gentamicin. [135] The same effect is seen in Fischer 344 rats in which concurrent administration of methoxyflurane and gentamicin produces greater nephrotoxicity than expected from either drug alone. [136]

Enflurane

Enflurane defluorination may occasionally result in serum F^- concentrations high enough to produce mild renal impairment. In a study with Fischer 344 rats, 6 to 10 hours of 2.5 percent enflurane anesthesia produced a mild vasopressin-resistant polyuric renal dysfunction. [27] Peak serum

F^- concentrations were 40 to 57 mumol/L, just reaching the threshold for renal toxicity. Surgical patients rarely show renal dysfunction following enflurane anesthesia. [13] Although postoperative serum F^- concentrations are significantly higher than background concentrations, they seldom reach the threshold for nephrotoxicity. In comparison with methoxyflurane, serum F^- concentrations following enflurane anesthesia peak earlier and fall more rapidly, emphasizing the important role that lipid solubility has in determining total F^- production (Fig. 6-3) . In one study, peak serum F^- concentrations from nine surgical patients averaged 22.2 mumol/L following enflurane exposures averaging 2.7 MAC-hours. [137] The only controlled human study to show mild renal dysfunction following enflurane anesthesia involved 11 healthy volunteers. [138] After 9.6 MAC-hours of enflurane, maximum urinary osmolality following antidiuretic hormone administration was reduced from approximately 1,050 to 800 mOsm; mean serum F^- concentration was 33.6 mumol/L. The mild impairment of renal concentrating ability was not associated with hypernatremia, serum hyperosmolality, or increased serum creatinine or urea nitrogen and therefore was not regarded as clinically significant.

Some clinicians have speculated that enflurane administered to patients with significant preexisting renal disease could produce additional renal dysfunction. Such fears have not been borne out in studies of Fischer 344 rats with surgically induced chronic renal insufficiency. [139] [140] Furthermore, results of a study of patients with mild to moderate renal

Figure 6-3 Serum inorganic fluoride (F^-) concentrations before and after administration of methoxyflurane, sevoflurane, enflurane, isoflurane, and desflurane anesthesia. Following 2 to 3 MAC-hours of methoxyflurane, mean peak serum F^- concentration was 61 ± 8 mumol/L, which slowly declined. Sevoflurane anesthesia of 3.7 MAC-hours resulted in a mean peak F^- concentration of 30.6 ± 2.2 mumol/L, which declined more rapidly than methoxyflurane but remained elevated for several days. After 2.7 MAC-hours of enflurane, mean peak F^- concentrations were 22.2 ± 2.8 mumol/L, which also declined over several days. There was no increase and almost no increase in F^- concentrations following desflurane and isoflurane administrations, respectively.

insufficiency showed no clinically significant difference between preoperative and postoperative renal function following either enflurane or halothane administration. [141] Another concern with enflurane is that F^- concentrations, and hence the risk of nephrotoxicity, may be higher in obese patients. In one study, the peak serum F^- concentration in an obese patient weighing 130 kg was 52 mmol/L after 5 hours of exposure to enflurane. [137] In another study, peak serum F^- concentrations averaged 28 mmol/L in morbidly obese patients compared with 17 mmol/L in nonobese patients. [142] Studies have not been performed in humans to determine whether nephrotoxicity is more common in obese patients receiving enflurane, but such has been shown to be the case in obese Fischer 344 rats. [143]

Enzyme induction does not significantly increase enflurane defluorination measured *in vitro* [28] or in surgical patients [9] receiving common enzyme-inducing drugs such as ethanol, phenobarbital, and phenytoin. In contrast, prior long-term treatment with isoniazid may result in higher than expected serum concentrations of F^- and a transient urinary concentrating defect following enflurane anesthesia. Work with Fischer 344 rats has shown that, unlike phenobarbital and phenytoin, isoniazid significantly increases enflurane defluorination. [11] [12] In addition, a study of surgical patients has shown that approximately one-half of those patients treated with isoniazid on a long-term basis prior to enflurane anesthesia had significantly higher serum F^- concentrations than predicted, [13] but these were not sufficiently high or sufficiently sustained to produce clinically significant renal impairment. An unsubstantiated theory is that fast acetylators metabolize isoniazid and induce the cytochrome P-450 isozyme responsible for enflurane metabolism.

Isoflurane

Isoflurane, an isomer of enflurane, is defluorinated much less than enflurane. In nine surgical patients receiving, on average, 3 MAC-hours of isoflurane, mean peak serum F^- concentration measured 6 hours after anesthesia was only 4.4 mumol/L. [74] Thus, isoflurane should not be associated with F^- nephrotoxicity in most clinical situations. For patients having prolonged anesthesia with isoflurane, however, caution is warranted. In patients who received about 19 MAC-hours of isoflurane, peak plasma F^- levels were much higher in the isoflurane group compared with the halothane group. [144] In fact, 40 percent of patients administered isoflurane had peak plasma F^- levels greater than 50 mmol/L. Caution may also be warranted in obese patients, because in a rat model, peak serum F^- concentrations averaged 27 mmol/L after 4 hours' exposure. [143] Enzyme induction does not appear to be a problem with isoflurane because phenobarbital pretreatment of rats only slightly enhances isoflurane defluorination and does not produce clinically significant increases in F^- concentration. [28] Prolonged isoflurane administration has been investigated for uses outside the operating room. Isoflurane was investigated for its ef-fectiveness in long-term sedation of patients on mechanical ventilation. [145] [146] In the first study, the highest serum F^- concentration was measured for a 2-year-old child who received 73 MAC-hours of isoflurane and had a serum F^- of 37 mumol/L. [145] In the second study, pediatric patients on mechanical ventilation received isoflurane for 13 to

497 MAC-hours. The highest serum F^- concentration was 26.1 mumol/L, with no alterations in serum creatinine or osmolality. [146] Although it appears that isoflurane can be administered for very long periods without producing clinically significant serum F^- concentrations, there are influences on metabolism, and renal and hepatic functions should be carefully followed.

Sevoflurane

Sevoflurane is moderately defluorinated to approximately the same extent as that of enflurane. Results of clinical studies show that serum F^- concentrations often peak above 50 mmol/L even when sevoflurane is administered during surgery of average duration. [89] [147] Because of sevoflurane's low blood/gas solubility (0.69) and its rapid elimination, F^- concentrations fall very quickly after surgery, and renal toxicities are not expected from sevoflurane administration. Defluorination of sevoflurane is induced with phenobarbital, [8] [84] [148] isoniazid, [11] [12] and ethanol [15] in rats. *In vivo* studies have shown that although peak F^- levels are comparable to those with enflurane, sevoflurane has less nephrotoxic potential, as measured by maximum urine concentrating ability and the production of *N*-acetyl-beta-glucosaminidase, an indicator of renal tubular damage. [149] Numerous clinical studies of F^- production and nephrotoxic potential of sevoflurane have been performed and have been reviewed elsewhere. [150] Many of the same issues were addressed with sevoflurane as with enflurane, including serum and urinary F^- levels after prolonged exposure, [147] [149] [151] urine concentrating ability, [149] [151] [152] [153] effect of obesity, [152] and the effect of preexisting renal impairment. [154] The consensus from these studies is that sevoflurane has little potential for nephrotoxicity, a conclusion supported by its apparently safe administration to many millions of patients worldwide. There is, however, concern because a decomposition product of sevoflurane, compound A, is nephrotoxic in rats at ppm concentrations that could potentially be achieved in a low-flow system. [155] [156] The lesion has been described as corticomedullary tubular necrosis.

Desflurane

Clinical studies thus far performed with desflurane show no evidence of nephrotoxicity. Desflurane is extremely resistant to defluorination and serum F^- concentrations in surgical patients after exposure to desflurane are not increased above background concentrations. [82] [157] As expected from these findings, desflurane does not appear to be nephrotoxic. [123] [158]

Halothane

Halothane is not significantly defluorinated under normal clinical conditions and is not nephrotoxic. In patients who received about 19 MAC-hours of halothane, peak plasma F^- levels were much higher in the isoflurane group compared with the halothane group. [144] Defluorination is enhanced slightly in rats under conditions of hypoxia and enzyme induction, but not to an extent that would be associated with renal damage.

There is no doubt that F^- is the causative agent in anesthetic-induced nephropathy; however, the lack of correlation between peak serum F^- levels and nephrotoxicity following administration of newer anesthetics such as sevoflurane has led one investigator to suggest that intrarenal production of F^- is more important in the etiology of nephrotoxicity than the total body production of F^-. [60] This question is open to debate at this point in time, but one hopes that it will be resolved. If the intrarenal production of F^- has a significant influence on toxicity, then the renal cytochrome P-450 isozymes become very important in any design considerations for new fluorinated anesthetics.

Effects on Hematopoietic and Neurologic Systems

N_2O is the only anesthetic reported to produce hematologic toxicity and neurotoxicity with long-term administration. Both these toxicities are the result of the interaction of N_2O with vitamin B_{12} and the disruption of several pathways involved in one-carbon chemistry. The biochemical basis of this effect is the oxidation of the cobalt in vitamin B_{12} by a physicochemical reaction with N_2O that was previously discussed (see Eq. 6-9).

The time required to produce megaloblastic hematopoiesis with N_2O exposure varies among patients and perhaps depends on their general state of health. In healthy patients undergoing routine surgery, mild megaloblastic bone marrow changes are not seen after 6 hours, but they are seen after about 12 hours of exposure to 50 percent N_2O; after 24 hours of exposure, changes are marked. [159] Complete bone marrow failure can be expected after several days of continuous exposure. [160] Limited evidence suggests that N_2O produces bone marrow changes earlier in seriously ill patients. [161] Evidence also suggests that the bone marrow changes are preventable by pretreating patients with large doses of folinic acid. [159] This drug is converted to the 5,10-methylene tetrahydrofolate needed for thymidine synthesis (Fig. 6-4) .

The neurologic disease, subacute combined degeneration of the spinal cord, develops only after several months of daily exposure to N_2O. The symptoms and signs include numbness and paresthesia in the extremities, loss of balance and unsteady gait, impairment of touch, and muscle weakness. In the late 1970s, the disease was recognized to be similar to vitamin B_{12} deficiency, but treatment with vitamin B_{12} did not alleviate the symptoms or enhance recovery. [162] Thus, it occurs in those who abuse N_2O on a long-term basis and in those rare individuals who work for many months in an environment grossly contaminated with the gas. Dental personnel who are occasionally exposed to greater than 1,000 ppm waste N_2O in poorly ventilated dental operatories for long periods are particularly at risk. In one study, 3 of 20 dentists exposed to mean concentrations up to 4,600 ppm had abnormal bone marrow. [163] Personnel in modern scavenged operating suites, however, are rarely exposed to such conditions and would not be expected to have problems. Epidemiologic surveys confirm that dental, but not operating room, personnel have a higher incidence of neurologic

Figure 6-4 Conversion of methyltetrahydrofolate and homocysteine to tetrahydrofolate and methionine.

disease, although exposure to waste N_2O has not definitely been shown to be the cause. [164]

In humans and animals, there is an irreversible inactivation of the enzyme methionine synthase, which requires vitamin B_{12} in the completely reduced form to act as its coenzyme. Methionine synthase catalyzes the conversion of methyltetrahydrofolate and homocysteine to tetrahydrofolate and methionine (see Fig. 6-4) . Failure to produce these products has a number of biochemical consequences including reduced synthesis of thymidine, which is an essential DNA base. The clinical syndrome associated with oxidation of vitamin B_{12} is essentially the same as that seen in pernicious anemia: megaloblastic hematopoiesis and subacute combined degeneration of the spinal cord. The time required for inactivation of methionine synthase depends on the species. In rats exposed to 50 percent N_2O, the half-time of inactivation

is about 5 minutes. [165] Recovery of activity takes 3 to 4 days because of oxidation of the vitamin B_{12}, which is irreversible and covalently bound to the enzyme. Thus, new enzyme must be synthesized to restore activity. In humans, the half-life of inactivation is much longer than in rats, about 45 minutes. [165] Nevertheless, after several hours of routine anesthesia with N_2O, methionine synthase activity is very low. The decrease of thymidine synthesis takes somewhat longer to develop but also lasts several days. Experimental data suggest that there is a threshold concentration of about 1,000 ppm (0.1%) below which N_2O has no biochemical effect. [166]

Reproduction and Development

The inhaled anesthetics present potential for adverse reproductive and developmental effects for both patients administered inhaled anesthetics and health care personnel exposed to waste anesthetics. In the United States, at least 50,000 pregnant women (
1.6%) undergo anesthesia and surgery during gestation for indications unrelated to pregnancy. [167] Operations for ovarian cysts, acute appendicitis, mammary tumors, and repair of incompetent cervix are most common. The risk of unexpected abortion or premature labor clearly is higher following anesthesia. What is not immediately obvious is whether the patient's disease, surgery, anesthesia, or a combination of these is the precipitating cause. Perhaps an even greater concern is that anesthesia during pregnancy may lead to an increased incidence of congenital abnormalities in the offspring of the patient. To assess the incidence of various anesthesia-and surgery-related hazards occurring during pregnancy, at least five major and several minor studies have been performed. [168] [169] [170] [171] [172] [173] [174]

The most extensive and thorough study links and analyzes data from three Swedish health care registries, the Medical Birth Registry, the Registry of Congenital Malformations, and the Hospital Discharge Registry for the years 1973 to 1981. [174] Among the 720,000 pregnant patients whose records were examined, there were 5,405 operations performed. The adverse reproductive and developmental outcomes examined were stillbirths, early postnatal deaths, low birth weight, and congenital anomalies. Women who had an operation did not have an increased incidence of stillbirths or of congenital anomalies among offspring. In contrast, the incidence of postnatal death within 7 days of delivery was increased when an operation occurred during the second or third trimester but not during the first trimester. The incidence of low birth weight and premature delivery was increased regardless of the trimester in which an operation occurred. The cause of these hazards was not determined, although the finding that no particular type of operation or anesthesia was associated with a higher incidence of adverse

outcome suggests that the patient's disease played the major role in determining the outcome.

In recent years, the increasing popularity of *in vitro* fertilization has afforded some opportunity to study the effects of anesthetics on ova. Various anesthetic regimens have been examined for their effects on rates of fertilization and cleavage of oocytes, pregnancy, and carriage to term. Results for general anesthesia have been variable, although there is some consensus that regimens that include inhaled anesthetics produce adverse effects. [175] [176] In a well-controlled study of *in vitro* fertilization, no difference in fertilization or pregnancy rates was found between patients having isoflurane anesthesia with or without N_2O, a finding implying that short exposures to N_2O are not harmful. [177] A publication on transvaginal oocyte retrieval and reproductive outcome [178] reported that general anesthesia with N_2O in combination with opiates, barbiturates, and halothane resulted in significantly lower clinical pregnancy rates (14.5%) compared with patients receiving local anesthesia (23.7%) or epidural block (25.8%). There were no adverse effects reported for oocyte collection, embryo yield, or embryo transfer. *In vitro* test systems of *Drosophila* larvae, sea urchin eggs, and mice embryos have shown significant adverse effects on development. [179] The relevance of these findings to the human situation is unknown at this time; however, the amount of anesthetic encountered by these test systems would be significantly greater than would be encountered in scavenged operating rooms.

Several studies have examined the effects of the inhaled anesthetics on sperm. In the only study of human sperm, semen was collected from 46 anesthesiologists who had worked for a minimum of 1 year in a scavenged operating suite. [180] Semen from 26 residents beginning an anesthesia training program were used as controls. The concentration of sperm and the percentage of abnormally shaped sperm were not different between the two groups. Furthermore, sperm collected from 13 of the 26 residents after they had been working for 1 year was not different from the first sample. Studies of mice and rats under various experimental conditions have provided both positive and negative results, but insufficient information is available to permit extrapolation to humans. Thus, despite some suggestive animal data, inhaled anesthetics have not been shown to have significant effects on sperm in humans. However, the scope of both animal and human studies so far performed has been limited, and only moderate assurance of no effect has been achieved.

Twenty reports have been published of epidemiologic surveys that have examined the reproductive performance of operating room and dental personnel exposed to waste gases. [181] [182] [183] [184] [185] [186] [187] [188] [189] [190] [191] [192] [193] [194] [195] [196] [197] [198] [199] [200] Table 6-1 . lists the overall outcome of these surveys. An evaluation of the merits of each of these studies is beyond the scope of this chapter, which summarizes the outcomes. The interested reader is referred to a review of these studies. [201] In a review of many of the studies prior to 1978, an estimate was made of the relative risks for particular adverse health effects. [202] The magnitude of the relative risk for spontaneous abortion among exposed women was approximately 1.3. The increase was reported to be both consistent and statistically significant. For congenital abnormalities among offspring of anesthetic-exposed women, the relative risk was approximately 1.2. The overall data for wives of exposed males and for congenital abnormalities among their offspring were less consistent than the data for spontaneous abortion. For both spontaneous abortion and congenital abnormalities, the increases observed were small and could not be attributed to a specific cause. Exposure to waste anesthetic gases, viruses, roentgenograms, a variety of chemicals other than anesthetics, or a combination of these factors could have accounted for the positive results. Furthermore, most surveys had serious methodologic faults, including failure to verify the medical data supplied by respondents.

To resolve whether there were adverse effects that had not been appropriately acknowledged, in 1985 Buring et al [203] performed a meta-analysis of five studies [182] [183] [184] [186] [195] in which these investigators analyzed spontaneous abortion and congenital abnormalities among female physicians and nurses potentially exposed to waste anesthetics. Risk ratios were 1.3 (95% confidence interval [CI], 1.2-1.4) for spontaneous abortion and 1.2 (95% CI, 1.0-1.4) for congenital abnormalities, both of which were statistically significant. Response or recall bias or both, however, could explain these significant associations because most of the studies relied on voluntary responses and self-reported outcomes. One of the

TABLE 6-1 -- Results of Epidemiologic Surveys of Adverse Reproductive Effects Among Personnel Exposed to Waste Anesthetic Gases and Their Spouses

INVESTIGATORS (YEAR)	EXPOSED WOMEN		WIVES OF EXPOSED MEN	
	SPONTANEOUS ABORTION	*MAJOR ANOMALY IN OFFSPRING*	*SPONTANEOUS ABORTION*	*MAJOR ANOMALY IN OFFSPRING*
Askrog and Harvald [181] (1970)	Negative	--	Positive	--
Cohen et al [182] (1971)	Positive	Negative	--	--
Knill-Jones et al [183] (1972)	Negative	Positive	--	--
Rosenberg and Kirves [184] (1973)	Positive	Negative	--	--
Corbett et al [185] (1974)	--	Positive	--	--
American Society of Anesthesiologists [186] (1974)	Positive	Positive	Negative	Positive
Knill-Jones et al [188] (1975) (1) (2)	Positive Positive	Negative Positive	Negative Negative	Negative Positive
Cohen et al [187] (1975)	Positive	Positive	Positive	Negative
Pharoah et al [189] (1977)	Positive	Positive	--	--

Positive, statistically significant association; negative, no association; --, not examined

acknowledged shortcomings of these studies (i.e., the lack of a quantitative measure of exposure) was addressed in two more recent retrospective studies [199] [200] that

attempted to quantitate N_2O exposure among female dental assistants. These investigators reported that in unscavenged dental suites, exposure to more than 5 and 3 hours of N_2O per day, respectively, was associated with reduced fertility and increased spontaneous abortion rates.

A retrospective cohort study design, which is subject to both selection and recall bias, was used for the majority of epidemiologic studies listed in Table 6-1 . One of the weakest links in the epidemiologic studies of adverse reproductive and developmental outcomes following occupational anesthetic exposure is the lack of quantification of the extent and duration of anesthetic exposure. Data generally were collected by self-administered questionnaire without verification of either exposure or outcome. In addition, the extent and duration of exposure to waste anesthetics has decreased in recent years, so it is difficult to draw conclusions on the likely adverse effects of current anesthetic exposure based on these earlier studies at conditions of higher exposure. In the only three studies in which medical records were used to confirm medical data, negative results were obtained for a number of adverse reproductive effects including spontaneous abortion. [191] [195] [196]

In addition to problems in quantification of exposure, there is also a problem of identifying the cause of any congenital malformation that is observed. Although human development is remarkably consistent, it is not always perfect, and congenital malformations, both severe and trivial, are found in 2 to 4 percent of all births in countries in which records are kept. [204] There are many mechanisms involved in abnormal development (Table 6-2) . Some, such as mutations that result in specific biochemical abnormalities and chromosomal nondisjunction, are well established. (See the section on genotoxicity later in this chapter for a brief discussion of mutations.) Others, such as interference with abnormal cell membrane states, are less certain mechanisms of teratogenicity. Although the cause of most defects remains unknown, chemical teratogenesis in humans is well established (Table 6-3) . Because of the difficulty in identifying causes and investigating mechanisms in humans, sophisticated animal studies have been developed over the last 30 years for examining the teratogenicity of chemicals. The complete assessment of a chemical now involves examining its effect on mating behavior, fertility, embryonic and fetal wastage, congenital anomalies, and postnatal survival and behavior. Animal studies provide useful information, but they are limited because of the difficulty of extrapolating animal data to humans and the relatively low statistical power to detect the presence of a weak teratogen.

TABLE 6-2 -- Teratogenic Mechanisms

Mutation
Interference with cell division
Alteration of nucleic acid function
Removal of cell precursors and substrates
Lack of energy source
Enzyme inhibition
Change in cell membrane characteristics

The developmental effects of the inhaled anesthetics have also been extensively studied in animals in an attempt to control conditions that cannot be controlled in epidemiologic studies. These studies tried to control for the many factors (e.g., genetic variability, environment, diet) that could contribute to the background incidence of congenital malformations in humans. Studies of the inhaled anesthetics on reproductive processes of experimental animals have been conducted at both trace and subanesthetic concentrations to simulate occupational exposure and at anesthetic concentrations to simulate surgical exposure. The large number of such studies precludes a complete discussion in this chapter. The interested reader is referred to several reviews. [201] [205] [206] In general, N_2O is the only inhaled anesthetic that has been convincingly shown to be directly teratogenic to experimental animals, but only under experimental conditions that are considered extreme. High concentrations (50-75%) delivered to rats for 24-hour periods during organogenesis and low concentrations (0.1%) delivered to rats continuously throughout pregnancy result in an increased incidence of fetal resorptions and visceral and skeletal abnormalities. [207] [208] A particularly interesting abnormality produced by high N_2O exposure is situs inversus, in which there is a disturbance of the left/right body axis so that organs such as the heart are on the wrong side of the body. [209] Although effects in rodents are seen only after extended periods of continuous exposure, it is not known whether humans are more sensitive than rodents and would show effects after shorter periods of exposure.

The mechanisms that produce teratogenic effects with N_2O are slowly being revealed. The former leading theory was that inhibition of methionine synthase causes critical shortages of intracellular thymidine and, hence, DNA, which is needed by the rapidly growing embryo. Certainly, both decreased DNA synthesis and decreased total DNA content have been observed in embryos immediately after N_2O exposure. [210] [211] It now appears that lack of methionine rather than the lack of thymidine plays the critical role in all the adverse reproductive effects other than situs inversus. [212] Furthermore, an entirely different mechanism accounts for the situs inversus, namely, stimulation of alpha $_1$ -adrenergic receptors by N_2O. [213] The effect is mediated by activation of calmodulin kinase II but not phosphokinase C (PKC). [214] N_2O teratogenesis is being actively investigated, not only because of its relevance to patient and occupational safety, but also because N_2O can be used to determine the importance of vitamin B_{12} , folates, one-carbon chemistry, and the adrenergic system in developmental processes.

Halothane, enflurane, and isoflurane are also teratogenic to rodents, but only when they are administered at anesthetizing

TABLE 6-3 -- Known Human Chemical Teratogens[a]

Androgenic hormones (e.g., diethylstilbestrol)
Anticonvulsants (e.g., phenytoin)
Cancer chemotherapeutic agents (e.g., methotrexate)
Thalidomide
Organic mercury
Hypoglycemics (?) (e.g., tolbutamine)

[a] Account for only 2 to 3 percent of known causes of developmental defects in humans

concentrations for many hours on several days during pregnancy. Desflurane and sevoflurane have not been tested, but they are expected to have the same effects. The consensus is that the teratogenic effects observed in animals exposed to the inhaled anesthetics are caused by physiologic changes associated with anesthesia, rather than by inherent terotologic properties of the anesthetics themselves. Nonetheless, all findings emphasize the potential for anesthetics to interfere with developmental processes regardless of the mechanism.

Developmental toxicity also encompasses the cognitive and functional deficits that may occur in the absence of observable morphologic changes. Organ systems are most sensitive to chemical teratogens during periods of development (organogenesis). The central nervous system may be particularly vulnerable during the period of myelination. In humans, this period is from the fourth intrauterine month through the second postnatal year. Thus, a chemical or drug may produce behavioral teratogenesis if administered late in gestation or even after birth. Anesthetics have not escaped scrutiny as possible behavioral teratogens. A study of 1-day-old rats exposed to 0.75 or 1.0 percent halothane with or without 50 or 75 percent N_2O for 6 hours demonstrated dose-dependent decrements in PKC activity in growth cone particles isolated from the forebrains. [215] There were no effects at 0.5 percent halothane or 25 percent N_2O. Although the anesthetic concentrations causing effects were high, the importance of PKC in signal transductions in developing brain and the potential disruption by anesthetics cannot be ignored. To date, although some rodent studies have shown behavioral deficits following exposure to the inhaled anesthetics, [216] [217] [218] the mechanism for these changes is unknown, and the applicability to humans is unclear. In general, the anesthetic exposure conditions can be considered extreme relative to any reasonably expected human exposure.

Human studies have generally focused on long-term behavioral effects of maternal obstetric medication, including epidural anesthesia. Claims have been made that the medication given at delivery to the mother produces depressed motor skills and impaired language ability in the infant and child for several years. Such claims,

however, are controversial. Behavioral abnormalities of offspring whose mothers received inhaled anesthetics at any time during delivery have not been well studied. Furthermore, studies have not been done to assess neurobehavioral function of children of operating room personnel who have been exposed to waste anesthetic gases. Firm conclusions about the risk of the occurrence of behavioral teratogenesis among the offspring of exposed personnel or in exposed patients therefore await further investigation. If the number of scientific articles published can be regarded as a measure of scientific concern, the behavioral effects following *in utero* and perinatal exposure to the inhaled anesthetics do not appear to be a significant problem.

DNA, Genetics, and Neoplasia

The potential long-term adverse health effects from occupational exposure to trace concentrations of waste anesthetic gases have been recognized for more than 20 years. Even if inhaled anesthetics have a low potential for causing long-term toxicity, exposure of a large population may represent a considerable public health hazard. In the United States, about 50,000 hospital operating room personnel, including anesthesiologists, nurse anesthetists, and operating room technicians, are exposed daily to waste anesthetic gases. [167] In addition, surgeons, dental personnel, and veterinarians and their technical assistants have a variable but sometimes heavy exposure to waste anesthetics. The total number of exposed or potentially exposed personnel in the United States each year is about 225,000. [167] Of particular concern have been the reports that inhaled anesthetics possess mutagenic and carcinogenic potentials.

Genotoxicity

Investigators have been interested in the mutagenic potential of inhaled anesthetics for several reasons. First, many chemical carcinogens are also mutagens, although the reverse is not necessarily true. Thus, finding that a particular anesthetic is a mutagen also implies a potential for carcinogenesis that should be evaluated. Second, mutagens may pose a threat to the integrity of the human genome (the totality of genes and chromosomes).

Mutations are heritable changes in genetic information. Unrepaired mutations in germ cells can be passed from generation to generation. Unrepaired mutations in somatic cells can result in diseases including cancer. The four types of mutations traditionally recognized are base-pair mutations, frame-shift mutations, deletions or rearrangements of chromosomal segments, and nondisjunction of chromosomes between daughter cells. In addition, a fifth and novel type of mutation has been recognized that involves continuous repeats of three nucleotides at a specific site in a gene. [219] *In vitro* assays for mutagenicity require much less time and expense than *in vivo* tests for carcinogenicity, and these assays have become popular screening methods for detecting carcinogens. A wide variety of test systems has been used to examine the mutagenicity of inhaled anesthetics including assays with bacteria, yeast, mammalian cells in culture, and intact mammals. Most studies of the anesthetic agents have been reviewed elsewhere [206] and are only summarized here.

Extensive work has been done with the Ames *Salmonella*/mammalian hepatic microsome system, which uses several strains of histidine-dependent *S. typhimurium* as tester organisms. This system is a well-validated assay for mutagenicity and often is regarded as the standard against which other systems are compared. It has been used to test most currently and formerly used anesthetics. Only divinyl ether and fluroxene give unequivocally positive mutagenic responses, whereas trichloroethylene gives a weak mutagenic response. Other anesthetics including N_2O, halothane, and enflurane are not mutagenic when tested under a wide variety of experimental conditions and anesthetic concentrations. The finding that some mutagenic anesthetic metabolites have a chemical structure reminiscent of vinyl chloride (CH_2 =CHCl) is consistent with the known high reactivity and mutagenicity of this class of chemicals. Of the many inhaled anesthetic metabolites that have been tested in the *Salmonella* assay, only 1,1-difluoro-2-bromo-2-chloroethylene (CF_2 =CBrCl) and 1,1-difluoro-2-chloroethylene (CF_2 =CHCl) have been found to be

even weakly mutagenic. In general, results from numerous studies with other test systems have confirmed those from studies with *Salmonella.* [206] [220] Although there are some anomalous results, the overwhelming evidence from *in vitro* tests indicates that all currently used and most previously used anesthetics are not mutagens.

Genotoxicity studies of humans exposed to inhaled anesthetics have generally been negative. In an early study from 1977, [221] no significant difference in the number of chromosomal aberrations could be detected between the lymphocytes obtained from operating room nurses and those obtained from surgical outpatient nurses. Mutagenic activity was not detected in the *Salmonella* assay either for urine of personnel working in scavenged or unscavenged operating rooms or for urine of anesthesiology residents during the first 15 months of training. [222] Finally, lymphocytes from personnel exposed to waste anesthetic gases for durations up to 312 months had no higher incidence of chromosomal aberrations or sister chromatid exchange compared with lymphocytes from unexposed individuals. [223] This later study was an extension of previous negative studies by the same authors of sister chromatid exchanges in lymphocytes of operating room personnel exposed to waste anesthetic gases and of patients anesthetized with halothane, enflurane, or fluroxene. In contrast to these negative results, studies in 1990 [224] and 1992 [225] showed cytogenic damage in operating room personnel exposed to waste anesthetic gases. Another study, in 1993, [226] showed DNA single-strand breaks in lymphocytes of patients immediately after anesthesia with isoflurane/nitrous oxide. Why these differences in results exist among the studies is at present unknown, although positive results could be explained by multiple factors unassociated with the anesthetics. As with the teratogenicity and carcinogenicity studies described elsewhere in this chapter, genotoxicity studies of operating room personnel are more realistically studies of the work environment, which is composed of many chemical and physical agents as well as anesthetic gases.

Carcinogenicity

Chemical carcinogenesis is a multistage, multistep process leading to the formation of malignant tumors. There are two general classes of carcinogens: genotoxic and nongenotoxic. The former directly interacts with DNA, and the latter does not. Chemical carcinogenesis consists of three operationally defined stages: initiation, promotion, and progression (Fig. 6-5) . Genotoxic carcinogens are often referred to as *initiators* because, in interacting with DNA, they initiate the process in normal cells. Initiation is most often accomplished in several steps, the first of which is the metabolic activation of the chemical to a reactive intermediate. The second step consists of the covalent binding of the reactive intermediate to DNA. One or more cell divisions are required to "set" or "fix" the mutation. Before the mutation is fixed, the DNA may still be repaired. Initiation is accomplished only when the mutation is fixed. Once initiation has occurred, there is still no guarantee that a cell with defective DNA will survive a sufficiently long period to proceed in the process of carcinogenesis because initiated cells are also subject to apoptosis (natural cell death).

Figure 6-5 Multistage, multistep chemical carcinogenesis.

Nongenotoxic carcinogens, unlike genotoxic carcinogens, do not initiate cells. Nongenotoxic agents act through other mechanisms to promote the growth of initiated cells; thus, the term *promoter* is often applied to these carcinogens. These agents may interact with other cellular components to promote the growth of these cells. A common mechanism is increased rate of cellular proliferation preventing the normal repair process. One thing in common with these agents is that the promotion of initiated cells into tumors requires the continued presence of the promoter. Without its presence, apoptosis results in the elimination of single initiated cells and natural regression of the preneoplastic tumors. The terms initiator and promoter are used to indicate the state of carcinogenesis in which a chemical is first active. An initiator may also have activity as a promoter. The phase of progression that results in the appearance of clinically apparent tumors involves additional phenotypic and genotypic changes to cells resulting in karyotypic instability. These mechanisms are not understood, and many cancers appear to occur over a prolonged period.

Covalent binding of reactive intermediates to tissue macromolecules is presumed to be a necessary requirement for initiation of chemical carcinogenesis. Covalent binding, however, is not sufficient for initiation because the binding must be specific to a DNA site that would result in miscoding of a necessary gene product or a regulatory gene. As previously discussed, the mutation caused by covalent binding must also be "fixed" in the DNA by cell division. Current techniques can distinguish specific binding sites, but the older literature did not, thus giving the impression that any covalent binding was paramount to carcinogenesis.

Structural evaluation of chemicals for similarities to known carcinogens is useful to identify potential mutagens, but often minor changes in structure have profound effects on mutagenic and carcinogenic activity. Methoxyflurane, enflurane, and isoflurane are alpha-haloethers, as are the nonanesthetic but carcinogenic chemicals bis(chloromethyl)ether,

chloromethyl methyl ether, and bis(alpha-chloroethyl)ether. The anesthetics, however, are not mutagenic. Halothane is an alkyl halide, as are the animal carcinogens methyl iodide, butyl bromide, and butyl chloride. Halothane, however, is not mutagenic. Fluroxene and divinyl ether also contain the vinyl moiety similar to the human and animal carcinogen, vinyl chloride. Although the structural similarity between the anesthetics and several chemical carcinogens provides suggestive evidence for an association between anesthetics and carcinogenicity, there are no epidemiologic or other data to support that suggestion. Despite the obvious advantage of surveying human populations to determine the carcinogenic risk of exposure to anesthetics, such surveys have provided little information on the carcinogenicity of specific anesthetics. The primary reason is that the doses of anesthetics to which surveyed individuals have been exposed have not been measured and at best have been estimated. Nonetheless, the studies thus far performed should indicate whether waste anesthetics are associated with a higher incidence of cancer.

There have been several surveys of cancer incidence among operating room and dental workers (Table 6-4) . [186] [192] [198] [227] [228] [229] [230] [231] In the largest, the American Society of Anesthesiologists conducted a retrospective survey of 49,595 operating room personnel working throughout the United States. [186] A 1.3- to 1.9-fold increase in cancer incidence was noted among female members of the American Society of Anesthesiologists and the American Association of Nurse Anesthetists compared with unexposed control female groups. No increase in cancer incidence was seen among surveyed males. In an earlier study, the incidence of cancer among 525 female nurse anesthetists in Michigan was compared with that of women participating in the Connecticut Tumor Registry. [228] The nurse anesthetists had a higher incidence of malignancies diagnosed during 1971 than did all the women of Connecticut during 1966 to 1969. In another large study, a national survey of health among dental personnel was reported. [193] The study population consisted of 30,650 dentists and 30,547 chairside assistants and was readily divided into those who used or did not use inhaled anesthetics to provide pain relief and sedation of patients. Otherwise, both groups did similar work under similar conditions. An estimate of anesthetic exposure was made by noting the number of hours per week spent by each respondent in the dental operatory. About 80 percent of inhaled anesthetics users were exposed to N_2O alone, whereas the remainder were also exposed to potent volatile anesthetics. The cancer incidence among female chairside assistants exposed to waste anesthetics for more than 8 hours per week was 50 percent greater than among those not exposed, although the increase was not statistically significant ($P = .056$). Analysis of various types of cancer showed that only cancer of the cervix occurred more frequently ($P = .06$) in exposed women than in unexposed women. However, a more recent study (1990) of health effects associated with waste anesthetic exposure in Ontario hospital personnel did not show an increased cancer incidence for either men or women compared with unexposed controls. [198] Collectively, the foregoing studies of cancer incidence appear to suggest a small risk to women directly exposed to waste anesthetic gases. However, because of problems with study design and the small increase in cancer incidence observed, reviewers have generally been unconvinced of the existence of a hazard to humans. [202] [205] [206] This lack of conviction is strengthened by the uniformly negative results from surveys of deaths from cancer [192] [227] [229] [230] [231] (see Table 6-4) .

Problems in interpreting epidemiologic surveys led many investigators to turn to animal studies to provide information on the carcinogenic potential of specific anesthetics. In early studies, chloroform was found to be a rodent carcinogen when the drug was administered in very high doses by oral gavage, but this route of administration is not relevant to inhaled exposure of patients or operating room personnel. It is now recognized that hepatic tumorigenesis in rodents with chloroform is related to high-dose cytotoxicity and the subsequent increased rate of reparative proliferation. At lower doses, at which cytotoxicity is not present, tumor formation is absent. Indeed, when halothane, methoxyflurane, enflurane, isoflurane, and N_2O have been administered by inhalation and assessed in adequate studies, results for carcinogenicity have been uniformly negative. [232] [233] [234] [235] [236] [237] Parenthetically, in none of these studies was there evidence of other types of organ toxicity on histologic examination. The conclusion from both animal and human studies is that there is no carcinogenic risk from exposure to the currently used inhaled anesthetics.

TABLE 6-4 -- Epidemiologic Surveys for Cancer Incidence or Deaths Among Personnel Exposed to Waste Anesthetic Gases

STUDIED RESULT	POPULATION	RESULTS	INVESTIGATORS (YEAR)
Deaths	ASA Members	Negative	Bruce et al [227] (1968)
Incidence	Nurse anesthetists	3.3-fold increase for 1971	Corbett et al [228] (1973)
Incidence	ASA members	1.3 to 1.9-fold increase for women; negative for men	American Society of Anesthesiologists [186] (1974)
Deaths	ASA members	Negative	Bruce et al [229] (1974)
Deaths	Anesthetists	Negative	Doll and Peto [230] (1977)
Deaths	Anesthetists and offspring	Negative	Tomlin [192] (1979)
Incidence	Dental personnel	1.5-fold increase for women; negative for men	Cohen et al [193] (1980)
Deaths	Anesthetists	Negative	Neil et al [231] (1987)
Incidence	Operating room personnel	Negative	Guirguis et al [198] (1990)

ASA, American Society of Anesthesiologists

SUMMARY

In summary, the inhaled anesthetics are not chemically inert or innocuous. As is the case with all drugs, there are risks that accompany their use. Historically, there have been significant toxicities associated with anesthetics that were for the most part first observed in humans. As more has been learned about how chemicals act in biologic systems, anesthetics have been designed that are more chemically stable and more resistant to biodegradation. The result has been inhaled anesthetics that are less toxic. Overall, the current-day inhaled anesthetics are not very toxic. The identification of both acute and chronic toxicities in humans associated with the use of the inhaled anesthetics is difficult because of myriad confounding factors. As in any field of study, it is essential that no one study, whether positive or negative, is taken as the definitive answer, but rather that all available information is evaluated for merit. In evaluating studies and data related to the toxicity of the inhaled anesthetics, it is helpful to remember that certain widely accepted formal criteria need to be met before the association between any agent and any adverse health outcome can be accepted as likely to be causal. These criteria evaluate the strength of the association, the dose-response relationship, the specificity of the association, the appropriate temporal association, the consistency of the association across multiple studies, the biologic plausibility of the association, and the coherence of the evidence.

References

1. Porter TD, Coon MJ: Cytochrome P450: Multiplicity of isoforms, substrates, and catalytic and regulatory mechanisms. J Biol Chem 266:13469, 1991.

2. Guengerich F: Human cytochrome P450 enzymes. Life Sci 50:1471, 1992.

3. Quinn GP, Axelrod J, Brodie BB: Species, strain and sex differences in metabolism of hexobarbitone, amidopyrine, antipyrine and aniline. Biochem Pharmacol 1:152, 1958.

4. Boobis AR, Davis DS: Human cytochromes P450. Xenobiotica 14:151, 1984.

5. Guengerich FP: Cytochrome P450 enzymes and drug metabolism. In Bridges JW, Chasseaud LF, Gibson GG (eds): Progress in Drug Metabolism, vol 10. New York, Taylor and Francis, 1987, p 3.

6. Mazze RI, Hitt BA, Cousins MJ: Effect of enzyme induction with phenobarbital on the *in vivo* and *in vitro* defluorination of isoflurane and methoxyflurane. J Pharmacol Exp Ther 190:523, 1974.

7. Ross WT, Cardell RR: Proliferation of smooth endoplasmic reticulum and induction of microsomal drug-metabolizing enzymes after ether or halothane. Anesthesiology 8:325, 1978.

8. Caughey GH, Rice SA, Kosek JC et al: Effect of phenytoin (DPH) treatment on methoxyflurane metabolism in rats. J Pharmacol Exp Ther 210:180, 1979.

9. Dooley JR, Mazze RI, Rice SA et al: Is enflurane defluorination inducible in man? Anesthesiology 50:213, 1979.

10. Ivanetich KM, Lucas SA, Marsh JA: Enflurane and methoxyflurane: Their interaction with hepatic cytochrome P450 *in vitro*. Biochem Pharmacol 28:785, 1979.

11. Rice SA, Talcott RE: Effects of isoniazid treatment on selected hepatic mixed function oxidases. Drug Metab Dispos 7:260, 1979.

12. Rice SA, Sbordone L, Mazze RI: Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following isoniazid administration. Anesthesiology 53:489, 1980.

13. Mazze RI, Woodruff RE, Heerdt ME: Isoniazid-induced enflurane defluorination in humans. Anesthesiology 57:5, 1982.

14. Van Dyke RA: Enflurane, isoflurane, and methoxyflurane metabolism in rat hepatic microsomes from ethanol-treated animals. Anesthesiology 58:22, 1983.

15. Rice SA, Dooley JR, Mazze RI: Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following ethanol consumption. Anesthesiology 58:237, 1983.

16. Biermann JS, Rice SA, Gallagher EJ et al: Effect of diazepam treatment on hepatic microsomal anesthetic defluorinase activity. Arch Int Pharmacodyn Ther 283:181, 1986.

17. Waskell L: Metabolism of the volatile anesthetics. In Rice SA, Fish KJ (eds): Anesthetic Toxicity. New York, Raven Press, 1994, p 49.

18. Koop D: Oxidative and reductive metabolism by cytochrome P450-2E1. FASEB J 6:728, 1992.

19. Miller RE, Guengerich FP: Metabolism of trichloroethylene in isolated hepatocytes, microsomes and reconstituted enzyme systems containing cytochrome P450. Cancer Res 43:1145, 1983.

20. Cascorbi HF, Vessel ES, Blake DA: Genetic and environmental influence on halothane metabolism in twins. Clin Pharmacol Ther 12:50, 1971.

21. Parkinson A: Biotransformation of xenobiotics. In Klaassen CD (ed): Casarett & Doull's Toxicology: The Basic Science of Poisons, 5th ed. New York, McGraw-Hill, 1996, p 113.

22. Conney AH: Pharmacological implications of microsomal enzyme induction. Pharmacol Rev 19:317, 1967.

23. Snyder R, Remmer H: Classes of hepatic microsomal mixed function oxidase inducers. In Schenkman JB, Kupfer D (eds): Hepatic Cytochrome P450 Monooxygenase System. New York, Pergamon Press, 1982, p 227.

24. Linde HW, Berman ML: Nonspecific stimulation of drug-metabolizing enzymes by inhalation anesthetic agents. Anesth Analg 50:656, 1971.

25. Brown BR Jr, Sagalyn AM: Hepatic microsomal enzyme induction by inhalation anesthetics: Mechanism in the rat. Anesthesiology 40:152, 1974.

26. Duvaldestin P, Mazze RI, Nivoche Y et al: Occupational exposures to halothane results in enzyme induction in anesthetists. Anesthesiology 54:57, 1981.

27. Barr GA, Cousins MJ, Mazze RI et al: A comparison of the renal effects and metabolism of enflurane and methoxyflurane in Fischer 344 rats. J Pharmacol Exp Ther 190:530, 1974.

28. Hitt BA, Mazze RI: Effect of enzyme induction on nephrotoxicity of halothane related compounds. Environ Health Perspect 21:179, 1977.

29. Greene NM: Halothane anesthesia and hepatitis in a high risk population. N Engl J Med 289:304, 1973.

30. Ortiz de Montellano PR, Reich NO: Inhibition of cytochrome P450 enzymes. In Ortiz de Montellano PR (ed): Cytochrome P450: Structure, Mechanism, and Biochemistry. New York, Plenum Press, 1986, p 273.

31. Ivanetich KM, Lucas S, Marsh JA et al: Organic compounds, their interaction with and degradation of hepatic microsomal drug-metabolizing enzymes in vitro. Drug Metab Dispos 6:218, 1978.

32. Baden JM, Rice SA: Metabolism and toxicity. In Miller RD (ed): Anesthesia, 3rd ed. New York, Churchill Livingstone, 1990, p 135.

33. Banks RGS, Henderson RJ, Pratt JM: Reactions of gases in solution. III. Some reactions of nitrous oxide with transition metal complexes. J Chem Soc 3(A):2886, 1968.

34. Hong K, Trudell JR, O'Neill JR et al: Metabolism of nitrous oxide by human and rat intestinal contents. Anesthesiology 52:16, 1980.

35. Amess JAL, Burman JF, Rees GM et al: Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 2:339, 1978.

36. Drummond JT, Matthews RG: Nitrous oxide degradation by cobalamin-dependent methionine synthase: Characterization of the reactants and products in the inactivation reaction. Biochemistry

33:3732, 1994.

37. Van Dyke RA: Biotransformation. In Chenoweth MB (ed): Handbook of Experimental Pharmacology. New York, Springer-Verlag, 1972, p 345.

38. Rao GS, Meridian DJ, Tong YS et al: Biochemical toxicology of chronic nitrous oxide exposures. Pharmacologist 21:216, 1979.

39. Rice SA, Mazze RI, Baden JM: Effects of subchronic intermittent exposure to nitrous oxide in Swiss Webster mice. J Environ Pathol Toxicol Oncol 6:271, 1985.

40. Greunke LD, Konopka K, Koop DR et al: Characterization of halothane oxidation by hepatic microsomes and purified cytochromes P450 using a gas chromatographic mass spectrometric assay. J Pharmacol Exp Ther 246:454, 1988.

41. Lind R, Gandolfi A, Hall P: The role of oxidative biotransformation of halothane in the guinea pig model of halothane-associated hepatotoxicity. Anesthesiology 70:649, 1989.

42. Muller R, Stier A: Modification of liver microsomal lipids by halothane metabolites: A multinuclear NMR spectroscopic study. Arch Pharmacol 321:234, 1982.

43. Cohen E, Trudell J, Edmonds H et al: Urinary metabolites of halothane in man. Anesthesiology 43:392, 1975.

44. Maiorino RM, Sipes IG, Gandolfi AJ et al: Factors affecting the formation of chlorotrifluoroethane and chlorodifluoroethylene from halothane. Anesthesiology 53:383, 1981.

45. Baker MT, Nelson RM, Van Dyke RA: The release of inorganic fluoride from halothane and halothane metabolites by cytochrome P450, hemin, and hemoglobin. Drug Metab Dispos 1:308, 1983.

46. Sipes IG, Brown BR Jr: An animal model of hepatotoxicity associated with halothane anesthesia. Anesthesiology 45:622, 1976.

47. Sharp JH, Trudell JR, Cohen EN: Volatile metabolites and decomposition products of halothane in man. Anesthesiology 50:2, 1979.

48. Ahr HJ, King LJ, Nastainczk W et al: The mechanism of reductive dehalogenation of halothane by liver cytochrome P450. Biochem Pharmacol 31:383, 1982.

49. Van Dyke RA, Baker MT, Jansson I et al: Reductive metabolism of halothane by purified cytochrome P450. Biochem Pharmacol 37:2357, 1988.

50. De Groot H, Harnisch U, Noll T: Suicidal activation of microsomal cytochrome P450 by halothane under hypoxic conditions. Biochem Biophys Res Commun 107:885, 1982.

51. Clauberg G: Untersuchugen uber den Einfluss von Inhalationsnarkose und Operation auf die Leberfunktion unter besonderer Berucksichtigung des Halothans. Anaesthesist 19:324, 1970.

52. Jee R, Sipes IG, Gandolfi AJ et al: Factors influencing an animal model of halothane hepatotoxicity. Toxicol Appl Pharmacol 52:267, 1980.

53. Rice SA, Maze M, Smith CM et al: Halothane hepatotoxicity in Fisher 344 rats pretreated with isoniazid. Toxicol Appl Pharmacol 87:411, 1987.

54. Holaday DA, Rudofsky S, Treuhaft PS: Metabolic degradation of methoxyflurane in man. Anesthesiology 33:579, 1970.

55. Van Dyke RA, Wood CL: Metabolism of methoxyflurane: Release of inorganic fluoride in human and rat hepatic microsomes. Anesthesiology 39:613, 1973.

56. Yoshimura N, Holaday DA, Fiserova-Bergerova V: Metabolism of methoxyflurane in man. Anesthesiology 44:372, 1976.

57. Waskell L, Gonzales J: Dependence of microsomal methoxyflurane *O*-demethylation on cytochrome P450 reductase and the stoichiometry of fluoride ion and formaldehyde release. Anesth Analg 61:609, 1982.

58. Waskell L, Canova-Davis E, Philpot R et al: Identification of the enzymes catalyzing metabolism of methoxyflurane. Drug Metab Dispos 14:643, 1986.

59. Canova-Davis E, Chiang JY, Waskell L: Obligatory role of cytochrome b5 in the microsomal metabolism of methoxyflurane. Biochem Pharmacol 34:1907, 1985.

60. Kharasch ED, Hankins DC, Thummel KE: Human kidney methoxyflurane and sevoflurane metabolism: Intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. Anesthesiology 82:689, 1995.

61. Madelian V, Warren WA: Defluorination of methoxyflurane by a glutathione-dependent enzyme. Res Commun Chem Pathol Pharmacol 16:385, 1977.

62. Warren W, Madelian V: Defluorination of methoxyflurane by glutathione and coenzyme B_{12}. Res Commun Chem Pathol Pharmacol 35:515, 1982.

63. Wang S-L, Rice SA, Serra MT, Gross B: Purification and identification of rat cytosolic enzymes responsible for defluorination of methoxyflurane and fluoroacetate. Drug Metab Dispos 14:392, 1986.

64. Burke TR Jr, Martin JL, George JW et al: Investigation of the mechanisms of defluorination of enflurane in rat liver microsomes with specifically deuterated derivatives. Biochem Pharmacol 29:1623, 1980.

65. Garton KJ, Yuen P, Meinwald J et al: Stereoselective metabolism of enflurane by human liver cytochrome P450 2E1. Drug Metab Dispos 23:1426, 1995.

66. Burke TR, Branchflower RV, Lees DE et al: Mechanism of defluorination of enflurane: Identification of an organic metabolite in rat and man. Drug Metab Dispos 9:19, 1981.

67. Miller MS, Gandolfi AJ: Enflurane biotransformation in humans. Life Sci 27:1465, 1980.

68. Christ DD, Satoh H, Kenna JG et al: Potential metabolic basis for enflurane hepatitis and the apparent cross-sensitization between enflurane and halothane. Drug Metab Dispos 16:135, 1988.

69. Hoffman J, Konopka K, Buckhorn C et al: Ethanol-inducible cytochrome P450 in rabbits metabolizes enflurane. Br J Anaesth 63:103, 1989.

70. Thummel K, Kharasch E, Podoll T et al: Human liver microsomal enflurane defluorination catalyzed by cytochrome P450 2E1. Drug Metab Dispos 21:350, 1993.

71. Wrighton S, Thomas P, Molowa D et al: Characterization of ethanol-inducible human liver *N*-nitrosodimethylamine demethylase. Biochemistry 25:6731, 1986.

72. Baden JM, Rice SA, Wharton RS et al: Metabolic and toxicologic studies with enflurane in Swiss/ICR mice. J Environ Pathol Toxicol 4:293, 1980.

73. Hitt BA, Mazze RI, Cousins MJ: Metabolism of isoflurane in Fischer 344 rats and man. Anesthesiology 40:62, 1974.

74. Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. Anesthesiology 40:536, 1974.

75. Holaday DA, Fiserova-Bergerova V, Latto IP et al: Resistance of isoflurane to biotransformation in man. Anesthesiology 54:383, 1981.

76. Eger EI II: Stability of I-653 in soda lime. Anesth Analg 66:983, 1987.

77. Kharasch ED, Thummel KE: Identification of cytochrome P450 2E1 as the predominant enzyme catalyzing human liver microsomal defluorination of sevoflurane, isoflurane, and methoxyflurane. Anesthesiology 79:795, 1993.

78. Koblin DD, Eger EI, Johnson BH et al: I-653 resists degradation in rats. Anesth Analg 67:534, 1988.

79. Bradshaw J, Ivanetich K: Isoflurane: A comparison of its metabolism by human and rat hepatic cytochrome P450. Anesth Analg 63:805, 1984.

80. Rice SA, Baden JM, Kundomal YR: Effects of subchronic intermittent exposure to isoflurane in Swiss Webster mice. J Environ Pathol Toxicol Oncol 6:285, 1986.

81. Sutton TS, Koblin DD, Gruenke LD et al: Fluoride metabolites after prolonged exposure of volunteers and patients to desflurane. Anesth Analg 73:180, 1991.

82. Eger EI II, Johnson BH, Strum DP et al: Studies of the toxicity of I-653, halothane, and isoflurane in enzyme-induced, hypoxic rats. Anesth Analg 66:1227, 1987.

83. Cook TL, Beppu WJ, Hitt BA et al: Renal effects and metabolism of sevoflurane in Fischer 344 rats: An *in vivo* and *in vitro* comparison with methoxyflurane. Anesthesiology 43:70, 1975.

84. Cook TL, Beppu WJ, Hitt BA et al: A comparison of renal effects and metabolism of sevoflurane and methoxyflurane in enzyme induced rats. Anesth Analg 54:829, 1975.

85. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 54:100, 1981.

86. Kharasch ED, Karol MD, Lanni C et al: Clinical sevoflurane metabolism and disposition. I. Sevoflurane and metabolite pharmacokinetics. Anesthesiology 82:1369, 1995.

87. Kharasch ED, Armstrong AD, Gunn K et al: Clinical sevoflurane metabolism and disposition. II. The role of cytochrome P450 2E1 in fluoride and hexafluoroisopropanol formation. Anesthesiology 82:1379, 1995.

88. Kikuchi H, Morio M, Fujii K et al: Clinical evaluation and metabolism of sevoflurane in patients. Hiroshima J Med Sci 36:93, 1987.

89. Frink EJ, Ghantous H, Malan TP et al: Plasma inorganic fluoride with sevoflurane anesthesia: Correlation with indices of hepatic and renal function. Anesth Analg 74:231, 1992.

90. Hanaki C, Fujii K, Morio M et al: Decomposition of sevoflurane by soda lime. Hiroshima J Med Sci 36:61, 1987.

91. Gregus Z, Klaassen CD: Mechanisms of toxicity. In Klaassen CD (ed): Casarett & Doull's Toxicology. The Basic Science of Poisons, 5th ed. New York, McGraw-Hill, 1996, p 35.

92. Pohl LR, Satoh H, Christ DD et al: The immunologic and metabolic basis of drug hypersensitivities. Annu Rev Pharmacol Toxicol 28:367, 1988.

93. Pryor WA: Free radical reactions and their importance in biochemical systems. FASEB J 32:1862, 1973.

94. Bus JS, Gibson JE: Lipid peroxidation and its role in toxicology. Rev Biochem Toxicol 1:125, 1979.

95. Brown BR Jr: Hepatic microsomal lipoperoxidation and inhalational anesthetics: A biochemical and morphologic study in the rat. Anesthesiology 36:458, 1972.

96. Gelman SI: Disturbances in hepatic blood flow during anesthesia and surgery. Arch Surg 111:881, 1976.

97. Brody GL, Sweet RB: Halothane anesthesia as a possible cause of massive hepatic necrosis. Anesthesiology 24:29, 1963.

98. Bunker JP, Blumenfeld CM: Liver necrosis after halothane anesthesia. Cause or coincidence? N Engl J Med 268:531, 1963.

99. Lindenbaum J, Leifer E: Hepatic necrosis associated with halothane anesthesia. N Engl J Med 268:525, 1963.

100. Subcommittee on the National Halothane Study of the Committee on Anesthesia, National Academy of Sciences-National Research Council: Summary of the National Halothane Study: Possible association between halothane anesthesia and postoperative necrosis. JAMA 197:775, 1966.

101. Dykes MHM, Bunker JP: Hepatotoxicity and anesthetics. Pharmacol Physicians 4:15, 1970.

102. Bottinger LE, Dalen E, Hallen B: Halothane-induced liver damage: An analysis of the material reported to the Swedish Adverse Drug Reaction Committee 1966-1973. Acta Anaesthesiol Scand 20:40, 1976.

103. Moult PJA, Sherlock S: Halothane related hepatitis: A clinical study of twenty-six cases. Q J Med 173:99, 1975.

104. Walton B, Simpson BR, Strunin L et al: Unexplained hepatitis following halothane. BMJ 1:1171, 1976.

105. Walton B: Halothane hepatitis in children. Anaesthesia 41:575, 1986.

106. Kenna JG, Neuberger J, Mieli-Vergani G et al: Halothane hepatitis in children. BMJ 294:1209, 1987.

107. Uetrecht J, Wood AJJ, Phythyon JM et al: Contrasting effects on halothane hepatotoxicity in the phenobarbital-hypoxia and triiodothyronine model: Mechanistic implications. Anesthesiology 59:196, 1983.

108. Baker MT, Van Dyke RA: Hepatotoxicity of halogenated anesthetics. In Rice SA, Fish KJ (eds): Anesthetic Toxicity. New York, Raven Press, 1994, p 73.

109. Gut J, Christen U, Frey N et al: Molecular mimicry in halothane hepatitis: Biochemical and structural characterization of lipoylated autoantigens. Toxicology 97:199, 1995.

110. Van Pelt FN, Straub P, Manns MP: Molecular basis of drug-induced immunological liver injury. Semin Liver Dis 15:283, 1995.

111. Vergani D, Mieli-Vergani G, Albert A et al: Antibodies to the surface of halothane-altered rabbit hepatocytes in patients with severe halothane-associated hepatitis. N Engl J Med 303:66, 1980.

112. Davis M, Eddleston ALWF, Neuberger JM et al: Halothane hepatitis. N Engl J Med 303:1123, 1980.

113. Kenna JG, Satoh H, Christ DD et al: Metabolic basis for a drug hypersensitivity: Antibodies in sera from patients with halothane hepatitis recognize liver neoantigens that contain the trifluoroacetyl group derived from halothane. J Pharmacol Exp Ther 245:1103, 1988.

114. Knight TL, Scatchard KM, Van Pelt F et al: Sera from patients with halothane hepatitis contain antibodies to halothane-induced liver antigens which are not detectable by immunoblotting. J Pharmacol Exp Ther 270:1325, 1994.

115. Kitteringham NR, Kenna JG, Park BK: Detection of autoantibodies directed against human hepatic endoplasmic reticulum in sera from patients with halothane-associated hepatitis. Br J Clin Pharmacol 40:379, 1995.

116. Eger EI II, Smuckler EA, Ferrell LD et al: Is enflurane hepatotoxic? Anesth Analg 65:21, 1986.

117. Sadove MS, Reis L, Askin SH, Freckner GN et al: Hepatitis after use of two different fluorinated anesthetic agents. Anesth Analg 53:336, 1974.

118. Sigurdsson J, Hriedarsson AB, Theodleifsson B: Enflurane hepatitis: A report of a case with a previous history of halothane hepatitis. Acta Anaesthesiol Scand 29:495, 1985.

119. Christ DD, Kenna JG, Kammerer W et al: Enflurane metabolism produces covalently bound liver adducts recognized by antibodies from patients with halothane hepatitis. Anesthesiology 69:833, 1988.

120. Stoelting RK, Blitt CD, Cohen PJ et al: Hepatic dysfunction after isoflurane anesthesia. Anesth Analg 66:147, 1987.

121. Scheider DM, Klygis LM, Tsang TK et al: Hepatic dysfunction after repeated isoflurane administration. J Clin Gastroenterol 17:168, 1993.

122. Joshi PH, Conn HO: The syndrome of methoxyflurane associated hepatitis. Ann Intern Med 80:395, 1974.

123. Jones RM, Koblin DD, Cashman JN et al: Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653). Br J Anaesth 64:482, 1990.

124. Wrigley SR, Fairfield JE, Jones RM et al: Induction and recovery characteristics of desflurane in day case patients: A comparison with propofol. Anaesthesia 46:615, 1991.

125. Martin JL, Plevak DJ, Flannery KD et al: Hepatoxicity after desflurane anesthesia. Anesthesiology 83:1125, 1995.

126. Lynch S, Martis L, Woods E: Evaluation of hepatotoxic potential of sevoflurane in rats. Pharmacologist 21:221, 1979.

127. Gingrich TF, Virtue RW: Postoperative liver damage: Is anesthesia involved? Surgery 57:241, 1965.

128. Herber R, Specht NW: Liver necrosis following anesthesia. Arch Intern Med 115:266, 1965.

129. Crandell WB, Pappas SG, MacDonald A: Nephrotoxicity associated with methoxyflurane anesthesia. Anesthesiology 27:591, 1966.

130. Mazze RI, Shue GL, Jackson SH: Renal dysfunction associated with methoxyflurane anesthesia: A randomized prospective clinical evaluation. JAMA 216:278, 1971.

131. Mazze RI, Cousins MJ, Kosek JC: Dose-related methoxyflurane nephrotoxicity in rats: A biochemical and pathologic correlation. Anesthesiology 36:571, 1972.

132. Smith FA (ed): Handbook of Experimental Pharmacology: Pharmacology of Fluorides. New York, Springer-Verlag, 1970.

133. Cousins MJ, Mazze RI: Methoxyflurane nephrotoxicity: A study of dose response in man. JAMA 225:1611, 1973.

134. Cousins MJ, Mazze RI, Kosek JC et al: The etiology of methoxyflurane nephrotoxicity. J Pharmacol Exp Ther 190:530, 1974.

135. Mazze RI, Cousins MJ: Combined nephrotoxicity of gentamicin and methoxyflurane anesthesia in man: A case report. Br J Anaesth 45:394, 1973.

136. Barr GA, Mazze RI, Cousins MJ et al: An animal model for combined methoxyflurane and gentamicin nephrotoxicity. Br J Anaesth 45:306, 1973.

137. Cousins MJ, Greenstein LR, Hitt BA et al: Metabolism and renal effects of enflurane in man. Anesthesiology 44:44, 1976.

138. Mazze RI, Calverley RK, Smith NT: Inorganic fluoride nephrotoxicity: Prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46:265, 1977.

139. Sievenpiper TS, Rice SA, McClendon F et al: Renal effects of enflurane anesthetics in Fischer 344 rats with pre-existing renal insufficiency. J Pharmacol Exp Ther 211:36, 1979.

140. Fish K, Sievenpiper TS, Rice SA et al: Renal function in Fischer 344 rats with chronic renal impairment after the administration of enflurane and gentamicin. Anesthesiology 53:481, 1980.

141. Mazze RI, Sievenpiper TS, Stevenson J: Renal effects of enflurane and halothane in patients with abnormal renal function. Anesthesiology 60:161, 1984.

142. Bentley JB, Vaughan RW, Miller MS et al: Serum inorganic fluoride levels in obese patients during and after enflurane exposure. Anesth Analg 58:409, 1979.

143. Rice SA, Fish KJ: Anesthetic metabolism and renal function in obese and nonobese Fischer 344 rats following enflurane or isoflurane anesthesia. Anesthesiology 65:28, 1986.

144. Murray JM, Trinick TR: Plasma fluoride concentrations during and after prolonged anesthesia: A comparison of halothane and isoflurane. Anesth Analg 74:236, 1992.

145. Troug RD, Rice SA: Inorganic fluoride and prolonged isoflurane anesthesia in the intensive care unit. Anesth Analg 69:843, 1989.

146. Arnold JH, Troug RD, Rice SA: Prolonged administration of isoflurane to pediatric patients during mechanical ventilation. Anesth Analg 76:520, 1993.

147. Kobayashi Y, Ryoichi O, Takeda J et al: Serum and urinary inorganic fluoride concentrations after prolonged inhalation of sevoflurane in humans. Anesth Analg 74:753, 1992.

148. Malan TP, Kadota Y, Mata H et al: Renal function after sevoflurane or enflurane anesthesia in the Fischer 344 rat. Anesth Analg 77:817, 1994.

149. Frink EJ, Malan TP, Isner J et al: Renal concentrating function with prolonged sevoflurane or enflurane anesthesia in volunteers. Anesthesiology 80:1019, 1994.

150. Malan TP: Sevoflurane and renal function. Anesth Analg 81:S39, 1995.

151. Nishiyama T, Hirasaki A: Effects of sevoflurane anesthesia on renal function: Duration of administration and area under the curve and rate of decrease of serum inorganic fluoride. Eur J Anaesthesiol 12:477, 1995.

152. Frink EJ, Malan TP, Brown EA et al: Plasma inorganic fluoride levels with sevoflurane anesthesia in morbidly obese and non obese patients. Anesth Analg 76:1333, 1993.

153. Higushi H, Arimura S, Sumikura H et al: Urine concentrating ability after prolonged sevoflurane anesthesia. Br J Anaesth 73:239, 1994.

154. Conzen PF, Nuscheler M, Melotte A et al: Renal function and serum fluoride concentrations in patients with stable renal insufficiency after anesthesia with sevoflurane or enflurane. Anesth Analg 81:569, 1995.

155. Gonsowski CT, Laster MJ, Eger EI et al: Toxicity of Compound A in rats: Effect of increasing duration of administration. Anesthesiology 80:566, 1994.

156. Kandel L, Laster MJ, Eger EI et al: Nephrotoxicity in rats undergoing a one-hour exposure to Compound A. Anesth Analg 81:559, 1995.

157. Smiley RM, Ornstein E, Pantuck EJ et al: Metabolism of desflurane and isoflurane to fluoride ion in surgical patients. Can J Anaesth 38:965, 1991.

158. Weiskopt RB, Eger EI, Ionescu P et al: Desflurane does not produce hepatic or renal injury in human volunteers. Anesth Analg 74:570, 1992.

159. O'Sullivan H, Jennings F, Ward K et al: Human bone marrow biochemical function and megaloblastic hematopoiesis after nitrous oxide anesthesia. Anesthesiology 55:645, 1981.

160. Lassen HCA, Hinriksen E, Neukirch F et al: Treatment of tetanus: Severe bone marrow depression after prolonged nitrous oxide anaesthesia. Lancet 1:527, 1956.

161. Amos RJ, Amess JAL, Hinds CJ et al: Incidence and pathogenesis of acute megaloblastic bone marrow change in patients receiving intensive care. Lancet 2:835, 1982.

162. Layzer RB: Myeloneuropathy after prolonged exposure to nitrous oxide. Lancet 2:1227, 1978.

163. Sweeney B, Bingham RM, Amos RJ et al: Toxicity of bone marrow in dentists exposed to nitrous oxide. BMJ 291:567, 1985.

164. Brodsky JB, Cohen EN, Brown BW Jr et al: Exposure to nitrous oxide and neurologic disease among dental professionals. Anesth Analg 60:297, 1981.

165. Royston BD, Nunn JF, Weinbren HK et al: Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. Anesthesiology 68:213, 1988.

166. Sharer NM, Nunn JF, Royston JP et al: Effects of chronic exposure to nitrous oxide on methionine synthase activity. Br J Anaesth 5:693, 1983.

167. National Institute for Occupational Safety and Health (NIOSH): Criteria for a recommended standard ... occupational exposure to waste anesthetic gases and vapors. NIOSH Publ No 77-140. Washington, DC, NIOSH, 1977.

168. Smith BE: Fetal prognosis after anesthesia during gestation. Anesth Analg 42:521, 1963.

169. Shnider SM, Webster GM: Maternal and fetal hazards of surgery during pregnancy. Am J Obstet Gynecol 92:891, 1965.

170. Brodsky JB, Cohen EN, Brown BW et al: Surgery during pregnancy and fetal outcome. Am J Obstet Gynecol 8:1165, 1980.

171. Aldridge LM, Tunstall ME: Nitrus oxide and the fetus: A review and the results of a retrospective study of 175 cases of anesthesia for insertion of Shirodkar suture. Br J Anaesth 58:1348, 1986.

172. Crawford JS, Lewis M: Nitrous oxide in early human pregnancy. Anaesthesia 41:900, 1986.

173. Duncan PG, Pope WDB, Cohen MM et al: Fetal risk of anesthesia and surgery during pregnancy. Anesthesiology 64:790, 1986.

174. Mazze RI, Kallen B: Reproductive outcome after anesthesia and operation during pregnancy: A registry study of 5405 cases. Am J Obstet Gynecol 161:1178, 1989.

175. Hayes MF, Sacco AG, Savoy-Moore RT et al: Effect of general anesthesia on fertilization and cleavage of human oocytes *in vitro.* Fertil Steril 48:975, 1987.

176. Critchlow BM, Ibrahim Z, Pollard BJ: General anaesthesia for gamete intra-fallopian transfer. Eur J Anaesthesiol 8:381, 1991.

177. Rosen MA, Roizen MF, Eger EI II et al: The effects of nitrous oxide on *in vitro* fertilization success rate. Anesthesiology 67:42, 1987.

178. Gonen O, Shulman A, Ghetler Y et al: The impact of different types of anesthesia on *in vitro* fertilization-embryo transfer treatment outcome. J Assist Reprod Genet 12:678, 1995.

179. Rice SA: Reproductive and developmental toxicity of anesthetics in animals. In Rice SA, Fish KJ (eds): Anesthetic Toxicity. New York, Raven Press, 1994, p 157.

180. Wyrobeck AJ, Brodsky J, Gordon L et al: Sperm studies in anesthesiologists. Anesthesiology 55:527, 1981.

181. Askrog V, Harvald B: Teratogen effect of inhalation anesthetics. Nord Med 83:498, 1970.

182. Cohen EN, Bellvile JW, Brown BW: Anesthesia, pregnancy and miscarriage: A study of operating room nurses and anesthetists. Anesthesiology 35:343, 1971.

183. Knill-Jones RP, Moir DB, Rodrigues LV et al: Anaesthetic practice and pregnancy: A controlled study of women anesthetists in the United Kingdom. Lancet 1:1326, 1972.

184. Rosenberg P, Kirves A: Miscarriages among operating theatre staff. Acta Anaesthesiol Scand 53:37, 1973.

185. Corbett TH, Cornell RG, Endres JL et al: Birth defects among children of nurse anesthetists. Anesthesiology 41:341, 1974.

186. American Society of Anesthesiologists: Report of an ad hoc committee on the effect of trace anesthetics on the health of operating room personnel. Occupational disease among operating room personnel: A national study. Anesthesiology 41:321, 1974.

187. Cohen EN, Brown BW, Bruce DL et al: A survey of anesthetic health hazards among dentists. J Am Dent Assoc 90:1291, 1975.

188. Knill-Jones RP, Newman BJ, Spence AA: Anaesthetic practice and pregnancy: Controlled survey of male anaesthetists in the United Kingdom. Lancet 2:807, 1975.

189. Pharoah PO, Alberman E, Doyle P: Outcome of pregnancy among women in anaesthetic practice. Lancet 1:34, 1977.

190. Rosenberg PH, Vanttinen H: Occupational hazards to reproduction and health in anaesthetics and paediatricians. Acta Anaesthesiol Scand 22:202, 1978.

191. Ericson A, Kallen B: Survey of infants born in 1973 or 1975 to Swedish women working in operating rooms during their pregnancies. Anesth Analg 58:302, 1979.

192. Tomlin PJ: Health problems of anaesthetists and their families in the West Midlands. BMJ 1:779, 1979.

193. Cohen EN, Brown BW, Wu M: Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 101:21, 1980.

194. Lauwerys R, Siddons M, Mison CB et al: Anaesthetic health hazards among Belgian nurses and physicians. Int Arch Occup Environ Health 48:195, 1981.

195. Axelsson G, Rylander R: Exposure to anesthetic gases and spontaneous abortion: Response in a postal questionnaire study. Int J Epidemiol 11:250, 1982.

196. Hemminki K, Kyyronen P, Lindbohm M-L: Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. J Epidemiol Commun Health 39:141, 1985.

197. Johnson JA, Buchan RM, Reif JS: Effect of waste anesthetic gas and vapor exposure on reproductive outcome in veterinary personnel. Am Ind Hyg Assoc J 48:62, 1987.

198. Guirguis SS, Pelmear PL, Roy ML et al: Health effects associated with exposure to anesthetic gases in Ontario hospital personnel. Br J Ind Med 47:490, 1990.

199. Rowland AS, Baird DD, Weinberg CR et al: Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. N Engl J Med 327:993, 1992.

200. Rowland AS, Baird DD, Shore DL et al: Nitrous oxide and spontaneous abortion in female dental assistants. Am J Epidemiol 141:531, 1995.

201. Ebi KL, Rice SA: Reproductive and developmental toxicity of anesthetics in humans. In Rice SA, Fish KJ (eds): Anesthetic Toxicity. New York, Raven Press, 1994, p 175.

202. Vessey MP: Epidemiological studies of the occupational hazards of anesthesia: A review. Anaesthesia 33:430, 1978.

203. Buring JE, Hennekens CH, Mayrent SL et al: Health experiences of operating room personnel. Anesthesiology 62:325, 1985.

204. Klingberg MA, Weatherall JA (eds): Epidemiological Methods for Detection of Teratogens. Basel, S Karger, 1979.

205. Ferstandig LL: Trace concentrations of anesthetic gases: A critical review of their disease potential. Anesth Analg 57:328, 1978.

206. Baden JM: Chronic toxicity of inhalation anaesthetics. In Mazze RI (ed): Clinics in Anaesthesiology, vol 1. London, WB Saunders, 1983, p 441.

207. Shepard TH, Fink BR: Teratogenic activity of nitrous oxide in rats. In Fink BR (ed): Toxicity of Anesthetics. Baltimore, Williams & Wilkins, 1968, p 308.

208. Vieria E, Cleaton-Jones P, Austin JC et al: Effects of low concentration of nitrous oxide on rat fetuses. Anesth Analg 59:175, 1980.

209. Fujinaga M, Baden JM, Shepard TH et al: Nitrous oxide alters body laterality in rats. Teratology 41:131, 1990.

210. Mazze RI, Wilson AI, Rice SA et al: Reproduction and fetal development in rats exposed to nitrous oxide. Teratology 30:259, 1984.

211. Fujinaga M, Mazze RI, Baden JM et al: Rat whole embryo culture: An *in vitro* model for testing nitrous oxide teratogenicity. Anesthesiology 69:401, 1988.

212. Baden JM, Fujinaga M: Mechanisms of nitrous oxide induced reproductive toxicity in rat embryos grown in culture. Anesthesiology 77:A329, 1992.

213. Fujinaga M, Maze M, Hoffman B et al: Activation of alpha-1 adrenergic receptors modulates the control of left/right sidedness in rat embryos. Dev Biol 150:419, 1992.

214. Fujinaga M, Hoffman BB, Baden JM: Receptor subtype and intracellular signal transduction pathway associated with situs inversus by alpha $_1$ adrenergic stimulation. Dev Biol 162:558, 1994.

215. Saito S, Fujita T, Igarashi M: Effects of inhalational anesthetics on biochemical events in growing neuronal tips. Anesthesiology 79:1338, 1993.

216. Rice SA: Anaesthesia in pregnancy and the fetus: Toxicological aspects. In Reynolds F (ed): Effects on the Baby of Maternal Analgesia and Anesthesia. London, WB Saunders, 1993, p 88.

217. Rice SA: Behavioral toxicity of inhalation anesthetic agents. In Mazze RI (ed): Inhalation Anesthesiology. Oxford, Alden Press, 1983, p 507.

218. Holson RR, Bates HK, LaBorde JB et al: Behavioral teratology and dominant lethal evaluation of nitrous oxide exposure in rats. Neurotoxicol Teratol 17:583, 1995.

219. Randall T: A novel, unstable DNA mutation cracks decades-old clinical enigma. JAMA 269:557, 1993.

220. Baden JM, Rice SA: Metabolism and toxicity. In Miller RD (ed): Anesthesia, 4th ed. New York, Churchill Livingstone, 1994, p 157.

221. Rosenberg PH, Kallio H: Operating-theatre gas pollution and chromosomes. Lancet 2:452, 1977.

222. Baden JM, Kelly MJ, Cheung A et al: Lack of mutagens in urine of operating personnel. Anesthesiology 53:195, 1980.

223. Husum B, Niebuhr E, Wulf HC et al: Sister chromatid exchanges and structural chromosome aberrations in lymphocytes in operating room personnel. Acta Anaesthesiol Scand 27:262, 1983.

224. Natarajan D, Santhiya ST: Cytogenic damage in operating theatre personnel. Anaesthesia 45:574, 1990.

225. Sardas S, Cuhruk H, Karakaya AE et al: Sister-chromatid exchanges in operating room personnel. Mutat Res 279:117, 1992.

226. Reitz M, Antonini-Rumpf E, Lanz E: DNA single strand breaks in peripheral lymphocytes after anesthesia with isoflurane-nitrous oxide-oxygen. Arzneimittelforschung 43:1258, 1993.

227. Bruce DL, Eide KA, Linde HW et al: Causes of death among anesthesiologists: A 20 year survey. Anesthesiology 29:565, 1968.

228. Corbett TH, Cornell RG, Lieding K et al: Incidence of cancer among Michigan nurse anesthetists. Anesthesiology 38:260, 1973.

229. Bruce DL, Eide KA, Smith NJ et al: A prospective study of anesthesiologist mortality, 1967-1971. Anesthesiology 41:71, 1974.

230. Doll R, Peto R: Mortality among doctors in different occupations. BMJ 1:779, 1977.

231. Neil HAW, Fairer JG, Coleman MP et al: Mortality among male anaesthetists in the United Kingdom, 1957-83. BMJ 295:360, 1987.

232. Eger EI II, White AE, Brown CL et al: A test of the carcinogenicity of enflurane, isoflurane, halothane, methoxyflurane and nitrous oxide in mice. Anesth Analg 57:678, 1978.

233. Baden JM, Kundomal YR, Mazze RI et al: Carcinogen bioassay of isoflurane in mice. Anesthesiology 69:750, 1988.

234. Baden JM, Mazze RI, Wharton RS et al: Carcinogenicity of halothane in Swiss/ICR mice. Anesthesiology 51:20, 1979.

235. Baden JM, Egbert B, Mazze RI: Carcinogen bioassay of enflurane in mice. Anesthesiology 56:9, 1982.

236. Baden JM, Kundomal YR, Luttropp ME Jr et al: Carcinogen bioassay of nitrous oxide in mice. Anesthesiology 64:747, 1986.

237. Coate WB, Ulland BM, Lewis TR: Chronic exposure to low concentrations of halothane-nitrous oxide: Lack of carcinogenic effect in the rat. Anesthesiology 50:306, 1979.

Chapter 7 - Inhaled Anesthetic Delivery Systems

J. Jeff Andrews

INTRODUCTION

An anesthesia system consists of the various components that communicate with each other during the administration of inhalation anesthesia. [1] System components include the anesthesia machine, the vaporizers, the anesthetic circuit, the ventilator, and the scavenging system. A thorough understanding of these parts is essential to the safe practice of anesthesia. Malpractice claims associated with gas delivery equipment are infrequent but severe and continue to occur in the 1990s. [2] This chapter discusses the normal operation, function, and integration of major system components. More importantly, it illustrates some problems and hazards associated with each and describes appropriate preoperative checks.

ANESTHESIA MACHINES

Anesthesia machines have evolved from simple, pneumatic devices to sophisticated, computer-based, fully integrated anesthesia systems (Figs. 7-1 (Figure Not Available) , 7-2) (Figure Not Available) . A few years ago, a rudimentary background in pneumatics sufficed, but today, an understanding of pneumatics, electronics, and even computer science is useful. Even though it is difficult for the anesthesiologist to achieve a thorough understanding of modern anesthesia machines, it is essential to the safe practice of anesthesia. The anesthesiologist must be aware of design differences between manufacturers so that appropriate preoperative checks can be performed. The only two major anesthesia machine manufacturers in the United States are Ohmeda and North American Drager.

Anesthesia Machine Standards

Anesthesia machine standards provide guidelines to manufacturers regarding minimum performance, design characteristics, and safety requirements for anesthesia machines. During the past 2 decades, the progression of anesthesia machine standards has been as follows:

1979: American National Standards Institute Z79.8-1979 [3]

1988: American Society for Testing and Materials (ASTM) F1161-88 [4]

1994: ASTM 1161-94 [5]

1998: ASTM F29.01.09 [6]

To comply with the new 1998 ASTM F29.01.09 standard, newly manufactured workstations must have monitors that have the following parameters: continuous breathing system pressure, exhaled tidal volume, ventilatory carbon dioxide (CO_2) concentration, anesthetic vapor concentration, inspired oxygen concentration, oxygen supply pressure, arterial hemoglobin oxygen saturation, arterial blood pressure, and continuous electrocardiogram. These monitors must be

Figure 7-1 (Figure Not Available) Ohmeda CD anesthesia system. *(Courtesy of Ohmeda, A Division of BOC Health Care, Madison, Wisconsin.)*

enabled and functioning automatically when the machine is in use. The anesthesia workstation must have a prioritized alarm system that groups the alarms into three categories: high, medium, and low priority. [6]

Generic Anesthesia Machine

A diagram of a generic two-gas anesthesia machine is shown in Figure 7-3 (Figure Not Available) . Both oxygen and nitrous oxide have two supply sources: a pipeline supply source and a cylinder supply source. The pipeline supply source is the primary gas source for the anesthesia machine. The hospital piping system provides gases to the machine at approximately 50 pounds per square inch gauge (psig), which is the normal working pressure of most machines. The cylinder supply source serves as a back-up if the pipeline fails. The oxygen cylinder source is regulated from 2,200 to approximately 45 psig, and the nitrous oxide cylinder source is regulated from 745 to approximately 45 psig. [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23]

A safety device traditionally referred to as the fail-safe valve is located downstream from the nitrous oxide supply source. It serves as an interface between the oxygen and nitrous oxide supply sources. This valve shuts off or proportionally

Figure 7-2 (Figure Not Available) North American Drager Narkomed 4 anesthesia system. *(Courtesy of North American Drager, Telford, Pennsylvania.)*

decreases the supply of nitrous oxide (and other gases) if the oxygen supply pressure decreases. Contemporary machines have an alarm device to monitor the oxygen supply pressure. An alarm is actuated at a predetermined oxygen pressure, such as 30 psig. [7] [8] [18] [23]

Most Ohmeda machines have a second-stage oxygen regulator located downstream from the oxygen supply source. It is adjusted to a precise pressure level, such as 14 psig. [8] [11] [12] [13] [14] [15] [16] [17] This regulator supplies a constant pressure to the oxygen flow control valve, regardless of fluctuating oxygen pipeline pressures. For example, the flow from the oxygen flow control valve is constant if the oxygen supply pressure is greater than 14 psig.

The flow control valves are an important anatomic landmark because they divide the anesthesia machine into two parts. The high-pressure circuit is the part of the machine that is upstream from the flow control valves, and the low-pressure circuit is the part of the machine that is downstream from the flow control valves. The operator regulates flow entering the low-pressure circuit by adjusting the flow control valves. The oxygen and nitrous oxide flow control valves are linked mechanically or pneumatically by a proportioning system to help prevent delivery of a hypoxic mixture. The flow travels through a common manifold and may be directed to a calibrated vaporizer. Precise amounts of inhaled anesthetic can be added, depending on the vaporizer setting.

Figure 7-3 (Figure Not Available) Diagram of a generic two-gas anesthesia machine. *(Modified from Check-Out, A Guide for Preoperative Inspection of an Anesthesia Machine. American Society of Anesthesiologists, Park Ridge, Illinois, 1987.)*

The total fresh gas flow travels toward the common gas outlet. [7] [8]

Many Ohmeda machines have a machine outlet check valve between the vaporizers and the common gas outlet. [8] [9] [10] [11] [12] [13] [14] [15] Its purpose is to prevent backflow into the vaporizer, thereby minimizing the effects of downstream intermittent pressure fluctuations on inhaled anesthetic concentration (see Intermittent Back Pressure). The presence or absence of a check valve profoundly influences the decision regarding the preoperative leak test that is indicated (see Checking Anesthesia Machines). The oxygen flush connection joins the mixed-gas pipeline between the one-way check valve and the machine outlet. Thus, the oxygen flush,

when activated, has a "straight shot" to the common gas outlet. [7] [8]

Pipeline Supply Source

The pipeline supply source is the primary gas source for the anesthesia machine. Most hospitals have a central piping system to deliver medical gases such as oxygen, nitrous oxide, and air to the operating room. The central piping system must supply the anesthesia machine with the appropriate gas at the appropriate pressure for the machine to function properly. Unfortunately, this does not always occur.

In a survey of approximately 200 hospitals in 1976, 31 percent reported difficulties with pipeline systems. [24] The most common problem was inadequate oxygen pressure, followed by excessive pipeline pressures. The most devastating reported hazard, however, was accidental crossing of oxygen and nitrous oxide pipelines, which caused several deaths. This problem caused 23 deaths in a newly constructed wing of a general hospital in Sudbury, Ontario, during a 5-month period. [24] [25]

The operator must take two actions if a pipeline crossover is suspected. First, the back-up oxygen cylinder must be turned on. Then, the pipeline supply must be disconnected. This second step is mandatory because the machine preferentially uses the inappropriate 50-psig pipeline supply source instead of the lower pressure (45-psig) oxygen cylinder source.

Gas enters the anesthesia machine through the pipeline inlet connections (Fig. 7-3 (Figure Not Available) ; see arrows). The pipeline inlet fittings are gas-specific Diameter Index Safety System threaded body fittings. The Diameter Index Safety System provides threaded noninterchangeable connections for medical gas lines, which minimizes the risk of misconnection. A check valve is located downstream from the inlet. It prevents reverse flow of gases from the machine to the pipeline or to the atmosphere. [6]

Cylinder Supply Source

Anesthesia machines have reserve E cylinders if a pipeline supply source is not available or if the pipeline fails. Color-coded cylinders are attached to the anesthesia machine through the hanger yoke assembly. The hanger yoke assembly orients and supports the cylinder, provides a gas-tight seal, and ensures a unidirectional flow of gases into the

machine. [7] Each hanger yoke is equipped with the Pin Index Safety System. The Pin Index Safety System is a safeguard introduced to eliminate cylinder interchanging and the possibility of accidentally placing the incorrect gas on a yoke designed to accommodate another gas. Two pins on the yoke are arranged so that they project into the cylinder valve. Each gas or combination of gases has a specific pin arrangement. [26]

Gas travels from the high-pressure cylinder source to the anesthesia machine when the cylinder is turned on (see Fig. 7-3 (Figure Not Available)). A check valve is located downstream from each cylinder if a double-yoke assembly is used. The check valve has several functions. First, it minimizes gas transfer from a cylinder at high pressure to one with lower pressure. Second, it allows an empty cylinder to be exchanged for a full one while gas flow continues from the other cylinder into the machine with minimal loss of gas. Third, it minimizes leakage from an open cylinder to the atmosphere if one cylinder is absent. [7] [8] A cylinder supply pressure gauge is located downstream from the check valves. The gauge indicates the pressure in the cylinder having the higher pressure when two reserve cylinders of the same gas are opened at the same time. [20]

Each cylinder supply source has a pressure-reducing valve known as the cylinder pressure regulator. It reduces the high and variable storage pressure present in a cylinder to a lower, more constant, pressure suitable for use in the anesthesia machine. The oxygen cylinder pressure regulator reduces the oxygen cylinder pressure from a high of 2,200 psig to approximately 45 psig. The nitrous oxide cylinder pressure regulator receives pressure of up to 745 psig and reduces it to approximately 45 psig. [7] [8]

The cylinders should be turned off except during the preoperative machine checking period or when a pipeline source is unavailable. If left on, the reserve cylinder supply can be silently depleted whenever the pressure inside the machine decreases to a value lower than the regulated cylinder pressure. Oxygen pressure within the machine can decrease below 45 psig with oxygen flushing or with ventilator use, particularly at high peak flow rates. The pipeline supply pressures of all gases can be less than 45 psig if problems exist in the central piping system. If the cylinders are left on, they eventually become depleted. Then, no reserve supply would be available if a pipeline failure occurs. [8] [27]

Oxygen Supply Pressure Failure Safety Devices

Oxygen and nitrous oxide supply sources existed as independent entities in older models of anesthesia machines, and they were not pneumatically or mechanically interfaced. Therefore, abrupt or insidious oxygen pressure failure had the potential to lead to the delivery of a hypoxic mixture. The ASTM F29.01.09-1998 standard states that "The anesthesia gas supply device shall be designed so that whenever oxygen supply pressure is reduced to below the manufacturer-specified minimum, the delivered oxygen concentration shall not decrease below 19 percent at the common gas outlet." [6] Contemporary anesthesia machines have a number of safety devices that act together to minimize the risk of hypoxia as oxygen pressure decreases. Several of these devices are described in the following sections.

Pneumatic and Electronic Alarm Devices

Many older anesthesia machines have a pneumatic alarm device that sounds a warning when the oxygen supply pressure decreases to a predetermined threshold value, such as 30 psig. The ASTM F29.01.09-1998 standard mandates that a medium-priority alarm shall be activated within 5 seconds when the oxygen pressure decreases below a manufacturer-specific pressure threshold. [6] Electronic alarm devices are now used to meet this guideline.

Fail-Safe Valves

A fail-safe valve is present in the gas line supplying each of the flowmeters except that for oxygen. Controlled by oxygen supply pressure, the valve shuts off or proportionally decreases the supply pressure of all other gases (nitrous oxide, air, CO_2 , helium, nitrogen) as the oxygen supply pressure decreases. Unfortunately, the misnomer "fail-safe" has led to the misconception that the device prevents administration of a hypoxic mixture. This is not the case. Machines that are not equipped with a flow proportioning system (see Proportioning Systems) can deliver a hypoxic mixture under normal working conditions. The oxygen flow control valve can be closed intentionally or accidentally. Normal oxygen pressure keeps other gas lines open so that a hypoxic mixture can result. [7] [8]

Ohmeda machines are equipped with a fail-safe valve known as the pressure-sensor shut-off valve (Fig. 7-4) (Figure Not Available) . The valve is threshold in nature, and it is either open or closed. Oxygen supply pressure opens the valve, and the valve return spring closes the valve. Figure 7-4 (Figure Not Available) shows a nitrous oxide pressure-sensor shut-off valve with a threshold pressure of 20 psig. [12] [13] [15] [16] [17] Figure 7-4 (Figure Not Available) A, an oxygen supply pressure greater than 20 psig is exerted on the mobile diaphragm. This pressure moves the piston and pin upward, and the valve opens. Nitrous oxide flows freely to the nitrous oxide flow control valve. In Figure 7-4 (Figure Not Available) B, the oxygen supply pressure is less than 20 psig, and the force of the valve return spring completely closes the valve. [8] Nitrous oxide flow stops at the closed fail-safe valve, and it does not advance to the nitrous oxide flow control valve.

North American Drager uses a fail-safe valve known as the oxygen failure protection device (OFPD) that interfaces the oxygen pressure with that of other gases, such as nitrous oxide, air, CO_2 , helium, and nitrogen. [18] [19] [20] [21] [22] [23] It differs from Ohmeda's oxygen pressure-sensor shut-off valve because the OFPD is based on a proportioning principle rather than a threshold principle. The pressures of all gases controlled by the OFPD decrease proportionally with the oxygen pressure. The OFPD consists of a seat-nozzle assembly connected to a spring-loaded piston (Fig. 7-5) (Figure Not Available) . The oxygen supply pressure in the left panel is 50 psig. This pressure pushes the piston upward, forcing the nozzle away from the valve seat. Nitrous oxide (or other gases) advance toward

Figure 7-4 (Figure Not Available) Pressure-sensor shut-off valve. The valve is open in A because the oxygen supply pressure is greater than the threshold value of 20 psig. The valve is closed in B because of inadequate oxygen pressure. *(Modified from Bowie and Huffman [6])*

the flow control valve at 50 psig. The oxygen pressure in the right panel is zero psig. The spring is expanded and forces the nozzle against the seat, preventing flow through the device. Finally, the center panel shows an intermediate oxygen pressure of 25 psig. The force of the spring partially closes the valve. The nitrous oxide pressure delivered to the flow control valve is 25 psig. There is a continuum of intermediate configurations between the extremes (0-50 psig) of oxygen supply pressure. These intermediate valve configurations are responsible for the proportional nature of the OFPD. [18]

Second-Stage Oxygen Pressure Regulator

Most contemporary Ohmeda machines have a second-stage oxygen pressure regulator set at a specific value ranging from 12 to 19 psig. [12] [13] [14] [15] [16] [17] Oxygen flowmeter output is constant when the oxygen supply pressure exceeds the set value. Ohmeda pressure-sensor shut-off valves are set at a higher threshold value (20-30 psig). This ensures that oxygen is the last gas flow to decrease if oxygen pressure fails.

Flowmeter Assembly

The flowmeter assembly (Fig. 7-6) (Figure Not Available) precisely controls and measures gas flow to the common gas outlet. The flow control valve regulates the amount of flow that enters a tapered, transparent flowtube known as a Thorpe tube. A mobile indicator float inside the flowtube indicates the amount of flow passing through the flow control valve. The quantity of flow is indicated on a scale associated with the flowtube. [7] [8]

Physical Principles of Flowmeters

Opening the flow control valve allows gas to travel through the space between the float and the flowtube. This space is known as the annular space (Fig. 7-7) (Figure Not Available) . The indicator float hovers freely in an equilibrium position where the upward force resulting from gas flow equals the downward force on the float resulting from gravity at a given flow rate. The float moves to a new equilibrium position in the tube when flow is changed. These flowmeters are commonly referred to as *constant pressure* flowmeters because the pressure

Figure 7-5 (Figure Not Available) Oxygen failure protection device, which responds proportionally to changes in oxygen supply pressure (see text for details). *(Modified from Narkomed 2A Anesthesia System [18])*

Figure 7-6 (Figure Not Available) Oxygen flowmeter assembly. The oxygen flowmeter assembly is composed of the flow control valve assembly plus the flowmeter subassembly. *(Modified from Bowie and Huffman [6])*

decrease across the float remains constant for all positions in the tube. [7] [26] [28]

Flowtubes are tapered, with the smallest diameter at the bottom of the tube and the largest diameter at the top. The term *variable orifice* designates this type of unit because the annular space between the float and the inner wall of the flowtube varies with the position of the float. Flow through the constriction created by the float can be laminar or turbulent, depending on the flow rate (Fig. 7-8) (Figure Not Available) . The characteristics

Figure 7-7 (Figure Not Available) The annular space. The clearance between the head of the float and the flowtube is known as the annular space. It can be considered an equivalent to a circular channel of the same cross-sectional area. *(Modified from Macintosh et al [26])*

of a gas that influence its flow rate through a given constriction are viscosity (laminar flow) and density (turbulent flow). Because the annular space is tubular at low flow rates, laminar flow is present, and *viscosity* determines the gas flow rate. The annular space simulates an orifice at high flow rates, and turbulent gas flow then depends predominantly on the *density* of the gas. [7] [28]

Components of Flowmeter Assembly

Flow Control Valve Assembly.

The flow control valve assembly (see Fig. 7-6 (Figure Not Available)) is composed of a flow control knob, a needle valve, a valve seat, and a pair of valve stops. [7] The assembly can receive its pneumatic input either directly from the pipeline source (50 psig) or from a second-stage pressure regulator. The location of the needle valve in the valve seat changes to establish different orifices when the flow control valve is adjusted. Gas flow increases when the flow control valve is turned counterclockwise, and it decreases when the valve is turned clockwise. Extreme clockwise rotation results in damage to the needle valve and

Figure 7-8 (Figure Not Available) Flowtube constriction. The lower pair of illustrations represents the lower portion of a flowtube. The clearance between the head of the float and the flowtube is narrow. The equivalent channel is tubular because its diameter is less than its length. Viscosity is dominant in determining gas flow rate through this tubular constriction. The upper pair of illustrations represents the upper portion of a flowtube. The equivalent channel is orificial because its length is less than its width. Density is dominant in determining gas flow rate through this orificial constriction. *(Modified from Macintosh et al [26])*

---

the valve seat. Therefore, flow control valves are equipped with valve "stops" to prevent this occurrence. [8]

Safety Features.

Contemporary flow control valve assemblies have numerous safety features. The oxygen flow control knob is physically distinguishable from other gas knobs. It is distinctively fluted, projects beyond the control knobs of the other gases, and is larger in diameter than the flow control knobs of other gases. All knobs are color coded for the appropriate gas, and the chemical formula or the name of the gas is permanently marked on each. Flow control knobs are recessed or protected with a shield or barrier to minimize inadvertent change from a preset position. If a single gas has two flowtubes, the tubes are arranged in series and are controlled by a single flow control valve. [6]

Flowmeter Subassembly.

The flowmeter subassembly (see Fig. 7-6 (Figure Not Available)) consists of the flowtube, the indicator float with float stops, and the indicator scale. [7]

Flowtubes.

Contemporary flowtubes are made of glass. Most have a single taper in which the inner diameter of the flowtube increases uniformly from bottom to top. Manufacturers provide double flowtubes for oxygen and nitrous oxide to provide better visual discrimination at low flow rates. A fine flowtube indicates flow from approximately 200 mL/min to 1 L/min, and a coarse flowtube indicates flow from approximately 1 L/min to 10 to 12 L/min. The two tubes are connected in series and

are supplied by a single flow control valve. The total gas flow is that shown on the higher flowmeter.

Indicator Floats and Float Stops.

Contemporary anesthesia machines use several different types of bobbins or floats, including plumb-bob floats, [11] [12] [13] [16] [17] rotating skirted floats, [14] [15] and ball floats. [18] [19] [20] [21] [22] Flow is read at the top of plumb-bob and skirted floats and at the center of the ball on the ball-type floats. [7] Flowtubes are equipped with float stops at the top and bottom of the tube. The upper stop prevents the float from ascending to the top of the tube and plugging the outlet. It also ensures that the float will be visible at maximum flows instead of being hidden in the manifold. The bottom float stop provides a central foundation for the indicator when the flow control valve is turned off. [7] [8]

Scale.

The flowmeter scale can be marked directly on the flowtube or located to the right of the tube. [6] Gradations corresponding to equal increments in flow rate are closer together at the top of the scale because the annular space increases more rapidly than does the internal diameter from bottom to top of the tube. Rib guides are used in some flowtubes with ball-type indicators to minimize this compression effect. They are tapered glass ridges that run the length of the tube. There are usually three rib guides that are equally spaced around the inner circumference of the tube. In the presence of rib guides, the annular space from the bottom to the top of the tube increases almost proportionally with the internal diameter. This results in a nearly linear scale. [7] Rib guides are employed on North American Drager flowtubes. [18] [19] [20] [22]

Safety Features.

The flowmeter subassembly for each gas on the Ohmeda Modulus I, Modulus II, Modulus II Plus, and CD is housed in an independent, color-coded, pin-specific module. The flowtubes are adjacent to a gas-specific, color-coded backing. The flow scale and the chemical formula or the name of the gas is permanently etched on the backing to the right of the flowtube. [11] [12] [13] [16] [17] Flowmeter scales are individually hand calibrated by use of the specific float to provide a high degree of accuracy. The tube, float, and scale make an inseparable unit. The entire set must be replaced if any component is damaged. [11] [12] [13] [16] [17]

North American Drager does not use a modular system for the flowmeter subassembly. The flow scale, the chemical symbol, and the gas-specific color codes are etched directly onto the flowtube. [18] [19] [20] [21] [22] The scale in use is obvious when two flowtubes for the same gas are used.

Problems with Flowmeters

Leaks.

Flowmeter leaks are a substantial hazard because the flowmeters are located downstream from all machine safety devices except the oxygen analyzer. [1] Leaks can occur at the O-rings between the glass flowtube and the metal manifold and in the glass flowtubes, the most fragile pneumatic component of the anesthesia machine. Gross damage to glass flowtubes is usually apparent, but subtle cracks and chips may be overlooked, resulting in errors of delivered flows. [29]

In 1963, Eger et al [30] demonstrated that in the presence of a flowmeter leak, a hypoxic mixture is less likely to occur if the oxygen flowmeter is located downstream from all other flowmeters. Figure 7-9 (Figure Not Available) is a contemporary version of the figure in Eger's original publication. The unused air flowtube has a large leak. Nitrous oxide and oxygen flow rates are set at a ratio of 3:1. A potentially dangerous arrangement is shown in Figures 7-9 (Figure Not Available) A and B because the nitrous oxide flowmeter is located in the downstream position. A hypoxic mixture can result because a substantial portion of oxygen flow passes through the leak, and all nitrous oxide is directed to the common gas outlet. A safer configuration that complies with the ASTM F29.01.09-1998 machine standard [6] is shown in Figures 7-9 (Figure Not Available) C and D. The oxygen flowmeter is located in the downstream position. A portion of the nitrous oxide flow escapes through the leak, and the remainder goes toward the common gas outlet. A hypoxic mixture is less likely because all the oxygen flow is advanced by the nitrous oxide. [30] North American Drager flowmeters are arranged as in Figure 7-9 (Figure Not Available) . C, and Ohmeda flowmeters are as in Figure 7-9 (Figure Not Available) D.

A leak in the oxygen flowtube can produce a hypoxic mixture even when oxygen is located in the downstream position (Fig. 7-10) . [1] [29] Oxygen escapes through the leak, and nitrous oxide flows toward the common outlet, particularly at high ratios of nitrous oxide to oxygen flow.

Inaccuracy.

Flow error can occur even when flowmeters are assembled properly with appropriate components. Dirt or static electricity can cause a float to stick, and the actual flow may be higher or lower than that indicated. Sticking

---

Figure 7-9 (Figure Not Available) Flowmeter sequence--a potential cause of hypoxia. In the event of a flowmeter leak, a potentially dangerous arrangement exists when nitrous oxide is located in the downstream position (A and B). The safest configuration exists when oxygen is located in the downstream position (C and D) (see text for details). *(Modified from Eger et al [30])*

is more common in the low flow range because the annular space is smaller. A damaged float can cause inaccurate readings because the precise relationship between the float and the flowtube is altered. Back pressure from the breathing circuit can cause a float to drop so that it reads less than the actual flow. Finally, if flowmeters are not aligned properly in the vertical position, readings can be inaccurate because tilting distorts the annular space. [7] [29] [31]

Ambiguous Scale.

Before the standardization of flowmeter scales and the widespread use of oxygen analyzers, at least two deaths resulted from confusion created by ambiguous scales. [29] [31] [32] The operator read the float position beside an adjacent but erroneous scale in both cases. Today, this error is less likely to occur because contemporary flowmeter scales are marked either directly onto, or to the right of, the appropriate flowtube. [6] Confusion is minimized when the scale is etched directly onto the tube.

Proportioning Systems

Manufacturers have equipped newer machines with proportioning systems in an attempt to prevent delivery of a hypoxic mixture. Nitrous oxide and oxygen are interfaced either mechanically or pneumatically so that the minimum oxygen concentration at the common outlet is 25 percent.

Figure 7-10 Oxygen flowtube leak. An oxygen flowtube leak can produce a hypoxic mixture regardless of the flowtube arrangement.

Ohmeda Link-25 Proportion Limiting Control System

Contemporary Ohmeda machines use the Link-25 System. The heart of the system is the mechanical integration of the nitrous oxide and oxygen flow control valves. It allows independent adjustment of either valve, yet automatically intercedes to maintain a minimum 25 percent oxygen concentration with a maximum nitrous oxide-oxygen flow ratio of 3:1. The Link-25 automatically increases oxygen flow to prevent delivery of a hypoxic mixture. [11] [12] [13] [14] [15] [16] [17]

Figure 7-11 (Figure Not Available) shows the Ohmeda Modulus II Link-25 System. The nitrous oxide and oxygen flow control valves are identical. A 14-tooth sprocket

is attached to the nitrous oxide flow control valve, and a 28-tooth sprocket is attached to the oxygen flow control valve. A chain physically links the sprockets. When the nitrous oxide flow control valve is turned through two revolutions, or 28 teeth, the oxygen flow control valve revolves once because of the 2:1 gear ratio. The final 3:1 flow ratio results because the nitrous oxide flow control valve is supplied by approximately 26 psig, whereas the oxygen flow control valve is supplied by 14 psig. Thus, the combination of the mechanical and pneumatic aspects of the system yields the final oxygen concentration. [12] [13]

Figure 7-11 (Figure Not Available) Ohmeda Link-25 proportion limiting control system (see text for details). *(Modified from Andrews JJ: Delivery systems for inhaled anesthetics. In Barash PG, Cullen BF, Stoelting RK [eds]: Clinical Anesthesia, 3rd ed. Philadelphia, New York, Lippincott-Raven, 1997, pp 535-572.)*

North American Dr a ger Oxygen Ratio Monitor Controller

North American Drager's proportioning system, the oxygen ratio monitor controller (ORMC), is used on the North American Drager Narkomed 2A, 2B, 3, and 4. [18] [19] [20] [21] [22] [23] It is a pneumatic oxygen-nitrous oxide interlock system designed to maintain a fresh gas oxygen concentration of at least 25 ± 3 percent. The device controls the fresh gas oxygen concentration to levels substantially higher than 25 percent at oxygen flow rates of less than 1 L/min. The ORMC limits nitrous oxide flow to prevent delivery of a hypoxic mixture. [18] [19] [20] [21] [22] This is unlike the Ohmeda Link-25, which actively increases oxygen flow.

A schematic of the ORMC is shown in Figure 7-12 (Figure Not Available) . It is composed of an oxygen chamber, a nitrous oxide chamber, and a nitrous oxide slave control valve; all are interconnected by a mobile horizontal shaft. The pneumatic input into the device is from the oxygen and the nitrous oxide flowmeters. These flowmeters are unique because they have specific resistors located downstream from the flow control valves. These resistors create back pressures directed to the oxygen and nitrous oxide chambers. The value of the oxygen flowtube resistor is three to four times that of the nitrous oxide flowtube resistor, and the relative value of these resistors determines the value of the controlled fresh gas oxygen concentration. The back pressure in the oxygen and nitrous oxide chambers pushes against rubber diaphragms attached to the mobile horizontal shaft. Movement of the shaft regulates the nitrous oxide slave control valve, which feeds the nitrous oxide flow control valve. [1] [19] [23]

If the oxygen pressure is proportionally higher than the nitrous oxide pressure, the nitrous oxide slave control valve opens more widely, allowing more nitrous oxide to flow. As the nitrous oxide flow is increased manually, the nitrous oxide pressure forces the shaft toward the oxygen chamber. The valve opening becomes more restrictive and limits the nitrous oxide flow to the flowmeter.

Figure 7-12 (Figure Not Available) illustrates the action of a single ORMC under different sets of circumstances. The back pressure exerted on the oxygen diaphragm, in the upper configuration, is greater than that exerted on the nitrous oxide diaphragm. This causes the horizontal shaft to move to the left, opening the nitrous oxide slave control valve. Nitrous oxide is then able to proceed to its flow control valve and out through the flowmeter. In the bottom configuration, the nitrous oxide slave control valve is closed because of inadequate oxygen back pressure. [1] [18] [23]

Limitations

Proportioning systems are not foolproof. Machines equipped with proportioning systems can still deliver a hypoxic mixture under the following conditions.

Wrong Supply Gas.

Both the Link-25 and the ORMC are fooled if a gas other than oxygen is present in the oxygen pipeline. In the Link-25 System, the nitrous oxide and oxygen flow control valves continue to be mechanically linked, and a hypoxic mixture proceeds to the common outlet. The oxygen rubber diaphragm of the ORMC recognizes adequate

Figure 7-12 (Figure Not Available) North American Drager oxygen ratio monitor controller (see text for details). *(Modified from Schreiber P: Safety Guidelines for Anesthesia Systems. Telford, Pennsylvania, North American Drager, 1984.)*

"oxygen" pressure, and flow of both the wrong gas plus nitrous oxide results. The oxygen analyzer is the only machine monitor that detects this condition in both systems.

Defective Pneumatics or Mechanics.

Normal operation of the Ohmeda Link-25 and the North American Drager ORMC is contingent on pneumatic and mechanical integrity. [33] Pneumatic integrity in the Ohmeda System depends on properly functioning second-stage regulators. A nitrous oxide-oxygen ratio other than 3:1 results if the regulators are not precise. The chain connecting the two sprockets must be intact. A 97-percent nitrous oxide concentration can occur if the chain is cut or broken. [34] In the North American Drager System, a functional OFPD is necessary to supply appropriate pressure to the ORMC. The mechanical aspects of the ORMC, such as the rubber diaphragms, the flowtube resistors, and the nitrous oxide slave control valve, must likewise be intact.

Leaks Downstream.

The ORMC and the Link-25 function at the level of the flow control valves. A leak down-stream from these devices, such as from a broken oxygen flowtube (see Fig. 7-10), can cause delivery of a hypoxic mixture. Oxygen escapes through the leak, and the predominant gas delivered at the common outlet is nitrous oxide. The oxygen analyzer is the only machine safety device that can detect the problem. [1] North American Drager recommends a preoperative positive-pressure leak test to detect such a leak. [18] [19] [20] [21] [22] Ohmeda recommends a preoperative negative-pressure leak test because of the check valve located at the common outlet (see Checking Anesthesia Machines). [9] [10] [11] [12] [13] [15]

Inert Gas Administration.

Administration of a third inert gas, such as helium, nitrogen, and CO_2 , can cause a hypoxic mixture because contemporary proportioning systems link only nitrous oxide and oxygen. [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [35] Use of an oxygen analyzer is mandatory if the operator uses a third inert gas.

Oxygen Flush Valve

The oxygen flush valve allows direct communication between the oxygen high-pressure circuit and the low-pressure circuit (see Fig. 7-3 (Figure Not Available)). Flow from the oxygen flush valve enters the low-pressure circuit downstream from the vaporizers and downstream from the Ohmeda machine outlet check valve. The spring-loaded valve stays closed until the operator opens it by depressing the oxygen flush button. Actuation of the valve delivers 35 to 75 L/min to the breathing circuit. [8]

The oxygen flush valve can provide effective jet ventilation if the anesthesia machine is equipped with a one-way check valve positioned between the vaporizer and the oxygen flush valve. Because the Ohmeda Modulus II has such a valve, the entire oxygen flow of 45 to 75 L/min is delivered to the common gas outlet at a high pressure of 50 psig. On the other hand, the Ohmeda Modulus II Plus, which does not have the check valve, provides only 7 psig at the common gas outlet because some oxygen flow travels retrograde through an internal relief valve located upstream from the oxygen flush valve. The North American Drager Narkomed 2A, which also does not have the check valve, provides an intermediate pressure of 18 psig to the common gas outlet because some oxygen flow travels retrograde through a pop-off valve located in the vaporizers. [36]

The oxygen flush valve is associated with several hazards. A defective or damaged valve can stick in the fully open position, causing barotrauma. [37] A valve sticking

in a partially open position can result in patient awareness because the oxygen flow from the incompetent valve dilutes the inhaled anesthetic. [38] Improper use of normally functioning oxygen flush valves also can result in problems. Overzealous intraoperative oxygen flushing can dilute inhaled anesthetics. Oxygen flushing during the inspiratory phase of positive-pressure ventilation can cause barotrauma. Excess volume cannot be vented from the breathing circuit because the ventilator relief valve is closed and the adjustable pressure-limiting (APL) valve is either out of circuit or closed. [39] If a machine is equipped with a freestanding vaporizer downstream from the common gas outlet, oxygen flushing can deliver large quantities of inhaled anesthetic to the patient. Finally, inappropriate preoperative use of the oxygen flush to evaluate the low-pressure circuit for leaks can be misleading, particularly on Ohmeda machines with a check valve at the common outlet. [40] Back pressure from the breathing circuit closes the check valve airtight, and major low-pressure circuit leaks can go undetected (see Checking Anesthesia Machines).

VAPORIZERS

Through the years, vaporizers have evolved from rudimentary ether inhalers to copper kettles to the present temperature-compensated, variable-bypass vaporizers. With the introduction of the new inhaled anesthetic desflurane, an even more sophisticated, electrically heated, pressurized, electronically controlled vaporizer has been introduced. Before variable-bypass vaporizers and the new Tec 6 desflurane vaporizer are discussed, certain physical principles are reviewed briefly to facilitate understanding of the operating principles, construction, and design of contemporary vaporizers.

Physics

Vapor Pressure

Contemporary inhaled volatile anesthetics exist in the liquid state below 20°C. When a volatile liquid is in a closed container, molecules escape from the liquid phase to the vapor phase until the number of molecules in the vapor phase is constant. These molecules bombard the wall of the container and create a pressure known as the saturated vapor pressure. As the temperature increases, more molecules enter the vapor phase, and the vapor pressure increases (Fig. 7-13) (Figure Not Available) . Vapor pressure is independent of atmospheric pressure and is contingent only on the temperature and the physical characteristics of the liquid. The boiling point of a liquid is that temperature at which the vapor pressure equals atmospheric pressure. [41] [42] [43] At 760 mm Hg, the boiling points for desflurane, isoflurane, halothane, enflurane,

Figure 7-13 (Figure Not Available) Vapor pressure versus temperature curves for desflurane, isoflurane, halothane, enflurane, and sevoflurane. The vapor pressure curve for desflurane is both steeper and shifted to higher vapor pressures when compared with the curves for other contemporary inhaled anesthetics. *(From inhaled anesthetic package insert equations and from Susay et al [74])*

and sevoflurane are approximately 22.8, 48.5, 50.2, 56.5, and 58.5°C, respectively. Unlike other contemporary inhaled anesthetics, desflurane boils at temperatures commonly encountered in clinical settings, such as pediatric and burn operating rooms. This unique physical characteristic mandates a special vaporizer design for the delivery of desflurane.

Latent Heat of Vaporization

Energy must be expended to convert a molecule from the liquid to the gaseous state because the molecules of a liquid tend to cohere. The latent heat of vaporization is defined as the number of calories required to change 1 g of liquid into vapor without a temperature change. The energy for vaporization must come from the liquid itself or from an outside source. The temperature of the liquid decreases during vaporization in the absence of an outside energy source. Energy loss can lead to significant decreases in temperature of the remaining liquid. This temperature drop greatly decreases vaporization. [41] [43] [44]

Specific Heat

The specific heat of a substance is the number of calories required to increase the temperature of 1 g of a substance by 1°C. [41] [43] [44] The substance can be solid, liquid, or gas. The concept of specific heat is important to the design, operation, and construction of vaporizers because it is applicable in two ways. First, the specific heat value for an inhaled anesthetic is important because it indicates how much heat must be supplied to the liquid to maintain a constant temperature when heat is lost during vaporization. Second, manufacturers select vaporizer metals that have a high specific heat to minimize temperature changes associated with vaporization.

Thermal Conductivity

Thermal conductivity is a measure of the speed with which heat flows through a substance. The higher the thermal conductivity, the better the substance conducts heat. [41] Vaporizers are constructed of metals that have relatively high thermal conductivity, a characteristic that helps maintain a uniform temperature.

Variable-Bypass Vaporizers

The Ohmeda Tec 4, the Ohmeda Tec 5, and the North American Drager Vapor 19.1 are classified as variable-bypass, flowover, temperature-compensated, agent-specific,

out-of-circuit vaporizers. [41] *Variable-bypass* refers to the method for regulating output concentration. As gas flow enters the vaporizer's inlet, the setting of the concentration control dial determines the ratio of flow that goes through the bypass chamber and through the vaporizing chamber. The gas channeled to the vaporizing chamber flows over the liquid anesthetic and becomes saturated with vapor. Thus, *flowover* refers to the method of vaporization. The Tec 4, the Tec 5, and the Vapor 19.1 are classified as *temperature-compensated* because they are equipped with an automatic temperature-compensating device that helps maintain a constant vaporizer output over a wide range of temperatures. These vaporizers are *agent specific* and *out of circuit* because they are designed to accommodate a single agent and to be located outside the breathing circuit. Variablebypass vaporizers are used to deliver halothane, enflurane, isoflurane, and sevoflurane, but not desflurane (see Electrically Heated, Pressurized Vaporizers).

Basic Operating Principles

A diagram of a generic, variable-bypass vaporizer is shown in Figure 7-14 (Figure Not Available) . Vaporizer components include the concentration control dial, the bypass chamber, the vaporizing chamber, the filler port, and the filler cap. Using the filler port, the operator fills the vaporizing chamber with liquid anesthetic. The maximum safe level is predetermined by the position of the filler port, which is positioned to minimize the chance of overfilling. If a vaporizer is overfilled or tilted, liquid anesthetic can spill into the bypass chamber, causing an overdose. The concentration control dial is a variable restrictor, and it can be located either in the bypass chamber or in the outlet of the vaporizing chamber. The function of the concentration control dial is to regulate the relative flow rates through the bypass and vaporizing chambers.

Flow from the flowmeters enters the inlet of the vaporizer. More than 80 percent of the flow passes straight through the bypass chamber to the vaporizer outlet, and

this accounts for the name "bypass chamber." Less than 20 percent of the flow from the flowmeters is diverted through the vaporizing chamber. Depending on the temperature and the vapor pressure of the particular inhaled anesthetic, the flow through the vaporizing chamber entrains a specific flow of inhaled anesthetic. All three flows, that is, flow through the bypass chamber, flow through the vaporizing chamber, and flow of entrained anesthetic, exit the vaporizer at the outlet. The final concentration of inhaled anesthetic is the ratio of the flow of the inhaled anesthetic to the total gas flow. [41] [46]

The vapor pressure of an inhaled anesthetic depends on the ambient temperature (see Fig. 7-13 (Figure Not Available) .). For example, at 20°C, the vapor pressure of isoflurane is 238 mm Hg, whereas at 35°C, the vapor pressure almost doubles (450 mm Hg). Variable-bypass vaporizers have an internal mechanism to compensate for different ambient temperatures. The temperature-compensating valve of the Ohmeda Tec 4 is shown in Figure 7-15 (Figure Not Available) [47] At high temperatures, such as those commonly used in pediatric or burn operating rooms, the vapor pressure inside the vaporizing chamber is high. To compensate for this increased vapor pressure, the bimetallic strip of the temperature-compensating valve leans to the right. This allows more flow to pass through the bypass chamber and less flow to pass through the vaporizing chamber. The net effect is a constant vaporizer output. In a cold operating room environment, the vapor pressure inside the vaporizing chamber decreases. To compensate for this decrease in vapor pressure, the bimetallic strip swings to the left, causing more flow to pass through the vaporizing chamber and less to pass through the bypass chamber. The net effect is a constant vaporizer output.

Factors That Influence Vaporizer Output

The output of an ideal vaporizer with a fixed dial setting would be constant, regardless of varied flow rates, temperatures, back pressures, and carrier gases. Designing such a

Figure 7-14 (Figure Not Available) Generic variable bypass vaporizer (see text for details). *(Modified from Andrews JJ: Delivery systems for inhaled anesthetics. In Barash PG, Cullen BF, Stoelting RK [eds]: Clinical Anesthesia, 3rd ed. Philadelphia, New York, Lippincott-Raven, 1997, pp 535-572.)*

Figure 7-15 (Figure Not Available) Simplified schematic of the Ohmeda Tec 4 vaporizer (see text for details). *(Modified from Andrews JJ: Delivery systems for inhaled anesthetics. In Barash PG, Cullen BF, Stoelting RK [eds]: Clinical Anesthesia, 3rd ed. Philadelphia, New York, Lippincott-Raven, 1997, pp 535-572.)*

vaporizer is difficult because as ambient conditions change, the physical properties of gases and of vaporizers themselves can change. [46] Contemporary vaporizers approach ideal but still have some limitations. Several factors listed below can influence vaporizer output.

Flow Rate.

With a fixed dial setting, vaporizer output varies with the rate of gas flowing through the vaporizer. This variation is particularly notable at extremes of flow rates. The output of all variable-bypass vaporizers is less than the dial setting at low flow rates (<250 mL/min). This results from the relatively high density of volatile inhaled anesthetics. The turbulence generated at low flow rates in the vaporizing chamber is insufficient to upwardly advance the vapor molecules. At extremely high flow rates, such as 15 L/min, the output of most variable-bypass vaporizers is less than the dial setting. This discrepancy is attributed to incomplete mixing and saturation in the vaporizing chamber. Also, the resistance characteristics of the bypass chamber and the vaporizing chamber can vary as flow increases. These changes can result in decreased output concentration. [46]

Temperature.

Because of improvements in design, the output of contemporary temperature-compensated vaporizers is almost linear over a wide range of temperatures. Automatic temperature-compensating mechanisms in bypass chambers maintain a constant vaporizer output with varying temperatures. [8] [47] [48] A bimetallic strip (see Fig. 7-15 (Figure Not Available)) or an expansion element (Fig. 7-16) (Figure Not Available) directs a greater proportion of gas flow through the bypass chamber as temperature increases. [46] Wicks are placed in direct contact with the metal wall of the vaporizer to help replace heat used for vaporization. Vaporizers are constructed with metals having relatively

Figure 7-16 (Figure Not Available) Simplified schematic of the North American Drager Vapor 19.1 vaporizer (see text for details). *(Modified from Andrews JJ: Delivery systems for inhaled anesthetics. In Barash PG, Cullen BF, Stoelting RK [eds]: Clinical Anesthesia, 3rd ed. Philadelphia, New York, Lippincott-Raven, 1997, pp 535-572.)*

high specific heat and high thermal conductivity in order to minimize heat loss.

Intermittent Back Pressure.

Intermittent back pressure associated with positive-pressure ventilation or with oxygen flushing can cause higher vaporizer output concentration than the dialed setting. This phenomenon, known as the pumping effect, [41] [46] [49] [50] [51] is more pronounced at low flow rates, low dial settings, and low levels of liquid anesthetic in the vaporizing chamber. Additionally, the pumping effect is increased by rapid respiratory rates, high peak inspired pressures, and rapid drops in pressure during expiration. [47] [48] [49] [50] [51] The Ohmeda Tec 4 and the North American Drager Vapor 19.1 are relatively immune from the pumping effect. [47] [48] One proposed mechanism for the pumping effect is dependent on retrograde pressure transmission from the patient circuit to the vaporizer during the inspiratory phase of positive-pressure ventilation. Gas molecules are compressed in both the bypass and the vaporizing chambers. When the back pressure is suddenly released during the expiratory phase of positive-pressure ventilation, vapor exits the vaporizing chamber via the vaporizing chamber outlet and retrograde through the vaporizing chamber inlet. This occurs because the output resistance of the bypass chamber is lower than that of the vaporizing chamber, particularly at low dial settings. The enhanced output concentration results from the increment of vapor that travels in the retrograde direction to the bypass chamber. [46] [49] [50] [51]

To decrease the pumping effect, the vaporizing chambers of the Tec 4 and the Vapor 19.1 are smaller than those of older variable-bypass vaporizers, such as the Fluotec Mark II (750 mL). [47] [48] [50] Therefore, no substantial volumes of vapor can be discharged from the vaporizing chamber into the bypass chamber during the expiratory phase. The North American Drager Vapor 19.1 (see Fig. 7-16 (Figure Not Available)) has a patented long spiral tube that serves as the inlet to the vaporizing chamber. [48] [50] When the pressure in the vaporizing chamber is released, some of the vapor enters this tube but does not enter the bypass chamber because of tube length. [50] The Tec 4 (see Fig. 7-15 (Figure Not Available)) has an extensive baffle system in the vaporizing chamber, and a one-way check valve has been inserted at the common outlet to minimize the pumping effect. This check valve attenuates but does not eliminate the pressure increase, because gas still flows from the flowmeters to the vaporizer during the inspiratory phase of positive-pressure ventilation. [41] [52]

Carrier Gas Composition.

Vaporizer output is influenced by the composition of the carrier gas that flows through the vaporizer. [47] [48] [53] [54] [55] [56] [57] [58] [59] [60] When the carrier gas is quickly switched from 100 percent oxygen to 100 percent nitrous oxide, there is a rapid transient decrease in vaporizer output followed by a slow increase to a new steady-state value (Fig. 7-17 (Figure Not Available) .B) [58] [59] The transient decrease in vaporizer output is attributed to nitrous oxide's being more soluble than oxygen in halogenated liquid. [58] Therefore, the quantity of gas leaving the vaporizing chamber is transiently diminished until the anesthetic liquid is totally saturated with nitrous oxide.

The explanation for the new steady-state output value is less well understood. [60] With contemporary vaporizers, such as the North American Drager Vapor 19.1 and the Ohmeda Tec 4, the steady-state output value is less when nitrous oxide rather than oxygen is the carrier gas (Fig. 7-17 (Figure Not Available) .B) [47] [48] Conversely,

Figure 7-17 (Figure Not Available) Halothane output of a North American Drager Vapor 19.1 vaporizer with different carrier gases. The initial output concentration is approximately 4% halothane when oxygen is the carrier gas at flows of 6 $L \cdot min^{-1}$ (A). When the carrier gas is quickly switched to 100% nitrous oxide (B), the halothane concentration decreases to 3% within 8-10 seconds. Then, a new

steady-state concentration of approximately 3.5% is attained within 1 minute (see text for details). *(Modified from Gould et al [55])*

the output of some older vaporizers is enhanced when nitrous oxide is the carrier gas instead of oxygen. [53] [55] The steady-state plateau is achieved more rapidly with increased flow rates, regardless of the ultimate output value. [59] Factors that contribute to the characteristic steady-state response resulting when various carrier gases are used include the viscosity and density of the carrier gas, the relative solubilities of the carrier gas in the liquid anesthetic, the flow splitting characteristics of the specific vaporizer, and the dial setting. [55] [58] [59] [60]

Safety Features

The North American Drager 19.1, the Ohmeda Tec 4, and the Ohmeda Tec 5 have many safety features that have minimized or eliminated many hazards that were once associated with variable-bypass vaporizers. Agent-specific, keyed filling devices help prevent a vaporizer from being filled with the wrong agent. Overfilling of these vaporizers is minimized because the filler port is located at the maximum safe liquid level. Today's vaporizers are firmly secured to the vaporizer manifold, and there is little need to move them. Thus, problems associated with tipping are minimized. Contemporary interlock systems prevent administration of more than one inhaled anesthetic. [47] [48] [61]

Hazards

Despite many safety features, some hazards are still associated with contemporary variable-bypass vaporizers.

Misfilling.

Vaporizers not equipped with keyed fillers have been occasionally misfilled with the wrong anesthetic liquid. [62] A potential for misfilling exists even on contemporary vaporizers equipped with keyed fillers. [63] [64]

Contamination.

Contamination of anesthetic vaporizer contents occurred when an isoflurane vaporizer was filled with a contaminated bottle of isoflurane. A potentially serious incident was avoided because the operator did not use the contaminated vaporizer after detecting an abnormal acrid odor. [65]

Tipping.

Tipping can occur when vaporizers are incorrectly "switched out" or moved. However, tipping is unlikely when a vaporizer is attached to a manifold in the upright position. Excessive tipping can cause the liquid agent to enter the bypass chamber and can cause a high output concentration. [66] The Tec 4 is slightly more immune to tipping than the Vapor 19.1 because of its extensive baffle system. However, if either vaporizer is tipped, it should not be used until it has been flushed for 20 to 30 minutes at high flow rates with the vaporizer set at a low concentration. [41]

Overfilling.

Improper filling procedures combined with failure of the vaporizer sight glass can cause overfilling and overdose. Liquid anesthetic enters the bypass chamber, and up to 10 times the intended vapor concentration can be delivered. [67]

Simultaneous Inhaled Anesthetic Administration.

Two inhaled anesthetics can be administered simultaneously when the center Tec 4 vaporizer is removed from Ohmeda machines equipped with the older style Selectatec vaporizer manifold. The left or right vaporizer should be moved to the central position if the central vaporizer is removed as indicated by the manifold label. The interlock system then functions properly because the two remaining vaporizers are adjacent. [12] [13] [14]

Leaks.

Leaks occur often with vaporizers, and vaporizer leaks can cause patient awareness. [41] [68] [69] A loose filler cap is the most common source of vaporizer leaks. Leaks can occur at the O-ring junction between the vaporizer and its manifold. A vaporizer must be in the on position to detect a leak within it. Vaporizer leaks in the North American Drager System can be detected with a conventional positive-pressure leak test because of the absence of check valves. Ohmeda recommends using a negative-pressure leak testing device (suction bulb) to detect vaporizer leaks in the Modulus I, Modulus II, and Excel models because of the check valve at the machine outlet [11] [12] [13] [15] (see Checking Anesthesia Machines).

Electrically Heated, Pressurized Vaporizers

Controlled vaporization of desflurane requires an electrically heated, pressurized vaporizer because of desflurane's unique physical properties. [70] [71] The vapor pressure of desflurane is three to four times that of contemporary inhaled anesthetics, and it boils at 22.8°C, [72] which is near room temperature (see Fig. 7-13 (Figure Not Available)). Desflurane has a minimum alveolar anesthetic concentration value of 6 to 7 percent. [72] Desflurane is valuable because it has a low blood gas solubility coefficient of 0.45 at 37°C, and recovery from anesthesia is more rapid than with other potent inhaled anesthetics. [72]

Unsuitability of Contemporary Variable-Bypass Vaporizers for Controlled Vaporization of Desflurane

Desflurane's high volatility and moderate potency preclude its use with contemporary variable-bypass vaporizers, such as Ohmeda Tec 4, Tec 5, or North American Drager Vapor 19.1, for two reasons [70] :

1. The vapor pressure of desflurane is near 1 atm. The vapor pressures of enflurane, isoflurane, halothane, and desflurane at 20°C are 172, 240, 244, and 669 mm Hg, [72] respectively (see Fig. 7-13 (Figure Not Available)). Normal flow through a traditional vaporizer would vaporize many more volumes of desflurane. For example, at 1 atm and 20°C, 100 mL/min passing through the vaporizing chamber entrains 735 mL/min of desflurane versus 29, 46, and 47 mL/min of enflurane, isoflurane, and halothane, respectively. [70] Under these same conditions, the amount of bypass flow necessary to achieve sufficient distribution of anesthetic vapor to produce 1 percent desflurane output would be approximately 73 L/min, compared with 5 L/min or less for the other three anesthetics. At greater than 22.8°C at 1 atm, desflurane boils. The amount of vapor produced would be limited only by the heat energy available from the vaporizer owing to its specific heat. [70]
2. Contemporary vaporizers lack an external heat source. Although desflurane has a heat of vaporization approximately equal to that of enflurane, isoflurane, and halothane, its minimum alveolar anesthetic concentration is four to nine times higher than that of the other three inhaled anesthetics. Thus, the absolute amount of desflurane vaporized over a given time period is considerably higher than that occurring with other anesthetics. Supplying desflurane in higher concentrations would cause excessive cooling of the vaporizer. In the absence of an external heat source, temperature compensation using traditional mechanical devices would be almost impossible over a broad clinical range of temperatures because of desflurane's steep vapor pressure versus temperature curve (see Fig. 7-13 (Figure Not Available)). [70]

Operating Principles of the Tec 6

To achieve controlled vaporization of desflurane, Ohmeda has introduced the Tec 6 vaporizer, which is electrically heated and pressurized. [73] The physical appearance and operation of the Tec 6 are similar to those of contemporary vaporizers, but some aspects of the internal design and operating principles are radically different. A simplified schematic of the Tec 6 is shown in Figure 7-18 (Figure Not Available) . The vaporizer has two independent gas circuits arranged in parallel. The

fresh gas circuit is shown in red, and the vapor circuit is shown in white.

Figure 7-18 (Figure Not Available) Simplified schematic of the Tec 6 desflurane vaporizer. *(Modified from Andrews JJ: Operating Principles of the Ohmeda Tec 6 Desflurane Vaporizer: A Collection of Twelve Color Illustrations. Washington, DC, Library of Congress, 1996.)*

The fresh gas from the flowmeters enters at the fresh gas inlet, passes through a fixed restrictor (R1), and exits at the vaporizer gas outlet. The vapor circuit originates at the desflurane sump, which is electrically heated and thermostatically controlled to 39°C, a temperature well above desflurane's boiling point. The heated sump assembly serves as a reservoir of desflurane vapor. At 39°C, the vapor pressure in the sump is approximately 1,300 mm Hg absolute, [74] or approximately 2 atm absolute (see Fig. 7-13 (Figure Not Available)). Just downstream from the sump is the shut-off valve. After the vaporizer warms up, the shut-off valve fully opens when the concentration control valve is turned to the "on" position. A pressure-regulating valve downstream from the shut-off valve downregulates the pressure to approximately 1.1 atm absolute (74 mm Hg gauge) at a fresh gas flow rate of 10 L/min. The operator controls desflurane output by adjusting the concentration control valve (R2) , which is a variable restrictor. [70]

The vapor flow through R2 joins the fresh gas flow through R1 at a point downstream from the restrictors. Until this point, the two circuits are physically divorced. They are interfaced pneumatically and electronically, however, through differential pressure transducers, a control electronics system, and a pressure-regulating valve. When a constant fresh gas flow rate encounters the fixed restrictor, R1, a specific back pressure that is proportional to the fresh gas flow rate pushes against the diaphragm of the control differential pressure transducer. The differential pressure transducer conveys the pressure difference between the fresh gas circuit and the vapor circuit to the control electronics system. The control electronics system regulates the pressure-regulating valve so that the pressure in the vapor circuit equals the pressure in the fresh gas circuit. This equalized pressure supplying R1 and R2 is the working pressure, and the working pressure is constant at a fixed fresh gas flow rate. If the operator increases the fresh gas flow rate, more back pressure is exerted on the diaphragm of the control pressure transducer, and the working pressure of the vaporizer increases. [70]

Table 7-1 (Table Not Available) shows the approximate correlation between fresh gas flow rate and working pressure for a typical vaporizer. At a fresh gas flow rate of 1 L/min, the working pressure is 10 millibars, or 7.4 mm Hg gauge. At a fresh gas flow rate of 10 L/min, the working pressure is 100 millibars, or 74 mm Hg gauge. Therefore, there is a linear relationship between fresh gas flow rate and working pressure. When the fresh gas

TABLE 7-1 -- Fresh Gas Flow Rate Versus Working Pressure

(Not Available)

From Andrews JJ, Johnston RV Jr: The new Tec 6 desflurane vaporizer. Anesth Analg 76:1338, 1993.

flow rate is increased tenfold, the working pressure increases tenfold. [70]

Listed below are two specific examples to demonstrate the operating principles of the Tec 6. [70]

Example A: Constant fresh gas flow rate of 1 L/min, with an increase in the dial setting. With a fresh gas flow rate of 1 L/min, the working pressure of the vaporizer is 7.4 mm Hg. That is, the pressure supplying R1 and R2 is 7.4 mm Hg. As the operator increases the dial setting, the opening at R2 becomes larger, allowing more vapor to pass through R2. Specific vapor flow values at different dial settings are shown in Table 7-2 (Table Not Available) .

Example B: Constant dial setting with an increase in fresh gas flow from 1 to 10 L/min. At a fresh gas flow rate of 1 L/min, the working pressure is 7.4 mm Hg, and at a dial setting of 6 percent, the vapor flow rate through R2 is 64 mL/min (see Tables 7-1 (Table Not Available) and 7-2) (Table Not Available) . With a tenfold increase in the fresh gas flow rate, there is a concomitant tenfold increase in the working pressure to 74 mm Hg. The ratio of resistances of R2 to R1 is constant at a fixed dial setting of 6 percent. Because R2 is supplied by 10 times more pressure, the vapor flow rate through R2 increases tenfold to 640 mL/min. Vaporizer output is constant because both the fresh gas flow and the vapor flow increase proportionally.

Factors That Influence Vaporizer Output

Varied altitude and carrier gas composition influence Tec 6 output and are discussed in the following sections.

Varied Altitudes.

Unlike contemporary variable-bypass vaporizers, the Tec 6 vaporizer requires manual adjustments of the concentration control dial at altitudes other than sea level to maintain a constant partial pressure of anesthetic. The Tec 6 itself works at absolute pressures; therefore, altitude makes no difference to the vaporizer's performance per se. It accurately delivers the dialed volume percent of desflurane. However, when this gas is brought to ambient atmosphere at high altitudes, the volume percent represents an absolute decrease in the partial pressure of the anesthetic, unlike with the contemporary variable-bypass vaporizers, which deliver a constant partial pressure of anesthetic. To compensate for the reduction of partial pressure of vapor at altitude, the Tec 6 rotary valve must be advanced to maintain

TABLE 7-2 -- Dial Setting Versus Flow Through Restrictor R2
From Andrews JJ, Johnston RV Jr: The new Tec 6 desflurane vaporizer. Anesth Analg 76:1338, 1993.

(Not Available)

the required anesthetic partial pressure. The required dial setting may be calculated by use of the following formula [73] :

Required dial setting = Normal dial setting (vol %) × 760 mm Hg/ambient pressure (mm Hg)

For example, at an altitude of 2,000 m, or 6,564 feet, where the ambient pressure is 608 mm Hg, the operator must advance the concentration control dial from 10 to 12.5 percent to maintain the required anesthetic partial pressure. [73] In hyperbaric settings, the operator must decrease the dial setting to prevent delivery of an overdose.

Carrier Gas Composition.

Vaporizer output approximates the dial setting when oxygen is the carrier gas because the Tec 6 vaporizer is calibrated by use of 100 percent oxygen. [73] At low flow rates when a carrier gas other than 100 percent oxygen is used, however, a clear trend toward reduction in vaporizer output emerges. This reduction parallels the proportional decrease in the viscosity of the carrier gas. Nitrous oxide has a lower viscosity than oxygen, so the back pressure generated by resistor R1 (see Fig. 7-18 (Figure Not Available)) is less when nitrous oxide is the carrier gas, and the working pressure is reduced. At low flow rates with nitrous oxide as the carrier gas, vaporizer output is approximately 20 percent less than the dial setting. This result suggests that at clinically useful fresh gas flow rates, the gas flow across resistor R1 is laminar, and the working pressure is proportional to both the fresh gas flow rate and the viscosity of the carrier gas. [75]

Safety Features

Because desflurane's vapor pressure is near 1 atm, misfilling contemporary vaporizers with desflurane can theoretically cause desflurane overdose and hypoxemia. [76] Ohmeda has introduced a unique anesthetic-specific filling system to minimize the occurrence of this hazard. The agent-specific filler cap of the desflurane bottle

prevents its use with traditional vaporizers. The filling system also minimizes spillage of liquid or vapor anesthetic by maintaining a "closed system" during the filling process. Each desflurane bottle has a spring-loaded filler cap with an O-ring on the tip. The spring seals the bottle until it is engaged in the filler port of the vaporizer. Thus, this anesthetic-specific filling system interlocks the vaporizer and the dispensing bottle, preventing loss of anesthetic to the atmosphere. [73]

Major vaporizer faults cause the shut-off valve located just downstream from the desflurane sump (see Fig. 7-18 (Figure Not Available)) to close, producing a no-output situation. The valve is closed and a "no output" alarm is activated immediately if any of the following conditions occur: (1) the anesthetic level decreases to below 20 mL, (2) the vaporizer is tilted, (3) a power failure occurs, or (4) there is a disparity between the pressure in the vapor circuit versus the pressure in the fresh gas circuit exceeding a specified tolerance. [73]

Summary

The Tec 6 vaporizer is an electrically heated, thermostatically controlled, constant-temperature, pressurized, electromechanically coupled, dual-circuit, gas-vapor blender. The

---

pressure in the vapor circuit is electronically regulated to equal the pressure in the fresh gas circuit. At a constant fresh gas flow rate, the operator regulates vapor flow by use of a conventional concentration control dial. When the fresh gas flow rate increases, the working pressure increases proportionally. At a specific dial setting at different fresh gas flow rates, vaporizer output is constant because the amount of flow through each circuit is proportional. [70]

ANESTHETIC CIRCUITS

Gas exits the anesthesia machine at the common gas outlet and then enters an anesthetic circuit. The function of an anesthetic circuit is not only to deliver oxygen and anesthetic gases to the patient but also to eliminate CO_2. CO_2 can be removed either by washout with adequate fresh gas inflow or by absorption with soda lime. This discussion is limited to semiclosed rebreathing circuits and the circle system.

Mapleson Systems

In 1954 Mapleson described and analyzed five different semiclosed anesthetic systems, and they are now classically referred to as the Mapleson systems and are designated A to E. [77] Willis et al [78] added the F system to the five original systems. The Mapleson systems are shown in Figure 7-19 (Figure Not Available) . System components can include a face mask, a spring-loaded pop-off valve, reservoir tubing, fresh gas inflow tubing, and a reservoir bag. Three distinct functional groups emerge, and they include the A, the BC, and the DEF groups. The Mapleson A, also known as the Magill circuit, has a spring-loaded pop-off valve located near the face mask, and the fresh gas flow enters the opposite end of the circuit near the reservoir bag. In the B and C systems, the spring-loaded pop-off valve is located near the face mask, but the fresh gas inlet tubing is located near the patient. The reservoir tubing and breathing bag serve as a blind limb where fresh gas, dead space gas, and alveolar gas can collect. Finally, in the Mapleson D, E, and F group, or the T-piece group, the fresh gas enters near the patient, and excess gas is popped off at the opposite end of the circuit.

Even though the component arrangement and components are simple, functional analysis of the Mapleson systems can be complex. [79] [80] The amount of CO_2 rebreathing associated with each system is multifactorial, and variables dictating the ultimate CO_2 concentration include the following: (1) fresh gas inflow rate, (2) minute ventilation, (3) mode of ventilation (spontaneous or controlled), (4) tidal volume, (5) respiratory rate, (6) inspiratory to expiratory ratio, (7) duration of the expiratory pause, (8) peak inspiratory flow rate, (9) volume of the reservoir tube, (10) volume of

Figure 7-19 (Figure Not Available) Gas disposition at end-expiration during spontaneous (left) and controlled (right) ventilation in circuits A-F. FGF, fresh gas flow. *(Modified from Sykes [81])*

the breathing bag, (11) ventilation by mask, (12) ventilation through an endotracheal tube, and (13) the CO_2 sampling site.

The performance of the Mapleson systems is best understood by studying the expiratory phase of the respiratory cycle (see Fig. 7-19 (Figure Not Available)). [81] During spontaneous ventilation, the Mapleson A has the best efficiency of the six systems, requiring a fresh gas inflow rate of only one times the minute ventilation to prevent rebreathing of CO_2. However, it has the worst efficiency during controlled ventilation, requiring a minute ventilation of as much as 20 L/min to prevent rebreathing. Systems D to F are slightly more efficient than systems B and C. To prevent rebreathing of CO_2, systems D to F require a fresh gas inflow rate of approximately 2.5 times the minute ventilation, whereas the fresh gas inflow rates required for systems B and C are somewhat higher. [80]

The relative efficiency of different Mapleson systems with respect to prevention of rebreathing during spontaneous ventilation can be summarized as follows: A > DFE > CB. During controlled ventilation, DFE > BC > A. [80] [82] The Mapleson A, B, and C systems are rarely used today, but the D, E, and F systems are commonly employed. In the United States, the most popular representative from the D, E, and F group is the Bain circuit.

Bain Circuit

The Bain circuit is a modification of the Mapleson D system. It is a coaxial circuit in which the fresh gas flows through a narrow inner tube within the outer corrugated tubing. [83] The central tube originates near the reservoir bag, but the fresh gas actually enters the circuit at the patient end (Fig. 7-20) (Figure Not Available) . Exhaled gases enter the corrugated tubing and are vented through the expiratory valve near the reservoir bag. The Bain circuit may be used for both spontaneous and controlled ventilation. The fresh gas inflow rate necessary to prevent rebreathing is 2.5 times the minute ventilation.

There are many advantages to this circuit. It is lightweight, convenient, easily sterilized, and reusable. Scavenging of the gases from the expiratory valve is facilitated because the overflow valve is located away from the patient. Exhaled gases in the outer reservoir tubing add warmth to inspired fresh gases. The hazards of the Bain circuit include unrecognized disconnection or kinking of the inner fresh gas hose. These problems can cause hypercarbia from inadequate gas flow or increased respiratory resistance.

The outer tube should be transparent to allow inspection of the inner tube. The integrity of the inner tube can be assessed, as described by Pethick. [84] High-flow oxygen is fed into the circuit while the patient end is occluded until the reservoir bag is filled. The patient end is opened, and oxygen is flushed into the circuit. If the inner tube is intact, the Venturi effect occurs at the patient end. This effect causes a decrease in pressure within the circuit, and the reservoir bag deflates. Conversely, a leak in the inner tube allows the fresh gas to escape into the expiratory limb, and the reservoir bag remains inflated. This test is recommended as a part of the preanesthesia check if a Bain circuit is used.

Circle System

The circle system is the most popular breathing system in the United States. It is so named because its components are arranged in a circular manner. This system prevents rebreathing of CO_2 by soda lime absorption but allows partial rebreathing of other exhaled gases. The extent of rebreathing of the other exhaled gases depends on component arrangement and the fresh gas flow rate.

A circle system can be semiopen, semiclosed, or closed, depending on the amount of fresh gas inflow. [85] A semiopen system has no rebreathing and requires a very high flow of fresh gas. A semiclosed system is associated with rebreathing of gases and is the most commonly used system in the United States. A closed system is one in which the inflow gas exactly matches that being taken up, or consumed, by the patient. There is complete rebreathing of exhaled gases after absorption of CO_2, and the overflow (pop-off) valve is closed.

The circle system (Fig. 7-21) consists of seven components: (1) a fresh gas inflow source; (2) inspiratory and expiratory unidirectional valves; (3) inspiratory and expiratory corrugated tubes; (4) a Y-piece connector; (5) an overflow or pop-off valve, referred to as the APL valve; (6) a reservoir bag; and (7) a canister containing a CO_2 absorbent. The unidirectional valves are placed in the system to ensure unidirectional flow through the corrugated hoses.

Figure 7-20 (Figure Not Available) The Bain circuit. *(Modified from Bain and Spoerel [85])*

Figure 7-21 Components of the circle system. B, reservoir bag; V, ventilator; APL, adjustable pressure limiting.

The fresh gas inflow enters the circle by a connection from the common gas outlet of the anesthesia machine.

Numerous variations of the circle arrangement are possible, depending on the relative positions of the unidirectional valves, the pop-off valve, the reservoir bag, the CO_2 absorber, and the site of fresh gas entry. However, to prevent rebreathing of CO_2, three rules must be followed: (1) a unidirectional valve must be located between the patient and the reservoir bag on both the inspiratory and the expiratory limbs of the circuit, (2) the fresh gas inflow cannot enter the circuit between the expiratory valve and the patient, and (3) the overflow (pop-off) valve cannot be located between the patient and the inspiratory valve. If these rules are followed, any arrangement of the other components prevents rebreathing of CO_2. [86]

The most efficient circle system arrangement that allows the highest conservation of fresh gases is one with the unidirectional valves near the patient and the pop-off valve just downstream from the expiratory valve. This arrangement conserves dead space gas and preferentially eliminates alveolar gas. A more practical arrangement, used on all contemporary anesthesia machines (see Fig. 7-21), is less efficient because it allows alveolar and dead space gas to mix before venting. [86] [87]

The advantages of the circle system include relative stability of inspired concentration, conservation of respiratory moisture and heat, and prevention of operating room pollution. Additionally, it can be used for closed-system anesthesia or with low oxygen flows. The major disadvantage of the circle system stems from its complex design. The circle system has approximately 10 connections, and the multiple connection sites set the stage for misconnections, disconnections, obstructions, and leaks. In a recent closed claim analysis of adverse anesthetic outcomes arising from gas delivery equipment, a third (25/72) of malpractice claims resulted from breathing circuit misconnections or disconnections. [2] Malfunctioning valves can cause serious problems. Rebreathing can occur if the valves stick in the open position. Total occlusion of the circuit can occur if they are stuck closed. Finally, the bulk of the circle offers less convenience and portability than the Mapleson systems.

CARBON DIOXIDE ABSORPTION

Different anesthesia systems eliminate CO_2 with varying degrees of efficiency. The closed and semiclosed circle systems both require CO_2 absorption. Desirable features of CO_2 absorbents include lack of toxicity with common anesthetics, low resistance to air flow, low cost, ease of handling, and efficiency.

The Absorber Canister

On modern anesthesia machines, the absorber canister (see Fig. 7-21) is composed of two clear plastic canisters arranged in series. The canisters can be filled either with bulk absorbent or with absorbent supplied by the factory in prefilled plastic disposable cartridges called prepacks. Free granules from bulk absorbent can create a clinically significant leak if they lodge between the clear plastic canister and the O-ring gasket of the absorber. Leaks have also been caused by defective prepacks that were larger than factory specifications. [88] Prepacks can also cause total obstruction of the circle system if the clear plastic shipping wrapper is not removed before use. [89]

Chemistry of Absorbents

Two formulations of CO_2 absorbents are commonly used today: soda lime and Baralyme.

By weight, the approximate composition of "high moisture" soda lime is 80 percent calcium hydroxide, 15 percent water, 4 percent sodium hydroxide, and 1 percent potassium hydroxide (an activator). Small amounts of silica are added in order to produce calcium and sodium silicate. This addition produces a hard compound and reduces dust formation. The efficiency of the soda lime absorption varies inversely with the hardness; therefore, little silicate is used in contemporary soda lime. Sodium hydroxide is the catalyst for the CO_2 absorptive properties of soda lime. [90] [91] Baralyme is a mixture of approximately 20 percent barium hydroxide and 80 percent calcium hydroxide. It may also contain some potassium hydroxide.

The size of the absorptive granules has been determined by trial and error, which represents a compromise between resistance to air flow and absorptive efficiency. [92] The smaller the granules, the more surface area available for absorption. However, air flow resistance increases. The granular size of soda lime and Baralyme in anesthesia practice is between 4 and 8 mesh, a size at which resistance to air flow is negligible. Mesh refers to the number of openings per linear inch in a sieve through which the granular particles can pass. A 4-mesh screen means that there are four quarter-inch openings per linear inch. An 8-mesh screen has eight eighth-inch openings per linear inch. [90]

The absorption of CO_2 by soda lime is a chemical process, not a physical process. CO_2 combines with water to form carbonic acid. Carbonic acid reacts with the hydroxides to

---

form sodium (or potassium) carbonate and water. Calcium hydroxide accepts the carbonate to form calcium carbonate and sodium (or potassium) hydroxide. The equations are as follows:

1. $CO_2 + H_2O$
 H_2CO_3

2. $H_2CO_3 + 2NaOH\ (KOH)$
 $Na_2CO_3\ (K_2CO_3) + 2H_2O + Heat$

3. $Na_2CO_3\ (K_2CO_3) + Ca(OH)_2$
 $CaCO_3 + 2NaOH\ (KOH)$

Some CO_2 may react directly with $Ca(OH)_2$, but this reaction is much slower.

The reaction with Baralyme differs from that with soda lime because more water is liberated by a direct reaction of barium hydroxide and CO_2 .

1. $Ba(OH)_2 + 8H_2O + CO_2$
 $BaCO_3 + 9H_2O + Heat$

2. $9H_2O + 9CO_2$
 $9H_2CO_3$

Then, by direct reactions and by KOH and NaOH,

3. $9H_2CO_3 + 9Ca(OH)_2$
 $CaCO_3 + 18H_2O + Heat$

Absorptive Capacity

The maximum amount of CO_2 that can be absorbed is 26 L of CO_2 per 100 g of absorbent. However, channeling of gas through granules may substantially decrease this efficiency and may allow only 10 to 20 L of CO_2 to be absorbed. [93]

Indicators

Ethyl violet, the pH indicator added to both soda lime and Baralyme to help assess the functional integrity of the absorbent, is a substituted triphenylmethane dye with

a critical pH of 10.3. [91] The color of ethyl violet changes from colorless to violet when the pH of the absorbent decreases as a result of CO_2 absorption. The pH of fresh absorbent exceeds the critical pH, and the dye exists in its colorless form (Fig. 7-22 (Figure Not Available) , left). As absorbent becomes exhausted, however, the pH decreases below 10.3, and ethyl violet changes to its violet form (see Fig. 7-22 (Figure Not Available) , right) through alcohol dehydration. Ethyl violet is not always a reliable indicator of the functional status of absorbent. Fluorescent lights can deactivate the dye so that the absorbent appears white even though it is exhausted. [94]

Interactions of Inhaled Anesthetics With Absorbents

It is important and desirable to have CO_2 absorbents that are neither intrinsically toxic nor toxic when exposed to common anesthetics. Soda lime and Baralyme generally fit this description, but inhaled anesthetics do interact with absorbents to some extent. Historically speaking, an uncommon anesthetic, trichloroethylene, reacts with soda lime to produce toxic compounds. In the presence of alkali and heat, trichloroethylene degrades into the cranial neurotoxin dichloroacetylene, which can cause cranial nerve lesions and encephalitis. Phosgene, a potent pulmonary irritant, is also produced and can cause adult respiratory distress syndrome. [95]

Sevoflurane has been shown to produce degradation products on interaction with CO_2 absorbents. [96] The major degradation product produced is fluoromethyl-2, 2-difluoro-1-(trifluoromethyl) vinyl ether, or compound A. During sevoflurane anesthesia, factors apparently leading to an increase in the concentration of Compound A include (1) low flow or closed circuit anesthetic techniques; (2) the use of Baralyme rather than soda lime; (3) higher concentrations of sevoflurane in the anesthetic circuit; (4) higher absorbent temperatures; and (5) fresh absorbent. [96] [97] [98] Baralyme dehydration increases the concentration of compound A, and soda lime dehydration decreases the concentration of compound A. [99] [100] Apparently, the degradation products do not cause toxic effects in humans, even during low-flow anesthesia, [97] but further studies are needed to verify this. [101] [102] [103]

Desiccated soda lime and Baralyme can degrade contemporary inhaled anesthetics to clinically significant concentrations of carbon monoxide (CO), which in turn can produce carboxyhemoglobin concentrations reaching 30 percent or more. Higher levels of CO are more likely after prolonged contact between absorbent and anesthetics and after disuse of an absorber for at least 2 days, especially over a weekend. Thus, case reports describing CO poisoning are most common in patients anesthetized on Monday morning, presumably

Figure 7-22 (Figure Not Available) (A and B) Ethyl violet (see text for details). *(Modified from Andrews JJ et al [94])*

because continuous flow from the anesthesia machine dehydrated the absorbents over the weekend. [104] [105]

Several factors appear to increase the production of CO, including (1) the inhaled anesthetic used (for a given minimum alveolar concentration multiple, the magnitude of CO production from greatest to least is desflurane
enflurane > isoflurane >> halothane = sevoflurane); (2) the absorbent dryness (completely dry absorbent produces more CO than hydrated absorbent); (3) the type of absorbent (at a given water content, Baralyme produces more CO than does soda lime); (4) the temperature (an increased temperature increases CO production); and (5) the anesthetic concentration (more CO is produced from higher anesthetic concentrations). [106]

In a study in swine in which partially dried Baralyme was used during desflurane anesthesia, extremely high levels of CO and carboxyhemoglobin occurred. [107] Interventions have been suggested to reduce the incidence of CO exposure in humans undergoing general anesthesia. [105] The interventions include (1) educating anesthesia personnel regarding the cause of CO production, (2) turning off the anesthesia machine at the conclusion of the last case of the day to eliminate fresh gas flow, which dries the absorbent, (3) changing the CO_2 absorbent if fresh gas was found flowing during the morning machine check, (4) rehydrating desiccated absorbent by adding water to the absorbent. [104]

ANESTHESIA VENTILATORS

The anesthesia ventilator can substitute for the breathing bag of the circle system, the Bain circuit, and other breathing systems. Ten years ago, anesthesia ventilators were mere adjuncts to the anesthesia machine. Today, they have attained a prominent central role in newer anesthesia systems. This discussion focuses on the classification, operating principles, and hazards of anesthesia ventilators.

Classification

Ventilators can be classified according to their power source, drive mechanism, cycling mechanism, and bellows type. [108] [109] The following section reviews ventilator classification and terminology before the discussion of individual anesthesia machine ventilators.

Power Source

The power source required to operate a mechanical ventilator is provided by compressed gas, electricity, or both. Older pneumatic ventilators required only a pneumatic power source to function properly. Contemporary North American Drager and Ohmeda electronic ventilators require both an electronic and a pneumatic power source. [16] [18] [19] [20] [21] [22] [110] [111]

Drive Mechanism

Most anesthesia machine ventilators are classified as double-circuit, pneumatically driven ventilators. In a double-circuit system, a driving force (compressed gas) compresses a bag or bellows, which in turn delivers gas to the patient. The driving gas in the Ohmeda 7000, 7810, and 7900 is 100 percent oxygen. [16] [110] [111] In the North American Drager AV-E, a Venturi device mixes oxygen and air. [18] [19] [20] [21] [22]

Cycling Mechanism

Most anesthesia machine ventilators are time cycled and provide ventilator support in the control mode. Inspiration is initiated by a timing device. Older pneumatic ventilators use a fluidic timing device. Contemporary electronic ventilators use a solid-state timing device and are thus classified as time cycled and electronically controlled.

Bellows Classification

The direction of bellows movement during the expiratory phase determines the bellows classification. Ascending (standing) bellows ascend during the expiratory phase (Fig. 7-23 (Figure Not Available) , right), whereas descending (hanging) bellows descend during the expiratory phase. Older pneumatic ventilators use weighted descending bellows, whereas most contemporary electronic ventilators have ascending bellows. Of the two configurations, the ascending bellows is safer. An ascending bellows does not fill if a total disconnection occurs. The bellows of a descending bellows ventilator, however, continues its upward and downward movement during a disconnection. The driving gas pushes the bellows upward during the inspiratory phase. During the expiratory phase, room air is entrained into the breathing system at the site of the disconnection because gravity acts on the weighted bellows. The disconnection pressure monitor and the volume monitor may be fooled even if a disconnection is complete (see Breathing Circuit Problems). [1]

Operating Principles of Ascending Bellows Ventilators

Contemporary examples of ascending bellows, double-circuit, electronic ventilators include the North American Drager AV-E and the Ohmeda 7000, 7800, and 7900 series. A generic ascending bellows ventilator is shown in Figure 7-23 (Figure Not Available) . It may be viewed as a breathing bag (bellows) located within a clear plastic box. The bellows physically separates the driving gas circuit from the patient gas circuit. The driving gas circuit is located outside the bellows, and the patient gas circuit is inside the bellows. During the inspiratory phase (see Fig. 7-23 (Figure Not Available) , left), the driving gas enters the bellows chamber, causing the pressure within it to increase. This increase in pressure is responsible for two events. First, the ventilator relief valve closes, preventing anesthetic gas from escaping into the scavenging system. Second, the bellows is compressed, and the anesthetic gas within the bellows is delivered to the patient's lungs. This compression action is analogous to that of the hand of the anesthesiologist squeezing the breathing bag. [39]

During the expiratory phase (see Fig. 7-23 (Figure Not Available) , right), the driving gas exits the bellows chamber. The pressure within the bellows chamber and the pilot line declines to zero,

Figure 7-23 (Figure Not Available) Inspiratory (left) and expiratory (right) phase gas flows of a generic ascending bellows anesthesia ventilator (see text for details). *(From Andrews [35])*

causing the mushroom portion of the ventilator relief valve to open. Exhaled patient gas fills the bellows before any scavenging occurs, because a weighted ball similar to those used in ball-type positive end-expiratory pressure valves is incorporated into the base of the ventilator relief valve. The ball produces 2 to 3 cm H_2O of back pressure; therefore, scavenging occurs only after the bellows fills completely and the pressure inside the bellows exceeds this pressure threshold. This design causes all ascending bellows ventilators to produce 2 to 3 cm H_2O of positive end-expiratory pressure within the breathing circuit. Scavenging occurs only during the expiratory phase because the ventilator relief valve is open only during expiration. [39]

Gas flow from the anesthesia machine into the breathing circuit is continuous and independent of ventilator activity. During the inspiratory phase of mechanical ventilation, the ventilator relief valve is closed, and the breathing system's APL valve (pop-off valve) is either closed or out of circuit. Therefore, the patient receives volume from the bellows and flowmeters during the inspiratory phase. Factors that influence the correlation between set tidal volume and exhaled tidal volume include the flowmeter settings, the inspiratory time, the compliance of the breathing circuit, the external leakage, and the location of the tidal volume sensor. [16] [17] [110] [111] Usually, the volume gained from the flowmeters during inspiration is counteracted by the volume lost to the breathing circuit compliance. The set tidal volume generally approximates the exhaled tidal volume. However, oxygen flushing during the inspiratory phase can result in barotrauma because excess volume cannot be vented. [39]

Problems and Hazards

Numerous hazards are associated with anesthesia ventilators. These include problems with the breathing circuit, the bellows assembly, and the control assembly.

Breathing Circuit Problems

Breathing circuit disconnection is a leading cause of critical incidents in anesthesia. [2] [112] The most common disconnection site is at the Y-piece. Disconnections can be complete or partial (leaks). A common source of leaks with older absorbers is failure to close the APL or pop-off valve when mechanical ventilation is initiated. The bag/ventilator switch on contemporary absorbers helps minimize this problem. Preexisting undetected leaks can be found in compressed, corrugated, disposable anesthetic circuits. For such a leak to be detected preoperatively, the circuit must be fully expanded before the circuit is checked for leaks. [113] As mentioned earlier, disconnections and leaks manifest more readily with the ascending bellows because the bellows does not fill. [1]

Several disconnection monitors exist. The most important is a vigilant anesthesia care provider who monitors breath sounds, chest wall excursion, and mechanical monitors.

Pneumatic and electronic pressure monitors are helpful in diagnosing disconnections. Factors that influence monitor effectiveness include the disconnection site, the pressure sensor location, the threshold pressure alarm limit, the inspiratory flow rate, and the resistance of the disconnected breathing circuit. [114] [115] Various anesthesia machines and ventilators have different locations for the pressure sensor and different values for the threshold pressure alarm limit (Table 7-3) . The threshold pressure alarm limit may be adjustable or preset at the factory. An audible or visual alarm is actuated if the peak inspiratory pressure of the breathing circuit does not exceed the threshold pressure alarm limit. When an adjustable threshold pressure alarm limit is available, such as on the North American Drager Narkomed 2A, 2B, 3, and 4, the operator should set the pressure alarm limit to within 5 cm H_2O of the peak inspiratory pressure. [18] [19] [20] [21] [22] Figure 7-24 (Figure Not Available) illustrates how a partial disconnection (leak) may be unrecognized by the low-pressure monitor if the

TABLE 7-3 -- Disconnection Pressure Monitors

MACHINE/VENTILATOR	LOCATION OF PRESSURE SENSOR	THRESHOLD PRESSURE ALARM LIMIT (CM WATER)
Ohmeda Modulus II GMS Absorber Ohmeda 7000 Vent	Patient side of expiratory valve	6
Ohmeda Modulus II Plus GMS Absorber Ohmeda 7810	Patient side of inspiratory valve	Delta4-9 PEEP compensated
NAD Narkomed 2A NAD AV-E	CO_2 absorber or Y-piece	8, 12, 26
NAD Narkomed 2B, 3 NAD AV-E	CO_2 absorber or Y-piece	5 30 (12 default)

Data from Ohmeda, [12] [13] [16] [110] [111] *North American Drager* [18] [19] [20] [21]

threshold pressure alarm limit is set too low or if the factory preset value is relatively low.

Respiratory volume monitors are useful in detecting disconnections. Volume monitors sense exhaled tidal volume, minute volume, or both. The user should bracket the high and low threshold volumes slightly above and below the exhaled volumes. For example, if the exhaled minute volume of a patient is 10 L/min, reasonable alarm limits would be 8 to 12 L/min.

Carbon dioxide monitors are probably the best devices for revealing patient disconnections. CO_2 concentration is measured near the Y-piece either directly or by aspiration of a gas sample to the instrument. A drastic change in the differences between the inspiratory and end-tidal CO_2 concentration or the absence of CO_2 indicates a disconnection, a nonventilated patient, or other problems. [1]

Misconnections of the breathing system are common, despite efforts by standards committees to eliminate this problem by assigning different diameters to various hoses and terminals. Anesthesia machines, breathing systems, ventilators, and scavenging systems incorporate a multitude of hose terminals. Hoses have been connected to inappropriate terminals and even to various solid cylindrically shaped protrusions of the anesthesia machine. [1]

Occlusion (obstruction) of the breathing circuit may occur. Tracheal tubes can become kinked. Hoses throughout the breathing circuit are subject to occlusion by external mechanical forces that can impinge on flow. Blockage of a bacterial filter in the expiratory limb of the circle system has caused a bilateral tension pneumothorax. [116] Incorrect insertion of flow direction-sensitive components can result in a no-flow state. [1] Examples of these components include some positive end-expiratory pressure valves and cascade humidifiers. Depending on the location of the occlusion and the pressure sensor, a high-pressure alarm may alert the anesthesiologist to the problem.

Excess inflow to the breathing circuit from the anesthesia machine during the inspiratory phase can cause barotrauma. The best example of this phenomenon is oxygen flushing. Excess volume cannot be vented from the system during inspiration

Figure 7-24 (Figure Not Available) Threshold pressure alarm limit. (Top) The threshold pressure alarm limit (dotted line) has been set appropriately. An alarm is actuated when a partial disconnection occurs (arrow) because the threshold pressure alarm limit is not exceeded by the breathing circuit pressure. (Bottom) A partial disconnection is unrecognized by the pressure monitor because the threshold pressure alarm limit has been set too low. *(Modified from Baromed Breathing Pressure Monitor. Operator's Instruction Manual. Telford, Pennsylvania, North American Drager, 1986.)*

because the ventilator relief valve is closed and the APL valve is either out of circuit or closed. [39] A high-pressure alarm, if present, may be activated when the pressure becomes excessive. In the North American Drager System, both audible and visual alarms are actuated if the high-pressure threshold is exceeded. [18] [19] [20] [21] [22] In the Modulus II Plus System, the Ohmeda 7810 ventilator automatically switches from the inspiratory to the expiratory phase when the adjustable peak pressure threshold is exceeded. [16] This minimizes the possibility of barotrauma if the peak pressure threshold is set appropriately by the anesthesiologist.

Bellows Assembly Problems

Leaks can occur in the bellows assembly. Improper seating of the plastic bellows housing can result in inadequate ventilation because a portion of the driving gas is vented to the atmosphere. A hole in the bellows can lead to alveolar hyperinflation and possibly to barotrauma in some ventilators because high-pressure driving gas can enter the patient circuit. The value on the oxygen analyzer may increase if the driving gas is 100 percent oxygen, or it may decrease if the driving gas is composed of an air/oxygen mixture. [117]

The ventilator relief valve can cause problems. Hypoventilation occurs if the valve is incompetent because anesthetic gas is delivered to the scavenging system during the inspiratory phase instead of to the patient. Gas molecules preferentially exit into the scavenging system because it represents the path of least resistance, and the pressure within the scavenging system can be subatmospheric. Ventilator relief valve incompetency can result from a disconnected pilot line, a ruptured valve, or a damaged flapper valve. [118] [119] A ventilator relief valve stuck in the closed position can produce barotrauma. Excessive suction from the scavenging system can draw the ventilator relief valve to its seat and close the valve during both the inspiratory and expiratory phases. [1] Breathing circuit pressure escalates because

excess anesthetic gas cannot be vented.

Control Assembly Problems

The control assembly can be the source of both electrical and mechanical problems. Electrical failure can be total or partial; the former is the more obvious. Some mechanical problems include leaks within the system, faulty regulators, and faulty valves. An occluded muffler on the North American Drager AV-E can cause barotrauma. Obstruction of driving gas outflow closes the ventilator relief valve, and excess patient gas cannot be vented. [120]

SCAVENGING SYSTEMS

Scavenging is the collection and subsequent removal of vented gases from the operating room. [121] The amount of gas used to anesthetize a patient commonly far exceeds the patient's needs. Therefore, scavenging minimizes operating room pollution. In 1977, the National Institute for Occupational Safety and Health prepared a document entitled "Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors." [122] Although it was maintained that a safe level of exposure could not be defined, the National Institute for Occupational Safety and Health recommendations are shown in Table 7-4 . [122] In 1991, the ASTM released the ASTM F1343-91 standard entitled "Standard Specification for Anesthetic Equipment--Scavenging Systems for Anesthetic Gases." [123] The document provided guidelines for devices that safely and effectively scavenge excess anesthetic gas to reduce contamination in anesthetizing areas. [123]

Components

Scavenging systems have five components (Fig. 7-25) (Figure Not Available) : (1) a gas collecting assembly, (2) a transfer means, (3) a scavenging interface, (4) a gas disposal assembly tubing, and (5) an active or passive gas disposal assembly. [123] An active system uses a central vacuum to eliminate waste gases. The pressure of the waste gas itself produces flow through a passive system.

Gas Collecting Assembly

The gas collecting assembly captures excess anesthetic gas and delivers it to the transfer tubing. [123] Excess gas is vented from the anesthesia system either through the APL valve or through the ventilator relief valve. All excess gas passes through these valves, accumulates in the gas collecting assembly, and is directed to the transfer means.

Transfer Means

The transfer means carries excess gas from the gas collecting assembly to the scavenging interface. The tubing must be either 19 or 30 mm, as specified by the ASTM F1343-91 standard. [123] The tubing should be sufficiently rigid to prevent kinking, and as short as possible to minimize the chance of occlusion. Some manufacturers color code the transfer tubing with yellow bands to distinguish it from 22-mm

TABLE 7-4 -- NIOSH Recommendations, 1977

ANESTHETIC GAS	MAXIMUM TWA[a] CONCENTRATION PARTS PER MILLION (PPM)
Halogenated agent alone	2
Nitrous oxide	25
Combination of halogenated agent plus nitrous oxide	
Halogenated agent	0.5
Nitrous oxide	25
Dental facilities (nitrous oxide alone)	50

TWA, time-weighted average; NIOSH, National Institute for Occupational Safety and Health.

Modified from US Department of Health, Education, and Welfare: Criteria for a recommended standard: Occupational exposure to waste anesthetic gases and vapors. March ed, Washington DC, 1977, with permission.

[a] Time-weighted average sampling, also known as time-integrated sampling, is a sampling method that evaluates the average concentration of anesthetic gas over a prolonged period of time, such as 1 to 8 hours.

Figure 7-25 (Figure Not Available) Components of a scavenging system. APL, adjustable pressure limiting. *(Modified from Andrews JJ: Delivery systems for inhaled anesthetics. In Barash PG, Cullen BF, Stoelting RK [eds]: Clinical Anesthesia, 3rd ed. Philadelphia. New York, Lippincott-Raven, 1997, pp 535-572.)*

breathing system tubing. Many machines have separate transfer tubes for the APL valve and for the ventilator relief valve. The two tubes frequently merge into a single hose before they enter the scavenging interface. Occlusion of the transfer means can be particularly problematic because it is upstream from the pressure-buffering scavenging interface. If the transfer means is occluded, breathing circuit pressure increases, and barotrauma can occur.

Scavenging Interface

The scavenging interface is the most important component of the system because it protects the breathing circuit or ventilator from excessive positive or negative pressure. [121] The interface should limit the pressures immediately downstream from the gas collecting assembly to between -0.5 and +10 cm H_2O under normal working conditions. [123] Positive-pressure relief is mandatory, irrespective of the type of disposal system used, to vent excess gas in case of occlusion downstream from the interface. If the disposal system is active, negative-pressure relief is necessary to protect the breathing circuit or the ventilator from excessive subatmospheric pressure. A reservoir is highly desirable with active systems because it stores excess waste gas until the evacuation system can eliminate it. Interfaces can be open or closed, depending on the method used to provide positive-pressure and negative-pressure relief. [121]

Open Interfaces.

An open interface contains no valves and is open to the atmosphere, allowing both positive-pressure and negative-pressure relief. Open interfaces should be used only with active disposal systems that utilize a central vacuum system. Open interfaces require a reservoir because waste gases are intermittently discharged in surges, whereas flow to the active disposal system is continuous. [121]

Many contemporary anesthesia machines are equipped with open interfaces like those in Figures 7-26A (Figure Not Available) and B. [124] An open canister provides reservoir capacity. The canister volume should be large enough to accommodate a variety of waste gas flow rates. Gas enters the system at the top of the canister and travels through a narrow inner tube to the canister base. Gases are stored in the reservoir between breaths. Positive-pressure and negative-pressure relief is provided by holes in the top of the canister. The open interface shown in Figure 7-26 (Figure Not Available) A differs somewhat from the one shown in Figure 7-26 (Figure Not Available) B. The operator can regulate the vacuum by adjusting the vacuum control valve shown in Figure 7-26 (Figure Not Available) .B [124]

The efficiency of an open interface depends on several factors. The vacuum flow rate per minute must equal or exceed the minute volume of excess gases for spillage to be prevented. The volume of the reservoir and the flow characteristics within the interface are important. Spillage occurs if the volume of a single exhaled breath exceeds the capacity of the reservoir. Leakage can occur long before the volume of waste gas delivered to the reservoir equals the reservoir volume if large-scale turbulence occurs within the interface. [125]

Closed Interfaces.

A closed interface communicates with the atmosphere through valves. All closed interfaces must have a positive-pressure relief valve to vent excess system pressure if obstruction occurs downstream from the interface. A negative-pressure relief valve is mandatory to protect the breathing system from subatmospheric pressure if an active disposal system is used. [121] Two types of closed interfaces are commercially available. One has positive-pressure relief only; the other has both positive-pressure and negative-pressure relief. Each type is discussed in the following sections.

Positive-Pressure Relief Only.

This interface (Fig. 7-27 (Figure Not Available) , left) has a single positive-pressure relief valve and is designed to be used only with passive disposal systems. Waste gas enters the interface at the waste gas inlets. Transfer of the waste gas from the interface to the disposal system relies on the pressure of the waste gas itself because a vacuum is not used. The positive-pressure relief valve opens at a preset value, such as 5 cm H_2O, if an obstruction between

---

Figure 7-26 (Figure Not Available) (A and B) Two open scavenging interfaces. Each requires an active disposal system. APL, adjustable pressure limiting valve (see text for details). *(Modified from Dorsch and Dorsch [121])*

the interface and the disposal system occurs. [126] A reservoir bag is not necessary.

Positive-Pressure and Negative-Pressure Relief.

This interface has a positive-pressure relief valve, at least one negative-pressure relief valve, and a reservoir bag. It is used with active disposal systems. Figure 7-27 (Figure Not Available) (right) is a schematic of North American Drager's closed interface for suction systems. A variable volume of waste gas intermittently enters the interface through the waste gas inlets. The reservoir stores transient excess gas until the vacuum system eliminates it. The operator should adjust the vacuum control valve so that the reservoir bag is properly inflated (A) and not overdistended (B) or completely deflated (C). Gas is vented to the atmosphere through the positive-pressure relief valve if the system pressure exceeds +5 cm H_2O. Room air is entrained through the negative-pressure relief valve if the system pressure is more negative than -0.5 cm H_2O. A back-up negative-pressure relief valve opens at 1.8 cm H_2O if the primary negative-pressure relief valve becomes occluded. [18]

The effectiveness of a closed system in preventing spillage depends on the inflow rate of excess gas, the vacuum flow rate, and the volume of the reservoir. Leakage of waste gases into the atmosphere occurs only if the reservoir bag becomes fully inflated and the pressure increases sufficiently to open the positive-pressure relief valve. In contrast, the effectiveness of an open system in preventing spillage depends not only on the volume of the reservoir but also on the flow characteristics within the interface. [125]

Gas Disposal Assembly Tubing

The gas disposal assembly tubing (see Fig. 7-25 (Figure Not Available)) conducts waste gas from the scavenging interface to the gas disposal assembly. It should be collapse proof and should run overhead, if possible, to minimize the chance of occlusion. [123]

Gas Disposal Assembly

The gas disposal assembly ultimately eliminates excess waste gas (see Fig. 7-25 (Figure Not Available)). There are two types of disposal systems: (1) active and (2) passive.

The most common method of gas disposal is the active assembly, which uses a central vacuum. The vacuum is a mechanical flow-inducing device that removes the waste gases. An interface with a negative-pressure relief valve is mandatory because the pressure within the system is negative. A reservoir is desirable, and the larger the reservoir, the lower the suction flow rate needed. [121] [125]

A passive disposal system does not use a mechanical flow-inducing device. Instead, the pressure of the waste gas itself produces flow through the system. Positive-pressure relief is mandatory, but negative-pressure relief and a reservoir are unnecessary. Excess waste gas can be eliminated in a number of ways, including venting through the wall, ceiling, or floor or to the room exhaust grill of a nonrecirculating air conditioning system. [121] [125]

Hazards

Scavenging systems minimize operating room pollution, yet they add complexity to the anesthesia system. A scavenging system extends the anesthesia circuit all the way from the anesthesia machine to the ultimate disposal site. This extension increases the potential for problems. Obstruction of scavenging pathways can cause excessive positive-pressure in the breathing circuit, and barotrauma can occur. Excessive

---

Figure 7-27 (Figure Not Available) Closed scavenging interfaces. (Left) Interface used with a passive disposal system. (Right) Interface used with an active system (see text for details). *(Modified [left] from Scavenger Interface for Air Conditioning: Instruction Manual [126] and [right] from Narkomed 2A Anesthesia System [18])*

vacuum applied to a scavenging system can cause negative pressures in the breathing system.

CHECKING ANESTHESIA MACHINES

A complete anesthesia apparatus checkout procedure should be performed each day before the first case. An abbreviated version should be performed before each subsequent case. Several checkout procedures exist, but the 1993 Food and Drug Administration (FDA) Anesthesia Apparatus Checkout Recommendations reproduced in Appendix I is the most popular. [127] [128] [129] [130] [131] The FDA checkout procedures serve only as generic guidelines because the designs of different machines vary considerably. Also, many machines have been modified in the field. Therefore, specific checks must be performed on specific machines. The user must refer to the operator's manual for special procedures or precautions.

The three most important preoperative checks are (1) oxygen analyzer calibration, (2) low-pressure circuit leak test, and (3) circle system test. Each is discussed in the following sections.

Oxygen Analyzer Calibration

The oxygen analyzer is the most important machine monitor because it is the only machine safety device that evaluates the integrity of the low-pressure circuit. Other machine safety devices, such as the fail-safe valve, the oxygen supply failure alarm, and the proportioning system, are all upstream from the flow control valves (see Fig. 7-3 (Figure Not Available)). The only machine monitor that detects problems downstream from the flow control valves is the oxygen analyzer. Calibration of this monitor is described in Appendix I, #9.

Low-Pressure Circuit Leak Test

The low-pressure circuit leak test checks the integrity of the anesthesia machine from the flow control valves to the common outlet. It evaluates the portion of the machine that is downstream from all safety devices except the oxy-gen analyzer. The components located within this area are precisely the ones that are most subject to breakage and leaks. Leaks in the low-pressure circuit can cause hypoxia or patient awareness. [132] Flowtubes, the most delicate pneumatic component of the machine, can crack or break. A typical three-gas anesthesia machine has 16 O-rings in the low-pressure circuit. Leaks can occur at the interface between the glass flowtube and the manifold and at the O-ring junction between the vaporizer and its manifold. Loose filler caps on vaporizers are a common source of leaks, and these leaks can cause patient awareness under anesthesia. [133]

Several different methods have been used to check the low-pressure circuit for leaks. They include the oxygen flush test, the common gas outlet occlusion test, the traditional positive-pressure leak test, the North American Drager positive-pressure leak test, the Ohmeda 8000 internal positive-pressure leak test, the Ohmeda negative-pressure

TABLE 7-5 -- Check Valves and Recommended Leak Tests

ANESTHESIA MACHINE	MACHINE OUTLET CHECK VALVE	VAPORIZER OUTLET CHECK VALVE	LEAK TEST RECOMMENDED BY MANUFACTURER	
			POSITIVE PRESSURE	*NEGATIVE PRESSURE (SUCTION BULB)*
North American Drager				
Narkomed 2A, 2B, 3, and 4	No	No	X	
Ohmeda Unitrol	Yes	Variable		X
Ohmeda 30/70	Yes	Variable		X
Ohmeda Modulus I	Yes	Variable		X
Ohmeda Modulus II	Yes	No		X
Ohmeda Excel series	Yes	No		X
Ohmeda Modulus II Plus	No	No		X
Ohmeda CD	No	No		X

Data from Ohio Medical Products, [9] [11] *Ohmeda,* [10] [12] [13] [15] [16] [17] *North American Drager* [18] [19] [20] [21] [22]

leak test, and the new 1993 FDA universal negative pressure leak test. One reason for the large number of methods is that the internal design of various machines differs considerably. The most notable example is that most Ohmeda machines have a check valve near the common gas outlet, whereas North American Drager machines do not. The presence or absence of the check valve profoundly influences which preoperative check is indicated.

Several mishaps have resulted from the application of the wrong leak test to a machine. [31] [68] [134] Therefore, it is mandatory to perform the appropriate low-pressure leak test before every case. To do this, it is essential to understand the exact location and operating principles of the Ohmeda check valve. Most Ohmeda anesthesia machines have a machine outlet check valve located in the low-pressure circuit (Table 7-5) . The check valve is located downstream from the vaporizers and upstream from the oxygen flush valve (see Fig. 7-3 (Figure Not Available)). It is open (Fig. 7-28 (Figure Not Available) , left) in the absence of back pressure. Gas flow from the manifold moves the rubber flapper valve off its seat and allows gas to proceed freely to the common outlet. The valve closes (Fig. 7-28 (Figure Not Available) , right) if back pressure is exerted on it. [8] Back pressure sufficient to close the check valve may occur with the following conditions: oxygen flushing, peak breathing circuit pressures generated during positive-pressure ventilation, or use of a positive-pressure leak test.

Generally, machines without check valves can be tested by use of a positive-pressure leak test, and machines with check valves must be tested using a negative-pressure leak test. When performing a positive-pressure leak test, the operator generates positive pressure in the low-pressure circuit by use of flow from the anesthesia machine or from a positive-pressure bulb to detect a leak. When performing a negative-pressure leak test, the operator creates negative pressure in the low-pressure circuit by use of a suction bulb to detect leaks. Two different low-pressure circuit leak tests are described in the following sections.

Figure 7-28 (Figure Not Available) Machine outlet check valve (see text for details). *(Modified from Bowie and Huffman [6])*

Oxygen Flush Positive-Pressure Leak Test

Historically, older anesthesia machines did not have check valves in the low-pressure circuit. Therefore, it was common practice to pressurize the breathing circuit and the low-pressure circuit with the oxygen flush valve to test for internal anesthesia machine leaks. Because many modern Ohmeda machines now have check valves in the lowpressure circuit, however, application of a positive-pressure leak test to these machines can be misleading or even dangerous (Fig. 7-29) (Figure Not Available) . Inappropriate use of the oxygen flush valve to evaluate the low-pressure circuit for leaks can lead to a false sense of security despite the presence of huge leaks. [31] [40] [68] [134] Positive pressure from the patient circuit closes the check valve, and the value on the airway pressure gauge does not decline. The system appears to be tight, but in actuality, only the circuitry downstream from the check valve is leak-free. [27] Thus, a vulnerable area exists from the check valve back to the flow control valves because this area is not tested by a positive-pressure leak test.

1993 FDA Universal Negative-Pressure Leak Test

In 1993, the FDA universal negative-pressure leak test [131] (Appendix I, #5) was named universal because it can be used to check all contemporary anesthesia machines, regardless of the presence or absence of check valves in the low-pressure circuit. It can be applied to Ohmeda machines, North American Drager machines, and others. The 1993 FDA check is based on the Ohmeda negative-pressure leak test (Fig. 7-30) (Figure Not Available) . It is performed by use of a negative-pressure leak testing device, which is a simple suction bulb. The machine master switch, the flow control valves, and the vaporizers are turned off. The suction bulb is attached to the common fresh gas outlet and is squeezed repeatedly until it is fully collapsed. This action creates a vacuum in the low-pressure circuitry. The machine is leak-free if the hand bulb remains collapsed for at least 10 seconds. A leak is present if the bulb reinflates during this period. The test is repeated with each vaporizer individually turned to the "on" position because internal vaporizer leaks can be detected only with the vaporizer turned on.

The FDA universal negative-pressure low-pressure circuit leak test has several advantages. [132] It helps eliminate the present confusion regarding which check should be performed on specific machines. The universal test is quick and simple to perform. It has an obvious end point, and it isolates the problem. For example, if the bulb reinflates in less than 10 seconds, a leak is present somewhere in the low-pressure circuit. Therefore, it differentiates between breathing-circuit leaks and low-pressure circuit leaks. The universal negative-pressure leak test is the most sensitive of all contemporary leak tests because it is not volume dependent, that is, it does not involve a compliant breathing bag or corrugated hoses. It can detect leaks as small as 30 mL/min. Finally, the operator does not need a detailed or in-depth

Figure 7-29 (Figure Not Available) Inappropriate use of the oxygen flush valve to check the low-pressure circuit of an Ohmeda machine equipped with a check valve. The area within the rectangle is not checked by the inappropriate use of the oxygen flush valve. The components located within this area are precisely the ones most subject to breakage and leaks. Positive pressure within the patient circuit closes the check valve, and the value on the airway pressure gauge does not decline, despite leaks in the low-pressure circuit. *(Modified from Andrews JJ: Delivery systems for inhaled anesthetics. In Barash PG, Cullen BF, Stoelting RK [eds]: Clinical Anesthesia, 3rd ed. Philadelphia, New York, Lippincott-Raven, 1997, pp 535-572.)*

Figure 7-30 (Figure Not Available) FDA negative pressure leak test. (Left) A negative pressure leak testing device is attached directly to the machine outlet. Squeezing the bulb creates a vacuum in the low-pressure circuit and opens the check valve. (Right) When a leak is present in the low-pressure circuit, room air is entrained through the leak and the suction bulb inflates. *(From Andrews JJ: Understanding anesthesia machines. In 1988 Review Course Lectures. Cleveland, International Anesthesia Research Society, 1988, p 78.)*

knowledge of proprietary design differences. If the operator performs the universal test correctly, the leak is detected.

Circle System Test

The circle system test (Appendix I, #11 and #12) evaluates the integrity of the circle breathing system, which extends from the common gas outlet to the Y-piece (see Fig. 7-21). It has two parts--the leak test and the flow test. To thoroughly check the circle system for leaks and for valve integrity, both tests must be performed preoperatively. The leak test is performed by closing the pop-off valve, occluding the Y-piece, and pressurizing the circuit to 30 cm H_2O by use of the oxygen flush valve. The value on the pressure gauge does not decline if the circle system is leak-free, but this does not ensure valve integrity. The value on the gauge reads 30 cm H_2O if the unidirectional valves are stuck shut or if the valves are incompetent.

The flow test checks the integrity of the unidirectional valves. It can be performed by removing the Y-piece from the circle system and breathing through the two corrugated hoses individually. The valves should be present, and they should move appropriately. The operator should be able to inhale but should not be able to exhale through the inspiratory limb. The operator should be able to exhale but not inhale through the expiratory limb. The flow test can also be performed by use of the ventilator and a breathing bag attached to the Y-piece as described in the 1993 FDA "Anesthesia Apparatus Checkout Recommendations" (Appendix 1, #12). [131]

SUMMARY

Rapid advances in the anesthesia industry make it increasingly difficult for the anesthesia care provider to keep up with anesthesia machine technology. Nevertheless, a thorough understanding of the machine is mandatory for the safe practice of anesthesia. Machines are equipped with dozens of safety features, yet none of them is foolproof. The anesthesia care provider must still check the machine preoperatively by use of appropriate checkout procedures.

References

1. Schreiber P: Safety Guidelines for Anesthesia Systems. Telford, Pennsylvania, North American Drager, 1984.

2. Caplan RA, Vistica MF, Posner KL et al: Adverse anesthetic outcomes arising from gas delivery equipment. Anesthesiology 87:741-748, 1997.

3. American National Standards Institute: Minimum Performance and Safety Requirements for Components and Systems of Continuous Flow Anesthesia Machines for Human Use. (ANSI Z79.81979). New York, American National Standards Institute, 1979.

4. American Society for Testing and Materials: Standard Specification for Minimum Performance and Safety Requirements for Components and Systems of Anesthesia Gas Machines. (ASTM F1161-88). Philadelphia, American Society for Testing and Materials, 1988.

5. American Society for Testing and Materials: Standard Specification for Minimum Performance and Safety Requirements for Components and Systems of Anesthetic Gas Machines. (ASTM 116194). Philadelphia, American Society for Testing and Materials, 1994.

6. American Society for Testing and Materials: Particular Requirements for Anesthesia Workstations and Their Components. (ASTM 29.01.09). West Conshohocken, Pennsylvania, American Society for Testing and Materials, 1998.

7. Dorsch JA, Dorsch SE: The anesthesia machine. In Dorsch JA, Dorsch SE (eds): Understanding Anesthesia Equipment, 3rd ed. Baltimore, Williams & Wilkins, 1994, p 51.

8. Bowie E, Huffman LM: The Anesthesia Machine: Essentials for Understanding. Madison, Ohmeda, The BOC Group, 1985.

9. 30/70 Proportionate Anesthesia Machine (Canadian version). Madison, Ohio Medical Products, 1982.

10. Ohmeda Unitrol Anesthesia System: Operation and Maintenance Manual. Madison, Ohmeda, The BOC Group, 1985.

11. Modulus Anesthesia Gas Machine: Operation Maintenance. Madison, Ohio Medical Products, The BOC Group, 1981.

12. Modulus II Anesthesia System: Operation and Maintenance Manual. Madison, Ohmeda, The BOC Group, 1985.

13. Modulus II Anesthesia System: Service Manual. Madison, Ohmeda, The BOC Group, 1985.

14. Ohmeda 8000 Anesthesia Machine: Operation and Maintenance Manual. Madison, Ohmeda, The BOC Group, 1985.

15. Ohmeda Excel 110 and 210: Operation and Maintenance Manual. Madison, Ohmeda, The BOC Group, 1987.

16. Modulus II Plus Anesthesia System: Operation and Maintenance Manual. Madison, Ohmeda, The BOC Group, 1988.

17. Ohmeda CD Anesthesia System: Operation and Maintenance Manual. Madison, Ohmeda, The BOC Group, 1990.

18. Narkomed 2A Anesthesia System: Technical Service Manual, 6th ed. Telford, Pennsylvania, North American Drager, 1985.

19. Narkomed 2A Anesthesia System: Instruction Manual, 7th ed. Telford, Pennsylvania, North American Drager, 1985.

20. Narkomed 2B Anesthesia System: Operator's Manual. Telford, Pennsylvania, North American Drager, 1988.

21. Narkomed 3 Anesthesia System: Operator's Instruction Manual. Telford, Pennsylvania, North American Drager, 1986.

22. Narkomed 4 Anesthesia System: Operations Instruction Manual. Telford, Pennsylvania, North American Drager, 1990.

23. Cicman JH, Jacoby MI, Skibo VF et al: Anesthesia systems. Part 1: Operating principles of fundamental components. J Clin Monit 8:295, 1992.

24. Feeley TW, Hedley Whyte J: Bulk oxygen and nitrous oxide delivery systems: Design and dangers. Anesthesiology 44:301, 1976.

25. Pelton DA: Nonflammable medical gas pipeline systems. In Wyant GM (ed): Mechanical Misadventures in Anesthesia. Toronto, University of Toronto Press, 1978, p 8.

26. Adriani J: Clinical application of physical principles concerning gases and vapors to anesthesiology. In Adriani J (ed): The Chemistry and Physics of Anesthesia, 2nd ed. Springfield, Illinois, Charles C Thomas, 1962, p 58.

27. Dorsch JA, Dorsch SE: Equipment checkout, management, and legal issues. In Dorsch JA, Dorsch SE (eds): Understanding Anesthesia Equipment, 3rd ed. Baltimore, Williams & Wilkins, 1994, p 693.

28. Macintosh R, Mushin WW, Epstein HG: Flowmeters. In Macintosh R, Mushin WW, Epstein HG (eds): Physics for the Anaesthetist, 3rd ed. Oxford, Blackwell Scientific Publications, 1963, p 196.

29. Eger EI II, Epstein RM: Hazards of anesthetic equipment. Anesthesiology 24:490, 1964.

30. Eger EI II, Hylton RR, Irwin RH et al: Anesthetic flowmeter sequence a cause for hypoxia. Anesthesiology 24:396, 1963.

31. Rendell-Baker L: Problems with anesthetic and respiratory therapy equipment. Int Anesthesiol Clin 20:1, 1982.

32. Mazze RI: Therapeutic misadventures with oxygen delivery systems: The need for continuous inline oxygen monitors. Anesth Analg 51:787, 1972.

33. Richards C: Failure of a nitrous oxide oxygen proportioning device. Anesthesiology 71:997, 1989.

34. Abraham ZA, Basagoitia B: A potentially lethal anesthesia machine failure. Anesthesiology 66:589, 1987.

35. Neubarth J: Another hazardous gas supply misconnection (Letter). Anesth Analg 80:206, 1995.

36. Gaughan SD, Benumof JL, Ozaki GT: Can an anesthesia machine flush valve provide for effective jet ventilation? Anesth Analg 76:800, 1993.

37. Anderson CE, Rendell Baker L: Exposed O_2 flush hazard. Anesthesiology 56:328, 1982.

38. Anonymous: Internal leakage from anesthesia unit flush valves. Health Devices 10:172, 1981.

39. Andrews JJ: Understanding your anesthesia machine and ventilator. In International Anesthesia Research Society (ed): 1989 Review Course Lectures. Cleveland, 1989, p 59.

40. Dodgson BG: Inappropriate use of the oxygen flush to check an anaesthetic machine. Can J Anaesth 35:336, 1988.

41. Dorsch JA, Dorsch SE: Vaporizers. In Dorsch JA, Dorsch SE (eds): Understanding Anesthesia Equipment, 3rd ed. Baltimore, Williams & Wilkins, 1994, p 91.

42. Macintosh R, Mushin WW, Epstein HG: Vapor pressure. In Macintosh R, Mushin WW, Epstein HG (eds): Physics for the Anaesthetist, 3rd ed. Oxford, Blackwell Scientific Publications, 1963, p 68.

43. Adriani J: Principles of physics and chemistry of solids and fluids applicable to anesthesiology. In Adriani J (ed): The Chemistry and Physics of Anesthesia, 2nd ed. Springfield, Illinois, Charles C Thomas, 1962, p 7.

44. Macintosh R, Mushin WW, Epstein HG: Vaporization. In Macintosh R, Mushin WW, Epstein HG (eds): Physics for the Anaesthetist, 3rd ed. Oxford, Blackwell Scientific Publications, 1963, p 26.

45. Macintosh R, Mushin WW, Epstein HG: Specific heat. In Macintosh R, Mushin WW, Epstein HG (eds): Physics for the Anaesthetist, 3rd ed. Oxford, Blackwell Scientific Publications, 1963, p 17.

46. Schreiber P: Anaesthetic Equipment: Performance, Classification, and Safety. New York, Springer-Verlag, 1972.

47. Tec 4 Continuous Flow Vaporizer: Operator's Manual. Steeton, England, Ohmeda, The BOC Group, 1987.

48. Drager Vapor 19.n Anaesthetic Vaporizer: Instructions for Use, 14th ed. Lubeck, Federal Republic of Germany, Dragerwerk, 1990.

49. Hill DW, Lowe HJ: Comparison of concentration of halothane in closed and semiclosed circuits during controlled ventilation. Anesthesiology 23:291, 1962.

50. Hill DW: The design and calibration of vaporizers for volatile anaesthetic agents. In Scurr C, Feldman S (eds): Scientific Foundations of Anaesthesia, 3rd ed. London, William Heinemann Medical Books, 1982, p 544.

51. Hill DW: The design and calibration of vaporizers for volatile anaesthetic agents. Br J Anaesth 40:648, 1968.

52. Morris LE: Problems in the performance of anesthesia vaporizers. Int Anesthesiol Clin 12:199, 1974.

53. Stoelting RK: The effects of nitrous oxide on halothane output from Fluotec Mark 2 vaporizers. Anesthesiology 35:215, 1971.

54. Diaz PD: The influence of carrier gas on the output of automatic vaporizers. Br J Anaesth 48:387, 1976.

55. Nawaf K, Stoelting RK: Nitrous oxide increases enflurane concentrations delivered by Ethrane vaporizers. Anesth Analg 58:30, 1979.

56. Prins L, Strupat J, Clement J: An evaluation of gas density dependence of anaesthetic vaporizers. Can Anaesth Soc J 27:106, 1980.

57. Lin CY: Assessment of vaporizer performance in low-flow and closed-circuit anesthesia. Anesth Analg 59:359, 1980.

58. Gould DB, Lampert BA, MacKrell TN: Effect of nitrous oxide solubility on vaporizer aberrance. Anesth Analg 61:938, 1982.

59. Palayiwa E, Sanderson MH, Hahn CEW: Effects of carrier gas composition on the output of six anaesthetic vaporizers. Br J Anaesth 55:1025, 1983.

60. Scheller MS, Drummond JC: Solubility of N_2O in volatile anesthetics contributes to vaporizer aberrancy when changing carrier gases. Anesth Analg 65:88, 1986.

61. Tec 5 Continuous Flow Vaporizer: Operation and Maintenance Manual. Steeton, England, Ohmeda, The BOC Group, 1990.

62. Karis JH, Menzel DB: Inadvertent change of volatile anesthetics in anesthesia machines. Anesth Analg 61:53, 1982.

63. Riegle EV, Desertspring D: Failure of the agent specific filling device (Letter). Anesthesiology 73:353, 1990.

64. George TM: Failure of keyed agent specific filling devices. Anesthesiology 61:228, 1984.

65. Lippmann M, Foran W, Ginsburg R et al: Contamination of anesthetic vaporizer contents. Anesthesiology 78:1175, 1993.

66. Munson WM: Cardiac arrest: A hazard of tipping a vaporizer. Anesthesiology 26:235, 1965.

67. Sinclair A: Vaporizer overfilling. Can J Anaesth 40:77, 1993.

68. Peters KR, Wingard DW: Anesthesia machine leakage due to misaligned vaporizers. Anesth Rev 14:36, 1987.

69. Meister GC, Becker KE Jr: Potential fresh gas flow leak through Drager vapor 19.1 vaporizer with key index fill port. Anesthesiology 78:211, 1993.

70. Andrews JJ, Johnston RV Jr: The new Tec 6 desflurane vaporizer. Anesth Analg 76:1338, 1993.

71. Weiskopf RB, Sampson D, Moore MA: The desflurane (Tec 6) vaporizer: Design, design considerations and performance evaluation. Br J Anaesth 72:474, 1994.

72. Eger EI: New inhaled anesthetics. Anesthesiology 80:906, 1994.

73. Tec 6 Vaporizer: Operation and Maintenance Manual. Steeton, England, The BOC Group, 1993.

74. Susay SR, Smith MA, Lockwood GG: The saturated vapor pressure of desflurane at various temperatures. Anesth Analg 83:864-866, 1996.

75. Johnston RV Jr, Andrews JJ: The effects of carrier gas composition on the performance of the Tec 6 desflurane vaporizer. Anesth Analg 79:548, 1994.

76. Andrews JJ, Johnston RV Jr, Kramer GC: Consequences of misfilling contemporary vaporizers with desflurane. Can J Anaesth 40:71, 1993.

77. Mapleson WW: The elimination of rebreathing in various semiclosed anaesthetic systems. Br J Anaesth 26:323, 1954.

78. Willis BA, Pender JW, Mapleson WW: Rebreathing in a T-piece: Volunteer and theoretical studies of the Jackson-Rees modification of Ayre's T-piece during spontaneous respiration. Br J Anaesth 47:1239, 1975.

79. Rose DK, Froese AB: The regulation of $PaCO_2$ during controlled ventilation of children with a T-piece. Can Anaesth Soc J 26:104-113, 1979.

80. Froese AB, Rose DK: A detailed analysis of T-piece systems. In Steward DJ (ed): Some Aspects of Paediatric Anaesthesia. Elsevier North-Holland Biomedical Press, 1982, pp 101-136, WO/200/M751/V.10/ 1982.

81. Sykes MK: Rebreathing circuits: A review. Br J Anaesth 40:666, 1968.

82. Dorsch JA, Dorsch SE: The breathing system II. The Mapleson systems. In Dorsch JA, Dorsch SE (eds): Understanding Anesthesia Equipment, 2nd ed. Baltimore, Williams & Wilkins, 1984, pp 182- 196.

83. Bain JA, Spoerel WE: A streamlined anaesthetic system. Can Anaesth Soc J 19:426, 1972.

84. Pethick SL: Letter to the editor. Can Anaesth Soc J 22:115, 1975.

85. Moyers J: A nomenclature for methods of inhalation anesthesia. Anesthesiology 14:609, 1953.

86. Eger EI II: Anesthetic systems: Construction and function. In Eger EI II (ed): Anesthetic Uptake and Action. Baltimore, Williams & Wilkins, 1974, p 206.

87. Eger EI II, Ethans CT: The effects of inflow, overflow and valve placement on economy of the circle system. Anesthesiology 29:93, 1968.

88. Kshatri AM, Kingsley CP: Defective carbon dioxide absorber as a cause for a leak in a breathing circuit. Anesthesiology 84:475-476, 1996.

89. Norman PH, Daley MD, Walker JR et al: Obstruction due to retained carbon dioxide absorber canister wrapping. Anesth Analg 83:425-426, 1996.

90. Adriani J: Carbon dioxide absorption. In Adriani J (ed): The Chemistry and Physics of Anesthesia, 2nd ed. Springfield, Illinois, Charles C Thomas, 1962, p 151.

91. Dewey & Almy Chemical Division: The Sodasorb Manual of CO_2 Absorption. New York, WR Grace & Company, 1962.

92. Hunt HE: Resistance in respiratory valves and canisters. Anesthesiology 16:190, 1955.

93. Brown ES: Performance of absorbents: Continuous flow. Anesthesiology 20:41, 1959.

94. Andrews JJ, Johnston RV Jr, Bee DE et al: Photodeactivation of ethyl violet: A potential hazard of Sodasorb. Anesthesiology 72:59, 1990.

95. Case History 39: Accidental use of trichloroethylene (Trilene, Trimar) in a closed system. Anesth Analg 43:740, 1964.

96. Morio M, Fujii K, Satoh N et al: Reaction of sevoflurane and its degradation products with soda lime. Anesthesiology 77:1155, 1992.

97. Frink EJ Jr, Malan TP, Morgan SE et al: Quantification of the degradation products of sevoflurane in two CO_2 absorbents during low-flow anesthesia in surgical patients. Anesthesiology 77:1064, 1992.

98. Fang ZX, Kandel L, Laster MJ et al: Factors affecting production of compound A from the interaction of sevoflurane with Baralyme and soda lime. Anesth Analg 82:775-781, 1996.

99. Eger EI II, Ion P, Laster MJ et al: Baralyme dehydration increases and soda lime dehydration decreases the concentration of compound A resulting from sevoflurane degradation in a standard anesthetic circuit. Anesth Analg 85:892-898, 1997.

100. Steffey EP, Laster MJ, Ionescu P et al: Dehydration of Baralyme increases compound A resulting from sevoflurane degradation in a standard anesthetic circuit used to anesthetize swine. Anesth Analg 85:1382-1386, 1997.

101. Eger EI II, Koblin DD, Bowland T et al: Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 84:160- 168, 1997.

102. Kharasch ED, Frink Jr EJ, Zager R et al: Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular toxicity. Anesthesiology 86:1238-1254, 1997.

103. Bito H, Ikeuchi Y, Ikeda K: Effects of low-flow sevoflurane anesthesia on renal function: Comparison with high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. Anesthesiology 86:1231-1237, 1997.

104. Baxter PJ, Kharasch ED: Rehydration of desiccated Baralyme prevents carbon monoxide formation from desflurane in an anesthesia machine. Anesthesiology 86:1061-1065, 1997.

105. Woehlck HJ, Dunning M, Connolly LA: Reduction in the incidence of carbon monoxide exposures in humans undergoing general anesthesia. Anesthesiology 87:228-234, 1997.

106. Fang ZX, Eger EI, Laster MJ et al: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth Analg 80:1187-1193, 1995.

107. Frink EJ, Nogami WM, Morgan SE et al: High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. Anesthesiology 87:308-316, 1997.

108. Spearman CB, Sanders HG: Physical principles and functional designs of ventilators. In Kirby RR, Smith RA, Desautels DA (eds): Mechanical Ventilation. New York, Churchill Livingstone, 1985, p 59.

109. McPherson SP, Spearman CB: Introduction to ventilators. In McPherson SP, Spearman CB (eds): Respiratory Therapy Equipment, 3rd ed. St. Louis, CV Mosby, 1985, p 230.

110. 7000 Electronic Anesthesia Ventilator: Operation Maintenance. Madison, Ohmeda, The BOC Group, 1985.

111. 7000 Electronic Anesthesia Ventilator: Service Manual. Madison, Ohmeda, The BOC Group, 1985.

112. Cooper JB, Newbower RS, Kitz RJ: An analysis of major errors and equipment failures in anesthesia management: Considerations for prevention and detection. Anesthesiology 60:34, 1984.

113. Reinhart DJ, Friz R: Undetected leak in corrugated circuit tubing in compressed configuration. Anesthesiology 78:218, 1993.

114. Raphael DT, Weller RS, Doran DJ: A response algorithm for the low-pressure alarm condition. Anesth Analg 67:876, 1988.

115. Slee TA, Pavlin EG: Failure of low pressure alarm associated with use of a humidifier. Anesthesiology 69:791, 1988.

116. McEwan AI, Dowell L, Karis JH: Bilateral tension pneumothorax caused by a blocked bacterial filter in an anesthesia breathing circuit. Anesth Analg 76:440, 1993.

117. Feeley TW, Bancroft ML: Problems with mechanical ventilators. Int Anesthesiol Clin 20:83, 1982.

118. Khalil SN, Gholston TK, Binderman J: Flapper valve malfunction in an Ohio closed scavenging system. Anesth Analg 66:1334, 1987.

119. Sommer RM, Bhalla GS, Jackson JM: Hypoventilation caused by ventilator valve rupture. Anesth Analg 67:999, 1988.

120. Roth S, Tweedie E, Sommer RM: Excessive airway pressure due to a malfunctioning anesthesia ventilator. Anesthesiology 65:532, 1986.

121. Dorsch JA, Dorsch SE: Controlling trace gas levels. In Dorsch JA, Dorsch SE (eds): Understanding Anesthesia Equipment, 3rd ed. Baltimore, Williams & Wilkins, 1994, p 281.

122. US Department of Health, Education, and Welfare: Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors, March ed. Washington, DC, 1977.

123. American Society for Testing and Materials: Standard Specification for Anesthetic Equipment--Scavenging Systems for Anesthetic Gases. (ASTM F134391). Philadelphia, American Society for Testing and Materials, 1991.

124. Open Reservoir Scavenger: Operator's Instruction Manual. Telford, Pennsylvania, North American Drager, 1986.

125. Gray WM: Scavenging equipment. Br J Anaesth 57:685, 1985.

126. Scavenger Interface for Air Conditioning: Instruction Manual. Telford, Pennsylvania, North American Drager, 1984.

127. Cooper JB: Toward prevention of anesthetic mishaps. Int Anesthesiol Clin 22:167, 1984.

128. Spooner RB, Kirby RR: Equipment related anesthetic incidents. Int Anesthesiol Clin 22:133, 1984.

129. Emergency Care Research Institute: Avoiding anesthetic mishaps through preuse checks. Health Devices 11:201, 1982.

130. Food and Drug Administration: Anesthesia Apparatus Checkout Recommendations, FDA, 8th ed. Rockville, Maryland, Food and Drug Administration, 1986.

131. Food and Drug Administration: Anesthesia Apparatus Checkout Recommendations. Rockville, Maryland, Food and Drug Administration, 1993.

132. Myers JA, Good ML, Andrews JJ: Comparison of tests for detecting leaks in the low-pressure system of anesthesia gas machines. Anesth Analg 84:179-184, 1997.

133. Dorsch JA, Dorsch SE: Hazards of anesthesia machines and breathing systems. In Dorsch JA, Dorsch SE (eds): Understanding Anesthesia Equipment, 3rd ed. Baltimore, Williams & Wilkins, 1994, p 325.

134. Comm G, Rendell-Baker L: Back pressure check valves a hazard. Anesthesiology 56:227, 1982.

Chapter 8 - Barbiturates

Robert J. Fragen
Michael J. Avram

INTRODUCTION

For more than 50 years, barbiturates have been a standard element of anesthesia practice. Their use has profoundly affected the way anesthesiologists administer drugs, because barbiturates have a rapid but short action and are safe and effective when administered properly.

Although barbituric acid was first synthesized in 1864 by von Baeyer, it was not until 1903, when Fischer and von Mering synthesized diethylbarbituric acid, that a barbiturate with hypnotic activity became available. The many hypnotic barbiturates introduced between 1903 and 1932 had little impact on intravenous anesthesia because they had slow onsets and long durations of action. [1] In 1932, Weese and Scharpff introduced the methylated oxybarbiturate hexobarbital, bringing a new era to anesthesia, because hexobarbital had a rapid onset and short duration of hypnotic effect despite its excitatory side effects. Another barbiturate, thiopental, which is fast-acting but devoid of excitatory side effects, was first administered in 1934 by Waters and Lundy. [1] Unfortunately, a lack of understanding of pharmacokinetics led to the use of hexobarbital and thiopental for induction and maintenance of general anesthesia in the manner of diethyl ether and chloroform, sometimes with disastrous results including hypotension and prolonged sleeping times. [2] Administration of hexobarbital and thiopental in this manner to the casualties at Pearl Harbor resulted in so many deaths that intravenous anesthesia was described as "an ideal method of euthanasia." [3] The negative impact of this report was perhaps moderated both by an accompanying case report by Adams and Gray [4] and by an anonymous editorial [5] suggesting that the method of drug administration rather than the drug's inherent toxicity caused the adverse outcomes. Brodie and colleagues [6] provided further insight into the use of intravenous barbiturates by demonstrating that the effects of small doses of thiopental were terminated, not by metabolism, but by redistribution from their sites of action to other body tissues. Price [7] clarified this concept in 1960 and explained that during prolonged administration, distribution becomes less effective in terminating the drug's action because redistribution sites approach equilibrium. An understanding of its pharmacokinetics [2] [5] [6] [7] and its desirable pharmacologic properties [8] made thiopental the standard hypnotic drug to induce anesthesia.

BASIC PHARMACOLOGY

Chemistry and Formulation

The barbiturates are derivatives of barbituric acid (2,4,6-trioxohexahydropyrimidine) (Fig. 8-1) , which is devoid of hypnotic activity, or of its 2-thio analogue. Although commonly called a cyclic ureide of malonic acid because of its synthesis from urea and malonic acid, barbituric acid is actually a pyrimidine nucleus. [9] Keto-enol tautomerization (see Fig. 8-1) (or its sulfur equivalent) lends acidic character to the oxygen (or sulfur) at position 2 of the barbiturate nucleus; the predominance of the enol form, or its sulfur equivalent, in alkaline solution allows the formation of water-soluble barbiturate salts. [10]

The barbiturates commonly used for induction of anesthesia are the thiobarbiturates thiopental [5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid] and thiamylal [5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid] and the methylated oxybarbiturate methohexital [alpha- *dl*-1-methyl-5-allyl-5-(1-methyl-2-pentynyl) barbituric acid] (Fig. 8-2) . The sodium salts of these drugs, which are mixed with 6 percent by

Figure 8-1 The keto and enol tautomeric forms of barbituric acid with the sites of substitution in the hypnotically active barbiturates identified as 1, 2, and 5.

weight anhydrous sodium carbonate, are reconstituted with either water or 0.9 percent sodium chloride to produce 2.5 percent, 2.0 percent, or 1.0 percent solutions of thiopental, thiamylal, or methohexital, respectively. The buffering action of the sodium carbonate in the presence of atmospheric carbon dioxide maintains the moderate alkalinity (pH 10 to 11) of the barbiturate solutions. A decrease in the alkalinity of the barbiturate solutions can result in their precipitation as free acids; therefore, they should not be reconstituted with lactated Ringer's solution, nor should the reconstituted solutions be mixed with acidic solutions of other drugs. Properly reconstituted thiobarbiturate solutions are stable for 1 week if refrigerated. Sterile water solutions of methohexital can be used up to 6 weeks after reconstitution. The bactericidal and bacteriostatic properties of thiopental solution (and, presumably, those of the other barbiturates) appear to be related to its relatively high pH. [11]

Solutions of thiopental may be incompatible with drugs in more acidic solution likely to be coadministered during the induction of anesthesia, including pancuronium, vecuronium, atracurium, alfentanil, sufentanil, and midazolam. [12] A simulation of a rapid sequence induction in which thiopental was coadministered with either vecuronium or pancuronium led to the formation of 15,000 to 20,000 17- to 39-mum particles/mL which appeared to dissolve readily in plasma but had the potential to occlude the intravenous line. [13] Such precipitation can be prevented by allowing a 30-second delay between the injection of thiopental and the injection of the muscle relaxants.

Figure 8-2 Hypnotically active barbiturates with asymmetric centers indicated by an asterisk.

Structure-Activity Relationships

Modifying the structure of the hypnotically inactive barbituric acid (see Fig. 8-1) can convert it into a hypnotic barbiturate with physicochemical properties that affect its ability to gain access to its sites of action and to interact with its receptor. The structure-activity relationships of the barbiturates are well described. [9] Hypnotic activity is introduced into the barbituric acid molecule by the addition of side chains, especially if at least one of them is branched, in positions 5 (see Figs. 8-1 and 8-2) . The length of the side chains in the 5 position influences both the potency and the duration of action of the barbituric acid derivatives; secobarbital and thiamylal are slightly more potent than pentobarbital and thiopental, respectively, because the former drugs have slightly longer (three-carbon versus two-carbon) side chains in position 5 (see Fig. 8-2) . Replacing the oxygen atom with a sulfur atom at position 2 of an active barbiturate produces a barbiturate with a more rapid onset and a shorter duration of action; the thiobarbiturates, thiopental and thiamylal, have faster onsets and shorter durations of action than their oxybarbiturate analogues, pentobarbital and secobarbital (see Fig. 8-2) . Methylation of an active barbiturate in position 1 produces a drug such as methohexital (see Fig. 8-2) with not only a rapid onset and short duration of action but also an increased incidence of excitatory side effects. Therefore, any chemical modification that increases the lipophilicity of a hypnotic barbiturate generally increases both its potency and its rate of onset while shortening its duration of action.

The effect of stereoisomerism on biologic activity is another important aspect of structure-activity relationships. Many barbiturates, including pentobarbital, secobarbital, thiopental, thiamylal, and methohexital, have asymmetric carbon atoms in one of the side chains attached to carbon 5 of the barbiturate ring [14] (see Fig. 8-2) . The *l* isomers of pentobarbital, secobarbital, thiopental, and thiamylal are nearly twice as potent as the *d* isomers despite their similar access to the central nervous system (CNS) [14] and, at least in the case of thiopental, despite having no clinically significant differences in pharmacokinetics. [15] These barbiturates are marketed as racemic mixtures. Methohexital has four stereoisomers because it has an asymmetric center at carbon 5, as well as an asymmetric carbon atom on one of the side chains attached to carbon 5 (see Fig. 8-2) . The most potent hypnotic stereoisomer of methohexital is the beta- *l,* which is four to five times as potent as the least active, alpha- *l;* however, the beta-isomers produce excessive motor activity, so methohexital is marketed as a racemic mixture of alpha-isomers. [16] Differences in the potency of stereoisomers suggest interaction with the chiral active center of a receptor or enzyme rather than a nonspecific action; side effects are often due to nonspecific actions of drugs. Therefore, some consider the less active stereoisomer to be an impurity in the drug formulation. [17]

Mechanism of Action

The gamma-aminobutyric acid ($GABA_A$) receptor complex is the most likely site of barbiturate action. [18] Of the various effects of barbiturates at the cellular level, only their effects on

Figure 8-3 (Figure Not Available) The hypothetic GABA $_A$ oligomeric complex. *(Modified from Olsen et al [20])*

the $GABA_A$ receptor complex occur at clinical drug concentrations, correlate with anesthetic potency, and are stereospecific.

GABA is the principal inhibitory neurotransmitter in the mammalian CNS. The GABA $_A$ receptor is an oligomeric complex consisting of at least five protein subunits, which assemble to form a chloride ion channel with a GABA $_A$ receptor, as well as benzodiazepine, barbiturate, steroid, and picrotoxin binding sites [18] [19] [20] (Fig. 8-3) (Figure Not Available) . Activation of the GABA $_A$ receptor increases chloride conductance through the ion channel, hyperpolarizing and thereby reducing the excitability of the postsynaptic neuron. Thus, GABA $_A$ receptors are referred to as *ligand-gated chloride ion channels.*[18] [19]

Barbiturates both enhance and mimic the action of GABA. [18] [19] By binding to their receptor, barbiturates decrease the rate of dissociation of GABA from its receptor and increase the duration of GABA-activated chloride ion channel openings. At slightly higher but still clinically relevant concentrations, barbiturates directly activate chloride channels, even in the absence of GABA. Barbiturate enhancement of the action of GABA may be responsible for its sedative-hypnotic effects, whereas the GABA-mimetic effect at slightly higher concentrations may be responsible for "barbiturate anesthesia." [18]

Pharmacokinetics/Pharmacodynamics

The physiologic pharmacokinetic models of thiopental disposition developed by Price and colleagues [7] [21] and by Bischoff and Dedrick [22] provide invaluable insight into the pharmacology of fast-acting drugs such as the barbiturates. Following intravenous administration, thiopental mixes rapidly within a central blood pool and is distributed by blood flow and molecular diffusion throughout the tissues of the body according to their rate of perfusion, their affinity for the drug, and the relative concentration of thiopental in the tissues and blood (Fig. 8-4) (Figure Not Available) . The highly perfused, relatively low-volume tissues such as the brain equilibrate rapidly with the high early concentrations of thiopental in the blood, resulting in the induction of anesthesia. Thiopental concentrations in the blood and highly perfused tissue then decrease rapidly as the drug redistributes to the large reservoir of less well perfused lean tissue such as muscle, terminating the effect of an induction dose. Despite its high affinity for thiopental, adipose tissue takes up drug slowly because of its poor perfusion; the amount of thiopental taken up by adipose tissue is not significant until long after its effects wane. The irreversible removal of thiopental from the body (i.e., the elimination clearance), like uptake into adipose tissue, is so slow relative to the uptake of drug by the lean tissue that it contributes minimally to the termination of the effect of an induction dose.

Compartmental pharmacokinetic models that mathematically characterize the blood drug concentration versus time relationships (Fig. 8-5) have largely replaced physiologic models [23] because physiologic models require extensive human data. Data from compartmental models of thiopental and methohexital disposition are presented in Table 8-1 . The central volumes of distribution (V_c) of these drugs exceed intravascular space in these models; the rapid onsets of

Figure 8-4 (Figure Not Available) Percentage of thiopental dose in the central blood pool, viscera, lean tissue, and fat after rapid intravenous administration. This model assumes there is no elimination clearance. *(From Price et al [21])*

TABLE 8-1 -- Pharmacokinetics of Thiopental and Methohexital (± SD)

DRUG	V_c (L/kg)	V_{dss} (L/kg)	Cl_e (mL/min/kg)	$t_{½beta}$ (h)	ESTIMATED HEPATIC EXTRACTION RATIO
Thiopental	0.38 ± 0.10	2.5 ± 1.0	3.4 ± 0.5	11.6 ± 6.0	0.15
Methohexital	0.35 ± 0.10	2.2 ± 0.7	10.9 ± 3.0	3.9 ± 2.1	0.50

± SD, mean ± standard deviation; V_c , central volume of distribution; V_{dss} , volume of distribution at steady state; Cl_e , elimination clearance; $t_{½beta}$, elimination half-life.

Data from Hudson et al [24]

the effects of the drugs suggest that the brain is part of their V_c . The action of an induction dose of thiopental or methohexital is terminated by redistribution from the relatively small V_c to the much larger total apparent volume of distribution (V_{dss}), suggesting extensive uptake by some body tissues. The low, restrictive elimination clearance (Cl_e) of thiopental is a reflection of its hepatic extraction ratio, which may be low because of its extensive protein binding. Methohexital has an intermediate hepatic extraction ratio and Cl_e despite extensive protein binding. Because the elimination half-life ($t_{½beta}$) is a pharmacokinetic variable that depends directly on the V_d and inversely on the Cl_e , the difference in $t_{½beta}$ between thiopental and methohexital is due to a difference in Cl_e .

Although Cl_e begins the moment a drug reaches its clearing organs, Cl_e becomes a dominant factor in the plasma drug concentration versus time relationship only after the end of the rapid decline in plasma drug concentrations during the redistribution phase (see Fig. 8-5) . Hudson et al [24] and Burch and Stanski [25] determined the relative importance of Cl_e and redistribution to the termination of the effect of an induction dose of either thiopental or methohexital. They found that despite the threefold difference in the Cl_e of the drugs (see Table 8-1) , redistribution is the primary process terminating the effect of an induction dose of either drug; this finding is consistent with the results of physiologic models. [21] [22] However, when methohexital or thiopental is administered in large doses, as multiple doses, or by continuous infusion, the capacity of the lean tissue to dilute the drugs decreases progressively as the tissue approaches equilibrium with the blood. Thus, termination of the drug action increasingly depends

Figure 8-5 Blood thiopental concentration versus time relationship after rapid intravenous drug administration. The circles represent measured thiopental concentrations, and the line represents a computer-generated fit to a quadriexponential equation. *(Data from Henthorn et al [26])*

on the slower processes of uptake into adipose tissues and Cl_e , resulting in a prolonged drug effect. [7] As an extreme example, when thiopental was administered for 2 to 4 days of cerebral resuscitation, redistribution sites reached equilibrium with the blood, drug-metabolizing enzymes approached saturation, and recovery depended entirely on nonlinear (Michaelis-Menten) drug metabolism and took nearly 4 days [26] (Fig. 8-6) (Figure Not Available) .

Pharmacokinetics is only part of the dose-response relationship. The other component of this relationship is pharmacodynamics, or the relationship between plasma drug concentrations and drug effect. An understanding of the pharmacodynamics of a drug such as thiopental ideally requires a continuous, noninvasive measure of drug effect. Such a measure can be provided by the electroencephalogram (EEG). Buhrer et al [27] studied this relationship in detail and determined that the number of waves per second, a variable obtained from aperiodic analysis of the EEG, best characterizes thiopental's activation of the EEG at low concentrations and its subsequent inhibition of the EEG at high concentrations. The same group then examined the relationship between clinical anesthetic depth assessed by noxious stimuli and the number of waves per second from aperiodic analysis of the EEG. [28] These investigators found that

Figure 8-6 (Figure Not Available) Decline in plasma thiopental concentrations with time after a 42-hour infusion of 40.2 g of the drug for cerebral resuscitation, illustrating nonlinear (Michaelis-Menten) elimination clearance. Note the difference between this postdrug administration relationship and that for a standard dose of thiopental (see Fig. 8-8) (Figure Not Available) , which has typical distributional phases followed by linear elimination clearance. *(Modified from Stanski et al [26])*

a unique relationship between all but the deepest clinical anesthetic depth and the number of waves per second could not be defined because of the biphasic nature of the EEG response (i.e., activation followed by inhibition). [28] Thus, the number of waves per second from aperiodic analysis of the EEG does not provide a useful index of anesthetic depth. It may, nonetheless, prove useful in combined pharmacokinetic-pharmacodynamic models that include a description of this biphasic response because it may still allow an estimate of the rate of equilibration between blood thiopental concentrations and those in the brain. [29] Combined pharmacokinetic-pharmacodynamic models can potentially establish the kinetic or dynamic basis of differences in the reactivity of individuals or groups of individuals (e.g., the elderly) to the barbiturates. [30]

A real-time index of the effect of thiopental may be provided by the bispectral index (BIS). [31] BIS is a measure of hypnotic effect that is computed from EEG data and is reported as a value between 0 and 100. A patient maintained at a BIS of less than 55 from the time of induction of anesthesia with thiopental until maintenance anesthetic concentrations are adequate would have a small probability of awareness. [31]

Plasma concentrations for thiopental's hypnotic effect and for its anesthetic effect have been determined by two different methods with remarkably good agreement in the results. Hung et al [26] used a computer-controlled infusion pump to maintain various constant target serum thiopental concentrations, which were verified by serum drug concentration measurement, and assessed response to verbal command, tetanic nerve stimulation, trapezius squeeze, laryngoscopy, and laryngoscopy and intubation. Shanks and colleagues [32] determined effective plasma thiopental concentrations from a combined pharmacokinetic-pharmacodynamic model that was based on both a study in which thiopental was infused until the patient first lost voluntary motor power and then had EEG burst suppression [33] and a separate study of thiopental pharmacokinetics following rapid intravenous administration. [34] The serum concentration producing a 50 percent probability of loss of voluntary motor power was predicted to be 11.3 mug/mL, [32] which is similar to that for loss of response to verbal command, 15.6 mug/mL. [28] The mean effective thiopental concentration producing EEG burst suppression in 50 percent of the population was predicted to be 33.9 mug/mL, whereas the 50 percent probability of no response to tetanic nerve stimulation and trapezius muscle squeeze was at 30.3 and 39.8 mug/mL, respectively. Much higher thiopental concentrations were needed in the study of Hung et al to produce a 50 percent probability of no response to laryngoscopy and laryngoscopy and intubation, 50.7 and 78.8 mug/mL, respectively. [28]

CLINICAL PHARMACOLOGY AND USES

Pharmacokinetic Bases of Altered Dose Requirements

Interindividual variability in response to thiopental is well known. [35] [36] Variability in response to induction doses of thiopental is not due to differences in V_{dss}, Cl_e, or $t_{½beta}$, because these minimally affect the plasma drug concentration versus time relationship when thiopental exerts its effect and when its effect is being terminated. Differences in thiopental dose requirements must be due to altered pharmacodynamics or early distribution pharmacokinetics because thiopental has a rapid onset of effect. For example, on the basis of his physiologic model, Price [7] reasoned that the dose requirement is less in patients in hemorrhagic shock because, in this condition, the fraction of the dose received by the brain is very high and its rate of removal from the brain is very low, owing to decreased blood flow to other tissues. Price's hypothesis was substantiated by a study showing changes in the physiologic kinetics of lidocaine in hypovolemic monkeys. [37]

A decrease in the initial distribution volume of thiopental could explain increased reactivity to a standard drug dose because it would lead to less dilution of the dose and higher plasma drug concentrations. While seeking the basis of the decreased thiopental dose requirements in the elderly, Homer and Stanski [38] found no change in the pharmacodynamics with age, but they reported an age-related decrease in the initial distribution volume. Although these observations could provide a pharmacokinetic rationale for the decreased dose requirements in the elderly, neither Avram et al [34] nor Stanski and Maitre [39] could reproduce them. Despite using different methods of drug administration and different pharmacokinetic models, these investigators found similar age-related differences in clearance to the rapidly equilibrating compartment. Stanski and Maitre [39] concluded this finding could account for the age-related decrease in thiopental induction dose requirement, whereas Avram et al [34] concluded it could not. This has led both groups to develop pharmacokinetic models that are able to describe drug distribution from the moment of injection; the model of Wada et al [40] is a sophisticated physiologic pharmacokinetic model based on a scale-up to humans of a model developed in rats, whereas that of Krejcie and colleagues [41] [42] is a recirculatory compartmental pharmacokinetic model based on the disposition of markers of known physiologic spaces.

Wulfsohn and Joshi [43] suggested that if the induction dose of thiopental is based on lean body mass rather than on total body mass, there is no need to adjust the dose with age because the proportion of lean body mass decreases with increasing age. Termination of the effect of an induction dose of thiopental by redistribution to muscle [21] and the increase in the slowly equilibrating volume of distribution with age [34] are consistent with this suggestion. Furthermore, the apparently increased response of the obese [35] and of females [35] may be eliminated if the induction dose of thiopental is based on lean body mass, which represents a smaller proportion of total body mass in these patients. [43]

When the hypothesis that lean body mass and cardiac output codetermine thiopental induction dose regardless of age and sex was tested, age and sex remained important variables. Avram et al [33] determined the combined effect of the patient-specific variables of age, sex, cardiac output, and either body weight or lean body mass on thiopental requirements to reach the end point of loss of voluntary motor power (syringe drop) or the end point of EEG burst suppression. They confirmed a greater thiopental potency in females and the progressive increase in thiopental potency with age (Fig. 8-7) (Figure Not Available) . However, the multiple linear regression

---

Figure 8-7 (Figure Not Available) Cumulative percentage of patients reaching each end point (loss of voluntary motor power, the clinical end point, and EEG burst suppression, the EEG end point) versus log of the thiopental dose at each end point when thiopental was infused at 150 mg/min in 30 male and 30 female patients (A) and 10 male and 10 female patients in each of three age ranges: 18 to 45 years, 46 to 65 years, and 66 to 83 years (B). *(From Avram et al [35])*

model, which accounted for 75 percent of the variability at the syringe drop end point, included not only lean body mass or body weight but also age and sex. The multiple linear regression model for the EEG burst suppression end point accounted for nearly 90 percent of the observed variability in dose requirements and included not only lean body mass or weight and cardiac output but also age. Although these relationships were determined by infusion of thiopental at 150 mg/min, a combined pharmacokinetic-pharmacodynamic model predicts that when the same dose is infused over 30 seconds, it would produce loss of consciousness at 1 minute, lasting for 4 minutes. [29]

Wada et al [40] used their physiologic pharmacokinetic model of drug disposition in humans, based on a scale-up of a model developed in rats, to simulate arterial plasma thiopental concentrations during and after administration of 250 mg of the drug over 1 minute to "patients" of different age, gender, and body habitus and to "patients" who differed only in their cardiac output. They predicted slightly higher peak concentrations in women and the elderly and a nearly 50 percent higher peak concentration in patients with a 50 percent decrease in cardiac output (Fig. 8-8) (Figure Not Available) . Patients who are 50 or 100 percent overweight or have a 50 percent increase in cardiac output were predicted to have lower peak concentrations (see Fig. 8-8) (Figure Not Available) . This study confirmed the importance of cardiac output as a determinant of early arterial thiopental concentrations. The authors went on to predict that adjusting the thiopental induction dose on the basis of either cardiac output or lean body mass will minimize interindividual differences in peak arterial thiopental concentrations in all but extremes of cardiac output (i.e., a 50% increase or a 50% decrease).

A study of the relationship of thiopental infusion rate with dose required to reach the end point of loss of voluntary motor power (syringe drop) also lends weight to the importance of cardiac output in determining induction dose requirements. Gentry et al [44] found that the relationship of the cumulative thiopental dose with the infusion rate is not a simple linear relationship; at infusion rates of 40 to 150 mg/min, thiopental doses were not different, but as the infusion rate increased to 1200 mg/min, the dose required to reach the clinical end point nearly doubled. These observations

---

Figure 8-8 (Figure Not Available) Physiologic pharmacokinetic model predictions of arterial plasma thiopental concentrations immediately after intravenous administration of 250 mg of the drug over 1 minute in patients with different cardiac outputs (A) and body habitus (B), in a male and a female (C), and in patients of different ages (D). *(From Wada et al [40])*

were best predicted by a combined pharmacokinetic-pharmacodynamic model that reflected cardiac output. [32] This model also predicts that the thiopental dose requirement will increase rapidly at infusion rates below 40 mg/min, which are lower than clinically useful rates.

There are strong suggestions in the literature that both cardiac output and its regional distribution are important determinants of thiopental induction dose requirements. A recent study by Gin and colleagues [45] found that the thiopental dose required to produce loss of consciousness and anesthesia in pregnant women of 7 to 13 weeks' gestation was 18 and 17 percent less than that in nonpregnant women, respectively. They postulated that dose requirement decreased despite a 20 percent increase in cardiac output at 13 weeks' gestation because of altered distribution of peripheral blood flow in early pregnancy. Studies of the importance of

cardiac output and its regional distribution in determining early drug concentration histories are under way. [46]

Acute Tolerance

Acute tolerance to thiopental was first described by Brodie et al [47] and subsequently by Dundee and associates [48] and by Toner et al. [49] According to these investigators, the plasma thiopental concentration at awakening is proportional to the dose used; that is, the depth of anesthesia is independent of the plasma thiopental concentration. This suggests that the higher the induction dose of thiopental, the less sensitive a patient will be to a subsequent dose. Hudson et al [50] evaluated the relationship between venous plasma thiopental concentrations and the EEG spectral edge, going from light to moderately deep anesthesia and back during and after three infusions administered over approximately 1 hour; they found no acute tolerance. The consistency of plasma thiopental concentrations on awakening after exponential infusions delivering 0.8 to 2.6 g of thiopental led Crankshaw and colleagues [51] to conclude that there was no acute tolerance to thiopental. The discrepancies among these studies were at least partially explained by Barratt et al, [52] [53] who found that shortly after rapid intravenous drug administration, peripheral venous plasma thiopental concentrations poorly reflect brain (i.e., jugular venous) thiopental concentrations. This accounts for the apparent acute tolerance reported by Toner et al. [49]

Nighttime Hypnosis and Premedication

Pentobarbital and secobarbital provided nighttime drowsiness (hypnosis) and premedication prior to surgery before benzodiazepines replaced them (Ch. 23) . Benzodiazepines cause less cardiovascular, respiratory, and CNS depression. [54] Benzodiazepines given orally or parenterally also replaced barbiturates given orally, rectally, or parenterally for premedication in children.

Induction of General Anesthesia

Drugs and Dosage

Thiopental, thiamylal, and methohexital can be injected intravenously to induce general anesthesia and can also be used to maintain unconsciousness as the hypnotic component of a balanced anesthetic technique or a total intravenous

anesthetic technique. These barbiturates continue to be commonly used anesthetic induction agents because they induce anesthesia rapidly and pleasantly and are less expensive than propofol or etomidate. When injected intravenously, these lipid-soluble drugs act in one arm-brain circulation time and have their maximum effect in about 1 minute. [7] Because barbiturates redistribute rapidly from the brain to the lean body tissue, the duration of effect from a single induction dose is about 5 to 8 minutes. Induction doses produce the highest blood concentrations and, as a result, the most profound effects on body systems and the most side effects.The usual induction dose of thiopental for healthy adults is 2.5 to 4.5 mg/kg (Fig. 8-9) (Figure Not Available) . Doses based on lean body mass, rather than actual body weight, compensate for age, gender, and body habitus differences. [33] [40] A slightly higher dose, 5 to 6 mg/kg, is recommended for children, and 7 to 8 mg/kg is used for infants [55] (Fig. 8-10) (Figure Not Available) . To identify persons who may be particularly sensitive to the barbiturates, one can inject 25 percent of the calculated dose initially and then observe the patient's level of consciousness, respiration, and cardiovascular response. If this small dose has a great effect, the calculated dose should be reduced.

Both the patient's premedication and general health (American Society of Anesthesiologists [ASA] physical status) can influence the dose of thiopental necessary to induce anesthesia [36] (Table 8-2) (Table Not Available) . Premedicated geriatric patients require a 30 to 35 percent reduction in dose as compared with younger patients. [35] [36] Unpremedicated pregnant women of 7 to 13 weeks' gestation require 18 percent less thiopental to induce anesthesia than do nonpregnant women of similar age. [45] Benzodiazepines, opioids, and, more recently, alpha $_2$ -agonists can be used for premedication before barbiturate induction of anesthesia. Midazolam given intravenously concomitantly with thiopental shifts the dose-response curve to the left in proportion to the dose of midazolam administered. [56] Fentanyl, 5 mug/kg, given intravenously to healthy adults a few minutes before induction with thiopental decreases the median effective dose (ED $_{50}$)

Figure 8-9 (Figure Not Available) This bar graph depicts the scatter of induction doses of thiopental (mg/kg) in 2,006 consecutive unselected anesthetic inductions. See the source reference for how the induction doses were determined. *(From Dundee et al [36])*

Figure 8-10 (Figure Not Available) Estimated ED $_{50}$ ± SEM of thiopental in children of different ages from a dose-response study performed with the "up and down method." The ED $_{50}$ is the dose at which anesthesia is induced in 50 percent of the children. The dashed lines do not represent data and are only added to facilitate visual observation of the actual data. *(From Jonmarker et al [57])*

for unconsciousness from 4 to 2.2 mg/kg without causing significant change in systolic blood pressure. [57] Oral clonidine, 2 or 4 mg, decreased the induction dose of thiamylal (mean ± standard deviation [SD]) in 7- to 12-year-old children from 5.4 ± 0.9 to 4.5 ± 1.1 and 3.4 ± 0.9, respectively. [58] Patients who have severe anemia or burns, malnutrition, advanced malignant disease, uremia, ulcerative colitis, or intestinal obstruction or who are in shock require lower anesthetic induction doses of any barbiturate. Hypothermia and circulatory failure slow the circulation time and prolong anesthetic induction; therefore, a much lower dose of barbiturate is necessary, and its effect is greater. The acutely inebriated patient requires less barbiturate to induce anesthesia, whereas the patient with chronic alcoholism requires a higher dose than normal.

An induction dose of 1.5 mg/kg of methohexital is equivalent to 4 mg/kg of thiopental; thus, methohexital appears to be about 2.7 times as potent. After reviewing a large number of cases with thiopental and thiamylal anesthetics, Tovall [59] concluded that there was no difference between the drugs in potency, incidence of laryngospasm and respiratory depression, cardiotoxicity, or recovery time. In the rest of this chapter, therefore, statements about thiopental also apply to thiamylal, unless stated otherwise.

TABLE 8-2 -- Mean Thiopental Dose Following Various Premedicants

(Not Available)

From Dundee et al [36]

Injection Complications

After injection of barbiturates, there may be an urticarial rash of the upper chest, neck, and face that fades after a few minutes. Anaphylactoid reactions such as hives, facial edema, bronchospasm, and shock occasionally occur after thiobarbiturate induction. [60] [61] The absence of reactions to oral barbiturates does not ensure a lack of sensitivity to intravenous barbiturates. Treatment of these reactions is symptomatic but should include 1-mL increments of 1:10,000 epinephrine and intravenous fluids. Aminophylline can be given to treat bronchospasm.

The incidence of pain on injection is 1 to 2 percent after thiopental and up to 5 percent after methohexital [62] when injected into small veins in the back of the hand or wrist and essentially none when injected into larger veins. If methohexital is injected into an artery or is extravasated in the subcutaneous tissue, there is mild discomfort and no sequelae occur. However, if the thiobarbiturates [63] are extravasated, pain, edema, and erythema ensue, and reactions ranging from slight soreness to extensive tissue necrosis can occur locally, depending on the concentration and total amount injected. [64]

If the intravenous thiobarbiturates, especially in concentrations greater than 2.5 percent, are injected intraarterially, intense arterial spasm results, and excruciating pain can be felt from the injection site to the hand and fingers. The onset of pain and burning is immediate and can persist for hours. Within the first 2 hours, anesthesia or hyperesthesia of the hand, edema, or motor weakness can occur. Depending on the dose of drug injected, its concentration, volume, rate of injection, and the patient's level of consciousness, a range of symptoms from mild discomfort to gangrene and loss of tissue in the hand can result. [64] The presence of a pulse

does not rule out later development of thrombosis. The pathologic process is a chemical endarteritis, which destroys the endothelium, subendothelial tissues, and possibly the muscle layer. To prevent permanent sequelae, treatment is necessary to dilute the barbiturate, relieve vascular spasm, and prevent thrombosis. Injection of papaverine (40 to 80 mg in 10 to 20 mL of normal saline) or 5 to 10 mL of 1 percent lidocaine or procaine into the artery may accomplish the first two objectives. Blocking the sympathetic nerves to the upper extremity with either a stellate ganglion block or a brachial plexus block can relieve spasm. Heparin can be given intravenously to prevent thrombosis.

Side Effects During Induction of Anesthesia

Approximately 40 percent of adult patients of either gender describe an onion or garlic taste between injection of thiopental and unconsciousness. This is more prevalent in younger patients. [65] Besides producing unconsciousness, the barbiturates can cause mild muscular excitatory movements such as hypertonus, tremor, or twitching and respiratory excitatory effects including cough and hiccup. The dosedependent incidence and severity of these effects are greater after methohexital than after thiopental, especially if

TABLE 8-3 -- Incidence of omplications in Unpremedicated Patients

(Not Available)

Modified from Clarke [66]

the dose of methohexital is more than 1.5 mg/kg [66] (Table 8-3) (Table Not Available) . Although these excitatory effects are not disturbing enough to limit the use of the barbiturates, atropine or opioids given just prior to anesthetic induction will minimize the excitatory effects, whereas premedication with phenothiazines or scopolamine exaggerates them. Inadequate induction doses can also evoke excitatory responses because inhibitory areas of the brain are the first to be depressed.

Specific Organ Function Effects

Central Nervous System Effects

The barbiturates may be hyperalgesic in subanesthetic concentrations, exaggerating the response to pain. [64] Clinical signs of their hyperalgesic effect include tachycardia, hypertension, diaphoresis, tearing, and tachypnea until pain becomes controlled. At a plasma concentration range of 2 to 20 mug/mL and brain and spinal cord concentrations of 1.7 ± 0.03 and 3.5 ± 1.7 mug/g, respectively (mean ± SD), antinociceptive effects were demonstrated in the rat. [67] However, in healthy patients, sedative infusions of thiopental or propofol were not associated with clinically relevant hyperalgesia to thermal pain. [68]

Thiopental produces a dose-related depression of the EEG [69] (Fig. 8-11) (Figure Not Available) . The awake alpha pattern progresses to higher-amplitude and slower-frequency delta and theta waves until there is burst suppression and finally a flat EEG. A flat EEG can be maintained with a continuous infusion of thiopental (4 mg/kg/h) [70] or a pentobarbital infusion that maintains a plasma concentration of 3 to 6 mg/dL. [71] There is a dose-dependent depression of cerebral metabolism of oxygen ($CMRO_2$), which reaches a maximum of 55 percent when the EEG becomes flat. This reflects a decrease in neuronal, but not metabolic, need for oxygen; hypothermia is the only way to decrease the metabolic requirement. In addition, there is a parallel reduction in cerebral blood flow and intracranial pressure (ICP) [72] ; this is particularly beneficial for patients with increased ICP. Cerebral perfusion pressure is uncompromised because ICP decreases more than mean arterial pressure. The direction and magnitude of these changes are appropriate for patients with intracranial lesions, making thiopental an appropriate drug to induce anesthesia for neurosurgical operations (Ch. 52) .

Figure 8-11 (Figure Not Available) EEG changes with increasing doses of thiopental from an awake state to a flat EEG. *(From Kiersey et al [69])*

Thiopental is the preferred barbiturate for high-dose administration or prolonged use for neuroanesthesia because patients have been reported to have had epileptiform seizures after very high doses of methohexital [73] and a 33 percent incidence of postoperative seizures when methohexital was given by continuous infusion. [74] Thiopental loading, to electroencephalographic burst suppression for cerebral artery aneurysms that require cardiopulmonary bypass and deep hypothermic circulatory arrest to be safely clipped, causes negligible cardiac impairment and does not impede separation from cardiopulmonary bypass if preoperative ventricular function is good. [75]

Although thiopental is a satisfactory agent for use with somatosensory evoked potential (SSEP) monitoring, it produces detrimental effects on amplitude of motor evoked potentials (MEP). The SSEP components remain even after administration of doses that cause a flat EEG. However, there is a dose-dependent change in median nerve SSEP response and brain-stem auditory evoked response associated with the use of thiopental. [76] [77] Thiopental and propofol depress MEP to a greater extent than do etomidate or methohexital. [78] A 2-mg/kg dose of thiopental decreased the MEP amplitude 42.8 percent, and subsequent doses caused a further dose-dependent decrease. [79]

Intravenous barbiturates are safe to use as anesthetic induction agents for ophthalmologic surgical procedures, including those for open eye injuries. Intraocular pressure (IOP) decreases about 40 percent after an induction dose of thiopental or methohexital is injected. If succinylcholine is

Figure 8-12 (Figure Not Available) Depression of the ventilatory response to CO_2 by pentobarbital and thiopental in the dog. The lines relate minute ventilation (V_E) to alveolar CO_2 tension (P_{ACO_2}). The slopes are normalized to the same starting point on the abscissa. STPD, standard temperature and pressure. *(Modified from Hirshman et al [81])*

given immediately after thiopental, IOP returns to preinduction values, but if as much as 2 minutes elapses, IOP exceeds preinduction values [80] (Ch. 63) .

Respiratory Effects

The barbiturate induction agents cause central respiratory depression, the nature and duration of which depend on the dose, rate of injection, and type and dose of premedication; both the rate and depth of breathing can be depressed until apnea occurs. Although respiration returns toward normal in a few minutes, the responses to hypercarbia (Fig. 8-12) (Figure Not Available) and hypoxemia (Fig. 8-13) (Figure Not Available) are depressed for a longer time. [81] Even 2 mg/kg of pentobarbital, a dose used for premedication, depresses the ventilatory response to hypoxemia. [82]

There is a low incidence of hypersalivation and rarely bronchospasm or laryngospasm after barbiturate induction of anesthesia. Usually, these side effects are due to the insertion of artificial airways, laryngeal masks, [83] or tracheal tubes in lightly anesthetized patients; unless very large doses of barbiturates are used, laryngeal and tracheal reflexes remain intact. [84] Laryngeal reflexes are, however, more active after induction with thiopental than with equivalent doses of propofol. [85] Thiopental and volatile anesthetic agents depress the mucociliary clearance of foreign material to the same degree. [86] Both methohexital [87] and thiopental are safe for asthmatic patients, but they do not cause bronchodilation, as ketamine does.

Figure 8-13 (Figure Not Available) Depression of O_2 -CO_2 interaction by barbiturates. Hypoxic ventilatory drive (HVD) is plotted as a function of the carbon dioxide tension (P_{ACO_2}) at which the studies were done. Each line represents the least-squares regression of about 40 studies. The circles represent the baseline P_{ACO_2} and HVD obtained with each agent. *(Modified from Hirshman et al [81])*

Cardiovascular Effects

The predominant cardiovascular effect of barbiturate induction is venodilation followed by pooling of blood in the periphery. [88] Myocardial contractility is depressed, but not to the extent seen after volatile anesthetics. [89] *In vitro,* using human atrial strips, thiopental inhibited contractility more than midazolam, etomidate, propofol, and ketamine. [90] Possible mechanisms for depressed myocardial contractility involve interference with calcium transport across myocardial cells and/or altering the

nitric oxide mechanism. From a study on isolated cat papillary muscle, the negative ionotropic effect may depend on the presence of an intact endocardial epithelium, a finding suggesting that it involved the nitric oxide pathway. [91] Thiopental, as well as other intravenous anesthetics, decreases neuronal nitric oxide synthase activity. [92] Other studies suggest that thiopental may interfere with the influx of transsarcolemmal calcium [93] and can decrease sarcoplasmic reticulum calcium release and inhibit the ryanodine-induced efflux of sarcoplasmic reticulum calcium. [94] Cardiac output decreases even though heart rate increases via the only slightly depressed baroreflex mechanism. Systemic vascular resistance usually remains unchanged, but in patients with preload-independent artificial hearts and a constant cardiac output, it decreased by 21 percent. In this model, thiopental also dilates pulmonary vessels and veins. [95] Heart rate increases more after methohexital than after equivalent doses of thiopental. No arrhythmias occur after induction of anesthesia by the barbiturates as long as hypoxemia and hypercarbia are avoided. The barbiturates also decrease sympathetic output from the CNS [96] and do not sensitize the heart to catecholamines.

Both thiopental and methohexital cause an increased heart rate, which results in an increased myocardial oxygen consumption. The arteriocoronary venous oxygen difference remains normal when aortic pressure is relatively unchanged because there is a proportional decrease in coronary vascular resistance and an increase in myocardial blood flow. [97] However, if systemic pressure is low enough, coronary blood flow decreases. The barbiturates, therefore, must be used cautiously if at all in conditions in which an increased heart rate or a decrease in preload could be detrimental to the patient. Such conditions include pericardial tamponade, hypovolemia, congestive heart failure, ischemic heart disease, and heart block, as well as a high resting sympathetic tone or myocardial ischemia.

Hypotension from a given dose is greater in both treated and untreated hypertensive patients than in normotensive patients. [98] An exaggerated hypotensive effect probably occurs in the presence of a blunted baroreflex or beta-adrenergic blockade.

Gastrointestinal, Renal, and Hepatic Effects

Healthy patients and those with preexisting liver disease have essentially no changes in gastrointestinal and liver function after barbiturate induction of anesthesia. [99] Hypoproteinemia in patients with hepatic or renal disease leads to a greater fraction of unbound thiopental than in healthy patients. [100] Thus, for patients with chronic renal failure, induction doses of thiopental should be injected at a slower rate, and maintenance doses should be decreased 50 to 75 percent, but these doses may have to be given more often than in healthy patients. A given dose can have a longer duration of effect in patients with hepatic failure, and recovery can be more rapid in patients in renal failure than in others. [101]

Thiopental can decrease urine output because it decreases blood flow to the kidney, causes renal artery constriction, and results in a small decrease in the glomerular filtration rate and urinary solute secretion. [8] Controversy exists about whether there is an increase in antidiuretic hormone (ADH) secretion from the pituitary. [8] [102] In dogs, methohexital impaired osmoregulation after an osmotic challenge by inhibiting ADH. [103] Correcting hypotension and administering adequate intravenous fluids prevent the renal effects of barbiturate induction from becoming a clinical problem.

Metabolic Effects

Although there is a slight, clinically insignificant increase in blood glucose levels and impairment of the glucose tolerance test after thiopental injection, serum insulin levels do not change. [104] Heat loss results from barbiturate-induced vasodilation of cutaneous and skeletal muscle vessels, which may contribute to postoperative shivering.

Endocrine Effects

Thiopental decreases plasma cortisol concentrations but does not prevent adrenocortical stimulation from the stress of surgery [105] (Fig. 8-14) . This finding contrasts with the effect

Figure 8-14 Normal cortisol and aldosterone response after thiopental during and after general anesthesia. The adrenocortical response to stress is preserved after thiopental but is depressed after etomidate. *(Data from Fragen et al [105])*

of an induction dose of etomidate, which suppresses the adrenocortical response to stress. [105] Both thiobarbiturates cause a dose-related histamine release, in contrast to methohexital and pentobarbital [106] (Fig. 8-15) (Figure Not Available) , but histamine release is rarely of clinical consequence.

Obstetric Effects

Thiopental neither depresses nor increases the tone of the gravid uterus (Ch. 57) . [64] Thiopental is not harmful to the fetus when the drug is given for anesthetic induction for

Figure 8-15 (Figure Not Available) Comparison of percent histamine release from human mast cells when in the presence of increasing concentrations of four barbiturates. Both thiobarbiturates produced significant dose-related histamine release. Histamine release by thiamylal was significantly greater than that by thiopental from 3.3×10^{-5} to 1×10^{-3} M ($P < .05$). *(From Hirshman et al [106])*

cesarean section in doses up to 6 mg/kg, but 8 mg/kg does depress the fetus. [107] Placental circulatory factors and redistribution of thiopental in the mother and fetus protect the fetal brain and spinal cord from high concentrations of barbiturates and explain why the umbilical cord blood concentration of thiopental at delivery is one-half that in maternal blood. Safe delivery of the fetus by cesarean section is possible if accomplished within 10 minutes after anesthetic induction with either thiopental or ketamine. [108] The neonatal condition is better after thiopental induction than after midazolam induction. [109] Neurobehavioral tests showed that newborns were more depressed after mothers received thiopental than after mothers received ketamine or epidural anesthesia for vaginal deliveries. [110]

Drug Interactions

Barbiturates given to patients taking other CNS-depressant drugs such as ethanol, antihistamines, isoniazid, methylphenidate, and monoamine oxidase inhibitors cause greater CNS depression than when barbiturates are given alone. Concomitant administration of 5.6 mg/kg of aminophylline reduces both the depth and the duration of sedation after thiopental administration. [111] Long-term barbiturate use induces hepatic microsomal enzymes, which accelerate the metabolism of other drugs metabolized by the P-450 system. [112]

Recovery

The time it takes for all CNS-depressant drug concentrations, not those of the intravenous hypnotic alone, to decrease below a particular threshold level determines the speed of recovery from general anesthesia. Recovery is rapid after many anesthetic regimens that include intravenous barbiturates. For example, if healthy patients have anesthesia induced with thiopental (4 mg/kg) and anesthesia maintained with 67 percent nitrous oxide, fentanyl (100 mug), and 50- to 100-mg increments of thiopental for operations lasting 30 minutes or less, they open their eyes in 3 to 4 minutes after the nitrous oxide is discontinued, and psychomotor tests recover in 15 to 75 minutes. [113] This technique is satisfactory for outpatient or inpatient anesthesia.

Clinical recovery was faster in infants less than 1 year old after equipotent doses of methohexital compared with thiopental [114] and in volunteers after single doses of methohexital (2 mg/kg) than after thiopental (6 mg/kg), but the ability to drive a motor vehicle was impaired for 8 hours after methohexital compared with 6 hours after thiopental [115] (Fig. 8-16) (Figure Not Available) . Furthermore, psychophysiologic tests were impaired for 8 hours after thiopental, and abnormal sleep patterns on the EEG occurred for 12 hours after methohexital. [115] The recommendation that patients not drive for 24 hours after general anesthesia is based on these data.

Naloxone (0.05 mg/kg) fails to antagonize the effects of thiopental. [116] At this time, there are no specific pharmacologic antagonists to treat barbiturate overdose; maintaining a patent airway, supporting ventilation, and supporting circulation are the appropriate symptomatic treatments.

Postoperative Sequelae

Venous sequelae include thrombosis and phlebitis and may not be seen until a few days postoperatively. Venous thrombosis is reported in 3 to 4 percent of patients receiving thiopental and in a slightly higher proportion of patients after methohexital. [117] An idea of the overall incidence of venous sequelae after barbiturates compared with other induction agents is shown in Table 8-4 (Table Not Available) . Venous sequelae are usually confined to an area of the vein in close proximity to the site of injection; they are treated symptomatically.

There are four reported cases of inadvertent epidural injections of up to 20 mL of 2- to 2.5-percent solutions of thiopental. The patients were successfully treated by injecting 0.5 percent bupivacaine into the epidural space to dilute thiopental and attempt to precipitate it. [118] Methohexital (1 percent) injected epidurally was treated with an epidural injection of saline plus methylprednisolone and hyaluronidase; no sequelae occurred. [119] The incidence of nausea and vomiting after barbiturate anesthesia is less than after inhaled anesthetics, ketamine, or etomidate, but the incidence is even lower after midazolam or propofol. [64]

Paralysis and death can occur if barbiturates are given to patients with acute intermittent porphyria or variegate porphyria. Barbiturates can precipitate acute and even fatal attacks of porphyria owing to the induction of

Figure 8-16 (Figure Not Available) Mean number of performance errors (neglected instructions, collisions, and driving off the road) during 30 minutes of simulated driving 2 to 8 hours after administration of 6 mg/kg of thiopental (
), 2 mg/kg of methohexital (
), 6.6 mg/kg of propanidid (
), and 85 muL/kg of alphadione (
). Ten subjects in each group.*, $P < .05$ in comparison with control group (
). *(From Korttila et al [115])*

TABLE 8-4 -- Incidence of Venous Sequelae After Intravenous Injection of Anesthetics

(Not Available)

Modified from Clarke [66]

delta-aminolevulinic acid synthetase, which catalyzes the rate-limiting step in the biosynthesis of porphyrins. [120]

ADMINISTRATION OF BARBITURATES BY INFUSIONS

Barbiturates administered by a continuous infusion for maintenance of hypnosis are seldom used for anesthesia because they may prolong recovery. This can be explained by looking at the context-sensitive half-time (i.e., the time it takes for the plasma concentration in the central compartment to decrease by 50 percent) for thiopental relative to other intravenous hypnotics used for anesthesia [94] (Fig. 8-17) (Figure Not Available) . Crankshaw et al [122] used the same concept in their "plasma drug efflux" method to achieve and maintain a steady plasma concentration of thiopental or methohexital rapidly. They believed that a thiopental infusion can be a major component of anesthesia when given as an exponential infusion based on lean body mass to prevent overdose in heavier patients. Even if this is possible, recovery after reasonably long barbiturate infusions is slow relative to that after propofol. A successful infusion achieves a blood concentration of 15 to 20 mug/mL on induction and 10 to 20 mug/mL during maintenance. The mean plasma concentration on awakening is 5.9 ± 1.1 mug/mL. Schwilden et al [123] developed a combined pharmacokinetic-pharmacodynamic model to provide a closed-loop feedback-control method of delivering methohexital to maintain a set EEG level of 2 to 3 Hz and to maintain unconsciousness. Thiopental infusions of 2 to 3 mg/kg/h have been used to treat refractory aminophylline seizures and to control a hyperdynamic state after coronary bypass surgery. [124]

OTHER USES OF BARBITURATES

Anticonvulsants

Both thiopental and phenobarbital can stop seizures abruptly in patients refractory to other anticonvulsant drugs, [125] but benzodiazepines have largely replaced barbiturates for the acute treatment of seizures. GABA augmentors have anticonvulsant effects, and both barbiturates and benzodiazepines facilitate the action of GABA [126] in prolonging hyperpolarization of the postsynaptic membrane.

Figure 8-17 (Figure Not Available) Context-sensitive half-times as a function of infusion duration for each of the pharmacokinetic models simulated. Note the longer context-sensitive half-time for thiopental as compared with propofol and midazolam as the infusion duration increases. *(Modified from Hughes et al [121])*

TABLE 8-5 -- Dose Structure of Antiseizure Phenobarbital Therapy

(Not Available)

From Vining [127]

Other postsynaptic effects include altered membrane conductance of chloride ions and antagonism of glutaminergic and cholinergic excitation. Presynaptically, these drugs block calcium entry into nerve terminals and diminish transmitter release. [127] Barbiturates also increase the threshold of normal brain structures during electrically induced afterdischarges and inhibit the kindling process more effectively than do other antiepileptic drugs. Furthermore, small barbiturate doses can reduce seizure activity by increasing beta- activity in the EEG. [127] Table 8-5 (Table Not Available) shows a dose schedule for phenobarbital treatment of seizures in different age groups with or without concomitant phenytoin therapy. The phenobarbital dose should be reduced in patients with hepatic or renal disease because a given dose can produce significantly higher blood concentrations in those patients.

Brain Protection

A number of actions of the barbiturates on the CNS can protect the brain in some clinical situations (Chs. 19 and 52) . [64] They decrease cerebral metabolism in areas of high brain activity until the EEG becomes flat, after which no further suppression occurs even with an increased dose. This decrease is nonlinear during a thiopental infusion (Fig. 8-18) (Figure Not Available) . [128] A possible mechanism for this protective effect may be suppression of excitatory transmission by interfering with the nitric oxide (NO)-cyclic guanosine monophosphate system. Barbiturates may either inhibit the action of NO or inactivate NO in vascular smooth muscle. [129] Another mechanism is attenuation of *N*-methyl- D-aspartate- and AMPA-mediated glutamate excitatotoxicity. [130] Other barbiturate protective actions include an inverse steal in which vasoconstriction in healthy areas of the brain shunts blood to diseased areas, a reduction of ICP and an increase in cerebral perfusion pressure, stabilization of liposomal membranes, free-radical scavenging, and an anticonvulsant effect. However, arterial hypotension must be avoided to maintain adequate cerebral perfusion pressure. The depression of cerebral metabolism neither alters the concentration of lactate, pyruvate, phosphocreatine, or adenosine triphosphate nor has important effects on the pathways of cerebral glucose metabolism. [131]

In animals, doses of thiopental sufficient to suppress EEG activity are more likely to cause hypotension or ventricular fibrillation than are equivalent doses of pentobarbital. [132] High doses of methohexital cause depression of mean arterial pressure, cerebral blood flow, and cerebral metabolism; thiopental has similar effects at equivalent EEG suppression. Methohexital causes less cerebral vasoconstriction, has less effect on cerebral metabolism, and causes blood flow to return toward control values more rapidly than equivalent doses of thiopental. [133]

In primates, barbiturates decrease cerebral infarction size after focal cerebral artery occlusion, but these agents offer no benefit after stroke or cardiac arrest. [131] In humans, thiopental provides protection if a 40 mg/kg dose, sufficient to maintain a flat EEG, is given to patients undergoing cardiac valvular surgery that is likely to have neuropsychiatric complications of emboli after normothermic cardiopulmonary bypass. However, these patients awaken more slowly and need more inotropic support than untreated patients. [134] Thiopental may also protect poorly perfused areas of the brain in patients with increased ICP secondary to carotid endarterectomy, thoracic aneurysm, and profound controlled hypotension. [135] Barbiturates may provide important brain protection for young patients by reducing hyperemic response to head injury, [136] but in adults they have

Figure 8-18 (Figure Not Available) Effect of thiopental on cerebral metabolism of oxygen ($CMRO_2$). $CMRO_2$ (percent of control) is plotted versus total dose of thiopental infused over time. Regression lines from changes in $CMRO_2$ are drawn for each EEG-determined area; for example, a decrease to 77 percent of control when the EEG is shifting and a slower decrease when an anesthetic pattern appears. *(Modified from Stulken et al [126])*

TABLE 8-6 -- Summary of the Important Clinical Properties of the Intravenous Sedative-Hypnotics Used for Anesthetic Induction [a]

(Not Available)

From Fragen and Avram [143]

[a] ++ to -- is a five-point qualitative scale describing the relative positive (+, ++), neutral (0), or negative (-, --) effect of each agent in each category.

failed to protect the brain after head trauma [137] or cardiac arrest.

Wada Test

A small dose of amobarbital (Amytal Sodium) can be injected into the carotid artery to lateralize cerebral speech dominance in neurosurgical patients; this is known as

the Wada test. [138] An alternative is injection of methohexital (3 to 5 mg) after a 1-mg test dose. [139]

Electroconvulsive Therapy

Propofol resulted in a shorter seizure duration, but blood pressure was more likely to rise above control values after methohexital, when either drug was used to provide hypnosis for electroconvulsive therapy. [140] [141] Methohexital is preferable to thiopental because transient premature atrial and ventricular contractions occur less frequently after methohexital, whether or not atropine is used for premedication. [142]

SUMMARY

The actions of thiopental and other barbiturates have not changed since they were first used by anesthesiologists. However, the understanding of their pharmacokinetics and mechanisms of action has changed. Anesthesiologists also have a better understanding of how the barbiturates affect the various body systems, thus enabling clinicians to use these drugs most effectively, yet with minimum side effects. Comparison of the anesthetic barbiturates with other sedative-hypnotics used to induce general anesthesia (Table 8-6) (Table Not Available) puts in perspective their important clinical properties. [143] Although thiopental is not the ideal intravenous drug to induce general anesthesia, its long-standing position as the standard anesthetic induction agent stems from its lack of major disadvantages.

References

1. Dundee JW: Historical vignettes and classification of intravenous anesthetics. In Aldrete JA, Stanley TH (eds): Trends in Intravenous Anesthesia. Chicago, Year Book Medical Publishers, 1980, p 1.

2. Dundee JW: Fifty years of thiopentone. Br J Anaesth 56:211, 1984.

3. Halford FJ: A critique of intravenous anesthesia in war surgery. Anesthesiology 4:67, 1943.

4. Adams RC, Gray HK: Intravenous anesthesia with pentothal sodium in the case of gunshot wound associated with accompanying severe traumatic shock and loss of blood: Report of a case. Anesthesiology 4:70, 1943.

5. Editorial: The question of intravenous anesthesia in war surgery. Anesthesiology 4:74, 1943.

6. Brodie BB, Mark LC, Papper EM et al: The fate of thiopental in man and a method for its estimation in biological material. J Pharmacol Exp Ther 98:85, 1950.

7. Price HL: A dynamic concept of the distribution of thiopental in the human body. Anesthesiology 21:40, 1960.

8. Guerra F: Thiopental forever after. In Aldrete JA, Stanley TH (eds): Trends in Intravenous Anesthesia. Chicago, Year Book Medical Publishers, 1980, p 143.

9. Dundee JW: Molecular structure-activity relationships of barbiturates. In Halsey MJ, Millar RA, Sutton JA (eds): Molecular Mechanisms in General Anesthesia. New York, Churchill Livingstone, 1974, p 16.

10. Hobbs WR, Rall TW, Verdoon TA: Hypnotics and sedatives; Ethanol. In Hardman JG, Limbird LE, Molinoff PB et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York, McGraw-Hill, 1996, p 361.

11. Crowther J, Hrazdil J, Jolly DT et al: Growth of microorganisms in propofol, thiopental, and a 1:1 mixture of propofol and thiopental. Anesth Analg 82:475, 1996.

12. Hadzija BW, Lubarsky DA: Compatibility of etomidate, thiopental sodium, and propofol injections with drugs commonly administered during induction of anesthesia. Am J Health Syst Pharm 52:997, 1995.

13. Mahisekar UL, Callan CM, Derasari M et al: Infusion of large particles of thiopental sodium during anesthesia induction. J Clin Anesth 6:55, 1994.

14. Andrews PR, Mark LC: Structural specificity of barbiturates and related drugs. Anesthesiology 57:314, 1982.

15. Nguyen KT, Stephens DP, McLeish MJ et al: Pharmacokinetics of thiopental and pentobarbital enantiomers after intravenous administration of racemic thiopental. Anesth Analg 83:552, 1996.

16. Gibson WR, Doran WJ, Wood WC et al: Pharmacology of stereoisomers of 1-methyl-5-(1-methyl-2-pentynyl)-5-allyl barbituric acid. J Pharmacol Exp Ther 125:23, 1959.

17. Ariens EJ: Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. Eur J Clin Pharmacol 26:663, 1984.

18. Carlson BX, Hales TG, Olsen RW: $GABA_A$ receptors and anesthesia. In Yaksh TL, Lynch C III, Zapol WM et al (eds): Anesthesia: Biologic Foundations. New York, Lippincott-Raven, 1998, p 259.

19. Tanelian DL, Kosek P, Mody I et al: The role of the $GABA_A$ receptor/ chloride channel complex in anesthesia. Anesthesiology 78:757, 1993.

20. Olsen RW, Sapp DM, Bureau MH et al: Allosteric actions of central nervous system depressants including anesthetics on subtypes of the inhibitory gamma-aminobutyric acid $_A$ receptor-chloride channel complex. Ann N Y Acad Sci 625:145, 1991.

21. Price HL, Kovnat PJ, Safer JN et al: The uptake of thiopental by body tissues and its relation to the duration of narcosis. Clin Pharmacol Ther 1:16, 1960.

22. Bischoff KB, Dedrick RL: Thiopental pharmacokinetics. J Pharm Sci 57:1346, 1968.

23. Henthorn TK, Avram MJ, Krejcie TC: Intravascular mixing and drug distribution: The concurrent disposition of thiopental and indocyanine green. Clin Pharmacol Ther 45:56, 1989.

24. Hudson RJ, Stanski DR, Burch PG: Pharmacokinetics of methohexital and thiopental in surgical patients. Anesthesiology 59:215, 1983.

25. Burch PG, Stanski DR: The role of metabolism and protein binding in thiopental anesthesia. Anesthesiology 58:146, 1983.

26. Stanski DR, Mihm FG, Rosenthal MH, et al: Pharmacokinetics of high dose thiopental used in cerebral resuscitation. Anesthesiology 53:169, 1980.

27. Buhrer M, Maitre PO, Hung OR et al: Thiopental pharmacodynamics. I. Defining pseudo-steady-state serum concentration-EEG effect relationship. Anesthesiology 77:225, 1992.

28. Hung OR, Varvel JR, Shafer SL et al: Thiopental pharmacodynamics. II. Quantitation of clinical and electroencephalographic depth of anesthesia. Anesthesiology 77:237, 1992.

29. Jacobs JR, Reves JG: Effect site equilibration time is a determinant of induction dose requirement. Anesth Analg 76:1, 1993.

30. Stanski DR: Pharmacodynamic modeling of anesthetic EEG drug effects. Annu Rev Pharmacol Toxicol 32:423, 1992.

31. Flaishon R, Windsor A, Sigl J et al: Recovery of consciousness after thiopental or propofol. Anesthesiology 86:613, 1997.

32. Shanks CA, Avram MJ, Krejcie TC et al: A pharmacokinetic-pharmacodynamic model for quantal responses with thiopental. J Pharmacokinet Biopharm 21:309, 1993.

33. Avram MJ, Sanghvi R, Henthorn TK et al: Determinants of thiopental induction dose requirements. Anesth Analg 76:10, 1993.

34. Avram MJ, Krejcie TC, Henthorn TK: The relationship of age to the pharmacokinetics of early drug distribution: The concurrent disposition of thiopental and indocyanine green. Anesthesiology 72:403, 1990.

35. Christiansen JH, Andreasen F: Individual variation in response to thiopental. Acta Anaesthesiol Scand 22:303, 1978.

36. Dundee JW, Hassard TH, McGowan WAW et al: The 'induction' dose of thiopentone: A method of study and preliminary illustrative results. Anaesthesia 37:1176, 1982.

37. Benowitz N, Forsyth RP, Melmon KL et al: Lidocaine disposition kinetics in monkey and man. II. Effects of hemorrhage and sympathomimetic drug administration. Clin Pharmacol Ther 16:99, 1974.

38. Homer TD, Stanski DR: The effect of increasing age on thiopental disposition and anesthetic requirement. Anesthesiology 62:714, 1985.

39. Stanski DR, Maitre PO: Population pharmacokinetics and pharmacodynamics of thiopental: The effect of age revisited. Anesthesiology 72:412, 1990.

40. Wada DR, Bjorkman S, Ebling WF et al: Computer simulation of the effects of alterations in blood flows and body composition on thiopental pharmacokinetics in humans. Anesthesiology 87:884, 1997.

41. Krejcie TC, Henthorn TK, Niemann CU et al: Recirculatory pharmacokinetic models of markers of blood, extracellular fluid and total body water administered concomitantly. J Pharmacol Exp Ther 278:1050, 1996.

42. Krejcie TC, Henthorn TK, Gentry WB et al: The concordance of the early distribution kinetics of antipyrine and thiopental. Anesthesiology 79:A341, 1993.

43. Wulfsohn NL, Joshi CW: Thiopentone dosage based on lean body mass. Br J Anaesth 41:516, 1969.

44. Gentry WB, Krejcie TC, Henthorn TK et al: Effect of infusion rate on thiopental dose-response relationships: Assessment of a pharmacokinetic-pharmacodynamic model. Anesthesiology 81:316, 1994.

45. Gin T, Mainland P, Chan MTV et al: Decreased thiopental requirements in early pregnancy. Anesthesiology 86:73, 1997.

46. Avram MJ, Krejcie TC, Niemann CU et al: The effects of halothane on the recirculatory pharmacokinetics of physiologic markers. Anesthesiology 97:138, 1997.

47. Brodie BB, Mark LC, Lief PA et al: Acute tolerance to thiopental. J Pharmacol Exp Ther 102:215, 1951.

48. Dundee JW, Price HL, Dripps RD: Acute tolerance to thiopentone in man. Br J Anaesth 28:344, 1956.

49. Toner W, Howard PJ, McGowan WAW et al: Another look at acute tolerance to thiopentone. Br J Anaesth 52:1005, 1980.

50. Hudson RJ, Stanski DR, Saidman LJ et al: A model for studying depth of anesthesia and acute tolerance to thiopental. Anesthesiology 59:301, 1983.

51. Crankshaw DP, Edwards NE, Blackman GL et al: Evaluation of infusion regimens for thiopentone as a primary anesthetic agent. Eur J Clin Pharmacol 28:543, 1985.

52. Barratt R, Graham GG, Torda TA: The influence of sampling site upon the distribution of phase kinetics of thiopentone. Anaesth Intensive Care 12:5, 1984.

53. Barratt RL, Graham GG, Torda TA: Kinetics of thiopentone in relation to the site of sampling. Br J Anaesth 56:1385, 1984.

54. DeJong RH, Heavner JE: Local anesthetic seizure prevention: Diazepam versus pentobarbital. Anesthesiology 36:449, 1972.

55. Jonmarker C, Westrin P, Larsson S et al: Thiopental requirements for induction of anesthesia in children. Anesthesiology 67:104, 1987.

56. Short TG, Galletly DC, Plummer JL: Hypnotic and anesthetic action of thiopental and midazolam alone and in combination. Br J Anaesth 66:13, 1991.

57. Wang LP, Hermann C, Westrin P: Thiopentone requirements in adults after varying preinduction doses of fentanyl. Anaesthesia 51:831, 1996.

58. Nishina K, Mikawa K, Maekawa N et al: Clonidine decreases the dose of thiamylal required to induce anesthesia in children. Anesth Analg 79:776, 1994.

59. Tovall RM: A comparative clinical and statistical study of thiopental and thiamylal in human anesthesia. Anesthesiology 16:910, 1965.

60. Thompson DS, Eason CN, Flacke JW: Thiamylal anaphylaxis. Anesthesiology 39:556, 1973.

61. Sprung J, Schoenwald PK, Schwartz LB: Cardiovascular collapse resulting from thiopental-induced histamine release. Anesthesiology 86:1006, 1997.

62. Whitwam JG: Methohexitone. Br J Anaesth 48:641, 1976.

63. Stone HH, Donnelly CC: The accidental intra-arterial injection of thiopental. Anesthesiology 22:995, 1961.

64. Dundee JW, Wyant GM: Intravenous Anaesthesia, 2nd ed. Edinburgh, Churchill Livingstone, 1988.

65. Nor NB, Fox MA, Metcalfe JR et al: The taste of intravenous thiopentone. Anaesth Intensive Care 24:483, 1996.

66. Clarke RSJ: Adverse effects of intravenously administered drugs used in anaesthetic practice. Drugs 22:26, 1981.

67. Archer DP, Ewen A, Roth SH et al: Plasma, brain, and spinal cord concentrations of thiopental associated with hyperalgesia in the rat. Anesthesiology 80:168, 1994.

68. Wilder-Smith OH, Kolletzki M, Wilder-Smith CH: Sedation with intravenous infusions of propofol or thiopentone: Effects on pain perception. Anaesthesia 50:218, 1995.

69. Kiersey DK, Bickford RG, Faulkner A: Electroencephalographic patterns produced by thiopental sodium during surgical operations: Description and classification. Br J Anaesth 23:141, 1951.

70. Turcant A, Delhumeau A, Premel-Cabic A et al: Thiopental pharmacokinetics under conditions of long-term infusions. Anesthesiology 63:50, 1985.

71. Rockhoff MA, Marshall LF, Shapiro HM: High dose barbiturate therapy in humans. Ann Neurol 6:194, 1979.

72. Albrecht RF, Miletich DJ, Rosenberg R et al: Cerebral blood flow and metabolic changes from induction to onset of anesthesia with halothane or pentobarbital. Anesthesiology 47:252, 1977.

73. Gumpert J, Paul R: Activation of the electroencephalogram with intravenous brietal (methohexitone): The findings in 100 cases. J Neurol Neurosurg Psychiatry 34:646, 1971.

74. Todd MM, Drummond JC, Sang H: The hemodynamic consequences of high-dose methohexital anesthesia in humans. Anesthesiology 61:495, 1984.

75. Stone JG, Young WL, Marans ZS et al: Cardiac performance preserved despite thiopental loading. Anesthesiology 79:36, 1993.

76. Drummond JC, Todd MM, U HS: The effect of high-dose sodium thiopental in brain stem auditory and median nerve somatosensory evoked responses in humans. Anesthesiology 63:249, 1985.

77. McPherson RW, Sell B, Traystman RJ: Effects of thiopental, fentanyl, and etomidate in upper extremity somatosensory evoked potentials in humans. Anesthesiology 65:584, 1986.

78. Taniguchi M, Nadstawek J, Langenbach U et al: Effects of four intravenous anesthetic agents on motor evoked potentials elicited by magnetic transcranial stimulation. Neurosurgery 33:407, 1993.

79. Kawaguchi M, Sakamoto T, Shimizu K et al: Effect of thiopentone on motor evoked potentials induced by transcranial magnetic stimulation in humans. Br J Anaesth 71:849, 1993.

80. Joshi C, Bruce DL: Thiopental and succinylcholine action on intraocular pressure. Anesth Analg 54:471, 1975.

81. Hirshman CA, McCullough RE, Cohen PJ et al: Hypoxic ventilatory drive in dogs during thiopental, ketamine, or pentobarbital anesthesia. Anesthesiology 43:628, 1975.

82. McCullough RE, Cohen PJ, Weil JV: Effect of pentobarbitone on hypoxic ventilatory drive in man: Preliminary study. Br J Anaesth 47:963, 1975.

83. Brown GW, Patel N, Ellen FR: Comparison of propofol and thiopental for laryngeal mask insertion. Anaesthesia 46:771, 1991.

84. Harrison GA: The influence of different anesthetic agents on the response to respiratory tract irritation. Br J Anaesth 34:804, 1962.

85. Barker P, Langston JA, Wilson IG et al: Movements of the vocal cords on induction of anaesthesia with thiopental or propofol. Br J Anaesth 69:23, 1992.

86. Forbes AR, Gamsu G: Depression of lung mucociliary clearance by thiopental and halothane. Anesth Analg 58:387, 1979.

87. Taylor C, Stoelting VK: Methohexital sodium: A new ultrashort acting barbiturate. Anesthesiology 21:29, 1960.

88. Eckstein JW, Hamilton WK, McCammond JM: The effect of thiopental on peripheral venous tone. Anesthesiology 22:525, 1961.

89. Frankle WS, Pool-Wilson PA: Effects of thiopental on tension development, action potential, and exchange of calcium and potassium in rabbit ventricular myocardium. J Cardiovasc Pharmacol 3:554, 1981.

90. Gelissen HPMM, Epema AH, Henning RH et al: Inotropic effects of propofol, thiopental, midazolam, etomidate and ketamine on isolated human atrial muscle. Anesthesiology 84:397, 1996.

91. Bettens KM, DeHert SG, Sys SU et al: Role of the endocardial endothelium in the negative inotropic effects of thiopental. Anesthesiology 85:1100, 1996.

92. Galley HF, Webster NR: Brain nitric oxide synthase activity is decreased by intravenous anesthetics. Anesth Analg 83:591, 1996.

93. Housmans PR, Kudsioglu ST, Bingham J: Mechanism of the negative inotropic effect of thiopental in isolated ferret ventricular myocardium. Anesthesiology 82:436, 1995.

94. Komai H, Rusy BF: Effect of thiopental on Ca^{2+} release from sarcoplasmic reticulum in intact myocardium. Anesthesiology 81:946, 1994.

95. Rouby J, Andreev A, Leger P et al: Peripheral vascular effects of thiopental and propofol in humans with artificial hearts. Anesthesiology 75:32, 1991.

96. Skovsted P, Price ML, Price HL: The effects of short-acting barbiturates on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 33:10, 1970.

97. Kettler D, Sonntag H, Wolfram-Donath U et al: Haemodynamics, myocardial function, oxygen requirements, and supply of the human heart after administration of etomidate. In Doenicke A (ed): Anesthesiology and Resuscitation: Etomidate, an Intravenous Hypnotic Agent. Berlin, Springer-Verlag, 1977, p 81.

98. Prys-Roberts C: Cardiovascular and ventilatory effects of intravenous anesthetics. Clin Anaesth 2:203, 1984.

99. Bittrick NM, Kane AVR, Mosher RE: Methohexital and its effect on liver function tests. Anesthesiology 24:81, 1963.

100. Ghoneim MM, Pandya H: Plasma protein binding of thiopental in patients with impaired renal or hepatic function. Anesthesiology 42:545, 1975.

101. Hudson RJ, Stanski DR: Barbiturates: Pharmacokinetics and pharmacodynamics. Clin Anaesth 2:27, 1984.

102. Marsland AR, Bradley JP: Anaesthesia for renal transplantation: 5 Years' experience. Anaesth Intensive Care 11:337, 1983.

103. Kasner M, Grosse J, Krebs M et al: Methohexital impairs osmoregulation. Anesthesiology 82:1396, 1995.

104. Kaniaris P, Katsilambros N, Castanas E et al: Relation between glucose tolerance and serum insulin levels in man before and after thiopental intravenous administration. Anesth Analg 54:718, 1975.

105. Fragen RJ, Shanks CA, Molteni A et al: Effects of etomidate on hormonal responses to surgical stress. Anesthesiology 61:652, 1984.

106. Hirshman CA, Edelstein RA, Ebertz JM et al: Thiobarbiturate-induced histamine release in human mast cells. Anesthesiology 63:353, 1985.

107. Kosaka Y, Takahashi T, Mark LC: Intravenous thiobarbiturate anesthesia for cesarean section. Anesthesiology 31:489, 1969.

108. Bernstein K, Gisselsson SL, Jacobson L et al: Influence of two different anaesthetic agents on the newborn and the correlation between foetal oxygenation and induction-delivery time in elective caesarean section. Acta Anaesthesiol Scand 29:157, 1985.

109. Bland BAR, Lawes EG, Duncan PW et al: Comparison of midazolam and thiopental for rapid sequence anesthetic induction for elective cesarean section. Anesth Analg 66:1165, 1987.

110. Hodgkinson R, Marx GF, Kim SS et al: Neonatal neurobehavioral tests following vaginal delivery under ketamine, thiopental, and extradural anesthesia. Anesth Analg 56:548, 1977.

111. Krintel JJ, Wegmann F: Aminophylline reduces the depth and duration of sedation with barbiturates. Acta Anaesthesiol Scand 31:352, 1987.

112. Harvey SC: Hypnotics and sedatives. In Gilman AG, Goodman LS, Rall TW et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York, Macmillan, 1985, p 339.

113. Fragen RJ, Caldwell N: Comparison of a new formula of etomidate with thiopental: Side effects and awakening times. Anesthesiology 50:242, 1979.

114. Beskow A, Werner O, Westrin P: Faster recovery after anesthesia in infants after intravenous induction with methohexital instead of thiopental. Anesthesiology 83:979, 1995.

115. Korttila K, Linnoila M, Ertama P et al: Recovery and simulated driving after intravenous anesthesia with thiopental, methohexital, propanidid, or alphadione. Anesthesiology 43:291, 1975.

116. Duncalf D, Nagashima H, Duncalf RM: Naloxone fails to antagonize thiopental anesthesia. Anesth Analg 57:558, 1978.

117. O'Donnell JF, Hewitt JC, Dundee JW: Clinical studies of induction agents. XXVIII. A further comparison of venous complications following thiopentone, methohexitone and propanidid. Br J Anaesth 41:681, 1969.

118. Cay DL: Accidental epidural thiopentone. Anaesth Intensive Care 12:61, 1984.

119. Wells D, Davies G, Wagner D: Accidental injection of epidural methohexital. Anesthesiology 67:846, 1987.

120. Remmer H: The role of the liver in drug metabolism. Am J Med 49:617, 1970.

121. Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 76:334, 1992.

122. Crankshaw DP, Boyd MD, Bjorksten AR: Plasma drug efflux: A new approach to optimization of drug infusion for constant blood concentration of thiopental and methohexital. Anesthesiology 67:32, 1987.

123. Schwilden H, Schuttler J, Stoeckel H: Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. Anesthesiology 67:341, 1987.

124. Katz RI, Skeen JT, Quartararo C et al: Varied uses of a thiopental infusion. Anesth Analg 66:1328, 1987.

125. Young GB, Blume WT, Bolton CF et al: Anesthetic barbiturates in refractory status epilepticus. J Sci Neurol 7:291, 1980.

126. Olsen RW, Snowman AM, Lee R et al: Role of the gamma-aminobutyric acid receptor-ionophore complex in seizure disorders. Ann Neurol 16:S90, 1984.

127. Vining EPG: Uses of barbiturates and benzodiazepines in treatment of epilepsy. Neurol Clin 4:617, 1986.

128. Stulken EH Jr, Milde JH, Michenfelder JD et al: The nonlinear response of cerebral metabolism to low concentrations of halothane, enflurane, isoflurane and thiopental. Anesthesiology 46:28, 1977.

129. Terasko K, Nakamura K, Toda H et al: Barbiturates inhibit endothelium-dependent and -independent relaxations mediated by cyclic GMP. Anesth Analg 78:823, 1994.

130. Zhu H, Cottrell JE, Kass IS: The effect of thiopental and propofol on NMDA- and AMPA-mediated L-glutamate excitotoxicity. Anesthesiology 87:944, 1997.

131. Smith AL: Barbiturate protection in cerebral hypoxia. Anesthesiology 47:285, 1977.

132. Roesch C, Haselby KA, Paradise RP et al: Comparison of cardiovascular effect of thiopental and pentobarbital at equivalent levels of CNS depression. Anesth Analg 62:749, 1983.

133. Boarini DJ, Kassel NF, Coester HC: Comparison of sodium thiopental and methohexital for high-dose barbiturate anesthesia. J Neurosurg 60:602, 1984.

134. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. Anesthesiology 64:165, 1986.

135. Bedford RF, Persing JA, Potereskin L et al: Lidocaine or thiopental for rapid control of intracranial hypertension. Anesth Analg 59:435, 1986.

136. Aitkenhead AR: Do barbiturates protect the brain? Br J Anaesth 53:1011, 1981.

137. Ward JD, Becker DP, Miller DJ et al: Failure of prophylactic barbiturate coma in the treatment of severe head trauma. J Neurosurg 62:383, 1985.

138. Wada J, Rasmussen T: Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: Experimental and clinical observations. J Neurosurg 17:226, 1960.

139. Willmore LJ, Wilder BJ, Mayersdorf A et al: Identification of speech lateralization by intracarotid injection of methohexital. Ann Neurol 4:86, 1978.

140. Rampton AJ, Griffin RM, Stuart CS et al: Comparison of methohexital and propofol for electroconvulsive therapy: Effects on hemodynamic responses and seizure duration. Anesthesiology 70:412, 1989.

141. Avramov MN, Husain MM, White PF: The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. Anesth Analg 81:596, 1995.

142. Mokriske BLK, Nagle SE, Cohen SM et al: ECT induced cardiac arrhythmias during anesthesia with different barbiturates. Anesthesiology 69A:617, 1988.

143. Fragen RJ, Avram MJ: Comparative pharmacology of drugs used for the induction of anesthesia. In Stoelting RR, Barash PG, Gallagher TJ (eds): Advances in Anesthesia. Chicago, Year Book Medical Publishers, 1986, p 303.

Chapter 9 - Nonbarbiturate Intravenous Anesthetics

J. Gerald Reves
Peter S. A. Glass
David A. Lubarsky

Uses

SUMMARY

/das/book/view/29494766/875/96.html

INTRODUCTION

The introduction of thiopental into clinical practice in 1934 marked the advent of modern intravenous anesthesia. Thiopental and other barbiturates, however, are not ideal intravenous anesthetics, primarily because they provide only hypnosis (Ch. 8) . The ideal intravenous anesthetic drug would provide hypnosis, amnesia, and analgesia. Because no single drug is ideal, many other drugs are used, often together, that offer some or all of the desired effects. These drugs were introduced steadily into clinical practice with varying degrees of acceptance. With an increasing number of compounds and superior methods of intravenous anesthetic drug delivery available (Ch. 11) , the use of intravenous anesthetics continues to grow.

The future of anesthetic management involves the simultaneous use of several drugs, including inhaled anesthetics together with intravenous drugs. A 1988 survey of mortality in 100,000 cases of anesthesia reveals that the practice of combined anesthetic drug use may be safer than the use of only one or two drugs [1] ; the relative odds of dying within 7 days was 2.9 times greater when one or two anesthetic drugs were used than when three or more were used. Although it is exceedingly difficult to interpret these data, the use of several drugs may be beneficial to anesthetic care. Thus, the skillful use of multiple intravenous anesthetics is not only possible but preferable in the optimal care of patients. The purpose of this chapter is to provide information on the major nonbarbiturate and nonopioid intravenous anesthetic drugs available for clinical use today.

BENZODIAZEPINES

History

Benzodiazepines were discovered accidentally to be ef-fective sedative-hypnotic drugs. [2] Sternbach synthesized chlordiazepoxide (Librium) in 1955, but it was discarded without testing because it was considered inert. However, in 1957 the drug was discovered to have entirely unexpected "hypnotic, sedative, and antistrychnine effects in mice." [3] This first benzodiazepine was released for oral use in 1960, and in that year it was clear that in sufficiently large doses, chlordiazepoxide possessed profound hypnotic and amnestic properties, although it was not available in parenteral form for use in anesthesia. However, a patient who was taking chlordiazepoxide was reported to have fallen and fractured her sacrum accidentally; [4] this accident, which was not remembered or painful, suggested the use of benzodiazepines as anesthetics during trauma (surgery). Diazepam (Valium) was synthesized by Sternbach in 1959 in a search for a new and better compound. Oxazepam (Serax), a metabolite of diazepam, was synthesized in 1961 by Bell and was marketed by a different pharmaceutical company. Lorazepam (Ativan), a 2
chloro-substitution product of oxazepam, was synthesized in 1971 in an attempt to produce a more potent benzodiazepine. The next major achievement was Fryer and Walser's 1976 synthesis of midazolam (Versed), the first clinically used water-soluble benzodiazepine. [5] It is not certain when benzodiazepines were first used to induce anesthesia, but in 1966 several groups reported the use of diazepam for anesthesia. [6] [7] [8] Midazolam was the first benzodiazepine that was produced primarily for use in anesthesia. [9]

The benzodiazepines produce many of the characteristics sought by anesthesiologists. They produce their actions by occupying the benzodiazepine receptor, which was first discussed in December of 1971 in Milan. [10] Barnett and Fiore [11] postulated a benzodiazepine receptor, and in 1977, specific benzodiazepine receptors were described when ligands were found to interact with a central receptor. [12] The discovery and understanding of the mechanism of the benzodiazepine receptor have enabled chemists to develop many agonist compounds and even to produce a specific antagonist for clinical use.

Physicochemical Characteristics

Three benzodiazepine receptor agonists are commonly used in the practice of anesthesia in the United States: midazolam, diazepam, and lorazepam (Fig. 9-1) and Table 9-1) . All these molecules are relatively small and are lipid soluble at physiologic pH. Each milliliter of diazepam solution (5 mg) contains propylene glycol 0.4 mL, alcohol 0.1 mL, benzyl alcohol 0.015 mL, and sodium benzoate/benzoic acid in water for injection (pH 6.2 to 6.9). Lorazepam solution (2 or 4 mg/mL) contains 0.18 mL polyethylene glycol, with 2 percent benzyl alcohol as a preservative. Midazolam solution contains 1 or 5 mg/mL of midazolam with 0.8 percent sodium chloride and 0.01 percent disodium edetate, with 1 percent benzyl alcohol as a preservative. The pH is adjusted to 3 with hydrochloric acid and sodium hydroxide. Midazolam is the most lipid soluble of the three drugs *in vivo*,[13] but because of its pH-dependent solubility, is water soluble as formulated in a buffered acidic medium (pH 3.5). The imidazole ring of midazolam accounts for its stability in solution and rapid metabolism. The high lipophilicity of all three accounts for the rapid central nervous system (CNS) effect, as well as for their relatively large volumes of distri-bution. [14]

Metabolism

Biotransformation of the benzodiazepines occurs in the liver. The two principal pathways involve either hepatic microsomal oxidation (*N*-dealkylation or aliphatic hydroxylation) or glucuronide conjugation. [2] [15] The difference in the two pathways is significant, because oxidation is susceptible to outside influences and can be impaired by certain population characteristics (e.g., old age), disease states (e.g., hepatic cirrhosis), or the coadministration of other drugs that can impair oxidizing capacity (e.g., cimetidine). Conjugation is less susceptible to these factors. [2] Both midazolam and diazepam undergo oxidation reduction or phase I reactions in the liver. [16] The fused imidazole ring of midazolam is oxidized rapidly by the liver, much more rapidly than the methylene group of the diazepine ring of other benzodiazepines. This accounts for the greater hepatic clearance of midazolam compared with diazepam. Lorazepam is less affected by enzyme induction and some of the other factors known to alter the cytochrome P-450 and other phase I enzymes. For example, cimetidine inhibition of oxidative enzyme function impairs the clearance of diazepam, [17] but it has no effect on lorazepam. [16] Age decreases and smoking increases the clearance of diazepam, [18] but neither has a significant effect on midazolam biotransformation. [18] [19] Habitual alcohol consumption increases the clearance of midazolam. [20] There is new evidence that race, because of differences in isoenzymes responsible for hydroxylations, has a genetic basis for differences in drug metabolism. [21] The high frequency of mutated alleles in Asians in the genes coding for *CYP2C19* may explain the reduced hepatic biotransformation of diazepam.

The metabolites of the benzodiazepines can be important. Diazepam forms two active metabolites, oxazepam and

Figure 9-1 The structures of four benzodiazepines used in clinical anesthesia practice.

TABLE 9-1 -- Physicochemical Characterization of Three Benzodiazepines

	DIAZEPAM	LORAZEPAM	MIDAZOLAM
Molecular weight (d)	284.7 [a]	321.2 [a]	362 [a]
p K_a	3.3 (20°)	11.5 (20°)	6.2 (20°) [a]
Water soluble	No [a]	Almost insoluble	Yes [b]
Lipid soluble	Yes [a]	Yes (less so, however)	Yes [b]
	Highly lipophilic	Relatively less lipophilic	Highly lipophilic

[a] *Data from Moffet* [581]
[b] pH dependent: pH >4, lipid soluble; pH < 4, water soluble

desmethyldiazepam, both of which add to and prolong the drug's effects. Midazolam is biotransformed to hydroxymidazolams, which have activity, and when given over a longer time can accumulate. [22] However, these metabolites are rapidly conjugated and excreted in the urine. The 1-hydroxymidazolam has an estimated clinical potency 20 to 30 percent of midazolam. [23] It is excreted by the kidneys largely and can cause profound sedation in patients with renal impairment. [24] The primary hydroxymetabolite is cleared more rapidly [23] than midazolam in healthy patients (Table 9-2) (Table Not Available) . Thus, the metabolites are less potent and normally more rapidly cleared than midazolam, making them of little concern in patients with normal hepatic and renal function. Lorazepam has five metabolites, but the principal one is conjugated to glucuronide. This metabolite is inactive, water soluble, and rapidly excreted via the kidney.

Pharmacokinetics

The three benzodiazepines used in anesthesia are classified as short- (midazolam), intermediate- (lorazepam), and long-lasting (diazepam), according to their metabolism and plasma clearance [18] [25] (Table 9-3) . The plasma disappearance curves of all the benzodiazepines can be fitted to a two- or three-compartment model. Protein binding and volumes of distribution are not importantly different among these three benzodiazepines, but the clearance is significantly different. The clearance rate of midazolam ranges from 6 to 11 mL/kg/min, whereas the clearance of lorazepam is 0.8 to 1.8 mL/kg/min, and that of diazepam is 0.2 to 0.5 mL/kg/min. [18] Because of these differences in clearance, the drugs have predictably different plasma disappearance curves (Figs. 9-2 , 9-3 , and 9-4) . They also have different context-sensitive half-times (Fig. 9-5) . Although the termination of action of these drugs is primarily a result of redistribution of the drug from the CNS to other tissues after use in anesthesia, after daily (long-term) repeated administration or after prolonged continuous infusion, midazolam blood levels will decrease more rapidly than blood levels of the other drugs because of its greater hepatic clearance. Thus, patients given continuous infusions of midazolam or repeated boluses over days should awaken faster than those given diazepam or lorazepam.

Factors known to influence the pharmacokinetics of benzodiazepines are age, gender, race, enzyme induction, and hepatic and renal disease. Diazepam is sensitive to some of these factors, particularly age. Increasing age tends to reduce the clearance of diazepam [26] significantly and the clearance of midazolam to a lesser degree. [27] Lorazepam is resistant to the effects of age, gender, and renal disease on pharmacokinetics. These drugs are all affected by obesity. The volume of distribution is increased as drug goes from the plasma into the adipose tissue. Although clearance is not altered, elimination half-lives are prolonged, owing to the delayed return of the drug to the plasma in obese persons. [27] On the basis of pharmacokinetics, complex and seemingly contradictory dosing recommendations are required. For example, the induction dose of midazolam (and other benzodiazepines) should take into consideration a heavy weight (increased dose) because of the increased fat depot for the drug. However, dosing for continuous infusion in obese patients should be based on lean body weight because clearance is unaffected by weight. [18] In general, sensitivity to benzodiazepines in some groups, such as the elderly, is greater despite relatively modest pharmacokinetic effects; thus, factors other than pharmacokinetics must be considered when these drugs are used.

Pharmacology

All benzodiazepines have hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle relaxant properties. The drugs differ in their potency and efficacy with regard to each of the pharmacodynamic actions.

TABLE 9-2 -- Pharmacokinetic and Pharmacodynamic Comparison of Midazolam and Active Metabolites[a]

(Not Available)

From Mandema et al [23]

[a] All values are significantly ($P < .05$) different between midazolam and alpha-hydroxymidazolam.

TABLE 9-3 -- Pharmacokinetic Variables of Commonly Used Intravenous Anesthetics

	ELIMINATION HALF-LIFE (H)	CLEARANCE (ML/KG/MIN)	VD_{SS} (L/KG)	REFERENCE
Diazepam	20-50	0.2-0.5	0.7-1.7	[18]
Droperidol	1.7-2.2	14	2.0	[515] [516]
Etomidate	2.9-5.3	18-25	2.5-4.5	[258] [259] [262] [263] [264]
Fentanyl	2.5-5	5-15	3-5	[582]
Flumazenil	0.7-1.3	5-20	0.6-1.6	[90] [92]
Ketamine	2.5-2.8	12-17	3.1	[125]
Lorazepam	11-22	0.8-1.8	0.8-1.3	[18]
Midazolam	1.7-2.6	6.4-11	1.1-1.7	[18]
Propofol	4-7	20-30	2-10	[329] [334] [335] [336] [337] [338] [339]

Vd_{SS} , apparent volume of distribution at steady state

The chemical structure of each drug dictates its particular physicochemical properties and pharmacokinetics as well as its receptor binding characteristics. The binding of benzodiazepines to their respective receptors is of high affinity and is stereospecific and saturable; the order of receptor affinity (thus potency) of the three agonists is lorazepam > midazolam > diazepam. Midazolam is approximately three to six [28] times and lorazepam five to ten times as potent as diazepam.

The mechanism of action of benzodiazepines is reasonably well understood. [29] [30] The interaction of ligands with the benzodiazepine receptor represents one of the few examples in which the complex systems of biochemistry, mo-lecular pharmacology, and clinical behavioral patterns can be explained. More is understood about the mechanism of action of benzodiazepines than about that of many other general anesthetics, although it is still not known how the different effects (amnesic, anticonvulsant, anxiolytic, and sleep) are mediated. However, it appears that different receptor subtypes mediate these different actions; for example, anxiolytic, anticonvulsant, and muscle relaxation effects are mediated at the benzodiazepine-gamma-aminobutyric acid (GABA) $_A$ receptor and the hypnotic effects are mediated elsewhere. [31] It also seems that drug effect is a function of blood level. By using plasma concentration data and pharmacokinetic

Figure 9-2 Simulated time course of plasma levels of midazolam following an induction dose of 0.2 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 100 to 200 ng/mL, with awakening usually occurring at levels lower than 50 ng/mL.

simulations, it has been estimated that a benzodiazepine receptor occupancy of less than 20 percent may be sufficient to produce the anxiolytic effect, sedation is observed with 30 to 50 percent receptor occupancy, and unconsciousness requires 60 percent or higher occupation of benzodiazepine agonist receptors. [32]

It is agreed that benzodiazepines exert their general effects by occupying the benzodiazepine receptor that modulates GABA, the major inhibitory neurotransmitter in the brain. GABA-adrenergic neurotransmission counterbalances the influence of excitatory neurotransmitters. The benzodiazepine receptors are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus, but lower densities are found in the striatum, lower brain stem, and spinal cord. Although there are two GABA receptors, it appears that the benzodiazepine receptor is part of the GABA $_A$ receptor complex on the

subsynaptic membrane of the effector neuron. This receptor complex is made up of three protein subunits--alpha, beta, and gamma--arranged as a pentameric aerolic glycoprotein complex (Fig. 9-6) (Figure Not Available) . These proteins contain the various ligand-binding sites of the $GABA_A$ receptor, such as the benzodiazepine, GABA, and barbiturate binding sites. The benzodiazepine binding site is located on the gamma $_2$ -subunit, [31] [33]

Figure 9-3 Simulated time course of plasma levels of diazepam following an induction dose of 0.5 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 0.6 to 1.0 mug/mL, with awakening usually occurring at levels lower than 0.5 mug/mL.

Figure 9-4 Simulated time course of plasma levels of lorazepam following an induction dose of 0.1 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are between 50 and 150 ng/mL, with awakening usually occurring at levels lower than 50 ng/mL.

and the beta-subunit is thought to contain the binding site for GABA. With activation of the $GABA_A$ receptor, gating of the channel for chloride ions is triggered. The cell becomes hyperpolarized and therefore resistant to neuronal excitation. It is now postulated that the hypnotic effects of benzodiazepines are mediated by alterations in a potential-dependent calcium ion flux. [31] The degree of modulation of GABA-receptor function has a built-in limitation, and this explains the relatively high degree of safety with benzodiazepines.

A fascinating and therapeutically significant discovery regarding the benzodiazepine receptor is that the pharmacologic spectrum of ligands includes three different types or classes, [29] which have been termed agonists, antagonists, and

Figure 9-5 The context-sensitive half-times for commonly used intravenous anesthetic drugs are displayed. The context-sensitive half-time is the time for the plasma level of the drug to drop 50 percent after cessation of infusion. The duration of infusion is plotted on the horizontal axis. Note that the rapidity with which the drug level drops is directly related to the time of infusion (i.e., the longer the drug is infused, the longer the half-time). Also note that etomidate, propofol, and ketamine have significantly shorter half-times than thiopental and diazepam, which makes them more suitable for prolonged infusion.

Figure 9-6 (Figure Not Available) Model of the GABA-benzodiazepine receptor complex. Current data suggest a pentameric protein composed of alpha-, beta-, and gamma-subunits; the proposed arrangement of subunits is arbitrary. There are two sites for GABA binding (on the beta-subunits) and a single site for benzodiazepine (BDZ) binding (depicted on the gamma $_2$ -subunit). Homology between the $GABA_{alpha}$ receptor and the nicotinic acetylcholine receptor suggests that the chloride ion channel is formed by contributions from each subunit. *(Modified from Zorumski and Isenberg, [578] copyright 1991, the American Psychiatric Association. Reprinted by permission.)*

inverse agonists (Fig. 9-7) (Figure Not Available) , names that connote their actions. Agonists (e.g., midazolam) alter the conformation of the $GABA_A$ receptor complex so that binding affinity for GABA is increased, with a resultant opening of the chloride channel. Agonist and antagonist bind to a common (or at least overlapping) area of the receptor by forming differing reversible bonds with the receptor. [34] The well-known effects of an agonist then occur (anxiolysis, hypnosis, and anticonvulsant action). Antagonists (e.g., flumazenil) occupy the benzodiazepine receptor, but they produce no activity and therefore block the actions of both the agonists and inverse agonists. Inverse agonists reduce the efficiency of GABA-adrenergic synaptic transmission, and because GABA is inhibitory, the result of decreased GABA is CNS stimulation. The potency of the ligand is dictated by its affinity for the benzodiazepine receptor and the duration of effect by the rate of clearance of the drug from the receptor.

Long-term administration of benzodiazepines produces tolerance, which is defined as the decrease of efficacy of the drug over time. [35] Although the mechanism of chronic tolerance is not fully understood, it appears that long-term exposure to benzodiazepines causes decreased receptor binding and function (i.e., downregulation of the benzodiazepine-$GABA_A$ receptor complex). This would explain the increased dose requirements for anesthesia of benzodiazepines in patients who take them on a long-term basis. Interestingly, it appears that after the cessation of long-term use of benzodiazepines, there is upregulation of the receptor complex, [35] which could mean an increased susceptibility to benzodiazepines during a period after recent use.

The onset and duration of action of a single bolus administration of a benzodiazepine depend on the lipid solubility of the drug, a finding that probably explains the differences in onset and duration of action of the three benzodiazepines used in clinical practice in the United States. Midazolam and diazepam have a more rapid onset (usually within 30-60 seconds) of action than lorazepam (60-120 seconds). The half-life of equilibrium between plasma concentration and electroencephalographic (EEG) effect of midazolam is approximately

Figure 9-7 (Figure Not Available) Spectrum of intrinsic activities of benzodiazepine-receptor ligands, which range from agonists to inverse agonists. Structures of agonist, partial agonist, antagonist, partial inverse agonist, and inverse agonist compounds are shown. Intrinsic activity is greatest among agonists and is least among inverse agonists. Intrinsic activities are schematically indicated as positive by a plus sign and as negative by a minus sign, with 0 indicating a lack of intrinsic activity. *(Modified from Mohler and Richards [25])*

2 to 3 minutes and is not affected by age. [36] [37] This is about two times longer than that of diazepam, but compared with diazepam midazolam has a sixfold greater intrinsic potency. [28] Similar data for other benzodiazepines are not available. Like onset, the duration of effect is also related to lipid solubility and blood level. [38] The more rapid redistribution of midazolam and diazepam compared with lorazepam (presumably because of the lower lipid solubility of lorazepam) [13] accounts for the shorter duration of their actions.

Effects on the Central Nervous System

The benzodiazepines in a dose-related manner reduce the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and cerebral blood flow (CBF) (Ch. 35) .

Midazolam and diazepam maintain a relatively normal ratio of CBF to $CMRO_2$. In healthy human volunteers, midazolam, 0.15 mg/kg, induces sleep and reduces CBF by 34 percent, despite a slight increase in arterial partial pressure of carbon dioxide (Pa_{CO_2}) from 34 to 39 mm Hg. [39] Brown et al [40] studied EEG tracings following 10 mg intravenous midazolam and showed the appearance of rhythmic beta activity at 22 Hz within 15 to 30 seconds of administration in healthy volunteers. Within 60 seconds, there was a second beta rhythm at 15 Hz. Alpha rhythm started to reappear at 30 minutes; however, after 60 minutes there was resistant rhythmic beta activity at 15- to 20-muV amplitude. The EEG changes were similar to EEG effects with diazepam and were not typical of light sleep, although the patients were clinically asleep.

Midazolam, diazepam, and lorazepam all increase the seizure initiation threshold to local anesthetics and lower the mortality rate in mice exposed to lethal doses of local anesthetics. [41] Midazolam and diazepam cause a dose-related protective effect against cerebral hypoxia, demonstrated by extending mouse survival time when mice were placed in 5 percent oxygen. The protection afforded by midazolam is superior to that of diazepam but less than that of pentobarbital. [41] Antiemetic effects are not a prominent action of the benzodiazepines.

Effects on the Respiratory System

Benzodiazepines, like most intravenous anesthetics, produce dose-related central respiratory system depression (Chs. 15 and 33) . The respiratory depression may be greater with midazolam than with diazepam and lorazepam, although comparative studies of the three do not exist. Lorazepam (2.5 mg IV) produces a similar but shorterlasting decrease in tidal volume and minute ventilation than diazepam (10 mg IV) in patients with lung disease. [42] Peak decrease in minute ventilation after midazolam (0.15 mg/kg) is almost identical to that produced in healthy patients given diazepam (0.3 mg/kg), as determined by carbon dioxide response data. [43] The slopes of the ventilatory response curves to carbon dioxide are flatter than normal (control) but not shifted to the right, as with opioids. Judging from the plasma level and steepness of the dose-response effect on Pa_{CO_2} curves [44] (Fig. 9-8) (Figure Not Available) , midazolam is about five to nine times as potent as diazepam. The

peak onset of ventilatory depression with midazolam (0.13-0.2 mg/kg) is rapid (about 3 min),

Figure 9-8 (Figure Not Available) (A) The increase of Pa CO_2 from baseline versus the plasma concentration after three intravenous bolus doses of diazepam (0.15 mg/kg) given at 20-minute intervals. (B) The increase of Pa CO_2 from baseline versus the midazolam plasma concentration after three intravenous bolus doses of midazolam (0.05 mg/kg) given at 20-minute intervals. The solid line represents a best fit model of the data from the three injections. Mean values are represented plus or minus standard error of the mean; open boxes are data from injection 1, cross-hatched boxes are data from injection 2, and solid boxes are data from injection 3. *(From Sunzel et al [44])*

and significant depression remains for about 60 to 120 minutes. [46] [46] The rate of midazolam administration affects the onset time of peak ventilatory depression; the faster the drug is given, the more quickly this peak depression occurs. [47] The respiratory depression of midazolam is more pronounced and of longer duration in patients with chronic obstructive pulmonary disease, and the duration of ventilatory depression is longer with midazolam (0.19 mg/kg) than with thiopental (3.3 mg/kg). [45] Lorazepam (0.05 mg/kg) alone does not depress the carbon dioxide response, but when lorazepam is combined with meperidine, there is predictable respiratory depression. [48] It is probable that benzodiazepines and opioids produce additive or supra-additive (synergistic) respiratory depression, even though they act at different receptors.

Apnea occurs with benzodiazepines. The incidence of apnea after thiopental or midazolam when these drugs are given for induction of anesthesia is similar. Apnea occurred in 20 percent of 1,130 patients given midazolam for induction and 27 percent of 580 patients given thiopental in clinical trials with midazolam. [9] Apnea is related to dose of benzodiazepine and is more likely to occur in the presence of opioids. Old age, debilitating disease, and other respiratory depressant drugs probably also increase the incidence and degree of respiratory depression and apnea with benzodiazepines.

Effects on the Cardiovascular System

The benzodiazepines used alone have modest hemodynamic effects (Chs. 16 and 30) . The hemodynamic changes reported with anesthetic induction doses of diazepam, midazolam, and lorazepam are shown in Table 9-4 . These values represent the peak hemodynamic effect in the first 10 minutes after administration and are derived from studies of both healthy subjects and patients with ischemic and valvular heart diseases. [49] [50] [51] [52] [53] [54] [55] [56] The predominant hemodynamic change is a slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The mechanism by which benzodiazepines maintain relatively stable hemodynamics involves the preservation of homeostatic

TABLE 9-4 -- Hemodynamic Changes After Induction of Anesthesia With Nonbarbiturate Hypnotics

	DIAZEPAM	DROPERIDOL	ETOMIDATE[a]	KETAMINE	LORAZEPAM	MIDAZOLAM	PROPOFOL
HR	-9-+13%	Unchanged	-5-+10%	0-59%	Unchanged	-14-+12%	-10-+10%
MBP	0--19%	0--10%	0--17%	0-+40%	-7--20%	-12--26%	-10--40%
SVR	-22-+13%	-5--15%	-10-+14%	0-+33%	-10--35%	0--20%	-15--25%
PAP	0--10%	Unchanged	-9-+8%	+44-+47%	--	Unchanged	0--10%
PVR	0--19%	Unchanged	-18-+6%	0-+33%	Unchanged	Unchanged	0--10%
PAO	Unchanged	+25-+50%	Unchanged	Unchanged	--	0--25%	Unchanged
RAP	Unchanged	Unchanged	Unchanged	+15-+33%	Unchanged	Unchanged	0--10%
CI	Unchanged	Unchanged	-20-+14%	0-+42%	0-+16%	0--25%	-10--30%
SV	0--8%	0--10%	0--20%	0--21%	Unchanged	0--18%	-10--25%
LVSWI	0--36%	Unchanged	0--33%	0-+27%	--	-28--42%	-10--20%
dP/dt	Unchanged	--	0--18%	Unchanged	--	0--12%	Decreased
References	[49] [50] [51] [581] [583] [584] [585]	[180] [196]	[290] [292] [293] [294] [295] [296]	[167] [586] [587] [588]	[56] [589]	[49] [250] [590] [591] [592]	[298] [426] [427] [428] [429] [433] [434] [435] [436] [437] [438]

CI, cardiac index; HR, heart rate; LVSWI, left ventricular stroke work index; MBP, mean blood pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PAO, pulmonary artery occluded pressures; RAP, right atrial pressure; SV, stroke volume; SVR, systemic vascular resistance

[a] The larger deviations are in patients with valvular disease.

reflex mechanisms, [57] but there is evidence that the baroreflex is impaired by both midazolam and diazepam. [58] Midazolam causes a slightly greater decrease in arterial blood pressure than do the other benzodiazepines, but the hypotensive effect is minimal and about the same as seen with thiopental. [59] Despite the hypotension, midazolam, even in doses as high as 0.2 mg/kg, is safe and effective for induction of anesthesia even in patients with severe aortic stenosis. [60] The hemodynamic effects of midazolam and diazepam are dose related: the higher the plasma level, the greater the decrease in systemic blood pressure [44] ; however, there is a plateau plasma drug effect above which little change in arterial blood pressure occurs. The plateau plasma level for midazolam is 100 ng/mL, and that for diazepam is about 900 ng/mL. [44] Heart rate, ventricular filling pressures, and cardiac output are maintained after induction of anesthesia with benzodiazepines. In patients with elevated left ventricular filling pressures, diazepam and midazolam produce a "nitroglycerin-like" effect by lowering the filling pressure and increasing cardiac output. [52] [54]

The stresses of endotracheal intubation and surgery are not blocked by midazolam. [49] Thus, adjuvant anesthetics, usually opioids, are often combined with benzodiazepines. The combination of benzodiazepines with opioids and nitrous oxide has been investigated in patients with ischemic and valvular heart diseases. [51] [56] [60] [61] [62] [63] [64] Whereas the addition of nitrous oxide to midazolam (0.2 mg/kg) and diazepam (0.5 mg/kg) has trivial hemodynamic consequences, the combination of benzodiazepines with opioids does have a supra-additive effect. [65] The combinations of diazepam with fentanyl or sufentanil, of midazolam with fentanyl [62] or sufentanil, [64] and lorazepam with fentanyl [56] or sufentanil [63] all produce greater decreases in systemic blood pressure than does each drug alone. Presumably, combinations of benzodiazepines with remifentanil will do the same. The mechanism for this synergistic hemodynamic effect is not completely understood, but it is probably related to a reduction in sympathetic tone when the drugs are given together. [61] There is evidence that diazepam and midazolam decrease catecholamines, [58] a finding consistent with this hypothesis.

Uses

Intravenous Sedation

Benzodiazepines are used for sedation as preoperative premedication, intraoperatively during regional or local anesthesia, and postoperatively (Chs. 40 , 42 , 43 , 44 , 65 , and 65) . The anxiolysis, amnesia, and elevation of the local anesthetic seizure threshold are desirable benzodiazepine actions. The drugs should be given by titration for this use; end points of titration are adequate sedation or dysarthria (Table 9-5) . The onset of action is more rapid with midazolam, usually with peak effect reached within 2 to 3 minutes of administration; time to peak effect is slightly longer with diazepam and is still longer with lorazepam. The duration of action of these drugs depends primarily on the dose used. Although the onset is more rapid with midazolam than with diazepam after bolus administration, the recovery is similar, [66] probably because both drugs have similar early plasma

TABLE 9-5 -- Uses and Doses of Intravenous Benzodiazepines

	MIDAZOLAM	DIAZEPAM	LORAZEPAM

Induction	0.05-0.15 mg/kg	0.3-0.5 mg/kg	0.1 mg/kg
Maintenance	0.05 mg/kg prn 1.0 mug/kg/min	0.1 mg/kg prn	0.02 mg/kg prn
Sedation [a]	0.5-1 mg repeated 0.07 mg/kg IM	2 mg repeated	0.25 mg repeated

prn, as required to keep patient hypnotic and amnestic

[a] Incremental doses given until desired degree of sedation is obtained

decay (redistribution) patterns (see Figs. 9-2 and 9-3) . With lorazepam, sedation and particularly amnesia are slower in onset [67] and are longer lasting than with the other two benzodiazepines. [22] [68] [69] There is often a disparity in the level of sedation as compared with the presence of amnesia (patients seem conscious and reasonably coherent, yet they are amnesic for events and instructions) with all three benzodiazepines. Lorazepam is particularly unpredictable with regard to duration of amnesia, and this is undesirable in patients who wish or need to have recall in the immediate postoperative period. [67] The degree of sedation and the reliable amnesia, as well as preservation of respiratory and hemodynamic function, are better overall with benzodiazepines than with other sedative-hypnotic drugs used for conscious sedation. Despite the wide safety margin with benzodiazepines, respiratory function must be monitored when these drugs are used for sedation to prevent undesirable degrees of respiratory depression. There may be a slight synergistic action between midazolam and spinal anesthesia with respect to ventilation. [70] Thus, the use of midazolam for sedation during regional and epidural anesthesia requires vigilance with regard to respiratory function, as when these drugs are given with opioids. Sedation for longer periods, for example in the intensive care unit (ICU), is accomplished with benzodiazepines. Prolonged infusion will result in accumulation of drug and, in the case of mid-azolam, significant concentration of the active metabolite. Reviews have pointed out concerns as well as advantages of benzodiazepine sedation. [22] [71] In a relatively small study comparing an infusion of midazolam with an intermittent bolus lorazepam, both drugs were equivalent in sedation and oxygenation effects, but the overall recovery from sedation over time was not examined. [72] The superiority of one drug over the other has not been established; both agents should always be titrated downward to maintain sedation as required. Dosing should not be fixed, but it should be reduced over time to avoid accumulation of parent or metabolites during prolonged infusion.

Induction and Maintenance of Anesthesia

Midazolam is the benzodiazepine of choice for use in anesthetic induction. Although both diazepam and lorazepam have been used for induction of general anesthesia, the faster onset and lack of venous complications make midazolam better suited for this use. With midazolam, induction

of anesthesia is defined as unresponsiveness to command and loss of the eyelash reflex. When midazolam is used in appropriate doses (see Table 9-5) , induction occurs less rapidly than with thiopental, [9] but the amnesia is more reliable. Numerous factors influence the rapidity of action of midazolam and the other benzodiazepines when used for induction of general anesthesia; these factors are dose, speed of injection, degree of premedication, age, American Society of Anesthesiologists (ASA) physical status, and concurrent anesthetic drugs. [9] [73] In a well-premedicated, healthy patient, midazolam (0.2 mg/kg given in 5-15 seconds) will induce anesthesia in 28 seconds, whereas with diazepam (0.5 mg/kg given in 5-15 seconds), induction occurs in 39 seconds. [49] Elderly patients require lower doses of midazolam than younger patients [74] [75] (Fig. 9-9) (Figure Not Available) . Patients older than 55 years and those with ASA physical status higher than III require a 20 percent or greater reduction in the induction dose of midazolam. [9] The usual induction dose of midazolam in premedicated patients is between 0.05 and 0.15 mg/kg. When midazolam is used with other anesthetic drugs (coinduction), there is a synergistic interaction, [38] [76] [77] and the induction dose is less than 0.1 mg/kg (Fig. 9-10) (Figure Not Available) . The synergy is seen when midazolam is used with opioids and/or other hypnotics such as thiopental and propofol. This combination therapy (use of two or more hypnotics) may be called *coinduction.*

Awakening after benzodiazepine anesthesia is the result of the redistribution of drug from the brain to other, less well-perfused tissues. The emergence (defined as orientation to time and place) of young, healthy volunteers who have received 10 mg of intravenous midazolam occurs in about 15 minutes, [40] and after an induction dose of 0.15 mg/kg, it occurs in about 17 minutes. [78] Emergence time is related to the dose of midazolam as well as to the dose of adjuvant anesthetic drugs. [9] Emergence from midazolam (0.32 mg/kg)/fentanyl anesthesia is about 10 minutes longer than that from thiopental (4.75 mg/kg)/fentanyl anesthesia [79] and is more prolonged than with propofol. [80] This difference accounts for some anesthesiologists' preference for barbiturates as induction drugs for short operations.

Benzodiazepines lack analgesic properties and must be used with other anesthetic drugs to provide sufficient analgesia; however, as maintenance anesthetic drugs during general anesthesia, benzodiazepines provide hypnosis and amnesia. Double-blind studies comparing midazolam and thiopental as the hypnotic component for balanced anesthesia [79] [81] have shown that midazolam is superior for this use because of better amnesia and a smoother hemodynamic course. Opioid requirements are less with midazolam. Midazolam (0.6 mg/kg) lowers the minimum alveolar concentration (MAC) of halothane by 30 percent [82] and presumably has a similar effect on other inhaled anesthetics. The question of an optimal redosing scheme after induction when midazolam is used as a maintenance hypnotic component of general anesthesia has not been answered. The amnesic period after an anesthetic dose is about 1 to 2 hours. Infusions of midazolam have been used to ensure a constant and appropriate depth of anesthesia. [82] Experience indicates that a plasma level of more than 50 ng/mL when used with adjuvant opioids (e.g., fentanyl) and/or inhalation anesthetics (e.g., nitrous oxide, volatile anesthetics) is achieved with a bolus loading dose of 0.05 to 0.15 mg/kg and a continuous infusion of 0.25 to 1 mug/kg/min. [83] This is sufficient to keep the patient asleep and amnesic but arousable at the end of surgery. Lower infusion doses may be required in some patients and with certain opioids. Midazolam as well as diazepam and lorazepam will accumulate in the blood with repeated bolus administrations or with continuous infusion, just as most intravenous anesthetics do on repeated injection. If the benzodiazepines do accumulate with repeated administrations, prolonged arousal time can be anticipated. This is less of a problem with midazolam than with diazepam and lorazepam because of the shorter context-sensitive half-time and greater clearance of midazolam.

Figure 9-9 (Figure Not Available) Simulated quantal concentration-response curves generated by the parameterized pharmacodynamic model for midazolam. *(From Jacobs et al [75])*

Figure 9-10 (Figure Not Available) Vertical axes all represent drug dose in milligrams per kilogram. On the right, median effective dose (ED_{50}) isobolograms for the hypnotic interactions among midazolam, alfentanil, and propofol are shown. The dotted lines are additive effect lines; note that all combinations fall within the line representing synergism or supra-additive effect. On the left, a triple interaction is depicted. The shaded area represents an additive plane passing through three single-drug ED_{50} points (small open circles). The largest closed circle (with arrows) is the ED_{50} point for the triple combination. The smaller closed circles are ED_{50} points for the binary combinations. R ratios on all graphs represent the interaction (1.0 indicates additive effect) of the various drug combinations. Note that the combination of midazolam and alfentanil produces the greatest synergism, but the combination of all three is also synergistic. *P* values denote the significance of the additive effects. *(Modified from Vinik et al [579])*

Side Effects and Contraindications

Benzodiazepines are remarkably safe drugs. They have relatively high margins of safety, especially compared with barbiturates. They are also free of allergenic effects and do not suppress the adrenal gland. [84] The most significant problem with midazolam is respiratory depression when the drug is given for conscious sedation. The major side effects of lor-azepam and diazepam are venous irritation and thrombophlebitis, problems related to aqueous insolubility and requisite solvents. [9] When used as sedatives or for induction and maintenance of anesthesia, benzodiazepines can produce an undesirable degree or prolonged interval of postoperative amnesia, sedation, and rarely, respiratory depression. These residual effects can be reversed with flumazenil.

New Benzodiazepines

The primary limitation of midazolam, which is the best suited benzodiazepine for use in anesthesia, is the slightly slower onset and prolonged offset compared with a hypnotic such as propofol. There are two benzodiazepine agonists that have been used in clinical trials, RO 48-6791 and RO 48-8684. [19] [37] Both are promising from a pharmacokinetic analysis because they have a larger volume of distribution and clearance than midazolam. Recovery is also faster, approximately 2-fold. It is

possible that one of these two drugs will undergo development with larger clinical trials, because a shorter-lasting benzodiazepine will be welcomed in clinical practice. The most welcome new benzodiazepine would be one rapidly metabolized by esterases, as seen with remifentanil.

FLUMAZENIL

Flumazenil (Anexate, Romazicon) is the first benzodiazepine antagonist approved for clinical use. [46] The preclinical pharmacologic studies with flumazenil revealed it to be a benzodiazepine receptor ligand with high affinity, great specificity, and by definition minimal intrinsic effect. [34] Flumazenil, like the agonists it replaces at the benzodiazepine receptor, interacts with the receptor in a concentration-dependent manner. Because it is a competitive antagonist at the benzodiazepine receptor, its antagonism is reversible and surmountable. Flumazenil has minimal intrinsic activity, [34] [85] which means that its benzodiazepine receptor agonist effects are very weak, significantly less than those of clinical agonists. Flumazenil, like all competitive antagonists at receptors, does not displace the agonist but rather occupies the receptor when an agonist dissociates from the receptor. The half-time (or half-life) of a receptor-ligand bond is a few milliseconds to a few seconds, and new ligand receptor bonds are then immediately formed. This dynamic situation accounts for the ability of either an agonist or an antagonist to occupy the receptor readily. The proportion

of receptors occupied by the agonist in the presence of an antagonist obeys the law of mass action and depends on the affinities and concentrations of the two ligands. [30] [34] Equation 1 expresses this relationship [86] :

where $[R_{Ago}]$ = receptor concentration of agonist, $[R_t]$ = total number of receptors, K_{Ago} = dissociation constant for agonist, K_{Ant} = dissociation constant for antagonist, [Ago] = concentration of agonist at the receptor, and [Ant] = concentration of antagonist at the receptor.

The ratio of agonist to total receptors produces the effects of the agonist drug, but the antagonist can alter this ratio, depending on its concentration and dissociation constant (see Eq. 1). Thus, flumazenil, which is an avid (high-affinity) li-gand, will replace a relatively weak agonist such as diazepam as long as it is given in sufficient dose (i.e., high [Ant]). However, flumazenil is cleared relatively rapidly, and the net result is that the [Ant] is reduced over time as compared with [Ago]; thus, the proportion of receptors occupied by agonist will increase, and the potential for resedation exists (Fig. 9-11) . This situation is less likely to happen when flumazenil is used to reverse midazolam, which has a more rapid clearance than other benzodiazepine agonists. [87] Another important finding is that in the presence of extremely high doses of agonist (e.g., when a mistake in dosing has occurred or suicide is attempted), flumazenil in a low dose attenuates the deep CNS depression (loss of consciousness, respiratory depression) by reducing the fractional receptor occupancy by the agonist without decreasing the agonist effects that occur at low fractional receptor occupancy (drowsiness, amnesia). Conversely, high doses of flumazenil in the presence of low doses of agonist completely

Figure 9-11 Schematic representation of the interaction of a short-acting antagonist with a longer-acting agonist, resulting in resedation. The upper curve shows agonist disappearance from blood, and the lower curve shows antagonist disappearance from plasma. Four conditions are represented: I, agonist response; II, antagonist response (the antagonist reverses the agonist effect); III, agonist response (resedation or resumption of agonist response with disappearance of short-lasting antagonist); and IV, no drug effect, with disappearance of both agonist and antagonist (both drugs are below the therapeutic level).

reverse virtually all the agonist effects. Flumazenil can precipitate withdrawal symptoms in animals or in humans physically dependent on a benzodiazepine receptor agonist. [88] This is not a problem when flumazenil is used to reverse benzodiazepine receptor agonists in anesthesia.

Physicochemical Characteristics

Flumazenil, synthesized in 1979, is similar to midazolam and other classic benzodiazepines except for the absence of the phenyl group, which is replaced by a carbonyl group [89] (see Fig. 9-1) . It forms a colorless, crystalline powder, has a dissociation constant of 1.7, and has weak but sufficient water solubility to permit its preparation in aqueous solution. Its octanol/aqueous buffer partition coefficient is 14, demonstrating moderate lipid solubility at pH 7.4 [89]

Metabolism

Flumazenil, like the other benzodiazepines, is metabolized in the liver, is rapidly cleared from the plasma, and has three known metabolites, *N*-desmethylflumazenil, *N*-desmethylflumazenil acid, and flumazenil acid. [90] The activities of these metabolites and their corresponding glucuronides are not known at present. The glucuronides probably are excreted in the urine. Because flumazenil is still under investigation, many details regarding the clinical metabolism of this drug have not been studied.

Pharmacokinetics

Flumazenil is a short-lived compound. Table 9-3 includes a summary of its pharmacokinetics, which have been described in a variety of clinical settings. [90] [91] [92] Of particular note is that, compared with benzodiazepine receptor agonists, flumazenil has the highest clearance and shortest elimination half-life. The plasma half-life of flumazenil is about 1 hour--it is the shortest-lived of all benzodiazepines used in anesthetic practice. This means that the potential exists for the antagonist to be cleared, leaving sufficient concentrations of agonist at the receptor site to cause resedation. [87] To maintain a constant therapeutic blood level over a prolonged time, either repeated administration or a continuous infusion is required. An infusion rate of 30 to 60 mug/min (0.5-1 mug/kg/min) has been used for this purpose. [93] The rapid blood clearance of flumazenil approaches hepatic blood flow, a finding that indicates that liver clearance is partially dependent on hepatic blood flow. Flumazenil, compared with other benzodiazepines, has a relatively high proportion of unbound drug; its protein binding is low, with the free fraction ranging from 54 to 64 percent. [90] This property of flumazenil could contribute to its rapid onset and greater clearance, but this hypothesis is unproven.

Pharmacology

When given in the absence of a benzodiazepine receptor agonist, flumazenil has little discernible CNS effect. Although

intrinsic (agonist and inverse agonist) effects have been ascribed to flumazenil, [85] they are clinically unimportant. It has been postulated that in low doses a stimulating effect can be seen, and in high doses a central depressant effect becomes more likely. [32] When given to volunteers and patients in clinically relevant doses, flumazenil has no effect on the EEG or cerebral metabolism. [92] [94] [95] In animals, flumazenil has no anticonvulsant properties and, in fact, reverses the anticonvulsant properties of benzodiazepines in local anesthetic-induced seizures. [96] When administered to patients who have benzodiazepine-induced CNS depression, flumazenil produces rapid and dependable reversal of unconsciousness, respiratory depression, sedation, amnesia, and psychomotor dysfunction. [32] [91] [97] [98] Flumazenil can be given prior to, during, or after the agonist to block or reverse the CNS effects of the agonist. The usual clinical need is to reverse the effects of agonists given prior to flumazenil. Flumazenil has successfully reversed the effects of the agonists midazolam, diazepam, lorazepam, and flunitrazepam. The onset is rapid, with peak effect occurring in 1 to 3 minutes, [32] which coincides with the detection of ^{11}C-flumazenil in human brain. [99] Flumazenil reverses the agonist by replacing it at the benzodiazepine receptor, and its onset and duration are governed by the law of mass action (see Eq. 1). A predicted therapeutic plasma level for flumazenil is 20 ng/mL [90] ; however, because the relative binding characteristics of agonist and antagonist in part dictate benzodiazepine receptor occupation by the residual agonist, different doses and plasma levels of flumazenil are required to reverse the effects of particular agonists. These reactions have not been fully studied, but it is known that higher doses of flumazenil are required for reversal of lorazepam than of diazepam, [97] lorazepam being more potent than diazepam. Although it is too soon to be certain, it does not appear that flumazenil administration after long-term benzodiazepine use produces severe withdrawal reactions.

The duration of action of flumazenil is determined by its dose, the dose of the agonist, and the specific agonist that is being reversed. The duration is dictated by the factors given in Equation 1. Studies have shown that during a constant infusion of agonist, the duration of flumazenil action is dependent on the dose, but 45 to 90 minutes of antagonism can be expected after an intravenous dose of 3.0 mg or 2 to 3 hours after a dose of 0.8 mg/kg. [100] [101] This is an artificial setting, because in clinical practice flumazenil is given after administration of agonist has been discontinued.

Flumazenil is devoid of the respiratory and cardiovascular depressant effects of benzodiazepine receptor agonists. A relatively large dose of flumazenil (0.1 mg/kg) given to volunteers did not produce significant respiratory depression. [102] However, when flumazenil is given in the presence of agonists, there are significant respiratory effects, because it reverses respiratory depression caused by the agonists (e.g., when given to volunteers made apneic with midazolam [103]). The reversal of midazolam-induced (0.13 mg/kg) respiratory depression with flumazenil (1.0 mg/kg) lasts between 3 and 30 minutes. [46] Other agonists and other doses would have different durations of antagonism of respiratory depression. If respiratory depression is related to opioid administration, flumazenil will not reverse it. [104] Incremental doses, up to 3 mg intravenously, in patients with ischemic heart disease had no significant effect on cardiovascular variables. [105] Administration of flumazenil to patients given agonists is remarkably free of cardiovascular effects, [32] [106] [107] [108] unlike the experience of opioid reversal with naloxone. Of particular interest is the effect on plasma catecholamines of benzodiazepine receptor agonist reversal with flumazenil, because this effect on catecholamines is the suspected mechanism of hyperdynamic response in opioid reversal. Although flumazenil does reverse sedation, it is not associated with significantly higher catecholamines than are found in patients receiving saline, [106] [107] [108] [109] [110] but the rise in catecholamines that accompanies arousal is more rapid after flumazenil. [109]

Uses and Doses

The relatively few uses for a benzodiazepine antagonist (Table 9-6) include the diagnostic and therapeutic reversal of the effects of benzodiazepine receptor agonists. [111] For diagnostic use in suspected benzodiazepine overdose, flumazenil may be given in incremental intravenous doses of 0.2 to 0.5 mg up to 3 mg. If there is no change in CNS sedation, it is unlikely that CNS depression is based solely on benzodiazepine overdose. More commonly in anesthesia, flumazenil is used to reverse the sedation of a patient who remains depressed after administration of a benzodiazepine for conscious sedation for a general anesthesia. Flumazenil reliably reverses the sedation, respiratory depression, and amnesia of benzodiazepines. However, there is now evidence of differential reversal effects on the different agonist actions. Thus, flumazenil tends to reverse the hypnotic and respiratory effects more than the amnesic effects of the agonist benzodiazepine. [104] [112] [113] The dosage guidelines are given in Table 9-6 , but it must be emphasized that large-scale dosing studies have not yet been completed. The dose varies with the particular benzodiazepine being reversed, and the duration of reversal is dependent on the kinetics both of the agonist and of flumazenil. Surveillance is recommended if a long-lasting benzodiazepine is reversed with a single administration of flumazenil because of the relatively short-lived effect. Flumazenil may be administered by continuous infusion to prevent resedation with longer-lasting benzodiazepine receptor agonists. It is postulated that the availability of flumazenil will extend the usefulness of benzodiazepine agonists, although it will not necessarily alter the safety of this class of drugs.

Side Effects and Contraindications

Flumazenil has been given in large oral and intravenous doses with remarkably few toxic reactions. [32] It is free of local

TABLE 9-6 -- Uses and Doses of Flumazenil

Reversal of benzodiazepines [a]	0.1-0.2 mg repeated [b] up to 3.0 mg
Diagnosis in coma	0.5 mg repeated up to 1.0 mg

[a] The dose required to reverse each benzodiazepine (BZD) depends on residual BZD and the particular BZD (i.e., higher doses are required for more potent BZDs) (see text).
[b] The degree of reversal should be titrated by repeating 0.2-mg increment every 1-2 min until desired level of reversal is achieved.

or tissue irritant properties, and there are no known organotoxicities. Like all benzodiazepines, it appears to have a high safety margin, probably higher than those of agonists, because it does not produce prominent CNS depression. Unless it is found that benzodiazepine reversal in patients who have a long-term history of benzodiazepine use causes withdrawal reactions, including seizures, there is no current contraindication for the use of flumazenil. An important caution is that resedation could occur because of the relatively short half-life of the drug.

PHENCYCLIDINES (KETAMINE)

History

Phencyclidine was the first drug of its class to be used for anesthesia. It was synthesized by Maddox and introduced into clinical use in 1958 by Greifenstein et al [114] and in 1959 by Johnstone et al. [115] Although phencyclidine proved useful as an anesthetic, it produced unacceptably high adverse psychologic effects (hallucinations and delirium) in the postanesthetic recovery period. Cyclohexamine, a congener of phencyclidine, was tried clinically in 1959 by Lear and coworkers, [116] but it was found to be less efficacious than phencyclidine in terms of analgesia and yet to have as many adverse psychotomimetic effects. Neither of these drugs is used clinically today, although phencyclidine is available for illicit recreational use. Ketamine (Ketalar) was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino. [117] It was chosen from among 200 phencyclidine derivatives and proved to be the most promising in laboratory animal testing. Ketamine was released for clinical use in 1970 and is still used in a variety of clinical settings. Ketamine is different from most other anesthetic induction agents because it has significant analgesic effect. It usually does not depress the cardiovascular and respiratory systems, [118] [119] but it does possess some of the worrisome adverse psychologic effects found with the other phencyclidines.

Physicochemical Characteristics

Ketamine (Fig. 9-12) has a molecular weight of 238 kd, is partially water soluble, and forms a white crystalline salt with a negative log of the acid ionization constant (pK_a) of 7.5. [118] [119] It has a lipid solubility five to ten times that of thiopental. [120] Ketamine is prepared in a slightly acidic (pH 3.5-5.5) solution and comes in concentrations of 10-, 50-, and 100-mg ketamine base per milliliter of sodium chloride solution containing the preservative benzethonium chloride. The ketamine molecule contains a chiral center and therefore occurs as two resolvable optical isomers or enantiomers (11-12), the commercial preparation being a racemic mixture of both isomers [S-(+) and R-(-)] in equal amounts. [118]

Metabolism

Ketamine is metabolized by the hepatic microsomal enzymes responsible for most drug detoxification. The major pathway involves *N*-demethylation to form norketamine (metabolite I), which is then hydroxylated to hydroxynorketamine. These products are conjugated to water-soluble glucuronide derivatives and are excreted in the urine. [118] [119] [121] The activity of the principal metabolites of ketamine has not been well studied, but norketamine (metabolite I) has been shown to have significantly less (between 20 and 30%) activity than the parent compound. [122] [123] [124] Little is known about the activity of the other metabolites, but it is probable that ketamine is the major active drug.

Pharmacokinetics

The pharmacokinetics of ketamine have not been as well studied as those of many other intravenous anesthetics. Ketamine pharmacokinetics have been examined after bolus administration of anesthetizing doses (2 to 2.5 mg/kg), [125] following a subanesthetic dose (0.25 mg/kg) [125] [126] and after continuous infusion (steady-state plasma level
2,000 ng/ mL). [127] Regardless of the dose, ketamine plasma disappearance can be described by a two-compartment model. Table 9-3 contains the pharmacokinetic values from bolus administration studies. [125] Of note is the rapid distribution reflected in the relatively brief slow distribution half-life of 11 to 16 minutes (Fig. 9-13) . The high lipid solubility of ketamine is reflected in its relatively large volume of distribution, nearly 3 L/kg. Clearance is also relatively high, ranging from 890 to 1,227 mL/min, which accounts for the relatively short elimination half-life of 2 to 3 hours. The mean total

Figure 9-12 Stereoisomers of ketamine as it is formulated.

Figure 9-13 Simulated time course of plasma levels of ketamine following an induction dose of 2.0 mg/kg. Plasma levels required for hypnosis and amnesia during surgery are 0.7 to 2.2 mug/mL, with awakening usually occurring at levels lower than 0.5 mug/mL.

body clearance (1.4 L/min) is approximately equal to liver blood flow, which means that changes in liver blood flow affect clearance. Thus, the administration of a drug such as halothane, which reduces hepatic blood flow, reduces ketamine clearance. [128] [129]

Pharmacology

Effects on the Central Nervous System

Ketamine produces dose-related unconsciousness and analgesia (Chs. 35 and 52) . The anesthetized state has been termed *dissociative anesthesia* because patients who receive ketamine alone appear to be in a cataleptic state, unlike other states of anesthesia that resemble normal sleep. The ketamine-anesthetized patients have profound analgesia but keep their eyes open and maintain many reflexes. Corneal, cough, and swallow reflexes may all be present but should not be assumed to be protective. [130] There is no recall of surgery or anesthesia, but amnesia is not as prominent with ketamine as with the benzodiazepines. Because ketamine has a low molecular weight, a pK_a near the physiologic pH, and relatively high lipid solubility, it crosses the blood-brain barrier rapidly and therefore has an onset of action within 30 seconds of administration. The maximal effect occurs in about 1 minute. After ketamine administration, pupils dilate moderately and nystagmus occurs. Lacrimation and salivation are common, as is increased skeletal muscle tone, often with coordinated but seemingly purposeless movements of the arms, legs, trunk, and head. Although there is great interindividual variability, plasma levels of 0.6 to 2.0 mug/mL are considered the minimum concentrations for general anesthesia, [127] [128] but children may require slightly higher plasma levels (0.8-4.0 mug/mL). [131] The duration of ketamine anesthesia after a single administration of a general anesthetic dose (2 mg/kg IV) is 10 to 15 minutes [119] (see Fig. 9-13) , and full orientation to person, place, and time occurs within 15 to 30 minutes. [132]

The S enantiomer enables quicker recovery (by a couple of minutes) than the racemic mixture. [133] This is thought to be due to the lower dose necessary to produce

an equianesthetic effect and to the 10 percent faster hepatic biotransformation. [134]

The duration of ketamine anesthesia is determined by the dose; higher doses produce more prolonged anesthesia, [135] and the concurrent use of other anesthetics also prolongs the time of emergence. Because there is a reasonably good correlation between blood level of ketamine and CNS effect, it appears that ketamine's relatively short duration of action is due to its redistribution from the brain and blood to the other tissues in the body. Thus, the termination of effect after a single bolus administration of ketamine is caused by drug redistribution from the well-perfused to the less well-perfused tissues. Concomitant administration of benzodiazepines, a common practice, may prolong ketamine's effect. [136] When used in combination with a benzodiazepine, the S enantiomer was no different in terms of awareness at 30 minutes, but it was significantly better at 120 minutes than the racemic mixture. [137] Analgesia occurs at considerably lower blood levels than loss of consciousness. The plasma level at which pain thresholds are elevated is 0.1 g/mL or higher. [128] This means that there is a considerable period of postoperative analgesia after ketamine general anesthesia and that subanesthetic doses can be used to produce analgesia.

The primary site of CNS action of ketamine appears to be the thalamoneocortical projection system. [138] The drug selectively depresses neuronal function in parts of the cortex (especially association areas) and thalamus while simultaneously stimulating parts of the limbic system, including the hippocampus. This process creates what is termed a *functional disorganization* [119] of nonspecific pathways in midbrain and thalamic areas. [139] [140] There is also evidence that ketamine depresses transmission of impulses in the medial medullary reticular formation, which is important to transmission of the affective-emotional components of nociception from the spinal cord to higher brain centers. [141] Blockade of CNS sodium channels has been shown not to be the mechanism of action by which ketamine produces anesthesia. [142] There is some evidence that ketamine occupies opiate receptors in the brain and spinal cord, and this property could account for some of the analgesic effects. [118] [119] [143] [144] The S-(+) enantiomer has been shown to have some opioid mu-receptor activity, accounting for part of its analgesic effect. [145] *N*-Methyl- D-aspartate (NMDA) receptor interaction may mediate the general anesthetic effects as well as some analgesic actions of ketamine. [146] [147] [148] The spinal cord analgesic effect of ketamine is postulated to be due to inhibition of dorsal horn wide dynamic range neuronal activity. [149] Although some drugs have been used to antagonize ketamine, no specific receptor antagonist is yet known that reverses all the CNS effects of ketamine.

Ketamine increases cerebral metabolism, CBF, and intracranial pressure (ICP). Because of its excitatory CNS effects, which can be detected by generalized EEG development of theta-wave activity [135] as well as by petit mal seizure-like activity in the hippocampus, [150] ketamine increases $CMRO_2$. Whereas theta-wave activity signals the analgesic activity of ketamine, alpha waves indicate its absence. There is an increase in CBF, which appears higher

than the increase in $CMRO_2$ would mandate. With the increase in CBF as well as the generalized increase in sympathetic nervous system response, there is an increase in ICP after ketamine. [151] [152] The increase in $CMRO_2$ and CBF can be blocked by the use of thiopental [153] or diazepam. [152] [154] Cerebrovascular responsiveness to carbon dioxide appears to be preserved with ketamine; therefore, reducing Pa CO_2 attenuates the rise in ICP after ketamine [152] (Ch. 56) .

Ketamine, like other phencyclidines, produces undesirable psychologic reactions, which occur during awakening from ketamine anesthesia and are termed *emergence reactions.* The common manifestations of these reactions, which vary in severity and classification, are vivid dreaming, extracorporeal experiences (sense of floating out of body), and illusions (misinterpretation of a real, external sensory experience). [155] These incidents of dreaming and illusion are often associated with excitement, confusion, euphoria, and fear. [119] They occur in the first hour of emergence and usually abate within 1 to several hours. It has been postulated that the psychic emergence reactions occur secondary to ketamine-induced depression of auditory and visual relay nuclei, leading to misperception and/or misinterpretation of auditory and visual stimuli. [118] Their incidence ranges from as low as 3 to 5 percent [118] [119] to as high as 100 percent. [155] A clinically relevant range is probably 10 to 30 percent of adult patients who receive ketamine as a sole or major part of the anesthetic technique.

Factors that affect the incidence of emergence reactions are age, [156] dose, [119] gender, [157] psychologic susceptibility, [158] and concurrent drugs. Playing music during anesthesia does not attenuate the incidence of psychotomimetic reactions. [159] Pediatric patients do not report as high an incidence of unpleasant emergence reactions as do adult patients, nor do men as compared with women. Larger doses and rapid administration of large doses seem to predispose patients to a higher incidence of adverse effects. [160] [161] Finally, certain personality types seem prone to the development of emergence reactions. Patients who score high in psychotism on the Eysenck Personality Inventory are prone to develop emergence reactions, [158] and people who commonly dream at home are more likely to have postoperative dreams in the hospital after ketamine. [160] Numerous drugs have been used to reduce the incidence and severity of postoperative reactions to ketamine [118] [119] [162] ; the benzodiazepines seem to be the most effective group of drugs to attenuate or to treat ketamine emergence reactions. Mid-azolam, [118] lorazepam, [163] and diazepam [164] are useful in reducing reactions to ketamine. The mechanism is not known, but it is probable that both the sedative and amnesic actions of the benzodiazepines make them superior to other sedative-hypnotics. Midazolam has also been shown to reduce the psychotomimetic effect of the S enantiomer. [165]

Effects on the Respiratory System

Ketamine has minimal effects on the central respiratory drive as reflected by an unaltered response to carbon dioxide. [166] There can be a transient (1-3-min) decrease in minute ventilation after the bolus administration of an anesthetizing dose of ketamine (2 mg/kg IV). [135] [167] [168] Unusually high doses can produce apnea, [169] but this is seldom seen. Arterial blood gases are generally preserved when ketamine is used alone for anesthesia or analgesia. However, with the use of adjuvant sedatives or anesthetic drugs, respiratory depression can occur. Ketamine has been shown to affect ventilatory control in children and should be considered a possible respiratory depressant when the drug is given to them in bolus doses. [170] [171]

Ketamine is a bronchial smooth muscle relaxant. When it is given to patients with reactive airway disease and bronchospasm, pulmonary compliance is improved. [172] [173] Ketamine is as effective as halothane or enflurane in preventing experimentally induced bronchospasm. [174] The mechanism for this effect is probably a result of the sympathomimetic response to ketamine, but there are isolated bronchial smooth muscle studies showing that ketamine can directly antagonize the spasmogenic effects of carbachol and histamine. [175] Owing to its bronchodilating effect, ketamine has been used to treat status asthmaticus unresponsive to conventional therapy. [176]

A potential respiratory problem, especially in children, is the increased salivation that follows ketamine administration. This can produce upper airway obstruction, which can be further complicated by laryngospasm. The increased secretions may also contribute to or may further complicate laryngospasm. In addition, although swallow, cough, sneeze, and gag reflexes are relatively intact after ketamine, there is evidence that silent aspiration can occur during ketamine anesthesia. [130]

Effects on the Cardiovascular System

Ketamine also has unique cardiovascular effects; it stimulates the cardiovascular system and is usually associated with increases in blood pressure, heart rate, and cardiac output (see Table 9-4) . Other anesthetic induction drugs either cause no change in hemodynamic variables or produce vasodilation with cardiac depression. The S enantiomer, despite hope that reducing the dose by half (equi-anesthetic potency) would attenuate side effects, is equivalent to the racemic mixture regarding hemodynamic response. [165] The increase in hemodynamic variables is associated with increased work and myocardial oxygen consumption. The healthy heart is able to increase oxygen supply by increased cardiac output and decreased coronary vascular resistance, so that coronary blood flow is appropriate for the increased oxygen consumption. [177] The hemodynamic changes are not related to the dose of ketamine (e.g., there is no hemodynamic difference between administration of 0.5 and 1.5 mg/kg IV). [178] It is also interesting that a second dose of ketamine produces hemodynamic effects less than or even opposite to those of the first dose. [179] The hemodynamic changes after anesthesia induction with ketamine tend to be the same in healthy patients and in those with a variety of acquired or congenital heart diseases. [168] [178] [180] [181] [182] In patients with congenital heart disease, there are no significant changes in shunt directions or fraction [183] or systemic oxygenation after ketamine induction of anesthesia. [184] In patients who have elevated pulmonary artery pressure (as with mitral valvular and some congenital lesions), ketamine

seems to cause a more pronounced increase in pulmonary than systemic vascular resistance. [182] [183] [185] [186]

The mechanism by which ketamine stimulates the circulatory system remains enigmatic. It appears not to be a peripheral mechanism such as baroreflex inhibition, [187] [188] but rather to be central. [189] [190] [191] There is some evidence that ketamine attenuates baroreceptor function via an effect on NMDA receptors in the nucleus tractus solitarius. [192] Ketamine injected directly into the CNS produces an immediate sympathetic nervous system hemodynamic response. [193] Ketamine also causes the

sympathoneuronal release of norepinephrine, which can be detected in venous blood. [194] Blockade of this effect is possible with barbiturates, benzo-diazepines, and droperidol. [191] [193] [194] [195] Ketamine *in vitro* probably has negative inotropic effects. Myocardial depression has been demonstrated in isolated rabbit hearts, [196] intact dogs, [197] chronically instrumented dogs, [198] and isolated canine heart preparations. [199] However, in isolated guinea pig hearts, ketamine was the least depressant of all the major induction drugs. [200] The finding that ketamine may exert its myocardial effects by acting on myocardial ionic currents (which may exert different effects from species to species or among tissue types) may explain the tissue and animal model variances in direct myocardial action. [201]

The centrally mediated sympathetic responses to ketamine usually override the direct depressant effects of ketamine. There are some peripheral nervous system actions of ketamine that play an undetermined role in the hemodynamic effects of the drug. Ketamine inhibits intraneuronal uptake of catecholamines in a cocaine-like effect [202] [203] and inhibits extraneuronal norepinephrine uptake. [204] [205]

Stimulation of the cardiovascular system is not always desirable, and certain pharmacologic methods have been used to block the ketamine-induced tachycardia and systemic hypertension. Successful methods include use of adrenergic antagonists (both alpha and beta), as well as a variety of vasodilators [206] and clonidine. [207] However, probably the most fruitful approach has been prior administration of benzodiazepines. Modest doses of diazepam, flunitrazepam, and midazolam all attenuate the hemodynamic effects of ketamine. It is also possible to lessen the tachycardia and hypertension caused by ketamine by using a continuous infusion technique with or without a benzodiazepine. [208] Other general anesthetics, particularly the inhalation anesthetics, [209] blunt the hemodynamic effect of ketamine. Ketamine can produce hemodynamic depression in the setting of deep anesthesia, when sympathetic responses do not accompany its administration.

Uses

The many unique features of ketamine pharmacology, especially its propensity to produce unwanted emergence reactions, have placed ketamine outside the realm of routine clinical use. Nevertheless, ketamine has an important niche in the practice of anesthesiology when its unique sympathomimetic activity and bronchodilating capabilities are indicated during induction of anesthesia. It is used for premedication, sedation, induction and maintenance of general anesthesia.

Induction and Maintenance of Anesthesia

Poor-risk patients (ASA class IV) with respiratory and cardiovascular system disorders (excluding ischemic heart disease), represent the majority of candidates for ketamine induction; this is particularly true for patients with bronchospastic airway disease or patients with hemodynamic compromise based either on hypovolemia or cardiomyopathy (not coronary artery disease). Ketamine bronchodilation and profound analgesia allowing the use of high oxygen concentrations make ketamine an excellent choice for induction in patients with reactive airway disease. Otherwise healthy trauma victims whose blood loss is extensive are also candidates for rapid-sequence anesthesia induction with ketamine. [210] Patients with septic shock may also benefit from ketamine. [211] However, ketamine's intrinsic myocardial depressant effect may manifest in this situation if trauma or sepsis has caused depletion of catecholamine stores prior to the patient's arrival in the operating room. Use of ketamine in these patients does not obviate the need for appropriate preoperative preparation, including restoration of blood volume. Other cardiac diseases that can be well managed with ketamine anesthesia are cardiac tamponade and restrictive pericarditis. [212] The finding that ketamine preserves heart rate and right atrial pressure through its sympathetic stimulating effects makes ketamine an excellent anesthetic induction and maintenance drug in this setting. Ketamine is also often used in patients with congenital heart disease, especially those in whom the propensity for right-to-left shunting exists. Use of ketamine has also been reported in a patient susceptible to malignant hyperthermia who had a large anterior mediastinal mass, [213] when spontaneous ventilation was required and inhalation anesthetics were contraindicated. [213] [214] [215]

Ketamine combined with diazepam or midazolam can be given by continuous infusion to produce satisfactory cardiac anesthesia for patients with valvular and ischemic heart disease (Ch. 49) . The combination of a benzodiazepine [206] or of a benzodiazepine plus sufentanil [216] with ketamine attenuates or eliminates the unwanted tachycardia and hypertension as well as postoperative psychologic derangements. With this technique, there are minimal hemodynamic perturbations, profound analgesia, dependable amnesia, and an uneventful convalescence. No comparison of this technique with a continuous benzodiazepine-opioid technique has been made.

Low-dose ketamine as an analgesic has been used following thoracic surgery, [217] in which its lack of respiratory depressant properties and its equivalent pain relief as compared with meperidine make it a third choice when one wishes to avoid narcotics because of their respiratory depressant effects and when there is reason also to avoid non-steroidal agents such as ketorolac. Additional analgesic use can be considered in asthmatic patients. [218]

Sedation

Ketamine is particularly suited for sedation of the pediatric patient undergoing procedures away from the operating

room. Pediatric patients have fewer adverse emergence reactions [156] than adults, and this feature makes the use of ketamine in pediatrics more versatile. Ketamine is used for sedation and/or general anesthesia for the following pediatric procedures: cardiac catheterization, radiation therapy, radiologic studies, dressing changes, [219] and dental work. [136] Caution is advised in use of ketamine for cardiac catheterization in pediatric patients with elevated pulmonary vascular resistance, because this can be increased by ketamine. [220]

Ketamine is often used repeatedly in the same patient. Unfortunately, the literature does not provide information on how many times ketamine anesthesia can safely be administered to one individual, whether frequency of administration is related to tolerance following multiple administrations, and whether or not there are detrimental effects of frequent/long-term use.

Usually, a subanesthetic dose (
1.0 mg/kg IV) is used for dressing changes; this dose gives adequate operating conditions but a rapid return to normal function, including the resumption of eating, which is important in maintaining proper nutrition in burn patients. [118] [119] Often, ketamine is combined with premedication of a barbiturate or benzodiazepine and an antisialagogue (e.g., glycopyrrolate) to facilitate management. The premedications reduce the dose requirement for ketamine, and the antisialagogue reduces the sometimes troublesome salivation.

In adults and children, ketamine can be used as a supplement or an adjunct to regional anesthesia, extending the usefulness of the primary (local anesthetic) form of anesthesia. In this setting, ketamine can be used prior to the application of painful blocks, [221] but more commonly it is used for sedation or supplemental anesthesia during long or uncomfortable procedures. When used for supplementation of regional anesthesia, ketamine (0.5 mg/kg IV) combined with diazepam (0.15 mg/kg IV) is better accepted by patients and is not associated with greater side effects as compared with unsedated patients. [222] Ketamine in low doses can also be combined with nitrous oxide and propofol for the supplementation of conduction or local anesthesia. These techniques of ketamine administration are used in outpatient and inpatient settings, and although patients are comfortable and cooperative, dreams and other unpleasant emergence reactions can occur. [118] In outpatients, premedication with midazolam, concurrent propofol infusion, and intermittent ketamine (for analgesia) in doses less than 3 mg/kg are recommended. [223]

Doses and Routes of Administration

Ketamine can be administered intravenously, intramuscularly, orally, nasally, and rectally. [224] Most clinical use involves the intravenous and intramuscular routes, by which the drug rapidly achieves therapeutic levels. The dose depends on the desired therapeutic effect and on the route of administration. Table 9-7 contains general recommended doses for the intravenous and intramuscular administration of ketamine for various therapeutic goals. [118] Because of their side effects, most anesthetic drugs require that dosage be reduced in elderly and seriously ill patients; such a recommendation probably is prudent with ketamine, although data supporting this are not available. Patients who have been

TABLE 9-7 -- Uses and Doses of Ketamine

Induction of general anesthesia [a]	
0.5-2 mg/kg IV	

4-6 mg/kg IM		
Maintenance of general anesthesia		
0.5-1 mg/kg IV	prn	with N_2O 50% in O_2
15-45 mug/kg/min IV		with N_2O 50-70% in O_2
30-90 mug/kg/min IV		without N_2O
Sedation and analgesia		
0.2-0.8 mg/kg IV		over 2-3 min
2-4 mg/kg IM		

[a] Lower doses are used if adjuvant drugs such as midazolam or thiopental are also given.

critically ill for a prolonged period may have exhausted their catecholamine stores and may exhibit the circulatory depressant effects of ketamine. [225] Ketamine can be given epidurally and intrathecally for operative and postoperative pain control. The dose used in cancer pain is 1.0 mg (with benzethorium chloride as preservative and 0.05 mg morphine) twice daily, with additional morphine as required. [226] The peak action after intravenous administration occurs in 30 to 60 seconds. Onset occurs in about 5 minutes, with peak effect in about 20 minutes after intramuscular administration. An oral dose of 3 to 10 mg/kg generates a sedative effect in 20 to 45 minutes. The continuous infusion of intravenous ketamine with or without concomitant drugs is a satisfactory method to keep blood levels in the therapeutic range. The use of concomitant drugs such as benzodiazepines permits a lower dose requirement for ketamine while enhancing recovery by reducing emergence reactions. The interaction of ketamine with propofol is strictly additive and not synergistic; thus, the dose of each would be reduced by about half when used together for induction. [227]

For sedation, ketamine may be given intramuscularly if the patient wishes to avoid awareness of intravenous catheter placement. It has also been administered orally in doses of 3 to 10 mg/kg, with 6 mg/kg providing optimal conditions in 20 to 25 minutes in one study and 10 mg/kg providing sedation in 87 percent of children within 45 minutes in another study. [228] [229] In at least one case, deep sleep was produced by a supposedly sedative oral dose. [230]

Side Effects and Contraindications

The common psychologic emergence reactions are discussed earlier. Contraindications to ketamine relate to specific pharmacologic actions and patient diseases. Patients with increased ICP and with intracranial mass lesions should not receive ketamine because it can increase ICP and has been reported to cause apnea on this basis. [231] The S-(+) enantiomer also increases CBF and is probably similarly contraindicated. [232] Ketamine is also contraindicated in patients with an open eye injury or other ophthalmologic disorder, in whom a ketamine-induced increase in intraocular pressure would be detrimental (Ch. 63) . Because ketamine has a propensity to cause hypertension and tachycardia, with a commensurate increase in myocardial oxygen consumption, it is contraindicated as the sole anesthetic in patients with ischemic heart disease. [181] Likewise, it is unwise to give

ketamine to patients with vascular aneurysms because of the possible sudden change in arterial pressure. Psychiatric disease such as schizophrenia or a history of adverse reaction to ketamine or one of its congeners also constitutes a contraindication. [119] One should also consider carefully using ketamine when there is a possibility of postoperative delirium from other causes (e.g., delirium tremens, possibility of head trauma) and a ketamine-induced psychomimetic effect would cloud the differential diagnosis.

Other side effects include potentiation of nondepolarizing neuromuscular blockade by an undefined mechanism. [233] [234] Finally, because ketamine's preservative, chlorobutanol, has been demonstrated to be neurotoxic, subarachnoid administration is contraindicated. [235] It is probably unwise to administer the drug epidurally for this reason.

ETOMIDATE

History

Etomidate (Amidate, Hypnomidate) was synthesized [236] in 1964 and was introduced into clinical practice [237] in 1972. Its properties include hemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetics enabling rapid recovery following either a single dose or a continuous infusion. In animals, etomidate also provides a wider margin of safety (median effective dose/median lethal dose [ED_{50} /LD_{50}]) than thiopental (26.4 versus 4.6). [238] These beneficial properties led to widespread use of etomidate for induction, for maintenance of anesthesia, and for prolonged sedation in critically ill patients. Anesthesiologists' enthusiasm for etomidate, however, was tempered by reports that the drug can cause temporary inhibition of steroid synthesis after both single doses and infusions. [239] [240] [241] This effect, combined with other minor disadvantages (e.g., pain on injection, superficial thrombophlebitis, myoclonus, and a relatively high incidence of nausea and vomiting) led to several editorials [242] [243] [244] questioning the role of etomidate in modern anesthetic practice. Use of the drug waned significantly following those editorials, but it has been expanding over the past several years owing to a rediscovery of etomidate's beneficial physiologic profile combined with a lack of any new reports describing clinically significant adrenocortical suppression.

Physicochemical Characteristics

Etomidate is an imidazole derivative (R-(+)-pentylethyl-1H-imidazole-5 carboxylate sulfate). [238] Its chemical structure is illustrated in Figure 9-14 . Etomidate exists as two isomers, but only the (+) isomer is active as a hypnotic. [245] Its molecular weight is 342.36 kd. [245] Etomidate is water insoluble and is unstable in a neutral solution. It therefore has been formulated with several solvents. [246] Currently, it is supplied as a 2-mg/mL propylene glycol (35% by volume) solution with a pH of 6.9 and an osmolality of 4,640 mOsm/L. Unlike sodium thiopental, when etomidate is mixed with other commonly used anesthetic agents such as neuromuscular blockers, vasoactive drugs, or lidocaine, it does not cause precipitation. [247]

Figure 9-14 The structure of etomidate, an imidazole derivative.

Metabolism, Induction, and Maintenance of Anesthesia

Etomidate is metabolized in the liver primarily by ester hydrolysis to the corresponding carboxylic acid of etomidate (major metabolite) or by *N*-dealkylation. [245] The main metabolite is inactive. [247] Only 2 percent of the drug is excreted unchanged, the rest being excreted as metabolites by the kidney (85%) and bile (13%). [247]

Etomidate has been used for both induction and maintenance of anesthesia (Table 9-8) . The induction dose of etomidate varies from 0.2 to 0.6 mg/kg, [237] [246] [248] [249] and it is reduced by premedication with an opiate, a benzodiazepine, or a barbiturate. [237] Onset of anesthesia following a routine induction dose of 0.3 mg/kg etomidate is rapid (one arm-brain circulation) and is equivalent to that obtained with an induction dose of thiopental or methohexital. [237] [246] [250] The duration of anesthesia following a single induction dose is linearly related to the dose--each 0.1 mg/kg administered provides about 100 seconds of sleep. [251] Repeat doses of etomidate, either by bolus or infusion, prolong the duration of hypnosis. Recovery following etomidate is still usually rapid. [237] [248] [252] [253] [254] [255] [256] The addition of small doses of fentanyl with etomidate for short surgical procedures reduces the required dose of etomidate and allows earlier awakening. In children, induction by rectal administration of etomidate has been obtained with 6.5 mg/kg. Hypnosis occurs in 4 minutes. At this dose, hemodynamics are unaltered, and recovery is still rapid. [257]

Various infusion schemes have been devised to utilize etomidate as a maintenance agent for the hypnotic component of anesthesia. Most regimens aim to achieve a plasma level of 300 to 500 ng/mL, which is the concentration necessary for hypnosis. [258] [259] [260] [261] Both two- and three-stage infusions have been successfully used. These consist of an initial rapid infusion of 100 mug/kg/min for 10 minutes followed by 10 mug/kg/min thereafter, [261] or of 100 mug/kg/min for 3 minutes, 20 mug/kg/min for 27 minutes, and 10 mug/kg/min thereafter. [258]

TABLE 9-8 -- Uses and Doses of Etomidate

Induction of general anesthesia	0.2-0.6 mg/kg IV
Maintenance of general anesthesia	10 mug/kg/min IV with N_2 o and an opiate
Sedation and analgesia	5-8 mug/kg/min IV only for short periods of sedation because of inhibition of corticosteroid synthesis

Loss of consciousness with these techniques occurs after 100 to 120 seconds. [258] The infusion is usually terminated 10 minutes prior to desired awakening. [258]

Pharmacokinetics

The pharmacokinetics of etomidate has been calculated following single bolus doses and following continuous infusion [258] [259] [262] [263] [264] (see Table 9-3) . The time course of plasma disappearance after a 0.3-mg/kg bolus is shown in Figure 9-15 . The kinetics of etomidate are best described by an open three-compartment model. [262] [263] [264] The drug has an initial distribution half-life of 2.7 minutes, a redistribution half-life of 29 minutes, [262] [264] and an elimination half-life that varies from 2.9 to 5.3 hours. [258] [259] [262] [263] [264] Clearance of etomidate by the liver is high (18-25 mL/kg/min), with a hepatic extraction ratio of 0.5:0.9. [246] [258] [262] [263] [264] Thus, drugs affecting hepatic blood flow alter its elimination half-life. Because redistribution is the mechanism whereby the effect of a bolus of etomidate is dissipated, hepatic dysfunction should not appreciably alter recovery from its hypnotic effect. The volume of distribution at steady state is 2.5 to 4.5 L/kg. [258] [259] [262] [263] [264] Etomidate is 75 percent protein bound. [265] Pathologic conditions altering serum proteins (e.g., hepatic or renal disease) vary the amount of the free (unbound) fraction and may cause a given dose to have an exaggerated pharmacodynamic effect. [265]

In patients with cirrhosis, the volume of distribution is doubled, whereas clearance is normal; the result is an elimination half-life that is twice normal. [266] It is likely that the initial distribution half-life and clinical effect are unchanged. Increasing age is associated with a smaller initial volume of distribution and a decreased clearance of etomidate. [267] The relatively short elimination half-life and the rapid clearance of etomidate make it suitable for administration in a single dose, in multiple doses, or in a continuous infusion.

Pharmacology

Effects on the Central Nervous System

The primary action of etomidate on the CNS is hypnosis (Ch. 52) , which is achieved in one arm-brain circulation following a normal induction dose (0.3 mg/kg). [246] [268] Etomidate has no analgesic activity. Plasma levels required during the maintenance of anesthesia are approximately 300 to 500 ng/mL, those for sedation are 150 to 300 ng/mL, and those for awakening are 150 to 250 ng/mL [258] [260] [261] [268] (see Fig. 9-15) . The mechanism by which etomidate produces hypnosis is not fully elucidated; however, it may be in part related to the GABA-adrenergic system, because its action may be antagonized by GABA antagonists. [269]

At a dose of 0.2 to 0.3 mg/kg, etomidate reduces CBF (by 34%) and $CMRO_2$ (by 45%) without altering mean arterial pressure. [270] Thus, cerebral perfusion pressure is maintained or increased, and there is a beneficial net increase in the cerebral oxygen supply/demand ratio. [270] Etomidate given in

Figure 9-15 Simulated time course of plasma levels of etomidate following an induction dose of 0.3 mg/kg. Plasma levels required for hypnosis during surgery are 300 to 500 ng/mL, with awakening usually occurring at levels lower than 225 ng/mL.

doses sufficient to produce EEG burst suppression acutely lowers ICP by up to 50 percent in patients with already raised ICP, returning raised ICP to almost normal values. [271] [272] The decrease in ICP is maintained in the period immediately following intubation [272] (Ch. 52) . To maintain the effects of etomidate on ICP, high infusion rates (60 mug/kg/min) are necessary. [273] In contrast to the situation with other neuroprotective agents such as thiopental, reduction of ICP and maintenance of burst suppression are not associated with a drop in mean arterial blood pressure. [272] Because cerebral vascular reactivity is still maintained following etomidate administration, [273] hyperventilation theoretically may further reduce ICP when used in conjunction with etomidate. In animals, etomidate has reduced brain disease following acute cortical ischemic insult. [274] In 1993, Takanobu et al [275] reported the neuroprotective qualities of etomidate to be equal to those of thiopental and superior to those of isoflurane in a rat model. Other investigators disagree on etomidate's neuroprotective qualities. [276] Deeper structures such as the brain stem may not be afforded ischemic protection by etomidate. [277]

A dose of 0.3 mg/kg rapidly reduces intraocular pressure by 30 to 60 percent. [278] The decrease in intraocular pressure following a single dose lasts 5 minutes, but the reduction may be maintained by an infusion of 20 mug/kg/min. [278] (Ch. 63) .

Etomidate produces changes in the EEG similar to those produced by the barbiturates. [279] There is an initial increase in alpha amplitude with sharp beta bursts followed by mixed delta-theta waves, with delta-wave activity predominating prior to the onset of periodic burst suppression. [279] The absence of beta waves in the initial phase of induction with etomidate is the major difference in EEG changes as compared with thiopental. [279] Etomidate has been associated with grand mal seizures [280] [281] and has been shown to produce increased EEG activity in epileptogenic foci. This feature has proved useful for intraoperative mapping of seizure foci prior to surgical ablation. [281] [282] Etomidate is also associated with a high incidence of myoclonic movement. [248] [253] Myoclonus is not thought to be associated with seizure-like EEG activity. [279] Giving etomidate to unpremedicated patients

caused an increase in EEG activity in 22 percent of patients versus 17 percent of those receiving thiopental. [283] The myoclonic movement is believed to result from activity either in the brain stem or in deep cerebral structures. [237]

The effect of etomidate on auditory evoked potentials is similar to that produced by the inhaled anesthetics, with a dose-dependent increase in latency and a decreasing amplitude of the early cortical components (Pa and Nb). [284] Amplitude and latency of upper limb cortical somatosensory evoked potentials are positively affected following 0.4 mg/kg etomidate, which could theoretically obscure neurologic injury during positioning immediately following induction of anesthesia. [285] Brain-stem evoked responses are unaltered following etomidate administration. [284] Because amplitude depression is less, etomidate may be superior to propofol as an induction agent when monitoring of motor evoked responses to transcranial stimulation monitoring is indicated. [286]

Effects on the Respiratory System

Etomidate has minimal effect on ventilation. It does not induce histamine release either in healthy patients or in patients with reactive airway disease. [287] Ventilatory response to carbon dioxide is depressed by etomidate, but the ventilatory drive at any given carbon dioxide tension is greater than that following an equipotent dose of methohexital. [288] Similarly, the response to occlusion pressure is less depressed following etomidate than following an equivalent dose of methohexital. [289] Induction with etomidate produces a brief period of hyperventilation, [290] [291] sometimes followed by a similarly brief period of apnea, [291] which results in a slight (±15%) increase in Pa CO_2 but no change in the partial pressure of arterial oxygen (Pa O_2). [290] [292] The incidence of apnea is altered by premedication. [254] [293] Hiccups or coughing may accompany etomidate induction, with an incidence similar to that following methohexital induction. [246]

Effects on the Cardiovascular System

The minimal effect of etomidate on cardiovascular function sets it apart from other fast-acting induction agents [290] [292] [293] [294] [295] [296] (see Table 9-4) . An induction dose of 0.3 mg/kg of etomidate given to cardiac patients for noncardiac surgery results in almost no change in heart rate, mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, stroke volume, cardiac index, and pulmonary and systemic vascular resistance. [292] A relatively large dose of etomidate, 0.45 mg/kg (which is 50% larger than a normal induction dose), [293] also produces minimal changes in cardiovascular parameters. In patients with ischemic heart disease or valvular disease, [292] [295] etomidate (0.3 mg/kg) produces similar minimal alterations in cardiovascular parameters. In patients with mitral or aortic valve disease, etomidate may produce greater changes in mean arterial pressure (an approximate 20% decrease) [290] [297] than in patients without cardiac valvular disease. Following induction (18 mg) and infusion (2.4 mg/min), etomidate produces a 50 percent decrease in myocardial blood flow and oxygen consumption and a 20 to 30 percent increase in coronary sinus blood oxygen saturation. [298] The myocardial oxygen supply/demand ratio is thus well maintained. [296] [298] There is minimal effect on the QT interval. [299]

The hemodynamic stability seen with etomidate may be due in part to its unique lack of effect both on the sympathetic nervous system and on baroreceptor function. [300] However, etomidate, lacking analgesic efficacy, may not totally ablate the sympathetic response to laryngoscopy and intubation. [250] [253] For the smoothest hemodynamic induction/intubation sequence, a low dose (1.5-5.0 mug/kg) of fentanyl is often combined with etomidate. [297] [301]

Endocrine Effects

The concern surrounding the endocrine effects of etomidate stems from a letter by Ledingham et al [302] in 1983 concerning ICU patients receiving long-term sedative infusions of etomidate while being mechanically ventilated for 5 days or longer. These investigators noted that in this subset of mechanically ventilated multiple trauma patients, the mortality rate was higher for 1981 to 1982 than among similar patients treated during 1979 to 1980. The earlier group had received primarily morphine and benzodiazepines for sedation, whereas patients in 1981 to 1982 had received primarily etomidate for sedation. It was postulated that adrenocortical suppression secondary to long-term etomidate infusion was the cause of the increased mortality. [239] Another ICU with similar patients receiving etomidate did not note an increased mortality; these patients received high-dose steroids as part of the trauma protocol. [302] This finding helped to confirm that hypothesis.

The specific endocrine effects manifested by etomidate are a dose-dependent reversible inhibition of the enzyme 11-beta-hydroxylase, which converts 11-deoxycortisol to cortisol, and a relatively minor effect on 17-alpha-hydroxylase [303] [304] (Fig. 9-16) . This results in an increase in the cortisol precursors 11-deoxycortisol and 17-hydroxyprogesterone as well as

Figure 9-16 Pathway for the biosynthesis of cortisol and aldosterone. The sites at which etomidate affects cortisol-aldosterone synthesis by its action on 11-beta-hydroxylase (major site) and

17-alpha-hydroxylase (minor site) are illustrated.

an increase in adrenocorticotropic hormone (ACTH). The blockade of 11-beta-hydroxylase and, to a lesser extent, 17-alpha-hydroxylase [303] appears to be related to the free imidazole radical of etomidate-binding cytochrome P-450. [304] [305] [306] This results in inhibition of ascorbic acid resynthesis, which is required for steroid production in humans. [305] [306] The blockade of the cytochrome P-450-dependent enzyme 11-beta-hydroxylase also results in decreased mineralocorticoid production and an increase in intermediaries (11- deoxycorticosterone). [240] [241] [243] Vitamin C supplementation restores cortisol levels to normal following the use of etomidate. [306] Because minor adrenocortical suppressive effects were shown to follow even single bolus doses, [240] [303] [307] concerns about the use of etomidate for anesthetic induction arose. [242] No large prospective studies have been done, but several smaller studies have provided some insight into the exact nature of adrenocortical suppression following an induction dose.

Duthie et al [308] demonstrated that in otherwise healthy patients undergoing minor peripheral surgery, plasma cortisol levels were slightly depressed from the preinduction levels for up to 1 hour postoperatively. The nadir of mean cortisol levels did not fall out of the normal range. 11- Deoxycorticosterone, substrate for the etomidate-inhibited 11-beta-hydroxylase, peaked at very high levels when compared with the thiopental control group. [308] In another study, patients undergoing orthopedic surgery were given an etomidate induction followed by an infusion of etomidate (average total dose 68 mg). Temporary adrenocortical suppression, as measured by a reduced response to ACTH stimulation, was documented for 6 hours postoperatively and returned to normal by 20 hours postoperatively. Postoperative cortisol levels in the etomidate study patients were not significantly different from those in a group who received a midazolam induction. As in the study of Duthie et al [308] mean cortisol levels in the etomidate group remained in the normal range at all times postoperatively. [309] Other studies have shown similar results when evaluating etomidate induction doses; none reported adverse outcomes secondary to short-term adrenocortical suppression. [240] [241] [303] [307] [308] [309] [310]

However, in each of the prospective etomidate studies documenting adrenocortical suppression without associated clinical sequelae, a conclusion of safety was not forthcoming. The reason was that these studies did not address high-stress procedures, in which the benefit of a high cortisol level in response to a major stress could be desirable and etomidate's blockade of the response to ACTH could be detrimental. As part of a quality assurance program, we addressed this issue with a small, retrospective analysis of etomidate induction for high-stress procedures (vascular, thoracic, major intra-abdominal, and major retroperitoneal surgery) in 1993. [249] Indices of adrenocortical function and perioperative outcome in patients who received induction doses of etomidate were compared with those in a control group who received thiopental. The incidence of perioperative wound infection, sepsis, miscellaneous infection, myocardial infarction, and hypotension and the need for perioperative vasopressor/inotropic support were evaluated, along with postoperative serum sodium levels. No difference was found between patients receiving etomidate and those receiving other induction agents for these high-stress procedures. In 1994, the cortisol levels during and after coronary artery bypass surgery were compared in patients receiving total intravenous anesthesia with etomidate/fentanyl (mean etomidate dose of 87 ± 3 mg) versus midazolam/fentanyl. Except for the first hour after induction, cortisol levels were the same or higher in the etomidate group compared with the midazolam group, a finding implying that the body's ability to respond to a high surgical stress was still intact despite relatively high doses of etomidate. This study is further proof that etomidate is probably safe for use in major surgery. [311]

In summary, three facts suggest that the issue of temporary adrenocortical suppression following induction doses of etomidate is not clinically significant: (1) there are no known reports of any negative clinical outcome associated with an etomidate induction despite millions of uses; (2) following etomidate induction, the nadir of cortisol levels usually remains in the low normal range and the adrenocortical suppression is a relatively short-lived phenomenon; and (3) high-stress surgery can overcome the temporary adrenocortical suppression caused by etomidate.

Other Effects

Although etomidate provides stable hemodynamics and minimal respiratory depression, it is associated with several adverse effects when it is used for induction. These are nausea and vomiting, pain on injection, myoclonic movement, and hiccups. [237] [246] [248] [252] [253] [254] [255] Etomidate has been associated with a high (30 to 40 percent) incidence of nausea and vomiting. [248] [253] [254] [255] [256] This compares with a reported incidence of 10 to 20 percent with methohexital [246] [254] or thiopental, [253] [312] but some studies have shown no difference. [249] [253] Addition of fentanyl to etomidate further increases the incidence of nausea and vomiting. [248] [253] Nausea and vomiting constitute the most common reasons for patients to rate anesthesia with etomidate unsatisfactory. [255] It seems prudent to avoid etomidate in patients predisposed to nausea and vomiting.

Superficial thrombophlebitis of the vein used may occur 48 to 72 hours after etomidate injection. [313] The incidence may be as high as 20 percent when etomidate is given alone through a small (21-gauge) intravenous needle. Intra-arterial injection of etomidate is not associated with local or vascular disease. [237] Pain on injection, similar in incidence to that with propofol, [314] can be essentially eliminated by injecting lidocaine immediately before injection of etomidate; as little as 20 to 40 mg may be enough. [315] Pain on injection is further reduced by using a large vein. [237] [252] Less successful but somewhat efficacious is premedication with benzodiazepine plus a narcotic. [253] [256] The incidence of pain on injection varies from 0 to 50 percent. The incidence of muscle movement (myoclonus) and of hiccups is also highly variable (0-70%), but myoclonus is reduced by premedication with either a narcotic or benzodiazepine. [256] Both fast and slow injection techniques have also been advocated for reducing myoclonus. [252] [256]

Etomidate enhances the neuromuscular blockade of nondepolarizing neuromuscular blockers. [316] [317] Hepatic function is unaltered by etomidate. [246] [262] *In vitro,* etomidate inhibits aminolivulinic acid synthetase, but it has been administered to patients with porphyria without inducing an acute attack of porphyria. [312]

The carrier for etomidate, propylene glycol, has also been reported to have some negative effects. Some reports suggest that propylene glycol can be associated with a small degree of hemolysis. [318] Additionally, high-dose prolonged infusion has been reported to result in propylene glycol toxicity (a hyperosmolar state). [319]

Uses

The use of etomidate is most appropriate in patients with cardiovascular disease, reactive airway disease, intracranial hypertension, or any combination of disorders indicating the need for an induction agent with limited or beneficial physiologic side effects. The hemodynamic stability of etomidate is unique among the rapid-acting induction agents.

Etomidate has been primarily used in sick patients. In multiple studies, etomidate has been used for induction in patients with a compromised cardiovascular system who are undergoing coronary artery bypass surgery or valve surgery, in patients requiring induction of general anesthesia for percutaneous transluminal coronary angioplasty, and in other similar situations. [297] [301] [320] In cardiovascular surgery, particularly surgery for aortic aneurysms, etomidate is an excellent anesthetic induction agent. When etomidate is used in combination with fentanyl, titrating etomidate up to 0.6 mg/kg maintains blood pressure and heart rate in a narrow range, preserving coronary perfusion pressure in these patients with probable coronary artery disease while blunting the response to intubation and avoiding unnecessary stress on the aneurysm. For cardiothoracic procedures, especially cardiac and lung transplantation, the required rapid-sequence induction and hemodynamic stability make etomidate the induction agent of choice. For patients with concomitant coronary artery disease and reactive airway disease, etomidate induction does not release histamine, and a relatively large dose (0.6 mg/kg) may be titrated to provide a deep level of anesthesia for intubation without compromising hemodynamics and coronary perfusion pressure. For cardioversion, the rapid onset, quick recovery, and maintenance of blood pressure in these sometimes hemodynamically tenuous patients, combined with continued spontaneous respiration, make etomidate an acceptable choice, [314] although there is one report of myoclonus interfering with electrocardiographic evaluation. [321] Although definitive proof of etomidate's neuroprotective effect in humans is lacking, the combination of animal data and anecdotal reports of successful use of etomidate in neurosurgical procedures such as giant aneurysm clippings makes etomidate a reasonable choice during neurosurgical induction. [261] [272] [274] [322] In addition, etomidate should be considered as an agent to reduce raised ICP when maintenance of cerebral or coronary perfusion pressure is also important. Trauma patients with questionable volume status may be well served by an etomidate induction. Although the indirect sympathomimetic effect seen with ketamine induction is absent, there is no direct myocardial depression and no confusion in the differential diagnosis of postoperative delirium. This is especially important in patients whose trauma may be related to drug and/or alcohol use.

During an infusion, hemodynamic status is well maintained, and adequate spontaneous ventilation is pres-ent. [88] [323] The incidence of pain on injection and of myoclonus and thrombophlebitis tends to be less with an infusion technique. [258] [260] [323] A concentrated form of etomidate used for continuous infusion in Europe is not

available in the United States.

Short-term sedation with etomidate is useful in hemodynamically unstable patients, such as those requiring cardioversion [314] or those requiring sedation following an acute myocardial infarction or with unstable angina for a minor operative procedure [301] or for intubation both in the emergency room and in the ICU. In addition, etomidate has been used to produce short-term sedation for placement of retrobulbar block and for electroconvulsive therapy instrumentation, during which maintenance of spontaneous respirations and quick recovery are important features. When used during electroconvulsive therapy, etomidate can produce longer seizures compared with other hypnotics. [324]

Prolonged sedation for patients in the ICU, although initially popular following the release of etomidate, is now contraindicated owing to inhibition of corticosteroid and mineralocorticoid production, with subsequent increase in morbidity. [239] [242] [302]

/das/book/view/29494766/875/101.html

PROPOFOL

History

Propofol (Diprivan) is the most recent intravenous anesthetic to be introduced into clinical practice. Work in the early 1970s on substituted derivatives of phenol with hypnotic properties resulted in the development of 2,6-di-isopropofol. [325] The first clinical trial, by Kay and Rolly [326] and reported in 1977, confirmed the potential of propofol as an anesthetic induction agent. Propofol is insoluble in water and therefore was initially prepared with Cremophor EL (BASF A.G.). Because of anaphylactoid reactions associated with Cremophor EL in this early formulation of propofol, [327] the drug was reformulated in an emulsion. Propofol has been used for induction and maintenance of anesthesia as well as for sedation.

Physicochemical Characteristics

Propofol (Fig. 9-17) is one of a group of alkylphenols that have hypnotic properties in animals. [328] The alkylphenols are oils at room temperature and are insoluble in aqueous solution, but they are highly lipid soluble. The present formulation consists of 1 percent (wt/vol) propofol, 10 percent soybean

Figure 9-17 The structure of propofol, an alkylphenol derivative.

oil, 2.25 percent glycerol, and 1.2 percent purified egg phosphatide. In the United States, disodium edetate (0.005%) was added as a retardant of bacterial growth. Propofol has a pH of 7 and appears as a slightly viscous, milky white substance. Propofol is available as a 1 percent solution in 20-mL clear glass ampules, 50- and 100-mL vials, and in 50-ml prefilled syringes. It is stable at room temperature and is not light sensitive. If a dilute solution of propofol is required, it is compatible with 5 percent dextrose in water.

Metabolism

Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulfate [329] to produce water-soluble compounds, which are excreted by the kidneys. [329] Less than 1 percent propofol is excreted unchanged in urine, and only 2 percent is excreted in feces. [329] The metabolites of propofol are thought not to be active. Because clearance of propofol exceeds hepatic blood flow, extrahepatic metabolism or extrarenal elimination has been suggested. Extrahepatic metabolism has been confirmed during the anhepatic phase of patients receiving a transplanted liver. [330] [331] The lungs do not seem to be the site of this extrahepatic metabolism; however, in *in vitro* studies with human kidney and small intestine, microsomes in these tissues demonstrated an ability to form propofol glucuronide. [332] Propofol itself results in a concentration-dependent inhibition of cytochrome P-450 and thus may alter the metabolism of drugs dependent on this enzyme system. [333]

Pharmacokinetics

The pharmacokinetics of propofol following a wide range of doses as well as following continuous infusions has been evaluated by numerous investigators, [329] [334] [335] [336] [337] [338] [339] and it has been described by both two- and three-compartment models (see Table 9-3) . Following a single bolus injection, whole blood propofol levels decrease rapidly as a result of both redistribution and elimination (Fig. 9-18) . The initial distribution

Figure 9-18 Simulated time course of whole blood levels of propofol following an induction dose of 2.0 mg/kg. Blood levels required for anesthesia during surgery are 2 to 5 mug/mL, with awakening usually occurring at a blood level lower than 1.5 mug/mL.

half-life of propofol is 2 to 8 minutes. [329] [335] In studies using a two-compartment model, the elimination half-life has varied from 1.0 to 3 hours. [329] [334] [336] [339] Studies in which the disposition of propofol was better described by a three-compartment model have given initial and slow distribution half-lives of 1 to 8 minutes and 30 to 70 minutes and an elimination half-life of 4 to 23.5 hours. [335] [336] [337] [339] [340] This longer elimination half-life is indicative of a deep compartment with limited perfusion, which results in a slow return of propofol back to the central compartment. Owing to the rapid clearance of propofol from the central compartment, the slow return of propofol from this deep compartment contributes little to the initial rapid decrease in propofol concentrations. The context-sensitive half-time for propofol (see Fig. 9-5) for infusions of up to 8 hours is less than 40 minutes. [341] Because the required decrease in concentration for awakening following anesthesia or sedation with propofol is generally less than 50 percent, recovery from propofol remains rapid even following prolonged infusions. The volume of distribution of the central compartment has been calculated as 20 to 40 L, and the volume of distribution at steady state has been calculated as 150 to 700 L. [329] [334] [335] [336] [337] [338] [339] The clearance of propofol is extremely high--1.5 to 2.2 L/min. [329] [334] [335] [336] [337] [338] [339] This exceeds hepatic blood flow, and extrahepatic metabolism has been demonstrated. [330] [331] The equilibrium constant for EEG effect for propofol is 0.291 min^{-1} , and the half-life of equilibrium between plasma concentration and EEG effect is 2.4 minutes based on suppression of the EEG. The time to peak effect is 92 seconds. [342]

The pharmacokinetics of propofol may be altered by a variety of factors (e.g., gender, weight, preexisting disease, age, and concomitant medication). [335] [336] [339] [343] [344] Propofol may impair its own clearance by decreasing hepatic blood flow. [345] Probably of greater clinical significance is that propofol may alter its own intercompartmental clearances because of its effects on cardiac output. Women have a higher volume of distribution and higher clearance rates, but the elimination half-life is similar for males and females. [335] [339] The elderly have decreased clearance rates but a smaller central compartment volume. [336] [339] In addition, patients presenting for coronary artery bypass surgery seem to have different pharmacokinetic parameters compared with other adult populations. When a patient is placed on a cardiopulmonary bypass machine, there is an increase in the central volume and initial clearance, thus necessitating higher initial infusion rates to maintain the same propofol plasma concentration. [346] Children have a larger central compartment volume (50%) and a more rapid clearance (25%). [347] In children older than 3 years, volumes and clearances should be weight adjusted [348] (Ch. 59) . Children less than 3 years of age also demonstrate weight-proportional pharmacokinetic parameters but with greater central compartment and systemic clearance values than in adults or older children [348] . This finding explains the higher dosing requirements in this age group. [349] Hepatic disease appears to result in a larger steady-state and central compartment volumes; clearance is unchanged, but the elimination half-life is slightly prolonged. [343] The effect of fentanyl administration on propofol pharmacokinetic parameters is controversial. Some studies suggest that fentanyl may reduce intercompartmental and total body clearance rates as well as volumes of distribution. [350] When propofol was administered with alfentanil at similar infusion rates, the measured propofol concentrations were 22 percent greater than

when propofol was administered alone. [351] A separate study found that fentanyl did not alter propofol pharmacokinetics following a single dose of both drugs. [352] Some of these differences in propofol pharmacokinetics when given with an opioid may be explained by studies in cats that showed that pulmonary uptake of propofol is reduced by 30 percent when propofol is administered immediately following fentanyl but not if it is administered 3 minutes later. [353] In addition, *in vitro* studies on human hepatocytes demonstrated that propofol inhibited in a dose-dependent manner the enzymatic degradation of both sufentanil and alfentanil. [354] Propofol kinetics are unaltered by renal disease. [344]

Pharmacology

Effects on the Central Nervous System

Propofol is primarily a hypnotic. The exact mechanism of its action has not yet been fully elucidated; however, evidence suggests that it acts by promoting the function of the beta$_1$ subunit of GABA through activation of the chloride channel and thereby enhancing inhibitory synaptic transmission. [355] [356] [357] Propofol also inhibits the NMDA subtype of glutamate receptor through modulation of channel gating. [358] [359] This action may also contribute to the drug's CNS effects. The hypnotic action of propofol is pressure reversible, and it adheres to the correlation exhibited by other general anesthetics between anesthetic potency and octanol/water distribution coefficient. [360] Unlike barbiturates, propofol is not antianalgesic. [361] Propofol at subhypnotic doses helps in the diagnosis and treatment of central, but not neuropathic, pain. [357]

The onset of hypnosis following doses of 2.5 mg/kg is rapid (one arm-brain circulation), with a peak effect seen at 90 to 100 seconds. [362] [363] The ED_{50} of propofol is 1 to 1.5 mg/kg following a bolus. [362] [364] [365] [366] The duration of hypnosis is dose-dependent, being 5 to 10 minutes following 2 to 2.5 mg/kg. [362] [367] Age markedly affects the 95 percent effective dose (ED_{95}) induction dose of propofol, being highest at ages less than 2 years (ED_{95} 2.88 mg/kg) and decreasing with increasing age. [368] At subhypnotic doses, propofol provides sedation and amnesia. [369] [370] [371] Propofol infusions of at least 2 mg/kg/h were necessary to provide amnesia in unstimulated volunteers. [372] Awareness during surgery at higher infusion rates has been reported. [373] During surgical procedures, extremely high infusion rates may be necessary to prevent awareness if propofol is used as the sole anesthetic. [374] Propofol alters mood following short surgical procedures to a lesser extent than thiopental. [375] Propofol also tends to produce a general state of well-being. [375] Hallucinations, [376] sexual fantasies, and opisthotonos [377] have been reported following propofol administration.

The effect of propofol on the EEG as assessed after 2.5 mg/kg followed by an infusion demonstrates an initial increase in alpha rhythm followed by a shift to gamma and theta frequency. High infusion rates produce burst suppression. [378] EEG power analysis indicates that amplitude increases after induction but is thereafter unaltered at propofol blood concentrations of 3 to 8 mug/mL. [379] At propofol concentrations greater than 8 mug/mL, amplitude markedly decreases, with periods of burst suppression. [379] There is a strong correlation between the logarithm of blood concentration of propofol and the percentage of activity content, and there is an inverse correlation with percentage of activity content. [379] The bispectral (BIS) index is a new derivative of the EEG. Propofol causes a concentration-dependent decrease in the BIS index, with 50 and 95 percent of patients unable to respond to a verbal command at a BIS value of 63 and 51, respectively (Fig. 9-19) . The propofol concentration at which 50 percent of volunteers failed to respond to verbal command was 2.35 mug/mL. Lack of recall was observed in

Figure 9-19 The relationship between the bispectral (BIS) index and probability of consciousness (i.e., response to verbal command) using the logistic regression analysis for volunteers receiving propofol, isoflurane, or midazolam. The probability of response was no different among the three different anesthetics used. It can also be noted that 95 percent of the volunteers were unconscious with a BIS index of 50 or less.

95 percent of patients at a BIS value of 77. [380] Propofol produces a decrease in amplitude of the early components of somatosensory evoked potentials, [381] as well as a small nonsignificant increase in latency of the P_{40} and N_{50} components. [381] Like other intravenous anesthetics, propofol does not alter brain-stem auditory evoked potentials. [382] There are, however, a dose-dependent prolongation of latency and a decrease in amplitude of cortical middle latency auditory potentials, which are concentration-dependent. [382] Auditory evoked potentials show an abrupt change in the auditory evoked potential index between awake and nonresponsive patients. This finding differs from the BIS index, which tends to show a trend of decreasing BIS values and increasing sedation and loss of consciousness with propofol administration. [383]

The effect of propofol on epileptogenic EEG activity is controversial. Initial studies in mice indicated that propofol neither induced convulsions nor provided anticonvulsant activity. [384] Several more recent reports have shown in a variety of models a direct anticonvulsant effect of propofol, which is dose-dependent. [385] [386] In a few reports, propofol has been used to treat epileptic seizures. [387] [388] Propofol also results in a shorter duration of motor and EEG seizure activity following electroconvulsive therapy as compared with methohexital. [389] Interestingly, propofol has been associated with grand mal seizures and has been used for cortical mapping of epileptogenic foci. [390] [391] In 17 patients undergoing cortical resection for intractable epilepsy, 2 mg/kg propofol resulted in markedly reduced or ablated seizure activity. [392] When propofol was administered at sedative doses in 14 patients with complex seizure disorders, no effect on seizure activity was noted. [393] There have been a few reports of convulsions following propofol administration that have occurred several (6) days following anesthesia. Although the majority of these patients had a history of previous convulsions, a few did not. The incidence of this adverse effect is rare (1 in 50,000 administrations). [394] There have also been reports of tolerance developing to propofol following either repeat anesthesia or prolonged infusions (days). [395] [396] There have not been reports of acute tolerance during a single case of anesthesia. In addition to tolerance, addiction to propofol has been reported. [397]

Propofol decreases ICP in patients with either normal or increased ICP [398] [399] [400] [401] [402] (Ch. 52) . In patients with normal ICP, the decrease in ICP (30%) is associated with a small decrease in cerebral perfusion pressure (10%). [401] The addition of small doses of fentanyl and of supplemental doses of propofol ablates the rise of ICP secondary to endotracheal intubation. [401] Normal cerebral reactivity to carbon dioxide and autoregulation are maintained during a propofol infusion. [398] [403] [404] In patients with elevated ICP, the decrease in ICP (30-50%) is associated with significant decreases in cerebral perfusion pressure [399] [405] and therefore may not be beneficial. Propofol reduces $CMRO_2$ 36 percent. [398] With a background of 0.5 percent enflurane, propofol still reduces $CMRO_2$ by 18 percent, whereas lactate and glucose metabolism remains unchanged. [402] By measuring arteriovenous oxygen content difference, cerebral metabolic autoregulation is maintained during burst suppression with propofol. [406] Propofol administered to burst suppression results in significantly better neurologic outcome and less brain tissue injury in an incomplete ischemia model in rats, as compared with fentanyl. [407] Propofol also provides cerebral protective effects following an acute ischemic insult to the same degree as either halothane or thiopental. [408] [409] The neuronal protective effect of propofol may be due to the attenuation of changes in adenosine triphosphate, calcium, sodium, and potassium caused by hypoxic injury. [410] Propofol acutely reduces intraocular pressure by 30 to 40 percent. [411] [412] As compared with thiopental, propofol produces a greater decrease in intraocular pressure, and following a small second dose, it is more effective in preventing a rise in intraocular pressure secondary to succinylcholine and endotracheal intubation. [412]

The propofol Cp_{50} for loss of response to verbal command in the absence of any other drug is 2.3 to 3.5 mug/mL. [413] [414] [415] The propofol Cp_{50} (arterial whole blood concentration) to prevent movement on skin incision is 16 mug/mL. This is markedly reduced by increasing concentrations of fentanyl or alfentanil. [413] [414] [416] The propofol Cp_{50} for skin incision when combined with benzodiazepine premedication (lorazepam 1-2 mg) and 66 percent nitrous oxide is 2.5 mug/mL (venous). [417] This concentration is reduced to 1.7 mug/mL when morphine (0.15 mg/kg) rather than lor-azepam is used for premedication. [418] The concentration of propofol (when combined with 66% nitrous oxide) required during minor surgery varies from 1.5 to 4.5 mug/mL, [338] [339] and that for major surgery varies from 2.5 to 6 mug/mL. [419] Awakening usually occurs at concentrations lower than 1.6 mug/mL, [338] [339] [367] and orientation occurs at concentrations lower than 1.2 mug/mL. [338] [339] Age also affects the propofol concentration required to provide adequate anesthesia. [339]

Effects on the Respiratory System

Propofol affects the respiratory system in a manner qualitatively similar to the action of barbiturates. [420] [421] [422] Apnea occurs after an induction dose of propofol; the incidence and duration of apnea appear dependent on dose, speed of injection, and concomitant premedication. An induction dose of propofol results in a 25 to 30 percent incidence of apnea. [419] [420] The apnea occurring with propofol, however, may be prolonged to more than 30 seconds. The incidence of prolonged apnea (>30

seconds) is further increased by addition of an opiate, either as premedication or just prior to induction, [419] [420] [423] and it is greater with propofol than with other commonly used intravenous induction agents. [420] [423] The onset of apnea is usually preceded by marked tidal volume reduction and tachypnea. [422] Following a 2.5-mg/kg induction dose of propofol, the respiratory rate is significantly decreased for 2 minutes, [420] and minute volume is significantly reduced for up to 4 minutes, a finding that indicates a more prolonged effect of propofol on tidal volume than on respiratory rate.

A maintenance infusion of propofol (100 mug/kg/min) results in a 40 percent decrease in tidal volume and a 20 percent increase in respiratory frequency, with an unpredictable change in minute ventilation. [422] Doubling the infusion rate from 100 to 200 mug/kg/min causes a further moderate decrease in tidal volume (455-380 mL) but no change in respiratory frequency. [422] The ventilatory response to carbon dioxide is also decreased during a maintenance infusion of propofol. [422] At 100 mug/kg/min, there is a 58 percent

reduction in the slope of the carbon dioxide-response curve. [422] This is similar to the 50 percent depression of carbon dioxide responsiveness measured with 1 MAC of halothane [424] or after a brief infusion of 3 mg/kg/min of thiopental. [425] Doubling the infusion rate (and presumably the blood level) of propofol results in only a minimal further decrease in carbon dioxide responsiveness. [422] This is in contrast to halothane, with which use of twice the MAC results in halving the carbon dioxide response. [424] Propofol, 1.5 to 2.5 mg/kg, results in an acute (13-22%) rise in Pa CO_2 and a decrease in pH. [426] [427] [428] Pa O_2 does not change significantly. [426] [427] [428] These changes are similar to those seen following an induction dose of thiopental. [427] [428] During a maintenance infusion of propofol (54 mug/kg/min), Pa CO_2 is moderately increased from 39 to 52 mm Hg. [429] Doubling this infusion rate does not result in a further increase in Pa CO_2 . [429] Propofol (50-120 mug/kg/min) also depresses the ventilatory response to hypoxia. [430]

Propofol induces bronchodilation in patients with chronic obstructive pulmonary disease. [431] Propofol, however, does not appear to provide as effective bronchodilating properties as halothane. [432]

Effects on the Cardiovascular System

The cardiovascular effects of propofol have been evaluated following its use both for induction and for maintenance of anesthesia [298] [426] [427] [428] [429] [433] [434] [435] [436] [437] [438] (see Table 9-4) . The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anesthesia. Independently of the presence of cardiovascular disease, an induction dose of 2 to 2.5 mg/kg produces a 25 to 40 percent reduction of systolic blood pressure. [298] [426] [427] [428] [429] [433] [434] [435] [436] [437] [438] Similar changes are seen in mean and diastolic blood pressure. The decrease in arterial pressure is associated with a decrease in cardiac output/cardiac index (15%), [427] [429] [436] [437] [438] stroke volume index (20%), [429] [437] [438] and systemic vascular resistance (15-25%). [427] [429] [436] [437] Left ventricular stroke work index is also decreased (by 30%). [437] When looking specifically at right ventricular function, propofol produces a marked reduction in the slope of the right ventricular end-systolic pressure-volume relationship. [439] In patients with valvular heart disease, pulmonary artery and pulmonary capillary wedge pressure are also reduced, a finding that implies that the resultant decrease in pressure is due to a decrease in both preload and afterload. [426] The decrease in systemic pressure following an induction dose of propofol appears to be due to both vasodilation and myocardial depression. Both the myocardial depressant effect and the vasodilation appear to be dose-dependent and plasma concentration-dependent. [440] The vasodilatory effect of propofol appears to be due both to a reduction in sympathetic activity [441] and to a direct effect on intracellular smooth muscle calcium mobilization. [442] [443]

Heart rate does not change significantly after an induction dose of propofol. It has been suggested that propofol either resets or inhibits the baroreflex, thus reducing the tachycardic response to hypotension. [300] [444] Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction. [445]

During maintenance of anesthesia with a propofol infusion, systolic pressure remains between 20 and 30 percent below preinduction levels. [429] [437] In patients allowed to breathe room air during a maintenance infusion of 100 mug/kg/min of propofol, there is a significant decrease in systemic vascular resistance (30%), but cardiac index and stroke index are unaltered. [437] In contrast, in patients receiving a narcotic premedication and nitrous oxide with an infusion of propofol (54 and 108 mug/kg/min) for maintenance during surgery, systemic vascular resistance is not significantly decreased from baseline, but cardiac output and stroke volume are decreased. [429] This is probably explained by the observation that propofol infusions produce a dose-dependent lowering of sympathetic nerve activity, thereby attenuating the reflex responses to hypotension. In the presence of hypercarbia, the reflex sympathetic responses are better maintained. [416] Increasing the infusion rate of propofol from 54 to 108 mug/kg/min (blood concentration 2.1-4.2 mug/mL) produces only a slightly greater decrease in arterial blood pressure (10%). [429] The peak plasma concentrations obtained following a bolus dose are substantially higher than those seen with a continuous infusion. Because the vasodilatory and myocardial depressant effects are concentration-dependent, the decrease in blood pressure from propofol during the infusion phase is much less than that seen following an induction bolus. When propofol was compared with midazolam for sedation after coronary revascularization, propofol resulted in a 17 percent lower incidence of tachycardia, a 28 percent lower incidence of hypertension, and a 17 percent greater incidence in hypotension. These differences in hemodynamic parameters resulted in no difference in the number or severity of ischemic events between the two groups. [439]

Heart rate may increase, [428] [435] decrease, [426] [434] or remain unchanged [433] when anesthesia is maintained with propofol. An infusion of propofol results in a significant reduction in both myocardial blood flow and myocardial oxygen consumption, [298] [435] a finding that suggests that the global myocardial oxygen supply/demand ratio is preserved.

Other Effects

Propofol, like thiopental, does not potentiate neuromuscular blockade produced by both nondepolarizing and depolarizing neuromuscular blocking agents. [446] [447] Propofol produces no effect on the evoked electromyogram or twitch tension [446] ; however, good intubating conditions after propofol alone have been reported. [448] Propofol does not trigger malignant hyperpyrexia and is probably the anesthetic of choice in patients with this condition. [449] [450]

Propofol following a single dose or a prolonged infusion does not affect corticosteroid synthesis or alter the normal response to ACTH stimulation. [451] Propofol in the emulsion formulation does not alter hepatic, hematologic, or fibrinolytic function. [452] [453] [454] However, lipid emulsion per se reduces *in vitro* platelet aggregation. [455] Anaphylactoid reactions to the present formulation of propofol have been reported. In at least some of the patients, the immune response was entirely due to propofol and not to the lipid emulsion. A high percentage of the patients developing the anaphylactoid response to propofol had a previous history of allergic responses. In patients with multiple drug allergies, propofol should be used with caution. [456] In most people, the present preparation does not trigger histamine release. [457]

Propofol also possesses significant antiemetic activity at low (subhypnotic) doses. [458] It has been used successfully to treat postoperative nausea in a bolus dose of 10 mg. [459] It has also been used successfully to treat refractory postoperative nausea and vomiting. [460] The median concentration of propofol that was associated with an antiemetic region was 343 ng/mL. [461] This concentration can be achieved by a propofol infusion of 10 to 20 ng followed by 10 mug/kg/min. Propofol used as a maintenance anesthetic during breast surgery was more effective than 4 mg of ondansetron given prophylactically in preventing postoperative nausea and vomiting. In the same study, the maintenance propofol infusion was also superior to adding propofol only at the end of the procedure (sandwich technique). [462] The difference in efficacy of propofol in preventing postoperative nausea and vomiting between the propofol maintenance method and the sandwich technique is that the propofol concentration drops rapidly after the sandwich technique below the therapeutic concentration, whereas with the maintenance technique, although the propofol concentration decreases rapidly to allow awakening, any further decrease is much slower and is maintained above therapeutic concentrations for several hours. Propofol as an infusion of 1 mg/kg/h (17 mug/kg/ min) has also provided excellent antiemetic action following anticancer chemotherapy. [463] The antiemetic effect of propofol has been shown not to be due to an action on dopamine-2 receptors. [464] Propofol at subhypnotic doses has also been reported to relieve cholestatic pruritus and was as effective as naloxone in treating pruritus induced by spinal opiates. [465] Propofol causes a dose-dependent decrease in the thermoregulatory threshold for vasoconstriction, but it has little effect on the sweating threshold. [466]

Propofol only decreases polymorphonuclear leukocyte chemotaxis but not adherence phagocytosis and killing. This action contrasts with the effect of thiopentone, which inhibits all these chemotactic responses. [467] However, propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli.*[468] These

findings are particularly pertinent in view of the observation of increased life-threatening systemic infections associated with the use of propofol. [464] [469] It was also noticed that opened vials and syringes of propofol in hospitals where these infections occurred had positive cultures for the offending organisms. The intralipid that acts as the solvent for propofol is an excellent culture medium. Ethylenediaminetetra-acetic acid has been added to the formulation of propofol in an attempt to retard such bacterial growth. Strict aseptic technique must still be observed.

Uses

Induction and Maintenance of Anesthesia

Propofol is suitable for both the induction and maintenance of anesthesia and has also been approved for use in neurologic and cardiac anesthesia (Table 9-9) . The induction dose varies from 1.0 to 2.5 mg/kg, [362] [470] [471] and the ED_{95} in unpremedicated adult patients is 2.25 to 2.5 mg/kg. [470] [472] Premedication with an opiate and or a benzodiazepine

TABLE 9-9 -- Uses and Doses of Propofol

Induction of general anesthesia	1-2.5 mg/kg IV dose reduced with increasing age
Maintenance of general anesthesia	50-150 mug/kg/min IV combined with N_2 o or an opiate
Sedation	25-75 mug/kg/min IV

markedly reduces the induction dose. [365] [366] [473] Increasing age also reduces the dose of propofol required to induce anesthesia. [474] [475] A dose of 1 mg/kg (with premedication) to 1.75 mg/kg (without premedication) is recommended for inducing anesthesia in patients older than 60 years of age. [475] To prevent hypotension in sicker patients or in patients presenting for cardiac surgery, a fluid load should be administered as tolerated, and the propofol should be administered in small incremental doses (10-30 mg) until the patients lose consciousness. The ED_{95} (2.0-3.0 mg/kg) for induction is increased in children, primarily because of pharmacokinetic differences. [472] [479]

Propofol, when used for induction of anesthesia in briefer procedures, results in a significantly quicker recovery and an earlier return of psychomotor function as compared with thiopental or methohexital, irrespective of the agent used for maintenance of anesthesia. [478] [479] [480] The incidence of nausea and vomiting when propofol is used for induction is also markedly lower than following the use of other intravenous induction agents, probably because of the antiemetic properties of propofol. [472] [479]

Because of its pharmacokinetics, propofol provides a rapid recovery and is thus superior to barbiturates for maintenance of anesthesia, [480] [481] [482] and it appears equal to enflurane and isoflurane. [364] [478] [483] Recovery from desflurane is slightly more rapid than recovery from propofol. [484] Propofol can be given as intermittent boluses or as a continuous infusion for maintenance. [453] Following a satisfactory induction dose, a bolus of 10 to 40 mg is needed every few minutes to maintain anesthesia. Because these doses need to be given frequently, it is more suitable to administer propofol as a continuous infusion.

Several infusion schemes have been used to achieve adequate plasma concentrations of propofol. [480] [485] Following an induction dose, an infusion of 100 to 200 mug/kg/min is usually needed. [339] [364] [417] [418] [478] [480] [481] [482] The infusion rate is then titrated to individual requirements and the surgical stimulus. When combined with propofol, morphine, fentanyl, or alfentanil reduces its required infusion rate and concentration. [413] [414] [417] [418] [486] Because opioids alter the concentration of propofol required for adequate anesthesia, the relative dose of either opioid and propofol will markedly affect the time from termination of drug to awakening and recovery. Illustrated in Figure 9-20 is the relationship between the concentration of propofol and alfentanil that will prevent a somatic response in 50 percent of patients combined with the time to awakening (on the Z axis) for that specific combination. [487] The infusion rate required to achieve the combination with the shortest recovery is propofol, 1 to 1.5 mg/kg followed by 140 mug/kg/min for 10 minutes followed by 100 mug/kg/min, and alfentanil, 30 mug/kg followed by an infusion of 0.25 mug/kg/min, or fentanyl, 3 mug/kg followed by

Figure 9-20 The interaction between propofol and alfentanil for movement at skin incision is shown. The solid line intersecting the X and Y axes represents the concentration of propofol and alfentanil at which 50 percent of patients did not move on skin incision. Noted as the concentration of alfentanil increases, the concentration of propofol required to prevent movement on skin incision decreases until a plateau is reached at an alfentanil concentration of approximately 200 ng/mL. At higher alfentanil concentrations, there is no further reduction in the amount of propofol required to ensure absence of movement at skin incision. This concentration of propofol is approximately 2.5 mug/mL, close to the concentration of propofol required for loss of consciousness in the absence of any opioid. The solid line on the Z axis represents the time to awakening and spontaneous ventilation when the indicated concentration of propofol and alfentanil is administered. Note the shortest recovery period with the optimal combination to prevent movement at 50 percent of patients is a propofol concentration of 3.5 mug/mL with an alfentanil concentration of 85 ng/mL. Note also that increasing either the propofol concentration or the alfentanil concentration from this ideal com-bination results in a prolongation in recovery time. This prolongation in recovery time is more marked with an increase in alfentanil concentration than with an increase in propofol concentration.

0.02 mug/kg/min. Propofol has also been used as a single mixture with alfentanil, containing 1 mg alfentanil (2 mL) to 400 mg propofol (40 mL). When this mixture was administered at infusion rates commonly used for propofol (i.e., 166 mug/kg/min for 10 min, 133 mug/kg/min for 10 min, and 100 mug/kg/min thereafter), it provided an outcome equal to that obtained by using the two drugs as separate infusions. [488]

Increasing age is associated with a decrease in propofol infusion requirements, [489] [490] whereas these requirements are higher in children and infants. [347] The blood levels of propofol alone for loss of consciousness are 2.5 to 4.5 mug/mL, and the blood concentrations (when combined with nitrous oxide) required for surgery are 2.5 to 8 mug/ mL. [338] [339] [367] [417] [418] [483] Similar concentrations are necessary when propofol is combined with an opioid for a total intravenous technique. The knowledge of these levels and of the pharmacokinetics of propofol has enabled the use of pharmacokinetic model-driven infusion systems to deliver propofol as a continuous infusion for the maintenance of anesthesia. [364] [485] [491] [492]

For short (<1 h) body surface procedures, the advantages of a more rapid recovery and decreased nausea and vomiting are still evident. [478] However, if propofol is used for longer or major procedures, both speed of recovery and the incidence of nausea and vomiting are similar to those following thiopental/isoflurane anesthesia. [364] [478] A meta-analysis of recovery data following either propofol for maintenance or the newer volatile anesthetics indicated only minor differences in times to reach recovery goals; however, the incidence of nausea and vomiting remained significantly lower in the patients administered propofol for maintenance. [493]

Several studies have investigated the utility of propofol as a maintenance infusion regimen for cardiac surgery. Using reduced and titrated doses of propofol for induction and titrated infusion rates of 50 to 200 mug/kg/min combined with an opioid for maintenance, propofol provided intraoperative hemodynamic control and ischemic episodes similar to those with either enflurane/opioid or a primary opioid technique. [494] [495] [496] [497]

Sedation

Propofol has been evaluated for sedation during surgical procedures [369] [370] [498] [499] and for patients receiving mechanical ventilation in the ICU. [500] [501] [502] Propofol by continuous infusion provides a readily titratable level of sedation and a rapid recovery once infusion is terminated, irrespective of the duration of the infusion. [370] [498] [501] [503] In a study of patients sedated in the ICU for 4 days with propofol, recovery to consciousness was rapid (
10 min). Both the rate of recovery and the decrease in plasma concentration were similar at 24 and at 96 hours, when the infusion was discontinued. In addition, the plasma concentrations required for sedation and for awakening were similar at 24 and 96 hours, a finding that implies that tolerance to propofol did not occur. [503] As noted earlier, there have been more recent reports of tolerance with propofol. Infusion rates required for sedation to supplement regional anesthesia in healthy patients are half or less than those required for general anesthesia (i.e., 30-60 mug/kg/min). [369] [498] In elderly patients (older than 65 years) and in sicker patients, the infusion

rates that are necessary are markedly reduced. [369] [500] [501] Thus, it is important to titrate the infusion individually to the desired effect. A 1992 report [504] linked propofol with several deaths in children requiring sedation for mechanical ventilation secondary to upper respiratory tract infections. The likelihood that propofol was the primary cause has been challenged. However, propofol is not yet approved for ICU sedation in children, and it should not be used for this purpose until definitive studies assessing the drug's safety in this population are completed. No such adverse experiences have been reported in adults. A potential advantage of propofol for sedation of ICU patients is that it appears to possess antioxidant properties. [505]

Generally, at propofol infusion rates greater than 30 mug/kg/min, patients are amnesic. [498] [501] In comparison with midazolam when used to maintain sedation, propofol provides equal or better control and more rapid recovery. [370] [498] [501] In mechanically ventilated patients, more rapid recovery translates to more rapid extubation when sedation is terminated. [501] The use of propofol for sedation following cardiac surgery to provide fast tracking has shown that patients can be extubated rapidly using this technique. [506] The incidence of unwanted cardiovascular changes and of ischemic events was similar when propofol or midazolam was used for sedation in patients after coronary artery bypass surgery. [439] Propofol has also been used successfully in patient-controlled sedation. Propofol was rated better than midazolam when used by this technique, probably owing to its much more rapid onset and offset. [507]

Side Effects and Contraindications

Induction of anesthesia with propofol is associated with several side effects. These include pain on injection, myoclonus, apnea, decrease in arterial blood pressure, and, rarely, thrombophlebitis of the vein into which propofol is injected. Pain on injection is less than or equal to that with etomidate, equal to that with methohexital, and greater than after thiopental. [314] [452] [477] Pain on injection is reduced by using a large vein, avoiding veins in the dorsum of the hand, and adding lidocaine to the propofol solution. [452] Myoclonus occurs more frequently following propofol than following thiopental but less frequently than following etomidate or methohexital. [477] Apnea following induction with propofol is common. The incidence of apnea may be similar to that following thiopental or methohexital; however, propofol produces a greater incidence of apnea lasting longer than 30 seconds. [417] [423] The addition of an opiate increases the incidence of apnea, especially prolonged apnea. [417] [419]

The most significant side effect on induction is the decrease in systemic blood pressure. Addition of an opiate just prior to induction of anesthesia appears to augment the decrease in arterial blood pressure. [438] Perhaps slow administration and lower doses in adequately prehydrated patients may attenuate the decrease in arterial blood pressure. Conversely, the effects of laryngoscopy and endotracheal intubation and the increases in mean arterial pressure, heart rate, and systemic vascular resistance are less significant following propofol than thiopental. [434] [438]

DROPERIDOL

History

General anesthesia with inhaled anesthetics and barbiturates depresses the entire CNS in a nonspecific manner. Laborit and Huguenard [508] [509] in the 1950s sought an anesthetic technique that would produce "artificial hibernation" devoid of circulatory and respiratory depression. Their concept was to use drugs that would produce neurovegetative blockade (multifocal inhibition) of cellular, autonomic, and endocrine mechanisms normally activated in response to stress. [510] The first attempt at developing this concept was the lytic cocktail, containing an analgesic (meperidine), two tranquilizers (chlorpromazine and promethazine), and atropine. Although this combination of drugs did enjoy widespread use for conscious sedation, it produced respiratory depression. It was not used for general anesthesia. Janssen [511] synthesized haloperidol, the first member of the butyrophenones, which became the primary neuroleptic component in neuroleptanesthesia (NLAN). DeCastro and Mundeleer [512] in 1959 combined haloperidol with phenoperidine (a meperidine derivative also synthesized by Janssen) in the forerunner to the current practice of NLAN. Droperidol, a derivative of haloperidol, and fentanyl (a phenoperidine congener), both again synthesized by Janssen, were used by DeCastro and Mundeleer [512] in a combination they reported to be superior to haloperidol and phenoperidine. This NLAN combination produced more rapid onset of analgesia, less respiratory depression, and fewer extrapyramidal side effects. The fixed combination of droperidol and fentanyl, marketed as Innovar in the United States, is the drug currently used for NLAN.

Droperidol is a butyrophenone, a fluorinated derivative of phenothiazines [510] (Fig. 9-21) . Butyrophenones produce CNS depression, characterized by marked apparent tranquility and cataleptic immobility. They are potent antiemetics. Droperidol is a potent butyrophenone, and like the others, it produces its action centrally at sites where dopamine, norepinephrine, and serotonin act. It has been postulated that butyrophenones may occupy GABA receptors on the postsynaptic membrane, thereby reducing synaptic transmission and resulting in a build-up of dopamine in the intersynaptic cleft. [510] [511] An imbalance in dopamine and acetylcholine is thought to occur, which results in alteration in normal transmission of signals in the CNS. The chemoreceptor trigger zone is the emetic center, and "red" astrocytes transport neurolept molecules from the capillary to dopaminergic synapses in the chemoreceptor trigger zone, where they occupy GABA receptors (Fig. 9-22) (Figure Not Available) . This is

Figure 9-21 Structure of droperidol, a butyrophenone derivative.

Figure 9-22 (Figure Not Available) Site of action of droperidol. Mode of action of neuroleptanesthetic drugs at the chemoreceptor trigger zone. *(Modified from Janssen [580])*

thought to be the mechanism by which droperidol exerts its antiemetic effect. [513]

Metabolism and Pharmacokinetics

Droperidol is biotransformed in the liver into two primary metabolites. [514] Its plasma decay can be described by a two-compartment model. The pharmacokinetics [515] is shown in Table 9-3 . The clearance of droperidol is relatively large (14 mL/kg/min), and its elimination half-life is relatively short (103-134 min). [515] [516] Its time course of disappearance from plasma is similar to that of fentanyl (Fig. 9-23) , yet the discrepancy in duration of effect of the two has been the subject of criticism, because both are formulated together in Innovar. The seemingly longer CNS action of droperidol has prompted some investigators to postulate that droperidol has a propensity to occupy CNS receptors [515] and that it has greater receptor binding than fentanyl.

Pharmacology

Effects on the Central Nervous System

The effects of neuroleptanesthetics on human CBF and $CMRO_2$ have not been studied. In dogs, droperidol causes potent cerebral vasoconstriction, producing a 40 percent reduction in CBF (Ch. 54) . No significant change in $CMRO_2$ occurs during droperidol administration. [517] The EEG in conscious patients shows some reduction in frequency in the range, with occasional slowing to the range. [518] The extrapyramidal and malignant neuroleptic syndrome that sometimes follows droperidol use is discussed later in connection with Innovar.

Effects on the Respiratory System

When used alone, droperidol has little effect on the respiratory system. [519] Droperidol (0.044 mg/kg) given to surgical patients produced a slight reduction in respiratory rate, [520] and droperidol (3 mg IV) had no significant effect on tidal volume in volunteers. [521] More detailed respiratory studies are not available.

Effects on the Cardiovascular System

The predominant cardiovascular effect of droperidol is vasodilation with a decrease in blood pressure (see Table 9-4) .

Figure 9-23 Simulated time course of plasma levels of fentanyl and droperidol after an induction dose of fentanyl 5 mug/kg and droperidol 25 mug/kg. Note the parallel plasma disappearance of the drugs.

This effect is considered to be a result of moderate alpha-adrenergic blockade. [514] [522] [523] Importantly, the dopamine-induced increase in renal blood flow (renal artery flowmeter methodology) is not significantly impaired by administration of droperidol. [524] Droperidol has little effect on myocardial contractility. [525] It seems to possess some antiarrhythmic effects that are much like those of quinidine. [525] [526]

Uses

Droperidol is used as an NLAN component (see *Innovar*) and as an antiemetic component in general anesthesia. It is an effective antiemetic, [527] the dose for this use varying between 10 and 20 mug/kg (0.6 and 1.25 mg for a 70-kg person). [528] These doses of droperidol, given at the start of anesthesia for operations lasting 1 hour, reduce the incidence of nausea and vomiting by about 50 percent. These doses given at induction have little effect on wake-up time, but should they be given at the end of surgery, there could be some residual hypnotic effect. Droperidol is also effective in pediatric patients [529] when the drug is given orally (300 mug/kg), and the effect can be enhanced when combining it with oral metoclopramide (0.15 mg/kg) Overall antiemetic efficacy of droperidol alone is probably less than that of ondansetron and is associated with more sedation, but costs are less.

A newer use for droperidol is as an antiemetic given as an adjunctive drug intermittently or with continuous infusion for postoperative pain relief as part of a patient-controlled regimen [530] [531] or as epidural supplements to opioids. [532] When used in this fashion, droperidol effectively reduces nausea, but it does increase sedation.

INNOVAR

Innovar is a combination of droperidol and fentanyl in a ratio of 5:1 (droperidol 2.5 mg/mL and fentanyl 50 mug/mL). Lactic acid is added for adjustment of pH to 3.5. The pharmacologic effects of Innovar are those of its two component drugs. Droperidol produces hypnosis, sedation, and anti-emetic effects, whereas fentanyl produces analgesia. There is no apparent synergistic or supra-additive effect of the two drugs, but simply an additive effect (i.e., the effects of each drug add to those of the other). Recovery from NLAN produced by Innovar is usually prompt after cessation of nitrous oxide administration, and consciousness returns within 3 to 5 minutes. [510] In the recovery period, patients tend to be drowsy, detached, and free of pain, nausea, and vomiting.

Pharmacology

Effects on the Respiratory System

Innovar produces respiratory depression in a dose-related fashion. The respiratory effects are peripheral and central and are due to fentanyl. The peripheral effects involve truncate rigidity, and the central respiratory depression is a result of fentanyl's action at the respiratory center. Both respiratory rate and tidal volume are reduced by Innovar [521] [533] [534] [535] the contribution of droperidol to this effect is limited. [536] Innovar and/or the combination of droperidol with fentanyl will reduce respiratory function more than droperidol alone. [520] [521] Respiratory depression can be antagonized by administration of an opioid competitive antagonist.

Effects on the Cardiovascular System

The primary cardiovascular effect of Innovar is a decrease in arterial blood pressure [534] because of the droperidol component, which produces alpha-adrenergic blockade. Heart rate decreases as a result of a fentanyl-induced increase in vagal tone. Despite these changes, Innovar does not significantly reduce cardiac output in patients with adequate blood volumes. The antiarrhythmic properties of droperidol are those present in Innovar. [537]

Uses

NLAN may be induced with droperidol and fentanyl (or other opioids) separately or with the drug Innovar. Innovar should be used with caution during induction because of possible vasodilation and hypotension. It is recommended that a test dose of 1 to 2 mL be administered prior to induction of NLAN with Innovar. If the components are given separately, droperidol should be administered first, in a dose of about 5 to 10 mg (5-150 mug/kg), and followed by incremental doses of fentanyl in 50- to 100-mug increments. The usual induction dose of Innovar is 0.1 to 0.15 mL/kg (Table 9-10) in fit adults, and this is almost always administered with nitrous oxide and a muscle relaxant. It is recommended that 200 to 300 mL of balanced salt solution be administered prior to induction and that hypotension be treated with further fluid administration. Elderly and other high-risk patients require less Innovar for induction of anesthesia. Supplementation of anesthesia during NLAN should be with fentanyl and not with Innovar. The reasons are that the prolonged duration of action of droperidol will produce postoperative somnolence if the drug is repeated during the operation, and analgesia is required to blunt stress responses.

Innovar in markedly reduced doses can be used for intravenous sedation during conduction anesthesia or selected diagnostic procedures performed using local anesthesia. The customary dose of Innovar for sedation is about 2 to 4 mL in divided doses titrated to the desired level of sedation. Innovar has been used for many types of procedures and can be safely used in most. Operations that are particularly suited for Innovar

TABLE 9-10 -- Uses and Doses of Innovar

Induction of general anesthesia	
0.1-0.15 mL/kg	with N_2O 50-66% in O_2 [a]
Maintenance of general anesthesia	
Fentanyl	1-2 mug/kg prn
Fentanyl	0.01-0.05 mug/kg/min
Sedation and analgesia	
0.5-1.0 mL IV repeated and titrated to desired effect	
1-2 mL IM	

[a] Dose should be reduced in hypovolemic and other high-risk patients. Each milliliter of Innovar contains droperidol 2.5 mug and fentanyl 50 mug.

are those with a high incidence of postoperative nausea and vomiting (e.g., middle ear surgery). Small doses of droperidol or Innovar may be helpful in outpatient procedures that are associated with nausea and vomiting. Innovar may also be used as a sedative-analgesic for sedation during diagnostic and surgical procedures. It does not produce reliable amnesia.

Side Effects and Contraindications

Innovar is not associated with organ toxicity or with tissue or venous irritation. However, it does have several adverse effects. Muscle rigidity is a consequence of the fentanyl component and is more of a problem if large doses are given rapidly. Treatment and prevention include giving a muscle relaxant with the Innovar. Respiratory depression is also a result of the fentanyl and can be reversed with an opioid antagonist, but this can also reverse the analgesia and may precipitate hypertension. Hypotension from the droperidol component is a common side effect of Innovar and can be treated with intravascular blood volume expansion or an alpha-adrenergic agonist (e.g., phenylephrine). Prolonged somnolence or detachment is a result of the droperidol and is related to dose. Although this has been reversed with physostigmine (2 mg), physostigmine is not a specific antagonist, and the possibility that resedation may occur is real, because droperidol clearance is less than that of physostigmine. Extrapyramidal complications, manifested by dyskinesia, especially of the face, neck, and pharyngeal muscles, with speech and swallowing difficulties, grimacing, trismus, oculogyric spasms, and torticollis, occur in a small percentage of patients given Innovar [538] and are due to the droperidol component. Droperidol in doses as low as 0.65 mg can produce extrapyramidal reactions, [539] which may be treated with diphenhydramine or benztropine. Some patients have an unusual psychologic reaction, particularly when Innovar is used as a premedicant, and patients have refused to have surgery after Innovar premedication. Patients

report hallucinations and bizarre sensations of weightlessness and loss of body image; these reactions can be successfully treated with a benzodiazepine. A final and rare complication of Innovar is the malignant neuroleptic syndrome, [540] [541] characterized by hyperthermia, muscular rigidity, and autonomic instability. The muscular hypertonicity is lead-pipe. Although this reaction can be distinguished from malignant hyperthermia by the temperature course (which is lower) and muscle biopsy studies, dantrolene has been successfully used to treat the syndrome. [542] Bromocriptine, a central dopamine agonist, has also been used (2.5-10 mg PO tid) to treat this syndrome, which is mostly encountered in patients taking butyrophenones and phenothiazines for psychiatric disturbances.

alpha-ADRENERGIC AGONISTS: DEXMEDETOMIDINE

History

Adrenergic receptors were first differentiated into alpha and beta by Ahlquist, based on their responses to various amines. [543] The alpha$_2$ -adrenergic agonists provide sedation, anxiolysis, and hypnosis, as well as analgesia and sympatholysis. An excellent review and an editorial concerning their pharmacology and potential uses in anesthesia have been published. [543] [544] The initial impetus for the use of alpha $_2$ -agonists in anesthesia resulted from observations made in patients during anesthesia who were receiving clonidine therapy. [543] [545] [546] This was soon followed by a description of the MAC reduction of halothane by clonidine. [547] Clonidine is currently the only available alpha $_2$ -agonist approved for administration, and this is only for the treatment of hypertension; however, dexmedetomidine is undergoing extensive evaluation for perioperative use.

Physicochemical Characteristics

Medetomidine is a highly selective alpha $_2$ -adrenergic agonist. Dexmedetomidine is its specific stereoisomer, which is available as a parenteral formulation. Its structure is illustrated in Figure 9-24 .

Metabolism and Pharmacokinetics

The exact metabolic pathways for dexmedetomidine in humans have not been fully described. It is believed that the drug is first hydroxylated and subsequently undergoes either dehydrogenation to form a carboxylic acid derivative or glucuronidation. Dexmedetomidine is 90 percent protein bound, and its concentration ratio between whole blood and plasma is 0.66. Dexmedetomidine has profound affects on cardiovascular parameters and thus appears to effect its own pharmacokinetics. At high doses, there is marked vasoconstriction, which probably reduces the drug's volumes of distribution. Thus, in essence, dexmedetomidine displays nonlinear pharmacokinetics. [548] Because it is likely that this agent will only be administered within a narrow therapeutic range of 0.5 to 1.0 ng/mL, it is preferable to describe the pharmacokinetic parameters within this dosage range. Within this range, Dyck et al [548] found that its pharmacokinetics is best described by a three-compartment model (Table 9-11) . These pharmacokinetic parameters appear to be unaltered by age or weight, but clearance is a function of height. [548] The elimination half-life of dexmedetomidine is 2 to 3 hours, with a context sensitive half-time ranging from 4 minutes after a 10-minute infusion to 250 minutes following an 8-hour infusion. An intramuscular injection of 2 mug/kg of dexmedetomidine into the deltoid muscle had a bioavailability of 73(±11) percent with a time to peak concentration of 13(±18) minutes and resulted in a peak plasma concentration

Figure 9-24 Chemical structure of dexmedetomidine.

TABLE 9-11 -- Pharmacokinetic Parameters of Dexmedetomidine Derived During Infusion at Therapeutic Concentrations Likely to be Used Within the Perioperative Period

V_1 (L)	7.99
V_2 (L)	13.8
V_3 (L)	18.7
Cl_1 ($L \cdot min^{-1}$)	(0.00791*Ht)-0.927
Cl_2 ($L \cdot min^{-1}$)	2.26
Cl_3 ($L \cdot min^{-1}$)	1.99

V_1 , central volume of distribution; Cl_1 , clearance in volume 1; Cl_2 , clearance in volume 2; Cl_3 , clearance in volume 3

of 0.8(±3) ng/mL. [549] Injection into the gluteus muscle, however, results in a much longer time to peak effect of approximately 90 minutes. [550]

Pharmacology

Effects on the Central Nervous System

The alpha$_2$ -agonists produce their sedative hypnotic effect by an action on alpha $_2$ -receptors in the locus caeruleus and an analgesic action both at alpha $_2$ -receptors within the locus caeruleus and the spinal cord. [551] The alpha$_2$ -agonists appear to inhibit ion conductance through L- or P-type calcium channels and facilitate conductance through voltage-gated calciumactivated potassium channels. [552] The alpha$_2$ -agonists have the advantage that their effects are readily reversible by alpha$_2$ -adrenergic antagonists (e.g., atipamezole). [553] Like other adrenergic receptors, the alpha $_2$ -agonists also demonstrate tolerance following prolonged administration. [554] Rats rendered tolerant to morphine also show a decrease in efficacy of both hypnotic and analgesic effects of dexmedetomidine. As tolerance to the opioid recovered, there was a more rapid recovery of the hypnotic effect of dexmedetomidine than its analgesic efficacy. [555] These data would tend to indicate a possible cross-tolerance across receptors.

In a model of focal ischemia in rabbits, dexmedetomidine, administered at doses that reduced the MAC of halothane by 50 percent, resulted in less cortical neuronal damage than when halothane was administered alone at equi-effective MAC concentrations. [556] Little is known of the effects of dexmedetomidine alone on ICP and CBF. In dogs, in the presence of volatile anesthetics and dexmedetomidine, CBF was decreased and oxygen consumption was maintained. [557] [558] CBF velocity, as measured by transcranial Doppler, decreased with increasing concentrations of dexmedetomidine in parallel with decreasing mean arterial pressure and increasing arterial carbon dioxide. [559] In a rat seizure model, dexmedetomidine demonstrated significant proconvulsant action, which is consistent with previous findings that inhibition of central nor-adrenergic transmission facilitates seizure expression. [560] This finding, however, is in contrast to an anticonvulsant effect shown in rats following kainic acid-induced seizures. [561] As yet, in the limited number of administrations of dexmedetomidine, there have been no reports of seizures in humans. Dexmede-tomidine is also able to reduce muscle rigidity following high-dose opioid administration. [562] In resting volunteers, dexmede-tomidine increased growth

hormone secretion in a dosedependent manner, but it had no effect on other pituitary hormones. [550] [563]

Effects on the Respiratory System

Doses of 1 to 2 mug/kg of dexmedetomidine induce a mild increase in Pa CO_2 (45 mm Hg) and a rightward shift and depression of the carbon dioxide-response curves. The changes in respiration are mainly a decrease in tidal volume with little change in respiratory frequency. [558] When combined with alfentanil, dexmedetomidine enhances analgesia without causing further respiratory depression.

Effects on the Cardiovascular System

The basic effects of alpha$_2$ -agonists on the cardiovascular system are decreased heart rate, decreased systemic vascular resistance, and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure. By developing highly selective alpha-agonists, it has been hoped to decrease some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. Thus far, dexmedetomidine is the most selective alpha $_2$ -agonist that is likely to be used in clinical practice. The hemodynamic effects of dexmedetomidine in humans have shown a biphasic response. An acute intravenous injection of 2 mug/kg resulted in an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at 5 minutes following injection. This initial increase in blood pressure is probably due to the effect of dexmedetomidine on peripheral alpha $_2$ -receptors. Heart rate returned to baseline by 15 minutes, and blood pressure gradually drifted down to approximately 15 percent below baseline by 1 hour. Following an intramuscular injection of the same dose, the initial increase in blood pressure was not seen, and both heart rate and blood pressure remained within 10 percent of baseline. [549] In dogs, oral doses of dexmedetomidine both alone and in the presence of halothane did not alter baroreflex activity. In several studies following both intramuscular and intravenous administration, dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/pause. Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. In animal models, dexmedetomidine demonstrated some beneficial effects on the ischemic heart through decreased oxygen consumption and redistribution of coronary flow from nonischemic zones to ischemic zones following acute brief occlusion. [564] Thus far, human studies have not shown clear clinical benefits of dexmedetomidine infusions in patients at risk for myocardial ischemia.

Other Effects

A frequently reported side effect of dexmedetomidine has been a dry mouth, which is due to a decrease in saliva production. [565]

Uses

Unlike the other drugs described in this chapter, dexmedetomidine is not indicated for the induction of anesthesia. Its role is likely to be as a preoperative sedative, an adjuvant during anesthesia to reduce hypnotic and opioid requirements, and possible postoperatively in patients at high risk for myocardial ischemia.

Sedation

As a premedicant, dexmedetomidine, at intravenous doses of 0.33 to 0.67 mug/kg given 15 minutes prior to surgery, appears efficacious while minimizing the cardiovascular side effects of hypotension and bradycardia. [566] Within this dosage range, dexmedetomidine reduces thiopental requirements (by 30%) for short procedures, [566] [567] reduces the requirements of volatile anesthetics (by 25%), and as compared with 2 mug/kg fentanyl, more effectively attenuates the hemodynamic response to endotracheal intubation. [568] Dexmedetomidine has also been evaluated as an intramuscular injection (2.5 mug/kg) with or without fentanyl administered 45 to 90 minutes prior to surgery. This regimen was compared with intramuscular midazolam plus fentanyl and was found to provide equal anxiolysis, reduced response to intubation, lower volatile anesthetic requirements, and a lower incidence of postoperative shivering but a higher incidence of bradycardia. Atipamezole, a selective alpha $_2$ -antagonist, at 50 mug/kg was effective in reversing the sedation of dexmedetomidine, 2 mug/kg intramuscularly, when used to provide sedation for brief operative procedures. [553] This reversal of effects resulted in a more rapid recovery than occurred after equi-sedative doses of midazolam.

Clonidine, in doses of 3 to 5 mug/kg orally, usually given 30 to 90 minutes prior to surgery, similarly reduces the MAC of the potent volatile anesthetics (by 30-50%), reduces opioid requirements, attenuates the hemodynamic responses to intubation, and generally provides a more stable hemodynamic profile intraoperatively, [543] [569] [570] although significant bradycardia and hypotension during and immediately after induction have been observed. This reduction in anesthetic requirements also translates into a more rapid awakening after surgery. [571] Clonidine also reduces intraocular pressure, reduces perioperative catecholamines, decreases postoperative analgesic requirements, and prevents the usual deterioration in renal function following aortocoronary bypass. [538] [543] [571] [572] As with clonidine, with dexmedetomidine intraocular pressure is decreased (33%), catecholamine secretion is reduced, perioperative analgesic requirements are less, and recovery is more rapid. [573] [574]

Maintenance of Anesthesia

Dexmedetomidine has also been used as a maintenance infusion starting with a loading dose of 170 ng/kg/min for 10 minutes followed by an infusion of 10 ng/kg/min. This resulted in a plasma concentration of slightly less than 1 ng/ mL, so that dexmedetomidine, after induction with thiopental and combined with 70 percent nitrous oxide, reduced isoflurane requirements by 90 percent as compared with a control group. [575] The interaction of dexmedetomidine, fentanyl, and enflurane on MAC reduction and hemodynamics has been evaluated in dogs. This triple combination is complex, but it appears that dexmedetomidine further enhances the MAC reduction of enflurane by fentanyl. This triple interaction, however, does not seem to reduce the likelihood of hypotension or bradycardia in providing adequate anesthesia. [576] In patients presenting for vascular surgery, three infusion rates of dexmedetomidine were compared with a placebo infusion starting 1 hour prior to surgery and administered until 48 hours after surgery. In the groups receiving dexmedetomidine, more vasoactive agents were required to maintain hemodynamics intraoperatively, but less tachycardia was noted postoperatively. No other significant differences were noted between the groups. [577] There are currently large studies evaluating the use of a maintenance infusion of dexmedetomidine for several surgical procedures. The results of these studies are likely to more clearly define the role of dexmedetomidine as a possibly useful adjuvant during anesthesia.

The alpha$_2$ -adrenergic agonists possess many important characteristics that are valuable for anesthesia. It would appear, however, that at anesthetic concentrations in humans, the cardiovascular effects (hypotension and/or bradycardia) of these drugs may be their major drawback, preventing them from being used as the primary anesthetic and thereby limiting their role to that of an adjuvant for other anesthetic drugs. The exact role of dexmedetomidine either as a premedicant or as an intravenous anesthetic adjuvant is still to be determined.

SUMMARY

Many different intravenous drugs are available for use in the care of patients requiring general anesthesia. The selection of a particular drug must be based on the individual patient's need for hypnosis, amnesia, and analgesia. Drug selection must match the physiology and/or the pathophysiology of the individual patient with the pharmacology of the particular drug. Thus, for example, a patient in shock who requires anesthesia induction should receive the drug that will produce rapid onset of effect without causing further hemodynamic compromise. The knowledge of the clinical pharmacology of each of the intravenous anesthetic drugs enables the clinician to induce and maintain sedation and/or general anesthesia safely and effectively. There is no single perfect drug for any particular patient, but rather the informed practitioner wisely employs the appropriate drug or drugs in the practice of good anesthesia care.

References

1. Cohen MM, Duncan PG, Tate RB: Does anesthesia contribute to operative mortality? JAMA 260:2859, 1988.

2. Greenblatt DJ, Shader RI: Benzodiazepines in Clinical Practice. New York, Raven Press, 1974.

3. Randall LO, Schallek W, Heise GA et al: The psychosedative properties of methaminodiazepoxide. J Pharmacol Exp Ther 129:163, 1960.

4. Lemere F: Toxic reactions to chlordiazepoxide. JAMA 174:893, 1960.

5. Walser A, Benjamin LES, Flynn T et al: Quinazolines and 1,4-benzodiazepines. 84. Synthesis and reactions of imidazo (1,5alpha)(1,4)-benzodiazepines. J Org Chem 43:936, 1978.

6. Urban BJ, Amaha K, Steen SN: Investigation of 1-4-benzodiazepine derivatives as basal anesthetic agents. Anesth Analg 45:733, 1966.

7. McClish A: Diazepam as an intravenous induction agent for general anesthesia. Can J Anaesth 13:562, 1966.

8. Stovner J, Endresen R: Intravenous anaesthesia with diazepam. Acta Anaesth Scand Suppl 24:223, 1966.

9. Reves JG, Fragen RJ, Vinik HR et al: Midazolam: Pharmacology and uses. Anesthesiology 62:310, 1985.

10. Haefely W, Hunkeler W: The story of flumazenil. Eur J Anaesthesiol 2:3, 1988.

11. Barnett A, Fiore JW: Acute tolerance to diazepam in cats and its possible relationship to diazepam metabolism. Eur J Pharmacol 13:239, 1971.

12. Squires RF, Braestrup C: Benzodiazepine receptors in rat brain. Nature 266:732, 1977.

13. Greenblatt DJ, Shader RI, Abernethy DR: Medical intelligence drug therapy: Current status of benzodiazepines. N Engl J Med 309:354, 1983.

14. Arendt RM, Greenblatt DJ, DeJong RH et al: In vitro correlates of benzodiazepine cerebrospinal fluid uptake, pharmacodynamic action and peripheral distribution. J Pharmacol Exp Ther 227:98, 1983.

15. Elliott HW: Metabolism of lorazepam. Br J Anaesth 48:1017, 1976.

16. Blitt CD: Clinical pharmacology of lorazepam. In Brown BRJ (ed): New Pharmacologic Vistas in Anesthesia. Philadelphia, FA Davis, 1983, p 135.

17. Klotz U, Reimann I: Elevation of steady-state diazepam levels by cimetidine. Clin Pharmacol Ther 30:513, 1981.

18. Reves JG: Benzodiazepines. In Prys-Roberts C, Hugg CC (eds): Pharmacokinetics of Anesthesia. Boston, Blackwell Scientific Publications, 1984, p 157.

19. Ihmsen H, Hering W, Albrecht S et al: Pharmacokinetics of the new benzodiazepines RO48-6791 and RO48-8684 in comparison with midazolam in young and elderly volunteers. Anesthesiology 85:A317, 1996.

20. Kassai A, Eichelbaum M, Klotz U: No evidence of a genetic polymorphism in the oxidative metabolism of midazolam. Clin Pharmacokinet 15:319, 1988.

21. Bertilsson L: Geographical/interracial differences in polymorphic drug oxidation: Current state of knowledge of cytochromes P450 (CYP) 2D6 and 2C19. Clin Pharmacokinet 29:192, 1995.

22. Barr J, Donner A: Optimal intravenous dosing strategies for sedatives and analgesics in the intensive care unit. Crit Care Clin 11:827, 1995.

23. Mandema JW, Tuk B, van Steveninck AL et al: Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of mid-azolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. Clin Pharmacol Ther 51:715, 1992.

24. Bauer TM, Ritz R, Haberthur C et al: Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet 346:145, 1995.

25. Greenblatt DJ, Shader RI, Harmatz JS: Benzodiazepines: A summary of pharmacokinetic properties. Br J Clin Pharmacol 11:11, 1981.

26. MacLeod SM, Giles HG, Bengert B: Age- and gender-related differences in diazepam pharmacokinetics. J Clin Pharmacol 19:15, 1979.

27. Greenblatt DJ, Abernethy DR, Loeniskar A et al: Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 61:27, 1984.

28. Mould DR, DeFeo TM, Reele S et al: Simultaneous modeling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam. Clin Pharmacol Ther 58:35, 1995.

29. Mohler H, Richards JG: The benzodiazepine receptor: A pharmacological control element of brain function. Eur J Anaesthesiol 2:15, 1988.

30. Amrein R, Hetzel W: Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). Acta Anaesthesiol Scand 92:6, 1990.

31. Mendelson WB: Neuropharmacology of sleep induction by benzodiazepines. Neurobiology 16:221, 1992.

32. Amrein R, Hetzel W, Harmann D, et al: Clinical pharmacology of flumazenil. Eur J Anaesthesiol 2:65, 1988.

33. Strange PG: D1/D2 dopamine receptor interaction at the biochemical level. Trends Pharmacol Sci 12:48, 1991.

34. Haefely W: The preclinical pharmacology of flumazenil. Eur J Anaesthesiol 2:25, 1988.

35. Miller LG: Chronic benaodiazepine administration: From the patient to the gene. J Clin Pharmacol 31:492, 1991.

36. Breimer LTM, Burm AGL, Danhof M et al: Pharmacokinetic-pharmacodynamic modelling of the interaction between flumazenil and midazolam in volunteers by aperiodic EEG analysis. Clin Pharmacokinet 20:497, 1991.

37. Hering W, Ihmsen H, Albrecht S et al: CNS effects of the new benzodiazepines RO48-6791 and RO48-8684 compared to midazolam in young and elderly volunteers. Anesthesiology 85:A189, 1996.

38. Persson MP, Nilsson A, Hartvig P: Relation of sedation and amnesia to plasma concentrations of midazolam in surgical patients. Clin Pharmacol Ther 43:324, 1988.

39. Forster A, Juge O, Morel D: Effects of midazolam on cerebral blood flow in human volunteers. Anesthesiology 53:A263, 1981.

40. Brown CR, Sarnquist FH, Canup CA et al: Clinical electroencephalographic and pharmacokinetic studies of water-soluble benzodiazepine, midazolam maleate. Anesthesiology 50:467, 1979.

41. de Jong RH, Bonin JD: Benzodiazepines protect mice from local anesthetic convulsions and deaths. Anesth Analg 60:385, 1981.

42. Denault M, Yernault JC, DeCoster A: Double-blind comparison of the respiratory effects of parenteral lorazepam and diazepam in patients with chronic obstructive lung disease. Curr Med Res Opin 2:611, 1975.

43. Forster A, Gardaz JP, Suter PM et al: Respiratory depression by midazolam and diazepam. Anesthesiology 53:494, 1980.

44. Sunzel M, Paalzow L, Berggren L et al: Respiratory and cardiovascular effects in relations to plasma levels of midazolam and diazepam. Br J Clin Pharmacol 25:561, 1988.

45. Gross JB, Zebrowski ME, Carel WD et al: Time course of ventilatory depression after thiopental and midazolam in normal subjects and in patients with chronic obstructive pulmonary disease. Anesthesiology 58:540, 1983.

46. Brodgen RN, Goa KL: Flumazenil. Drugs 42:1061, 1991.

47. Alexander CM, Teller LE, Gross JB: Slow injection does not prevent midazolam-induced ventilatory depression. Anesth Analg 74:260, 1992.

48. Paulson BA, Becker LD, Way WL: The effects of intravenous lorazepam alone and with meperidine on ventilation in man. Acta Anaesthesiol Scand 27:400, 1983.

49. Samuelson PN, Reves JG, Kouchoukos NT et al: Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. Anesth Analg 60:802, 1981.

50. Rao S, Sherbaniuk RW, Prasad K et al: Cardiopulmonary effects of diazepam. Clin Pharmacol Ther 14:182, 1973.

51. Samuelson PN, Lell WA, Kouchoukos NT et al: Hemodynamics during diazepam induction of anesthesia for coronary artery bypass grafting. South Med J 73:332, 1980.

52. Cote P, Gueret P, Courassa MG: Systemic and coronary hemodynamic effects of diazepam in patients with normal and diseased coronary arteries. Circulation 50:1210, 1974.

53. Reves JG, Samuelson PN, Lewis S: Midazolam maleate induction in patients with ischaemic heart disease: Haemodynamic observations. Can J Anaesth 26:402, 1979.

54. Reves JG, Samuelson PN, Linnan M: Effects of midazolam maleate in patients with elevated pulmonary artery occluded pressure. In Aldrete JA, Stanley TH (eds): Trends in Intravenous Anesthesia. Chicago, Year Book, 1980, p 253.

55. Elliott HW, Nomof N, Navarro G et al: Central nervous system and cardiovascular effects of lorazepam in man. Clin Pharmacol Ther 12:468, 1971.

56. Ruff R, Reves JG: Hemodynamic effects of a lorazepam-fentanyl anesthetic induction for coronary artery bypass surgery. J Cardiothorac Anesth 4:314, 1990.

57. Reves JG, Gelman S: Cardiovascular effects of intravenous anesthetic drugs. In Covino BG, Fozzard HA, Rehder K, et al (eds): Effects of Anesthesia. Bethesda, Md, American Physiological Society, 1985, p 179.

58. Marty J, Gauzit R, Lefevre P et al: Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans. Anesth Analg 65:113, 1986.

59. Lebowitz PW, Core ME, Daniels AL et al: Comparative cardiovascular effects of midazolam and thiopental in healthy patients. Anesth Analg 61:771, 1982.

60. Croughwell N, Reves JG, Hawkins E: Cardiovascular changes after midazolam in patients with aortic stenosis: Effects of nitrous oxide. Anesth Analg 67:S1, 1988.

61. Tomichek RC, Rosow CE, Schneider RC et al: Cardiovascular effects of diazepam-fentanyl anesthesia in patients with coronary artery disease. Anesth Analg 61:217, 1982.

62. Heikkila H, Jalonen J, Arola M et al: Midazolam as adjunct to high-dose fentanyl anaesthesia for coronary artery bypass grafting operation. Acta Anaesthesiol Scand 28:683, 1984.

63. Benson KT, Tomlinson DL, Goto H et al: Cardiovascular effects of lorazepam during sufentanil anesthesia. Anesth Analg 67:966, 1988.

64. Windsor JPW, Sherry K, Feneck RO et al: Sufentanil and nitrous oxide anaesthesia for cardiac surgery. Br J Anaesth 61:662, 1988.

65. Reves JG, Croughwell N: Valium-fentanyl interaction. In Reves JG, Hall K (eds): Common Problems in Cardiac Anaesthesia. Chicago, Year Book, 1987, p 356.

66. Cole SG, Brozinsky S, Isenberg JI: Midazolam, a new more potent benzodiazepine, compared with diazepam: A randomized, double-blind study of preendoscopic sedatives. Gastrointest Endosc 29:219, 1983.

67. George KA, Dundee JW: Relative amnestic actions of diazepam, flunitrazepam and lorazepam in man. Br J Clin Pharmacol 4:45, 1977.

68. Fragen RJ, Caldwell N: Lorazepam premedication: Lack of recall and relief anxiety. Anesth Analg 55:792, 1976.

69. McNulty SE, Gratch D, Costello D et al: The effect of midazolam and lorazepam on postoperative recovery after cardiac surgery. Anesth Analg 81:404, 1995.

70. Gauthier RA, Dyck B, Chung F et al: Respiratory interaction after spinal anesthesia sedation with midazolam. Anesthesiology 77:909, 1992.

71. Shapiro BA, Warren J, Egol AB et al: Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: An executive summary. Crit Care Med 23:1596, 1995.

72. Cernaianu AC, DelRossi AJ, Flum DR et al: Lorazepam and midazolam in the intensive care unit: A randomized, prospective, multicenter study of hemodynamics, oxygen transport, efficacy, and cost. Crit Care Med 24:222, 1996.

73. Kanto J, Sjovall S, Vuori A: Effect of different kinds of premedication on the induction properties of midazolam. Br J Anaesth 54:507, 1982.

74. Gamble JAS, Kawar P, Dundee JW et al: Evaluation of midazolam as an intravenous induction agent. Anaesthesia 36:868, 1981.

75. Jacobs JR, Reves JG, Marty J et al: Aging increases pharmacodynamic sensitivity to the hypnotic effects of midazolam. Anesth Analg 80:143, 1995.

76. Vinik HR, Bradley EL, Kissin I: Midazolam-alfentanil synergism for anesthetic induction in patients. Anesth Analg 69:213, 1989.

77. Vinik HR, Bradley JEL, Kissin I: Triple anesthetic combination: Propofol-midazolam-alfentanil. Anesth Analg 78:354, 1994.

78. Forster A, Gardaz JP, Suter PM et al: I.V. midazolam as an induction agent for anaesthesia: A study in volunteers. Br J Anaesth 52:907, 1980.

79. Reves JG, Vinik R, Hirschfield AM et al: Midazolam compared with thiopentone as a hypnotic component in balanced anaesthesia: A randomized, double-blind study. Can J Anaesth 26:42, 1979.

80. Norton AC, Dundas CR: Induction agents for day-case anaesthesia. Anaesthesia 45:198, 1990.

81. Crawford ME, Carl P, Andersen RS et al: Comparison between mid-azolam and thiopentone-based balanced anaesthesia for day-care surgery. Br J Anaesth 56:165, 1984.

82. Melvin MA, Johnson BH, Quasha AL et al: Induction of anesthesia with midazolam decreases halothane MAC in humans. Anesthesiology 57:238, 1982.

83. Theil DR, Stanley TE, White WD et al: Continuous intravenous anesthesia for cardiac surgery: A comparison of two infusion systems. J Thorac Cardiovasc Anesth 7:300, 1993.

84. Nilsson A, Persson MP, Hartvig P et al: Effect of total intravenous anaesthesia with midazolam/alfentanil on the adrenocortical and hyperglycaemic response to abdominal surgery. Acta Anaesthesiol Scand 32:379, 1988.

85. File SE, Pellow S: Intrinsic actions of the benzodiazepine receptor antagonist RO 15-1788. Psychopharmacology (Berl) 88:I, 1986.

86. Limbird LE: Cell Surface Receptors: A Short Course on Theory and Methods. Boston, 1986, p 42.

87. Lauven P, Schwilden H, Stoeckel H et al: The effect of a benzodiazepine antagonist Ro15-1788 in the presence of stable concentrations of midazolam. Anesthesiology 63:61, 1985.

88. Cumin R, Bonetti EP, Scherschlicht R et al: Use of the specific benzodiazepine antagonist, Ro15-1788, in studies of physiological dependence on benzodiazepines. Experientia 38:833, 1982.

89. Hunkeler W: Preclinical research findings with flumazenil (Ro15-1788, Anexate): Chemistry. Eur J Anaesthesiol 2:37, 1988.

90. Klotz U: Drug interactions and clinical pharmacokinetics of flumazenil. Eur J Anaesthesiol 2:103, 1988.

91. Klotz U, Kanto J: Pharmacokinetics and clinical use of flumazenil (Ro15-1788). Clin Pharmacokinet 14:1, 1988.

92. Breimer LTM, Hennis PJ, Burm AGL et al: Pharmacokinetics and EEG effects of flumazenil in volunteers. Clin Pharmacokinet 20:491, 1991.

93. Kleinberger G, Grimm G, Laggner A et al: Weaning patients from mechanical ventilation by benzodiazepine antagonist Ro15-1788. Lancet 2:268, 1986.

94. Knudsen L, Cold GE, Holdgard HO et al: Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy. Br J Anaesth 67:277, 1991.

95. Wolf J, Friberg L, Jensen J et al: The effect of the benzodiazepine antagonist flumazenil on regional cerebral blood flow in human volunteers. Acta Anaesthesiol Scand 34:628, 1990.

96. Yokoyama M, Benson KT, Arakawa K et al: Effects of flumazenil on intravenous lidocaine-induced convulsions and anticonvulsant property of diazepam in rats. Anesth Analg 75:87, 1992.

97. Dunton AW, Schwam E, Pitman V et al: Flumazenil: U.S. clinical pharmacology studies. Eur J Anaesthesiol 2:81, 1988.

98. Forster A, Juge O, Louis M et al: Effects of a specific benzodiazepine antagonist (Ro15-1788) on cerebral blood flow. Anesth Analg 66:309, 1987.

99. Samson Y, Hantraye P, Baron JC et al: Kinetics and displacement of (11C) Ro15-1788, a benzodiazepine antagonist, studied in human brain in vivo by positron tomography. Eur J Pharmacol 110:247, 1985.

100. Dunton AW, Schwam E, Pitman V et al: The relationship between dose and duration of action of intravenous flumazenil in reversing sedation induced by a continuation infusion of midazolam. Eur J Anaesthesiol 2:97, 1988.

101. Philip BK, Simpson TH, Hauch MA et al: Flumazenil reverses sedation after midazolam-induced general anesthesia in ambulatory surgery patients. Anesth Analg 71:371, 1990.

102. Forster A, Crettenand G, Morel DR: Absence of ventilatory agonist or inverse agonist effects of an overdose of Ro15-1788: A specific benzodiazepine antagonist. Anesthesiology 67:A144, 1987.

103. Rouiller M, Forster A, Gemperle M: Evaluation de l'efficacite et de la tolerance d'un antagoniste des benzodiazepines (Ro15-1788). Ann Fr Anesth Reanim 6:1, 1987.

104. Weinbrum A, Geller E: The respiratory effects of reversing midazolam sedation with flumazenil in the presence or absence of narcotics. Acta Anaesthesiol Scand 92:65, 1990.

105. Croughwell N, Reves JG, Will CJ et al: Safety of flumazenil in patients with ischemic heart disease. Eur J Anaesthesiol 2:177, 1988.

106. Duka T, Achenheil M, Noderer J et al: Changes in noradrenaline plasma levels and behavioral responses induced by benzodiazepine agonists with the benzodiazepine antagonist Ro15-1788. Psychopharmacology (Berl) 90:351, 1986.

107. Geller E, Halpern P, Chernilas J et al: Cardiorespiratory effects of antagonism of diazepam sedation with flumazenil in patients with cardiac disease. Anesth Analg 72:207, 1991.

108. Nilsson A: Autonomic and hormonal responses after the use of mid-azolam and flumazenil. Acta Anaesthesiol Scand 92:51, 1990.

109. Marty J, Joyon D: Haemodynamic responses following reversal of benzodiazepine-induced anaesthesia or sedation with flumazenil. Eur J Anaesthesiol 2:167, 1988.

110. White PF, Shafer A, Boyle WA et al: Benzodiazepine antagonism does not provoke a stress response. Anesthesiology 70:636, 1989.

111. Whitwam JG, Amrein R: Pharmacology of flumazenil. Acta Anaesthesiol Scand Suppl 108:3, 1995.

112. Ghoneim MM, Dembo JB, Block RI: Time course of antagonism of sedative and amnesic effects of diazepam by flumazenil. Anesthesiology 70:899, 1989.

113. Curran HV, Birch B: Differentiating the sedative, psychomotor and amnesic effects of benzodiazepines: A study with midazolam and the benzodiazepine antagonist, flumazenil. Psychopharmacology (Berl) 103:519, 1991.

114. Greifenstein FE, DeVault M, Yoshitake J et al: A study of a 1-aryl cyclo hexyl amine for anesthesia. Anesth Analg 37:283, 1958.

115. Johnstone M, Evans V, Baigel S: Sernyl (CI-395) in clinical anesthesia. Br J Anaesth 31:433, 1959.

116. Lear E, Suntay R, Pallin IM et al: Cyclohexamine (CI-400): A new intravenous agent. Anesthesiology 20:330, 1959.

117. Corssen G, Domino EF: Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg 45:29, 1966.

118. White PF, Way WL, Trevor AJ: Ketamine: Its pharmacology and therapeutic uses. Anesthesiology 56:119, 1982.

119. Corssen G, Reves JG, Stanley TH: Dissociative anesthesia. In Intravenous Anesthesia and Analgesia. Philadelphia, Lea & Febiger, 1988, p 99.

120. Cohen ML, Trevor AJ: On the cerebral accumulation of ketamine and the relationship between metabolism of the drug and its pharmacological effects. J Pharmacol Exp Ther 189:351, 1974.

121. Chang T, Glazko AJ: Biotransformation and disposition of ketamine. Int Anesthesiol Clin 12:157, 1974.

122. Cheng G: The pharmacology of ketamine. In Kreuscher E (ed): Ketamine. Berlin, Springer-Verlag, 1969, p 1.

123. White PF, Johnston RR, Pudwill CR: Interaction of ketamine and halothane in rats. Anesthesiology 42:179, 1975.

124. Cohen ML, Chan SL, Bhargava HN et al: Inhibition of mammalian brain acetylcholinesterase by ketamine. Biochem Pharmacol 23:1647, 1974.

125. Clements JA, Nimmo WS: The pharmacokinetics and analgesic effect of ketamine in man. Br J Anaesth 53:27, 1981.

126. Grant IS, Nimmo WS, Clements JA: Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth 53:805, 1981.

127. Idvall J, Ahlgren I, Aronsen KF et al: Ketamine infusions: Pharmacokinetics and clinical effects. Br J Anaesth 51:1167, 1979.

128. Nimmo WS, Clements JA: Ketamine. In Prys-Roberts C, Hug CC, (eds): Pharmacokinetics of Anesthesia. Boston, Blackwell Scientific Publications, 1984, p 235.

129. White PF, Marietta MP, Pudwill CR et al: Effects of halothane anesthesia on the biodisposition of ketamine in rats. J Pharmacol Exp Ther 196:545, 1976.

130. Taylor PA, Towey RM: Depression of laryngeal reflexes during ketamine anesthesia. BMJ 2:688, 1971.

131. Grant IS, Nimmo WS, McNicol LR et al: Ketamine disposition in children and adults. Br J Anaesth 55:1107, 1983.

132. Corssen G, Miyasaka M, Domino EF: Changing concepts in pain control during surgery: Dissociative anesthesia with CI-581: A progress report. Anesth Analg 47:746, 1968.

133. Adams HA, Thiel A, Jung A et al: Studies using S-(+)-ketamine on probands: Endocrine and circulatory reactions, recovery and dream experiences. Anaesthesist 41:588, 1992.

134. Kharasch ED, Labroo R: Metabolism of ketamine stereoisomers by human liver microsomes. Anesthesiology 77:1201, 1992.

135. Domino EF, Chodoff P, Corssen G: Pharmacologic effects of CI-581, a new dissociative anesthetic in man. Clin Pharmacol Ther 6:279, 1965.

136. Okamoto GU, Duperon DF, Jedrychowski JR: Clinical evaluation of the effects of ketamine sedation on pediatric dental patients. J Clin Pediatr Dent 16:253, 1992.

137. Doenicke A, Kugler J, Mayer M et al: Ketamineracemate or S-(+)-ketamine and midazolam: The effect on vigilance, efficacy and subjective findings. Anaesthesist 41:610, 1992.

138. Miyasaka M, Domino EF: Neuronal mechanisms of ketamine-induced anesthesia. Neuropharmacology 7:557, 1968.

139. Sparkes DL, Corssen G, Aizenman B et al: Further studies of the neural mechanisms of ketamine-induced anesthesia in the rhesus monkey. Anesth Analg 54:189, 1975.

140. Massopust LC, Wolin LR, Albin MS: Electrophysiologic and behavioral responses to ketamine hydrochloride in the rhesus monkey. Anesth Analg 51:329, 1972.

141. Ohtani M, Kikuchi H, Kitahata LM et al: Effects of ketamine on nociceptive cells in the medial medullary reticular formation of the cat. Anesthesiology 51:414, 1979.

142. Frenkel C, Urban BW: Molecular actions of racemic ketamine on human CNS sodium channels. Br J Anaesth 69:292, 1992.

143. Finck AD, Ngai SH: A possible mechanism of ketamine-induced analgesia. Anesthesiology 51:S34, 1979.

144. Fratta W, Casu M, Belestrieri A et al: Failure of ketamine to interact with opiate receptors. Eur J Pharmacol 61:389, 1980.

145. Freye E, Latasch L, Schmidhammer H: Pharmacodynamic effects of S-(+)-ketamine on EEG, evoked potentials and respiration: A study in the awake dog. Anaesthesist 41:527, 1992.

146. Irifune M, Shimizu T, Nomoto M et al: Ketamine-induced anesthesia involves the *N*-methyl-D-aspartate receptor-channel complex in mice. Brain Res 596:1, 1992.

147. Klepstad P, Maurset A, Moberg ER: Evidence of a role for NMDA receptors in pain perception. Eur J Pharmacol 187:513, 1990.

148. Oye I, Paulsen O, Maurset A: Effects of ketamine on sensory perception: Evidence for a role of *N*-methyl-D-aspartate receptors. J Pharmacol Exp Ther 260:1209, 1992.

149. Nagasaka H, Nagasaka I, Sato I et al: The effects of ketamine on the excitation and inhibition of dorsal horn WDR neuronal activity induced by bradykinin injection into the femoral artery in cats after spinal cord transection. Anesthesiology 78:722, 1993.

150. Kayama Y, Iwama K: The EEG, evoked potentials, and single-unit activity during ketamine anesthesia in cats. Anesthesiology 36:316, 1972.

151. Gardner AE, Dannemiller FJ, Dean D: Intracranial cerebrospinal fluid pressure in man during ketamine anesthesia. Anesth Analg 51:741, 1972.

152. Shapiro HM, Wyte SR, Harris AB: Ketamine anaesthesia in patients with intracranial pathology. Br J Anaesth 44:1200, 1972.

153. Dawson B, Michenfelder D, They A: Effects of ketamine on canine cerebral blood flow and metabolism: Modification by prior administration of thiopental. Anesth Analg 50:443, 1971.

154. Thorsen T, Gan L: Ketamine/diazepam infusion anaesthesia with special attention to the effect on cerebrospinal fluid pressure and arterial blood pressure. Acta Anaesthesiol Scand 24:1, 1980.

155. Garfield JM: A comparison of psychologic responses to ketamine and thiopental-nitrous oxide-halothane anesthesia. Anesthesiology 36:329, 1972.

156. Sussman DR: A comparative evaluation of ketamine anesthesia in children and adults. Anesthesiology 40:459, 1974.

157. Dundee JW, Bovill JG, Clarke RSJ et al: Problems with ketamine in adults. Anaesthesia 26:86, 1971.

158. Khorramzadeh E, Lofty AO: Personality predisposition and emergence phenomena with ketamine. Psychosomatics 17:94, 1976.

159. Kumar A, Bajaj A, Sarkar P et al: The effect of music on ketamine induced emergence phenomena. Anaesthesia 47:438, 1992.

160. Hejja P, Galloon S: A consideration of ketamine dreams. Can J Anaesth 22:100, 1975.

161. Wulfsohn NL: Ketamine dosage for induction based on lean body mass. Anesth Analg 51:299, 1972.

162. Johnson M: The prevention of ketamine dreams. Anaesth Intensive Care 1:70, 1972.

163. Dundee JW, Lilburn JK: Ketamine-lorazepam: Attenuation of the psychic sequelae of ketamine by lorazepam. Anaesthesia 37:312, 1977.

164. Kothary SP, Zsigmond EK: A double-blind study of the effective anti-hallucinatory doses of diazepam prior to ketamine anesthesia. Clin Pharmacol Ther 21:108, 1977.

165. Doenicke A, Angster R, Mayer M et al: The action of S-(+)-ketamine on serum catecholamine and cortisol: A comparison with ketamine racemate. Anaesthesist 41:597, 1992.

166. Soliman MG, Brinale GF, Kuster G: Response to hypercapnia under ketamine anaesthesia. Can Anaesth Soc J 22:486, 1975.

167. Virtue RW, Alanis JM, Mori M et al: An anesthetic agent: 2-Orthochlorophenyl, 2-methylamino cyclohexanone CI-581. Anesthesiology 28:823, 1967.

168. Stanley V, Hunt J, Wilis KW et al: Cardiovascular and respiratory function with CI-581. Anesth Analg 47:760, 1968.

169. Dillon JB: Clinical experience with repeated ketamine administration for procedures requiring anesthesia. In Kreuscher H (ed): Ketamine. Berlin, Springer-Verlag, 1969.

170. Hamza J, Ecoffey L, Gross JB: Ventilatory response to CO_2 following intravenous ketamine in children. Anesthesiology 70:422, 1989.

171. Greene CA, Gillette PC, Fyfe DA: Frequency of respiratory compromise after ketamine sedation for cardiac catheterization in patients <21 years of age. Am J Cardiol 68:1116, 1991.

172. Huber FC, Reves JG, Gutierrez J et al: Ketamine: Its effect on airway resistance in man. South Med J 65:1176, 1972.

173. Corssen G, Gutierrez J, Reves JG et al: Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 51:588, 1972.

174. Hirshman CA: Ketamine block of bronchospasm in experimental canine asthma. Br J Anaesthesiol 51:713, 1979.

175. Wanna HT, Gergis SD: Procaine, lidocaine and ketamine inhibit his-tamine-induced contracture of guinea pig tracheal muscle in vitro. Anesth Analg 57:25, 1978.

176. Sarma VJ: Use of ketamine in acute severe asthma. Acta Anaesthesiol Scand 36:106, 1992.

177. Sonntag H, Heiss HW, Knoll D et al: Coronary blood flow and myocardial oxygen consumption in patients during induction of anesthesia with droperidol/fentanyl or ketamine. Z Kreislaufforsch 61:1092, 1972.

178. Zsigmond EK, Domino EF: Clinical pharmacology and current uses of ketamine. In Aldrete JA, Stanley TH (eds): Trends in Intravenous Anesthesia. Chicago, Year Book, 1980, p 283.

179. Savege TM, Colvin MP, Weaver EJM et al: A comparison of some cardiorespiratory effects of althesin and ketamine when used for induction of anaesthesia in patients with cardiac disease. Br J Anaesth 48:1071, 1976.

180. Gooding JM, Dimick AR, Tavakoli M et al: A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. Anesth Analg 56:813, 1977.

181. Reves JG, Lell WA, McCracken LE Jr et al: Comparison of morphine and ketamine anesthetic techniques for coronary surgery: A randomized study. South Med J 71:33, 1978.

182. Spotoft H, Korshin JD, Sorensen MB et al: The cardiovascular effects of ketamine used for induction of anaesthesia in patients with valvular heart disease. Can J Anaesth 26:463, 1979.

183. Morray JP, Lynn AM, Stamm SJ et al: Hemodynamic effects of ketamine in children with congenital heart disease. Anesth Analg 63:895, 1984.

184. Greeley WJ, Bushman GA, Davis DP et al: Comparative effects of halothane and ketamine on systemic oxygen saturation in children with cyanotic heart disease. Anesthesiology 65:666, 1986.

185. Faithfull NS, Haider R: Ketamine for cardiac catheterization: An evaluation of its use in children. Anaesthesia 26:318, 1971.

186. Hickey PR, Hansen DD, Cramolini GM et al: Pulmonary and systemic hemodynamic responses to ketamine in infants with normal and elevated pulmonary vascular resistance. Anesthesiology 62:287, 1985.

187. Slogoff S, Allen GW: The role of baroreceptors in the cardiovascular response to ketamine. Anesth Analg 53:704, 1974.

188. Dowdy EG, Kaya K: Studies of the mechanism of cardiovascular responses to CI-581. Anesthesiology 29:931, 1968.

189. Chodoff P: Evidence for central adrenergic action of ketamine. Anesth Analg 51:247, 1972.

190. Wong DHW, Jenkins LC: An experimental study of the mechanism of action of ketamine on the central nervous system. Can J Anaesth 21:57, 1974.

191. Iwatsuki M, Aoba Y, Sato K et al: Clinical study of CI-581, a phencyclidine derivative. Tohoku J Exp Med 93:39, 1967.

192. Ogawa A, Uemura M, Kataoka Y et al: Effects of ketamine on cardiovascular responses mediated by *N*-methyl-D-aspartate receptor in the rat nucleus tractus solitarius. Anesthesiology 78:163, 1993.

193. Ivankovich AD, Miletich DJ, Reimann C et al: Cardiovascular effects of centrally administered ketamine in goats. Anesth Analg 53:924, 1974.

194. Zsigmond EK, Kothary SP, Matsuki A et al: Diazepam for prevention of the rise in plasma catecholamines caused by ketamine. Clin Pharmacol Ther 15:223, 1974.

195. Balfors E, Haggmark S, Nyhman H et al: Droperidol inhibits the effects of intravenous ketamine on central hemodynamics and myocardial oxygen consumption in patients with generalized atherosclerotic disease. Anesth Analg 62:193, 1983.

196. Miletich DJ, Ivankovich AD, Albrecht RF et al: The effect of ketamine on catecholamine metabolism in the isolated perfused rat heart. Anesthesiology 39:271, 1973.

197. Valicenti JF, Newman WH, Bagwell EE et al: Myocardial contractility during induction and steady-state ketamine anesthesia. Anesth Analg 52:190, 1973.

198. Pagel PS, Kampine JP, Schmeling WT et al: Ketamine depresses myocardial contractility as evaluated by the preload recruitable stroke work relationship in chronically instrumented dogs with autonomic nervous system blockade. Anesthesiology 76:564, 1992.

199. Urthaler F, Walker AA, James TN: Comparison of the inotropic action of morphine and ketamine studied in canine cardiac muscle. J Thorac Cardiovasc Surg 72:142, 1976.

200. Stowe DF, Bosnjak ZJ, Kampine JP: Comparison of etomidate, ketamine, midazolam, propofol, and thiopental on function and metabolism of isolated hearts. Anesth Analg 74:547, 1992.

201. Endou M, Hattori Y, Nakaya H et al: Electrophysiologic mechanisms responsible for inotropic responses to ketamine in guinea pig and rat myocardium. Anesthesiology 76:409, 1992.

202. Hill GE, Wong KC, Shaw CL et al: Interactions of ketamine with vasoactive amines at normothermia and hypothermia in the isolated rabbit heart. Anesthesiology 48:315, 1978.

203. Nedergaard OA: Cocaine-like effect of ketamine on vascular adrenergic neurones. Eur J Pharmacol 23:153, 1973.

204. Salt PJ, Barnes PK, Beswick FJ: Inhibition of neuronal and extraneuronal uptake of noradrenaline by ketamine in the isolated perfused rat heart. Br J Anaesth 51:835, 1979.

205. Cook DJ, Housmans PR, Rorie D: Effect of ketamine HCl on norepinephrine disposition in isolated ferret ventricular myocardium. J Pharmacol Exp Ther 261:101, 1992.

206. Reves J, Flezzani P, Kissin I: Pharmacology of intravenous anesthetic induction drugs. In Kaplan JA (ed): Cardiac Anesthesia. Orlando, Fla, Grune & Stratton, 1987, p 125.

207. Munro HM, Sleigh JW, Paxton LD: The cardiovascular response to ketamine: The effects of clonidine and lignocaine. Acta Anaesthesiol Scand 37:75, 1993.

208. Hatano S, Keane DM, Boggs RE et al: Diazepam-ketamine anaesthesia for open heart surgery: A "micro-mini" drip administration technique. Can J Anaesth 23:648, 1976.

209. Bidwal AV, Stanley TH, Graves CL et al: The effects of ketamine on cardiovascular dynamics during halothane and enflurane anesthesia. Anesth Analg 54:588, 1975.

210. Corssen G, Reves JG, Carter JR: Neuroleptanesthesia, dissociative anesthesia, and hemorrhage. Int Anesthesiol Clin 12:145, 1974.

211. Van der Linden P, Gilbart E, Engelman E et al: Comparison of halothane, isoflurane, alfentanil, and ketamine in experimental septic shock. Anesth Analg 70:608, 1990.

212. Kingston HG, Bretherton KW, Holloway AM et al: A comparison between ketamine and diazepam as induction agents for pericardectomy. Anesth Intensive Care 6:66, 1978.

213. Allen GC, Byford LJ, Shamji FM: Anterior mediastinal mass in a patient susceptible to malignant hyperthermia. Can J Anaesth 40:46, 1993.

214. Fletcher JE, Rosenberg H, Lizzo FH: Effects of droperidol, haloperidol and ketamine on halothane, succinylcholine and caffeine contractures: Implications for malignant hyperthermia. Acta Anaesthesiol Scand 33:187, 1989.

215. Dershwitz M, Sreter FA, Ryan JF: Ketamine does not trigger malignant hyperthermia in susceptible swine. Anesth Analg 69:501, 1989.

216. Raza SM, Masters RW, Zsigmond EK: Haemodynamic stability with midazolam-ketamine-sufentanil analgesia in cardiac surgical patients. Can J Anaesth 36:617, 1989.

217. Dich-Nielsen JO, Svendsen LB, Berthelsen P: Intramuscular low-dose ketamine versus pethidine for postoperative pain treatment after thoracic surgery. Acta Anaesthesiol Scand 36:583, 1992.

218. Jahangir SM, Islam F, Aziz L: Ketamine infusion for postoperative analgesia in asthmatics: A comparison with intermittent meperidine. Anesth Analg 76:45, 1993.

219. Groeneveld A, Inkson T: Ketamine: A solution to procedural pain in burned children. Can Nurse 88:28, 1992.

220. Wolfe RR, Loehr JP, Schaffer MS et al: Hemodynamic effects of ketamine, hypoxia and hyperoxia in children with surgically treated congenital heart disease residing greater than or equal to 1,200 meters above sea level. Am J Cardiol 67:84, 1991.

221. Thompson GE, Moore DC: Ketamine, diazepam, and Innovar: A computerized comparative study. Anesth Analg 50:458, 1971.

222. Korttila K, Levanen J: Untoward effects of ketamine combined with diazepam for supplementing conduction anaesthesia in young and middle-aged adults. Acta Anaesthesiol Scand 22:640, 1978.

223. Friedberg BL: Propofol-ketamine technique. Aesthetic Plast Surg 17:297, 1993.

224. Fuchs C, Schwabe M: Rectal premedication using ketamine-dehydrobenzperidol-atropine in childhood. Anaesthesiol Reanim 15:322, 1990.

225. Waxman K, Shoemaker WC, Lippmann M: Cardiovascular effects of anesthetic induction with ketamine. Anesth Analg 59:355, 1980.

226. Yang CY, Wong CS, Chang JY et al: Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth 43:379, 1996.

227. Hui TW, Short TG, Hong W et al: Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. Anesthesiology 82:641, 1995.

228. Gutstein HB, Johnson K, Heard MB et al: Oral ketamine preanesthetic medication in children. Anesthesiology 76:28, 1992.

229. Tobias JD, Phipps S, Smith B et al: Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. Pediatrics 90:537, 1992.

230. Neckel W, Jacobs FE, Tolksdorf W: Oral ketamine as preferred preanesthetic medication of uncooperative patients (in German). Anasthesiol Intensivmed Notfallmed Schmerzther 27:381, 1992.

231. Shapiro HM: Intracranial hypertension: Therapeutic and anesthetic considerations. Anesthesiology 43:445, 1971.

232. Thiel A, Adams HA, Fengler G et al: Studies using S-(+)-ketamine on probands. Computerized EEG-analysis and transcranial Doppler ultrasonography. Anaesthesist 41:604, 1992.

233. Tsai SK, Liao KT, Lee CM: Modification by ketamine of the neuromuscular actions of magnesium, vecuronium, pancuronium and alpha-bungarotoxin in the primate. Can J Anaesth 39:79, 1992.

234. Tsai SK, Lee C: Ketamine potentiates nondepolarizing neuromuscular relaxants in a primate. Anesth Analg 68:5, 1989.

235. Malinovsky JM, Lepage JY, Cozian A et al: Is ketamine or its preservative responsible for neurotoxicity in the rabbit? Anesthesiology 78:109, 1993.

236. Godefroi EF, Janssen PA, Van Der Eycken CA et al: DL-1-(1- arylalkyl)imidazole-5-carboxylate esters: A novel type of hypnotic agents. J Med Chem 8:220, 1965.

237. Doenicke A: Etomidate, a new intravenous hypnotic. Acta Anaesthesiol Belg 25:307, 1974.

238. Janssen PAJ, Niemegeers JE, Schellekens KHL et al: Etomidate, R-(+)-Ethyl-1-(alpha-methyl-benzyl)imidazole-5-carboxylate (R 16659): A potent, short-acting and relatively atoxic intravenous hypnotic agent in rats. Arzneimittelforschung 21:1234, 1971.

239. Ledingham IM, Watt I: Influence of sedation on mortality in critically ill multiple trauma patients (letter). Lancet 1:1270, 1983.

240. Wagner RL, White PF: Etomidate inhibits adrenocortical function in surgical patients. Anesthesiology 61:647, 1984.

241. Fragen RJ, Shanks CA, Molteni A et al: Effects of etomidate on hormonal responses to surgical stress. Anesthesiology 61:652, 1984.

242. Longnecker DE: Stress free: To be or not to be? Anesthesiology 61:643, 1984.

243. Owen H, Spence AA: Etomidate. Br J Anaesth 56:555, 1984.

244. Anonymous: Etomidate (editorial). Lancet 2:24, 1983.

245. Corssen G, Reves JG, Stanley TH: Etomidate. In Intravenous Anesthesia and Analgesia. Philadelphia, Lea & Febiger, 1988, p 285.

246. Nimmo WS, Miller M: Pharmacology of etomidate. In Brown BR (ed): New Pharmacologic Vistas in Anesthesia. Philadelphia, FA Davis, 1983, p 83.

247. Hadzija BW, Lubarsky DA: Compatibility of etomidate, thiopental sodium, and propofol injections with drugs commonly administered during induction of anesthesia. Am J Health Syst Pharm 52:997, 1995.

248. Fragen RJ, Caldwell N: Comparison of a new formulation of etomidate with thiopental: Side effects and awakening times. Anesthesiology 50:242, 1979.

249. Carli F, Stribley GC, Clark MM: Etomidate infusion in thoracic anaesthesia. Anaesthesia 38:784, 1983.

250. Nauta J, Stanley TH, de Lange S et al: Anaesthetic induction with alfentanil: Comparison with thiopental, midazolam, and etomidate. Can J Anaesth 30:53, 1983.

251. Dundee JW, Zacharias M: Etomidate. p. 46. In Dundee JW (ed): Current Topics in Anaesthesia Series. 1. Intravenous Anaesthetic Agents. London, Arnold, 1979, p 46.

252. Famewo CE, Odugbesan CO: Further experience with etomidate. Can Anaesth Soc J 25:130, 1978.

253. Giese JL, Stockham RJ, Stanley TH et al: Etomidate versus thiopental for induction of anesthesia. Anesth Analg 64:871, 1985.

254. Craig J, Cooper GM, Sear JW: Recovery from day-case anaesthesia: Comparison between methohexitone, Althesin and etomidate. Br J Anaesth 54:447, 1982.

255. Wells JKG: Comparison of ICI 35868, etomidate and methohexitone for day-case anaesthesia. Br J Anaesth 57:732, 1985.

256. Zacharias M, Dundee JW, Clarke RSJ et al: Effect of preanaesthetic medication on etomidate. Br J Anaesth 51:127, 1979.

257. Linton DM, Thornington RE: Etomidate as a rectal induction agent. Part II. A clinical study in children. S Afr Med J 64:309, 1983.

258. Fragen RJ, Avram MJ, Henthorn TK et al: A pharmacokinetically designed etomidate infusion regimen for hypnosis. Anesth Analg 62:654, 1983.

259. Schuttler J, Schwilden H, Stoeckel H: Infusion strategies to investigate the pharmacokinetics and pharmacodynamics of hypnotic drugs: Etomidate as an example. Eur J Anaesthesiol 2:133, 1985.

260. Schuttler J, Schwilden H, Stoeckel H: Pharmacokinetics as applied to total intravenous anaesthesia. Anaesthesia 38(suppl):53, 1983.

261. Sear JW, Walters FJM, Wilkins DG et al: Etomidate by infusion for neuroanaesthesia. Anaesthesia 39:12, 1984.

262. Van Hamme MJ, Ghoneim MM, Ambre JJ: Pharmacokinetics of etomidate, a new intravenous anesthetic. Anesthesiology 49:274, 1978.

263. Hebron BS, Edbrooke DL, Newby DM et al: Pharmacokinetics of etomidate associated with prolonged i.v. infusion. Br J Anaesth 55:281, 1983.

264. De Ruiter G, Popescu DT, De Boer AG et al: Pharmacokinetics of etomidate in surgical patients. Arch Int Pharmacodyn Ther 249:180, 1981.

265. Meuldermans WEG, Heykants JJP: The plasma protein binding and distribution of etomidate in dog, rat and human blood. Arch Int Pharmacodyn Ther 221:150, 1976.

266. Van Beem H, Manger FW, Van Boxtel C et al: Etomidate anaesthesia in patients with cirrhosis of the liver: Pharmacokinetic data. Anaesthesia 38(suppl):61, 1983.

267. Arden JR, Holley FO, Stanski DR: Increased sensitivity to etomidate in the elderly: Initial distribution versus altered brain response. Anesthesiology 65:19, 1986.

268. Doenicke A, Loffler B, Kugler J et al: Plasma concentration and E.E.G. after various regimens of etomidate. Br J Anaesth 54:393, 1982.

269. Evans RH, Hill RG: GABA: Mimetic action of etomidate. Br J Pharmacol 61:484, 1977.

270. Cold GE, Eskesen V, Eriksen H et al: CBF and CMRO2 during continuous etomidate infusion supplemented with N_2O and fentanyl in patients with supratentorial cerebral tumour: A dose-response study. Acta Anaesthesiol Scand 29:490, 1985.

271. Dearden NM, McDowall DG: Comparison of etomidate and althesin in the reduction of increased intracranial pressure after head injury. Br J Anaesth 57:361, 1985.

272. Modica PA, Tempelhoff R: Intracranial pressure during induction of anaesthesia and tracheal intubation with etomidate-induced burst suppression on EEG. Can J Anaesth 39:236, 1992.

273. Renou AM, Vernhiet J, Macrez P et al: Cerebral blood flow and metabolism during etomidate anaesthesia in man. Br J Anaesth 50:1047, 1978.

274. Tulleken CAF, van Dieren A, Jonkman J et al: Clinical and experimental experience with etomidate as a brain protective agent. J Cereb Blood Flow Metab 2:S92, 1982.

275. Takanobu S, Piyush MP, Drummond JC et al: A comparison of the cerebral protective effects of etomidate, thiopental, and isoflurane in a model of forebrain ischemia in the rat. Anesth Analg 76:990, 1993.

276. Drummond JC, Cole DJ, Patel PM et al: Focal cerebral ischemia during anesthesia with etomidate, isoflurane, or thiopental: A comparison of the extent of cerebral injury. Neurosurgery 37:742, 1995.

277. Guo J, White JA, Batjer HH: Limited protective effects of etomidate during brainstem ischemia in dogs. J Neurosurg 82:278, 1995.

278. Thomson MF, Brock-Utne JG, Bean P et al: Anaesthesia and intraocular pressure: A comparison of total intravenous anaesthesia using etomidate with conventional inhalation anaesthesia. Anaesthesia 37:758, 1982.

279. Ghoneim MM, Yamada T: Etomidate: a clinical and electroencephalographic comparison with thiopental. Anesth Analg 56:479, 1977.

280. Lees NW, Hendry JGB: Etomidate in urological outpatient anaesthesia. Anaesthesia 32:592, 1977.

281. Ebrahim EY, DeBoer GE, Luders H et al: Effect of etomidate on the electroencephalogram of patients with epilepsy. Anesth Analg 65:1004, 1986.

282. Gancher S, Laxer KD, Krieger W: Activation of epileptogenic activity by etomidate. Anesthesiology 61:616, 1984.

283. Reddy RV, Moorthy SS, Dierdorf SF et al: Excitatory effects and electroencephalographic correlation of etomidate, thiopental, methohexital, and propofol. Anesth Analg 77:1008, 1993.

284. Thornton C, Heneghan CPH, Navaratnarajah M et al: Effect of etomidate on the auditory evoked response in man. Br J Anaesth 57:554, 1985.

285. McPherson RW, Sell B, Traystman RJ: Effects of thiopental, fentanyl, and etomidate on upper extremity somatosensory evoked potentials in humans. Anesthesiology 68:584, 1986.

286. Kalkman CJ, Drummond JC, Ribberink AA et al: Effects of propofol, etomidate, midazolam, and fentanyl on motor evoked responses to transcranial electrical or magnetic stimulation in humans. Anesthesiology 76:502, 1992.

287. Guldager H, Sondergaard I, Molke Jensen F et al: Basophil histamine release in asthma patients after in vitro provocation with althesin and etomidate. Acta Anaesthesiol Scand 29:352, 1985.

288. Choi SD, Spaulding BC, Gross JB et al: Comparison of the ventilatory effects of etomidate and methohexital. Anesthesiology 62:442, 1985.

289. Kay B: The measurement of occlusion pressure during anaesthesia: A comparison of the depression of respiratory drive by methohexitone and etomidate. Anaesthesia 34:543, 1979.

290. Colvin MP, Savege TM, Newland PE et al: Cardiorespiratory changes following induction of anaesthesia with etomidate in patients with cardiac disease. Br J Anaesth 51:551, 1979.

291. Morgan M, Lumley J, Whitwam JG: Respiratory effects of etomidate. Br J Anaesth 49:233, 1977.

292. Gooding JM, Weng J, Smith RA et al: Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. Anesth Analg 58:40, 1979.

293. Criado A, Maseda J, Navarro E et al: Induction of anaesthesia with etomidate: Haemodynamic study of 36 patients. Br J Anaesth 52:803, 1980.

294. Gooding JM, Corssen G: Effect of etomidate on the cardiovascular system. Anesth Analg 56:717, 1977.

295. Lindeburg T, Spotoft H, Bredgaard Sorensen M et al: Cardiovascular effects of etomidate used for induction and in combination with fentanyl-pancuronium for maintenance of anaesthesia in patients with valvular heart disease. Acta Anaesthesiol Scand 26:205, 1982.

296. Kettler D, Sonntag H, Donath U et al: Haemodynamics, myocardial mechanics, oxygen requirement and oxygenation of the human heart during induction of anaesthesia with etomidate. Anaesthesist 23:116, 1974.

297. Haessler R, Madler C, Klasing S et al: Propofol/fentanyl versus etomidate/fentanyl for the induction of anesthesia in patients with aortic insufficiency and coronary artery disease. J Cardiothorac Vasc Anesth 6:173, 1992.

298. Larsen R, Rathgeber J, Bagdahn A et al: Effects of propofol on cardiovascular dynamics and coronary blood flow in geriatric patients: A comparison with etomidate. Anaesthesia 435:25, 1988.

299. Lischke V, Wilke HJ: Prolongation of the QT-interval during induction of anesthesia in patients with coronary artery disease. Acta Anaesthesiol Scand 38:144, 1994.

300. Ebert TJ, Muzi M, Berens R et al: Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology 76:725, 1992.

301. De Bruijn NP, Hlatky MA, Jacobs JR et al: General anesthesia during percutaneous transluminary coronary angioplasty for acute myocardial infarction: Results of a randomized controlled clinical trial. Anesth Analg 68:201, 1989.

302. Ledingham IM, Finlay WEI, Watt I et al: Etomidate and adrenocortical function (letter). Lancet 1:1434, 1983.

303. Allolio B, Dorr H, Stuttmann R et al: Effect of a single bolus dose of etomidate upon eight major corticosteroid hormones and plasma ACTH. Clin Endocrinol (Oxf) 22:281, 1985.

304. Lamberts SWJ, Bons EG, Bruining HA et al: Differential effects of the imidazole derivatives etomidate, ketoconazole and miconazole and of metyrapone on the secretion of cortisol and its precursors by human adrenocortical cells. J Pharmacol Exp Ther 240:259, 1987.

305. Boidin MP: Steroid response to ACTH and to ascorbinic acid during infusion of etomidate for general surgery. Acta Anaesthesiol Belg 36:15, 1985.

306. Boidin MP, Erdmann WE, Faithfull NS: The role of ascorbic acid in etomidate toxicity. Eur J Anaesthesiol 3:417, 1986.

307. Wagner RL, White PF, Kan PB et al: Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 310:1415, 1984.

308. Duthie DJR, Fraser R, Nimmo WS: Effect of induction of anaesthesia with etomidate on corticosteroid synthesis in man. Br J Anaesth 57:156, 1985.

309. Crozier TA, Beck D, Schlaeger M et al: Endocrinological changes following etomidate, midazolam, or methohexital for minor surgery. Anesthesiology 66:628, 1987.

310. Fragen RJ, Shanks CA, Molteni A: Effect on plasma cortisol concentration of a single induction dose of etomidate or thiopentone. Lancet 2:625, 1983.

311. Crozier TA, Schlaeger M, Wuttke W et al: TIVA with etomidate-fentanyl versus midazolam-fentanyl: The perioperative stress of coronary surgery overcomes the inhibition of cortisol synthesis caused by etomidate-fentanyl anesthesia. Anaesthesist 43:605, 1994.

312. Famewo CE: Induction of anaesthesia with etomidate in a patient with acute intermittent porphyria. Can Anaesth Soc J 32:171, 1985.

313. Korttila K, Aromaa U: Venous complications after intravenous injection of diazepam, flunitrazepam, thiopentone and etomidate. Acta Anaesth Scand 24:227, 1980.

314. Canessa R, Lema G, Urzua J et al: Anesthesia for elective cardioversion: A comparison of four anesthetic agents. J Cardiothorac Vasc Anesth 5:566, 1991.

315. Galloway PA, Nicoll JMV, Leiman BC: Pain reduction with etomidate injection (letter). Anaesthesia 37:352, 1982.

316. Olkkola KT, Tammisto T: Quantitation of the interaction of rocuronium bromide with etomidate, fentanyl, midazolam, propofol, thiopentone, and isoflurane using closed-loop feedback control of infusion of rocuronium. Eur J Anaesthesiol Suppl 9:99, 1994.

317. Olkkola KT, Tammisto T: Quantifying the interaction of rocuronium (Org 9426) with etomidate, fentanyl, midazolam, propofol, thiopental, and isoflurane using closed-loop feedback control of rocuronium infusion. Anesth Analg 78:691, 1994.

318. Doenicke A, Roizen MB, Nebauer AE et al: A comparison of two formulations for etomidate, 2-hydroxypropyl-beta-cyclodextrin (HPCD) and propylene glycol. Anesth Analg 79:933, 1994.

319. Van de Wiele B, Rubinstein E, Peacock W et al: Propylene glycol toxicity caused by prolonged infusion of etomidate. J Neurosurg Anesthesiol 7:259, 1995.

320. Liem TH, Booij LHDJ, Hasenbos MAWM et al: Coronary artery bypass grafting using two different anesthetic techniques. Part I. Hemodynamic results. J Cardiothorac Vasc Anesth 6:148, 1992.

321. Shulman MS, Edelmann R: Use of etomidate for elective cardioversion (letter). Anesthesiology 68:656, 1988.

322. Batjer HH, Frankfurt AI, Purdy PD et al: Use of etomidate, temporary arterial occlusion, and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms. J Neurosurg 68:234, 1988.

323. Lees NW, Glasser J, McGroarty FJ et al: Etomidate and fentanyl for maintenance of anaesthesia. Br J Anaesth 53:959, 1981.

324. Avramov MN, Husain MM, White PF: The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. Anesth Analg 81:596, 1995.

325. Fragen RJ: Diprivan (propofol): A historical perspective. Semin Anesth 7:1, 1988.

326. Kay B, Rolly G: ICI 35 868, a new intravenous induction agent. Acta Anaesthesiol Belg 28:303, 1977.

327. Briggs LP, Clarke RSJ, Watkins J: An adverse reaction to the administration of disoprofol (Diprivan). Anesthesia 37:1099, 1982.

328. James R, Glen JB: Synthesis, biological evaluation, and preliminary structure-activity considerations of a series of alkylphenols as intravenous anesthetic agents. J Med Chem 23:1350, 1980.

329. Simons PJ, Cockshott ID, Douglas EJ et al: Blood concentrations, metabolism and elimination after a subanesthetic intravenous dose of (14)C-propofol (Diprivan) to male volunteers (abstract). Postgrad Med J 61:64, 1985.

330. Veroli P, O'Kelly B, Bertrand F et al: Extrahepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. Br J Anaesth 68:183, 1992.

331. Gray PA, Park GR, Cockshott ID et al: Propofol metabolism in man during the anhepatic and reperfusion phases of liver transplantation. Xenobiotica 22:105, 1992.

332. Raoof AA, van Obbergh LJ, de Ville de Goyet J et al: Extrahepatic glucuronidation of propofol in man: Possible contribution of gut wall and kidney. Eur J Clin Pharmacol 50:91, 1996.

333. Chen TL, Ueng TH, Chen SH et al: Human cytochrome P450 mono-oxygenase system is suppressed by propofol. Br J Anaesth 74:558, 1995.

334. Adam HK, Briggs LP, Bahar M et al: Pharmacokinetic evaluation of ICI 35 868 in man: Single induction doses with different rates of injection. Br J Anaesth 55:97, 1983.

335. Kay NH, Sear JW, Upington J et al: Disposition of propofol in patients undergoing surgery: A comparison in men and women. Br J Anaesth 58:1075, 1986.

336. Kirkpatrick T, Cockshott ID, Douglas EJ et al: Pharmacokinetics of propofol (Diprivan) in elderly patients. Br J Anaesth 60:146, 1988.

337. Gepts E, Camu F, Cockshott ID et al: Disposition of propofol administered as constant rate intravenous infusions in humans. Anesth Analg 66:1256, 1987.

338. Schuttler J, Stoeckel H, Schwilden H: Pharmacokinetic and pharmacodynamic modeling of propofol (Diprivan) in volunteers and surgical patients. Postgrad Med J 61:53, 1985.

339. Shafer A, Doze VA, Shafer SL et al: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology 69:348, 1988.

340. Bailie GR, Cockshott ID, Douglas EJ et al: Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. Br J Anaesth 68:486, 1992.

341. Hughes MA, Jacobs JR, Glass PSA: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthesia. Anesthesiology 76:334, 1992.

342. Dyck JG, Varvel J, Hung O et al: The pharmacokinetics of propofol vs age. Anesthesiology 75:A315, 1991.

343. Servin F, Desmonts JM, Farinttir EA: Pharmacokinetics of propofol given as a continuous infusion in a cirrhotic patient: Preliminary results. Ann Fr Anesth Reanim 6:228, 1987.

344. Morcos WE, Payne JP: The induction of anaesthesia with propofol (Diprivan) compared in normal and renal failure patients. Postgrad Med J 61:62, 1985.

345. Leslie K, Daniel IS, Bjorksten AR et al: Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg 80:1007, 1995.

346. Bailey JM, Mora CT, Shafer SL: Pharmacokinetics of propofol in adult patients undergoing coronary revascularization: The Multicenter Study of Perioperative Ischemia Research Group. Anesthesiology 84:1288, 1996.

347. Marsh B, White MNM, Kenny GNC: Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 67:41, 1991.

348. Kataria BK, Ved SA, Nicodemus HF et al: The pharmacokinetics of propofol in children using three different data analysis approaches (see comments). Anesthesiology 80:104, 1994.

349. Murat I, Billard V, Vernois J et al: Pharmacokinetics of propofol after a single dose in children aged 1-3 years with minor burns: Comparison of three data analysis approaches. Anesthesiology 84:526, 1996.

350. Benoni G, Cuzzolin L, Gilli E et al: Pharmacokinetics of propofol: Influence of fentanyl administration, (abstract). Eur J Pharmacol 183:1457, 1990.

351. Pavlin DJ, Coda B, Shen DD et al: Effects of combining propofol and alfentanil on ventilation, analgesia, sedation, and emesis in human volunteers. Anesthesiology 84:23, 1996.

352. Gill SS, Wright EM, Reilly CS: Pharmacokinetic interaction of propofol and fentanyl: Single bolus injection study. Br J Anaesth 65:760, 1990.

353. Matot I, Neely CF, Katz RY et al: Fentanyl and propofol uptake by the lung: Effect of time between injections. Acta Anaesthesiol Scand 38:711, 1994.

354. Janicki PK, James MFM, Erskine WAR: Propofol inhibits enzymatic degradation of alfentanil and sufentanil by isolated liver microsomes in vitro. Br J Anaesth 68:311, 1992.

355. Sanna E, Garau F, Harris RA: Novel properties of homomeric beta 1 gamma-aminobutyric acid type A receptors: Actions of the anesthetics propofol and pentobarbital. Mol Pharmacol 47:213, 1995.

356. Hara M, Kai Y, Ikemoto Y: Enhancement by propofol of the gamma-aminobutyric acid $_{A}$ response in dissociated hippocampal pryamidal neurons of the rat. Anesthesiology 81:988, 1994.

357. Canavero S, Bonicalzi V, Pagni CA et al: Propofol analgesia in central pain: Preliminary clinical observations. J Neurol 242:561, 1995.

358. Orser BA, Bertlik M, Wang LY et al: Inhibition by propofol (2,6 di-isopropylphenol) of the *N*-methyl- $_{D}$-aspartate subtype of glutamate receptor in cultured hippocampal neurones. Br J Pharmacol 116:1761, 1995.

359. Yamakura T, Sakimura K, Shimoji K et al: Effects of propofol on various AMPA-, kainate- and NMDA-selective glutamate receptor channels expressed in *Xenopus* oocytes. Neurosci Lett 188:187, 1995.

360. Tonner PH, Poppers DM, Miller KW: The general anesthetic potency of propofol and its dependence on hydrostatic pressure. Anesthesiology 77:926, 1992.

361. Briggs LP, Dundee JW, Bahar M et al: Comparison of the effect of diisopropylphenol (ICI 35 868) and thiopentone on response to somatic pain. Br J Anaesth 54:307, 1982.

362. Major E, Verniquet AJW, Waddell TK et al: A study of three doses of ICI 35 868 for induction and maintenance of anaesthesia. Br J Anaesth 53:267, 1981.

363. Rolly G, Versichelen L, Huyghe L et al: Effect of speed of injection on induction of anesthesia using propofol. Br J Anaesth 57:743, 1985.

364. Glass P, Ginsberg B, Hawkins ED et al: Comparison of sodium thiopental/isoflurane to propofol (delivered by means of a pharmacokinetic model-driven device) for the induction, maintenance, and recovery from anesthesia. Anesthesiology 69:A575, 1988.

365. McIune S, McKay AC, Wright PMC et al: Synergistic interaction between midazolam and propofol. Br J Anaesth 68:240, 1992.

366. Short TG, Plummer JL, Chui PT: Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. Br J Anaesth 69:162, 1992.

367. Adam HK, Kay B, Douglas EJ: Blood disoprofol levels in anesthetized patients. Correlation of concentration after single or repeated doses with hypnotic activity. Anaesthesia 37:536, 1982.

368. Aun CST, Short SM, Leung DHY et al: Induction dose response of propofol in unpremedicated children. Br J Anaesth 68:64, 1992.

369. Mackenzie N, Grant IS: Propofol for intravenous sedation. Anaesthesia 42:3, 1987.

370. Wilson E, Mackenzie N, Grant IS: A comparison of propofol and mid-azolam by infusion to provide sedation in patients who receive spinal anaesthesia. Anaesthesia 43:91, 1988.

371. Veselis RA, Reinsel RA, Wronski M et al: EEG and memory effects of low dose infusions of propofol. Br J Anaesth 69:246, 1992.

372. Zacny JP, Lichtor JL, Coalson DW et al: Subjective and psychomotor effects of subanesthetic doses of propofol in healthy volunteers. Anesthesiology 76:696, 1992.

373. Kelly JS, Roy RC: Intraoperative awareness with propofol-oxygen total intravenous anesthesia for microlaryngeal surgery. Anesthesiology 77:207, 1992.

374. Glass PSA: Prevention of awareness during total intravenous anesthesia. Anesthesiology 78:399, 1993.

375. McDonald NJ, Mannion D, Lee P et al: Mood evaluation and outpatient anesthesia. Anaesthesia 43:68, 1988.

376. Nelson VM: Hallucinations after propofol. Anaesthesia 43:170, 1988.

377. Cameron AE: Opisthotonos again. Anaesthesia 42:1124, 1987.

378. Hazeau C, Tisserant D, Vespignani H et al: Electroencephalographic changes produced by propofol. Ann Fr Anesth Reanim 6:261, 1987.

379. Yate PM, Maynard DE, Major E et al: Anaesthesia with ICI 35-868 monitored by the cerebral function analyzing monitor (CFAM). Eur J Anaesthesiol 3:159, 1986.

380. Glass PSA, Bloom M, Kearse L et al: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. Anesthesiology 86:836, 1997.

381. Maurette P, Simeon F, Castagnera L: Propofol anaesthesia alters somatosensory evoked cortical potentials. Anaesthesia 43:44, 1988.

382. Savoia G, Esposito C, Belfiore F: Propofol infusion and auditory evoked potentials. Anaesthesia 43:46, 1988.

383. Doi M, Gajraj RJ, Mantzaridis H et al: Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: Comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. Br J Anaesth 78:180, 1997.

384. Glen JB, Hunter SC, Blackburn TP et al: Interaction studies and other investigations of the pharmacology of propofol (Diprivan). Postgrad Med J 61:7, 1985.

385. Al Hader A, Hasan M, Hasan Z: The comparative effects of propofol, thiopental, and diazepam administered intravenously, on pentylene-tetrazol seizure threshold in the rabbit. Life Sci 51:779, 1992.

386. Heavner JE, Arthur J, Zou J et al: Propofol vs. thiopental for treating bupivicaine induced seizures in rats. Anesthesiology 77:A802, 1992.

387. Wood PR, Browne GPR, Pugh S: Propofol infusion for the treatment of status epilepticus (letter). Lancet 1:480, 1988.

388. Chilvers CR, Laurie PS: Successful use of propofol in status epilepticus (letter). Anaesthesia 45:995, 1990.

389. Dwyer R, McCaughey W, Lavery J: Comparison of propofol and methohexitone as anesthetic agents for electroconvulsive therapy. Anaesthesia 43:459, 1988.

390. Hodkinson BP, Frith RW, Mee EW: Propofol and the electroencephalogram. Lancet 2:1518, 1987.

391. Committee on Safety of Medicines: Propofol. Curr Probl 20:1987.

392. Ebrahim ZY, Schubert A, Van Ness P et al: The effect of propofol on the electroencephalogram of patients with epilepsy. Anesth Analg 78:275, 1994.

393. Samra SK, Sneyd JR, Ross DA et al: Effects of propofol sedation on seizures and intracranially recorded epileptiform activity in patients with partial epilepsy. Anesthesiology 82:843, 1995.

394. Anonymous: Convulsions after propofol. Pharm J 249:745, 1992.

395. Deer TR, Rich GF: Propofol tolerance in a pediatric patient. Anesthesiology 77:828, 1992.

396. Boyle WA, Shear JM, White PF et al: Tolerance and hyperlipemia during long term sedation with propofol. Anesthesiology 73:A245, 1990.

397. Follette JW, Farley WJ: Anesthesiologist addicted to propofol. Anesthesiology 77:817, 1992.

398. Stephan H, Sonntag H, Schenk HD et al: Effects of Disoprivan on cerebral blood flow, cerebral oxygen consumption and cerebral vascular reactivity. Anaesthesist 36:60, 1987.

399. Hartung HJ: Intracranial pressure after propofol and thiopental administration in patients with severe head trauma. Anaesthesist 36:285, 1987.

400. Hartung HJ: Effect of propofol (Disoprivan) on intracranial pressure. Anaesthesist 36:66, 1987.

401. Ravussin P, Guinard JP, Ralley F et al: Effect of propofol on cerebrospinal fluid pressure and cerebral perfusion pressure in patients undergoing craniotomy. Anaesthesia 43:37, 1988.

402. Vandesteene A, Trempont V, Engelman E: Effect of propofol on cerebral blood flow and metabolism in man. Anaesthesia 43:42, 1988.

403. Enns J, Gelb AW, Manninen PH: Cerebral autoregulation is maintained during propofol-nitrous oxide anaesthesia in humans. Can J Anaesth 39:A43, 1992.

404. Jansen GFA, Kagenaar D, Kedaria MB et al: Effects of propofol on the relation between CO_2 and cerebral blood flow velocity. Anesth Analg 76:S163, 1993.

405. Herregods L, Verberke J, Rolly G et al: Effect of propofol on elevated intracranial pressure: Preliminary results. Anaesthesia 43:107, 1988.

406. Newman MF, Murkin JM, Roach G et al: Cerebral physiologic effects of burst suppression doses of propofol during nonpulsatile cardiopulmonary bypass: CNS Subgroup of McSPI. Anesth Analg 81:452, 1995.

407. Kochs E, Hoffman WE, Werner C: The effects of propofol on brain electrical activity, neurologic outcome and neuronal damage following incomplete ischemia in rats. Anesthesiology 76:245, 1992.

408. Gelb AW, Zhang C, Henderson SM: A comparison of the cerebral protective effects of propofol, thiopental, and halothane in temporary feline focal cerebral ischemia. Anesth Analg 76:S115, 1993.

409. Ridenour TR, Warner DS, Todd MM et al: Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. Anesthesiology 76:807, 1992.

410. Amorim P, Chambers GJC, Kass IS: Propofol reduces neuronal transmission damage and attenuates the changes in calcium, potassium, and sodium during hyperthermic anoxia in the rat hippocampal slice. Anesthesiology 83:1254, 1995.

411. Mirakhur RK, Shepherd WFI: Intraocular pressure changes with propofol (Diprivan): Comparison with thiopentone. Postgrad Med J 61:41, 1985.

412. Mirakhur RK, Shepherd WFI, Darrah WC: Propofol or thiopentone: Effects on intraocular pressure associated with induction of anaesthesia and tracheal intubation (facilitated with suxamethonium). Br J Anaesth 59:431, 1987.

413. Vuyk J, Engbers FHM, Lemmens HJM: Pharmacodynamics of propofol in female patients. Anesthesiology 77:3, 1992.

414. Smith C, McEwan AI, Jhaveri R: Reduction of propofol Cp50 by fentanyl. Anesthesiology 77:A340, 1992.

415. Forrest FC, Tooley MA, Saunders PR et al: Propofol infusion and the suppression of consciousness: The EEG and dose requirements. Br J Anaesth 72:35, 1994.

416. Ebert TJ, Muzi M: Propofol and autonomic reflex function in humans. Anesth Analg 78:369, 1994.

417. Turtle MJ, Cullen P, Prys-Roberts C: Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man. II. Patients premedicated with lorazepam. Br J Anaesth 59:283, 1987.

418. Spelina KR, Coates DP, Monk CR: Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man. I. Patients premedicated with morphine sulphate. Br J Anaesth 58:1080, 1986.

419. Sanderson JH, Blades JF: Multicentre study of propofol in day case surgery. Anaesthesia 43:70, 1988.

420. Taylor MB, Grounds RM, Dulrooney PD et al: Ventilatory effects of propofol during induction of anesthesia: Comparison with thiopentone. Anaesthesia 41:816, 1986.

421. Grounds RM, Maxwell DL, Taylor MB et al: Acute ventilatory changes during IV induction of anaesthesia with thiopentone or propofol in man: Studies using inductance plethysmography. Br J Anaesth 59:1098, 1987.

422. Goodman NW, Black AMS, Carter JA: Some ventilatory effects of propofol as sole anesthetic agent. Br J Anaesth 59:1497, 1987.

423. Gold MI, Abraham EC, Herrington C: A controlled investigation of propofol, thiopentone and methohexitone. Can J Anaesth 34:478, 1987.

424. Munson ES, Larson CP, Babad AA: The effects of halothane, fluroxene and cyclopropane on ventilation: A comparative study in man. Anesthesiology 27:716, 1966.

425. Knill RL, Clement JL, Gelb AW: Ventilatory responses mediated by chemoreceptors in anaesthetized man. Adv Exp Med Biol 99:67, 1978.

426. Aun C, Major E: The cardiorespiratory effects of ICI 35 868 in patients with valvular heart disease. Anaesthesia 39:1096, 1984.

427. Grounds RM, Twigley AJ, Carli F: The haemodynamic effects of thiopentone and propofol. Anaesthesia 40:735, 1985.

428. Al-Khudhairi D, Gordon G, Morgan M, et al: Acute cardiovascular changes following disoprofol: Effects in heavily sedated patients with coronary artery disease. Anaesthesia 37:1007, 1982.

429. Coates DP, Monk CR, Prys-Roberts C et al: Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. Anesth Analg 66:64, 1987.

430. Blouin RT, Seifert HA, Conrad PF et al: Propofol significantly depresses hypoxic ventilatory drive during conscious sedation. Anesthesiology 77:A1215, 1992.

431. Conti G, DellUtri D, Vilardi V: Propofol induces bronchodilation in mechanically ventilated chronic obstructive pulmonary disease (COPD) patients. Acta Anaesthesiol Scand 37:105, 1993.

432. Mehr EH, Hirshman CA, Lindeman KS: The effect of halothane, propofol and thiopental on peripheral airway reactivity. Anesthesiology 77:A1212, 1992.

433. Vermeyen KM, Erpels FA, Janssen LA: Propofol-fentanyl anaesthesia for coronary bypass surgery in patients with good left ventricular function. Br J Anaesth 59:1115, 1987.

434. Patrick MR, Blair IJ, Feneck RO et al: A comparison of the haemodynamic effects of propofol (Diprivan) and thiopentone in patients with coronary artery disease. Postgrad Med J 61:23, 1985.

435. Stephan H, Sonntag H, Schenk HD: Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. Br J Anaesth 58:969, 1986.

436. Coates DP, Prys-Roberts C, Spelina KR: Propofol (Diprivan) by intravenous infusion with nitrous oxide: Dose requirements and hemodynamic effects. Postgrad Med J 61:76, 1985.

437. Claeys MA, Gepts E, Camu F: Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 60:3, 1983.

438. Van Aken H, Meinshausen E, Prien T: The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N_2O in humans. Anesthesiology 68:157, 1988.

439. Wahr JA, Plunkett JJ, Ramsay JG et al: Cardiovascular responses during sedation after coronary revascularization: Incidence of myocardial ischemia and hemodynamic episodes with propofol versus midazolam. Institutions of the McSPI Research Group. Anesthesiology 84:1350, 1996.

440. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology 78:100, 1993.

441. Ebert TJ, Muzi M, Goff DR et al: Does propofol really preserve baroreflex function in humans? Anesthesiology 77:A337, 1992.

442. Xuan YT, Zhang J, Glass PSA: Propofol regulation of calcium entry pathways in cultured A10 and rat aortic smooth muscle cells. Br J Pharmacol 117:5, 1996.

443. Chang KSK, Davis RF: Propofol produces endothelium-independent vasodilatation and may act as a Ca^{2+} channel blocker. Anesth Analg 76:24, 1993.

444. Cullen PM, Turtle M, Prys-Roberts C: Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 66:1115, 1987.

445. Sharpe MD, Dobkowski WB, Murkin JM et al: Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction in Wolff-Parkinson-White syndrome during alfentanil/midazolam anesthesia. Anesthesiology 82:888, 1995.

446. De Grood PMRM, Van Egmond J, Van De Wetering M: Lack of effects of emulsified propofol (Diprivan) on vecuronium pharmacodynamics: Preliminary results in man. Postgrad Med J 61:28, 1985.

447. Nightingale P, Petts NV, Healy TEJ: Induction of anaesthesia with propofol (Diprivan) or thiopentone and interactions with suxamethonium, atracurium and vecuronium. Postgrad Med J 61:31, 1985.

448. McKeating K, Bali IM, Dundee JW: The effects of thiopentone and propofol on upper airway integrity. Anaesthesia 43:638, 1988.

449. Richardson J: Propofol infusion for coronary artery bypass surgery in a patient with suspected malignant hyperpyrexia (letter). Anaesthesia 42:1125, 1987.

450. Hopkinson KC, Denborough M: Propofol and malignant hyperpyrexia (letter). Lancet 1:191, 1988.

451. Van Hemelrijck J, Weekers F, Van Aken H et al: Propofol anesthesia does not inhibit stimulation of cortisol synthesis. Anesth Analg 80:573, 1995.

452. Stark RD, Binks SM, Dukka VN: A review of the safety and tolerance of propofol (Diprivan). Postgrad Med J 61:152, 1985.

453. Robinson FP: Propofol (Diprivan) by intermittent bolus with nitrous oxide in oxygen for body surface operations. Postgrad Med J 61:116, 1985.

454. Sear JW, Uppington J, Kay NH: Haemotological and biochemical changes during anaesthesia with propofol (Diprivan). Postgrad Med J 61:165, 1985.

455. Aviram M, Deckelbaum RJ: Intralipid infusion into humans reduces in vitro platelet aggregation and alters platelet lipid composition. Metabolism 38:343, 1989.

456. Laxenaire MC, Mata Bermejo E, Moneret Vautrin DA et al: Life-threatening anaphylactoid reactions to propofol ('Diprivan'). Anesthesiology 77:275, 1992.

457. Doenicke A, Lorenz W, Stanworth D: Effects of propofol (Diprivan) on histamine release, immunoglobulin levels and activation of complement in healthy volunteers. Postgrad Med J 61:15, 1985.

458. McCollum JSC, Milligan KR, Dundee JW: The antiemetic action of propofol. Anaesthesia 43:239, 1988.

459. Borgeat A, Wilder Smith OHG, Saiah M et al: Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. Anesthesiology 76:510, 1992.

460. Schulman SR, Rockett CB, Canada AT et al: Long-term propofol infusion for refractory postoperative nausea: A case report with quantitative propofol analysis. Anesth Analg 80:636, 1995.

461. Gan TJ, Glass PSA, Howell ST et al: Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. Anesthesiology (In press, 1997).

462. Gan TJ, Ginsberg B, Grant AP et al: A double-blind randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology 85:1036, 1996.

463. Borgeat A, Wilder Smith OHG, Rifat K: Adjuvant propofol is effective in preventing refractory chemotherapy associated nausea and vomiting. Anesthesiology 77:A344, 1992.

464. Appadu BL, Strange PG, Lambert DG: Does propofol interact with D2 dopamine receptors? Anesth Analg 79:1191, 1994.

465. Saiah M, Borgeat A, Wilder-Smith OH et al: Epidural-morphine-induced pruritus: Propofol versus naloxone. Anesth Analg 78:1110, 1994.

466. Leslie K, Sessler DI, Bjorksten AR et al: Propofol causes a dose-dependent decrease in the thermoregulatory threshold for vasoconstriction but has little effect on sweating. Anesthesiology 81:353, 1994.

467. Skoutelis A, Lianou PEP, Papageorgiou E. et al: Effects of propofol and thiopentone on polymorphonuclear leukocyte functions in vitro. Acta Anaesthesiol Scand 38:858, 1994.

468. Krumholz W, Endrass J, Hempelmann G: Propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli* by polymorphonuclear leukocytes in vitro. Can J Anaesth 41:446, 1994.

469. Bennett SN, McNeil MM, Bland LA et al: Postoperative infections traced to contamination of an intravenous anesthetic, propofol. N Engl J Med 333:147, 1995.

470. Cummings GC, Dixon J, Kay NH: Dose requirements of ICI 35, 868 (propofol, Diprivan) in a new formulation for induction of anaesthesia. Anaesthesia 39:1168, 1984.

471. Kay B, Stephenson DK: Dose response relationship for disoprofol (ICI 35 868; Diprivan): Comparison with methohexitone. Anaesthesia 36:863, 1981.

472. Rutter DV, Morgan M, Lumley J et al: ICI 35 868 (Diprivan): A new intravenous induction agent. Anaesthesia 35:1188, 1980.

473. Briggs LP, White M: The effects of premedication on anaesthesia with propofol (Diprivan). Postgrad Med J 61:35, 1985.

474. Dundee JW, Robinson FP, McCollum JSC et al: Sensitivity to propofol in the elderly. Anaesthesia 41:482, 1986.

475. Steib A, Freys G, Curzola U et al: Propofol in elderly high risk patients: A comparison of haemodynamic effects with thiopentone during induction of anaesthesia. Anaesthesia 43:111, 1988.

476. Purcell-Jones G, Yates A, Baker JR et al: Comparison of the induction characteristics of thiopentone and propofol in children. Br J Anaesth 59:1431, 1987.

477. Mirakhur RK: Induction characteristics of propofol in children: Comparison with thiopentone. Anaesthesia 43:593, 1988.

478. Doze VA, Shafer A, White PF: Propofol-nitrous oxide versus thiopental-isoflurane-nitrous oxide for general anesthesia. Anesthesiology 69:63, 1988.

479. Heath PJ, Kennedy DJ, Ogg TW: Which intravenous induction agent for day surgery? A comparison of propofol, thiopentone, methohexitone and etomidate. Anaesthesia 43:365, 1988.

480. Mackenzie N, Grant IS: Propofol (Diprivan) for continuous intravenous anaesthesia: A comparison with methohexitone. Postgrad Med J 61:70, 1985.

481. Doze VA, Westphal L, White P: Comparison of propofol with methohexital for outpatient anesthesia. Anesth Analg 65:1189, 1986.

482. Kay B: Propofol and alfentanil infusion: A comparison with methohexitone and alfentanil for major surgery. Anaesthesia 41:589, 1986.

483. Sear JW, Shaw I, Wolf A et al: Infusions of propofol to supplement nitrous oxide-oxygen for the maintenance of anaesthesia: A comparison with halothane. Anaesthesia 43:18, 1988.

484. Van Hemelrijck J, Smith I, White PF: Use of desflurane for outpatient anesthesia: A comparison with propofol and nitrous oxide. Anesthesiology 75:197, 1991.

485. Roberts FL, Dixon J, Lewis GTR: Induction and maintenance of propofol anaesthesia: A manual infusion scheme. Anaesthesia 43:14, 1988.

486. Thomas VL, Saunders DA: The effect of fentanyl on propofol requirements for day case anaesthesia. Anaesthesia 43:73, 1988.

487. Vuyk J, Lim T, Engbers FHM et al: The interaction of propofol and alfentanil during lower abdominal surgery in female patients. Anesthesiology 83:8, 1995.

488. Taylor IN, Kenny GNC, Glen JB: Pharmacodynamic stability of a mixture of propofol and alfentanil. Br J Anaesth 69:168, 1992.

489. Hilton P, Dev VJ, Major E: Intravenous anaesthesia with propofol and alfentanil: The influence of age and weight. Anaesthesia 41:640, 1986.

490. Schuttler J, Kloos S, Roepcke H et al: Age dependent dose requirements of propofol in total intravenous anesthesia as quantified by closed-loop EEG feedback infusion strategies. Anesthesiology 77:A338, 1992.

491. Schuttler J, Kloos S, Schwilden H et al: Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Anaesthesia 43:2, 1988.

492. Tackley RM, Lewis GTR, Prys-Roberts C: Open loop control of propofol infusions, abstracted. Br J Anaesth 59:935, 1987.

493. Dexter F, Tinker JH: Comparisons between desflurane and isoflurane or propofol on time to following commands and time to discharge. Anesthesiology 83:77, 1995.

494. Mora CT, Dudek C, Epstein R et al: Cardiac anesthesia techniques, fentanyl alone or in combination with enflurane or propofol. Anesth Analg 68:S202, 1989.

495. Russell GN, Wright EL, Fox MA et al: Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass. Anaesthesia 44:205, 1989.

496. Underwood SM, Davies SW, Feneck RO et al: Anaesthesia for myocardial revascularization: A comparison of fentanyl/propofol with fentanyl/enflurane. Anaesthesia 47:939, 1992.

497. Hall RI, Murphy JT, Moffitt EA et al: A comparison of the myocardial and metabolic and haemodynamic changes produced by propofol-sufentanil and enflurane-sufentanil anaesthesia for patients having coronary artery bypass graft surgery. Can J Anaesth 38:996, 1991.

498. Fanard L, Van Steenberge A, Demeire X et al: Comparison between propofol and midazolam as sedative agents for surgery under regional anaesthesia. Anaesthesia 42(S):87, 1988.

499. Gepts E, Claeys MA, Camu F et al: Infusion of propofol (Diprivan) as sedative technique for colonoscopies. Postgrad Med J 61:120, 1987.

500. Newman LH, McDonald JC, Wallace PGM et al: Propofol infusion for sedation in intensive care. Anaesthesia 42:929, 1987.

501. Grounds RM, Lalor JM, Lumley J: Propofol infusion for sedation in the intensive care unit: Preliminary report. BMJ 294:397, 1985.

502. Beller JP, Pottecher T, Manigin P: Long-term sedation with propofol during intensive care: Preliminary results of the study of recovery and pharmacokinetics. Ann Fr Anesth Reanim 6:334, 1987.

503. Beller JP, Pottecher T, Lugnier A: Prolonged sedation with propofol in ICU patients: Recovery and blood concentration changes during periodic interruptions in infusion. Br J Anaesth 61:583, 1988.

504. Parke TJ, Stevens JE, Rice ASC: Metabolic acidosis and fatal myocardial failure after propofol infusion in children: Five case reports. BMJ 305:613, 1992.

505. Murphy PG, Myers DS, Davies MJ: The antioxidant potential of propofol (2,6-diisopropylphenol). Br J Anaesth 68:613, 1992.

506. Chong JL, Grebenik C, Sinclair M et al: The effect of a cardiac surgical recovery area on the timing of extubation. J Cardiothorac Vasc Anesth 7:137, 1993.

507. Rudkin GE, Osborne GA, Finn BP: Intra-operative patient-controlled sedation: Comparison of patient-controlled propofol with patient-controlled midazolam. Anaesthesia 47:376, 1992.

508. Laborit H, Huguenard P: Practique de l'hibernotherapie en chirurgie et en medicine. Paris, Masson, 1954.

509. Laborit H: Stress and Cellular Function. Philadelphia, JB Lippincott, 1959.

510. Corssen G, Reves JG, Stanley TH: Neuroleptanalgesia and neurolept-anesthesia. Intravenous Anesthesia and Analgesia. Philadelphia, Lea & Febiger, 1988, p 175.

511. Janssen PAJ: The pharmacology of haloperidol. Int J Neuropsychiatry 3(suppl 1):10, 1967.

512. DeCastro J, Mundeleer P: Anesthesie sans barbituriques: la neuroleptanalgesie (R1406, R1625, hydergine, procain). Anesth Analg 16:1022, 1959.

513. Borison HL, Wang SC: Physiology and pharmacology of vomiting. Pharmacol Rev 5:193, 1953.

514. Janssen PAJ: Zur Frage des Abbaus und der Ausscheidung der bei Neuroleptanalgesie zur Anwendung kommenden Pharmaka. In Henschel WF (ed): Die Neuroleptanalgesie. Berlin, Springer-Verlag, 1966.

515. Fischler M, Bonnet F, Trang H: The pharmacokinetics of droperidol in anesthetized patients. Anesthesiology 64:486, 1986.

516. Cressman WA, Plostnieks J, Johnson PC: Absorption, metabolism and excretion of droperidol by human subjects following intramuscular and intravenous administration. Anesthesiology 38:363, 1973.

517. Michenfelder JD, Theye RA: Effects of fentanyl, droperidol, and Innovar on canine cerebral metabolism and blood flow. Br J Anaesth 43:630, 1971.

518. Barker J, Harper AM, McDowall DG: Cerebral blood flow, cerebrospinal fluid pressure and EEG activity during neuroleptanalgesia induced with dehydrobenzperidol and phenoperidine. Br J Anaesth 40:143, 1968.

519. Prys-Roberts C, Kelman GR: The influence of drugs used in neuroleptanalgesia on cardiovascular and ventilatory function. Br J Anaesth 39:134, 1967.

520. Corssen G, Domino EF, Sweet RB: Neuroleptanalgesia and anesthesia. Anesth Analg 43:748, 1964.

521. Israel JS, Jansen GT, Dobkin AB: Circulatory and respiratory response to tilt with pentazocine (Win 20, 228), droperidol (R4749), droperidol-fentanyl (Innovar), and methotrimeprazine in normal healthy male subjects. Anesthesiology 26:253, 1965.

522. Janssen PAJ, Niemegeers CJE, Schellekens KHL: The pharmacology of dehydrobenzperidol (R4749), a new potent and short-acting neuroleptic agent chemically related to haloperidol. Arzneimittelforschung 13:205, 1963.

523. Stanley TH: Cardiovascular effects of droperidol during enflurane and enflurane-nitrous oxide anaesthesia in man. Can J Anaesth 25:26, 1978.

524. Birch AA, Boyce WH: Effects of droperidol-dopamine interaction on renal blood flow in man. Anesthesiology 47:70, 1977.

525. Yelonsky J, Katz R, Dietrich E: A study of some of the pharmacologic actions of droperidol. Toxicol Appl Pharmacol 6:37, 1964.

526. Long G, Dripps RD, Price HL: Measurements of anti-arrhythmic potency of drugs in man: Effects of dehydrobenzperidol. Anesthesiology 28:318, 1967.

527. Wetchler BV, Collins IS, Jacob L: Antiemetic effects of droperidol on the ambulatory surgery patient. Anesthesiol Rev 9:23, 1982.

528. Pandit SK, Kothary SP, Pandit UA et al: Dose-response study of droperidol and metoclopramide as antiemetics for outpatient anesthesia. Anesth Analg 68:798, 1989.

529. Kymer PJ, Brown RE Jr, Lawhorn CD et al: The effects of oral droperidol versus oral metoclopramide versus both oral droperidol and metoclopramide on postoperative vomiting when used as a premedicant for strabismus surgery. J Clin Anesth 7:35, 1995.

530. McKenzie R, Tantisira B, Jackson D et al: Antiemetic efficacy of a droperidol-morphine combination in patient-controlled analgesia. J Clin Anesth 7:141, 1995.

531. Gan TJ, Alexander R, Fennelly M et al: Comparison of different methods of administering droperidol in patient-controlled analgesia in the prevention of postoperative nausea and vomiting. Anesth Analg 80:81, 1995.

532. Aldrete JA: Reduction of nausea and vomiting from epidural opioids by adding droperidol to the infusate in home-bound patients. J Pain Symptom Manage 10:544, 1995.

533. Yelnosky J, Gardocki JF: A study of some of the pharmacologic actions of fentanyl citrate and droperidol. Toxicol Appl Pharmacol 6:48, 1964.

534. Stoelting RK, Gibbs PS, Creasser CW et al: Hemodynamic and ventilatory responses to fentanyl, fentanyl-droperidol and nitrous oxide in patients with acquired valvular heart disease. Anesthesiology 42:319, 1975.

535. Harper MH, Hickey RF, Cromwell TH et al: The magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. J Pharmacol Exp Ther 199:464, 1976.

536. Corssen G, DeKornfield TJ: Comparison of the respiratory depressant effects of fentanyl, fentanyl and droperidol, and morphine. Anesthesiology 27:213, 1966.

537. Ivankovich AD, El-Etr AA, Janeczko GF et al: The effect of ouabaine and of Innovar anesthesia on digitalis tolerance in dogs. Anesth Analg 54:106, 1975.

538. Lieper DJ, Townsend GE: Improved hemodynamic and renal function with clonidine in coronary artery bypass grafting. Anesth Analg 70:S240, 1990.

539. Melnick BM: Extrapyramidal reactions to low-dose droperidol. Anesthesiology 69:424, 1988.

540. Guze BH, Baxter LRJ: Current concepts: Neuroleptic malignant syndrome. Med Intell 313:163, 1985.

541. Parikh AM, Camara E: Neuroleptic malignant syndrome. Am Fam Physician 37:296, 1988.

542. Segal IS, Vickery RG, Walton JK: Dexmedetomidate diminishes halothane anesthetic requirements in rats through a postsynaptic alpha $_2$ adrenergic receptor. Anesthesiology 69:818, 1988.

543. Maze M, Tranquilli W: Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. Anesthesiology 74:581, 1991.

544. Peden CJ, Prys-Roberts C: Dexmedetomidine: A powerful new adjunct to anaesthesia? Br J Anaesth 68:123, 1992.

545. Kaukinen S, Kaukinen L, Eerola R: Postoperative use of clonidine with neuroleptanaesthesia. Acta Anaesthesiol Scand 23:113, 1979.

546. Kaukinen S, Pyykko K: The potentiation of halothane anesthesia by clonidine. Acta Anaesthesiol Scand 23:107, 1979.

547. Bloor BC, Flacke WE: Reduction in halothane anesthetic requirement by clonidine, an alpha adrenergic agonist. Anesth Analg 61:741, 1982.

548. Dyck JB, Maze M, Haack C et al: Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 78:821, 1993.

549. Dyck JB, Maze M, Haack C et al: The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 78:813, 1993.

550. Scheinin H, Karhuvaara S, Olkkola KT et al: Pharmacodynamics and pharmacokinetics of intramuscular dexmedetomidine. Clin Pharmacol Ther 52:537, 1992.

551. Guo TZ, Jiang JY, Buttermann AE et al: Dexmedetomidine injection into the locus ceruleus produces antinociception. Anesthesiology 84:873, 1996.

552. Nacif-Coelho C, Correa-Sales C, Chang LL et al: Perturbation of ion channel conductance alters the hypnotic response to the alpha 2-adrenergic agonist dexmedetomidine in the locus coeruleus of the rat. Anesthesiology 81:1527, 1994.

553. Aho M, Erkola O, Kallio A et al: Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. J Clin Anesth 5:194, 1993.

554. Reid K, Hayashi Y, Guo TZ et al: Chronic administration of an alpha 2 adrenergic agonist desensitizes rats to the anesthetic effects of dexmedetomidine. Pharmacol Biochem Behav 47:171, 1994.

555. Hayashi Y, Guo TZ, Maze M: Hypnotic and analgesic effect of the alpha 2-adrenergic agonist dexmedetomidine in morphine-tolerant rats. Anesth Analg 83:606, 1996.

556. Maier C, Steinberg GK, Sun GH et al: Neuroprotection by the alpha 2-adrenoreceptor agonist dexmedetomidine in a focal model of cerebral ischemia. Anesthesiology 79:306, 1993.

557. Karlsson BR, Forsman M, Roald OK et al: The effect of dexmedetomidine, a selective and potent a $_2$ -agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 71:125, 1990.

558. Zornow M, Fleischer J, Scheller M et al: Dexmedetomidine, an a $_2$ -adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. Anesth Analg 70:624, 1990.

559. Zornow MH, Maze M, Dyck JB et al: Dexmedetomidine decreases cerebral blood flow velocity in humans. J Cereb Blood Flow Metab 13:350, 1993.

560. Mirski MA, Rossell LA, McPherson RW et al: Dexmedetomidine decreases seizure threshold in a rat model of experimental generalized epilepsy. Anesthesiology 81:1422, 1994.

561. Halonen T, Kotti T, Tuunanen J et al: Alpha-2-adrenoceptor agonist, dexmedetomidine, protects against kainic acid-induced convulsions and neuronal damage. Brain Res 693:217, 1995.

562. Weinger MB, Segal IS, Maze M: Dexmedetomidine, acting through central alpha-2 adrenoceptors, prevents opiate-induced muscle rigidity in the rat. Anesthesiology 71:242, 1989.

563. Karhuvaara S, Kallio A, Koulu M et al: No involvement of a $_2$ -adrenoceptors in the regulation of basal prolactin secretion in healthy men. Psychoneuroendocrinology 15:125, 1990.

564. Roekaerts P, Prinzen F, Willigers H et al: The effect of dexmedetomidine on systemic haemodynamics, regional myocardial function and blood flow during coronary artery stenosis in acute anaesthetized dogs. J Cardiothorac Vasc Anesth 8:58, 1994.

565. Karhuvaara S, Kallio JH, Salonen M et al: Rapid reversal of a $_2$ -adrenoceptor agonist effects by atipamezole in human volunteers. Br J Clin Pharmacol 31:160, 1991.

566. Aantaa RE, Kanto JH, Scheinin M: Dexmedetomidine premedication for minor gynecological surgery. Anesth Analg 70:407, 1990.

567. Aantaa RE, Kanto J, Scheinin M et al: Dexmedetomidine, an alpha 2-adrenoreceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. Anesthesiology 73:230, 1990.

568. Aho M, Lehtinen AM, Erkola O et al: The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. Anesthesiology 74:997, 1991.

569. Flacke JW, Bloor BC, Flacke WE: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 67:11, 1987.

570. Ghignone M, Quintin L, Duke PC: Effect of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 64:36, 1986.

571. Segal IS, Jarvis DA, Duncan SR: Clinical efficacy of oral-transdermal clonidine combinations during the perioperative period. Anesthesiology 74:220, 1991.

572. Ghignone M, Noe C, Calvillo O et al: Anesthesia for ophthalmic surgery in the elderly: The effects of clonidine on intraocular pressure, perioperative hemodynamics, and anesthesia requirements. Anesthesiology 68:707, 1988.

573. Jaakola ML, Ali-Melkkila T, Kanto J: Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. Br J Anaesth 68:570, 1992.

574. Scheinin B, Lindgren L, Randell T: Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and perioperative fentanyl. Br J Anaesth 68:126, 1992.

575. Aho M, Erkola O, Kallio A: Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. Anesth Analg 75:940, 1992.

576. Salmenpera MT, Szlam F, Hug CC Jr: Anesthetic and hemodynamic interactions of dexmedetomidine and fentanyl in dogs. Anesthesiology 80:837, 1994.

577. Talke P, Li J, Jain U et al: Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery: The Study of Perioperative Ischemia Research Group. Anesthesiology 82:620, 1995.

578. Zorumski CF, Isenberg KE: Insights into the structure and function of GABA-benzodiazepine receptors: Ion channels and psychiatry. Am J Psychiatry 148:162, 1991.

579. Vinik HR, Bradley EL Jr, Kissin I: Triple anesthetic combination: Propofol-midazolam-alfentanil. Anesth Analg 76:S450, 1993.

580. Janssen PAJ: Pharmacological aspects. In Bente D, Bradley P (eds): Neuropsychopharmacology. Amsterdam, Elsevier Science, 1965, p 151.

581. Moffet ACE: Clarke's Isolation and Identification of Drugs. 2nd ed. London, Pharmaceutical Press, 1986.

582. McClain DA, Hug CC: Intravenous fentanyl kinetics. Clin Pharmacol Ther 28:106, 1980.

583. Dhadphale PR, Behrendt DM, Jackson PF: The effect of diazepam on contractility in the intact human heart. In Abstracts of Scientific Papers, American Society of Anesthesiology Annual Meeting, New Orleans, 1977.

584. Prakash R, Thurer R, Vargas A: Cardiovascular effects of diazepam induction in patients for aortocoronary saphenous vein bypass grafts. In Abstracts of Scientific Papers, American Society of Anesthesiology Annual Meeting, 1976.

585. Jackson APF, Dhadphale PR, Callaghan ML: Haemodynamic studies during induction of anaesthesia for open-heart surgery using diazepam and ketamine. Br J Anaesth 50:375, 1978.

586. Cote P, Noble J, Bourassa MG: Systemic vasodilation following diazepam after combined sympathetic and parasympathetic blockade in patients with coronary heart disease. Cathet Cardiovasc Diagn 2:369, 1976.

587. Tweed WA, Minuck M, Mymin D: Circulatory responses to ketamine anesthesia. Anesthesiology 37:613, 1972.

588. Tweed WA, Mymin D: Myocardial force-velocity relations during ketamine anesthesia at constant heart rate. Anesthesiology 41:49, 1974.

589. Nishimura K, Kitamura Y, Hamai R: Pharmacological studies of ketamine hydrochloride in the cardiovascular system. Osaka City Med J 19:17, 1973.

590. Schmucker P, van Ackern K, Franke N et al: Einwirkung von intravenos appliziertem Lormetazepam auf Hamodynamik und arterielle Blutgase bei Patienten mit koronarer Herzerkrankung. Anaesthesist 31:557, 1982.

591. Lebowitz PW, Cote ME, Daniels AL et al: Cardiovascular effects of midazolam and thiopentone for induction of anesthesia in ill surgical patients. Can J Anaesth 30:19, 1983.

592. Marty J, Nitenberg A, Blancet F: Effects of midazolam on the coronary circulation in patients with coronary artery disease. Anesthesiology 64:206, 1986.

Chapter 10 - Intravenous Opioid Anesthetics

Peter L. Bailey
Talmage D. Egan
Theodore H. Stanley

INTRODUCTION

Significant advances continue to be made in the science and practice of anesthesia. The number of scientific reports concerning opioids continues to exceed 3,000 citations per year. Research interests range from molecular genetics and the biology of opioids through the neurosciences to many clinical specialties. Such a voluminous amount of information presents obvious difficulties for the writer as well as the reader of textbook chapters on opioid pharmacology. It has thus become impossible to create a chapter that is simultaneously comprehensive and useful for clinical anesthesia practitioners. In this fifth edition chapter, discussions of older agents and techniques, which are no longer a part of modern practice, are minimized. The interested reader should refer to earlier editions of this textbook for discussions of formerly used agents and techniques.

Opioids have been administered for hundreds of years to allay anxiety and to reduce the pain associated with surgery. Many of these compounds not only are used as premedicants and analgesics during and after anesthesia and surgery, but also serve as intravenous (IV) anesthetics. In this chapter, the pharmacology and use of opioids in contemporary anesthetic practice are reviewed. The terms "opioid" and "opiate" are used to describe drugs that specifically bind to any of several subspecies of opioid receptors and share some of the properties of one or more of the naturally occurring endogenous opioids. The term "narcotic" is Greek in origin and means "to numb or deaden." It can refer to non-opioid compounds as well and is avoided.

HISTORY

Although morphine-like alkaloids had been used for analgesia and sedation for centuries, the isolation of morphine as the active ingredient from opium by Serturner in the early 1800s and the introduction of the syringe and hollow needle to clinical practice by Wood in 1853 finally permitted opioids to be administered in more precisely measured doses. [1] Morphine was, at that time, frequently injected intramuscularly (IM) for preoperative medication, as a supplement during ether or chloroform anesthesia, and postoperatively for analgesia. Late in the nineteenth century, large amounts of morphine (1 to 2 mg kg^{-1}) plus scopolamine (1 to 3 mg 70 kg^{-1}) were administered in divided doses IV, IM, or both, as a complete anesthetic. [2] Although initially popular, this technique rapidly fell into disfavor because of an increase in operative morbidity and mortality. [3] For the next 30 to 40 years, anesthesiologists rarely used opioids intraoperatively.

Introduction of the short-acting barbiturates as IV anesthetics and popularization of the concept of "balanced anesthesia" led to renewed interest in opioids as anesthetic agents. [4] Important events in this development were the synthesis of meperidine in 1939 and its use for anesthesia with nitrous oxide (N_2O), with or without *d*-tubocurarine. [5] In 1942, nalorphine (N-allylnormorphine), a mixed agonistantagonist, was introduced. Although an analgesic itself, nalorphine was recognized as an antagonist capable of reversing morphine-induced respiratory depression and inducing abstinence syndrome in addicted individuals. [6] The development of naloxone, as a purer antagonist, followed shortly.

Many variations of the "N_2O-narcotic" or balanced anesthesia technique became popular. At first, thiopental for induction and maintenance of anesthesia, *d*-tubocurarine, and opioids such as morphine, meperidine, or alphaprodine were commonly employed. After the introduction of Innovar-N_2O anesthesia [7] (Innovar consists of the butyrophenone droperidol and the opioid fentanyl), various IV supplements were employed, including hypnotics, sedatives, tranquilizers, and additional analgesics. These techniques were often termed "balanced anesthesia," because each IV compound was selected and administered to achieve a specific effect, such as analgesia, unconsciousness, amnesia, muscle relaxation, or abolition of autonomic reflexes.

Following this, opioids and sedative-hypnotics were, and continue to be, administered IV during anesthesia in combination with potent inhaled anesthetics. Benefits attributed to such techniques are that IV agents reduce the concentrations of inhaled anesthetics required for anesthesia, result in less depression of cardiovascular and other organ systems, and allow for better recovery from anesthesia.

Lowenstein et al [8] and Stanley and Webster [9] reintroduced the practice of administering large doses of opioids as primary or sole anesthetics. Morphine (0.5 to 3.0 mg kg^{-1}), administered IV to patients while they breathed 100 percent O_2, did not alter the cardiovascular dynamics in those patients who did not have cardiac disease and in many cases improved the cardiovascular status of those with significant valvular disease. [8] These reports led to additional studies evaluating morphine and other opioids as sole anesthetics for patients with poor cardiovascular reserve who were undergoing major operative procedures. [10] [11] [12] Unfortunately, problems with incomplete amnesia, [13] histamine release, [14] prolonged postoperative respiratory depression, [15] [16] increased blood volume requirements secondary to marked venovasodilation, [11] hypotension, and hypertension [10] diminished the popularity of morphine as a sole anesthetic. [13] Large doses of fentanyl do not produce many of the unwanted adverse hemodynamic effects associated with large doses of morphine.

The synthetic opioid fentanyl remains popular as an IV supplement in combination with an inhaled anesthetic, as a component of balanced anesthesia, and also administered in larger doses as a primary or sole anesthetic. Unfortunately, large doses of fentanyl also cause significant postoperative respiratory depression, which militates against this application

TABLE 10-1 -- Lowest ED_{50} Values in the Tail-Withdrawal Test in Rats, LD_{50} Values, and Safety Margins of Different Opioids After Intravenous Administration

COMPOUNDS	LOWEST ED_{50} mg kg^{-1}	LD_{50} mg kg^{-1}	THERAPEUTIC INDEX (SAFETY MARGIN)
Meperidine	6.0	29.0	4.8
Alfentanil	0.044	47.5	1,080
Fentanyl	0.011	3.1	277
Sufentanil	0.007	17.9	25,211
Lofentanil	0.0059	0.066	112
Carfentanil	0.0034	3.4	10,000

ED_{50}, median effective dose; LD_{50}, median lethal dose.

in patients who may otherwise meet tracheal extubation criteria shortly after surgery.

More recently, sufentanil, alfentanil, and remifentanil were introduced into clinical practice. Each of these agents offers potentially significant clinical advantages, in addition to greater therapeutic indexes in animal models (Table 10-1) . Sufentanil alone is more potent and is possibly more effective than fentanyl as a primary or sole anesthetic. Alfentanil is very rapid in its onset and may be more predictable in terms of determining the dose required to produce effective plasma drug levels and to obtund the response to many surgical stimuli when it is administered with N_2O. [17] Predictability has been a problem with opioids: plasma concentrations following a standard dose can vary up to 5-fold. Similarly, variability in therapeutic plasma levels, which effectively block a defined response to a stimulus in 50 percent of patients (i.e., Cp_{50}), has also been 3- to 5-fold. Both plasma concentrations of sufentanil and alfentanil decline more rapidly than those of fentanyl and result in more rapid patient recovery after the termination of IV infusions of these drugs. [18]

Remifentanil is also very rapid in its onset and has an ultrashort duration of action, which is independent of the length of time the drug is administered. Among the modern opioids currently employed, this feature is unique and allows for the rapid dissipation of even profound opioid action at the end of surgery.

Other developments include continued improvements in the understanding of drug pharmacokinetics and pharmacodynamics and advances in computer-assisted mechanical drug delivery systems (Ch. 11) . In addition, anesthesiologists continue to play an important role in advancing the treatment of pain. Resistance to the

concept of opioids as acceptable and appropriate agents for the treatment of severe chronic pain persists despite expert opinion. However, opioids remain at the center of new and exciting pain control therapies. Newer routes of drug delivery, including the skin and buccal, sublingual, nasal, and rectal mucosal surfaces, continue to be investigated for administering opioid analgesics. These approaches have resulted in transdermal fentanyl patches, sufentanil nasal sprays, oral transmucosal fentanyl citrate applications, and a variety of other approaches.

Reports that postoperative outcome is favorably altered by sufentanil anesthesia or analgesia suggest that opioid-induced stress reduction may be clinically significant. [19] [20] However, numerous other investigations have failed to find outcome differences associated with one anesthetic agent or anesthetic technique compared with another. [21] [22] [23] The lack of compelling evidence that large doses of opioids confer any major advantage, combined with efforts to make anesthesia as cost-effective as possible, have led to moderation in the doses of opioids administered as anesthetics. Nevertheless, opioids continue to occupy an important niche in the anesthesiologist's armamentarium of anesthetic and therapeutic agents.

The prediction and discovery of opioid receptors in the early 1970s preceded the recognition and documentation of endogenous opiate-like compounds (see later). These landmark discoveries introduced an era of prolific research that continues to this day. Ultimately, genetically based investigations will delineate the DNA coding of opioid receptors, the molecular structure of opioid receptors, and will result in definitive descriptions of the molecular biology of opioids. Numerous difficulties that have plagued opioid research are now being solved as a result of genetic research. Cloning of opioid receptors, with expression of single receptor types in separate cell lines, will allow their pharmacologic, functional, and biochemical characteristics to be determined. [24] Ultimately, although an elusive goal to date, the development of pharmacologic agents with the analgesic potency of opioids but without their adverse effect profile is anticipated. Undoubtedly, exciting advances remain on the horizon.

CLASSIFICATION

Several classification systems are available to describe opioids. Opioids can be classified as naturally occurring, semisynthetic, and synthetic (Table 10-2) . Morphine, codeine, and papaverine, the only naturally occurring opioids of clinical significance, are obtained from the poppy plant, *Papaver somniferum.*[*]

Papaverine is devoid of opiate activity, but it does relax smooth muscle. The naturally occurring opioids of significance can be divided into two chemical classes, five-ring structures, entitled the phenanthrenes (morphine and

* Papaveretum is a preparation containing the water-soluble alkaloids of opium with 50 percent anhydrous morphine and the remaining 50 percent a mixture of papaverine, codeine, and thebaine. Papaveretum on a weight basis is approximately half as potent as morphine.

TABLE 10-2 -- Classification of Opioid Compounds

Naturally occurring
Morphine
Codeine
Papaverine
Thebaine
Semisynthetic
Heroin
Dihydromorphone/morphinone
Thebaine derivatives (e.g., etorphine, buprenorphine)
Synthetic
Morphinan series (e.g., levorphanol, butorphanol)
Diphenylpropylamine series (e.g., methadone)
Benzomorphan series (e.g., pentazocine)
Phenylpiperidine series (e.g., meperidine, fentanyl, sufentanil, alfentanil, remifentanil)

codeine), and three-ring compounds, the benzylisoquinoline derivatives (papaverine). Of the naturally occurring opioids, only morphine is of clinical importance in anesthesia.

The semisynthetic opioids are derivatives of morphine in which any one of several changes has been made, such as etherification of one hydroxyl group (codeine), esterification of both hydroxyl groups (heroin), oxidation of the alcoholic hydroxyl to a ketone drug, or reduction of a double bond on the benzene ring (hydromorphone). Thebaine, a relatively inactive opium derivative itself, is a precursor of several derivative compounds used clinically including oxymorphone, oxycodone, and naloxone. Etorphine (M99), another thebaine derivative, is several thousand times more potent than morphine; this compound has been used successfully for immobilization and anesthesia in wildlife management. [25]

Synthetic opioid compounds are divided into four groups: the morphinan derivatives (levorphanol), the diphenyl or methadone derivatives (methadone, *d*-propoxyphene), the benzomorphans (phenazocine, pentazocine), and the phen-ylpiperidine derivatives (meperidine, fentanyl, alfentanil, sufentanil, and remifentanil). The general phenylpiperidine skeletal structure and derivatives meperidine and fentanyl are illustrated in Figure 10-1 . Important opiate receptor research compounds (ketocyclazocine and SKF 10,047) also belong to this group. Although many of these synthetic opioids have been used for IV analgesia or anesthesia experimentally, the phenylpiperidine derivatives currently occupy the predominant role in anesthesia.

Opioids can also be classified as agonists, partial agonists, mixed agonist-antagonists, and antagonists. Although agonist and antagonist opioids alike may bind to effector (receptor) sites, only agonists elicit any effect. Thus, pure antagonist opioids have intrinsic activities or efficacies of 0, and agonist opioids, which at some concentration elicit the full spectrum and magnitude of pharmacophysiologic effects, have intrinsic activities of 1. Partial agonists exhibit intrinsic activities of less than 1. Figure 10-2 (Figure Not Available) illustrates schematically these various types of compounds and their interactions.

Agonists are used most commonly in anesthesia, because the majority of opioid actions sought can be produced in a dose-dependent fashion (see later). Partial agonists, such as buprenorphine, regardless of dose, cannot produce the full magnitude of opioid (mu-receptor-mediated) effects. Nalbuphine is a mixed agonist-antagonist compound that acts as an agonist at one receptor (kappa), thereby producing effects

Figure 10-1 The phenylpiperidine skeleton structure and the synthetic phenylpiperidine opioids meperidine and fentanyl.

such as weak, spinally mediated analgesia, and as an antagonist at another (mu), resulting in its ability to reverse agonist-induced respiratory depression. Naloxone is a relatively pure antagonist that elicits few or no effects on its own at clinical doses, but it acts competitively to displace agonists from opioid receptors, although to different degrees.

Matters are, however, quite complex. For example, low doses of naloxone can effectively reduce adverse effects associated with morphine administration for postoperative pain and, interestingly, can decrease morphine requirements for pain relief, too. [26] Furthermore, the range of intrinsic activities produced by a given

drug can vary depending on numerous factors, such as receptor reserve and differences in coupling systems (e.g., receptor subtypes, G protein systems). Thus, the apparent classification of certain drugs as partial agonists, for example, to explain decreased intrinsic activity may instead simply represent differences in conditions and models studied. [27]

A third and most modern and relevant classification of opioid drugs describes these agents according to their interactions with opioid receptor types and spectrum of elicited effects. The following section details these receptors and what they reveal to us about the pharmacophysiology of opioids.

MECHANISMS OF ACTION

Structure-Activity Relationships

The structural dissimilarities among compounds displaying opiate activity almost defy a common mechanism as the basis for opioid structure-activity relationships. However, a detailed analysis of opioid stereospecificity has been used to

Figure 10-2 (Figure Not Available) Receptor interactions of opioids. Opioid-receptor interactions are illustrated in terms of a lock-and-key diagram with two receptor sites, mu and kappa, and a representative dose-response (DR) curve of analgesic effects. (A) An opioid agonist stimulates both mu- and kappa-receptors. The steep portion of the DR curve is in the clinical dose range (CDR), and analgesia is unlimited. (B) Partial agonists such as buprenorphine combine with the mu-receptor, but they have only limited activity. The DR curve is flatter, with a lower maximum effect. The partial agonist shifts the DR curve for an agonist to the right. (C) The opioid antagonist naloxone can occupy both mu- and kappa-receptors, but it has no intrinsic activity. The antagonist shifts the DR curve for an agonist to the right. (D) The agonist-antagonist opioids (e.g., nalbuphine) may have mixed effects at the mu- and kappa-receptor. Analgesia is kappa-receptor related, whereas blockade occurs at the mu-receptors. This naloxone-like effect would shift the DR curve to a mu-agonist to the right. *(From Hare. [121] Reproduced with permission from Formulary, Vol. 22, 1987. Copyright by Avanstar Communications Inc. Avanstar Communications Inc. retains all rights to this article.)*

describe a hypothetic three-dimensional model of the opiate receptor responsible for opioid activity. [28] Structurally, opioids are complex, three-dimensional compounds that sometimes exist as two optical isomers (e.g., morphine). [29] Usually, only the *l*-rotary isomer is capable of producing analgesia.

A close relationship exists between the stereochemical structure of an opioid compound and the presence or absence

of analgesic activity. [30] In addition, even relatively minor molecular changes, such as the degree of ionization produced by variations in pH, may cause significant alteration in pharmacologic activity of opioid compounds. [30]

The prototype opioid is morphine. Its rigid pentacyclic structure conforms to a T-shape [28] (Fig. 10-3) (Figure Not Available) . Morphine demonstrates several other structural characteristics common to most opioids: a tertiary positively charged basic nitrogen, a quaternary carbon (^{13}C in morphine) that is separated from the basic nitrogen by an ethane chain (-CH_2 -CH_2 -) and is attached to a phenyl group, a phenolic hydroxyl group (in morphine derivatives), or a ketone group (meperidine, methadone), and the presence of an aromatic ring whose center is 4.55 A from the nitrogen atom. [28]

The morphine molecule also contains a phenylpiperidine structure (an aromatic ring attached to a six-membered ring containing five carbons and one nitrogen). This moiety is present in opioids that otherwise seem unrelated to morphine, such as fentanyl (see Fig. 10-1) . [28] Short-chain alkyl group substitution at the basic amino group (the group essential for opioid activity) results in mixed opioid agonistantagonists. [31] Additional hydroxylation of ^{14}C produces opioids with antagonist and no agonist properties. [32] Phenylalanine and, especially, the tyrosine moiety are important structural elements of all opioid compounds (see later), as well as endogenous opioid-like neurotransmitters and modulators. [33] [34] Interestingly, morphine is synthesized by the poppy plant from two tyrosine molecules, and many opiates contain a moiety that bears a configurational similarity to alanine. [28]

Site and Mechanism of Opioid Action

Opioid Receptors

In 1973, three independent teams of investigators described the presence of an "opioid receptor" in nervous tissue and hypothesized that endogenous substances probably stimulate this structure. [35] [36] [37] This rationale was supported by numerous observations, including the finding that naloxone could reverse footshock-induced analgesia. A few years later, the endogenous opiates were discovered (see later).

The original classification of opioid receptors was based on response patterns to three different opioid compounds in the chronic spinal dog model [38] and resulted in the description of three receptor types, named after the drugs used in

Figure 10-3 (Figure Not Available) The T-shaped molecule of morphine. *(From Thorpe [28])*

the studies: mu (morphine), kappa (ketocyclazocine), and sigma (SKF 10,047 or *N*-allylnormetazocine). The "sigma" receptor is no longer considered an opioid receptor but rather a highaffinity binding site for phencyclidine and related compounds. [39] In addition, sigma-receptor-mediated effects are enantio-selective for dextrorotatory, instead of levorotatory, compounds. Finally, sigma-receptor-mediated effects are not naloxone-reversible. In 1977, Lord and colleagues described a binding site in the isolated mouse vas deferens with high affinity for enkephalins. This opioid receptor site was named the delta receptor, after deferens.

The profile of effects thought to be associated with a specific receptor is derived in numerous ways, including the potency and physiologic effects of a variety of agonist and agonist-antagonist interactions, the results of various bioassay and binding studies, structure-activity relationship data, and numerous other screening evaluations. For example, potency often correlates with receptor affinity and is described by the IC_{50} value, defined as the concentration of an agent that lowers the specific binding of ^{3}H-naloxone by 50 percent. The greater the affinity of such an agent for a receptor, the lower the IC_{50} , [31] and the smaller the dose and number of molecules necessary to occupy enough receptors to elicit a certain level of effect. Intrinsic efficacy, a property of drug-receptor interaction, is directly related to the number of spare receptors: the greater the intrinsic efficacy of a drug, the greater the receptor reserve.

Bioassay systems are used to help evaluate potency. The response to transmural electrical stimulation of a number of isolated tissues can be inhibited by opioids. This effect is most likely mediated by the presynaptic inhibition of transmitter release (neuromodulation). The two most important of these systems are the guinea pig ileum and mouse vas deferens. For example, morphine inhibits electrically induced contractions of the isolated guinea pig ileum. Data from these systems correlate well with opioid analgesic potency, [40] as determined by numerous intact animal and clinical evaluations. Biochemical characterizations of opiate receptors also have been used in receptor research. [31] Attempts to purify opioid receptors have been thwarted by their paucity in most tissues and chemical instability during isolation. Some investigators have reported the cloning and sequencing of opioid receptor types. [24] Five cDNAs that belong to the opioid receptor gene family have been cloned, but only three opioid receptor types (mu, delta, kappa), each arising from their own gene, have been pharmacologically defined. Three subtypes of each

receptor have been proposed but have not yet been cloned (Table 10-3) .

The mu-opioid receptor manifests a high affinity for endogenous enkephalin, and the distribution of mu-receptors and enkephalin mRNA is highly correlated. Investigations utilizing opiate receptor knockout mice demonstrate that morphine-induced analgesia is mu-receptor-mediated. [41] Enkephalins also interact with delta-receptors. kappa-Receptors, on the other hand, have high affinity for the endogenous opiate dynorphin.

mu-Receptors are located in both the brain and spinal cord, with highest concentrations in the periaqueductal gray and substantia gelatinosa, respectively. mu-Receptor opioidinduced analgesia is dose-dependent. Pharmacologic distinction of an analgesic mu-receptor (mu_1) and a respiratory depression mu-receptor (mu_2) is suggested, but it remains in

TABLE 10-3 -- Characteristics of Opioid Receptors

	mu	delta	kappa
Tissue bioassay	Guinea pig ileum	Mouse vas deferens	Rabbit vas deferens
Endogenous ligand	Enkephalin beta-Endorphin (?)	Enkephalin	Dynorphin
Exogenous agonist ligand	Morphine Phenylpiperidines DAMGO, DAGO	DPDPE DADLE 1 Deltorphin	U 50,488 Butorphanol Bremazocine
Antagonist	Naloxone Naltrexone	Naloxone Naltrindole	Naloxone NorBNI
Cloned (human)	Yes	Yes	Yes
Subtypes	1,2,3	1,2,3	1,2,3
G protein-coupled	Yes	Yes	Yes
Adenylate cyclase	Inhibits	Inhibits	Inhibits
Voltage-dependent calcium channels	Inactivates	Inactivates	Inactivates
Potassium channel conductance	Increases	Increases	?
Actions	Analgesia, sedation, respiratory depression, miosis, bradycardia, nausea, vomiting, decreased gastrointestinal mobility	Supraspinal analgesia Respiratory depression (?)	Spinal analgesia Diuresis Dysphoria Respiratory depression, (weak)

DAGO, [Tyr-D-Ala-Gly-McPhe-Gly-ol]; DAMGO, [D-Ala^2, $MePhe^4$, $Gly(ol)^5$]; DPDPE, [D-Pen^2, D-Pen^5].

question. [42] [43] A mu_3 -receptor may be involved in immune processes because it has significant distribution in astrocytes, endothelial cells, and macrophages. It is not clear whether or not these various receptor subtypes originate from separate genes or from post-translational modifications.

There is no selective systemic agonist available for delta- receptors, and the enkephalins are rapidly degraded. The degree of analgesia that is produced by stimulation of the delta-receptor is unclear (and may be more important at the spinal cord level). mu_1 -Receptors also appear more prominent in supraspinal analgesia, whereas delta-receptors may be more important for spinal analgesia. [44] kappa-Receptors appear to play a role in producing mild to moderate analgesia at the spinal cord level for nonthermal painful stimuli (Table 10-4) . The kappa-receptor agonist ethylketocyclazocine produces sedation and analgesia without causing much respiratory depression. [45] kappa-Receptor activation may explain in part some of the effects (analgesia with limited respiratory depression)

TABLE 10-4 -- Supraspinal and Spinal Sites and Opioid Receptor Types Mediating Analgesia [a]

LOCATION	RECEPTOR SELECTIVITY
Supraspinal	
Periaqueductal gray area	mu, kappa >delta
Raphe nuclei	
Caudal linear	kappa
Dorsal	kappa > mu
Median	mu > kappa
Magnus	mu > kappa
Pallidus	delta
Gigantocellular reticular	mu, kappa, delta
Spinal	
Spinal cord	mu, delta, kappa
Dorsal root ganglia	mu, delta, kappa

[a] Analgesic effects are mediated by mu-, delta-, and kappa-receptors. Receptor-mRNA expression suggests that mu-, delta-, and kappa-receptor-mediated analgesics can act at both supraspinal and spinal levels.

of some mixed agonist-antagonists such as enalbuphine. [38] At least three separate kappa-receptor subtypes have been isolated. $kappa_3$ -receptors are of particular interest because of their high density within the brain and association with supraspinal analgesia, whereas other kappa-receptors relate to spinal analgesia. [46]

Cellular Mechanisms

Opioid receptors belong to the superfamily of G protein- coupled receptors, all of which possess seven membrane-spanning regions. [24] [47] This group constitutes 80 percent of all known receptors and includes muscarinic, adrenergic, gamma-aminobutyric acid (GABA), and somatostatin receptors. The three opioid receptors have high amino acid sequence similarity to somatostatin receptors and very low similarity with all other receptors. The amino acid sequences of the opioid receptors are approximately 60 percent identical to one another, with greatest similarities existing in transmembrane and intracellular regions (Fig. 10-4) (Figure Not Available) . Specific amino acid sequences of the extracellular loops of opioid receptors are key in determining ligand-specific actions. Phosphorylation and glycosylation sites are responsible for a host of opioid-related effects including agonist-induced analgesia and desensitization or uncoupling of the receptor from G proteins. [48] Extracellular

signal-related kinase activation may also contribute to opioid-induced biologic effects. [49]

Studies indicate both presynaptic (indirect) and post-synaptic (direct) facilitatory and inhibitory actions of opioids on synaptic transmission in many regions of the nervous system. Direct inhibitory actions of opioids are mediated by opioid receptors coupled to pertussis toxin-sensitive G_i/G_o proteins and direct excitatory effects via a cholera toxin-sensitive G_s-like protein. The opioid receptor-activated G protein effector systems can be divided into two categories: short-term effectors (K^+ and Ca^{2+} channels) and longer-term effectors involving second messengers such as adenylate cyclase/cyclic adenosine monophosphate (cAMP) and

Figure 10-4 (Figure Not Available) Proposed model for membrane topography of the rat mu-opioid receptor. Amino acid residues of mu-opioid receptor conserved in both delta- and kappa-receptors, in either delta- and kappa-receptors, and in neither delta- nor kappa-receptor are shown by black, gray, and white circles, respectively. Branched structures show the potential *N*-linked glycosylation sites. *(Reprinted from Minami and Satoh, [51] with permission of Elsevier Science.)*

phosphatidylinositol. Both mu- and delta-receptors activate inwardly rectifying K^+ channels and all opioid receptor types can inhibit the opening of voltage-dependent Ca^{2+} channels. mu-Opioid agonists can also directly increase Ca^{2+} entry and cellular Ca^{2+} concentrations. [50] Changes in cAMP may underlie opioid-induced modulation of the release of neurotransmitters such as substance P. These previously mentioned actions account for many of the effects of opioids. For example, K^+ channel effects result in hyperpolarization of neuronal membranes and decreased synaptic transmission. Decreases in Ca^{2+} influx can decrease neurotransmitter mobilization and release. Opioid-induced changes in Ca^{2+} concentration are likely to be a component of the mechanisms of opioid analgesia.

Opioids also have excitatory actions, indirectly by interneuron disinhibition and directly by neuronal excitation, via G_s proteins. This may explain some neuroexcitatory responses to opioids.

Mechanisms of Analgesia

There is significant concordance between specific receptor mRNA expression in the central nervous system (CNS) and binding of specific receptor ligands [51] [52] (see Table 10-4) . Many of these areas are in major ascending and descending pain pathways (Fig. 10-5) . The transport of opioid receptors is thought frequently to underlie differences that exist in receptor mRNA and ligand binding distributions. Research on opioid receptors has entered a new era in which receptors can be examined with dual labeling techniques utilizing both specific ligands and gene structure and mRNA expression. Resultant anatomic studies will help to characterize the phenotype and function of CNS centers, nuclei, and even individual cells. [52]

Numerous studies do demonstrate opioid action and behaviorally defined analgesia in many CNS sites. These include the amygdala, the mesencephalic reticular formation, the periaqueductal gray matter, and the rostral ventral medulla. However, the role of some of the higher brain structures containing opioid receptors in opioid analgesia remains obscure and controversial. The proposed mechanisms by which opioids alter nociception are summarized in Figure 10-5 .

The periaqueductal gray area is one of the regions in the brain stem where microinjections of morphine or direct electrical stimulation produce analgesia that can be blocked with naloxone. [53] [54] [55] Stimulation of periaqueductal gray receptors with morphine, electricity, or endogenous opiate-like peptides results in impulses that alter the degrees of inhibition of different neuronal pools and contribute to reducing the transmission of nociceptive information from peripheral nerves into the spinal cord and up the neuraxis. [55] Opioid actions at the periaqueductal gray area influence, through direct neural connections, the rostral ventromedial region of the medulla. This region of the medulla, in turn, modulates nociceptive transmission neurons in the dorsal horn of the spinal cord. The integrity of such neurotransmitter

Figure 10-5 Diagram illustrating proposed antinociceptive mechanisms of morphine in the central nervous system.

systems connecting the pain-inhibiting system in the brain to the spinal cord is necessary for morphine to exert its full analgesic action. Thus, opioids do not only produce analgesia by direct actions. Whereas opioid application at the spinal cord, for example, produces analgesia at the level of administration, neurally mediated actions at distant CNS sites also enhance analgesia. The systemic administration of opioids activates the analgesic "system" in the CNS. [56]

Local spinal mechanisms, in addition to descending inhibition, underlie the analgesic action of opioids. Opioids act at nerve synapses either presynaptically (as neuromodulators) or postsynaptically (as neurotransmitters) (Fig. 10-6) (Figure Not Available) . [57] The substantia gelatinosa of the spinal cord possesses a dense collection of opiate receptors. [29] [58] Direct application of opioids to these receptors creates intense analgesia. Spinal cord presynaptic substance P release in primary sensory neurons is inhibited by mu-, kappa-, and delta- agonists and is one neuraxial mechanism of opioid analgesia. [59]

Opiate receptors are also localized in the substantia gelatinosa of the caudal spinal trigeminal nucleus, the nucleus receiving pain fibers from the face and hands via branches of the fifth, seventh, ninth, and tenth cranial nerves. [53] Opioids inhibit neuronal excitation of the dorsal horn in response to

Figure 10-6 (Figure Not Available) A schematic diagram illustrating the release of the excitatory transmitters from C fibers and the subsequent effects on a dorsal horn nociceptive neuron. The predominant presynaptic action of opioids (reducing the release of these transmitters) and the postsynaptic action (reducing neuronal activity) are shown. *(From Dickenson [57])*

painful sharp stimulation, and sensations via A delta fibers are reduced. Excitatory postsynaptic potential summation is also blocked by opioids in the dorsal horn blocking the development of dull persistent pain transmitted via C fibers. This summation is much easier to block than to treat and underlies the concept of preemptive analgesia as well as the clinical observation that patient responses to surgery are easier to control with opioids before rather than after stimulation. Opioids also affect second-order neurons by preventing excitatory threshold reductions and receptive field expansions at the spinal cord level. Opioids may also inhibit the early expression of DNA that is integral to transforming cellular characteristics necessary for the development of chronic or persistent pain (see Fig. 10-6) (Figure Not Available) .

Opioids may also produce some analgesia via peripheral mechanisms outside the CNS [60] (Fig. 10-7) (Figure Not Available) . Not all studies confirm this capacity in humans, [61] and the clinical relevance of this phenomenon appears to be negligible. [62] Factors affecting the efficacy of opioid action in the periphery, such as inflammation, may be important. Opioid receptors located on primary afferent neurons are likely sites of action, and immune cells infiltrating inflamed tissue may produce the endogenous ligands for these peripheral receptors.

Several other mechanisms of opioid action have been suggested. Opioid agonists produce a local anesthetic-like effect on the surface of excitable cell membranes that does not involve a stereospecific receptor and may contribute to some of their actions. [63] More recent work suggests that the local anesthetic effects of opioids, most prominent with meperidine, occur at the proximal end of the dorsal root as it passes the dorsal root entry zone. [64] Serotoninergic pathways may also in part modulate opioid-mediated analgesia. [65] Some opioid effects may be elicited at GABA receptors. Finally, it has also been postulated that opioid anesthesia may involve a general membrane effect because of much closer correlations between electroencephalographic (EEG) or anesthetic effects and membrane lipid content as opposed to serum opioid levels. [66]

Tolerance is a diminished response to opioid action and occurs within hours to days or weeks. Tolerance may represent an uncoupling of the usual drug-receptor effect. It may result from downregulation of the number of receptors and/or their affinity for agonists or an uncoupling between the receptor and intracellular second messengers via increases in adenyl cyclase activity. Tolerance may also develop as a result of other compensatory cellular responses to the presence of continuous opioid action that result in the restoration of cAMP homeostasis. [67] The level of expression of mu-opioid receptor mRNA is not static, and its regulation by protein

kinase C activation, with subsequent phosphorylation of opioid receptor protein, contributes to alterations in responsiveness to opioid agents in long-term opioid use. [68] Interestingly, there is little cross-tolerance between most receptor subtypes. In addition, the most potent opioid agonists with the largest receptor reserve, such as sufentanil, appear to be least prone to producing tolerance. [69] Tolerance is surmountable by increasing dose, at least initially.

Receptorology has also helped delineate, through receptor pharmacokinetic studies, how certain drugs can have a duration of action that extends well beyond what the plasma

Figure 10-7 (Figure Not Available) Schematic representation of possible peripheral opioidergic mechanisms. The neuronal cell body is located in the dorsal root ganglion. Opioid receptors are transported toward its central (right) and peripheral (left) terminals. After stimulation with cytokine (interleukin-1) or corticotropinreleasing hormone, opioid peptides are released from monocytes or macrophages (M) or lymphocytes (L). Occupation of neuronal opioid receptors by these ligands decreases the release of excitatory (proinflammatory) neuropeptides (e.g., substance P or calcitonin-gene-related peptide) and the excitability of the primary afferent neuron. *(From Stein [60])*

half-life would predict. For example, buprenorphine's dissociation from the mu-receptor is much slower than fentanyl's and does not parallel plasma concentrations. [70] The high affinity of buprenorphine for mu-receptors also accounts for the difficulty of reversing its effects with naloxone.

Other pharmacologic phenomena have been explained by radioligand-receptor studies. The concentration and proportion of the receptor subtypes can change with time. For example, mu_1 -receptors increase in number and concentration as newborn mice grow and thus provide more analgesia after a similar dose of an opioid agonist. [71] A marked and widespread disappearance of mu- and delta-receptors has been shown to occur in the aging brain. [72] Interestingly, the opposite occurs with benzodiazepine receptors during aging, a finding indicating that these effects are specific and are not representative of a general phenomenon.

The presence of opioid receptors in other areas of the CNS (e.g., basal ganglia, limbic area, cerebral cortex) suggests other roles for the endogenous opiates and their receptors. The cardiovascular system possesses opioid receptors that have been documented by radioligand studies to exist in the heart, the cardiac branches of the vagus and sympathetic nerves, the central cardiovascular regulatory centers, and the adrenal medulla. [73] Receptor-mediated opioid effects, as discussed later, indicate potential roles for and implications of opioids in shock, myocardial ischemia, ischemic preconditioning, and other cardiovascular events.

Endogenous Opioids

Hughes et al [74] first described two brain pentapeptides, methionine-enkephalin and leucine-enkephalin, that shared a four-amino acid sequence (Tyr-Gly-Gly-Phe), had potent affinities for opiate binding sites, and had opiate effects that were reversed by naloxone. Large endogenous opioid peptides, beta-endorphin [75] and dynorphin, [76] have also been described.

Three distinct precursor molecules (coded for by three distinct genes) are at the origin of three families of endogenously produced opioids in humans. The biosynthesis of all these endogenous opiates is complex. Pro-opiomelanocortin, a prohormone with a molecular weight of 30,000, is cleaved to form adrenocorticotropic hormone (ACTH) and beta-lipotropin (beta-LPH). [31] beta-LPH is devoid of opioid activity and, in turn, is cleaved to yield beta-endorphin. [77] The enkephalins have different precursors from those of beta-endorphin, although the amino acid sequence for methionine-enkephalin is contained in beta-LPH (amino acid sequence 61-65). Proenkephalin, a peptide with a molecular weight of 30,000, is the precursor for met-enkephalin and several other enkephalins. [78] Dynorphin, as well as leu-enkephalin, is derived from a third precursor, called prodynorphin. The differential biochemical processing of endogenous opiates parallels regional anatomic differences in endogenous opiate compounds, distribution, and concentration. [31] In spite of their differences, all three families of endogenous opioids possess the common amino acid sequence, *Tyr-Gly-Gly-Phe.*

The endogenous opioids exist in virtually all vertebrate species and in many invertebrates as well. [79] The highest concentrations of beta-endorphin occur in the pituitary gland (anterior and intermediate lobes greater than posterior lobe) and in the medial, basal, and arcuate regions of the hypothalamus. [80] Some long-axoned endorphin-releasing neurons synapse at upper brain-stem locations implicated in nociceptive processes such as the septum, the periaqueductal gray area, and the thalamus. It is unclear whether beta- endorphin exists functionally in the spinal cord. beta-Endorphin also exists outside the CNS, in the small intestine, placenta, and plasma. [81] [82] By contrast, enkephalins are widely distributed in many areas of the CNS (amygdala, globus pallidus, striatum, hypothalamus, thalamus, brain stem, and spinal cord dorsal horn laminae I, II, and V) that receive afferent nociceptive information. Met-enkephalin applied to the ventral surface of the brain stem in cats rapidly depresses ventilation and, to a lesser degree, heart rate and blood pressure. These actions are short-lived and are reversible by naloxone. [83] Enkephalins have also been isolated in the peripheral nervous system (peripheral ganglia, autonomic nervous system, adrenal medulla), as well as the gastrointestinal (GI) tract and plasma. [31]

Dynorphin is found in the hypothalamoneurohypophyseal axis, but as with the other two families of opioids, the role and importance of this finding remain unclear. Dynorphins may function primarily as neuromodulators in the CNS by interacting with mu-, delta-, and kappa-receptors. [84] Electrophysiologic, biochemical, and pharmacologic data support the hypothesis that dynorphin is implicated in specific types of seizures, most notably complex partial (limbic) seizures, that is, those characteristic of temporal lobe epilepsy. [85] kappa-Opioid agonists are effective against limbic seizures. Dynorphins may also play a role in the central control of the cardiovascular system. Dynorphin injected intrathecally at the thoracic level in the rat stimulates blood pressure and heart rate via a nonopioid receptor mechanism. [86] Dynorphin appears to be distributed in other CNS areas relevant to nociception: the periaqueductal gray, limbic system, thalamus, and laminae I and V of the dorsal horn in the spinal cord.

A functional hierarchy exists in nociception and with the endogenous opioids. Primary processing of afferent nociceptive information occurs from peripheral nerve endings to the dorsal horn of the spinal cord. Both dynorphins and enkephalins are active in these areas. Key ascending and descending relay stations for nociception reside in the midbrain, brain stem, and thalamus, and high concentrations of dynorphins, enkephalins, and beta-endorphin can be found in these areas. Higher brain centers involved in the affective dimension of pain (limbic system, amygdala, and cortex) contain significant populations of neurons where dynorphin, enkephalin, and beta-endorphin are found.

beta-Endorphin probably does not play a role in basal nociceptive thresholds but rather modulates nociception during stress, midbrain periaqueductal gray stimulation, and acupuncture. beta-Endorphin administered supraspinally or spinally produces analgesia. [87] Complete elucidation of the role of beta-endorphin in pain perception is still awaited. Enkephalins may play some role in acupuncture-mediated analgesia. Enkephalins may also elicit analgesia through the modulation of substance P release in the dorsal horn. Enkephalins act as inhibitory neurotransmitters. This is consistent with their wide distribution and rapid inactivation throughout the neuraxis. Dynorphin is thought to play a more important role in nociception at the spinal cord level (through activation of the kappa-receptor) than in the brain.

There have been many other roles postulated for endogenous opioids, but they are incompletely defined. For example, mu-receptors can mediate antidiuresis, whereas kappa-receptor activation elicits free water diuresis. The physiologic importance of these phenomena is unknown. Other roles include the modulation of respiratory responses to various stimuli and drugs [88] and participation in the cardiovascular depression seen in shock. [89] beta-Endorphin and met-enkephalin both depress ventilation, whereas dynorphin may not. [90] Several studies demonstrate increases in endogenous opioids in patients with chronic obstructive pulmonary disease. It has been suggested that these opioids serve a protective mechanism that lessens the stress of prolonged dyspnea and reduces excessive increases in the work of breathing. [88] This is especially true in advanced chronic obstructive pulmonary disease in which abnormal ventilation/ perfusion relations do not improve with increased ventilation. [88] Conversely, naloxone may improve ventilation in certain cases of respiratory failure. In certain pathologic conditions (Leigh syndrome, sudden infant death syndrome), increased cerebrospinal fluid (CSF) concentrations of endogenous opioids seem to be associated with apnea. [91] Endogenous opioids may also mediate the placebo effect. [92] The clinical implications of these and other roles for the endogenous opiates remain controversial and unclear. Further information may be obtained in published reviews. [73] [88] [93] [94]

/das/book/view/29494766/875/112.html

PHARMACODYNAMICS: NEUROPHYSIOLOGIC ACTIONS

In healthy, pain-free volunteers, the administration of IV opioids produces dizziness, drowsiness, lethargy, apathy, and sleep. For example, fentanyl, in low doses resulting in analgesic plasma concentrations (1-2 ng/mL), produces similar sedative, but weaker amnesic effects compared with propofol or midazolam. [95] Initially on IV injection, opioids frequently stimulate coughing, which is of brief duration, followed by cough suppression. Opioids relieve anxiety and the distress of dyspnea. Other respiratory actions, including those that are neurophysiologic, are reviewed in a separate section. Pruritus almost always accompanies other opioid effects. Nausea and vomiting also can result after opioids. More rarely, opioids produce euphoria or dysphoria. [96] Morphine and meperidine, via histamine release, can cause a transient flushing or a hot sensation. The neurophysiologic mechanisms of opioid-induced analgesia and anesthesia are discussed earlier under mechanisms of action.

Are Opioids Anesthetics?

Whether or not opioids alone are capable of producing anesthesia was a subject of debate in the past. [97] [98] [99] Reports of patient awareness during high-dose fentanyl anesthesia highlighted the potential for this problem. [100] [101] A popular model used to examine the anesthetic potential of opioids determines their ability to substitute for volatile anesthetics in dogs subjected to tail-clamp minimum alveolar anesthetic (MAC) evaluations. [102] A consistent reduction, in the range of 60 to 70 percent, in the MAC of potent inhaled anesthetics has been demonstrated with numerous opioids. Although analgesic doses of opioids can decrease the MAC of potent inhaled agents by approximately 50 percent, further, and even very large, increases in opioid doses result in relatively small additional MAC reductions. This finding suggests that, in these models, opioid effects reach a ceiling that is subanesthetic.

Studies in rats demonstrate that opioids reduce the MAC of volatile anesthetics to a greater degree than in other animals [103] (Fig. 10-8) (Ch. 29) . In contrast to investigators using the dog model, these authors concluded that "sufentanil is essentially a complete anesthetic." [103] Sufentanil does result in the greatest MAC reduction of the opioids in the dog, too. [102] Interspecies differences in opioid actions are significant. [104] Some authors argue that a similarity between opioids and associated cardiovascular effects in humans and dogs supports the conclusion that responses of the two species to opioids are similar. [105] [106] Other investigators have found that dogs are not only more resistant to the actions of opioids, but also demonstrate a markedly different profile of effects compared with humans. [107] The rhesus monkey appears to respond to opioids in a fashion more similar to that seen in humans. [108] In addition, the results of motor response evaluations to noxious stimulation in MAC reduction studies do not necessarily predict anesthetic capabilities.

Reports in humans that demonstrate lower thiopental requirements to produce loss of consciousness after sufentanil compared with fentanyl support the notion that sufentanil has greater anesthetic potential compared with fentanyl (Fig. 10-9) (Figure Not Available) . Bowdle and Ward [109] reported that sufentanil (1.3 mug/kg IV) minimized the need for sodium thiopental to produce unconsciousness in nine of ten patients.

The hypnotic effects of midazolam are also significantly potentiated by alfentanil. [110] McEwan et al [111] demonstrated that fentanyl can reduce the MAC of isoflurane at skin incision in patients at least 80 percent (Table 10-5) (Table Not Available) . The relationship between plasma fentanyl concentration and MAC reduction was not linear, and the authors suggested a sub-MAC ceiling exists to the effect of fentanyl on isoflurane MAC reduction. The potency ratios for fentanyl/sufentanil/alfentanil/remifentanil, based on MAC reduction studies in humans, is approximately 1:12: 1/16: 1.2. [112] Although unconsciousness in humans, as defined by unresponsiveness to verbal command, can be produced with opioids

TABLE 10-5 -- MAC and MAC Reduction of Isoflurane by Increasing Concentrations of Fentanyl in Humans

(Not Available)

From McEwan et al [111]

Figure 10-8 Reduction of halothane minimum alveolar concentration in the rat observed with progressively increased sufentanil dosage. *(From Hecker et al [103])*

Figure 10-9 (Figure Not Available) Plot of thiopental requirement for induction of sleep versus opioid dose in surgical patients. Thiopental was administered intravenously in 25-mg increments every 30 seconds until the patient was unconscious. The thiopental requirement was plotted against the opioid dose. Sufentanil and fentanyl doses were plotted on the same scale, using a potency ratio of 1:8. The thiopental requirement was significantly smaller ($P < .0001$) for sufentanil, 0.7 and 1.3 mug/kg, than for equipotent doses of fentanyl (5 and 10 mug/kg, respectively). Only one of the ten patients receiving sufentanil, 1.3 mug/kg, required any thiopental as compared with ten of ten in the fentanyl, 10 mug/kg, group, and eight of ten in the fentanyl, 13 mug/kg, group ($P < .0001$). *(From Bowdle and Ward [109])*

TABLE 10-6 -- Unconsciousness as a Function of Age in 72 Patients Given Fentanyl (30 mug kg^{-1}) for Induction of Anesthesia

(Not Available)

From Bailey et al [217]

alone [113] [114] (Table 10-6) (Table Not Available) , opioid anesthesia can be unpredictable and inconsistent.

The presumed mechanism by which opioids act leaves doubt as to whether they should be expected to produce amnesia or anesthesia. However, the ability of opioids to produce analgesia in subanesthetic concentrations, and loss of consciousness in higher concentrations, may be mediated, at least in part, by different processes. [115] A dual mechanism in the anesthetic action of opioids has been proposed and requires that, in addition to receptor-mediated effects, an opioid must be lipid soluble enough to function as a general anesthetic. [116] Interestingly, a biphasic response has been noted with sufentanil [103] and fentanyl [107] (see Fig. 10-8) .

Awareness Under General Anesthesia

The subject of patient awareness during anesthesia and surgery continues to receive much attention (Ch. 29) . [117] Most clinicians define awareness as "the spontaneous recall of events occurring during general anesthesia and surgery." This is known as explicit memory. There are numerous studies documenting that the registration or retention of mental images or information under general anesthesia also can occur without conscious recollection. [118] [119] This is known as implicit memory. Notably, auditory functioning is left largely intact, even under inhalational anesthesia. [120] It is therefore not necessary or perhaps even possible to block the registration or retention of all information in patients who undergo general anesthesia, irrespective of the anesthetic used. It is rather the consolidation of such material and the conscious recollection of intraoperative events that concern anesthesiologists and patients most.

Awareness has been reported with many anesthetic techniques. [121] [122] Although reports of awareness, particularly with high-dose fentanyl anesthesia, highlighted the significance of this problem, it is now recognized that several factors contribute to its occurrence (Table 10-7) . Particular surgical patient populations, such as those individuals requiring anesthesia for obstetric, major trauma, and cardiac surgery are known to experience a high incidence (7-43%) of awareness. [123] Overall, it appears that up to 1 percent of all patients may experience awareness during general anesthesia.

The ability to monitor for intraoperative awareness remains limited. Clinical signs suggestive of awareness are

TABLE 10-7 -- Factors Cited as Contributing to Awareness

Inadequate anesthetic technique
No premedication
Ultrashort-acting intravenous induction agent
Excessive or unnecessary neuromuscular blockade
Difficult and/or prolonged intubation
Equipment failure
American Society of Anesthesiologists physical status IV or V
Obstetric procedure
Morbid obesity
Cardiac surgery
Inexperience of the anesthesiologist
Bronchoscopy
Pharmacologic autonomic blockade
Anesthesia at high altitude
Increased anesthetic requirement

generally motor and autonomic. Eyelid motion, swallowing, increased spontaneous respiratory effort, coughing, facial grimacing, and extremity or head motion are signs often assumed to indicate inadequate amnesia. Hypertension, tachycardia, mydriasis, tearing, sweating, or salivation may also indicate too light a level of anesthesia. Monitoring for muscle activity as an indicator of awareness is useful because muscle movements usually occur before awareness occurs. Motor signs also frequently occur prior to hemodynamic or autonomic indications of possible awareness. [124]

Other approaches for detecting awareness include evaluation of esophageal motility, isolated forearm technique, and measurement of facial muscle activity. [125] Various measures of CNS activity have included auditory evoked responses and some of its derivatives and the EEG. The raw EEG is complex and of limited value as an awareness monitor. Mathematic techniques and EEG transformations (i.e., power spectrum analysis) have produced some success. [126] Bispectral analysis uses a processed EEG to obtain an index (BIS) that can correlate with sedation and depth of anesthesia for certain drugs, but probably not opioids. [127] Although opioids alone do not substantially alter the BIS except at very high doses, the synergism between opioids and sedative-hypnotics is reflected by the BIS. Whether or not BIS monitoring can improve the detection of awareness and can allow strategies that reduce it remains unproven.

Several measures can be taken to minimize the occurrence of awareness under general anesthesia or the problems that can arise when a patient has such an experience. Preoperative evaluation of patients should include an assessment of their ability to tolerate anesthesia and the role opioids should play in intraoperative management. In selected cases (e.g., cardiac anesthesia) in which opioids may be the primary anesthetic, preoperative discussion of the possibility of awareness may be appropriate. Although pain is not always associated with awareness, a national inquiry in Great Britain documented that 41 percent of patients felt pain during their awareness episode. [120]

The use and misuse of muscle relaxants are thought to contribute often to awareness. The administration of muscle relaxants during balanced anesthesia is often routine, although it is frequently unnecessary, and it removes important motor signs of awareness. Limiting the use of muscle

relaxants to appropriate indications and not employing them as substitutes for anesthesia or to prevent movement in all patients should help to prevent awareness.

Some clinicians attempt to reduce the possibility of awareness by administering one or more sedative-hypnotic drugs during premedication, induction, and/or the maintenance of anesthesia. The administration of supplements (N_2O, diazepam, droperidol) or larger doses of opioids increases the likelihood of amnesia. [128] The use of 0.3 to 0.6 MAC or "MAC awake" concentrations of potent inhalation agents prevents recall and responses to verbal commands in volunteers and may eliminate awareness in patients. However, the doses and concentrations of IV drugs and inhaled agents required to eliminate awareness in patients remain difficult to predict with certainty. [122]

Intraoperative conversation, especially that which contains material meaningful to the patient, should be curtailed during anesthesia and surgery. Although potent stimuli such as laryngoscopy, intubation, skin incision, sternotomy, and aortic root dissection are considered to be the events most frequently associated with awareness, comments about a patient's size or discussion of clinical aspects of the patient's case can cause EEG arousal and are thought to be more likely be recalled. [120]

Intraoperative awareness may or may not be reported by patients postoperatively. In addition, understanding of intraoperative awareness as a phenomenon by medical personnel remains poor. The absence of spontaneous recall or of reports of it from medical colleagues, therefore, does not ensure that awareness under anesthesia did not occur. Traumatic neurosis consisting of nightmares, anxiety, preoccupation with death, and reluctance to discuss the incident is a symptom complex often associated with awareness during surgery. [129] [130] There is a lack of epidemiologic information concerning this and other possible sequelae. Awareness associated with anesthesia is best dealt with by informing patients of its possibility preoperatively and by frank and open discussion of such an episode after an occurrence. Direct explanation and support are considered to be the most helpful approach to a reluctant and fearful patient. [130] Medicolegal actions based on awareness during anesthesia in the United States have occurred.

Finally, many studies have evaluated the potential for intraoperative suggestions (e.g., audiotaped messages) to alter postoperative behavior and events such as pain perception or nausea and vomiting. [122] Results of these reports remain conflicting and controversial, and the implications and potential utility of implicit awareness as a means to modify behavior and outcome remain incompletely defined.

Electroencephalography

The neurophysiologic state produced by large doses of opioids differs from the "general anesthetic" state resulting from inhaled anesthetics (Chs. 29 and 35) . [131]

Increasing concentrations of inhaled anesthetics produce a continuum of EEG changes, eventually resulting in burst suppression and a flat EEG. In contrast, a "ceiling effect" is reached with fentanyl, morphine, sufentanil, and other opioids. Increasing opioid dosage, once this ceiling has been obtained, does not further affect the EEG. [132] Overall, the effects of the mu-agonists fentanyl, alfentanil, sufentanil, and remifentanil on the EEG are consistent among the opioids after allowing for differences in potency and rate of plasma-CNS equilibrium. [133]

Opioids can produce neuroexcitation or arousal. [134] In animals (cats), opioid-induced increases in cerebral oxidative metabolism have implied an analeptic-like effect. Species differences (opioids produce EEG seizure discharges in cats and mice) are now known to account for much of the discrepant findings in EEG studies between animals and humans.

Small doses of fentanyl (200 mug) produce minimal EEG changes, [135] whereas higher doses (30-70 mug kg^{-1}) result in high-voltage slow (delta) waves, suggesting a state consistent with anesthesia. [131] Although transient isolated (usually frontotemporal) sharp wave activity can be observed after large doses of fentanyl and other opioids, it is not generalized.

Sufentanil produces EEG changes that are similar to those seen with fentanyl. These changes are achieved at lower opioid plasma concentrations in the elderly. [136] [137] EEG states consistent with surgical anesthesia have been produced with doses of sufentanil as low as 2.5 mug kg^{-1}. [138] High doses of both fentanyl and sufentanil produce greater EEG changes than morphine. [139]

Although high doses of fentanyl or sufentanil produce similar EEG changes, [139] the effects of large alfentanil doses may be different. [140] Alfentanil (125 mug kg^{-1}) produces less synchronization of the EEG and less change in the relative EEG power in the delta band, a finding suggesting a lesser depth of anesthesia. [140] In addition, EEG spindle activity is common with alfentanil and rare with fentanyl or sufentanil. The latter may represent a specific or unique effect of alfentanil.

EEG is useful in several ways. As an effect site measure, it can be employed to assess onset of drug action and drug potency ratios. For example, EEG data confirm that alfentanil is more rapid acting than fentanyl. Scott et al [141] reported that the lag time between plasma drug concentration and change in the spectral edge is only 1 minute for alfentanil (84 mug kg^{-1} over 6 min) and 6 minutes for fentanyl (8.8 mug kg^{-1} over 6 min) (Figs. 10-10 (Figure Not Available) , 10-11) (Figure Not Available) .

The serum concentration ratio that results in a similar EEG pattern is 75:1 for alfentanil/fentanyl. [141] This contrasts with the reported IV dose ratio in which fentanyl is only three to five times as potent as alfentanil. In a similarly performed study, Scott et al [142] found the half-time of blood-brain equilibration ($t½_{2ke0}$) was not statistically different between fentanyl and sufentanil. Serum drug concentration ratios were 12:1 (fentanyl/sufentanil) at equal (halfmaximal) EEG slowing. Similar studies suggest that fentanyl and remifentanil are 75 and 16 times as potent as alfentanil, respectively. [143] Bowdle and Ward [109] also found similar times to onset of EEG effects for fentanyl and sufentanil. With more rapid sufentanil infusion rates (0.7 mug/kg/min), near maximal EEG effects, corresponding with a failure of patients to respond to command, can be obtained within 3 minutes. [132]

Potency ratios based on EEG studies are similar to those obtained from studies determining the plasma (or whole blood, in the case of remifentanil) drug levels of each opioid necessary to reduce the MAC of isoflurane by 50 percent. Potency ratios for sufentanil/fentanyl/remifentanil/alfentanil

Figure 10-10 (Figure Not Available) Time course of spectral edge and serum alfentanil concentrations. Note the inverted spectral edge axis. Spectral edge changes closely parallel serum concentrations. The alfentanil infusion rate is 1,500 mug/min (solid bar). *(From Scott et al [141])*

are 1: 1/10: 1/80. [111] [144] [145] [146] [147] [148] Based on EEG studies and experimental pain studies performed in humans, trefentanil has a potency that is very similar to that of alfentanil. [149] [150]

EEG analysis may be useful in monitoring the depth of anesthesia. [131] [139] [140] [141] Plasma opioid levels correlate reasonably well with EEG changes, [141] and some patterns (Kcomplexes or an increase in frequency and decrease in wave amplitude) can be used to indicate a possible return of awareness or light anesthesia. [140] However, problems with lead placement and signal processing, as well as high cost and reliability, need to be resolved before EEG analysis can be used as a routine monitor of opioid anesthesia depth. For example, Long et al [151] found emergence of patients from isoflurane but not fentanyl anesthesia to be predictably associated with obvious changes in the overall EEG frequency power spectrum.

Whether or not other forms of EEG, such as BIS, accurately reflect opioid action remains incompletely investigated

Figure 10-11 (Figure Not Available) Time course of spectral edge and serum fentanyl concentrations. Note the inverted spectral edge axis. The spectral edge changes lag behind the serum concentrations changes. The fentanyl infusion rate is 150 mug/min (solid bar). *(From Scott et al [141])*

to date. Work continues toward defining EEG parameters that correlate well with opioid effect. [133] Furthermore, it has been postulated that the EEG may eventually allow determination of the therapeutic windows for many opioid effects. [152]

Sensory Evoked Potentials

Opioids do not appreciably alter somatosensory evoked potentials (SEP) elicited at the posterior tibial or median nerve (Ch. 35) . [153] [154] [155] [156] [157] [158] [159] Changes produced in SEP latencies (increases usually less than 3 ms) and amplitudes (reductions of usually 30-40%) after administration of opioids with or without N_2O are compatible with successful clinical monitoring. Supplementation of alfentanil (100 mug/kg/10 min, then 2 mug/kg/min) with propofol (6 mg/kg/h) instead of N_2O results in a better preservation of early posterior tibial nerve-SEP peaks. [160] Median nerve SEP monitoring is also possible after sufentanil (5 mug/kg). Kimovec et al [161] found this dose of sufentanil produced acceptable and stable SEP alterations that permitted latency changes typically associated with neurologic injury to be noted. Some investigators believe the signal-to-noise ratio is also better preserved with opioid-based techniques than during anesthesia with potent inhaled agents. [153]

Although opioids do not interfere with SEP interpretation, they do inhibit both the velocity and the amplitude of nerve action potential transmission. [154] It follows that opioid-induced SEP changes may occasionally be confused with neurologic injury. [158] Significant variability in opioid effects on SEP amplitude has been reported. Amplitude has been found to decrease, increase, or remain unchanged. [154] [162] Thus, it has been recommended that the administration of opioids should be timed to avoid confusion with other possible causes of SEP change. [162] Fortunately, changes induced by large doses of opioids occur rapidly, and then elicited SEP usually remain stable. [163] In addition, slow IV infusions of opioids generally produce fewer SEP changes than large boluses. [154] Repeated boluses produce less change than the initial injection. [155] Sebel et al [164] did not find a significant correlation between increasing doses of fentanyl and SEP changes. These findings confirm the stability of the SEP signals once opioid-based anesthesia has been established. In addition, the early portions of the SEP signal are more significant in monitoring and are less affected by fentanyl than the latter parts of the SEP. [162]

Combinations of opioids and other IV anesthetics may or may not be compatible with reliable SEP monitoring. Fentanyl (10 mug kg^{-1}), administered as a bolus after midazolam (0.3 mg kg^{-1}), and followed by a fentanyl infusion, causes little change in SEP. [159] Thiopental (5-mg kg^{-1} bolus plus a 2-mg kg^{-1}

h^{-1} infusion), followed by fentanyl (10 mug
kg^{-1}), further decreases SEP amplitudes, but causes little change in latencies. [159] After etomidate (0.3-mg
kg^{-1} bolus plus 2 mg
kg^{-1}
h^{-1} as an infusion), fentanyl (10 mug
kg^{-1}) increases latency and reverses etomidate-induced increases in amplitude. [159] The effects of remifentanil on evoked potentials are similar to those of other fentanyl congeners. [165]

Brain-stem auditory evoked potentials are also minimally altered by analgesic and anesthetic doses of morphine, fentanyl, or sufentanil. [166] [167] [168] Visual evoked potentials during sodium thiopental-fentanyl-N_2O anesthesia show transiently decreased amplitudes and modest but persistent increases in latencies. Much of the disturbance in visual evoked potentials in this technique is due to barbiturate action. [169]

Although some reports document little or no effect of opioids on auditory evoked potentials, others have found dose-dependent effects. [165] Midlatency auditory evoked potentials are similarly affected by the modern opioids and reveal only a slight slowing of cortical stimulus transmission and processing. [170]

Cerebral Blood Flow

Opioids generally produce modest decreases (10-25%) in cerebral metabolic rate (CMR) and intracranial pressure (ICP), although these changes are influenced by the concomitant administration of other agents and anesthetics, as well as by patient conditions (Ch. 19) . Thus, in reports in which vasodilatation is produced by the background anesthetic (e.g., potent inhalation agents), opioids are more likely to cause cerebral vasoconstriction. Opioids also decrease cerebral blood flow (CBF) when combined with N_2O. When there is no background anesthetic, or when the background anesthetic causes cerebral vasoconstriction, opioids usually have no influence or result in a small increase in CBF.

Opioids, in general, are not thought to uncouple CBF and CMR. Endogenous opioids contribute to the regulation of arterial tone, at least in certain experimental models. [171] Endogenous opioid activity is present in cerebral arteries, although exogenously administered opioids were found to exert little effect on pial artery diameter in several animal models. [172] However, differences in species and conditions can affect the results of investigations.

Wahl [173] did find that morphine, as well as some endogenous opiates, produced dose-dependent pial arterial dilatation that became significant at higher drug concentrations. In dogs, intracarotid morphine decreases neurohypophyseal blood flow by up to 40 percent. Intraventricular morphine causes a similar neurohypophyseal effect while increasing CBF to other brain regions. [174]

Fentanyl (100 mug
kg^{-1}) causes dose-related reductions in CBF (maximum 50%) and $CMRO_2$ (maximum 35%) in rats receiving N_2O in O_2. [175] In the piglet, fentanyl and, to lesser degrees, alfentanil and sufentanil decrease arteriolar diameter in a dose-dependent naloxone-reversible manner. [176] Fentanyl alone causes little change in CBF in the dog [177] or lamb. [178] Phenobarbital-fentanyl anesthesia also preserves cerebrovascular responsivity to changes in arterial pressures of CO_2 (Pa_{CO_2}) and O_2 (Pa_{O_2}) and mean arterial blood pressure in the dog. [179]

In human volunteers, positron emission tomography demonstrates that after fentanyl (1.5 mug/kg IV), CBF effects are regionally heterogeneous. [180] In patients undergoing carotid artery surgery, CBF during fentanyl-N_2O or isoflurane (0.75%)-N_2O anesthesia is significantly less than with halothane (0.5%)-N_2O anesthesia (19±2, 24±2, and 34±5 mL/100 g/min, respectively). [181] Balanced anesthesia with fentanyl-N_2O better preserves the cerebrovascular response

to CO_2 in patients with an edematous brain than isoflurane-N_2O anesthesia. [182] Other balanced anesthetic techniques also maintain cerebrovascular CO_2 reactivity in humans. [183] [184]

Sufentanil causes dose-related decreases in CBF (maximum 53%) and $CMRO_2$ (maximum 40%) in the rat. [185] The effect of sufentanil on CBF in the dog may be dose- and time-dependent. [186] [187] Werner et al [186] found that sufentanil (20 mug/kg IV) produces modest (35-40%) decreases in CBF 5 and 10 minutes after opioid administration coupled with decreases in cerebral O_2 consumption. On the other hand, Milde [187] found that sufentanil (10-200 mug/kg) produces transient increases in CBF that peak 2 minutes after drug administration. In a primate model, which is more sensitive to opioids, Bunegin et al [188] found that sufentanil significantly decreases CBF, cerebral perfusion pressure, and $CMRO_2$.

In humans, both sufentanil and fentanyl can, however, increase middle cerebral artery blood flow velocity by approximately 25 percent. [189] Other investigators report that in healthy human volunteers, sufentanil (0.5 mug/kg IV) produces no significant effect on CBF. [190] In patients undergoing carotid endarterectomy, sufentanil (1.5-2.0-mug/kg bolus plus 0.2-0.3-mug/kg/h infusion)-N_2O anesthesia produces CBF effects similar to those of isoflurane (0.75%)-N_2O anesthesia, and CO_2 cerebrovascular reactivity is maintained. [191] In brain-injured patients, sufentanil (3 mug/kg by IV bolus) minimally affects middle cerebral artery blood flow velocity. [192]

In the dog, alfentanil and remifentanil both decrease regional blood flow 40 to 50 percent in the cortex, hippocampus, and caudate, even if blood pressure is maintained with phenylephrine. [193] Alfentanil (25 or 50 mug/kg IV), administered to patients receiving isoflurane (0.4-0.6%)-$N_2$0 anesthesia, produces minimal reductions in middle cerebral artery flow velocity. [194] Absolute CBF values during remifentanil-N_2O anesthesia are similar to CBF values during fentanyl-N_2O and isoflurane-N_2O anesthesia, and cerebrovascular reactivity to CO_2 remains intact. [195]

Cerebral Metabolic Rate

As reviewed earlier in the section on CBF, opioids usually produce mild to moderate decreases in CMR that remain coupled to CBF. Nevertheless, opioid-induced neuroexcitation (see later) and, rarely, focal seizure activity can result in regional increases in brain metabolism. In the rat, for example, fentanyl-induced EEG spike, seizure, and post-EEG seizure phases are all associated with significant increases in CBF. [196] Regional increases in glucose utilization induced by high doses of alfentanil in the rat are associated not only with epileptiform activity, but also with neuropathic lesions. [197]

Intracranial Pressure

Opioids are generally thought to affect ICP minimally (Ch. 52) . For example, under background anesthetic conditions (isoflurane-N_2O), opioids do not cause significant increases in ICP or CSF pressure in patients undergoing craniotomy for supratentorial space-occupying lesions. [198] [199] Some authors report that opioid sedation, in general, does not alter ICP in head-injured patients. [200] However, some reports suggest that potentially deleterious opioid-induced ICP effects can be produced. In patients undergoing craniotomy for excision of supratentorial space-occupying lesions, opioids may produce increases in ICP by one or more mechanisms, especially if intracranial compliance is compromised.

Marx et al [201] reported that CSF pressure increased 190 percent after sufentanil (1 mug/kg) and 120 percent after alfentanil (50 mug/kg) in patients with brain tumors who were anesthetized with thiopental-N_2O-vecuronium. Similar patients experienced a 5 percent decrease in CSF pressure after fentanyl (5 mug/kg). These findings were confirmed for fentanyl and alfentanil by Jung et al. [202] In contrast, Markovitz et al [203] found no impact of alfentanil (70 mug/kg over 6 min) on ICP in hydrocephalic patients aged 1.3 to 20 years who were undergoing shunt revision under isoflurane (0.5%)-N_2O anesthesia. Sperry et al [204] reported that both sufentanil (0.6 mug/kg) and fentanyl (3 mug/kg) caused significant ICP increases in fully resuscitated patients with severe head trauma.

Fentanyl has been reported to exacerbate ICP elevations by others. [205] Still other investigators have demonstrated that sufentanil causes no change in ICP in patients. [206] Whether these discrepancies are due to different ICP or CSF pressure assessment methods, the presence of other drugs, or other reasons is unclear. [204] In addition, if opioids do increase ICP, whether the mechanism is due to direct cerebrovascular dilation and/or is indirectly related to decreases in mean blood and

cerebral perfusion pressure and subsequent compensatory cerebrovasodilation is not resolved. Rapid treatment of opioid-induced cardiovascular effects may attenuate or eliminate associated adverse ICP effects. Regional increases in CMR (see later) may also underlie opioid-induced increases in CBF and ICP. Opioidinduced rigidity can also increase ICP. [207] CSF production and reabsorption do not appear to be affected by fentanyl and, presumably, other opioids. [208] [209] Brain retraction pressure, a clinical correlate of regional cerebral dysfunction, is not affected by fentanyl, sufentanil, or alfentanil in patients. [210] In patients undergoing craniotomy with isoflurane N_2 O-O_2 anesthesia, neither remifentanil (0.5 or 1.0 mug/kg) nor alfentanil (10 or 20 mug/kg) caused an increase in ICP. [198]

Neuroprotection

Although certain early studies suggested potentially adverse effects of mu-opioid agonists on ischemic brain, other studies document that at least certain opioid agents, such as the kappa-agonists, can be neuroprotective (Chs. 19 and 52) at least in animal models of focal ischemia. [211] [212] Animal studies of neurologic injury suggest that anesthesia with opioids improves neurologic outcome compared with the awake state. [213] In addition, spinal cord protection by fentanyl-N_2 O anesthesia is equal to that provided by halothane or spinal lidocaine. [214]

Opioids offer considerable advantages in neuroanesthesia, including the promotion of intraoperative systemic hemodynamic, as well as cerebrovascular stability and a rapid but smooth emergence. Although many studies suggest the

possibility of adverse effects of opioids on regional CMR, CBF, and ICP, opioid-based anesthesia has had an extensive and safe clinical record. The significance of reported opioid-induced changes in CBF and/or ICP and the impact, if any, of such changes on patient outcome is unknown. In the near future, tests that provide direct measures of local brain activity, such as positron emission tomography and functional magnetic resonance imaging, will further advance our understanding of CNS opioid actions.

Muscle Rigidity

Opioids can increase muscle tone and may cause muscle rigidity. Corssen et al [215] reported an 80 percent incidence of some rigidity in patients receiving dehydrobenzperidol (0.44 mg
kg^{-1}) and fentanyl (8.8 mug
kg^{-1}). Grell et al [216] found that a single IV dose of fentanyl (0.5-0.8 mg) consistently produced chest-wall rigidity within 60 to 90 seconds of IV administration. The incidence of rigidity noted with opioid anesthetic techniques varies greatly because of differences in dose and speed of opioid administration, the concomitant use of N_2 O, the presence or absence of muscle relaxants, and patient age. [7] [217] [218] [219] [220]

Opioid-induced rigidity is characterized by increased muscle tone progressing at times to severe stiffness. Clinically significant opioid-induced rigidity usually begins just as, or after, a patient loses consciousness. Mild manifestations of rigidity, such as hoarseness, can occur in conscious patients. Clinically, rigidity is most frequently first observed as wrist flexion. Rigidity can decrease pulmonary compliance and functional residual capacity, may diminish or preclude adequate ventilation, and may cause hypercarbia, hypoxia, and an elevated ICP. [207] [221] [222] [223] Opioid-induced rigidity also increases pulmonary artery and central venous pressures and pulmonary vascular resistance (Table 10-8) . [224] [225] Changes in arterial blood pressure and cardiac output are usually small. [225] Transient increases in plasma fentanyl levels may be induced by rigidity. [226]

Rigidity of the abdominal and/or thoracic muscles (wooden chest syndrome) was thought to underlie opioid-induced impairment of spontaneous or controlled ventilation in the nonparalyzed patient. [224] However, it has been demonstrated that vocal cord closure is primarily responsible for difficult ventilation with bag and mask that follows opioid administration. [227]

TABLE 10-8 -- Potential Problems Associated with Opioid-Induced Rigidity

SYSTEM	PROBLEM
Hemodynamic	
	CVP, PAP, PVR
Pulmonary	
	Compliance, FRC, ventilation
	Hypercarbia
	Hypoxemia
Miscellaneous	
	Oxygen consumption
	Intracranial pressure
	Occluded or dislodged intravenous lines
	Fentanyl plasma levels

CVP, central venous pressure; FRC, functional residual capacity; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

Rigidity occasionally occurs on emergence from anesthesia [228] and may rarely occur hours after the last dose of opioid has been administered. [229] Delayed or postoperative rigidity is probably related to second peaks that can occur in plasma opioid concentrations, as well as other possible causes similar to those underlying the recurrence of respiratory depression. Rigidity has also been reported in a neonate whose mother was anesthetized with an opioid [230] and in newborn infants receiving alfentanil. [221]

Abnormal muscle movements ranging from extremity flexion to single or multiple extremity tonic-clonic movements to global tonic-clonic motions can also occur after the use of opioids. [217] Indeed, tonic-clonic muscle movements and/or rigidity may explain reports describing seizure-like movements after fentanyl and sufentanil. [231] Whether such muscle movements (including rigidity) are part of a spectrum of neuromuscular activity associated with opioids or are manifestations of subcortical seizure activity is unclear (see the next section of this chapter).

The precise mechanism by which opioids cause muscle rigidity is not clearly understood. Muscle rigidity is not due to a direct action on muscle fibers, because it can be decreased or prevented by pretreatment with muscle relaxants. In addition, opioid-induced muscle rigidity is not associated with increases in creatinine kinase, [218] a finding suggesting that little or no muscle damage occurs during this period. Opioids do not have significant effects on neuromuscular conduction and result in only minimal depression of monosynaptic reflexes associated with muscle stretch receptors. [218] [219] Opioid-induced rigidity is probably related to a catatonic state, which can be induced by opioids. [232] Some investigators have suggested that opioids produce rigidity by altering dopamine concentrations within the striatum of the brain. [233] [234] mu-Receptor agonists induce rigidity in the rat, whereas delta- and kappa-agonists do not. [235] Rigidity may be the result of stimulation of GABAergic interneurons, which can be blocked by lesions in the striatum. Striatonigral GABA pathways involved with rigidity can also be affected by both GABA agonists and antagonists. [236] The nucleus pontis raphae is an integral central site concerning opioid-induced rigidity. [222] [237]

Some aspects of opioid-induced catatonia and rigidity (increased incidence with age, muscle movements resembling extrapyramidal side effects) are similar to

Parkinson disease and suggest similarities in neurochemical mechanisms. For example, some components of Parkinson disease not responsive to levodopa may involve endogenous opioid neurotransmitters. [238] Perturbations in endogenous opioid concentrations exist in parkinsonian patients. Parkinsonian patients, particularly if inadequately treated, may experience reactions like dystonia following opioid administration. [239]

Succinylcholine reliably and rapidly terminates rigidity (provided the IV infusion is not impaired by a rigid flexed extremity), eliminates associated cardiovascular changes, and usually permits controlled ventilation. Nevertheless, the unpleasant aesthetics and potential risk posed by opioidinduced rigidity episodes have stimulated the search for preventive measures.

Pretreatment or concomitant use of nondepolarizing muscle relaxants significantly decreases the incidence and severity of rigidity (Table 10-9) (Table Not Available) . [217] [240] [241] Induction doses of

TABLE 10-9 -- Incidence (Percentage) of Patients and Degrees of Rigidity After 30 mug kg^{-1} of Fentanyl in 72 Patients

(Not Available)

From Bailey et al [217]

sodium thiopental and less than anesthetic doses of diazepam and midazolam have also been reported to prevent, attenuate, or successfully treat rigidity. However, other reports discount the reliability of the benzodiazepines in reducing opioid-induced rigidity. [217] Other experimental compounds (ketanserin, amantadine, and $alpha_2$ -agonists) have been suggested to reduce opioid-induced rigidity. Avoidance of rigidity in clinical practice is best achieved by the concomitant administration of a "priming" size dose of a nondepolarizing muscle relaxant and avoiding the rapid administration of large doses of any of the opioids. Although the concomitant administration of a full dose of nondepolarizing muscle relaxant with an opioid during anesthetic induction has been recommended, [242] this method can result in the onset of muscle relaxation prior to unconsciousness. Opioid-induced rigidity, on the other hand, accompanied by apnea, usually indicates unconsciousness. [113]

It is common practice for an anesthesiologist to demonstrate the ability to mask ventilate a patient after the induction of anesthesia prior to the administration of a muscle relaxant. This practice is of questionable utility when opioid-induced rigidity occurs during induction and patients become difficult or impossible to ventilate manually. If a patient presents with the possibility of a difficult airway or other circumstances in which it is important to ascertain that the patient can be manually ventilated prior to neuromuscular blockade, then only small doses of an opioid should be given during induction. Persisting in an attempt to mask ventilate a patient with opioid-induced rigidity will likely result in gastric insufflation and inadequate ventilation or oxygenation until a muscle relaxant is administered. Clinicians should anticipate the need for rapid neuromuscular blockade when doses of opioids are administered that produce rigidity in order to minimize its occurrence and to allow for ventilation and airway management.

Neuroexcitatory Phenomena

Opioids, as well as inhalation (diethyl ether, enflurane, and isoflurane) and other IV (ketamine, methohexital, and propofol) anesthetic agents, can cause neuroexcitatory phenomena. [134] [234] [243] [244] [245] [246] [247] [248] [249] Fentanyl can cause neuroexcitation ranging from delirium to grand mal seizure-like activity. [250] [251] [252] Sufentanil (
5 mug
kg^{-1}) can also produce neuroexcitation including tonic-clonic movements and seizure-like activity. [253] [254] [255] [256] Interestingly, most reports of neuroexcitation with fentanyl or sufentanil involve the elderly, although these responses are occasionally observed in young patients aged 4 to 12 years. [257]

Fentanyl causes EEG seizure activity in cats (20-80 mug
kg^{-1}), [134] rats (200-400 mug
kg^{-1}), [232] and dogs (>1,250 mug
kg^{-1}). [243] Opioids have been implicated as causative in a variety of other types of neuroexcitation ranging from nystagmus, nonspecific eye movements, single extremity flexion, single or multiple extremity tonic or clonic-tonic activity and global (truncal and extremity myoclonic-tonic grand mal seizure-like) activity. [258] [259] [260] [261] However, EEG evidence of seizure activity after fentanyl (
150 mug
kg^{-1}), alfentanil (175 mug
kg^{-1}), and sufentanil (
15 mug
kg^{-1}) is generally lacking in humans. [131] [139] [225] [262] [263] Neither fentanyl nor sufentanil alters thresholds for pilocarpine-induced seizures in the rat. [264]

Animal studies demonstrate that in certain species, opioids cause focal CNS excitation rather than global CNS depression. [265] [266] Generally, these areas are subcortical (in particular the limbic system, which is rich in opiate receptors) and may in part explain the difficulty in documenting neuroexcitatory opioid effects by surface EEG. Focal neuroexcitation on EEG (e.g., sharp and spike wave activity) occasionally occurs in humans after large doses of fentanyl, sufentanil, and alfentanil. [262] The implications of such epileptiform activity are unclear. Such activity is usually of short duration (1-2 min) and is self-limited. It can be terminated by anticonvulsants such as midazolam. Fentanyl (25 mug/kg) has been demonstrated to induce EEG seizure activity documented via epidural electrodes in either temporal lobe in patients with a history of temporal lobe seizures. [267]

Reports of jerking movements and hyperexcitability after morphine are rare, but they are probably similar in origin to rigidity after fentanyl. [10] Morphine has also been reported to produce tonic-clonic activity after epidural and intrathecal administration. [268] [269] Meperidine may also cause CNS excitability. The mechanism is unique and is related to its *N*-demethylation metabolite, normeperidine, which is twice as likely to cause CNS excitation and convulsions as meperidine. Normeperidine has a long elimination half-life (15-40 h) and is chiefly eliminated by the kidney. Normeperidine is also hydrolyzed to normeperidinic acid, which is inactive. [270] Convulsions and myoclonic jerking movements that occur after large doses of meperidine, especially in patients with decreased renal function, are most likely caused by normeperidine and are not antagonized by naloxone. [270]

The mechanisms underlying neuroexcitatory phenomena are not clear. Changes in central catecholamine concentrations in dopaminergic pathways have been proposed as a possible explanation. [271] Other purported mechanisms include opioid-induced increases in glutamate-activated currents, disinhibition of pyramidal cells of the hippocampus, [272] and an increase in the release of excitatory neurotransmitters, such as met- and leu-enkephalin, which possess epileptogenic properties. [245] At least some forms of neuroexcitation are reversible by naloxone. [250] More recent work suggests that certain excitatory opioid actions may be related to their coupling to mitogen-activated protein kinase cascades. [49]

Clinical circumstances do not usually allow for naloxone treatment of opioid-induced neuroexcitation following induction of anesthesia. Such therapy may preclude continuing anesthesia and surgery, or it may result in undesirable hemodynamic alterations. The discontinuation of surgery is also not recommended because there is no known CNS morbidity associated with opioid-related neuroexcitation. Instead, if rigidity or neuroexcitation occurs in an unanticipated fashion, control of the airway and completion of anesthetic induction should proceed. Nevertheless, concern about the potential risk or sequelae of seizures is legitimate. Neuroexcitatory phenomena can alarm operating personnel, lead to physical harm, [273] or at least disconnect IV lines and make appropriate treatment difficult. Local increases in CBF [274] and metabolism [265] are also of theoretical concern because prolonged seizure activity, even if focal, could lead to neuronal injury and/or cellular death. [275] [276] [277] Opioids have been demonstrated to produce limbic system brain damage in rats. [278] To date, no neurologic deficit in humans has been associated with neuroexcitatory opioid effects.

Pupil Size and Opioid Action

Many stimuli and most anesthetic agents, including atropine, barbiturates, opioids, ephedrine, and halothane, affect pupillary diameter. These effects are mediated via several mechanisms, including alterations in sympathetic and parasympathetic tone. Opioids constrict the iris, and the time course of the response appears related to plasma opioid levels, even in the presence of potent inhalation agents. [279] [280] Opioids release cortical inhibition of the Edinger-Westphal nucleus, resulting in pupillary constriction. Direct effects on the iris are also possible.

Few studies have systematically examined the response of the pupil to different anesthetic techniques. The changes in pupil size associated with opioid action may be too small to be of clinical utility in assessing the degree of opioid effect. Cardiac surgery or neurologic deficit and other factors such as eye color, age, pain, and ambient light can affect the size and/or rate of change of pupillary diameter to stimuli. [281] [282] Nevertheless, clinicians often use pupillary size to assess opioid action. Peacock et al [283] did find a significant inverse correlation between pupil size and plasma codeine concentrations in volunteers. It has been demonstrated that, in a dose-dependent manner, alfentanil attenuates the reflex pupillary dilatation that normally follows noxious stimulation in anesthetized individuals. [284]

Thermoregulation and Shivering

Studies demonstrate that opioid ligands and receptors have a functional role in thermoregulation. [285] Opioid-based anesthesia probably reduces thermoregulatory thresholds to a degree similar to that of the potent inhaled agents. [286] [287] However, meperidine is unique among opioids in its ability effectively to terminate or attenuate shivering in approximately 70 to 80 percent of patients. [288] [289] [290] This is likely related to non-mu-opioid receptor-related actions of meperidine. The special antishivering effect of meperidine is primarily related to a reduction in the shivering threshold. [291] From 25 to 50 mg of meperidine IV is usually effective. Meperidine (IV or epidurally) is also effective in treating shivering that occurs during epidural anesthesia. [289] [292] Shivering related to blood product transfusions can also be treated with meperidine. [293] Alfentanil, morphine, and fentanyl are not as effective as meperidine in the treatment of postoperative shivering, although epidural sufentanil and fentanyl may reduce or prevent shivering in obstetric patients receiving regional anesthesia. [294] [295]

Pruritus

The mechanism and physiologic significance of opioid-induced pruritus are unknown. Histamine release, once thought to underlie this phenomenon, is not causative because non-histamine-releasing opioids also produce pruritus. Opioid-induced pruritus is not a manifestation of an allergic reaction, although medical records frequently indicate this. Drug solution preservatives do not cause the itching associated with opioid administration. Naloxone reverses opioid-induced itching, and this finding supports a receptor-mediated central mechanism for pruritus. A "scratching center" that lies in the medulla oblongata in animals may have an anatomic correlate in humans. [296] In addition, pruritus induced by spinal opioid actions in the substantia gelatinosa may be referred to a remote site by neural transmission. Thus, facial itching may not necessarily be a manifestation of direct opioid action at the level of the trigeminal nucleus, but rather, it may be a reflection of opioid-triggered neural transmission at a distant site. Why the face, and in particular the nose, is so prone to pruritus, even after spinal opioids, is unclear. Teleologically, nasal scratching may stimulate ventilation, may counter opioid-induced respiratory depression, and may be protective. Interestingly, cholestasis is ameliorated by opiate antagonists. [297]

PHARMACODYNAMICS: RESPIRATORY ACTIONS

The roles and actions of opioid receptors and endogenous, as well as exogenous opioids, in respiration have been thoroughly reviewed. [90] The respiratory-depressant actions of opioids represent their single most serious adverse effect. Although significant adverse events related to opioid-induced respiratory depression are presumably preventable, they persist with a perioperative incidence of approximately 0.1 to 1 percent, no matter what the route of administration. [298] A review of the respiratory actions of opioids should also consider the potentially beneficial respiratory effects obtained by the use of opioids.

Therapeutic Effects

Pain and/or anxiety can induce excessive spontaneous ventilation resulting in respiratory alkalosis. Certain brain-stem diseases also induce hyperventilation. [299] [300] Opioids, by decreasing both pain and central ventilatory drive, are effective agents in such conditions. [299] [300] The lack of adequate

pain relief can also cause postoperative respiratory dysfunction. [301] Although large doses of opioids can impair ventilation and decrease pulmonary compliance (see the section on rigidity), opioid analgesic therapy can improve synchronous breathing and decrease voluntary muscle tone, resulting in improved dynamic total respiratory compliance in awake but mechanically ventilated patients in the intensive care unit. [302]

The antitussive actions of opioids are well known and central in origin. Curiously, fentanyl, sufentanil, and alfentanil elicit a brief cough in up to 50 percent of patients when injected by IV bolus. [303] A pulmonary chemoreflex, mediated by C-fiber receptors (also known as J receptors), may underlie this phenomenon. The cough reflex after opioid injection is not likely to be vagally mediated because atropine pretreatment does not effect it. [304] Opioids may elicit cough by stimulating irritant receptors in tracheal smooth muscle. Interestingly, pretreatment with inhaled beta-adrenergic agonists significantly reduces the incidence of cough associated with IV opioid injection. [304]

Opioids are also excellent agents for depressing upper airway, tracheal, and lower respiratory tract reflexes. The exact mechanisms underlying this clinical observation are not clear. Opioid receptors have been demonstrated in smooth muscles of the trachea and bronchi, as well as alveolar walls, but not in the small airways. [305] Alveolar wall receptors may be associated with J receptors, and the tracheal receptors may be prejunctional opioid receptors on C-afferent nerve fibers. It has been suggested that trachealis muscle contractile responses can be attenuated by kappa- and mu-opioid receptor agonists, [306] although other investigators suggest that opioids can cause constriction. The clinical significance and relevance of opioid-induced effects on airway resistance remain controversial. [307]

Opioids blunt or eliminate somatic and autonomic responses to tracheal intubation. Opioids allow patients to tolerate endotracheal tubes without coughing or "bucking," which when pronounced can lead to hypoxemia, hypercarbia, hemodynamic instability, and other deleterious effects. Impaired gas exchange results from the marked disturbance in ventilatory pattern as well as loss of lung volume that bucking produces. Thus, on emergence from general anesthesia, patients anesthetized with a potent inhalation agent and no opioid routinely cough and buck prior to regaining consciousness and responsiveness, whereas patients adequately treated with opioids can awaken without such disturbances, even while they are still tracheally intubated.

Opioids can also help to avoid increases in bronchomotor tone. Opioids have long been used in the treatment of acute asthma because of these actions. Opioids also relieve dyspnea and other symptoms of respiratory distress associated with conditions such as asthma and heart failure. Fentanyl also has antimuscarinic, antihistaminergic, and antiserotoninergic actions and may be more effective than morphine in patients with asthma or other bronchospastic diseases. [308] Opioids can blunt the pulmonary vasoconstrictive response to tracheobronchial stimulation that can occur with suctioning. [309]

Certain IV agents, including opioids, minimally alter pulmonary gas exchange. [310] The minimal impact of opioids on hypoxic pulmonary vasoconstriction [311] (in contrast to the potent inhalation agents), coupled with associated hemodynamic and bronchomotor stability, as well as the stability of tone, contributes to the minimal interference with pulmonary gas exchange observed after opioids and many other IV anesthetics. Opioids such as fentanyl also do not impair the lungs' ability to prevent venous air emboli from reach-ing the systemic arterial circulation as much as does halothane. [312]

Nontherapeutic Effects

Endogenous opioid peptides are widely distributed in brain-stem nuclei regulating respiration. [91] High concentrations of opiate receptors have been found in many of the supraspinal brain respiratory centers including the nucleus solitarius, nucleus retroambigualis, and nucleus ambiguus. [90] [313] Specific chemosensitive brain areas also mediate opioid-induced respiratory effects. [88] [91] Opioids interfere with pontine and medullary respiratory centers that regulate respiratory rhythmicity.

All mu-receptor stimulating opioids cause dose-dependent depression of respiration in humans [314] primarily through a direct action on brain-stem respiratory centers. [315] [316] Controversy persists as to whether different subclasses of mu- opioid receptors have disparate roles in opioid-induced respiratory depression. [317] How the various respiratory centers involved with ventilatory drive, respiratory rhythm generation, chemoreception, and neural integration are affected by opioids is also unclear. The stimulatory effect of CO_2 on ventilation is significantly reduced by opioids. Thus, the slopes of the ventilatory and occlusion pressure responses to CO_2 are decreased, and minute ventilatory responses to increases in Paco2 are shifted to the right (Fig. 10-12) . In addition, the apneic threshold and resting end-tidal P_{CO_2} are increased by opioids.

Opioids also decrease hypoxic ventilatory drive. [318] [319] In fact, carotid body chemoreception and hypoxic drive are

Figure 10-12 A graphic representation of the ventilatory response to progressive hypercapnia. In this illustration, the slope of line A is approximately 2 L min^{-1} $mm\ Hg^{-1}$, although a wide range of responses in humans exists. The slope of the ventilatory response to CO_2 is reduced to 1 and 0.5 in lines B and C, respectively. Lines B and C are also shifted to the right of line A. Lines B and C have the same intercept along the X axis, indicating no displacement or shift of line C compared with line B.

blunted or eliminated by low, analgesic doses of opioids. Opioids also blunt the increase in respiratory drive normally associated with increased loads such as increased airway resistance. [318]

Respiratory rate is usually drastically slowed in overt opioid overdose, although hypoxic CNS insult can counter this effect. Opioids can usually be titrated to effect, especially in anesthetized patients, by observing dose-dependent decreases in the spontaneous respiratory rate. However, respiratory rate, especially in the postoperative setting, cannot serve as a reliable index of the magnitude of opioid-induced respiratory depression. [9C] [320] High doses of opioids usually eliminate spontaneous respirations without necessarily producing unconsciousness. Patients receiving high doses of opioids may still be responsive to verbal command and often breathe when directed to do so.

Opioid-induced effects on the control of respiratory rhythm and pattern include increased respiratory pauses, delays in expiration, irregular and/or periodic breathing, and decreased, normal, or increased tidal volume. The prolonged expiratory time in the respiratory cycle induced by opioids frequently results in greater reductions in respiratory rate than in tidal volume. Fentanyl depresses respiratory drive, phase timing, and activation of respiratory muscles, whereas enflurane only decreases respiratory drive. [321]

Peak onset of respiratory depression after an analgesic dose of morphine is slower than after comparable doses of fentanyl: 30±15 minutes versus 5 to 10 minutes. [314] This effect is due in part to the lower lipid solubility of morphine. Because of its low lipid solubility, plasma concentrations and onset of action of morphine are nearly identical after IV and IM administration. [322] Thus, it could be argued that the selection of morphine as an IV analgesic is not the most ration-al choice for acute pain control in the immediate postoperative period.

Respiratory depression induced by small doses of morphine usually lasts longer than after equipotent doses of fentanyl. [323] Downes et al [324] found that IV fentanyl (100 and 200 mug
70 kg^{-1}). These investigators also noted a faster onset and peak effect after fentanyl than after meperidine. [324] Even though fentanyl has a shorter onset and quicker recovery than morphine and meperidine, small doses (2 mug
kg^{-1}) produce respiratory depression for longer than is generally appreciated (>1 h). Sufentanil (0.1-0.4 mug
kg^{-1}) produces shorter-lasting respiratory depression and longer-lasting analgesia than fentanyl (1.0-4.0 mug
kg^{-1}). [325]

Although fentanyl (4-8 mug
kg^{-1}) given during induction of anesthesia does not usually produce troublesome postoperative respiratory depression, some investigators have found significant residual respiratory depression 5 or more hours later. [326] [327] Recovery from the ventilatory effects of fentanyl closely parallels the decline of plasma levels (Ch 69). [259] Large or repeated doses, or continuous infusions, increase the time required for lower plasma levels (below the threshold for significant respiratory effects) to be established. Plasma fentanyl concentrations of 1.5 to 3.0 ng
mL^{-1} are usually associated with significant decreases in CO_2 responsiveness. [326]

As discussed earlier, with higher doses of fentanyl (50-100 mug
kg^{-1}), respiratory depression can persist for many hours. Indeed, ventilation may need to be assisted or supported for 6 to 18 hours after induction of anesthesia with large doses of fentanyl. [328] [329] When moderately large (20-50 mug
kg^{-1}) or greater doses of fentanyl are used, the potential need for postoperative mechanical ventilation should be anticipated.

Pharmacokinetic data predict, and studies have demonstrated, that both alfentanil and sufentanil allow more rapid recovery of respiratory function than fentanyl. [18] Alfentanil has more rapid receptor dissociation kinetics than other opioids, thus making respiratory depression less likely after it is employed in anesthesia. [330] Although adequate spontaneous ventilation after alfentanil-N_2O is likely with plasma alfentanil concentrations of less than 200 ng/mL, [331] significant residual respiratory depression can exist at lower levels. The effects of remifentanil, no matter what the dose, dissipate rapidly and completely within 5 to 15 minutes following termination of its administration. The pharmacodynamic effects of alfentanil, sufentanil, and remifentanil on respiratory function are not significantly different from those of fentanyl. High doses of morphine (and probably other opioids) decrease bronchiociliary motion. [332]

Factors Affecting Opioid-Induced Respiratory Depression

Many factors can change both the magnitude and duration of respiratory depression after opioid administration (Table 10-10) . Patients who are sleeping are usually more sensitive to the respiratory-depressant effects of opioids. [333] [334] Even small doses of opioids markedly potentiate the normal right shift of the Pa CO_2 -alveolar ventilation curve that occurs during natural non-rapid eye movement sleep. [333] [334] For several days postoperatively, sleep is associated with hypoxemia. [335] The mechanisms and implications of postoperative sleep disturbances are complex and relate not only to respiratory problems, but also to cognitive and hemodynamic disturbances. [336] Both sleep and morphine relatively spare the diaphragmatic, but decrease the thoracic (ribcage), component of breathing. [337] Sleep also impairs tonic and phasic upper airway muscle activity that accompanies breathing. [338] This can be troublesome when patients have an opioid-based anesthetic and an operation that results

TABLE 10-10 -- Factors Increasing the Magnitude and/or Duration of Opioid-Induced Respiratory Depression

Dose
Intermittent bolus (versus continuous infusion)
Brain penetration/drug delivery
Distribution (cardiac output)
Un-ionized fraction (respiratory alkalosis)
Reuptake from the brain (intraoperative respiratory alkalosis)
Clearance (hepatic blood flow, e.g., intra-abdominal surgery)
Secondary peaks in plasma opioid levels (reuptake of opioid from muscle, lung, fat, intestine)
Ionized opioid at receptor site (postoperative respiratory acidosis)
Sleep
Age
Metabolic alkalosis

in little or no postoperative pain. In such patients, apparently adequate breathing can become insufficient with the onset of sleep. In patients with conditions that impair abdominal breathing or airway function, such as patients with marked obesity or sleep apnea, an increased risk of adverse respiratory events is likely with the administration of opioid analgesia.

Older patients are more sensitive to the anesthetic [217] and respiratory-depressant effects of opioids. [1] Older patients experience higher plasma concentrations of opioids administered on a weight basis. [322] Although older patients tend to have a lower blood volume than younger patients, the precise reason for higher plasma concentrations after similar doses is unknown. Conflicting reports argue for or against differences in pharmacokinetics (decreased clearance, increased elimination half-life) and/or pharmacodynamics (increased brain sensitivity) as the basis for the presence or absence of agerelated increases in sensitivity to fentanyl. [136] [339] Older patients also have more frequent apnea, periodic breathing, and obstruction after morphine than young adults. [340]

Morphine alone produces greater respiratory depression on a weight basis in neonates than adults. Its low lipid solubility normally limits blood-brain barrier penetration. In neonates and infants with incomplete blood-brain barriers, morphine easily penetrates the brain. Neonates are not unduly sensitive to the more lipid-soluble opioids (meperidine, fentanyl, and sufentanil) because penetration of these drugs into the brain is not affected by blood-brain barrier maturity. [341] Endogenous opioid activity may also be increased in the neonate and possibly contributes to the depressed ventilatory response to hypoxia observed in such young individuals. Support for this hypothesis comes from studies demonstrating that naloxone shortens the apneic phase and stimulates the response to hypoxia in newborns but not in older infants. [91]

The respiratory-depressant effects of opioids are increased and/or prolonged when administered with other CNS depressants, including the potent inhaled anesthetics, [342] alcohol, [1] barbiturates, [1] benzodiazepines, [343] and most of the IV sedatives and hypnotics. Drug interactions and synergistic depression of the ventilatory response to hypercarbia and/or hypoxia can result in bradypnea or apnea. Exceptions are droperidol, scopolamine, and clonidine, which do not enhance the respiratory-depressant effects of fentanyl or other opioids. [324] [344] [345] [346] [347] Sedation and sleep may accompany alpha$_2$ -adrenergic agonists and possibly may explain some of their reported mild respiratory-depressant actions. [348]

Pain, particularly surgically induced pain, is thought to counteract the respiratory-depressant effects of opioids. However, the contrary has been suggested by some investigators. [301] [349] For example, certain postsurgical breathing patterns are not predominantly determined by the level or mode of pain relief. [350] Acute pain does not reverse the depression of the ventilatory response to hypoxemia that is produced by sedation with sevoflurane. [351] An investigation of the effect of experimental pain on ventilatory control suggests that pain causes a chemoreflex-independent increase in tonic ventilatory drive. [352]

It is interesting to note that although some acute tolerance to opioid-induced respiratory depression can develop, 5 to 8 months of opioid exposure may be necessary for significant tolerance to the respiratory-depressant actions of opioids on hypoxic ventilatory responses to develop. [90] Cross-tolerance to the respiratory-depressant actions of different opioids also may be neither complete nor predictable. [91] Infants of mothers receiving methadone maintenance demonstrate impaired central chemosensitivity to CO_2 . They may also be at higher than normal risk for sudden infant death syndrome.

Although opioid action is usually dissipated via redistribution and hepatic metabolism, rather than by urinary excretion (see the section on pharmacokinetics), adequacy of renal function may influence the duration of opioid activity. It was previously thought that in renal insufficiency, the more potent respiratory-depressant properties of the morphine metabolite morphine-6-glucuronide (M6G) would become evident as it accumulated. [353] However, one study indicates that M6G is a somewhat weaker respiratory depressant than morphine. [354] Nevertheless, morphine or meperidine and/or some of their metabolites can accumulate in patients with renal insufficiency and may result in greater respiratory depression (see later).

Hypocapnic hyperventilation has been shown to enhance and prolong postoperative respiratory depression after fentanyl (10 and 25 mug kg^{-1}). [326] Intraoperative hypercarbia produces the opposite effects. [355] Possible explanations for these findings include increased brain opioid penetration (increased un-ionized fentanyl with hypocarbia) and removal (decreased CBF with hypocarbia). Decreased liver clearance related to decreased cardiac output and hepatic blood flow may also explain this phenomenon. In addition, intraoperative hyperventilation depletes CO_2 stores and can result in a posthyperventilation hypoventilation syndrome. Following hyperventilation, CO_2 stores are repleted. This process removes CO_2 from the blood and lowers minute ventilatory requirements, resulting in hypoventilation. In this circumstance, a normal Pa $_{CO_2}$ does not necessarily indicate normal or adequate minute ventilatory volumes. In patients who hyperventilate because of anxiety and/or pain, even small doses of IV opioids can result in transient apnea because of acute shifts in apneic thresholds.

Some authors suggest that the administration of opioids in anesthesia leads to increased respiratory problems. [356] [357] However, most of the studies performed to date have failed to isolate perioperative opioid administration as particularly associated with increased respiratory problems [358] Although Beard et al [356] found an increase in adverse respiratory events in the recovery room associated with the use of muscle relaxants and fentanyl, the frequency of a serious problem with fentanyl was rare (1/886 patients). In another study, patients receiving IV morphine for postoperative pain after general anesthesia experienced more respiratory side effects than those who received regional anesthesia. Interestingly, desaturations of significance were always associated with sleep and were related to obstruction, paradoxic breathing, or slow respiratory rates. [359] The analgesic dose of morphine used in the latter study was large (>12 mg $70\ kg^{-1}$ IM).

Recurrence of Respiratory Depression

Delayed or recurring respiratory depression has been reported with most opioids including fentanyl, [344] [360] morphine, [361] meperidine, [362] alfentanil, [363] and sufentanil, [364] [365]

but not remifentanil. Explanations for this phenomenon are not clear and are confounded by the simultaneous occurrence of a variety of clinical events. These include stimulation and pain or their absence, the concomitant administration of different supplemental analgesics and other medications, sleep, level of activity, hypothermia, and hemodynamic alterations. For example, even small doses of benzodiazepines given prior to induction of anesthesia can increase postoperative respiratory problems after balanced anesthesia with an opioid.

Numerous investigators have also noted the occurrence of significant secondary peaks and fluctuations in plasma opioid levels during the elimination phase. [366] [367] The existence of large peripheral compartments (e.g., skeletal muscle) and the variability in drug uptake from them contributes to and can augment this phenomenon. Some investigators have shown secondary peaks in plasma fentanyl levels with parallel changes in CO_2 sensitivity and breathing (Fig. 10-13) (Figure Not Available) . [368] [369] Interestingly, McQuay et al [369] found a higher incidence of second peaks in plasma fentanyl levels (increases of $0.5\ ng/mL^{-1}$) with an infusion technique than after intermittent boluses.

The stomach can sequester up to 20 percent of an IV dose of fentanyl via ion trapping in its acid milieu. It has been postulated that subsequent passage of stomach contents into the alkaline medium of the small intestine leads to reabsorption of significant amounts of fentanyl and results in secondary peaks in fentanyl plasma concentrations and recurrent respiratory depression. This mechanism appears unlikely in view of the high hepatic extraction ratios for fentanyl and most opioids. [370] Other mechanisms for renarcotization include augmented release of fentanyl or other opioids from skeletal muscle into the systemic circulation on rewarming, shivering, motion, or any other condition that enhances muscle perfusion. Plasma fentanyl and probably other opioid levels can also increase significantly on the release of a thigh tourniquet. [371] The pharmacologic management

Figure 10-13 (Figure Not Available) The top panel depicts fentanyl plasma concentrations over time, and the bottom panel depicts the slope of the ventilatory response to CO_2 as a percentage of control over time. Note the second peak in plasma fentanyl concentrations and the corresponding second decrease in the slope of the ventilatory response to CO_2 . *(From Stoeckel et al [366])*

of troublesome respiratory depression is addressed later (see the section on naloxone).

/das/book/view/29494766/875/114.html

PHARMACODYNAMICS: CARDIOVASCULAR ACTIONS

Opioids are administered not only to provide analgesia, but also to produce or promote stable hemodynamics both in the presence and the absence of noxious stimuli (Ch. 29) . Potent inhaled agents can only suppress hemodynamic responses to noxious stimuli if prestimulation blood pressures are depressed to a point that may be clinically unacceptable. [372] Numerous reports have demonstrated that large doses of opioids, administered as the sole or primary anesthetic, do result in hemodynamic stability throughout the operative period. Other investigators claim the opposite, and the issue remains a matter of debate that is unlikely to be fully resolved.

Many factors can alter the hemodynamic profile achieved during anesthetic induction, tracheal intubation, and surgery, including (1) the degree of beta-adrenergic and/or Ca^{2+} channel blockade, (2) preoperative ventricular function, (3) volume status, (4) patient habits, (5) the administration and type of premedication, and (6) the presence or absence of awareness. [129] [329] [373] [374] [375] [376] In addition, the choice of opioid can have an impact. For example, although some investigators find little difference between fentanyl and sufentanil as primary anesthetics for cardiac surgery, [377] [378] others believe that sufentanil provides better control of intraoperative hemodynamics. [376] [379] [380] [381] [382] [383] Sufentanil also decreases the need for vasodilators during cardiopulmonary bypass (CPB), the post-bypass period, and postoperatively. [376] [384] Although sufentanil alone is probably more effective than equipotent doses of fentanyl, its use does not guarantee complete control of intraoperative blood pressure. [99] [385]

Alfentanil is less reliable than fentanyl and sufentanil in blocking increases in heart rate and blood pressure during anesthetic induction, sternotomy, sternal spread, and aortotomy in patients with ischemic heart disease who undergo coronary artery surgery. [386] [387] [388] Cardiovascular stimulation can occur during and after anesthetic induction with alfentanil. [114] A higher incidence of ischemia during alfentanil anesthesia than with comparable doses of fentanyl or sufentanil has also been reported. [379] The following descriptions summarize the modes and sites of action that underlie the cardiovascular effects of opioids.

Neurologic Mechanisms

The anatomy of opioid receptor distribution within the neuraxis and the widespread association between opioid receptors and cardiovascular and autonomic regulatory areas within the CNS define much of the pharmacophysiologic basis for opioid-induced hemodynamic effects. Endogenous opioid peptides also are associated with the sympathetic and parasympathetic nervous systems, particularly in areas of the brain stem involved in the control of cardiovascular function. [73]

Key areas of the brain stem that integrate cardiovascular responses and maintain cardiovascular homeostasis are the

nucleus solitarius, the dorsal vagal nucleus, the nucleus ambiguus, and the parabrachial nucleus. The nucleus solitarius is the primary central synapse for baroreceptor-mediated reflexes and is an important relay station for peripheral information destined for hypothalamic sympathetic control centers. The nucleus solitarius also projects directly to the intermediolateral nucleus in the spinal cord, the common pathway for preganglionic sympathetic outflow. The nucleus solitarius and parabrachial nucleus play an important role in the hemodynamic control of vasopressin secretion. [389] The nucleus solitarius, dorsal vagal nucleus, nucleus ambiguus, and parabrachial nucleus all have enkephalin-containing neurons and high concentrations of opioid receptors. mu- Opioid receptors dominate in areas such as the nucleus solitarius. The direct administration of mu-agonists into the CNS of animals most commonly, but not always, produces hypotension and bradycardia. [73] [390]

The ventrolateral periaqueductal gray region, a key central site mediating analgesia, also affects hemodynamic control. Different opiate receptor subtypes occupy this site. Direct injection of mu-agonists elicits hypertension and tachycardia in the rat, whereas delta- or kappa-agonists have the opposite or no effect. [391] In addition, activation of mu-opioid receptors suppresses somatosympathetic reflexes transmitted by unmyelinated C-afferent fibers at the level of the spinal cord and modulates them at the brain stem. [392] These actions contribute to the anesthetic capabilities of opioids.

Opioids also can modulate the stress response through receptor-mediated actions on the hypothalamic-pituitary-adrenal axis (see later). Most opioids reduce sympathetic and enhance vagal and parasympathetic tone. If not countered by indirect effects (e.g., catecholamine release) or the coadministration of drugs with anticholinergic or sympa-thomimetic activity (e.g., atropine, ephedrine, or pancuronium), opioids can result in hypotension. Patients who are volume depleted, or individuals depending on high sympathetic tone or exogenous catecholamines to maintain cardiovascular function, are predisposed to hypotension after opioid administration.

Ablation of sympathetic tone can occur after all the modern opioids. Flacke et al [393] have postulated that cardiovascular depression after fentanyl is due to inhibition of central sympathetic outflow that is apart from analgesia or other sensory-depressant effects of the opioid. These investigators found that naloxone reversal of fentanyl-induced cardiovascular depression is blocked by clonidine, an alpha $_2$ -agonist. After eliminating all autonomic tone in dogs, Flacke et al [394] found minimal hemodynamic changes after fentanyl or fentanyl plus large doses of diazepam. They concluded that hypotension induced by fentanyl was indirect, that is, mediated by a decrease in CNS sympathetic vasoregulatory outflow.

Occasionally, opioids produce paradoxic effects. Thomson et al [395] reported the occurrence of a hyperdynamic cardiovascular response to anesthetic induction with high-dose fentanyl in 10 percent of patients and attributed it to central sympathetic activation. Fentanyl increases norepinephrine release from some sympathetic nerve endings, and it may also inhibit its neuronal uptake in dogs.

The predominant and usual effect of opioids on heart rate is to produce bradycardia resulting from stimulation of the central vagal nucleus. [396] [397] [398] Opioid-induced bradycardia is almost totally prevented by bilateral vagotomy or vagal block with atropine. [399] Blockade of sympathetic chronotropic actions may also play a role in opioid-induced bradycardia. [396] In addition, many, even minor, nasal or maxillofacial or other stimuli can also induce or exacerbate bradyarrhythmias via parasympathetic reflexes. [400] [401] Meperidine, in contrast to other opioids, rarely results in bradycardia, but it can cause tachycardia. [402] Tachycardia after meperidine may be related to its structural similarity to atropine, to normeperidine, its principal metabolite, or to early manifestations of its toxic CNS effects.

Cardiac Mechanisms

The direct cardiac actions of opioids, and in particular the effects on myocardial contractile mechanisms, are significantly less than those of many other IV and inhalation anesthetics. Opioid receptors have been demonstrated to exist in cardiac myocytes of several species. Preliminary investigations of the direct effects of opioids on myocytes report complex and conflicting results. For example, Ela et al [403] found that morphine acts by two different pathways in cultured cardiac myocytes, causing both an increase in Ca^{2+} transients and a decrease in myocyte responsiveness to Ca^{2+} .

Contractility

The state of myocardial contractility has an impact on the efficacy of opioids as anesthetics. For example, Wynands et al [404] showed that patients with good left ventricular function become hypertensive more frequently than patients with poor left ventricular function during fentanyl anesthesia for coronary artery surgery. Patients with good myocardial function could increase cardiac index in response to increases in systemic vascular resistance induced by surgical stimuli. Patients with limited myocardial reserve could not always maintain cardiac output in the face of increased systemic vascular resistance. Their blood pressure did not increase and at times decreased.

Some investigators suggest that opioids produce direct positive inotropic effects on the heart. [405] Others report negative inotropic actions with some agents (meperidine) and no direct effects with others (morphine). [406] Vasko and coworkers [407] found that morphine has a significant positive inotropic effect that is dependent on endogenous catecholamine release in dogs. Meperidine has been reported to produce decreases, [408] increases [406] or mixed effects on myocardial contractility in isolated cardiac preparations and intact animals. The ability of meperidine to produce positive inotropic actions may be related to class III antiarrhythmic properties or the mediation of increased intracellular Na^{+} activity via actions on the Na-K pump. [406] However, Strauer [408] found equianalgesic doses of meperidine 20 times more depressant to the contractile element of the isolated cat papillary muscle than morphine. Some investigators suggest that local anesthetic-like effects, and not receptor-related opioid actions, mediate some of the negative inotropic effects of opioids, especially with high drug concentrations. [409] This suggestion is consistent with the greater local anesthetic-like action of meperidine compared with other opioids.

Most evidence indicates that fentanyl produces little or no change in myocardial contractility. [9] [328] [380] [381] Other investigators

have reported negative inotropic effects, [410] [411] [412] [413] positive inotropic effects, [409] or myocardial depression-sparing actions of fentanyl during halothane and enflurane anesthesia. [414] [415] Possible mechanisms of the dose-dependent positive inotropic effects of fentanyl, as well as sufentanil, include catecholamine release or direct myocardial adrenergic activation. Usually, most hemodynamic variables, including heart rate, arterial blood pressure, cardiac output, systemic and pulmonary vascular resistance, and pulmonary artery occlusion or wedge pressure, remain unchanged after large doses of fentanyl. [9] [328] [380] [381] [404] [411] [412] [416]

Miller et al [379] compared anesthetic induction with fentanyl (75 mug kg^{-1}), sufentanil (15 mug kg^{-1}), and alfentanil (125 mug kg^{-1} followed by 5 mug kg^{-1} min^{-1}) in patients premedicated with lorazepam scheduled for coronary artery surgery. Anesthetic induction with fentanyl was associated with the least change in mean arterial pressure and myocardial performance. Although sufentanil did not produce hemodynamic instability, it did cause myocardial depression (Figs. 10-14 (Figure Not Available) , 10-15) (Figure Not Available) . Mild to no depression of cardiac index and pump function has been reported after sufentanil in humans. [380] [381] [385]

Studies in dogs have demonstrated little change in hemodynamics with moderate doses (160 mug kg^{-1}) of alfentanil and transient cardiac stimulation (increases in left ventricular contractility, aortic blood flow velocity, and acceleration) with very large doses (5 mg kg^{-1}). [243] Heart rate, cardiac output, and pulmonary and systemic vascular resistance increased following 5 mg kg^{-1} of alfentanil. Other investigators have reported increases in myocardial contractility, mean aortic, pulmonary artery, left and right atrial pressures, and systemic vascular resistance with lower doses (200 mug kg^{-1}) of alfentanil in dogs. [417] [418] Alfentanil also has direct positive inotropic effects in the rabbit. [405] Some authors have found that alfentanil causes similar decreases in heart rate, blood pressure, and cardiac index as fentanyl, [419] [420] whereas others have reported that alfentanil produces the least desirable hemodynamic profile (more hypotension as well as myocardial ischemia) compared with fentanyl and sufentanil in patients undergoing coronary artery grafting. [379] [413] [421] [422] [423] In dogs, remifentanil produces hemodynamic effects that include decreases in contractility and cardiac output, as well as in heart rate and blood pressure. [424]

Heart Rate and Rhythm

Central neurally mediated mechanisms are the primary mechanism of opioid-induced bradycardia (see earlier). Morphine also has a direct effect on the sinoatrial node [425] [426] and atrioventricular conduction. [427] Asystole may follow opioid-induced bradycardia, and several case reports illustrate predisposing factors (Table 10-11) . [428] [429] [430] [431] [432] Sufentanil and alfentanil appear to be more likely than fentanyl to result in asystole. [379] Premedication with, or concomitant administration of, beta-adrenergic or Ca^{2+} entry blockers can exacerbate bradycardias and may result in asystole after sufentanil. [433] Severe bradycardia and asystole often appear prior to or during laryngoscopy and intubation. Laryngoscopy can relieve or exacerbate bradyarrhythmias or asystole. Periods of asystole, 10 to 12 seconds in duration, may resolve on their own, but they usually respond to atropine (0.4-0.8 mg IV). On occasion, much larger doses of atropine (>1.0 mg), isoproterenol, or a precordial thump may be required to treat severe bradycardia/asystole.

Cardiac Conduction

Opioids may depress cardiac conduction. Fentanyl slows atrioventricular node conduction and prolongs the RR interval, the atrioventricular node refractory period, and Pur-kinje fiber action potential duration. [434] [435] Sufentanil also prolongs action potential duration in isolated canine cardiac

Figure 10-14 (Figure Not Available) Graphic display of the changes in mean arterial pressure (MAP) (A) and heart rate (HR) (B) after anesthetic induction (IND) with sufentanil, fentanyl, and alfentanil. Baseline (BL) and preinduction (PRE) hemodynamics, as well as responses to intubation (INT) and volume loading (VL_1 , VL_2) are also shown for each drug. *(From Miller et al [379])*

Figure 10-15 (Figure Not Available) Systolic function after anesthetic induction with sufentanil, fentanyl, and alfentanil and in response to volume loading (VL). Systolic function, described by the relationship between systolic blood pressure (SBP) and end-systolic volume index (ESVI), was significantly more depressed with sufentanil when compared with alfentanil and fentanyl. *(From Miller et al [379])*

Purkinje fibers. This effect may be related to enhanced Ca^{2+} entry during the plateau phase of the action potential or depression of the outward K^{+} current during terminal repolarization. [436] These effects have been suggested to be mediated via direct membrane actions, as opposed to opioid receptor interactions. [434] [435] [437]

Opioids can also prolong the QT interval. The risk of opioid use in patients with QT abnormalities or taking medications such as quinidine is unknown. [438] However, both sufentanil and alfentanil have been demonstrated to be devoid of electrophysiologic effects on the normal or accessory pathways in patients with Wolff-Parkinson-White syndrome. [439] [440]

Clinically, cardiac conduction disturbances due to opioids are very rare, but they may be more likely to occur in the presence of Ca^{2+} entry or beta-adrenergic blockers. [433] Although the effects of opioids on cardiac conduction could

TABLE 10-11 -- Factors Predisposing Patients to Bradycardia and Asystole During Induction of Anesthesia with Opioids

Presence of beta-adrenergic and/or calcium entry blockade
Premedication with or concomitant use of benzodiazepines
Muscle relaxants with little or no vagolytic properties (e.g., vecuronium)

Muscle relaxants with vagotonic properties (e.g., succinylcholine)
Added vagal stimuli (e.g., laryngoscopy)
Rapid administration of the opioid

theoretically lead to the development of reentry-type dysrhythmias, in practice this rarely occurs. Indeed, the overall effect of opioid anesthesia is antiarrhythmic. [441] [442] Antifi-brillatory effects have been suggested to be produced by fentanyl. [442] [443]

Opioid antagonists (delta and kappa) appear more antiarrhythmogenic than agonists in rats. [444] Although doses of epinephrine sufficient to induce dysrhythmias in dogs are the same during balanced anesthesia with opioids versus halothane or enflurane plus N_2O, the incidence of malignant dysrhythmias (ventricular tachycardia and ventricular fibrillation) is lower with opioids plus N_2O. [436] Studies in humans also demonstrate a lower incidence of severe ventricular dysrhythmias in patients receiving fentanyl versus halothane anesthesia. [445] Some of the electrophysiologic actions of opioids resemble those of class III antiarrhythmic compounds and may underlie the antiarrhythmogenic potential of opioids.

Ischemia

Determining the effects and consequences of opioid action on myocardial ischemia is complex. Results can depend on such factors as the species studied and experimental design. For example, compared with isoflurane, fentanyl anesthesia allows better preservation of myocardial function in a ventricular region subjected to experimental ischemia. [446] During myocardial ischemia in dogs, fentanyl, compared with halothane, also allows better functional compensation in nonischemic left ventricular walls. [447] On the other hand, functional recovery of the stunned myocardium is greater in dogs anesthetized with halothane, compared with fentanyl. [448] Opioids have been found not to protect against ischemia in animal models by some investigators. [449] [450]

Most recently, it has been suggested that opioids can mimic ischemic preconditioning. Schultz et al [451] demonstrated that opioid receptor stimulation results in a reduction in infarct size similar to that produced by ischemic preconditioning. It appears that this phenomenon may be delta-opioid receptor mediated. It also has been reported that the maintenance of intense analgesia into the postoperative period with sufentanil can reduce myocardial ischemia following coronary artery surgery. [20] Further studies are required to better our understanding of the role of exogenously administered opioids, as well as endogenous opioid systems, in myocardial ischemia.

High doses of opioids can maintain myocardial perfusion and the O_2 supply/demand ratio as well as or better than inhalation-based techniques. [452] [453] Helman et al [452] found hemodynamic instability and myocardial ischemia to be more frequent during induction of anesthesia with desflurane compared with sufentanil. Other studies suggest that fentanyl and sufentanil do not provide adequate hemodynamic control in humans during coronary artery surgery, [454] when compared with a potent inhalation agent. [455] [456]

Among the opioids, alfentanil is associated with more myocardial ischemia (as indicated by reversal of myocardial lactate extraction to production and worsening ventricular dia-stolic compliance) than fentanyl or sufentanil in patients having coronary artery surgery. [379] Interestingly, hemodynamic conditions do not reliably indicate ischemia. Kleinman

et al [457] reported that hemodynamic changes were most often absent during ischemia in patients anesthetized with either fentanyl or halothane. Data from a prospective randomized comparison of sufentanil versus enflurane, isoflurane, and halothane for coronary artery surgery revealed no difference in new intraoperative ischemia, the incidence of postoperative myocardial infarction, or death. [22] These results occurred in spite of a greater (2-fold) incidence of hypotension associated with the inhalation agent techniques and a greater (2-fold) incidence of hypertension associated with sufentanil. Tachycardia, the only hemodynamic parameter significantly related to ischemia, occurred with the same frequency with all agents.

Coronary Circulation

Opioids appear to have no significant effect on coronary vasomotion or myocardial metabolism, they do not produce steal phenomena, and they do not diminish the ability of large coronary arteries or coronary arterioles to respond to vasoactive agents. [458] [459] In the dog, although coronary blood flow and myocardial O_2 consumption are reduced by fentanyl, the delivery and use of O_2 remain commensurate with demands of the heart. Regional blood flow distribution ratios also are not altered, and myocardial tissue perfusion is not compromised. [460] Direct intracoronary fentanyl has no effect on left ventricular mechanoenergetics in the dog. [461]

In a study of the effects of opioids and neuroendocrine modulators on porcine coronary arteries, fentanyl, but neither sufentanil nor morphine, antagonized acetylcholineinduced contractions. [462] In this study, none of these opioids affected histamine-induced contractions. The effects of fentanyl were not reversible by naloxone and were thus thought to represent a direct smooth muscle effect. Another report documents that, in humans, fentanyl anesthesia slows the rate of change in coronary vascular resistance induced by pacing. [463] Conclusions regarding the relevance and significance of this finding were limited by the lack of comparative studies. Although the potent inhalation agents do produce coronary artery dilatation, even patients with steal-prone anatomy do not appear to experience more ischemia when anesthetized with isoflurane, halothane, or enflurane versus sufentanil. [464]

Baroreception

Low-pressure baroreceptors at the junction of the great vessels and atria are sensitive to decreases in filling pressure. Stimulation of baroreceptors causes reflex increases in systemic vascular resistance in order to maintain arterial blood pressure. Potent opioids applied in anesthesia usually produce minimal to no decreases in preload and after-load, [9] [385] [465] and little depression of great vessel and atrial baroreceptors, whereas potent inhalation agents such as halothane do. [466]

Opioids may depress arterial baroreflex control of the heart rate induced by hypotension or hypertension, [467] but other reports suggest that this reflex is preserved under opioid anesthesia. [468] Infants, after receiving 10 mug kg^{-1} of fentanyl, do demonstrate significant depression of baroreflex responses. [469] This finding is significant because of the relationship between heart rate and cardiac output, especially in infants.

Cardiogenic Reflex

Some authors have suggested that aortic root dissection causes hypertension via stimulation of a specific cardiogenic reflex. [470] This cardiogenic hypertensive reflex is elicited by serotonin and causes powerful positive inotropic, chronotropic, and dromotropic responses that are neurally mediated. [471] In humans, this reflex may underlie new hypertension during myocardial ischemia, infarct, or surgery. Chemoreceptors between the aorta and the pulmonary artery are the source of the reflex. Many authors have found, for example, that aortic root manipulation is the most provocative stimulus for intraoperative hypertension. Corroborating the role of this reflex is the finding that hypertension after aortic root dissection is not associated with increases in plasma catecholamine concentrations or light levels of anesthesia. [419] Although higher doses of fentanyl or sufentanil can decrease the occurrence of intraoperative hypertension, no dose of any opioid has been shown to prevent all hypertensive responses reliably, especially during cardiac surgery in humans. [99]

Hormonal Mechanisms

Morphine (1-3 mg kg^{-1}) causes histamine release and sympathoadrenal activation. [472] The release of catecholamines by morphine and meperidine follows and parallels histamine release, which can be marked in some patients. [473] [474] Hasbrouck [475] administered up to 595 mg of morphine to patients and documented significant increases in plasma epinephrine and norepinephrine. Increases in blood and urine catecholamine concentrations after morphine are also dose-dependent. [476] [477]

Evaluations of the effects of opioids on histamine release from basophils and mast cells reveal a spectrum of differing effects depending on the cell, its tissue of

origin, and the opioid tested. [478] Increases in plasma histamine after morphine also cause dilatation of terminal arterioles. Histamine can produce direct positive cardiac chronotropic and inotropic actions that are receptor mediated. Stimulation of the renin-angiotensin mechanism also occurs after large doses of morphine. [479]

Hormonal alterations contribute to the cardiovascular changes seen after morphine and include an increase in cardiac index and a decrease in arterial blood pressure and systemic vascular resistance. [480] Increases in sympathetic activity could be detrimental in some patients. Moffitt et al [481] showed that 1 mg kg^{-1} of morphine does not inhibit cardiac lactate production and can produce ischemia with surgical stimulation in patients undergoing coronary artery bypass operations.

Cardiovascular changes after morphine are similar when patients are pretreated with diphenhydramine (a histamine H_1 -antagonist) or cimetidine (a histamine H_2 -antagonist). However, in patients pretreated with both H_1 - and H_2 - antagonists, the cardiovascular responses are significantly attenuated

despite comparable increases in plasma histamine concentrations.

Meperidine also causes histamine release more frequently than most other opioids, including morphine, fentanyl, sufentanil, and alfentanil. Flacke et al [474] found that 5 of 16 patients experienced increased plasma histamine concentrations after meperidine, whereas only 1 of 10 patients receiving morphine had similar changes. Increases in plasma histamine occur most often in females and are highly correlated to the magnitude of subsequent hypotension. [474] Unlike morphine or meperidine, fentanyl, sufentanil, alfentanil, and remifentanil do not produce increases in plasma histamine, and hypotension is less frequent with these opioids.

Although large doses of fentanyl produce significant increases in plasma catecholamines in dogs, [482] large doses of fentanyl (24-75 mug kg^{-1}) decrease rather than increase plasma catecholamine and cortisol concentrations in humans. [483] The effect of fentanyl on plasma catecholamines may be dose-dependent. Hicks et al [410] noted elevated plasma norepinephrine levels after 15 mug kg^{-1} of fentanyl, but normal (baseline) values after 50 mug kg^{-1} in human subjects. Similarly, anesthetic doses of sufentanil usually do not change circulating catecholamine concentrations.

Opioids also may have direct effects on adrenal secretory mechanisms. Met-enkephalin, for example, can be found in the adrenal medulla. Gaumann et al [484] have reported that sufentanil produced 6- to 20-fold increases in adrenal vein concentrations of catecholamines and parallel increases in arterial blood pressures in cats. Interestingly, sufentanil and the accompanying increase in catecholamine levels prevented the hypotension that normally occurred in these animals after a 25 percent loss of blood volume. Thus, although mu-opioid agonists do modulate the adrenal secretory response to pain, the adrenal secretory response to hemorrhage is preserved after sufentanil administration. [484] This may be of clinical benefit when patients hemorrhage, but it also underlies, in part, the inability of opioids to suppress completely some sympathetic responses to major surgical stimuli. [378] [485]

Vascular Mechanisms

Investigations of the effects of opioids on vascular tone in isolated vessels have yielded varying results, depending on such factors as the species studied, the vascular bed examined, and the opioid and particular dose evaluated. [486] Zelis and coworkers [487] found that morphine selectively impairs certain sympathetic reflexes involving peripheral veins. Their data suggest that this response is due to a CNS action of the drug with secondary withdrawal of sympathetic tone. Vasodilation after morphine may also result from a direct effect of morphine on vascular smooth muscle. [488] At high doses, morphine inhibits the presynaptic release of norepinephrine in saphenous vein rings and results in a decreased contractile response to electrical stimulation. [489] This effect is not reversed by naloxone or attenuated by histamine blockers.

Sufentanil can directly relax vascular smooth muscle. [490] Vascular studies evaluating alfentanil, fentanyl, and sufentanil in the dog demonstrate similar direct peripheral vessel smooth muscle relaxation. [491] In the rat aorta, mu-opioid receptor stimulation may modulate norepinephrine-induced responses at low doses, and it may have a direct contractile effect at higher doses. [486] During fentanyl anesthesia, alpha $_1$ -adrenergic responsiveness to phenylephrine is better in patients with good left ventricular function, compared with those with poor left ventricular function. [492]

PHARMACODYNAMICS: HORMONAL RESPONSE

There was considerable interest in the past in the pharmacologic modification of hormonal and metabolic indexes of the stress response to surgical trauma. [493] [494] The term "stress response" has been used extensively to describe the total physiologic process that occurs when patients encounter a significant insult. [495] [496] [497] The main components of the neuroendocrine stress response are the corticotropinreleasing hormone brain centers (e.g., paraventricular hypothalamic nucleus) and the locus caeruleus-norepinephrine/autonomic nervous system. [494] Despite great variability in stimuli, the body's response to an insult has common denominators. These include the release of trophic hormones from the hypothalamus that stimulate the pituitary to release ACTH, growth hormone (GH), renin, prolactin, endorphins, and antidiuretic hormone (ADH). Catabolic hormones including cortisol, catecholamines, glucagon, and thyroxine are also secreted in increased amounts, and plasma concentrations of anabolic hormones such as insulin and testosterone are usually decreased. [497] Plasma concentrations of stress hormones increase during general anesthesia and surgery, often in proportion to the severity of the operative trauma. [483] [498] [499] Increased levels of stress hormones are considered undesirable because they promote hemodynamic instability and intraoperative and postoperative metabolic catabolism. In some circumstances, hormonal and metabolic responses to surgery are extreme and are thought to contribute to operative mortality. [500]

It is thought that there is normal tonic inhibition of specific components of the hypothalamic-pituitary part of the stress response axis by endogenous opioids. Although inhalation anesthetics, in general, do not suppress the stress response, [493] and opioids, to a certain degree, can, it is likely that combinations of different anesthetic agents and techniques provide the best control.

Opioids are capable of reducing the stress response by modulating nociception at several different levels of the neuraxis (see earlier), as well as by influencing centrally mediated neuroendocrine responses. [501] Opioids are potent inhibitors of the pituitary-adrenal axis. [502] Endogenous opioid peptides may serve as stress hormones themselves and not just as modulators of other hormone secretion. This activity is suggested by the finding that beta-endorphin and ACTH are cosynthesized and cosecreted during stress and are in fact derived from the same precursor pro-opiomelanocortin. [503] Different hypothalamic opiate receptors can be stimulated by morphine and may alter hormone secretion. [504] Hall et al [505] believe that the inhibitory effect of fentanyl on surgically induced pituitary hormone secretion is mediated via the hypothalamus. Additionally, there is evidence that distinct

opiate receptors selectively act to impede pain signals arising from different forms of injury. [506] [507]

Morphine

Morphine modifies hormonal responses to surgical trauma in a dose-related fashion. [508] Morphine can prevent ACTH release, suppress surgically induced increases in plasma cortisol, and attenuate the pituitary-adrenal response to surgical stress. [508] [509] Large doses of morphine (4 mg kg^{-1}) can prevent increases in plasma concentrations of cortisol and GH in the pre-bypass period, but not during or after CPB. [508] [510]

Morphine can increase some stress-responding hormones due to increases in plasma histamine release, adrenal medullary release mechanisms, [511] [512] and catecholamine release from sympathetic nerve endings. [513] Morphine increases concentrations of catecholamines in both blood and urine in patients undergoing cardiac valve surgery. [476] Plasma ADH concentrations rise significantly during morphine (1 mg kg^{-1}) plus N_2O anesthesia in humans during surgery before CPB and increase further during bypass. [514] Plasma renin activity also increases markedly in patients anesthetized with morphine (1-3 mg kg^{-1}) and N_2O during cardiac surgery. [479]

Fentanyl

Fentanyl and its congeners are more effective than morphine in modifying hormonal responses to surgery. Fentanyl can abolish the hyperglycemic response to surgery and may reduce cortisol and GH responses better than halothane. [515] [516] The efficacy of fentanyl in controlling the hormonal manifestations of the stress response can be dose-dependent. [517]

Fentanyl, in doses of at least 50 mug kg^{-1}, prevents increases in blood glucose, plasma catecholamine, ADH, renin, aldosterone, cortisol, and GH concentrations before, but not consistently during or after, CPB, even in the presence of maintained opioid blood levels. [483] [518] [519] [520] Fentanyl can stimulate the secretion of some hormones including atrial natriuretic peptide.

In preterm infants undergoing cardiac surgery, fentanyl-N_2O-curare anesthesia is more effective than N_2O-curare anesthesia in suppressing hormonal responses to surgery and postoperative protein breakdown and in decreasing circulatory and metabolic complications. [521] Fentanyl doses greater than or equal to 50 mug/kg can help to reduce the hyperglycemic response to cardiac surgery in pediatric patients to less than 200 mg/dL throughout operation. [522]

Sufentanil

Sufentanil may be superior to fentanyl in modifying the stress response. [383] [523] Sufentanil can eliminate most, if not all, significant hormonal stress responses prior to CPB. [496] [524] However, it has been demonstrated that neither fentanyl nor sufentanil alone can completely block sympathetic and hormonal stress responses and that perhaps no dose-response relationship exists for opioid-associated stress response control. [99] [378] The stress response to CPB is difficult to suppress with sufentanil, as with fentanyl, anesthesia. [496] [524]

Alfentanil

Alfentanil can cause hormone-modifying effects similar to those of sufentanil. [524] Alfentanil (30 mug/kg IV), combined with thiopental (4 mg/kg IV), produces maximal suppression of the catecholamine response to tracheal intubation. [525] Alfentanil (20 mug/kg IV), combined with propofol (2.5 mg/kg IV), effectively blunts the hemodynamic effect, but not the efferent sympathetic nerve activity, associated with rapid increases in the inspired concentration of desflurane. [485] Alfentanil can suppress increases in plasma cortisol and catecholamines before but not during CPB and may prevent increases in ADH and GH throughout coronary artery bypass surgery. [523] Acute hypertensive responses and neuroendocrine responses to surgical stimulation are more effectively suppressed with alfentanil compared with isoflurane or trimethaphan during balanced anesthesia. [526] High-dose alfentanil-N_2O anesthesia (150-mug/kg loading dose plus 3-mug/kg/min infusion) better

suppresses intraoperative cortisol and glucose elevation than droperidol-fentanyl-N_2O anesthesia in patients undergoing abdominal surgery. [527]

Stress Reduction and Outcome

Increases in metabolism and substrate mobilization are part of the stress response. Such responses may be deleterious, especially in very ill patients undergoing major procedures. Increases in plasma catecholamine concentrations may increase cardiac risk, and increases in protein catabolism may delay recovery. Some evidence suggests that anesthetic techniques or agents that minimize this stress response may reduce morbidity and mortality in a variety of circumstances. [19] [20] [528] [529]

Sufentanil appears to be the most likely opioid to modify stress responses and outcome successfully. [19] [20] [529] Other investigators suggest that neither the opioid administered nor the anesthetic technique has an impact on outcome. [22] [23] Anand et al [19] evaluated the impact of sufentanil versus morphine-halothane anesthesia on hormonal and metabolic responses and morbidity and mortality in neonates undergoing cardiac surgery [19] (Ch. 50) . Neonates receiving sufentanil anesthesia (total intraoperative dose was 37±2 mug/kg) also received either infusions of sufentanil (49.3±1.3 mug/kg/24 h) or fentanyl (178±25 mug/kg/24h) for analgesia for the first postoperative day. Neonates anesthetized with halo-thane and morphine (total intraoperative morphine dose was 0.35±0.05 mg/kg) received intermittent morphine (1.45±0.34 mg/kg/24 h) plus diazepam postoperatively. (Curiously, the authors of this study referred to the halothane-morphine anesthesia as a "light" technique and the sufentanil anesthesia as a "deep" technique.) Significant reductions and improvements in hormonal profiles were measured in neonates anesthetized with sufentanil versus halothane-morphine. In addition, neonates anesthetized with sufentanil versus halothane-morphine experienced a

lower incidence of sepsis, metabolic acidosis, and disseminated intravascular coagulation. Most strikingly, a statistically significant difference in postoperative mortality was observed (0 of 30 given sufentanil versus 4 of 15 given halothane plus morphine).

Mangano et al [20] also reported that, after myocardial revascularization, patients receiving intense postoperative analgesia with sufentanil (1 mug/kg/h) experience a decrease in the incidence and severity of electrocardiographically documented ischemia compared with patients receiving intermittent IV morphine (2.2±2.1 mg/h) for postoperative analgesia. This finding may relate in part to the fact that anesthesia-induced reductions in metabolic responses to surgery are usually short-lived. [516] [518] [520]

Major investigative challenges remain in the area of stress response research: many different hormonal changes have been described; the concomitant neural, cellular, immune, and chemical changes have been less well defined, and little is understood or proven with regard to how modifying hormonal responses alters outcome. [530] Interest in cytokines and the inflammatory response to trauma and surgery and in modifying it raises similar issues. [531] Only with additional studies can the question of altering outcome with different anesthetic and/or analgesic techniques be appropriately addressed.

Opiate Tolerance

Patients with a history of opiate tolerance or substance abuse and painful conditions are frequently undertreated with appropriate doses of opioids. [532] Lack of knowledge, legal implications, separation of pain management and addiction specialties of medicine, and associated stigmas all contribute to this problem.

The mechanisms of dependence and tolerance are genetic, molecular, cellular, physiologic, and functional. The molecular and cellular mechanisms of addiction have been reviewed. [533] Long-term opiate agonist administration produces downregulation of prodynorphin gene expression in the brain. [534] In the locus caeruleus, the major noradrenergic nucleus in the brain, long-term opioid exposure results in inhibition of adenylyl cyclase, reduced activity of protein kinase A, and upregulation of the cAMP pathway. These changes restore normal neuronal activity in the presence of the opioid. On removal of the opioid, the upregulated and now unopposed cAMP pathway contributes to activation of locus caeruleus neurons (Fig. 10-16) (Figure Not Available) . This is but one of several mechanisms suggested as contributing to the development of opioid tolerance and withdrawal. [535]

In certain models, receptor downregulation is not essential for the development of tolerance. Changes in mu- receptor density that occur prior to or during the development of tolerance also do not appear to be essential. [536] This finding suggests that some cellular mechanisms that are downstream from the receptor contribute to the development of tolerance. Possible mechanisms involve protein kinase signal transduction cascades that link extracellular signals to cellular changes by regulating target gene expression (see Fig. 10-16) (Figure Not Available) . Interestingly, hibernation reduces the manifestations of opiate dependence in certain animal models. Endogenous opiates also play a role. For example, morphine withdrawal can be attentuated by inhibition of endogenous

Figure 10-16 (Figure Not Available) Scheme illustrating opiate actions in the locus caeruleus (LC). Opiates acutely inhibit LC neurons by increasing the conductance of a K^+ channel (light crosshatch) via coupling with subtypes of G_i and/or G_o proteins and the consequent inhibition of adenylyl cyclase. Reduced levels of cyclic adenosine monophosphate (cAMP) decrease protein kinase A (PKA) activity and the phosphorylation of the responsible channel or pump. Inhibition of the cAMP pathway also decreases phosphorylation of numerous other proteins and thereby affects many additional processes in the neuron. For example, it reduces the phosphorylation state of cAMP response element-binding protein (CREB), which may initiate some of the longer-term changes in LC function. Upward bold arrows summarize the effects of long-term morphine in the LC. Long-term morphine administration increases levels of adenylyl cyclase, PKA, and several phosphoproteins, including CREB. These changes contribute to the altered phenotype of the drug-addicted state. For example, the intrinsic excitability of LC neurons is increased via enhanced activity of the cAMP pathway and Na^+ -dependent inward current, which contributes to the tolerance, dependence, and withdrawal exhibited by these neurons. This altered phenotypic state may be maintained in part by upregulation of CREB expression. *(Reprinted with permission from Nestler. [535] Copyright 1996 American Association for the Advancement of Science.)*

enkephalin catabolism. [537] Much work remains to elucidate fully the complex mechanisms of tolerance. [538] [539]

The implications of acute tolerance to opioids in the clinical setting remain controversial and poorly understood. [540] Acute tolerance to the analgesic actions of opioids can occur rapidly, whereas tolerance to the respiratory-depressant actions of opioids may take months to develop. [541] The more potent opioids, such as sufentanil, because of their greater intrinsic activity and low percentage of receptor occupancy, result in less tolerance. However, morphine does not appear in general to have a clinically relevant ceiling to its analgesic effects, although the severity of side effects may limit dose escalation. Peripheral morphine effects have been suggested to be less prone to tolerance. [542] In animals, intrinsic efficacy is inversely related to the degree of tolerance when opioids are administered by continuous infusion but not once-daily dosing. Thus, the method and schedule of drug

administration may also affect the development of tolerance. [543] [544] However, modifying an opioid administration schedule to modulate the development of tolerance may not always be useful or effective. [545]

Certain patients may appear to be tolerant to opioids, but instead they may suffer from pathophysiologic conditions, such as neuropathies, that are poorly responsive to opioids. [546] Morphine-3-glucuronide (M3G), previously thought to be inert, has been argued to produce functional antagonism of morphine and M6G, especially in certain individuals predisposed to produce large amounts of M3G. However, animal and human data do not support this theory. [546]

Management of the Opioid-Dependent Patient

The anesthetic management of the opioid-addicted patient should be tailored to the patient's specific complex of problems and the planned surgery. Common cardiopulmonary problems include endocarditis, cardiac tamponade, cardiac dysrhythmias, thrombophlebitis, mycotic aneurysm, septic pulmonary and systemic emboli, sepsis, pulmonary edema, bacterial pneumonia, pulmonary aspiration and abscesses, pulmonary hypertension, and talc granulomas. Restrictive lung disease and increased alveolar-arterial O_2 gradients are also not uncommon in addicted patients. [547] [548] [549] Renal disease, especially the nephrotic syndrome, is seven times more prevalent in addicted than in nonaddicted patients. Likewise, addicted patients have a higher incidence of other genitourinary problems [547] and anemia. Long-term morphine administration causes adrenal hypertrophy and impairs corticosteroid secretion. [1] Other problems that occur with increased incidence in opioid abusers are viral and nonviral hepatitis, acquired immunodeficiency syndrome, osteomyelitis, muscle weakness associated with rhabdomyolysis and myoglobinuria, and neurologic complications such as transverse myelitis, encephalitis, and cerebral abscess.

Anesthetic management for the opiate-dependent or addicted patient should include adequate premedication, with opioids, if indicated. There is no ideal anesthetic agent or technique to employ in the chronic addict or in the patient with an acute opiate overdose. Although some opiate addicts may be managed with local or regional anesthesia, associated behavioral and psychologic problems make general anesthesia frequently easier and safer. The patient with an acute opiate overdose manifests hypotension, bradycardia, hypoventilation, relative hypovolemia, meiosis, and a GI tract that must be considered arrested and full of recently ingested material. Maximum effects will produce a comatose and apneic patient who is cyanotic with pinpoint pupils unless anoxic pupillary dilatation has supervened. If spontaneous ventilation has persisted, hypotension, bradycardia, and hypothermia are additional likely signs. Treatment of such a patient follows basic life support. Cardiovascular and respiratory changes can be reversed with increments of naloxone (40-80 mug every 1-2 min IV) until vital signs are adequate. Naloxone has a shorter duration of action than most abused opioids, and renarcotization can occur. Complete opioid reversal may turn the patient into an uncontrollable menace. Support of the circulatory system with fluids and monitoring of arterial blood gases and pulmonary function are also important.

Individuals intoxicated but not overdosed with opioids present in a sedated, "nodding" state with pinpoint pupils, normal to euphoric moods, and a revealing history. Patients who are withdrawing from opiates initially (3-4 h after last "fix") are anxious, fearful, and exhibit drug-seeking behavior. Early withdrawal (8-12 h later) reveals restlessness, sweating, nausea, nasal congestion, rhinorrhea, lacrimation, mydriasis, stomach cramps, and continued drug-seeking behavior. Overt, fully developed withdrawal develops within 1 to 3 days of abstinence and along with early symptoms includes piloerection ("cold turkey"), vomiting, diarrhea, muscle spasms (hence the term "kicking the habit"), fever, chills, hypertension, tachycardia, and severe behavioral disturbances. [550] Commonly used medications for detoxification and/or stabilization of the withdrawing addict are meth-adone, clonidine, acetaminophen, and chloral hydrate (for sleep). Cardiovascular stimulation and some of the other signs and symptoms of acute opiate withdrawal can be treated with beta-adrenergic antagonists and alpha $_2$ -agonists.

Pain relief during the postoperative period should be appropriate for the degree of pain and should end with the resolution of the acute surgical condition. Methadone maintenance can be instituted for more gradual opiate withdrawal. Complete reviews of the anesthetic management of addicted patients are available. [551] [552] [553] Substance abuse among anesthesiologists is reviewed in Chapter 84 .

PHARMACODYNAMICS: RENAL EFFECTS

The control of water and electrolyte balance and of blood pressure has been demonstrated to be influenced in various animal models by opioids. mu-Receptor activation causes antidiuresis and decreases electrolyte excretion. kappa-Receptor stimulation predominantly produces diuresis with little change in electrolyte excretion. Whether these renal-induced opioid actions are directly and/or indirectly mediated via neurohumoral factors is uncertain. Indirect actions may involve inhibiting or altering the secretion of ADH and atrial natriuretic peptide. [554] Animal studies utilizing an opioid with selective peripheral actions suggest that diuretic, natriuretic, and kaliuretic opioid effects are mediated via atrial natriuretic factor release. [555] Dynorphin may be a natural endogenous opiate ligand with kappa-receptor renal actions. The stable dynorphin analogue E-2078 causes kappa-mediated diuretic effects in the isolated perfused rat kidney. [556] Dynorphin analogues may have potential as diuretics of significance.

Antidiuresis after morphine administration has been attributed to a decrease in renal blood flow and glomerular filtration rate. [557] [558] Increases in urine volume and decreases in urinary Na^{+} excretion and urine osmolality have also been reported during fentanyl-O_2 anesthesia. Hunter et al [559] reported decreases in renal plasma flow, glomerular filtration rate, urine volume, and increases in renovascular resistance in dogs anesthetized with N_2O after 25 mug kg^{-1} of fentanyl. Kien et al [560] also noted a 25 percent decrease in renal cortical blood flow that paralleled changes in blood pressure suggesting impairment of autoregulation. Morphine

and meperidine have been reported to decrease renovascular resistance. [561] [562] The relevance of these animal studies is unclear in light of the presence of background anesthetics and species differences.

Anecdotal reports suggest that rarely opioids may contribute to renal failure by a mechanism that is unclear but that is reversible by naloxone. [563] However, in a study comparing halothane and high-dose morphine anesthesia, intraoperative and postoperative urine outputs of 61 patients undergoing similar open heart operations did not differ. [564] Other work has confirmed that large doses of morphine and fentanyl probably do not stimulate ADH release in humans. [7] [258] The absence of increases in plasma ADH, renin, and aldosterone indicate that fentanyl, sufentanil, alfentanil, and probably remifentanil most likely preserve or minimally alter renal function in humans. [519] [523] If renal function does change during opioid anesthesia and surgery, it is probably due to secondary changes in systemic and renal hemodynamics.

Lower urinary tract opioid effects include disturbances of micturition characterized by urinary retention, especially after intrathecal opioid administration. Opioids cause relaxation of bladder smooth muscle. Not all opioid agonists behave similarly, and morphine appears to be particularly potent with regard to producing urodynamic problems. [565] Patients who receive opioids and whose bladders are not catheterized may experience urinary retention.

PHARMACODYNAMICS: GASTROINTESTINAL EFFECTS

Motility

Opioids decrease GI motility, and this action underlies their use as antidiarrheal agents. Whether or not long-term opioid use, the use of opioids for several days prior to sur-gery, or the administration of opioids as part of a rapid sequence anesthetic induction increases the risk of pulmonary aspiration is unknown. [566] Patients receiving parenteral opioid therapy preoperatively are more likely to have "full stomachs" regardless of their "NPO" status.

Opioids produce widespread effects throughout the GI tract by several central and peripheral mechanisms. Such effects are a mixture of inhibitory and excitatory actions. Opioid peptides and their receptors are found throughout the GI tract, especially in the gastric antrum and proximal duodenum. Several opiate receptor subtypes can be demonstrated on myenteric neurons, and both kappa- and mu-receptor agonists regulate cholinergic transmission in the myenteric plexus. kappa-Agonists appear more powerful, and they modulate acetylcholine release by inhibition of *N*-type voltage-sensitive Ca^{2+} channels via a pertussis toxin-sensitive G protein in guinea pig ileum. [567]

Opioids alter lower esophageal sphincter activity, resulting in sphincter relaxation. [568] This probably accounts for the unreliability of spontaneous lower esophageal sphincter contractions as predictors of patient movement to skin incision when opioid-based anesthetics are used, as opposed to potent inhalation agent anesthesia. [569]

Gastric emptying is delayed by opiates, via supraspinal (vagus nerve-mediated) and spinal, as well as peripheral, mechanisms. [570] Morphine and related opioids inhibit electrically evoked acetylcholine release from nerves in the GI tract. Even small doses of alfentanil (5 mug kg^{-1}) slow gastric emptying, but for a shorter period than morphine. Both fentanyl and meperidine reduce antroduodenal motility during balanced anesthesia, but at least partial recovery occurs relatively early (0.5-2.0 h) postoperatively. [571] Both opioids are also associated with an increase in gastric pH.

Fentanyl-supplemented (21 mug/kg total) anesthesia for cardiac surgery delays postoperative recovery of bowel motility in a dose-dependent manner and surprisingly longer than morphine (0.7 mg/kg) (15.2±7.3 versus 8.2±6 h). [572] Epidural opioids reduce GI motility more so than epidural bupivacaine. [573] Intrathecal morphine also reduces GI tract motility, [574] as do mixed agonist-antagonist opioids. Naloxone reverses opioid-induced delays in gastric emptying. [575] [576] Methylnaltrexone, a quaternary naloxone derivative that does not cross the blood-brain barrier, can attenuate morphine-induced delays in gastric emptying. [566] IV, but not IM, metoclopramide (10 mg) also can reverse morphine-induced delays in gastric emptying. [577] Droperidol (2.5 mg IV) does not appear to reverse slowed gastric emptying induced by fentanyl. [578]

Opioid effects on the intestine are complex. The ileum appears to be less sensitive to opioids than the jejunum. In fact, morphine enhances ileal propulsion before decreasing motility. As a result, mouth-to-ileum transit time may not be significantly altered. [579] Opioid effects on the ileum are blocked by naloxone. [579] Opioids increase tone and decrease propulsive activity in most of the intestine (small and large). Electromyographically, this is reflected by an increase in rhythmic stationary (tone) bursts and a decrease in sporadic (propagating) bursts. Some clinicians believe that opioids may be indicated during surgical construction of a continent urinary reservoir because they are superior to anticholinergic drugs for terminal ileal relaxation. [580] GI secretions can be increased by opioids. [552]

Biliary Tree Effects

All opioid agonists increase biliary duct pressure and sphincter of Oddi (choledochoduodenal sphincter) tone in a dose- and drug-dependent manner through opiate receptor-mediated mechanisms [581] [582] (Fig. 10-17) (Figure Not Available) . Morphine-induced spasm of the common bile duct has been documented with ultrasound. [583] Opioid-induced reductions in common bile duct caliber in anesthetized patients are greatest (60% of predrug dimension) with morphine (0.2 mg/kg) and are insignificant after fentanyl (1.5 mug/kg) or sufentanil (0.3 mug/kg). [584] Increases in biliary pressure after opioids are small. [585] There is only a 3 percent incidence of failed intraoperative cholangiograms during fentanyl supplemented (10 mug kg^{-1}) anesthesia. These facts suggest that clinical consequences of opioid-induced biliary tract actions are usually minimal. [586]

Opioid-induced biliary spasm rarely produces severe epigastric pain which can be confused with cholecystitis or myocardial ischemia. [587] Increases in biliary pressure caused by opioids are, with the exception of meperidine, reversible with naloxone. [588] [589] Glucagon (1-3 mg IV), carefully titrated, also reverses opioid-induced biliary spasm.

Although some reports suggest that mixed agents such as nalbuphine and butorphanol can raise biliary pressure as

Figure 10-17 (Figure Not Available) Changes in common bile duct pressure after administration of alfentanil 7.5 ( ) and 15 (Delta) mug/kg and fentanyl, 1.5 ( ) mug/kg (mean values ± SEM). Statistically significant difference in changes from baselines among the groups are indicated as follows: *, $P < .05$; **, $P < .01$; ***, $P < .001$. *(From Hynynen et al [1214])*

much as pure agonists, [585] most studies show that they produce less or little pressure change. [581] [589]

Meperidine has a dual effect on the biliary tract. [588] Meperidine (10^{-6} mol/L) produces an inhibitory effect on the response of the common bile duct to electrical stimulation (antimuscarinic mechanism). Higher concentrations (10^{-4} mol/L) produce an excitatory effect and increase spontaneous contractions via direct smooth muscle stimulation. Neither of these responses is affected by naloxone. In spite of these contrasting actions, meperidine increases biliary pressure in humans.

Intestinal Circulation

The effects of opioids on intestinal circulation are complex and are not completely understood. [590] Low doses of morphine (0.5-1.0 mg kg^{-1}) increase intestinal blood flow (perhaps secondary to histamine release), whereas high doses (1-3 mg kg^{-1}) decrease flow. [591] [592] Decreases in blood flow after morphine are likely related to hypotension or increases in plasma catecholamines. Fentanyl increases intestinal blood flow in a dose-dependent fashion. The increase in blood flow coupled with a substantial and dose-related decrease in intestinal O_2 uptake represents a state of "luxury perfusion" that has been hypothesized possibly to increase mesenteric and portal venous O_2 content, thereby improving hepatic O_2 supply. [591]

Hepatic Effects

Opioids produce mild effects on liver function during anesthesia and surgery. Fentanyl produces some postanesthetic liver dysfunction (small increases in serum glutamate oxaloacetate transaminase or serum glutamate pyruvate transaminase) in rats that is independent of the presence of cirrhosis. [593] These changes are similar to those caused by potent inhalation agents. There is evidence that fentanyl, as well as other anesthetics, can produce hepatic dysfunction or injury in some animal models. [594] Bromosulfophthalein breakdown by the liver, for example, is decreased by morphine in rats. [595]

Alfentanil can also reduce hepatic artery blood flow by more than 50 percent in the dog. [560] Similar decreases in hepatic blood flow caused by morphine, fentanyl, and other opioids can increase the blood levels of other drugs whose elimination depends on hepatic blood flow. [596]

Nausea and Vomiting

The "big little problem" of postoperative nausea and vomiting continues to attract a great deal of interest and to create controversy. [597] [598] Opioids usually increase the incidence of nausea and vomiting when these drugs are used as premedicants, intraoperative agents, or postoperative analgesics. The physiology and prevention of nausea and vomiting are summarized in Figure 10-18 . The interested reader is referred to an extensive review. [599]

Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla, possibly through delta-receptors. [600] This action, combined with their actions on the GI tract, promotes nausea and vomiting. Opioids may also have antiemetic properties related to the existence of both emetic and antiemetic brain centers possessing different opiate receptor profiles. [601] There is very little evidence suggesting that any one opioid is consistently more emetogenic

Figure 10-18 Physiology of emesis. The chemoreceptor trigger zone (CRTZ) and the vomiting center (VC) stimulate the upper gastrointestinal tract (UGIT), resulting in emesis. Cholinergic (Chol.) and dopaminergic pathways are integral, and many factors influence nausea and vomiting through these and other mechanisms. RF, reticular formation; ADR, adrenergic. Serotoninergic actions at the chemoreceptor, underlying the efficacy of antiemetics such as ondansetron, are not illustrated.

than another. Nevertheless, in any one particular patient, changing from one opioid to another can influence associated nausea and vomiting. [599]

Many other factors are associated with nausea and vomiting. These include age (emesis is greater in pediatric patients), female gender, surgery during the first 8 days of the menstrual cycle, [602] obesity, history of motion sickness, anxiety, gastroparesis, certain operative procedures (e.g., lapa-roscopy), duration of surgery, and ambulation. Anesthesia-associated factors that increase nausea and vomiting include opioid premedication, pain, gastric distention, airway trauma, balanced anesthesia, and the agents etomidate and N_2O. The use of propofol in balanced or total IV anesthesia (TIVA) significantly reduces the incidence of nausea and vomiting. [603] The incidence of postoperative nausea and vomiting can be as low as 5 to 20 percent after propofol-alfentanil anesthesia.

When opioids are employed, antiemetic prophylaxis should be considered because postoperative nausea and vomiting are of great concern to many patients, can increase cost, and may delay patient recovery and discharge. Some of the more efficacious antiemetic therapies commonly used in anesthesia are as follows:

1. Drugs with anticholinergic activity, in particular sco-polamine [604] (IM, IV, or as a transdermal patch) and, to a lesser degree, atropine. Glycopyrrolate is not effective because it does not penetrate the blood-brain barrier.
2. Butyrophenones, in particular droperidol (0.005-0.07 mg kg^{-1} IV), are most likely effective because of their antidopaminergic properties.
3. Dopamine antagonists, in particular metoclopramide (0.1-0.3 mg kg^{-1} IV), which acts both centrally at the chemoreceptor trigger zone and peripherally on the GI tract. Metoclopramide has a rapid onset but is short acting and thus is more effective if administered at the end of an anesthetic regimen.
4. Serotonin antagonists (e.g., ondansetron) may be among the most efficacious drugs available. They are most effective in high-risk populations, but because ondansetron is associated with a low (3%) incidence of headache and liver enzyme elevation, potential costs and benefits remain controversial. [597] [598]
5. Acupressure at the pericardium 6 meridian point (P-6, Nei-Guan) with acupressure bands. [605]

The appropriate application of these therapies, along with skilled and gentle handling of the airway (which includes appropriate but minimal suctioning and associated trauma), can lead to an acceptable and low incidence of nausea and vomiting even after anesthetic techniques that include opioids.

OTHER OPIOID EFFECTS

Obstetrics

Specific concerns regarding the use of opioids in obstetrics include the question of opioid-induced reproductive or teratogenic actions and the maternal, fetal, and newborn consequences of the use of opioids during and after labor and delivery (Ch. 57).

Morphine, but not fentanyl, can adversely affect *in vitro* fertilization of sea urchin eggs. Thus, fentanyl has been recommended as clinically useful during the harvesting of human ova for subsequent *in vitro* fertilization. [606] Other investigators question whether opioid-induced increases in prolactin may disfavor implantation. [607] Although alfentanil penetrates follicular fluid to a greater extent than fentanyl, it has no effect on cleavage rate and has also been recommended as useful in providing analgesia for oocyte retrieval. [608]

Teratogenic actions of opioids, including fentanyl, sufentanil, and alfentanil, at least in animal models, appear to be

minimal. [609] [610] Older studies evaluating morphine, meperidine, and methadone suggest some teratogenic potential with these drugs, but concomitant respiratory depression and the administration of very high drug doses may have affected study results.

The parenteral administration of opioids prior to delivery in obstetrics remains a commonly used method of analgesia despite known adverse maternal, fetal, and neonatal effects (see later), as well as arguably superior alternatives. In addition to typical adverse effects, aortocaval compression and associated hypotension may be exacerbated by parenteral opioids, especially following morphine or meperidine. Fetal manifestations of maternal opioid administration include decreases in heart rate variability.

Meperidine (12.5-50 mg IV or 50-125 mg IM) has been suggested to result in less neonatal depression than morphine (2-6 mg IV or 4-10 mg IM). [341] Fetal blood-brain barrier immaturity may permit greater than normal brain penetration of the relatively lipophobic morphine compared with meperidine. However, both morphine and meperidine rapidly cross the placenta and result in significant drug levels in the fetus and neonate soon after maternal injection, and drug elimination for both opioids is impaired in the neonate. [611] [612] The elimination half-life of meperidine in the newborn can be as long as 23 hours. [613] Multiple maternal doses of meperidine can result in significant accumulation of the drug and its metabolite normeperidine in the fetus. [614] The neonatal effects of maternally administered meperidine can last up to 3 days. [615] Adverse neonatal effects can occur after either morphine or meperidine administration to mothers. [614] Attempts to minimize neonatal effects of opioids include restricting opioid administration to the first stage of labor.

Because of its high lipid solubility, sufentanil transfer across the placenta should be enhanced. As with most anesthetics, placental transfer is passive for opioids. However, sufentanil is highly bound to plasma proteins, and this impedes placental transfer. In addition, the placenta takes up more sufentanil compared with other opioids such as fentanyl or alfentanil, and this action further blunts its transfer to the fetus. [616] Sufentanil transfer to the fetus may be least when delivery is within 45 minutes of drug administration. Because the placenta can act as a drug depot, it may continue to supply the fetus with sufentanil, especially if delivery occurs more than 45 minutes after drug administration. Fetal acidosis increases opioid transfer from the mother.

Morphine has little effect on the pregnant rat uterus, whereas meperidine can increase uterine contractions in a dose-dependent fashion that is not reversible by naloxone. [617] It has been suggested that labor may be shorter in women receiving meperidine compared with those receiving morphine. Fentanyl (50-100 mug) is devoid of actions on uterine blood flow and tone in sheep. [618] Although fentanyl is a successful agent for analgesia during labor, it is less frequently employed. [619] Fentanyl (50-100 mug q1h IV), compared with meperidine (25-50 mg IV q2-3h), results in less nausea, vomiting, and sedation in the mother and in lower naloxone requirements in newborns. [620]

Opioids have traditionally been omitted from general anesthetic techniques for cesarean section until fetal delivery. More recently, however, mothers with severe pregnancy-induced hypertension or other severe cardiovascular problems have had alfentanil included in the inductionintubation sequence to promote hemodynamic stability. [621] [622] Although at times naloxone reversal of neonatal depression has been required after alfentanil, maternal effects were deemed beneficial. Remifentanil is probably rapidly metabolized by the newborn, and it may offer advantages because of this property.

Morphine and meperidine have been found in the breast milk of mothers receiving IV opioid analgesia. In at least one study, morphine administered to mothers produced less neonatal neurobehavioral depression than meperidine. [623] Repeated dosing with meperidine may produce detrimental effects in a suckling newborn. [624] The potential actions of M6G in the fetus have not been evaluated. Preliminary reports document that a fentanyl infusion of 25 mug/h IV provides effective maternal analgesia and few unwanted maternal or nursing neonatal effects. [625] Although both fentanyl and morphine are concentrated in breast milk in milk-to-plasma ratios of 2 to 3:1, newborn exposure is reported to be insignificant. [626] [627]

Newborns of addicted mothers can exhibit opioid withdrawal and require observation and appropriate treatment. The severity of withdrawal is related to maternal methadone dose and neonatal gestational age. [628] Seizures are more common in term (13/178) than in preterm infants (1/34).

Allergic and Adverse Reactions

True allergic reactions to opioids are rare. [629] Patients often complain of being "allergic" to opioid analgesics because they have experienced adverse side effects, most frequently nausea, vomiting, or pruritus. Most of the adverse reactions to opioids that fall into the category of side effects are discussed in their respective sections of this chapter.

Papaveretum, fentanyl, and meperidine have on occasion been associated with anaphylactic-type reactions [630] [631] [632] [633] and positive intradermal skin tests. Harle et al [633] suggested that compounds likely to cross-react with morphine-reactive antibodies do so because of structural similarities of immunoglobulin E binding sites and include codeine, meperidine, and methadone. Fentanyl, buprenorphine, and naltrexone were predicted to cross-react poorly with morphine-reactive antibodies.

Systemic anaphylactoid reactions to opioids are also rare. More commonly, local reactions occur, and these may be caused by preservatives or histamine. (Ampules of fentanyl do not contain preservatives; however, vials of fentanyl do contain methylparasept and propylparasept.) Levy et al [634] demonstrated that wheal and flare responses on intradermal injection of morphine, meperidine, fentanyl, and sufentanil, but not alfentanil, naloxone, and nalbuphine, were greater than those due to saline. The intensity of the responses was not related to the potency of the mu-receptor agonists, and it was due to a combination of histamine release and direct

vascular actions. Naloxone and antihistamines both only partially attenuated these opioid-induced reactions.

Meperidine is metabolized by the liver to meperidinic acid and normeperidine. Normeperidine is active and has half the analgesic potency and twice the neurotoxicity of meperidine. Oral meperidine produces particularly high normeperidine blood levels. Normeperidine is slow to accumulate (days) and is dependent on renal excretion for elimination. Because of these factors, meperidine is often recommended

only for short-term use in healthy individuals. Meperidine should be avoided in patients with renal dysfunction. CNS adverse effects associated with meperidine include disorientation, hallucinations, tremors, twitches, myoclonus, psychosis, and seizures. The adverse effect rate after meperidine is dose related even in normal dose ranges. Meperidine-induced neurotoxicity is reversible, although effects may persist for several days after terminating drug administration. Treatment is supportive and includes cessation of meperidine, substitution with another opioid for analgesia, and administration of a benzodiazepine for signs or symptoms of CNS irritability. Naloxone administration should be avoided because it can elicit seizures by unmasking excitatory effects when depressant effects are antagonized.

It is now recognized that the pharmacology of morphine is complicated by the fact that at least two of its metabolites, M6G and M3G, are active. This can lead to an increased incidence of adverse effects in some patients. The pharmacology of these metabolites has been the subject of much interest, but their effects remain incompletely understood. M6G, like morphine, is relatively selective for mu-opioid receptors. It is thought that M6G, although not more potent than morphine as a respiratory depressant, may have a longer half-life, and that, especially in patients with renal dysfunction, the accumulation of M6G can lead to an increased incidence of adverse effects, including respiratory depression. Patients with renal dysfunction who receive morphine analgesic therapy may require additional attention. M3G may actually antagonize morphine, and this effect may contribute to both variability in response and resistance to morphine analgesic therapy.

Finally, use and abuse of illicit "designer" opiates, such as 3-methylfentanyl ("China white"), [635] has probably caused several hundred drug overdose deaths. This agent is as potent as sufentanil. The number of deaths related to 3-methylfentanyl has declined. Rapid treatment for drug overdose follows that for other opioids.

Ocular Effects

The use of fentanyl, sufentanil, and alfentanil during induction of anesthesia can help to prevent increases in intraocular pressure. Induction techniques without opioids can lead to increases in intraocular pressure associated with succinylcholine and/or tracheal intubation, whereas pretreatment with an opioid can prevent such problems. [636] [637] Fentanyl, alfentanil, and sufentanil doses as small as 2.5, 10, and 0.1 mug/kg, respectively, and remifentanil, 0.1 to 0.5 mug/kg/min, may be sufficient as long as appropriate anesthetic depth is achieved prior to tracheal intubation. Opioid-droperidol sedation alone also reduces intraocular pressure. [638]

Immune Effects

It is now firmly established that opioids influence neuroimmune function as well as autoimmune regulation. Evidence includes the finding that opioid receptors, with the mu_3 -receptor perhaps most significant, are present on inflammatory cells. Direct effects of opioid agonists and opiate signal molecules include modulation of immune cellular activity, as well as that of specific enzymatic degradation and regulation processes. [639] Opioids also can affect immune function indirectly through neuroendocrine or neuroimmune actions mediated through the hypothalamic-pituitary- adrenal axis and the autonomic nervous system. [640]

Several immune cell populations serve as targets for the effects of opioids including T cells, macrophages, and NK cells. The production of lymphokines and cytokines is also altered following opioid treatment. Met-enkephalin affects both immunocyte activation and chemotaxis. Morphine can suppress monocyte chemotaxis, and long-term exposure to morphine can increase the lethality of certain infections. How opioids alter resistance to infection and what are the details of the mechanisms and effects of opioids on immune function are among the research problems under current investigation. [639] [640]

PHARMACOKINETIC-PHARMACODYNAMIC CONSIDERATIONS

Pharmacokinetic-Pharmacodynamic Variability

Humans exhibit substantial intersubject variability in their response to opioids. [641] [642] This variability is at least 3- to 5-fold and is a function of both pharmacokinetic and pharmacodynamic parameters. Therefore, a single opioid dosage regimen is not appropriate for all patients. Figure 10-19 (Figure Not Available) illustrates the pharmacokinetic (left panel) and pharmacodynamic (right panel) variability for alfentanil and is typical for opioids. Combined pharmacokinetic-dynamic models help to identify sources of variability and strategies to manage them.

Pharmacokinetic-Pharmacodynamic Modeling

Traditionally, the clinical pharmacology of opioids was characterized by simple phenomenologic experiments in which a dose of opioid was administered to an experimental subject and the effects were observed (Ch. 2) . Although such "dose-response" experiments could provide general guidelines for safe and efficacious opioid administration, they could not specifically identify the mechanisms responsible for variability in response. With the advent of modern drug assay technology and the widespread availability of computers, it is now possible to analyze pharmacologic data with combined pharmacokinetic-pharmacodynamic models.

Pharmacokinetic-pharmacodynamic modeling separates drug response into pharmacokinetic and pharmacodynamic components, allowing precise identification of the mechanisms responsible for the variability in drug response. In addition, modeling yields mathematically defined pharmacokinetic-dynamic parameters, which can be employed in computer simulations of opioid pharmacology in a variety of settings.

Figure 10-19 (Figure Not Available) Two examples of opioid pharmacologic variability. The left panel represents alfentanil's pharmacokinetic variability after injection of an identical dose of alfentanil to 45 subjects. The observed concentrations for some subjects at any given time after injection are many times greater than those of other subjects. The right panel shows alfentanil's pharmacodynamic variability when alfentanil is used with nitrous oxide to prevent untoward responses to surgical manipulation during intra-abdominal surgery. Note that the potency of alfentanil for some subjects is several times greater than for others. *(From Maitre et al [743] and Ausems et al [874])*

Pharmacokinetic parameters govern the relationship between opioid dose and the opioid concentrations in the blood (or other body fluid). Pharmacodynamic parameters describe the relationship between opioid concentration in the blood (or other fluid) and opioid effect. Expectations regarding opioid response, including latency to peak effect, and its magnitude and duration are made possible by careful analysis of these pharmacokinetic-dynamic parameters. Dosing schemes that target the appropriate "therapeutic window" in the patient population of interest can then be developed.

Physicochemical Properties

The physicochemical properties of opioids have important pharmacologic implications. Opioids are weak bases. When dissolved in solution, they are dissociated into protonated and free-base fractions, with the relative proportions depending on the pH and pKa. The free base form is always more lipid soluble than the ionized form. Hence, opioid lipid solubility is strongly influenced by the pKa.

A high lipid solubility facilitates opioid transport into the biophase or site of action. Thus, in general, highly lipid-soluble opioids have a more rapid onset of action. However, because the opioid receptor "recognizes" an opioid molecule in the protonated form, the intensity of opioid effect is closely related to the ionized concentration of drug in the biophase. Thus, speed of onset and receptor agonism are complex functions of lipid solubility and the percentage ionized at physiologic pH (Fig. 10-20) .

All opioids are to some extent bound to plasma proteins, including albumin and alpha $_1$ -acid glycoprotein. Opioid molecules that are bound to plasma proteins cannot move from the blood to opioid receptors in the CNS or elsewhere. It is only the un-ionized, unbound fraction that constitutes the "diffusible fraction" and provides the concentration gradient that promotes diffusion of opioid from the blood to the tissue of interest. The concentration of this diffusible fraction (and other factors such as lipid solubility and plasma-tissue partition coefficients) determines the rate at which opioid diffusion takes place.

Differences in the speed of onset of effect between morphine and alfentanil illustrate the impact of lipid solubility and diffusible fraction. Morphine has a high diffusible fraction but is a slow-onset opioid because of its low lipid solubility. Alfentanil, on the other hand, has a high diffusible fraction and adequate lipid solubility, a combination that makes it a very rapid-onset opioid.

Common Pharmacokinetic Features of Opioids

Although each opioid has unique pharmacokinetic features, as a group they share a general pattern of pharmacokinetic behavior. Representative pharmacokinetic parameters for the opioids commonly used in anesthesia are displayed in Table 10-12 .

After IV injection, arterial plasma concentrations of opioids rise to a peak within one circulation time. Thereafter, they exhibit a rapid redistribution phase (sometimes two) and a slower elimination phase typical of drugs whose pharmacokinetics is described by compartmental models.

Opioid pharmacokinetics can be conceptualized in schematic and graphic forms as summarized in Figure 10-21 (Figure Not Available) . [643] After administration into a central compartment, opioids are either eliminated from the central compartment (by excretion or biotransformation) or distributed to peripheral compartments, as depicted in the schematic panel of Figure 10-21 (Figure Not Available) . An alternative representation of these pharmacokinetic processes is shown in the concentration versus time plot in the middle panel of Figure 10-21 (Figure Not Available) , graphically illustrating the distinct distribution and elimination phases characteristic of opioids. These compartments are mathematic

---

Figure 10-20 Distribution of fentanyl within the body compartments at an extracellular pH of 7.4. The accumulation of fentanyl by the tissue is assumed to increase the tissue concentration 13-fold. In

the extracellular space, an equilibrium exists between the ionized fentanyl (F^+), the free base (F), and the fentanyl molecules bound to macromolecules (F_b). The concentration of ionized fentanyl within the interstitial fluid (encircled F^+) determines the pharmacologic effect, because the opioid receptors (U U) are located at the cell surface. Fentanyl as the free base readily penetrates the cells and becomes bound to cytomembranes, lysosomes, and other structures (thick arrows) and thus accumulates in the cell. A small decrease of the extracellular pH shifts the equilibrium between F and F^+ toward higher F^+ concentrations and induces a marked release of fentanyl from the cellular compartment as a result of the decrease of the concentration of F in the interstitium. An increase of the extracellular H^+ concentration by pH 0.2 may roughly double the concentration of ionized fentanyl within the interstitial fluid and accordingly enhance its pharmacologic effect.

constructs and do not represent any particular anatomic region or organ system.

The biexponential equation depicted in the right panel of Figure 10-21 (Figure Not Available) is the mathematic form of the concepts illustrated by the schematic diagram and graphic portions of the figure. This equation (and various modifications of it) provides the quantitative foundation for the computerized modeling process used to estimate opioid pharmacokinetic parameters.

In general, opioids are cleared from the plasma by biotransformation in the liver. For most opioids, the hepatic extraction ratio is high enough that liver blood flow has a substantial influence on opioid clearance. Extrahepatic metabolism is important for some opioids. For example, the kidney plays a role in the conjugation of morphine, whereas blood and tissue esterases are responsible for remifentanil metabolism (discussed later).

As a rule, because of their high lipid solubility, opioids are widely distributed in body tissues. In pharmacokinetic terms, this means that opioids typically have a high apparent volume of distribution at steady state. Because opioids are distributed so widely and so rapidly to various body tissues,

TABLE 10-12 -- Physicochemical and Pharmacokinetic Data of Commonly Used Opioid Agonists

	MORPHINE	MEPERIDINE	FENTANYL	SUFENTANIL	ALFENTANIL	REMIFENTANIL
pKa	8.0	8.5	8.4	8.0	6.5	7.1
% Un-ionized at pH 7.4	23	<10	<10	20	90	67?
Octanol/H_2O partition coefficient	1.4	39	813	1,778	145	17.9
% Bound to plasma protein	20-40	39	84	93	92	80?
Diffusible fraction (%)	16.8	2.2	1.5	1.6	8.0	13.3?
$t_{½\ alpha}$, (min)	1-2.5	--	1-2	1-2	1-3	0.5-1.5
$t_{½\ beta}$, (min)	10-20	5-15	10-30	15-20	4-17	5-8
$t_{½\ gamma}$, (h)	2-4	3-5	2-4	2-3	1-2	0.7-1.2
Vd_c (L/kg)	0.1-0.4	1-2	0.4-1.0	0.2	0.1-0.3	0.06-0.08
Vd_{ss} (L/kg)	3-5	3-5	3-5	2.5-3.0	0.4-1.0	0.2-0.3
Clearance (mL/min/kg)	15-30	8.18	10-20	10-15	4-9	30-40
Hepatic extraction ratio	0.6-0.8	0.5-0.7	0.8-1.0	0.7-0.9	0.3-0.5	NA

$t_{½}$ alpha, beta, gamma are the half-lives of a three compartment model; Vd_c, volume of distribution of the central compartment; Vd_{ss}, volume of distribution at steady state.

Figure 10-21 (Figure Not Available) A summary of pharmacokinetic modeling theory for a two compartment model. Depicted schematically, after intravenous administration into a central compartment, drug can either be eliminated or distributed to a peripheral compartment. The process results in distinct distribution and elimination phases of the concentration versus time curve when plotted graphically. The mathematical representation of curves of this shape is the polynomial equation noted. This equation is the basis for the computerized pharmacokinetic modeling process typically applied to opioids. *(Reprinted with permission from Egan, [643] St. Louis, Mosby.)*

redistribution has a prominent impact on the decline of opioid concentration, particularly in the early period after injection.

Opioid uptake by the lung is a significant nuance of opioid pharmacokinetics. The rise-time to peak concentration of an opioid is influenced by the percentage of pulmonary uptake. A very substantial proportion of the initial dose of a highly lipophilic opioid such as fentanyl is taken up by the lung (75%) and subsequently is rapidly released. [644] This process influences peak blood concentration and the time to achieve it.

Pharmacokinetic Features of Individual Drugs

Morphine

Morphine pharmacokinetics is notably different from that of the fentanyl congeners. This difference is in large part due to morphine's comparatively low lipid solubility. Both biexponential and triexponential equations have been used to describe the pharmacokinetics of morphine. After IV injection, morphine is rapidly distributed. [361] [645] [646] [647] [648] [649] [650] In contrast to the fentanyl series, there is relatively little transient first-pass uptake of morphine by the lung. [644] [651]

Morphine's physicochemical properties have important clinical implications. The pKa of morphine (8.0) is greater than physiologic pH, and thus after IV injection only a small percentage (10-20%) is un-ionized. This property, combined with its low lipid solubility, limits the ability of morphine to penetrate tissues. Thus, penetration of morphine into and out of the brain is presumably slower compared with that of other opioids. Morphine's slow brain penetration means that analgesia and respiratory effects are not reflected by plasma levels. Approximately 20 to 40 percent of morphine is bound to plasma proteins, mostly albumin. [649]

Morphine is principally metabolized by conjugation and has a hepatic extraction ratio that is equal to or greater than hepatic blood flow indicating a high clearance (15-30 mL
kg^{-1}
min^{-1}). [652] The kidney appears to play a key role in the extrahepatic metabolism of morphine and may account for nearly 40 percent of its clearance, [653] although there is some controversy about the importance of renal morphine metabolism. [654] [655]

M3G is the major metabolite of morphine, but it does not bind to opioid receptors and possesses little or no analgesic activity. [656] [657] However, M6G accounts for nearly 10 percent of morphine's metabolism and is a more potent mu- receptor agonist than morphine with a similar duration of action. It is now clear the M6G contributes substantially to morphine's analgesic effects even in patients with normal renal function. [658] Interestingly, M6G appears to have a more favorable side effect profile than morphine. [659] *N*-demeth-ylation metabolites of morphine also represent a small percent of its metabolism.

Because of morphine's high hepatic extraction ratio, the bioavailability of orally administered morphine is significantly lower (20-30%) than after IM or subcutaneous injection. [650] As demonstrated in Figure 10-22 (Figure Not Available) , in contrast to IV administration, the hepatic first-pass effect on an orally administered dose of morphine results in substantial levels of M6G. It appears that M6G is in fact the primary active compound when morphine is administered orally. [660]

Meperidine

The plasma concentration versus time decay curve of meperidine is best characterized by a two-compartment model. [661] [662] [663] [664] [665] [666] Unlike morphine, after IV injection, first-pass uptake of meperidine by the lungs is approximately 65 percent. [644] The volume of distribution of meperidine is similar to that of morphine (4±1 L
kg^{-1}), [661] [662] [663] [664] [665] as is its clearance (8-18 mL
kg^{-1}

min^{-1}). [661] [662]

Meperidine's physicochemical properties are similar to those of the fentanyl congeners. Meperidine is more highly bound to plasma proteins than morphine, principally (70%) to alpha$_1$ -acid glycoprotein. In contrast to morphine, meperidine binds only to a minor extent to plasma albumin.

Figure 10-22 (Figure Not Available) Mean plasma concentrations of morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) after intravenous and oral administration. Note the high concentrations of morphine-6-glucuronide after oral administration. *(From Osborne et al [660])*

Meperidine is even less un-ionized (<10%) than morphine at physiologic pH, but it is significantly more lipid soluble.

As with morphine, a relatively high hepatic extraction ratio results in biotransformation that is dependent on hepatic blood flow. The principal metabolic pathways of meperidine are *N*-demethylation and diesterification, which produces normeperidine, meperidinic acid, and normeperidinic acid as the major metabolites. Little meperidine (<5%) is excreted unchanged in the urine. Normeperidine has analgesic activity and is roughly twice as potent as the parent compound in producing seizures in animals. [667] The greater epileptogenic properties of meperidine cause its therapeutic index to be less than one-tenth that of morphine (5 versus 70).

Normeperidine is dependent on renal clearance mechanisms for elimination. The elimination half-life of normeperidine is considerably greater than that of meperidine, and thus repeated doses can easily produce accumulation of this toxic metabolite in patients with renal disease, potentially producing seizures (see later). [668]

Fentanyl

A three-compartment model is typically used to describe plasma fentanyl concentration decay. [339] [366] [669] [670] The lungs exert a significant first-pass effect and transiently take up approximately 75 percent of an injected dose of fentanyl. [644] [671] As is typical of the fentanyl congeners, at steady state fentanyl's volume of distribution (3-6 L
kg^{-1}) and clearance (10-20 mL
kg^{-1}
min^{-1}) are both high.

Approximately 80 percent of fentanyl is bound to plasma proteins, and significant amounts (40%) are taken up by red blood cells. [672] Because the pKa of fentanyl is high (8.4) at physiologic pH, it exists mostly in the ionized form (>90%). Fentanyl's lipid solubility is also high (see Table 10-12) , a finding that explains in part its large volume of distribution. Bjorkman et al [673] found the tissue/blood partition coefficients of fentanyl to be 2- to 30-fold higher than those of alfentanil. Because fentanyl is distributed so widely in the body, it must ultimately be returned to the blood to be metabolized in the liver. Fentanyl is relatively long acting, in large part because of this widespread distribution in body tissues.

Fentanyl is primarily metabolized in the liver by *N*-dealkylation and hydroxylation. [674] Fentanyl has a high hepatic clearance (approaching hepatic blood flow) and a high hepatic extraction ratio (approaching 1.0). [370] Metabolites begin to appear in the plasma as early as 1.5 minutes after injection. [675] Norfentanyl, the primary metabolite, is detectable in the urine for up to 48 hours after IV fentanyl in humans. [676] The activity of fentanyl's metabolites is unclear, but it is thought to be minimal. Little fentanyl is excreted in the urine unchanged. [366]

Alfentanil

Perhaps more than any other opioid, the pharmacokinetics of alfentanil has been extensively evaluated [370] [677] [678] [679] [680] [681] and discussed. [17] [682] [683] [684] Following IV injection, alfentanil plasma concentrations are described by either two-compartment [370] [677] [678] [681] or three-compartment models. [679] [680] Alfentanil's clearance (4-9 mL
min^{-1}
kg^{-1}) is less than that of fentanyl. A small volume of distribution at steady state (0.4-1.0 L
kg^{-1}) limits drug distribution and tissue drug accumulation and is largely responsible for the short elimination half-life of alfentanil in spite of a lower clearance than fentanyl.

Alfentanil's physicochemical properties make it unique compared with the other fentanyl congeners. Alfentanil is lipid soluble but significantly less so than fentanyl. [682] [685] Alfentanil is also bound to plasma proteins (mostly glycoproteins) in higher proportions (90%) than fentanyl. [370] [678] [680] Alfentanil's most unique physicochemical feature is that at physiologic pH, it is mostly (90%) un-ionized because of its relatively low pKa (6.5). [686] Thus, despite more intense protein binding, the diffusible fraction of alfentanil is higher

---

than fentanyl. This explains, in part, its short latency to peak effect after IV injection. Although not proven, it may be that alfentanil's lower lipid solubility compared with fentanyl makes for less uptake of alfentanil by lipid-rich brain tissue. This may also contribute to alfentanil's rapid onset and offset of effect. [141] [682] [687]

The main metabolic pathways of alfentanil are similar to those of sufentanil and include oxidative *N*-dealkylation and *O*-demethylation, aromatic hydroxylation, and ether glucuronide formation. [688] Reported hepatic extraction ratios vary from 0.3 to 0.5. [370] [680] [689] Oxidative- *N*-dealkylation of alfentanil produces its major metabolite, noralfentanil. Other metabolites include desmethylalfentanil, desmethylnoralfentanil, and a number of other products. [690] [691] The degradation products of alfentanil have little, if any, opioid activity. Little alfentanil (<1%) appears in the urine unchanged due to its protein binding, renal tubular reabsorption and hepatic metabolism.

Patients deficient in the cytochrome P-450 form involved in debrisoquin metabolism do not have an altered disposition of alfentanil. [690] [691] This is consistent with the finding that human alfentanil metabolism may be predominantly, if not exclusively, by cytochrome P-450 3A3/4. [692] Cytochrome P-450 3A3/4 is one of a family of cytochrome P-450 isoenzymes that have distinct but overlapping substrate specificities. [693] This enzyme is known to display at least an 8-fold difference in activity in humans. This may be why patients are occasionally found to have a very low alfentanil clearance and unexpected prolonged effects.

Sufentanil

Until recently, the pharmacokinetics of sufentanil had been inadequately characterized because of poor assay sensitivity. For example, in carefully designed and conducted studies, Bovill et al [694] and Hudson et al [695] reported sufentanil pharmacokinetic parameter sets that had a similar central clearance but a 5-fold difference in steady-state distribution volumes. This difference likely reflected that it is difficult to estimate accurately the distribution and elimination properties of a drug unless it can be detected at the low levels present during the later stages of the concentration decay.

Sufentanil's potency is so great that it continues to exert its effects when the concentrations in the plasma are at very low levels. In order to estimate pharmacokinetic parameters that are meaningful, it was necessary to develop an assay that could measure sufentanil at the low levels observed during the elimination phase. A radioimmunoassay was developed that made adequate characterization of sufentanil's pharmacokinetics possible. [696]

As was suggested by the earlier work of Bovill and Hudson and their colleagues, the pharmacokinetics of sufentanil is adequately described by a three-compartment model. [697] After IV injection, first-pass pulmonary extraction, retention, and release are similar to those of fentanyl. [651] Representative pharmacokinetic parameters include an apparent steady-state distribution volume of 262 L and a central clearance of 0.92 L
min^{-1} in a typical adult. [697]

The pKa of sufentanil at physiologic pH is the same as that of morphine (8.0), and, therefore, only a small amount (20%) exists in the un-ionized form. Sufentanil is twice as lipid soluble as fentanyl and is highly bound (93%) to plasma proteins including alpha $_1$ -acid glycoprotein. This combination of physicochemical properties means that sufentanil has a diffusible fraction that is very similar to that of fentanyl.

Sufentanil's hepatic extraction ratio is very high (0.8), and thus changes in liver blood flow can significantly alter its elimination. The major metabolic pathways of sufentanil include *N*-dealkylation, oxidative *N*-dealthylation, oxidative *O*-demethylation, and aromatic hydroxylation. [698] Major metabolites include *N*-phenylpropanamide. Extensive renal tubular reabsorption leads to little unchanged sufentanil in the urine.

Remifentanil

Remifentanil is a synthetic opioid that has been approved for clinical use in the United States and Europe. [699] Although chemically related to the fentanyl congeners, remifentanil is structurally unique because of its ester linkages. Remifentanil's ester structure renders it susceptible to hydrolysis by blood- and tissue-nonspecific esterases, resulting in rapid metabolism. Remifentanil thus constitutes the first "ultrashort"-acting opioid for use as a supplement to general anesthesia.

Remifentanil's pharmacokinetics is best described by a three-compartment model. It appears that the lungs do not represent a site of significant remifentanil metabolism or sequestration. [700] Its clearance is several times greater than normal hepatic blood flow, consistent with widespread extrahepatic metabolism. Several high-resolution studies in both volunteers and patients have confirmed its very short-acting pharmacokinetic profile. [701] [702] [703] Figure 10-23 (Figure Not Available) contrasts the fall in blood concentrations when remifentanil and alfentanil are given in a crossover fashion to a group of adult male volunteers in doses sufficient to produce profound slowing of the EEG during a 10-minute infusion. [703] Remifentanil concentrations fall very rapidly after termination of an infusion.

Remifentanil's physicochemical properties are characteristic of drugs in the fentanyl family. [704] It is a weak base with a pKa of 7.07. It is highly lipid soluble with an octanol/water partition coefficient of 19.9 at pH 7.4. Like the other fentanyl congeners, remifentanil is highly bound (
70%) to plasma proteins (mostly alpha$_1$ -acid glycoprotein). The remifentanil free base is formulated with glycine. Because glycine has been shown to act as an inhibitory neurotransmitter that causes a reversible motor weakness when injected intrathecally in rodents, remifentanil is not approved for spinal or epidural use. [705] In addition, because remifentanil is unstable in solution for long periods of time, the lyophilized powder must be reconstituted within 24 hours prior to use.

After IV injection, remifentanil undergoes widespread extrahepatic hydrolysis by nonspecific blood and tissue esterases. As depicted in Figure 10-24 (Figure Not Available) , the primary metabolic pathway of remifentanil is de-esterification to form a carboxylic acid metabolite, GI-90291. [699] GI-90291 is dependent on renal clearance mechanisms. *N*-dealkylation of remifentanil to GI-94219 is a minor metabolic pathway. Almost 90 percent of the drug is recovered in the urine in the form of the acid metabolite. Although specific human data

Figure 10-23 (Figure Not Available) The raw concentration versus time data when a group of ten volunteers received (in a cross-over trial) remifentanil and alfentanil in doses sufficient to produce profound slowing of the electroencephalogram. *(From Egan et al [703])*

are not available, evidence from dogs suggests that the remifentanil metabolites are, for practical purposes, completely inactive, even in the face of renal failure. [706] A unique feature of remifentanil metabolism is that its pharmacokinetics is not appreciably influenced by renal or hepatic failure. [707] [708]

Remifentanil metabolism is mediated by nonspecific esterases in blood and tissue. In blood, remifentanil is metabolized primarily by enzymes within the red cell. [709] Remifentanil

Figure 10-24 (Figure Not Available) Remifentanil's metabolic pathway. De-esterification by nonspecific plasma and tissue esterases to form a carboxylic acid metabolite (GI-90291) is the primary metabolic pathway. *N*-dealkylation of remifentanil to GI-94219 is a minor metabolic pathway. *(From Egan [699])*

is not a good substrate for pseudocholinesterase and, therefore, is not influenced by pseudocholinesterase deficiency. [710]

NEW PHARMACOKINETIC-DYNAMIC CONCEPTS IN OPIOID PHARMACOLOGY

Irrelevance of the Terminal Half-Life

Half-life, perhaps the most familiar and widely used concept in pharmacokinetics, is the parameter employed to describe the rate at which drug concentrations decline. However, unlike clearance and volume of distribution, half-life is not a fundamental pharmacokinetic parameter. It is, instead, a derived or calculated parameter. Because the value of half-life is dependent on the primary pharmacokinetic parameters volume of distribution and clearance, half-life is not independently influenced by changes in patient physiology. [643] Alterations in volume of distribution, clearance, or both these parameters that come about as a result of changes in patient physiology affect the value of half-life secondarily.

The clinical relevance of half-life is even more obscure when dealing with opioid multicompartmental models because there are as many half-lives as there are compartments. Although the terminal half-life from multicompartmental models has traditionally been the pharmacokinetic parameter relied on for predictions regarding the duration of opioid effect, it can be grossly misleading. Distribution volumes and clearances can be similarly confusing to apply clinically. This confusion relates to the complex way in which these multiple pharmacokinetic parameters interact.

An opioid whose pharmacokinetics is described by a three-compartment model, for example, has three half-lives, three clearances, and four distribution volumes (the steady-state distribution volume is the sum of the three compartment volumes). Which of these multiple parameters is important? How do they interact? To the dismay of clinicians and pharmacokineticists alike, the interaction of these parameters is not easily predicted. In fact, in most cases, it is virtually impossible to predict without the aid of computers. [643]

No single parameter from a multicompartmental model can be relied on to make predictions about the overall opioid pharmacokinetic profile. The terminal elimination half-life is often used clinically as if it constituted the only pharmacokinetic parameter of importance in predicting the duration of opioid effect. [711] In fact, for drugs described by multicompartmental models, there are numerous half-lives that must be considered, along with a host of other parameters. Each half-life, or other parameter, contributes variably to the prediction of drug concentration at a given time after drug administration. [712] For most opioids, the terminal elimination half-life has very minimal impact on the overall decline in drug concentration within the range of clinical significance because most of the concentration decrease is accounted for by other components of the model. The popularity of the terminal elimination half-life as an indicator of duration of drug effect, given its lack of usefulness, is a clinical tradition that requires reexamination. [701]

The primary shortcoming of half-lives in opioid pharmacology is that they fail to account for the important influence of distribution processes on drug disposition. [713] Distribution processes refer to the net transfer of drug between the central compartment and the peripheral compartments. Depending on the size of the peripheral compartment and the rate at which drug transfer occurs, distribution into or out of the peripheral compartments can have a major impact on the concentration versus time profile.

Figure 10-25 (Figure Not Available) is a hydraulic representation of a pharmacokinetic model for a drug such as sufentanil that illustrates how distribution processes influence the concentration versus time profile. For sufentanil, the volume of one of the peripheral compartments is large, and the rate of transfer into it from the central compartment is slow. Thus, the concentrations in the two compartments come to equilibrium very slowly. If equilibrium has not been reached when a sufentanil infusion is terminated, both elimination from the central compartment and distribution into the slowly equilibrating peripheral compartment can combine to lower central drug concentration. Conversely, if the two compartments have come to equilibrium, the peripheral compartment serves as a reservoir of sufentanil that reenters the central compartment after termination of an infusion, thus impeding the decrease in sufentanil concentration produced by elimination from the central compartment.

Context-Sensitive Half-Time

Computer simulation techniques predict the time necessary to achieve a 50 percent decrease in drug concentration after termination of a variable length continuous infusion to a steady-state drug level (Fig. 10-26) (Figure Not Available) . Using concepts developed by Shafer and Varvel, these simulations are an attempt

Figure 10-25 (Figure Not Available) A hydraulic representation of a three-compartment model in which drug administration and elimination occur in the central compartment. This model could represent the pharmacokinetics of a drug such as sufentanil. The model is composed of three cylindric areas (CA_1) representing the volume of the pharmacokinetic compartments (or buckets using this hydraulic analogy). The height (h_1) of the water level in each compartment represents drug concentrations. The pipes connecting the compartments transfer drug from one compartment to another and to the outside at a rate characterized by the conductance (G_1), denoted by the diameter of the pipe. The water entering the system at a specified rate (r[t]) represents drug administration (see text for complete explanation). *(From Hughes et al [713])*

Figure 10-26 (Figure Not Available) A graphic representation of the context-sensitive half-times for the fentanyl congeners. It simulates the time required for a 50 percent decrease in plasma concentration after termination of a continuous infusion. *(From Egan et al [701])*

to provide "context-sensitive half-times" as proposed by Hughes et al. [713] In this case, the "context" is the duration of a continuous infusion. The context-sensitive half-time has also been referred to as the 50 percent decrement time. [714] Such simulations are intended to provide more clinically relevant meaning to pharmacokinetic parameters.

For example, and perhaps contrary to contemporary established notions, alfentanil does not exhibit a more rapid 50 percent decrease in plasma concentration compared with sufentanil after termination of a continuous infusion until after approximately 8 hours of infusion, despite its short terminal elimination half-life. Thus, sufentanil appears to have more favorable pharmacokinetics for infusions lasting less than 8 hours when the goal is to achieve a rapid 50 percent decrease in concentration. As noted previously, in terms of pharmacokinetic theory, this surprising difference between alfentanil and sufentanil can be explained by the fact that sufentanil's pharmacokinetic model has a large, slowly equil-ibrating peripheral compartment that continues to fill after termination of an infusion, thus contributing to the faster decrease in sufentanil's central compartment concentration.

Remifentanil has a context-sensitive half-time that is markedly shorter than those of the other fentanyl congeners. [701] Remifentanil's context-sensitive half-time is also independent of infusion duration. Hence, despite very long infusions, remifentanil concentrations decrease by 50 percent within 3 to 5 minutes of stopping drug

administration. Clinically, when rapid offset of opioid effect is important, or when the need for opioid effect is highly variable, remifentanil's unique pharmacokinetic profile can be exploited.

Interestingly, for cases of very brief duration, the context-sensitive half-times for sufentanil, alfentanil, and fentanyl are nearly identical. Thus, for brief cases, when the opioid is administered by infusion, there would not be any substantial differences among the three drugs in the time to a 50 percent drop in concentration after stopping a continuous infusion. It should be noted that the shapes and relationships of these curves vary depending on the percentage decrease in concentration required. For some anesthetic techniques, a 50 percent decrease in concentration is not sufficient to permit spontaneous ventilation at the end of the operation (e.g., "high dose" opioid anesthesia for cardiac surgery). In such cases, the 80 percent decrement time (or some other percentage) may be more clinically useful. [714]

Biophase and Latency to Peak Effect

Equilibration delay between peak drug concentration in the blood or plasma and peak drug effect must also be considered in understanding the implications of opioid pharmacokinetic simulations. For many opioids, there is a significant time lag between peak concentration in the plasma and peak drug effect. This time lag, or hysteresis, is a function of drug movement into and action within the effect site, or biophase. [715] [716] The hysteresis is a summation of all the events that can conceivably affect the onset of pharmacologic effect such as drug diffusion to the effect site and receptor binding. Because effect site concentrations lag behind plasma or blood concentrations, pharmacologic effect also lags behind plasma or blood concentrations.

In short, opioids do not act in the plasma or blood. Thus, this lag time must be considered when using plasma or blood simulations of drug concentration in forecasting drug effect. The time lag is particularly important when giving opioids by bolus administration such as during patientcontrolled analgesia (PCA) therapy, whereas for long infusions, the time lag assumes less importance because the biophase and plasma are generally much closer to equilibrium.

For many of the opioids in widespread clinical use, the equilibration delay between peak concentration in the plasma and peak effect has been characterized. Flow of drug to the effect compartment is a first-order process and can be elucidated by estimating k_{ec}, a first-order rate constant for

---

Figure 10-27 (Figure Not Available) A simulation of plasma and effect site concentrations after intravenous fentanyl administration during typical anesthesia. Plasma concentrations are indicated by the solid line and are designated C_p. The effect site concentrations are represented by the dotted line and are labeled C_e. The effect site concentrations lag behind the plasma concentrations. *(Reprinted with permission from Egan, [643] St. Louis, Mosby)*

elimination of drug from the effect compartment. When the k_{ec} parameter is available for an opioid, theoretic effect compartment concentrations can be simulated along with plasma or blood concentrations, thus making the implications of the time lag easily appreciated.

Figure 10-27 (Figure Not Available) is a simulation of fentanyl administration, showing both the plasma and effect site concentrations based on parameters from the literature. Recognizing that drug effect best correlates with effect site concentration, the simulation is quite revealing, illustrating that the time course of drug concentration in the effect site is much smoother than in the plasma. In general, the fentanyl congeners (especially alfentanil and remifentanil) have a short k_{eo} half-life ($t_{1/2}\,k_{eo}$), whereas morphine's blood-brain equilibration time is much longer. [717] Hence, when administered in "equipotent" doses, the fentanyl congeners reach peak effect considerably faster than morphine.

Figure 10-28 (Figure Not Available) contrasts the implications of plasma effect site equilibration delay on the achievement of peak concentrations in the effect site for the fentanyl congeners. Note that alfentanil and remifentanil reach peak concentrations very shortly after bolus administration, whereas fentanyl and sufentanil are slower to reach peak concentration in the effect site. [718] When equipotent doses are given, this simulation is a general guide to the speed of onset of the fentanyl congeners. Alfentanil and remifentanil can be regarded as

---

Figure 10-28 (Figure Not Available) A computer simulation of the time required to reach peak effect site concentration after bolus administration of fentanyl, alfentanil, sufentanil, and remifentanil using pharmacokinetic parameters from the literature. This is a graphic illustration of the plasma-biophase equilibration process for these drugs. C_e is the effect site concentration; a bolus injection was made at time 0. *(From Egan [716])*

very rapid-onset opioids (i.e., short latency to peak effect). Interestingly, after single bolus administration, alfentanil and remifentanil also exhibit a rapid speed of offset because effect site concentrations begin to fall immediately after the rapid peak. [18] Note that gross overdosage of any of these drugs renders these simulations irrelevant because opioid receptor saturation may occur before peak effect site levels are reached.

Slope of the Concentration-Effect Relationship

Although clinicians have traditionally relied on pharmacokinetic parameters in predicting the time course of drug effect, the temporal profile of drug effect is a function of both pharmacokinetic and pharmacodynamic parameters. Computer modeling research has focused attention on the steepness of the concentration-effect relationship as an important parameter in predicting duration of drug effect.

For opioids, the concentration-effect relationship is usually described graphically by a sigmoidal maximum-effect curve in which drug concentration in the site of action is plotted against drug effect. This sigmoid curve is represented mathematically by the following equation:

where E is the predicted effect, E_0 is the baseline effect level, E_{max} is maximal effect, C_e is effect site concentration, gamma is a measure of curve steepness, and EC_{50} is the effect site concentration that produces 50 percent of maximal effect. EC_{50} is the measure of drug potency, which can be compared with other drugs of the same class.

This mathematic representation of the concentrationeffect relationship is appealing not only because it is harmonious with experimental observations, but also because it is consistent with the receptor concept of opioid action. When sufficient numbers of receptors are highly activated, the maximal possible effect is achieved; that is, biologic systems are not capable of an infinite response. Thus, the opioid concentration-effect relationship is well described by a sigmoidal maximum effect curve in which a plateau in drug effect is eventually observed despite enormous increases in opioid concentration.

The gamma parameter of the sigmoidal maximum effect equation is a measure of curve steepness. When gamma is large, the concentration-effect relationship is steep. For drugs with a steep concentration-effect relationship, small changes in drug concentration within the steep portion of the curve produce large changes in drug effect. For drugs that exhibit concentration-effect relationships in which gamma is small, a small change in concentration does not result in such obvious changes in the magnitude of drug effect.

For drugs such as opioids that have a steep concentration-effect relationship, the correlation of effect with concentration is often observed to be binary. In other words, the degree of drug effect is either substantial or it is near negligible. This is because when drug concentration drops much lower than the EC_{50}, the probability of substantial drug effect is minimal, whereas when concentrations are much higher than EC_{50}, the probability of near maximum drug effect is high. When the concentration-effect relationship is less steep, the correlation of concentration with effect is more continuous.

One very important practical application of this concept is that pharmacokinetic parameters cannot be interpreted in isolation in predicting the duration of drug effect.

Although knowledge of the predicted decline in drug concentration based on pharmacokinetic parameters is helpful, it must be interpreted with knowledge about the drug potency and steepness of the concentration-effect relationship.

For example, in Figure 10-29 (Figure Not Available) , the predicted decline in fentanyl concentration after a steady-state infusion is terminated is plotted versus time. The probability of drug effect is also plotted for two different theoretic concentration-effect relationships; one that is steep (gamma = 10) and another that is not steep (gamma = 2). When the concentration-effect relationship is steep, there is a rapid dissipation in the probability of drug effect with declining drug concentration, whereas when the concentration-effect relationship is not steep, there is a much more gradual decline in the probability of drug effect with falling drug concentration. This notion has been quantified mathematically and has been designated the mean effect time. [719]

The implications of context-sensitive half-time (or 50% decrement time) must thus be interpreted in concert with knowledge of the concentration-effect relationship. Duration of drug effect as predicted by the context-sensitive half-time closely parallels that predicted by the mean effect time when the concentration-effect relationship is steep. When the concentration-effect relationship is less steep, the context-sensitive half-time may be less useful in predicting the time course of drug effect. For alfentanil, a drug whose concentration-effect relationship is steep, the mean effect time and context-sensitive half-time predict a similar time course of drug effect. Conversely, for midazolam, a drug whose concentration-effect relationship is less steep, the mean effect time and context-sensitive half-time predict a different time course of drug effect after termination of an infusion. [719]

The clinical application of these concepts with regard to opioid pharmacology relates to the steepness of the concentration-effect relationship of opioids. Opioids are known to be drugs with relatively steep concentration-effect relationships; that is, the gamma parameter is relatively large. Thus, very small changes in opioid concentration can produce large changes in the degree of drug effect. This means that for patients in whom a typical analgesic regimen fails, sometimes very small increases in dosage can result in adequate analgesia. [720] Figure 10-30 (Figure Not Available) illustrates how small increases in meperidine concentration resulted in an abrupt change from inadequate to good analgesia because of the steepness of the concentration-effect relationship. Patient response to opioids is often binary. Analgesia is either adequate or it is not.

Computerized Delivery Methods in Opioid Research and Clinical Practice

Until recently, the most sophisticated delivery device for the administration of opioids was the calculator pump, a device that enabled an accurate and precise delivery of fluid

---

Figure 10-29 (Figure Not Available) The decline in fentanyl concentration in the plasma after stopping a 60-minute infusion and targeting a concentration of 10 ng/mL versus the probability of drug effect for two concentration-effect relationships, one steep (gamma = 10) and the other less steep (gamma = 2). Note that when the slope of the concentration-effect relationship is steep, the probability of substantial drug effect as a function of concentration is nearly a binary response (see text for complete explanation). *(From Bailey [719])*

per unit of time. Used in both clinical and research settings, the physician operator of these devices simply specifies a delivery rate in terms of milliliters per hour or micrograms per kilogram per minute. The PCA machine is a hybrid of the calculator pump that permits patient control of opioid administration within physician-constrained parameters. The primary limitation of these calculator pumps is that they do not achieve the pharmacokinetic exactness possible with more advanced methods of administration.

Advances in pharmacologic modeling and infusion pump technology have made it possible to administer opioids (and other drugs) via a computer-controlled infusion pump (CCIP). [721] By coding a pharmacokinetic model into a computer program and linking it to an electronic pump modified to accept computerized commands, delivery according to a drug's specific pharmacokinetic parameters can be achieved. The physician operating a CCIP designates a target concentration to achieve rather than specifying an infusion rate. The CCIP then calculates the necessary infusion rates to achieve the targeted concentration. This process is somewhat akin to delivering inhaled anesthetic through the lungs using a vaporizer.

Borrowing from inhalation anesthesia concepts, the CCIP makes progress toward the concept of a "vaporizer" for opioids because they address the fundamental limitation associated with delivering drugs directly into the circulation. Constant

Figure 10-30 (Figure Not Available) Blood meperidine concentration-response curves for three individual patients (A, B, C) illustrating the steepness of the typical opioid concentration-effect relationship. Postoperative patients rated their pain from 0 (no pain) to 2 (severe pain) in response to meperidine therapy. As meperidine concentrations increased, eventually a small increase produced a dramatic improvement in the patient's pain. *(From Austin et al [720])*

---

rate infusions result in continuous drug uptake. The CCIP, in contrast, gradually decreases the rate of infusion based on the drug's pharmacokinetics. Known in its general form as the BET method (i.e., bolus, elimination, and transfer), [722] the dosing scheme determined by a CCIP accounts for the initial concentration after a bolus dose and the subsequent drug distribution and clearance while an infusion is ongoing.

Delivery of an opioid via CCIP requires a different approach by clinicians. Rather than setting an infusion rate based on clinical experience and literature recommendations, the anesthesiologist using a CCIP designates a target concentration, and the CCIP calculates the infusion rates necessary to achieve the concentration over time. The CCIP changes the infusion rates at frequent intervals, sometimes as often as every 10 seconds. Successful use of a CCIP thus requires knowledge of the therapeutic concentrations appropriate for the clinical setting.

Computer-controlled drug delivery is an exciting area with promising potential in anesthesiology and pain management. Available CCIP prototypes typically perform quite well, as exemplified by Figure 10-31 (Figure Not Available) , a fentanyl CCIP application. [723] Pharmacokinetic model-based PCA analgesia is also being developed with optimism. [724] This application of CCIP technology requires the patient to specify whether pain relief is adequate or not. The CCIP raises or lowers the target concentration accordingly.

Surrogate Measures of Opioid Potency

Because a high-resolution measure of analgesia is not available, opioid potencies are usually estimated in terms of some surrogate measure. Surrogate measures are used when the drug effect of clinical interest cannot be directly or conveniently measured. In the case of opioids, although many investigators employ experimental pain models with success, [725] surrogate measures have been extremely useful in providing an accurate and precise measure of potency.

Reduction of the MAC required to produce lack of movement to skin incision (see earlier) has been a frequently utilized surrogate measure in the estimation of opioid potency. [144] [148] [726] [727] Because they quantitate the interaction between opioids and inhaled anesthetics, the estimations of opioid potency determined by MAC reduction methodology have obvious implications for the intraoperative use of opioids, but their application outside the operating room is less clear.

The EEG has been another widely utilized surrogate measure in estimating opioid potency. [141] [142] [152] In contrast to more clinically oriented measures of opioid effect such as respiratory depression or analgesia, the EEG is attractive to investigators seeking to characterize opioid pharmacodynamics because it is an objective, continuous, reproducible, high-resolution signal. The EEG is also advantageous because it can be used as an effect measure when an experimental subject is unconscious or apneic, whereas many of the more clinically oriented measurements require awake, cooperative subjects. The EEG also offers the advantage of relative noninvasiveness. For example, it does not require a skin incision, as MAC reduction studies do, and thus it can be used in volunteer studies.

At relatively high levels, potent mu-receptor opioid agonists produce characteristic changes in the EEG waveform that can be processed into univariate descriptors of drug effect. Figure 10-32 (Figure Not Available) illustrates the changes in the raw EEG that are characteristic of the fentanyl family of opioids. When processed by Fourier spectral analysis, these raw EEG changes translate into a significant decrease in the value of the spectral edge, a parameter that quantitates the frequency

below which a given percentage (usually 95%) of the power in the EEG signal is found. [728]

Figure 10-31 (Figure Not Available) The best, median, and worst performances of a computer-controlled fentanyl delivery device in 21 patients. The line represents the predicted concentration (the computer's target), and the diamonds represent the actual measured concentrations. *(From Shafer et al [723])*

Figure 10-32 (Figure Not Available) The raw electroencephalographic (EEG) changes produced by remifentanil (asleep) compared with the awake state in a representative volunteer. These changes are representative of the EEG effects produced by all the fentanyl congeners. muV, microvolts. *(From Egan et al [703])*

Despite their theoretic appeal, the use of surrogate measures in clinical trials and pharmacodynamic studies is controversial. [729] The obvious concern over surrogate measures is whether or not the surrogate measure actually provides a clinically meaningful representation of what the investigators would really prefer to measure but cannot. Many clinical end points, particularly those that translate into an actual change in patient outcome or cost savings, are extremely difficult to measure. Surrogate measures are obviously useless if no meaningful connection exists between the surrogate measure and the actual clinical effects.

Evidence demonstrates that the EEG as a surrogate measure of opioid effect does, in fact, relate in a proportionally consistent way to clinical measures of opioid potency. [730] Figure 10-33 (Figure Not Available) compares the EEG EC_{50} for three fentanyl congeners with their therapeutic windows measured in numerous clinical studies. Note that each clinical therapeutic window is a relatively constant fraction of the EEG EC_{50} . Thus, although the clinical meaning of the EEG changes produced by opioids is unclear, the opioid potencies estimated using the EEG as a surrogate measure appear to be clinically reliable because they relate to clinically determined potencies in a proportional, reproducible fashion. As illustrated in Figure 10-33 (Figure Not Available) , the same appears to be true for the MAC reduction surrogate measure.

The clinical importance of this surrogate measure issue in anesthesiology is straightforward. For opioids, because the surrogate measures do not always assess the drug effect of clinical interest (e.g., analgesia in the conscious patient), estimations of potency based on surrogate measures must be interpreted with some caution. Because practitioners rely on potency ratios of one drug to another in formulating dosage regimens, it is important to understand how these potencies are estimated and to recognize their limitations.

Figure 10-33 (Figure Not Available) Depiction of the electroencephalographic potency (EC_{50}) versus other clinical measures of potency for the fentanyl congeners. The vertical line in each therapeutic window (horizontal bar) represents the mean value for each window. Note that the therapeutic windows for each fentanyl congener are a relatively constant fraction of its EEG EC_{50} . *(From Egan et al [730])*

For practical purposes, it appears that potency estimates based on the EEG and MAC reduction surrogates are reliable and can be applied clinically.

FACTORS THAT ALTER PHARMACOKINETICS AND PHARMACODYNAMICS

Age

The influence of age on opioid pharmacokinetics and pharmacodynamics has been extensively investigated (Ch. 61) . Unfortunately, conflicting data from these numerous studies make it difficult to draw definitive conclusions. The difficulty in synthesizing this literature is largely a function of methodologic differences among the numerous studies, especially with regard to data analysis techniques. Another limitation is that many studies were simply not sufficiently powerful or relied on historical controls. However, the available data do permit a few generalizations that apply to most opioids.

It is clear that neonates exhibit a reduced rate of elimination of essentially all opioids. [731] This is presumably due to immature metabolic mechanisms, including the cytochrome P-450 system. [732] For example, neonates are known to have poor morphine clearance, resulting in extended elimination half-times. [733] Similarly, the elimination of fentanyl has also been shown to be prolonged in neonates. [367]

The prolonged elimination of opioids observed in the neonatal period quickly normalizes toward adult values within the first year of life. [731] By the end of the first decade of life, maximal opioid metabolic capacity is achieved, and the clearance of most opioids is at least as great as, and often is greater than, in typical adults. [734] For example, clearance of alfentanil in children 1 to 7 years of age is substantially greater than in adults. [735]

With advanced age, although pharmacokinetic changes may play a minor role, pharmacodynamic differences are primarily responsible for the decreased dose requirement in the elderly. In other words, the aging brain is in fact more sensitive to a given concentration of opioid. Scott and Stanski [136] showed that the concentration of fentanyl and alfentanil necessary to produce half of maximal slowing of the EEG (i.e., the EC_{50}) is lower in the elderly compared with younger adults, as illustrated in Figure 10-34 (Figure Not Available) . The hypothesis that pharmacodynamic and not pharmacokinetic differences account for the greater part of the reduced dosage requirement in the elderly is also supported by clinical studies in patients. [736]

However, it is possible to demonstrate pharmacokinetic changes in the disposition of opioids in the elderly. Many studies show a small but significant decrease in opioid clearance. For example, Helmers et al [737] demonstrated that alfentanil clearance was reduced in the elderly. Similar reductions in fentanyl clearance were reported by Bentley et al. [339] Other investigators have shown that the elderly achieve a higher peak concentration after a bolus dose of fentanyl, presumably because of a lower cardiac output that results in a smaller central volume of distribution. [738] Overall, however, the clinical impact of these pharmacokinetic changes is thought to be less important than the pharmacodynamic changes in the elderly (i.e., increased potency of the opioids in the elderly).

Data from studies investigating the pharmacology of remifentanil support the generalization that the elderly exhibit both pharmacokinetic and pharmacodynamic changes in opioid behavior. Minto et al [739] confirmed that age was inversely correlated with remifentanil central volume of distribution, clearance, and potency. When translated into dosage strategy, these combined pharmacokinetic and pharmacodynamic changes mandate a reduction in remifentanil dosage by at least 50 percent or more in the elderly.

Weight

The effect of body weight on opioid pharmacokinetics has not been conclusively investigated, even though opioid dosage regimens are often based on total body weight. Available

Figure 10-34 (Figure Not Available) The relationship of age and opioid potency as measured by the EEG. For both fentanyl and alfentanil, as age increases the concentration required to achieve 50 percent of maximal, brain depression (i.e., the IC_{50}) on the EEG decreases. *(From Scott and Stanski [136])*

literature suggests that opioid pharmacokinetic param-eters are not closely related to total body weight, except perhaps distribution parameters. Instead, many opioid pharmacokinetic parameters, especially clearance, appear to be more closely related to lean body mass. This means that opioid dosage regimens may best be based on lean body mass and not total body weight.

A preliminary report by Bentley et al [740] demonstrated that fentanyl pharmacokinetics is not grossly different in lean versus obese subjects. Schwartz et al [741] reported that sufentanil exhibits more extensive distribution in obese patients, whereas clearance was unchanged. However, this study reported total body weight-normalized pharmacokinetic parameters, and therefore the results must be interpreted with caution because weight-normalized parameters can sometimes achieve a statistically significant difference when none exists. [143] [742] A sophisticated analysis by Maitre et al [743] of a large group of patients who received alfentanil suggests that its volume of the central compartment does correlate with total body weight.

As illustrated by Figure 10-35 (Figure Not Available) , total body weight-based dosing in an obese patient results in much higher remifentanil effect site concentrations than does lean body mass-based dosing. In contrast, for lean patients, the concentrations that result from total body weight-based dosing are not much greater than those based on lean body mass.

The recommendation that opioid dosing be based on lean body mass is consistent with current knowledge regarding the effect of body weight on pharmacokinetics. There is mounting evidence to suggest that lean body mass is a better predictor of metabolic capacity than total body weight. [742] This is probably related to the concept that more than 90 percent of the body's metabolic processes is thought to occur in lean tissue. [744] For practical purposes, because the estimation of lean body mass requires a somewhat cumbersome calculation that is not well suited to the clinical environment, ideal body weight, a parameter closely related to lean body mass and one that is perhaps more easily "guesstimated" by the clinician, is probably an acceptable alternative.

Renal Failure

The impact of renal failure on opioid pharmacokinetics has been extensively evaluated (Ch. 53) . Renal failure has implications of major clinical importance with respect to morphine and meperidine. For the fentanyl congeners, the clinical importance of kidney failure is less marked but is nonetheless measurable. [745]

Morphine is a prototypical example of an opioid with active metabolites that are dependent on renal clearance mechanisms for elimination. Morphine is principally metabolized by conjugation in the liver and is eliminated via renal excretion of water-soluble glucuronides (M3G and M6G). [652] The kidney also plays a role in the conjugation of morphine, accounting for nearly 40 percent of its metabolism. [653] Although the actions of M3G are poorly understood, M6G is a mu-agonist with similar

or greater potency than morphine. [746] Patients with renal failure can develop very high levels of M6G and life-threatening respiratory depression. [747] [748] [749] Figure 10-36 (Figure Not Available) contrasts the morphine and metabolite concentrations that result when morphine is

Figure 10-35 (Figure Not Available) A computer simulation of a typical remifentanil "balanced" anesthetic regimen (i.e., remifentanil in combination with nitrous oxide, inhaled vapor, or propofol) when the dosage is calculated based on lean body mass (LBM) or total body weight (TBW) for lean (57-kg) and obese (159-kg) female patients who are the same height (5 feet, 5 inches). The dosage scheme was 1 mg/kg bolus injection followed by an infusion of 0.5 mug/kg/min for 15 minutes and 0.25 mug/kg/min for an additional 105 minutes. Note that TBW-based dosing in an obese patient results in dramatically higher concentrations. *(From Egan et al [1215])*

Figure 10-36 (Figure Not Available) An example of kidney failure and its effect on the elimination of morphine metabolites. The top panel shows the concentration versus time profile of patients in renal failure who received morphine (0.1 mg/kg) intravenously during arterio-venous fistula surgery. The bottom panel shows the same profile for patients with normal kidney function. Note the prolonged elimination of the morphine glucuronides in the kidney failure group. This delayed elimination is reversed with renal transplantation. *(From Osborne et al [750])*

given to patients in kidney failure who are undergoing arteriovenous fistula procedures compared with subjects with normal renal function. [750] In view of these changes induced by renal failure, morphine may not be a good choice in patients with severely altered renal clearance mechanisms. At the very least, morphine dosages should be decreased, and patients should be carefully monitored.

The clinical pharmacology of meperidine is also significantly altered by renal failure. Like morphine, meperidine is metabolized in the liver to several metabolites that are subsequently rendered soluble by glucuronidation and are eventually excreted by the kidney. Normeperidine, the chief metabolite, has analgesic and CNS excitatory effects. [751] These excitatory effects can range from anxiety and tremulousness to multifocal myoclonus and frank seizures. [752] As with morphine, because the active metabolites are subject to renal excretion, this potential CNS toxicity secondary to normeperidine accumulation is especially a concern in patients in renal failure. [668] Fatal and near fatal CNS toxicities including convulsions and extreme tachycardia and hypertension in patients receiving meperidine who coincidentally developed acute renal failure have been reported. [753] [754] [755] It should be emphasized, however, that the CNS toxicity of meperidine can also be observed in patients with normal renal function. [752]

In contrast to morphine and meperidine, the clinical pharmacology of the fentanyl congeners is not grossly altered by kidney failure, although a decrease in plasma protein binding may potentially alter the free fraction of the fentanyl class of opioids. [745] For example, fentanyl clearance is not altered by renal failure. [756] Although fentanyl metabolites may accumulate, they are thought to be inactive and nontoxic. Patients with renal failure and hyperlipoprotein-emia do, in fact, bind more fentanyl to plasma proteins, but they do not demonstrate a change in clinical effect. [757]

As with fentanyl, sufentanil pharmacokinetics is not altered in any consistent fashion by renal disease, although greater variability exists in its clearance and elimination half-life when patients have impaired renal function. [758] The available data suggest that a substantial dose modification does not appear to be necessary for sufentanil in patients with renal failure. [759] [760]

Two studies have reported alfentanil's pharmacokinetics in patients with renal failure. [761] [762] Both suggested that an increased clinical effect was likely with alfentanil because of a decreased initial volume of distribution and an increased alfentanil free fraction. [761] [762] Discrepancies exist in the results of the two studies, but clearance was unchanged in both. Variations in plasma protein abnormalities (hypoproteinemia, hyperlipoproteinemia, and various accumulated endogenous and exogenous substances) could possibly explain the differing results. Both reports concluded that no delay in recovery after alfentanil should be expected.

Data regarding the effect of renal failure on remifentanil pharmacology suggest that neither the pharmacokinetics nor the pharmacodynamics of remifentanil is altered by impaired renal function. [708] Evidence suggests that the metabolite GI-90291, which is eliminated by the kidney, is at least three orders of magnitude less potent than remifentanil. Levels of GI-90291 that develop during a remifentanil infusion in patients in renal failure are not likely to produce any clinically significant effects. [706] [708]

Hepatic Failure

Even though the liver is the metabolic organ primarily responsible for opioid biotransformation, the degree of liver failure typically observed in perioperative patients, with the exception of patients undergoing liver transplantation, does not have a major impact on the pharmacokinetics of most opioids (Chs. 54 and 55). This reflects the substantial metabolic reserve of the liver, particularly with regard to conjugation reactions (e.g., glucuronidation). [763]

Liver disease can influence opioid pharmacokinetics in a host of ways. In addition to reduced metabolic capacity (i.e., cytochrome P-450 system and conjugation), liver disease may also lead to reductions in hepatic blood flow, hepatocellular mass, and plasma protein binding. The increase in total body water and the edema of advanced liver disease may alter the distribution characteristics of a drug. Finally, enzyme induction such as observed in early alcoholism can actually increase the liver's metabolic capacity. Some of these derangements have opposing pharmacokinetic effects that together may be offsetting.

Because of the numerous mechanisms by which liver disease may alter opioid pharmacokinetics, it can be difficult to predict exactly how an individual patient with liver disease will respond to opioid administration. However, based on the opioid's hepatic extraction ratio and the percent that is protein bound, it is possible to predict the likely impact of liver failure. This notion can be graphically depicted by constructing what is known as the Blaschke triangle, relating hepatic extraction ratio to protein binding. [764] Inspecting the Blaschke triangle makes it possible to categorize drugs according to whether their hepatic metabolism is sensitive to changes in hepatic blood flow, enzyme capacity, or protein binding, as illustrated in Figure 10-37 .

An opioid that is highly extracted by the liver, such as fentanyl or morphine, is substantially influenced by changes in hepatic blood flow, regardless of the amount that is protein bound. Drugs with a low hepatic extraction ratio and low protein binding, such as pancuronium, are especially sensitive to reduced metabolic capacity, but they are not greatly influenced

Figure 10-37 The Blaschke triangle for opioids and other commonly used anesthetics and muscle relaxants. Opioids (and most drugs) can be classified in three general categories with regard to the impact of altered liver function on pharmacokinetics: flow limited, capacity limited-binding insensitive, and capacity limited-binding sensitive. Most, but not all opioids, are flow limited, so that decreased hepatic metabolic capacity does not affect their pharmacokinetics significantly. AL, alfentanil; AT, atracurium; D, diazepam; F, fentanyl; K, ketamine; MID, midazolam; MP, meperidine; MS, morphine; P, pancuronium; S, sufentanil; STP, thiopentone; V, vecuronium.

by reductions in liver blood flow or protein binding. Because none of the common opioids is similar to a drug such as pancuronium in terms of its position on the Blaschke triangle (low protein binding and low hepatic extraction ratio), opioid pharmacology in general is not substantially affected by reduced hepatic metabolic capacity. Opioids such as alfentanil (high protein binding and moderate to low hepatic extraction) are to some extent similar to drugs such as diazepam and thiopentone in that their pharmacokinetics is substantially influenced by changes in protein binding but is relatively unchanged by reductions in hepatic blood flow. Using the Blaschke triangle, opioids can be classified as flow-limited or capacity-limited and binding-sensitive.

In terms of the individual opioids, morphine pharmacokinetics is relatively unchanged by liver failure. [765] This is in part a function of the substantial extrahepatic metabolism of morphine by the kidney. Mazoit et al [766] reported a reduction in morphine clearance in cirrhotic patients, but the pharmacokinetic parameters they reported were similar to those of other investigators in normal subjects. As noted earlier, a reduction in hepatic blood flow would be expected to slow the decline of morphine plasma concentrations.

As an exception to the rule, meperidine is an opioid whose pharmacokinetics is altered by liver failure (perhaps more so than predicted by the Blaschke triangle). Hepatic cirrhosis is associated with reduced clearance and a longer terminal half-time. [767] Other investigators have also documented decreased meperidine

clearance and prolonged elimination half-lives in patients with cirrhosis [768] [769] and acute viral hepatitis. [770] It is not clear how clinically important these changes are.

The disposition of fentanyl is not altered in patients with cirrhosis during general anesthesia. [771] As predicted by the

Blaschke triangle, reductions in liver blood flow that result from either liver disease or some other disorder (e.g., shock) will delay the decline of fentanyl plasma concentrations. Interestingly, although not necessarily related to liver disease, a positive correlation exists between alcohol consumption and the need for fentanyl supplementation during N_2O-O_2-relaxant anesthesia. [772] Up to 70 percent more fentanyl (6.4 versus 3.8 mum
kg
h) was needed in individuals with a mean annual consumption of 31 L pure alcohol.

As with meperidine, alfentanil's pharmacokinetics is also altered by hepatic failure. Ferrier et al [773] reported that patients with alcoholic cirrhosis have reduced alfentanil plasma clearance and prolonged terminal half-times. Thus, an augmented and prolonged alfentanil effect can be anticipated in patients with cirrhosis. Surprisingly, children with cholestatic liver disease who were scheduled to undergo orthotopic liver transplantation showed no changes in alfentanil clearance and volume of distribution at steady state. [774] Although not necessarily related to liver disease, changes in protein binding are thought to account for a substantial proportion of the intersubject pharmacodynamic variability of alfentanil. [775] There is an obvious inverse correlation between unbound alfentanil and the EC_{50} (i.e., the measure of potency). As noted with fentanyl, patients with high alcohol consumption rates require higher plasma alfentanil levels than nondrinking patients. Decreased CNS sensitivity to opioid effects is the likely cause of these pharmacodynamic differences in alcoholics. [776]

Although liver blood flow does not affect the kinetics of alfentanil as much as morphine and fentanyl, decreases in hepatic blood flow can still decrease alfentanil elimination. [689] Major intra-abdominal surgery has been shown to prolong alfentanil effects by reducing clearance from 6.8 to 2.6 mL
min^{-1}
kg^{-1}. [777] Greater elimination half-lives (3.7±2.6 h) have also been observed for alfentanil in patients undergoing abdominal aortic surgery. [778]

As with morphine and fentanyl, sufentanil's pharmacokinetics appears to be minimally changed in cirrhotic patients. [779] However, major intra-abdominal surgery can increase the volume of distribution at steady state and the elimination half-life of sufentanil. [695]

Remifentanil is perhaps the prototype example of an opioid whose pharmacokinetics is completely unchanged by liver disease. Dershwitz et al [707] studied the impact of severe liver disease on remifentanil pharmacokinetics and pharmacodynamics in volunteers. They found no difference in remifentanil pharmacokinetics between the two groups. However, the liver disease cohort appeared to be more sensitive to the respiratory depressive effects of remifentanil. Perhaps the most compelling evidence of no effect of hepatic dysfunction on the pharmacokinetics of remifentanil is that its kinetics does not change during the anhepatic phase of orthotopic liver transplantation. [780]

Cardiopulmonary Bypass

CPB produces significant alterations in the pharmacokinetics of most opioids (Ch. 49) . [755] [781] These alterations are a result of CPB-induced modifications in distribution volumes (secondary to priming), changes in acid-base balance, organ blood flow, plasma protein concentrations, and body temperature. The binding of drugs to components of the bypass circuit is another mechanism by which CPB may alter opioid pharmacokinetics.

There has been little work on the impact of CPB on morphine pharmacokinetics. A single study demonstrated that when morphine is given as a premedicant before cardiac anesthesia, its concentrations decline significantly on initiation of CPB. [782]

Fentanyl pharmacokinetics during CPB has been extensively studied and can serve as a prototype representing the fentanyl family of opioids. Fentanyl pharmacokinetics is extensively altered by CPB. Plasma concentrations of fentanyl decrease by 30 to 60 percent within minutes of starting CPB. This decrease is greater than can be attributed to hemodilution alone. [226] [328] *In vitro* experiments have shown that some of the initial concentration decline after starting CPB can be attributed to sequestration of fentanyl on components of the bypass circuit, especially the oxygenators. [783] [784] Typically, the concentrations of fentanyl during CPB are steady. After termination of CPB, there is usually a rise in fentanyl concentration toward pre-bypass levels. [785] [786] Overall, the elimination of fentanyl is prolonged because of increased distribution and decreased clearance. [226] [785] These changes are attributed to hypothermia, hemodilution, and decreased hepatic blood flow.

Sufentanil's pharmacokinetics during CPB is thought to be very similar to that of fentanyl. Figure 10-38 illustrates the temporal profile of sufentanil concentrations in relation to the CPB events when sufentanil is given in several different doses. [787] Like fentanyl, sufentanil is sequestered in bypass circuit components, although less so. [788] [789] As with fentanyl, sufentanil's elimination is thought to be somewhat prolonged by CPB. [787]

Alfentanil's pharmacokinetics is similarly influenced by CPB. Its elimination is prolonged primarily because of increased distribution. [387] [790] Because the drug's hepatic extraction ratio is relatively low, CPB-induced reductions in liver blood flow do not contribute much to the overall pharmacokinetic changes of CPB. Importantly, the free fraction of alfentanil during CPB remains constant despite complex changes in binding protein concentrations. [791] In contrast to fentanyl, alfentanil is not as likely to be bound by CPB bypass components. [783]

Comparatively little is known about remifentanil's pharmacokinetics during CPB. For example, how much remifentanil is sequestered by the CPB circuit is unknown. It is clear, however, that remifentanil remains a very short-acting drug despite CPB. During the hypothermic portion of CPB, remifentanil's clearance decreases by about 20 percent and then returns to pre-bypass levels after rewarming. [792] Table 10-13 summarizes the pharmacokinetic consequences of CPB.

Acid-Base Changes

The overall clinical impact of acid-base changes on opioid pharmacokinetics is complex, difficult to predict, and incompletely evaluated (Ch. 38) . For example, respiratory acidosis during fentanyl administration has multiple effects including increases in ionization and CBF and decreases in plasma protein binding. [793] [794] [795] How a change in pH can affect opioid kinetics has been described by Lullmann et al. [796]

Figure 10-38 Plasma sufentanil levels after 30-mug/kg bolus (Delta), a 10-mug/kg/min infusion (
), a 20-mug/kg bolus plus a 0.1-mug/kg/min infusion (
), and a 40-mug/kg bolus plus a 0.2-mug/kg/min infusion (
) and the influence of cardiopulmonary bypass.

When mechanical ventilation is abruptly terminated, respiratory acidosis rapidly decreases the pH of the extracellular (blood and interstitial) space. More fentanyl in the interstitial compartment will be ionized, as determined by the Henderson-Hasselbalch equation for weak bases:

More opioid receptors, on cell membranes that interact with ionized fentanyl, are stimulated, producing an enhanced

TABLE 10-13 -- Pharmacokinetic Consequences of CPB

EVENT	CONSEQUENCE
Hemodilution	50% Plasma opioid level; Vd_{ss}
Decreased plasma proteins	Opioid free fraction Vd_{ss}
Hypotension	- Hepatic blood flow - Drug distribution - Opioid clearance
Membrane oxygenator	Plasma opioid levels
Decreased muscle perfusion	Opioid accumulation in muscle
Lung isolation	Opioid trapping
Hypothermia	Opioid potency, need for anesthesia, drug metabolism
Decreased hepatic blood flow, opioid clearance and distribution	Opioid levels constant after initial decrease
Terminating cardiopulmonary by- pass and improved tissue perfusion	Opioid reuptake from tissues and plasma levels
Post-cardiopulmonary bypass	Prolonged $t_{½\ beta}$ persists

$t_{½\ beta}$, elimination half-life; Vd_{ss}, volume of distribution at steady state.

opioid effect (see Fig. 10-20) . Additional respiratory acidosis due to opioid-induced depression of respiratory centers could produce a vicious cycle of ventilatory depression-acidosis-increased ionized fentanyl and increased ventilatory depression. In addition, the acidosis (and shift from free base to ionized fentanyl in the interstitial space) draws un-ionized fentanyl out of the intracellular compartment, where a 13-fold accumulation of fentanyl occurs, further augmenting opioid effects. Finally, increased ionization decreases the amount of fentanyl available for hepatic metabolism or renal excretion. [796] Alfentanil, with a pKa of 6.5, is not as greatly influenced by either pH changes or tissue accumulation. [796]

Intraoperative hyperventilation can also increase the duration of respiratory depression. [326] Brain fentanyl levels are higher with respiratory alkalosis. [355] Alkalosis also increases the lipophilicity (increased octanol/water partition coefficient) of several opioids. Serum and brain levels of morphine are elevated by 10 to 30 percent and 30 to 70 percent, respectively, in hypocapnic, alkalotic dogs. [793] Similar findings have been reported for morphine in rats subjected to alkalosis. [797] Alkalosis favors un-ionized morphine and may enhance brain penetration in spite of decreased CBF and increased plasma protein binding. [793] Nishitateno et al [793] reported a decreased clearance of morphine, and Schwartz et al [798] noted an increased volume of distribution for sufentanil after hyperventilation. Both changes could explain documented increases in elimination half-life and duration of action. Hypercapnia also increases CNS morphine levels in the dog, although to a lesser degree. Hypercapnia also prolongs the removal of morphine from the brain, probably because of CNS acidosis and increased morphine ionization within the brain. Thus, both intraoperative respiration alkalosis

and respiratory acidosis, especially in the immediate postoperative period, can prolong and exacerbate opioid-induced respiratory depression.

ANESTHETIC TECHNIQUES

Sedation and Analgesia

Opioids are frequently used to relieve pain during monitored anesthesia care and regional or general anesthesia (Ch. 65) . For short but painful procedures such as field or retrobulbar nerve blocks, a single bolus injection of an opioid can provide significant relief. Morphine is slow in onset and does not allow rapid titration to effect. Meperidine (50-100 mg IV) produces variable degrees of pain relief and is not always effective in patients with severe pain. [720] IV boluses of fentanyl (1-3 mug/kg), alfentanil (10-20 mug/kg), or sufentanil (0.1-0.3 mug/kg) can produce potent, short-lasting analgesia. For example, the administration of 1 to 2 mL of alfentanil 1 to 2 minutes prior to a short but painful injection or procedure can significantly reduce, if not completely eliminate, associated patient discomfort. Infusion rates range from 0.01 to 0.05 mug
kg^{-1}
min^{-1} for fentanyl, 0.0015 to 0.01 mug
kg^{-1}
min^{-1} for sufentanil, 0.25 to 0.75 mug
kg^{-1}
min^{-1} for alfentanil, and 0.05 to 0.25 mug
kg^{-1}
min^{-1} . Remifentanil can also produce sedation and analgesia at infusion rates of 0.05 to 0.2 mug/kg/min and is approved by the U.S. Food and Drug Administration (FDA) for this indication. Plasma concentrations of these opioids that produce analgesia are detailed in Table 10-14 .

One of the most exciting developments in pain research over the past decade has been the recognition that changes in the excitability of central neurons play an important role in the generation of pain. The neurophysiologic concepts and mechanisms that underlie the concept of preemptive analgesia are complex. [799] Even the definition of preemptive analgesia and the way in which to demonstrate its existence remain confusing, if not controversial. [800] Whether or not preemptive analgesia can be effectively achieved clinically by the early administration of opioids remains uncer-tain. [801] [802] However, reductions in postoperative pain and improved recovery have been attributed to preemptive analgesia with either epidural fentanyl or bupivacaine after radical prostatectomy. [803]

The administration of systemic opioids postoperatively is commonplace. Practice guidelines, developed by the American Society of Anesthesiologists (ASA), help to define important issues surrounding pain management with opioids. [804] PCA with opioids is now a cornerstone of postoperative analgesia. Besides its obvious appeal in providing patients with a sense of control as well as allowing patients to self-titrate pain-relieving medication, PCA with opioids may improve outcome. [805] Nevertheless, pharmacokinetic optimization of opioid treatment in acute pain is a complex matter. [806] For example, PCA therapy with morphine may require an initial loading dose in order to optimize dosing intervals and patient relief. Modern pharmacologic approaches to opioid pain therapy attempt to incorporate the concept that small, frequent doses produce the most stable blood drug concentrations, best relief, and fewest adverse effects. However, without considering effect site drug concentrations over time, the choice of opioid and the amount, method, and frequency of its administration can be suboptimal. [806] Morphine remains a popular and rational choice for PCA therapy. [807]

Balanced Anesthesia

The concept of balanced anesthesia dates back to 1910, when George W. Crile introduced his theory of anociassociation. [808] Crile taught that psychic stimuli associated with operations could be prevented by light general anesthesia, whereas painful stimuli could be blocked by local analgesia. The term "balanced anesthesia" was introduced by Lundy in 1926. [4] Lundy suggested that a balance of agents and techniques (e.g., premedication, regional anesthesia, and general anesthesia with one or more agents) be used to produce the different components of anesthesia (i.e., analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance of homeostasis) [809] (Fig. 10-39) .

Neff et al in 1947 [5] introduced meperidine as a supplement during N_2O anesthesia. Variations of these techniques using meperidine [810] [811] and other opioids were subsequently described [812] [813] and continue to be developed. All the fentanyl congeners have been successfully employed as components of balanced anesthesia.

Which Opioid?

The ideal opioid would permit rapid titration to effect, successfully prevent unwanted responses to noxious stimuli, require little supplementation, not depress cardiovascular function, permit the return of adequate spontaneous ventilation in a timely manner, and produce residual if not complete postoperative analgesia with minimal side effects. Numerous studies have evaluated one or more of these facets for the fentanyl congeners and have compared one opioid

TABLE 10-14 -- Range of Approximate Plasma (or Whole Blood for Remifentanil) Opioid Concentration (ng/mL) Required for Total Intravenous Anesthesia

	FENTANYL	SUFENTANIL	ALFENTANIL	REMIFENTANIL
Predominant agent	15-30	5-10	400-800	--
Major surgery	4-10	1-3	200-400	2-4
Minor surgery	3-6	0.25-1	50-200	1-3
Spontaneous ventilation	1-3	<0.4	<200	0.3-0.6
Analgesia	1-2	0.2-0.4	50-150	0.2-0.4

Figure 10-39 Balanced anesthesia: addressing the four components of anesthesia.

with another as a component of balanced anesthesia. [814] [815] [816] [817] [818] [819] [820] [821] [822] [823] [824] [825] [826] [827] [828] Fewer studies have compared three or more opioids in balanced anesthesia. [124] [327] [829] Fentanyl and alfentanil have been frequently compared. [815] [820] [827]

Alfentanil and remifentanil provide the greatest ability to titrate opioids rapidly because of their extremely rapid time to onset (1-2 min) of peak effect. The

administration of these two agents can be timed much like anesthetic induction agents.

It is a commonly held perception that all the fentanyl congeners are pharmacodynamically the same. However, differences exist among opioids that can not always be explained by pharmacokinetic characteristics alone. Alfentanil, compared with fentanyl, produces greater decreases in heart rate and blood pressure during induction. [815] [322] [830] Although some investigators reported no significant differences between fentanyl and alfentanil during emergence, [824] most studies have found that alfentanil results in a more rapid recovery and a decreased need for naloxone. [815] [820] [822] [823] [826] [827] In many studies, dose-equivalency and timing of drug administration are confounding factors creating questions about the accuracy of comparisons.

Studies comparing fentanyl and sufentanil indicate that sufentanil provides greater intraoperative hemodynamic stability, [816] [819] more rapid emergence, [817] and less respiratory depression in the immediate postoperative period than fentanyl. [817] [818] Compared with alfentanil, sufentanil provides greater hemodynamic stability and requires less supplementation. [816]

Flacke et al [829] compared morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia for general or orthopedic surgery. Hemodynamic and plasma catecholamine changes were greatest with morphine and meperidine and least with sufentanil. Only patients receiving sufentanil as the opioid component of their anesthetic did not require potent inhalation agent supplementation. Approximately one-third of patients in each other group required such supplementation. Meperidine produced the most side effects, including hypotension, tachycardia, and urticaria, especially during anesthetic induction. On emergence, respiratory depression was greatest with morphine and least with fentanyl and sufentanil. Other investigators [124] have reported similar results in comparisons of these four opioids. These data suggest that fentanyl and sufentanil are preferable to morphine or meperidine in balanced anesthesia. [124] [829]

Sufentanil, alfentanil, and remifentanil are arguably superior to fentanyl in most respects except cost. [18] [687] Onset of action is faster with alfentanil or remifentanil, and thus control is enhanced. Duration of action and time for drug effect to dissipate are shortest and most consistent for remifentanil and are shorter for both alfentanil and sufentanil compared with fentanyl, especially after repeated administration or infusions. Efficacy may be greatest for sufentanil. The ability to administer doses of remifentanil that produce profound opioid action without prolonged effect is unique to this drug. Alfentanil is more easily antagonized with naloxone because of its low receptor affinity. Antagonism of opioid action with naloxone for troublesome respiratory depression is required less frequently after alfentanil and sufentanil compared with fentanyl. Pharmacologic antagonism is rarely required after remifentanil administration.

Currently, fentanyl remains a good choice if the goal of including opioids as part of an anesthetic regimen is to provide basal analgesia and to minimize drug costs. In clinical situations in which a prolonged opioid effect is desired postoperatively, fentanyl is also a rational choice. If opioids are to be employed as "anesthetic" agents, sufentanil, alfentanil, and remifentanil offer significant advantages over fentanyl. Whether or not these advantages translate to benefits that justify their use and increased drug acquisition cost remains unclear.

General Principles

The inclusion of an opioid as a component of balanced anesthesia can reduce preoperative pain and anxiety, decrease somatic and autonomic responses to airway manipulations, improve hemodynamic stability, lower requirements for inhaled anesthetics, and provide immediate postoperative analgesia. [831] [832] [833] Proper anticipation should lead to the administration of any opioid at the right time prior to a stimulus. Fentanyl and sufentanil should be administered for 4 to 6 minutes, and alfentanil and remifentanil should be given 1 to 2 minutes prior to stimulation. Once a stress response is activated and catecholamines are released, opioids are less effective in maintaining hemodynamic stability. [829] In a similar fashion, as mentioned earlier, the administration of an opioid prior to, rather than after, noxious stimulation attenuates physiologic responses.

Opioids interact synergistically and markedly reduce the dose of propofol and other sedative-hypnotics required for loss of consciousness and during noxious stimulation such as skin incision. [834] Opioids can ameliorate or eliminate responses to a rapid sequence induction and other noxious stimuli, [835] [836] [837] controlling changes in heart rate, blood pressure, pulmonary capillary wedge pressure, and other aspects of the stress response that occur during laryngoscopy and intubation. Heart rate response to laryngoscopy is better controlled with an opioid than with esmolol. [833] Frequently,

however, inadequate doses (100 mug) of fentanyl are administered and insufficient time is allowed for effective onset of drug action.

Anesthesia with a single agent can require doses that produce excessive hemodynamic depression. For example, the concentrations of propofol or isoflurane required to eliminate movement after skin incision frequently produce undesirable hypotension prior to such stimulation. [372] [838] Although the intent of combining opioids with sedativehypnotics and/or volatile anesthetics is to produce anesthetic conditions with stable hemodynamics prior to as well as after noxious stimulation, this ideal is not always achieved. For example, combinations of propofol and fentanyl can result in as much or more hypotension than propofol alone prior to tracheal intubation. [839] However, the hypertensive response to intubation is better attenuated with the drug combination than with propofol alone. [840] [841]

The timing, rate of administration, and dose of supplemental opioid should also be tailored to the specific condition of the patient and the expected duration of the operation in order to avoid problems. The duration of action and magnitude of effect of an opioid are determined not only by pharmacokinetic properties but also by timing, dosage, and interaction with other compounds used, as well as patient factors such as age and intensity of pain (see later). Giving a large dose of any opioid shortly before the end of surgery is very likely to result in postoperative respiratory depression or to potentiate and prolong already existing respiratory depression. However, analgesic concentrations of opioids have little effect on the MAC awake of potent inhaled anesthetics. [842] Troublesome opioid-induced respiratory depression needs to be avoided if fentanyl and its congeners are to be optimally employed in most patients. In balanced anesthesia, this means that, at the appropriate time, adequate spontaneous ventilation has returned without the frequent use of opioid antagonists.

Fentanyl

Anesthetic induction is usually achieved by combining a loading dose of fentanyl (2-6 mug kg^{-1}) with a sedativehypnotic, most commonly thiopental or propofol, and a muscle relaxant. The dose of sedative-hypnotic should be significantly reduced. [109] [843] Agents such as etomidate (0.1-0.3 mg/kg) or ketamine (0.5-2.0 mg/kg) are more likely to provide hemodynamic stability compared with thiopental or propofol after fentanyl or other opioids, especially in patients with cardiovascular disease. [837]

Maintenance of anesthesia can be achieved with N_2O (60-70%) in O_2, low concentrations of potent inhalation agents, plus additional fentanyl (intermittent boluses of 25-50 mug every 15 to 30 min or a constant infusion of 0.5-5.0 mug kg 1 h^{-1}). Shorter procedures may require lower bolus doses or infusion rates. [844] Premedication, typically with a benzodiazepine, reduces the need for supplements. Propofol infusions can also be administered as part of balanced anesthesia (see later).

Fentanyl plasma concentrations of 1.0 to 2.0 ng mL^{-1} provide analgesia, [641] but levels of at least 2 to 3 ng mL^{-1} are usually required during surgery (at sea level) if the only inhaled agent is N_2O. Higher plasma opioid concentrations may be necessary at high altitude, where N_2O is less effective. [845] [846] In unpremedicated patients anesthetized with a fentanyl infusion and N_2O in O_2, the CP_{50}* and the CP_{50}-BAR* for fentanyl at skin incision are 3.26 and 4.17 ng/mL, respectively. [847] The MAC of isoflurane at skin incision can be reduced by 50 and 63 percent with plasma fentanyl concentrations of 1.67 and 3.0 ng/mL, respectively [111] (see Table 10-5) (Table Not Available) . Others have reported the fentanyl plasma concentration that reduces the MAC of isoflurane 50 percent to be lower (0.5 ng/mL) but have also noted a wide range of effective concentrations. [144] With greater doses or plasma fentanyl concentrations, further MAC reductions become proportionately less. For example, McEwan et al [111] found that increasing plasma fentanyl concentrations from 3.0 to 10 ng/mL only further reduced the MAC of isoflurane from 63 to 82 percent.

Patient pharmacokinetics varies significantly (up to 5-fold), and predicting plasma levels after a given dose of an opioid can be challenging. Pharmacodynamic actions are also variable; the opioid plasma concentration necessary to block increases in blood pressure and heart rate can be unpredictable. [641] [848] Nevertheless, a balanced technique with fentanyl, titrating the opioid in anticipation of various stimuli and patient responses with pharmacokinetic guidelines in mind, will often result

in a stable hemodynamic course and rapid awakening in a pain-free patient. Low doses of fentanyl (4-8 mug kg^{-1}), followed by a continuous infusion of 2 to 4 mug kg^{-1} h^{-1}, will often result in adequate plasma levels (3-6 ng mL^{-1}) for anesthesia when combined with N_2O.

Repeated doses or continuous infusions of fentanyl are most likely to result in significant depression of spontaneous ventilation. [18] [325] This is especially likely if fentanyl is dosed in an empiric manner without titration to some clinical endpoint. Administering fentanyl boluses toward the latter part of an operation also increases the likelihood of troublesome respiratory actions. Others have reported that fentanyl (1-2 mug/kg), administered at the time of peritoneal closure in women undergoing gynecologic surgery, can significantly attenuate hemodynamic responses to tracheal extubation. [849] A useful clinical approach is to wait for spontaneous ventilation to resume, then administer additional titrated doses (25-50 mug) of fentanyl to produce a respiratory rate of 8 to 12 breaths per minute prior to tracheal extubation. Plasma fentanyl levels associated with adequate analgesia after abdominal surgery have been reported to range 5-fold from 0.23 to at least 1.18 ng/mL. [641]

Sufentanil

Sufentanil (0.25-1.0 mug/kg), administered several minutes prior to induction of anesthesia, effectively prevents significant hemodynamic responses to laryngoscopy and intubation. Marty et al [850] studied 14 patients who were premedicated with lorazepam (2.5 mg) and then anesthetized

* CP_{50} is the steady-state plasma drug concentration that prevents a somatic response in 50 percent of patients.

** CP_{50} -BAR is the steady-state plasma drug concentration that prevents a hemodynamic and autonomic response in 50 percent of patients.

with sufentanil (2-mug/kg bolus plus 0.66-mug kg^{-1} /h infusion). These patients were ventilated with 66 percent N_2O in O_2 and received vecuronium or succinylcholine for muscle relaxation. The mean plasma sufentanil concentration reported to be the CP_{50} for prevention of hemodynamic responses to laryngoscopy and tracheal intubation was 1.08 ng/mL with a range of 0.73 to 2.55 ng/mL.

Maintenance of anesthesia can be achieved with N_2O (60-70%) in O_2 and further sufentanil (intermittent boluses, 0.1-0.25 mug kg^{-1} ; or constant infusion, 0.5-1.5 mug kg^{-1} h^{-1}). The CP_{50} for sufentanil during skin incision is twice as great as that for intubation in unpremedicated patients (2.08±0.62 ng/mL). [145] CP_{50} value ratios at skin incision for sufentanil, fentanyl, and alfentanil in N_2O-O_2 anesthesia are approximately 1:2:150 and represent different and probably more accurate potency ratios than those traditionally published based on drug dose. During surgery, sufentanil plasma levels less than 0.5 ng mL^{-1} can lead to an increased need for supplements. [831]

Sufentanil infusions of less than 1.0 mug/kg/h are associated with fewer postoperative problems than infusions of at least 1.0 mug/kg/h in adults and children. [851] Sufentanil levels less than 0.25 ng mL^{-1} often allow for adequate spontaneous ventilation. [850] Titration of sufentanil to respiratory rate prior to emergence, or minimizing infusion rate to less than 0.25 to 0.5 mug/kg for the last hour of anesthesia are approaches that allow timely emergence.

Alfentanil

Small to moderately large doses (5-50 mug kg^{-1}) of alfentanil used to supplement a sedative-hypnotic induction attenuate or eliminate hemodynamic responses to laryngoscopy and intubation. Because alfentanil penetrates the brain so rapidly, equilibration of alfentanil between the plasma and the CNS can be achieved while plasma alfentanil levels are relatively high compared with sufentanil and fentanyl (Fig. 10-40) (Figure Not Available) . This property, combined with the significant synergism between alfentanil or other opioids and propofol and/or midazolam, [852] [853] explains how low doses (10-30 mug/kg) of alfentanil, administered just before or simultaneously with a sedative-hypnotic, are effective.

Alfentanil (16 mug/kg) is more effective than esmolol (2 mg/kg) in blunting the hemodynamic response to tracheal intubation after induction with propofol (2.5 mg/kg). [854] Alfentanil (25-50 mug/kg IV), followed by small titrated sleep doses of any sedative-hypnotic (e.g., 50-100 mg sodium thiopental), is usually successful in preventing significant hemodynamic stimulation from laryngoscopy and intubation. Indeed, 25 to 35 mug/kg of alfentanil, combined with propofol or etomidate for induction of anesthesia, usually results in good to excellent conditions and allows tracheal intubation without the use of muscle relaxants. [855] [856] Combining alfentanil and propofol can reduce propofol requirements for loss of consciousness by 50 to 75 percent. [839]

Anesthesia is often maintained after such an induction with 60 to 70 percent N_2O in O_2 . Further opioid supplementation can be achieved with an alfentanil infusion (0.5-2.0 mug kg^{-1} min^{-1}) or intermittent boluses of alfentanil (5-10 mug kg^{-1}) for shorter procedures. An alfentanil bolus of 7 mug kg^{-1} will increase plasma alfentanil concentrations

Figure 10-40 (Figure Not Available) Computer-simulated plasma and effect site concentrations for fentanyl, alfentanil, and sufentanil, for the first 10 minutes after a bolus injection, as a percentage of initial plasma concentrations. *(Adapted from Shafer and Varvel [18])*

by 50 ng mL^{-1} (range 20-100 ng mL^{-1}) if a relatively steady plasma level of alfentanil already exists. In balanced anesthetic techniques in which potent inhalation agents are also employed, relatively low plasma alfentanil concentrations (e.g., 29 ng/mL) can reduce the MAC of isoflurane approximately 50 percent. [144]

Failure to institute N_2O and/or an alfentanil infusion may lead to inadequate anesthesia at the time of surgical incision (Fig. 10-41) . The duration of surgery and strength of the surgical stimulus are important influences on alfentanil requirements. Ausems et al [331] determined the plasma concentrations of alfentanil required to supplement N_2O anesthesia for several types of surgery. The CP_{50} , defined as the concentration needed to obtund responses to stimuli adequately in 50 percent

Figure 10-41 Plasma alfentanil levels after three different bolus injections and one bolus plus continuous infusion for 1 hour.

of patients, for several stimuli is listed in Table 10-15 (Table Not Available) . The Cp_{50} for spontaneous ventilation was 223±13 ng mL^{-1} . Interestingly, the more potent the stimulus, the greater the variability in the Cp_{50} . This is depicted in the flatter curve for upper abdominal surgery in Figure 10-42 (Figure Not Available) . These numbers define target plasma concentrations. However, because of considerable variability in effective concentrations, clinicians must still titrate both alfentanil infusions and the frequency and magnitude of boluses to clinical response.

Interestingly, the EC_{50} of alfentanil for various stimuli in patients premedicated with temazepam (10 mg orally) and receiving propofol (plasma concentrations targeted to be 3 mug/mL) was only one-fourth to one-half that required in patients receiving N_2O-O_2 instead of propofol. [857] Balanced anesthesia with a sedative-hypnotic, alfentanil, and N_2O-O_2 in appropriately premedicated patients has been recommended for short and minor operations, [858] as well as for major vascular procedures. [859]

Alfentanil infusions or repeated doses should be minimized 15 to 30 minutes prior to the end of surgery, [331] in order to avoid problematic residual respiratory depression. If no alfentanil is administered toward the latter part of an anesthetic regimen, inadequate analgesia will exist in some patients shortly after they regain consciousness, unless steps

TABLE 10-15 -- Stimuli and Corresponding Cp_{50} for Alfentanil During Alfentanil-Nitrous Oxide Anesthesia

(Not Available)

From Ausems et al [331]

have been taken to ensure analgesia. Although alfentanil infusions should be reduced as permitted during balanced anesthesia, they should not be completely terminated until the operation is nearly finished. Alfentanil plasma concentrations that permit the return of spontaneous ventilation have been reported to be 223±13 ng/mL. [331] Alfentanil infusion rates of 0.5±0.25 mug
kg^{-1}
min^{-1}, administered until surgery is nearly complete, do not usually interfere with the return of adequate spontaneous ventilation and emergence.

Remifentanil

Remifentanil has been administered as a bolus of 1 mug/kg in combination with propofol for induction of anesthesia with favorable results. [860] Combinations of propofol (0.5-1.0- mg/kg

Figure 10-42 (Figure Not Available) Mean alfentanil plasma concentration-effect curves for the intraoperative period in each surgical group of patients during nitrous oxide anesthesia. The mean plasma clearance (Cp_{50}) and slope of these curves were determined by averaging the estimates of individual patients. Bar indicates the standard deviation and Cp_{50}. *(From Ausems and Hug* [1216] *)*

bolus plus a 75-mug/kg/min infusion) and remifentanil (1-mug/kg bolus plus a 0.5-1.0-mug/kg/min infusion) for induction and maintenance of anesthesia can result in hypotension and bradycardia in 10 to 30 percent of healthy patients. [861] It is now recognized that these doses are too high. Remifentanil's very short duration of action mandates that an infusion (0.1-1.0 mug/kg/min) be started prior to or soon after the bolus dose to ensure sustained opioid effect. Another approach is to administer remifentanil only by continuous infusion for induction and maintenance of anesthesia.

Remifentanil maintenance infusion rates range from 0.1 to 1.0 mug/kg/min for balanced anesthesia. Numerous clinical trials, comparing remifentanil with alfentanil or other opioids, document that remifentanil can more reliably suppresses autonomic, hemodynamic, and somatic responses to noxious stimulation and allows the most predictable and rapid trouble-free emergence from anesthesia. [862]

The use of remifentanil as the opioid component of balanced anesthesia should allow a rapid (5-15 min) emergence without troublesome respiratory depression in light of its very short duration of action. [861] Infusion rates of 0.1±0.05 mug/kg/min should permit the return of spontaneous ventilation and responsiveness with maintenance of analgesia. A unique problem associated with emergence from remifentanil anesthesia is the possibility of an excessively rapid dissipation of opioid effect with undesirable consequences. The need for alternative analgesic therapies should be anticipated and administered in a timely fashion, but definitive approaches remain to be determined. [863] Discharge from, or completely bypassing the postanesthetic care unit can also be expedited by the use of remifentanil. Tables 10-14 and 10-16 depict the range of loading and maintenance doses and plasma levels required for fentanyl, alfentanil, sufentanil, and remifentanil in balanced anesthesia.

Neuroleptanalgesia-Anesthesia

In 1949, Laborit and Huygenard [864] introduced the concept of an anesthetic technique that blocked not only cerebrocortical responses but also some cellular, endocrine, and autonomic mechanisms usually activated by surgical stimulation. This state was called "ganglioplegia" or "neuroplegia" (artificial hibernation) and was achieved by the use of a lytic cocktail consisting of chlorpromazine, promethazine, and meperidine. From this idea, De Castro and Mundeleer [865] derived the concept of neuroleptanalgesia, which involved the combination of a major tranquilizer (usually the butyrophenone droperidol) and a potent opioid analgesic (fentanyl) to produce a detached, pain-free state of immobilization and insensitivity to pain. Neuroleptanalgesia is characterized by analgesia, absence of clinically apparent motor activity, suppression of autonomic reflexes, maintenance of cardiovascular stability, and amnesia in most, but not all, patients. The addition of an inhalation agent, usually N_2O, improves amnesia and has been called neuroleptanesthesia.

"Neuroleptic" drugs traditionally include the phenothiazines (e.g., chlorpromazine) and the butyrophenones (e.g., haloperidol and droperidol). The phenothiazines are rarely used as an anesthetic adjuvant in the United States because of associated hypotension. Droperidol can also cause hypotension, but it is usually less severe and transient. Sedation after droperidol, especially after at least 0.1 mg
kg^{-1}, may last much longer than the analgesic used (e.g., fentanyl) and may result in a patient who is apparently calm yet suffering from pain and mental anguish. [866] The commercial preparation of droperidol-fentanyl (Innovar) is frequently the principal component of neuroleptanalgesia for monitored anesthesia care when analgesia and a tranquil patient are desirable. Innovar is also commonly used in a balanced anesthetic technique that usually employs N_2O.

Butyrophenones cause sedation, tranquility, immobility, and antiemesis. One of their side effects includes an extrapyramidal syndrome with face and neck dyskinesia, oculogyric crises, torticollis, agitation, and hallucinations. Droperidol, like other butyrophenones, affects GABA receptors and alters the balance of dopamine and acetylcholine in certain brain sites. Droperidol's effects on dopamine receptors (antidopaminergic) not only account for much of the drug's behavioral effects but also cause its side effects. Administering droperidol alone, without analgesics or other sedatives, often produces feelings of discomfort or dysphoria in patients. The cardiovascular effects of droperidol are most often limited to mild hypotension that is thought to be mediated through alpha-adrenergic blockade. Droperidol has an antiarrhythmic action that is effective during halothane anesthesia or following epinephrineinduced arrhythmias. [867] Droperidol may be of some benefit in patients with Wolff-Parkinson-White syndrome. [868] There is little respiratory depression induced by droperidol, although significant variability exists, and occasional respiratory depression may be noted. Droperidol and other butyrophenones may enhance hypoxic-induced increases in ventilation in humans because of their antidopaminergic effects at the carotid body. [869]

Droperidol can be used as a premedicant (0.025-0.075 mug
kg^{-1} IM), an antiemetic (0.01-0.02 mug
kg^{-1} IV), an adjunct for awake intubations (0.025-0.1 mug
kg^{-1} IV) and as treatment for agitated, belligerent, or psychotic patients (0.05-0.2 mg
kg^{-1} IV or IM). Neuroleptanalgesia with droperidol and an opioid such as fentanyl may still be useful for "monitored anesthesia care" in a variety of clinical circumstances

TABLE 10-16 -- Approximate Opioid Loading (Bolus) Doses, Maintenance Infusion Rates, and Additional Maintenance Doses for Total Intravenous Anesthesia

	LOADING DOSE (mu g/kg)	MAINTENANCE INFUSION RATE	ADDITIONAL BOLUSES
Alfentanil	25-100	0.5-2 mug/kg/min	5-10 g/kg
Sufentanil	0.25-2	0.5-1.5 mug/kg/h	2.5-10 mug

Fentanyl	4-20	2-10 mug/kg/h	25-100 mug
Remifentanil	1-2	0.1-1.0 mug/kg/min	0.1-1.0 mug/kg

including ophthalmic operations, endoscopic and bronchoscopic examinations, neurodiagnostic procedures, and excision of epileptogenic foci. Combining alfentanil (5 mug
kg^{-1} as a bolus and/or an infusion, 1.5 mug
kg^{-1}
min^{-1}) with droperidol and N_2O has been reported to be useful in providing patient comfort for awake craniotomies. More recently, remifentanil, in combination with propofol, has been used successfully as an anesthetic technique for awake craniotomy. [870]

In the past, neuroleptanesthesia with droperidol and fentanyl proved useful in patients undergoing neurologic, cardiac, and general surgical procedures. Neuroleptanesthesia has also been proposed for removal of pheochromocytomas. [871] [872]

Neuroleptanalgesia or neuroleptanesthesia is contraindicated in patients receiving monoamine oxidase inhibitors (MAOI), in those who abuse drugs or alcohol, or those with Parkinson disease. The introduction of newer drugs with superior pharmacologic properties, combined with "fast track" approaches in most surgical patients, has reduced the utility of neuroleptic techniques.

Total Intravenous Anesthesia

TIVA is a natural extension of balanced anesthesia. Newer IV drugs now allow reliable anesthesia to be produced entirely with IV anesthetics and rapid recovery to occur even after long infusions. Additionally, hardware and software also now exist that permit delivery of these agents in a manner superior to manual injection. Although TIVA does not necessarily require an opioid component, especially in minimally stimulating procedures, the fentanyl congeners most often are an important part of TIVA.

Several challenges exist to the successful application of TIVA. Variability in patient drug requirements is significant. [873] The "light" nature of many TIVA techniques often creates an environment with which many anesthesiologists are neither comfortable nor satisfied. Common solutions to this problem are to eliminate the possibility of patient motor responses with the routine use of muscle relaxants. The routine application of muscle relaxants with TIVA predisposes patients to experiencing awareness.

The complexity of delivering TIVA with one, two, and even three simultaneous infusion pumps and programs remains a technical burden compared with the simplicity of modern inhalation agent vaporizers. Most experts agree that continuous infusions are a necessary part of TIVA if benefits are to be maximized and disadvantages minimized. Numerous advantages exist when drugs are administered by infusion (Table 10-17) . [874] [875] [876] [877]

Some researchers and clinicians utilize and recommend the use of population-based or other pharmacokinetic data, [878] software programs, pocket calculator approaches, or other methods to enhance drug infusion accuracy. However, TIVA and drug infusions can be and are most often successfully administered by clinical titration and without mathematic and/or computer-assisted calculations of drug re-quirements. [879] Much progress has been made in the development of pharmacologic models that help us better to understand drug disposition and administration. [687] [712] [713] However, the persistent inability to predict and/or to

TABLE 10-17 -- Potential Advantages of Continuous Infusions over Intermittent Boluses of Opioids in Anesthesia

Decreased total dose
Greater hemodynamic stability
Decreased side effects (e.g., rigidity)
Decreased need for supplementation
More rapid recovery of consciousness
Less respiratory depression and need for antagonists
Less pain in the immediate postoperative period
Decreased discharge time

measure drug levels and effects in individual patients continues to dampen widespread enthusiasm for TIVA techniques. [699] [880]

Another hurdle TIVA enthusiasts must confront is the cost-to-benefit analysis to which many anesthetic regimens are likely to be subjected. Newer, and arguably superior, agents are more expensive by drug acquisition cost analysis. Deciding whether benefits justify the greater costs of these drugs is complex and not always obvious. Potential benefits of new anesthetics include less pain, less nausea and vomiting, and a more rapid recovery and hospital discharge (along with lower resultant overall hospital charges). Benefits more difficult to measure include a decreased use of reversal agents, fewer morbid events, greater patient satisfaction, and a more rapid return of patients to work. [881] Unfortunately, issues such as the superior control of a patient's anesthetic regimen that is provided by the clinician, or the reduced stress on the patient and the anesthesiologist, are largely neglected. [882]

Many different IV compounds can be employed in a number of combinations to provide TIVA. Most commonly, an opioid is combined with another drug more likely to provide hypnosis and amnesia. Propofol-opioid TIVA is popular. For example, both alfentanil and propofol are similarly short-acting agents and have excellent synergism pharmacodynamically. Alfentanil provides analgesia and hemodynamic stability while blunting responses to noxious stimuli. Propofol provides hypnosis and amnesia and is anti-emetic. [603] Profound synergism also exists when more than two agents, such as propofol-alfentanil-midazolam, are combined. [852] [883]

Anesthetic induction with alfentanil (25-50 mug/kg) and propofol (0.5-1.5 mg/kg) followed by infusions of 0.5 to 1.5 mug
kg^{-1}
min^{-1} of alfentanil and 80 to 120 mug
kg^{-1}
min^{-1} of propofol will produce complete anesthesia in patients ventilated with air and O_2 with or without N_2O for a variety of procedures. Although many alternatives to propofol exist, its pharmacokinetic profile and short duration of action, antiemetic properties, and association with a general sense of well-being in patients postoperatively make it popular. Several opioids can be successfully employed, depending on the patient, the proposed operation, and other considerations.

Vuyk et al [883] evaluated the significant synergism between propofol and alfentanil and explored numerous combinations of blood drug concentrations. They proposed that alfentanil concentrations as low as 85 ng/mL, when combined with a blood propofol concentration of 3.5 mug/mL, can produce both optimal anesthetic conditions and speed

of recovery. In an accompanying editorial, Stanski and Shafer [884] suggested that bolus doses and initial infusion rates would be 30 mug/kg and 0.35 mug
kg^{-1}
min^{-1} for alfentanil and 0.7 mg/kg and 180 mug
kg^{-1}
min^{-1} for propofol. Decreasing infusion rates to eventually achieve rates of approximately 0.25 and 100 mug

kg^{-1}
min^{-1} for alfentanil and propofol respectively were also recommended. Recognizing that these calculations were based on EC_{50} data in patients undergoing only moderately painful procedures, clinicians should adjust these doses accordingly. Thus, a plausible infusion regimen would increase the alfentanil infusion rate somewhat in order to enhance suppression of responses to noxious stimuli.

Vuyk et al [885] also determined the optimal propofol-opioid concentrations that ensure adequate anesthesia and rapid emergence with computer modeling for all the modern fentanyl congeners. The optimal propofol concentration decreases in the order of fentanyl > alfentanil > sufentanil >> remifentanil. These conclusions are somewhat intuitive and coincide with ordering based on the context-sensitive half-time of opioids. In essence, a shorter context-sensitive half-time allows the administration of greater amounts of opioid (and less propofol) during anesthesia without creating prolonged opioid effects.

Premedication prior to alfentanil-propofol anesthesia can prolong postoperative recovery and should be avoided if appropriate. [886] [887] Drug infusion devices should be prepared and infusing prior to induction of anesthesia, so that clinician efforts can be appropriately focused on airway management yet anesthesia can be adequately maintained. Induction of anesthesia may proceed with the administration of a defasciculating or priming dose of a nondepolarizing muscle relaxant and alfentanil (10 to 25 mug/kg IV). Additional similar doses of alfentanil may be administered up to a total dose of 25 to 75 mug/kg and immediately followed by a sleep dose of propofol of 0.5 to 1.5 mg/kg. Additional propofol (0.25-1.0 mg/kg) may be required to produce unconsciousness. Lidocaine requirements to reduce pain associated with propofol injection are significantly reduced when propofol is administered after alfentanil. [888] [889]

Figure 10-41 illustrates the plasma alfentanil concentrations over time from four different studies [678] [680] [681] [890] Bolus injections of alfentanil (80-200 mug/kg) produce initial plasma levels proportional to the dose. Although lower doses of alfentanil than illustrated in the figure are frequently administered, the point remains that if alfentanil maintenance infusions are not instituted, plasma drug levels rapidly decline and become subtherapeutic. After 50 mug/kg, plasma levels of alfentanil are less than 300 ng
mL^{-1} within 3 to 5 minutes. [679]

Maintenance infusions vary according to patient condition and surgical stimuli. Propofol (75-125 mug/kg/min) and alfentanil (1.0-2.0 mug/kg/min) are initially recommended. Intraoperatively, propofol and/or alfentanil infusions should be manipulated in an effort to obtain the lowest required rates. Drug infusions should be terminated 10 to 20 minutes prior to end of anesthesia if N_2O is employed in a similar but balanced anesthesia technique. Otherwise, propofol infusions should be terminated 5 to 10 minutes before anticipated patient awakening. Alfentanil infusion rates do not need to be less than 0.25 to 0.5 mug/kg/min until surgery is terminated.

As mentioned earlier, many agents can be used for TIVA. Midazolam-opioid combinations can also provide complete anesthesia. However, midazolam-alfentanil TIVA has not been found to compare favorably to propofol-alfentanil TIVA even with flumazenil reversal of residual benzodiazepine actions. [891] On the other hand, TIVA for major (cardiac) and/or long operations may be effectively achieved with midazolam and sufentanil [892] or midazolam-fentanyl (see later). [893] TIVA with sufentanil and midazolam has also been employed in patients susceptible to malignant hyperthermia [894] and for pheochromocytoma resection. [895] TIVA techniques are especially useful when delivery of inhaled agents is compromised. Examples include patients with significant V/Q abnormalities or requiring one-lung ventilation, as well as patients requiring specialized ventilation techniques such as jet ventilation. The complete description of the application of TIVA techniques is be-yond the scope of this chapter. Nevertheless, by keeping the goals of balanced anesthesia in mind, combining modern opioids and other drugs, utilizing infusion pumps, and employing an increased understanding of pharmacokinetics, clinicians can successfully administer a variety of TIVA techniques.

Continuous Opioid Infusions

The classic pharmacokinetic descriptions of drug disposition have major limitations in anesthesia. [713] The context-sensitive half-time, more modern pharmacokinetic descriptions, and computer simulations have helped clinicians to select opioids in a more rational fashion. [712] [713] [885] The context-sensitive half-time, for example, illustrates how the duration of a drug infusion influences the time needed for dissipation of drug effect (Fig. 10-43) (Figure Not Available) . [18]

Analyses based on effect site concentrations can also be more helpful than those based on plasma concentration. For example, although plasma opioid concentrations over time after a bolus injection of fentanyl, sufentanil, and alfentanil decrease at a similar rate, effect site concentrations both rise and fall faster after alfentanil (see Fig. 10-40) (Figure Not Available) . The more rapid rise in effect site drug concentrations means that more drug will reach the brain because plasma levels will be higher when brain-blood equilibration occurs.

Continuous infusions of fentanyl, sufentanil, and alfentanil have been evaluated as alternatives to intermittent bolus techniques in anesthesia, and the former approach provides many advantages [875] [876] [877] [896] (see Table 10-17) . Some anesthesiologists still prefer to administer large IV boluses of opioids, thus producing high plasma concentrations that are effective for nearly all stimuli. The high therapeutic index of most opioids permits this approach. In addition, in cardiac anesthesia, in which the application of high doses of opioids first achieved popularity, significant postoperative respiratory depression is not a problem because postoperative controlled mechanical ventilation is most often practiced. However, the use of opioids as a key component of anesthesia in many other surgical areas is most often limited by the potential for troublesome postoperative depression of ventilatory drive. For this reason, as well as others reviewed later, some anesthesiologists believe that limiting the dose of opioids, as well as optimizing their use, is better achieved by

Figure 10-43 (Figure Not Available) Computer simulation of recovery curves for fentanyl, alfentanil, and sufentanil describing the time required (Y axis) for 20, 50, and 80 percent decreases in effect site concentrations after intravenous infusions of variable duration (X axis). *(Adapted from Shafer and Varvel [16])*

administering a loading "bolus" dose followed by a continuous infusion (see Tables 10-14 and 10-16) .

Various mathematic models and calculations have been used to predict, establish, and maintain the desired plasma concentration of a drug, but the objective is the same: to achieve a desired plasma and effect site drug concentration and to maintain that state by replacing drug removed by redistribution and metabolism. [722] [897] [899] More recent investigations offer better but more complex regimens [879] or computer-assisted delivery methods. [875] Continuous infusions are often slowed decrementally not only to seek the lowest effective concentration, but also to avoid opioid accumulation when redistribution of the drug declines as the peripheral compartment is filled. The necessity or presumed benefit of invoking complicated pharmacokinetic equations has been questioned as unduly cumbersome and complicated. [685] Titration, based on a dose-response relationship with limited attention to pharmacokinetic equations or concern about "ideal plasma levels," may be equally effective. Nevertheless, computer-assisted continuous infusions that deliver drugs based on population-based pharmacokinetic data and target plasma or effect site concentrations not only are accurate but also are becoming increasingly popular. [699] [900] [901]

Opioid-Based (High-Dose) Anesthesia

Opioids can be administered as the primary or sole anesthetic in opioid-based anesthetic techniques. Several factors have diminished the popularity of high-dose opioid anesthesia, even in cardiac anesthesia, in which it has been most commonly employed. These include the lack of evidence substantiating any significant outcome benefit associated with the use of large doses of opioids, [22] [23] the added drug costs, and the trend toward "fast track" approaches to the cardiac patient that can be impeded by large doses of opioids, especially fentanyl. [21] [902] [903] Anesthesia with an opioid as the sole anesthetic is also less frequently practiced for the same reasons, as well as because such a technique is not consistently reliable. [99] [848] [904]

The concept of a "cardiac" anesthetic has become more, not less, obscure over time. [905] However, the lack of compelling evidence that one anesthetic agent, or combination of anesthetic agents, is not superior or preferred does not negate the need to provide stable intraoperative hemodynamics for patients with cardiac disease. Opioids, particularly when administered by continuous infusion, are still among the most effective anesthetics for patients undergoing cardiac or other extensive operations. In addition, the efficacy of opioid-based anesthesia can be optimized intraoperatively with the administration of moderate drug doses and not result in prolonged postoperative respiratory depression.

Fentanyl

The popularity of high-dose opioid anesthesia was first established with morphine. [8] Problems with intraoperative hemodynamic instability, the need to intervene with vasoactive agents, excessive postoperative respiratory depression, and prolonged emergence have been noted to be more frequent with morphine than with fentanyl or sufentanil. [380] [382] Morphine is not recommended for high-dose opioid anesthesia.

Many different techniques have been used by clinicians and investigators to achieve anesthesia with fentanyl. [9] [10] [101] [129] [240] [252] [374] [380] [482] [786] [848] [902] [906] [907] [908] [909] [910] [911] [912] [913] [914] Rapid or slow bolus injections of fentanyl range from 5 to 75 mug
kg^{-1} . There is little benefit accrued by administering loading bolus doses of more than 5 to 30 mug/kg. These doses will establish sufficient plasma fentanyl concentrations (10-30 ng
mL^{-1}) that are often sufficient to provide stable hemodynamics throughout the induction/intubation sequence

Figure 10-44 (Figure Not Available) The plasma fentanyl concentration and the number of patients with a hypertensive response at each event studied.
, hypertensive; O, normotensive. *(From Wynands et al [374])*

(Fig. 10-44). Continuous infusions of fentanyl for cardiac surgery range from 0.1 to 1.0 (Figure Not Available) mug
kg^{-1}
min^{-1} up to or continuing through CPB (Fig. 10-45) (Figure Not Available) .

Other simple infusion schemes, such as those reported by Hall et al, [915] employing a modified Wagner method, [897] demonstrate that target and anesthetic fentanyl plasma concentrations can be maintained throughout surgery. A priming solution of 2.4 mug/kg/min for 20 minutes in combination with a simultaneously started and maintained infusion of 0.3 mug/kg/min produced fentanyl plasma concentrations between 20 and 27 ng/mL and effectively eliminated the need for supplements.

High dose fentanyl anesthesia has also proved effective and safe in premature infants for repair of patent ductus arteriosus (
50 mug
kg^{-1}) [916] [917] and for pediatric heart surgery (50-100 mug
kg^{-1}). [918] [919] [920] Intraoperative reduction in ventricular fibrillation in neonates undergoing surgery for hypoplastic left heart syndrome has been described as an advantage of high-dose fentanyl anesthesia. [442]

Figure 10-45 (Figure Not Available) Mean plasma fentanyl concentration (ng/mL) after fentanyl:
, 30 mug/kg/min;
, 40 mug/kg followed by 0.4 mug/kg/min;
, 50 mug/kg followed by 0.5 mug/kg/min;
, 75 mug/kg followed by 0.75 mug/kg/min. *(Composite figure adapted from Wynands et al [374] and Sprigge et al [786])*

Alfentanil

The induction of anesthesia with large doses of alfentanil has been applied to cardiac surgery. [379] [386] [388] [921] [922] [923] Large doses of alfentanil (150 mug
kg^{-1}) may be used with or without thiopental to induce anesthesia. The loss of verbal response ED_{50} for alfentanil in young unpremedicated adults is 111 mug
kg^{-1} . [114] Other investigators claim that anesthesia cannot be reliably induced with alfentanil alone, at least in young and healthy adults. [904] Continuous infusions of alfentanil (2-12 mug
kg^{-1}
min^{-1}) have been employed to maintain moderate to very high plasma alfentanil concentrations (
3,000 ng
mL^{-1}) during cardiac surgery. [921] [923] Hemodynamic control with alfentanil is more difficult with intermittent bolus techniques. [921] Enthusiasm for high-dose alfentanil anesthesia techniques is limited by the amount (and cost) of drug required and suggestions that alfentanil anesthesia for cardiac surgery is inadequate [388] and is associated with more cardiovascular adverse effects compared with fentanyl and sufentanil. [379]

More modest doses of alfentanil have been successfully administered in combination with sedative-hypnotics such as propofol for cardiac anesthesia. [924] Induction and maintenance of anesthesia with alfentanil (25-75-mug/kg loading dose plus 1-2-mug/kg/min infusion) and propofol (0.25-1.0- mg/kg bolus plus 80-100 mug/kg/min) is reliable and stable.

Sufentanil

Several reports suggest that high doses of sufentanil are superior to fentanyl in anesthesia for cardiac surgery. Purported advantages include more rapid induction, [382] better blunting or elimination of hypertensive episodes, [376] [925]

greater reduction in left ventricular stroke work, [381] with higher cardiac outputs [925] and more stable hemodynamics intraoperatively and/or postoperatively. [382] [925] Patients anesthetized with sufentanil instead of fentanyl also regain consciousness sooner and are extubated earlier. [382] [384] High-dose sufentanil anesthesia may produce lower blood pressures than equivalent doses of fentanyl. [379] Other investigators do not believe clinical differences between the two opioids to be significant. [99] [922] [926]

High doses of sufentanil have been employed in anesthesia for coronary artery and cardiac valvular sur-gery. [138] [376] [496] [922] [927] Induction doses of sufentanil range from 2 to 20 mug
kg^{-1} administered as a bolus or infused over 2 to 10 minutes. Although larger doses are sometimes administered during or early after induction, many anesthesiologists give additional sufentanil in anticipation of provocative stimuli, that is, before skin incision and sternotomy. Total doses of sufentanil employed in high-dose techniques usually range from 15 to 30 mug
kg^{-1} . However, as with other opioids, the trend is to reduce opioid doses and employ drug synergism to advantage. No additional benefit could be demonstrated in terms of hemodynamic control or EEG signs by increasing the dose of sufentanil from 3 to 15 mug/kg for the induction of anesthesia in patients premedicated with lorazepam. [928]

Zurick et al [138] showed that infusions of sufentanil are useful for induction of anesthesia. They found that the total dose of sufentanil needed was less and emergence was faster with an infusion versus a multiple bolus technique. The amount of sufentanil required can be markedly influenced by the supplements employed concomitantly. In a multicenter report of computer-assisted continuous infusion techniques for patients undergoing coronary artery surgery, modest induction (0.4±0.2 mug/kg) and total maintenance (2.4±0.8 mug/kg) doses of sufentanil were used in combination with propofol (1.5±1 mug/kg for induction and 32±12 mg/kg total). [929] Interestingly, sufentanil requirements tripled when midazolam was employed instead of propofol.

Etomidate has been recommended for the induction of anesthesia in patients with significant cardiovascular disease. Etomidate, combined with an opioid, can provide excellent anesthetic conditions with minimal hemodynamic perturbation. [913] Inducing anesthesia with sufentanil (0.5-1.0 mug/kg) plus etomidate (0.1-0.2 mg/kg) frequently confers hemodynamic stability. Maintenance of anesthesia, utilizing an infusion of sufentanil (1.0-2.0 mug/kg/h), in a balanced anesthetic technique, achieves the advantages of an opioid-based anesthetic and avoids prolonged opioid action into the postoperative period.

Remifentanil has been employed in cardiac anesthesia. [792] Insufficient data preclude drawing conclusions about this application of remifentanil. Whether the cost or risks of using an ultrashort-acting opioid would be outweighed by any benefit remains to be seen.

Other Applications of Opioids

New systems and sites for drug delivery have the potential to improve analgesic therapies by improving convenience and patient compliance, reducing pain associated with drug delivery, and increasing drug bioavailability and analgesic efficacy.

Transdermal Drug Delivery

Transdermal drug delivery generally requires high solubility in both water and oil (lipid solubility to pass through the stratum corneum and aqueous solubility to move through the dermis), low molecular weight, high potency (requiring absorption of only small amounts for clinical effect), and little or no skin irritation. Under basal conditions, 450 mL of blood, approximately 10 percent of the cardiac output, passes through the skin. Under thermal stress, skin blood flow can increase as much as 10-fold. Cutaneous vasoconstriction from cold stress can virtually abolish skin blood flow. The transdermal permeability of a drug may vary over different areas of the body. In some formulations, attempts to reduce variability in drug absorption have been made by adding a rate-controlling membrane to the transdermal drug delivery apparatus, which limits the release of drug to a fraction of the uncontrolled rate of absorption of the skin.

Fentanyl is available in a transdermal delivery system. Potential advantages of delivering fentanyl transdermally include no first-pass drug metabolism by the liver, improved patient compliance, convenience and comfort, and consistent analgesia. Other theoretic advantages include its simple, noninvasive nature, reduced nursing efforts, and less interruption of sleep. Transdermal fentanyl is approved by the FDA, but for use only in opioid-tolerant patients. Results of clinical trials utilizing fentanyl for postoperative analgesia have demonstrated a high incidence of significant respiratory depression, and this application is not recommended. [930] [931] [932] The development of other types of fentanyl patches has not eliminated problems with wide variability in fentanyl concentrations produced or in episodes of troublesome respiratory depression. [933] [934]

Doses of transdermal fentanyl include 25, 50, 75, and 100 mug/h and achieve blood levels ranging from less than 1.0 to 2.0 ng/mL, although significant variability exists. Plasma fentanyl levels rise and usually reach a plateau within 8 to 16 hours. Steady-state fentanyl concentrations are achieved by the time a second patch is applied. Fentanyl blood levels fall slowly after patch removal because absorption of drug deposited in the skin continues. [935] The half-life for the decline in fentanyl levels after patch removal is high (17±2.3 h).

Transdermal fentanyl is effective in cancer pain management. Patients should have analgesia provided by fasteracting opioid preparations, then be converted to transdermal fentanyl, with allowances made for drug conversions. Most patients with cancer experience 72 hours of analgesia following application of the patch, but some individuals only obtain about 48 hours of analgesia from each unit. This may be due to tumor fever, a common phenomenon that occurs in about 40 percent of patients with active cancer. Elevated body temperature accelerates either the release of fentanyl from the patch or the distribution from the subcutaneous fat depot.

Because of the difficulties encountered in the passive delivery of drugs through the skin, physical and chemical methods of enhancing transdermal drug delivery are being investigated. [936] Iontophoresis is a technique by which drug passage through the skin is augmented by an external electric current. Morphine HCl has been delivered iontophoretically for postoperative pain control. Patients who received morphine by iontophoresis required fewer additional opioid analgesics than patients receiving a placebo after orthopedic

surgery. [937] After a short delay, plasma morphine levels are directly proportional to the electric current employed in the iontophoretic device. Similar results have been achieved with fentanyl. [938]

Transmucosal Drug Delivery

Similar to transdermal drug delivery, transmucosal delivery through the oropharynx and nasopharynx eliminates hepatic first-pass metabolism (drugs are absorbed directly into the systemic circulation) and improves patient comfort, convenience, and compliance. The oral and nasal cavities are rich in blood vessels and lymphatics; thus, drug absorption is faster and onset of action is more rapid compared with oral (swallowed) and transdermal routes. Possible applications for this mode of administration include premedication, acute postoperative pain relief, and treatment of chronic pain.

Sites for transmucosal delivery in the mouth include sublingual, buccal, and gingival surfaces. Although the sublingual route is easier for patients to use, increased salivary production and swallowing limit systemic availability with this approach.

Buprenorphine, a potent, synthetic morphine analogue with mixed opioid agonist-antagonist properties and a long half-life, is readily absorbed from sublingual mucosal tissues. Buprenorphine is well absorbed across mucosal membranes and is quite suitable for sublingual and buccal administration. The portion of the drug that is swallowed is almost completely metabolized by the liver, and only a small fraction can reach the systemic circulation when swallowed. It has been used successfully for premedication and treatment of postoperative and cancer pain. [939] [940] [941] [942] Sublingual buprenorphine, given 1 hour preoperatively, provides reliable preoperative sedation and postoperative analgesia similar to IM morphine. [941] In several studies, sublingual buprenorphine (0.4 mg) was compared with conventional intramuscular morphine or meperidine and found to provide comparable and satisfactory postoperative analgesia. [942] However, onset of drug effect was slow (3 h) and thus not effective for the immediate postoperative period. [939] [941] Systemic bioavailability after sublingual buprenorphine is approximately 50 percent of that following IV administration. [940] Although the percentage of patients achieving adequate pain relief after cholecystectomy with sublingual buprenorphine alone is high (
80%), other supplemental methods (e.g., PCA) may be required for higher success rates or after more painful operations. [943] Sublingual buprenorphine is not approved for use in the United States.

Initial experience with buccal morphine for postoperative analgesia had been promising. Bell et al [944] demonstrated that buccal morphine has a 50 percent bioavailability. However, subsequent studies by Fisher et al [945] have questioned the reliability and systemic availability of buccal morphine. These investigators showed that IM morphine provided more effective premedication than a buccal tablet of morphine. Furthermore, 81 percent of patients receiving buccal morphine complained of its bitter taste, and plasma drug concentration-time curves were markedly different than those reported by Bell. In addition, peak plasma levels after buccal morphine were lower (9.1 versus 36.0 ng
mL^{-1}), time to peak levels was longer (408 versus 60 min) and bioavailability (area under the curve) was less (1.6 versus 14.8 mug-min
mL^{-1}) than after IM morphine. [944] [945] Reasons for these markedly differing results are unclear, but those offered by Fisher and others [946] include the wide variability in morphine absorption by the buccal route, differences in the pH of the formulation tested and morphine assay methods, and poor adherence and dissolution of the tablet on the buccal mucosa in patients with a dry mouth. [945] In addition, the bitter taste of morphine elicits salivation and swallowing that negate the objective of avoiding first-pass drug metabolism. [946] Bioavailability after sublingual morphine is six times lower than when the same dose is given IM or nebulized and administered intratracheally. [947] Morphine's low lipid solubility makes it an unlikely candidate for effective transmucosal absorption (Fig. 10-46) (Figure Not Available) . Opioids with a high lipid solubility, such as buprenorphine, fentanyl, and methadone are more effectively absorbed sublingually than those with low lipid solubilities such as morphine. [948]

Oral transmucosal fentanyl citrate (OTFC) is a solid dosage form of fentanyl that consists of fentanyl incorporated into a sweetened lozenge on a stick. When consumed, a portion of fentanyl is absorbed through the oral mucosa and the rest is swallowed and absorbed through the GI tract. OTFC gained regulatory approval in 1993 for use as a premedication before surgery and painful procedures (not requiring general anesthesia) in both children and adults. [949] [950] [951] [952] [953]

OTFC is available in 200-, 300-, and 400-mug units. The recommended doses range from 5 to 15 mug/kg, depending on the desired degree of sedation. Patients should be instructed to consume OTFC quickly (within 15 min) because longer consumption times may decrease fentanyl absorption. In addition, OTFC should be administered approximately 30 minutes before surgery (or painful procedure) to obtain peak effect.

Plasma concentrations after OTFC administration peak at 2.0±0.5 ng/mL, 15 to 30 minutes after OTFC administration, then decline to less than 1 ng/mL an hour later (Fig. 10-47) (Figure Not Available) . [954] Plasma concentrations rapidly reach concentrations associated with analgesia (0.63-1.0 ng/mL) during OTFC consumption. The elimination half-life of OTFC is 7.7 hours, similar to the IV route. Unlike transdermal fentanyl, OTFC leaves no significant depot in the mucosal tissues after it is

removed. However, some absorption of fentanyl continues after OTFC is removed or consumed because of the absorption of swallowed fentanyl from the GI tract. Swallowed fentanyl has a low bioavailability because of hepatic first-pass metabolism. The systemic bioavailability of OTFC is 50 percent and reflects both buccal and GI absorption. OTFC bioavailability is similar to that of buprenorphine (55%), but much greater than buccal morphine and other opioids with low lipid solubility.

OTFC was developed because of the need for less painful and frightening methods of obtaining analgesia in children. Because many children do not have IV access, analgesia may be obtained by the transmucosal route. For example, premedication with OTFC can reduce pain in children undergoing lumbar puncture or bone marrow aspiration, and it can also reduce pain associated with laceration repair, dermatologic surgery, and burn dressing changes.

Enthusiasm for OTFC as a premedicant has been tempered by associated side effects, which include perioperative emesis. Decreasing patient activity and timing OTFC

Figure 10-46 (Figure Not Available) The mean absorption (± SE) of the test opioids after 10 minutes in the oral cavity of normal subjects (*n* = 10 for each test condition). The pH of the dosing solution was 6.5. BUP, buprenorphine; FENT, fentanyl; HER, heroin; HM, hydromorphone; LEVO, levorphanol; METH, methadone; MS, morphine sulfate; NAL, naloxone; OXY, oxycodone. *(From Weinberg et al [948])*

administration so that patients are moved to the operating room before the peak effects occur can reduce this side effect. Respiratory depression can also occur, and patients need to be adequately monitored and treated for this side effect.

OTFC is also being evaluated for treatment of acute postoperative analgesia [955] and breakthrough cancer pain. For example, the speed of onset of analgesia with OTFC is equal to that of IV morphine in patients after abdominal hysterectomy. OTFC may be ideally suited to treat breakthrough cancer pain because fentanyl is rapidly absorbed from OTFC and patients can easily self-administer OTFC. Onset of analgesia for breakthrough pain occurs as early as 5 minutes after OTFC administration. Clinical trials examining

Figure 10-47 (Figure Not Available) Plasma concentration of fentanyl (mean ± SEM) after oral transmucosal fentanyl (OTFC) versus oral (swallowed) fentanyl. Total fentanyl administered via each route was 15 mug/kg. OTFC oralets were consumed in 15 minutes, and solutions were swallowed within 10 seconds. Systemic bioavailability was greater for OTFC (0.52±0.1) than for swallowed fentanyl (0.32±0.1) (*P* = .01). *(From Streisand et al [954])*

the safety and efficacy of OTFC in breakthrough cancer pain are completed, and FDA approval is pending. Reviews on OTFC are available. [956]

Delivery of opioids through the nasal mucosa has also been investigated. [957] Although intranasal sufentanil (1.5, 3.0, 4.5 mug kg^{-1}) in children allows easy separation from parents, many of the children cried on drug administration. [958] Side effects of intranasal sufentanil include reduced ventilatory compliance (chest wall rigidity) with higher doses (3.0-4.5 mug kg^{-1}). Intranasal sufentanil (2 mug/kg) in pediatric patients before surgery can cause hypoxemia and impair manual ventilation. [959] Intranasal sufentanil (2 mug/kg) and midazolam (0.2 mg/kg) have been compared as premedicants for pediatric outpatients. [960] Sufentanil provided better conditions during induction and emergence and was associated with less nasal irritation, but more nausea and vomiting postoperatively than intranasal midazolam.

In adults, too, 10 to 15 mug of intranasal sufentanil induces moderate sedation with few side effects 20 to 40 minutes after administration. [961] [962] Plasma sufentanil levels 5 and 10 minutes after intranasal sufentanil are 36 and 56 percent of those after IV dosing respectively. After 30 minutes, plasma levels were the same after both routes. Bioavailability of intranasal sufentanil is 78 percent of IV sufentanil.

Butorphanol, a partial mu- and kappa-agonist, has also been administered nasally. A metered-dose spray pump delivers 1 mg/spray (0.1 mg/mL), the approximate therapeutic dose. Peak blood concentrations occur 15 minutes after administration and bioavailability is relatively high (50-70%). Transnasal butorphanol provides superior and more prolonged analgesia than similar doses given IV for postoperative pain after cesarean section. [963] In human volunteers, transnasal butorphanol (1-2 mg) produced psychomotor, cognitive, and subjective effects for 1 to 3 hours. [964] The application of transnasal butorphanol has proven efficacious after cesarean section, episiotomy, orthopedic surgery in children, and in the emergency room.

Postoperative pain management with self-administered meperidine [965] and PCA with intranasal fentanyl [966] have been demonstrated to be as effective as more traditional pain therapies. Intranasal oxycodone is also rapidly and effectively absorbed, but with significant variability. [967] It appears that further exploration of the transnasal approach to drug delivery for pain management is merited.

Morphine (10 mg) and fentanyl (300 mg) inhalation produces low plasma drug levels (10 and 0.2-0.4 ng/mL, respectively) and analgesia that may be disproportionately greater than expected. [947] [968] Inhaled liposome-encapsulated fentanyl may allow analgesia to be rapidly produced and sustained. [969]

Successful inhalation of any drug requires proper coordination with inspiration, and some devices include strategies toward this goal. One device for the pulmonary administration of morphine (AERx, Aradigm Corp., Hayward, Calif) only releases drug when the correct inhalation pattern is accomplished. Inhaled doses of 2.2, 4.4, and 8.8 mg of morphine, aerosolized in an aqueous solution, provide dosedependent, analgesic blood concentrations of morphine within 5 minutes of administration. Technologic advances in drug delivery are likely to continue to stimulate research in analgesic therapies.

The rectal mucosa is another site for transmucosal drug delivery. Rectal methohexital was frequently used in the past for premedication in young children. Rectal suppositories containing morphine, hydromorphone and oxymorphone, and oxycodone are available.

Morphine is only poorly absorbed from the rectal mucosa of children. [970] However, sustained-release morphine hydrogel suppositories (MHS) may be more promising. [971] Two suppositories have been designed. The first releases a bolus, then a smaller quantity of morphine at a constant rate to achieve initially and then maintain plasma drug concentrations. A second sustained-release-only suppository has also been developed to permit administration for successive 12-hour periods after administration of the first type of rectal morphine. Plasma morphine levels after MHS are lower than after IM morphine, but linear analogue scales for pain were lower, and the incidence of nausea was reduced after rectal sustained-release therapy. [971] The hydrogel formulation of rectal morphine may also be useful for premedication and analgesia in pediatric patients. [972] Although rectal administration of drugs is complicated by interruption of absorption by defecation, mucosal irritation, variable systemic availability (venous drainage of the rectum is in part to the portal system), and poor patient acceptability, further investigation with MHS seems warranted.

Oral Controlled-Release Medications

Despite the high first-pass metabolism of opioid analgesics, morphine has been formulated into an oral, sustained-release tablet (MST) and has been evaluated for premedication, [973] postoperative analgesia [974] [975] and as an analgesic for chronic cancer pain. [976] [977] Early clinical trials have suggested that MST provides unreliable preoperative anxiolysis [973] and postoperative pain relief, [974] [975] possibly because of delayed time to onset of peak effects (3-5 h), which can be increased by impaired gastric emptying and absorption from the small intestine. On the other hand, patients with chronic cancer pain perceived that analgesia was superior and side effects were fewer with MST. [976]

/das/book/view/29494766/875/123.html

OTHER OPIOID AGONISTS

Many other opioid agonists exist (Table 10-18) , but their use in operative anesthesia is usually limited. Some of these agents are used primarily for analgesia. The following is a brief synopsis of many, but not all, available opioid agonists.

Alphaprodine (Nisentil) is a phenylpiperidine derivative that is approximately one-fourth as potent as morphine. Alphaprodine has a rapid onset and a relatively short duration of action (2 h). Some clinicians compare alphaprodine to meperidine but believe the former causes less nausea and vomiting. Alphaprodine has been a popular analgesic for labor pain. [978] Respiratory depression, fetal bradycardia, and depressed progression of labor can occur when the drug is given for analgesia during labor. Murakawa et al, [978] on the other hand, found alphaprodine (39±4 mg IV) to produce no neonatal effects when given to parturients 197±96 minutes prior to delivery.

Codeine (methylmorphine) is one-half as potent as morphine, has a high oral-parenteral potency ratio (2:3) and a plasma half-life of 2 to 3 hours. Codeine has mild to moderate

TABLE 10-18 -- Partial List of Other Opioid Agonists

Heroin
Codeine
Oxymorphone (Numorphan)
Phenoperidine
Methadone (Dolophine)
Alphaprodine (Nisentil)
Hydromorphone (Dilaudid)
Pentamorphone
Bremazocine
GI 87084B (remifentanil)
A-4492 (pentamorphone)
A-3508
A-3217 (ocfentanil)
A-3665
Tramadol
Etorphine
Carfentanil
Dextromoramide
Piritramide
Dihydrocodeine
Levorphanol tartrate
Phenazocine

analgesic but strong cough-suppressant properties after oral administration. Hepatic conversion to morphine (demethylation) is necessary for codeine's activity. Cytochrome P-450 2D6 (CYP2D6) is the enzyme responsible for *O*-demethylation of codeine to morphine. [979] IV codeine produces profound hypotension and is neither approved nor recommended. [980] Its use as a preferred opioid in neurosurgical patients is not substantiated.

Dextromoramide was developed by Janssen Pharmaceutica in 1956. Though unavailable in the United States, dextromoramide is still used in a few European countries. It can be administered orally or parenterally, has a duration of action similar to that of methadone, and is 25 times more potent than morphine. [981]

Etorphine and carfentanil are wild game-immobilizing opioids not available for use in humans and are several thousand times more potent than morphine. [982]

Heroin, diacetylmorphine, is approximately twice as potent as morphine and has a 4- to 5-hour duration of action. Heroin is rapidly hydrolyzed to 6-acetylmorphine and morphine. These metabolites account for a significant portion of heroin's effects. Because of its high solubility and lipophilicity, heroin lends itself to subcutaneous injection. Heroin is excreted in the urine mostly as free and conjugated morphine. Manufacture and importation of heroin is illegal in the United States, but not in the United Kingdom or Canada.

Hydromorphone (dihydromorphinone or Dilaudid) is structurally related to morphine but is approximately five to ten times as potent. The onset and duration of action of hydromorphone is similar to that of morphine. [983] [984] Analgesia after hydromorphone lasts 4 to 5 hours. The effects of hydromorphone are essentially indistinguishable from those of heroin. [985] Hydromorphone does not result in an increase in plasma histamine. [986] It can be administered by oral, rectal, subcutaneous, and other parenteral routes.

Levorphanol is a semisynthetic opioid with a long (12- 16-h) half-life. It is 5 times as potent as morphine with an IM/oral potency ratio of 1:2. Discrepancies between half-life and apparent duration of clinical analgesia (4-6 h) create conditions in which repeated doses may lead to drug accumulation and toxicity. Levorphanol may have particular utility in patients with chronic pain and who demonstrate morphine tolerance, perhaps because of differences in opiate receptor activity.

Methadone (Dolophine) has an equivalent potency but longer duration of action than morphine. [987] Methadone's efficacy is reduced by 50 percent after oral administration, compared with IM delivery. Its major clinical applications are in the prevention of opioid withdrawal symptoms and in the treatment of chronic pain. It can also provide postoperative pain relief. [987] Prolonged and potentially troublesome postoperative respiratory depression can occur, possibly because of the long duration of action of methadone. [988] This may be related to increases in apparent potency that occur with repeated administration. The plasma half-life of methadone is very long and variable (13-100 h). Despite this property, many patients require dosing every 4 to 8 hours to maintain analgesic effects. It is a difficult drug to titrate successfully. Methadone should not be administered subcutaneously because of local skin toxicity.

Oxymorphone (dihydrohydroxymorphinone or Numorphan), also structurally related to morphine, is almost ten times as potent, but has a similar duration of action. Oxymorphone is less likely to cause the release of histamine than morphine and may have particular utility in patients who experience excessive with opioid analgesics.

Pentamorphone, a morphinan derivative, is two to eight times as potent as fentanyl and produces similarly lasting analgesia without hemodynamic disturbances or increases in plasma histamine. [989] Although respiratory depression may be limited with analgesic doses (0.1 mug/kg), greater doses produce typical opioid-induced respiratory depression. [990] Pentamorphone does not appear to offer significant advantages over better-established opioid agents.

Phenoperidine is chemically related to meperidine but is 100 times as potent as an analgesic. Onset of effect is rapid and duration is moderate (2-6 h). Doses of 2 to 5 mg IV produce significant respiratory depression. Metabolism of phenoperidine results in significant levels of meperidine and its metabolites. Phenoperidine has been frequently employed in balanced anesthesia in Europe, but it is unavailable in the United States.

Piritramide, the first 4-amino-piperidine derivative among opioids to be synthesized, is interestingly devoid of emetic activity. In fact, it blocks apomorphine-induced emesis. [981] It is slightly less potent than morphine.

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine with a dual mechanism of action. [991] [992] Tramadol stimulates the mu-receptor, and to a lesser extent the delta- and kappa-opioid receptors, and like tricyclic antidepressants, it also activates spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin. Tramadol is a racemic mixture. It is unlikely to produce troublesome respiratory depression at recommended doses, but it can at greater doses. Tramadol is one-fifth to one-tenth as potent as morphine and can be given by numerous parenteral routes. Recommended dosing ranges from 50 to 100 mg every 4 to 6 hours with a maximum daily dose of 400 mg. A onetime dose of tramadol, 150 mg IV, for immediate postthoracotomy pain can be as effective as thoracic epidural

TABLE 10-19 -- Hemodynamic Effects of Agonist-Antagonist Compounds Compared with Morphine

(Not Available)

From Zola and McLeod [1026]

morphine. [993] Bioavailability of tramadol ranges from 70 to 100 percent. To date, evidence suggests that tramadol has low abuse potential. Analgesic doses of tramadol may produce less respiratory depression in part because of its non-opioid receptor-mediated actions. [994] Other common adverse effects are typical for opioids; however, tramadol may interfere less with GI function. [995] Several warnings should be noted concerning tramadol. Seizures have been reported in patients taking the drug. Caution should be exercised when combining tramadol with MAOI, neuroleptic agents, and other drugs that lower the seizure threshold.

AGONIST-ANTAGONIST COMPOUNDS

The first recorded specific opioid antagonist was developed by Pohl in 1914, who, in an attempt to improve the analgesic properties of codeine, synthesized *N*-allylnorcodeine. [996] This compound mildly antagonized the respiratory depression and sleep produced by morphine. Pohl's discovery went unnoticed for 26 years, until McCawley et al, [997] in a search for a strong analgesic with "built-in" antagonistic action, attempted to prepare *N*-allylmorphine (nalorphine) in 1940. Nalorphine was successfully synthesized by Weijland and Erickson [998] in 1942 and was found to be strongly antagonistic to almost all the properties of morphine. [999] [1000] It was also found to possess fairly strong analgesic properties in humans [1001] and animals. [1002] [1003] Unfortunately, doses of nalorphine sufficient to produce analgesia were accompanied by severe psychotomimetic effects rendering it unsuitable for clinical use as an analgesic. However, nalorphine was used in lower doses as an opioid antagonist.

Agonist-antagonist opioids are usually produced by alkylation of the piperidine nitrogen and addition of a threecarbon side chain such as a propyl, allyl, or methyl allyl to morphine. Changing the side chain to an amyl group restores agonist activity. Currently, there are several agonist-antagonist opioids in use in the United States including pentazocine, butorphanol, nalbuphine, dezocine, and buprenorphine. Buprenorphine is a partial agonist at the mu-receptor. The other compounds are mu-antagonists and full or partial agonists at the kappa-receptors. The differing degrees of interaction at the receptors contribute to the unique hemodynamic and respiratory effects of these compounds (Tables 10-19 (Table Not Available) , 10-20) (Table Not Available) . Buprenorphine has an especially high affinity at the mu-receptor. Its actions at kappa-receptors are probably minimal. Agonist-antagonist opioids are less prone (but not immune) to abuse because they cause less euphoria and are associated with less drug-seeking behavior and physical dependence.

Pentazocine

Pentazocine, a benzomorphan derivative, was the first opioid agonist-antagonist to be widely used in humans. Analgesia produced by pentazocine is primarily related to kappa-receptor stimulation. [1004] [1005] Pentazocine is one-half to one-fourth as potent as morphine. Moderate analgesia results from 10 to 30 mg IV or 50 mg orally. Ceilings to both analgesia and respiratory depression occur after 30 to 70 mg of pentazocine. Although the potential for abuse is less than with morphine, [1005] prolonged use of pentazocine can lead to physical dependence. [1004] [1006] Pentazocine is not particularly useful in reversing the respiratory-depressant effects of fentanyl, [1007] but it can precipitate opioid withdrawal in addicts. [1008] Nalorphine-like dysphoric side effects are common, especially after high doses (>60 mg) of pentazocine in the elderly. The dysphoric effects of pentazocine can be reversed with naloxone. Although the hemodynamic effects of morphine make it a useful analgesic for patients with myocardial failure, ischemia, or infarction, [1009] pentazocine depresses myocardial contractility [1010] and increases arterial blood pressure, heart rate, systemic vascular resistance, pulmonary artery pressure, and left ventricular work index. [1011] [1012] Pentazocine also increases blood catecholamine levels. In Europe, pentazocine (1 mg kg^{-1}) has been used in a general anesthetic technique called "sequential analgesic anesthesia." In this technique, the drug is administered after moderate doses of fentanyl (10-15 mug kg^{-1}). Overall, pentazocine has limited application because it is associated with a high incidence of postoperative nausea and vomiting, it provides limited analgesia, it partially antagonizes other opioids, and it can produce undesirable cardiovascular and psychotomimetic effects.

TABLE 10-20 -- Respiratory Depressant Effects of Agonist-Antagonists Compared with Morphine [a]

(Not Available)

From Zola and McLeod [1026]

[a] Low or moderate naloxone doses readily reverse the respiratory effects produced by therapeutic doses of all drugs listed, except buprenorphine.

Butorphanol

Butorphanol is an agonist at kappa-receptors. Its activity at mu-receptors is either antagonistic or partially agonistic. It is five to eight times as potent as morphine and is only available in parenteral form. After IM injection, onset of effect is rapid, and peak analgesia occurs within 1 hour. Whereas butorphanol's duration of action is similar to morphine, its plasma half-life is only 2 to 3 hours. [1013] Bioavailability after oral administration is only 17 percent of a similar IV dose. Although butorphanol (10 mg IM) causes as much respiratory depression as the same dose of morphine, higher doses reach a ceiling. [1014] Side effects after butorphanol include drowsiness, sweating, nausea, and CNS stimulation. The latter are qualitatively similar but occur less frequently than after pentazocine.

In healthy volunteers, butorphanol (0.03 or 0.06 mg kg^{-1} IV) produces no or minimal cardiovascular changes. [1014] However, in patients with cardiac disease, butorphanol causes significant increases in cardiac index, left ventricular end-diastolic pressure, and pulmonary artery pressure. [1015] These cardiovascular changes are quite similar to those produced by pentazocine. [1011] Thus, butorphanol is not particularly useful in patients with congestive heart failure or at risk for myocardial ischemia.

Butorphanol has been reported to provide adequate analgesia when used as a supplement in N_2O-opioid-O_2 anesthetic or balanced techniques. [1016] [1017] Because butorphanol decreases the MAC for enflurane by only a small fraction (11%), it cannot serve like the fentanyl congeners as an anesthetic agent. [1018] Butorphanol (0.17 mg kg^{-1}) will result in greater immediate postoperative respiratory depression than nalbuphine (0.085 mg kg^{-1}) when used as a supplement with N_2O. [1019] The antagonistic properties of butorphanol at the mu-receptor are weak and do not usually interfere with the use of other opioid agonists in anesthesia. [1020] However, butorphanol does partially antagonize fentanylinduced respiratory depression. [1021] The use of butorphanol as an epidural agent has achieved some popularity, as has its transnasal administration (see earlier).

Butorphanol is subject to less abuse and has less addictive potential than morphine or fentanyl, but it still has some potential for abuse. [1022] Withdrawal symptoms can occur after prolonged use and usually increase in severity for several days. [1023] Hepatic metabolism and urinary and a small amount of biliary excretion account for drug elimination. Acute biliary spasm can occur after butorphanol, but increases in biliary pressure are less than after equipotent doses of fentanyl or morphine. [1024]

Buprenorphine

Buprenorphine is a thebaine derivative, mu-receptor partial agonist, and similar in structure to morphine but approx-imately 33 times more potent. It also binds to delta- and kappa- receptors, but activity at the latter two sites is relatively insignificant. [70] Although buprenorphine is highly lipophilic, its opiate receptor association and dissociation are slow. Whereas fentanyl dissociates rapidly from mu-receptors (half-life of 6.8 min), buprenorphine has a higher affinity and takes much longer (half-life of 166 min). Thus, plasma levels do not parallel CNS effects. [70] Buprenorphine's onset of action is slow, and its peak effect may not occur until 3 hours. Duration of effect is prolonged (
10 h). Metabolism occurs in the liver with biliary excretion of most metabolites. The metabolites of buprenorphine, buprenorphine-3-glucuronide and norbuprenorphine are significantly less potent and have lower affinities for the mu-receptor. Their accumulation in patients with renal failure is unlikely to exert significant pharmacologic activity. [1025] Buprenorphine's volume of distribution is 2.8 L
kg^{-1} and clearance is 20 mL
kg^{-1}
min^{-1} . Recommended initial analgesic doses are 0.3 to 0.4 mg. [1026]

Subjective effects (e.g., euphoria) of buprenorphine are similar to morphine. Buprenorphine produces respiratory depression with a ceiling after 0.15 to 1.2 mg in adults. Higher doses do not produce further respiratory depression and may actually result in increased ventilation (predominance of antagonistic actions). [1027] Respiratory depression can be significant after buprenorphine. Reversal with naloxone is limited by buprenorphine's high affinity for and slow dissociation from the mu-opiate receptor. Very high doses of naloxone and/or doxapram may be required for full reversal. [1026] [1028] Buprenorphine (0.6 mg IV) has been reported to reverse troublesome fentanyl-induced postoperative respiratory depression as well as naloxone (0.4 mg) and to preserve analgesia better. [1029]

Buprenorphine has been successfully used for premedication (0.3 mg IM), [1030] as the analgesic component in balanced anesthesia (4.5 to 12 mug kg^{-1}) [1031] and for postoperative pain control (0.3 mg IM). Sublingual administration (0.4 mg) has also proved effective. [1032] Buprenorphine, like the other agonist-antagonist compounds, is not acceptable as a sole anesthetic, and its receptor kinetic profile restricts its usefulness if other mu-agonists are used. Buprenorphine has been administered via alternate routes (see earlier), epidurally, and it may be of value as an alternative to methadone for maintenance therapy in opiate addicts.

The hemodynamic effects of buprenorphine are similar to those of morphine (see Table 10-19) (Table Not Available) . Opioid withdrawal symptoms develop slowly (5-10 days) after buprenorphine is discontinued following long-term use. In contrast to other agonist-antagonists, buprenorphine produces minimal effects in methadone-maintained opioid abusers. [1033]

Nalbuphine

Nalbuphine is an agonist-antagonist opioid that is structurally related to oxymorphone and naloxone. [1034] Autoradiography studies indicate that nalbuphine binds to mu- receptors as well as to kappa- and delta-receptors. [1035] Nalbuphine acts as an antagonist at the mu-receptor and an agonist at the kappa-receptor. Activation of supraspinal and spinal kappa-receptors results in limited analgesia, respiratory depression, and sedation. [46] [1035] Although 10 mg of nalbuphine produces similar sedation, analgesia, and respiratory depression as 10 mg of morphine, this equivalency does not persist at higher doses. Maximal analgesia occurs after approximately 30

mg
70 kg^{-1} of nalbuphine. Nalbuphine also causes other typical opioid side effects. [1036]

Nalbuphine is only available for parenteral use. Onset of effect is rapid (5 to 10 min), and duration is long (3 to 6 h) because of a long plasma elimination half-life (5 h). Hepatic metabolism and fecal excretion account for most of the drug's elimination. Nalbuphine does not increase plasma histamine levels. Nalbuphine (0.6 mg kg^{-1}) produces no or minimal hemodynamic changes in ASA class I and II patients or those undergoing cardiac catheterization when administered alone. [1037] Premedication with nalbuphine (0.1 mg
kg^{-1}) in patients scheduled for cardiac surgery results in similar sedation, relief of anxiety, and respiratory depression as morphine (0.1 mg
kg), but it causes no significant hemodynamic changes. [1037] In patients experiencing a myocardial infarction, 10 mg of nalbuphine causes small decreases in heart rate (82-72 beats/min) and cardiac index (3.16-2.75 l
min^{-1}
m^{2-1}) and small increases in systemic vascular resistance (1204-1461 dynes
s
cm^{-} [5]). [1038] Changes in systemic, pulmonary arterial, and pulmonary capillary wedge pressures are not significant. [1038]

In addition to occasionally being used as a premedicant, nalbuphine has been administered as an analgesic supplement for conscious sedation or balanced anesthesia and as a analgesic for postoperative and chronic pain problems. Conscious sedation during monitored anesthesia care has also been recommended with combinations of nalbuphine (20-30 mg
70 kg^{-1}) and droperidol (2.5 mg) [1039] or nalbuphine (0.05-0.2 mg
kg^{-1}) and midazolam (0.05 mg
kg^{-1}). [1040] Apnea and/or slow respiratory rates (less than 8) are occasional problems with the latter drug combination. [1040]

Balanced anesthesia with nalbuphine as an IV analgesic supplement is effective for surgical procedures not associated with severe pain. [1041] Postoperative sedation, dreaming, anxiety, and a longer recovery room stay are more common when nalbuphine (0.3 to 0.5 mg
kg^{-1}) is used with N_2O for laparoscopy than when fentanyl (1.5 mug
kg^{-1}) is employed as the opioid. [1041] Other investigators have found that nalbuphine is not as effective as fentanyl in attenuating responses to intubation and surgery, but it provides similar levels of postoperative analgesia with less respiratory depression in women having lower abdominal surgery. [1042] Anesthesia with nalbuphine (3 mg
kg^{-1}), diazepam (0.4 mg
kg^{-1}), and N_2O has been reported to provide hemodynamic stability during cardiac surgery by some investigators, [1043] but not others. [1044] [1045] Nalbuphine's inability to decrease the MAC of potent inhalation agents [1018] (maximum 10-30%) suggests it has little or no role as a sole or primary anesthetic.

Nalbuphine provides good analgesia for mild to moderate, but not severe, postoperative pain. Nalbuphine, like other agonist-antagonist compounds, interferes with the analgesia produced by pure mu-agonists. Addiction, abuse, and withdrawal occur less frequently after nalbuphine than after the pure mu-agonist, but they occur as frequently as after the other agonist-antagonist compounds.

Nalbuphine as an Antagonist of Opioid Drugs

Preservation of analgesia following reversal of opioidinduced respiratory depression has long been a goal of researchers and clinicians. [1046] Although numerous opioid antagonists have been studied in attempts to find the "ideal" compound (including nalorphine, levallorphan, naloxone, and numerous others), none is optimal. Nalbuphine has been extensively evaluated for this purpose. [316] [1047] [1048] [1049] [1050] [1051] [1052] [1053] [1054] Nalbuphine restores normal inspiratory neuronal activity after fentanyl in cats, [316] but respiratory depression induced by oxymorphone (1.5 mg) is only partially reversed by nalbuphine in humans (0.1 mg
kg^{-1}). Nalbuphine (0.21 mg
kg^{-1}) does not reverse and may actually increase respiratory depression after morphine (0.21 mg
kg^{-1}) (Fig. 10-48) (Figure Not Available) . [1052]

Latasch et al [1047] reported that nalbuphine (20 mg IV) adequately reversed respiratory depression but not analgesia in patients who had received 7 mug

kg^{-1} of fentanyl and N_2O for general surgery. Zsigmond et al [1054] found that nalbuphine (0.1 mg kg^{-1}) did not elicit significant cardiovascular changes or pain in patients given fentanyl-N_2O anesthesia for abdominal surgery. Unfortunately, many other investigators have documented the occurrence of significant pain, hypertension, and tachycardia (often requiring pharmacologic intervention) following opioid reversal with nalbuphine. [1049] [1050] [1055] Many of these reports involved patients undergoing cardiovascular procedures (abdominal vascular surgery or coronary artery bypass grafting [1049] [1050] [1054]). Patients at risk for myocardial ischemia or other cardiovascular problems are not good candidates for opioid reversal.

Restoration of spontaneous ventilation using small titrated doses of nalbuphine (2.5 mg q 2-3 min) results in less pain than naloxone (0.08 mg titrated similarly) after fentanyl (mean dose 25 mug kg^{-1}), isoflurane and N_2O anesthesia. [1053] Renarcotization is likely to be less frequent after nalbuphine (Table 10-21) (Table Not Available).

Figure 10-48 (Figure Not Available) Resting end-tidal CO_2 (P_{ECO_2}) at baseline and at 5 and 30 minutes after morphine (0.21 mg/kg IV) and after nalbuphine (0.21 mg/kg IV), naloxone (0.014 mg/kg IV), and saline given 55 minutes after morphine. *(From Bailey et al [1052])*

TABLE 10-21 -- Percentage of Patients Requiring Analgesics and Renarcotizing After Nalbuphine or Naloxone Reversal of Fentanyl

(Not Available)

From Bailey et al [1053]

Dezocine

Dezocine is slightly more potent and faster-acting than morphine, with a similar duration. [1056] It is active at mu-receptors, and side effects are similar to those of morphine. Respiratory depression and analgesia reach a plateau after approximately 0.3 mg kg^{-1}. [1056] Dezocine may prove superior to other agonist-antagonists as an anesthetic supplement because it is more effective in reducing the MAC of potent inhalation agents (50% with cyclopropane or 58% with enflurane) than other agonist-antagonists. [1057] [1058] In addition, dezocine potentiates rather than antagonizes morphine and other pure mu-agonist analgesics. Dezocine is a partial agonist at mu- and probably delta-receptors. [1057] Affinity at mu-receptors is high. Dezocine does not increase plasma histamine and produces less hypotension than morphine or pentazocine in dogs. [1059] Dezocine can be effective for moderate and severe pain, [1060] but it can cause myocardial depression and hypotension.

Meptazinol

Meptazinol is an investigational synthetic analgesic with opioid agonist-antagonist properties. Meptazinol has been reported to cause minimal respiratory depression because of its selectivity for mu_1 - (high-affinity) receptors. [1061] However, other investigators have found significant respiratory depression after meptazinol, as well as significant cholinomimetic effects. [1062] Controversy persists concerning the existence and significance of mu_1 -opiate receptors. Meptazinol has a rapid onset of action that lasts approximately 2 to 4 hours. There are conflicting reports concerning the efficacy of meptazinol as a postoperative analgesic. [1061] [1063] Meptazinol, 120 mg, is equianalgesic to 10 mg of morphine. Side effects (nausea and vomiting) after meptazinol increase with dosage and limit its ability to relieve severe pain. [1061]

OPIOID ANTAGONISTS

Naloxone

Opioid antagonists are essential tools in scientific evaluations of opiates and opiate receptors. [1064] Clinically, opioid antagonists are used to restore spontaneous ventilation in patients who breathe inadequately after opioid overdoses or opioid anesthesia. In addition, opioid antagonists can reduce or reverse opioid-induced nausea and vomiting, pruritus, urinary retention, rigidity, and biliary spasm associated with numerous therapies employing opioids, such as neuraxial analgesic techniques.

The most common side effects of opioids, administered by any route, are nausea, vomiting, and pruritus. These effects can be very disturbing to patients, as well as costly to treat. Numerous strategies utilizing antagonists or mixed agonist-antagonists have been employed in attempts to reduce or eliminate these side effects. In one study, it was suggested that low doses (0.25 mug/kg/h) of naloxone administered via continuous infusion reduced adverse effects associated with PCA analgesia with morphine. In addition, morphine requirements were significantly less in patients receiving naloxone, and the authors of the study concluded that naloxone enhanced analgesia. Proposed possible mechanisms for this apparent paradoxic effect of naloxone include enhanced release of endogenous opiates and opioid receptor upregulation. [26] There is great variability in the requirements and efficacies of opioid reversal agents when they are administered to reduce side effects. [1065]

Reversal of Respiratory Depression

In the early 1950s, nalorphine [1066] and levallorphan [1067] were evaluated as opioid antagonists. They were often found unacceptable because of a high incidence of side effects, as well as incomplete reversal. [1046] Naloxone was introduced into clinical practice in the late 1960s, and numerous studies demonstrated its efficacy as an antagonist of opioid-induced respiratory depression. Reports of side effects (increases in heart rate and blood pressure) and more serious complications (e.g., pulmonary edema) soon followed (Table 10-22) . [1068] [1069] [1070] [1071] [1072] [1073] [1074] [1075] [1076] Initial naloxone dose recommendations ranged from 0.4 to 0.8 mg. These high doses contribute to exaggerated cardiovascular responses after naloxone and are rarely necessary after anesthesia. Initial and required doses of naloxone in emergency room patients who present with possible opiate overdose may be 1 to 2 mg or more. If IV access is not available, naloxone, in doses similar to those

TABLE 10-22 -- Reported Severe Complications Following Naloxone Administration

AUTHOR	NALOXONE DOSE (IV, mg)	COMPLICATION
Azar [1068]	0.4	Hypertension (270/140)
Estilo [1069]	0.4	Hypertension (260/140); cerebrovascular accident
Flacke [1070]	0.4	Pulmonary edema
Tanaka [1071]	0.4	Hypertension (340/150)
Andree [1072]	0.4	Cardiac arrest, death
	0.4	Cardiac arrest, death
Prough [1073]	0.1	Pulmonary edema
	0.2 (+0.3 IM)	Pulmonary edema
Michaelis [1074]	0.1	Ventricular tachycardia, ventricular fibrillation
	0.4	Ventricular fibrillation
Partridge [1075]	0.08	Pulmonary edema
Taff [1076]	0.3	Pulmonary edema

given IV, is effectively absorbed after intratracheal administration. [1077]

Several mechanisms produce increases in arterial blood pressure, heart rate, and other significant hemodynamic alterations after naloxone reversal of opioids. These include pain, rapid awakening, and sympathetic activation not necessarily due to pain. Nausea and vomiting increase when opioid-induced analgesia is antagonized with naloxone. Naloxone administered by itself may not alter mean arterial pressure, heart rate, or plasma catecholamine concentrations in normotensive or hypertensive patients (not treated with clonidine) anesthetized without an opioid. [1078] However, Patschke et al [1079] showed that naloxone reversal of morphine in halothane-anesthetized dogs produces the same hemodynamic changes as it does in unanesthetized animals. These investigators reasoned that pain and awakening did not cause the increases in heart rate, blood pressure, left ventricular dP/dt, O_2 consumption, and coronary artery blood flow that were observed. They postulated that patients with coronary artery disease could be adversely affected by naloxone because of sympathetic activation.

Metabolic stress is also more likely when patients receiving naloxone for opioid agonist reversal are hypothermic. Shivering can occur, and O_2 consumption and minute ventilation can increase 2- to 3-fold. [1080] Such metabolic demands also stress the cardiovascular system, increasing cardiac output. [1081] In addition, greater degrees of hypercapnia at the time of opioid antagonism will result in greater degrees of cardiovascular stimulation because of associated sympathetic stimulation. Often, only modest levels of hypercapnia (P_{CO_2} 46-50 mm Hg) are required to allow for adequate ventilatory drive yet avoid excessive cardiovascular stimulation when opioid antagonism is carefully applied. Opioids decrease sympathetic outflow through their central (brain system and spinal) actions. [393] alpha-Adrenergic agonists (e.g., clonidine) and opioids decrease transmission through the same preganglionic sympathetic neurons. [1082] This mechanism may explain clonidine's effectiveness in blocking hemodynamic stimulation following naloxone reversal of fentanyl. [393] Naloxone also reverses clonidine-induced decreases in potent inhalation agent requirements. [1083] In addition, many hypertensive patients demonstrate reversal of the antihypertensive effects of clonidine by naloxone with concomitant increases in heart rates, peripheral vascular resistance, plasma renin activity, plasma epinephrine, and norepinephrine. [1084] Naloxone may also have a nonspecific analeptic effect through activation of a CNS arousal system. [1085] [1086]

Opioid reversal is perhaps best avoided in patients in whom increases in arterial blood pressure and heart rate could be detrimental. Although naloxone has been used safely in neuroanesthesia, [1087] significant increases in CBF and $CMRO_2$ can occur, [1088] and careful titration is required. Opioid reversal may be particularly

hazardous in patients with pheochromocytoma or chromaffin tissue tumors. [1089]

Onset of action of IV naloxone is rapid (1-2 min), and half-life and duration of effect are short, approximately 30 to 60 minutes. [1090] [1091] Naloxone is primarily metabolized in the liver via glucuronidation. Most often, 1.0 to 2.0 mug
kg^{-1} titrated in 0.5- to 1.0-mug
kg^{-1} boluses every 2 to 3 minutes will restore adequate spontaneous ventilation. [1053] Even smaller doses of naloxone may be adequate after alfentanil. Careful titration of naloxone may obviously not be appropriate if a patient is hypoxic.

Recurrence of respiratory depression after naloxone is due to the agent's short half-life as well as reuptake of opioid from peripheral compartment tissues (e.g., muscle) and other factors (see earlier). Attempts to compensate for naloxone's short duration of action by increasing the size of a single dose risk increasing the incidence and severity of unwanted side effects. "Renarcotization" occurs more frequently after the use of naloxone to reverse longer-acting opioids such as morphine. In these circumstances, an additional IM dose or continuous infusion of naloxone may be helpful. In the immediate postoperative setting, these modes of administering naloxone should not supplant good nursing care and attentive observations of respiratory function. Short-lasting opioids such as alfentanil rarely pose a danger of renarcotization, because of a rapid plasma decay curve, less chance of second plasma peaks due to reuptake of drug from peripheral tissues, and weak opiate receptor binding compared with fentanyl and sufentanil. [1092]

Although other agents (see under nalbuphine) may be somewhat better as antagonists, a rational use of reversal agents includes the following:

1. Use opioids in anesthesia so that reversal agents are rarely necessary.
2. Avoid intraoperative iatrogenic hypocapnia and posthyperventilation-hypoventilation syndrome so that body CO_2 stores are not be depleted and adequate ventilatory drive remains after anesthesia and surgery.
3. Carefully titrate opioid antagonists.
4. Avoid reversal agents in patients with severe or worrisome hypertension or cardiac or cerebrovascular disease.

Naloxone, although active at mu-, delta-, and kappa-receptors, has greatest affinity for mu-receptors, through which most potent opioid effects, including respiratory depression and analgesia, are mediated. Although it is unlikely that analgesia can always be spared following reversal of respiratory depression, careful titration of naloxone often can restore adequate spontaneous ventilation without reversal of adequate analgesia.

Naloxone: Other Applications

The potential roles of opioid receptor antagonists such as naloxone in disorders such as septic and hemorrhagic shock, alcoholism, and other conditions continue to be explored. Naloxone may be useful in the treatment of postanesthetic apnea in infants, even when exogenous opioids have not been administered. [1093] Primary apnea and periodic breathing associated with hypoxemia [1094] may also be ameliorated by naloxone; however, roles for opioid antagonists in other disorders of ventilatory control (e.g., sudden infant death syndrome) await definition. [1095] Naloxone does restore flow-resistive load compensation in patients with chronic obstructive pulmonary disease, [1096] and it may be beneficial in other forms of respiratory failure. [1097]

Alcohol interacts with many neurotransmitter systems, including the endogenous opioid peptide system. The mesolimbic dopamine system is central to drug-induced reward, and it has been suggested that alcohol-opioid system

links may play an important role in alcohol addiction. [1098] The frequency and severity of relapses in alcoholics have been demonstrated to be decreased by treatment with naltrexone, a long-acting opioid antagonist.

Although many conflicting reports and opinions exist, high doses of naloxone may reverse the effects of some nonopioid CNS depressants. [1099] Benzodiazepine reversal has been reported after naloxone and may be related to GABA receptor effects, a nonspecific analeptic effect, or reversal of concomitantly released endogenous opiates. Barbiturate and alcohol reversal have also been reported after naloxone. Certain metabolic products of alcohol (isoquinolines) have opioid-like actions and may account for this interaction. Opioid-GABA receptor interactions could also explain barbiturate antagonism. Naloxone may also partially antagonize ketamine and N_2O analgesia. The MAC of potent inhalational agents is unaffected by naloxone. However, pretreatment of rats with naloxone does counteract halothane-induced depression of sympathetic nerve activity, but interestingly, not halothane-induced analgesia. [1100]

Naloxone increases arterial blood pressure in laboratory animals, primates, and some patients in hypovolemic and septic shock. Purported mechanisms include centrally mediated increases in sympathetic tone and decreases in parasympathetic output and/or antagonism of endogenous opioids. [1101]

Naloxone may ameliorate the neurologic deficit following an ischemic or traumatic neurologic insult in animals. For example, hemorrhage-induced cerebral ischemia and SEP depression in the rat is reversed by naloxone, whereas CBF decreases are not. [1102] Such improvements in neurologic function, attributed to reversal of endogenous opiate effects, may underlie reported benefits. Results have not, however, been consistent, and further research is needed. [1101] Naloxone may also have a therapeutic role in heat stroke disorders, [1103] Alzheimer disease, schizophrenia, intractable pruritus, and thalamic pain syndrome.

Other Opioid Antagonists

New antagonists continue to be developed. [1104] [1105] However, the number of clinically available pure opioid receptor antagonists remains limited.

Naltrexone

Naltrexone is a mu-, delta-, and kappa-opioid receptor antagonist and provides two possible advantages when compared with naloxone. It is longer acting (plasma half-life of 8-12 versus 0.5-1.5 h), and it is active when taken orally. A single oral dose results in a constant plasma concentration for up to 24 hours. Naltrexone is not subject to as much first-pass hepatic metabolism as naloxone. Oral naltrexone (5-10 mg) reduces the frequency and severity of pruritus, nausea, and vomiting associated with epidural morphine without diminishing analgesia. [1106] Abboud et al [1107] found that 6 mg of naltrexone significantly reduces pruritus associated with epidural morphine and better preserves analgesia than 9 mg. Whether or not urinary retention or delayed respiratory depression can also be decreased or eliminated with naltrexone remains to be proven. Higher doses of naltrexone (e.g., 100 mg) are used to prevent opioid activity during maintenance treatment of opioid addicts. Naltrexone, like naloxone, can stimulate the cardiovascular system. [1108]

Nalmefene

Nalmefene is a pure opioid antagonist structurally similar to naloxone and naltrexone. Like naloxone and naltrexone, nalmefene has a greater preference for mu- than delta- or kappa- receptors, as demonstrated by IC_{50} studies. [1109] Nalmefene is long acting after oral (0.5-3.0 mg
kg^{-1}) and parenteral (0.2-2.0 mg
kg^{-1}) administration. It produces little effect when administered by itself. Duration of reversal of fentanyl and morphine-induced respiratory depression is dosedependent. [1110] [1111] Nalmefene is equipotent to naloxone. [1112] Reports of the plasma half-life for nalmefene range from 3 to 8 to 10 hours and reflect differences in doses studied and assay sensitivity. [1112] Bioavailability after oral administration is 40 to 50 percent, and peak plasma concentrations are reached in 1 to 2 hours. The drug undergoes hepatic metabolism and is excreted via the biliary and renal systems. Nalmefene's steady-state volume of distribution and elimination half-life are significantly increased in patients with renal failure because of decreased renal clearance. [1113]

/das/book/view/29494766/875/126.html

DRUG INTERACTIONS

General Principles

No one drug or agent produces optimal anesthetic conditions. At least two drugs are required. [884] [1114] Opioids are frequently combined with other anesthetic agents toward this end. However, the possibility of adverse drug interactions increases exponentially with the number of drugs a patient receives. In anesthesia, most drugs concomitantly administered interact. Some of these interactions are intentionally sought; others are unwanted and adverse.

There are three general types of mechanisms of drug interactions. [1115] Pharmaceutical-type interactions are chemical in nature, as illustrated when an alkaline solution of thiopental and an acidic solution of succinylcholine precipitate when simultaneously administered IV.

Pharmacokinetic-type interactions are probably commonplace in anesthesia. They occur when the administration of one agent alters the pharmacokinetics or disposition of another. Hemodynamic changes, for example, induced by one agent are likely to alter one or more factors that determine the pharmacokinetics of another agent. Sufentanil, which has a greater hepatic extraction ratio than alfentanil, is more likely to be affected by decreases in hepatic blood flow. Benzodiazepine administration can result in higher opioid plasma levels secondary to the pharmacokinetic consequences of decreased cardiac output. [1116] Opioid plasma levels also increase in the presence of propofol. [1117] Decreased opioid metabolism, by the CYP 3A4 isoform of the cytochrome P-450 enzyme responsible for the oxidative metabolism of more than 50 drugs, may underlie these effects, too. Liver enzyme induction, by substances such as alcohol, antiepileptics, and barbiturates, can also markedly alter the metabolism and disposition

of anesthetic agents, in particular midazolam. Enzyme inhibitors, such as erythromycin, may be more likely to prolong the action of alfentanil than sufentanil. [1115]

A third general mechanism underlying drug interactions is pharmacodynamic. Pharmacodynamic interactions can be adverse, such as when a patient experiences profound hypotension on receiving an opioid and a sedative-hypnotic for the induction of anesthesia. However, understanding and optimally using pharmacodynamic interactions is a cornerstone of clinical practice. Studies have quantified the pharmacodynamic interaction between opioids and inhalation anesthetics with classic MAC reduction evaluations in animals and humans (see earlier). Although marked synergism between opioids and inhalation agents occurs with analgesic doses of opioids, there is a ceiling effect to MAC reduction by opioids. The ceiling to opioid action with opioid- sedative-hypnotic interactions and synergism is much less apparent. Other evaluations of opioid-sedative-hypnotic interactions have focused primarily on suppression of somatic responses to surgery and optimizing recovery, with the aid of computer simulations. [853] [885]

The pharmacodynamic synergism between opioids and sedative-hypnotics such as propofol is profound. Thus, when combined, the amounts administered and the effect site concentrations needed for both agents are significantly reduced. Intuitively, and demonstrated in published studies, choosing an opioid with a short context-sensitive half-life allows greater doses of that opioid to be administered, along with reduced doses of propofol, without compromising the time for recovery from anesthesia. Thus, the optimal plasma level of propofol is estimated to be approximately 30 percent less when it is combined with remifentanil instead of alfentanil. [1117] When a potent opioid effect is sought, the use of remifentanil allows the greatest flexibility in opioid dosing without necessarily prolonging emergence.

Other questions remain to be addressed. For example, what drug dosing regimens and plasma concentrations of an opioid and a sedative-hypnotic will provide optimal hemodynamic control during a range of noxious stimuli? This is of particular interest especially when opioids are employed with the aim of providing hemodynamic control and stability. Complicating our understanding of drug interactions is the observation that the same degree of interaction does not apply across different types of stimuli.

Specific Agents

Sedative-Hypnotics

Benzodiazepines are potent anxiolytics and amnesics, and they produce few significant hemodynamic alterations when administered alone. They are considered by some to be the ideal agents to combine with opioids. Benzodiazepines potentiate the effects of opioids and decrease opioid requirements for loss of consciousness, often in a synergistic fashion. [1118] [1119] Not all benzodiazepine-opioid interactions are synergistic. On the contrary, antinociceptive interaction between these two types of drugs may be less than additive. [1120] [1121] Substantial or convincing proof of this in humans is, however, lacking. [1122] [1123] In addition, many studies reveal benzodiazepine-opioid interactions for many properties other than analgesia to be synergistic (supraadditive). [1124]

As reviewed previously, both the cardiovascular and respiratory actions of opioids can be significantly altered by the concomitant administration of benzodiazepines (Fig. 10-49) (Figure Not Available) . Combinations of benzodiazepines and opioids, although occasionally preserving ventricular function, [1125] can cause significant and occasionally profound decreases in

Figure 10-49 (Figure Not Available) Bar graph of the incidence of hypoxemia (Sp O_2 <90%) and apnea (no spontaneous respiratory effort for 15 sec) in healthy volunteers breathing room air who received 2 mug/kg fentanyl and/or 0.05 mg/kg midazolam intravenously. *(From Bailey et al [343])*

blood pressure, cardiac index, heart rates, and systemic vascular resistances. [9] [217] [1116] [1126] Sudden dramatic hypotension has been reported when midazolam and sufentanil are combined. [1127] [1128] In patients with poor left ventricular function, this drug regimen may be particularly hazardous. Some investigators have found IV lorazepam, if administered after tracheal intubation and high-dose fentanyl anesthesia, to cause less severe hemodynamic changes than other benzodiazepines. [1129] [1130] The slow onset of action of lorazepam may contribute to an apparent reduction of associated adverse hemodynamic effects. Other investigators have suggested that fluid loading may attenuate decreases in blood pressure, ventricular filling, and cardiac output that occur when benzodiazepines are combined with opioids. [1131]

Barbiturates, droperidol, ketamine, etomidate, and propofol are some of the other sedative-hypnotics combined with opioids. Either thiopental or propofol can be employed safely in combination with opioids. However, either drug can potentiate or produce hypotension if too large a dose is administered. This is true in healthy patients as well as in those with coronary artery disease. [1132] Hypotension after barbiturate-opioid combination is due to venodilatation and decreased cardiac filling. Other mechanisms include myo-cardial depression and decreased sympathetic nervous system activity. Attempts to ensure amnesia by combining barbiturates with

opioids can significantly compromise hemodynamic stability. [1132] [1133] Significantly reducing induction doses of barbiturate administered concomitantly with opioids is recommended.

The administration of propofol-opioid combinations is born of the same logic as benzodiazepine-opioid combinations: together they provide unconsciousness and block responses to noxious stimuli, whereas alone neither drug reliably does both. In addition, with the trend toward early tracheal extubation after cardiac surgery, short-acting agents such as propofol can be useful in cardiac anesthesia. Propofol does, however, produce significant cardiovascular depression that may not resolve immediately with decreasing blood drug levels. [1134] Initial reports of hypotension after anesthetic induction with propofol [1135] have been followed by investigations demonstrating minimal changes in blood pressure when propofol is administered via infusion. [1136]

Several clinical studies of cardiac anesthesia with propofol and moderate doses of opioids report favorable outcomes. [902] [924] [1137] [1138] [1139] [1140] [1141] [1142] Propofol-fentanyl [1138] and propofol-sufentanil [1143] anesthesia for coronary artery bypass surgery may provide acceptable conditions, but mean arterial pressure can decrease to levels that may jeopardize coronary perfusion, especially during the induction of anesthesia. [1138] When a propofol infusion is followed by opioid administration, mean arterial pressure and heart rate can decrease by as much as 35 and 16 percent, respectively. [1138] These changes can be associated with similar decreases in systemic vascular resistance and cardiac index. Comparisons of propofol-opioid anesthesia with potent inhaled agent-opioid anesthesia demonstrate that bolus induction doses, but not infusions, of propofol produce greater degrees of hypotension. [1143] [1144]

Other anesthetic induction agents such as etomidate and ketamine can be combined in low doses with opioids with little loss of cardiovascular stability. In patients scheduled for coronary artery bypass grafting, Haessler et al [1145] found etomidate (0.25 mg/kg) plus fentanyl (6 mug/kg) results in less hypotension after induction and intubation than propofol (1 mg/kg) plus fentanyl (6 mug/kg).

Inhaled Anesthetics

Cardiovascular function is frequently preserved during N_2O administration. However, decreases in cardiac output, heart rate and arterial pressure, as well as increases in pulmonary and systemic vascular resistance, can occur. [12] [328] [1146] [1147] Deterioration of cardiac function with N_2O-opioid combinations may be due to increases in afterload (systemic and pulmonary vascular resistance increases), [328] [1148] increases in coronary vascular resistance resulting in impaired coronary blood flow, [1149] lower inspired O_2 concentration associated with the use of N_2O, [1150] or direct myocardial depression. [1151] [1152] [1153] See Chapter 5 .

Other studies demonstrate that N_2O does not exacerbate myocardial ischemia. [1154] [1155] Myocardial dysfunction with N_2O may not be evident with routine monitoring, that is, blood pressure, because of the elevated systemic vascular resistance. [1156] Segmental wall motion abnormalities in areas of marginal myocardial perfusion can be demonstrated in animals when N_2O and opioids are combined. [1156] However, in clinical studies of patients with ischemic cardiac disease, the addition of N_2O to fentanyl or sufentanil is reported not to be associated with any new ST-segment changes or segmental wall motion abnormalities. [1157]

N_2O produces analgesia that is in part mediated through opioidergic systems. [1158] This may explain suggested infra-additive interactions between opioids and N_2O. In addition, N_2O is a weak amnesic, and its use is associated with nausea and vomiting. Combining N_2O with an opioid in a balanced technique may not best employ drug interaction synergism. Although amnesia and intraoperative conditions may be somewhat improved, N_2O does not produce any effects that are not already produced by either an opioid or a sedative-hypnotic. The advent of shorter-acting IV anesthetics, as well as volatile anesthetics with bloodgas partition coefficients equal to that of N_2O, has decreased the popularity of N_2O in balanced anesthesia.

Volatile anesthetics are frequently combined in low doses (one-third to one-half MAC) with opioids in order to ensure amnesia and to promote immobility and hemodynamic stability. Their intrinsic ability to produce cardiovascular depression in a dose-dependent manner often allows their titration toward these goals. [1143] [1159] With the exception of halothane, [1160] low concentrations of volatile anesthetics in combination with opioids are usually well tolerated in patients with normal, as well as compromised, ventricular function. [1159] The newer volatile anesthetics isoflurane, desflurane, and sevoflurane cause only modest myocardial depression at concentrations of less than 1 MAC. Low concentrations of isoflurane have also been effectively and safely used to treat intraoperative hypertension during high-dose sufentanil anesthesia for coronary artery surgery. [1161] [1162]

In general, clinical trials of opioids supplemented with newer volatile anesthetics for cardiac surgery demonstrate well-preserved cardiac output and minimal decreases in mean arterial blood pressure. [1139] [1142] [1163] [1164] The hemodynamic effects of combining opioids with modest doses of

these inhalational agents are usually additive and do not resemble the exaggerated effect on hemodynamics that has been described with agents such as the benzodiazepines. In addition, the added advantage of being able to remove, as well as to introduce, potent inhaled anesthetics results in greater flexibility and perhaps safety.

Myocardial ischemia may not, however, always be ameliorated by approaches that combine opioids with potent inhaled agents in spite of apparent "good" hemodynamic control. [1165] For example, adding halothane to a sufentanil (10-20 mug kg^{-1}) anesthetic to control increases in arterial blood pressure may produce hemodynamic alterations (decreased blood pressure, cardiac output) that exacerbate regional myocardial hypoperfusion and increase lactate production. [1166] In addition, undesirable cardiovascular depression can result from combining these agents. [1165]

Some of the potent inhaled anesthetics can increase sympathetic nervous system activity and may increase the risk of myocardial ischemia in the cardiac patient. For example, the administration of either desflurane or isoflurane can increase heart rate and mean arterial pressure during induction of anesthesia or with rapid increases in drug concentration. [1167] [1168] Theses findings are most pronounced with desflurane, but they can occur with isoflurane. Prior administration of fentanyl, in doses as low as 1.5 mug/kg, can markedly attenuate such responses (Fig. 10-50) (Figure Not Available) . [1167] Alfentanil (10 mug/kg) is also effective in attenuating these effects. [485]

Muscle Relaxants

Autonomic actions of muscle relaxants can alter hemodynamics unfavorably during opioid-based anesthesia (Ch. 12) . Pancuronium bromide has been frequently used for muscle relaxation during high-dose opioid anesthesia and has been reported to provide superior hemodynamics than vecuronium, [1169] metocurine, or metocurine-pancuronium combinations. [1170] The vagolytic actions of pancuronium tend to attenuate opioid-induced bradycardias and to support blood

Figure 10-50 (Figure Not Available) The effect of fentanyl, 1.5 and 4.5 mug/kg, in attenuating the increases in heart rate (HR) and mean arterial pressure (MAP) that are associated with a rapid change in the end-tidal desflurane concentration from 4 to 8 percent. Compared with control (without fentanyl), fentanyl significantly decreases these hyperdynamic responses. *(From Weiskopf et al [1167])*

pressure. [1171] However, other investigators have cautioned against using pancuronium because it can cause significant increases in heart rate and myocardial ischemia. [454] [1172] [1173] [1174] [1175] [1176] One study reported detecting no myocardial ischemia as assessed by transesophageal echocardiography after bolus injections of pancuronium in patients undergoing coronary artery bypass surgery, even though increases in heart rate, blood pressure and cardiac output occurred. [1177] Many factors alter the impact of pancuronium and other muscle relaxants on hemodynamics when combined with opioids: the dose, timing, and rate of administration of each relaxant as well as the premedication, intravascular volume, left ventricular function, and presence of other drugs with autonomic nervous system actions. [1178] For example, beta-adrenergic blockade often attenuates or eliminates significant pancuronium-induced tachycardias. [1172] [1179] [1180] [1181]

Vecuronium can potentiate decreases in heart rate and cardiac index after fentanyl, [1182] [1183] although alone it has minimal cardiovascular side effects. Combinations of vecuronium and high doses of opioids produce negative chronotropic and inotropic effects resulting in decreases in heart rate, cardiac output, and blood pressure

and increases in the need for vasopressor support. [1176] [1184] Stimuli enhancing vagal tone may also predispose patients to bradycardia after vecuronium. [1185]

O'Connor et al [1186] found that, compared with vecuronium (0.15 mg
kg^{-1}), pancuronium (0.15 mg
kg^{-1}) produced tachycardia more often (32 versus 7%) in patients undergoing coronary artery surgery. However, pancuronium-induced tachycardia was easily and rapidly treated and caused no differences in ischemia or perioperative myocardial infarction. Others have found more stable hemodynamics with vecuronium than pancuronium or atracurium during opioid anesthesia. [1175] Still other investigators have found no significant differences in the frequency of intraoperative ischemic events with pancuronium and vecuronium. [1181]

Metocurine (0.5 mg
kg^{-1}) alone has also been reported to produce less hemodynamic fluctuation [1187] than pancuronium during opioid anesthesia, although high doses (>0.3 mg
kg^{-1}) may cause hypotension. [1173] Combining metocurine and pancuronium has several advantages (e.g., increased speed of onset and less tachycardia and hypotension). [1173] [1175] [1188] Doxacurium causes no circulatory changes during sufentanilmidazolam anesthesia effects. [1189] Small decreases in blood pressure and heart rate were observed by Murray et al [1190] in healthy patients receiving doxacurium during balanced anesthesia with fentanyl (2-10 mug/kg). Opioid-based anesthesia does not reduce the ED [95] of doxacurium. [1191]

Pipecuronium, in doses as high as three times the ED [95] , has also been found to be devoid of circulatory actions in patients undergoing coronary artery bypass grafting surgery under midazolam-fentanyl anesthesia. [1192] Starr et al [1193] reported that neither pipecuronium nor vecuronium produced significant hemodynamic changes in such patients who were receiving sufentanil anesthesia. Opioid-based anesthesia does not affect the duration of action of pipecuronium. [1194]

Mivacurium chloride produces modest decreases in blood pressure when larger doses (e.g., twice ED_{95}) are injected rapidly (<30 s). [1195] [1196] This response likely results from histamine release. [1195] Few significant circulatory changes were associated with mivacurium (0.15-0.25 mg/kg over 60 s) in patients undergoing coronary artery bypass grafting surgery and receiving sufentanil-midazolam anesthesia. [1197] These changes were modest and were limited to decreases in heart rate and increases in stroke volume. Opioids do not affect the duration of action of mivacurium. [1198]

Miscellaneous

MAOI can underlie the most serious and potentially fatal opioid-other drug interaction. Although at times this warning was thought to pertain to all opioids, only meperidine is consistently implicated as capable of this severe interaction. [1199] [1200] MAO mediates norepinephrine turnover rate, and treatment with MAOI results in the accumulation of norepinephrine within the CNS. Indirect acting sympa- thomimetics can cause exaggerated norepinephrine release.

Meperidine-MAOI interactions are either excitatory or depressive. The former result in agitation, headache, hemodynamic instability, fever, rigidity, convulsions, and coma. This interaction is thought to be due to excessive central serotoninergic activity. Meperidine, but not morphine, blocks neuronal uptake of serotonin. The depressive form consists of respiratory depression, hypotension, and coma as a result of MAOI inhibition of hepatic microsomal enzymes and meperidine accumulation. [1200]

Treatment of these drug interaction syndromes is supportive. Opioid antagonism may be hazardous, especially in the excitatory form. Suggested therapeutic approaches include administering antipyretics, antihypertensive agents, sedatives, and steroids. [1200]

Although Ca^{2+} entry blockers (CEB) can significantly depress cardiac function and may cause regional wall motion abnormalities during potent inhalation anesthesia, opioid-CEB interactions are usually mild. Mean arterial pressure and cardiac function and conduction have been reported not to change appreciably in dogs when opioids and verapamil are combined. [1201] [1202] Diltiazem-fentanyl interactions in the dog, however, frequently result in hypotension and second-degree heart block. [1203] Regional systolic and diastolic cardiac dysfunction results from verapamil-fentanyl interactions if coronary blood flow is critically limited in the dog. [1204] Fentanyl anesthesia causes minimal decreases in cardiac index and only modest decreases in blood pressure and systemic vascular resistance in patients receiving verapamil. [1205] On the other hand, the presence of beta- adrenergic blockade, the quality of left ventricular function, and the presence of other anesthetics will influence the response to CEB. In addition, CEB have different profiles of effects and can result in persistent hypotension or unpredictable responses when used as an adjunct to opioid anesthesia for controlled hypotension. [1206] *N*-type CEB may also functionally interact with morphine at the level of the spinal cord to influence nociception. [1207]

Nitroglycerin is often used with high-dose opioid anesthesia to treat increases in blood pressure and ischemia. Nitroglycerin infusion during high-dose fentanyl anesthesia for coronary artery surgery has been reported to reduce ischemia by some investigators, [1208] but not others. [1209] These or larger doses of nitroglycerin can result in hypotension, tachycardia, and decreases in ventricular filling pressures.

Erythromycin can inhibit the metabolism of several compounds including theophylline and the histamine $_2$ blockers. It supposedly reduces the oxidizing activity of cytochrome P-450. Alfentanil, but not sufentanil, may have its action prolonged as a result of impaired metabolism in patients receiving erythromycin. [1210] [1211]

Cimetidine can prolong opioid effects by decreasing hepatic blood flow and/or diminishing hepatic metabolism. Ranitidine can also reduce hepatic blood flow but binds less to the cytochrome P-450 system and has less impact on opioid metabolism than cimetidine. [1212] Other drugs that inhibit certain cytochrome systems can increase endogenous morphine production from codeine. [979]

References

1. Foldes FF, Swerdlow M, Siker ES (eds): Narcotics and Narcotic Antagonists. Springfield, Ill, Charles C Thomas, 1964.

2. Smith RR: Scopolamine-morphine anesthesia, with report of two hundred and twenty-nine cases. Surg Gynecol Obstet 7:414, 1908.

3. Sexton JC: Death following scopolamine-morphine injection. Lancet Clin 55:582, 1905.

4. Lundy JS: Balanced anesthesia. Minn Med 9:399, 1926.

5. Neff W, Mayer EC, de la Luz Perales M: Nitrous oxide and oxygen anesthesia with curare relaxation. Calif Med 66:67, 1947.

6. Brownstein MJ: A brief history of opiates, opioid peptides, and opioid receptors. Proc Natl Acad Sci U S A 90:5391, 1993.

7. Holderness MC, Chase PE, Dripps RD: A narcotic analgesic and a butyrophenone with nitrous oxide for general anesthesia. Anesthesiology 24:336, 1963.

8. Lowenstein E, Hallowell P, Levine FH et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389, 1969.

9. Stanley TH, Webster LR: Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anaesthesia in man. Anesth Analg 57:411, 1978.

10. Arens JF, Benbow BP, Ochsner JL et al: Morphine anesthesia for aorto-coronary bypass procedures. Anesth Analg 51:901, 1972.

11. Stanley TH, Gray NJ, Staford W et al: The effects of high-dose morphine on fluid and blood requirements in open-heart operations. Anesthesiology 38:536, 1973.

12. Stoelting RK, Gibbs PS, Creasser CW et al: Hemodynamic and ventilatory response to fentanyl, fentanyl-droperidol, and nitrous oxide in patients with acquired valvular heart disease. Anesthesiology 42:319, 1975.

13. Lowenstein E: Morphine "anesthesia": A perspective. Anesthesiology 35:563, 1971.

14. Thompson WL, Walton RP: Elevation of plasma histamine levels in the dog following administration of muscle relaxants, opiates and macromolecular polymers. J Pharmacol Exp Ther 143:131, 1964.

15. Bedford RF, Wollman H: Postoperative respiratory effects of morphine and halothane anesthesia: A study in patients undergoing cardiac surgery. Anesthesiology 43:1, 1975.

16. Stanley TH, Lathrop GD: Urinary excretion of morphine during and after valvular and coronary-artery surgery. Anesthesiology 46:166, 1977.

17. Stanski DR, Hug CC Jr: Alfentanil: A kinetically predictable narcotic analgesic. Anesthesiology 57:435, 1982.

18. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 74:53, 1991.

19. Anand KJS, Philbin D, Hickey PR: Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 326:1, 1992.

20. Mangano DT, Siliciano D, Hollenberg M et al: Postoperative myo-cardial ischemia: Therapeutic trials using intensive analgesia following surgery. Anesthesiology 76:342, 1992.

21. Mora CT, Dudek C, Torjman MC et al: The effects of anesthetic technique on the hemodynamic response and recovery profile in coronary revascularizaton patients. Anesth Analg 81:900, 1995.

22. Slogoff S, Keats AS: Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 70:179, 1989.

23. Tuman KJ, McCarthy RJ, Spiess BD et al: Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 70:189, 1989.

24. Reisine T: Review: Neurotransmitter receptors. V. Neuropharmacology 34:463, 1995.

25. Woolf A: Immobilization of captive and free ranging white-tailed deer with etorphine hydrochloride. J Am Vet Med Assoc 156:636, 1970.

26. Gan TJ, Ginsberg B, Glass PSA et al: Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 87:1075, 1997.

27. Hoyer D, Boddeke HW: Partial agonists, full agonists, antagonists: Dilemmas of definition. Trends Pharmacol Sci 14:270, 1993.

28. Thorpe AH: Opiate structure and activity: A guide to understanding the receptor. Anesth Analg 63:143, 1984.

29. Snyder SH: Opiate receptors and internal opiates. Sci Am 236:44, 1977.

30. Beckett AH: Analgesics and their antagonists: Some steric and chemical considerations. I. The dissociation constants of some tertiary amines and synthetic analgesics, the conformations of methadone-type compounds. J Pharm Pharmacol 8:848, 1956.

31. Pasternak GW, Childers SR: Opiates, Opioid peptides and their receptors. In Shoemaker W (ed): Critical Care: State of the Art. Fullerton, Calif, Society of Critical Care Medicine, 1984, p 1.

32. Osei-Gyimah P, Archer S: Some 14-beta-substituted analogues of *N*-(cyclopropylmethyl)nor-morphine. J Med Chem 24:212, 1981.

33. Portoghese PS, Alreja BD, Larson DL: Allylprodine analogues as receptor probes. Evidence that phenolic and nonphenolic ligands interact with different subsites on identical opioid receptors. J Med Chem 24:782, 1981.

34. Gorin FA, Balasubramanian TM, Cicero TJ et al: Novel analogues of enkephalin: Identification of functional groups required for biological activity. J Med Chem 23:113, 1980.

35. Pert CB, Snyder SH: Opiate receptor: Demonstration in nervous tissue. Science 179:1011, 1973.

36. Terenius L: Characteristics of the "receptor" for narcotic analgesics in synaptic plasma membrane fractions from rat brain. Acta Pharmacol Toxicol 13:377, 1973.

37. Simon EJ, Hiller JM, Edelman I: Stereospecific binding of the potent narcotic analgesia [3H]-etorphine to rat-brain homogenate. Proc Natl Acad Sci U S A 70:1947, 1973.

38. Martin WR, Eades CG, Thompson JA et al: The effects of morphine- and nalorphine-like drugs in the nondependent and morphinedependent chronic spinal dog. J Pharmacol Exp Ther 197:517, 1976.

39. Atcheson: Update on opioid receptors. Br J Anaesth 73:132, 1994.

40. Creese I, Snyder SH: Receptor binding and pharmacological activity of opiates in the guinea pig ileum intestine. J Pharmacol Exp Ther 194:205, 1975.

41. Sora I, Takahashi N, Funada M et al: Opiate receptor knockout mice define mu receptor roles in endogenous nociceptive responses and morphine-induced analgesia. Proc Natl Acad Sci U S A 94:1544, 1997.

42. Pasternak GW, Snyder SH: Identification of novel high affinity opiate receptor binding in rat brain. Nature 253:563, 1975.

43. Wolozin BL, Pasternak GW: Classification of multiple morphine and enkephalin binding sites in the central nervous system. Proc Natl Acad Sci U S A 78:6181, 1981.

44. Ling GSF, Pasternak GW: Spinal and supraspinal analgesia in the mouse: The role of subpopulations of opioid binding sites. Brain Res 271:152, 1983.

45. Kuhar MJ, Pert CB, Snyder SH: Regional distribution of opiate receptor binding in monkey and human brain. Nature 245:447, 1973.

46. Pick CG, Paul D, Pasternak GW: Nalbuphine, a mixed kappa $_1$ and kappa$_3$ analgesic in mice. J Pharmacol Exp Ther 262:1044, 1992.

47. Pleuvry BJ: Opioid receptors and their ligands: Natural and unnatural. Br J Anaesth 66:370, 1991.

48. Kanjhan R: Opioids and pain. Clin Exp Pharmacol Physiol 22:397, 1995.

49. Gutstein HB, Ribue EA, Mansour A et al: Opioid effects on mitogen-activated protein kinase signaling cascades. Anesthesiology 87:1118, 1997.

50. Wandless AL, Smart D, Lambert DG: Fentanyl increases intracellular Ca $^{2+}$ concentrations in SH-SY5y cells. Br J Anaesth 76:461, 1996.

51. Minami M, Satoh M: Molecular biology of the opioid receptors: Structures, functions and distributions. Neurosci Res 23:121, 1995.

52. Mansour A: Opioid-receptor distribution. Trends Neurosci 18:24, 1995.

53. Goldstein A: Opiate receptors. Life Sci 14:615, 1974.

54. Snyder SH: Opiate receptors in the brain. N Engl J Med 296:266, 1977.

55. Mayer DJ, Wolfle TL, Akil H et al: Analgesia from electrical stimulation in the brainstem of the rat. Science 174:1351, 1971.

56. Fields HL: Brainstem mechanisms of pain modulation: Anatomy and physiology. In Herz A (ed): Opioids II: Handbook of Experimental Pharmacology. Berlin, Springer-Verlag, 1993, p 3.

57. Dickenson AH: Spinal cord pharmacology of pain. Br J Anaesth 75:193, 1995.

58. Yaksh TL, Rudy TA: Studies on the direct spinal action of narcotics in the production of analgesia in the rat. J Pharmacol Exp Ther 202:411, 1977.

59. Chang HM, Berde CB, Holz GG et al: Sufentanil, morphine, met-enkephalin, and kappa-agonist (U-50, 488H) inhibit substance P release from primary sensory neurons: A model for presynaptic spinal opioid actions. Anesthesiology 70:672, 1989.

60. Stein C: The control of pain in peripheral tissue by opioids. N Engl J Med 332:1685, 1995.

61. Heard SO, Edwards WT, Ferrari D et al: Analgesic effect of intraarticular bupivacaine or morphine after arthroscopic knee surgery: A randomized prospective, double-blind study. Anesth Analg 74:822, 1992.

62. Picard PR, Tramer MR, McQuay HJ et al: Analgesic efficacy of peripheral opioids (all except intra-articular): A qualitative systematic review of randomised controlled trials. Pain 72:309, 1997.

63. Frank GB: Stereospecific opioid drug receptors on excitable cell membranes. Can J Physiol Pharmacol 63:1023, 1985.

64. Jaffe RA, Rowe MA: A comparison of the local anesthetic effects of meperidine, fentanyl, and sufentanil on dorsal root axons. Anesth Analg 83:776, 1996.

65. Althaus JS, Miller ED, Moscicki JC et al: Analgetic contribution of sufentanil during halothane anesthesia: A mechanism involving serotonin. Anesth Analg 64:857, 1985.

66. Stone DJ, DiFazio CA: Anesthetic action of opiates: Correlations of lipid solubility and spectral edge. Anesth Analg 67:663, 1988.

67. Bovill JG: Mechanisms of actions of opioids and non-steroidal anti-inflammatory drugs. Eur J Anaesthesiol 14:9, 1997.

68. Gies EK, Peters DM, Gelb CR et al: Regulation of mu opioid receptor mRNA levels by activation of protein kinase c in human SH-SY5Y neuroblastoma cells. Anesthesiology 87:1127, 1997.

69. Christie MJ, Williams JT, North RA: Cellular mechanisms of opioid tolerance: Studies in simple brain neurons. Mol Pharmacol 32:633, 1987.

70. Boas RA, Villiger JW: Clinical actions of fentanyl and buprenorphine: The significance of receptor binding. Br J Anaesth 57:192, 1985.

71. Pasternak GW, Zhang AZ, Tecott L: Developmental differences between high and low affinity opiate binding sites: Their relationship to analgesia and respiratory depression. Life Sci 27:1185, 1980.

72. Agnati LF, Fuxe K, Benfenati F et al: Studies on aging processes. III. Acta Physiol Scand 532:45, 1984.

73. Parratt JR: Opioid receptors in the cardiovascular system. In van Zwielen P, Schonbaum E (eds): Progress in Pharmacology. Stuttgart, Gustav Fischer, 1986.

74. Hughes J, Smith TW, Kosterlitz HW et al: Identification of two related pentapeptides from the brain with potent opiate agonist activity. Nature 258:577, 1975.

75. Cox BM, Opheim KE, Teschemaker H et al: A peptide-like substance from pituitary that acts like morphine: Purification and properties. Life Sci 16:1777, 1975.

76. Goldstein A, Fischli W, Lowney LI et al: Porcine pituitary dynorphin: Complete amino acid sequence of the biologically active heptadecapeptide. Proc Natl Acad Sci U S A 78:7219, 1981.

77. Mains RE, Eipper BA, Ling N: Common precursor to corticotropins and endorphins. Proc Natl Acad Sci U S A 74:3014, 1977.

78. Gubler U, Kilpatrick DL, Seeburg PH et al: Detection and partial characterization of proenkephalin in mRNA. Proc Natl Acad Sci U S A 78:5484, 1981.

79. Olson GA, Olson RD, Kastin AJ et al: Endogenous opiates: 1980.Peptides 2:349, 1981.

80. Rossier J, Vargo TM, Minick S et al: Regional dissociation of betaendorphin and enkephalin contents in rat brain and pituitary. Proc Natl Acad Sci U S A 74:5162, 1977.

81. Orwall ES, Kendall JW: B-endorphin and ACTH in extra-adrenocorticotropin pituitary sites: Gastrointestinal tract. Endocrinology 107:438, 1980.

82. Houck JC, Kimball C, Chang C et al: Placental beta-endorphin-like peptides. Science 207:78, 1980.

83. Florez J, Hurle MA, Mediavilla A: Respiratory responses to opiates applied to the medullary ventral surface. Life Sci 31:2189, 1977.

84. Paquette NC, Young GA: Relationship between regulation of morphine-induced EEG effects and changes in naloxone sensitivity. Eur J Pharmacol 196:61, 1991.

85. Simonato M, Romualdi P: Dynorphin and epilepsy. Prog Neurobiol 50:557, 1996.

86. Rochford J, Godin C, Henry JL: Intrathecal administration of dynorphin A and its fragments increase heart rate and arterial pressure in the urethane anesthetized rat: Mediation by a nonopioid mechanism. Brain Res 565:67, 1991.

87. Bach FW: beta-endorphin in the brain: A role in nociception. Acta Anaesthesiol Scand 41:133, 1997.

88. Santiago TV, Edelman NH: Opioids and breathing. J Appl Physiol 59:1675, 1985.

89. Tuggle DW, Horton JW: Cardiocirculatory effects of physiological doses of beta-endorphin. Circ Shock 18:215, 1986.

90. Shook JE, Watkins WD, Camporesi EM: Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. Am Rev Respir Dis 142:895, 1990.

91. Florez J, Hurle MA: Opioids in respiration and vomiting. In Herz A (ed): Opioids II: Handbook of Experimental Pharmacology. Berlin, Springer-Verlag, 1993, p 263.

92. Sher L: The placebo effect on mood and behavior: The role of the endogenous opioid system. Med Hypotheses 48:347, 1997.

93. Millan MJ: Multiple opioid systems and pain. Pain 27:303, 1986.

94. Akil H, Watson SJ, Young E et al: Endogenous opioids: Biology and function. Annu Rev Neurosci 7:223, 1984.

95. Veselis RA, Reinsel RA, Feshchenko VA et al: The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. Anesthesiology 87:749, 1997.

96. Veselis RA, Reinsel RA, Feshchenko VA et al: Impaired memory and behavioral performance with fentanyl at low plasma concentrations. Anesth Analg 79:952, 1994.

97. Lowenstein E, Philbin D: Narcotic "anesthesia" in the eighties (editorial). Anesthesiology 55:195, 1981.

98. Hug CC Jr: Does opioid "anesthesia" exist? (editorial). Anesthesiology 73:1, 1990.

99. Philbin DM, Rosow CE, Schneider RC et al: Fentanyl and sufentanil anesthesia revisited: How much is enough? Anesthesiology 73:5, 1990.

100. Hilgenberg JC: Intraoperative awareness during high-dose fentanyl-oxygen anesthesia. Anesthesiology 54:341, 1981.

101. Mummanemi N, Rao T, Montoya A: Awareness and recall with high-dose fentanyl oxygen anesthesia. Anesth Analg 59:943, 1980.

102. Michelsen LG, Salmenpera M, Hug CC Jr et al: Anesthetic potency of remifentanil in dogs. Anesthesiology 84:865, 1996.

103. Hecker BR, Lake CL, DiFazio CA et al: The decrease of the minimum alveolar anesthetic concentration produced by sufentanil in rats. Anesth Analg 62:987, 1983.

104. Steffey EP: Isoflurane-sparing effect of fentanyl in swine. Anesthesiology 83:446, 1995.

105. Hall RI, Szlam F, Hug CC Jr: The enflurane-sparing effect of alfentanil in dogs. Anesth Analg 66:1287, 1987.

106. Arndt JO, Mikat M, Parasher C: Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. Anesthesiology 61:355, 1984.

107. Bailey PL, Port DJ, McJames S et al: Is fentanyl an anesthetic in the dog? Anesth Analg 66:542, 1987.

108. Nussmeier NA, Benthuysen JL, Steffey EP et al: Cardiovascular, respiratory, and analgesic effects of fentanyl in unanesthetized rhesus monkeys. Anesth Analg 72:221, 1991.

109. Bowdle TA, Ward RJ: Induction of anesthesia with small doses of sufentanil or fentanyl: Dose versus EEG response, speed of onset and thiopental requirement. Anesthesiology 70:26, 1989.

110. Kissin I, Vinik HR, Castillo R et al: Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. Anesth Analg 71:65, 1990.

111. McEwan AI, Smith C, Dyar O et al: Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology 78:864, 1993.

112. Glass PSA, Gan TJ, Howell S et al: Drug interactions: Volatile anesthetics and opioids. J Clin Anesth 9:18S, 1997.

113. Streisand JB, Bailey PL, LeMaire L et al: Fentanyl-induced rigidity and unconsciousness in human volunteers. Anesthesiology 78:629, 1993.

114. McDonnell TE, Bartkowski RR, Williams JJ: ED_{50} of alfentanil for induction of anesthesia in unpremedicated young adults. Anesthesiology 60:136, 1984.

115. Dundee JW, Nichol RM, Black GW: Alterations in response to somatic pain associated with anesthesia. X. Further studies with inhalation agents. Br J Anaesth 34:158, 1962.

116. Dodson BA, Miller KW: Evidence of a dual mechanism in the anesthetic action of an opioid peptide. Anesthesiology 62:615, 1985.

117. Aitkenhead AR: Awareness during anaesthesia: When is an anaesthetic not an anaesthetic? Can J Anaesth 43:206, 1996.

118. Levinson BW: States of awareness during general anesthesia. Br J Anaesth 37:544, 1965.

119. Bennett HL, Davis HS, Giamnini JA: Non-verbal response to intraoperative conversation. Br J Anaesth 57:174, 1985.

120. Jones JG: Use of evoked responses in EEG to measure depth of anesthesia. In Lunn J, Rosen M (eds): Consciousness, Awareness and Pain in General Anesthesia. Boston, Butterworth, 1987, p 99.

121. Heier T, Steen PA: Awareness in anaesthesia: Incidence, consequences and prevention. Acta Anaesthesiol Scand 40:1073, 1996.

122. Ghoneim MM, Block RI: Learning and memory during general anesthesia. Anesthesiology 87:387, 1997.

123. Ghoneim MM, Block RI: Learning and consciousness during general anesthesia. Anesthesiology 76:2795, 1992.

124. Ghoneim MM, Dhanaraj J, Choi WW: Comparison of four opioid analgesics as supplements to nitrous oxide anesthesia. Anesth Analg 63:405, 1984.

125. Heier T, Steen PA: Assessment of anaesthesia depth. Acta Anaesthesiol Scand 40:1087, 1996.

126. Schneider G, Sebel PS: Monitoring depth of anaesthesia. Eur J Anaesth 14:21, 1997.

127. Sebel PS, Lang E, Rampil IJ et al: A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg 84:891, 1997.

128. Siebert BS, Rosow CE, Keegan CR et al: The effect of diazepam on induction of anesthesia with alfentanil. Anesth Analg 67:717, 1986.

129. Mark JB, Greenberg LM: Intraoperative awareness and hypertensive crisis during high-dose fentanyl-diazepam-oxygen anesthesia. Anesth Analg 62:698, 1983.

130. Blacher RS: On awakening paralyzed during surgery: A syndrome of traumatic neurosis. JAMA 234:67, 1975.

131. Sebel PS, Bovill JG, Wauquier A et al: Effects of high dose fentanyl anesthesia on the electroencephalogram. Anesthesiology 55:203, 1981.

132. Chi OZ, Sommer W: Power spectral analysis of EEG during sufentanil infusion in humans. Can J Anaesth 38:275, 1991.

133. Gambus PL, Gregg KM, Shafer SL: Validation of the alfentanil canonical univariate parameter as a measure of opioid effect on the electroencephalogram. Anesthesiology 83:747, 1995.

134. Freeman J, Ingvar DH: Effects of fentanyl on cerebral cortical blood flow and EEG in the cat. Acta Anaesthesiol Scand 11:381, 1967.

135. Ghoneim MM, Mewaldt SP, Thatcher JW: The effect of diazepam and fentanyl on mental, psychomotor and electroencephalographic functions and their rate of recovery. Psychopharmacologia (Berl) 44:61, 1975.

136. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 240:159, 1987.

137. Matteo RS, Ornstein E, Schwartz AE et al: Effects of low-dose sufentanil on the EEG: Elderly vs. young. Anesthesiology 65:A553, 1986.

138. Zurick AM, Khoury GF, Estafanous FG et al: Sufentanil requirement of surgical anesthesia (as determined by EEG) and its effect on awakening time. Anesth Analg 62:292, 1983.

139. Smith NT, Dec-Silver H, Sanford TJ et al: EEGs during high-dose fentanyl-, sufentanil-, or morphine-oxygen anesthesia. Anesth Analg 63:386, 1984.

140. Bovill JG, Sebel PS, Wauquier A et al: Influence of high-dose alfentanil anaesthesia on the electroencephalogram: Correlation with plasma concentrations. Br J Anaesth 55:199S, 1983.

141. Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234, 1985.

142. Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioid effect: Comparative pharmacodynamics of fentanyl and sufentanil. Anesthesiology 74:34, 1991.

143. Egan TD, Minto CF, Hermann DJ et al: Remifentanil versus alfentanil: Comparative pharmacokinetics and pharmacodynamics. Anesthesiology 84:821, 1996.

144. Westmoreland CL, Sebel PS, Gropper A: Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients. Anesth Analg 78:23, 1994.

145. Glass PSA, Doherty MA, Jacobs JR et al: CP_{50} for sufentanil. Anesthesiology 73:A378, 1990.

146. Westmoreland CW, Sebel PS, Gropper A et al: Reduction of isoflurane MAC by fentanyl or alfentanil. Anesthesiology 77:A394, 1992.

147. Kapila A, Lang E, Glass P et al: MAC reduction of isoflurane by remifentanil. Anesthesiology 81:A378, 1994.

148. Brunner MD, Braithwaite P, Jhaveri R: MAC reduction of isoflurane by sufentanil. Br J Anaesth 72:42, 1994.

149. Lemmens HJM, Dyck JB, Shafer SL et al: Pharmacokineticpharmacodynamic modeling in drug development: Application to the investigational opioid trefentanil. Clin Pharmacol Ther 56:261, 1994.

150. Cambareri JJ, Afifi MS, Glass PSA et al: A-3665, a new short-acting opioid: A comparison with alfentanil. Anesth Analg 76:812, 1993.

151. Long CW, Shah NK, Loughlin C et al: A comparison of EEG determinants of near-awakening from isoflurane and fentanyl anesthesia: Spectral edge, median power frequency, and delta ratio. Anesth Analg 69:169, 1989.

152. Egan TD, Miur KT, Stanski DR et al: The EEG versus clinical measures of opioid potency: Defining the EEG-clinical potency. Anesthesiology 85:A349, 1996.

153. Kalkman CJ, Rheineck AR, Bovill JG: Influence of high-dose opioid anesthesia on posterior tibial nerve somatosensory cortical evoked potentials: Effects of fentanyl, sufentanil, and alfentanil. J Cardiothorac Anesth 2:758, 1998.

154. Pathak KS, Brown RH, Cascorbi HF et al: Effects of fentanyl and morphine on intraoperative somatosensory cortical-evoked potentials. Anesth Analg 63:833, 1984.

155. van Rheineck Leyssius A, Kalkman C, Hesselink E et al: Effects of high dose fentanyl anesthesia on posterior tibial nerve somatosensory evoked potentials. Anesth Analg 66:S183, 1987.

156. McPherson RW, Sell B, Traystman RJ: Effects of thiopental, fentanyl, and etomidate on upper extremity somatosensory evoked potentials in humans. Anesthesiology 65:584, 1986.

157. McPherson RW, Mahla M, Johnson R et al: Effects of enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials during fentanyl anesthesia. Anesthesiology 62:626, 1985.

158. Schubert A, Drummond JC, Peterson DO et al: The effect of high-dose fentanyl on human nerve somato-sensory-evoked responses. Can Anaesth Soc J 34:35, 1987.

159. Koht A, Schutz W, Schmidt G et al: Effects of etomidate, midazolam, and thiopental on median nerve somatosensory evoked potentials and the additive effects of fentanyl and nitrous oxide. Anesth Analg 67:435, 1988.

160. Kalkman CJ, Traast H, Zuurmond WWA et al: Differential effects of propofol and nitrous oxide on posterior tibial nerve somatosensory cortical evoked potentials during alfentanil anaesthesia. Br J Anaesth 66:483, 1991.

161. Kimovec MA, Koht A, Sloan TB: Effects of sufentanil on median nerve somatosensory evoked potentials. Br J Anaesth 65:169, 1990.

162. Grundy BL: Fentanyl alters somatosensory cortical evoked potentials. Anesth Analg 59:544, 1980.

163. Koht A, Kimovec MA, Sloan TB et al: The effects of sufentanil on median nerve somatosensory evoked potentials. Anesth Analg 65:S81, 1986.

164. Sebel PS, De Bruijn N, Jacobs J et al: Median nerve somatosensory evoked potentials during anesthesia with sufentanil or fentanyl. Anesthesiology 69:A312, 1988.

165. Crabb I, Thornton C, Konieczko KM et al: Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anesthesia in a dose-dependent manner. Br J Anaesth 76:795,

1996.

166. Samra SK, Lilly DJ, Rush NL et al: Fentanyl anesthesia and human brain-stem auditory evoked potentials. Anesthesiology 61:261, 1984.

167. Samra SK, Krutak-Krol H, Pohorecki R et al: Scopolamine, morphine, and brain-stem auditory evoked potentials in awake monkeys. Anesthesiology 62:437, 1985.

168. Hyman SA, Berman ML, Bullington JC et al: Brainstem auditory evoked potentials during balanced anesthesia with a sufentanil infusion. Anesth Analg 66:S85, 1987.

169. Chi OZ, Ryterband S, Field C: Visual evoked potentials during thiopentone-fentanyl-nitrous oxide anaesthesia in humans. Can J Anaesth 36:637, 1989.

170. Schwender D, Weninger E, Daunderer M et al: Anesthesia with increasing doses of sufentanil and midlatency auditory evoked potentials in humans. Anesth Analg 80:499, 1995.

171. Rossberg M, Armstead W: The role of cyclic nucleotides in vasopressin-induced pial artery dilation and opioid release. Anesthesiology 85:A558, 1996.

172. Thorogood MC, Armstead WM: Influence of polyethylene glycol superoxide dismutase/catalase on altered opioid-induced pial artery dilation after brain injury. Anesthesiology 84:614, 1996.

173. Wahl M: Effects of enkephalins, morphine, and naloxone on pial arteries during perivascular microapplication. J Cereb Blood Flow Metab 5:451, 1985.

174. Hoehner PJ, Whitson JT, Kirsch JR et al: Effect of intracarotid and intraventricular morphine on regional cerebral blood flow and metabolism in anesthetized dogs. Anesthesiology 71:A146, 1989.

175. Carlsson C, Smith DS, Keykhah M et al: The effects of high dose fentanyl on cerebral circulation and metabolism in rats. Anesthesia 57:375, 1982.

176. Monitto CL, Kurth CD: The effect of fentanyl, sufentanil, and alfentanil on cerebral arterioles in piglets. Anesth Analg 76:985, 1993.

177. Milde LN, Milde JH, Gallagher WJ: Cerebral effects of fentanyl in dogs. Br J Anaesth 63:710, 1989.

178. Yaster M, Koehler RC, Traystman RJ: Effects of fentanyl on peripheral and cerebral hemodynamics in neonatal lambs. Anesthesiology 66:524, 1987.

179. McPherson RW, Traystman RJ: Fentanyl and cerebral vascular responsivity in dogs. Anesthesiology 60:180, 1984.

180. Adler LJ, Gyulai FE, Diehl DJ et al: Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. Anesth Analg 84:120, 1997.

181. Young WL, Prohovnik I, Correll JW et al: Cerebral blood flow and metabolism in patients undergoing anesthesia for carotid endarterectomy. Anesth Analg 68:712, 1989.

182. Shah N, Long C, Marx W et al: Cerebrovascular response to CO_2 in edematous brain during either fentanyl or isoflurane anesthesia. J Neurosurg Anesth 2:11, 1990.

183. Cold GE, Christensen KJS, Nordentoft J et al: Cerebral blood flow, cerebral metabolic rate of oxygen and relative CO_2 reactivity during neurolept anaesthesia in patients subjected to craniotomy for supratentorial cerebral tumors. Acta Anaesthesiol Scand 32:310, 1988.

184. Vernhiet J, Renou AM, Orgogozo JM et al: Effects of diazepamfentanyl mixture on cerebral blood flow and oxygen consumption in man. Br J Anaesth 50:165, 1978.

185. Keykhah MM, Smith DS, Carlsson C et al: Influence of sufentanil on cerebral metabolism and circulation in the rat. Anesthesiology 63:274, 1985.

186. Werner C, Hoffman WE, Baughman VL et al: Effects of sufentanil on cerebral blood flow, cerebral blood flow velocity, and metabolism in dogs. Anesth Analg 72:177, 1991.

187. Milde LN, Milde JH, Gallagher WJ: Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg 70:138, 1990.

188. Bunegin L, Albin MS, Ernst PS et al: Cerebrovascular responses to sufentanil citrate (SC) in primates with and without intracranial hypertension. Anesth Analg 70:S42, 1990.

189. Trindle MR, Dodson BA, Rampil IJ: Effects of fentanyl versus sufentanil in equianesthetic doses on middle cerebral artery blood flow velocity. Anesthesiology 78:454, 1993.

190. Mayer N, Weinstabl C, Podreka I et al: Sufentanil does not increase cerebral blood flow in healthy human volunteers. Anesthesiology 73:240, 1990.

191. Young WL, Prohovnik I, Correll JW et al: A comparison of the cerebral hemodynamic effects of sufentanil and isoflurane in humans undergoing carotid endarterectomy. Anesthesiology 71:863, 1989.

192. Werner C, Kochs E, Bause H et al: Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. Anesthesiology 83:721, 1995.

193. Hoffman WE, Cunningham F, James MK et al: Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. Anesthesiology 79:107, 1993.

194. Mayberg TS, Lam AM, Eng CC et al: The effect of alfentanil on cerebral blood flow velocity and intracranial pressure during isoflurane-nitrous oxide anesthesia in humans. Anesthesiology 78:288, 1993.

195. Baker KZ, Ostapkovich N, Sisti MB et al: Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia. J Neurosurg Anesthesiol 9:134, 1997.

196. Maekawa T, Tommasino C, Shapiro HM: Local cerebral blood flow with fentanyl-induced seizures. J Cereb Blood Flow Metab 4:88, 1984.

197. Kofke WA, Garman RH, Tom WC et al: Alfentanil-induced hypermetabolism, seizure, and histopathology in rat brain. Anesth Analg 75:953, 1992.

198. Warner DS, Hindman BJ, Todd MM et al: Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. Anesth Analg 83:348, 1996.

199. Jamali S, Ravussin P, Archer D et al: The effects of bolus administration of opioids on cerebrospinal fluid pressure in patients with supratentorial lesions. Anesth Analg 82:600, 1996.

200. Lauer KK, Connolly LA, Schmeling WT: Opioid sedation does not alter intracranial pressure in head injured patients. Can J Anaesth 44:929, 1997.

201. Marx W, Shah N, Long C et al: Sufentanil, alfentanil, and fentanyl: Impact on cerebrospinal fluid pressure in patients with brain tumors. J Neurosurg Anesth 1:3, 1989.

202. Jung R, Shah N, Reinsel R et al: Cerebrospinal fluid pressure in patients with brain tumors: Impact of fentanyl versus alfentanil during nitrous oxide-oxygen anesthesia. Anesth Analg 71:419, 1990.

203. Markovitz BP, Duhaime A-C, Sutton L et al: Effects of alfentanil on intracranial pressure in children undergoing ventriculoperitoneal shunt revision. Anesthesiology 76:71, 1992.

204. Sperry RJ, Bailey PL, Reichman MV et al: Fentanyl and sufentanil increase intracranial pressure in head trauma patients. Anesthesiology 77:416, 1992.

205. Knuttgen D, Doehn M, Eymer D et al: Fentanyl-induced increase in intracranial pressure. Anaesthesist 38:73, 1989.

206. Weinstabl C, Mayer N, Richling B et al: Effect of sufentanil on intracranial pressure in neurosurgical patients. Anaesthesia 46:837, 1991.

207. Benthuysen JL, Kien ND, Quam DD: Intracranial pressure increases during alfentanil-induced rigidity. Anesthesiology 68:438, 1988.

208. Artru AA: Effects of halothane and fentanyl anesthesia on resistance to reabsorption of CSF. J Neurosurg 60:252, 1984.

209. Artru AA: Effect of halothane and fentanyl on the rate of CSF production in dogs. Anesth Analg 62:581, 1983.

210. Herrick IA, Gelb AW, Manninen P et al: Effects of fentanyl, sufentanil, and alfentanil on brain retractor pressure. Anesth Analg 72:359, 1991.

211. Baskin DS, Widmayer MA, Browning JL et al: Evaluation of delayed treatment of focal cerebral ischemia with three selective kappa-opioid agonists in cats. Stroke 25:2047, 1994.

212. Takahashi H, Traystman RJ, Hashimoto J et al: Postischemic brain injury is affected stereospecifically by pentazocine in rats. Anesth Analg 85:353, 1997.

213. Cole DJ, Drummond JC, Shapiro HM et al: The effect of fentanyl anesthesia and intrathecal naloxone on neurologic outcome following spinal cord injury in the rat. Anesthesiology 71:426, 1989.

214. Cole DJ, Shapiro HM, Drummond JC et al: Halothane, fentanyl/ nitrous oxide, and spinal lidocaine protect against spinal cord injury in the rat. Anesthesiology 70:967, 1989.

215. Corssen G, Domino EF, Sweet RB: Neuroleptanalgesia and anesthesia. Anesth Analg 43:748, 1964.

216. Grell FL, Koons DA, Denson JS: Fentanyl in anesthesia: A report of 500 cases. Anesth Analg 49:523, 1970.

217. Bailey PL, Wilbrink J, Zwanikken P et al: Anesthetic induction with fentanyl. Anesth Analg 64:48, 1985.

218. Gergis SD, Hoyt JL, Sokoll MD: Effects of Innovar and Innovar plus nitrous oxide on muscle tone and "H" reflex. Anesth Analg 50:743, 1971.

219. Sokoll MD, Hoyt JL, Gergis SD: Studies in muscle rigidity, nitrous oxide, and narcotic analgesic agents. Anesth Analg 51:1620, 1972.

220. Freund FG, Martin WE, Wong KC et al: Abdominal muscle rigidity induced by morphine and nitrous oxide. Anesthesiology 38:358, 1973.

221. Pokela ML, Ryhanen P, Koivisto ME et al: Alfentanil-induced rigidity in newborn infants. Anesth Analg 75:252, 1992.

222. Blasco TA, Lee D, Amalric M et al: The role of the nucleus raphe pontis and the caudate nucleus in alfentanil rigidity in the rat. Brain Res 386:280, 1986.

223. Kallos T, Wyche MQ, Garman JK: The effects of Innovar on functional residual capacity and total chest compliance in man. Anesthesiology 39:358, 1975.

224. Comstock MK, Carter JG, Moyers JR et al: Rigidity and hypercarbia associated with high-dose fentanyl induction of anesthesia. Anesth Analg 60:362, 1981.

225. Benthuysen JL, Smith NT, Sanford TJ et al: Physiology of alfentanil-induced rigidity. Anesthesiology 64:440, 1986.

226. Bovill JG, Sebel PS: Pharmacokinetics of high dose fentanyl. Br J Anaesth 52:795, 1980.

227. Bennett JA, Abrams JT, Van Riper DF et al: Difficult or impossible ventilation after sufentanil-induced anethesia is caused primarily by vocal cord closure. Anethesiology 87:1070, 1997.

228. Christian CM, Waller JL, Moldenhauer CC: Postoperative rigidity following fentanyl anesthesia. Anesthesiology 58:275, 1983.

229. Goldberg M, Ishak S, Garcia C et al: Postoperative rigidity following sufentanil administration. Anesthesiology 63:199, 1985.

230. Jarvis AP, Arancibia CU: A case of difficult neonatal ventilation (letter). Anesth Analg 66:196, 1987.

231. Sebel PS, Bovill JG: Fentanyl and convulsions (letter). Anesth Analg 62:858, 1983.

232. Mavrojammis M: L'action cataleptique de la morphine chez les rats: Contribution a la theorie toxique de la catalepsie. CR Soc Biol (Paris) 55:1092, 1903.

233. Jurna I, Ruzdic N, Nell T et al: The effect of alpha-methyl-p-tyrosine and substantia nigra lesions on spinal motor activity in the rat. Eur J Pharmacol 20:341, 1972.

234. Freye E, Kuschinsky K: Effects of fentanyl and droperidol on the dopamine metabolism of the rat striatum. Pharmacology 14:1, 1976.

235. Bronson JB, Weinger B, Weinger M: Opiate-induced muscle rigidity is mediated by mu, and not delta or kappa receptors, in the rat. Anesthesiology 71:A599, 1989.

236. Havemann U, Kuschinsky K: Further characterization of opioid receptors in the striatum mediating muscular rigidity in rats. Naunyn Schmiedebergs Arch Pharmacol 317:321, 1981.

237. Weinger MB, Koob GF: Further elucidation of brain sites which mediate alfentanil-induced muscle rigidity in the rat. Anesthesiology 69:A610, 1988.

238. Baronti F, Conant KE, Giuffra M et al: Opioid peptides in Parkinson's disease: Effects of dopamine repletion. Brain Res 560:92, 1991.

239. Mets B: Acute dystonia after alfentanil in untreated Parkinson's disease. Anesth Analg 72:557, 1991.

240. Hill AB, Nahrwold ML, de Rosayro M et al: Prevention of rigidity during fentanyl-oxygen induction of anesthesia. Anesthesiology 55:452, 1981.

241. Jaffe TB, Ramsey FM: Attenuation of fentanyl-induced truncal rigidity. Anesthesiology 58:562, 1983.

242. Horrow JC, Abrams JT, Van Riper DF et al: Ventilatory compliance after three sufentanil-pancuronium induction sequences. Anesthesiology 75:969, 1991.

243. De Castro J, Van de Water A, Wouters L et al: Comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Acta Anaesthesiol Belg 30:5, 1979.

244. Poulton TJ, Ellingson RJ: Seizure associated with induction of anesthesia with clonidine: Effects on stress responses during general anesthesia. Anesthesiology 61:471, 1984.

245. Frenk H, Urca G, Liebeskind JC: Epileptic properties of leucine and methionine-enkephalin: Comparison with morphine and reversibility by naloxone. Brain Res 147:327, 1978.

246. Myers RR, Shapiro HM: Local cerebral metabolism during enflurane anesthesia: Identification of epileptogenic foci. Electroencephalogr Clin Neurophysiol 47:153, 1979.

247. Crosby G, Crane AM, Sokoloff L: Local changes in cerebral glucose utilization during ketamine anesthesia. Anesthesiology 56:437, 1982.

248. DeFriez CB, Wong HC: Seizures and opisthotonos after propofol anesthesia. Anesth Analg 75:630, 1992.

249. Cochran D, Price W, Gwinnutt CL: Unilateral convulsion after induction of anaesthesia with propofol. Br J Anaesth 76:570, 1996.

250. Crawford RD, Bashoff JD: Fentanyl associated delirium in man. Anesthesiology 53:168, 1980.

251. Rao TLK, Mummanemi N, El-Etr AA: Convulsions: An unusual response to intravenous fentanyl administration. Anesth Analg 61:1020, 1982.

252. Safwat AM, Daniel D: Grand-mal seizure after fentanyl administration. Anesthesiology 59:78, 1983.

253. Brian JE, Seifen AB: Tonic-clonic activity after sufentanil. Anesth Analg 66:481, 1987.

254. Bowdle TA: Myoclonus following sufentanil without EEG seizure activity. Anesthesiology 67:593, 1987.

255. Molbegott LP, Flashburg MH, Karasic L et al: Probable seizures after sufentanil. Anesth Analg 66:91, 1987.

256. Katz RI, Eide TR, Hartman A et al: Two instances of seizure-like activity in the same patient associated with two different narcotics. Anesth Analg 67:289, 1988.

257. Moore RA, Yang SS, McNicholas KW et al: Hemodynamic and anesthetic effects of sufentanil as the sole anesthetic for pediatric cardiovascular surgery. Anesthesiology 62:725, 1985.

258. Stanley TH, Philbin DM, Coggins CH: Fentanyl-oxygen anaesthesia for coronary artery surgery: Cardiovascular and antidiuretic hormone responses. Can Anaesth Soc J 26:168, 1979.

259. Hug CC Jr, Murphy MR: Fentanyl disposition in cerebrospinal fluid and plasma and its relationship to ventilatory depression in the dog. Anesthesiology 50:342, 1979.

260. Hall GM: Analgesia and the metabolic response to surgery. Proc R Soc Med 3:19, 1978.

261. Florence A: Attenuation of stress and haemodynamic stability. Proc R Soc Med 3:23, 1978.

262. Bovill JG, Sebel PS, Wauquier A et al: Electroencephalographic effects of sufentanil anaesthesia in man. Br J Anaesth 54:45, 1982.

263. Murkin JM, Moldenhauer CC, Hug CC et al: Absence of seizures during induction of anesthesia with high-dose fentanyl. Anesth Analg 63:489, 1984.

264. Logas WG, McCarthy RJ, Forde D et al: Effect of inhalation, narcotic and neuroleptic anesthesia on seizure threshold in rats. Anesth Analg 70:S247, 1990.

265. Tommasino C, Mackawa T, Shapiro HM: Fentanyl-induced seizures activate subcortical brain metabolism. Anesthesiology 60:283, 1984.

266. Young ML, Smith DS, Greenberg J et al: Effects of sufentanil on regional cerebral glucose utilization in rats. Anesthesiology 61:564, 1984.

267. Tempelhoff R, Modica PA, Bernardo KL et al: Fentanyl-induced electrocorticographic seizures in patients with complex partial epilepsy. J Neurosurg 77:201, 1992.

268. Borgeat A, Biollaz J, Depierraz B et al: Grand mal seizure after extradural morphine analgesia. Br J Anaesth 60:733, 1988.

269. Parkinson SK, Bailey SL, Little WL et al: Myoclonic seizure activity with chronic high-dose spinal opioid administration. Anesthesiology 72:743, 1990.

270. Armstrong PJ, Bersten A: Normeperidine toxicity. Anesth Analg 65:536, 1986.

271. Berryhill RE, Benumof JL, Janowsky DS: Morphine-induced hyperexcitability in man. Anesthesiology 50:65, 1979.

272. Gloor P, Vera CL, Sperti L et al: Investigations on the mechanism of epileptic discharges in the hippocampus. Epilepsia 2:4262, 1961.

273. Hoien AO: Another case of grand mal seizure after fentanyl administration. Anesthesiology 60:387, 1984.

274. Safo Y, Greenberg J, Young M et al: Effects of high dose fentanyl on regional cerebral blood flow. Anesthesiology 59:A306, 1983.

275. Ingvar MK, Shaprio HM: Selective metabolic activation of the hippocampus during lidocaine-induced pre-seizure activity. Anesthesiology 54:33, 1981.

276. Siesjo B (ed): Brain Energy Metabolism. New York, John Wiley & Sons, 1978.

277. Dam A: Hippocampal neuron loss in epilepsy and after experimental seizures. Acta Neurol Scand 66:601, 1982.

278. Kofke WA, Garman RH, Stiller RL et al: Opioid neurotoxicity: Fentanyl dose-response effects in rats. Anesth Analg 83:1298, 1996.

279. Martin WR: Pharmacology of opioids. Pharmacol Rev 35:283, 1983.

280. Asbury AJ: Pupil response to alfentanil and fentanyl. Anaesthesia 41:717, 1986.

281. Thompson SH: The pupil. In Moses R (ed): Adler's Physiology of the Eye: Clinical Application. London, CV Mosby, 1981, p 326.

282. Woodall NM, Maryniak JK, Gilston A: Pupillary signs during cardiac surgery. Anaesthesia 44:885, 1989.

283. Peacock JE, Henderson PD, Nimmo WS: Changes in pupil diameter after oral administration of codeine. Br J Anaesth 61:598, 1988.

284. Larson MD, Kurz A, Sessler DI et al: Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. Anesthesiology 87:849, 1997.

285. Adler MW, Geller EB: Physiological functions of opioids: Temperature regulation. In Herz A (ed): Opioids II: Handbook of Experimental Pharmacology. Berlin, Springer-Verlag, 1993, p 205.

286. Sessler DI, Olofsson CI, Rubinstein EH: The thermoregulatory threshold in humans during nitrous oxide-fentanyl anesthesia. Anesthesiology 69:357, 1988.

287. Kurz A, Go JC, Sessler DI et al: Alfentanil slightly increases the sweating threshold and markedly reduces the vasocontriction and shivering thresholds. Anesthesiology 83:293, 1995.

288. MacIntyre PE, Pavlin EG, Dwersteg JF: Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in postanesthesia shivering. Anesth Analg 66:751, 1987.

289. Casey WF, Smith CE, Katz JM et al: Intravenous meperidine for control of shivering during caesarean section under epidural anaesthesia. Can Anaesth Soc J 35:128, 1988.

290. Pauca AL, Savage RT, Simpson S et al: Effect of pethidine, fentanyl and morphine on post-operative shivering in man. Acta Anaesthesiol Scand 28:138, 1984.

291. Ikeda T, Sessler DI, Tayafeh F et al: Meperidine and alfentanil do not reduce the gain or maximum intensity of shivering. Anesthesiology 88:858, 1998.

292. Brownridge P: Shivering related to epidural blockade with bupivicaine in labour, and the influence of epidural pethidine. Anaesth Intensive Care 14:412, 1986.

293. Friedlander M, Noble WH: Meperidine to control shivering associated with platelet transfusion reaction. Can J Anaesth 36:460, 1989.

294. Sevarino FB, Johnson MD, Lema MJ et al: The effect of epidural sufentanil on shivering and body temperature in the parturient. Anesth Analg 68:530, 1989.

295. Liu WHD, Luxton MC: The effect of prophylactic fentanyl on shivering in elective caesarean section under epidural analgesia. Anaesthesia 46:344, 1991.

296. Scott PV, Fischer HBJ: Spinal opiate analgesia and facial pruritus: A neural theory. Postgrad Med J 58:531, 1982.

297. Jones EA, Bergasa NV: The pruritus of cholestasis and the opioid system. JAMA 268:3359, 1992.

298. Etches RC: Respiratory depression associated with patientcontrolled analgesia: A review of eight cases. Can J Anaesth 41:125, 1994.

299. Jaeckle KA, Digre KB, Jones CR et al: Central neurogenic hyperventilation: Pharmacologic intervention with morphine sulfate and correlative analysis of respiratory, sleep and ocular motor dysfunction. Neurology 40:1715, 1990.

300. Tobias JD, Heideman RL: Primary central hyperventilation in a child with a brainstem glioma: Management with continuous intravenous fentanyl. Pediatrics 88:818, 1991.

301. Tyler DC: Respiratory effects of pain in a child after thoracotomy. Anesthesiology 70:873, 1989.

302. Irazuzta J, Pascucci R, Perlman N et al: Effects of fentanyl administration on respiratory system complicance in infants. Crit Care Med 21:1001, 1993.

303. Bohrer H, Fleischer F, Werning P: Tussive effect of a fentanyl bolus administered through a central venous catheter. Anaesthesia 45:18, 1990.

304. Liu P-W, Hsing C-H, Chu Y-C: Terbutaline inhalation supresses fentanyl induced coughing. Can J Anaesth 43:1216, 1996.

305. Cabot PJ, Cramond T, Smith MT: Quantitative autoradiography of peripheral opioid binding sites in rat lung. Eur J Pharmacol 310:47, 1996.

306. Zappi L, Nicosia F, Rocchi D et al: Opioid agonists modulate release of neurotransmitters in bovine trachealis muscle. Anesthesiology 83:543, 1995.

307. Neto PPR: Respiratory mechanical properties during fentanyl and alfentanil anaesthesia. Can J Anaesth 39:458, 1992.

308. Toda N, Hatano Y: Contractile responses of canine tracheal muscle during exposure to fentanyl and morphine. Anesthesiology 53:93, 1980.

309. Hickey PR, Hansen DD, Wessel DL et al: Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Anesth Analg 64:1137, 1985.

310. Anjou-Lindskog E, Broman L, Broman M et al: Effects of intravenous anesthesia on Va/Q distribution: A study performed during ventilation with air and with 50% oxygen, supine and in the lateral position. Anesthesiology 62:485, 1985.

311. Bjertraes LJ: Hypoxia-induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalation anesthetics. Acta Anaesthesiol 21:133, 1977.

312. Yahagi N, Furuya H, Sai Y et al: Effect of halothane, fentanyl, and ketamine on the threshold for transpulmonary passage of venous air emboli in dogs. Anesth Analg 75:720, 1992.

313. Wamsley JK: Opioid receptors: Autoradiography. Pharmacol Rev 35:69, 1983.

314. Hickey RF, Severinghaus JW: Regulation of breathing: Drug effects. In Hornbein T (ed): Lung Biology in Health and Disease. New York, Marcel Dekker, 1981, p 1251.

315. Ngai SH: Effects of morphine and meperidine on the central respiratory mechanisms in the cat, the action of levallorphan in antagonizing these effects. J Pharmacol Exp Ther 131:91, 1961.

316. Tabatabai M, Kitahata LM, Collins JG: Disruption of the rhythmic activity of the medullary inspiratory neurons and phrenic nerve by fentanyl and reversal with nalbuphine. Anesthesiology 70:489, 1989.

317. Chen S-W, Maguire PA, Daview MF et al: Evidence for mu $_1$ -opioid receptor involvement in fentanyl-mediated respiratory depression. Eur J Pharmacol 312:241, 1996.

318. Kryger MH, Yacoub O, Dosman J et al: Effect of meperidine on occlusion pressure responses to hypercapnia and hypoxia with and without external inspiratory resistance. Am Rev Respir Dis 114:333, 1976.

319. Weil JV, McCullough RE, Kline JS et al: Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. N Engl J Med 292:1103, 1975.

320. Bailey PL, Rhondeau S, Schafer PG et al: Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology 79:49, 1993.

321. Drummond GB: Comparison of decreases in ventilation caused by enflurane and fentanyl during anesthesia. Br J Anaesth 55:825, 1983.

322. Berkowitz BA, Ngai SH, Yang JC et al: The disposition of morphine in surgical patients. Clin Pharamcol Ther 17:629, 1975.

323. Nielsen CH, Camporesi EM, Bromage PR et al: CO_2 sensitivity after epidural and IV morphine. Anesthesiology 55:A372, 1981.

324. Downes JJ, Kemp RA, Lambertsen CJ: The magnitude and duration of respiratory depression due to fentanyl and meperidine in man. J Pharmacol Exp Ther 158:416, 1967.

325. Bailey PL, Streisand JB, East KA et al: Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. Anesth Analg 70:8, 1990.

326. Cartwright P, Prys-Roberts C, Gill K et al: Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesth Analg 62:966, 1983.

327. Holmes CM: Supplementation of general anaesthesia with narcotic analgesics. Br J Anaesth 48:907, 1976.

328. Lunn JK, Stanley TH, Webster LR et al: High dose fentanyl anesthesia for coronary artery surgery: Plasma fentanyl concentration and influence of nitrous oxide on cardiovascular responses. Anesth Analg 58:390, 1979.

329. de Lange S, Stanley T, Boscoe M: Comparison of anesthetic requirements and cardiovascular responses in Salt Lake City and Leiden, Holland. In Zindler M, Rugheimer E (eds): Seventh World Congress of Anaesthesiology. Amsterdam, Excerpta Medica, 1980, p 313.

330. Cookson RF, Niemegeers CJE, Vanden Bussche G: The development of alfentanil. Br J Anaesth 55:147S, 1983.

331. Ausems ME, Hug CC Jr, Stanski DR et al: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. Anesthesiology 65:362, 1986.

332. Van Dongen K, Leusink H: The action of opium-alkaloids and expectorants on the ciliary movements in the air passages. Arch Int Pharmacodyn 93:261, 1953.

333. Reed DJ, Kellog RH: Changes in respiratory response to CO_2 during natural sleep at sea level and at altitude. J Appl Physiol 13:325, 1958.

334. Forrest WH, Bellville JW: The effect of sleep plus morphine on the respiratory response to carbon dioxide. Anesthesiology 25:137, 1964.

335. Kurth CD: Postoperative arterial oxygen saturation: What to expect. Anesth Analg 80:1, 1995.

336. Rosenberg-Adamsen S, Kehlet H, Dodds C et al: Postoperative sleep disturbances: Mechanisms and clinical implications. Br J Anaesth 76:552, 1996.

337. Rigg JRA, Rondi P: Changes in rib cage and diaphragm contribution to ventilation after morphine. Anesthesiology 55:507, 1981.

338. Longobardo GE, Gothe B, Goldman MD et al: Sleep apnea considered as a control system instability. Respir Physiol 50:311, 1982.

339. Bentley JB, Borel JD, Nenad REJ et al: Age and fentanyl pharmacokinetics. Anesth Analg 61:968, 1982.

340. Arunasalam K, Davenport HT, Painter S et al: Ventilatory response to morphine in young and old subjects. Anaesthesia 38:529, 1983.

341. Way WL, Costley EC, Way EL: Respiratory sensitivity of the newborn to meperidine and morphine. Clin Pharmacol Ther 6:454, 1965.

342. Eckenhoff JE, Oech SR: The effects of narcotics and antagonists upon respiration and circulation in man. Clin Pharmacol Ther 1:483, 1960.

343. Bailey PL, Pace NL, Ashburn MA et al: Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 73:826, 1990.

344. Becker LD, Paulson BA, Miller RD et al: Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. Anesthesiology 44:291, 1976.

345. Harper MH, Hickey RF, Cromwell TH et al: The magnitude and duration of respiratory depression produced by fentanyl and fentanyl plus droperidol in man. J Pharmacol Exp Ther 199:464, 1976.

346. Bailey PL, Sperry RJ, Johnson GK et al: Respiratory effects of clonidine alone and combined with morphine, in humans. Anesthesiology 74:43, 1991.

347. Furst SR, Weinger MB: Dexmedetomidine, a selective alpha $_2$ -agonist, does not potentiate the cardiorespiratory depression of alfentanil in the rat. Anesthesiology 72:882, 1990.

348. Belleville JP, Ward DS, Bloor BC et al: Effects of intravenous dexmedetomidine in humans. Anesthesiology 77:1125, 1992.

349. Rawal N, Wattwil M: Respiratory depression after epidural morphine: An experimental and clinical study. Anesth Analg 63:8, 1984.

350. Nishino T, Hiraga K, Fujisato M et al: Breathing patterns during postoperative analgesia in patients after lower abdominal operations. Anesthesiology 69:967, 1988.

351. Sarton E, Dahan A, Teppema L et al: Acute pain and central nervous system arousal do not restore impaired hypoxic ventilatory response during sevoflurane sedation. Anesthesiology 85:295, 1996.

352. Sarton E, Dahan A, Teppeman L et al: Influence of acute pain induced by activation of cutaneous nociceptors on ventilatory control. Anesthesiology 87:289, 1997.

353. Pelligrino DA, Riegler FX, Albrecht RF: Ventilatory effects of fourth cerebroventricular infusions of morphine-6- or morphine-3- glucuronide in the awake dog. Anesthesiology 71:936, 1989.

354. Peat SJ, Hanna MH, Woodham M et al: Morphine-6-glucuronide: Effects on ventilation in normal volunteers. Pain 45:101, 1991.

355. Ainslie SG, Eisele JH, Corkill G: Fentanyl concentrations in brain and serum during respiratory acid-base changes in the dog. Anesthesiology 51:293, 1979.

356. Beard K, Hershel J, Walker AM: Adverse respiratory events occuring in the recovery room after general anesthesia. Anesthesiology 64:269, 1986.

357. Severinghaus JW, Kelleher JF: Recent developments in pulse oximetry. Anesthesiology 76:1018, 1992.

358. Bailey PL: The use of opioids in anesthesia is not especially associated with nor predictive of postoperative hypoxemia (letter). Anesthesiology 77:1235, 1992.

359. Catley DM, Thornton C, Jordan C et al: Pronounced episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. Anesthesiology 63:20, 1985.

360. Adams AP, Pybus DA: Delayed respiratory depression after use of fentanyl during anaesthesia. BMJ 1:278, 1978.

361. Stanski DR, Greenblatt DJ, Lowenstein E: Kinetics of intravenous and intramuscular morphine. Clin Pharmacol Ther 24:52, 1978.

362. Chan K, Kendall MJ, Mitchard M et al: The effect of aging on plasma pethidine concentration. Br J Clin Pharmacol 2:297, 1975.

363. Mahla ME, Maj MC, Maj SEW et al: Delayed respiratory depression after alfentanil. Anesthesiology 69:593, 1988.

364. Chang J, Fish KJ: Acute respiratory arrest and rigidity after anesthesia with sufentanil: A case report. Anesthesiology 63:710, 1985.

365. Robinson D: Respiratory arrest after recovery from anaesthesia supplemented with sufentanil (letter). Can J Anaesth 35:101, 1988.

366. McClain DA, Hug CC Jr: Intravenous fentanyl kinetics. Clin Pharmacol Ther 28:106, 1980.

367. Koehntop DE, Rodman JH, Brundage DM et al: Pharmacokinetics of fentanyl in neonates. Anesth Analg 65:227, 1986.

368. Stoeckel H, Schuttler J, Magnussen H et al: Plasma fentanyl concentrations and occurrence of respiration depression in volunteers. Br J Anaesth 54:1087, 1982.

369. McQuay HJ, Moore RA, Paterson GMC et al: Plasma fentanyl concentrations and clinical observations during and after operation. Br J Anaesth 51:543, 1979.

370. Bower S, Hull CJ: Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 54:871, 1982.

371. Schmitt H, Batz G, Knoll R et al: Plasma level changes of fentanyl and midazolam after release of a prolonged thigh tourniquet. Acta Anaesthesiol Scand 34:104, 1990.

372. Zbinden AM, Petersen-Felix S, Thomson DA: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. Anesthesiology 80:261, 1994.

373. Stanley TH, de Lange S: The effect of patient habits on dosage requirements during high dose fentanyl anesthesia. Can Anaesth Soc J 31:368, 1985.

374. Wynands JE, Townsend GE, Wong P et al: Blood pressure response and plasma fentanyl concentrations during high- and very high-dose fentanyl anesthesia for coronary artery surgery. Anesth Analg 62:661, 1983.

375. Edde RR: Hemodynamic changes prior to and after sternotomy in patients anesthetized with high-dose fentanyl. Anesthesiology 55:444, 1981.

376. de Lange S, Stanley TH, Boscoe MJ et al: Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology 56:112, 1982.

377. Howie MB, Reitz J, Reilley TE et al: Does sufentanil's shorter half-life have any clinical significance? Anesthesiology 59:A146, 1983.

378. Sonntag H, Stephan H, Lange H et al: Sufentanil does not block sympathetic responses to surgical stimuli in patients having coronary artery revascularization surgery. Anesth Analg 68:584, 1989.

379. Miller DR, Wellwood M, Teasdale SJ et al: Effects of anaesthetic induction on myocardial function and metabolism: A comparison of fentanyl, sufentanil and alfentanil. Can J Anaesth 35:219, 1988.

380. Benthuysen JL, Foltz BD, Smith NT et al: Prebypass hemodynamic stability of sufentanil-O_2, fentanyl-O_2 and morphine-O_2 anesthesia during cardiac surgery: A comparison of cardiovascular profiles. J Cardiothorac Anesth 12:749, 1988.

381. Mathews HML, Furness G, Carson IW et al: Comparison of sufentanil-oxygen and fentanyl-oxygen anaesthesia for coronary artery bypass grafting. Br J Anaesth 60:530, 1988.

382. Sanford TJ, Smith NT, Dec-Silver H et al: A comparison of morphine, fentanyl, and sufentanil anesthesia for cardiac surgery: Induction, emergence, and extubation. Anesth Analg 65:259, 1986.

383. Boulton AJ, Wilson N, Turnbull KW et al: Haemodynamic and plasma vasopressin responses during high-dose fentanyl or sufentanil anaesthesia. Can Anaesth Soc J 33:475, 1986.

384. Stanley TH, de Lange S: Comparison of sufentanil-oxygen and fentanyl-oxygen anesthesia for mitral and aortic valvular surgery. J Cardiothorac Anesth 2:6, 1988.

385. Sebel PS, Bovill JG: Cardiovascular effects of sufentanil anesthesia: A study in patients undergoing cardiac surgery. Anesth Analg 61:115, 1982.

386. de Lange S, Stanley TH, Boscoe MJ: Alfentanil-oxygen anaesthesia for coronary artery surgery. Br J Anaesth 53:1291, 1981.

387. Robbins GR, Wynands JE, Whalley DG et al: Pharmacokinetics of alfentanil and clinical responses during cardiac surgery. Can J Anaesth 37:52, 1990.

388. Hug CC Jr, Hall RI, Angert KC et al: Alfentanil plasma concentration v. effect relationships in cardiac surgical patients. Br J Anaesth 61:435, 1988.

389. Iwasaki Y, Gaskill MB, Fu R et al: Opioid antagonist diprenorphine microinjected into parabrachial nucleus selectively inhibits vasopressin response to hypovolemic stimuli in the rat. J Clin Invest 92:2230, 1993.

390. Feldman PD, Parveen N, Sezen S: Cardiovascular effects of Leu-enkephalin in the nucleus tractus solitarius of the rat. Brain Res 709:331, 1996.

391. Keay KA, Crowfoot LJ, Floyd NS et al: Cardiovascular effects of microinjections of opioid agonists into the "depressor region" of the ventrolateral periaqueductal gray region. Brain Res 762:61, 1997.

392. Sato A, Sato Y, Schmidt RF: Modulation of somatocardiac sympathetic reflexes mediated by opioid receptors at the spinal and brainstem level. Exp Brain Res 105:1, 1995.

393. Flacke JW, Flacke WE, Bloor BC et al: Effects of fentanyl, naloxone, and clonidine on hemodynamics and plasma catecholamine levels in dogs. Anesth Analg 62:305, 1983.

394. Flacke JW, David LJ, Flacke WE et al: Effects of fentanyl and diazepam in dogs deprived of autonomic tone. Anesth Analg 64:1053, 1985.

395. Thomson IR, Putnins CL, Friesen RM: Hyperdynamic cardiovascular response to anesthetic induction with high dose fentanyl. Anesth Analg 65:91, 1986.

396. Reitan JA, Stengert KB, Wymore ML et al: Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. Anesth Analg 57:31, 1978.

397. Cohn AE: The effect of morphine on the mechanism of the dog's heart after removal of one vagus nerve. Proc Soc Exp Biol Med 10:93, 1913.

398. Robbins BH, Fitzhugh OG, Baxter JH Jr: The action of morphine in slowing the pulse. J Pharmacol Exp Ther 66:216, 1939.

399. Liu WS, Bidwai AV, Stanley TH et al: Cardiovascular dynamics after large doses of fentanyl and fentanyl plus N_2O in the dog. Anesth Analg 55:168, 1976.

400. Bailey PL: Sinus arrest induced by trivial nasal stimulation during alfentanil-nitrous oxide anesthesia. Br J Anaesth 65:718, 1990.

401. Lang S, Lanigan DT, van der Wal M: Trigeminocardiac reflexes: Maxillary and mandibular variants of the oculocardiac reflex. Can J Anaesth 38:757, 1991.

402. King BD, Elder JD, Dripps RD: The effect of the intravenous administration of meperidine upon the circulation of man and upon the circulatory response to tilt. Surg Gynecol Obstet 94:591, 1952.

403. Ela C, Hasin Y, Eilam Y: Opioid effects on contractility, Ca^{2+} - transients and intracellular pH in cultured cardiac myocytes. J Mol Cell Cardiol 26:599, 1993.

404. Wynands JE, Wong P, Whalley DG et al: Oxygen-fentanyl anesthesia in patients with poor left ventricular function, hemodynamics and plasma fentanyl concentrations. Anesth Analg 62:476, 1983.

405. Zhang C-C, Su JY, Calkins D: Effects of alfentanil on isolated cardiac tissues of the rabbit. Anesth Analg 71:268, 1990.

406. Helgesen KG, Ellingsen O, Ilebekk A: Inotropic effect of meperidine: Influence of receptor and ion channel blockers in the rat atrium. Anesth Analg 70:499, 1990.

407. Vasko JS, Henney RP, Brawley RK et al: Effects of morphine on ventricular function and myocardial contractile force. Am J Physiol 210:329, 1966.

408. Strauer BE: Contractile responses to morphine, piritramide, meperidine and fentanyl: A comparative study of effects on the isolated ventricular myocardium. Anesthesiology 37:304, 1972.

409. Rendig SV, Amsterdam EA, Henderson GL et al: Comparative cardiac contractile actions of six narcotic analgesics: Morphine, meperidine, pentazocine, fentanyl, methadone and l-alpha-acetylmethadol (LAAM). J Pharmacol Exp Ther 215:259, 1980.

410. Hicks HC, Mowbray AG, Yhap EO: Cardiovascular effects of and catecholamine responses to high dose fentanyl-O_2 for induction of anesthesia in patients with ischemic coronary artery disease. Anesth Analg 60:563, 1981.

411. Rosow CE, Moss J, Philbin DM et al: Histamine release during morphine and fentanyl anesthesia. Anesthesiology 56:93, 1982.

412. Motomura S, Kissin I, Aultman D et al: Effects of fentanyl and nitrous oxide on contractility of blood-perfused papillary muscle of the dog. Anesth Analg 63:47, 1984.

413. Rucquoi M, Camu F: Cardiovascular responses to large doses of alfentanil and fentanyl. Br J Anaesth 55:223S, 1983.

414. Hamm D, Freedman B, Pellom G et al: The maintenance of myocardial contractility by fentanyl during enflurane administration. Anesthesiology 59:A86, 1983.

415. Freedman B, Hamm D, Pellom G et al: Fentanyl-halothane anesthesia maintains myocardial contractility. Anesthesiology 59:A35, 1983.

416. Waller JL, Hug CC, Nagle DM et al: Hemodynamic changes during fentanyl-oxygen anesthesia for aortocoronary bypass operations. Anesthesiology 55:212, 1981.

417. Schauble JF, Chen BB, Murray PA: Marked hemodynamic effects of bolus administration of alfentanil in conscious dogs. Anesthesiology 59:A85, 1983.

418. de Bruijn ND, Christian C, Fagraeus L et al: The effects of alfentanil on global ventricular mechanics. Anesthesiology 59:A33, 1983.

419. Sebel PS, Bovill JG: Opiate anaesthesia fact or fallacy (editorial). Br J Anaesth 54:1149, 1982.

420. Ausems ME, Hug CC Jr, de Lange S: Variable rate infusion of alfentanil as a supplement to nitrous oxide anesthesia for general surgery. Anesth Analg 62:982, 1983.

421. Moldenhauer CC, Griesemer RW, Hug CC et al: Hemodynamic changes during rapid induction of anesthesia with alfentanil. Anesth Analg 62:276, 1983.

422. Bartkowski RR, McDonnell TE: Alfentanil as an anesthetic induction agent: A comparison with thiopental-lidocaine. Anesth Analg 63:330, 1984.

423. Lemmens HJM, Bovill JG, Burm AGL et al: Alfentanil infusion in the elderly. Anaesthesia 43:850, 1988.

424. James MK, Vuong A, Grizzle MK et al: Hemodynamic effects of GI 87084B, an ultra-short acting mu-opioid analgesic, in anesthetized dogs. J Pharmacol Exp Ther 263:84, 1992.

425. Kennedy BL, West TC: Effect of morphine on electrically induced release of autonomic mediators in the rabbit sinoatrial node. J Pharmacol Exp Ther 157:149, 1967.

426. Tomichek RC, Rosow C, Schneider RC et al: Cardiovascular effects of diazepam-fentanyl anesthesia in patients with coronary artery disease. Anesth Analg 61:217, 1982.

427. De Silva RA, Verrierm RL, Lown B: Protective effect of vagotonic action of morphine sulfate on ventricular vulnerability. Cardiovasc Res 12:167, 1978.

428. Starr NJ, Sethna DH, Estafanous FG: Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. Anesthesiology 64:521, 1986.

429. Maryniak JK, Bishop VA: Sinus arrest after alfentanil (letter). Br J Anaesth 59:390, 1987.

430. Sherman EP, Lebowitz PW, Street WC: Bradycardia following sufentanil-succinylcholine. Anesthesiology 66:106, 1987.

431. Rivard JC, Lebowitz PW: Bradycardia after alfentanil-succinylcholine. Anesth Analg 67:907, 1988.

432. Egan TD, Brock-Utne JG: Asystole after anesthesia induction with fentanyl, propofol, and succinylcholine sequence. Anesth Analg 73:818, 1991.

433. Schmeling WT, Kampine JP, Warltier DC: Negative chronotropic actions of sufentanil and vecuronium in chronically instrumented dogs pretreated with propranolol and/or diltiazem. Anesth Analg 69:4, 1989.

434. Royster RL, Keeler DK, Haisty WK et al: Cardiac electrophysiologic effects of fentanyl and combinations of fentanyl and neuromuscular relaxants in pentobarbital anesthetized dogs. Anesth Analg 67:15, 1988.

435. Blair JR, Pruett JK, Introna RPS et al: Cardiac electrophysiologic effects of fentanyl and sufentanil in canine cardiac Purkinje fibers. Anesthesiology 71:565, 1989.

436. Puerto BA, Wong KC, Puerto AX et al: Epinephrine-induced dysrhythmias: Comparison during anaesthesia with narcotics and with halogenated agents in dogs. Can Anaesth Soc J 26:263, 1979.

437. Weber G, Stark G, Stark U: Direct cardiac electrophysiologic effects of sufentanil and vecuronium in isolated guinea-pig hearts. Acta Anaesthesiol Scand 39:1071, 1995.

438. Blair JR, Pruett JK, Crumrine RS et al: Prolongation of QT interval in association with large doses of opiates. Anesthesiology 67:442, 1987.

439. Sharpe MD, Dobkowski WB, Murkin JM et al: Alfentanil-midazolam anaesthesia has no electrophysiological effects upon the normal conduction system or accessory pathways in patients with WolffParkinson-White syndrome. Can J Anaesth 39:816, 1992.

440. Sharpe MD, Dobkowski WB, Murkin JM et al: The electrophysiologic effects of volatile anesthetics and sufentanil on the normal atrioventricular conduction system and accessory pathways in Wolff-Parkinson-White syndrome. Anesthesiology 80:63, 1994.

441. Atlee JL, Bosnjak ZJ: Mechanisms for cardiac dysrhythmias during anesthesia. Anesthesiology 72:347, 1990.

442. Hickey PR, Hansen DD: High-dose fentanyl reduces intraoperative ventricular fibrillation in neonates with hypoplastic left heart syndrome. J Clin Anesth 3:295, 1991.

443. Saini V, Carr DB, Hagestad EL et al: Antifibrillatory action of the narcotic agonist fentanyl. Am Heart J 115:598, 1988.

444. McIntosh M, Kane K, Parratt J: Effects of selective opioid receptor agonists and antagonists during myocardial ischaemia. Eur J Pharmacol 210:37, 1992.

445. Forrest JB, Cahalan MK, Rehder K et al: Multicenter study of general anesthesia. II. Results. Anesthesiology 72:262, 1990.

446. Chinzei M, Morita S, Chinzei T et al: Effects of isoflurane and fentanyl on ischemic myocardium in dogs: Assessment by end-systolic measurements. J Cardiothorac Vasc Anesth 5:243, 1991.

447. Kim YD, Danchek M, Myers AK et al: Anaesthetic modification of regional myocardial functional adjustments during myocardial ischaemia: Halothane vs fentanyl. Br J Anaesth 68:286, 1992.

448. White JL, Myers AK, Analouei A et al: Functional recovery of stunned myocardium is greater with halothane than fentanyl anaesthesia in dogs. Br J Anaesth 73:214, 1994.

449. MacLeod BA, Augereau P, Walker MJA: Effects of halothane anesthesia compared with fentanyl anesthesia and no anesthesia during coronary ligation in rats. Anesthesiology 58:44, 1983.

450. Frank LP, Davis RF: The effect of fentanyl on myocardial salvage in dogs after coronary artery occlusion. Anesth Analg 65:S50, 1986.

451. Schultz JE, Hsu AK, Gross GJ: Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. Circ Res 78:1100, 1996.

452. Helman JD, Leung JM, Bellows WH et al: The risk of myocardial ischemia in patients receiving desflurane versus sufentanil anesthesia for coronary artery bypass graft surgery. Anesthesiology 77:47, 1992.

453. Leung JM, Goehner P, O'Kelly BF et al: Isoflurane anesthesia and myocardial ischemia: Comparative risk versus sufentanil anesthesia in patients undergoing coronary artery bypass graft surgery. Anesthesiology 74:838, 1991.

454. Sonntag H, Larsen R, Hilfiker O et al: Myocardial blood flow and oxygen consumption during high-dose fentanyl anesthesia in patients with coronary artery disease. Anesthesiology 56:417, 1982.

455. Moffitt EA, McIntyre AJ, Barker RA et al: Myocardial metabolism and hemodynamic responses with fentanyl-enflurane anesthesia for coronary arterial surgery. Anesth Analg 65:46, 1986.

456. Heikkila H, Jalonen J, Arola M et al: Haemodynamics and myocardial oxygenation during anaesthesia for coronary artery surgery: Comparison between enflurane and high-dose fentanyl anaesthesia. Acta Anaesthesiol Scand 29:457, 1985.

457. Kleinman B, Henkin RE, Glisson SN et al: Qualitative evaluation of coronary flow during anesthetic induction using thallium-201 perfusion scans. Anesthesiology 64:157, 1986.

458. Beland A, Blaise GA, Lenis SG et al: Effect of fentanyl on the coronary circulation in an isolated heart. Can Anaesth Soc J 34:S72, 1987.

459. Blaise GA, Witzeling TM, Sill JC et al: Fentanyl is devoid of major effects on coronary vasoreactivity and myocardial metabolism in experimental animals. Anesthesiology 72:535, 1990.

460. Hirsch LJ, Rooney MW, Mathru M et al: Effects of fentanyl on coronary blood flow distribution and myocardial oxygen consumption in the dog. J Cardiothorac Vasc Anesth 7:50, 1993.

461. Kohno K, Takaki M, Ishioka K et al: Effects of intracoronary fentanyl on left ventricular mechanoenergetics in the excised cross-circulated canine heart (revised publication). Anesthesiology 87:658, 1997.

462. Yamanoue T, Brum J, Estafanous FG et al: Effects of opioids on vasoresponsiveness of porcine coronary artery. Anesth Analg 74:889, 1992.

463. van Wezel HB, Kal JE, Vergroesen I et al: Rate of coronary flow adaptation in response to changes in heart rate before and during anesthesia for coronary artery surgery. Anesthesiology 84:1107, 1996.

464. Slogoff S, Keats AS, Dear WE et al: Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. Anesth Analg 72:22, 1991.

465. Nauta J, Stanley TH, de Lange S et al: Anaesthetic induction with alfentanil: Comparison with thiopental, midazolam, and etomidate. Can Anaesth Soc J 30:53, 1983.

466. Ebert TJ, Kotrly KJ, Madsen KE et al: Fentanyl-diazepam anesthesia with or without N_2O does not attenuate cardiopulmonary baroreflex-mediated vasoconstrictor responses to controlled hypovolemia in humans. Anesth Analg 67:548, 1988.

467. Kotrly KJ, Ebert TJ, Vucins EJ et al: Baroreceptor reflex control of heart rate during morphine sulfate, diazepam, N_2O/O_2 anesthesia in humans. Anesthesiology 61:558, 1984.

468. Zimpfer M, Kotal E, Mayer N et al: Effects of morphine on circulatory adjustments to acute, progressive haemorrhage. Anaesthesist 32:259, 1983.

469. Murat JM, Levron J-C, Berg A et al: Effects of fentanyl on baroreceptor reflex control of heart rate in new born infants. Anesthesiology 68:717, 1988.

470. James TN, Isobe JH, Urthaler F: Analysis of components in a cardiogenic hypertensive chemoreflex. Circulation 52:179, 1975.

471. James TN: A cardiogenic hypertensive chemoreflex. Anesth Analg 69:633, 1989.

472. Hoar PF, Nelson NT, Mangano DT et al: Adrenergic response to morphine-diazepam anesthesia for myocardial revascularization. Anesth Analg 60:406, 1981.

473. Fahmy NR, Sinder N, Soter NA: Role of histamine in the hemodynamic and plasma catecholamine responses to morphine. Clin Pharmacol Ther 33:615, 1983.

474. Flacke JW, Van Etten AP, Bloor BC et al: Histamine release by four narcotics: A double blind study in humans. Anesth Analg 66:723, 1987.

475. Hasbrouck JD: Morphine anesthesia for open heart surgery. Ann Thorac Surg 10:364, 1970.

476. Stanley TH, Isern-Amaral J, Lathrop GD: Urine norepinephrine excretion in patients undergoing mitral or aortic valve replacement with morphine anesthesia. Anesth Analg 54:509, 1975.

477. Balasariswathi K, Glisson SN, El-Etr AA et al: Serum epinephrine and norepinephrine during valve replacement and aortocoronary bypass. Can Anaesth Soc J 25:198, 1978.

478. Stellato C, Cirillo R, de Paulis A et al: Human basophil/mast cell releasability. IX. Heterogeneity of the effects of opioids on mediator release. Anesthesiology 77:932, 1992.

479. Bailey DR, Miller ED, Kaplan JA et al: The renin-angiotensinaldosterone system during cardiac surgery with morphine-nitrous oxide anesthesia. Anesthesiology 42:538, 1975.

480. Moss J, Rosow CE: Histamine release by narcotics and muscle relaxants in humans. Anesthesiology 59:330, 1983.

481. Moffitt EA, Sethna DH, Bussell JA et al: Myocardial metabolism and hemodynamic responses to halothane or morphine anesthesia for coronary artery surgery. Anesth Analg 61:979, 1982.

482. Liu WS, Bidwai AV, Lunn JK et al: Urine catecholamine excretion after large doses of fentanyl, fentanyl and diazepam and fentanyl, diazepam and pancuronium. Can Anaesth Soc J 24:371, 1977.

483. Stanley TH, Berman L, Green O et al: Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary-artery operations. Anesthesiology 53:250, 1980.

484. Gaumann DM, Yaksh TL, Tyce GM et al: Opioids preserve the adrenal medullary response evoked by severe hemorrhage: Studies on adrenal catecholamines and Met-enkephalin secretion in halothane anesthetized cats. Anesthesiology 68:743, 1988.

485. Yonker-Sell AE, Muzi M, Hope WG et al: Alfentanil modifies the neurocirculatory responses to desflurane. Anesth Analg 82:162, 1996.

486. Parra L, Perez-Vizcaino F, Alsasua A et al: mu- and delta-opioid receptor-mediated contractile effects on rat aortic vascular smooth mucle. Eur J Pharmacol 277:99, 1995.

487. Zelis R, Mansour EJ, Capone RJ et al: The cardiovascular effects of morphine: The peripheral capacitance and resistance vessels in human subjects. J Clin Invest 54:1247, 1974.

488. Lowenstein E, Whiting RB, Bittar DA et al: Local and neurally mediated effects of morphine on skeletal muscle vascular resistance. J Pharmacol Exp Ther 180:359, 1972.

489. Hsu HO, Hickey RF, Forbes AR: Morphine decreases peripheral vascular resistance and increases capacitance in man. Anesthesiology 50:98, 1979.

490. Starck T, Hall D et al: Peripheral vascular depression with sufentanil in the dog. Anesth Analg 68:S277, 1989.

491. White DA, Reitan JA, Kien ND et al: Decrease in vascular resistance in the isolated canine hindlimb after graded doses of alfentanil, fentanyl, and sufentanil. Anesth Analg 71:29, 1990.

492. Schwinn DA, McIntyre RW, Hawkins ED et al: $Alpha_1$-adrenergic responsiveness during coronary artery bypass surgery: Effect of preoperative ejection fraction. Anesthesiology 69:206, 1988.

493. Weissman C: The metabolic response to stress: An overview and update. Anesthesiology 73:308, 1990.

494. Chrousos GP, Gold PW: The concepts of stress and stress system disorders. JAMA 267:1244, 1992.

495. Anand KJS, Ward-Platt MP: Neonatal and pediatric stress responses to anesthesia and operation. Int Anesthesiol Clin 26:218, 1988.

496. Bovill JG, Sebel PS, Fiolet JW et al: The influence of sufentanil on endocrine and metabolic responses to cardiac surgery. Anesth Analg 62:391, 1983.

497. Oyama T, Wakayama S: The endocrine responses to general anesthesia. Int Anesthesiol Clin 26:176, 1988.

498. Madsen SN, Engquist A, Badwai I et al: Cyclic AMP, glucose and cortisol in plasma during surgery. Horm Metab Res 8:483, 1976.

499. Clarke RSJ, Johnston H, Sheridan B: The influence of anaesthesia and surgery on plasma cortisol, insulin and free fatty acids. Br J Anaesth 42:295, 1970.

500. Anand KJS, Hansen DD, Hickey PR: Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. Anesthesiology 73:661, 1990.

501. Carr DB, Murphy MT: Operation, anesthesia and the endorphin system. Int Anesthesiol Clin 26:199, 1988.

502. Delitala G, Trainer PJ, Oliva O et al: Opioid peptide and alpha-adrenoceptor pathways in the regulation of the pituitary-adrenal axis in man. J Endocrinol 141:163, 1994.

503. Eipper BA, Mains RE: Structure and biosynthesis of pro-adrenocorticotropin/endorphin and related peptides. Endocrine Rev 1:1, 1980.

504. Koenig JI, Mayfield MA, McCann SM et al: Differential role of the opioid mu and delta receptors in the activation of prolactin (PRL) and growth hormone (GH) secretion by morphine in the male rat. Life Sci 34:1829, 1984.

505. Hall GM, Lacoumenta S, Hart GR et al: Site of action of fentanyl in inhibiting the pituitary-adrenal response to surgery in man. Br J Anaesth 65:251, 1990.

506. Przewlocki R, Stala L, Greczek M et al: Analgesic effects of mu-, delta- and kappa-opiate agonists and, in particular, dynorphin at the spinal level. Life Sci 33:649, 1983.

507. Schmauss C, Yaksh TL: *In vivo* studies on spinal opiate receptor systems mediating antinociception. II. Pharmacological profiles suggesting a differential association of mu, delta and kappa receptors with visceral chemical and cutaneous thermal stimuli in the rat. J Pharmacol Exp Ther 228:1, 1984.

508. George JM, Reier CE, Lanese RR et al: Morphine anesthesia blocks cortisol and growth hormone response to surgical stress in humans. J Clin Endocrinol Metab 38:736, 1974.

509. Briggs FN, Munson PL: Studies on the mechanism of stimulation of ACTH secretion with the aid of morphine as a blocking agent. Endocrinology 57:205, 1955.

510. Brandt MR, Korshin J, Prange Hansen A et al: Influence of morphine anesthesia on the endocrine-metabolic response to open heart surgery. Acta Anaesthesiol Scand 22:400, 1978.

511. Kayaalp SO, Kaymakcalan S: Studies on the morphine-induced release of catecholamine from the adrenal glands in the dog. Arch Int Pharmacodyn Ther 172:139, 1968.

512. Fennessey MR, Ortiz A: The behavioral and cardiovascular actions of intravenously administered morphine in the conscious dog. Eur J Pharmacol 3:177, 1968.

513. Reier CE, George JM, Kilman JW: Cortisol and growth hormone response to surgical stress during morphine anesthesia. Anesth Analg 52:1003, 1973.

514. Philbin DM, Wilson NE, Sokoloski J et al: Radioimmunoassay of antidiuretic hormone during morphine anaesthesia. Can Anaesth Soc J 23:290, 1976.

515. Hall GM, Young C, Holdcroft A et al: Substrate mobilisation during surgery: A comparison between halothane and fentanyl anesthesia. Anaesthesia 33:924, 1978.

516. Cooper GM, Paterson JL, Ward ID et al: Fentanyl and metabolic response to gastric surgery. Anaesthesia 36:667, 1981.

517. Giesecke K, Hamberger B, Jarnberg P-O et al: High- and low-dose fentanyl anaesthesia: Hormonal and metabolic responses during cholecystectomy. Br J Anaesth 61:575, 1988.

518. Sebel PS, Bovill JG, Schellekens APM et al: Hormonal responses of high-dose fentanyl anaesthesia: A study in patients undergoing cardiac surgery. Br J Anaesth 53:941, 1981.

519. Kono K, Philbin DM, Coggins CH et al: Renal function and stress response during halothane or fentanyl anesthesia. Anesth Analg 60:552, 1981.

520. Walsh ES, Patterson JL, O'Riordan JBA et al: Effects of high dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. Br J Anaesth 53:1155, 1981.

521. Anand KJS, Sippell WG, Aynsley-Green A: Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: Effects on the stress response. Lancet 1:243, 1987.

522. Ellis DJ, Steward DJ: Fentanyl dosage is associated with reduced blood glucose in pediatric patients after hypothermic cardiopulmonary bypass. Anesthesiology 72:812, 1990.

523. de Lange S, Boscoe M, Stanley TH et al: Antidiuretic and growth hormone responses during coronary artery surgery with sufentanil-oxygen and alfentanil-oxygen anesthesia in man. Anesth Analg 61:434, 1982.

524. de Lange S, Stanley TH, Boscoe MJ et al: Catecholamine and cortisol responses to sufentanil-O_2 and alfentanil-O_2 anaesthesia during coronary artery surgery. Can Anaesth Soc J 30:248, 1983.

525. Miller DR: Effects of alfentanil on the hemodynamic and catecholamine response to tracheal intubation. Anesth Analg 76:1040, 1993.

526. Monk TG, White PF, Mueller M et al: Stress response during balanced anesthesia: Optimal therapy. Anesthesiology 71:A129, 1989.

527. Moller IW, Krantz T, Wandall E et al: Effect of alfentanil anaesthesia on the adrenocortical and hyperglycaemic response to abdominal surgery. Br J Anaesth 57:591, 1985.

528. Yeager MP, Glass DD, Neff RK et al: Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 66:729, 1987.

529. Benefiel DJ, Roizen MF, Lampe GH et al: Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology 65:A516, 1986.

530. Plunkett JJ: Urine and plasma catecholamine and cortisol concentrations after myocardial revascularization. Anesthesiology 86:785, 1997.

531. Salo M: Cytokines and attenuation of responses to surgery. Acta Anaesthesiol Scand 40:141, 1996.

532. Portenoy RK: Pain management and chemical dependency. JAMA 278:592, 1997.

533. Nestler EJ, Aghajanian GK: Molecular and cellular basis of addiction. Science 278:58, 1997.

534. Romualdi P, Lesa G, Ferri S: Chronic opiate agonists down-regulate prodynorphine gene expression in rat brain. Brain Res 563:132, 1991.

535. Nestler EJ: Under siege: The brain on opiates. Neuron 16:897, 1996.

536. Chan KW, Duttory A, Yoburn BC: Magnitude of tolerance to fentanyl is independent of mu-opioid receptor density. Eur J Pharmacol 319:225, 1996.

537. Maldonado R, Fournie-Zaluski MC, Roques BP: Attenuation of the morphine withdrawal syndrome by inhibition of catabolism of endogenous enkephalins in the periaqueductal gray matter. Naunyn Schmiedebergs Arch Pharmacol 345:466, 1992.

538. Maze M: Why does insensitivity to opioid narcotics develop? Anesthesiology 87:1033, 1997.

539. Kissin I, Lee SS, Arthur GR et al: Time course characteristics of acute tolerance development to continuously infused alfentanil in rats. Anesth Analg 83:600, 1996.

540. Arnold JH, Truog RD, Orav EJ et al: Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. Anesthesiology 73:1136, 1990.

541. Kissin I, Brown PT, Robinson A et al: Acute tolerance in morphine analgesia: Continuous infusion and single injection in rats. Anesthesiology 74:166, 1991.

542. Stein C, Pfluger M, Yassouridis A et al: No tolerance to peripheral morphine analgesia in presence of opioid expression in inflamed synovia. J Clin Invest 98:793, 1996.

543. Gebhart GF: Some mechanistic insights into opioid tolerance (editorial). Anesthesiology 73:1065, 1990.

544. Duttaroy A, Yoburn BC: The effect of intrinsic efficacy on opioid tolerance. Anesthesiology 82:1226, 1995.

545. Ouellet DMC: Pharmacodynamics and tolerance development during multiple intravenous bolus morphine administration in rats. J Pharmacol Exp Ther 281:713, 1997.

546. Hanks GW, Forbes K: Opioid responsiveness. Acta Anaesthesiol Scand 41:154, 1997.

547. Thornton WE, Thornton BP: Narcotic poisoning: A review of the literature. Am J Psychiatry 131:867, 1974.

548. Cherubin CE: The medical sequelae of narcotics addiction. Ann Intern Med 67:23, 1967.

549. Fracchia C: Medical complications of heroin use: Anesthetic considerations. Anesth Rev 4:45, 1977.

550. Ling W, Wesson DR: Drugs of abuse: Opiates. West J Med 152:565, 1990.

551. Caldwell TB III: Anesthesia for patients with behavioral and environmental disorders: Anesthetic management of the narcotic addict. In Katz J, Benumof J, Kadis L (eds): Anesthesia and Uncommon Diseases. Philadelphia, WB Saunders, 1981, p 681.

552. Giuffrida JG, Bizzarri DV, Saure AC et al: Anesthetic management of drug abusers. Anesth Analg 49:272, 1970.

553. Jenkins LC: Anaesthetic problems due to drug abuse and dependence. Can Anaesth Soc J 19:461, 1972.

554. Pesonen A, Leppaluoto J, Ruskoaho H: Mechanism of opioidinduced atrial natriuretic peptide release in conscious rats. J Pharmacol Exp Ther 254:690, 1990.

555. Gutkowska J, Schiller PW: Renal effects of TAPP, a highly selective mu-opioid agonist. Br J Pharmacol 119:239, 1996.

556. Salas SP, Roblero JS, Lopez LF et al: [N-methyl-tyr ^{1} ,N-methyl-arg^{7} ,-D-leu^{8}]-dynorphin-A-(1-8) ethylamide, a stable dynorphin analog, produces diuresis by *kappa*-opiate receptor activation in the rat. J Pharmacol Exp Ther 262:979, 1992.

557. Deutch S, Bastron RD, Pierce EC et al: The effects of anaesthesia with thiopentone, nitrous oxide, narcotics and neuromuscular blocking drugs on renal function in normal man. Br J Anaesth 41:807, 1969.

558. Papper S, Papper EM: The effects of pre-anesthetic, anesthetic, and postoperative drugs on renal function. Clin Pharmacol Ther 5:205, 1964.

559. Hunter JM, Jones RS, Utting JE: Effect of anaesthesia with nitrous oxide in oxygen and fentanyl on renal function in the artificially ventilated dog. Br J Anaesth 52:343, 1980.

560. Kien ND, Reitan JA, White DA et al: Hemodynamic responses to alfentanil in halothane-anesthetized dogs. Anesth Analg 65:765, 1986.

561. Priano LL, Vatner SF: Morphine effects on cardiac output and regional blood flow distribution in conscious dogs. Anesthesiology 55:236, 1981.

562. Priano LL, Vatner SF: Generalized cardiovascular and regional hemodynamic effects of meperidine in conscious dogs. Anesth Analg 6:649, 1981.

563. Hill SA, Quinn K, Shelly MP et al: Reversible renal failure following opioid administration. Anaesthesia 46:938, 1991.

564. Stanley TH, Gray NH, Isern-Amaral J et al: Comparison of blood requirements during morphine and halothane anesthesia for open-heart surgery. Anesthesiology 41:34, 1974.

565. Drenger B, Magora F: Urodynamic studies after intrathecal fentanyl and buprenorphine in the dog. Anesth Analg 69:348, 1989.

566. Murphy DB, Sutton JA, Prescott LF et al: Opioid-induced delay in gastric emptying. Anesthesiology 87:765, 1997.

567. Kojima Y, Takahashi T, Fujina M et al: Inhibition of cholingergic transmission by by opiates in ileal myenteric plexus is mediated by kappa receptor: Involvement of regulatory inhibitory G protein and calcium n-channels. J Pharmacol Exp Ther 268:965, 1994.

568. Dowlatshahi K, Evander A, Walther B et al: Influence of morphine on the distal oesophagus and the lower oesophageal sphincter: A manometric study. Gut 26:802, 1985.

569. Sessler DI, Stoen R, Olofsson CI et al: Lower esophageal contractility predicts movement during skin incision in patients anesthetized with halothane, but not with nitrous oxide and alfentanil. Anesthesiology 70:42, 1989.

570. Lamki L, Sullivan S: A study of gastrointestinal opiate receptors: The role of the mu receptor on gastric emptying. Concise communication. J Nucl Med 24:689, 1983.

571. Schurizek BA, Willacy LHO, Kraglund K et al: Antroduodenal motility, pH and gastric emptying during balanced anaesthesia: Comparison of pethidine and fentanyl. Br J Anaesth 62:674, 1989.

572. Yukioka H, Tanaka M, Fujimori M: Recovery of bowel motility after high dose fentanyl or morphine anaesthesia for cardiac surgery. Anaesthesia 45:353, 1990.

573. Thorn SE, Wickbom G, Philipson L et al: Myoelectric activity in the stomach and duodenum after epidural administration of morphine or bupivacaine. Acta Anaesthesiol Scand 40:773, 1996.

574. Thorn SE, Wattwil M, Lindberg G et al: Systemic and central effects of morphine on gastroduodenal motility. Acta Anaesthesiol Scand 40:177, 1996.

575. Nimmo WS, Wilson J, Prescott LF: Narcotic analgesics and delayed gastric emptying during labour. Lancet 1:890, 1975.

576. Frame WT, Allison RH, Moirand DD et al: Effect of naloxone on gastric emptying during labour. Br J Anaesth 56:2636, 1984.

577. McNeill MJ, Ho ET, Kenny GNC: Effect of I.V. metoclopramide on gastric emptying after opioid premedication. Br J Anaesth 64:450, 1990.

578. Petring OU, Adelhoj B, Crawford M et al: The effect of droperidol on fentanyl-induced gastric emptying in man. Acta Anaesthesiol Scand 32:21, 1988.

579. Borody TJ, Quigley EEM, Phillips SF et al: Effects of morphine and atropine on motility and transit in the human ileum. Gastroenterology 89:5620, 1985.

580. Thangathurai D, Oyos T, Nelson D et al: The effect of papaverine and scopolamine on small bowel relaxation during surgery. Anesthesiology 69:A445, 1988.

581. Radnay PA, Duncalf D, Novakovic M et al: Common bile duct pressure changes after fentanyl, morphine, meperidine, butorphanol, and naloxone. Anesth Analg 63:441, 1984.

582. Vatashsky E, Haskel Y, Nissan S et al: Effect of morphine on the mechanical activity of common bile duct isolated from the guinea pig. Anesth Analg 66:245, 1987.

583. Vieira ZG, Duarte B, Renigers SA et al: Double-blind ultrasonographic demonstration of morphine-induced spasm of the common bile duct. Anesthesiology 69:A347, 1988.

584. Vieira ZG, Duarte B, Renigers SA et al: Double-blind ultrasonographic study of the effect of five analgesics on the common bile duct. Anesthesiology 71:A232, 1989.

585. Martin DE, Joehl RJ: Butorphanol and nalbuphine cause human bile duct obstruction. Anesthesiology 59:A324, 1983.

586. Jones R, Detmer M, Hill AB et al: Incidence of choledochoduodenal sphincter spasm during fentanyl-supplemented anesthesia. Anesth Analg 60:638, 1981.

587. Maltby JR, Williams RT: Morphine-induced cardiac pain? (letter). Anesthesiology 64:527, 1986.

588. Goldberg M, Vatashsky E, Haskel Y et al: The effect of meperidine on the guinea pig extrahepatic biliary tract. Anesth Analg 66:1282, 1987.

589. McCammon RL, Stoelting RK, Madura JA: Effects of butorphanol, nalbuphine and fentanyl on intrabiliary tract dynamics. Anesth Analg 63:139, 1984.

590. Granger DN, Richardson PDI, Kvietys PR et al: Intestinal blood flow. Gastroenterology 78:837, 1980.

591. Tverskoy M, Gelman S, Fowler KC et al: Influence of fentanyl and morphine on intestinal circulation. Anesth Analg 64:577, 1985.

592. Leaman DM, Levenson L, Zelis R et al: Effect of morphine on splanchnic blood flow. Br Heart J 40:569, 1978.

593. Baden JM, Kundomal YR, Luttropp ME et al: Effects of volatile anesthetics or fentanyl on hepatic function in cirrhotic rats. Anesth Analg 64:1183, 1985.

594. Shingu K, Eger EI II, Johnson BH et al: Hepatic injury induced by anesthetic agents in rats. Anesth Analg 62:140, 1983.

595. Hurwitz A, Fischer HR: Effects of morphine and respiratory depression on sulfobromophthalein disposition in rats. Anesthesiology 60:537, 1984.

596. Hurwitz A: Narcotic effects on phenol red disposition in mice. J Pharmacol Exp Ther 216:90, 1981.

597. Fisher DM: The "big little problem" of postoperative nausea and vomiting. Anesthesiology 87:1271, 1997.

598. Tramer MR, Reynolds JM, Moore A et al: Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting. Anesthesiology 87:1277, 1997.

599. Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment, and prevention. Anesthesiology 77:162, 1992.

600. Wang SC, Glaviano VV: Locus of emetic action of morphine and hydergine in dogs. J Pharmacol Exp Ther 111:329, 1954.

601. Harris AL: Cytotoxic therapy induced vomiting is mediated via enkephalin pathways. Lancet 1:714, 1982.

602. Beattie WS, Lindblad T, Buckley DN et al: Menstruation increases the risk of nausea and vomiting after laparoscopy. Anesthesiology 78:272, 1993.

603. Raftery S, Sherry E: Total intravenous anaesthesia with propofol and alfentanil protects against postoperative nausea and vomiting. Can J Anaesth 39:37, 1992.

604. Bailey PL, Streisand JB, Pace NL et al: Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. Anesthesiology 72:977, 1990.

605. Fan C-F, Tanjiu E, Joshi S et al: Acupressure treatment for prevention of postoperative nausea and vomiting. Anesth Analg 84:821, 1997.

606. Bruce DL, Hinkley R, Norman PF: Fentanyl does not inhibit fertilization or early development of sea urchin eggs. Anesth Analg 64:498, 1985.

607. Watson WJ: Fentanyl and fertilization (letter). Anesth Analg 65:102, 1986.

608. Palot M, Levron JC, Gabriel R et al: Follicular concentration of alfentanil during ultrasonically guided oocyte retrieval: Influence on cleavage rate. Anesthesiology 71:A888, 1989.

609. Fujinaga M, Stevenson JB, Mazze RI: Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats. Teratology 34:51, 1986.

610. Fujinaga M, Mazze RI, Jackson EL et al: Reproductive and teratogenic effects of sufentanil and alfentanil in Sprague-Dawley rats. Anesth Analg 67:166, 1988.

611. Kuhnert BR, Kuhnert PM, Philipson EH et al: Disposition of meperidine and normeperidine following multiple doses during labor. II. Fetus and neonate. Am J Obstet Gynecol 151:410, 1985.

612. Crawford JS, Rudofsky S: The placental transmission of pethidine. Br J Anaesth 37:929, 1965.

613. Caldwell J, Wakile LA, Notarianni LJ et al: Maternal and neonatal disposition of pethidine in childbirth: A study using quantitative gas chromatography-mass spectrometry. Life Sci 22:589, 1978.

614. Kuhnert BR, Linn PL, Kennard MJ et al: Effects of low doses of meperidine on neonatal behavior. Anesth Analg 64:335, 1985.

615. Hodgkinson R, Husain FJ: The duration of effect of maternally administered meperidine on neonatal neurobehavior. Anesthesiology 56:51, 1982.

616. Krishna BR, Zakowski MI, Grant GJ: Sufentanil transfer in the human placenta during *in vitro* perfusion. Can J Anaesth 44:996, 1997.

617. Sivalingam T, Pleuvry BJ: Actions of morphine, pethidine and pentazocine on the oestrus and pregnant rat uterus *in vitro.* Br J Anaesth 57:430, 1985.

618. Craft JB, Coaldrake LA, Bolan JC et al: Placental passage and uterine effects of fentanyl. Anesth Analg 62:894, 1983.

619. Rayburn W, Rathke A, Leuschen P et al: Fentanyl citrate analgesia during labor. Am J Obstet Gynecol 161:202, 1989.

620. Rayburn WF, Smith CV, Parriott JE et al: Randomized comparison of meperidine and fentanyl during labor. Obstet Gynecol 74:604, 1989.

621. Ashton WB, Janicki JP, Uys PC: Attenuation of the pressor response to tracheal intubation by magnesium sulfate with and without alfentanil in hypertensive proteinuric patients undergoing caesarean section. Br J Anaesth 67:741, 1991.

622. Batson MA, Longmire S, Csontos E: Alfentanil for urgent caesarean section in a patient with severe mitral stenosis and pulmonary hypertension. Can J Anaesth 37:685, 1990.

623. Wittels B, Scott DT, Sinatra RS: Exogenous opioids in human breast milk and acute neonatal neurobehavior: A preliminary study. Anesthesiology 73:864, 1990.

624. Spigset O: Anaesthetic agents and excretion in breast milk. Acta Anaesthesiol Scand 38:94, 1994.

625. Rosaeg OP, Kitts JB, Koren G et al: Maternal and fetal effects of intravenous patient-controlled fentanyl analgesia during labor in a thrombocytopenic parturient. Can J Anaesth 39:277, 1992.

626. Feilberg VL, Rosenborg D, Boren CC et al: Excretion of morphine in human breast milk. Acta Anaesthesiol Scand 33:426, 1989.

627. Steer PL, Biddle CJ, Marley WS et al: Concentration of fentanyl in colostrum after an analgesic dose. Can J Anaesth 39:231, 1992.

628. Doberczak TM, Kandall SR, Wilets I: Neonatal opiate abstinence syndrome in term and preterm infants. J Pediatr 118:933, 1991.

629. Fisher MM: The diagnosis of acute anaphylactoid reactions to anesthetic drugs. Anaesth Intensive Care 9:234, 1981.

630. Bennett MJ, Anderson LK, McMillar JC et al: Anaphylactic reaction during anaesthesia associated with positive intradermal skin test to fentanyl. Can Anaesth Soc J 33:75, 1986.

631. Levy JH, Rockoff MA: Anaphylaxis to meperidine. Anesth Analg 61:301, 1982.

632. Zucker-Pinchoff B, Ramanathan S: Anaphylactic reaction to epidural fentanyl. Anesthesiology 71:599, 1989.

633. Harle DG, Baldo BA, Coroneos NJ et al: Anaphylaxis following administration of papaveretum. Case report: Implication of IgE antibodies that react with morphine and codeine, and identification of an allergenic determinant. Anesthesiology 71:489, 1989.

634. Levy JH, Brister NW, Shearin A et al: Wheal and flare responses to opioids in humans. Anesthesiology 70:756, 1989.

635. Hibbs J, Perper J, Winek CL: An outbreak of designer drug-related deaths in Pennsylvania. JAMA 265:1011, 1991.

636. Feneck RO, Durkin MA: A comparison between the effects of fentanyl, droperidol with fentanyl, and halothane anaesthesia on intra-ocular pressure in adults. Anaesthesia 42:266, 1987.

637. Sweeney J, Underhill S, Dowd T et al: Modification by fentanyl and alfentanil of the intraocular pressure response to suxamethonium and tracheal intubation. Br J Anaesth 63:688, 1989.

638. Coley S, Jones GW, Lassey D et al: A comparison of the effects of alfentanil/droperidol or fentanyl/droperidol on intra-ocular pressure. Anaesthesia 45:477, 1990.

639. Stefano GB, Scharrer B, Smith EM et al: Opioid and opiate immunoregulatory processes. Crit Rev Immunol 16:109, 1996.

640. Carr DJJ, Rogers TJ, Weber RJ: The relevance of opioids and opioid receptors on immunocompetence and immune homeostasis. Proc Soc Exp Biol Med 213:248, 1993.

641. Gourlay GK, Kowalski SR, Plummer JL et al: Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 67:329, 1988.

642. Reilly CS, Wood AJJ, Wood M: Variability of fentanyl pharmacokinetics in man: Computer predicted plasma concentrations for three intravenous dosage regimens. Anaesthesia 40:837, 1984.

643. Egan TD: Pharmacokinetics and rational intravenous drug selection and administration in anesthesia. Adv Anesth 12:363, 1995.

644. Roerig DL, Kotrly KJ, Vucins EJ et al: First pass uptake of fentanyl, meperidine, and morphine in the human lung. Anesthesiology 67:466, 1987.

645. Dahlstrom B, Bolme P, Feychting H et al: Morphine kinetics in children. Clin Pharmacol Ther 26:354, 1979.

646. Stanski DR, Paalzow L, Edlund PO: Morphine pharmacokinetics: GLC assay versus radio immunoassay. J Pharm Sci 71:314, 1982.

647. Murphy MR, Hug CC Jr: Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. Anesthesiology 54:187, 1981.

648. Dahlstrom B, Tamsen A, Paalzow L et al: Patient controlled analgesia therapy. IV. Pharmacokinetics and analgesic plasma concentrations of morphine. Clin Pharmacokinet 7:266, 1982.

649. Hug CC Jr, Murphy MR, Rigel EP et al: Pharmacokinetics of morphine injected intravenously into the anesthetized dog. Anesthesiology 54:38, 1981.

650. Berkowitz BA: The relationship of pharmacokinetics to pharmacological activity: Morphine, methadone, and naloxone. Clin Pharmacokinet 1:219, 1976.

651. Boer F, Bovill JG, Burm AGL et al: Uptake of sufentanil, alfentanil and morphine in the lungs of patients about to undergo coronary artery surgery. Br J Anaesth 68:370, 1992.

652. Brunk SF, Delle M: Morphine metabolism in man. Clin Pharmacol Ther 16:51, 1974.

653. Mazoit JX, Sandouk P, Scherrmann J-M et al: Extrahepatic metabolism of morphine occurs in humans. Clin Pharmacol Ther 48:613, 1990.

654. Merrell WJ, Gordon L, Wood AJJ et al: The effect of halothane on morphine disposition: Relative contributions of the liver and kidney to morphine glucuronidation in the dog. Anesthesiology 72:308, 1990.

655. Sloan PA, Mather LE, McLean CF et al: Physiological disposition of I.V. morphine in sheep. Br J Anaesth 67:378, 1991.

656. Sasajima M: Analgesic effect of morphine-3-g1ucuronide. Keio Ogaka 47:421, 1970.

657. Frances B, Gout R, Monsarrat B et al: Further evidence that morphine-6beta-glucuronide is a more potent opioid agonist than morphine. J Pharmacol Exp Ther 262:25, 1992.

658. Portenoy RK, Thaler HT, Inturrisi CE et al: The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. Clin Pharmacol Ther 51:422, 1992.

659. Hanna MH, Peat SJ, Knibb AA et al: Disposition of morphine-6- glucuronide and morphine in healthy volunteers. Br J Anaesth 66:103, 1991.

660. Osborne R, Joel S, Trew D et al: Morphine and metabolite behavior after different routes of morphine administration: Demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol Ther 47:12, 1990.

661. Mather LE, Tucke GT, Pflug AE et al: Meperidine kinetics in man: Intravenous injection in surgical patients and volunteers. Clin Pharmacol Ther 17:21, 1975.

662. Klotz U, McHorse TS, Wilkinson GR et al: The effect of cirrhosis on the disposition and elimination of meperidine in man. Clin Pharmacol Ther 16:667, 1974.

663. Verbeeck RK, Branch RA, Wilkinson GR: Meperidine disposition in man: Influence of urinary pH and route of administration. Clin Pharmacol Ther 30:619, 1981.

664. Stambaugh JE, Wainer IW, Sanstead J et al: The clinical pharmacology of meperidine: Comparison of routes of administration. J Clin Pharmacol 16:245, 1976.

665. Austin KL, Stapleton JV, Mather LE: Multiple intramuscular injections: A major source of variability in analgesic response to meperidine. Pain 8:47, 1980.

666. Fung DL, Asling JH, Eisele JH et al: A comparison of alpha-prodine and meperidine pharmacokinetics. J Clin Pharmacol 20:37, 1980.

667. Miller JW, Anderson HH: The effect of N-demethylation on certain pharmacologic actions of morphine, codeine and meperidine in the mouse. J Pharmacol Exp Ther 112:191, 1954.

668. Szeto HH, Inturrisi CE, Houde R et al: Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. Ann Intern Med 86:738, 1977.

669. Fung DL, Eisele JH: Fentanyl pharmacokinetics in awake volunteers. J Clin Pharmacol 20:652, 1980.

670. Schleimer R, Benjamin E, Eisele J et al: Pharmacokinetics of fentanyl as determined by radioimmunoassay. Clin Pharmacol Ther 23:188, 1978.

671. Taeger K, Weninger E, Schmelzer F et al: Pulmonary kinetics of fentanyl and alfentanil in surgical patients. Br J Anaesth 61:425, 1988.

672. Meuldermans WEG, Hurkmans RMA, Heykants JJP: Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. Arch Int Pharmacodyn Ther 257:4, 1982.

673. Bjorkman S, Stanski DR, Verotta D et al: Comparative tissue concentration profiles of fentanyl and alfentanil in humans predicted from tissue/blood partition data obtained in rats. Anesthesiology 72:865, 1990.

674. Mather LE: Clinical pharmacokinetics of fentanyl and its newer derivatives. Clin Pharmacokinet 8:422, 1983.

675. Hug CC, Murphy MR: Tissue redistribution of fentanyl and termination of its effects in rats. Anesthesiology 55:369, 1981.

676. Silverstein JH, Reiders MF, McMullin M et al: Norfentanyl is detectable in urine for >48 hours; an advance for urine drug testing in anesthesia. Anesthesiology 75:A895, 1991.

677. Shafer A, Sun M-L, White PF: Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. Anesth Analg 65:1021, 1986.

678. Schuttler J, Stoeckel H: Alfentanil (R 39209) ein neues kurwirkendes opioid. Anaesthetist 31:10, 1982.

679. Bovill JG, Sebel PS, Blackburn CL et al: The pharmacokinetics of alfentanil (R39209): A new opioid analgesic. Anesthesiology 57:439, 1982.

680. Camu F, Gepts E, Rucquoi M et al: Pharmacokinetics of alfentanil in man. Anesth Analg 61:657, 1982.

681. Fragen RJ, Booij LHD, Braak GJJ et al: Pharmacokinetics of the infusion of alfentanil in man. Br J Anaesth 55:1077, 1983.

682. Hug CC Jr: Lipid solubility, pharmacokinetics, and the EEG: Are you better off today than you were four years ago? Anesthesiology 62:221, 1985.

683. Grevel J, Whiting B: The relevance of pharmacokinetics to optimal intravenous anesthesia. Anesthesiology 66:1, 1987.

684. Brater DC: Bayesian dosing of anesthetic agents: Esoteric or practical? Anesthesiology 69:641, 1988.

685. Waud BE, Waud DR: Dose-response curves and pharmacokinetics. Anesthesiology 65:355, 1986.

686. Hull CJ: The pharmacokinetics of alfentanil in man. Br J Anaesth 55:157S, 1983.

687. Ebling WF, Lee EN, Stanski DR: Understanding pharmacokinetics and pharmacodynamics through computer simulation. I. The comparative clinical profiles of fentanyl and alfentanil. Anesthesiology 72:650, 1990.

688. Meuldermans W, Hendrickx J, Lauwers W et al: Excretion and biotransformation of alfentanil and sufentanil in rats and dogs. Drug Metab Dispos 15:905, 1987.

689. Chauvin M, Bonnet F, Montembault C et al: The influence of hepatic plasma flow on alfentanil plasma concentration plateaus achieved with an infusion model. Anesth Analg 65:999, 1986.

690. Lavrijsen KLM, Van Houdt JMG, Van Dyck DMJ et al: Is the metabolism of alfentanil subject to debrisoquine polymorphism? Anesthesiology 69:535, 1988.

691. Meuldermans W, van Peer A, Hendricks J et al: Alfentanil pharmacokinetics and metabolism in humans. Anesthesiology 69:527, 1988.

692. Kharasch ED, Thummel KE: Human alfentanil metabolism by cytochrome P450 3A3/4: An explanation for the interindividual variability in alfentanil clearance? Anesth Analg 76:1033, 1993.

693. Wrighton SA, Ring BJ, Watkins PB et al: Identification of a polymorphically expressed member of the human cytochrome P-450III family. Mol Pharmacol 36:97, 1989.

694. Bovill JG, Sebel PS, Blackburn CL et al: The pharmacokinetics of sufentanil in surgical patients. Anesthesiology 61:502, 1984.

695. Hudson RJ, Bergstrom RG, Thomson IR et al: Pharmacokinetics of sufentanil in patients undergoing abdominal aortic surgery. Anesthesiology 70:426, 1989.

696. Woestenborghs RJ, Timmerman PM, Cornelissen ML et al: Assay methods for sufentanil in plasma: Radioimmunoassay versus gas chromatography-mass spectrometry. Anesthesiology 80:666, 1994.

697. Gepts E, Shafer SL, Camu F et al: Linearity of pharmacokinetics and model estimation of sufentanil. Anesthesiology 83:1194, 1995.

698. Lavrijsen K, Van Houdt J, Van Dyck D et al: Biotransformation of sufentanil in liver microsomes of rats, dogs, and humans. Drug Metab Dispos 18:704, 1990.

699. Egan TD: Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal. Clin Pharmacokinet 29:80, 1995.

700. Duthie DJ, Stevens JJ, Doyle AR et al: Remifentanil and pulmonary extraction during and after cardiac anesthesia. Anesth Analg 84:740, 1997.

701. Egan TD, Lemmens HJM, Fiset P et al: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 79:881, 1993.

702. Westmoreland CL, Hoke JF, Sebel PS et al: Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology 79:893, 1993.

703. Egan TD, Minto CF, Hermann DJ et al: Remifentanil versus alfentanil: Comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers (erratum appears in Anesthesiology 85:695, 1996). Anesthesiology 84:821, 1996.

704. Glass PS: Remifentanil: A new opioid. J Clin Anesth 7:558, 1995.

705. Buerkle H, Yaksh TL: Continuous intrathecal administration of shortlasting mu opioids remifentanil and alfentanil in the rat. Anesthesiology 84:926, 1996.

706. Cunningham FE, Hoke JF, Muir KT: Pharmacokinetic/pharmacodynamic evaluation of remifentanil, GI90291 and alfentanil. Anesthesiology 83:A376, 1995.

707. Dershwitz M, Hoke JF, Rosow CE et al: Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease. Anesthesiology 84:812, 1996.

708. Hoke JF, Shlugman D, Dershwitz M et al: Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers. Anesthesiology 87:533, 1997.

709. Selinger K, Nation RL, Smith A: Enzymatic and chemical hydrolysis of remifentanil. Anesthesiology 83:A385, 1995.

710. Stiller RL, Davis PJ, McGowan FX et al: *In vitro* metabolism of remifentanil: The effects of pseudocholinesterase deficiency. Anesthesiology 83:A381, 1995.

711. Fisher DM: (Almost) everything you learned about pharmacokinetics was (somewhat) wrong! (editorial; comment). Anesth Analg 83:901, 1996.

712. Shafer SL, Stanski DR: Improving the clinical utility of anesthetic drug pharmacokinetics (editorial). Anesthesiology 76:327, 1992.

713. Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 76:334, 1992.

714. Youngs EJ, Shafer SL: Pharmacokinetic parameters relevant to recovery from opioids (erratum appears in Anesthesiology 82:326, 1995). Anesthesiology 81:833, 1994.

715. Verotta D, Sheiner LB: Simultaneous modeling of pharmacokinetics and pharmacodynamics: An improved algorithm. Comput Appl Biosci 3:345, 1987.

716. Verotta D, Beal SL, Sheiner LB: Semiparametric approach to pharmacokinetic-pharmacodynamic data. Am J Physiol 256:R1005, 1989.

717. Kramer TH, d'Amours RH, Buetner C: Pharmacodynamic model of the effects of morphine and morphine-6-glucuronide during patient-controlled analgesia. Clin Pharmacol Ther 59:132, 1996.

718. Egan TD: The clinical pharmacology of the new fentanyl congeners. Anesth Analog (IARS Supplement to 71 st Annual Meeting) 1997.

719. Bailey J: Technique for quantifying the duration of intravenous anesthetic effect. Anesthesiology 83:1095, 1995.

720. Austin KL, Stapleton JV, Mather LE: Relationship between blood meperidine concentrations and analgesic response: A preliminary report. Anesthesiology 53:460, 1980.

721. Egan TD: Intravenous drug delivery systems: Toward an intravenous "vaporizer." J Clin Anesth 8:952, 1996.

722. Schwilden H: A general method for calculating the dosage scheme in linear pharmacokinetics. Eur J Clin Pharmacol 20:379, 1981.

723. Shafer SL, Varvel JR, Aziz N et al: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. Anesthesiology 73:1091, 1990.

724. van den Nieuwenhuyzen MC, Engbers FH, Burm AG et al: Computer-controlled infusion of alfentanil versus patient-controlled administration of morphine for postoperative analgesia: A double-blind randomized trial (see comments). Anesth Analg 81:671, 1995.

725. Hill HF, Saeger L, Bjurstrom R et al: Steady-state infusions of opioids in human volunteers. I. Pharmacokinetic tailoring. Pain 43:57, 1990.

726. McEwan AI, Smith C, Dyar O et al: Isoflurane minimum alveolar concentration reduction by fentanyl (see comments). Anesthesiology 78:864, 1993.

727. Lang E, Kapila A, Shlugman D et al: Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 85:721, 1996.

728. Levy DL, Warriner RAI, Burgess GE: Fetal response to cardiopulmonary bypass. Obstet Gynecol 56:112, 1980.

729. Fisher DM: Surrogate end points. Are they meaningful? (editorial; comment; see comments). Anesthesiology 81:795, 1994.

730. Egan TD, Muir KT, Stanski DR et al: Using the EEG fingerprint to define the clinical pharmacology of a new opioid: Application to remifentanil. Clin Pharmacol Ther 59:129, 1996.

731. Olkkola KT, Hamunen K, Maunuksela EL: Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. Clin Pharmacokinet 28:385, 1995.

732. Mannering FJ: Drug metabolism in the newborn. Fed Proc 44:2302, 1985.

733. Lynn AM, Slattery JT: Morphine pharmacokinetics in early infancy. Anesthesiology 66:136, 1987.

734. Goresky GV, Koren G, Sabourin MA et al: The pharmacokinetics of alfentanil in children. Anesthesiology 67:654, 1987.

735. Roure P, Jean N, Leclerc A-C et al: Pharmacokinetics of alfentanil in children undergoing surgery. Br J Anaesth 59:1437, 1987.

736. Matteo RS, Schwartz AE, Ornstein E et al: Pharmacokinetics of sufentanil in the elderly surgical patient. Can J Anaesth 37:852, 1990.

737. Helmers H, Van Peer A, Woestenborghs R et al: Alfentanil kinetics in the elderly. Clin Pharmacol Ther 36:239, 1984.

738. Singleton MA, Rosen JI, Fisher DM: Pharmacokinetics of fentanyl in the elderly. Br J Anaesth 60:619, 1988.

739. Minto CF, Schnider TW, Egan TD et al: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 86:10, 1997.

740. Bentley JB, Borel JD, Gillespie TJ et al: Fentanyl pharmacokinetics in obese and nonobese patients. Anesthesiology 55:A177, 1981.

741. Schwartz AE, Matteo RS, Ornstein E et al: Pharmacokinetics of sufentanil in obese patients. Anesth Analg 73:790, 1991.

742. Morgan DJ, Bray KM: Lean body mass as a predictor of drug dosage: Implications for drug therapy. Clin Pharmacokinet 26:292, 1994.

743. Maitre PO, Vozeh S, Heykants J et al: Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. Anesthesiology 66:3, 1987.

744. Roubenoff R, Kehayias JJ: The meaning and measurement of lean body mass. Nutr Rev 49:163, 1991.

745. Davies G, Kingswood C, Street M: Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet 31:410, 1996.

746. Pasternak GW, Bodnar RJ, Clark JA et al: Morphine-6-glucuronide, a potent mu agonist. Life Sci 41:2845, 1987.

747. Osborne RJ, Joel SP, Slevin ML: Morphine intoxication in renal failure: The role of morphine-6-glucuronide. BMJ 292:1548, 1986.

748. D'Honneur G, Gilton A, Sandouk P et al: Plasma and cerebrospinal fluid concentrations of morphine and morphine glucuronides after oral morphine: The influence of renal failure. Anesthesiology 81:87, 1994.

749. Mostert J, Evers J, Hobika J et al: Cardiorespiratory effects of anaesthesia with morphine or fentanyl in chronic renal failure and cerebral toxicity after morphine. Br J Anaesth 43:1053, 1985.

750. Osborne R, Joel S, Grebenik K et al: The pharmacokinetics of morphine and morphine glucuronides in kidney failure (see comments). Clin Pharmacol Ther 54:158, 1993.

751. Shochet RB, Murray GB: Neuropsychiatric toxicity of meperidine. J Intensive Care Med 3:246, 1988.

752. Kaiko RF, Foley KM, Grabinski PY: Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol 13:180, 1983.

753. Jiraki K: Lethal effects of normeperidine. Am J Forensic Med Pathol 13:42, 1992.

754. Geller RJ: Meperidine in patient-controlled analgesia: A near-fatal mishap. Anesth Analg 76:655, 1993.

755. Gedney JA, Ghosh S: Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. Br J Anaesth 75:344, 1995.

756. Coral IM, Moore AR, Struinin L: Plasma concentrations of fentanyl in normal surgical patients with severe renal failure. Br J Anaesth 52:101, 1980.

757. Bower S: Plasma protein binding of fentanyl: The effect of hyperlipoproteinaemia and chronic renal failure. J Pharm Pharmacol 34:102, 1981.

758. Davis PJ, Stiller RL, Cook DR et al: Pharmacokinetics of sufentanil in adolescent patients with chronic renal failure. Anesth Analg 67:268, 1988.

759. Sear JW: Sufentanil disposition in patients undergoing renal transplantation: Influence of choice of kinetic model. Br J Anaesth 63:60, 1989.

760. Fyman PN, Reynolds JR, Moser F et al: Pharmacokinetics of sufentanil in patients undergoing renal transplantation. Can J Anaesth 35:312, 1988.

761. van Peer A, Vercauteren M, Noorduin H et al: Alfentanil kinetics in renal insufficiency. Eur J Clin Pharmacol 30:245, 1986.

762. Chauvin M, Lebrault C, Levron JC et al: Pharmacokinetics of alfentanil in chronic renal failure. Anesth Analg 66:53, 1987.

763. Klotz U, Antonin KH, Brugel H et al: Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease. Clin Pharmacol Ther 21:430, 1977.

764. Blaschke TF: Protein binding and kinetics of drugs in liver diseases. Clin Pharmacokinet 2:32, 1977.

765. Parwardhan RV, Johnson RF, Hoyumpa A: Normal metabolism of morphine in cirrhosis. Gastroenterology 81:1006, 1981.

766. Mazoit J-X, Sandouk P, Zetlaoui P et al: Pharmacokinetics of unchanged morphine in normal and cirrhotic subjects. Anesth Analg 66:293, 1987.

767. Klotz I, Avant G, Hoyumpa A et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 55:347, 1975.

768. Neal EA, Meffin PJ, Gregory PB et al: Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. Gastroenterology 77:96, 1979.

769. Pond SM, Tong T, Benowitz NL et al: Presystemic metabolism of meperidine to normeperidine in normal and cirrhotic subjects. Clin Pharmacol Ther 30:183, 1981.

770. McHorse TS, Wilkinson GR, Johnson RF et al: Effect of acute viral hepatitis in man on the disposition and elimination of meperidine. Gastroenterology 68:775, 1975.

771. Haberer JP, Schoeffler P, Couderc E et al: Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. Br J Anaesth 54:1267, 1982.

772. Tammisto T, Tigerstedt I: The need for fentanyl supplementation of N_2O-O_2 relaxant anaesthesia in chronic alcoholics. Acta Anaesthesiol Scand 21:216, 1977.

773. Ferrier C, Marty J, Bouffard Y et al: Alfentanil pharmacokinetics in patients with cirrhosis. Anesthesiology 62:480, 1985.

774. Davis PJ, Stiller RL, Cook DR et al: Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. Anesth Analg 68:579, 1989.

775. Lemmens HJ, Burm AGL, Bovill JG et al: Pharmacodynamics of alfentanil. Anesthesiology 76:65, 1992.

776. Lemmens HJM, Bovill JG, Hennis PJ et al: Alcohol consumption alters the pharmacodynamics of alfentanil. Anesthesiology 71:669, 1989.

777. Reitz J, MacKichan JJ, Hoffer L et al: Reduced plasma clearance of alfentanil associated with prolonged major intra-abdominal surgery. Anesth Analg 63:265, 1984.

778. Hudson RJ, Thomson IR, Burgess PM et al: Alfentanil pharmacokinetics in patients undergoing abdominal aortic surgery. Can J Anaesth 38:61, 1991.

779. Chauvin M, Ferrier C, Haberer JP et al: Sufentanil pharmacokinetics in patients with cirrhosis. Anesth Analg 68:1, 1989.

780. Navapurkar VU, Archer S, Frazer NM et al: Pharmacokinetics of remifentanil during hepatic transplantation. Anesthesiology 83:A382, 1995.

781. Buylaert WA, Herregods LL, Mortier EP et al: Cardiopulmonary bypass and the pharmacokinetics of drugs: An update. Clin Pharmacokinet 17:10, 1989.

782. Kentala E, Kaila T, Arola M et al: Pharmacokinetics and clinical response of hyoscine plus morphine premedication in connection with cardiopulmonary bypass surgery. Eur J Anaesthesiol 8:135, 1991.

783. Skacel M, Knott C, Reynolds F et al: Extracorporeal circuit sequestration of fentanyl and alfentanil. Br J Anaesth 58:947, 1986.

784. Rosen D, Rosen K, Davidson B et al: Fentanyl uptake by the Scimed membrane oxygenator. J Cardiothorac Anesth 2:619, 1988.

785. Koska AJ III, Romagnoli A, Kramer WG: Effect of cardiopulmonary bypass on fentanyl distribution and elimination. Clin Pharmacol Ther 29:100, 1981.

786. Sprigge JS, Wynands JE, Whalley DG et al: Fentanyl infusion anesthesia for aortocoronary bypass surgery: Plasma levels and hemodynamic response. Anesth Analg 61:972, 1982.

787. Okutani RYU, Philbin DM, Rosow CE et al: Effect of hypothermic hemodilutional cardiopulmonary bypass on plasma sufentanil and catecholamine concentrations in humans. Anesth Analg 67:667, 1988.

788. Rosen KR, Rosen DA: Absorption of sufentanil by the membrane oxygenator. Anesthesiology 65:A224, 1986.

789. Durkan W, Lonergan M, Schwartz S et al: Effect of membrane oxygenators on sufentanil blood levels during cardiopulmonary bypass. Anesth Analg 67:S54, 1988.

790. Hug CC Jr, Burm AG, de Lange S: Alfentanil pharmacokinetics in cardiac surgical patients. Anesth Analg 78:231, 1994.

791. Hynynen M, Hynninen M, Soini H et al: Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. Br J Anaesth 72:571, 1994.

792. Russell D, Royston D, Rees PH et al: Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil. Br J Anaesth 79:456, 1997.

793. Nishitateno K, Ngai SH, Finck AD et al: Pharmacokinetics of morphine: Concentrations in the serum and brain of the dog during hyperventilation. Anesthesiology 50:520, 1979.

794. Benson DW, Kaufman JJ, Koski WS: Theoretic significance of pH dependence of narcotics and narcotic antagonists in clinical anesthesia. Anesth Analg 55:253, 1976.

795. Finck AD, Berkowitz BA, Hempstead J et al: Pharmacokinetics of morphine: Effects of hypercarbia on serum and brain morphine concentrations in the dog. Anesthesiology 47:407, 1977.

796. Lullmann H, Martins B-S, Peters T: pH-dependent accumulation of fentanyl, lofentanil, and alfentanil by beating guinea pig atria. Br J Anaesth 57:1012, 1985.

797. Schulman DS, Kaufman JJ, Eisenstein MM et al: Blood pH and brain uptake of ^{14}C-morphine. Anesthesiology 61:540, 1984.

798. Schwartz AE, Matteo RS, Ornstein E et al: Pharmacokinetics of sufentanil in neurosurgical patients undergoing hyperventilation. Br J Anaesth 63:385, 1989.

799. Woolf CJ: Windup and central sensitization are not equivalent (editorial). Pain 66:105, 1996.

800. Kissin I: Preemptive analgesia: Why its effect is not always obvious. Anesthesiology 84:1015, 1996.

801. Katz J, Clairoux M, Redahan C et al: High dose alfentanil pre-empts pain after abdominal hysterectomy. Pain 68:109, 1996.

802. Woolf CJ, Chong M-S: Preemptive analgesia: Treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:362, 1993.

803. Gottschalk A, Smith DS, Jobes DR et al: Preemptive epidural analgesia and recovery from radical prostatectomy: A randomized controlled trial. JAMA 279:1076, 1998.

804. Ready LB, Ashburn M, Caplan RA et al: Practice guidelines for acute pain management in the perioperative setting. Anesthesiology 82:1071, 1995.

805. Wasylak TJ, Abbott FV, English MJM et al: Reduction of post-operative morbidity following patient-controlled morphine. Can J Anaesth 37:726, 1990.

806. Upton RN, Semple TJ, Macintyre P: Pharmacokinetic optimisation of opioid treatment in acute pain therapy. Clin Pharmacokinet 33:225, 1997.

807. Plummer JL, Owen H, Ilsley AH et al: Morphine patient-controlled analgesia is superior to meperidine patient-controlled analgesia for postoperative pain. Anesth Analg 84:794, 1997.

808. Crile GW: Phylogenetic association in relation to certain medical problems. Boston Med Surg J 163:893, 1910.

809. Woodbridge PD: Changing concepts concerning depth of anesthesia. Anesthesiology 18:536, 1957.

810. Mushin WW, Rendell-Baker L: Pethidine as a supplement to nitrous oxide anaesthesia. BMJ 2:472, 1949.

811. Brotman M, Cullen SC: Supplementation with demerol during nitrous oxide anesthesia. Anesthesiology 10:696, 1949.

812. Siker ES, Foldes FF, Pahk NM et al: Nisentil (1, 3, dimethyl-4-phenyl-4-propionoxypiperidine): A new supplement for nitrous oxide oxygen thiopentone (Pentothal sodium) anaesthesia. Br J

Anaesth 26:405, 1954.

813. Dundee JW, Brown SS, Hamilton RC et al: Analgesic supplementation of light general anesthesia: A study of its advantages using sequential analysis. Anaesthesia 24:52, 1969.

814. Kay B, Rolly G: Duration of action of analgesic supplement to anesthesia. Acta Anaesthesiol Belg 28:25, 1977.

815. Coe V, Shafer A, White PF: Techniques for administering alfentanil during outpatient anesthesia: A comparison with fentanyl. Anesthesiology 59:A347, 1983.

816. Kuperwasser B, Dahl M, McSweeney TD et al: Comparison of alfentanil and sufentanil in the ambulatory surgery procedure when used in balanced anesthesia technique. Anesth Analg 67:S122, 1988.

817. Kalenda Z, Scheijground HW: Anaesthesia with sufentanil-analgesia in carotid and vertebral arteriography. A comparison with fentanyl. Anaesthesist 25:380, 1976.

818. Clark NJ, Meuleman T, Liu W et al: Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology 66:130, 1987.

819. van de Walle J, Lauwers P, Adriaensen H: Double blind comparison of fentanyl and sufentanil in anesthesia. Acta Anaesthesiol Belg 27:129, 1976.

820. Patrick M, Eagar B, Toft DF et al: Alfentanil supplemented anesthesia for short procedures: A double blind comparison with fentanyl. Anesthesiology 59:A346, 1983.

821. Rosow CE, Latta WB, Keegan CR et al: Alfentanil and fentanyl in short surgical procedures. Anesthesiology 59:A345, 1983.

822. White PF, Coe V, Shafer A et al: Comparison of alfentanil with fentanyl for outpatient anesthesia. Anesth Analg 64:99, 1986.

823. Kallar SK, Keenan RL: Evaluation and comparison of recovery time from alfentanil and fentanyl for short surgical procedures. Anesthesiology 61:A379, 1984.

824. Cooper GM, O'Connor M, Mark J et al: Effect of alfentanil and fentanyl on recovery from brief anaesthesia. Br J Anaesth 55:179S, 1983.

825. Stanley TH, Pace NL, Liu WS et al: Alfentanil-N_2O vs fentanyl-N_2O balanced anesthesia: Comparison of plasma hormonal changes, early postoperative respiratory function, and speed of postoperative recovery. Anesth Analg 62:285, 1983.

826. Kay B, Cohen AT: Intravenous anaesthesia for minor surgery. A comparison of etomidate or althesin with fentanyl and alfentanil. Br J Anaesth 55:165S, 1983.

827. Kestin IG, Dorje P: Anaesthesia for evacuation of retained products of conception: Comparison between alfentanil plus etomidate and fentanyl plus thiopentone. Br J Anaesth 59:364, 1987.

828. McKay RD, Varner PD, Hendricks PL et al: The evaluation of sufentanil-N_2O-O_2 anesthesia for craniotomy. Anesth Analg 63:250, 1984.

829. Flacke JW, Bloor BC, Flacke WE et al: Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: A double-blind study. Anesth Analg 64:897, 1985.

830. From RP, Warner DS, Todd MM et al: Anesthesia for craniotomy: A double-blind comparison of alfentanil, fentanyl, and sufentanil. Anesthesiology 73:896, 1990.

831. O'Connor M, Sear JW: Sufentanil to supplement nitrous oxide in oxygen during balanced anaesthesia. Anaesthesia 43:749, 1988.

832. Glenski JA, Friesen RH, Lane GA et al: Low-dose sufentanil as a supplement to halothane/N_2O anesthesia in infants and children. Can J Anaesth 35:379, 1988.

833. Ebert JP, Pearson JD, Gelman S et al: Circulatory responses to laryngoscopy: The comparative effects of placebo, fentanyl and esmolol. Can J Anaesth 36:301, 1989.

834. Smith C, McEwan AI, Jhaveri R et al: The interaction of fentanyl on the Cp_{50} of propofol for loss of consciousness and skin incision. Anesthesiology 81:820, 1994.

835. Martin DE, Rosenberg H, Aukberg SJ et al: Low-dose fentanyl blunts circulatory responses to tracheal intubation. Anesth Analg 61:680, 1982.

836. Cork RC, Weiss JL, Hameroff SR et al: Fentanyl preloading for rapid-sequence induction of anesthesia. Anesth Analg 63:60, 1984.

837. Van Aken H, Meinshausen E, Prien T et al: The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N_2O in humans. Anesthesiology 68:157, 1988.

838. Andrews DT, Leslie K, Sessler DI et al: The arterial blood propofol concentration preventing movement in 50% of healthy women after skin incision. Anesth Analg 85:414, 1997.

839. Vuyk J, Engbers FHM, Burm AGL et al: Pharmacodynamic interaction between propofol and alfentanil when given for induction of anesthesia. Anesthesiology 84:288, 1996.

840. Billard V, Moulla F, Bourgain JL et al: Hemodynamic response to induction and intubation. Anesthesiology 81:1384, 1994.

841. Kazama T, Ikeda K, Morita K: Reduction by fentanyl of the CP_{50} Values of propofol and hemodynamic responses to various noxious stimuli. Anesthesiology 87:231, 1997.

842. Katoh T, Uchiyama T, Ikeda K: Effect of fentanyl on awakening concentration of sevoflurane. Br J Anaesth 73:322, 1994.

843. Ben-Shlomo I, Abd-El-Khalim H, Ezry J et al: Midazolam acts synergistically with fentanyl for induction of anaesthesia. Br J Anaesth 64:45, 1990.

844. Griffiths G: In reply (letter). Anesthesiology 64:667, 1986.

845. Hilberman M, Hyer D: Potency of sufentanil (letter). Anesthesiology 64:665, 1986.

846. Lehmann KA, Heinrich C, van Heiss R: Balanced anesthesia and patient controlled postoperative analgesia with fentanyl: Minimum effective concentrations, accumulation and acute tolerance. Acta Anaesthesiol Belg 39:11, 1988.

847. Glass PSA, Doherty M, Jacobs JR et al: Plasma concentration of fentanyl, with 70% nitrous oxide, to prevent movement at skin incision. Anesthesiology 78:842, 1993.

848. Wynands JE, Wong P, Townsend GE et al: Narcotic requirements for intravenous anesthesia. Anesth Analg 63:101, 1984.

849. Nishina K, Mikawa K, Markawa N et al: Fentanyl attenuates cardiovascular responses to tracheal extubation. Acta Anesthesiol Scand 39:85, 1995.

850. Marty J, Couderc E, Servin F et al: Plasma concentrations of sufentanil required to suppress hemodynamic responses to noxious stimuli during nitrous oxide anesthesia. Anesthesiology 69:A631, 1988.

851. Murkin JM: Multicentre trial. Sufentanil anaesthesia for major surgery: The multicentre Canadian clinical trial. Can J Anaesth 36:343, 1989.

852. Vinik HR, Bradley EL Jr, Kissin I: Triple anesthetic combination: Propofol-midazolam-alfentanil. Anesth Analg 78:354, 1994.

853. Vuyk J, Lim T, Engbers FHM et al: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 83:8, 1995.

854. Smith I, Jan Hemelrijck J, White PF: Efficacy of esmolol versus alfentanil as a supplement to propofol-nitrous oxide anesthesia. Anesth Analg 73:540, 1991.

855. Stevens JB, Vescovo MV, Harris KC et al: Tracheal intubation using alfentanil and no muscle relaxant: Is the choice of hypnotic important? Ambulatory Anesth 84:1222, 1997.

856. Scheller MS, Zornow MH, Saidman LJ: Tracheal intubation without the use of muscle relaxants: A technique using propofol and varying doses of alfentanil. Anesth Analg 75:788, 1992.

857. Vuyk J, Lim T, Engbers FHM et al: The pharmacodynamics of alfentanil as a supplement to propofol or nitrous oxide for lower abdominal surgery. Anesthesiology 77:A402, 1992.

858. Bernstein K, Wirpszo R, Djarv L: Anesthesia with alfentanil and methohexitone for short gynecological surgery. Acta Anaesthesiol Scand 33:458, 1989.

859. Miller DR, Martineau RJ, Ewing D et al: Cardiovascular response of a continuous variable rate alfentanil infusion for abdominal aortic surgery. Can J Anaesth 37:844, 1990.

860. Randel GI, Fragen RJ, Librojo ES: Remifentanil blood concentration effect relationship at intubation and skin incision in surgical patients compared to alfentanil (abstract). Anesthesiology 81:A375, 1994.

861. Hogue CW Jr, Bowdle TA, O'Leary C et al: A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery. Anesth Analg 83:279, 1996.

862. Patel SS, Spencer CM: Remifentanil. Drugs 52:417, 1996.

863. Yarmush J, D'Angelo R, Kirkhart B et al: A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifantanil and propofol. Anesthesiology 87:235, 1997.

864. Laborit H, Huygenard P: Practique de l'hibernotherapie en chirurgie et en medicine. Paris, Masson, 1954.

865. De Castro J, Mundeleer R: Anesthesie sans barbituratiques: La neuroleptanalgesie. Anaesth Analg (Paris) 16:1022, 1959.

866. Edmonds-Seal J, Prys-Roberts C: Pharmacology of drugs used in neuroleptanalgesia. Br J Anaesth 42:207, 1970.

867. Long G, Dripps RD, Price HL: Measurements of anti-arrhythmic potency of drugs in man: Effects of dehydrobenzperidol. Anesthesiology 28:318, 1967.

868. Gomez-Arnau J, Marquez-Montes J, Avello F: Fentanyl and droperidol effects on the refractoriness of the accessory pathway in the Wolff-Parkinson-White syndrome. Anesthesiology 58:307, 1983.

869. Welsh MJ, Heistad DD, Abboud PM: Depression of ventilation by dopamine in man. J Clin Invest 61:708, 1978.

870. Johnson KB, Egan TD: Remifentanil and propofol combination for awake craniotomy: Case report with pharmacokinetic simulations. J Neurosurg Anesthesiol 10:25, 1998.

871. Clarke AD, Tobias MA, Challen PDP: The use of neuroleptanalgesia during surgery of pheochromocytoma. Br J Anaesth 44:1093, 1972.

872. Ogawa R, Fujita T: Neuroleptanaesthesia for the surgery of pheochromocytomas. Masui 21:174, 1972.

873. Wood M: Editorial: Variability of human drug response. Anesthesiology 71:631, 1989.

874. Ausems ME, Vuyk J, Hug CC Jr et al: Comparison of a computerassisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 68:851, 1988.

875. Alvis JM, Reves JG, Govier AV et al: Computer-assisted continuous infusions of fentanyl during cardiac anesthesia: Comparison with a manual method. Anesthesiology 63:41, 1985.

876. Pathak KS, Brown RH, Nash CL Jr et al: Continuous opioid infusion for scoliosis fusion surgery. Anesth Analg 62:841, 1983.

877. White PF: Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology 59:294, 1983.

878. Raemer DB, Buschman A, Varvel JR et al: The prospective use of population pharmacokinetics in a computer-driven infusion system for alfentanil. Anesthesiology 73:66, 1990.

879. Maitre PO, Shafer SL: A simple pocket calculator approach to predict anesthetic drug concentrations from pharmacokinetic data. Anesthesiology 73:332, 1990.

880. Jenstrup M, Fruegard K, Nielsen J et al: Alfentanil infusion in total intravenous anaesthesia (TIVA): Population pharmacokinetics fails to predict plasma concentration of alfentanil. Acta Anaesthesiol Scand 36:846, 1992.

881. White PF: Are new drugs cost-effective for patients undergoing ambulatory surgery? (editorial). Anesthesiology 78:2, 1993.

882. Lubarsky DA, Glass PSA, Ginsberg B et al: The successful implementation of pharmaceutical practice guidelines. Anesthesiology 86:1145, 1997.

883. Vuyk J, Lim T, Engbers F et al: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 83:8, 1995.

884. Stanski DR, Shafer SL: Quantifying anesthetic drug ineraction. Anesthesiology 83:1, 1995.

885. Vuyk J, Mertens MJ, Olofsen E et al: Propofol anesthesia and ration-al opioid selection. Anesthesiology 87:1549, 1997.

886. Bailie R, Christmas L, Price N et al: Effects of temazepam premedication on cognitive recovery following alfentanil-propofol anaesthesia. Br J Anaesth 63:68, 1989.

887. Richards MJ, Skues MA, Jarvis AP et al: Total I.V. anaesthesia with propofol and alfentanil: Dose requirements for propofol and the effect of premedication with clonidine. Br J Anaesth 65:157, 1990.

888. Saarnivaara L, Klemola UM: Injection pain, intubating conditions and cardiovascular changes following induction of anaesthesia with propofol alone or in combination with alfentanil. Acta Anaesthesiol Scand 35:19, 1991.

889. Hiller A, Saarnivaara L: Injection pain, cardiovascular changes and recovery following induction of anaesthesia with propofol in combination with alfentanil and lignocaine in children. Acta Anaesthesiol Scand 36:564, 1992.

890. McDonnell TE, Bartkowski RR, Bonilla FA et al: Evidence for polymorphic oxidation of alfentanil in man. Anesthesiology 61:A284, 1984.

891. Vuyk J, Hennis PJ, Burm AGL et al: Comparison of midazolam and propofol in combination with alfentanil for total intravenous anesthesia. Anesth Analg 71:645, 1990.

892. Raza SMA, Masters RW, Vasireddy AR et al: Haemodynamic stability with midazolam-sufentanil analgesia in cardiac surgical patients. Can J Anaesth 35:518, 1988.

893. Reves JG, Croughwell ND, Jacobs J et al: Continuous infusion of fentanyl and midazolam for cardiac surgery. Anesth Analg 70:S323, 1990.

894. Tuman KJ, Spiess BD, Wong CA et al: Sufentanil-midazolam anesthesia in malignant hyperthermia. Anesth Analg 67:405, 1988.

895. Shapiro JD, El-Ganzouri A, White PF et al: Midazolam-sufentanil anaesthesia for phaeochromocytoma resection. Can J Anaesth 35:190, 1988.

896. Cork RC, Gallo JA, Weiss LB: Sufentanil infusion: Pharmacodynamics compared to bolus. Anesth Analg 67:S40, 1988.

897. Wagner JG: A safe method for rapidly achieving plasma concentration plateaus. Clin Pharmacol Ther 16:691, 1974.

898. Vaughn DP, Tucker GT: General derivation of the ideal intravenous drug input required to achieve and maintain a constant plasma drug concentration. Eur J Clin Pharmacol 10:433, 1976.

899. Rigg JRA, Wong TY: A method for achieving rapidly steady-state blood concentrations of IV drugs. Br J Anaesth 53:1247, 1981.

900. Glass PSA, Jacobs JR, Smith LR et al: Pharmacokinetic model-driven infusion of fentanyl: Assessment of accuracy. Anesthesiology 73:1082, 1990.

901. Schwieger IM, Bailey JM, Hug CC Jr: Evaluation of a computercontrolled infusion of sufentanil for cardiac surgery. Anesth Analg 70:S358, 1990.

902. Bell J, Sartain J, Wilkinson GAL et al: Propofol and fentanyl anaesthesia for patients with low cardiac output state undergoing cardiac surgery: Comparison with high-dose fentanyl anaesthesia. Br J Anaesth 73:162, 1994.

903. Tuman KJ, Keane DM, Spiess BD et al: Effects of high-dose fentanyl on fluid and vasopressor requirements after cardiac surgery. J Cardiothorac Anesth 2:419, 1988.

904. Jhaveri R, Joshi P, Batenhorst R et al: Dose comparison of remifentanil and alfentanil for loss of consciousness. Anesthesiology 87:253, 1997.

905. Reves JG, Sladen RN, Newman MF: Cardiac anesthetic: Is it unique? Anesth Analg 81:895, 1995.

906. Kentor ML, Schwalb AJ, Lieberman RW: Rapid high dose fentanyl induction for CABG. Anesthesiology 3:S95, 1980.

907. Quinton L, Whalley DG, Wynands JE et al: Oxygen-high dose fentanyl-droperidol anesthesia for aortocoronary bypass surgery. Anesth Analg 60:412, 1981.

908. Sebel PS, Bovill JG, Boekhorst RAA et al: Cardiovascular effects of high dose fentanyl anesthesia. Acta Anesthesiol Scand 26:308, 1982.

909. Tuman KJ, Keane DM, Silins AI et al: Effects of high dose fentanyl on fluid and vasopressor requirements after cardiac surgery. Anesth Analg 67:S236, 1988.

910. Murkin JM, Moldenhauer CC, Hug CC Jr: High-dose fentanyl for rapid induction of anaesthesia in patients with coronary artery disease. Can Anaesth Soc J 32:320, 1984.

911. Bergstrom RG, Thomson IR, Rosenbloom M et al: Premedication and high-dose fentanyl anaesthesia for myocardial revascularization. Can Anaesth Soc J 34:S114, 1987.

912. Bazaral MG, Wagner R, Abi-Nader E et al: Comparison of effects of 15 and 60 mug/kg fentanyl used for induction of anesthesia in patients with coronary artery disease. Anesth Analg 64:312, 1985.

913. Weiss-Bloom L, Reich DL: Haemodynamic responses to tracheal intubaton following etomidate and fentanyl for anaesthetic induction. Can J Anaesth 39:780, 1992.

914. Howie MB, Black HA, Romanelli VA et al: A comparison of isoflurane versus fentanyl as primary anesthetics for mitral valve surgery. Anesth Analg 83:941, 1996.

915. Hall RI, Moldenhauer CC, Hug CC Jr: Fentanyl plasma concentrations maintained by a simple infusion scheme in patients undergoing cardiac surgery. Anesth Analg 76:957, 1993.

916. Robinson S, Gregory GA: Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. Anesth Analg 60:331, 1981.

917. Walter RR, Kim YD, Macnamara TE et al: Comparison of isoflurane vs fentanyl anesthesia in ligation of the patent ductus arteriosus in preterm infants. Anesth Analg 65:S165, 1986.

918. Hickey PR, Hansen DD: Fentanyl- and sufentanil-oxygen-pancuronium anesthesia for cardiac surgery in infants. Anesth Analg 63:117, 1984.

919. Glenski JA, Foresen RH, Berglund NL et al: Comparison of the cardiovascular effects of sufentanil, fentanyl, isoflurane and halothane during pediatric cardiac surgery. Anesthesiology 65:A438, 1986.

920. Morgan P, Lynn AM, Parrot C et al: Hemodynamic and metabolic effects of two anesthetic techniques in children undergoing surgical repair of acyanotic congenital heart disease. Anesth Analg 66:1028, 1987.

921. de Lange S, de Bruijn N: Alfentanil-oxygen anesthesia: Plasma concentration and clinical effects during variable rate continuous infusion for coronary artery surgery. Br J Anaesth 55:S183, 1983.

922. Bovill JG, Warren PJ, Schuller JL et al: Comparison of fentanyl, sufentanil, and alfentanil anesthesia in patients undergoing valvular heart surgery. Anesth Analg 63:1081, 1984.

923. Mantz J, Abi-Jaoude, Ceddaha A et al: High-dose alfentanil for myocardial revascularization: A hemodynamic and pharmacokinetic study. J Cardiothorac Vasc Anesth 5:107, 1991.

924. Roekaerts PMHJ, Gerrits HJ, Timmerman BE et al: Continuous infusions of alfentanil and propofol for coronary artery surgery. J Cardiothorac Vasc Anesth 9:362, 1995.

925. Howie MB, Smith DF, Reiley TE et al: Postoperative course after sufentanil or fentanyl anesthesia for coronary artery surgery. J Cardiothorac Vasc Anesth 5:485, 1991.

926. Crosby ET, Miller DR, Hamilton PP et al: A randomized double-blind comparison of fentanyl- and sufentanil-oxygen anesthesia for abdominal aortic surgery. J Cardiothorac Anesth 4:168, 1990.

927. Howie MB, McSweeney TD, Lingam RP et al: A comparison of fentanyl-O_2 and sufentanil-O_2 for cardiac anesthesia. Anesth Analg 64:877, 1985.

928. Sareen J, Hudson RJ, Rosenbloom M et al: Dose-response to anaesthetic induction with sufentanil: Haemodynamic and electroencephalographic effects. Can J Anaesth 44:19, 1997.

929. Jain U, Body SC, Bellows W et al: Multicenter study of targetcontrolled infusion of propofol-sufentanil or sufentanil-midazolam for coronary artery bypass graft surgery. Anesthesiology 85:522, 1996.

930. Duthie DJR, Rowbotham DJ, Wyld R et al: Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. Br J Anaesth 60:614, 1988.

931. Rowbotham DJ, Wyld R, Peacock JE et al: Transdermal fentanyl for the relief of pain after upper abdominal surgery. Br J Anaesth 63:56, 1989.

932. Sandler AN, Baxter AD, Katz J et al: A double-blind, placebocontrolled trial of transdermal fentanyl after abdominal hysterectomy. Anesthesiology 81:1169, 1994.

933. Miguel R, Kreitzer JM, Reinhart D et al: Postoperative pain control with a new transdermal fentanyl delivery system. Anesthesiology 83:470, 1995.

934. Fiset P, Cohane C, Browne S et al: Biopharmaceutics of a new transdermal fentanyl device. Anesthesiology 83:459, 1995.

935. Varvel JR, Shafer SL, Hwang SS et al: Absorption characteristics of transdermally administered fentanyl. Anesthesiology 70:928, 1989.

936. Rolf D: Chemical and physical methods of enhancing transdermal drug delivery. Pharm Tech 12:130, 1988.

937. Ashburn MA, Stephen RL, Petelenz TJ et al: Controlled iontophoretic delivery of morphine HCL for postoperative pain relief. Anesthesiology 69:A348, 1988.

938. Ashburn MA, Streisand J, Zhang J et al: The iontophoresis of fentanyl citrate in humans. Anesthesiology 82:1146, 1995.

939. Edge WG, Cooper GM, Morgan M: Analgesic effects of sublingual buprenorphine. Anaesthesia 34:463, 1979.

940. Bullingham RES, McQuay HJ, Porter EJB et al: Sublingual buprenorphine used postoperatively: Ten hour plasma drug concentration analysis. Br J Clin Pharmacol 13:665, 1982.

941. Risbo A, Chraemmer JB, Kolby P et al: Sublingual buprenorphine for premedication and postoperative pain relief in orthopaedic surgery. Acta Anaesthesiol Scand 29:180, 1985.

942. Moa G, Zetterstrom H: Sublingual buprenorphine as postoperative analgesic: A double-blind comparison with pethidine. Acta Anaesthesiol Scand 34:68, 1990.

943. Witjes WPJ, Crul BJP, Vollaard EJ et al: Application of sublingual buprenorphine in combination with naproxen or paracetamol for post-operative pain relief in cholecystectomy patients in a double-blind study. Acta Anaesthesiol Scand 36:323, 1992.

944. Bell MDD, Mishra P, Weldon BD et al: Buccal morphine: A new route for analgesia? Lancet 1:71, 1985.

945. Fisher AP, Vine P, Whitlock J et al: Buccal morphine premedication. Anaesthesia 41:1104, 1986.

946. Manara AR, Shelly MP, Quinn KG et al: Pharmacokinetics of morphine following administration by the buccal route. Br J Anaesth 62:498, 1989.

947. Chrubasik J, Wust H, Friedrich G et al: Absorption and bioavailability of nebulized morphine. Br J Anaesth 61:228, 1988.

948. Weinberg DS, Inturrisi CE, Beidenberg B et al: Sublingual absorption of selected opioid analgesics. Clin Pharmacol Ther 44:335, 1988.

949. Stanley TH, Hague BH, Mock DL et al: Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. Anesth Analg 69:21, 1989.

950. Streisand JB, Stanley TH, Hague B et al: Oral transmucosal fentanyl citrate premedication in children. Anesth Analg 69:28, 1989.

951. Friesen RH, Lockhart CH: Oral transmucosal fentanyl citrate for preanesthetic medication of pediatric day surgery patients with and without droperidol as a prophylactic anti-emetic. Anesthesiology 76:46, 1992.

952. Feld LH, Champeau MW, van Steennis CA et al: Preanesthetic medication in children: A comparison of oral transmucosal fentanyl citrate versus placebo. Anesthesiology 71:374, 1989.

953. Goldstein-Dresner MC, Davis PJ, Kretchman E et al: Double-blind comparison of oral transmucosal fentanyl citrate with oral meperidine, diazepam, and atropine as preanesthetic medication in children with congenital heart disease. Anesthesiology 74:28, 1991.

954. Streisand J, Varvel JR, Stanski DR et al: Absorption and bioavailability of oral transmucosal fentanyl citrate. Anesthesiology 75:223, 1991.

955. Ashburn MA, Fine PG, Stanley TH: Oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: A case report. Anesthesiology 71:615, 1989.

956. Rosenberg H: A multi-disciplinary perspective on oral transmuscosal drug delivery in adult and pediatric patients. Am J Anesthesiol 24(suppl):1, 1997.

957. Ralley FE: Intranasal opiates: Old route for new drugs (editorial). Can J Anaesth 36:491, 1989.

958. Henderson JM, Brodsky DA, Fisher DM et al: Pre-induction of anesthesia in pediatric patients with nasally administered sufentanil. Anesthesiology 68:671, 1988.

959. Karl HW, Keifer AT, Rosenberger JL et al: Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients. Anesthesiology 76:209, 1992.

960. Zedie N, Amory DW, Wagner BKJ et al: Comparison of intranasal midazolam and sufentanil premedication in pediatric outpatients. Clin Trials Ther 59:341, 1996.

961. Vercauteren M, Boeckx E, Hanegreefs G et al: Intranasal sufentanil for pre-operative sedation. Anaesthesia 43:270, 1988.

962. Helmers JHJH, Noorduin H, Van Peer A et al: Comparison of intravenous and intranasal sufentanil absorption and sedation. Can J Anaesth 36:494, 1989.

963. Abboud TK, Zhu J, Gangolly J et al: Transnasal butorphanol: A new method for pain relief in post-cesarean section pain. Acta Anaesthesiol Scand 35:14, 1991.

964. Zacny JP, Lichtor JL, Klafta JM et al: The effects of transnasal butorphanol on mood and psychomotor functioning in healthy volunteers. Anesth Analg 82:931, 1996.

965. Striebel HW, Bonillo B, Schwagmeier R et al: Self-administered intranasal meperidine for postoperative pain management. Can J Anaesth 42:287, 1995.

966. Striebel HW, Oelmann T, Spies C et al: Patient-controlled intranasal analgesia: A method for noninvasive postoperative pain management. Anesth Analg 83:548, 1996.

967. Takala A, Kaasalainen V, Seppala T et al: Pharmacokinetic comparison of intravenous and intranasal administration of oxycodone. Acta Anaesthesiol Scand 41:309, 1997.

968. Worsley MH, Macleod AD, Brodie MJ et al: Inhaled fentanyl as a method of analgesia. Anaesthesia 45:449, 1990.

969. Hung OR, Whynot SC, Varvel JR et al: Pharmacokinetics of inhaled liposome-encapsulated fentanyl. Anesthesiology 83:277, 1995.

970. Lindahl S, Olsson A-K, Thomson D: Rectal premedication in children: Use of diazepam, morphine and hyoscine. Anaesthesia 36:376, 1981.

971. Hanning CD, Vickers AP, Smith G et al: The morphine hydrogel suppository. Br J Anaesth 61:221, 1988.

972. Lundeberg S, Beck O, Olsson GL et al: Rectal administration of morphine in children: Pharmacokinetic evaluation after a single-dose. Acta Anaesthesiol Scand 40:445, 1996.

973. Simpson KH, Dearden MJ, Ellis FR et al: Premedication with slow release morphine (MST) and adjuvants. Br J Anaesth 60:825, 1988.

974. Banning AM, Schmidt JF, Chraemmer-Jorgensen B et al: Comparison of oral controlled-release morphine and epidural morphine in the management of postoperative pain. Anesth Analg 65:385, 1986.

975. Derbyshire DR, Bell A, Parry PA et al: Morphine sulfate slow release: A comparison with IM morphine for postoperative analgesia. Br J Anaesth 57:858, 1985.

976. Khojasteh A, Evans W, Reynolds RD et al: Controlled-release oral morphine sulfate in the treatment of cancer pain with pharmacokinetic correlation. J Clin Oncol 5:956, 1987.

977. Hoskin PJ, Poulain P, Hanks GW: Controlled-release morphine in cancer pain. Anaesthesia 44:897, 1989.

978. Murakawa K, Abboud TK, Yanagi T: Neonatal responses to alphaprodine administered during labor. Anesth Analg 65:392, 1986.

979. Caraco Y, Tateishi T, Guengerich FP et al: Microsomal codeine N-demethylation: Cosegregation with cytochrome P45032A4 activity. Drug Metab Dispos 24:761, 1996.

980. Parke TJ, Nandi PR, Bird KJ et al: Profound hypotension following intravenous codeine phosphate. Anaesthesia 47:852, 1991.

981. Janssen PAJ: Potent, new analgesics, tailor-made for different purposes. Acta Anaesthesiol Scand 26:262, 1982.

982. Bailey PL, Port JD, Pace NL: The ED_{50} of carfentanil for elk immobilization with and without the tranquilizer R51703. J Wildl Manage 49:931, 1985.

983. Welti RS, Moldenhauer CC, Hug CC Jr et al: High-dose hydromorphine (Dilaudid) for coronary artery bypass surgery. Anesth Analg 63:55, 1984.

984. Hill HF, Coda BA, Tanaka A et al: Multiple-dose evaluation of intravenous hydromorphine pharmacokinetics in normal human subjects. Anesth Analg 72:330, 1991.

985. Wallenstein SL, Houde RW, Portenoy R et al: Clinical analgesic assay of repeated and single doses of heroin and hydromorphine. Pain 41:5, 1990.

986. Fahmy NR, Bottros MR, Charchaflieh J et al: A double-blind comparison of oxymorphone and fentanyl as supplements to nitrous oxide anesthesia. Anesth Analg 66:S53, 1987.

987. Gourlay GK, Willis RJ, Lamberty J: A double-blind comparison of the efficacy of methadone and morphine in postoperative pain control. Anesthesiology 64:322, 1986.

988. Wangler MA, Rosenblatt RM: Methadone titration to avoid excessive respiratory depression (letter). Anesthesiology 59:363, 1983.

989. Glass PSA, Camporesi EM, Shafron D et al: Evaluation of pentamorphine in humans: A new potent opiate. Anesth Analg 68:302, 1989.

990. Camporesi EM, Glass PSA, Moon RE et al: Evaluation of hypoxic and of hypercapnic responses after A-4492. Anesthesiology 69:A816, 1988.

991. Lee CR, McTavish D, Sorkin EM: Tramadol: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs 46:313, 1993.

992. Eggers KA, Power I: Tramadol (editorial). Br J Anaesth 74:247, 1995.

993. James MF, Heijke SA, Gordon PC: Intravenous tramadol versus epidural morphine for postthoracotomy pain relief: A placebocontrolled double-blind trial. Anesth Analg 83:87, 1996.

994. Vickers MD, O'Flaherty D, Szekely SM et al: Tramadol: Pain relief by an opioid without depression of respiration. Anaesthesia 47:291, 1992.

995. Wilder-Smith CH, Bettiga A: The anlagesic tramadol has minimal effect on gastrointestinal motor function. Br J Clin Pharmacol 43:71, 1997.

996. Pohl J: Uber das N-allylnorecodeine, einen Antagonisten des Morphins. J Exp Path Ther 17:370, 1915.

997. McCawley WL, Hart ER, Marsh DF: The preparation of Nallylnormorphine. J Am Chem Soc 63:314, 1941.

998. Weijland J, Erickson AE: N-allylnormorphine. J Am Chem Soc 64:869, 1942.

999. Unna K: Antagonistic effect of N-allylnormorphine upon morphine. J Pharmacol Exp Ther 79:27, 1943.

1000. Hart ER, McCawley EL: The pharmacology of N-allylnormorphine as compared with morphine. J Pharmacol Exp Ther 82:339, 1944.

1001. Schnider, Hellerback J: Synthese von Morphinan. Helv Chem Acta 33:1437, 1950.

1002. Pearl J, Stander H, McKean DB: Effects of analgesics and other drugs on mice in phenylquinone and rotarod tests. J Pharmacol Exp Ther 167:9, 1969.

1003. Perrin TD, Atwell L, Tice IB et al: Analgesic activity as determined by the Nilsen method. J Pharm Sci 61:86, 1972.

1004. Jasinski DR, Martin WR, Hoeldtke RD: Effects of short- and long-term administration of pentazocine in man. Clin Pharmacol Ther 11:335, 1970.

1005. Fraser HF, Rosenberg DE: Studies on the human addiction liability of 2-hydroxy-5,9-dimethyl-2-(3,3-dimethylallyl)-6,7-benzomorphan (Win 20,228): A weak narcotic antagonist. J Pharmacol Exp Ther 143:149, 1964.

1006. Parwatikar S, Gomez H, Knowles RR: Pentazocine dependency. Int J Addict 8:87, 1973.

1007. Kaukinen L, Kaukinen S, Eerola R et al: The antagonistic effect of pentazocine on fentanyl-induced respiratory depression compared with nalorphine and naloxone. Ann Clin Res 13:396, 1981.

1008. Beaver WT, Wallenstein SL, Houde RW et al: A comparison of the analgesic effects of pentazocine and morphine in patients with cancer. Clin Pharmacol Ther 7:740, 1966.

1009. Leaman DM, Nellis SH, Zelis R et al: Effect of morphine sulfate on human coronary blood flow. Am J Cardiol 41:324, 1978.

1010. Jewitt DE, Maurer RJ, Sonnenblick EJ et al: Pentazocine: Effect on ventricular muscle and hemodynamic changes in ischemic heart disease. Circulation 44:118, 1971.

1011. Alderman EL, Barry WH, Graham AF: Hemodynamic effects of morphine and pentazocine differ in cardiac patients. N Engl J Med 287:623, 1972.

1012. Jewitt DE, Maurer BJ, Hubner PJB: Increased pulmonary arterial pressures after pentazocine in myocardial infarction. BMJ 1:795, 1970.

1013. Dobkin AB, Eamkaow S, Zak S et al: Butorphanol: A double-blind evaluation in postoperative patients with moderate or severe pain. Can Anaesth Soc J 21:600, 1974.

1014. Nagashima H, Karamanian A, Malovany R et al: Respiratory and circulatory effects of intravenous butorphanol and morphine. Clin Pharmacol Ther 19:738, 1976.

1015. Popio KA, Jackson DH, Ross AM et al: Hemodynamic and respiratory effects of morphine and butorphanol. Clin Pharmacol Ther 23:281, 1978.

1016. Del Pizzo A: A double-blind study of the effects of butorphanol compared with morphine in balanced anaesthesia. Can Anaesth Soc J 25:392, 1978.

1017. Zauder HL: Butorphanol, a new non-narcotic analgesic. In Aldrete JA, Stanley TH (eds): Trends in Intravenous Anesthesia. Chicago, Year Book, 1980, p 367.

1018. Murphy MR, Hug CC: The enflurane sparing effect of morphine, butorphanol and nalbuphine. Anesthesiology 57:489, 1982.

1019. Zucker JR, Neuenfeldt T, Freund PR: Respiratory effects of nalbuphine and butorphanol in anesthetized patients. Anesth Analg 66:879, 1987.

1020. Laffey DA, Kay NH: Premedication with butorphanol. Br J Anaesth 56:363, 1984.

1021. Bowdle TA, Greichen SL, Bjurstrom RL et al: Butorphanol improves CO_2 responses and ventilation after fentanyl anesthesia. Anesth Analg 66:517, 1987.

1022. Vandam L: Drug therapy: Butorphanol. N Engl J Med 302:381, 1980.

1023. Heel RC, Brogden RN, Speight TM et al: Butorphanol: A review of its pharmacological properties and therapeutic efficacy. Drugs 16:473, 1978.

1024. Dolan PF: Butorphanol and biliary spasm. Anesthesiology 63:340, 1985.

1025. Hand CW, Sear JW, Uppington J et al: Buprenorphine disposition in patients with renal impairment: Single and continuous dosing, with special reference to metabolites. Br J Anaesth 64:276, 1990.

1026. Zola EM, McLeod DC: Comparative effects of analgesic efficacy of the agonist-antagonist opioids. Drug Intell Clin Pharm 17:411, 1983.

1027. Pedersen JE, Chraemmer-Jorgensen B, Schmidt JF et al: Naloxone: A strong analgesic in combination with high-dose buprenorphine? Br J Anaesth 57:1045, 1985.

1028. Gal T: Naloxone reversal of buprenorphine-induced respiratory depression. Clin Pharmacol Ther 45:66, 1989.

1029. Boysen K, Hertel S, Chraemmer-Jorgensen B et al: Buprenorphine antagonism of ventilatory depression following fentanyl anaesthesia. Acta Anaesthesiol Scand 32:490, 1988.

1030. Sear JW, Alexander JI: Comparison of buprenorphine-hyoscine and papaveretum-hyoscine as premedicants for gynaecological surgery. Br J Anaesth 55:319, 1983.

1031. Obel D, Hansen LK, Huttel MS et al: Buprenorphine-supplemented anaesthesia. Br J Anaesth 57:271, 1985.

1032. Bullingham RES, O'Sullivan G, McQuay HJ et al: Mandatory sublingual buprenorphine for post-operative pain. Anaesthesia 39:329, 1984.

1033. Strain EC, Preston KL, Liebson IA et al: Acute effects of buprenorphine, hydromorphone and naloxone in methadone-maintained volunteers. J Pharmacol Exp Ther 261:985, 1991.

1034. Beaver WT, Feise GA: A comparison of the analgesic effect of intramuscular nalbuphine and morphine in patients with postoperative pain. J Pharmacol Exp Ther 204:487, 1978.

1035. De Souza EB, Schmidt WK, Kukor MJ: Nalbuphine: An autoradiographic opioid receptor binding profile in the central nervous system of an agonist/antagonist analgesic. J Pharmacol Exp Ther 244:391, 1988.

1036. Romagnoli A, Keats AS: Ceiling effect for respiratory depression by nalbuphine. Clin Pharmacol Ther 27:478, 1980.

1037. Lake C, Duckworth EN, DiFazio CA et al: Cardiorespiratory effects of nalbuphine and morphine premedication in adult cardiac surgical patients. Acta Anaesthesiol Scand 28:305, 1984.

1038. Lee G, Low R, Amsterdam E et al: Hemodynamic effects of morphine and nalbuphine in acute myocardial infarction. Clin Pharmacol Ther 29:576, 1981.

1039. Klein DS: Nalbuphine and droperidol combination for local standby sedation. Anesthesiology 58:397, 1983.

1040. Sury MRJ, Cole PV: Nalbuphine combined with midazolam for outpatient sedation. Anaesthesia 43:281, 1988.

1041. Garfield JM, Garfield FB, Philip BK et al: A comparison of clinical and psychological effects of fentanyl and nalbuphine in ambulatory gynecologic patients. Anesth Analg 66:1303, 1987.

1042. Rawal N, Wennhager M: Influence of perioperative nalbuphine and fentanyl on postoperative respiration and analgesia. Acta Anaesthesiol Scand 34:197, 1990.

1043. Zsigmond EK, Winnie AP, Raza SMA et al: Nalbuphine as an analgesic component in balanced anesthesia for cardiac surgery. Anesth Analg 66:1155, 1987.

1044. Lake CL, Duckworth EN, Difazio CA et al: Cardiovascular effects of nalbuphine in patients with coronary or valvular heart disease. Anesthesiology 57:498, 1982.

1045. Welch GW, Feldman HS: Intravenous nalbuphine. Anesth Analg 60:168, 1981.

1046. Telford J, Keats AS: Narcotic-narcotic antagonist mixtures. Anesthesiology 22:465, 1961.

1047. Latasch L, Probst S, Duziak R: Reversal by nalbuphine of respiratory depression caused by fentanyl. Anesth Analg 63:814, 1984.

1048. Blaise GA, McMichan JC, Nugent M et al: Nalbuphine produces side-effects while reversing narcotic-induced respiratory depression. Anesth Analg 65:S19, 1986.

1049. Ramsay JG, Wynands JE, Robbins R et al: Early extubation after high-dose fentanyl anaesthesia for aortocoronary bypass surgery: Reversal of respiratory depression with low-dose nalbuphine. Can Anaesth Soc J 32:597, 1985.

1050. Moldenhauer CC, Roach GW, Finlayson DC et al: Nalbuphine antagonism of ventilatory depression following high dose fentanyl anesthesia. Anesthesiology 62:647, 1985.

1051. Tabatabai M, Javadi P, Tadjziechy M et al: Effect of nalbuphine hydrochloride on fentanyl-induced respiratory depression and analgesia. Anesthesiology 61:A475, 1984.

1052. Bailey PL, Clark NJ, Pace NL et al: Failure of nalbuphine to antagonize morphine. Anesth Analg 65:605, 1986.

1053. Bailey PL, Clark NJ, Pace NL et al: Antagonism of postoperative opioid induced respiratory depression: Nalbuphine vs. naloxone. Anesth Analg 66:1109, 1987.

1054. Zsigmond EK, Durrani Z, Barabas E et al: Endocrine and hemodynamic effects of antagonism of fentanyl-induced respiratory depression by nalbuphine. Anesth Analg 66:421, 1987.

1055. Jaffe RS, Moldenhauer CC, Hug CC Jr et al: Nalbuphine antagonism of fentanyl-induced ventilatory depression: A randomized trial. Anesthesiology 68:254, 1988.

1056. Gal TJ, DiFazio CA: Ventilatory and analgesic effects of dezocine in humans. Anesthesiology 61:716, 1984.

1057. Rowlingson JC, Moscicki JC, DiFazio CA: Anesthetic potency of dezocine and its interaction with morphine in rats. Anesth Analg 62:899, 1983.

1058. Hall RI, Murphy MR, Szlam F et al: Dezocine MAC reduction and evidence for myocardial depression in the presence of enflurane. Anesth Analg 66:1169, 1987.

1059. Lewis AJ, Kirchner A: A comparison of the cardiorespiratory effects of ciramadol, dezocine, morphine and pentazocine in the anesthetized dog. Arch Int Pharmacodyn 250:73, 1981.

1060. Galloway FM, Varma S: Double-blind comparison of intravenous doses of dezocine, butorphanol, and placebo for relief of postoperative pain. Anesth Analg 65:283, 1986.

1061. Kaiko RF, Wallenstein SL, Rogers AG et al: Intramuscular meptazinol and morphine in postoperative pain. Clin Pharmacol Ther 37:589, 1985.

1062. Wilkinson DJ, O'Connor SA, Dickson GR et al: Meptazinol: A cause of respiratory depression in general anaesthesia. Br J Anaesth 57:1077, 1985.

1063. Slattery PJ, Harmer M, Rosen H et al: Comparison of meptazinol and pethidine given IV on demand in the management of postoperative pain. Br J Anaesth 53:927, 1981.

1064. Yaksh TL, Howe JR: Opiate receptors and their definition by antagonists. Anesthesiology 56:246, 1982.

1065. Kendrick WD, Woods AM, Daly MY et al: Naloxone versus nalbuphine infusion for prophylaxis of epidural morphine-induced pruritus. Anesth Analg 82:641, 1996.

1066. Eckenhoff JE, Elder JD, King BD: N-allyl-normorphine in the treatment of morphine or demerol narcosis. Am J Med Sci 223:191, 1952.

1067. Costa PJ, Bonnycastle DD: Effect of levallorphan tartrate, nalorphine Hcl and WIn 7681 (1-allyl-4-pheno-4-carbethoxypiperidine) on respiratory depression and analgesia induced by some active analgesics. J Pharmacol Exp Ther 113:310, 1955.

1068. Azar I, Turndorf H: Severe hypertension and multiple atrial premature contractions following naloxone administration. Anesth Analg 58:524, 1979.

1069. Estilo AE, Cottrell JE: Naloxone, hypertension, and ruptured cerebral aneurysm. Anesthesiology 54:352, 1981.

1070. Flacke JW, Flacke WE, Williams GD: Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. Anesthesiology 47:376, 1977.

1071. Tanaka GY: Hypertensive reaction to naloxone. JAMA 228:25, 1974.

1072. Andree RA: Sudden death following naloxone administration. Anesth Analg 59:782, 1980.

1073. Prough DS, Roy R, Bumgarner J et al: Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. Anesthesiology 60:485, 1984.

1074. Michaelis LL, Hickey PR, Clark TA et al: Ventricular irritability associated with the use of naloxone hydrochloride. Ann Thorac Surg 18:608, 1974.

1075. Partridge BL, Ward CF: Pulmonary edema following low-dose naloxone administration. Anesthesiology 65:709, 1986.

1076. Taff RH: Pulmonary edema following naloxone administration in a patient without heart disease. Anesthesiology 59:576, 1983.

1077. Kulig K: Initial management of ingestions of toxic substances. N Engl J Med 326:1677, 1992.

1078. Estilo AE, Cottrell JE: Hemodynamic and catecholamine changes after administration of naloxone. Anesth Analg 61:349, 1982.

1079. Patschke D, Eberlein HJ, Tarnow J et al: Antagonism of morphine with naloxone in dogs: Cardiovascular effects with special reference to the coronary circulation. Br J Anaesth 49:525, 1977.

1080. Just B, Delva E, Camus Y et al: Oxygen uptake during recovery following naloxone. Anesthesiology 76:60, 1992.

1081. Tigerstedt I, Tammisto T: Effect of naloxone reversal on CO_2, output, oxygen uptake and cardiac index during recovery from fentanyl-supplemented anaesthesia. Acta Anaesthesiol Scand 22:158, 1978.

1082. Franz DN, Hare BD, McCloskey KL: Spinal sympathetic neurons: Possible sites of opiate withdrawal suppression by clonidine. Science 215:1643, 1982.

1083. Raybould D, Bloor BC, McIntee DF et al: Naloxone reverses the potentiation of inhalational anesthesia and hemodynamic changes induced by the acute administration of clonidine. Anesthesiology 67:A392, 1987.

1084. Farsang C, Kapocsi J, Vajda L et al: Reversal by naloxone of the antihypertensive action of clonidine: Involvement of the sympathetic nervous system. Circulation 69:461, 1984.

1085. Kraynack BJ, Gintautas JG: Naloxone: Analeptic action unrelated to opiate receptor antagonism? Anesthesiology 56:251, 1982.

1086. Aldrete JA, Goldman E: Is naloxone a nonspecific analeptic? Anesthesiology 50:270, 1979.

1087. Shupak RC, Harp JR, Stevenson-Smith W et al: High-dose fentanyl for neuroanesthesia. Anesthesiology 58:579, 1983.

1088. Keykhah MM, Smith DS, Englebach I et al: Effects of naloxone on cerebral blood flow and metabolism. Anesthesiology 59:A309, 1983.

1089. Mannelli M, Maggi M, De Feo ML et al: Naloxone administration releases catecholamines. N Engl J Med 308:654, 1982.

1090. Ngai SH, Berkowitz BA, Yang JC et al: Pharmacokinetics of naloxone in rats and man. Anesthesiology 44:398, 1976.

1091. Kaufman R: Relative potencies and durations of action with respect to respiratory depression of intravenous meperidine, fentanyl and alphaprodine in man. J Pharmacol Exp Ther 208:73, 1979.

1092. Brown JH, Pleuvry BJ: Antagonism of the respiratory effects of alfentanil and fentanyl by naloxone in the conscious rabbit. Br J Anaesth 53:1033, 1981.

1093. Beilin B, Vatashsky E, Aronson HB et al: Naloxone reversal of postoperative apnea in a premature infant. Anesthesiology 63:317, 1985.

1094. Chadha T, Birch S, Sackner MA: Periodic breathing triggered by hypoxia in normal awake adults. Chest 88:16, 1985.

1095. Chernick V: Endorphins and ventilatory control. N Engl J Med 304:122, 1981.

1096. Santiago TV, Remolina C, Scoles V III et al: Endorphins and the control of breathing. N Engl J Med 304:1190, 1981.

1097. Williams AJ, Tarn AC, de Belder MA et al: Naloxone in acute respiratory failure. Lancet 25:1470, 1982.

1098. Terenius L: Alcohol addiction (alcoholism) and the opioid system. Alcohol 13:31, 1996.

1099. Jordan C, Lehane JR, Jones JG: Respiratory depression following diazepam: Reversal with high-dose naloxone. Anesthesiology 53:293, 1980.

1100. Delle M, Ricksten SE, Thoren P: The opiate antagonist naloxone counteracts the inhibition of sympathetic nerve activity caused by halothane anesthesia in rats. Anesthesiology 70:309, 1989.

1101. Smith G, Pinnock C: Naloxone: Paradox or panacea? Br J Anaesth 57:547, 1985.

1102. Sharphendinsson JO, Delle M, Hoffman P et al: The effects of naloxone on cerebral blood flow and cerebral function during relative cerebral ischemia. J Cereb Blood Flow Metab 9:515, 1989.

1103. Romanovsky AA, Blatteis CM: Heat stroke: Opioid-mediated mechanisms. J Appl Physiol 81:2565, 1996.

1104. Comer SD, Burke TF, Lewis JW et al: Clocinnamox: A novel, systemically-active, irreversible opioid antagonist. J Pharmacol Exp Ther 262:1051, 1992.

1105. Horan P, Taylor J, Yamamura HI et al: Extremely long-lasting antagonistic actions of nor-binaltorphimine (nor-BNI) in the mouse tail-flick test. J Pharmacol Exp Ther 260:1237, 1992.

1106. Cullen M, Altstatt AH, Kwon NJ et al: Naltrexone reversal of the side effects of epidural morphine. Anesthesiology 69:A336, 1988.

1107. Abboud TK, Afasiabi A, Davidson J et al: Prophylactic oral naltrexone with epidural morphine: Effect on adverse reactions and ventilatory responses to carbon dioxide. Anesthesiology 72:233, 1990.

1108. Amaral JLG, Saragoca MA, Burnier MNN et al: Effect of naltrexone chloride upon arterial pressure during pregnancy in rats. Anesth Analg 70:S8, 1990.

1109. Michel ME, Bolger G, Weisman B-A: Binding of a new opiate antagonist nalmefene to rat brain membranes. Pharmacologist 26:201, 1988.

1110. Konieczko KM, Jones JG, Barrowcliffe MP et al: Antagonism of morphine induced respiratory depression with nalmefene. Br J Anaesth 61:318, 1988.

1111. Gal TJ, DiFazio CA: Prolonged antagonism of opioid action with intravenous nalmefene in man. Anesthesiology 64:175, 1986.

1112. Glass PSA, Jhaveri RM, Smith LR: Comparison of potency and duration of action of nalmefene and naloxone. Anesth Analg 78:536, 1994.

1113. Matzke GR, Frye RF, Alexander ACM et al: The effect of renal insufficiency and hemodialysis on the pharmacokinetics of nalmefene. J Clin Pharmacol 36:144, 1996.

1114. Zbinden AM, Maggiorini M, Petersen-Felix S et al: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions (see comments). Anesthesiology 80:253, 1994.

1115. Bovill JG: Adverse drug interactions in anesthesia. J Clin Anesth 9:3S, 1997.

1116. Thomson IR, Bergstrom RG, Rosenbloom M et al: Premedication and high-dose fentanyl anesthesia for myocardial revascularization: A comparison of lorazepam versus morphine-scopolamine. Anesthesiology 68:194, 1988.

1117. Vuyk J: Pharmacokinetic and pharmacodynamic interactions between opioids and propofol. J Clin Anesth 9:23S, 1997.

1118. Tverskoy M, Fleyshman G, Ezry J et al: Midazolam-morphine sedative interaction in patients. Anesth Analg 68:282, 1989.

1119. Kissin I, Brown P, Bradley E et al: Diazepam-morphine hypnotic synergism in rats. Anesthesiology 70:689, 1989.

1120. Schwieger IM, Hall RI, Hug CC: Less than additive antinociceptive interaction between midazolam and fentanyl in enfluraneanesthetized dogs. Anesthesiology 74:1060, 1991.

1121. Kissin I, Brown PT, Bradley EL: Morphine and fentanyl anesthetic interactions with diazepam: Relative antagonism in rats. Anesth Analg 71:236, 1990.

1122. Kitahata LM, Saberski L: Are barbiturates hyperalgesic? (editorial). Anesthesiology 77:1059, 1992.

1123. Wilder-Smith OHG, Kolletzki M, Wilder-Smith CH: Sedation with intravenous infusions of propofol or thiopentone. Anaesthesia 50:218, 1995.

1124. Vinik HR, Bradley EL, Kissin I: Midazolam-alfentanil synergism for anesthetic induction in patients. Anesth Analg 69:213, 1989.

1125. Dauchot PJ, van Heeckeren DW, Bastulli J et al: Sufenta requirements, plasma Sufenta and catecholamine levels after diazepam during CABG surgery. Anesth Analg 67:S45, 1988.

1126. Tomichek RC, Rosow CE, Philbin DM et al: Diazepam-fentanyl interaction: Hemodynamic and hormonal effects in coronary artery surgery. Anesth Analg 62:881, 1983.

1127. Spiess BD, Sathoff RH, El-Ganzouri ARS et al: High-dose sufentanil: Four cases of sudden hypotension on induction. Anesth Analg 65:703, 1986.

1128. West JM, Estrada S, Heerdt M: Sudden hypotension associated with midazolam and sufentanil (letter). Anesth Analg 66:693, 1987.

1129. Heikkila H, Jalonen J, Laaksonen V et al: Lorazepam and high-dose fentanyl anaesthesia: Effects on haemodynamics and oxygen transportation

in patients undergoing coronary revascularization. Acta Anaesthesiol Scand 28:357, 1984.

1130. Benson KT, Tomlinson DL, Goto H et al: Cardiovascular effects of lorazepam during sufentanil anesthesia. Anesth Analg 67:996, 1988.

1131. Komatsu T, Shibutani K, Okamoto K et al: Comparison of sufentanil-diazepam and fentanyl-diazepam anesthesia for induction. Anesth Analg 65:S82, 1986.

1132. Takkunen O, Meretoja OA: Thiopentone reduces the haemodynamic response to induction of high-dose fentanyl-pancuronium anaesthesia in coronary artery surgical patients. Acta Anaesthesiol Scand 32:222, 1988.

1133. Pomane C, Paulin M, Lena P et al: Comparison of the haemodynamic effects of a midazolam-fentanyl and thiopental-fentanyl combination for induction of general anesthesia. Anesthesiology 2:75, 1983.

1134. Coetzee A, Fourie P, Coetzee J et al: Effect of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. Anesth Analg 69:473, 1989.

1135. Claeys MA, Gepts E, Camu F: Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 60:3, 1988.

1136. Hullander RM, Leivers D, Wingler K: A comparison of propofol and etomidate for cardioversion. Anesth Analg 77:690, 1993.

1137. Gordon PC, Morrell DF, Pamm JD: Total intravenous anesthesia using propofol and alfentanil for coronary artery bypass surgery. J Cardiothorac Vasc Anesth 8:284, 1994.

1138. Lepage J-Y, Pinaud M, Helias J et al: Left ventricular function during propofol and fentanyl anesthesia in patients with coronary artery disease: Assessment with a radionuclide approach. Anesth Analg 67:949, 1988.

1139. Phillips AS, McMurray TJ, Mirakhur RK et al: Propofol-fentanyl anesthesia: A comparison with isoflurane-fentanyl anesthesia in coronary artery bypass grafting and valve replacement surgery. J Cardiothorac Vasc Anesth 8:289, 1994.

1140. Russell GN, Wright EL, Fox MA et al: Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass. Anaesthesia 44:205, 1989.

1141. Sherry KM, Sartain J, Bell JH et al: Comparison of the use of a propofol infusion in cardiac surgical patients with normal and low cardiac output states (see comments). J Cardiothorac Vasc Anesth 9:368, 1995.

1142. Sorbara C, Pittarello D, Rizzoli G et al: Propofol-fentanyl versus isoflurane-fentanyl anesthesia for coronary artery bypass grafting: Effect on myocardial contractility and peripheral hemodynamics (see comments). J Cardiothorac Vasc Anesth 9:18, 1995.

1143. Hall RI, Murphy JT, Moffitt EA et al: A comparison of the myocardial metabolic and haemodynamic changes produced by propofol-sufentanil and enflurane-sufentanil anaesthesia for patients having coronary artery bypass graft surgery. Can J Anaesth 38:996, 1991.

1144. Underwood SM, Davies SW, Feneck RO et al: Anaesthesia for myocardial revascularisation: A comparison of fentanyl/propofol with fentanyl/enflurane. Anaesthesia 47:939, 1992.

1145. Haessler R, Madler C, Klasing S et al: Propofol/fentanyl versus etomidate/fentanyl for the induction of anesthesia in patients with aortic insufficiency and coronary artery disease. J Cardiothorac Vasc Anesth 6:173, 1992.

1146. Stoelting RK, Gibbs PS: Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary artery disease. Anesthesiology 38:45, 1973.

1147. McDermott RW, Stanley TH: Cardiovascular effects of low concentrations of nitrous oxide during morphine anesthesia. Anesthesiology 41:89, 1974.

1148. Wong KC, Martin WE, Hornbein TF et al: The cardiovascular effects of morphine sulfate with oxygen and with nitrous oxide in man. Anesthesiology 38:542, 1973.

1149. Moffitt EA, Scovil JE, Barker RA et al: Myocardial metabolism and hemodynamics of nitrous oxide in fentanyl or enflurane anesthesia in coronary patients. Anesthesiology 59:A31, 1983.

1150. Michaels I, Barash PG: Does nitrous oxide or a reduced FiO_2 alter hemodynamic function during high-dose sufentanil anesthesia? Anesth Analg 62:275, 1983.

1151. Lawson D, Frazer MJ, Lynch C: Nitrous oxide effects on isolated myocardium: A reexamination *in vitro.* Anesthesiology 73:930, 1990.

1152. Reves JG, Kissin I, Fournier SE et al: Additive negative inotropic effect of a combination of diazepam and fentanyl. Anesth Analg 63:97, 1984.

1153. Stowe DF, Monroe SM, Marijic J et al: Effects of nitrous oxide on contractile function and metabolism of the isolated heart. Anesthesiology 73:1220, 1990.

1154. Mitchell MM, Prakash O, Rulf EN et al: Nitrous oxide does not induce myocardial ischemia in patients with ischemic heart disease and poor ventricular function. Anesthesiology 71:526, 1989.

1155. Kozmary SV, Lampe GH, Benefiel D et al: No finding of increased myocardial ischemia during or after carotid endarterectomy under anesthesia with nitrous oxide. Anesth Analg 71:591, 1990.

1156. Philbin DM, Foex P, Drummond G et al: Postsystolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. Anesthesiology 62:166, 1985.

1157. Cahalan MK, Prakash O, Rulf E et al: Addition of nitrous oxide to fentanyl anesthesia does not induce myocardial ischemia in patients with ischemic heart disease. Anesthesiology 67:925, 1987.

1158. Finck AD, Samaniego E, Ngai SH: Nitrous oxide selectively releases met ^{5} -enkephalin and met^{5} -enkephalin-arg^{6} phe^{7} into canine third ventricular cerebrospinal fluid. Anesth Analg 80:664, 1995.

1159. Heikkila H, Jalonen J, Arola M et al: Low-dose enflurane as adjunct to high-dose fentanyl in patients undergoing coronary artery surgery: Stable hemodynamics and maintained myocardial oxygen balance. Anesth Analg 66:111, 1987.

1160. Stoelting RK, Creasser CW, Gibbs PS et al: Circulatory effects of halothane added to morphine anesthesia in patients with coronary-artery disease. Anesth Analg 53:449, 1974.

1161. O'Young J, Mastrocostopoulas G, Hilgenberg A et al: Myocardial circulatory and metabolic effects of isoflurane and sufentanil during coronary artery surgery. Anesthesiology 66:653, 1987.

1162. Vermeyen KM, Erpels FA, Beeckman CP et al: Low-dose sufentanil-isoflurane anaesthesia for coronary artery surgery. Br J Anaesth 63:44, 1989.

1163. Ramsay JG, DeLima LG, Wynands JE et al: Pure opioid versus opioid-volatile anesthesia for coronary artery bypass graft surgery: A prospective, randomized, double-blind study. Anesth Analg 78:867, 1994.

1164. Searl NR, Martineau RJ, Conzen P et al: Comparison of sevoflurane/fentanyl and isoflurane/fentanyl during elective coronary artery bypass surgery. Can J Anaesth 43:890, 1996.

1165. O'Brien DJ, Moffitt EA, McIntyre AJ et al: Myocardial metabolism and hemodynamic responses with fentanyl-halothane anaesthesia in hypertensive patients undergoing coronary arterial surgery. Can Anaesth Soc J 33:S101, 1986.

1166. Mastrocostopoulos G, Athanasiadis C, Skourtis C et al: Regional and global myocardial metabolic and coronary hemodynamic effects of halothane in cardiac patients during high dose sufentanil anesthesia. Anesth Analg 65:S93, 1986.

1167. Weiskopf RB, Eger EI II, Noorani M et al: Fentanyl, esmolol, and clonidine blunt the transient cardiovascular stimulation induced by desflurane in humans. Anesthesiology 81:1350, 1994.

1168. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane (see comments). Anesthesiology 79:444, 1993.

1169. Gravlee GP, Ramsey FM, Roy RC et al: Pancuronium is hemodynamically superior to vecuronium for narcotic/relaxant induction. Anesthesiology 65:A46, 1986.

1170. Hill AEG, Muller BJ: Optimum relaxant for sufentanil anesthesia. Anesthesiology 61:A393, 1984.

1171. Cote D, Martin R, Tetrault JP: Haemodynamic interactions of muscle relaxants and sufentanil in coronary artery surgery. Can J Anaesth 38:324, 1991.

1172. Thomson IR, MacAdams CL, Hudson RJ et al: Drug interactions with sufentanil: Hemodynamic effects of premedication and muscle relaxants. Anesthesiology 76:922, 1992.

1173. Atlee JL, Laravuso RB: Muscle relaxants and high-dose fentanyl: Hemodynamics during coronary bypass surgery. Anesth Analg 63:181, 1984.

1174. Thomson IR, Putnins CI: Adverse effects of pancuronium during high-dose fentanyl anesthesia for coronary artery bypass grafting. Anesthesiology 62:708, 1985.

1175. Sethna DH, Starr NJ, Estafanous FG: Cardiovascular effects of non-depolarizing neuromuscular blockers in patients with coronary artery disease. Can Anaesth Soc J 33:280, 1986.

1176. Paulissian R, Mahdi M, Joseph NJ et al: Hemodynamic responses to pancuronium and vecuronium during high-dose fentanyl anesthesia for coronary artery bypass grafting. J Cardiothorac Vasc Anesth 5:120, 1991.

1177. Shorten GD, Siever T, Maslow AD et al: Left ventricular regional wall motion and haemodynamic changes following bolus administration of pipecuronium or pancuronium to adult patients undergoing coronary artery bypass grafting. Can J Anaesth 42:695, 1995.

1178. Gravlee GP, Ramsey FM, Roy RC et al: Rapid administration of a narcotic and neuromuscular blocker: A hemodynamic comparison of fentanyl, sufentanil, pancuronium, and vecuronium. Anesth Analg 67:39, 1988.

1179. Zahl K, Ellison N: Rapid induction and intubation with pancuronium or vecuronium and sufentanil for cardiac surgery. Anesthesiology 65:A519, 1986.

1180. McDonald DH, Zaidan JR: Hemodynamic effects of pancuronium and pancuronium plus metocurine in patients taking propranolol. Anesthesiology 60:359, 1984.

1181. Waldmann CS, Wark KJ, Sebel PS et al: Hemodynamic effects of atracurium, vecuronium and pancuronium during sufentanil anesthesia for coronary artery bypass. Acta Anaesthesiol Scand 30:351, 1986.

1182. Salmenpera M, Peltola K, Takkunen O et al: Cardiovascular effects of pancuronium and vecuronium during high-dose fentanyl anesthesia. Anesth Analg 62:1059, 1983.

1183. Inoue K, El-Banayosy A, Stolarski L et al: Vecuronium induced bradycardia following induction of anaesthesia with etomidate or thiopentone, with or without fentanyl. Br J Anaesth 60:10, 1988.

1184. Heinonen J, Salmenpera M, Suomivuori M: Contribution of muscle relaxant to the haemodynamic course of high-dose fentanyl anaesthesia: A comparison of pancuronium, vecuronium and atracurium. Can Anaesth Soc J 33:597, 1986.

1185. Cozanitis DA, Lindgren L, Rosenberg PH: Bradycardia in patients receiving atracurium or vecuronium in conditions of low vagal stimulation. Anaesthesia 44:303, 1989.

1186. O'Connor JP, Ramsay JG, Wynands JE et al: The incidence of myo-cardial ischemia during anesthesia for coronary artery bypass surgery in patients receiving pancuronium or vecuronium. Anesthesiology 70:230, 1989.

1187. Khoury GF, Estafanous FG, Zurick AM et al: Sufentanil/pancuronium versus sufentanil/metocurine anesthesia for coronary artery surgery. Anesthesiology 57:A47, 1982.

1188. Lebowitz PW, Ramsey FM, Savarese JJ et al: Combination of pancuronium and metocurine: Neuromuscular and hemodynamic advantages over pancuronium alone. Anesth Analg 60:12, 1981.

1189. Stoops CM, Curtis CA, Kovach DA et al: Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentanil anesthesia for coronary artery bypass grafting or valve replacement. Anesthesiology 69:365, 1988.

1190. Murray DJ, Mehta MP, Choi WW et al: The neuromuscular blocking and cardiovascular effects of doxacurium chloride in patients receiving nitrous oxide narcotic anesthesia. Anesthesiology 69:472, 1988.

1191. Katz JA, Fragen RJ, Shanks CA et al: Dose-response relationships of doxacurium chloride in humans during anesthesia with nitrous oxide and fentanyl, enflurane, isoflurane, or halothane. Anesthesiology 70:432, 1989.

1192. Tassonyi E, Neidhart P, Pittet J-F et al: Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 69:793, 1988.

1193. Starr NJ, Kraenzler EJ, Wong D et al: Comparison of cardiovascular effects of pipecuronium versus vecuronium in patients receiving sufentanil anesthesia for myocardial revascularization. J Cardiothorac Vasc Anesth 5:116, 1991.

1194. Wierda JMKH, Richardson FJ, Agoston S: Dose-response relation and time course of action of pipecuronium bromide in humans anesthetized with nitrous oxide and isoflurane, halothane, or droperidol and fentanyl. Anesth Analg 68:208, 1989.

1195. Savarese JJ, Ali HH, Basta SJ et al: The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide-opiate-barbiturate anesthesia. Anesthesiology 70:386, 1989.

1196. Choi WW, Mehta MP, Murray DJ et al: Neuromuscular and cardiovascular effects of mivacurium chloride in surgical patients receiving nitrous oxide-narcotic or nitrous oxide-isoflurane anaesthesia. Can J Anaesth 36:641, 1989.

1197. Stoops CM, Curtis CA, Kovach DA et al: Hemodynamic effects of mivacurium chloride administered to patients during oxygensufentanil anesthesia for coronary artery bypass grafting or valve replacement. Anesth Analg 68:333, 1989.

1198. Caldwell JE, Kitts JB, Heier T et al: The dose-response relationship of mivacurium chloride in humans during nitrous oxide-fentanyl or nitrous oxide-enflurane anesthesia. Anesthesiology 70:31, 1989.

1199. Wells DG, Bjorksten AR: Monoamine oxidase inhibitors revisited. Can J Anaesth 36:64, 1989.

1200. Stack CG, Rogers P, Linter SPK: Monoamine oxidase inhibitors and anaesthesia. Br J Anaesth 60:222, 1988.

1201. Ramsay JG, Arvieux CC, Foex P et al: Global and regional myocardial effect of verapamil when added to fentanyl. Can Anaesth Soc J 33:S100, 1986.

1202. Hill DC, Chelly JE, Dlewati A et al: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. VI. Verapamil and fentanyl-pancuronium. Anesthesiology 68:874, 1988.

1203. Griffin RM, Dimich I, Jurado R et al: Haemodynamic effects of diltiazem during fentanyl-nitrous oxide anaesthesia. Br J Anaesth 60:655, 1988.

1204. Diedericks J, Leone BJ, Philbin DM et al: Effect of verapamil on canine left ventricular function in the presence of fentanyl when apical blood flow is critically limited. Br J Anaesth 63:458, 1989.

1205. Kapur PA, Norel EJ, Dajee H et al: Haemodynamic effects of verapamil administration after large doses of fentanyl in man. Can Anaesth Soc J 33:138, 1986.

1206. Bernard JM, Pinaud M, Carteau S et al: Hypotensive actions of diltiazem and nitroprusside compared during fentanyl anaesthesia for total hip arthroplasty. Can Anaesth Soc J 33:308, 1986.

1207. Omote K, Kawamata M, Satoh O et al: Spinal antinociceptive action of an n-type voltage-dependent calcium channel blocker and the synergistic interaction with morphine. Anesthesiology 84:636, 1996.

1208. Coriat P, Daloz M, Bousseau D et al: Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous nitroglycerin. Anesthesiology 61:193, 1984.

1209. Thomson IR, Mutch AC, Culligan JD: Failure of intravenous nitroglycerin to prevent intraoperative myocardial ischemia during fentanyl-pancuronium anesthesia. Anesthesiology 61:385, 1984.

1210. Bartowski RR, McDonnell TE: Prolonged alfentanil effect following erythromycin administration. Anesthesiology 73:566, 1990.

1211. Bartkowski RR, Goldberg ME, Huffnagle S et al: Sufentanil disposition: Is it affected by erythromycin administration? Anesthesiology 78:260, 1993.

1212. Sedman AJ: Cimetidine-drug interactions. Am J Med 76:109, 1984.

1213. Hare BD: The opioid analgesics: Rational selection of agents for acute and chronic pain. Hosp Formul 22:64, 1987.

1214. Hynynen MJ, Turunen MT, Korttila KT: Effects of alfentanil and fentanyl on common bile duct pressure. Anesth Analg 65:370, 1986.

1215. Egan TD, Huizinga B, Gupta SK et al: Remifentanil pharmacokinetics in obese versus lean elective surgery patients. Anesthesiology 89:562, 1998.

1216. Ausems ME, Hug CC Jr: Plasma concentrations of alfentanil required to supplement nitrous oxide anaesthesia for lower abdominal surgery. Br J Anaesth 55:191S, 1983.

Chapter 11 - Intravenous Drug Delivery Systems

Peter S. A. Glass
Steven L. Shafer
J. G. Reves

INTRODUCTION

For anesthetic drugs to be effective, they must reach their site of action. In 1628, William Harvey proved in *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* that venous blood was transported to the arterial circulation and thus to the organs of the body by the heart. It was recognized almost immediately that this meant that drugs given into veins could be rapidly carried to the entire body. Indeed, in 1657, Christopher Wren injected opium intravenously by means of a quill and bladder (Fig. 11-1A) in dogs and humans, rendering them unconscious. It is doubtful that Wren recognized this unconsciousness as "anesthesia" as we think of it today. Eight years later, Sigismund Elsholtz gave an opioid solution for the purpose of rendering subjects insensitive, but it was not until 1874 that Pierre-Cyprien Ore administered chloral hydrate intravenously for a surgical procedure. This landmark occasion followed the unsuccessful attempts by the Russian surgeon Pirogoff to administer ether intravenously in 1846, shortly after Crawford Long and William Morton had independently demonstrated the efficacy of ether insufflation for surgery. [1]

Intravenous methods of anesthetic drug delivery have depended on a steady improvement in technology. The quill and bladder used by Wren were not significantly improved on until Alexander Wood employed a needle and syringe to give intravenous medications in 1853. The hollow hypodermic needle was developed by Frances Rynd and a functional syringe, by Charles Pravaz. [1] Contemporary needles, catheters, and syringes are descendants of these early devices. The latest technologic development in intravenous anesthesia has been the introduction of computerized pharmacokinetic model-driven continuous-infusion devices (Fig. 1B) , first published by Helmut Schwilden [2] in 1981. Schwilden demonstrated the ability to attain desired plasma levels of an intravenous anesthetic drug by using a computer-controlled infusion pump driven by the published pharmacokinetics of the drug. These efforts have resulted in the release in Europe of the first commercial targetcontrolled infusion (TCI) device, developed by Zeneca, specifically for the administration of propofol. The March 1998 issue of the journal *Anaesthesia* was devoted entirely to a review of TCI, with a focus on the "Diprifusor" and the role of TCI devices in clinical practice.

The ultimate development will be devices for the closed-loop administration of intravenous drugs during anesthesia. Systems have been developed for closed-loop administration of sodium nitroprusside [3] [4] [5] [6] [7] and muscle relaxants. [8] [9] [10] [11] [12] [13] [14] The drug effect is easily measured for vasoactive drugs and muscle relaxants, facilitating closed-loop control. The lack of an obvious readily available measure of mental status has hindered the development of closed-loop anesthetic delivery systems. Clinical assessment of anesthetic depth requires integration of the patient's physiology, the drug dosing history, the level of noxious stimulation, and measurement of the patient's response to stimulation (hemodynamics, movement, electroencephalogram [EEG], tearing, and so on). It seems unlikely that a closed-loop device will perform this complex heuristic assessment in the near future. However, increasing understanding of the physiology involved in providing anesthesia and the development of monitoring devices for specific components of the anesthetic state have resulted in increasing efforts to develop such closed-loop devices. Schwilden has developed closed-loop systems for infusion of methohexital [15] [16] and propofol [17] on the basis of the median EEG frequency. Other closed-loop systems have been based on auditory evoked potentials [18] or the bispectral index [19] developed by Aspect Medical Systems. [20]

The development of new techniques has coincided with the development of new drugs. Rapid intravenous induction became popular with the introduction of sodium thiopental in 1934. The pharmacokinetics of thiopental prevented its becoming popular for the maintenance of anesthesia. During the past 30 years, numerous intravenous hypnotics

Figure 11-1 Intravenous drug delivery, past and future. (A) A depiction of the first intravenous injection of opium, utilizing the quill and bladder. (B) The future of intravenous drug delivery, in which drugs are delivered with the aid of a small, sophisticated infusion pump, which permits dosing in terms of plasma drug concentration rather than amount.

(methohexital, 1957; propanidid, 1957; althesin, 1971; etomidate, 1973; propofol, 1977), anxiolytics (diazepam, 1966; midazolam, 1978), and analgesics (fentanyl, 1959; ketamine, 1966; sufentanil, 1979; alfentanil, 1980; remifentanil, 1996) have been introduced. The general trend in the introduction of these newer agents has been to provide drugs with shorter and shorter times for recovery from drug effect. The newer intravenous agents propofol, etomidate, alfentanil, sufentanil, and remifentanil have all been shown to provide a rapid onset of anesthesia, a stable maintenance phase, and a rapid recovery.

Before a review of intravenous anesthesia delivery techniques and devices, it is essential that the relevant pharmacokinetics and pharmacodynamics be understood so that intravenous drugs may be given to their best advantage. Therefore, we develop these concepts and then show how intravenous anesthesia delivery systems can be used to ration-ally dose the intravenous drugs used in clinical practice.

PHARMACOKINETIC CONSIDERATIONS

One objective of anesthetic administration is to produce the clinically desired *time course of anesthetic effect.* Often, this includes rapid onset, smooth maintenance, and rapid recovery after termination of the anesthetic. Conventional pharmacokinetic models assume that a bolus of drug is instantaneously mixed into the plasma, producing an immediate peak in the plasma concentration. The concentration then continuously declines until the next bolus. Except for a transient perioperative stimulus (intubation, incision, bowel traction), it is unlikely that the patient's anesthetic requirements follow the saltatory time course of anesthetic effect seen with repeated bolus injections. Thus, the technique of intermittent boluses results in excessive drug effect at the time of the bolus, inadequate drug effect before the next bolus, or both (Fig. 11-2) . The technique of giving the entire anesthetic as an initial bolus, as was popular several years ago with massive doses of opioids for cardiac surgery, represents the reductio ad absurdum of the intermittent bolus technique. This technique produces a needlessly huge initial peak and, depending on the dose, grossly excessive or possibly subtherapeutic levels later in the case. Fortunately, opioids are enormously forgiving drugs in paralyzed patients whose lungs are mechanically ventilated.

The oscillating effect produced by intermittent bolus injection may be clinically undesirable when drugs that depress hemodynamics are used or when prompt emergence is desirable. To produce a time course of drug effect that follows the time course of anesthetic requirement, it is necessary to use a continuous infusion that is titrated to perceived anesthetic requirement. Ideally, just enough drug is given to achieve the therapeutic blood or plasma drug concentration, which is then titrated until the end of surgery (Fig. 11-3) . This method of drug delivery avoids the peaks and valleys in drug concentration seen with intermittent drug boluses. Theoretical advantages of continuous infusions over intermittent bolus injections include fewer periods of poor anesthetic control, a reduction in the total amount of drug used, and a more rapid recovery from anesthesia. These advantages have been documented by several investigators. [21] [22]

The goal of intravenous administration is to administer anesthetic drugs so that the resulting plasma concentration produces the desired time course of drug effect. By use of pharmacokinetic models, it is possible to calculate the dose of drug needed to produce the desired time course of plasma concentration. The medical literature is replete with articles describing pharmacokinetic models for every drug administered in the course of providing anesthesia. Anesthesiologists have found little use for these models. In this chapter, we demonstrate how pharmacokinetic models *can* be used to develop rational dosing guidelines for use with intravenous infusion delivery systems. We first review some basic pharmacokinetic concepts and define the relevant pharmacology terminology. The reader can find more detail about pharmacokinetics in Chapter 2 .

Pharmacokinetic models are mathematical descriptions of how the body "disposes" of drugs. The parameters describing this disposing process are estimated by administering a known dose of the drug and measuring the resulting plasma

Figure 11-2 Pharmacokinetic simulation of (upper curve) a single large bolus (50 mug/kg) and (lower curve) of a smaller bolus (8 mug/kg) followed by small intermittent boluses (1.5 mug/kg), using fentanyl as an example. The single large bolus results in plasma drug concentrations far in excess of those required, whereas the intermittent scheme results in plasma concentrations that periodically fall below those required. Ideally, the plasma drug concentration should be just within the therapeutic range, which can be best accomplished by an appropriately administered continuous infusion.

concentrations. A mathematical model then relates the input, I(t), with the concentrations, C(t). These models can take many forms. Figure 11-4 shows the concentrations in the plasma over time after a single intravenous bolus of drug at time 0. The drug concentrations continuously decrease after the bolus, and the rate of decrease is approximately proportional to the amount of drug in the plasma. Typically, it is convenient to describe this behavior by use of exponential models. The curve might have a single exponent, in which case the plasma concentrations over time might be described by the function $C(t) = A\ e^{-kt}$, where A is the concentration at time 0, and k is a constant that describes the rate that the concentrations decrease. The relationship appears to be a straight line when graphed as the log of concentration versus time. The pharmacokinetics of intravenous anesthetic drugs are more complex because after a bolus of any anesthetic drug, one observes a period of rapid decrease before the terminal "log-linear" portion (e.g., the part that is a straight line when graphed as log concentration versus time is reached). We can model this by taking several

Figure 11-3 Landscape of surgical anesthesia. The stimuli of surgery are not constant; therefore, the plasma concentration of the anesthetic drug should be titrated to match the needs of the patient. ICU, intensive care unit.

Figure 11-4 Steps involved in pharmacokinetic model-driven infusion. Typically, pharmacokinetic models are derived from experiments in which plasma drug concentrations are measured at intervals after bolus administration of the drug. Nonlinear regression is used to fit a mono-, bi-, or tri-exponential curve to the resulting concentration versus time data. There is an algebraic relationship between the exponential decay curves and a 1-, 2-, or 3-compartment pharmacokinetic model. The BET infusion scheme is derived from the 2-compartment model by use of contour integration. A BET infusion results in the maintenance of a constant specified plasma drug concentration. Practical implementation of the BET scheme using real infusion pumps and infusion rates that change only at discrete intervals of time results in a plasma drug concentration profile that approximates that resulting from a BET infusion. V_1, volume of the central compartment.

monoexponential (i.e., one-exponent) curves and adding them together. The result is a polyexponential curve. For example, the concentrations after an intravenous bolus might be described by an equation with two exponents, $C(t) = A\ e^{-alpha\ t} + B\ e^{-beta\ t}$, or an equation with three exponents, $C(t) = Ae^{-alpha\ t} + B\ e^{-beta\ t} + C\ e^{-gamma\ t}$.

There are many uses of intravenous anesthetic drugs besides single boluses. A more general way to think of pharmacokinetics is to decompose the input into a series of bits (boluses) and consider each bit of drug separately. The general pharmacokinetic model of drug disposition commonly used in anesthesia treats each bit of administered drug to a polyexponential decay over time. The formal mathematical description of treating each bit of drug to a polyexponential decay over time is the relationship

where C(t) is the plasma concentration at time t and I(t) is the drug input (i.e., a bolus or infusion). The summation after the * (described later) is the function describing how the drug is disposed of (hence its name, the "disposition" function). Note that this is again a sum of exponentials, as described in the prior paragraph. Pharmacokinetic modeling is the process of estimating the parameters within this function. The integer n is the number of exponentials (i.e., compartments) and is usually two or three for the drugs used in anesthesia. Each exponential term is associated with a coefficient A_i and an exponent $lambda_i$. The lambda values are the inverse of the half-lives (half-life = 0.693/lambda), with the smallest lambda representing the longest (terminal) half-life. The A values are the relative contribution of each half-life to overall drug disposition. If a drug has a very long terminal half-life but a coefficient that is much smaller than the other coefficients, then the long half-life is likely to be clinically meaningless. The * means the mathematical process called convolution, which can be thought of as multiplication, but for functions rather

than for simple numbers. For a bolus at time 0, convolution simply is multiplication. For infusions, the math implied by the $*$ gets more complicated, but the A's and lambda's estimated are the same.

Constructing pharmacokinetic models represents a trade-off among accurately describing the data, having confidence in the results, and achieving mathematical tractability. It is usually the case that adding exponentials (i.e., increasing n) to the model provides a better description of the data. However, adding exponential terms usually decreases our confidence in how well we know each coefficient and exponential. Additionally, each exponential greatly increases the mathematical burden of pharmacokinetic models. This is why most models of anesthetic drugs are limited to two or three exponential terms.

The pharmacokinetic model shown has some useful characteristics, accounting for its enduring popularity in pharmacokinetic analysis. Most important, the model describes the observations from studies reasonably well, obviously the sine qua non for models. Second, these models have the useful characteristic of linearity. Consider the aforementioned equation for two values of I (the drug input), one exactly twice the magnitude (over the same time course) of the other. The equation predicts that C(t) will be twice as large for twice the input. Simply stated, if you double the dose (e.g., a bolus twice as large or an infusion twice as fast), then you double the concentrations.

More generally, linearity implies that the system (i.e., the body acting to produce a plasma drug concentration output from a drug dosage input) behaves in accordance with the principle of superposition. The superposition principle states that the response of a linear system having multiple inputs can be computed by determining the response to each individual input and then summing the individual responses. In other words, when the body treats each bit of drug to a polyexponential decay over time, the disposing of each bit of drug does not influence the disposing of other bits of drug.

The third reason for the continuing popularity of these models is that they can be mathematically transformed from the admittedly unintuitive exponential form shown earlier to a more easily intuitive compartmental form, as shown in Figure 11-5 .The fundamental parameters of the compartment model are the volumes of distribution (central, rapidly, and slowly equilibrating peripheral volumes) and clearances (systemic, rapid, and slow intercompartmental). The central compartment (compartment 1) represents a distribution volume and includes the rapidly mixing portion of the blood and the first-pass pulmonary uptake. The peripheral compartments are composed of those tissues and organs that show a time course and extent of drug accumulation (or dissipation) different from that of the central compartment. In the three-compartment model, the two peripheral compartments may correspond roughly to splanchnic and muscle tissues (rapidly equilibrating) and fat stores (slowly equilibrating). The sum of the compartment volumes is the apparent volume of distribution at steady state (Vd_{SS}) and is the proportionality constant relating the plasma drug concentration at steady state to the total amount of drug in the body. The intercompartmental rate constants (k_{12}, k_{21}, and so on) describe the exchange of drug between the central and the peripheral compartments. The elimination rate constant (k_{10}) encompasses processes acting through biotransformation or elimination that irreversibly remove drug from the central compartment.

Despite the physiologic flavor of compartmental models, compartmental models are simply mathematical transformations of the polyexponential disposition functions that are computed entirely from observed plasma concentrations. Thus, physiologic interpretation of the volumes and clearances, with the possible exception of systemic clearance and Vd_{SS} (the algebraic sum of the volumes), are entirely speculative.

The last reason that these models have been popular is that they can be used to design infusion regimens. If we abbreviate the disposition function

Figure 11-5 Three-compartment model (including the effect site) schematizing the basic pharmacokinetic processes that occur after intravenous drug administration. V_1, central compartment volume, usually expressed in liters or liters per kilogram. I (mug/kg/min or mug/kg), the dosing scheme as a function of time; k_{10}/min, rate constant reflecting all processes acting to irreversibly remove drug from the central compartment; k_{ij}/min, intercompartmental rate constants.

as simply D(t), then we can rewrite the relationship among concentration, dose, and the pharmacokinetic model D(t) as

where $*$ is the convolution operator, as noted earlier. In the usual pharmacokinetic study, we know I(t) (what we gave the patient), and we measured C(t). Our goal is to find D(t), the pharmacokinetic disposition function. Pharmacokinetic analysis can be thought of as a simple rearrangement of the above equation to solve for D(t):

where the horizontal bar means deconvolution, which is like division, but of functions rather than of simple numbers. When we design dosing regimens from known pharmacokinetic models and a desired course for the plasma concentration over time, then the known values are D(t) (the pharmacokinetics) and C_T (t) (the desired target concentrations), and the drug dosing scheme is

Thus, knowing the desired concentration time course and the pharmacokinetics, we can design an infusion rate to achieve any result. Unfortunately, such a solution might require some negative infusion rates, which is obviously impossible. Because we cannot suck drug out of the body (i.e., give negative infusions), we must restrict ourselves to those plasma concentrations over time that can be achieved with nonnegative infusion rates. The fundamental point is that given desired target concentrations, C_T (t), one can calculate the necessary infusion rates, I(t), from the pharmacokinetics, D(t), by use of the same set of tools used to calculate the

pharmacokinetics, D(t), when we know the infusion rates, I(t), and measured plasma concentrations, C(t).

The standard pharmacokinetic model has one glaring shortcoming. It assumes that after a bolus injection there is complete mixing within the central compartment, so that the peak concentration occurs precisely at time 0. It actually takes about 30 to 45 seconds for the drug to make its transit from the venous injection site to the arterial circulation. This model misspecification of 30 to 45 seconds may not seem significant, but it can cause some problems when one is trying to relate the drug effect after a bolus to the drug concentrations in the body. Researchers are modifying the standard polyexponential pharmacokinetic models to provide more accurate models of plasma drug concentration in the 1st minute after bolus injection.

PHARMACODYNAMIC CONSIDERATIONS

Although the plasma concentration after an intravenous bolus peaks nearly instantaneously, no anesthesiologist would induce a healthy patient with an intravenous bolus of hypnotic and immediately intubate the patient's trachea. The reason, of course, is that although the plasma concentration peaks almost instantly, additional time is required for the drug concentration in the brain to rise and induce unconsciousness. This delay between peak plasma concentration and peak concentration in the brain is called hysteresis. Hysteresis is the clinical manifestation of the fact that the plasma is not the site of anesthetic action, only the mechanism of transport. It is at the biophase that intravenous anesthetic drugs exert their pharmacologic effect. Physically, the biophase is the immediate milieu in which the drug acts on the body, including membranes, receptors, and enzymes.

The concentration of drug in the biophase cannot be measured for two reasons. First, it is usually inaccessible, at least in human subjects. Second, even if we could take tissue samples, the drug concentration in the microscopic environment of the receptive molecules would not be the same as the concentration grossly measured in, say, homogenated brain and cerebrospinal fluid. Although it is not possible to actually measure drug concentration in the biophase, by use of rapid measures of drug effect we can characterize the time course of drug effect. Knowing the time course of drug effect, we can characterize the rate of drug flow in and out of the biophase (or "effect site") by use of mathematical models. [23] [24] Knowing the rate of equilibration between the plasma and the biophase, we can characterize the apparent drug concentration in the biophase in terms of the steady state-plasma concentration that would produce the same effect.

Just as shown for the plasma pharmacokinetics earlier, if we know the time course of drug input and the time course of drug concentration, we can compute how the biophase disposes of drug, that is, the disposition function of the biophase. [25] [26] The direct input to the biophase is not the drug infusion, I(t), but is the arterial plasma concentration over time, $C_{plasma}(t)$. We can estimate the disposition function of the biophase, $D_{biophase}(t)$, on the basis of the plasma drug concentrations and the biophase concentrations:

where the horizontal bar is deconvolution, the inverse operation of deconvolution. Of course, $C_{biophase}(t)$ is an unknown quantity because we cannot directly measure drug concentrations in the biophase. As an alternative, we can postulate that drug concentration in the biophase relates to drug effect through one of several pharmacodynamic models. In this sense, the biophase concentrations over time can be thought of as a function of the observed effect over time, E(t), and several additional pharmacodynamic parameters, P, that relate concentration to effect. The parameters, P, are simultaneously estimated with D(t). We can rewrite the relationship stated earlier in terms of the time course of drug effect:

where F is the function relating the effect-site concentration to drug effect, according to parameters P. Just as developed for plasma pharmacokinetics, we assume that the effect site

treats each bit of drug to an exponential decay over time. However, the data almost never justify more than a single exponential term, and so the disposition function of the effect site is

where k_{e0} is the rate constant for transfer of drug from the site of drug effect to the environment. The monoexponential disposition function implies that the effect site is simply an additional compartment in the standard compartmental model, connected to the plasma compartment(see Fig. 11-5) . The effect site is the hypothetical compartment that relates the time course of plasma drug concentration to the time course of drug effect, and k_{e0} is the rate constant of drug elimination from the effect site. By definition, the effect compartment receives such tiny amounts of drug from the central compartment that it has no influence on the plasma pharmacokinetics.

If a constant plasma concentration is maintained, then the time required for the biophase concentration to reach 50 percent of the plasma concentration ($t½k_{e0}$) can be calculated as $0.693/k_{e0}$. After a bolus dose, the time to peak effect-site concentration is a function of both the plasma pharmacokinetics and k_{e0} . For drugs with a very rapid decline in plasma concentration after a bolus (e.g., adenosine, which has a half-life of several seconds), the effect-site concentration peaks within several seconds of the bolus, regardless of the k_{e0} . For drugs with a rapid k_{e0} and a slow decrease in concentration after bolus injection (e.g., pancuronium), the peak effect-site concentration is determined more by the k_{e0} than by the plasma pharmacokinetics. The time to peak effect and the $t½k_{e0}$ for several intravenous anesthetics are listed in Table 11-1 .

This delay in onset has important clinical implications. After a bolus, the plasma concentration peaks nearly instantly and then steadily declines. The effect-site concentration starts at zero and increases over time until it equals the descending plasma concentration. The plasma concentration continues to fall, and after that moment of identical concentrations, the gradient between the plasma and the effect site favors drug removal from the effect site, and the effect-site concentrations decrease. The rate at which the effect site rises toward the peak after a bolus dictates how much drug must be injected into the plasma to produce a given effect.

TABLE 11-1 -- The $t½k_{e0}$ and Time to Peak Drug Effect Following a Bolus Dose

DRUG	TIME TO PEAK EFFECT (MIN)	$t½\ k_{e0}$ (MIN)
Fentanyl	3.6	4.7
Alfentanil	1.4	0.9
Sufentanil	5.6	3

Remifentanil	1.6	1.3
Propofol	2.2	2.4
Thiopental	1.7	1.5
Midazolam	2.8	4
Etomidate	2	1.5

t½k_{e0} , rate constant for the transfer of drug from the site of drug effect to the environment.

For alfentanil, the rapid plasma-effect-site equilibration (large k_{e0}) causes the effect-site concentration to rise rapidly, producing a peak in about 90 seconds. At the time of the peak, about 60 percent of the alfentanil bolus has distributed into the peripheral tissues or has been eliminated from the body. For fentanyl, the effect site rises much more slowly and peaks 3 to 4 minutes after the bolus. [27] At the time of the peak, more than 80 percent of the initial bolus of fentanyl has been distributed into the tissues or eliminated. As a result of the slower equilibration with the effect site, relatively more fentanyl than alfentanil must be injected into the plasma, which slows the rate of drug offset from a fentanyl bolus compared with an alfentanil bolus.

This suggests that the k_{e0} must be incorporated into dosing strategies. For a rapid onset of effect, a drug with a short k_{e0} should be chosen. For example, for a rapid-sequence induction, alfentanil or remifentanil may be the opioid of choice when given as part of the rapid induction sequence because the peak opioid effect-site concentration coin-cides with endotracheal intubation. However, for a slower induction, in which a nondepolarizing neuromuscular blocking drug is used, it may be appropriate to choose an opioid with a slower onset of drug effect to coincide with the peak effect of the muscle relaxant. In this case, a bolus of fentanyl or sufentanil at the time of induction may be appropriate. The time to peak effect for the commonly used opioids is shown in Figure 11-6 . Knowing the k_{e0} (or time to peak effect) also improves titration of the drug by identifying the time at which the clinician should make the assessment of drug effect. For example, midazolam has a slow time to peak effect, and repeat bolus doses should be spaced at least 5 to 7 minutes apart to avoid inadvertent overdosing.

Figure 11-6 The simulated onset and time to peak effect of commonly used opioids based on their k_{e0} and pharmacokinetic parameters. k_{e0} , rate constant for transfer of drug from the site of drug effect to the environment.

To summarize:

1. If we know $D_{plasma}(t)$, the plasma pharmacokinetics, and I(t), the drug given to the patient, we can calculate the resulting concentrations, $C_{plasma}(t)$, as the convolution of $D_{plasma}(t)$ with I(t).

2. If we know $D_{biophase}(t)$, the biophase pharmacokinetics, and $C_{plasma}(t)$, the input to the biophase, we can calculate the resulting concentrations in the biophase as the convolution of $D_{biophase}(t)$ with $C_{plasma}(t)$.

It follows that we can relate the biophase concentration to drug input by the relationship

From this relationship, it follows that we can calculate the infusion rate necessary to produce any desired concentration time course in the biophase, $C_T(t)$, the target concentration, as

where the horizontal line represents deconvolution, provided we restrict our choice of $C_T(t)$ to those biophase concentrations that can be achieved without negative infusion rates. [25] [26]

Having established that we can produce almost any desired concentration time course in the effect site, what concentration should we choose? The pharmacokinetics and pharmacodynamics of the inhalational anesthetics are greatly simplified by the equilibrium established at the alveolar gas/blood interface, permitting the measurement of the minimum alveolar concentration (MAC) associated with 50 percent likelihood of movement in response to noxious stimulation. [28] Considerable effort has gone into developing a concept equivalent to MAC for intravenous anesthetic drugs.

Because of the difficulty measuring the concentration of intravenous drugs, early investigators related infusion rate to clinical effects, such as the response to skin incision. These studies defined the minimum infusion rate (MIR) necessary to prevent a somatic response to surgical skin incision in 50 percent of patients. This simple approach is pharmacokinetically naive. It ignores the accumulation of drug in the plasma that necessarily occurs over time during intravenous infusions. The result is that MIR is a time-dependent measure of dose adequacy. Additionally, the variability in MIR reflects both pharmacokinetic and pharmacodynamic variability between individuals, whereas the variability in MAC measures only pharmacodynamic variability between individuals.

Because MIR depends on the patient's pharmacokinetics, and MIR changes over time, investigators have developed more general measures to relate intravenous drugs to drug effect. The most common approach is to report pharmacodynamics in terms of C_{50} . The C_{50} is, by definition, *the concentration that produces 50 percent of the maximum possible drug effect.* There are many ways of thinking about C_{50} . It might be the drug concentration that prevents response (e.g., movement, hypertension, and catecholamine release) to a particular stimulus (e.g., incision, intubation, and sternal spreading) in 50 percent of patients. In this case, each combination of stimulus and response may have a unique C_{50} . For example, Ausems and colleagues [29] defined the C_{50} for several noxious stimuli for alfentanil in the presence of 66 percent nitrous oxide. When C_{50} is defined as the drug concentration that produces a given response in 50 percent of the patients, it is also the concentration associated with a 50 percent probability of response in a given patient. Note that defining C_{50} as the concentration that produces a given effect in 50 percent of individuals implicitly assumes that the effect can be achieved in all individuals. Some drugs exhibit a ceiling effect. For example, there appears to be a ceiling on the ability of opioids to suppress response to noxious stimulation. When a ceiling exists in drug effect, even at infinite concentrations, some patients may not exhibit the drug effect. In this case, the C_{50} is not the concentration that causes the drug effect in 50 percent of patients but is the concentration associated with the drug effect in half of whatever fraction of patients are able to show the drug effect.

Several studies have been performed to establish appropriate concentrations for intravenous anesthetics. The C_{50} for skin incision for alfentanil, fentanyl, and remifentanil in the presence of 70 percent nitrous oxide have been defined (Table 11-2) . The C50 values for loss of consciousness and skin incision have also been defined for the hypnotics thiopental, [30] [31] propofol, [32] [33] [34] and midazolam [35] (see Table 11-2). Defining the C_{50} , like MAC, provides a measure of relative potency between the intravenous anesthetics.

Another means of evaluating the relative potency of an intravenous anesthetic during anesthesia is to define the plasma concentration of the intravenous anesthetic (once it has equilibrated with the biophase) required to reduce the MAC of a volatile anesthetic by a set percentage. The MAC reduction of isoflurane by fentanyl, [36] sufentanil, [37] alfentanil, [38] and remifentanil [39] have all been defined. The concentrations of these opioids that provide a 50 percent MAC reduction are listed in Table 11-2 .

Another interpretation of C_{50} is the concentration that produces 50 percent of the maximum possible physiologic response. For example, the C_{50} for an EEG response is the drug concentration that provides 50 percent of the maximal EEG effect. The C_{50} for EEG response has been measured for the opioids alfentanil, [40] fentanyl, [40] sufentanil, [41] remifentanil, [42] [43] and trefentanil. [44] It has also been determined for thiopental, [30] [45] [46] etomidate, [47] propofol, [48] and benzodiazepines [49] (see Table 11-2) .

The EEG is a surrogate measure of anesthetic effect. The utility of the EEG as a surrogate measure of opioid drug effect comes from the consistency between the relative potency of the opioids based on the C_{50} for EEG response and the relative potency based on clinical measures, such as the C_{50} for ablation of response to a noxious stimulation and the C_{50} for 50 percent MAC reduction. Although the C_{50} values for all combinations of stimuli and measures have not been experimentally determined for each opioid, these can be accurately estimated by scaling the values of C_{50} determined experimentally for other opioids by the relative potency. For example, the C_{50} of alfentanil for spontaneous ventilation is about 40 percent of the C_{50} for the EEG response (Table 11-1) . Knowing this, we can estimate the C_{50} for spontaneous ventilation of sufentanil (which has not yet been determined experimentally) as 0.2 to 0.3 ng/mL, that is, 40 percent of the C_{50} for EEG response (0.7 ng/mL).

To be entirely independent of dosing history, the C_{50} must be determined at steady state. This is rarely possible

TABLE 11-2 -- Steady-State Concentrations or Predefined Effects [a]

DRUG	C_{50} FOR EEG DEPRESSION [b]	C_{50} FOR INCISION OR PAINFUL STIMULUS [c]	C_{50} FOR LOSS OF CONSCIOUSNESS [d]	C_{50} FOR SPONTANEOUS VENTILATION [e]	C_{50} FOR 50% ISOFLURANE MAC REDUCTION	MEAC
Alfentanil (ng/mL)	500-600	200-300	--	175-225	50	10-30
Fentanyl (ng/mL)	6-10	4-6	--	2-3	1.67	0.5-1
Sufentanil (ng/mL)	0.5-0.75	(0.3-0.4)	--	(0.15-0.2)	0.145	0.025-0.05
Remifentanil (ng/mL)	10-15	4-6	--	2-3	1.23	0.5-1
Thiopental (mug/mL)	15-20	35-40	8-16	--	--	--
Midazolam (ng/mL)	250-350	--	125-250	--	--	--

MEAC, minimum effective plasma concentration providing postoperative analgesia.

[a] Values in parentheses are estimated by scaling to the alfentanil C_{50} (see text for details).

[b] C_{50} for EEG depression is the steady-state serum concentration that causes a 50% slowing of the maximal EEG.

[c] C_{50} for skin incision is the steady-state plasma concentration that prevents somatic or autonomic response in 50% of patients.

[d] C_{50} for loss of consciousness is the steady-state plasma concentration for absence of a response to a verbal command in 50% of patients.

[e] C_{50} for spontaneous ventilation is the steady-state plasma concentration associated with adequate spontaneous ventilation in 50% of patients.

because most anesthetic drugs do not reach steady state during a continuous infusion until many hours have passed. However, if the drug has rapid equilibration between the plasma and the effect site and the investigator waits long enough after starting the infusion, this choice can be reasonably satisfactory. For example, Ausems and colleagues [29] [50] used a continuous infusion but chose a rapidly equilibrating drug, alfentanil, for their experiments and waited sufficiently long before taking measurements to ensure that the plasma and effect-site concentrations were nearly in equilibrium.

One alternative to performing a true steady-state experiment is to simply measure the plasma drug concentrations in non-steady-state conditions and to calculate C_{50} from these values. This is a poor choice because the extent of equilibration between the site of drug effect and the plasma influences the value of C_{50} . Thus, if C_{50} is based on non-steady-state plasma drug concentrations, it has exactly the same dependence on dosing history and time of measurement that taints the use of MIR.

A second alternative to performing a true steady-state experiment is to use mathematical modeling to calculate the effect-site concentrations of drug at the time of the measurement, as proposed by Hull et al [23] and Sheiner et al. [24] The relationship between the effect site and the plasma concentrations is represented graphically in Equation 5 and mathematically in Equation 9. Calculating effect-site concentrations is nothing more than attempting to determine the steady-state plasma concentrations that would produce the observed drug effect. Sometimes, when the C_{50} reflects effect-site concentrations, it is represented as Ce_{50} , to distinguish it from values of C_{50} that are based on plasma concentrations, which are then termed Cp_{50} . However, the distinction is artificial. In both cases, the C_{50} is intended to represent the steady-state plasma drug concentration associated with a given drug effect.

A third alternative to performing a steady-state experiment is to establish a pseudo-steady state by use of computer-controlled drug delivery. This has become the present state-of-the-art method for determining the C_{50} for anesthetic drugs, and many of the C_{50} values referenced earlier were determined at pseudo-steady state by use of computer-controlled drug delivery. Typically, this requires maintaining a constant plasma concentration steady state for four to five plasma-effect-site equilibration half-lives (e.g., 10-15 minutes for fentanyl). Such a long delay is not necessarily required when computer-controlled drug delivery is used. For example, Glass et al [51] used computer controlled infusions to target initially higher plasma target concentrations to provide more rapid achievement of the desired effect-site concentration. This can be automated by having the computer actually target the concentration in the effect-site rather than the plasma, rapidly establishing plasma-effect-site equilibration. [25] [26]

Thus, there are several ways to establish C_{50} in terms of steady-state concentrations. C_{50} can be estimated through mathematical effect-site modeling or can be measured experimentally by use of computer-controlled drug delivery to quickly establish a pseudo-steady state. Regardless, when C_{50} is referenced to steady-state plasma concentrations, it is superior to MIR because it is independent of the dosing history and the pharmacokinetic variability.

When C_{50} is defined in terms of the concentration associated with a response in half of a population, then that same C_{50} is the concentration associated with a 50 percent probability of response in the typical individual. However, the individual patient is not the typical individual but rather will have his or her own value for C_{50} . Expressed in clinical terms, different patients have different anesthetic requirements for the same stimulus. For example, the minimal effective analgesic concentration of fentanyl is 0.6 ng/mL but varies from 0.2 to 2.0 ng/mL between patients. [52] The minimal effective analgesic concentration of alfentanil [53] [54] and sufentanil [55] similarly varies between patients by a factor of five to ten times. This range encompasses both variability in the intensity of the stimulus and variability of the individual

patient. However, this wide range reflects the clinical reality that must be accounted for when dosing regimens are designed. Because of this variability, intravenous anesthetics should be titrated to each patient's unique anesthetic requirement for the given stimulus.

Pharmacodynamic Drug Interactions in Providing Anesthesia

A common residency experience for the authors, and perhaps for the reader as well, was the attempt to administer "pure" techniques: pure inhalational anesthesia (e.g., isoflurane/oxygen), pure nitrous/narcotic anesthesia (nitrous oxide/fentanyl/oxygen), pure ketamine anesthesia, and so on. We rapidly discovered that pure anesthetics required huge doses of drugs to achieve anesthetic conditions that were often unsatisfactory. The only benefit of struggling with pure techniques is the appreciation one gets for the essential role of drug interactions in the practice of anesthesia.

Drug interactions cause the C_{50} of one drug to shift in response to administration of a second drug. We have already referred to the ability of opioids to reduce MAC, a clinically useful drug interaction with a long history. In 1901, George Crile suggested that opioids should be administered with supplemental drugs for intravenous anesthesia. In 1959, DeCastro and Mundeleer introduced the term "neurolept anesthesia," consisting of a tranquilizer, opioid, and nitrous oxide. Today, the concept and term coined by John Lundy, "balanced anesthesia," is used to describe the concurrent administra-tion of several anesthetic drugs so that no single drug is given in a dosage sufficient to produce toxicity during or after surgery. Contemporary anesthesia consists of at least two components--analgesia and loss of consciousness. Combining an opioid with a volatile anesthetic provides both components. The interaction of volatile anesthetics and opioids in producing the anesthetic is complex but predictable. In addition, because two drugs are being used to provide anesthesia, recovery to an awake state is dependent on both drugs. Thus, to provide adequate anesthesia and appropriate recovery, it is important to incorporate both the pharmacodynamic interactions that occur between these drugs and their relative offset, as demonstrated by their context-sensitive decrement times.

Drug interactions are species dependent. Thiopental and opioids show relative antagonism to analgesic end points in rats, [56] [57] whereas their effects are synergistic in humans. [58] Just as C_{50} must be defined for very specific end points, drug interactions must also be clearly defined in terms of end points. For example, Kissin et al [57] observed that "the combination of a barbiturate and an opioid gives different outcomes for different end-points of anesthesia." Often, we differentiate between analgesic end points (i.e., analgesia to noxious stimulation) and hypnotic end points (e.g., sedation and loss of consciousness). In a study of morphine-midazolam interactions on sedation and loss of righting reflex in rats, Kissin et al [59] observed that the conventional bifurcation into hypnotic and analgesic end points may be inadequate. Both sedation and loss of righting reflex appear to be "hypnotic" end points, but they were associated with different degrees of synergy between morphine and analgesia. Kissin et al concluded that "differences in the outcomes of midazolammorphine interactions regarding sedation and hypnosis (loss of righting reflex) suggest that underlying mechanisms for these two effects are different. Therefore, they should not be regarded as only increasing depths of the same action."

The MAC of volatile anesthetics appears additive when several inhalational anesthetics are administered concurrently. [60] [61] In other words, 30 percent MAC of drug A combined with 40 percent MAC of drug B produce the same effect as 70 percent MAC of A or B. The additivity of MAC suggests a uniform mechanism of action for the inhalational anesthetics, although the "unitary theory" of inhalational anesthesia has fallen into disfavor. [62] [63] The intravenous anesthetics encompass categories of drugs (hypnotics, opioids, psychotomimetics, anxiolytics, neuroleptics, local anesthetics, and so on) with different receptors and mechanisms of action. In the absence of a uniform mechanism of action, there is no reason to anticipate simple additivity, for example, that maintaining 30 percent C_{50} of drug A plus 40 percent C_{50} of drug B will produce the same effect as 70 percent C_{50} of either drug A or drug B.

The assumption of balanced anesthesia is that combinations of drug will be synergistic in anesthetic effect (however defined) but not in toxicity. Such synergism has been demonstrated for a variety of drug combinations but not for others. [64] In an interesting set of studies, Glass and colleagues [34] observed minimal synergy between propofol and fentanyl for a hypnotic end point, loss of consciousness (Fig. 11-7) , but profound synergy between propofol and fentanyl for an analgesic end point, loss of response to skin incision (Fig. 11-8) More profound synergy for analgesic end points than hypnotic end points has also been demonstrated for the interaction between propofol and alfentanil [33] and sevoflurane and fentanyl. [65] Thus, when anesthetic regimens are designed that rely on synergy to produce the anesthetic state, it is important to distinguish the desired end point--loss of consciousness or ablation of response to noxious stimulation. Different combinations of drugs may be required to achieve each end point.

Mean alveolar concentration is defined as the steady-state alveolar concentration of anesthetic gas that inhibits movement to incision in 50 percent of patients. It is an excellent measure of potency. MAC is also a useful guideline for clinical

Figure 11-7 The interaction of propofol and fentanyl in providing loss of consciousness. The solid lines represent the concentrations of propofol and fentanyl when administered together that are required to prevent a response to a verbal command in 50% of patients at each decade of age.

Figure 11-8 The interaction of propofol and fentanyl in preventing a somatic response at skin incision. The solid line represents the concentrations of propofol and fentanyl when administered together that are required to prevent purposeful movement in 50% of patients at skin incision. The dashed line represents the concentration of propofol and fentanyl when administered together that is required to prevent purposeful movement in 95% of patients at skin incision.

dosage, provided the clinician remembers that it is the concentration *in 50 percent of patients* that inhibits a movement response and that it is defined in terms of an analgesic end point--loss of movement in response to noxious stimulation. To establish the interaction between volatile anesthetics and opioids, the reduction in MAC can be utilized. When such studies are performed, it is important that both the volatile anesthetic and the opioid be maintained at stable concentrations and have equilibrated with their effect site. For the volatile anesthetic, this is readily achieved by use of a calibrated vaporizer. For the opioid, targetcontrolled delivery devices as described in this chapter are used to maintain constant opioid concentrations within the effect compartment.

Probably the most commonly used combination of anesthetics is isoflurane and fentanyl. McEwan et al [36] demonstrated that the MAC of isoflurane is reduced by 50 percent at a fentanyl concentration of 1.7 ng/mL (Figure 11-9) This corresponds with a fentanyl loading dose of 4 mug/kg followed by 1.75 mug/kg/h. Because the minimum effective analgesic concentration of fentanyl is 0.6 ng/ml, [52] and because clinically significant respiratory depression may occur with plasma fentanyl concentrations above 2 ng/mL, [66] the steepest reduction in MAC occurred within the useful analgesic range for fentanyl (i.e., 0.6-2 ng/mL). In other words, just maintaining fentanyl within an analgesic range reduces MAC by 50 percent. The study by McEwan et al also demonstrated that beyond a fentanyl plasma concentration

Figure 11-9 The interaction of isoflurane and fentanyl in preventing a somatic response at skin incision (i.e., MAC reduction of isoflurane). The solid line represents the concentrations of isoflurane and fentanyl when administered together that are required to prevent purposeful movement in 50% of patients at skin incision. The dashed line represents the 95% confidence interval of the MAC at each combination of fentanyl and isoflurane. MAC, minimum alveolar concentration.

of 5 ng/mL, a plateau is seen with a maximum MAC reduction of approximately 80 percent. The maximum reduction in isoflurane was to a concentration of ±0.3 percent, that is, a value close to the MAC awake for isoflurane. [67]

Alfentanil, [38] sufentanil, [37] and remifentanil [39] produce similar reductions in isoflurane MAC, with an initial steep reduction at lower concentrations and a plateau effect at higher concentrations. Remifentanil is a new esterase-metabolized opioid. [51] [68] The MAC reduction of isoflurane by remifentanil has been published and is illustrated in Figure 11-10 . [39] The results of this drug interaction are identical to those with the other opioids tested. Again, even with these very high plasma concentrations (>30 ng/mL), a ceiling effect was observed, and the MAC of isoflurane was not reduced lower than 0.2 to 0.3 percent. The interactions between propofol and fentanyl [34] (Fig. 11-8) and propofol and alfentanil [33] have also been studied. The reduction of the C_{50} of propofol by these opioids is almost identical to their interaction with isoflurane in preventing a somatic response at skin incision.

Adequate anesthesia provides for loss of consciousness (a hypnotic end point) and reduction in response to noxious stimulation (an analgesic end point). Loss of consciousness is achieved at hypnotic concentrations well below the concentration that suppresses response to noxious stimulation (e.g., MAC). If a slightly higher dose of hypnotic is combined with an analgesic dose of opioid, the profound interaction between opioids and hypnotics reduces or ablates the response to noxious

stimulation. There is very little advantage in administering the opioid to higher concentrations once the ceiling effect is reached. This occurs at a concentration of 3 to 5 ng/mL for fentanyl and remifentanil, 200 to 400 ng/mL for alfentanil, and 0.25 to 0.5 ng/mL for sufentanil.

Figure 11-10 The interaction of isoflurane and remifentanil in preventing a somatic response at skin incision (i.e., MAC reduction of isoflurane). The solid line represents the concentrations of isoflurane and remifentanil when administered together that are required to prevent purposeful movement in 50% of patients at skin incision.

Additionally, keeping the opioid dose within an analgesic range prevents the very slow recovery that is associated with high opioid concentrations.

Although these principles are likely true for all patients, there is still variability in sensitivity from patient to patient, as well as variability in the level of stimulation associated with different surgical procedures. Thus, each patient is an experiment, with the clinician learning the individual patient's C_{50} for the combination of drugs employed during the administration of each anesthetic. Despite this variability, dosing guidelines still have an important role to play in the practice of anesthesia. The concentration ranges for the intravenous anesthetics for anesthesia, sedation, and analgesia are given in Table 11-3 . These ranges should be viewed as starting estimates on which subsequent titration can be based. They also provide a means of estimating whether the patient is having a typical response or an atypical response. If the patient's dosing requirements deviate greatly from established guidelines, it is reasonable to stop and wonder whether something else might be going on with either the patient or the drug delivery system.

DESIGNING DOSING REGIMENS

Bolus Dose Calculations

The definition of concentration is amount divided by volume. We can rearrange the definition of concentration to find the amount of drug required to produce any desired concentration for a known volume:

where C_T is the desired or "target" concentration. Many introductory pharmacokinetic texts suggest using this formula to calculate the loading bolus required to achieve a given concentration. The problem with applying this concept to the anesthetic drugs is that there are several volumes: V_1 (central compartment), V_2 and V_3 (the peripheral compartments), and Vd_{SS}, the sum of the individual volumes. V_1 is usually much smaller than Vd_{SS}, and so it is tempting to say that the loading dose should be something between $C_T \times V_1$ and $C_T \times Vd_{SS}$.

Consider the dose of fentanyl required to attenuate the hemodynamic response to intubation when combined with thiopental. The C_{50} for fentanyl, combined with thiopental for intubation, is approximately 3 ng/mL. The V_1 and Vd_{SS} for fentanyl are 13 L and 360 L, respectively. The aforementioned equations can thus be interpreted as suggesting that an appropriate dose of fentanyl to attenuate the hemodynamic response is between 39 mug (3 ng/mL × 13 L) and 1080 mug (3 ng/mL × 360 L). A fentanyl bolus of 39 mug achieves the desired concentration in the plasma for an initial instant, but the plasma levels almost instantly decrease below the desired target. The levels in the effect site will never be close to the desired target concentration of 3 ng/mL. A fentanyl bolus of 1080 mug, not surprisingly, produces an enormous overshoot

TABLE 11-3 -- Plasma Drug Concentration Ranges

DRUG[a]	STIMULUS					
	SKIN INCISION	***MAJOR SURGERY***	***MINOR SURGERY***	***SPONTANEOUS VENTILATION***	***AWAKENING***	***ANALGESIA OR SEDATION***
Alfentanil (ng/mL)	200-300	250-450	100-300	<200-250	--	50-100
Fentanyl (ng/mL)	3-6	4-8	2-5	<1-2	--	1-2
Sufentanil (ng/mL)	1-3	2-5	1-3	<0.2	--	0.02-0.2
Remifentanil (ng/mL)	4-8	4-8	2-4	<1-3	--	1-2
Propofol (mug/mL)	2-6	2.5-7.5	2-6	--	0.8-1.8	1.0-3.0
Methohexital (mug/mL)	5-10	5-15	5-10	--	1-3	2-5
Thiopental (mug/mL)	7.5-12.5 (with N_2O) 35-45 (without N_2O)	10-20	10-20	--	4-8	7.5-15.0
Etomidate (ng/mL)	400-600	500-1000	300-600	--	200-350	100-300
Midazolam (ng/mL)	--	50-250 (combined with an opioid)	50-250 (combined with an opioid)	--	150-200 (reduced to 20- 70 in the presence of an opioid)	40-100
Ketamine (mug/mL)	--	--	1-2	--	--	0.1-1

[a] Drug levels are when combined with 65-70% nitrous oxide (N_2O) unless otherwise stated. Effective plasma concentrations may differ markedly, depending on premedication and intraoperative drug combinations.

in the plasma levels that persists for hours (Fig. 11-11) Additionally, it is clearly absurd to use equations to calculate the fentanyl dose if the resulting recommendation is "pick a dose between 39 and 1080mug."

The usual dosing guidelines for bolus dose, presented earlier, are designed to produce a specific plasma concentration. Because the plasma is not the site of drug effect, it is illogical to base the calculation of the initial bolus on a desired plasma concentration. As pointed out previously, by knowing the k_{e0} of an intravenous anesthetic, we can design a dosing regimen that yields the desired concentration at the site of drug effect. If we do not want to overdose the patient, we should select the bolus that produces the desired peak concentration in the effect site.

The decline in plasma concentration between the initial concentration after the bolus (amount/V_1) and the concentration at the time of peak effect can be thought of as a dilution of the bolus into a larger volume than the volume of the central compartment. This introduces the concept of Vd_{pe}, the apparent volume of distribution at the time of peak effect, [25] [69] (Table 11-4) or pseudo-equilibration between the plasma and the site of drug effect. [70] The size of this volume can be readily calculated

from the observation that the plasma and effect-site concentrations are the same at the time of peak effect:

where C_{pe} is the plasma concentration at the time of peak effect.

Figure 11-11 Pharmacokinetic simulation demonstrating the limitations of infusion regimens based on simple pharmacokinetic parameters, using fentanyl as an example. These infusion schemes were designed to achieve a plasma fentanyl concentration of 3 ng/mL. The upper curve shows that a regimen using a loading dose based on the volume of distribution followed by a constant infusion based on clearance results in a transient period of extremely high plasma concentrations. If the same maintenance infusion is given but the loading dose is based on the volume of the central compartment, distribution of drug to the peripheral compartments causes the plasma concentration to fall below the desired level until the compartments reach steady-state concentrations, as shown in the lower curve. Cp, plasma drug concentration.

TABLE 11-4 -- Volume of Distribution at the Time of Peak Effect

DRUG	V_1 (L)	VD_{PE} (L)
Fentanyl	12.7	75
Alfentanil	2.19	5.9
Sufentanil	17.8	89
Remifentanil	5.0	17
Propofol	6.7	37

V_1 , volume of the central compartment; Vd_{pe} , apparent volume of distribution at the time of peak effect.

Returning to the goal of selecting the dose required to produce a certain drug effect, without producing an overdose, by definition, the plasma concentration at the time of peak effect is the bolus amount/Vd_{pe} . This can be rearranged to calculate the size of the initial bolus:

The Vd_{pe} for fentanyl is 75 L. Producing a peak fentanyl effect-site concentration of 3.0 ng/mL requires 225 mug, which produces a peak effect in 3.6 minutes. This is a much more reasonable dosing guideline than the previous recommendation of picking a dose between 39 and 1080 mug. Table 11-4 lists V_1 and Vd_{pe} for fentanyl, alfentanil, sufentanil, remifentanil, thiopental, and propofol. Table 11-1 lists the k_{e0} , $t½k_{e0}$ /2 k_{e0} , and time to peak effect of the commonly used intravenous anesthetics.

Maintenance Infusion Rate

By definition, the rate at which drug exits from the body is the systemic clearance, Cl_S , times the plasma concentration. To maintain a given target concentration, C_T , drug must be delivered at the same rate that drug is exiting the body. Thus, the maintenance infusion rate is

For drugs with multicompartmental pharmacokinetics, which includes all of the intravenous drugs used in anesthetic practice, drug is distributed into the peripheral tissues as well as cleared from the body. The rate of distribution into tissues changes over time as the tissues equilibrate with the plasma. Equation 14 is correct only after the peripheral tissues have fully equilibrated with the plasma, which requires many hours. At all other times, this maintenance infusion rate underestimates the actual infusion rate to maintain a target concentration.

However, in some situations, this simple maintenance rate calculation may be acceptable. For example, if an infusion at this rate is used along with a bolus dose based on Vd_{pe} , and the drug has a long delay between the bolus and peak effect, then much of the distribution of drug into the tissues may have occurred by the time the effect-site concentration reaches the target concentration. In this case, the maintenance infusion rate calculated as clearance times target concentration may be fairly accurate because Vd_{pe} is sufficiently higher than V_1 to account for much of the distribution of drug into peripheral tissues. Unfortunately, most drugs used in anesthesia have sufficiently rapid equilibration between the plasma and the effect site that Vd_{pe} does not adequately encompass the distribution process, making this approach fairly unsuitable.

Another example for calculating infusion rates for drugs with multicompartmental pharmacokinetics is the two-step approach proposed by Wagner. [71] In this method, two infusions, Q_1 and Q_2 , are administered in sequence. The loading infusion, Q_1 , is selected on the basis of a combination of convenience and degree of overshoot in plasma concentration that will be clinically acceptable. The second infusion, Q_2 , is calculated as C_T times Cl_S , exactly as noted earlier. The Wagner two-step approach does not consider the time course of drug effect and thus is probably not appropriate for most anesthetic drugs.

Having offered to the reader several simple approaches that do not work very well, we now turn to approaches that are mathematically sound. Because the net flow of drug into peripheral tissues decreases over time, the infusion rate required to maintain any desired concentration must also decrease over time. If the initial bolus has been based on Vd_{pe} , no infusion need be administered until the effect-site concentrations peak. After the peak in effect-site concentration, the correct equation to maintain the desired concentration is (unfortunately)

This equation indicates that a high infusion rate is initially required to maintain C_T . Over time, the infusion rate gradually decreases (Fig. 11-4) At equilibrium (t

), the infusion rate decreases to $C_T V_1 k_{10}$, which is the same as $C_T Cl_S$. Few anesthesiologists would choose to mentally solve such an equation during administration of an anesthetic. Fortunately, there are a few simple techniques that can be used in place of solving such a complex expression.

Figure 11-12 is a nomogram in which the Equation 15 has been solved, showing the infusion rates over time necessary to maintain any desired concentration of fentanyl, alfentanil, sufentanil, and propofol. This nomogram is complex, so we will review it in detail. The Y axis represents the C_T , selected in "pharmacodynamic considerations." The X axis is the time since the beginning of the anesthetic (i.e., since the initial bolus). Envision a horizontal line drawn from the target concentration (on the Y axis) across the graph to the right edge. The correct rate is given by the diagonal line that most closely intersects with this imaginary horizontal line (desired

target concentration) at the desired point in time. Each diagonal line is associated with a particular infusion rate. The suggested target initial concentrations are based on the work of Vuyk and colleagues [33] with propofol and alfentanil and are scaled to fentanyl and sufentanil based on their relative potencies. [69]

For example, to maintain a fentanyl concentration of 1.5 ng/mL, the appropriate rates are 4.5 mug/kg/h at 15 minutes, 3.6 mug/kg/h at 30 minutes, 2.7 mug/kg/h at 60 minutes, 2.1 mug/kg/h at 120 minutes, and 1.5 mug/kg/h at 180 minutes. Of course, you can select different times of rate adjustment, depending on clinical convenience and your assessment of how accurately the intravenous drug needs to be titrated.

Figure 11-12 Nomogram for calculating the maintenance infusion rates to maintain a stable concentration of fentanyl, alfentanil, sufentanil, or propofol. The Y axis is the desired concentration. The X axis is the time relative to the initial bolus. The diagonal lines show the infusion rates at different times required to maintain the desired concentration selected on the Y axis.

Recovery from Anesthesia

Recovery from anesthesia is similarly determined by the pharmacokinetic principles that determine the rate of decrease of drug from the effect compartment, once drug administration is terminated, as well as by the pharmacodynamics of the drug. Although the terminal elimination half-life is often interpreted as a measure of how short or long lasting a drug is, the rate at which drug decreases is dependant both on elimination and on redistribution of the drug from the central compartment. The contribution of both redistribution and elimination toward the rate of decrease of drug concentration varies according to the duration for which the drug has been administered. [69] [72]

In 1985, Schwilden [73] developed a mathematical model to relate the time course of offset of the inhalational anesthetics to the duration of anesthetic drug delivery. Similarly, Fisher and Rosen [74] demonstrated how accumulation of muscle relaxants in peripheral volumes of distribution resulted in slowed recovery with increasing duration of administration.

Figure 11-13 Context-sensitive half-times as a function of infusion duration (the "context") derived from pharmacokinetic models of fentanyl, sufentanil, alfentanil, propofol, midazolam, and thiopental.

They introduced two measures of the time course of recovery, the time for twitch tension to recover from 5 to 25 percent and the time for twitch tension to recover from 25 to 75 percent.

Since then, the time for the plasma concentration to decrease by 50 percent from an infusion that maintains a constant concentration (e.g., the infusion given by Equation 15) has been termed the "context-sensitive half-time" [72] (Fig. 11-13) , with the context being the duration of the infusion. The 50 percent decrease was chosen both for tradition (e.g., half-lives are the time for a 50 percent decrease with a one-compartment model) and because, very roughly, a 50 percent reduction in drug concentration appears necessary for recovery after administration of most intravenous hypnotics at the termination of surgery. Depending on the circumstances, decreases other than 50 percent may be clinically relevant. Additionally, sometimes it is the plasma concentration that is of interest, and sometimes it is the effect-site concentration that is of interest. A more general term is the context-sensitive "decrement time," [75] in which the decrement in concentration is specifically noted, as is the compartment where the decrease is modeled (plasma effect site). For example, the relationship between infusion duration and time required for a 70 percent decrease in fentanyl effect-site concentration is the "context-sensitive 70 percent effect-site decrement time."

Context-sensitive effect-site decrement times for varying percent decreases in alfentanil, fentanyl, and remifentanil concentration are illustrated in Figure 11-14 To determine when an infusion should be terminated (to enable awakening of the patient at the end of surgery), the clinician needs to bear in mind the decrease in concentration necessary for recovery, the duration of the infusion (the context), and the context-sensitive effect-site decrement time required for the necessary decrease.

Context-sensitive decrement times provide a clinically useful framework for understanding the relationship between infusion duration and time course of recovery. The context-sensitive half-time is fundamentally different from the elimination half-life. With a monoexponential decay, each 50 percent decrease in concentration requires the same amount of time, and this time is independent of how the drug was given. This is not true for the context-sensitive

Figure 11-14 Context-sensitive effect-site decrement times for alfentanil, fentanyl, sufentanil, and remifentanil showing the time required for decreases of a given percentage (labeled for each curve) from the maintained effect-site concentration after termination of the infusion.

decrement times. First, as the name is intended to imply, the time for a 50 percent decrease is absolutely dependent on how the drug was given, with infusion duration being the context to which the name refers. Also, small changes in percent decrement can result in surprisingly large increases in the time required. As can be seen from Figure 11-14 , in some situations, the time required for a 60 percent decrease in drug concentration can be more than twice the time required for a 50 percent decrease.

Context-sensitive decrement times are based on the assumption that the plasma or effect site is maintained at a constant concentration. This is rarely the case clinically, but maintenance of constant concentrations is a necessary assumption to provide a unique mathematical solution to the time required for a given percent decrement in plasma or effect-site concentration. Because plasma and effect-site concentrations are rarely kept constant, it is important that the context-sensitive decrement times be used as general guidelines for interpreting the pharmacokinetics of intravenous drugs and not as absolute predictions for any given case or infusion regimen. Automated drug delivery systems can provide more precise predictions of the time required for the plasma or effect-site concentration to decrease to any desired concentration, based on the actual drug dosing in the individual patient. This provides the clinician with guidance for the most appropriate time to terminate the infusion.

The context-sensitive decrement times focus on the role of pharmacokinetics in recovery from anesthesia. Pharmacodynamics plays an important role in recovery as well. Bailey [76] used integrated pharmacokinetic/pharmacodynamic models to define the "mean effect time" as the average time to responsiveness after maintenance of anesthesia at the 90 percent probability of unresponsiveness. The mean effect time demonstrates that when drugs have a very shallow concentration-versus-response relationship, the concentrations must fall a great distance to provide adequate emergence. This delays recovery from anesthesia. In contrast, recovery is hastened by a steep concentration-versus-response relationship, in which emergence from anesthesia occurs after a small decrease in concentration.

Pharmacodynamic drug interactions play a role in the recovery from anesthesia. Interaction relationships predict that the same anesthetic state can be achieved by different ratios of two drugs. One way of selecting the best ratio might be the combination that offers the most rapid recovery. For example, when an opioid is combined with a hypnotic, recovery from anesthesia depends on the opioid and the hypnotic concentrations, the rate of decrease of both drugs, and the relative synergy between loss of response to noxious stimulation (i.e., the state maintained during anesthesia) versus the relative synergy for loss of consciousness. Although the time course of decrease in opioid and hypnotic concentrations can be approximately described by their respective context-sensitive decrement times for both drugs (Fig. 11-15) , the influence of relative synergy for different end points must be captured by separate models of the interaction of the drugs for adequate anesthesia and emergence from anesthesia.

Vuyk et al [77] modeled the predicted time to awakening when propofol is combined with fentanyl, sufentanil, alfentanil, or remifentanil on the basis of the interaction

between

Figure 11-15 The interaction between hypnotic and opioid for prevention of movement to a noxious stimulus and for awakening and adequate spontaneous ventilation at the end of a surgical procedure. From this it can be seen that the time to recover at the end of a procedure is dependent on the concentration of both drugs used during surgery and the time for both to decrease below that required for consciousness and adequate spontaneous ventilation (i.e., their context-sensitive decrement times).

propofol and these opioids to provide adequate anesthesia and the interaction between propofol and opioids on emergence from anesthesia, as seen in Figures 11-16 and 11-17 The recovery times vary according to the selection of opioid and the relative balance of opioid and propofol during maintenance of anesthesia. For example, in the upper right of Figure 11-16 is a simulation of emergence from a propofol/fentanyl anesthetic of 15 minutes' duration. The simulations assume a steady concentration of fentanyl and propofol throughout the anesthetic, similar to the underlying assumption of context-sensitive decrement times. The curve in the lower plane is the interaction curve between fentanyl and propofol, ranging from no fentanyl and 10 mug/mL of propofol on the left to 1.8 mug/mL of propofol and 5.33 ng/mL of fentanyl on the right. In theory, any point along this curve would provide equivalent maintenance of anesthesia. When the infusion is turned off after 15 minutes of anesthesia, the concentration of both drugs decreases. The decreasing concentrations of propofol and fentanyl when the infusion is turned off can be found by the upward lines drawn from different points on the interaction curve, with the distance away from the lower plane representing time. Taken together, these upward lines represent a "recovery surface." The line drawn on the recovery surface shows the points at which the fentanyl-propofol interaction model predicts emergence.

Figure 11-16 shows that after 15 minutes of maintaining 1.8 mug/mL of propofol and 5.33 ng/mL of fentanyl (right edge of interaction curve), it takes approximately 20 minutes for the concentrations of both drugs to decrease enough to permit emergence. However, if one maintains concentrations of 3.0 mug/mL of propofol and 1.5 ng/mL of fentanyl (toward the middle of the interaction curve), then emergence can be expected just 10 minutes after the infusions are turned off. Examination of the curves for 60, 300, and 600 minutes of fentanyl/propofol anesthesia suggests that the fentanyl target concentration that provides the most rapid emergence is approximately 1.0 to 1.5 ng/mL, which requires a propofol concentration of approximately 3.0 mug/mL to maintain adequate anesthesia. This is consistent with the earlier observation that most of the MAC reduction benefit of fentanyl occurs within the analgesic range, and exceeding this range is of little benefit during anesthesia. In similar simulations, Vuyk and colleagues demonstrated that maintaining alfentanil and sufentanil concentrations in excess of the analgesic range (i.e., approximately 80 ng/mL for alfentanil and 0.15 ng/mL for sufentanil) is of little clinical benefit but can be expected to delay recovery from anesthesia. A second conclusion from these simulations is that if the patient demonstrates inadequate anesthesia, to prevent prolongation of recovery, it is preferable to increase the hypnotic concentration than to increase the opioid concentration beyond the analgesic range.

The situation is different for remifentanil, owing to its unusual pharmacokinetic properties (Fig. 11-17) The extraordinary clearance of remifentanil results in a very rapid offset of opioid drug effect when a remifentanil infusion is terminated. In Figure 11-17 , the lower plane again shows equivalent anesthetic states during maintenance with an opioid, remifentanil, and propofol. High doses of remifentanil permit a modest reduction in the dose of propofol necessary for adequate anesthesia. However, the recovery surfaces show that high doses of remifentanil, with a modest reduction in propofol dose, permit considerably faster emergence from anesthesia. For example, it takes approximately 12 minutes to awaken from 600 minutes of anesthesia maintained with 3 mug/mL of propofol and 2.5 ng/mL of remifentanil (Fig. 11-17 , lower left graph). If the remifentanil concentration is increased to 5 ng/mL, the propofol concentration can be reduced to 2 to 2.5 ng/mL, and emergence can be anticipated within 6 minutes of discontinuation of the infusions. It is unclear whether such a technique places patients at increased risk for awareness because a propofol concentration of 2 mug/mL is below the C_{50} value for wakefulness. [32] [34] Thus, a technique utilizing high doses of opioids with low doses of hypnotics depends on the opioid/hypnotic interaction to maintain unconsciousness.

Figure 11-16 Simulation of the interaction of propofol and fentanyl in preventing a somatic response at skin incision and time to recovery. On the X axis is fentanyl concentration, and on the Y axis, the propofol concentration. The curve in the lower plane shows the propofolfentanyl interaction required to provide adequate anesthesia. When the infusion is turned off, the concentrations of each drug decrease, as shown on the Z axis. The curve drawn on the recovery surface shows the time to emergence from anesthesia for combinations of fentanyl and propofol after an anesthetic of 15 minutes' (A), 60 minutes' (B), 180 minutes' (C), or 600 minutes' (D) duration. Note that the optimal combination for the most rapid recovery is a propofol concentration of 3.0-3.5 mug/mL of propofol combined with 1.5 ng/mL of fentanyl. As the concentration of propofol or fentanyl increases, the time for recovery increases. Also, the longer the duration of drug infusion, the longer recovery takes, especially if the optimal combination is not used.

The offset of isoflurane and sevoflurane is similar to that of propofol. The offset of desflurane is slightly quicker than that of propofol. We can draw some logical extrapolations from these propofol/opioid simulations to anesthetics consisting of volatile anesthetics combined with opioids. When fentanyl, alfentanil, or sufentanil is combined with a volatile anesthetic, the most rapid recovery occurs when the opioid concentration is maintained at an analgesic concentration equivalent to 1 to 2 ng/mL of fentanyl (Table 11-5) Concurrently, the volatile anesthetic should be administered to the lowest concentration required to provide adequate anesthesia but no less than an end-tidal concentration of 0.3 MAC, the MAC value for return of consciousness. If the patient demonstrates signs of inadequate anesthesia, it is

TABLE 11-5 -- Infusion Rates for Opioids to Achieve Preset Concentrations

DRUG	PLASMA TARGET CONCENTRATION (ng/m L)	BOLUS (mu g/kg)	INFUSION RATE mu g/kg/min)
Fentanyl	1	3	.020
	4	10	.070
Alfentanil	40	20	0.25
	160	80 [a]	1.00
Sufentanil	0.15	0.15	0.003
	0.50	0.50	0.010
Remifentanil	6	1 [a]	0.02
	12-20	1-2 [a]	0.4-1.0

[a] Give as a rapid infusion over 1-2 min.

Figure 11-17 Simulation of the interaction of propofol and remifentanil in preventing a somatic response at skin incision and time to recovery. Note that with remifentanil, the optimal combination is a propofol concentration of 2.5 mug/mL, and remifentanil, 5-7 ng/mL, and that increasing the duration of the infusion has minimal impact on recovery time if the optimal dose of remifentanil is not used. However, if the propofol dose is increased, recovery is prolonged.

preferable to increase the volatile anesthetic because this has less of an effect on prolonging wake-up time than does increasing the opioid (with the exception of remifentanil) and is more likely to ensure that awareness does not occur.

/das/book/view/29494766/875/133.html

MANUAL INFUSION SCHEMES FOR INTRAVENOUS ANESTHETIC DRUG ADMINISTRATION

The following infusion schemes are developed from integrated pharmacokinetic-pharmacodynamic models. However, it is the patient's response, demonstrating adequate or inadequate anesthesia, that ultimately determines the rate of drug administration. Individuals vary markedly in their response to a given drug dose or concentration, and therefore it is essential to maintain an adequate drug level for each individual patient. Drug concentrations required to provide adequate anesthesia vary according to the type of surgery (e.g., surface surgery versus upper abdominal surgery). Thus, the infusion scheme should try to obtain higher or lower concentrations, depending on the planned surgery. The end of surgery requires lower drug levels, and therefore continuously titrating the infusion rate to a pharmacodynamic end point provides lower drug concentrations at the end of surgery and thus facilitates a rapid recovery. Common dosing schemes for administering intravenous anesthetics by infusion are given in Table 11-6 .

If the infusion rate proves to be insufficient to maintain adequate anesthesia, then both a further loading (bolus) dose and an increase in infusion are required to rapidly raise the plasma (biophase) drug concentration. Various interventions also require greater drug concentrations, usually for brief periods (e.g., laryngoscopy, endotracheal intubation, skin incision) (Fig. 11-3) Therefore, the infusion scheme should be tailored to provide peak concentrations during these brief periods of intense stimulation. An adequate drug level for endotracheal intubation is often achieved by the initial loading dose, but for procedures such as skin incision, a further bolus dose may be necessary. When the initial loading dose is based on the central compartment volume, a high initial infusion rate or several repeat doses are initially required to replace drug loss resulting from distribution.

TABLE 11-6 -- Manual Infusion Schemes[a]

DRUG	ANESTHESIA		SEDATION OR ANALGESIA	
	***LOADING DOSE* (mu *g/kg*)**	***MAINTENANCE INFUSION* (mu *g/kg/min*)**	***LOADING DOSE* (mu *g/kg*)**	***MAINTENANCE INFUSION* (mu *g/kg/min*)**
Alfentanil	50-150	0.5-3	10-25	0.25-1
Fentanyl	5-15	0.03-0.1	1-3	0.01-0.03
Sufentanil	1-5	0.01-0.05	0.1-0.5	0.005-0.01
Remifentanil	0.5-1.0	0.1-0.4	* [b]	0.025-0.1
Ketamine	1500-2500	25-75	500-1000	10-20
Propofol	1000-2000	50-150	250-1000	10-50
Midazolam	50-150	0.25-1.5	25-100	0.25-1
Methohexital	1500-2500	50-150	250-1000	10-50

[a] After the loading dose, an initially high infusion rate to account for redistribution should be used and then titrated to the lowest infusion rate that will maintain adequate anesthesia or sedation.
[b] For analgesia or during sedation, an initial loading dose is not required with remifentanil.

Opioids

Alfentanil

As shown by the work of Ausems et al, [22] the highest alfentanil concentrations (in combination with 70 percent nitrous oxide) are required for endotracheal intubation. The concentration of alfentanil required for skin closure is less than that required for skin incision or spontaneous ventilation. This allows the opioid to be gradually titrated downward toward the end of the procedure.

Several schemes have been advocated for the infusion of alfentanil when it is used as part of a nitrous-narcotic technique. [78] [79] [80] Most schemes vary in the sequence of the initial loading dose, although most provide 100 mug/kg within the first 10 minutes. Thus, the loading dose may be given as an initial rapid infusion of 50 mug/kg/min over 2 minutes or two 50-mug/kg doses given before endotracheal intubation and skin incision or as a slower infusion of 10 mug/kg/min over 10 minutes. The initial loading dose is followed by an infusion of 0.5 to 2 mug/kg/min. If the plasma concentration needs to be raised, an incremental bolus of 7 to 15 mug/kg with a 0.5- to 1-mug/kg/min increase in infusion rate is usually successful. For the aforementioned infusion scheme, alfentanil is usually combined with 66 percent nitrous oxide. If a hypnotic is used with alfentanil to induce anesthesia, the dose of the hypnotic can usually be markedly reduced. Alfentanil can be infused with nitrous oxide or combined with a hypnotic for a total intravenous technique. If combined with midazolam (loading dose, 0.05-0.2 mg/kg, and maintenance infusion, 0.05-0.15 mug/kg/min) or propofol (loading dose, 1-2 mg/kg, and maintenance infusion, 50-150 mug/kg/min), the loading dose and infusion rate of alfentanil can be reduced to 10 to 50 mug/kg followed by 0.5 to 1 mug/kg/min. If given with a potent inhalational anesthetic at 0.3 to 0.5 MAC, both the loading dose and the infusion rate can be reduced to approximately 30 to 50 percent of that used with nitrous oxide alone. When alfentanil is combined with a volatile anesthetic or forms part of a total intravenous anesthetic (TIVA) technique, alfentanil is dosed to achieve plasma concentrations of 75 to 150 ng/mL. When these doses are used, the infusion of alfentanil should be discontinued approximately 10 to 20 minutes before the expected end of surgery.

For cardiac anesthesia, in the absence of adjuvant anesthetic drugs, much larger infusion rates are required. An initial infusion of 40 mug/kg/min to loss of consciousness is followed by 10 mug/kg/min until cooling. On patient rewarming, the infusion rate can be restarted at 2.5 mug/kg/min. If inadequate anesthesia occurs, a bolus of 30 mug/kg usually ablates a response. Alfentanil has also been used for sedation in intensive care units. An initial loading dose of 25 mug/kg is followed by 0.25 to 0.5 mug/kg/min for 20 minutes and then titrated according to patient needs (0.1-2.0 mug/kg/min). A bolus of 3 mug/kg can be given when further supplementation is needed. In general, the doses of alfentanil, as listed earlier, should be reduced in elderly or debilitated patients.

Fentanyl

Infusion of fentanyl has classically been used for cardiac surgery. Again, various schemes have been advocated for the loading dose that vary from a bolus of 50 mug/kg to a rapid infusion of 4 to 5 mug/kg/min for 5 minutes or 2 to 3 mug/kg/min over 10 minutes. [79] [80] This is followed by continuous infusion of 0.1 to 1.0

mug/kg/min. These infusion schemes are designed to obtain a plasma fentanyl concentration of 20 to 40 ng/mL. Such a high dose of fentanyl has not demonstrated advantage over infusion schemes that provide fentanyl concentrations of 5 to 10 ng/mL and are combined with low-dose volatile anesthetic or propofol. This approach also facilitates fast tracking of cardiac patients. An initial loading dose of 10 to 20 mug/kg is followed by an infusion of 0.05 to 0.1 mug/kg/min. For noncardiac surgery in which a nitrous narcotic technique is used, the loading dose can be reduced to 5 to 15 mug/kg, followed by continuous infusion of 0.03 to 0.1 mug/kg/min to provide plasma concentrations of 3 to 10 ng/mL. [51] These concentrations combined with 66 percent nitrous oxide provide adequate anesthesia for intraabdominal and body surface surgery but may result in prolonged respiratory depression.

Analgesic concentrations of fentanyl are obtained at a plasma concentration of 1 to 2 ng/mL. [52] This concentration is optimal when combined with an intravenous hypnotic or potent inhalational agent or postoperatively for analgesia and is obtained after a loading dose of 1.5 to 3 mug/kg is administered,

followed by continuous infusion of 0.01 to 0.04 mug/kg/min.

Sufentanil

Sufentanil has been successfully used by infusion during cardiac anesthesia. [79] [80] For cardiac surgery, an initial loading dose of 15 mug/kg followed by an infusion of 0.75 mug/kg/min has been used. When combined with midazolam (midazolam loading dose, 100 mug/kg, and maintenance infusion, 1.0 to 2.5 mug/kg/min), the sufentanil dose is reduced to 2 mug/kg/min for 5 minutes, followed by 0.010 to 0.025 mug/kg/min thereafter. Even smaller doses of midazolam and sufentanil may be adequate for cardiac surgery. Very little has been published on the plasma concentrations or infusion rates of sufentanil required for noncardiac surgery. Several studies have established that in the concentration domain, sufentanil is approximately ten times more potent than fentanyl. Thus, for noncardiac surgery, infusion rates are based on achieving concentrations approximately one-tenth those of fentanyl. When combined with 70 percent nitrous oxide, a loading dose of 1 to 2 mug/kg of sufentanil followed by an infusion of 0.01 to 0.04 mug/kg/min can be used. As the analgesic component of a total intravenous technique or combined with a volatile anesthetic, an initial loading dose of 0.2 to 0.5 mug/kg followed by an infusion of 0.005 to 0.01 mug/kg/min of sufentanil is generally appropriate to achieve sufentanil concentrations within the analgesic range of 0.1 to 0.3 ng/mL.

Remifentanil

Remifentanil is the newest mu-agonist available for administration as an analgesic during surgery. Because of its metabolism by general body esterases, the drug is best administered as an infusion. Also, as a result of this unique metabolism, the decrease in concentration and dissipation of opioid effect are very rapid after termination of its administration. This enables the clinician to administer remifentanil at relatively higher analgesic concentrations than is possible with other opioids without the likelihood of prolonged respiratory depression. An initial loading infusion of 0.5 to 1 mug/kg/min is usually administered. Because the offset of the drug is so rapid, to ablate the response to endotracheal intubation, the infusion must be maintained at 0.2 to 0.5 mug/kg/min. When it is used in combination with a volatile anesthetic or propofol for noncardiac surgery, the infusion rate can then be reduced to 0.1 to 0.2 mug/kg/min. When it is used as a nitrous-narcotic technique, an infusion rate of 0.3 to 0.6 mug/kg/min is necessary. The infusion should be terminated only 5 to 10 minutes before the end of surgery. If postoperative pain is likely to be present, it is important that the clinician initiate other forms of pain management either before or on termination of the remifentanil infusion. For cardiac surgery, infusion rates of 1 mug/kg/min have been used successfully with marked ablation of the stress response. Infusion rates of 0.5 mug/kg/min combined with low-dose propofol or volatile anesthetic are also likely to be useful for cardiac surgery. Remifentanil, like all the other opioids, requires lower infusion rates to produce the same effect in elderly subjects. [43] [81] In general, by the age of 50 years, the remifentanil infusion rate should be reduced by half of that given to a 21-year-old patient. An 80-year-old patient requires a remifentanil infusion rate that is just ^{1} 1/3 of that required in a 21-year-old patient.

Hypnotics

Thiopental

Thiopental is rarely used by infusion for the maintenance of surgical anesthesia because the context-sensitive half-time is prolonged when an infusion of more than just a brief duration is used. Thiopental has been successfully used by infusion for short body surface procedures in combination with fentanyl. [82] An initial loading dose of 2 to 4 mg/kg is followed by an infusion of 200 to 300 mug/kg/min for the first 20 minutes and 30 to 70 mug/kg/min thereafter. For sedation, an initial loading dose of 2 to 4 mg/kg is followed by an infusion of 30 to 80 mug/kg/min. When thiopental is used by infusion, its metabolism results in the formation of pentobarbital. It is uncertain whether this is of clinical significance.

Methohexital

Methohexital (unlike thiopental) can be used effectively by infusion for the maintenance of anesthesia for surgical procedures of up to 2 hours' duration. A loading (induction) dose of 1 to 2 mg/kg is followed by an infusion of 50 to 150 mug/kg/min. Methohexital (at these infusion rates) is combined with 66 percent nitrous oxide and/or an opioid. For total intravenous anesthesia, alfentanil (10 mug/kg followed by 1 mug/kg/min) can be utilized with methohexital, 1.5 mg/kg, followed by a variable rate of infusion of 50 to 150 mug/kg/min. After premedication with morphine (0.15 mg/kg) or diazepam (10 mg orally), the MIR_{95} of methohexital (combined with 66 percent nitrous oxide and after a loading dose of 1.5 mg/kg) is 80 mug/kg/min. [83] Methohexital may also be used by infusion for sedation. A loading dose of 0.5 to 1 mg/kg given over 5 to 10 minutes followed by an infusion of 15 to 25 mug/kg/min usually provides an adequate level of sedation.

Etomidate

The use of etomidate by infusion is controversial (Ch. 9). Most infusions with etomidate for general anesthesia are designed to provide a plasma concentration of etomidate of 500 ng/mL. [84] This may be achieved with either a two-stage or a three-stage infusion scheme. In the two-stage scheme, etomidate is infused at 100 mug/kg/min for 10 minutes and then at 10 mug/kg/min. In the three-stage regimen, etomidate is infused at 100 mug/kg/min for 3 minutes, 20 mug/kg/min for 27 minutes, and 10 mug/kg/min thereafter. Etomidate is combined with nitrous oxide and usually an opioid given either intermittently or by continuous infusion. Etomidate plus fentanyl (loading dose 2-3 mug/kg, and maintenance infusion, 0.03-0.06 mug/kg/min) or alfentanil (loading dose, 10-20 mug/kg and maintenance infusion, 0.5-1 mug/kg/min) can be

combined to provide a total intravenous anesthesia. The etomidate infusion can usually be terminated 10 to 15 minutes before the anticipated end of the surgical procedure. Etomidate has been used by infusion for cardiac surgery. An initial loading dose (used for induction) is followed by an infusion of etomidate at 20 mug/kg/min. This results in a plasma level of 550 to 900 ng/mL. The use of etomidate for prolonged sedation is contraindicated, but it can be used for brief periods of sedation (i.e., for regional anesthesia). For sedation, a loading dose of 15 to 20 mug/kg/min for 10 minutes is followed by a maintenance infusion of 2.5 to 7.5 mug/kg/min.

Ketamine

Ketamine, although it possesses both hypnotic and analgesic properties as well as suitable pharmacokinetics, is not a popular agent for the maintenance of general anesthesia because of the psychotomimetic action of the currently available racemic mixture. When combined with a benzodiazepine, ketamine can provide suitable anesthesia (with or without nitrous oxide). The loading (induction) dose is 1 to 2 mg/kg followed by an infusion of 10 to 50 mug/kg/min. [85] In the absence of nitrous oxide and for more invasive surgery, higher infusion rates of 30 to 100 mug/kg/min may be necessary. Ketamine has also been used by infusion during cardiac surgery with similar infusion rates. An infusion of ketamine is also useful for analgesia and/or sedation. The loading dose can be reduced to 0.2 to 0.75 mg/kg and the infusion to 5 to 20 mug/kg/min. Ketamine has been successfully used with propofol for a TIVA technique. The ketamine infusion consists of a loading dose of 1 to 3 mg/kg followed by an infusion of 5 to 20 mug/kg/min. The propofol infusion is the same regimen used when propofol is combined with nitrous oxide.

Propofol

Propofol is best administered by continuous infusion. Plasma concentrations necessary during surgery and for awakening have been established (Table 11-6) .[32] [33] [34] [86] [87] To obtain a plasma level of 3 to 4 mug/mL, a four-stage infusion scheme can be utilized. This consists of a loading dose of 1 mg/kg over 20 seconds, followed by 170 mug/kg/min (10 mg/kg/h) for 10 minutes, then 130 mug/kg/min (8 mg/kg/h) for 10 minutes, and 100 mug/kg/min (6 mg/kg/h) thereafter. More simply, a loading dose of 1 to 2 mg/kg can be followed by an initial infusion of 150 to 200 mug/kg/min, which is then titrated to about 100 mug/kg/min. For short surgical procedures, generally higher average infusion rates are required, but for longer procedures, the average infusion rate is 100 to 150 mug/kg/min when combined with nitrous oxide.

When propofol is given with an opioid (rather than nitrous oxide) as part of a total intravenous anesthetic, the infusion rate of propofol remains similar to that required with nitrous oxide (i.e., an initial induction dose followed by a decreasing infusion rate of 150 to 100 mug/kg/min). Propofol has been combined with alfentanil (loading dose, 10-25 mug/kg, and maintenance infusion, 0.5-1 mug/kg/min), fentanyl (loading dose, 2-5 mug/kg, and maintenance infusion, 0.025-0.075 mug/kg/min), sufentanil (loading dose, 0.2-0.5 mug/kg, and maintenance infusion, 0.005-0.03 mug/kg/min), or remifentanil (loading dose, 1 mug/kg, and maintenance infusion, 0.1-0.4 mug/kg/min) for total intravenous anesthesia. The required infusion rate of propofol during anesthesia demonstrates a negative correlation with age, that is, elderly patients need lower infusion rates.

For sedation during regional or topical anesthesia, an initial loading infusion of 0.5 mg/kg is given over 5 minutes, followed by a maintenance infusion of 25 to 75 mug/kg/min. Propofol has been used for up to 2 weeks for continuous sedation of patients in intensive care units. [88] In critically ill patients, a loading dose may not be desirable, and therefore, an infusion can be started at 25 to 50 mug/kg/min. This rate is subsequently titrated to the desired level of sedation.

The bispectral monitor has recently been shown to correlate well with sedation and loss of consciousness [89] [90] [91] and thus has been introduced as a monitor for the hypnotic component of the anesthetic. Several studies have demonstrated that it may potentially facilitate the titration of the hypnotic component of the anesthetic, resulting in a decrease in the amount of hypnotic administered versus standard practice and shortening recovery time. [92]

Midazolam

Midazolam can be administered by infusion for sedation or for provision of the hypnotic component of a balanced anesthetic. [93] The effects of an opioid plus a benzodiazepine appear to be synergistic rather than additive for both loss of consciousness and anesthesia. [64] [94] The loading (induction) dose of midazolam can therefore be reduced to 0.05 to 0.1 mg/kg when combined with fentanyl (2-5 mug/kg) or alfentanil (10-25 mug/kg). The midazolam maintenance infusion rate during surgical anesthesia can then be titrated between 0.25 and 1 mug/kg/min with either fentanyl (maintenance infusion, 0.03-0.06 mug/kg/min) or alfentanil (maintenance infusion, 0.5-1.5 mug/kg/min). Nitrous oxide, if added to the aforementioned combinations, further decreases the required infusion rates of both midazolam and the opioid. For cardiac surgery, similar doses of midazolam can be combined with slightly larger doses of the chosen opioid. [95] For sedation, a loading dose of 0.02 to 0.1 mg/kg of midazolam is administered. This is best given as 10-mug/kg doses until the desired level of sedation is achieved. The maintenance infusion is then titrated between 0.25 and 1 mug/kg/min. At the termination of a prolonged (days') infusion, there is a possibility of a benzodiazepine withdrawal syndrome. Therefore, the infusion might need to be slowly tapered, or a long-acting benzodiazepine may need to be given.

INFUSION DEVICES

Manual Delivery

When an infusion of an intravenous anesthetic is administered, the infusion regimen can be controlled by a variety of mechanisms. These vary from the simple CAIR clamp or Dial-a-Flo (Abbott Laboratories) to complex computer-controlled infusion pumps. Simplicity of mechanical design, however, is not necessarily correlated with ease of use. This has prompted ongoing advances in infusion device technology.

Infusion devices can be classified as either controllers or positive displacement pumps. Explicit in their title, controllers contain mechanisms that control the rate of flow produced by gravity, whereas positive displacement pumps contain active pumping mechanisms.

The most commonly used pumps for the administration of intravenous anesthetics are positive displacement syringe pumps that utilize a screw mechanism. These pumps can be made extremely accurate and have the convenience of not requiring specialized tubing. Many of these pumps have included several new features that make infusion pumps more suitable for anesthetic delivery. An important advance has been the introduction of a calculator feature within the pump so that the clinician sets the weight of the patient, the drug concentration, and the infusion rate in dose/unit weight/unit time, and the pump then calculates the infusion in volume/unit time. These pumps also allow simple application of a stage infusion scheme (cf. Wagner [71]) by allowing a loading dose and a maintenance infusion rate to be programmed into the pump. Numerous syringe pumps also now include automated recognition of syringe size. Major advances have been made in pump technology and design, enabling intravenous anesthetics to be conveniently delivered. However, no commercially available device for the delivery of intravenous anesthetics approaches the convenience of the present-day vaporizer. It is therefore desirable to take intravenous drug delivery systems one step further beyond a "calculator" pump to a truly "smart" pump by utilizing truly automated drug delivery.

Automated Delivery

Automated drug delivery implies that some form of electronic and/or mechanical instrumentation performs dose rate adjustments independent of human intervention (in contrast to the manual devices described earlier). The desired target (e.g., drug concentration and clinical response) is still chosen by the clinician. Preprogrammed dosing (either bolus or infusion) is the simplest form of automated drug delivery. This consists of a preprogrammed infusion (usually calculated to provide a single target blood or effect concentration) that is automatically implemented by the microprocessor in the pump. Preprogrammed devices are limited in their application for intravenous anesthetic drugs because of their inability to allow the user to vary the target concentration. Generally, two methods may be applied for automated target anesthetic drug delivery: model-based (a form of open-loop control) and closed-loop systems.

Terms and Definitions

Both model-based and closed-loop systems require a set-point (Fig. 11-18) . [96] The set-point may best be defined as the quantifiable end point (e.g., plasma concentration or % T1 of the electromyogram) related to the clinical objective (level of anesthesia, neuromuscular blockade, and so on). Accordingly, the set-point is the value (i.e., target) that the automated system is attempting to maintain. The feedback signal is the measured (e.g., % T1 of the electromyogram) or predicted (e.g., predicted plasma concentration from pharmacokinetic

Figure 11-18 The components of a typical automated drug delivery system.

simulation) value that has resulted from the automated delivery process.

Although closed loop is the ideal means of automated drug delivery, as previously observed, there is no quantifiable signal that incorporates both the hypnotic and the analgesic requirements to provide an adequate anesthetic. Model-based drug delivery, therefore, provides an important alternative in circumstances in which the feedback signal cannot be measured and an appropriate model is available. A mathematical equation that can simulate the process that produces the set-point provides the model. Consequently, the accuracy of any model-based control system is dependent on how well the model represents the process under control. The control signal (which for automated drug delivery is the dosing scheme) is generated by a set of instructions known as an algorithm. An algorithm is ordinarily designed to keep the control variable as close as possible to the set-point value. The set-point and feedback values, in turn, act on the algorithm to generate the control signal. The control signal directs the actuator (i.e., the infusion pump), producing the intervention necessary to obtain the set-point (i.e., delivers the dosage regimen prescribed by the algorithm to the patient). This intervention results in a new feedback control signal, and the process repeats itself to maintain the patient at the target. In an adaptive control system, the algorithm is altered/adapted to the individual's unique response to the intervention produced by the actuator. For example, in a closed-loop system to control blood pressure, the algorithm may prescribe an increase in the infusion of sodium nitroprusside of 1 mug/kg/min when the blood pressure exceeds 5 mm Hg above the target. Although this may generally be an appropriate prescription, a change of this magnitude may cause a much greater drop in blood pressure than desired in a sensitive individual. After experience with the patient, an adaptive controller learns the individual's sensitivity and, utilizing this, changes the algorithm so that the control signal (dosing scheme) results in an intervention by the actuator that brings the feedback signal more closely to the target.

Target Control Infusion Systems

Devices

In 1968, Kruger-Thiemer [97] described the infusion regimen theoretically required to quickly achieve and maintain a constant plasma concentration of an intravenously administered

---

drug whose kinetics are described by a twocompartment model. This regimen has become known as the "BET scheme" and consists of an initial *B*olus of $C_T V_1$, an infusion at a rate of $C_T Cl_S$ to replace drug *E*liminated from the body, and an exponential decreasing infusion at a rate given by Equations 13 to 15 to replace drug

*T*ransferred to the peripheral tissues. The section on designing dosage regimens demonstrates that the bolus portion, calculated as $C_T V_1$, will likely be inadequate for reaching the desired effect-site concentration. Mathematically, the "ET" portion of the BET scheme is identical to the exponentially declining maintenance infusion rate shown in the section on designing dosing regimens. Precise implementation of this complex dosage regimen requires infusion rates that change continuously as a function of time until steady state is achieved.

More than a decade after publication of Kruger-Thiemer's classic paper, Schwilden and colleagues, [2] [98] [99] in Bonn, interfaced a microcomputer to an infusion pump and demonstrated clinical application of the BET infusion scheme. Many other groups have since implemented either the BET algorithm or modifications of this algorithm on microcomputers connected to infusion pumps. These algorithms are based on the same polyexponential equations or compartment models described previously and calculate the infusion rates theoretically required to obtain the desired plasma drug concentration (Fig. 11-4) . In implementing these algorithms, it is necessary to consider the physical limitations of the system. Drug cannot be removed from the system by the pump, and infusion rates must be positive or zero. Additionally, some pumps have limitations on precision and accuracy that can reduce the accuracy of the infusion.

Although there are minor differences in the approaches taken by different investigators using pharmacokinetic model-driven infusion systems, all are conceptually similar. Each consists of a microcomputer interfaced to an infusion pump (Fig. 11-19) The microcomputer executes a program that incorporates the pharmacokinetic model. In using the device, the anesthesiologist enters a target plasma or effect-site drug concentration (Fig. 11-20) This target concentration

Figure 11-19 The present CACI system used at Duke University Medical Center. It consists of a laptop computer electronically linked to an infusion pump. The desired drug plasma or effect-site concentration is entered via the keyboard.

is based on knowledge of the pharmacokinetic-dynamic relationship of the drug and the desired effect, as well as on the individual responses of the patient. At frequent intervals (e.g., every 9-15 seconds), the program compares the target concentration with the current prediction of the plasma or effect-site drug concentration, which is computed by real-time simulation of a pharmacokinetic model of the drug being infused. The computer calculates the infusion rate required to achieve the desired target concentration and transmits this rate to the pump, after adjusting the rate to reflect the physical capabilities of the pump. The pump then delivers drug to the patient at the desired rate.

At each step, the computer makes sure that the pump has delivered the drug it was instructed to give and checks for errors reported by the infusion pump (e.g., air in line, out of drug). The computer then calculates what the pump did during the previous interval and updates the internal pharmacokinetic model on the basis of the reported drug delivered. The cycle is completed when the computer calculates the infusion rate required over the next interval to reach the desired target concentration and transmits this rate to the infusion pump. Concurrently, the computer supplies the anesthesiologist with information about the state of the model, the state of the pump, any problems reported by the pump, the anticipated time course for elimination of drug from the patient, the total amount of drug delivered, the current infusion rate, and other information that may be of assistance in providing clinical care.

As a result of the increasing popularity of intravenous anesthesia and continuous-infusion techniques, the inherent reasonableness of pharmacokinetically based drug delivery, and the promising results achieved with automated administration of a variety of drugs by research groups around the world, pharmacokinetic model-driven infusion has now become a commercial device for the administration of propofol. This system consists of a commercial pump and the "Diprifusor" software that provides the control algorithm. This device is available in Europe and is awaiting approval in several countries, including the United States. It is expected that further devices consisting of standard infusion pumps, most of which already contain powerful microprocessors, will be equipped with the capability to perform pharmacokinetic model-driven infusions as a software-selectable option. Pharmacokinetic parameters for various drugs will be programmed into the device. Additionally, such devices will be able to target the concentration at the site of drug effect, rather than the plasma drug concentration, resulting in a system that is better adapted to the need for rapid titration in anesthesia. The user will use the pump's keypad or soft keys to select the drug to be infused and to enter pharmacokinetically relevant information about the patient, such as weight, age, and sex, and will ensure that the infusion setup is primed with drug at a specified concentration. Then, the keypad will be used to enter target concentrations in the same manner that the dial on a calibrated vaporizer is utilized in titrating the administration of an inhalation anesthetic. Alternatively, the pharmacokinetic model may be built into a future generation of anesthesia workstations. These workstations could then control many different brands of infusion pumps and could provide a common platform for implementing precise titration of intravenous anesthetics in the concentration domain.

Figure 11-20 Schematic illustration of pharmacokinetic model-driven drug delivery. The physician enters the target plasma or biophase drug concentration (Cp_d). An infusion device control algorithm uses a pharmacokinetic model for the drug being infused to determine what the infusion rate should be for the next infusion interval (e.g., 9-15 s). The infusion device delivers drug to the patient, and the infusion rate is fed into a simulation of the pharmacokinetic model to compute the current predicted plasma drug concentration (Cp_p). The variables computed in the simulation are available to the infusion algorithm, which then calculates the infusion rate necessary for the next 9-15 s to achieve the target concentration. On the basis of monitored and anticipated patient response, knowledge of approximate therapeutic plasma drug concentrations (e.g., Cp_{50}) and on Cp_p, the physician can titrate Cp_d as necessary.

Evaluation of Target-Controlled Drug Delivery

Acceptance of target-controlled drug delivery of intravenous anesthetics requires evaluation of both accuracy, defined as the difference between the predicted and the measured concentrations, and outcome of patients in whom automated drug delivery has been used. The sources of inaccuracy with pharmacokinetic model-driven devices include the software, the hardware, and the pharmacokinetic variability (Fig. 11-21) .

Inaccuracy in the software results from incorrect mathematical implementation of the pharmacokinetic model. Computer simulations can be used to test the infusion rates calculated by a software program, and thus software errors are fairly simple to identify and correct. [100] Inaccurate drug delivery from the infusion pump is small with present syringe-pump technology and thus contributes little to the overall inaccuracy of these devices. The major cause of inaccuracy is pharmacokinetic variability. There are two sources of this variability: (1) the pharmacokinetic model is always wrong and (2) the patient's pharmacokinetics are never those programmed into the model. The first source of variability reflects the fact that individuals are far more complex than implied by simple compartmental models, and thus no such model can precisely predict the concentrations, even if the pharmacokinetic parameters in the individual were known absolutely precisely. The second source of variability reflects that the parameters incorporated in TCI systems are average estimates in the population, and these estimates necessarily differ from the estimates that would best describe the model in any individual. Thus, the pharmacokinetic variability fundamentally precludes the possibility of precisely achieving the desired target concentration when automated drug delivery devices are used.

Optimization of Target-Controlled Drug Delivery

The performance of computer-controlled drug administration must be interpreted in terms of the therapeutic expectations of the clinician. Possible goals include accurately producing a desired concentration in the plasma, precisely titrating the plasma drug concentration, producing the desired drug effect, and producing the desired time course of

Figure 11-21 Major sources of potential error in pharmacokinetic model-driven drug delivery. In a commercial device, the computer functions would be incorporated into the infusion device itself.

drug effect. Over the past decade, investigators have addressed each of these goals and have refined the performance of automated drug delivery devices in light of these goals.

The ability of an automated drug delivery system to rapidly achieve and then maintain a selected target concentration is a logical measure of the performance of such a device. There are several ways of expressing the difference between the measured and the target concentrations. The most simple means is either to diagram a plot of the target and measured concentration of each sample in each individual patient (Fig. 11-22) or to diagram an XY plot of the measured to target concentration and observe how much the plots vary from the line of identity (Fig. 11-23) [66] The primary concern is how far the measured concentration is from the predicted one, and this is now most frequently described in terms of the performance error, which is the difference between the measured and the target concentrations as a percent of the desired target (i.e., [measured-target]/target * 100%). [101] The median value of the performance error for a patient or a population is referred to as the median performance error (MDPE) and represents the average overshoot or undershoot of the system. The median absolute performance error (MDAPE) is the median of the absolute value of all performance errors. The MDAPE is commonly used as a measure of the inaccuracy of an automated drug delivery device. An MDAPE of zero is perfect performance, and an MDAPE of 20 percent means that half the plasma concentrations will be within 20 percent of the target and half will be outside that range. A further assessment of accuracy is whether the system maintains a stable target concentration. This is best measured by the wobble of the system. Varvel et al [101] asked a group of clinicians to evaluate the performance of automated drug delivery devices and demonstrated that the MDAPE best predicted the adequacy of the performance of the automated delivery device, as judged by experienced clinicians.

As observed earlier, it is not reasonable to expect all performance errors to be zero percent. However, it would be desirable if positive and negative errors offset each other, so that the MDPE of an automated drug delivery device were zero percent. The MDPE does not indicate the range of performance errors (because positive and negative performance errors offset each other), but it does indicate whether the plasma concentrations achieved with the device tend to overshoot the desired target (+MDPE) or undershoot the desired target (-MDPE).

Table 11-7 summarizes the accuracy of pharmacokinetic model-driven devices administering several of the intravenous drugs in anesthetic. [29] [66] [102] [103] [104] [105] [106] [107] [108] [109] [110] It is clear from Table 11-7 that the expected performance of such devices, at best, tends to be around 20 to 30 percent MDAPE. The pharmacokinetics of propofol have probably been the most frequently tested. Coetzee et al [109] tested the accuracy of three parameter sets and found those of Marsh et al [110] and Tackley et al [111] to provide the best accuracy in adult patients (Fig. 11-24) . To demonstrate the actual impact of the three different pharmacokinetic parameters on propofol dosing, the infusion rates required to produce a set of target concentrations are plotted in Figure 11-25 . The pharmacokinetic parameter set of Marsh are those included in the Diprifusor software. Better accuracy has been obtained in

Figure 11-22 Individual plots of the target plasma fentanyl concentration (solid line) and measured concentration (dots) in four separate patients.

Figure 11-23 Plot of the measured to the predicted concentration of fentanyl administered via CACI in 24 patients. The solid line represents the line of identity, i.e., the target concentration is equal to the measured. The dashed lines represent a bias of ±30%.

children [110] because they may have less pharmacokinetic variability as a result of their general lack of chronic disease and more narrow distribution of weight at any given age (than found in adults).

Interest has focused on the impact of a second drug on the pharmacokinetics of the first. Several studies have shown that opioids may alter the pharmacokinetic parameters of propofol. [112] [113] [114] The exact mechanism for this is unclear but may be the result of alterations in cardiac output, reductions of hepatic blood flow, or first-pass pulmonary uptake of drug. It is unlikely to be related to any interaction with cytochrome P-450 systems because the pharmacokinetics of propofol are limited by liver blood flow and thus are unlikely to be affected by modest alterations in hepatic metabolic capacity. Although these drug interactions have not had a major impact on the utility of TCI devices, to enhance their accuracy, different pharmacokinetic sets should be determined for each of the commonly used drugs that result in a significant pharmacokinetic drug interaction.

The best performance with an automated drug delivery device is that reported by Crankshaw et al [103] [115] (Table 11-7) . The Crankshaw device is not based on a pharmacokinetic model but rather targets a single concentration by use of a series of preprogrammed infusion rates (i.e., this is a preprogrammed automated infusion device as described earlier). In a series of iterations with successive populations

TABLE 11-7 -- Accuracy of Target-Controlled Infusion Devices for Intravenous Anesthetics Using Different Pharmacokinetic Parameter Sets

DRUG	AUTHOR OF PHARMACOKINETIC PARAMETER SET	AUTHOR OF STUDY	COMMENTS	MDAPE[a] (%)	MDPE[a] (%)
Alfentanil	Schuttler and Stoeckel [134]	Ausems et al [29]			22-32
	Schuttler and Stoeckel [134]	Schuttler et al [104]		28	0
	Maitre et al [117]	Raemer et al [102]		53	+53
	Scott et al [27]	Raemer et al [102]		17	+1
	Estimated	Crankshaw et al [115] [b]		10	+3
	Helmers et al [135]	Lemmens et al [105]		24	+12
Fentanyl	McClain and Hug [116]	Alvis et al [108]	Single target	20	0
	McClain and Hug [116]		Multiple targets	26	+11
	McClain and Hug [116]	Glass et al [124]		21	+4
	McClain and Hug [116]	Shafer et al [107]		61	+61
	Scott et al [27]	Shafer et al [107]		33	+19
	Estimated			21 [c]	-13 [b]
	McClain and Hug [116]	Veselis et al [106]		40	40
Sufentanil	Greeley et al [136]	Kern et al [137]	Pre-CPB		49
	Greeley et al [136]	Kern et al [137]	Post-CPB		32
Thiopental	Ghoneim and Van Hamme [138]	Veselis et al [106]	Volunteers	50	-50
Midazolam	Smith et al [139]	Kern et al [137]	Pre-CPB		44

	Smith et al [139]	Kern et al [137]	Post-CPB		32
	Greenblatt et al [140]	Veselis et al [106]	Volunteers		
				100	100
Propofol	Schuttler et al [104]	Schuttler et al [104]			
				22	-12
	Dyck et al [141]	Coetzee et al [105]		20	42
	Tackley et al [111]	Coetzee et al [105]		20	-1
	Marsh et al [110]	Coetzee et al [105]		23	-6
	Marsh et al [110]	Marsh et al [110]	Pediatric patients	25	-18.5
	Estimated	Marsh et al [110]	Pediatric patients	16 [d]	+3 [d]
	Gepts et al [142]	Veselis et al [106]	Volunteers		0
				25	
	Gepts et al [142]	Glass et al [143]		29	+5

MDPE, median performance error; MDAPE, median absolute performance error.

[a] MDAPE and MDPE were not calculated or only provide as a figure, and so the reported numbers are approximately inferred from the measure of performance reported by the authors.
[b] Not model-based (see text for details).
[c] Retrospectively applied to same data set.
[d] Prospectively tested.

Figure 11-24 The evaluation of 3 pharmacokinetic parameter sets for propofol. Plotted is the measured/predicted ratio for samples obtained during administration of propofol using a target-controlled infusion device programmed with the pharmacokinetics derived by Dyck, Marsh, or Tackley (*n* = 10 per group). A ratio of 1 means measured = predicted. Note that the pharmacokinetic parameters of Dyck provide a consistently positive bias.

of patients, the preprogrammed rates are adjusted by the ratio between the desired and the observed concentrations. Crankshaw et al demonstrated that after several honing iterations, the MDAPE can be decreased to 10 to 15 percent, which is superb performance. However, the device cannot achieve arbitrary targets at arbitrary times, as can the model-dependent devices, and so the very accurate performance comes at the cost of flexibility.

There are a variety of published parameter sets for most of the drugs used in anesthesia. If the pharmacokinetic parameters are highly biased, then one might expect large errors to occur in performance. Several studies in Table 11-7 show the importance of selecting the proper pharmacokinetic parameters (or at least the cost of selecting the wrong set). Shafer et al [107] examined the performance of a pharmacokinetic model-driven infusion device using the fentanyl pharmacokinetics described by McClain and Hug [116] and demonstrated

Figure 11-25 Infusion rates (mL/h) calculated to achieve propofol target concentrations of 4 (10 min), 3 (10 min), 4 (20 min), and 2 mug/mL (20 min) based on the 3 pharmacokinetic parameter sets of Dyck, Marsh, and Tackley.

an MDAPE of 61 percent and an MDPE of +61 percent. The large positive MDPE indicates that nearly all fentanyl concentrations greatly exceeded the target. The performance errors over time with the use of the McClain and Hug pharmacokinetics are shown in Figure 11-26 . Shafer et al also examined the performance of a pharmacokinetic model-driven infusion device by use of the fentanyl pharmacokinetic parameters described by Scott et al. [27] This second parameter set produced an MDAPE of 33 percent and an MDPE of +19 percent, as shown in the performance errors over time in Figure 11-26B . Although the measured concentrations tended to be higher than the target concentrations with the Scott and Stanski fentanyl parameter set, the performance was much better than obtained with the parameter set reported by McClain and Hug. This study demonstrated that selection of the proper parameter set influenced the performance of pharmacokinetic model- driven infusion. Raemer and colleagues [102] demonstrated the same for alfentanil, when they compared the performance of the alfentanil pharmacokinetic parameters reported by Maitre et al [117] with the alfentanil pharmacokinetic parameters reported by Scott et al. [27]

Glass et al [66] examined the performance of a pharmacokinetic model-driven infusion device by use of the same fentanyl pharmacokinetics described by McClain and Hug. [116] They demonstrated an MDAPE of 21 percent and an MDPE of +4 percent (i.e., an almost completely unbiased performance). It is important to realize that there were major differences in methodology between the study by Glass et al and that by Shafer et al, such as arterial versus venous samples, rapid sampling after changes in target concentration versus sampling only when a pseudo-steady state was achieved, and a different set of patients--cardiac versus noncardiac. It is these differences in methodology that result in differences in performance of pharmacokinetic model-driven infusion device using the same pharmacokinetic parameters being reported by different investigators.

With the goal of improving pharmacokinetic model- driven infusion device performance, Shafer et al recalculated

Figure 11-26 Performance errors over time for fentanyl by use of the pharmacokinetics reported by McClain and Hug (A) and Scott and Stanski (B) and a parameter set derived from these observations (C).

the optimal pharmacokinetic parameters of fentanyl directly from the observed concentrations that were obtained when fentanyl was administered via a pharmacokinetic model-driven infusion device by use of the initial pharmacokinetics of McLean and Hug. [116] Figure 11-26C shows the performance errors over time for the optimal fentanyl pharmacokinetics estimated for that population of patients (as compared with those of McLean and Hug [116] and Scott et al [27] in the same group of patients). The optimal pharmacokinetic parameter set still had a median residual error of 21 percent when retrospectively tested against the same group of patients. This represents the limit imposed by pharmacokinetic variability on the possible performance of any fentanyl parameter set for dosing to a similar adult population. In other words, it is unlikely that any fentanyl pharmacokinetic parameter set would produce less than 21 percent MDAPE.

Marsh et al [110] took the same approach to optimizing the performance of a pharmacokinetic model-driven infusion device administering propofol in children. They initially used a pharmacokinetic parameter set derived from adult subjects in their device and obtained an MDAPE of 25 percent and an MDPE of -18.5 percent. They subsequently derived new propofol pharmacokinetics for children and prospectively demonstrated that they had decreased the MDAPE to 16 percent, with a bias of less than 3 percent. This is highly accurate performance for a model-based device. Ginsberg et al [118] similarly derived a pharmacokinetic set for fentanyl in children, as did Fiset et al [119] for alfentanil.

Several other studies have also demonstrated that pharmacokinetic parameters vary with certain subsets of patients. For example, the pharmacokinetic parameters of propofol for patients presenting for open heart surgery are different from the previously verified pharmacokinetic parameters of the general population. These new pharmacokinetic parameters for fentanyl also vary both during bypass and after bypass. [120] The pharmacokinetics of intravenous

anesthetics may also be altered by age and possibly by gender. Not only is there interindividual variability, but there may also be significant intraindividual variability. Hill and colleagues [121] studied volunteers to learn the individual's own pharmacokinetics for morphine and alfentanil. These investigators then used that volunteer's unique pharmacokinetic values to subsequently control a pharmacokinetic model-driven infusion device. With this technique of personalized pharmacokinetics, they reduced the average error to just less than 20 percent. It appears that studies determining the pharmacokinetics of an individual to be used to infuse the same drug to the same individual later result in a bias and MAPE similar to those seen when an optimal pharmacokinetic set derived from the general population is used. The implication of these data is that although highly specific pharmacokinetic sets are desirable, they may not necessarily improve overall accuracy, and such systems can never be relied on to provide absolute accuracy.

It is unlikely that we will have the opportunity to conduct a full pharmacokinetic study on patients undergoing anesthesia. Bayesian forecasting is a statistical technique by which a few measured plasma concentrations from an individual can be incorporated into pharmacokinetic parameters to improve the performance of a pharmacokinetic model- driven infusion device. Maitre and Stanski [122] demonstrated the theoretical improvement in such devices when using bayesian forecasting for alfentanil. In this study, Maitre and Stanski demonstrated that measurement of a single plasma alfentanil concentration could potentially reduce the inaccuracy by half, to 14 percent average performance error. Unfortunately, a rapid assay does not exist for any of the intravenous drugs used in anesthetic practice. However, there are rapid assays for lidocaine, and at least one pharmacokinetic model-driven infusion device (STANPUMP, developed by Shafer and Maitre at Stanford) performs real-time bayesian forecasting using measured lidocaine levels for use in coronary care units.

In the absence of rapid assays for anesthetic drugs, the obvious method to decrease variability is to observe the drug effect and to adjust the target to the concentration that produces the desired level of drug effect. [25] [26] As discussed under "Pharmacodynamic Considerations," by knowing the rate constant k_{e0}, it is possible to model the concentration at the site of drug effect. Figure 11-27 (Figure Not Available) shows the plasma fentanyl concentrations that could theoretically be obtained over the course of a brief operation. Figure 11-27B (Figure Not Available) shows the fentanyl concentrations at the effect site for the same anesthetic shown in Figure 11-27A (Figure Not Available) . Even if the pump produced precisely the concentrations shown in Figure 11-27A (Figure Not Available) (i.e., had perfect performance), the lag between the plasma and the site of drug effect would, at best, produce a very slurred response because of the equilibration delay between the plasma and the effect site. Several pharmacokinetic model-driven infusion devices now simultaneously display both the plasma and the effect-site concentrations. Such devices permit the clinician to target the concentration in the effect site, rather than the plasma, in order to provide more precise control of drug effect.

Targeting the effect site rather than the plasma may make titration more precise by permitting the clinician to determine whether the levels are higher or lower than desired by observing drug effect. The next step is then to feed the measured drug effect directly back into the automated drug delivery device and to permit the model to be updated based on

Figure 11-27 (Figure Not Available) Simulated plasma fentanyl concentrations over time for a brief anesthetic, showing the rapid rise and fall and impression of precise titration that can be created by a target-controlled drug delivery device (A). (B) Effect-site concentrations for the same anesthetic course, demonstrating that precise control of plasma concentration does not necessarily translate into precise control at the site of drug effect. *(Adapted from Shafer and Gregg [25])*

---

observed measures of drug effect, thus providing a closed-loop system. [4] [7] [15] [16] [17] [18] [19] This is the same concept as using observed plasma concentrations for improving performance, except that assays are not available for most of the drugs used in anesthesia practice. Thus, several investigators have developed closed-loop target control of anesthesia. [15] [16] [17] [18] [123] As mentioned earlier, the ability to measure adequacy of anesthesia is limited; however, both median EEG frequency and auditory evoked responses, as well as the bispectral index, have been used successfully to provide closed-loop anesthesia in patients during surgery. Schwilden et al [15] [16] [17] used the EEG to adjust the infusion rates of anesthetic drugs with their automated drug delivery device. Their device does not maintain any drug target concentration either in the plasma or at the site of drug effect but rather uses a proportional controller to maintain a target median EEG frequency from 2 to 3 Hz. They found that this approach works well clinically for methohexital and propofol. Since then, it has become apparent that anesthesia may be composed of both hypnosis and analgesia. The bispectral index, which is a derived parame-ter of the EEG, has been shown to correlate well with level of sedation and loss of consciousness. Several investigators have started to implement closed-loop anesthesia using the bispectral index as the measure of effect, with the understanding that the analgesic component needs to be addressed separately. This approach moves automated delivery of anesthetic drugs away from pharmacokinetic models entirely and toward the closed-loop systems that have been developed and have been well described for the vasoactive drugs, nitroprusside in particular. [4] [5] [6] [7]

In summary, automated drug delivery devices appear to be able to achieve and maintain desired plasma concentrations with a median expected error of about 20 to 30 percent of the target. Although pharmacokinetic analysis after automated drug delivery results in a reduction in the median error to closer to 20 percent in adults and possibly lower in children, biologic variability sets a limit on the expected accuracy of these devices. More accurate performance could be obtained with bayesian feedback by use of rapid intraoperative assays, but this is unavailable for the intravenous drugs used in anesthetic practice. However, the equilibration delay between the plasma and the effect site is such that excessive focus on plasma concentrations may be unwarranted. Instead, learning about the pharmacokinetic/pharmacodynamic characteristics of the specific patient, by titrating to a readily measured drug effect, appears to be the most promising method for optimizing the performance of automated drug delivery devices to the clinical needs of the individual patient.

Outcome

The evaluation of outcome with TCI devices is more difficult than the evaluation of accuracy because of the difficulty of precisely measuring patient outcome. Because contemporary anesthetic practice produces very little morbidity, outcome measures are usually based on the process variables, such as blood pressure, heart rate, and duration of recovery room stay, rather than on substantive measures of patient morbidity. The evaluation of outcome with automated drug delivery devices requires a comparison of manual methods of administration with the same drug with automated drug delivery of intravenous anesthetics and volatile anesthetics. There have now been numerous studies evaluating automated drug delivery device administration of intravenous anesthetics for both brief and complex surgery, in children and in adults, in short-term sedation, in prolonged sedation (days), and in chronic pain management. Unfortunately, there have so far been very few comparative outcome studies between automated drug delivery devices and manual delivery systems.

Ausems et al [22] compared pharmacokinetic model-driven administration with intermittent bolus administration of alfentanil. Automated drug delivery produced fewer incidences of muscular rigidity, hypotension, and bradycardia on induction. Automated drug delivery during maintenance resulted in significantly fewer incidences of hemodynamic response, resulting in a greater percentage of anesthesia time within 15 percent of the desired blood pressure and heart rate. Recovery after TCI was associated with significantly less use of naloxone for adequate ventilation.

Pharmacokinetic model-driven infusion of fentanyl during cardiac surgery resulted in greater hemodynamic control with fewer additional drug interventions and significantly fewer episodes of either hypotension or hypertension than occurred with bolus dose administration. [108] A small study comparing manual alfentanil administration to pharmacokinetic model-driven infusion of alfentanil showed no statistical differences during maintenance or recovery. [124] Theil et al [95] compared double-blind manual administration of fentanyl/midazolam to pharmacokinetic model-driven infusion of these two anesthetics in a small group of patients presenting for cardiac surgery. Both systems were titrated simultaneously (one containing placebo), with the aim of maintaining hemodynamics within 20 percent of baseline values. Both systems were equally effective in providing hemodynamic control as dictated by the protocol. The most significant difference between the two modes of delivery was the greater variability in drug plasma concentrations in the manual group. This suggested that pharmacokinetic model- driven infusion maintained patients within a narrower therapeutic range. The advantages of this would be most important with drugs that have a narrow therapeutic window. This small comparative study, although it did not show many differences in outcome, demonstrated that targetcontrolled drug delivery was at least equal to manual drug delivery. Many pertinent outcome parameters, such as recovery times, were not measured in this study. Thus, there remains a need to establish which of the theoretical patient benefits will be realized with model-based target controlled delivery over manual delivery of intravenous drugs. With the introduction of a commercial TCI device for propofol, several more comparative studies have been performed. Struys et al [125] ($n = 90$), Russel et al [126] ($n = 160$), and Servin, in a large multicenter study ($n = 562$), found when they compared a manual infusion of propofol to TCI administration there were small differences between the two means of propofol administration. Interestingly, in the TCI groups, the maintenance infusion rate tended to be higher in the TCI groups but was associated with a lower incidence of movement by patients. Both Servin and Russel et al noted that there was a marked preference of the user for the TCI system, even though this was their first use of the device.

Pharmacokinetic model-driven infusion of propofol compares favorably with thiopental/isoflurane anesthesia for general surgery lasting several hours. [127] Induction, maintenance, and recovery were similar between the two groups. This implies that given the appropriate means for administration, intravenous anesthesia can be equal to inhalational anesthetics in providing the objectives of anesthesia, that is, rapid induction and recovery with stable maintenance.

In noncomparative studies, pharmacokinetic modeldriven infusion has been used to administer most of the potent opioids as well as the hypnotics. Different anesthetic techniques have also been tested with pharmacokinetic model-driven infusion devices, including nitrous-narcotic anesthesia, supplementation of volatile anesthetics, total intravenous anesthesia and sedation for monitored anesthesia care, and intensive care unit sedation. In all these studies, outcome, as measured by hemodynamics and recovery, has been within the expectations of normal clinical care. Etomidate, methohexital, midazolam, propofol, thiopental, alfentanil, fentanyl, remifentanil, and sufentanil have all been used with TCI. When these drugs were used with target-controlled drug delivery systems for total intravenous anesthesia or to supplement nitrous oxide or volatile anesthetics, hemodynamics were well maintained during induction and intubation, as well as during maintenance. Recovery milestones were reached that were at times comparable to those of similar drug combinations used in manual infusion schemes. In none of these numerous studies have authors commented on adverse outcome resulting from target-controlled drug delivery. The clinical experience with TCI devices is now enormous, with probably several hundred thousand patient exposures. It is thus likely that TCI will become a part of routine practice.

Most of the studies thus far published have targeted plasma/blood concentrations. Although systems are available to target the effect site, there have been no publications of the clinical utility when the effect site is targeted. As discussed earlier, targeting the effect site may even further enhance outcome with model-based target-controlled devices.

Target-controlled infusion devices have also been used to provide patient-controlled analgesia. Hill and colleagues demonstrated patient-controlled anesthesia devices using morphine, fentanyl, or alfentanil [121] [128] and the clinical utility of such devices. [129] [130] [131] [132] Van den Nieuwenhuyzen et al [53] demonstrated advantages of such a system with alfentanil over routine morphine patient-controlled anesthesia.

From the body of literature presently available, it appears that automated drug delivery of intravenous anesthetics is at least equal to manual delivery of these drugs. Intravenous drug administration using target-controlled drug delivery is analogous to inhalational vapor delivery using a calibrated vaporizer. Like the vaporizer, pharmacokinetic model- driven infusion facilitates drug delivery based on plasma or biophase concentration rather than on drug dosage. There is variability with the use of a calibrated vaporizer, including variability in the accuracy of drug delivery with vaporizers, slow equilibration between the fresh gas flow and the circuit at low flow rates, and variable uptake by the patient. This variability does not particularly complicate titration of the inhalational anesthetics. The variability with targetcontrolled drug delivery is of a similar magnitude. Just as with the vaporizers, the variability with target-controlled drug delivery does not particularly complicate titration of intravenous anesthetics. Indeed, the time-varying stresses of surgery and the variability in patient response require that the anesthesiologist titrate the administration of the potent inhalation anesthetics, using the calibrated vaporizer as a tool. These same factors require that the anesthesiologist vigilantly titrate the infusion of intravenous anesthetic drugs when using automated drug delivery as a tool.

Target-controlled drug delivery has advantages beyond a delivery system to simplify the clinical administration of intravenous anesthetics. Probably the most significant contribution of these delivery devices is their use in research. The pseudo-steady state that can be almost instantly achieved with these devices permits the plasma and effect site to rapidly come into equilibrium. This is critically important in studies examining the concentration-response relationships (i.e., the C_{50} values) for anesthetic drugs. [22] [30] [51] In addition, these systems enable interactions involving intravenous drugs to be clearly defined. [36] [37] [38] Closed-loop target delivery will eventually enable unbiased and more precise comparisons between drugs. Lastly, as noted earlier, targetcontrolled delivery has provided us with the ability to prospectively test pharmacokinetic parameter sets and modeling approaches and ultimately may provide the most suitable pharmacokinetic parameters for any intravenous drug delivery. [107] [110] [119] [133] Purely as a research tool, automated drug delivery has already had a major impact on anesthetic practice.

SUMMARY

In comparison with intermittent bolus administration, the continuous infusion of intravenous anesthetic drugs provides greater control of anesthetic depth, thus ensuring (1) better hemodynamic control with fewer incidences of hemodynamic instability, (2) lower total drug doses, and (3) more rapid return to an awake state. Improved drug administration techniques combined with several new intravenous anesthetic agents have provided greater impetus for the use of intravenous anesthesia in clinical practice. The devices for the administration of intravenous anesthesia are undergoing rapid evolution. The introduction of pumps designed specifically for continuous intravenous anesthetic drug delivery is likely to further enhance intravenous anesthesia. "Calculator" pumps enhance manual means of continuous intravenous drug administration. These pumps, although a major step forward for intravenous drug delivery, fall short of enabling the clinician to titrate drug concentration to drug effect.

Automated drug delivery provides this ability. There are several theoretical advantages of pharmacokinetic model- driven infusion over manual infusion systems, such as further improvements in hemodynamic control and a more predictable rapid awakening. The actual advantages of automated drug delivery of intravenous anesthetics over manual methods, or in comparison with inhalational anesthesia, are not yet fully established but, under all circumstances, are at least equal to them, with greater user preference for such devices. It also appears that pharmacokinetics used with pharmacokinetic model-driven infusion, although not yet optimal, are adequate for clinical use. The initial data, however,

indicate that pharmacokinetic model-driven infusion provides advantages as a system for intravenous drug delivery, but well-controlled studies with large patient populations are needed to fully establish its ultimate role in the clinical practice of anesthesia. The introduction of commercial TCI systems is a strong indication that automated drug delivery is now likely to become an everyday part of anesthesia practice.

REFERENCES

1. Corssen G, Reves JG, Stanley T: Intravenous Anesthesia and Analgesia. Philadelphia, Lea & Febiger, 1988.

2. Schwilden H: A general method for calculating the dosage scheme in linear pharmacokinetics. Eur J Clin Pharmacol 20:379-386, 1981.

3. Reves JG, Sheppard LC, Wallach R et al: Therapeutic uses of sodium nitroprusside and an automated method of administration. Int Anesthesiol Clin 16:51-88, 1978.

4. Meline LJ, Westenskow DK, Pace NL et al: Computer-controlled regulation of sodium nitroprusside infusion. Anesth Analg 64:38, 1985.

5. Reid JA, Kenny GN: Evaluation of closed-loop control of arterial pressure after cardiopulmonary bypass. Br J Anaesth 59:247-255, 1987.

6. Colvin JR, Kenny GN: Development and evaluation of a dual-pump microcomputer-based closed-loop arterial pressure control system. Int J Clin Monit Comput 6:31-35, 1989.

7. Grosmaire EK: Computer-controlled sodium nitroprusside infusions in patients after cardiac surgery. Heart Lung 21:214, 1992.

8. de Vries JW, Ros HH, Booij LH: Infusion of vecuronium controlled by a closed-loop system. Br J Anaesth 58:1100-1103, 1986.

9. Olkkola KT, Schwilden H: Quantitation of the interaction between atracurium and succinylcholine using closed-loop feedback control of infusion of atracurium. Anesthesiology 73:614-618, 1990.

10. O'Hara DA, Derbyshire GJ, Overdyk FJ et al: Closed-loop infusion of atracurium with four different anesthetic techniques. Anesthesiology 74:258-263, 1991.

11. Schwilden H, Olkkola KT: Use of a pharmacokinetic-dynamic model for the automatic feedback control of atracurium. Eur J Clin Pharmacol 40:293-296, 1991.

12. Uys PC, Morrell DF, Bradlow HS et al: Self-tuning, microprocessor-based closed-loop control of atracurium-induced neuromuscular blockade. Br J Anaesth 61:685- 692, 1988.

13. Wait CM, Goat VA, Blogg CE: Feedback control of neuromuscular blockade: A simple system for infusion of atracurium. Anaesthesia 42:1212-1217, 1987.

14. Webster NR, Cohen AT: Closed-loop administration of atracurium: Steady-state neuromuscular blockade during surgery using a computer controlled closed-loop atracurium infusion. Anaesthesia 42:1085-1091, 1987.

15. Schwilden H, Schuttler J, Stockel H: Closed-loop feedback control of methohexital anesthesia by quantitative EEG analysis in humans. Anesthesiology 67:341, 1987.

16. Schwilden H, Stoeckel H: Effective therapeutic infusions produced by closed-loop feedback control of methohexital administration during total intravenous anesthesia with fentanyl. Anesthesiology 73:225-229, 1990.

17. Schwilden H, Stoeckel H, Schuttler J: Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. Br J Anaesth 62:290-296, 1989.

18. Kenny GNC, Davies FW, Mantzardis H et al: Closed-loop control of anesthesia. Anesthesiology 77:A328, 1992.

19. Struys M, Desmet T, Audenaert S et al: Development of a closed loop system for propofol using bispectral analysis and a patient-individual pharmacokinetic-dynamic (PK-PD) model: Preliminary results [abstract]. Br J Anaesthesia 78(suppl 1):23, 1997.

20. Sigl JC, Chamoun NG: An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 10:392-404, 1994.

21. White PF: Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology 59:294, 1983.

22. Ausems ME, Vuyk J, Hug CC et al: Comparison of a computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 68:851-861, 1988.

23. Hull CJ, Van Beem HB, McLeod K et al: A pharmacodynamic model for pancuronium. Br J Anaesth 50:1113-1123, 1978.

24. Sheiner LB, Stanski DR, Vozeh S et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. Clin Pharmacol Ther 25:358-371, 1979.

25. Shafer SL, Gregg K: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer controlled infusion pump. J Pharmacokinet Biopharm 20:147-169, 1992.

26. Jacobs JR, Williams EA: Algorithm to control "effect compartment" drug concentrations in pharmacokinetic model-driven drug delivery. IEEE Trans Biomed Eng 40:993-999, 1993.

27. Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234-241, 1985.

28. Eger EID, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. Anesthesiology 26:756-763, 1965.

29. Ausems ME, Stanski DR, Hug CC: An evaluation of the accuracy of pharmacokinetic data for the computer assisted infusion of alfentanil. Br J Anaesth 57:1217-1225, 1985.

30. Hung OR, Varvel JR, Shafer SL et al: Thiopental pharmacodynamics II. Quantitation of clinical and electroencephalographic depth of anesthesia. Anesthesiology 77:237-244, 1992.

31. Telford RJ, Glass PSA, Goodman D et al: Fentanyl does not alter the "sleep" plasma concentration of thiopental. Anesth Analg 75:523-529, 1992.

32. Vuyk J, Engbers FHM, Lemmens HJM et al: Pharmacodynamics of propofol in female patients. Anesthesiology 77:3-9, 1992.

33. Vuyk J, Lim T, Engbers FH et al: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 83:8-22, 1995.

34. Smith C, McEwan AI, Jhaveri R et al: Reduction of propofol Cp50 by fentanyl. Anesthesiology 77:A340, 1992.

35. Jacobs JR, Reves JG, Marty J et al: Aging increases pharmacodynamic sensitivity to the hypnotic effects of midazolam. Anesth Analg 80:143-148, 1995.

36. McEwan AI, Smith C, Dyar O et al: Isoflurane MAC reduction by fentanyl. Anesthesiology 78:864-869, 1993.

37. Brunner MD, Braithwaite P, Jhaveri R et al: The MAC reduction of isoflurane by sufentanil. Br J Anaesth 72:42-46, 1994.

38. Westmoreland C, Sebel PS, Groper A et al: Reduction of isoflurane MAC by fentanyl or alfentanil. Anesthesiology 77:A394, 1992.

39. Lang E, Kapila A, Shlugman D et al: Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 85:721-728, 1996.

40. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 240:159-166, 1987.

41. Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioid effect: Comparative pharmacodynamics of fentanyl and sufentanil. Anesthesiology 74:34, 1991.

42. Egan TD, Lemmens HJM, Fiset P et al: The pharmacokinetics and pharmacodynamics of GI 87084B. Anesthesiology 77:A369, 1992.

43. Minto CF, Schnider TW, Egan TD et al: The influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 86:10-23, 1997.

44. Lemmens HJM, Dyck JB, Shafer SL et al: The application of pharmacokinetics dynamics and computer simulations to drug development: A3665 versus fentanyl and alfentanil. Anesthesiology 77:A456, 1992.

45. Homer TD, Stanski DR: The effect of increasing age on thiopental disposition and anesthetic requirement. Anesthesiology 62:714-724, 1985.

46. Stanski DR, Maitre PO: Population pharmacokinetics and pharmacodynamics of thiopental: The effect of age revisited [see comments]. Anesthesiology 72:412-422, 1990.

47. Arden JR, Holley FO, Stanski DR: Increased sensitivity to etomidate in the elderly: Initial distribution versus altered brain response. Anesthesiology 65:19, 1986.

48. Billard V, Gambus PL, Chamoun N et al: A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol, and midazolam drug effect. Clin Pharmacol Ther 61:45-58, 1997.

49. Schnider TW, Minto CF, Fiset P et al: Semilinear canonical correlation applied to the measurement of the electroencephalographic effects of midazolam and flumazenil reversal. Anesthesiology 84:510-519, 1996.

50. Ausems ME, Hug CC Jr, Stanski DR et al: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. Anesthesiology 65:362-373, 1986.

51. Glass PSA, Doherty M, Jacobs JR et al: Plasma concentration of fentanyl, with 70% nitrous oxide, to prevent movement at skin incision. Anesthesiology 78:842-847, 1993.

52. Gourlay GK, Kowalski SR, Plummer JL et al: Fentanyl blood concentration analgesic response relationship in the treatment of postoperative pain. Anesth Analg 67:329-337, 1988.

53. Van den Nieuwenhuyzen MCO, Engbers FHM, Burm AGL et al: Computer-controlled infusion of alfentanil versus PCA-morphine for postoperative analgesia: A double-blind study. Anesth Analg 40:1112-1118, 1995.

54. Lehmann KA: Patient-controlled analgesia for postoperative pain. Adv Pain Res Ther 14:297, 1990.

55. Lehmann KA, Gerhard A, Horrichs-Haermeyer G et al: Postoperative patient-controlled analgesia with sufentanil: Analgesic efficacy and minimum effective concentrations. Acta Anaesthesiol Scand 35:221, 1991.

56. Kissin I, Mason JOD, Bradley EL Jr: Morphine and fentanyl interactions with thiopental in relation to movement response to noxious stimulation. Anesth Analg 65:1149-1154, 1986.

57. Kissin I, Mason JO, Bradley EL: Morphine and fentanyl hypnotic interactions with thiopental. Anesthesiology 67:331-335, 1987.

58. Mehta D, Bradley Jr, EL, Kissin I: Effect of alfentanil on hypnotic and antinociceptive components of thiopental sodium anesthesia. J Clin Anesth 3:280-284, 1991.

59. Kissin I, Brown PT, Bradley Jr: EL: Sedative and hypnotic midazolam-morphine interactions in rats. Anesth Analg 71:137-143, 1990.

60. Ropcke H, Schwilden H: The interaction of nitrous oxide and enflurane on the EEG median of 2-3 Hz is additive, but weaker than at 1.0 MAC [see comments]. Anaesthesist 45:819-825, 1996.

61. Gonsowski CT, Eger 2nd EI: Nitrous oxide minimum alveolar anesthetic concentration in rats is greater than previously reported. Anesth Analg 79:710-712, 1994.

62. Deady JE, Koblin DD, Eger EI 2nd et al: Anesthetic potencies and the unitary theory of narcosis. Anesth Analg 60:380-384, 1981.

63. Targ AG, Yasuda N, Eger EI 2nd et al: Halogenation and anesthetic potency [see comments]. Anesth Analg 68:599-602, 1989.

64. Kissin I: General anesthetic action: An obsolete notion? Anesth Analg 76:215-218, 1993.

65. Katoh T, Ikeda I: The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. Anesthesiology 88:18-24, 1998.

66. Glass PSA, Jacobs JR, Smith RL et al: Pharmacokinetic model-driven infusion of fentanyl: Assessment of accuracy. Anesthesiology 73:1082-1090, 1990.

67. Dwyer R, Bennett HL, Eger EI 2nd et al: Isoflurane anesthesia prevents unconscious learning. Anesth Analg 75:107-112, 1992.

68. Egan TD, Lemmens HJM, Fiset P et al: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 79:881-892, 1993.

69. Shafer SL, Varvel JR: Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology 74:53-63, 1991.

70. Henthorn TK, Krejcie TC, Shanks CA et al: Time-dependent distribution volume and kinetics of the pharmacodynamic effector site [letter]. J Pharm Sci 81:1136, 1992.

71. Wagner JG: A safe method for rapidly achieving plasma concentration plateaus. Clin Pharmacol Ther 16:691-700, 1974.

72. Hughes MA, Glass PSA, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 76:334-341, 1992.

73. Schwilden H: Optimization of the dosage of volatile anesthetics based on pharmacokinetic and dynamic models. Anasth Intensivther Notfallmed 20:307-315, 1985.

74. Fisher DM, Rosen JI: A pharmacokinetic explanation for increasing recovery time following larger or repeated doses of nondepolarizing muscle relaxants. Anesthesiology 65:286-291, 1986.

75. Youngs EJ, Shafer SL: Pharmacokinetic parameters relevant to recovery from opioids. Anesthesiology 81:833-842, 1994.

76. Bailey JM: Technique for quantifying the duration of intravenous anesthetic effect [see comments]. Anesthesiology 83:1095-1103, 1995.

77. Vuyk J, Mertens MJ, Olofsen E et al: Propofol anesthesia and rational opioid selection: Determination of optimal EC50-EC95 propofolopioid concentrations that assure adequate anesthesia and a rapid return of consciousness. Anesthesiology 87:1549-1562, 1997.

78. Heykants J, Geerts P, Noorduin H et al: The pharmacokinetic basis of alfentanil infusion. Eur J Anaesth 1:17, 1987.

79. Moldenhauer CC, Hug CC Jr: Use of narcotic analgesics as anaesthetics. Clin Anaesth 2:107, 1984.

80. Sebel PS, Bovill JG: Opioid analgesics in cardiac anesthesia. In Kaplan JA (ed): Cardiac Anesthesia. Orlando, Florida, Grune & Stratton, 1987, p 67.

81. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 86:24-33, 1997.

82. White PF, Dworsky WA, Horai V et al: Comparison of continuous infusion fentanyl or ketamine versus thiopental--determining the mean effective serum concentrations for outpatient surgery. Anesthesiology 59:564, 1983.

83. Prys-Roberts C, Sear JW: Non-barbiturate intravenous anesthetics and continuous infusion anaesthesia. In Prys-Roberts C, Hug CC, Jr (eds): Pharmacokinetics of Anaesthesia. St. Louis, Blackwell Scientific Publishers, 1984, p 128.

84. Glass PS, Leiman BC, Reves JG: Etomidate: What is its present role in anesthesia? Semin Anesth 7:143, 1988.

85. White PF, Way WL, Trevor AJ: Ketamine: Its pharmacology and therapeutic uses. Anesthesiology 56:119, 1982.

86. White P: Propofol: Pharmacokinetics and pharmacodynamics. Semin Anesth 7:4, 1988.

87. Shafer A, Doze VA, Shafer SL et al: Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology 69:348-356, 1988.

88. Barr J, Egan T, Feeley T et al: Depth of sedation vs. propofol concentration in mechanically ventilated ICU patients. Anesthesiology 77:A313, 1992.

89. Liu J, Singh H, White PF: Electroencephalographic bispectral analysis predicts the depth of midazolam-induced sedation. Anesthesiology 84:64-69, 1996.

90. Liu J, Harbhej S, White PF: Electroencephalographic bispectral index correlates with recall and depth of propofol-induced sedation. Anesth Analg 84:185-189, 1997.

91. Glass PSA, Bloom M, Kearse L et al: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 86:836-847, 1997.

92. Gan TJ, Glass PS, Windsor A et al: BIS Utility Study Group, bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology 87:808-815, 1997.

93. Reves J, Glass PSA, Jacobs J: Midazolam and alfentanil: New anesthetic drugs for continuous infusion and an automated method of administration. Mt Sinai J Med 56:99, 1989.

94. Kissin I, Brown PT, Bradley EL et al: Diazepam-morphine hypnotic synergism in rats. Anesthesiology 70:689-694, 1989.

95. Theil DR, Stanley TE III, White WD et al: Midazolam and fentanyl continuous infusion anesthesia for cardiac surgery: A comparison of computer-assisted vs. manual infusion systems. J Cardiothorac Vasc Anesth 7:300-306, 1993.

96. Reves JG, Jacobs JR, Glass PSA: Automated drug delivery in anesthesia. ASA Refresher Course in Anesthesiology 19, 1991, p 19.

97. Kruger-Thiemer E: Continuous intravenous infusion and multicompartment accumulation. Eur J Pharmacol 4:317-324, 1968.

98. Schwilden H, Schuttler J, Stoekel H: Pharmacokinetics as applied to total intravenous anaesthesia: Theoretical considerations. Anaesthesia 38(suppl):51-52, 1983.

99. Schuttler J, Schwilden H, Stoekel H: Pharmacokinetics as applied to total intravenous anaesthesia: Practical implications. Anaesthesia 38(suppl):53-56, 1983.

100. Shafer SL, Siegel LC, Cooke JE et al: Testing computer-controlled infusion pumps by simulation. Anesthesiology 68:261-266, 1988.

101. Varvel JR, Donoho DL, Shafer SL: Measuring the predictive performance of computer-controlled infusion pumps. J Pharmacokinet Biopharm 20:63, 1992.

102. Raemer DB, Buschman A, Varvel JR et al: The prospective use of population pharmacokinetics in a computer-driven infusion system for alfentanil. Anesthesiology 73:66-72, 1990.

103. Crankshaw DP, Morgan DJ, Beemer GH et al: Preprogrammed infusion of alfentanil to constant arterial plasma concentration. Anesth Analg 76:556, 1993.

104. Schuttler J, Kloos S, Schwilden H et al: Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Anaesthesia 43 (suppl):2-7, 1988.

105. Lemmens HJM, Bovill JG, Burm AGL et al: Alfentanil infusion in the elderly. Anaesthesia 43:850-856, 1988.

106. Veselis RA, Glass P, Dnistrian A et al: Performance of computer-assisted continuous infusion at low concentrations of intravenous sedatives. Anesth Analg 84:1049-1057, 1997.

107. Shafer SL, Varvel SL, Aziz N et al: The pharmacokinetics of fentanyl administered by computer controlled infusion pump. Anesthesiology 73:1091-1102, 1990.

108. Alvis JM, Reves JG, Govier AV et al: Computer assisted continuous infusions of fentanyl during cardiac anesthesia: Comparison with a manual method. Anesthesiology 63:41-49, 1985.

109. Coetzee JF, Glen JB, Wium CA et al: Pharmacokinetic model selection for target controlled infusions of propofol: Assessment of three parameter sets. Anesthesiology 82:1328-1345, 1995.

110. Marsh B, White M, Morton N et al: Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth 67:41, 1991.

111. Tackley RM, Lewis GTR, Prys-Roberts C et al: Computer controlled infusion of propofol. Br J Anaesth 62:46, 1989.

112. Pavlin DJ, Coda B, Shen DD et al: Effects of combining propofol and alfentanil on ventilation, analgesia, sedation, and emesis in human volunteers. Anesthesiology 84:23-37, 1996.

113. Kharasch ED, Russell M, Mautz D et al: The role of cytochrome P450 3A4 in alfentanil clearance. Anesthesiology 87:36-50, 1997.

114. Vuyk J, Mertens MJ, Vletter AA et al: Alfentanil modifies the pharmacokinetics of propofol in volunteers [abstract]. Anesthesiology 87:A300, 1997.

115. Crankshaw DP, Boyd MD, Bjorksten AR: Plasma drug efflux: A new approach to optimization of drug infusion for constant blood concentration of thiopental and methohexital. Anesthesiology 67:32-41, 1987.

116. McClain DA, Hug CC Jr: Intravenous fentanyl kinetics. Clin Pharmacol Ther 28:106, 1980.

117. Maitre PO, Vozeh S, Heykants J: Population pharmacokinetics of alfentanil: The average dose-plasma concentration relationship and interindividual variability in patients. Anesthesiology 66:3-12, 1987.

118. Ginsberg B, Howell S, Glass PSA et al: Pharmacokinetic model- driven infusion of fentanyl in children. Anesthesiology 85:1268-1275, 1996.

119. Fiset P, Mathers L, Engstrom R et al: Pharmacokinetics of computer controlled alfentanil administration in children undergoing cardiac surgery. Anesthesiology 83:944-955, 1995.

120. Bailey JM, Mora CT, Shafer SL et al: Pharmacokinetics of propofol in adult patients undergoing coronary revascularization. Anesthesiology 81:1288-1297, 1996.

121. Hill HF, Saeger L, Bjurstrom R et al: Steady-state infusions of opioids in human volunteers. I. Pharmacokinetic tailoring. Pain 43:57, 1990.

122. Maitre PE, Stanski DR: Bayesian forecasting improves the prediction of intraoperative plasma concentrations of alfentanil. Anesthesiology 69:652-659, 1988.

123. Struys M, Versichelen L, Byttebier G et al: Clinical usefulness of the bispectral index for titrating propofol target effect-site concentration. Anaesthesia 53:4-12, 1998.

124. Glass PSA, Jacobs J, Alvis M et al: Computer assisted continuous infusion of alfentanil during noncardiac anesthesia: A comparison with a manual method. Anesthesiology 65:A546, 1986.

125. Struys M, Versichelen L, Thas O et al: Comparison of computer-controlled propofol administration with two manual infusion methods [abstract]. Br J Anaesth 76(suppl 2):87, 1996.

126. Russel D, Wilkes MP, Hunter SC et al: Manual compared with target-controlled infusion of propofol. Br J Anaesth 75:562-566, 1995.

127. Glass PSA, Ginsberg B, Hawkins ED et al: Comparison of sodium thiopental/isoflurane to propofol (delivered by means of a pharmacokinetic model-driven device) for the induction, maintenance, and recovery from anesthesia. Anesthesiology 69:A575, 1988.

128. Hill HF, Chapman CR, Saeger LS et al: Steady-state infusions of opioids in human. II. Concentration-effect relationships and therapeutic margins. Pain 43:69-79, 1990.

129. Hill HF, Mather LE: Patient-controlled analgesia: Pharmacokinetic and therapeutic considerations. Clin Pharmacokinet 24:124-140, 1993.

130. Hill H, Mackie A, Coda B et al: Evaluation of the accuracy of a pharmacokinetically-based patient-controlled analgesia system. Eur J Clin Pharmacol 43:67-75, 1992.

131. Hill HF, Jacobson RC, Coda BA et al: A computer-based system for controlling plasma opioid concentration according to patient need for analgesia. Clin Pharmacokinet 20:319-330, 1991.

132. Hill HF, Mackie AM, Coda BA et al: Patient-controlled analgesic administration: A comparison of steady-state morphine infusions with bolus doses. Cancer 67:873-882, 1991.

133. Schnider TW, Gaeta R, Brose W et al: Derivation and cross-validation of pharmacokinetic parameters for computer-controlled infusion of lidocaine in pain therapy. Anesthesiology 84:1043-1050, 1996.

134. Schuttler J, Stoeckel H: Alfentanil (R39209) ein neues kurzwirkendes opioid. Pharmakokinetik und erste klinische erfahrungen. Anaesthesist 31:10, 1982.

135. Helmers H, Van Peer A, Woestenborghs R et al: Alfentanil kinetics in the elderly. Clin Pharmacol Ther 36:239-243, 1984.

136. Greeley WJ, de Bruijn NP, Davis DP: Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesth Analg 66:1067-1072, 1987.

137. Kern FH, Ungerleider RM, Jacobs JR et al: Computerized continuous infusion of intravenous anesthetic drugs during pediatric cardiac surgery. Anesth Analg 72:487-492, 1991.

138. Ghoneim MM, Van Hamme MJ: Pharmacokinetics of thiopentone: Effects of enflurane and nitrous oxide anaesthesia and surgery. Br J Anaesth 50:1237-1242, 1978.

139. Smith MT, Eadie MJ, Brophy TO: The pharmacokinetics of midazolam in man. Eur J Clin Pharmacol 19:271-278, 1981.

140. Greenblatt DJ, Abernathy DR, Locniskar A et al: Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 61:27-35, 1984.

141. Dyck JB, Varvel J, Hung O et al: The pharmacokinetics of propofol versus age [abstract]. Can Anaesth J 38(suppl):A129, 1991.

142. Gepts E, Camu F, Cockshott ID et al: Disposition of propofol administered as constant rate intravenous infusions in humans. Anesth Analg 66:1256-1263, 1987.

143. Glass PSA, Goodman DK, Ginsberg B et al: Accuracy of pharmacokinetic model-driven infusion of propofol. Anesthesiology 71:A277, 1989.

Chapter 12 - Pharmacology of Muscle Relaxants and Their Antagonists

John J. Savarese
James E. Caldwell
Cynthia A. Lien
Ronald D. Miller

INTRODUCTION

History

In 1942 Griffith and Johnson [1] suggested that *d*-tubocurarine (dTc) is a safe drug to use during surgery to ensure good skeletal muscle relaxation. One year later, Cullen [2] reported that dTc had been given to 131 patients under general anesthesia to produce additional skeletal muscle relaxation greater than that provided by the anesthetic alone. In 1954, however, Beecher and Todd [3] published a clinical report in which a 6-fold increase in mortality rate was found in patients who received muscle relaxants versus those who did not receive muscle relaxants. This study created undeserved negative publicity and dampened growing enthusiasm for the clinical use of muscle relaxants, largely because the clinical pharmacology of the drugs was very imprecise in that era. At that time the value of supported or controlled ventilation was not adequately understood, the effects of residual neuromuscular blockade in the recovery room were not at all appreciated, the importance of antagonism of residual blockade was unknown, and the need for careful monitoring was not yet established. During subsequent years, as the clinical pharmacology of the neuromuscular blocking drugs has been refined, and as the drugs themselves have been improved, the use of muscle relaxants has become a vitally important aspect of modern anesthesia practice. The development of new synthetic relaxants has greatly increased the clinician's options for providing skeletal muscle relaxation. Safer, more efficient, and more precise practice patterns have evolved as a result of the development of both a vastly expanded knowledge base and greatly improved drugs and monitoring techniques.

Succinylcholine, introduced by Thesleff [4] and Foldes et al [5] in 1952, revolutionized anesthetic practice by providing intense neuromuscular blockade of very rapid onset and ultra-short duration, thereby greatly easing the maneuver of tracheal intubation. The synthetic and semisynthetic nondepolarizing drugs gallamine, dimethyltubocurarine, and alcuronium, introduced over the next decade, were alternatives to dTc. They were not considered as dramatic improvements or as replacements for dTc (see the sections on individual nondepolarizing relaxants), because they as well as dTc produced cardiovascular side effects and because they showed long durations of action similar to that of dTc. This extended neuromuscular blocking effect occurs as a result of little or no metabolism and dependence on organ-based (liver and kidney) elimination.

In 1967 Baird and Reid [6] first reported on the clinical administration of the synthetic aminosteroid pancuronium. Although also similar in duration of action to dTc, this drug provided an improved cardiovascular and autonomic side-effect profile--lack of ganglionic blocking and histaminereleasing properties--in addition to having a mild to moderate vagolytic effect. The resulting lack of hypotensive action and mild stimulation of heart rate and arterial blood pressure were considered significant improvements over dTc. The structure of pancuronium (see Fig. 12-4) also allows a small degree of liver metabolism via deacetylation of the acetoxy groups. This minor degree of destruction in the body was considered an advance with respect to dTc (which is not metabolized) because pancuronium was the first nondepolarizing relaxant in clinical practice that was intentionally designed to follow a theoretical metabolic pathway.

The nearly simultaneous introduction in the early 1980s of two new muscle relaxants of intermediate duration--atracurium [7] [8] and vecuronium [9] [10] --revolutionized clinical practice by providing relaxation with little or no dependence on the kidney for elimination; faster onset; a more rapid, measurable recovery; and faster and more complete antagonism of residual block than in the case of the longer-lasting drugs. The development of atracurium and vecuronium (1) encouraged tracheal intubation by the use of nondepolarizing relaxants, (2) made it more convenient to provide paralysis by continuous infusion of relaxants, and (3) most importantly, enabled significantly improved postoperative neuromuscular function, resulting in a measurably shorter period of risk of weakness in the postanesthetic care unit. (ch. 72).

The virtual lack of cardiovascular effect of vecuronium over a very wide dose-range established a benchmark for other relaxants. [11] The degradation of atracurium via the chemical mechanism of Hofmann elimination [12] removed any important influence of biologic disorders such as advanced age, organ failure, or biochemical abnormalities on the pattern of neuromuscular blockade.

The early 1990s witnessed the introduction in the United States of two long-acting muscle relaxants found to be free of side effects: pipecuronium [13] and doxacurium. [14] A short-acting relaxant hydrolyzed by plasma cholinesterase (mivacurium [15]) and an intermediate-duration substance with rapid onset (rocuronium [16]) were also added to the armamentarium. Mivacurium facilitates maintenance of relaxation by continuous infusion with rapid spontaneous recovery, making antagonism of residual blockade an option rather than a requirement. Rocuronium is the first nondepolarizer considered to be an acceptable substitute for succinylcholine in facilitating rapid intubation of the trachea. An atracurium isomer, cisatracurium, [17] introduced in 1996, does not release histamine, and retains the intermediate duration of action of atracurium, facilitated by the Hofmann elimination reaction. A new steroidal material, rapacuronium (ORG 9487), now in the latter stages of clinical trial, shows fast onset, approaching that of succinylcholine, enabling rapid tracheal intubation. It has a short-to-intermediate duration of action.

Clinical Use

Two philosophies govern the clinical administration of muscle relaxants. One end of the scale, first popularized by Cecil Gray and coworkers in Liverpool, England, in the early 1950s, employs nitrous oxide, oxygen, and large doses of muscle relaxants as the anesthetic prescription. With this type of anesthesia, patients are usually amnesic, but occasionally some recall may occur. [18] Awareness during surgery has been vividly described in an editorial [19] : a trained medical person under general anesthesia described being awake during a cesarean section. She specifically stated that when she moved she was given more muscle relaxant (pancuronium) rather than more anesthesia. This pattern of giving muscle relaxants, instead of analgesics or hypnotics, to prevent movement in response to surgical stimulation is completely unacceptable practice. Although this practice may be considered

as an essential part of general anesthetic technique in a patient who has an unstable circulatory status, in our opinion, muscle relaxants must not be given without adequate dosage of analgesic and hypnotic drugs, no matter how precarious the patient's physical state. As stated by Cullen and Larson, [20] "muscle relaxants given inappropriately may provide the surgeon with optimal [operating] conditions in ... a patient [who] is paralyzed but not anesthetized--a state that [is] wholly unsatisfactory for the patient."

A further quote from Cullen and Larson [20] expresses our philosophy concerning muscle relaxant administration: "Relaxants used to cover up deficiencies in total anesthetic management ... represent an ... inappropriate use of these valuable adjuncts to anesthesia." Muscle relaxants should be viewed as adjuncts, not as substitutes, for anesthesia. They should be given only to adequately anesthetized patients as an integral part of a prescription that includes hypnosis, analgesia, and amnesia as well as relaxation. Neuromuscular function must be monitored, and appropriate doses should be given in order to minimize the possibility of residual paralysis in the postanesthetic care unit.

The importance of proper monitoring of neuromuscular function calls for special emphasis (Ch. 39) . Recent developments in monitoring that are changing attitudes toward clinical practice include (1) the introduction of a new evoked response, double-burst stimulation [21] ; (2) the observation of significantly faster evolution of

blockade in the airway musculature (jaw, [22] larynx, [23] diaphragm [24]) as compared with that in the thumb; and (3) measurements emphasizing the longer time requirement for, and greater difficulty of, antagonism of residual blockade due to long-acting relaxants. [25] [26] There is also most likely overall reduced cost and greater safety in practice with the newer shorter-acting relaxants. Proper attention to careful monitoring will certainly lead to greater precision, safety, and economy of practice (see the section on economics of relaxation).

This chapter discusses the clinical pharmacology and clinical use of muscle relaxants in the operating room and in the intensive care unit, incorporating the overall philosophy that these drugs are adjuvants, not substitutes, for anesthesia and/or sedation and analgesia. Diseases of the neuromuscular system, with which anesthesiologists are often confronted, are discussed with respect to their influence on the actions of the relaxants. The economics of providing relaxation are discussed, and new outcome studies comparing relaxants of different duration are summarized. The latter two topics, namely, economics and outcome, are distinctly and directly related.

MONITORING NEUROMUSCULAR FUNCTION

Details of monitoring clinical neuromuscular function are described in Chapter 36 . In this section general concepts are presented.

Peripheral Nerve Stimulation

Stimulating a peripheral nerve (usually the ulnar nerve at the wrist or elbow) and visually observing contraction of the fingers (adductor pollicis and flexor digitorum muscles) is the most commonly advocated method of monitoring neuromuscular function clinically. This stimulation need not be restricted to the arm; any superficially located neuromuscular unit may be monitored. Stimulating the facial nerve or the motor nerves of a lower extremity, such as the peroneal nerve, and observing the magnitude of resultant muscular contraction can also be used for monitoring neuromuscular function. As will be discussed later in more detail, different neuromuscular units should be monitored to assess onset of and recovery from neuromuscular block (Table 12-1) .

Peripheral nerve stimulation can be used to detect both magnitude and type of neuromuscular blockade. Quantitative conclusions must be guarded, however. Because of the wide margin of safety of neuromuscular function, a reduction in the contractile response to peripheral nerve stimulation is not quantitatively proportional to the action of relaxants at the receptor. For example, Waud and Waud [27] demonstrated that the twitch response of the tibialis anterior muscle of the cat in response to a single supramaximal stimulus is not reduced unless more than 70 percent of the receptors are occupied by a nondepolarizing relaxant. Twitch is completely eliminated when 90 percent of the receptors are occupied. Furthermore, as Kopman [27A] demonstrated, regardless of a clinician's expertise, fade in the train-of-four (TOF) response is not reliably detected at TOF values above .40. This may lead to extubation of the trachea before adequate recovery of neuromuscular function. Despite these limitations, the response to peripheral nerve stimulation can be extremely useful. Four important questions can be answered by observing the response to peripheral nerve stimulation: (1) Is the neuromuscular blockade adequate? (2) Is the neuromuscular blockade excessive? (3) Can the neuromuscular blockade be antagonized? (4) Is the neuromuscular blockade adequately antagonized?

Whatever form of nerve stimulation is used, subtle slight degrees of neuromuscular blockade cannot be detected by observing the response of a peripheral muscle. Especially in light of recent claims that even a TOF ratio of .70 is inadequate to be considered "complete" recovery, detection of subtle degrees of neuromuscular block is important.

In order to detect subtle residual neuromuscular blockade, the neuromuscular junction must be stressed by a stimulus that is greater and longer in intensity than that used to elicit a single twitch. While a 5-second tetanic stimulus would accomplish this, tetanic stimuli are painful and are, therefore, of limited value in detecting shallow residual blockade in the unanesthetized patient.

There are multiple types of peripheral nerve stimulation. The specific pattern of stimulation used depends on the clinical purpose (e.g., monitoring of adequate relaxation versus adequate antagonism).

Muscle contraction is an all-or-none phenomenon. Each fiber either contracts maximally or does not contract at all. Therefore, when twitch height (adduction of the thumb, for example) is reduced, some fibers are contracting normally, and others are blocked and remain flaccid. The stronger the response, the fewer fibers exist in a blocked state. Fade of muscular contraction in response to tetanic stimuli suggests that some fibers are more susceptible to being blocked by relaxants and need a greater release of acetylcholine (ACh) to trigger their response.

TABLE 12-1 -- Tests of Neuromuscular Transmission

TEST	ACCEPTABLE CLINICAL RESULT TO SUGGEST NORMAL FUNCTION	APPROXIMATE PERCENTAGE OF RECEPTORS OCCUPIED WHEN RESPONSE RETURNS TO NORMAL VALUE	COMMENTS/DISADVANTAGES/ADVANTAGES
Tidal volume	At least 5 mL/kg	80	Insensitive as an indicator of peripheral neuromuscular function.
Single twitch strength	Qualitatively as strong as baseline	75-80	Uncomfortable, need to know twitch strength before relaxant administration. Insensitive as an indicator of recovery, but useful as a gauge of deep neuromuscular blockade.
Train-of-four (TOF)	No palpable fade	70-75	Still uncomfortable, but more sensitive as an indicator of recovery than single twitch. Useful as a gauge of depth of block by counting the number of responses perceptible.
Sustained tetanus at 50 Hz for 5 seconds	No palpable fade	70	Very uncomfortable, but a reliable indicator of adequate recovery.
Vital capacity	At least 20 mL/kg	70	Requires patient cooperation, but is the goal for achievement of full clinical recovery.
Double-burst stimulation	No palpable fade	60-70	Uncomfortable, but more sensitive than TOF as an indicator of peripheral function. No perceptible fade indicates TOF of at least recovery of 60%.
Sustained tetanus at 100 Hz	No palpable fade	50	Very painful, a "stress test" for the neuromuscular junction. It is not always possible to achieve or to demonstrate lack of fade at 100 Hz.
Inspiratory force	At least -40 cm H_2O	50	Sometimes difficult to perform without endotracheal intubation, but a reliable gauge of normal diaphragmatic function.
Head lift	Must be performed un-aided with patient supine at 180° and sustained for 5 sec-onds	50	Requires patient cooperation, but remains the standard test of nor-mal clinical function. Must be performed with the patient in a completely supine position.

Hand grip	Sustained at a level qualitatively similar to preinduction baseline	50	Sustained strong grip, though also requiring patient cooperation.Is another good gauge of normal function.
Sustained bite	Sustained jaw clench on tongue blade	50	Very reliable with patient cooperation.Corresponds with TOF of 85%.

Stimulus Variables

Because the interaction of nondepolarizing relaxants with ACh binding sites is competitive, neuromuscular blockade can be overcome by increasing, or intensified by reducing, the concentration of ACh. This basic concept is important in clinical monitoring of neuromuscular blockade. Another fundamental concept is the economy of ACh synthesis, storage, and release. The quantity of ACh released with each nerve action potential is inversely proportional to the number of action potentials reaching the nerve terminal per unit time, or the stimulus frequency. For this reason, low concentrations of nondepolarizing relaxants block responses to high-frequency peripheral nerve stimulation (e.g., 100 Hz), whereas relatively high concentrations of relaxant are required to abolish responses elicited by low-frequency stimulation (e.g., 0.1 Hz). The depth of blockade of evoked neuromuscular responses in the presence of nondepolarizing relaxants is directly proportional to the stimulus frequency. Thus, stimuli of increasing frequency are able to detect increasingly shallow degrees of neuromuscular blockade. With rapid rates of stimulation such as tetanus at 100 Hz, very subtle degrees of block can be detected because the response to this stimulus is diminished with only very slight clinical evidence of weakness.

The pattern of response during depolarizing neuromuscular blockade is the same during slow and high rates of stimulation. Therefore, twitch and tetanic response provide essentially the same information during this type of blockade.

While monitoring nondepolarizing blockade during a typical surgical procedure, the following pattern is advised: single twitch or TOF should be followed during onset of neuromuscular blockade. TOF should be monitored during maintenance of blockade and recovery until fade in the response is no longer perceptible. Double-burst stimulation, followed by tetanic stimulation at 50 to 100 Hz, may subsequently be employed to detect more subtle degrees of residual paralysis during the final stages of recovery. Inability to reliably detect shallow residual neuromuscular blockade with either of these stimulus patterns may be due to the second and third responses to TOF stimulation influencing the clinician's interpretation of the response as well as displacement of the thumb from its baseline position with repetitive stimulation. [27B] [27C] It is imperative to confirm adequacy of function following either spontaneous or pharmacologically augmented recovery with a reliable clinical test, such as head lift for 5 seconds. This test must be performed properly, with the patient's head being lifted unaided from a true horizontal (180-degree) position. If the clinician is concerned about even more shallow degrees of block and would like to be certain that the patient has a TOF ratio greater

than 85%, the ability of the patient to appose his incisor teeth should be tested. [27C]

Receptor Occlusion Techniques

Work on the subject of the fraction of receptors that may be occupied during responses to various tests of neuromuscular function was performed primarily by Waud and Waud. [27] [28] Although this approach is based on fundamental agonist-antagonist relationships, its main clinical value is that it allows estimation of the sensitivity of many of the tests used clinically (see Table 12-1) . Even though the number of receptors occupied by a relaxant cannot be counted, Waud and Waud estimated the fraction of receptors (without knowing the absolute number of receptors) that must be unblocked by relaxant for tests of neuromuscular function to be normal. The technique estimates the fraction of receptors blocked by a nondepolarizing muscle relaxant by determining a dose-response depolarization curve from various agonist doses (succinylcholine) both in the absence and in the presence of the nondepolarizing blocker or antagonist (dTc, pancuronium). The fraction of receptors unblocked by the nondepolarizing muscle relaxant or still available for neuromuscular transmission can be estimated from the dose ratio of the agonist and blocker. For example, in the presence of dTc, 100 nmol of succinylcholine might be required to produce the same degree of depolarization produced by 10 nmol without dTC. Because ten times more succinylcholine is required with dTc, 10 percent of the receptors are still free (or 90 percent of the receptors are blocked). All other tests permit a normal response with a significant number of receptors still blocked, even at a tetanic stimulus of 200 Hz. These results suggest that no test is available to determine whether all receptors are free of a relaxant.

Respiration

The ability of a patient to maintain sustained adequate ventilation and to protect the airway, particularly during stresses such as airway obstruction or vomiting, is a main concern when looking at adequacy of recovery of neuromuscular function. Despite the enormous number of relaxant studies in the literature, few correlate tests of neuromuscular function with adequacy of ventilation, and the conclusions are often incomplete.

Johansen et al [29] found head-lift and hand-grip strength to be 38 and 48 percent of control when both inspiratory and expiratory flow rates are greater than 90 percent of control. Furthermore, Ali et al [30] found inspiratory force to be only 70 percent of control when vital capacity and expiratory flow rate are greater than 90 percent of control. Pavlin et al [31] found that many of the recommended tests can return to normal while the pharyngeal and neck muscles necessary to protect the airway can still be partially paralyzed (Fig. 12-1) (Figure Not Available) . As a result, they recommend that patients should be considered to be partially paralyzed until they can lift their head for 5 seconds or achieve a maximum negative inspiratory pressure of 35 cm H_2O (Pavlin EG, Holle RH, Schoene RB, personal communication). A negative inspiratory force of 50 cm

Figure 12-1 (Figure Not Available) Levels of neuromuscular blockade from *d*-tubocurarine as measured by maximum inspiratory pressure (MIP) below which the indicated clinical maneuver could not be accomplished. Obviously, head lift and straight-leg raising are the most sensitive indicators of neuromuscular blockade. *(From Pavlin et al [31])*

H_2O was found to correlate well with recovery of peripheral muscle strength.

Most recently D'Honneur et al [31A] found that with a TOF ratio of 50 percent or greater in volunteers airway patency remained at baseline values. However, in two, more recent, studies with a TOF ratio less than 90 percent, 40 percent of volunteers aspirated, [31B] and the incidence of pulmonary complications is increased in patients who had a TOF ratio less than 70 percent postoperatively. [31C] Therefore, although clinicians cannot readily detect subtle degrees of block, and patients can sustain adequate respiration before the TOF ratio has reached 90 percent, it is imperative that neuromuscular blockers be chosen and dosed in a fashion that allows for prompt recovery. Recovery room personnel need to observe the patient closely until all evidence of residual neuromuscular blockade has dissipated, [32] and head-lift for 5 seconds is unequivocally demonstrated.

Pattern of Blockade in Muscles of the Airway

Several groups of investigators, most notably Donati et al [23] and Pansard et al, [24] have shown that the evolution of both depolarizing and nondepolarizing block proceeds more rapidly in the central muscles of the airway, such as the larynx (Fig. 12-2), (Figure Not Available) the jaw, and the diaphragm (Fig. 12-3 (Figure Not Available) , than in the more peripheral adductor of the thumb. Neuromuscular blockade develops faster, lasts a shorter time, and recovers more quickly in these muscles. Since several studies have been done (Table 12-2) that have measured the effects of neuromuscular blockers in the larynx, these data can be very useful clinically in precisely determining dosage for intubation, timing of intubation, and recovery time to levels of function compatible with airway protection.

Because neuromuscular blockade develops more rapidly in the airway than in the thumb, tracheal intubation can be performed before onset of complete block at the adductor

Figure 12-2 (Figure Not Available) Evolution of neuromuscular blockade in the larynx and thumb (adductor pollicis) following vecuronium (0.07 mg/kg). Onset and recovery from block occur more rapidly in the larynx. *(From Donati et al [23])*

pollicis. Onset of block in the larynx occurs 1 to 2 minutes earlier than at the adductor pollicis following administration of nondepolarizing neuromuscular blocking agents. The pattern of blockade (onset, depth, speed of recovery) in the orbicularis oculi is similar to that in the larynx. [33] By monitoring the onset of neuromuscular blockade at the orbicularis oculi, the quality of intubating conditions can be predicted. The onset of maximal block in the larynx also corresponds with the point where the adductor pollicis is beginning to show palpable evidence of weakening. Furthermore, because recovery in the airway musculature is faster than in the thumb, one can be sure that, once monitored responses in the thumb have been correctly diagnosed as having returned to normal, the identical responses in the airway musculature have already reached that point. In other words, return of thumb responses to normal suggests that the efferent muscular arc of protective airway reflexes is intact.

Clinical Conclusion: Choice of Relaxant and Testing of Recovery

It is not known what proportion of receptors must be available or how sensitive a test must be to ensure adequate

Figure 12-3 (Figure Not Available) Evolution of atracurium-induced blockade in the adductor pollicis and diaphragm following a dose of 0.6 mg/kg. Block develops and recovers more quickly in the diaphragm. *(From Pansard et al [24])*

muscle strength to overcome airway obstruction and permit effective coughing. The anesthesiologist should not rely on one test but should use as many tests as is practically possible (see Table 12-1) . For example, when the operative procedure is nearly finished and the patient is still under anesthesia, a tetanic stimulus of 50 Hz, TOF, twitch height, and inspiratory force may be used to determine whether a neuromuscular blockade has been antagonized completely. Then, with the patient awake, other tests, such as a 5-second head lift, can be employed. It is important to use several tests that stress the neuromuscular junction to detect subtle degrees of neuromuscular blockade. The results of Pavlin et al [31] and the frequent return to the recovery room of patients with partial paralysis [34] (i.e., not recognized by the anesthesiologist) emphasize the difficulty in clinically ensuring that no residual neuromuscular blockade exists after surgery and anesthesia. [35]

Several studies have found a much higher incidence of residual weakness in the postanesthesia care unit (PACU) following the administration of the long-acting drug pancuronium than following the use of the intermediateduration drugs vecuronium and atracurium. [36] [37] The findings of these studies document the much longer time required for adequate antagonism of deep levels of block induced

TABLE 12-2 -- Approximate Dose-Response of Some Neuromuscular Blocking Drugs in the Larynx[a]

DRUG	DOSE (mg/kg)	ONSET(s)	RECOVERY CHARACTERISTICS (min)		APPROXIMATE ED_{95} (mg/kg)
			TO 25% T_1	TO 90- 95% T_1	
SUCCINYLCHOLINE	1.0	34	4.3	8.0	0.50
VECURONIUM	0.07	88	9.3	23.3	0.10
ROCURONIUM	0.8	96	25.0	NA	0.8
	1.2	54	43.0	NA	
RAPACURONIUM (ORG 9487)	2.0	52	7.4	16.7 [b]	1.5-2.0
MIVACURIUM	0.14	137	5.7	16.4	0.16

[a] All studies done with train-of-four stimulation and recording of laryngeal adductor pressure responses. See text for references.
[b] To 75% recovery of T_1

by long-acting muscle relaxants than by those of intermediate duration. These observations suggest that the administration of long-acting relaxants to patients whose tracheas are to be extubated at the end of a procedure should be avoided. In such cases, even in rather long procedures (4 hours), it may be wiser to provide relaxation by infusion of intermediate or short-acting agents. The use of long-acting nondepolarizing neuromuscular blocking agents should be reserved for patients scheduled to remain intubated following lengthy and complicated procedures in order to facilitate continued mechanical ventilation in an intensive care unit or in the PACU.

Conversely, patients who are scheduled to undergo ambulatory surgical procedures and who are to be expected to function normally within minutes following the completion of the procedure should receive short- or intermediateacting relaxants for reasons of both safety and economy (see below).

CHEMISTRY

Molecular Features and Physiochemical Properties

Neuromuscular blocking drugs are quaternary ammonium compounds. Positive charges at these sites in the molecules mimic the quaternary nitrogen atom of the transmitter ACh and are the principal reason for the attraction of these drugs to cholinergic nicotinic receptors at the neuromuscular junction. These receptors are also located at other physiologic sites of action of ACh in the body, such as at nicotinic receptors in autonomic ganglia and at as many as three different muscarinic receptors on both the parasympathetic and sympathetic sides of the autonomic nervous system.

All relaxants are structurally related to ACh because of the quaternary groups. In some cases, such as pancuronium and vecuronium, entire ACh-like structures are intentionally incorporated into the molecule. The depolarizing relaxant succinylcholine is actually two molecules of ACh linked back-to-back through the acetate methyl groups (Fig. 12-4) ; hence, the older name "diacetylcholine."

Nearly all muscle relaxants contain two positive charges. In most of the drugs, the positive charges are permanent quaternary ammonium cations. In a few drugs, such as vecuronium, rocuronium, and dTc, there is one permanent quaternary cation and one tertiary amine that is protonated and therefore positively charged at physiologic pH. The two positive charges are separated by a bridging structure that is lipophilic and that varies in size. The bridging structure is different for various series of muscle relaxants and is also a major determinant of potency (see *Structure-Activity Relationships*).

Muscle relaxants are generally quite water-soluble, especially because of the quaternary groups. The water solubility of relaxants inhibits uptake into hepatocytes, so metabolism and/or excretion in the liver is usually not a major pathway of elimination. Furthermore, the cytochrome P-450 oxidative enzyme system in liver microsomes requires lipophilic substrates, generally excluding the relatively hydrophilic muscle relaxants. There are a few minor exceptions to this general

Figure 12-4 Structural relationship of succinylcholine, a depolarizing agent, and pancuronium, a nondepolarizing agent, to acetylcholine, the neuromuscular transmitter. Succinylcholine, originally called diacetylcholine, is simply two molecules of acetylcholine linked through the acetate methyl groups. Like acetylcholine, succinylcholine stimulates cholinergic receptors at the neuromuscular junction and at nicotinic (ganglionic) and muscarinic autonomic sites. Pancuronium may be viewed as two acetylcholine-like fragments properly oriented on a steroid nucleus. Pancuronium and other nondepolarizers inhibit the actions of acetylcholine at neuromuscular and autonomic cholinergic receptors.

lack of liver elimination, such as vecuronium, rocuronium, and ORG 9487 (rapacuronium) among the steroid-based relaxants.

The muscle relaxants display the hydrophilic physicochemical properties of cations in watery media such as the plasma and urine. Other chemical features of relaxants that promote either water solubility or hydrophilic properties or both are various oxygen-bearing groups. Some of these are the ester linkages of succinylcholine, mivacurium, cisatracurium, and atracurium; the acetate groups of pancuronium, vecuronium, rocuronium, and ORG 9487; the ether linkages of metocurine and dTc; the hydroxyl groups of dTc and alcuronium; and the methoxy groups of dTC, metocurine, doxacurium, mivacurium, cisatracurium, and atracurium (see *Individual Nondepolarizing Relaxants* for chemical formulas).

Because of their water solubility, the muscle relaxants are easily excreted by glomerular filtration in the urine. Urinary excretion is the principal route of elimination for the entire class of drugs as a whole. Similarly, their high water solubility generally prevents the passage of relaxants across lipoid membranous barriers, such as the blood-brain and placental barriers, and the lipid membranes of most cells, such as renal tubular cells, hepatocytes, nerve and muscle cells, and red blood cells.

Sources and Synthesis

Several relaxants are still purified from naturally occurring sources. For example, although dTc can be synthesized,

it is still the least expensive to obtain from the amazonian vine *Chondodendron tomentosum.* Similarly, the intermediates for the production of metocurine and alcuronium, which are semisynthetic, are obtained from *Chondodendron* and *Strychnos toxifera.* In fact, although pancuronium and vecuronium are entirely synthesized, their ancestor, Malouetine, the first steroidal neuromuscular blocking drug, was originally isolated from *Malouetia bequaertiana,* which grows in the jungles of Zaire in central Africa.

Atracurium, succinylcholine, pipecuronium, doxacurium, vecuronium, ORG 9487, mivacurium, rocuronium, cisatracurium, and gallamine are entirely synthetic. In any case, the final step in the synthesis of muscle relaxants is quaternization, which converts lipophilic tertiary amines into neuromuscular blocking drugs. In two cases, those of atracurium and cisatracurium, this final synthetic step has been taken advantage of as a source of potential drug degradation and inactivation, namely the Hofmann elimination reaction (see the section titled *Metabolism*).

Structure-Activity Relationships

There are many classic structure-activity relationships among neuromuscular blocking drugs. Bovet [38] originally noted structural differences between depolarizing muscle relaxants (leptocurares), which are long, thin, flexible molecules, and nondepolarizing muscle relaxants (pachycurares), which are large, heavy, rigid ring systems into which the quaternary groups are incorporated.

An optimum interonium distance (between two quaternary nitrogen atoms) of 12 to 14 angstrom (A) units (1.2-1.4 nm) was thought to be required for high neuromuscular blocking activity. Since the early 1960s, however, this concept has gradually lost importance. Although succinylcholine and decamethonium in their "extended" conformations may show interonium distances of 12 to 14 A, dTc, the toxiferines (alcuronium), and the steroids (pancuronium, vecuronium, and others) show internitrogen distances of only 10 to 11 A (1.0-1.1 nm). In addition, the second nitrogen of dTc, vecuronium, and rocuronium is a tertiary amine that is protonated at physiologic pH. These drugs are therefore really monoquaternaries, and gallamine is a trisquaternary structure. Thus, neuromuscular blocking potency need not be associated with a bisquaternary structure. Nevertheless, mivacurium, cisatracurium, and atracurium are bisquaternaries, but their internitrogen distances are between 21 A and 18 A. Thus, many of the old rules obviously no longer apply as to what structures are required to impose neuromuscular blocking properties on a compound.

Some other structure-activity correlations are:

Steroids/Ganglion Blockade.

A fixed interonium distance of 8 A seems to promote ganglion-blocking activity in steroidal bisquaternaries. [39] On the other hand, this type of side effect is minimized at 10, 18, and 21 A (pancuronium, rocuronium, vecuronium, atracurium, cisatracurium, mivacurium).

Gallamine/Muscarinic Blockade.

Muscarinic blocking properties (vagolytic effect) appear prominent in trisquaternary substances (gallamine).

Steroids/Muscarinic Blockade.

In steroidal-based neuromuscular blocking drugs, muscarinic blockade has always been a notable side effect (pancuronium) until recently, when this side effect was found to be largely due to the ACh-like substitution at positions 2 and 3 of the A-ring. This was corrected by Savage and colleagues simply by removing the quaternizing methyl group in the 2-position. This eliminates the positive charge, reducing the ACh-like character, and markedly reduces the antimuscarinic (vagolytic) property (vecuronium). [9] [10] [40] [41]

Potency/Onset.

Removal of both acetoxy groups from vecuronium results in an experimental relaxant of low potency but high affinity for cardiac muscarinic receptors. Although such a compound is clinically not useful because of its cardiovascular effects, Bowman et al [42] noted that lowpotency compounds have a rapid onset of action (see Fig. 12-6) . This original hypothesis is being proven clinically, where steroidal relaxants of low potency such as rocuronium and ORG 9487 (rapacuronium) do promote faster onset of blockade than the more potent drugs pancuronium and vecuronium.

Benzylisoquinolines/Histamine Release.

Benzylisoquinoline substances (dTc, metocurine, atracurium, and mivacurium) tend to cause release of histamine. In metocurine, mivacurium, and atracurium, this tendency is reduced by the methoxy group substitutions. It is further reduced in atracurium by the electron-withdrawing effect of the carboxyl groups in the chain and by specific stereochemistry (*cis* orientation) at the 1- to 2-positions in the benzylisoquinoline structure. [43] [44] For example, cisatracurium, the R- *cis,* R - *cis* isomer of atracurium, does not cause histamine release in the clinical dose-range and is the second benzylisoquinolinium (after doxacurium) to be largely free of this side effect. [45] [46]

Stereochemistry.

Studies of atracurium's isomers have shown that the phenomenon of histamine release may be stereospecific. The original observations of Wastila and colleagues [45] [46A] may lead to reduction of this side effect in other compounds related to cisatracurium and mivacurium.

PHARMACOLOGY OF SUCCINYLCHOLINE

Pharmacokinetics and Pharmacodynamics

The extremely brief duration of action of succinylcholine is primarily due to its rapid hydrolysis by pseudocholinesterase (plasma cholinesterase, butyrylcholinesterase), an enzyme of the liver and plasma. The initial metabolite (succinylmonocholine) is a much weaker neuromuscular blocker that is metabolized much more slowly to succinic acid and choline. Pseudocholinesterase has an enormous capacity to hydrolyze succinylcholine at a very rapid rate such that only a small fraction of the original intravenous dose actually reaches the neuromuscular junction. Because there is little or no pseudocholinesterase at the neuromuscular junction, the neuromuscular block of succinylcholine is terminated

by its diffusion away from the neuromuscular junction back into the circulation. Pseudocholinesterase, therefore, influences the onset and duration of action of succinylcholine by controlling the rate at which the drug is hydrolyzed before and after it reaches the neuromuscular junction.

Neuromuscular block induced by succinylcholine can be prolonged by a decreased concentration of normal enzyme or by the presence of an atypical form of the enzyme. Factors that have been described as lowering pseudocholinesterase concentration are liver disease, [47] pregnancy, burns, oral contraceptives, monoamine oxidase inhibitors, echothiophate, cytotoxic drugs, neoplastic disease, [37] anticholinesterase drugs, [48] [49] tetrahydroaminacrine, [50] hexafluorenium, [51] [52] and metoclopramide. [53] The histamine type 2 receptor antagonists have no effect on pseudocholinesterase activity or duration of succinylcholine effect. [54] Bambuterol, a pro-drug of terbutaline, produces marked inhibition of pseudocholinesterase activity and causes prolongation of succinylcholine-induced block. [55] [55A] The beta blocker esmolol inhibits pseudocholinesterase but causes only an insignificant prolongation of succinylcholine block. [55B] [55C]

Although not yet demonstrated in all cases, those drugs that influence the duration of action of succinylcholine by inhibiting pseudocholinesterase probably have a broadly similar effect on the nondepolarizing drug mivacurium, which is also hydrolyzed by pseudocholinesterase (see section on mivacurium).

Despite all the publications and efforts identifying those situations in which the normal pseudocholinesterase enzyme concentration may be low, this is not a major concern in clinical practice. In a study conducted by Foldes et al, [47] it was found that when pseudocholinesterase activity was reduced to 20 percent of normal by severe liver disease, the duration of apnea after the administration of succinylcholine was increased from a normal duration of 3 minutes to almost 9 minutes. Even when glaucoma treatment with echothiophate decreased pseudocholinesterase activity from 49 percent of control to no activity, the increase in duration of neuromuscular blockade varied from 2 to 14 minutes. In no patient did the total duration of neuromuscular blockade exceed 23 minutes. [55D] In an extensive clinical study, VibyMogensen [56] confirmed these observations that duration of blockade from the usual clinical dose of succinylcholine is only moderately increased by low cholinesterase levels (Fig. 12-5) (Figure Not Available) . Thus, if repeated doses are given only when recovery from the previous dose of succinylcholine is evident, low pseudocholinesterase levels should only slightly prolong a succinylcholine or mivacurium-induced blockade.

Figure 12-5 (Figure Not Available) Correlation between duration of succinylcholine neuromuscular blockade and pseudocholinesterase activity. Normal range of activity lies between arrows. *(From Viby-Mogensen [56])*

Dibucaine Number and Pseudocholinesterase Activity

A succinylcholine neuromuscular blockade can be prolonged if the patient has an abnormal genetic variant of pseudocholinesterase. The variant was found by Kalow and Genest [57] to respond to dibucaine differently than does normal pseudocholinesterase. Dibucaine inhibits normal pseudocholinesterase to a far greater extent than the abnormal enzyme. This observation led to the development of the test for dibucaine number. Under standardized test conditions, dibucaine inhibits the normal enzyme about 80 percent and the abnormal enzyme about 20 percent (Table 12-3) . Subsequently, many other genetic variants of pseudocholin- esterase have been identified, although the dibucaineresistant variants are the most important. Reviews by Pantuck [58] and Jensen and Viby-Mogensen [58A] can be consulted for more detailed information on this topic.

Although the dibucaine number indicates the genetic makeup of an individual with respect to pseudocholinesterase, it does not measure the concentration of the enzyme in the plasma, nor does it indicate the *efficiency* of the enzyme in hydrolyzing a substrate such as succinylcholine or mivacurium. Both the latter factors are accounted for in measurements of pseudocholinesterase *activity.* The activity of the enzyme refers to the number of substrate molecules (mumol) hydrolyzed per unit of time, often expressed in international units (IU). Pseudocholinesterase

TABLE 12-3 -- Relationship Between Dibucaine Number and Duration of Succinylcholine or Mivacurium Neuromuscular Block

TYPE OF PSEUDOCHOLINESTERASE	GENOTYPE	INCIDENCE	DIBUCAINE NUMBER[a]	RESPONSE TO SUCCINYLCHOLINE OR MIVACURIUM
Homozygous typical	$E_1^{u} E_1^{u}$	Normal	70-80	Normal
Heterozygous atypical	$E_1^{u} E_1^{a}$	1/480	50-60	Lengthened by about 50-100%
Homozygous atypical	$E_1^{a} E_1^{a}$	1/3,200	20-30	Prolonged to 4-8 hours

[a] The dibucaine number indicates the percentage of enzyme inhibited.

activity is certainly markedly influenced by the genotype but is also dependent on the concentration of enzyme in plasma. The latter may vary due to nutritional factors as well as to genetic background. A number of well-known drug interactions with pseudocholinesterase may lower its activity in plasma. Among those are the standard anticholinesterases neostigmine and pyridostigmine (but not edrophonium), pancuronium, alkylating agents, and echothiophate as well as other organophosphates used as active ingredients in insecticides.

The molecular biology of pseudocholinesterase is now well understood. The amino acid sequence of the enzyme is well known, and the coding errors responsible for most genetic variations have been identified. [58] [58A] Most variants are due to a single amino acid substitution error or sequencing error at or near the active site of the

enzyme. For example, in the case of the "atypical" dibucaine-resistant (A) gene, a mutation occurs at nucleotide 209, where guanine is substituted for adenine. The resultant change in this codon causes substitution of glycine for aspartic acid at position 70 in the enzyme. In the case of the fluoride-resistant (F) gene, two amino acid substitutions are possible, namely, methionine for threonine at position 243 and valine for glycine at position 390. Table 12-4 (Table Not Available) summarizes many of the known genetic variants of plasma cholinesterase: the amino acid substitution at position 70 is written as Asp
Gly. New variants of pseudocholinesterase genotypes continue to be discovered. [58B] [58C]

Cardiovascular Effects

Succinylcholine-induced cardiac arrhythmias are many and varied. The drug stimulates all cholinergic autonomic receptors: nicotinic receptors on both sympathetic and parasympathetic ganglia [59] and muscarinic receptors in the sinus node of the heart. In low doses, both negative inotropic and chronotropic responses may occur. These can be attenuated by prior administration of atropine. With large doses of succinylcholine, these effects may become positive. [60] One prominent clinical manifestation of this generalized autonomic stimulation is the development of cardiac arrhythmias. These are principally manifested as sinus bradycardia, junctional rhythms, and ventricular arrhythmias, ranging from unifocal premature ventricular contractions to ventricular fibrillation in certain special circumstances such as burns. Reports of clinical studies have noted these arrhythmias under various conditions in the presence of the intense autonomic stimulus of tracheal intubation; it is not entirely clear whether the cardiac irregularities are due to the action of succinylcholine alone or to the added presence of extraneous autonomic stimulation.

Sinus Bradycardia

The autonomic mechanism involved in sinus bradycardia is stimulation of cardiac muscarinic receptors in the sinus node, particularly in individuals with high sympathetic tone, such as children who have not received atropine. [61] [62] Sinus bradycardia has also been noted in adults and appears more commonly after a second dose of the drug is given approximately 5 minutes after the first. [63] The bradycardia may be prevented by thiopental, [64] [64A] atropine, [64] ganglion-blocking drugs, and nondepolarizing muscle relaxants, [64] [65] the implication being that direct myocardial effects, increased muscarinic stimulation, and ganglionic stimulation may all be involved in the bradycardiac response. The higher incidence of bradycardia after a second dose of succinylcholine [65] suggests that the hydrolysis products of succinylcholine (succinylmonocholine and choline) may sensitize the heart to a subsequent dose.

Nodal (Junctional) Rhythms

Nodal rhythms commonly occur as bradycardias that are slower than the sinus rate measured before the administration of succinylcholine and intubation of the trachea. The mechanism probably involves relatively greater stimulation of muscarinic receptors in the sinus node, suppressing the sinus mechanism and allowing the emergence of the atrioventricular node as the pacemaker. The incidence of junctional rhythm is greater after a second dose of succinylcholine but is prevented by prior administration of dTc. [64] [65]

TABLE 12-4 -- Human Plasma Cholinesterase Variants[a]

(Not Available)

Modified from Pantnel [58]

[a] Shown are variants whose structures were published before 1993

Ventricular Arrhythmias

Under stable anesthetic conditions, succinylcholine lowers the threshold of the ventricle to catecholamine-induced arrhythmias in the monkey and the dog. Circulating catecholamine concentrations increase 4-fold and potassium increases by one-third after succinylcholine administration in dogs. [66] Similar increases in catecholamines in response to succinylcholine are also observed in humans. [66A] [66B] Other autonomic stimuli, such as endotracheal intubation, [66C] hypoxia, hypercarbia, and surgery, are probably additive to the effect of succinylcholine. To these stimuli must be added the possible influence of drugs such as digitalis, tricyclic antidepressants, monoamine oxidase inhibitors, exogenous catecholamines, and anesthetic drugs such as halothane and cyclopropane, all of which may lower the ventricular threshold for ectopic activity or increase the arrhythmogenic effect of the catecholamines. Ventricular escape beats may also occur as a result of severe sinus and atrioventricular nodal slowing secondary to succinylcholine administration. The incidence of ventricular arrhythmias is further encouraged by the release of potassium from skeletal muscle as a consequence of the depolarizing action of the drug.

Complications

Pediatric

In recent years, attention has been called to the development of intractable cardiac arrest in hitherto apparently healthy children and adolescents who were given succinylcholine. [66D] In many of these cases, hyperkalemia, rhabdomyolysis, and acidosis have been documented. From muscle biopsy samples obtained after the event, subclinical Duchenne muscular dystrophy is a frequently associated pathologic feature.

Because these catastrophic events have occurred in previously asymptomatic children and have led to death in as many as 60 percent of such cases, the Malignant Hyperthermia Associations of the United States and Germany have strongly advised the discontinuation of succinylcholine administration to children. In the United States, the U.S. Food and Drug Administration has responded by including the following wording in the Glaxo-Wellcome package insert for succinylcholine: "it is recommended that the use of succinylcholine in children should be reserved for emergency intubation or instances where immediate securing of the airway is necessary...." It is still not clearly defined what age group is defined by "children," but in practice the group at highest risk is males 8 years old and younger (see package insert; also see sections on hyperkalemia and neuromuscular disease and Ch. 31). In view of the currently, available supply of nondepolarizing relaxants that may readily be substituted for succinylcholine, this seems a prudent and timely change in policy. In particular, the place of succinylcholine as the sole relaxant for intramuscular use has now been occupied as well by rocuronium. [66E] The administration into the deltoid of rocuronium 1.0 mg/kg (infants) and 1.8 mg/kg (children) permitted tracheal intubation in 2.5 to 3.0 minutes, albeit with a duration of action of approximately 2 hours. [66E] The new drug ORG 9487 (rapacuronium) has a shorter duration of action than rocuronium and may be more suitable as an alternative to succinylcholine for intramuscular administration. This possibility has yet to be investigated.

Hyperkalemia

Clinical reports and experimental studies have clearly shown that, in patients with certain diseases or conditions, an exaggerated release of potassium in response to succinylcholine may occur, occasionally of such magnitude that cardiac arrest ensues. [66D] [66G] Conditions that render the patient especially susceptible to the hyperkalemic response from succinylcholine are burns, trauma, nerve damage, neuromuscular disease, closed head injury, intra-abdominal infections, and renal failure. [66G]

Burns

See the section on burns for a full discussion.

Trauma

In studying soldiers who had undergone trauma associated with the Vietnam War, Birch et al [67] found that a significant increase in serum potassium did not occur in 59 patients until about 1 week after the injury, at which time a progressive increase in the serum potassium level occurred after the infusion of succinylcholine. Three

weeks after injury, three of these patients with especially severe injuries showed a marked hyperkalemia with increase in serum potassium of > 3.6 mEq/L, sufficient to cause cardiac arrest. Birch and coworkers [67] found that administration of dTc (6 mg IV) prevented the hyperkalemic response to succinylcholine. As with burns, in the absence of infection or persistent degeneration of tissue, a patient is susceptible to the hyperkalemic response probably for at least 60 days following massive trauma or until adequate healing of damaged muscle has occurred.

Nerve Damage or Neuromuscular Disease

Cooperman [68] described 40 patients with neuromuscular disease, 15 of whom had an increase in serum potassium of from 1 to 6 mEq/L after intravenous administration of succinylcholine (1 mg/kg). In another instance, Cooperman et al [69] reported a hyperkalemic response, one of which was 9.05 mEq/L, in three patients with hemiplegia or paraplegia secondary to upper motor neuron lesions. These investigators concluded that the vulnerable period appears to be within the first 6 months after the onset of hemiplegia or paraplegia and within a longer period of time in patients with progressive disease such as muscular dystrophy. Cooperman and colleagues speculated that in the latter instance, progressive muscle-wasting or other structural change accounted for the prolonged susceptibility. [69] They also found the degree of hyperkalemia to correlate with the degree and

extent of muscle affected. The greatest extent of hyperkalemia was found in those patients with greater neurologic deficit and involvement of more muscle mass. For an in-depth discussion of the clinical and pathophysiologic aspects of succinylcholine-induced hyperkalemia, the reader is referred to the review by Gronert and Theye. [70]

Closed Head Injury

Stevenson and Birch [71] described a single, well-documented case of a marked hyperkalemic response to succinylcholine in a patient with a closed head injury without peripheral paralysis.

Intra-Abdominal Infections

Kohlschutter et al [72] found that four of nine patients with severe abdominal infections had an increase in serum potassium (2.5 to 3.1 mEq/L) from succinylcholine. These researchers concluded that in the case of intra-abdominal infection that persisted longer than 1 week, the possibility of hyperkalemic response to succinylcholine should be considered.

Renal Failure

Several early case reports have suggested that patients with renal failure may be susceptible to a hyperkalemic response to succinylcholine. [73] [74] Nevertheless, more controlled studies have shown that renal failure patients are no more susceptible to an exaggerated response to succinylcholine than are those with normal renal function. [75] [76] [77] [78] [79] [80] In one author's (RDM) experience, in anesthetizing hundreds of patients with renal failure, succinylcholine may be a suitable alternative because of its lack of dependence on renal excretion for its elimination. One might postulate that patients who have uremic neuropathy may be susceptible to succinylcholine-induced hyperkalemia, although the evidence supporting this view is scanty. [79] [80] [80A] Because a number of nondepolarizing relaxants are now available that depend little or only partially on the kidney for elimination (e.g. atracurium, mivacurium, cisatracurium, vecuronium, and rocuronium), there are many alternatives to succinylcholine for muscle relaxation in patients with renal disease.

Metabolic Acidosis

It is less well appreciated that severe hyperkalemia may also follow the administration of succinylcholine to patients with severe metabolic acidosis and hypovolemia. [80B] In rabbits, the combination of metabolic acidosis and hypovolemia results in a high resting potassium and an exaggerated hyperkalemic response to succinylcholine. [80C] In this situation, the potassium originates from the gastrointestinal tract and not from muscle as in the classic hyperkalemic response. [80D] In patients with metabolic acidosis and hypovolemia, correction of the acidosis by hyperventilation and sodium bicarbonate administration should be attempted before succinylcholine administration. Should severe hyperkalemia occur, it can be treated with immediate hyperventilation, calcium chloride 1.0 to 2.0 mg intravenously, sodium bicarbonate 1 mEq/kg, and glucose (25-50 g) plus soluble insulin (10-20 U). [80E]

Increased Intraocular Pressure

Succinylcholine usually causes an increase in intraocular pressure (IOP). The increased IOP is manifested within 1 minute after injection, peaks at 2 to 4 minutes, and subsides by 6 minutes. [81] The mechanism by which succinylcholine increases IOP has not been clearly defined, but it is known to involve contraction of tonic myofibrils and/or transient dilatation of choroidal blood vessels. Apparently, sublingual administration of nifedipine will attenuate the increase in IOP from succinylcholine, suggesting a circulatory mechanism. [82] Despite this increase in IOP, the use of succinylcholine for eye operations is not contraindicated unless the anterior chamber is open. Although Meyers et al [83] were unable to confirm the efficacy of precurarization in attenuating increases in IOP following succinylcholine, numerous other investigators have found that prior administration of a subparalyzing dose of nondepolarizing relaxant (3 mg dTc, or 1 mg pancuronium) will prevent a succinylcholine-induced increase in IOP. [84] [85] Despite this discrepancy, one author (RDM) has successfully used this approach many times in providing anesthesia for patients undergoing eye surgery. Furthermore, Libonati et al [86] described the anesthetic management of 73 patients with penetrating eye injuries who received succinylcholine: no loss of global contents resulted. Thus, despite the theoretical objections expressed by Meyers and coworkers, [83] Libonati et al [86] and the authors of this chapter conclude that the use of succinylcholine in patients with penetrating eye injuries with a carefully controlled rapidsequence induction of anesthesia (including pretreatment with a nondepolarizing muscle relaxant) is an acceptable technique (Ch. 67) . As part of the total picture, succinylcholine is only one of many factors, which include endotracheal intubation and "bucking" on the tube, that may elevate IOP. [83] Of prime importance is ensuring that the patient is well anesthetized and is not straining. There are several approaches to accomplishing this goal, such as additional intravenous anesthetic drugs, deeper inhalation anesthesia, topical anesthesia to the trachea, or additional muscle relaxant, preferably a nondepolarizer.

There are probably three situations in which succinylcholine should either be avoided or the above measures taken to prevent its increasing IOP: if the patient is about to undergo repair of an ocular laceration, if the patient is about to have repair of a recent ocular surgical incision that is coming apart, or if the patient's anesthesia lightens during intraocular surgery. In the last case, succinylcholine should not be given to quiet the patient, but the surgeon should be asked to pause while anesthesia is deepened without the use of muscle relaxants or while the depth of nondepolarizing block is increased. [87]

Increased Intragastric Pressure

Unlike the rather consistent increase in IOP, the increase in intragastric pressure (IGP) from succinylcholine is quite

variable. In fact, Miller and Way [88] found that 11 of 30 patients essentially had no increase in IGP. Yet 5 of 30 patients had an increase in IGP greater than 30 cm H_2O. The increase in IGP from succinylcholine appeared to be related to the intensity of fasciculations. Accordingly, when fasciculations were prevented by prior administration of gallamine (20 mg) or dTc (3 mg), no increase in IGP was observed.

The increase in IGP from succinylcholine is presumed to be due to fasciculations of the abdominal skeletal muscle. This is not surprising because more coordinated abdominal skeletal muscle activity (e.g. straight leg-raising) may increase IGP to values as high as 120 cm H_2O. In addition to skeletal muscle fasciculations, the ACh-like effect of succinylcholine may be partly responsible for the observed increases in IGP. Greenan [89] observed consistent increases in IGP of 4 to 7 cm H_2O with direct vagal stimulation. Therefore, prior administration of vagolytic drugs may partly inhibit succinylcholine-based increases in IGP.

Are the increases in IGP following succinylcholine administration enough to cause incompetence of the gastroesophageal junction? Generally, IGP of greater than 28 cm H_2O is required to overcome the competence of the gastroesophageal junction. However, when the normal oblique angle of entry of the esophagus into the stomach is altered, as may occur with pregnancy, an abdomen distended by ascites, bowel obstruction, or a hiatus hernia, the IGP required to cause incompetence of the gastroesophageal junction is frequently less than 15 cm H_2O. [88] In these circumstances, regurgitation of stomach contents following succinylcholine is a distinct possibility, and precautionary measures should be taken to prevent fasciculation, or an appropriate nondepolarizing relaxant technique may be substituted (see the section *Dosage for Rapid Intubation of the Trachea*).

Apparently, succinylcholine does not increase IGP appreciably in infants and children. This may be related to the minimal or absent fasciculations from succinylcholine in these age groups. [90]

Muscle Pains

The incidence of muscle pain following administration of succinylcholine varies from 0.2 to 89 percent. [91] It occurs more frequently following minor surgery, especially in women and in ambulatory rather than bedridden patients. [92] Waters and Mapleson [92] postulated that pain is secondary to damage produced in muscle by the unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis. That damage to muscle may occur has been substantiated by finding myoglobinemia and increases in serum creatine kinase following succinylcholine administration. [93] [93A] [93B] Prior administration of a subparalyzing dose of nondepolarizing muscle relaxant clearly prevents fasciculations from succinylcholine. [94] But the efficacy of this approach in preventing muscle pain is questionable. Although some investigators claim that pretreatment with a subparalyzing dose of nondepolarizing muscle relaxant has no effect, [91] most believe that the pain from succinylcholine is at least attenuated. [94A] [94B] [94C]

Miller [95] believes that the practice of preceding succinylcholine administration with a small dose of nondepolarizing muscle relaxant should be routine. The fasciculations certainly in no way are desirable. Furthermore, postoperative muscle pains and elevated IOP and IGP will be decreased or eliminated. Succinylcholine-induced increases in serum creatine phosphokinase and myoglobinuria may be attenuated as well. Although the succinylcholine dose should be increased by 50 percent, this appears to present no problems. [95] However, the use of a defasciculating dose of a nondepolarizing relaxant may slow the onset of succinylcholine and produce poorer conditions for tracheal intubation. [94B] [94C] The incidence of myalgia can reportedly be reduced without the use of a nondepolarizing relaxant by increasing the dose of succinylcholine to 3.0 mg/kg, which in addition produces excellent conditions for tracheal intubation. [93B] The incidence of myalgia can reportedly be reduced without affecting fasciculations or running the risk of the patient developing premature muscle weakness if succinylcholine 1.5 mg/kg is administered just 1 minute after dTc in a dose of 3 mg/70 kg. [95A]

Intracranial Pressure

Succinylcholine clearly has the potential to increase intracranial pressure (Ch. 56) . [95B] The mechanisms and clinical significance of this transient increase are unknown, but the rise in intracranial pressure does not occur following pretreatment with dTc. [95C] In patients in whom an increase in intracranial pressure may be harmful, an appropriate nondepolarizing relaxant should be substituted (see *Dosage for Rapid Intubation of the Trachea*).

Masseter Spasm

Succinylcholine causes masseter spasm, especially in children. [95D] [96] In all likelihood, this is an exaggerated contractile response at the neuromuscular junction and cannot be used to establish a diagnosis of malignant hyperthermia. There is currently no evidence that masseter spasm is a prodrome of malignant hyperthermia and no indication to change to a "nontriggering" anesthetic. [95D]

Interactions With Nondepolarizing Muscle Relaxants, Neostigmine, and Pyridostigmine

The interaction of succinylcholine with nondepolarizing muscle relaxants is complex, depending on whether succinylcholine is administered before or after the nondepolarizer. Both types of relaxants are administered concomitantly in three possible situations:

1. Succinylcholine is commonly given to facilitate intubation of the trachea, and then a nondepolarizing relaxant is administered. Succinylcholine given first may enhance the depth of block induced by a subsequent dose of nondepolarizing relaxant. [97] [98] [99] However, the effect on duration of action is variable; succinylcholine has no effect on pancuronium,

pipecuronium, or mivacurium [99] [100] but increases the duration of atracurium and rocuronium. [97] [98] The causes of these differences are not clear.
2. A small dose of nondepolarizing relaxant is commonly given before administration of succinylcholine to prevent some of the adverse affects of the latter. This approach is discussed in the section on myalgia.
3. A nondepolarizing relaxant can be injected for prolonged relaxation, and then the shorter-acting succinylcholine can be given to facilitate closure of the peritoneum. The amount of succinylcholine required for adequate relaxation in this case is directly dependent on the amount of residual effect of nondepolarizer present. [101] Despite the questionable pharmacologic reasoning, concomitant administration of an AChR-antagonist (the nondepolarizing relaxant) and an AChR-agonist (succinylcholine) appears to be clinically effective. [95] Whether it is the best way to solve the problem is the subject of considerable debate. Many prefer to give an additional dose of nondepolarizer that can be easily antagonized at the end of the operation or to deepen anesthesia. The latter two approaches seem more reasonable, certainly make better sense from a pharmacologic point of view, and are recommended by the authors.

In fact, current practice with intermediate- and shortacting nondepolarizing relaxants allows for greater control of the depth of neuromuscular blockade, such that block depth at the end of the procedure should have been adjusted to reach levels easily antagonized by anticholinesterases. Maintenance of relaxation by continuous infusion readily facilitates control of block depth. The latest studies of antagonism of residual blockade have clearly shown a more rapid and complete antagonism of blockade produced by intermediate- and short-acting relaxants than by longacting drugs. [36] [37] [102] The speed of antagonism of blockade is probably related to the rate of clearance of the relaxant and is inversely related to the half-life (see *Antagonism of Residual Neuromuscular Blockade*). Taken together, these factors suggest that (1) the practice of deepening block at the end of a case (e.g. for peritoneal closure) by injecting succinylcholine following long-acting nondepolarizers is not only pharmacologically incorrect, it is probably obsolete; and (2) maintenance of blockade for long cases (3-4 hours) with long-acting drugs may no longer be the preferred technique if the trachea is to be extubated early and rapid recovery of normal neuromuscular function is to be produced. It may be wiser and safer to maintain the blockade by administration of intermediate- or short-acting drugs in such cases, either by repetitive bolus dosing or by infusion.

Another interaction with succinylcholine involves neostigmine or pyridostigmine. For example, after dTc has been used for an intra-abdominal surgery of long-duration and the neuromuscular blockade has been reversed by neostigmine, the surgeon announces another 15 minutes is needed to retrieve a missing sponge. Should succinylcholine be given? The authors' experience is that succinylcholine (100 mg/70 kg IV) produces a neuromuscular blockade that normally lasts 5 to 10 minutes but may last up to 60 minutes when given soon after administration of neostigmine (5 mg). Sunew and Hicks [49] found that the effect of succinylcholine (1 mg/kg) was prolonged from 11 to 35 minutes when given 5 minutes after administration of neostigmine (5 mg). This can partly be explained by inhibition of pseudocholinesterase by neostigmine and, to a lesser extent, by pyridostigmine.

Clinical Management

The changing characteristics of succinylcholine neuromuscular blockade from a clinical point of view have been nicely reviewed by Lee and Katz [103] (Table 12-5) (Table Not Available) .

TOF stimulation has proven to be a very safe and useful guide in detecting the transition from a phase 1 to a phase 2 block (see Table 12-5) (Table Not Available) . Clearly, both the dose and the duration of administration of succinylcholine are important variables, although the relative contribution of each has not been established. Practically, if the administration of the drug is terminated shortly after TOF fade is clearly evident, rapid return of normal neuromuscular function should ensue. Also, the decision whether to attempt antagonism of a phase 2 block has always been controversial. However, it is now clear that if the TOF ratio is less than 0.4, administration of edrophonium or neostigmine should result in prompt antagonism. Ramsey et al [104] recommended that antagonism of a succinylcholine-induced

phase 2 block with edrophonium or neostigmine be attempted after spontaneous recovery

TABLE 12-5 -- Clinical Characteristics of Phase 1 and Phase 2 Neuromuscular Blockade During Succinylcholine Infusion

(Not Available)

Adapted from Lee and Katz [103]

of the twitch has been observed for 20 to 30 minutes and has reached a plateau phase with further recovery proceeding slowly. These researchers state that, in this situation, edrophonium and neostigmine invariably produce "dramatic" acceleration of the return of the TOF ratio toward normal. According to Ramsey et al, the dosage guideline in Table 12-5 (Table Not Available) applies only to halothane or to enflurane anesthesia. With nitrous oxide anesthesia supplemented by intravenous drugs, the dosage guidelines are more variable. In any event, monitoring neuromuscular function via peripheral nerve stimulation, such as with the TOF response, will help avoid succinylcholine overdose, detect development of phase 2 block, observe its rate of recovery, and assess the effect of edrophonium or neostigmine on recovery. The authors no longer see good reason for administration of succinylcholine for maintenance of neuromuscular blockade because of the availability of intermediate- and shortacting nondepolarizing relaxants such as atracurium, cisatracurium, vecuronium, rocuronium, and mivacurium. These drugs may be conveniently administered by repeated bolus or by infusion for periods of hours, with little concern for tachyphylaxis. After either infusion or repeated bolus administration of these intermediate- or short-acting drugs, spontaneous recovery occurs rapidly and/or residual blockade is readily antagonized.

PHARMACOLOGY OF NONDEPOLARIZING MUSCLE RELAXANTS

Introduction

Available nondepolarizing relaxants include a variety of agents that can be classified according to chemical class (the steroidal compounds and the benzylisoquinolinium substances) or according to duration of action (long-, intermediate-, and short-acting drugs). All the nondepolarizers block the neuromuscular junction by competitive inhibition of ACh at nicotinic receptors. The block is antagonized by conventional doses of anticholinesterases. In addition, the clinical effects of all the nondepolarizers may be monitored in the same way, using twitch, tetanus, TOF, and double-burst modes of stimulation. Recommended dosing is summarized in Tables 12-2 , 12-6 , and 12-7 .

The clinical pharmacology of each individual nondepolarizing relaxant is summarized in a later section. A general discussion of these drugs follows. For comparative reviews of the clinical and basic pharmacology of this group of relaxants, see later sections on pharmacokinetics and pharmacodynamics, metabolism, autonomic and cardiovascular effects, and renal and hepatobiliary disease.

TABLE 12-6 -- Guide to Nondepolarizing Relaxant Dosage (mg/kg) Under Different Anesthetic Techniques [a]

DRUG	ED_{95} UNDER N_2O/O_2	DOSE FOR INTUBATION	SUPPLEMENTAL DOSE AFTER INTUBATION	DOSAGE FOR RELAXATION	
				N_2O	ANESTHETIC VAPORS[b]
Long-acting					
Pancuronium	0.07	0.08-0.12	0.02	0.05	0.03
Metocurine	0.28	0.3-0.4	0.05	0.2	0.1
d-Tubocurarine	0.5	0.5-0.6	0.1	0.3	0.15
Gallamine	3.0	4.0-6.0	0.5	2.0	1.0
Alcuronium	0.25	0.3	0.05	0.2	0.08
Doxacurium	0.025	0.05-0.08	0.005-0.01	0.025	0.02
Pipecuronium	0.05	0.08-0.1	0.01-0.015	0.04	0.03
Intermediate-acting					
Vecuronium	0.05	0.1-0.2	0.02	0.05	0.03
Atracurium	0.23	0.5-0.6	0.1	0.3	0.15
Cisatracurium	0.05	0.15-0.2	0.02	0.05	0.04
Rocuronium	0.3	0.6-1.0	0.1	0.3	0.15
Short-acting					
Mivacurium	0.08	0.2-0.25	0.05	0.1	0.08
Rapacuronium (ORG 9487)	1.15	1.5-2.0	0.3-0.5 [c]	1.0	0.6
Continuous infusions	Dosage (mug/kg/min) required to maintain 90-95% twitch inhibi-tion under N_2O/O_2 with intrave-nous agents				
Mivacurium	3-15				
Atracurium	4-12				
Cisatracurium	1-2				
Vecuronium	0.8-2				
Rocuronium	9-12				
Rapacuronium	40-60				

[a] Suggested dosages provide good intubating conditions under light anesthesia. Satisfactory abdominal relaxation may be achieved at dosages listed after intubation without a relaxant or with succinylcholine. This table is intended as a general guide to dosage. Individual relaxant requirement should be confirmed with a peripheral nerve stimulator.
[b] The potentiation of nondepolarizing relaxants by different anesthetic vapors has been reported to vary 20-50 percent. Recent data suggest, however, that this variation may be much less, particularly in the case of the intermediate- and short-acting relaxants. Therefore, for the sake of simplicity, this table assumes a potentiation of 40 percent in the case of all volatile anesthetics.
[c] Cumulation may occur on repeat dosage as early as after first "topping-up" dose.

TABLE 12-7 -- Rapid Tracheal Intubation [a] With Succinylcholine or Nondepolarizing Relaxants [b]

DRUG	PRIMING DOSE[c] (mg/kg)	INTUBATING DOSE[d] (mg/kg)	CLINICAL DURATION[e]	FULL RECOVERY[f]
Succinylcholine	None	1.0	5-10	12-15
Succinylcholine	Nondepolarizer pretreatment	1.5	5-10	12-15
Rapacuronium (ORG 9487)	None	1.5-2.0	15-30	35-55
Rocuronium	None	0.6-1.0	30-60	60-120

Mivacurium	0.02	0.25-0.3	15-20	25-35
Vecuronium	0.01	0.2	60-75	90-120
Vecuronium	None	0.3-0.4	90-150	120-180
Cisatracurium	0.01	0.25	55-75	75-100
Cisatracurium	None	0.4	75-100	100-120

[a] Intubation within 60 to 90 seconds following injection of the intubating dose of the relaxant
[b] The administration of adequate dosage of intravenous anesthetic is assumed.
[c] This dose is given as preoxygenation is begun.
[d] This dose is given 2 to 4 minutes following the priming dose. For atracurium and mivacurium, slower injection (30 seconds) is recommended to minimize circulatory effects.
[e] Minutes from injection of the intubating dose to recovery of twitch to 25 percent of control
[f] Minutes from injection of the intubating dose to recovery of twitch to 95 percent of control and train-of-four of .70

Classification by Chemical Structure

Steroidal Compounds: Pancuronium, Pipecuronium, Vecuronium, Rocuronium and ORG 9487 (Rapacuronium)

The advantages of this class of compounds include high potency and lack of histamine release. This class generally exhibits a vagolytic property. This side effect is moderate in pancuronium and ORG 9487, slight to moderate in rocuronium, and absent within the clinical dose range in pipecuronium and vecuronium. All steroidal relaxants are excreted by the kidney. The duration of action may be altered by modification of the lipophilic/hydrophilic balance in the molecule, with the more lipophilic substances such as vecuronium, rocuronium, and ORG 9487 showing intermediate or short-to-intermediate durations of effect because of greater uptake by the liver. The onset of action of steroidal substances is shortened in less potent molecules such as rocuronium and ORG 9487 (Fig. 12-6) . [42]

The steroidal relaxants are generally not extensively metabolized: about 30 to 40 percent of an injected dose of vecuronium undergoes deacetylation in the liver at the 3- position to an active metabolite, 3-OH vecuronium. Similarly, about 15 to 20 percent of pancuronium undergoes 3-deacetylation to 3-OH pancuronium. Both metabolites are active, having neuromuscular blocking potencies of 50 to 80 percent those of the parent compounds. Pipecuronium and rocuronium are not metabolized to any known significant extent. ORG 9487 undergoes a moderate amount of deacetylation at the 3-position to a metabolite (ORG 9488), which is longer lasting than, and two to three times as potent as, the parent compound (see sections on kinetics and dynamics, metabolism, and hepatic and renal disease).

Benzylisoquinolinium Compounds: d-Tubocurarine, Metocurine, Doxacurium, Atracurium, Cisatracurium, and Mivacurium

Advantages of this class include high potency and lack of vagolytic effect. This class generally exhibits a tendency to cause release of histamine. [44] This side effect is promi-nent in dTc, moderate in metocurine, slight in atracurium and mivacurium, and absent (beyond the clinical dose range) in doxacurium and cisatracurium. [14] [17] [44] [105] [106] The benzylisoquinolinium compounds are excreted by the kidney. There is a relatively unimportant biliary excretory pathway for dTc and doxacurium. In the benzylisoquinolinium esters, degradation by Hofmann elimination (atracurium and cisatracurium) or metabolism by cholinesterasecatalyzed hydrolysis (mivacurium) occurs in the plasma. [15] [106A] (see sections on kinetics and dynamics, metabolism, and hepatic and renal disease.)

Phenolic Ether: Gallamine

Gallamine, a phenolic ether introduced in 1948, was the first synthetic relaxant used in clinical practice. This compound is a long-acting drug excreted entirely by the kidney and is strongly vagolytic. Consequently, it is no longer popular.

Strychnos Alkaloid: Alcuronium

Introduced in 1964, alcuronium is a long-acting agent that is the semisynthetic diallyl derivative of toxiferine. The latter is purified from *Strychnos toxifera.* Its advantage at the time of its introduction was a relative lack of side effects. It is mildly vagolytic and is excreted unchanged by the kidney with a minor secondary biliary pathway. Alcuronium is

Figure 12-6 Linear regression of onset of neuromuscular blockade (ordinate) versus potency of a series of steroidal relaxants studied in the cat model by Bowman and associates. [42] The data show that onset may be increased in compounds of low potency and encouraged the eventual development of rocuronium and rapacuronium (ORG 9487).

moderately popular in Europe, the Far East, and Australia. It is not available in the United States.

Classification by Duration of Action

The duration of action of the nondepolarizing relaxants is governed mainly by the pattern(s) of metabolism and elimination of each drug. See the sections on pharmacokinetics and pharmacodynamics, metabolism, and renal and hepatobiliary disease.

Long-Acting Relaxants

Long-acting relaxants include dTc, metocurine, doxacurium, pancuronium, pipecuronium, gallamine, and alcuronium. They generally show relatively slow onsets to maximum blockade of 3 to 6 minutes following doses given for tracheal intubation (1.5 to 2 times the ED_{95} for twitch inhibition). The clinical duration of action (to recovery of twitch to 25% of baseline) ranges from 80 to 120 minutes following intubating doses. All the long-acting relaxants require careful antagonism of residual blockade at the end of nearly every case. Selection of a long-acting relaxant is based primarily on the prominence or absence of the cardiovascular side effect. All the long-acting agents are primarily excreted unchanged by glomerular filtration in the urine, having undergone little or no metabolism.

Relaxants of Intermediate Duration

Intermediate-acting relaxants include vecuronium, rocuronium, atracurium, and cisatracurium. Onset of block following doses typically given for tracheal intubation is about 2 to 2½ minutes. Clinical duration is 30 to 60 minutes, and 95 percent twitch recovery occurs in 45 to 90 minutes. Vecuronium and rocuronium owe their intermediate duration to their dual excretory pathways (kidney and liver). Atracurium and cisatracurium are intermediate-acting because they undergo the chemical breakdown process of the Hofmann elimination in the plasma.

Short-Acting Relaxants

Mivacurium and rapacuronium (ORG 9487) are relatively short-acting. Mivacurium shows medium onset of about 2 minutes for intubation. The onset of ORG 9487 is fast, enabling intubation in 1 minute. The clinical duration of mivacurium is about 12 to 20 minutes, and 95 percent twitch recovery occurs in 25 to 35 minutes; corresponding times for rapacuronium are about 15 to 20 minutes and 25 to 50 minutes. The lower range of times for ORG 9487 is achieved after doses of 1.5 mg/kg, with the higher durations occurring following 2.0 to 2.5 mg/kg. Mivacurium is nearly completely destroyed by plasma cholinesterase at about 70 to 88 percent the rate of succinylcholine. [15] Less than 5 percent is excreted in the urine. ORG 9487 is partially deacetylated

at the 3-position and excreted in the bile and urine as the parent compound or the more active metabolite, ORG 9488. The metabolite is longer-acting than the parent compound and is most likely the cause of cumulation of the effect of ORG 9487, resulting in longer duration of action and slower recovery following repetitive dosage or periods of infusion of 30 minutes or more.

Pharmacokinetics and Pharmacodynamics

The principal action of nondepolarizing neuromuscular blocking drugs is competitive antagonism of acetylcholine at nicotinic receptors on the postjunctional membrane of the neuromuscular junction. [107] The potency of the drugs as antagonists is commonly expressed by the dose-response relationship. The drugs have different potencies as illustrated in Table 12-6 and Figure 12-7 . The dose-response relationship is sigmoidal in shape (see Fig. 12-7) and has been derived in a variety of ways. The simplest method is to perform simple linear regression over the approximately linear portion of a semilogarithmic plot between 25 and 75 percent effect. Alternatively, the curve can be subjected to probit or logic transform to linearize it over its whole length or be subjected to nonlinear regression using the sigmoid E_{max} model of the form:

This can be applied to the raw data. [109] [108] More complex models relating the concentration of muscle relaxant at the neuromuscular junction to their pharmacologic effect have been developed, and they will be discussed later. [110] [111]

Several factors can alter the potency of muscle relaxants, but in clinical practice the greatest effect is mediated by the halogenated anesthetics that increase the potency of the muscle relaxants. The magnitude of this effect may allow up to a 50 percent decrease in the required dose of muscle relaxant, halothane having the least effect and isoflurane and

Figure 12-7 Schematic representation of a semilogarithmic plot of muscle relaxant dose versus neuromuscular block. A drug of high potency would be represented by doxacurium, one of medium potency by atracurium, and one of low potency by gallamine. The graph illustrates that the relative potencies of the muscle relaxants span a range of approximately two orders of magnitude.

Figure 12-8 (Figure Not Available) Rates at which the plasma concentration of *d*-tubocurarine (dTc) and pancuronium decrease in patients with and without renal failure. Distribution of drug from plasma to the tissues is primarily responsible for the rapid decline in plasma concentrations in the first 30 minutes after administration. Thereafter, further decrease in plasma concentration is due to elimination, a slower process. *(Data for pancuronium from McLeod et al [119] and those for dTc are from Miller et al [120])*

enflurane having greater, approximately equal effects. [111A] Traditionally, doses used to facilitate tracheal intubation are two times the ED_{95} (this also approximates to four times the ED_{50}). Doses for maintenance are usually in the order of one-tenth to one-fourth of the intubating dose.

Following its injection into the circulation, the concentration of a muscle relaxant in the plasma decreases rapidly at first, then more slowly (Fig. 12-8) (Figure Not Available) . The shape of this curve is determined by the processes of distribution and elimination. Classically, this curve is divided into an initial (distribution) phase and a terminal (elimination) phase. In Figure 12-8 (Figure Not Available) the log-linear terminal phase is obvious from 60 minutes on. This curve can be represented mathematically by bi- or triexponential equations in the form

These multiexponential equations express the concept of drug distributing between two or three theoretical compartments.

Figure 12-9 illustrates the classic model whereby drug is administered intravenously into a central compartment with volume V1 and is distributed and eliminated only from this compartment. Drug distributes very rapidly throughout this central compartment, which includes the plasma volume and the organs of elimination, e.g., in the case of muscle relaxants, the kidneys and liver. The terms "k" are the rate constants for drug movement between compartments, in the direction of the arrows. The peripheral compartments (usually one or two in number, here represented by V2 and V3) can be thought of as the "tissues." The effect compartment, which will be discussed later, is the neuromuscular junction; for computational purposes, it has infinitesimal volume; therefore, it does not influence overall drug distribution. Drug administration and elimination are unidirectional; distribution is bidirectional.

Figure 12-9 Schematic representation of drug disposition into different compartments. These compartments are mathematical concepts only and do not represent real physiologic spaces. The effect compartment in this case would be the neuromuscular junction; for computational purposes, it has infinitesimal volume. The terms k_{nm} are the rate constants for drug movement, in the direction of the arrow, between these theoretical compartments. See text for further discussion.

Initially, drug concentration in the central compartment (plasma concentration) will exceed that in the peripheral compartment (tissue concentration), and drug will move from the plasma to the tissues. Later, as plasma concentration decreases, it becomes less than tissue concentration, and the net direction of drug movement is now from tissues to plasma. In general, this conceptual model is appropriate for all the muscle relaxants, with the exception of atracurium and cisatracurium, which also undergo elimination (by degradation) from the tissues. [113] For simplicity, the following discussion will assume only one peripheral compartment.

Volume of distribution is the volume to which the drug has distributed when the processes of distribution and elimination are in equilibrium. Elimination is represented by the variable, plasma clearance, i.e., the volume of plasma from which drug is irreversibly and completely eliminated per unit time. For most nondepolarizing muscle relaxants, the process of distribution is more rapid than that of elimination, and the initial rapid decline in plasma concentration is due primarily to distribution of the drug to the tissues. An exception to this rule is mivacurium, which has such a rapid clearance, due to metabolism by plasma cholinesterase, that elimination is the principal determinant of the initial decline in plasma concentration. [114]

Following the initial process of drug distribution to the tissues, the plasma concentration falls more slowly (terminal phase). The rate of decrease in plasma concentration during this terminal phase is often expressed in terms of elimination half-life, which equals the natural logarithm of 2 divided by the rate constant of decline (i.e., the slope of the terminal phase). During this terminal phase, the tissue drug concentration exceeds that of the plasma, and the rate of decrease of the plasma concentration is determined by two factors, the rate at which drug can move from the tissues back to the plasma and the clearance of drug from the plasma. In classic theory for muscle relaxants, drug can move rapidly from the tissues to the plasma, and elimination from the plasma (clearance) is the rate-limiting step. For this reason, the terminal portion of the curve is often termed the elimination phase, even though distribution of drug from tissues to the plasma is occurring continually throughout. Volume of distribution can also influence the terminal portion of the curve; the greater the volume of distribution, the slower the decline in plasma concentration.

The muscle relaxants are polar drugs, and their volume of distribution is classically thought to be limited to a volume roughly equivalent to a portion of the extracellular fluid space, i.e., 150 to 450 $mL \cdot kg^{-1}$ (see tables in renal and hepatobiliary sections). [112] With this model of drug distribution, the potential rate of drug movement from the tissues to the plasma exceeds the rate of elimination, and plasma clearance is the process that limits the rate of decline of plasma drug concentration. However, there is evidence that muscle relaxants distribute more widely, into tissues with low blood flows, e.g., connective tissue, [115] and the true volume of distribution of

tubocurarine has been estimated as high as 3.4 $L \cdot kg^{-1}$ and the elimination half-life as long as 40 hours (compare with values in Tables 12-13 and 12-14) . [116] Because the rate of drug movement from such tissues is slow, less than that of plasma clearance, this becomes the rate-limiting step in the rate of decline in plasma drug concentration.

This phase only becomes obvious when drug is administered for many days or when sampling is continued for 24 to 96 hours after drug administration. In normal operating room use of muscle relaxants, the amount of drug distributing to this compartment does not affect the clinical response to the drug. In conditions where clearance of the muscle relaxant is reduced, e.g., renal or hepatic disease, it is the terminal portion of the plasma concentration versus time curve that is most affected (see Figs. 12-8 (Figure Not Available) and 12-39 (Figure Not Available)). [117] The rate of decline of plasma concentration is slowed, and recovery from paralysis is potentially delayed. [117] In conditions associated with an increased distribution volume, e.g., renal or hepatic disease, early plasma concentrations of drug may be less than those observed when organ function is normal (see Fig. 12-38) (Figure Not Available) . However, during the terminal phase, the increased volume of distribution will result in a higher plasma concentration, which decreases more slowly (see Fig. 12-38) (Figure Not Available) Decreased protein binding of a drug results in a larger distribution volume, but as the degree of protein binding of muscle relaxants is small, changes in protein binding will have minimal effect on their distribution. [118]

Recovery of neuromuscular function takes place as plasma concentration declines, and Figure 12-8 (Figure Not Available) shows that the greater part of this decrease occurs primarily because of distribution, and early recovery of neuromuscular function, e.g., to 10 or 25 percent of control, often occurs during this phase. Thus, processes that primarily affect elimination of the drug, e.g., renal failure, may not be associated with prolonged duration of block. Observe that at 30 minutes, plasma concentrations are little different for patients with and without renal failure. [119] [120] However, as recovery comes to rely more on drug elimination than distribution, i.e., recovery from 25 to 75 percent or more or after administration of larger or repeated doses, the duration of action may be prolonged. [113] [121]

Following injection of a muscle relaxant, plasma drug concentration immediately starts to decrease. The effect (neuromuscular blockade) takes approximately 1 minute to begin, increases initially, and does not begin to recover for many more minutes despite continually decreasing plasma concentration of drug. This discrepancy between plasma concentration and drug effect occurs because the action of muscle relaxants is not in the plasma but at the neuromuscular junction. To produce paralysis, the drug must diffuse from the plasma to the neuromuscular junction, and the effect is terminated later by drug diffusion back into the plasma (see Fig. 12-9) . Thus, concentrations at the neuromuscular junction lag behind those in the plasma, and they are less during onset of block and greater during recovery. The plasma concentration-effect relationship exhibits hysteresis, i.e., for a given level of block, plasma concentrations are greater during onset than during recovery. For this reason, a concentration-effect relationship cannot be obtained simply by directly relating plasma concentration to level of neuromuscular blockade.

To overcome this problem, pharmacodynamic models have been developed to incorporate a factor for the delay caused by drug diffusion to and from the neuromuscular junction. [110] This factor, k_{e0} , is the rate-constant for drug equilibration between plasma and the neuromuscular junction. By measuring plasma drug concentrations and neuromuscular blockade, during both onset and recovery phases, and using the technique of simultaneous pharmacokinetic/ pharmacodynamic modeling, it is possible to collapse the hysteresis in the plasma concentration-effect curve, to estimate actual neuromuscular junction drug concentrations, and to derive true concentration-effect relationships ($Cpss_{50}$ and k_{e0}) for the neuromuscular relaxants (Table 12-8) . [110]

Results from studies using these techniques indicate that the potency of the muscle relaxants is increased by the volatile anesthetics in a dose-dependent manner (isoflurane > halothane) and is increased by prior administration of succinylcholine. The potency is less in neonates and infants than in older children and adults and in burned patients (see Table 12-6 and Fig. 12-40) (Figure Not Available) .

The long-acting muscle relaxants undergo minimal or no metabolism, and they are eliminated, largely unchanged, mostly by renal excretion. Hepatic pathways are less important. Vecuronium undergoes deacetylation at the 3-position of the steroid nucleus to 3-desacetylvecuronium. This compound has approximately 80 percent of the neuromuscular blocking potency of vecuronium, and it can accumulate and cause prolonged paralysis during long-term administration of vecuronium to patients with renal failure in the intensive care unit. [122] Atracurium and cisatracurium are extensively degraded by Hofmann elimination, principally to laudanosine. Degradation comprises at least 50 percent of the total clearance for atracurium. [113] Both vecuronium and atracurium have greater clearance than do the long-acting muscle relaxants (see Tables 12-13 and 12-14) . Mivacurium is cleared rapidly and almost exclusively by metabolism by plasma cholinesterase, resulting in a plasma clearance much greater than of any other nondepolarizing muscle relaxant (see Tables 12-13 and 12-14) . [15] In addition, because of its rapid metabolism in the plasma, there is limited opportunity for distribution, and its volume of distribution is small.

Clinical Management

There are two important safety issues in practice with muscle relaxants: cardiovascular side effects and adequacy of recovery to normal neuromuscular function. Of the two, the latter is by far the more important. It has been difficult to demonstrate that one muscle relaxant is truly "safer" than another. [123] [124] [125] To avoid prolonged residual paralysis or inadequate antagonism of residual blockade or both, the main goal should be to use the lowest possible dose that will provide adequate relaxation for surgery. The rational use of muscle relaxants depends on administration by an anesthesiologist who is familiar with the operative procedure, who knows when to use muscle relaxants, who correctly applies monitoring techniques to assess the magnitude and duration of action of the specific muscle relaxant, and who understands the clinical pharmacology of the drug, including its side effects and complications. The key factor again is to avoid overdosage. For example, in an adequately anesthetized and monitored patient, there is little reason to completely obliterate twitch or TOF responses to peripheral nerve stimulation during maintenance of relaxation. Supplemental doses of relaxants should be about one-fourth to one-tenth the initial dose and should not be given until there is clear evidence of beginning recovery from the previous

TABLE 12-8 -- Pharmacodynamic Parameters Derived Using Simultaneous Pharmacokinetic/ Pharmacodynamic Modeling

	STUDY GROUP	Cp_{ss50}[a] ($ng \cdot mL^{-1}$)	k_{e0}[b] (min^{-1})	REFERENCE
ATRACURIUM	Infants	363	0.19	Fisher DM, 1990
	Children	444	0.16	
	Young adults	449	0.13	Kitts JB, 1990
	Elderly adults	436	0.12	
	Standard model	359	0.12	Parker CJ, 1992
	Threshold model	357	0.12	
	Isoflurane anesthesia	357 [c]	0.12	Parker CJ, 1993
	Halothane anesthesia	432 [c]	0.12	
	Midazolam anesthesia	524 [c]	0.12	
	Young adults	669 [c]	0.07	Marathe PH, 1989
	Burn patients	2,270 [c]	0.10	
	No succinylcholine	454 [c]	0.07	Donati F, 1991
	After succinylcholine	305 [c]	0.09	
VECURONIUM	Young adults	94	--	Cronnelly R, 1983
	Young adults	92	0.17	Rupp SM, 1987

	Elderly adults		106	0.17	
d-*TUBOCURARINE:*	Normal renal function		370	0.13	Sheiner LB, 1979 [110]
	Renal failure		380	0.16	
	Halothane 0.5-0.7%		360 [c]	0.09 [c]	Stanski DR, 1979 [e]
	Halothane 1.0-1.2%		220 [c]	0.12	
	Narcotic anesthesia		600 [c]	0.15 [c]	
	Neonates		180 [d]	0.11	Fisher DM, 1982 [e]
	Infants		270 [d]	0.09	
	Children		420 [d]	0.09	
	Adults		530 [d]	0.10	
PANCURONIUM	Young adults		88	--	Cronnelly R, 1983

[a] Cp_{ss50} is the neuromuscular junction concentration of each drug that produces a 50 percent decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle following ulnar nerve stimulation.
[b] k_{eo} is the rate constant for equilibration of drug between the plasma and the neuromuscular junction.
[c] All groups different from each other
[e] k_{eo} values calculated as $0.693/t_{½}$ keo
[d] Neonates and infants different from children and adults

dose. This practice will help to avoid an excessive neuromuscular blockade that cannot be readily antagonized by anticholinesterases (see Tables 12-2 , 12-6 , and 12-9 for dosage guidelines). *The management of individual patients should always be guided by monitoring with a peripheral nerve stimulator.*

Several clinical alternatives to muscle relaxants are available to provide adequate surgical relaxation. It is important to keep them all in mind to avoid relying only on neuromuscular blockade to achieve a desired degree of relaxation. These options include adjustment of the depth of general anesthesia, regional anesthesia, proper positioning of the patient on the operating table, and proper adjustment of the depth of neuromuscular blockade. The choice of one or several of these options is determined by the estimated remaining duration of surgery, the anesthetic technique, and the surgical maneuver required.

Control of Depth of Anesthesia

Inhaled anesthetics are known to produce relaxation of skeletal muscle by multiple inhibitory influences on reflex pathways in the CNS that are responsible for maintenance of muscle tone. This action of anesthetics is dose-related but usually does not cause measurable neuromuscular blockade. Very deep anesthesia with isoflurane, desflurane, enflurane, and diethyl ether may cause a slight reduction of neuromuscular transmission, as measured by depression of sensitive indicators of clinical neuromuscular function, such as tetanus and TOF. [126] [127] There is a relationship between relaxation and anesthetic depth during all types of anesthesia. Thus, relaxation may be increased by deepening anesthesia using either inhaled or intravenous anesthetics for various surgical maneuvers such as peritoneal closure, fracture or dislocation reduction, and tracheal intubation. The effectiveness of neuromuscular blocking drugs increases proportionally with depth of inhalational anesthesia. [128] [129]

Control of Depth of Neuromuscular Blockade

The level of clinical neuromuscular blockade is demonstrable by appropriate use of a nerve stimulator (Ch. 39) . Relaxation is generally inadequate for most situations if all four responses are clearly visible or palpable during TOF monitoring. If one or two responses are visible or palpable, relaxation should be sufficient for abdominal surgery under adequate depth of anesthesia. If only one twitch is faintly visible or palpable, relaxation should be deep enough to permit intubation of the trachea under already-established general

TABLE 12-9 -- Dose-Response Relationships of Nondepolarizing Neuromuscular Blocking Drugs in Human Subjects

	ED_{50} (mg· kg^{-1})	ED_{90} (mg· kg^{-1})	ED_{95} (mg· kg^{-1})	REFERENCES
DOXACURIUM	0.012 (0.006-0.016)	0.022 (0.021-0.024)	0.024 (0.016-0.033)	Basta SJ, 1988; Murray DJ, 1988; Katz JA, 1989;Koscielniak NZ, 1992;Maddineni VR, 1992
PIPECURONIUM	0.021 (0.013-0.032)	0.032 (0.022-0.033)	0.042 (0.024-0.059)	Azad SS, 1989; Pittet JF,1989; Stanley JC, 1989;Wierda JM, 1989;Foldes FF, 1990; Naguib M, 1992
VECURONIUM	0.027 (0.015-0.031)	0.042 (0.023-0.055)	0.043 (0.037-0.059)	Shanks CA, 1986
PANCURONIUM	0.036 (0.022-0.042)	0.056 (0.044-0.070)	0.067 (0.059-0.080)	Shanks CA, 1986
MIVACURIUM	0.039 (0.027-0.052)	----------	0.067 (0.045-0.081)	Savarese JJ, 1988; Weber S, 1988; Caldwell JE, 1989; Choi WW, 1989; From RP, 1990; Pearson C, 1992
ALCURONIUM	0.11 (0.07-16)	0.18 (0.12-0.25)	0.22 (0.14-0.29)	Shanks CA, 1986
ATRACURIUM	0.12 (0.08-0.15)	0.18 (0.19-0.24)	0.21 (0.13-0.28)	Shanks CA, 1986
METOCURINE	0.14 (0.13-0.15)	0.25 (0.24-0.26)	0.30 (0.28-0.32)	Shanks CA, 1986
ROCURONIUM	0.147 (0.069-0.220)	0.268 (0.200-0.419)	0.305 (0.257-0.521)	Booij LH, 1991; Foldes FF, 1991; Lambalk LM, 1991; Quill TJ, 1991; Cooper RA, 1992; Bartkowski RR,1993; Bevan DR, 1993; Oris B, 1993
d-*TUBOCURARINE*	0.23 (0.16-0.26)	0.41 (0.27-0.45)	0.48 (0.34-0.56)	Shanks CA, 1986
GALLAMINE	1.30	2.30	2.82	Shanks CA, 1986

Data are the median and range of reported values.

ED_{50} , ED_{90} , and ED_{95} are the doses of each drug that produce, respectively, 50%, 90%, and 95% decrease in the force of contraction or amplitude of the electromyogram of the adductor pollicis muscle following ulnar nerve stimulation.

anesthesia. *If anesthesia is too light, on the other hand, relaxation may prove inadequate, even if the indicators of monitoring seem appropriate.*

Regional Anesthesia

Regional anesthesia (Chs. 46 and 47) should always be considered alone or in combination with light general anesthesia as a means of achieving relaxation localized to the area of surgery. For example, continuous epidural or spinal anesthesia will provide good relaxation for lower abdominal surgery or for surgery on the hip. The patient may be spared the discomforts of abdominal exploration during epidural or spinal anesthesia by the supplemental administration of 0.5 to 1.0 MAC

levels of inhaled anesthetics or intravenous supplements such as propofol and/or opioids such as remifentanil.

Patient Positioning

Adequate relaxation for peritoneal closure, laryngoscopy, and other maneuvers depends considerably on suitable positioning (Ch. 30). The operating table may be flexed slightly to make it easier to close an abdominal wound. Placement of the head in the sniffing position for laryngoscopy and placement of the height of the operating table at a level slightly above the waist of the anesthesiologist can very much improve conditions for intubation of the trachea.

Dosage

General Dosage Guidelines

It is important to select the proper dose of a nondepolarizing relaxant in order to ensure that the desired effect is achieved without excessive overdosage. A general dosage guideline for administration of nondepolarizing relaxants is presented in Table 12-6 . In addition to a general knowledge of the guidelines, precise practice requires the use of a peripheral nerve stimulator to adjust relaxant dosage to the individual patient. Overdosage must be avoided for two reasons: (1) to limit the duration of drug effect to match the anticipated length of surgery and (2) to avoid unwanted cardiovascular side effects. The development of new relaxants with different lengths of action and lack of effect on the circulation

has made overdosage both easier to avoid and more safely tolerated.

Initial and Maintenance Dosage

The initial dosage is determined by the purpose of administration. If the trachea has already been intubated without a relaxant or with succinylcholine and the purpose is simply to produce surgical relaxation, a dose slightly less than the ED_{95} (Table 12-6) should be given, with adjustment upward as indicated by responses evoked by peripheral nerve stimulation. Downward adjustment of the initial dose is necessary in the presence of any of the potent inhaled anesthetics, which probably potentiate all the nondepolarizers to a similar extent (by 30-50%) (see Fig. 12-40) (Figure Not Available) when given in concentrations of about 1 MAC.

Supplemental (maintenance) doses of nondepolarizers range from 20 to 30 percent of the initial dose in the case of long-acting drugs to 35 to 50 percent of the initial dose in the case of intermediate- and short-acting relaxants.

Maintenance of relaxation by continuous infusion of intermediate and short-acting drugs can be performed and is useful to keep relaxation smooth and to rapidly adjust the depth of relaxation to surgical needs. By contrast, the depth of block in each patient is kept moderate, if possible, to ensure prompt spontaneous recovery or easy reversal at the end of the procedure. Table 12-6 lists approximate dose ranges that are usually required during infusion to maintain 90 to 95 percent block of the twitch (one twitch visible on TOF stimulation) under nitrous oxide-oxygen anesthesia supplemented with intravenous anesthetics. Infusion dosage is usually decreased by about 30 to 50 percent in the presence of potent inhaled anesthetics.

Dosage for Tracheal Intubation

If the purpose of the initial dose is to provide the very deep paralysis needed for tracheal intubation, bronchoscopy, or other manipulations of the airway, dosage in the range of two to three times the ED_{95} is usually given to facilitate the maneuver within 1 to 3 minutes, depending on the choice and dose of muscle relaxant (see Tables 12-2 , 12-6 , and 12-7) .

Dosage for Priming

Several groups of investigators have recommended that a small subparalyzing dose of the nondepolarizer (about 20% of the ED_{95} or about 10% of the intubating dose) be given 2 to 4 minutes before giving a second large dose for tracheal intubation. [130] [131] [132] [133] [134] This procedure, termed priming, has been shown to accelerate the onset of block of most nondepolarizing relaxants by about 30 to 60 seconds, with the result that intubation can be performed within approximately 90 seconds following the second dose (see Table 12-7) . Doses in Table 12-7 , which are recommended for rapid intubation following priming, are 50 to 100 percent higher than conventional doses recommended for intubation. This increase in dosage will ensure that conditions will be satisfactory within 90 seconds or less. Although priming in conjunction with such large doses clearly does shorten the onset time of nondepolarizers, the shortest onset is still produced by succinylcholine > rapacuronium (ORG 9487) > rocuronium.

With priming, intubating conditions at 60 to 90 seconds will be satisfactory following two to three times ED_{95} , provided that the patient has also received adequate dosage of intravenous anesthetic agents to produce hypnosis, amnesia, and analgesia, or a state of light general anesthesia. Considerably larger doses of intravenous anesthetics and neuromuscular blocking drugs may be required in healthy young adults and in children.

A caution in the use of the priming technique is the potential development of weakness or loss of airway control by the patient before induction of anesthesia. [134A] To prevent this, the following is suggested: the patient should be instructed, before receiving the priming dose, to report the development of diplopia after the dose is given. Once the patient reports diplopia, the priming effect may be considered to be in place, and induction of anesthesia with cricoid pressure should immediately follow. If diplopia is not reported within 2 to 4 minutes, induction should proceed at that time in any case. Needless to say, oxygen administration should be begun before administration of the priming dose of relaxant.

Dosage for Rapid Intubation of the Trachea

Succinylcholine is still preferred for this critical maneuver (Chs. 29 and 42). Now, however, there are suitable alternatives among the nondepolarizing relaxants (Tables 12-2 and 12-7) but as yet no replacement. There are five caveats in any case, whichever technique of rapid intubation is elected: (1) preoxygenation must be performed; (2) adequate dosage of intravenous drugs must be administered to ensure that the patient is adequately anesthetized; (3) intubation within 60 to 90 seconds is considered acceptable; (4) priming should be considered to shorten the onset of action of nondepolarizers; and (5) cricoid pressure should be applied subsequent to the injection of the induction agent.

When rapid tracheal intubation is performed with nondepolarizing relaxants, priming is recommended, with doses listed in Table 12-7 given 2 to 4 minutes before injection of the intubating dose in order to speed the onset of action. [130] [131] [132] [133] [134] (In the case of rocuronium and ORG 9487, onset is probably fast enough to make priming unnecessary. [135] [136] [137]) Large doses in the range of two to four times ED_{95} are advised for rapid intubation following priming. Following doses greater than five times ED_{95} , priming is probably not necessary with any of the short- or intermediateacting drugs. [138] Rapid intubation using long-acting drugs is no longer advised because of the unacceptably long period of block that results. Once again, the practitioner must remember that the price to be paid for giving large doses of muscle relaxants is longer duration of action and/or potentially increased circulatory effect. Lengthening of the duration of effect is more noticeable in drugs with longer half-lives, such as vecuronium (t½beta 50-60 minutes). Potentially increased circulatory effect in the case of the weak histamine-releasing property of atracurium (t½beta 20 minutes) and mivacurium (t½beta 2-3 minutes) should be dealt with by injecting three

times ED_{95} doses more slowly (e.g., over a 20- to 30-second period). [139] [140]

Table 12-7 also gives the approximate clinical duration following dosage for rapid intubation for each muscle relaxant. At this point the evoked twitch response has

recovered to about 25 percent of its baseline strength. Residual block by nondepolarizers can then be easily antagonized with neostigmine or edrophonium. The clinical duration is therefore a useful guideline for practice. The approximate time to full recovery is also a useful guideline. If spontaneous recovery from the particular muscle relaxant has appeared to have occurred within this period, then administration of an anticholinesterase may not be necessary. The decision not to give an anticholinesterase drug dictates that complete recovery from neuromuscular blockade must be verified by confirmatory monitoring data via a nerve stimulator; by adequate clinical evaluation, such as sustained head lift for 5 seconds; and by proper documentation on the anesthetic record and on the patient's chart.

Metabolism and Elimination

The specific pathways of metabolism (biotransformation) and elimination of neuromuscular blocking drugs are summarized in Table 12-10 . The following description is intended to give a general understanding of the various processes of clearance that affect the duration of neuromuscular block and contribute toward recovery from paralysis. Metabolism and elimination of specific drugs is also discussed in the sections on individual agents and in the sections on renal and hepatobiliary disease.

TABLE 12-10 -- Metabolism and Elimination of Neuromuscular Blocking Drugs

DRUG	DURATION	METABOLISM (%)	ELIMINATION		METABOLITES
			KIDNEY (%)	LIVER (%)	
Succinylcholine	Ultrashort	Plasma cholinesterase (98-99%)	< 2%	None	Monoester (succinyl monocholine) and choline. The monoester is metabolized much more slowly than succinylcholine.
Mivacurium	Short	Plasma cholinesterase (95-99%)	< 5%	None	Monoester and quaternary alcohol. The metabolites are inactive. They are most likely not themselves metab-olized any further.
			(Metabolites eliminated in urine and bile)		
Rapacuronium (ORG 9487)	Short-intermediate	to 3-desacetyl metabolite	20%	Unknown	The 3-OH derivative, ORG 9488, is two to three times more potent than the parent compound and has a longer half-life (see section on kinetics and section on rapacuronium).
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60-90%)	10-40%	None	Laudanosine, acrylates, alcohols, and acids (see Fig. 12-11) (Figure Not Available) . Although laudanosine has CNS-stimulating properties, the clinical relevance of this effect is negligible.
			(Metabolites eliminated in urine and bile)		
Cisatracurium	Intermediate	Hofmann elimination (77%?)	Renal clearance is 16% of total		Laudanosine and acrylates. Ester hydrolysis of the quaternary monoacrylate occurs secondarily (see Fig. 12-11 (Figure Not Available)). Because of the greater potency of cisatracurium, laudanosine quantities produced by Hofmann elimination are five to ten times lower than in the case of atracurium, making this a non-issue in practice.
Vecuronium	Intermediate	Liver (30-40%)	40-50%	50-60%	The 3-OH metabolite accumulates, particularly in renal failure. It has about 80% the potency of vecuro-nium and may be responsible for delayed recovery in ICU patients.
			(Metabolites excreted in urine and bile)		
			~40%	~60%	
Rocuronium	Intermediate	None	< 10%	> 70%	None
Pancuronium	Long	Liver (10-20%)	85%	15%	The 3-OH metabolite may accu-mulate, particularly in renal failure. It is about two-thirds as potent as the parent compound.
d-Tubocurarine	Long	None	80% (?)	20%	None
Pipecuronium	Long	Approximately 10%	> 90% (?)	< 10%	The 3-OH metabolite is produced in small quantities (~5%).
Metocurine	Long	None	> 98%	< 2%	None
Doxacurium	Long	None	> 90% (?)	< 10%	None
Alcuronium	Long	None	80-90% (?)	10-20%	None
Gallamine	Long	None	100%	0%	None

All relaxants are positively charged cations because they contain quaternary nitrogen atoms. [107] Nearly all relaxant molecules also contain ester linkages, acetoxy groups, and hydroxyl or methoxy groups. These substitutions, especially the quaternary nitrogen groups, confer a high degree of water solubility with only a slight lipid solubility. The hydrophilic nature of relaxant molecules enables easy elimination in the urine via glomerular filtration with no tubular resorption or secretion. Therefore, all muscle relaxants show elimination of the parent molecule in the urine as a basic route of elimination. Muscle relaxants with a long duration of action are eliminated predominantly in the urine and thus have a clearance rate limited by glomerular filtration (1-2 mL/kg/min).

Other processes of clearance may be added to renal elimination. Pancuronium and pipecuronium undergo a small amount of metabolism by deacetylation at the 3-position, [140A] [140B] [140C] [140D] but this makes a minimal contribution to their total clearance.

Vecuronium, the 2-desmethyl derivative of pancuronium, is more lipid-soluble than pancuronium because of the absence of the quaternizing methyl group at the 2-position. As a result, it undergoes a greater amount of metabolism (3-deacetylation). About 12 percent of vecuronium clearance is by conversion to 3-desacetylvecuronium, [141] and about 30 to 40 percent is cleared in the bile as parent compound. [142] [143] Vecuronium is also eliminated in the urine, and this combined organ elimination gives it a clearance of 3 to 6 mL/kg/min, [141] [143] [144] i.e., about twice that of pancuronium (Fig. 12-10) (Figure Not Available) .

In undergoing Hofmann elimination in the plasma (Fig. 12-11) (Figure Not Available) and interstitial fluid, atracurium is cleared two to three times more rapidly than the longacting drugs. [113] [145] [146] [147] [148] [149] Similar clearance values have been obtained for rocuronium [150] [151] [152] [152A] [152B] [152C] and cisatracurium. [153] [153A] [153B] [153C] [153D] In summary, relaxants such as vecuronium, rocuronium, atracurium, and cisatracurium, have clearances in the range 3 to 6 mL/kg/min because of multiple pathways of degradation, metabolism, and/or elimination, and these drugs have an intermediate duration of action.

Mivacurium is hydrolyzed in the plasma by plasma cholinesterase (Fig. 12-12) (Figure Not Available) . [15] [154] Mivacurium consists of three stereoisomers, and the clearances of the two most pharmacologically active isomers, the *cis-trans* and *trans-trans,* are approximately 100 and 50 to 70 mL/kg/min, respectively. [154A] [154B] [154C] This rapid enzymatic clearance of mivacurium accounts for its short duration. [15] [154B] The clearance of these two isomers is decreased by approximately 50 percent in patients with cirrhosis, [154C] and by approximately 20 percent in those with renal failure. [154D] The third stereoisomer, the *cis-cis* isomer, is present as only 4 to 8 percent of the mivacurium mixture and has less than 10 percent of the neuromuscular blocking potency of the other two isomers. [154B] Consequently, even though it has a much lower clearance (~4 mL/kg/min) than the two other isomers, it does not contribute significantly to the duration of action of mivacurium.

It is clear from the above discussion that renal elimination is basic to all muscle relaxants. Additional processes of clearance (e.g., biliary clearance) shorten the duration of effect. Very active metabolism and/or degradation shortens the action still further. All processes of clearance are additive.

Figure 12-10 (Figure Not Available) Metabolism of vecuronium as it occurs in the liver. About 30 to 40 percent of an injected dose is deacetylated at the 3- and 17-positions. The major metabolite is 3-OH vecuronium (heavy arrow). The metabolites are excreted in the urine and bile. The 3-OH metabolite is nearly as potent as the parent compound and is probably cleared from blood at a rate slightly slower than that of vecuronium. *(From Agoston et al [144A])*

Figure 12-11 (Figure Not Available) Degradation pathways of atracurium. The major metabolite, laudanosine, is excreted in urine and bile. Laudanosine is a tertiary amine that may enter the CNS. Less than 10 percent of atracurium is excreted as the parent compound. *(From Basta et al [293C])*

Of the nondepolarizing muscle relaxants listed in Table 12-10 , pancuronium, pipecuronium, vecuronium, atracurium, cisatracurium, mivacurium, and rapacuronium (ORG 9487) are the only ones that are metabolized or degraded. About 15 to 20 percent of an injected dose of pancuronium is deacetylated, almost entirely at the 3-position. It is a theoretical possibility that deacetylation occurs also at the 17-position, but this occurs to such a small extent as to be clinically irrelevant. The metabolites have been individually studied in anesthetized humans. [154D] The 3-desacetyl metabolite is the most potent of the three (approximately two-thirds the potency of pancuronium) and the only one present in detectable concentrations in the plasma. This metabolite has pharmacokinetics and duration of action similar to those of pancuronium. [154D]

Vecuronium is metabolized in a manner similar to that of pancuronium, with 3-desacetylvecuronium being the primary metabolite (see Fig 12-10) (Figure Not Available) . Other putative metabolites are 17-desacetylvecuronium and 3,17- *bis*desacetylvecuronium, neither of which occurs in clinically significant amounts. [140A] The 3-desacetylvecuronium is 80 percent as potent as the parent compound and has a total clearance of 3.5 mL/kg/min. Renal clearance accounts for approximately one-sixth of its elimination. [141] In the isolated perfused rat liver, about 40 percent of an injected dose of vecuronium appears unchanged in the bile. About 15 percent is recovered in the urine in the intact animal. [155] An additional 30 to 40 percent appears in the bile as 3-desacetylvecuronium. [155] In patients with renal failure in the intensive care unit (ICU) who receive vecuronium for more than 2 days, high concentrations of 3-desacetylvecuronium can be achieved. These concentrations may persist for several days after vecuronium administration is stopped and vecuronium concentrations have declined to almost zero. [122] Thus, the excretory pathways of vecuronium and its 3-desactyl metabolite may be different.

Theoretically, atracurium is metabolized via two pathways (see Fig 12-11) (Figure Not Available) . The drug undergoes Hofmann elimination, a purely chemical process that results in loss of the positive charges by molecular fragmentation to laudanosine (a tertiary amine) and a monoquaternary acrylate. [156] [157] Under the proper chemical conditions, these breakdown products may actually be used to synthesize the parent compound. They were thought to have no neuromuscular and little or no cardiovascular activity of clinical relevance. [156] [157] The Hofmann elimination process is nonbiologic and does not require renal, hepatic, or enzymatic function. It occurs at physiologic pH and temperature and is slowed by a decrease in pH and especially by a decrease in temperature. [158] [159] In fact, atracurium's duration of action is markedly prolonged by hypothermia. [159A] (Alterations in pH within the physiologic range do not cause a significant increase in the duration

Figure 12-12 (Figure Not Available) Metabolism of mivacurium by plasma cholinesterase. The reaction occurs at about 70 to 88 percent the rate of succinylcholine *in vitro.* The metabolites are inactive and carry positive charges, suggesting minimal CNS entry. *(From Savarese et al [15])*

of action.) Thus, atracurium is relatively stable at pH 3.0 and 4°C and becomes unstable when injected into the blood stream. Early observations of the breakdown of the drug in buffer and plasma showed a faster degradation in plasma, suggesting a possible enzymatic hydrolysis of the ester groups. [160] Further evidence suggests that this second pathway, ester hydrolysis, may be of more importance than was originally realized in the breakdown of atracurium. [161] By using a pharmacokinetic analysis, Fisher et al [162] concluded that a significant amount of clearance of atracurium may be by routes other than ester hydrolysis and Hofmann elimination. Atracurium's metabolism is complicated and may not be completely resolved. [162] [163]

Because of its central nervous system (CNS)-stimulating properties, laudanosine, the main metabolite of atracurium, has received much attention and has been the subject of multiple studies, some of which are cited here. Clearly, the ability of laudanosine to cause CNS stimulation depends on the total dose of atracurium given. Unlike atracurium, laudanosine is dependent on the liver and kidney for its elimination and has a longer elimination half-life. [164] [165] Laudanosine concentrations are elevated in patients with liver disease [166] and those who have received atracurium for many hours in an ICU. [167] Laudanosine freely crosses the blood-brain barrier. [164] Beemer et al [168] found that patients awakened at a 20 percent higher arterial concentration of thiopental when atracurium had been given; this was attributed to the CNS stimulatory effect of laudanosine. These relatively low concentrations of laudanosine, however, did not influence an animal model of epilepsy [169] or lidocaineinduced seizures. [170] In the ICU, blood levels of laudanosine can be as high as 5 to 6 mug/mL. [167] Although not known in humans, the seizure threshold in animals ranges from 5.0 mug/mL in rabbits [171] to 17 mug/mL in dogs. [172] Thus, no adverse effects are likely to occur with atracurium use in the operating room, but the issue may still be unresolved following prolonged use in the ICU. Laudanosine also has cardiovascular effects. In dogs, hypotension occurs at a blood concentration of about 6 mug/mL, [164] [172] a level higher than usually found in patients in the ICU. However, there is one case report of a patient who had severe hypotension and bradycardia while receiving atracurium, which resolved only when vecuronium was substituted. [173] Laudanosine enhances stimulation-evoked release of norepinephrine, [174] [175] which also may partly account for its CNS-stimulating effect.

Atracurium is a mixture of 10 optical isomers. Cisatracurium, on the other hand, is the single 1R- *cis* 1R - *cis* isomer. [175A] Like atracurium, it is metabolized by Hofmann elimination. There is no ester hydrolysis of the parent molecule. [175B] Hofmann elimination accounts for 77 percent of the total clearance of 5 to 6 mL/kg/min. [153B] Clearance of cisatracurium and laudanosine formation is little affected by liver dysfunction. [153A] Because cisatracurium is about four to five times as potent as atracurium, about five times less laudanosine is produced, and accumulation of this metabolite is not thought to be of any consequence in clinical practice.

Mivacurium, a benzylisoquinolinium ester, is rapidly hydrolyzed by plasma cholinesterase (see Fig. 12-12) (Figure Not Available) at a rate slower than that of succinylcholine. [15] Specifically, the hydrolysis rate of mivacurium is 70 to 88 percent that of succinylcholine. [15] [154] This mechanism of metabolism allows mivacurium to have a duration of action much shorter than that of vecuronium and atracurium but about twice that of succinylcholine. [175D] However, when plasma cholinesterase activity is severely deficient, e.g., in rare patients (1/3,000) who are homozygotes with genetically atypical enzyme, the duration of action of mivacurium can be prolonged by several hours. [175E] [175F] [175G] [175H] The metabolites of mivacurium have no neuromuscular blocking potency and do not cause CNS simulation.

ORG 9487 (rapacuronium) is a new muscle relaxant with a fast onset and short-to-intermediate duration of action. [175I] It has a clearance of between 8 and 11 mL/kg/min. [176] [177] It likely undergoes metabolism to its 3-desacetyl derivative (ORG 9488), which contributes significantly to its neuromuscular blocking effect. [176] The metabolite (ORG 9488) is more potent and shows considerably longer kinetics than the parent compound. Accumulation of the metabolite may be a reason for cumulation of ORG 9487 during clinical use. [178] The pharmacokinetic and pharmacodynamic interaction of the parent drug and its metabolite is complex and requires further elucidation.

Autonomic Effects

Cholinoceptive Interactions (Nicotinic and Muscarinic Effects)

Neuromuscular blocking drugs interact with the transmitter acetylcholine at nicotinic and muscarinic cholinergic receptors within the sympathetic and parasympathetic nervous systems and at the nicotinic receptors of the neuromuscular junction. Important interactions also occur at esteratic receptors: the active sites of both

acetylcholinesterase and pseudocholinesterase (plasma cholinesterase). These are collectively termed cholinoceptive sites (listed in Table 12-11) .

Interactions with cholinergic receptors form the basis for some of the classic cardiovascular side effects of the relaxants. For example, the depolarizing agent succinylcholine stimulates both nicotinic and muscarinic receptors. All the nondepolarizing drugs can potentially block all autonomic receptors. However, the likelihood of autonomic blockade by nondepolarizing relaxants, especially by the newer agents, is remote because the dose-response curves for autonomic inhibition lie far to the right of the curve for neuromuscular blockade.

Dose ratios comparing the neuromuscular blocking potency of relaxants (ED_{95}) with their potencies in blocking vagal (parasympathetic) or sympathetic ganglionic transmission (ED_{50}) can be constructed (Table 12-12) . These ratios are termed the autonomic margin of safety of the relaxant in question. The higher the dose ratio, the lower the likelihood of or the greater the safety ratio for the occurrence of the particular autonomic effect. For example, in the case of pancuronium, vagal inhibition (ED_{50}) becomes prominent in the cat at about three times the ED_{95} for neuromuscular blockade (twitch inhibition). [179] The vagal margin of safety is therefore 3.0. Similarly, blockade of vagal transmission by doxacurium is not measurable in the cat unless at least 100 times the ED_{95} for neuromuscular blockade is given. The autonomic effects of the neuromuscular blocking drugs when used in clinical practice are summarized in Table 12-12 A. Interpretation of this table is as follows and should be correlated with safety ratios listed in Table 12-12 . The side effect is absent (none) in clinical practice if the safety ratio is greater than 5. The side effect is weak or slight if the safety ratio is 3 or 4, moderate if 2 or 3, and strong or prominent if the ratio is 1 or less.

These autonomic responses are not reduced by slower injection of the relaxant. They are dose-related and are additive over time if divided doses are given. If identical to the original dose, subsequent doses will produce a similar response, that is, no tachyphylaxis will occur. This is not the case when the side effect of histamine release is in question. Cardiovascular responses secondary to histamine release are decreased by slowing the injection rate, and the response undergoes rapid tachyphylaxis. That side effect is discussed below.

TABLE 12-11 -- Cholinoceptive Sites That Interact With Neuromuscular Blocking Drugs

TYPE RECEPTOR	LOCATION	FUNCTION	RELAXANT INTERACTIONS
Nicotinic	Neuromuscular junction: postsynaptic	Initiates depolarization in muscle end plate	Succinylcholine stimulates: nondepolarizers block
Nicotinic	Neuromuscular junction: presynaptic	Maintains ACh release during high-frequency stimulation	Succinylcholine stimulates, nondepolarizers block
Nicotinic	Autonomic ganglion: ganglion cell bodies	Initiates depolarization of ganglion cell	Succinylcholine stimulates: *d*-tubocurarine blocks
Nicotinic	Postganglionic neuron terminal of autonomic nerves	Positive feedback for transmitter release	Succinylcholine stimulates: *d*-tubocurarine and other nondepolarizers may block
Muscarinic	Sinus node of heart	Slows cardiac rate	Succinylcholine stimulates: gallamine, pancuronium, alcuronium, rocuronium block, and rapacuronium (ORG 9487)
Muscarinic (M1)	Autonomic ganglia: interneuron cell bodies	Inhibits depolarization by hyper-polarization	Pancuronium and gallamine block
Muscarinic (M2)	Autonomic ganglia: ganglion cell bodies	Augments depolarization: slow, delayed depolarization	Atropine blocks: not affected by nondepolarizing muscle relaxants
Muscarinic	Postganglionic neuron terminal of autonomic nerves	Negative feedback for transmitter release	Pancuronium and gallamine block
Esteratic	AChE	Hydrolysis of ACh	Not significantly affected by relaxants
Esteratic	Pseudocholinesterase	Hydrolysis of ACh, succinylcholine, and mivacurium	Succinylcholine and mivacurium are substrates Inhibited by pancuronium Weakly inhibited by vecuronium and atracurium

ACh, acetylcholine; AChE, acetylcholinesterase

TABLE 12-12 -- Approximate Autonomic Margins of Safety of Nondepolarizing Relaxants[a]

DRUGS	VAGUS[b]	SYMPATHETIC GANGLIA[b]	HISTAMINE RELEASE[c]
Benzylisoquinolinium compounds			
d-Tubocurarine	0.6	2.0	0.6
Metocurine	3.0	16.0	2.0
Doxacurium	>50	>100	>4.0
Atracurium	16	40	2.5
Mivacurium	>50	>100	3.0
Cisatracurium	>50	>50	None
Steroidal compounds			
Pancuronium	3.0	>250	None
Vecuronium	20	>250	None
Pipecuronium	25	>200	None
Rocuronium	3.0-5.0	>10	None
Rapacuronium	2.0-3.0	? 5-20	? 3.0
Others			
Alcuronium	3.0	4.0	None
Gallamine	0.6	>100	None

[a] Definition: number of multiples of the ED_{95} for neuromuscular blockade required to produce the autonomic side effect (ED_{50})
[b] In the cat
[c] In human subjects

Specific Autonomic Mechanisms

Ganglionic Stimulation

The depolarizing relaxant succinylcholine may produce an elevation in heart rate and in arterial pressure secondary to the mechanism of ganglionic stimulation, [59] [60] which is probably mediated by activation of nicotinic receptors on ganglion cells on both sides of the autonomic nervous system. In patients who have received an anticholinergic drug, e.g., atropine, the chief cardiovascular response is elevated heart rate and arterial pressure. In subjects not given an anticholinergic drug beforehand, the result of ganglionic stimulation by succinylcholine may be either bradycardia and a decrease in blood pressure or increased heart rate and blood pressure, depending on the activity of the patient's autonomic nervous system at the time of administration of succinylcholine. For example, the cardiovascular response to succinylcholine in a patient who is very anxious before induction of anesthesia or who is receiving a catecholamine infusion may include ventricular arrhythmias. In patients receiving beta-adrenergic blockers, on the other hand, bradycardia after succinylcholine should be expected.

Succinylcholine produces a dose-related positive chronotropic effect through stimulation of the sinoatrial node by the release of catecholamines from adrenergic nerve endings. By contrast, succinylmonocholine causes a decrease in heart rate. [180]

TABLE 12-12A -- Clinical Autonomic Effects of Neuromuscular Blocking Drugs

DRUG TYPE	AUTONOMIC GANGLIA	CARDIAC MUSCARINIC RECEPTORS	HISTAMINE RELEASE
Depolarizing substance			
Succinylcholine	Stimulates	Stimulates	Slight
Benzylisoquinoline class			
d-Tubocurarine	Blocks	None	Moderate
Metocurine	Blocks weakly	None	Slight
Doxacurium	None	None	None
Atracurium	None	None	Slight
Mivacurium	None	None	Slight
Cisatracurium	None	None	None
Steroid class			
Pancuronium	None	Blocks moderately	None
Vecuronium	None	None	None
Pipecuronium	None	None	None
Rocuronium	None	Blocks weakly	None
Rapacuronium [a]	? None	Blocks moderately	? Slight
Others			
Alcuronium	Blocks weakly	Blocks weakly	None
Gallamine	None	Blocks strongly	None

[a] Has not been extensively studied; may also block calcium channels

Ganglionic Blockade

The ganglion-blocking effect of dTc occurs closer to the neuromuscular blocking effects than in the case of any other muscle relaxant. [177] [181] Nevertheless, the principal reason for the hypotensive property of dTc in humans is its histamine-releasing action. [182] Tables 12-12 and 12-12A show that the dose ratio of dTc for histamine release is about 0.6, well within the neuromuscular blocking dose range.

Muscarinic Blockade

Vagal block, resulting in tachycardia, is produced by muscarinic receptor blockade at the sinus node of the heart in response to pancuronium and gallamine. Gallamine is a potent vagolytic substance in which this side effect occurs within a lower dose range than that for neuromuscular blockade. [179] The dose-response curve for the vagolytic property of pancuronium lies slightly to the right of its neuromuscular blocking effects, [179] so that in clinical practice pancuronium is probably only partially vagolytic. The result is usually only a moderate rise in heart rate (10 to 25 beats/min) when high doses of pancuronium are administered. [183] [184] The new steroidal relaxant rocuronium shows a dose ratio of vagal block to neuromuscular block of about 5.0. Some clinical studies have shown dose-related increases in heart rate, suggesting that rocuronium may be slightly vagolytic at high dosage in human subjects. [185] The new short-to-intermediate-acting steroidal agent ORG 9487 (rapacuronium) is also moderately vagolytic within the clinical dose range. The vagolytic effect of relaxants is limited to receptors in the sinus node of the heart. Other classic muscarinic sites in the parasympathetic nervous system, such as bowel, bladder, bronchi, and pupils, are not affected.

Muscarinic Blockade Within the Sympathetic Nervous System

There are at least three sets of muscarinic receptors in the sympathetic nervous system (Fig. 12-13) (Figure Not Available) . Two of these are blocked by neuromuscular blocking agents, such as pancuronium and gallamine, that have a vagolytic property. That is, these relaxants can block muscarinic receptors in the sinus node of the heart, on the parasympathetic side of the autonomic nervous system. One mechanism, muscarinic receptor blockade on a dopaminergic interneuron within a pathway responsible for inhibitory input to sympathetic ganglion cells, [186] results in less modulation of augmented ganglionic traffic during periods of relatively intense stimulation; and another mechanism, muscarinic receptor blockade at adrenergic neuron terminals, results in reduction of a negative feedback mechanism regulating catecholamine output. [187] Both mechanisms may not only contribute to increases in heart rate normally seen with pancuronium but may also represent supportive mechanisms facilitating exaggerated cardiovascular responses sometimes seen in the presence of pancuronium block under light anesthesia during intense surgical stimulation (including laryngoscopy and tracheal intubation).

Inhibition of Catecholamine Reuptake

Pancuronium inhibits reuptake of norepinephrine by adrenergic nerves. [188] [189] [190] [191] This mechanism may also contribute

Figure 12-13 (Figure Not Available) Muscarinic receptors within the autonomic nervous system. These are labeled M1, M2, and M3. Vagolytic neuromuscular blocking drugs classically block M2 receptors at the sinus node of the heart. They may also block at M2 receptors at postganglionic neuroeffector junctions, where blockade of receptors located on postganglionic nerve terminals facilitates release of transmitter. Blockade of M2 receptors on a dopaminergic interneuron in the sympathetic nervous system augments ganglionic transmission by inhibiting a "braking" mechanism. N, nicotinic receptor; dTC, *d*-tubocurarine; F, fazadinium; P, pancuronium; G, gallamine. *(From Birdsall et al [185A])*

to exaggerated cardiovascular responses during pancuronium block.

Histamine Release

Quaternary ammonium compounds, such as muscle relaxants, are generally weak histamine-releasing substances relative to tertiary amines, such as morphine. Nevertheless, when large doses of certain muscle relaxants are injected rapidly by the intravenous route, some degree of erythema of the face, neck, and upper torso may develop, possibly together with a brief fall in arterial pressure and a slight-to-moderate rise in heart rate. Bronchospasm is very rare. The side effect of histamine release is most often noted following administration of the benzylisoquinolinium class of muscle relaxants, although it has been noted in steroidal relaxants of low potency. The effect is usually of short duration (1-5 minutes), is dose-related, and is clinically insignificant in healthy patients. The side effect may be reduced considerably by a slower injection rate. It is also prevented by prophylaxis with combinations of histamine $_1$ - and histamine$_2$ - blockers. If a minor degree of histamine release such as described above occurs after an initial dose of muscle relaxant, subsequent doses will generally cause no response at all, as long as they do not exceed the original dose. This is clinical evidence of tachyphylaxis, an important characteristic of histamine release.

A much more significant degree of histamine release occurs during anaphylactic or anaphylactoid reactions; these reactions are very rare. Anaphylactic reactions are mediated through immune responses involving IgE antibodies fixed to mast cells. Anaphylactoid reactions probably are not immune-mediated and represent exaggerated pharmacologic responses in very rare and very sensitive individuals.

For an excellent review of the topic of histamine release by muscle relaxants, see the paper by Basta. [192] The side effect of histamine release by the benzylisoquinolinium class of muscle relaxants may be viewed as a pharmacologic response wherein, as dosage is increased, the percentage of individuals responding with some manifestation of the side effect increases. This type of response involves chemical displacement of the contents of mast cell granules containing histamine, prostaglandin, and possibly other vasoactive substances. [192] The serosal mast cell, located in the skin and connective tissue and near blood vessels and nerves, is principally involved in the degranulation process. [192]

Hatano et al [193] showed that the hypotensive cardiovascular response to dTc (0.6 mg/kg) in humans is prevented (Fig. 12-14) (Figure Not Available) not only by antihistamines but also by NSAIDs (e.g., aspirin). These investigators concluded that the final step in dTc-induced hypotension is modulated by prostaglandins that are vasodilators. [193]

When an increase of histamine levels in plasma to 200 to 300 percent of baseline levels occurs, a brief decrease in arterial blood pressure (1-5 minutes), an increase in heart rate, and skin erythema about the face and neck may occur. The benzylisoquinolinium substances dTc, metocurine, mivacurium, and atracurium release these amounts of histamine in a dose range of 0.5 to 3 times the ED_{95} for each compound. Thus, the safety margin for this side effect is about three times greater for atracurium and mivacurium

Figure 12-14 (Figure Not Available) Inhibition by aspirin or diphenhydramine of the blood pressure decrease in anesthetized patients following *d*-tubocurarine (dTc) (0.6 mg/kg). The corresponding rise in $PGF_{1\ alpha}$ was also prevented by aspirin or diphenhydramine, suggesting that prostaglandin-induced vasodilation is the final step in dTc-induced hypotension. AP, aspirin-treated; DH, diphenhydramine-treated. *(From Hatano et al [193])*

and two times greater for metocurine than for dTc. [192] [193] [194] [195] The side effect occurs well within the clinical dose range for dTc and is therefore common during its use. It is less prominent with metocurine, atracurium, and mivacurium, unless doses in the range of three times the ED_{95} are injected rapidly (5-10 seconds). As in the case of dTc, [182] any decrease in blood pressure that may develop during the use of these drugs is probably directly related to elevation of serum histamine levels. The amount of histamine released by any of these drugs is both dose-related and related to the speed of injection. [182] [192] [193] [194] [195] Thus, cardiovascular responses to a very large dose of atracurium (0.6 mg/kg) may be prevented by slow injection or by prophylaxis with antihistamines (both histamine $_1$ - and histamine$_2$ -blockers are necessary). [196] Although multiple cardiovascular studies have been performed with atracurium, the most aggressive was that conducted by Hosking et al. [197] They gave atracurium (1.5 mg/kg) (six times the ED_{95}) as an intravenous bolus. Not surprisingly, they observed an average decrease in mean arterial blood pressure of 30 percent and a large (10- to 20-fold) increase in plasma histamine concentrations. Scott et

al [196] and Hosking et al [197] found that combined histamine$_1$ - and histamine$_2$ -receptor blockade attenuated these histamine-induced changes. Mivacurium releases histamine in about the same multiples of the ED_{95} as does atracurium. When 0.15 mg/kg (two times the ED_{95}) is given over 60 seconds to patients with coronary artery disease, only minimal cardiovascular changes occur. [198] When mivacurium is given more rapidly or in larger doses to these patients, hypotension is more likely to occur. In healthy patients, a brief decrease in arterial pressure may develop at a dosage greater than two times ED_{95} when these larger doses are injected rapidly [140] [195] (Fig. 12-15) (Figure Not Available) .

Clinical Cardiovascular Manifestations of Autonomic Mechanisms

Hypotension

d-Tubocurarine causes hypotension, probably as a result of the liberation of histamine; in larger doses, it produces ganglionic blockade. [199] [200] [201] [202] Dowdy et al [202] proposed that hypotension is not caused by the dTc itself but by the preservative in its formulation. However, in anesthetized patients, Stoelting [203] [204] disproved this theory. Premedication with promethazine, an antihistamine drug, will attenuate dTcinduced hypotension. [204] Hypotension is directly related to dose of dTc and to anesthetic depth, [201] especially if the anesthetic is itself a sympathetic nervous system depressant such as halothane or isoflurane. With a light level of surgical anesthesia and the use of smaller doses of dTc (15 mg/70 kg), the incidence of significant hypotension is markedly attenuated. Although hypotension can occur after administration of metocurine, the incidence and magnitude are much less than those associated with dTc. Atracurium in doses greater than 0.4 mg/kg and mivacurium in doses greater than 0.15 mg/kg occasionally cause transient hypotension due to histamine release. Histamine release can be minimized by slower administration (20-30 seconds at three times ED_{95}) of these muscle relaxants [195] [196] [198] (see Fig. 12-15) (Figure Not Available) .

Tachycardia

Pancuronium causes a moderate increase in heart rate and, to a lesser extent, in cardiac output, with little or no change in systemic vascular resistance. [183] [184] Although pancuronium-induced tachycardia has been attributed to a vagolytic action, [179] [183] numerous investigators have implicated the sympathetic nervous system as well. Both indirect (release of norepinephrine from adrenergic nerve endings) [188] [205] and direct (blockade of neuronal uptake of norepinephrine) mechanisms have been suggested. [188] [189] [190] Vercruysse et al [191] suggested that both gallamine and pancuronium augment the release of norepinephrine in vascular tissues under vagal control. In studies in humans, Roizen et al [206] surprisingly found a decrease in plasma norepinephrine levels after administration of either pancuronium or atropine. These researchers postulated that the increase in heart rate or rate-pressure product occurs because

Figure 12-15 (Figure Not Available) Dose response to mivacurium in patients under nitrous oxide-oxygen-opioid anesthesia. Maximum changes at each dose are shown; *n* = 9 subjects per group. (A), With fast injection a 15 to 20 percent decrease in arterial pressure occurred at 2.5 to 3 times ED_{95} (0.20 to 0.25 mg/kg). (B) The changes were less than 10 percent when slower injection (30 seconds) was done. *(From Savarese et al [140])*

pancuronium (or atropine) acts through baroreceptors to reduce sympathetic outflow. More specifically, the vagolytic effect of pancuronium increases heart rate and, hence, blood pressure and cardiac output (Fig. 12-16) (Figure Not Available) , in turn influencing the baroreceptors to decrease sympathetic tone. Support for this concept is provided by the fact that prior administration of atropine will attenuate or eliminate the cardiovascular effects of pancuronium. [183] Gallamine increases heart rate by both a vagolytic effect [179] [207] and sympathetic stimulation. [208] Specifically, gallamine releases norepinephrine from adrenergic nerve endings in the heart by an unknown mechanism. [208] However, a positive chronotropic effect that places emphasis on the vagolytic mechanism has not been found in humans. [209] It would not be surprising to find out ultimately that gallamine and pancuronium act by similar mechanisms.

Figure 12-16 (Figure Not Available) Hemodynamic responses to pancuronium (0.1 mg/kg) and to pipecuronium (0.05, 0.1, or 0.15 mg/kg) in patients under opioid anesthesia. Injection was done at time = 0. Expected increases in heart rate and cardiac index were noted after pancuronium (open circles). These changes were not seen after any of the three doses of pipecuronium (squares, closed

circles). *(From Tassonyi et al [235])*

Arrhythmias

Gallamine, dTc, and succinylcholine actually reduce the incidence of epinephrine-induced arrhythmias. [210] Possibly because of enhanced atrioventricular conduction, [211] the incidence of arrhythmias from pancuronium appears to increase during halothane anesthesia. [183] Edwards et al [212] observed a rapid tachycardia (more than 150 beats/min) that progressed to atrioventricular dissociation in two patients anesthetized with halothane. The only factor common to these two patients was that both were receiving tricyclic antidepressants. In further studies, Edwards et al found the incidence of severe ventricular arrhythmia to be common in response to administration of pancuronium to dogs receiving halothane (but not enflurane) and chronically administered tricyclic antidepressants. In conclusion, the drug interaction among tricyclic antidepressants, halothane, and pancuronium must be avoided. Use of another nonvagolytic muscle relaxant, such as vecuronium or cisatracurium, is probably the most convenient approach in a patient receiving tricyclic antidepressants who must have halothane anesthesia.

Bradycardia

Several case reports [213] [214] have described severe bradycardia and even asystole following vecuronium or atracurium administration. All of these cases were associated with opioid administration. Subsequent studies indicate that vecuronium or atracurium alone does not cause bradycardia, [215] but when combined with other drugs (e.g., fentanyl) that do cause bradycardia, the nonvagolytic relaxants such as vecuronium, cisatracurium, and atracurium simply allow this mechanism to occur unopposed. The moderate vagolytic effect of pancuronium is often used to counteract opioid-induced bradycardia.

Individual Nondepolarizing Relaxants

d-Tubocurarine

d-Tubocurarine (curare, dTc) was the first relaxant introduced into clinical practice (1942). It was introduced by Griffith and Johnson [1] in Montreal, where it was first administered during an appendectomy. The corrected formula is shown in Figure 12-17 , where dTc is depicted as a monoquaternary compound. Curare remained popular until the early 1970s, when pancuronium became the most commonly prescribed nondepolarizer. The drug is indicated for longer operations (3-4 hours) in which early extubation is not important and in which a decrease in blood pressure is acceptable or desired.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.5	
Intubation (at t = +3 min)	0.5-0.6	60-100
Relaxation (N_2O/O_2)	0.3-0.5	30-60
Relaxation (Vapor)	0.2-0.3	30-60
Maintenance	0.1-0.15	30-45

Cardiovascular Side Effect

The most common side effect of dTc is release of histamine, [182] [192] [193] [199] which occurs when a dosage of more

Figure 12-17 The chemical formula of *d*-tubocurarine shows that it is a monoquaternary compound. The tertiary nitrogen at the lower right is shown in the protonated form.

Figure 12-18 (Figure Not Available) Relationship of decrease in blood pressure to increase in plasma histamine concentration following *d*-tubocurarine administration to patients under nitrous oxide-oxygen-barbiturate-opioid anesthesia. There is a highly significant correlation, which is dose-related. *(From Moss et al [182])*

than 0.3 mg/kg is given rapidly as a bolus (10-15 seconds). Plasma histamine levels may increase as much as 10-fold (Fig. 12-18) (Figure Not Available) , causing a transient decrease in blood pressure of 30 to 50 percent. [182] Although a ganglion-blocking effect is easily demonstrable in animals, [179] [199] this side effect is probably beyond the clinical dose range. *d*-Tubocurarine is nonvagolytic; as such, increases in heart rate are uncom-mon, except as part of the syndrome of histamine release. [179] [182] [199] Histamine release is prevented by slow administration of the drug (e.g., at a rate of 0.3 mg/kg/min) or by administration of smaller doses of the drug.

Metabolism and Elimination

There is no active metabolism of dTc. The kidney is the major pathway of elimination, with approximately 50 percent of a dose being eliminated through renal pathways. The liver is probably a secondary route of elimination. The drug is not indicated for use in patients with either renal [120] or hepatic [216] failure, as more suitable agents are available.

PHARMACOLOGY OF NONDEPOLARIZING MUSCLE RELAXANTS - continued

Individual Nondepolarizing Relaxants

Metocurine

Metocurine (Fig. 12-19) is a semisynthetic derivative of dTc, first synthesized by King [217] in 1935 as part of the work that first suggested a chemical structure for dTc. It is the N,O,O-trimethylated compound. Unlike dTc, it is a bisquaternary molecule. It was introduced into clinical practice in 1948 by V.K. Stoelting et al, [218] who recognized its lesser cardiovascular effect in comparison with dTc. Metocurine is about twice as potent as curare in human subjects, with a similarly long duration of action. [219] Its principal advantage over curare is its weaker histamine-releasing property--less than one-half that of dTc. [194] [199] Metocurine is indicated for longer operations (3-4 hours) in which early extubation is unnecessary and in which no change in heart rate is desirable.

Figure 12-19 Chemical formula of metocurine. Metocurine is a bisquaternary compound. With respect to *d*-tubocurarine (dTc), it is additionally methylated at both phenolic hydroxyl groups and at the tertiary nitrogen. It is therefore the trimethylated derivative of dTc.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.28	
Intubation (at t = +3 min)	0.3-0.4	60-120
Relaxation (N_2O/O_2)	0.15-0.2	40-60
Relaxation (Vapor)	0.1-0.15	40-60
Maintenance	0.05-0.1	30-45

Cardiovascular Side Effects

The only effect pertinent to clinical practice is histamine release, which may occur at a dosage in the range of 0.3 to 0.4 mg/kg or more. [194] [199] A brief decrease in blood pressure may result from rapid administration of these doses. [219] Metocurine has no ganglion-blocking or vagolytic effect. [179] [199]

Metabolism and Elimination

Metocurine is excreted only by the kidney. It has no alternate biliary pathway, and no metabolism occurs in the liver. [220]

Gallamine

Gallamine is a long-acting drug (Fig. 12-20) . It was the first synthetic neuromuscular blocking drug to be introduced into clinical practice. Gallamine was synthesized originally by Bovet [38] and colleagues as part of an extensive

Figure 12-20 Chemical formula of gallamine, a trisquaternary ether of gallic acid. Gallamine is the only trisquaternary compound zavailable. Its strong vagolytic property is likely due to the trisquaternary structure.

structure-activity study that helped evolve the concepts of "pachycurares" and "leptocurares." Succinylcholine also evolved from this work, for which Bovet received the Nobel Prize.

The trisquaternary structure of gallamine confers a strong vagolytic property. [179] Although gallamine might be indicated for longer operations (3-4 hours), its obligatory renal excretion [221] and vagolysis may render it less suitable than other agents, particularly when a distinct increase in heart rate is not desirable.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	3.0	
Intubation (at t = +2 min)	4.0-6.0	90-120
Relaxation (N_2O/O_2)	2.0-3.0	40-60
Relaxation (Vapor)	1.0-2.0	40-60
Maintenance	0.3-0.5	30-40

Cardiovascular Side Effects

The strong vagolytic effect of gallamine [179] and the increased release of myocardial catecholamines that is associated with its use [208] result in an increased heart rate. The tachycardia may be marked and is very evident, even at low doses that do not produce any neuromuscular blockade (0.2-0.3 mg/kg), because the dose-response curve for the vagolytic property actually lies considerably to the left of that for neuromuscular blockade. [179] Blood pressure, as well as heart rate, is

often elevated. [209] Gallamine does not release histamine or block autonomic ganglia [179] and therefore does not cause a decrease in blood pressure.

Metabolism and Elimination

Gallamine is not metabolized and is excreted unchanged in the urine only. There is no alternative biliary excretory pathway. [221]

Alcuronium

Alcuronium (Fig. 12-21) is the semisynthetic diallyl derivative of toxiferine I. It is a long-acting drug with few cardiovascular side effects and, therefore, is indicated for longer operations (3-4 hours) in which cardiovascular stability is desired and early extubation is not needed.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.2	
Intubation (at t = +3 min)	0.25-0.3	60-120
Relaxation (N_2O/O_2)	0.15-0.2	40-60
Relaxation (Vapor)	0.1-0.15	40-60
Maintenance	0.05-0.1	30-45

Figure 12-21 Chemical formula of alcuronium, the semisynthetic diallyl derivative of toxiferine. The quaternizing allyl groups actually reduce the potency by a factor of 3 to 5.

Cardiovascular Side Effects

Alcuronium is a very weak ganglion blocker and is very weakly vagolytic. [179] A slight increase in heart rate is occasionally observed following its administration. Decreases in blood pressure are rare. [222] The drug does not cause release of histamine.

Metabolism and Elimination

There is little or no metabolism. The urine is the major excretory pathway. There is a small amount of biliary clearance of unchanged drug. [223]

Pancuronium

Pancuronium (Fig. 12-22) is a long-acting drug. The drug was originally designed by Hewett and Savage. [224] In a brilliant medicinal-chemical maneuver, they appended two acetylcholine-like moieties to the rigid steroidal androstane framework. [225] [226] The drug was an instant success [6] because its high potency, lack of hypotensive effect, and mild-to-moderate vagolytic property contrasted markedly with the cardiovascular side effects of dTc and gallamine, the only two commonly used nondepolarizers in the United States at that time (1970-1971). Its administration is ideally suited to longer operations (3-4 hours) in which prompt extubation is not necessarily important and in which a slight-to-moderate increase in heart rate and blood pressure might be desirable.

Figure 12-22 Chemical formula of pancuronium. The introduction of acetylcholine-like fragments into the A and D rings of pancuronium is a unique feature that is retained in all other clinically available steroidal relaxants. The vagolytic property is largely due to the A-ring substitutions.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.06-0.07	
Intubation (at t = +2-3 min)	0.08-0.12	60-120
Relaxation (N_2O/O_2)	0.05-0.06	30-60
Relaxation (Vapor)	0.03	30-60
Maintenance	0.01-0.015	30-40

Cardiovascular Side Effects

A moderate vagolytic effect [179] and stimulation of the sympathetic nervous system [186] [187] [188] [189] [190] [191] [205] usually cause an increase in heart rate, blood pressure, [183] [184] and cardiac output (see Fig. 12-15) (Figure Not Available) . The mechanisms that contribute to sympathetic nervous system stimulation include facilitation of ganglionic transmission, increased catecholamine release, and decreased reuptake of catecholamines [186] [187] [188] [189] [191] [205] (see Fig. 12-16) (Figure Not Available) .

Metabolism and Elimination

Pancuronium is cleared largely by the kidney. [227] A small amount (10-20%) is deacetylated at the 3-position in the liver. [143] [228] The parent compound and the 3-OH metabolite are cleared in small [143] [228] amounts via the minor liver pathway. The total clearance is delayed, and the duration of action is significantly lengthened by severe disorders of renal or hepatic function. [119] [229] [230] [231] [232] The 3-OH metabolite is about half as potent a neuromuscular blocking agent as the parent compound. [233] It has a duration of action and kinetic pattern similar to that of pancuronium. The 3-OH metabolite is also most likely excreted largely by the kidney. [233]

Pipecuronium

Pipecuronium (Fig. 12-23) is a pancuronium derivative in which the 2,16-substitutions are piperazinium groups. It was introduced in eastern Europe during the early 1980s and in the United States nearly 10 years later. [234] Pipecuronium is about 20 to 30 percent more potent than pancuronium. Like pancuronium, it is a long-acting drug. Therefore, it is suited to longer operations (3-4 hours) in which early extubation is not mandatory.

Figure 12-23 Chemical formula of pipecuronium. The positive charge on the quaternary nitrogens is further separated by two carbon atoms from the carboxyl groups than in the case of pancuronium. This chemical change reduces the vagolytic effect by a factor of about 10.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)

ED_{95}	0.04-0.05	
Intubation (at t = +2-3 min)	0.08-0.12	80-120
Relaxation (N_2 O/O_2)	0.04-0.06	40-60
Relaxation (Vapor)	0.2-0.3	40-60
Maintenance	0.005-0.01	30-45

Cardiovascular Side Effects

Because in pipecuronium the 2,16-substitutions are piperazinium groups, the quaternary nitrogens are moved farther away from the 3,17-acetoxy substitutions. This lessens the vagolytic property of the relaxant by a factor of about 10 when compared with pancuronium. Additionally, pipecuronium does not block autonomic ganglia, nor does it release histamine. As such, it does not affect cardiovascular responses in the clinical dose range. Tassonyi et al [235] compared the hemodynamic responses following administration of pipecuronium or pancuronium in anesthetized patients (see Fig. 12-16) (Figure Not Available) . As expected, a significant increase in heart rate (30%) and cardiac index (12%) was observed after somewhat less than two times ED_{95} of pancuronium (0.10 mg/kg), whereas hemodynamic changes were minimal following pipecuronium doses of up to 0.15 mg/kg (three times ED_{95}).

Metabolism and Elimination

There is very little metabolism of pipecuronium. Only a very small amount of the drug (5%) may be deacetylated at the 3-position. The major excretory pathway is the kidney. The liver is possibly a minor secondary pathway. Excretion is delayed, clearance is decreased, and the elimination half-life is lengthened in the presence of major disorders of renal or hepatic function. [236] [237] [238]

Doxacurium

Doxacurium (Fig. 12-24) is a very potent, very longacting benzylisoquinolinium ester. Interestingly, although it is an ester of succinic acid, it undergoes no hydrolysis by pseudocholinesterase. [14] This may be due to its very high neuromuscular blocking potency and the relatively small

Figure 12-24 Chemical formula of doxacurium. Although an ester of succinic acid, this very potent benzylisoquinolinium compound is not metabolized in human subjects. Consequently, it is a long-lasting substance.

amount of drug administered with each dose. It was introduced in 1991 as the first benzylisoquinolinium relaxant free of side effects. [14] [239] It is about 20 times as potent as dTc and is indicated for longer operations (3-4 hours) in which cardiovascular stability is important and in which early extubation is not necessary.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.025	
Intubation (at t = +3-4 min)	0.05-0.08	90-150
Relaxation (N_2 O/O_2)	0.02-0.03	45-60
Relaxation (Vapor)	0.015-0.02	45-60
Maintenance	0.005-0.01	30-60

Cardiovascular Side Effects

There is no vagolytic or ganglion-blocking effect associated with the administration of doxacurium. Doses of up to four times ED_{95} do not cause histamine release. [14] Consequently, there are no cardiovascular side effects of note in clinical practice. [14] [239] [240] Stoops et al [240] demonstrated minimal changes in hemodynamic variables (cardiac output, right- and left-sided filling pressure, heart rate, mean arterial pressure) following doxacurium doses up to and including three times ED_{95} (0.075 mg/kg).

Metabolism and Elimination

There is no metabolism of doxacurium in humans. The drug is excreted in the urine and bile as the unchanged parent molecule. The urine is the major route of elimination, with the bile a minor secondary pathway. [241] [242]

Vecuronium

Vecuronium (Fig. 12-25) , the 2-desmethyl analogue of pancuronium, was recognized in the mid-1970s by Savage, Durant, Bowman, and Marshall [9] [40] [243] as having much less vagolytic effect and a shorter duration of action than pancuronium in the cat. These pharmacologic properties were subsequently confirmed in surgical patients. [244] [245] The identification of vecuronium represents a noteworthy collaborative

Figure 12-25 Chemical formula of vecuronium. Vecuronium is the monoquaternary analogue of pancuronium. The lack of a quaternizing methyl group in the 2-position removes the vagolytic effect and enables greater liver uptake with regard to pancuronium.

effort between industrial chemists and academic pharmacologists working at the University of Strathclyde in Glasgow, Scotland, and at Organon's chemical laboratories at nearby Newhouse. Remarkably, in a similar collaborative effort at Strathclyde, atracurium was discovered during the same period by Stenlake and coworkers (see below). The two groups of investigators were working on separate floors in the same building of the university.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.5	
Intubation (at t = +1.5-3 min)	0.1-0.2	45-90
Relaxation (N_2 O/O_2)	0.05	25-40
Relaxation (Vapor)	0.03-0.04	25-40
Maintenance	0.01-0.02	15-30
Infusion	0.8-2.0 mug/kg/min	

Vecuronium and atracurium, together, revolutionized clinical practice as the first nondepolarizers of intermediate duration. [246] The major contributions of the

intermediate-acting drugs are (1) more facile tracheal intubation with nondepolarizers; (2) easier administration by infusion for maintenance of blockade during surgery; and (3) faster and more complete antagonism of residual blockade at the end of the case. In addition, vecuronium's remarkable lack of cardiovascular effect established a benchmark for future relaxants.

Cardiovascular Side Effects

Vecuronium is about 20 times weaker as a vagolytic substance than pancuronium. The structural feature responsible for this difference is the absence of the 2-methyl quaternizing group. This markedly reduces the ACh-like character of the A-ring substitutions, resulting in less attraction to cardiac muscarinic receptors. The markedly reduced vagolytic property, together with absent ganglionic blocking and histamine-releasing effects, results in a noteworthy lack of cardiovascular responses throughout a wide clinical dose range from one to eight times the ED_{95} (0.05 to 0.40 mg/kg). [247] [248]

Metabolism and Elimination

The metabolic pathways of vecuronium are shown in Figure 12-10 (Figure Not Available) . Vecuronium is taken up into the liver by a carrier-mediated transport system. [249] Vecuronium is deacetylated at the 3-position by liver microsomes. Vecuronium undergoes two to three times as much metabolism as pancuronium, such that 12 to 30 percent of vecuronium is eventually excreted as the metabolite 3-desacetylvecuronium (3-OH vecuronium). [250] [251] [252] Although the liver is the principal organ of elimination for vecuronium, the drug also undergoes significant (up to 25%) renal excretion. [250] [252]

The principal metabolite, 3-desacetylvecuronium, is a potent (
80% of vecuronium) neuromuscular blocking drug

in its own right. The metabolite, however, has a lower plasma clearance and longer duration of action than vecuronium. [252] In patients in the ICU who have renal failure, 3desacetylvecuronium can accumulate and produce prolonged neuromuscular blockade. [253]

The excretion of vecuronium is diminished in the presence of decreased renal or hepatic function in the elderly and in children younger than 1 year of age. [254] The duration of action of vecuronium is longer in these groups of patients, and recovery is slower than in young healthy individuals. Despite its lengthening of action in patients with hepatic or renal dysfunction, vecuronium can be given to these patients provided its administration is guided by neuromuscular monitoring (Ch. 39).

Rocuronium

Rocuronium (ORG 9426) (Fig. 12-26) is a steroidal relaxant of intermediate duration, with an onset of action that is faster than that of vecuronium. [255] [256] [257] [258] It has become popular because of its faster onset. It is seven to eight times less potent than vecuronium [255] [256] [257] [258] [259] but has about the same molecular weight; thus, a greater number of drug molecules are able to reach junctional receptors within a few circulation times, enabling faster development of neuromuscular blockade. Weaker binding to receptors (lower potency), however, prevents *buffered diffusion,* a process that occurs with potent drugs, which causes repetitive binding and unbinding to receptors, keeping potent drugs in the neighborhood of effector sites and potentially lengthening the duration of effect. Diffusion of less potent drugs away from receptors very likely occurs much more readily, thereby helping to limit the duration of blocking effect. This is most likely the reason why the duration of action of rocuronium remains intermediate. [260] [261] The duration of action of rocuronium is also limited by avid liver uptake and elimination into the bile, [262] due to an increase in the lipophilic nature of the molecule with respect to vecuronium. The relationship of lower potency to faster onset of block in steroidal molecules has been described by Bowman et al [42] (see Fig. 12-6) and in the use of drugs in the clinic by Kopman. [138A] At appropriate dosage, 0.9 to 1.2 mg/kg, rocuronium enables tracheal intubation within 60 to 90 seconds, [263] [264] [265] and may be used as a substitute for succinylcholine in rapid intubation of the trachea. [266] [267] Other aspects of the clinical neuromuscular pharmacology of rocuronium seem similar to the properties of vecuronium.

Figure 12-26 Chemical formula of rocuronium, a vecuronium derivative of faster onset and intermediate duration. The faster onset is conferred by lowered potency induced by the D- and A-ring modifications (see Figs. 12-6 and 12-25).

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.3-0.4	
Intubation (at t = +60-90 s)	0.6-1.0	35-75
Relaxation (N_2 O/O_2)	0.3-0.4	30-40
Relaxation (Vapor)	0.2-0.3	30-40
Maintenance	0.1-0.15	15-25
Infusion	8-12 mug/kg/min	

Cardiovascular Side Effects

The autonomic safety ratio for vagal block (3.0-5.0) is about 10 times less than that of vecuronium. [268] [269] In doses up to 1.2 mg/kg, rocuronium has minimal cardiovascular effects both in healthy patients [270] [271] [272] [273] and in those with cardiovascular disease. [275] There is no detectable histamine release following rocuronium in doses up to 1.2 mg/kg. [270] Reports of slight to moderate increases in heart rate may be due either to the fact that rocuronium produces pain on injection [276] [277] or to its weak vagolytic effect. The heart rate increase may be controlled by the prior administration of fentanyl. [276] [277] In summary, rocuronium in doses up to 0.6 mg/kg has cardiovascular effects that are negligible. At higher dosage (0.9-1.2 mg/kg), increases in heart rate of 10 to 25 percent may occasionally be observed due to the weak vagolytic effect.

Metabolism and Elimination

Rocuronium is eliminated primarily by the liver, with a small fraction (
10%) eliminated in the urine. [262] It is taken up into the liver by a carrier-mediated active transport system. [278] [279] The putative metabolite, 17-desacetylrocuronium, has not been detected in significant quantities. In patients with hepatic disease (most commonly cirrhosis), the distribution volume of rocuronium is increased, [265] [280] [281] [282] and its clearance may be decreased. [282] The duration of action of rocuronium is prolonged in hepatic disease, [280] [281] [282] and its onset may be prolonged. [280] Consequently, dosing in patients with hepatic disease should be conservative and guided by careful monitoring of neuromuscular function. In patients with renal failure, the plasma clearance of rocuronium may be decreased, [283] and its distribution volume increased, [284] but the duration of action of single and repeated doses is not significantly affected. [285] In the elderly, the clearance of rocuronium is decreased and its distribution volume increased, and as a consequence, its duration of action is prolonged. [286]

Rapacuronium (ORG 9487)

Rapacuronium (ORG 9487) (Fig. 12-27) is a steroidal muscle relaxant, the 16N-allyl, 17beta propionate analogue of vecuronium. [287] It has low potency (ED_{90} 1.15 mg/kg), a fast onset, and short-to-intermediate duration of action depending on dosage. [287] [288] [289] Compared with vecuronium, rapacuronium has an onset of action that it twice as fast and a duration of action about one-half as long. [289] The peak effect of a

Figure 12-27 Chemical formula of rapacuronium (ORG 9487). The lower potency of this compound enables a speed of onset that approaches that of succinylcholine. The duration is short-to-intermediate, depending on dosage.

dose of 1.5 mg/kg occurs in 62 seconds at the laryngeal muscles and 96 seconds at the adductor pollicis during TOF stimulation. [290] Rapacuronium in doses of 1.5 to 2.0 mg/kg produces good intubating conditions at 60 seconds, [280] [291] which are similar to those of succinylcholine 1 mg/kg [288] and which have a clinical duration of action (recovery to 25% twitch height) of about 20 minutes, depending on dosage. [291] Intubating conditions at 60 and 90 seconds are comparable in young and elderly adults, respectively. There is an increased duration of action with increasing age. [291] With continued infusion for an hour, the time of recovery increases to that of an intermediate-duration relaxant. [292] This observation may be due to the accumulation of the 3-desacetyl metabolite (ORG 9488), which is more potent and longer-acting than the parent compound. [292] There is little clinical experience with this drug as yet, but it seems suitable for tracheal intubation and procedures lasting less than 60 minutes and may serve as an acceptable alternative to succinylcholine for emergent intubation of the trachea.

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	1.0-1.3	
Intubation (at t = +60-90 s)	1.5-2.5	15-35
Relaxation (N_2O/O_2)	1.0-1.5	15-20
Relaxation (Vapor)	0.6-1.0	15-20
Maintenance	0.2-0.5	15-20
Infusion [a]	12 9 mug/kg/min	

[a] Cumulation and slowed recovery tend to develop.

Cardiovascular and Other Side Effects

Despite its low potency and the consequent need to administer large amounts of the drug, some animal data suggest that rapacuronium may have little cardiovascular effect. [293] On the other hand, in early studies in anesthetized patients, doses in the range of 2-3 mg/kg were shown by Pitts et al [293A] to cause 20 to 22 percent decreases in blood pressure lasting more than 5 minutes. The dose of 3 mg/kg in this study was associated with an increase of plasma histamine of approximately 1 mug/mL. No cutaneous flushing or bronchospasm was noted in this study. Yamaguchi et al [293B] have shown that ORG 9487 can produce vasodilation in isolated human mammary arteries as a result of blockade of both receptor- and voltage-activated calcium channels. The effect on voltage-activated calcium channels is greater than that of vecuronium. [293B] In another study involving intubation of almost 200 patients after doses of up to 2.5 mg/kg, adverse cardiovascular effects were not common [291] ; bronchospasm was reported, however, at an incidence of about 5 percent during that study.

In any event, these early impressions of the effects of rapacuronium on vessels and bronchi in humans require further study, and greater experience with the drug in the clinic is needed.

Metabolism and Elimination

Rapacuronium has a plasma clearance of 8.5 to 11.1 mL/kg/min, which is consistent with its short-to-intermediate duration of action. [292] It has a steady-state volume of distribution of 457 mL/kg and an elimination half-life of 72 to 88 minutes. [287] Renal excretion amounts to 22 percent of an administered dose, [292] so it is possible that its principal route of elimination may be via the liver. The principal metabolite is 3-desacetylrapacuronium (ORG 9488), which is approximately twice as potent as the parent drug. With continued administration of rapacuronium, the metabolite may make a proportionately greater contribution to the neuromuscular blockade and more than likely cause delayed recovery. [287] [292]

Atracurium

Atracurium (Fig. 12-28) , a benzylisoquinolinium diester relaxant of intermediate duration of action, emerged from a series of studies by Stenlake and colleagues [43] in the mid-1970s that were designed to produce a nondepolarizing relaxant that might undergo Hofmann elimination. In this chemical reaction, a cyclic quaternary nitrogen grouping, under the influence of high pH and temperature, opens to a tertiary amine. In atracurium, Stenlake et al adapted the reaction to a molecule that not only has good neuromuscular blocking potency but also undergoes the reaction at physiologic pH and temperature. [106A] The drug was introduced into

Figure 12-28 Chemical formula of atracurium, a benzylisoquinolinium diester that undergoes Hofmann degradation (see Fig. 12-11) (Figure Not Available) . The reaction is facilitated at physiologic pH by the orientation of the ether oxygens toward the center of the chain, enabling the rupture of the linkage of the chain with the terminal ring system (laudanosine).

clinical practice in Britain by Payne and Hughes [293C] in 1981 and in the United States by Basta et al in 1982. [293D]

Atracurium is the first nondepolarizing muscle relaxant to be largely broken down in the blood stream; perhaps the most significant advance made with atracurium is its degradation by a chemical reaction (Hofmann elimination) that is not affected by biologic disorders (see Fig. 12-11) (Figure Not Available) .

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.23	
Intubation (at t = +2-3 min)	0.5-0.6	30-45
Relaxation (N_2O/O_2)	0.3-0.4	30-45
Relaxation (Vapor)	0.2-0.3	30-45
Maintenance	0.1-0.15	15-20
Infusion	4-12 mug/kg/min	

Cardiovascular Side Effect

Atracurium, being a benzylisoquinolinium, may cause the release of histamine at high dosage. This may occur when doses of more than 0.5 mg/kg (more than two times ED_{95}) are injected rapidly [139] [192] [194] [196] [293D] (Fig. 12-29). (Figure Not Available) When plasma histamine levels increase to over 1,000 pg/mL, facial erythema

and a transient decrease in blood pressure may be noted. Histamine release may be decreased by slower injection of the relaxant (30-60 seconds) [139] [192] [196] (see the section titled *Mivacurium*[140] [195] or by administration of smaller or divided doses of the relaxant. Combined histamine$_1$ - and histamine$_2$ -receptor blockade effectively prevents the cardiovascular manifestations of histamine release, which may be associated with the rapid administration of high doses of atracurium. [192] [196] [197] For example, Hosking et al [197] treated patients with intravenous diphenhydramine (1 mg/kg) and cimetidine (4 mg/kg) 30 minutes before giving a very large dose of atracurium (1.5 mg/kg or six times the ED_{95}). Atracurium-induced decreases in mean arterial pressure were reduced from 30 mm Hg (37% below baseline) in control subjects to 8 mm Hg (10% below baseline) in treated patients, despite a 10- to 20-fold increase in plasma

Figure 12-29 (Figure Not Available) Dose response to atracurium in patients under nitrous oxide-oxygen-barbiturate-opioid anesthesia. Curves represent maximum responses in at least nine patients per group. At two times ED_{95} for twitch inhibition (0.5 mg/kg), a decrease in arterial pressure and a slight increase in heart rate was noted. The divergence of arterial pressure and heart rate responses is characteristic of histamine release. *(From Basta et al [293C])*

histamine levels. Scott et al [196] obtained similar results in patients pretreated with chlorpheniramine and cimetidine 15 minutes before an atracurium dose of 0.6 mg/kg. Atracurium is nonvagolytic and does not block autonomic ganglia. [106A]

Metabolism and Elimination

Atracurium is degraded by the Hofmann elimination (see Fig. 12-11) (Figure Not Available) . The reaction is a purely chemical process that is accelerated by alkaline pH and increase in temperature. In fact, pH changes during clinical practice probably have very little effect on the speed of the reaction, whereas a decrease in the temperature of the patient below 34°C will slow the reaction and lengthen the blocking effect considerably. Some degree of enzymatic ester hydrolysis, not related to plasma cholinesterase, probably also occurs. [157] [160] [161] Although the actual amounts remain debated, [162] the majority of atracurium is destroyed in the plasma, and a much smaller amount is eliminated through renal pathways. There is no biliary excretion of atracurium.

A major metabolite of atracurium, laudanosine is a tertiary amine that can enter the central nervous system (CNS). Very high doses of laudanosine itself (5-15 mg/kg) may cause CNS excitation in laboratory animals, [164] [169] [170] [171] [172] but no clear-cut cases have been noted in humans, even when renal and hepatic failure are present. [167] [168] The potential effects of this metabolite of atracurium in the CNS in human subjects are likely subclinical, although difficult to determine in the ICU in patients who are partially paralyzed and/or sedated. Laudanosine is excreted in the urine and bile and is cleared more slowly than atracurium itself. [165]

Cisatracurium

Cisatracurium, the 1R- *cis,* 1R
- *cis* configuration of atracurium (Fig. 12-30) , is one of the ten stereoisomers that comprise atracurium. The atracurium mixture of isomers consists of approximately 15 percent cisatracurium. Cisatracurium is about four times more potent than atracurium and has minimal cardiovascular side effects. [46A] [294] [294E] Like atracurium, it has an intermediate duration of action. [294A] [294B]

A comparison of the speed of onset of blockade versus the potency of the various isomers of atracurium yields a very cogent proof that onset is accelerated in less potent compounds and decreased in compounds of higher potency in the benzylisoquinolinium series of relaxants (Fig. 12-31) (Figure Not Available) . The proof is so compelling because all stereoisomers of atracurium, of course, have the same molecular weight. [46A]

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.05	
Intubation (at t = +1.5-3 min)	0.15-0.2	40-75
Relaxation (N_2O/O_2)	0.05	30-45
Relaxation (Vapor)	0.03-0.04	30-45
Maintenance	0.01-0.02	15-20
Infusion	1-2 mug/kg/min	

Figure 12-30 Chemical formula of cisatracurium (51W89). This compound is one of the stereoisomers of atracurium. The R- *cis,*R
- *cis* conformation confers greater potency and significantly reduces the side effect of histamine release in comparison with atracurium.

Cardiovascular Side Effects

The autonomic safety ratios for cisatracurium, atracurium, and vecuronium were compared in the cat. [45] [469] Cisatracurium had higher autonomic safety ratios than atracurium. Furthermore, it had less propensity to cause histamine release. Atracurium was shown to cause marked elevations of plasma histamine at doses of 25 to 50 times ED_{95} in the cat, whereas cisatracurium did not affect plasma histamine concentrations in doses as high as 80 times ED_{95} . [45] [469]

In humans as well as animals, cisatracurium does not cause histamine release. [294C] [294D] [295] Doses of eight times ED_{95} do not cause cardiovascular changes suggestive of histamine release or increases in plasma histamine concentration even when administered as a rapid (5-second) intravenous bolus. Doses of two times ED_{95} have been given to patients with coronary artery disease, and hemodynamic

Figure 12-31 (Figure Not Available) Regression of onset (ordinate) versus potency in atracurium and its individual isomers. As in the case of steroidal relaxants (see Fig. 12-6) , onset is faster in substances of low potency. The relationship is very compelling in this series of benzylisoquinolinium molecules because their molecular weights are identical. *(From Wastila et al [175A])*

Figure 12-32 Slopes of spontaneous recovery of twitch following 0.1, 0.2, and 0.4 mg/kg of cisatracurium. These doses represent 2x, 4x, and 8x ED_{95} . All the slopes are parallel, including the slope of recovery from infusions, and average 30 to 35 minutes. The data indicate constant speed of recovery unrelated to dose or to duration of administration, suggesting lack of cumulative effect.

changes were indistinguishable from those seen in a similar group of patients receiving vecuronium. [295A]

Like atracurium, cisatracurium undergoes Hofmann elimination to yield laudanosine and a monoquaternary alcohol metabolite. [295B] [295C] [296] As a result of this degradation, which occurs in the plasma and extracellular fluid, the slope of recovery from blockade is unaffected by dosage or by duration of administration (Fig. 12-32) . Cisatracurium does not undergo hydrolysis by nonspecific plasma esterases. Twenty-three percent of the drug is cleared through organ-dependent means, with renal elimination accounting for 16 percent of this. [296] In patients with chronic renal failure, the duration of action of cisatracurium is not prolonged. [296A] The clearance of the drug is slightly decreased (by 13%) in this patient population. [296B] In patients in hepatic failure, there is an increased volume of distribution that is offset by greater clearance of cisatracurium. The result is minimal net change in pharmacodynamics. [296C] Recovery from cisatracuriuminduced block is not prolonged in patients in the intensive care unit. [297]

Mivacurium

Mivacurium (Fig. 12-33) is a benzylisoquinolinium diester. This nondepolarizing relaxant is hydrolyzed by plasma cholinesterase at 70 to 88 percent the rate of succinylcholine. [15] [154] Enzymatic hydrolysis gives the drug its short duration of action. [15] The duration of relaxation is one-half to one-third that of the

intermediate-acting nondepolarizers and about two to three times that of succinylcholine. [15] [297] [297B]

The short duration of action of mivacurium enables maintenance of relaxation by continuous infusion for short- to intermediate-length surgical procedures of 30 to 90 minutes

Figure 12-33 Chemical formula of mivacurium, a benzylisoquinolinium diester that is hydrolyzed by pseudocholinesterase at about 70 to 88 percent the rate of succinylcholine. Cholinesterase-catalyzed hydrolysis is facilitated by orientation of the ether oxygen of the carboxyl group toward the quaternary nitrogen atom.

or more. [297D] [297e] Longer infusions may be given with minimal increase in recovery time. [15] [297D] The slope of recovery is not affected by dose or by duration of administration by infusion (Fig. 12-34) (Figure Not Available) . The block is antagonized by anticholinesterases [15] [298] or by administration of pseudocholinesterase [298A] [298B] (see *Antagonism of Residual Neuromuscular Blockade*).

	DOSAGE (mg/kg)	CLINICAL DURATION (min)
ED_{95}	0.07-0.08	
Intubation (at t = +2.0-3.0 min)	0.2-0.25	15-20
Relaxation (N_2 O/O_2)	0.1	10-15
Relaxation (Vapor)	0.08	10-15
Maintenance	0.05-0.1	5-10
Infusion	3-15 (average 6) mug/kg/min	

Cardiovascular Side Effects

Mivacurium can cause histamine release. Following rapid injection of doses of 0.2 to 0.25 mg/kg, transient facial erythema and a brief decrease in blood pressure may occur [198] [298C] (see Fig. 12-15 (Figure Not Available) A). Because these doses are used to facilitate tracheal intubation within about 120 seconds, [299] [299A] [299B] a slower rate of administration of the drug (30 seconds) should be used if histamine release is to be minimized [298C]

Figure 12-34 (Figure Not Available) Slopes of spontaneous recovery of twitch following mivacurium. Four different bolus doses from 1.5 to 4 times ED_{95} are shown, together with recovery following infusion (average duration of infusion is 92 minutes); *n* = at least 9 per bolus group and 38 for the infusion group. Recovery times from 5 to 95 percent twitch height do not differ significantly and average 13 to 14 minutes. *(From Savarese et al [15])*

(Fig. 12-15 (Figure Not Available) B). There is no blockade of autonomic ganglia, nor is there any vagolytic effect. [299C]

Isomers of Mivacurium

Mivacurium consists of three stereoisomers. The more potent *cis-trans* and *trans-trans* isomers make up about 95 percent of the preparation. These isomers are rapidly hydrolyzed by plasma cholinesterase and show elimination half-lives of 2 to 3 minutes. [299D] The *cis-cis* isomer is more slowly hydrolyzed, and its elimination half-life is 55 minutes. As this isomer constitutes only 5 percent of the preparation of mivacurium and is 10 to 15 times less potent than the more active *cis-trans* and *trans-trans* isomers, [299C] it is not likely to contribute significantly to the blocking activity of mivacurium in human subjects. [297D]

Metabolism and Elimination

Mivacurium is nearly completely metabolized in the plasma (see Fig. 12-12) (Figure Not Available) by hydrolysis by pseudocholinesterase. Less than 5 percent is excreted as the parent compound in the urine. The metabolites of hydrolysis are the mivacurium monoester and the amino alcohol Fig. 12-12) (Figure Not Available) . These are excreted in urine and bile. [300] The metabolites are positively charged, making CNS entry unlikely. They show less than 1/100 the neuromuscular blocking activity of the parent compound. They do not affect the autonomic nervous system. [300]

Although not directly dependent on the kidney or the liver for elimination from the body, the dynamics of the relaxant are altered in patients with hepatic or renal failure. The duration of action of mivacurium is lengthened (by 10-15 minutes) in renal failure. [114] In anhepatic subjects undergoing liver transplantation, its duration of action is lengthened by a factor of 3. These alterations are likely due to decreased pseudocholinesterase activity. [114] Plasma cholinesterase is synthesized in the normal liver and is decreased in the presence of uremia.

Atypical Pseudocholinesterase Case

In the case of persons who carry atypical forms of pseudocholinesterase, the action of mivacurium is lengthened. In patients heterozygous for the atypical enzyme, mivacurium's duration of action is lengthened by 30 to 100 percent (10-30 minutes). In patients homozygous for the atypical enzyme (incidence 1 in 3,000), the duration of action of mivacurium is markedly prolonged. In these patients, mivacurium is extremely potent and long-lasting. Full paralysis after an ordinary intubating dose of 0.2 mg/kg will last 3-4 hours. [300A] [300B] Once signs of the beginning of recovery are noted, antagonism of residual block should be attempted as if antagonizing a long-acting nondepolarizing agent. A large dose of neostigmine (60-70 mug/kg) together with atropine or glycopyrrolate should be administered once spontaneous recovery of neuromuscular function has begun. Alternatively, pseudocholinesterase may be given (see *Antagonism of*

Residual Neuromuscular Blockade) to induce metabolism of mivacurium in these patients. [298A]

GW 280430A

GW 280430A (Fig. 12-35) represents a new class of nondepolarizing relaxants, called asymmetric mixed-onium chlorofumarates that are rapidly degraded by chemical mechanisms in blood *in vitro*. The compound has an ultra-short duration of action in the monkey, the dog, and the cat. A study in anesthetized human volunteers evaluated the onset and recovery profiles of GW 280430 in the thumb and larynx. The pattern of blockade resembles that of succinylcholine, with fully paralyzing doses (2-3 times ED_{95} or 0.3-0.5 mg/kg) producing 100 percent block of TOF within 50 to 60 seconds in the larynx. Spontaneous recovery to TOF of 0.9 develops in the thumb within about 12 to 15 minutes following administration. The recovery is accelerated by edrophonium. The cardiovascular changes following rapid (5-second) bolus doses in these volunteers have averaged less than 10 percent from baseline.

Further careful evaluation of GW 280430 therefore seems needed in patients, with respect to its dosage requirements, pharmacodynamics and kinetics, and cardiovascular properties.

Figure 12-35 The chemical formula of GW 280430. This substance represents a new chemical class of relaxants called asymmetric mixed-onium chlorofumarates, which are degraded chemically *in*

vitro. The rapid breakdown may explain an ultra-short duration of action noted in animals and in human volunteers (see text).

EFFECTS IN THE CENTRAL NERVOUS SYSTEM

Despite being ionized, intravenously administered nondepolarizing muscle relaxants do pass into the cerebrospinal fluid (CSF). [301] Neuromuscular blocking doses of gallamine given intravenously have been found to increase the seizure threshold to lidocaine in dogs. [302] Forbes et al [303] found intravenously administered pancuronium to reduce halothane anesthetic requirement by 25 percent. However, more recent studies indicate that muscle relaxants do not alter anesthetic requirement. [304]

When neuromuscular blocking drugs have been administered accidentally into the CSF (i.e., wrong drug given for a spinal anesthetic), myotonia, autonomic changes, and even convulsions have occurred. [305] [306] Furthermore, prolonged administration of vecuronium, and probably of other muscle relaxants, will result in these drugs entering the CSF in critical care patients. [306A] On the basis of these limited data, the authors of this chapter conclude that small amounts of intravenously administered muscle relaxants do pass into the CSF, but the clinical significance is unclear. Also, laudanosine, a metabolite of atracurium, crosses the blood-brain barrier. [164] In large doses in animals, laudanosine may cause central nervous system stimulation.

During the clinical use of atracurium, however, the accumulation of quantities of this metabolite sufficient to cause CNS stimulation has not been documented even in the most arcane of circumstances. Furthermore, because the new isomer cisatracurium is four to five times as potent as the parent compound atracurium, quantities of laudanosine produced during breakdown of cisatracurium are theoretically four times less than during the use of atracurium. In fact, measured laudanosine quantities produced during cisatracurium administration are five to ten times lower than during atracurium use, making laudanosine accumulation a nonissue in clinical practice with cisatracurium.

Whether the CNS effects of muscle relaxants contribute to the morbidity and mortality of critical care patients is another matter. Further studies are very much needed in this area, since critical care patients may receive relaxants continuously for many weeks (see also *Muscle Relaxants in the Intensive Care Unit, Metabolism and Elimination,* and *Individual Nondepolarizing Relaxants: Atracurium* and *Cisatracurium*).

SPECIAL POPULATIONS

Pediatric Patients

The development of the neuromuscular junction is not complete at birth. [307] [307A] Goudsouzian [308] pointed out that maturation of neuromuscular transmission in humans occurs after the first 2 months of age. In spite of this, muscle relaxants can be used safely in term and preterm infants.

It is not apparent from older studies whether the newborn is more sensitive than adults to nondepolarizing muscle relaxants. [309] [310] [311] [312] [313] [314] [315] More recent studies by Fisher and colleagues [316] [316A] [316B] of the pharmacokinetics and pharmacodynamics of relaxants in infants, children, and adults, however, have made it possible to better understand the

clinical pharmacology of these drugs in pediatric patients (Ch. 63). Neonates and infants are more sensitive than adults to the neuromuscular blocking effects of dTc. [316] A lower plasma concentration of this muscle relaxant is required to achieve a desired level of neuromuscular blockade in these young patients. However, dosage should not be decreased because infants have a larger volume of distribution. The increased volume of distribution and slower clearance (Fig. 12-36) (Figure Not Available) contribute to a longer elimination half-life, [316] [317] which means that in infants dTc may require less frequent dosing (longer dosing intervals) than in older children.

Atracurium, vecuronium, cisatracurium, and rocuronium are commonly administered to children. The popularity of these drugs in children most likely stems from the following points: they are intermediate-acting muscle relaxants, minimal residual paralysis is seen in the postoperative period, [318] and a faster onset of action occurs in children than in adults.

Atracurium and vecuronium, in comparison, show very different kinetic and dynamic patterns in infants. As with the long-acting relaxants, the sensitivity of infants to vecuronium is greater than it is in children (ED_{95} 0.047 versus 0.081 mg/kg, respectively). [319] An increased duration of action in infants is most likely secondary to the increased volume of distribution of vecuronium because its clearance is unchanged. [316A] [317] Vecuronium therefore acts as a longacting muscle relaxant in the neonate. [316A] [317] [320]

In contrast, the duration of action of atracurium is not significantly different in the pediatric patient from that in the adult. [321] [322] [323] As with vecuronium and dTc, the volume of distribution is increased in infants. [316B] However, the clearance of atracurium is also more rapid. [316B] Therefore, the same dose (0.5-0.6 mg/kg) can be used in infants, children, and adults for tracheal intubation without any major difference in its duration of action in the three groups. Cisatracurium is a single isomer of atracurium. In children a dose of 0.1 mg/kg has an onset of just over 2 minutes and a clinical duration of approximately 30 minutes during balanced or halothane anesthesia. [324] Although further studies need to be done, the authors recommend an intubating dosage of 0.2 mg/kg of cisatracurium in children (as in adults) to facilitate good intubating conditions within 90 seconds. The clinical duration at this dosage should be in the neighborhood of 45 to 50 minutes.

The short-acting muscle relaxant mivacurium can be safely used in children. The ED_{95} of mivacurium is greater in children than in adults (0.10 mg/kg during narcotic anesthesia and 0.09 mg/kg during halothane anesthesia). [325] Children, therefore, require larger doses of mivacurium than adults to achieve a given depth of neuromuscular block. [325] [326] Onset time, as with atracurium [322] and vecuronium, [327] is faster in children than in adults, so maximal block is achieved in less than 2 minutes. A dose of 0.25 to 0.30 mg/kg facilitates tracheal intubation in about 90 seconds in children. A dose of twice the ED_{95} (0.2 mg/kg) results in only a 20 percent increase in the duration of block as compared with the ED_{95} . [326] And, in contrast to adults, with this dose there is less hemodynamic instability. At doses of 0.25 mg/kg, facial flushing and transient hypotension secondary to histamine release are observed less often (in about 10-15% of the pediatric population who receive this amount as a rapid 5-10 second injection). [325]

Mivacurium's clinical duration of action is shorter in children than in adults (12 versus 15-20 minutes). Although halothane potentiates mivacurium-induced neuromuscular block, it does not prolong its duration of action. [325] [326] Because of its short duration of action, mivacurium is best used as an infusion in children for maintenance of relaxation. Infusion rates required by children (10-20 mug/kg/min) are about twice those required by adults, probably because of a significantly higher plasma cholinesterase activity. [328] [329] [330]

Rocuronium in adults is an intermediate-acting relaxant with a fast onset of action, and this is also true in infants and children. [330A] [330B] Its potency is greater in infants than in children, but its onset is faster in the latter age group. [330B] In children, rocuronium 0.6 mg/kg produces better conditions for rapid tracheal intubation than does vecuronium 0.1 mg/kg or atracurium 0.5 mg/kg. [330A] If given by intramuscular injection into the deltoid (1.0 mg/kg in infants and 1.8 mg/kg in children), rocuronium allows for tracheal intubation in approximately 3 minutes. [330C] As with adults, for rapid-sequence intubation (60 seconds) in the presence of a full stomach, high doses of 1.2-1.5 mg/kg are suggested.

Antagonism of residual neuromuscular blockade in the

Figure 12-36 (Figure Not Available) Correlation between age, glomerular filtration, and clearance of curare. *(From Fisher et al [316])*

case of the various nondepolarizers is similar in children and adults. Fisher et al [331] [332] described some minor variations in neostigmine and edrophonium dosage for pediatric patients. For example, the ED_{50} of neostigmine for antagonism of a dTc-induced 90 percent block of the adductor pollicis twitch was 22.9 mug/kg in adults, compared with 15.5 mug/kg in infants. [331] In the case of edrophonium, the ED_{50} for antagonism of dTc-induced 90 percent block was 128 mug/kg in adults. In children, the ED_{50} was 233 mug/kg, and in infants the ED_{50} was 145 mug/kg. [332]

It seems that despite the above variations, neostigmine and edrophonium dosage in various age groups should be liberal enough to ensure return of monitoring variables such as TOF to clinical adequacy within a reasonable time, i.e., 10-15 min. The authors recommend neostigmine dosage of 50 to 60 mug/kg for reversal in children and edrophonium dosage of 500 to 1,000 mug/kg. In all cases, tests of clinical recovery, such as head lift, leg lift, and cry, should be performed and documented for pediatric patients and adults.

The routine administration of succinylcholine to healthy children should be discontinued. In apparently healthy children, intractable cardiac arrest with hyperkalemia, rhabdomyolysis, and acidosis may develop following succinylcholine administration, particularly in patients with unsuspected muscular dystrophy of the Duchenne type. [332A] In response to this, the U.S. Food and Drug Administration and Glaxo-Wellcome have modified the package insert for succinylcholine, warning against the use of succinylcholine in children except for emergent control of the airway (see the section on complications of succinylcholine; see also Ch. 31).

Elderly Patients

The pharmacodynamics of muscle relaxants are altered in elderly patients (Ch. 65). There are a number of physiologic changes that accompany the aging process, including decreases in total body water, increases in total body fat, decreases in hepatic and renal blood flow, and decreases in cardiac reserve, which account for the altered responses of the elderly to muscle relaxants. A number of physiologic and anatomic changes at the neuromuscular junction also occur with aging. These include an increase in the distance between the junctional axon and the motor endplate, a flattening of the folds of the motor endplate, a decreased concentration of ACh receptors at the motor endplate, a decrease of the amount of ACh in each vesicle in the prejunctional axon, and decreased release of ACh from the preterminal axon in response to a neural impulse. [333] As shown by Matteo et al, [334] despite all these changes, ACh receptor sensitivity to nondepolarizing muscle relaxants is not altered by advancing age (Fig. 12-37) (Figure Not Available) . That is, the elderly as well as young adults have similar degrees of neuromuscular blockade at the same plasma concentration of a muscle relaxant. Rather, it appears that, in the elderly, decreased splanchnic and renal blood flow, decreased glomerular filtration rate, and decreased hepatic function are responsible for the prolonged durations of action of most muscle relaxants. However, the impact of aging per se versus disease states often associated with the aging process may be difficult to distinguish in identifying mechanisms of altered muscle relaxant action in the elderly.

Figure 12-37 (Figure Not Available) Correlation of plasma metocurine concentration versus percentage paralysis (twitch depression) in young and elderly patients (open and closed squares). Differences are not significant. *(From Matteo et al [334])*

Pancuronium, [335] [336] metocurine, [334] dTC, [334] vecuronium, [336A] [337] and rocuronium [338] all show altered pharmacodynamics and pharmacokinetics in the elderly patient population. Decreased clearance of each of these drugs from the plasma explains their prolonged duration of action in these patients. These muscle relaxants depend on the kidney and/or the liver for their metabolism and elimination.

Surprisingly, the pharmacokinetics and pharmacodynamics of the newer long-acting muscle relaxants doxacurium [339] and pipecuronium, [340] which rely almost exclusively on the kidney for their elimination, do not seem to be significantly different in the elderly. The duration of neuromuscular blockade induced with doxacurium has been found to be more variable in the elderly than in younger patients and tends to be longer. However, clearance and elimination half-lives are the same in the two patient groups. Similarly, recovery from pipecuronium-induced neuromuscular blockade, volume of distribution, clearance, and elimination half-life of the drug are the same in young and old patients. Further studies in the elderly with doxacurium and pipecuronium may be needed to better define the issue.

In the case of drugs whose elimination is independent of hepatic or renal blood flow, pharmacokinetics and pharmacodynamics should be unaffected by age. This is true of atracurium, which depends on Hofmann degradation for its clearance. [341] [342] Cisatracurium, which also undergoes Hofmann elimination, has a delayed onset of effect in elderly patients. [342A] [342B] Duration of action of the relaxant appears not to be influenced by advanced age. The prolonged elimination half-life of the drug in the elderly is due to an increased volume of distribution. Clearance is not decreased with advanced age.

Plasma cholinesterase activity in the elderly, although in the normal range, is decreased by approximately 26 percent when compared with that in young adults. [343] Because mivacurium

is metabolized by plasma cholinesterase, its clearance is likely to be slightly reduced in the elderly, resulting in a 20 to 25 percent longer duration of action [343A] and a decreased infusion requirement to maintain a stable depth of block. [343B]

Obese Patients

There are conflicting reports concerning the effect of obesity on the pharmacodynamics of nondepolarizing neuromuscular blockade [344] [345] [346] Although the duration of action of pancuronium is unaffected by patient weight, [346] obese patients recover more slowly from metocurine- , [347] doxacurium- , [347A] or vecuronium-induced [348] neuromuscular blockade. The duration of action of rocuronium is prolonged in obese patients. [348A] These findings imply that the elimination of these drugs is decreased. The recovery from atracurium-induced neuromuscular blockade is not affected by obesity, [348] which is most likely secondary to its lack of dependence on end-organ function for its elimination.

Muscle relaxants should be dosed in the obese patient more precisely on the basis of about 20 percent more than lean body mass, rather than on actual body weight [349] to ensure that these patients are not receiving relative overdoses.

Severe Renal Disease

Renal failure influences the pharmacology of nondepolarizing muscle relaxants by producing either decreased elimination of the drug or its metabolites via the kidney, or decreased activity of enzymes that metabolize the drug, e.g., mivacurium (Table 12-13) . Consequently, the duration of action of muscle relaxants may be prolonged in patients with renal failure. An early example of prolonged neuromuscular blockade due to renal failure was a case of postoperative respiratory failure following gallamine, reported in 1950. [350]

Renal failure does not alter the *sensitivity* (doseresponse) of patients to the neuromuscular blocking action of gallamine, [351] dTc, [352] pancuronium, [352A] atracurium, [352B] vecuronium, [352C] or mivacurium, [352D] but it does cause resistance to metocurine. [352E]

Gallamine [351] and metocurine, [352E] which rely almost exclusively on the kidney for their elimination, have reduced plasma clearance and potentially a very long duration in patients with renal failure (see Table 12-13) . Pancuronium and dTc are eliminated predominantly via the kidney, and renal failure is associated with a reduced plasma clearance and increased elimination half-life for these drugs. [353] [353A] As a consequence of these pharmacokinetic changes, the duration of neuromuscular blockade produced by these drugs is longer and more variable than in patients with normal renal function. [353] For doxacurium, in renal failure its plasma clearance is decreased, its elimination half-life is increased, and its duration of action is prolonged. [354] [354A] Pipecuronium is eliminated predominantly by the kidney. In the 24 hours after its administration, approximately 40 percent is excreted in the urine and only 2 percent in the bile. [354B] Its plasma clearance is decreased by one-third, and its elimination half-life is increased 2-fold in patients with renal failure. [354C] Although the duration of action of a dose of 0.07 mg/kg was not prolonged by renal failure, the pharmacokinetic changes observed suggest that larger or repeat doses are quite likely to produce prolonged neuromuscular blockade. [354C] Because of the potential for prolonged block and the availability of intermediate- and short-acting relaxants, there is no longer any reason to recommend the use of the long-acting relaxants in patients with renal failure.

The pharmacokinetics and duration of action of atracurium are unaffected by renal failure. [355] [356] [357] This lack of effect is in part because atracurium undergoes spontaneous chemical degradation (Hofmann elimination) and ester hydrolysis, [357B] processes that account for 50 percent of its total clearance. [357C] The elimination half-life of laudanosine, the principal metabolite of atracurium, increases significantly in renal failure. [357] [358] Concern has been expressed about possible accumulation of laudanosine in patients with renal failure, [358A] but recent evidence suggests that significant concentrations of laudanosine are not achieved during the administration of atracurium in the operating room setting. [357] [358] However, the accumulation of laudanosine during atracurium administration in the ICU is not as clear (see the section on the ICU).

Vecuronium relies principally on hepatic, not renal, mechanisms for its elimination. [358B] [358C] However, its clearance is reduced and its elimination half-life is increased in patients with renal failure. [359] [359A] [360] In one study, the duration of action of vecuronium, 0.1 mg/kg, was both longer and more variable in patients with renal failure than in those with normal renal function. [360] In three other studies, the duration of action of vecuronium, 0.05-0.14 mg/kg, was not prolonged by renal failure, but this result was probably obtained because relatively small doses were administered or because the sample sizes were too small to detect a difference. [358C] [359] [359A] The principal metabolite of vecuronium, 3-desacetylvecuronium, has 80 percent of the neuromuscular blocking activity of vecuronium [361] ; it may cause prolonged paralysis in patients with renal failure in the intensive care unit. [362] [363] Although their pharmacokinetics differ, in clinical use for patients with renal failure, the duration

of action and rate of recovery from vecuronium or atracuriuminduced neuromuscular blockade are similar. [364] [365] [366]

Mivacurium is a short-acting nondepolarizing muscle relaxant metabolized by plasma cholinesterase at approximately 70 percent of the rate of succinylcholine. [367] [368] Mivacurium is a mixture of three stereoisomers; the pharmacokinetics of the two most pharmacologically active isomers (the *trans-trans* and *cis-trans*) are unaffected by renal failure; the clearance of the third isomer *(cis-cis),* which has little clinical effect, is decreased by renal failure. [369] The effect of renal failure on the duration of action and recovery from mivacurium-induced block is variable. In some studies renal failure had no effect, [369] [369A] whereas in another the duration of action and recovery were lengthened and the infusion dose requirements were decreased by renal failure. [370] The effect of renal failure on mivacurium's duration of action is most probably mediated through its effect on plasma cholinesterase. Renal failure can decrease plasma cholinesterase activity, [370A] and this decrease would be expected to lengthen the duration of mivacurium effect. [370B] In the studies where renal failure had no effect on mivacurium's duration, plasma cholinesterase activity in patients with and without renal failure was not different. [369] [369A] In contrast, where patients with renal failure had decreased

TABLE 12-13 -- Pharmacokinetics of Neuromuscular Blocking Drugs in Patients With Normal Renal Function or Renal Failure

		PLASMA CLEARANCE (mL/kg/min)		VOLUME OF DISTRIBUTION (mL/kg)		ELIMINATION HALF-LIFE (min)	
		NORMAL FUNCTION	RENAL FAILURE	NORMAL FUNCTION	RENAL FAILURE	NORMAL FUNCTION	RENAL FAILURE
GALLAMINE	Ramzan MI, 1981	1.20	0.24 [a]	240	280	132	750 [a]
METOCURINE	Brotherton WP, 1981	1.2	0.4 [a]	472	353	300	684 [a]
PANCURONIUM	Mcleod K, 1976 [b]	74	20 [a]	148	236 [a]	97	475 [a]
	Somogyi A, 1977	1.7	0.9	261	296 [a]	132	257 [a]
d-*TUBOCURARINE*	Sheiner LB, 1979	2.4	1.5	250	250	84	132
DOXACURIUM	Cook DR, 1991	2.7	1.2 [a]	220	270	99	221 [a]
PIPECURONIUM	Caldwell JE, 1989	2.4	1.6 [a]	309	442 [a]	137	263 [a]
ATRACURIUM	Fahey MR, 1984	6.1	6.7	182	224	21	24
	Ward S, 1987 [357A] [357B]	5.5	5.8	153	141	19	20
	Vandenbrom RH, 1990 [357]	10.9	7.8	280	265	17.3	19.7
CISATRACURIUM	Kisor DF, 1996	5.2	--	31	--	--	--
VECURONIUM	Fahey MR, 1981	3.0	2.5	194	239	78	97
	Bencini AF, 1986	3.2	2.6	510	471	117	149
	Meistelman C, 1986	3.6	4.5	242	347	51	68
	Lynam DP, 1988	5.3	3.1 [a]	199	241	53	83 [a]
MIVACURIUM	Head-Rapson, AG 1995						
	Cis-trans	106	80	278	475	2.0	4.3
	Trans-trans	57	48	211	270	2.3	4.3
	Cis-cis	3.8	2.4 [a]	227	244	68	80
ROCURONIUM	Szenohradszky J 1992	2.9	2.9	207	264 [a]	71	97 [a]

Bencini AF, Scaf AH, Sohn YJ et al: Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. Anesth Analg 65:245, 1986.

Brotherton WP, Matteo RS: Pharmacokinetics and pharmacodynamics of metocurine in humans with and without renal failure. Anesthesiology 55:273, 1981.

Caldwell JE, Canfell PC, Castagnoli KP et al: The influence of renal failure on the pharmacokinetics and duration of action of pipecuronium bromide in patients anesthetized with halothane and nitrous oxide. Anesthesiology 70:7, 1989.

Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with hepatic or renal failure. Anesth Analg 72:145, 1991.

Fahey MR, Morris RB, Miller RD et al: Pharmacokinetics of ORG NC 45 (NORCURON) in patients with and without renal failure. Br J Anaesth 53:1049, 1981.

Fahey MR, Rupp SM, Fisher DM et al: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 61:699, 1984.

Head-Rapson AG, Devlin JC, Parker CJ et al: Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal function. Br J Anaesth 75:31, 1995.

Kisor DF, Schmith VD, Wargin WA et al: Importance of the organ-independent elimination of cisatracurium. Anesth Analg 83:1065, 1996.

Lynam DP, Cronnelly R, Castagnoli KP et al: The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. Anesthesiology 69:227, 1988.

Mcleod K, Watson MJ, Rawlins MD: Pharmacokinetics of pancuronium in patients with normal and impaired renal junction. Br J Anaesth 48:341, 1976.

Meistelman C, Lienhart A, Leveque C et al: Pharmacology of vecuronium in patients with end-stage renal failure. Eur J Anaesthesiol 3:153, 1986.

Ramzan MI, Shanks CA, Triggs EJ: Gallamine disposition in surgical patients with chronic renal failure. Br J Clin Pharmacol 12:141, 1981.

Sheiner LB, Stanski DR, Vozeh S et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to *d*-tubocurarine. Clin Pharmacol Ther 25:358, 1979.

Somogyi A, Shanks CA, Triggs EJ: The effect of renal failure on the disposition and neuromuscular blocking action of pancuronium bromide. Eur J Clin Pharmacol 12:23, 1977.

Szenohradszky J, Fisher DM, Segredo V et al: Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology 77:899, 1992.

[a] Significant difference normal renal function versus renal failure
[b] Values expressed as mL/min, not weight-adjusted

cholinesterase activity, the duration of mivacurium was longer. [370] [370C] Because a patient's plasma cholinesterase activity is not known preoperatively, when mivacurium is used in patients with renal failure, doses should be conservative, and its effect should be carefully monitored.

When rocuronium is administered to patients with renal failure undergoing renal transplantation, compared with patients with normal renal function, plasma clearance is unchanged (2.89 mL/kg/min), volume of distribution is increased by 28 percent, and elimination half-life is lengthened by 37 percent (Fig. 12-38) (Figure Not

Available) . [370D] [370E] In patients with renal failure the duration of action of rocuronium is not prolonged, and it shows no evidence of cumulation. [370F]

Cisatracurium is the single R- *cis,* R
- *cis* isomer of atracurium. Organ-independent mechanisms (Hofmann elimination) account for 77 percent of the total clearance of cisatracurium. [371] Because renal excretion accounts for only 16 percent of cisatracurium elimination, renal failure should have little impact on its duration of action. [371]

Hepatobiliary Disease

Patients with hepatobiliary disease may exhibit prolonged block with *d*-tubocurarine, [372] pancuronium, [372A] doxacurium, [372B] vecuronium, [372C] rocuronium, [372D] [372E] and mivacurium.

Figure 12-38 (Figure Not Available) "Average" plasma concentration (Cp) versus time following rocuronium (0.6 mg/kg) in patients with normal renal function (solid line) or patients undergoing renal transplantation (dashed line). *(From Szenohradszky et al [15C])*

[372F] [372G] In the case of pancuronium, [372A] vecuronium, [372C] and mivacurium, [372F] [372G] this prolonged action is associated with a decreased plasma clearance of the drug. However, this is not a consistent relationship, and many studies have described a reduction in clearance without a prolonged duration. In the case of atracurium, one study even reports increased clearance in patients with cirrhosis, but the duration of action was normal. [372H]

A concern raised about administering atracurium to patients with hepatic disease was the possible cumulation of its principal metabolite, laudanosine. [373] However, although laudanosine relies principally on hepatic mechanisms for its elimination, the concentrations encountered during liver transplantation are unlikely to be associated with clinical sequelae. [373] [374]

The influence of hepatobiliary disease on the pharmacokinetics of muscle relaxants is complex (Table 12-14) . In most studies, hepatic disease is associated with an increased volume of distribution, and as a result, there is an apparent resistance to the effect of dTc, [372] [374A] pancuronium [375] [375A] atracurium, [376] and rocuronium. [376A] The effect of hepatic disease on the pharmacokinetics of the muscle relaxants (see Table 12-14) suggests that initial doses may need to be greater than for patients with normal hepatic function but that once the desired level of block has been achieved, subsequent recovery may be slower. This is illustrated in the case of vecuronium, in which doses up to 0.15 mg/kg have a normal duration of action, [377] [378] [378A] but a dose of 0.2 mg/kg has a prolonged action [378] [378B] (Fig. 12-39) (Figure Not Available) .

There are several mechanisms by which hepatic disease can alter the elimination of muscle relaxants. The principal route of metabolism of pancuronium and vecuronium is deacetylation at the 3-position. [379] [380] [380A] This metabolic process is presumed to occur in the liver because 10 to 20 percent of the total dose of pancuronium and 40 percent of that of vecuronium is found in the liver and bile as both parent drug and metabolite. [379] [380] [380A] [380B] In hepatic disease, increased plasma concentration of bile salts can reduce the hepatic uptake of pancuronium and vecuronium, [380C] [380D]

Figure 12-39 (Figure Not Available) Disappearance of vecuronium from the plasma following a single bolus dose of 0.2 mg/kg. Semilogarithmic plot of the mean concentration versus time for patients with normal hepatic function (filled circles) and cirrhotic patients (open circles). Error bars are the SD for that value. *(From Lebrault et al [142])*

and this may be an explanation for the decreased clearance of these drugs observed by some investigators. [372A] [378B] [380E]

In patients with severe liver disease, plasma cholinesterase activity is decreased probably due to decreased synthesis of the enzyme in the liver. [372F] [372G] Consequently, the plasma clearances of the isomers of mivacurium are decreased (see Table 12-14) , and its duration of action is prolonged and may be almost tripled. [372F] [372G]

Atracurium and cisatracurium share organ-independent modes of elimination, namely, Hofmann elimination and ester hydrolysis. [380F] [380G] As a consequence, their clearance should be little affected by hepatic disease. In fact, and in contrast to all other muscle relaxants, the plasma clearances of atracurium and cisatracurium are increased slightly (see Table 12-14) in patients with liver disease. [372H] [380H] Because elimination of atracurium and cisatracurium occurs outside of, as well as from within, the central compartment, it has been suggested that a larger distribution volume should be associated with a larger clearance. [380G] In two studies, [372H] [380H] volumes of distribution and clearances of the drugs increased with liver disease, lending support to the theory of Kisor et al. [380G] This increased clearance with liver disease is not reflected by a decrease in the drugs' durations of action. [372H] [380H]

TABLE 12-14 -- Pharmacokinetics of Neuromuscular Blocking Drugs in Patients With Normal Liver Function or Hepatobiliary Disease

		PLASMA CLEARANCE (mL/ kg/ min)		VOLUME OF DISTRIBUTION (mL/ kg)		ELIMINATION HALF-LIFE (min)		HEPATIC PATHOLOGY
		NORMAL	DISEASE	NORMAL	DISEASE	NORMAL	DISEASE	
GALLAMINE	Westra P, 1981	1.22	0.90	237	259	162	220	Cholestasis
	Ramzan IM, 1981	1.20	1.21	206	247 [a]	135	160	Cholestasis
PANCURONIUM	Somogyi AA, 1977 [b]	123	59 [a]	261	307 [a]	133	267 [a]	Cholestasis
	Duvaldestin P, 1978	1.86	1.45 [a]	279	416 [a]	114	208 [a]	Cirrhosis
	Westra P, 1981	1.76	1.47	284	425 [a]	141	224 [a]	Cholestasis
DOXACURIUM	Cook DR, 1991	2.7	2.3	220	290	99	115	Transplantation
PIPECURONIUM	D'Honneur G, 1993	3.0	2.6 [a]	350	452	111	143	Cirrhosis
ATRACURIUM	Ward S, 1983	5.3	6.5	159	207 [a]	21	22	Hepatorenal
	Parker CJ, 1989	6.6	8.0 [a]	202	282 [a]	21	25	Cirrhosis
VECURONIUM	Lebrault C, 1985	4.26	2.73 [a]	246	253	58	84 [a]	Cirrhosis
	Lebrault C, 1986	4.30	2.36 [a]	247	206	58	98 [a]	Cholestasis
	Arden JR, 1988	4.5	4.4	180	220	58	51	Cirrhosis
MIVACURIUM	Head-Rapson AG, 1994							Cirrhosis
	Cis-trans	95	44 [a]	210	188	1.53	2.48 [a]	
	Trans-trans	70	32 [a]	200	199	2.32	11.1 [a]	
	Cis-cis	5.2	4.2	266	237	50.3	60.8	
ROCURONIUM	Khalil M, 1994	2.79	2.41	184	234	87.5	96.0	Cirrhosis
	Magorian T, 1995 [b]	217	217	16.4	23.4 [a]	76.4	111.5 [a]	Mixed
	Servin FS, 1996 [b]	296	189	151	264 [a]	56	98 [a]	Cirrhosis
	van Miert MM, 1997	3.70	2.66 [a]	211	248	92	143 [a]	Cirrhosis

CISATRACURIUM	De Wolf AM, 1996	5.7	6.6 [a]	161	195 [a]	23.5	24.4	Transplantation

Arden JR, Lynam DP, Castagnoli KP et al: Vecuronium in alcoholic liver disease: A pharmacokinetic analysis. Anesthesiology 68:771, 1988.

Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with hepatic or renal failure. Anesth Analg 72:145, 1991.

D'Honneur G, Khalil M, Dominique C et al: Pharmacokinetics and pharmacodynamics of pipecuronium in patients with cirrhosis. Anesth Analg 77:1203, 1993.

De Wolf AM, Freeman JA, Scott VL et al: Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth 76:624, 1996.

Duvaldestin P, Agoston S, Henzel D et al: Pancuronium pharmacokinetics in patients with liver cirrhosis. Br J Anaesth 50:1131, 1978.

Head-Rapson AG, Devlin JC, Parker CJR et al: Pharmacokinetics of the three isomers of mivacurium and pharmacodynamics of the chiral mixture in hepatic cirrhosis. Br J Anaesth 73:613, 1994.

Khalil M, d'Honneur G, Duvaldestin P et al: Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. Anesthesiology 80:1241, 1994.

LeBrault C, Berger JL, D'Hollander AA et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 62:601, 1985.

Lebrault C, Duvaldestin P, Henzel D et al: Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. Br J Anaesth 58:983, 1986.

Magorian T, Wood P, Caldwell J et al: The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg 80:754, 1995.

Parker CJ, Hunter JM: Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth:177, 1989.

Ramzan IM, Shanks CA, Triggs EJ: Pharmacokinetics and pharmacodynamics of gallamine triethiodide in patients with total biliary obstruction. Anesth Analg 60:289, 1981.

Servin FS, Lavaut E, Kleef U et al: Repeated doses of rocuronium bromide administered to cirrhotic and control patients receiving isoflurane: A clinical and pharmacokinetic study. Anesthesiology 84:1092, 1996.

Somogyi AA, Shanks CA, Triggs EJ: Disposition kinetics of pancuronium bromide in patients with total biliary obstruction. Br J Anaesth 49:1103, 1977.

van Miert MM, Eastwood NB, Boyd AH et al: The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. Br J Clin Pharmacol 44:139, 1997.

Ward S, Neill EA: Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). Br J Anaesth 55:1169, 1983.

Westra P, Vermeer GA, de Lange AR et al: Hepatic and renal disposition of pancuronium and gallamine in patients with extrahepatic cholestasis. Br. J Anaesth 53:331, 1981.

[a] Significant difference normal hepatic function versus hepatobiliary disease
[b] Values expressed as mL/min, or L, not weight-adjusted

IMPORTANT INTERACTIONS

Anesthetics

Inhaled anesthetics augment the neuromuscular blockade from nondepolarizing muscle relaxants in a dose-dependent fashion [381] [381A] (Fig. 12-40) (Figure Not Available) , which may also depend on the duration of anesthesia. [382] Not all types of anesthetics enhance neuromuscular block to the same extent. For example, isoflurane, and enflurane may have a greater effect than halothane, which in turn has a greater effect than nitrous oxide-barbiturate-opioid or propofol anesthesia [383] [384] (Fig. 12-41) (Figure Not Available) . Sevoflurane enhances blockade produced by vecuronium, pancuronium, or atracurium to a degree similar to that of isoflurane. [384A] [384B] Desflurane appears to have a slightly greater effect than isoflurane on vecuroniuminduced blockade. [384C]

Interestingly, not all muscle relaxants are affected to the same degree by the presence of volatile anesthetics. The reason may be partly due to differences in experimental design. However, atracurium and vecuronium do not seem to be as much affected by the choice of general anesthesia as are dTc and pancuronium. [385] There is an approximately 20 percent difference in the dose-response curves of these two intermediate-acting relaxants with nitrous oxide-barbiturateopioid anesthesia compared with isoflurane anesthesia. In contrast, with dTc and pancuronium, there may be as much as a 50 percent difference. Isoflurane and enflurane do, however, markedly reduce the infusion rate of vecuronium [385A] or rocuronium [385B] required to maintain a stable depth of neuromuscular blockade compared with opioidnitrous oxide anesthesia (Fig. 12-42) (Figure Not Available) . In addition, the presence of isoflurane will slow recovery from vecuronium [386] [386A] and apparently mivacurium-induced neuromuscular blockade as compared with opioid anesthesia, [386A] [387] such that,

Figure 12-40 (Figure Not Available) Effect of anesthetics on a *d*-tubocurarine dose-response curve. *(From Ali and Savarese [381B])*

Figure 12-41 (Figure Not Available) Shift of pancuronium dose response to the left as the end-tidal concentration of Forane (isoflurane) is increased from 0.5 to 1.5 percent. *(From Miller et al [128])*

pharmacodynamically, they behave more like long- and intermediate-acting relaxants, respectively, particularly at the end of lengthy procedures.

Gencarelli et al [388] demonstrated that a stepwise decrease in enflurane concentration from 2.2 to 0.5 percent during a constant infusion of dTc resulted in a reduction of neuromuscular blockade from 92 to 8 percent twitch inhibition. This suggests that when potent inhaled anesthetics are used, a significant fraction of the neuromuscular blockade can be removed by simply decreasing the anesthetic concentration.

Several mechanisms have been proposed by which inhaled anesthetics may affect the neuromuscular blockade from muscle relaxants. The mechanisms that are probably most important are those due to the following actions of inhaled anesthetics: (1) to increase muscle blood flow, so that a greater fraction of the injected relaxant may reach the neuromuscular junction, [389] probably a factor mainly with isoflurane; (2) to induce relaxation at sites proximal to the neuromuscular junction, obviously the CNS [390] ; (3) to maintain release of ACh from the motor nerve terminal [391] ; (4) to exert

Figure 12-42 (Figure Not Available) Infusion rates of vecuronium necessary to maintain constant 90 percent depression of control twitch tension during three different anesthetics. I, standard deviation;
, range of infusion rates. *(From Cannon et al [129])*

no demonstrable effect on the ACh receptor [392] [393] (5) to decrease the sensitivity of the postjunctional membrane to depolarization [394] ; and (6) possibly to act at a site distal to the cholinergic receptor and the postjunctional membrane, such as the muscle membrane. [390] [393] [394]

In generally healthy individuals, volatile anesthetics do not decrease twitch tension. Desflurane is an exception to this and at end-tidal concentrations of up to 2.0 MAC has been reported to cause as much as 30 percent depression of the TOF response in healthy humans. [381] [395] Although the majority of volatile anesthetics do not depress twitch tension, they reduce the margin of safety of neuromuscular transmission. Waud and Waud [391] [392] indicate that halothane acts at a site beyond the cholinergic receptor, perhaps on either calcium conductance or ACh release via depolarization. Other studies indicate that inhaled anesthetics have specific effects on the ACh receptor channels. Using a patch clamp technique, Brett et al [396] found that isoflurane reduces the average open duration of the ACh receptor channels during activation. The end-plate current is reduced in amplitude by the muscle relaxant and, because of isoflurane, has an accelerated decay. Both factors reduce the net charge transfer across the end plate, which impairs neuromuscular transmission.

Because of their action on the CNS, volatile anesthetics often produce adequate relaxation with minimal neuromuscular blockade. Therefore, when potent anesthetic vapors are used, good surgical conditions can exist in the absence of deep neuromuscular blockade.

Some potent anesthetics (e.g., isoflurane) increase muscle blood flow. Diversion of a larger fraction of the cardiac output to muscle may result in a proportionally greater quantity of relaxant being delivered to muscle. This mechanism has been proposed as a factor to explain why the potentiating effect of isoflurane is greater than that of halothane. [389] Clearly the most important mechanism is that anesthetics inhibit motor end-plate depolarization; the effect is directly related to anesthetic concentration. [397]

Despite changes in regional, renal, and hepatic blood flow, inhaled anesthetics have little or no effect on the pharmacokinetics of muscle relaxants in humans. [385A] [398] The ability of inhaled anesthetics to augment a nondepolarizing neuromuscular block is a pharmacodynamic one, that is, the blood concentration of muscle relaxants required to produce paralysis is decreased by inhaled anesthetics (see Fig. 12-42) (Figure Not Available) .

The ability of enflurane to enhance a dTc neuromuscular block is time-dependent. Stanski et al [399] found that, despite a constant blood level of dTc, paralysis increased at a rate of 9 ± 4 percent/h. They speculated that halothane achieves its maximum effect so rapidly because it acts on neural tissue (e.g., neuromuscular junction) where blood flow is high. Conversely, they speculated that, in addition to the neuromuscular junction, enflurane may also act on skeletal muscle, where blood flow is less. Thus, a longer time would be required for enflurane to achieve its maximal enhancement of nondepolarizing neuromuscular blockade. The specificity of enflurane in this time-dependent potentiating effect is now less certain because Kelly et al [381] have shown a similar time-dependent action of desflurane as well. A time- dependent effect of halothane and isoflurane on maintenance dosage of mivacurium given by infusion has also been demonstrated. [400] [400A]

There is still debate about the influence of volatile anesthetics on reversal of neuromuscular blockade. Some studies have suggested that maintenance of anesthesia with anesthetic vapors can impede reversal of nondepolarizing neuromuscular blockade by neostigmine or edrophonium. [400B] [400C] [400D] [401] It has even been suggested that the effect is different for different anesthetics and that sevoflurane may impede neostigmine-induced antagonism more than isoflurane. [400C] That so many factors may act to impede adequate reversal stresses the need for close clinical monitoring of neuromuscular function and the avoidance of attempting antagonism with no

evidence of at least the beginning of spontaneous recovery. However, it has also been suggested that withdrawal of the anesthetic vapor at the end of surgery (and consequently reduction of its enhancement of the neuromuscular blockade) will speed pharmacologic reversal. [386]

Temperature

The force of contraction of the adductor pollicis decreases by 10 to 16 percent per degree centigrade decrease in muscle temperature below 35.2°C, during both nitrous oxide/isoflurane and nitrous oxide/fentanyl anesthesia. [402] [403] To maintain the muscle temperature above 35.2°C, central temperature must be maintained at 36.0°C. [404] Mild hypothermia significantly prolongs the duration of action of both vecuronium and atracurium in humans. [404] [405] The duration of action (recovery to 10% twitch height) of vecuronium, 0.1 mg/kg, increases from 28 minutes at a mean central temperature of 36.4°C to 64 minutes at 34.4°C (see Fig. 12-39) (Figure Not Available) . [404] For atracurium, 0.5 mg/kg, the duration of action is 44 minutes at 37°C and 68 minutes at 34.0°C. [405] In contrast, in cats, the durations of both pancuronium and dTc are similar at 39 and 34°C. [406] [407] However, reduction of central temperature in the cat to 28 to 29°C is associated with increased duration of action of both drugs. [406] [407] The prolonged action at these lower temperatures is associated with diminished renal and hepatic excretion, and for pancuronium, serum clearance decreases with decreasing temperature. [406] [407] In humans, there are no differences in the pharmacokinetics or pharmacodynamics of dTc at 31.8°C versus 35.8°C. [408]

The influence of temperature on the sensitivity of a muscle to neuromuscular blockade is complex. In cats, the neuromuscular junction is more sensitive to pancuronium at 29°C than at 39°C, [407] in contrast to dTc, for which the opposite is true. [406] In humans, the sensitivity to dTc is similar at 31.8°C and 35.8°C, [408] and for vecuronium, sensitivity at 34.4° and 36.8°C is similar. [409] The dose of muscle relaxants producing 50 percent decrease in force of contraction of a rat hemidiaphragm preparation, the ED_{50} , was studied at a control temperature of 37°C and over the range 27° to 42°C. [410] Compared to control, the ED_{50} of pipecuronium did not change over the temperature range 27° to 42°C. [410] The ED_{50} of vecuronium and pancuronium decreased with both increasing and decreasing temperature. [410] Succinylcholine was potentiated at 17° and 27°C but not at higher temperatures. [410] *d*-Tubocurarine showed a biphasic response. [410] The ED_{50} decreased by half at 32°C, and increased back to normal at 27°C, and decreased again at

Figure 12-43 (Figure Not Available) Clinical duration of action of vecuronium in 10 normothermic and in 10 hypothermic patients. Duration of action was significantly prolonged during hypothermia (62 ± 8 minutes compared with 28 ± 4 minutes at normothermia; mean ± SD). *(From Heier et al [404])*

17°C. It did not change with hyperthermia. Thus, the effect of hypothermia on neuromuscular junction sensitivity to block will vary with species studied, with different muscle relaxants, and at different temperatures.

Changes in temperature will affect interpretation of the results of monitoring neuromuscular blockade. The duration of action of vecuronium measured in an arm cooled to a skin temperature of 27°C is prolonged, and monitoring by post-tetanic count in that arm is unreliable. [411] In the same patient, TOF responses are different if the arms are at different temperatures, and the correlation of responses in the two arms becomes progressively poorer as the temperature difference between the arms increases. [412]

In summary, the effects of altered temperature on the course of neuromuscular blockade in humans seem to vary widely from one relaxant to another. As hypothermia invariably lengthens the duration of block (Fig. 12-43) (Figure Not Available) , maintenance of normal temperature both centrally and in the limb being monitored will promote improved precision of practice.

Drug Interactions

So many drugs have been shown to interact with neuromuscular blockers and/or their antagonists in animals that it is beyond the scope of this chapter to review them all. The reader is referred to excellent reviews on drug interactions for more detailed information. [413] [414] Some of the more important drug interactions are discussed in the following sections.

Antibiotics

Antibiotics can cause neuromuscular blockade in the absence of neuromuscular blocking agents, [414A] and many reports concerning enhancement of neuromuscular blockade from muscle relaxants by antibiotics have appeared in the literature. Some of the antibiotics have been shown to cause a magnesium-like depression of the evoked release of ACh (a prejunctional effect). Yet these same antibiotics exhibit postjunctional activity. [415] [416] [417] [418] Many investigators have attempted to classify antibiotics according to whether the prejunctional or postjunctional activity is dominant. There may, however, be no common mechanism of antibiotic-induced neuromuscular blockade as different antibiotics have their effect on neuromuscular blockade through different mechanisms. This makes recommendation of a standard therapy for antibiotic-augmented neuromuscular blockade difficult, leading some to conclude that continued mechanical ventilation is the preferred treatment in this clinical setting. [417]

All aminoglycosides can potentiate neuromuscular blockade. Antagonism of rocuronium-induced neuromuscular blockade has been reported to be more difficult following oral neomycin. [418A] Dupuis et al [419] found that gentamicin and tobramycin prolong a vecuronium- but not an atracurium-induced neuromuscular blockade. It is difficult to imagine that antibiotics would affect nondepolarizing muscle relaxants differently; and a more recent study [419A] demonstrated potentiation of atracurium-induced neuromuscular blockade by gentamicin. One approach to a prolonged neuromuscular blockade involving antibiotics is straightforward. Administer neostigmine up to 5 mg/70 kg. If this is ineffective in facilitating full recovery, ventilation should be controlled until the neuromuscular blockade terminates spontaneously. Calcium should not be used to hasten recovery of neuromuscular function for two reasons: the antagonism it produces is not sustained, and it may prevent the antibacterial effect of the antibiotics.

Magnesium and Calcium

The effects of magnesium- and calcium-induced alterations of neuromuscular blockade have been studied in animals and in humans. Magnesium sulfate, given for treatment of preeclampsia and eclamptic toxemia, enhances the neuromuscular blocking properties of both dTC and succinylcholine. [420] [421] Magnesium decreases the amount of ACh released from the motor nerve terminal, the depolarizing action of ACh on the postjunctional membrane, the excitability of the muscle fiber itself, and the amplitude of the end-plate potential. [422] Thus, magnesium enhances dTCinduced blockade by reducing ACh output from the motor nerve terminal and by reducing sensitivity of the postjunctional membrane.

Enhancement of succinylcholine block probably involves the same mechanisms; reduced transmitter output and reduced postjunctional membrane sensitivity will delay the return of normal function. Magnesium may also inhibit plasma cholinesterase.

Although calcium enhances the release of ACh from the motor nerve terminal and enhances excitation-contraction coupling in muscle, [423] it also stabilizes the postjunctional membrane. This stabilization may explain why calcium only partially antagonizes combined magnesium- and dTCinduced blockade. [421] Calcium is less effective in antagonizing combined magnesium- and succinylcholine-induced blockade and will augment a desensitization block from succinylcholine. This is probably explained by membrane stabilization. [424] A prolonged block should be anticipated when a relaxant is administered to a patient receiving magnesium. In these patients, neostigmine and calcium are only partially effective antagonists.

Local Anesthetics and Antiarrhythmics

In large doses given intravenously, most local anesthetics block neuromuscular transmission; in smaller doses, they enhance the neuromuscular block from both nondepolarizing and depolarizing muscle relaxants. [425] [426] Telivuo and Katz [425] found an additional decrease in twitch height and tidal volume from lidocaine, mepivacaine, prilocaine, and bupivacaine in patients partially paralyzed with alcuronium. Local anesthetics, therefore, particularly when given intravenously as

antiarrhythmic agents intraoperatively or postoperatively, may augment a residual neuromuscular blockade. The ability of neostigmine to antagonize a combined local anesthetic-relaxant neuromuscular blockade has not been studied.

In small intravenous doses, local anesthetics depress post-tetanic potentiation, and this is thought to be a neural, prejunctional effect. [427] With higher doses, local anesthetics block ACh-induced muscular contractions, and this suggests that local anesthetics have a stabilizing effect on the postjunctional membrane. [428] Local anesthetics also have a direct effect on the muscle membrane. They decrease the strength of contraction of a curarized or denervated muscle in response to a single shock. [429] Procaine has been shown to displace calcium from the sarcolemma and thus inhibit caffeine-induced contracture of skeletal muscle. [430] Most of these mechanisms of action probably apply to all the local anesthetics. Local anesthetics have actions on the presynaptic, postjunctional, and muscle membranes. Additionally, procaine inhibits plasma cholinesterase and may augment the effects of succinylcholine and mivacurium by decreasing their hydrolysis by the enzyme.

Several drugs used for the treatment of arrhythmias augment the block from muscle relaxants, particularly that of dTC. [431] For example, patients have become "recurarized" after receiving quinidine in the recovery room. These cases may represent unrecognized residual curarization augmented by the administration of quinidine. Quinidine potentiates the neuromuscular block from both nondepolarizing and depolarizing muscle relaxants. [432] Edrophonium is ineffective in antagonizing a nondepolarizing blockade after quinidine. In clinical doses, quinidine appears to act at the prejunctional membrane as judged by its lack of effect on ACh-evoked twitch. However, large, nonclinical doses of quinidine given intra-arterially produce a neuromuscular blockade of the depolarizing type, augmented by edrophonium. [433]

Any drug that influences conduction and the electrical properties of the heart may also influence ion transport at the neuromuscular junction and, therefore, the action of muscle relaxants. Examples of such drugs include betaadrenergic blockers and calcium channel blockers. Although there can be no doubt that these cardiovascular drugs may influence the action of muscle relaxants, the clinical significance of these interactions is probably minor.

Antiepileptic Drugs

Chronic phenytoin or carbamazepine therapy ac- celerates recovery from long-acting and intermediateacting relaxants. It has been well documented by Ornstein and colleagues [434] [435] [436] that metocurine-, doxacurium-, and vecuronium-induced blockades recover as much as 50 percent faster in patients receiving chronic anticonvulsants. Patients receiving two anticonvulsants were very resistant to the blocking effects of atracurium and recovered remarkably quickly from blockade (25-75% recovery index 2 minutes versus 8 minutes in control patients), [435] and those receiving only carbamazepine were not resistant to atracurium-induced block. [436A]

The mechanism of the relative resistance to nondepolarizing neuromuscular blockade in patients receiving anticonvulsants remains unclear, and CNS effects as well as peripheral effects of antiepileptic drugs have been suggested. The clearance of vecuronium in patients receiving carbamazepine is twice as high as it is in patients not receiving carbamazepine. [436B] This, coupled with the lack of a relationship between drug-induced resistance and alpha $_1$ -acid glycoprotein levels [436C] suggests a kinetic rather than a pharmacodynamic reason for the effects of anticonvulsant agents.

Calcium Channel Blockers

A number of observations in experimental animals and in human subjects suggest that any effect of calcium channel blockers on the evolution of neuromuscular blockade in patients is likely subclinical. No interaction between nifedipine and atracurium or vecuronium was found by Bell et al, [437] who studied patients under anesthesia with fentanyl and nitrous oxide. Neither nicardipine nor verapamil affected the recovery index of vecuronium in patients under halothane. [438]

Dantrolene

Dantrolene (Ch. 31), a drug used for the treatment of malignant hyperthermia, depresses skeletal muscle directly and also blocks excitation-contraction coupling. Although it does not block neuromuscular transmission, the mechanical response will be depressed without demonstrating any effect on the electromyogram. [439] [440] The effects of nondepolarizing muscle relaxants are enhanced by dantrolene. [441]

Diuretics

In patients undergoing renal transplantation, the intensity and duration of dTC neuromuscular blockade was increased following a dose of furosemide (1 mg/kg intravenously). [442] This has been investigated further with the rat diaphragm and cat soleus preparations. In the rat diaphragm, the concentration of dTC required for neuromuscular blockade is markedly reduced at clinically relevant doses of furosemide. This diuretic has an effect on the nerve terminal (presynaptic), probably relating to the cyclic nucleotide system.

Furosemide appears to inhibit the production of cyclic adenosine monophosphate. The breakdown of ATP is inhibited, resulting in a reduced output of transmitter, causing enhanced dTC blockade. This effect has been documented as clinically significant. [442]

By contrast, mannitol appears to have no effect on a nondepolarizing neuromuscular blockade. Furthermore, increasing urine output by administration of mannitol or other osmotic or tubular diuretics has no effect on the rate at which dTC and presumably other muscle relaxants are eliminated in the urine. [443] However, this lack of effect on the excretion of dTC should not be surprising. Urinary excretion of all relaxants that are long-acting depends primarily on glomerular filtration. Mannitol is an osmotic diuretic that exerts its effects by altering the osmotic gradient within the proximal tubules so that water is retained within the tubules. An increase in urine volume in patients with adequate glomerular filtration, therefore, would not be expected to increase excretion of muscle relaxants.

Azathioprine

Azathioprine, an immunodepressant drug used in renal transplantation, has a minor antagonistic action on muscle relaxant-induced neuromuscular blockade. [444] [445]

Interactions Among Nondepolarizing Relaxants

The authors of this chapter believe there is little reason to combine nondepolarizing relaxants, particularly as few of the possible multiple combinations [446] [447] have been studied for the presence of either potentiation or a simple additive effect. The original clinical reason for combining pancuronium and metocurine was the resulting lack of cardiovascular side effect of the combination. [448] [449] Vecuronium, pipecuronium, and doxacurium, all with minimal cardiovascular side effects, are now available, making the original combination seem less appropriate.

Although little has yet been published on the subject, it is important to consider the sequential administration of long- and short-acting nondepolarizers.

The general rule is the following: the changeover from one drug to another, when the durations are dissimilar, is a matter of simple kinetics. Three half-lives will be required for a clinical changeover (so that 95% of the first drug has been cleared) and for the block duration to begin to take on the characteristics of the second drug. Consequently, the change in blocking characteristics (most noticeable as change in the speed of recovery) will occur within only 10 to 15 minutes following mivacurium but will require 4 to 6 hours if change from long- to short-acting drug is attempted. A few pertinent examples follow.

Change from Short- to Intermediate- or Long-Acting Drug

When the short-acting nondepolarizer mivacurium is given for tracheal intubation with the intention of continuing maintenance of relaxation with a longer-acting drug, the following approach is recommended. A maintenance dose of the long-acting muscle relaxant (e.g., 0.5 mg [0.01 mg/kg] of doxacurium) should be given when the TOF response has begun to recover (e.g., to two or three twitches visible). The clinician will note that the duration of effect of this first maintenance dose is much shorter than commonly observed. Only after the second maintenance dose of longer-acting muscle relaxant will the expected longer duration establish itself. This changeover, however, does make sense in clinical practice, more so if the change intended is from short- to intermediate-acting drug than if the change is from short-

to long-acting drug. Definitive studies are needed to support these considerations.

Change from Longto Short-Acting Drug

When relaxation has been maintained, for example, for 3 hours with dTC or any other long-acting relaxant, if the clinician wishes to administer a maintenance dose of mivacurium to obtain a shorter duration of block, a very small dose should be given (10-20 mug/kg). The clinician will note that this dose will have an unexpectedly long duration of action, nearly as though another small dose of dTC were given. This should not be surprising; the established kinetics are those of the long-acting drug, with its 1½ to 2-hour half-life. Addition of a small amount of mivacurium at this point will have very little effect on this kinetic pattern. Therefore, this change of drug sequence makes little clinical sense and is probably not worth attempting.

"Priming" with a Long-Acting Muscle Relaxant

If a priming dose of long-acting muscle relaxant (e.g., 10 mug/kg of pancuronium, 50 mug/kg of dTc, 5 mug/kg of doxacurium) is given prior to an intubating dose of mivacurium (0.25 mg/kg), then the clinician will note a much longer-than-usual duration of action of mivacurium. This should be expected, because the priming dose of the long-acting drug still has a half-life of 1½ to 2 hours. Therefore, the subclinical effect of the priming dose of the long-acting drug will be additive to the action of mivacurium throughout the normal course of action of the long-acting drug, in effect lengthening the duration of action of mivacurium considerably. Consequently, priming with a long-acting or intermediate-acting muscle relaxant prior to mivacurium (or even prior to an intermediate-acting drug) does not seem to make any clinical sense, unless the intent is to lengthen the action of the endotracheal intubating drug.

In summary, few actual measurements have been made of the consequences of changing from one nondepolarizer to another with a different duration of action. The switch from the short-acting mivacurium to the longer-acting drugs seems to make the most clinical sense, because here the kinetic changes are most appropriate to clinical practice patterns. Change from one of the relaxants of intermediate duration (atracurium, vecuronium, cisatracurium, or rocuronium) to one of the long-acting relaxants also seems reasonable, although the time differences will not be as noticeable. Certainly, whenever such changeover is undertaken, careful monitoring with a peripheral nerve stimulator is mandatory. Clinical studies are certainly needed to better define these scenarios.

ANTAGONISM OF RESIDUAL NEUROMUSCULAR BLOCKADE

The criteria for determining whether a block has been adequately antagonized have been described in the section *Monitoring Neuromuscular Function*. The drugs used to antagonize residual neuromuscular block, neostigmine, edrophonium, and pyridostigmine are anticholinesterases. They antagonize a nondepolarizing neuromuscular blockade primarily by increasing the concentration of ACh at the muscle end plate mainly by inhibition of acetylcholinesterase. In addition, they may also increase release of ACh from the motor nerve terminals, block neural potassium channels, and have a direct agonist effect. [449A] The reader should consult Chapter 22 and the following review articles for more details regarding the mechanisms of action of these antagonists. [450] [451]

Major Determinants of Speed and Completeness of Reversal

Antagonism of nondepolarizing block requires a certain amount of time. Reversal occurs at a rate that depends primarily on five factors: (1) depth of block at the time of administration of the antagonist, (2) the particular antagonist administered, (3) the dose of the antagonist, (4) the rate of spontaneous recovery from the muscle relaxant, and (5) the concentration of the inhaled anesthetic present during reversal.

Depth of Block

The deeper the block, the longer the time required for restoration of adequate neuromuscular function. [451A] [451B] [451C] Figure 12-44 (Figure Not Available) presents data for antagonism of pancuronium block by a standard dose of 2.5 mg (about 35 mug/kg) of neostigmine. The data shown in the figure are for antagonism of the *single twitch response* of the adductor pollicis, a peripheral muscle. Note that antagonism of TOF to 0.7 or more would take longer. Figure 12-44 (Figure Not Available) shows that the relationship of reversal time (speed of reversal) to depth of block is apparently hyperbolic, with a "knee" in the curve occurring at 80 to 90 percent twitch inhibition. At block depth of less than 80 percent, only 8 to 12 minutes are required for antagonism of pancuronium. Deeper blocks require much longer times (15-30 minutes) for adequate reversal. Therefore, it is recommended that one bear in mind the longer period (15-30 minutes), with the further understanding that even longer time may be required for restoration of TOF ratio to more than 0.7 when block by longacting drugs is being antagonized.

The maximum antagonistic effect of neostigmine occurs in about 10 minutes or less. [452] [452A] If adequate recovery does not occur within this time, then subsequent recovery is slow. For profound vecuronium-induced block in which no twitch recovery has occurred, the administration of neostigmine, 70 mug/kg, produces an initial reversal that falls far short of adequate recovery. [453] Subsequent recovery is at the same rate as spontaneous recovery and is due to the decrease

Figure 12-44 (Figure Not Available) Correlation between twitch height when a bolus of neostigmine (2.5 mg) was given intravenously and time it took for twitch height to return to its control height. *(From Katz [451A])*

in plasma concentration of vecuronium as the drug is eliminated. [453] Administration of a second dose of neostigmine has no further effect on recovery. [453]

If the block at the time of neostigmine administration is sufficiently deep that adequate recovery does not occur within 10 minutes, then the time until full recovery does occur will depend on the inherent duration of action of the relaxant. [451C] With long-acting drugs this period of inadequate neuromuscular function can be 30 to 60 minutes or longer, whereas with intermediate-duration drugs it will be much shorter (e.g., 15-30 minutes). [453A]

Antagonist Administered

Under conditions of moderate depth of block (e.g., two to three twitches palpable by TOF), the order of rapidity of antagonism of residual blockade by anticholinesterases is edrophonium > neostigmine > pyridostigmine. [452] [453B] For this reason, and because of its lesser atropine requirement, edrophonium regained popularity as an antagonist during the 1980s. [452] However, Rupp et al [454] found that edrophonium is not as effective as neostigmine in antagonizing profound blockade of greater than 90 percent twitch depression (only one twitch palpable by TOF). When the dose of edrophonium was increased from 0.5 to 1.0 mg/kg, edrophonium was more active but possibly still not as effective as neostigmine. [454] To be equivalent to neostigmine 40 mug/kg as an antagonist of deep vecuronium blockade, edrophonium has to be administered in a dose of 1.5 mg/kg. [454A]

Donati et al [455] showed that the relative potencies of edrophonium and neostigmine differ at various intensities of block (Fig. 12-45) (Figure Not Available) . In fact, edrophonium becomes less potent with respect to neostigmine as the depth of blockade becomes more intense. In other words, the dose-response curves are not parallel and become increasingly divergent (i.e., the dose ratio increases) as the depth of blockade intensifies. This difference does indicate that edrophonium may be less effective than neostigmine at very deep levels of blockade.

Figure 12-45 (Figure Not Available) First twitch height (logit scale) versus dose (log scale) 10 minutes after administration of neostigmine and edrophonium given at either 1 percent (99% block) or 10 percent (90% block) first twitch recovery. Thin dashed lines represent the standard error of estimate for the mean. *(From Donati [455])*

Dose of Antagonist

Larger doses of anticholinesterases should antagonize neuromuscular blockade more rapidly and more completely than smaller doses. This relationship is true up to the point of maximum effective dose, beyond which further amounts of anticholinesterase will not produce any greater antagonism. For neostigmine, this maximum dosage is in the range 60 to 80 mug/kg. [453] [455A] For edrophonium, this dose is in the range 1.0 to 1.5 mg/kg. [454] [454A] The maximum effect of the anticholinesterase occurs within 10 minutes; further recovery to normal function subsequently occurs at a rate that is largely dependent on the rate of spontaneous recovery. [453] [455B]

One of the better recent demonstrations of the relationship of dose of neostigmine to speed of reversal is the work of Donati et al [456] (Fig. 12-46) (Figure Not Available) , who studied reversal of 90 percent block induced by either dTC or pancuronium. They showed that increasingly greater amounts of antagonism of

Figure 12-46 (Figure Not Available) Rate of antagonism of 90 percent pancuronium block by increasing doses of neostigmine. Note that even after 0.05 mg/kg of neostigmine, only 80 percent twitch height had been reached within 10 minutes. *(From Donati [456])*

neuromuscular block occurred over the course of 10 minutes as neostigmine dosage was increased from 5 to 50 mug/kg. Note, however, that even after 50 mug/kg, the twitch had reached only 80 percent of normal strength 10 minutes after neostigmine administration.

Mixing or combining antagonists is not advisable. Neostigmine and edrophonium do not potentiate each other; in fact, their effects in combination may not even be

additive. [457] Therefore, when inadequate reversal occurs, one should not be tempted to add a different anticholinesterase but should ensure only that the maximum dose of the original drug has been administered. Ventilation should then be supported until adequate neuromuscular function is achieved, e.g., head lift. If function is not adequate 30 to 60 minutes following antagonist administration, then an additional dose of antagonist (about half the original dose) may be given. This time-frame is somewhat less than one half-life of any of the antagonists.

Rate of Spontaneous Recovery of the Relaxant

Following administration of an anticholinesterase, two processes contribute to recovery of neuromuscular function. The first is antagonism induced by the effect of the anticholinesterase at the neuromuscular junction; the second is the natural process of decrease in plasma (and hence neuromuscular junction) concentration of the relaxant consequent on its elimination (spontaneous recovery). [451C] [451B] As a result, the more rapid the elimination of the relaxant, in general, the faster the recovery of adequate neuromuscular function following administration of an antagonist (Fig. 12-47) (Figure Not Available) . A clear illustration of this principle is the difference in antagonizing the block induced by relaxants with an intermediate versus a long duration of action. The plasma concentrations of drugs with an intermediate duration of action

Figure 12-47 (Figure Not Available) Comparative mean speed of antagonism by neostigmine of neuromuscular blockade induced by long-acting agents (doxacurium, pancuronium, pipecuronium), intermediate-acting drugs (atracurium and others), and the short-acting agent mivacurium. Antagonism is more rapid as processes of clearance increase (see text). *(From Savarese [457A])*

decrease more rapidly than those with a long duration, [457B] and consequently recovery of neuromuscular function is more rapid. [452A] [458] [458A] The incidence of inadequate neuromuscular function in the postoperative period is less with intermediate-acting than with long-acting relaxants. [453A] [459] This difference in speed of reversal between intermediate- and long-acting drugs is due to the effect of different rates of spontaneous recovery and not due to a difference in response to neostigmine. [459A] The proof is that when neostigmine is administered to antagonize a stable level of block maintained by continuous infusion of either vecuronium or pancuronium, the rate and degree of recovery are similar in the case of each relaxant. [459A]

The interaction of spontaneous recovery and anticholinesterase-induced reversal of mivacurium is more complex. The inherent rate of spontaneous recovery of mivacurium is more rapid than that of any other nondepolarizing relaxant because of its rapid hydrolysis by plasma (butyryl) cholinesterase. [459B] Neostigmine-induced reversal of mivacurium is similar to or faster than that of atracurium. [459B] [459C] In the circumstance of profound (<3% twitch recovery) mivacurium-induced block, the administration of neostigmine may possibly prolong recovery. [460] [460A] This complexity exists in theory because neostigmine has two major effects relevant to mivacurium. First, it inhibits acetylcholinesterase at the neuromuscular junction and facilitates recovery. Second, it inhibits plasma cholinesterase, the enzyme responsible for the metabolism of mivacurium, and slows the normally rapid decrease in the plasma concentration of mivacurium. [460B] A similar effect is less likely with edrophonium because edrophonium has little inhibitory effect on plasma cholinesterase. [460C] Regardless of the complexity of the pharmacologic interactions, if there is already easily detectable recovery (twitch height 10% or greater), then administration of neostigmine 20 to 40 mug/kg, or edrophonium 0.3-0.5 mg/kg, will certainly accelerate recovery from mivacurium. [450] [461] [461A] [461B]

It has been suggested that routine administration of an anticholinesterase may often be omitted because spontaneous recovery from mivacurium is so rapid. [461C] However, this strategy may possibly lead to inadequate recovery and postoperative weakness *unless enough time is allowed (at least 20 minutes) for spontaneous recovery.* [461] [461A] The authors advise against attempting anticholinesterase-induced reversal of mivacurium when no twitch or TOF responses are present and suggest that small doses of neostigmine or edrophonium should be used if mivacurium administration has continued till near the end of the surgical procedure, and acceleration of already-present spontaneous recovery is desired.

Because mivacurium is extensively metabolized by plasma cholinesterase, its recovery might, in theory, be made more rapid by the administration of exogenous human butyryl-cholinesterase. The administration of purified human cholinesterase does produce some antagonism of mivacurium-induced block, [462] but it is ineffective in profound block [462A] and no better than edrophonium alone. [462B] It may be justified to administer purified butyrylcholinesterase to patients with genetic abnormality of the enzyme who have prolonged block, [463] but this therapy has yet to be adequately tested and is expensive.

Concentration of Inhaled Anesthetic

Several recent studies have documented that antagonism of residual block is actually retarded by anesthetizing concentrations of anesthetic vapors (this does make sense, because the nondepolarizers are potentiated by the potent vapors). Thus, for example, Delisle and Bevan [400B] showed that pancuronium reversal by neostigmine under enflurane occurred more slowly than under nitrous oxide and intravenous anesthetics. [463A] However, a study by Baurain [464] showed that the situation is complex. The presence of isoflurane during the reversal of vecuronium by neostigmine resulted in a lower TOF ratio but a similar degree of fade to 50 Hz tetanus and a lesser degree of fade at 100 Hz, compared with an anesthetic without vapor. [464] The current state of knowledge is incomplete, but there is evidence that isoflurane may impair some, but not all, parameters of neuromuscular recovery after neostigmine reversal of neuromuscular block. [464] [465] In any event, it is good clinical practice to reduce concentrations of potent anesthetic vapors as much as possible to facilitate reversal at the end of a case.

Other Factors That May Interfere With Antagonism

It is not advisable to administer further antagonist if maximal doses of edrophonium (1.5 mg/kg), neostigmine (70 mug/kg), or pyridostigmine (350 mug/kg) fail to antagonize residual block. [454A] [455A] These doses inhibit acetylcholinesterase completely, and if they fail to fully antagonize residual block, the most likely cause of the inadequate antagonism should be sought. Some of these additional potential causes follow.

Acid-Base State

Both metabolic and respiratory acidosis may augment a nondepolarizing neuromuscular blockade, but only respiratory acidosis prevents adequate antagonism. [453B] [467] [467A] In other words, the probability of achieving adequate antagonism of a nondepolarizing neuromuscular blockade in the presence of significant respiratory acidosis (Pa CO_2 greater than 50 mm Hg) is low. For example, if a patient hypoventilates in the recovery room, attempts to antagonize a residual block may fail. Administration of narcotics to relieve pain may, by producing hypoventilation, increase the likelihood of this adverse event. Such a sequence contains an element of potential undesirable and potentially dangerous positive feedback in which respiratory depression produces more acidosis and greater block--hence, more respiratory depression, etc.

Although metabolic acidosis might also be predicted to prevent antagonism by neostigmine, this theory has not been substantiated. [453B] [467] [467A] To the authors' surprise, metabolic alkalosis, but not metabolic acidosis, prevented neostigmine antagonism of dTC and pancuronium. [453B] [466] [467] These results suggest that extracellular hydrogen ion concentration (pH) per se may not be as important as changes in electrolytes and intracellular pH. Because so many factors are involved,

the simplest and most obvious objective of the clinician should be the maintenance of a normal acid-base state in the patient.

Electrolyte Imbalance

Although it has been the subject of several review articles, [468] few data are available on the effect of electrolyte imbalance on a nondepolarizing neuromuscular blockade and its antagonism by neostigmine. Low extracellular concentrations of potassium do enhance the blockade from nondepolarizing muscle relaxants and diminish the ability of neostigmine to antagonize the blockade. This effect is based on the increase in end-plate transmembrane potential that results from a higher ratio of intracellular to extracellular potassium. Thus, a decrease in extracellular potassium causes hyperpolarization and produces resistance to depolarization. Patients with an imbalance in potassium may have other diseases or injuries that alter their response to muscle relaxants (e.g., patients with burns). Cohen [469] and Feldman [468] speculated that, in chronic diseases, both intracellular and extracellular potassium is depleted with little net effect on transmembrane potential. Therefore, the response to muscle relaxants and their antagonists should be normal. However, the muscle transmembrane potentials are changed in patients who are

severely ill or bedridden for a few days. [470] Also, severe dehydration should concentrate the relaxant present in plasma, in effect decreasing the volume of distribution, thereby increasing muscle relaxant activity. In an animal model of chronic hypokalemia, cats were given a diuretic without potassium supplement for 15 days. Less pancuronium was required for neuromuscular blockade and more neostigmine for antagonism. [470A] Even though the differences were small, the blockade was always antagonized completely. Assuming that this animal model approximates the clinical situation, changes in potassium appear to be of relatively minor consequence with respect to the clinical question of adequacy of reversal.

Other Factors

The calcium channel blocker verapamil will potentiate nondepolarizing neuromuscular blocking drugs and may produce difficulty with obtaining adequate reversal. [470B] [470C] [471] When attempting reversal of neuromuscular blockade in patients receiving verapamil, edrophonium may be more effective than neostigmine. [470B] [470C] Other factors that may interfere with antagonism are hypothermia or the administration of antibiotics, particularly of the aminoglycoside or polypeptide classes. [453A] [455A] [471A] [471B] In the case of the antibiotics, the administration of an anticholinesterase may in fact deepen the blockade. [453A]

In general, any significant perturbation of homeostasis may be regarded as potentially interfering with antagonism of residual neuromuscular blockade and should raise a level of suspicion that reversal may prove to be inadequate. In the situation where reversal appears incomplete, and maximum doses of the chosen anticholinesterase have been administered, the following management will provide the best route to a safe and trauma-free outcome for the patient: (1) leave or reinsert the endotracheal tube in the patient's trachea; (2) if respiration is inadequate, support ventilation; (3) explain the situation to the patient, and administer a sedative/anxiolytic and, if indicated, an analgesic; (4) correct metabolic and acid-base disorders and return the patient's temperature to normal. Continue these supportive measures until there is good clinical evidence for adequate recovery of neuromuscular function, at which point the patient's trachea may be extubated. Clinical criteria should be used to assess adequacy of recovery; monitoring with a nerve stimulator may give misleading results, particularly if aminoglycosides have been administered. [472] This management strategy is simple, safe, and, if handled appropriately, with proper attention to sedation and personal attention to psychologic support, should prove to be minimally traumatic for the patient. Other approaches involving calculations of half-lives of the relaxants and antagonists to allow repeat doses of the latter to be given may present other potential problems. The administration of calcium is unlikely to result in a more rapid and safe resolution of the problem and is no longer recommended.

Cardiovascular Effects of Antagonism

Because only the nicotinic effects of edrophonium, neostigmine, and pyridostigmine are desired, the muscarinic effects must be blocked by atropine or glycopyrrolate. [449A] Atropine induces its vagolytic effect much more rapidly than does glycopyrrolate. To minimize cardiovascular changes, the authors believe atropine is better suited together with the rapid-acting edrophonium, [472A] and glycopyrrolate is better suited with the slower-acting neostigmine and pyridostigmine. [472B] In general, 7 to 10 mug/kg of atropine should be given with 0.5 to 1.0 mg/kg of edrophonium. [452] Glycopyrrolate (7-15 mug/kg) should be given with neostigmine (40-70 mug/kg). Administration of atropine with pyridostigmine will induce an initial tachycardia, [473] and giving glycopyrrolate with edrophonium may result in an initial bradycardia unless it is administered at least 1 minute earlier. [473A] Arrhythmias can occur, [473A] [473B] [474] [475] [476] and anticholinesterases should be used with caution in patients with autonomic neuropathy. [473B] When cardiac arrhythmias are a concern, glycopyrrolate may be preferable to atropine, [476] and the anticholinesterases and anticholinergics may be administered over a longer time (e.g., 2-5 minutes) in order to help reduce the incidence and severity of the disorders of rhythm.

Pharmacokinetics of Neostigmine, Pyridostigmine, and Edrophonium

The pharmacokinetics of edrophonium, neostigmine, and pyridostigmine are summarized in Table 12-15 . [477] [478] [479] [479A] Several important clinical conclusions can be derived from these data.

1. The longer duration of action of pyridostigmine probably has a pharmacokinetic basis in view of the longer elimination half-life. [477] [478]

2. By comparing elimination half-lives in patients with and without renal failure, the authors conclude that renal excretion accounts for about 50 percent of excretion of neostigmine and about 75 percent of that of pyridostigmine and edrophonium. Of prime importance clinically is that renal failure decreases plasma clearance of neostigmine, pyridostigmine, and edrophonium as much as, if not more than, that of the long-acting relaxants such as pancuronium and dTc. Therefore, if proper doses of anticholinesterase drugs are given and overdoses of muscle relaxants are avoided, renal failure should not be associated with "recurarization." [477] [478] This remote possibility is further diminished if the clinician restricts relaxant administration to intermediate- or short-acting drugs in patients with renal failure. There is no longer any justification for giving long-acting drugs, which are excreted almost exclusively by the kidneys, to patients with markedly decreased renal function.
3. Edrophonium was once believed to be an unsuitable antagonist in clinical practice because its duration of action might be too short. However, when larger doses (i.e., 0.5-1.0 mg/kg) are given, sustained antagonism of a nondepolarizing neuromuscular blockade results. [480] [481] In fact the elimination half-life of edrophonium is similar to that of neostigmine or pyridostigmine [479A] (see Table 12-15) . That edrophonium has a quicker onset of action and probably fewer side effects may justify more frequent use of this drug when antagonizing a nondepolarizing neuromuscular blockade.

TABLE 12-15 -- Pharmacokinetics of Neostigmine (N), Pyridostigmine (P), and Edrophonium (E) in Patients Without and With Renal Failure

MEASURE	WITHOUT RENAL FAILURE			WITH RENAL FAILURE		
	N	P	E	N	P	E
Distribution half-life (t½alpha, min)	3.4	6.7	7.2	2.5	3.9	7.0
Elimination half-life (t½beta, min)	77	113	110	181	379	304
Volume of central compartment (L/kg)	0.2	0.3	0.3	0.3	0.4	0.3
Total plasma clearance (mL/kg/min)	9.1	8.6	9.5	4.8	3.1	3.9

Data from Cronnelly et al [477] ; Cronnelly et al [478] ; Morris et al [479] ; Morris et al [479A]

Mild hypothermia (i.e., 34-35°C), as commonly occurs intraoperatively, has detrimental effects on the pharmacokinetics of neostigmine. The clearance is decreased from 16.2 mL/kg/min at 36.5°C to 13.5 mL/kg/min at 34.5°C. [481A] Also, the onset of peak effect is prolonged by mild hypothermia from 4.2 to 5.5 minutes. [481A] The peak effect and duration of effect were unchanged by hypothermia. Thus, if hypothermia has any influence on the effectiveness of neostigmine-induced reversal, it is more likely to be due to the effect of temperature on the muscle relaxant (e.g. prolonged duration of action [481B]) than to the pharmacology of neostigmine.

The pharmacokinetics of the anticholinesterases depend on several factors, including metabolism as well as distribution and elimination. In the case of neostigmine, a carbamylated complex with acetylcholinesterase is formed, [481C] [481D] and it is the rate of dissociation of neostigmine from this complex, i.e., its metabolism, that is probably the major determinant of its duration of action. The decay in its plasma concentration, i.e., its distribution and elimination, [481E] may not be as pertinent a determinant of the duration of action of the drug.

DISEASES THAT MAY ALTER MUSCLE RELAXANT ACTION

The following diseases show complex pathophysiology. Only that aspect directly relating to the use of muscle relaxants is discussed.

Myasthenia Gravis

Excellent reviews of this topic are presented in references [482] [483] [484] [485] . Because myasthenia is an autoimmune disease where there is decreased postjunctional receptor substance, myasthenic patients are often extremely sensitive to nondepolarizing relaxants and are usually somewhat resistant to succinylcholine. [486] [487] Not all the musculature is affected to the same degree. Careful monitoring with a peripheral nerve stimulator is mandatory when relaxants are to be given to these patients; more effective management must include (1) a preoperative consultation with the patient's neurologist to learn of the recent history and progress of management; (2) knowledge of current medications (usually an anticholinesterase such as pyridostigmine, also commonly referred to by the trade name Mestinon) and/or corticosteroids; (3) counseling and preparation of the patient for possible postoperative endotracheal intubation and mechanical ventilation; (4) monitoring at several sites with a nerve stimulator, such as at the ulnar nerve-adductor pollicis, the facial nerve and musculature, and the peroneal nerve-extensor hallucis-tibialis anterior (dorsiflexion of the toe and ankle); and (5) clinical judgment of adequacy of neuromuscular function when a decision to discontinue mechanical ventilation and to extubate the trachea is being considered postoperatively. Once again, at this point, consultation with the patient's neurologist is mandatory in order to ensure smooth transition and continuation of management.

Often, surgical relaxation can be provided for the myasthenic patient using only a potent inhaled anesthetic. However, many patients are very well compensated on medication and show surprisingly adequate neuromuscular function and a virtually normal response to nondepolarizing relaxants. It may be safer and more convenient to intubate the trachea and to provide abdominal relaxation with the aid of relaxants in these patients than to use deep anesthesia.

Short-acting or intermediate-acting drugs should be used in low dosage as guided by monitoring with a nerve stimulator. About one-tenth to one-fifth the ED_{95} should be given as a test dose to estimate the patient's requirement. Again, individual response will vary from extreme sensitivity, such that the test dose is all that is needed, to nearly normal relaxant requirements.

Because the myasthenic patient is usually receiving pyridostigmine therapy, the medication should be continued preoperatively. Pyridostigmine will modify the response to relaxants as follows: (1) the sensitivity to nondepolarizers will be diminished; (2) the response to succinylcholine or mivacurium may be lengthened somewhat, because therapeutic levels of pyridostigmine may partially inhibit pseudocholinesterase; and (3) reversal of residual block at the end of the case may be ineffective because much acetylcholinesterase inhibition already exists as a result of chronic pyridostigmine therapy. Consequently, it is probably safer to allow spontaneous recovery from relaxation postoperatively while continuing supportive mechanical ventilation. This recommendation is consistent with the authors' experience and is in agreement with the literature. [488] [489] Conservatism in postoperative management of the disease is mandatory because surgery and anesthesia may exacerbate the myasthenic state in an unpredictable manner. [488] [489]

Myasthenic Syndrome (Eaton-Lambert Syndrome)

Eaton-Lambert syndrome is an association between carcinomatous conditions (especially oat cell carcinoma of the bronchus) and motor neuropathy and clinically resembles myasthenia gravis. The disease is differentiated from myasthenia by electromyography, in which facilitation of the electromyogram (EMG) response, rather than fade, occurs during high-frequency (30-50 Hz) stimulation. These patients are unusually sensitive to both nondepolarizing and depolarizing muscle relaxants.

Myotonia

The myotonic syndromes include myotonia congenita, myotonia dystrophica, and paramyotonia congenita. With the latter condition, myotonia appears only on exposure to cold.

Myotonic dystrophy (atrophica), the most common of the three, is an inherited, autosomal-dominant disease. Clinical features include weakness and wasting of the facial, cervical, and proximal limb muscles; frontal baldness; cataracts; gonadal atrophy; thyroid nodules; endocrine failure; and voluntary and percussion myotonia. Continuous, low-voltage activity with high-voltage, fibrillation-like potential bursts will be evident on the EMG. A mechanical stimulus will evoke a burst of rhythmic EMG potentials at 90 to 100/s, which eventually slows to low-voltage activity. Cardiac conduction defects and myocardial failure are commonly present as the disease progresses. Respiratory involvement, secondary to skeletal muscle weakness, is also common. While the carbon dioxide response curves are normal, mechanical ability to ventilate is impaired, as reflected by a diminished vital capacity and forced vital capacity in 1 second, as well as reduced maximum expiratory force. Some patients have weakness of pharyngeal muscles with recurrent aspiration pneumonitis. The onset of the disease is most common in the 2nd to 4th decade and progresses to muscular atrophy in later years.

Anesthetic and operative mortality is increased for several reasons. The most common complication is postoperative respiratory failure due to decreased mechanical ability, which interferes with deep breathing and coughing. Intraoperatively, cardiac conduction abnormalities may cause hemodynamic instability. Generalized myotonia may follow administration of succinylcholine in some patients. Occasionally, the severity of the myotonic response has precluded attempts to control ventilation. Although it is difficult to collect a large clinical experience, [490] Mitchell et al [491] thoroughly evaluated three patients with myotonia dystrophica and their response to muscle relaxants and concluded that (1) the response to nondepolarizing muscle relaxants is normal, (2) patients with myotonia are more likely than normal patients to develop apnea after administration of sedative or anesthetic drugs, and (3) the use of depolarizing muscle relaxants is hazardous because marked generalized contracture of skeletal muscle may develop, preventing adequate airway maintenance and ventilation. The use of anticholinesterases may exacerbate myotonia. This last point, though, is not well documented and was not confirmed by Mitchell et al. Should myotonia develop intraoperatively, nondepolarizing neuromuscular blocking drugs will not attenuate it, as the disease is primarily a disorder of the muscle membrane. Myotonia may also develop in response to percussion or to shivering postoperatively. Local infiltration of the involved muscles with local anesthetics may help to attenuate percussion myotonia. Quinine and procainamide have been used for generalized myotonia.

Familial Periodic Paralysis

Familial periodic paralysis is associated with hyperkalemia, hypokalemia, or normokalemia and is characterized by intermittent attacks of skeletal muscle weakness and flaccid paralysis, usually sparing the bulbar musculature. With the hypokalemic type, intravenous fluids should be chosen to avoid a large carbohydrate or salt load and should treat hypokalemia. Postoperatively, if such a patient is weak, the weakness is usually secondary to hypokalemia. Muscle relaxants should generally be avoided, although Siler and Discavage [492] noted a normal response to succinylcholine. By contrast, in hyperkalemic patients, carbohydrate stores should be

maintained with dextrose-rich, potassium-free intravenous solutions. Muscle relaxants, especially succinylcholine, should be avoided. Succinylcholine can cause myotonia in these patients. [493]

Upper and Lower Motor Neuron Disease

The potential hazards of giving succinylcholine to patients with upper or lower motor neuron disease is described earlier in this chapter. These patients' response to nondepolarizing

muscle relaxants is exaggerated. This was well documented by Rosenbaum et al, [494] who found that dTC (1.5 mg) given over 30-minutes to a man with amyotrophic lateral sclerosis caused difficulty with speech and swallowing.

Lower motor neuron denervation results in a resistance to nondepolarizing muscle relaxants because of a proliferation of ACh receptors. [495] By administering small doses of nondepolarizing muscle relaxants plus monitoring with a peripheral nerve stimulator, the anesthesiologist should be able to avoid significant problems in these patients. However, monitoring with a peripheral nerve stimulator may not be reliable in patients with an upper motor neuron lesion because a paretic limb is relatively resistant to nondepolarizing block. [496] [497] Monitoring of the unaffected limb and other confirmatory clinical measures of depth of neuromuscular blockade and adequacy of recovery should be undertaken in these patients.

Burns

Patients with burn injuries have abnormal responses to both depolarizing and nondepolarizing muscle relaxants.

The rise in serum potassium that normally follows succinylcholine administration is markedly exaggerated in burned victims. [498] Potassium levels as high as 13 mEq/L, resulting in ventricular tachycardia, fibrillation, and cardiac arrest, have been reported. [499] [500] [501] The mechanism of this exaggerated response to depolarizing relaxants seems to be similar to that in victims of denervation injuries. Apparent proliferation of extrajunctional acetylcholine receptors occurs. [502] [503] Stimulation of these receptors by succinylcholine causes massive potassium release sufficient to cause cardiac arrhythmias and death.

When in the course of the burn injury this hyperkalemic response appears and later subsides remains unclear. Succinylcholine has been safely administered within 24 hours of a burn injury. Following this initial 24 hours, however, sufficient alteration in muscle response may have occurred such that the use of succinylcholine is best avoided. The magnitude of the hyperkalemic response does not appear to closely correlate with the magnitude of the burn injury. A marked hyperkalemic response has been noted following only an 8 percent total body surface area burn. [502] The length of time during which a burn patient may be at risk for the hyperkalemic response is also not well defined. Whereas susceptibility to hyperkalemia may persist only several weeks to months, an altered response to nondepolarizing relaxants has been reported in one patient as long as 463 days after the thermal injury. [504]

The time course of abnormal muscle membrane function corresponds with that of the healing process. Once normal skin has regrown, and any infection subsides, return of normal ACh receptor populations appears to occur. [502] Normal responses to succinylcholine have been demonstrated in burn patients studied 3 years postinjury. [502] A conservative guideline therefore would be to avoid the use of succinylcholine in patients 24 to 48 hours following a thermal injury and for at least 1 to 2 years after the burned skin has healed.

TABLE 12-16 -- Reported Indications for Use of Muscle Relaxants in the ICU

Facilitate mechanical ventilation
Facilitation of endotracheal intubation
Enable patient to tolerate mechanical ventilation
High pulmonary inflation pressures, e.g., acute respiratory distress syndrome
Hyperventilation for elevated intracranial pressure
Facilitate therapeutic or diagnostic procedures
Tetanus
Status epilepticus
Reduce oxygen consumption
Abolish shivering
Reduce work of breathing

MUSCLE RELAXANTS IN THE INTENSIVE CARE UNIT

Currently, neuromuscular blocking drugs are used in many intensive care units (ICU). [505] [506] [507] Pancuronium and vecuronium were the most commonly used nondepolarizing drugs, but atracurium, cisatracurium, rocuronium, and doxacurium are now are being used commonly. [505] [508] [509] [510] The indications for use of muscle relaxants in the ICU are outlined in Table 12-16 . There are few data to support their use, and evidence for a beneficial effect on pulmonary function or patient oxygenation is inconclusive. [511] [511A] [511B]

Complications associated with both short- and long-term use of muscle relaxants for ICU patients are outlined in Table 12-17 . The specific, short-term side effects of muscle relaxants are covered elsewhere in this chapter. Of particular concern in the ICU setting is the risk of paralyzed patients receiving inadequate analgesia and sedation. [512] [513] [514] Inadequate analgesia and sedation occur in part because in

TABLE 12-17 -- Complications of Muscle Paralysis in the ICU

Short-term use
Specific, known drug side effects
Inadequate ventilation
Circuit disconnection
Ventilator failure
Inadequate analgesia and/or sedation
Long-Term Use
Complications of immobility
Deep venous thrombosis and pulmonary embolus
Peripheral nerve injuries
Decubitus ulcers
Inability to cough
Retention of secretions and atelectasis
Pulmonary infection
Prolonged paralysis after stopping relaxant
Persistent neuromuscular blockade
Steroid-associated myopathy
Motor neuropathy
Neuromuscular dysfunction
Combination of the above
Unrecognized effects of drug or metabolites
Succinylcholine and metabolic acidosis/hypovolemia
3-desacetylvecuronium and neuromuscular blockade
Laudanosine and cerebral excitation
CNS effects of muscle relaxants

up to 15 percent of ICUs, sedative drugs are not normally administered to paralyzed patients, and also because ICU nurses and physicians may be unfamiliar with the pharmacology of the drugs they are using. [506] [513] Pancuronium was thought to be an anxiolytic by 50 to 70 percent of ICU nurses and house staff, and 5 to 10 percent thought it was an analgesic. [513] In addition, diazepam was considered to be an analgesic by 40 to 80 percent. [513] Such misconceptions explain why patients sometimes report frightening experiences while paralyzed in the ICU. [512]

The complications of long-term administration of muscle relaxants in the ICU are outlined in Table 12-17 . The first two categories are consequences of immobilization and loss of the ability to cough. Preventing these complications relies on skilled nursing care and intensive physical therapy and is not in the realm of the physician; consequently, they will not be discussed. The complications of long-term use of muscle relaxants of relevance to this section are prolonged paralysis after the relaxant is stopped and effects, either unrecognized or not fully investigated, of the drugs or their metabolites.

When long-term relaxant administration is stopped, most patients recover full muscle strength within a few hours. [515] [516] However, a subgroup of patients who receive muscle relaxants for periods of several days or weeks have persistent weakness after relaxant administration is stopped. [516A] [516B] Because muscle strength may not return, weaning from mechanical ventilation can be delayed, full recovery of muscle strength may not occur for months, and the impact on the patients can be devastating. [516A] [516B] The additional health-care cost of one case of persistent weakness was estimated as almost $67,000. [516C] Personnel caring for ICU patients must attempt to minimize the risk of this serious complication.

Muscle relaxant-associated persistent weakness is a distinct pathologic entity and is not simply a manifestation of critical illness polyneuropathy. [517] The prospective study by Kupfer et al [517A] showed a 70 percent incidence of persistent weakness in ICU patients who received muscle relaxants for more than 2 days, compared with 0 incidence in similar ICU patients who got no muscle relaxant. This is compelling evidence for the role of relaxants in this complication. Persistent weakness has several pathologic forms.

Weakness may be due to persistent pharmacologic neuromuscular blockade. After muscle relaxant administration is stopped, the persistence of the drug itself, or a metabolite with muscle relaxant properties, results in persistent paralysis. [517B] [517C] The principal metabolite of vecuronium is 3-desacetylvecuronium, which has 80

percent of the muscle relaxant potency of vecuronium. [517D] This metabolite has been identified as a likely cause of persistent paralysis in patients who received vecuronium for more than 2 days. [517B] Additional risk factors for persistent paralysis were renal failure and female gender. [517B] Pancuronium and pipecuronium also have 3-desacetyl metabolites, and despite an absence of specific data, it would seem wise to avoid long-term administration of these drugs to patients with renal failure.

There is a striking clinical picture of flaccid quadriplegia following administration of muscle relaxants to patients with severe asthma who are receiving high doses of corticosteroid. [518] [519] [520] [521] [522] [523] [524] The syndrome is characterized by severe flaccid paralysis, increased creatine kinase (CK) concentrations, myonecrosis, and slow recovery that can take several months to complete. The incidence of myopathy in asthmatics who require mechanical ventilation is 15 to 40 percent. [518] [522] The syndrome is more likely to occur the greater the dose of muscle relaxant and the greater the dose of steroid administered. [518] [522] Initial reports of this myopathy involved pancuronium or vecuronium, leading to a belief that the complication was due to their steroidal structure, and thus the belief that it might not occur with atracurium. More recently, myopathy has also been reported in patients who received atracurium, [521] [523] so the complication therefore appears unrelated to the structural class of the muscle relaxant. Plasma CK concentrations usually increase with the development of myopathy. [525] The authors recommend daily monitoring of CK concentrations in ICU patients who receive muscle relaxants and high-dose steroids. Doses of steroid and muscle relaxant should be kept to a minimum, and if CK concentrations increase, muscle relaxant administration should be stopped.

Another syndrome, motor neuropathy without myopathy, can follow the long-term use of vecuronium or pancuronium. [517A] [526] The neuropathy affects the upper and lower limbs and may be accompanied by absent tendon reflexes and muscle wasting. Weaning from mechanical ventilation may be delayed, and full recovery may take several months. The motor neuropathy is more likely to occur as the dose and duration of relaxant administration increase. [517A] [526]

Yet another clinical syndrome consisting of persistent motor weakness without sensory involvement has followed long-term use of pancuronium, vecuronium, or metocurine. [527] Electrodiagnostic studies were consistent with failed neuromuscular transmission, and the weakness took several months to resolve.

The incidence of prolonged paralysis following long-term use of muscle relaxants will vary among institutions, depending on their patient populations, but it is of the order of 5 percent overall, 20 percent for patients who receive muscle relaxants for more than 6 days, [516A] 15 to 40 percent for asthmatic patients who also receive high-dose steroids, [518] [522] and almost 50 percent in female patients with renal failure who receive vecuronium. [517B] Risk factors for prolonged weakness are: (1) use of vecuronium by female patients with renal failure; (2) concomitant high-dose steroid administration; and (3) large doses and long duration of relaxant administration. The phenomenon affects the motor system only and probably reflects pathologic effects due to chronic pharmacologic denervation of the muscle. It is not yet resolved whether the syndromes described (with the exception of persistent pharmacologic neuromuscular blockade) represent distinct pathologic processes or are simply different manifestations of a common underlying cause. Regardless of the cause, the impact for the patient is severe. Weaning from mechanical ventilation will be delayed, and their ICU stay will be prolonged. This will result in increased costs, increased risk of the complications of mechanical ventilation, and the need to remain in an ICU. Because recovery of muscle strength often takes several months, the impact on the patient's career and finances may be significant.

For most patients, the initial doses of relaxant that patients

require are similar to the doses used in the operating room (e.g., vecuronium, 0.1 mg/kg / h, or atracurium, 0.5 mg/kg/h. [528] [529] [530] [531] These initial doses will often need to be increased within 1 to 3 days because of the development of tolerance. [528] [529] [530] [531] Tolerance develops in the first 24 to 72 hours of administration, occurs in children as well as adults, and is such that vecuronium doses as high as 32 mg/h have been required. [530] The likely cause of tolerance is upregulation of acetylcholine receptors consequent to chronic pharmacologic denervation. [532] The clinical problem is that patients who seem to require large doses for clinical relaxation may subsequently go on to develop prolonged paralysis when relaxant administration is stopped. [533]

The effect of muscle relaxant administration is most commonly monitored clinically in the ICU by the use of a nerve stimulator with assessment of TOF responses. [533A] [533B] There is evidence that monitoring versus no monitoring results in decreased amounts of muscle relaxant used, decreased costs, and decreased incidence of prolonged weakness. [533C] It is not clear whether monitoring by clinical criteria or by use of a nerve stimulator is superior. In one study comparing monitoring by clinical criteria with the use of a nerve stimulator, the amounts of drug used and comparative patient recovery times were similar. [533D] A different study concluded that the use of a nerve stimulator with TOF monitoring resulted in less drug use and lower costs than monitoring using clinical criteria. [533E] Whatever form of monitoring is used, the principle should be to administer the minimum amount of drug needed to achieve the desired therapeutic effect.

In most, but not all, of the reports of prolonged weakness, no monitoring was used. In one study in which neuromuscular function was monitored with a peripheral nerve stimulator and at least one twitch in the TOF response was maintained, all patients recovered rapidly from vecuronium-induced block. [534] However, in that study the average length of administration of vecuronium was only 40 hours, and prolonged weakness would not be expected after such a relatively short period of administration. In addition, none of the patients had organ dysfunction. Therefore, prolonged weakness would not have been expected to occur in that group of patients, and the effectiveness of monitoring to reduce the incidence of prolonged weakness cannot be judged from that study. It is possible for patients to have TOF responses throughout the whole period of relaxant administration and still to have persistent weakness occur. [521]

Succinylcholine is often used to facilitate emergent tracheal intubation in the ICU. Several well-recognized conditions predispose to severe acute hyperkalemia and are contraindications to the use of succinylcholine (see the section on succinylcholine). The risk of hyperkalemia in patients who have hypovolemia and metabolic acidosis is not well recognized. [535] [535A] Schwartz et al [535] reported a case of hyperkalemic cardiac arrest in a postpartum patient who had severe blood loss and metabolic acidosis. The risk of hyperkalemia following succinylcholine in the setting of severe blood loss and metabolic acidosis was confirmed in a study in rabbits. [536] It appears that in this situation the source of potassium is the splanchnic circulation. [536A] Before administration of succinylcholine to a hypovolemic, acidotic patient in the ICU, consideration should be given to hyperventilation of the patient and to the administration of sodium bicarbonate. Alternatively, if it is considered appropriate, rocuronium may replace succinylcholine to facilitate rapid-sequence intubation. [510] [536B] [536C]

Because of the reports of complications involving vecuronium and pancuronium, atracurium became popular for long-term use in the ICU, and this raised concerns regarding its principal metabolite, laudanosine. This metabolite has no muscle relaxant effects, but it is an analeptic. The toxic dose in humans is not known, but there are case reports of patients having seizures while receiving atracurium, and laudanosine has not been ruled out as a cause of these seizures. [537] [537A] [538] The infusion of atracurium in the ICU has been associated with recurrent episodes of bradycardia and hypotension, effects that may be due to the CNS effects of laudanosine and that resolved when vecuronium was substituted for atracurium. [539] [540] Cisatracurium is a single isomer of atracurium, and because it is four to five times more potent than atracurium, it is given in smaller doses. Consequently, the risk of laudanosine-related adverse effects, even with long-term administration of cisatracurium, should be minimal. [508] [540A] [540B]

The muscle relaxants are polar molecules and do not readily cross the blood-brain barrier, but vecuronium and 3-desacetylvecuronium have been detected in the CSF of patients in the ICU, and laudanosine is found in the CSF of ICU patients who receive atracurium. [540C] The CNS effects of muscle relaxants and their metabolites in humans have not been well studied, but in rats atracurium, pancuronium, and vecuronium injected into the CSF will cause dose-related cerebral excitation culminating in seizures. [541] Cerebral excitation with consequent increased cerebral oxygen demand is undesirable in ICU patients at risk of cerebral ischemia.

Currently there are insufficient data to conclude that the long-term administration of muscle relaxants to patients in the ICU is safe or even efficacious. Indeed, the problems so far identified--principally, persistent weakness--have such grave consequences for the patient that they may be considered as a contraindication to the long-term use of muscle relaxants in certain "at risk" patients. Until the cause of the complications is better understood and more is known about the safe use of muscle relaxants in the ICU, the authors believe that relaxant administration should be minimized whenever possible. When relaxants are used, then the guidelines in Table 12-18 may help to minimize the incidence of complications.

TABLE 12-18 -- Recommendations for the Use of Muscle Relaxants in the ICU

Avoid the use of muscle relaxants by
Maximal use of analgesics and sedatives
Manipulation of ventilatory parameters and modes

Minimize the dose of relaxant

Do not administer for more than 2 days continuously

Administer by bolus rather than infusion

Administer only when required and to achieve a well-defined goal

Continually allow recovery from paralysis

Consider alternative therapies

Avoid vecuronium in female patients with renal failure

Isoflurane in place of muscle relaxants in severe asthmatics

Minimize the dose of steroid in asthmatics

ECONOMICS AND OUTCOME IN PRACTICE WITH NEUROMUSCULAR BLOCKING DRUGS

The introduction of vecuronium and atracurium heralded a new age in the use of neuromuscular blocking drugs. These were the first drugs with an intermediate duration of action and rapidly became the first-line drugs for most clinical situations. [542] However, the acquisition costs of the intermediate-acting relaxants is considerably greater than that of long-acting drugs like pancuronium, and in recent years there has been pressure to reduce health-care costs by reverting to more widespread use of long-acting relaxants. [543] [544] However, merely comparing acqusition cost of drugs is simplistic and potentially misleading, and a more complete pharmacoeconomic analysis must take into consideration the impact of different drugs on patient outcome and thus the overall cost to the health-care institution. [545]

The most significant outcome difference between long-acting and intermediate-acting drugs is the relative incidence of residual neuromuscular block in the postoperative period. In 1979, a study by Viby-Mogensen and colleagues [546] showed that the incidence of residual weakness in the recovery room was more than 40 percent. At that time only long-acting drugs were available. With the introduction of vecuronium and atracurium, the incidence of residual weakness declined significantly to less than 10 percent. [547]

The greater incidence of residual blockade with longacting relaxants is because reversal of their neuromuscular blocking effect takes longer than with intermediate-acting drugs. [548] [549] This difference in ease of reversal is crucial as even minor degrees of residual neuromuscular blockade have significant adverse effects. [550] [551] [552] [553] The muscles of airway protection are very sensitive to residual block, [550] and this predisposes patients to pulmonary aspiration. [552] In addition, residual neuromuscular blockade may compromise a patient's "street readiness" in the postoperative recovery period. [553] There is mounting evidence that the standard for acceptable recovery of neuromuscular function is no longer a TOF ratio of 0.7, but in fact greater safety might be achieved at 0.9. [552] [553] As the level of neuromuscular recovery considered adequate increases, so will the differential between relaxants with long versus intermediate durations of action become greater.

As a result of these adverse effects of residual neuromuscular blockade, the use of long-acting versus intermediateacting relaxants can predispose patients to a greater risk of postoperative pulmonary complications. [554] These complications constitute the greatest potential added expenses, which accrue as a result of the choice of long-acting relaxants over shorter-acting drugs. Delayed discharge from the PACU [555] also has a significant cost impact. The increased length of stay in the PACU with long-acting relaxants has an estimated cost penalty to the institution of $40 per patient. [555]

There is an argument that the use of long-acting relaxants is without adverse effect if strict practice guidelines regarding their use and dosing are implemented and continuously enforced. [556] However, even with strict regulation, the use of pancuronium in place of an intermediate-acting relaxant is associated with a delay (a mean of 3 minutes) in the time from the end of the surgical procedure until the patient reaches the PACU. Much debate has been generated about the importance of this 3-minute delay.

The risks of residual weakness associated with use of long-acting relaxants apply to the situation where the patient's trachea will be extubated at the end of the surgical procedure. Following cardiac surgery, for instance, where the endotracheal tube will remain in place and the patient's ventilation will be supported for hours or days postoperatively, there is no cost penalty in the use of long-acting relaxants. [557]

With the current state of knowledge, the use of intermediate- and short- versus long-acting relaxants comes down to a philosophic debate. On one side, there is a body of evidence that strongly suggests but does not absolutely prove that a greater risk to patients is incurred with the use of long-acting relaxants. This potential added risk may translate to greatly increased expense of anesthetic care as a result of a higher incidence of complications. [554] On the other side is the rather simple economic argument whereby it is easy to demonstrate a reduction in drug acquisition costs by using long-acting relaxants, even though the full pharmacoeconomic impact of this is not established because all the risk and safety issues and all the added efficiencies are not carefully cost-accounted. Perhaps we can be guided by this excerpt from the Hippocratic oath--"I will prescribe regimen for the good of my patients according to my ability and my judgment and never do harm to anyone." Where evidence for one position over another is conclusive, the authors believe that one should always take the option that involves the least risk of harm to the patient.

References

1. Griffith HR, Johnson GE: The use of curare in general anesthesia. Anesthesiology 3:418, 1942.

2. Cullen SC: The use of curare for improvement of abdominal relaxation during cyclopropane anesthesia: Report on 131 cases. Surgery 14:216, 1943.

3. Beecher HK, Todd DP: A study of deaths with anesthesia and surgery. Ann Surg 140:2, 1954.

4. Thesleff S: Farmakologiska och kliniska forsok med L.T.I. (O,Osuccinylcholine jodid). Nord Med 46:1045, 1951.

5. Foldes FF, McNall PG, Borrego-Hinojosa JM: Succinyl-choline, a new approach to muscular relaxation in anaesthesiology. N Engl J Med 247:596, 1952.

6. Baird WLM, Reid AM: Neuromuscular blocking properties of a new steroidal compound, pancuronium bromide: A pilot study in man. Br J Anaesth 39:775, 1967.

7. Stenlake JB, Waigh RD, Dewar GH et al: Biodegradable neuromuscular blocking agents. Part 4: Atracurium besylate and related polyalkylene di-esters. Eur J Med Chem 16:515, 1981.

8. Stenlake JB: Atracurium: A contribution to anaesthetic practice. Pharm J 229:116, 1982.

9. Savage DS, Sleigh T, Carlyle I: The emergence of ORG NC 45, 1-[(2 beta, 3 alpha, 5 alpha, 16 beta, 17 beta)-3,17-bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1 methylpiperidinium bromide, from the pancuronium series. Br J Anaesth 52:3S, 1980.

10. Durant NN, Savage DS, Nelson DN et al: The neuromuscular and autonomic blocking activities of pancuronium, ORG NC 45, and other pancuronium analogues in the cat. J Pharm Pharmacol 31:831, 1979.

11. Booij LHDJ, Edwards RP, Sohn YJ et al: Cardiovascular and neuromuscular effects of ORG NC 45, pancuronium, metocurine, and *α*-tubocurarine in dogs. Anesth Analg 59:26, 1980.

12. Neill EAM, Chapple DJ: Metabolic studies in the cat with atracurium: A neuromuscular blocking agent designed for nonenzymatic inactivation at physiological pH. Xenobiotica 12:203, 1982.

13. Karpati E, Biro K: Pharmacological study of a new competitive neuromuscular blocking steroid, pipecuronium bromide. Arzneimittelforschung 30:346, 1980.

14. Basta SJ, Savarese JJ, Ali HH et al: Clinical pharmacology of doxacurium chloride (BW A 938U): A new long-acting nondepolarizing muscle relaxant. Anesthesiology 69:478, 1988.

15. Savarese JJ, Ali HH, Basta SJ et al: The clinical pharmacology of mivacurium chloride (BW B1090U): A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 68:723, 1988.

16. Wierda JMKH, De Wit APM, Kuizenga K et al: Clinical observations on the neuromuscular blocking action of ORG 9426, a new steroidal non-depolarizing agent. Br J Anaesth 64:521, 1990.

17. Wastila WB, Maehr RB, Turner GL et al: Comparative pharmacology of cisatracurium (51W89), atracurium, and five isomers in cats. Anesthesiology 85:169, 1996.

18. Bogetz MS, Katz JA: Recall of surgery for major trauma. Anesthesiology 61:6, 1984.

19. Editorial: On being aware. Br J Anaesth 51:711, 1979.

20. Cullen SC, Larson CP Jr (eds): Essentials of Anesthetic Practice. Chicago, Year Book Medical, 1974.

21. Drenck NE, Ueda N, Olsen NV et al: Manual evaluation of residual curarization using double-burst stimulation: A comparison with train-of-four. Anesthesiology 70:578, 1989.

22. Smith CE, Donati F, Bevan DR: Differential effects of pancuronium on masseter and adductor pollicis muscles in humans. Anesthesiology 71:57, 1989.

23. Donati F, Plaud B, Meistelman C: Vecuronium neuromuscular blockade at the adductor muscle of the larynx and the adductor pollicis. Anesthesiology 74:833, 1991.

24. Pansard JL, Chauvin M, Lebreault C et al: Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and adductor pollicis muscle in humans. Anesthesiology 67:326, 1987.

25. Bartkowski RR: Incomplete reversal of pancuronium neuromuscular blockade by neostigmine, pyridostigmine, and edrophonium. Anesth Analg 66:594, 1987.

26. Beemer GH, Bjorksten AR, Dawson PJ et al: Determinants of the reversal time of competitive neuromuscular block by anticholinesterases. Br J Anesth 66:469, 1991.

27. Waud BE, Waud DR: The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. Anesthesiology 35:456, 1971.

27A. Kopman AF: Tactile evaluation of train-of-four count as an indicator of reliability of antagonism of vecuronium- or atracurium-induced neuromuscular blockade. Anesthesiology 75:558, 1991.

27B. Brull SJ, Silverman DG. Real time versus slow-motion train-of-four monitoring: A theory to explain the inaccuracy of visual assessment. Anesth Analg 80:548, 1995.

27C. Saitoh Y, Nazakawa K, Makita K et al: Evaluation of residual neuromuscular block using train-of-four and double-burst stimulation at the index finger. Anesth Analg 84:1354, 1997.

27D. Kopman AF, Yee PS, Neuman GG: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 86:765, 1997.

28. Waud BE, Waud DR: The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block. Anesthesiology 37:413, 1972.

29. Johansen SH, Jorgensen M, Molbeck S: Effect of tubocurarine on respiratory and nonrespiratory muscle power in man. J Appl Physiol 19:990, 1964.

30. Ali HH, Wilson RS, Savarese JJ et al: The effect of tubocurarine on indirectly elicited train-of-four muscle responses and respiratory measurements in humans. Br J Anaesth 47:570, 1975.

31. Pavlin EG, Holle RH, Schoene RB: Recovery of airway protection compared with ventilation in humans after paralysis with curare. Anesthesiology 70:381, 1989.

31A. D'Honneur G, Lofaso F, Drummond GB et al: Susceptibility to upper airway obstruction during partial neuromuscular block. Anesthesiology 88:371, 1998.

31B. Eriksson LI, Sundman E, Olsson R et al: Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans. Anesthesiology 87:1035, 1997.

31C. Viby-Mogensen J, Roed J, Mortensen CR et al: Residual neuromuscular block is a risk factor for postoperative pulmonary complications: A prospective, randomized, and blinded study of postoperative pulmonary complications after atracurium, vecuronium, and pancuronium. Acta Anaesthsiol Scand 41:1095, 1997.

32. Miller RD: Antagonism of neuromuscular blockade. Anesthesiology 44:293, 1976.

33. Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. Anesthesiology 73:870, 1990.

33A. Debaene B, Beaussier M, Meistelman C, et al: Monitoring the onset of neuromuscular block at the orbicularis oculi can predict good intubating conditions during atracurium-induced neuromuscular block. Anesth Analg 80:360, 1995.

34. Viby-Mogensen J, Jorgensen BC, Ording H: Residual curarization in the recovery room. Anesthesiology 50:539, 1979.

35. Miller RD: How should residual neuromuscular blockade be detected? Anesthesiology 70:379, 1989.

36. Kopman AF: Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions. Anesthesiology 65:572, 1986.

37. Bevan DR, Smith CE, Donati F: Postoperative neuromuscular blockade: A comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 69:272, 1988.

38. Bovet D: Some aspects of the relationship between chemical constitution and curare-like activity. Ann NY Acad Sci 54:107, 1951.

39. Marshall IG, Paul D, Singh H: Steroids and related studies: Some actions of 4,17-dimethyl-4,17 diaza- *d*-homo-5-androstane dimethiodide (HS-342), a new neuromuscular blocking drug. J Pharm Pharmacol 25:441, 1973.

40. Durant NN, Houwertjes MC, Crul JF: Comparison of the neuromuscular blocking properties of ORG NC 45 and pancuronium in the rat, cat, and rhesus monkey. Br J Anaesth 52:723, 1980.

41. Marshall IG, Agoston S, Booij LH et al: Pharmacology of ORG NC 45 compared with other non-depolarizing neuromuscular blocking drugs. Br J Anaesth 52:11S, 1980.

42. Bowman WC, Rodger IW, Houston J et al: Structure/action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetized cat. Anesthesiology 69:57, 1988.

43. Stenlake JB, Waigh RD, Urwin J et al: Atracurium: Conception and inception. Br J Anaesth 55:3S, 1983.

44. Basta SJ, Savarese JJ, Ali HH et al: Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. Br J Anaesth 55:105S, 1983.

45. Wastila WB, Maehr RB, Turner GL et al: Comparative pharmacology of 51W89, atracurium, and five isomers of atracurium in cats. Anesthesiology 85:169, 1996.

46. Lien CA, Belmont MR, Abalos A et al: The cardiovascular effects and histamine-releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 82:1131, 1995.

46A. Maehr RB, Wastila WB: Comparative pharmacology of atracurium and six isomers in cats. Anesthesiology 79:A950, 1993.

47. Foldes FF, Rendell-Baker L, Birch JH: Causes and prevention of prolonged apnea with succinylcholine. Anesth Analg 35:609, 1956.

48. Kopman AF, Strachovsky G, Lichtenstein L: Prolonged response to succinylcholine following physostigmine. Anesthesiology 49:142, 1978.

49. Sunew KY, Hicks RG: Effects of neostigmine and pyridostigmine on duration of succinylcholine action and pseudocholinesterase activity. Anesthesiology 49:188, 1978.

50. Lindsay PA, Lumley J: Suxamethonium apnoea masked by tetrahydroaminacrine. Anaesthesia 33:620, 1978.

51. Walts LF, DeAngelis J, Dillon JB: Clinical studies of the interaction of hexafluorenium and succinylcholine in man. Anesthesiology 33:503, 1970.

52. Baraka A: Hexafluorenium-suxamethonium interaction in patients with normal versus atypical cholinesterase. Br J Anaesth 47:885, 1975.

53. Kao YJ, Tellez J, Turner DR: Dose-dependent effect of metoclopramide on cholinesterases and suxamethonium metabolism. Br J Anaesth 65:220, 1990.

54. Woodworth GE, Sears DH, Grove TM et al: The effect of cimetidine and ranitidine on the duration of action of succinylcholine. Anesth Analg 68:295, 1989.

55. Fisher DM, Caldwell JE, Sharma M et al: The influence of bambuterol (carbamylated terbutaline) on the duration of action of succinylcholine-induced paralysis in humans. Anesthesiology 69; 757, 1988.

55A. Bang U, Viby-Mogensen J, Wiren JE et al: The effect of bambuterol (carbamylated terbutaline) on plasma cholinesterase activity and suxamethonium-induced neuromuscular blockade in genotypically normal patients. Acta Anaesthesiol Scand 34:596, 1990.

55B. Barabas E, Zsigmond EK, Kirkpatrick AF: The inhibitory effect of esmolol on human plasma cholinesterase. Can Anaesth Soc J 33:332, 1986.

55C. Murthy VS, Patel KD, Elangovan RG, et al: Cardiovascular and neuromuscular effects of esmolol during induction of anesthesia. J Clin Pharmacol 26:351, 1986.

55D. Pantuck EJ: Ecothiopate iodide eye drops and prolonged response to suxamethonium. Br J Anaesth 38:406, 1966.

56. Viby-Mogensen J: Correlation of succinylcholine duration of action with plasma cholinesterase activity in subjects with the genotypically normal enzyme. Anesthesiology 53:517, 1980.

57. Kalow W, Genest K: A method for the detection of atypical forms of human serum cholinesterase: Determination of dibucaine numbers. Can J Biochem 35:339, 1957.

58. Pantuck EJ: Plasma cholinesterase: Gene and variations. Anesth Analg 77:380, 1993.

58A. Jensen FS, Viby-Mogensen J: Plasma cholinesterase and abnormal reaction to succinylcholine: Twenty years' experience with the Danish Cholinesterase Research Unit. Acta Anaesthesiol Scand 39:150, 1995.

58B. Primo-Parmo SL, Bartels CF, Wiersema B et al: Characterization of 12 silent alleles of the human butyrylcholinesterase (BCHE) gene. Am J Hum Genet 58:52, 1996.

58C. Primo-Parmo SL, Lightstone H, La Du BN: Characterization of an unstable variant (BChE115D) of human butyrylcholinesterase. Pharmacogenetics 7:27, 1997.

59. Galindo AHF, Davis TB: Succinylcholine and cardiac excitability. Anesthesiology 23:32, 1962.

60. Goat VA, Feldman SA: The dual action of suxamethonium on the isolated rabbit heart. Anaesthesia 27:149, 1972.

61. Craythorne NWB, Turndorf H, Dripps RD: Changes in pulse rate and rhythm associated with the use of succinylcholine in anesthetized patients. Anesthesiology 21:465, 1960.

62. Leigh MD, McCoy DD, Belton KM et al: Bradycardia following intravenous administration of succinylcholine chloride to infants and children. Anesthesiology 18:465, 1960.

63. Stoelting RK, Peterson C: Heart-rate slowing and junctional rhythm following intravenous succinylcholine with and without intramuscular atropine preanesthetic medication. Anesth Analg 54:705, 1975.

64. Schoenstadt DA, Witcher CE: Observations on the mechanism of succinylcholine-induced cardiac arrythmias. Anesthesiology 24:358, 1963.

64A. Badgwell JM, Cunliffe M, Lerman J: Thiopental attenuates dysrhythmias in children: Comparison of induction regimens. Tex Med 86:36, 1990.

65. Mathias JA, Evans-Prosser CD, Churchill-Davidson HC: The role of the non-depolarizing drugs in the prevention of suxamethonium bradycardia. Br J Anaesth 42:609, 1970.

66. Leiman BC, Katz J, Butler BD: Mechanisms of succinylcholine-induced arrhythmias in hypoxic or hypoxic:hypercarbic dogs. Anesth Analg 66:1292, 1987.

66A. Nigrovic V, McCullough LS, Wajskol A et al: Succinylcholine-induced increases in plasma catecholamine levels in humans. Anesth Analg 62:627, 1983.

66B. Derbyshire DR: Succinylcholine-induced increases in plasma catecholamine levels in humans [letter]. Anesth Analg 63:465, 1984.

66C. Derbyshire DR, Chmielewski A, Fell D et al: Plasma catecholamine responses to tracheal intubation. Br J Anaesth 55:855, 1983.

66D. Larach MG, Rosenberg H, Gronert GA et al: Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. Clin Pediatr (Phila) 36:9, 1997.

66E. Reynolds LM, Lau M, Brown R et al: Intramuscular rocuronium in infants and children: Dose-ranging and tracheal intubating conditions. Anesthesiology 85:231, 1996.

66F. Bevan DR, Smith CE, Donati F: Postoperative neuromuscular blockade: A comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 69:272, 1988.

66G. Bevan DR, Bevan JC, Donati F (eds): Muscle Relaxants in Clinical Anesthesia. Chicago, Year Book Medical, 1988.

67. Birch AA, Jr., Mitchell GD, Playford GA et al: Changes in serum potassium response to succinylcholine following trauma. JAMA 210:490, 1969.

68. Cooperman LH: Succinylcholine-induced hyperkalemia in neuromuscular disease. JAMA 213:1867, 1970.

69. Cooperman LH, Strobel GE Jr, Kennell EM: Massive hyperkalemia after administration of succinylcholine. Anesthesiology 32:161, 1970.

70. Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 43:89, 1975.

71. Stevenson PH, Birch AA: Succinylcholine-induced hyperkalemia in a patient with a closed head injury. Anesthesiology 51:89, 1979.

72. Kohlschutter B, Baur H, Roth F: Suxamethonium-induced hyperkalaemia in patients with severe intra-abdominal infections. Br J Anaesth 48:557, 1976.

73. Roth F, Wuthrich H: The clinical importance of hyperkalaemia following suxamethonium administration. Br J Anaesth 41:311, 1969.

74. Powell JN: Suxamethonium-induced hyperkalemia in a uremic patient. Br J Anaesth 42:806, 1970.

75. Walton JD, Farman JV: Suxamethonium, potassium and renal failure. Anaesthesia 28:626, 1973.

76. Miller RD, Way WL, Hamilton WK et al: Succinylcholine-induced hyperkalemia in patients with renal failure? Anesthesiology 36:138, 1972.

77. Powell DR, Miller R: The effect of repeated doses of succinylcholine on serum potasssium in patients with renal failure. Anesth Analg 54:746, 1975.

78. Koide M, Waud BE: Serum potassium concentrations after succinylcholine in patients with renal failure. Anesthesiology 36:142, 1972.

79. Walton JD, Farman JV: Suxamethonium hyperkalaemia in uraemic neuropathy. Anaesthesia 28:666, 1973.

80. Powell JN, Golby M: The pattern of potassium liberation following a single dose of suxamethonium in normal and uraemic rats. Br J Anaesth 43:662, 1971.

80A. Zahl K, Apfelbaum JL: Muscle pain occurs after outpatient laparoscopy despite the substitution of vecuronium for succinylcholine. Anesthesiology 70:408, 1989.

80B. Schwartz DE, Kelly B, Caldwell JE et al: Succinylcholine-induced hyperkalemic arrest in a patient with severe metabolic acidosis and exsanguinating hemorrhage. Anesth Analg 75:291, 1992.

80C. Antognini JF, Gronert GA: Succinylcholine causes profound hyperkalemia in hemorrhagic, acidotic rabbits. Anesth Analg 77:585, 1993.

80D. Antognini JF: Splanchnic release of potassium after hemorrhage and succinylcholine in rabbits. Anesth Analg 78:687, 1994.

80E. Stoelting RK, Miller RD: Fluid and blood therapy. In Basics of Anesthesia, 3rd ed. New York, Churchill Livingstone, 1994.

81. Pandey K, Badola RP, Kumar S: Time course of intraocular hypertension produced by suxamethonium. Br J Anaesth 44:191, 1972.

82. Indu B, Batra YK, Puri GD et al: Nifedipine attenuates the intraocular pressure response to intubation following succinylcholine. Can J Anaesth 36:269, 1989.

83. Meyers EF, Krupin T, Johnson M et al: Failure of nondepolarizing neuromuscular blockers to inhibit succinylcholine-induced increased intraocular pressure: A controlled study. Anesthesiology 48:149, 1978.

84. Konchigeri HN, Lee YE, Venugopal K: Effect of pancuronium on intraocular pressure changes induced by succinylcholine. Can Anaesth Soc J 26:479, 1979.

85. Miller RD, Way WL, Hickey RF: Inhibition of succinylcholine-induced increased intraocular pressure by non-depolarizing muscle relaxants. Anesthesiology 29:123, 1968.

86. Libonati MM, Leahy JJ, Ellison N: The use of succinylcholine in open eye surgery. Anesthesiology 62:637, 1985.

87. Joshi C, Bruce DL: Thiopental and succinylcholine: Action on intraocular pressure. Anesth Analg 54:471, 1975.

88. Miller RD, Way WL: Inhibition of succinylcholine-induced increased intragastric pressure by nondepolarizing muscle relaxants and lidocaine. Anesthesiology 34:185, 1971.

89. Greenan J: The cardio-oesophageal junction. Br J Anaesth 33:432, 1961.

90. Salem MR, Wong AY, Lin YH: The effect of suxamethonium on the intragastric pressure in infants and children. Br J Anaesth 44:166, 1972.

91. Brodsky JB, Brock-Utne JG, Samuels SI: Pancuronium pretreatment and post-succinylcholine myalgias. Anesthesiology 51:259, 1979.

92. Waters DJ, Mapelson WW: Suxamethonium pains: Hypothesis and observation. Anaesthesia 26:127, 1971.

93. Ryan JF, Kagen LJ, Hyman AI: Myoglobinemia after a single dose of succinylcholine. N Engl J Med 285:824, 1971.

93A. Maddineni VR, Mirakhur RK, Cooper AR: Myalgia and biochemical changes following suxamethonium after induction of anaesthesia with thiopentone or propofol. Anaesthesia 48:626, 1993.

93B. McLoughlin C, Leslie K, Caldwell JE: Influence of dose on suxamethonium-induced muscle damage. Br J Anaesth 73:194, 1994.

94. Jansen EC, Hansen PH: Objective measurement of succinylcholine-induced fasciculations and the effect of pretreatment with pancuronium or gallamine. Anesthesiology 51:159, 1979.

94A. Marr AT, Sosis M: Effectiveness of atracurium in preventing succinylcholine myalgia. AANA J 57:128, 1989.

94B. McLoughlin C, Elliott P, McCarthy G et al: Muscle pains and biochemical changes following suxamethonium administration after six pretreatment regimens. Anaesthesia 47:202, 1992.

94C. Demers-Pelletier J, Drolet P, Girard M et al: Comparison of rocuronium and *d*-tubocurarine for prevention of succinylcholineinduced fasciculations and myalgia. Can J Anaesth 44:1144, 1997.

95. Miller RD: The advantages of giving *d*-tubocurarine before succinylcholine. Anesthesiology 37:568, 1972.

95A. Horrow JC, Lambert DH: The search for an optimal interval between pretreatment dose of *d*-tubocurarine and succinylcholine. Can Anaesth Soc J 31:528, 1984.

95B. Minton MD, Grosslight K, Stirt JA et al: Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. Anesthesiology 65:165, 1986.

95C. Haigh JD, Nemoto EM, DeWolf AM et al: Comparison of the effects of succinylcholine and atracurium on intracranial pressure in monkeys with intracranial hypertension. Can Anaesth Soc J 33:421, 1986.

95D. Littleford JA, Patel LR, Bose D et al: Masseter muscle spasm in children: Implications of continuing the triggering anesthetic [see comments]. Anesth Analg 72:151, 1991.

96. Habre W, Sims C: Masseter spasm and elevated creatine kinase after intravenous induction in a child. Anaesth Intensive Care 24:496, 1996.

97. Donati F, Gill SS, Bevan DR et al: Pharmacokinetics and pharmacodynamics of atracurium with and without previous suxamethonium administration. Br J Anaesth 66:557, 1991.

98. Dubois MY, Lea DE, Kataria B et al: Pharmacodynamics of rocuronium with and without prior administration of succinylcholine. J Clin Anesth 7:44, 1995.

99. Naguib M, Abdulatif M, Selim M, et al: Dose-response studies of the interaction between mivacurium and suxamethonium. Br J Anaesth 74:26, 1995.

100. Erkola O, Rautoma P, Meretoja OA: Interaction between mivacurium and succinylcholine. Anesth Analg 80:534, 1995.

101. Walts LF, Dillon JB: Clinical studies of the interaction between *d*-tubocurarine and succinylcholine. Anesthesiology 31:35, 1969.

102. Larijani GE, Gratz I, Minassian SS et al: Comparative evaluation of the neuromuscular and cardiovascular effects of pipecuronium, pancuronium, atracurium, and vecuronium under isoflurane anesthesia. Pharmacotherapy 12: 278, 1992.

103. Lee C, Katz RL: Neuromuscular pharmacology: A clinical update and commentary. Br J Anaesth 52:173, 1980.

104. Ramsey FM, Lebowitz PW, Savarese JJ et al: Clinical characteristics of long term succinylcholine neuromuscular blockade during balanced anesthesia. Anesth Analg 59:110, 1980.

105. Moss J, Philbin DM, Roscow CE et al: Histamine release by neuromuscular blocking agents in man. Klin Wochenschr 60:891, 1982.

106. Murray DL, Mehta MP, Choi WW et al: The neuromuscular blocking and cardiovascular effects of doxacurium chloride in patients receiving nitrous oxide-narcotic anesthesia. Anesthesiology 69:472, 1988.

106A. Hughes R, Chapple DJ: The pharmacology of atracurium: A new competitive neuromuscular blocking agent. Br J Anaesth 53:31, 1981.

107. Bowman WC: Neuromuscular-blocking agents. In Pharmacology of Neuromuscular Function. London, Wright, 1990.

108. Holford NH, Sheiner LB: Understanding the dose-effect relationship: Clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet 6:429, 1981.

109. Bevan DR, Bevan JC, Donati F: Pharmacodynamic principles. In Muscle Relaxants in Clinical Anesthesia. Chicago Year Book, 1988.

110. Sheiner LB, Stanski DR, Vozeh S et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to *d*-tubocurarine. Clin Pharmacol Ther 25:358, 1979.

111. Holford NH, Sheiner LB: Kinetics of pharmacologic response. Pharmacol Ther 16:143, 1982.

111A. Viby-Mogensen J: Interaction of other drugs with muscle relaxants. Sem Anesth 4:52, 1985.

112. Bevan DR, Bevan JC, Donati F: Pharmacokinetic principles. In Muscle Relaxants in Clinical Anesthesia. Chicago Year Book, 1988.

113. Fisher DM, Rosen JI: A pharmacokinetic explanation for increasing recovery time following larger or repeated doses of nondepolarizing muscle relaxants. Anesthesiology 65:286, 1986.

114. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 69:580, 1992.

115. Waser PG, Wiederkehr H, Sin RA et al: Distribution and kinetics of 14 C-vecuronium in rats and mice. Br J Anaesth 59:1044, 1987.

116. Matteo RS, Nishitateno K, Pua EK et al: Pharmacokinetics of *d*-tubocurarine in man: Effect of an osmotic diuretic on urinary excretion. Anesthesiology 52:335, 1980.

117. Lebrault C, Berger JL, D'Hollander AA et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 62:601, 1985.

118. Wood M: Plasma drug binding: Implications for anesthesiologists. Anesth Analg 65:786, 1986.

119. McLeod K, Watson MJ, Rawlins MD: Pharmacokinetics of pancuronium in patients with normal and impaired renal function. Br J Anaesth 48:341, 1976.

120. Miller RD, Matteo R, Benet LZ et al: Influence of renal failure on the pharmacokinetics of *d*-tubocurarine in man. J Pharmacol Exp Ther 202:1, 1977.

121. Wright PMC, Hart PS, Fisher DM et al: Cumulative effects of atracurium vs. vecuronium: A clinical and kinetic confirmation. Anesthesiology 79:A915, 1993.

122. Segredo V, Caldwell JE, Matthay MA et al: Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 327:524, 1992.

123. Hull CJ: The safety of new drugs. Br J Anaesth 62:587, 1989.

124. Jick H, Andrews EB, Tilson HH et al: Atracurium--a post-marketing surveillance study: Methods and US experience. Br J Anaesth 62:590, 1989.

125. Lawson DH, Paice FM, Glavin RJ et al: Atracurium--a post-marketing surveillance study: UK study and discussion. Br J Anaesth 62:596, 1989.

126. Caldwell JE, Laster MJ, Magorian T et al: The neuromuscular effects of desflurane, alone or in combination with pancuronium or succinylcholine in humans. Anesthesiology 74:412, 1991.

127. Kelly RE, Lien CA, Savarese JJ et al: Depression of neuromuscular function in a patient during desflurane anesthesia. Anesth Analg 76:868, 1993.

128. Miller RD, Way WL, Dolan WM et al: The dependence of pancuronium and *d*-tubocurarine induced neuromuscular blockades on alveolar concentrations of halothane and Forane. Anesthesiology 37:573, 1972.

129. Cannon JE, Fahey MR, Castagnoli KP et al: Continuous infusion of vecuronium: The effect of anesthetic agents. Anesthesiology 67:503, 1987.

130. Miller RD: The priming principle. Anesthesiology 62:381, 1985.

131. Foldes FF: Rapid tracheal intubation with non-depolarizing neuromuscular blocking drugs: The priming principle [letter]. Br J Anaesth 56:663, 1984.

132. Schwarz S, Ilias W, Lackner F et al: Rapid tracheal intubation with vecuronium: The priming principle. Anesthesiology 62:288, 1985.

133. Mehta MP, Choi W, Gergis SD et al: Rapid sequence endotracheal intubation with non-depolarizing muscle relaxants. Anesthesiology 62:392, 1985.

134. Taboada JA, Rupp SM, Miller RD: Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. Anesthesiology 64:243, 1986.

134A. Jones RM: The priming principle: How does it work and should we be using it? Br J Anaesth 63:1, 1989.

135. Magorian T, Flannery KB, Miller RD: Comparison of rocuronium,

succinylcholine and vecuronium for rapid-sequence induction of anesthesia in adult patients. Anesthesiology 79:913, 1993.

136. Booij LH, Knape HTA: The neuromuscular blocking effect of ORG 9426. Anaesthesia 46:341, 1991.

137. Rolly G, DeBrock M, DeMey JC: Intubating conditions and time course of action of rocuronium bromide. Anesthesiology 77:A963, 1992.

138. Kopman AF: The effect of priming on onset time of neuromuscular blockade as a function of the total dose of relaxant administered: A computer simulation. (in preparation)

138A. Kopman AF: Gallamine, pancuronium, and *d*-tubocurarine compared: Is onset time related to drug potency? Anesthesiology 70:915, 1989.

139. Scott RPF, Savarese JJ, Basta SJ et al: Clinical pharmacology of atracurium given in high dose. Br J Anaesth 58:834, 1986.

140. Savarese JJ, Ali HH, Basta SJ et al: The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide-opiate-barbiturate anesthesia. Anesthesiology 70:386, 1989.

140A. Bowman WC: Neuromuscular-blocking agents. In Pharmacology of Neuromuscular Function. London, Wright, 1990.

140B. Marshall IG, Gibb AJ, Durant NN: Neuromuscular and vagal blocking actions of pancuronium bromide, its metabolites, and vecuronium bromide (Org NC45) and its potential metabolites in the anaesthetized cat. Br J Anaesth 55; 703, 1983.

140C. Wierda JM, Karliczek GF, Vandenbrom RH et al: Pharmacokinetics and cardiovascular dynamics of pipecuronium bromide during coronary artery surgery. Can J Anaesth 37; 183, 1990.

140D. Wierda JM, Szenohradszky J, De WA et al: The pharmacokinetics and urinary and biliary excretion of pipecuronium bromide. Eur J Anaesthesiol 8; 451, 1991.

141. Caldwell JE, Szenohradszky J, Segredo V et al: The pharmacodynamics and pharmacokinetics of the metabolite 3-desacetylvecuronium (ORG 7268) and its parent compound, vecuronium, in human volunteers. J Pharmacol Exp Ther 270:1216, 1994.

142. Lebrault C, Berger JL, D'Hollander AA et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 62:601, 1985.

143. Bencini AF, Scaf AHJ, Sohn YJ et al: Hepatobiliary disposition of vecuronium bromide in man. Br J Anaesth 58:988, 1985.

144. Arden JR, Lynam DP, Castagnoli KP et al: Vecuronium in alcoholic liver disease: A pharmacokinetic and pharmacodynamic analysis. Anesthesiology 68:771, 1988.

144A. Agoston S, Seyr M, Khuenl-Brody KS et al: Use of neuromuscular blocking agents in the intensive care unit. Anesth Clin North Am 11:345, 1993.

145. Fahey MR, Rupp SM, Fisher DM et al: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 61:699, 1984.

146. Ward S, Boheimer N, Weatherley BC et al: Pharmacokinetics of atracurium and its metabolites in patients with normal renal function and in patients with renal failure. Br J Anaesth 59:697, 1987.

147. Ward S, Wright D, Corall et al: Combined pharmacokinetic and pharmacodynamic studies with atracurium besylate (in normal patients and in patients with hepatic and renal failure). Can J Anaesth 30:S81, 1983.

148. Parker CJ, Hunter JM: Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 62:177, 1989.

149. Bion JF, Bowden MI, Chow B et al: Atracurium infusions in patients with fulminant hepatic failure awaiting liver transplantation. Intensive Care Med 19(suppl):S94, 1993.

150. Szenohradszky J, Fisher DM, Segredo V et al: Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology 77:899, 1992.

151. Khalil M, d'Honneur G, Duvaldestin P et al: Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. Anesthesiology 80; 1241, 1994.

152. Matteo RS, Ornstein E, Schwartz AE: Pharmacokinetics and pharmacodynamics of ORG 9426 in elderly surgical patients. Anesthesiology 75:A1065, 1991.

152A. Wierda JM, Proost JH, Schiere S et al: Pharmacokinetics and pharmacokinetic/dynamic relationship of rocuronium bromide in humans. Eur J Anaesthesiol 9(suppl):66, 1994.

152B. Magorian T, Wood P, Caldwell J et al: The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. Anesth Analg 80:754, 1995.

152C. van Miert MM, Eastwood NB: The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. Br J Clin Pharmacol 44:139, 1997.

153. Lien CA, Schmith VD, Belmont MR et al: Pharmacokinetics of cisatracurium in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 84:300, 1996.

153A. De Wolf AM, Freeman JA, Scott VL et al: Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth 76:624, 1996.

153B. Kisor DF, Schmith VD, Wargin WA et al: Importance of the organ-independent elimination of cisatracurium. Anesth Analg 83:1065, 1996.

153C. Ornstein E, Lien CA, Matteo RS et al: Pharmacodynamics and pharmacokinetics of cisatracurium in geriatric surgical patients. Anesthesiology 84:520, 1996.

153D. Sorooshian SS, Stafford MA, Eastwood NB et al: Pharmacokinetics and pharmacodynamics of cisatracurium in young and elderly adult patients. Anesthesiology 84:1083, 1996.

154. Cook DR, Stiller RL, Weakly NJ: In vitro metabolism of mivacurium chloride (BW B1090U) and succinylcholine. Anesth Analg 68:452, 1989.

154A. Head-Rapson AG, Devlin JC, Parker CJ et al: Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal function. Br J Anaesth 75:31, 1995.

154B. Lien CA, Schmith VD, Embree PB et al: The pharmacokinetics and pharmacodynamics of the stereoisomers of mivacurium in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 80:1296, 1994.

154C. Head-Rapson AG, Devlin JC, Parker CJR et al: Pharmacokinetics of the three isomers of mivacurium and pharmacodynamics of the chiral mixture in hepatic cirrhosis. Br J Anaesth 73:613, 1994.

154D. Miller RD, Agoston S, Booij LH et al: The comparative potency and pharmacokinetics of pancuronium and its metabolites in anesthetized man. J Pharmacol Exp Ther 207:539, 1978.

155. Bencini AF, Mol WEM, Scaf AHJ et al: Uptake and excretion of vecuronium bromide and pancuronium and its metabolites in anesthetized man. J Pharmacol Exp Ther 207:539, 1978.

156. Neill EAM, Chapple DJ, Thompson CW: Metabolism and kinetics of atracurium: An overview. Br J Anaesth 55:23S, 1983.

157. Chapple DJ, Clark JS: Pharmacologic action of breakdown products of atracurium and related substances. Br J Anaesth 55:115, 1983.

158. Stenlake JB, Hughes R: In vitro degradation of atracurium in human plasma [letter]. Br J Anaesth 59:806, 1987.

159. Stenlake JB, Waigh RD, Urwin J et al: Atracurium: Conception and inception. Br J Anaesth 55(suppl):3S, 1983.

159A. Leslie K, Sessler DI, Bjorksten AR et al: Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg 80:1007, 1995.

160. Merrett RA, Thompson CW, Webb FW: In vitro degradation of atracurium in human plasma. Br J Anaesth 55:61, 1983.

161. Stiller RL, Cook DR, Chakravorti S: In vitro degradation of atracurium in human plasma. Anesth Analg 64:289, 1985.

162. Fisher DM, Canfell PC, Fahey MR et al: Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. Anesthesiology 65:6, 1985.

163. Nigrovic V, Fox JL: Atracurium decay and the formation of laudanosine in humans. Anesthesiology 74: 446, 1991.

164. Hennis PJ, Fahey MR, Canfell PC et al: Pharmacology of laudanosine in dogs. Anesthesiology 65:56, 1986.

165. Canfell PC, Castagnoli N, Fahey MR et al: The metabolic disposition of laudanosine in dog, rabbit, and man. Drug Metab Dispos 14:703, 1986.

166. Parker CJR, Hunter JM: Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 62:177, 1989.

167. Yate PM, Flynn PJ, Arnold RW et al: Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. Br J Anaesth 59:211, 1987.

168. Beemer GH, Bjorksten AR, Dawson PJ et al: Production of laudanosine following infusion of atracurium in man and its effect on awakening. Br J Anaesth 63:26, 1989.

169. Tateishi A, Zornow MH, Scheller MS et al: Electroencephalographic

effects of laudanosine in an animal model of epilepsy. Br J Anaesth 62:548, 1989.

170. Lanier WL, Sharbrough GN, Michenfelder JD: Effects of atracurium, vecuronium or pancuronium pretreatment on lignocaine seizure thresholds in cats. Br J Anaesth 60:74, 1988.

171. Shi WZ, Fahey MR, Fisher DM et al: Modification of central nervous system effects of laudanosine by inhalation anaesthetics. Br J Anaesth 63: 598, 1989.

172. Chapple DJ, Miller AA, Ward JB et al: Cardiovascular and neurological effects of laudanosine. Br J Anaesth 59:218, 1987.

173. Powles AB, Ganta R: Use of vecuronium in the management of tetanus. Anaesthesia 40:879, 1985.

174. Kinjo M, Nagashima H, Vizi ES: Effect of atracurium and laudanosine on the release of 3 H-noradrenaline. Br J Anaesth 62:683, 1989.

175. Pittet JF, Tassonyi E, Schopfer C et al: Elevated plasma levels of laudanosine are associated with high plasma concentration of norepinephrine during orthotopic liver transplantation. Anesthesiology 69:A484, 1988.

175A. Wastila WB, Maehr RB, Turner GL et al: Comparative pharmacology of cisatracurium (51W89), atracurium, and five isomers in cats. Anesthesiology 85:169, 1996.

175B. Welch RM, Brown A, Ravitch J et al: The in vitro degradation of cisatracurium, an R, *cis*-R
-isomer of atracurium, in human and rat plasma. Clin Pharmacol Ther 58:132, 1995.

175C. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 69:580, 1992.

175D. Caldwell JE, Heier T, Kitts JB et al: Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. Br J Anaesth 63:393, 1989.

175E. Goudsouzian NG, d'Hollander AA, Viby MJ: Prolonged neuromuscular block from mivacurium in two patients with cholinesterase deficiency. Anesth Analg 77:183, 1993.

175F. Maddineni VR, Mirakhur RK: Prolonged neuromuscular block following mivacurium. Anesthesiology 78:1181, 1993.

175G. Mangar D, Kirchhoff GT, Rose PL et al: Prolonged neuromuscular block after mivacurium in a patient with end-stage renal disease. Anesth Analg 76:866, 1993.

175H. Ostergaard D, Jensen FS, Jensen E et al: Mivacurium-induced neuromuscular blockade in patients with atypical plasma cholinesterase. Acta Anaesthesiol Scand 37:314, 1993.

175I. Wierda JMKH, van den Broek L, Proost JH et al: Time course of action and endotracheal intubating conditions of ORG 9487, a new short-acting steroidal muscle relaxant: A comparison with succinylcholine. Anesth Analg 77:579, 1993.

176. van den Broek L, Wierda WMKH, Smeulers NJ et al: Pharmacodynamics and pharmacokinetics of an infusion of ORG 9487, a new short-acting steroidal neuromuscular blocking agent. Br J Anaesth 73:331, 1994.

177. Wierda JM, Beaufort AM, Kleef UW et al: Preliminary investigations of the clinical pharmacology of three short-acting non-depolarizing neuromuscular blocking agents, ORG 9453, ORG 9489 and ORG 9487. Can J Anaesth 41; 213, 1994.

178. Schiere S, Proost JH, Wierda JMKH: Pharmacokinetic and pharmacokinetic/dynamic (PK/PD) relationship of ORG 9488, the 3desacetyl metabolite of ORG 9487. Anesthesiology 87:A377, 1997.

179. Hughes R, Chapple DJ: Effects of non-depolarizing neuromuscular blocking agents on autonomic mechanisms in cats. Br J Anaesth 48:59, 1976.

180. Yasuda I, Hirano T, Amaha K et al: Chronotropic effects of succinylcholine and succinylmonocholine on sinoatrial node. Anesthesiology 57:289, 1982.

181. Harrison GA: The cardiovascular effects and some relaxant properties of four relaxants in patients about to undergo cardiac surgery. Br J Anaesth 44:485, 1972.

182. Moss J, Rosow CE, Savarese JJ et al: Role of histamine in the hypotensive action of *d*-tubocurarine in humans. Anesthesiology 55:19, 1981.

183. Miller RD, Eger EI II, Stevens WC: Pancuronium-induced tachycardia in relation to alveolar halothane, dose of pancuronium, and prior atropine. Anesthesiology 42:352, 1975.

184. Stoelting RK: The hemodynamic effects of pancuronium and *d*-tubocurarine in anesthetized patients. Anesthesiology 36:612, 1972.

185. Mellinghoff H, Diefenbach C, Buzello W: Neuromuscular and cardiovasuclar properties of ORG 9426. Anesthesiology 75:A807, 1991.

185A. Birdsall NJM, Hulme EC: Biochemical studies on the muscarinic acetylcholine receptor. J Neurochem 27:7, 1976.

186. Gardier RW, Tsevdos EJ, Jackson DB: Effects of gallamine and pancuronium on inhibitory transmission in cat sympathetic ganglion. J Pharmacol Exp Ther 204:46, 1978.

187. Vercruysse P, Hanegreefs G, Vanhoutte PM: Influence of skeletal muscle relaxants on the prejunctional effects of acetylcholine in adrenergically-innervated blood vessels. Arch Int Pharmacodyn Ther 232:350, 1978.

188. Docherty JR, McGrath JC: Sympathomimetic effects of pancuronium bromide on the cardiovascular system of the pithed rat. Br J Pharmacol 64:589, 1978.

189. Quintana A: Effect of pancuronium bromide on the adrenergic reactivity of the isolated rat vas deferens. Eur J Pharmacol 46:275, 1977.

190. Ivankovich AD, Milevich DJ, Albrecht RF et al: The effect of pancuronium on myocardial contraction and catecholamine metabolism. J Pharm Pharmacol 27:837, 1975.

191. Vercruysse P, Bossuyt P, Hanegreefs G et al: Gallamine and pancuronium inhibit pre- and postjunctional muscarinic receptors in canine saphenous veins. J Pharmacol Exp Ther 209:225, 1979.

192. Basta SJ: Modulation of histamine release by neuromuscular blocking drugs. Curr Opinion Anaesth 5:572, 1992.

193. Hatano Y, Arai T, Noda J et al: Contribution of prostacyclin to *d*-tubocurarine-induced hypotension in humans. Anesthesiology 72:28, 1990.

194. Basta SJ, Savarese JJ, Ali HH et al: Histamine-releasing potencies of atracurium, dimethyl-tubocurarine, and tubocurarine. Br J Anaesth 55:105S, 1983.

195. Choi WW, Mehta MP, Murray DJ et al: Neuromuscular and cardiovascular effects of mivacurium chloride in surgical patients receiving nitrous oxide-narcotic or nitrous oxide-isoflurane anesthesia. Can J Anaesth 36:641, 1989.

196. Scott RPF, Savarese JJ, Ali HH et al: Atracurium: Clinical strategies for preventing histamine release and attenuating the hemodynamic response. Br J Anaesth 52:550, 1985.

197. Hosking MP, Lennon RL, Gronert GA: Combined H1 and H2 receptor blockade attenuates the cardiovascular effects of high-dose atracurium for rapid sequence endotracheal intubation. Anesth Analg 67:1089, 1988.

198. Stoops CM, Curtis CA, Kovach DA et al: Hemodynamic effects of mivacurium chloride administered to patients during oxygen-sufentanil anesthesia for coronary artery bypass grafting or valve replacement. Anesth Analg 68:333, 1989.

199. Savarese JJ: The autonomic margins of safety of metocurine and *d*-tubocurarine in the cat. Anesthesiology 50:40, 1979.

200. McCullough LS, Reier CE, Delauaois AL et al: The effects of *d*-tubocurarine on spontaneous postganglionic sympathetic activity and histamine release. Anesthesiology 33:328, 1970.

201. Munger WL, Miller RD, Stevens WC: The dependence of *d*-tubocurarine-induced hypotension on the alveolar concentration of halothane, dose of *d*-tubocurarine and nitrous oxide. Anesthesiology 40:442, 1974.

202. Dowdy EG, Holland WC, Yamaka I: Cardioactive properties of *d*-tubocurarine with and without preservatives. Anesthesiology 34:256, 1971.

203. Stoelting RK: Blood-pressure responses to *d*-tubocurarine and its preservatives in anesthetized patients. Anesthesiology 35:315, 1971.

204. Stoelting RK, Longnecker DE: Effects of promethazine on hypotension following *d*-tubocurarine use in anesthetized patients. Anesth Analg 51:509, 1972.

205. Domenech JS, Garcia RC, Sasiain JMR et al: Pancuronium bromide: An indirect sympathomimetic agent. Br J Anaesth 48:1143, 1976.

206. Roizen MF, Forbes AR, Miller RD et al: Similarity between effects of pancuronium and atropine on plasma norepinephrine levels in man. J Pharmacol Exp Ther 211:419, 1979.

207. Eisele JH, Marta JA, Davis HI: Quantitative aspects of the chronotropic and neuromuscular effects of gallamine in anesthetized man. Anesthesiology 35:630, 1971.

208. Brown BR Jr, Crout JR: The sympathomimetic effect of gallamine on the heart. J Pharmacol Exp Ther 172:266, 1970.

209. Reitan JA, Fraser AI, Eisele JH: Lack of cardiac inotropic effects of gallamine in anesthetized man. Anesth Analg 52:974, 1973.

210. Wong KC, Wyte SR, Martin WE et al: Antiarrhythmic effects of skeletal muscle relaxants. Anesthesiology 34:458, 1971.

211. Geha DG, Cozelle BC, Raessler KL et al: Pancuronium bromide enhances

atrioventricular conduction in halothane-anesthetized dogs. Anesthesiology 46:342, 1977.

212. Edwards R, Miller RD, Roizen MF et al: Cardiac effects of imipramine and pancuronium during halothane and enflurane anesthesia. Anesthesiology 50:42, 1979.

213. Clayton D: Asystole associated with vecuronium. Br J Anaesth 58:937, 1986.

214. Starr NJ, Sethna DH, Estafanous FG: Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. Anesthesiology 64:521, 1986.

215. Cozanitis DA, Erkola O: A clinical study into the possible intrinsic bradycardiac activity of vecuronium. Anaesthesia 44:648, 1989.

216. Dundee JW, Gray TC: Resistance to *d*-tubocurarine chloride in the presence of liver damage. Lancet 2:16, 1953.

217. King H: Curare alkaloids: I. Tubocurarine. J Chem Soc 1381, 1935.

218. Stoelting VK, Graf JP, Vieira Z: Dimethyl ether of *d*-tubocurarine iodide as an adjunct to anesthesia. Proc Soc Exp Biol Med 69:565, 1948.

219. Savarese JJ, Ali HH, Antonio RP: The clinical pharmacology of metocurine: Dimethyltubocurarine revisited. Anesthesiology 47:277, 1977.

220. Brotherton WP, Matteo RS: Pharmacokinetics and pharmacodynamics of metocurine in humans with and without renal failure. Anesthesiology 55:273, 1981.

221. Ramzan MI, Shanks CA, Triggs EJ: Gallamine disposition in surgical patients with chronic renal failure. Br J Clin Pharmacol 12:141, 1981.

222. Kennedy BR, Kelman GR: Cardiovascular effects of alcuronium in man. Br J Anaesth 42:625, 1970.

223. Shanks CA: Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimens. Anesthesiology 64:72, 1986.

224. Hewett CL, Savage DS: Amino steroids--Part III: 2- and 3-amino-5-androstanes. J Chem Soc (C), 1134, 1968.

225. Buckett WR, Marjoribanks CEB, Marwick FA et al: The pharmacology of pancuronium bromide (ORG NA 97), a new potent steroidal neuromuscular blocking agent. Br J Pharmacol 32:671, 1968.

226. Buckett WR, Hewett CL, Savage DS: Potent steroidal neuromuscular blocking agents. Chem Ther 2:186, 1967.

227. Agoston S, Vermeer GA, Kersten UW et al: The fate of pancuronium bromide in man. Acta Anaesthesiol Scand 17:267, 1973.

228. Bencini AF, Mol WEM, Scaf AHJ et al: Uptake and excretion of vecuronium bromide and pancuronium bromide in the isolated perfused rat liver. Anesthesiology 69:487, 1988.

229. Duvaldestin P, Agoston S, Henzel D et al: Pancuronium pharmacokinetics in patients with liver cirrhosis. Br J Anaesth 50:1131, 1978.

230. Somogyi A, Shanks CA, Triggs EJ: The effect of renal failure on the disposition and neuromuscular blocking action of pancuronium bromide. Eur J Clin Pharmacol 12:23, 1977.

231. Somogyi AA, Shanks CA, Triggs EJ: Disposition kinetics of pancuronium bromide in patients with total biliary obstruction. Br J Anaesth 49:1103, 1977.

232. Ward ME, Adu-Gyamfi Y, Strunin L: Althesin and pancuronium in chronic liver disease. Br J Anaesth 47:1199, 1975.

233. Miller RD, Agoston S, Booij LDHJ et al: The comparative potency and pharmacokinetics of pancuronium and its metabolites in anesthetized man. Anesthesiology 207:539, 1978.

234. Tassonyi E, Szabo G, Vimiati L: Pipecuronium bromide (Arduan). In Kharkevitch DA (ed): Handbook of Experimental Pharmacology, vol 19. Berlin, Springer-Verlag, 1965.

235. Tassonyi E, Neidhart P, Pittet JF et al: Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 69:793, 1988.

236. Caldwell JE, Canfell PC, Castagnoli KP et al: The influence of renal failure on the pharmacokinetics and duration of action of pipecuronium bromide in patients anesthetized with halothane and nitrous oxide. Anesthesiology 70:7, 1988.

237. Wierda JM, Szenohradszky J, De Wit AP et al: The pharmacokinetics and urinary and biliary excretion of pipecuronium bromide. Eur J Anaesthesiol 8:451, 1991.

238. Dominique C, D'Honneur G, Khalil M et al: Pipecuronium pharmacokinetics and pharmacodynamics in patients with cirrhosis. Anesthesiology 77:A938, 1992.

239. Reich DL, Thys DM, Griffin AV et al: The hemodynamic effects of doxacurium during abdominal aortic surgery. J Cardiothorac Anesth 4(suppl):28, 1990.

240. Stoops CM, Curtis CA, Kovach DA et al: Hemodynamic effects of doxacurium chloride in patients receiving oxygen-sufentanil anesthesia for cornary artery bypass grafting or valve replacement. Anesthesiology 69:365, 1988.

241. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with hepatic or renal failure. Anesth Analg 72:145, 1991.

242. Freeman JA, Cook DR, Robertson KA et al: Pharmacokinetics of doxacurium chloride (BW A938U) in patients with organ failure. Anesth Analg 68:590, 1989.

243. Marshall IG, Gibb AJ, Durant NN: Neuromuscular and vagal blocking actions of pancuronium bromide, its metabolites and vecuronium bromide (ORG NC 45) and its potential metabolites in the anaesthetized cat. Br J Anaesth 55:703, 1983.

244. Agoston S, Salt P, Newton D et al: The neuromuscular blocking action of ORG NC 45, a new pancuronium derivative in anaesthetized patients: A pilot study. Br J Anaesth 52:53S, 1980.

245. Fahey MR, Morris RB, Miller RD et al: Clinical pharmacology of ORG NC 45 (Norcuron): A new nondepolarizing muscle relaxant. Anesthesiology 55:6, 1981.

246. Miller RD, Rupp SR: Clinical pharmacology of vecuronium and atracurium. Anesthesiology 61:444, 1984.

247. Morris RB, Cahalan MK, Miller RD et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 58:438, 1983.

248. Tullock WC, Diana P, Cook DR et al: Neuromuscular and cardiovascular effects of high-dose vecuronium. Anesth Analg 70:86, 1990.

249. Mol WE, Fokkema GN: Mechanisms for the hepatic uptake of organic cations: Studies with the muscle relaxant vecuronium in isolated rat hepatocytes. J Pharmacol Exp Ther 244:268, 1988.

250. Bencini AF, Scaf AHJ, Sohn YJ et al: Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. Anesth Analg 65:245, 1986.

251. Bencini AF, Mol WEM: Uptake and excretion of vecuronium bromide and pancuronium bromide in the isolated perfused rat liver. Anesthesiology 69:487, 1988.

252. Caldwell JE, Szenohradszky J: The pharmacodynamics and pharmacokinetics of the metabolite 3-desacetylvecuronium (ORG 7268) and its parent compound, vecuronium, in human volunteers. J Pharmacol Exp Ther 270:1216, 1994.

253. Segredo V, Caldwell JE: Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 327:524, 1992.

254. Fisher DM, Castagnoli K, Miller RD: Kinetics and dynamics of vecuronium in anesthetized infants and children. Clin Pharmacol Ther 37:402, 1985.

255. Wierda JM: Clinical observations on the neuromuscular blocking action of ORG 9426, a new steroidal non-depolarizing agent. Br J Anaesth 64:521, 1990.

256. Bartkowski RR, Witlkowski TA, Azad S et al: Rocuronium onset of action: A comparison with atracurium and vecuronium. Anesth Analg 77:574, 1993.

257. Foldes FF, Nagashima H, Nguyen HD et al: The neuromuscular effects of ORG 9426 in patients receiving balanced anesthesia. Anesthesiology 75:191, 1991.

258. Quill TJ, Begin M, Glass PS et al: Clinical responses to ORG 9426 during isoflurane anesthesia. Anesth Analg 72:203, 1991.

259. Cooper RA, Mirakhur RK, Elliott P et al: Estimation of the potency of ORG 9426 using two different modes of nerve stimulation. Can J Anesth 39:139, 1992.

260. Min JC, Bekavac I, Glavinovic MI et al: Iontophoretic study of speed of action of various muscle relaxants. Anesthesiology 77:351, 1992.

261. Armstrong DL, Lester HA: The kinetics of tubocurarine action and restricted diffusion within the synaptic cleft. J Physiol 294:365, 1979.

262. Khuenl-Brady K, Castagnoli KP, Canfell PC et al: The neuromuscular blocking effects and pharmacokinetics of ORG 9426 and ORG 9616 in the cat. Anesthesiology 72:669, 1990.

263. Puhringer FK, Khuenl-Brady KS, Koller J et al: Evaluation of the endotracheal intubating conditions of rocuronium (ORG 9426) and succinylcholine in outpatient surgery. Anesth Analg 75:37, 1992.

264. Huizinga AC, Vandenbrom RH, Wierda JM et al: Intubating conditions and onset of neuromuscular block of rocuronium (ORG 9426): A comparison with suxamethonium. Acta Anaesthesiol Scand 36:463, 1992.

265. Magorian T, Wood P: The pharmacokinetics and neuromuscular effects

of rocuronium bromide in patients with liver disease. Anesth Analg 80:754, 1995.

266. Sparr HJ: Rapid-sequence intubation with non-depolarizing muscle relaxants. Acta Anaesthesiol Scand Suppl 111:111, 1997.

267. Weiss JH, Gratz I: Double-blind comparison of two doses of rocuronium and succinylcholine for rapid-sequence intubation. J Clin Anesth 9:379, 1997.

268. Muir AW, Houston J, Green KL et al: Effects of a new neuromuscular blocking agent (ORG 9426) in anesthetized cats and pigs and in isolated nerve-muscle preparation. Br J Anaesth 63:400, 1989.

269. Muir AW, Houston J: A comparison of the neuromuscular blocking and autonomic effects of two new short-acting muscle relaxants with those of succinylcholine in the anesthetized cat and pig. Anesthesiology 70:533, 1989.

270. Levy JH, Davis GK: Determination of the hemodynamics and histamine release of rocuronium (ORG 9426) when administered in increased doses under N_2O/O_2 -sufentanil anesthesia. Anesth Analg 78:318, 1994.

271. Robertson EN, Hull JM: A comparison of rocuronium and vecuronium: The pharmacodynamic, cardiovascular and intra-ocular effects. Eur J Anaesthesiol Suppl 9:116, 1994.

272. Stevens JB, Hecker RB: The haemodynamic effects of rocuronium and vecuronium are different under balanced anaesthesia. Acta Anaesthesiol Scand 41:502, 1997.

273. Wierda JM, Schuringa M: Cardiovascular effects of an intubating dose of rocuronium 0.6 mg/kg in anaesthetized patients, paralysed with vecuronium. Br J Anaesth 78:586, 1997.

274. Hudson CJ, Banner M: Nursing assessment of intermittent mandatory ventilation. Int Anesthesiol Clin 18:143, 1980.

275. Nitschmann P, Oberkogler W: Comparison of haemodynamic effects of rocuronium bromide with those of vecuronium in patients undergoing CABG surgery. Eur J Anaesthesiol Suppl 9:113, 1994.

276. Borgeat A: Spontaneous movements associated with rocuronium: Is pain on injection the cause? Br J Anaesth 79:382, 1997.

277. Borgeat A: Spontaneous movements associated with rocuronium injection: The effects of prior administration of fentanyl. J Clin Anesth 9:650, 1997.

278. Schwarz LR: Uptake of taurocholate, a vecuronium-like organic cation, ORG 9426, and ouabain into carcinogen-induced diploid and polyploid hepatocytes obtained by centrifugal elutriation. Biochem Pharmacol 43:1195, 1992.

279. Smit JW: Interactions between P-glycoprotein substrates and other cationic drugs at the hepatic excretory level. Br J Pharmacol 123:361, 1998.

280. Khalil M: Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. Anesthesiology 80:1241, 1994.

281. Servin FS: Repeated doses of rocuronium bromide administered to cirrhotic and control patients receiving isoflurane: A clinical and pharmacokinetic study. Anesthesiology 84:1092, 1996.

282. van Miert MM: The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. Br J Clin Pharmacol 44:139, 1997.

283. Cooper RA: Pharmacokinetics of rocuronium bromide in patients with and without renal failure. Eur J Anaesthesiol Suppl 11:43, 1995.

284. Szenohradszky J: Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology 77:899, 1992.

285. Khuenl-Brady KS: The use of rocuronium (ORG 9426) in patients with chronic renal failure. Anaesthesia 48:873, 1993.

286. Matteo RS, Ornstein E, Schwartz AE: Pharmacokinetics and pharmacodynamics of rocuronium in elderly surgical patients. Anesth Analg 27:1193, 1993.

287. Wierda JM: Preliminary investigations of the clinical pharmacology of three short-acting non-depolarizing neuromuscular blocking agents, ORG 9453, ORG 9489 and ORG 9487. Can J Anaesth 41:213, 1994.

288. Weirda JM: Time course of action and endotracheal intubating conditions of ORG 9487, a new short-acting steroidal muscle relaxant: A comparison with succinylcholine. Anesth Analg 77:579, 1993.

289. Schiere S: Comparison of vecuronium with ORG 9487 and their interaction. Can J Anaesth 44:1138, 1997.

290. Debaene B: ORG 9487 neuromuscular block at the adductor pollicis and the laryngeal adductor muscles in humans. Anesthesiology 86:1300, 1997.

291. Kahwaji R: Dose-ranging study in younger adult and elderly patients of ORG 9487, a new, rapid-onset, short-duration muscle relaxant. Anesth Analg 84:1011, 1997.

292. van den Broek L: Pharmacodynamics and pharmacokinetics of an infusion of ORG 9487, a new short-acting steroidal neuromuscular blocking agent. Br J Anaesth 73:331, 1994.

293. Muir A. W: Neuromuscular blocking and cardiovascular effects of ORG 9487, a new short-acting aminosteroidal blocking agent, in anaesthetized animals and in isolated muscle preparations. Eur J Anaesthesiol 15:467, 1998.

293A. Pitts ME, Thanapoulos A, Kim J et al: The cardiovascular and histamine releasing properties of organon 9487. Anesth Analg 86:110, 1998.

293B. Yamaguchi K, Huraux C, Szlam F et al: Vascular effects of ORG 9487 in human mammary arteries, a new short-acting muscle relaxant. Anesth Analg 86:109, 1998

293C. Payne JP, Hughes R: Evaluation of atracurium in anaesthetized man. Br J Anaesth 53:45, 1981.

293D. Basta SJ, Ali HH, Savarese JJ et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 61:723, 1982.

294. Belmont MR, Beemer G, Bownes P et al: Comparative pharmacology of atracurium and one of its isomers, 51W89, in rhesus monkeys. Anesthesiology 79:A947, 1993.

294A. Belmont MR, Lien CA, Quessy S et al: The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/ opioid/barbiturate anesthesia. Anesthesiology 82:1139, 1995.

294B. Lepage JY, Malinovsky JM, Malinge M et al: Pharmacodynamic dose-response and safety study of cisatracurium (51W89) in adult surgical patients during N_2O-O_2 -opioid anesthesia. Anesth Analg 83:823, 1996.

294C. Lien CA, Belmont MR, Abalos A et al: The cardiovascular effects and histamine-releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 82:1131, 1995.

294D. Doenicke A, Soukup J, Hoernecke R et al: The lack of histamine release with cisatracurium: A double-blind comparison with vecuronium. Anesth Analg 84:623, 1997.

295. Schramm WM, Paponsek A, Mickalet-Sauberber A et al: The cerebral and cardiovascular effects of cisatracurium and atracurium in neurosurgical patients. Anesth Analg 86:123, 1998.

295A. Konstadt SN, Reich DL, Stanley TE et al: A two-center comparison of the cardiovascular effects of cisatracurium (Nimbex
) and vecuronium in patients with coronary artery disease. Anesth Analg 81:1010, 1995.

295B. Welch RM, Brown A, Ravitch J et al: The in vitro degradation of cisatracurium, the R, *cis*-R
isomer of atracurium, in human and rat plasma. Clin Pharmacol Ther 58:132, 1995.

295C. Lien CA, Schmith VD, Belmont MR et al: Pharmacokinetics of cisatracurium in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 84:300, 1996.

296. Kisor DF, Schmith VD, Wargin WA et al: Importance of the organ-independent elimination of cisatracurium. Anesth Analg 83:1065, 1996.

296A. Boyd AH, Eastwood NB, Parker CJR et al: Pharmacodynamnics of the R, *cis*-R
isomer of atracurium (51W89) in health and chronic renal failure. Br J Anaesth 74:400, 1995.

296B. Eastwood NB, Boyd AH, Parker CJR et al: Pharmacodynamics of the R, *cis*-R
atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. Br J Anaesth 75:431, 1995.

296C. DeWolf AM, Freeman JA, Scott VL et al: Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth 76:624, 1996.

297. Prielipp RC, Coursin DB, Scuderi PE et al: Comparison of the infusion requirements and recovery profiles of vecuronium and cisatracurium 51W89 in intensive care unit patients. Anesth Analg 81:3, 1995.

297A. Diefenbach C, Mellinghoff H, Lynch J, et al: Mivacurium: Dose-response relationships and administration by repeated injection or infusion. Anesth Analg 74:420, 1992.

297B. Caldwell JE, Heir T, Kitts JB et al: Comparison of the neuromuscular block induced by mivacurium, suxamethonium, and atracurium during nitrous oxide-fentanyl anaesthesia. Br J Anaesth 63:393, 1989.

297C. Ali HH, Savarese JJ, Embree PB et al: Clinical pharmacology of mivacurium chloride (BW B1090U) infusion: Comparison with vecuronium and atracurium. Br J Anaesth 61:541, 1988.

297D. Goudsouzian NG, Chakravorti S, Denman W et al: Prolonged mivacurium infusion in young and elderly adults. Can J Anaesth 44:955, 1997.

298. Naguib M, Abdulatif M, Al-Ghamdi A et al: Dose-response relationships for edrophonium and neostigmine antagonism of mivacurium-induced neuromuscular block. Br J Anaesth 71:709, 1993.

298A. Naguib M, Daoud W, el-Gammal M et al: Enzymatic antagonism of mivacurium-induced neuromuscular blockade by human plasma cholinesterase. Anesthesiology 83:694, 1995.

298B. Ostergaard D, Jensen FS, Viby-Mogensen J: Reversal of intense mivacurium block with human plasma cholinesterase in patients with atypical plasma cholinesterase. Anesthesiology 82:1295, 1995.

298C. Savarese JJ, Basta SJ, Ali HH et al: Cardiovascular effects of BW B1090U in patients under nitrous oxide-oxygen-thiopental-fentanyl anesthesia. Anesthesiology 63:A319, 1985.

299. Savarese JJ, Ali HH, Basta SJ et al: Sixty-second tracheal intubation with BW B1090U after fentanyl-thiopental induction. Anesthesiology 67:A351, 1987.

299A. Savarese JJ, Ali HH, Basta SJ et al: Ninety and 120-second tracheal intubation with BW B1090U: Clinical conditions with and without priming after fentanyl-thiopental induction. Anesthesiology 65:A283, 1986.

299B. Ali HH, Lien CA, Witkowski T et al: Efficacy and safety of divided dose administration of mivacurium for a 90-second tracheal intubation. J Clin Anesth 8:276, 1996.

299C. Maehr RB, Belmont MR, Wray DW et al: Autonomic and neuromuscular effects of mivacurium and isomers in cats. Anesthesiology 75:A772, 1991.

299D. Lien CA, Schmith VD, Wargin WA et al: Pharmacokinetics and pharmacodynamics of mivacurium stereoisomers during a two-step infusion. Anesthesiology 77:A910, 1992.

300. Wastila WB: Data on file, Burroughs Wellcome Co., Research Triangle Park, NC.

300A. Ostergaard D, Jensen FS, Skovgaard LT et al: Dose-response relationship for mivacurium in patients with phenotypically abnormal plasma cholinesterase activity. Acta Anaesthesiol Scand 39:1016, 1995.

300B. Goudsouzian NG, D'Hollander AA, Viby-Mogensen J: Prolonged neuromuscular block from mivacurium in two patients with cholinesterase deficiency. Anesth Analg 77:183, 1993.

301. Matteo RS, Pua EK, Khambatta HJ et al: Cerebrospinal fluid levels of *d*-tubocurarine in man. Anesthesiology 46:396, 1977.

302. Munson ES, Wagman IH: Elevation of lidocaine seizure threshold by gallamine. Arch Neurol 28:329, 1973.

303. Forbes AR, Cohen NH, Eger EI: Pancuronium reduces halothane requirement in man. Anesth Analg 58:497, 1979.

304. Fahey MR, Sessler DI, Cannon JE et al: Atracurium, vecuronium and pancuronium do not alter the minimum alveolar concentration (MAC) of halothane in humans. Anesthesiology 71:53, 1989.

305. Peduto VA, Gungui P, Di Martino MR et al: Accidental subarachnoid injection of pancuronium. Anesth Analg 69:516, 1989.

306. Goonewardene TW, Sentheshanmuganathan S, Kamalathan S et al: Accidental subarachnoid injection of gallamine. Br J Anaesth 47:889, 1975.

306A. Segredo V, Matthay MA, Sharma ML et al: Prolonged neuromuscular blockade after long-term administration of vecuronium in two critically ill patients. Anesthesiology 72:566, 1990.

307. Kelly SS, Robert DV: The effect of age on the safety factor in neuromuscular transmission in the isolated rat diaphragm. Br J Anaesth 149:271, 1977.

307A. Kelly SS: The effect of age on neuromuscular transmission. J Physiol (Lond) 274:51, 1978.

308. Goudsouzian NG: Maturation of neuromuscular transmission in the infant. Br J Anaesth 52:205, 1980.

309. Bennet EJ, Ignacio A, Patel K et al: Tubocurarine and the neonate. Br J Anaesth 48:687, 1976.

310. Bennett EJ, Ramamurthy S, Dalal FY et al: Pancuronium and the neonate. Br J Anaesth 47:75, 1975.

311. Churchill-Davidson HC, Wise RP: The response of the newborn infant to muscle relaxants. Can J Anaesth 11:1, 1964.

312. Long G, Bachman L: Neuromuscular blockade by *d*-tubocurarine in children. Anesthesiology 28:723, 1967.

313. Goudsouzian NG, Ryan JF, Savarese JJ: The neuromuscular effects of pancuronium in infants and children. Anesthesiology 41:95, 1974.

314. Goudsouzian NG, Donlon JV, Savarese JJ et al: Re-evaluation of dosage and duration of action of *d*-tubocurarine in the pediatric age group. Anesthesiology 43:416, 1975.

315. Goudsouzian NG, Liu L, Savarese JJ: Metocurine in infants and children. Anesthesiology 49:266, 1978.

316. Fisher DM, O'Keefe CO, Stanski DR et al: Pharmacokinetics and pharmacodynamics of *d*-tubocurarine in infants, children and adults. Anesthesiology 57:203, 1982.

316A. Fisher DM, Castagnoli K, Miller RD: Vecuronium kinetics and dynamics in anesthetized infants and children. Clin Pharmacol Ther 37:402, 1985.

316B. Fisher DM, Canfell PC, Spellman MJ et al: Pharmacokinetics and pharmacodynamics of atracurium in infants and children. Anesthesiology 73:33, 1990.

317. Fisher DM, Miller RD: Neuromuscular effects of vecuronium (ORG NC 45) in infants and children during N_2O, halothane anesthesia. Anesthesiology 58:519, 1983.

318. Baxter MRN, Bevan JC, Samuel J et al: Postoperative neuromuscular function in pediatric care patients. Anesth Analg 72:504, 1991.

319. Meretoja OA, Wirtavouri K, Neuvonen PJ: Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. Anesth Analg 67:21, 1988.

320. Meretoja OA: Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? Br J Anaesth 62:184, 1989.

321. Brandon BW, Woelfel SK, Cook DR et al: Clinical pharmacology of atracurium in infants. Anesth Analg 63:309, 1984.

322. Goudsouzian NG, Liu LMP, Cote CJ et al: Safety and efficacy of atracurium in adolescents and children anesthetized with halothane. Anesthesiology 59:459, 1983.

323. Meretoja OA, Kalli I: Spontaneous recovery of neuromuscular function after atracurium in infants. Anesth Analg 65:1042, 1986.

324. Meretoja OA, Taivainen T, Wirtavuori K: Cisatracurium during halothane and balanced anaesthesia in children. Paediatr Anaesth 6:373, 1996.

325. Sarner JB, Brandom BW, Woelfel SK et al: Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide-halothane and nitrous oxide-narcotic anesthesia. Anesth Analg 68:116, 1989.

326. Goudsouzian NG, Alifimoff JK, Eberly C et al: Neuromuscular and cardiovascular effects of mivacurium in children. Anesthesiology 70:237, 1989.

327. Goudsouzian NG, Martyn JAJ, Liu LMP et al: Safety and efficacy of vecuronium in adolescents and children. Anesth Analg 62:1083, 1983.

328. Hart PS, McCarthy GJ, Brown R et al: The effect of plasma cholinesterase activity on mivacurium infusion rates. Anesth Analg 80:760, 1995.

329. Markakis DA, Hart PS, Lau M et al: Does age or pseudocholinesterase activity predict mivacurium infusion rate in children? Anesth Analg 82:39, 1996.

330. Brandom BW, Sarner JB, Woelfel SK et al: Mivacurium infusion requirements in pediatric surgical patients during nitrous oxide- halothane and during nitrous oxide-narcotic anesthesia. Anesth Analg 71:16, 1990.

330A. Scheiber G, Ribeiro FC, Marichal A et al: Intubating conditions and onset of action after rocuronium, vecuronium, and atracurium in young children. Anesth Analg 83:320, 1996.

330B. Taivainen T, Meretoja OA, Erkola O et al: Rocuronium in infants, children and adults during balanced anaesthesia. Paediatr Anaesth 6:271, 1996.

330C. Reynolds LM, Lau M, Brown R et al: Intramuscular rocuronium in infants and children. Anesthesiology 85:231, 1996.

330D. Berry FA (editorial): Intramuscular rocuronium in infants and children-is there a need? Anesthesiology 85:229, 1996.

331. Fisher DM, Cronnelly R, Sharma M et al: Clinical pharmacology of edrophonium in infants and children. Anesthesiology 61:428, 1984.

332. Fisher DM, Cronnelly R, Miller RD et al: The neuromuscular pharmacology of neostigmine in infants and children. Anesthesiology 59:220, 1983.

332A. Larach MG, Rosenberg H, Gronert GA et al: Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. Clin Pediatr (Phila) 36:9, 1997.

333. Frolkis VV, Martynenko OA, Zamostyan VP: Aging of the neuromuscular apparatus. Gerontology 22:244, 1976.

334. Matteo RS, Backus WW, McDaniel DD et al: Pharmacokinetics and pharmacodynamics of *d*-tubocurarine and metocurine in the elderly. Anesth Analg 64:23, 1985.

335. McLeod K, Hull CJ, Watson MJ: Effects of aging on the pharmacokinetics of pancuronium. Br J Anaesth 51:435, 1979.

336. Duvaldestin P, Saada J, Berger JL et al: Pharmacokinetics, pharmacodynamics and dose-response relationships of pancuronium in control and elderly subjects. Anesthesiology 56:36, 1982.

336A. Lien CA, Matteo RS, Ornstein E et al: Distribution, elimination, and action of vecuronium in the elderly. Anesth Analg 73:39, 1991.

337. D'Hollander AA, Masseaux F, Nevelsteen M et al: Age-dependent dose-response relationship of ORG NC 45 in anaesthetized patients. Br J Anaesth 54:653, 1982.

338. Matteo RS, Ornstein E, Schwartz AE et al: Pharmacokinetics and pharmacodynamics of rocuronium (ORG 9426) in elderly surgical patients. Anesth Analg 77:1193, 1993.

339. Dresner DL, Basta SJ, Ali HH et al: Pharmacokinetics and pharmacodynamics of doxacurium in young and elderly patients during isoflurane anesthesia. Anesth Analg 71:498, 1990.

340. Ornstein E, Matteo RS, Schwartz AE et al: Pharmacokinetics and pharmacodynamics of pipecuronium bromide (Arduan) in elderly surgical patients. Anesth Analg 74:841, 1992.

341. D'Hollander AA, Luyckx C, Barvais L et al: Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: Lack of age-related effects. Anesthesiology 59:237, 1983.

342. Kitts JB, Fisher DM, Canfell PC et al: Pharmacokinetics and pharmacodynamics of atracurium in the elderly. Anesthesiology 72:272, 1990.

342A. Ornstein E, Lien CA, Matteo RS et al: Pharmacodynamics and pharmacokinetics of cisatracurium in geriatric surgical patients. Anesthesiology 84:520, 1996.

342B. Sorooshian SS, Stafford MA, Eastwood NB et al: Pharmacokinetics and pharmacodynamics of cisatracurium in young and elderly adult patients. Anesthesiology 84:1083, 1996.

343. Maddineni VR, Mirakhur RK, McCoy EP. Plasma cholinesterase activity in elderly and young adults. Br J Anaesth 72: 1994.

343A. Maddineni VR, Mirakhur RK, McCoy EP et al: Neuromuscular and haemodynamic effects of mivacurium in elderly and young adult patients. Br J Anaesth 73:608, 1994.

343B. Goudsouzian N, Chakravorti S, Denman W et al: Prolonged mivacurium infusion in young and elderly adults. Can J Anaesth 44:955, 1997.

344. Tsueda K, Warren JE, McCafferty LA et al: Pancuronium bromide requirement during anesthesia for the morbidly obese. Anesthesiology 48:438, 1978.

345. Feingold A: Pancuronium requirements of the morbidly obese. Anesthesiology 50:269, 1979.

346. Soderberg M, Thomson D, White T: Respiration, circulation and anaesthetic management in obesity. Acta Anaesthesiol Scand 21:55, 1977.

347. Schwartz AE, Matteo RS, Ornstein E et al: Pharmacokinetics and dynamics of metocurine in the obese. Anesthesiology 65:295A, 1986.

347A. Schmith VD, Fiedler-Kelly J, Abou-Donia M et al: Population pharmacodynamics of doxacurium. Clin Pharmacol Ther 52:528, 1992.

348. Weinstein JA, Matteo RS, Ornstein E et al: Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. Anesth Analg 67:1149, 1988.

348A. Puhringer FK, Khuenl-Brady KS, Mitterschiffhaler G: Rocuronium bromide: Time-course of action in underweight, normal weight, overweight and obese patients. Eur J Anaesthesiol Suppl 11:107, 1995.

349. Beemer GH, Bjorksten AR, Crankshaw DP: Effect of body build on the clearance of atracurium: Implication for drug dosing. Anesth Analg 76:1296, 1993.

350. Fairley HB: Prolonged intercostal paralysis due to a relaxant. BMJ 76:1296, 1950.

351. Ramzan MI, Shanks CA, Triggs EJ: Gallamine disposition in surgical patients with chronic renal failure. Br J Clin Pharmacol 12:141, 1981.

352. Orko R, Heino A, Rosenberg PH et al: Dose-response of tubocurarine in patients with and without renal failure. Acta Anaesthesiol Scand 28:452, 1982.

352A. Miller RD, Matteo RS, Benet LZ et al: The pharmacokinetics of *d*-tubocurarine in man with and without renal failure. J Pharmacol Exp Ther 202:1, 1977.

352B. Ward S, Neill EA: Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). Br J Anaesth 55:1169, 1983.

352C. Bevan DR, Donati F, Gyasi H et al: Vecuronium in renal failure. Can Anaesth Soc J 31:491, 1984.

352D. Blobner M, Jelen-Esselborn S, Schneider G et al: Effect of renal function on neuromuscular block induced by continuous infusion of mivacurium. Br J Anaesth 74:452, 1995.

352E. Brotherton WP, Matteo RS: Pharmacokinetics and pharmacodynamics of metocurine in humans with and without renal failure. Anesthesiology 55:273, 1981.

353. Ramzan MI, Somogyi AA, Walker JS et al: Clinical pharmacokinetics of the non-depolarizing muscle relaxants. Clin Pharmacokinet 6:25, 1981.

353A. Shanks CA: Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to calculation of bolus and infusion regimens. Anesthesiology 64:72, 1986.

354. Cashman JN, Luke JJ, Jones RM: Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function. Br J Anaesth 64:186, 1990.

354A. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with hepatic or renal failure. Anesth Analg 72:145, 1991.

354B. Wierda JM, Szenohradszky J, De WA et al: The pharmacokinetics, urinary and biliary excretion of pipecuronium bromide. Eur J Anaesthesiol 8:451, 1991.

354C. Caldwell JE, Canfell PC, Castagnoli KP et al: The influence of renal failure on the pharmacokinetics and duration of action of pipecuronium bromide in patients anesthetized with halothane and nitrous oxide. Anesthesiology 70:7, 1989.

355. Mongin-Long D, Chabrol B, Baude C et al: Atracurium in patients with renal failure. Br J Anaesth 58:44S, 1986.

356. Hunter JM, Jones RS, Utting JE: Use of atracurium in patients with no renal function. Br J Anaesth 54:1251, 1982.

357. Vandenbrom RH, Wierda JM, Agoston S: Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal renal function. Clin Pharmacokinet 19:230, 1990.

357A. Fahey MR, Rupp SM, Fisher DM et al: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 61:699, 1984.

357B. Ward S, Boheimer N, Weatherley BC et al: Pharmacokinetics of atracurium and its metabolites in patients with normal renal function and in patients in renal failure. Br J Anaesth 59:697, 1987.

357C. Fisher DM, Canfell PC, Fahey MR et al: Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. Anesthesiology 65:6, 1986.

358. Parker CJ, Jones JE, Hunter JM: Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in an ITU. Br J Anaesth 61:531, 1988.

358A. Fahey MR, Rupp SM, Canfell C et al: Effect of renal failure on laudanosine excretion in man. Br J Anaesth 57:1049, 1985.

358B. Bencini AF, Scaf AH, Sohn YJ et al: Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. Anesth Analg 65:245, 1986.

358C. Bencini AF, Scaf AHJ, Sohn YJ et al: Hepatobiliary disposition of vecuronium bromide in man. Br J Anaesth 58:988, 1986.

359. Meistelman C, Lienhart A, Leveque C et al: Pharmacology of vecuronium in patients with end-stage renal failure. Eur J Anaesthesiol 3:153, 1986.

359A. Fahey MR, Morris RB, Miller RD et al: Pharmacokinetics of ORG NC 45 (NORCURON) in patients with and without renal failure. Br J Anaesth 53:1049, 1981.

360. Lynam DP, Cronnelly R, Castagnoli KP et al: The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. Anesthesiology 69:227, 1988.

361. Caldwell JE, Szenohradszky J, Segredo V et al: The pharmacodynamics and pharmacokinetics of the metabolite 3-desacetylvecuronium (ORG 7268) and its parent compound, vecuronium, in human volunteers. J Pharmacol Exp Ther 270:1216, 1994.

362. Segredo V, Caldwell JE, Matthay MA et al: Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 327:524, 1992.

363. Segredo V, Matthay MA, Sharma ML et al: Prolonged neuromuscular blockade after long-term administration of vecuronium in two critically ill patients. Anesthesiology 72:566, 1990.

364. Hunter JM, Jones RS, Utting JE: Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. Br J Anaesth 56:941, 1984.

365. Gramstad L: Atracurium, vecuronium and pancuronium in end-stage renal failure. Br J Anaesth 59:995, 1987.

366. Lepage JY, Malinge M, Cozian A et al: Vecuronium and atracurium in patients with end-stage renal failure. Br J Anaesth 59:1004, 1987.

367. Savarese JJ, Ali HH, Basta SJ et al: The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 68:723, 1988.

368. Cook DR, Stiller RL, Weakly JN et al: In vitro metabolism of mivacurium chloride (BW B1090U) and succinylcholine. Anesth Analg 68:452, 1989.

369. Head-Rapson AG, Devlin JC, Parker CJ et al: Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal

function. Br J Anaesth 75:31, 1995.

369A. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 69:580, 1992.

370. Phillips BJ, Hunter JM: Use of mivacurium chloride by constant infusion in the anephric patient. Br J Anaesth 68:492, 1992.

370A. Ryan DW: Preoperative serum cholinesterase concentration in chronic renal failure. Br J Anaesth 49:945, 1977.

370B. Ostergaard D, Jensen FS, Jensen E et al: Influence of plasma cholinesterase activity on recovery from mivacurium-induced neuromuscular blockade in phenotypically normal patients. Acta Anaesthesiol Scand 36:702, 1992.

370C. Mangar D, Kirchhoff GT, Rose PL et al: Prolonged neuromuscular block after mivacurium in a patient with end-stage renal disease. Anesth Analg 76:866, 1993.

370D. Szenohradszky J, Caldwell JE, Sharma ML et al: Interaction of rocuronium (ORG 9426) and phenytoin in a patient undergoing cadaver renal transplantation: A possible pharmacokinetic mechanism? Anesthesiology 80:1167, 1994.

370E. Szenohradszky J, Fisher DM, Segredo V et al: Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology 77:899, 1992.

370F. Khuenl-Brady KS, Pomaroli A, Puhringer F et al: The use of rocuronium (ORG 9426) in patients with chronic renal failure. Anaesthesia 48:873, 1993.

371. Kisor DF, Schmith VD, Wargin WA et al: Importance of the organ-independent elimination of cisatracurium. Anesth Analg 83:1065, 1996.

372. El-Hakim M, Baraka A: *d*-Tubocurarine in liver disease. Kasr-El-Aini J 4:99, 1963.

372A. Somogyi AA, Shanks CA, Triggs EJ: Disposition kinetics of pancuronium bromide in patients with total biliary obstruction. Br J Anaesth 49:1103, 1977.

372B. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with hepatic or renal failure. Anesth Analg 72:145, 1991.

372C. Lebrault C, Berger JL, D'Hollander AA et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) in patients with cirrhosis. Anesthesiology 62:601, 1985.

372D. Khalil M, d'Honneur G, Duvaldestin P et al: Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. Anesthesiology 80:1241, 1994.

372E. van Miert MM, Eastwood NB, Boyd AH et al: The pharmacokinetics and pharmacodynamics of rocuronium in patients with hepatic cirrhosis. Br J Clin Pharmacol 44:139, 1997.

372F. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 69:580, 1992.

372G. Head-Rapson AG, Devlin JC, Parker CJR et al: Pharmacokinetics of the three isomers of mivacurium and pharmacodynamics of the chiral mixture in hepatic cirrhosis. Br J Anaesth 73:613, 1994.

372H. Parker CJ, Hunter JM: Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 62:177, 1989.

373. Pittet JF, Tassonyi E, Schopfer C et al: Plasma concentrations of laudanosine, but not of atracurium, are increased during the anhepatic phase of orthotopic liver transplantation in pigs. Anesthesiology 72:145, 1990.

374. Lawhead RG, Matsumi M, Peters KR et al: Plasma laudanosine levels in patients given atracurium during liver transplantation. Anesth Analg 76:569, 1993.

374A. Dundee JW, Gray TC: Resistance to *d*-tubocurarine chloride in the presence of liver damage. Lancet 2:16, 1953.

375. Nana A, Cardan E, Leitersdorfer T: Pancuronium bromide: Its use in asthmatics and patients with liver disease. Anaesthesia 27:154, 1972.

375A. Ward ME, Adu-Gyamfi Y, Strunin L: Althesin and pancuronium in chronic liver disease. Br J Anaesth 47:1199, 1975.

376. Gyashi HK, Naguib M: Atracurium and severe hepatic disease: A case report. Can Anaesth Soc J 32:161, 1985.

376A. Servin FS, Lavaut E, Kleef U et al: Repeated doses of rocuronium bromide administered to cirrhotic and control patients receiving isoflurane: A clinical and pharmacokinetic study. Anesthesiology 84:1092, 1996.

377. Bell CF, Hunter JM, Jones RS et al: Use of atracurium and vecuronium in patients with oesophageal varices. Br J Anaesth 57:160, 1985.

378. Hunter JM, Parker CJ, Bell CF et al: The use of different doses of vecuronium in patients with liver dysfunction. Br J Anaesth 57:758, 1985.

378A. Arden JR, Lynam DP, Castagnoli KP, et al: Vecuronium in alcoholic liver disease: A pharmacokinetic and pharmacodynamic analysis. Anesthesiology 68:771, 1988.

378B. Lebrault C, Duvaldestin P, Henzel D et al: Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. Br J Anaesth 58:983, 1986.

379. Hewett CL, Savage DS: Amino steroids: 2- and 3-amini-5a-androstanes. J Chem Soc (C):1134, 1968.

380. Agoston S, Vermeer GA, Kertsten UW et al: The fate of pancuronium bromide in man. Acta Anaesthesiol Scand 17:267, 1973.

380A. Bencini AF, Mol WEM, Scaf AHJ et al: Uptake and excretion of vecuronium bromide and pancuronium bromide in the isolated perfused rat liver. Anesthesiology 69:487, 1988.

380B. Bencini AF, Scaf AHJ, Sohn YJ et al: Hepatobiliary disposition of vecuronium bromide in man. Br J Anaesth 58:988, 1986.

380C. Westra P, Keulemans GTP, Houwertjes MC et al: Mechanisms underlying the prolonged duration of action of muscle relaxants caused by extrahepatic cholestasis. Br J Anaesth 53:217, 1981.

380D. Westra P, Vermeer GA, de Lange AR et al: Hepatic and renal disposition of pancuronium and gallamine in patients with extrahepatic cholestasis. Br J Anaesth 53:331, 1981.

380E. Duvaldestin P, Agoston S, Henzel D et al: Pancuronium pharmacokinetics in patients with liver cirrhosis. Br J Anaesth 50:1131, 1978.

380F. Fisher DM, Canfell PC, Fahey MR et al: Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. Anesthesiology 65:6, 1986.

380G. Kisor DF, Schmith VD, Wargin WA et al: Importance of the organ-independent elimination of cisatracurium. Anesth Analg 83:1065, 1996.

380H. De Wolf AM, Freeman JA, Scott VL et al: Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth 76:624, 1996.

381. Kelly RE, Lien CA, Savarese JJ et al: Depression of neuromuscular function in a patient during desflurane anesthesia. Anesth Analg 76:868, 1993.

381A. Miller RD, Way WL, Dolan WM et al: The dependence of pancuronium- and *d*-tubocurarine-induced neuromuscular blockades on alveolar concentrations of halothane and forane. Anesthesiology 37:573, 1972.

381B. Ali HH, Savarese JJ: Monitoring of neuromuscular function. Anesthesiology 45:216, 1976.

382. Miller RD, Crique M, Eger EI: Duration of halothane anesthesia and neuromuscular blockade with *d*-tubocurarine. Anesthesiology 44:206, 1976.

383. Miller RD, Eger EI, Way WL et al: Comparative neuromuscular effects of Forane and halothane alone and in combination with *d*-tubocurarine in man. Anesthesiology 35:38, 1971.

384. Fogdall RP, Miller RD: Neuromuscular effects of enflurane, alone and combined with *d*-tubocurarine, pancuronium, and succinylcholine, in man. Anesthesiology 42:173, 1975.

384A. Morita T, Tsukagoshi H, Sugaya T et al: The effects of sevoflurane are similar to those of isoflurane on the neuromuscular block produced by vecuronium. Br J Anaesth 72:465, 1994.

384B. Vanlinthout LE, Booij LH, van Egmond J et al: Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium pancuronium and atracurium. Br J Anaesth 76:389, 1996.

384C. Wright PM, Hart P, Lau M et al: The magnitude and time course of vecuronium potentiation by desflurane versus isoflurane. Anesthesiology 82:404, 1995.

385. Miller RD, Rupp SR, Fisher DM et al: Clinical pharmacology of vecuronium and atracurium. Anesthesiology 61:444, 1984.

385A. Cannon JE, Fahey MR, Castagnoli KP et al: Continuous infusion of vecuronium: The effect of anesthetic agents. Anesthesiology 67:503, 1987.

385B. Shanks CA, Fragen RJ, Ling D: Continuous intravenous infusion of rocuronium (ORG 9426) in patients receiving balanced, enflurane, or isoflurane anesthesia. Anesthesiology 78:649, 1993.

386. Baurain MJ, d'Hollander AA, Melot C et al: Effects of residual concentrations of isoflurane on the reversal of vecuronium-induced neuromuscular blockade. Anesthesiology 74:474, 1991.

386A. Jellish WS, Thalji ZA, Murdoch JR: Recovery from mivacuriuminduced neuromuscular blockade after neurosurgical procedures of long duration. J Clin Anesth 7:643, 1995.

387. Savarese JJ, Ali HH, Basta SJ et al: The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 68:723, 1988.

388. Gencarelli PJ, Miller RD, Eger EI et al: Decreasing enflurane concentrations and *d*-tubocurarine neuromuscular blockade. Anesthesiology 56:192, 1982.

389. Vitez TS, Miller RD, Eger EI et al: Comparison of in vitro isoflurane and halothane potentiation of *d*-tubocurarine and succinylcholine neuromuscular blockades. Anesthesiology 41:53, 1974.

390. Gergis SD, Dretchen KL, Sokoll MD et al: Effect of anesthetics on acetylcholine release from the myoneural junction. Proc Soc Exp Biol Med 141:629, 1972.

391. Waud BE, Waud DR: The effects of diethyl ether, enflurane, and isoflurane at the neuromuscular junction. Anesthesiology 42:275, 1975.

392. Waud BE, Cheng MC, Waud DR: Comparison of drug-receptor dissociation constants at the mammalian neuromuscular junction in the presence and absence of halothane. J Pharmacol Exp Ther 187:40, 1973.

393. Karis JH, Gissen AJ, Nastuk WL: Mode of action of diethyl ether in blocking neuromuscular transmission. Anesthesiology 27:42, 1966.

394. Gissen AJ, Karis JH, Nastuk WL: Effect of halothane on neuromuscular transmission. JAMA 197:770, 1966.

395. Caldwell JE, Laster MJ, Magorian T et al: The neuromuscular effects of desflurane, alone and combined with pancuronium or succinylcholine, in humans. Anesthesiology 74:412, 1991.

396. Brett RS, Dilger JP, Yland KF: Isoflurane causes "flickering" of the acetylcholine receptor channel: Observations using the patch clamp. Anesthesiology 69:161, 1988.

397. Waud BE, Waud DR: Comparison of the effects of general anesthetics on the end-plate of skeletal muscle. Anesthesiology 43:540, 1975.

398. Stanski DR, Ham J, Miller RD et al: Pharmacokinetics and pharmacodynamics of *d*-tubocurarine during nitrous oxide-narcotic and halothane anesthesia in man. Anesthesiology 51:235, 1979.

399. Stanski DR, Ham J, Miller RD et al: Time-dependent increase in sensitivity to *d*-tubocurarine during enflurane anesthesia in man. Anesthesiology 52:483, 1980.

400. Meretoja OA, Wirtavuori K, Taivainen T et al: Time course of potentiation of mivacurium by halothane and isoflurane in children. Br J Anaesth 76:235, 1996.

400A. Jalkanen L, Meretoja OA: The influence of the duration of isoflurane anaesthesia on neuromuscular effects of mivacurium. Acta Anaesthesiol Scand 41:248, 1997.

400B. Delisle S, Bevan DR: Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. Br J Anaesth 54:441, 1982.

400C. Morita T, Tsukagoshi H, Sugaya T et al: Inadequate antagonism of vecuronium-induced neuromuscular block by neostigmine during sevoflurane or isoflurane anesthesia. Anesth Analg 80:1175, 1995.

400D. Morita T, Kurosaki D, Tsukagoshi H et al: Sevoflurane and isoflurane impair edrophonium reversal of vecuronium-induced neuromuscular block. Can J Anaesth 43:799, 1996.

401. Morita T, Kurosaki D, Tsukagoshi H et al: Factors affecting neostigmine reversal of vecuronium block during sevoflurane anaesthesia. Anaesthesia 52:538, 1997.

402. Heier T, Caldwell JE, Sessler DI et al: The relationship between adductor pollicis twitch tension and core, skin, and muscle temperature during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 71:381, 1989.

403. Heier T, Caldwell JE, Sessler DI et al: The effect of local surface and central cooling on adductor pollicis twitch tension during nitrous oxide/isoflurane and nitrous oxide/fentanyl anesthesia in humans. Anesthesiology 72:807, 1990.

404. Heier T, Caldwell JE, Sessler DI et al: Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 74:815, 1991.

405. Leslie K, Sessler DI, Bjorksten AR et al: Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg 80:1007, 1995.

406. Ham J, Miller RD, Benet LZ et al: Pharmacokinetics and pharmacodynamics of *d*-tubocurarine during hypothermia in the cat. Anesthesiology 49:324, 1978.

407. Miller RD, Agoston S, van der Pol F et al: Hypothermia and the pharmacokinetics and pharmacodynamics of pancuronium in the cat. J Pharmacol Exp Ther 207:532, 1978.

408. Ham J, Stanski DR, Newfield P et al: Pharmacokinetics and dynamics of *d*-tubocurarine during hypothermia in humans. Anesthesiology 55:631, 1981.

409. Heier T, Caldwell JE, Sharma ML et al: Mild intraoperative hypothermia does not change the pharmacodynamics (concentration-effect relationship) of vecuronium in humans. Anesth Analg 78:973, 1994.

410. Yoneda I, Okamoto T, Aoki T et al: [The effect of temperature on the action of several neuromuscular blocking agents in vitro]. Masui 40:743, 1991.

411. Eriksson LI, Viby MJ, Lennmarken C: The effect of peripheral hypothermia on a vecuronium-induced neuromuscular block. Acta Anaesthesiol Scand 35:387, 1991.

412. Thornberry EA, Mazumdar B: The effect of changes in arm temperature on neuromuscular monitoring in the presence of atracurium blockade. Anaesthesia 43:447, 1988.

413. Argov Z, Mastaglia FL: Disorders of neuromuscular transmission caused by drugs. N Engl J Med 301:409, 1979.

414. Miller RD: Factors affecting the action of muscle relaxants. In Katz RL (ed): Muscle Relaxants, Amsterdam, Excerpta Medica, 1975.

414A. Ahdal O, Bevan DR: Clindamycin-induced neuromuscular blockade. Can J Anaesth 42:614, 1995.

415. Lee C, de Silva AJC: Acute and subchronic neuromuscular blocking characteristics of streptomycin: A comparison with neomycin. Br J Anaesth 51:431, 1979.

416. Singh YN, Harvey AL, Marshall IG: Antibiotic-induced paralysis of the mouse phrenic nerve-hemidiaphragm preparation, and reversibility by calcium and by neostigmine. Anesthesiology 48:418, 1978.

417. Singh YN, Marshall IG, Harvey AL: Depression of transmitter release and postjunctional sensitivity during neuromuscular block produced by antibiotics. Br J Anaesth 51:1027, 1979.

418. Sokoll MD, Gergis SD: Antibiotics and neuromuscular function. Anesthesiology 55:148, 1981.

418A. Hasfurther DL, Bailey PL: Failure of neuromuscular blockade reversal after rocuronium in a patient who received oral neomycin. Can J Anaesth 43:617, 1996.

419. Dupuis JY, Martin R, Tetrault JP: Atracurium and vecuronium interaction with gentamicin and tobramycin. Can J Anaesth 36:407, 1989.

419A. Martinez EA, Mealey KL, Woolridge AA et al: Pharmacokinetics, effects on renal function, and potentiation of atracurium-induced neuromuscular blockade after administration of a high dose of gentamicin in isoflurane-anesthetized dogs. Am J Vet Res 57:1623, 1996.

420. Giesecke AH, Morris RE, Dalton MD et al: Of magnesium, muscle relaxants, toxemic parturients and cats. Anesth Analg 47:689, 1968.

421. Ghoneim MM, Long JP: The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 32:23, 1970.

422. del Castillo J, Engbaek L: The nature of the neuromuscular block produced by magnesium. J Physiol 124:370, 1954.

423. Manthey AA: The effect of calcium on the desensitization of membrane receptors at the neuromuscular junction. J Gen Physiol 49:963, 1966.

424. Badola RP, Chatterji S, Pandey K et al: Effects of calcium on neuromuscular block by suxamethonium in dogs. Br J Anaesth 43:1027, 1971.

425. Telivuo LL, Katz RL: The effects of modern intravenous local analgesics

on respiration during partial neuromuscular block in man. Anaesthesia 25:30, 1970.

426. Usubiaga JE, Wikinski JA, Morales RL: Interaction of intravenously administered procaine, lidocaine and succinylcholine in anesthetized subjects. Anesth Analg 46:39, 1967.

427. Usubiaga JE, Standaert F: The effects of local anesthetics on motor nerve terminals. J Pharmacol Exp Ther 159:353, 1968.

428. Kordas M: The effect of procaine on neuromuscular transmission. J Physiol 209:689, 1970.

429. Gelser RM, Matsuba M: Neuromuscular blocking actions of local anesthetics. J Pharmacol Exp Ther 103:314, 1951.

430. Thorpe WR, Seeman P: The site of action of caffeine and procaine in skeletal muscle. J Pharmacol Exp Ther 179:324, 1971.

431. Harrah MD, Way WL, Katzung BG: The interaction of *d*-tubocurarine with antiarrhythmic drugs. Anesthesiology 33:406, 1970.

432. Miller RD, Way WL, Katzung BG: The potentiation of neuromuscular blocking agents by quinidine. Anesthesiology 28:1036, 1967.

433. Miller RD, Way WL, Katzung BG: The neuromuscular effects of quinidine. Proc Soc Exp Biol Med 129:215, 1968.

434. Ornstein E, Matteo RS, Weinstein JA et al: Accelerated recovery from doxacurium-induced neuromuscular blockade in patients receiving chronic anticonvulsant therapy. J Clin Anesth 3:108, 1991.

435. Ornstein E, Matteo RS, Schwartz AE et al: The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. Anesthesiology 67:191, 1987.

436. Ornstein E, Matteo RS, Young WL et al: Resistance to metocurine-induced neuromuscular blockade in patients receiving phenytoin. Anesthesiology 63:294, 1985.

436A. Spacek A, Neiger FX, Spiss CK et al: Atracurium-induced neuromuscular block is not affected by chronic anticonvulsant therapy with carbamazepine. Acta Anaesthesiol Scand 41:1308, 1997.

436B. Alloul K, Whalley DG, Shutway F et al: Pharmacokinetic origin of carbamazepine-induced resistance to vecuronium neuromuscular blockade in anesthetized patients. Anesthesiology 84:330, 1996.

436C. Hans P, Brichant JF, Pieron F et al: Elevated plasma alpha l-acid glycoprotein levels: Lack of connection to resistance to vecuronium blockade induced by anticonvulsant therapy. J Neurosurg Anaesth 9:3, 1997.

437. Bell PF, Mirakhur RK, Elliott P: Onset and duration of clinical relaxation of atracurium and vecuronium in patients on chronic nifedipine therapy. Eur J Anaesthesiol 6:343, 1989.

438. Kanaya N, Sato Y, Tsuchida H et al: The effects of nicardipine and verapamil on the recovery time of vecuronium-induced neuromuscular blockade. Masui 40:246, 1991.

439. Nott NW, Bowman WC: Actions of dantrolene sodium on contractions of the tibialis anterior and soleus muscles of cats under chloralose anesthesia. Clin Exp Pharmacol Physiol 1:113, 1974.

440. Morgan KG, Bryant SD: The mechanism of action of dantrolene sodium. J Pharmacol Exp Ther 201:138, 1977.

441. Lee C, Katz RL: Neuromuscular pharmacology: A clinical update and commentary. Br J Anaesth 52:173, 1980.

442. Miller RD, Sohn YJ, Matteo RS: Enhancement of *d*-tubocurarine neuromuscular blockade by diuretics in man. Anesthesiology 45:442, 1976.

443. Matteo RS, Nishitateno K, Pua EK et al: Pharmacokinetics of *d*-tubocurarine in man: Effects of an osmotic diuretic on urinary excretion. Anesthesiology 52:335, 1980.

444. Glidden RS, Martyn JAJ, Tomera JD: Azathioprine fails to alter the dose-response curve of *d*-tubocurarine in rats. Anesthesiology 68:595, 1988.

445. Gramstad L: Atracurium, vecuronium, and pancuronium in end-stage renal failure. Br J Anaesth 59:995, 1987.

446. Schuh FT: On the interaction of combinations of nondepolarizing neuromuscular blocking drugs. Anaesthetist 30:537, 1981.

447. Van der Spek AFL, Zupan JT, Pollard BJ et al: Interactions of vecuronium and atracurium in an in vitro nerve-muscle preparation. Anesth Analg 67:240, 1987.

448. Lebowitz PW, Ramsey FM, Savarese JJ et al: Potentiation of neuromuscular blockade in man produced by combinations of pancuronium and metocurine or pancuronium and *d*-tubocurarine. Anesth Analg 59:604, 1980.

449. Lebowitz PW, Ramsey FM, Savarese JJ et al: Combination of pancuronium and metocurine: Neuromuscular and hemodynamic advantages over pancuronium alone. Anesth Analg 60:12, 1981.

449A. Bowman WC: Neuromuscular-blocking agents. In Pharmacology of Neuromuscular Function. London, Wright, 1990.

450. Bevan DR, Donati F, Kopman AF: Reversal of neuromuscular blockade. Anesthesiology 77:785, 1992.

451. Mirakhur RK: Basic pharmacology of reversal agents. Anesth Clin North Am 11:237, 1993.

451A. Katz RL: Clinical neuromuscular pharmacology of pancuronium. Anesthesiology 34:550, 1971.

451B. Beattie WS: Continuous infusions of atracurium and vecuronium, compared with intermittent boluses of pancuronium: Dose requirements and reversal. Can J Anaesth 39:925, 1992.

451C. Beemer GH: The maximum depth of an atracurium neuromuscular block antagonized by edrophonium to effect adequate recovery. Anesthesiology 82:852, 1995.

452. Cronnelly R: Edrophonium: Duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261, 1982.

452A. Beemer GH: Determinants of the reversal time of competitive neuromuscular block by anticholinesterases. Br J Anaesth 66:469, 1991.

453. Magorian TT: Can early administration of neostigmine, in single or divided doses, alter the course of neuromuscular recovery from a vecuronium-induced neuromuscular blockade? Anesthesiology 73:410, 1990.

453A. Viby-Mogensen J: Residual neuromuscular block is a risk factor for postoperative pulmonary complications: A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 41:1095, 1997.

453B. Miller RD: Comparative times to peak effect and durations of action of neostigmine and pyridostigmine. Anesthesiology 41:27, 1974.

454. Rupp SM, McChristian J, Miller RD: Neostigmine and edrophonium antagonism of varying intensity neuromuscular blockade induced by atracurium, pancuronium, or vecuronium. Anesthesiology 64:711, 1986.

454A. Engbaek J: Edrophonium and neostigmine for reversal of the neuromuscular blocking effect of vecuronium. Acta Anaesthesiol Scand 29:544, 1985.

455. Donati F, Smith CE, Bevan DR: Dose-response relationships for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. Anesth Analg 68:13, 1989.

455A. Cronnelly R: Muscle relaxant antagonists. Sem Anesth 4:31, 1985.

455B. Caldwell JE: Antagonism of vecuronium and atracurium: Comparison of neostigmine and edrophonium administered at 5% twitch height recovery. Br J Anaesth 59:478, 1987.

456. Donati F, McCarroll SM, Antzaka C et al: Dose-response curves for edrophonium, neostigmine, and pyridostigmine after pancuronium and *d*-tubocurarine. Anesthesiology 66:471, 1987.

457. Naguib M, Abdulatif M: Priming with anti-cholinesterases: The effect of different combinations of anti-cholinesterases and different priming intervals. Can J Anaesth 35:47, 1988.

457A. Savarese JJ: Reversal of nondepolarizing blocks: More controversial than ever? Review Course Lectures, 67th Congress, International Anesthesia Research Society. Cleveland, OH, 1993.

457B. Cronnelly R: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC 45) and pancuronium in anesthetized humans. Anesthesiology 58:405, 1983.

458. Kopman AF: Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions. Anesthesiology 65:572, 1986.

458A. Larijani GE: Comparative evaluation of the neuromuscular and cardiovascular effects of pipecuronium, pancuronium, atracurium, and vecuronium under isoflurane anesthesia. Pharmacotherapy 12:278, 1992.

459. Bevan DR, Smith CE, Donati F: Postoperative neuromuscular blockade: A comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 69:272, 1988.

459A. Gencarelli PJ, Miller RD: Antagonism of ORG NC 45 (vecuronium) and pancuronium neuromuscular blockade by neostigmine. Br J Anaesth 54:53, 1982.

459B. Savarese JJ, Ali HH, Basta SJ et al: The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 68:723, 1988.

459C. Caldwell JE: Comparison of the neuromuscular block induced by

mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. Br J Anaesth 63:393, 1989.

460. Abdulatif M: Recovery characteristics after early administration of anticholinesterases during intense mivacurium-induced neuromuscular block. Br J Anaesth 74:20, 1995.

460A. Kao YJ, Le ND: The reversal of profound mivacurium-induced neuromuscular blockade. Can J Anaesth 43:1128, 1996.

460B. Szenohradszky J: The effect of neostigmine on twitch tension and muscle relaxant concentration during infusion of mivacurium or vecuronium. Anesthesiology 83:83, 1995.

460C. Hart PS: Edrophonium increases mivacurium concentrations during constant mivacurium infusion, and large doses minimally antagonize paralysis. Anesthesiology 82:912, 1995.

461. Baurain MJ: Comparison of neostigmine-induced recovery with spontaneous recovery from mivacurium-induced neuromuscular block. Br J Anaesth 73:791, 1994.

461A. Bevan DR: Residual block after mivacurium with or without edrophonium reversal in adults and children. Anesthesiology 84:362, 1996.

461B. Lessard MR: Neostigmine requirements for reversal of neuromuscular blockade following an infusion of mivacurium. Can J Anaesth 44:836, 1997.

461C. Mirakhur RK: Spontaneous recovery or evoked reversal of neuromuscular block. Acta Anaesthesiol Scand Suppl 106:62, 1995.

462. Naguib M: Enzymatic antagonism of mivacurium-induced neuromuscular blockade by human plasma cholinesterase. Anesthesiology 83:694, 1995.

462A. Naguib M: Enzymatic versus pharmacologic antagonism of profound mivacurium-induced neuromuscular blockade. Anesthesiology 84:1051, 1996.

462B. Naguib M: Edrophonium and human plasma cholinesterase combination for antagonism of mivacurium-induced neuromuscular block. Br J Anaesth 77:424, 1996.

463. Ostergaard D: Reversal of intense mivacurium block with human plasma cholinesterase in patients with atypical plasma cholinesterase. Anesthesiology 82:1295, 1995.

463A. Delisle S: Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. Br J Anaesth 54:441, 1982.

464. Baurain MJ: Effects of residual concentrations of isoflurane on the reversal of vecuronium-induced neuromuscular blockade. Anesthesiology 74:474, 1991.

465. Dernovoi B: Neostigmine antagonism of vecuronium paralysis during fentanyl, halothane, isoflurane, and enflurane anesthesia. Anesthesiology 66:698, 1987.

466. Miller RD, Van Nyhuis LS, Eger EI II et al: The effect of acid-base balance on neostigmine antagonism of *d*-tubocurarine-induced neuromuscular blockade. Anesthesiology 42:377, 1975.

467. Miller RD, Roderick L: The influence of acid-base changes on neostigmine antagonism of pancuronium neuromuscular blockade. Br J Anaesth 50:317, 1978.

467A. Biro K: Effects of respiratory and metabolic alkalosis and acidosis on pipecuronium neuromuscular block. Eur J Pharmacol 154:329, 1988.

468. Feldman S: Effect of changes in electrolytes, hydration, and pH upon the reactions to muscle relaxants. Br J Anaesth 35:546, 1963.

469. Cohen EN: The choice and mode of administration of relaxants: Patients with altered sensitivity. Clin Anesth 2:75, 1966.

470. Cunningham JN Jr, Carter NW, Rector FC Jr et al: Resting transmembrane potential difference of skeletal muscle in normal subjects and severely ill patients. J Clin Invest 50:49, 1971.

470A. Miller RD, Roderick LL: Diuretic-induced hypokalemia, pancuronium neuromuscular blockade, and its antagonism by neostigmine. Br J Anaesth 50:541, 1978.

470B. Jones RM: Verapamil potentiation of neuromuscular blockade: Failure of reversal with neostigmine but prompt reversal with edrophonium. Anesth Analg 64:1021, 1985.

470C. Wali FA: Interaction of verapamil with gallamine and pancuronium and reversal of combined neuromuscular blockade with neostigmine and edrophonium. Eur J Anaesthesiol 3:385, 1986.

471. Wali FA: Interaction of verapamil with atracurium and reversal of combined neuromuscular blockade with edrophonium and neostigmine. Ir J Med Sci 156:215, 1987.

471A. Mackie K, Pavlin EG: Recurrent paralysis following piperacillin administration. Anesthesiology 72:561, 1990.

471B. Hasfurther DL, Bailey PL: Failure of neuromuscular blockade reversal after rocuronium in a patient who received oral neomycin. Can J Anaesth 43:617, 1996.

471C. Viby-Mogensen J: Interaction of other drugs with muscle relaxants. Sem Anesth 4:52, 1985.

472. Pavlin EG: T4/T1 does not predict recovery from vecuronium in the presence of gentamycin (abstract). Anesthesiology 79:A918, 1993.

472A. Mirakhur RK: Antagonism of the muscarinic effects of edrophonium with atropine or glycopyrrolate: A comparative study. Br J Anaesth 57:1213, 1985.

472B. Salem MG: Comparison between glycopyrrolate and atropine in a mixture with neostigmine for reversal of neuromuscular blockade: Studies in patients following open heart surgery. Br J Anaesth 57:184, 1985.

473. Fogdall RP, Miller RD: Antagonism of *d*-tubocurarine and pancuroniuminduced neuromuscular blockades by pyridostigmine in man. Anesthesiology 39:504, 1973.

473A. Dodd P: Glycopyrronium requirements for antagonism of the muscarinic side effects of edrophonium. Br J Anaesth 62:77, 1989.

473B. Triantafillou AN: Refractory bradycardia after reversal of muscle relaxant in a diabetic with vagal neuropathy. Anesth Analg 65:1237, 1986.

474. Caldwell JE: Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. Anesth Analg 80:1168, 1995.

475. Parlow JL: The duration of impairment of autonomic control after anticholinergic drug administration in humans. Anesth Analg 84:155, 1997.

476. van Vlymen JM: The effects of reversal of neuromuscular blockade on autonomic control in the perioperative period. Anesth Analg 84:148, 1997.

477. Cronnelly R, Stanski DR, Miller RD et al: Renal function and the pharmacokinetics of neostigmine in anesthetized man. Anesthesiology 51:222, 1979.

478. Cronnelly R, Stanski DR, Miller RD et al: Pyridostigmine kinetics with and without renal function. Clin Pharmacol Ther 28:78, 1980.

479. Morris RB, Cronnelly R, Miller RD et al: Pharmacokinetics of edrophonium and neostigmine when antagonizing *d*-tubocurarine neuromuscular blockade in man. Anesthesiology 54:399, 1981.

479A. Morris RB, Cronnelly R, Miller RD et al: Pharmacokinetics of edrophonium in anephric and renal transplant patients. Br J Anaesth 53:1311, 1981.

480. Kopman AF: Edrophonium antagonism of pancuronium-induced neuromuscular blockade in man: A reappraisal. Anesthesiology 51:139, 1979.

481. Bevan DR: Reversal of pancuronium with edrophonium. Anaesthesia 34:614, 1979.

481A. Heier T, Caldwell JE, Bhatia S et al: The influence of mild hypothermia on the efficacy and pharmacokinetics of neostigmine in volunteers. Anesthesiology 85:A812, 1996.

481B. Heier T, Caldwell JE, Sessler DI et al: Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 74:815, 1991.

481C. Wilson IB, Harrison MA, Ginsberg S: Carbamyl derivatives of acetylcholinesterase. J Biol Chem 238:1498, 1961.

481D. Barber HE, Calvey TN, Muir KT: The relationship between the pharmacokinetics, cholinesterase inhibition and facilitation of twitch tension of the quaternary ammonium anticholin- esterase drugs, neostigmine, pyridostigmine, edrophonium and 3hydroxyphenyltrimethylammonium. Br J Pharmacol 66:525, 1979.

481E. Verotta D, Kitts J, Rodriguez R et al: Reversal of neuromuscular blockade in humans by neostigmine and edrophonium: A mathematical model. J Pharmacokinet Biopharm 19:713, 1991.

482. Grob D, Namba T: Characteristics and mechanisms of neuromuscular block in myasthenia gravis. Ann N Y Acad Sci 274:143, 1976.

483. Engel WK: Myasthenia gravis, corticosteroids, anticholinesterase. Ann N Y Acad Sci 274:623, 1976.

484. Gracey DR, Howard FM Jr, Divertie B: Plasmapheresis in the treatment of ventilator-dependent myasthenia gravis. Chest 85:739, 1984.

485. Seybold ME: Myasthenia gravis: A clinical and basic science review. JAMA 250:2516, 1983.

486. Buzello W, Noeldge G, Krieg N et al: Vecuronium for muscle relaxation in patients with myasthenia gravis. Anesthesiology 64:507, 1986.

487. Eisenkraft JB, Mann SM, Book WJ et al: Succinylcholine doseresponse in myasthenia gravis. Anesthesiology 69:760, 1988.

488. Feldman SA: Muscle relaxants in pathologic states. In Muscle Relaxants. Philadelphia, WB Saunders, 1979, p 108.

489. Hedley-Whyte J, Burgess GE III, Feeley TW et al: Respiratory management of peripheral neurologic disease. In Applied Physiology of Respiratory Care. Boston, Little, Brown, 1976, p 245.

490. Hook R, Anderson EF, Noto P: Anesthetic management of a parturient with myotonia atrophica. Anesthesiology 43:689, 1975.

491. Mitchell MM, Ali HH, Savarese JJ: Myotonia and neuromuscular blocking agents. Anesthesiology 49:44, 1978.

492. Siler JN, Discavage WJ: Anesthetic management of hypokalemic periodic paralysis. Anesthesiology 43:489, 1975.

493. Flewellen EH, Bodensteiner JB: Anesthetic experience in a patient with hyperkalemic periodic paralysis. Anesth Rev 7:44, 1980.

494. Rosenbaum KJ, Neigh JL, Strobel GE: Sensitivity to nondepolarizing muscle relaxants in amyotrophic lateral sclerosis: Report of two cases. Anesthesiology 35:638, 1971.

495. Hogue CW, Itani MS, Martyn JAJ: Resistance of *d*-tubocurarine in lower motor neuron injury is related to increased acetylcholine receptors at the neuromuscular junction. Anesthesiology 71:A1203, 1989.

496. Graham DH: Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. Anesthesiology 52:74, 1980.

497. Moorthy SS, Hilgenberg JC: Resistance to nondepolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia. Anesth Analg 59:624, 1980.

498. Allen CM, Cullen WG, Gillies DMW: Ventricular fibrillation in a burned boy. Can Med Assoc J 85:432, 1961.

499. Schaner PJ, Brown RL, Kirksey TD et al: Succinylcholine-induced hyperkalemia in burned patients. Anesth Analg 48:764, 1969.

500. Lowenstein E: Succinylcholine administration in the burned patient. Anesthesiology 27:494, 1966.

501. Belin KP, Carleen CI: Cardiac arrest in the burned patient following succinylcholine administration. Anesthesiology 27:516, 1966.

502. Martyn JAJ, White DA, Gronert GA et al: Up-and-down regulation of skeletal muscle acetylcholine receptors. Anesthesiology 76:822, 1992.

503. Kim C, Fuke N, Martyn JAJ: Thermal injury to rat increases nicotinic acetylcholine receptors in diaphragm. Anesthesiology 68:401, 1988.

504. Martyn JAJ, Matteo RS, Szyfelbien SK et al: Unprecedented resistance to neuromuscular blocking effects of metocurine with persistence after complete recovery in a burned patient. Anesth Analg 61:614, 1982.

505. Reeves ST, Turcasso NM: Nondepolarizing neuromuscular blocking drugs in the intensive care unit: A clinical review. South Med J 90:769, 1997.

506. Hansen-Flaschen JH, Brazinsky S, Basile C et al: Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure: A national survey. JAMA 266:2870, 1991.

507. Klessig HT, Geiger HJ, Murray MJ et al: A national survey on the practice patterns of anesthesiologist intensivists in the use of muscle relaxants. Crit Care Med 20:1341, 1992.

508. Newman PJ, Quinn AC, Grounds RM et al: A comparison of cisatracurium (51W89) and atracurium by infusion in critically ill patients. Crit Care Med 25:1139, 1997.

509. Prielipp RC, Robinson JC, Wilson JA et al: Dose response, recovery, and cost of doxacurium as a continuous infusion in neurosurgical intensive care unit patients. Crit Care Med 25:1236, 1997.

510. Sparr HJ, Wierda JMKH, Proost JH et al: Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients. Br J Anaesth 78:267, 1997.

511. Bishop MJ: Hemodynamic and gas exchange effects of pancuronium bromide in sedated patients with respiratory failure. Anesthesiology 60:369, 1984.

511A. Coggeshall JW, Marini JJ, Newman JH: Improved oxygenation after muscle relaxation in adult respiratory distress syndrome. Arch Intern Med 145:1718, 1985.

511B. Conti G, Vilardi V, Rocco M et al: Paralysis has no effect on chest wall and respiratory system mechanics of mechanically ventilated, sedated patients. Intensive Care Med 21:808, 1995.

512. Parker MM, Schubert W, Shelhamer JH et al: Perceptions of a critically ill patient experiencing therapeutic paralysis in an ICU. Crit Care Med 12:69, 1984.

513. Loper KA, Butler S, Nessly M et al: Paralyzed with pain: The need for education. Pain 37:315, 1989.

514. Hallenberg B, Bergbom EI, Haljamae H: Patients' experiences of postoperative respirator treatment: Influence of anaesthetic and pain treatment regimens. Acta Anaesthesiol Scand 34:557, 1990.

515. Khuenl-Brady KS, Reitstatter B, Schlager A et al: Long-term administration of pancuronium and pipecuronium in the intensive care unit. Anesth Analg 78:1082, 1994.

516. Murray MJ, Coursin DB, Scuderi PE et al: Double-blind, randomized, multicenter study of doxacurium vs. pancuronium in intensive care unit patients who require neuromuscular-blocking agents. Crit Care Med 23:450, 1995.

516A. Op de Coul AAW, Lambregts PCLA, Koeman J et al: Neuromuscular complications in patients given Pavulon (pancuronium bromide) during artifical ventilation. Clin Neurol Neurosurg 87:17, 1985.

516B. Hansen-Flaschen J, Cowen J, Raps EC: Neuromuscular blockade in the intensive care unit: More than we bargained for. Am Rev Respir Dis 147:234, 1993.

516C. Rudis MI, Guslits BJ, Peterson EL et al: Economic impact of prolonged motor weakness complicating neuromuscular blockade in the intensive care unit. Crit Care Med 24:1749, 1996.

517. Zochodne DW, Bolton CF, Wells GA et al: Critical illness polyneuropathy: A complication of sepsis and multiple organ failure. Brain 110:819, 1987.

517A. Kupfer Y, Namba T, Kaldawi E et al: Prolonged weakness after long-term infusion of vecuronium bromide. Ann Intern Med 117:484, 1992.

517B. Segredo V, Caldwell JE, Matthay MA et al: Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 327:524, 1992.

517C. Segredo V, Matthay MA, Sharma ML et al: Prolonged neuromuscular blockade after long-term administration of vecuronium in two critically ill patients. Anesthesiology 72:566, 1990.

517D. Caldwell JE, Szenohradszky J, Segredo V et al: The pharmacodynamics and pharmacokinetics of the metabolite 3-desacetylvecuronium (ORG 7268) and its parent compound, vecuronium, in human volunteers. J Pharm Exp Ther 270:1216, 1994.

518. Shee CD: Risk factors for hydrocortisone myopathy in acute severe asthma. Respir Med 84:229, 1990.

519. Danon MJ, Carpenter S: Myopathy with thick filament (myosin) loss following prolonged paralysis with vecuronium during steroid treatment. Muscle Nerve 14:1131, 1991.

520. De Smet Y, Jaminet M, Jaeger U et al: [Acute corticosteroid myopathy in patient with asthma]. Rev Neurol (Paris) 147:682, 1991.

521. Meyer KC, Prielipp RC, Grossman JE et al: Prolonged weakness after infusion of atracurium in two intensive care unit patients. Anesth Analg 78:772, 1994.

522. Douglass JA, Tuxen DV, Horne M et al: Myopathy in severe asthma. Am Rev Respir Dis 146:517, 1992.

523. Tousignant CP, Bevan DR, Eisen AA et al: Acute quadriparesis in an asthmatic treated with atracurium. Can J Anaesth 42:224, 1995.

524. Hirano M, Ott BR, Raps EC et al: Acute quadriplegic myopathy: A complication of treatment with steroids, nondepolarizing blocking agents, or both. Neurology 42:2082, 1992.

525. Giostra E, Magistris MR, Pizzolato G et al: Neuromuscular disorder in intensive care unit patients treated with pancuronium bromide: Occurrence in a cluster group of seven patients and two sporadic cases, with electrophysiologic and histologic examination. Chest 106:210, 1994.

526. Op de Coul AA, Verheul GA, Leyten AC et al: Critical illness polyneuromyopathy after artifical respiration. Clin Neurol Neurosurg 93:27, 1991.

527. Gooch JL, Suchyta MR, Balbierz JM et al: Prolonged paralysis after treatment with neuromuscular junction blocking agents. Crit Care Med 19:1125, 1991.

528. Yate PM, Flynn PJ, Arnold RW et al: Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. Br J Anaesth 59:211, 1987.

529. Callanan DL: Development of resistance to pancuronium in adult respiratory distress syndrome. Anesth Analg 64:1126, 1985.

530. Coursin DB, Klasek G, Goelzer SL: Increased requirements for continously infused vecuronium in critically ill patients. Anesth Analg 69:518, 1989.

531. Kushimo OT, Darowski MJ, Morris P et al: Dose requirements of atracurium in paediatric intensive care patients. Br J Anaesth 67:781, 1991.

532. Hogue CJ, Ward JM, Itani MS et al: Tolerance and upregulation of

acetylcholine receptors follow chronic infusion of *d*-tubocurarine. J Appl Physiol 72:1326, 1992.

533. Vanderheyden BA, Reynolds HN, Gerold KB et al: Prolonged paralysis after long-term vecuronium infusion. Crit Care Med 20:304, 1992.

533A. Appadu BL, Greiff JM, Thompson JP: Postal survey on the long-term use of neuromuscular block in the intensive care. Intensive Care Med 22:862, 1996.

533B. Kleinpell R, Bedrosian C, McCormick L et al: Use of peripheral nerve stimulators to monitor patients with neuromuscular blockade in the ICU. Am J Crit Care 5:449, 1996.

533C. Couch NS, Dorgan NE: Vecuronium use in MICU: A quality improvement study. Nurs Manage 24:96J, 1993.

533D. Strange C, Vaughan L, Franklin C et al: Comparison of train-of-four and best clinical assessment during continuous paralysis. Am J Respir Crit Care Med 156:1556, 1997

533E. Zarowitz BJ, Rudis MI, Lai K et al: Retrospective pharmacoeconomic evaluation of dosing vecuronium by peripheral nerve stimulation versus standard clinical assessment in critically ill patients. Pharmacotherapy 17:327, 1997.

534. Darrah WC, Johnston JR, Mirakhur RK: Vecuronium infusions for prolonged muscle relaxation in the intensive care unit. Crit Care Med 17:1297, 1989.

535. Schwartz DE, Kelly B, Caldwell JE et al: Succinylcholine-induced hyperkalemic arrest in a patient with severe metabolic acidosis and exsanguinating hemorrhage. Anesth Analg 75:291, 1992.

535A. Castillo J, Sierra P, Escolano F, et al: [Succinlycholine induces hyperpotassemia in patients in critically ill patients]. Rev Esp Anestesiol Reanim 43:349, 1996.

536. Antognini JF, Gronert GA: Succinylcholine causes profound hyperkalemia in hemorrhagic, acidotic rabbits. Anesth Analg 77:585, 1993.

536A. Antognini JF: Splanchnic release of potassium after hemorrhage and succinylcholine in rabbits. Anesth Analg 78:687, 1994.

536B. Sparr HJ, Giesinger S, Ulmer H et al: Influence of induction technique on intubating conditions after rocuronium in adults: Comparison with rapid-sequence induction using thiopentone and suxamethonium. Br J Anaesth 77:339, 1996.

536C. Sparr HJ, Luger TJ, Heidegger T et al: Comparison of intubating conditions after rocuronium and suxamethonium following "rapid-sequence induction" with thiopentone in elective cases. Acta Anaesthesiol Scand 40:425, 1996.

537. Griffiths RB, Hunter JM, Jones RS: Atracurium infusions in patients with renal failure on an ITU. Anaesthesia 41:375, 1986.

537A. Beemer GH, Dawson PJ, Bjorksten AR et al: Early postoperative seizures in neurosurgical patients administered atracurium and isoflurane. Anaesth Intensive Care 17:504, 1989.

538. Eddleston JM, Harper NJ, Pollard BJ et al: Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma during intracranial surgery. Br J Anaesth 63:525, 1989.

539. Powles AB, Ganta R: Use of vecuronium in the management of tetanus. Anaesthesia 40:879, 1985.

540. Chapple DJ, Miller AA, Ward JB et al: Cardiovascular and neurological effects of laudanosine: Studies in mice and rats and in conscious and anaesthetized dogs. Br J Anaesth 59:218, 1987.

540A. Dear GJ, Harrelson JC, Jones AE et al: Identification of urinary and biliary conjugated metabolites of the neuromuscular blocker 51W89 by liquid chromatography/mass spectrometry. Rapid Commun Mass Spectrom 9:1457, 1995.

540B. Pearson AJ, Harper NJ, Pollard BJ: The infusion requirements and recovery characteristics of cisatracurium or atracurium in intensive care patients. Intensive Care Med 22:694, 1996.

540C. Gwinnutt CL, Eddleston JM, Edwards D et al: Concentrations of atracurium and laudanosine in cerebrospinal fluid and plasma in three intensive care patients. Br J Anaesth 65:829, 1990.

541. Szenohradszky J, Trevor AJ, Bickler P et al: Central nervous system effects of intrathecal muscle relaxants in rats. Anesth Analg 76:1304, 1993.

542. Miller RD: Clinical pharmacology of vecuronium and atracurium. Anesthesiology 61:444, 1984.

543. Durfee DD: A practical approach to achieving a $950,000 cost savings from a joint anesthesia-pharmacy program. Hosp Pharm 30:957, 1995.

544. Gora-Harper ML: Effect of prescribing guidelines on the use of neuromuscular blocking agents. Am J Health Syst Pharm 52:1900, 1995.

545. Souetre EJ: Methodological approaches to pharmaco-economics. Fundam Clin Pharmacol 8:101, 1994.

546. Viby-Mogensen J: Residual curarization in the recovery room. Anesthesiology 50:539, 1979.

547. Bevan DR: Postoperative neuromuscular blockade: A comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 69:272, 1988.

548. Kopman AF: Recovery times following edrophonium and neostigmine reversal of pancuronium, atracurium, and vecuronium steady-state infusions. Anesthesiology 65:572, 1988.

549. Larijani GE: Comparative evaluation of the neuromuscular and cardiovascular effects of pipecuronium, pancuronium, atracurium, and vecuronium under isoflurane anesthesia. Pharmacotherapy 12:278, 1992.

550. Pavlin EG: Recovery of airway protection compared with ventilation in humans after paralysis with curare. Anesthesiology 70:381, 1989.

551. Eriksson LI: Reduced hypoxic chemosensitivity in partially paralysed man: A new property of muscle relaxants? Acta Anaesthesiol Scand 40:520, 1996.

552. Eriksson LI: Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: Simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology 87:1035, 1997.

553. Kopman AF: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 86:765, 1997.

554. Viby-Mogensen J: Residual neuromuscular block is a risk factor for postoperative pulmonary complications: A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 41:1095, 1997.

555. Ballantyne JC: The impact of choice of muscle relaxant on postoperative recovery time: A retrospective study. Anesth Analg 85:476, 1997.

556. Lubarsky DA: The successful implementation of pharmaceutical practice guidelines: Analysis of associated outcomes and cost savings. SWiPE Group. Systematic Withdrawal of Perioperative Expenses. Anesthesiology 86:1145, 1997.

557. Butterworth J: Do shorter-acting neuromuscular blocking drugs or opioids associate with reduced intensive care unit or hospital lengths of stay after coronary artery bypass grafting? CABG Clinical Benchmarking Data Base Participants. Anesthesiology 88:1437, 1998.

Chapter 13 - Local Anesthetics

Charles B. Berde
Gary R. Strichartz

INTRODUCTION

Local anesthesia may be produced by many tertiary amine bases, certain alcohols, and a variety of other drugs and toxins. However, all currently available clinically useful agents are either aminoesters or aminoamides. These drugs, when applied in sufficient concentration at the site of action, prevent conduction of electrical impulses by the membranes of nerve and muscle. When local anesthetics are given systemically, the functions of cardiac, skeletal, and smooth muscle, as well as the transmission of impulses in the peripheral nervous system and the central nervous system (CNS) and within the specialized conducting system of the heart, may all be altered. Local anesthetics may provide analgesia in various parts of the body by topical application, injection in the vicinity of peripheral nerve endings and major nerve trunks, or instillation within the epidural or subarachnoid spaces. Toxicity may be local or systemic. The CNS and cardiovascular system are most commonly involved in acute clinical toxicity.

BASIC PHARMACOLOGY

Chemistry

Local Anesthetic Molecule

The typical local anesthetic molecule, exemplified by lidocaine and procaine (Fig. 13-1) , is a tertiary amine attached to a substituted aromatic ring by an intermediate chain. The tertiary amine is a base (proton acceptor). The chain always contains either an ester

or amide

linkage; local anesthetics may therefore be classified as aminoester or aminoamide compounds. The aromatic ring system gives a lipophilic character to its portion of the molecule, whereas the tertiary amine end is relatively hydrophilic, particularly because it is partially protonated and thus bears some positive charge in the physiologic pH range. Lidocaine, for example, is 65 percent protonated at pH 7.4. The structures of commonly administered local anesthetic drugs are given in

TABLE 13-1 -- Representative Local Anesthetic Agents in Common Clinical Use

(Not Available)

Modified from Covino and Vassallo [1,2,3]

Figure 13-1 Structures of two local anesthetics, the aminoamide lidocaine and the aminoester procaine. In both drugs, a hydrophobic aromatic group is joined to a more hydrophilic base, the tertiary amine, by an intermediate bond.

Table 13-1 (Table Not Available) , and their physicochemical properties are listed in Table 13-2 (Table Not Available) .

Structure-Activity Relations and Physicochemical Properties

The intrinsic potency and duration of action of local anesthetics are clearly dependent on certain features of the molecule.

Lipophilic-Hydrophilic Balance

The lipophilic versus hydrophilic character of the local anesthetic depends on the size of alkyl substituents on or near the tertiary amine and on the aromatic ring. Lipophilicity expresses the tendency of a compound to associate with membrane lipids, usually approximated by the equilibrium partitioning into a hydrophobic solvent such as octanol. [1] Such octanol/buffer partition coefficients are comparable with membrane/buffer partition coefficients for the uncharged species of local anesthetics, but they greatly underestimate the membrane partitioning for the charged, protonated species, octanol being a poor model for the polar regions near the membrane surface. [2] In this chapter, we use the term hydrophobicity, expressed by octanol/buffer partitioning, to describe a physicochemical property of local anesthetics.

Compounds with a more hydrophobic nature are obtained by increasing the size of the alkyl substituents. These agents are more potent and produce longer-lasting blocks than their less hydrophobic congeners. [3] [4] [5] For example, etidocaine, which has three more carbon atoms than lidocaine in the amine end of the molecule, is four times as potent and five times as long-lasting when these compounds are compared in the isolated frog sciatic nerve.

Hydrogen Ion Concentration

Local anesthetics in solution exist in a chemical equilibrium between the basic uncharged form (B) and the charged cationic form (BH^+). At a certain hydrogen ion concentration ($\log_{10}{}^{-1}$ [-pH]) specific for each drug, the concentration of local anesthetic base is equal to the concentration of charged cation. This hydrogen ion concentration is called the pK_a . The relationship is defined by

The pK_a values for standard local anesthetic agents are listed in Table 13-2 (Table Not Available) . The tendency to be protonated also depends on environmental factors, such as temperature and ionic strength, and on the medium surrounding the drug. [1] In the relatively apolar milieu of a membrane, the average pK_a of local anesthetics is lower than in solution. [6] This is chemically equivalent to saying that the membrane concentrates the base form of the local anesthetic more than it

concentrates the protonated cations.

TABLE 13-2 -- Relative In Vitro Conduction Blocking Potency and Physiochemical Properties of Local Anesthetic Drugs

(Not Available)

From Strichartz, et al [131]

Figure 13-2 (Figure Not Available) The fraction of local anesthetic in the protonated, cationic form of aqueous solution at physiologic pH (7.4) as a function of the pK_a of the drug. *(From Covino and Vassallo* [123] *)*

The pH of the medium into which the local anesthetic is injected influences drug activity by altering the relative percentage of agent present in the basic or protonated forms. The relationship between pK_a and the percentage of local anesthetic present in the cationic form is shown in Figure 13-2 (Figure Not Available) . As described later, there are dual effects of pH, depending on where the local anesthetic is injected and on the importance of the base form for tissue penetration.

ANATOMY OF THE PERIPHERAL NERVE

Each peripheral nerve axon possesses its own cell membrane, the axolemma. Nonmyelinated nerves, such as autonomic postganglionic and nociceptive afferent C fibers, are encased in a single Schwann cell sheath. Most large motor and sensory fibers are enclosed in many layers of myelin, which consists of plasma membranes of specialized Schwann cells that wrap themselves around the axon during axonal outgrowth. Myelin greatly increases the speed of nerve conduction by insulating the axolemma from the surrounding conducting salt medium and forcing the action current to flow through the axoplasm to the nodes of Ranvier, which are periodic interruptions in the myelin sheath where the action currents are regenerated (Fig. 13-3) . The Na^+ channels that serve impulse generation and propagation are highly concentrated at the nodes of Ranvier of myelinated fibers, [7] but they are distributed all along the axon of nonmyelinated fibers (see Fig. 13-3) . A classification of peripheral nerves according to fiber size and physiologic properties is presented in Table 13-3 (Table Not Available) .

A typical peripheral nerve consists of several axon bundles, or fascicles. Each axon has its own connective tissue covering, the endoneurium. Each fascicle of axons is encased by a second connective tissue layer, the perineurium, and the entire nerve is wrapped in a loose outer sheath called the epineurium (Fig. 13-4) . To reach its site of action (the nerve axon), a local anesthetic molecule must traverse four or five layers of connective tissue and/or lipid membranous barriers.

Structure of the Axonal Membrane

Biologic membranes consist of a molecular lipid bilayer containing proteins adsorbed on the surfaces as well as embedded in or spanning the hydrocarbon core (Fig. 13-5) . The bilayer character is imposed by the amphiphilic phospholipids, which have long hydrophobic fatty acyl tails that lie in the center of the membrane and polar hydrophilic head groups composed of zwitterionic (containing positive and negative charges) components that project into the cytoplasm or the interstitial fluid. Within the membrane there is some lateral and rotational diffusion, which allows lipids and certain proteins to migrate in a fluid mosaic, but most membrane proteins are fixed within specific regions of a membrane. [7]

A dynamic interaction exists between the cell's membrane and cytoplasm. Although we focus here on the channel-blocking actions of local anesthetics, it is noteworthy that many other cellular activities are inhibited by these drugs.

Physiology of Nerve Conduction

The neural membrane is able to maintain a voltage difference of 60 to 90 mV between its inner and outer aspects because at rest it is relatively impermeable to sodium ions but is selectively permeable to potassium ions. An active, energy-dependent

Figure 13-3 The direction of action currents flowing in a large nonmyelinated axon (e.g., of the squid) **(A)** and in a myelinated axon **(B).** During propagation of impulses from left to right, current entering the axon at the initial rising phase of the impulse (open arrows) passes down the axoplasm (local circuit current) and depolarizes the adjacent membrane. This ionic current passes uniformly along the nonmyelinated axon but is funneled from one node of Ranvier to another in the myelinated axon.

TABLE 13-3 -- Classification of Peripheral Nerves According to Fiber Size and Physiologic Properties

(Not Available)

Modified from Bonica [234]

mechanism, the Na^+ -K^+ pump, sustains the ion gradients that drive this potential difference by constant extrusion of sodium from within the cell in exchange for a net uptake of potassium, using adenosine triphosphate as an energy source. Although the membrane is relatively permeable to potassium ions, an intracellular-to-extracellular potassium ratio of 150 mmol/L to 5 mmol/L, or 30:1, is maintained because of the membrane's impermeability to other, potentially cotransported ions and the active removal of potassium.

The nerve at rest behaves largely as a potassium electrode, according to the Nernst equation:

where E_m is the membrane potential; E_k is the potassium equilibrium potential; R is the gas constant; T is temperature (Kelvin); F is Faraday's constant; and $[K^+]$ is the potassium ion concentration inside (i) and outside (o) the cell. For potassium, therefore,

An opposite situation exists for Na^+ , which is at higher concentration outside the cell and has a Nernst potential, E_{Na} , of about +60 mV. During an action potential, the nerve membrane transiently switches its permeability from K^+ selective to Na^+ selective, thus changing the membrane potential from negative to positive, and back again. [8] The progress of this potential change and the underlying events are graphed in Figure 13-6 . They provide a basis for understanding local anesthetic conduction block.

Ion permeation through membranes occurs via special proteins called ion channels. [9] The conformation of these channels is often sensitive to the membrane potential; both Na^+ and K^+ channels in nerve membranes are activated to an open conformation by membrane depolarization. Sodium channels, in addition, close to an inactivated conformation following their initial activation. A small membrane depolarization, extending along an axon from a region of excited membrane for example, begins to open both Na^+ and K^+

Figure 13-4 Transverse sections of a peripheral nerve **(A)** showing the outermost epineurium, the inner perineurium that collects nerve axons in fascicles, and the endoneurium that surrounds each myeli-nated fiber. Each myelinated axon **(B)** is encased in the multiple membranous wrappings of myelin formed by one Schwann cell, each of which stretches longitudinally over approximately 100 times the diameter of the axon. The narrow span of axon between these myelinated segments, the node of Ranvier, contains the ion channels that support action potentials. Nonmyelinated fibers (C) are enclosed in bundles of 5 to 10 axons by a chain of Schwann cells that tightly embrace each axon with but one layer of membrane.

Figure 13-5 Drawing of a typical plasma membrane showing the lipid bilayer composed of phospholipids and cholesterol molecules (in a 10:1 ratio), embedding the membrane integral proteins, and the relationship of the cytoplasmic peripheral proteins and the carbohydrate moieties facing the extracellular medium. Probable sites for local anesthetics are also shown.

channels. The Na^+ channels open faster, however, and because the membrane potential is initially much further from the Nernst potential for Na^+ than from that for K^+, the inwardly directed Na^+ current is larger (see Fig. 13-6) . Sodium ions thus entering the nerve depolarize it further, leading to the opening of more Na^+ channels and increasing the current even further (Fig. 13-7) . This sequence of events continues in the *positive feedback of the depolarizing phase* until some of the Na^+ channels have become inactivated and enough of the potassium channels have opened to change the balance of current, resulting in a net outward current that produces membrane repolarization (see Fig. 13-7) . After one action potential, the concentrations of Na^+ and K^+ have changed very little. The small amount of Na^+ entering and K^+ leaving the cell as a result of this process is restored by the Na^+-K^+ pump. [10]

Depolarizations too weak to activate enough Na^+ channels to produce a net inward current are below the membrane's excitability threshold. The precise value of the threshold varies among different regions of the cell and also changes with time. Directly after an impulse, when some Na^+ channels are still inactivated and some K^+ channels still activated, the threshold is higher than the resting value, and the membrane is refractory to stimulation. In the immediately repolarized membrane, as Na^+ inactivation decays and as K^+ channels return to their closed conformation, the original threshold value is progressively restored.

The impulse is a wave of depolarization that is propagated along the axon by a continuous coupling between excited and nonexcited regions of membrane. Ionic current (the action current) entering the axon in the excited, depolarized region flows down the axoplasm and exits through the surrounding membrane, thus passively depolarizing the adjacent region (see Fig. 13-3) . Although this *local circuit current* spreads away from the excited zone in both directions, the region behind the impulse, having just been depolarized, is absolutely refractory, and impulse propagation is thus unidirectional.

The local circuit current spreads rapidly along a length of insulated internode in a myelinated axon (see Fig. 13-3) , and many nodes of Ranvier in sequence are depolarized to threshold with little intervening delay. Single impulses do not jump from node to node as separate, discrete events, but instead the active depolarization occurs simultaneously along several centimeters of the largest axons [11] (see Fig. 13-10) (Figure Not Available) . Indeed, the local circuit current is so robust that it can skip past two completely nonexcitable nodes and may successfully stimulate a third. [12] If nodal excitability is partially reduced, by inhibition of some of the Na^+ channels for example, the amplitude of impulses in successive nodes falls decrementally, a process that can continue for many centimeters. [13] This situation probably occurs during certain phases of local anesthesia, as discussed later. However, when the inhibition of Na^+ channels is sufficient, so that local circuit current fails to bring the adjacent resting region to threshold, then the impulse is extinguished.

Figure 13-6 Membrane potential (E_m), conductances of sodium (g_{Na}) and potassium (g_K), and the corresponding membrane currents (I_{Na} and I_K) that occur during a propagated action potential. Modeled from the original studies of Hodgkin and Huxley on the squid giant axon (see Hodgkin [9]), these relationships hold for almost all invertebrate and vertebrate nerve fibers. The direction of the total ionic current (I_t), which is the sum of I_{Na} and I_K, is inward (negative values) for the depolarizing phase of the action potential and outward (positive values) for the repolarizing phase.

MECHANISM OF ACTION OF LOCAL ANESTHETICS (PHARMACODYNAMICS)

Active Form

Local anesthetic bases are poorly to sparingly soluble in water, but they are soluble in relatively hydrophobic organic solvents. Therefore, as a matter of convenience, most of these drugs are marketed as the hydrochloride salts. The pK_a of the drug and the tissue pH determine the amount of drug that exists in solution as free base or as positively charged cation when injected into living tissue (see earlier). Furthermore, the uptake of the drug by the tissue, largely resulting from lipophilic adsorption, also alters its activity, both by shifting the effective pK_a downward, and thereby favoring the neutral base form, and by limiting the diffusion of the anesthetic away from the site of injection. Moderately hydrophobic local anesthetics act more rapidly than either hydrophilic or highly hydrophobic agents, delivered at the same concentration, for the following reasons. Moderately hydrophilic local anesthetics, such as lidocaine, are less bound to tissues than are very hydrophobic drugs (i.e., tetracaine), but they still are more membrane permeant than very hydrophilic ones (e.g., chlorprocaine). The highly hydrophobic local anesthetics also have higher intrinsic potency [4] (see Table 13-2) (Table Not Available) , they are used in lower concentrations, and their rate of onset is correspondingly reduced.

A lengthy debate has taken place over the issue of which form of the local anesthetic, charged cation or neutral base, is actually responsible for impulse blockade. Early observations showed that alkaline solutions of local anesthetics more effectively blocked nerve conduction. [14] In the desheathed nerve and in the isolated single axon, the rate of inhibition by tertiary amine anesthetics also was greater at alkaline than at neutral external pH. [15] [16] From these observations, it was concluded that either the neutral base in the external solution is the active species or membrane penetration and transport, highly favored by base over cation species, are essential for the channel-blocking action. The second possibility is, in fact, the explanation for the acceleration of rate in alkaline media. [15] [16] [17] Direct control of axoplasmic pH [18] or internal perfusion with permanently charged quaternary amine homologues shows the dominant potency of the cationic species acting from the cytoplasmic surface. [19] [20] The uncharged base also has intrinsic pharmacologic activity, however, and in addition to those molecules with tertiary amine moieties, those having hydroxyl (alcohols) or alkyl groups (e.g., benzocaine) can also inhibit Na^+ channels and may block impulses. [16] [17] [21] [22]

To obtain a clear picture of the mechanism, the channel-inhibitory kinetics are necessary, but it is almost impossible to measure the rate of binding of local anesthetics to the receptor after their addition to a bathing solution. Drug diffusion through the unstirred layer of solution next to the membrane and the membrane itself present steps that limit the

Figure 13-7 Factors contributing to the regenerative, depolarizing phase of the action potential. Positive factors (solid arrows) increase the rate of depolarization, each element in the cycle favoring the subsequent one. Negative factors (open arrows) decrease the depolarization rate by reducing or opposing the related positive factor.

rate of receptor binding. [16] [23] However, once the drug has equilibrated with membranes and solutions, it is possible to perturb the channels by depolarizing the membrane and to follow the phasic inhibition by local anesthetics in order to clarify the details of the binding reaction, as described later.

Electrophysiologic Effect of Local Anesthetics

The resting membrane potential of nerve is little affected by local anesthetics. [24] As the concentration of local anesthetic applied to the nerve is increased, a decrease in the rate and degree of impulse depolarization is produced. Until the impulse is abolished, however, it is not possible to derive direct data on the binding of local anesthetics to Na^+ channels from measurement of nerve impulses.

By using a voltage-clamp procedure instead, Na^+ currents and their inhibition by local anesthetics can be directly assayed (Fig. 13-8) (Figure Not Available) . When the membrane is rapidly depolarized to a constant value by voltage-clamp, the time course of ionic currents is observed. Sodium currents are reduced during one initial depolarization by subclinical doses of local anesthetic (e.g., 0.2 mmol/L lidocaine) and are totally abolished by clinical doses (e.g., 1% lidocaine, which equals about 40 mmol/L). If the test depolarization is repeatedly applied, for example, at frequencies higher than 5 Hz (5 pulses/s), the partially depressed (tonically inhibited) Na^+ current is further reduced, incrementally for each pulse, until a new steady-state level of inhibition is reached. [20] [25] This frequency-dependent inhibition, also called *phasic inhibition*, is reversed when stimulation is slowed or stopped, and currents return to the level of tonic inhibition observed in the resting nerve. The potency for local anesthetics to produce both tonic and phasic inhibition is similarly dependent on their structure, hydrophobicity, and pK_a . [25] [26] At its simplest, there appears to be a single binding site for local anesthetics on the Na^+ channel, with a tonic affinity at rest and increased phasic affinity occurring as a result of depolarization. The phasic blocking mode can thus be used to reveal the true kinetics of local anesthetic binding to the functional receptor, the Na^+ channel itself.

There are two fundamental mechanisms of inhibition. Na^+ currents are reduced by local anesthetics primarily because the drug-bound channels fail to open. Investigations with neutral and cationic compounds show that the channel-activation process is disrupted by local anesthetics. [27] [28] A sodium channel inhibited by a local anesthetic is functionally similar to an inactivated channel; both inactivation and anesthetic binding prevent the complete conformational changes of the activation process by partially immobilizing the channel. [29] Blockade of the ion-conducting pore, the second mechanism, plays a part in channel inhibition, but the contribution from this action seems minor.

Figure 13-8 (Figure Not Available) Inhibition of Na^+ currents in myelinated nerves exposed to lidocaine or to bupivacaine. Traces show the inward ionic currents during a 16-ms-long depolarization to -20 mV, before drug addition (control), for the first depolarization imposed 5 minutes after beginning drug exposure (0, tonic inhibition), and for the subsequent pulses in a train of depolarizations applied to 10 Hz (identified numerically by their order in the sequence; use-dependent inhibition). T = 13°C. Toad node of Ranvier. *(From Chernoff [38])*

Figure 13-9 Schematic drawing of drug access routes to a putative local anesthetic binding site on the Na^+ channel. The hydrophilic route, from the cytoplasmic phase, mediates binding of aqueous drug (L_a) directly to the receptor site. The hydrophobic route mediates binding to membrane-associated drug (L_m) to the site. The activated channel (induced by membrane depolarization) binds drug more tightly than the resting channel, but both states of the protein appear to favor the hydrophobic route.

Are inactivated channels essential for local anesthetic binding and action? No, because when inactivation is prevented by various chemical reagents or toxins, there

is only a small change in the tonic and phasic actions of local anesthetics. [30] Phasic channel inhibition occurs during depolarizations that are as short as neuronal impulses (1-5 ms) because local anesthetics bind more rapidly and with higher affinity to activated channels (some open, some in intermediate activated conformations preceding the open state) than to resting channels. During longer depolarizations, additional binding to drug-free inactivated channels also can occur [17] [25] ; this mode of binding probably accounts for much of the cardiotherapeutic action of local anesthetic-like class I antiarrhythmics. [31] [32]

Regardless of the channel state that binds the drug, by its very binding the local anesthetic stabilizes that state. During phasic block, therefore, more channels become drug-bound during activation, and reciprocally, less activation can occur. Thus, overall binding of anesthetic is increased by channel activation for two reasons: more binding sites become accessible during activation (the guarded receptor model), [33] and drug dissociation from activated channels is slower than from resting channels (the modulated receptor model). [17]

The specific binding rates and affinities for the different conformations of the sodium channel depend on the particular local anesthetic drug. When the details of this dependence are correlated with the physicochemical properties of the drug and with the experimental conditions, they provide insight into the nature of the local anesthetic binding site. [4] [5]

Nature of the Local Anesthetic Binding Site

Kinetic and equilibrium measurements of inhibition by diverse local anesthetics reveal much about the binding site. Like the rate of onset of tonic block, the rate of binding for phasic block is greater at more alkaline external pH. [26] Curiously, cytoplasmic pH has almost no effect on phasic inhibition. [34] Drugs of greater hydrophobicity are proportionately more potent for both tonic and phasic block than less hydrophobic congeners. [4] [35] [36] However, at equipotent doses for channel blockade of two local anesthetics that differ 100-fold in hydrophobicity and in intrinsic potency (but have very similar pK_a), the rate of phasic binding is almost the same despite the 100-fold difference in their concentrations in solution. The apparent discrepancy between rates and concentrations can be reconciled by postulating that the primary blocking reaction occurs from drugs that are in the membrane phase, in which the more potent drug is concentrated (even 100-fold) by hydrophobic uptake [17] [26] (Fig. 13-9) .

Dissociation of local anesthetic from the open channel depends little on hydrophobicity, pK_a, or external pH, but it is faster for smaller molecules. In contrast, drug dissociation from the closed channels depends strongly on all these factors. Dissociation is slightly faster for more hydrophobic compounds, [4] [37] [38] markedly faster at more alkaline than at neutral external pH, [38] [39] and faster for drugs of lower pK_a. The latter observation suggests that extracellular H^+ can bind to the amine portion of the bound local anesthetic molecule and trap it in the Na^+ channel. [26] [37] [40] One interpretation of these findings is that anesthetics can leave their blocking site by either a hydrophobic or a hydrophilic pathway. [17] The former accommodates the uncharged base primarily and is 20 to 50 times as fast as the latter, which accommodates the cationic species and is the preferred exit route from open channels.

Integrating these physicochemical findings resolves a dynamic picture of local anesthetic action (see Fig. 13-9) . The binding of tertiary amine compounds occurs primarily from the membrane phase and favors the neutral base species. Dissociation of drug involves primarily the closed conformations of the channel (excitation occurring only briefly) and is slowed by extracellular protons. In brief, hydrophobicity delivers the drug to the receptor and charge keeps it there. Studies with intentionally mutated Na^+ channels show that decreasing the hydrophobicity of certain amino acid residues near the putative pore decreases local anesthetic affinity, indicating a locus for drug binding at the molecular level. [41] [42]

Neurophysiologic Aspects of Phasic Inhibition

Impulse blockade is also increased by repetitive stimulation. As the frequency of impulse traffic in an axon is increased, the probability of impulse blockade by local anesthetic also rises. This phenomenon develops along the length of axon exposed to drug, as shown by the simulation in Figure 13-10 (Figure Not Available) . The first impulse to traverse the fiber, where 16 consecutive nodes have been exposed to lidocaine at a concentration that blocks 50 percent of the Na^+ channels

Figure 13-10 (Figure Not Available) Decremental inhibition of conducted impulses modeled in a myelinated axon shows use-dependent block. In this computer simulation, the membrane potential at each of 26 sequential nodes of Ranvier is plotted as the impulse, stimulated at the leftmost node, propagating to the right. Fifteen nodes in the middle of this fiber are exposed to local anesthetics, which reduces both Na^+ and K^+ conductances to tonically inhibited levels (see Fig. 13-8) (Figure Not Available) for the first impulse in a train (top frame). Although this impulse's amplitude decrements continuously over the exposed length, local current at the last exposed node is still sufficient to stimulate the next, unexposed node, and conduction continues. Use-dependent drug binding during this spike lowers the Na^+ conductance available for subsequent impulses in the train, which therefore decreases further (compare spike 2 and spike 10) and fails to sustain conduction within the exposed region. *(From Raymond et al. [44] Reproduced with permission of S. Karger AG, Basel.)*

at rest, suffers decreasing conduction along the drug-exposed region [43] ; yet the reduced impulse still provides enough current at the last anesthetized node to raise the adjacent drug-free region to threshold. Impulse propagation is thus slowed, but it does not fail. However, the second impulse in the train encounters an exposed region of axon rendered less excitable by the residual phasic inhibition of the first impulse. Action currents at the end of the exposed region are now lower than the margin of safety, and propagation fails. [44] The third impulse propagates along a path of an even more sharply decreasing excitability. Each subsequent impulse in the train similarly fails to traverse the drugged axon; impulse activity entering the anesthetized region thus maintains its own failure.

An identical phenomenon occurs *in vivo.* In this situation, the pattern of impulses encodes neuronal information (e.g., in sensory fibers, the intensity of the physiologic stimulation is encoded in the frequency of the discharge). Local anesthetics significantly disrupt this pattern, as shown by the example in Figure 13-11 (Figure Not Available) of an afferent A fiber coupled to a slowly adapting mechanoreceptor in the rat's footpad. [44] Application of a subclinical dose of lidocaine to the ensheathed sciatic nerve *in vivo* leads to a progressive reduction in the average frequency of impulses propagated by one axon, even though the mechanical stimulus intensity is increased beyond the original control level.

Different fiber types in the nerve are affected differently during local anesthesia. At least part of this difference arises from pharmacokinetic factors. At the onset of and during recovery from clinical block, in particular, the longitudinal and radial diffusion of drug produces concentration variations within and along the nerve. [45] This variation is superimposed on the dynamic use-dependent inhibition to provide variable propagation, which depends on a fiber's geometry, position within the nerve, and functional as well as electrophysiologic properties. Different fiber types are also differentially

Figure 13-11 (Figure Not Available) The pattern of impulses *in vivo* in a cutaneous afferent fiber of the rat is strongly modified by local anesthetic. Discharge frequency (upper traces, shown on a logarithmic scale) in response to increasing pressure on the rat's footpad (lower traces) maintains a relatively constant value (50/s, average) in this slowly adapting mechanoreceptor before drug. Bathing the ensheathed sciatic nerve with lidocaine (0.01% over a 2- to 3-cm length) inhibits impulse conduction through the exposed region, so that after 24 minutes of drug exposure, the average frequency has fallen by 90 percent, despite the faster and larger mechanical stimulation. *(From Raymond et al. [44] Reproduced with permission of S. Karger AG, Basel.)*

sensitive to local anesthetic blockade. No clear relationship has been established between an axon's diameter and its absolute susceptibility to block by local anesthetics. [46] Despite many claims to the contrary, the smallest sensory afferents, nociceptive C fibers, are actually less susceptible to local anesthetic blockade than are the larger-diameter mechanosensitive A beta or nociceptive A delta fibers. [47] Nevertheless, the temporal sequence of loss of various sensory and sympathetic functions during regional block is well documented. [48] [49] For an explanation of the clinical observation, we must look beyond the strictly geometric aspects of an axon. A consideration of fiber functions and physiologic properties, as well as the relationship between relative impulse blockade among different types of fiber and functional deficits, may provide a basis for developing functionally selective nerve blocks.

Summary of Local Anesthetic Mechanisms

Impulse blockade by local anesthetics may be summarized by the following chronology: [4]

1. Solutions of local anesthetic are deposited near the nerve. Diffusion of drug molecules away from this locus is a function of tissue binding, removal by the circulation, and local hydrolysis of aminoester anesthetics. The net result is penetration of the nerve sheath by the remaining drug molecules.

2. Local anesthetic molecules then permeate the nerve's axon membranes and equilibrate there and in the axoplasm. The speed and extent of these processes depend on a particular drug's pK_a and on the lipophilicity of its base and cation species.
3. Binding of local anesthetic to sites on voltage-gated Na^+ channels prevents opening of the channels by inhibiting conformational changes that underlie channel activation.
4. During onset of and recovery from local anesthesia, impulse blockade is incomplete, and partially blocked fibers are further inhibited by repetitive stimulation, which produces an additional, use-dependent binding to Na^+ channels.
5. One local anesthetic binding site on the Na^+ channel may be sufficient to account for the drug's resting (tonic) and use-dependent (phasic) actions. The access to this site may potentially involve multiple pathways, but for clinical local anesthetics, the primary route is the hydrophobic approach from within the axon membrane.
6. The clinically observed rates of onset and recovery from blockade are governed by the relatively slow diffusion of local anesthetic molecules into and out of the whole nerve, not by their much faster binding and dissociation to ion channels.

CLINICAL PHARMACOLOGY

The successful use of regional anesthesia requires knowledge of the pharmacologic properties of the various local anesthetic drugs, as well as technical skill in the performance of the nerve block. Local anesthetic requirements vary considerably, depending on factors such as type of block, surgical procedure, and physiologic status of the patient.

The clinically useful aminoester local anesthetics are procaine, chloroprocaine, tetracaine, and cocaine. The aminoamides consist of lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. The ester and amide local anesthetics differ in their chemical stability, locus of biotransformation, and allergic potential. Amides are extremely stable, whereas esters are relatively unstable in solution. The aminoesters are hydrolyzed in plasma by the cholinesterase enzymes, whereas the amide compounds undergo enzymatic degradation in the liver. The exception to this trend is cocaine, an ester

that is metabolized predominantly by hepatic carboxylesterase. [50] [51]

p-Aminobenzoic acid is one of the metabolites of ester-type compounds that can induce allergic-type reactions in a small percentage of patients. The aminoamides are not metabolized to *p*-aminobenzoic acid, and reports of allergic reactions to these agents are extremely rare.

General Considerations

The clinically important properties of the various local anesthetics include potency, speed of onset, duration of anesthetic action, and differential sensory/motor blockade. As previously indicated, the profile of the individual drugs is determined by their physicochemical characteristics (see Table 13-2) (Table Not Available) .

Anesthetic Potency

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency, [5] [35] [51] [52] because the anesthetic molecule must penetrate the nerve membrane and must bind at a partially hydrophobic site on the Na^+ channel. Clinically, however, the correlation between hydrophobicity and anesthetic potency is not as precise as in an isolated nerve. For example, etidocaine is more potent than bupivacaine in an isolated nerve whereas, clinically, etidocaine is actually less active than bupivacaine. [53] [54] [55] The difference between *in vitro* and *in vivo* results is related to a number of factors such as the vasodilator or tissue redistribution properties of the various local anesthetics. For example, lidocaine causes a greater degree of vasodilation than prilocaine, resulting in its more rapid vascular uptake, so that fewer lidocaine molecules are available for neural blockade. [56] The extremely high lipid solubility of etidocaine may result in a greater uptake of this agent by adipose tissue, such as in the epidural space, which again causes fewer molecules to be available for neural blockade as compared with bupivacaine.

Onset of Action

The onset of conduction block in isolated nerves is related to the physicochemical properties of the individual agents. *In vivo* latency is also dependent on the dose or concentration of local anesthetic. For example, 0.25 percent bupivacaine possesses a slow onset of action, but increasing the concentration to 0.75 percent results in a significant acceleration of anesthetic effect. [55] Chloroprocaine demonstrates a rapid onset of action in humans even though its pK_a is approximately 9, its proportion of charged molecules is high (97%), and thus its onset of action in isolated nerves is relatively slow. [57] However, the low systemic toxicity of this agent allows its use in high concentrations (e.g., 3%). Therefore, the rapid onset *in vivo* of chloroprocaine may be related simply to the large number of molecules placed in the vicinity of peripheral nerves. In humans, 1.5 percent lidocaine produced a more rapid onset of epidural anesthesia than 1.5 percent chloroprocaine [58] ; however, 3 percent chloroprocaine resulted in a more rapid onset than 2 percent lidocaine.

Duration of Action

The duration of action of the various local anesthetics differs markedly. Procaine and chloroprocaine demonstrate a short duration of action. Lidocaine, mepivacaine, and prilocaine produce a moderate duration of anesthesia, whereas tetracaine, bupivacaine, and etidocaine have the longest durations. For example, with procaine, the duration of brachial plexus blockade is 30 to 60 minutes, whereas up to approximately 10 hours of anesthesia has been reported following the use of bupivacaine or etidocaine for brachial plexus blockade. [59]

In humans, the duration of anesthesia is markedly influenced by the peripheral vascular effects of the local anesthetic drugs. Many local anesthetics have a biphasic effect on vascular smooth muscle; at low concentrations, these agents tend to cause vasoconstriction, whereas at clinically employed concentrations, they cause vasodilation. [60] [61] However, differences exist in the degree of vasodilator activity produced by the various drugs. For example, lidocaine is a more potent vasodilator than mepivacaine or prilocaine. Although little difference in the duration of conduction block is apparent among these agents in an isolated nerve, *in vivo* the anesthesia produced by lidocaine is of shorter duration than that produced by mepivacaine or prilocaine. In spinal cord, the pial vessels are dilated by bupivacaine, but they are constricted by ropivacaine, a finding suggesting a stereoselective effect on vascular tone independent of nerve block per se. [62]

Differential Sensory/Motor Blockade

Another important clinical consideration is the ability of local anesthetic agents to cause a differential inhibition of sensory and motor activity. Bupivacaine became popular in the 1980s for epidural blocks because it was better than previously available agents in producing adequate antinociception without profound inhibition of motor activity, particularly when dilute solutions are employed. Bupivacaine and etidocaine provide an interesting contrast in their differential sensory and motor blocking activity, although they are both potent, long-acting anesthetics [63] (Fig. 13-12) . Bupivacaine is widely used epidurally for obstetric analgesia and postoperative pain management because it can provide acceptable analgesia with only mild muscle weakness, particularly when it is used in concentrations of 0.125 percent or less (Ch. 57) . Ropivacaine appears to provide greater sensory selectivity than bupivacaine in some studies, but not in others (see later).

Traditional texts often state that small-diameter axons, such as C fibers, are more susceptible to local anesthetic block than are larger-diameter fibers. However, when careful measurements are made of single-impulse annihilation in individual nerve fibers, exactly the opposite differential susceptibility is seen. [64] [65] Repetitive stimulation, such as occurs during propagation of trains of impulses--the normal mode of operation for neuronal information coding (see Fig. 13-11) (Figure Not Available) --produces a further, phasic inhibition of excitability, but it is unclear how this will effect a functionally selective failure of impulses. The length of drug-exposed nerve in the intrathecal space, imposed by anatomic restrictions,

Figure 13-12 Comparative inhibition of sensory and motor activity following the epidural administration of varying concentrations of bupivacaine and etidocaine.

can explain clinically documented differential spinal or epidural blockade, [45] because longer drug-exposed regions yield block by lower concentrations of local anesthetic. [66] However, this reasoning does not explain the functionally differential loss from peripheral nerve block. Other factors may include the actual spread of the drug along the nerve, [67] or its selective ability to inhibit Na^+ channels over K^+ channels, [68] which in itself can produce a differential block because these channels are present in very different proportions in different types of nerves. [69] Because of these confounding factors, clinicians should be discouraged from making conclusions about fiber type involvement in chronic pain syndromes based on the dose or concentration requirement for pain relief in diagnostic nerve blockade. [70]

Factors Influencing Anesthetic Activity in Humans

Dosage of Local Anesthetic

As the dosage of local anesthetic is increased, the probability and duration of satisfactory anesthesia increase, and the time to onset of block is shortened. The dosage of local anesthetic can be increased by administering either a larger volume or a more concentrated solution. For example, increasing the concentration of epidurally administered bupivacaine from 0.125 to 0.5 percent while maintaining the same volume of injectate (10 mL) resulted in shorter latency, improved incidence of satisfactory analgesia, and produced a longer duration of sensory analgesia. [71] Similarly, an increase in the concentration of epidural bupivacaine in surgical patients from 0.5 to 0.75 percent with a concomitant increase in dosage from approximately 100 to 150 mg produced a more rapid onset and prolonged sensory anesthesia, a greater frequency of satisfactory sensory anesthesia, and more profound motor blockade [55] (see Fig. 13-12) . The volume per se of anesthetic solution probably influences the spread of anesthesia. For example, 30 mL of 1 percent lidocaine administered into the epidural space produced a level of anesthesia that was 4.3 dermatomes higher than that achieved when 10 mL of 3 percent lidocaine was given. [48]

Addition of Vasoconstrictors

Vasoconstrictors, usually epinephrine (5 mug/mL or 1:200,000), are frequently included in local anesthetic solutions to decrease the rate of vascular absorption, thereby allowing more anesthetic molecules to reach the nerve membrane and so improve the depth and duration of anesthesia, as well as to provide a marker for inadvertent intravascular injection. [72] Epinephrine in a concentration of 1:200,000 has been reported to provide the optimal degree of vasoconstriction when it is employed with lidocaine for epidural or intercostal use. [67] Other vasoconstrictor agents, such as norepinephrine and phenylephrine, have been used, but they do not appear to be superior to epinephrine. For example, equipotent concentrations, for vasoconstriction, of epinephrine and phenylephrine prolong to a similar extent the duration of spinal anesthesia produced by tetracaine. [73]

The extent to which epinephrine prolongs the duration of anesthesia depends on the specific local anesthetic employed and on the site of injection. Epinephrine significantly extends the duration of both infiltration anesthesia and peripheral nerve blocks with many agents, such as lidocaine. [74] [75] Epinephrine does not markedly prolong the duration of motor blockade by epidural bupivacaine or etidocaine; however, it does extend sensory blockade by these epidural agents. [63] The depth and duration of epidural analgesia in obstetric patients were improved slightly when epinephrine 1:300,000 was added to 0.25 percent bupivacaine. [76] alpha-Adrenergic receptors in the spinal cord are known to activate endogenous analgesic mechanisms, [77] and the increased depth of analgesic action produced by epinephrine with both epidural and intrathecal local anesthetics may arise both from this pharmacodynamic mechanism and from the pharmacokinetic (vasoconstrictive) action.

Site of Injection

The most rapid onset but the shortest duration of action occurs following intrathecal or subcutaneous administration of local anesthetics. The longest latencies and durations are observed following brachial plexus blocks. For example, intrathecal bupivacaine usually produces anesthesia within 5 minutes that persists for 3 to 4 hours. However, when bupivacaine is administered for brachial plexus blockade, the onset time is approximately 20 to 30 minutes, whereas the duration of anesthesia averages 10 hours. These differences

---

in the onset and duration of anesthesia are due in part to the particular anatomy of the area of injection, which influences the rates of diffusion and vascular absorption and, in turn, affects the amount of drug employed for various types of regional anesthesia. In the subarachnoid space, for example, the lack of a nerve sheath around the spinal cord and the deposition of the local anesthetic solution in the immediate vicinity of the spinal cord are responsible for the rapid onset of action, whereas the relatively small amount of drug employed for spinal anesthesia probably accounts for the short duration of conduction block.

On the other hand, the onset of brachial plexus blockade is slow, because the anesthetic agent is usually deposited at some distance from the nerve and must diffuse through various tissue barriers before reaching the nerve membrane. The prolonged blockade is probably related to the decreased rate of vascular absorption from that site and to the much larger doses of drug required for this regional anesthetic technique.

Carbonation and pH Adjustment of Local Anesthetics

The presence of bicarbonate carbon dioxide in a solution of local anesthetic applied to an isolated nerve results in a more rapid onset and a decrease in the minimum concentration required for conduction blockade. [78] [79] [80] Although the effect of carbon dioxide on local anesthetic activity is easily demonstrable in isolated nerve, [78] [79] controversy exists concerning the clinical utility of carbonated local anesthetic solutions. For example, some studies have failed to demonstrate a significantly more rapid onset of action for lidocaine carbonate as compared with lidocaine hydrochloride for epidural blockade, [81] whereas others have reported a significant reduction in onset time of epidural blockade with lidocaine carbonate. [82] Similar discrepancies existed when bupivacaine hydrochloride and bupivacaine carbonate were evaluated clinically. [83] [84] Although the general effect of carbon dioxide on the latency of conduction blockade may be controversial, carbonated solutions appear to improve the depth of sensory and motor blockade when they are administered into the epidural space. [81] [82] In addition, these solutions may produce a more complete blockade of the radial, median, and ulnar nerves when they are employed for brachial plexus blockade. [85]

Addition of sodium bicarbonate to local anesthetic solutions has also been reported to decrease the onset time of conduction blockade. [85] [86] An increase in the pH of the local anesthetic solution increases the amount of drug in the uncharged base form and thus should enhance the rate of diffusion across the nerve sheath and nerve membrane, resulting in a more rapid onset of anesthesia. Alkalinization of solutions of bupivacaine or lidocaine reportedly does significantly decrease the latency of onset of brachial plexus and epidural blockade. [85] [86] On the other hand, at least one study failed to demonstrate an improved onset of brachial plexus blockade when the pH of bupivacaine solution was increased by addition of sodium bicarbonate. [87]

Studies on isolated, desheathed nerves using a variety of impulse blocking agents at constant extracellular pH have shown that un-ionized anesthetics (e.g., benzocaine) and ionizable tertiary amines are potentiated by bicarbonate carbon dioxide buffers. [80] In contrast, the potency of permanently cationic (quaternary) local anesthetics is unaffected by bicarbonate carbon dioxide. Therefore, the mechanism of ion trapping, whereby the ionized form of the drug is concentrated in the axoplasm by the internal acidification wrought by membrane-permeant carbon dioxide molecules, does not fully account for potentiation by bicarbonate carbon dioxide. Furthermore, this potentiation in isolated, desheathed nerve is strongly dependent on bicarbonate concentration but is almost independent of carbon dioxide tension (P_{CO_2}). At present, there is no easy explanation for the potentiation of local anesthetics by bicarbonate buffers, nor has a clear connection been established between *in vitro* results and clinical phenomena.

Mixtures of Local Anesthetics

The use of mixtures of local anesthetics for regional anesthesia has become relatively popular in recent years. The basis for this practice is to compensate for the short duration of action of certain rapidly acting agents such as chloroprocaine and lidocaine and the long latency of other agents such as tetracaine and bupivacaine.

Mixtures of chloroprocaine and bupivacaine theoretically should offer significant clinical advantages, owing to the rapid onset and low systemic toxicity of chloroprocaine and the long duration of action of bupivacaine. A mixture of 3 percent chloroprocaine and 0.5 percent bupivacaine was reported to produce a short latency and prolonged duration of brachial plexus blockade. [88] However, subsequent studies indicated that the duration of epidural anesthesia produced by a mixture of chloroprocaine and bupivacaine was significantly shorter than that obtained with bupivacaine alone, whereas time to onset of anesthesia was longer than that of chloroprocaine alone. [89] Isolated nerve studies suggest that a metabolite of chloroprocaine may inhibit the binding of bupivacaine to membrane sites. [90] At present, there do not appear to be any clinically significant advantages to the use of mixtures of local anesthetic agents. Etidocaine and bupivacaine provide clinically acceptable onsets of action and prolonged durations of anesthesia. In addition, the use of catheter techniques for many forms of regional anesthesia makes it possible to extend the duration of action of rapidly acting agents such as chloroprocaine or lidocaine indefinitely. Conversely, clinicians should be cautioned not to use maximum doses of two local anesthetics in combination in the mistaken belief that toxicities of these agents are independent. [91] In the absence of additional data, the toxicities should be presumed to be additive.

Pregnancy

The spread and depth of epidural and spinal anesthesia are reported to be greater in pregnant than in nonpregnant women [92] (Ch. 57) . This finding was originally attributed to mechanical factors associated with pregnancy; that is, dilated epidural veins decrease the diameter of the epidural and subarachnoid space. Hormonal alterations may also play a role in the apparent increase in local anesthetic sensitivity

during pregnancy, because a greater spread of epidural anesthesia occurs during the first trimester of pregnancy, preceding any gross change in vascular dimensions within the epidural or subarachnoid spaces. [93] A correlation appears to exist between progesterone concentrations in cerebrospinal fluid and the milligrams per segment requirement of lidocaine for spinal anesthesia in pregnant and nonpregnant patients. [94] Lidocaine's block of sciatic nerve functions in pregnant rats significantly outlasts that in age-matched nonpregnant female or male rats. [95] Isolated nerve studies have shown a more rapid onset and an increased sensitivity to local anesthetic-induced conduction blockade in vagus nerves obtained from pregnant rabbits as compared with nonpregnant control subjects. [96] [97] However, direct measures of lidocaine uptake kinetics in isolated rat nerve show no effect of pregnancy, [95] a finding suggesting that any pharmacokinetic differences are not due to the nerve per se. These results suggest that hormonal changes associated with pregnancy enhance the apparent potency of local anesthetics; thus, the dosage probably should be reduced in patients in all stages of pregnancy.

CHOICE OF LOCAL ANESTHETIC FOR VARIOUS REGIONAL ANESTHETIC PROCEDURES

On the basis of anatomic considerations, regional anesthesia may be divided into infiltration anesthesia, intravenous regional anesthesia, peripheral nerve blockade, central neural blockade, and topical anesthesia (Chs. 42 to 44 , 69 , and 70) . An additional method of local anesthetic injection, tumescent anesthesia, is included, because it is widely used in office plastic surgery practice.

Infiltration Anesthesia

Any local anesthetic may be employed for infiltration anesthesia. Onset of action is almost immediate for all agents following intradermal or subcutaneous administration; however, duration of anesthesia varies (Table 13-4) . Epinephrine markedly prolongs the duration of infiltration anesthesia by all local anesthetic drugs, although this effect is most pronounced when epinephrine is added to lidocaine. Choice of a specific drug for infiltration anesthesia basically depends on the desired duration of action.

The dosage of local anesthetic required for adequate infiltration anesthesia depends on the extent of the area to be anesthetized and on the expected duration of the surgical procedure. When large surface areas have to be anesthetized, large volumes of dilute anesthetic solutions should be used. These considerations are particularly important when performing infiltration anesthesia in infants and smaller children. As an example, consider a 4-kg infant receiving infiltration anesthesia using the maximum safe dose of lidocaine, 5 mg/kg. Dosing to 5 mg/kg × 4 kg permits 20 mg, which is 1 mL of 2 percent solution, or 4 mL of 0.5 percent solution. Lidocaine is effective for infiltration in concentrations as dilute as 0.3 to 0.5 percent, so the more dilute solution can be used to anesthetize a larger area.

Patients frequently experience pain immediately after subcutaneous injection of local anesthetic solutions. [98] This response is due in part to the acidic nature of these solutions. [95] [100] For example, neutralization of lidocaine solutions by addition of sodium bicarbonate reduces pain on skin infiltration and may improve onset (see earlier). In addition, certain agents such as etidocaine are associated with a greater frequency and intensity of pain, whereas lidocaine is perceived as less painful. [6] [99]

Intravenous Regional Anesthesia

Intravenous regional anesthesia involves intravenous administration of a local anesthetic into a tourniquet-occluded limb (i.e., Bier block). The local anesthetic diffuses from the peripheral vascular bed to nonvascular tissue such as axons and nerve endings. Both the safety and efficacy of this regional anesthetic procedure depend on the interruption of blood flow to the involved limb and on the gradual release of the occluding tourniquet. Intravenous regional anesthesia has been used primarily for surgical procedures on the upper limbs. Shorter procedures on the foot can also be successfully performed with the patient under intravenous regional anesthesia. If a lower leg tourniquet is used, it should be applied just below the fibular neck to avoid pressure over the superficial peroneal nerve.

TABLE 13-4 -- Infiltration Anesthesia

DRUG	CONCENTRATION (%)	PLAIN SOLUTION		EPINEPHRINE-CONTAINING SOLUTION	
		MAXIMUM DOSE (mg)	*DURATION (min)*	*MAXIMUM DOSE (mg)*	*DURATION (min)*
Short duration					
Procaine					
Chloroprocaine	1.0-2.0	800	15-30	1,000	30
Moderate duration					
Lidocaine	0.5-1.0	300	30-60	500	120
Mepivacaine	0.5-1.0	300	45-90	500	120
Prilocaine	0.5-1.0	500	30-90	600	120
Long duration					
Bupivacaine	0.25-0.5	175	120-240	225	180
Etidocaine	0.5-1.0	300	120-180	400	180

Lidocaine has been the drug most frequently used for intravenous regional anesthesia and is the only drug officially approved by the U.S. Food and Drug Administration for intravenous regional anesthesia in the United States. Prilocaine, mepivacaine, chloroprocaine, procaine, bupivacaine, and etidocaine have also been used successfully. One could suppose a safety advantage with the amino-ester linked compounds, because of their hydrolysis in blood; however, thrombophlebitis has been reported in several patients in whom chloroprocaine was used. [101] Cardiovascular collapse has been reported following the use of bupivacaine for intravenous regional anesthesia, and this use of bupivacaine is discouraged. [102]

In general, approximately 3 mg/kg (40 mL of 0.5% solution) of preservative-free lidocaine without epinephrine is used for upper extremity procedures. For surgical procedures on the lower limbs, 50 to 100 mL of 0.25 percent lidocaine has been used.

Peripheral Nerve Blockade

Regional anesthetic procedures that inhibit conduction in fibers of the peripheral nervous system can be classified together under the general category of peripheral nerve blockade (Chs. 43 and 44) . This form of regional anesthesia has been subdivided arbitrarily into minor and major nerve blocks. Minor nerve blocks are defined as procedures involving single nerve entities such as the ulnar or radial nerve, whereas major nerve blocks involve the blocking of two or more distinct nerves or a nerve plexus.

Most local anesthetic drugs can be used for minor nerve blocks. The onset of block is rapid with most drugs, and the choice of drug is determined primarily by the required duration of anesthesia. A classification of the various drugs according to their duration of action is shown in Table 13-5 (Ch. 43) . The duration of both

sensory analgesia and motor blockade is prolonged significantly when epinephrine is added to the various local anesthetic solutions.

In 1986, a technique of intrapleural regional analgesia was described as an alternative to multiple intercostal nerve blocks. [103] This procedure involves administration of local anesthetic solution into the pleural space. An epidural needle is inserted into the pleural space, usually by way of the fourth to the ninth intercostal space. An epidural catheter is then passed into the pleural space approximately 5 cm beyond the tip of the needle. The needle is removed, and the local anesthetic is administered through the catheter. Intrapleural analgesia can also be positioned by the surgeon through the open chest during thoracotomy. Although this technique appeared useful for unilateral postoperative analgesia following cholecystectomy, mastectomy, and nephrectomy, [104] [105] its efficacy for post-thoracotomy pain is doubtful. [106] Most frequently, 22 to 30 mL of 0.5 percent bupivacaine with epinephrine is employed in this technique; the duration of analgesia averages approximately 8 hours with a range of 4 to 24 hours. The advantage of the technique is the ability to administer subsequent injections of local anesthetics via catheter to provide long-lasting analgesia without subjecting patients to repeated multiple intercostal nerve blocks. Caution is advised, however, because this technique has been associated with extremely high plasma concentrations of anesthetic, with an associated risk of convulsions. [103]

Brachial plexus blockade for upper limb surgery is the most common major peripheral nerve block technique. A significant difference exists among the onset times of various agents when these blocks are used (Table 13-6) (Ch. 43) . In general, the agents of intermediate potency exhibit a more rapid onset than the more potent compounds. Onset times of approximately 14 minutes for lidocaine and mepivacaine have been reported, compared with approximately 23 minutes for bupivacaine. [107] Etidocaine may be an exception, because it produces a relatively rapid onset and a long duration of block.

Epinephrine prolongs the duration of most local anesthetics employed for brachial plexus blockade, but it is less effective with drugs having intrinsically longer durations of action. The variation in duration of anesthesia after brachial plexus blockade is also considerably greater than that observed with other types of conduction block. For example, durations of anesthesia varying from 4 to 30 hours have been reported for bupivacaine. It would be prudent to forewarn patients who are about to be given a major nerve block about the possibility of prolonged sensory and motor block in the involved region, particularly when agents such as bupivacaine and etidocaine are employed. Knowledge shapes expectation and can often relieve anxiety over unusual sensations and may thus increase comfort and reduce pain.

TABLE 13-5 -- Minor Nerve Blocks

DRUG	USUAL CONCENTRATION (%)	PLAIN SOLUTIONS			EPINEPHRINE-CONTAINING SOLUTIONS
		USUAL VOLUME (mL)	*DOSAGE (mg)*	*AVERAGE DURATION (min)*	*AVERAGE DURATION (min)*
Prilocaine	2	5-20	100-400	15-30	30-60
Chloroprocaine	2	5-20	100-400	15-30	30-60
Lidocaine	1	5-20	50-200	60-120	120-180
Mepivacaine	1	5-20	50-200	60-120	120-180
Prilocaine	1	5-20	50-200	60-120	120-180
Bupivacaine	0.25	5-20	12.5-50	180-360	240-480
Etidocaine	0.5	5-20	25-100	120-240	180-420

TABLE 13-6 -- Major Nerve Blocks

DRUG WITH EPINEPHRINE 1: 200,000	USUAL CONCENTRATION (%)	USUAL VOLUME (mL)	MAXIMAL DOSE (mg)	USUAL ONSET (min)	USUAL DURATION (min)
Lidocaine	1-1.5	30-50	500	10-20	120-240
Mepivacaine	1-1.5	30-50	500	10-20	180-300
Prilocaine	1-2	30-50	600	10-20	180-300
Bupivacaine	0.25-0.5	30-50	225	15-30	360-720
Etidocaine	0.5-1.0	30-50	400	10-20	360-720
Tetracaine	0.25-0.5	30-50	200	20-30	300-600

Central Neural Blockade

Any of the local anesthetic drugs may be used for epidural anesthesia (Table 13-7) , although procaine and tetracaine are rarely used, owing to their long onset times (Ch. 42) . The drugs of intermediate potency produce surgical anesthesia of 1 to 2 hours' duration, whereas the long-acting drugs usually produce 3 to 5 hours of anesthesia. The duration of short- and intermediate-acting drugs is significantly prolonged by the addition of epinephrine (1:200,000), whereas the long-acting drugs benefit little from its addition. Onset of lumbar epidural anesthesia occurs within 5 to 15 minutes following administration of chloroprocaine, lidocaine, mepivacaine, and prilocaine. Bupivacaine has a slower onset of action.

Bupivacaine at 0.125 and 0.25 percent produces adequate analgesia with minimal motor deficit. These solutions of bupivacaine are useful for obstetric epidural analgesia and postoperative analgesia. Bupivacaine at 0.5 to 0.75 percent is associated with a more profound degree of motor block, which makes these solutions most suitable for major surgical procedures. Etidocaine produces adequate sensory analgesia and profound, long-lasting motor block and is primarily useful for surgical procedures in which muscle relaxation is required.

Drugs available for subarachnoid administration are shown in Table 13-8 (Ch. 42) . Tetracaine is available both as crystals and as a 1 percent solution, which may be diluted with 10 percent glucose to obtain a 0.5 percent hyperbaric solution.

Hypobaric solutions of tetracaine (tetracaine in sterile water) may be used for specific operative situations; for example, anorectal or hip surgery. Isobaric tetracaine obtained by mixing 1 percent tetracaine with cerebrospinal fluid or normal saline is occasionally used. Bupivacaine is widely used as a spinal anesthetic, either as a hyperbaric solution at a concentration of 0.75 percent with 8.25 percent dextrose or by using the nearly isobaric 0.5 percent solution.

Intrathecal bupivacaine possesses an anesthetic profile similar to that of tetracaine. [108] [109] However, differences do exist between the two drugs. Although two-segment regression of anesthesia is similar for bupivacaine and tetracaine, the total duration of sensory anesthesia is significantly longer following the subarachnoid administration of tetracaine. The depth and duration of motor blockade are also greater with tetracaine than with bupivacaine. On the other hand, bupivacaine has been reported in some studies to be associated with less hypotension than tetracaine. In addition, the frequency of tourniquet pain in the lower limbs during certain orthopedic surgical procedures has been reported to be significantly reduced when bupivacaine instead of tetracaine is employed for spinal anesthesia. [110] [111]

Whereas tetracaine and bupivacaine are considered to be agents of long duration, lidocaine provides a short duration of spinal anesthesia. Onset of spinal anesthesia is extremely rapid with a drug such as lidocaine. The addition of vasoconstrictors may prolong the duration of spinal anesthesia: for example, addition of 0.2 mg of epinephrine to tetracaine solutions produces a 50 percent or greater increase in duration. The duration of spinal anesthesia produced by tetracaine can also be increased to a similar extent by adding 1 mg of phenylephrine. The addition of epinephrine to bupivacaine or lidocaine may not significantly prolong the duration of

surgical anesthesia (e.g., in thoracic segments [112] [113]) although the total duration of anesthesia (e.g., lower extremity motor block) is significantly increased.

Topical Anesthesia

Several local anesthetic formulations are available for topical anesthesia (Table 13-9) (Table Not Available) , most commonly lidocaine,

TABLE 13-7 -- Epidural Anesthesia

DRUG WITH EPINEPHRINE 1: 200,000	USUAL CONCENTRATION (%)	USUAL VOLUME (mL)	MAXIMAL DOSE (mg)	USUAL ONSET (min)	USUAL DURATION (min)
Chloroprocaine	2-3	15-30	300-900	5-15	30-90
Lidocaine	1-2	15-30	150-500	5-15	
Mepivacaine	1-2	15-30	150-500	5-15	60-180
Prilocaine	1-3	15-30	150-600	5-15	
Bupivacaine	0.25-0.75	15-30	37.5-225	10-20	180-300
Etidocaine	1.0-1.5	15-30	150-300	5-15	

TABLE 13-8 -- Spinal Anesthesia

DRUG	USUAL CONCENTRATION (%)	USUAL VOLUME (mL)	TOTAL DOSE (mg)	BARICITY	GLUCOSE CONCENTRATION (%)	USUAL DURATION (min)
Procaine	10.0	1-2	100-200	Hyperbaric	0	30-60
Lidocaine	1.5, 5.0	1-2	30-100	Hyperbaric	7.5	30-90
Mepivacaine	4	1-2	40-80	Hyperbaric	9.0	30-90
Tetracaine	0.25-1.0	1-4	5-20	Hyperbaric	5.0	75-200
	0.25	2-6	5-20	Hypobaric	0	75-200
	1.0	1-2	5-20	Isobaric	0	75-200
Dibucaine	0.25	1-2	2.5-5.0	Hyperbaric	5.0	75-180
	0.5	1-2	5-10	Isobaric	0	--
	0.06	5-20	3-12	Hypobaric	0	--
Bupivacaine	0.5	3-4	15-20	Isobaric	0	75-200
	0.75	2-3	15-22.5	Hyperbaric	8.25	75-200

dibucaine, tetracaine, and benzocaine. In general, these preparations provide effective but relatively short durations of analgesia when they are applied to mucous membranes or abraded skin. In addition, lidocaine and tetracaine sprays have been employed for endotracheal anesthesia prior to intubation. A topical anesthetic formulation, Emla, which is a eutectic mixture of 2.5 percent lidocaine base and 2.5 percent prilocaine base, is widely used for cutaneous analgesia. [114] Clinical studies have demonstrated that this preparation can decrease the pain associated with the percutaneous insertion of intravenous needles and cannulas. [115] In addition, Emla has been successfully employed for cutaneous anesthesia in skin grafting procedures. [116] This preparation must be applied under an occlusive bandage for 45 to 60 minutes to obtain effective cutaneous anesthesia. Emla appears quite safe in neonates, and methemoglobinemia from prilocaine is exceedingly uncommon. Emla is more effective for newborn circumcision than placebo, but it is less effective than dorsal penile nerve block. Several alternative topical local anesthetic formulations also are in use, including tetracaine. Physical methods to accelerate local anesthetic transit across skin are also under study, including iontophoresis and electrophoration.

Topical anesthesia through cut skin may be provided by a mixture of tetracaine, epinephrine (adrenaline), and cocaine, known as TAC. TAC is widely used in pediatric emergency rooms in the United States for liquid application into lacerations that require suturing. TAC is usually supplied as tetracaine 0.5 percent, epinephrine 1:2,000, and cocaine 10 to 11.8 percent, although studies suggest that more dilute concentrations may be almost equally effective and are less likely to cause toxicity. The generally recommended safe

TABLE 13-9 -- Various Preparations Intended for Topical Anesthesia

(Not Available)

Modified from Covino and Vassallo [123]

maximum dose is 3 to 4 mL for adults or 0.05 mL/kg for children. TAC is ineffective through intact skin; in contrast, it can be absorbed rapidly from mucosal surfaces, thus leading to toxic reactions. There is a report of a fatal reaction following application to a nasal laceration, with presumed dripping into the mouth and rapid mucosal absorption. [117] [118]

Because of concerns regarding cocaine toxicity and the potential for diversion and abuse, several groups have investigated alternative cocaine-free topical preparations. Tetracaine-phenylephrine preparations were found to be as effective as TAC. [119]

Tumescent Anesthesia

A technique of local anesthesia most commonly employed by plastic surgeons during liposuction procedures involves subcutaneous injection of large volumes of dilute local anesthetic in combination with epinephrine and other agents. Total doses of lidocaine ranging from 35 to 55 mg/kg have been reported to produce safe plasma concentrations, which may peak more than 8 to 12 hours after infusion. [120] Despite these seemingly huge doses, very good outcomes have been reported in large series. [121] The factors governing uptake and clearance from this method of local anesthetic delivery deserve further study. Clinicians should use great caution in administering additional local anesthetics by infiltration or other routes for at least 12 to 18 hours following use of this technique.

/das/book/view/29494766/875/159.html

PHARMACOKINETICS

The concentration of local anesthetics in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of tissue distribution, and the rate of biotransformation and excretion of the specific drug. Patient-related factors such as age, cardiovascular status, and hepatic function influence the physiologic disposition and the resultant blood concentrations of local anesthetics.

Absorption

The systemic absorption of local anesthetics is determined by the site of injection, dosage and volume, addition of a vasoconstrictor agent, and pharmacologic profile of the agent itself. A comparison of the blood concentration of local anesthetics following various routes of administration reveals that the anesthetic drug level is highest after intercostal nerve blockade, followed, in order of decreasing concentration, by injection into the caudal epidural space, lumbar epidural space, brachial plexus, and subcutaneous tissue [122] (Fig. 13-13) (Figure Not Available) . When a local anesthetic solution is exposed to an area of greater vascularity, a greater rate and degree of absorption occur. This relationship is of clinical significance because use of a fixed dose of a local anesthetic agent may be potentially toxic in one area of administration but not in others. For example, the use of 400 mg of lidocaine without epinephrine for intercostal nerve block results in an average peak venous plasma level of approximately 7 mug/mL, which is sufficiently high to cause symptoms of

Figure 13-13 (Figure Not Available) Peak venous blood concentrations of various local anesthetics following injection into different sites. *(From Covino and Vassallo [123])*

CNS toxicity in some patients. [122] By comparison, this same dose of lidocaine employed for brachial plexus block yields a mean maximum blood level of approximately 3 mug/mL, which is rarely associated with signs of toxicity.

The maximum blood level of local anesthetic drugs is related to the total dose of drug administered for any particular site of administration. For most drugs, there is a linear relationship between the amount of drug administered and the resultant peak anesthetic blood levels. [123] Higher blood levels also follow from administration of larger volumes of a correspondingly dilute solution than from the same dose in a smaller volume.

Local anesthetic solutions frequently contain a vasoconstrictor agent, usually epinephrine, in concentrations varying from 5 to 20 mug/mL. Epinephrine decreases the rate of absorption of certain agents from various sites of administration and thus lowers their potential systemic toxicity. A 5 mug/mL dose of epinephrine (1:200,000) significantly reduces the peak blood levels of lidocaine and mepivacaine irrespective of the site of administration. The peak blood levels of bupivacaine and etidocaine are minimally influenced by addition of a vasoconstrictor following injection into the lumbar epidural space. [124] However, epinephrine significantly reduces the rate of vascular absorption of these drugs when they are used for peripheral nerve blocks such as brachial plexus blockade. [125]

Differences also exist in the rate of absorption of various local anesthetic drugs. For example, a comparison of drugs of similar anesthetic profiles reveals that lidocaine is absorbed more rapidly following brachial plexus blockade than

TABLE 13-10 -- Pharmacokinetic Properties of Various Amide Local Anesthetics

AGENT	$t_{1/2alpha}$ (min)	$t_{1/2beta}$ (min)	V_{DSS} (L)	$t_{1/2gamma}$ (h)	CLEARANCE (L/min)
Prilocaine	0.5	5.0	261	1.5	2.84
Lidocaine	1.0	9.6	91	1.6	0.95
Mepivacaine	0.7	7.2	84	1.9	0.78
Bupivacaine	2.7	28.0	72	3.5	0.47
Etidocaine	2.2	19.0	133	2.6	1.22

$t_{1/2\ alpha}$, $t_{1/2\ beta}$, elimination half-life; $t_{1/2\ gamma}$, V_{dss} , volume of distribution at steady state

is prilocaine, whereas bupivacaine is absorbed more rapidly than etidocaine. [123]

Distribution

The systemic distribution of local anesthetics can be described sufficiently by a two-compartment model. [126] The rapid disappearance phase is believed to be related to uptake by rapidly equilibrating tissues (i.e., tissues that have a high vascular perfusion). The slower phase of disappearance from blood is mainly a function of the particular compound [127] (Table 13-10) . The half-lives of lidocaine and mepivacaine are similar, but a comparison of bupivacaine and etidocaine reveals that etidocaine has a more rapid rate of tissue redistribution and biotransformation than does bupivacaine. [128]

Local anesthetic drugs are distributed throughout all body tissues, but the relative concentration in different tissues varies. In general, the more highly perfused organs show higher concentrations of local anesthetic drug than the less well perfused organs. Local anesthetics are rapidly extracted by lung tissue, so that the whole blood concentration of local anesthetics decreases markedly as these agents pass through the pulmonary vasculature. [129] [130] The highest percentage of an injected dose of a local anesthetic is found in skeletal muscle. Although this tissue does not show any particular affinity for this class of drugs, the mass of skeletal muscle makes it the largest reservoir for local anesthetic drugs.

Biotransformation and Excretion

The pattern of metabolism of local anesthetic agents varies according to chemical classification. The ester, or procaine-like, drugs undergo hydrolysis in plasma by the pseudocholinesterase enzymes. Chloroprocaine shows the fastest rate (4.7 mol/mL/h), compared with a rate of 1.1 mol/mL/h for procaine and 0.3 mol/mL/h for tetracaine. [131] [132]

The aminoamide drugs undergo enzymatic degradation primarily in the liver. Lidocaine is metabolized more rapidly than mepivacaine, [132] and bupivacaine is

metabolized more slowly than either lidocaine or mepivacaine. [133] Some degradation of the amide-type compounds may take place in tissues other than liver; in particular, the metabolism of lidocaine is discussed in detail elsewhere. [132]

The excretion of the metabolites of amide-type local anesthetics occurs via the kidney. Less than 5 percent of the unchanged drug is excreted via the kidney into the urine.

Pharmacokinetic Alterations by Patient Status

A patient's age may influence the physiologic disposition of local anesthetics. The half-life of lidocaine following intravenous administration averaged 80 minutes in human volunteers whose ages varied from 22 to 26 years. On the other hand, volunteers 61 to 71 years of age demonstrated a significantly prolonged lidocaine half-life of 138 minutes [134] (Ch. 61) .

Newborn infants have immature hepatic enzyme systems and prolonged elimination of lidocaine and bupivacaine [135] [136] (Chs. 58 and 59) . Prolonged elimination is particularly an issue for continuous infusions of local anesthetics in infants, and seizures have been associated with high bupivacaine infusion rates. [137] [138] Based on analysis of these cases, a maximum infusion rate of 0.4 mg/kg/h for prolonged bupivacaine infusions has been proposed for children and adults, whereas prolonged infusion rates for neonates and young infants should not exceed 0.2 mg/kg/h. Even at 0.2 mg/kg/h, plasma bupivacaine concentrations were found to be rising toward a toxic range in some younger infants after 48 hours. Similarly, prolonged lidocaine infusions in neonates should not exceed 0.8 mg/kg/h.

The rate of degradation of the amide type of local anesthetic drugs is influenced by the hepatic status of the individual patient. In those patients in whom liver blood flow is abnormally low or liver function is poor, significantly higher blood levels of the amide drugs occur. An average lidocaine half-life of 1.5 hours was reported in volunteers with normal hepatic function, whereas patients with liver disease demonstrated an average half-life of 5.0 hours. [139] The rate of lidocaine disappearance from blood has also been shown to be markedly prolonged in patients with congestive heart failure. [140]

TOXICITY

Local anesthetic drugs are relatively free of side effects if these agents are administered in an appropriate dosage and in the correct anatomic location. However, systemic and localized toxic reactions can occur, usually owing to accidental

intravascular or intrathecal injection or to administration of an excessive dose. In addition, specific adverse effects are associated with the use of certain drugs, such as allergic reactions to the aminoester drugs and methemoglobinemia following the use of prilocaine.

Systemic Toxicity

Systemic reactions to local anesthetics primarily involve the CNS and the cardiovascular system (Chs. 42 to 44 and 70) In general, the CNS is more susceptible to the actions of systemic local anesthetics than the cardiovascular system, and thus the dose and blood level of local anesthetic required to produce CNS toxicity are usually lower than those resulting in circulatory collapse (Fig. 13-14) (Figure Not Available) .

Central Nervous System Toxicity

The initial symptoms of local anesthetic-induced CNS toxicity are feelings of lightheadedness and dizziness, followed frequently by visual and auditory disturbances such as difficulty in focusing and tinnitus. Other subjective CNS symptoms include disorientation and occasional feelings of drowsiness. Objective signs of CNS toxicity are usually excitatory and include shivering, muscle twitching, and tremors initially involving muscles of the face and distal parts of the extremities. Ultimately, generalized convulsions of a tonic-clonic nature occur. If a sufficiently large dose or a rapid intravenous injection of a local anesthetic is administered, the initial signs of CNS excitation are rapidly followed by a state of generalized CNS depression. Seizure activity ceases, and respiratory depression and, ultimately, respiratory arrest may occur. In some patients, CNS depression without a preceding

Figure 13-14 (Figure Not Available) Relationship between plasma concentration of lidocaine and various signs and symptoms of toxicity. (*Modified from Mather and Cousins* [235])

excitatory phase is seen, particularly if other CNS depressant drugs have been administered.

CNS excitation is thought to be the result of an initial blockade of inhibitory pathways in the cerebral cortex by local anesthetic drugs. [141] The blockade of inhibitory pathways allows facilitatory neurons to function in an unopposed fashion, which results in an increase in excitatory activity leading to convulsions. An increase in the dose of local anesthetic leads to an inhibition of activity of both inhibitory and facilitatory circuits, resulting in a generalized state of CNS depression.

In general, a correlation exists between anesthetic potency and intravenous CNS toxicity of various drugs (Fig. 13-15) . For example, in cats, the dose of intravenous procaine required to cause convulsions is approximately seven times greater than the convulsive dose of bupivacaine. [142] However, bupivacaine is also approximately eight times more potent than procaine as a local anesthetic. [143] Intravenous infusion studies in human volunteers have also demonstrated an inverse relationship between the intrinsic anesthetic potency of various drugs and the dosage required to induce CNS toxicity. [143] [144]

The rate of injection and the rapidity with which a particular blood level is achieved alter the toxicity of local anesthetic drugs. For example, in human volunteers, an average dose of 236 mg of etidocaine and a venous blood level of 3.0 mug/mL resulted in CNS symptoms when an infusion rate of 10 mg/min was employed. [143] When the infusion rate was increased to 20 mg/min, an average of 161 mg of etidocaine, which produced a venous plasma level of approximately 2 mug/mL, caused symptoms of CNS toxicity.

Respiratory or metabolic acidosis increases the risks of CNS toxicity from local anesthetics in animals and patients. In cats, the convulsive threshold of various local anesthetics was inversely related to the arterial P_{CO_2} level [142] (see Fig. 13-15) . An increase in Pa $_{CO_2}$ from 25 to 40 mm Hg to 65 to 81 mm Hg decreases the convulsive threshold of procaine, mepivacaine, prilocaine, lidocaine, and bupivacaine by approximately 50 percent.

An elevation of Pa $_{CO_2}$ enhances cerebral blood flow, so that more anesthetic is delivered more rapidly to the brain. In addition, diffusion of carbon dioxide into neuronal cells decreases intracellular pH and thus facilitates the conversion of the base form of the drugs to the cationic form. The cationic form does not diffuse well across the nerve membrane, so that ion trapping occurs and increases the apparent CNS toxicity of local anesthetics.

Hypercarbia and/or acidosis also decreases the plasma protein binding of local anesthetic agents. [145] [146] Accordingly, an elevation in Pa $_{CO_2}$ or a decrease in pH increases the proportion of free drug available for diffusion into the brain. On the other hand, acidosis increases the cationic form of the local anesthetic, a change that should decrease the rate of diffusion through lipoid barriers. The clinical implication of this effect of hypercapnia and acidosis on toxicity deserves emphasis. Seizures and CNS depression produce hypoventilation and respiratory acidosis, which further exacerbates the CNS toxicity. In the setting of local anesthetic toxic reactions, it is essential to provide prompt assisted ventilation and circulatory support as needed to prevent or correct hypercapnia and acidosis.

Figure 13-15 Relationship between convulsive dose of procaine, lidocaine, and bupivacaine in cats and their relative *in vivo* anesthetic potency. The open bar represents convulsive dose during normocarbia, and the hatched bar is the convulsive dose under hypercarbic conditions.

Cardiovascular System Toxicity

Local anesthetic agents can exert a direct action on both the heart and the peripheral blood vessels.

Direct Cardiac Effects

The primary cardiac electrophysiologic effect of local anesthetics is a decrease in the rate of depolarization in the fast conducting tissues of Purkinje fibers and

ventricular muscle. [141] [142] This reduction in rate is believed to be due to a decrease in the availability of fast Na^+ channels in cardiac membranes. Action potential duration and the effective refractory period are also decreased by local anesthetics. [147] However, the ratio of effective refractory period to action potential duration is increased both in Purkinje fibers and in ventricular muscle.

Qualitative differences may exist among the electrophysiologic effects of various agents. Bupivacaine depresses the rapid phase of depolarization (V_{max}) in Purkinje fibers and ventricular muscle to a greater extent than does lidocaine. [147] In addition, the rate of recovery from a use-dependent block is slower in bupivacaine-treated papillary muscles than in lidocaine-treated muscles. [148] This slow rate of recovery results in an incomplete restoration of Na^+ channel availability between action potentials, particularly at high heart rates. In contrast, recovery from lidocaine is complete, even at rapid heart rates. These differential effects of lidocaine and bupivacaine have been advanced as explanations of the antiarrhythmic properties of lidocaine and the arrhythmogenic potential of bupivacaine.

Electrophysiologic studies in intact dogs and in humans have shown that high blood levels of local anesthetics prolong conduction time through various parts of the heart, as indicated in the electrocardiogram by an increase in the PR interval and QRS complex duration. Extremely high concentrations of local anesthetics depress spontaneous pacemaker activity in the sinus node, resulting in sinus bradycardia and sinus arrest.

Local anesthetic drugs also exert profound effects on the mechanical activity of cardiac muscle. All local anesthetics exert a dose-dependent negative inotropic action on isolated cardiac tissue. [149] [150] This depression of cardiac contractility is proportional to the conduction blocking potency of the various agents in isolated nerves [150] and in dogs [151] [152] [153] (Table 13-11) . Thus, bupivacaine and tetracaine are more potent cardiodepressants than lidocaine, which, in turn, is a more potent cardiodepressant than chloroprocaine.

Local anesthetics may depress myocardial contractility by affecting calcium influx and triggered release. For example, procaine blocks the intracellular release of calcium in isolated sarcoplasmic reticular preparations. [154] However, in the isolated guinea pig heart, an increase in the extracellular concentration of calcium failed to reverse the negative inotropic action of bupivacaine or lidocaine. [155]

Voltage-clamp studies show that lidocaine inhibits cardiac sarcolemmal Ca^{2+} currents as well as Na^+ currents. [156] This action alone should be antagonized by an increase in extracellular Ca^{2+}, so it is likely that the negative inotropy of local anesthetics involves several mechanisms, not just the blockade of inward currents.

Direct Peripheral Vascular Effects

Local anesthetic drugs exert a biphasic effect on peripheral vascular smooth muscle. Low concentrations of lidocaine and bupivacaine produced vasoconstriction in the cremaster muscle of rats, whereas high concentrations increased arteriolar diameter, indicative of vasodilation. [60] [61]

In vivo studies have also demonstrated that small doses of

TABLE 13-11 -- Comparative Effect of Various Local Anesthetic Drugs on Cardiac Contractility and Cardiac Output

DRUG	RELATIVE ANESTHETIC POTENCY	ISOLATED GUINEA PIG ATRIA (50%) (mu g/mL)	CARDIAC OUTPUT IN DOGS (50%) (mg/kg)
Procaine	1	277	100
Chloroprocaine	1	102	30
Cocaine	2	56	--
Lidocaine	2	67	30
Prilocaine	2	42	40
Mepivacaine	2	55	40
Etidocaine	6	--	20
Bupivacaine	8	6	10
Tetracaine	8	6	20

local anesthetics decrease peripheral arterial flow without any change in arterial blood pressure, whereas larger doses increased blood flow. [56] Cocaine is the only local anesthetic that consistently causes vasoconstriction at all concentrations, owing to its ability to inhibit the uptake of norepinephrine by storage granules and thus to potentiate neurogenic vasoconstriction. [157] [158]

Some studies in anesthetized animals and in isolated heart-lung preparations have found increases in pulmonary vascular resistance from local anesthetic infusions. [152] [153] [159] Addition of lidocaine to cultured smooth muscle cells acutely elevates intracellular Ca^{2+} and could be a mechanism for local vasoconstriction. How many of these pulmonary vascular effects are direct actions and how much they reflect responses to circulatory or respiratory depression from drug acting on the CNS are not determined.

Comparative Cardiovascular Toxicity

In recent years, the more potent drugs (i.e., bupivacaine and etidocaine) have been reported to cause rapid and profound cardiovascular depression (Ch. 57) . The cardiotoxicity of the more potent drugs such as bupivacaine appears to differ from that of lidocaine in the following manner: [49]

1. The ratio of the dosage required for irreversible cardiovascular collapse (CC) and the dosage that produces CNS toxicity (convulsions)--that is, the CC/CNS ratio--is lower for bupivacaine and etidocaine than for lidocaine.
2. Ventricular arrhythmias and fatal ventricular fibrillation may occur often following rapid intravenous administration of a large dose of bupivacaine, but they occur far less frequently with lidocaine.
3. The pregnant animal or patient may be more sensitive to the cardiotoxic effects of bupivacaine than the nonpregnant animal or patient.
4. Cardiac resuscitation is more difficult following bupivacaine-induced cardiovascular collapse.
5. Acidosis and hypoxia markedly potentiate the cardiotoxicity of bupivacaine.

Cardiovascular Collapse/CNS Ratio

In sheep, the CC/CNS dose and blood level ratios for bupivacaine and etidocaine were found to be lower than those for lidocaine. [160] A CC/CNS dose ratio of 7.1 ± 1.1 was found for lidocaine, a finding indicating that seven times as much drug was required to induce irreversible cardiovascular collapse as was needed to produce convulsions (Fig. 13-16) . The CC/CNS dose ratio for bupivacaine was 3.7 ± 0.5, whereas that for etidocaine was 4.4 ± 0.9, and the CC/CNS blood level ratio for lidocaine was 3.6 ± 0.3, compared with 1.6 to 1.7 for bupivacaine and etidocaine. At the time of cardiovascular collapse, higher concentrations of bupivacaine and etidocaine than of lidocaine were present in the myocardium, a finding that suggests that some of the enhanced cardiac toxicity of these more potent agents is due to greater myocardial uptake.

Ventricular Arrhythmias

Bupivacaine and, to a lesser degree, etidocaine may produce severe cardiac arrhythmias, including ventricular fibrillation, in various animal species [155] [161] [162] [163] [164] [165] (Table 13-12) . Ventricular arrhythmias were rarely seen with lidocaine, mepivacaine, or tetracaine. [166] These electrophysiologic effects of bupivacaine may result

in conduction abnormalities, leading to a reentrant type of arrhythmia similar to torsades de pointes arrhythmias. [162] Although the cardiac arrhythmias observed in bupivacaine-treated animals are due in part to a direct cardiac effect, injection of bupivacaine directly into certain regions of the brain resulted in the development of cardiac arrhythmias, a finding that may indicate a relationship between the CNS and cardiotoxic effects of bupivacaine. [167] [168]

Enhanced Cardiotoxicity in Pregnancy

A number of the cardiotoxic reactions reported following the use of bupivacaine occurred in pregnant patients (Ch. 57) . As a result, the 0.75 percent solution is no longer recommended for use in obstetric anesthesia in the United States. In studies in pregnant and nonpregnant sheep, the CC/CNS dose ratio of bupivacaine decreased from 3.7 ± 0.5 in nonpregnant to 2.7 ± 0.4 in pregnant animals. [160] However, little difference was observed in the CC/CNS blood level ratio, which varied from 1.6 ± 1.0 in nonpregnant animals to 1.4 ± 0.1 in pregnant ewes. The blood level of bupivacaine

Figure 13-16 Dose of lidocaine, bupivacaine, and etidocaine that produces convulsive activity (CD) and cardiovascular collapse (CC) in sheep.

at which circulatory collapse occurred was lower in pregnant animals, but no difference in the myocardial uptake of bupivacaine in pregnant and nonpregnant sheep was observed at the time of cardiovascular collapse. Thus, if the pregnant patient is more susceptible to the cardiotoxic effects of bupivacaine, this effect apparently is not related to a greater myocardial uptake of drug.

Subsequent electrophysiologic studies in rabbits *in vivo* have shown that both pregnancy and prolonged (4-day) progesterone treatment of previously ovariectomized females

TABLE 13-12 -- Ventricular Arrhythmias Following the Use of Lidocaine and Bupivacaine in Various Animal Preparations

ANIMAL MODEL	VENTRICULAR ARRHYTHMIAS	
	LIDOCAINE	***BUPIVACAINE***
Unanesthetized paralyzed cat	6% PVC	100% PVC
Anesthetized dog	0	0
Unanesthetized dog	0	40%--VT, VF
Unanesthetized sheep	0	80-100%--PVC, VT
Hypoxic, acidotic sheep	0	17-50%--VT, VF
Isolated guinea pig heart	0	33-50%--PVC bigeminy, trigeminy
Intracoronary injection in anesthetized pigs	VF at 64 mg	VF at 4 mg
Intracranial injections in cats	17% VT	100% VT
Intracranial injections in rats	55% VT No deaths	55% VT 50% deaths

PVC: premature ventricular contractions; VF: ventricular fibrillation; VT: ventricular tachycardia

lead to increased myocardial [169] [170] and peripheral nerve [165] [166] conduction block by local anesthetics. In the myocardium of these animals, there are a reduction of excitability and the occasional appearance of secondary slow waves in response to a single stimulus that could develop into a circus rhythm and could support ventricular tachycardia, leading to fibrillation and cardiac collapse.

Cardiac Resuscitation

Studies in acidotic and hypoxic sheep have demonstrated that cardiac resuscitation following bupivacaine-induced toxicity is difficult. [171] Studies in cats and hypoxic dogs rendered toxic with bupivacaine indicate that resuscitation is possible [172] [173] if massive doses of epinephrine and atropine are employed. In addition, bretylium, but not lidocaine, could raise the ventricular tachycardia threshold that was lowered by bupivacaine. [174] Other agents have been tested for their effects in resuscitation from bupivacaine cardiotoxicity. Amrinone was found to be effective in two studies in dogs, but it was ineffective in a study in rats. Case reports have suggested that either bretylium or phenytoin may be effective.

Ropivacaine

In response to reports of cardiovascular toxicity from accidental intravenous injections of bupivacaine, [102] a long-lasting amide local anesthetic was developed. Ropivacaine (Naropin) differs from bupivacaine both in the substitution of a propyl for the butyl group on the piperidine ring's tertiary nitrogen atom and in that it consists of a single enantiomer, the *S*-stereoisomer. Commercial bupivacaine is a

racemic mixture of both isomers, whereas lidocaine, lacking a chiral center, has no stereosymmetry. With these designed changes in molecular structure, it was hoped that ropivacaine would be less intrinsically cardiotoxic. The hope that it would be cleared more rapidly from the circulation if the drug were injected intravenously has, however, been confounded by the evidence that the *S*-enantiomers of mepivacaine and bupivacaine are metabolized by the liver more slowly than the corresponding *R*-enantiomers, as well as having a slower rate of total body clearance. [175] [176]

The cardiovascular toxicity of local anesthetics is complex, involving direct effects on the myocardium, [150] on vascular tissue [156] (both smooth muscle and its neuronal supply), and on the central innervation of the heart. [167] [177] In both neuronal and cardiac Na^+ channels, the S-isomers of these piperidine-containing local anesthetics are less potent than the *R*-isomers, [178] [179] but the stereopotency of the cardiovascular effects mediated through vascular tissue and CNS is not known. Because of the smaller propyl substituent, (S-)ropivacaine is slightly less potent than S-bupivacaine in its effect on single sodium channels [180] and on isolated nerve action potentials. [181] More germane to the direct cardiotoxic actions is that the very slow reversal of Na^+ channel blockade after a cardiac action potential, a hallmark of bupivacaine, is considerably faster with ropivacaine. [182] Such slow drug reversal has been related to persistent conduction slowing, reentry circuits, and the development of ventricular tachycardias leading to fibrillation. [148] In addition to these electrical differences, the negative inotropic potency of ropivacaine on isolated cardiac tissue appears to be considerably less than that of bupivacaine. [182] [183] Both electrical and mechanical differences in the toxic profiles may arise from the selective inhibition of Ca^{2+} currents by bupivacaine. [149] [166] [184]

Do the data so far support the claim of a greater therapeutic index for ropivacaine than bupivacaine, particularly with regard to cardiotoxicity? In clinical studies comparing potencies of ropivacaine and bupivacaine administered for brachial plexus [185] or lumbar epidural block, [186] [187] the anesthetic profiles of the drugs were almost identical. A third study comparing lumbar epidural 0.5 percent bupivacaine with 0.75 percent ropivacaine also found no significant differences in motor or sensory effects between the drugs at these different concentrations. [188] Overall, it appears that ropivacaine is slightly less potent than (11.3 to 11.5) or as potent as bupivacaine for regional anesthesia. In laboratory animals and in humans, ropivacaine also produces blocks of shorter duration than those due to bupivacaine. [187] [189] [190]

At the projected equipotent doses for nerve block, are the drugs equally toxic? The overall impression is that ropivacaine is less cardiotoxic than bupivacaine. In contrast to the studies on isolated tissues, ropivacaine and bupivacaine injected intravenously *in vivo* were cardiodepressant in the order of their nerve blocking potency. [191] [192] Electrical signs of conduction slowing *in vivo* are less with intravenous ropivacaine than with bupivacaine, [191] and cardiac collapse and ventricular

fibrillation in dogs were far more frequent with bupivacaine than with ropivacaine delivered at the same doses. [193] Chirality rather than the difference between propyl and butyl *N*-piperidine substituent may account for the greater safety of ropivacaine, for many fewer cardiotoxic events also occur when *S*-bupivacaine (levobupivacaine) rather than racemic bupivacaine is administered to sheep. In contrast, death from ventricular arrhythmias is comparable between ropivacaine and bupivacaine at equipotent doses in sheep. Convulsant doses of ropivacaine are larger than those of bupivacaine, but they are smaller than those of lidocaine. [194] [195]

Perhaps the most notable difference between these two drugs is that aggressive cardiac resuscitation after an intentional intravenous bolus in dogs led to effective reversal of the toxic effects far more frequently with ropivacaine than with bupivacaine. [193] Furthermore, intravenous ropivacaine is cleared from the circulation more rapidly than intravenous bupivacaine. [196] This feature enhances the safety of ropivacaine relative to bupivacaine when the drugs are used for repeated dosing or by infusion. Finally, the major problem with intravenous bupivacaine that prompted the search for a new long-lasting local anesthetic, namely, increased cardiovascular toxicity during pregnancy, [197] [198] appears to have been overcome with ropivacaine. The cardiotoxic profile of ropivacaine in pregnant ewes is the same as the corresponding profile in nonpregnant ewes. [198] For these several reasons, it appears that ropivacaine may be a significantly safer drug than bupivacaine for local and regional anesthesia.

Acidosis and Hypoxia

Hypercarbia, acidosis, and hypoxia potentiate the negative chronotropic and inotropic actions of lidocaine and bupivacaine in isolated cardiac tissue, and the combination of hypoxia and acidosis markedly potentiates the cardiodepressant effects of bupivacaine. Hypoxia and acidosis also increased the frequency of cardiac arrhythmias and the mortality rate in sheep following intravenous administration of bupivacaine. [171] [199] Hypercarbia, acidosis, and hypoxia occur very rapidly in some patients following seizure activity owing to the rapid accidental intravascular injection of local anesthetic agents. [200] Thus, the cardiovascular depression observed in some patients following accidental intravenous injection of bupivacaine may be related in part to the severe acid-base changes that occur during toxic reactions to this agent.

Methemoglobinemia

A unique systemic side effect associated with a specific local anesthetic is the development of methemoglobinemia following administration of large doses of prilocaine. [201] A dose-response relationship exists between the amount of prilocaine administered epidurally and the degree of methemoglobinemia; in general, 600-mg doses are required for development of clinically significant levels of methemoglobinemia. The metabolism of prilocaine in the liver results in the formation of *o*-toluidine, which is responsible for the oxidation of hemoglobin to methemoglobin. [202] The methemoglobinemia associated with the use of prilocaine is spontaneously reversible or may be treated by intravenous administration of methylene blue. With increased use of Emla (which contains prilocaine) for neonates and young infants, there has been a concern regarding the risk of methemoglobinemia. [203]

Standard dosing of Emla in term newborns produced minimal amounts of methemoglobin, and Emla should be regarded as very safe in the great majority of newborns. Risks may be increased in rare newborns made more susceptible by metabolic disorders and concomitant administration of other drugs that impair reduction of methemoglobin. [203]

Allergies

The aminoester drugs such as procaine may produce allergic-type reactions. These drugs are derivatives of *p*-aminobenzoic acid, which is known to be allergenic. The aminoamide local anesthetics are not derivatives of *p*-aminobenzoic acid, and allergic reactions to the amino- amides are extremely rare. Intradermal injections of aminoester anesthetics in patients without a presumptive history of local anesthetic allergy resulted in positive skin reactions in 30 percent of the patients, [204] but no cutaneous reactions occurred following the use of the aminoamide drugs. Similarly, the majority of patients with a history of alleged local anesthetic allergy showed a positive skin reaction to procaine, tetracaine, or chloroprocaine, but no positive cutaneous response was seen following administration of lidocaine, mepivacaine, or prilocaine. No signs of systemic anaphylaxis occurred in any of the patients. Although the aminoamide anesthetics appear to be relatively free of allergic-type reactions, solutions of these drugs may contain a preservative, methylparaben, whose chemical structure is similar to that of *p*-aminobenzoic acid.

Local Tissue Toxicity

Local anesthetic drugs employed clinically rarely produce localized nerve damage. Concentrations of lidocaine required to produce irreversible conduction blockade in isolated desheathed peripheral nerves overlap the concentrations used clinically, such as 2 percent, but these are applied clinically to ensheathed nerve *in situ,* embedded in drugabsorbing tissue. Irreversible block in desheathed nerve by lidocaine has a threshold of 20 mmol/L and a 50 percent effective concentration (EC_{50}) of 45 mmol/L (1.1%) as compared with the EC_{50} of 1 mmol/L for reversible impulse blockade *in vivo.*[205] The intrathecal administration of tetracaine or etidocaine in rabbits resulted in histopathologic spinal cord changes following the use of 2 percent tetracaine, which exceeds the maximum concentration of 1 percent employed for spinal anesthesia in humans. [206]

Although local anesthetics are usually packaged and injected at concentrations much higher than their physiologically effective range, in the process of delivery they are usually diluted sufficiently that no harm is done. If this dilution does not occur, however, long-term or permanent neural deficits do result. Thus, the application of 5 percent (200 mmol/L) lidocaine in viscous, dense solutions through narrow intrathecal catheters has been associated with a high frequency of cauda equina syndrome. [207] Laboratory investigations showed that such high concentrations of local anesthetics alone applied directly to bare nerve fibers produced irreversible conduction block in less than 5 minutes. [208] Indeed, previous studies on ensheathed peripheral nerves *in vivo* had shown neurologic and histologic changes following infiltration of the space surrounding the nerve with local anesthetics at concentrations as low as 1 to 2 percent. [209] Clinicians should be aware that the concentrations of formulated local anesthetic solutions are neurotoxic per se, and that their dilution, *in situ* or in the tissue, is essential for safe use.

In the late 1970s and early 1980s, prolonged sensory and motor deficits were reported in some patients following the epidural or subarachnoid injection of large doses of chloroprocaine. [210] [211] Studies in animals have proved contradictory regarding the potential neurotoxicity of chloroprocaine [212] [213] [214] [215] [216] [217] (Table 13-13) . The results of these studies suggest that the combination of low pH, sodium bisulfite, and inadvertent intrathecal dosing is responsible in part for the neurotoxic reactions observed following use of large amounts of chloroprocaine solution. Chloroprocaine itself at high concentrations may also be neurotoxic, but these concentrations are not achieved during properly positioned epidural anesthesia. The currently available commercial solutions of chloroprocaine do not contain sodium bisulfite. This was initially replaced by EGTA, a preservative and a high-affinity calcium chelator, which was occasionally reported to cause local muscle spasms after epidural administration. More recently, chloroprocaine has become available in an entirely preservative-free preparation. Chloroprocaine has unique utility when rapid plasma clearance is required to prevent excessive systemic accumulation of local anesthetic. Chloroprocaine has been used by epidural infusion in young infants when lidocaine and bupivacaine could not provide an effective therapeutic index. [218]

Concerns regarding local anesthetic-associated neurotoxicity were increased following studies of continuous spinal anesthesia using microcatheters. [207] A number of patients in these initial studies developed transient or longer-term radicular irritation or, in some cases, cauda equina syndrome. Investigations suggested that microcatheters may facilitate localized injection of high concentrations of drug, which are inadequately dispersed and diluted in cerebrospinal fluid, leading to high intraneural drug concentrations around sacral roots and consequent toxicity.

TABLE 13-13 -- Animal Studies Concerning Potential Neurotoxicity of 2-Chloroprocaine and Other Local Anesthetics

TYPE OF STUDY	RESULTS
In vitro rabbit vagus nerve	Local irritation with 2-CP but not lido and bup
In vivo rat sciatic nerve	No irritation with 2-CP and lido
In vitro rabbit vagus nerve	Irreversible block with commercial 2-CP and Na bisulfite but not with pure 2-CP
Spinal dog	Paralysis with 2-CP, but not with bup or low pH saline
Spinal rabbit	Paralysis with commercial 2-CP and Na bisulfite but not with pure 2-CP
Spinal sheep	Minimal toxicity with 2-CP, lido, bup, and control solution

Spinal monkey	Minimal toxicity with 2-CP and bup

bup, bupivacaine; 2-CP, 2-chloroprocaine; lido, lidocaine

Related investigations showed that single-shot spinal anesthesia with commonly recommended doses and concentrations of local anesthetics can produce more limited and transient neurologic symptoms (back pain, paresthesias, radicular pain, or hypesthesia). [219] Transient neurologic symptoms have since been observed with many different local anesthetics. Some studies have found that mepivacaine and lidocaine, at a range of dilutions, cause more frequent symptoms than bupivacaine. [220] The risk of transient neurologic symptoms following spinal anesthesia was not diminished by dilution of lidocaine from 5 to 1 to 2 percent. Differences in study design, method of questioning, and criteria for inclusion may be partially responsible for differences in prevalence of radicular sequelae in different studies. Intraoperative positioning also appears to be a risk factor. Patients having surgery in the lithotomy position appear at increased risk of neurologic symptoms following either spinal or epidural anesthesia. It is unknown at present why this association produces increased risk. Lithotomy position per se can produce neurologic sequelae and lower extremity compartment syndromes, particularly with prolonged surgery and use of the Trendelenburg position. Neurotoxicity appears to be unrelated to conduction block per se, because tetrodotoxin, a highly potent blocker of sodium channels, can produce intense conduction blockade without histologic or behavioral signs of nerve injury. [221]

Skeletal muscle changes have been observed following the intramuscular injection of local anesthetic agents such as lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. [222] [223] [224] In general, the more potent, longer-acting agents bupivacaine and etidocaine appear to cause more localized skeletal muscle damage than the less potent, shorter-acting agents lidocaine and prilocaine. This effect on skeletal muscle is reversible, and muscle regeneration occurs rapidly and is complete within 2 weeks following injection of local anesthetic agents. Furthermore, such skeletal muscle processes have not been associated with overt signs of local irritation and probably cannot account for transient neurological syndromes.

Prolonged Infusions of Local Anesthetics, Tachyphylaxis, and Development of Long-Duration Local Anesthetics

Local anesthetics are used increasingly by continuous infusion for several days following surgery or for weeks to months in the treatment of chronic malignant and nonmalignant pain. With prolonged infusions, there is the potential for delayed systemic accumulation and toxicity. Continuous infusions of bupivacaine up to 30 mg/h in adults for up to 2 weeks produced no overt CNS or cardiac toxicity, despite total plasma bupivacaine concentrations in the range from 2 to 5 mug/mL in several patients.

Apparent reductions in effectiveness of local anesthetic infusions may be due to a number of causes unrelated to tolerance per se, including dislodgement of epidural catheters and changes in the dermatomal origin or intensity of nociceptive inputs. In obstetric patients receiving epidural bolus injections, recurrence of pain prior to the next injection resulted in a reduction in the intensity and duration of block, whereas repeat injection prior to return of pain prevented this rapidly occurring form of tolerance, or tachyphylaxis. In postoperative patients, coadministration of systemic opioids prevented regression of segmental block in patients receiving thoracic epidural bupivacaine infusions. [225] Studies in rats suggest that both pharmacokinetic and pharmacodynamic mechanisms are involved. In a rat model, tachyphylaxis was linked to development of hyperalgesia, [226] and drugs that inhibit hyperalgesia, including *n*-methyl- D-aspartate receptor antagonists [227] and nitric oxide synthase inhibitors, [228] also prevented tachyphylaxis. Conversely, repeated sciatic injections of lidocaine produced reduced intraneural lidocaine content along with reduced duration of block. [229] In addition, compound action potential recordings from rat sciatic nerve following repeated blocks *in vivo* show diminished suppression of the compound action potential with repeated blocks (C. Wang, C. Berde, R. Wilder, unpublished observations, 1998).

Several methods are under investigation to produce long-duration nerve blockade. Liposomal encapsulation can prolong block, depending on the dose and the physical properties of the liposome (surface charge, size, lamellar structure). [230] [231] Local anesthetics can be incorporated into biodegradable polymer microspheres for sustained release. These preparations produce peripheral nerve block in animal models ranging from 2 to 8 days, depending on the dose, site, and species. [232] Prolonged duration local anesthesia also appears feasible by use of site 1 sodium channel toxins, e.g., tetrodotoxin, in combination with either local anesthetics or adrenergics. [233]

It remains to be determined whether prolonged-duration local anesthetics will receive widespread use in clinical practice. If they prove safe and effective, they may have potential utility in peripheral nerve blockade and wound infiltration, particularly for surgery of the thorax and abdomen, in which protective sensation is comparatively less important than for limb surgery.

References

1. Sanchez V, Arthur G, Strichartz G: Fundamental properties of local anesthetics. I. The dependence of lidocaine's ionization and octanol: buffer partitioning on solvent and temperature. Anesth Analg 66:159, 1987.

2. Sanchez V, Ferrante F, Cibotti N et al: Partitioning of tetracaine base and cation into phospholipid membranes: relevance to anesthetic potency (abstract). Reg Anesth 13(suppl):81, 1988.

3. Gissen A, Covino B, Gregus J: The differential sensitivities of mammalian nerve fibers to local anesthetic agents. Anesthesiology 53:467, 1980.

4. Courtney K: Structure-activity relations for frequency-dependent sodium channel block in nerve by local anesthetics. J Pharmacol Exp Ther 213:114, 1980.

5. Courtney K, Strichartz G: Structural elements which determine local anesthetic activity. In Strichartz G (ed): Handbook of Experimental Pharmacology: Local Anesthetics. Heidelberg, Springer, 1987, p 53.

6. Schreier S, Frezzatti WA, Araujo P et al: Effect of lipid membranes on the apparent pK of the local anesthetic tetracaine: Spin label and titration studies. Biochim Biophys Acta 769:231, 1984.

7. Ritchie J, Rogart R: Density of sodium channels in mammalian myelinated nerve fibers and nature of the axonal membrane under the myelin sheath. Proc Natl Acad Sci USA 74:74, 1977.

8. Hodgkin A: The Conduction of the Nervous Impulse. Springfield, Ill, Charles C Thomas, 1964.

9. Hille B: Ionic Channels of Excitable Membranes. Sunderland, Mass, Sinauer Associates, 1991.

10. Skou J: Enzymatic basis for active transport of Na^+ and K^+ across cell membrane. Physiol Rev 45:496, 1965.

11. Rushton W: A theory of the effects of fibre size in medullated nerve. J Physiol (Lond) 115:101, 1951.

12. Tasaki I: Nervous Transmission. Springfield, Ill, Charles C Thomas, 1953.

13. Condouris G, Goebel R, Brady T: Computer simulation of local anesthetic effects using a mathematical model of myelinated nerve. J Pharmacol Exp Ther 196:737, 1976.

14. Trevan J, Boock E: The relation of hydrogen ion concentration to the action of local anesthetics. Br J Exp Pathol 8:307, 1927.

15. Ritchie J, Ritchie B, Greengard P: The effect of the nerve sheath on the action of local anesthetics. J Pharmacol Exp Ther 150:160, 1965.

16. Hille B: The pH-dependent rate of action of local anesthetics on the node of Ranvier. J Gen Physiol 69:475, 1977.

17. Hille B: Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. J Gen Physiol 69:497, 1977.

18. Narahashi T, Frazier D, Yamada M: The site of action and active form of local anesthetics. I. Theory and pH experiments with tertiary compounds. J Pharmacol Exp Ther 171:32, 1970.

19. Frazier D, Narahashi T, Yamada M: The site of action and active form of local anesthetics. II. Experiments with quaternary compounds. J Pharmacol Exp Ther 171:45, 1970.

20. Strichartz G: The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. J Gen Physiol 62:37, 1973.

21. Ritchie J, Ritchie B: Local anaesthetics: effect of pH on activity. Science 162:1394, 1968.

22. Chernoff D, Strichartz G: Tonic and phasic block of neuronal sodium channels by 5-hydroxyhexano-2
6
-xylidide, a neutral lidocaine homologue. J Gen Physiol 93:1075, 1989.

23. Ulbricht W: Kinetics of drug action and equilibrium results at the node of Ranvier. Physiol Rev 61:785, 1981.

24. Shanes A, Freygang W, Grundfest H et al: Anesthetic and calcium action in the voltage-clamped squid giant axon. J Gen Physiol 42:793, 1959.

25. Courtney K, Kendig J, Cohen E: The rates of interaction of local anesthetics with sodium channels in nerve. J Pharmacol Exp Ther 207:594, 1978.

26. Chernoff D: Kinetics of local anesthetic binding to sodium channels: Role of pK_a. Boston, Massachusetts Institute of Technology, 1988.

27. Cahalan M, Almers W: Interactions between quaternary lidocaine, the sodium channel gates and tetrodotoxin. Biophys J 27:39, 1979.

28. Neumcke B, Schwarz W, Stampfli R: Block of Na channels in the membrane of myelinated nerve by benzocaine. Pflugers Arch 390:230, 1981.

29. Bekkers J, Greeff N, Keynes R et al: The effect of local anaesthetics on the components of the asymmetry current in the squid giant axon. J Physiol (Lond) 352:653, 1984.

30. Wang G, Brodwick M, Eaton D et al: Inhibition of sodium currents by local anesthetics in chloramine-T treated squid axons: The role of Na channel activation. J Gen Physiol 89:645, 1987.

31. Chernoff D, Strichartz G: Binding kinetics of local anesthetics to closed and open sodium channels during phasic inhibition: Relevance to anti-arrhythmic actions. In Hondeghem L (ed): Molecular and Cellular Mechanisms of Anti-Arrhythmic Agents. Mount Kisco, NY, Futura, 1989, p 307.

32. Bean B, Cohen C, Tsien R: Lidocaine block of cardiac sodium channels. J Gen Physiol 81:613, 1983.

33. Starmer C, Courtney K: Modeling ion channel blockade at guarded binding sites: Application to tertiary drugs. J Am Physiol Soc 251 H848, 1986.

34. Schwarz W, Palade P, Hille B: Local anesthetics: Effect of pH on use-dependent block of sodium channels in frog muscle. Biophys J 20:343, 1977.

35. Bokesch P, Post C, Strichartz G: Structure-activity relationship of lidocaine homologs producing tonic and frequency-dependent impulse blockade in nerve. J Pharmacol Exp Ther 237:773, 1986.

36. Yeh J, TenEick R: Molecular and structural basis of resting and use-dependent block of sodium current defined using disopyramide analogues. Biophys J 51:123, 1987.

37. Chernoff D, Strichartz G: Kinetics of local anesthetic inhibition of neuronal sodium channels: pH- and hydrophobicity-dependence. Biophys J 93:1075, 1990.

38. Chernoff D: Kinetic analysis of phasic inhibition of neuronal sodium currents by lidocaine and bupivacaine. Biophys J 58:53, 1990.

39. Butterworth J, Strichartz G: Molecular mechanism of local anesthesia: A review. Anesthesiology 72:711, 1990.

40. Schwarz W, Palade PT, Hille B: Local anesthetics: Effect of pH on use-dependent block of sodium channels in frog muscle. Biophys J 203:343, 1977.

41. Ragsdale D, McPhee J, Scheuer T et al: Molecular determinants of state-dependent block of Na^+ channels by local anesthetics. Science 265:1724, 1994.

42. Sunami A, Dudley S, Fozzard H: Sodium channel selectivity filter regulates antiarrhythmic drug binding. Proc Natl Acad Sci USA 94:14126, 1997.

43. Raymond S, Steffensen S, Gugino L et al: The role of length of nerve exposed to local anesthetics in impulse blocking action. Anesth Analg 68:563, 1989.

44. Raymond S, Thalhammer J, Strichartz G: Axonal excitability: endogenous and exogenous modulation. In Dimitrijevic MR (ed): Altered Sensation and Pain: Recent Achievements in Restorative Neurology. Basel, Karger, 1990, p 112.

45. Fink B: Toward the mathematization of spinal anesthesia. Reg Anesth 17:263, 1992.

46. Raymond S, Gissen A: Mechanisms of differential nerve block. In Strichartz G (ed): Handbook of Experimental Pharmacology: Local Anesthetics. Heidelberg, Springer, 1987, p 95.

47. Huang J, Thalhammer J, Raymond S et al: Susceptibility to lidocaine of impulses in different somatosensory afferent fibers of rat sciatic nerve. J Pharmacol Exp Ther 292:802, 1997.

48. Erdemir H, Soper L, Sweet R: Studies of factors affecting peridural anesthesia. Anesth Analg 44:400, 1965.

49. Rocco A, Raymond S, Murray E et al: Differential spread of blockade of touch, cold, and pinprick during spinal anesthesia. Anesth Analg 64:917, 1985.

50. Brzezinski M, Spink B, Dean R et al: Human liver carboxylesterase hCE-1: Binding specificity for cocaine, heroin, and their metabolites and analogs. Drug Metab Dispos 25:1089, 1997.

51. Pindel E, Kedishvili N, Abraham T et al: Purification and cloning of a broad substrate specificity human liver carboxylesterase that catalyzes the hydrolysis of cocaine and heroin. J Biol Chem 272:14769, 1997.

52. Wildsmith J, Gissen A, Gregus J et al: Differential nerve blocking activity of amino-ester local anaesthetics. Br J Anaesth 57:612, 1985.

53. Wildsmith J, Gissen A, Takman B et al: Differential nerve blockade: esters vs amides and the influence of pK_a. Br J Anaesth 59:379, 1987.

54. Gissen A, Covino B: Differential sensitivity of fast and slow fibres in mammalian nerve. III. Effect of etidocaine and bupivacaine on fast/slow fibres. Anesth Analg 61:570, 1982.

55. Scott D, McClure J, Giasi R et al: Effects of concentration of local anesthetic drugs in extradural block. Br J Anaesth 52:1033, 1980.

56. Blair M: Cardiovascular pharmacology of local anesthetics. Br J Anaesth 47(suppl):247, 1975.

57. Rosenberg P, Heinonen E, Jansson S et al: Differential nerve block by bupivacaine and 2-chloroprocaine. Br J Anaesth 52:1183, 1980.

58. Galindo A, Benavides O, Ortega de Munos S et al: Comparison of anesthetic solutions used in lumbar and caudal peridural anesthesia. Anesth Analg 57:175, 1978.

59. Covino B: Pharmacology of local anaesthetic agents. Br J Anaesth 58:701, 1986.

60. Johns R, DiFazio C, Longnecker D: Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. Anesthesiology 62:141, 1985.

61. Johns R, Seyde W, DiFazio C et al: Dose-dependent effects of bupivacaine on rat muscle arterioles. Anesthesiology 65:186, 1986.

62. Iida H, Watanabe Y, Dohi S et al: Direct effects of ropivacaine and bupivacaine on spinal pial vessels in canine. Anesthesiology 87:75, 1997.

63. Sinclair C, Scott D: Comparison of bupivacaine and etidocaine in extradural blockade. Br J Anaesth 56:147, 1984.

64. Fink B, Cairns A: Differential slowing and block of conduction by lidocaine in individual afferent myelinated and unmyelinated axons. Anesthesiology 60:111, 1984.

65. Fink B, Cairns A: Lack of size-related differential sensitivity to equilibrium conduction block among mammalian myelinated axons exposed to lidocaine. Anesth Analg 66:948, 1987.

66. Raymond SA, Steffensen SC, Gugino LD et al: The role of length of nerve exposed to local anesthetics in impulse blocking action. Anesth Analg 68:563, 1989.

67. Braid D, Scott D: The systemic absorption of local analgesic drugs. Br J Anaesth 37:394, 1965.

68. Drachman D, Strichartz G: Potassium channel blockers potentiate impulse inhibition by local anesthetics. Anesthesiology 75:1051, 1991.

69. Kocsis J: Functional characteristics of potassium channels of normal and pathological mammalian axons. In Ritchie J, Keynes R, Bolis L (eds): Ion Channels in Neural Membranes. New York, Alan R. Liss, 1986, p 123.

70. Hogan Q, Abram S: Neural blockade for diagnosis and prognosis: A review. Anesthesiology 86:216, 1997.

71. Littlewood D, Buckley P, Covino B et al: Comparative study of various local anaesthetic solutions in extradural block in labour. Br J Anaesth 51:475, 1979.

72. Moore D, Batra M: The components of an effective test dose prior to epidural block. Anesthesiology 55:693, 1981.

73. Concepcion M, Maddi R, Francis D et al: Vasoconstrictors in spinal anesthesia with tetracaine: A comparison of epinephrine and phenylephrine. Anesth Analg 63:134, 1984.

74. Swerdlow M, Jones R: The duration of action of bupivacaine, prilocaine and lignocaine. Br J Anaesth 42:335, 1970.

75. Albert J, Lofstrom B: Bilateral ulnar nerve blocks for the evaluation of local anesthetic agents. Acta Anaesthesiol Scand 9:203, 1965.

76. Eisenach J, Grice S, Dewan D: Epinephrine enhances analgesia produced by epidural bupivacaine during labor. Anesth Analg 66:447, 1987.

77. Eisenach J, Lysak S, Viscomi C: Epidural clonidine analgesia following surgery: Phase I. Anesthesiology 71:640, 1989.

78. Gissen A, Covino B: Differential sensitivity of fast and slow fibres in mammalian nerve. IV. Effect of carbonation of local anesthetics. Reg Anesth 10:68, 1985.

79. Bokesch P, Raymond S, Strichartz G: Dependence of lidocaine potency on pH and P_{CO_2}. Anesth Analg 66:9, 1987.

80. Wong K, Strichartz G, Raymond S: On the mechanism of potentiation of local anesthetics by bicarbonate buffer: Drug structure-activity studies on isolated peripheral nerve. Anesth Analg 76:131, 1993.

81. Morrison D: A double-blind comparison of carbonated lidocaine and lidocaine hydrochloride in epidural anaesthesia. Can J Anaesth 28:387, 1981.

82. Nickel P, Bromage P, Sherrill D: Comparison of hydrochloride and carbonated salts of lidocaine for epidural analgesia. Reg Anesth 11:62, 1986.

83. Eckstein K, Vincente-Eckstein A, Steiner R et al: Klinische Erprobung von Bupivacaine CO_2. Anaesthesist 27:1, 1978.

84. McClure J, Scott D: Comparison of bupivacaine hydrochloride and carbonated bupivacaine in brachial plexus block by the interscalene technique. Br J Anaesth 53:523, 1981.

85. Hilgier M: Alkalinization of bupivacaine for brachial plexus block. Reg Anaesth 10:59, 1985.

86. DiFazio C, Carron H, Grosslight K et al: Comparison of pH adjusted lidocaine solutions for epidural anesthesia. Anesth Analg 65:760, 1986.

87. Bedder M, Kozody R, Carig D: Comparison of bupivacaine and alkanized bupivacaine in brachial plexus anesthesia. Anesth Analg 67:48, 1988.

88. Cunningham N, Kaplan J: A rapid onset long acting regional anesthetic technique. Anesthesiology 41:509, 1974.

89. Cohen S, Thurlow A: Comparison of chloroprocaine-bupivacaine mixture with chloroprocaine and bupivacaine use individually for obstetric epidural analgesia. Anesthesiology 51:288, 1979.

90. Corke B, Carlson C, Detbarn W: The influence of 2-chloroprocaine on the subsequent analgesic potency of bupivacaine. Anesthesiology 60:25, 1984.

91. Badgwell JM, Heavner JE, Kytta J: Cardiovascular and central nervous system effects of co-administered lidocaine and bupivacaine in piglets. Reg Anesth 16:89, 1991.

92. Bromage P: Spread of analgesic solutions in the epidural space and their site of action: A statistical study. Br J Anaesth 34:61, 1962.

93. Fagraeus L, Urban B, Bromage P: Spread of analgesia in early pregnancy. Anesthesiology 58:184, 1983.

94. Datta S, Hurley R, Naulty J et al: Effect of pregnancy on bupivacaine induced conduction blockade in the rabbit vagus nerve. Anesth Analg 66:123, 1987.

95. Popitz-Bergez F, Leeson S, Thalhammer J et al: Intraneural lidocaine uptake compared to analgesic differences between pregnant and nonpregnant rats. Reg Anesth 22:363, 1997.

96. Datta S, Lambert D, Gregus J et al: Differential sensitivities of mammalian nerve fibers during pregnancy. Anesth Analg 62:1070, 1983.

97. Flanagan H, Datta S, Lambert D et al: Effect of pregnancy on bupivacaine induced conduction blockade in the rabbit vagus nerve. Anesth Analg 66:123, 1987.

98. Morris R, McKay W, Mushlin P: Comparison of pain associated with intradermal and subcutaneous infiltration with various local anesthetic solutions. Anesth Analg 66:1180, 1987.

99. McKay W, Morris R, Mushlin P: Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. Anesth Analg 66:572, 1987.

100. Bromage P, Pettigrew R, Crowell D: Tachyphylaxis in epidural analgesia. I. Augmentation and decay of local anesthesia. J Clin Pharmacol 9:30, 1969.

101. Harris W, Slater E, Bell H: Regional anesthesia by the intravenous route. JAMA 194:1273, 1965.

102. Albright G: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 51:285, 1979.

103. Reistad F, Stromskag K: Interpleural catheter in management of postoperative pain: A preliminary report. Reg Anesth 11:89, 1986.

104. Brismar B, Pettersson N, Tokies L et al: Postoperative analgesia with intrapleural administration of bupivacaine-adrenaline. Acta Anaesthesiol Scand 31:515, 1987.

105. Stromskag K, Reistad F, Holmquist E et al: Intrapleural administration of 0.25%, 0.375% and 0.5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg 67:430, 1988.

106. Rosenbert P, Schleinin B, Lepantalo M et al: Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 67:811, 1987.

107. Bromage P, Gertel M: An evaluation of two new local anaesthetics for major conduction blockade. Can J Anaesth 17:557, 1970.

108. Rocco A, Mallampati S, Boon J et al: Double blind evaluation of intrathecal bupivacaine and tetracaine. Reg Anaesth 9:183, 1984.

109. Bigler D, Hjortso N, Edstrom H et al: Comparative effects of intrathecal bupivacaine and tetracaine. Reg Anesth 9:183, 1984.

110. Concepcion M, Lambert D, Welch K et al: Tourniquet pain during spinal anesthesia: A comparison of plain solutions of tetracaine and bupivacaine. Anesth Analg 67:828, 1988.

111. Stewart A, Lambert D, Concepcion M et al: Decreased incidence of tourniquet pain during spinal anesthesia with bupivacaine: A possible explanation. Anesth Analg 67:833, 1988.

112. Chambers W, Littlewood D, Logan M et al: Effect of added epinephrine on spinal anesthesia with lidocaine. Anesth Analg 60:417, 1981.

113. Chambers W, Littlewood D, Scott D: Spinal anaesthesia with hyperbaric bupivacaine: Effect of added vasoconstrictors. Anesth Analg 61:49, 1982.

114. Evers H, Von Dardel O, Juhlin L: Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine (EMLA). Br J Anesth 57:997, 1985.

115. Hallen B, Uppfeldt A: Does lidocaine-prilocaine cream permit pain free insertion of catheters in children? Anesthesiology 57:340, 1982.

116. Ohlsen L, Englesson S, Evers H: An anaesthetic lidocaine/prilocaine cream (EMLA) for epicutaneous application tested for split skin grafts. Scand J Plast Reconstr Surg Hand Surg 19:201, 1985.

117. Bonadio W, Wagner V: TAC (tetracaine, adrenaline, cocaine) for the repair of minor dermal lacerations (letter). Pediatr Emerg Care 4:82, 1988.

118. Bonadio W: TAC: A review. Pediatr Emerg Care 5:128, 1989.

119. Smith G, Strausbaugh S, Harbeck-Weber C et al: New non-cocaine-containing topical anesthetics compared with tetracaine-adrenaline-cocaine during repair of lacerations. Pediatrics 100:825, 1997.

120. Burk RW 3rd, Guzman-Stein G, Vasconez LO: Tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction. Dermatol Surg 22:921, 1996.

121. Choi RH, Birknes JK, Popitz-Bergez FA et al: Safety of tumescent liposuction in 15,336 patients: National survey results. Dermatol Surg 21:459, 1995.

122. Covino B: Pharmacokinetics of local anesthetic drugs. In Prys-Roberts C, Hug CJ (eds): Pharmacokinetics of Anesthesia. Oxford, Blackwell Scientific Publications, 1984, p 202.

123. Covino B, Vassallo H: Local Anesthetics: Mechanisms of Action and Clinical Use. Orlando, Fla, Grune & Stratton, 1976.

124. Abdel-Salam A, Vonwiller J, Scott D: Evaluation of etidocaine in extradural block. Br J Anaesth 47:1081, 1975.

125. Wildsmith J, Tucker G, Cooper S et al: Plasma concentrations of local

anaesthetics after interscalene brachial plexus block. Br J Anaesth 49:461, 1977.

126. Tucker G: Pharmacokinetics of local anaesthetic agents. Br J Anaesth 47:213, 1975.

127. Tucker G, Mather L: Clinical pharmacokinetics of local anesthetics. Clin Pharmacokinet 4:241, 1979.

128. Tucker G, Mather L: Pharmacokinetics of local anaesthetics. Br J Anaesth 58:717, 1986.

129. Lofstrom J, Alm B, Bertler A et al: Lung uptake of lidocaine. Acta Anaesthesiol Scand 70:80, 1978.

130. Lofstrom J: Tissue distribution of local anesthetics with special reference to the lung. Int Anesthesiol Clin 16:53, 1978.

131. Strichartz G, Sanchez V, Arthur G et al: Fundamental properties of local anesthetics. II. Measured octanol: buffer partition coefficients and pK_a values of clinically-used drugs. Anesth Analg 71:158, 1990.

132. Boyes R: A review of the metabolism of amide local anaesthetic agents. Br J Anaesth 47:225, 1975.

133. Tucker G, Wiklund L, Berlin-Wahlen A et al: Hepatic clearance of local anesthetics in man. J Pharmacokinet Biopharm 5:111, 1977.

134. Nation R, Triggs E, Selig M: Lignocaine kinetics in cardiac and aged subjects. Br J Clin Pharmacol 4:439, 1977.

135. Mazoit J, Denson D, Samii K: Pharmacokinetics of bupivacaine following caudal anesthesia in infants. Anesthesiology 63:A465, 1992.

136. Yaster M, Aronoff D, Kornhauser D et al: The pharmacokinetics of lidocaine during caudal anesthesia in children. Anesthesiology 63:A465, 1985.

137. Agarwal R, Gutlove D, Lockhart C: Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine [with comments]. Anesth Analg 75:284, 1992.

138. McCloskey J, Haun S, Deshpande J: Bupivacaine toxicity secondary to continuous caudal epidural infusion in children [with comments]. Anesth Analg 75:287, 1992.

139. Stenson R, Constantino R, Harrison D: Interrelationships of hepatic blood flow, cardiac output and blood levels of lidocaine in man. Circulation 43:205, 1971.

140. Thomson P, Melmon K, Richardson J et al: Lidocaine pharmacokinetics in advanced heart failure, liver disease and renal failure in humans. Ann Intern Med 78:499, 1973.

141. Wagman I, DeJong R, Prince D: Effects of lidocaine on the central nervous system. Anesthesiology 28:155, 1967.

142. Englesson S: The influence of acid-base changes on central nervous system toxicity of local anesthetic agents. I. An experimental study in cats. Acta Anaesthesiol Scand 18:79, 1974.

143. Scott D: Evaluation of clinical tolerance of local anaesthetic agents. Br J Anaesth 47:328, 1975.

144. Arthur G, Scott D, Boyes R et al: Pharmacokinetic and clinical pharmacological studies with mepivacaine and prilocaine. Br J Anaesth 51:481, 1979.

145. Burney R, DiFazio C, Foster J: Effects of pH on protein binding of lidocaine. Anesth Analg 57:478, 1978.

146. Apfelbaum J, Shaw L, Gross J et al: Modification of lidocaine protein binding with CO. Can J Anaesth 32:468, 1985.

147. Moller R, Covino B: Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 67:107, 1988.

148. Clarkson C, Hohdeghem L: Mechanisms for bupivacaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 62:396, 1985.

149. Lynch C: Depression of myocardial contractility *in vitro* by bupivacaine, etidocaine and lidocaine. Anesth Analg 65:551, 1986.

150. Block A, Covino B: Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth 6:55, 1982.

151. Stewart D, Rogers W, Mahaffrey J et al: Effect of local anesthetics on the cardiovascular system in the dog. Anesthesiology 24:620, 1963.

152. Liu P, Feldman H, Covino B et al: Acute cardiovascular toxicity of procaine, chloroprocaine and tetracaine in anesthetized ventilated dogs. Reg Anesth 7:14, 1982.

153. Liu P, Feldman H, Covino B et al: Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Reg Anesth 61:317, 1982.

154. Chamberlain B, Volpe P, Fleischer S: Inhibition of calcium induced release from purified cardiac sarcoplasmic reticulum vesicles. J Biol Chem 259:7547, 1984.

155. Tanz R, Heskett T, Loehning W et al: Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart. Anesth Analg 63:549, 1984.

156. Josephson I: Lidocaine block of Na, Ca and K currents of chick ventricular myocytes. J Mol Cell Cardiol 20:593, 1988.

157. MacMillan W: A hypothesis concerning the effect of cocaine on the action of sympathomimetic amines. Br J Pharmacol 14:385, 1959.

158. Lofstrom J: The effect of local anesthetics on the peripheral vasculature. Reg Anesth 17:1, 1992.

159. Wollenberger A, Krayer O: Experimental heart failure caused by central nervous system depressants and local anesthetics. J Pharmacol Exp Ther 94:439, 1948.

160. Morishima H, Pedersen H, Finster M et al: Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 63:134, 1985.

161. Dejong R, Ronfeld R, DeRosa R: Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 61:3, 1982.

162. Kotelko D, Shnider S, Dailey P et al: Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 60:10, 1984.

163. Kasten G: High serum bupivacaine concentrations produce rhythm disturbances similar to torsades de pointes in anesthetized dogs. Reg Anesth 11:20, 1986.

164. Sage D, Feldman H, Arthur G et al: The cardiovascular effects of convulsant doses of lidocaine and bupivacaine in the conscious dog. Reg Anesth 10:175, 1985.

165. Reiz S, Nath S: Cardiotoxicity of local anaesthetic agents. Br J Anaesth 58:736, 1986.

166. Coyle D, Sperelakis N: Bupivacaine and lidocaine blockade of calcium mediated slow action potentials in guinea pig ventricular muscle. J Pharmacol Exp Ther 242:1001, 1987.

167. Heavner J: Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricle of cats. Anesth Analg 65:444, 1986.

168. Thomas R, Behbehani M, Coyle D et al: Cardiovascular toxicity of local anesthetics: An alternative hypothesis. Anesth Analg 65:133, 1986.

169. Moller R, Datta S, Fox J et al: Effects of progesterone on the cardiac electrophysiologic action of bupivacaine and lidocaine. Anesthesiology 76:604, 1992.

170. Moller R, Covino B: Effects of progesterone on the cardiac electrophysiologic alteration produced by ropivacaine and bupivacaine. Anesthesiology 76:604, 1992.

171. Rosen M, Thigpen J, Shnider S et al: Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 64:491, 1985.

172. Chadwick H: Toxicity and resuscitation in lidocaine or bupivacaine infused cats. Anesthesiology 63:385, 1985.

173. Kasten G, Martin S: Successful cardiovascular resuscitation after massive intravenous bupivacaine overdosage in anesthetized dogs. Anesth Analg 64:491, 1985.

174. Kasten G, Martin S: Bupivacaine cardiovascular toxicity: Comparison of treatment with bretylium and lidocaine. Anesth Analg 64:491, 1985.

175. Mather L: Disposition of mepivacaine and bupivacaine enantiomer in sheep. Br J Anaesth 67:239, 1991.

176. Rutten A, Mather L, McLean C: Cardiovascular effects and regional clearances of I.V. bupivacaine in sheep: Enantiomeric analysis. Br J Anaesth 67:247, 1991.

177. Bernards C, Artru A: Hexamethonium and midazolam terminate dysrhythmias and hypertension caused by intracerebroventricular bupivacaine in rabbits. Anesthesiology 74:89, 1991.

178. Vanhoutte F, Vereecke J, Verbeke N et al: Stereoselective effects of enantiomers of bupivacaine on the electrophysiological properties of guinea pig papillary muscle. Br J Pharmacol 193:1275, 1991.

179. Lee-Son S, Wang G, Concus A et al: Stereoselective inhibition of neuronal sodium channels by local anesthetics. Anesthesiology 77:324, 1992.

180. Wang G: Binding affinity and stereoselectivity of local anesthetics in single batrachotoxin-activated Na channels. J Gen Physiol 96:1105, 1990.

181. Covino B, Datta S, Flanagan H et al: Comparison of bupivacaine- and ropivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 68:724, 1989.

182. Arlock P: Actions of three local anaesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (V_{max}). Pharmacol Toxicol 63:1, 1988.

183. Pitkanen M, Feldman H, Arthur G et al: Chronotropic and inotropic effects of ropivacaine, bupivacaine and lidocaine in the spontaneously

beating and electrically paced isolated perfused rabbit heart. Reg Anesth 17:183, 1992.

184. Moller R, Covino B: Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiology 72:322, 1990.

185. Hickey R, Hoffman J, Ramamurthy S: A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block. Anesthesiology 74:639, 1991.

186. Brown D, Carpenter R, Thompson G: Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. Anesthesiology 72:633, 1990.

187. Kerkamp H, Gielen M, Edstrom H: Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar anesthesia. Reg Anesth 15:204, 1990.

188. Katz J, Knarr D, Bridenbaugh P: A double-blind comparison of 0.5% bupivacaine and 0.75% ropivacaine administered epidurally in humans. Reg Anesth 15:250, 1990.

189. Feldman H, Covino B: Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amide local anesthetic, in the rat and dog. Anesth Analg 67:1047, 1988.

190. Nolte H, Fruhstorfer H, Edstrom HH: Local anesthetic efficacy of ropivacaine (Lea 103) in ulnar nerve block. Reg Anesth 15:118, 1990.

191. Reiz S, Haggmark S, Johansson G et al: Cardiotoxicity of ropivacaine: A new amide local anaesthetic agent. Acta Anaesthesiol Scand 33:93, 1989.

192. Hurley R, Feldman H, Latka C et al: The effects of epinephrine on the anesthetic and hemodynamic properties of ropivacaine and bupivacaine after epidural administration in the dog. Reg Anesth 16:303, 1991.

193. Feldman H, Arthur G, Pitkanen M et al: Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. Anesth Analg 73:373, 1991.

194. Feldman H, Arthur G, Covino B: Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine and lidocaine in the conscious dog. Anesth Analg 69:794, 1989.

195. Rutten A, Nancarrow C, Mather L et al: Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine in sheep. Anesth Analg 69:291, 1989.

196. Arthur G, Feldman H, Covino B: Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. Anesth Analg 67:1053, 1988.

197. Santos A, Pedersen H, Harmon T et al: Does pregnancy alter the systemic toxicity of local anesthetics? Anesthesiology 70:991, 1989.

198. Santos A, Arthur G, Pedersen M et al: Systemic toxicity of ropivacaine during ovine pregnancy. Anesthesiology 75:137, 1991.

199. Sage D, Feldman H, Arthur G et al: Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia. Anesth Analg 63:1, 1984.

200. Moore D, Crawford R, Scurlock J: Severe hypoxia and acidosis following local anesthetic-induced convulsions. Anesthesiology 53:259, 1980.

201. Lund P, Cwik J: Propitocaine (Citanest) and methemoglobinemia. Anesthesiology 53:259, 1980.

202. Hjelm M, Holmdahl M: Biochemical effects of aromatic amines. Acta Anaesthesiol Scand 2:99, 1965.

203. Taddio A, Stevens B, Craig K et al: Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. N Engl J Med 336:1197, 1997.

204. Aldrete J, Hohnson D: Evaluation of intracutaneous testing for investigation of allergy to local anesthetic agents. Anesth Analg 49:173, 1970.

205. Bainton C, Strichartz G: Concentration dependence of lidocaineinduced irreversible conduction loss in frog nerve. Anesthesiology 81:657, 1994.

206. Adams H, Mastri A, Eicholzer A et al: Morphologic effects of intrathecal etidocaine and tetracaine on the rabbit spinal cord. Anesth Analg 53:904, 1974.

207. Rigler M, Drasner K, Krejcie T et al: Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 72:275, 1991.

208. Lambert L, Lambert D, Strichartz G: Irreversible conduction block in isolated nerve by high concentrations of local anesthetics. Anesthesiology 80:1082, 1994.

209. Kalichman M, Powell H, Myers R: Pathology of local anestheticinduced nerve injury. Acta Neuropathol (Berl) 75:583, 1988.

210. Ravindran R, Bond V, Tasch M et al: Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 58:447, 1980.

211. Reisner L, Hochman B, Plumer M: Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 58:452, 1980.

212. Barsa J, Batra M, Fink B et al: Prolonged neurologic blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 61:961, 1982.

213. Pizzolato D, Renegar O: Histopathological effects of long term exposure to local anesthetics on peripheral nerves. Anesth Analg 61:961, 1982.

214. Rosen M, Baysinger C, Shnider S et al: Evaluation of neurotoxicity of local anesthetics on peripheral nerves. Anesth Analg 62:802, 1983.

215. Ravindran R, Turner M, Miller I: Neurological effects of subarachnoid administration of 2-chloroprocaine-CE, bupivacaine and low pH normal saline in dogs. Anesth Analg 61:279, 1982.

216. Wang B, Hillman D, Spiedholz N et al: Chronic neurologic deficits and Nesacaine-CE: an effect of the anesthetic, 2-chloroprocaine, or the antioxidant, sodium bisulfate? Anesth Analg 63:445, 1984.

217. Gissen A, Datta S, Lambert D: The chloroprocaine controversy. II. Is chloroprocaine neurotoxic? Reg Anesth 9:135, 1984.

218. Henderson K, Sethna NF, Berde CB: Continuous caudal anesthesia for inguinal hernia repair in former preterm infants. J Clin Anesth 5:129, 1993.

219. Sakura S, Bollen AW, Ciriales R et al: Transient neurologic symptoms after spinal anesthesia [see comments]. Anesth Analg 81:1148, 1995.

220. Hampl KF, Schneider MC, Ummenhofer W et al: Transient neurological symptoms after spinal anaesthesia with 4% mepivacaine and 0.5% bupivacaine. Br J Anaesth 79:301, 1997.

221. Sakura S, Bollen A, Ciriales R et al: Local anesthetic neurotoxicity does not result from blockade of voltage-gated sodium channels. Anesth Analg 81:338, 1995.

222. Libelius R, Sonesson B, Stamenovic B et al: Denervation-like changes in skeletal muscle after treatment with a local anesthetic (Marcaine). J Anat 106:297, 1970.

223. Benoit P, Belt W: Destruction and regeneration of skeletal muscle after treatment with a local anesthetic, bupivacaine (Marcaine). J Anat 107:547, 1970.

224. Benoit P, Belt W: Some effects of local anesthetic agents on skeletal muscle. Exp Neurol 34:264, 1972.

225. Lund C, Mogensen T, Hjortso NC et al: Systemic morphine enhances spread of sensory analgesia during postoperative epidural bupivacaine infusion. Lancet 2:1156, 1985.

226. Lee KC, Wilder RT, Smith RL et al: Thermal hyperalgesia accelerates and MK-801 prevents the development of tachyphylaxis to rat sciatic nerve blockade. Anesthesiology 81:1284, 1994.

227. Sholas M, Wilder RT, Berde CB: Tachyphylaxis to sciatic nerve blockade persists in spinalized rats. Anesthesiology 81:A964, 1994.

228. Wilder R, Sholas M, Berde C: NG-nitro- L-arginine methyl ester (L-NAME) prevents tachyphylaxis to local anesthetics in a dosedependent manner. Anesth Analg 83:1251, 1996.

229. Choi R, Birknes J, Popitz-Bergez F et al: Pharmacokinetic nature of tachyphylaxis to lidocaine: Peripheral nerve blocks and infiltration anesthesia in rats. Life Sci Pharmac Lett 61:177, 1997.

230. Boogaerts J, Lafont N, Carlino S et al: Biodistribution of liposomeassociated bupivacaine after extradural administration to rabbits. Br J Anaesth 75:319, 1995.

231. Mowat J, Mok M, MacLeod B et al: Liposomal bupivacaine: Extended duration nerve blockade using large unilamellar vesicles that exhibit a proton gradient. Anesthesiology 85:635, 1996.

232. Curley J, Castillo J, Hotz J et al: Prolonged regional nerve blockade: Injectable biodegradable bupivacaine/polyester microspheres. Anesthesiology 846:1401, 1996.

233. Kohan DS, Yieh J, Lu NT et al: A re-examination of tetrodotoxin for prolonged duration local anesthesia. Anesthesiol 89:119, 1998.

234. Bonica JJ: Principles and Practice of Obstetric Analgesia and Anesthesia. Philadelphia, FA Davis, 1967.

235. Mather LE, Cousins MJ: Local anesthetics and their current clinical use. Drugs 18:185, 1979.

Chapter 14 - The Autonomic Nervous System

Jonathan Moss
Cheryl L. Renz

INTRODUCTION

Much of the action of the body in maintaining cardiovascular, gastrointestinal, and thermal homeostasis occurs through the autonomic nervous system (ANS). The ANS is also our primary defense against challenges to that homeostasis. It provides involuntary (outside of consciousness) control and organization of both maintenance and stress responses. In the words of Claude Bernard, "... nature thought it provident to remove these important phenomena from the capriciousness of an ignorant will." Activation of the sympathetic nervous system elicits what is traditionally called the "fight or flight" response, including redistribu-tion of blood flow from the viscera to skeletal muscle, increased cardiac function, sweating, salivation, and pupillary dilatation. The parasympathetic system governs activities of the body more closely associated with maintenance of function, such as digestive and genitourinary functions. A major goal of anesthetic administration is maintaining optimum homeostasis in the patient, in spite of powerful challenges to a sometimes tenuous physiologic balance. The intelligent administration of anesthetic care to patients requires a knowledge of ANS pharmacology in order to achieve desirable interactions of anesthetics with the involuntary control system and to avoid responses or interactions with deleterious effects. In addition, disease states may impair ANS function to a significant extent and may thereby alter the expected responses to surgery and anesthesia. Last, pos-sible negative effects of the human stress response have long been appreciated, and considerable effort has been expended in examining the possibility that modification or ablation of the stress response may improve perioperative outcome.

History and Definitions

Initially, nerves were thought to be connected in a giant syncytium. Claude Bernard, a student of Magendie, postulated the theory of chemical synapse transmission. Later, Sherrington initiated a systemic study of reflexes describing some characteristics of reflex function. A chemist, J.J. Abel, first synthesized epinephrine (EPI) in 1899, and his student Langley demonstrated that EPI caused the same effect as stimulating postganglionic sympathetic neurons. Langley found that when the nerve was cut and EPI was injected there was a more profound effect, thus demonstrating de-nervation supersensitivity. From these observations, the concept of chemical transmission in the ANS developed. Sir Henry Dale isolated choline and studied an ester, acetylcholine (ACh), in animals. He demonstrated that it caused a marked decrease in blood pressure and vasodilatation, mimicking parasympathetic activity.

Nerves are traditionally classified by the chemical transmitters they contain. Nerves containing ACh are called cholinergic, whereas those containing norepinephrine (NE) or EPI are called adrenergic. In addition to classifying nerves, the term "cholinergic" refers to other structures or functions that relate in some way to ACh. For instance, *cholinergic receptors (*or *cholinoceptors*) are proteins in cell membranes that react with ACh and cause the cell to respond in a characteristic way (e.g., muscles contract, glands secrete). *Cholinergic agonists* are drugs that act like ACh on cholinoceptors to cause the cell to react in its characteristic way. They are sometimes referred to as *cholinomimetic* drugs. *Cholinergic antagonists* are drugs that react with cholinoceptors to block the access by ACh and so prevent its action. These drugs may also be referred

to as *cholinolytic, cholinergic-blocking,* or *anticholinergic drugs.*

Because muscarine, a chemical isolated from a mushroom, causes effects similar to those produced by activation of the parasympathetic nervous system, it was thought to be the endogenous parasympathetic transmitter. Since then, drugs that mimic the effects of muscarine on the parasympathetically innervated structures, including the heart, smooth muscles, and glands, have been called *muscarinic* drugs. Because muscarinic drugs act mainly in the parasympathetic system, agonists sometimes are called *parasympathomimetic* drugs, whereas antagonists are called *parasympatholytic* drugs. As yet, there are no drugs marketed that are selective for one muscarinic effect or another.

In the early years of this century, nicotine was found to act on ganglionic and skeletal muscle synapses and on nerve membranes and sensory endings. Accordingly, drugs that act on these parts of the cholinergic system are called *nicotinic* drugs. Nicotinic drugs that are more specific in their action have been discovered and are referred to by the name of the system they affect, such as ganglionic drugs or neuromuscular drugs. Both agonists and antagonists exist in each category, with little crossover of effect between drugs acting at the ganglia and those acting at the neuromuscular junction.

For purposes of this chapter, cholinergic nerves include the following (Fig. 14-1) :

1. All the motor nerves that innervate skeletal muscle.
2. All postganglionic parasympathetic neurons.
3. All preganglionic parasympathetic and sympathetic neurons.
4. Some postganglionic sympathetic neurons, such as those that innervate sweat glands and certain blood vessels.
5. Preganglionic sympathetic neurons that arise from the greater splanchnic nerve and innervate the adrenal medulla.
6. Central cholinergic neurons.

Drugs mimicking the action of NE are referred to as *sympathomimetic,* whereas drugs inhibiting these effects of NE are called *sympatholytic.* NE is the transmitter acting at adrenergic nerves, whereas both EPI and NE are released by the adrenal medulla. Adrenergic receptors have been identified and subdivided into alpha- and beta-receptors and further subdivided into $alpha_1$, $alpha_2$, $beta_1$, $beta_2$, and so forth. $alpha_2$ -Receptors are primarily located on the presynaptic membrane, whereas $alpha_1$ -receptors mediate smooth muscle vasoconstriction. $beta_1$ -Receptors are found primarily on cardiac tissue, and $beta_2$ - receptors mediate smooth muscle relaxation in some organs. We define adrenergic neurons as follows:

1. Postganglionic sympathetic neurons.
2. Some interneurons.
3. Certain central neurons.

New Concepts of Transmitter Action

Until recently, nervous control of the vasculature was considered predominantly in terms of classic transmitters: NE and ACh. For many years, these were the only transmitters recognized in perivascular nerves. Beginning in the early 1960s, various other compounds, including monoamines, purines, amino acids, and polypeptides, were identified that fulfilled the criteria of functional neurotransmitters. [1] [2] Furthermore, as reviewed by Burnstock, [3] nonadrenergic, noncholinergic components are part of the ANS. Other transmitter candidates demonstrated in perivascular nerves using histochemical and immunohistochemical techniques include adenosine 5
-triphosphate (ATP), vasoactive intestinal polypeptide (VIP), substance P (SP), 5-hydroxytryptamine (5-HT), neuropeptide Y (NPY), and calcitonin gene-related peptide (CGRP). Immunocytochemical studies show that more than one transmitter or putative transmitter may be *colocalized* in the same nerve. *The most common*

combinations of transmitters in perivascular nerves are NE, ATP, and NPY in sympathetic nerves; ACh and VIP in parasympathetic nerves; and SP, CGRP, and ATP in sensory-motor nerves. Many of these putative transmitters act through *cotransmission,* which is the synthesis, storage, and release of more than one transmitter by a nerve. [4] Initially, the multiplicity

Figure 14-1 Autonomic nervous sys-tem neurotransmission. ACh, acetylcholine; NE, norepinephrine; Epi, epinephrine.

of transmitters released in various combinations appears random and bewildering, but a pattern is now emerging that clarifies the situation. Autonomic nerves exhibit "chemical coding": individual neurons subserving a specific physiologic function contain distinct combinations of transmitter substances. [5]

The concepts of cotransmission and neuromodulation have become accepted mechanisms in autonomic nervous control. In order to establish that transmitters coexisting in the same nerves act as cotransmitters, it is necessary to demonstrate that, on release, each substance acts postjunctionally on its own specific receptor to produce a response.

In the case of many, but not all, perivascular sympathetic nerves, there is evidence that NE and ATP act as cotransmitters, being released from the same nerves but acting on alpha$_1$ -adrenoceptors and P_2 -purinoceptors, respectively, to produce vasoconstriction [6] [7] (Fig. 14-2) (Figure Not Available) . ATP, once thought to act only as an electrical buffer for the charged NE, now is believed to mediate contraction through P $_{2X}$ -receptors by voltage-dependent calcium channels. The fast component of contraction appears to be mediated by these purinoceptors, whereas NE itself sustains contraction of muscle by acting on the alpha $_1$ -adrenoreceptor via receptor-operated calcium channels. Specific drugs have been designed to interact with this purinergic component. [8]

Neuromodulators modify the process of neurotransmission. Such neuromodulators may be circulating neurohormones, local agents, or neurotransmitter substances released from the same nerves or from others nearby. Neuromodulation can occur either prejunctionally, by decreasing or increasing the amount of transmitter released during transmission, or postjunctionally, by altering the extent or time course of neurotransmitter effect. In all known examples in which both prejunctional and postjunctional neuromodulation occur, these substances act in concert either to attenuate or to augment effective transmission. The rationale for such may reflect the variable geometry of the autonomic neuroeffector junction. [9] [10] Unlike the neuromuscular junction, the autonomic neuroeffector junction exists in a dynamic state and manifests only modest postjunctional specialization. Biogenic amines often must traverse wide distances. Given their short half-lives, neuromodulation provides a biologic mechanism for augmentation and prolongation of their action. [11]

NPY is also colocalized with NE and ATP. However, in some vessels, NPY has little, if any, direct action; instead, NPY acts as a neuromodulator, prejunctionally to inhibit the release of NE from the nerve and/or postjunctionally to enhance the action of NE [12] [13] (Fig. 14-3 (Figure Not Available) A). In other vessels, notably those of the spleen, skeletal muscle, and cerebral and coronary vasculature, NPY has direct vasoconstrictor actions. In the heart and brain, local intrinsic (nonsympathetic) neurons use NPY as the principal transmitter (Fig. 14-3 (Figure Not Available) B). In the spleen, NPY appears to act as a genuine cotransmitter with NE in perivascular sympathetic nerves [14] (Fig. 14-3 (Figure Not Available) C). The frequency of stimulation determines which vesicles are mobilized to release their transmitters.

Figure 14-2 (Figure Not Available) Diagram showing that adenosine triphosphate (ATP) and norepinephrine (NE) are released as cotransmitters from the sympathetic nerves supplying the vas deferens and some blood vessels. ATP acts on P_2 -purinoceptors on the smooth muscles to initiate excitatory junction potentials, action potentials, and a fast initial contraction involving electromechanical coupling via voltage-dependent calcium channels. In contrast, NE acts on alpha $_1$ -adrenoceptors to produce the second, slower phase of the contraction by pharmacomechanical (or at least spike-independent) coupling via receptor-operated calcium channels. Prejunctional alpha$_2$ -adrenoceptors and P_1 -purinoceptors can reduce transmitter release when activated by NE and adenosine (AD), respectively (prejunctional neuromodulation), whereas NE and ATP enhance each other's actions (postjunctional neuromodulation). *(Modified from Burnstock [7])*

Figure 14-3 (Figure Not Available) Schematic representation of different interactions that occur between neuropeptide Y (NPY) and adenosine triphosphate (ATP), and norepinephrine (NE) released from single sympathetic nerve varicosities. (A) Diagram showing what occurs in the vas deferens and many blood vessels, where NE and ATP, probably released from small granular vesicles, act synergistically to contract (+) the smooth muscle via alpha $_1$ -adrenoceptors and P_2 -purinoceptors, respectively. (B and C) Sympathetic neurotransmission in the heart and brain (B) and the spleen (C). *(Modified from Lincoln and Burnstock [15])*

A classic transmitter such as ACh coexists with VIP in the parasympathetic nerves of many organs, but in this instance the two transmitters are stored in separate vesicles. They can be released differentially at different stimulation frequencies, depending on where they are located. [15] [16] For example, in the salivary gland, they can act independently on acinar cells and glandular blood vessels [7] (Fig. 14-4) (Figure Not Available) . Cooperation is achieved by the selective release of ACh at low frequencies and of VIP at high frequencies of stimulation. Elements of pre- and postjunctional modulation have also been described. It is becoming increasingly apparent that in many biologic states, including pregnancy, [17] hypertension, and aging, the relationships among cotransmitters may be an important determinant of a compensatory response, allowing finer control of important physiologic function.

FUNCTIONAL ANATOMY

Sympathetic Nervous System

The sympathetic nervous system originates from the spinal cord in the thoracolumbar region, from the first thoracic through the second or third lumbar segment. The preganglionic sympathetic neurons have cell bodies within the horns of the spinal gray matter (the intermediolateral columns). Nerve fibers from these cell bodies extend to three types of ganglia, grouped as paired sympathetic chains, various unpaired distal plexus, or terminal or collateral ganglia near the target organ.

The 22 paired ganglia lie along either side of the vertebral column. Nerve trunks connect these ganglia to each other, and gray rami communicantes connect the ganglia to the spinal nerves. The preganglionic fibers leave the cord in the anterior nerve roots, join the spinal nerve trunks, and enter the ganglion at that level via the white (myelinated) ramus. Leaving the ganglion, postsynaptic fibers reenter the spinal nerve via the gray (unmyelinated) ramus, then go on to innervate pilomotor and sudomotor (sweat gland) effectors and blood vessels of the skeletal muscle and skin (Fig. 14-5) (Figure Not Available) . Sympathetic innervation of the trunk and limbs is thus carried by the spinal nerves.

The sympathetic distribution to the head and neck, enabling and mediating vasomotor, pupillodilator, secretory, and pilomotor functions, comes from the three ganglia of the cervical sympathetic chain. Preganglionic fibers of these cervical structures originate in the upper thoracic segments. In 80 percent of people, the stellate ganglion is formed by

Figure 14-4 (Figure Not Available) A classic transmitter, acetylcholine (ACh), coexists with vasoactive intestinal polypeptide (VIP) in parasympathetic nerves supplying the cat salivary gland. ACh and VIP are stored in separate vesicles; they can be released differentially at different stimulation frequencies to act on acinar cells and glandular blood vessels. Cooperation is achieved by the selected release of ACh at low-impulse frequencies and of VIP at high frequencies. Pre- and postjunctional modulation is indicated. *(Modified from Burnstock [7])*

Figure 14-5 (Figure Not Available) Autonomic nervous system. Pre, preganglionic neuron; post, postganglionic neuron; RC, ramus communicans. *(Modified from Ganong [149])*

the fusion of the inferior cervical ganglion with the first thoracic ganglion on each side (Chs. 43 and 70).

The unpaired prevertebral ganglia reside in the abdomen and pelvis anterior to the vertebral column and are primarily the celiac, superior mesenteric, aorticorenal, and inferior mesenteric ganglia. The celiac ganglion is innervated by T5-T12 and innervates the liver, spleen, kidney, pancreas, small bowel, and proximal colon. Many preganglionic fibers from T5 to T12 may pass through the paired paravertebral ganglia to form the splanchnic nerves; most do not synapse until in the celiac ganglion, whereas others innervate the adrenal medulla. The superior mesenteric ganglion innervates the distal colon, whereas the inferior mesenteric ganglion subserves the rectum, bladder, and genitals (Fig. 14-6) (Figure Not Available) . Postganglionic fibers arising from the synaptic links of upper thoracic sympathetic fibers in vertebral ganglia form terminal cardiac, esophageal, and pulmonary plexus. These fibers also innervate the viscera of the abdomen and pelvis. Ganglia of the third type, the terminal or collateral ganglia, are small, few in number, and near their target organs. The adrenal medulla and other chromaffin tissue are homologous to sympathetic ganglia and all are derived embryonically from neural crest cells; unlike sympathetic ganglia, the adrenal medulla releases both EPI and NE.

Sympathetic preganglionic fibers are relatively short, because sympathetic ganglia are generally close to the central nervous system (CNS), but they are distant from the effector organs; therefore, postganglionic fibers run a long course before innervating effector organs (see Fig. 14-1) . The distribution is also diffuse and is capable of amplification: preganglionic

Figure 14-6 (Figure Not Available) Schematic representation of the autonomic nervous system depicting the functional innervation of peripheral effector organs and the anatomic origin of peripheral autonomic nerves from the spinal cord. Although both paravertebral sympathetic ganglia chains are presented, the sympathetic innervation to the peripheral effector organs is shown only on the right part of the figure, whereas the parasympathetic innervation of peripheral effector organs is depicted on the left. The roman numerals on nerves originating in the tectal region of the brain stem refer to the cranial nerves that provide parasympathetic outflow to the effector organs of the head, neck, and trunk. *(From Ruffolo [21])*

sympathetic fibers may pass through multiple ganglia before actually synapsing, so terminal fibers may contact large numbers of postganglionic neurons. Terminal fibers of preganglionic axons may synapse with more than 20 ganglia; in addition, one cell may be supplied by several preganglionic fibers. *Sympathetic nerves need not synapse solely in the ganglion of their origin, but they can course up and down the paired ganglia of the spinal cord.* Thus, sympathetic response is not confined to segments from which the stimulus originates. This allows for a more dramatic response, with diffuse discharge of the sympathetic system.

Autonomic reflexes remain after transection of the spinal cord. The autonomic reflexes are normally inhibited by supraspinal feedback, but this supraspinal inhibition is lost with the division of the spinal tracts. Thus, after transection, trivial stimuli may elicit an exaggerated sympathetic discharge. (See the discussion of spinal cord transection in the section *Autonomic Dysfunction.*)

Parasympathetic Nervous System

The parasympathetic nervous system arises from cranial nerves III, VII, IX, and X, as well as from sacral segments. *Unlike in the sympathetic nervous system, the ganglia of the parasympathetic nervous system occur proximal to or within the innervated organ.* This location of ganglia makes the parasympathetic nervous system more targeted and less robust than the sympathetic nervous system.

Preganglionic fibers of the parasympathetic nervous system originate in three areas of the CNS: the midbrain, medulla oblongata, and the sacral part of the spinal cord. Fibers arising in the Edinger-Westphal nucleus of the oculomotor nerve course in the midbrain to synapse in the ciliary ganglion. This pathway innervates the smooth muscle of the iris and the ciliary muscle. In the medulla oblongata lie parasympathetic components of the facial (lacrimatory nucleus), glossopharyngeal, and vagus (dorsal nucleus) nerves. The facial nerve gives off parasympathetic fibers to the chorda tympani and greater superficial petrosal nerve, which subsequently synapse in the ganglia of the submaxillary or sublingual glands and the sphenopalatine ganglion, respectively. The glossopharyngeal nerve synapses in the otic

ganglion. These postganglionic fibers innervate the mucous, salivary, and lacrimal glands; they also carry vasodilator fibers.

The vagus is unquestionably the most important of the parasympathetic nerves. The vagus transmits fully three-fourths of the traffic of the parasympathetic nervous system. It supplies the heart, tracheobronchial tree, liver, spleen, kidney, and all the gastrointestinal tract except the distal colon. The preganglionic fibers of the vagus are long, whereas the postganglionic fibers are short. Most vagal fibers do not synapse until they arrive at small ganglia on and about the thoracic and abdominal viscera. Although the parasympathetic nerves may synapse with a 1:1 ratio of nerve to effector cells, the vagal innervation of the Auerbach plexus may connect 1 nerve fiber to 8,000 cells.

Finally, the second through fourth sacral segments contribute the nervi erigentes, or pelvic splanchnic nerves. They synapse in terminal ganglia associated with the rectum and genitourinary organs.

Enteric Nervous System

Given the importance of clinical phenomena such as nausea, vomiting, and alterations in bowel and bladder function associated with anesthesia, it is surprising how little is understood about the third branch of the ANS. The enteric nervous system is the system of neurons and their supporting cells found within the walls of the gastrointestinal tract, including the neurons within the pancreas and gallbladder. [18] The history of this system is as rich as its innervation: Meissner (1829-1903) and Auerbach (1828-1897) first described the ganglionated plexus of the system; Dogiel (1852-1922) recognized and classified the unique morphologies of enteric neurons and correctly predicted that differences in shape would indicate differences in function; Bayliss (1860-1924) and Starling (1866-1927) showed the existence of polarized reflexes operating in the intestine independent of extrinsic influences; John Langley defined the unusual features of the enteric nervous system and classified it as the "third division of the autonomic nervous system." *The enteric nervous system contains as many nerve cells as the spinal cord.* It is derived from neuroblasts of the neural crest that migrate to the gastrointestinal tract along the vagus nerve.

One major difference between the enteric nervous system and the sympathetic and parasympathetic branches of the ANS is its extraordinary degree of local autonomy. Digestion and peristalsis occur after spinal cord transection or during spinal anesthesia, although sphincter function may be impaired (see later).

Although functionally discrete, the gut is influenced by sympathetic and parasympathetic activity. The sympathetic preganglionic fibers from T5 through L1 are inhibitory to gut action; a spinal anesthetic to the midthoracic levels removes this inhibition, yielding a contracted small intestine that may afford superior surgical conditions in combination with the profound muscle relaxation of a spinal anesthetic. [19] The sphincters are relaxed, and peristalsis is normally active.

NE present within the gut is the transmitter of postganglionic sympathetic neurons to the gut. For example, if the contents of the upper intestine become overly acidic or hypertonic, an adrenergically mediated enterogastric reflex occurs, reducing the rate of gastric emptying. The adrenergic neurons, which run to the myenteric ganglia of the gastrointestinal tract from the thoracic and lumbar spinal segments, are usually inactive in the resting individual. Reflex pathways both within and external to the alimentary tract cause discharge of these neurons. During abdominal surgery, when the viscera are handled, a reflex firing of the adrenergic inhibitory nerves inhibits the motor activity of the intestine for an extended period of time. This adrenergic inhibition is thought to be the basis of the common condition known as postoperative ileus. Loss of parasympathetic nervous control usually decreases bowel tone and peristalsis, but, over time, compensation is provided by the increased activity of the enteric plexus. Spinal cord lesions may remove sacral parasympathetic input, but cranial *parasympathetics* may still be carried by the branches of the vagus nerve down to the end-organ ganglia: colonic dilatation and fecal impaction (which may precipitate hypertension in autonomic dysreflexia) occur more often than small intestinal dysfunction.

Enteric neurons can be *sensory* (monitoring such factors as tension in the wall of the intestine or the chemical nature of its contents), *associative* (acting like interneurons), or *motor* (activating intestinal functions, for example, causing muscles to contract, vessels to dilate, or water and electrolytes to be transported). The motor neurons in the enteric nervous system may be either excitatory or inhibitory.

Certain plexus play important roles in the enteric nervous system. The *myenteric plexus,* also called the Auerbach plexus, is a network of nerve strands and small ganglia lying in the plane between the external longitudinal and circular muscle coats of the intestine. The *submucus plexus* (Meissner plexus) consists of nerve cell bodies, glial cells, and glial and neuronal processes, but they do not contain connective tissue or blood vessels. Within the ganglia, many neuronal processes contain vesicles that are the presumed storehouses of neurotransmitters.

What is the organizational pattern of these neurons, which can contain up to a dozen neurotransmitters? Unlike the sympathetic and parasympathetic nervous systems, in which geographic location can confer selective action, this is anatomically impossible in the gut. Hence, an alternative pattern, that of chemical coding for function, assumes an important organizational role. The combination of amines and peptides within the enteric neuron is thought to code for its function.

ACh is the principal excitatory trigger of the nonsphincteric portion of the enteric nervous system, causing muscle contraction. Cholinergic neurons have several roles in the enteric nervous system, including excitation of external muscle, activation of motor neurons augmenting water and electrolyte secretion, and stimulation of gastric cells. Neural control of gastrointestinal motility is mediated through two types of motor neurons: excitatory and inhibitory. These neurons act in concert on the circular smooth muscle layer, on sphincteric and nonsphincteric regions throughout the digestive tract, and supply the muscle of the biliary tree and the muscularis mucosae. Although excitatory motor neurons supply the external longitudinal muscle, it is not well established that all regions of the longitudinal muscle are supplied by inhibitory motor neurons. Enteric motor neurons to the circular muscle of the small and large intestine are activated by local reflex pathways contained within the wall of the intestine. Distention evokes polarized reflexes, including contraction orally and relaxation anally, which in synchrony constitute peristalsis. Nicotinic antagonists abolish enteric reflexes, suggesting that the sensory neurons or interneurons in the pathway are cholinergic. Thus, in cases of cholinergic overload, such as insecticide poisoning or "overreversal" of muscle relaxants, there is a tendency for the gut (in which cholinesterase is inhibited) to become hyperreactive.

There are, however, many other compounds that also participate in intestinal function. These include SP, a variety of opiate peptides, VIP, and a growing population of peptide hormones. There is evidence for *nonadrenergic, noncholinergic (NANC)* neurons in the small intestine and for similar cells that mediate gastrin release. Evidence also indicates that nitric oxide (NO), the same compound that dilates the vasculature and is secreted by the endothelial cells, may be an important component of interneurons and may be cosecreted with VIP (NO-containing-NANC neurons also mediate penile erection. [20]) In the sphincters, SP, opioid peptides, and ACh may be involved in excitatory transmission, although their relative roles may vary from sphincter to sphincter.

FUNCTION

Organization and Integration

The sympathetic system, in response to internal or external challenges, acts to increase heart rate, blood pressure, and cardiac output, to dilate the bronchial tree, and to shunt blood away from the intestines and other viscera to better supply voluntary muscles: teleologically, the body is now better prepared to deal with the challenge. Parasympathetic nervous input acts primarily to conserve energy and maintain organ function and to support the vegetative processes.

Most organs of the body exhibit dual innervation, with input from the sympathetic and parasympathetic systems frequently mediating opposing effects (Table 14-1) (Table Not Available) . [21] Stimulation of one system may have an excitatory effect on the end organ, whereas stimulation of the other system may have an inhibitory effect. The eye, heart, bronchial tree, and gastrointestinal and genitourinary systems are thus innervated. For example, sympathetic stimulation acts on the heart to increase rate and vigor of contraction and to enhance conduction through the atrioventricular (AV) node, whereas parasympathetic stimulation acts to decrease rate and contractility and to slow conduction through the AV node. One of the two systems normally dominates the organ's function, providing its "resting tone" (Table 14-2) . In a few organs, the sympathetic system alone provides innervation: certain blood vessels, the spleen, and piloerector muscles are examples.

To predict the effects of drugs, the interaction of the sympathetic and parasympathetic system in different organs must be understood. *Blockade of sympathetic function unmasks preexisting parasympathetic activity, and the converse relation is true.* For example, administration of atropine blocks the resting muscarinic tone of the parasympathetically dominated heart, and unopposed sympathetic tone then causes tachycardia. Autonomic denervation, which may occur with neuraxial anesthesia, diabetes, and myocardial infarction (MI), can be assessed by traditional methods, such as orthostatic hypotension, or more recently by changes in the time interval between successive heart beats, that is, beat-to-beat or heart rate variability, as a measure of sympathovagal balance. [22]

Adrenergic Function

Overview of Effects of Epinephrine

The adrenergic neurons influence many bodily functions, but the effects on circulation and respiration are among the most important. The effects of sympathetic nervous stimulation on the body's physiology are designed to facilitate fight or flight (Table 14-3) . Ventilation is increased by both a central effect on the ventilatory centers and bronchodilation. Cardiac output is increased through an increase in the contractile force of the heart as well as in the rate of contraction,

TABLE 14-1 -- Responses Elicited in Effector Organs by Stimulation of Sympathetic and Parasympathetic Nerves

(Not Available)

From Ruffolo [21]

and perfusion pressure for vital organs is increased by constriction of vessels to nonvital organs. Function of both the gastrointestinal and genitourinary systems is decreased as a result of a relaxation of the smooth muscle in these organs and contraction of their sphincters. Gastrointestinal secretory activity is inhibited, and adrenal medullary output is increased. Metabolism is generally stimulated to provide more fuel for bodily function in the form of glucose and fatty acids.

Both endogenous catecholamines, NE and EPI, possess alpha- and beta-receptor agonistic activity. However, NE has minimal

TABLE 14-2 -- Usual Sympathetic or Parasympathetic Dominance at Specific Effector Sites

SITE	PREDOMINANT TONE
Ciliary muscle	Parasympathetic
Iris	Parasympathetic
Sinoatrial node	Parasympathetic
Arterioles	Sympathetic
Veins	Sympathetic
Gastrointestinal tract	Parasympathetic
Uterus	Parasympathetic
Urinary bladder	Parasympathetic
Salivary glands	Parasympathetic
Sweat glands	Sympathetic (cholinergic)

$beta_2$ -receptor activity, whereas EPI stimulates both the $beta_1$ - and $beta_2$ -receptors (Table 14-4) . Fundamental differences exist between infusion of exogenous catecholamines and release of endogenous catecholamines. For example, NE, when infused, can elicit bradycardia, but when released in response to stress, it evokes tachycardia.

The physiologic responses mediated by alpha-adrenoceptors are wide ranging and important. alpha-Receptor-mediated activity is responsible for most of the sympathetically induced smooth muscle contraction throughout the body, including the ciliary muscle of the eye, vascular smooth muscle, bronchial smooth muscle, and ureteral smooth muscle. [23] In addition, the gastrointestinal and genitourinary sphincter mechanisms are also stimulated by alpha-adrenergic receptors. alpha-Receptor agonism also mediates sympathetic nervous system control of pancreatic insulin secretion. In the peripheral vasculature, postjunctional alpha $_1$ - and $alpha_2$ -receptors are found on both arteries and veins and act to mediate vasoconstriction independent of nerve supply.

beta-Receptor agonism appears to be primarily responsible for sympathetic stimulation of the heart, relaxation of vascular and bronchial smooth muscle, stimulation of renin secretion by the kidney, and several metabolic consequences, including lipolysis and glycogenolysis. The beta $_1$ -receptor mechanism is thought to be primarily

involved in the cardiac effects [24] and release of fatty acids and renin, whereas the beta$_2$-receptors are primarily responsible for smooth muscle

TABLE 14-3 -- Effects of Sympathetic Nervous System Activation

	STIMULATION	INHIBITION
Heart	Rate, conduction, contractility	
Blood vessels	Vasoconstriction (skin, gut, liver, heart, kidney)	Vasodilation (skeletal muscle, heart, brain)
Respiration	Respiratory center	Bronchodilation
Gastrointestinal tract	Sphincters	Smooth muscle
Genitourinary tract	Sphincters	Ureteral and uterine muscle
Metabolic and endocrine effects	Glycogenolysis (muscle, liver)	Insulin release (alpha stimulation or beta$_1$ antagonism)
	Lipolysis	
	Gluconeogenesis	
	Insulin release (beta$_1$)	
	Renin release	
	ADH release	

ADH, antidiuretic hormones or arginine vasopressin.

relaxation and hyperglycemia. In specialized circumstances, however, beta$_2$-receptors may also mediate cardiac activity (see later). Although acute changes in blood pressure or heart rate can be caused by NE or EPI, chronic hypertension does not appear to be related to levels of these hormones. [25] It is estimated that 85 percent of resting blood pressure is controlled by renin (Fig. 14-7) . An additional important effect of EPI includes increasing gap junctions in bone, causing an increase in circulating blood elements. [26] [27]

Psychologic and physical stimuli may evoke different compensatory responses. Whereas public speaking activates both the adrenal gland and the sympathetic nervous system, physical exercise elicits primarily a sympathetic response. [28]

TABLE 14-4 -- Adrenergic-Receptor Differentiation

	STIMULATION	INHIBITION
ALPHA		
Heart		
Blood vessels	Vasoconstriction (skin, gut, kidney, liver, heart)	
Gastrointestinal tract	Sphincters	
Genitourinary tract	Sphincters	
Metabolic and endocrine effects		Insulin release
BETA		
Heart	(1) Rate, conduction contractility	
Blood vessels		(2) Vasodilation (skeletal muscle, heart, brain)
Respiration	(?) Respiratory center	(2) Bronchodilation
Gastrointestinal tract		(2) Smooth muscle
Genitourinary tract		(2) Ureteral and uterine muscle
Metabolic and endocrine effects	(2) Glycogenolysis (muscle, liver)	
	(1) Lipolysis	
	(2) Gluconeogenesis	
	(1) Insulin release	
	(?) Renin release	
	(?) Antidiuretic hor-mone release	

1, mediated by beta$_1$-receptors; 2, mediated by beta$_2$-receptors; ?, controversial.

Thus, the stress response should not be conceived of as a uniform response, but it can vary in intensity and manifestations.

Blood Glucose

Catecholamines are released to mobilize glucose in the face of systemic hypoglycemia and thus normalize glucose values, providing cells with energy. Overall, sympathetic nervous stimulation via beta-receptor stimulation increases glycogenolysis in liver and muscle and liberates free fatty acids from adipose tissue, ultimately increasing blood glucose. In neonates, EPI plays an additional role in the exothermic breakdown of brown fat to maintain body temperature (nonshivering thermogenesis).

In addition, alpha$_2$- and beta$_2$-receptors are present in the pancreas. alpha$_2$-Receptor activation suppresses insulin secretion by pancreatic islets and inhibits lipolysis; blockade of these receptors may increase insulin release and may be associated with significant lowering of blood glucose levels. beta-Receptor stimulation increases glucagon and insulin secretion.

Potassium Shift

An additional function of plasma EPI involves regulation of serum potassium. beta-Adrenergic stimulation can initiate transient hyperkalemia, as potassium shifts out of hepatic cells with the glucose efflux produced by beta$_2$-stimulation. This effect is followed by a more prolonged hypokalemia as beta$_2$-stimulation drives potassium into red blood cells and muscle cells. Exogenously administered or endogenously released EPI stimulates the beta$_2$-receptors of red blood cells, activating adenylate cyclase and the sodium-potassium ATPase, driving potassium into cells. This leads to a reduction in serum potassium concentration and may contribute to the cardiac dysrhythmias accompanying MI and other stresses. beta$_2$-Adrenergic blockade has the theoretic advantage of inhibiting this potassium shift. However, the selective and nonselective beta blocker(s) have been shown to be equivalent in protecting the postinfarction heart against arrhythmias. [29] [30] [31] [32] [33]

Figure 14-7 The interactions of the renin-angiotensin-aldosterone and sympathetic nervous systems in maintaining blood pressure and volume. +, stimulating effects; -, inhibiting effects; RBF, renal blood flow; NE, norepinephrine; AI, angiotensin I; AII, angiotensin II; CE, converting enzyme.

Cholinergic Function

Overview of Effects of Acetylcholine

In contrast to the diffuse discharge of the sympathetic nervous system that constitutes the fight or flight response, the parasympathetic system is anatomically and functionally more localized in its effects. Parasympathetic activation conserves energy and maintains organ function. A massive parasympathetic response would only prostrate the organism, leaving it helplessly salivating, weeping, wheezing, vomiting, urinating, defecating, and seizing. Although the sympathetic system is needed for the emergency response to stressful situations, it is not necessary for survival; the parasympathetic system is, however, essential for the maintenance of life.

ACh release is the hallmark of parasympathetic activation. The actions of ACh are almost diametrically opposed to those of NE and EPI. In general, the muscarinic effects of ACh are qualitatively the same as the effects of vagal stimulation. *ACh is the only endogenous compound that causes simultaneous bradycardia and hypotension.*

The dose of ACh determines the effect or effects: a small intravenous (IV) dose of ACh causes generalized vasodilatation (including the coronary and pulmonary circulation), whereas a larger dose is required to demonstrate negative chronotropic and dromotropic effects. Significant numbers of muscarinic receptors exist in these vascular beds despite the apparent absence of cholinergic nerve supply to most vessels. Cholinergic receptor stimulation of the endothelium releases endothelium-derived relaxing factors (EDRF) causing vasodilation. However, if the endothelium is damaged, receptor stimulation by ACh causes vasoconstriction. A second mechanism of vessel relaxation by ACh is its inhibition of NE release from adrenergic nerve terminals.

ACh decreases the rate of cardiac contraction, the velocity of conduction in the sinoatrial (SA) and AV nodes, and contractility (although not as marked as the increase produced by sympathetic stimulation) in the atria. In the SA node, ACh causes membrane hyperpolarization, delaying resumption of the threshold potential and the ability to generate another action potential. This action slows the heart rate. Although the duration of the action potential and the effective refractory period are increased, the rate of conduction through atrial myocardium is unchanged. In the AV node, ACh decreases conduction velocity and increases the effective refractory period. This decrease in nodal conduction usually accounts for the complete heart block seen when large amounts of cholinergic agonists are given. In the ventricle, ACh decreases the Purkinje system automaticity, thereby increasing the fibrillation threshold. In the heart, muscarinic receptors present both pre- and postsynaptically are involved in these effects. ACh inhibits adrenergic stimulation of the heart, presynaptically by inhibiting the release of NE from sympathetic nerve endings and postsynaptically by opposing the effects of catecholamines on the myocardium.

Parasympathetic activation has many effects aside from the cardiovascular system. ACh stimulates the chemoreceptors of the carotid and aortic bodies. Cholinergic stimulation causes smooth muscle constriction, including that of bronchial walls. In the gastrointestinal and genitourinary tracts, there is constriction of the smooth muscle in the walls but relaxation of the sphincters. Topically administered, ACh constricts the smooth muscle of the iris, causing miosis.

Signs and symptoms of cholinergic overload reflect all these effects, with nausea and vomiting, intestinal cramps, belching, urination, and urgent defecation. All parasympathetic glands are stimulated to produce secretions, including the lacrimal, tracheobronchial, salivary, digestive, and exocrine glands.

Local Control of Vascular Tone

In addition to the pharmacologic effects of ACh that are mediated by the parasympathetic nervous system, ACh has a

significant effect on blood vessels, dilating virtually all vessels *in vivo.* In 1980, Furchgott and Zawadzki [34] noted that blood vessels that had intact endothelium would *dilate* when ACh was applied. If the endothelial cells were damaged, the vessels would *constrict.* Endothelial cells respond to ACh stimulation by producing one or more EDRF. [35] It now appears that the endothelial cells have receptors to numerous agonists including serotonin, adenosine, histamine, and catecholamines (Fig. 14-8) (Figure Not Available) . The radical NO is the first identified EDRF. It is produced by the endothelial cells in minute quantities, but it acts to relax the vascular smooth muscle cell and to limit or modify the actions of many vasoconstrictors. Nitroglycerin is degraded to NO in the vascular myo-cyte. The mechanism of this vasodilator action is mediated through activation of guanylate cyclase, through a protein phosphorylation cascade to phosphorylate actinomyosin directly. Thus, when the endothelium is damaged, as in ath-erosclerosis, there is diminished production of EDRF and increased constriction. This change explains why patients with damaged or diseased vessels react differently.

The biology of NO appears to be important. [36] It now appears that this simple compound, the mechanism of whose storage and release is still poorly understood, plays a prominent role in signal transduction and is a neurotransmitter in the cerebellum and gut (*N*-methyl- D-aspartate [NMDA] induces release of NO in cerebellum). [37] [38] NO is produced during the conversion of arginine to citrulline, by a class of enzymes known as NO synthases (NOS). This family of enzymes, now numbering five isoforms, has been identified, and the most common form, found in the cerebellum, has been cloned. [39] There is a requirement for flavins, reduced nicotinamide adenine dinucleotide phosphate (NADPH), and calmodulin. Some isoforms are inducible, and in septic (but not traumatic) shock or during chemotherapy, there is evidence that NO causes the hypotension that occurs. [40] Other isoforms of the enzyme, such as those in the brain, are constitutive and appear to reside in a population of cells that are tonically active. Curiously, the structure of NOS closely resembles that of cytochrome P-450. [41] There is also the suggestion that the head of the enzyme contains the NOS function, whereas the tail contains an NADPH diaphorase function. *Preclinical studies with NOS inhibitors suggest that the systemic vasculature is in a state of constant active vasodilation.*[42]

Endothelial cells exert important controls over the circulation in addition to producing NO. Endothelial cells metabolize many vasoactive amines, convert angiotensin I to angiotensin II, and secrete NO, prostacyclin, and the vasoconstrictive peptide endothelin-1 (ET-1). All three of these mediators (NO, ET-1, and prostacyclin) are local hormones released by endothelial cells to influence their immediate microenvironment. Prostacyclin and NO cause relaxation of underlying smooth muscle on the *abluminal* side, whereas in the lumen they act separately or in concert to prevent platelets from clumping onto the endothelium. There is clear synergism between the antiaggregating effect of prostacyclin and subthreshold concentrations of NO. Substances that activate prostacyclin generally stimulate NO release. Shear stress increases NO as an adaptive mechanism to dilate the circulation actively. Whereas NO works by the guanylate cyclase mechanism, prostacyclin works by activation of adenylate cyclase. Thus, although they work in concert, they activate different second messengers. [43]

Whereas prostacyclin and NO are short-lived vasodilators, injection of the vasoconstrictor ET-1 causes a powerful and long-lasting pressor effect. ET-1, which consists of 21 amino acids bound by 2 disulfide bonds, is enzymatically generated from the 39 amino acid pre-ET-1, known as big ET-1. The vasoconstrictor action of ET-1 is due to activation of endothelium receptors on smooth muscle. [44]

These three local hormones (NO, prostacyclin, and ET-1) appear to be operative in local control of the circulation. The prostacyclin system may be a mechanism reserved to reinforce the NO system in the presence of endothelial damage. Acting together, these two dilators provide an important defense mechanism against intravascular thrombosis.

Figure 14-8 (Figure Not Available) Schematic representation of potential modes of regulation of vascular tone by endothelial-related mechanisms. Norepinephrine (NA), adenosine triphosphate (ATP), calcitonin gene-related peptide (CGRP), substance P (SP), and vasoactive intestinal polypeptide (VIP) can be released from nerves in the adventitia (ADV) to act on their respective receptors in the media (MED) to cause vasoconstriction or vasodilation. ATP, acetylcholine (ACh), 5-hydroxytryptamine (5-HT), and SP released from endothelial cells (END) by shear stress or hypoxia act on their receptors on endothelial cells to cause release of endothelium-derived relaxing factors (EDRF) or prostaglandins (PG), which, in turn, act on the smooth muscle to cause relaxation. In areas denuded of endothelial cells, opposite effects may be produced by receptors on the smooth muscle. alpha, norepinephrine receptor; P_{2x} , P_{2x} -purinoceptor; P_{2y} , P_{2y} -purinoceptor; M, muscarinic receptor.

(Modified from Lincoln and Burnstock [13])

On the other hand, ET-1 can be produced locally in response to trauma such as wounds to the vessel wall. Long-term functions of these local hormones are of considerable interest in the pathophysiology of many disease states, including septic shock, pulmonary hypertension, and renal failure. [45] [46] [47]

PHARMACOLOGY

Adrenergic Pharmacology

Synthesis of Norepinephrine

NE is synthesized from tyrosine, which is actively transported into the varicosity of the postganglionic sympathetic nerve ending (Fig. 14-9) (Figure Not Available) . Tyrosine is synthesized from phenylalanine. One would therefore expect that in phenylketonuric patients, who lack phenylalanine hydroxylase, there would be a significant defect in the ANS. However, tyrosine is available from the diet as well as from phenylalanine, and no autonomic defect exists in phenylketonuric patients. In hypertensive rats, tyrosine may increase central adrenergic transmission, decreasing peripheral sympathetic outflow. [48] In hypotensive (hemorrhaged) rats, tyrosine may increase peripheral synthesis and release of catecholamines. Precursors are taken up in greater amounts in shock and may have beneficial effects on the efforts of the sympathetic nervous system to maintain perfusion pressure.

A series of steps results in the conversion of tyrosine to NE and (in the adrenal medulla) EPI. The first of these steps involves tyrosine hydroxylase (TH). *This cytoplasmic enzyme is the rate-controlling step for NE biosynthesis.* High levels of NE inhibit TH, and low levels stimulate the enzyme. Evidence indicates that during sympathetic nervous system stimulation, an increased supply of tyrosine also increases synthesis of NE. TH activity is modified by phosphorylation. TH depends on both a pteridine cofactor and the presence of molecular oxygen. Molecular oxygen, when in reduced quantity, may significantly reduce NE synthesis and may account for changes in wakefulness. Whereas acute control of TH occurs by altering enzyme activity, chronic stress can elevate TH levels by stimulating *synthesis* of new enzyme. Tyrosine is converted by the enzyme TH to dehydroxyphenylalanine (DOPA), which, in turn, is decarboxylated to dopamine by aromatic amino acid decarboxylase (DOPA decarboxylase), a relatively promiscuous enzyme in its substrate specificity. In Parkinson disease, central dopaminergic function is impaired. Administration of DOPA attempts to improve dopaminergic function in the

Figure 14-9 (Figure Not Available) Biosynthesis of norepinephrine and epinephrine in sympathetic nerve terminal (and adrenal medulla). (A) Perspective view of molecules. (B) Enzymatic processes. *(Modified from Tollenaere, [455] as modified by Vanhoutte [456])*

brain, because DOPA, but not dopamine, crosses the blood-brain barrier. Dopamine can and does act as a neurotransmitter in some cells, but in most adrenergic neurons dopamine is catabolized quickly by the enzyme monoamine oxidase (MAO), found particularly in mitochondria. Subsequently, dopamine is beta-hydroxylated within the vesicles to NE by the enzyme dopamine beta-hydroxylase (DBH).

In the adrenal medulla and to a limited extent in discrete regions of the brain, there is an additional enzyme, phenylethanolamine *N*-methyl transferase (PNMT), which methylates about 85 percent of the NE in the adrenal medulla to EPI. Glucocorticoids from the adrenal cortex pass through the adrenal medulla and can activate the system, so that stress-induced steroid release can cause increased EPI production. This local circulation amplifies the effects of glucocorticoid release. [49]

Storage of Norepinephrine

NE is stored within large, dense-core vesicles. Electron microscopy demonstrates that the dense cores in these vesicles are not due to NE but perhaps to other binding proteins also contained in the vesicle. The vesicles also contain calcium and a variety of peptides and ATP. Depending on the nature and frequency of physiologic stimuli, the ATP can be selectively released to cause an immediate postsynaptic effect via purinoreceptors.

Synaptic vesicles are heterogeneous and exist within functionally defined compartments. There appears to be an actively recycling population of synaptic vesicles and a reserve population of vesicles that is mobilized only on extensive stimulation. *Newly synthesized or taken up transmitters are preferentially incorporated into the actively recycling vesicles and thus are preferentially released on stimulation.* Therefore, drugs that mimic the neurotransmitter and are taken up presynaptically may be disproportionally represented in release. Functionally, NE is stored in compartments, of which 10 percent is readily releasable. *In general, 1 percent of stored NE is released with each depolarization, implying a significant functional reserve.* On stimulation, the contents of the vesicle are released into the synaptic cleft. Approximately 10 percent of stored NE is resistant to depletion, such as occurs with reserpine.

Synaptic vesicles have two fundamentally different functions: they take up and store neurotransmitters, and they both fuse with and bud from the presynaptic plasma terminal membrane. The proteins of synaptic vesicles can be divided into two functionally discrete classes. The first class consists of transport proteins providing the channels and pumps needed for the uptake and storage of neurotransmitters. The second class consists of proteins involved in the directed movement and docking reactions of the synaptic vesicle membrane.

Release of Norepinephrine

There are two fundamentally different processes by which the contents of the vesicle enter the synaptic cleft. The first of these occurs by leakage from the vesicles into the presynaptic cytoplasm and subsequent release. This mechanism, known as *indirect release,* occurs with drugs such as ephedrine or bretylium, which displace NE from the vesicles. Drugs that inhibit vesicular uptake, such as reserpine, also facilitate indirect release. Although it is easy to underestimate vesicular leakage, NE leakage from storage vesicles into the axoplasm actually exceeds leakage into the synaptic cleft by 100-fold and presynaptic reuptake by 10-fold, explaining the initial hypertension seen with drugs such as reserpine. [50]

The physiologic mechanism of release is known as exocytosis, in which the vesicle responds to the entry of calcium by initiating a process of vesicle docking, fusion, and endocytosis (the process by which vesicular membrane and proteins are recaptured) (Fig. 14-10) (Figure Not Available) . [47] Proof of the physiologic relevance of exocytosis in adrenergic release resides in numerous studies that demonstrate that the vesicular contents (DBH and NE) are present in the identical ratio in the stimulated superfusate as in the intact isolated vesicle preparations. Thus, the entire contents of the vesicle are liberated on nerve stimulation. Angiotensin II, prostacyclin, and histamine

Figure 14-10 (Figure Not Available) Release and reuptake of norepinephrine at sympathetic nerve terminals. aad, aromatic L-amino decarboxylase; DbetaH, dopamine beta-hydroxylase; dopa, L-dihydroxyphenylalanine; NE, norepinephrine; tyr hyd, tyrosine hydroxylase; solid circle, active carrier. *(Modified from Vanhoutte, [456] as modified by Shepherd and Vanhoutte [47])*

may potentiate release, whereas ACh and prosta-glandin E inhibit release. Because of its generalized importance in neurotransmitter release, the process of exocytosis has been extensively investigated in the past decade.

In this model, the vesicle merges with the cell membrane, a process dependent on microfilaments and influenced by calcium. A widely accepted view of the role of synaptic vesicles in transmitter release is as follows: when an action potential reaches a nerve terminal, the presynaptic plasma membrane depolarizes, and the voltage-gated calcium channels open at the active zone. Although only small amounts of calcium are required to initiate the process, the concentration of calcium in the specialized zones of active release, nanodomains, is very high. This concept of calcium nanodo-mains is postulated to represent the biologic explanation underlying augmentation and post-tetanic potentiation [51] in that the gradual diffusion of these high calcium levels from the nanodomains recruits new vesicles for release on subsequent stimulations (Ch. 20) . The dynamics of calcium levels in causing this phenomenon now appears well accepted. [52] The ensuing rise in intracellular calcium triggers exocytosis of synaptic vesicles, resulting in the release of neurotransmitters. [53] The synaptic vesicle membranes are reclaimed from the plasma membrane by endocytosis, and the vesicles eventually refill with neurotransmitters. A more detailed examination of this process can be seen in Figure 14-11 (Figure Not Available) . [54]

Various specific soluble and membrane-bound proteins have been identified that participate in docking, fusion, and endocytosis. There is increasing evidence that synaptotagmin serves as the intermediate between calcium entry and docking, because it binds calcium. [55] Microinjection of this protein participates in the step between docking and fusion, [56] and transgenic mice deficient in this protein exhibit attenuated neurotransmitter release. [57] Anatomic and molecular studies reveal vesicles that are predocked adjacent to the presynaptic membrane and permit rapid response. [54] [58] [59] The short latency between presynaptic excitation and vesicle release [60] has important functional implications, particularly in facilitating rapid transmission in the sympathetic nervous system.

The process by which docking and fusion occurs is incompletely understood, but it is thought to include two soluble proteins, *N*-ethylmaleimide-sensitive factor (NSF) and soluble NSF attachment protein (SNAP). These membrane proteins bind to cell membrane-bound SNAP receptors (SNARE), of which synaptobrevin, syntaxin, and 25-kd synaptasome-associated proteins (SNAP-25) have been identified. Syntaxin may serve to couple calcium channels and vesicle proteins. [61] It is now believed that the initial events involve activation of vesicles by the NSF-SNAP-SNARE complex, which synaptotagmin activates as soon as calcium entry reaches a critical level. [62] Evidence for the biologic relevance of these proteins derives from observations that tetanus toxin and botulinus toxin block vesicular release by binding to the docking and fusion proteins, [63] whereas microinjection of SNAP into neurons enhances exocytosis. [55] [64] Synaptic vesicles also contain guanosine triphosphate (GTP) binding proteins, which also participate in docking and fusion. [65] Recent evidence based on the uptake of fluorescent membrane dye and measurement of capacitance in nerve terminals demonstrates that the entire process of exocytosis, endocytosis, and vesicular reconstitution occurs in seconds. [66] [67] [68] [69]

The intimate chemistry of vesicular release is not a random event, but a highly differentiated process. The fact that exocytosis is so highly conserved from species to species indicates the biologic importance of this process. However, exocytosis is distinct from the generalized secretory process. First, exocytosis is a local pathway of the nerve terminal that is *independent* of organelles such as the Golgi complex, whereas regulated secretion, particularly of peptide hormones, typically requires repackaging of secretory vesicles via the Golgi complex. Second, exocytosis is far faster than secretion. Release of neurotransmitter from a single nerve

Figure 14-11 (Figure Not Available) Pathway of synaptic vesicle movement in the nerve terminal. Synaptic vesicles accumulate neurotransmitters (NT) by active transport (stage I) and then move to the plasma membrane (stage II), where they become docked at the active zone (stage III). Calcium (Ca^{2+}) influx after membrane depolarization triggers synaptic vesicle exocytosis and release of neurotransmitters (stage IV), after which the empty synaptic vesicles are endocytosed by clathrin-coated pits (stage V) and are recycled (stage VI) via an endosomal intermediate (stage VII). Stages V and VII have not been definitely proved, but they are probable on the basis of morphologic observations. *(Modified from Sudhof and Jahn [54])*

terminal can occur 50 times a second, requiring a coordinated and tightly linked regulation of underlying biochemical processes.

Although chromaffin cells in the adrenal medulla synthesize both EPI and NE, the two compounds are actually stored in and secreted from distinct chromaffin cell subtypes. Pharmacologic differences between cells containing NE and EPI have been described, and data suggest that there may be a preferential release from one or another form of chromaffin cell contingent on the nature of the stimulus. [70] Nicotinic agonists or depolarizing agents may cause the preferential release of NE, whereas histamine elicits predominantly EPI release. [71] [72] [73] Protein kinase C plays an important role in regulating catecholamine secretion from NE-containing chromaffin cells. [74]

Inactivation

Most of the NE released is rapidly removed from the synaptic cleft by either an amine uptake mechanism (uptake 1) or uptake by nonneuronal tissue (uptake 2). If a transmitter is to exert fine control over an effector system, as when NE controls blood pressure via the baroreceptor reflex, its half-life in the biophase (i.e., the extracellular space in close proximity of the receptor) must be very short. The uptake-1 mechanism represents the first and most important step in the inactivation of released NE. The majority of released NE is transported into the storage vesicle for reuse. This neurotransmitter uptake into synaptic vesicles is driven by an electrochemical proton gradient across the synaptic vesicle membrane. The vacuolar proton pump is a large, hetero-oligomeric complex, containing eight to nine different subunits. Following reuptake, the small amounts of NE not taken up into the vesicle are deaminated by MAO. There are several organ-specific forms of this enzyme.

In 1991, isolation and cloning of the human NE transporter were reported. [75] The cDNA sequence predicts a protein of molecular weight (MW) 69 kd with 12 to 13 highly hydrophobic regions compatible with membrane-spanning domains. The pharmacologic characteristics of this binding protein identify it as the cocaine binding site (K_i = 140 nm), although tricyclic antidepressants (desipramine and nortriptyline) were also potent antagonists.

Uptake of NE into the nerve varicosity and its return to the storage vesicle, albeit efficient, is not specific for the neurotransmitter. Some compounds structurally similar to NE may enter the nerve by the same mechanism and may result in depletion of the neurotransmitter. These false transmitters can be of great clinical importance. Moreover, some drugs that block reuptake either into the vesicle or into the synaptic ending itself may cause an enhanced response to catecholamines, that is, more NE is available to receptors. These drugs include cocaine and tricyclic antidepressants (Table 14-5). (Table Not Available)

Activity of the uptake-1 system varies greatly among different tissues. *Peripheral blood vessels, because of anatomic barriers, have almost no reuptake of NE, but they have the highest rate of synthesis in the body, whereas the highest rate of reuptake is found in the heart.* Thus, those drugs or disease states that alter biosynthesis or storage (e.g., alpha-methyldopa decreases storage) would be expected to have a more profound effect on blood pressure, whereas those that affect reuptake (e.g., cocaine) would be expected to affect cardiac rate and rhythm.

Typically, the lungs remove 25 percent of the NE that passes through their circulation, whereas EPI and dopamine pass through unchanged. Pulmonary uptake of NE appears to be a sodium-dependent, facilitated-transport process occurring in the endothelial cells of pre- and postcapillary vessels and pulmonary veins. There is no significant uptake by nerve endings. Pulmonary hypertension causes the diminution of NE uptake, presumably because of concomitant thickening of the pulmonary vasculature. [76] Diminished uptake is seen in patients with either primary or secondary pulmonary hypertension with elevated pulmonary vascular resistance. Although the functional significance of the endothelial uptake mechanism of the pulmonary vasculature is unknown, this occurs for other powerful vasoactive compounds, suggesting that the pulmonary endothelium functions

TABLE 14-5 -- Comparison of Direct- and Indirect-Acting Sympathomimetics

(Not Available)

Modified from Moore K: Drugs affecting the sympathetic nervous system. In Wingard L, Brody T, Larner J, et al (eds): Human Pharmacology: Molecular to Clinical. St. Louis, Mosby-Year Book, 1991, p 114.

to protect the left heart. Defects in the ANS are common in patients with congestive heart failure (CHF). The reuptake of NE is decreased, both at rest and during sympathetic activation, even more than with aging. Sustained sympathoexcitation results in increased neuronal release of NE. The spillover of cardiac NE is increased, predominantly attributable to increased rates of sympathetic nerve firing, rather than faulty neuronal reuptake of NE. [77] Cardiac NE spillover rates differ widely, even among patients with end-stage heart failure awaiting cardiac transplantation. [77] Studies of patients with CHF demonstrate that the heart is depleted of catecholamines. [78] Decreased vesicular leakage of NE in the failing heart because of depleted cardiac NE stores limits the increase in cardiac NE turnover that results from increased NE release. Because their ability to augment catecholamine release further is markedly impaired, patients with CHF compensate for decreases in systemic vascular resistance by further activation of the reninangiotensin system. Decreased clearance of catecholamines also occurs, and indeed some studies suggest that plasma catecholamine levels may provide a better guide to prognosis than traditional cardiovascular indices. [79] [80] Together, these events result in increased adrenergic drive, desensitization of beta-receptors, and depletion of NE stores, which contribute to insufficient inotropic function. [81] [82]

Metabolism

During storage and reuptake, a small amount of NE escapes uptake into the nerve ending and enters the circulation, where it is metabolized by MAO and/or catechol-*O*-methyl transferase (COMT). This metabolism occurs in the blood, liver, and kidney [83] (Fig. 14-12) (Figure Not Available) .

EPI, which is released by the adrenal medulla, is inactivated by the same enzymes. The final metabolic product of these inactivations is vanillylmandelic acid (VMA). The two catabolic enzymes and the vigorous uptake system account for an efficient clearance of catecholamines. *Because of this rapid clearance, the half-life of NE (and in fact most biogenic amines) in plasma is very short, less than 1 minute.* This short half-life necessitates administration of these agents by infusion. Another consequence of their short half-life is that measuring metabolic products, rather than catecholamines themselves, may be a more ideal measure of catecholamine production. For example, screening for an NE-producing pheochromocytoma is frequently done by measuring urine metanephrine and VMA. Only a small percentage of NE appears in the urine for assay.

Inhibition of MAO would be expected to have a great impact on the sympathetic function of a patient. MAO inhibitors (MAOI) are generally well tolerated, but the stability of the patient belies the fact that amine handling is fundamentally changed. Clinically important life-threatening drug interactions have been noted and are discussed in the section *Drugs and the Autonomic Nervous System.*

Other compounds can be metabolized by catabolic enzymes to produce "false transmitters." Although it is not used therapeutically, tyramine is the prototypic drug studied. Tyramine is present in many foods, particularly aged cheese and wines, or it can be synthesized from tyrosine. Tyrosine is decarboxylated in the liver and gut. Tyramine enters the sympathetic

Figure 14-12 (Figure Not Available) Metabolism of catecholamines. *(Modified from Lake et al [83])*

nerve terminal via the uptake-1 mechanism, displacing NE from the vesicles into the cytoplasm. This released NE leaks out from the cytoplasm and is responsible for the sympathomimetic effect of tyramine. However, a secondary effect can occur. In the vesicle, tyramine is converted by DBH into octopamine, which is eventually released as a false transmitter in place of NE, but without the expected effects, because it has only 10 percent of the potency of NE. [84] It is probably also clinically important to note that sodium plays a key role in the transport of NE into the cell. [85]

Adrenergic Receptors

Ahlquist originally identified alpha- and beta-receptors by their differing response to pharmacologic agents. Initially, alpha-adrenergic receptors were distinguished from beta-adrenergic receptors by their greater response to EPI and NE than to isoproterenol. The development of alpha- and beta-antagonists further supported the existence of separate alpha-receptors. The advent of radioligand binding techniques signaled an era of pharmacology in which subtypes of receptors could be more readily assessed.

Although it has long been traditional to classify adrenergic receptors as either alpha- or beta-, and more recently as alpha $_1$, alpha$_2$, beta$_1$, or beta$_2$ based on available drugs, the advent of molecular biology has suggested a more rational classification into three major subtypes and nine sub-subtypes [86] (Fig. 14-13) . Justification for such a scheme is derived from pharmacologic analyses of drug affinity patterns (see later), functional differences in signal transduction mechanisms, and primary structural differences in the receptors. Although such a classification is consistent with the available scientific evidence, the drugs currently available for clinical use may still be classified in the more traditional pattern. (Table 14-6) describes the distribution, response, typical agonists, and antagonists of the alpha $_1$ -, alpha$_2$ -, beta$_1$ -, and beta$_2$ -receptors.

alpha-Receptors

Whereas alpha$_1$ - and alpha$_2$ -receptors are traditionally differentiated based on pharmacologic characteristics, radioligand binding affinities have more recently been examined. At the alpha$_1$ -receptor prazosin is more potent than yohimbine, whereas the reverse is true at alpha $_2$ -receptors. Functional and binding assays and molecular biologic approaches have unequivocally confirmed the classification of alpha-adrenoceptors into subtypes. [87] Within alpha $_1$ -adrenergic receptors, alpha$_{1A/D}$ -, alpha$_{1B}$ - and alpha$_{1C}$ -receptors have been characterized. Several alpha $_2$ -isoreceptors (alpha$_{2A}$, alpha$_{2B}$, and alpha$_{2C}$) have been described. alpha$_2$ -Receptors can be expressed presynaptically or even in nonneuronal tissue. alpha $_2$ -Receptors are found in the peripheral nervous system and the CNS and in a variety of organs, including platelets, liver, pancreas, kidney, and the eye, where specific physiologic functions have been identified. [88] More recently, the predominant alpha$_2$ -receptor of the human spinal cord was identified as the alpha $_{2A}$ -subtype. [86] It appears that mammalian genomes contain two sets of at least three unique genes encoding the alpha-adrenoceptors. The genes encoding alpha $_2$ -receptors have been localized in chromosomes 2, 4, and 10.

There is more than theoretic relevance in subclassification of receptors. For example, the alpha-adrenergic receptors in the prostate gland are predominantly alpha $_{1A}$. Thus, therapy with selective alpha$_{1A}$ -antagonists for benign prostatic hypertrophy may avoid some of the postural hypotension and other deleterious effects that occur with less specific alpha-antagonists Localization of beta $_3$ -receptors to fat cells suggests a new therapy for obesity. Polymorphism of this beta-receptor subtype is associated with obesity and the potential for the development

Figure 14-13 Classification of adrenergic receptors.

TABLE 14-6 -- Distribution of alpha- and beta-Receptors

RECEPTOR	DISTRIBUTION	RESPONSE	AGONIST	ANTAGONIST
alpha$_1$	Smooth muscle	Constriction	Methoxamine Phenylephrine	Prazosin
alpha$_2$	Presynaptic	Inhibit norepinephrine release	Clonidine	Yohimbine

			Dexmedetomidine	
$beta_1$	Heart	Inotropy	Dobutamine	Metoprolol
		Chronotropy		
$beta_2$	Smooth muscle	Dilation	Terbutaline	
		Relaxation		

of diabetes. [89] [90] [91] There are also examples of point mutations in genes encoding beta $_2$ -receptors that are correlated with decreased downregulation of beta-receptors and nocturnal asthma. [92] [93]

Amino acid sequence comparisons indicate that alpha- receptors are members of the seven transmembrane segment gene superfamily utilizing G protein for signal transduction. A core of 175 amino acids constitutes the seven transmembrane regions that are highly conserved among different family members. [94] The plethora of receptor subtypes remains incompletely explained, although the observation that different signal transduction mechanisms are used suggests finer control and physiologic significance. It may be important that there is considerable variability in alpha-adrenergic receptor subtypes among species. [95]

Receptors can be presynaptic as well as postsynaptic. Presynaptic receptors may act as either heteroreceptors or autoreceptors. An *autoreceptor* is a presynaptic receptor that reacts with the neurotransmitter released from its own nerve terminal, providing feedback regulation. A *heteroreceptor* is a presynaptic receptor that responds to substances other than the neurotransmitter released from that specific nerve terminal.

Although several presynaptic receptors have been identified, the alpha $_2$ -receptor may be of the greatest clinical import. Presynaptic alpha $_2$ -receptors regulate the release of NE and ATP through a negative feedback mechanism. [96] Thus, activation of presynaptic alpha $_2$ -receptors by NE inhibits subsequent NE release in response to nerve stimulation. Clonidine is a prototype alpha $_2$ -agonist. In the human brain, ligand studies reveal a high density of alpha $_2$ -receptors, particularly in cerebral cortex and medulla. [97] This latter distribution may account for the bradycardiac and hypotensive responses to alpha $_2$ -agonist drugs. Whereas presynaptic $alpha_2$ -receptors and cholinergic receptors inhibit release, presynaptic beta- receptors stimulate release of NE.

beta-Receptors

The structure of the beta-adrenergic receptor was among the first to be ascertained and is well characterized. Like the alpha-receptor, the beta-receptor is one of the superfamily of proteins that have seven helices woven through the cellular membrane. These transmembrane domains are labeled M $_1$ through M_7 ; antagonists have specific binding sites, whereas agonists are more diffusely attached to hydrophobic membrane-spanning domains (Fig. 14-14) (Figure Not Available) . The extracellular portion of the receptor ends in an amino group. A carboxyl group occupies the intracellular terminus, and it is here that phosphorylation occurs. At these cytoplasmic domains, interaction with G proteins and kinases, including beta-adrenergic receptor kinase, occurs (see later). Interestingly, the beta- receptor has mechanistic and structural similarities with muscarinic, but not nicotinic, receptors, primarily in the transmembrane sections. Both muscarinic and beta-receptors are coupled to adenylate cyclase through G proteins, and both can initiate the opening of ion channels.

beta-receptors have been further divided into beta $_1$ -, $beta_2$ -, and $beta_3$ -subtypes, all of which increase cyclic adenosine monophosphate (cAMP) through adenylate cyclase and the mediation of G proteins. [99] Traditionally, the beta $_1$ -receptors were thought isolated to cardiac tissue, and beta $_2$ -receptors were believed to be restricted to vascular and bronchial smooth muscle. Although this model of distribution is still useful because it reflects the primary clinical effects of pharmacologic manipulation of the $beta_1$ - and $beta_2$ -receptor subtypes, the role of beta $_2$ -receptors in cardiac function is more important than indicated by this model. The beta $_2$ -receptor population in human cardiac tissue is sizable, accounting for 15 percent of the beta-receptors in the ventricles and 30 to 40 percent in the atria. [100] These $beta_2$ -receptors may play an important role in compensation for disease, helping to maintain response to catecholamine stimulation as beta $_1$ -receptors are downregulated during chronic catecholamine stimulation and CHF. [101] The $beta_2$ -population is almost unaffected in end-stage congestive cardiomyopathy. [102] In addition to positive inotropic effects, beta $_2$ -receptors in the human atria participate in the regulation of heart rate. The generation of cAMP in the human heart appears to be mediated primarily by $beta_2$ -receptors, although this may be an artifact related to lability of beta $_1$ -receptors. [102] Thus, $beta_2$ -agonism may have significant effects on cardiac contractility and rate. [101]

Dopamine Receptors

Dopamine not only exists as an intermediate in NE biosynthesis, but also exerts alpha- or beta-effects (depending on the dose administered). Further, Goldberg and Rajfer [103] demonstrated physiologically distinct dopamine-1 (DA_1)- and dopamine-2 (DA_2)-receptors, the most important of the five dopamine receptors cloned to date (Fig. 14-15) (Figure Not Available) . DA_1 -receptors are postsynaptic and act on renal, mesenteric, splenic, and coronary vascular smooth muscle to mediate vasodilatation through stimulated adenylate cyclase and increased cAMP production. The vasodilatory effect tends to be strongest in the renal arteries. It is for this action, particularly

Figure 14-14 (Figure Not Available) Molecular structure of the beta-adrenergic receptor. Note the three domains. The transmembrane domains act as a ligand-binding pocket. Cytoplasmic domains can interact with G proteins and kinases, such as beta-adrenergic receptor kinase (beta-ARK). The latter can phosphorylate and desensitize the receptor. *(Modified from Opie [96])*

the redistribution of renal blood flow, that dopamine is most frequently used. Additional renal DA_1 -receptors located in the tubules modulate natriuresis through the sodium-potassium ATPase pump and the sodium-hydrogen exchanger. [103] [104] [105] [106] The DA_2 -receptors are presynaptic; their action may be to inhibit NE and perhaps ACh release. There are also central DA_2 -receptors that may mediate nausea and vomiting. The antiemetic activity of droperidol is thought to be related to its DA_2 activity.

G Proteins

After adrenergic receptor stimulation, the extracellular signal is transformed into an intracellular signal by a process known as *signal transduction* in which $alpha_1$ - and beta-receptors are coupled to G proteins. When activated, the G proteins can modulate either the synthesis or the availability of intracellular second messengers (Fig. 14-16) (Figure Not Available) . The activated second messenger diffuses through the cytoplasm and stimulates an enzymatic cascade. The sequence first messenger
receptor
G protein
effector
second messenger
enzymatic cascade is found in a wide variety of cells; the specific entities that fulfill the separate roles vary from cell to cell. [107] G proteins located on the inner surface of the cell membrane can also directly modify the activity of transmembrane ion channels.

The structure of G proteins has been the subject of intense scrutiny. Three types of subunits (alpha, beta, and gamma) have been described. The alpha-subunit is most variable and determines the

Figure 14-15 (Figure Not Available) Location of dopamine-1-(DA_1) receptors, $alpha_1$ - and $alpha_2$ -adrenoceptors on postganglionic vascular effector cells, and DA_2 -receptors and $alpha_2$ -adrenoceptors on the prejunctional sympathetic nerve terminal. When dopamine is administered, activation of DA_1 -receptors causes vasodilation, whereas activation of DA_2 -receptors causes inhibition (-) of norepinephrine (NE) release from storage granules. A larger dose of dopamine activates alpha $_1$ - and $alpha_2$ -adrenoceptors on the postjunctional effector cells to cause vasoconstriction and on $alpha_2$ -adrenoceptors on the prejunctional sympathetic terminal to inhibit release of NE. NE released from the prejunctional sympathetic terminal also acts on alpha $_1$ - and $alpha_2$ -adrenoceptors. *(Modified from Goldberg and Rajfer [103])*

Figure 14-16 (Figure Not Available) Epinephrine-stimulated glycogenolysis in a liver cell demonstrates the role of G proteins in cellular function. The first messenger (epinephrine) binds to its specific receptor, stimulating the G protein (in this case Gs) to activate the effector, adenylyl cyclase. This enzyme converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), the second messenger, which then triggers a cascade of enzymatic reactions that stimulates the enzyme phosphorylase (phos-a) to convert glycogen into glucose, which the cell finally extrudes. *(Modified from Linder and Gilman [107])*

activity of the protein--whether it is stimulatory (G_s), inhibitory (G_i), G_o or the recently-described $G_{q/11}$. [108] [109] The alpha-subunit may split off and behave independently, whereas the beta- and gamma-subunits remain together. Although 20 alpha-subunits, 5 beta-subunits, and 6 gamma-subunits have been cloned, the constellation of G proteins used by any individual receptor is more limited. Each class of adrenergic receptor couples to a different major subfamily of G proteins, which are, in turn, linked to different effectors. The major subtypes of alpha$_1$ -, alpha$_2$ - and beta-receptors are linked to G_q, G_i, and G_s, respectively, which, in turn, are linked to phospholipase C activation (alpha$_1$), adenylyl cyclase inhibition (alpha$_2$), or adenylyl cyclase stimulation (beta) (see Fig. 14-13) . The pertussis-resistant G_q protein was identified in 1991 [109] and subsequently was observed to mediate alpha$_1$ -adrenergic receptor signal transduction by activation of phospholipase C and generation of inositol triphosphate (ITP) and diacylglycerol (DAG). [110] The physiologic relevance of the subunits is all the more important when one recognizes that the pharmacologic tools for dissecting signal transduction are all associated with diseases that have been scourges of humankind *(Bordetella pertussis, Vibrio cholerae,* and *Clostridium botulinum).*

In its resting state, the G protein is bound to guanosine diphosphate (GDP) and is not in contact with the receptor. When the receptor is activated by the first messenger, it stimulates the G protein to release GDP and bind GTP to its alpha-subunit, activating itself. The bound GTP signals the G protein to split into two parts consisting of the alpha-GTP structure and the beta-gamma-subunit. The released alpha-subunit binds to the effector and activates it, then converts its attached GTP to GDP thus returning itself to the resting state. The alpha- subunit joins with the beta-gamma-unit, and once again the reconstructed G protein waits at the inner membrane.

beta-Receptor stimulation activates G proteins, enhancing adenylate cyclase activity and cAMP formation. The briefest encounter of plasma membrane beta-adrenergic receptors with EPI or NE results in profound increases (up to 400-fold higher than the basal level within minutes) in the intracellular levels of cAMP. Increased cAMP synthesis, in turn, activates protein kinases, which phosphorylate target proteins. This phosphorylation elicits various cellular responses that complete the path between receptor and effect. Stimulation of alpha$_2$ -receptors results in G_i inhibition of the adenylate cyclase. There is a relative abundance of G proteins, resulting in amplification of receptor agonism at the signal transduction step. The number of G protein molecules greatly exceeds the number of beta-adrenergic receptors and adenylate cyclase molecules. Thus, it is the receptor concentration and ultimately adenylate cyclase activity that limit the response to catecholamines, perhaps providing an explanation for the efficacy of phosphodiesterase inhibitors. [111] [112]

Other transduction pathways are known. The alpha$_{1B}$ - receptor acts through G proteins, but it activates phospholipase C in the inner cell membrane, which then increases hydrolysis of the diphosphate form of phosphoinosotol (PIP_2) to the triphosphate and diacyglycerol. These two compounds then mobilize intracellular calcium stores from the sarcoplasmic reticulum and probably the subsarcolemma, resulting in a marked increase in intracellular calcium ion concentration. Ultimately, the calcium ions bind to calmodulin. This calcium-sensitive intracellular protein then activates a myosin light-chain kinase that phosphorylates the myosin light chain and facilitates the interaction between actin and myosin, resulting in the contraction of the smooth muscle. In other cells, calmodulin stimulates other kinases, resulting in effector activity.

Myocardial cells respond to receptor stimulation differently depending on the identity of the first messenger. Two opposing effects, inhibition or stimulation of contractility, are produced by the sequence of receptor
G protein
effector
enzymatic cascade, but the identity of the chemicals in the sequence differs. [113] NE causes myocardial cells to contract with more vigor when the alpha-subunit of the stimulatory protein (G_s) activates adenylate cyclase. The alpha-subunits of this protein cause potassium channels to open and permit efflux of potassium ion. The force of contraction is diminished when ACh acts as a first messenger, stimulating its receptor to activate the inhibitory protein G_i or G_o. Clinically important second-to-second changes in heart rate can be explained by the simultaneous activation of G_s and G_o. The current caused by G_o is larger than that of G_s, which explains the clinical impression that vagal inhibition of heart

---

rate is augmented in the presence of sympathetic stimulation, such as may occur in unpremedicated patients. [113]

Interaction of anesthetics with G proteins has been suggested as a mechanism for the negative inotropic effects of halothane and other volatile anesthetics. Although halothane attenuates neurotransmitter release from peripheral sympathetic neurons, [114] [115] [116] [117] other important postsynaptic effects may be involved in its negative inotropic action. [118] [119] [120] [121] [122]

Although an effect on cAMP formation would be a plausible explanation for halothane's negative inotropic effects, studies suggest that this effect is unrelated to adenylate cyclase. [123] Halothane blocks slow calcium channels in the heart, [124] [125] alters calcium fluxes in sarcoplasmic reticulum, [126] [127] and inhibits cAMP-dependent protein kinase. [119] Thus, at this time it appears that the negative inotropic effect of inhalational anesthetics occurs at several sites.

Upregulation and Downregulation

beta *-Adrenergic receptors are not fixed, but they change significantly in dynamic response to the amount of NE present in the synaptic cleft or in plasma.* For beta-adrenergic receptors, this response is fast: within 30 minutes of denervation or adrenergic blockade, there is an increased number of receptors. This upregulation may explain why sudden discontinuation of beta-adrenergic receptor blocking drugs causes rebound tachycardia and increases the incidence of myocardial infarction and ischemia. Many chronic phenomena, such as varicose veins [128] or aging, can decrease adrenergic receptor number or responsiveness systemically.

Clinically, and at the cellular level, responses to many hormones and neurotransmitters wane rapidly despite continuous exposure to adrenergic agonists. [129] This phenomenon, termed *desensitization,* has been particularly well studied for the stimulation of cAMP levels by plasma membrane beta-adrenergic receptors. [94] Mechanisms postulated for desensitization include uncoupling (phosphorylation), sequestration, and downregulation. The molecular mechanisms underlying *rapid* beta-adrenergic receptor desensitization do not appear to require internalization of the receptors, but rather an alteration in the functioning of beta-receptors themselves that uncouples the receptors from the stimulatory G_s protein. Agonist-induced desensitization involves phosphorylation of G protein-coupled receptors by two classes of serine-threonine kinases. One of these initiates receptor-specific or homologous desensitization. The other works through second messenger-dependent kinases, thus mediating a general cellular hyporesponsiveness, termed *heterologous desensitization.* Ultimately, an inhibitory arrestin protein binds to the phosphorylated receptor, causing desensitization by blocking signal transduction. Because GPK only phosphorylate receptors in the activated state, there has been an attempt to utilize transient beta blockade in states of receptor desensitization such as CHF or cardiopulmonary bypass in order to achieve a "a receptor holiday." [11] [95] [130] Regeneration of a functional beta-adrenergic receptor is contingent on sequestration of the receptor, with dephosphorylation and presumed recycling. There has been some evidence that the arrestins contribute to desensitization not only by uncoupling signal transduction, but also by contributing to the process of receptor internalization. [131] [132] Rapid changes in receptor populations can occur with such sequestration, which does not require protein synthesis. Downregulation may be distinguished from these rapid mechanisms because it occurs after hours of exposure to an agonist (e.g., as in chronic stress or CHF), and receptors are actually destroyed. New receptors must be synthesized before a return to a baseline state is possible.

Chronic CHF is one of the most important and best studied pathophysiologic situations in which tolerance or downregulation occurs. Initially, it was noted that the density of cardiac beta-receptors was markedly decreased in patients with terminal heart failure in response to the elevated plasma catecholamine levels. This finding explained why administration of exogenous beta-agonists was relatively ineffectual in this syndrome. Subsequently, with the demonstration that beta$_1$ - and beta$_2$ -receptors coexisted in human ventricles, Bristow and coworkers, [134] using radioligand techniques, documented that beta$_1$ -receptor density was decreased without

change in the density of beta$_2$ -receptors in human ventricles affected by CHF. Consequently, beta$_2$ -agonism accounted for 60 percent of the total inotropic response stimulated by isoproterenol in the failing heart, as contrasted with 40 percent in the nonfailing heart. [134]

Another disease in which adrenergic receptor function is altered is hyperthyroidism. The activity of the thyroid gland influences the receptor density, with hyperthyroidism increasing density and hypothyroidism decreasing density. There is some evidence that corticosteroids decrease receptor density. [24] Consequently, the reaction of the body to well-characterized sympathetic agonists may be considerably different, depending on the pathologic and environmental circumstances. [135] However, the structural similarity of thyroid hormone and tyrosine suggests that false transmitters may play a role. [136]

Cholinergic Pharmacology

Acetylcholine Synthesis

Many of our presumptions about cholinergic pharmacology are drawn from what is known about the neuromuscular junction, where detailed electrophysiologic information on cholinergic transmission is readily available. ACh is synthesized intraneurally from acetyl coenzyme A (CoA) and choline via the enzyme choline acetyl transferase in the synaptosomal mitochondria (Fig. 14-17) (Figure Not Available) . [137] Despite the presence of this enzyme, it should be noted that choline itself is not made in the brain, but it appears to be transported. Sources of choline include dietary phospholipids, hepatic synthesis of phosphatidylcholine from dietary precursors such as ethanolamines, and choline released by hydrolysis of ACh. Most choline originates in the liver. Choline is transported as the phospholipid and is taken up by a high-affinity transport system. This system appears to be largely responsible for determining ACh levels, although there is some evidence that precursor availability may limit cholinergic activity. The level of circulating choline can affect the release of ACh when rapid firing is taking place at cholinergic motor neurons. In one interesting experiment, plasma choline levels were measured in marathon runners before

Figure 14-17 (Figure Not Available) Synthesis of acetylcholine (ACh). Choline and acetyl coenzyme A (CoA) bind to the surface of choline acetyltransferase (ChAT). An imidazole on ChAT promotes proton removal and generates a more nucleophilic choline, thereby facilitating condensation with the acetyl group of acetyl CoA. The products of the reaction are CoA and ACh, which are rapidly packaged in vesicles for immediate release on proper stimulation. ChAT also catalyzes the reverse reaction between ACh and CoASH, although at a much slower rate than the forward reaction. *(Modified from Doukas [137])*

and immediately after a race; running a marathon decreased choline levels to well below those usually seen in fasting individuals, potentially lowering performance ability by possibly decreasing ACh release at the neuromuscular junction or cholinergic sites. [138] Choline analogues are being developed to enhance neuromuscular performance and to treat Alzheimer disease.

Storage and Release

The neuromuscular junction includes the nerve ending, the muscle, and the synaptic cleft, which is a space between the nerve and the muscle. On the nerve or presynaptic side, the nerve ending contains many synaptic vesicles (quanta) that contain ACh. On the muscle membrane, there are many infoldings of the postjunctional membrane. Studies have demonstrated that there are presynaptic release sites located opposite the junctional folds at the shoulders of the junctional folds. Vesicles containing ACh move toward these specific release sites and then fuse with the presynaptic membrane and open, spilling their contents across the synaptic cleft onto the receptors on the postsynaptic membrane (Fig. 14-18) (Figure Not Available) . [139]

ACh is stored in vesicles approximately 300 mum in diameter each containing 10,000 molecules of ACh. Central cholinergic transmission is different from the neuromuscular model in that few vesicles are present in the presynaptic terminal. These vesicles are "clear" on electron microscopy.

The spontaneous release of the ACh in one vesicle causes a miniature end-plate potential of 0.5 millivolts (mV) and 2,000 channels open in the membrane of a muscle cell, permitting sodium influx and potassium efflux. Twelve thousand ions enter the postsynaptic cell each millisecond each channel is open.

When a nerve impulse arrives at the presynaptic nerve terminal, it causes an influx of calcium ions across the membrane. This induces 100 to 300 synaptic vesicles to fuse with the presynaptic membrane at specific release sites at the active zone, resulting in the liberation of ACh from vesicles into the synaptic cleft.

Although the original hypothesis proposed by Katz of calcium as the exocytotic trigger has stood the test of time, *calcium entrance is necessary but not sufficient:* the presynaptic terminal must also be depolarized. Within 0.3 ms after the vesicle release occurs, the ACh in each vesicle causes 2,000 channels in the postsynaptic muscle cell membrane to open, with sodium entering the cell and potassium leaving. This ion flow gives rise to an electrical current and changes the normal resting potential of -90 mV. This nerve impulseinduced brief depolarization of 100 to 300 vesicles is known as an end-plate potential (EPP) but it is also a synaptic potential or an excitatory postsynaptic potential (EPSP), terms used to describe synaptic transmission in general. The EPP (50-100 mV) triggers a muscle action potential.

Normally, in the absence of a nerve impulse, there is a series of miniature end-plate potentials (MEPP) resulting from the spontaneous release of one quantum of ACh (10,000 molecules, or the contents of one vesicle). Each channel that is opened results in a depolarization of 0.00022 mV. The MEPP involves 1,500 ion channels being opened and causes a deflection of 0.5 mV. The EPP, which is summated, involves 500,000 ion channels opening and represents a depolarization of 50 to 100 mV.

Figure 14-18 (Figure Not Available) Acetylcholine (ACh) release, diffusion across the synaptic cleft, binding to receptors on end-plate membrane, and hydrolysis by acetylcholine esterase (AChE) in the absence of blocking drugs. *(From Stiller [135])*

Inactivation

ACh is an ester that hydrolyzes spontaneously in alkaline solutions into acetate and choline, neither of which has significant pharmacologic action. *In vivo,* the rate of hydrolysis is increased enormously by enzymatic catalysis. (Web sites: www.uoguelph.ca/GTI/urbanpst/cholin t.htm and www.biology.bnl.gov/disk$3/giles/che.html). The two most important enzymes are acetylcholinesterase and butyrylcholinesterase.

Sometimes called "tissue esterase" or "true esterase," *acetylcholinesterase* is a membrane-bound enzyme that is present in all cholinergic synapses, where it functions to destroy the neurotransmitter released from the nerve endings. Acetylcholinesterase is one of the most efficient of enzymes and destroys ACh, terminating transmission within milliseconds after its release. The enzyme also is present in tissues that are not innervated, such as erythrocytes. Its function in these tissues is not known.

Butyrylcholinesterase, sometimes called "plasma esterase" or "pseudocholinesterase," is a soluble enzyme that is made primarily in the liver and circulates in the blood. Its function in normal situations is not known; individuals who are genetically incapable of making the enzyme are normal in all other regards.

Of these two enzymes, acetylcholinesterase is the more important in terms of the function of ACh. Not only is it present in all cholinergic synapses, where it destroys neurally released ACh, but also it is the more efficient of the two enzymes. The substrate turnover is 2,500 molecules per second, and one catalytic event lasts 40 mus. Butyrylcholinesterase is important for the destruction of some cholinergic drugs, many of which are not destroyed by acetylcholinesterase.

Both forms of cholinesterase have been cloned. It is of more than passing interest that the first example of gene amplification in humans occurred in this enzyme system. The offspring of Israeli farmers exposed to insecticide expressed abnormal cholinesterase. [140] [141]

Traditionally, the catalytic part of the enzyme has been thought to contain two areas: an anionic site (which carries a strong negative charge) and an esteratic site (which contains electrophilic amino acids). It has been believed that, during its hydrolysis, ACh is attracted to the enzyme because the negative charge of the anionic

site attracts the positive charge in the quaternary nitrogen of ACh. The ester group of ACh aligns with the esteratic site of the enzyme. An electrophilic attack on the molecule occurs, and the acetate link is transferred from the choline to an amino acid in the enzyme. The choline drifts away, leaving a covalently bound, acetylated enzyme. The acetate link is subsequently attacked and broken by a hydroxyl group from water. The acetate drifts away, and the regenerated enzyme is ready to interact with another molecule of ACh.

However, the atomic structure of acetylcholinesterase has been found to be different from what had been previously thought, and our understanding of the binding of ACh to its

hydrolytic enzyme has altered. [142] The new model predicts that the quaternary ammonium binds to some of the 14 aromatic amino acids lining a deep gorge in the enzyme.

Inhibition of acetylcholinesterase prevents the destruction of ACh in cholinergic synapses and so can activate all cholinergic systems simultaneously. In addition to their therapeutic use, cholinesterase inhibitors are the active ingredients in insecticides and many nerve gases.

Cholinergic Receptors

Traditionally, cholinergic receptors have been organized into two major subdivisions, nicotinic and muscarinic, that predict most clinical effects. Muscarinic receptors are mostly present in peripheral visceral organs, whereas nicotinic receptors are present on parasympathetic and sympathetic ganglia and on the neuromuscular junctions of skeletal muscle.

Although these two structurally and functionally distinct classes of receptors have significantly different responses to ACh, ACh itself exhibits no specificity. However, specific antagonists can exploit the difference between the muscarinic and nicotinic receptors. As a result, structure-activity relationships have emerged. All cholinergic agonists appear to need a quaternary ammonium group as well as an atom capable of forming a hydrogen bond through an unshared pair of electrons. The distance between the two may determine whether the agonism is nicotinic or muscarinic. With muscarinic agonists, the distance appears to be about 4.4 A, whereas for nicotinic agonists, the distance is 5.9 A.

The nicotinic receptors on ganglia and motor end plates differ, and they are blocked by different drugs. *d*- Tubocurarine predominantly blocks the neuromuscular junction, whereas hexamethonium acts to block the ganglionic receptors. Methonium compounds were developed to explore the structure-activity relationships of the curare alkaloids. The most potent depolarizing neuromuscular blocking structure contained ten carbon atoms (decamethonium); in contrast, the structure containing six carbon atoms, hexamethonium, was an active ganglionic blocking agent but had little effect at the neuromuscular junction.

ACh receptors on the neuromuscular junctions of mature mammals belong to the superfamily of receptor-gated ion channels, which includes glutamate and glycine. The nicotinic receptors are pentameric membrane proteins, which form nonselective cation channels. There are two alpha-units, each 40 kd, and one each of the beta-, epsilon-, and delta-units (Fig. 14-19) (Figure Not Available) . Although different subunits may be expressed developmentally, the alpha-subunits represent the binding sites for ACh or nicotinic antagonists. At birth, a gamma-subunit occupies the position that will be taken by the epsilon-subunit within the first 2 weeks of life. This change in subunits converts the receptor from one with a low conductance and a relatively long duration of opening to a receptor with a high conductance but a brief duration of opening. [143] There are therefore important functional differences in ACh receptors during development, but the important drug-binding subunits remain constant.

These five subunits surround each ion channel through which sodium or calcium may enter the cell or potassium may exit. Each ion has its own separate channel, a unique characteristic of the neuromuscular junction. In order for the channel to open, ACh must occupy a receptor site on each of the two alpha-subunits. When ACh occupies both alpha-subunits, the channel opens; if only one site is occupied and the other is empty, the channel remains closed and there is no flow of ions and no change in electrical potential. In addition, if one site is occupied by ACh and the other site is occupied by an antagonist such as *d*-tubocurarine, the channel remains closed. If both sites are occupied by *d*-tubocurarine, the channel also remains closed. The ion channel response to ACh is instantaneous and usually lasts only a few milliseconds because ACh is rapidly destroyed by acetylcholinesterase in the synapse. This time course lends a rapidity and flexibility of response of motor end plates to neural stimulation that contributes profoundly not only to the viability of an organism, but also to its ability to control its own movements precisely and subsequently its environment.

In addition to binding of the alpha-subunit binding site by competing, non-ACh structures, there are two types of channel block (open and closed). With open-channel block, a drug enters a channel opened by ACh but cannot travel all the way through the channel. Thus, it impedes ionic flow and so prevents depolarization. Because only an open channel

Figure 14-19 (Figure Not Available) Sketch of postjunctional nicotinic acetylcholine receptors with an acetylcholinesterase (AChoE) molecule nearby. *(Modified from Standaert [457])*

may be entered, the intensity of this block depends on how often the channels are open and how active the system is; thus, it is "use dependent." Open-channel block is driven by the electrical potential difference across the membrane and the charge inherent in the molecular structure. In addition, drugs penetrating an open channel may temporarily bind at some point on the wall of the channel. The duration of effect, therefore, is partially dependent on the identity of molecule. Closed-channel blockade is harder to study and is less well understood. In this case, a drug may react with the mouth of a closed channel and prevent ion flow. Channel opening is not required, and blockade is, therefore, not use dependent. Because block does not occur at the ACh receptor site, closed-channel block is not due to a competitive antagonism of ACh. Therefore, the classic agents that inhibit cholinesterase may not be completely effective.

In adult skeletal muscle and postganglionic cells, cholinoceptors and their associated ion channels are present only in the immediate synaptic area and are absent from the rest of the cell membrane. The high density (10,000 molecules/mum^{-2}) of nicotinic acetylcholine receptors at the motor end plate is central to accomplishing successful neuromuscular transmission. Studies have demonstrated that agrin, a nerve-derived extracellular basal lamina protein, provides the signal that directs formation of presynaptic terminals [144] [145] and results in a 1,000-fold increase in nicotinic receptors in the motor end plate within hours of the presynaptic terminals reaching the myoctye. A series of ACh receptor (AChR)-associated proteins has been identified, but the precise way in which these extracellular [146] (agrin, laminin, and dystroglycan) and intracellular (utrophin and syntrophin) membrane-associated proteins maintain the necessary AChR clustering and integrity of motor end plate and bind to the cytoskeleton is unclear. Only the synaptic area is depolarized by ACh. This depolarization usually leads to the generation of action potentials that spread along the whole membrane of the cell and cause muscles to contract or neurons to transmit. However, if ACh action is prolonged, such as by inhibition of acetylcholinesterase, or if a longacting cholinomimetic drug is administered, the initial activation is quickly followed by blockade of transmission. This biphasic effect occurs because sodium channels in the membrane around the synapse, which are unaffected by ACh, accommodate to the continued depolarization of the synaptic membrane. They become inactivated and will not open again until the synaptic potential disappears. Propagated action potentials cannot be generated without sodium flow across the membrane, and so the message sent across the synapse is blocked from propagating through the postsynaptic cell.

Compared with adrenergic receptors, the cholinergic receptors turn over slowly. When a nerve to a muscle is transected, it takes 1 to 3 days to increase the number of cholinergic receptors. In the diaphragm, the number may increase 8 fold. These new receptors will no longer be confined to the motor end plate; that change has important clinical ramifications, especially in burn-induced denervation.

In contrast to the ion-gated nicotinic receptors, muscarinic receptors belong to the superfamily of G protein-coupled receptors. As noted earlier, it is of some interest that muscarinic receptors have a greater homology to alpha- and beta-adrenergic receptors than to nicotinic receptors. Like the other members of the family of receptors with seven helices (alpha$_2$, beta$_1$, beta$_2$, serotonin, rhodopsin, and opsin), muscarinic receptors utilize G proteins for signal transduction. Five muscarinic receptors (M_1 -M_5) exist with the primary structural variability residing in a huge cytoplasmic loop between the fifth and sixth membrane-spanning domains. Although molecular studies have described five forms, of which four are defined pharmacologically (M_1 , M_2 , M_3 , and M_4), selective muscarinic drugs are not available. The M_2 cholinergic postjunctional receptor predominates in visceral organs. M_2 and M_3 receptors have been identified in the airway smooth muscle of many species. *In vitro*

studies reveal that the M_3 receptor mediates the contractile and secretory response. However, the excess of M_2 receptors could explain the relative ineffectiveness of beta-adrenergic agonists in reversing cholinergic bronchoconstriction. [147]

The muscarinic receptors have diverse signal transduction mechanisms. The odd-numbered receptors (M_1, M_3, and M_5) work predominantly through the hydrolysis of polyphosphoinositide, whereas the even-numbered receptors work primarily through G_i proteins to regulate adenylate cyclase. [148]

When the M_3 muscarinic receptor is activated, G_q activates phospholipase C, which catalyzes the hydrolysis of phosphatidylinositol biphosphate into diacylglycerol and inositol triphosphate. Receptors in the muscarinic series are coupled to second messenger systems, such as cyclic nucleotides or phosphoinositides. These, in turn, are coupled to ion channels. In other cases, the influx of a cation is the trigger for cellular response. In some cases, however, an influx of calcium ions is initiated, and these ions act as messengers that react with and open other ion channels. The nature of the response is determined by the specific cation. If calcium or sodium is permitted to flow, then the membrane depolarizes; if only potassium is permitted to flow, then the membrane hyperpolarizes. In addition to affecting ion channels, the messenger calcium can stimulate various intracellular proteins to alter cell activity. In cardiac atria, activation of muscarinic receptors leads to the efflux of potassium and hyperpolarization of the cell membrane. This efflux slows conduction and slows or stops pacemakers. In glands, an influx of calcium and/or sodium activates intracellular events and causes the cells to secrete. Similarly, the influx of these ions into smooth muscle cells causes them to contract.

Muscarinic receptors are found on both central and peripheral neurons; a single neuron may have muscarinic receptors with excitatory as well as inhibitory effects. Prejunctional autoreceptors are perhaps not as well studied in the parasympathetic nervous system as in the sympathetic nervous system. Exogenous alpha $_2$ -agonists may act on prejunctional cholinergic receptors to decrease ACh release. As in the sympathetic system, presynaptic inhibition is of clinical relevance. Presynaptic muscarinic receptors may inhibit the release of ACh from postganglionic parasympathetic neurons, whereas prejunctional nicotinic receptors may act to increase the release of ACh.

Because of the complex coupling, the response of the muscarinic system is sluggish; no response is seen for seconds to minutes after the application of ACh. Similarly, the effect long outlives the presence of the agonist. Even though the transmitter is destroyed rapidly, the train of events it initiated causes the cellular response to continue for many minutes. Desensitization of muscarinic receptors occurs via agonist-dependent phosphorylation in a mechanism similar to that described earlier for beta-adrenergic receptors.

Ganglionic Pharmacology

Ganglia subserve far more complex functions than that of a simple connection between the nerve process of one cell and the cell body of its next connection. Integrative and processing functions may contribute to the subtlety of response and organization of the ANS. The electrophysiology of ganglionic stimulation is complex, with at least four different types of responses to electrical stimulation (Table 14-7) (Table Not Available) . [149] [150]

The central event at the ganglion is the EPSP, which occurs when ACh interacts with a nicotinic receptor to cause a rapid depolarization of the postsynaptic membrane. This depolarization primarily results from the influx of sodium ions through the nicotinic receptor channel, and it is sensitive to nondepolarizing nicotinic blocking drugs such as hexa-methonium. The other changes in electrical potential are related to secondary or subsidiary pathways that serve to augment or suppress; these pathways are insensitive to classic nicotinic antagonists.

The secondary pathways are indicated by the following changes in potential elicited by electrical stimulation of the ganglia:

1. A slow EPSP.
2. A late slow EPSP.
3. An inhibitory postsynaptic potential (IPSP).

The slow EPSP is slower in onset than the EPSP and lasts 30 to 60 seconds, because of a decrease in potassium ion conductance. The interaction of ACh with nicotinic receptors leads to closing of a potassium channel (m-channel). The slow EPSP is associated with the reduction or suppression of a potassium current through this channel. This wave is initiated by muscarinic receptor agonists and can be blocked by atropine and the selective M_1 muscarinic antagonists.

Like the slow EPSP, the late slow EPSP is due to a decrease in potassium ion conductance. It lasts for several minutes after being initiated by peptides in specialized ganglia. Peptides have special properties as neurotransmitters, showing prolonged stability and thus extending their influence to other postsynaptic sites, not just those in the immediate vicinity of the nerve ending. Depolarization of the membrane activates the potassium channel; the conductance of potassium ion has been labeled the "M current" and appears to act to regulate the cell's response to repetitive fast depolarizations.

The IPSP is inhibitory because the membrane is hyperpolarized and therefore is more resistant to depolarization. The slow IPSP seems to be mediated by the activation of an interneuron interposed between the preganglionic fiber and the ganglionic cell. The preganglionic nerve ending releases ACh, which stimulates the catecholamine-containing interneurons to release dopamine and NE. Catecholamine released by the interneuron then causes hyperpolarization of the ganglion cell membrane, or an IPSP. M_2 -receptors appear to be involved, as are SIF cells (*s*mall, *i*ntensely *f*luorescent cells). IPSP and catecholamine-induced hyperpolarization are both blocked by adrenergic blocking drugs. IPSP is not affected by classic nicotinic blocking agents, but is frequently sensitive to block by atropine.

The impact of the secondary pathways on the initial EPSP and the identity of the involved neurotransmitter varies among ganglia and differs between the parasympathetic and sympathetic ganglia. Many peptides have been identified in the ganglia and shown to be released on stimulation of preganglionic nerves, including gonadotropin-releasing hormone (GnRH), substance P, angiotensin, VIP, NPY, and the enkephalins. As mentioned, the peptides seem to be primarily associated with the late slow EPSP and inhibition of the M current. In addition, 5-HT and gamma-aminobutyric acid (GABA) appear to modify ganglionic transmission.

Autonomic ganglia may be stimulated by two groups of drugs, the nicotinic and muscarinic agonists. Nicotinic agonists cause the rapid onset of excitatory effects, mimic the initial EPSP, and are blocked by classic nondepolarizing ganglionic blocking drugs. Muscarinic agonists cause the delayed onset of these excitatory effects, are blocked by atropine, and mimic the slow EPSP.

Blockade of ganglionic transmission results primarily from action at the nicotinic receptor to stop or inhibit transmission. There are two groups of drugs that block ganglionic transmission. The first group is classically represented by nicotine and initially stimulates the receptor, then blocks it. This action is similar to the action of persistent depolarization. The second group causes no prior stimulation of the ganglia or change in ganglionic potentials and includes the drugs hexamethonium, trimethaphan, and mecamylamine. Trimethaphan appears to act by competing with ACh at the cholinergic receptor sites on the ganglia; hexamethonium blocks the channel when it is open. Either mechanism blocks the initial EPSP and ganglionic transmission.

Muscarinic antagonists or alpha-agonists are incapable of completely blocking transmission, but they may act to inhibit normal modulation of the nerve impulse. beta-Adrenergic stimulation appears to facilitate both nicotinic and muscarinic transmission, whereas alpha-adrenergic stimulation inhibits this transmission. 5-HT is mostly facilitative, but it can be inhibitory in certain areas. Dopamine may also be inhibitory through stimulation of the IPSP. It should be remembered that the adrenal medulla is a specialized ganglionic synapse and is therefore under influences similar to those arising on the autonomic ganglia.

TABLE 14-7 -- Fast and Slow Responses of Postganglionic Neurons in Sympathetic Ganglia

(Not Available)

From Ganong [149]

/das/book/view/29494766/875/167.html

DRUGS AND THE AUTONOMIC NERVOUS SYSTEM

The structure and function of the sympathetic and parasympathetic systems are discussed in the preceding sections. Pharmacologic manipulation of autonomic function is the basis of therapy in many acute and chronic illnesses. The complex pharmacology allows many points for intervention, including enhancement or inhibition of synthesis, storage, or receptor-mediated activity (Table 14-8) (Table Not Available) . [149] In the following section, specific autonomic drugs of interest to anesthesiologists and the mechanisms by which they work are discussed.

Drugs Affecting Adrenergic Transmission

Endogenous Catecholamines

The endogenous sympathetic transmitters NE, EPI, and dopamine are catecholamines and are an important subclass of the sympathomimetic drugs (Fig. 14-20) . The parent compound of this sympathomimetic group is beta-phenylethylamine, the structure of which includes a benzene ring and ethylamine side chain. Substitution of hydroxyl groups at the 3 and 4 positions of the benzene ring converts benzene to catechol, and thus these compounds are known as *catecholamines.* Although synthetic, isoproterenol and dobutamine are also catecholamines. Noncatecholamine drugs may also act as sympathomimetics and have a similar structure.

The catecholamines are primarily metabolized by catechol- *O*-methyl transferase (COMT). The loss of either hydroxyl group enhances oral effectiveness and duration of action because the drug is no longer metabolized by COMT. Noncatecholamines are primarily metabolized by MAO. The noncatecholamines that have a substituted alpha-carbon have a longer duration of action because they are not metabolized by either COMT or MAO. [151]

Epinephrine

EPI is used IV in life-threatening circumstances, including the treatment of cardiac arrest, circulatory collapse, and anaphylaxis, but it is also commonly used locally to limit the spread of local anesthetics or to reduce blood loss. The systemic effects of EPI are variable and are related to blood levels. Therefore, the choice of dosing and the route of administration are determined by the indication for use and its urgency.

EPI activates all adrenergic receptors: alpha $_1$, alpha $_2$, beta $_1$, beta $_2$, and beta $_3$. Potential therapeutic effects of EPI include positive intropy, chronotropy, and enhanced conduction in the heart (beta $_1$); smooth muscle relaxation in the vasculature and bronchial tree (beta $_2$); and vasoconstriction (alpha $_1$). As a result of

TABLE 14-8 -- Some Drugs and Toxins That Affect Autonomic Activity[a]

(Not Available)

Modified from Ganong [149]

[a] Only the principal actions are listed. Note that guanethidine is believed to have two principal actions.

Figure 14-20 Catecholamine structures. A benzene ring with two adjacent hydroxyl groups forms the catechol nucleus.

this vasoconstriction, aortic diastolic pressure is increased, promoting coronary flow during cardiac arrest, which may be the single most important determinant of survival. [152] Endocrine and metabolic effects of EPI include increased levels of glucose, lactate, and free fatty acids (see Table 14-1) (Table Not Available) .

EPI may be given IV as a bolus or by infusion. Usual bolus doses for pressure support begin at 2 to 8 mug IV; 0.02 mg/kg or approximately 1.0 mg is given for cardiovascular collapse, asystole, ventricular fibrillation, and electromechanical dissociation or anaphylactic shock. This higher dose range is recommended in these critical situations in order to maintain myocardial and cerebral perfusion through peripheral vasoconstriction. High-dose EPI (0.1-0.2 mg/kg) has been studied in resuscitation from cardiac arrest, but it does not appear to improve rates of survival in adults. High-dose EPI may be given in adults if usual doses fail to generate a response. [153] In pediatric patients, outcome from asystole and pulseless cardiac arrest is abysmal, and current recommendation is that high-dose EPI (0.1 mg/kg) be administered within 3 to 5 minutes after the initial dose (0.01 mg/kg) and repeated every 3 to 5 minutes throughout resuscitative attempts. [154] Doses as large as 0.2 mg/kg may be effective. [155] Endotracheal or intraosseous administration is an option in urgent situations such as cardiac arrest while IV access is obtained. Endotracheal doses should be at least tripled and diluted in 10 mL of normal saline in adult patients. [156] In pediatric patients, ten times the IV dose may be needed. [154] When continued cardiovascular support is required, infusion rates can be adjusted to elicit specific receptor stimulation. EPI should not be administered in alkaline solutions, because it is rapidly degraded to its biologically inactive metabolite, adrenochrome. If adrenochrome is present, the vial will have a pink hue and should be discarded. [151]

It should be remembered that patients vary tremendously in their response to these agents, and given rates of infusion cannot guarantee the expected serum levels in all patients; therefore, the "pressors" should be carefully titrated, and appropriate measures to monitor renal, cerebral, and myo-cardial perfusion are more critical than adherence to a rigid dosing scheme (Table 14-9) . A rate of 1 to 2 mug/min, though rarely used, should predominantly activate beta $_2$ -receptors with resulting vascular and bronchial smooth muscle relaxation. A rate of 2 to 10 mug/min (25-120 ng/kg/min) will, in addition, increase heart rate, contractility, and conduction through the AV node and decrease the refractory period. Doses in excess of 10 mug/min (100 ng/kg/min) cause marked alpha-stimulation with resultant generalized vasoconstriction. EPI is a potent renal vasoconstrictor acting directly by alpha- receptor stimulation and indirectly by stimulation of renin release. It is frequently used in combination with "renal dose" dopamine in an attempt to avoid renal ischemia. Although low-dose EPI increases heart rate by direct beta $_1$ - stimulation, reflex bradycardia is seen with higher doses, because of marked elevation of blood pressure through peripheral vasoconstriction.

In the past, inhaled EPI was used in a 1 percent (1 g:100 mL) solution to treat bronchospasm, but it has been largely supplanted by beta $_2$ -specific agonists. Racemic EPI (a mixture of the levo- and dextrorotary isomers) acts to constrict edematous mucosa and is used in the treatment of severe

TABLE 14-9 -- Dose-Dependent Actions of Inotropes and Chronotropes

DRUG[a] (PROPRIETARY NAME)	RECEPTORS	USUAL INFUSION RATE
Epinephrine (Adrenalin)	$beta_2$	1-2 mug/min
	$beta_1$ + $beta_2$	2-10 mug/min
	$alpha_1$	>10 mug/min[b] (bolus: 2-10 mug; 0.5-1.0 mg[c])
Norepinephrine (Levophed)	$alpha_1$, $beta_1$, $beta_2$	4-12 mug/min[b]
Dopamine (Intropin)	Dopaminergic	0-3 mug/kg/min
	beta	3-10 mug/kg/min
	alpha	>10 mug/kg/min[b]
Dobutamine (Dobutrex)	$beta_1$ $beta_2$, alpha	2.5-10 mug/kg/min[b]
Isoproterenol (Isuprel)	$beta_1$ > $beta_2$	0.5-10 mug/min
Amrinone (Inocor)	Increase cyclic adenosine monophosphate through phosphodiesterase inhibition	0.75 mg/kg/load over 2-3 min 5-10 mug/kg/min infusion

Data from Hoffman and Lefkowitz [151]

[a] All agents have elimination half-lives of a few minutes, except amrinone ($t_{½}$, 3.6 h; 5.8 h in congestive heart failure).

[b] Much higher doses have been used in clinical practice.

[c] With anaphylaxis or cardiac arrest.

croup [157] and of postextubation and traumatic airway edema. A 2.25 percent solution (microNefrin/Vaponefrin) is diluted with water or saline in a 1:8 ratio and is nebulized. Treatments may be given as frequently as every 2 hours, with effects lasting 30 to 60 minutes; the patient should remain under observation for at least 2 hours, because initial improvement may be followed by rebound swelling up to 2 hours after administration. [151] Although it is common clinical practice to utilize the racemic form of EPI for these clinical applications, data show that (levo)-EPI is 15 to 30 times more potent than the mixture [158] [159] and is equally effective and less expensive in treating these clinical complications. [160]

Bronchospasm may also be treated by subcutaneous (SQ) administration of EPI in doses of 300 mug every 20 minutes up to three doses. In addition to its direct bronchodilatory effects, EPI may decrease antigen-induced release of endogenous bronchospastic substances from mast cells and is particularly useful in anaphylactic reactions. [161] Relative contraindications include advanced age, significant tachycardia, hypertension, and coronary occlusive disease. Absorption of SQ EPI is extremely slow because of intense local vasoconstriction, and the effect of a very large SQ dose of 0.5 to 1.5 mg is roughly equivalent to an IV infusion of 10 to 30 mug/min. [151] IV injection of EPI in a dose appropriate for SQ administration can result in life-threatening ventricular arrhythmias, hypertension, and cerebral hemorrhage. Sus-Phrine, a sustained-release form of EPI, may be used in children by SQ injection but should never be given IV.

EPI is often applied locally to mucosal surfaces to decrease bleeding in the operative site. It is mixed with local anesthetics for infiltration into tissues or intrathecal injection. The alpha-mediated vasoconstriction decreases bleeding in the area and slows vascular uptake of local anesthetic, prolonging both the duration of effect and decreasing the peak serum level of the local anesthetic. Although clinicians express concern over the systemic effects of such injections, several studies have shown that, barring intravascular injection, resultant elevations in plasma levels due to vascular uptake are relatively modest and are substantially less than levels seen in psychologic stress. [28] [162]

Drug interactions with EPI are often predictable. Cocaine and other uptake inhibitors enhance the effect and duration of exogenous EPI. Preexisting alpha $_1$ -blockade can cause the paradoxic phenomenon of "EPI reversal" as the beta$_2$ -vasodilating effects are unmasked. Patients receiving nonselective beta blockers may demonstrate unopposed alpha-responses. Cardioselective (beta $_1$) blockade does not have this effect. [163]

Halothane is known to sensitize the heart to catecholamines, and the potential for troublesome arrhythmias under light inhalational anesthesia has long been appreciated by clinicians. EPI decreases the refractory period, rendering the heart more susceptible to arrhythmias. In adults, the EPI ED_{50} (dose required to produce three premature ventricular contractions in 50 percent of patients) at 1.25 minimum alveolar concentration (MAC) was 2.1 mug/kg for halothane, 6.7 mug/kg for isoflurane, and 10.9 mug/kg for enflurane. [164] Children appear to tolerate higher doses than do adults. It has been suggested that children receiving a halothane anesthetic can receive a maximum of 10 to 15 mug/kg SQ of EPI every 10 minutes. [157] Hypocapnia potentiates this drug interaction.

Norepinephrine

NE differs structurally from EPI only in its lack of a methyl group. Like EPI, NE acts at both alpha- and beta- receptors, but it is usually used for its potent alpha-agonism. It is frequently the pressor of last resort in supporting the systemic vascular resistance. Because of its short half-life of 2.5 minutes, a continuous infusion is preferred. Whereas less than 2 mug/min (30 ng/kg/min) may uncover beta $_1$ -stimulation effects, the usual infusion rates of greater than 3 mug/min (50 ng/kg/min) elicit peripheral vasoconstriction from alpha- stimulation. [165]

The peripheral vasoconstriction increases blood pressure and may cause reflex bradycardia. Venous return is increased by the powerful venoconstriction. Cardiac output is frequently unchanged or decreased; oxygen consumption is markedly increased. Pulmonary vascular resistance may be increased, and NE should be used with caution in patients with pulmonary hypertension. [166]

Like EPI, NE is a potent constrictor of the renal and mesenteric vascular beds and can cause renal failure,

mesenteric infarction, and peripheral hypoperfusion. The decrease in hepatic flow is of clinical relevance because plasma levels of hepatically metabolized drugs (such as lidocaine) are markedly increased. [167] To ameliorate the renal effects, low-dose dopamine infusion may be added to NE. [168] Extravasation can cause tissue necrosis and may be treated with local infiltration of phentolamine. Prolonged infusion has caused gangrene of the digits. The potential for profound vasoconstriction makes careful patient selection and close monitoring mandatory.

Dopamine

Dopamine acts at alpha-, beta-, and dopaminergic receptors; it also acts to release NE and therefore has mixed direct and indirect effects. Although dopamine is a precursor of NE, its most important effect may be to cause peripheral vasodilation. Improvement of blood flow through the renal and mesenteric beds in shock-like states is expected through its action at dopamine receptors on the postjunctional membrane. It is rapidly metabolized by MAO and COMT, and so has a short half-life of about 1 minute. Therefore, like other endogenous catecholamines, it is given as a continuous IV infusion and without a loading dose. At low doses (0.5-2.0 mug/kg/min), DA_1 -receptors are stimulated, and renal and mesenteric vascular beds dilate. [169] In addition to an improvement in renal blood flow, glomerular filtration

rate and sodium excretion increase. With an infusion rate of 2 to 10 mug/kg/min, beta $_1$ -receptor stimulation is seen, with resultant increases in cardiac contractility and output. Rates higher than 5 mug/kg/min stimulate release of endogenous NE, which contributes to cardiac stimulation. At higher doses, (10-20 mug/kg/min), both alpha- and beta$_1$ -receptors are stimulated, the alpha-vasoconstrictive effect predominates, and the benefit to renal perfusion may be lost. [170] Patients' responses to dopamine are extremely variable, and dosages must be individualized. Appropriate monitoring to ensure organ and peripheral perfusion is critical. The dose should be significantly decreased in patients treated previously with an MAOI or tricyclic antidepressant.

Dopamine is frequently the initial agent used in the treatment of shock, particularly in vasodilated states such as sepsis; as discussed earlier, it is frequently used to protect the kidney and also to aid in diuresis. It is particularly useful for this purpose in severe CHF. [171] Infusion in combination with dobutamine for the therapy of cardiogenic shock may be more effective than either agent given alone. [172]

Dopexamine hydrochloride (Dopacard), an inotropic vasodilator, is a synthetic parenteral dopamine analogue that may be of use in CHF. Intrinsic activity of dopexamine relative to dopamine is approximately 60 times more potent at beta$_2$ -adrenoreceptors and one-third at DA$_1$ -receptors and one-seventh at DA$_2$ -receptors. [173] [174] Unlike dopamine, it shows no alpha- and negligible beta $_1$ -adrenergic effects and is therefore devoid of any vasoconstrictive activity. [173] [175] Dopexamine has a reported half-life of 3 to 7 minutes in healthy patients and approximately 11 minutes in patients with low cardiac output. [176] beta$_2$ -Agonism produces systemic vasodilatation and indirect inotropic activity (via inhibition of neuronal uptake of NE). [173] [175] [177] [178] [179] The stimulation of dopaminergic receptors produces selective vasodilatation of renal and splanchnic vessels and increased glomerular filtration rate, diuresis, and natriuresis. [175] [180] [181] [182] [183]

The use of dopexamine seems preferable when vascular resistance is high. Within the dose range of 1 to 6 mug/kg/min, the combined inotropic, vasodilative, diuretic, and natriuretic effects have shown benefit in the management of CHF, [184] [185] [186] [187] but they have had an indeterminant outcome in the treatment of septic shock. [186] [188] [189] [190] [191] [192] Use of this agent has been limited by dose-dependent tachycardia, mainly at doses higher than 4 mug/kg/min. [193] [194] The effects of dopexamine on intestinal mucosal and hepatic perfusion remain controversial. [195] [196] [197] [198] [199] [200] In general, systemic vasodilatation appears more pronounced with dopexamine, and positive ino-tropic effects appear more marked with dopamine [201] and dobutamine. [202]

Fenoldopam is a selective DA$_1$ -agonist and potent vasodilator (6-9 times as potent as dopamine) that enhances natriuresis, diuresis, and renal blood flow. [203] [204] [205] [206] [207] Because of its poor bioavailability and varied results in clinical trials, fenoldopam is no longer being investigated as a candidate for therapy of chronic hypertension or CHF. Instead, IV fenoldopam, given by infusion at rates of 0.1 to 0.8 mug/kg/min with incremental titration at 0.1 mug/kg/min, has recently been approved to treat severe hypertension. It is an alternative to sodium nitroprusside, with potentially fewer side effects (no thiocyanate toxicity, rebound effect, or "coronary steal") and improved renal function. Its peak effects occur within 15 minutes. [208] [209]

Noncatecholamine Sympathomimetic Amines

Whereas the beta-agonist isoproterenol and the alpha-agonists phenylephrine and methoxamine act predominantly at only one type of receptor, most of the sympathomimetic drugs act at both alpha- and beta-receptors. Most noncatecholamine sympathomimetic amines act at alpha- and beta-receptors because they have two mechanisms of action: directly at a receptor and indirectly by releasing endogenous NE.

Mephentermine (Wyamine), ephedrine, and metaram-inol (Aramine) are mixed-acting drugs. Ephedrine increases blood pressure and has a positive inotropic effect. Because it does not have detrimental effects on uterine blood flow, ephedrine is widely used as a pressor in the hypotensive parturient patient. [210] Because of its beta$_1$ -stimulating effects, ephedrine is helpful in treating moderate hypotension, particularly if accompanied by bradycardia. It also has some direct beta $_2$ -stimulating effects and has been used orally as a bronchodilator. The usual dose is 2.5 to 25 mg IV, or 25 to 50 mg intramuscularly (IM). Mephentermine is similar to ephedrine in its effects, whereas metaraminol has relatively stronger direct alpha $_1$ -stimulating effects and may be associated with reflex bradycardia.

Tachyphylaxis to the indirect effect may develop through depletion of NE stores. Although all sympathomimetic amines are capable of producing tolerance or tachyphylaxis, the mechanism has been best studied with metaraminol. Metaraminol is taken up into the sympathetic nerve ending, displacing NE and producing the sympathomimetic effect. However, after a period of time, the drug acts as a false

transmitter, and subsequent sympathetic nerve stimulation results in much less effect. Consequently, the drug probably should not be used widely when other, more effective drugs are available. Indirect action is attenuated in the presence of long-term reserpine or cocaine use, but these drugs may still be efficacious, although at higher doses. Although indirect-acting agents are widely used as a first-line therapy for intraoperative hypotension, epidemiologic studies of adverse reactions under anesthesia suggest that dependence on these agents in life-threatening events may contribute to morbidity. [211]

alpha-Agonists

Phenylephrine and methoxamine are selective alpha$_1$ -agonists. These drugs are commonly used when peripheral vasoconstriction is needed, sometimes when cardiac output is adequate, as in the hypotension that may accompany spinal anesthesia, and at other times in patients with coronary artery disease or aortic stenosis to increase coronary perfusion pressure without chronotropic side effects. Phenyl-ephrine (Neo-Synephrine) has a rapid onset and a relatively short duration of action (5-10 min) when given intravenously. It may be given by bolus doses of 40 to 100 mug or by infusion at a starting rate of 10 to 20 mug/min. Higher doses of up to 1 mg may be used to slow supraventricular tachycardia through reflex action. Phenylephrine is also used as a mydriatic and nasal decongestant. In anesthetic practice, it is applied topically either alone or mixed with local anesthetic gel to prepare the nose for intubation. It is also added to local anesthetic to prolong subarachnoid block. In contrast, methoxamine (Vasoxyl) is a much longer-acting drug (30-60 min). [212] At high doses, the drug possesses some membrane-stabilizing properties and even beta-adrenergic blocking properties.

The alpha$_2$ -agonists are assuming greater importance as anesthetic adjuvants and analgesics. Their primary effect is sympatholytic. They reduce peripheral NE release by stimulation of prejunctional inhibitory alpha $_2$ -adrenoreceptors, and they inhibit central neural transmission in the dorsal horn, by both presynaptic and postsynaptic mechanisms, and directly in spinal preganglionic sympathetic neurons. Although traditionally they have primarily been used as antihypertensive drugs, new roles based on sedative, anxiolytic, and analgesic properties are being developed.

Clonidine, the prototypic drug of this class (Table 14-10) , is a selective partial agonist for alpha $_2$ -adrenoreceptors, with a ratio of approximately 200:1 (alpha $_2$:alpha$_1$). The antihypertensive effects are due to central and peripheral attenuation of sympathetic outflow and central activation of nonadrenergic imidazoline-preferring receptors. [164] [253] [254] [255] The decrease in central sympathetic outflow reduces activity in peripheral sympathetic neurons without affecting baroreceptor reflexes. [256] Arterial blood pressure is thereby decreased without the accompanying orthostatic hypotension seen with many antihypertensive drugs. [257] Because clonidine is lipid soluble, it is able to penetrate the blood-brain barrier to reach the hypothalamus and medulla, and thus, unlike alpha-methyldopa, it does not require transformation into another substance. [258] Clonidine withdrawal may precipitate hypertensive crises, and clonidine should be continued throughout the perioperative period (perhaps by patch) or at the least replaced by close monitoring of blood pressure and ready ability to treat hypertension. The administration of nonselective beta blockers during clonidine withdrawal could worsen hypertension by leaving alpha $_1$ -receptor- mediated vasoconstriction unopposed. Labetalol has been used to treat this withdrawal syndrome.

Although the use of alpha$_2$ -agonists as the sole anesthetic agents has not been demonstrated in humans, these drugs can reduce the anesthetic requirement and may provide a more stable cardiovascular course, presumably because of the sympatholytic effect of the drug and the need for lower doses of cardioactive anesthetic. [213] [214] [259] Clonidine reduced halothane MAC by up to 50 percent in a dosedependent fashion, [260] limited by alpha$_1$ -adrenoreceptor activation at higher concentrations, whereas dexmedetomidine, the prototype of novel superselective alpha $_2$ -agonists (alpha$_1$:alpha$_2$ of 10:1), decreased halothane MAC by more than 95 percent in animals. [260] [261] [262] Data suggest that oral, IV, epidural, and intrathecal administration of clonidine potentiates the anesthetic action of other agents, either volatile or injectable, and reduces both general and regional anesthetic requirements with correspondingly fewer side effects, [213] [214] [215] [222] [223] [224] [225] [238] [239] [240] [241] [242] [243] [260] [261] [262] [263] [264] [265] [266] [267] [268] [269] [270] [271] [272] although it has not been shown to reduce perioperative ischemia. [273] Clonidine also attenuates the rise in intraocular pressure associated with laryngoscopy and endotracheal intubation. [274] [275] [276]

alpha$_2$ -Agonists provide effective analgesia for acute and chronic pain, particularly as adjuncts to local anesthestics and opioids. The addition of clonidine results both in increased duration of analgesia and reduced doses of each component. [218] [219] [220] [222] [224] [225] [226] [277] [278] [279] [280] [281] [282] [283] [284] [285] [286] [287] [288] Epidural clonidine is indicated for the treatment of intractable pain, which is the basis for the approval of parenteral clonidine in the United States as an orphan drug. [289] Patients with intractable pain, unresponsive to maximal doses of oral or epidural opioids, benefit from oral, patch, IM, and neuraxial administration of clonidine, [228] [229] [230] [231] [232] as do patients with reflex sympathetic dystrophy [294]

TABLE 14-10 -- Clonidine Dosing

ROUTE	BOLUS	CONTINUOUS INFUSION	REFERENCES
Oral	150 mug, 4-5 mug/kg	--	[213] [214] [215] [216] [217]
Intramuscular	2 mug/kg	--	[218]
Intravenous	150 mug, 4-8 mug/kg	2 mug/kg/h	[219] [220] [221]
Epidural	150-450 mug	12.5-70 mug/h	[218] [222] [223] [224] [225] [226] [228] [229] [230] [231] [232] [233] [234] [235] [236]
	6-8 mug/kg	1-2 mug/kg/h	
Intrathecal	30-225 mug	8-400 mug/d	[237] [238] [239] [240] [241] [242] [243] [244] [245] [246] [247] [248] [249] [250] [251] [252]

and neuropathic pain. [229] [291] The intrinsic analgesic effects of alpha $_2$ -agonists have been demonstrated with large doses of clonidine alone, administered either intrathecally (as much as 450 mg) or epidurally (1-2 mug/kg/h) to control intraoperative and postoperative pain. Clonidine decreases postoperative oxygen consumption and adrenergic stress response. [292] [293] Although there are dose-dependent side effects such as hypotension and sedation and idiosyncratic side effects with clonidine such as bradycardia, it does not induce profound respiratory depression and only mildly potentiates opiate-induced respiratory depression. [216] [295] [298]

Aside from its role as an anesthetic adjuvant and antihypertensive agent, clonidine has been used to treat panic disorder; [296] symptoms of opiate, benzodiazepine, and ethanol withdrawal; [297] [298] cigarette craving after heavy smoking cessation; [299] [300] [301] and as an antiemetic in cancer chemotherapeutic regiment. Its use in diabetic diarrheas is based on the presence of alpha $_2$ -receptors on gut epithelial cells. Normally, stimulation of ileal mucosal alpha $_2$ -receptors by EPI promotes sodium chloride absorption and inhibits bicarbonate secretion. In diabetes, in which intractable diarrhea can be a major problem, there is a depletion of mucosal NE stores and a denervation hypersensitivity, resulting in increased numbers of postsynaptic alpha $_2$ -receptors. Clonidine may increase blood glucose concentrations by inhibiting insulin release. [302] Further, unlike spinal opioids, clonidine does not cause urinary retention and may actually hasten time to first micturition after spinal anesthesia. [244] [245] [246] [302]

beta-Agonists

Nonselective: Dobutamine

Although at clinical doses it can act at beta $_2$ - and alpha$_1$ - receptors, this synthetic analogue of dopamine has predominantly beta $_1$ -effects. Compared with isoproterenol, it is reported to have more inotropy than chronotropy, but it increases conduction velocity through nodal tissue to the same extent. [303] It exerts less beta$_2$ -effect than does isoproterenol and less alpha $_1$ -effect than NE. Unlike dopamine, it does not directly release endogenous NE, nor does it act at dopaminergic receptors.

Dobutamine is particularly useful in CHF and MI complicated by a low-output state, although in cases of severe hypotension it may not be effective because of a lack of a significant alpha$_1$ -pressor effect. Although dobutamine increases cardiac contractility in the failing heart, its ability to lower filling pressures contrasts with the effects of dopamine and NE. It is relatively safe to use in myocardial ischemia without increasing the size of the infarct or causing arrhythmias. [304] Tachycardia does not usually occur with doses less than 20 mug/kg/min, but in especially severe CHF, significant tachycardia may occur and is the primary side effect. Because dobutamine directly stimulates beta$_1$ -receptors, it does not rely on NE stores and may still be effective in catecholamine-depleted states such as chronic CHF. However, in severe chronic CHF, the downregulation of beta-adrenergic receptors may hamper its effectiveness.

The beta$_2$ -vasodilating effects of dobutamine are almost exactly offset by its alpha $_1$ -constricting effects, which experimentally can be revealed by administering a nonselective beta blocking drug. [305] Its modest ability to dilate the peripheral vasculature is probably more closely connected with its ability to relieve the high-adrenergic state of decompensated CHF than to a specific beta $_2$ -mediated vasodilative effect. [306] Clinical situations that call for distinct afterload reduction may be better served by an agent such as nitroprusside.

Prolonged treatment with dobutamine causes downregulation of beta-receptors; tolerance to its hemodynamic effects is significant after 3 days and may be temporarily offset by increasing the rate of infusion. [307] Intermittent infusions of dobutamine have been used in the long-term treatment of heart failure and have been shown to cause some persistent improvement in exercise tolerance, [308] but they do not improve survival. [309]

Nonselective: Isoproterenol

Isoproterenol (Isuprel) provides relatively pure nonselective beta-stimulation with no significant effect at alpha-receptors. Its beta $_1$ -stimulation is significantly stronger than beta$_2$, but it still causes more beta$_2$ -activity than does dobutamine. Since the development of other inotropes, its popularity has declined because of its side effects of tachycardia and arrhythmias. These side effects have limited its use in myocardial ischemia or when ventricular irritability is a concern. Isoproterenol has been used in aerosol form to treat bronchospasm, but it has been replaced by beta $_2$ -selective drugs with their lower risk of cardiac side effects. Its lack of alpha-agonist properties renders it ineffective to raise perfusion pressure in shock. In the past, isoproterenol was used in bradycardia or heart block resistant to atropine, but it is no longer part of the American Heart Association Advanced Cardiac Life Support protocol. Infusion rates start at 0.5 to 5 mug/min for adults. It is metabolized primarily by COMT. It is not taken up into adrenergic nerve endings, so its duration of action is slightly longer than that of the natural catecholamines.

Selectivebeta$_2$ -Agonists

As mentioned earlier, isoproterenol was used in the treatment of bronchospasm for its beta $_2$ -stimulating properties, but unpleasant and dangerous beta $_1$ -mediated side effects limited its use. The development of beta $_2$ -selective agents has made beta-stimulants a cornerstone of the treatment of bronchospasm. However, it should be noted that this beta$_2$ -selectivity is only relative, and it may be lost at higher doses; in addition, beta $_2$ - receptors in the SA node may cause tachycardia when stimulated. The structures of these drugs have also been modified to slow their metabolism, thus prolonging therapeutic benefit and enabling oral administration. In particular, the addition of bulky structures on the catecholamine amino group increases beta $_2$ -selectivity, decreases affinity for alpha-receptors, and protects against metabolism by COMT. These agents are preferentially given by inhalation aerosol both for reasons of rapid onset and to minimize systemic drug levels and side effects by reducing drug levels. However, a well-documented increase in the annual number of deaths from asthma has been described, and it has been suggested that this increase may be related to beta $_2$ -agonist use, [310] [311] [312] in part because of the

TABLE 14-11 -- Pharmacokinetics and Pharmacology of Selected beta-Adrenoceptor Blockers

	ATENOLOL	METOPROLOL	NADOLOL	PINDOLOL	TIMOLOL	PROPRANOLOL HCl	ACEBUTOLOL	LABETALOL	ESMOLOL	BISOPROLOL
Proprietary name	Tenormin	Lopressor	Corgard	Visken	Blocadren	Inderal Ipran	Sectral	Trandate Normodyne	Brevibloc	Zebeta
Relative beta sensitivity	+	+	0	0	0	0	+	0	+	+
Intrinsic sympathetic activity	0	0	0	+	0	0	+	+	0	0
Membrane-stabilizing activity	0	0	0	+	0	++	+	0	0	0
Lipophilicity [b]	Low	Moderate	Low	Moderate	Low	High	Low	Low	Low	High
Predominant route of elimination	RE (mostly un-changed)	HM	RE	RE and HM	HM	HM	HM [c]	HM	Hydrolysis by RBC esterase	RE and HM
Drug accumulation in renal disease	Yes	No	Yes	No	No	No	Yes	No	No	Yes
Elimination half-life (h)	6-9	3-4	14-25	3-4	3-4	3-4	3-4 [d]	6	9 min	9-13
Usual oral maintenance dose	50-100 mg qd	50-100 mg qid	40-80 mg qd	5-20 mg tid	20 mg bid	60 mg qid	200-600 mg bid	100-600 mg bid	N/A	2.5-20 mg qd
Usual intravenous dose (caution)		5 mg q5min ×3				0.1 mg/kg (maximum)		1-2 mg/kg	50-300 mug/kg/min infusion	

HM, hepatic metabolism; N/A, not applicable; RE, renal excretion.

Modified from Rutherford and Braunwald [318]

[a] Data not available.
[b] Determined by the distribution ratio between octanol and water.
[c] Acebutolol is mainly eliminated by the liver, but its major metabolite, diacetolol, is excreted by the kidney.
[d] Half-life of the active metabolite, diacetolol, is 12 to 15 hours.

severity of illness and patient factors. A susceptibility to arrhythmia caused by these agents either by direct cardiac stimulation or by beta $_2$ -induced hypokalemia is one suggested mechanism, although it has been hypothesized that the long-term use of these drugs may increase airway hyperreactivity. Nonetheless, the safe use of these drugs in many thousands of patients is well documented. Commonly used drugs include metaproterenol (Alupent, Metaprel), terbutaline (Brethine, Bricanyl), and albuterol (Proventil, Ventolin). Metaproterenol is probably less beta $_2$ -selective than albuterol or terbutaline. Terbutaline is the only beta $_2$ -selective agent that can be given SQ and therefore may have particular use in status asthmaticus; the normal SQ dose is 0.25 mg, which may be repeated after 15 to 30 minutes.

beta$_2$ -Agonists are also used to treat premature labor. [313] Ritodrine (Yutopar) has been marketed for this purpose. beta $_1$ -side effects are common, particularly when the drugs are used IV. The other beta$_2$ -selective drugs have also been used as tocolytics, and all have been associated with significant beta $_1$ -side effects as well as the occasional incidence of pulmonary edema. [314] Their use for this purpose has recently been questioned. [315]

alpha-Receptor Antagonists

alpha$_1$ -Antagonists have long been utilized clinically as antihypertensives, but they have become less popular over the years. Alpha $_1$ -blockade vasodilates by blocking the effect of endogenous catecholamines on arterial and venous constriction. The effects are potentiated when standing or in the presence of hypovolemia. Reflex tachycardia and fluid retention can ensue. alpha $_2$ -Antagonists may act presynaptically to release NE.

Phenoxybenzamine (Dibenzyline) is a prototype alpha $_1$ - antagonist, although it irreversibly binds to both alpha $_1$ - and alpha$_2$ -receptors. New receptors must be synthesized before complete offset of its effects occurs. Its half-life after oral administration is unknown, but that after an IV dose is about 24 hours. Effects include a decrease in peripheral resistance and an increase in cardiac output; blood flow to skin and viscera is increased. As would be expected, its primary side effect is orthostatic hypotension; nasal stuffiness may occur. In addition to receptor blockade, phenoxybenzamine inhibits neuronal and extraneuronal uptake of the catecholamines. Phenoxybenzamine is used to treat pheochromocytoma through relatively long-term preoperative treatment ("chemical sympathectomy") that aids in blood pressure control, but also permits correction of a contracted plasma volume and protects against catecholamine-induced cardiac damage, yielding a smoother perioperative course. Total daily dose is 40 to 360 mg in two or three divided doses. When exogenous sympathomimetics are administered after alpha $_1$ -receptor blockade, their vasoconstrictive effects are inhibited. The effect of phenylephrine is completely blocked, whereas that of NE is limited to its beta $_1$ -effect of cardiac stimulation. There is potential "EPI reversal" caused by unopposed beta $_2$ -agonism, seen as severe hypotension and tachycardia. Despite its irreversible binding to the receptor, the recommended treatment for overdosage of phenoxybenzamine is NE infusion, because some receptors would still be free of the drug. [316]

Phentolamine (Regitine) is a shorter-acting agent that blocks both alpha $_1$ - and alpha$_2$ -receptors. Historically of use in pulmonary hypertension, it has been largely supplanted by nitroglycerin and nitroprusside. It is used to treat hypertension associated with clonidine withdrawal or with tyramine ingestion during MAOI therapy, but few real data have been collected on its efficacy and safety for these indications. The dose is 1 to 5 mg IM or slowly IV. Its plasma half-life is 19 minutes after IV administration. Phentolamine has also been infiltrated into affected tissues after extravasation of agents such as NE in an attempt to relax vasoconstriction: 5

to 10 mg is diluted in 10 mL of saline. Adverse effects of phentolamine include hypotension and gastrointestinal distress; reflex tachycardia and arrhythmias may be seen, at least partly resulting from action at alpha $_2$ -receptors. Coronary artery disease and peptic ulcer disease are relative contraindications. As in phenoxybenzamine overdosage, severe hypotension may require treatment with NE rather than EPI. Tolazoline (Priscoline) is a related drug used in persistent pulmonary hypertension of the newborn. [316]

Prazosin (Minipress) is a potent selective alpha $_1$ -adrenergic blocker often used as a prototypic antagonist in pharmacologic experiments. It antagonizes the vasoconstrictor effects of NE and EPI, causing a fall in peripheral vascular resistance and venous return to the heart. Although there is usually no increase in heart rate, orthostatic hypotension is a major problem. Unlike other antihypertensive drugs, prazosin improves lipid profiles, lowering lower-density lipid levels while raising the level of high-density lipids. It is primarily used to treat hypertension. It has also been used in CHF, but unlike the angiotensin-converting enzyme inhibitors (ACEI), prazosin does not prolong life. It is extensively hepatically metabolized. Supplied as 1-, 2-, and 5-mg tablets, its starting dose is usually 0.5 to 1 mg, given at bedtime only because of the orthostatic hypotension, and eventually it is given twice daily. [316]

alpha$_2$ -Antagonists, such as yohimbine, increase sympathetic outflow by enhancing release of NE. Although these drugs have proven to be of little clinical utility in anesthesia, they are used in urology.

beta-Receptor Antagonists

beta-Adrenergic receptor antagonists ("beta blockers") are among the most commonly prescribed drugs and are frequently taken by patients presenting for surgery. Current indications for the use of beta-blockade include ischemic heart disease, postinfarction management, arrhythmias, hypertrophic cardiomyopathy, hypertension, and prophylaxis of migraine headache. Initial concern that patients treated with beta blockers would be hemodynamically unstable under anesthesia has proven to be largely unjustified. In addition, these drugs are an important part of the armamentarium of the anesthesiologist in the ongoing attempt to limit stress responses perioperatively and to protect the cardiovascular system.

There is a confusing spectrum of beta blockers currently available to the clinician. The most important properties to consider in choosing a beta blocker for long-term use are cardioselectivity, intrinsic sympathomimetic activity, and lipid solubility. [317] [318] In anesthetic practice, cardioselectivity, duration of action, and a formulation suitable for IV use are crucial factors to consider (Table 14-11) . The beta-antagonists all resemble isoproterenol in structure and bind competitively to the beta-receptor, blocking access by more potent beta-agonists (Fig. 14-21) (Figure Not Available) . [316] Competitive inhibition at the beta-receptor can be overcome by increasing the available concentration of beta-agonist. In fact, the potency of a beta blocker is often determined

Figure 14-21 (Figure Not Available) Structures of isoproterenol and propranolol. *(From Tollenaere [455])*

by its ability to inhibit induction of tachycardia by isoproterenol. Propranolol is assigned a potency of 1, and the other drugs are evaluated in relation to it.

Nonselective beta blockers act at both the $beta_1$ - and $beta_2$ - receptors. The nonselective beta blockers include propranolol, nadolol, pindolol, sotalol, oxprenolol, penbutolol, and timolol. [306] [318] Cardioselective beta blockers have a stronger affinity for $beta_1$ - than for $beta_2$ -adrenergic receptors, and therefore the predominant effects are cardiac. Velocity of AV conduction, heart rate, and cardiac contractility are decreased, as well as the release of renin by the juxtaglomerular apparatus and lipolysis at the adipocytes. At higher doses, the relative selectivity for $beta_1$ -adrenergic receptors is lost, and $beta_2$ -receptors are also blocked, [319] with potential bronchoconstriction, peripheral vasoconstriction, and decreased glyco-genolysis. Cardioselective agents include atenolol, betaxolol, bevantolol, esmolol, and metoprolol. [306] [318] These drugs may be preferable in patients with obstructive pulmonary disease, peripheral vascular disease, Raynaud phenomenon, and diabetes mellitus. However, because the selectivity is only relative and may be lost at conventional clinical doses, extreme care must be used in administering a beta blocker in the presence of pulmonary disease, because death may result. Some beta-antagonists also have vasodilatory effects, making them particularly useful in the treatment of hypertension. [306] Labetalol vasodilates by blocking $alpha_1$ -receptors, as well as by direct $beta_2$ -agonism.

As mentioned, some beta blockers exert a partial agonist effect at the receptor while blocking access by more potent agonists and thus possess intrinsic sympathomimetic activity (ISA). Agents with ISA include acebutolol, carteolol, celiprolol, dilevalol, oxprenolol, penbutolol, and pindolol. [318] Of these, acebutolol and pindolol are more often used in the United States, but neither is commonly used in anesthetic practice. These agents lower blood pressure with less decrease in *resting* heart rate and left ventricular function. When sympathetic activity is high, such as during exercise, these drugs behave more like conventional beta blockers. The partial $beta_2$ -agonism of pindolol induces bronchodilation. [320] ISA may therefore be useful if beta blockade is required in a patient with bradycardia, peripheral vascular disease, or very mild hyperreactive airway disease. Beta blockers with ISA appear not to have the adverse effects on triglyceride and high-density lipoprotein levels seen after use of the other agents, although the clinical significance of this finding is unclear. [321] Agents with ISA may not be as effective in controlling symptoms in severe angina or in reducing mortality after MI. [322] ISA may protect against beta blocker withdrawal syndrome. [323]

The degree of lipid solubility greatly affects absorption and metabolism. Propranolol, metoprolol, and pindolol are the most lipid-soluble agents, are readily absorbed from the gastrointestinal tract, and are metabolized in the liver, undergoing extensive first-pass metabolism. Thus, propranolol and metoprolol are given IV in a much lower dose than that used orally because up to 70 percent of the orally administered drug is removed on the first pass of portal blood through the liver. [317] In addition, altered hepatic function may have a profound effect on plasma levels. The oral or IV dose of these agents required to reach a clinical end point varies greatly between patients. Because of a relatively short half-life, lipid-soluble agents are usually given at least twice a day. [316] The extremely short half-life of esmolol, however, is due to its metabolism by esterases.

The non-lipid-soluble, or hydrophilic, drugs are atenolol, sotalol, and nadolol. They are not as readily absorbed from the gastrointestinal tract, not as extensively metabolized, and are excreted unchanged by the kidneys. Because of a relatively long half-life, daily dosing may be adequate. There is less interpatient variability in plasma drug level and clinical effect because of the lack of hepatic metabolism and first-pass effect. [318] The lipid-insoluble drugs are slower to cross the blood-brain barrier and so may be chosen in an attempt to avoid the CNS side effects associated with beta blocker therapy (depression, sleep disturbances, nightmares, and fatigue). However, the relationship between lipid solubility and the occurrence of these symptoms is not consistent. [324] [325]

Propranolol and acebutolol possess membrane stabilizing activity (MSA), also referred to as the quinidine-like or local anesthetic effect. This reduces the rate of rise of the cardiac action potential. However, MSA is seen only at very high concentrations (ten times that required for blockade of beta receptors) [326] and is probably of little clinical consequence. Overdose with agents with MSA is associated with a higher incidence of fatality. [327]

Indications for Use

Myocardial Ischemia

Propranolol was initially introduced for treatment of myocardial ischemia three decades ago, and beta blocking drugs remain an important part of drug therapy for myocardial ischemia. This class of drugs reduces oxygen demand by decreasing heart rate and cardiac contractility. Both cardio-selective and nonselective beta blockers are effective: atenolol, metoprolol, nadolol, and propranolol have been approved in the United States for the treatment of angina; metoprolol and atenolol are the only beta blockers approved for IV use in acute MI. [316] Although initially there was concern that $beta_2$ -receptor blockade could worsen ischemia through unopposed alpha-mediated vasoconstriction, this phenomenon is rarely seen even in patients with variant angina. In usual clinical practice, the dose is increased until the heart rate is 60 to 80 beats/min at rest, and there is no tachycardia with exercise. Although in theory a nonselective antagonist may seem a better choice in acute MI, because the blockade of $beta_2$ -receptors may protect against stressinduced potassium shifts and hypokalemia-associated arrhythmias, cardioselective and nonselective drugs appear equally useful. [306] Agents with ISA are not as beneficial in this situation. [306] beta-antagonists are used both acutely in MI and on a long-term basis in postinfarction patients to reduce reinfarction and mortality. [328] [329] [330] [331] Early administration of IV beta blocking agents to patients receiving thrombolytic therapy appears to lower the incidence of ischemia and reinfarction [332] and may reduce the incidence of serious ventricular arrhythmias. [333] The long-term use of beta blockers (timolol, propranolol, metoprolol, and atenolol) has been shown unequivocally to decrease mortality after MI.

Hypertension

Although beta blockers are now recognized by the Joint National Council of the USA Guidelines as one of the two

preferred first-line therapies for hypertension (the other being diuretics), [334] the mechanisms by which beta-antagonists treat hypertension are incompletely understood. The blood pressure reduction is specific to hypertensive patients because long-term treatment of normotensive individuals does not lower blood pressure. Reduced cardiac output and renin release have been suggested as mechanisms. In hypertensive patients, beta-antagonists without ISA may cause a 15 to 20 percent reduction in cardiac output and a 60 percent reduction in renin release. However, pindolol, which has ISA and minimal effect on renin, is successful in treating hypertension. [335] In addition, maximum renin suppression precedes significant changes in arterial blood pressure. [336] Generally, beta blockade initially increases peripheral vascular resistance, then over time lowers it. [337] The decrease in cardiac output and eventual lowering of peripheral resistance may account for much of the antihypertensive efficacy of these drugs. However, this too is an incomplete explanation because labetalol is an effective antihypertensive despite its lack of effect on cardiac output. A primary CNS effect is not likely to be a major mechanism because of the similarity of antihypertensive efficacy of lipophilic and hydrophilic

compounds. Generally, beta blockade is ineffective as monotherapy in African-American patients more than 60 years of age.

Cardiac Arrhythmias

Beta blockers are also widely used in the therapy of tachyarrhythmias as class II agents (Ch.32) . Two possible mechanisms of action are blockade of catecholamine effects and MSA, although the latter is most likely not clinically significant, because antiarrhythmic effects are present in agents without MSA. [338] beta-Antagonists slow the rate of depolarization of the sinus node and any ectopic pacemakers, slow conduction through atrial tissue and the AV node, and increase the refractory period of the AV node. These drugs can convert atrial arrhythmias to sinus rhythm, [339] but beta blockade is primarily used to slow the ventricular response. Reentrant tachyarrhythmias and those associated with Wolff-Parkinson-White syndrome, mitral valve prolapse, and prolonged QT interval may also respond to these drugs. [326] Care should be exercised if AV block is present, as in digitalis toxicity, although these drugs are useful in the treatment of digitalis-associated tachyarrhythmias. [326] Sotalol, a beta blocker with added class III activity, is effective against ventricular tachyarrhythmias. A trial comparing racemic sotalol to *d*-sotalol in post-MI patients to protect against ventricular fibrillation showed an *increased* mortality with *d*-sotalol. [340] This finding suggests that beta-antagonists may perform differently as racemates than as optically pure agents.

Tachycardia

beta-Antagonists are frequently used as adjuvants to moderate the reflex tachycardia associated with vasodilators. This tachycardia can limit the effectiveness of blood pressure control or may cause myocardial ischemia. It is particularly crucial that appropriate beta blockade be administered during vasodilator therapy of aortic dissection because, in addition to potentiating blood pressure reduction, beta blockade reduces the velocity of left ventricular ejection (dp/dt) to attenuate the shearing force associated with tachycardia. [341] Nitroprusside used without concomitant beta blockade may propagate the dissection. Labetalol has been particularly useful in this situation. [342]

Perioperative Use

The safety of continuing beta blockade perioperatively is well established, and initial concerns regarding interaction with general anesthesia have not been confirmed. [343] In addition, attempts to discontinue beta blockers increase the risk of rebound tachycardia and myocardial ischemia in patients with coronary disease. These drugs should be given up to the time of surgery, and IV forms in appropriate dosages should be used whenever gastrointestinal absorption may be in question. As noted earlier, doses for IV administration vary less among patients because of the absence of first-pass hepatic effects. If beta blockers have been omitted from the preoperative regimen, esmolol or labetalol may be used acutely to blunt tachycardia and hypertension. Both cardio-selective and nonselective beta blockers appear effective in blocking chronotropic effects of endotracheal intubation and surgical stress. [344]

Thyrotoxicosis

Cardiac complications are a primary cause of morbidity in thyrotoxicosis. Beta blockade can suppress the tachycardia and rhythm disturbances, although very large doses may be required. beta-Antagonists also may be combined with digitalis for their synergistic effect on AV node conduction. Care should be exercised in the presence of CHF, but if the cause is tachyarrhythmia and ventricular function is adequate, beta blockers with or without digitalis may be helpful. Propranolol has been shown to inhibit conversion of thyroxine to the active form, triiodothyronine, in the periphery. [345]

Miscellaneous Conditions

Timolol (Timoptic) and betaxolol (Betoptic) are beta blocking drugs used topically in the eye to treat glaucoma through their reduction of the production of aqueous humor. Even topical use of these agents has been associated with significant systemic effects of beta blockade. Beta blockers are used in idiopathic hypertrophic subaortic stenosis in order to reduce the obstruction to left ventricular outflow and in the medical management of acute dissecting aortic aneurysm. The drugs are also effective in prophylaxis, but not therapy, of migraine headaches and in controlling acute panic symptoms and essential tremor.

Adverse Effects

The adverse effects of most concern are those involving cardiopulmonary function. Severe noncardiopulmonary reactions such as cutaneous reactions or anaphylaxis are extremely rare. Life-threatening bradycardia, even asystole, may occur; decreased contractility may precipitate CHF in

vulnerable individuals. Beta $_2$ blockade in patients with bronchospastic lung disease may be fatal. CNS effects, although an appropriate consideration in long-term therapy, are not a concern in the usual anesthetic use of these agents. Diabetes mellitus is a relative contraindication to the long-term use of beta-antagonists, because hypoglycemia in the face of sympathetic blockade is not accompanied by warning signs such as tachycardia and tremor, and compensatory glycogenolysis is blunted. However, most non-insulindependent diabetic patients can tolerate these drugs, although beta blockade may rarely cause insulin resistance. In addition to the potential worsening of peripheral perfusion by beta $_2$ blockade in patients with peripheral vascular disease, Raynaud phenomenon may be triggered in susceptible patients. Sudden withdrawal of beta blockers may cause myocardial ischemia and possibly infarction, although this is less of a problem with beta blockers with ISA such as pindolol. [323] [346] [347] Although beta-antagonists may reduce renal blood flow and glomerular filtration rate, these agents can be used in renal failure. In this case, the doses of lipidinsoluble drugs should be reduced. Use in pheochromocytoma should be avoided unless alpha-receptors have previously been blocked, to avoid worsening of hypertension. Hypertensive responses to nonselective agents may occur in cases of high sympathetic stimulation. [348]

Important drug interactions may occur. [316] [318] Verapamil has rate and contractility effects that are additive with those of the beta blockers, [349] [350] and care should be used in combining these agents, especially when using the IV forms in acute situations such as supraventricular tachycardia. The combination of digoxin and beta blockers can have powerful effects on heart rate and conduction and should be used with special care. Pharmacokinetic interactions are of note and are predictable from the degree of lipid solubility of the drug. Cimetidine and hydralazine may reduce hepatic perfusion, thereby increasing plasma levels and half-lives of the lipid-soluble beta-antagonists. Barbiturates, phenytoin, rifampin, and smoking may induce hepatic enzymes, thus enhancing metabolism. Propranolol may reduce hepatic clearance of lidocaine, increasing the risk of toxicity.

Overdose of beta blocking drugs may be treated with atropine, but isoproterenol, dobutamine, and/or glucagon infusions may be required, as well as cardiac pacing, to ensure an adequate rate of contraction.

Specific Drugs

The drugs propranolol, metoprolol, labetalol, and esmolol are particularly useful in anesthetic practice because they are widely available in IV formulation and have wellcharacterized effects. They are discussed in further detail in the following sections. If the drug the patient has taken on a long-term basis is propranolol, metoprolol, or labetalol, then that drug may be continued in IV form, if the clinical situation is relatively stable. In deciding which intravenous beta blocker to substitute in a patient taking a beta blocker on a long-term basis, the need for cardioselectivity is a primary consideration. Cardioselectivity is provided by metoprolol or esmolol. If the long-term agent has ISA, oxprenolol and acebutolol have IV forms, but they are not readily available. In many situations, esmolol may be substituted and titrated to effect, with the expectation that, if it is not well tolerated, its effects will fade relatively rapidly.

Propranolol

Propranolol (Inderal, Ipran) is the prototypic beta blocker, and its actions and its use are well characterized. [338] It is a nonselective beta blocking drug with MSA but no ISA. [318] It readily penetrates the CNS. Because of its high lipid solubility, it is extensively metabolized in the liver, but to an extent that varies greatly from patient to patient. Therefore, its effective dose is extremely variable: 10 mg to as much as 1 g may be given orally each day. Clearance of the drug can be affected by liver disease or altered hepatic blood flow. Renal impairment does not require adjustment of dosing. Despite its half-life of 4 hours, its antihypertensive effect is long-lived

enough to permit dosing once or twice a day. [338] [351] Inderal LA is a sustained-release formulation given once a day. [316]

Propranolol is available in IV form; although initially used as either bolus or infusion, the latter use has been largely supplanted by esmolol. For bolus administration, doses of 0.1 mg/kg may be given, although most practitioners initiate therapy with much smaller doses, typically 0.25 to 0.5 mg, and titrate to effect. Interestingly, propranolol shifts the oxyhemoglobin dissociation curve to the right, perhaps accounting for its efficacy in vasospastic disorders. [352] [353] [354]

Metoprolol

Metoprolol (Lopressor) is approved for the treatment of angina pectoris and is the only IV beta blocker formally approved by the U.S. Food and Drug Administration for treatment of acute myocardial infarction. Lacking either ISA or MSA, it is cardioselective. Because it is metabolized in the liver by the monooxygenase system, doses need not be adjusted in the presence of renal failure. [318] The usual oral dose is 100 to 200 mg per day, once or twice a day for hypertension and twice a day for angina pectoris. It may be administered IV in doses of 2.5 to 5 mg every 2 to 5 minutes up to about 15 mg, titrating to control of heart rate and acceptable blood pressure.

Labetalol

Labetalol (Trandate, Normodyne) is representative of a class of drugs that act as competitive antagonists at both alpha $_1$ - and beta-adrenergic receptors. Labetalol consists of four isomers that block the alpha$_1$ -, beta$_1$ -, and beta$_2$ -receptors, inhibit neuronal uptake of NE (uptake 1), act as a partial agonist at beta $_2$ -receptors, and possibly have some direct dilating abilities. [316] The potency of the mixture for beta blockade is 5- to 10-fold that for alpha blockade. [355] The usual oral dose of labetalol is 200 to 400 mg twice a day, although much larger doses have been used. It is hepatically metabolized, and therefore clearance is affected by hepatic perfusion. The dose need not be adjusted for renal dysfunction. [318] Labetalol may be given IV every 5 minutes in 5- to 10-mg doses or up to a 2-mg/min infusion. It significantly blunts cardiovascular responses

to tracheal intubation. [356] It can be effective in treatment of aortic dissection, [342] hypertensive emergencies, [357] [358] and postoperative cardiac surgical patients, [359] particularly because its vasodilatation is not accompanied by tachycardia. It may be used in pregnancy to treat hypertension, both on a long-term basis and in more urgent situations. [360] Uterine blood flow is not affected even with significant reduction of blood pressure. [361] Carvedilol, a mixed alpha- and beta-antagonist, has been introduced as therapy for mild to moderate hypertension, [362] [363] [364] [365] [366] [367] [368] [369] [370] for management of stable or unstable angina, and after acute MI. [371] [372] [373] [374] [375] Clinical trials of carvedilol use in the treatment of controlled CHF (New York Heart Association class II-IV) suggest a significant reduction in the risk of mortality, [376] [377] [378] [379] especially for patients with diabetes. [380]

Esmolol

Because of its hydrolysis by esterases, esmolol (Brevibloc) has a uniquely short half-life of 9 to 10 minutes, which makes it particularly useful in anesthetic practice. It is administered when beta blockade of short duration is desired or in critically ill patients for whom adverse effects of bradycardia, heart failure, or hypotension may necessitate rapid withdrawal of the drug. Peak effects of a loading dose are seen within 5 to 10 minutes and diminish rapidly (within 20-30 min). It is cardioselective. It may be given as a bolus of 0.5 mg/kg to blunt cardiovascular responses to tracheal intubation. If used as an infusion for the treatment of supraventricular tachycardia, 500 mug/kg is given over 1 minute, followed by an infusion of 50 mug/kg/min for 4 minutes. If the rate is not controlled, a repeat loading dose followed by a 4-minute infusion of 100 mug/kg/min is given, and this sequence is repeated, increasing the infusion in 50-mug/kg/min increments, up to 200 or 300 mug/kg/min if needed. It should be remembered that the clinical effect may persist for 20 to 30 minutes after discontinuation of the infusion. Compared with verapamil, esmolol may be more likely to convert atrial fibrillation to sinus rhythm. [339] Esmolol is safe and effective in treatment of intraoperative and postoperative hypertension and tachycardia. [381] [382] [383] If continuous use is required, it may be reasonably replaced by a longer-lasting cardioselective drug such as IV metoprolol. It has been used safely even in patients with compromised left ventricular function. [384] [385]

Drugs that Inhibit Synthesis, Storage or Release of Norepinephrine

Some early antihypertensive drugs acted by replacing NE in the nerve ending with a much less potent false transmitter. alpha-Methyldopa (Aldomet) is such a drug and was, in fact, the most popular nondiuretic antihypertensive used prior to the development of beta blockers. [317] Like DOPA, alpha- methyldopa enters the biosynthetic pathway for NE (see Fig. 14-9) (Figure Not Available) . It is then decarboxylated to alpha-methyl-NE. Initially, this chemical was thought to act as a false transmitter, but it was found to be almost as potent as NE. In the CNS, alpha-methyldopa may be further metabolized to alpha-methylepinephrine, [386] and it acts at alpha$_2$ -receptors to decrease sympathetic outflow, [387] thus reducing blood pressure. Because of its sedating qualities, fluid retention, postural hypotension, and occasional reports of hepatic necrosis, alpha-methyldopa is now used much less often. [317]

Methylparatyrosine (metyrosine, Demser) is a potent inhibitor of tyrosine hydroxylase, which catalyzes the formation of DOPA from tyrosine (see Fig. 14-9) (Figure Not Available) . Because this is the rate-limiting step in the biosynthesis of NE, the drug significantly decreases levels of endogenous catecholamines and is useful in treating inoperable or malignant pheochromocytomas. [388]

Reserpine affects the uptake of NE not at the neuronal membrane but at the vesicular membrane, thereby inhibiting transport and storage of NE and dopamine. Eventually, NE stores are depleted, and postsynaptic receptors increase in number, which may increase the effects of EPI in patients who have been given reserpine (see Table 14-5) (Table Not Available) . In these patients who require a sympathomimetic drug, direct-acting agents may be more useful, whereas mixed-acting drugs would only be efficacious at higher doses, if at all. Although the agent has central effects that lead to side effects such as sedation and depression, its peripheral effects are responsible for its utility as an antihypertensive drug.

Guanethidine (Ismelin) is taken up into adrenergic nerve endings by the uptake-1 mechanism and depletes NE stores, after initially blocking release of NE. It is used in therapy of hypertension, usually after trial of many other drugs. Its inability to cross the blood-brain barrier accounts for its lack of sedative effect. Guanadrel (Hylorel) is similar to guanethidine, but it has a shorter onset and duration of action.

Bretylium is a class III antiarrhythmic used parenterally to treat life-threatening ventricular tachyarrhythmias. Like guanethidine, it is taken up into adrenergic nerve terminals, but its mechanism of action is otherwise quite different. Bretylium initially causes NE release, then subsequently blocks that release by decreasing sympathetic nerve excitability. Unlike guanethidine, bretylium does not deplete NE stores. [389] The initial catecholamine release may worsen some arrhythmias, such as those associated with digitalis toxicity and myocardial ischemia. [326]

MAO and COMT are enzymes important in degradation of the catecholamines. MAOI bind irreversibly to the enzyme and cause increased amine concentration within the presynaptic terminal. This increase is associated with antihypertensive, antidepressant, and antinarcoleptic effects. [390] MAOI are thought to exert their antihypertensive effect through a false transmitter mechanism. Tyramine is usually oxidatively deaminated in the gut by MAO. With administration of an MAOI, tyramine levels rise. When tyramine is taken up into the sympathetic nerve terminal via uptake 1, it enters the varicosities and is transformed by DBH into octopamine. On its subsequent release in place of NE, octopamine is only weakly reactive at sympathetic receptors, resulting in a lowering of blood pressure. The MAOI are no longer used as antihypertensives because many other drugs with better risk-benefit ratios have been developed.

MAOI are now primarily used in psychiatric practice. The use of MAOI as antidepressants is based on the theory that depression is due to decreased amine in the synapses of the CNS. Inhibition of MAO thus makes more amine available

for release. MAOI currently available for treatment of depression include isocarboxazid (Marplan), phenelzine sulfate (Nardil), and tranylcypromine sulfate (Parnate).

There are at least two forms of this enzyme, based on substrate specificity. MAO-A acts on 5-HT, NE, and dopamine, whereas MAO-B is specific for tyramine. A specific MAO-B inhibitor, selegiline hydrochloride (deprenyl), has been developed for the treatment of Parkinson disease, in hopes that by blocking central dopamine breakdown, more dopamine will be preserved in the affected areas. [391]

Drug and food reactions have been of great concern in patients taking MAOI. Ingestion of tyramine-containing foods such as red wine and aged cheese must be avoided by patients taking these drugs. Consumption delivers a huge amount of tyramine to the adrenergic nerve terminal, with a subsequent massive release of NE. This is manifest clinically as a hypertensive crisis with potential for MI, cerebral hemorrhage, and death. Any intake of biogenic amine precursors would be expected to increase catecholamine levels greatly, as seen with the concurrent administration of levodopa with MAOI. The effects of sympathomimetic amines, particularly the indirect-acting drugs, are enhanced. [390] Of commonly used drugs, narcotics, in particular meperidine, have been associated with hyperpyrexic coma and death in patients treated with MAOI. Depressant effects of agents such as sedatives, alcohol, and general anesthetics are enhanced in these patients. Interaction between MAOI and tricyclic antidepressants can be disastrous. [390] Anesthetic interactions with deprenyl have not been reported, but experience with this drug is currently limited. [391] Great concern has been expressed that patients receiving long-term therapy with MAOI risk life-threatening drug interactions during anesthesia. Emergency surgery in patients given MAOI can be punctuated by marked hemodynamic instability. Severe reactions to narcotics and indirect-acting sympathomimetics, as well as altered metabolism of endogenous and exogenous catecholamines, make these patients potentially difficult to manage. Because of the possibly dangerous interactions of many drugs with MAOI, controversy exists over the best way to anesthetize these patients. [392] [393] It has been suggested that the level of concern expressed over the years may be excessive. Although prudence and custom dictate discontinuation of MAOI well in advance of elective procedures (2 weeks), there appear to be rational anesthetic choices based on pharmacology and risk-benefit considerations in patients in whom surgery cannot be delayed.

Drugs Affecting the Renin-Angiotensin System

The renin-angiotensin system is important in maintaining blood pressure and fluid balance (see Fig. 14-7) . The major end product of the system, angiotensin II, is a potent vasoconstrictor that stimulates the release of aldosterone from the adrenal cortex. Aldosterone causes salt and water retention by the kidney. The mechanism by which angiotensin II is produced is as follows. The juxtaglomerular cells of the renal cortex secrete the proteolytic enzyme called renin, which cleaves angiotensinogen, a protein produced in the liver, producing the decapeptide angiotensin I. Angiotensin I is converted almost immediately to angiotensin II by ACE. This converting enzyme is located predominantly in the endothelial tissue of the lung. In addition to its direct vasoconstrictive activity, angiotensin II enhances the prejunctional release of NE from the adrenergic nerve ending and increases efferent sympathetic nerve activity. Angiotensin II also affects sodium and water homeostasis by directly decreasing tubular reabsorption of sodium, increasing ADH and adrenocorticotropic hormone secretion, and stimulating the secretion of aldosterone. ACE is also a kinase that degrades the vasodilator bradykinin. Therefore, ACE inhibition blocks angiotensin II formation and delays bradykinin breakdown along with effects on associated prostaglandins. [394]

A few patients with hypertensive vascular disease have high circulating plasma renin levels, but many more, 70 percent of patients, respond to the antihypertensive effects of ACEI, and there is no dramatic difference in hypertensive response among patients with low or high renin levels. [317] The ACEI have proven to be useful in the treatment of hypertension and CHF and have decreased mortality after MI [395] (Table 14-12) . Captopril (Capoten), was the first active oral agent available, followed by enalapril (Vasotec) and lisinopril (Prinivil, Zestril). Four new ACEI have been marketed: benazepril (Lotensin), fosinopril (Monopril), quinapril (Accupril), and ramipril (Altace). The ACEI affect the renin-angiotensin aldosterone system by inhibiting ACE activity. [394] [396] [397] Enalapril is the only ACEI available in a parenteral dosage at this time. Lisinopril offers once-a-day dosing.

Although all the ACEI are approved for the treatment of hypertension, only captopril and enalapril are approved for the treatment of CHF. Both these agents have been shown to decrease morbidity and mortality in patients with CHF. Captopril is associated with more frequent adverse effects than enalapril, may have a few more drug interactions, and has a two- to three-times daily dosing regimen as compared with enalapril, which has a once-daily to twice-daily dosing regimen.

Some adverse effects observed with ACEI are common to the entire class, such as cough, angioedema, acute renal failure, and hyperkalemia. Angioedema has occurred, especially after the first dose, affecting the face, extremities, lips, mucous membranes, tongue, glottis, or larynx. [394] [398] [399] Some occurrences may be fatal. [394] [398] [400] This common side effect has led to the approval of the angiotensin II receptor antagonist, losartan. Rash and taste disturbance occur more frequently with captopril than with the other ACEI. Renal function impairment has occurred with ACEI, but it is usually reversible after withdrawal of the drug. Renal function should be monitored. [396] [399] Because hyperkalemia may result from inhibition of aldosterone secretion, it is recommended that serum potassium levels be monitored. [394] [397] [398] [399] ACEI have demonstrated fetal morbidity and mortality in humans. It is advised not to use these agents at all during the second or third trimester of pregnancy. [400]

Cholinergic Drugs

Overview of Mechanisms of Action

The cholinergic drugs act by mimicking, amplifying, or inhibiting the effects of ACh. Cholinergic drugs do not behave exactly as does ACh: their drug action is more specific, affecting

TABLE 14-12 -- Comparative Pharmacokinetics of Angiotensin-Converting Enzyme Inhibitors

	BENAZEPRIL	CAPTOPRIL	ENALAPRIL	FOSINOPRIL	LISINOPRIL	QUINAPRIL	RAMIPRIL
Prodrug	Yes	No	Yes	Yes	No	Yes	Yes
Lipid solubility	No data	Not very lipophilic	Lipophilic	Very lipophilic	Very lipophilic	No data	Somewhat lipophilic
Absorption	37%	75%	60% (53-73%)	36%	25% (6-60%)	60%	50-60%
Serum $t_{1/2}$ (h)	Benazeprilat 10-12	<2	Enalapril 1.3, enalaprilat 11	Fosinoprilat 12	12	Quinapril 0.8, quinaprilat 2	Ramipril 1-2 ramiprilat 13/17
Serum protein binding	>95%	25-30%	<50%	>95%	0	0.97	Ramipril 73%, ramiprilat 56%
Elimination	Primarily renal, some biliary	Metabolized to disulfide, then renal	Renal	Renal 50%, hepatic 50%	Renal	Renal 61%, hepatic 37%	Renal
Onset of hypotensive action (h)	1	0.25	1	1	1	1	1-2
Peak hypotensive effects (h)	2-4	1-1.5	4-6	2-6	6	2	3-6
Duration of hypotensive effects (h)	>20 mg/day, 24	Dose-related	24 (18-30)	24	24 (18-30)	24	24 (24-60)
Dosage	20-80 mg daily, dosed 1-2 × day, maximum 80 mg daily	25-150 mg/dose, dosed 2-3 × day, maximum 450 mg daily	5-40 mg daily, dosed 1-2 × day, maximum 40 mg daily	10-40 mg daily, dosed 1-2,m × day, maxi- mum 80 mg daily	10-40 mg daily, dosed 1-2 × day, maxi- mum 80 mg daily	10-80 mg daily, dosed 1-2 × day, maxi- mum 80 mg daily	2.5-20 mg daily, dosed 1-2 × day, maximum 20 mg daily

fewer sites than ACh, and their duration of action is generally longer than that of ACh.

Unlike adrenergic pharmacology, in which the clinician can select from a wide choice of drugs, there is a relative paucity of drugs that influence parasympathetic function. In general, drugs that affect the parasympathetic system act in one of four ways:

1. As an agonist, stimulating cholinergic receptors.
2. As an antagonist, blocking or inhibiting the actions mediated by the cholinergic receptor.
3. Blocking or stimulating receptors on autonomic ganglia.
4. Inhibiting the metabolism of ACh, thus increasing and prolonging the effect of ACh.

There are currently no effective clinically used drugs that act through mechanisms affecting synthesis of ACh (e.g., by inhibiting choline acetyltransferase) or by causing indirect release of ACh (as tyramine, ephedrine, and amphetamine may release NE). Hemicholinium does interfere with choline uptake and could deplete ACh stores, but it is not used clinically. Adenosine may inhibit the release of ACh by decreasing the affinity of binding sites for calcium ions; aminoglycoside antibiotics may compete with calcium for membrane calcium channels, as does magnesium ion. Exocytotic release of ACh is inhibited by botulinum toxin; this toxin is sometimes given by local injection to treat strabismus and blepharospasm. In a full-blown botulism poisoning syndrome, fatalities may result from muscle weakness and respiratory failure.

Agonists

Cholinergic agonists have limited therapeutic use because of their detrimental effects. ACh, as a result of its diffuse, nonselective actions and rapid hydrolysis by both acetylcholinesterase and butyrylcholinesterase, has had almost no therapeutic use other than as an intraocular medication for transient constriction of the pupil during ophthalmic surgery.

Cholinergic agonists in clinical use have been derived from ACh, but they resist hydrolysis by cholinesterase, permitting a useful duration of action. The different systemic effects of the cholinergic agonists are more quantitative than qualitative, but some limited organ selectivity is useful therapeutically, as is seen with the synthetic choline esters bethanechol and carbachol. Methacholine and bethanechol are primarily muscarinic agonists; carbachol has significant nicotinic and muscarinic effects. The simple maneuver of adding a methyl group to the beta-position of the choline in ACh produces methacholine, which is almost purely muscarinic and is almost totally resistant to hydrolysis by either of the cholinesterases. An IV infusion of methacholine causes hypotension and bradycardia; a small SQ dose causes a more transient hypotension with a reflex increase in heart rate. The sole current use of methacholine (Provocholine) is as a provocative agent in diagnosing hyperreactive airways, making positive use of the deleterious bronchoconstrictive effect of muscarinic agonists. It is administered only by inhalation; serious side effects including gastrointestinal symptoms, chest pain, hypotension, loss of consciousness,

and complete heart block have occurred when the drug is given orally or parenterally. Excessive bronchoconstrictive response should be treated by an inhaled beta-agonist; coexisting beta blockade is considered a contraindication to the use of methacholine.

The carbamate derivative of methacholine, bethanecol (Urecholine), is occasionally used postoperatively to reinstitute peristaltic activity in the gut or to force the extrusion of urine from an atonic bladder. It is administered SQ or orally to avoid effects in other organ systems.

Carbachol is used topically or intraocularly to constrict the pupil, for long-term treatment of wide-angle glaucoma. When used topically, it is often better tolerated than the ophthalmic anticholinesterase agents, and it may be effective in patients resistant to pilocarpine and physostigmine. The rapid pupillary constriction is due to the combination of ganglionic block and muscarinic effects. Another natural alkaloid, pilocarpine, was used to treat glaucoma until the advent of more modern drugs.

Muscarinic Antagonists

Muscarinic antagonists are the active ingredients in some common plants used since antiquity for both medicinal and poisonous effects. It has been suggested that atropine poisoning figures in the American classic, *The Scarlet Letter.*[401] Despite their age, muscarinic antagonists still represent important drugs in anesthesia and critical care (Fig. 14-22) .

Muscarinic antagonists compete with neurally released ACh for access to muscarinic cholinoceptors and block its effects. They also antagonize the actions of muscarinic agonists at noninnervated, muscarinic cholinoceptors. Presyn-aptic muscarinic receptors on the adrenergic nerve terminal may inhibit NE release. Hence, muscarinic antagonists may enhance sympathetic activity. With the exception of quaternary ammonium compounds that do not readily cross the blood-brain barrier and so have few CNS actions, there is no significant specificity of action among these drugs; they block all muscarinic effects with equal efficacy, although some quantitative differences in effect may be seen (Table 14-13) . Research has revealed several subtypes of muscarinic receptors, and agonists and antagonists have been synthesized that bind preferentially to one or another. None of these selective agents is yet available commercially, but this is a rapidly developing area of research, and there will soon be drugs that selectively act on one site or another, such as the heart, bronchial system, smooth muscle, gastric mucosa, or some particular area of the CNS.

Historically, these drugs were used in peptic ulcer disease, various forms of "spastic bowel syndrome," upper respiratory illness, and asthma. However, with the availability of the specific histamine (H_2) drug cimetidine for peptic ulcer disease and inhaled beta-agonists and steroids for asthma, these uses have markedly decreased. Historically, atropine was one of the important drugs used to treat bronchospasm, but it was displaced with the introduction of beta $_2$ -agonist drugs that did not cause drying of secretions or diminished ciliary motility. Topical use of atropine analogues in ophthalmologic practice to dilate the pupil is still common.

The addition of a muscarinic anticholinergic drug to anesthetic premedication to decrease secretions and to prevent harmful vagal reflexes was mandatory in the era of ether anesthesia, but it is no longer necessary with modern inhalational agents. Scopolamine combined with an opiate, usually morphine, is still used by cardiac anesthesiologists to sedate a patient while minimizing cardiorespiratory effects. Routine preoperative use of these drugs as antisialogogues continues in some pediatric and otorhinolaryngologic cases.

Atropine is a tertiary structure that easily crosses the blood-brain barrier (see Fig. 14-22) . CNS effects have been seen with the relatively large doses (1-2 mg) given to block

Figure 14-22 Structural formulas of the clinically useful antimuscarinic drugs.

TABLE 14-13 -- Muscarinic Anticholinergic Drugs

	DURATION	CENTRAL NERVOUS SYSTEM[a]	ANTISIALAGOGUE	HEART RATE
Atropine	Short	Stimulation	+	++
Glycopyrrolate	Long	0	++	+

Scopolamine	Short	Sedation	++	0/+

0, no effect; +, mild effect, ++ moderate effect.

[a] Effects of atropine are limited with usual clinical doses, but they can be significant in the elderly.

the muscarinic side effects of the anticholinesterase drugs used for reversal or neuromuscular blockade reversal (Ch. 12) . In contrast, one of the synthetic antimuscarinic drugs, glycopyrrolate (Robinul), does not cross the blood-brain barrier and has gained popularity for this use. In addition, glycopyrrolate has a longer duration of action than does atropine.

Scopolamine, which resembles the others of this class in peripheral actions, has pronounced CNS effects. It is the active ingredient in most over-the-counter preparations sold as soporifics, and it is effective in preventing motion sickness. The patch preparation of scopolamine can be used prophylactically for motion sickness and postoperative nausea and vomiting, but like oral and parenteral forms, it may be associated with eye, bladder, skin and psychologic side effects. [402] [403]

The development of ipratropium (Atrovent) reestablished antimuscarinic drugs as an important therapeutic approach in asthma and bronchospastic disorders. [404] Although ipra-tropium is structurally similar to atropine and has essentially the same effects when administered parenterally, an important difference is that ipratropium is a quarternary ammonium compound. Thus, it is very poorly absorbed when delivered via inhalation and essentially has few extrapulmonary effects even when given in extremely large doses by this route. Ninety percent of inhaled drug is swallowed, but only 1 percent of the total dose is absorbed systemically.

When administered to normal volunteers, ipratropium provides almost complete protection against bronchospasm induced by a variety of provocative agents. However, in asthmatic patients, results are more variable. The bronchospastic effects of some agents, such as methacholine or sulfur dioxide, are completely blocked, whereas there is little effect on leukotriene-induced bronchoconstriction. Further, there is considerable variability among patients. The onset of bronchodilation is slow, and the maximal effect is less than that seen with beta-agonists. Unlike atropine, ipratropium has no negative effect on ciliary clearance. In general, more therapeutic effect from antimuscarinics, including ipra-tropium, is seen in patients with chronic obstructive pulmonary disease than in asthmatic patients. [404] [405] Ipra-tropium is supplied as a metered-dose inhaler supplying 18 mug per puff. Dosage is two puffs orally four times a day. Maximum bronchodilation occurs in 30 to 90 minutes, but the duration may be 4 hours. [405]

The toxic effects of the muscarinic antagonists are due to the blockade of muscarinic cholinoceptors in the periphery and the CNS. The peripheral effects (e.g., dry mouth) may be irritating, but not life-threatening, in healthy adults. However, children are more dependent than adults on sweating for thermoregulation and easily become dangerously hyperthermic. Moreover, older individuals may not be able to tolerate the cardiac, ocular, or urinary effects of muscarinic blockade.

The CNS effects are the usual cause of death or injury. Increasing doses of atropine or scopolamine cause greater distortions of mentation, progressing from thought disorders to hallucinations, delusions, delirium, and severe psychoses. These effects are reversible, but the mental dysfunction can persist for weeks. Left alone, the intoxicated individual will die of starvation, dehydration, and/or trauma. However, recovery will be complete if the individual receives appropriate supportive and protective care until the drug is eliminated. Volunteers have received more than 500 mg of atropine, more than 1,000 times the usual dose, and, although they have been disabled for weeks, they have recovered fully.

Small doses of atropine (0.05 mg) can evoke bradycardia, a finding that has led some clinicians to increase the dose in children. It was thought that a CNS effect of atropine could be responsible, but the time course, as well as the fact that it occurred in vagotomized animals, cast doubt on this mechanism. Whether this paradoxic bradycardia is a central or peripheral effect, or both, and the role of muscarinic subtypes, are still subjects of debate. [406]

Atropine and scopolamine toxicity have been treated for decades by the use of the naturally occurring alkaloid physostigmine (Antilirium), which is an anticholinesterase that penetrates the blood-brain barrier. [407] Consequently, the use of this drug in doses of 1 to 2 mg IV to treat the postoperative CNS effects of IV atropine or scopalamine has been successful. Physostigmine may also reverse the CNS effects of other compounds with anticholinergic activity, including the tricyclic antidepressants, several major tranquilizers, and antihistamine drugs. [408] Physostigmine may antagonize the sedative effects of the benzodiazepines as well, but the specific benzodiazepine antagonist, flumazenil (Romazicon), will undoubtedly supplant physostigmine for this use. [409] [410] Physostigmine must be administered with care because of its potentially lethal nicotinic effects, which are not prevented by the muscarinic antagonists, and because its half-life rarely matches that of the intoxicant.

Cholinesterase Inhibitors

Anticholinesterase drugs provide the most commonly used means of producing sustained systemic cholinergic agonism. These drugs are used to reverse neuromuscular blockade, to treat myasthenia gravis, and to treat certain tachyarrhythmias.

The first anticholinesterase agent available was physostigmine (see earlier). There are currently three chemical

classes of compounds used as cholinesterase inhibitors: carbamates, organophosphates, and quaternary ammonium alcohols. Neostigmine was first used as a gastrointestinal tract stimulant and later as a treatment for myasthenia gravis.

Physostigmine, neostigmine, and pyridostigmine are carbamates, whereas edrophonium is a quaternary ammonium alcohol. The cholinesterase enzyme is inhibited so long as the esteratic site is bound to an acetate, carbamate, or phosphate. Carbamate and phosphate bonds are much more resistant to attack by hydroxyl groups than are acetate bonds. The acetylated form lasts for only microseconds, whereas the carbamylated form lasts for 15 to 20 minutes. Organophosphates include diisopropylfluorophosphate, parathion, malathion, soman, sarin, VX, and a variety of other compounds used as insecticides. Although the toxicity of the organophosphate insecticides is primarily related to their anticholinesterase activity, the mechanism of this effect is different from the clinically used anticholinesterase drugs. The organophosphates produce an irreversible enzyme inhibition and have CNS effects as well. [411] Consequently, treatment of organophosphate insecticide poisoning relies on chemical compounds capable of displacing the insecticides from the enzyme and therefore of reactivating the cholinesterase activity. The best-documented of these chemicals is pralidoxime (2-PAM). Physostigmine and most of the organophosphates are not quaternary ammonium compounds and have major effects on cholinergic functions in the CNS.

Edrophonium is unique in that it lacks an acetate, carbamate, or a phosphate group. It acts because the positive charge of the nitrogen is attracted strongly by the anionic site and physically blocks the esteratic site. Thus, the edrophonium molecule is postulated to be held in place only by an ionic bond. The duration of inhibition provided by each molecule is short (e.g. milliseconds), but because they are not changed in the reaction, the molecules can hop onto and off the enzyme repeatedly and consequently render the enzyme unavailable to ACh.

Aside from reversal of neuromuscular blockade, there are few other therapeutic uses of these compounds. Because these compounds can increase the effect and duration of neurally released ACh, they are useful in situations in which such release is deficient, such as myasthenia gravis. Further, anticholinesterase drugs are occasionally used to stimulate intestinal function and topically in the eye as a miotic. An irreversible organophosphate anticholinesterase that is used clinically is echothiophate iodide (Phospholine), which is available as topical drops for the treatment of glaucoma. Its major advantage over other topical agents is its prolonged duration of action. Because this chemical also inactivates plasma cholinesterase, it may prolong the action of succinylcholine. Although prudence dictates discontinuation of echothiophate for 1 week prior to surgery, there are numerous case reports of successful anesthesia performed under emergency conditions.

Ganglionic Drugs

Agonists

The agonists are essential for analyzing the mechanism of ganglionic function, but they have no therapeutic use. Nicotine is the classic ganglionic agonist, and its

effects have been well described. [412]

Parasympathetic drugs stimulate ganglia, but this action is usually masked by the other parasympathomimetic effects. Experimentally, relatively large doses of ACh administered IV after blockade of muscarinic receptors by atropine causes ganglionic stimulation and release of EPI by the adrenal medulla. [412]

Antagonists

The ganglionic antagonists were the first effective therapy for the management of hypertension and were used extensively during the 1950s and 1960s. However, because of interference with transmission through both sympathetic and parasympathetic ganglia, antihypertensive action was accompanied by numerous undesirable side effects. Hexa-methonium is the prototypic drug of this class, and it has minimal neuromuscular and muscarinic activity. Paton [413] provided a vivid description of the clinical effects of chronic ganglionic blockade with his "hexamethonium man." The systemic effects of ganglionic blockade are determined by the "resting tone" of a specific body system prior to the application of ganglionic blockade (see Table 14-2) .

Although not as reliable or as potent as nitroprusside, trimethaphan has a quick onset and short duration of action that makes it useful in situations in which moment-to-moment control of blood pressure is critical, while avoiding some of the toxicity and side effects associated with agents such as nitroprusside and beta blockers. Because it does not increase cerebral blood flow, it may be used in hypertensive encephalopathy without worsening cerebral edema and also in intracranial hem-orrhage associated with hypertension. In acute aortic dissection, trimethaphan may lower blood pressure without causing significant tachycardia, avoiding the increase in shearing forces (dp/dt) seen with increased heart rate. [341]

Trimethaphan may be used for controlled hypotension under certain circumstances, as an alternative to or in combination with nitroprusside. The two agents combined may avoid the sympathoadrenal stimulation and rebound hypertension seen with nitroprusside alone. The dosages are also decreased with the use of combination therapy, thus avoiding cyanide toxicity in patients who have renal insufficiency or who require large cumulative doses of trimethaphan. Side effects and rapidly developing tolerance limit its use. Other noncardiovascular side effects related to effects of ganglionic blockade include blurred vision, persistent pupillary dilatation (which may interfere with neurologic evaluation), and gastrointestinal and urinary atony. Orthostatic hypotension occurs, but it may not be a serious concern in these usually critically ill patients. Histamine release also occurs at clinically relevant concentrations.

AUTONOMIC DYSFUNCTION

Plasma Catecholamines

Accurate and sensitive techniques for measuring plasma catecholamines have existed for three decades, but interpretation of the data they yield has been controversial. Plasma EPI and NE levels are typically in the 100 to 400 pg/mL normal range, but they can easily increase 6-fold or more in stress.

Plasma concentrations of EPI reflect adrenal medullary activity, [414] if not overall sympathetic activity, and are labile. The uncontrolled stress experienced by experimental subjects has clouded the meaning of measured levels. Significant isolated adrenal medullary secretion can occur in certain stressful situations, such as public speaking. [28] Moreover, venous samples may reflect the EPI kinetics in the organ being sampled rather than in the whole body, and arterial samples may be more reliable. [415]

The significance of plasma NE concentration is even more controversial. Although the adrenal medulla secretes some NE, plasma NE levels generally reflect spillover from sympathetic stimulation because most of the plasma NE released at the nerve ending is taken up again by the nerve terminal. Although reuptake may be tissue-specific and markedly influenced by alterations in physiology or diseases, this spillover in humans is 10 to 20 percent of the NE synthesis rate at baseline and may be greatly enhanced in periods of sympathetic activation. [416] The most compelling argument for use of plasma NE as a marker for sympathetic activity comes from animal studies in which plasma NE levels directly mirrored nerve stimulation. [417] Many important studies have correlated elevations in plasma catecholamines with acute and chronic stress and have led to the concept of stress-free anesthesia. The landmark study showing a striking relationship between mortality in CHF and plasma NE levels resulted in attempts to utilize beta-adrenergic antagonists in the treatment of ventricular dysfunction. [79] [418] [419]

The development of experimental radiotracer techniques to assess the *in vivo* kinetics of catecholamines has provided additional information that is of clinical importance, particularly in relation to regional kinetics. For example, studies relying only on arterial and venous catecholamines suggested that the hepatomesenteric bed contributed significantly to the total body clearance of catecholamines but only minimally (<8%) to the spillover. However, more recent studies of regional NE kinetics demonstrate that the gut release of NE (
25% of the total body) is largely obscured by efficient extraction (>80%) in the liver. Similarly, selective elevations in NE release from the heart, which may be associated with ischemia, the early onset of CHF, and tachyarrhythmias may not be apparent in measuring arterial or venous levels. [420] The observations involving regional spillover have led to the realization that although stress may activate a generalized sympathetic response, there may be different patterns contingent on the stimulus. Thus, it is possible that the lack of association of plasma NE levels in the presence of clinically significant sympathetic activation may be a function of the measurement technique or the particular stressor. Although there are increasing data that many anesthetic techniques, including inhalational, opiate, and regional, can attenuate the stress response, the question whether this represents a benefit or liability in patient care remains a matter of controversy. [421] [422] Until recently, there were few data to suggest that the attenuation of the stress response altered outcome, with the exception of prolonged postoperative epidural anesthesia or special surgical situations. However, results of several studies in infants and adults undergoing heart surgery suggest that the use of high-dose opiates or other strategies to diminish perioperative stress may improve outcome. [423] [424] [425] [426] Since the last edition of this book, several studies have reported that the ability of neur-axial analgesia to attenuate the sustained increase in perioperative catecholamines usually associated with general anesthesia leads to decreased ischemic and thrombotic complications. [427] [428] [429] [430]

It is our belief that, given the effects of age, posture, and hydration, small changes in plasma catecholamines levels correlate poorly with hemodynamic changes and merit cautious interpretation, whereas significant increases (>1,000 pg) in levels are good markers of sympathetic nervous system activation.

Clinical Syndromes

Diabetes Mellitus

Diabetes mellitus is the most common cause of autonomic neuropathy. Early small-fiber damage is revealed by loss or impairment of vagally controlled normal heart rate variability, decreased peripheral sympathetic tone with subsequent increase in blood flow, and diminished sweating. The diabetic neuropathic foot demonstrates early loss of pain and temperature sense before loss of touch or vibration. With sympathetic denervation, sympathetic nerves normally found supplying small arterioles are either entirely absent or are abnormally distant from their effector sites. The neuropathic foot may show increased blood flow with arteriovenous shunting, whereas peripheral arteries are dilated and stiff; despite the total increase in flow, capillaries may be "missed," with distal ischemia the result. The arterial walls may be stiff from calcification in the media; interestingly, calcification has been reported after surgical sympathectomy.

Mechanisms maintaining normal standing blood pressure are altered, and normal precapillary vasoconstriction in the foot on standing may be diminished. When healthy people stand, roughly 700 mL of the blood volume may pool in the legs and splanchnic circulation, with an associated 20 percent decrease in cardiac output. In healthy individuals, baroreceptors in the carotid sinus and aortic arch detect the decrease and mediate sympathetic impulses to the heart and blood vessels. The sympathetic denervation associated with diabetes may cause loss of the normal compensatory vasoconstriction in the peripheral and gut tissues, and this may be potentiated also by a failure of appropriate acceleration of heart rate and reduced cardiac output. Diabetic patients with orthostatic hypotension usually have lower NE levels.

Most clinicians recognize that diabetic patients with autonomic neuropathy may be at additional risk in general anesthesia. The increased cardiovascular casualty is shown in a number of case reports and at least one prospective study. [431] Gastroparesis is most probably due to vagal degeneration and is of clinical relevance, because awake or rapidsequence intubation may be required.

Autonomic Changes with Aging

Although numerous studies have examined the effects of maturation and aging on vascular reactivity, the human paradigm is one of exaggerated changes in blood pressure. [432] Aging is associated with alterations in vascular reactivity manifest clinically as exaggerated changes in blood pressure, namely, hypertension and orthostatic hypotension. Orthostatic hypotension is quite common (
20%) in the elderly

and may result largely from diminished baroreceptor responsiveness. Heart rate response to changes in blood pressure, Valsalva maneuver, and the respiratory cycle are blunted with aging. [433] [434] [435] [436] [437]

Resting and exercise-induced NE levels increase with age in healthy subjects (by 13% per decade), [438] in part owing to decreased clearance. [438] [439] Previously a matter of controversy, it now appears that besides the well-documented reduction in vagal function associated with aging, [440] [441] the primary autonomic defect in aging is an impairment in NE reuptake, perhaps as a function of decreased nerve density. Although there is no apparent age-dependent decrement in nerve firing rates from sympathetic efferents in skeletal muscle, [442] kinetic studies reveal selective and dramatic increases in cardiac NE spillover attributable to decreased reuptake in elderly patients subjected to mental stress or exercise. [416] The augmented synaptic concentration of NE in the setting of age-related reduction in vagal function can precipitate clinical complications (arrhythmogenesis and sudden cardiac death) in patients with cardiac disease. However, end-organ responsiveness is blunted by compensatory downregulation of the beta $_1$ -adrenoreceptors (decreased receptor density and affinity) and uncoupling of beta $_2$ -adrenoreceptors (via decreased G_s activity). [443] [444] [445] Despite increased cardiac spillover cardiac oxygen consumption was not altered. [446]

Attenuation of presynaptic alpha$_2$ -adrenoreceptor-mediated inhibition of neuronal NE release [447] [448] [449] also accounts for increased NE levels observed with age. Reduced postsynaptic alpha$_2$ -adrenoreceptor activity decreases contractile responses and further attenuates vasoconstrictor tone. In a seemingly vicious cycle, the increase in circulating NE levels are associated with downregulation of platelet alpha $_2$ -adrenoreceptor density and responsiveness. [450] The loss of adrenergic control via the reduction of alpha$_2$ - and beta-receptor-mediated responses with age causes a loss in the efficacy of the sympathetic system to control cardiovascular responsiveness with advancing age, implying a relationship with or an explanation of the increased incidence of cardiovascular disorders, such as CHF, in the elderly.

Autonomic Changes in Spinal Cord Transection

The most drastic of all alterations in the ANS an anesthesiologist may encounter is complete spinal cord transection. Spinal cord transection not only may affect motor and sensory function, but also may exhibit profound alterations and autonomic activity that can alter anesthetic care. As is obvious from the anatomy of the sympathetic and parasympathetic outflow, spinal cord injuries or transection can cause varying degrees of autonomic dysfunction, depending on the site, extent, and timing of the lesion.

In patients with cervical spinal cord transection, both sympathetic and parasympathetic outflows are detached from central control mechanisms. Thus, in addition to expected motor and sensory changes, there are profound abnormalities altering the cardiovascular, thermoregulatory, gastrointestinal, and urinary systems. The autonomic consequences of transection are not always apparent because the distal portion of the spinal cord may retain some function, resulting in unanticipated autonomic abnormalities.

There are fundamental differences between the acute and chronic effects of spinal cord transection. Initially, a transient state of decreased excitability occurs. This phenomenon, known as "spinal shock," usually occurs immediately after the lesion and may last from days to weeks. In these patients, the periphery is generally atonic, and the peripheral blood vessels are largely dilated. Investigators have suggested that methylprednisolone may be of some use in treating this phase of spinal shock. [451] In patients with high thoracic lesions who have sustained recent injury, the basal supine blood pressure is usually low and is accompanied by plasma catecholamine levels that are approximately 35 percent of normal. [452] Patients with recent low spinal injuries may exhibit compensatory tachycardia from intact parts of the ANS.

In contrast, patients with high spinal lesions may fail to respond to hypovolemia with an increased heart rate and may actually exhibit bradycardia. The only intact efferent component of baroreflex pathways in quadriplegic patients is the vagus. Bradycardia occurs not only with changes in position, but also with Valsalva maneuvers or increased intrathoracic pressure. [453]

One aspect of care that is frequently overlooked is the effect of tracheal suctioning on patients with high spinal transection. Given that many of these patients are dependent on artificial respiration because of their respiratory muscle paralysis, there may be unopposed vagal stimuli contributing to profound bradycardia in these patients. This vagal response is particularly accentuated during hypoxemia.

Because the sympathetic nervous system may be dysfunctional in these patients, there is a compensatory enhancement of the renin-angiotensin-aldosterone system for the maintenance of blood pressure. Therefore, patients who have spinal cord transection may be exquisitely sensitive to ACEI, even with modest changes in intravascular volume or posture. It should be emphasized that the release of renin may be independent of sympathetic stimulation and may be due to renal baroreceptor stimulation that accompanies the fall in renal perfusion pressure.

Although pressure stimuli above the lesion do not usually cause a change in blood pressure, the phenomenon of *autonomic dysreflexia* can occur when stimulation occurs below the lesion. Thus, bladder or bowel distention can elicit the so-called "mass reflex." This autonomic reflex includes a dramatic rise in blood pressure, a marked reduction in flow to the periphery, and flushing and sweating in areas above the lesion. The patient's heart rate may fall as a reflex. Surprisingly, evidence from microneurography studies indicates that there is only a modest rise in sympathetic nerve activity during activation of the mass reflex, [454] and plasma levels increase only modestly. Thus, speculation has arisen that the exaggerated blood pressure response may be due to supersensitivity of adrenoreceptors. As would be anticipated, there is an increase in sensitivity to exogenously administered pressors in quadriplegic patients. [452] It is interesting to note, however, that quadriplegic patients may exhibit a 5- to 10-fold increase in blood pressure in response to the exogenous administration of angiotensin as well as to catecholamines. It is thus possible that impairment of descending inhibitory reflex pathways that are activated during hypertension may contribute to the supersensitivity. This hypothesis is supported by the finding that lesions below T5 only infrequently exhibit the increased sensitivity. Further,

there is apparently a normal level of adrenoreceptors even in patients with chronic quadriplegia.

The management of autonomic dysreflexia is of clinical importance. Although the anesthesiologist may be tempted to utilize minimal anesthesia in a patient without sensory or motor function, significant visceral reflexes can be evoked. For these reasons, one may utilize spinal anesthesia, general anesthesia, or a vasodilator such as nitroprusside or nitroglycerin to attenuate this reflex even if pain is not appreciated. There has been some enthusiasm for using clonidine prophylactically to diminish this response.

An additional problem arising from the autonomic denervation occurring with spinal cord transection involves thermogenesis. Hypothermia may occur readily in such patients resulting from cutaneous vasodilatation and the inability to shiver. Similarly, hyperthermia can occur because the normal sweating mechanism can be impaired. It is therefore important to monitor temperature assiduously in these patients during the course of anesthesia.

References

1. Burnstock G: The first von Euler lecture in physiology: The changing face of autonomic neurotransmission. Acta Physiol Scand 126:67, 1986.

2. Burnstock G: Autonomic neuromuscular junctions: Current developments and future directions. J Anat 146:1, 1986.

3. Burnstock G: Sympathetic purinergic transmission in small blood vessels. Trends Pharmacol Sci 9:116, 1988.

4. Burnstock G: Do some nerve cells release more than one transmitter? Neuroscience 1:239, 1976.

5. Bartfai T, Iverfeldt K, Fisone G: Regulation of the release of coexisting neurotransmitters. Annu Rev Pharmacol Toxicol 28:285, 1988.

6. Von Kugelgen I, Starke K: Noradrenaline-ATP co-transmission in the sympathetic nervous system. Trends Pharmacol Sci 12:319, 1991.

7. Burnstock G: Local mechanisms of blood flow control by perivascular nerves and endothelium. J Hypertens Suppl 8:95, 1990.

8. Jacobson KA, Trivedi BK, Churchill PC et al: Novel therapeutics acting via purine receptors. Biochem Pharmacol 41:1399, 1991.

9. Burnstock G: Overview: Purinergic mechanisms. Ann N Y Acad Sci 603:1, 1990.

10. Goncalves J, Guimaraes S: Influence of neuronal uptake on pre- and postjunctional effects of alpha-adrenoceptor agonists in tissues with noradrenaline: ATP cotransmission. Arch Pharmacol 344:532, 1991.

11. Hirst G, Bramich N, Edwards F et al: Transmission at autonomic neuroeffector junctions. Trends Neurosci 15:40, 1992.

12. Walker P, Grouzmann E, Burnie M et al: The role of neuropeptide Y in cardiovascular regulation. Trends Pharmacol Sci 12:111, 1991.

13. Lincoln J, Burnstock G: Neural-endothelial interactions in control of local blood flow. In Warren J (ed): The Endothelium: An Introduction to Current Research. New York, Wiley-Liss, 1990, p 21.

14. Lundberg JM, Rudehill A, Sollevi A et al: Frequency- and reserpine-dependent chemical coding of sympathetic transmission: Differential release of noradrenaline and neuropeptide Y from pig spleen. Neurosci Lett 63:96, 1986.

15. Bloom S, Edwards A: Vasoactive intestinal polypeptide in relation to atropine resistant vasodilatation in the submaxillary gland of the cat. J Physiol 300:41, 1980.

16. Lundberg JM: Evidence for coexistence of vasoactive intestinal polypeptide (VIP) and acetylcholine in neurons of cat exocrine glands: Morphological, biochemical and functional studies. Acta Physiol Scand Suppl 112:1, 1981.

17. Mione M, Cavanagh J, Lincoln J et al: Pregnancy reduces noradrenaline but not neuropeptide levels in the uterine artery of the guinea-pig. Cell Tissue Res 259:503, 1990.

18. Furness JB, Costa M: The Enteric Nervous System. New York, Churchill Livingstone, 1987.

19. Bridenbaugh PO, Greene NM: Spinal (subarachnoid) neural blockade. In Cousins M, Bridenbaugh P (eds): Neural Blockade in Clinical Anesthesia and Pain Management. 2nd ed. Philadelphia, JB Lippincott, 1988, p 213.

20. Rajfer J, Aronson WJ, Bush PA et al: Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. N Engl J Med 326:90, 1992.

21. Ruffolo R: Physiology and biochemistry of the peripheral autonomic nervous system. In Wingard L, Brody T, Larner J et al (eds): Human Pharmacology: Molecular-to-Clinical. St. Louis, Mosby-Year Book, 1991, p 77.

22. Fleisher LA, Frank SM, Shir Y et al: Cardiac sympathovagal balance and peripheral sympathetic vasoconstriction: Epidural versus general anesthesia. Anesth Analg 79:165, 1994.

23. Lefkowitz R, Hoffman B, Taylor P: Drugs acting at synaptic and neuroeffector junctional sites. In Gilman A, Rall T, Nies A et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990, p 84.

24. Hoffman B, Lefkowitz R: Adrenergic receptors in the heart. Annu Rev Physiol 44:475, 1982.

25. Goldstein DS, Ziegler MG, Lake CR: Plasma norepinephrine in essential hypertension. In Ziegler M, Lake C (eds): Frontiers of Clinical Neuroscience, vol. 2. Baltimore, Williams & Wilkins, 1984, p 389.

26. Ottolenghi D: Su i nervi del midollo delle ossa. Atti R Accad Sci Torino 36:939, 1903.

27. Radu A, Dahl G, Loewenstein WR: Hormonal regulation of cell junction permeability: Upregulation by catecholamine and prostaglandin E_1. J Membr Biol 70:239, 1982.

28. Dimsdale J, Moss J: Plasma catecholamines in stress and exercise. JAMA 243:340, 1980.

29. Kharasch ED, Bowdle T: Hypokalemia before induction of anesthesia and prevention by beta $_2$ adrenoceptor antagonism. Anesth Analg 72:216, 1991.

30. Williams ME, Gervino EV, Rosa RM et al: Catecholamine modulation of rapid potassium shifts during exercise. N Engl J Med 312:823, 1985.

31. Struthers AD, Reid JL: The role of adrenal medullary catecholamines in potassium homoeostasis. Clin Sci 66:377, 1984.

32. Brown M: Hypokalemia from beta $_2$ -receptor stimulation by circulating epinephrine. Am J Cardiol 56:3D, 1985.

33. Vincent HH, ManIn't Veld AJ, Boomsma F et al: Prevention of epinephrine-induced hypokalemia by nonselective beta blockers. Am J Cardiol 56:10D, 1985.

34. Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288:373, 1980.

35. Johns RA: EDRF/nitric oxide: The endogenous nitrovasodilator and a new cellular messenger. Anesthesiology 75:927, 1991.

36. Snyder SH, Bredt DS: Biological roles of nitric oxide. Sci Am 266:68, 1992

37. Bredt DS, Hwang PM, Snyder SH: Localization of nitric oxide synthase indicating a neural role for nitric oxide. Nature 347:768, 1990.

38. Bredt DS, Snyder S: Nitric oxide, a novel neuronal messenger. Neuron 8:3, 1992.

39. Forstermann U, Schmidt H, Pollock J et al: Isoforms of nitric oxide synthase: Characterization and purification from different cell types. Biochem Pharmacol 42:1849, 1991.

40. Petros A, Bennett D, Vallance P: Effect of nitric oxide synthase inhibitors on hypotension in patients with septic shock. Lancet 338:1557, 1991.

41. Bredt DS, Hwang PM, Glatt CE et al: Cloned and expressed nitric oxide synthase structurally resembles cytochrome P-450 reductase. Nature 351:714, 1991.

42. Rees DD, Palmer R, Moncada S: Role of endothelium-derived nitric oxide in the regulation of blood pressure. Proc Natl Acad Sci U S A 86:3375, 1989.

43. Koesling D, Bohme D, Schultz G: Guanylyl cyclases, a growing family of signal-transducing enzymes. FASEB J 5:2785, 1991.

44. Sakurai T, Yanagisawa M, Masaki T: Molecular characterization of endothelin receptors. Trends Pharmacol Sci 13:103, 1992.

45. Nava E, Palmer R, Moncada S: Inhibition of nitric oxide synthesis in septic shock: How much is beneficial? Lancet 338:1555, 1991.

46. Moore K, Wendon J, Frazer M et al: Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. N Engl J Med 327:1774, 1992.

47. Shepherd J, Vanhoutte P: Neurohumoral regulation. In Shepherd S, Vanhoutte P (eds): The Human Cardiovascular System: Facts and Concepts. New York, Raven Press, 1979, p 107.

48. Conlay L, Maher TJ, Wurtman RJ: Tyrosine increases blood pressure in hypotensive rats. Science 212:559, 1981.

49. Nussdorfer GG: Pancrine control of adrenal cortical function by medullary chromaffin cells. Pharmacol Rev 48:495, 1996.

50. Eisenhofer G: In vivo kinetics of catecholamines. J Auton Pharmacol 14:7, 1994

51. Kamiya H, Zucker RS: Residual Ca^{2+} and short-term synaptic plasticity. Nature 371:603, 1994.

52. Zucker RS: Exocytosis: A molecular and physiological perspective. Neuron 17:1049, 1996.

53. Katz B: Nerve, Muscle, and Synapse. New York, McGraw-Hill, 1966.

54. Sudhof TC, Jahn R: Proteins of synaptic vesicles involved in exocytosis and membrane recycling. Neuron 6:665, 1991.

55. DeBello WM, O'Connor V, Dresbach T et al: SNAP-mediated protein-protein interactions essential for neurotransmitter release. Nature 373:626, 1995.

56. Bommert K, Charlton MP, DeBello WM et al: Inhibition of neurotransmitter release by C2-domain peptides implicates synaptotagmin in exocytosis. Nature 363:163, 1993.

57. Geppert M, Goda Y, Hammer RE et al: Synaptotagmin I: A major Ca^{2+} sensor for transmitter release at a central synapse. Cell 79:717, 1994.

58. Bennett MK, Scheller RH: A molecular description of synaptic vesicle membrane trafficking. Annu Rev Biochem 63:63, 1994.

59. Rothman JE: Mechanisms of intracellular protein transport. Nature 372:55, 1994.

60. Katz B, Miledi R: The effect of temperature on the synaptic delay at the neuromuscular junction. J Physiol 181:656, 1965.

61. Yoshida A, Oho C, Omori A et al: HPC-1 is associated with synaptotagmin and omega-conotoxin receptor. J Biol Chem 267:24925, 1992.

62. O'Connor V, Augustine GJ, Betz H: Synaptic vesicle exocytosis: Molecules and models. Cell 76:785, 1994.

63. Schiavo G, Rossetto O, Montecucco C: Clostridial neurotoxins as tools to investigate the molecular events of neurotransmitter release. Semin Cell Biol 5:221, 1994.

64. Morgan A, Burgoyne RD: A role for soluble NSF attachment proteins (SNAPs) in regulated exocytosis in adrenal chromaffin cells. EMBO J 14:232, 1995.

65. Novick P, Brennwald P: Friends and family: The role of the Rab GTP-ases in vesicular traffic. Cell 76:597, 1993.

66. Betz WJ, Bewick GS: Optical monitoring of transmitter release and synaptic vesicle recycling at the frog neuromuscular junction. J Physiol 460:287, 1993.

67. Ryan TA, Smith SJ: Vesicle pool mobilization during action potential firing at hippocampal synapses. Neuron 14:983, 1995.

68. Ryan TA, Reuter H, Wendland B et al: The kinetics of synaptic vesicle recycling measured at single presynaptic boutons. Neuron 11:713, 1993.

69. Von Gersdorff H, Matthews G: Dynamics of synaptic vesicle fusion and membrane retrieval in synaptic terminals. Nature 367:735, 1994.

70. Moro MA, Lopez MG, Gandia L et al: Separation and culture of living adrenaline and noradrenaline-containing cells from bovine adrenal medulla. Anal Biochem 185:243, 1990.

71. Livett BG, Marley PD: Effects of opioid peptides and morphine on histamine-induced catecholamine secretion from cultured, bovine adrenal chromaffin cells. Br J Pharmacol 89:327, 1986.

72. Marley PD, Livett BG: Differences between the mechanism of adrenaline and noradrenaline secretion from isolated, bovine, adrenal chromaffin cells. Neurosci Lett 77:81, 1987.

73. Owen PJ, Plevin R, Boarder MR: Characterization of bradykinin-stimulated release of noradrenaline from cultured bovine adrenal chromaffin cells. J Pharmacol Exp Ther 248:1231, 1989.

74. Cahill A, Perlman RL: Phorbol esters cause preferential secretion of norepinephrine from bovine chromaffin cells. J Neurochem 58:768, 1992.

75. Pacholczyk T, Blakely RD, Amara SG: Expression cloning of a cocaine and antidepressant sensitive human noradrenaline transporter. Nature 350:350, 1991.

76. Sole MJ, Drobac M, Schwartz L et al: The extraction of circulating catecholamines by the lungs in normal man and in patients with pulmonary hypertension. Circulation 60:160, 1979.

77. Kaye DM, Lambert GW, Lefkovits J et al: Neurochemical evidence of cardiac sympathetic activation and increased central nervous system norepinephrine turnover in severe congestive heart failure. J Am Coll Cardiol 23:570, 1994.

78. Moss J, Lappas D, Slater E: Role of the renin catecholamine system in hemodynamic performance in man. In Usdin E, Kvetnansky R, Kopin IJ (eds): Catecholamines and Stress: Recent Advances in Neurosciences. New York, Elsevier, 1980, p 513.

79. Cohn J, Levine T, Olivari M et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 311:819, 1984.

80. Bristow M: The adrenergic nervous system in heart failure (editorial). N Engl J Med 311:850, 1984.

81. Eisenhofer G, Friberg P, Rundqvist B et al: Cardiac sympathetic nerve function in congestive heart failure. Circulation 93:1667, 1996.

82. Port JD, Gilbert EM, Larrabee P et al: Neurotransmitter depletion compromises the ability of indirect-acting amines to provide inotropic support in the failing human heart. Circulation 81:929, 1990.

83. Lake CR, Chernow B, Feuerstein G et al: The sympathetic nervous system in man, its evaluation and the measurement of plasma norepinephrine. In Ziegler M, Lake C (eds): Frontiers of Clinical Neuroscience, vol. 2. Baltimore, Williams & Wilkins, 1984, p 1.

84. Kopin IJ: False neurochemical transmitters and the mechanism of sympathetic blockade by monoamine oxidase inhibitors. J Pharmacol Exp Ther 147:186, 1965.

85. Trendelenburg U: Functional aspects of the neuronal uptake of noradrenaline. Trends Pharmacol Sci 12:334, 1991.

86. Lawhead R, Blaxall H, Bylund D: $alpha_{2A}$ Is the predominant $alpha_2$ -adrenergic receptor subtype in human spinal cord. Anesthesiology 77:983, 1992.

87. Bylund DB: Subtypes of $alpha_1$ and $alpha_2$ adrenergic receptors. FASEB J 832, 1992.

88. Szabo B, Hedler L, Starke K: Peripheral presynaptic and central effects of clonidine, yohimbine and rauwolscine on the sympathetic nervous system in rabbits. Naunyn Schmiedebergs Arch Pharmacol 340:648, 1989.

89. Walston J, Silver K, Bogardus C: Time of onset of non-insulin dependent diabetes mellitus and genetic variation in the beta-adrenergic-receptor gene. N Engl J Med 333:343, 1995.

90. Widen E, Lehto M, Kanninen T et al: Association of a polymorphism in the beta-adrenergic receptor gene with features of the insulin resistance syndrome in Finns. N Engl J Med 333:348, 1995.

91. Clement K, Vaisse C, Manning BSF: Genetic variation in the beta-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity. N Engl J Med 333:352, 1995.

92. Halt IP, Wheatley A, Widling P et al: Association of Glu27 beta-adrenoceptor polymorphism with lower airway reactivity in asthmatic subjects. Lancet 345:1213, 1995.

93. Turki J, Pak J, Martin RJ et al: Genetic polymorphism of the beta-adrenergic receptor in nocturnal and non-nocturnal asthma: Evidence that Gly 16 correlates with the nocturnal phenotype. J Clin Invest 95:1635, 1995.

94. Hausdorf WP, Caron MG, Lefkowitz RJ: Turning off the signal desensitization of beta-adrenergic receptor function. FASEB J 4:2881, 1990.

95. Michel MC, Kenny B, Schwinn DA: Classification of $alpha_1$ -adrenoceptor subtypes. Arch Pharmacol 352:1, 1995.

96. Szabo B, Schramm A, Starke K: Effect of yohimbine on renal sympathetic nerve activity and renal norepinephrine spillover in anesthetized rabbits. J Pharmacol Exp Ther 260:780, 1992.

97. Limberger N, Singer EA, Starke K: Only activated but not non-activated presynaptic $alpha_2$ -autoreceptors interfere with neighbouring presynaptic receptor mechanisms. Naunyn Schmiedebergs Arch Pharmacol 338:62, 1988.

98. Opie L: Receptors and signal transduction. In Opie LH (ed): The Heart: Physiology and Metabolism. New York, Raven Press, 1991.

99. Raymond J, Hratowich M, Lefkowitz R et al: Adrenergic receptors: Models for regulation of signal transduction processes. Hypertension 15:119, 1990.

100. Vanhees L, Auleert A, Iagard R et al: Influence of $beta_2$ -adrenoceptor blockade on left ventricular function in humans. J Cardiovasc Pharmacol 8:1086, 1986.

101. Opie L: Ventricular overload and heart failure. In Opie LH (ed): The Heart: Physiology and Metabolism. 2nd ed. New York, Raven Press, 1991, p 386.

102. Brodde O: The functional importance of $beta_1$ and $beta_2$ adrenoceptors in the human heart. Am J Cardiol 62:24C, 1988.

103. Goldberg LI, Rajfer SI: Dopamine receptors: Applications in clinical cardiology. Circulation 72:245, 1985.

104. Bertorello A, Aperia A: Both DA_1 and DA_2 receptor agonists are necessary to inhibit Na^+ /K^+ ATPase activity in proximal tubules from the rat kidney. Acta Physiol Scand 132:441, 1988.

105. Bertorello A, Aperia A: Regulation of Na^+ /K^+ ATPase activity in kidney tubules: Involvement of GTP binding proteins. Am J Physiol 256:F57, 1989.

106. Gesek FA, Schoolwerth AC: Hormonal interactions with the Na^+ /K^+ exchanger. Am J Physiol 258:F514, 1990.

107. Linder ME, Gilman AG: G Proteins. Sci Am 56, 1992.

108. Pang I-H, Sterweis PC: Purification of unique alpha subunits of GTP-binding regulatory proteins (G proteins) by affinity chromatography with immobilized betagamma subunits. J Biol Chem 265:18707, 1990.

109. Blank JL, Ross AH, Exton JH: Purification and characterization of two G-proteins that activate the $beta_1$ isozyme of phosphoinositide-specific phospholipase C. J Biol Chem 266:18206, 1991.

110. Gutowski S, Smrcka A, Nowak L et al: Antibodies to the alphaq subfamily of guanine nucleotide-binding regulatory protein alpha subunits attenuate activation of phosphatidylinositol 4,5-bisphosphate hydrolysis by hormones. J Biol Chem 266:20519, 1991.

111. Alousi AA, Jasper JR, Insel PA et al: Stoichiometry of receptor G_s -adenylate cyclase interactions. FASEB J 5:2300, 1991.

112. Post SR, Hilal-Dandan R, Urasawa K et al: Quantification of signaling components and amplification in the beta-adrenergic receptor-adenylyl cyclase pathway in isolated adult rat ventricular myocytes. Biochem J 311:75, 1995.

113. Yatani A, Okabe K, Codina J et al: Heart rate regulation by G proteins acting on the cardiac pacemaker channel. Science 249:1163, 1990.

114. Roizen M, Horrigan R, Frazier B: Anesthetic doses blocking adrenergic stress and cardiovascular responses to incision: MAC BAR. Anesthesiology 54:390, 1981.

115. Roizen MF, Thoa NB, Moss J et al: Inhibition by halothane of release of norepinephrine, but not of dopamine-beta-hydroxylase, from guinea pig vas deferens. Eur J Pharmacol 31:313, 1975.

116. Rorie DK, Tyce GM, Mackenzie RA: Evidence that halothane inhibits norepinephrine release from sympathetic nerve endings in dog saphenous vein by stimulation of presynaptic inhibitory muscarinic receptors. Anesth Analg 63:1059, 1984.

117. Lunn JJ, Rorie DK: Halothane-induced changes in the release and disposition of norepinephrine at adrenergic nerve endings in dog saphenous vein. Anesthesiology 61:377, 1984.

118. Bernstein KJ, Gangat Y, Verosky M et al: Halothane effect on beta-adrenergic receptors in canine myocardium. Anesth Analg 60:401, 1981.

119. Bernstein K, Verosky M, Triner L: Halothane inhibition of canine myocardial adenylate cyclase: Modulation by endogenous factors. Anesth Analg 63:285, 1984.

120. Gangat Y, Vulliemoz Y, Verosky M et al: Action of halothane on myocardial adenylate cyclase of rat and cat. Proc Soc Exp Biol Med 60:154, 1979.

121. Narayanan TK, Confer RA, Dennison RL et al: Halothane attenuation of muscarinic inhibition of adenylate cyclase in rat heart. Biochem Pharmacol 37:1219, 1988.

122. Vulliemoz V, Verosky M, Triner L: Effect of halothane on myocardial cyclic AMP and cyclic GMP content of mice. J Pharmacol Exp Ther 236:181, 1986.

123. Thurston T, Glusman S: Halothane myocardial depression: Interactions with the adenylate cyclase system. Anesth Analg 75:63, 1993.

124. Terrar DA, Victory JG: Effects of halothane on membrane currents associated with contraction in single myocytes from guinea-pig ventricle. Br J Pharmacol 94:500, 1988.

125. Lynch C, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. Anesthesiology 55:360, 1988.

126. Komai H, Rusy BF: Direct effect of halothane and isoflurane on the function of the sarcoplasmic reticulum in intact rabbit atria. Anesthesiology 72:694, 1990.

127. Su JY, Kerrick GL: Effects of halothane on caffeine-induced tension transients in functionally skinned myocardial fibers. Pflugers Arch 380:29, 1979.

128. Blochl-Daum B, Schuller-Petrovic S, Wolzt M et al: Primary defect in alpha-adrenergic responsiveness in patients with varicose veins. Clin Pharmacol Ther 49:49, 1991.

129. Insel PA: Adrenergic receptors: Evolving concepts and clinical implications. N Engl J Med 334:580, 1996.

130. Bristow MR, Ginsburg R, Minobe W et al: Decreased catecholamine sensitivity and beta-adrenergic receptor density in failing human hearts. N Engl J Med 307:205, 1982.

131. Menard L, Ferguson SS, Zhang J et al: Synergistic regulation of $beta_2$ -adrenergic receptor sequestration: Intracellular complement of beta-adrenergic receptor kinase and beta-arrestin determine kinetics of internalization. Mol Pharmacol 51:800, 1997.

132. Ferguson SS, Barak LS, Zhang J et al: G-protein-coupled receptor regulation: Role of G-protein-coupled receptor kinases and arrestins. Can J Physiol Pharmacol 74:1095, 1996.

133. Hedberg A, Kemp FF, Josephson ME et al: Co-existence of $beta_1$ and $beta_2$ -adrenergic receptors in the human heart: Effects of treatment with receptor antagonists or calcium entry blockers. J Pharmacol Exp Ther 234:561, 1985.

134. Bristow M, Ginsburg R, Umans V et al: beta and $beta_2$ -adrenergic receptor subpopulations in non-failing and failing human ventricular myo-cardium: Coupling of both receptor subtypes to muscle contraction and selective beta receptor downregulation in heart failure. Circ Res 59:297, 1986.

135. Hedberg A: Adrenergic receptors: Methods of determination and mechanisms of regulation. Acta Med Scand Suppl 672:7, 1983.

136. Dratman M, Crutchfield F, Axelrod J et al: Triiodothyronine in nerve ending fractions in rat brain. Proc Natl Acad Sci U S A 73:940, 1976.

137. Doukas PH: Drugs affecting the parasympathetic nervous system. In Wingard L, Brody T, Larner J et al (eds): Human Pharmacology: Molecular to Clinical. St. Louis, Mosby-Year Book, 1991.

138. Conlay L, Wurtman RJ, Blusztaj K et al: Decreased plasma choline concentrations in marathon runners. N Engl J Med 86:892, 1986.

139. Stiller R: Neuromuscular blocking agents. In Wingard L, Brody T, Larner J et al (eds): Human Pharmacology: Molecular to Clinical. St. Louis, Mosby-Year Book, 1991.

140. Soreq H, Zakut H: Amplification of butyrylcholinesterase and acetylcholinesterase genes in normal and tumor tissues: Putative relationship to organophosphorous poisoning. Pharm Res 7:1, 1990.

141. Prody CA, Dreyfus P, Zamir R et al: De novo amplification within a "silent" human cholinesterase gene in a family subjected to prolonged exposure to organophosphorous insecticides. Proc Natl Acad Sci U S A 86:690, 1989.

142. Sussman JL, Harel M, Frolow F et al: Atomic structure of acetylcholinesterase from *Torpedo californica:* A prototypic acetylcholine-binding protein. Science 253:872, 1991.

143. Martinou J-C, Falls DL, Fischbach GD et al: Acetylcholine receptor-inducing activity stimulates expression of the epsilon-subunit gene of the muscle acetylcholine receptor. Proc Natl Acad Sci U S A 87:7669, 1991.

144. McMahan UJ, Horton SE, Werle MJ et al: Agrin isoforms and their role in synaptogenesis. Curr Opin Cell Biol 4:869, 1992.

145. Nastuk MA, Fallon JR: Agrin and the molecular choreography of synapse formation. Trends Neurosci 16:72, 1993.

146. Apel ED, Merlie JP: Assembly of the postsynaptic apparatus. Curr Opin Neurobiol 5:62, 1995.

147. Eglen RM, Hedge SS, Watson N: Muscarinic receptor subtypes and smooth muscle function. Pharmacol Rev 48:531, 1996.

148. Hosey MM: Diversity of structure, signaling and regulation within the family of muscarinic cholinergic receptors. FASEB J 12:845, 1992.

149. Ganong W: The autonomic nervous system. In Ganong W (ed): Review of Medical Physiology. 15th ed. E. Norwalk, Conn, Appleton & Lange, 1991, p 210.

150. Glusman S: Electrophysiology of ganglionic transmission in the sympathetic nervous system. Int Anesthesiol Clin 27:273, 1989.

151. Hoffman BB, Lefkowitz RJ: Catecholamines and sympathetic drugs. In Goodman A, Rall T, Nies A et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990, p 187.

152. Paradis NA, Martin GB, Rivers EP et al: Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA 263:1106, 1990.

153. Emergency Cardiac Care Committee: Guidelines for cardiopulmonary resuscitation and emergency cardiac care. III. Adult advanced cardiac life support. JAMA 268:2199, 1992.

154. Emergency Cardiac Care Committee: Guidelines for cardiopulmonary resuscitation and emergency cardiac care. VI. Pediatric advanced life support. JAMA 268:2262, 1992.

155. Goetting M, Paradis N: High-dose epinephrine improves outcome from pediatric cardiac arrest. Ann Emerg Med 20:22, 1991.

156. Aitkenhead A: Drug administration during CPR: What route? Resuscitation 22:191, 1991.

157. Berry F: Clinical pharmacology of inhalational anesthetic, muscle relaxants, vasoative agents, and narcotics, and techniques of general anesthesia. In Berry F (ed): Anesthetic Management of Difficult and Routine Pediatric Patients. 2nd ed. New York, Churchill Livingstone, 1990, p 64.

158. Ziment I: Pharmacology of sympathomimetic agents. In Ziment I (ed): Respiratory Pharmacology and Therapeutics. Philadelphia, WB Saunders, 1978.

159. Waisman Y, Klein BL, Boenning DA et al: Prospective randomized double-blind study comparing *l*-epinephrine and racemic epinephrine aerosols in the treatment of laryngotracheitis (croup). Pediatrics 89:302, 1992.

160. Nutman J, Brooks LJ, Deakins KM et al: Racemic versus *l*-epinephrine aerosol in the treatment of postextubation laryngeal edema: Results from a prospective, randomized double-blind study. Crit Care Med 22:1591, 1994.

161. Bochner BS, Lichtenstein L: Anaphylaxis. N Engl J Med 324:1785, 1991.

162. Donlon J, Moss J: Plasma catecholamine levels during local anesthesia for cataract operations. Anesthesiology 51:471, 1979.

163. Houben H, Thien T, van't Laar A: Effect of low-dose epinephrine on hemodynamics after selective and nonselective beta-blockade in hypertension. Clin Pharmacol Ther 31:685, 1982.

164. Johnston R, Eger E, Wilson C: A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man. Anesth Analg 55:709, 1976.

165. Zaritsky A, Chernow B: Catecholamines, sympathetomimetics. In Chernow B, Lake C (eds): The Pharmacologic Approach to the Critically Ill Patient. Baltimore, Williams & Wilkins, 1983, p 481.

166. O'Neil MJ, Pennock JL, Seaton JF et al: Regional endogenous catecholamine concentration in pulmonary hypertension. Surgery 84:140, 1978.

167. Benowitz N, Forsyth RP, Melman KL et al: Lidocaine disposition kinetics in monkey and man: Effects of hemorrhage and sympathomimetic drug administration. Clin Pharmacol Ther 16:19, 1974.

168. Schafer G, Fink M, Parillo J: Norepinephrine alone versus norepinephrine plus low dose dopamine: Enhanced renal blood flow with combination pressor therapy. Crit Care Med 13:492, 1985.

169. Goldberg L: Dopamine: Clinical uses of an endogenous catecholamine. N Engl J Med 291:707, 1974.

170. Goldberg LI, Hsieh Y-Y, Resnekov L: Newer catecholamines for treatment of heart failure and shock: An update on dopamine and a first look at dobutamine. Prog Cardiovasc Dis 19:327, 1977.

171. Maskin C, Ocken S, Chadwick B et al: Comparative systemic and renal effects of dopamine and angiotensin-converting enzyme inhibitor with enalapril in patients with heart failure. Circulation 72:846, 1985.

172. Richard C, Ricome J, Rimailho A et al: Combined hemodynamic effects of dopamine and dobutamine in cardiogenic shock. Circulation 67:620, 1983.

173. Brown RA, Dixon J, Farmer JB et al: Dopexamine: A novel agonist at peripheral dopamine receptors and beta $_2$ -adrenoceptors. Br J Pharmacol 85:599, 1985.

174. Foulds RA: Clinical development of dopexamine hydrochloride (Dopacard) and an overview of its hemodynamic effects. Am J Cardiol 62:41C, 1988.

175. Smith GW, O'Connor SE: An introduction to the pharmacologic properties of Dopacard (dopexamine hydrochloride). Am J Cardiol 62:9C, 1988.

176. Fitton A, Benfield P: Dopexamine hydrochloride: A review of its pharmacodynamics and pharmacokinetic properties and therapeutic potential in acute cardiac insuffiency. Drugs 39:308, 1990.

177. Foalds RA: Clinical development of dopexamine hydrochloride (Dopacard) and an overview of its hemodynamic effects. Am J Cardiol 62:41C, 1988.

178. Smith GW, Hall JC, Farmer JB et al: The cardiovascular actions of dopexamine hydrochloride, an agonist at dopamine receptors and beta $_2$ adrenoceptors in the dog. J Pharm Pharmacol 39:636, 1987.

179. Mitchell PD, Smith GW, Wells E et al: Inhibition of uptake 1 by dopexamine hydrochloride *in vitro.* Br J Pharmacol 92:265, 1987.

180. Lokhandwala MF: Renal actions of dopexamine hydrochloride. Clin Intensive Care 1:163, 1990.

181. Vyas SJ, Lokhandwala MF: Role of tubular dopamine-1 receptors in the natriuretic and diuretic response to dopexamine. Pharmacologist 31:378, 1989.

182. Bass AS: Contrasting effects of dopexamine hydrochloride on electrolyte excretion in canine kidneys. J Pharmacol Exp Ther 253:798, 1990.

183. Chintala MS, Lokhandwala MF, Jandhyala BS: Protective effects of dopexamine hydrochloride in renal failure after acute hemorrhage in anesthetized dogs. J Auton Pharmacol 10(suppl):S95, 1990.

184. Leier CV, Binkley PF, Carpenter J et al: Cardiovascular pharmacology of dopexamine in low output congestive heart failure. Am J Cardiol 62:94, 1988.

185. Baumann G, Felix SB, Filcek SAL: Usefulness of dopexamine hydrochloride versus dobutamine in chronic congestive heart failure and the effects on hemodynamics and urine output. Am J Cardiol 65:748, 1990.

186. Colardyn FC, Vandenbogaerde FE: Use of dopexamine hydrochloride in intensive care patients with low-output left ventricular heart failure. Am J Cardiol 62:68C, 1988.

187. Friedl N, Wenzel R, Matheis G et al: Haemodynamic effects of different doses of dopexamine hydrochloride in low cardiac output states following cardiac surgery. Eur Heart J 13:1271, 1992.

188. Bredle DL, Cain SM: Systemic and muscle oxygen uptake delivery after dopexamine infusion in endotoxic dogs. Crit Care Med 19:198, 1991.

189. Cain SM, Curtis SE: Systemic and regional oxygen uptake and delivery and lactate flux in endotoxic dogs infused with dopexamine. Crit Care Med 19:1552, 1991.

190. Colardyn FC, Vandenbogaerde JF, Vogelaers DP et al: Use of dopexamine hydrochloride in patients with septic shock. Crit Care Med 17:999, 1989.

191. Preiser JC, Arminstead C, Le Minh T et al: Increase in oxygen supply during experimental septic shock: The effects of dobutamine versus dopexamine. J Crit Care 4:40, 1989.

192. Webb AR, Moss RF, Tighe D et al: The effects of dobutamine, dopexamine and fluid on hepatic histological response to porcine faecal peritonitis. Int Care Med 17:487, 1991.

193. Hakim M, Foulds R, Latimer RD et al: Dopexamine hydrochloride, a beta $_2$ -adrenergic and dopaminergic agonist: Haemodynamic effects following cardiac surgery. Eur Heart J 9:853, 1988.

194. Macgregor DA, Butterworth JF IV, Zaloga GP et al: Hemodynamic and renal effects of dopexamine and dobutamine in patients with reduced cardiac output following coronary artery bypass grafting. Chest 106:835, 1994.

195. Smithies M, Yee TH, Jackson L et al: Protecting the gut and the liver in the critically ill: Effects of dopexamine. Crit Care Med 22:789, 1994.

196. Lund N, Asia RJ, Papadakos PJ et al: Dopexamine hydrochloride in septicemia: Effects on gut, liver and muscle oxygenation. Crit Care Med 20(suppl 4):46, 1992.

197. Trinder TJ, Lavery GG, Fee JPH et al: Correction of splanchnic oxygen deficit in the intensive care unit: Dopexamine and colloid versus placebo. Anaesth Intensive Care 23:178, 1995.

198. Kuhly P, Oschmann G, Specht M et al: Dopexamine hydrochloride does not improve gastric and sigmoid mucosal acidosis. Br J Anesth 74(suppl 1):121, 1995.

199. Schmidt H, Secchi A, Wellmann R et al: Dopexamine maintains intestinal villus blood flow during endotoxemia in rats. Crit Care Med 24:1233, 1996.

200. Maynard N, Bihari D, Dalton RN et al: Increasing splanchnic blood flow in the critically ill. Chest 108:1648, 1995.

201. Jackson NC, Taylor SH, Frais MA: Hemodynamic comparison of dopexamine hydrochloride and dopamine in ischemic left ventricular dysfunction. Am J Cardiol 62:73, 1988.

202. Tan LB, Littler WA, Murray RG: Comparison of the haemodynamic effects of dopexamine and dobutamine in patients with severe congestive heart failure. Int J Cardiol 30:203, 1991.

203. Young JB, Leon CA: Fenoldopam. In Messerli FH (ed): Cardiovascular Drug Therapy. Philadelphia, WB Saunders, 1990.

204. Lokhandwala MF: Pre-clinical and clinical studies on the cardiovascular and renal effects of fenoldopam: A DA-1 receptor agonist. Drug Devel Res 10:123, 1987.

205. Goldberg LI: Dopamine and new dopamine analogs: Receptors and clinical applications. J Clin Anesth 1:66, 1988.

206. Aronson S, Goldberg L, Roth S et al: Preservation of renal blood flow during hypotension induced with fenoldopam in dogs. Can J Anaesth 37:380, 1990.

207. Aronson S, Goldberg LI, Roth S et al: Effects of fenoldopam on renal blood flow and systemic hemodynamics during isoflurane anesthesia in dogs. J Cardiothorac Vasc Anesth 5:29, 1991.

208. Shusterman NH, Elliott WJ, White WB: Fenoldopam, but not nitroprusside, improves renal function in severely hypertensive patients with impaired renal function. Am J Med 95:161, 1993.

209. Pilmer BL, Green JA, Panacek EA et al: Fenoldopam mesylate versus sodium nitroprusside in the acute management of severe systemic hypertension. J Clin Pharmacol 33:549, 1993.

210. Schnider S, Levinson G, Cosmi E: Obstetric anesthesia and uterine blood flow. In Schnider S, Levinson G (eds): Anesthesia for Obstetrics. 3rd ed. Baltimore, Williams & Wilkins, 1993, p 29.

211. Caplan R, Ward R, Posner K et al: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

212. Shibata S, Seriguchi DG, Iwadare S et al: The regional and species differences on the activation of myocardial alpha-adrenoreceptors by phenylephrine and methoxamine. Gen Pharmacol 11:173, 1980.

213. Flacke J, Bloor BC, Flacke WE et al: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 67:11, 1987.

214. Ghignone M, Quintin L, Duke P et al: Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 64:36, 1986.

215. Ghignone M, Calvillo O, Quintin L: Anesthesia and hypertension: The effect of clonidine on perioperative hemodynamics and isoflurane requirements. Anesthesiology 67:3, 1987.

216. Bailey PL, Sperry RJ, Johnson GK et al: Respiratory effects of clonidine alone and combined with morphine in humans. Anesthesiology 74:43, 1991.

217. Ota K, Namiki A, Ujike Y et al: Prolongation of tetracaine spinal anesthesia by oral clonidine. Anesth Analg 75:262, 1992.

218. Bonnet F, Boico O, Rostaining S: Clonidine-induced analgesia in postoperative patients: Epidural versus intramuscular administration. Anesthesiology 72:423, 1990.

219. DeKock M, Pichon G, Scholtes JL: Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia. Can J Anaesth 39:537, 1992.

220. Tryba M, Zenz M, Strumpf M: Clonidine i.v. is equally effective as morphine i.v. for postoperative analgesia: A double-blind study. Anesthesiology 75:A1085, 1991.

221. DeKock M, Lavandhomme P, Scholtes JL: Intraoperative and postoperative analgesia using intravenous opioid, clonidine and lignocaine. Anaesth Intensive Care 22:15, 1994.

222. Bonnet F, Brun-Buisson V, Saada M: Dose-related prolongation of hyperbaric tetracaine spinal anesthesia by clonidine in humans. Anesth Analg 68:619, 1989.

223. Murga G, Samso E, Valles J et al: The effect of clonidine on intraoperative requirements of fentanyl during combined epidural/general anesthesia. Anaesthesia 49:999, 1994.

224. Klimscha W, Chiari A, Drafft P et al: Hemodynamic and analgesic effects of clonidine added repetitively to continuous epidural and spinal blocks. Anesth Analg 80:322, 1995.

225. Delaunay L, Leppert C, Dechaubry V et al: Epidural clonidine decreases postoperative requirements for epidural fentanyl. Reg Anesth 18:176, 1993.

226. Carabine UA, Milligan KR, Mulholland D et al: Extradural clonidine infusions for analgesia after total hip replacement. Br J Anaesth 68:338, 1992.

228. Petros AJ, Wright RMB: Epidural and oral clonidine in domiciliary control of deafferentation pain. Lancet 1:1034, 1987.

229. Eisenach JC, Rauck RL, Buzzanell C et al: Epidural clonidine analgesia for intractable cancer pain: Phase I. Anesthesiology 71:647, 1989.

230. Ferit PA, Aydinli I, Akra S: Management of cancer pain with epidural clonidine (abstract). Reg Anesth 17(suppl 3S):173, 1992.

231. Lund C, Hansen O, Kehlet H: Effect of epidural clonidine on somatosensory evoked potentials to dermatomal stimulation. Eur J Anaesth 6:207, 1989.

232. Strube PJ, Lavies NG, Rubin J: Epidural clonidine (letter). Anaesthesia 39:834, 1984

233. Mendez R, Eisenach JC, Kashtan K: Epidural clonidine analgesia after cesarean section. Anesthesiology 73:848, 1990.

234. Filos KS, Goudas LC, Patroni O et al: Intrathecal clonidine as a sole analgesic for pain relief after cesarean section. Anesthesiology 77:267, 1990.

235. Bernard JM, Kick O, Bonnet F: Comparison of intravenous and epidural clonidine for postoperative patient-controlled analgesia. Anesth Analg 81:706, 1995.

236. Huntoon M, Eisenach JC, Boese P: Epidural clonidine after cesarean section: Appropriate dose and effect of prior local anesthetic. Anesthesiology 76:187, 1992.

237. Bouguet D: Caudal clonidine added to local anesthetics enhances post-operative analgesia after anal surgery in adults (abstract). Anesthesiology 81:A942, 1994.

238. Bonnet F, Diallo A, Saada M et al: Prevention of tourniquet pain by spinal isobaric bupivacaine with clonidine. Br J Anaesth 63:93, 1989.

239. Racle JP, Benkhadra A, Poy JY et al: Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. Anesth Analg 66:442, 1987.

240. Bonnet F, Catoire P, Brun-Buison V et al: Effects of oral and subarachnoid clonidine on spinal anesthesia with bupivacaine. Reg Anesth 15:211, 1990.

241. Fogarty DJ, Carabine UA, Milligan KR: Comparison of the analgesic effects of intrathecal clonidine and intrathecal morphine after spinal anesthesia in patients undergoing total hip replacement. Br J Anaesth 71:661, 1993.

242. Niemi L: Effects of intrathecal clonidine on duration of bupivacaine spinal anaesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. Acta Anaesthesiol Scand 38:724, 1994.

243. Fukuda T, Dohi S, Naito H: Comparisons of tetracaine spinal anesthesia with clonidine or phenylephrine in normotensive and hypertensive humans. Anesth Analg 78:106, 1994.

244. Gentili M, Bonnet F: Incidence of urinary retention after spinal anesthesia: Comparison of morphine and clonidine (abstract). Anesthesiology 81:A945, 1994.

245. Gentili M, Mamelle JC, Le Foll G: Combination of low-dose bupivacaine and clonidine for unilateral spinal anesthesia in arthroscopic knee surgery. Reg Anesth 20:169, 1995.

246. Kapral S, Kocek S, Krafft P et al: Intrathecal clonidine delays motor onset of bupivacaine (abstract). Anesthesiology 81:A935, 1994.

247. Coombs DW, Saunders RL, Fratkin JD et al: Continuous intrathecal hydromorphone and clonidine for intractable cancer pain. J Neurosurg 64:890, 1986.

248. van Essen EJ, Bovill JG, Ploeger EJ et al: Intrathecal morphine and clonidine for control of intractable cancer pain: A case report. Acta Anaesthesiol Belg 39:109, 1988.

249. Hardy PAJ, Wells JCD: Pain after spinal intrathecal clonidine: An adverse interaction with tricyclic antidepressants? Anaesthesia 43:1026, 1988.

250. Grace D, Milligan KR, Morrow BJ et al: Co-administration of pethidine and clonidine: A spinal anaesthetic technique for total hip replacement. Br J Anaesth 73:628, 1994.

251. Boico O, Bonnet F, Bazoit JX: Effects of epinephrine and clonidine on plasma concentrations of spinal bupivacaine. Acta Anaesthesiol Scand 36:684, 1992.

252. Grace D, Bunting H, Milligan KR et al: Postoperative analgesia after co-administration of clonidine and morphine by the intrathecal route in patients undergoing hip replacement. Anesth Analg 80:86, 1995.

252A. Sucu Y, Kanbak O, Gogus N et al: Comparison of intrathecal clonidine and alfentanil (abstract). Br J Anaesth 74:131, 1995.

253. DeVos H, Bricca G, DeKreyser J et al: Imidazoline receptors, non-adrenergic idazoxan binding sites and alpha $_2$ -adrenoceptors in the human central nervous system. Neuroscience 59:589, 1994.

254. Hamilton CA: The role of imidazoline receptors in blood pressure regulation. Pharmacol Ther 54:231, 1992.

255. Guyenet PG, Cabot JB: Inhibition of sympathetic preganglionic neurons by catecholamines and clonidine: Mediation by an alpha-adrenergic receptor. J Neurosci 1:908, 1981.

256. Ruffolo RR Jr: Distribution and function of peripheral alpha-adrenoceptors on the cardiovascular system. Pharmacol Biochem Behav 22:827, 1985.

257. Muzi M, Goff D, Kampine J et al: Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology 77:864, 1992.

258. Aho M, Erkola O, Korttila K: alpha $_2$ -Adrenergic agonists in anaesthesia. Curr Opin Anesthesiol 5:481, 1992.

259. Maze M, Tranguilli W: alpha $_2$ -Adrenoreceptor agonists: Defining the role in clinical anesthesia. Anesthesiology 74:581, 1991.

260. Bloor BC, Flacke WE: Reduction in halothane anesthetic requirement by clonidine, an alpha $_2$ adrenergic agonist. Anesth Analg 61:741, 1982.

261. Segal IS, Vickery RG, Walton JK: Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha $_2$ adrenergic receptor. Anesthesiology 69:818, 1988.

262. Vickery RG, Sheridan BS, Segal IS et al: Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha $_2$ -adrenergic agonist, in halothane-anesthetized dogs. Anesth Analg 67:611, 1988.

263. Orko R, Pouttu J, Ghignone M: Effect of clonidine on hemodynamic responses to endotracheal intubation and gastric acidity. Acta Anaesthesiol Scand 31:325, 1987.

264. Aantaa RE, Jaakola ML, Kallio A et al: A comparison of dexmedetomidine, an alpha $_2$ adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery. Br J Anaesth 67:402, 1991.

265. Aantaa RE, Kanto JH, Scheinen M: Dexmedetomidine premedication for minor gynecological surgery. Anesth Analg 70:407, 1990.

266. Aantaa RE, Kanto JH, Scheinen M: Dexmedetomidine, an alpha $_2$ adrenergic agonist, reduces anesthetic requirements for patients undergoing minor gynecological surgery. Anesthesiology 73:230, 1990.

267. Richard MJ, Skues MA, Jarvis AP et al: Total i.v. anaesthesia with propofol and alfentanil: Dose requirements for propranolol and the effect of premedication with clonidine. Br J Anaesth 65:157, 1990.

268. Singelyn FJ, Dangoisse M, Bartholomee S et al: Adding clonidine to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Reg Anesth 17:148, 1992.

269. Macaire P, Bernard JM, LeRoux D et al: Dose-ranging study of clonidine added to lidocaine for axillary plexus block in outpatients (abstract). Anesthesiology 83:A774, 1995.

270. Singelyn FJ, Muller G, Gouverneur JM: Adding fentanyl and clonidine to mepivacaine results in a rapid in onset and prolonged anesthesia and analgesia after brachial plexus blockade (abstract). Anesthesiology 75:A653, 1991.

271. Bartholomee S, Singelyn FJ, Broka S et al: Clonidine added to mepivacaine for brachial plexus blockade: Its minimal effective dose prolonging the duration of both anesthesia and analgesia (abstract). Anesthesiology 75:A1084, 1991.

272. Tschernko E, Benditte H, Kritzinger M et al: Clonidine added to the anesthetic solution prolongs analgesia and improves arterial oxygen tension after intercostal nerve blockade (abstract). Anesthesiology 83:A846, 1995.

273. Breslow MJ: The role of stress hormones in perioperative myocardial ischemia. Int Anesthesiol Clin 30(1):81, 1992.

274. Ghignone MC, Cavillo O, Quintin L: Anesthesia for ophthalmic surgery in the elderly: The effects of clonidine on intraocular pressure, perioperative hemodynamics, and anesthesia requirement. Anesthesiology 68:707, 1988.

275. Jaakola ML, Ali-Melkkila T, Kanto J: Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. Br J Anaesth 68:570, 1992.

276. Kumar A, Bose S, Phattacharya A: Oral clonidine premedication for elderly patients undergoing intraocular surgery. Acta Anaesthesiol Scand 36:159, 1992.

277. DeKock M, Pichon G, Scholtes JL: Intraoperative clonidine enhances postoperative morphine patient controlled analgesia. Anesthesiology 75:A654, 1991.

278. Motsh J, Graber E, Ludwig K: Addition of clonidine enhances postoperative analgesia from epidural morphine: A double blind study. Anesthesiology 73:1066, 1990.

279. Bernard JM, Hommeril JL, Passuti N et al: Postoperative analgesia by intravenous clonidine. Anesthesiology 75:577, 1991.

280. Carabine UA, Milligan KR, Moore J: Extradural clonidine and bupivacaine for postoperative analgesia. Br J Anaesth 68:132, 1992.

281. Rostaing S, Bonnet F, Levron JC: Effect of epidural clonidine on analgesia and pharmacokinetics of epidural fentanyl in postoperative patients. Anesthesiology 75:420, 1991.

282. DeKock M, Crochet B, Morimont C et al: Intravenous or epidural clonidine for intra- and postoperative analgesia. Anesthesiology 79:525, 1993.

283. Mogensen T, Eliasen K, Ejlersen E et al: Epidural clonidine enhances postoperative analgesia from a combined low-dose epidural bupivacaine and morphine regimen. Anesth Analg 75:607, 1992.

284. Vercauteren M, Lauwers E, Meert T et al: Comparison of epidural sufentanil plus clonidine with sufentanil alone for postoperative pain relief. Anaesthesia 45:531, 1990.

285. Rockemann MG, Seeling W, Brinkmann A et al: Analgesic and hemodynamic effects of epidural clonidine, clonidine/morphine and morphine after pancreatic surgery: A double-blind study. Anesth Analg 80:869, 1995.

286. O'Meara ME, Gin T: Comparison of 0.125% bupivacaine with 0.125% bupivacaine and clonidine as extradural analgesia in the first stage of labour. Br J Anaesth 71:651, 1993.

287. Brichant JF, Bonhomme V, Mikulski M et al: Admixture of clonidine to epidural bupivacaine for analgesia during labor: Effect of varying clonidine doses (abstract). Anesthesiology 81:A1136, 1994.

288. Cigarini I, Kaba A, Bonnet F et al: Epidural clonidine combined with bupivacaine for analgesia in labor: Effects on mother and neonate. Reg Anesth 20:113, 1995.

289. Eisenach JC, DePen S, Dubois M et al: Epidural clonidine study group: Epidural clonidine anesthesia for intractable cancer pain. Pain 61:391, 1995.

290. Rauck RL, Eisenach JC, Jackson K: Epidural clonidine treatment for refractory reflex sympathetic dystrophy. Anesthesiology 79:1163, 1993.

291. Zeigler D, Lynch SA, Muir J: Transdermal clonidine versus placebo in painful diabetic neuropathy. Pain 48:403, 1992.

292. Slogoff S: Perioperative ischemia. Semin Anesth 9:107, 1990.

293. Quintin L, Viale JP, Annat G: Oxygen uptake after major abdominal surgery: Effect of clonidine. Anesthesiology 74:236, 1991.

294. Marruecos I, Roglan A, Frati ME et al: Clonidine overdose. Crit Care Med 11:959, 1988.

295. Ooi R, Pattison J, Feldman SA: The effects of intravenous clonidine on ventilation. Anaesthesia 46:632, 1991.

296. Uhde TW, Stein MB, Vittone BJ: Behavioral and physiologic effects of short-term and long-term administration of clonidine in panic disorder. Arch Gen Psychiatry 46:170, 1989.

297. Gold MS, Pottash AC, Sweeney DR et al: Opiate withdrawal using clonidine: A safe, effective, and rapid nonopiate treatment. JAMA 243:343, 1980.

298. Franz DN, Hare BD, McCloskey KL: Spinal sympathetic neurons: Possible sites of opiate-withdrawal suppression by clonidine. Science 215:1643, 1982.

299. Davison R, Kaplan K, Fintel D et al: The effect of clonidine on the cessation of cigarette smoking. Clin Pharmacol Ther 44:265, 1988.

300. Glassman AH, Stetner F, Walsh BT: Heavy smokers, smoking cessation, and clonidine: Results of a double-blind, randomized trial. JAMA 259:2863, 1988.

301. Hughes JR: Clonidine, depression, and smoking cessation. JAMA 259:2901, 1988.

302. Metz SA, Halter JB, Robertson RP: Induction of defective insulin secretion and impaired glucose tolerance by clonidine: Selective stimulation of metabolic alpha-adrenergic pathways. Diabetes 27:554, 1978.

303. Sonnenblick EH, Frishman WH, LeJemtel TH: Dobutamine: A new synthetic cardioactive sympathetic amine. N Engl J Med 300:17, 1979.

304. Gillespie T, Ambos H, Sobel B et al: Effects of dobutamine in patients with acute myocardial infarction. Am J Cardiol 39:588, 1977.

305. Ruffolo R, Yaden E: Vascular effects of the stereoisomers of dobutamine. J Pharmacol Exp Ther 224:46, 1982.

306. Opie L, Sonnenblick E, Kaplan N et al: Beta-blocking agents. In Opie LH: Drugs for the Heart. 3rd ed. Philadelphia, WB Saunders, 1991.

307. Unverferth DV, Blanford M: Tolerance to dobutamine after a 72 hour continuous infusion. Am J Med 69:262, 1980.

308. Leier CV, Huss P, Lewis RP et al: Drug-induced conditioning in congestive heart failure. Circulation 65:1382, 1982.

309. Krell MJ, Kline EM, Bates ER et al: Intermittent, ambulatory dobutamine infusions in patients with severe congestive heart failure. Am Heart J 112:787, 1986.

310. Spitzer W, Suissa S, Ernst P et al: The use of beta-agonists and the risk of death and near death from asthma. N Engl J Med 326:501, 1992.

311. Robin E, McCauley R: Sudden cardiac death in bronchial asthma, and inhaled with beta-adrenergic agonists. Chest 101:1699, 1992.

312. Zimert I: Infrequent cardiac deaths accour in bronchial asthma. Chest 101:1703, 1992.

313. Caritis SN, Edelstone DI, Mueller-Heubach E: Pharmacologic inhibition of preterm labor. Am J Obstet Gynecol 133:557, 1979.

314. Wagner JM, Morton MJ, Johnson KA et al: Terbutaline and maternal cardiac function. JAMA 246:2697, 1981.

315. Canadian Preterm Labor Investigators Group: Treatment of preterm labor with the beta-adrenergic agonist ritodrine. N Engl J Med 327:308, 1992.

316. Hoffman B, Lefkowitz R: Adrenergic receptor antagonists. In Gilman A, Rall T, Nies A et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990, p 221.

317. Kaplan N: Treatment of hypertension: Drug therapy. In Kaplan N (ed): Clinical Hypertension. 5th ed. Baltimore, Williams & Wilkins, 1990, p 182.

318. Rutherford J, Braunwald E: Chronic ischemic heart disease. In Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 1292.

319. Conolly ME, Kersting F, Dollery CT: The clinical pharmacology of beta-adrenoreceptor blocking drugs. Prog Cardiovasc Dis 19:203, 1976.

320. Kostis JB, Frishman W, Hosler MH et al: Treatment of angina pectoris with pindolol: The significance of intrinsic sympathomimetic activity of beta blockers. Am Heart J 104:496, 1982.

321. Miller N: Effects of adrenoceptor-blocking drugs on plasma lipoprotein concentrations. Am J Cardiol 60:17E, 1987.

322. Furberg C: Secondary prevention trials after antimyocardial infarction. Am J Cardiol 60:28A, 1987.

323. Rango R, Langlois S: Comparison of withdrawal phenomena after propranolol, metroprolol, and pindolol. Am Heart J 104:437, 1982.

324. Streufert S, DePadova A, McGlynn T et al: Impact of beta-blockade on complex cognitive functioning. Am Heart J 116:311, 1988.

325. Gengo FM, Huntoor L, McHugh WB: Lipid-soluble and watersoluble beta-blockers: Comparison of the central nervous system depressant effect. Arch Intern Med 147:39, 1987.

326. Zipes DG: Management of cardiac arrhythmias: Pharmacological, electrical and surgical techniques. In Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB Saunders, 1992, p 628.

327. Henry J, Cassidy S: Membrane stabilizing activity: A major cause of fatal poisoning. Lancet 1:1414, 1986.

328. Olsson G, Rehnqvist N, Sjogren A et al: Long-term treatment with metoprolol after myocardial infarction: Effect on 3 year mortality and morbidity. J Am Coll Cardiol 5:1428, 1985.

329. Yusuf S: Interventions that potentially limit myocardial infarct size: Overview of clinical trials. Am J Cardiol 60:11A, 1987.

330. ISIS-1 (First International Study of Infarct Survival) Collaborative Group: Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. Lancet 1:57, 1986.

331. Yusuf S, Peto R, Lewis J et al: Beta blockade during and after myocardial infarction: An overview of the randomized trials. Prog Cardiovasc Dis 27:335, 1985.

332. TIMI Study Group: Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 320:618, 1989.

333. Ryden L, Ariniego R, Arnman K et al: A double-blind trial of metoprolol in acute myocardial infarction: Effects on ventricular tachyarrhythmias. N Engl J Med 308:614, 1983.

334. Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: The fifth report of the Joint National Committee on detection, evaluation and treatment of high blood pressure (JNC-V). Arch Intern Med 153:154, 1993.

335. Frishman W: Pindolol: A new beta-adrenoceptor antagonist with partial agonist activity. N Engl J Med 308:940, 1983.

336. Van den Meiracker AH, Man in't Veld AJ, Ritsema van Eck HJ et al: Hemodynamic and hormonal adaptations to beta-adrenoceptor blockade: A 24-hour study of acebutolol, atenolol, pindolol, and propranolol in hypertensive patients. Circulation 78:957, 1988.

337. Man in't Veld AJ, Van den Meiracker AH, Schalekamp MA: Do beta blockers really increase peripheral vascular resistance? Review of the literature and new observations under basal conditions. Am J Hypertens 1:91, 1988.

338. Shand D: Propanolol. N Engl J Med 293:280, 1975.

339. Platia E, Fitzpatrick P, Wallis D et al: Esmolol vs verapamil for the treatment of recent-onset atrial fibrillation/flutter. J Am Coll Cardiol 11:170A, 1988.

340. Waldo AL, Camm AJ, deRuyter H et al: Effect of *d*-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. Lancet 348:7, 1996.

341. DeSanctis RW, Doroghazi RM, Austen WG et al: Aortic dissection. N Engl J Med 317:1060, 1987.

342. Grubb BP, Sirio C, Zelis R: Intravenous labetalol in acute aortic dissection. JAMA 258:78, 1987.

343. Viljoen JF, Estafanous G, Kellner GA: Propanolol and cardiac surgery. J Thorac Cardiovasc Surg 64:826, 1972.

344. DeBruijn N, Reves JG, Croughnell N et al: Comparison of hemodynamic responses to isoproterenol infusion and surgical stress in patients given cardioselective and noncardioselective beta-adrenergic antagonists. Anesth Analg 66:637, 1987.

345. Wiersinga WM, Touber JL: The influence of beta-adrenergic blocking agents on plasma thyroxine and triiodothyronine. J Clin Endocrinol Metab 45:293, 1977.

346. Miller RR, Olson HG, Amsterdam EA et al: Propanolol-withdrawal rebound phenomenon: Exacerbation of coronary events after abrupt cessation of antianginal therapy. N Engl J Med 292:416, 1975.

347. Psaty B, Koepsell T, Wagner E et al: The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. JAMA 263:1653, 1990.

348. Cleophas T, Kauw F: Pressor responses from noncardioselective beta-blockers. Angiology 39:587, 1988.

349. Strauss W, Parisi A: Combined use of calcium-channel and beta- adrenergic blockers for the treatment of chronic stable angina. Ann Intern Med 109:570, 1988.

350. Wayne VS, Harper RW, Laufer E et al: Adverse interaction between beta-adrenergic blocking drugs and verapamil: Report of three cases. Aust N Z J Med 12:285, 1982.

351. Douglas-Jones A, Baber N, Lee A: Once daily propranolol in the treatment of mild to moderate hypertension: A dose range finding study. Eur J Clin Pharmacol 14:163, 1978.

352. Lichtman M, Cohen J, Murphy M et al: Effect of propranolol on oxygen binding to hemoglobin in vitro and in vivo. Circulation 49:881, 1974.

353. Schrumpf JD, Sheps DS, Wolfson S et al: Altered hemoglobin-oxygen affinity with long-term propranolol therapy in patients with coronary artery disease. Am J Cardiol 40:76, 1977.

354. Pendleton RG, Newman DJ, Sherman SS et al: Effect of propranolol upon the hemoglobin-oxygen dissociation curve. J Pharmacol Exp Ther 180:647, 1972.

355. Hoffman BB, Lefkowitz RJ: Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In Hardman JG, Limbird LE, Molinoff PB, et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, McGraw-Hill, 1996.

356. Bernstein JS, Ebert TJ, Stone DF et al: Partial attenuation of hemodynamic responses to rapid sequence induction and intubation with labetalol. J Clin Anesth 1:444, 1989.

357. Huey J, Thomas JP, Hendricks DR et al: Clinical evaluation of labetalol for the treatment of hypertensive urgency. Am J Hypertens 1:284S, 1988.

358. Gabrielson G, Lingham R, Dimich I et al: Comparative study of labetalol and hydralazine in the treatment of postoperative hypertension. Anesth Analg 66:S63, 1987.

359. Skrobic J, Cruise C, Webster R et al: Labetalol vs nitroprusside in hypertension post coronary-bypass surgery. Am J Hypertens 2:1295, 1989.

360. Lavies NG, Meiklejohn BH, May AE et al: Hypertensive and catecholamine response to tracheal intubation in patients with pregnancy-induced hypertension. Br J Anaesth 63:429, 1989.

361. Jouppilla P, Kirkinen P, Koivula A: Labetalol does not alter the placental and fetal blood flow or maternal prostanoids in pre-eclampsia. Br J Obstet Gynaecol 93:543, 1986.

362. Dupont AG, Van der Niepen P, Taeymans Y et al: Effect of carvedilol on ambulatory blood pressure, renal hemodynamics, and cardiac function in essential hypertension. J Cardiovasc Pharmacol 10(suppl 1):S130, 1987.

363. Eggertsen R, Sivertsson R, Adren L et al: Haemodynamic effects of carvedilol, a new beta-adrenoceptor blocker and precapillary vasodilator in essential hypertension. J Hypertens 2:529, 1984.

364. Leonetti G, Sempieri L, Cuspidi C et al: Resting and postexercise hemodynamic effects of carvedilol, a beta-adrenergic blocker and precapillary vasodilator in hypertensive patients. J Cardiovasc Pharmacol 10(suppl 11):S94, 1987.

365. Omvik P, Lund-Johansen P: Acute haemodynamic effects of carvedilol in essential hypertension at rest and during exercise. Eur Heart J 12:736, 1991.

366. Cervantes Escarcega JL, Ruiz de Chavez A, Guadalajara Boo J: Double-blind study of the efficacy and tolerability of carvedilol vs nifedi-pine S.R. in uncomplicated essential hypertension (in Spanish). Invest Med Int 19:142, 1992.

367. Ostergren J, Storstein L, Karlberg BE: Quality of life in hypertensive patients treated with either carvedilol or enalapril. Blood Press 5:41, 1996.

368. Ruilope LM: Comparison of a new vasodilating beta blocker, carvedilol, with atenolol in the treatment of mild to moderate essential hypertension. Am J Hypertens 7:129, 1994.

369. Weber K, Bohmeke T, van der Does R et al: Comparison of the hemodynamic effects of metoprolol and carvedilol in hypertensive patients. Cardiovasc Drug Ther 10:113, 1996.

370. Albergati F, Paterno E, Venuti RP et al: Comparison of the effects of carvedilol and nifedipine in patients with essential hypertension and non-insulin-dependent diabetes mellitus. J Cardiovasc Pharmacol 19(suppl 1):S86, 1992.

371. Louis WJ, Krum H, Conway EL: A risk-benefit assessment of carvedilol in the treatment of cardiovascular disorders. Drug Saf 11:86, 1994.

372. Van der Does R, Eberhardt R, Derr I et al: Efficacy and safety of carvedilol in comparison with nifedipine sustained-release in chronic stable angina. J Cardiovasc Pharmacol 19(suppl 1):S122, 1992.

373. Basu S, Senior R, van der Does R et al: Carvedilol reduces adverse cardiac events following acute myocardial infarction (abstract). Circulation 92(suppl I):I-20, 1995.

374. Senior R, Basu S, Lahiri A: Carvedilol prevents remodeling and improves prognosis in patients with left ventricular dysfunction following acute myocardial infarction (abstract). J Am Coll Cardiol 27(suppl A):319A, 1996.

375. Zehender M, Faber T, Schnabel P et al: Benefits and hazards of carvedilol in unstable angina: A double-blind placebo controlled, randomized study (abstract). Circulation 92(suppl I):I-20, 1995.

376. Bristow MR, Gilbert EM, Abraham WT et al: Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 94:2807, 1996.

377. Cohn JN, Fowler MB, Bristow MR et al: Effect of carvedilol in severe chronic heart failure (abstract). J Am Coll Cardiol 27(suppl A):169A, 1996.

378. Colucci WS, Packer M, Bristow MR et al: Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation 94:2800, 1996.

379. Packer M, Colucci WS, Sackner-Bernstein JD et al: Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure: The PRECISE trial. Circulation 94:2793, 1996.

380. Bristow MR, Gilbert EM, Abraham WT et al: Effects of carvedilol on LV function and mortality in diabetic versus nondiabetic patients with ischemic or nonischemic dilated cardiomyopathy (abstract). Circulation 94(suppl I):I-664, 1996.

381. Gray R, Bateman T, Czer L: Comparison of esmolol and nitroprusside for acute post-cardiac surgical hypertension. Am J Cardiol 59:887, 1987.

382. Reves JG, Croughwell ND, Hawkins E et al: Esmolol for treatment of intraoperative tachycardia and/or hypertension in patients having cardiac operations, bolus loading technique. J Thorac Cardiovasc Surg 100:221, 1990.

383. Oxorn D, Knox JW, Hill J: Bolus doses of esmolol for the prevention of perioperative hypertension and tachycardia. Can J Anaesth 37:206, 1990.

384. Wallis DE, Littman WJ, Scanlon PJ: Safety and efficacy of esmolol for unstable angina pectoris. Am J Cardiol 62:1033, 1988.

385. Kirshenbaum JM, Kloner RJ, McGowan N et al: Use of an ultrashort-acting beta-receptor blocker (esmolol) in patients with acute myocardial ischemia and relative contraindications to beta-blockade therapy. J Am Coll Cardiol 12:773, 1988.

386. Beart PM, Rowe PR, Louis WJ: Alphamethyl adrenaline is a central metabolite of alpha-methyldopa. J Pharm Pharmacol 35:519, 1980.

387. Tung C-S, Goldberg MR, Hollister AS et al: Central and peripheral cardiovascular effects of alpha-methylepinephrine. J Pharmacol Exp Ther 227:484, 1983.

388. Triner L, Baer L, Gallagher R et al: Use of metyrosine in the anesthetic management of patients with catecholamine-secreting tumors. Br J Anaesth 54:1333, 1982.

389. Bigger J, Hoffman B: Antiarrhythmic drugs. In Gilman A, Rall T, Nies A et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990, p 840.

390. Baldessarini R: Drugs and the treatment of psychiatric disorders. In Gilman A, Rall T, Nies A et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990.

391. Parkinson Study Group: Effect of deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 321:1364, 1989.

392. Roizen MF: Monoamine oxidase inhibitors: Are we condemned to relive history, or is history no longer relevant? J Clin Anesth 2:293, 1990.

393. Doyle DJ: Ketamine induction and monoamine oxidase inhibitors. J Clin Anesth 2:324, 1990.

394. Materson BJ: Adverse effects of angiotensin-converting enzyme inhibitors in antihypertensive therapy with focus on quinapril. Am J Cardiol 69:46C, 1992.

395. ISIS-4 (Fourth International Study of Infarct Survival) Study Group: A randomised factorial trial assessing early oral captopril, oral mono-nitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet 345:669, 1995.

396. Nash DT: Comparative properties of angiotensin-converting enzyme inhibitors: Relations with inhibition of tissue angiotensin-converting enzyme and potential clinical implications. Am J Cardiol 69:26C, 1989.

397. Raia JJ, Barone JA, Byerly WG et al: Angiotensin-converting enzyme inhibitors: A comparative review. DICP Ann Pharmacother 24:506, 1990.

398. Weber MA: Safety issues during antihypertensive treatment with angiotensin converting enzyme inhibitors. Am J Med 84(suppl 4A):16, 1988.

399. Warner JN, Rush JE: Safety profiles of the angiotensin-converting enzyme inhibitors. Drugs 35(suppl 5):89, 1988.

400. Ferner RE: Adverse effects of angiotensin-converting-enzyme inhibitors. Adverse Drug React Acute Poisoning Rev 141:528, 1990.

401. Khan JA: Atropine poisoning in Hawthorne's *The Scarlet Letter.* N Engl J Med 311:414, 1984.

402. Ziskind A: Transdermal scopolamine-induced psychosis. Postgrad Med 84:73, 1988.

403. Wilkinson JA: Side-effects of transdermal scopolamine. J Emerg Med 5:389, 1987.

404. Gross NJ: Ipratropium bromide. N Engl J Med 319:486, 1988.

405. Brown JH: Atropine, scopolamine and related antimuscarinic drugs. In Gilman A, Rall T, Nies A et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990, p 150.

406. Alcalay M, Izraeli S, Wallach-Kapon R et al: Paradoxical pharmacodynamic effect of atropine on parasympathetic control: A study by spectral analysis of heart rate fluctuations. J Clin Pharmacol Ther 52:518, 1992.

407. Cromwell EB, Ketchum JS: The treatment of scopolamine-induced delirium with physostigmine. Clin Pharmacol Ther 8:409, 1967.

408. Heiser JF, Wilbert D: Reversal of delirium induced by tricyclic antidepressant drugs with physostigmine. Am J Psychiatry 131:1275, 1974.

409. Bidwai AV, Stanley TH, Rogers C et al: Reversal of diazepam-induced post-anesthetic somnolence with physostigmine. Anesthesiology 51:256, 1979.

410. Ghoneim MM, Dembo JB, Block RI: Time course of antagonism of sedative and amnesic effects of diazepam by flumazenil. Anesthesiology 70:899, 1989.

411. Flacke WE, Flacke JE: Cholinergic and anticholinergic agents. In Smith NT, Corbascio A (eds): Drug Interactions in Anesthesia. 2nd ed. Philadelphia, Lea & Febiger, 1986, p 160.

412. Taylor P: Agents acting at the neuromuscular junction and autonomic ganglia. In Gilman A, Rall T, Nies A et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, Pergamon Press, 1990.

413. Paton W: The principles of ganglionic block. In Scientific Basis of Medicine Annual Reviews. London: University of London, Athlone Press, 1954.

414. Thomas J, Fouad FM, Tarazi RC et al: Evaluation of plasma catecholamines in humans: Correlation of resting levels with cardiac responses to beta-blocking and sympatholytic drugs. Hypertension 5:858, 1983.

415. Best JD, Halter JB: Release and clearance rates of epinephrine in man: Importance of arterial measurements. J Clin Endocrinol Metab 55:263, 1982.

416. Esler M, Thompson J, Kaye D et al: Effects of aging on the responsiveness of the human cardiac sympathetic nerves to stressors. Circulation 91:351, 1995.

417. Yamaguchi I, Kopin IJ: Plasma catecholamine and blood pressure responses to sympathetic stimulation in pithed rats. Am J Physiol 237:H305, 1979.

418. Adams K: Current perspectives on beta-receptor antagonists in the treatment of symptomatic ventricular dysfunction. Pharmacotherapy 16:69S, 1996.

419. Eichhorn EJ: Do beta-blockers have a role in patients with congestive heart failure? Cardiol Clin 12:133, 1994.

420. Rundqvist B, Eisenhofer G, Elam M et al: Attenuated cardiac sympathetic responsiveness during dynamic exercise in patients with heart failure. Circulation 95:940, 1997.

421. Klassen G, Bramwell R, Bromage P et al: Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. Anesthesiology 52:8, 1980.

422. Bland J, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 45:287, 1976.

423. Anand K, Hickey P: Halothane-morphine combined with high dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 326:1, 1992.

424. Roizen MF, Lampe GH, Benefiel DJ et al: Is increased operative stress associated with worse outcome? Anesthesiology 67:A1, 1987.

425. Scott NB, Kehlet H: Regional anaesthesia and surgical morbidity. Br J Surg 75:299, 1988.

426. Yeager M, Glass D, Neff R et al: Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 66:729, 1987.

427. Breslow MJ, Jordan DA, Christopherson R et al: Epidural morphine decreases postoperative sympathetic nervous system hyperactivity. JAMA 261:3577, 1989.

428. Rosenfeld BA, Beattie C, Christopherson R et al: The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Anesthesiology 79:435, 1993.

429. Christopherson R, Beattie C, Frank SM et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Anesthesiology 79:422, 1993.

430. Parker SD, Breslow MJ, Frank SM et al: Catecholamine and cortisol responses to lower extremity revascularization: Correlation with outcome variables. Crit Care Med 23:1954, 1995.

431. Burgos L, Ebert T, Asiddao C et al: Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. Anesthesiology 70:591, 1989.

432. Docherty JR: Cardiovascular responses in aging: A review. Pharmacol Rev 42:103, 1990.

433. Davies HEF: Respiratory change in heart rate, sinus arrhythmia in the elderly. Gerontol Clin 17:96, 1975.

434. Gribbin B, Pickering TG, Sleight P et al: Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 29:424, 1971.

435. Kalflusch JH, Stowe DF, Smith W: Evaluations of heart rate response to the Valsalva maneuver. Am Heart J 95:707, 1978.

436. Rothbaum RA, Shaw DS, Angell CS et al: Cardiac performance in the unanesthetized male rat. J Gerontol 28:287, 1974.

437. Sata I, Hasegawa Y, Takahashi N et al: Age-related changes of cardiac control function in man: With special reference to heart rate control at rest and during exercise. J Gerontol 36:564, 1981.

438. Esler M, Skews H, Leonard P et al: Age-dependence of noradrenaline kinetics in normal subjects. Clin Sci (Lond) 60:217, 1981.

439. Esler MD, Turner AG, Kaye DM et al: Aging effects on human sympathetic neuronal function. Am J Physiol 268:R278, 1995.

440. Nafelski LA, Brown CFG: Action of atropine on the cardiovascular system in normal persons. Arch Intern Med 86:898, 1950.

441. Mancia G, Ferrari A, Gregorini L et al: Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. Circ Res 53:96, 1983.

442. Ng AV, Callister R, Johnson DG et al: Sympathetic neural reactivity to stress does not increase with age in healthy humans. Am J Physiol 267:H344, 1994.

443. White M, Roden R, Minobe W et al: Age-related changes in beta- adrenergic neuroeffector systems in the human heart. Circulation 90:1225, 1994.

444. Guaneri T, Filburn CR, Zitnik G et al: Contractile and biochemical correlates of beta-adrenergic stimulation of the aged heart. Am J Physiol 239:H501, 1980.

445. Krall JF, Connelly M, Weisbart R et al: Age-related elevation of plasma catecholamine concentration and reduced responsiveness of lymphocyte adenylate cyclase. J Clin Endocrinol Metab 52:863, 1981.

446. Vaz M, Rajkumar C, Wong J et al: Oxygen consumption in the heart, hepatomesenteric bed, and brain in young and elderly human subjects, and accompanying sympathetic nervous activity. Metabolism 45:1487, 1996.

447. Buchholz J, Duckles SP: Effect of age on prejunctional modulation of norepinephrine release. J Pharmacol Exp Ther 252:159, 1990.

448. Hyland L, Docherty JR: Further examination of the effects of aging on the adrenoceptor responsiveness of the rat vas deferens. Eur J Pharmacol 110:241, 1985.

449. Fernandes F, Salaices CF, Sanchez-Ferrer JL et al: Effect of aging and hypertension on [^{3} H]noradrenaline release in rat mesenteric artery. J Hypertens 10(suppl 4):S65, 1992.

450. Supiano MA, Neubig RR, Linares OA et al: Effects of low-sodium diet on regulation of platelet alpha $_{2}$ -adrenergic receptors in young and elderly humans. Endocrinol Metab 19:E339, 1989.

451. Bracken MB, Shepard MJ, Collins WF et al: A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. N Engl J Med 322:1405, 1990.

452. Mathias CJ, Christensen NJ, Spalding JMK: Cardiovascular control in recently injured tetraplegics in spinal shock. Q J Med 48:273, 1979.

453. Van Lieshout JJ, Imholz BPM, Wesseling KH et al: Singing-induced hypotension: A complication of high spinal cord lesion. Neth J Med 38:76, 1991.

454. Stjernberg L, Blumberg H, Wallin B: Sympathetic activity in man after spinal cord injury: Outflow to muscle below the lesion. Brain 109:695, 1986.

455. Tollenaere JP: Atlas of the Three-Dimensional Structure of Drugs. Amsterdam, Elsevier North-Holland, 1979.

456. Vanhoutte PM: Adrenergic neuroeffector interaction in the blood vessel wall. Fed Proc 37:181, 1978.

457. Standaert F: Donuts and holes: Molecules and muscle relaxants. In Katz R (ed): Muscle Relaxants: Basic and Clinical Aspects. Orlando, Fla, Grune & Stratton, 1984.

Chapter 15 - Respiratory Physiology and Respiratory Function During Anesthesia

Jonathan L. Benumof

INTRODUCTION

Respiratory Physiology

Understanding normal respiratory physiology is a prerequisite to understanding mechanisms of impaired gas exchange during anesthesia and surgery. Toward this end, the normal (gravity-determined) distribution of perfusion and ventilation, the major nongravitational determinants of resistance to perfusion and ventilation, the transport of the respiratory gases, and the pulmonary reflexes and special functions are presented first in this chapter. These processes and concepts are then discussed in relation to the general mechanisms of impaired gas exchange during anesthesia and surgery.

Normal (Gravity-Determined) Distribution of Perfusion, Ventilation, and the Ventilation/Perfusion Ratio

Distribution of Pulmonary Perfusion

Contraction of the right ventricle imparts kinetic energy to the blood in the main pulmonary artery. As the kinetic energy in the main pulmonary artery is dissipated in climbing a vertical hydrostatic gradient, the absolute pressure in the pulmonary artery (Ppa) decreases by 1 cm H_2O per centimeter of vertical distance up the lung (Fig. 15-1) (Figure Not Available) . At some height above the heart, Ppa becomes zero (atmospheric), and still higher in the lung, the Ppa becomes negative. [1] In this region, alveolar pressure (P_A) then exceeds Ppa and pulmonary venous pressure (Ppv), which is very negative at this vertical height. Because the pressure outside the vessels is greater than the pressure inside the vessels, the vessels in this region of the lung are collapsed, and there is no blood flow (zone 1, $P_A > Ppa > Ppv$). Because there is no blood flow, no gas exchange is possible, and the region functions as alveolar dead space, or "wasted" ventilation. Little or no zone 1 exists in the lung under normal conditions, [2] but the amount of zone 1 lung may be greatly increased if Ppa is reduced, as in oligemic shock, or if P_A is increased, as in positive-pressure ventilation.

Further down the lung, absolute Ppa becomes positive, and blood flow begins when Ppa exceeds P_A (zone 2, $Ppa > P_A > Ppv$). At this vertical level in the lung, P_A exceeds Ppv, and blood flow is determined by the mean Ppa - P_A difference rather than by the more conventional Ppa - Ppv difference (see later). [3] The zone 2 blood flow-alveolar pressure relationship has the same physical characteristics as a waterfall flowing over a dam. The height of the upstream river (before reaching the dam) is equivalent to Ppa, and the

Figure 15-1 (Figure Not Available) Schematic diagram showing distribution of blood flow in the upright lung. In zone 1, alveolar pressure (P_A) exceeds pulmonary artery pressure (Ppa), and no flow occurs because the intra-alveolar vessels are collapsed by the compressing alveolar pressure. In zone 2, Ppa exceeds P_A, but P_A exceeds venous pressure (Ppv). Flow in zone 2 is determined by the Ppa-P_A difference (Ppa - P_A) and has been likened to an upstream river waterfall over a dam. Because Ppa increases down zone 2 and P_A remains constant, the perfusion pressure increases, and flow steadily increases down the zone. In zone 3, Ppv exceeds P_A, and flow is determined by the Ppa-P_A difference (Ppa - Ppv), which is constant down this portion of the lung. However, the transmural pressure across the wall of the vessel increases down this zone so that the caliber of the vessels increases (resistance decreases), and therefore flow increases. Finally, in zone 4 pulmonary interstitial pressure becomes positive and exceeds both Ppv and P_A. Consequently, flow in zone 4 is determined by the Ppainterstitial pressure difference (Ppa - P_{ISF}). *(Modified from West [14])*

height of the dam is equivalent to P_A. The rate of water flow over the dam is only proportional to the difference between the height of the upstream river and the dam (Ppa - P_A), and it does not matter how far below the dam the downstream river bed (Ppv) is. This phenomenon has various names, including the waterfall, Starling resistor, weir (dam made by beavers), and "sluice" effect. Because mean Ppa increases down this region of the lung but mean P_A is relatively constant, the mean driving pressure (Ppa - P_A) increases linearly, and therefore mean blood flow increases linearly. However, respiration and pulmonary blood flow are cyclic phenomena. Therefore, absolute instantaneous Ppa, Ppv, and P_A are changing continuously, and the relationships among Ppa, Ppv, and P_A are dynamically determined by the phase lags between the cardiac and respiratory cycles. Consequently, a given point in zone 2 may actually be in either a zone 1 or a zone 3 condition at a given moment, depending on whether the patient is in respiratory systole or diastole or in cardiac systole or diastole.

Still lower in the lung, there is a vertical level at which Ppv becomes positive and also exceeds P_A. In this region, blood flow is governed by the pulmonary arteriovenous pressure difference (Ppa - Ppv) (zone 3, $Ppa > Ppv > P_A$), for here both these vascular pressures exceed the P_A, and the capillary systems are thus permanently open and blood flow is continuous. In descending zone 3, gravity causes both absolute Ppa and Ppv to increase at the same rate, so that the perfusion pressure (Ppa - Ppv) is unchanged. However, the pressure outside the vessels, namely, pleural pressure (Ppl), increases less than Ppa and Ppv, so that the transmural distending pressures (Ppa - Ppl and Ppv - Ppl) increase down zone 3, the vessel radii increase, vascular resistance decreases, and blood flow therefore increases further.

Finally, whenever pulmonary vascular pressures are extremely high, as they are in a severely volume-overloaded patient, in a severely restricted and constricted pulmonary vascular bed, in an extremely dependent lung (far below the vertical level of the left atrium), and in patients with pulmonary embolism or mitral stenosis, fluid may transude out of the pulmonary vessels into the pulmonary interstitial compartment. In addition, pulmonary interstitial edema can be caused by extremely negative Ppl and perivascular hydrostatic pressure, such as may occur in a vigorously spontaneously breathing patient with an obstructed airway (upper airway masses [tumors, hematoma, abscess, edema], laryngospasm [most common], strangulation, infectious processes [epiglottitis, pharyngitis, croup], and vocal cord paralysis), by rapid reexpansion of lung, and by application of very negative Ppl during thoracentesis. [4] [5] Transuded pulmonary interstitial fluid may significantly alter the distribution of pulmonary blood flow.

When the flow of fluid into the interstitial space is excessive and cannot be cleared adequately by lymphatics, it accumulates in the interstitial connective tissue compartment around the large vessels and airways, forming peribronchial and periarteriolar edema fluid cuffs. The transuded pulmonary interstitial fluid fills the pulmonary interstitial space and may eliminate the normally present negative and radially expanding interstitial tension on the extra-alveolar pulmonary vessels. The expansion of the pulmonary interstitial space by fluid causes pulmonary interstitial pressure (P_{ISF}) to become positive and to exceed Ppv (zone 4, $Ppa > P_{ISF} > Ppv > P_A$). [6] [7] In addition, the vascular resistance of

extra-alveolar vessels may be increased at a very low lung volume (i.e., the residual volume), at which the tethering action of the pulmonary tissue on the vessels is also lost, causing P_{ISF} to increase positively (see lung volume discussion later). [8] [9] Consequently, zone 4 blood flow is governed by the arteriointerstitial pressure difference (Ppa - P_{ISF}), which is less than the Ppa - Ppv difference, and therefore zone 4 blood flow is less than zone 3 blood flow. In summary, zone 4 is a region of the lung from which a large amount of fluid has transuded into the pulmonary interstitial compartment or is possibly at a very low lung volume. Both these circumstances produce a positive interstitial pressure, causing extra-alveolar vessel compression, increased extra-alveolar vascular resistance, and decreased

regional blood flow.

It should be evident that as Ppa and Ppv increase, three important changes take place in the pulmonary circulation, namely, recruitment or opening of previously unperfused vessels, distention or widening of previously perfused vessels, and transudation of fluid from very distended vessels. [10] [11] Thus, as mean Ppa increases, zone 1 arteries may become zone 2 arteries, and as mean Ppv increases, zone 2 veins may become zone 3 veins. The increase in both mean Ppa and Ppv distends zone 3 vessels according to their compliance and decreases the resistance to flow through them. Zone 3 vessels may become so distended that they leak fluid and become converted to zone 4 vessels. In general, recruitment is the principal change as Ppa and Ppv increase from low to moderate levels; distention is the principal change as Ppa and Ppv increase from moderate to high levels; and finally, transudation is the principal change when Ppa and Ppv increase from high to very high levels.

Distribution of Ventilation

Gravity also causes vertical Ppl differences that, in turn, cause regional alveolar volume, compliance, and ventilation differences. The vertical gradient of Ppl can be best understood by imagining the lung as a plastic bag filled with semifluid contents; in other words, it is a viscoelastic structure. Without the presence of a supporting chest wall, the effect of gravity on the contents of the bag would cause the bag to bulge outward at the bottom and inward at the top (it would assume a globular shape). With the lung inside the supporting chest wall, the lung cannot assume a globular shape. However, gravity still exerts a force on the lung to assume a globular shape; the force creates a relatively more negative pressure at the top of the pleural space (where the lung pulls away from the chest wall) and a relatively more positive pressure at the bottom of the lung (where the lung is compressed against the chest wall) (Fig. 15-2) . The magnitude of this pressure gradient is determined by the density of the lung. Because the lung has about one-fourth of the density of water, the gradient of Ppl (in cm H_2O) is about one-fourth the height of the upright lung (30 cm). Thus, Ppl increases positively by 30/4 = 7.5 cm H_2O from the top to the bottom of the lung. [12]

Because P_A is the same throughout the lung, the Ppl gradient causes regional differences in transpulmonary distending pressures (P_A - Ppl). Because Ppl is most positive (least negative) in the dependent basilar lung regions, alveoli in these regions are more compressed and therefore are considerably

Figure 15-2 Schematic diagram of the lung within the chest wall, showing the tendency of the lung to assume a globular shape owing to the lung's viscoelastic nature. The tendency of the top of the lung to collapse inward creates a relatively negative pressure at the apex of the lung, and the tendency of the bottom of the lung to spread outward creates a relatively positive pressure at the base of the lung. Thus, pleural pressure increases by 0.25 cm H_2O per centimeter of lung dependency.

smaller than superior, relatively noncompressed apical alveoli (there is an approximately fourfold volume difference). [13] If the regional differences in alveolar volume are translated to a pressure-volume curve for normal lung (Fig. 15-3) , the dependent small alveoli are on the midportion and the nondependent large alveoli are on the upper portion of the S-shaped pressure-volume curve. Because the different regional slopes of the composite curve are equal to the different regional lung compliances, dependent alveoli are relatively compliant (steep slope), and nondependent alveoli are relatively noncompliant (flat slope). Thus, most of the tidal volume (V_T) is preferentially distributed to dependent alveoli, because they expand more per unit pressure change than do nondependent alveoli.

Distribution of the Ventilation/Perfusion Ratio

Both blood flow and ventilation (both on the left-hand vertical axis of Fig. 15-4) (Figure Not Available) increase linearly with distance down the normal upright lung (horizontal axis, reverse polarity). [14] Because blood flow increases from a very low value and more rapidly than ventilation with distance down the lung, the ventilation/perfusion (V_A/Q) ratio (right-hand vertical axis) decreases rapidly at first and then more slowly.

The V_A/Q ratio best expresses the amount of ventilation relative to perfusion in any given lung region. Thus, alveoli at the base of the lung are overperfused in relation to their ventilation ($V_A/Q < 1$). Figure 15-5 (Figure Not Available) shows the calculated ventilation (V_A) and blood flow (Q) in liters per minute, the V_A/Q ratio, and the alveolar partial pressure of oxygen (P_{AO_2}) and partial pressure of carbon dioxide (P_{ACO_2}) in mm Hg for horizontal slices from the top (7% of lung volume), middle (11% of lung volume), and bottom (13% of lung volume) of the

Figure 15-3 Pleural pressure increases by 0.25 cm H_2O every centimeter down the lung. The increase in pleural pressure causes a fourfold decrease in alveolar volume. The caliber of the air passages also decreases as lung volume decreases. When regional alveolar volume is translated over to a regional transpulmonary pressure-alveolar volume curve, small alveoli are on a steep (large slope) portion of the curve, and large alveoli are on a flat (small slope) portion of the curve. Because the regional slope equals regional compliance, the dependent small alveoli normally receive the largest share of the tidal volume. Over the normal tidal volume range (lung volume increases by 500 mL from 2,500 mL [normal functional residual capacity] to 3,000 mL), the pressure-volume relationship is linear. Lung volume values in this diagram relate to the upright position.

Figure 15-4 (Figure Not Available) Distribution of ventilation and blood flow (left-hand vertical axis) and the ventilation/perfusion ratio (V_A/Q, right-hand vertical axis) in normal upright lung. Both blood flow and ventilation are expressed in liters per minute per percentage of alveolar volume and have been drawn as smoothed-out linear functions of vertical height. The closed circles mark the /V_A/Q ratios of horizontal lung slices (three of which are shown in Fig. 15-5) (Figure Not Available) . A cardiac output of 6 L/min and a total minute ventilation of 5.1 L/min was assumed. *(Modified from West [14])*

Figure 15-5 (Figure Not Available) The ventilation/perfusion ratio (V_A/Q) and the regional composition of alveolar gas. Values for the regional flow (Q), ventilation (V_A), P_{O_2} , and P_{CO_2} were derived from Figure 15-4 (Figure Not Available) . P_{N_2} was obtained by what remains from the total gas pressure (which, including water vapor, equals 760 mm Hg). The volumes [Vol. (%)] of the three lung slices are also shown. Compared with the top of the lung, the bottom of the lung has a low V_A/Q and is relatively hypoxic and hypercarbic. *(From West [15])*

lung. [15] The P_{AO_2} increases by more than 40 mm Hg from 89 mm Hg at the base to 132 mm Hg at the apex, whereas P_{CO_2} decreases by 14 mm Hg from 42 mm Hg at the bottom to 28 mm Hg at the top. Thus, in keeping with the regional V_A/Q , the bottom of the lung is relatively hypoxic and hypercarbic as compared with the top of the lung.

V_A/Q inequalities have different effects on arterial P_{CO_2} (Pa_{CO_2}) as compared with arterial P_{O_2} (Pa_{O_2}). Blood passing through underventilated alveoli tends to retain its CO_2 and does not take up enough O_2 ; blood traversing overventilated alveoli gives off an excessive amount of CO_2 but cannot take up a proportionately increased amount of O_2 , owing to the flatness of the oxyhemoglobin (oxy-Hb) dissociation curve in this region (see Fig. 15-25) . Hence, a lung with uneven V_A/V relationships can eliminate CO_2 from the overventilated alveoli to compensate for the underventilated alveoli. Thus, with uneven V_A/Q relationships, P_{ACO_2} to Pa_{CO_2} gradients are small, and P_{AO_2} to Pa_{O_2} gradients are usually large.

In 1974, Wagner and colleagues [16] described a method of determining the continuous distribution of V_A/Q ratios within the lung based on the pattern of elimination of a series of intravenously infused inert gases. Gases of differing solubility are dissolved in physiologic saline solution and infused into a peripheral vein until a steady state is achieved (20 minutes). Toward the end of the infusion period, samples of arterial and mixed expired gas are collected, and total ventilation and cardiac output (Q_T) are measured. For each gas, the ratio of arterial to mixed venous concentration (retention) and the ratio of expired to mixed venous concentration (excretion) are calculated, and retention-solubility and excretion-solubility curves are drawn. The retention- and excretion-solubility curves can be regarded as fingerprints of the particular distribution of V_A/Q ratios that give rise to them.

Figure 15-6 (Figure Not Available) shows the type of distributions found in young, healthy subjects breathing air in the semirecumbent position. [17] The distributions of both ventilation and blood flow are relatively narrow. The upper and lower 95 percent limits shown (vertical interrupted lines) correspond to V_A/Q ratios of 0.3 and 2.1, respectively. Note that these young, healthy subjects had no blood flow perfusing areas with very low V_A/Q ratios, nor did they have any blood flow to unventilated or shunted areas ($V_A/Q = 0$) or unperfused areas ($V_A/Q =$

). Figure 15-6 (Figure Not Available) also shows P_{AO_2} and P_{ACO_2} in respiratory units having different V_A/Q ratios. Within the 95 percent range of V_A/Q ratios (0.3-2.1), the P_{O_2} ranges from 60 to 123 mm Hg, whereas the corresponding P_{CO_2} range is 44 to 33 mm Hg.

Other (Nongravitational) Important Determinants of Pulmonary Vascular Resistance and Blood Flow Distribution

Cardiac Output

As Q_T increases, pulmonary vascular pressures increase [18] (Fig. 15-7) (Figure Not Available) . Because the pulmonary vasculature is distensible, an increase in Ppa increases the radius of the pulmonary vessels, causing pulmonary vascular resistance to decrease. Exactly the opposite effect applies to the passive effect of a

Figure 15-6 (Figure Not Available) (A) The average distribution of ventilation/perfusion ratios (V_A/Q) in young semirecumbent normal subjects. The 95 percent range covers V_A/Q from 0.3 to 2.1 (between dashed lines). (B) The corresponding variations of P_{O_2} and P_{CO_2} in the alveolar gas. *(From West [17])*

decrease in Q_T on the pulmonary circulation. As Q_T decreases, pulmonary vascular pressures decrease. The decrease in pulmonary vascular pressure reduces the radii of the pulmonary vessels, causing pulmonary vascular resistance to increase.

Understanding the relationship among Ppa, pulmonary vascular resistance, and Q_T during passive events is a prerequisite to recognition of active vasomotion in the pulmonary circulation. Active vasoconstriction occurs whenever Q_T decreases, and Ppa either remains constant or increases. Increased Ppa and pulmonary vascular resistance have been found to be "a universal feature of acute respiratory failure." [19] Active pulmonary vasoconstriction can increase Ppa and Ppv, thereby contributing to the formation of pulmonary edema, and in that way has a role in the genesis of the adult respiratory distress syndrome (ARDS). Active vasodilation occurs any time Q_T increases and Ppa either remains constant or decreases. When deliberate hypotension is achieved with sodium nitroprusside, Q_T often remains constant or increases, but Ppa decreases and, therefore, so does pulmonary vascular resistance.

Alveolar Hypoxia

Alveolar or environmental hypoxia of *in vivo* and *in vitro* whole lung, unilateral lung, lobe, or lobule of lung causes localized

Figure 15-7 (Figure Not Available) Passive changes in pulmonary vascular resistance (PVR) as a function of pulmonary artery pressure (Ppa) and pulmonary blood flow (Q_T) (PVR = Ppa/Q_T). As Q_T increases, Ppa also increases, but to a lesser extent, so that PVR decreases. As Q_T decreases, Ppa also decreases, but to a lesser extent, so that PVR increases. *(Modified from Fishman [18])*

pulmonary vasoconstriction. This phenomenon is called hypoxic pulmonary vasoconstriction (HPV) and is present in all mammalian species.

The HPV response occurs primarily in the pulmonary arterioles of about 200-mum diameter. These vessels are advantageously situated anatomically in close relation to the small bronchioles and alveoli, which permits rapid and direct detection of alveolar hypoxia. Indeed, blood may actually become oxygenated in small pulmonary arteries, owing to the ability of oxygen to diffuse directly across the small distance between the contiguous air spaces and vessels. [20] This direct access that gas in the airways has to small arteries makes possible a rapid and localized vascular response to changes in gas composition.

The oxygen tension at the HPV stimulus site (Ps_{O_2}) is a function of both P_{AO_2} and mixed venous O_2 pressure (Pv_{O_2}). [21] The Ps_{O_2} - HPV response is sigmoid, with a 50 percent response when P_{AO_2}, Pv_{O_2}, and Ps_{O_2} are approximately 30 mm Hg. Usually, P_{AO_2} has a much greater effect than Pv_{O_2}, because O_2 uptake is from the alveolar space to the blood in the small pulmonary arteries. [21] However, in those regions of the lung that are atelectatic, the only stimulus for HPV is Pv_{O_2}.

There are two major theories how alveolar hypoxia may cause pulmonary vasoconstriction. [22] [23] [24] [25] [26] First, alveolar hypoxia may cause the release of vasoconstrictor substances into the pulmonary interstitial compartment, where the substances may then cause vasoconstriction. Over the past years, many vasoactive substances have been proposed as the mediators of HPV (e.g., leukotrienes, prostaglandins, catecholamines, serotonin, histamine, angiotensin, and bradykinin), but none has been proved to be involved primarily in the process. In 1992, nitric oxide (endothelialderived relaxing factor) was proposed to have a pivotal role in modulating pulmonary vascular resistance. [27]

Although the precise mediator of HPV is not known, it is certain that the prostaglandin products of arachidonic acid metabolism can inhibit the HPV response, and it is possible that the leukotriene products of arachidonic acid metabolism mediate, or are at least required for, the HPV response. The general scheme of arachidonic acid metabolism is shown in Figure 15-8 . On an appropriate stimulus, such as alveolar hypoxia, phospholipase A_2 converts the phospholipid in the cell membrane (possibly in all 40 lung cell types) [28] to arachidonic acid. The released arachidonic acid can be metabolized in two ways. First, the enzyme cyclooxygenase can convert arachidonic acid to prostaglandins; the major prostaglandin is prostaglandin I_2 (prostacyclin). [29] [30] Prostacyclin is a potent pulmonary vasodilator, which can abolish HPV. [29] [30] The cyclooxygenase pathway can also produce thromboxane; this product is not shown in Figure 15-8 because it is thought not to be important with regard to HPV. [31] [32] Second, the enzyme lipoxygenase can convert arachidonic acid to leukotrienes. All the leukotrienes are potent pulmonary vasoconstrictors and can enhance HPV; indeed, the leukotrienes have received considerable attention as the mediator of HPV. [32] The amount of pulmonary vasoconstriction caused by hypoxia is regulated by a balance between leukotriene agonist and prostaglandin antagonist effects.

There are many experimental data that support and are consistent with the foregoing relationship between the products of arachidonic acid metabolism and HPV (see Fig. 15-8) . Blockage of cyclooxygenase with acetylsalicylic acid, [30] [33] [34] [35] indomethacin, [33] [34] [35] [36] meclofenamate, [37] [38] or ibuprofen [39] [40] results in increased HPV (predominance of leukotrienes). Infusion of prostaglandins [41] [42] and prostacyclin [40] during regional HPV and prostacyclin during regional pneumonia [33] [36] [43] [44] decreases HPV (predominance of prostaglandins). Blockage of lipoxygenase results in decreased HPV (predominance of prostaglandins). [45] [46] [47] Blockage of leukotriene receptors with FPL 55713 causes decreased HPV (predominance of prostaglandins). [30] [48] [49] If both the cyclooxygenase-prostaglandin and the lipoxygenase-leukotriene systems are inhibited (as with BW755C), but the cyclooxygenase-prostaglandin system is inhibited to a greater extent (resulting in predominance of leukotrienes), HPV is increased. [50] If cyclooxygenase is already blocked by ibuprofen, addition of BW755C relatively selectively blocks lipoxygenase (relative increase in the cyclooxygenase-prostaglandin system), and

Figure 15-8 The leukotriene products of arachidonic acid metabolism can increase hypoxic pulmonary vasoconstriction (HPV), and the prostaglandin products of arachidonic acid metabolism can decrease HPV. The amount of HPV is determined by a balance between these agonist and antagonist effects of the leukotrienes and prostaglandins, respectively.

HPV is relatively decreased. [39] Thus, maneuvers that promote the use of the cyclooxygenase-prostaglandin pathway decrease HPV, and maneuvers that promote the use of the lipoxygenase-leukotriene pathway increase HPV. Although most studies support the cyclooxygenase-prostaglandin-decreased HPV and lipoxygenase-leukotriene-increased HPV theory, a few studies do not. [51] [52] [53] [54] [55]

Second and/or alternatively, hypoxia also appears to stimulate metabolic activity of pulmonary vascular smooth muscle directly and to accelerate production of adenosine triphosphate (ATP), whereas in systemic vascular beds, the action of hypoxia on metabolism is depressant. Low O_2 tension also maintains the membrane of pulmonary vascular smooth muscle cells in a state of partial depolarization and influences the role of calcium in excitation-contraction coupling. [26] Thus, alveolar hypoxia may directly cause ion fluxes, which cause or contribute to the vasoconstriction. In this way, elements of the vascular wall could serve both as a sensor and as an effector of vasoconstriction. [32] In summary, HPV may be due to either a direct action of alveolar hypoxia on pulmonary vasculature or an alveolar hypoxia-induced release of vasoactive substances. These two mechanisms for the production of HPV are not necessarily mutually exclusive.

There are three ways in which HPV operates in humans. First, life at high altitude or whole-lung respiration of a low inspired concentration of O_2 (F_{IO_2}) increases

Ppa. This is true for newcomers to high altitude, for the acclimatized, and for natives. [26] The vasoconstriction is considerable, and in healthy people breathing 10 percent O_2, Ppa doubles, whereas pulmonary wedge pressure remains constant. [56] The increased Ppa increases perfusion of the apices of the lung (recruitment of previously unused vessels) and results in gas exchange in a region of lung not normally utilized (i.e., zone 1). Thus, with a low F_{IO_2}, the Pa_{O_2} is greater and the alveolar-arterial O_2 tension difference and V_T/V_T ratio are less than would be expected or predicted on the basis of a normal (sea level) distribution of ventilation and blood flow. High-altitude pulmonary hypertension is an important component in the development of mountain sickness subacutely (hours to days) and cor pulmonale chronically (weeks). [57] In fact, there is now good evidence that in patients with chronic obstructive pulmonary disease, even nocturnal episodes of arterial O_2 desaturation (caused by episodic hypoventilation) are accompanied by elevations in Ppa and may account for or lead to sustained pulmonary hypertension and cor pulmonale. [58] Second, hypoventilation (low V_A/Q), atelectasis, or nitrogen ventilation of any region of the lung (one lung, lobe, lobule) generally causes a diversion of blood flow away from the hypoxic to the nonhypoxic lung (40-50%, 50-60%, 60-70%, respectively) [59] [60] (Fig. 15-9) . The regional vasoconstriction and blood flow diversion are of great importance in minimizing transpulmonary shunt and in normalizing regional V_A/Q ratios during disease of one lung, one-lung anesthesia (Ch. 48) , and inadvertent intubation of a main stem bronchus. Third, in patients who have chronic obstructive pulmonary disease, asthma, pneumonia, or mitral stenosis but not bronchospasm, administration of pulmonary vasodilator drugs such as isoproterenol, sodium nitroprusside, and nitroglycerin causes a decrease in Pa_{O_2} and pulmonary vascular resistance and an increase in right-to-left transpulmonary shunt. [61] The mechanism for

Figure 15-9 Schematic drawing of regional hypoxic pulmonary vasoconstriction (HPV); one-lung ventilation is a common clinical example of regional HPV. HPV in the hypoxic atelectatic lung causes a redistribution of blood flow away from the hypoxic lung to the normoxic lung, thereby diminishing the amount of shunt flow (Q_S/Q_T) that can occur through the hypoxic lung. Inhibition of hypoxic lung HPV causes an increase in the amount of shunt flow through the hypoxic lung, thereby decreasing Pa_{O_2}.

these changes is thought to be deleterious inhibition of preexisting and, in some of the lesions, geographically widespread HPV without a concomitant and beneficial bronchodilation. [61] In accordance with the latter two lines of evidence (one-lung or regional hypoxia and vasodilator drug effects on whole-lung or generalized disease), HPV is thought to divert blood flow away from hypoxic regions of the lung, thereby serving as an autoregulatory mechanism that protects Pa_{O_2} by favorably adjusting regional V_A/Q ratios. Factors that inhibit regional HPV are extensively discussed elsewhere. [62]

Lung Volume

The functional residual capacity (FRC) is the volume of lung that exists at the end of a normal exhalation after a normal V_T and when there is no muscle activity or pressure difference between alveoli and atmosphere. Total pulmonary vascular resistance is increased when lung volume is either increased or decreased from FRC (Fig. 15-10) . [63] [64] [65] The increase in total pulmonary vascular resistance above FRC is due to alveolar compression of small intra-alveolar vessels, which results in an increase in small vessel pulmonary vascular resistance (i.e., creation of zone 1 or zone 2). [66] As a relatively small mitigating or counterbalancing effect to the small vessel compression, the large extra-alveolar vessels may be expanded by the increased negativity of the perivascular pressure at high FRC. The increase in total pulmonary vascular resistance below FRC is due to an increase in pulmonary vascular resistance of large extraalveolar vessels. The increase in large vessel pulmonary vascular resistance was previously thought to be due to a mechanical tortuosity or kinking of these vessels. However, small or grossly atelectatic lungs are hypoxic, and it has been shown that the

Figure 15-10 An asymmetric U-shaped curve relates total pulmonary vascular resistance to lung volume. The trough of the curve occurs when lung volume equals functional residual capacity (FRC). Total pulmonary resistance is the sum of resistance in small vessels (increased by increasing lung volume) and the resistance in large vessels (increased by decreasing lung volume). The end point for increasing lung volume (toward total lung capacity [TLC]) is the creation of zone 1 conditions, and the end point for decreasing lung volume (toward residual volume [RV]) is the creation of low ventilation/perfusion (V_A/Q) and atelectatic (atel) areas that have hypoxic pulmonary vasoconstriction (HPV). The curve represents a composite of data from Benumof, [62] Simmons et al, [63] and Burton and Patel. [64]

mechanism of increased large-vessel pulmonary vascular resistance in these lungs is due entirely to HPV. [67] This conclusion has been found to be true whether the chest is open or closed and whether ventilation is by positive pressure or is spontaneous. [68]

Alternate (Nonalveolar) Pathways of Blood Flow Through the Lung

There are several possible pathways for blood to travel from the right side of the heart to the left side of the heart without being fully oxygenated or oxygenated at all. Blood flow through poorly ventilated alveoli (low V_A/Q regions at F_{IO_2} <0.3 have a right-to-left shunt effect on oxygenation) and blood flow through nonventilated alveoli (atelectatic or consolidated regions;V_A/Q = 0 at all F_{O_2}) are sources of right-to-left shunt. Low V_A/Q and atelectatic lung units occur in conditions in which the FRC is less than the closing capacity of the lung (see the section *Lung Volumes, Functional Residual Capacity, and Closing Capacity*).

There are several right-to-left blood flow pathways through the lungs and heart that do not pass by or involve alveoli at all. The bronchial and pleural circulations originate from systemic arteries and empty into the left side of the heart without being oxygenated, constituting the 1 to 3 percent true right-to-left shunt normally present. With chronic bronchitis, the bronchial circulation may carry 10 percent of the cardiac output, and with pleuritis, the pleural circulation may carry 5 percent of the cardiac output. Consequently, there may be as much as a 10 percent and a 5 percent obligatory right-to-left shunt present, respectively, under these conditions. Intrapulmonary arteriovenous anastomoses are normally closed, but in the face of acute pulmonary hypertension, such as may be caused by a pulmonary embolus, they may open and may cause a direct increase in right-to-left shunt. The foramen ovale is patent in 20 to 30 percent of individuals, but it normally remains functionally closed because left atrial pressure exceeds right atrial pressure. However, any condition that causes right atrial pressure to be greater than left atrial pressure may produce a right-to-left shunt, with resultant hypoxemia and possible paradoxic embolization. Such conditions include the use of high levels of positive end-expiratory pressure (PEEP), pulmonary embolization, pulmonary hypertension, chronic obstructive pulmonary disease, pulmonary valvular stenosis, congestive heart failure, and postpneumonectomy states. [69] Indeed, even such common events as mechanical ventilation [70] and breath-holding and reaction to the presence of an endotracheal tube during the excitement phase of emergence from anesthesia [71] [72] have caused right-to-left shunting across a patent foramen ovale and severe arterial desaturation (with the potential for paradoxic embolization). [72] Esophageal to mediastinal to bronchial to pulmonary vein pathways have been described and may explain in part the hypoxemia associated with portal hypertension and cirrhosis. There are no known conditions that selectively increase thebesian channel blood flow (thebesian vessels nourish the left portion of the myocardium and originate and empty into the left side of the heart.)

Other (Nongravitational) Important Determinants of Pulmonary Compliance, Resistance, Lung Volume, and Ventilation

Pulmonary Compliance

For air to flow into the lungs, a pressure gradient (DeltaP) must be developed to overcome the elastic resistance of the lungs and chest wall to expansion. These structures are arranged concentrically, and their elastic resistances are therefore additive. The relationship between the DeltaP and the resultant volume increase (DeltaV) of the lungs and thorax is independent of time and is known as total compliance (C_T), as expressed in the following equation:

The C_T of lung plus chest wall is related to the individual compliances of lungs (C_L) and chest wall (C_{CW}) according to the following expression:

Normally, C_L and C_{CW} each equal 0.2 L/cm H_2O; thus, C_T = 0.1 L/cm H_2O. To determine C_L, DeltaV and the *transpulmonary pressure gradient* (P_A - Ppl, the DeltaP for the lung) must be known; to determine C_{CW}, DeltaV and the *transmural pressure gradient* (Ppl - Pambient, the DeltaP for the chest wall) must be known; to determine C_T, DeltaV and the *transthoracic pressure gradient* (P_A - Pambient, the DeltaP for the lung and chest wall together) must be known. In clinical practice, only C_T is measured, which can be done dynamically or statically, depending on whether a peak or plateau inspiratory DeltaP (respectively) is used for the C_T calculation.

During a positive or negative pressure inspiration of sufficient duration, the transthoracic DeltaP first increases to a peak value and then decreases to a lower plateau value. The peak transthoracic pressure value is due to pressure required to overcome both elastic and airway resistance (see the section *Airway Resistance*). The transthoracic pressure decreases to a plateau value following the peak value, because with time, gas redistributes from stiff alveoli (which expand only slightly and therefore have only a short inspiratory period) into more compliant alveoli (which expand a great deal and therefore have a long inspiratory period). Because the gas redistributes into more compliant alveoli, less pressure is required to contain the same amount of gas, and this explains why the pressure decreases. In practical terms, dynamic compliance is the volume change divided by the peak inspiratory transthoracic pressure, and static compliance is the volume change divided by the plateau inspiratory transthoracic pressure. Therefore, static C_T is usually greater than dynamic C_T, because the former calculation uses a smaller denominator (lower pressure) than the latter. However, if the patient is receiving PEEP, this must be first subtracted from the peak or plateau pressure before calculating thoracic compliance (i.e., compliance = volume delivered/ peak or plateau pressure - PEEP).

The P_A deserves special comment. The alveoli are lined with a layer of liquid. The lining of a curved surface (sphere or cylinder, as are the alveoli, bronchioles, and bronchi) with liquid creates a surface tension that tends to make the surface area that is exposed to the atmosphere as small as possible. Simply stated, water molecules crowd much closer together on the surface of a curved layer of water than elsewhere in the fluid. As lung or alveolus size decreases, the degree of curvature and the retractive surface tension increase.

According to the Laplace equation, the pressure in an alveolus (P, in dynes per square centimeter) is higher than ambient pressure by an amount depending on the surface tension of the lining liquid (T, in dynes per centimeter) and the radius of curvature of the alveolus (R, in centimeters). This is expressed in the following equation:

Although surface tension contributes to the elastic resistance and retractive forces of the lung, two difficulties must be resolved. First, the pressure inside small alveoli should be higher than that inside large alveoli, a conclusion that stems directly from the Laplace equation (R in the denominator). From this reasoning, one would expect a progressive discharge of each small alveolus into a larger one, until eventually only one gigantic alveolus would be left (Fig. 15-11 A). The second problem concerns the relationship between lung volume and the transpulmonary DeltaP (P_A - Ppl). Theoretically, the retractive forces of the lung should increase as the lung volume decreases. If this were true, lung volume should decrease in a vicious circle, with the tendency to collapse

Figure 15-11 Relationship among surface tension (T), alveolar radius (R), and alveolar transmural pressure (P). (A) The pressure relationship in two alveoli of different size but with the same surface tension in their lining fluids. The direction of gas flow is from the higher-pressure small alveolus to the lower-pressure large alveolus, and the result is one large alveolus (Rfinal = SigmaRinitial). (B) The pressure relationships of two alveoli of different size when allowance is made for the expected changes in surface tension (less tension in smaller alveolus). The direction of gas flow is from the larger alveolus to the smaller alveolus until the two alveoli are of equal size and are volume stable (R_K). SigmaR, sum of all individual radii; K, constant.

increasing progressively as the lung volume diminished.

These two problems are resolved by the fact that the surface tension of the fluid lining the alveoli is variable and decreases as its surface area is reduced. The surface tension of alveolar fluid can reach levels that are well below the normal range for body fluids such as water and plasma. When an alveolus decreases in size, the surface tension of the lining fluid falls to an extent greater than the corresponding reduction of radius, so that the transmural pressure gradient (= 2T/R) diminishes. This explains why small alveoli do not discharge their contents into large alveoli (Fig. 15-11 B) and why the elastic recoil of small alveoli is less than that of large alveoli.

The substance responsible for the reduction (and variability) of alveolar surface tension is secreted by the intraalveolar type II pneumocyte and is a lipoprotein called *surfactant,* which floats as a 50-A-thick film on the surface of the fluid lining the alveoli. When the surface film is reduced in area and the concentration of surfactant at the surface is increased, there is an increased surface-reducing pressure, which counteracts the surface tension of the fluid lining the alveoli.

Airway Resistance

For air to flow into the lungs, a DeltaP must also be developed to overcome the nonelastic airway resistance of the lungs to airflow. The relationship between the DeltaP and the rate of airflow (V) is known as airway resistance (R):

The DeltaP along the airway depends on the caliber of the airway and the rate and pattern of airflow. There are three main patterns of airflow. Laminar flow occurs when the gas passes down parallel-sided tubes at less than a certain critical velocity. With laminar flow, the pressure drop down the tube is proportional to the flow rate and may be calculated from the equation derived by Poiseuille: $P = V \times 8L \times mu/pir^4 \times 980$, where P = pressure drop (in cm H_2O), V = volume flow rate (in mL/s), L = length of tube (in cm), r = radius of tube (in cm), and mu = viscosity (in poises).

When flow exceeds the critical velocity, it becomes turbulent. The significant feature of turbulent flow is that the pressure drop along the airway is no longer directly proportional to flow rate but is proportional to the square of flow rate according to the equation $P = V^2 pfL/4pi^2 r^5$, where p is a gas or fluid density term and f is a friction factor that depends on the roughness of the tube wall. [73] Thus, with increases in turbulent flow (and/or orifice flow; see the next paragraph), P increases much more than V, and therefore R increases, as shown in equation 4.

Orifice flow occurs at severe constrictions such as a nearly closed larynx. In these situations, the pressure drop is also proportional to the square of the flow rate, but density replaces viscosity as the important factor in the numerator. This explains why a low-density gas such as helium diminishes the resistance to flow (by threefold as compared with air) in severe obstruction of the upper airway.

Because the total cross-sectional area of the airways increases as branching occurs, the velocity of airflow decreases; laminar flow is therefore chiefly confined to the airways below the main bronchi. Orifice flow occurs at the larynx, and flow in the trachea is turbulent during most of the respiratory cycle. Viewing the components that constitute each of the preceding airway pressure equations, one can see that many factors obviously may affect the pressure drop down the airways during respiration. However, variations in diameter of the smaller bronchi and bronchioles are particularly critical (bronchoconstriction may convert laminar flow to turbulent

flow), and the pressure drop along the airways may become much more closely related to flow rate.

Different Regional Lung Time Constants

So far, the compliance and airway resistance properties of the chest have been discussed separately. In the following analysis, the pressure at the mouth is assumed to increase suddenly to a fixed positive value [74] (Fig. 15-12) (Figure Not Available) that overcomes both elastic and airway resistance and to be maintained at this value during inflation of the lungs. The DeltaP required to overcome nonelastic airway resistance is the difference between the fixed mouth pressure and the instantaneous height of the dashed line in Figure 15-12 (Figure Not Available) and is proportional to the flow rate during most of the respiratory cycle. Thus, the DeltaP required to overcome nonelastic airway resistance is maximal initially but then decreases exponentially (Fig. 15-12 (Figure Not Available) A), hatched lines). The rate of filling therefore also declines in an approximately exponential manner. The remainder of the pressure gradient overcomes the elastic resistance (the instantaneous height of the dashed line in Fig. 15-12 (Figure Not Available) A) and is proportional to the change in lung volume. Thus, the DeltaP required to overcome elastic resistance is minimal initially but then increases exponentially, as does lung volume. Alveolar filling ceases (lung volume remains constant) when the pressure resulting from the retractive elastic forces balances the applied (mouth) pressure (see Fig. 15-12 (Figure Not Available) A, dashed line).

Because there is only a finite time available for alveolar filling and because alveolar filling occurs in an exponential manner, the degree of filling obviously depends on the duration of the inspiration. The rapidity of change in an exponential curve can be described by its time constant tau, which is the time required to complete 63 percent of an exponentially changing function if the total time allowed for the function change is unlimited (2tau = 87%, 3tau = 95%, and 4tau = 98%). For lung inflation, tau = $C_T \times R$; normally, C_T = 0.1 L/cm H_2O, R = 2.0 cm H_2O/L/s, tau = 0.2 second, and 3tau = 0.6 second.

When this equation is applied to individual alveolar units, the time taken to fill such a unit clearly increases as airway resistance increases. The time to fill an alveolar unit also increases as compliance increases, because a greater volume of air will be transferred into a more compliant alveolus before

Figure 15-12 (Figure Not Available) (A-C) Artificial ventilation by intermittent application of a constant pressure (square wave). Expiration is passive. The pressure required to overcome airway resistance (hatched lines, A) and airflow rate (V of Equation 4, C), which are proportional to one another, decreases exponentially. The pressure required to overcome elastic resistance (height of dashed line, A) and lung volume (B), which are proportional to one another, increases exponentially. Values shown are typical for an anesthetized supine paralyzed patient: total dynamic compliance, 50 mL/cm H_2O; pulmonary resistance, 3 cm H_2O/L/s; apparatus resistance, 7 cm H_2O/L/s; total resistance, 10 cm H_2O/L/s; time constant, 0.5 second. *(From Nunn [74])*

the retractive force equals the applied pressure. The compliance of individual alveoli differs from top to bottom of the lung, and the resistance of individual airways varies widely depending on their length and caliber. Therefore, various time constants for inflation exist throughout the lung.

Pathways of Collateral Ventilation

Collateral ventilation is another nongravitational determinant of the distribution of ventilation. There are four known pathways of collateral ventilation. First, interalveolar communications (pores of Kohn) exist in most species; they may range from 8 to 50 per alveolus and may increase with age and with the development of obstructive lung disease. Their precise role has not been defined, but they probably function to prevent hypoxia in neighboring but obstructed lung units. Second, distal bronchiolar-to-alveolar communications are known to exist (channels of Lambert), but their function *in vivo* is speculative (may be similar to pores of Kohn). Third, respiratory bronchiole-to-terminal bronchiole connections have been found in adjacent lung segments (channels of Martin) in healthy dogs and in humans with lung disease. Fourth, there are interlobar connections; the functional characteristics of interlobar collateral ventilation through these connections have been described in dogs, [75] and they have been observed in humans as well. [76]

The Work of Breathing

The pressure-volume characteristics of the lung also determine the work of breathing.Because

and ventilatory work may be analyzed by plotting pressure against volume. [77] In the presence of increased airway resistance or decreased C_L, increased transpulmonary pressure is required to achieve a given V_T with consequent increase in the work of breathing. The metabolic cost of the work of breathing at rest constitutes only 1 to 3 percent of the total O_2 consumption in healthy subjects, but it is increased considerably (up to 50%) in patients with pulmonary disease.

Two different pressure-volume diagrams are shown in Figure 15-13. During normal inspiration (left graph), transpulmonary pressure increases from 0 to 5 cm H_2O while 500 mL of air is drawn into the lung. Potential energy is stored by the lung during inspiration and is expended during

Figure 15-13 Lung volume plotted against transpulmonary pressure in a pressure-volume diagram for an awake (healthy) and an anesthetized patient. The lung compliance of the awake patient (slope of line AB = 100 mL/cm H_2O) equals that shown for the small dependent alveoli in Figure 15-3. The lung compliance of the anesthetized patient (slope of line AB = 50 mL/cm H_2O) equals that shown for the medium midlung alveoli in Figure 15-3 . and for the anesthetized patient in Figure 15-12 (Figure Not Available) The total area within the oval and triangles has the dimensions of pressure multiplied by volume and represents the total work of breathing. The hatched area to the right of lines AB and AB represents active inspiratory work necessary to overcome resistance to airflow during inspiration (INSP). The hatched area to the left of the triangle AB C represents active expiratory work necessary to overcome resistance to airflow during expiration (EXP). Expiration is passive in the healthy subject because sufficient potential energy is stored during inspiration to produce expiratory airflow. The fraction of total inspiratory work necessary to overcome elastic resistance is shown by the triangles ABC and AB C. The anesthetized patient has a decreased compliance and increased elastic resistance work (triangle AB C) compared with the healthy patient's compliance and elastic resistance work (triangle ABC). The anesthetized patient shown in this figure has an increased airway resistance to both inspiratory and expiratory work.

expiration; as a consequence, the entire expiratory cycle is passive. The hatched area plus the triangular area ABC represents pressure multiplied by volume and is the work of breathing. Line AB is the lower section of the pressurevolume curve of Figure 15-13 . The triangular area ABC is the work required to overcome elastic forces (C_T), whereas the hatched area is the work required to overcome airflow or frictional resistances (R). The graph on the right applies to an anesthetized patient with diffuse obstructive airway disease resulting from the accumulation of mucous secretions. There is a marked increase in both the elastic (triangle AB C) and airway (hatched area) resistive components of respiratory work. During expiration, only 250 mL of air leaves the lungs during the passive phase when intrathoracic pressure reaches the equilibrium value of 0 cm H_2O. Active effort-producing work is required to force out the remaining 250 mL of air, and intrathoracic pressure actually becomes positive.

For a constant minute volume, the work done against elastic resistance is increased when breathing is deep and slow. On the other hand, the work done against airflow resistance is increased when breathing is rapid and shallow. If the two components are summated and the total work is plotted against respiratory frequency, there is an optimal respiratory frequency at which the total work of breathing is minimal [78] (Fig. 15-14) (Figure Not Available) . [79] In patients with diseased lungs in which elastic resistance is high (pulmonary fibrosis, pulmonary edema, infants), the optimum frequency is increased, and rapid, shallow breaths are favored. When airway resistance is high (asthma, obstructive lung disease), the optimum frequency is decreased, and slow, deep breaths are favored.

Figure 15-14 (Figure Not Available) The diagrams show the work done against elastic and airflow resistance separately and summated to indicate the total work of breathing at different respiratory frequencies. The total work of breathing has a minimum value at about 15 breaths/min under normal circumstances. For the same minute volume, minimum work is performed at higher frequencies with stiff (less compliant) lungs and at lower frequencies when the airflow resistance is increased. *(Modified from Nunn [75])*

Lung Volumes, Functional Residual Capacity, and Closing Capacity

Lung Volumes and Functional Residual Capacity

The FRC is defined as the volume of gas in the lung at the end of a normal expiration when there is no airflow and P_A equals the ambient pressure. Under these conditions, expansive chest wall elastic forces are exactly balanced by retractive lung tissue elastic forces [80] (Fig. 15-15) (Figure Not Available) .

The expiratory reserve volume is part of the FRC; it is that additional gas beyond the end-tidal volume that can be consciously exhaled, resulting in the minimum volume of lung possible, known as the residual volume. Thus, the FRC equals the residual volume plus the expiratory reserve volume (Fig. 15-16) . With regard to the other lung volumes shown in Figure 15-16 , V_T, vital capacity, inspiratory capacity, inspiratory reserve volume, and expiratory reserve volume can all be measured by simple spirometry. Total lung volume, FRC, and residual volume all contain a fraction (the residual volume) that cannot be measured by simple spirometry. However, if one of these three volumes is measured, the others can be easily derived because the other

Figure 15-15 (Figure Not Available) (A) The resting state of normal lungs when they are removed from the chest cavity; that is, elastic recoil causes total collapse. (B) The resting state of a normal chest wall and diaphragm when the thoracic apex is open to the atmosphere and the thoracic contents are removed. (C) The lung volume that exists at the end of expiration is the functional residual capacity (FRC). At FRC, the elastic forces of lung and chest walls are equal and in opposite directions. The pleural surfaces link these two opposing forces. *(Modified from Shapiro et al [80])*

lung volumes, which relate these three volumes to one another, can be measured by simple spirometry.

FRC can be measured by one of three techniques. The first method is to wash the nitrogen out of the lungs by several minutes of O_2 breathing and to measure the total quantity of nitrogen eliminated. Thus, if 2 L of nitrogen is eliminated and the initial alveolar nitrogen concentration was 80 percent, the initial volume of the lung was 2.5 L. The second method uses the washin of a tracer gas such as helium. If 50 mL of helium is introduced into the lungs and, after equilibration, the helium concentration is found to be 1 percent, the volume of the lung is 5 L. The third method uses Boyle's law (i.e., PV = K, where P = pressure, V = volume, and K = a constant). The subject is confined within a gas-tight box (plethysmograph), so that changes in the volume of the body may be readily determined as a change in pressure within the box. Disparity between FRC as measured in the body plethysmograph and by the helium method is often used as a way of detecting large, nonventilating air-trapped blebs. [81] Obviously, there are difficulties in applying the body plethysmograph to anesthetized patients.

Airway Closure and Closing Capacity

As discussed earlier in the section on the distribution of ventilation, Ppl increases from the top to the bottom of the lung and determines regional alveolar size, compliance, and ventilation. Of even greater importance to the anesthesiologist is the recognition that these gradients in Ppl may lead to airway closure and collapse of alveoli.

Airway Closure in Patients with Normal Lungs

Figure 15-17 (Figure Not Available) A illustrates the normal resting endexpiratory (FRC) position of the lung-chest wall combination. The distending transpulmonary and the intrathoracic air passage transmural DeltaP are 5 cm H_2O, and the airways remain patent. During the middle of a normal inspiration (Fig. 15-17, (Figure Not Available) B) there is an increase in the transmural DeltaP (to 6.8 cm H_2O), which encourages distention of intrathoracic air passages. During the middle of a normal expiration (Fig. 15-17 (Figure Not Available) C), expiration is passive; P_A is attributable only to the elastic recoil of the lung (2 cm H_2O), and there is a decrease (to 5.2 cm H_2O) but still a favorable (distending) intraluminal transmural DeltaP. During the middle of a severe forced expiration (Fig. 15-17 (Figure Not Available) D), Ppl increases far higher than atmospheric pressure and is communicated to the alveoli, which have a pressure that is higher still owing to the elastic recoil of the alveolar septa (an additional 2 cm H_2O). At high gas flow rates, the pressure drop down the air passage is increased, and there will be a point at which intraluminal pressure equals either surrounding parenchymal pressure or Ppl; that point is termed the *equal pressure point* (EPP). If the EPP occurs in small intrathoracic air passages (distal to the 11th generation, the airways have no cartilage and are called *bronchioles*), they may be held open at that particular point by the tethering effect of the elastic recoil of the immediately adjacent or surrounding lung parenchyma. If the

Figure 15-16 The dynamic lung volumes that can be measured by simple spirometry are the tidal volume, inspiratory reserve volume, expiratory reserve volume, inspiratory capacity, and vital capacity. The static lung volumes are the residual volume, functional residual capacity, and total lung capacity. The static lung volumes cannot be measured by observation of a spirometer trace and require separate methods of measurement.

EPP occurs in large extrathoracic air passages (proximal to the 11th generation, the airways have cartilage and are called *bronchi*), they may be held open at that particular point by their cartilage. Downstream of the EPP (in either small or large airways), the transmural DeltaP is reversed (-6 cm H_2O) and results in airway closure. Thus, the patency of airways distal to the 11th generation is a function of lung volume, and the patency of airways proximal to the 11th generation is a function of intrathoracic (pleural) pressure. In extrathoracic bronchi with cartilage, the posterior membranous sheath appears to give first by invaginating into the lumen. [82] If lung volume were abnormally decreased (for example, owing to splinting) and expiration were still forced, the caliber of the airways would be relatively reduced at all times, causing the EPP and point of collapse to move progressively from larger to smaller air passages (closer to the alveolus).

In patients with normal lungs, airway closure may still occur even if exhalation is not forced, provided residual volume is approached closely enough. Even in patients with normal lungs, as lung volume decreases toward residual volume during expiration, the small airways (0.5-0.9 mm in diameter) show a progressive tendency to close, whereas larger airways remain patent. [83] [84] Airway closure occurs first in the dependent lung regions (as directly observed by computed tomography [CT]), [85] because the distending transpulmonary pressure is less and the volume change during expiration is greater. The airway closure is most likely to occur in

Figure 15-17 (Figure Not Available) Pressure gradients across the airways. The airways consist of a thin-walled intrathoracic portion (near the alveoli) and a more rigid (cartilaginous) intrathoracic and extrathoracic portion. During expiration, the pressure due to elastic recoil is assumed to be +2 cm H_2O in normal lungs (A-D) and +1 cm H_2O in abnormal lungs (E and F). The total pressure inside the alveolus is pleural pressure plus the elastic recoil. The arrows indicate direction of airflow. EPP, equal pressure point. See text for explanation. *(Modified from Benumof [189])*

the dependent regions of the lung whether the patient is in the supine or lateral decubitus position, [85] and whether ventilation is spontaneous or positive-pressure ventilation. [86] [87]

Airway Closure in Patients with Abnormal Lungs

Airway closure occurs with milder active expiration, lower gas flow rates, and higher lung volumes and occurs closer to the alveolus in patients with emphysema, bronchitis, asthma, and pulmonary interstitial edema. In all four conditions, airway resistance is increased, causing a larger pressure decrease from the alveoli to the larger bronchi, thereby creating the potential for negative intrathoracic transmural DeltaP and narrowed and collapsed airways. In addition, the structural integrity of the conducting airways may be diminished owing to inflammation and scarring, and therefore these airways may close more readily for any given lung volume or transluminal DeltaP.

In emphysema, the elastic recoil of the lung is reduced (to 1 cm H_2O in Fig. 15-17 (Figure Not Available) E), the air passages are poorly supported by the lung

parenchyma, the point of airway resistance is close to the alveolus, and the transmural DeltaP can become negative quickly. Therefore, during only a *mild* forced expiration in an emphysematous patient, the EPP and the point of collapse are near the alveolus (see Fig. 15-17 (Figure Not Available) E). Use of pursed lip or grunting expiration (the equivalents of partly closing the larynx during expiration), PEEP, and a continuous positive airway pressure in an emphysematous patient restores a favorable (distending) intrathoracic transmural air DeltaP (Fig. 15-17 (Figure Not Available) F). In bronchitis, the airways are structurally weakened and may close when only a small negative transmural DeltaP is present (as with a mild forced expiration). In asthma, the middle-size airways are narrowed by bronchospasm, and if expiration is forced, they are further narrowed by a negative transmural DeltaP. Finally, with pulmonary interstitial edema, perialveolar interstitial edema compresses alveoli and acutely decreases FRC; the peribronchial edema fluid cuffs (within the connective tissue sheaths around the larger arteries and bronchi) compress the bronchi and acutely increase closing volume. [88] [89] [90]

Measurement of Closing Capacity

Closing capacity (CC) is a sensitive test of early smallairway disease and is performed by having the patient exhale to residual volume [91] (Fig. 15-18). (Figure Not Available) An inhalation from residual volume toward total lung capacity is begun, and at the beginning of the inhalation a bolus of tracer gas (xenon-133 [^{133} Xe], helium) is injected into the inspired gas. During the initial part of this inhalation from residual volume, the first gas to enter the alveolus is the V_D gas and the tracer bolus. The tracer gas will only enter alveoli that are already open (presumably the apices of the lung; see hatched lines, Fig. 15-18) (Figure Not Available) . and does not enter alveoli that are already closed (presumably the bases of the lung; see no hatched lines, Fig. 15-18) (Figure Not Available) As the inhalation continues, apical alveoli complete filling and basilar alveoli begin to open and fill, but with gas that does not contain any tracer gas.

Figure 15-18 (Figure Not Available) Measurement of closing capacity by the use of a tracer gas such as xenon-133 (^{133} Xe). The bolus of tracer gas is inhaled near residual volume and, owing to airway closure in the dependent lung, is distributed *only* to those nondependent alveoli whose air passages are still open (shown crosshatched in diagram). During expiration, the concentration of the tracer gas becomes constant after the dead space is washed out. This plateau (phase 3) gives way to a rising concentration of tracer gas (phase 4) when there is once again closure of the dependent airways because the only contribution made to the expired gas is by the nondependent alveoli with a high ^{133} Xe concentration. *(Modified from Nunn [91])*

A differential tracer gas concentration is thus established; the gas in the apices has a higher tracer concentration (see Fig. 15-18 (Figure Not Available) , hatched lines) than that in the bases (see Fig. 15-18 (Figure Not Available) , no hatched lines). As the subject exhales and the diaphragm ascends, a point is reached at which the small airways just above the diaphragm start to close, limiting airflow from these areas. The airflow now comes more from the upper lung fields, where the alveolar gas has a much higher tracer concentration, which results in a sudden increase in the tracer gas concentration toward the end of exhalation (phase 4)

The closing volume (CV) is the difference between the onset of phase 4 and residual volume; because it represents part of a vital capacity maneuver, it is expressed as a percentage of the vital lung capacity. The CV plus the residual volume is known as the CC and is expressed as a percentage of total lung capacity. Smoking, obesity, aging, and the supine position increase the CC. [92] In healthy individuals at a mean age of 44 years, CC = FRC in the supine position, and at a mean age of 66 years, CC = FRC in the upright position. [93]

Relationship Between Functional Residual Capacity and Closing Capacity

The relationship between FRC and CC is far more important than consideration of the FRC or CC alone because

it is this relationship that determines whether a given respiratory unit is normal or atelectatic or has a low V_A/Q ratio. The relationship between FRC and CC is as follows. When the volume of lung at which some airways close is greater than the whole of the V_T, lung volume never increases enough during tidal inspiration to open any of these airways. Thus, these airways stay closed during the entire tidal respiration. Airways that are closed all the time are equivalent to atelectasis (Fig. 15-19) (Figure Not Available) . If the CV of some airways lies within the V_T, then as lung volume increases during inspiration, some previously closed airways will open for a short time until lung volume recedes once again below the CV of these airways. Because these opening and closing airways are open for a shorter time than normal airways, they have less chance or time to participate in fresh gas exchange, a circumstance equivalent to a low V_A/Q region. If the CV of the lung is below the whole of tidal respiration, no airways are closed at any time during tidal respiration; this is a normal circumstance. Anything that decreases FRC relative to CC or increases CC relative to FRC will convert normal areas to low V_A/Q and atelectatic areas, [94] which causes hypoxemia.

Mechanical intermittent positive-pressure breathing (IPPB) may be efficacious because it can take a previously spontaneously breathing patient with a low V_A/Q relationship (in which CC is greater than FRC but still within the tidal volume, as depicted in Fig. 15-20 , right panel) and increase the amount of inspiratory time that some previously closed (at end exhalation) airways spend in fresh gas exchange and thereby increase the V_A/Q relationship (Fig. 15-20 , middle panel). However, if PEEP is added to the IPPB, the PEEP increases FRC to or above a lung volume greater than CC, thereby restoring a normal FRC to CC relationship, so that no airways are closed at any time during the tidal respiration depicted in Figure 15-20 (left panel) (IPPB + PEEP). Thus, anesthesia-induced atelectasis (CT scan shows crescent-shaped densities) in the dependent regions of patients' lungs has not been reversed with IPPB alone but has been reversed with IPPB plus PEEP (5-10 cm H_2O). [85]

Figure 15-19 (Figure Not Available) Relationship between the functional residual capacity (FRC), which is the percentage of total lung capacity that exists at the end of exhalation, shown by the level of each trough of the sine wave tidal volume, and the closing capacity (CC) of the lung (three different closing capacities are indicated by the three different straight lines). See text for explanation of why the three different FRC to CC relationships depicted result in normal or low ventilation/perfusion relationships (V_A/Q) or atelectasis. The abscissa is time. *(From Benumof [189])*

Figure 15-20 The functional residual capacity to closing capacity relationship during spontaneous ventilation (SPON), intermittent positive-pressure breathing (IPPB), and intermittent positive-pressure breathing and positive end-expiratory pressure (IPPB + PEEP). See text for explanation of the effect of the two ventilatory maneuvers (IPPB and PEEP) on the functional residual capacity to closing capacity relationship. TLC, total lung capacity.

Oxygen and Carbon Dioxide Transport

Alveolar and Dead Space Ventilation and Alveolar Gas Tensions

In patients with normal lungs, approximately two-thirds of each breath reach perfused alveoli to take part in gas exchange. This constitutes the effective or alveolar ventilation. The remaining one-third of each breath takes no part in gas exchange and is therefore termed the total (or effective or physiologic) dead space ventilation. The total V_D ventilation may be divided into two components: a volume of gas that ventilates the conducting airways (the anatomic V_D ventilation) and a volume of gas that ventilates unperfused alveoli (e.g., as in zone 1, pulmonary embolus, and destroyed alveolar septa) and therefore does not take part in gas exchange (the alveolar dead space ventilation). Figure 15-21 shows a two-compartment model of the lung in which the anatomic and alveolar dead space compartments have been combined into the total (physiologic) dead space compartment; the other compartment is the alveolar ventilation compartment, whose idealized V_A/Q ratio is 1.0. *

* Figure 15-21 indicates that in a steady state, the volume of CO_2 entering the alveoli (V_{CO_2}) must equal the volume of CO_2 eliminated in the expired gas (V_E) (FE_{CO_2}). Thus $V_{CO_2} = (V_E)(FE_{CO_2})$. However, the expired gas volume consists of alveolar gas (V_A)(F_{ACO_2}) and V_D gas (V_D)(F_{ICO_2}). Thus, $V_{CO_2} = (V_A)(F_{ACO_2}) + (V_D)(F_{ICO_2})$. Setting the first equation equal to the second equation and using the relationship $V_E = V_A + V_D$, subsequent algebraic manipulation (including setting $P_{ACO_2} = Pa_{CO_2}$) results in the V_D equation:

Figure 15-21 Two-compartment model of the lung in which the anatomic and alveolar dead space compartments have been combined into the total (physiologic) dead space (V_D).V_A, alveolar ventilation; V_E, expired minute ventilation; V_{CO_2}, carbon dioxide (CO_2) production; F_{ICO_2}, inspired CO_2 fraction; F_{ACO_2}, alveolar CO_2 fraction; FE_{CO_2}, mixed expired CO_2 fraction;$V_A/Q = 1$, equal

ventilation and perfusion in liters per minute. Normally, the amount of CO_2 eliminated at the airway ($V_E \times FE_{CO_2}$) equals the amount of CO_2 removed by alveolar ventilation ($V_A \times F_{ACO_2}$) because there is no CO_2 elimination from alveolar dead space ($F_{ICO_2} = 0$).

The anatomic dead space varies with lung size and is approximately 2 mL/kg of body weight. In the healthy patient lying supine, the anatomic and total dead space are approximately equal to each other because alveolar dead space is minimal. In the erect posture, the uppermost alveoli may not be perfused (zone 1), and alveolar dead space may increase from a negligible amount to 60 to 80 mL.

In severe lung disease, the physiologic V_D/V_T provides a useful expression of the inefficiency of ventilation. In the healthy patient, this ratio is usually less than 30 percent; that is, ventilation is more than 70 percent efficient. In the patient with obstructive airway disease, V_D/V_T may increase to 60 to 70 percent. Under these conditions, ventilation is obviously grossly inefficient. Figure 15-22 shows the relationship between minute ventilation (V_E) and Pa_{CO_2} for several V_D/V_T values. As V_E decreases, Pa_{CO_2} increases for all V_D/V_T. As V_D/V_T increases, a given decrease in V_E causes a much greater increase in Pa_{CO_2}. If Pa_{CO_2} is to remain constant while V_D/V_T increases, V_E must increase.

The alveolar concentration of a gas is equal to the difference between the inspired concentration of a gas and the ratio of the output (or uptake) of the gas to the V_A. Thus, for gas X during dry conditions, $P_{AX} = (Pdry\ atm)(F_{IX}) \pm V_X$ (output or uptake)$/V_A$, where P_{AX} = alveolar partial pressure of gas X; F_{IX} = inspired concentration of gas X; Pdry atm = dry atmospheric pressure = Pwet atm - PH_2O = 760 - 47 = 713 mm Hg; V_X = output or uptake of gas X; V_A = alveolar ventilation. For CO_2, $P_{ACO_2} = 713(F_{ICO_2} + V_{CO_2}/V_A)$. Because $F_{ICO_2} = 0$ and using standard conversion factors

For example, 36 mm Hg = (713)(200/4,000).

For O_2,

For example, 100 mm Hg = 713(0.21 - 225/3,200).

Figure 15-23 (Figure Not Available) shows the hyperbolic relationships expressed in equations (7) and (8) between Pa_{CO_2} and V_A (and Fig. 15-22) and between P_{AO_2} and V_A for different levels of V_{CO_2} and V_{O_2}, respectively. Pa_{CO_2} is substituted for P_{ACO_2}, because P_{ACO_2} to Pa_{CO_2} gradients are small (as opposed to P_{AO_2} to Pa_{O_2} gradients, which can be large). Note that as V_A increases, the second term of the right-hand side of equations 7 and 8 approaches zero and the composition of the alveolar gas approaches that of the inspired gas. In addition, it should be noted from Figures 15-22 through 15-24 that because anesthesia is usually administered with an oxygen-enriched gas mixture, hypercarbia is a more common result of hypoventilation than hypoxemia.

Oxygen Transport

Overview of Oxygen Transport

The principal function of the heart and lungs is supporting O_2 delivery to, and CO_2 removal from, the tissues in accordance

Figure 15-22 Relationship between the minute ventilation (V_E, L/min) and Pa_{CO_2} for a family of ratios of total dead space to tidal volume (V_D/V_T). These curves are hyperbolic (see equation 7) and rise steeply at low V_E values.

Figure 15-23 (Figure Not Available) Relationship between alveolar ventilation and P_{AO_2} and Pa_{O_2} for a family of different O_2 consumption (V_{O_2}) and CO_2 production (V_{CO_2}) is derived from Equations 7 and 8 in the text and is hyperbolic. As alveolar ventilation increases, the P_{AO_2} and Pa_{CO_2} approach inspired concentrations. Decreases in alveolar ventilation to less than 4 L/min are accompanied by precipitous decreases in P_{AO_2} and increases in Pa_{CO_2}. *(From Nunn [79])*

with metabolic requirements while maintaining arterial blood O_2 and CO_2 partial pressures within a narrow range. The respiratory and cardiovascular systems are series-linked to accomplish this function over a wide range of metabolic requirements, which may increase 30-fold from rest to heavy exercise. The steps in this functional linkage are as follows: (1) ventilation and distribution of ventilation with respect to perfusion, (2) diffusion of O_2 into blood, (3) chemical reaction of O_2 with Hb, (4) Q_T of arterial blood, and (5) distribution of blood to tissues and release of O_2 (Table 15-1) (Table Not Available) . The system is seldom stressed except at exercise, and the earliest symptoms of cardiac or respiratory diseases are often seen only during exercise.

The maximum functional capacity of each link can be determined independently. Table 15-1 (Table Not Available) lists these measured functional capacities for healthy, young men. Because theoretical maximum O_2 transport at the ventilatory step or the diffusion and chemical reaction steps (about 6 L/min in healthy humans at sea level) exceeds the O_2 transportable by maximum cardiac output and distribution steps, the limit to O_2 transport is the cardiovascular system. Respiratory diseases would not be expected to limit maximum O_2 transport until their functional capacities were reduced nearly 40 to 50 percent.

Oxygen-Hemoglobin Dissociation Curve

As a red blood cell (RBC) passes by the alveolus, O_2 diffuses into the plasma, increasing the Pa_{O_2}. As Pa_{O_2} increases, O_2 diffuses into the RBC and combines with Hb. Each Hb molecule consists of four heme molecules attached

Figure 15-24 For any given O_2 concentration in the inspired gas, the relationship between alveolar ventilation and P_{AO_2} is hyperbolic. As the inspired O_2 concentration is increased, the amount that alveolar ventilation must decrease to produce hypoxemia is greatly increased.

TABLE 15-1 -- Functional Capacities and Potential Maximum Oxygen (O_2) Transport of Each Link in the O_2 Transport Chain in Normal Humans[a] at Sea Level

(Not Available)

From Cassidy SS: Heart-lung interaction in health and disease. Am J Med Sci 30:451-461, 1987.

[a] Hemoglobin = 15 g/dL; physiologic dead space in percentage of tidal volume = 0.25; partial alveolar pressure of oxygen > 110 mm Hg.

to a globin molecule. Each heme molecule consists of glycine, alpha-ketoglutaric acid, and iron in the ferrous (Fe^{++}) form. Each ferrous ion has the capacity to bind with one O_2 molecule in a loose, reversible combination. As the ferrous ions bind to O_2, the Hb molecule begins to become saturated.

The oxy-Hb dissociation curve relates the saturation of Hb (rightmost Y axis in Fig. 15-25) to the Pa o_2. Hb is fully saturated (100%) by a P o_2 of about 700 mm Hg. The normal arterial point on the right side and flat part of the oxy-Hb curve in Figure 15-25 is 95 to 98 percent saturation by a Pa o_2 of about 90 to 100 mm Hg. When the P o_2 is less than 60 mm Hg (90% saturation), the saturation falls steeply, so that the amount of Hb uncombined with O_2 increases greatly for a given decrease in P o_2. Mixed venous blood has a P o_2 (Pv o_2) of about 40 mm Hg and is approximately 75 percent saturated; this is indicated by the middle of the three points on the oxy-Hb curve in Figure 15-25.

The oxy-Hb curve can also relate the O_2 content (C o_2) (volume percent, mL of O_2 /0.1 L of blood; secondmost right Y axis in Fig. 15-25) to the P o_2. Oxygen is carried in solution in the plasma, 0.003 mL of O_2 /mm Hg P o_2 /0.1 L, and is combined with Hb, 1.39 mL of O_2 /g of Hb * to the extent (percentage) Hb is saturated. Thus

For a patient with an Hb of 15 g/0.1 L, Pa o_2 of 100 mm Hg, and Pv o_2 of 40 mm Hg, arterial O_2 content (Ca o_2) = (1.39) (15)(1) + (0.003)(100) = 20.9 + 0.3 = 21.2 mL of O_2 /0.1 L; mixed venous O_2 content (Cv o_2) = (1.39)(15)(0.75) - (0.003)(40) = 15.6 + 0.1 = 15.2 mL of O_2 /0.1 L. Thus, the normal arteriovenous O_2 content difference is approximately 5.5 mL/0.1 L.

The oxy-Hb curve can also relate the O_2 transport (L/min) to the peripheral tissues (see thirdmost right Y axis in Fig. 15-25) to the P o_2. This value is obtained by multiplying O_2 content by the Q t (O_2 transport = Q t × Ca o_2). To do this multiplication, one must convert the content unit of mL/0.1 L to mL/L by multiplying the usual O_2 content by 10 (results in ml of O_2 /L of blood); subsequent multiplication of mL/L against Q t in L/min yields mL/min. Thus, if Q t = 5 L/min and Ca o_2 = 20.4 mL of O_2 /0.1 L, then the arterial point corresponds to 1,060 mL/min going to the periphery and the venous point corresponds to 785 mL/min returning to the lungs, with V o_2 = 275 mL/min.

The oxy-Hb curve can also relate the O_2 actually available to the tissues (see leftmost Y axis in Fig. 15-25) as a function of P o_2. Of the 1,000 mL/min of O_2 normally going to the periphery, 200 mL/min of O_2 cannot be extracted because it would lower the P o_2 below the level (see rectangular dashed line in Fig. 15-25) at which organs such as the brain can survive; the O_2 available to the tissues is therefore 800 mL/min. This amount is approximately three to four times the normal resting V o_2. When Q t = 5 L/min and the arterial saturation is less than 40 percent, the total flow of O_2 to the periphery is reduced to 400 mL/min, so that the available O_2 is now 200 mL/min and O_2 supply just equals O_2 demand. Consequently, with low arterial saturation, tissue demand can only be met by an increase in Q t or, in the longer term, by an increase in Hb concentration.

The position of the oxy-Hb curve is best described by the P o_2 level at which Hb is 50 percent saturated (P_{50}). The normal adult P_{50} (see the point on the left side and steep portion of the oxy-Hb curve in Fig. 15-24) is 26.7 mm Hg.

The effect on Hb saturation of a shift in the position of the oxy-Hb curve depends greatly on the P o_2. In the region of the normal Pa o_2 (75 to 100 mm Hg), the curve is relatively horizontal, so that shifts of the curve have little effect on saturation. In the region of the mixed venous P o_2, where the curve is relatively steep, a shift of the curve leads to a much greater difference in saturation. A P_{50} lower than 27 mm Hg describes a left-shifted oxy-Hb curve, which means that at any given P o_2, Hb has a higher affinity for O_2 and is therefore more saturated than normal. This lower P_{50} may require a higher than normal tissue perfusion to produce the normal amount of O_2 unloading. The causes of a left-shifted oxy-Hb curve are alkalosis (metabolic and respiratory-- the Bohr effect), hypothermia, abnormal and fetal Hb, carboxyhemoglobin, methemoglobin, and decreased RBC 2,3-diphosphoglycerate (2,3-DPG) content (which may occur with transfusion of old acid-citrate-dextrose [ACD]-

* Controversy exists over the magnitude of this number. Originally, 1.34 had been used, [95] but with the determination of the molecular weight of Hb (64,458), the theoretic value of 1.39 has become popular. [96] Following extensive human studies, Gregory [97] observed in 1974 that the applicable value was 1.306 mL/g% in human adults. Most of the literature still, however, uses 1.39.

Figure 15-25 The oxygen-hemoglobin dissociation curve. Four different ordinates are shown as a function of oxygen partial pressure (the abscissa). In order from right to left, they are: saturation (%), O_2 content (mL of O_2 /0.1 L) of blood; O_2 supply to the peripheral tissues (mL/min); and O_2 available to the peripheral tissues (mL/min), which is O_2 supply minus approximately 200 mL/min that cannot be extracted below a partial pressure of 20 mm Hg. Three points are shown on the curve: a, normal arterial; v, normal mixed venous; and P_{50}, the partial pressure (27 mm Hg) at which hemoglobin is 50 percent saturated.

stored blood; storage of blood in citrate-phosphate-dextrose [CPD] minimizes changes in 2,3-DPG with time).

A P_{50} higher than 27 mm Hg describes a right-shifted oxy-Hb curve, which means that at any given P o_2, Hb has a low affinity for O_2 and is less saturated than normal. This higher P_{50} may allow a lower tissue perfusion than normal to produce the normal amount of O_2 unloading. The causes of a right-shifted oxy-Hb curve are acidosis (metabolic and respiratory--the Bohr effect), hyperthermia, abnormal Hb, increased RBC 2,3-DPG content, and inhalation anesthetics (see later).

Abnormalities in acid-base balance result in alteration of 2,3-DPG metabolism to shift the oxy-Hb curve to its normal position. This compensatory change in 2,3-DPG requires between 24 and 48 hours. Thus, with acute acid-base abnormalities, O_2 affinity and the position of the oxy-Hb curve change. However, with more prolonged acid-base changes, the altered levels of 2,3-DPG shift the oxy-Hb curve and therefore O_2 affinity back toward normal.

Many inhalation anesthetics have been shown to shift the oxy-Hb dissociation curve to the right. [98] [99] Isoflurane shifts the P_{50} to the right by 2.6±0.07 mm Hg at a vapor pressure of approximately 1 MAC (1.25 percent). [100] On the other hand, high-dose fentanyl, morphine, and meperidine do not alter the position of the curve.

Effect of QS/QT on the PaO_2

Figure 15-26 (Figure Not Available) shows the relationship between F IO_2 and Pa o_2 for a family of right-to-left transpulmonary shunts (Q s/Q t); the calculations assume a constant and normal Q t and Pa co_2. With no Q s/Q t, a linear increase in F IO_2 results in a linear increase in Pa o_2 (solid straight line). As the shunt is increased, the Q s/Q t lines relating F IO_2 to Pa o_2 become progressively flatter. [101] With a shunt of 50 percent of Q t, an increase in F IO_2 results in almost no increase in Pa o_2. The solution to the problem of hypoxemia secondary to a large shunt is not increasing the F IO_2, but rather causing a reduction in the shunt (fiberoptic bronchoscopy, PEEP, patient positioning, antibiotics, suctioning, diuretics).

Effect of QT and Vo_2 on Cao_2

In addition to an increased Q s/Q t, the Ca o_2 is decreased by a decreased Q t (for a constant V o_2) and by an increased V o_2 (for a constant Q t). In either case (decreased Q t or increased

Figure 15-26 (Figure Not Available) Effect of changes in inspired oxygen concentration on Pa o_2 for various right-to-left transpulmonary shunts. Cardiac output (Q t), hemoglobin (Hb), oxygen

consumption (V O_2), and arteriovenous oxygen content differences [C(a - v) O_2] were assumed to be normal. *(From Nunn [75])*

Figure 15-27 Effect of a decrease in cardiac output or an increase in oxygen consumption on mixed venous and arterial oxygen contents. Mixed venous blood (v) either perfuses ventilated alveolar (ALV O_2) capillaries and becomes oxygenated end-pulmonary capillary blood (c
) or perfuses whatever true shunt pathways exist and remains the same in composition (desaturated). These two pathways must ultimately join together to form mixed arterial (a) blood. If the cardiac output (Q T) decreases and/or the oxygen consumption (V O_2) increases, the tissues must extract more oxygen per unit volume of blood than under normal conditions. Thus, the primary effect of a decrease in Q T or an increase in V O_2 is a decrease in mixed venous oxygen content. The mixed venous blood with a decreased oxygen content must flow through the shunt pathway as before (which may remain constant in size) and lower the arterial content of oxygen. Thus, the secondary effect of a decrease in Q T or an increase in V O_2 is a decrease in arterial oxygen content.

V O_2), along with a constant right-to-left shunt, the tissues must extract more O_2 from the blood per unit blood volume, and therefore, the Cv O_2 must primarily decrease (Fig. 15-27) . When the blood with lower Cv O_2 passes through whatever shunt exists in the lung and remains unchanged in its O_2 composition, it must inevitably mix with oxygenated end-pulmonary capillary blood (c
flow) and secondarily decrease the Ca O_2 (Fig. 15-27) * The larger the intrapulmonary shunt, the greater is the decrease in Ca O_2 because more venous blood with lower Cv O_2 can admix with end-pulmonary capillary blood [102] [103] (see Fig. 15-37) (Figure Not Available) . Thus, the P(A - a) O_2 is a function both of the size of the Q S/Q T and of what is flowing through the Q S/Q T, namely, Cv O_2 , and Cv O_2 is a primary function of Q T and V O_2 .

Figure 15-28 shows the equivalent circuit of the pulmonary circulation in a patient with a 50 percent shunt, a normal Cv O_2 of 15 vol percent, and a moderately low Ca O_2 of 17.5 vol percent. Decreasing Q T and/or increasing V O_2 causes a larger primary decrease in Cv O_2 to 10 vol percent and a smaller, but still significant, secondary decrease in Ca O_2 to 15 vol percent; the ratio of change in Cv O_2 to Ca O_2 in this example of 50 percent Q S/Q T is 2:1.

Figure 15-28 The equivalent circuit of the pulmonary circulation in a patient with a 50 percent right-to-left shunt. Oxygen content is in mL/100 mL of blood (vol percent). A decrease in cardiac output (Q T) or an increase in O_2 consumption (V O_2) can cause a decrease in mixed venous oxygen content (from 15 to 10 vol percent in this example), which, in turn, will cause a decrease in the arterial content of oxygen (from 17.5 to 15.0 vol percent). In this 50 percent shunt example, the decrease in mixed venous oxygen content was twice the decrease in arterial oxygen content.

If a decrease in Q T or an increase in V O_2 is accompanied by a decrease in Q S/Q T, there may be no change in Pa O_2 (a decreasing effect on Pa O_2 is offset by an increasing effect on Pa O_2) (Table 15-2) . These changes sometimes occur in diffuse lung disease. If a decrease in Q T or an increase in V O_2 is accompanied by an increase in Q S/Q T, Pa O_2 may be greatly decreased (a decreasing effect on Pa O_2 is compounded by another decreasing effect on Pa O_2) (see Table 15-2) . These changes sometimes occur in regional ARDS and atelectasis. [105]

Fick Principle

The Fick principle allows calculation of V O_2 and states that the amount of O_2 consumed by the body (V O_2) is equal

TABLE 15-2 -- Cardiac Output (Q T), Shunt (Q S/Q T), and Venous (Pv O_2) and Arterial PaO_2 Oxygenation

CHANGES	CLINICAL SITUATION
If Q T	Classic theory, normal lung
Pv O_2 and Q S/Q T = K Pa O_2	
If Q T	Diffuse lung disease
Pv O_2 and Q S/Q T Pa O_2 = K	
If Q T	Regional ARDS and atelectasis
Pv O_2 and Q S/Q T Pa O_2	

ARDS, adult respiratory distress syndrome; K, constant;
, decrease;
, increase.

* The amount of O_2 flowing through any given channel per minute in Figure 15-27 is a product of the blood flow times the O_2 content. Thus, from Figure 15-27 Q TCa O_2 = Qc
Cc
O_2 + QsCv O_2 . With Qc
= Q T - Qs and further algebraic manipulation [104]

to the amount of O_2 leaving the lungs (Q T)(Ca O_2) minus the amount of O_2 returning to the lungs (Q T)(Cv O_2). Thus

Condensing the content symbols yields the usual expression of the Fick equation:

This equation states that O_2 consumption is equal to the Q_T times the arteriovenous O_2 content difference. Normally, (5 L/min)(5.5 mL)/0.1 L = 0.27 L/min (see the section *Oxygen-Hemoglobin Dissociation Curve*).

Similarly, the amount of O_2 consumed by the body (V_{O_2}) is equal to the amount of O_2 brought into the lungs by ventilation (V_I)(F_{IO_2}) minus the amount of O_2 leaving the lungs by ventilation (V_E)(FE_{O_2}), where V_E is expired minute ventilation and FE_{O_2} is mixed expired O_2 fraction. Thus, $V_{O_2} = (V_I)(F_{IO_2}) - (V_E)(FE_{O_2})$. Because the difference between V_I and V_E is due to the difference between V_{O_2} (normally 270 mL/min) and V_{CO_2} (normally 200 mL/min) and is only 70 mL/min (see below), V_I essentially equals V_E. Substituting V_E for V_I:

Normally, V_{O_2} = 5.0 L/min (0.21 - 0.16) = 0.25 L/min. In determining V_{O_2} in this way, V_E can be measured with a spirometer, F_{IO_2} can be measured with an O_2 analyzer or from known fresh gas flows, and FE_{O_2} can be measured by collecting expired gas in a bag for a few minutes. A sample of the mixed expired gas is used to measure PE_{O_2}. To convert PE_{O_2} to FE_{O_2}, simply divide PE_{O_2} by dry atmospheric pressure: $PE_{O_2}/713 = FE_{O_2}$.

Additionally, the Fick equation is useful in understanding the impact of changes in Q_T on Pa_{O_2} and Pv_{O_2}. If V_{O_2} remains constant (K) and Q_T decreases (
), the arteriovenous O_2 content difference has to increase (
):

The $C(a - v)_{O_2}$ difference increases because a decrease in Q_T causes a much larger and primary decrease in Cv_{O_2} as compared with a smaller and secondary decrease in Ca_{O_2}:

Thus, the Cv_{O_2} (and Pv_{O_2}) are much more sensitive indicators of Q_T, because they change more with the changes in Q_T than does Ca_{O_2} (or Pa_{O_2}) (see Figs. 15-27 and 15-37) (Figure Not Available) .

Carbon Dioxide Transport

The amount of CO_2 circulating in the body is a function of both CO_2 elimination and production. Elimination of CO_2 depends on pulmonary blood flow and alveolar ventilation. Production of CO_2 parallels O_2 consumption according to the respiratory quotient (R):

Under normal resting conditions, R is 0.8; that is, only 80 percent as much CO_2 is produced as O_2 is consumed. However, this value changes as the nature of the metabolic substrate changes. If only carbohydrate is utilized, the respiratory quotient is 1.0. Conversely, with the sole use of fat, more O_2 combines with hydrogen to produce water and the R value drops to 0.7.

CO_2 is transported from the mitochondria to the alveoli in a number of forms. In plasma, CO_2 exists in physical solution, hydrated to carbonic acid (H_2CO_3) and as bicarbonate (HCO_3^-). In the RBC, CO_2 combines with Hb as carbaminohemoglobin (Hb-CO_2). The approximate relative values of H_2CO_3 ($H_2O + CO_2$), HCO_3^-, and Hb-CO_2 to the total CO_2 transported are 7, 80, and 13 percent, respectively.

In plasma, CO_2 exists both in physical solution and as H_2CO_3:

The CO_2 in solution can be related to P_{CO_2} by use of Henry's law [106]:

where alpha is the solubility coefficient of CO_2 in plasma (0.03 mmol/L/mm Hg at 37°C). However, the major fraction of CO_2 produced passes into the RBC. As in plasma, CO_2 combines with water to produce H_2CO_3. However, unlike the slow reaction in plasma, in which the equilibrium point lies toward the left, the reaction in the RBC is catalyzed by the enzyme carbonic anhydrase. This zinc-containing enzyme moves the reaction to the right at a rate 1,000 times faster than in plasma. Furthermore, nearly 99.9 percent of the H_2CO_3 dissociates to the HCO_3^- and hydrogen ions (H^+):

The H^+ produced from H_2CO_3 in the production of HCO_3^- is buffered by Hb (H^+ + Hb i HHb). The HCO_3^- produced passes out of the RBC into the plasma to perform its function as a buffer. To maintain electrical neutrality within the RBC, chloride ion (Cl^-) moves in as HCO_3^- moves out (Cl^- shift). Finally, CO_2 can combine with Hb in the erythrocyte (to produce Hb-CO_2). Again, as in the HCO_3^- release, an H^+ ion is formed in the reaction of CO_2 and Hb. This H^+ ion is also buffered by Hb.

Bohr and Haldane Effects

Just as the percent saturation of Hb with O_2 is related to P_{O_2}, so is the total CO_2 in blood related to P_{CO_2}. The Bohr effect is the dependence of the position of the oxy-Hb curve

on P $_{CO_2}$ and pH; hypercapnia and acidosis shift the curve to the right, and hypocapnia and alkalosis shift the curve to the left. The Haldane effect is the shift in the relationship of P $_{CO_2}$ to total CO_2 (i.e., the CO_2 dissociation curve) caused by altered levels of O_2. Low P $_{O_2}$ shifts the CO_2 dissociation curve to the left so that the blood is able to pick up more CO_2.

Pulmonary Microcirculation, Pulmonary Interstitial Space, and Pulmonary Interstitial Fluid Kinetics (Pulmonary Edema)

The ultrastructural appearance of an alveolar septum [107] is schematically depicted in Figure 15-29 (Figure Not Available) . Capillary blood is separated from alveolar gas by a series of anatomic layers: capillary endothelium, endothelial basement membrane, interstitial space, epithelial basement membrane, and alveolar epithelium (of the type I pneumocyte).

On one side of the alveolar septum (the thick, upper [see Fig. 15-29] (Figure Not Available) , fluid- and gas-exchanging side), the epithelial and endothelial basement membranes are separated by a space of variable thickness containing connective tissue fi-brils, elastic fibers, fibroblasts, and macrophages. This connective tissue is the backbone of the lung parenchyma; it forms a continuum with the connective tissue sheaths around the conducting airways and blood vessels. Thus, the pericapillary perialveolar interstitial space is continuous with the interstitial tissue space that surrounds terminal bronchioles and vessels, and both spaces constitute the connective tissue space of the lung. There are no lymphatics in the interstitial space of the alveolar septum. Instead, lymphatic capillaries first appear in the interstitial space surrounding terminal bronchioles, small arteries, and veins.

The opposite side of the alveolar septum (the thin, down [see Fig. 15-29] (Figure Not Available) , gas-exchanging-only side) contains only

Figure 15-29 (Figure Not Available) Schematic summary of the ultrastructure of the pulmonary capillary. The upper side of the capillary has the endothelial and epithelial basement membranes separated by an interstitial space, whereas the lower side of the capillary contains only fused endothelial and epithelial basement membranes. The dashed arrows indicate a potential pathway for fluid to move from the intravascular space to the interstitial space (through loose junctions in the endothelium) and from the interstitial space to the alveolar space (through tight junctions in the epithelium). RBC, red blood cell; ENDO, endothelium; BM, basement membrane; IS, interstitial space; EPI, epithelium; LJ, loose junction; TJ, tight junction; ALV, alveolus. *(From Fishman [107])*

fused epithelial and endothelial basement membranes. The interstitial space is thus greatly restricted on this side owing to fusion of the basement membranes. Interstitial fluid cannot separate the endothelial and epithelial cells from one another, and as a result the space and distance barrier to fluid movement from the capillary to alveolar compartment is reduced and is composed only of the two cell linings with their associated basement membranes. [108] [109]

Between the individual endothelial and epithelial cells are holes or junctions that provide a potential pathway for fluid to move from the intravascular space to the interstitial space and finally from the interstitial space to the alveolar space. The junctions between endothelial cells are relatively large and are therefore termed *loose;* the junctions between epithelial cells are relatively small and therefore termed *tight.* Pulmonary capillary permeability (K) is a direct function of and essentially equivalent to the size of the holes in the endothelial and epithelial linings.

To understand how pulmonary interstitial fluid is formed, stored, and cleared, it is necessary to first develop the concepts that (1) the pulmonary interstitial space is a continuous space between a periarteriolar and peribronchial connective tissue sheath and the space between the endothelial and epithelial basement membranes in the alveolar septum, and (2) the space has a progressively negative distal to proximal DeltaP.

The concepts of a continuous connective tissue sheath-alveolar septum interstitial space and a negative interstitial space DeltaP are prerequisite to understanding interstitial fluid kinetics (Fig. 15-30) (Figure Not Available) . After entering the lung parenchyma, both the bronchi and arteries run within a connective tissue sheath, which is formed by an invagination of the pleura at the hilum and which ends at the level of the bronchioles (Fig. 15-30 (Figure Not Available) A). Thus, there is a potential perivascular and peribronchial space, respectively, between the arteries and the bronchi and the connective tissue sheath. The negative pressure in the pulmonary tissues surrounding the perivascular connective tissue sheath exerts a radial outward traction force on the sheath. The radial traction creates a negative pressure within the sheath, which is transmitted to the bronchi and arteries, tending to hold them open and increase their diameters (see Fig. 15-30). (Figure Not Available) [219] The alveolar septum interstitial space is the space between the capillaries and alveoli (or more precisely, the space between the endothelial and epithelial basement membranes) and is continuous with the interstitial tissue space that surrounds the larger arteries and bronchi (see Fig. 15-30 (Figure Not Available) A). Studies indicate that the alveolar interstitial pressure is also uniquely negative but not as much as the negative interstitial space pressure around the larger arteries and bronchi. [110]

The forces governing net transcapillary-interstitial space fluid movement are as follows. The net transcapillary flow of fluid (F) out of pulmonary capillaries is equal to the difference between pulmonary capillary hydrostatic pressure (Pinside) and the interstitial fluid hydrostatic pressure (Poutside) and to the difference between the capillary colloid oncotic pressure (piinside) and the interstitial colloid oncotic pressure (pioutside). These four forces produce a steady-state fluid flow (F) during a constant capillary permeability (K).

Figure 15-30 (Figure Not Available) (A) Schematic diagram of the concept of a continuous connective tissue sheath-alveolar septum interstitial space. The entry of the main stem bronchi and pulmonary artery into the lung parenchyma invaginates the pleura at the hilum, forming a surrounding connective tissue sheath (heavy black line). The connective tissue sheath ends at the level of the bronchioles. The space between the pulmonary arteries and bronchi and the interstitial space is continuous with the alveolar septum interstitial space. The alveolar septum interstitial space is contained within the endothelial and epithelial basement membranes of the capillaries and alveoli, respectively. (B) Schematic diagram showing how interstitial fluid moves from the alveolar septum interstitial space to the connective tissue interstitial space. The mechanisms are a negative pressure gradient (sump), the presence of one-way valves in the lymphatics, and the massaging action of arterial pulsations. *(Modified from Benumof [185])*

K is a capillary filtration coefficient expressed in mL/min/mm Hg/100 g. The filtration coefficient is the product of the effective capillary surface area in a given mass of tissue and the permeability per unit surface area of the capillary wall to filter the fluid. Under normal circumstances and at a vertical height in the lung that is at the junction of zones 2 and 3, the intravascular colloid oncotic pressure (
26 mm Hg) acts to keep water in the capillary lumen, and working against this force, the pulmonary capillary hydrostatic pressure (
10 mm Hg) acts to force water across the loose endothelial junctions into the interstitial space. If these were the only operative forces, the interstitial space, and consequently the alveolar surfaces, would be constantly dry, and there would be no lymph flow. In fact, alveolar surfaces are moist, and lymphatic flow from the interstitial compartment is constant (
500 mL/d). This can be explained in part by the pioutside (8 mm Hg) and in part by the negative Poutside (
8 mm Hg). Negative (subatmospheric) interstitial space pressure would promote, by suction, a slow loss of fluid across the endothelial holes. [111] Indeed, extremely negative pleural (and perivascular hydrostatic) pressure, such as may occur in a vigorously spontaneously breathing patient with an obstructed airway, can cause pulmonary interstitial edema [112] (Table 15-3) . Relative to the vertical level of the junction of zones 2 and 3, as lung height decreases (lung dependency), absolute Pinside increases, and fluid has a propensity to transudate; as lung height increases (lung nondependency), absolute Pinside decreases, and fluid has a propensity to be reabsorbed. However, fluid transudation induced by an increase in Pinside is limited by a concomitant dilution of proteins in the interstitial space and therefore a decrease in pioutside. [113] Any change in the size of the endothelial junctions, even if the foregoing four forces remain constant, changes the magnitude and perhaps even the direction of fluid movement; increased size of endothelial junctions (increased permeability) promotes transudation, and decreased size of endothelial junctions (decreased permeability) promotes reabsorption.

There are no lymphatics in the interstitial space of the alveolar septum. Instead, lymphatic capillaries first appear in the interstitial space sheath surrounding terminal bronchioles and small arteries. Interstitial fluid is normally removed from the alveolar interstitial space into the lymphatics by a sump (pressure gradient) mechanism, which is caused by the presence of the more negative pressure surrounding the larger arteries and bronchi. [114] [115] The sump mechanism is aided by the presence of valves in the lymph vessels. In addition, because the lymphatics run in the same sheath as the pulmonary arteries, they are exposed to the massaging action of the arterial pulsations. The differential negative pressure, the lymphatic valves, and the arterial pulsations all help to propel the lymph proximally toward the hilum through the lymph nodes (pulmonary to bronchopulmonary to tracheobronchial to paratracheal to scalene and cervical nodes) to the central venous circulation depot (Fig. 15-30 (Figure Not Available) B). An increase in central venous pressure, which is the back pressure for lymph to flow out of the lung, would decrease lung lymph flow

and perhaps promote pulmonary interstitial edema.

If the rate of entry of fluid into the pulmonary interstitial space exceeds the capability of the pulmonary interstitial space to clear the fluid, the pulmonary interstitial space will fill with fluid; the fluid, now under an increased and positive

TABLE 15-3 -- Causes of Extremely Negative Pulmonary Interstitial Fluid Pressure (Poutside) Pulmonary Edema

Vigorous spontaneous ventilation against an obstructed airway
Upper airway mass (tumor, hematoma, abscess, foreign body, etc.)
Laryngospasm
Infection, inflammation, edema
Vocal cord paralysis
Strangulation
Rapid reexpansion of lung
Vigorous pleural suctioning (thoracentesis, chest tube)

driving force (P_{ISF}), will cross the relatively impermeable epithelial wall holes and the alveolar space will fill. Intra-alveolar edema fluid will additionally cause alveolar collapse and atelectasis, thereby promoting further fluid accumulation.

RESPIRATORY FUNCTION DURING ANESTHESIA

Introduction

Arterial oxygenation is impaired in most patients during anesthesia, with either spontaneous or controlled ventilation. [116] [117] [118] [119] [120] [121] In otherwise normal patients it is generally accepted that the impairment of arterial oxygenation during anesthesia is more severe in the elderly, [122] [123] the obese, [124] and smokers. [125] In various studies of healthy young to middle-aged, generally anesthetized patients, venous admixture (shunt) has been found to average 10 percent, and the scatter in V_A/Q ratios has been found to be small to moderate [123] [126] whereas in patients with more marked deterioration in preoperative pulmonary function, general anesthesia causes considerable widening of V_A/Q distribution and large increases in both low V_A/Q ($0.005 < V_A/Q < 0.1$) (underventilated) regions and shunt. [122] [125] [127] The magnitude of shunt correlates closely with the degree of atelectasis. [122] [127]

In addition to the foregoing generalizations concerning respiratory function during anesthesia, the effect of a given anesthetic on respiratory function depends on the depth of general anesthesia, the patient's preoperative respiratory condition, and the presence of special intraoperative anesthetic and surgical conditions.

Effect of Anesthetic Depth on Respiratory Pattern

The respiratory pattern is altered by the induction and deepening of anesthesia. When the depth of anesthesia is inadequate (less than minimum alveolar concentration [MAC]), the respiratory pattern may vary from excessive hyperventilation and vocalization to breathholding. As anesthetic depth approaches or equals MAC (light anesthesia), irregular respiration progresses to a more regular pattern, which is associated with a larger than normal V_T. However, during light but deepening anesthesia, the approach to a more regular respiratory pattern may be interrupted by a pause at the end of inspiration (a "hitch" in the inspiration), followed by a relatively prolonged and active expiration in which the patient seems to exhale forcefully rather than passively. As anesthesia deepens to moderate levels, respiration becomes faster and more regular but shallower. The respiratory pattern is a sine wave losing the inspiratory hitch and lengthened expiratory pause. There is little or no inspiratory or expiratory pause, and the inspiratory and expiratory periods are equivalent. Intercostal muscle activity is still present, and there is normal movement of the thoracic cage with lifting of the chest during inspiration. The respiratory rate is generally slower and the V_T larger with nitrous oxide-narcotic anesthesia as compared with anesthesia with halogenated drugs. During deep anesthesia with halogenated drugs, increasing depression of respiration is manifested by even more rapid, shallow breathing (panting). On the other hand, with deep nitrous oxide-narcotic anesthesia, respirations become slower but may remain deep. With very deep anesthesia with all drugs, respirations are jerky or gasping in character and irregular in pattern. This situation results from loss of active intercostal muscle contribution to inspiration. As a result, a rocking boat movement occurs in which there is an out-of-phase depression of the chest wall during inspiration, a flaring of the lower chest margins, and a billowing of the abdomen. The reason for this type of movement is that inspiration is dependent solely on diaphragmatic effort. Independently of anesthetic depth, similar chest movements may be simulated by upper and lower airway obstruction and by partial paralysis.

Effect of Anesthetic Depth on Spontaneous Minute Ventilation

Despite the variable changes in respiratory pattern and rate as anesthesia deepens, overall spontaneous V_E progressively decreases. The normal awake response to breathing CO_2 (the X axis in Fig. 15-31 (Figure Not Available) shows increasing end-tidal concentration of CO_2) causes a linear increase in V_E (see the Y axis in Fig. 15-31) (Figure Not Available) . In Figure 15-31 (Figure Not Available) the slope of the line relating V_E to end-tidal CO_2 concentration in awake individuals is 2 L/min/mm Hg. (There is a large variation in the slope of this response in healthy individuals.) Figure 15-31 (Figure Not Available) also shows that increasing halothane concentration displaces the end-tidal CO_2 concentration P_{CO_2} -ventilation response curve progressively to the right (meaning that at any CO_2 concentration, ventilation is less than before), decreases the slope of the curve, and shifts the apneic threshold to a higher end-tidal CO_2 concentration level. [128] Similar alterations are observed with other halogenated anesthetics and

Figure 15-31 (Figure Not Available) In conscious controls (heavy solid line), increasing end-expiratory P_{CO_2} increases pulmonary minute volume. The dashed line is an extrapolation of the CO_2 -response curve to zero ventilation and represents the apneic threshold. An increase in anesthetic (halothane) concentration (end-expiratory concentration) progressively diminishes the slope of the CO_2 -response curve and shifts the apneic threshold to a higher P_{CO_2} . The heavy line interrupted by dots shows the decrease in minute ventilation and the increase in P_{CO_2} that occur with increasing depth of anesthesia. *(Modified from Munson et al [128])*

narcotics. Figures 15-22 to 15-24 show that decreases in V_E cause increases in Pa_{CO_2} and decreases in Pa_{O_2} . In healthy, unstimulated, spontaneously breathing male volunteers, 1 MAC halothane, isoflurane, and enflurane causes a Pa_{CO_2} of approximately 46, 48, and 62 mm Hg, respectively.

Effect of Preexisting Respiratory Dysfunction on the Respiratory Effects of Anesthesia

Anesthesiologists are frequently required to care for (1) patients with acute chest disease (pulmonary infection, atelectasis) or systemic diseases (sepsis, cardiac and renal failure, or multiple trauma) who require emergency operations; (2) heavy smokers with subtle pathologic airway and parenchymal conditions and hyperreactive airways; (3) patients with classic emphysematous and bronchitic problems; (4) obese people prone to decreases in FRC during anesthesia; [129] [130] (5) patients with chest deformities; and (6) extremely old patients.

The nature and magnitude of these preexisting respiratory conditions determine, in part, the effect of a given standard anesthetic on respiratory function. For example, in Figure 15-32 , the FRC-CC relationship is depicted for normal, obese, bronchitic, and emphysematous patients. In the healthy patient, FRC exceeds CC by approximately 1 L. In the latter three respiratory conditions, CC is 0.5 to 0.75 L less than FRC. If anesthesia causes a 1-L decrease in FRC, the healthy patient will have no change in the qualitative relationship

Figure 15-32 The lung volume (ordinate) at which the tidal volume is breathed decreases (by 1 L) from the awake state to the anesthetized state. The functional residual capacity (FRC), which is the volume of lung existing at the end of the tidal volume, therefore also decreases (by 1 L) from the awake to the anesthetized state. In healthy, obese, bronchitic, and emphysematous patients, the awake FRC considerably exceeds the closing capacity (CC). In obese, bronchitic, and emphysematous patients, the anesthetized state causes FRC to be less than CC. In healthy patients, anesthesia causes the FRC to equal the CC.

between FRC and CC. In the patients with special respiratory conditions, a 1-L decrease in FRC will cause CC to exceed FRC and will change the previous marginally normal FRC-CC relationship to either a grossly low V_A/Q or an atelectatic FRC-CC relationship. Similarly, patients with chronic bronchitis, who have copious airway secretions, may suffer more from an anesthetic-induced decrease in mucus velocity flow than other patients. Finally, if an anesthetic drug inhibits HPV,

the drug may increase shunting more in patients with than in those without preexisting HPV. Thus, the effect of a standard anesthetic can be expected to produce varying degrees of respiratory change among patients who have different degrees of preexisting respiratory dysfunction.

Effect of Special Intraoperative Conditions on the Respiratory Effects of Anesthesia

Some special intraoperative conditions (such as surgical position, massive blood loss, and surgical retraction on the lung), may cause impaired gas exchange. For example, some of the surgical positions (i.e., the lithotomy, jackknife, and kidney rest positions) and surgical exposure requirements may decrease Q_T, may cause hypoventilation in a spontaneously breathing patient, and may reduce the FRC. The respiratory depressant effects of any anesthetic will be magnified by the type and severity of preexisting respiratory dysfunction as well as by the number and severity of special intraoperative conditions that can embarrass respiratory function.

Mechanisms of Hypoxemia During Anesthesia

Malfunction of Equipment

Mechanical Failure of Anesthesia Apparatus to Deliver Oxygen to the Patient

Hypoxemia resulting from mechanical failure of the O_2 supply system (also see Ch. 7) or the anesthesia machine is a recognized hazard of anesthesia. Disconnection of the patient from the O_2 supply system (usually at the juncture of the endotracheal tube and elbow connector) is by far the most common cause of mechanical failure to deliver O_2 to the patient. Other reported causes of O_2 supply failure during anesthesia include the following: an empty or depleted O_2 cylinder; substitution of a nonoxygen cylinder at the O_2 yoke because of absence or failure of the pin index; an erroneously filled O_2 cylinder; insufficient opening of the O_2 cylinder (which hinders a free flow of gas as pressure decreases); failure of gas pressure in a piped O_2 system; faulty locking of the piped O_2 system to the anesthesia machine; inadvertent switching of the Schrader adapters on piped lines; crossing of piped lines during construction; failure of a reducing valve or gas manifold; inadvertent disturbance of the setting of the O_2 flowmeter; employment of the fine O_2

flowmeter instead of the coarse flowmeter; fractured or sticking flowmeters; transposition of rotameter tubes; erroneous filling of a liquid O_2 reservoir with nitrogen; and fresh gas line disconnection from machine to in-line hosing. [131] [132] [133] [134] [135] Monitoring of the inspired O_2 concentration with an in-line F_{IO_2} analyzer and monitoring of airway pressure should detect most of these causes of failure to deliver O_2 to the patient. [131] [132] [133] [134] [135]

Mechanical Failure of Endotracheal Tube: Main Stem Bronchus Intubation

Esophageal intubation results in almost no ventilation. Virtually all other mechanical problems (except disconnect) with endotracheal tubes (such as kinking, secretion blockage, and herniated or ruptured cuffs) cause an increase in airway resistance and may result in hypoventilation. Intubation of a main stem bronchus (also see Ch. 39) results in the absence of ventilation of the contralateral lung. Although potentially minimized by HPV, some perfusion to the contralateral lung always remains, and shunting increases and Pa_{O_2} decreases. A tube previously well positioned in the trachea may enter a bronchus after the patient or a patient's head is turned or moved into a new position. [136] Flexion of the head causes caudad movement, and extension of the head causes cephalad movement of an endotracheal tube. [136] A high incidence of main stem bronchial intubation following institution of a 30-degree Trendelenburg position has been reported. [137] Cephalad shift of the carina during the Trendelenburg position caused the previously "fixed" endotracheal tube to become located in a main stem bronchus. A main stem bronchial intubation may obstruct the ipsilateral upper lobe in addition to the contralateral lung. [138] [139] Infrequently, the right upper bronchus or one of its segmental bronchi branches from the lateral wall of the trachea and may be occluded by a properly positioned, endotracheal tube.

Hypoventilation (Decreased Tidal Volume)

Patients under general anesthesia may have a reduced spontaneous V_T for two reasons. First, it may be more difficult to breathe during general anesthesia because of increased airway resistance and decreased C_L. Airway resistance may be increased because of reduced FRC, endotracheal intubation, the presence of external breathing apparatus and circuitry, and possible airway obstruction in patients whose tracheas are not intubated. [140] [141] [142] C_L is reduced owing to some (or all) of the factors that can decrease FRC. [143] Second, the patients may be less willing to breathe spontaneously during general anesthesia (decreased chemical control of breathing) (see Fig. 15-31) (Figure Not Available) .

There are two ways a decreased V_T may cause hypoxemia. First, shallow breathing may promote atelectasis and cause a decrease in FRC (see the section *Ventilation History*). [144] [145] Second, decreased V_E decreases the overall V_A/Q ratio of the lung, which decreases Pa_{O_2} (see Figs. 15-23 (Figure Not Available) and 15-24) . This is likely to occur with spontaneous ventilation during moderate to deep levels of anesthesia, in which the chemical control of breathing is significantly altered.

Hyperventilation

Hypocapnic alkalosis (hyperventilation) may result in a decreased Pa_{O_2} via several mechanisms. These mechanisms are decreased Q_T, [102] [103] and increased O_2 consumption [146] [147] (see the section *Decreased Cardiac Output and Increased Oxygen Consumption*), a left-shifted oxy-Hb curve (see the section *Oxygen-Hemoglobin Dissociation Curve*), decreased HPV [148] (see the section *Inhibition of Hypoxic Pulmonary Vasoconstriction*), and/or increased airway resistance and decreased compliance [149] (see the section *Increased Airway Resistance*).

Decrease in Functional Residual Capacity

Induction of general anesthesia is consistently accompanied by a significant (15-20%) decrease in FRC, [85] [94] [150] which usually causes a decrease in compliance. [143] The maximum decrease in FRC appears to occur within the first few minutes of anesthesia [85] [151] [153] and in the absence of any other complicating factor does not seem to decrease progressively during anesthesia. During anesthesia, the reduction in FRC is of the same order of magnitude whether ventilation is spontaneous or controlled. Conversely, in awake patients FRC is only slightly reduced during controlled ventilation. [153] The reduction of FRC continues into the postoperative period. [154] For individual patients, the reduction in FRC correlates well with an increase in the alveolar-arterial P_{O_2} gradient during anesthesia with spontaneous breathing, [155] during anesthesia with artificial ventilation, [152] and in the postoperative period. [154] The reduced FRC may be restored to normal or above normal by application of PEEP. [84] [156] The following discussion considers all possible causes of reduced FRC.

Supine Position

Anesthesia and surgery are usually performed with the patient in the supine position (Ch. 26) . In changing from the upright to the supine position, FRC decreases by 0.5 to 1.0 L [85] [94] [150] because of a 4-cm cephalad displacement of the diaphragm by the abdominal viscera (Fig. 15-33) (Figure Not Available) . Pulmonary vascular congestion may also contribute to the decrease in FRC in the supine position, particularly in patients who experienced orthopnea preoperatively.

Induction of General Anesthesia: Change in Thoracic Cage Muscle Tone

At the end of a normal (awake) exhalation, there is slight tension in the inspiratory muscles and no tension in the expiratory muscles. Thus, at the end of a normal exhalation, there is a force tending to maintain lung volume and no

Figure 15-33 (Figure Not Available) Anesthesia and surgery may cause a progressive cephalad displacement of the diaphragm. The sequence of events involves assumption of the supine position,

induction of anesthesia, causation of paralysis, the assumption of several surgical positions, and displacement by retractors and packs. The cephalad displacement of the diaphragm results in a decreased functional residual capacity (
FRC). P_{ab} , pressure of the abdominal contents. *(Modified from Benumof [189])*

force decreasing lung volume. After induction of general anesthesia, there is a loss of the inspiratory tone and an appearance of end-expiratory tone in the abdominal expiratory muscles at the end of exhalation. The end-expiratory tone in the abdominal expiratory muscles increases intra-abdominal pressure, forces the diaphragm cephalad, and decreases FRC [151] [157] (see Fig. 15-33) (Figure Not Available) . Thus, after the induction of general anesthesia, there is loss of a force tending to maintain lung volume and gain of a force tending to decrease lung volume. Indeed, Innovar (droperidol and fentanyl citrate) may increase tone in expiratory muscles to such an extent that the reduction in FRC with Innovar anesthesia alone is greater than that with Innovar plus paralysis induced by succinylcholine. [157] [158]

With emphysema, exhalation may be accompanied by pursing the lips or grunting (partially closed larynx). The emphysematous patient exhales in either of these ways because both these maneuvers cause an expiratory retard that produces PEEP in the intrathoracic air passage and decreases the possibility of airway closure and decrease in FRC (see Fig. 15-17 (Figure Not Available) F). Endotracheal intubation bypasses the lips and glottis and may abolish normally present pursed-lip or grunting exhalation and in that way contribute to airway closure and a loss in FRC in some spontaneously breathing patients.

Paralysis

In the upright subject, the FRC and the position of the diaphragm are determined by the balance between the lung elastic recoil pulling the diaphragm cephalad and the weight of the abdominal contents pulling it caudad. [159] There is no transdiaphragmatic pressure gradient.

The situation is more complex in the supine position. The diaphragm separates two compartments of markedly different hydrostatic gradients. On the thoracic side, pressure increases by approximately 0.25 cm H_2O/cm of lung height, [6] [7] and on the abdominal side by 1.0 cm H_2O/cm of abdominal height. [159] This means that in horizontal postures, progressively higher transdiaphragmatic pressures must be generated toward dependent parts of the diaphragm to keep the abdominal contents out of the thorax. In the unparalyzed patient, this tension is developed either by passive stretch and shape changes of the diaphragm (causing an increased contractile force) or by neurally mediated active tension. With acute muscle paralysis, neither of these two mechanisms can operate, and a shift of the diaphragm to a more cephalad position occurs [160] (see Fig. 15-33) (Figure Not Available) . The latter position must express the true balance of forces on the diaphragm, unmodified by any passive or active muscle activity.

The cephalad shift in the FRC position of the diaphragm owing to expiratory muscle tone during general anesthesia is equal to the shift observed during paralysis (awake or anesthetized patients). [151] [161] The equal shift suggests that the pressure on the diaphragm caused by an increase in expiratory muscle tone during general anesthesia is equal to the pressure on the diaphragm caused by the weight of the abdominal contents during paralysis. It is quite probable that the magnitude of these changes in FRC due to paralysis also depends on the body habitus.

Light or Inadequate Anesthesia and Active Expiration

The induction of general anesthesia can result in increased expiratory muscle tone, [157] but the increased expiratory muscle tone is not coordinated and does not contribute to the exhaled volume of gas. In contrast, spontaneous ventilation during light general anesthesia usually results in a coordinated and moderately forceful active exhalation and larger exhaled volumes. Excessively inadequate anesthesia (relative to a given stimulus) results in very forceful active exhalation, which may produce exhaled volumes of gas equal to an awake expiratory vital capacity.

As during an awake expiratory vital capacity maneuver, a forced expiration during anesthesia raises the intrathoracic and alveolar pressures considerably above atmospheric pressure (see Fig. 15-17) (Figure Not Available) . This results in a rapid outflow of gas, and because part of the expiratory resistance lies in the smaller air passages, a pressure drop occurs between the alveoli and the main bronchi. Under these circumstances, the intrathoracic pressure rises considerably above the pressure within the main bronchi. Collapse will occur if this reversed pressure gradient is sufficiently high to overcome the tethering effect of the surrounding parenchyma on the small intrathoracic bronchioles or the structural rigidity of cartilage in the large extrathoracic bronchi. Such collapse occurs in the normal subject during a maximal forced expiration and is responsible for the associated wheeze in both awake and anesthetized patients. [162]

In the paralyzed anesthetized patient, use of a subatmospheric expiratory pressure phase is analogous to a forced expiration in the conscious subject; the negative phase may set up the same adverse DeltaP, which can cause airway closure, gas trapping, and a decrease in FRC. An excessively rapidly descending bellows of a ventilator during expiration has caused a subatmospheric expiratory pressure and resulted in wheezing. [163]

Figure 15-34 (Figure Not Available) The anesthetized patient in the supine position has an increased airway resistance owing to decreased functional residual capacity, decreased caliber of the airways, endotracheal intubation, and connection of the endotracheal tube to external breathing apparatus and circuitry. *(Modified from Benumof [189])*

Increased Airway Resistance

The overall reduction in all components of lung volume during anesthesia results in a reduced caliber of airway, which increases airway resistance and any tendency toward airway collapse (Fig. 15-34) (Figure Not Available) . The relationship between airway resistance and lung volume is well established (Fig. 15-35). (Figure Not Available) The decreases in FRC caused by the supine position (
0.8 L) and the induction of anesthesia (
0.4 L) are often sufficient to explain the increased resistance seen in the healthy anesthetized patient. [140]

In addition to this expected increase in airway resistance in anesthetized patients, there are a number of additional special potential sites of increased airway resistance. These consist of the endotracheal tube (if present), the upper and lower airway passages, and the external anesthesia apparatus. Endotracheal intubation reduces the size of the trachea, usually by 30 to 50 percent (see Fig. 15-34) (Figure Not Available) . Pharyngeal obstruction, which can be considered to be a normal feature of unconsciousness, is most common. A minor degree of this

Figure 15-35 (Figure Not Available) Airway resistance is an increasing hyperbolic function of decreasing lung volume. Functional residual capacity (FRC) decreases in changing from the upright to the supine position. *(From Nunn [91])*

type of obstruction occurs in snoring. Laryngospasm and obstructed endotracheal tubes (secretions, kinking, herniated cuffs) are not uncommon and may be life-threatening.

Respiratory apparatus often causes resistance that is considerably higher than the resistance in the normal human respiratory tract [91] (see Fig. 15-34) (Figure Not Available) . When certain resistors such as those shown in Figure 15-34 (Figure Not Available) are joined in a series to form an anesthetic gas circuit, they generally add to produce a larger resistance (as with resistances in series in an electrical circuit). The increase in resistance associated with commonly used breathing circuits and endotracheal tubes may impose an additional work of breathing that is two to three times normal. [142]

Supine Position, Immobility, and Excessive Intravenous Fluid Administration

Patients undergoing anesthesia and surgery are often kept supine and immobile for long periods of time. Thus, some of the lung may be continually dependent and below the left atrium and therefore in zone 3 or 4 condition. Being in a dependent position, the lung is predisposed to fluid accumulation. Coupled with excessive fluid administration, conditions sufficient to promote transudation of fluid into the lung are present and will result in pulmonary edema and a decreased FRC. When mongrel dogs were placed in a lateral decubitus position and were anesthetized for several hours (Fig. 15-36 (Figure Not Available) , bottom horizontal axis), expansion of the extracellular space with fluid (top horizontal axis) caused the P_{O_2} (left-hand axis) of blood draining the dependent lung (closed circles) to decrease precipitously to mixed venous levels (no O_2 uptake). [164] Blood draining the nondependent lung maintained its P_{O_2} for a period of time but in the face of the extracellular fluid expansion also suffered a decline in its P_{O_2} after 5 hours. Transpulmonary shunt (right-hand axis) progressively increased. If the animals were

turned every hour (and received the same fluid challenge), only the dependent lung, at the end of each hour period, suffered a decrease in oxygenation. If the animals were turned every half-hour and received the same fluid challenge, neither lung suffered a decrease in oxygenation. In patients undergoing surgery in the lateral decubitus position (e.g., pulmonary resection, in which they have, or will have, a restricted pulmonary vascular

Figure 15-36 (Figure Not Available) Mongrel dogs anesthetized with pentobarbital (bottom axis), placed in a lateral decubitus position, and subjected to progressive extracellular fluid expansion (top axis) have a marked decrease in the P_{O_2} (left vertical axis) of blood draining the dependent lung (solid circles) and a smaller, much slower decrease in P_{O_2} of blood draining the nondependent lung (open circles). The pulmonary arteriovenous shunt (right vertical axis) rises progressively (triangles). *(From Ray et al [164])*

bed) who receive excessive intravenous fluids, the risk of the dependent lung becoming edematous is certainly increased. These considerations also explain, in part, the beneficial effect of a continuously rotating (side-to-side) bed on the incidence of pulmonary complications in critically ill patients. [165]

High Inspired Oxygen Concentration and Absorption Atelectasis

General anesthesia is usually administered with an increased F_{IO_2}. In patients who have areas of moderately low V_A/Q ratios (0.1 to 0.01), administration of F_{IO_2} greater than 0.3 adds enough O_2 into the alveolar space in these areas to eliminate the shunt-like effect that they have, and total measured right-to-left shunt decreases. However, when patients with a significant amount of blood flow perfusing lung units with very low V_A/Q ratios (0.01-0.0001) have a change in F_{IO_2} from room air to 1.0, the very low V_A/Q units virtually disappear, and a moderately large right-to-left shunt appears. [16] [17] [166] In these studies, the increase in shunting was equal to the amount of blood flow previously perfusing the areas with low V_A/Q ratios during the breathing of air. Thus, in these studies the effect of breathing O_2 was to convert units that had low V_A/Q ratios into shunt units. The pathologic basis for this data is the conversion of low V_A/Q units into atelectatic units.

The cause of the atelectatic shunting during O_2 breathing is presumably a large increase in O_2 uptake by lung units with low V_A/Q ratios. [166] [167] A unit that has a low V_A/Q ratio during breathing of air will have a low P_{AO_2}. When an enriched O_2 mixture is inspired, P_{AO_2} rises, causing the rate at which O_2 moves from the alveolar gas to the capillary blood to increase greatly. The O_2 flux may increase so much that the net flow of gas into the blood exceeds the inspired flow of gas, and the lung unit will become progressively smaller. Collapse is most likely to occur if the F_{IO_2} is high, the V_A/Q ratio is low, the time of exposure of the unit with low V_A/Q to high F_{IO_2} is long, and the Cv_{O_2} is low. Thus, given the right V_A/Q ratio and time of administration, an F_{IO_2} as low as 50 percent can produce absorption atelectasis. [166] [167] This phenomenon is of considerable significance in the clinical situation for two reasons. First, enriched O_2 mixtures are often used therapeutically, and it is important to know whether this therapy is causing atelectasis. Second, the amount of shunt is often estimated during breathing of 100 percent O_2, and if this maneuver results in additional shunt, the measurement will be hard to interpret.

Surgical Position

In the supine position, the abdominal contents force the diaphragm cephalad and reduce FRC (Ch. 26). [94] [151] [157] [161] The Trendelenburg position allows the abdominal contents to push the diaphragm further cephalad, so that the diaphragm not only must ventilate the lungs, but it also must lift the abdominal contents out of the thorax. The result is a predisposition to decreased FRC and atelectasis. [168] Increased pulmonary blood volume and gravitational force on the mediastinal structures are additional factors that may decrease pulmonary compliance and FRC. In the steep Trendelenburg position, most of the lung may be below the left atrium and therefore in a zone 3 or 4 condition. As such, the lung may be susceptible to the development of pulmonary interstitial edema. Thus, patients with elevated Ppa, such as those with mitral stenosis, do not tolerate the Trendelenburg position well. [169]

In the lateral decubitus position, the dependent lung experiences a moderate decrease in FRC and is predisposed to atelectasis, whereas the nondependent lung may have an increased FRC. The overall result is usually a slight to moderate increase in total lung FRC. [170] The kidney and lithotomy positions also cause small decreases in FRC above that caused by the supine position. The prone position may increase FRC moderately. [170]

Ventilation History (Rapid Shallow Breathing)

Rapid shallow breathing is often a regular feature of anesthesia. Monotonous shallow breathing may cause a decrease in FRC, promote atelectasis, and decrease compliance. [144] [145] [171] These changes with rapid shallow breathing are likely due to progressive increases in surface tension. [171] Initially, these changes may cause hypoxemia with normocarbia and may be prevented and/or reversed by periodic large mechanical inspirations, spontaneous sighs, and/or PEEP. [171] [172] [173]

Decreased Removal of Secretions (Decreased Mucociliary Flow)

Tracheobronchial mucous glands and goblet cells produce mucus, which is swept by cilia up to the larynx, where

it is swallowed or expectorated. This process clears inhaled organisms and particles from the lungs. The secreted mucus consists of a surface gel layer lying on top of a more liquid sol layer in which the cilia beat. The tips of the cilia propel the gel layer toward the larynx (upward) during the forward stroke. As the mucus streams upward and the total cross-sectional area of the airways diminishes, absorption takes place from the sol layer to maintain a constant depth of 5 mm. [174]

Poor systemic hydration and low inspired humidity reduce mucociliary flow by increasing the viscosity of secretions and by slowing the ciliary beat. [175] [176] [177] Mucociliary flow varies directly with body or mucosal temperature (low inspired temperature) over a range of 32 to 42°C. [178] [179] A high F_{IO_2} decreases mucociliary flow. [180] Inflation of an endotracheal tube cuff suppresses tracheal mucous velocity, [181] an effect that occurs within 1 hour, and apparently it does not matter whether a low- or high-compliance cuff is used. Passage of an uncuffed tube through the vocal cords and keeping it *in situ* for several hours does not affect tracheal mucous velocity. [181]

The mechanism for endotracheal tube cuff suppression of mucociliary clearance is speculative. In the report of Sackner et al, [181] mucous velocity was decreased in the distal trachea, whereas the cuff was inflated in the proximal portion. Thus, the phenomenon cannot be attributed solely to damming of mucus at the cuff site. One possibility is that the endotracheal tube cuff caused a critical increase in the thickness of the layer of mucus proceeding distally from the cuff. Another possibility is that mechanical distention of the trachea by the endotracheal tube cuff initiated a neurogenic reflex arc, which altered mucous secretions or frequency of ciliary beating.

Other investigators showed that when all the foregoing factors are controlled, halothane reversibly and progressively decreases, but does not stop, mucus flow over an inspired concentration of 1 to 3 MAC. [182] The halothaneinduced depression of mucociliary clearance was likely due to depression of the ciliary beat, an effect that caused slow clearance of mucus from the distal and peripheral airways. In support of this hypothesis is the finding that cilia are morphologically similar throughout the animal kingdom, and in clinical dosages, inhaled anesthetics, including halothane, have been found to cause reversible depression of the ciliary beat of protozoa. [183]

Decreased Cardiac Output and Increased Oxygen Consumption

A decreased Q_T in the presence of a constant O_2 consumption (V_{O_2}), or an increased V_{O_2} in the presence of a constant Q_T, or a decreased Q_T and an increased V_{O_2} must all result in a lower Cv_{O_2}. The venous blood with lowered Cv_{O_2} then flows through whichever shunt pathways exist, mixes with the oxygenated end-pulmonary capillary blood, and lowers the Ca_{O_2} (see Figs. 15-27 and 15-28). Figure 15-37 (Figure Not Available) shows these relationships quantitatively for several different intrapulmonary shunts. [102] [103] The larger the intrapulmonary shunt, the greater the decrease in Ca_{O_2} because more venous blood with lower Cv_{O_2} can admix with end-pulmonary

Figure 15-37 (Figure Not Available) Effects of changes in cardiac output (Q) on the O_2 content of end-pulmonary capillary, arterial, and mixed venous blood for a family of different transpulmonary

right-to-left shunts. The magnitude of the right-to-left shunt is indicated by the various numbered percent symbols for arterial (solid line) and mixed venous (dashed line) blood; the oxygen content of end-capillary blood is unaffected by the degree of shunting. Note that a decrease in Q results in a greater decrease in the arterial content of O_2, the larger the shunt. *(From Kelman et al [102])*

capillary blood. Decreased Q_T may occur with myocardial failure and hypovolemia; the specific causes of these two conditions are beyond the scope of this chapter. Increased V_{O_2} may occur with excessive sympathetic nervous system stimulation, hyperthermia, or shivering and can further contribute to impaired oxygenation of arterial blood. [184]

Inhibition of Hypoxic Pulmonary Vasoconstriction

Decreased regional P_{AO_2} causes regional pulmonary vasoconstriction, which diverts blood flow away from hypoxic regions of the lung to better ventilated normoxic regions of the lung. The diversion of blood flow minimizes venous admixture from the underventilated or nonventilated lung regions. Inhibition of regional HPV could impair arterial oxygenation by permitting increased venous admixture from hypoxic or atelectatic areas of the lung (see Fig. 15-9) .

Because the pulmonary circulation is poorly endowed with smooth muscle, any condition that increases the pressure against which the vessels must constrict (i.e., the Ppa) will decrease HPV. There are numerous clinical conditions that can increase Ppa and therefore decrease HPV. Mitral stenosis, [185] volume overload, [185] low (but >room air) F_{IO_2} in nondiseased lung, [186] a progressive increase in the amount of diseased lung, [186] thromboembolism, [186] hypothermia, [187] and vasoactive drugs [188] can all increase Ppa. Direct vasodilating drugs (such as isoproterenol, nitroglycerin, and sodium nitroprusside), [61] [188] inhaled anesthetics, [189] and hypocapnia [148] [188] can directly decrease HPV. The selective application of PEEP to only the nondiseased lung can selectively increase nondiseased lung pulmonary vascular resistance and may divert blood flow back into the diseased lung. [190]

Figure 15-38 (Figure Not Available) Mechanisms of hypoxemia during pulmonary embolism. See text for explanation of pathophysiologic flow diagram. AV, arteriovenous; CAP PERM, capillary permeability; CC, closing capacity; FRC, functional residual capacity; HPV, hypoxic pulmonary vasoconstriction; PA, pulmonary artery. *(Modified from Benumof [189])*

Paralysis

In the supine position, the weight of the abdominal contents pressing against the diaphragm is greatest in the dependent or posterior part of the diaphragm and is least in the nondependent or anterior part of the diaphragm. In the awake patient breathing spontaneously, the active tension in the diaphragm is capable of overcoming the weight of the abdominal contents, and the diaphragm moves the most in the posterior portion (because the posterior diaphragm is stretched higher into the chest, it has the smallest radius of curvature and therefore it contracts most effectively) and least in the anterior portion. This is a healthy circumstance because the greatest amount of ventilation occurs where there is the most perfusion (posteriorly or dependently), and the least amount of ventilation occurs where there is the least perfusion (anteriorly or nondependently). During paralysis and positive-pressure breathing, the passive diaphragm is displaced by the positive pressure preferentially in the anterior nondependent portion (where there is the least resistance to diaphragmatic movement) and is displaced minimally in the posterior dependent portion (where there is the most resistance to diaphragmatic movement). This is an unhealthy circumstance because the greatest amount of ventilation now occurs where there is the least perfusion, and the least amount of ventilation now occurs where there is the most perfusion. [161] However, the magnitude of the change in the diaphragmatic motion pattern with paralysis varies with body position. [191] [192]

Right-to-Left Interatrial Shunting

Acute arterial hypoxemia from a transient right-to-left shunt through a patent foramen ovale has been described, particularly during emergence from anesthesia. [193] [194] However, unless there is a real-time technique of imaging the cardiac chambers (color-flow Doppler mapping), it is difficult to document an acute and transient right-to-left intracardiac shunt as a cause of arterial hypoxemia. Nevertheless, right-to-left shunting through a patent foramen ovale has been described in virtually every conceivable clinical situation that afterloads the right heart and increases right atrial pressure.

Involvement of Mechanisms of Hypoxemia in Specific Diseases

In any given pulmonary disease, many of the mechanisms of hypoxemia listed earlier may be involved. Pulmonary embolism (air, fat, thrombi) (Fig. 15-38) (Figure Not Available) (Ch. 52) and the evolution of ARDS (Ch. 72) (Fig. 15-39) (Figure Not Available) will be used to illustrate this point. A significant pulmonary embolus can cause severe increases in pulmonary artery pressure, and these increases can cause right-to-left transpulmonary shunting through opened arteriovenous anastomoses and the foramen ovale (possible in 20% of patients), pulmonary edema in nonembolized regions of the lung, and inhibition of HPV.

Figure 15-39 (Figure Not Available) Mechanisms of hypoxemia during the adult respiratory distress syndrome (ARDS). See text for explanation of pathophysiologic flow diagram. CAP PERM, capillary permeability; CC, closing capacity; FRC, functional residual capacity; HPV, hypoxic pulmonary vasoconstriction; PA, pulmonary artery. *(Modified from Benumof [189])*

The embolus may cause hypoventilation via increased dead space ventilation. If the embolus contains platelets, serotonin may be released, and this release can cause hypoventilation via bronchoconstriction and pulmonary edema via increased pulmonary capillary permeability. Finally, the pulmonary embolus can increase pulmonary vascular resistance and decrease the cardiac output.

After major hypotension, shock, or blood loss, respiratory failure often ensues, and this is the syndrome called ARDS (Chs. 71 and 72) . The syndrome can evolve during and after anesthesia and has the hallmark characteristics of decreased FRC and compliance and hypoxemia. Following shock and trauma, plasma levels of serotonin, histamine, plasmakinins, lysozymes, superoxides, fibrin degradation products, products of complement metabolism, and fatty acids increase. Sepsis and endotoxemia may be present. Increased levels of activated complement activate neutrophils into chemotaxis in patients with trauma and pancreatitis; activated neutrophils can damage endothelial cells. These factors, along with pulmonary contusion (if it occurs), may individually or collectively increase pulmonary capillary permeability. After shock, acidosis, increased circulating catecholamines and sympathetic nervous system activity, leukotriene and prostaglandin release, histamine release, microembolism (with serotonin release), increased intracranial pressure (with head injury), and alveolar hypoxia may occur and may individually or collectively, particularly after resuscitation, cause a moderate increase in Ppa. After shock, the normal compensatory response to hypovolemia is movement of a protein-free fluid from the interstitial space into the vascular space to restore vascular volume. The dilution of vascular proteins by protein-free interstitial fluid can cause a decreased capillary colloid oncotic pressure. Increased pulmonary capillary permeability and Ppa along with decreased capillary colloid oncotic pressure will cause fluid transudation and pulmonary edema. Additionally, decreased Q_T, inhibition of HPV, immobility, supine position, excessive fluid administration, and an excessively high F_{IO_2} can contribute to the development of ARDS.

Mechanisms of Hypercapnia and Hypocapnia During Anesthesia

Hypercapnia

Hypoventilation, increased dead space ventilation, increased CO_2 production, and inadvertent switching off of a CO_2 absorber can all cause hypercapnia (Fig. 15-40) (Figure Not Available) .

Hypoventilation

Patients spontaneously hypoventilate during anesthesia because it is more difficult to breathe (abnormal surgical position, increased airway resistance, decreased compliance) and they are less willing to breathe (decreased respiratory drive due to anesthetics). Hypoventilation results in hypercapnia (see Figs. 15-22 and 15-23) (Figure Not Available) .

Increased Dead Space Ventilation

A *decrease* in Ppa, as during deliberate hypotension, [195] may cause an increase in zone 1 and alveolar dead space ventilation. An *increase* in *airway pressure* (as with PEEP) may cause an increase in zone 1 and alveolar dead space ventilation. *Pulmonary embolus, thrombosis,* and *vascular obliteration* (kinking, clamping, blocking of pulmonary artery during surgery) may increase the amount of lung that is ventilated but unperfused. Vascular obliteration may be

Figure 15-40 (Figure Not Available) Schematic diagram of the causes of hypercapnia during anesthesia. An increase in carbon dioxide (CO_2) production (V_{CO_2}) will increase Pa_{CO_2} with a constant minute ventilation (V_E). There are several events that can increase alveolar dead space, and they consist of a decrease in pulmonary artery pressure (Ppa), the application of positive end-expiratory pressure, thromboembolism, and mechanical interference with pulmonary arterial flow (ligatures and kinking of vessels). A decrease in V_E causes an increase in Pa_{CO_2} with a constant V_{CO_2}. It is possible for some anesthesia systems to cause rebreathing of CO_2. Finally, the anesthesia apparatus may increase the anatomic dead space, and inadvertent switching off of a CO_2 absorber in the presence of low fresh gas flows can increase Pa_{CO_2}. *(Modified from Benumof [185])*

responsible for the increase in dead space ventilation with age (V_D/V_T = 33 + age/3). *Rapid short inspirations* may be distributed preferentially to noncompliant (short time constant for inflation) and badly perfused alveoli, while a slow inspiration allows time for distribution to more compliant (long time constant for inflation) and better perfused alveoli. Thus, rapid, short inspirations may have a dead space ventilation effect.

The *anesthesia apparatus* increases total dead space (V_D/V_T) for two reasons. First, the apparatus simply increases the anatomic dead space. Inclusion of normal apparatus dead space increases the total V_D/V_T ratio from 33 percent to about 46 percent in intubated patients and to about 64 percent in patients breathing via a mask. [196] Second, anesthesia circuits cause rebreathing of expired gases, which is equivalent to dead space ventilation. The rebreathing classification by Mapleson is widely accepted. [197] The order of increasing rebreathing (decreasing clinical merit) with spontaneous ventilation with Mapleson circuits is A (Magill), D, C, and B. The order of increasing rebreathing (decreasing clinical merit) with controlled ventilation is D, B, C, and A. There will be no rebreathing in system E (Ayre T-piece) if the patient's respiratory diastole is long enough to permit washout with a given fresh gas flow (common event) or if the fresh gas flow is greater than the peak inspiratory flow rate (uncommon event).

The effects of an increase in dead space can usually be counteracted by a corresponding increase in the respiratory V_E. If, for example, the V_E is 10 L/min and the V_D/V_T ratio is 30 percent, the alveolar ventilation will be 7 L/min. If a pulmonary embolism occurred, resulting in an increase of the V_D/V_T ratio to 50 percent, the V_E would need to be increased to 14 L/min to maintain an alveolar ventilation of 7 L/min (14 L/min × 0.5).

Increased Carbon Dioxide Production

All the causes of increased O_2 consumption also increase CO_2 production: hyperthermia, shivering, catecholamine release (light anesthesia), hypertension, and thyroid storm. If V_E, total dead space, and V_A/Q relationships are constant, an increase in CO_2 production will result in hypercapnia.

Inadvertent Switching Off of a Carbon Dioxide Absorber

Many factors, such as patient ventilatory responsiveness to CO_2 accumulation, fresh gas flow, circle system design, and CO_2 production, determine whether hypercapnia will result from accidental switching off or using up of a circle CO_2 absorber (Ch. 7) . However, high fresh gas flows (> 5 L/min) minimize the problem with almost all systems for almost all patients.

Hypocapnia

The mechanisms of hypocapnia are the reverse of those that produce hypercapnia. Thus, all other factors being equal, hyperventilation (spontaneous or controlled ventilation), decreased V_D ventilation (change from mask airway to endotracheal tube airway, decreased PEEP, increased Ppa, or decreased rebreathing), and decreased CO_2 production (hypothermia, deep anesthesia, hypotension) will lead to hypocapnia. By far the most common mechanism of hypocapnia is passive hyperventilation by mechanical means.

Physiologic Effects of Abnormalities in the Respiratory Gases

Hypoxia

The end products of aerobic metabolism (oxidative phosphorylation) are CO_2 and water, both of which are easily diffusible and lost from the body. The essential feature of hypoxia is the cessation of oxidative phosphorylation when mitochondrial P_{O_2} falls below a critical level. Anaerobic pathways, which produce energy (ATP) inefficiently, are then utilized. The main anaerobic metabolites are hydrogen and lactate ions, which are not easily excreted. They accumulate in the circulation, where they may be quantified in terms of the base deficit and the lactate/pyruvate ratio.

Because the various organs have different blood flow and O_2 consumption rates, the presentation and clinical diagnosis of hypoxia is usually related to symptoms arising from the most vulnerable organ. This organ is usually the brain in an awake patient and the heart in an anesthetized patient (see later), but in special circumstances it may be the spinal cord (aortic surgery), kidney (acute tubular necrosis), liver (hepatitis), or limb (claudication, gangrene).

The cardiovascular response to hypoxemia [198] [199] [200] is a product of both reflex (neural and humoral) and direct effects (Table 15-4) . The reflex effects occur first and are excitory and vasoconstrictive. The neuroreflex effects result from aortic and carotid chemoreceptor, baroreceptor, and central cerebral stimulation, and the humoral reflex effects result from catecholamine and renin-angiotensin release. The direct local vascular effects of hypoxia are inhibitory and vasodilatory and occur late. The net response to hypoxia in a subject depends on the severity of the hypoxia, which determines the magnitude of and balance between the inhibitory and excitory components; the balance may vary according to the type and depth of anesthesia and the degree of preexisting cardiovascular disease.

Mild arterial hypoxemia (arterial saturation less than normal but still 80 percent or higher) causes a general activation of the sympathetic nervous system and release of catecholamines. Consequently, heart rate, stroke volume, Q_T, and myocardial contractility (as measured by a shortened preejection period [PEP], left ventricular ejection time [LVET], and a decreased PEP/LVET ratio) are increased [201] (Fig. 15-41) (Figure Not Available) . Changes in systemic vascular resistance are usually slight. However, in patients under anesthesia with beta-blockers, hypoxia (and hypercapnia when present) may cause circulating catecholamines to have only an alpha-receptor effect, the heart may be unstimulated (even depressed by a local hypoxia effect), and systemic vascular resistance may be increased. Consequently, Q_T may be decreased in these patients. With moderate hypoxemia (arterial O_2 saturation

TABLE 15-4 -- Cardiovascular Response to Hypoxemia

O_2 SATURATION (%)	HEMODYNAMIC VARIABLE					PREDOMINANT RESPONSE
	HR	***BP***	***SV***	***CO***	***SVR***	
>80					No change	Reflex, excitatory
60-80	Baroreceptor		No change	No change		Local, depressant

						>
						Reflex, excitatory
<60						Local, depressant

BP, systemic blood pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance;
, increase;
, decrease.

60 to 80 percent), local vasodilation begins to predominate and systemic vascular resistance and blood pressure decrease, but heart rate may continue to be increased owing to a systemic hypotension-induced stimulation of baroreceptors. Finally, with severe hypoxemia (arterial saturation less than 60 percent), local depressant effects dominate and blood pressure falls rapidly, the pulse slows, shock develops, and the heart either fibrillates or becomes asystolic. Significant preexisting hypotension will convert a mild hypoxemia-hemodynamic profile into a moderate hypoxemia-hemodynamic profile and a moderate hypoxemia-hemodynamic profile into a severe hypoxemia-hemodynamic profile. Similarly, in well anesthetized and/or sedated patients, early sympathetic nervous system reactivity to hypoxemia may be reduced and the effects of hypoxemia may be expressed only as bradycardia with severe hypotension and ultimately, circulatory collapse. [202]

Figure 15-41 (Figure Not Available) Changes in the minute ventilation and circulation of healthy awake humans during progressive isocapnic hypoxia and hyperoxic hypercapnia. P_{ETCO_2}, end-tidal P_{CO_2}; P_{ETO_2}, end-tidal P_{O_2}; Q, minute cardiac output; S_1, slope during the first phase of slowly increasing ventilation and/or circulation; S_2, slope during the second phase of sharply increasing ventilation and/or circulation. V_E, expired minute ventilation. *(From Serebrovskaya, [201] reproduced with permission of S. Karger AG, Basel)*

Hypoxemia may also cause cardiac arrhythmias which may in turn potentiate the already mentioned deleterious cardiovascular effects. Hypoxemia-induced arrhythmias may be caused by multiple mechanisms; the mechanisms are interrelated because they all cause a decrease in the myocardial O_2 supply/demand ratio, which in turn increases myocardial irritability. First, arterial hypoxemia may directly decrease myocardial O_2 supply. Second, early tachycardia may cause an increased myocardial O_2 consumption, and a decreased diastolic filling time may cause a decreased myocardial O_2 supply. Third, early increased systemic blood pressure may cause an increased afterload on the left ventricle, which increases left ventricular O_2 demand. Fourth, late systemic hypotension may decrease myocardial O_2 supply owing to decreased diastolic perfusion pressure. Fifth, coronary blood flow reserve may be exhausted by a late maximally increased coronary blood flow due to maximal coronary vasodilation). [203] The level of hypoxemia that will cause cardiac arrhythmias cannot be predicted with certainty because the myocardial O_2 supply and demand relationship in a given patient is not known (i.e., the degree of coronary artery atherosclerosis may not be known). However, if a myocardial area (or areas) become hypoxic and/or ischemic, unifocal or multifocal premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation may occur.

The cardiovascular response to hypoxia includes a number of other important effects. Cerebral blood flow increases (even if hypocapnic hyperventilation is present). Ventilation will be stimulated no matter why hypoxia exists (see Fig. 15-41) (Figure Not Available) . The pulmonary distribution of blood flow is more homogeneous owing to an increased pulmonary artery pressure. Chronic hypoxia causes an increased Hb concentration and a right-shifted oxy-Hb curve (due to either an increase in 2,3-DPG or acidosis), which tends to raise tissue P_{O_2}.

Hyperoxia (Oxygen Toxicity)

The dangers associated with the inhalation of excessive O_2 are multiple (Ch. 67) . Exposure to a high O_2 tension clearly causes pulmonary damage in healthy individuals. [204] [205] A dose-time toxicity curve for humans is available from a number of studies. [204] [205] [206] Because the lungs of normal human volunteers cannot be directly examined to determine the rate of onset and course of toxicity, indirect measures such as the onset of symptom formation have been

employed to construct the dose-time toxicity curves. Examination of the curve indicates that 100 percent O_2 should not be administered for more than 12 hours, 80 percent O_2 should not be administered for more than 24 hours, and 60 percent O_2 should not be administered for more than 36 hours. [204] [205] [206] No measurable changes in pulmonary function or blood-gas exchange occur in humans during exposures to less than 50 percent O_2 even for long periods. [206] Nevertheless, it is important to note that in the clinical setting, these dose-time toxicity relationships are often generally obscured, [207] owing to the complex multivariable nature of the clinical setting.

The dominant symptom of O_2 toxicity in human volunteers is substernal distress, which begins as a mild irritation in the area of the carina and may be accompanied by occasional coughing. [208] As exposure continues, pain becomes more intense, and the urge to cough and to deep breathe also becomes more intense. These symptoms will progress to severe dyspnea, paroxysmal coughing, and decreased vital capacity when the F_{IO_2} has been 1.0 for longer than 12 hours. At this point, recovery of mechanical lung function usually occurs within 12 to 24 hours, but it may require more than 24 hours in some individuals. [206] As toxicity progresses, other pulmonary function studies such as compliance and blood gases deteriorate. Pathologically, in animals, the lesion progresses from tracheobronchitis (exposure for 12 hours to a few days), to involvement of the alveolar septa with pulmonary interstitial edema (exposure for a few days to 1 week), to pulmonary fibrosis of the edema (exposure for more than 1 week). [209]

Ventilatory depression may occur in those patients who, by reason of drugs or disease, have been ventilating in response to a hypoxic drive. By definition, ventilatory depression resulting from removal of a hypoxic drive by increasing the inspired O_2 concentration will cause hypercapnia but does not necessarily produce hypoxia (owing to the increased F_{IO_2}).

Absorption atelectasis is previously earlier (see the section *High Inspired Oxygen Concentration and Absorption Atelectasis*). Retrolental fibroplasia, an abnormal proliferation of the immature retinal vasculature of the prematurely born infant, can occur after exposure to hyperoxia. Extremely premature infants are most susceptible to retrolental fibroplasia (i.e., those of less than 1.0 kg birth weight and 28 weeks' gestation). The risk of retrolental fibroplasia exists whenever an F_{IO_2} causes Pa_{O_2} to be more than 80 mm Hg for more than 3 hours in an infant whose gestational age plus life age combined is less than 44 weeks. If the ductus arteriosus is patent, arterial blood samples should be drawn from the right radial artery (umbilical or lower extremity Pa_{O_2} is lower than the Pa_{O_2} to which the eyes are exposed owing to ductal shunting of unoxygenated blood).

The mode of action of toxicity of O_2 in tissues is complex, but interference with metabolism seems to be widespread. Most importantly, there is O_2-derived free radicals inactivation of many enzymes, particularly those with sulfhydryl groups. [207] Neutrophil recruitment and release of mediators of inflammation occur next and greatly accelerate the extent of endothelial and epithelial damage and impairment of the surfactant systems. [207] The most acute toxic enzyme effect of O_2 in humans is a convulsive effect, which occurs during exposure to pressures in excess of 2 atm absolute.

High inspired O_2 concentrations can be of use therapeutically. Clearance of gas loculi in the body may be greatly accelerated by inhalation of 100 percent O_2. Inhalation of 100 percent O_2 creates a large nitrogen gradient from the gas space to the perfusing blood. As a result, nitrogen leaves the gas space and the space diminishes in size. Administration of O_2 to remove gas may be used to ease intestinal gas pressure in patients with intestinal obstruction, to hasten recovery from pneumoencephalography, to decrease the size of an air embolus, and to aid in absorption of pneumoperitoneum and pneumothorax.

Hypercapnia

The effects of CO_2 on the cardiovascular system are as complex as those of hypoxia. Like hypoxemia, hypercapnia appears to cause direct depression of both the cardiac muscle and vascular smooth muscle, but at the same time it causes reflex stimulation of the sympathoadrenal system, which compensates to a greater or lesser extent for the primary cardiovascular depression [200] [203] (see Fig. 15-41) (Figure Not Available) . With moderate to severe hypercapnia a hyperkinetic circulation results with increased Q_T and systemic blood pressure (see Fig. 15-41) (Figure Not Available) . [201] Even in patients under halothane anesthesia, plasma

catecholamine levels increase in response to increased CO_2 levels in much the same way as conscious subjects. Thus, hypercapnia, like hypoxemia, may cause increased myocardial O_2 demand (tachycardia, early hypertension) and decreased myocardial O_2 supply (tachycardia, late hypotension).

Table 15-5 summarizes the interaction of anesthesia with hypercapnia in humans; increased Q_T and decreased systemic vascular resistance should be emphasized. [210] [211] The increase in Q_T is most marked during anesthesia with drugs that enhance sympathetic activity and least marked with halothane and nitrous oxide. The decrease in systemic vascular resistance is most marked during enflurane anesthesia and hypercapnia. Hypercapnia is a potent pulmonary vasoconstrictor even after inhalation of 3 percent isoflurane for 5 minutes. [212]

Arrhythmias have been reported in unanesthetized humans during acute hypercapnia, but they have seldom been of serious import. A high Pa_{CO_2} level is, however, more dangerous during general anesthesia. With halothane anesthesia, arrhythmias frequently occur above a Pa_{CO_2} arrhythmic threshold that is often constant for a particular patient.

The maximal stimulant respiratory effect is attained by a Pa_{CO_2} of about 100 mm Hg. With a higher Pa_{CO_2}, stimulation is reduced, and at extremely high levels, respiration is depressed and later ceases altogether. The P_{CO_2}-ventilation response curve is generally displaced to the right, and its slope is reduced by anesthetics and other depressant drugs. [213] With profound anesthesia, the response curve may be flat or even sloping downward, and CO_2 then acts as a respiratory depressant. In patients with ventilatory failure, CO_2 narcosis occurs when the Pa_{CO_2} rises to more than 90 to 120 mm Hg. A 30 percent CO_2 concentration is sufficient for the production of anesthesia, and this concentration causes total but reversible flattening of the electroencephalogram. [214] As expected, hypercapnia causes bronchodilation in both healthy persons and patients with lung disease. [215]

TABLE 15-5 -- Cardiovascular Responses to Hypercapnia (Pa_{CO_2} = 60 to 83 mm Hg) during Various Types of Anesthesia (1 MAC Equivalent Except for Nitrous Oxide)[a]

ANESTHESIA	HEART RATE	CONTRACTILITY	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE
Conscious	++	++	+++	-
Nitrous oxide	0	+	++	--
Fluroxene	+	+++	+++	-
Halothane	0	+	+	-
Enflurane	+	+	++	---
Isoflurane	++	+++	+++	-

+, <10% increase; ++, 10 to 25% increase; +++, >25% increase; 0, no change; -, <10% decrease; -- 10 to 25% decrease; ---, >25% decrease; MAC, minimum alveolar concentration for adequate anesthesia in 50% of subjects.

[a] The increase in partial arterial pressure of carbon dioxide (Pa_{CO_2}) in the conscious subjects was 11.5 mm Hg from a normal level of 38 mm Hg.

Quite apart from the effect of CO_2 on ventilation, it exerts two other important effects that influence the oxygenation of the blood. First, if the concentration of nitrogen (or other inert gas) remains constant, the concentration of CO_2 in the alveolar gas can only increase at the expense of O_2, which must be displaced. Thus, P_{AO_2} and Pa_{O_2} may decrease. Second, hypercapnia shifts the oxy-Hb curve to the right, facilitating tissue oxygenation.

Chronic hypercapnia results in increased resorption of bicarbonate by the kidneys, further raising the plasma bicarbonate level and constituting a secondary or compensatory metabolic alkalosis. Chronic hypocapnia decreases renal bicarbonate resorption, resulting in further fall of plasma bicarbonate and producing a secondary or compensatory metabolic acidosis. In each case arterial pH returns toward the normal value, but the bicarbonate ion concentration departs even further from normal.

Hypercapnia is accompanied by a leakage of potassium from the cells into the plasma. Much of the potassium comes from the liver, probably from glucose release and mobilization, which occur in response to the rise in plasma catecholamine levels. [216] Because the plasma potassium level takes an appreciable time to return to normal, repeated bouts of hypercapnia at short intervals result in a stepwise rise in plasma potassium.

Hypocapnia

In this section, hypocapnia is considered to be produced by passive hyperventilation (by the anesthesiologist or ventilator). Hypocapnia may cause a decrease in Q_T by three separate mechanisms. First, if it is present, an increase in intrathoracic pressure will decrease the cardiac output. Second, hypocapnia is associated with a withdrawal of sympathetic nervous system activity, and this can decrease the ionotropic state of the heart. Third, hypocapnia can increase pH, which can in turn decrease ionized calcium, which may, in turn, decrease the ionotropic state of the heart. Hypocapnia with an alkalosis also shifts the oxy-Hb curve to the left, which increases the Hb affinity for O_2, impairing O_2 unloading at the tissue level. The decrease in peripheral flow and impaired ability to unload O_2 to the tissues is compounded by an increase in whole body O_2 consumption caused by an increased pH-mediated uncoupling of oxidation from phosphorylation. [217] A Pa_{CO_2} of 20 mm Hg will increase tissue O_2 consumption by 30 percent. Consequently, hypocapnia may simultaneously increase tissue O_2 demand and decrease tissue O_2 supply. Thus, to have the same amount of O_2 delivery to the tissues, Q_T or tissue perfusion has to increase at a time when it may not be possible to do so. The cerebral effects of hypocapnia may be related to a state of cerebral acidosis and hypoxia, because hypocapnia may cause a selective reduction in the cerebral blood flow and also shifts the oxy-Hb curve to the left.

Hypocapnia may cause V_A/Q abnormalities by inhibiting HPV or by causing bronchoconstriction and decreased C_L. Finally, passive hypocapnia produces apnea.

References

1. West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung: Relation to vascular and alveolar pressures. J Appl Physiol 19:713, 1964.

2. Puri GD, Venkataranan RK, Singh H et al: Physiological dead space and arterial to end-tidal CO_2 difference under controlled normocapnic ventilation in young anaesthetized subjects. Indian J Med Res 94:41, 1991.

3. Permutt S, Bromberger-Barnea B, Bane HN: Alveolar pressure, pulmonary venous pressure and the vascular waterfall. Med Thorac 19:239, 1962.

4. Willms D, Shure D: Pulmonary edema due to upper airway obstruction in adults. Chest 94:1090, 1988.

5. Lang SA, Duncan PG, Shephard DAE et al: Pulmonary oedema associated with airway obstruction. Can J Anaesth 37:210, 1990.

6. West JB, Dollery CT, Heard BE: Increased pulmonary vascular resistance in the dependent zone of the isolated dog lung caused by perivascular edema. Circ Res 17:191, 1965.

7. West JB (ed): Regional Differences in the Lung. Orlando, Fla, Academic Press, 1977.

8. Hughes JMB, Glazier JB, Maloney JE et al: Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol 4:58, 1968.

9. Hughes JM, Glazier JB, Maloney JE et al: Effect of extra-alveolar vessels on the distribution of pulmonary blood flow in the dog. J Appl Physiol 25:701, 1968.

10. Permutt S, Caldini P, Maseri A et al: Recruitment versus distensibility in the pulmonary vascular bed. In Fishman AP, Hecht H (eds): The Pulmonary Circulation and Interstitial Space. Chicago, University of Chicago Press, 1969, p 375.

11. Maseri A, Caldini P, Harward P et al: Determinants of pulmonary vascular volume: Recruitment versus distensibility. Circ Res 31:218, 1972.

12. Hoppin FG Jr, Green ID, Mead J: Distribution of pleural surface pressure. J Appl Physiol 27:863, 1969.

13. Milic-Emili J, Henderson JAM, Dolovich MB et al: Regional distribution of inspired gas in the lung. J Appl Physiol 21:749, 1966.

14. West JB: Ventilation/Blood Flow and Gas Exchange, 4th ed. Oxford, Blackwell Scientific Publications, 1970.

15. West JB: Regional differences in gas exchange in the lung of erect man. J Appl Physiol 17:893, 1962.

16. Wagner PD, Saltzman HA, West JB: Measurement of continuous distributions of ventilation-perfusion ratios: Theory. J Appl Physiol 36:588, 1974.

17. West JB: Blood flow to the lung and gas exchange. Anesthesiology 41:124, 1974.

18. Fishman AP: Dynamics of the pulmonary circulation. In Hamilton WF (ed): Handbook of Physiology, section 2. Circulation, vol. 2. Baltimore, Williams & Wilkins, 1963, p 1667.

19. Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476, 1977.

20. Reid L: Structural and functional reappraisal of the pulmonary arterial system. In The Scientific Basis of Medicine Annual Reviews. London, Athlone Press, 1968.

21. Marshall C, Marshall BE: Site and sensitivity for stimulation of hypoxic pulmonary vasoconstriction. J Appl Physiol 55:711, 1983.

22. Benumof JL, Mathers JM, Wahrenbrock EA: The pulmonary interstitial compartment and the mediator of hypoxic pulmonary vasoconstriction. Microvasc Res 15:69, 1978.

23. Bohr D: The pulmonary hypoxic response. Chest 71(suppl):244, 1977.

24. Bergofsky EH: Ions and membrane permeability in the regulation of the pulmonary circulation. In Fishman AP, Hecht H (eds): The Pulmonary Circulation and Interstitial Space. Chicago, University of Chicago Press, 1969, p 269.

25. Bergofsky EH: Mechanisms underlying vasomotor regulation of regional pulmonary blood flow in normal and disease states. Am J Med 57:378, 1974.

26. Fishman AP: Hypoxia on the pulmonary circulation: How and where it works. Circ Res 38:221, 1976.

27. Xuan DAT: Endothelial modulation of pulmonary vascular tone. Eur Respir J 5:757, 1992.

28. Hanley SP: Prostaglandins and the lung. Lung 164:65, 1986.

29. Gerber JG, Voelkel N, Nies AS et al: Moderation of hypoxic vasoconstriction by infused arachidonic acid: Role of PGI. J Appl Physiol 49:107, 1980.

30. Leeman M, Naeije R, Lejeune P et al: Influence of cyclo-oxygenase inhibition and of leukotriene receptor blockade on pulmonary vascular pressure/cardiac index relationships in hyperoxic and in hypoxic dogs. Clin Sci 72:717, 1987.

31. Weir EK, McMurtry IF, Tucker A et al: Prostaglandin synthetase inhibitors do not decrease hypoxic pulmonary vasoconstriction. J Appl Physiol 41:714, 1976.

32. Voelkel NF: Mechanisms of hypoxic pulmonary vasoconstriction. Am Rev Respir Dis 133:1186, 1986.

33. Light RB: Indomethacin and ASA reduce intrapulmonary shunt in experimental pneumococcal pneumonia. Am Rev Respir Dis 134:520, 1986.

34. Hales CA, Rouse E, Slate JL: Influence of aspirin and indomethacin on variability of alveolar hypoxic vasoconstriction. J Appl Physiol 45:33, 1978.

35. Kadowitz PJ, Chapnick BM, Joiner PD: Influence of inhibitors of prostaglandin synthesis on the canine pulmonary vascular bed. Am J Physiol 229:941, 1975.

36. Hanley PJ, Roberts D, Dobson K et al: Effect of indomethacin on arterial oxygenation in critically ill patients with severe bacterial pneumonia. Lancet 1:351, 1987.

37. Schulman LL, Lennon PF, Ratner SJ et al: Meclofenamate enhances blood oxygenation in acute oleic acid injury. J Appl Physiol 64:710, 1988.

38. Garrett RC, Thomas HM III: Meclofenamate uniformly decreases shunt fraction in dogs with lobar atelectasis. J Appl Physiol 54:284, 1983.

39. Marshall C, Kim SD, Marshall BE: The actions of halothane, ibuprofen and BW755C on hypoxic pulmonary vasoconstriction. Anesthesiology 66:537, 1987.

40. Hallemans R, Naeji R, Melot C et al: Do cyclo-oxygenase products mediate hypoxic pulmonary vasoconstriction in man? Am Rev Respir Dis 129A:341, 1984.

41. Wagner WW Jr, Lathan LP, Capen RL: Capillary recruitment during airway hypoxia: Role of pulmonary artery pressure. J Appl Physiol 47:383, 1979.

42. Sprague RS, Stephenson AH, Lonigro AJ: Prostaglandin I_2 supports blood flow to hypoxic alveoli in anesthetized dogs. J Appl Physiol 56:1246, 1984.

43. Hanly P, Sienko A, Light RB: Effect of indomethacin on gas exchange, pulmonary perfusion and hemodynamics in experimental *Pseudomonas* pneumonia. Am Rev Respir Dis 133A:282, 1986.

44. Hanly P, Sienko A, Light RB: Role of endogenous prostaglandins in the hemodynamic changes during acute experimental *Pseudomonas* pneumonia with bacteremia. Am Rev Respir Dis 133A:77, 1986.

45. Kobayashi T, Newman JH, Zadoff AD et al: Diethylcarbamazine attenuates hypoxic vasoconstriction but not the pressor response to endotoxin or PGH_2 analog in awake sheep. Am Rev Respir Dis 131A:400, 1985.

46. Morganroth ML, Stenmark KR, Zirrolli JA et al: Leukotriene C_4 production during hypoxic pulmonary vasoconstriction in isolated rat lungs. Prostaglandins 28:867, 1984.

47. Morganroth ML, Reeves JT, Murphy RC et al: Leukotriene synthesis and receptor blockers block hypoxic pulmonary vasoconstriction. J Appl Physiol 56:1340, 1984.

48. Ahmed T, Oliver W: Does slow-reacting substance of anaphylaxis mediate hypoxic pulmonary vasoconstriction? Am Rev Respir Dis 127:566, 1983.

49. Ahmed T, Oliver W, Frank BL et al: Hypoxic pulmonary vasoconstriction in conscious sheep: Role of mast cell degranulation. Am Rev Respir Dis 126:291, 1982.

50. Garrett RC, Foster S, Thomas HM III: Lipoxygenase and cyclooxygenase blockade by BW755C enhances pulmonary hypoxic vasoconstriction. J Appl Physiol 62:129, 1987.

51. Gottlieb JE, McGeady M, Adkinson NF et al: Effects of cyclo- and lipoxygenase inhibitors on hypoxic pulmonary vasoconstriction in isolated ferret lungs. J Appl Physiol 64:936, 1988.

52. Scherer RW, Vigfusson G, Hultsch E et al: Prostaglandin F_2 improves oxygen tension and reduces venous admixture during one lung ventilation in anesthetized paralyzed dogs. Anesthesiology 62:23, 1985.

53. Scherer R, Vigfusson G, Lawin P: Pulmonary blood flow reduction by prostaglandin $F_{2\ alpha}$ and pulmonary artery balloon manipulation during one lung ventilation in dogs. Acta Anaesthesiol Scand 30:2, 1986.

54. Pearl RG, Prielipp RC: Leukotriene synthesis inhibition and receptor blockade do not inhibit pulmonary vasoconstriction in sheep. Anesth Analg 72:169, 1991.

55. Chen L, Miller FL, Malmkvist G et al: Intravenous PGF_{2alpha} infusion does not enhance hypoxic pulmonary vasoconstriction during canine one-lung hypoxia. Anesthesiology 68:226, 1988.

56. Doyle JT, Wilson JS, Warren JV: The pulmonary vascular responses to short-term hypoxia in human subjects. Circulation 5:263, 1952.

57. Fishman AP: State of the art: Chronic cor pulmonale. Am Rev Respir Dis 114:775, 1976.

58. Boysen PG, Block AJ, Wynne JW et al: Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. Chest 76:536, 1979.

59. Zasslow MA, Benumof JL, Trousdale FR: Hypoxic pulmonary vasoconstriction and the size of the hypoxic compartment. J Appl Physiol 53:626, 1982.

60. Marshall BE, Marshall C: Continuity of response to hypoxic pulmonary vasoconstriction. J Appl Physiol 49:189, 1980.

61. Benumof JL: Hypoxic pulmonary vasoconstriction and sodium nitroprusside perfusion. Anesthesiology 50:481, 1979.

62. Benumof JL: Anesthesia for Thoracic Surgery. 3rd ed. Philadelphia, WB Saunders, 1994, chaps. 4 and 8.

63. Simmons DH, Linde CM, Miller JH et al: Relation of lung volume and pulmonary vascular resistance. Circ Res 9:465, 1961.

64. Burton AC, Patel DJ: Effect on pulmonary vascular resistance of inflation of the rabbit lungs. J Appl Physiol 12:239, 1958.

65. Wittenberger JL, McGregor M, Berglund E et al: Influence of state of inflation of the lung on pulmonary vascular resistance. J Appl Physiol 15:878, 1960.

66. Benumof JL, Rogers SN, Moyce PR et al: Hypoxic pulmonary vasoconstriction and regional and whole lung PEEP in the dog. Anesthesiology 52:503, 1979.

67. Benumof JL: Mechanism of decreased blood flow to the atelectatic lung. J Appl Physiol 46:1047, 1978.

68. Pirlo AF, Benumof JL, Trousdale FR: Atelectatic lobe blood flow: Open vs. closed chest, positive pressure vs. spontaneous ventilation. J Appl Physiol 50:1022, 1981.

69. Hagen PT, Scholz DG, Edwards WD: Incidence and size of patent foramen ovale during the first ten decades of life: An autopsy study of 965 normal hearts. Mayo Clin Proc 59:17, 1984.

70. Jaffe RA, Pinto FJ, Schnittger I et al: Intraoperative ventilatorinduced right-to-left intracardiac shunt. Anesthesiology 75:153, 1991.

71. Dubourg O, Bourdarias JP, Farcot JC et al: Contrast echocardiographic visualization of cough-induced right-to-left shunt through a patent foramen ovale. J Am Coll Cardiol 4:587, 1984.

72. Moorthy SS, Haselby KA, Caldwell RL et al: Transient right-left interatrial shunt during emergence from anesthesia: Demonstration by color flow Doppler mapping. Anesth Analg 68:820, 1989.

73. Sykes MK: The mechanics of ventilation. In Scurr C, Feldman S (eds): Scientific Foundations of Anesthesia. Philadelphia, FA Davis, 1970, p 174.

74. Nunn JF: Mechanisms of pulmonary ventilation. In Nunn JF (ed): Applied Respiratory Physiology, 3rd ed. London, Butterworths, 1987, p 64.

75. Scanlon TS, Benumof JL: Demonstration of interlobar collateral ventilation. J Appl Physiol 46:658, 1979.

76. Kent EM, Blades B: The surgical anatomy of the pulmonary lobes. J Thorac Surg 12:18, 1941.

77. Peters RM: Work of breathing following trauma. J Trauma 8:915, 1968.

78. Nunn JF: The minute volume of pulmonary ventilation. In Nunn JF (ed): Applied Respiratory Physiology, 3rd ed. London, Butterworths, 1987, p 65.

79. Nunn JF: Oxygen. In Nunn JF (ed): Applied Respiratory Physiology, 3rd ed. London, Butterworths, 1987, p 109.

80. Shapiro BA, Harrison RA, Trout CA: The mechanics of ventilation. In Clinical Application of Respiratory Care, 3rd ed. Chicago, Year Book, 1985, p 57.

81. Comroe JH, Forster RE, Dubois AB et al: The Lung, 2nd ed. Chicago, Year Book, 1962.

82. Macklem PT, Fraser RG, Bates DV: Bronchial pressures and dimensions in health and obstructive airway disease. J Appl Physiol 18:699, 1983.

83. Craig DB, Wahba WM, Don HF et al: "Closing volume" and its relationship to gas exchange in seated and supine positions. J Appl Physiol 31:717, 1971.

84. Burger EJ Jr, Macklem P: Airway closure: demonstration by breathing 100% O_2 at low lung volumes and by N_2 washout. J Appl Physiol 25:139, 1968.

85. Brismer B, Hedenstierna G, Lundquist H et al: Pulmonary densities during anesthesia with muscular relaxation: A proposal of atelectasis. Anesthesiology 62:422, 1985.

86. Strandberg A, Hedenstierna G, Tokics L et al: Densities in dependent lung regions during anaesthesia: Atelectasis or fluid accumulation? Acta Anaesthesiol Scand 30:256, 1986.

87. Strandberg A, Tokics L, Brismar B et al: Atelectasis during anesthesia and in the postoperative period. Acta Anaesthesiol Scand 30:154, 1986.

88. Hales CA, Kazemi H: Small airways function in myocardial infarction. N Engl J Med 290:761, 1974.

89. Harken AH, O'Connor NE: The influence of clinically undetectable edema on small airway closure in the dog. Ann Surg 184:183, 1976.

90. Biddle TL, Yu PN, Hodges M et al: Hypoxemia and lung water in acute myocardial infarction. Am Heart J 92:692, 1976.

91. Nunn JF: Resistance to gas flow. In Nunn JF (ed): Applied Respiratory Physiology, 3rd ed. London, Butterworths, 1987, p 397.

92. Rehder K, Marsh HM, Rodarte JR et al: Airway closure. Anesthesiology 47:40, 1977.

93. Leblanc P, Ruff F, Milic-Emili J: Effects of age and body position on "airway closure" in man. J Appl Physiol 28:448, 1970.

94. Craig DB, Wahba WM, Don HF et al: "Closing volume" and its relationship to gas exchange in seated and supine positions. J Appl Physiol 31:717, 1971.

95. Foex P, Prys-Roberts C, Hahn CEW et al: Comparison of oxygen content of blood measured directly with values derived from measurement of oxygen tension. Br J Anaesth 42:803, 1970.

96. Sykes MK, Adams AP, Finley WEI et al: The cardiorespiratory effects of hemorrhage and overtransfusion in dogs. Br J Anaesth 42:573, 1970.

97. Gregory IC: The oxygen and carbon monoxide capacities of foetal and adult blood. J Physiol 236:625, 1974.

98. Gilles IDS, Bard BD, Norman J: The effect of anesthesia on the oxyhemoglobin dissociation curve. Br J Anaesth 42:561, 1970.

99. Smith TC, Sotton ET, Behar MG: Does anesthesia alter the hemoglobin dissociation curve? Anesthesiology 35:5, 1970.

100. Kambam JR: Effect of isoflurane on P_{50} and on P_{O_2} measurement. Anesthesiol Rev 14:40, 1987.

101. Lawler PGP, Nunn JF: A re-assessment of the validity of the iso-shunt graph. Br J Anaesth 56:1325, 1984.

102. Kelman GF, Nunn JF, Prys-Roberts C et al: The influence of the cardiac output on arterial oxygenation: A theoretical study. Br J Anaesth 39:450, 1967.

103. Philbin DM, Sullivan SF, Bowman FO et al: Post-operative hypoxemia: Contribution of the cardiac output. Anesthesiology 32:136, 1970.

104. Berggren SM: The oxygen deficit of arterial blood caused by nonventilating parts of the lung. Acta Physiol Scand Suppl 4:11, 1942.

105. Cheney FW, Colley PS: The effect of cardiac output on arterial blood oxygenation. Anesthesiology 52:496, 1980.

106. Henry W: Experiments on the quantity of gases absorbed by water at different temperatures and under different pressures. Philos Trans R Soc 93:29, 1803.

107. Fishman AP: Pulmonary edema: The water-exchanging function of the lung. Circulation 46:390, 1972.

108. Low FN: Lung interstitium, development, morphology, fluid content. In Staub NC (ed): Lung Water and Solute Exchange. New York, Marcel Dekker, 1978, p 17.

109. Weibel ER: Morphological basis of alveolar-capillary gas exchange. Physiol Rev 53:419, 1973.

110. Guyton AC: A concept of negative interstitial pressure based on pressures in implanted perforated capsules. Circ Res 12:399, 1963.

111. Smith-Erichsen N, Bo G: Airway closure and fluid filtration in the lung. Br J Anaesth 51:475, 1979.

112. Oswalt CE, Gates GA, Holmstrom EMG: Pulmonary edema as a complication of acute airway obstruction. Rev Surg 34:364, 1977.

113. Staub NC: Pulmonary edema: Physiologic approaches to management. Chest 74:559, 1978.

114. Permutt S: Effect of interstitial pressure of the lung on pulmonary circulation. Med Thorac 22:118, 1965.

115. Staub NC: "State of the art" review: Pathogenesis of pulmonary edema. Am Rev Respir Dis 109:358, 1974.

116. Marshall BE, Wyche MO: Hypoxemia during and after anesthesia. Anesthesiology 37:178, 1972.

117. Nunn JF, Bergman NA, Coleman AJ: Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation. Br J Anaesth 37:898, 1965.

118. Sykes MK, Young WE, Robinson BE: Oxygenation during anaesthesia with controlled ventilation. Br J Anaesth 37:314, 1965.

119. Rehder K, Sessler AD, Marsh HM: General anesthesia and the lung. In Murray JF (ed): Lung Disease: State of the Art. New York, American Lung Association, 1975-1976, p 367.

120. Nunn JF: Respiratory aspects of anaesthesia. In Nunn JF (ed): Applied Respiratory Physiology, 3rd ed. London, Butterworths, 1987, p 350.

121. Hedenstierna G: Gas exchange during anaesthesia. Br J Anaesth 64:507, 1990.

122. Gunnarsson L, Tokics L, Gustavsson H et al: Influence of age on atelectasis formation and gas exchange impairment during general anesthesia. Br J Anaesth 66:423, 1991.

123. Nunn JF (ed): Applied Respiratory Physiology, 3rd ed. London, Butterworths, 1987, p 370.

124. Vaughan RW, Wise L: Intraoperative arterial oxygenation in obese patients. Ann Surg 184:35, 1976.

125. Dueck R, Young I, Clausen J et al: Altered distribution of pulmonary ventilation and blood flow following induction of inhalational anesthesia. Anesthesiology 52:113, 1980.

126. Rehder K, Knopp TH, Sessler AD et al: Ventilation-perfusion relationships in young healthy awake and anesthetized-paralyzed man. J Appl Physiol 47:745, 1979.

127. Tokics L, Hedenstierna G, Strandberg A et al: Lung collapse and gas exchange during general anesthesia: Effects of spontaneous breathing, muscle paralysis and positive end-expiratory pressure. Anesthesiology 66:157, 1987.

128. Munson ES, Larson CP Jr, Babad AA et al: The effects of halothane, fluroxene and cyclopropane on ventilation: A comparative study in man. Anesthesiology 27:716, 1966.

129. Couture J, Picken J, Trop D et al: Airway closure in normal, obese, and anesthetized supine subjects. FASEB J 29:269, 1970.

130. Don HF, Craig DB, Wahba WM et al: The measurement of gas trapped in the lungs at functional residual capacity and the effects of posture. Anesthesiology 35:582, 1971.

131. Ward CS: The prevention of accidents associated with anesthetic apparatus. Br J Anaesth 40:692, 1968.

132. Mazze RI: Therapeutic misadventures with oxygen delivery systems: The need for continuous in-line oxygen monitors. Anesth Analg 51:787, 1972.

133. Epstein RM, Rackow H, Lee ASJ et al: Prevention of accidental breathing of anoxic gas mixture during anesthesia. Anesthesiology 23:1, 1962.

134. Sprague DH, Archer GW: Intraoperative hypoxia from an erroneously filled liquid oxygen reservoir. Anesthesiology 42:360, 1975.

135. Eger EI II, Epstein RM: Hazards of anesthetic equipment. Anesthesiology 25:490, 1964.

136. Martin JT: Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1978.

137. Heinonen J, Takki S, Tammisto T: Effect of the Trendelenburg tilt and other procedures on the position of endotracheal tubes. Lancet 1:850, 1969.

138. Seto K, Goto H, Hacker D et al: Right upper lobe atelectasis after inadvertent right main bronchial intubation. Anesth Analg 62:851, 1983.

139. Halpern NA, Siegal RE, Papadakos PJ et al: Right upper lobe collapse following uneventful endotracheal intubation. J Cardiothorac Vasc Anesth 3:620, 1989.

140. Mead J, Agostoni E: Dynamics of breathing. In Fenn WO, Rahn H (eds): Handbook of Physiology, section 3. Respiration, vol. 1. Baltimore, Williams & Wilkins, 1964, p 411.

141. Wright PE, Marini JJ, Bernard GR: In vitro versus in vivo comparison of endotracheal tube airflow resistance. Am Rev Respir Dis 140:10, 1989.

142. Bersten AD, Rutten AJ, Vedig AE et al: Additional work of breathing imposed by endotracheal tube, breathing circuits and intensive care ventilators. Crit Care Med 17:671, 1989.

143. Don HF, Robson JG: The mechanics of the respiratory system during anesthesia. Anesthesiology 26:168, 1965.

144. Bendixen HH, Hedley-Whyte J, Chir B et al: Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. N Engl J Med 269:991, 1963.

145. Bendixen HH, Bullwinkel B, Hedley-Whyte J et al: Atelectasis and shunting during spontaneous ventilation in anesthetized patients. Anesthesiology 25:297, 1964.

146. Cain SM: Increased oxygen uptake with passive hyperventilation of dogs. J Appl Physiol 28:4, 1970.

147. Karetzky MS, Cain SM: Effect of carbon dioxide on oxygen uptake during hyperventilation in normal man. J Appl Physiol 28:8, 1970.

148. Benumof JL, Mathers JM, Wahrenbrock EA: Cyclic hypoxic pulmonary vasoconstriction induced by concomitant carbon dioxide changes. J Appl Physiol 41:466, 1976.

149. Cutillo A, Omboni E, Perondi R et al: Effect of hypocapnia on pulmonary mechanics in normal subjects and in patients with chronic obstructive lung disease. Am Rev Respir Dis 110:25, 1974.

150. Don H: The mechanical properties of the respiratory system during anesthesia. Int Anesthesiol Clin 15:113, 1977.

151. Don HF, Wahba M, Cuadrado L et al: The effects of anesthesia and 100 percent oxygen on the functional residual capacity of the lungs. Anesthesiology 32:521, 1970.

152. Hewlett AM, Hulands GH, Nunn JF et al: Functional residual capacity during anaesthesia. III. Artificial ventilation. Br J Anaesth 46:495, 1974.

153. Westbrook PR, Stubbs SE, Sessler AD et al: Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J Appl Physiol 34:81, 1973.

154. Alexander JI, Spence AA, Parikh RK et al: The role of airway closure in postoperative hypoxemia. Br J Anaesth 45:34, 1973.

155. Hickey RF, Visick W, Fairley HB et al: Effects of halothane anesthesia on functional residual capacity and alveolar-arterial oxygen tension difference. Anesthesiology 38:20, 1973.

156. Wyche MQ, Teichner RL, Kallos T et al: Effects of continuous positive-pressure breathing on functional residual capacity and arterial oxygenation during intra-abdominal operation. Anesthesiology 38:68, 1973.

157. Freund F, Roos A, Dodd RB: Expiratory activity of the abdominal muscles in man during general anesthesia. J Appl Physiol 19:693, 1964.

158. Kallos T, Wyche MQ, Garman JK: The effect of Innovar on functional residual capacity and total chest compliance. Anesthesiology 39:558, 1973.

159. Campbell EJM, Agostini E, David JN: The Respiratory Muscles: Mechanics and Neural Control, 2nd ed. Philadelphia, WB Saunders, 1970.

160. Milic-Emili J, Mead J, Tanner JM: Topography of esophageal pressure as a function of posture in man. J Appl Physiol 19:212, 1964.

161. Froese AB, Bryan CA: Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242, 1974.

162. Dekker E, Defares JG, Heemstra H: Direct measurement of intrabronchial pressure: Its application to the location of the check-valve mechanism. J Appl Physiol 13:35, 1958.

163. Ward CF, Gagnon RL, Benumof JL: Wheezing after induction of general anesthesia: Negative expiratory pressure revisited. Anesth Analg 58:49, 1979.

164. Ray JF, Yost L, Moallem S et al: Immobility, hypoxemia, and pulmonary arteriovenous shunting. Arch Surg 109:537, 1974.

165. Gentilello L, Thompson DA, Tonnesen et al: Effect of a rotating bed on the incidence of pulmonary complications in critically ill patients. Crit Care Med 16:783, 1988.

166. Wagner PD, Laravuso RB, Uhl RR et al: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2. J Clin Invest 54:54, 1974.

167. Briscoe WA, Cree EM, Filler et al: Lung volume, alveolar ventilation and perfusion interrelationships in chronic pulmonary emphysema. J Appl Physiol 15:785, 1960.

168. Slocum HC, Hoeflich EA, Allen CR: Circulatory and respiratory distress from extreme positions on the operating table. Surg Gynecol Obstet 84:1065, 1947.

169. Laver MB, Hallowell P, Goldblatt A: Pulmonary dysfunction secondary to heart disease: Aspects relevant to anesthesia and surgery. Anesthesiology 33:161, 1970.

170. Lumb AB, Nunn JF: Respiratory function and ribcage contribution to ventilation in body positions commonly used during anesthesia. Anesth Analg 73:422, 1991.

171. Huang YC, Weinmann GG, Mitzner W: Effect of tidal volume and frequency on the temporal fall in lung compliance. J Appl Physiol 65:2040, 1988.

172. Tweed WA, Phua WT, Chong KY et al: Large tidal volume ventilation improves pulmonary gas exchange during lower abdominal surgery in Trendelenburg's position. Can J Anaesth 38:989, 1991.

173. Grim PS, Freund PR, Cheney FW: Effect of spontaneous sighs on arterial oxygenation during isoflurane anesthesia in humans. Anesth Analg 66:839, 1987.

174. Yeaker H: Tracheobronchial secretions. Am J Med 50:493, 1971.

175. Forbes AR: Humidification and mucous flow in the intubated trachea. Br J Anaesth 45:874, 1973.

176. Bang BG, Bang FB: Effect of water deprivation on nasal mucous flow. Proc Soc Exp Biol Med 106:516, 1961.

177. Hirsch JA, Tokayer JL, Robinson MJ et al: Effects of dry air and subsequent humidification on tracheal mucous velocity in dogs. J Appl Physiol 39:242, 1975.

178. Dalhamn T: Mucous flow and ciliary activity in the tracheas of rats exposed to respiratory irritant gases. Acta Physiol Scand Suppl 36:123, 1956.

179. Hill L: The ciliary movement of the trachea studies *in vitro.* Lancet 2:802, 1928.

180. Sackner MA, Landa J, Hirsch J et al: Pulmonary effects of oxygen breathing. Ann Intern Med 82:40, 1975.

181. Sackner MA, Hirsch J, Epstein S: Effect of cuffed endotracheal tubes on tracheal mucous velocity. Chest 68:774, 1975.

182. Forbes AR: Halothane depresses mucociliary flow in the trachea. Anesthesiology 45:59, 1976.

183. Nunn JF, Sturrock JE, Wills EJ et al: The effect of inhalation anaesthetics on the swimming velocity of *Tetrahymena pyriformis.* J Cell Sci 15:537, 1974.

184. Prys-Roberts C: The metabolic regulation of circulatory transport. In Scurr C, Feldman S (eds): Scientific Foundation of Anesthesia. Philadelphia, FA Davis, 1970, p 87.

185. Benumof JL, Wahrenbrock EA: Blunted hypoxic pulmonary vasoconstriction by increased lung vascular pressures. J Appl Physiol 38:846, 1975.

186. Scanlon TS, Benumof JL, Wahrenbrock EA et al: Hypoxic pulmonary vasoconstriction and the ratio of hypoxic lung to perfused normoxic lung. Anesthesiology 49:177, 1978.

187. Benumof JL, Wahrenbrock EA: Dependency of hypoxic pulmonary vasoconstriction on temperature. J Appl Physiol 42:56, 1977.

188. Benumof JL: Anesthesia for Thoracic Surgery. Philadelphia, WB Saunders, 1987, Chap. 4 .

189. Benumof JL: Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, chap. 8 .

190. Benumof JL: One lung ventilation: Which lung should be PEEPed? Anesthesiology 56:161, 1982.

191. Krayer S, Rehder K, Vettermann et al: Position and motion of the human diaphragm during anesthesia-paralysis. Anesthesiology 70:891, 1989.

192. Froese AB: Anesthesia-paralysis and the diaphragm: In pursuit of an elusive muscle. Anesthesiology 70:887, 1989.

193. Moorthy SS, Dierdorf SF, Krishna G et al: Transient hypoxemia from a transient right-to-left shunt in a child during emergence from anesthesia. Anesthesiology 66:234, 1987.

194. Moorthy SS, Haselby KA, Caldwell RL et al: Transient right-left interatrial shunting during emergence from anesthesia: demonstration by color flow Doppler mapping. Anesth Analg 68:820, 1989.

195. Eckenhoff JE, Enderby GEH, Larson A et al: Pulmonary gas exchange during deliberate hypotension. Br J Anaesth 35:750, 1963.

196. Kain ML, Panday J, Nunn JF: The effect of intubation on the dead space during halothane anaesthesia. Br J Anaesth 41:94, 1969.

197. Conway CM: Anesthetic circuits. In Scurr C, Feldman S (eds): Scientific Foundations of Anesthesia, 2nd ed. London, William Heinemann Medical Books, 1974, p 509.

198. Heistad DD, Abboud FM: Circulatory adjustments to hypoxia: Dickinson W. Richards Lecture. Circulation 61:463, 1980.

199. Roberts JG: The effect of hypoxia on the systemic circulation during anaesthesia. In Prys-Roberts E (ed): The Circulation in Anaesthesia: Applied Physiology and Pharmacology. Oxford, Blackwell Scientific Publications, 1980, p 311.

200. Rothe CF, Flanagan AD, Maass-Moreno R: Reflex control of vascular capacitance during hypoxia, hypercapnia, or hypoxic hypercapnia. Can J Physiol Pharmacol 68:384, 1990.

201. Serebrovskaya TV: Comparison of respiratory and circulatory human responses to progressive hypoxia and hypercapnia. Respiration 59:35, 1992.

202. Dohzaki S, Ohtsuka H, Yamamura T et al: Comparative effects of volatile anesthetics on the sympathetic activity to acute hypoxemia or hypercarbia in dogs. Anesth Analg 70:S87, 1990.

203. Lehot JJ, Leone BJ, Foex P: Effects of altered Pa O_2 and Pa CO_2 on left ventricular function and coronary hemodynamics of sheep. Anesth Analg 72:737, 1991.

204. Winter PM, Smith G: The toxicity of oxygen. Anesthesiology 37:210, 1972.

205. Lambertsen CJ: Effects of oxygen at high partial pressure. In Fenn WO, Rahn H (eds): Handbook of Physiology, section 3. Respiration, vol. 2. Baltimore, Williams & Wilkins, 1965, p 1027.

206. Clark JM: Pulmonary limits of oxygen tolerance in man. Exp Lung Res 14:897, 1988.

207. Klein J: Normobaric pulmonary oxygen toxicity. Anesth Analg 70:195, 1990.

208. Montgomery AB, Luce JM, Murray JF: Retrosternal pain is an early indicator of oxygen toxicity. Am Rev Respir Dis 139:1548, 1989.

209. Nash G, Blennerhasset JB, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 276:368, 1967.

210. Waltwil LMT, Olsson JG: Circulatory effects of isoflurane during acute hypercapnia. Anesth Analg 66:1234, 1987.

211. Prys-Roberts C: Hypercapnia. In Gray TC, Nunn JF, Utting JE (eds): General Anaesthesia, 4th ed. London, Butterworth, 1980, p 435.

212. Wattwil LMT, Olsson JG: Circulatory effects of isoflurane during hypercapnia. Anesth Analg 66:1234, 1987.

213. Severinghaus JW, Larson CP: Respiration in anesthesia. In Fenn WO, Rahn H (eds): Handbook of Physiology, section 3. Respiration, vol. 2. Baltimore, Williams & Wilkins, 1965, p 1219.

214. Clowes GHA, Hopkins AL, Simeone FA: A comparison of the physiological effects of hypercapnia and hypoxia in the production of cardiac arrest. Ann Surg 142:446, 1955.

215. Parson PE, Grunstein MM, Fernandez E: The effects of acute hypoxia and hypercapnia on pulmonary mechanics in normal subjects and patients with chronic pulmonary disease. Chest 96:96, 1989.

216. Fenn WO, Asano T: Effects of carbon dioxide inhalation on potassium liberation from the liver. Am J Physiol 185:567, 1956.

217. Patterson RW: Effect of Pa CO_2 on O_2 consumption during cardiopulmonary bypass in man. Anesth Analg 55:269, 1976.

Chapter 16 - Cardiac Physiology *

Thomas J. J. Blanck
David L. Lee

INTRODUCTION

Cardiac physiology today concerns a broad range of issues extending from systems physiology to molecular biology. In this chapter, we examine a few of the issues pertinent to the understanding of cardiac contraction, the regulation of contraction, and the assessment of cardiac contractility.

The heart is a pump that works continuously from before birth until death; this requires approximately 2.6 billion contractions over a lifetime (assuming a life-span of 73 years and a heart rate of 70 beats/min). With a cardiac output of 3 to 5 L/min, the heart is required to pump 100 to 200 million L of blood in a lifetime in order to deliver approximately 9.6 billion L of oxygen to the tissues of the body. Obviously, the heart is a pump that is dependable and durable, and it is quite remarkable that more problems related to cardiac dysfunction do not appear in view of the incredible workload the heart must perform. The following discussion deals with the average mechanisms of cardiac contraction and does not consider the differences that exist in cardiac function at the extremes of youth and old age (Chs. 58 , 59 , and 61).

CELLULAR STRUCTURE

Anatomic Considerations

The heart can be considered as two parallel pumps, each consisting of an atrium and a ventricle, acting in unison to propel blood into the pulmonary and systemic circulations from the right and left sides, respectively. Anatomically, the walls of the cardiac chambers consist of three parts: the endocardium, a thin inner layer of endothelial cells in direct contact with the blood; the myocardium, a middle layer consisting predominantly of muscle tissue; and the epicardium, an outer layer that is actually the inner portion of the double-layered pericardium, a fibrous sheath composed of mesothelial cells encasing the heart.

Blood return from the body enters the right atrium (RA) through the superior and inferior vena cava. It is then pumped through the tricuspid valve into the right ventricle (RV) and through the pulmonic valve into the pulmonary circulation, where oxygen-carbon dioxide exchange occurs within lung alveoli. Newly oxygenated blood returns to the left atrium (LA) via the pulmonary veins and passes through the mitral valve into the left ventricle (LV). The blood is then propelled through the aortic valve into the systemic circulation in order to meet the metabolic demands of peripheral tissues. Elaborate nervous and endocrine feedback loops carefully regulate the function of the heart and circulatory systems.

Structurally, the atria are thin-walled, low-pressure chambers that essentially serve as conduits to the ventricles. [1] The interatrial septum, which divides the two chambers, is embryologically derived from the foramen ovale and is the thinnest portion of the heart. Pacemaker activity of the conduction system of the heart originates in the sinoatrial (SA) and atrioventricular (AV) nodes, both of which are located within the RA. RA and LA chamber pressures vary anywhere from 0 to 10 mm Hg. [2]

Between each atrium and its respective ventricle lies an AV valve. As its name implies, the tricuspid valve, which separates the RA from the RV, is composed of three leaflets (anterior, medial, and posterior) arranged to open into the ventricle to allow one-way flow of blood from the atrium. The normal tricuspid valve has an 8- to 11-cm^2 area. [2] At the tip of each leaflet are the chordae tendineae, strong fibrous filaments that are anchored within the papillary muscles of the ventricles. They act to hold the leaflets together in a closed position during ventricular ejection to prevent prolapse of the valves and regurgitation of the blood back into the atria.

---

* *See Practice Guideliness for Pulmonary Artery Catheterization*

The mitral valve, which separates the LA from the LV, is composed of two leaflets (anterior and posterior), also arranged in an inverted fashion connected by chordae tendineae to the papillary muscles. The normal mitral valve has a 6- to 8-cm^2 area. [3]

The ventricles are thick-walled, muscular, high-pressure chambers that serve to propel blood forward into the pulmonary and systemic circulations. Because the LV must pump against higher pressure, its walls are considerably thicker than those of the RV. *In utero,* the ratio of LV to RV thickness is approximately 1:1. After delivery, pulmonary vascular resistance rapidly decreases with expansion of the lungs and increased oxygen saturation, and systemic vascular resistance increases with loss of the placenta, such that over the first month of extrauterine life, the LV/RV thickness ratio increases to 2:1, which is similar to that of the adult. [4] The ventricles are separated by the interventricular septum, consisting of a thinner membranous portion along the uppermost segment of the septum, which is contiguous with the RA, and a thicker muscular portion, which forms the major body of the septum and is structurally identical to the rest of the LV free wall. Normal RV pressures are in the ranges 15 to 30/0 to 10 mm Hg, whereas normal LV pressures are in the ranges 100 to 140/3 to 12 mm Hg.

Between each ventricle and its respective outflow tract is a semilunar (half-moon-shaped) valve. The pulmonic valve, which separates the RV from the pulmonary artery, comprises three cusps (anterior, right, and left), which are arranged to allow unidirectional flow of blood by pushing the individual cusps up and outward into the pulmonary artery during ventricular systole, only to have them snap back together during diastole. Normal pulmonic valve area is 4 cm^2. A similar arrangement occurs in the aortic valve, which separates the LV from the aorta, except that the three cusps (posterior, right, and left) are slightly thicker, owing to the increased stress placed on the valve by higher systemic pressures. Normal aortic valve area is 3 to 4 cm^2. Normal pulmonary artery pressures are 15 to 30/3 to 12 mm Hg, and normal aortic pressures are 100 to 140/60 to 90 mm Hg. [2]

Behind the cusps of the aortic valve and, to a lesser extent, the pulmonic valve, small outpouchings in the aorta and pulmonary artery known as the *sinuses of Valsalva* produce tiny eddy currents, which tend to keep the cusps away from the vessel walls. These sinuses are of significance because they prevent occlusion of the right and left coronary ostia, which originate behind the right and left aortic cusps, respectively. [1]

The right coronary artery originates from the aorta behind the right aortic cusp and travels anteriorly behind the pulmonary artery into the groove between the RA and RV [5] (Fig. 16-1). (Figure Not Available) It gives off several branches, including the acute marginal, and continues circumferentially until it reaches the posterior interventricular groove. It is primarily responsible for blood supply to the RA and RV, and in 50 percent of the population, it gives rise to the posterior descending artery, which courses along the interventricular septum, providing blood supply to the AV node and the posterior third of the septum. This is termed a right dominant distribution pattern despite some overlapping blood supply from the left circumflex artery in an additional 30 percent of individuals. [6] [7]

The left main coronary artery originates from the aorta behind the left cusp of the aortic valve and courses laterally behind the pulmonary artery, where it divides into the left anterior descending artery and the left circumflex artery (see Fig. 16-1). (Figure Not Available) The left anterior descending artery travels anteriorly and courses down the anterior interventricular groove toward the apex, where it gives off branches, including the ramus intermedius, septal perforators, and diagonals, that are responsible for the blood supply to the anterior free wall of the LV and the anterior two-thirds of the septum. Meanwhile, the left circumflex artery extends posteriorly along the groove between the LA and the LV, giving off the obtuse marginal branches, until it connects with the right coronary artery at the posterior interventricular groove. It is primarily responsible for blood supply to the LA and posterolateral segments of the LV, and in 20 percent of individuals, it gives rise to the posterior descending artery. This is termed a left dominant distribution pattern. Blood supply to the SA node is provided by a branch of either the right coronary artery (59% of cases) or the left circumflex artery (38% of cases). [8] Blood supply to the AV node is provided by a branch of the right coronary artery (90% of cases) or the left circumflex artery (10% of cases). [8A]

Most venous blood from the heart returns to the RA via the coronary sinus, which drains the great and middle cardiac veins and the posterior LV vein. However, some return occurs via the anterior coronary veins, in addition to direct blood return into the cardiac chambers via arteriosinusoidal, arterioluminal, and thebesian vessels. [9] Arteriosinusoidal channels are small arteries that divide into endothelium-lined sinuses that connect with other sinuses and capillaries and filter into the chambers. Arterioluminal vessels are small arterioles in direct communication with the chambers. Thebesian vessels are small veins that connect capillaries directly to the chambers as well as between other capillaries and cardiac veins. All three vessel types form an extensive subendocardial vascular network, which possibly plays a

role in added myocardial oxygen and nutrient delivery.

Cellular Anatomy

At the cellular level, the heart itself can be divided into the cardiac muscle tissue, the conduction system, and the extracellular connective tissue, which consists mainly of collagen. The cardiac muscle cell is unique in that it incorporates characteristics present in both skeletal and smooth muscle, yet it remains morphologically distinct. As in skeletal muscle, cross-striations or Z lines are present in cardiac tissue, demarcating the sarcomere borders. The sarcomeres are the smallest units of the contractile complex and are separated from one another at each end by Z lines; each sarcomere consists of an ordered array of thick (myosin molecules) and thin (actin molecules) filaments [10] [11] (Fig. 16-2) (Figure Not Available) and a third filament system that imparts stiffness to the myocyte (see (Fig. 16-2) (Figure Not Available) A, B). The third filament system consists of the giant protein, titin, with a molecular weight of
30,000 kd, that imparts structural integrity and passive tension response to stretched muscle. [12] Titin is the third most abundant muscle protein after myosin and actin, and it constitutes approximately 10 percent of muscle protein. Titin has two important domains that appear to impart elastic and passive tension properties to the protein and the muscle: an immunoglobulin domain (Ig) and a PEVK domain consisting of repeating residues of proline (P), glutamate (E), valine (V), and lysine (K). Cardiac muscle is the stiffest of the striated muscles, and its stiffness appears related

Figure 16-1 (Figure Not Available) The anatomic distribution of the coronary arteries and veins along the surface of the heart and their relationship to the great vessels. *(From Berne and Levy [5])*

to the smaller complement of Ig and PEVK residues relative to skeletal muscle. Unlike the fibers of striated muscle, the individual muscle fibers in the heart are contained within discrete cell membranes. These membranes contain extensive networks of interdigitating folds, which link the ends of individual fibers together along their Z lines in areas known as *intercalated disks.* These disks form a tight connection between longitudinally arranged fibers and allow for tension to be transferred uniformly between cells in that particular axis. In addition, the presence of fused cell membranes, or gap junctions, between laterally adjacent muscle fibers provides a low-resistance pathway for propagation of depolarization potentials between fibers. The gap junction connects adjacent myocytes and is responsible for the electrical continuity that exists between cells in the heart. [13] [14]

The gap junction has a permeability that is several orders of magnitude greater than that of normally juxtaposed plasma membranes. The major protein component of the gap junction is connexin, which appears to make up the six subunits of the channel structure (the *connexon*) that links

Figure 16-2 (Figure Not Available) (A) Contractile elements of the sarcomere. Individual actin fibers form the thin filament, a double helical structure that houses the troponin and tropomyosin complex. Individual myosin molecules form the thick filament, the articulated region that allows for cross-bridging of the two structures during contraction. *(Fig. A from Langer [10])* (B) Electron micrograph of mammalian cardiac muscle in longitudinal section. A sarcomere, the smallest contractile unit, is defined from Z line to Z line. The light areas adjacent to the Z line are made up of thin filaments (actin filaments), which are anchored to the Z line, and the dark central zone is due to the interdigitation of thick (myosin molecules) and thin filaments. The H zone is due solely to thick filaments. The section on the left shows muscle at the optimum length on its length-tension curve (no H zone), and that on the right is muscle that has been stretched. *(Fig. B from Fawcett and McNutt [11])*

the cytoplasm of adjacent cells. [15] The connexins consist of a family of related proteins that contain conserved and unique regions. Connexin 40, connexin 43, and connexin 45 are all found in cardiomyocytes. The individual connexins form channels with different permeability, voltage dependence, and conductance properties. [16] The gating properties (i.e., the regulation of opening) of these channels are under intense investigation, but the channels appear to remain in an open conformation for more time than do other ion channels found in the myocyte plasma membrane. [17] The gap

junction effectively allows for cardiac muscle to act in a synchronous manner as a syncytium, similar to that of smooth muscle, while maintaining cellular integrity.

The myocardial cell is surrounded by its plasma membrane, which has proteoglycans and connective tissue attached to its outer surface. Together, the plasma membrane and its outer constituents comprise the sarcolemma. The plasma membrane is typical of lipid bilayers found in mammalian cells. Imbedded within this lipid bilayer and extending from the extracellular to the intracellular space are receptors, ion channels, and ionic pumps that allow the cells to communicate with each other and their extracellular environment.

In the myocardial cell, invaginations of the plasma membrane result in the extension of extracellular space into more central portions of the myocardial cell [11] (Fig. 16-3) (Figure Not Available) . These invaginations are called *transverse tubules* (T tubules). The T tubules are in close proximity to an intracellular membrane system, the sarcoplasmic reticulum (SR), which is the major storage area for ionized calcium (Ca^{2+}) within the cell. Although the SR is a contiguous membrane structure, it can be further divided into two functional types, longitudinal and junctional SR. A large protein complex termed the *calcium release channel* resides within the junctional SR membrane. It responds to the depolarization-stimulated influx of Ca^{2+} through the sarcolemmal L-type Ca^{2+} channel

Figure 16-3 (Figure Not Available) Electron micrograph of mammalian cardiac muscle in cross-section. TT indicates the T tubule, which extends into the body of the muscle from the outer sarcolemma. *(From Fawcett and McNutt [11])*

by releasing large amounts of Ca^{2+} from the SR stores into the myoplasm, resulting in an increase in intracellular Ca^{2+} concentration from 10^{-7} to 10^{-5} mol/L.

Electrical Activity and Conduction System

As seen in Figure 16-4 , the conduction system of the heart consists of the SA and AV nodes, the bundle of His, and Purkinje fibers of the right and left bundle branches, which initiate, transmit, and propagate impulses and subsequent contraction in a sequential fashion. [18]

Electrophysiology

In the normal heart the action potential originates at the SA node. Contraction of the heart is initiated by the action potential, of which two types present within the heart: fast-response action potentials, which occur in most myocardial tissue, including the atria, ventricles, and Purkinje cells of the conduction system; and slow-response action potentials, which are found in the specialized cells responsible for the internal automaticity or pacemaker activity of the heart, namely the SA and AV nodes. [19] The difference between the two types of action potential lies in the resting membrane potential (V_m) present in the various cells and the rate of rise

Figure 16-4 The components of the conduction system and their anatomic relationship to the chambers of the heart. *(From Berne and Levy [18])*

Figure 16-5 (Figure Not Available) The four phases of an action potential and the various ion movements that occur along electrostatic and electrochemical gradients with membrane depolarization.

(Modified from Berne and Levy [18])

of upstroke of the action potential, which subsequently determines the propagation velocity of the action potential through the heart. [19]

The action potential can be divided into four phases, [18] as depicted in Figure 16-5 (Figure Not Available) . In the fast-response action potential, the resting V_m in a cardiac muscle cell is -80 to -90 mV, and phase 0 represents initial depolarization of the cell through the voltage-dependent fast sodium (Na^+) channels. [20] These sarcolemmal Na^+ channels operate in a double-gated fashion in which initially the outer, or m-gate (activation gate) is closed until a threshold V_m of -60 to -70 mV is achieved [21] (Fig. 16-6) (Figure Not Available) . The gate then opens, and Na^+

Figure 16-6 (Figure Not Available) Schematic of sodium channel dynamics that occur during a cardiac cycle. The channel is initially closed but not inactivated; depolarization leads to activation, which opens the m-gate, allowing entry of ions. Subsequently the h-gate closes, inactivating the channel and preventing ion flow. Deactivation then occurs, with both the m-gate and h-gate closed. This is followed by removal of inactivation, with opening of the h-gate, priming the channel for voltagesensitive activation. *(Modified from Levitan and Kazcmarek [21])*

is allowed to enter the cell along its concentration and electrostatic gradient, contributing to the brisk upstroke seen in the V_m. As the V_m reaches +30 mV, the inner, or h-gate (inactivation gate) closes, preventing further influx of Na^+ (inhibition of Na^+ channels) and effectively ending phase 0. At a V_m of 0, there are no further electrostatic forces pulling Na^+ into the cell, but Na^+ nonetheless continues to enter the cell because of the persistent concentration gradient, which accounts for the overshoot seen in the V_m. These fast Na^+ channels are inhibited by tetrodotoxin. [22]

Partial repolarization (phase 1) and the plateau (phase 2) at a V_m of around 0 are dominated by the influx of Ca^{2+} through slow L-type voltage-dependent Ca^{2+} and to a lesser extent, of Na^+ along its slow channel. These channels open initially at a V_m of -30 mV during the rapid depolarization upstroke of phase 0 and allow Ca^{2+} and to a lesser extent, Na^+, to enter the cell along its concentration gradient. [23] The entry of Ca^{2+} via these channels triggers further release of Ca^{2+} from the SR. [24] Free intracellular Ca^{2+} is then able to bind contractile proteins and to initiate contractile force. Catecholamines, such as epinephrine and norepinephrine, increase slow inward Ca^{2+} currents, and this represents one of the mechanisms by which catecholamines increase contractile force. These slow Ca^{2+} channels are inhibited by manganese and by dihydropyridine and phenylalkylamine-type Ca^{2+} channel antagonists. [25]

Repolarization, or phase 3, occurs as the ionized potassium (K^+) permeability increases, leading to an efflux of K^+ along its concentration gradient out of the cell. This has the effect of lowering V_m to its resting potential and causing the closure and inactivation of the slow Ca^{2+} and Na^+ channels. During this period, which is known as the *effective* or *absolute refractory* period, no further depolarization of the cell can take place. Restoration of Na^+ and K^+ to their preexcitation concentration gradients occurs via an active transport Na^+/K^+ membrane adenosine triphosphatase (ATPase) pump at a ratio of 6 Na^+ ions out for every 3 K^+ ions in. Ca^{2+} homeostasis is achieved by the SR, Ca^{2+}, Mg^{2+} ATPase and the sarcolemmal Ca^{2+} ATPase and Na^+, Ca^{2+} exchange mechanism.

Finally, phase 4 represents the period between completion of repolarization and initiation of the next action potential. During this period, K^+ continues to leak slowly from the cell along its concentration gradient.

In contrast, in the slow-response action potential, cell resting V_m are approximately -60 mV [18] (Fig. 16-7) (Figure Not Available) . Fast Na^+ channel activation is virtually absent, and depolarization occurs in a manner similar to that of phase 2 of the fast-response action potential, with the predominance of slow inward Ca^{2+} and Na^+ currents. [26] Phase 3 repolarization and phase 4 are virtually identical between the two types of action potentials, although the absolute refractory period in cells exhibiting slow-type action potentials is much longer.

Components of the Conduction System

The SA node is a disk-shaped structure, approximately 15 × 5 × 2 mm, which lies in the sulcus terminalis at the junction of the superior vena cava and the RA on the posterior

Figure 16-7 (Figure Not Available) An example of the slow-response action potential seen in a pacemaker-type cell. Note the resting transmembrane potential of -60 mV. The slope of diastolic depolarization is dependent on the degree of sympathetic (a) and parasympathetic (b) stimulation. *(From Berne and Levy [18])*

aspect of the heart. [27] Anatomically, it developed from right-sided embryologic structures, and this origin accounts for the predominance of right vagal innervation to it. [28] As noted earlier, its action potential tracing is characteristic of the slow-response type, with a V_m of -60 mV and a slower velocity upstroke of phase 1, indicating little involvement of the fast Na^+ channels. However, in contrast to the constant V_m seen in phase 4 of fast-response action potentials, such as that of ventricular free wall muscle, the SA node exhibits a slow, steady depolarization of phase 4, known as *prepotential* or *pacemaker potential,* which continues until the next action potential threshold is reached and triggered. During phase 4 in the slow-response tissue, a steady increase in net inward current is occurring. This phase 4 pattern is characteristic and represents the internal automaticity present among pacemaker-type cells. [29]

Automaticity

The basis of automaticity lies in the outward K^+ current, which serves to return the V_m to its resting baseline during phase 3 repolarization. As mentioned earlier, K^+ continues to leak out of the cell during phase 4, but its membrane permeability is markedly reduced, a factor that contributes to this steady depolarization. [29] Factors that alter the frequency of pacemaker depolarization include changes in the rate (slope) of phase 4 depolarization and changes in the resting potential. For example, sympathetic stimulation from catecholamines, such as norepinephrine, act to raise heart rate by increasing the rate of phase 4 depolarization. [30] Conversely, parasympathetic (vagal) stimulation from cholinergics, such as acetylcholine, act to hyperpolarize pacemaker cells, an action that lengthens the time of phase 4 depolarization [31] (see Fig. 16-7) (Figure Not Available) .

A phenomenon known as *overdrive suppression* occurs when the automaticity of pacemaker-type cells is depressed after a period in which action potentials are triggered at a frequency greater than its intrinsic rate. [18] For example, an ectopic atrial pacemaker site may fire at a rate of 150 times per minute, causing overdrive suppression of the SA node, which normally fires at a rate of between 60 and 100 times per minute. As the ectopic site stops firing, a brief period, called the *sinus node recovery time,* may intervene between the end of the period of overdrive suppression and the resumption of pacemaker activity by the SA node. This concept

is important in understanding the origin of conduction abnormalities, such as sick sinus syndrome, in which rapid heart rates inhibit normal SA node pacemaker activity and lead to periods of asystole in which the ectopic focus discharge slows. [18]

The SA nodal discharges are passed through the atria via three bundles of fibers, which conduct impulses to the AV node: the anterior internodal tract of Bachmann, the middle internodal tract of Wenckebach, and the posterior internodal tract of Thorec. [32] [33] [34] Of these, the most important is probably the anterior pathway, which also conducts impulses directly to the LA. [32] The atrial muscle tissue for the most part exhibits the fast-response-type action potentials, with a shorter phase 2 plateau and a slightly slower rate of phase 3 repolarization as compared with ventricular muscle tissue.

The AV node is a button-shaped structure approximately 22 × 10 × 3 mm, which lies on the right posterior side of the interatrial septum near the ostium of the coronary sinus. [35] Anatomically, it developed from left-sided embryologic structures, an origin that accounts for the predominance of left vagal innervation to the AV node. [28] Impulses from the three internodal tracts converge on the AV node, which is divided into three discrete functional zones: the AN region, joining the atrium to the node; the nodal (N) region; and the NH region, joining the node to the bundle of His. [36] The AN and, to a lesser degree, the N regions, are important because of the delay that occurs in transmission of the atrial impulses to the distal conduction system, allowing for adequate filling time for the ventricle between the onset of

atrial and ventricular contraction. This area is responsible for the PR interval on the electrocardiogram (ECG).

As with the pacemaker-type cells, the action potential tracing of AV nodal cells is of the slow-response type, with a V_m of -50 to -60 mV and a very slow phase 1 upstroke, particularly in the N region. In addition, the absolute and relative refractory periods tend to be prolonged in the AV node. This property acts as a protective mechanism against rapid ventricular depolarization, which could otherwise occur in rapid atrial rhythms such as atrial fibrillation and flutter.

Like the SA node, the AV node is also subject to overdrive suppression. Its intrinsic pacemaker rate is approximately 60 per minute, so its automaticity tends to be suppressed by the higher SA nodal discharge rate. Moreover, the AV node is also subject to similar autonomic regulation of conduction. For example, sympathetic stimulation from norepinephrine decreases conduction time through the AV node, enhancing the rhythmicity, or regularity, of pacemaker activity of the node. As in the SA node, it also increases the rate of rise of phase 4 depolarization. Meanwhile, parasympathetic stimulation from acetylcholine acts in an opposite manner, to delay or block impulses through the node. [28]

The AV node gives rise distally to the bundle of His, which travels subendocardially along the right side of the interventricular septum, divides, and continues as the right bundle branch (see Fig. 16-4) . Meanwhile, the left bundle branch arises in a perpendicular path from the bundle of His, passes through the interventricular septum, and is further divided into a thin anterior fascicle and a thick posterior fascicle, which courses subendocardially along the left side of the interventricular septum. Ultimately, the right bundle and two left fascicles continue to subdivide to form the complex Purkinje fiber network, which allows conduction of impulses to all parts of the ventricle. Because of their somewhat thicker cellular diameter, the Purkinje fibers have a faster conduction velocity than any other portion of the conduction system. [18] This property allows for rapid propagation of action potentials to all regions of the ventricular myocardium to coordinate contraction. The action potential configuration for Purkinje fibers and for ventricular muscle is virtually identical; both are of the fast-response type.

As the action potential passes through the Purkinje fibers, the myocardial tissue of the interventricular septum and papillary muscle are the first to contract. Septal contraction serves to anchor the heart as the rest of the ventricular free wall begins contracting, and papillary muscle tightening prevents prolapse of the tricuspid and mitral valves during the early portion of systole. Excitation of muscle fibers spreads outward from endocardium to epicardium, and owing to the relative differences in wall thickness, the RV contracts earlier than the LV. [18]

CARDIAC CYCLE

As seen in Figure 16-8 (Figure Not Available) , the cardiac cycle can be divided into four distinct segments. It begins in the latter half of diastole with ventricular filling (points A to B). Blood returns to the RA and LA from the pulmonary and systemic circulations, respectively, and accumulates during the time of the previous ventricular systole. When the atrial pressure exceeds that within the ventricle, the AV valves open, and blood enters the ventricular chambers. This passive flow accounts for roughly 75 percent of total ventricular filling, with the balance contributed by active atrial contraction, also known as the atrial "kick." [37] This occurs with atrial systole, which begins with the depolarization of the sinus

Figure 16-8 (Figure Not Available) The cardiac cycle and its phases. *(From Berne and Levy [1])*

node and propagation of the action potential through the atria along the internodal tracts, and corresponds to the P wave on ECG (Fig. 16-9) (Figure Not Available) . The shape of the curve of the ventricular filling segment (see Fig. 16-8 (Figure Not Available) , A to B) is dependent on the compliance or elasticity of the ventricular wall muscle. Certain conditions or disease states, such as after cardiopulmonary bypass or in LV hypertrophy secondary to aortic stenosis or prior myocardial infarction, can make the ventricle stiffer and less compliant, a property that impedes passive filling. In these circumstances, the atrial kick may be very important in achieving adequate ventricular filling.

While the ventricles fill, the valves are displaced upward, and ventricular systole begins with the closure of the tricuspid and mitral valves, corresponding to the end of the R wave on the ECG (point B). Ventricular systole can be divided into two parts. In the first part, known as *isovolumic* or *isometric contraction* (points B to C), the initial impulse has traveled through the AV node and down the right and left bundles into the Purkinje fibers, which stimulate the ventricular muscle to contract. The AV valves are held closed by the initial tightening of the papillary muscles, and pressure within the ventricle increases as progressively more ventricular myocardium is stimulated to contract. When the developed pressures within the two ventricles exceed the pulmonary artery and aortic pressures (point C), the pulmonic and aortic valves open to allow flow into their respective circulations. The latter portion of systole, termed *ventricular ejection* (points C to E), has an initial rapid phase (points C to D), characterized by maximal forward flow and developed artery and aortic pressures, which tapers while systole progresses (points D to E).

With ejection of blood from the heart, the pressures within the RV and LV fall, and ventricular diastole begins with the closure of the pulmonic and aortic valves (point E). Ventricular diastole can also be divided into two periods. Initially during the first half, known as *isovolumic* or *isometric relaxation* (points E to A), the conduction system and myocardial cells have repolarized and are in the relative refractory period, corresponding to the end of the T wave on ECG. The ventricular pressures continue to drop until they fall below that of the RA and LA, at which point the tricuspid and mitral valves reopen (point A), ventricular filling commences, and the cycle repeats itself.

MECHANISMS OF MYOCARDIAL CONTRACTION

Biochemical Components

The heartbeat is initiated at the SA node, which is a strip of fine muscle fibers located posteriorly near the junction of the superior vena cava with the RA. [37] The nodal cells undergo spontaneous depolarization. The impulse passes out from the SA node to the atria and down the conduction system through the AV node into the ventricular cells. Phase 0 of the action potential in both atrial and ventricular cells is due to the opening of Na^+ channels and the rapid influx of

Figure 16-9 (Figure Not Available) A single cardiac cycle. AORTA, PULM. A., L.V., R.V. indicate the pressures in the respective vessels and chambers of the heart. The hatched lines mark the periods of isovolumic contraction and relaxation. Heart sounds and the ECG are pictured in register with the pressure and flow curves. *(From Patton HD et al (eds): Textbook of Physiology, vol. 2. Philadelphia, WB Saunders, 1989.)*

Na^+ . Soon thereafter, as a result of depolarization, Ca^{2+} channels open. The Ca^{2+} channel, designated the L-type channel because it is activated by low voltage, allows entry of Ca^{2+} into the myoplasm (see Fig. 16-5) (Figure Not Available) .

Sarcoplasmic Reticulum

The SR is the intracellular storage site of Ca^{2+} used for contraction. The Ca^{2+} entering through the sarcolemma is scant and acts solely as a trigger to initiate Ca^{2+} release from the SR. [38]

Electron micrographs have shown that L-type Ca^{2+} channels are closely associated with the Ca^{2+} release channel (CRC) of the junctional SR. The CRC is a huge protein of 565,000 molecular weight with foot processes that appear to be involved in release, perhaps by giving directionality to the outflow of Ca^{2+} (Fig. 16-10) (Figure Not Available) . The short distance from the L-type Ca^{2+} channel in the T-tubular membrane to the foot process of the CRC in the junctional SR allows Ca^{2+} entry through the L channel to immediately initiate Ca^{2+} release from the SR CRC. [39] The rise of Ca^{2+} as measured by luminescent or fluorescent intracellular Ca^{2+} dyes indicates that little, if any, measurable lag exists between the initiation of the action potential and the increase in intracellular Ca^{2+} . Measurements of myoplasmic Ca^{2+} by luminescent and fluorescent techniques measure free Ca^{2+} ; the quantity and time course of Ca^{2+} that is bound to troponin C qualitatively follows the time course of free Ca^{2+} . [40] Approximately 99 percent of cytosolic Ca^{2+} is bound to Ca^{2+} buffering proteins, so the measurement of free Ca^{2+} by spectroscopic means underestimates the Ca^{2+} that is available for contraction. As noted earlier, the CRC is localized to the heavy or junctional SR and is responsible for release of Ca^{2+} stores from the SR during contraction.

The other equally important function of the SR is the reaccumulation of Ca^{2+} . This is accomplished by a 105,000-molecular weight Ca/Mg-ATPase pump, which is imbedded in the membrane of the longitudinal SR. Because removal of free intracellular Ca^{2+} from the myoplasm to generate a Ca^{2+} gradient is an active, energy-consuming process, hydrolysis of ATP is required. The myoplasmic Ca^{2+} concentration is restored to 10^{-7} mol/L at diastole, and a high Ca^{2+} concentration within the SR membrane space results. The activity of the SR Ca^{2+} pump can be augmented by the cyclic adenosine monophosphate (cAMP)-dependent phosphorylation

Figure 16-10 (Figure Not Available) Model of the approximation of the dihydropyridine receptor in the T tubule to the calcium release channel (ryanodine receptor) in the junctional sarcoplasmic reticulum. Ca^{2+} , which enters through the dihydropyridine receptor or L-type Ca^{2+} channel, acts upon the ryanodine receptor to initiate calcium release channel opening and the efflux of Ca^{2+} into the myoplasm. Calsequestrin in the SR binds Ca^{2+} and adds to the storage capacity of the SR. *(From McPherson and Campbell [39])*

of an associated SR protein, phospholamban. beta-Adrenergic stimulation leads to increased phospholamban phosphorylation, increased Ca^{2+} pump activity, and a shorter relaxation time. [41]

The continuity of the SR membrane, from junctional to longitudinal, and the separation of CRC and the Ca^{2+} pump from each other along the course of the SR membrane suggests the importance of movement of Ca^{2+} within the SR membrane space from the longitudinal to the junctional region. This movement could simply depend on diffusion of Ca^{2+} down a concentration gradient and suggests a temporal limitation to the availability of the Ca^{2+} for contraction.

Contractile Elements

The purpose of the elaborate system of Ca^{2+} delivery and removal is to control the availability of Ca^{2+} for the contractile process (see Fig. 16-2) (Figure Not Available) . For cardiac muscle to contract, actin and myosin must interact. These two contractile proteins make up, respectively, the thin and thick filaments seen in electron micrographs of cardiac and skeletal muscle. Actin is a small protein with a molecular weight of 43,000. Individual actin molecules combine to form long polymer chains in a double-helical structure that make up the thin filament. Interposed at a regular spacing along the thin filament is a complex of tropomyosin (Tm) and troponin (Tn). Tm is a linear protein of approximately 70,000 molecular weight that lies within the sulcus of the thin filament. Tn is a protein consisting of three distinct polypeptides: TnT, TnI, and TnC. It is found at the amino-terminal of Tm, with which it forms a complex. Each polypeptide of troponin fulfills a different function in the regulation of contraction. TnT binds to Tm, TnI is believed to inhibit the reaction of actin with myosin, and TnC binds Ca^{2+} , which results in a conformational change of several proteins and leads to contraction.

TnC, a small protein (molecular weight 18,000), is the target at which Ca^{2+} activates contraction. This protein is similar to TnC found in skeletal muscle, but cardiac TnC has one less Ca^{2+} binding site, which leads to the less steep Ca^{2+} concentration dependence of tension development found in cardiac muscle. [42] TnC is an example of a ubiquitous class of Ca^{2+} binding proteins called EF-hand proteins, all of which contain a particular amino acid sequence that results in a pocket with multiple oxygen atoms to coordinate the binding of the Ca^{2+} ion with high specificity and affinity. [43] Another example of this class of proteins is calmodulin, which confers Ca^{2+} sensitivity on many enzymatic processes in the heart and central nervous system. The binding of Ca^{2+} to TnC is the trigger that initiates a chain reaction of conformational changes and leads to the development of mechanical activity.

The thick filament observed in electron micrographs of cardiac muscle is made up of myosin, which is a large, asymmetric molecule consisting of two heavy chains,

each of 220,000 molecular weight, and four light chains, each of approximately 20,000 molecular weight. The functions of the light chains are still uncertain but may include regulation of cross-bridge formation. The myosin molecule consists of two globular heads containing the enzymatic ATPase activity, a hinge area, and a tail area resulting from the intertwining of the two heavy chains [44] (Fig. 16-11) (Figure Not Available) . The head interacts with actin to form cross-bridges and hydrolyse ATP, the hinge area appears to be involved in tension development, and the tail anchors the molecule to other myosin molecules in the thick filament.

A complex cycle of actin-myosin interactions, shortening, and tension development occurs on binding of Ca^{2+} to TnC. This active process requires ATP and utilizes approximately 70 percent of the ATP available in the myocyte. [45] The hydrolysis of ATP to adenosine diphosphate (ADP) and the formation of a high-energy phosphate intermediate of actin-myosin

Figure 16-11 (Figure Not Available) Diagram of a possible mechanism of force generation due to the interaction of the myosin head (S1) with the actin thin filament. Upon attachment of the head, P_i is released, followed by release of ADP during the power stroke. This results in a change in the angle of attachment of the head, S1, and the hinge area S2. The binding of another ATP molecule leads to detachment, and the cycle of hydrolysis and reattachment begins again. *(Modified from Stryer [44])*

ATPase drives the three parts of the contractile cycle: (1) detachment of the myosin head from actin; (2) reattachment of myosin to actin with a different conformation and higher free energy at the beginning of the work stroke; and (3) development of force and the performance of mechanical work. [46]

The transduction of the energy released by ATP hydrolysis into mechanical force occurs during the release of ADP and inorganic phosphorus (P_i) from the myosin head. The substrate, Mg^{2+} ATP, causes the dissociation of the actomyosin complex by binding to the ATPase active site of myosin. Myosin hydrolyses ATP, forming a complex with ADP and P_i . Actin is able to recombine with another myosin head, displacing ADP and P_i . Force is generated in this last step. [47]

Metabolic Considerations

The metabolic function of the cardiac myocyte serves a 2-fold purpose: to generate energy to maintain cell integrity by maintaining ionic gradients across membranes and to generate energy to maintain a physiologic pump that must work nonstop for, on average, 73 years.

Substrates and Energy Sources

The heart is able to metabolize glucose, carbohydrates, lactate, and fatty acids to form its metabolic energy source, ATP. During fasting, free fatty acids (FFA) are elevated in the serum, and the substrates utilized by the heart in fasting patients are mainly FFA and glucose. In fact, FFA in these circumstances inhibit the utilization of glucose. [48] These substrates are used to form ATP and creatine phosphate, molecules with high energy, which are then used by the heart to perform mechanical and chemical work, such as contraction and ion transport.

Mitochondria

The mitochondrion contains the enzymatic constituents to synthesize the ATP used by the cell for all its energy requirements. Approximately 23 percent of the volume of the myocardial cell is occupied by mitochondria, a finding that reflects the importance of a continuous supply of ATP for continuous cardiac function (Fig. 16-12) (Figure Not Available) . The mitochondrion is an elongated structure with an outer and inner membrane system. The inner membrane system consists of a multiplex of folds, which contain the enzymes for aerobic metabolism and the cytochromes involved in electron transport. Modified FFA and the intermediary products of glucose metabolism are further metabolized by the mitochondria, yielding reduced nictotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH), which are fed into the electron transport chain.

Utilization Pathways

Glucose and FFA are the primary substrates. Glucose is metabolized by the glycolytic pathway to yield pyruvate when the oxygen supply is sufficient and lactate when oxygen is in short supply. Pyruvate then enters the citric acid cycle in the mitochondrion, where it is broken down to carbon dioxide and water and ATP is generated. Pyruvate is enzymatically transformed to acetylcoenzyme A (acetyl-CoA) and NADH. The enzyme responsible for this transformation is pyruvate dehydrogenase, which is a highly regulated enzyme found in the inner mitochondrial membrane. Acetyl-CoA enters the citric acid cycle in the mitochondrion, where it is oxidized, yielding NADH, $FADH_2$, and two ATP molecules from what is called substrate level phosphorylation. The NADH and $FADH_2$ then enter the respiratory chain, where they are oxidized and provide reducing equivalents (a reducing equivalent is a hydrogen atom

Figure 16-12 (Figure Not Available) Mammalian cardiac muscle in crosssection, demonstrating the large number of mitochondria (MI) found in cardiac muscle in order to fulfill the metabolic requirements of contraction. The mitochondria are surrounded by myofilaments (MfI). *(From Fawcett and McNutt [11])*

[$H^+ + e^-$]). The basic equations of oxidative phosphorylation are as follows:

which is coupled to the oxidation of ADP

such that three molecules of ATP are formed for each atom of oxygen. This refers to the concept of a phosphate/oxygen (P/O) ratio of 3, but in fact, depending on the energy substrate, the ratio varies from 2.83 to 3.17. For example, with FFA as substrates, the P/O ratio is 2.83 because one of the products of FFA metabolism is $FADH_2$ rather than NADH alone. $FADH_2$ enters the respiratory chain at one phosphorylation site further downstream than NADH, yielding less ATP per molecule of FFA than per molecule of glucose (Fig. 16-13) (Figure Not Available) . The function of oxygen in this metabolic scheme is to act as an acceptor of electrons, allowing the cycling of the electron transport chain to continue.

Regulators

FFA, which are normally present in the blood, are elevated during fasting, and, as noted earlier, the result is in an inhibition of glucose metabolism and a preferential metabolism of FFA. FFA metabolism accounts for approximately 60 to 70 percent of the oxygen utilized, whereas glucose accounts for the remaining 30 to 40 percent. [49] FFA are found in the blood highly bound to albumin. Myocardial cells have albumin receptors, which permit the interaction of FFAs with the sarcolemma. Because the FFA are lipid soluble, they can cross the sarcolemma freely and enter the cytoplasm of the cell, where they are transformed by thiokinase to acyl-CoA derivatives. The enzyme, acylcarnitine transferase, then adds a carnitine moiety to the FFA. An enzymatic translocation system, carnitine translocase, transports

Figure 16-13 (Figure Not Available) Schematic of mitochondrial metabolism, depicting the entry of substrates into the mitochondrial matrix and the addition of electrons, via NADH and $FADH_2$, to the electron transport chain. (CPT, carnitine palmitoyltransferase; PDHC, pyruvate dehydrogenase complex; CoA, coenzyme A; TCA, tricarboxylic acid; NADH, nicotinamide adenine dinucleotide, reduced; $FADH_2$, flavin adenine dinucleotide, reduced; I, II, III, IV, V, complexes of the respiratory chain; CoQ, coenzyme Q; Cyt c, cytochrome c.) *(From DiMauro S: The mitochondrial disorders. In*

the acyl-carnitine derivatives into the mitochondrial matrix, where the long-chain acyl-CoA derivatives are oxidized, two carbons at a time, by the citric acid cycle, producing reducing equivalents and yielding ATP.

CARDIAC OUTPUT

Definition

Cardiac output is defined as the rate of blood flow (Q), or the amount of blood pumped by the heart per unit time. It has been traditionally calculated by the Fick principle, derived from the law of conservation of mass, which states that the amount of oxygen present in the blood returned to the heart from the body plus the amount of oxygen transported across the alveoli into the blood equals the amount of oxygen carried away from the heart. [50] This concept is diagrammed in Figure 16-14 (Figure Not Available) , [51] where q_1 represents the rate of oxygen delivery to the alveoli via the pulmonary artery, which is equivalent to a certain rate of blood flow Q multiplied by the mixed venous oxygen content ($[O_2]_{ven}$). Meanwhile, q_3 represents the rate of oxygen delivery to the left side of the heart and subsequent peripheral tissues via the pulmonary vein, which is equivalent to the same rate of Q multiplied by the arterial oxygen content ($[O_2]_{art}$). The difference between the two, q_2 , represents the rate of oxygen consumption by the body and is equivalent to the rate of oxygen transported across the alveoli.

Thus, mathematically by the Fick principle

which converts to

Therefore, the rate Q, or cardiac output, is equivalent to

At a resting basal oxygen consumption rate of 250 mL/min, with an average arterial oxygen content of 20 vol percent and an average venous oxygen content of 15 vol percent, the cardiac output is 5,000 mL/min. [52]

Determinants

Cardiac output can also be thought of in anatomic terms. Because stroke volume reflects the amount of blood ejected from the heart per beat, cardiac output is mathematically equal to the stroke volume multiplied by the heart rate, or number of beats per minute. Stroke volume is defined as the difference between LV end-diastolic volume and LV end-systolic volume, corresponding to the change in volume seen during the ejection phase of the cardiac cycle. Typical values for stroke volume in healthy adults range from 60 to 90 mL per beat.

Thus, based on the foregoing definitions, cardiac output changes to accommodate changes in oxygen consumption, as reflected by alterations in oxygen delivery (arterial oxygen content) or oxygen utilization (venous oxygen content), and this may be manifested as a change in stroke volume, heart rate, or both.

Classic teaching has been that cardiac output is determined by four separate parameters: preload, afterload, heart rate, and contractility. *Preload* is defined as the end-diastolic fiber length or end-diastolic volume of the heart. It is influenced by intravascular volume status, capacity of the venous system, and ventricular function as related to compliance, afterload, and contractility. *Afterload* is defined as the force opposing ventricular ejection and translates into the wall tension developed as ventricular muscle fibers shorten during both isovolumic contraction and ejection phases of systole. It is influenced by ventricular size and volume, including chamber radius and wall thickness, as well as by systemic vascular

Figure 16-14 (Figure Not Available) An illustration of the Fick principle, in which q_1 represents the rate of oxygen delivery to the alveoli (venous return) and q_3 represents the rate of oxygen delivery to the periphery (systemic circulation). By the law of conservation of mass, q_2 must represent the rate of oxygen consumption that is equivalent to the rate of oxygen transport across the alveoli. *(Modified from Berne and Levy [51])*

resistance and aortic compliance. *Heart rate,* as previously discussed, is defined as the number of beats per minute and is heavily influenced by the autonomic nervous system. Increases in heart rate increase cardiac output up until the point at which a rapid heart rate does not permit for adequate ventricular filling during diastole, and cardiac output consequently falls. This occurs at a heart rate of approximately 160 beats/min. [53] *Contractility* is defined as the inherent inotropic ability of the heart independent of changes in the other codeterminants of cardiac output. It is influenced by the regulation of intracellular calcium concentration, as discussed previously, and ventricular compliance, including relaxation, which determines the ability of the ventricle to fill. Indices of contractility include the rate of change of ventricular pressure with respect to time (dP/dt), the rate of shortening of mean circumferential fiber length during ejection, ventricular function curves, and the cardiac cycle pressure-volume loops and force-velocity curves, as discussed later. *Ejection fraction,* a term often associated with the discussion of contractility, is defined as the stroke volume divided by the left ventricular end-diastolic volume, or the percentage of blood ejected with each beat during systole. Typical values for ejection fraction in healthy adults range from 60 to 70 percent, whereas values lower than 40 percent represent severe ventricular contractile dysfunction.

Several other factors influence the actual cardiac output primarily through changes in contractility. The term *heterometric autoregulation* refers to adaptive adjustments used by the heart that improve ventricular function dependent on changes in myocardial fiber length. The Frank-Starling curve, as described later, is an example of heterometric autoregulation, in which an increase in preload or stretch on the heart results in an increase in cardiac output.

Conversely, the term *homeometric autoregulation* refers to compensatory mechanisms that result in improved ventricular performance that is independent of changes in myocardial fiber length. The Anrep effect is an example of homeometric autoregulation. It occurs when afterload or systemic vascular resistance increases abruptly and produces a resultant increase in LV end-diastolic and diastolic pressures. These increased values are transient and return to baseline as contractile function

increases in response to the pressure challenge. [54]

Another example of homeometric autoregulation is the treppe (staircase) effect. This phenomenon was first described by Bowditch in frog ventricle, in which he noted a negative correlation between time interval between stimuli (heart rate) and developed myocardial tension (as a measure of contractile function). This finding is believed to be due to an increased intracellular calcium concentration, as noted by studies using aequorin, a Ca^{2+} -sensitive bioluminescent protein indicator, which demonstrated an increased signal in response to an increased heart rate. [55] A related contradictory phenomenon is the reverse, or negative, staircase effect in which myocardial performance increases in response to a long pause between beats, as is seen with the compensatory pause following premature ventricular contractions. [56]

Moreover, there are also several factors that worsen myocardial performance and hence cardiac output. These include hypoxia, myocardial ischemia or infarction, acidosis, cardiomyopathy, volatile anesthetics, and various negative inotropic drugs.

Measurement

In addition to the Fick principle described earlier, cardiac output can be measured by several other techniques. Injection of an indicator dye such as indocyanine green into the venous blood allows determination of cardiac output by calculating the area under the dye dilution curve as measured by densitometry of the arterial blood. The major limitation of this method is the recirculation of dye, which then requires extrapolation of the downward slope of the dilution curve to estimate the area under the peak and hence cardiac output. Thus, repeated injections cause build-up of dye levels and further hinder the usefulness of this method. This problem, however, has a hidden advantage in that it can be used to determine the presence of shunts. The initial bolus of dye injected into the blood normally produces a second or recirculation peak after the primary dilution curve from the second passage of dye through the heart. The presence of a right-to-left shunt results in the appearance of a more prominent initial peak as well as a secondary recirculation peak, which occurs much earlier than normal. Conversely, the presence of a left-to-right shunt results in the appearance of a diminished initial dye curve and a barely detectable recirculation peak, which occurs much later than normal, with marked prolongation of dye elimination.

Another method of determining cardiac output is Doppler echocardiography. This noninvasive technique is based on measuring the cross-sectional area of the aortic valve and the velocity of blood flow by ultrasound. Although it has shown good experimental correlation with other methods of determining cardiac output, its use in clinical situations has been limited by reliability issues. [57]

Currently, the most widely used technique for measuring cardiac output is the thermodilution method. Like the dye method, it relies on dilutional measurements of a substance injected as a bolus. In this case, a thermistor sensor measures changes in temperature of a known quantity of injectate of normal saline or dextrose at either 4°C or room temperature and calculates the cardiac output as the area under the curve. Although it only measures output from the right side of the heart, this is assumed to correlate well with that of the left. Thus, the limitations of this method include the presence of shunts, the use of varying quantities of injectate, the speed of injection, and the baseline temperature, all of which may overestimate or underestimate the actual cardiac output.

CONTROL OF CARDIAC FUNCTION

Neural Regulation of the Heart

Control of Heart Rate

As described earlier, the SA and AV nodes receive autonomic nervous system input via parasympathetic and sympathetic innervation to the heart, eliciting changes in heart rate in response to physiologic changes within the body that vary with a person's age and particular situation [58] (ch. 14) .

In the adult, the normal heart rate varies between 60 and 80 beats/min. The SA node, because of its origin from right-sided embryologic structures, receives its innervation predominantly

from the right vagus nerve and right stellate ganglion, although there is usually some overlap of distribution between right and left sides. Cholinergic parasympathetic simulation from the vagus nerve causes a decrease in the heart rate via muscarinic receptors, which hyperpolarize pacemaker cells and slow phase 4 depolarization. Meanwhile, adrenergic sympathetic stimulation from the cardiac accelerator fibers via the stellate ganglion causes an increase in the heart rate via beta receptors that speed phase 4 depolarization.

Most changes in heart rate usually involve a coordinated reciprocal action between the two branches of the autonomic nervous system, such that situations that increase sympathetic activity (e.g., exercise) elicit a concomitant decrease in parasympathetic activity and vice versa. Under normal resting circumstances in the adult heart, parasympathetic tone predominates. When parasympathetic and sympathetic innervation is completely blocked through denervation (e.g., transplant surgery) or pharmacologic intervention, the underlying or intrinsic heart rate has been found to average around 105 beats/min.

There are three types of parasympathetic reflex receptors found in the atria that function to regulate changes in heart rate or volume status. Type A receptors are innervated by myelinated vagal afferent fibers and are located throughout the atria as well as at the junction between the vena cava and the RA and the pulmonary vein and the LA. [58A] [58B] [58C] These receptors seem to be more responsive to heart rate rather than atrial chamber volume, and they discharge impulses continuously throughout the normal cardiac cycle that correspond to the timing of the a wave. Type B receptors are also innervated by myelinated vagal afferent fibers and occur in a similar distribution to that of type A receptors. These receptors seem to be more responsive to atrial stretch and changes in intravascular volume than to heart rate, and they discharge impulses late in systole that correspond to the timing of the v wave. [58C] These receptors are normally inactive in atrial contraction, but they increase their activity in conditions such as tachyarrhythmias, in which the rate of rise of intra-atrial pressure increases. Finally, a group of receptors innervated by group C parasympathetic fibers and located throughout the atria respond to changes in atrial pressure with a threshold of 2 to 3 mm Hg, but in general they are much less responsive and have a lower rate of activity than type B receptors. [59]

There are also ventricular receptors mediated by myelinated vagal afferent fibers, which are located throughout the ventricular chambers and coronary arteries and respond to changes in pressure either by bradycardia and hypotension or by reflexive sympathetic cardiovascular stimulation. These receptors are sensitive to changes in the rate of rise of ventricular pressure and fire impulses at the onset of ventricular ejection. They may play a role in the reported myocardial depressant effects seen with parasympathetic stimulation, as discussed later. In addition, there are two types of receptors innervated by unmyelinated vagal afferent fibers: chemoreceptors that respond to capsaicin or veratridine and mechanoreceptors that respond to aortic constriction and ventricular stimuli.

Most sympathetic afferent nerves are unmyelinated, although the significance of myelinated versus unmyelinated nerve fibers remains unclear. [60] Both myelinated and unmyelinated spinal afferents have been detected in the atria, fire throughout the cardiac cycle, and appear to be sensitive to both mechanical and chemical stimulation including K^+ and bradykinin. [61] The myelinated nerve fibers in the ventricles are also sensitive to mechanical and chemical stimuli, with increased firing during periods of increased ventricular pressure and with the detection of vasoactive peptides such as bradykinin and veratridine. [62]

The pain of myocardial ischemia is presumably related to stimulation of spinal afferent pathways. Specifically, various compounds, such as bradykinin, are released by ischemic myocardium and activate both chemosensitive and mechanosensitive sympathetic afferent fibers. [63] This effect is attenuated by vagal afferents, which can modulate the sensation of cardiac pain, and it serves as an explanation for silent ischemia and infarction. [64] In humans, myocardial ischemic pain can be relieved by the bilateral removal of the T1 to T5 sympathetic ganglia. [65]

Control of Myocardial Performance

As would be expected, left-sided structures in the heart are predominantly autonomically innervated by the left vagus and left stellate ganglion. Distribution of the left vagus nerve terminates near the AV node, where it elicits its greatest influence, producing variable degrees of nodal conduction block. Meanwhile, the branches of the left stellate ganglion form an extensive plexus network over the epicardium of the heart and penetrate the myocardium along the various branches of the coronary vessels. Thus in general, sympathetic adrenergic activity from the cardiac augmenter fibers via the left stellate ganglion has a greater effect on contractility, whereas the accelerator fibers from the right have a greater effect on heart rate. [66] The tissue concentration of norepinephrine in the atria is roughly three times that in the ventricle, reflecting the differences in the relative density of sympathetic innervation to those respective areas of the heart. Moreover, if the heart is denervated, as in transplanted hearts, the tissue levels of norepinephrine are virtually nonexistent.

Stimulation of beta receptors increases heart rate and contractility via increases in cyclic adenosine monophosphate (cAMP) [67] (Fig. 16-15) (Figure Not Available) . This process occurs as norepinephrine, the neurotransmitter released by postganglionic sympathetic nerve terminals, binds the receptor and causes a conformational change that subsequently activates a specific guanylnucleotide-binding stimulatory coupling protein (G_s). G proteins are a family of heterotrimeric structures composed of alpha-, beta-, and gamma-subunits, of which the alpha-subunits vary in molecular weight and function. Binding of the beta receptor causes dissociation of the alpha-subunit of G_s (molecular weight 43,000) from the betagamma complex (molecular weight 35,000) with the concomitant expenditure of guanosine triphosphate, and this alpha-subunit then stimulates adenylate cyclase to increase intracellular cAMP levels. [68] Increases in cAMP, in turn, act on certain protein kinases that function to phosphorylate various intracellular proteins, especially those related to the SR, that ultimately raise intracellular Ca^{2+} concentration.

Although both $beta_1$ - and $beta_2$ -receptors cause increases in heart rate and contractility, $beta_1$ -receptors specifically increase

Figure 16-15 (Figure Not Available) A schematic of the coupling of the beta receptor (R_s) via a stimulatory guanyl-nucleotide-binding protein (G_s) to adenylate cyclase. Note the heterotrimeric structure of the G protein. The muscarinic receptor (R_i) is also coupled to adenylate cyclase via an inhibitory guanyl-nucleotide-binding protein (G_i). Ultimately, cAMP levels are affected by the balance of stimulatory and inhibitory input from sympathetic and parasympathetic influences. *(From Susanni et al [67])*

conduction velocity of the heart, whereas $beta_2$-receptors specifically cause smooth muscle relaxation, which is responsible for its usefulness in the control of asthma and reactive airway diseases as well as in premature labor [69] (ch. 72) . This becomes important when selecting certain drugs that have preferentially selective $beta_1$- and $beta_2$-agonist and antagonist activity.

As mentioned earlier, parasympathetic stimulation also seems to influence contractility, even though the parasympathetic nervous system has a relatively low level of innervation to the ventricles as compared with that of the sympathetic nervous system. The specific mechanism by which the parasympathetic neurotransmitter acetylcholine acts is unclear; however, there are several potential pathways, all of which ultimately lower the levels of intracellular cAMP. [70] Binding of acetylcholine to muscarinic receptors on myocardial cells has a dual effect. The first is to elevate cyclic guanosine monophosphate (cGMP) levels by activation of guanylate cyclase. Increases in this nucleotide have been shown to accelerate the breakdown of cAMP, perhaps by activation of phosphodiesterase, although the exact mechanism by which this occurs is not known. The second effect occurs via an inhibitory G protein (G_i). Like G_s, the corresponding stimulatory coupling protein linking the beta receptor to adenylate cyclase, G_i couples the muscarinic receptor to adenylate cyclase. However, unlike G_s, the alpha- subunit of G_i (molecular weight 41,000), which dissociates from the betagamma complex on binding of the muscarinic receptor, then inhibits adenylate cyclase, leading to a decrease in cAMP synthesis. [71] Finally, acetylcholine released from parasympathetic postganglionic nerve terminals that lie in close proximity to sympathetic postganglionic nerve terminals may actually inhibit their release of norepinephrine, and this, in turn, decreases beta receptor stimulation and ultimately cAMP levels. [72]

Starling's Law of the Heart

As mentioned earlier, ventricular function curves illustrate the principle of heterometric autoregulation wherein an increase in stretch on a muscle fiber produces an increase in the tension developed. This serves as the basis for Starling's Law of the heart, or the Frank-Starling relationship, as it is more commonly known. [73] Experimentally, maximal developed tension in cardiac muscle fibers occurs at a resting sarcomere length of 2.0 to 2.3 mum, which allows for optimal cross-bridge formation between the contractile proteins that make up the thick and thin filaments. Clinically, this translates into peak ventricular output occurring at filling pressures of 10 to 12 mm Hg. [74] If the sarcomere length is less than ideal, the thin filaments may be compressed or may overlap, and this may interfere with adequate cross-bridge formation and generation of force. Conversely, if the sarcomere length is greater than optimal, there may be insufficient cross-bridges formed between thick and thin filaments, and this may result in impaired contractile performance. In fact, at a sarcomere length of 3.6 mum, there are no cross-bridges formed, and developed tension in these cardiac muscle fibers is zero [75] (Fig. 16-16) .

There exists some ambiguity regarding the applicability of the Frank-Starling relationship to periods, such as exercise, when the myocardial contractile state is high. This is related to the interaction of reflexive mechanisms in healthy persons (i.e., catecholamines) that regulate heart rate, vascular tone, coronary blood flow, and overall myocardial performance. With the diminution of catecholamine modulation of myocardial performance that occurs with advancing age, however, the heart reverts back to increased reliance on augmenting end-diastolic volume to improve cardiac output. [76] [77]

In addition, experimental evidence using Ca^{2+} and other inotropic substances suggests that changes in myocardial performance are closely linked to the effectiveness of excitation-contraction coupling. [78] Moreover, these pharmacologic interventions appear to depend on length and are more effective at longer rather than shorter resting muscle fiber lengths. [79]

Assessment of Contractile Function

Systolic Properties

Assessment of contractile function in the intact heart *in vivo* is a complex task because many factors such as preload, afterload, heart rate, and autonomic activity can modify contractility and are difficult to control. To measure the intrinsic contractile activity of the heart, several strategies have been attempted, with varying degrees of success. The simplest and most straightforward means of assessing contractile function is by differentiating the ventricular pressure (P) trace with respect to time (t). Maximum positive dP/dt has been used frequently to judge contractile function of the left

Figure 16-16 (A) Schematic diagram of the thick (myosin) and thin (actin) filaments, and of the spacing lateral projections from myosin that attach to actin to form cross-bridges. Sarcomere length is the distance between two lines, which are dense areas resulting from the overlap of actin fibers of sarcomeres in series. Note that when the sarcomere length is 3.65 mum, no cross-bridge attachment between thick and thin filaments can occur; when sarcomere length is 2.20 to 2.25 mum, the maximum number of bridges is formed. Reduction of sarcomere length from 2.20 to 2.05 mum does decrease the number of cross-bridges, because the central part of myosin (C band) has no projections. Reduction of sarcomere length from 2.05 mum to 1.85-1.65 mum does not reduce the number of cross-bridges from the maximum number but does result in double actin overlap. (B) Force measured during a tetanic activation at 0°C as a function of sarcomere length (as in 1 to 5 in Fig. A) in tetanized skeletal muscle. Note that force is zero at zero myofilament overlap, that is, at sarcomere length of 3.6 mum at which no cross-bridges exist between myosin and actin. Maximum force occurs when the number of cross-bridges is maximum and no double overlap of actin occurs (2.0 to 2.25). Force decreases 20 percent when sarcomere length is reduced from 2.0 to 1.65 mum, a length range where the *number* of cross-bridges does not change.

ventricle. Although this value is simple to obtain, its interpretation must be made with several caveats. Of primary importance is the measurement system. The passage of a high-fidelity micromanometer into the LV is required for accurate assessment of dP/dt. The micromanometer can be passed into the LV in at least three ways: (1) retrograde through the aorta and aortic valve; (2) through the pulmonary veins into the LA and across the mitral valve into the LV; and (3) through the apex of the LV. Each of these procedures obviously has its own set of drawbacks. The disadvantage of using dP/dt as a measure of contractility is that it is dependent on heart rate, afterload, and preload. If all these factors can be controlled during the course of the measurement, changes in dP/dt can be used to monitor contractile function.

Although dP/dt gives one an initial assessment of contractile activity, other methods have been developed to assess contractility independently of the effects of preload and afterload. In 1895, Frank published the first pressure-volume loops for frog hearts. He showed the extremes of curves for isovolumic maxima and isobaric maxima curves. He concluded that a simple relationship between length and tension did not exist, but the history (i.e., the preexisting conditions of the contractile process) were important in determining the instantaneous contractile activity. [80] An interest in pressure-volume curves was revived in the 1960s and 1970s. In 1978, when it became clear that a linear relationship existed between the end-systolic volume and the end-systolic ventricular pressure, Sagawa [81] suggested the use of the end-systolic pressure-volume relationship (ESPVR) as a means of comparing intrinsic contractile activity (Fig. 16-17) (Figure Not Available) . These studies [82] were performed in isolated hearts, and the linear relationship obtained in both the ejecting mode and the isovolumic contracting mode was formulated as follows:

where P_{ES} and V_{ES} are end-systolic pressure and end-systolic volume, respectively, E_{ES} is the slope, and V_d is the volume axis intercept. This linear formulation and its relation to the pressure-volume curve are demonstrated in Figure 16-17 (Figure Not Available) . [82] Although extensive use has been made of the concepts of the pressure-volume curve and the ESPVR as a

Figure 16-17 (Figure Not Available) Pressure-volume loops of the left ventricle, demonstrating the difference between the ESPVR in the control and epinephrine-treated isolated heart. The ESPVR is represented by the straight solid line connecting the upper left-hand corners of the pressure-volume loops obtained at different filling volumes of the heart. Epinephrine shifts the pressure-volume loops such that the ESPVR is shifted to the left with a steeper slope, indicating the positive inotropic effect. *(Modified from Suga et al [82])*

means of assessing contractile activity, the application of these tools to intact animals and humans has had less convincing results. [83] Investigations have, in fact, demonstrated that the ESPVR is dependent on heart rate, showing a 25 percent change over a heart rate of 60 to 160 beats/min. Furthermore, E_{ES} was found to yield inconsistent and statistically nonsignificant results when comparing control and inotropic-stimulated hemodynamics in the conscious dog. Overall, the results in intact animals and humans have been inconsistent in terms of assessing contractility changes with either E_{ES} or V_d alone. [83] [84] [85]

As a result, investigators have continued to search for other indices of contractility based on the ESPVR with more complete use of all the data available in a pressure-volume loop (i.e., not using either E_{ES} or V_d alone). Crottogini et al [83] demonstrated the utility of the area under the ESPVR within defined limits. They pointed out that in the positive inotropic state the ESPVR is always above and to the left of the control line, whereas in the negative inotropic state, the ESPVR is always below and to the right of the control loop. These investigators therefore calculated the area under the ESPVR from an upper limit defined by the end-systolic volume of the animal with no manipulations of volume status to a lower limit obtained from the occlusion of the inferior vena cava to limit preload during measurement of control ESPVR. Figure 16-18 (Figure Not Available) demonstrates the two trapezoidal areas calculated to compare inotropic states. [85] This determination of the $ESPVR_{area}$ as an index of contractility resulted in a statistically significant determination of positive and negative inotropic activity even when either the slope E_{ES} or the volume intercept V_d alone gave inconsistent results. Using the area under the ESPVR within defined limits as a means of assessing contractile states allowed Pagel et al [85] to obtain a dose-dependent and statistically significant decrease in this index of contractility in response to halothane and isoflurane while observing no consistent change in either E_{ES} or V_d from the ESPVR. In this set of experiments, consistent and dose-dependent decreases were also noted in dP/dt_{50} (i.e., the time derivate of pressure when pressure has reached one-half of its maximal value).

Some investigations have employed a new index of contractility, which is based on the speculation of Sarnoff and Berglund [86] that a linear relationship should exist between stroke work and end-diastolic volume. Because of the technical difficulties in measuring end-diastolic volume, these investigators were unable to obtain this linear relationship. However, in 1985, Glower et al, [87] using the best current technology, demonstrated that a linear relationship did in fact exist between stroke work and end-diastolic volume, and they termed this relationship the *preload recruitable stroke work* (PRSW) (Fig. 16-19) (Figure Not Available) . In fact, they used both global and regional measures of end-diastole and showed that linearity was maintained with either measure. Global ventricular volume was measured by placing dimensional transducers on the epicardial surface across the longitudinal and transverse axes of the LV, assuming that the volume of the ventricle could be represented by an ellipsoid. Global stroke work was then calculated as the integral of the LV pressure curve (i.e., the area within the curve). Regional stroke work was determined by employing segment length measurements and integrating the LV pressure over the segment length for a contractile cycle. Changes in preload and afterload were achieved with occlusions of the inferior vena cava and infusions of phenylephrine or nitroprusside, respectively. The resulting relationship remained linear over extremes of diastolic filling and ventricular pressure. However, these experimental conditions required autonomic blockade with 2 mg/kg of propranolol and 3 mg/kg of atropine and 20 mg/kg of hexamethonium to prevent the interference of hemodynamic reflexes from confounding the assessment of the factors regulating contractility.

Figure 16-18 (Figure Not Available) Pressure-segment length loops were generated with a transducer in the left ventricle and sonomicrometry crystals on the ventricular surface by occluding the inferior vena cava. The area under the curve was obtained by integration from the minimum segment length (L_m) to the maximum segment length (L_M) beneath the slope of the end-systolic pressure-length relationship. *(Modified from Pagel et al [85])*

Figure 16-19 (Figure Not Available) Example of the preload recruitable stroke work (PRSW) relationship. Pressure-length loops were obtained as in Figure 16-18 (Figure Not Available) . The shaded area represents regional stroke work and, as shown in the insert, was plotted versus the corresponding end-diastolic length (EDL, large dot). *(From Pagel et al [85])*

The concept of PRSW has appeared in the anesthesia literature and has been used as a means of demonstrating the negative inotropic effects of several anesthetics, in particular, halothane, isoflurane, and propofol. [85] [88] [89] Pagel and Warltier [88] compared the ESPVR, $ESPVR_{area}$, and PRSW in autonomically blocked, chronically instrumented canines. These investigators found that either the slope or the volume intercept of the ESPVR gave inconsistent results, whereas both $ESPVR_{area}$ and the PRSW gave results that were consistent and demonstrated the dose-dependent negative inotropic effects of the volatile anesthetics halothane and isoflurane and the intravenous anesthetic propofol.

Current data suggest that we have two load-insensitive measures of contractility, $ESPVR_{area}$ and PRSW; however, both indices, while giving valuable and reproducible measures of contractility, cannot, at this time be directly applied to clinical evaluation of the patient because of the invasive requirements of the measurements. Thus, as the quantitative aspects of transesophageal echocardiography improve, allowing accurate dimensional measurements to be performed, and as the reliability and use of volume catheters increase, and as the placement of high-fidelity transducers into the ventricular cavities becomes less an experimental procedure, clinical monitoring will likely benefit from these concepts.

Diastolic Properties

Intense investigations have demonstrated that alterations in diastole can markedly alter cardiac performance. It has been shown that diastolic function can be modified directly by certain pathologic processes such as ischemia and hypertrophy and also indirectly by alterations in systolic function. Diastole is a complex process, which can be divided into four phases: (1) isovolumic relaxation; (2) rapid ventricular filling; (3) diastasis or slow filling; and (4) atrial systole. Each phase is the result of independent mechanisms, but it is interrelated with the other processes [90] (Fig. 16-20) (Figure Not Available) .

Assessment of diastole can be performed in a number of ways, most requiring invasive monitoring for accurate measures of chamber pressure, segment length, and transcardiac pressure. One index of diastolic function is the maximum rate of fall of LV pressure, maximum negative dP/dt. Unfortunately, this index is highly dependent on the maximum ventricular pressure and loading conditions, is only measured at a single time point, and, therefore, disregards much of the available data that are obtainable during relaxation. A second, more encompassing index reflecting the

Figure 16-20 (Figure Not Available) The phases of left ventricular diastole: (1) isovolumic relaxation from aortic valve closure to initial valve opening; (2) rapid filling time from mitral valve opening to plateau of ventricular volume curve; (3) slow filling period; and (4) atrial systole. *(From Plotnick [90])*

Figure 16-21 (Figure Not Available) Determination of the time constant for relaxation obtained from a plot of dP/dt versus left ventricular pressure during one heart beat. The slope of the line from maximum negative dP/dt to mitral valve opening yields the constant T as the negative inverse of the slope. *(From Humphrey et al [91])*

rate of pressure decline is tau, or its inverse, T, which describes the time constant of the exponential decay of LV pressure from maximum -dP/dt to its asymptote. The following equation and method were developed by Thompson et al [91] to describe exponential decay of ventricular pressure:

where P(t) is the pressure at variable time, P_0 is the initial pressure, P_{asym} is the asymptotic pressure as t approaches infinity, and A is the reciprocal of the time

constant T. [91] This formula can be reconfigured by differentiation and substitution to yield

and plotting dP/dt versus P will result in a straight line with a slope of -1/T ms $^{-1}$ and an intercept of P_{asym} [92] (Fig. 16-21) (Figure Not Available) . The time constant T has the units of milliseconds, and an increase in T indicates prolongation of the relaxation process. Volatile anesthetics have been shown to prolong T, as do hemodynamic factors such as ischemia. [93] [94]

The relaxation processes reflected by T include the basic mechanisms of Ca^{2+} sequestration by the SR, unbinding of Ca^{2+} from TnC, detachment of the actin-myosin cross-bridges, and overcoming of the viscoelastic properties of the myocardium. Relaxation includes both passive and active mechanisms, and the multiple indices of relaxation reflect varying aspects of the processes enumerated earlier.

Ventricular chamber stiffness and myocardial stiffness are two indices that reflect the passive components of diastolic function. Chamber stiffness is defined as the change in ventricular pressure for a given change in ventricular volume (dP/dV) from the nadir of the ventricular pressure to the beginning of atrial systole. The reciprocal of chamber stiffness is compliance, dV/dP. LV pressure can be plotted as a function of ventricular volume or some aspect of ventricular dimensional change during the diastolic filling phase. The data can be fitted by linear regression analysis to the following formula:

where P is ventricular pressure, b is a constant, L is a volume or segment measurement, and k_c is the chamber stiffness constant [95] (Fig. 16-22) (Figure Not Available) .

To obtain an accurate assessment of the stiffness constant, it is important to obtain data over a wide range of diastolic ventricular pressures and volumes. [96] Several factors contribute to chamber stiffness, including the passive elastic properties of the myocardium, the extent of myocardial relaxation, viscoelastic forces, coronary turgor, geometric factors such as ventricular shape, and wall thickness. The k_c has units of the reciprocal of either volume, area, or length, depending on which dimension has been measured.

Figure 16-22 (Figure Not Available) Left ventricular chamber stiffness. Chamber stiffness is estimated from LV diastolic pressure versus LV diastolic volume curves. The data at increasing volumes are fitted to a simple exponential equation $P = be^{k_c L}$, where P equals LV diastolic pressure, b is a constant, L is a volume or segment measurement, and k_c represents the modulus for chamber stiffness. The stiffness curve is steeper and the value of k_c greater in the hypertrophic cardiomyopathy (HCM) patient than in the healthy patient. *(From Gaasch et al [95])*

Although chamber stiffness gives an overall synthesis of many factors involved in the global ventricular diastolic properties, myocardial stiffness refers directly to the muscle and connective tissue itself. Myocardial stiffness is defined as the ratio of myocardial stress to myocardial strain. Stress is defined as the force per unit cross-sectional area, whereas strain is the deformation of a material produced by a force. A plot of myocardial stress versus strain yields a curvilinear relationship, where the slope of any tangent to the line represents the elastic stiffness k_m . Myocardial stiffness represents the intrinsic molecular properties of the myocardium. Hypertrophy leads to an increase not only in muscle mass but also in extracellular connective tissue and perhaps in the intracellular cytoskeletal components and results in an increase in myocardial stiffness and in k_m . Similarly, following chronic ischemia and infarction, myocardial stiffness increases and k_m is higher. The measurement of myocardial strain is variable, because in some circumstances (e.g., localized ischemia or infarction) strain results from the local deformation caused by a stress placed on that area of tissue. One can therefore understand that because strain varies in particular areas of the ventricle, myocardial elasticity, and, in particular, the modulus of stiffness k_p , can be considerably different in different areas of the ventricle.

Cardiac Reflexes

Before discussing specific reflexes, it is important to understand the various pathways by which cardiac mechanoreceptors elicit their physiologic responses. These receptors, which can be found throughout the atria, ventricles, pericardium, and coronary arteries, are linked via either myelinated or unmyelinated afferent fibers that travel through the vagus to the brain stem or the dorsal root ganglia to the spinal cord. [62] It is presumably the central integration and processing of these various sympathetic and parasympathetic nerve inputs that determine the particular response or reflex elicited on the heart and systemic circulation.

Baroreceptor Reflex

The baroreceptor reflex, also called the carotid sinus reflex, responds to changes in blood pressure via circumferential and longitudinal stretch receptors present in the carotid sinus and aortic arch. Increases in blood pressure stimulate these two receptors, which send impulses along the afferent limbs of the glossopharyngeal nerve (nerve of Hering) and vagus nerve, respectively, to the nucleus solitarius in the medullary cardiovascular center. This center actually comprises two functional areas: a lateral and rostrally located pressor center and a central and caudally located depressor center, in which hypothalamic and limbic system inputs are then integrated. The response is decreased sympathetic activity, which, in turn, decreases contractility, heart rate, and vascular tone, and increased parasympathetic activity, which also decreases heart rate and further depresses contractility. Typically, these receptors begin to respond at pressures in excess of 170 mm Hg; however the set point shifts upward in patients with chronic or poorly controlled hypertension. Meanwhile, decreases in blood pressure have the reverse effect, and these receptors play an important role in the response of the cardiovascular system to acute blood loss and shock. However, at pressures lower than 50 to 60 mm Hg, the baroreceptors lose much of their functional capacity. [97]

Chemoreceptor Reflex

The chemoreceptor reflex responds to changes in pH status and blood oxygen tension at an arterial partial pressure of oxygen (P_{O_2}) of less than 50 mm Hg via receptors in the carotid and aortic bodies. [98] Conditions of acidosis and hypoxia stimulate these receptors, especially those within the carotid body, which also send their impulses along the glossopharyngeal and vagus nerves to the chemosensitive area of the medulla, located bilaterally just beneath its ventral surface. This area responds by stimulating respiratory centers to increase ventilation and also by increasing parasympathetic activity, which produces significant bradycardia and decreased contractility. [99] If hypoxia persists, direct central nervous stimulation will lead to improved ventricular performance independent of parasympathetic activity.

Bainbridge Reflex

The Bainbridge reflex responds to changes in RA or central venous pressure via stretch receptors present within the RA wall and cavoatrial junction. Increases in intravascular volume or right-sided filling pressures stimulate these receptors, which also send their impulses through vagal afferents to inhibit parasympathetic activity and to increase heart rate. [59] The changes in heart rate, however, are dependent on the underlying rate prior to stimulation, and relatively fast heart rates are less sensitive to further increase. In addition, there is also a direct effect of stretching on the SA node, which leads to enhanced automaticity and increased heart rate.

Bezold-Jarisch Reflex

The Bezold-Jarisch reflex responds to noxious ventricular stimuli via chemoreceptors and mechanoreceptors present within the LV wall. The activated receptors send their impulses along unmyelinated vagal afferent type C fibers, which reflexively increase parasympathetic tone, leading to bradycardia, hypotension, and coronary artery vasodilation. [100] Conditions under which ischemic myocardium is then reperfused, such as the aftermath of treatment with nitrates or heparin, thrombolytic therapy following infarction, or coronary bypass grafting, may also elicit this reflex. [101] [102]

Valsalva Maneuver

The Valsalva maneuver occurs with forced expiration against a closed glottis, producing increased intrathoracic pressure, increased central venous pressure, and decreased venous return to the heart. [103] The resulting decrease in cardiac output and blood pressure is then sensed by baroreceptors, which respond by reflexively increasing heart rate via

---

sympathetic stimulation. As the glottis opens and venous return subsequently increases, the heart responds by vigorous contraction, which increases cardiac output and blood pressure, thereby causing baroreceptors to reflexively decrease heart rate via parasympathetic stimulation.

Cushing Reflex

Cushing reflex occurs in response to cerebral ischemia that is secondary to increased intracranial pressure from increased cerebrospinal fluid production, decreased resorption, or a mass effect. The initial reflex is a direct central nervous system sympathetic stimulation leading to increased heart rate, contractility, and blood pressure in an effort to increase cerebral perfusion. This is followed by reflex bradycardia mediated by baroreceptors present within the carotid sinus and aortic arch as a result of the increased peripheral vascular tone.

Oculocardiac Reflex

The oculocardiac reflex responds to pressure on the globe of the eye or traction on the surrounding structures via stretch receptors within the extraocular muscles. Increases in tension on these muscles, especially the medial rectus, activate these receptors, which send their afferent impulses via the short and long ciliary nerves to the ciliary ganglion and, eventually, via the ophthalmic division of the trigeminal nerve, to the gasserian ganglion, which results in increased parasympathetic tone and profound reflex bradycardia. The incidence of this condition ranges from 30 to 90 percent of all ophthalmic surgical cases and can be attenuated by pretreatment with an antimuscarinic agent such as atropine or glycopyrrolate.

CORONARY BLOOD FLOW

Coronary blood flow, like blood flow in other vessels, is dependent on a pressure gradient, principally driven by mean arterial pressure. However, because aortic pressure can vary widely and because the heart beats continuously, the pressure gradient and, hence, coronary blood flow fluctuate depending on the state of contraction. During systole, especially on the left side of the heart, the pressure within the coronary artery secondary to extravascular compression from the squeezing effect of the contracting myocardium virtually eliminates antegrade coronary blood flow. This situation is diagrammed in Figure 16-23 (Figure Not Available) , in which the coronary blood flow goes to zero just prior to ventricular ejection, corresponding to isovolumic contraction and increased extravascular compression. [104] Conversely, coronary blood flow through the left side is maximal during early diastole, corresponding to the period of isovolumic relaxation (see Fig. 16-8 (Figure Not Available) , E to A) and minimal extravascular compression. Coronary blood flow through the right side, however, is maximal during peak systole, because developed pressure and consequently extravascular compression within the RV are considerably less than in the LV, thus allowing for antegrade flow during both systole and diastole. [5]

Figure 16-23 (Figure Not Available) The differences in coronary blood flow through the left and right sides of the heart during systole and diastole occur because of differences in ventricular muscle mass. *(From Berne and Levy [6])*

The difference between resting and maximal coronary blood flow is termed the *coronary flow reserve.* Hence, factors that decrease maximal coronary blood flow (e.g., tachycardia, increased blood viscosity, increased myocardial contractility, and increased ventricular size) also decrease coronary flow reserve. This is important because basal cardiac oxygen consumption is 6 to 10 mL O_2 /mm/100 g, and transcoronary extraction of oxygen is near the limits allowable by the oxyhemoglobin dissociation curve. Thus, unlike the kidney, which can compensate for increased oxygen consumption by increasing oxygen extraction, the heart has little "extraction reserve" and must increase oxygen delivery via increasing coronary blood flow to meet increased metabolic demands.

Under normal circumstances, the myocardial wall pressure is highest near the endocardium and is lowest near the epicardium. Thus, endocardial blood flow is greatly influenced by diastolic ventricular muscle relaxation, which decreases myocardial wall pressure and enhances the pressure gradient. This maximizes perfusion to the inner wall of the ventricle, thus making the endocardium relatively more sensitive to pathologic changes such as hypotension, partial coronary occlusion and ischemia, myocardial hypertrophy, and severe aortic stenosis.

The presence of stenosis tends to cause vasodilation in an effort to maintain coronary blood flow across the lesion.

However, as the extent of stenosis increases to more than 90 percent of the luminal cross-sectional area, the compensatory vasodilatory properties of the artery are exceeded, and the blood flow decreases. Thus, if a coronary artery provides blood flow to two distal branches and one of the branches is tightly occluded by a stenotic lesion, administration of a pharmacologic vasodilator or endogenous release of local mediators may cause preferential vasodilation of the normal vessel, because the stenotic vessel is already maximally dilated. This results in a phenomenon known as *coronary steal,* in which there is a relative increase in blood flow to the area of the heart served by the normal anatomy and a relative decrease in blood flow to the area of the heart served by the stenotic vessel.

Consequently, the coronary arteries, like the carotid and renal arteries, exhibit some degree of autoregulation, which acts to maintain coronary blood flow within tightly controlled limits over a perfusion pressure range of 0 to 140 mm Hg independent of myocardial oxygen demand. [105] [105A] Coronary perfusion pressure is defined as the difference between diastolic aortic pressure and LV end-diastolic pressure. [106] Factors influencing coronary artery autoregulation include neural, metabolic, and humoral inputs, as well as numerous myocardial reflexes, which are the result of parasympathetic and sympathetic innervation of the coronary vessels. [107] Parasympathetic stimulation of muscarinic receptors in coronary arteries produces direct vasodilation, whereas sympathetic stimulation of adrenergic receptors induces coronary dilation secondary to increased metabolic demand. Although unopposed alpha $_1$ -adrenergic stimulation may produce coronary artery spasm, the overall contribution of alpha-adrenergic stimulation on basal coronary tone is relatively small. In fact, the vasodilating properties of beta receptor activation appear to predominate over the alpha-adrenergic effects. [108]

Locally produced metabolites also appear to be important mediators of coronary vascular resistance. One hypothesis is that vasodilatory substances are released by myocytes in proportion to their level of work, thus ensuring an adequate supply of fresh substrate to meet existing metabolic demands. These vasodilatory substances presumably act on opposite mechanisms that generate basal vascular tone. In addition, vascular endothelium also produces vasoregulators that act independently of cardiac metabolism to influence coronary blood flow. [109] Some of the mediators of vascular tone that have been proposed include adenosine, ATP, prostaglandins, nitric oxide, endothelin, oxygen, and K^+ . [110]

Adenosine was first proposed as a physiologic regulator of coronary blood flow approximately 60 years ago. [111] [112] Over the past quarter-century, many data support its role as the most important mediator coupling coronary blood flow with myocardial oxygen consumption. In fact, adenosine release has been postulated to be an indicator of an imbalance between oxygen supply and demand. [113] Production of adenosine in the heart has three sources: one coupled to the cytosolic phosphate potential as a representation of the cellular energy state and the other two independent of it. Within the cardiomyocyte, adenosine is generated by the dephosphorylation of AMP by the enzyme, 5
-nucleotidase. High levels of ATP increase the activity of this enzyme and result in an increase in production of adenosine. [114] [115] [116] Adenosine can then diffuse out of the cell and may cause an increase in coronary blood flow to match metabolic demands. Extracellular adenosine production occurs by the hydrolysis of interstitial AMP and interstitial *S*-adenosylhomocysteine. Adenosine receptors are found in both the smooth muscle and the endothelial cells of the coronary arteries. [117] [118] The exact mechanism of action of adenosine in producing coronary vasodilation is unknown; however, it is postulated that alpha $_2$ -adenosine receptors are coupled to adenylate cyclase and increase levels of cAMP, thereby promoting coronary relaxation. Meanwhile, others have postulated that the alpha $_1$ -adenosine receptors are linked to guanylate cyclase, and they produce coronary vasodilation by a mechanism similar to that of nitric oxide. [119] Prostaglandin E_1 , a potent coronary vasodilator, probably acts through adenosine to achieve its vasomotor activity. [120]

In 1987, a substance that was previously known as endothelium-derived relaxing factor was identified as nitric oxide. Production of this labile substance from vascular endothelium was first noted to be the mechanism by which acetylcholine elicited relaxation of the smooth muscle in blood vessels. Since then, nitric oxide has been the subject of numerous investigations because it is linked to many cellular functions. Nitric oxide activates guanylate cyclase, which, in turn, increases intracellular production of cGMP. Cyclic GMP is known to initiate a cascade of phosphorylation/dephosphorylation reactions, most notably the dephosphorylation of myosin light chains, resulting in smooth muscle relaxation. [121] Arteriolar vascular beds are more sensitive to the relaxant effects of nitric oxide than venous beds. [122] Thus, nitric oxide released from vascular endothelium plays an important role in overall vascular tone.

Endothelin is a vasoconstrictor that was first noted to be released from endothelial cells grown in culture. It is a 21-amino acid peptide containing 2 intrachain disulfide bridges. Endothelin receptors have been found in both cardiac and smooth muscle cells, as well as in endothelial cells. Ironically, binding of endothelin to its receptor

in vascular beds also triggers the production of nitric oxide and prostacyclin, so it appears that endothelin regulates vascular tone by both direct and indirect mechanisms. [123] [124] [125] Endothelin induces vasoconstriction via activation of phosphoinositide-selective phospholipase C. Activation of this enzyme in smooth muscle leads to the breakdown of inositol triphosphate, which causes the release of calcium from intracellular stores and generalized vasoconstriction. Another byproduct of inositol triphosphate turnover, diacylglycerol, stimulates protein kinase C, which phosphorylates numerous intracellular proteins and leads to vasoconstriction. [126]

Oxygen, and more specifically a mixed venous oxygen tension at a P_{O_2} threshold of 32 mm Hg, plays an important role in coronary autoregulation. [127] In fact, arteriolar resistance varies directly with tissue P_{O_2}. [109] The hypothesis is that ATP-sensitive K^+ channels present in vascular smooth muscle open in response to a reduction in ambient tissue oxygen levels. The resultant efflux of K^+ from vascular myocytes produces hyperpolarization of the cell membrane such that Ca^{2+} channels are less likely to open. The slow inward current is therefore reduced, and cytosolic Ca^{2+} levels are decreased, a process that promotes smooth muscle relaxation and an overall decrease in vascular resistance. Sulfonylureas, such as glibenclamide, block the opening of ATP-sensitive K^+ channels and virtually abolish the coronary vasodilation that normally results from hypoxia and ischemia. [128]

References

1. Berne RM, Levy MN: The cardiac pump. In: Cardiovascular Physiology, 4th ed. St. Louis, CV Mosby, 1981, p 71.

2. Kelman GR: The heart. In: Applied Cardiovascular Physiology, 2nd ed. London, Appleton-Century-Crofts, 1977, p 52.

3. Westaby S, Karp RB, Blackstone EH et al: Adult valve dimensions and their surgical significance. Am J Cardiol 53:552, 1984.

4. Keen EH: The postnatal development of human cardiac ventricles. J Anat 89:484, 1955.

5. Berne RM, Levy MN: Coronary circulation. In: Cardiovascular Physiology, 4th ed. St. Louis, CV Mosby, 1981, p 211.

6. James TN: Blood supply of the human interventricular septum. Circulation 17:391, 1958.

7. Schesinger MJ: Relation of anatomic pattern to pathologic conditions of the coronary arteries. Arch Pathol 30:403, 1941.

8. Nevantzis CE, Toutouzas P, Avgoustakis D: The importance of the sinus node artery in the blood supply of the atrial myocardium. Acta Cardiol 38:35, 1983.

8A. Katz AM: Physiology of the Heart, 2nd ed. New York, Raven Press, 1992.

9. Wearn JT, Mettier SR, Klump TG et al: The nature of the vascular communications between the coronary arteries and the chambers of the heart. Am Heart J 9:143, 1933.

10. Langer GA: The Myocardium. New York, Academic Press, 1997.

11. Fawcett DW, McNutt NS: The ultrastructure of the cat myocardium. J Cell Biol 42:1, 1969.

12. Labeit S, Kolmerer B, Linke WA: The giant protein titin: Emerging roles in physiology and pathophysiology. Circ Res 80:290, 1997.

13. Engelmann TW: Uber die Leitung der Erregung im Herzmuskel. Pflugers Arch Physiol 11:465, 1875.

14. Sjostrand FS, Andersson-Cedergren E, Dewey MM: The ultrastructure of the intercalated disc of frog, mouse, and guinea pig cardiac muscle. J Ultrastruct Mol Struct Res 1:271, 1958.

15. Fishman GI, Moreno AP, Spray DC et al: Functional analysis of human cardiac gap junction channel mutants. Proc Natl Acad Sci U S A 88:3525, 1991.

16. Beyer EC, Davis LM, Veenstra RD: Cardiac intercellular communication: Consequences of connexin distribution and diversity. Braz J Med Biol Res 28:415, 1995.

17. Spray DC, Bennett MVL: Physiology and pharmacology of gap junctions. Annu Rev Physiol 47:281, 1985.

18. Berne RM, Levy MN: Electrical activity of the heart. In: Cardiovascular Physiology, 4th ed. St. Louis, CV Mosby, 1981, p 5.

19. Wit AL, Rosen MR, Hoffman BF: Electrophysiology and pharmacology of cardiac arrythmias. II. Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias. Am Heart J 88:515, 1974.

20. Noble D: A modification of the Hodgkin-Huxley equations applicable to Purkinje fiber action and pacemaker potentials. J Physiol 160:317, 1962.

21. Levitan IB, Kazcmarek LK: The Neuron. New York, Oxford University Press, 1991.

22. Cohen CJ, Bean BP, Colatsky TJ et al: Tetrodotoxin block of sodium channel in rabbit Purkinje fibers: Interactions between toxin binding and channel gating. J Gen Physiol 78:383, 1981.

23. Mitchell MR, Powell T, Terror DA et al: Characteristics of the second inward current in cells isolated from rat ventricular muscle. Proc R Soc Lond (Biol) 219:447, 1983.

24. Shen SS, Blaustein MP: Sodium/calcium exchange and control of cell calcium and contractility in cardiac and vascular smooth muscles. In Fozzard HA, Haber E, Jennings RB et al (eds): The Heart and Cardiovascular System, 2nd ed. New York, Raven Press, 1992, p 904.

25. Zobrist RH, Giacomini KM, Nelson WL et al: The interaction of phenylalkylamine calcium channel blockers with the 1,4 dihydropyridine binding site. J Mol Cell Cardiol 18:943, 1986.

26. Lake CL: Pharmacology of cardiac drugs. In: Cardiovascular Anesthesia. New York, Springer-Verlag, 1985, p 250.

27. Anderson RH, Ho SY, Smith A et al: The internodal atrial myocardium. Anat Rec 201:75, 1981.

28. Ganong WF: The heart. In: Review of Medical Physiology, 11th ed. Los Altos, Cal, Lange Medical Publications, 1983, p 435.

29. Vassale M: An analysis of cardiac pacemaker potential by means of a voltage clamp technique. Am J Physiol 210:1335, 1966.

30. Gadsby DC: Beta adrenergic agonists increase membrane K^+ conductance in cardiac Purkinje fibers. Nature 306:691, 1959.

31. Rayner B, Weatherall M: Acetylcholine and potassium movements in rabbit auricles. J Physiol (Lond) 146:392, 1959.

32. Bachmann G: The inter-auricular time interval. Am J Physiol 41:309, 1916.

33. Thorec C: Uber den Aufbau des Sinuskotens and seine Verbindung mit der Cava Superior und den Wenckebachschen Bundeln. Munch Med Wochenschr 57:183, 1910.

34. Wenkebach KF: Beitrage zur Kenntnis der menschlichen Herztagigkeit. Arch Physiol (suppl 3):53, 1908.

35. James TN: Morphology of the human atrioventricular node, with remarks pertinent to its electrophysiology. Am Heart J 62:756, 1961.

36. Woods WT, Sherf L, James TM: Structure and function of specific regions in the canine atrioventricular node. Am J Physiol 243:H41, 1982.

37. Noble D: The Initiation of the Heartbeat, 2nd ed. Oxford, Clarendon Press, 1979.

38. Fabiato A: Time and calcium independence of activation and inactivation of calcium-induced release of calcium from the sarcoplasmic reticulum of a skinned cardiac Purkinje cell. J Gen Physiol 85:247, 1985.

39. McPherson PS, Campbell KP: The ryanodine receptor/Ca^{2+} release channel. J Biol Chem 268:13765, 1993.

40. Peterson JN, Hunter WC, Berman MR: Estimated time course of Ca^{2+} bound to troponin C during relaxation in isolated cardiac muscle. Am J Physiol 260:1013, 1991.

41. Davis BA, Edes I, Gupta RC et al: The role of phospholamban in the regulation of calcium transport by cardiac sarcoplasmic reticulum. Mol Cell Biochem 99:83, 1990.

42. Putkey JA, Sweeney HL, Campbell ST: Site-directed mutation of the trigger calcium-binding sites in cardiac troponin C. J Biol Chem 264:12370, 1979.

43. Falke JJ, Snyder EE, Thatcher KC et al: Quantitating and engineering the ion specificity of an EF-hand-like Ca^{2+} binding site. Biochemistry 30:8690, 1991.

44. Stryer L: Muscle contraction and cell motility. In: Biochemistry, 3rd ed. New York, WH Freeman, 1988, p 931.

45. Opie LH: The Heart: Physiology and Metabolism. New York, Raven Press, 1991.

46. Eisenerg E, Hill TL: Muscle contraction and free energy transduction in biological systems. Science 227:999, 1985.

47. Rayment T, Holden HM, Whittaker M et al: Structure of the actin-myosin complex and its implications for muscle contraction. Science 261:58, 1993.

48. Neely JR, Morgan HE: Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle. Annu Rev Physiol 36:418, 1974.

49. Tahiliani AG: Myocardial fatty acid metabolism. In Fozzard HA, Haber E, Jennings RB et al (eds): The Heart and Cardiovascular System, 2nd ed. New York, Raven Press, 1992, p 1599.

50. Fagand R, Conway J: Measurement of cardiac output: Fick principle using catheterization. Eur Heart J 11 (suppl I):1, 1990.

51. Berne RM, Levy MN: Cardiac output and the venous system. In: Cardiovascular Physiology, 4th ed. St. Louis, CV Mosby, 1981, p 183.

52. Chambers CE, Skeehan TM, Hensley FA Jr: The Cardiac Catheterization Laboratory. In Kaplan JA (ed): Cardiac Anesthesia, 3rd ed. Philadelphia, WB Saunders, 1933, p 59.

53. Wetzel RC, Rogers MC: Pediatric hemodynamic monitoring. In Shoemaker WC, Thompson WL (eds): Critical Care State of the Art, vol 2. Fullerton, Cal, Society of Critical Care Medicine, 1981, p II(L)1.

54. Sarnoff SJ, Gilmore JP, Mitchell JH et al: Potassium changes in the heart during homeometric autoregulation and acetyl strophanthidin. Am J Med 34:440, 1963.

55. Koch-Weser J, Blinks JR: The influence of the interval between beats on myocardial contractility. Pharmacol Rev 15:601, 1963.

56. Woodworth RS: Maximal contraction, "staircase" contraction, refractory period, and compensatory pause of the heart. Am J Physiol 8:213, 1902.

57. Rose JS, Nanna M, Rahimtoola SH et al: Accuracy of determination of changes in cardiac output by transcutaneous continuous-wave Doppler computer. Am J Cardiol 54:1099, 1984.

58. De Marneffe M, Jacobs P, Haardt R et al: Variations of normal sinus node function in relation to age: Role of autonomic influence. Eur Heart J 7:662, 1986.

58A. Coleridge JCG, Hemingway A, Holmes RL et al: The location of atrial receptors in the dog: A physiological and histological study. J Physiol (Lond) 136:174, 1957.

58B. Mark AL, Kioschos JM, Abboud FM et al: Abnormal vascular responses to exercise in patients with aortic stenosis. J Clin Invest 52:1138, 1973.

58C. Miller MR, Kasahara K: Studies on the nerve endings in the heart. Am J Anat 115:217, 1964.

58D. Recordati G, Lombardi F, Bishop VS et al: Response of type B atrial vagal receptors to changes in wall tension during atrial filling. Circ Res 36:682, 1975.

59. Longhurst JC: Cardiac receptors: Their function in health and disease. Prog Cardiovasc Dis 27:201, 1984.

60. Seagard JL, Kampine JP: Electrophysiological investigation of sympathetic cardiac afferent fibers. Proc Soc Exp Biol Med 164:93, 1980.

61. Bishop VS, Malliani A, Thoren P: Cardiac mechanoreceptors. In Shepard JT, Abboud FM (eds): Handbook of Physiology: Peripheral Circulation and Organ Blood Flow. Washington, DC, American Physiological Association, 1983, p 497.

62. Shepard JT: Cardiac mechanoreceptors. In Fozzard HA, Haber E, Jennings RB et al (eds): The Heart and Cardiovascular System, 2nd ed, vol 2. New York, Raven Press, 1991, p 1481.

63. Kimura E, Hashimoto K, Furukawa S et al: Changes in bradykinin level in coronary sinus blood after the experimental occlusions of a coronary artery. Am Heart J 85:635, 1973.

64. Ammons WS, Blair RW, Foreman RD: Vagal afferent inhibition of spinothalamic cell responses to sympathetic afferents and bradykinin in the monkey. Circ Res 53:603, 1983.

65. White JC: Cardiac pain: Anatomic pathways and physiologic mechanisms. Circulation 16:644, 1957.

66. Perloff WH: Physiology of the heart and circulation. In Swedlow DB, Raphaely RC (eds): Cardiovascular Problems in Pediatric Critical Care. New York, Churchill Livingstone, 1986, p 1.

67. Susanni ES, Vatner DE, Homcy CJ: Beta-adrenergic receptor/adenyl cyclase system. In Fozzard HA, Haber E, Jennings RB et al. (eds): The Heart and Cardiovascular System. New York, Raven Press, 1992, p 1695.

68. Gilman AG: G proteins: Transducers of receptor-generated signals. Annu Rev Biochem 56:615, 1987.

69. Weiner N: Norepinephrine, epinephrine, and the sympathomimetic amines. In Gilman AG, Goodman LS (eds): The Pharmacological Basis of Therapeutics. 7th ed. New York, Macmillan, 1985, p 155.

70. Levy MN: Neural control of the heart: Sympathetic-vagal interactions. In Baan J, Noodergraaf A, Raines J (eds): Cardiovascular System Dynamics. Cambridge, Mass, MIT Press, 1976, p 365.

71. Katada T, Bokoch GM, Smigel MD et al: The inhibitory guanine nucleotide binding regulatory component of adenylate cyclase, subunit dissociation and the inhibition of adenylate cyclase in S49 lymphoma cyc- and wild type membranes. J Biol Chem 259:3586, 1984.

72. Levy MN, Blattberg B: Effect of vagal stimulation on the overflow of norepinephrine into the coronary sinus during cardiac nerve stimulation in the dog. Circ Res 38:81, 1976.

73. Patterson SW, Piper H, Starling EH: The regulation of the heart beat. J Physiol (Lond) 48:465, 1914.

74. Parker JO, Case RB: Normal left ventricular function. Circulation 60:4, 1979.

75. Frank JS, Winegrad S: Effect of muscle length on 45Ca efflux in resting and contracting skeletal muscle. Am J Physiol 231:555, 1976.

76. Lakatta EG: Age-related alterations in the cardiovascular response to adrenergic mediated stress. Fed Proc 39:3173, 1980.

77. Lakatta EG: Catecholamines and cardiovascular function in aging. Endocrinol Metab Clin North Am 16:877, 1987.

78. Koch-Weser J, Blinks JR: The influence of the interval between beats on myocardial contractility. Pharmacol Res 15:601, 1963.

79. Lakatta EG: Length modulation of muscle performance. In Fozzard HA, Haber E, Jennings RB et al (eds): The Heart and Cardiovascular System, 2nd ed, vol 2. New York, Raven Press, 1991, p 1327.

80. Sagawa K: The ventricular pressure-volume diagram revisited. Circ Res 43:677, 1978.

81. Sagawa K: The end-systolic pressure-volume relation of the ventricle: Definition, modifications and clinical use. Circulation 63:1223, 1981.

82. Suga H, Sagawa K, Shoukas AA: Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 32:314, 1973.

83. Crottogini AJ, Willshaw P, Barra JG et al: Inconsistency of the slope and the volume of the end-systolic pressure-volume relationship as individual indexes of inotropic state in conscious dogs: Presentation of an index combining variables. Circulation 76:1115, 1987.

84. Mahler F, Ross J, O'Rourke RA et al: Effects of changes in preload, afterload and inotropic state on ejection and isovolumic phase measures of contractility in the conscious dog. Am J Cardiol 35:626, 1975.

85. Pagel PS, Campine JP, Schmeling WT et al: Comparisons of end-systolic pressure-length relations and preload recruitable stroke work as indices of myocardial contractility in the conscious and anesthetized chronically instrumented dog. Anesthesiology 73:278, 1990.

86. Sarnoff SJ, Berglund E: Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation 9:706, 1954.

87. Glower DD, Spratt JA, Snow ND et al: Linearity of the Frank-Starling relationship in the intact heart: The concept of preload recruitable stroke work. Circulation 71:994, 1985.

88. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. Anesthesiology 78:100, 1993.

89. Pagel PS, Kampine JP, Schmeling WT et al: Reversal of volatileinduced depression of myocardial contractility by extracellular calcium also enhances left ventricular diastolic function. Anesthesiology 78:141, 1978.

90. Plotnick GD: Changes in diastolic function: Difficult to measure, hard to interpret. Am Heart J 118:637, 1989.

91. Thompson DS, Waldron CB, Coltart DF et al: Estimation of time constant of left ventricular relaxation. Br Heart J 49:250, 1983.

92. Beattie L, Marushak G, Humphrey LS: Determination of decay constants from time-varying pressure data. Anesthesiology 70:159, 1989.

93. Humphrey LS, Stinson DC, Humphrey MJ et al: Volatile anesthetic effect on left ventricular relaxation in swine. Anesthesiology 73:731 1990.

94. Rousseau MF, Veriter JM, Detry LB et al: Impaired early left ventricular relaxation in coronary artery disease: Effects of intracoronary nifedipine. Circulation 62:764, 1980.

95. Gaasch WH, Apstein CS, Levine HJ: Diastolic properties of the left ventricle. In Levine HJ, Gaasch WH (eds): The Ventricle. Boston, Martinus Nijhoff, 1985, p 148.

96. Lew WYW: Evaluation of left ventricular diastolic function. Circulation 79:1393, 1989.

97. Aviado DM, Schmidt CF: Reflexes from stretch receptors on blood vessels, heart, and lungs. Physiol Rev 35:247, 1955.

98. Coleridge JCG, Coleridge HM: Chemoreflex regulation of the heart. In Berne RM (ed): Handbook of Physiology, sect 2: The Cardiovascular System, vol 2: The Heart. Bethesda, Md, American Physiological Society, 1979, p 653.

99. Daly MD, Hazzledine JL: The effects of artificially induced hyperventilation of the primary cardiac reflex response to stimulation of the carotid bodies in the dog. J Physiol (Lond) 168:872, 1963.

100. Mark AL: The Bezold-Jarisch reflex revisited: Clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1:90, 1983.

101. Wei JY, Mrkis JE, Malagold M et al: Cardiovascular reflexes stimulated by reperfusion of ischemic myocardium in acute myocardial infarction. Circulation 67:796, 1983.

102. Koren G, Weiss AT, Ben-David Y et al: Bradycardia and hypotension following reperfusion with streptokinase (Bezold-Jarisch reflex): A sign of coronary thrombolysis and myocardial salvage. Am Heart J 112:468, 1986.

103. Santamore WP, Hickman JL, Bove AA: Right and left ventricular pressure-volume response to respiratory maneuvers. J Appl Physiol 57:1520, 1984.

104. Steinhausen M, Tillmanns H, Thederan H: Microcirculation of the epimyocardial layer of the heart. Pflugers Arch 378:9, 1978.

105. Dole WP: Autoregulation of the coronary circulation. Prog Cardiovasc Dis 43:105, 1975.

105A. Olsson RA, Bunger R, Spaan JAE: Coronary circulation. In: Fozzard HA, Haber E, Jennings RB et al (eds): The Heart and Cardiovascular System, 2nd ed. New York, Raven Press, 1991, p 1404.

106. Kirk ES, Sonnenblick EH: Newer concepts in the pathophysiology of ischemic heart disease. Am Heart J 103:756, 1982.

107. Vatner SF: Alpha adrenergic regulation of the coronary circulation in the conscious dog. Am J Cardiol 56:16E, 1985.

108. Shepard JT, Vanhoutte PM: Mechanisms responsible for coronary vasospasm. J Am Coll Cardiol 8:50A, 1986.

109. Olsson RA, Bunger R, Spaan JAE: Coronary circulation. In Fozzard HA, Haber E, Jennings RB et al (eds): The Heart and Cardiovascular System, 2nd ed, vol 2. New York, Raven Press, 1991, p 1393.

110. Wilken DEL: Local factors controlling coronary circulation. Am J Cardiol 52:8A, 1983.

111. Drury AN, Szent-Gyorgi A: The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J Physiol (Lond) 68:213, 1929.

112. Lindner F, Rigler R: Uber die Beeinflussung der Weite der Herzkranzgefasse durch Produkte des Zellkernstoffwechsels. Pflugers Arch 226:697, 1931.

113. Bardenheuer H, Schrader J: Supply-to-demand ratio for oxygen determines formation of adenosine by the heart. Am J Physiol 250:H173, 1986.

114. Burger RM, Lowenstein JM: 5
-Nucleotidase from smooth muscle of small intestine and from brain: Inhibition by nucleotides. Biochemistry 14:2362, 1975.

115. Collinson AR, Peuhkurinen KJ, Lowenstein JM: Regulation and function of 5
-nucleotidases. In Gerlach E, Becker CE (eds): Topics and Perspectives in Adenosine Research. Berlin, Springer-Verlag, 1987, p 133.

116. Newby AC: The pigeon heart 5
-nucleotidase responsible for ischaemia-induced adenosine formation. Biochem J 253:123, 1988.

117. Goldman SJ, Dickinson ES, Slakey LL: The effect of adenosine on synthesis and release of cyclic AMP by cultured vascular cells from swine. J Cyclic Nucleotide Protein Phosphor Res 9:69, 1983.

118. Nees S, Bock M, Herzog V et al: The adenine nucleotide metabolism of the coronary endothelium: Implications for the regulation of coronary flow by adenosine. In Stefanovich V, Rudolphi K, Schulbert P (eds): Adenosine: Receptors and Modulation of Cell Function. Oxford, 1985, p 419.

119. Kurtz A: Adenosine stimulates guanylate cyclase activity in vascular smooth muscle cells. J Biol Chem 262:6296, 1987.

120. Karmazyn M, Dhalla NS: Physiological and pathophysiological aspects of cardiac prostaglandins. Can J Physiol Pharmacol 62:1207, 1983.

121. Rapoport RM, Murad F: Agonist-induced endothelium-dependent relaxation in rat thoracic aorta may be mediated through cGMP. Circ Res 52:352, 1983.

122. De Mey JG, Vanhoutte PM: Heterogeneous behavior of the canine arterial and venous wall: Importance of the endothelium. Circ Res 51:439, 1982.

123. DeNucci G, Thomas R, D'Orleans-Juste P et al: Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci U S A 85:9797, 1988.

124. Warner TD, Mitchell JA, DeNucci G et al: Endothelin-1 and endothelin-3 release EDRF from isolated perfused arterial vessels of the rat and rabbit. J Cardiovasc Pharmacol 13:585, 1989.

125. Whittle BJR, Lopez-Belmonte J, Rees DD: Modulation of the vasodepressor actions of acetylcholine, bradykinin, substance P and endothelin in the rat by a specific inhibitor of nitric oxide formation. Br J Pharmacol 98:646, 1989.

126. Rasmussen H, Takuwa Y, Park S: Protein kinase C in the regulation of smooth muscle contraction. FASEB J 1:177, 1987.

127. Hoffman JIE: Determinants and prediction of transmural myocardial perfusion. Circulation 58:381, 1978.

128. Daut J, Maier-Rudolph W, von Beckerath N et al: Hypoxic dilation of coronary arteries is mediated by ATP-sensitive potassium channels. Science 247:1341, 1990.

Chapter 17 - Hepatic Physiology

Dale A. Parks
Kelly A. Skinner
Simon Gelman
Mervyn Maze

INTRODUCTION: LIVER BLOOD FLOW

Gross Anatomy and Vascular Supply

The liver lies in the right upper quadrant of the abdominal cavity and is attached to the diaphragm. It is the largest gland in the human body and weighs approximately 1.5 kg, which represents 2 percent of body weight in adults and almost 5 percent in neonates. The liver is also a vital blood reservoir by virtue of its large vascular capacity. Ordinarily, it contains 25 to 30 mL blood per 100 g tissue, which is 10 to 15 percent of total blood volume, [1] of which approximately 20 percent is in the arterial system, 10 percent is in the capillaries, and 70 percent is in the venous system. [2] In addition to serving as a reservoir, the venous bed plays a major role in fluid homeostasis. Small changes in hepatic venous pressure result in massive fluid transudation into the lymph and leakage into the outer surface of the capsule and into the peritoneal cavity. This fluid contains 80 to 90 percent of the protein concentration of normal plasma protein.

Under normal resting conditions in humans, total hepatic blood flow is 1,200 to 1,400 mL/min (~100 mL/min/100 g), which represents about 25 percent of cardiac output. Blood flow to the four lobes of the liver is derived from two major sources, the portal vein and the hepatic artery (Fig. 17-1) (Figure Not Available) . The hepatic artery is a branch of the celiac axis and accounts for 25 to 30 percent of total hepatic blood flow and 45 to 50 percent of the oxygen supply. The portal vein is a valveless afferent nutrient vessel of the liver that carries blood from the entire capillary system of the stomach, spleen, pancreas, and intestine. The portal vein supplies 70 to 75 percent of total hepatic blood flow but only 50 to 55 percent of the oxygen supply because this blood is partially deoxygenated in the preportal organs and tissues. The sinusoids are the hepatic capillaries formed by the merging of the hepatic arterial and the portal streams (Fig. 17-2) (Figure Not Available) . The sinusoids, which are lined by thin endothelial cells, large Kupffer cells, and fat-storing Ito cells, comprise the principal blood flow conduit in the liver parenchyma. [3] Fenestration of the endothelium facilitates passage of blood constituents into the space of Disse, whereby they gain access to the hepatic parenchymal cells. Blood flows along the sinusoids to the terminal hepatic venule (central vein) of the hepatic veins, which drain the liver and empty into the inferior vena cava. Three major hepatic veins (right, middle, and left) and numerous smaller branches empty into the inferior vena cava on the posterior surface of the liver.

Microcirculation of the Liver

Within the liver, the portal vein and hepatic artery give rise to progressively smaller intrahepatic branches and ultimately form terminal portal venules and hepatic arterioles. These terminal blood vessels supply a small, irregular cluster of parenchymal cells referred to as the *liver acinus.* This liver acinus is the functional microvascular unit of the liver and is formed about a vertical axis consisting of a terminal portal venule, a hepatic arteriole, a bile duct, lymph vessels, and nerves. The terminal portal venule and hepatic arteriole course along with a bile ductule and are jointly referred to as

Figure 17-1 (Figure Not Available) Schematic representation of splanchnic circulation. *(Modified from Gelman, [151] reproduced with permission of S. Karger AG, Basel)*

the *portal axis.* Blood enters the acinus at its center, flows outward, and empties either directly into the sinusoidal capillaries or through a complex peribiliary plexus (supplying the bile ducts), which subsequently drains into the sinusoids.

The parenchymal cells of the liver acinus can be subdivided into three circulatory zones (Fig. 17-3) (Figure Not Available) , based on orientation with regard to the afferent vessels (portal axis). Zone 1 encompasses the hepatocytes close to the portal axis and the origin of the sinusoid. These cells are bathed in blood that is rich in oxygen and nutrients. The cells in zone 3 are situated at the periphery of the acinus and receive blood that has already

Figure 17-2 (Figure Not Available) Relations of branches of the portal vein (PV), hepatic artery (HA), and bile duct (BD). Note the peribiliary capillary plexus associated with the bile duct. *(From Jones [152])*

exchanged gases and metabolites with cells in zones 1 and 2, zone 2 being the arbitrary intermediary transition zone. This unique microvascular arrangement results in metabolic heterogeneity from zone 1 to zone 3. The cells of zone 1 contain numerous mitochondria and are ideally suited

Figure 17-3 (Figure Not Available) The blood supply of the hepatic structural unit, which occupies adjacent sectors of neighboring hexagonal fields. Zones 1, 2, and 3 represent areas supplied with blood of first, second, and third quality, respectively, with regard to oxygen and nutrients. These zones cluster about the terminal afferent vascular twigs and extend into the periportal field from which these twigs originate. Zones 1
, 2
, and 3
designate corresponding areas in a portion of an adjacent structural unit. In zones 1 and 1
, the afferent vascular twigs empty into the sinusoids. The circles A, B, and C delimit concentric bands of the hepatic parenchyma arranged around a small portal field. PS, portal spaces; THV, terminal hepatic venule. *(From Rappaport et al [153])*

for oxidative metabolism and synthesis of glycogen. Zone 3 cells receive the blood with the lowest oxygen tension and are optimum for anaerobic metabolism. Biotransformation of the majority of drugs, chemicals, and toxins occurs in zone 3, owing to the abundance of smooth endoplasmic reticulum, reduced nicotinamide adenine dinucleotide phosphate, and cytochrome P-450. The cells of zone 3 are the most sensitive to damage from circulatory disturbances (ischemia, hypoxia, and congestion) and to injury by toxic byproducts of biotransformation. Consequently, drug biotransformation is compromised early in the ischemic process.

Measurement of Liver Blood Flow

The techniques for measurement of hepatic blood flow can be broadly divided into three categories: (1) methods based on the clearance of a substance from the circulation, (2) techniques based on indicator dilution methodology, and (3) miscellaneous measurement techniques.

Parenchymal Clearance Techniques

The unique capacity of the liver to remove substances from the circulation makes clearance techniques well suited for measurement of hepatic blood flow. Hepatic clearance is a measure of the overall efficiency of hepatic extraction and depends on blood flow as well as on the intrinsic ability of the liver to eliminate the compound. If a substance is cleared from the circulation exclusively by the liver, the indirect Fick principle can be used to derive total hepatic blood flow. Several substances with a high hepatic extraction ratio (e.g., propranolol, lidocaine, indocyanine green, and colloidal particles) have been used to estimate hepatic blood flow.

In spite of the high expense and limited stability, constant infusion of indocyanine green is regarded as the most reliable method. [4]

Reticuloendothelial Particle Clearance

Radiolabeled colloidal particles such as those of gold 198 are very efficiently phagocytosed by the reticuloendothelial cells in the liver; the area under the initial curve is used as a measure of blood flow, assuming a normally functioning reticuloendothelial system. [5]

Indicator Dilution Techniques

Indicator dilution methods for assessing hepatic blood flow have an advantage over clearance methods in that hepatic function is not a dependent variable. Radiolabeled marker substances, especially iodinated serum albumin, are injected intrasplenically; the flow through the liver is then estimated from indicator dilution curves obtained either by continuous sampling from one hepatic vein or by external gamma-scintillation counting. [6] This technique is valid when the marker substance is not metabolized by the liver and when there is uniform mixing. [6] [7]

Miscellaneous Techniques

Square-wave electromagnetic flow probes provide the most reliable direct method for the measurement of hepatic artery and portal vein blood flow. [8] This method does require invasive techniques for implantation that can perturb the system. However, once implanted, these probes can be left *in situ,* and measurements can then be made in the unanesthetized patient by telemetry.

Regulation of Liver Blood Flow

Intrinsic Regulation

Intrinsic regulation occurs by mechanisms that regulate blood flow independently of the influence of nerves and blood-borne vasoactive compounds. Three major mechanisms are primarily responsible for intrinsic regulation of hepatic blood flow: autoregulation, metabolic control, and the hepatic arterial buffer response.

Autoregulation

Autoregulation is due to the tendency for local blood flow to remain constant in spite of changes in arterial pressure. It is hypothesized that increased arterial perfusion pressure results in hepatic artery vasoconstriction, presumably because of a myogenic response of the arteriolar smooth muscle to stretch imposed by the increased perfusion pressure. Pressure-flow autoregulation in the hepatic arterial system exists to some extent in the metabolically active (postprandial) liver, but probably not in the unstimulated (fasted) liver. [9] [10] However, because surgery is most often performed when the patient is in the fasted state, it is likely that pressure-flow autoregulation does not exist to any great degree during anesthesia and surgery. There is no evidence of autoregulation in the portal venous system; instead of the nonlinear pressure-flow relationship associated with autoregulation, there exists a linear pressure-flow relationship. [11] Arterial or portal venous autoregulation is probably not a principal mechanism for control of hepatic blood flow.

Metabolic Control

Changes in the composition of the portal venous and systemic blood composition affect liver blood flow. These changes include arterial hypoxemia, [12] systemic hypercarbia, [13] and alkalosis. [14] Hepatic arterial blood flow is increased by decreased portal oxygen tension and pH. Postprandial hyperosmolarity increases both hepatic arterial and portal venous blood flow. [15]

Hepatic Arterial Buffer Response

Hepatic arterial buffer response is the phenomenon by which decreases in portal blood flow are associated with increased hepatic arterial blood flow. [16] This reciprocal relationship between the hepatic artery and portal vein tends to

maintain the constancy of the hepatic oxygen supply (which is essential for hepatocyte function) and of the total hepatic blood flow (which is essential for clearance of exogenous and endogenous substances). [16] Thus, when portal venous flow decreases, hepatic arterial resistance decreases and hepatic arterial flow increases, and vice versa. It has been suggested that washout of locally produced adenosine can account for the hepatic arterial buffer response. Other factors--neural, myogenic, and metabolic, as well as the oxygen content or pH of portal venous blood--may also significantly influence the buffer response. [17] In spite of significant increases in hepatic arterial blood flow, this compensatory mechanism is unable to compensate completely for a decrease in portal venous flow.

Extrinsic Regulation

Neural Control

Branches of the vagus, splanchnic, and sometimes phrenic nerves enter the liver mainly in association with the blood vessels and bile ducts. The sympathetic and parasympathetic nerves form an intercommunicating plexus, which terminates on arterioles and venules. Stimulation of the outflow of the sympathetic nervous system (e.g., hypercarbia, pain, hypoxia) reduces liver blood flow and blood volume abruptly, and 80 percent, or approximately 500 mL, of the hepatic blood can be expelled within a matter of seconds. [2] [18] The liver in this way represents a major reservoir of whole blood, which can be rapidly distributed in a precise and controlled manner in response to the activity of its autonomic innervation. Functional vagal innervation does exist in the dog and influences regional distribution within the liver by exerting effects on presinusoidal sphincters, [19] rather than by affecting total liver blood flow.

Humoral Factors

Of the systemic hormones, epinephrine is the most likely to attain vasoactive concentrations physiologically. Both alpha- and beta-adrenergic receptors are present in the hepatic arterial bed, whereas only alpha receptors exist in the portal vasculature. [20] Thus, epinephrine injected directly into the hepatic artery initially induces vasoconstriction via the alpha receptors, followed by vasodilation mediated by the beta receptors; the portal bed only vasoconstricts in response to intraportal epinephrine. Any action of dopamine on the liver circulation is of little physiologic significance, because any vascular effect it possesses alone would be overwhelmed by the concomitant presence of epinephrine, norepinephrine, and sympathetic activation. [20] [21] Glucagon causes a graded and long-lasting hepatic arterial vasodilation and can antagonize the hepatic arterial vasoconstrictor responses to a wide range of physiologic stimuli, including stress-induced sympathoadrenal outflow. [22] Angiotensin II evokes profound vasoconstriction of both hepatic arterial and portal beds, together with a significant reduction in mesenteric outflow, and this translates into a substantial reduction in total liver blood flow. [23] Vasopressin also induces marked splanchnic vasoconstriction; consequently, reduction in venous outflow into the portal system and a reduction in inflow resistance in the portal vasculature occurring after vasopressin administration make this hormone very effective in alleviating portal hypertension. [24]

Effects of Anesthesia on Liver Blood Flow

Apart from the specific effects of individual anesthetics on liver blood flow, ancillary influences, including surgery [25] and the mode of ventilation, need to be considered. During upper abdominal surgery, total hepatic blood flow can be decreased by up to 60 percent by surgery alone; this is considerably more than any alteration produced by anesthetics. When ventilation is controlled, portal venous blood flow decreases because of an increase in splanchnic vascular resistance with hypocarbia. [26] The application of positive endexpiratory pressure decreases hepatic blood flow even further by increasing hepatic venous pressure. [27]

All anesthetics and techniques that decrease cardiac output produce at least proportional decrements in total hepatic blood flow. In addition, some anesthetics have

more specific effects on hepatic blood flow that either mitigate or accentuate these changes. Halothane anesthesia usually decreases hepatic blood flow to a greater extent than other commonly used volatile anesthetics. [28] Isoflurane increases hepatic artery blood flow at both 1 and 2 minimum alveolar concentration (MAC), in contrast to halothane. [29] In 1988, Payen et al [30] reported the demonstration of isofluraneinduced increases in total hepatic blood flow in humans by a pulsed Doppler method.

Regional anesthesia may decrease hepatic blood flow. The extent to which subarachnoid block decreases hepatic blood flow depends on the level of the block; a T4 level of anesthesia results in a 20 percent reduction in liver blood flow, which closely parallels the decrease in systemic blood pressure. [31] The effects of induced hypotension on liver blood flow have also been examined. When the mean arterial blood pressure is decreased by 40 percent with a sodium nitroprusside infusion, there is no net change in liver blood flow, although there is an inversion in the contributions from the portal and hepatic vascular beds. [32] However, when more profound hypotension is induced, ischemic injury may ensue. [33] Although all forms of anesthesia decrease liver blood flow, oxygen requirements by the liver also decrease, so that anoxic metabolism does not routinely occur. [34] [35]

METABOLIC FUNCTION OF THE LIVER

Protein

The liver is the major site of amino acid metabolism, encompassing both the breakdown of amino acids to form substrates for the carbohydrate and fat metabolic pathways and the synthesis of a large number of biologically essential proteins.

Albumin, the major protein in human serum, accounts for 15 percent of the total hepatic protein synthesis. Albumin synthesis ranges from 120 to 300 mg/kg/dL. The higher figure is noted in the neonatal liver, and there is a progressive decline in synthesis rate with age. [36] Factors that regulate albumin

synthesis include dietary availability of amino acids, [37] hormonal balance, and plasma oncotic pressure. [38] Intravascular albumin accounts for about 40 percent of the exchangeable albumin pool, and in this location it exerts its principal function, maintenance of normal oncotic pressure. Various substances bind to albumin in the serum, a feature that makes albumin an important transport vehicle for drugs, hormones, metals, and metabolites. The half-life of albumin is approximately 20 days, so that a decrease in serum albumin is unlikely to occur within a short time of acute liver injury. In patients with ascites and chronic liver disease, the total exchangeable pool of albumin may be normal, but the serum level is often low. [39]

The vitamin K-dependent coagulation factors II, VII, IX, and X are synthesized in the liver, together with factors V, XI, XII, and XIII and fibrinogen, which are not dependent on vitamin K for synthesis. If the fat-soluble vitamin K is deficient, as in obstructive jaundice, or if it is antagonized by one of the coumarin anticoagulants, the coagulation factors are synthesized at the normal rate, but they lack the gamma-carboxylglutamic acid residues, which are attached in a post-translational event under the influence of vitamin K. The half-lives of the coagulation factors are relatively short; thus, abnormalities in coagulation quickly become apparent in acute liver damage. The actual level of clotting factors in the plasma represents a balance between synthesis and catabolism, and because the liver also synthesizes inhibitors of both coagulation and fibrinolysis, a combination of decreased synthesis and increased removal may arise in acute liver disease. Thus, prolongation of prothrombin time resulting from a deficiency of factors II, V, VII, and X is observed in parenchymal liver disease. When used as a liver function test, the prothrombin time has proved of some value in predicting the outcome of patients suffering from acute liver cell failure after hepatotoxin ingestion, [40] as well as that of patients with liver disease who are undergoing surgery. [41]

Ceruloplasmin, the copper-containing alpha-globulin, is synthesized in the liver. The plasma level is increased in biliary cirrhosis, Hodgkin's disease, pregnancy, and myocardial infarction, and as such it is considered an acute-phase reactant protein. [42]

Breakdown of amino acids by transamination and oxidative deamination leads to the formation of keto acids, ammonia, and glutamine within the liver. The Krebs-Henseleit urea cycle converts the ammonia and most of the other nitrogenous excretory products into urea. Both severe acute and chronic liver disease are characterized by a failure to synthesize urea, as a result of which its blood concentration is significantly reduced. There is also an excessive accumulation of ammonia, which in some way contributes to the encephalopathy often noted in hepatic failure. [43]

Carbohydrates

The liver is especially important for maintaining a normal blood glucose level in the circulation, especially after a carbohydrate meal, and also for releasing glucose into the blood stream during a diurnal fast or sustained exercise. [44] The rate of uptake or release of glucose by the liver is proportional to the degree of hypoglycemia or hyperglycemia, and thus the blood glucose concentration determines whether the liver is a glucose-producing or glucose-using organ.

The liver responds to conditioning of carbohydrate deprivation by increasing the rate of glucose production from endogenous sources. Liver glycogen is degraded to provide glucose, which is then released into the blood. Glycogen metabolism within the liver is regulated by two rate-limiting enzymes: (1) glycogen synthase, which synthesizes chains of glucose residues from uridine diphosphate (UDP)-glucose units, and (2) glycogen phosphorylase, which degrades glycogen, one glucose residue at a time, to glucose 1- phosphate. [45] Catecholamines probably stimulate the rate of gluconeogenesis via cyclic adenosine monophosphate (cAMP)-dependent (beta-mimetic) and cAMP-independent (alpha-mimetic) mechanisms. [46] Insulin antagonizes the action of both glucagon and catecholamines on hepatic gluconeogenesis. After glycogen stores in the liver have been exhausted by starvation (~24 h) or prolonged exercise, the only remaining endogenous source of glucose is by gluconeogenesis from lactate, glycerol, and certain amino acid (especially alanine and glutamine) precursors. The actions of glucagon and catecholamines on the gluconeogenic pathway are mediated by an increase in the cAMP concentration and therefore an increase in the activity of cAMP-dependent protein kinase. [47]

Fat

Lipid reaches the liver via the lymph and the blood in the form of chylomicrons, where it is broken down by stepwise degradation to acetylcoenzyme A (acetyl-CoA). This is a key molecule in a number of metabolic processes involving fat in the tricarboxylic acid cycle or the synthesis of triglyceride phospholipid, cholesterol, and lipoproteins. Glucose in excess of that needed to saturate hepatic glycogen stores, as well as other pathways, is converted very efficiently to fatty acids in the liver. The two pathways available for the metabolic disposal of fatty acids in the liver are esterification and oxidation. [48] Glucagon markedly stimulates the rate of fatty acid oxidation in liver, whereas insulin inhibits it. The beta oxidation of fatty acids proceeds to acetyl-CoA in the mitochondria, where the acetyl-CoA is further oxidized in the tricarboxylic acid cycle to carbon dioxide and water or is converted to ketone bodies. However, the liver lacks the enzyme required for oxidation of ketones, which is present in abundance in most other tissues. The amount of ketosis in the fasted state is self-limited, because ketones stimulate insulin secretion from the pancreas, [49] thereby limiting lipolysis in adipose tissue and thus the availability and oxidation of fatty acids in the liver. This fail-safe mechanism is obviously lacking in states of insulin deficiency and can result in diabetic ketoacidosis.

Fatty acids are esterified with glycerol in the liver to form triglycerides, which are then incorporated into lipoproteins, principally very-low-density lipoprotein (VLDL), that are secreted by the liver. The principal factor affecting VLDL production is the amount of free fatty acids reaching the liver. Secretion of VLDL is also stimulated by insulin [50] and estrogens. [51]

Bilirubin

About 300 mg bilirubin is formed daily, mostly from the destruction of senescent erythrocytes. The heme part of the myoglobin molecule is converted to bilirubin and is carried to the liver tightly bound to albumin. Within the liver cell, bilirubin is conjugated with glucuronic acid. Unlike unconjugated bilirubin, the conjugated form is nontoxic, and the pigment is now readily secreted by the liver into the bile and then into the alimentary tract. A small portion of the conjugated bilirubin formed by the hepatic cells returns to the plasma, either directly into the liver sinusoids or indirectly by absorption into the blood from the bile ducts or lymphatics. Appreciable amounts of conjugated bilirubins in plasma reflect defective hepatic secretion, which, in the presence of minor liver damage, may occur without increasing the plasma level of total bilirubins to more than 1 mg/dL. [52]

Effects of Anesthesia on Hepatic Metabolism

In response to fasting and surgical trauma, there is an increase in the circulating concentrations of catabolic hormones such as catecholamines, glucagon, and cortisol and a concomitant decrease in plasma concentrations of the anabolic hormones insulin and testosterone. These endocrine changes result in substrate mobilization and ultimately produce a catabolic state with negative nitrogen balance. Surgical trauma increases protein degradation and urea production and excretion and decreases protein synthesis. [53] The severity of these changes largely depends on the extent of the surgery and on the patient's initial status. [54] Hyperglycemia is ubiquitously associated with surgery, but whether this is due to increased hepatic glycogenolysis is in dispute. Hepatic fat metabolism is only slightly affected by surgery. Inasmuch as anesthetics can influence the release of these stress hormones (e.g., catecholamines, cortisol), hepatic metabolism will also be altered. If the afferent neurogenic impulses from the area of surgical trauma are blocked, these endocrine-metabolic responses can be attenuated, a change that results in improved nitrogen balance. This block can be most effectively accomplished with epidural analgesia, [55] with lesser effects noted with halothane, [56] enflurane, [57] morphine, [58] and either thiopental [59] or fentanyl [60] used to supplement nitrous oxide.

Few studies, most of which have used halothane, have examined the direct effects of anesthetics on intermediary metabolism. Halothane inhibits oxygen consumption of urea synthesis and gluconeogenesis in the isolated perfused liver. [61] Because the major pathways for clearing lactate from the plasma are also inhibited by halothane, there is an increase in lactate concentration above that normally observed after the addition of fructose to the medium of the isolated perfused liver. [62] The 1982 study of Rannels et al [63] revealed that exposure to halothane inhibits the peptide chain initiation step in protein synthesis within 15 minutes, whereas the process of protein secretion is unaffected. In isolated rat hepatocytes, clinically relevant concentrations of either halothane or enflurane (0.5-1.0 mmol/L), inhibited protein synthesis in a dose-dependent manner. [64]

BILE FORMATION

Bile eliminates many endogenous and exogenous substances from the liver while at the same time fulfilling an important function as a digestive fluid. [65] The bile is primarily formed by the hepatocyte (canalicular bile) and is then modified downstream in the ductules, ducts, and gallbladder mucosa by reabsorption and secretion of electrolytes and water. By this process, constituents such as bile salts, cholesterol, and phospholipids become highly concentrated in the gallbladder bile. Narcotics cause spasm in the sphincter of Oddi and an increase in pressure in the common bile duct. [66] This effect can be largely attenuated by halothane and, to a lesser extent, by enflurane, [67] as well as by nitroglycerin, naloxone, atropine, and glucagon. [68]

HEMATOLOGIC FUNCTION

Erythropoietic activity is largely confined to the liver from the 9th to the 24th week of gestation and continues to be an important site for hematopoiesis until approximately 2 months after birth. However, with the development of the bone marrow, recognizable hematopoietic cells completely disappear from the liver and only persist in the setting of congenital hemolytic anemias. Those cells may reappear in response to bone marrow failure or in the presence of myeloproliferative disorders. Heme is synthesized predominantly in the bone marrow and the liver by way of porphyrin metabolites. Patients with acute hepatic porphyrias have a defect in hepatic heme synthesis and may have their illness exacerbated by many anesthetics, including barbiturates, benzodiazepines, ketamine, pentazocine, and halothane. [69]

HUMORAL FUNCTION

The liver plays a vital role in the biotransformation of many hormones; for example, 50 percent of insulin secreted by the pancreas is degraded by the liver in a single passage and does not reach the systemic circulation. [70] Thyroxine (T_4), the major secretory product of the thyroid gland, is actively taken up by the liver, where it is converted to triiodothyronine (T_3) and can also be inactivated. In addition, the liver synthesizes the plasma proteins that bind the thyroid hormones. Thus, the liver can influence the distribution of the thyroid hormones between the intracellular and extracellular compartments. Aldosterone, estrogens, androgens, and antidiuretic hormone are all inactivated by the liver; thus, liver disease results in profound endocrine abnormalities.

IMMUNOLOGIC FUNCTION

The liver is the largest organ in the reticuloendothelial system; as much as 10 percent of its weight is derived from the Kupffer cell mass. Teleologically, the importance of this system relates to its ability to phagocytose antigens absorbed from the gastrointestinal tract, thus acting as a filter for the systemic circulation.

DRUG BIOTRANSFORMATION

Most xenobiotics contain lipophilic functional groups to facilitate penetration of membrane barriers, thereby expediting intestinal absorption. Excretion of these compounds would occur slowly, owing to a high degree of protein binding and renal tubular reabsorption. Thus, a function of drug biotransformation is to render molecules more polar so that the products can be efficiently eliminated. Drug metabolism is primarily a hepatic event, although it also occurs in the kidney and, to a lesser extent, in the intestine, lung, and skin. By converting lipophilic substances to excretable metabolites, hepatic enzymes detoxify drugs by terminating their pharmacologic activity. Unfortunately, reactive intermediates, which themselves are responsible for some toxic effects, may be formed during metabolism.

Enzymatic Reactions

The enzymatic reactions involved in hepatic drug metabolism may be divided into functionalization reactions (phase 1) and conjugation or synthetic reactions (phase 2). Phase 1 reactions often generate reactive species because they introduce carboxyl, epoxide, or hydroxyl groups into the parent compound. In phase 2 reactions, catalyzed by transferase enzymes, the chemical groups generated by phase 1 reactions serve as receptors for polar substances such as acetate, amino acid, sulfate, glucuronic acid, and glutathione. [71] The products of phase 2 reactions are usually less toxic and less biologically active than those of the parent compound. Furthermore, the water solubility of the phase 2 product is enhanced beyond that achieved by phase 1 reactions alone.

Phase 1 Reactions

Oxidation is the most common form of drug biotransformation, accounting for more than 90 percent of all reactions. It is catalyzed by the cytochrome P-450 system and, to a lesser extent, by the mixed-function oxidases. Many of the reductive pathways in the liver are catalyzed by cytochrome P-450. [72]

Phase 2 Reactions

Frequently, the final step in the metabolism of a foreign compound involves conjugation with a water-soluble metabolite. The most common conjugate encountered is the glucuronic acid adduct catalyzed by UDP-glucuronyl transferase, which is localized to the endoplasmic reticulum. Glutathione, a cysteine-containing tripeptide, is conjugated to xenobiotics by its free thiol group. Under adverse conditions (e.g., starvation), the available glutathione substrate may be rapidly depleted, so that potentially toxic compounds accumulate. Administration of cysteamine (mercaptoethylamine) or *N*-acetylcysteine (glutathione precursors) enhances the rate of synthesis of glutathione and is effective in combating the toxicity of certain electrophilic compounds.

Factors Affecting Hepatic Drug Metabolism

Perfusion models of hepatic drug elimination address the important determinants of hepatic drug disposition, such as hepatic blood flow, intrinsic hepatic clearance, and protein binding [73] [74] ; however, these models weight the importance of a specific variable, depending on whether the drug is efficiently or poorly extracted by the liver. Thus, elimination of a drug that has a high extraction ratio is influenced more directly by changes in hepatic blood flow than by changes in intrinsic hepatic clearance or protein binding. Whereas elimination may not be affected by changes in protein binding, changes in protein binding of highly extracted drugs may alter their pharmacologic effect. The disposition of poorly extracted drugs is more sensitive to changes in the intrinsic ability of the liver to eliminate a drug and in binding of the drug to blood constituents than it is to hepatic blood flow. Table 17-1 (Table Not Available) presents a compilation of frequently employed drugs with high and low extraction ratios. [75]

More than 300 compounds, including drugs, insecticides, organic solvents, carcinogens, and other environmental contaminants, are known to stimulate some type of microsomal xenobiotic-metabolizing activity. [76] These enzyme-inducing compounds result in an increase in the cellular amount of RNA coding for the appropriate enzyme in the cell. Clinical effects of enzyme induction only become apparent when the rate-controlling step in detoxification or elimination is affected. However, induction may have major effects in enhancing the metabolism of xenobiotics to toxic intermediates. For example, isoniazid enhances defluorination of enflurane, thereby increasing the risk of fluoride nephrotoxicity. The rate and manner in which an individual substance affects drug metabolism are determined in part by genetic factors, [77] but these factors are rarely apparent unless they result in toxicity.

Delayed development of xenobiotic metabolism in fetal liver, which extends into the newborn period, has a protective role. Polar compounds that would otherwise be formed by xenobiotic metabolic reactions in the liver would accumulate

TABLE 17-1 -- Drugs that Are Efficiently and Poorly Extracted from the Blood by the Liver

(Not Available)

Modified from Williams and Benet [75]

in the fetus because of lack of transfer across the fetoplacental barrier. The cytochrome P-450 content in the liver of newborns is only 28 percent of what is normally present. Phase 2 reaction rates are exceedingly slow, as reflected by the development of neonatal hyperbilirubinemia because of delayed development of bilirubin-UDP-glucuronyltransferase. At the other end of the life cycle, there appear to be decreased metabolic rates for meperidine [78] and amylobarbital. [79] More often, increased plasma half-lives of drugs in geriatric patients are due to changes in drug distribution rather than in metabolism. [80]

Certain factors in the perioperative period are known to decrease hepatic drug-metabolizing activity, including inflammation, [81] fever, [82] and the infusion of nitrogen-free [83] and nitrogen-rich [84] solutions.

Effects of Anesthesia on Drug Metabolism

Ketamine is capable of inducing its own metabolism, a feature that may account for the rapid development of tolerance to this agent. [85] Diazepam has been reported to both increase and decrease its own metabolism. [86]

Anesthetics capable of decreasing hepatic blood flow influence the clearance of perfusion-dependent drugs with high extraction ratios. More important, the volatile anesthetics, especially halothane, inhibit drug biotransformation by direct effects on the cytochrome P-450 and glucuronyltransferase systems. Halothane impairs the metabolism of phenytoin, [87] warfarin, [88] and ketamine. [89] Halothane also decreases the metabolism of enflurane in rats, possibly by competing for the same

drug-metabolizing sites on microsomal enzymes. [90] Fentanyl clearance is also decreased by concomitant halothane administration, possibly by the effect of halothane on hepatic blood flow. [91] Similar findings have been noted with verapamil [92] and propranolol clearance during halothane anesthesia. [93] In isolated rat hepatocytes, both halothane and enflurane were found to inhibit the metabolism of acetaminophen, antipyrine, and sulfanilamide in a dose-dependent manner over a clinically relevant range. [64] However, in a study involving long-term exposure of human patients to trace anesthetic concentrations of halothane, Duvaldestin et al [94] demonstrated a 29 percent increase in antipyrine metabolism, which is highly suggestive of enzyme induction. Subsequent observations suggest that the cytochrome c reductase activity is most likely to be altered by chronic low-level exposure. [95]

EVALUATION OF LIVER FUNCTION

Clinical Evaluation

The clinical evaluation of the liver and biliary tract should include a complete history and physical examination with appropriate laboratory tests to identify subclinical abnormalities and to define the disease process at a higher level of resolution. Particular attention in the history should be devoted to information regarding drug and alcohol intake; exposure to chemicals and/or toxic agents; receipt of injections and transfusions; family history of liver or biliary tract disease; itch, jaundice, abnormal pain, and indigestion; and alteration in stool or urine color. Physical examination should concentrate on establishing the size and texture of the liver and spleen and on detecting jaundice, ascites, collateral portal circulation, spider angiomas, hepatic encephalopathy, and fetor hepaticus.

Laboratory Tests

Hepatic function is extremely complex; therefore, there are a number of different biochemical tests that can be used to evaluate hepatic function. Generally speaking, some tests characterize hepatic function, some characterize liver damage, and some deal with specific markers of hepatic disease (Table 17-2) (Table Not Available) .

Aminotransferases

Elevated plasma levels of intracellular enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), are suggestive of hepatocellular damage. The highest ALT levels are in the liver, whereas AST levels are similar in liver, heart, and skeletal muscles. [96] [97] However, some organs other than liver, for example, heart, skeletal muscle, adipose tissue, brain, and kidney, contain aminotransferases, and this lack of tissue specificity limits the clinical usefulness of these enzymes as indicators of hepatic injury.

TABLE 17-2 -- Blood Tests and the Differential Diagnosis of Hepatic Dysfunction

(Not Available)

From Gelman [68]

Acute liver necrosis is accompanied by markedly elevated AST and ALT with the degree of the elevation reflecting the acuteness and severity of the injury but not necessarily hepatic function or prognosis. Marked elevations of AST and ALT are better indicators of acute injury than in chronic conditions, in which aminotransferase activity may be normal. Liver-specific enzymes, such as ornithine carbamoyl transferase and alcohol dehydrogenase, [96] [97] [98] have been used experimentally but are not yet widely available for clinical application. Although serum AST and ALT levels are valuable in the diagnosis of liver disease, they are best used in conjunction with other enzyme assays (e.g., LDH, CK) and measures of hepatic and renal function (e.g., blood urea, creatinine, ammonia, and bilirubin).

Alkaline Phosphatase

Alkaline phosphatase (AP) is actually a group of as many as 11 isoenzymes that are typically membrane-associated and have been identified in most body tissues. [96] [97] The activity of AP is greatest in the liver, bone, intestine, kidney, and placenta. Measurement of AP is useful in diagnosis of hepatobiliary disease, including acute hepatitis, cholestatic disease, and hepatomas. The activity of AP is markedly elevated by extrahepatobiliary obstruction (e.g., cholelithiasis or gallstones) and, to a lesser extent, by intrahepatic biliary obstruction. Liver disease that results in parenchymal cell necrosis does not typically elevate AP unless there is associated damage to the canaliculi or biliary stasis. Interpretation of serum AP can be complicated by nonhepatic elevations in AP associated with bone disease (e.g., Paget's disease, ricketts, and osteomalacia), rapid bone growth during puberty, and release from the placenta during the third trimester of pregnancy (see Table 17-2) (Table Not Available) .

Serum Albumin and Coagulation Factors

Serum albumin is a fairly good indicator of hepatocyte function, but abnormal distribution, changes in plasma volume, and alterations in albumin degradation may also contribute to hypoalbuminemia in liver disease. Serum albumin concentration is a more useful index of the severity of cellular dysfunction in chronic liver disease, because the plasma half-life is approximately 20 days, and changes in synthesis are detectable only after an appreciable time lag. The half-lives of the liver-derived coagulation factors, unlike that of albumin, are very short, ranging from 4 days for fibrinogen to a few hours for factor VII. Therefore, a decrease in hepatic synthesis of coagulation factors is quickly reflected in decreased plasma concentrations. The best estimate of hepatic function is provided by estimation of prothrombin time. Abnormalities of the prothrombin time indicate impaired hepatic synthesis of some or all of the clotting factors I, II, V, VII, and X. Failure to correct this abnormality readily by administration of vitamin K indicates that severe hepatocellular disease is present and that the impaired absorption of the fat-soluble vitamin from the gastrointestinal tract may be only partially responsible for the clotting abnormality. In acute liver failure, prothrombin time correlates with the degree of encephalopathy. Dye removal tests with Bromsulphalein, indocyanine green, or rose bengal have also been used to test hepatic function. Systemic retention of dye will occur if blood flow, uptake, intracellular binding, metabolic transformation, or biliary excretion is disordered. For quantitative assessment of specific functions of the hepatocyte, more complicated techniques can be employed, including galactose elimination and bile acid disappearance tests.

Serum Bilirubin

The functional status of the excretory apparatus of the liver is best assessed by measuring the bilirubin in the serum, which in the majority of the normal population does not exceed 1 mg/dL. However, as many as 10 percent of otherwise healthy persons have mildly elevated values for serum total bilirubin that are entirely accounted for by an increase in unconjugated bilirubin. These persons may have Gilbert syndrome (benign unconjugated hyperbilirubinemia) and probably represent the lowermost pole of the normal distribution of hepatic bilirubin UDP-glucuronyltransferase in the population. When the serum bilirubin level is higher than 4 mg/dL, this abnormality may be detected clinically as a yellow discoloration of body tissues, which is best appreciated in the sclerae by use of natural light. Conjugated bilirubin in serum indicates dysfunction of either the liver parenchyma or the bile ducts. Even in unconjugated hyperbilirubinemia from acute hemolysis, there may be an increase in the conjugated fraction. An increase in urine bilirubin indicates the presence of conjugated bilirubin in the serum, because unconjugated bilirubin is not excreted by the kidney.

Transport Function

Disturbances in the transport function of the hepatocyte, particularly with regard to the excretion of conjugated bile acids or mechanical obstruction of the biliary tree,

cause increased amounts of AP to enter plasma. Because the placenta, bone, and intestines also contribute to AP activity in the plasma, it is important to identify the tissue of origin when increased concentrations occur. Procedures available to differentiate the sources of the increased enzyme include simultaneous determination of 5
-nucleotidase or leucine aminopeptidase and/or gamma-glutamyl transpeptidase. Even though 5
-nucleotides can also be found in other tissues such as the placenta, bone, and the aorta, the activity of these substances in the serum does not rise during normal pregnancy, during the period of normal bone growth, or in diseases of the bone. In known hepatobiliary diseases, elevations in AP and 5
-nucleotidase tend to parallel each other, and for these reasons estimates of 5
-nucleotidase concentrations in serum are most useful in distinguishing between hepatic and nonhepatic causes of increased AP activity.

Radiologic Techniques

Radiologic techniques for demonstrating the biliary tract include percutaneous and endoscopic cholangiography. Percutaneous

transhepatic cholangiography is especially of value when dilated bile ducts are present. Endoscopic cholangiography is useful in localizing the site of biliary tract disease before surgery. Furthermore, papillotomy via the endoscope can obviate the need for surgical treatment of common bile duct stones. Esophagogastroscopy is a reliable and simple method for detecting submucosal varices in the upper digestive tract. Hepatic venous pressure measurements are useful in defining the level of block in patients with portal hypertension, whereas splenoportography delineates the splenic and portal veins. Radionuclide and ultrasonic scanning are useful for detecting space-occupying lesions of the hepatobiliary system. For evaluation of the immunologic status of the patient with suspected liver disease, the presence of high serum gamma-globulin levels is a strong indicator of significant chronic liver disease.

Antinuclear Antibody

Antinuclear antibody is present in 75 percent of patients with chronic active hepatitis, and the antimitochondrial antibody is present in nearly all patients with primary biliary cirrhosis. Alpha-fetoprotein is a marker of primary liver cell cancer. Infection with the virus of type A or B hepatitis is associated with the appearance of specific antigens and antibodies in serum.

PATHOPHYSIOLOGY OF LIVER DISEASE

Mechanisms of Hepatocellular Injury

Death of hepatic parenchymal cells, or hepatocytes, is common to virtually all hepatic diseases, but the mechanisms responsible for the cell death are poorly understood. Hepatocellular degeneration and mechanisms of cell death and target structures are discussed in detail in the literature. [99] [100] [101]

Cholestatic Injury

Cholestasis is an (intrahepatic) impairment in the secretion of bile or an (extrahepatic) impairment of the flow of bile from the liver to the intestine. Characteristically, substances that are normally secreted into bile, such as bile acids, cholesterol, and bilirubin, are increased in the serum. [67] Enzymes and proteins normally found in bile--AP, gamma-glutamyltranspeptidase, 5
-nucleotidase, leucine aminopeptidase, and immunoglobulin A--are also generally increased in the serum. [102] Bilirubin is probably the most toxic of the bile constituents and interferes with many enzyme systems, including those of respiration and oxidative phosphorylation, with glycogenesis, and with the tricarboxylic acid cycle. Bilirubin also interferes with heme biosynthesis and lipid, amino acid, and protein metabolism. At high concentrations, bilirubin may also interfere with membrane function. [67]

Hypoxia/Ischemia

Hypoxic injury is a consequence of circulatory disorders in which the oxygen supply to the tissue is compromised. Hypoxia is one of the most frequent causes of cellular apoptosis and necrosis in human disease. The effects of hypoxia on the liver have been studied in experimental animals, in which the duration and severity of the oxygen deprivation can be controlled. In these studies, hypoxia has been associated with decreased adenosine triphosphate, which stimulates glycolysis, depletes glycogen stores, and leads to accumulation of lactate and a consequent decrease in intracellular pH. The loss of high-energy phosphates also leads to decreased protein synthesis and interference with the ion pumps responsible for maintaining potassium and sodium homeostasis. The end result is cellular swelling and a loss in plasma membrane integrity, which facilitates release of intracellular hepatic enzymes into plasma.

Although most normal cellular aerobic metabolism results in tetravalent reduction to water, a small percentage of oxygen is univalently or divalently reduced to oxygen and hydrogen peroxide. [103] Endogenous antioxidant enzymatic defenses and expendable soluble or lipophilic scavengers typically maintain intracellular concentrations of oxidants in the nanomolar range. [104] However, hepatic ischemia results in a pathologic condition in which tissue antioxidant defense capabilities can become overwhelmed and essential biochemical processes are impaired. There has been a surge of interest in the effects of ischemia or hypoxemia that has focused on minimizing the hepatic damage associated with preservation and transplantation. The preservation and reperfusion damage are blamed for the primary nonfunction of transplants and the relatively high rate of complications and rejections. [105] There is accumulating evidence that reactive oxygen and nitrogen species play a significant role in postreperfusion injury in transplanted organs. Indirect evidence for oxidants in preservation injury has been provided by the observation that lipid peroxides are elevated in plasma of human patients following liver transplantation and that alpha-tocopherol levels were inversely related to oxidant production. [106] The appearance of an oxidation product of uric acid (allantoin) provides additional indirect evidence for involvement of oxidants following human liver transplantation. [107] [108] Humans lack the enzyme responsible for conversion of uric acid to allantoin. Therefore, detection of allantoin in plasma suggests that its formation was due to reactive oxidants and provides strong evidence for the production of reactive oxygen species during transplantation of the human liver. Electron paramagnetic resonance spin trapping has been utilized to demonstrate that storage of livers in hypothermic preservation solution results in formation of both carbon- and oxygen-centered radical adducts, [109] providing direct evidence for oxidants in perfusion and transplantation. Radical adducts increased three to four times following liver transplantation, a finding indicative of enhanced rates of oxidant formation. Electron paramagnetic resonance evidence of free radical formation has also been observed in Kupffer cells following preservation and transplantation. [110] Reactive nitrogen species also appear to play a role in graft dysfunction following preservation and transplantation because the plasma concentration of nitrogen oxides

increases with allograft rejection [111] and correlates with allograft cellular response in recipients. It has been suggested that excess production of oxidants coupled with depletion of endogenous tissue antioxidants renders the preserved liver susceptible to the reactive oxygen metabolites formed on reperfusion of the preserved liver. [112] [113]

Although reactive oxygen metabolites can arise from a number of sources, the enzyme xanthine oxidase (XO) has frequently been implicated as a significant intracellular source of toxic oxygen radicals. Much of the evidence for involvement of XO in ischemia-reperfusion is based on the protective effects of allopurinol, an XO inhibitor. [112] [114] The significant improvement of the quality of livers preserved in University of Wisconsin solution has been attributed to the inclusion of antioxidants and allopurinol. [114] [115] [116] Although there is considerable evidence that XO is a significant intracellular source of oxidant stress, there is accumulating evidence that it can also exert oxidant stress to remote tissues (e.g., lung and heart) via extracellular routes following release of XO into the circulation. Human liver and intestine contain the greatest specific activity of XDH+XO. [98] Immunolocalization studies have demonstrated that XO is predominantly in hepatocytes, endothelial cells, and Kupffer cells (Parks, unpublished data).

Hepatocellular damage resulting from hepatic ischemia, acute hepatitis, or cholecystitis has been associated with increased concentrations of circulating XO, along with other hepatocellular enzymes. [117] [118] We have provided evidence that human liver releases significant amounts of XO into the systemic circulation on reperfusion. [119] In animal models, we have demonstrated that, following liver transplantation, XO staining was intense in pericentral hepatocytes, intermediate in midzonal regions, and lowest adjacent to portal vein and to a lesser extent in Kupffer cells. The regions of highest XO/AO staining correspond to those regions in which ischemia and hypoxia would be most severe, because oxygen is extracted as blood flows from the portal triads (zone 1) to central vein branches (zone 3). Circulating XO can bind and concentrate on vascular endothelial cell surfaces, [98] [120] [121] [122] and it may involve tissues with low endogenous XO (e.g., heart and lung). The binding of circulating XO to endothelium and the subsequent generation of vascular cell-derived oxygen may react with nitric oxide (NO) to produce peroxy-nitrite ($ONOO^-$) and may result in extrahepatic tissue damage.

Free Radicals and Lipid Peroxidation

Free radicals can also be formed by the oxidation of organic molecules. It is well established that carbon tetrachloride forms the highly reactive trichloromethyl radical. The toxicity of nitrofurantoin, paraquat, and other aromatic compounds may also involve production of free radicals. One of the proposed mechanisms for halothane toxicity involves formation of reactive oxygen species. It is also possible that certain compounds could deplete essential antioxidants and thereby render the hepatocyte susceptible to oxidant stress. Such is the case in the depletion of reduced glutathione by acetaminophen and bromobenzene. [123] [124]

Bacterial, Viral, and Immunologic Injury

Bacterial products such as endotoxin can produce degeneration and subsequent death of hepatocytes. Endotoxins are lipopolysaccharides consisting of a hydrophilic carbohydrate portion, a bacterial strain-specific oxygen chain, a less variable core, and a common lipid A. [99] The lipid portion is responsible for the biologic reactions common to endotoxins and for the binding to high-density lipoproteins in blood and cells. In the liver, binding of endotoxin is greater for Kupffer cells than for the hepatocyte. Although the binding of endotoxin to the hepatocyte may produce some direct toxicity, the stimulation of Kupffer cells to produce eicosanoids and other cytotoxic mediators may lead to cholestasis and to hepatocellular injury. Viruses can also elicit hepatocellular injury, which can be direct or, more likely, indirect through the production of cytokines, resulting in lymphocyte- or macrophage-dependent cytotoxicity. The best examples are the hepatitis viruses and certain herpesviruses. Liver membrane antigens may be the target of cell-mediated injury because antibodies to these antigens are typically found in autoimmune hepatitis and primary biliary cirrhosis. [125] Other potential membrane antigens for cell-mediated cytotoxicity include liver-specific lipoproteins and hepatic lectin, antigens to which hepatitis B and other liver diseases may be directed. [99]

Alcohol

Hepatic dysfunction is the primary manifestation of long-term chronic ethanol consumption, but there are also strong links between alcohol consumption and cardiovascular effects, such as cardiomyopathies, arrhythmias, coronary heart disease, stroke, hypertension, and respiratory distress syndrome. [126] [127] Damage to liver and other tissues associated with chronic ethanol consumption has been attributed to (1) acetaldehyde-associated toxicities, (2) altered metabolism and relative hypoxia at a microvascular level, (3) formation of reactive oxygen and nitrogen species, (4) depletion in antioxidant defenses, and (5) formation of protein adducts with consequent alterations in function and structure.

The major pathway for ethanol metabolism involves alcohol dehydrogenase (ADH), a zinc metalloenzyme, with at least five molecular isoforms. [110] [128] Various tissues contain ADH isozymes; however, extrahepatic metabolism accounts for less than 5 percent of total ethanol metabolism. [128] Once in the liver, ethanol is metabolized by the (1) cytoplasmic ADH pathway, (2) microsomal ethanol oxidizing system in the endoplasmic reticulum, and (3) catalase located in the peroxisomes, [128] to result in formation of acetaldehyde. Acetaldehyde is then oxidized to acetate in hepatic mitochondria, but long-term ethanol consumption diminishes the ability of mitochondria to remove acetaldehyde, thus allowing tissue and plasma levels to increase. [130] Acetaldehyde may form adducts with proteins that impair normal function. [130] Acetaldehyde may also induce chemotactic substances (e.g., leukotriene B_4), which attract cytotoxic neutrophils to the hepatic parenchyma. [131] In addition, acetaldehyde can alter the hepatocellular plasma membrane, [132]

---

increase formation of superoxide, a cytotoxic reactive oxygen species, [133] and directly bind to the antioxidant glutathione, thereby reducing hepatic antioxidant levels. [134]

Ethanol administration has a profound "hypermetabolic" effect on liver that results in a marked increase in hepatic oxygen consumption. The resulting hypoxia, especially around the perivenular region (zone 3) where alcohol dehydrogenase activity is concentrated, could ultimately contribute to liver damage. [110] [128] This "ischemic" component could explain many of the similarities between ethanol-induced and ischemia-induced liver injury. In fact, it is suggested that the increase in nitric oxide (·NO) production associated with ethanol administration may be a compensatory mechanism to counteract ethanol-induced vasoconstriction of the hepatic microcirculation, [135] [136] and it may involve induction of nitric oxide synthase. It is postulated that the hepatic hypoxia is responsible for the release of proinflammatory cytokines, tumor necrosis factor, and interleukins 1 and 6, which are elevated in alcoholic liver disease. [106] [109] The proinflammatory mediators may increase expression of adhesion molecules, decrease leukocyte velocity, increase margination and platelet adherence, and reduce hepatic blood flow. [137] Complement may also be activated, further amplifying the inflammatory process. [138] This inflammatory cascade could be responsible for the pulmonary and cardiac injury associated with hepatoenteric ischemia-reperfusion, [103] [104] [106] and ultimately could result in chronic manifestations.

Chronic ethanol consumption results in a pathologic condition in which oxidant production is increased while essential tissue antioxidant defenses are diminished; consequently, essential biochemical processes become impaired. [139] Chronic ethanol administration may (1) increase $O_2^{\cdot -}$ production by the microsomal ethanol oxidizing system, (2) increase $O_2^{\cdot -}$ production by cytosolic oxidases (aldehyde oxidase, xanthine oxidase), and (3) activate inflammatory cells, such as Kupffer cells. [140] The ethanolinduced increase in oxidant production has been demonstrated indirectly by increased lipid peroxidation [129] [141] and directly by electron spin resonance. [142] Production of ·NO is also increased by chronic ethanol administration and presumably reflects increased iNOS activity in hepatocytes,macrophages (including Kupffer cells), vascular endothelial cells, and vascular smooth muscle. [143] The ·NO can react with $O_2^{\cdot -}$ to form peroxynitrite ($ONOO^-$), which also exhibits toxicity, including oxidation and nitration of lipids and proteins and oxidation of sulfhydryl groups. [144] [145] [146]

Essential tissue and plasma antioxidants are depleted on long-term exposure to ethanol administration, partially because of malnutrition, but also through interaction with oxidants. [139] [147] [147] Oxygen radical-mediated ethanol toxicity may be accentuated by the reduction of glutathione or hepatic alpha-tocopherol levels by long-term ethanol consumption. [129] [148] [149] Furthermore, the gene expression of antioxidant-producing enzymes [150] is modulated by long-term ethanol administration and may influence whether oxidant-induced tissue damage is manifested.

Chronic Liver Diseases

Although the previous discussion focuses on acute hepatocellular injury, almost all the mechanisms discussed can also result in chronic liver dysfunction. In chronic injury, the injury process has been modified by adaptive changes in spite of the continuation of the noxious stimulus. Microsomal, mitochondrial, and even antioxidant enzymes may be induced. Other adaptive changes include lysosome alterations, cellular hypertrophy, fatty acid metamorphosis, changes in transcription and translation, and altered transport and storage function. [99] The failure of adaptive changes to compensate for the injury ultimately leads to fibroplasia, which encircles hepatocytes, and to cirrhosis, which interferes with parenchymal perfusion and leads to loss of hepatic function. Acute and chronic diseases of the liver can be silent (subclinical) or clinically overt. Subclinical disease is usually detected when abnormal biochemical test results are reported during routine screening procedures. Clinically overt disease, regardless of origin, is typically characterized by portal hypertension, jaundice, variceal bleeding, ascites, hepatorenal syndrome, and portosystemic encephalopathy.

References

1. Campra JL, Reynolds TB: The hepatic circulation. In Arias IM, Jakoby WB, Popper H et al (eds): The Liver: Biology and Pathobiology. New York, Raven Press, 1988, p 911.

2. Greenway CV, Lautt WW: Hepatic circulation. In Schultz SG (ed): In Handbook of Physiology. Section 6: The Gastrointestinal System. Bethesda, Md, American Physiological Society, 1989, p 1519.

3. Rappaport AM: Hepatic blood flow. In Javitt NB (ed): Liver and Biliary Test Physiology. Baltimore, University Park Press, 1980, p 1.

4. Caesar J, Sheldon S, Chiandussi L et al: The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. Clin Sci 21:43, 1961.

5. Szabo G, Benyo I, Sandor J et al: Estimation of hepatic blood flow in the dog with the Xe and hydrogen washout, Au-colloid uptake techniques and with the electromagnetic flowmeter. Res Exp Med (Berl) 169:69, 1976.

6. Reichman S, Davis WE, Storaasli JP et al: Measurement of hepatic blood flow by indicator dilution techniques. J Clin Invest 37:1848, 1958.

7. Huet P-M, Lavoie P, Viallet A: Simultaneous estimation of hepatic and portal flows by an indicator dilution technique. J Lab Clin Med 82:836, 1973.

8. Hopkinson BR, Schenk WG: The electromagnetic measurement of liver blood flow and cardiac output in conscious dogs during feeding and exercise. Surgery 63:970, 1968.

9. Norris CP, Barnes GE, Smith EE et al: Autoregulation of superior mesenteric blood flow in fasted and fed dogs. Am J Physiol 237:H174, 1979.

10. Greenway CV, Lawson AE, Mellander S: The effects of stimulation of the hepatic nerves, infusions of noradrenaline and occlusion of the carotid artery on liver blood flow in the anaesthetized cat. J Physiol (Lond) 192:21, 1967.

11. Richardson PDI, Withrington PG: Liver blood flow. Pflugers Arch 299:311, 1968.

12. Hughes RL, Mathie RT, Campbell D: Systemic hypoxia and hyperoxia and liver blood flow in the greyhound. Pflugers Arch 381:151, 1979.

13. Scholtholt J, Shiraishi T: The reaction of liver and intestinal blood flow to a generalized hypoxia, hypocapnia in the anesthetized dog. Pflugers Arch 318:185, 1979.

14. Richardson PDI, Withrington PG: Physiologic regulation of the hepatic circulation. Annu Rev Physiol 44:57, 1982.

15. Richardson PDI, Withrington PG: Effects of intraportal infusions of hypertonic solutions on hepatic hemodynamics in the dog. J Physiol (Lond) 301:82, 1980.

16. Lautt WW: Mechanism and role of intrinsic regulation of hepatic arterial blood flow: Hepatic arterial buffer response. Am J Physiol 249:6549, 1988.

17. Gelman S, Ernst E: Role of pH, PCO_2 and O_2 content of portal blood in hepatic circulatory autoregulation. Am J Physiol 233:E255, 1977.

18. Carneiro JJ, Donald DE: Changes in liver blood flow and blood content in dogs during direct nerve activity. Circ Res 40:150, 1977.

19. Rappaport AM, Schneiderman JH: The function of the hepatic artery. Rev Physiol Biochem Pharmacol 76:130, 1976.

20. Richardson PDI, Withrington PG: The role of beta receptors in the responses of the hepatic arterial bed of the dog to phenylephrine, isoprenaline, noradrenaline and adrenaline. Br J Pharmacol 60:239, 1977.

21. Richardson PDI, Withrington PG: Physiologic regulation of the hepatic circulation. FASEB J 41:2111, 1982.

22. Richardson PDI, Withrington PG: Glucagon inhibition of hepatic arterial responses to hepatic nerve stimulation. Am J Physiol 233:H647, 1977.

23. Cohen MM, Sitar DS, McNeil JR et al: Vasopressin and angiotensin and resistance vessels of spleen, intestine and liver. Am J Physiol 218:1704, 1970.

24. Richardson PDI, Withrington PG: Effects of intra-arterial and intra-portal injections of vasopressin on the hepatic arterial and portal venous vascular beds of the dog. Circ Res 43:496, 1978.

25. Gelman SI: Disturbances in hepatic blood flow during anesthesia and surgery. Arch Surg 111:881, 1976.

26. Cooperman LH, Warden JC, Price HL: Splanchnic circulation during N_2O anesthesia and hypocarbia in normal man. Anesthesiology 29:254, 1968.

27. Johnson EE, Hedley-Whyte J: Continuing positive-pressure ventilation and choledochoduodenal flow resistance. J Appl Physiol 39:937, 1975.

28. Gelman S: General anesthesia and hepatic circulation. Can J Physiol Pharmacol 252:1762, 1987.

29. Gelman S, Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 61:726, 1984.

30. Payen D, Gatecel C, Dupuy P et al: Effects of isoflurane vs. halothane on human arterial hepatic blood flow (AHBF) and portal vein blood flow (PVBF) after surgical stress. Anesthesiology 69A:77, 1988.

31. Kennedy WF, Everett GB, Cobb LA et al: Simultaneous systemic and hepatic hemodynamic measurements during high spinal anesthesia in normal man. Anesth Analg 49:1016, 1970.

32. Gelman S, Ernst EA: Hepatic circulation during sodium nitroprusside infusion in the dog. Anesthesiology 49:182, 1978.

33. Dong WK, Bledsoe SW, Eng DY et al: Profound arterial hypotension in dogs. Anesthesiology 58:61, 1983.

34. Price HL, Davidson IA, Clement AF et al: Can general anesthetics produce splanchnic visceral hypoxia by reducing regional blood flow? Anesthesiology 27:24, 1966.

35. Nagano K, Gelman S, Parks DAA et al: Hepatic oxygen supply-uptake relationship and metabolism during anesthesia in miniature pigs. Anesthesiology 72:902, 1990.

36. Rothschild MA, Oratz M, Schreiber SS: Albumin synthesis. N Engl J Med 286:748, 1975.

37. Kirsch R, Frith L, Black E et al: Regulation of albumin synthesis by alteration of dietary protein. Nature 217:578, 1968.

38. Schreiber G, Urban J: Synthesis and secretion of albumin. Rev Physiol Biochem Pharmacol 82:27, 1978.

39. Rothschild MA, Oratz M, Zimmon D et al: Albumin synthesis in cirrhotic subjects with ascites studied by carbonate-14C. Clin Invest 8:344, 1969.

40. Clarke R, Rake MO, Flute PT et al: Coagulation abnormalities in acute liver failure: Pathogenic and therapeutic implications. Scand J Gastroenterol Suppl 19:63, 1973.

41. Aranha GV, Greenlee HB: Intraabdominal surgery in patients with advanced cirrhosis. Arch Surg 121:275, 1986.

42. Laurie SH, Mohammed ES: Ceruloplasmin: The enigmatic copper protein. Coord Chem Rev 33:279, 1980.

43. Zieve L: Amino acids in liver failure. Gastroenterology 76:219, 1979.

44. Cahill GF, Ashmore J, Renold AE et al: Blood glucose and the liver. Am J Med 26:264, 1959.

45. Stanley JC: The regulation of glucose production. Br J Anaesth 53:137, 1981.

46. Hems DA, Whitton PD: Control of hepatic glycogenolysis. Physiol Rev 60:1, 1980.

47. Pilkis SF, Park CR, Clans TH: Hormonal control of hepatic gluconeogenesis. Vitam Horm 36:383, 1978.

48. Zakim D: Metabolism of glucose and fatty acids by the liver. In Zakim D, Boyer TD (eds): Hepatology: A Textbook of Liver Disease. Philadelphia, WB Saunders, 1982, p 77.

49. Williamson DH, Hems R: Metabolism and function of ketone bodies. In Bartley W, Kornherb HL, Quayle JR (eds): Essays in Cell Metabolism. London, Wiley Interscience, 1970, p 275.

50. Olesky JM, Farquhar JW, Reaven GM: Reappraisal of the role of insulin in hypertriglyceridemia. Am J Med 57:551, 1974.

51. Chan L, Jackson RL, O'Malley BW et al: Synthesis of very low density lipoprotein in the cockerel: Effects of estrogen. Clin Invest 58:368, 1976.

52. Schmid R: Bilirubin metabolism: State of the art. Gastroenterology 74:1307, 1978.

53. Traynor C, Hall GM: Endocrine and metabolic changes during surgery: Anaesthetic implication. Br J Anaesth 53:153, 1981.

54. Flack A: Protein metabolism after surgery. Proc Nutr Soc 39:125, 1981.

55. Brandt MR, Fernandez A, Morhorst R et al: Epidural analgesia improves postoperative negative nitrogen balance. Br Med J 1:1106, 1978.

56. Oyama T, Takazawa T: Effects of halothane anesthesia and surgery on growth hormone and insulin levels in plasma. Br J Anaesth 23:179, 1972.

57. Oyama T, Matsuki A, Kudo M: Effects of enflurane anesthesia and surgery on carbohydrate and fat metabolism in man. Anaesthesia 27:179, 1972.

58. Brandt MR, Korshin J, Prange-Hansen J et al: Influence of morphine anesthesia on the endocrine-metabolic response to open-heart surgery. Acta Anaesthesiol Scand 22:400, 1978.

59. Clarke RSJ: The hyperglycemic response to different types of surgery and anesthesia. Br J Anaesth 42:45, 1970.

60. Hall GM, Young C, Holdcroft A et al: Substrate mobilization action during surgery. Anaesthesia 33:924, 1978.

61. Biebuyck JF, Lund P, Krebs HA: The effects of halothane on glycolysis and biosynthetic processes of the isolated perfused rat liver. Biochem J 128:711, 1972.

62. Biebuyck JF: Effects of anesthetic agents on metabolic pathways. Br J Anaesth 45:263, 1973.

63. Rannels DE, Flaim KE, Jefferson LS: Halothane inhibits synthesis of retained and secreted proteins in perfused rat liver. Anesthesiology 57A:231, 1982.

64. Aune H, Bessesen A, Olsen H et al: Acute effects of halothane and enflurane on drug metabolism and protein synthesis in isolated rat hepatocytes. Pharmacol Toxicol 53:363, 1983.

65. Guyton AC: Textbook of Medical Physiology. Philadelphia, WB Saunders, 1982, p 871.

66. Radnay PA, Duncalf D, Novakovic M et al: Common bile duct pressure changes after fentanyl, morphine, meperidine, butorphanol and naloxone. Anesth Analg 63:441, 1984.

67. Zylanoff PF, Mark-Savage P, Martucci RW et al: Common bile duct responses to anesthetic agents in dogs. Anesthesiology 51:S32, 1979.

68. Gelman S: Anesthesia and the liver. In Barash PG, Cullen BF, Stoelting RK (eds): Clinical Anesthesia. Philadelphia, JB Lippincott, 1992, p 1185.

69. Bonkowsky HL: Porphyrin and heme metabolism and the porphyrias. In Zakim D, Boyer TD (eds): Hepatology: A Textbook of Liver Disease. Philadelphia, WB Saunders, 1982, p 351.

70. Rojdmarke S, Bloom G, Chou MCY et al: Hepatic extraction of exogenous insulin and glucagon in the dog. Endocrinology 102:806, 1978.

71. Tucker GR: Drug metabolism. Br J Anaesth 51:603, 1979.

72. Bentley P, Oesch F: Foreign compound metabolism in the liver. In Popper H, Schaffner F (eds): Progress in Liver Disease. Orlando, Fla, Grune & Stratton, 1982, p 157.

73. Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377, 1976.

74. Williams RL: Drug administration in hepatic disease. N Engl J Med 309:1616, 1983.

75. Williams RL, Benet LZ: Hepatic function and pharmacokinetics. In Zakim D, Boyer TD (eds): Hepatology: A Textbook of Liver Disease. Philadelphia, WB Saunders, 1982, p 230.

76. Conney A: Pharmacological implications of microsomal enzyme induction. Pharmacol Rev 19:317, 1967.

77. Smith RE, Rawlins MD: Variability in Human Drug Response. London, Butterworths, 1973.

78. Chan K, Kendall MJ, Mitchard M et al: The effect of ageing on plasma pethidine concentrations. Br J Clin Pharmacol 2:297, 1975.

79. Irvine RE, Grove J, Toseland PA et al: The effect of age on the hydroxylation of amylobarbitone sodium in man. Br J Clin Pharmacol 1:41, 1974.

80. Nation RL, Triggs EJ, Selig M: Lignocaine kinetics in cardiac patients and aged subjects. Br J Clin Pharmacol 4:439, 1977.

81. Whitehouse MW, Beck FJ: Impaired drug metabolism in rats with adjuvant-induced arthritis. Drug Metab Dispos 1:251, 1973.

82. Elin RJ, Vesell ES, Wolff SM: Effects of etiocholanolone-induced fever on plasma antipyrine half-lives and metabolic clearance. Clin Pharmacol Ther 17:337, 1975.

83. Alvares AP, Anderson GE, Conney AH et al: Interactions between nutritional factors and drug biotransformation in man. Proc Natl Acad Sci U S A 73:2501, 1976.

84. Pantuck EJ, Pantuck CB, Weissman C et al: Effects of parenteral nutritional regimens on oxidative drug metabolism. Anesthesiology 60:534, 1984.

85. Livingstone A, Waterman AE: The development of tolerance to ketamine in rats and the significance of hepatic metabolism. Br J Pharmacol 64:63, 1978.

86. Kanto J, Lisalo E, Lehtinen V et al: Concentration of diazepam after an acute and chronic administration. Psychopharmacology (Berl) 36:123, 1974.

87. Karlin JM, Kutt H: Acute diphenylhydantoin intoxication following halothane anesthesia. J Pediatr 76:941, 1970.

88. Ghoneim MM, Delle M, Wilson WR et al: Alteration of warfarin kinetics in man associated with exposure to an operating room environment. Anesthesiology 43:333, 1975.

89. White PF, Johnstone RR, Pudwell CR: Interaction of ketamine and halothane in rats. Anesthesiology 42:179, 1975.

90. Fish KJ, Rice SA: Halothane inhibits metabolism of enflurane in Fischer 344 rats. Anesthesiology 59:417, 1983.

91. Borel JD, Bently JB, Nenad RE et al: Influence of halothane on fentanyl pharmacokinetics. Anesthesiology 57A:239, 1982.

92. Rogers K, Chelly J, Merin RG et al: Verapamil halothane interaction in the chronically instrumented dog. Anesth Analg 63:268, 1984.

93. Reilly CS, Wood AJJ, Kashakjn RP et al: The effect of halothane on drug disposition: Contribution of changes in intrinsic drug metabolizing capacity and hepatic blood flow. Anesthesiology 63:70, 1985.

94. Duvaldestin P, Mazze RI, Nivoche Y et al: Occupational exposure to halothane results in enzyme induction in anesthesia. Anesthesiology 54:57, 1981.

95. Dale O, Nielsen K, Westgaard G et al: Drug metabolizing enzymes in the rat after inhalation of halothane and enflurane. Br J Anaesth 55:1217, 1983.

96. Sherwin JE, Soberman RJ: Liver function. In Kaplan LA, Pesce AJ (eds): Clinical Chemistry: Theory, Analysis, Correlation. St. Louis, CV Mosby, 1996, p 505.

97. Moss DW, Henderson AR: Enzymes. In Burtis CA, Ashwood ER (eds): Tietz Textbook of Clinical Chemistry. Philadelphia, WB Saunders, 1994, p 735.

98. Yokoyama Y, Beckman JS, Beckman TK et al: Circulating xanthine oxidase: Potential mediator of ischemic injury. Am J Physiol 258:G564, 1990.

99. Popper H: Hepatocellular degeneration and death. In Arias IM, Jakoby WB, Popper H et al (eds): The Liver: Biology and Pathobiology. New York, Raven Press, 1988, p 1087.

100. Toledo-Pereyra LH, Suzuki S: Cellular and biomolecular mecha-nisms of liver ischemia and reperfusion injury. Transplant Proc 26:325, 1994.

101. Kurokawa T, Nonami T, Harada A et al: Mechanism and prevention of ischemia-reperfusion injury of the liver. Semin Surg Oncol 12:179, 1996.

102. Reichen J, Simon FR: Cholestasis. In Arias IM, Jakoby WB, Popper H et al (eds): The Liver: Biology and Pathobiology. New York, Raven Press, 1988, p 1105.

103. Nielsen VG, McCammon AT, Tan S et al: Xanthine oxidase inactivation attenuates postocclusion shock after descending thoracic aorta occlusion and reperfusion in rabbits. J Thorac Cardiovasc Surg 110:715, 1995.

104. Weinbroum A, Nielsen VG, Tan S et al: Liver ischemia-reperfusion increases pulmonary permeability in the rat: Role of circulating xanthine oxidase. Am J Physiol 268:G988, 1995.

105. Parks DA, Freeman BA: Organ preservation. In Gelman S (ed): Anesthesia and Organ Preservation. Philadelphia, WB Saunders, 1987, p 23.

106. Carden DL, Young JA, Granger DN: Pulmonary microvascular injury after intestinal ischemia-reperfusion: Role of P-selectin. J Appl Physiol 75:2529, 1993.

107. Parks DA, Tan S, Poplawski SC et al: Ascorbate oxidation products: Indicator for involvement of oxidants in human liver transplantation. FASEB J 5:A1824, 1992.

108. Parks DA, Tan S, Poplawski SC et al: Uric acid oxidation products: Indicator of oxidant stress in human liver transplantation. Gastroenterology 102:A232, 1992.

109. McClain CJ, Hill D, Schmidt J et al: Cytokines and alcoholic liver disease. Semin Liver Dis 13:170, 1993.

110. Weiner FR, Esposti SD, Zern MA: Ethanol and the liver. In Arias IM, Boyer JL, Fausto N et al (eds): The Liver: Biology and Pathobiology, 2nd ed. New York, Raven Press, 1994, p 1383.

111. Bird GL, Sheron N, Goka AK et al: Increased plasma tumor necrosis factor in severe alcoholic hepatitis. Ann Intern Med 112:917, 1990.

112. Adkison D, Hollwarth ME, Benoit JN et al: Role of free radicals in ischemia-reperfusion injury to the liver. Acta Physiol Scand 548:101, 1986.

113. Jaeschke H: Reactive oxygen and ischemia/reperfusion injury of the liver. Chem Biol Interact 79:115, 1991.

114. Toledo-Peereyra JL: Liver preservation: Experimental and clinical observations. Transplant Proc 20:965, 1988.

115. Jamieson NV, Sundberg R, Lindell S et al: The 24- to 48-hour preservation of canine liver by simple cold storage using UW lactobionate solution. Transplant Proc 21:1292, 1989.

116. Den Butter G, Marsh DC, Lindell SL et al: Amino acids to suppress reperfusion injury after liver preservation. Transplant Proc 23:2378, 1991.

117. Ramboer C, Piessens F, DeGroote J: Serum xanthine oxidase and liver disease. Digestion 7:183, 1972.

118. Giler S, Sperling O, Brosh S et al: Serum xanthine oxidase in jaundice. Clin Chim Acta 63:37, 1975.

119. Tan S, Gelman S, Poplawski SC et al: Xanthine oxidase: Release into the circulation following human liver transplantation. Gastroenterology 102:A246, 1992.

120. Tan S, Yokoyama Y, Dickens E et al: Xanthine oxidase activity in the circulation of rats following hemorrhagic shock. Free Radic Biol Med 15:407, 1993.

121. Radi R, Rubbo H, Bush K et al: Xanthine oxidase binding to glycosaminoglycans: Kinetics and superoxide dismutase interactions of immobilized xanthine oxidase-heparin complexes. Arch Biochem Biophys 339:125, 1997.

122. Adachi T, Fukushima T, Usami Y et al: Binding of human xanthine oxidase to sulphated glycosaminoglycans on the endothelial-cell surface. Biochem J 289:523, 1993.

123. Gerson RJ, Casini A, Gilfor D et al: Oxygen-mediated cell injury in the killing of cultured hepatocytes by acetaminophen. Biochem Biophys Res Commun 126:1129, 1985.

124. Casini A, Giorli M, Hyland RJ et al: Mechanisms of cell injury in the killing of cultured hepatocytes by bromobenzene. J Biol Chem 257:6721, 1982.

125. Mackay IR, Frazer IH: Autoantibodies, autoimmunity, and chronic hepatitis. In Chisari FV (ed): Advances in Hepatitis Research. New York, Masson, 1984, p 179.

126. Klatsky AL: Cardiovascular effects of alcohol. Sci Am Sci Med 2:28- 37, 1995.

127. Moss M, Bucher B, Moore FA et al: The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 275:50-54, 1996.

128. Lieber CS: Alcohol and the liver: 1994 update. Gastroenterology 106:1085-1105, 1994.

129. Nordmann R: Alcohol and antioxidant systems [Review]. Alcohol 29:513-522, 1994.

130. Tuma DJ, Thiele GM, Xu D et al: Acetaldehyde and malondialdehyde react together to generate distinct protein adducts in the liver during long-term ethanol administration. Hepatology 23:872-880, 1996.

131. Roll FJ, Bissell DM, Perrez HD: Human hepatocytes metabolizing ethanol generate a non-polar chemotactic factor for human neutrophils. Biochem Biophys Res Commun 137:688, 1986.

132. Williams AJK, Barry RE: Superoxide anion production and degranulation of rat neutrophils in response to acetaldehyde-altered liver cell membranes. Clin Sci 71:313, 1986.

133. Lewis KO, Paton A: Could superoxide cause cirrhosis? Lancet 2:188, 1982.

134. Shaw S, Rubin KP, Lieber CS: Depressed hepatic glutathione and increased diene conjugates in alcoholic liver disease: Evidence of lipid peroxidation. Dig Dis Sci 28:585, 1983.

135. Oshita M, Takei Y, Kawano S et al: Endogenous nitric oxide attenuates ethanol-induced perturbation of hepatic circulation in the isolated perfused rat liver. Hepatology 20:961, 1994.

136. Nanji AA, Greenberg SS, Tahan SR et al: Nitric oxide production in experimental alcoholic liver disease in the rat: Role in protection from injury. Gastroenterology 109:899, 1995.

137. Granger DN, Korthuis RJ: Physiologic mechanisms of postischemic tissue injury. Annu Rev Physiol 57:311, 1995.

138. Mulligan MS, Smith CW, Anderson DC et al: Role of leukocyte adhesion molecules in complement-induced lung injury. J Immunol 150:2401, 1993.

139. Grootveld M, Halliwell B: Measurement of allantoin and uric acid in human body fluids: A potential index of free-radical reactions in vivo. Biochem J 243:803, 1987.

140. Rosser BG, Gores GJ: Liver cell necrosis: Cellular mechanisms and clinical implications. Gastroenterology 108:252, 1995.

141. Nordmann R: Alcohol and antioxidant systems. Alcohol 29:513, 1994.

142. Reinke LA, Kotake Y, McCay PB et al: Spin-trapping studies of hepatic free radicals formed following the acute administration of ethanol to rats: In vivo detection of 1-hydroxyethyl radicals with PBN. Free Radic Biol Med 11:31, 1991.

143. Wang JF, Greenberg SS, Spitzer JJ: Chronic alcohol administration stimulates nitric oxide formation in the rat liver with or without pretreatment by lipopolysaccharide. Alcohol Clin Exp Res 19:387, 1995.

144. Beckmann JS, Ye YZ, Anderson PG et al: Extensive nitration of protein tyrosines in human atherosclerosis detected by immunohistochemistry. Biol Chem Hoppe Seyler 375:81, 1994.

145. Beckman JS, Beckman TW, Chen J et al: Apparent hydroxyl radical production by peroxynitrite: Implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci U S A 87:1620, 1990.

146. Skinner KA, Crow JP, Skinner HB et al: Free and protein associated nitrotyrosine formation following rat liver transplantation. Arch Biochem Biophys 342:282, 1997.

147. Wayner DDM, Burton GW, Ingold KU et al: The relative contributions of vitamin E, urate, ascorbate and proteins to the total peroxyl radical-trapping antioxidant activity of human blood plasma. Biochim Biophys Acta 924:408, 1987.

148. Lieber CS, Leo MA, Mak KM et al: Choline fails to prevent liver fibrosis in ethanol-fed baboons but causes toxicity. Hepatology 5:561, 1985.

149. Lauterburg BH, Davies S, Mitchell JR: Ethanol suppresses hepatic glutathione synthesis in rats in vivo. J Pharmacol Exp Ther 230:7, 1984.

150. Nanji AA, Griniuviene B, Sadrzadeh SM et al: Effect of type of dietary fat and ethanol on antioxidant enzyme mRNA induction in rat liver. J Lipid Res 36:736, 1995.

151. Gelman S: Effects of anesthetics on splanchnic circulation. In Altura BM, Halevy S (eds): Cardiovascular Action of Anesthetics and Drugs Used in Anesthesia. Basel, Karger, 1986, p 127.

152. Jones AL: Anatomy of the normal liver. In Zakim D, Boyer TD (eds): Hepatology: A Textbook of Liver Disease. Philadelphia, WB Saunders, 1982.

153. Rappaport AM, Borowy ZJ, Lougheed WM et al: Subdivision of hexagonal liver lobules into a structural and functional unit. Anat Rec 119:16, 1954.

Chapter 18 - Renal Physiology

Robert N. Sladen

INTRODUCTION

The kidneys contain approximately 2 ×10^6 nephrons, each of which consists of a glomerulus and a tubule, which empties into a collecting duct. Urine is formed by the combination of glomerular ultrafiltration and tubular reabsorption and secretion. These functional units collectively enable the kidneys to maintain a remarkably stable interior milieu despite large fluctuations in fluid and solute intake. Together they regulate intravascular volume, osmolality, and acid-base and electrolyte balance and excrete end products of metabolism and drugs. The nephron also elaborates hormones that contribute to fluid homeostasis (renin, prostaglandins, kinins), bone metabolism (1,25-dihydroxycholecalciferol) and hematopoiesis (erythropoietin). The function of the nephron is closely integrated with the vascular supply of the kidney (Fig. 18-1) (Figure Not Available) .

The Glomerulus (Renal Corpuscle)

The glomerulus consists of five distinct components: capillary endothelium, glomerular basement membrane, visceral epithelium, parietal epithelium, and mesangium. [1] [2] The afferent arteriole supplies a highly convoluted tuft of capillary loops, which subsequently drains into the efferent arteriole (Fig. 18-2) (Figure Not Available) . The capillary endothelium is fenestrated with pores about 70 to 100 nm in diameter. It lies on the glomerular basement membrane, which consists of a thick lamina densa sandwiched between two thin laminae rarae, externa and interna, with a total cross-section of about 350 nm. The blind epithelial sac of the renal tubule is invaginated around the capillary tuft as the Bowman capsule. The visceral layer, which is applied to the basement membrane, consists of podocytes with filamentous, interdigitating foot processes, which contain actin and abut the basement membrane. The gaps between the foot processes (filtration slits, about 25-60 nm) are bridged by a membrane, or slit diaphragm, whose size and permeability may be altered by contraction of the foot processes. The visceral layer is reflected back at the vascular pole of the glomerulus to form the parietal squamous epithelium of the Bowman capsule. The Bowman space, between the visceral and parietal layers of the capsule, becomes the lumen of the proximal tubule at the urinary pole of the glomerulus, and the parietal endothelium merges with the cuboidal cells of the proximal tubule. The central mesangial cells are specialized pericytes with numerous functions, including structural support, matrix elaboration, and phagocytosis. They contain myofilament-like threads consisting of actin and myosin, which contract in response to a number of vasoactive substances, especially angiotensin II, and restrict blood flow to fewer capillary loops. The mesangial cells thereby regulate the effective surface area for filtration and, as a consequence, glomerular permeability. [3]

Formation of the Glomerular Ultrafiltrate

To cross from the plasma to the tubular fluid, a molecule must pass in succession through the fenestrated capillary endothelium, the glomerular basement membrane, and the epithelial slit diaphragm. The capillary endothelium restricts the passage of cells only, but the basement membrane filters plasma proteins. All three layers contain negatively

Figure 18-1 (Figure Not Available) Anatomic relationships of the nephron and the renal vasculature. The left side of the diagram represents the renal vasculature as distributed through the inner medulla, outer medulla, and cortex. Arteries are drawn as solid lines, veins as hollow tubes. The renal artery divides serially into interlobar arteries (1), arcuate arteries (2), and interlobular arteries (3). The afferent arterioles (5) branch off laterally and provide the capillary tufts of the renal glomeruli in the outer cortex (7a), whose efferent arterioles (6) supply the cortical capillary network (not shown). In the juxtamedullary zone (7b), the efferent arterioles become the vasa recta, which are closely applied to the long loops of Henle (8, 8a, 9). The venous drainage consists of stellate veins (4), interlobular veins (3a), arcuate veins (2a), and interlobar veins (1a). The right side of the diagram represents two nephrons. On the left is the more numerous superficial cortical nephron with a short loop of Henle. On the right is the juxtamedullary nephron with a long loop of Henle, which dives deep into the inner medulla to generate the hyperosmotic interstitium required for tubular urine concentration. G, glomerulus; PT, proximal tubule; DTL, descending thin loop of Henle; ATL, ascending thin loop of Henle; TAL, thick ascending loop; DT, distal tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct. *(From Kriz and Bankir [174])*

charged glycoproteins, which retard the passage of other negatively charged proteins. Thus, the filtration barrier is both size-selective and charge-selective. [2] Molecules with an effective radius of less than 1.8 nm (water, sodium, urea, glucose, inulin) are freely filtered. Molecules larger than 3.6 nm (hemoglobin, albumin) are not filtered. Filtration of molecules between 1.8 and 3.6 nm depends on their electrical charge. Cations are filtered, whereas anions are not. In glomerulonephritis the negatively charged glycoproteins are destroyed, polyanionic proteins are filtered, and proteinuria ensues.

Glomerular ultrafiltration and the formation of tubular fluid depends on the balance of Starling forces regulating fluid flux across the filtration barrier. [2] Glomerular filtration rate (GFR) depends on the permeability of the filtration barrier and the net difference between the hydrostatic forces pushing fluid into the Bowman space and the osmotic forces keeping fluid in the plasma:

where uf = ultrafiltration, gc = glomerular capillary, and bs = Bowman space.

The ultrafiltration coefficient, K_f , reflects capillary permeability and glomerular surface area. The hydrostatic pressure in the glomerular capillary, P_{gc} , is effectively determined by the renal arterial pressure. The plasma oncotic pressure (pi_{gc}) is determined by afferent arteriolar plasma flow. Rapid blood flow washes out osmotically effective molecules and keeps the plasma osmotic pressure low, and vice versa.

Renal Autoregulation

In 1951 the classic dog studies of Shipley and Study [4] demonstrated that the kidney maintains a constant renal blood flow and GFR through an arterial pressure range of 80 to 180 mm Hg (Fig. 18-3) (Figure Not Available) . They also showed that urinary flow rate is not subject to autoregulation. Tubular water reabsorption, which determines urinary flow rate, is closely related to the hydrostatic pressure in the peritubular capillaries. Hypotension, whether induced or inadvertent, results in decreased urinary flow rate, which may be correctable only when the arterial blood pressure is restored toward normal.

The precise mechanism for renal autoregulation has still not been defined. In the vascular tree from the renal artery to the renal vein, most of the pressure decrease occurs in the afferent and efferent arterioles. Renal vascular resistance appears to be mediated by variable resistance of the preglomerular afferent arteriole. As mean arterial pressure decreases, renal vascular resistance decreases and renal blood

Figure 18-2 (Figure Not Available) Photomicrograph of a cast of a glomerulus without Bowman's capsule. At lower left the afferent arteriole (A) originates from an interlobular artery and enters the glomerulus with its many capillary loops. At upper left the efferent arteriole (E) leaves the glomerulus and branches to form the peritubular capillary plexus. Magnification ×300. *(From Tisher and Madsen [1])*

flow (RBF) is maintained. The most plausible explanation is that the arterioles constrict in response to increased arterial pressure and vice versa (i.e., a myogenic response). It is unlikely that the renin-angiotensin system plays a role: as arterial pressure falls, renin release and renal vascular resistance increase, which is the opposite of autoregulation.

It has also been postulated that tubuloglomerular feedback

Figure 18-3 (Figure Not Available) Autoregulation of glomerular filtration rate (GFR) and renal blood flow (RBF), based on the original work of Shipley and Study. [4] GFR and RBF remain constant between renal arterial pressures of 80 and 180 mm Hg. *(From Pitts [175])*

via the juxtaglomerular apparatus may play a role (see below). When arterial pressure increases through the autoregulatory range, it enhances delivery of sodium chloride to the cells of the macula densa, which induces afferent arteriolar constriction and decreased RBF and GFR. [2] The opposite effect occurs when arterial pressure declines. Autoregulation enables the kidney to maintain solute and water regulation independently of wide fluctuations of arterial blood pressure.

Although not to be abolished by most anesthetic agents, autoregulation appears to be impaired in severe sepsis, [5] acute renal failure, [6] and possibly during cardiopulmonary bypass. [7] In these situations, RBF is strikingly reduced during hypotension and is restored by normalization of renal perfusion pressure, even if this is achieved by vasoconstrictor therapy.

The Tubule

The tubule has four distinct segments: the proximal tubule, the loop of Henle, the distal tubule, and the connecting segment. The loop of Henle itself is divided into the pars recta (the straight portion of the proximal tubule), the descending and ascending thin limb segments, and the thick ascending limb. Each distal tubule drains into a collecting duct, which courses through the cortex, outer medulla, and inner medulla before entering the renal pelvis at the papilla (see Fig. 18-1) (Figure Not Available) .

There are two populations of nephrons. Those that occupy the outer and middle renal cortex are far more numerous, receive about 85 percent of the renal blood flow, and have short loops of Henle. Their efferent arterioles drain into a peritubular capillary plexus. Those that occupy the juxtamedullary renal cortex receive about 10 percent of the RBF and have larger glomeruli and long loops of Henle, which dive deeply into the inner medulla. Their efferent arterioles drain into elongated vascular conduits, the vasa recta, which are closely applied to the loops of Henle. Although the vasa recta receive less than 1 percent of the renal blood flow, they play an important role in generating the countercurrent mechanism for medullary hypertonicity and renal concentrating ability (see below).

The Juxtaglomerular Apparatus

The juxtaglomerular apparatus provides a remarkable integration of tubular and glomerular structure and function (Fig. 18-4) (Figure Not Available) . A modified portion of the thick ascending loop, the macula densa, is applied to the glomerulus at the vascular pole between the afferent and efferent arterioles. The cells of the macula densa appear to have a chemoreceptor function, which senses the concentration of sodium chloride (NaCl) in the tubular lumen of the thick ascending loop. The juxtaposed segments of the afferent and efferent arterioles contain modified smooth muscle cells (granular cells), which produce renin. The arterioles are innervated with sympathetic nerve fibers and contain baroreceptors, which respond to intraluminal pressure changes. Renin catalyzes the formation of angiotensin, which modulates efferent and afferent arteriolar tone and GFR. The relationship of the

Figure 18-4 (Figure Not Available) The juxtaglomerular apparatus. *(From Stanton and Koeppen [2])*

juxtaglomerular apparatus to the sympathoadrenal system is discussed later in the section on neurohormonal regulation of renal function.

Tubuloglomerular Feedback

When NaCl delivery to the macula densa is increased, renin-angiotensin elaboration is triggered, and arteriolar constriction ensues, which decreases GFR (tubuloglomerular feedback). The true role of tubuloglomerular feedback is unknown. Some have suggested that it is involved in renal autoregulation, [2] and others have postulated that it may be a compensatory mechanism to prevent polyuria in acute renal failure ("acute renal success"). When the thick ascending loop becomes ischemic, reabsorption of NaCl ceases, the ability of the tubule to concentrate urine is lost and, theoretically, intractable polyuria should result. Thurau and Boylan [8] suggested that the increased delivery of NaCl to the macula densa triggers angiotensin-mediated arteriolar constriction, which decreases GFR, induces oliguria, conserves intravascular volume, and protects the organism from dehydration.

Tubular Reabsorption and Secretion

The tubule has an enormous capacity for reabsorption of water and NaCl. Of the 180 L/d protein-free glomerular ultrafiltrate, 98 to 99 percent of the water and 99 percent of the sodium is reabsorbed. Many other filtered substances are completely reabsorbed, but some, such as glucose, have a maximum rate of tubular reabsorption (tubular maximum). Tubular reabsorption of glucose increases at a rate equal to that of the filtered load, which, if the GFR is constant, is directly proportional to that of plasma glucose. Once plasma glucose exceeds the tubular maximum (375 mg/dL), no further glucose is reabsorbed, and glycosuria results. Thereafter, the amount of glucose excreted in the urine increases in direct proportion to the filtered load.

Many important endogenous and exogenous solutes are secreted into the tubular lumen from the capillary blood. Some also have a tubular maximum for secretion, such as para-amino hippurate (PAH), which is used to calculate renal plasma flow. This is discussed further in the section on renal function tests.

There is a striking relationship between the structure and function of the different segments of the tubule (Fig. 18-5) (Figure Not Available) .

Figure 18-5 (Figure Not Available) Structure-function relationships in the renal tubule. The most metabolically active components of the tubule are the proximal tubule, the thick ascending loop of Henle, and the first part of the distal tubule. Their cells are large, and on the capillary surface (basolateral membrane) there are many invaginations rich in mitochondria. The cells of the proximal tubule have a brush-border on the luminal surface (apical cell membrane), whereas the cells of the descending and thin ascending loops of Henle are flattened with few mitochondria. The second part of the distal tubule and collecting duct are intermediate in nature. The intercalated cells of the distal tubule have many mitochondria, the principal cells few. *(From Stanton and Koeppen [2])*

The most metabolically active components of the tubule are the proximal tubule, the thick ascending loop of Henle, and the first part of the distal tubule. Figure 18-6 (Figure Not Available) illustrates a tubular cell in the thick ascending loop of Henle, which encompasses all the major mechanisms of reabsorption and secretion. The tubular lumen abuts the apical cell membrane, which joins adjacent cells at the right junctions. The remainder of the cell is lined by the basolateral cell membrane, which interfaces with the lateral interstitial spaces on either side and with the peritubular capillary at its base. There are a number of protein-based active transport systems. Of these the most important is the sodium-potassium adenosine triphosphatase (Na-K-ATPase) system, situated in the basolateral membrane, which, in exchange for potassium from inside the tubular cell, pumps sodium out of the tubular cell into the interstitial fluid (and capillary blood) against a concentration and an electrical gradient. The consequent decrease in intracellular sodium concentration in turn facilitates passive reabsorption of sodium from the tubular lumen into the

cell. The transport of virtually all solutes is coupled to that of sodium. Active transport systems that move solutes in the same direction into or out of the cell are called symporter systems, and those that move solutes in opposite directions are called antiporter systems. Whereas solutes are transported by both active and passive mechanisms, water always diffuses passively along an osmotic gradient.

Proximal Tubule

The first part of the proximal tubule reabsorbs about 100 percent of the filtered glucose, lactate, and amino acids as well as some phosphate by coupling with sodiumsymporter systems. [2] Hydrogen ions are extruded into the tubule by a sodium-H^+ antiporter system in exchange for bicarbonate. The absorption of organic anions and bicarbonate in the first part of the proximal tubule results in a relatively high chloride concentration downstream, promoting passive ingress of chloride. This leaves the tubular fluid positively charged relative to blood, further promoting the movement of sodium from the tubular fluid into the cell.

Most NaCl is absorbed transcellularly by a sodium-H^+ and chloride-based antiporter system in the apical cell membrane. Sodium is pumped into the interstitial space by the Na-K-ATPase pump, and chloride is pumped by a potassium-chloride symporter system, and the resulting increase in osmolality draws water across as well. In all, about two-thirds of the filtered water, chloride, and potassium are reabsorbed by the proximal tubule, coupled with and strongly influenced by sodium absorption. [2]

The proximal tubule is also an important site of secretion of many endogenous anions (bile salts, urate), cations (creatinine, dopamine) and drugs (diuretics, penicillin,

Figure 18-6 (Figure Not Available) Mechanisms of tubular secretion and reabsorption. This tubular cell in the thick ascending loop of Henle encompasses the major mechanisms of secretion and reabsorption, one or more of which is used by various segments of the tubule. The most ubiquitous and important transport mechanism is the energy-requiring Na-K-ATPase pump in the basolateral cell membrane (1), which pumps sodium out into the interstitium against its concentration gradient and maintains a low intracellular concentration. This favors inward movement of sodium from the tubular lumen, facilitated by a sodium chloride symporter system on the apical cell membrane (2), which creates enough potential energy to draw in potassium against its concentration gradient and which is the primary inhibitory site of action of loop diuretics. A sodium-H^+ antiporter system on the apical cell membrane (3) aids sodium reabsorption and extrudes H^+, thereby promoting reaction of water with carbon dioxide to form H^+ and bicarbonate ion under the influence of carbonic anhydrase (CA). Bicarbonate diffuses out into the capillary. Sodium reabsorption is thereby coupled to H^+ loss and bicarbonate reabsorption. The transport proteins create a positive charge in the lumen, which drives ions such as sodium, calcium, potassium, and magnesium passively through the tight junctions by paracellular diffusion. The thick ascending loop of Henle is uniquely highly water-impermeable so that luminal osmolality progressively falls to less than 150 mOsm/kg (the "diluting segment"). *(Modified from Stanton and Koeppen [2])*

probenecid, cimetidine). Organic ions compete for protein transport systems. Thus, administration of probenecid impairs tubular secretion of penicillin and prolongs its action. In chronic renal insufficiency there is an accumulation of organic acids that compete with drugs such as furosemide for secretor proteins, thereby conferring the "resistance" to loop diuretics encountered in this condition.

Thick Ascending Loop of Henle

The metabolically active component of the loop of Henle is the thick ascending loop, which reabsorbs about 20 percent of the filtered sodium, chloride, potassium, and bicarbonate. Only the descending loop is permeable to water. In the water-impermeable thick ascending loop, sodium is actively reabsorbed, but water remains. In this so-called diluting segment of the kidney, tubular fluid osmolality decreases to less than 150 mOsm/kg H_2O.

As in the proximal tubule, the Na-K-ATPase pump in the basolateral membrane is the engine that drives the resorptive capacity of the thick ascending loop. [2] Sodium moves from the tubular lumen by passive diffusion along its concentration gradient. A sodium-H^+ antiporter system in the apical cell membrane mediates the net secretion of H^+ and reabsorption of bicarbonate.

An important symporter protein system couples the reabsorption of sodium, chloride, and potassium (the latter against its concentration gradient) across the apical membrane. This system is the major site of action of loop diuretics in their inhibition of NaCl reabsorption in the thick ascending loop of Henle.

Oxygen Balance in the Medullary Thick Ascending Loop

The kidneys receive 20 percent of the total cardiac output but extract relatively little oxygen. The renal arteriovenous oxygen difference [(a-v)O_2] is only 1.5 mL/dL. However, there is a marked discrepancy between the renal cortex and medulla with regard to blood flow, oxygen delivery, and oxygen consumption (Table 18-1) . The medulla receives only 6 percent of the RBF and has an average oxygen tension (P_{O_2}) of 8 mm Hg. Thus, it is possible that severe hypoxia could develop in the medulla despite a relatively adequate total

TABLE 18-1 -- Distribution of Renal Blood Flow Between Cortex and Medulla

	CORTEX	MEDULLA
Percent of renal blood flow	94	6
Blood flow (mL/min/g)	5.0	0.03
P_{O_2} (mm Hg)	50	8
O_2 extraction ratio (V_{O_2}/D_{O_2})	0.18	0.79

O_2 = oxygen; V_{O_2} = oxygen consumption; D_{O_2} = oxygen delivery; P_{O_2} = oxygen tension. The renal medulla receives only a small fraction of the total renal blood flow, and flow rates are extremely slow. As a result, the tissue oxygen tension is extremely low, and the medulla extracts almost 80 percent of the oxygen delivered to it. A very mild reduction in total and cortical renal blood flow may therefore induce ischemia and hypoxia in the renal medulla. *Data from Brezis, Rosen, and Epstein.* [9]

RBF, and the metabolically active medullary thick ascending loop of Henle is particularly vulnerable. [9]

The medullary thick ascending loop is also a potential site for nephrotoxic injury. Intrarenal blood flow is regulated by endogenous vasoactive compounds. In the outer cortex, adenosine induces vasoconstriction. In the juxtamedullary zone, generation of prostaglandins and nitric oxide promote vasodilation. The net effect is to direct as much available blood flow to the medulla as possible. Drugs that inhibit prostaglandin synthesis, such as nonsteroidal antiinflammatory agents, can upset this compensatory mechanism and result in medullary ischemia.

Any stress resulting in activation of the sympathoadrenal system (pain, trauma, hemorrhage, hypoperfusion, sepsis, congestive heart failure) results in renal cortical constriction and potential tubular ischemia. The kidney is relatively devoid of beta $_2$ -receptors so that endogenous or exogenous epinephrine induces vasoconstriction through alpha receptors or angiotensin activation. In hemodynamically mediated renal injury, the initial response to renal hypoperfusion is increased active NaCl absorption in the thick ascending limb. This increases oxygen consumption in the face of decreased oxygen delivery. Subsequent sympathoadrenal responses and renal cortical vasoconstriction may be a compensatory attempt to redistribute blood flow to the medulla. Ultimately, ATP stores become depleted, and active NaCl reabsorption winds down. This increases the NaCl concentration in tubular fluid reaching the macula densa in the distal tubule, resulting in angiotensin release and afferent arteriolar constriction (i.e., tubuloglomerular feedback). Teleologically, the resultant decrease in GFR benefits renal oxygen balance by decreasing solute reabsorption and oxygen consumption in the medullary thick ascending loop and by preserving intravascular volume. [9]

This hypothesis implies that ischemic or nephrotoxic insults to the renal tubules could be alleviated by the administration of loop diuretics or dopaminergic agents. These drugs inhibit active sodium reabsorption in the thick ascending limb, thereby decreasing oxygen consumption and enhancing tubular oxygen balance. [10]

Distal Tubule and Collecting Duct

The proximal segment of the distal tubule is structurally and functionally similar to the thick ascending loop. An apical cell membrane NaCl symporter system is the site of action of thiazide diuretics.

The last part of the distal tubule is composed of two types of cells. Principal cells reabsorb sodium and water and secrete potassium via the Na-K-ATPase pump. Intercalated cells secrete H^+ and reabsorb bicarbonate by an H^+ -ATPase pump in the apical cell membrane.

Regulatory Mechanisms in Salt and Water Reabsorption

Osmotic Equilibrium

The ability of the kidney to concentrate urine is dependent on three factors: (1) the development of a hypertonic medullary interstitium by the countercurrent mechanism and urea recycling, (2) the impermeability to water of the ascending loop of Henle, and (3) the action of antidiuretic hormone (ADH) in increasing water permeability in the last part of the distal tubule and collecting ducts and active NaCl reabsorption in the thick ascending loop of Henle.

The medullary interstitium is rendered hypertonic by the countercurrent multiplier effect of the loop of Henle. The primary mechanism is the separation of solute from water (the single effect) by the combination of NaCl reabsorption and water impermeability in the ascending limb. This results in increased NaCl concentration and osmolality in the medullary interstitium. The descending limb is freely permeable to water, which diffuses into the interstitium along the osmotic gradient, and the tubular fluid becomes progressively hyperosmotic at the bend of the loop.

The vasa recta, which are closely applied to the long loops of Henle of juxtamedullary nephrons, maintain this condition by removing water and adding solute as they pass through the medullary interstitium. A standing osmotic gradient is thereby set up between the cortex (300 mOsm/kg), juxtamedullary zone (600 mOsm/kg), and deep medulla (1,200 mOsm/kg). This process is enhanced by the passive recycling of urea, which diffuses out of the inner medullary collecting duct into the interstitium and thence into the distal loop of Henle. These processes are summarized in Figure 18-7 (Figure Not Available) .

Tubular Concentration and Dilution

Hypovolemia

The tubular response to hypovolemia (contracted extracellular volume) is controlled by a series of vasoconstrictor, salt-retaining neurohormonal systems. Initially, the GFR and filtered load of sodium decrease. Sodium reabsorption in the proximal tubule is increased from about 66 to 80 percent by sympathetic activity and angiotensin II as well as by the decline in peritubular capillary pressure induced by renal vasoconstriction. Sodium delivery to the thick ascending loop of Henle, distal tubule, and collecting duct is decreased as is the relative proportion of extraction, but release of aldosterone and ADH causes avid reabsorption of sodium at these sites. Under the influence of ADH, water is also avidly reabsorbed in the collecting duct so that the urine becomes

---

Figure 18-7 (Figure Not Available) Tubular concentration of urine in the juxtamedullary nephrons, which have long loops of Henle associated with the vasa recta. Dashed arrows represent passive movement of fluid or solutes along concentration or osmolar gradients; solid arrows represent active transport. (1) Tubular fluid enters the distal proximal tubule iso-osmotic with plasma (300 mOsm/kg). In the descending limb of Henle (2), water rapidly diffuses out into the increasingly hypertonic medulla and is removed by the vasa recta so that the tubular fluid becomes hypertonic, owing largely to concentration of sodium chloride (NaCl). Urea diffuses in from the hypertonic interstitium, further increasing tubular fluid osmolality (1,200 mOsm/kg). In the thin ascending loop of Henle (3), NaCl passively diffuses into the interstitium along its concentration gradient, but water is trapped in the water-impermeable tubule, which progressively decreases tubular fluid osmolality. Urea passively diffuses into the tubular fluid (urea recycling). Tubular dilution is accelerated by active reabsorption of NaCl in the thick ascending loop (the diluting segment) and proximal distal tubule (4). The fluid entering the distal tubule is quite hypo-osmotic (100 mOsm/kg). In the collecting segment (5), the osmolality of the tubular fluid returns to that of plasma (300 mOsm/kg), but unlike the contents of the proximal tubule, the solute component consists largely of urea, creatinine, and other excreted compounds. Increased plasma ADH renders the cortical and medullary collecting ducts (6) permeable to water, which passively diffuses into the hypertonic medullary interstitium. Even though some urea diffuses out into the medulla, the maximal osmolality of concentrated urine (7) approaches that of the hypertonic medullary interstitium, about 1,200 mOsm/kg. In the absence of ADH, the collecting ducts remain impermeable to water, and the urine is diluted. *(From Stanton and Koeppen [24])*

highly concentrated (osmolality 600 mOsm/kg) but with virtually no sodium (10 mEq/L).

Diuretic agents abolish the kidney's ability to concentrate urine by washing out the hypertonic medulla. They do this either by an osmotic effect that prevents water reabsorption (mannitol) or by inhibition of active NaCl transport in the thick ascending loop (furosemide) or the first part of the distal tubule (hydrochlorthiazide). An early and important manifestation of acute tubular necrosis is the loss of urinary concentrating ability caused by the breakdown of the energy-requiring Na-K-ATPase pump in the thick ascending loop of Henle.

Hypervolemia

The tubular response to an expanded extracellular volume is controlled by a series of vasodilator, salt-excreting neurohormonal systems. Decreases in sympathetic and angiotensin II activity and the release of atrial natriuretic peptide (ANP) cause renal plasma flow (RPF), GFR, and the filtered sodium load to increase. The same effects, along with an increase in peritubular capillary hydrostatic pressure, cause sodium reabsorption in the proximal tubule to decrease from 67 to 50 percent. The declines in aldosterone and ADH decrease sodium absorption in the thick ascending loop of Henle, distal tubule, and collecting duct, although the absolute sodium load increases as does the relative proportion of sodium absorption at these sites. ANP, together with the absence of ADH, impairs water absorption at the collecting duct so that a dilute urine (osmolality 300 mOsm/kg) with abundant sodium (80 mEq/L) is produced. This urine profile (low osmolality, high urinary sodium) may be seen in hypovolemia if tubular resorptive capacity is depressed by loop diuretics or lost completely, as in acute tubular necrosis.

RENAL FUNCTION TESTS

Renal hemodynamic function is defined by RBF, RPF, intrarenal distribution of flow, filtration fraction, and renal vascular resistance. Glomerular function is defined by GFR. Tubular functions include concentrating ability, water conservation,

and sodium conservation. For practical purposes, however, tests of renal function can be described as those based on clearance techniques (the most commonly used), those that test tubular function, and those that are largely used for clinical and laboratory investigation.

Renal Clearance Techniques

Renal function is most frequently assessed by clearance techniques, [11] which provide an indirect estimate of function based on the Fick principle:

That is, the amount of substance *x* excreted by the kidney equals the amount delivered to the kidney by the renal arterial flow minus the amount returning from the kidney in the renal venous flow. Therefore

The amount of substance *x* delivered to the kidney is the product of the arterial plasma concentration ($P_a x$) and RBF, and the amount returning from the kidney is the product of the venous plasma concentration ($P_v x$) and RBF. The amount of substance *x* excreted is the product of the kidney's urine concentration (U_x) and the urine flow rate in milliliters per minute (V). Note that $U_x \times V$ (urine concentration times flow rate) represents the urinary excretion rate of substance *x*. Therefore,

However, in practice, RBF and venous return are not measured, and the removal of substance *x* by the kidney is expressed by the concept of clearance, which is defined as the virtual volume of plasma cleared of substance *x* per unit time, in milliliters per minute. This allows the urinary excretion rate to be equated to the renal arterial plasma concentration:

By rearrangement, clearance of substance *x* may be calculated:

where U_x is the concentration of substance *x* in the urine in mg/dL, V is the urine flow rate in milliliters per minute, and P_x is the concentration of substance *x* in the plasma, assuming that the substance's concentration is identical in the renal arterial plasma and in an arm vein.

Para-Amino Hippurate Clearance

PAH is an organic anion that is almost completely cleared from the plasma in a single pass through the kidney by means of a combination of glomerular filtration and proximal tubular secretion. Calculated clearance of PAH (C_{PAH}) therefore represents renal plasma flow. To obtain maximal PAH extraction, a steady state with a low plasma PAH level must be achieved by giving an intravenous loading dose followed by an infusion to maintain a plasma PAH concentration of about 2 mg/dL. [11] A carefully timed catheter urine collection is required. Because only 90 percent of the renal plasma flow enters the peritubular capillaries surrounding the proximal tubule, PAH clearance underestimates true renal plasma flow, and it is known as the effective renal plasma flow ($_{E}RPF$).

where U_{PAH} is the concentration of PAH in the urine, and P_{PAH} is its concentration in the plasma. The normal effective renal plasma flow is 660 mL/min/1.73 m^2.

Effective renal blood flow ($_{E}RBF$) may be derived if the hematocrit level (Hct) is known:

There are a number of circumstances in which C_{PAH} provides misleading information about renal plasma flow. If the plasma PAH concentration exceeds the tubular maximum of 12 mg/dL, the excess PAH is returned to the renal vein, the secreted fraction declines, and renal plasma flow is underestimated. [2] About 80 percent of

PAH is cleared by tubular secretion, so if proximal tubule function deteriorates, PAH clearance declines and again underestimates renal plasma flow.

These errors can be overcome if arterial and renal vein PAH levels are accessible. The renal extraction of PAH (E_{PAH}) can be calculated and serves as an indicator of proximal tubule function:

where A_{PAH} is arterial PAH concentration, and V_{PAH} is renal vein PAH concentration. When renal function is normal, renal vein PAH is close to zero, and PAH extraction approaches 1.0. As proximal tubule function declines, the concentration of PAH in the renal vein increases, and PAH extraction progressively decreases below 1.0. True RPF is calculated by dividing PAH clearance by PAH extraction:

PAH clearance may also misrepresent renal plasma flow in the presence of hypovolemia (PAH is sequestered in the kidney) and oliguria. Thus, despite its relative convenience as an experimental tool, PAH clearance may be an unreliable indicator of RBF during the perturbations induced by anesthesia and surgical stress.

Inulin Clearance

Inulin is an inert polyfructose sugar that is completely filtered by the glomerulus and is neither secreted nor reabsorbed by the renal tubules. The volume of plasma cleared of inulin (mL/min) represents the GFR. Inulin clearance is

measured identically to PAH clearance, and an indwelling intravenous cannula and urinary catheter must be in place. After an intravenous loading dose of 30 to 50 mg/kg, a continuous infusion of inulin is given to establish a steady-state plasma concentration of 15 to 20 mg/dL. The bladder is usually flushed with air to eliminate any pooled urine. Then, a very carefully timed urine collection is made, which can be as short as 30 minutes. It is generally accepted that inulin clearance (C_{IN}) provides the most accurate available determination of GFR (i.e., it represents the gold standard):

where U_{IN} is urinary inulin in mg/dL, P_{IN} is plasma inulin in mg/dL, and V is urine flow rate in mL/min. This relationship also implies that the renal excretion of inulin (urinary inulin times urine flow rate) is determined solely by the GFR and the plasma inulin concentration:

Although inulin clearance is the standard measure of GFR in experimental situations, it is seldom used clinically because its accurate measurement is laborious and requires meticulous attention to detail. The inulin assay is timeconsuming, and inulin itself is in short supply because of lack of demand. Inulin meets all the criteria of an ideal filtration marker, but large changes in blood glucose during the test may interfere with its measurement, and its accuracy in reflecting GFR cannot be directly assessed, only inferred. The predicted variability of inulin clearance is 20 percent when measurements are compared at two different times in the same individual and 40 percent when measurements are compared between two individuals. [11]

Normal values for inulin clearance are 110 to 140 mL/min/1.73m^2 (males) and 95 to 125 mL/min/1.37m^2 (females).

Filtration Fraction

The filtration fraction (FF) is the fraction of the RPF that is filtered by the glomerulus:

Normally, GFR is about 125 mL/min, and RPF is about 660 mL/min so that the FF approximates 125/660, or about 0.2. Changes in FF are considered to represent changes in periglomerular arteriolar tone. An increase in FF indicates that GFR is increased relative to RPF. This could be achieved by efferent arteriolar constriction or afferent arteriolar dilation and maintains glomerular filtration pressure in the face of decreased RPF. Conversely, a decrease in FF implies that GFR is decreased relative to RPF by afferent arteriolar constriction or efferent arteriolar dilation.

Creatinine Clearance

Creatinine is the endogenous end product of creatine phosphate metabolism, is normally generated from muscle at a very uniform rate, and is handled by the kidney in a manner similar to that of inulin. Thus, creatinine clearance (C_{CR}) provides a simple, inexpensive bedside estimate of GFR. A single blood sample is drawn at the midpoint of a carefully timed urine collection:

where U_{CR} is the urinary creatinine concentration in mg/dL, P_{CR} is the plasma creatinine concentration in mg/dL, and V is urine flow rate in mL/min.

Bedside use of creatinine clearance has been restricted by the belief that a prolonged (12-24-hour) urine collection is necessary to eliminate error induced by residual urine in the bladder neck after spontaneous voiding, a practice both tedious and cumbersome. The estimated creatinine clearance depends on when the blood sample is drawn, so if the serum creatinine changes rapidly during the time of urine collection, a misleading result may be obtained.

It is not the duration of urine collection that is critical, but rather the fact that its timing is precise. [12] The variability of creatinine clearance with a 1-hour urine collection is no greater than of 24-hour collection if a good urine flow is induced by diuresis, and care is taken to empty the bladder. [13] In catheterized patients with urine flow rates of more than 15 mL/h, creatinine clearance obtained with 2-hour urine collections gives values equivalent to those obtained with 12- to 24-hour collections. [14] [15] Moreover, a 2-hour creatinine clearance enables rapid, repeated estimates of GFR to be obtained. This not only makes it a viable bedside test in critically ill patients but also implies that a changing GFR can be closely tracked by serial estimations of creatinine clearance (Figs. 18-8 (Figure Not Available) , 18-9 , and 18-10) . For example, in trauma patients, a 1-hour creatinine clearance of less than 25 mL/min determined within 6 hours of surgery reliably

Figure 18-8 (Figure Not Available) Creatinine clearance: 2- versus 22-hour values. There is a close and significant correlation in creatinine clearance estimation from a 2-hour and a 22-hour urine

collection. CC02, 2-hour urine collection; CC22, 22-hour urine collection. *(From Sladen, Endo, and Harrison [15])*

Figure 18-9 New-onset acute renal failure. In a patient developing acute renal failure in the intensive care unit, the exponential decline in creatinine clearance is tracked equally well whether a 2-hour (CC02) or a 22-hour (CC22) urine collection is used. However, data from the 2-hour collection are available well before those from the 22-hour collection.

predicted postoperative acute renal failure, despite the absence of oliguria. [16]

There is considerable variation in the normal range of creatinine clearance, as wide as the range of normal values of body size. [13] Tobias et al [12] reported a variation in creatinine clearance between 88 and 148 mL/min and in serum creatinine between 0.9 and 1.5 mg/dL in a single healthy individual over 5 years. There is a diurnal variation in creatinine clearance, with higher values in the afternoon and a variance of up to 25 percent around mean values. [17] It is prudent to obtain short-collection creatinine clearance estimations at the same time each day to minimize diurnal variability. "Normal" creatinine clearance is related to body surface area and weight, so values may fluctuate widely in patients with cachexia or edema.

Figure 18-10 Renal revascularization. Patient with renovascular hypertension and renal insufficiency admitted to the intensive care unit for preoperative monitoring and stabilization. Bilateral renal revascularization was performed, and following return from the operating room there was a substantial decline in renal function. These changes were tracked equally well by creatinine clearance derived from a 2-hour (CC02) and a 22-hour (CC22) collection.

Creatinine clearance has a number of inherent limitations even if collection error is carefully avoided. Creatinine generation rate varies with muscle mass, physical activity, protein intake, and catabolism. The most commonly used serum creatinine assay is the Jaffe reaction, which is based on the red color of the creatinine complex with alkaline picrate. It also measures other normally-occurring chromogens, such as glucose, protein, ketones, and ascorbic acid, which represent about 14 percent of total creatinine when renal function is normal, although substantially less when serum creatinine is elevated. Ketoacidosis, barbiturates, and cephalosporin antibiotics may artifactually increase serum creatinine by as much as 100 percent and falsely decrease measured creatinine clearance. Unlike inulin, about 20 percent of creatinine is secreted by the proximal tubule, so that creatinine clearance overestimates GFR, and the ratio between the clearance of creatinine and inulin is 1.2:1. As the GFR declines, tubular secretion of creatinine increases. When GFR is less than 40 mL/min/1.73m ^{2} , a creatinine/inulin clearance ratio as high as 1.81 to 2.51 may be achieved. [18] [19] [20] In patients with normal renal function, the underestimate of GFR induced by the Jaffe reaction is balanced by the overestimate of GFR induced by tubular creatinine secretion, and creatinine clearance provides a reasonable representation of GFR. However, widely used drugs such as trimethoprim, H_2 -antagonists, and salicylates block tubular secretion of creatinine and may elevate serum creatinine and decrease creatinine clearance. When serum levels of creatinine are very high, it is excreted into the gut and undergoes extrarenal metabolism by intestinal organisms.

For all these reasons, an isolated creatinine clearance estimation may not diagnose lesser degrees of renal dysfunction. Nonetheless, serial estimations of creatinine clearance provide a useful clinical guide to alterations in renal function and prognosis. The variability of creatinine clearance diminishes as GFR declines; in fact, loss of variability is a clue to deteriorating renal function. If the GFR is rapidly declining, the creatinine clearance alerts the physician earlier and more compellingly than the serum creatinine because it reflects creatinine excretion rate (i.e., urine creatinine content times urine flow rate [$U_{CR}V$]). Directional changes between creatinine clearance and inulin clearance show good agreement. [18] At low levels of GFR a creatinine/inulin clearance ratio as high as 2:1 (e.g., 12 versus 6 mL/min) would induce little actual difference in clinical management.

Serum Creatinine

Serum creatinine is a useful marker of stable renal function, but it is unreliable when GFR is rapidly changing. [18] [19] [20] Serum creatinine concentration depends on its volume of distribution (total body water), creatinine generation rate (muscle mass and rate of catabolism), and creatinine excretion rate (GFR). Perioperative fluid administration increases total body water and dilutes serum creatinine, which underestimates renal dysfunction. In a cachectic patient with very low muscle mass, creatinine generation may be so feeble that the serum creatinine remains subnormal even in the face of a markedly decreased GFR. In some patients with a serum creatinine of less than 0.9 mg/dL, creatinine clearance may be less than 25 mL/min. [13] [14] The relationship

Figure 18-11 (Figure Not Available) The relationship between serum creatinine and GFR as measured by creatinine clearance is reciprocal and exponential. Doubling of the serum creatinine corresponds to halving of the GFR. Relatively large declines in GFR from normal are associated with small increases in serum creatinine until GFR decreases below 60 mL/min; further decrements are associated with large increases in serum creatinine. *(From Alfrey and Chan [176])*

between serum creatinine and GFR is inverse and exponential. An increase in serum creatinine from 0.8 to 1.6 mg/dL implies a 50 percent decrease in GFR, and early renal dysfunction may be missed. A much larger increase from 4 to 8 mg/dL also represents a 50 percent decrease in GFR, but by this time renal insufficiency is well established (Fig. 18-11) (Figure Not Available) . After a transient renal insult, such as that caused by suprarenal aortic cross-clamping, serum creatinine may increase for a few days while GFR is actually recovering. [21] In oliguric acute renal failure, serum creatinine is directly proportional to creatinine generation rate. Creatinine clearance is reliably low but is associated with a wide variability of serum creatinine.

Serum Creatinine-Based Nomograms

Cockroft and Gault [22] formulated a nomogram for the rapid estimate of creatinine clearance without urine collection. The nomogram was based on population studies incorporating serum creatinine, age, weight, and gender.

For females, the derived creatinine clearance is multiplied by 0.85.

In these formulas, the body weight that is used may substantially alter the derived creatinine clearance. In obese or edematous patients, the total body weight is much greater than the lean body mass from which creatinine is derived, and creatinine clearance is overestimated. In cachectic patients with depleted lean body mass, creatinine production is so low that serum creatinine is frequently less than 1.0 mg/dL and overestimates the true GFR. Robert et al [23] demonstrated that when the Cockroft and Gault equation incorporates ideal body weight (from a nomogram) and serum creatinine corrected to 1.0 mg/dL if it is less than 1.0 mg/dL, single measurements in hemodynamically stable patients correlate more closely with inulin clearance than either a 30-minute or a 24-hour creatinine clearance.

Serum creatinine-based nomograms are subject to the same limitations as serum creatinine itself in tracking changing renal function. Rapid alterations in GFR are reflected by rapid changes in the creatinine excretion rate, which is incorporated into measured creatinine clearance as $U_{CR}V$. In contrast, serum creatinine itself changes much more slowly and depends on the equilibrium point between creatinine production and excretion. In fact, serum creatinine does not begin to increase above normal levels until the GFR declines below 50 mL/min/1.73m ^{2} , and occasionally it will remain normal even when the GFR dips as low as 20 to 40 mL/min/1.73m ^{2} .

Tubular Function Tests

Tests of renal tubular function can define states of diuresis and antidiuresis and natriuresis and antinatriuresis. Under certain circumstances the tests can distinguish oliguria due to prerenal azotemia, which is reversed by restoration of hemodynamic status to normal, from that due to established acute renal failure, which persists

despite restoration of normal renal blood flow. In the former, tubular conservation mechanisms are enhanced, and in the latter they are lost. However, in nonoliguric renal dysfunction, which accounts for more than 50 percent of cases encountered clinically, the differences in tubular function are less distinct from prerenal azotemia. Diuretic therapy overcomes tubular conserving function. Thus, treatment with loop diuretics, osmotic diuretics, saline loading, or natriuretic vasodilators (low-dose dopamine, fenoldopam, prostaglandin E1, or ANP) may render tubular function tests uninterpretable.

Urinary Concentrating Ability

Concentrating ability is a very sensitive index of tubular function. In prerenal states, urinary osmolar concentration is markedly increased. In acute tubular necrosis, the ability to concentrate urine may be lost 24 to 48 hours before serum creatinine or blood urea nitrogen (BUN) starts to increase.

Urine-to-Plasma Osmolar Ratio

The normal tubular response to dehydration or hypovolemia is to generate a urine-to-plasma osmolar ratio ($U:P_{OSM}$) of 1.5 or greater. Isosthenuria ($U:P_{OSM} = 1.0$) in the presence of oliguria implies loss of tubular function and

established acute renal failure. However, isosthenuria can occur in a prerenal state following diuretic administration.

Free Water Clearance

Free water clearance (C_{H_2O}) attempts to represent the degree of urinary concentration or dilution by distinguishing the clearance of solute from that of free water. The solute or osmolar clearance (C_{OSM}) is calculated by standard methods, using urine osmolality in mOs/kg (U_{OSM}), plasma osmolality in mOs/kg (P_{OSM}), and urine flow in mL/min (V):

Then, the osmolar clearance is subtracted from the urine flow rate to give free water clearance:

If the urine is isosmotic with plasma, the osmolar clearance equals the urine flow rate so that C_{H_2O} is zero. If the urine is dilute (hypo-osmotic), the urine flow rate exceeds osmolar clearance, and the difference is the free water clearance. If the kidney is able to concentrate urine normally (hyperosmotic urine), urine flow rate is less than osmolar clearance, which results in a negative free water clearance (i.e., free water retention), also known as tubular conservation of water (TC_{H_2O}). Conceptually, TC_{H_2O} represents the volume of fluid that would have to be added to the urine to make its osmolality equivalent to that of plasma. [24]

With the onset of acute tubular necrosis and loss of concentrating ability, the urine becomes isosmotic, and C_{H_2O} approaches zero (±0.25 mL/min). However, in distinguishing between prerenal and intrarenal oliguria, C_{H_2O} does not really provide any more information about concentrating ability than $U:P_{OSM}$, and in addition it requires a timed urine collection.

The concept of free water excretion emphasizes that renal regulation of solute and of water balance are independent of each other. The kidney has an enormous range in its ability to handle water. The maximum excretion of water, or positive free water clearance, is 18 L/d, about 10 percent of the GFR. The maximum conservation of water, or negative free water clearance, is 8 L/d. [24]

Water Conservation

Urine-to-Plasma Creatinine Ratio

The urine-to-plasma creatinine ratio ($U:P_{CR}$) represents the proportion of water filtered by the glomerulus that is abstracted by the distal tubule. Normally, about 98 percent of water is abstracted, and urine creatinine is much greater than plasma creatinine. The ratio can increase a hundred-fold in severe prerenal states. When tubular function is lost, the ratio declines to less than 20:1. For example, two patients have a serum creatinine of 2.0 mg/dL. In one, urine creatinine is 100 mg/dL, which implies a prerenal state ($U:P_{CR}$ 50:1). In the other, urine creatinine is 20 mg/dL, which suggests acute tubular necrosis ($U:P_{CR}$ only 10:1). Similar information may be obtained during the performance of an inulin clearance test by calculating the urine-to-plasma inulin ratio.

Sodium Conservation

Urine Sodium

During dehydration or hypovolemia, the tubules intensely reabsorb sodium so that urine sodium (U_{Na}) declines to less than 20 mEq/L. In established acute renal failure, the ability to conserve sodium and protect the intravascular volume is lost, and U_{Na} exceeds 60 to 80 mEq/L. Diuretic therapy overcomes tubular sodium conservation so that a high U_{Na} does not necessarily imply loss of tubular function. However, if U_{Na} remains low in the face of diuretic therapy, an intense prerenal state exists.

Fractional Excretion of Sodium

Fractional excretion of sodium (FE_{Na}) expresses sodium clearance as a percentage of creatinine clearance:

Based on the relationship expressed in Equation 5:

Urine flow rate (V) is identical in the numerator and denominator and it cancels out:

Thus, FE $_{Na}$ may be calculated from a spot sample of blood and urine without requiring a timed urine collection.

During dehydration or hypovolemia, sodium clearance and FE $_{Na}$ are decreased to less than 1 percent of creatinine clearance. When tubular ability to conserve sodium is lost in acute renal failure, FE $_{Na}$ increases to more than 3 percent. However, FE $_{Na}$ increases with normal tubular function after diuretic therapy and during postoperative sodium mobilization. Sequential increases in FE $_{Na}$ associated with declining creatinine clearance indicate more reliably deteriorating renal function than an isolated high FE $_{Na}$.

Investigational Tests of Renal Function

Glomerular Filtration Rate

Radioisotopic Filtration Markers

The use of intravascularly injected radiolabeled compounds to define GFR is potentially simpler and more

precise than the methods discussed above because it involves detection of decay in radiation and avoids the necessity for a timed urine collection. These compounds include sodium iothalamate (I^{125}), diethylenetriaminepenta-acetic acid (DTPA) (Tc^{99m}), and ethylenediaminetetra-acetic acid (EDTA) (Cr^{51}). However, none of these compounds are inherently superior to inulin in their renal handling, the tests require great attention to detail and quality control, and there is the constant risk, albeit low, of radiation exposure. [11]

Total Renal Blood Flow

Flow Probes

Flow measurement by electromagnetic flow probes is based on the creation of a magnetic field around the circumference of the vessel. The field is disrupted by blood flow, and a voltage output proportional to blood velocity is generated. Ultrasonic flow probes use the Doppler technique, in which high-frequency sound is transmitted across the lumen of the vessel. A shift in sound frequency is created by the movement of blood and is proportional to blood velocity.

Flow-probe placement is invasive and requires direct surgical exposure of the renal arteries. Probes must be calibrated in vitro before and after measurements. However, they are generally very accurate.

Thermodilution Estimation of Renal Vein Effluent

Schaer et al [25] used a double-lumen pigtail catheter with a thermistor placed in the renal vein of dogs under direct vision or with fluoroscopy. RBF was calculated by thermodilution with cold saline, which allowed repeated measurements in conscious animals. The effect of the presence of the probe itself on RBF is unknown. A similar technique was used by Haywood et al [26] to measure RBF for the assessment of renal oxygen delivery and consumption during septic shock in pigs.

Contrast Ultrasonography

Aronson et al [27] attempted to measure RBF in vivo using contrast ultrasound. They injected sonicated albumin microspheres into the aorta of anesthetized dogs and then recorded simultaneous ultrasonography images of the kidney and aorta and calculated RBF using a mathematical model. RBF was altered by means of a renal artery occluder or vasoactive drugs (dopamine or fenoldopam), and the results were compared with direct measurements by electromagnetic flow probe. Although the correlation between ultrasonography and flow probe measurements of RBF was reasonable (0.84), there was a large bias (in many cases greater than 200 mL/min) and variance. Ultrasonography tended to overestimate RBF, especially when cardiac output was changing. The authors concluded that this method allows estimation of trends in RBF and may be helpful in the qualitative assessment of regional distribution of blood flow between the renal cortex and medulla.

Intrarenal Blood Flow Distribution

Diffusible Gas Tracers

A great deal of supposition about the intrarenal distribution of RBF within and between the renal cortex and medulla was based on studies using the radioactive gases xenon [133] and krypton [85] . The gases are injected into the renal artery, and radioactivity is counted externally. Renal radioactivity disappears faster the higher the blood flow, and flow is calculated mathematically from washout curves. In 1963 Thorburn et al [28] extrapolated four monoexponential components from these curves, said to represent the outer renal cortex (zone I), juxtamedullary cortex (zone II), medulla (zone III), and perihilar fat (zone IV). Blood flow was greatest in zone I and progressively diminished through zones II to IV.

During the next decade studies, such as those by Hollenberg et al, [29] using this technology suggested that ischemia and stress cause intrarenal redistribution of blood flow from zones I to II. Juxtamedullary nephrons are relatively saltretaining and have loops of Henle that penetrate the hypertonic medulla. Thus, this finding explained the retention of NaCl and edema observed during states of relative renal cortical hypoperfusion. However, the shortcomings of gas tracer techniques have generated skepticism about the validity of these studies. [30] The washout curves have not been matched to any specific anatomic area; xenon [133] itself decreases RBF, and the inert gases may diffuse out into the interstitium, especially in pathologic states.

Radioactive Microspheres

This is a terminal experimental procedure, which consists of injection of radioactive microspheres--radiolabeled polystyrene beads 9 to 50 mum in diameter--into the central circulation. It is presumed that the microspheres are distributed to and within organs proportional to blood flow. The animal is then sacrificed, the organs are removed and dissected, and radioactivity is counted.

Intrarenal localization of the microspheres truly represents regional blood flow. However, it is assumed that the injection does not itself interfere with renal hemodynamics and that all microspheres come to rest in the glomeruli without passing through the kidney or plugging arteries. Inner cortical afferent arterioles run at right angles to interlobular arteries, and microspheres may bypass them because of axial streaming. This error would give an overestimation of outer cortical blood flow.

Figure 18-12 Neurohormonal regulation of renal function. Normally, there is a balance between those systems promoting renal vasoconstriction and sodium retention versus those systems promoting renal vasodilation and sodium excretion. Surgical stress, ischemia, and sepsis tip the balance in favor of vasoconstriction and sodium retention. On the other hand, hypervolemia (or the induction of atrial stretch) tips the balance in favor of vasodilation and sodium excretion.

NEUROHORMONAL REGULATION OF RENAL FUNCTION

The role of the kidney in controlling the interior milieu appears to be modulated by two mutually dependent but opposing neurohormonal systems that maintain blood pressure, intravascular volume, and salt and water homeostasis by a complex set of interactions (Fig. 18-12) . The sympathoadrenal axis, the renin-angiotensin-aldosterone system, and ADH defend against hypotension and hypovolemia by promoting vasoconstriction and salt and water retention. The prostaglandins, bradykinins, and ANPs defend against hypertension and hypervolemia by promoting vasodilation and salt and water excretion (Fig. 18-13) (Figure Not Available) .

Anesthesia does not perturb these systems to any substantial degree. Most recent work suggests that in the intact organism, anesthetics affect renal function by the extrarenal circulatory changes that they induce rather than by their direct actions on the kidney. [31] Surgical or traumatic injury,

Figure 18-13 (Figure Not Available) Neurohormonal renal regulatory systems. RBF, renal blood flow; GFR, glomerular filtration rate; Na, sodium; x, decreased; y, increased. *(Modified from Sladen [177])*

on the other hand, induces profound vasoconstriction and salt and water retention, which may persist for several days. The clinical sequel is postoperative oliguria and edema. Renal vasoconstriction also predisposes the kidney to further perioperative ischemic and nephrotoxic insults. Elucidation of the role of ANP enhances the concept that these changes can be prevented or modified by maintenance of normal or increased intravascular (and thereby atrial) volume.

Systems Promoting Vasoconstriction and Salt Retention

The Sympathoadrenal Axis

Sympathetic effects on the kidney are mediated by circulating epinephrine and neuronal release of norepinephrine. The renal cortex has a dense plexus of autonomic nerve fibers derived from the T12 to L4 spinal segments via the celiac plexus. The primary stimulus to the sympathetic response is a decrease in arterial blood pressure sensed by baroreceptors in the aortic arch, carotid sinus, and afferent arteriole. Afferent fibers travel via the vagus nerve and decrease impulse transmission rate to the mediating centers in the hypothalamus, which results in increased adrenergic nerve activity. The kidney does not have any parasympathetic innervation.

A G-protein coupled phospholipase-C receptor mediates vasoconstrictor responses in vascular smooth muscle and the mesangium. It responds not only to alpha-adrenergic stimulation (epinephrine, norepinephrine) but also to a wide variety of other hormones and peptides, including angiotensin II, vasopressin, endothelin, platelet-activating factor, and leukotrienes. [3] The receptor subunit in the cell membrane is coupled through G_q protein to phospholipase C, which hydrolyzes phosphatidylinositol biphosphate (PIP_2) to inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG activates protein kinase, which opens a calcium channel in the membrane. IP_3 triggers the release of calcium from the sarcoplasmic or endoplasmic reticulum. Both mechanisms result in a rapid increase in intracellular calcium, which binds with calmodulin and thereby activates myosin light-chain kinase, resulting in smooth muscle contraction. The calcium-calmodulin complex simultaneously activates phospholipase A_2, resulting in the production of vasodilator prostaglandins (see below).

Mild alpha-adrenergic stimulation appears to cause preferential efferent arteriolar constriction, which preserves the filtration fraction. Severe alpha-adrenergic stimulation causes predominant afferent arteriolar constriction, and decreases filtration fraction. [32] Thus, the adrenergic response to a moderate decrease in renal perfusion (e.g., general anesthesia) favors the preservation of the GFR. In contrast, the adrenergic response to shock exacerbates the decrease in GFR already induced by renal hypoperfusion.

Adrenergic nerves also supply the proximal tubule, thick ascending limb of Henle, and collecting duct, and their stimulation enhances NaCl reabsorption at these sites. Gas tracer studies suggested that sympathetic activation caused sodium retention by intrarenal redistribution of RBF from the outer cortex to salt-retaining juxtamedullary nephrons, but this was not confirmed by microsphere studies. [29] [30]

There is a close relationship between sympathetic stimulation and activation of the renin-angiotensin system. Adrenergic stimulation releases renin from the juxtaglomerular apparatus, and adrenergically induced vasoconstriction can be blocked by angiotensin-converting enzyme (ACE) inhibitor drugs such as captopril.

The effects of the administration of exogenous adrenergic agents depend on their agonist activity. Drugs with predominantly alpha-adrenergic effects, such as norepinephrine, epinephrine, phenylephrine, and high-dose dopamine (>10 mug/kg/min) exacerbate the endogenous sympathetic responses to hypotension. Drugs with predominantly $beta_1$ - and $beta_2$ -adrenergic activity (dobutamine, isoproterenol) cause marked increases in cardiac output and thus RBF, but it is difficult to ascertain their intrarenal effects. Dopaminergic agonists, such as low-dose dopamine (<3 mug/kg/min), dopexamine, and fenoldopam, selectively increase RBF and may oppose alpha-adrenergic renal vasoconstriction. [25] They induce a quite different response in the kidney and will be discussed separately.

The Renin-AngiotensinAldosterone System

Renin and Angiotensin

As already discussed, the juxtaglomerular apparatus consists of three groups of juxtaposed specialized tissues: modified fenestrated endothelial cells of the afferent arterioles, which produce renin; modified distal tubular cells, which have chemoreceptors (the macula densa); and the mesangial cells of the glomerulus, which have contractile properties (see Fig. 18-4) (Figure Not Available) . Together these provide an important regulating system for blood pressure, salt, and water homeostasis. [33]

Renin release is controlled by several mechanisms. A decrease in renal artery perfusion pressure triggers baroreceptors in the afferent arterioles. Sympathetic nerve stimulation and circulating catecholamines act on beta-adrenergic receptors in the afferent arterioles. The cells of the macula densa of the distal tubule sense increases in chloride concentration in the tubular fluid, which triggers renin release from the afferent arteriole. As discussed previously, this tubuloglomerular feedback appears to play a role in modulating GFR during normal and abnormal renal function through a continuous feedback loop. [8] [24] Thus, renin secretion is stimulated by actual hypovolemia (hemorrhage, diuresis, sodium loss or restriction) or effective hypovolemia (positive pressure ventilation, congestive heart failure, sepsis, or cirrhosis with ascites).

Renin acts on angiotensinogen, a large circulating glycoprotein released from the liver, and cleaves off a decapeptide, angiotensin I. In the kidney and in the lung

angiotensin I is further cleaved by endothelial-based ACE to form an octapeptide, angiotensin II, a potent vasoconstrictor (Fig. 18-14) . Renin is the rate-limiting enzyme in the production of angiotensin II. [34]

Activation of modest amounts of angiotensin II causes renal cortical vasoconstriction, predominantly at the level of the efferent arterioles. This acts to maintain glomerular filtration fraction in the face of mild to moderate decreases in RBF or perfusion pressure. The importance of this protective mechanism is emphasized by the deterioration in GFR

Figure 18-14 Renin-angiotensin system. For explanation, see text. ACE, angiotensin-converting enzyme.

that occurs when ACE inhibitors are administered to patients with hypotension, renal insufficiency, or unilateral renal artery stenosis. [35] [36] Severe stress induces the release of high levels of angiotensin II, which constricts the glomerular mesangial cells and decreases the glomerular filtration fraction. Angiotensin II promotes systemic vasoconstriction at about one-tenth of its renal effect, yet systemic arterial pressure can be markedly decreased by ACE inhibitors such as captopril and enalapril or angiotensin receptor antagonists. The effect of angiotensin II in causing salt and water retention is enhanced by its actions in stimulating aldosterone secretion by the adrenal cortex, ADH secretion by the posterior pituitary, and NaCl reabsorption by the proximal tubule. [33]

Angiotensin II triggers a number of mechanisms that modulate or oppose its own actions. It inhibits renin secretion by a negative feedback mechanism. Blockade of angiotensin formation by ACE inhibitors causes vasodilation but increases plasma renin levels. Angiotensin II activates phospholipase A_2, which triggers the synthesis of intrarenal prostaglandins. Vasodilator prostaglandins modulate the action of angiotensin II and may be responsible for its preferential activity on the efferent arteriole at low plasma levels. [34] Angiotensin-induced vasoconstriction increases atrial pressure and releases ANP, which opposes the reninangiotensin-aldosterone system.

The consequences of ACE inhibition on renal function depend on the patient's volume status, systemic hemodynamics, and baseline renal function and the presence of renovascular stenoses. In the long-term treatment of hypertension and CHF, especially in diabetics, the administration of ACE inhibitors such as captopril, enalapril, or lisinopril decreases renal vascular resistance and appears to benefit renal function. Preliminary data suggest that short-term pretreatment with captopril may prevent a decrease in RBF and GFR and preserves sodium excretion during cardiopulmonary bypass. [37] However, deterioration in renal function and hyperkalemia have been reported with the use of ACE inhibitors in patients with hypotension, renal insufficiency, or unilateral renal artery stenosis, probably related to the block of compensatory angiotensin-mediated efferent arteriolar constriction. [35] [36] It may be prudent to avoid their use in the immediate perioperative period.

Aldosterone

Aldosterone is a steroid hormone secreted by the zona glomerulosa of the adrenal cortex in response to hypokalemia, angiotensin II, and adrenocorticotropic hormone (ACTH). It acts at the thick ascending limb of the loop of Henle, the principal cells of the distal tubule, and the collecting duct to increase active absorption of sodium and passive absorption of water, culminating in an expanded blood volume. Sodium retention in vessel walls appears to enhance their response to vasoconstrictor agents.

In the principal cells, aldosterone induces cytoplasmic transcription of messenger ribonucleic acid (mRNA) to synthesize proteins that form sodium channels in the apical cell membrane and enhance the Na-K ATPase pump in the basolateral cell membrane. [24] Sodium is transported from the tubular fluid into the peritubular capillary, with chloride following along the electrical gradient thus created. This process involves protein synthesis, and there is a delay of about 1 to 2 hours from the secretion of aldosterone to its action on sodium reabsorption. Contrast this to sympathetic activity and angiotensin II, whose effects are immediate.

Antidiuretic Hormone (Arginine Vasopressin)

Antidiuretic hormone (ADH) regulates urinary volume and osmolality and controls diuresis or antidiuresis. It is a nine-amino-acid peptide, 8-arginine-vasopressin (AVP), which is synthesized in the supraoptic and paraventricular nuclei of the anterior hypothalamus. From there it undergoes

Figure 18-15 Synthesis of renal prostaglandins. Phospholipase A_2 is stimulated by ischemia, norepinephrine, and angiotensin II and cleaves arachidonic acid from its bond with membrane phospholipid. Cyclooxygenase acts on arachidonic acid to form evanescent cyclic endoperoxides (PGG_2 and PGH_2). Action of isomerase and prostacyclin synthetase culminate in the formation of vasodilator prostaglandins PGD_2, PGE_2, and PGI_2 (prostacyclin), which oppose the actions of the renin-angiotensin system on the kidney and protect against ischemic stress. Inhibition of cyclooxygenase by nonsteroidal anti-inflammatory drugs predisposes the kidney to damage. Under hypoxic or ischemic conditions, cyclic endoperoxides undergo reduction to the vasoconstrictor PGF_2, which acts on thromboxane receptors. Endotoxin increases the activity of leukocyte lipooxygenase and thromboxane synthetase. Leukotrienes (especially C_4 and D_4) and thromboxane (TXA_2) induce renal vasoconstriction and contribute to the vasomotor nephropathy of sepsis.

neuroaxonal transport to the posterior pituitary gland, where it is stored in granules before it is released into the circulation. [38] AVP acts on specific V_2-receptors in the collecting ducts to induce water reabsorption and a decreased flow of concentrated urine. It also increases NaCl reabsorption in the thick ascending loop of Henle, which maintains the hypertonicity of the medullary interstitium and facilitates movement of water out of the collecting duct along the osmotic gradient. This results in tubular conservation of water, increased urine osmolality, decreased plasma osmolality, and negative free water clearance without significant alteration in solute excretion.

The V_2-receptor on the basolateral cell membrane of the collecting duct responds to AVP via a receptor mechanism analogous to the beta-adrenergic receptor. [24] Through activation of G protein-coupled adenylyl cyclase, ATP is converted to cyclic adenosine monophosphate (cAMP), which activates protein kinase. Protein kinase causes preformed vesicles containing water channels to migrate and fuse with the apical cell membrane, resulting in a dramatic increase in its permeability to water. Water is reabsorbed into the cell and passes through the freely permeable basolateral membrane into the peritubular capillary. This process is rapidly reversed when plasma AVP levels decline: AVP plasma half-life is between 5 and 15 minutes.

Regulation of AVP Secretion

Hypothalamic osmoreceptors are sensitive to increases in serum osmolality of as little as 1 percent above normal. As illustrated in Figure 18-16A (Figure Not Available) , the threshold for AVP secretion (and the sensation of thirst) is between 280 and 290 mOsm/kg; once this is exceeded, the secretion rate has a very steep gain. [39] Even mild dehydration results in antidiuresis, with urine osmolality rapidly increasing as plasma AVP levels rise from 0 to 5 pg/mL (Fig. 18-16B) (Figure Not Available) .

AVP secretion is also stimulated by decreases in intravascular volume (mediated by stretch receptors with vagal afferents in the left atrium and pulmonary veins) and psychic stress (via cortical input). Hypovolemia-induced secretion of AVP overrides osmolar responses and contributes to the perioperative syndrome of inappropriate ADH secretion: fluid retention, hypoosmolality and hyponatremia. [40] The situation is exacerbated by administration of large volumes of hypotonic solutions that decrease serum osmolality.

Systemic arterial hypotension is a very potent trigger for AVP release, mediated by aortic and carotid baroreceptors. Plasma AVP may reach levels ten- to a thousand-fold greater than normal (Fig. 18-16C) (Figure Not Available) . At these concentrations AVP acts as a vasoconstrictor, especially in the outer renal cortex. It does so by stimulating the V_1-receptor, which exists on vascular smooth muscle, glomerular mesangial cells, and the vasa recta and promotes vasoconstriction via the phosphatidylinositol pathway. [38]

Anesthetic agents have little direct effect on AVP secretion, except via the changes that they induce in arterial blood pressure, venous volume, and serum osmolality. Surgical stimulation is a major stimulus to AVP secretion. This stress response, whether mediated by pain or by volume changes, is profound and lasts at least 2 to 3

days after the surgical procedure.

Figure 18-16 (Figure Not Available) Physiologic regulation of arginine vasopressin (AVP). For explanation, see text. *(From Landry [39])*

Patients in septic shock have inappropriately low plasma levels of AVP, about 3 pg/mL compared with patients in congestive heart failure (CHF) (about 22 pg/mL). [41] The mechanism is unknown but appears to reflect an impaired baroreflex secretion of AVP from the hypothalamus. At the same time, septic patients are profoundly sensitive to the vasoconstrictor effects of even low levels of AVP, presumably because of downregulation of the V_1-receptor. A similar phenomenon has been observed in patients with vasodilatory shock (i.e., low systemic vascular resistance [SVR] and hypotension despite increased cardiac index [CI] and norepinephrine infusion) in the postoperative period after placement of a left ventricular assist device. [42] Argenziano et al postulated that AVP deficiency may have been the result of excessive preoperative baroreceptor-mediated release in these patients with end-stage cardiac failure, compounded by downregulation of alpha-adrenergic receptors in CHF and after cardiopulmonary bypass.

Mets et al [43] reported profound refractory vasodilation after heart transplantation in two patients who had previously been on a combination of amiodarone and an ACE inhibitor. Blood pressure improved with infusion of low-dose AVP. The authors suggested that two of the three vasoconstrictor systems that normally maintain blood pressure were impaired: the sympathoadrenal system by amiodarone and the renin-angiotensin system by the ACE inhibitor. However, the endogenous AVP response was also inadequate, and exogenous AVP was therapeutic.

Systems Promoting Vasodilation and Salt Excretion

Prostaglandins

Intrarenal prostaglandins play an important role in endogenous renal protection. [44] [45] [46] [47] Prostaglandins are classified as autocoids because, unlike true hormones, they are produced in minute amounts and have a local, evanescent action. They are also referred to as eicosanoids because their structure is based on a 20-carbon fatty acid (eicosa is 20 in Greek). Vasodilator prostaglandins are important not so much to maintain normal renal function as to preserve it during the ischemic insults of acute trauma and surgery. The synthesis of intrarenal prostaglandins is summarized in Figure 18-15 .

Phospholipase A_2, which resides in the inner lipid layer of the cell membrane, controls prostaglandin production. It is stimulated by ischemia and hypotension and also by norepinephrine, angiotensin II, and AVP. Thus, the factors that induce and mediate the stress response simultaneously activate prostaglandins, which defend the kidney against their actions. Arachidonic acid is converted to PGG_2, the precursor of the vasodilator prostaglandins, by cyclooxygenase, which is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin, meclofenamate, and ketorolac.

The important vasodilator renal prostaglandins are PGD_2, PGE_2, and PGI_2 (prostacyclin). They oppose the actions of norepinephrine and angiotensin II, antagonize AVP, and block distal tubule sodium reabsorption. Prostaglandins may be particularly important in decreasing the vasoconstrictor activity of angiotensin II on the afferent arteriole and glomerular mesangial cells. [34] Production of prostaglandins promotes renal vasodilation, maintains intrarenal hemodynamics, and enhances sodium and water excretion. At the same time that they modulate the actions of the reninangiotensin system, prostaglandins stimulate renin secretion so that there is a constant "yin and yang" between the two systems. [48]

Exogenous infusion of synthetic prostaglandins such as PGE_1 prevents ischemia-induced acute renal failure in animals and may have a role in the preservation of the donor kidney in renal transplantation. [49] The renal vasodilator response to mannitol during hypoperfusion appears to be mediated through prostaglandin activation. [50]

The renal protective effect of prostaglandins is illustrated by the fact that NSAIDs cause nephrotoxicity in ischemic

but not in normal kidneys. Cyclooxygenase is reversibly inhibited by NSAIDs for about 8 to 24 hours. A single dose of aspirin causes its irreversible acetylation. In platelets the impact lasts for the lifetime of these cells (7 to 10 days), but the kidney resynthesizes cyclooxygenase within 24 to 48 hours. During conditions of stress, NSAIDs or aspirin compromises prostaglandin-dependent renal function, resulting in decreased RBF and GFR and increased renal vascular resistance. Diuretic-induced sodium excretion is attenuated, and hyperkalemia may occur. Adverse effects of NSAIDs and aspirin have been demonstrated in animal models of hemorrhage, endotoxemia, increased venous pressure, and low cardiac output and in humans with mild underlying renal dysfunction who also have congestive heart failure, ascites, or systemic lupus erythematosus. [51]

Derivatives of arachidonic acid that induce vasoconstriction may be important in pathologic states. Thromboxane (TXA_2) is derived from cyclic endoperoxides by the action of thromboxane synthetase. It induces vasoconstriction and platelet aggregation, and in the kidney it causes mesangial cell contraction. This decreases GFR by diminishing the effective glomerular surface area and filtration constant (K_f). Renal levels of thromboxane are increased in experimental acute renal failure and sepsis. In animal experiments, the administration of a specific thromboxane synthetase inhibitor prevents the deterioration in renal function induced by injection of endotoxin. Another vasoconstrictor prostaglandin, PGF_2, which acts on the thromboxane receptor, is formed when arachidonic acid is oxidized by free radicals liberated by leukostasis during acute inflammation. The leukotrienes, arachidonic acid derivatives formed by lipooxygenase, are also released from endotoxin-activated leukocytes. Like thromboxane, leukotrienes C_4 and D_4 induce mesangial cell contraction and decrease GFR.

Kinins

Kinins act as vasodilators, which enhance the actions of prostaglandins and modulate the renin-angiotensin system. [52] They closely interact with these systems. For example, kinins stimulate phospholipase A_2, and kininase (which controls intrarenal kinin concentration) is blocked by ACE inhibitors. The two important intrarenal kinins, bradykinin and kallidin, appear to decrease renal vasoconstriction induced by adrenergic hormones and angiotensin II.

Atrial Natriuretic Peptide

The potential role of an endogenous natriuretic hormone was postulated for many years before atrial natriuretic peptide (ANP) was identified. For example, in 1972 Gorfinkel et al [53] demonstrated a profound difference in the renal response to different forms of shock induced in dogs. Hypovolemic shock resulted in low atrial pressure and a rapid diminution of RBF to 10 percent of control, whereas in their cardiogenic shock model atrial pressures were elevated and RBF was preserved at 75 percent of control despite low cardiac output. This suggested that atrial distention caused the release of a renal protective hormone. In 1981 de Bold et al [54] confirmed the existence of ANP by demonstrating that an extract of atrial tissues caused natriuresis in rats. In the subsequent decades the important actions of ANP on renal hemodynamics and sodium excretion have been well characterized. [55] An entire series of peptides with a similar precursor has been identified, with a core of 25 to 28 amino acids required for ANP-like activity.

ANP is released from electron-dense granules in atrial myocytes in response to local wall stretch and increased atrial volume. [34] It dilates vascular smooth muscle through guanylate cyclase activation and formation of cyclic guanosine monophosphate (cGMP). In addition, ANP competitively blocks norepinephrine at the phospholipase C-linked receptor and induces a noncompetitive blockade to angiotensin II at the same site. It thereby reverses vascular smooth muscle constriction induced by these compounds. ANP causes a prompt, sustained increase in GFR and glomerular filtration fraction, even when RBF is not increased or when arterial pressure is decreased. This suggests that it causes afferent arteriolar dilation with or without efferent arteriolar constriction. The increased GFR increases the filtered load of sodium, but natriuresis may be due to increased medullary blood flow, which washes out the concentration gradient. [56]

The "yin and yang" of the systems controlling the internal milieu is epitomized by the release of ANP as a result of vasoconstriction and salt retention induced by epinephrine, angiotensin, aldosterone, and AVP which ultimately results in atrial stretch. ANP may have a mutually antagonistic interaction with endothelin, the

endogenous vasoconstrictor peptide produced by vascular endothelium. [34] ANP appears to oppose the renin-angiotensin-aldosterone system on several fronts (Fig. 18-17) . It inhibits renin secretion and decreases angiotensin-stimulated aldosterone release. It also inhibits aldosterone release directly at the zona glomerulosa

Figure 18-17 Interactions between ANP and the renin-angiotensinaldosterone system. Hypotension or hypovolemia triggers release of renin from the afferent arteriole, causing the formation of angiotensin II, which stimulates release of aldosterone from the adrenal cortex. Angiotensin II and aldosterone cause vasoconstriction and sodium retention, ultimately resulting in reexpansion of the intravascular volume; this causes atrial distention, which triggers release of ANP. ANP inhibits release of renin, renin's action on angiotensinogen to form angiotensin II, angiotensininduced vasoconstriction, stimulation of aldosterone secretion by angiotensin II, and the actions of aldosterone on the collecting duct. Thus, the actions of ANP promote vasodilation and sodium excretion. Therapeutic administration of fluids to distend the atrium and release ANP is an important intervention to curtail renal vasoconstriction and sodium retention.

of the adrenal cortex and blocks the salt-retaining action of aldosterone at the distal tubule and collecting duct. It acts directly at the medullary portion of the collecting duct to inhibit NaCl reabsorption via cGMP activation. [24] ANP inhibits AVP secretion from the posterior pituitary and antagonizes its effect on the V_2 -receptor in the collecting duct, thereby promoting diuresis.

The protective role of endogenous ANP is illustrated in a study by Shannon et al, [57] who had noticed that patients undergoing mitral valve replacement appeared to have poorer urine output after cardiac surgery than those undergoing aortic valve replacement or coronary revascularization. They discovered that patients whose postoperative mean left atrial pressure declined by more than 7 mm Hg from preoperative values (which commonly occurs with correction of mitral valve disease) had significantly decreased postoperative urine sodium excretion and flow rate. Furthermore, there was a direct correlation between the quantitative decrease in left atrial pressure with surgery and a postoperative decline in circulating ANP levels (Fig. 18-18) (Figure Not Available) . In other words, patients with mitral valve disease and high left atrial pressure have a constant stimulus to ANP release. Valve replacement or repair results in decreased left atrial pressure, decreased ANP, and declining salt excretion and urine flow rate.

Exogenous administration of ANP decreases systemic blood pressure, probably through venodilation and decreased cardiac preload. It increases GFR, induces natriuresis, and can also reverse renovascular hypertension. Urodilatin, an ANP congener produced by the kidney and excreted in the urine, lacks the systemic vasodilator effects of the parent compound but has similar action on renal function.

There has been considerable interest in the ability of infused ANP to reverse established acute renal failure (ARF) ("renal rescue"). Animal studies of both ischemic [58] [59] and nephrotoxic [60] ARF have demonstrated that ANP infusion improves RBF and GFR, induces natriuresis, and decreases azotemia and renal histologic damage.

In a small uncontrolled human study, Cedidi et al [61] infused urodilatin in eight patients with oliguric ARF after liver transplantation. Blood pressure remained stable, but central venous pressure declined, all patients developed a marked natriuresis within 2 to 4 hours, and in 6 patients hemodialysis was avoided. In a controlled pilot study [62] on 53 patients with established intrinsic ARF, ANP infusion doubled creatinine clearance from 10 to 21 mL/min in 24 hours and decreased the incidence of dialysis from 52 to 23 percent ($P < .05$). This was followed by a large randomized, controlled, multicenter study in which 504 patients were prospectively identified as having oliguric (urine output <400 mL/d) or nonoliguric acute tubular necrosis (ATN). [63] Anaritide, a 25-amino acid synthetic analog of ANP, or placebo was infused for 24 hours. In patients with oliguric ARF, anaritide infusion induced significantly greater dialysis-free survival than in those with placebo, 27 versus 8 percent ($P < .008$). However, in nonoliguric ARF anaritide actually appeared to worsen survival (48% versus 59% with placebo). It is noteworthy that in the nonoliguric patients anaritide induced a decrease in blood pressure and urine flow rate, whereas in the oliguric patients blood pressure was less affected, and urine flow rate increased. This suggests

Figure 18-18 (Figure Not Available) Correlation between left atrial pressure and plasma ANP in a group of patients undergoing cardiac surgery. (A) There is significant correlation (r = 0.8, $P < .001$) between absolute preoperative left atrial pressure and plasma ANP. (B) There is a significant correlation (r = 0.72, $P < .002$) between the postoperative decrease in left atrial pressure and postoperative decrease in plasma ANP, ANF, atrial natriuretic factor, synonymous with ANP. Delta, change. *(From Shannon et al [57])*

that there may be intrinsic pathologic differences between oliguric and nonoliguric ATN. It also emphasizes the importance of maintenance of renal perfusion pressure in ARF, given the loss of renal autoregulation that occurs. [6]

The Dopaminergic System

There are two subtypes of dopaminergic (DA) receptors. [64] At the end-organ, DA_1 -receptors occur not only on the renal and splanchnic vasculature but also on the proximal tubule itself. [65] Stimulation of the DA_1 -receptor causes renal vasodilation, increased RBF and GFR, natriuresis, and diuresis. Neuronal DA_2 -receptors exist on the presynaptic

TABLE 18-2 -- Dopaminergic Agonists and Antagonists

RECEPTOR	AGONIST	ANTAGONIST
DA_1 , DA_2	Dopamine	Haloperidol, chlorpromazine, metoclopromide
DA_1	Fenoldopam	SCH 23390
DA_2	Bromocriptine	Domperidone

DA_1 = dopamine-1 receptor. DA_2 = dopamine-2 receptor. Dopamine is a nonselective dopaminergic agonist; haloperidol, chlorpromazine, and metoclopromide are nonselective dopaminergic antagonists (the clinical importance of this property is not known). Fenoldopam is a selective DA_1 -receptor agonist, which shows promise as a vasodilator agent that preserves renal blood flow. Bromocriptine is a selective DA_2 - receptor agonist used in Parkinson's disease to enhance central dopaminergic activity. SCH 23390 and domperidone are selective DA_1 - and DA_2 -receptor antagonists.

terminal of postganglionic sympathetic nerves. Stimulation inhibits the release of norepinephrine from presynaptic vesicles, a mechanism analogous to stimulation of the presynaptic alpha$_2$ -receptor. Through inhibition of norepinephrine, DA_2 -receptor activation facilitates vasodilation. Dopaminergic agonists and antagonists may be classified on the basis of their selective or nonselective action on DA_1 - and DA_2 - receptors (Table 18-2) .

Dopaminergic receptors form an integral part of the endogenous vasodilator-natriuresis system. Dopamine produced in the kidney acts as a natriuretic hormone by inhibiting tubular Na^+ -K^+ -ATPase activity. It appears to constitutively activate the DA_2 -receptor, which then synergistically enhances the activation of the DA_1 -receptor. [66] It has been suggested that decreased dopaminergic activity contributes to the pathogenesis of idiopathic edema, which manifests as retention of salt and water in the upright position. [67]

Dopamine

Low-dose dopamine (1-3 mug/kg/min) has a nonselective agonist effect on DA_1 - and DA_2 -receptors, causing renal and splanchnic vasodilation. [68] [69] Its action may also involve inhibition of sodium reabsorption by the proximal tubule, resulting in brisk saliuresis. [65] When dopamine was compared with dobutamine in equi-inotropic doses after cardiac surgery, effects on GFR, effective RPF, renal vascular resistance, and FF were similar. However, dopamine caused greater urine flow rate, natriuresis, fractional excretion of sodium, and potassium excretion, suggesting that tubular dopaminergic receptors exist. [70] Dopamine has also been shown to block the renal vasoconstrictor effects of norepinephrine. [25]

Clinically, dopamine is indicated as a diuretic when urine output is low (<0.5 mL/kg/h) despite apparently adequate intravascular volume and cardiac output. Dopamine's effectiveness is limited by its mixed adrenergic activity, with overlapping dose-response curves. From 3 to 10 mug/kg/min beta $_1$ -adrenergic effects predominate but can cause unwanted tachycardia even at lower doses. At doses above 10 mug/kg/min, dopamine has an increasing activity on the alpha $_1$ -adrenergic receptor. In part this is due to its biotransformation to norepinephrine. The net effect is progressive renal vasoconstriction and diminished urine flow rate. Haloperidol, chlorpromazine, and metoclopramide are nonselective dopaminergic antagonists, but there are few data on their clinical inhibition of dopamine action. [71]

There are few data on the perioperative protective effect of low-dose dopamine. Dog studies did not demonstrate any improvement in RBF, GFR, or urine flow rate when low-dose dopamine was infused during thoracic aortic cross-clamping. [72] Dopamine does not significantly increase GFR or RBF in chronic renal insufficiency when the baseline GFR is less than 50 mL/min/1.73M^{-2} . [73] In a retrospective study on patients undergoing orthotopic liver transplantation, prophylactic low-dose dopamine decreased the incidence of dialysis-dependent ARF from 27 to 9.5 percent of patients. [74] In a subsequent controlled prospective study, Swygert et al [75] failed to find that it had any benefit on intraoperative urine flow, postoperative creatinine clearance, ARF, or mortality. Grundmann et al [76] randomized 50 cadaveric kidney graft recipients into two equal groups; one received dopamine 2 mug/kg/min for 4 days. Although the dopamine group had higher urine flow, postoperative creatinine clearance and requirement for dialysis were identical. Moreover, dopamine frequently caused tachycardia.

Dopexamine

Dopexamine is a synthetic analogue of dopamine. It is a potent beta $_2$ -receptor agonist and nonselective dopaminergic agonist, with about one-third of dopamine's effect on the renal vasculature [77] (Table 18-3) . Its effects are predominantly chronotropic, with moderate inotropic effect and intense arterial vasodilation (inodilation). Used in the dose range of 1 to 5 mug/kg/min, it provides left and right ventricular afterload reduction in acute and chronic heart failure while augmenting RBF. [78] Tachycardia is common, but tachyarrhythmias are not. Potential advantages include improved myocardial efficiency through its vasodilator and lusitropic actions (enhanced diastolic relaxation and decreased wall stress) while it promotes renal perfusion. Dopexamine provides the pharmacologic profile of a phosphodiesterase inhibitor such as amrinone, with the rapid onset and offset of action of a catecholamine.

Fenoldopam

Fenoldopam, a benzazepine dopamine analogue, is a selective DA $_1$ -receptor agonist and is devoid of DA$_2$ -, beta-, or alpha-adrenergic activity. When administered between 0.03 to 0.3 mug/kg/min, there is a dose-related increase in renal

TABLE 18-3 -- Dopamine Derivatives

RECEPTOR	DA$_1$	DA$_2$	beta $_1$	beta $_2$	alpha $_1$
Dopamine	+++	++	++	±	+++
Dobutamine	0	0	+++	++	±
Dopexamine	++	+	±	+++	0
Fenoldopam	++++	0	0	0	0

DA$_1$ = dopamine-1 receptor, DA$_2$ = dopamine-2 receptor, beta$_1$ = beta-1 receptor, beta$_2$ = beta-2 receptor, alpha$_1$ = alpha-1 receptor.

blood flow and natriuresis. In vitro, it antagonizes norepinephrine-induced vasoconstriction. It is rapidly metabolized, with a half-life of 10 minutes, and when administered by intravenous infusion has a rapid onset and offset of effect.

Fenoldopam is as effective as sodium nitroprusside in controlling severe hypertension, but unlike nitroprusside it induces significant increases in GFR, urine flow, and saliuresis, without rebound hypertension. [79] [80] [81] In 1998 fenoldopam was approved for the short-term parenteral treatment of severe hypertension. The selective DA$_1$ -receptor agonist activity of fenoldopam suggests that it may confer protection against nephrotoxic or ischemic renal insults without the beta-adrenergic side effects of dopamine. [82] At present this remains a theoretical rather than practical concept.

PERIOPERATIVE ISCHEMIC AND NEPHROTOXIC INJURY

This section will review perioperative agents and events that may disrupt normal renal physiology. If the disruption is severe enough or occurs in susceptible individuals, it may induce ischemic or nephrotoxic renal injury.

Perioperative Events

Anesthetic Agents

The choice of an anesthetic technique to preserve renal function during and after surgery is predicated on the preservation of RBF and perfusion pressure, the suppression of vasoconstrictor, salt-retaining stress responses to surgical stimulation and postoperative pain, and the avoidance or curtailment of nephrotoxic insults. No single anesthetic drug alone meets these criteria.

Regional Anesthesia

Spinal or epidural anesthesia (Ch. 42) that achieves sympathetic blockade of the fourth through tenth thoracic segments is extremely effective in suppressing the sympathoadrenal stress response and release of catecholamines, renin and AVP. During major surgery, RBF and GFR are preserved as long as adequate renal perfusion pressure is maintained. [83] [84] [85] This implies careful titration of the block, especially in elderly patients with cardiovascular disease, and a 25- to 50-percent increase in intraoperative fluid requirement. [86] However, Gamulin et al [87] found that renal sympathetic blockade obtained by epidural anesthesia did not block increases in renal vascular resistance induced by infrarenal aortic cross-clamping nor did it prevent postoperative decreases in creatinine clearance.

General Anesthesia

The overall effect on renal function of anesthetic drugs in common use (Chs. 6 and 34) has been well summarized by Priano. [31] All anesthetic techniques and agents tend to decrease GFR and intraoperative urine flow. Some drugs also decrease RBF, but FF is usually increased, which implies that angiotensin-induced efferent arteriolar constriction limits the decrease in GFR. However, these effects are much less significant than those caused by surgical stress or aortic cross-clamping, and after emergence from anesthesia usually resolve promptly. Any anesthetic technique that induces hypotension will result in decreased urine flow because of altered peritubular capillary hydrostatic gradients, regardless of the maintenance of RBF and GFR by autoregulation (which is usually preserved during anesthesia). Permanent injury seldom results, unless the kidneys are abnormal to begin with or the hypovolemic insult is prolonged and exacerbated by nephrotoxins.

Halothane, enflurane, or isoflurane with nitrous oxide induce mild to moderate reductions in RBF and GFR, primarily due to their effects on the central circulation (myocardial depression, peripheral pooling). [88] [89] These effects can be modified by prior hydration. [90] High-dose opioid techniques using fentanyl or sufentanil do not depress myocardial contractility and have minimal effect on RBF and GFR. They are considerably more effective in suppressing the release of catecholamines, angiotensin II, aldosterone, and AVP during surgery than are volatile agents. However, during cardiopulmonary bypass both AVP and catecholamine levels rise markedly despite high-dose opioid anesthesia. [91] [92] [93] Intravenous agents such as thiopental and diazepam cause minor changes in renal function, about 10 to 15 percent deviation from control. Ketamine increases RBF but decreases urine flow rate, possibly through sympathetic activation; it preserves RBF during hemorrhagic hypovolemia. [94]

Nephrotoxicity of Volatile Anesthetics

The potential nephrotoxicity of volatile anesthetics (Ch. 6) is due to their metabolic production of free fluoride ions, which cause a tubular lesion that results in loss of concentrating ability and polyuric acute renal failure. [95] Toxicity is exacerbated by aminoglycosides or prior renal dysfunction. Peak fluoride levels less than 50 mum/L seldom induce injury, whereas levels >150 mum/L are associated with a high incidence of polyuric acute renal failure. [96] Administration of methoxyflurane at more than 1 minimum alveolar concentration (MAC) for more than 2 hours is capable of generating a peak fluoride level greater than 100 mum/L; for this reason, this anesthetic is no longer used. Enflurane is metabolized more rapidly, and most studies have indicated that peak fluoride levels seldom rise above 25 mum/L. However, the antituberculotic agent isoniazid enhances fluoride production. Only isolated reports of fluoride-induced nephrotoxicity due to enflurane have appeared. [97] [98] Isoflurane produces peak fluoride levels less than 4 m/L, and halothane is not metabolized to fluoride at all. [99]

The potential nephrotoxicity of sevoflurane remains controversial. Although its metabolism generates more fluoride than enflurane, clinically significant fluoride-induced nephrotoxicity has not been detected. Compound A, a vinyl ether formed by degradation of sevoflurane at low flow through carbon dioxide absorbents, is capable of inducing renal injury in rats. Although ARF has not been reported in humans, Eger et al reported evidence of transient renal injury

(albuminuria, tubular enzymuria) in volunteers subjected to 8 hours of 1.25 MAC sevoflurane at 2 L/min gas flow. There were no changes in urinary concentrating ability, serum creatinine, or blood urea nitrogen (BUN).

Eger's findings have been disputed by other laboratories. Bito et al compared 6-hour patient exposure to low- and high-flow sevoflurane and low-flow isoflurane exposure and found no differences in BUN, creatinine, or tubular enzymes for 3 days postoperatively. [100] Kharasch et al [101] had similar results with the use of sevoflurane or isoflurane at 1 L/min in 73 patients undergoing procedures lasting longer than 2 hours, and they concluded that moderate duration of low-flow sevoflurane anesthesia, even with the formation of compound A, is as safe as low-flow isoflurane anesthesia. [101] Ebert et al [102] attempted to duplicate the original 8-hour Eger sevoflurane study in volunteers at two sites with blinded laboratory analyses. [102] Biochemical derangements were minimal and transient, and there were no significant changes in BUN, creatinine, or creatinine clearance. Despite the similarity in experimental design, the mean level of compound A was about 25 percent lower, and the mean arterial pressure about 10% higher than the Eger study and may have accounted for the difference in results.

Subsequently, Eger et al [103] described a dose-response relationship between biochemical markers of glomerular and tubular injury (urinary albumin, alpha-glutathione-Stransferase) and compound A exposure expressed as parts per million-hours (ppm/h). They suggested that the threshold of renal injury is 80 to 168 ppm/h; they observed alteration in biochemical markers with 1.25 MAC sevoflurane at 2 L/min for 4 hours (but not for 2 hours) and none with desflurane.

In summary, clinically significant renal injury with the use of low-flow sevoflurane anesthesia has not been reported in patients, even with moderate preexisting renal dysfunction. The relationship between compound A formation, biochemical injury, and clinically relevant renal dysfunction remains unclear and unproven. Nonetheless it appears prudent to follow current FDA guidelines, which recommend a fresh gas flow of at least 2 L/min to inhibit compound A formation and rebreathing and to

enhance its washout.

Positive Pressure Ventilation

Positive pressure ventilation (Ch. 72) and positive endexpiratory pressure (PEEP) decrease RBF, GFR, sodium excretion, and urine flow rate. [104] [105] The extent of depression of renal function depends on the mean airway pressure. Thus, the impact on the kidney is greater with inverse ratio ventilation than with intermittent mandatory ventilation (IMV) and greater with IMV than spontaneous ventilation with PEEP (continuous positive airway pressure).

These changes are largely mediated by transmission of airway and intrapleural pressures to the intravascular space, leading to decreases in venous return, transmural (i.e., effective) cardiac filling pressures, and cardiac output. Transmission may actually be attenuated in acute lung injury because of poor lung compliance. High levels of mean airway pressure may compress the pulmonary arterial circulation, increase right ventricular afterload, and induce the intraventricular septum to shift into the left ventricle and decrease its filling and cardiac output. [106] Positive pressure ventilation increases inferior vena caval pressure and renal venous pressure and might increase tubular sodium reabsorption by increases in peritubular capillary pressure.

The decrease in cardiac output and systemic arterial pressure results in a carotid and aortic baroreceptor-mediated increase in sympathetic nerve tone to the kidney, with renal vasoconstriction, antidiuresis, and antinatriuresis. Volume receptors in the atria respond to decreased filling by decreased ANP secretion, resulting in increased sympathetic tone, renin activation, and AVP activity.

Salt and water retention during airway pressure therapy was originally thought to be due to an AVP effect, [107] but it is now considered that sympathetic responses are more important and that sodium retention is largely the result of decreased sodium delivery to the tubules. The reninangiotensin-aldosterone system undoubtedly augments the renal responses to positive pressure ventilation. Annat et al [108] found that 15 cm H_2O PEEP depressed cardiac output, RBF, GFR, and urine volume by 20 to 30 percent and was associated with increases in renin and aldosterone but not AVP. The impairment in renal function induced by airway pressure therapy can be prevented or reversed by preserving normal circulatory status, either by hydration or by use of dopamine. [109] [110]

Induced Hypotension

During anesthesia with induced hypotension (Ch. 41) , substantial reduction of GFR and urine flow rate is common. However, when the duration of hypotension is less than 2 hours, no permanent impairment of renal function occurs, even in elderly patients. [111] Vasodilator agents used to induce hypotension differ in their effect on RBF. The ganglionic blocker trimethaphan camsylate abolishes autoregulation and causes the greatest decrease in RBF. [112] Sodium nitroprusside has a lesser impact on renal vascular resistance, but its administration is associated with marked renin-angiotensin activation and catecholamine release (inhibited by propranolol), which results in rebound hypertension if the infusion is suddenly discontinued. [113] Nitroglycerin decreases RBF less than sodium nitroprusside. [114] The selective DA_1 -dopaminergic agonist fenoldopam is capable of providing induced hypotension without any significant decrease in RBF. [115]

Aortic Cross-Clamping

The effects of suprarenal and infrarenal aortic cross-clamping (Ch. 51) on renal function in patients undergoing major vascular surgery were compared by Myers et al. [21] Regardless of the position of the aortic cross-clamp, RBF was decreased to 50 percent of normal during surgical preparation of the aorta, presumably due to direct compression or reflex spasm of the renal arteries. After release of the suprarenal cross-clamp, RBF increased above normal (reflex hyperemia), but GFR remained depressed to one-third of control for up to 2 hours. After 24 hours GFR was still only two-thirds of control. Tubular functions (concentrating ability, sodium and water conservation) were markedly impaired,

but urine flow was maintained. Myers and Moran [116] observed that these changes resembled an attenuated form of acute tubular necrosis. All patients received mannitol pretreatment, which probably limited the tubular insult because oliguria was uncommon and recovery was relatively rapid. However, cross-clamp times longer than 50 minutes were associated with prolonged depression of GFR and transient azotemia.

Infrarenal aortic cross-clamping may also impair RBF and GFR by inducing decreases in cardiac output in response to increased systemic vascular resistance. [117] Atheromatous embolism of the renal arteries may be induced by cross-clamping or manipulation in areas of dense aortic plaque. Partial or complete cortical necrosis may occur, which is usually irreversible.

Renal Protection During Aortic Cross-Clamping

Mannitol has been used for more than 40 years to provide renal protection during aortic cross-clamping. [118] Its protective effects have been clearly demonstrated in animal models of ischemic acute tubular necrosis (ATN), [119] but few prospective controlled human studies exist. Low-dose dopamine is also commonly used during major vascular surgery, but in an animal study of thoracic aortic cross-clamping it did not prevent the impairment and delayed recovery of RBF, GFR, and urine flow observed after cross-clamp release. [72] In a human study of infrarenal cross-clamping, Paul et al [120] compared diuretic therapy with a combination of mannitol and dopamine versus fluid loading with saline to a pulmonary artery occlusion pressure (PAOP) of 12 to 15 mm Hg. Although mannitol and dopamine substantially increased urine flow and sodium excretion during cross-clamping, they were no better than saline on attenuating residual GFR depression after cross-clamp release.

Cardiopulmonary Bypass

Cardiopulmonary bypass (Ch. 49) induces hypotension with nonpulsatile flow, which promotes renal vasoconstriction and decreased RBF. Norepinephrine levels increase progressively during bypass, and the renin-angiotensin system is activated. Acute renal failure has been associated with persistent elevation of plasma renin levels. [121] Thromboxane, released from activated platelets, and vascular elaboration of endothelin could possibly contribute to renal vasoconstriction during extracorporeal circulation. Tubular enzymuria and microalbuminuria, an index of subclinical injury to the nephron, is consistently observed during cardiopulmonary bypass. [122] Despite these observations, the incidence of acute renal failure remains less than 2 percent of all patients. Nonetheless, when it does occur after cardiac surgery, ARF is associated with a forbidding mortality rate--60 to 90 percent.

Renal Protection During Cardiopulmonary Bypass

Pulsatile perfusion during cardiopulmonary bypass does not appear to offer an advantage with respect to RBF or catecholamine release. Although plasma renin activity is suppressed by pulsatile perfusion, microalbuminuria persists, and there is no evidence that outcome is better. [123] Badner et al [124] found no difference in postoperative renal function in a group of patients with normal kidneys undergoing pulsatile or nonpulsatile CPB. Case series that claim that pulsatile CPB confers protection to patients with chronic renal insufficiency undergoing cardiac surgery do exist, but unfortunately they are neither randomized nor prospective. [125] [126]

It has been observed in animal studies of cardiopulmonary bypass that RBF is dependent on renal perfusion pressure, and infusion of dopamine does not increase RBF during low pressure states. [7] This suggests that autoregulation may be impaired during cardiopulmonary bypass. However, Hilberman et al [127] found no relationship between low flow (<50 mL/kg/min) and mean arterial pressure (<50 mm Hg) and postoperative ARF. Instead, the severity of postoperative renal dysfunction and its outcome correlated with the severity of cardiac dysfunction after cardiopulmonary bypass. [128]

Other important risk factors for postoperative renal dysfunction after cardiac surgery include the complexity of surgery (e.g., combined procedures versus simple revascularization) and preoperative renal function. In a prospective review of more than 4,000 cases at the Cleveland Clinic, Higgins et al [129] demonstrated that the risk of renal morbidity and mortality increases exponentially when the preoperative serum creatinine is greater than 1.9 mg/dL.

There is little evidence that the "prophylactic" administration of low-dose dopamine has a protective role during cardiopulmonary bypass in patients with normal [130] or impaired renal function [131] undergoing cardiac surgery. Moreover, dopamine may induce tachycardia even in the low-dose range and is associated with a higher incidence of supraventricular and ventricular arrhythmias. [132]

Nephrotoxic Insults

Drug-Induced Nephrotoxicity

Nephrotoxic injury by drugs (aminoglycosides, cyclosporin A, amphotericin B, cisplatinum, etc.) or contrast dyes seldom occurs unless coexisting risk factors exist. [9] These may be acute (shock, hypovolemia, congestive heart failure) or chronic (advanced age, diabetes, chronic renal insufficiency). The risk of nephrotoxicity increases exponentially with the number of risk factors and nephrotoxic combinations.

Nephrotoxic acute renal failure is usually nonoliguric, with loss of concentrating ability and slowly progressive azotemia. As GFR declines, toxic serum levels of renally excreted drugs exacerbate nephrotoxicity unless drug levels are carefully monitored and dosage repeatedly adjusted. However, the prognosis for recovery is good if these agents are discontinued in time and no coexistent organ failure exists.

Aminoglycosides

Polycationic aminoglycosides (gentamicin, tobramycin, amikacin) are filtered into the proximal tubule, where they bind to the anionic brush-border membrane phospholipids.

Their nephrotoxicity is directly related to their polycationic status; neomycin (six cationic sites) is more destructive than gentamicin (five sites) or streptomycin (three sites). [133] They are absorbed into intracellular lysosomes by endocytosis and thence released into the cytosol. Within the cell they induce defects in lysosomes, plasma membranes, and mitochondria and, in particular, inhibit oxidative phosphorylation and the synthesis of high-energy phosphate compounds such as ATP.

Aminoglycoside-induced nephrotoxicity is directly related to sustained high-trough serum levels, especially when associated with advanced age, preexisting renal disease, renal vasoconstrictive states (sepsis, hypovolemia, liver disease, congestive heart failure), adjuvant drug therapy (loop diuretics, vancomycin, cephalosporins, NSAIDs, cyclosporin A, amphotericin B), and electrolyte disorders (hypokalemia, hypomagnesemia, hypercalcemia, and metabolic acidosis). [134] A vicious cycle may develop because as the GFR declines secondary to nephrotoxicity, aminoglycoside is retained and exacerbates renal injury.

Prevention of aminoglycoside nephrotoxicity depends on maintenance of adequate hydration, avoidance or removal of the risk factors enumerated above, and careful monitoring of serum aminoglycoside levels. A daily 2-hour creatinine clearance can also be helpful in the early detection of aminoglycoside-induced nephrotoxicity and appropriate dose adjustment for GFR. Once-daily administration of aminoglycosides to achieve a high therapeutic level with an adequate trough period for renal recovery may limit the occurrence of nephrotoxicity. [135] Low-dose dopamine increases renal clearance of aminoglycosides, but it is not known whether this protects against tubular injury.

Cyclosporine A

Cyclosporine A is a remarkably potent immunosuppressive agent and, together with steroids and azathioprine, is routinely used to prevent rejection after organ transplantation. Indeed, heart, lung, and liver transplantation increased exponentially after its release in 1981. It causes renal injury in part because it induces sympathetic hyperreactivity, hypertension, and renal vasoconstriction. Its nephrotoxic effects are exacerbated by preexisting renal dysfunction, hypovolemia, and other nephrotoxic insults. Many transplant patients must tolerate a moderately elevated serum creatinine (1.5-2 mg/dL) in order to sustain adequate immunosuppression. A number of alternative immunosuppressive agents (e.g., CellCept) have been developed in an effort to decrease or eliminate cyclosporine requirement.

Radiocontrast Dyes

The nephrotoxicity of dyes probably involves microvascular obstruction by crenated red cells as well as direct tubular toxicity. The risk is markedly increased in diabetic renal insufficiency, hypovolemia, congestive heart failure, and myeloma. [136] [137] Radiocontrast dyes are hypertonic and cause an osmotic diuresis, which induces a false sense of security but exacerbates hypovolemia and renal damage. Azotemia commences 24 to 48 hours after exposure and peaks at 3 to 5 days. Surgery performed during this period greatly increases the risk of perioperative acute renal failure.

Prevention of nephrotoxicity depends on adequate hydration with or without intravenous mannitol during the study and deferral of elective surgical procedures until the effects of the dye have been evaluated and treated. [138] [139] Calcium channel blockers appear to be protective (see below). Nonionic, low-osmolar radiocontrast agents have been developed, but they are quite expensive and appear to offer the best cost-benefit ratio when used in high-risk situations only, e.g., diabetic nephropathy. [135]

Role of Calcium Channel Blockers

Calcium channel blockers prevent ischemic renal injury by a number of mechanisms, including the prevention of reflow-induced vasoconstriction after ischemia, inhibition of angiotensin action in the glomerulus, and decrease in circulating interleukin-2 receptors. [140] They may reduce the accumulation of oxygen-free radicals and reperfusion injury through prevention of intracellular calcium influx and the calcium/calmodulin-dependent conversion of xanthine dehydrogenase to xanthine oxidase.

However, calcium blockers may overcome renal autoregulation and worsen renal function when they induce hypotension. Administration of nifedipine to patients with renal insufficiency has been reported to cause nonoliguric renal failure that improved when the drug was discontinued. [141] In contrast, in hypertensive patients diltiazem and nifedipine promoted natriuresis and increased RBF and GFR. [142]

Calcium channel blockers confer important protection against nephrotoxins such as cyclosporin, cisplatinum, and radiocontrast dyes. [143] [144] [145] [146] [147] In patients undergoing cadaveric renal transplantation, diltiazem was added to the graft preservative solution, infused into the donor for 48 hours, and then given orally. [143] The incidence of transplant acute tubular necrosis (ATN) decreased from 41 to 10 percent, and when ARF did occur, hemodialysis requirement was significantly less. Diltiazem impairs cyclosporin metabolism so that plasma cyclosporin levels are higher, with fewer episodes of early acute rejection, but it protects against cyclosporin nephrotoxicity. [147] Cyclosporin dosage may be reduced by 30 percent to achieve the same drug levels, representing a substantial cost-savings to patients.

Pigment Nephropathy

Pigment nephropathy implies acute renal injury due to the nephrotoxic effect of the heme pigments myoglobin, hemoglobin, and bilirubin.

Rhabdomyolysis and Myoglobinemia

Muscle necrosis (rhabdomyolysis) occurs most commonly with direct trauma involving major crush or thermal injury. However, it also occurs with acute muscle ischemia induced by vascular disease or injury or by prolonged immobilization. Compartment syndromes exacerbate rhabdomyolysis. They are particularly likely to occur with major hemorrhage in an extremity or when vascular insufficiency coexists with tissue edema (e.g., femoral placement of an intra-aortic balloon after vein harvesting). Dramatic increases in metabolic

rate (caused by severe prolonged fever, status epilepticus or myoclonus, or severe exercise with hypokalemia), severe hypophosphatemia, or direct proteolysis (as in

acute pancreatitis) can all precipitate rhabdomyolysis. [148]

Myoglobin, the oxygen-carrying heme pigment of muscle, is released into the blood stream (myoglobinemia) and rapidly excreted by the glomerulus at a plasma threshold of 0.03 mg/dL. Delivery of myoglobin to the proximal tubule is greater in a well-muscled individual with normal GFR than in a cachectic patient with low GFR. At a urine pH less than 5.6, myoglobin is transformed into ferrihematin, which precipitates in the proximal tubule. [149] Renal damage is facilitated by hypovolemia (i.e., low tubular flow) and acidic urine. Because of the associated hypercatabolic state, oligoanuria is associated with acute hyperkalemia, hypocalcemia, anion-gap metabolic acidosis, and rapid azotemia. Serum creatinine and BUN increase very rapidly (1.0-1.5 mg/dL/d and 20-30 mg/dL/d, respectively).

The most important aid to the diagnosis of rhabdomyolysis is a high index of suspicion. The affected muscle may be obviously ischemic or swollen, painful, and edematous. Urine myoglobin often tests positive without reddish urine. The serum is clear because of the low renal threshold for myoglobin excretion, whereas hemoglobinemia is associated with pink serum. Serial total creatinine phosphokinase (CPK) is a helpful guide to the severity of rhabdomyolysis (i.e., CPK-MM release). [150] Renal damage is much more likely when total CPK exceeds 10,000 U/L.

Prevention of acute nephrotoxic tubular necrosis is dependent on the maintenance of high RBF and tubular flow. Urine flow should be kept between 100 to 150 mL/h by osmotic diuresis with intravenous mannitol, 6.25 to 12.5 g every 6 hours, with or without intravenous furosemide, 10 to 20 mg as required. [151] Urine pH should be kept above pH 5.6 with intravenous sodium bicarbonate, 50 mEq intravenously, as required, and/or acetazolamide, 250 mg every 6 hours. However, because there are no prospective data that confirm the beneficial effect of urinary alkalinization, urine pH should not be increased at the expense of causing significant acid-base imbalance. Calcium should be given to treat hyperkalemia only.

Hemolysis and Hemoglobinemia

Acute intravascular hemolysis due to mismatched blood transfusion (ABO incompatibility) represents a direct and devastating renal insult. Renal damage is thought to be predominantly due to red blood cell stroma rather than to free hemoglobin. Management is essentially the same as for rhabdomyolysis.

Jaundice and Bilrubinemia

There is a direct correlation between the degree of preoperative obstructive jaundice and postoperative renal dysfunction. [152] [153] When cholestasis causes the conjugated bilirubin to increase above 8 mg/dL, bile salt excretion effectively ceases, resulting in portal septicemia and renal damage. This situation is analogous to hepatorenal syndrome and sepsis, in which circulating endotoxins induce renal vasoconstriction and damage (vasomotor nephropathy).

Perioperative protection in jaundiced patients may be provided by giving preoperative oral bile salts (e.g., sodium taurocholate) or intravenous mannitol. In a prospective, randomized study on patients with obstructive jaundice undergoing surgery, Plusa and Clark [154] found no difference in renal outcome between these two regimens. However, mannitol provokes a brisk osmotic diuresis, and it is important to replace urinary losses appropriately. Diuresis-induced hypovolemia negates the protective effect of mannitol. [155] Parks et al [153] reported a prevalence of postoperative oliguria of less than 20 percent of jaundiced patients who received 3 L intravenous crystalloid preoperatively and who were given furosemide with or without low-dose dopamine intraoperatively.

Sepsis

Sepsis is the most common cause of new onset ARF in the postoperative period. [156] Renal function may deteriorate progressively without defined episodes of hypotension. In addition, sepsis predisposes the kidney to further ischemic and nephrotoxic insults; for example, from concomitant aminoglycoside usage. [157] [158] ARF itself and hemodialysis perpetuate sepsis by activating leukocytes. Sepsis may induce renal damage by hypotension and vasomotor nephropathy and through the direct and indirect effects of endotoxin.

There is a reasonable amount of evidence to suggest that renal autoregulation may be impaired in sepsis and that RBF and GFR decline *pari passu* with systemic vascular resistance and mean arterial pressure. Hypotension in turn sets off a cascade of neurohormonal responses (sympathoadrenal activity; renin-angiotensin, vasopressin, and thromboxane activation) that result in decreased RBF, GFR, sodium excretion, and urine flow. The severity of renal dysfunction appears to be directly related to the severity of sepsis and the degree of plasma renin activation. [159]

Renal dysfunction in sepsis is characterized as a vasomotor nephropathy, which implies renal vasoconstriction in the face of increased total cardiac index. Renal vasoconstriction, mesangial cell contraction, decreased ultrafiltration coefficient, and decreased GFR are induced by endotoxin and by compounds activated in sepsis. [160] These include endothelin and eicosanoids, such as thromboxane, prostaglandin F_2, and the leukotrienes C4 and D4. Prostaglandin F_2, which mimics the action of thromboxane, is formed during leukostasis when arachidonic acid is oxidized by free oxygen radicals.

Endotoxin causes leukocyte arachidonic acid to undergo lipooxygenation to form leukotrienes; it also impairs their biliary elimination. In addition, experimental infusion of lipopolysaccharide (endotoxin) directly decreases RBF, GFR, and tubular concentrating ability and increases urinary loss of tubular enzymes. It causes sequestration of leukocytes in peritubular capillaries, induces endothelial lesions by releasing neutrophil-derived elastase (enhanced by reperfusion injury), and potentiates renal ischemia such that brief hemodynamic instability causes rapid loss of renal function. It also potentiates nephrotoxicity. The changes caused by endotoxin are mimicked by the cytokine, tumor necrosis factor-alpha.

It has been estimated that about 10 to 26 percent of septic patients receiving aminoglycoside antibiotics (gentamicin, tobramycin and amikacin) will develop nephrotoxic renal insufficiency. [161] Aminoglycosides are filtered into the proximal tubule, bind to the anionic brush-border membrane phospholipids, become absorbed by endocytosis into intracellular lysosomes, and are released into cytosol. There, they damage lysosomes and membranes, inhibit mitochondrial oxidative phosphorylation, and deplete tubular ATP.

Aminoglycoside nephrotoxicity is enhanced by the interaction of fever, renal vasoconstriction, hypovolemia, and endotoxin. It is also exacerbated by toxic drug levels, prolonged therapy, concomitant drug toxicity (NSAIDs, cyclosporine A, amphotericin B), and electrolyte disorders such as hypercalcemia, hypomagnesemia, hypokalemia, and metabolic acidosis. In the presence of these risk factors, alternative non-nephrotoxic antibiotics should be considered to cover gram-negative infections, including penicillins (ticarcillin), cephalosporins (ceftazidime), carbapenems (imipenem), or monobactams (aztreonam).

Renal Protection in Septic Shock

Supranormal Oxygen Delivery

Over the last decade there has been considerable interest in the concept of supranormal oxygen delivery to the tissues to overcome the defect that exists in oxygen utilization by septic tissues. This approach utilizes inotropic support and blood transfusion to drive global oxygen delivery (DO_2) to one of three end points: (1) DO_2 reaches levels consistently found in survivors, i.e., 600 mL/min/m^2; (2) global oxygen consumption (VO_2) no longer increases with increasing DO_2 (consumption independence); or (3) blood lactate levels start to decline. However, renal DO_2 and VO_2 differ markedly from systemic indices. Renal VO_2 is largely determined by tubular metabolic function, which is regulated by fluid and electrolyte changes. In a volume-loaded septic porcine model, inotropic support with dobutamine increased systemic DO_2 and VO_2 but did not increase renal DO_2 and VO_2. [26] Furthermore, decreased global renal DO_2 does not appear to cause tubular damage, possibly because tubular work and VO_2 are decreased when GFR declines. [162]

Dopaminergic Agents

Low-dose dopamine (1-3 mug/kg/min) is frequently administered to septic patients in the belief that it confers renal protection through renal vasodilation or perhaps by inhibition of the Na^+-K^+-ATPase pump and decrease in renal tubular VO_2.

It is also administered in combination with more potent pressors (dobutamine, epinephrine, and norepinephrine) in sepsis in the hope of enhancing hepatic, renal, and mesenteric perfusion. There are some animal data to support this practice. In a nonseptic dog study in which RBF was measured by thermodilution, the addition of low-dose dopamine to a norepinephrine infusion of 0.2-1.6 mug/kg/min increased RBF by 40 to 50 percent. [25] However, a subsequent study demonstrated that, although low-dose dopamine increased RBF when added to an epinephrine infusion in healthy sheep, this benefit could not be found in an intraperitoneal sepsis model. [163] Other studies have shown that low-dose dopamine can increase hepatic DO_2, possibly at the expense of splanchnic oxygenation.

In patients with sepsis syndrome (signs of sepsis without hypotension), low-dose dopamine infusion doubled urine flow rate and increased creatinine clearance by 60 percent without any change in systemic hemodynamics. [164] However, the renal response to dopamine decreased significantly after 48 hours of dopamine infusion, possibly due to downregulation of the renal dopaminergic receptors or diuresis-induced contraction of the intravascular volume. In patients with established septic shock who required catecholamines for blood pressure support, low-dose dopamine did not alter systemic hemodynamics or renal function.

The potential role of dopexamine in septic shock remains speculative. Most studies have examined its role in splanchnic and hepatic perfusion rather than in renal protection. In animal models of sepsis, it has been shown to have beneficial effects on splanchnic and hepatic DO_2, but its $beta_2$-adrenergic activity in causing tachycardia and hypotension may limit dopexamine's application in clinical sepsis. Smithies et al [165] administered dopexamine to patients with sepsis syndrome, acute respiratory failure, and at least one other organ system failure. Cardiac index increased and gastric intramucosal pH (an index of splanchnic perfusion) improved significantly.

Norepinephrine

In patients with septic shock, profound hypotension, and oliguria, vasopressor therapy with norepinephrine may actually improve renal function by enhancing renal perfusion pressure. Desjars et al [5] evaluated a group of septic patients who remained oliguric despite volume resuscitation and the use of dopamine up to doses of 15 mug/kg/min. The addition of norepinephrine and reduction of dopamine to a low-dose level resulted in an improvement in mean arterial pressure from 50 to 70 mm Hg, a tripling of urine flow, and a doubling of creatinine clearance. Norepinephrine increased the systemic vascular resistance (SVR) with little change in cardiac index or DO_2. Subsequent studies have confirmed that the use of norepinephrine to keep mean arterial pressure greater than 60 mm Hg results in improved cardiac function (increase in stroke volume and decrease in heart rate) and GFR without deleterious effects on cardiac index (CI), oxygen extraction, or VO_2. [166] These findings strongly support the concept that renal autoregulation is impaired in sepsis and that maintenance of adequate renal perfusion pressure is an important component of renal protection.

Vasopressin (AVP)

Landry et al [41] observed unusual sensitivity to the vasoconstrictor effects of infused AVP in patients with septic shock with profound hypotension despite catecholamine infusion. Plasma AVP levels were remarkably low (3.1 ± 1.0 pg/mL) and significantly lower than in a cohort of patients in cardiogenic shock also receiving catecholamines (22.7 ± 2.2 pg/mL, $P < .001$). Infusion of AVP at doses of 2.4 U/h, less

than one-tenth of those used in the treatment of bleeding esophageal varices, resulted in a dramatic increase in systolic blood pressure from 92 ± 4 to 146 ± 4 mm Hg (mean ± SEM, $P < .001$), and catecholamine infusions were able to be discontinued. In an associated report [167] the authors observed that urine flow increased concomitantly in three of five patients, from an average of 30 mL/h to 110 mL/h.

The inappropriately low plasma AVP in septic shock may be attributed to sustained baroreceptor-mediated AVP release as a response to hypotension. It is possible that upregulation of the V_1-receptor could quickly develop and explain the enhanced sensitivity to the vasoconstrictor effects of infused AVP. The beneficial effect of AVP on renal function could in part be due to enhanced renal perfusion pressure in the face of abnormal autoregulation (see above) and also due to the fact that AVP appears to preferentially constrict the efferent arteriole, thereby improving filtration fraction and GFR. [168]

Anti-Inflammatory Agents

Cumming et al [169] demonstrated a marked renal protective effect of a selective thromboxane synthetase inhibitor (U63557A) in laparotomy on a volume-loaded sheep peritonitis model. Administration of the selective inhibitor either before or 30 minutes after surgery prevented deterioration in creatinine clearance, urinary sodium excretion, and urine flow rate. Beneficial effects have also been observed with aprotonin, perhaps through its anti-inflammatory action. [170] In contrast, nonselective cyclooxygenase inhibition by NSAIDs worsens renal function in sepsis by decreasing the synthesis of the renal vasodilator prostacyclin. [47]

The use of pharmacologic doses of methylprednisolone in septic shock was discredited by two large multicenter studies showing no beneficial effect on outcome. [171] [172] Moreover, patients who received steroids had significant increases in BUN but not in serum creatinine, suggesting a prerenal state induced by increased protein catabolism. [173] Other potentially adverse effects of high-dose steroids include impaired mitochondrial function, impaired leukocyte function, and inhibition of phospholipase A_2, resulting in decreased synthesis of intrarenal vasodilator prostaglandins.

References

1. Tisher CC, Madsen KM: Anatomy of the kidney. In Brenner BM, Rector FCJ (eds): The Kidney, 4th ed. Philadelphia, WB Saunders Co., 1991, pp 3-75.

2. Stanton BA, Koeppen BM: Elements of renal function. In Berne RM, Levy MN (eds): Physiology, 3rd ed. St Louis, Mosby-Year Book, 1993, pp 719-753.

3. Maddox DA, Brenner BM: Glomerular ultrafiltration. In Brenner BM, Rector FCJ (eds): The Kidney, 4th ed. Philadelphia, WB Saunders Co., 1992, pp 215-231.

4. Shipley RE, Study RS: Changes in renal blood flow, extraction of inulin, glomerular filtration rate, tissue pressure and urine flow with acute alterations of renal artery pressure. Am J Physiol 167:676-688, 1951.

5. Desjars PH, Pinaud M, Bugnon D et al: Norepinephrine has no deleterious renal effects in human septic shock. Crit Care Med 17:426-429, 1989.

6. Kelleher SP, Robinette JB, Miller F et al: Effect of hemorrhagic reduction in blood pressure on recovery from acute renal failure. Kidney Int 31:725-730, 1987.

7. Mackay JH, Feerick AE, Woodson LC et al: Increasing organ blood flow during cardiopulmonary bypass in pigs: Comparison of dopamine and perfusion pressure. Crit Care Med 23:1090-1098, 1995.

8. Thurau K, Boylan JW: Acute renal success: The unexpected logic of oliguria in acute renal failure. Am J Med 61:308-315, 1976.

9. Brezis M, Rosen S, Epstein F: The pathophysiologic implications of medullary hypoxia. Am J Kid Dis 13:253-258, 1989.

10. Gelman S: Preserving renal function during surgery. Anesth Analg 74(suppl):88-92, 1992.

11. Levey AS, Madaio MP, Perrone RD: Laboratory assessment of renal disease: Clearance, urinalysis and renal biopsy. In Brenner BM, Rector FCJ (eds): The Kidney, 4th ed. Philadelphia, WB Saunders Co., 1991, pp 919-968.

12. Tobias GJ, McLaughlin RF, Hopper J: Endogenous creatinine clearance: A valuable clinical test of glomerular filtration and a prognostic guide in chronic renal disease. New Engl J Med 266:317-323, 1962.

13. Doolan PD, Alpen EL, Theil GB: A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 32:65-81, 1962.

14. Wilson RF, Soullier G: The validity of two-hour creatinine clearance studies in critically ill patients. Crit Care Med 8:281-284, 1980.

15. Sladen RN, Endo E, Harrison T: Two-hour versus 22-hour creatinine clearance in critically ill patients. Anesthesiology 67:1013-1016, 1987.

16. Shin B, Mackenzie C, Helrich M: Creatinine clearance for early detection of posttraumatic renal dysfunction. Anesthesiology 64: 605-609, 1986.

17. Wesson LG, Lauler DP: Diurnal cycle of glomerular filtration rate and sodium and chloride excretion during responses to altered salt and water balance in man. J Clin Invest 40:1967-1977, 1961.

18. Kim KE, Onesti G, Ramirez O et al: Creatinine clearance in renal disease. A reappraisal. BMJ 4:11-14, 1969.

19. Bjornsson TD: Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinetics 4:200-222, 1979.

20. Moran SM, Myers BD: Course of acute renal failure studied by a model of creatinine kinetics. Kidney Int 27:928-937, 1985.

21. Myers BD, Miller DC, Mehigan JT et al: Nature of the renal injury following total renal ischemia in man. J Clin Invest 73:329-341, 1984.

22. Cockroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41, 1976.

23. Robert S, Zarowitz BJ, Peterson EL et al: Predictability of creatinine clearance estimates in the critically ill. Crit Care Med 21:1487-1495, 1993.

24. Stanton BA, Koeppen BM: Control of body fluid osmolality and volume. In Berne RM, Levy MN: Physiology, 3rd ed. St Louis, Mosby-Year Book, 1993, pp 754-783.

25. Schaer GL, Fink MP, Parrillo JE: Norepinephrine alone versus norepinephrine plus low-dose dopamine: Enhanced renal blood flow with combination pressor therapy. Crit Care Med 13:492-496, 1985.

26. Haywood GA, Tighe D, Moss R et al: Goal-directed therapy with dobutamine in a porcine model of septic shock: Effects on systemic and renal oxygen transport. Postgrad Med J 67(suppl):S36-S39, 1991.

27. Aronson S, Wiencek JG, Feinstein SB et al: Assessment of renal blood flow with contrast ultrasonography. Anesth Analg 76:964, 1993.

28. Thorburn GD, Kopald HH, Herd JA et al: Intrarenal distribution of nutrient blood flow determined by krypton-85 in the unanesthetized dog. Circ Res 13:290-307, 1963.

29. Hollenberg NK, Epstein M, Rosen SM, et al: Acute oliguric failure in man: Evidence for preferential renal cortical ischemia. Medicine 47:455-474, 1988.

30. Aukland K: Methods for measuring renal blood flow: Total flow and regional distribution. Ann Rev Physiol 42:543-555, 1980.

31. Priano LL: Effects of anesthetic agents on renal function. In Barash PG (ed): Refresher Courses in Anesthesiology. Philadelphia, Lippincott, 1985, pp 143-156.

32. Schrier RW: Effects of the adrenergic nervous system and catecholamines on systemic and renal hemodynamics, sodium and water excretion and renin secretion. Kidney Int 6:291-306, 1974.

33. Levens NR, Peach MJ, Carey RM: Role of the intrarenal reninangiotensin system in the control of renal function. Circ Res 48:157-167, 1981.

34. Ballerman BJ, Zeidel ML, Gunning ME et al: Vasoactive peptides and the kidney. In Brenner BM, Rector FCJ (eds): The Kidney, 4th ed. Philadelphia, W.B. Saunders Co., 1991, pp 510-583.

35. Hricik D, Browning P, Kopelman R et al: Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. New Engl J Med 308:373-376, 1983.

36. Bender W, La France N, Walker W: Mechanism of deterioration of renal function in patients with renovascular hypertension treated with enalapril. Hypertension 6(suppl):I193-I197, 1984.

37. Colson P, Ribstein J, Mimran A et al: Effect of angiotensin-converting enzyme inhibition on blood pressure and renal function during open heart surgery. Anesthesiology 72:23-27, 1990.

38. Hays RM, Levine SD: Vasopressin. Kidney Int 6:307-322, 1974.

39. Landry DW: Vasopressin deficiency and hypersensitivity in vasodilatory shock: Discovery of a new clinical syndrome. P & S Med Rev 3:3-7, 1996.

40. Bartter FC, Schwartz WB: The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 42:790-806, 1967.

41. Landry DW, Levin HR, Gallant EM et al: Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 95:1122-1125, 1997.

42. Argenziano M, Choudri AF, Oz MC et al: A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 96 (suppl 2):286-290, 1997.

43. Mets B, Michler RE, Delphin ED et al: Refractory vasodilation after cardiopulmonary bypass for heart transplantation in recipients on combined amiodarone and angiotensin-converting enzyme inhibitor therapy: A role for vasopressin administration. J Cardiothorac Vasc Anesth 12:326-329, 1998.

44. Anggard E, Oliw E: Formation and metabolism of prostaglandins in the kidney. Kidney Int 19:771-780, 1981.

45. Lifschitz MD: Prostaglandins and renal blood flow: In vivo studies. Kidney Int 19:781-785, 1981.

46. Levenson DJ, Simmons CEJ, Brenner BM: Arachidonic acid metabolites, prostaglandins and the kidney. Am J Med 72:354-374, 1982.

47. Garella S, Matarese RA: Renal effects of prostaglandins and clinical adverse effects of nonsteroidal anti-inflammatory agents. Medicine 63:165-181, 1984.

48. Gerber JG, Olsen RD, Nies AS: Interrelationship between prostaglandins and renin release. Kidney Int 19:816-821, 1981.

49. Tobimatsu M, Konomi K, Saito S et al: Protective effect of prostaglandin E_1 on ischemia-induced acute renal failure in dogs. Surgery 98:45-52, 1985.

50. Johnston P, Bernard D, Perrin N et al: Prostaglandins mediate the vasodilatory effect of mannitol in the hypoperfused rat kidney. J Clin Invest 68:127-133, 1981.

51. Clive D, Stoff J: Renal syndromes associated with nonsteroidal antiinflammatory drugs. New Engl J Med 310:563-572, 1984.

52. Nasjletti A, Malik KU: Renal kinin-prostaglandin relationship: Implications for renal function. Kidney Int 19:860-868, 1981.

53. Gorfinkel HJ, Szidon JP, Hirsch LJ et al: Renal performance in experimental cardiogenic shock. Am J Physiol 222:1260-1268, 1972.

54. de Bold AJ, Borenstein HB, Veress AT, et al: A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 28:89-94, 1981.

55. Laragh J: Atrial natriuretic hormone, the renin-angiotensin axis, and blood-pressure electrolyte homeostasis. New Engl J Med 313: 1330-1340, 1985.

56. Maack T, Camargo MJF, Kleinert HD et al: Atrial natriuretic factor: Structure and functional properties. Kidney Int 27:607-615, 1985.

57. Shannon RP, Libby E, Elahi D: Impact of acute reduction in chronically elevated left atrial pressure on sodium and water excretion. Ann Thorac Surg 46:430-437, 1988.

58. Conger JD, Falk SA, Hammond WS: Atrial natriuretic peptide and dopamine in established acute renal failure in the rat. Kidney Int 40:21-28, 1991.

59. Atanasova I, Girchev R, Dimitrov D et al: Atrial natriuretic peptide and dopamine in a dog model of acute renal ischemia. Acta Physiologica Hungarica 82:75-85, 1994.

60. Seki G, Suzuki K, Nonaka T et al: Effects of atrial natriuretic peptide on glycerol-induced acute renal failure in the rat. Jpn Heart J 33:383-393, 1992.

61. Cedidi C, Meyer M, Kuse ER et al: Urodilatin: A new approach for the treatment of therapy-resistant acute renal failure after liver transplantation. Eur J Clin Invest 24:632-639, 1994.

62. Rahman SN, Kim GE, Mathew AS et al: Effects of atrial natriuretic peptide in clinical acute renal failure. Kidney Int 45:1731-1738, 1994.

63. Allgren RL, Marbury TC, Rahman SN et al: Anaritide in acute tubular necrosis. N Engl J Med 336:828-834, 1997.

64. Goldberg L, Rajfer S: Dopamine receptors: Applications in clinical cardiology. Circulation 72:245-248, 1985.

65. Bello-Reuss E, Higashi Y, Kaneda Y: Dopamine decreases fluid reabsorption in the straight portions of the rabbit proximal tubule. Am J Physiol 242:F634-F640, 1982.

66. Eklof AC: The natriuretic response to a dopamine DA1 agonist requires endogenous activation of dopamine DA2 receptors. Acta Physiol Scand 160:311-314, 1997.

67. Kuchel O, Buu NT, Unger T: Dopamine-sodium relationship: Is dopamine part of the endogenous natriuretic system? Contrib Nephrol 13:27-36, 1978.

68. Hollenberg N, Adams D, Mendell P et al: Renal vascular responses to dopamine: Hemodynamic and angiographic observations in normal man. Clin Sci Mol Med 45:733-742, 1973.

69. Rosenblum R, Tai A, Lawson D: Dopamine in man: Cardiorenal hemodynamics in normotensive patients with heart disease. J Pharm Exp Therap 183:256-263, 1972.

70. Hilberman M, Maseda J, Stinson EB et al: The diuretic properties of dopamine in patients after open-heart operation. Anesthesiology 61:489-494, 1984.

71. Goldberg L, Volkman P, Kohli J: A comparison of the vascular dopamine receptor with other dopamine receptors. Annu Rev Pharmacol Toxicol 18:57-79, 1978.

72. Pass L, Eberhart R, Brown J et al: The effect of mannitol and dopamine on the renal response to thoracic aortic cross-clamping. J Thor Cardiovasc Surg 95:608-612, 1988.

73. Ter Wee PM, Smit AJ, Rosman JB et al: Effect of intravenous infusion of low-dose dopamine on renal function in normal individuals and in patients with renal disease. Am J Nephrol 6:42-46, 1986.

74. Polson RJ, Park GR, Lindop MJ et al: The prevention of renal impairment in patients undergoing orthotopic liver grafting by infusion of low-dose dopamine. Anaesthesia 42:15-19, 1987.

75. Swygert TH, Roberts LC, Valek TR et al: Effect of intraoperative low-dose dopamine on renal function in liver transplant recipients. Anesthesiology 75:571-576, 1991.

76. Grundmann R, Kindler J, Meider G et al: Dopamine treatment of human cadaver kidney graft recipients: A prospectively randomized trial. Lancet ii:827-828, 1980.

77. Olsen NV, Lund J, Jensen PF et al: Dopamine, dobutamine, and dopexamine: A comparison of renal effects in unanesthetized human volunteers. Anesthesiology 79:685-694, 1993.

78. Ghosh S, Gray B, Oduro A et al: Dopexamine hydrochloride: Pharmacology and use in low cardiac output states. J Cardiothorac Vasc Anesth 5:382-389, 1991.

79. Panacek EA, Bednarczyk EM, Dunbar LM et al: Randomized, prospective trial of fenoldopam vs sodium nitroprusside in the treatment of acute severe hypertension: Fenoldopam Study Group. Acad Emerg Med 2:959-965, 1995.

80. Brogden RN, Markham A: Fenoldopam: A review of its pharmacodynamic and pharmacokinetic properties and intravenous clinical potential in the management of hypertensive urgencies and emergencies. Drugs 54:634-650, 1997.

81. Post JB, Frishman W: Fenoldopam: A new dopamine agonist for the treatment of hypertensive urgencies and emergencies. J Clin Pharmacol 38:2-13, 1998.

82. Singer I, Epstein M: Potential of dopamine A-1 agonists in the management of acute renal failure. Am J Kidney Dis 31:743-755, 1998.

83. Ecoffey C, Edouard A, Pruszczynski W et al: Effects of epidural anesthesia on catecholamines, renin activity and vasopressin changes induced by tilt in elderly men. Anesthesiology 62:294-297, 1985.

84. Kennedy W, Sawyer T, Gerbershagen H et al: Simultaneous systemic cardiovascular and renal haemodynamic measurements during high spinal anaesthesia in normal man. Acta Anaesthesiol Scand 37: 163-171, 1970.

85. Silvarjan M, Amory D, Lindbloom L et al: Systemic and regional blood flow changes during spinal anesthesia in the rhesus monkey. Anesthesiology 43:78-88, 1975.

86. Lunn J, Dannemiller FJ, Stanley TH: Cardiovascular responses to clamping of the aorta during epidural and general anesthesia. Anesth Analg 58:372-376, 1979.

87. Gamulin Z, Forster A, Simonet F et al: Effects of renal sympathetic blockade on renal hemodynamics in patients undergoing major aortic abdominal surgery. Anesthesiology 65:688-692, 1986.

88. Gelman S, Gowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 63:557-565, 1984.

89. Tranquilli WJ, McAndhar N, Parks CM et al: Systemic and regional blood flow distribution in the unanesthetized swine and swine anesthetized with halothane and nitrous oxide, halothane or enflurane. Anesthesiology 56:369-379, 1982.

90. Barry KG, Mazze RI, Schwartz FD: Prevention of surgical oliguria and renal hemodynamic suppression by sustained hydration. N Engl J Med 270:1371-1377, 1964.

91. Kono K, Philbin DM, Coggins CH et al: Renal function and stress response during halothane or fentanyl anesthesia. Anesth Analg 60:552-556, 1981.

92. Stanley TH, Philbin DM, Coggins CH: Fentanyl-oxygen anesthesia for coronary artery surgery: Cardiovascular and antidiuretic hormone responses. Can Anaesth Soc J 26:168-172, 1979.

93. Stanley TH, Berman L, Green O et al: Plasma catecholamine responses to fentanyl-oxygen anesthesia for coronary artery operation. Anesthesiology 53:250-253, 1980.

94. Priano LL: Alteration of renal hemodynamics by thiopental, diazepam and ketamine in conscious dogs. Anesth Analg 61:853-862, 1982.

95. Mazze RI, Trudell JR, Cousins MJ: Methoxyflurane metabolism and renal dysfunction: Clinical correlation in man. Anesthesiology 35:247-252, 1971.

96. Cousins MJ, Mazze RI: Methoxyflurane nephrotoxicity: A study of dose response in man. JAMA 225:1611-1616, 1973.

97. Loehning RW, Mazze RI: Possible nephrotoxicity from enflurane in a patient with severe renal disease. Anesthesiology 40:203-205, 1974.

98. Eichhorn JH, Hedley-White J, Steinman TI et al: Renal failure following enflurane anesthesia. Anesthesiology 45:557-560, 1976.

99. Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. Anesthesiology 40:536-542, 1974.

100. Bito H, Ikeuchi Y, Ikeda K: Effects of low-flow sevoflurane anesthesia on renal function. Anesthesiology 86:1231-1237, 1997.

101. Kharasch ED, Frink EJ, Zager R et al: Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular toxicity. Anesthesiology 86:1238-1253, 1997.

102. Ebert TJ, Frink EJ, Kharasch ED: Absence of biochemical evidence for renal and hepatic dysfunction after 8 hours of 1.25 minimum alveolar concentration sevoflurane anesthesia in volunteers. Anesthesiology 88:601-610, 1998.

103. Eger EI, Gong D, Koblin DD et al: Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 85:1154-1163, 1997.

104. Jarnberg P-O, De Villota DE, Eklund J et al: Effects of positive and expiratory pressure on renal function. Acta Anaesthesiol Scand 22:508-514, 1978.

105. Berry A: Respiratory support and renal function. Anesthesiology 55:655-667, 1981.

106. Jardin F, Forest JC, Boisante L et al: Influence of positive endexpiratory pressure on left ventricular performance. N Engl J Med 304:387-392, 1981.

107. Sladen A, Laver MB, Pontoppidan H: Pulmonary complications and water retention in prolonged mechanical ventilation. N Engl J Med 279:448-453, 1968.

108. Annat G, Viale JP, Xuan BB et al: Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology 58:136-141, 1983.

109. Venus B, Mathru M, Smith RA et al: Renal function during application of positive end-expiratory pressure in swine: Effects of hydration. Anesthesiology 62:765-769, 1985.

110. Hemmer M, Suter PM: Treatment of cardiac and renal effects of PEEP with dopamine in patients with acute respiratory failure. Anesthesiology 50:399-403, 1979.

111. Thompson GE, Miller RD, Stevens WC et al: Hypotensive anesthesia for total hip arthroplasty: A study of blood loss and organ function, brain, heart, liver and kidneys. Anesthesiology 48:91-96, 1978.

112. Wang HH, Liu LMP, Katz RL: A comparison of the cardiovascular effects of sodium nitroprusside and trimethaphan. Anesthesiology 46:40-48, 1977.

113. Khambatta HJ, Stone JG, Khan E: Propranolol alters renin release during nitroprusside-induced hypotension and prevents hypotension on discontinuation of nitroprusside. Anesth Analg 60:569-573, 1981.

114. Colley PS, Silvarjan M: Regional blood flow in dogs during halothane anesthesia and controlled hypotension produced by nitroprusside or nitroglycerin. Anesth Analg 63:503-510, 1984.

115. Aronson S, Goldberg LI, Glock D et al: Effects of fenoldopam on renal blood flow and systemic hemodynamics during isoflurane anesthesia. J Cardiothorac Vasc Anesth 5:29-32, 1991.

116. Myers BD, Moran SM: Hemodynamically mediated acute renal failure. N Engl J Med 314:97-105, 1986.

117. Gamulin Z, Forster A, Morel D et al: Effects of infra-renal aortic cross-clamping on renal hemodynamics in humans. Anesthesiology 61:394-399, 1984.

118. Barry K, Cohen A, Knochel J et al: Mannitol infusion: The prevention of acute functional renal failure during resection of an aneurysm of the abdominal aorta. N Engl J Med 264:967-971, 1961.

119. Burke T, Cronin R, Duchin K et al: Ischemia and tubule obstruction during acute renal failure in dogs: Mannitol in protection. Am J Physiol 238:F305-F314, 1980.

120. Paul MD, Mazer CD, Byrick RJ et al: Influence of mannitol and dopamine on renal function during elective infrarenal aortic cross-clamping in man. Am J Nephrol 6:427-434, 1986.

121. Taylor KM, Morton IJ, Brown JJ et al: Hypertension and the reninangiotensin system following open heart surgery. J Thorac Cardiovasc Surg 74:840-845, 1977.

122. Ip-Yam PC, Murphy S, Baines M et al: Renal function and proteinuria after cardiopulmonary bypass: The effects of temperature and mannitol. Anesth Analg 78:842-847, 1994.

123. Canivet JL, Larbuisson R, Damas P et al: Plasma renin activity and urine beta $_2$ -microglobulin during and after cardiopulmonary bypass: Pulsatile vs non-pulsatile perfusion. Eur Heart J 11:1079-1082, 1990.

124. Badner NH, Murkin JM, Lok P: Differences in pH management and pulsatile/nonpulsatile perfusion during cardiopulmonary bypass do not influence renal function. Anesth Analg 75:696-701, 1992.

125. Matsuda H, Hirose H, Nakano S et al: Results of open heart surgery in patients with impaired renal function as creatinine clearance below 30 mL/min: The effects of pulsatile perfusion. J Cardiovasc Surg 27:595-599, 1986.

126. Olinger G, Hutchinson L, Bonchek L: Pulsatile cardiopulmonary bypass for patients with renal insufficiency. Thorax 38:543-550, 1983.

127. Hilberman M, Myers B, Carrie G et al: Acute renal failure following cardiac surgery. J Thorac Cardiovasc Surg 77:880-888, 1979.

128. Hilberman M, Derby GC, Spencer RJ et al: Sequential pathophysiological changes characterizing the progression from renal dysfunction to acute renal failure following cardiac operation. J Thorac Cardiovasc Surg 79:838-844, 1980.

129. Higgins TL, Estafanous FG, Loop FD et al: Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients: A clinical severity score. JAMA 267:2344-2348, 1992.

130. Myles PS, Buckland MR, Schenk NJ et al: Effect of "renal-dose" dopamine on renal function following cardiac surgery. Anaesth Intensive Care 21:56-61, 1993.

131. Costa P, Ottino GM, Matani A et al: Low-dose dopamine during cardiopulmonary bypass in patients with renal dysfunction. J Cardiothorac Anesth 4:469-473, 1990.

132. Chiolero R, Borgeta A, Fisher A: Postoperative arrhythmias and risk factors after open heart surgery. Thorac Cardiovasc Surg 39:81-84, 1991.

133. Wardle N: Acute renal failure in the 1980s: The importance of septic shock and of endotoxemia. Nephron 30:193-200, 1982.

134. Zager RA, Foerder C, Bredl C: The influence of mannitol on myoglobinuric acute renal failure: Functional, biochemical, and morphological assessments. J Am Soc Nephrol 2:848-855, 1991.

135. Wetzels JF, Burke TJ, Schrier RW: Prevention and attenuation of acute renal failure: Review. Curr Opin Nephrol Hyperten 1:133-140, 1992.

136. Parfrey PS, Griffiths SM, Barrett BJ et al: Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency or both: A prospective, controlled study. N Engl J Med 320:143-149, 1989.

137. Van Zee BE, Hoy WE, Talley TE et al: Renal injury associated with intravenous pyelography in nondiabetic and diabetic patients. Ann Intern Med 89:51-54, 1978.

138. Eisenberg RL, Bank WO, Hedgecock MW: Renal failure after major angiography can be avoided with hydration. Am J Radiol 136:859-861, 1981.

139. Snyder HE, Killen DA, Foster JH: The influence of mannitol in toxic reactions to contrast angiography. Surgery 64:640-642, 1968.

140. Neumayer HH, Gellert J, Luft FC: Calcium antagonists and renal protection. Ren Fail 15:353-358, 1993.

141. Diamond J, Cheung J, Fang L: Nifedipine-induced renal dysfunction. Am J Med 77:905-909, 1984.

142. Bauer J, Sunderrajan S, Reams G: Effects of calcium entry blockers on renin-angiotensin-aldosterone system, renal function and hemodynamics, salt and water excretion and body fluid composition. Am J Cardiol 56:62H-67H, 1985.

143. Wagner K, Albrecht S, Neumayer H-H: Prevention of post-transplant acute tubular necrosis by the calcium antagonist diltiazem: A prospective, randomized study. Am J Nephrol 7:287-291, 1987.

144. Neumayer HH, Junge W, Kufner A et al: Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: A prospective randomised clinical trial. Nephrol Dial Transplant 4:1030-1036, 1989.

145. Neumayer HH, Kunzendorf U: Renal protection with the calcium antagonists: Review. J Cardiovasc Pharmacol 18(suppl):S11-S18, 1991.

146. Kunzendorf U, Walz G, Brockmoeller J et al: Effects of diltiazem upon metabolism and immunosuppressive action of cyclosporine in kidney graft recipients. Transplantation 52:280-284, 1991.

147. Neumayer HH, Kunzendorf U, Schreiber M: Protective effects of calcium antagonists in human renal transplantation. Kidney Int 36(suppl):87-93, 1992.

148. Gabow PA, Kaehny WD, Kelleher SP: The spectrum of rhabdomyolysis. Medicine (Baltimore) 61:141-152, 1982.

149. Clyne DH, Kant KS, Pesce AJ et al: Nephrotoxicity of low molecular weight serum proteins: Physicochemical interactions between myoglobin, hemoglobin, Bence-Jones protein and Tamm-Horsfall mucoprotein. Curr Prob Clin Biochem 9:299-308, 1979.

150. Ellinas PA, Rosner F: Rhabdomyolysis: Report of eleven cases. JAMA 84:617-624, 1992.

151. Ron D, Taitelman U, Michaelson M et al: Prevention of acute renal failure in traumatic rhabdomyolysis. Arch Intern Med 144:277-280, 1984.

152. Wait RB, Kahng KU: Renal failure complicating obstructive jaundice. Am J Surg 157:256-263, 1989.

153. Parks RW, Diamond T, McCrory DC et al: Prospective study of postoperative renal function in obstructive jaundice and the effect of perioperative dopamine. Br J Surg 81:437-439, 1994.

154. Plusa SM, Clark NW: Prevention of postoperative renal dysfunction in patients with obstructive jaundice: A comparison of mannitol-induced diuresis and oral sodium taurocholate. J R Coll Surg Edinb 36: 303-305, 1991.

155. Gubern JM, Martinez-Rodenas F, Sitges-Serra A: Use of mannitol as a measure to prevent postoperative renal failure in patients with obstructive jaundice: Letter. Am J Surg 159:444-445, 1990.

156. Biesenbach G, Zazgornik J, Kaiser W et al: Improvement in prognosis of patients with acute renal failure over a period of 15 years: An analysis of 710 cases in a dialysis center. Am J Nephrol 12:319-325, 1992.

157. Johnson JP, Rokaw MD: Sepsis or ischemia in experimental acute renal failure: What have we learned? New Horiz 3:608-614, 1995.

158. Zager RA: Sepsis-associated acute renal failure: Some potential pathogenetic and therapeutic insights: Review. Nephrol Dial Transplant 4:164-167, 1994.

159. Cumming AD, Driedger AA, McDonald JW et al: Vasoactive hormones in the renal response to systemic sepsis. Am J Kidney Dis 11:23-32, 1988.

160. Badr KF: Sepsis-associated renal vasoconstriction: Potential targets for future therapy. Am J Kidney Dis 20:207-213, 1992.

161. Zager RA: Endotoxemia, renal hypoperfusion, and fever: Interactive risk factors for aminoglycoside and sepsis-associated acute renal failure. Am J Kidney Dis 20:223-230, 1992.

162. Weber A, Schwieger IM, Poinsot O et al: Sequential changes in renal oxygen consumption and sodium transport during hyperdynamic sepsis in sheep. Am J Physiol 262:F965-F971, 1992.

163. Bersten AD, Rutten AJ: Renovascular interaction of epinephrine, dopamine, and intraperitoneal sepsis. Crit Care Med 23:537-544, 1995.

164. Lherm T, Troche G, Rossignol M et al: Renal effects of low-dose dopamine in patients with sepsis syndrome or septic shock treated with catecholamines. Intensive Care Med 22:213-219, 1996.

165. Smithies M, Yee TH, Jackson L et al: Protecting the gut and the liver in the critically ill: Effects of dopexamine. Crit Care Med 22:789-795, 1994.

166. Hesselvik JF, Brodin B: Low-dose norepinephrine in patients with septic shock and oliguria: Effects on afterload, urine flow and oxygen transport. Crit Care Med 17:179-180, 1989.

167. Landry DW, Levin HR, Gallant EM et al: Vasopressin pressor hypersensitivity in vasodilatory septic shock. Crit Care Med 25:1279-1282, 1997.

168. Edwards RM, Rizna W, Kinter LB: Renal microvascular effects of vasopressin and vasopressin antagonist. Am J Physiol 256:F526-534, 1989.

169. Cumming AD, McDonald JW, Lindsay RM et al: The protective effect of thromboxane synthetase inhibition on renal function in systemic sepsis. Am J Kidney Dis 13:114-119, 1989.

170. Cumming AD, Nimmo GR, Craig KJ et al: Vasoactive effects of aprotinin. Agents Actions (suppl) 38:211-218, 1992.

171. Veterans Administration Systemic Sepsis Cooperative Study Group: Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 317:659-665, 1987.

172. Bone RC, Fisher CJ, Clemmer TP et al: A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:653-658, 1987.

173. Slotman GJ, Fisher CJ, Bone RC et al: Detrimental effects of high-dose methylprednisolone sodium succinate on serum concentrations of hepatic and renal function indicators in severe sepsis and septic shock: The Methylprednisolone Severe Sepsis Study Group. Crit Care Med 21:191-195, 1993.

174. Kriz W: A standard nomenclature for structures of the kidney. Kidney Int 33:1-7, 1988.

175. Pitts RF: Physiology of the Kidney and Body Fluids. Chicago, Year Book Medical Publishers, 1974.

176. Alfrey AC, Chan L: Chronic renal failure: Manifestations and pathogenesis. In Schrier RW (ed): Renal and Electrolyte Disorders, 4th ed. Boston, Little, Brown, 1992, p 541.

177. Sladen RN: Effect of anesthesia and surgery on renal function. Crit Care Clin 3:380, 1987.

178. Barry KG, Mazze RI, Schwartz FD: Prevention of surgical oliguria and renal hemodynamic suppression by sustained hydration. New Engl J Med 270:1371-1377, 1964.

Chapter 19 - Cerebral Physiology and the Effects of Anesthetics and Techniques

John C. Drummond
Piyush M. Patel

INTRODUCTION

This chapter reviews the effects of anesthetic agents and techniques on cerebral physiology, and, in particular, their effects on cerebral blood flow (CBF) and metabolism (Table 19-1) . The final section presents a brief discussion of pathophysiologic states including cerebral ischemia and of cerebral protection. The chapter gives greatest emphasis to information that is of immediate relevance to the rationale for the anesthetic and intensive care management of patients with intracranial disease. Chapter 52 presents the clinical management of these patients in detail. Neurologic monitoring, including the effects of anesthetic agents on the electroencephalogram (EEG) and evoked responses, is reviewed in Chapter 35 .

REGULATION OF CEREBRAL BLOOD FLOW

Anesthetic agents cause dose-related and reversible alterations in many aspects of cerebral physiology including CBF, cerebral metabolic rate (CMR) and electrophysiologic function (EEG, evoked responses). The changes in CBF and CMR can be of clinical importance in patients with neurosurgical diseases. Certain anesthetic agents and techniques have the potential to affect the diseased brain and the conduct of the neurosurgical procedure adversely. However, in certain instances, the effects of general anesthesia on CBF and CMR can be manipulated to improve both the operative course and the clinical outcome of patients with neurologic disorders.

The adult human brain weighs approximately 1,350 g and therefore represents about 2 percent of total body weight. However, it receives 12 to 15 percent of cardiac output. This high flow rate is a reflection of the brain's high metabolic rate. At rest, the brain consumes O_2 at an average rate of approximately 3.5 mL of O_2 per 100 g of brain tissue per minute. Whole-brain O_2 consumption (13.5 × 3.5 = 47 mL/min) represents about 20 percent of total-body O_2 utilization. Normal values for CBF, CMR, and other physiologic variables are provided in Table 19-2 .

Approximately 60 percent of the brain's energy consumption [1] is used to support electrophysiologic function. The depolarization-repolarization activity that occurs and that is reflected in the EEG requires energy expenditure for the maintenance and restoration of ionic gradients and for the synthesis, transport, and reuptake of neurotransmitters. The remainder of the energy consumed by the brain is involved in cellular homeostatic activities. Local CBF (l-CBF) and local CMR (l-CMR) within the brain are very heterogeneous, and both are approximately four times greater in gray matter than in white matter. The cell population of the brain is also heterogeneous in its O_2 requirements. Glial cells make up about half of the brain's volume and require less energy than neurons. Besides providing a physically supportive latticework for the brain, the glial cells are important in the reuptake

TABLE 19-1 -- Abbreviations

BBB	Blood-brain barrier
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CBV	Cerebral blood volume
CMR	Cerebral metabolic rate
CMRg	Cerebral metabolic rate for glucose
$CMRO_2$	Cerebral metabolic rate for oxygen
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CSFP	Cerebrospinal fluid pressure
CVR	Cerebral vascular resistance
EEG	Electroencephalogram
ICP	Intracranial pressure
l-CBF	Local cerebral blood flow
l-CMR	Local cerebral metabolic rate
LLA	Lower limit of autoregulation
MAP	Mean arterial pressure
MCA	Middle cerebral artery
NO	Nitric oxide
N_2O	Nitrous oxide
PET	Positron emission tomography
r-CBF	Regional cerebral blood flow
TCD	Transcranial Doppler

of neurotransmitters and in the delivery and removal of metabolic substrates and wastes.

The brain's substantial demand for substrate must be met by adequate delivery of O_2 and glucose. However, the space constraints imposed by the noncompliant cranium and meninges require that blood flow not be excessive. Not surprisingly, there are elaborate mechanisms for the regulation of CBF. These mechanisms, which include chemical, myogenic, and neurogenic factors, are listed in Table 19-3 . The precise mechanisms of these effects are for the most part not well understood. However, a substantial volume of research indicates that modulation of the arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) system [2] [3] is central to the changes in cerebral vascular tone caused by several processes including hypercarbia, [4] [5] increased CMR, [6] [7] volatile agents, [8] [9] [10] and neurogenic mechanisms. [11] [12] [13]

Chemical Regulation

Several factors cause changes in the cerebral biochemical environment that result in adjustments of CBF. These include changes in CMR, arterial CO_2 tension (Pa

$_{CO_2}$) and arterial O_2 tension (Pa $_{O_2}$).

TABLE 19-2 -- Normal Cerebral Physiologic Values

Cerebral blood flow	
Global	45-55 mL/100 g/min
Cortical (mostly gray matter)	75-80 mL/100 g/min
Subcortical (mostly white matter)	20 mL/100 g/min
Cerebral metabolic rate for oxygen	3-3.5 mL/100 g/min
Cerebral vascular resistance	1.5-2.1 mmHg · 100 g · min/mL
Cerebral venous oxygen tension	32-44 mm Hg
Cerebral venous oxygen saturation	55-70%
Intracranial pressure (supine)	8-12 mm Hg

TABLE 19-3 -- Factors Influencing Cerebral Blood Flow [a]

FACTOR	COMMENT
Chemical/Metabolic/Humoral	
Cerebral metabolic rate	The cerebral metabolic rate influence assumes intact flow-metabolism coupling, the mechanism of which is not fully understood
Anesthetics	
Temperature	
Arousal/seizures	
Pa $_{CO_2}$	
Pa $_{O_2}$	
Vasoactive agents	
Anesthetics	
Vasodilators	
Pressors	
Myogenic	
Autoregulation/mean arterial pressure	The autoregulation mechanism is fragile, and in many pathologic states, cerebral blood flow is regionally pressure-passive
Rheologic	
Blood viscosity	
Neurogenic	
Extracranial sympathetic and parasympathetic pathways	Contribution and clinical significance poorly defined
Intra-axial pathways	

[a] See text for discussion.

Cerebral Metabolic Rate

Increased neuronal activity results in increased local brain metabolism, and this increase in CMR is associated with a well-matched, proportional change in CBF. [14] [15] Regional CBF and CMR measurements performed during maneuvers designed to activate specific brain regions provide evidence of the strict local "coupling" of CMR and CBF. [16] [17] [18] [19] Although it is clear that local metabolic factors play a major role in these adjustments in CBF, and whereas there is evidence that NO of neuronal origin contributes to the vasodilation that occurs, [6] [7] the complete mechanism of flowmetabolism coupling remains undefined. [20] CMR is influenced by several phenomena in the neurosurgical environment, including the functional state of the nervous system, anesthetic agents, and temperature.

Functional State.

CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any cause. During epileptoid activity, CMR increases may be extreme, whereas CMR may be substantially reduced in coma.

Anesthetics.

The effect of individual anesthetics on CMR is presented in greater detail later in this chapter. In general, anesthetic agents suppress CMR, with ketamine and nitrous oxide (N_2O) the notable exceptions. It appears that the component of CMR on which they act is that associated with electrophysiologic function. [21] With several agents, including barbiturates, [21] isoflurane, [22] and etomidate [23] (and probably propofol, sevoflurane and desflurane), increasing plasma concentrations cause progressive suppression of EEG activity and a concomitant reduction in CMR. However, increasing the plasma level beyond that required first to achieve suppression of the EEG results in no further depression

Figure 19-1 The interdependency [21] of cerebral electrophysiologic function and cerebral metabolic rate for oxygen (CMRO $_2$). Administration of various anesthetic agents [21] [22] [23] including barbiturates results in a dose-related reduction in $CMRO_2$ and cerebral blood flow (CBF). The maximum reduction occurs with the dose that results in electrocerebral silence. At this point, energy utilization associated with electrophysiologic activity has been reduced to zero, but energy utilization for cellular homeostasis persists unchanged. Additional barbiturate administration causes no further decrease in CBF or $CMRO_2$. EEG, electroencephalogram.

of CMR. The component of CMR required for the maintenance of cellular integrity, the "housekeeping" component, is apparently unaltered by intravenous anesthetics (Fig. 19-1) .

The $CMRO_2$ values observed when complete suppression of the EEG is achieved with different anesthetic agents are very similar. The inference that

anesthetic-induced EEG suppression represents a single physiologic state no matter what agent is employed follows easily. However, there is evidence to the contrary. When barbiturates are administered to the point of EEG suppression, a uniform depression of CBF and CMR occurs throughout the brain. When suppression occurs during isoflurane administration, the relative reductions in CMR and CBF are greater in the neocortex than in other portions of the cerebrum. [24] [25] [26] Electrophysiologic responsiveness also varies. Cortical somatosensory evoked responses to median nerve stimulation can be recorded readily at doses of thiopental far in excess of those required to cause complete suppression of the EEG, [27] but they are difficult to elicit at concentrations of isoflurane associated with a burst-suppression pattern, such as 1.5 minimum alveolar concentration (MAC) [28] (Fig. 19-2) . In addition, the EEG characteristics of the burst-suppression states that occur just before complete suppression differ among anesthetic agents. [29] These differences may be of some relevance to discussions of differences in the "protective" potential of agents that can produce EEG suppression because it is apparent that burst suppression does not represent a uniform physiologic state, irrespective of the agent used to produce it.

Temperature.

The effects of hypothermia on both normal and ischemic brain have been reviewed in detail. [1] [30] [31] CMR decreases by 6 to 7 percent per Celsius degree of temperature reduction. [1] As is the case with some anesthetic agents, hypothermia can also cause complete suppression of the EEG (at 20°C). However, in contrast to anesthetic agents, temperature reduction beyond that at which EEG suppression first occurs *does* produce a further decrease in CMR (Fig. 19-3) . This occurs because, whereas anesthetic agents reduce only the component of CMR associated with neuronal function, hypothermia decreases the rate of energy utilization associated with both electrophysiologic function and the basal component associated with the maintenance of cellular integrity. These decreases were once assumed to be proportional. However, it has been demonstrated that mild hypothermia preferentially suppresses the basal component of CMR. [32] [33] $CMRO_2$ at 18°C is less than 10 percent of normothermic control values, and this probably accounts for the brain's tolerance for moderate periods of circulatory arrest at these and lower temperatures.

Figure 19-2 Cortical somatosensory evoked responses to median nerve stimulation in human patients before induction and during anesthesia with thiopental and isoflurane nitrous oxide (N_2O). In spite of an equivalent or greater degree of cerebral metabolic rate (CMR) reduction with thiopental, cortical evoked responses are better preserved [27] than during anesthesia with isoflurane. [28] This finding suggests that the electroencephalographic (EEG) suppression achieved with different anesthetic agents should not be assumed to be equivalent electrophysiologic states. The cumulative thiopental doses and expired concentrations of isoflurane and N_2O are indicated.

Figure 19-3 The effect of temperature reduction on the cerebral metabolic rate for oxygen ($CMRO_2$). Hypothermia reduces both the components of cerebral metabolic activity identified in Figure 19-1 : that associated with neuronal electrophysiologic activity ("function") and that associated with the maintenance of cellular homeostasis ("integrity"). This is in contrast to anesthetic agents, which alter only the function component. *(Data from Michenfelder [1])*

Hyperthermia has an opposite influence on cerebral physiology. Between 37 and 42°C, CBF and CMR increase. However, at temperatures higher than 42°C a dramatic reduction in cerebral O_2 consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may occur as a result of protein (enzyme) degradation.

Partial Pressure of Carbon Dioxide

CBF varies directly with Pa co_2 (Fig. 19-4) . The effect is greatest within the range of physiologic Pa co_2 variation. CBF changes 1 to 2 mL/100 g/min for each 1 mm Hg of change in Pa co_2 around normal Pa co_2 values. [34] This response is attenuated below a Pa co_2 of 25 mm Hg. [34] Under normal circumstances, CBF sensitivity to changes in Pa co_2 (DeltaCBF/DeltaPa co_2) appears to be positively correlated with resting levels of CBF. [35] Accordingly, anesthetic agents that alter resting CBF cause changes in the CO_2 response of the cerebral circulation. However, CO_2 responsiveness has been observed in normal brain during anesthesia with all the numerous anesthetic agents that have been studied.

The changes in CBF caused by Pa co_2 are apparently dependent on pH alterations in the extracellular fluid of the brain. [36] NO, in particular NO of neuronal origin, is an important, although not exclusive, mediator of CO_2 -induced vasodilatation. [4] [5] [37] [38] [39] In particular, in primates, the available data indicate that NO's relevance may be limited to the cerebral cortex. [5] The changes in extracellular fluid (ECF) pH and CBF occur rapidly after Pa co_2 adjustments because CO_2 diffuses freely across the cerebrovascular endothelium. Note that in contrast to *respiratory* acidosis, acute systemic *metabolic* acidosis has little immediate effect on CBF because the blood-brain barrier (BBB) excludes the hydrogen ion from the perivascular space. Although the CBF changes in response to Pa co_2 alteration occur rapidly, they are not sustained. In spite of the maintenance of an elevated arterial pH, CBF returns to normal over 6 to 8 hours [40] [41] [42] because cerebrospinal fluid (CSF) pH gradually normalizes as a result of the extrusion of bicarbonate. As a result, the patient who has sustained periods of hyperventilation or hypoventilation deserves special consideration. Acute normalization of Pa co_2 results in a significant CSF acidosis (after hypocapnia) or alkalosis (after hypercapnia). The former results in increased CBF with a concomitant intracranial pressure (ICP) increase that will depend on the prevailing intracranial compliance. The latter conveys the theoretic risk of ischemia.

Partial Pressure of Oxygen

Changes in Pa o_2 from 60 to more than 300 mm Hg have little influence on CBF. When the Pa o_2 is less than 60 mm Hg, CBF increases rapidly (see Fig. 19-4) . The mechanisms mediating the cerebral vasodilation during hypoxia are not fully understood, but they may include neurogenic effects initiated by peripheral and/or neuraxial chemoreceptors as well as local humoral influences. At high Pa o_2 values, CBF decreases modestly. [43] At 1 atm O_2 , CBF is reduced by 12 percent. [44]

Figure 19-4 Changes in cerebral blood flow (CBF) caused by independent alterations in arterial pressures of carbon dioxide and oxygen (Pa co_2 and Pa o_2) and mean arterial pressure (MAP).

Myogenic Regulation (Autoregulation)

Autoregulation refers to the capacity of the cerebral circulation to adjust its resistance in order to maintain CBF constant over a wide range of mean arterial pressure (MAP). In normal human subjects, the limits of autoregulation occur at MAPs of approximately 70 and 150 mm Hg (Fig. 19-5) . The lower limit of autoregulation (LLA) has been widely quoted as an MAP of 50 mm Hg. Although this number may be correct for some animal species, the available data argue that the LLA is considerably higher in humans. [45] Note that the units used on the X axis of "autoregulation curves" influence the correct inflection points of the curve. When the X axis is MAP, the normal average LLA is not less than 70 mm Hg (with considerable interindividual variation). [46] [47] [48] [49] [50] However, cerebral perfusion pressure (CPP) is the ideal independent variable. However, because ICP is usually not measured in healthy subjects, CPP (MAP - ICP) is rarely available. Assuming a normal ICP in a supine subject of 10 to 15 mm Hg, an LLA of 70 expressed as MAP corresponds to an LLA of 55 to 60 mm Hg expressed as CPP.

Above and below the autoregulatory plateau, CBF is pressure dependent (pressure passive) and varies linearly with CPP. Autoregulation is influenced by various pathologic processes and, in addition, by the time course over which CPP changes occur. Even within the range over which autoregulation normally occurs, a rapid change in arterial pressure will result in a transient (3 to 4 minutes) alteration of CBF. [51]

The precise mechanism by which autoregulation is accomplished is not known. NO may participate in the vasodilation

Figure 19-5 Schematic representation of the effect of increasing concentrations of a typical volatile anesthetic agent on cerebral blood flow (CBF) autoregulation. Both the upper and lower thresholds are shifted to the left. MAP, mean arterial pressure.

associated with hypotension in some species, [52] [53] but not, according to a single study, in primates. [54]

Neurogenic Regulation

There is considerable evidence of extensive innervation of the cerebral vasculature. [55] The density of innervation declines with vessel size, and the greatest neurogenic influence appears to be exerted on larger cerebral arteries. [56] This innervation includes cholinergic (parasympathetic [57] and nonparasympathetic [58] [59] [60]), adrenergic (sympathetic [61] and nonsympathetic [62]), serotonergic, [63] [64] and vasoactive intestinal peptide-ergic (VIPergic) [65] systems of extra-axial and intra-axial origin. It is certain that in animals there is an extracranial sympathetic influence via the superior cervical ganglion [61] [66] [67] [68] [69] and parasympathetic innervation via the sphenopalatine ganglion. [57] The intra-axial pathways are less well defined, although there is considerable evidence of innervation arising from several nuclei in animals including the locus caeruleus, [62] the fastigial nucleus [60] the dorsal raphe nucleus [64] and the basal magnocellular nucleus of Mey-nert. [58] [59] Evidence of the functional significance of neurogenic influences has been derived from studies of CBF autoregulation [66] [68] [70] [71] [72] and ischemic injury. [73] [74] Hemorrhagic shock, a state of high sympathetic tone, results in a lower CBF at a given MAP than occurs when hypotension is produced with sympatholytic drugs. This is presumably because, during shock, a sympathetically mediated vasoconstrictive effect shifts the lower end of the "autoregulatory" plateau (see Fig. 19-4) to the right. It is not clear what the relative contributions of humoral and neural mechanisms are to this phenomenon; however, there is certainly a neurogenic component in some species because sympathetic denervation increases CBF during hemorrhagic shock in baboons [70] and rabbits [66] and in head injury in piglets. [75] Activation of cerebral sympathetic innervation also shifts the upper limit of autoregulation to the right and offers some protection against hypertensive breakthrough of the BBB. [71] [72] Experimental interventions that alter these neurogenic control pathways have also been shown to influence outcome after standardized ischemic insults, [73] [74] presumably via influences on vascular tone and therefore CBF. The nature and influence of such pathways in humans are not known, and at present there are no clinical interventions intended to manipulate them that are relevant to the neurosurgical patient. [76]

Viscosity Effects

Blood viscosity can influence CBF. Hematocrit is the single most important determinant of blood viscosity. [77] In healthy subjects, hematocrit variation within the normal range (33-45%) probably results in only trivial alteration of CBF. Beyond this range, changes are more substantial. [77] [78] In anemia, cerebral vascular resistance is reduced and CBF increases. However, this may result not only from reduction in viscosity, but also in response to reduced O_2 -carrying capacity of blood. [79] The effect of viscosity reduction on CBF is more obvious in the setting of focal cerebral ischemia when vasodilation in response to impaired O_2 delivery is probably

already maximal. In this setting, viscosity reduction accomplished by hemodilution results in increases in CBF in the ischemic territory. [80] [81] [82] [83] The best available information suggests that, in the setting of focal cerebral ischemia, a hematocrit of 30 to 34 percent will result in optimal O_2 delivery. [84] [85]

Vasoactive Agents

Many agents with intrinsic vascular effects are employed in contemporary anesthetic practice. These include both anesthetic agents and numerous vasoactive drugs used specifically for hemodynamic manipulation. This section deals with the latter. The actions of anesthetics are discussed in a later section.

Systemic Vasodilators

Most of the drugs used to induce hypotension (including sodium nitroprusside, nitroglycerin, hydralazine, adenosine, calcium channel blockers) also cause cerebral vasodilation. As a result, CBF either increases or is maintained at prehypotensive levels. In addition, CBF is maintained to lower MAP when hypotension is induced with a cerebral vasodilator than with either hemorrhage or a noncerebral vasodilator, such as the ganglionic blocker trimethaphan. [86] Agents that vasodilate the cerebral circulation simultaneously cause increases in cerebral blood volume (CBV) with the potential to increase ICP. The ICP effects of these agents are empirically less dramatic when hypotension is induced slowly. [87] This probably reflects the more effective interplay of compensatory mechanisms (CSF and venous blood shifts) when changes occur more slowly.

Catecholamine Agonists/Antagonists

Numerous drugs with agonist and antagonist activity at catecholamine receptors (alpha $_1$, alpha$_2$, beta, and dopamine) are in common use (Ch 14) . The data regarding the effects of these agents on cerebral physiology contain numerous apparent inconsistencies. In part, these arise because of differences among species, [69] because of differences in the receptor populations on different vessels (e.g., intraparenchymal versus extraparenchymal) within a given species, [69] and because of model differences (e.g., *in vivo* versus *in vitro*). However, other variables have probably contributed. These include the magnitude of the systemic blood pressure changes that occurred as a result of administration of the agent of interest, the status of the autoregulation mechanism (as determined by the anesthetic agents employed and/or damage inherent to the preparation), the status of the BBB, and, in *in vitro* studies, the status of the endothelium. Readers who intend to review this literature should also appreciate that the effects of pressors are reported by various authors in terms of effects on either CBF or CVR. An increase in CVR is occasionally presented as prima facie evidence that the agent in question is a cerebral vasoconstrictor. However, the normal autoregulatory response to a rising MAP entails cerebral vasoconstriction (an increase in CVR) in order to maintain a constant CBF. Accordingly, an increase in CVR may indicate that the agent has a direct effect on the cerebral vasculature, but alternatively, it may indicate the absence of a direct effect and preservation of autoregulation. It is probably most practical to think in terms of changes in CBF rather than changes in CVR because CBF is the variable that is most important to the clinician. The information given later in the discussion and in Table 19-4 emphasizes data obtained in investigations of pressor agents in intact preparations and gives greatest weight to results obtained in humans and higher primates.

alpha$_1$ -Agonists

A frequently encountered clinical concern is that the administration of agents with alpha $_1$ -agonist effects (phenyl-ephrine, norepinephrine) will lead to a reduction of CBF. Data derived from studies in both humans and nonhuman primates do not support this belief. Olesen [88] measured CBF

TABLE 19-4 -- Best Estimates of the Influence of Pure Catecholamine Receptor Agonists and Specific Pressor Substances on Cerebral Blood Flow and Cerebral Metabolic Rate[a]

AGONIST	CEREBRAL BLOOD FLOW	CEREBRAL METABOLIC RATE
Pure		
alpha$_1$	0/-	0
alpha$_2$	--	0
beta	+	+
beta (BBB open)	+++	+++
Dopamine	++	0
Dopamine (high dose)	?-	?0

Mixed		
Norepinephrine	0/-	0/+
Norepinephrine (BBB open)	+	+
Epinephrine	+	+
Epinephrine (BBB open)	+++	+++

BBB, blood-brain barrier; + indicates increase; - indicates decrease; the number of symbols indicates the magnitude of the effect; 0 indicates no effect.

[a] Where species differences occurred, data from primates were given preference. See text for complete discussion.

in human patients during intracarotid or intravenous infusion of norepinephrine. Intracarotid infusion in doses that raised peripheral MAP from 95 to 117 mm Hg and intravenous infusion that raised MAP from 95 to 142 mm Hg resulted in no change in CBF. King et al [89] administered sufficient norepinephrine to increase average MAP from 91 to 117 mm Hg and observed a reduction in global CBF from 61 to 56 mL/100 g/min, that is, a very small change. Rogers et al [90] saw no reduction of CBF during administration of phenylephrine to patients receiving cardiopulmonary bypass. Intracarotid infusion of norepinephrine in phencyclidine-anesthetized baboons in a dose sufficient to increase MAP by 10 percent had no effect on CBF. [91] alpha$_1$ -Agonists also do not appear to cause cerebral vasoconstriction in rats. [92] [93] [94] [95] The notion that they reduce CBF may be the product of species differences. In both dogs and goats, norepinephrine infusion at rates resulting in a moderate increase in MAP *is* associated with a reduction in CBF that can be blocked by alpha $_1$ -antagonists. [96] [97] [98] [99] Nonetheless, the concern that CBF will be reduced in patients appears unfounded.

CBF increases have been attributed to norepinephrine. These could occur if autoregulation were defective or its limit exceeded. In some instances, the increases may be the result of BBB abnormalities. There are data to suggest that beta-mimetic agents (norepinephrine has some beta-activity) cause activation of cerebral metabolism, [100] with a parallel "coupled" increase in CBF, and this effect is likely to be most apparent when they can gain greater access to the brain parenchyma via a defective BBB [91] [93] [101] (see the epinephrine section later). In summary, it seems likely that circulating alpha $_1$ -agonists will have little direct influence on CBF in humans, with the exception that norepinephrine may cause vasodilation when the BBB is defective.

beta-Agonists

The available data suggest that beta-receptor agonists, in low doses, have little direct effect on the cerebral vasculature, but in larger doses and in association with physiologic stress, they can cause an increase in CMR with an accompanying increase in CBF. [102] An investigation in rabbits by Sercombe et al, [103] who administered isoproterenol with and without selective and nonselective beta-antagonists indicates that the beta $_1$ -receptor is probably the mediator of these effects. The effects are probably enhanced by increased permeability of the BBB (see later). Olesen [88] observed no change in CBF in unanesthetized human volunteers in response to an intra-carotid infusion of approximately 6 mug/min of epinephrine, a dose that caused no change in MAP. However, when King et al [89] administered a larger dose of epinephrine, 37 mug/min intravenously (a dose sufficient to increase MAP from 91 to 109 mm Hg), CBF and CMRO $_2$ rose by 22 and 24 percent, respectively. A similar pattern was observed in rats by Berntman et al, [93] who found that 2 mug/kg/min of epinephrine had no effect on CBF and CMR, whereas 8 mug/kg/min caused increases in both.

There is evidence that a BBB defect enhances the effect of beta-agonists. [91] [101] [104] MacKenzie et al [91] observed no effect of intracarotid norepinephrine (which has some beta-effect) on CBF and CMR in normal baboons. However, when these researchers disrupted the BBB by the intracarotid injection of hypertonic urea, norepinephrine caused increases in CBF and CMR. Artru et al [101] demonstrated that epinephrine caused CMRO$_2$ elevation in dogs but only when BBB permeability to Evans blue was present. Note that in neither of these studies were CBF/CMR changes observed without BBB abnormality. In addition, in the previously described investigation of Berntman et al, [93] CBF and CMR increased, and, although the BBB was not known to be abnormal, MAP was transiently very high (180 mm Hg), and such transient changes can open the BBB. [105] These observations beg the interpretation that beta-agonist increase CBF and CMR *only* when the BBB is injured. However, in the aforementioned clinical study of King et al, [89] MAP was apparently not excessively high, and CBF/CMR increases nonetheless occurred. Accordingly, it does not appear that BBB injury is a necessary condition in humans for the occurrence of beta-mediated increases in CBF and CMR, although such a defect probably exaggerates the phenomenon.

beta-Blockers

beta-Blockers have been reported variously to reduce or to have no effect on CBF and/or CMR. In investigations in several species, including baboons, propranolol has been reported to prevent or to attenuate CBF and CMR effects attributed to beta-agonists. [93] [99] [106] In two investigations in humans, propranolol, 5 mg intravenously, [107] and labetalol, 0.75 mg/kg intravenously [108] had no effect on CBF and CBFV, respectively. Dubois et al [109] observed modest reductions in CBF when labetalol was administered to patients undergoing craniotomy who became hypertensive during emergence from anesthesia. Esmolol has been reported to shorten seizures induced by electroconvulsive therapy, a finding suggesting that it does cross the normal BBB. [110] Esmolol was reported in abstract form to have no effect on CBF and CMR as long as CPP was maintained. [111] Catecholamine levels at the time of beta-blocker administration and/or the status of the BBB may influence the effect of these agents. The database with respect to these possibilities is incomplete. However, the data suggest that beta-blockers are unlikely to have adverse effects on patients with intracranial disorders, other than effects secondary to changes in perfusion pressure.

Dopamine

Dopamine is widely employed in the treatment of hemodynamic dysfunction. In addition, it is commonly used to augment the function of the normal cardiovascular system when MAP elevation is desired as an adjunct to the treatment of focal cerebral ischemia, especially in the setting of vasospasm. Nonetheless, its effects on CBF and CMR have not been defined with certainty. Taken together, the available data [94] [97] [112] [113] [114] [115] suggest that the predominant effect of dopamine in the normal cerebral vasculature is probably vasodilation with minimal CMR change. There is a possibility of a vasoconstrictive effect at high doses. However, vasoconstriction was not evident in rhesus monkeys given doses up to 100 mug/kg/min. In that same investigation, the same doses of dobutamine were associated with CBF and CMR increases of 20 to 30 percent. [115]

alpha$_2$ -Agonists

There is considerable interest in alpha $_2$ -agonists because of their apparent analgesic and sedative effects. This class includes dexmedetomidine and clonidine, with the latter a much less specific and less potent alpha $_2$ -agonist. It appears likely that their predominant effect is reduction of CBF with no effect on CMRO $_2$. [116] [117] [118] [119] [120] The mechanism of the CBF effect is not clear. Dexmedetomidine has been shown to cause constriction of isolated cerebral vessels, [121] a finding suggesting the presence of postsynaptic alpha $_2$ -receptors causing vasoconstriction. [122] It is also possible that alpha $_2$ -agonists act at a central site, such as the locus caeruleus, [62] to cause neurogenically mediated vasoconstriction.

Age

Aging (Chs. 59 and 61) , from childhood to late adulthood, is associated with progressive reduction of CBF and CMRO $_2$. [123] [124] This change may reflect the progressive neuronal loss that occurs with age.

/das/book/view/29494766/875/203.html

EFFECTS OF ANESTHETIC AGENTS ON CEREBRAL BLOOD FLOW AND CEREBRAL METABOLIC RATE

This section deals with the effect of anesthetic agents on CBF and CMR. It includes limited mention of influences on autoregulation, CO_2 responsiveness, and CBV. Discussions of effects on CSF dynamics, the BBB, and epileptogenesis appear later in this chapter.

In neuroanesthesia, considerable emphasis is placed on the manner in which anesthetic agents and techniques influence CBF. The rationale is 2-fold. First, the delivery of energy substrates is dependent on CBF, and, in the setting of ischemia, modest alterations in CBF can substantially influence neuronal outcome. Second, the control and manipulation of CBF are central to the management of ICP because, as CBF varies in response to vasoconstrictor-vasodilator influences, such as Pa CO_2 and volatile anesthetics, CBV varies linearly with it, albeit with some variation among anesthetic agents in the CBF/CBV ratio. [125] In normal brain, CBV is approximately 5 mL/100 g of brain, [126] and over a Pa CO_2 range of approximately 20 to 80 mm Hg, CBV changes by about 0.049 mL/100 g for each 1 mm Hg change in Pa CO_2 . [127] [128] In an adult brain weighing about 1,400 g, this can amount to a 20-mL change in total CBV for a Pa CO_2 range of 25 to 55 mm Hg.

Whereas CBV and CBF usually vary in parallel, there are exceptions. CBV increases during cerebral ischemia, [129] [130] and CBV may vary independently of CBF when MAP is the manipulated variable. Autoregulation normally serves to prevent MAP-related increases in CBV. In fact, as the cerebral circulation constricts to maintain a constant CBF in the face of a rising MAP, CBV actually decreases. [131] When autoregulation is impaired, or its upper limit (150 mm Hg) is exceeded, CBF and CBV then increase in parallel as arterial pressure rises (see Fig. 19-4) . A declining MAP results in a progressive increase in CBV as the cerebral circulation dilates to maintain constant flow, and exaggerated increases in CBV occur as MAP falls below the lower limit of autoregulation. [131] This increase in CBV in the face of falling MAP is almost certainly the principal reason for ICP increases attributed to narcotics (see the later discussion of sufentanil and alfentanil). In healthy subjects, the initial increases in CBV do not result in significant ICP elevation because there is latitude for compensatory adjustments by other intracranial compartments (e.g., translocation of venous blood and CSF to extracerebral vessels and the spinal CSF space, respectively). When intracranial compliance * is reduced, a CBV increase can cause herniation or may reduce CPP sufficiently to cause ischemia.

There have been several investigations of the effects of anesthetic agents on CBV in normal brain. [133] [134] [135] In general, the observed effects confirm a parallel relationship between CBF and CBV. However, the relationship is not consistently one to one, [125] [136] and CBF-independent influences on CBV may occur. It is also an unexplored possibility that anesthetic agents may influence the venous side of the cerebral circulation. Although the intracranial veins are a largely passive compartment, there is evidence, in some species, of some active control of venous caliber by either neurogenic or humoral mechanisms. [67] [69] [137] At present, there is no evidence that these direct effects have clinical significance. Nonetheless, the importance of blood volume on the venous side of the cerebral circulation should not be overlooked. Passive engorgement of these vessels as a result of the head-down posture, compression of the jugular venous system, or high intrathoracic pressure can have dramatic effects on ICP (see Fig. 52-4) .

Intravenous Anesthetic Agents

The general pattern of the effect of intravenous anesthetic agents is one of parallel alterations in CMR and CBF. Most intravenous agents cause a reduction of both. Ketamine, which causes an increase in CMR and CBF, is the exception. The effects of selected intravenous anesthetic agents on human CBF are compared in Figure 19-6 .

It is probable that intravenous agent-induced changes in CBF are largely the result of effects on CMR with parallel (coupled) changes in CBF. If this were the entire explanation, the CBF/CMR ratio would be the same for all agents. It is not. It is therefore likely that there are also direct effects on cerebral vascular smooth muscle (e.g., vasoconstriction, vasodilation, alteration of autoregulatory function) that make contributions to the net effect. For instance, although barbiturates are generally thought of as cerebral vasoconstrictors, some barbiturates actually cause relaxation of cerebral vascular smooth muscle in isolated vessel preparations. [138] [139] [140] However, *in vivo,* a substantial reduction in CMR occurs, and the net effect at the point of EEG suppression

* Note a well-entrenched misuse of terminology. [132] The "compliance" curve that is commonly drawn to describe the intracranial pressure-volume relationship (see Fig. 52-2) actually depicts the relationship DeltaP/DeltaV (elastance) and not DeltaV/DeltaP (compliance). What is here referred to as "reduced compliance" is more correctly described as "increased elastance." Not all disciplines, including most notably neurosurgery, have adopted the revised terminology. The authors have therefore left the misuse uncorrected here.

is vasoconstriction and a substantial decrease in CBF. [21] It appears that, in general, autoregulation and CO_2 responsiveness are preserved during administration of intravenous anesthetic agents.

Barbiturates

A dose-dependent reduction in CBF and CMR occurs with barbiturates. With the onset of anesthesia, CBF and $CMRO_2$ are reduced by about 30 percent. [141] [142] When large doses of thiopental cause complete EEG suppression, CBF and CMR are reduced by about 50 percent. [21] [143] [144] Further increases in the dose of barbiturate have no additional effect on CMR. [21] [145] These observations suggest that the major effect of nontoxic doses of depressant anesthetics is a reduction in the component of cerebral metabolism that is linked to brain function (e.g., neurophysiologic activity), with only minimal effects on the second component, that related to cellular homeostasis (see Fig. 19-1) .

Tolerance to the CBF/CMR effects of barbiturates may develop quickly. [146] [147] In patients with severe head injury in whom "barbiturate coma" was maintained for 72 hours, the thiamylal blood concentration required to maintain EEG burst suppression was observed to be increased by the end of the first 24 hours and continued to increase over the next 48 hours. [148] During deep pentobarbital anesthesia, autoregulation is maintained to arterial pressures as low as 60 mm Hg. [149] CO_2 responsiveness also persists. [150]

Propofol

The effects of propofol (2,6-di-isopropylphenol) on CBF and CMR appear to be quite similar to those of the barbiturates. Three investigations in humans have revealed substantial reductions in both CBF and CMR after propofol administration. [151] [152] Stephan et al [152] administered propofol by bolus plus infusion (2 mL/kg and 0.2 mL/kg/min, respectively) and observed average CBF and CMR decreases of 51 and 36 percent, respectively. Alkire et al [153] assessed cerebral glucose metabolism in volunteers using positron emission tomography (PET) before and during infusion of propofol to the point of unresponsiveness. Whole-brain metabolic rate decreased by 48 to 58 percent, with limited regional heterogeneity observed. Ravussin et al [154] measured lumbar CSF pressure during induction of anesthesia by slow bolus administration of propofol (1.5 mL/kg over 30 s) in patients scheduled for craniotomy. These investigators observed maximal average reductions in lumbar

CSF pressure and in CPP of 32 and 10 percent, respectively.

Both CO_2 responsiveness and autoregulation appear to be preserved during the administration of propofol in humans. [155] [156] Seizures and opisthotonos have been reported to occur after propofol anesthesia. [157] [158] [159] [160] [161] However, systematic studies in both humans [162] [163] [164] and animals, [165] [166] although identifying the occurrence of occasional dystonic and choreiform [162] movements, have failed to confirm the notion that propofol is proconvulsant. In fact, propofol appears to be anticonvulsant in animals (mice). [165] [166] Furthermore, seizures from electroconvulsive therapy were shorter after induction of anesthesia with propofol than with methohexital, [167] a finding that is more consistent with an anticonvulsant effect. In addition, propofol sedation has been widely employed during "awake" resections of seizure foci and other intracranial lesions. [163] [164] [168] Although pronounced high-amplitude beta-frequency activity in the EEG has been observed, [169] there has not been an unexpected incidence of seizures.

Etomidate

The effects of etomidate on CBF and CMR are also superficially similar to those of barbiturates. Roughly parallel reductions in CBF and CMR occur in humans, [170] [171] and they are in general accompanied by progressive suppression of the EEG. [172] The CBF/CMR changes are substantial. Renou et al [170] gave approximately 0.2 mg/kg of etomidate to adults and observed mean reductions in CBF and CMR of 34 and 45 percent, respectively. In dogs, as is the case with barbiturates, no further reduction of CMR occurs when additional drug is administered beyond a dose sufficient to produce EEG suppression. [23] This latter phenomenon has not been demonstrated in humans. However, Bingham et al [173] observed that etomidate lowered ICP when administered to severely head-injured patients in whom EEG activity was well preserved but was ineffective when there was substantial antecedent EEG suppression. Canine data reviewed by Milde et al [23] suggested that, although the global CMR suppression attainable with etomidate is substantial, it is slightly less profound than that achieved with isoflurane and barbiturates. This finding is consistent with the observations of Davis et al [174] that, unlike barbiturates, which cause CMR suppression throughout the brain, the CMR suppression caused by etomidate is regionally variable and occurs predominantly in forebrain structures.

Etomidate has been shown to be effective in reducing ICP without causing reduction of CPP in patients with intracranial tumors [175] and in head-injured patients. [176] However, concerns regarding the occurrence of adrenocortical suppression and renal injury caused by the propylene glycol vehicle [177] probably preclude more than episodic use.

Reactivity to CO_2 is preserved in humans during etomidate administration. [170] [171] Autoregulation has not been evaluated. Myoclonus and epileptogenesis are discussed in a later section.

Narcotics

There are inconsistencies in the available information, but it is likely that narcotics have relatively little effect on CBF and CMR in the normal, unstimulated nervous system. [178] When changes occur, the general pattern is one of modest reductions in both CBF and CMR. The inconsistencies in the literature probably arise largely because, in many studies, the "control" state entailed paralysis and nominal sedation, often with N_2O alone. In these studies, in which substantial reductions of CBF and CMR were frequently observed, the effect of the narcotic was probably a combination of the inherent effect of the agent plus a substantial component resulting from reduction of arousal. Comparable effects related to reduction of arousal may occur and may be

important clinically. However, they should be viewed as nonspecific effects of sedation and/or pain control rather than as specific properties of narcotics. The following discussion emphasizes investigations in which control measurements were unlikely to have been markedly influenced by arousal phenomena.

Morphine.

When morphine (
1 mg/kg) was administered as the sole agent in human patients, Moyer et al [179] observed no effect on global CBF and a 41 percent decrease in $CMRO_2$. The latter is a substantial reduction, and the absence of a simultaneous CBF adjustment is surprising. There have been no other such investigations of morphine alone in humans. Jobes et al [180] gave morphine (1 and 3 mg/kg) with 70 percent N_2O to patients and observed no significant change in CBF or CMR. The N_2O that was used could be expected to have caused a tendency toward increases in CBF and CMR. The relative absence of *net* changes in these variables from the awake control measurements suggests a small to moderate depressive effect of morphine on CBF and CMR at this large dose. Takeshita et al [181] gave morphine, 3 mg/kg, to dogs sedated with 70 percent N_2O (
0.6 MAC). These researchers observed reductions of global CBF and $CMRO_2$ of approximately 60 and 17 percent, respectively. These data cannot be completely reconciled, and the data of Jobes et al [180] are probably relevant to the most common clinical situations. However, morphine can cause substantial histamine release in individual patients. Histamine is a cerebral vasodilator that causes an increase in CBV and a CBF effect that varies depending on the systemic blood pressure response. Autoregulation was observed to be intact between MAP of 60 and 120 mm Hg in human volunteers anesthetized with morphine, 2 mg/kg and 70 percent N_2O. [182]

Fentanyl.

Limited human data are available. Vernhiet et al [183] measured CBF and $CMRO_2$ before and during anesthesia with 12 to 30 (mean, 16) mug/kg of fentanyl with 50 percent N_2O to patients about to undergo cerebral angiography. Atropine and pancuronium were the only other agents administered. Neither CBF nor $CMRO_2$ changed significantly from awake control values in this group of six subjects. However, one of the patients (an epileptic patient with a normal computed tomography [CT] scan) had dramatic and unexplained increases in both CBF and $CMRO_2$. For the remaining five patients, CBF and $CMRO_2$ decreased by 21 and 26 percent, respectively ($P < .05$). The data for fentanyl and N_2O presented in Figure 19-6 are derived from these five patients who received an average of 17 mug/kg of fentanyl. Murkin et al [184] measured CBF before and after induction of anesthesia with high-dose fentanyl, 100 mug/kg, and diazepam, 0.4 mg/kg. CBF fell by 25 percent, although part of this effect may well have been the result of the benzodiazepine (see later) rather than of the fentanyl. Firestone et al, [185] using PET, observed a heterogeneous CBF response to 1.5 mug/kg of fentanyl in healthy volunteers. Increases occurred in frontal, temporal, and cerebellar areas simultaneous with decreases in discrete areas associated with pain-related processing. [185] There are additional data derived from animal experiments. McPherson et al [186] administered fentanyl (25 mug/kg) to pentobarbital-anesthetized dogs and observed no effect on CBF and

Figure 19-6 Changes in cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) caused by intravenous anesthetic agents. The data are derived from human investigations and are presented as a percentage of change from unanesthetized control values. See text for details. No data for the $CMRO_2$ effects of midazolam in humans are available. The data were derived from references [143] [152] [170] [180] [183] [197] [221] [223] and [240]. n.s., not statistically significant.

CMR. CO_2 responsiveness and autoregulation were unaffected, and the hyperemic CBF response to hypoxia also remained intact. Several investigations in lightly anesthetized animals [187] [188] [189] demonstrated much larger fentanyl-induced reductions in CBF and/or CMR than those observed in humans. These data taken together suggest that fentanyl causes a moderate global reduction in CBF and CMR in the normal quiescent brain and, like morphine, causes larger reductions when administered during arousal.

Alfentanil: CBF Effects.

McPherson et al [190] administered alfentanil, 320 mug/kg, to pentobarbital-anesthetized dogs. These researchers observed no changes in CBF, CMR, CO_2 responsiveness, autoregulation, or the CBF response to hypoxia. There have been no studies of the CMR effects of alfentanil in humans. Schregel et al [191] administered 25 to 50 mug/kg of alfentanil to patients receiving 60 percent N_2O after induction of anesthesia with thiopental. CBF velocity (CBFV) decreased transiently. A Doppler measure of middle cerebral artery (MCA) diameter was simultaneously unchanged, a finding suggesting that the CBFV reduction was indicative

of a CBF decrease. Mayberg et al [192] also observed no change in CBFV in response to 25 to 50 mug/kg of alfentanil given to patients during maintenance of anesthesia with isoflurane and N_2O.

Sufentanil: CBF Effects.

Although some laboratory investigations have revealed apparent sufentanil-induced increases in CBF and CMR, [193] most investigations in both animals [194] [195] [196] and humans have indicated that sufentanil

causes, depending on dose, either no change or reductions in CBF and CMR. Stephan et al [197] measured CBF and $CMRO_2$ in patients before and after induction of anesthesia with 10 mug/kg of sufentanil. These investigators observed a 29 percent reduction of CBF and a 22 percent reduction in $CMRO_2$. Murkin et al, [198] in a study involving the same dose of sufentanil and a similar design, made essentially identical observations. Mayer et al [199] gave 0.5 mug/kg of sufentanil to volunteers and observed no change in CBF. Weinstabl et al [200] observed reductions in CBFV when 1.0 and 2.0 mug/kg of sufentanil were given to patients in the intensive care unit (ICU) who had increased ICP. Neither Weinstabl et al [200] nor Mayer et al, [199] who administered sufentanil to healthy volunteers, observed changes in CBFV after 0.5 mug/kg of sufentanil.

Sufentanil: ICP Effects.

The data from the foregoing studies led to the anticipation of no change or a reduction in ICP as a result of administration of either sufentanil or alfentanil. With respect to sufentanil, the bulk of the data derived in animals [193] [195] [196] [201] and in humans [200] [202] [203] [204] [205] have revealed no change in ICP following its administration. However, in some investigations in humans, sufentanil was associated with modest increases in neuraxis pressure. [206] [207] [208] Subsequent investigations appear to indicate that the ICP increases associated with sufentanil are at least in large part the consequence of a normal autoregulatory response to the sudden MAP reduction that can occur as a consequence of sufentanil administration. [209] The message for the clinician should probably be that sufentanil (and, for that matter, fentanyl as well [204]) are best administered in a manner that does not produce a sudden reduction of MAP. MAP reduction clearly reduces CPP and may increase ICP, each of which, in sufficient extreme, may be deleterious. However, it should be noted that the ICP increases attributed to sufentanil have been small. Furthermore, four investigations [210] [211] [212] [213] that compared conditions in the surgical field, including pressure under brain retractors, [210] identified no adverse influences attributable to sufentanil. Accordingly, sufentanil need not be viewed as in any way contraindicated, although it should be used with attention to its effect on MAP.

Alfentanil: ICP Effects.

Although there are fewer data for this drug, the general pattern is similar, and the conclusions should be the same as for sufentanil (preceding paragraph). [206] [214] [215] [216] [217] Alfentanil was included with fentanyl and sufentanil in two of the investigations of conditions in the surgical field mentioned in connection with sufentanil. [210] [211] No adverse effects were noted.

Remifentanil.

Investigations of moderate doses of remifentanil in humans have revealed minimal effects that are very similar to those of the other synthetic narcotics (with the exception of its substantially shorter duration of action). In patients undergoing craniotomy for supratento-rial space-occupying lesions, 1 mug/kg of remifentanil caused no change in ICP. [218] In a second investigation in patients undergoing craniotomy, approximately 0.35 mug/kg/min of remifentanil resulted in CBF values comparable to those observed with moderately deep anesthesia with either isoflurane/N_2O or fentanyl/N_2O, [219] and CO_2 responsiveness was preserved. [219] Greater doses of remifentanil may have more substantial effects. CBFV in the MCA decreased 30 percent in response to 5 mug/kg, followed by 3 mug/kg/min of remifentanil at a constant MAP in patients being anesthetized for bypass surgery. [220] Quantitatively similar observations were made after a large dose of sufentanil in patients undergoing cardiac anesthesia (see earlier). [197]

Benzodiazepines

Benzodiazepines cause parallel reductions in CBF and CMR in humans and monkeys. CBF and $CMRO_2$ decreased by 25 percent when 15 mg of diazepam was given to head-injured patients. [221] Lorazepam given to monkeys in doses sufficient to cause sedation reduced CBF by 24 percent and $CMRO_2$ by 21 percent. [222] The effects of midazolam on CBF (but not CMR) have also been studied in humans. Forster et al [223] [224] observed a 30 to 34 percent reduction in CBF after administration of 0.15 mg/kg of midazolam to awake healthy human volunteers. Veselis et al, [225] using PET, observed a global CBF reduction of 12 percent after a similar dose and noted that the decreases occurred preferentially in the brain regions associated with arousal attention and memory. CO_2 responsiveness was preserved. [226]

The foregoing studies indicate that benzodiazepines should cause moderate reduction of CBF in humans and suggest that the effect may be metabolically coupled. The extent of the maximal CBF and CMR reductions produced by benzodiazepines is probably intermediate between the decreases caused by narcotics (modest) and barbiturates (substantial). [21] [227] [228] It appears that benzodiazepines should be safe to administer to patients with intracranial hypertension provided respiratory depression and an associated increase in Pa CO_2 do not occur.

Flumazenil

Flumazenil is a highly specific, competitive benzodiazepine receptor antagonist. It had no effect on CBF when administered to unanesthetized human volunteers. [224] In two investigations in dogs with normal intracranial compliance, [227] [229] flumazenil resulted in reversal of the CBF-, CMR-, and ICP-lowering effects of midazolam. Whereas Knudsen et al [230] observed no change in either CBF or CMR when patients were aroused from flumazenil midazolam anesthesia at the conclusion of craniotomy for brain tumor resection, Chiolero et al [231] reported severe increases in ICP when flumazenil was given to midazolam-sedated head-injured patients in whom ICP was poorly controlled prior to administration of flumazenil. These latter observations are consistent with two animal investigations. In the investigation of Fleischer et al, [227] mentioned earlier, flumazenil not only reversed the CBF and CMR effects of midazolam, but also caused a substantial, although short-lived, overshoot above premidazolam levels in both CBF (by 44-56%) and ICP (by 180-217%). CMR did not rise higher than control levels, a finding indicating that the CBF increase was not metabolically coupled. A similar increase in CBF after flumazenil reversal of midazolam has also been observed in cats. [232] The CBF overshoot effect is unexplained, but it may

be a neurogenically mediated arousal phenomenon. [233] Flumazenil should probably be avoided or used very cautiously to reverse benzodiazepine sedation in patients with impaired intracranial compliance.

Droperidol

There have been no human investigations of the CBF and CMR effects of droperidol in isolation. However, the available information from animal investigations and drug combination administration in humans [189] [234] [235] [236] [237] taken together suggests that droperidol is not a cerebral vasodilator and probably has little effect on CBF and CMR in humans. The occasional ICP increases that have been observed [235] probably reflect a normal autoregulation-mediated vasodilation in response to an abrupt fall in MAP.

Ketamine

Among the intravenous agents, ketamine is unique in its ability to cause increases in both CBF and CMR. [238] [239] [240] [241] [242] Animal studies indicate that the changes

in CMR are regionally variable. In rats, substantial increases occur in limbic system structures simultaneous with modest changes or small decreases in cortical structures. [239] [243] Depth-electrode studies of ketamine-induced convulsive phenomena suggest that similar preferential activation of thalamic and limbic structures also occurs in humans. [244] The CMR increases that have been repeatedly demonstrated in animals, [239] [243] [245] however, have not been verified in humans. In the only investigation of CMR effects in humans, Takeshita et al [240] observed a 62 percent increase in CBF and no change in CMR, and the explanation for this discrepancy is unclear.

The anticipated ICP correlate of the CBF increase has been confirmed to occur in humans. [246] [247] However, anesthetic agents (diazepam, midazolam, isoflurane/N_2O) have been shown to blunt or to eliminate the ICP or CBF increases associated with ketamine. [242] [246] [248] [249] In fact, decreases in ICP have been reported in response to relatively large doses of ketamine (1.5-5 mg/kg) administered to propofol-sedated head-injured patients. [250] Autoregulation during ketamine administration has not been directly tested. CO_2 responsiveness is preserved. [247] Accordingly, although ketamine is probably best avoided as the sole anesthetic agent in patients with impaired intracranial compliance, it may be reasonable to use it cautiously in patients who are simultaneously receiving the other agents mentioned earlier.

Lidocaine

Lidocaine produces a dose-related reduction of $CMRO_2$ in experimental animals. [251] In dogs, 3 mg/kg lowered $CMRO_2$ by 10 percent, and 15 mg/kg reduced it by 27 percent. When very large doses (160 mg/kg) were given to dogs receiving cardiopulmonary bypass, the reduction in $CMRO_2$ was apparently greater than that seen with high-dose barbiturates. [145] This may arise because the membrane-stabilizing effect of lidocaine also reduces the energy requirement for the maintenance of membrane integrity. In unanesthetized human volunteers, Lam et al [252] observed CBF and CMR reductions of 24 and 20 percent, respectively, after administration of 5 mg/kg of lidocaine over 30 minutes, followed by infusion of 45 mug/kg/min.

Bedford et al [253] compared the effectiveness of bolus doses of thiopental sodium, 3 mg/kg, and lidocaine, 1.5 mg/kg, in controlling the acute increase in ICP that occurred following application of a pin head holder or skin incision in patients undergoing craniotomy. The two regimens were equally effective in causing ICP reduction. However, the MAP decrease was greater with thiopental. Accordingly, a bolus dose of lidocaine is a reasonable adjunct to the prevention or treatment of acute ICP elevation, and it has been recommended for use in the prevention of ICP increases associated with endotracheal suctioning. [254] Note that large doses of lidocaine can produce seizures in humans and in some experimental animals. [255] Lidocaine-induced seizures have not been reported in anesthetized humans. Nonetheless, it seems appropriate to restrict lidocaine doses to amounts that achieve serum levels less than the seizure threshold (>5-10 mug/mL) in awake humans. [256] Viegas et al [257] reported peak serum concentrations of 6.6 to 8.5 mug/mL after a 2-mg/kg bolus of lidocaine. Bolus doses of 1.5 to 2.0 mg/kg therefore seem appropriate.

Inhaled Anesthetics

Volatile Anesthetics

The pattern of volatile agent effects on cerebral physiology is a striking departure from that observed with the intravenous agents, which cause generally parallel changes in CMR and CBF. All the volatile agents produce a dose-related reduction in CMR while simultaneously causing no change or an increase in CBF. [22] [258] [259] [260] [261] [262] As a consequence of this pattern, it has been said that volatile agents cause "uncoupling" of flow and metabolism. However, there is considerable evidence that coupling (CBF adjustments paralleling changes in CMR) persists during volatile agent anesthesia. [259] [263] [264] [265] [266] [267] Accordingly, it is probably more accurate to say that the CBF/CMR ratio is altered (increased) by volatile anesthetics. This alteration is dose related, and under steady-state conditions, there is a positive correlation between MAC multiples and the $CBF/CMRO_2$ ratio. [34] [260] [268] [269] In other words, higher MAC levels cause greater "luxury" perfusion.

The important clinical consequences of volatile agent administration are derived from the increases in CBF and CBV, and consequently ICP, that can occur. Of the commonly employed volatile agents, the order of vasodilating potency is approximately halothane >> enflurane > isoflurane = sevoflurane = desflurane. [26] [262] [267] [270] [271] [272] [273]

CBF Effects.

Because volatile anesthetics modify autoregulation, their effects on CBF and ICP should only be compared when arterial pressure is supported to a common level. In humans, when MAP is maintained at 80 mm Hg, equipotent (1.1 MAC) levels of halothane, enflurane, and isoflurane caused CBF increases of 191, 37, and 18 percent, respectively (Fig. 19-7) . [270] A similar potency scale was observed in a study that compared the degree of brain surface

Figure 19-7 Estimated changes in cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) caused by volatile agents. The CBF data for halothane, enflurane, and isoflurane were obtained during 1.1 MAC anesthesia (with blood pressure support) in human patients, [270] expressed as a percentage of change from awake control values. The $CMRO_2$ data for halothane, enflurane, and isoflurane were obtained in the cat [260] [277] and are expressed as a percentage of change from nitrous oxide (N_2O)-sedated control values. The data for sevoflurane were obtained during 1.1 MAC anesthesia in the rabbit and are expressed as a percentage of change from a morphine/N_2O-anesthetized control state. [262]

protrusion through a craniectomy in cats. [274] The combined results of other studies in humans, most using transcranial Doppler (TCD), indicate that the effects of isoflurane, desflurane (Fig. 19-8) , and sevoflurane are very similar, [267] [273] [275] with relatively little change in CBF (versus baseline determinations in the awake state) at 1.0 MAC concentrations. However, because of variations in blood pressure among study groups and among investigations, a strictly quantitative comparison is not possible. Note that there is some discrepancy among studies in the literature as to the magnitude of the effects of the volatile agents on CBF. Much of this may occur as a result of the interaction of regionally selective CBF methods with the heterogeneity within the cerebrum of the CBF effects of volatile agents. See the discussion on distribution of CBF/CMR changes later.

The effect of volatile anesthetics on CBF is probably the sum of several influences. These include a tendency toward CBF reduction caused by a depression of CMR and a CBF-increasing effect due to vasodilation caused by a substantial direct effect on vascular smooth muscle. [264] As noted previously, NO may be involved in both processes. [7] [8] [9] [10] [20] [276] The effect on smooth muscle apparently predominates, and the net effect of the volatile anesthetics is an increase in global CBF. The suppression of CMR caused by equi-MAC concentrations of the volatile agents differs (isoflurane, enflurane, desflurane, sevoflurane > halothane) (see Figs. 19-7 and 19-8) , and it seems likely that this is the basis of the difference in the magnitude of the CBF increases they cause (halothane > enflurane, isoflurane, desflurane, and sevoflurane).

CMR Effects.

All the volatile agents cause reductions in CMR. The degree of $CMRO_2$ reduction that occurs at a given MAC level is less with halothane than with the other four agents (see Fig. 19-7) . Sevoflurane's effect on CMR is very similar to that of isoflurane [262] (see Fig. 19-7) . The available information, derived in separate investigations in dogs, suggests that desflurane causes slightly less suppression of $CMRO_2$ than does isoflurane, especially at concentrations higher than 1.0 MAC. [22] [261] No direct comparisons of the $CMRO_2$ effects of all of the volatile agents have been

Figure 19-8 A comparison of the effects of desflurane and isoflurane on cerebral blood flow (CBF) (mL/100 g/min) and cerebral metabolic rate for oxygen ($CMRO_2$) (mL/100 g/min). The CBF data were obtained by Ornstein et al [272] in patients anesthetized with the volatile agent in air/oxygen. The $CMRO_2$ data were derived in separate investigations of desflurane by Lutz et al [261] and of isoflurane by Newberg et al [22] performed in the same laboratory using the same canine model.

performed in humans. The administration of 1.0 MAC of each agent to N_2O-sedated cats resulted in approximate $CMRO_2$ reductions of 25 percent with halothane and 50 percent with isoflurane and enflurane. [260] [277] The $CMRO_2$ reduction is dose related. With isoflurane (and almost certainly desflurane and sevoflurane as well), maximal reduction is attained simultaneously with the occurrence of EEG suppression. [22] [261] This occurs at clinically relevant concentrations, that is, 1.5 to 2.0 MAC in humans. [267] [278] In dogs, additional isoflurane up to 6.0 percent end-tidal results in no further CMR reduction and no indication of metabolic toxicity. [22] Halothane presents a contrast to this pattern. Halothane concentrations in excess of 4.0 MAC are required to achieve EEG isoelectricity in dogs, and additional halothane causes further reduction of $CMRO_2$ in concert with alterations in energy charge. The latter changes, which are reversible, suggest interference with oxidative phos-phorylation. [258] These data indicate that, unlike isoflurane, halothane can produce reversible toxicity when administered in very high concentrations.

There is some alinearity in the CBF and CMR dose-response relationships for volatile anesthetics. The initial appearance of an EEG pattern associated with the onset of anesthesia with halothane, enflurane, and isoflurane is accompanied by a precipitous decline in $CMRO_2$. [141] Thereafter, $CMRO_2$ declines in a slower dose-dependent manner. Other studies during anesthetic induction with halothane found marked increases in CBF prior to any alteration in CMR. [142] This finding suggests that the direct effect of a volatile agent on smooth muscle may develop more rapidly than influences related to depression of CMR.

Distribution of CBF/CMR Changes.

The regional distribution in anesthetic-induced changes in CBF and CMR differs markedly with halothane and isoflurane. Halothane produces relatively homogeneous changes throughout the brain. CBF is globally increased, and CMR is globally depressed. The changes caused by isoflurane are more heterogeneous. CBF increases are greater in subcortical areas and hindbrain structures than in the neocortex [25] [26] [279] (Fig. 19-9) (Figure Not Available) . For CMR, the converse is true, with greater reduction in the neocortex than in the subcortex. [24] Desflurane and sevoflurane have not been submitted to similar local CBF (l-CBF) studies. However, given their various similarities, including the similarity of their effects on the EEG (suggesting similar cortical CMR and CBF effects), the interim assumption of similar heterogeneity of CBF distribution seems reasonable. These distribution differences may explain certain apparent contradictions in reported CBF effects in the existing literature for isoflurane. Methods that assess the entire cerebrum and can measure true global CBF (microspheres, PET, autoradiography) will reveal greater increases in CBF than those that emphasize the cortical compartment (radioactive xenon techniques, TCD, venous outflow). For instance, Eintrei et al [271] reported no increase in CBF when isoflurane was administered to patients undergoing craniotomy, yet Adams et al, [280] Grosslight et al, [281] and Campkin et al [282] reported that administration of isoflurane to normocapnic subjects with intracranial disease can result in increases in CSF pressure. The CBF methodology used by Eintrei et al [271] measured cortical flow exclusively, and accordingly, these results of the three investigations are again consistent with a pattern of minimal vasodilation in the cortex and greater increases in CBF in the remainder of the brain.

Cerebral Vasodilation by Volatile Agents: Clinical Implications.

The data presented thus far, in sum, indicate that although isoflurane and, probably, desflurane and sevoflurane may have little cerebral vasodilating effect in cortex, they nonetheless probably cause net cerebral vasodilation in a dose-dependent fashion. Are isoflurane and desflurane and sevoflurane therefore contraindicated in the face of abnormal intracranial compliance? No. Note that the instances of CSF pressure (CSFP)/ICP increases in response to the administration of isoflurane observed in the studies of Adams et al [280] and Campkin et al [282] were usually readily prevented or reversed by the induction of hypocapnia. This indicates that, particularly in the sub-MAC concentrations typical of balanced anesthesia, the use of these drugs is reasonable when there is proper attention to the other important determinants of ICP, in particular CO_2 tension. One report does, however, describe the occurrence of apparent isoflurane-induced increases of ICP in the setting of large cerebral tumors in spite of the induction of hypocapnia. [281] Accordingly, there should be discretion in the setting of large mass lesions, unstable ICP, or sufficient derangement of cerebral physiology that CO_2 responsiveness and flow-metabolism coupling may be impaired in some or all of the brain. When these situations occur (the somnolent, vomiting patient with papilledema, a large mass, and compressed basal cisterns) the clinician may be well advised

Figure 19-9 (Figure Not Available) Regional differences in the cerebral blood flow (CBF) effects of isoflurane (ISO) and halothane (HAL). [25] The figure is a schematic representation of CBF in a coronal autoradiographic image of rat brain. The key indicates the approximate CBF (mL/100 g/min). In the cortex, CBF is less during anesthesia with isoflurane than with halothane. In the subcortex, CBF is similar during anesthesia with the two agents in some structures, and in others it is greater with isoflurane. The average hemispheric CBF with the two agents is very similar. Similar CBF distribution differences occur in humans, although the mean global CBF is greater for halothane than for isoflurane. [26] Amg, amygdala; CPu, caudate-putamen; Ctx, cortex; Hip, hippocampus; Thl, thalamus. *(From Hansen et al [25])*

to use a predominantly intravenous technique until such time as the cranium and dura are open and the effect of the anesthetic technique can be directly assessed. These events are relatively rare in elective neurosurgery.

Situations in which there has been substantial antecedent lowering of CMR by drug administration or disease processes should also justify caution in the use of volatile agents. If a volatile agent has a substantial direct vasodilating effect on the cerebral vasculature that is normally offset by an opposing metabolically mediated vasoconstricting influence, it may be surmised that, when near maximal reduction of CMR has occurred, introduction or an increase in the volatile agent will have a predominantly vasodilating effect. [264] [283] There are data to support this prediction. Murphy et al [270] observed no increase in CBF (versus awake control measurements) during anesthesia with 0.6 and 1.1 MAC isoflurane (with blood pressure support) but at 1.6 MAC, CBF had increased by 100 percent. Maekawa et al [24] measured CBF and l-CMR for glucose (l-CMRg) in rats both awake and during anesthesia with increasing concentrations of isoflurane; 1 MAC isoflurane resulted in an average CMRg decrease in five cortical areas of 54 percent of the awake control value and no change in average CBF. An additional 1.0 MAC (i.e., a total of 2.0 MAC) caused a further CMRg reduction of only 20 percent of the control value, and CBF simultaneously increased by 70 percent (Fig. 19-10) . These data together suggest that isoflurane is a significant cerebral vasodilator when administered in concentrations at and higher than those associated with near maximal CMR suppression or, perhaps, when administered when the component of CMR that is associated with electrophysiologic function is already suppressed by other drugs [264] [283] or pathologic processes.

The net vasodilating effect of equi-MAC concentrations of isoflurane, desflurane, and sevoflurane is less in humans than that of halothane, and the former drugs are probably

Figure 19-10 The relationship between changes in local cerebral metabolic rate for glucose (l-CMRg) and local cerebral blood flow (l-CBF) in the motor-sensory cortex in rats during isoflurane anesthesia. The majority of the CMR suppression caused by isoflurane has occurred by 1.0 MAC, and in this concentration range, CBF is not increased. Thereafter, additional isoflurane causes little further CMR reduction, and cerebral vasodilation occurs. These data (±SD), from Maekawa et al, [24] suggest the importance of metabolic coupling in determining the CBF effects of isoflurane. MAP, mean arterial pressure.

therefore preferable if a volatile agent is to be used in the setting of impaired intracranial compliance. That is not to say that halothane is contraindicated in these circumstances. It has been clearly demonstrated that, when hypocapnia is established prior to the introduction of halothane, the increases in ICP that could otherwise occur in a normocapnic patient with poor intracranial compliance can be prevented or greatly attenuated. [284] Nonetheless, most clinicians prefer isoflurane, desflurane, or sevoflurane because the margin for error is probably wider than with halothane. In addition, it has been demonstrated that avoidance of major ICP elevation can be accomplished by the induction of hypocapnia *simultaneously* with the introduction of isoflurane, [280] whereas CO_2 reduction should be instituted *before* exposure to halothane [284] if ICP increases are to be prevented in a patient population at risk.

Time Dependence of CBF Effects.

The effect of volatile anesthetic agents on CBF has been shown to be time dependent in animal investigations. After an initial increase, CBF falls substantially, reaching a steady state near prevolatile agent levels between 2½ and 5 hours after exposure. [40] [279] [285] The mechanism of this effect is not understood, and the phenomenon was not evident in humans studied during 3- or 6-hour exposures to halothane, isoflurane, desflurane, or sevoflurane. [267] [286]

CO_2 Responsiveness and Autoregulation.

CO_2 responsiveness is well maintained during anesthesia with all the volatile anesthetic agents. [34] [272] [287] [288] [289] By contrast, autoregulation of CBF in response to rising arterial pressure is impaired. This impairment appears to be most apparent with the agents that cause the greatest cerebral vasodilation, [260] [270] and it is dose related [290] [291] (see Fig. 19-5) . Sevoflurane may cause less impairment of autoregulation than other volatile agents. Two studies surprisingly reported no change in CBFV in response to phenylephrine-induced MAP increases during anesthesia with 1.2 to 1.5 MAC sevoflurane. [289] [292] The autoregulatory response to rising pressure is, however, rarely of significance in clinical neuroanesthesia. If anything, it is the CBF response to falling pressure that is important and, as with all vasodilators, CBF is preserved to lower MAP during administration of volatile agents, with no evidence of differences among the various agents. Direct comparisons of CBF with isoflurane, desflurane, and sevoflurane during hypotension are not available.

Epileptogenesis.

Enflurane is potentially epileptogenic in the clinical setting. Of particular relevance to neuroanesthesia is the observation that hypocapnia potentiates seizure-type discharges during enflurane anesthesia. [293] A 50 percent decrease in $CMRO_2$ was noted in human volunteers anesthetized with 3 percent enflurane, but with the onset of seizure activity, $CMRO_2$ returned to normal, [294] indicating the preservation of flow-metabolism coupling. Note that there is no evidence that this type of EEG activity is deleterious when O_2 delivery is maintained during the event. However, because seizure activity can elevate brain metabolism by as much as 400 percent, the use of enflurane, especially in high doses and with hypocapnia, should probably be avoided in patients predisposed to seizures and/or with occlusive cerebrovascular disease.

The EEG-activating property of enflurane has been used intraoperatively to activate and to identify seizure foci that are to be surgically resected, and in this situation, spike activity not present preoperatively has been observed to persist after surgery. [295] There have also been two reports of seizures in the immediate postoperative period following enflurane anesthesia in both predisposed [296] and nonpredisposed individuals. [297] There have been no apparent permanent sequelae from these events, and, in fact, this association is not rigorously proven. At worst, such occurrences are extremely uncommon.

Isoflurane can cause EEG spiking and myoclonus, but, in the experimental setting, it has not been associated with the frank epileptoid activity induced by enflurane. The clinical experience with isoflurane is very large, and unexplained "seizure-like activity" has been reported in only two patients. One occurrence was intraoperative, [298] and the other was immediately postoperative. [299] It therefore appears that epileptogenesis is not a clinical concern with isoflurane. In fact, isoflurane has been successfully employed to control EEG seizure activity in refractory status epilepticus. [300]

Seizures have been reported to occur during induction of anesthesia with high concentrations of sevoflurane in children, including children without a recognized seizure diathesis. [301] [302] Seizure induction in response to intense peripheral stimulation has also been demonstrated in cats receiving 5 percent sevoflurane. [303] No events in response to maintenance concentrations have been reported.

Brain Glucose Concentration.

Kofke et al [304] compared the brain concentrations of glucose and several other intermediary metabolites during administration of halothane, enflurane, and isoflurane in rats. Brain glucose was greater with isoflurane than with halothane and enflurane, but there were no differences in any of the other markers. Plasma glucose concentration was also increased in the isoflurane group and the plasma/brain glucose ratio did not differ among the three agents. There have been no evaluations of brain glucose concentration in humans; however, an increased plasma glucose concentration (versus halothane) has been reported to occur during isoflurane anesthesia. [305] The concern is that increased glucose availability has been shown in both clinical and experimental circumstances to worsen outcome following an episode of cerebral ischemia. However, the clinical significance of this effect of isoflurane is completely unknown, and, at present, the issue should be viewed as a matter of laboratory interest only.

Nitrous Oxide

The available data indicate unequivocally that N_2O can cause increases in CBF, CMR, and ICP. At least some of the CBF and CMR increases may be the result of a sympatho-adrenal-stimulating effect of N_2O. [306] The magnitude of the effect varies considerably according to the presence or absence of other anesthetic agents (Fig. 19-11) . When N_2O is administered alone, very substantial increases in CBF and ICP can occur. In sharp contrast, when N_2O is administered in combination with intravenous agents, including barbiturates, benzodiazepines, narcotics, and propofol, its cerebral vasodilating effect is attenuated or even completely inhibited.

Figure 19-11 Mean percentage increases in cerebral blood flow velocity (CBFV) in the middle cerebral artery of normocapnic subjects exposed to 60 percent nitrous oxide (N_2O) after control recording in three conditions: awake [311] ; 1.1 MAC isoflurane [324] ; and propofol, 150 mug/kg/min. [317]

The addition of N_2O to an established anesthetic with a volatile agent results in moderate CBF increases.

N_2O Administered Alone.

The most dramatic reported increases in ICP or CBF in humans [307] [308] and experimental animals [306] [309] [310] have occurred when N_2O was administered alone or with minimal background anesthesia. For instance, Henriksen et al [307] recorded ICP before and during spontaneous breathing of 66 percent N_2O by patients with intracranial tumors. Mean ICP rose from 13 to 40 mm Hg. The CBF increases observed in humans are more modest than those observed in animals, but they are still substantial. [311] Whether these substantial increases represent the effects of N_2O per se or whether they reflect the nonspecific effects of a "second-stage" arousal phenomenon is not known.

N_2O Administered with Intravenous Agents.

When N_2O is administered in conjunction with certain intravenous anesthetic agents, its CBF effect may be considerably reduced. Phirman and Shapiro [312] observed that a reproducible increase in ICP that had occurred in response to 70 percent N_2O administration to a comatose patient was prevented by prior administration of a combination of thiopental and diazepam in spite of no change in baseline ICP. In an investigation of patients with intracranial tumors and poor intracranial compliance (mean preinduction ICP, 27 mm Hg), [313] 50 percent N_2O introduced during barbiturate anesthesia and after the induction of hypocapnia had a negligible effect on ICP. Jung et al [314] compared lumbar CSFP in patients with brain tumors during administration of 0.7 percent isoflurane or 70 percent N_2O after induction of anesthesia with a barbiturate. Lumbar CSFP was modestly but significantly greater with N_2O. That the increase was less dramatic than those cited earlier for N_2O alone may reflect

the presence of residual barbiturate. Benzodiazepines administered alone have been shown to blunt the CBF response to N_2O in both animals and humans. [315] [316] Narcotics appear to have a similar effect. Jobes et al [180] reported that anesthesia with 1 mg/kg of morphine plus 70 percent N_2O resulted in no change in CBF from awake control values. Because of the very minor effect of morphine on CBF, these data suggest that N_2O did not cause substantial cerebral vasodilation. In a study using TCD, Eng et al [317] observed no change in CBFV when N_2O was introduced in patients anesthetized with propofol.

N_2O Administered with Volatile Anesthetics.

In the majority of the investigations, including several in humans, in which N_2O has been added to an anesthetic of 1.0 MAC or greater, substantial CBF increases have been recorded. [268] [318] [319] [320] [321] [322] [323] [324] [325] Algotsson et al [326] examined the effect of an approximately equi-MAC substitution of N_2O for isoflurane. They compared CBF in patients anesthetized with 1.5 MAC isoflurane and 0.75 MAC isoflurane with 65 percent N_2O. They observed a 43 percent greater CBF with the latter, a finding again consistent with a substantial vasodilating effect by N_2O in the presence of a volatile agent. Similar observations were made by Lam et al [324] and by Strebel et al. [325] Several investigations confirm that CBF will be less with 1.0 MAC of isoflurane than with a 1.0 MAC combination achieved with 50 to 65 percent N_2O and isoflurane. [324] [326] [327] The results of three investigations, including one in humans, indicate that this vasodilating effect of N_2O may be positively correlated with inhaled agent concentration, [320] [321] [325] and they suggest that, in general, the CBF increase caused by N_2O is exaggerated at higher concentrations of both halothane and isoflurane.

N_2O Effects on CMR.

There is not uniform agreement on the effect of N_2O on CMR. Parallel changes in CBF and CMR, [306] [309] CBF increases without alteration of CMR [323] [328] [329] and CMR alteration occurring without changes in CBF [330] have all been reported. This is doubtless the product of differences in species, methods, depth of background anesthesia, and interactions with simultaneously administered agents. There are few data derived from humans. Wollman et al [330] reported that 70 percent N_2O caused a 15 percent reduction in $CMRO_2$ in human volunteers. However, both premedication and induction of anesthesia were accomplished with barbiturates, and the control group was nonconcurrent. Algotsson et al, [326] mentioned earlier, reported no difference in $CMRO_2$ between the two anesthetic conditions studied (1.5 MAC isoflurane versus 0.75 MAC isoflurane/65% N_2O, see previous paragraph) and concluded that N_2O had no effect on CMR. [326] However, given the recognized depressive effect of isoflurane on CMR, the absence of net change in CMR can be interpreted as indicative of an N_2O-mediated CMR increase. From animal experimentation, it appears likely that, at least in some circumstances, N_2O causes increases in CMR. The "cleanest" investigation is that of Pelligrino et al, [309] who measured cortical CBF and CMR in awake goats that received N_2O without premedication or other supplements. After 60 minutes of N_2O inhalation, cortical $CMRO_2$ was increased to 170 percent of control, and global CBF was increased to 143 percent of control. The goats showed no evidence of an excitement stage. They became lethargic and experienced a fall in plasma epinephrine levels suggesting the absence of stress. The CBF response to CO_2 is preserved during administration of N_2O. [321] [323] [330]

Clinical Implications.

In spite of the evident inconsistencies, the data indicate that the vasodilatory action of N_2O can be clinically significant in neurosurgical patients with reduced intracranial compliance. [307] However, it appears that N_2O-induced cerebral vasodilation can be considerably blunted by the simultaneous administration of intravenous agents, although not all agents have been evaluated, and the dose-response relationships are not well defined. N_2O has been widely used in neurosurgery, and banishing it is inconsistent with accumulated experience. Nonetheless, when ICP is persistently elevated or the surgical field is persistently "tight," N_2O should be viewed as a potential contributing factor. In addition, the ability of N_2O to enter a closed gas space rapidly should be recalled, and this drug should be avoided or omitted when a closed intracranial gas space may exist.

Muscle Relaxants

Nondepolarizing Relaxants

The only recognized effect of nondepolarizing relaxants (Ch. 12) on the cerebral vasculature occurs via the release of histamine. Histamine can result in a reduction in CPP because of the simultaneous increase in ICP (caused by cerebral vasodilation) and decrease in MAP. [331] It is not entirely clear, when the BBB is intact, whether histamine directly causes cerebral vasodilation or whether it is a secondary (autoregulatory) response to a reduction in MAP. *d*-Tubocurarine is the most potent histamine releaser among available muscle relaxants. Metocurine, atracurium, and mivacurium also release histamine in lesser quantities. [332] [333] This effect is likely to be clinically inconsequential, [334] unless these agents are administered in the large doses necessary to achieve intubating conditions rapidly. Of this group of drugs, cisatracurium has the weakest histamine-releasing effect. No evidence of histamine release was seen after administration of 0.15 mg/kg (three times the ED_{95} for twitch depression) of cisatracurium in neurosurgical ICU patients. [335]

Vecuronium, in relatively large doses 0.1 to 0.14 mg/kg, had no significant effect on cerebral physiology in patients with brain tumors. [336] [337] Pipecuronium and rocuronium have not been studied, but they should similarly be without direct effect, and no adverse events have been reported.

The indirect actions of muscle relaxants may also have effects on cerebral physiology. Pancuronium given as a large bolus dose can cause an abrupt increase in arterial pressure. This could elevate ICP in the circumstances of impaired intracranial compliance and defective autoregulation; however, no significant clinical event has ever been reported. Muscle relaxation may reduce ICP because coughing and straining are prevented, and this results in a lowering of central venous pressure with a concomitant reduction in cerebral venous outflow impedance. [338]

A metabolite of atracurium, laudanosine, may be epileptogenic. However, whereas large doses of atracurium caused

an EEG arousal pattern in dogs, CBF, CMR, and ICP were unaltered. [339] In cats, the seizure threshold for lidocaine-induced seizures was not different during paralysis with atracurium, vecuronium, or pancuronium. [340] In rabbits, laudanosine administration did not increase the severity of the epileptoid activity caused by direct application of a cephalosporin to the cortical surface. [341] It appears highly unlikely that epileptogenesis will occur in humans with atracurium. [342] [343]

In summary, vecuronium, pipecuronium, rocuronium, atracurium, mivacurium, cisatracurium, metocurine, and pancuronium (if acute MAP increase is prevented with pancuronium) are all reasonable agents for use in the patient with or at risk of intracranial hypertension. Doses of metocurine, atracurium, and mivacurium should be limited to ranges not associated with hypotension. Curare (for the diehards) is best administered slowly and in small divided doses to avoid substantial histamine release.

Succinylcholine

Succinylcholine can produce an increase of ICP in lightly anesthetized human patients. Minton et al [344] studied patients with intracranial tumors. Their subjects received morphine, 0.1 mg/kg 1 hour prior to induction of anesthesia with thiopental, 6 mg/kg. The patients were ventilated by mask with 70 percent N_2O to maintain normocapnia, and then they received succinylcholine, 1 mg/kg. ICP increased from 15 ± 1 (SE) to a maximum of 20 ± 2 mm Hg after 1 to 3 minutes and returned to baseline in 8 to 10 minutes. The effect appears to be the result of cerebral activation (as evidenced by EEG changes and CBF increases) caused by afferent activity from the muscle spindle apparatus. [345] [346] [347] Note, however, that there is a poor correlation between the occurrence of visible muscle fasciculations and an increase in ICP. As could be expected with what appears to be an arousal phenomenon, deep anesthesia has been observed to prevent succinylcholine-induced ICP increases in the dog. [345] In humans, the ICP increase is also blocked by paralysis with vecuronium [344] and by "defasciculation" with metocurine, 0.03 mg/kg. [348] The efficacy of other defasciculating agents has not been examined in humans. However, defasciculation with pancuronium did not prevent ICP increases in the dog. [346]

Although succinylcholine *can* produce ICP increases, it need not be viewed as contraindicated when its use for rapid attainment of paralysis is otherwise seen as appropriate. Kovarik et al [349] observed no ICP change after administration of succinylcholine, 1 mg/kg, to nonparalyzed, ventilated neurosurgical ICU patients, six of ten of whom had sustained head injury. Their observations are very relevant because it is in precisely this population of patients that the issue of the use of succinylcholine arises most frequently. Given that the ICP effects of succinylcholine may be an arousal phenomenon caused by increased afferent traffic from muscle spindles, [347] it is not unreasonable that disease processes that substantially blunt the level of consciousness may similarly blunt this response. As with many agents, the concern should be not whether it is used but how it is used. If succinylcholine is administered with proper attention to the control of CO_2 tension, blood pressure,

and depth of anesthesia, and following defasciculation, preferably with metocurine pending additional information, little hazard should attend its use.

/das/book/view/29494766/875/204.html

OTHER EFFECTS OF ANESTHETICS ON CEREBRAL PHYSIOLOGY

Cerebrospinal Fluid Dynamics

There is approximately 150 mL of CSF in the adult human, half within the cranium and half in the spinal CSF space. The CSF, which is formed in the choroid plexuses and, to a lesser extent, by transependymal diffusion from the brain's interstitium into the ventricular system, is replaced about three times per day. [350] It functions both as a cushion for the central nervous system (CNS) and as an excretory pathway. Anesthetics have been shown to influence both the rate of formation and the rate of reabsorption of CSF. Table 19-5 provides nonquantitative information on the direction of the influences of common anesthetic agents. All the information has been derived from animals, [351] [352] [353] [354] [355] [356] [357] and these processes have not been examined in humans. They may be of relevance when a prolonged closed cranium procedure is to be performed in a patient with poor intracranial compliance. The most deleterious potential combination of effects in the setting of poor intracranial compliance is one of increased CSF production and decreased reabsorption. In the dog, this pattern occurs with enflurane, and this is perhaps another reason (in addition to the potential for epileptogenesis in the presence of cerebral injury and hypocapnia) for omission of enflurane in this circumstance.

The time course of these effects on CSF dynamics is slow. In clinical situations in which the CSF space is to be opened (most craniotomies) or in which a ventriculostomy is in

TABLE 19-5 -- Effects of Anesthetic Agents on the Rate of Cerebrospinal Fluid Secretion and Absorption [a]

	HALOTHANE	ENFLURANE	ISOFLURANE	DESFLURANE	FENTANYL	ETOMIDATE
Secretion			O	[b]	O	
Absorption				O		

Data from various investigations in animals. [351] [352] [353] [354] [355] [356] [357] [527]

[a] Upward arrows indicate an increase in the rate of cerebrospinal fluid absorption or secretion, downward arrows indicate a decrease, and O indicates no effect. The information is presented nonquantitatively, and effects may vary with dose.
[b] Hypocapnia only.

place, these effects are probably of relatively little clinical importance. The exception may occur with desflurane. Muzzi et al [358] measured lumbar CSF pressure (L-CSFP) during approximately 1 hour of 1.0 MAC anesthesia with isoflurane or desflurane in patients with supratentorial tumors. Anesthesia was induced with thiopental; the patients were paralyzed with vecuronium; hypocapnia (Pa CO_2 24-28 mm Hg) was maintained. After introduction of the volatile agent, L-CSFP were initially similar in the two groups. However, over the ensuing 50 minutes, L-CSFP rose progressively in the desflurane group. At the time of dural incision, L-CSFP in the two groups were as follows: isoflurane, 8 ± 2 (SD), and desflurane, 18 ± 6 mm Hg. This difference is neither as trivial nor as transient as many that have been trumpeted as significant in other studies of anesthetic agents in neurosurgery. Subsequently, an investigation revealed that desflurane causes increased CSF formation under conditions of increased ICP and hypocapnia. [357] The clinical results of Muzzi et al are nonetheless surprising because, in a study of similar design by the same investigators, [359] there were no differences in L-CSFP in groups that received either 0.5 MAC isoflurane/50 percent N_2O or 0.5 MAC desflurane/50 percent N_2O. Furthermore, two subsequent studies involving patients without large intracranial lesions [360] [361] revealed either no or trivial differences in the effects of isoflurane and desflurane on L-CSFP. In particular, because of methodologic weaknesses in the 1.0 MAC study of Muzzi et al (nonconcurrent experimental groups, nonblinded investigators [362]), clarifying investigation is necessary. In the meantime, it seems prudent to await a larger experience in situations in which desflurane is administered in patients undergoing ICP monitoring or with an open cranium (to permit observation of conditions in the surgical field) before undertaking prolonged closed cranium use of desflurane in patients with impaired intracranial compliance.

Blood-Brain Barrier

In the majority of the body's capillary beds, there are fenestrations approximately 65 A in diameter between endothelial cells. In the brain, with the exception of the choroid plexus, the pituitary, and the area postrema, tight junctions reduce this pore size to approximately 8 As. As a result, large molecules and most ions are prevented from entering the brain's interstitium. There is little evidence that anesthetic agents alter the function of this "blood-brain barrier" in most circumstances. However, it has been repeatedly demonstrated that acute hypertension can breach the barrier, [363] [364] [365] and certain anesthetics facilitate this phenomenon. [366] Forster et al [105] observed that Evans blue extravasation into rabbit brain was greater when acute hypertension occurred during anesthesia with halothane than with thiopental. It is probable that the effect is the nonspecific result of cerebral vasodilation, [367] rather than a specific effect of halothane. These results were obtained in the setting of extreme, abrupt hypertension in animals with an initially normal BBB. There is also evidence that anesthetics may influence the leakiness of an abnormal BBB at normotension. Smith and Marque [368] submitted dogs to 5 hours of anesthesia following a freeze lesion (which causes an opening of the BBB). Cerebral water accumulation at 24 hours was less in animals anesthetized with pentobarbital or fentanyl/droperidol/N_2O than with halothane, enflurane, or isoflurane. To our knowledge, no peer-reviewed investigation has attempted a comparison of anesthetic effects on BBB function during anesthesia in normotensive human patients.

Epileptogenesis

An extensive review of the convulsant and anticonvulsant effects of anesthetic agents and adjuvants is available. [369] [370] Several commonly employed anesthetic agents have some epileptogenic potential, particularly in predisposed individuals. A concern is that seizure activity may go unrecognized in an anesthetized and paralyzed patient and may result in neuronal injury if substrate demand (CMR) exceeds supply for a prolonged period. [371] A second concern is that the epileptogenic effect will persist in the postanesthesia period, when seizures may occur in less well-controlled circumstances than exist in the operating room. In practice, it appears that spontaneous seizures during or following anesthesia have been extremely rare events. Nonetheless, in patients with processes that may predispose them to seizures, it seems prudent to avoid the use of potentially epileptogenic agents in situations where there are reasonable alternatives.

Enflurane and Sevoflurane

The epileptogenic properties of these drugs are discussed earlier in the section on volatile anesthetics.

Methohexital

Myoclonic activity is sometimes observed with methohexital, and this agent has been used to activate seizure foci during cortical mapping. [372] [373] One clinical report [374] describes the occurrence of seizures in two pediatric patients following induction doses of methohexital administered rectally in one and intramuscularly in the other. Both these patients had temporal lobe lesions and had had previous seizures. It appears that it is specifically patients with seizures of temporal lobe origin, typically of the psychomotor variety, that are at risk of seizure activation by methohexital. [374] [375] It may be noteworthy that recurrent spontaneous seizures after methohexital anesthesia for electroconvulsive therapy have never been reported.

Ketamine

Ketamine can elicit seizures in patients with an epileptic diathesis. [376] Depth-electrode recordings in epileptic patients revealed the occurrence of isolated subcortical seizure activity originating in limbic and thalamic areas during ketamine anesthesia and demonstrated that this subcortical activation may not be reflected in surface EEG recordings. [244] The occurrence of seizures following ketamine anesthesia in neurologically normal subjects has also been reported on

only two occasions, [377] [378] and in one of those instances, seizure thresholds may have been lowered by aminophylline.

Etomidate

Etomidate frequently produces myoclonus that is not associated with epileptiform activity in the EEG. [379] A single instance of severe, sustained myoclonus immediately following anesthesia with etomidate by infusion has been reported. [380] Etomidate has also been shown to precipitate generalized epileptic EEG activity in epileptic patients, [381] and its use in this population should probably be avoided. However, it can be used electively, in low doses, to activate seizure foci for the purposes of intraoperative EEG localization. [382] In the authors' experience (unpublished), selective activation of a quiescent focus can be achieved with 0.1 mg/kg. Larger doses are more likely to lead to generalized activation.

Etomidate has also been noted to be associated with longer seizures in response to electroconvulsive therapy than occur after methohexital or propofol. Remarkably, etomidate, in the dose range of 0.15 to 0.3 mg/kg, does not cause dose-related electroconvulsive therapy seizure inhibition, as is readily demonstrated with the other two agents. [383] The preceding information notwithstanding, there are no convincing reports to indicate epileptogenesis in healthy subjects, and etomidate's use need not be restricted on this basis. In fact, it has been used to control refractory status epilepticus. [384]

Narcotics

Seizures and/or limbic system hypermetabolism can be elicited readily with narcotics in some animal species. [194] [385] [386] [387] [388] Although a CBF increase in deep brain structures associated with pain processing has been observed in human volunteers, [185] humans do not have a clinically apparent correlate of the hypermetabolism effect seen in animals. Several anecdotal reports, unaccompanied by EEG recordings, report that grand mal convulsions have occurred in patients who received both high [389] and low doses of fentanyl. [390] [391] However, systematic investigations of EEG changes during administration of relatively large doses of fentanyl, sufentanil, and alfentanil in humans have *not* documented neuroexcitatory activity, [392] [393] [394] and the "seizures" may been an exaggerated rigidity phenomenon. The exception is the observation that alfentanil, 50 mug/kg, can augment temporal lobe spike activity in patients with temporal lobe epilepsy. [395] Note that untreated rigidity may itself also have important CNS consequences. ICP elevation was observed when alfentanilinduced rigidity occurred in rats during controlled ventilation. [338] The effect probably arose because the associated increase in CVP caused cerebral venous congestion. In the absence of ventilatory support, both hypercapnia and hypoxemia may also occur.

Atracurium

See the discussion of the atracurium metabolite, laudanosine, in the earlier section on nondepolarizing muscle relaxants. All of the advantages of atracurium can be obtained from cisatracurium, which does not release nearly as much laudanosine (Ch. 12) .

CEREBRAL PHYSIOLOGY IN PATHOLOGIC STATES

Cerebral Ischemia

Introduction/Pathophysiology

The brain has a high rate of energy utilization and a very limited energy storage capacity. It is therefore extremely vulnerable in the event of interruption of substrate (O_2 , glucose) supply. Reviews of the pathophysiology of ischemic neuronal injury are available. [396] [397] [398] [399] [400] Only a simplified overview is presented here. Calcium is probably central to this complex process. [400] Calcium is present in the cytosol of normal neurons, where it performs important functions, such as second messenger, coenzyme. Calcium gains access to the cytosol in several ways (Fig. 19-12 A). It enters via both neurotransmitter-gated and voltage-dependent channels. Calcium is also released from intracellular storage sites in the endoplasmic reticulum through the actions of second messengers such as inositol triphosphate (IP3) that have been generated by the action of various neurotransmitters at cell-surface receptors. Calcium's normal concentration range is tightly regulated by energy-consuming processes that extrude it from the cell, resequester it in the mitochondria or endoplasmic reticulum, and inactivate the factors that liberate calcium from storage sites.

In the event of cerebral ischemia, there are two simultaneous impacts on these processes. There is excess release into the synaptic cleft of the neurotransmitters that activate the various calcium influx processes (see Fig. 19-12 A), and there is a failure of the supply of adenosine triphosphate (ATP) that is necessary to clear the calcium from the cytosol (Fig. 19-12 B). Among calcium's normal intracellular functions is the activation of various lipases, nucleases, and proteases. The sustained activation of these and other enzymes by elevated cytosolic calcium during ischemia has many consequences, including direct structural damage, the liberation of fatty acids from membranes, and the initiation of gene transcription. In addition, electron-hungry free radicals that are generated during the reperfusion process contribute to the further degradation of membrane lipids and other structural elements. Among the liberated free fatty acids is arachidonic acid, which is the substrate for the generation, by the action of cyclooxygenase and lipoxy-genase, of various prostaglandins and leukotrienes. These "eicosanoids" have numerous effects including vasoconstriction, vasodilation, alteration of membrane permeability, and leukotaxis, all of which can contribute to the evolution of the ischemic neuronal insult. In particular, the recruited white blood cells that initially adhere to damaged endothelium and subsequently enter brain parenchyma may make a substantial contribution to the progression of injury after ischemia. Some of the gene transcription initiated by ischemia inevitably contributes to restorative processes. However, in some circumstances that are not yet well defined, the transcription leads on to apoptosis (genetically mediated cell death).

Figure 19-12 (A) Neuronal calcium (Ca^{2+}) homeostasis. Cytosolic Ca^{2+} concentration is tightly regulated. Increases result from three primary mechanisms: depolarization of neurons opens voltage-dependent Ca^{2+} channels; ligand-gated channels, e.g., the *N*-methyl- D-aspartate (NMDA) subtype of the glutamate (Glu) receptor, open when activated by their specific neurotransmitter agonists; and, neurotransmitters that may also activate surface receptors leading to generation of inositol triphosphate (IP3), which, in turn, increases Ca^{2+} release from the endoplasmic reticulum (ER) and mitochondria. Ca^{2+} is removed from the cytosol by two adenosine triphosphate (ATP)-driven processes, a Ca^{2+} -ATPase pump and resequestration within the ER/mitochondria, and by a Ca^{2+} -sodium (Na^{+}) exchanger. (B) During ischemia, ATP depletion leads to neuronal depolarization and the subsequent release of supranormal quantities of neurotransmitters, especially glutamate. Excessive stimulation of ligand-gated channels and the simultaneous opening of voltage-dependent Ca^{2+} channels permits rapid entry of Ca^{2+} into neurons. Stimulation of metabotropic glutamate receptors generates IP3, causing release of Ca^{2+} from ER/mitochondria. Activation of the AMPA-gated subset of glutamate receptors also permits excessive entry of Na^{+} . The energy requiring Ca^{2+} extrusion/resequestration processes is inhibited by the lack of ATP, and high intracellular Na^{+} levels may result in the reversal of the Na^{+} -Ca^{2+} exchanger. Excessive free Ca^{2+} results in activation of numerous enzymes: protease activation causes breakdown of the cytoskeleton of the neuron; lipases damage plasma membrane lipids and release arachidonic acid (AA), which is metabolized by cyclooxygenases and lipooxygenases to yield free radicals (FR) and other mediators of cell injury; activation of nitric oxide synthase (NOS) leads to release of NO and, in turn, the generation of peroxynitrite, a highly reactive free radical; and, activated endonucleases damage DNA, rendering the neuron susceptible to apoptosis. Certain protein kinases are also activated, and some of these lead to synthesis of transcription factors that initiate gene transcription and protein synthesis. Some of these new proteins contribute to restorative functions, but others may initiate biochemical processes that culminate in cell suicide, or apoptosis. G, G protein; PLC, phospholipase C; Pi, inorganic phosphate; ADP, adenosine diphosphate; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazopropionic acid.

Lactate formation is an additional element of the pathophysiologic process. Lactic acid is formed as a result of the anaerobic glycolysis that takes place after the failure of the supply of O_2 . The associated pH decline contributes to the deterioration of the intracellular environment. An increased preischemic serum glucose concentration may accelerate this process by providing additional substrate for anaerobic glycolysis. [401] [402] [403] [404]

NO, [2] [3] [405] which has emerged as a probable mediator of CBF changes in many normal physiologic states (see preceding sections), is also of relevance to the pathophysiology of ischemia. NO is, in fact, a weak free radical, [405] [406] which, in turn, leads to the generation of a more reactive species (peroxynitrite) and is a "killer substance" used by macrophages. [2] In cerebral ischemia, NO is probably both friend and foe. [407] It is likely that during a period of focal ischemia, the vasodilating effect of NO (probably constitutively elaborated NO of endothelial origin) serves to augment collateral CBF. [408] However, in the postischemic phase, NO (probably inducible NO of neuronal origin) appears to contribute to neuronal injury. [408]

Much has been made of the difference between complete cerebral ischemia, as occurs during cardiac arrest, and incomplete cerebral ischemia, as may occur during occlusion of a major cerebral vessel or severe hypotension. However, from the clinician's vantage, the important difference is that the residual blood flow during incomplete ischemia may result in enough O_2 delivery to allow for some generation of ATP and thereby to prevent the catastrophic irreversible membrane failure that occurs within minutes during normothermic complete cerebral ischemia. This difference in the rate of failure of energy supply [409] [410] (Fig. 19-13) can result in a much greater apparent tolerance for focal or incomplete ischemia than for complete global ischemia, such as cardiac arrest. The difference is a matter of severity, rather than of the actual initial pathophysiology of the insult, with the exception that limited residual perfusion may potentially be detrimental in the event of hyperglycemia. There is also a theoretic concern that low levels of residual flow will provide sufficient O_2 delivery to permit the formation of O_2 radicals. However, the observation that focal

ischemia is better tolerated than complete global ischemia argues against major importance.

Critical CBF Levels and the Ischemic Penumbra Concept

In the face of a declining O_2 supply, neuronal function deteriorates progressively, rather than in an all-or-none fashion (Fig. 19-14) . There is a substantial reserve at less than normal CBF levels (>50 mL/100 g/min). It is not until CBF has fallen to approximately 22 mL/100 g/min that EEG evidence of ischemia begins to appear. At a CBF level of approximately 15 mL/100 g/min, the cortical EEG is isoelectric. However, only when CBF is reduced to about 6 mL/100 g/min are indications of potentially irreversible membrane failure (elevated extracellular potassium [411] and loss of the direct cortical response [412]) rapidly evident. As CBF decreases in the flow range between 15 and 6 mL/100 g/min, a progressive deterioration of energy supply occurs, leading eventually, with a time course that may encompass hours, [413] [414] rather than minutes, to membrane failure and neuronal death. The brain regions falling within this CBF range (6-15 mL/100 g/min) are

Figure 19-13 A comparison of the rates of failure of energy supply (adenosine triphosphate [ATP]) in complete global ischemia (produced by decapitation in dogs [410]) and in incomplete focal ischemia (middle cerebral artery [MCA] occlusion in monkeys [409]). In the presence of residual cerebral blood flow (CBF), energy supply failure is substantially delayed.

referred to as the "ischemic penumbra"--a region within which the neuronal dysfunction is temporarily reversible but within which neuronal death will occur if flow is not restored. [411] [415] It is the ischemic penumbra phenomenon that accounts for instances, such as in carotid endarterectomy, in which neurologic recovery occurs when the EEG was "flat" for periods longer than those normally associated with neurologic injury. The studies defining this progression have been performed principally in the cerebral cortex of baboons [411] [416] and monkeys, [413] and the actual CBF levels at which the various decrements in function occur may vary with both anesthetic [417] [418] and species. However, in humans anesthetized with halothane and N_2O, the CBF threshold for the initial EEG change [419] is similar to that observed in the animal investigations.

Brain Protection

As outlined earlier, cerebral ischemic injury involves a process whereby energy supply falls short of energy demand, wherein the intracellular environment deteriorates (increased calcium, decreased pH), membrane damage occurs, and secondary processes (eicosanoids, free radicals, white cells, apoptosis) that aggravate the injury are initiated. The numerous brain-protection strategies that have been studied in both the laboratory and the clinic can be classified according to the phase of this sequence that each addresses. They are listed in Table 19-6 . Brain-protection regimens are logically most effective when instituted prior to the onset of ischemia. However, it is reasonable to anticipate some efficacy of certain therapies initiated after the beginning of the insult because many of the insult processes are ongoing in the ischemic and reperfusion phases. The literature dealing with cerebral protection/resuscitation is enormous and cannot be thoroughly reviewed here. Reviews of brain protection are available. [397] [398] [399] [400] Of the many promising protection/resuscitation strategies, only a limited number (discussed later) have reached the stage of human application. Some are relevant to both complete global ischemia (e.g., cardiac arrest) and incomplete focal ischemia (e.g., thromboembolism, vessel occlusion), as mentioned later.

Figure 19-14 The relationships among cerebral perfusion, cerebral blood flow (CBF), the electroencephalogram (EEG), and the functional status/viability of neurons. Note that in the approximate CBF range of 6 to 12 mL/kg/min, the energy supply is insufficient to support electrophysiologic activity (i.e., EEG flat), but it can prevent complete membrane failure and neuronal death for extended periods (see Fig. 19-13) . These areas are referred to as the ischemic penumbra. [411] The data are derived from studies in the cerebral cortex of barbiturate anesthetized baboons [411] [416] and unanesthetized monkeys. [413] The CBF and mean arterial pressure (MAP) thresh-olds may vary with anesthetic agent and with species. [417]

TABLE 19-6 -- Ischemic Neuronal Injury: Pathophysiologic Sequence and Related Protection Strategies

INSULT MECHANISM	PROTECTION STRATEGY	THERAPY EXAMPLE[a]
Failure of energy supply	Decrease energy demand (cerebral metabolic rate)	Hypothermia*
		Barbiturates*
		Other anesthetics
	Increase energy supply (cerebral blood flow)	Induced hypertension*
		Hemodilution*
		Mannitol [528]
		Thrombolysis [529]
	Prevent supranormal energy demand	Seizure prophylaxis and control*
Increased cytosolic Ca^{2+}	Prevent neurotransmitter release	Hypothermia [421] [530]
		Adenosine agonists [531]
		$alpha_2$ -Agonists [532]
		Riluzole [533]
		Lubeluzole* [491]
	Oppose excitatory effects	gamma-Aminobutyric acid agonists [534]
	Block neurotransmitter receptor	Dopamine antagonists [535]
		Glutamate (AMPA) antagonists [536]
		Glutamate (NMDA) antagonists [537]
		Glycine antagonists [538]
		Serotonin antagonists [539]
	Block second messenger (inositol triphosphate) formation	Phospholipase C inhibitors [540]
	Block Ca^{2+} entry into neuron	Ca^{2+} channel blockers*
		Noncompetitive glutamate antagonists [541]
		Potassium channel activator [542]
	Block Ca^{2+} activated processes	Calpain inhibitors [543]
		Protein kinase C inhibitors [544]
Intracellular acidosis	Avoid hyperglycemia	Omit glucose solutions*
		Insulin to normalize plasma glucose [545]
Membrane damage	Inhibit free radical formation	Iron chelators (e.g., deferoxamine [546])
		Xanthine oxidase inhibitors (e.g., allopurinol [546])
	Inhibit nitric oxide	Nitric oxide synthase inhibitors [547]

	Scavenge free radicals	Superoxide dismutase [548]
		Catalase [549]
		Dimethylthiourea [550]
	Act as antioxidants	Aminosteroids [490]
		Vitamin E [551]
	Stabilize membranes	Gangliosides [552]
Fatty acid metabolite-mediated damage	Inhibit formation of prostaglandins and leukotrienes thromboxane synthetase [555]	Inhibitors of lipoxygenase [553] and cyclo-oxygenase [554]
Vascular injury/occlusion	Act as anticoagulants	Heparinoids [556]
	Inhibit platelets	Platelet-activating factor inhibitors [557]
	Inhibit white cell adhesion	Antibody to ICAM (intercellular adhesion molecule) [558]
	Act as thrombolytics	Tissue-plasminogen activators [529]
Apoptosis	Inhibit protein synthesis	Cycloheximide [559]
	Inhibit caspase	z-VAD.FMK [560]

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazopropionic acid; NMDA, *N*-methyl- D-aspartate

[a] Note that although each of the "therapy examples" has shown efficacy in at least one laboratory investigation, only those designated with an asterisk have been proven or are accepted as clinically applicable. For items not discussed in the text, a single reference is provided.

Others are of greater relevance only in focal ischemia, wherein energy supply failure may be more gradual and wherein there is potential for manipulation of collateral CBF.

Considerations Relevant to Both Complete and Incomplete Ischemia

Temperature.

Hypothermia is firmly and justifiably established as the principal cerebral protective technique for circulatory arrest procedures. It unequivocally enhances cerebral tolerance for episodes of ischemia. For deep hypothermia, this effect has been presumed to be largely a function of reduction of CMR. Although pharmacologic agents, such as barbiturates, reduce only that component of CMR associated with electrophysiologic "work" (about 60% of the $CMRO_2$ in the awake state), hypothermia causes a reduction of both electrophysiologic energy consumption and the energy utilization related to maintenance of cellular integrity, and mild hypothermia may preferentially suppress the latter. [32] [33] There has been a surge of interest in *mild* hypothermia as a cerebral protective technique. Laboratory studies have demonstrated that mild degrees of hypothermia (2-4°C) during an episode of ischemia can confer substantial protection, as measured histologically. [30] [420] [421] [422] [423] [424] [425] In addition, there is also evidence from animal studies that hypothermia

initiated in the immediate postischemic period confers protective benefits. [426] [427] [428] [429] [430]

These observations regarding mild hypothermia have cast doubt on the notion that CMR suppression is the sole mediator of the cerebral protective effects of hypothermia. This arises because the amount of CMR suppression associated with protective degrees of hypothermia is in some instances less than that associated with pharmacologic interventions that have been less clearly protective. Microdialysis investigations in the setting of cerebral ischemia have revealed that hypothermia has a very striking inhibitory effect on the release of various neurotransmitters [421] (recall the pathophysiologic cascade discussion earlier), and it may well be that the protective effects of hypothermia are far more dependent on influences on several steps in the biochemistry of ischemia (Table 19-7) than on suppression of CMR. [431] On the strength of the animal investigations cited earlier, mild hypothermia (32-34°C) is being used in some centers in anticipation of possible focal ischemic events, such as aneurysm surgery. There are, however, no data derived in humans to confirm the efficacy of the practice. There have also been several small, single-institution trials of mild hypothermia in head injury [432] [433] [434] [435] (conducted with the rationale that ischemia contributes to the pathophysiology of head injury [436] [437]). The results have been sufficiently favorable that a large, multicenter trial is being conducted.

Hyperthermia has been shown to be deleterious to outcome from standardized ischemic events. [422] [438] [439] [440] Hyperthermia before, during, and after ischemic events should be prevented or treated.

Glucose.

The withholding of glucose-containing solutions in situations in which cerebral ischemia may occur is now an established practice. The practice is based on numerous demonstrations in animal models of brain and spinal cord ischemia that elevation of plasma glucose concentrations prior to episodes of either complete or incomplete ischemia results in an aggravation of neurologic injury. [401] [402] [403] [441] [442] [443] [444] However, it should be noted that most investigations have involved adult animals, and there is less certainty as to the adverse effects of hyperglycemia in immature subjects, such as neonates. [445] Furthermore, it should be noted that only some, [446] [447] and not all, [448] [449] [450] [451] [452] of the investigations in humans have provided confirmation of an independent effect of serum glucose on neurologic outcome. A recurrent theme in the discussion of these studies is

TABLE 19-7 -- Possible Mechanisms of Cerebral Protection by Mild Hypothermia [a]

Reduction of cerebral metabolic rate
Decreased release of excitatory neurotransmitters
Inhibition of activation of protein kinase C (early)
Preservation of late postischemic enzyme function
Protein kinase C
Calcium-calmodulin kinase II
Ubiquitin
Reduction of free radical formation
Inhibition of DNA transcription
Inhibition of apoptosis
Inhibition of proinflammatory cytokines

[a] See published reviews for further details. [30] [561]

that glucose elevation may be the *result* of the stress associated with a severe insult, either ischemic or traumatic, rather than its *cause.* In addition, the inevitable

questions of whether and how quickly immediate pre-risk treatment with insulin of an elevated plasma glucose level reduces risk to normoglycemic levels have not been examined thoroughly. It is these authors' opinion that short-term insulin administration (with its attendant risk of hypoglycemia) in patients with modest glucose elevation, such as 175 to 250 mg/dL, is not yet justified.

Seizures and pH.

Although normalization of systemic pH, prevention and treatment of seizures, which dramatically increase CMR, and control of ICP and CPP are all mundane and lacking in the appeal of the pharmacologic silver bullet, they are important elements of brain protection and resuscitation.

Considerations Relevant to Focal (Incomplete) Ischemia

Protection by Anesthetic Agents.

Before discussing individual agents, it should be noted that a general theme that can be extracted from the literature on this topic, in particular for anesthesia with volatile agents, is that anesthesia per se is protective. It appears that, for undefined reasons, reducing the level of systemic stress associated with a standardized experimental insult results in an improved outcome. [453] [454] In reviewing the literature, readers should be conscious of the possibility that the protective benefit ascribed to an intervention with an anesthetic agent may, in fact, be the product of exaggeration of the injury in a high-stress control state, such as N_2O "sedation."

Barbiturates.

There have been numerous demonstrations of the protective efficacy of barbiturates in focal cerebral ischemia in animals [455] [456] [457] [458] [459] [460] [461] and a single demonstration of effectiveness in humans. [462] The effect has been attributed principally to suppression of CMR. However, CBF redistribution effects and free radical scavenging [463] have been suggested to contribute to this effect, and there is evidence that CMR suppression is not the sole mechanism. [464] [465] [466] Suppression of CMR could logically be expected to benefit brain regions in which O_2 delivery was inadequate to meet normal demands but was sufficient to allow energy consumption by some ongoing electrophysiologic activity, that is, in which the EEG was abnormal but not flat. Such regions are likely to be limited in size in the setting of focal ischemia, yet several animal investigations suggest a very substantial protective effect. [455] [457] [458] [459] Review of these experiments reveals that the methods used to monitor and maintain temperature, although accepted at the time, were below the standards that have evolved from more recent understanding of the effects of both deliberate [420] [424] and inadvertent [427] hypothermia. Unrecognized cerebral hypothermia may well have been a factor in some of the cited investigations, and it is possible therefore that the protective efficacy of barbiturates may have been overestimated. Although more recent publications involving suitable temperature-control methods do, in fact, indicate a protective effect

by barbiturates, [466] [467] [468] the magnitude of that effect was modest by comparison with the results of earlier studies. Barbiturate-induced EEG suppression in an already anesthetized patient may still be logical therapy when it can be applied before or early in the course of a period of temporary focal ischemia, such as temporary occlusion during aneurysm surgery. However, the judgment to institute such therapy should be made after consideration of the risk of the occlusive event, of the patient's cardiovascular status, and of the physicians' willingness to accept the possible prolongation of arousal and with an objective view of the likely magnitude of the protective effect. Numerous investigations in animals and humans have failed to demonstrate any protective effect of barbiturates in the setting of global cerebral ischemia, such as in cardiac arrest. [469] [470]

Because CMR suppression has been the presumed mechanism of effect, barbiturates have traditionally been administered to produce maximal reduction of CMR, which is near complete when EEG burst suppression has been achieved. However, data presented by Warner et al [466] demonstrated that the same protective benefit (expressed as reduction of infarct volume) could be achieved with one-third of the burst-suppression dose. This finding raises a clinically important issue. The various barbiturates (e.g., thiopental, thiamylal, methohexital, pentobarbital) have similar effects on CMR and have generally been assumed to have equal protective efficacy. However, if the mechanism of protection is a pharmacologic effect other than CMR reduction, is it reasonable to assume equivalence among the barbiturates? Probably not. In the opinion of the authors of this chapter, rational use of barbiturates for clinical cerebral protection requires further laboratory investigations. These analyses should entail concurrent comparisons, including dose-response evaluations, for thiopental, methohexital, and pentobarbital.

Isoflurane/Volatile Anesthetics.

Isoflurane is also a potent suppressant of CMR in cerebral cortex, and EEG evidence suggestive of a protective effect in hu- mans has been reported. [417] However, the available laboratory data have not provided consistent confirmation of a protective effect of isoflurane relative to other anesthetics. [424] [439] [454] [461] [467] [468] [471] [472] [473] [474] [475] The available literature suggests that adequate anesthesia per se may have a protective effect [453] [454] versus the awake state, but it does not confirm any advantage of isoflurane over any other volatile agent.

Propofol.

EEG suppression can also be achieved with clinically feasible doses of propofol. Anecdotal information suggests that the drug is being used to provide "protection" during both aneurysm surgery [476] and carotid endarterectomy. However, a search for experimental data using models of focal cerebral ischemia with histologic end points (infarct size) revealed only two relevant investigations. Ridenour et al [477] performed 2 hours of MCA occlusion followed by a 3-day survival period with subsequent determination of infarct volume in rats anesthetized either with 0.5 MAC halothane or propofol in sufficient concentration to produce burst suppression. There was no difference in infarct volume. Young et al [478] compared histologic injury 4 hours after a 2-hour period of temporary MCA occlusion in rats anesthetized with either propofol or isoflurane in burst-suppression inducing doses. There was less injury in the propofol-treated group, but CPP was neither measured nor controlled, thus leaving the conclusion suspect. Accordingly, it is difficult to assert that propofol has proven cerebral protective effects.

Etomidate.

Etomidate was proposed as early as 1988 as a potential protective agent in the setting of aneurysm surgery. [479] It, too, produces CMR suppression to an extent equivalent to that of barbiturates, and, like the barbiturates, etomidate is an agonist at the (inhibitory) gamma-aminobutyric acid ($GABA_A$) receptor. At that time, there were no investigations of etomidate using histologic end points. Subsequently, in a model of temporary forebrain ischemia, a very small protective effect, relative to anesthesia with 1.1 MAC halothane or isoflurane or thiopental, was demonstrated in the hippocampus, but no protective effects were seen in other brain regions including cortex, reticular nucleus of thalamus, and striatum. [480] [481] In a later investigation using a model of temporary MCA occlusion, [468] the volume of injury was not reduced by etomidate relative to a 1.2 MAC-anesthetized halothane control group. In fact, the volume of injury with etomidate was significantly larger than in the control group. Data [482] support the suspicion that this aggravation of injury by etomidate may be related to direct binding of NO as a consequence of etomidate-induced hemolysis, [483] combined with a direct inhibition of the NO synthase enzyme by etomidate, an imidazole. [484] This aggravation of injury may be a phenomenon peculiar to rats. Nonetheless, there is no scientific support for the current use [485] of etomidate for "cerebral protection."

Calcium Channel Blockers.

It is now an established clinical practice to administer nimodipine orally (the intravenous preparation is not approved for clinical use in North America) for 21 days beginning as soon as possible after subarachnoid hemorrhage. [486] However, it has not yet become a standard practice to administer nimodipine or any other calcium channel blocker routinely after neurologic stroke occurring in the operating room or in any other environment. In spite of favorable results in small trials, [487] [488] not all investigations in stroke victims have confirmed the benefits of nimodipine. [489] Those that did reveal beneficial effects saw them only in limited post hoc patient subsets, that is, patients in whom therapy was initiated quickly. [487] [488] An ongoing clinical trial of very early nimodipine use in stroke (VENUS) should provide clarification.

Other Agents.

In spite of the multitude of studies that have revealed "protective" effects in animals, the number of additional pharmacologic agents that have actually been proven effective in attenuating ischemic injury by large, prospective, randomized double-blind clinical trials is remarkably small. These include tirilazad [490] (an antioxidant of the 21-aminosteroid type) in the setting of subarachnoid hemorrhage and lubeluzole [491] (a sodium channel blocker) in clinical stroke.

Manipulation of CBF.

Measures designed to augment CBF (an important determinant of energy supply) are also important. In the ischemic penumbra described earlier, small improvements in CBF have the potential to prolong neuronal survival substantially. The maintenance of a high-normal

CPP can augment collateral CBF [92] and has been shown to result in improvement of various neurophysiologic parameters including neurologic function. [492] [493] [494] Note, however, that this practice carries the inadequately explored risks of increased edema and hemorrhagic infarction if used as support during more than brief periods of ischemia, particularly when several hours have elapsed since the onset of ischemia.

Carbon Dioxide Tension.

Normocapnia should be maintained. Hypercapnia has the potential to cause an intracerebral steal and may worsen intracellular pH. Hypocapnia, in spite of some support for the occurrence of a favorable so-called Robin Hood or inverse steal, [495] [496] has not generally proven effective in either laboratory or clinical settings. [497] [498] [499] [500] [501] Pending further information, normocapnia remains the standard practice.

Intravascular Volume/Hematocrit Manipulation.

Al- though hemodilution has not proven effective in studies of human stroke, both laboratory and clinical data support the practice, and it is an established part of the management of the ischemia associated with vasospasm. However, the data do not currently justify routine hemodilution (a hematocrit of 30-35% is the theoretic optimum) in patients in whom focal ischemia may occur in the operating room. [502] On the other hand, the potentially deleterious effects of hemoconcentration should help to suppress further the out-of-date notion that neurosurgical patients should be "run dry." An elevated hematocrit, because of viscosity effects, reduces CBF. [77] It is the authors' unsubstantiated opinion that in anticipation of a procedure wherein incomplete ischemia may occur, such as carotid endarterectomy, a hematocrit in excess of 55 percent should be lowered by preoperative phlebotomy.

Deferring Elective Procedures After Stroke.

The risks of extension of cerebral infarction in the event of subsequent anesthesia and surgery have not been studied systematically. In patients who have suffered a stroke, CBF undergoes marked changes. Areas of both high and low CBF occur, and stabilization of CBF and CMR is apparent after about 2 weeks. [503] Loss of normal vasomotor responses (CO_2 responsiveness, autoregulation) in the early postinsult period is very common, [504] [505] [506] and changes persist beyond 2 weeks in a small percentage of stroke victims. [505] [506] BBB abnormalities, as reflected by accumulation of CT contrast or brain scan isotopes, are still present 4 weeks after insult, [507] and the histologic resolution of large infarcts is not complete for several months. The available information does not allow a definite statement on how long elective procedures should be deferred. A 6-week delay should give some assurance of the likely recovery of autoregulation, CO_2 responsiveness, and BBB integrity. However, the size and location of the infarction should be weighed. A small infarction in silent cortex may give wider latitudes than a large lesion that has resulted in paresis that is still resolv-ing. Pending other information, it seems reasonable to defer elective surgery for at least 6 weeks after a cerebral vascular accident and preferably for 6 weeks from the point at which a stable postinsult neurologic state has been achieved.

Considerations Relevant to Complete Global Ischemia (Cardiac Arrest)

Maintenance of adequate perfusion pressures following cardiac arrest is of considerable importance (Ch. 75) . Hypotension developing after resuscitation from cardiac arrest may aggravate microcirculatory and vasospastic processes occurring at this time and may increase brain damage. A late phase of intracranial hypertension may occur and is due to the development of extensive cerebral edema, probably both vasogenic and cytotoxic in origin, associated with brain necrosis. Attempts to control this type of intracranial hypertension with osmotherapy usually fail. ICP monitoring is not generally employed because the patients who develop these delayed ICP increases have sustained massive tissue damage.

Both barbiturates and calcium channel blockers have been administered after cardiac arrest. The former are ineffective. [469] [470] [508] The calcium channel blocker nimodipine improved neurologic outcome when administered after complete global ischemia in a primate model, [509] but it was ineffective following complete global ischemia in the cat [510] [511] and the dog. [512] In a small cohort (51 patients) of cardiac arrest victims, nimodipine was shown to improve CBF but not neurologic outcome. [513] In a second trial in approximately 150 cardiac arrest victims, no overall benefit in neurologic outcome was observed. [514] However, a subset of patients in whom initiation of advanced life support was delayed for more than 10 minutes demonstrated improved survival. This single study cannot serve as a justification for the administration after cardiac arrest of nimodipine, especially in the face of the unequivocally negative results of the multicenter lidoflazine cardiac arrest study. [515] Once again, the important therapeutic objectives are maintenance of normocarbia and normotension, normalization of systemic pH, avoidance of hyperthermia, and prevention and treatment of seizures.

Chronic Arterial Hypertension

A recurrent concern is that of acceptable levels of blood pressure reduction in chronically hypertensive patients (Ch. 25) . Firm guidelines have not been established. However, from the vantage of cerebral well-being, limiting elective MAP reduction to 30 to 35 percent of resting mean levels seems appropriate for both hypertensive and normotensive patients. It is reasonable that the same guidelines may apply in both populations because, in chronic hypertension, both the upper limit of autoregulation and the LLA are shifted to the right with apparently little distortion. [46]

The rationale for a limit of 30 to 35 percent is as follows. It has been demonstrated that MAP reductions of 50 percent in nonanesthetized patients, both normotensive and hypertensive, commonly produce reversible symptoms of cerebral hypoperfusion. [46] [516] [517] Although even greater reductions are probably tolerated provided

plateau. It has been demonstrated that a MAP reduction of 25 percent brings both normotensive and hypertensive patients to the LLA. [46] Because MAP reduction exceeds 25 percent of baseline, CBF values are below normal, albeit, in subjects free of occlusive vascular disease, above the threshold for neurophysiologic dysfunction or injury (see Fig. 19-14) . However, physiologic reserve is being encroached on, leaving little margin for error or for other causes of impaired cerebral O_2 delivery (low hematocrit, unrecognized cerebrovascular disease).

It has been demonstrated in animals that treatment of chronic hypertension can restore the LLA to normal. [518] [519] A similar phenomenon has been observed in humans by Strandgaard, [46] although restoration was incomplete and had failed to occur after as much as 12 months of treatment in some subjects. It is an unexplored possibility that the extent of restoration of the LLA with antihypertensive therapy depends on the agent. Some drugs may restore the LLA more effectively than others. In particular, angiotensin-converting enzyme inhibitors have been shown to decrease the LLA acutely in both normotensive and hypertensive subjects. [47] [520]

Intracranial Hypertension

The control of intracranial hypertension is discussed in detail in Chapter 52 .

Brain Tumors

There are few data regarding the physiology of intracranial tumors. Arbit et al [521] measured CBF in cerebral tumors using laser-Doppler technology. In general, they found that tumors had a lower CBF than normal brain. Autoregulation was occasionally apparent, and CO_2 responsiveness was usually present. The investigation of Schregel et al, [522] who measured MCA velocity and vessel area in tumor patients, also revealed that CO_2 responsiveness was occasionally abnormal and that, ipsilateral to the tumor, hyperventilation was sometimes associated with paradoxic increases in MCA flow velocity. There is often considerable edema in association with intracranial tumors. Bedford et al [523] showed that the radiologic extent of the edema (which presumably represents the extent of abnormal vessel leakiness) correlated with the severity of the ICP elevation that occurred in association with intubation-related hypertension. Empirically, the edema associated with tumors is improved by steroids, [524] and it has been shown in patients with intracranial tumors [525] that, over a time course as short as 6 hours, BBB function is improved by administration of dexamethasone (Ch. 52) .

Coma and Epilepsy

Coma, regardless of its cause, is associated with reductions in brain metabolism. In the case of lesions occurring in the reticular activating system, the reduction in CMR probably represents a normal physiologic adjustment to reduced functional activity. During generalized seizure activity, CMR and CBF may increase dramatically. [371] The intensive motor and brain activity accompanying generalized seizures leads to the development of systemic and cerebral acidosis, often accompanied by a reduction in arterial oxygenation, an increase in Pa_{CO_2}, and peripheral lactic acidosis. If generalized seizure activity continues unabated, arterial hypotension ensues. With muscular relaxation and measures ensuring adequate oxygenation and ventilation, the systemic acidosis and hypotension can be avoided, and the severity of cerebral acidosis can be diminished. During relatively brief episodes of continuous seizures, the brain seems able to meet the high metabolic demands. [371] However, even with effective ventilation and maintenance of perfusion pressure, when seizures continue for a prolonged period, they can lead to the development of irreversible neuronal damage. [526] Therapy aimed at interrupting the seizure and restoring a normal balance between cerebral metabolic demand and CBF is indicated. Barbiturates, benzodiazepines, and other potent anticonvulsants are appropriate. Adequate ventilation, oxygenation, and maintenance of blood pressure are important adjunctive measures. Muscle relaxants must be viewed as purely symptomatic therapy, because they do not alter the abnormal cerebral electrical activity.

The potentially injurious nature of seizures justifies attention to prevention. Practices vary. However, patients who have sustained a severe head injury or subarachnoid hemorrhage and any patient in whom a substantial cortical incision is planned are at risk, and prophylactic anticonvulsants should be considered.

ACKNOWLEDGMENT

The authors gratefully acknowledge the contribution of Harvey M. Shapiro to the development of this chapter.

References

1. Michenfelder JD: Anesthesia and the brain: Clinical, functional, metabolic, and vascular correlates. New York, Churchill Livingstone, 1988.

2. Moncada S, Palmer RMJ, Higgs EA: Nitric oxide: Physiology, pathophysiology, and pharmacology. Pharmacol Rev 43:109, 1991.

3. Snyder SH, Bredt DS: Biological roles of nitric oxide. Sci Am 266:68, 1992.

4. Wang Q, Pelligrino DA, Baughman VL et al: The role of neuronal nitric oxide synthase in regulation of cerebral blood flow in normocapnia and hypercapnia in rats. J Cereb Blood Flow Metabol 15:774, 1995.

5. McPherson RW, Kirsch JR, Ghaly RF et al: Effect of nitric oxide synthase inhibition on the cerebral vascular response to hypercapnia in primates. Stroke 26:682, 1995.

6. Ayata C, Ma J, Meng W et al: L-NA-sensitive rCBF augmentation during vibrissal stimulation in type III nitric oxide synthase mutant mice. J Cereb Blood Flow Metab 16:539, 1996.

7. Cholet N, Seylaz J, Lacombe P et al: Local uncoupling of the cerebrovascular and metabolic responses to somatosensory stimulation after neuronal nitric oxide synthase inhibition. J Cereb Blood Flow Metab 17:1191, 1997.

8. McPherson RW, Kirsch JR, Traystman RJ: Effect of *N*-nitro- L-arginine on cerebral vasodilation by halothane and isoflurane (abstract). Anesthesiology 77:A173, 1992.

9. Koenig HM, Pelligrino DA, Albrecht RF: Halothane vasodilatation and nitric oxide in rat pial vessels (abstract). Anesthesiology 77:A751, 1992.

10. Koenig HM, Pelligrino DA, Wang Q et al: Role of nitric oxide and endothelium in rat pial vessel dilation response to isoflurane. Anesth Analg 79:886, 1994.

11. Iadecola C: Nitric oxide participates in the cerebrovasodilation elicited from cerebellar fastigial nucleus. Am J Physiol 263:R1156, 1992.

12. Raszkiewicz JL, Linville DG, Kerwin JF et al: Nitric oxide synthase is critical in mediating basal forebrain regulation of cortical cerebral circulation. J Neurosci Res 33:129, 1992.

13. Kimura T, Yu J-G, Edvinsson L et al: Cholinergic, nitric oxidergic innervation in cerebral arteries of the cat. Brain Res 773:117, 1997.

14. Lou HC, Edvinsson L, MacKenzie ET: The concept of coupling blood flow to brain function: Revision required? Ann Neurol 22:289, 1987.

15. Miyauchi Y, Sakabe T, Maekawa Y et al: Responses of EEG, cerebral oxygen consumption and blood flow to peripheral nerve stimulation during thiopentone anaesthesia in the dog. Can Anaesth Soc J 32:491, 1985.

16. Cameron OG, Modell JG, Hichwa RD et al: Changes in sensory-cognitive input: Effects on cerebral blood flow. J Cereb Blood Flow Metab 10:38, 1990.

17. Frostig RD, Lieke EE, Ts'o DY et al: Cortical functional architecture and local coupling between neuronal activity and the microcirculation revealed by *in vivo* high-resolution optical imaging of intrinsic signals. Proc Natl Acad Sci USA 87:6082, 1990.

18. Perlmutter JS, Lich LL, Margenau W et al: PET measured evoked cerebral blood flow responses in an awake monkey. J Cereb Blood Flow Metab 11:229, 1991.

19. Hyder F, Behar KL, Martin MA et al: Dynamic magnetic resonance imaging of the rat brain during forepaw stimulation. J Cereb Blood Flow Metab 14:649, 1994.

20. Dirnagl U, Niwa K, Lindauer U et al: Coupling of cerebral blood flow to neuronal activation: Role of adenosine and nitric oxide. Am J Physiol 267:H296, 1994.

21. Michenfelder J: The interdependency of cerebral function and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 41:231, 1974.

22. Newberg LA, Milde JH, Michenfelder JD: The cerebral metabolic effects of isoflurane at and above concentrations that suppress cortical electrical activity. Anesthesiology 59:23, 1983.

23. Milde LN, Milde JH, Michenfelder JD: Cerebral functional, metabolic and hemodynamic effects of etomidate in dogs. Anesthesiology 63:371, 1985.

24. Maekawa T, Tommasino C, Shapiro HM et al: Local cerebral blood flow and glucose utilization during isoflurane anesthesia in the rat. Anesthesiology 65:144, 1986.

25. Hansen TD, Warner DS, Todd MM et al: Distribution of cerebral blood flow during halothane versus isoflurane anesthesia in rats. Anesthesiology 69:332, 1988.

26. Reinstrup P, Ryding E, Algotsson L et al: Distribution of cerebral blood flow during anesthesia with isoflurane or halothane in humans. Anesthesiology 82:359, 1995.

27. Drummond JC, Todd MM, U HS: The effect of high dose sodium thiopental on brain stem auditory and median nerve somatosensory evoked potentials in humans. Anesthesiology 63:249, 1985.

28. Peterson DO, Drummond JC, Todd MM: The effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 65:35, 1986.

29. Akrawi WP, Drummond JC, Kalkman CJ et al: A comparison of the electrophysiologic characteristics of EEG burst-suppression as produced by isoflurane, thiopental, etomidate and propofol. J Neurosurg Anesthesiol 8:40, 1996.

30. Maher J, Hachinski V: Hypothermia as a potential treatment for cerebral ischemia. Cerebrovasc Brain Metab Rev 5:277, 1993.

31. Kataoka K, Mitani A, Yanese H et al: Ischemic neuronal damage: How does mild hypothermia modulate it? Mol Chem Neuropathol 28:191, 1996.

32. Nemoto EM, Klementavicius R, Melick JA et al: Suppression of cerebral metabolic rate for oxygen ($CMRO_2$) by mild hypothermia compared with thiopental. J Neurosurg Anesthesiol 8:52, 1996.

33. Klementavicius R, Nemoto EM, Yonas H: The Q10 ratio basal cerebral metabolic rate for oxygen in rats. J Neurosurg 85:482, 1996.

34. Smith AL, Wollman H: Cerebral blood flow and metabolism: Effects of anesthetic drugs and techniques. Anesthesiology 36:378, 1972.

35. Sato M, Pawlik G, Heiss WD: Comparative studies of regional CNS blood flow autoregulation and responses to CO_2 in the cat. Stroke 15:91, 1984.

36. Koehler RC, Traystman RJ: Bicarbonate ion modulation of cerebral blood flow during hypoxia and hypercapnia. Am J Physiol 243:H33, 1982.

37. Iadecola C, Zhang F: Nitric oxide-dependent and -independent components of cerebrovasodilation elicited by hypercapnia. Am J Physiol 266:R546, 1994.

38. Iadecola C, Xu X: Nitro- L-arginine attenuates hypercapnic cerebrovasodilation without affecting cerebral metabolism. Am J Physiol 266:R518, 1994.

39. Smith JJ, Lee JG, Hudetz AG et al: The role of nitric oxide in the cerebrovascular response to hypercapnia. Anesth Analg 84:363, 1997.

40. Albrecht RF, Miletich DJ, Madala LR: Normalization of cerebral blood flow during prolonged halothane anesthesia. Anesthesiology 58:26, 1983.

41. Raichle ME, Posner JB, Plum F: Cerebral blood flow during and after hyperventilation. Arch Neurol 23:394, 1970.

42. Plum F, Siesjo BK: Recent advances in CSF physiology. Anesthesiology 42:708, 1975.

43. Omae T, Ibayashi S, Kusuda K et al: Effects of high atmospheric pressure and oxygen on middle cerebral blood flow velocity in humans measured by transcranial doppler. Stroke 29:94, 1998.

44. Jacobson I, Harper AM, McDowall DG: The effects of oxygen at 1 and 2 atmospheres on the blood flow and oxygen uptake of the cerebral cortex. Surg Gynecol Obstet 119:737, 1964.

45. Drummond JC: The lower limit of autoregulation: Time to revise our thinking? (letter). Anesthesiology 86:1431, 1997.

46. Strandgaard S: Autoregulation of cerebral blood flow in hypertensive patients: The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation 53:720, 1976.

47. Waldemar G, Schmidt JF, Andersen AR et al: Angiotensin converting enzyme inhibition and cerebral blood flow autoregulation in normotensive and hypertensive man. J Hypertens 7:229, 1989.

48. Larsen FS, Olsen KS, Hansen BA et al: Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. Stroke 25:1985, 1994.

49. Olsen KS, Svenden LB, Larsen FS et al: Effect of labetalol on cerebral blood flow, oxygen metabolism and autoregulation in healthy humans. Br J Anaesth 75:51, 1995.

50. Olsen KS, Svendsen LB, Larsen FS: Validation of transcranial near-infrared spectroscopy for evaluation of cerebral blood flow autoregulation. J Neurosurg Anesth 8:280, 1996.

51. Greenfield JC, Rembert JC, Tindall GT: Transient changes in cerebral vascular resistance during the Valsalva maneuver in man. Stroke 15:76, 1984.

52. Toyoda K, Fujii K, Ibayashi S et al: Role of nitric oxide in regulation of brain stem circulation during hypotension. J Cereb Blood Flow Metab 17:1089, 1997.

53. Kobari M, Fukuuchi Y, Tomita M et al: Role of nitric oxide in regulation of cerebral microvascular tone and autoregulation of cerebral blood flow in cats. Brain Res 667:255, 1994.

54. Thompson BG, Pluta RM, Girton ME et al: Nitric oxide mediation of chemoregulation but not autoregulation of cerebral blood flow in primates. J Neurosurg 84:71, 1996.

55. Branston NM: Neurogenic control of the cerebral circulation. Cerebrovasc Brain Metab Rev 7:338, 1995.

56. Dahl E: The innervation of the cerebral arteries. J Anat 115:53, 1973.

57. Hara H, Zhang Q-J, Kuroyanagi T et al: Parasympathetic cerebrovascular innervation: An anterograde tracing from the sphenopalatine ganglion in the rat. Neurosurgery 32:822, 1993.

58. Sato A, Sato Y: Cerebral cortical vasodilatation in response to stimulation of cholinergic fibres originating in the nucleus basalis of Meynert. J Auton Nerv Syst 30:S137, 1990.

59. Adachi T, Biesold D, Inanami O et al: Stimulation of the nucleus basalis of Meynert and substantia innominata produces widespread increases in cerebral blood flow in the frontal, parietal and occipital cortices. Brain Res 514:163, 1990.

60. Iadecola C, Reis DJ: Continuous monitoring of cerebrocortical blood flow during stimulation of the cerebellar fastigial nucleus: A study by laser-Doppler flowmetry. J Cereb Blood Flow Metab 10:608, 1990.

61. Tuor UI: Local distribution of the effects of sympathetic stimulation on cerebral blood flow in the rat. Brain Res 529:224, 1990.

62. Reddy SVR, Yaksh TL, Anderson RE Jr et al: Effect in cat of locus coeruleus lesions on the response of cerebral blood flow and cardiac output to altered Pa CO_2 . Brain Res 365:278, 1985.

63. Edvinsson L, Dequeurce A, Duverger D et al: Central serotonergic nerves project to the pial vessels of the brain. Nature 306:55, 1983.

64. Underwood MD, Bakalian MJ, Arango V et al: Regulation of cortical blood flow by the dorsal raphe nucleus: Topographic organization of

cerebrovascular regulatory regions. J Cereb Blood Flow Metab 12:664, 1992.

65. Hara H, Jansen I, Ekman R et al: Acetylcholine and vasoactive intestinal peptide in cerebral blood vessels: Effect of extirpation of the sphenopalatine ganglion. J Cereb Blood Flow Metab 9:204, 1989.

66. Busija DW: Sympathetic nerves reduce cerebral blood flow during hypoxia in awake rabbits. Am J Physiol 247:H446, 1984.

67. Auer LM, Edvinsson L, Johansson BB: Effect of sympathetic nerve stimulation and adrenoceptor blockade on pial arterial and venous calibre and on intracranial pressure in the cat. Acta Physiol Scand 119:213, 1983.

68. MacKenzie ET, McGeorge AD, Graham DI et al: Effects of increasing arterial pressure on cerebral blood flow in the baboon, influence of the sympathetic nervous system. Pflugers Arch 378:189, 1979.

69. Bevan JA: Autonomic pharmacologist's guide to the cerebral circulation. Trends Pharmacol Sci 5:234, 1984.

70. Fitch W, MacKenzie ET, Harper AM: Effects of decreasing arterial blood pressure on cerebral blood flow in the baboon: Influence of the sympathetic nervous system. Circ Res 37:550, 1975.

71. Johansson BB, Auer LM: Neurogenic modification of the vulnerability of the blood-brain barrier during acute hypertension in conscious rats. Acta Physiol Scand 117:507, 1983.

72. Tuor UI: Acute hypertension and sympathetic stimulation: Local heterogeneous changes in cerebral blood flow. Am J Physiol 263:H511, 1992.

73. Reis DJ, Berger SB, Underwood MD et al: Electrical stimulation of cerebellar fastigial nucleus reduces ischemic infarction elicited by middle cerebral artery occlusion in rat. J Cereb Blood Flow Metab 11:810, 1991.

74. Koketsu N, Moskowitz MA, Kontos HA et al: Chronic parasympathetic sectioning decreases regional cerebral blood flow during hemorrhagic hypotension and increases infarct size after middle

cerebral artery occlusion in spontaneously hypertensive rats. J Cereb Blood Flow Metab 12:613, 1992.

75. Shibata M, Einhaus S, Schweitzer JB et al: Cerebral blood flow decreased by adrenergic stimulation of cerebral vessels in anesthetized newborn pigs with traumatic brain injury. J Neurosurg 79:696, 1993.

76. MacFarlane R, Moskowitz MA, Sakas DE et al: The role of neuroeffector mechanisms in cerebral hyperperfusion syndromes. J Neurosurg 75:845, 1991.

77. Harrison MG: Influence of haematocrit in the cerebral circulation. Cerebrovasc Brain Metab Rev 1:55, 1989.

78. Thomas DJ, Marshall J, Russell RW et al: Effect of haematocrit on cerebral blood-flow in man. Lancet 2:941, 1977.

79. Cole DJ, Drummond JC, Patel PM et al: Effects of viscosity and oxygen content on cerebral blood flow in ischemic and normal rat brain. J Neurol Sci 124:15, 1994.

80. Cole DJ, Drummond JC, Shapiro HM et al: The effect of hyper-volemic-hemodilution with and without hypertension on cerebral blood flow following middle cerebral artery occlusion in the rat. Anesthesiology 71:580, 1989.

81. Korosue K, Ishida K, Matsuoka H et al: Clinical, hemodynamic, and hemorrheological effects of isovolemic hemodilution in acute cerebral infarction. Neurosurgery 23:148, 1988.

82. Origitano TC, Wascher TM, Reichman H et al: Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. Neurosurgery 27:729, 1990.

83. Korosue K, Heros RC: Mechanism of cerebral blood flow augmentation by hemodilution in rabbits. Stroke 23:1487, 1992.

84. Kee DB, Wood JH: Rheology of the cerebral circulation. Neurosurgery 15:125, 1984.

85. Lee SH, Heros RC, Mullan JC et al: Optimum degree of hemodilution for brain protection in a canine model of focal cerebral ischemia. J Neurosurg 80:469, 1994.

86. Maekawa T, McDowall DG, Okuda Y: Brain-surface oxygen tension and cerebral cortical blood flow during hemorrhagic and drug-induced hypotension in the cat. Anesthesiology 51:313, 1979.

87. Marsh ML, Shapiro HM, Smith RW et al: Changes in neurologic status and intracranial pressure associated with sodium nitroprusside administration. Anesthesiology 51:336, 1979.

88. Olesen J: The effect of intracarotid epinephrine, norepinephrine, and angiotensin on the regional cerebral blood flow in man. Neurology 22:978, 1972.

89. King BD, Sokoloff L, Wechsler RL: The effects of *l*-epinephrine and *l*-norepinephrine upon cerebral circulation and metabolism in man. J Clin Invest 31:273, 1951.

90. Rogers AT, Stump DA, Gravlee GP et al: Response of cerebral blood flow to phenylephrine infusion during hypothermic cardiopulmonary bypass: Influence of Pa CO_2 management. Anesthesiology 69:547, 1988.

91. MacKenzie ET, McCulloch J, O'Keane M et al: Cerebral circulation and norepinephrine: Relevance of the blood-brain barrier. Am J Physiol 231:483, 1976.

92. Drummond JC, Oh Y-S, Cole DJ et al: Phenylephrine-induced hypertension decreases the area of ischemia following middle cerebral artery occlusion in the rat. Stroke 20:1538, 1989.

93. Berntman L, Dahlgren N, Siesjo BK: Influence of intravenously administered catecholamines on cerebral oxygen consumption and blood flow in the rat. Acta Physiol Scand 104:101, 1978.

94. Tuor UI, Edvinsson L, McCulloch J: Catecholamines and the relationship between cerebral blood flow and glucose use. Am J Physiol 251:H824, 1986.

95. Sokrab TE, Johansson BB: Regional cerebral blood flow in acute hypertension induced by adrenaline, noradrenaline and phenylephrine in the conscious rat. Acta Physiol Scand 137:101, 1989.

96. Ekstrom-Jodal B, vonEssen C, Haggendal E: Effects of noradrena-line on the cerebral blood flow in the dog. Acta Neurol Scand 50:11, 1974.

97. vonEssen C: Effects of dopamine, noradrenaline and 5-hydroxytryp-tamine on the cerebral blood flow in the dog. J Pharm Pharmacol 24:G68, 1972.

98. Oberdorster G, Lang R, Zimmer R: Direct effects of alpha- and beta-sympathomimetic amines on the cerebral circulation of the dog. Pflugers Arch 340:145, 1973.

99. Lluch S, Reimann C, Glick G: Evidence for the direct effect of adrenergic drugs on the cerebral vascular bed of the unanesthetized goat. Stroke 4:50, 1973.

100. Nemoto EM, KIemantavicius R, Melick JA et al: Norepinephrine activation of basal cerebral metabolic rate for oxygen ($CMRO_2$) during hypothermia in rats. Anesth Analg 83:1262, 1996.

101. Artru A, Nugent M, Michenfelder JD: Anesthetics affect the cerebral metabolic response to circulatory catecholamines. J Neurochem 36:1941, 1981.

102. Bryan RM: Cerebral blood flow and energy metabolism during stress. Am J Physiol 259:H269, 1990.

103. Sercombe R, Aubineau P, Edvinsson L et al: Pharmacological evidence *in vitro* and *in vivo* for functional $beta_1$ receptors in the cerebral circulation. Pflugers Arch 368:241, 1977.

104. Abdul-Rahman A, Dahlgren N, Johansson BB et al: Increase in local cerebral blood flow induced by circulating adrenaline: Involvement of blood-brain barrier dysfunction. Acta Physiol Scand 107:227, 1979.

105. Forster A, Horn KV, Marshall LF et al: Anesthetic effects on blood-brain barrier function during acute arterial hypertension. Anesthesiology 49:26, 1978.

106. MacKenzie ET, McCulloch J, Harper AM: Influence of endogenous norepinephrine on cerebral blood flow and metabolism. Am J Physiol 231:489, 1976.

107. Madsen PL, Vorstrup S, Schmidt JF et al: Effect of acute and prolonged treatment with propranolol on cerebral blood flow and cerebral oxygen metabolism in healthy volunteers. Eur J Clin Pharmacol 39:295, 1990.

108. Schroeder T, Schierbeck J, Howardy P et al: Effect of labetalol on cerebral blood flow and middle cerebral arterial flow velocity in healthy volunteers. Neurol Res 13:10, 1991.

109. Dubois M, Caputy A, MacCosbe P et al: Cerebral blood flow measurements during blood pressure control with intravenous labetalol following craniotomy. J Neurosurg Anesth 4:176, 1992.

110. Howie MB, Black HA, Zvara D et al: Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. Anesth Analg 71:384, 1990.

111. Bunegin L, Albin MS, Gelineau EF: Effect of esmolol on cerebral blood flow during intracranial hypertension and hemorrhagic hypo-volemia. Anesthesiology 67:A424, 1987.

112. vonEssen C, Zervas NT, Brown DR et al: Local cerebral blood flow in the dog during intravenous infusion of dopamine. Surg Neurol 13:181, 1980.

113. vonEssen C: Effects of dopamine on the cerebral blood flow in the dog. Acta Neurol Scand 50:39, 1974.

114. Toda N: Dopamine vasodilates human cerebral artery. Experientia 39:1131, 1983.

115. Bandres J, Yao L, Nemoto EM et al: Effects of dobutamine and dopamine on whole brain blood flow and metabolism in unanesthetized monkeys. J Neurosurg Anesth 4:250, 1992.

116. Karlsson B, Forsman M, Roald OK et al: Effect of dexmedetomidine, a selective and potent alpha2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 71:125, 1990.

117. James IM, Larbi E, Zaimis E: The effect of acute intravenous administration of clonidine on cerebral blood flow in man. Br J Pharmacol 39:198P, 1970.

118. Kanawati IS, Yaksh TL, Anderson RE et al: Effects of clonidine on cerebral blood flow and the response to arterial CO_2. J Cereb Blood Flow Metab 6:358, 1985.

119. Crosby G, Russo MA, Szabo MD et al: Subarachnoid clonidine reduces spinal cord blood flow and glucose utilization in conscious rats. Anesthesiology 73:1179, 1990.

120. Lee H-W, Caldwell JE, Dodson B et al: The effect of clonidine on cerebral blood flow velocity, carbon dioxide cerebral vasoreactivity, and response to increased arterial pressure in human volunteers. Anesthesiology 87:553, 1997.

121. Coughlan MG, Lee JG, Bosnjak ZJ et al: Direct coronary and cerebral vascular responses to dexmedetomidine: Significance of endogenous nitric oxide synthesis. Anesthesiology 77:998, 1992.

122. Busija DW, Leffler CW: Exogenous norepinephrine constricts cerebral arterioles via alpha $_2$ -adrenoceptors in newborn pigs. J Cereb Blood Flow Metab 7:184, 1987.

123. Marchal G, Rioux P, Petit-Taboue M-C et al: Regional cerebral oxygen consumption, blood flow, and blood volume in healthy human ageing. Arch Neurol 49:1013, 1992.

124. Meyer JS, Terayama Y, Takashima S: Cerebral circulation in the elderly. Cerebrovasc Brain Metabol Rev 5:122, 1993.

125. Todd MM, Weeks J: Comparative effects of propofol, pentobarbital, and isoflurane on cerebral blood flow and blood volume. J Neurosurg Anesthesiol 8:296, 1996.

126. Powers WJ, Raichle ME: Positron emission tomography and its application to the study of cerebrovascular disease in man. Stroke 16:361, 1985.

127. Greenberg JH, Alavi A, Reivich M et al: Local cerebral blood volume response to carbon dioxide in man. Circ Res 43:324, 1978.

128. Grubb RL, Raichle ME, Eichling JO et al: The effects of changes in Pa $_{CO_2}$ on cerebral blood volume, blood flow, and vascular mean transit time. Stroke 5:630, 1974.

129. Gibbs JM, Wise RJS, Leenders KL et al: Evaluation of cerebral perfusion reserve in patients with carotid-artery occlusion. Lancet 1:310, 1984.

130. Montgomery EB, Grubb RL, Raichle ME: Cerebral hemodynamics and metabolism in postoperative cerebral vasospasm and treatment with hypertensive therapy. Ann Neurol 9:503, 1981.

131. Ferrari M, Wilson DA, Hanley DF et al: Effects of graded hypotension on cerebral blood flow, blood volume, and mean transit time in dogs. Am J Physiol 262:H1908, 1992.

132. Lanier WL, Warner DO: Intracranial elastance versus intracranial compliance: Terminology should agree with that of other disciplines [letter]. Anesthesiology 77:403, 1992.

133. Artru AA: Relationship between cerebral blood volume and CSF pressure during anesthesia with isoflurane or fentanyl in dogs. Anesthesiology 60:575, 1984.

134. Artru AA: Relationship between cerebral blood volume and CSF pressure during anesthesia with halothane or enflurane in dogs. Anesthesiology 58:533, 1983.

135. Archer DP, Labreque P, Tyler JL et al: Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. Anesthesiology 67:642, 1987.

136. Weeks JB, Todd MM, Warner DS et al: The influence of halothane, isoflurane, and pentobarbital on cerebral plasma volume in hypocapnic and normocapnic rats. Anesthesiology 73:461, 1990.

137. Ulrich K, Kuschinsky W: *In vivo* effects of alpha-adrenoceptor agonists and antagonists on pial veins of cats. Stroke 16:880, 1985.

138. Marin J, Lobato RD, Rico ML et al: Effect of pentobarbital on the reactivity of isolated human cerebral arteries. J Neurosurg 54:521, 1981.

139. Ogura K, Takayasu M, Dacey RG: Differential effects of pentobarbital on intracerebral arterioles and venules of rats *in vitro.* Neurosurgery 28:537, 1991.

140. Moriyama S, Nakamura K, Hatano Y et al: Responses to barbiturates of isolated dog cerebral and mesenteric arteries contracted with KCl and prostaglandin F_{2alpha}. Acta Anaesthesiol Scand 34:523, 1990.

141. Stulken EH, Milde JH, Michenfelder JD et al: The nonlinear responses of cerebrospinal metabolism to low concentrations of halothane, enflurane, isoflurane, and thiopental. Anesthesiology 46:28, 1977.

142. Albrecht RF, Miletich DJ, Rosenberg R et al: Cerebral blood flow and metabolic changes from induction to onset of anesthesia with halothane or pentobarbital. Anesthesiology 47:252, 1977.

143. Pierce EC, Lambertsen CJ, Deutsch S et al: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. J Clin Invest 41:1664, 1962.

144. Astrup J, Rosenorn J, Cold GE et al: Minimum cerebral blood flow and metabolism during craniotomy: Effect of thiopental loading. Acta Anaesthesiol Scand 28:478, 1984.

145. Astrup J, Sorensen PM, Sorensen HR: Inhibition of cerebral oxygen and glucose consumption in the dog by hypothermia, pentobarbital, and lidocaine. Anesthesiology 55:263, 1981.

146. Altenburg BM, Michenfelder JD, Theye RA: Acute tolerance to thiopental in canine cerebral oxygen consumption studies. Anesthesiology 31:443, 1969.

147. Gronert GA, Michenfelder JD, Sharbrough FW et al: Canine cerebral metabolic tolerance during 24 hours of deep pentobarbital anesthesia. Anesthesiology 55:110, 1981.

148. Sawada Y, Sugimoto H, Kobayash H et al: Acute tolerance to high-dose barbiturate treatment in patients with severe head injuries. Anesthesiology 56:53, 1982.

149. Reivich M: Regulation of the cerebral circulation. Clin Neurosurg 1:378, 1969.

150. Kassell NF, Hitchon PW, Gerk MK et al: Influence of changes in arterial P $_{CO_2}$ on cerebral blood flow and metabolism during high-dose barbiturate therapy in dogs. J Neurosurg 54:615, 1981.

151. Vandesteene A, Trempont V, Engelman E et al: Effect of propofol on cerebral blood flow and metabolism in man. Anaesthesia 43:42, 1988.

152. Stephan H, Sonntag H, Schenk HD et al: Effects of Disoprivan on cerebral blood flow, cerebral oxygen consumption and cerebral vascular reactivity. Anesthetist 36:60, 1987.

153. Alkire MT, Haier RJ, Barker SJ et al: Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology 82:393, 1995.

154. Ravussin P, Guinard JP, Ralley F et al: Effect of propofol on cerebrospinal fluid pressure and cerebral perfusion pressure in patients undergoing craniotomy. Anaesthesia 43:37, 1988.

155. Fox J, Gelb AW, Enns J et al: The responsiveness of cerebral blood flow to changes in arterial carbon dioxide is maintained during propofol-nitrous oxide anesthesia in humans. Anesthesiology 77:453, 1992.

156. Craen RA, Gelb AW, Murkin JM et al: Human cerebral autoregulation is maintained during propofol air/O_2 anesthesia (abstract). J Neurosurg Anesthesiol 4:298, 1992.

157. Cameron AE: Opisthotonus again (letter). Anaesthesia 42:1124, 1987.

158. Hopkins CS: Recurrent opisthotonus associated with anaesthesia (letter). Anaesthesia 43:904, 1988.

159. Jones GW, Boykett MH, Klok M: Propofol, opisthotonus and epilepsy (letter). Anaesthesia 43:905, 1988.

160. DeFriez CB, Wong HC: Seizures and opisthotonos after propofol anesthesia. Anesth Analg 75:630, 1992.

161. Bevan JC: Propofol-related convulsions. Can J Anaesth 40:805, 1993.

162. Borgeat A, Dessibourg C, Popovic V et al: Propofol and spontaneous movements: An EEG study. Anesthesiology 74:24, 1991.

163. Cheng MA, Tempelhoff R, Silbergeld DL et al: Large-dose propofol alone in adult epileptic patients: Electrocorticographic results. Anesth Analg 83:169, 1996.

164. Samra SK, Sneyd JR, Ross DA et al: Effects of propofol sedation on seizures and intracranially recorded epileptiform activity in patients with partial epilepsy. Anesthesiology 82:843, 1995.

165. Lowson S, Gent JP, Goodchild CS: Anticonvulsant properties of propofol and thiopentone: Comparison using two tests in laboratory mice. Br J Anaesth 64:59, 1990.

166. Lowson S, Gent JP, Goodchild CS: Convulsive thresholds in mice during the recovery phase from anaesthesia induced by propofol, thiopentone, methohexitone and etomidate. Br J Pharmacol 102:879, 1991.

167. Rampton AJ, Griffin RM, Stuart CS et al: Comparison of methohexital and propofol for electroconvulsive therapy: Effects on hemodynamic responses and seizure duration. Anesthesiology 70:412, 1989.

168. Herrick IA, Craen RA, Gelb AW et al: Propofol sedation during awake craniotomy for seizures: Patient-controlled administration versus neurolept analgesia. Anesth Analg 84:1285, 1997.

169. Drummond JC, Iragui-Madoz VJ, Alksne JF et al: Masking of epileptiform activity by propofol during seizure surgery. Anesthesiology 76:652, 1992.

170. Renou AM, Vernhiet J, Macrez P et al: Cerebral blood flow and metabolism during etomidate anaesthesia in man. Br J Anaesth 50:1047, 1978.

171. Cold GE, Eskesen V, Eriksen H et al: CBF and $CMRO_2$ during continuous etomidate infusion supplemented with N_2O and fentanyl in patients with supratentorial cerebral tumour: A dose-response study. Acta Anaesthesiol Scand 29:490, 1985.

172. Cold GE, Eskesen V, Eriksen H et al: Changes in $CMRO_2$, EEG and concentration of etomidate in serum and brain tissue during cra-niotomy with continuous etomidate supplemented with N_2O and fentanyl. Acta Anaesthesiol Scand 30:159, 1986.

173. Bingham RM, Procaccio F, Prior PF et al: Cerebral electrical activity influences the effects of etomidate on cerebral perfusion pressure in traumatic coma. Br J Anaesth 57:843, 1985.

174. Davis DW, Mans AM, Biebuyck JF et al: Regional brain glucose utilization in rats during etomidate anesthesia. Anesthesiology 64:751, 1986.

175. Modica PA, Tempelhoff R: Intracranial pressure during induction of anaesthesia and tracheal intubation with etomidate-induced EEG burst suppression. Can J Anaesth 39:236, 1992.

176. Dearden NM, McDowall DG: Comparison of etomidate and althesin in the reduction of increased intracranial pressure after head injury. Br J Anaesth 57:361, 1985.

177. Levy ML, Aranda M, Zelman V et al: Propylene glycol toxicity following continuous etomidate infusion for the control of refractory cerebral edema. Neurosurgery 37:363, 1995.

178. Hoehner PJ, Whitson JT, Kirsch JR et al: Effect of intracarotid and intraventricular morphine on regional cerebral blood flow and metabolism in pentobarbital-anesthetized dogs. Anesth Analg 76:266, 1993.

179. Moyer JH, Pontius R, Morris G et al: Effect of morphine and *n*-allylnormorphine on cerebral hemodynamics and oxygen metabolism. Circulation 15:379, 1957.

180. Jobes DR, Kennell EM, Bush GL et al: Cerebral blood flow and metabolism during morphine-nitrous oxide anesthesia in man. Anesthesiology 47:16, 1977.

181. Takeshita H, Michenfelder JD, Theye RA: The effects of morphine and *n*-allylnormorphine on canine cerebral metabolism and circulation. Anesthesiology 37:605, 1972.

182. Jobes DR, Kennell E, Bitner R et al: Effects of morphine-nitrous oxide anesthesia on cerebral autoregulation. Anesthesiology 42:30, 1975.

183. Vernhiet J, Macrez P, Renou AM et al: Effets des fortes doses de morphinomimetiques (fentanyl et fentathienyl) sur la circulation cerebrale du sujet normal. Ann Anesth Fr 18:803, 1977.

184. Murkin JM, Farrar JK, Tweed WA et al: Relationship between cerebral blood flow and O_2 consumption during high-dose narcotic anesthesia for cardiac surgery. Anesthesiology 63:A44, 1985.

185. Firestone LL, Gyulai F, Mintun M et al: Human brain activity response to fentanyl imaged by positron emission tomography. Anesth Analg 82:1247, 1996.

186. McPherson RW, Traystman RJ: Fentanyl and cerebral vascular responsivity in dogs. Anesthesiology 60:180, 1984.

187. Baughman VL, Hoffman WE, Albrecht RF et al: Cerebral vascular and metabolic effects of fentanyl and midazolam in young and aged rats. Anesthesiology 67:314, 1987.

188. Safo Y, Young ML, Smith DS et al: Effects of fentanyl on local cerebral blood flow in the rat. Acta Anaesthesiol Scand 29:594, 1985.

189. Michenfelder JD, Theye RA: Effects of fentanyl, droperidol and Innovar on canine cerebral metabolism and blood flow. Br J Anaesth 43:630, 1971.

190. McPherson RW, Krempasanka E, Eimerl D et al: Effects of alfentanil on cerebral vascular reactivity in dogs. Br J Anaesth 57:1232, 1985.

191. Schregel W, Schafermeyer H, Muller C et al: The effect of halothane, alfentanil and propofol on blood flow velocity, blood vessel cross section and blood volume flow in the middle cerebral artery. Anaesthetist 41:21, 1992.

192. Mayberg TS, Lam AM, Eng CC et al: The effect of alfentanil on cerebral blood flow velocity and intracranial pressure during isoflurane-nitrous oxide anesthesia in humans. Anesthesiology 78:288, 1993.

193. Milde LN, Milde JH, Gallagher WJ: Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg 70:138, 1990.

194. Keykhah MM, Smith DS, Carlsson C et al: Influence of sufentanil on cerebral metabolism and circulation in the rat. Anesthesiology 63:274, 1985.

195. Werner C, Hoffman WE, Baughman VL et al: Effects of sufentanil on cerebral blood flow, cerebral blood flow velocity, and metabolism in dogs. Anesth Analg 72:177, 1991.

196. Bunegin L, Albin MS, Ernst PS et al: Cerebrovascular responses to sufentanil citrate in primates with and without intracranial hypertension (abstract). Anesth Analg 70:S42, 1990.

197. Stephan H, Groger P, Weyland A et al: The effect of sufentanil on cerebral blood flow, cerebral metabolism and the CO_2 reactivity of the cerebral vessels in man. Anaesthetist 40:153, 1991.

198. Murkin JM, Farrar JK, Tweed WA: Sufentanil anaesthesia reduces cerebral blood flow and cerebral oxygen consumption (abstract). Can J Anaesth 35:S131, 1988.

199. Mayer N, Weinstabl C, Podreka I et al: Sufentanil does not increase cerebral blood flow in healthy human volunteers. Anesthesiology 73:240, 1990.

200. Weinstabl C, Mayer N, Spiss CK: Sufentanil decreases cerebral blood flow velocity in patients with elevated intracranial pressure. Eur J Anaesthesiol 9:481, 1992.

201. Sheehan PB, Zornow MH, Scheller MS et al: The effects of fentanyl and sufentanil on intracranial pressure and cerebral blood flow in rabbits with an acute cryogenic brain injury. J Neurosurg Anesthesiol 4:261, 1992.

202. Weinstabl C, Mayer N, Richling B et al: Effect of sufentanil on intracranial pressure in neurosurgical patients. Anaesthesia 46:837, 1991.

203. Werner C, Kochs E, Hoffman WE et al: Sufentanil does not change cerebral hemodynamics and ICP in head injured patients (abstract). J Neurosurg Anesthesiol 4:313, 1992.

204. Jamali S, Ravussin P, Archer D et al: The effects of bolus administration of opioids on cerebrospinal fluid pressure in patients with supratentorial lesions. Anesth Analg 82:600, 1996.

205. Lauer KK, Connolly LA, Schmeling WT: Opioid sedation does not alter intracranial pressure in head injured patients. Can J Anaesth 44:929, 1997.

206. Marx W, Shah N, Long C et al: Sufentanil, alfentanil, and fentanyl: Impact on cerebrospinal fluid pressure in patients with brain tumors. J Neurosurg Anesthesiol 1:3, 1989.

207. Sperry RJ, Bailey PL, Reichman MV et al: Fentanyl and sufentanil increase intracranial pressure in head trauma patients. Anesthesiology 77:416, 1992.

208. Albanese J, Durbec O, Viviand X et al: Sufentanil increases intracranial pressure in patients with head trauma. Anesthesiology 79:493, 1993.

209. Werner C, Kochs E, Bause H et al: Effects of sufentanil on cerebral hemodynamics and intracranial pressure in patients with brain injury. Anesthesiology 83:721, 1995.

210. Herrick I, Gelb A, Manninen PH et al: Effects of fentanyl, sufentanil, and alfentanil on brain retractor pressure. Anesth Analg 72:359, 1991.

211. From RP, Warner DS, Todd MM et al: Anesthesia for craniotomy: A double-blind comparison of alfentanil, fentanyl, and sufentanil. Anesthesiology 73:896, 1990.

212. Bristow A, Shalev D, Rice B et al: Low-dose synthetic narcotic infusions for cerebral relaxation during craniotomies. Anesth Analg 66:413, 1987.

213. Shupak RC, Harp JR: Comparison between high-dose sufentanil-oxygen and high-dose fentanyl-oxygen for neuroanaesthesia. Br J Anaesth 57:375, 1985.

214. Jung R, Shah N, Reinsel R et al: Cerebrospinal fluid pressure in patients with brain tumors: Impact of fentanyl versus alfentanil during nitrous oxide-oxygen anesthesia. Anesth Analg 71:419, 1990.

215. Moss E: Alfentanil increases intracranial pressure when intracranial compliance is low. Anaesthesia 47:134, 1992.

216. Markovitz BP, Duhaime A-C, Sutton L et al: Effects of alfentanil on intracranial pressure in children undergoing ventriculoperitoneal shunt revision. Anesthesiology 76:71, 1992.

217. Souter MJ, Andrews PJD, Piper IR et al: Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury. Br J Anaesth 79:97, 1997.

218. Warner DS, Hindman BJ, Todd MM et al: Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supratentorial craniotomy. Anesth Analg 83:348, 1996.

219. Baker KZ, Ostapkovich N, Sisti MB et al: Intact cerebral blood flow reactivity during remifentanil/nitrous oxide anesthesia. J Neurosurg Anesthesiol 9:134, 1997.

220. Knobelsdorff GV, Paris A, Tonner PH et al: The effects of moderate vs. high dose remifentanil on cerebral hemodynamics during induction of anesthesia. Anesthesiology 87:A180, 1997.

221. Cotev S, Shalit MN: Effects of diazepam on cerebral blood flow and oxygen uptake after head injury. Anesthesiology 43:117, 1975.

222. Rockoff MA, Naughton KVH, Shapiro HM et al: Cerebral circulatory and metabolic responses to intravenously administered lorazepam. Anesthesiology 53:215, 1980.

223. Forster A, Juge O, Morel D: Effects of midazolam on cerebral blood flow in human volunteers. Anesthesiology 56:453, 1982.

224. Forster A, Juge O, Louis M et al: Effects of a specific benzodiazepine antagonist (RO 15-1788) on cerebral blood flow. Anesth Analg 66:309, 1987.

225. Veselis RA, Reinsel RA, Beattie BJ et al: Midazolam changes cerebral blood flow in discrete brain regions: An $H_2{}^{15}O$ positron emission tomography study. Anesthesiology 87:1106, 1997.

226. Forster A, Juge O, Morel D: Effects of midazolam on cerebral hemodynamics and cerebral vasomotor responsiveness to carbon dioxide. J Cereb Blood Flow Metab 3:246, 1983.

227. Fleischer JE, Milde JH, Moyer TP et al: Cerebral effects of high-dose midazolam and subsequent reversal with RO 15-1788 in dogs. Anesthesiology 68:234, 1988.

228. Nugent M, Artru AA, Michenfelder JD: Cerebral metabolic, vascular and protective effects of midazolam maleate. Anesthesiology 56:172, 1982.

229. Artru AA: Flumazenil reversal of midazolam in dogs: Dose-related changes in cerebral blood flow, metabolism, EEG, and CSF pressure. J Neurosurg Anesthesiol 1:46, 1989.

230. Knudsen L, Cold GE, Holdgard HO et al: Effects of flumazenil on cerebral blood flow and oxygen consumption after midazolam anaesthesia for craniotomy. Br J Anaesth 67:277, 1991.

231. Chiolero RL, Ravussin P, Anderes JP et al: The effects of midazolam reversal by RO 15-1788 on cerebral perfusion pressure in patients with severe head injury. Intensive Care Med 14:196, 1988.

232. Kumano H, Shimomura T, Furuya H et al: Effects of flumazenil during administration of midazolam on pial vessel diameter and regional cerebral blood flow in cats. Acta Anaesthesiol Scand 37:567, 1993.

233. Lanier WL, Albrecht RF, Iaizzo PA: Divergence of intracranial and central venous pressures in lightly anesthetized, tracheally intubated dogs that move in response to a noxious stimulus. Anesthesiology 84:605, 1996.

234. Sari A, Okuda Y, Takeshita H: The effects of Thalamonal on cerebral circulation and oxygen consumption in man. Br J Anaesth 44:330, 1972.

235. Misfeldt BB, Jorgensen PB, Spotoft H et al: The effects of droperidol and fentanyl on intracranial pressure and cerebral perfusion. Br J Anaesth 48:963, 1976.

236. Miller R, Tausk HC, Stark DCC: Effect of Innovar, fentanyl and droperidol on the cerebrospinal fluid pressure in neurosurgical patients. Can J Anaesth 22:502, 1975.

237. Fitch W, Barker J, Jennett WB et al: The influence of neuroleptanalgesic drugs on cerebrospinal fluid pressure. Br J Anaesth 41:800, 1969.

238. Fukuda S, Murakawa T, Takeshita H, et al: Direct effects of ketamine on isolated canine cerebral and mesenteric arteries. Anesth Analg 62:553, 1983.

239. Cavazzuti M, Porro CA, Biral GP et al: Ketamine effects on local cerebral blood flow and metabolism in the rat. J Cereb Blood Flow Metab 7:806, 1987.

240. Takeshita H, Okuda Y, Sari A: The effects of ketamine on cerebral circulation and metabolism in man. Anesthesiology 36:69, 1972.

241. Hougaard K, Hansen A, Brodersen P: The effect of ketamine on regional cerebral blood flow in man. Anesthesiology 41:562, 1974.

242. Strebel S, Kaufmann M, Maitre L et al: Effects of ketamine on cerebral blood flow velocity in humans: Influence of pretreatment with midazolam or esmolol. Anaesthesia 50:223, 1995.

243. Crosby G, Crane AM, Sokoloff L: Local changes in cerebral glucose utilization during ketamine anesthesia. Anesthesiology 56:437, 1982.

244. Ferrer-Allado T, Brechner VL, Dymond A et al: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 38:333, 1973.

245. Davis DW, Mans AM, Biebuyck JF et al: The influence of ketamine on regional brain glucose use. Anesthesiology 69:199, 1988.

246. Belopavlovic M, Buchthal A: Modification of ketamine-induced intracranial hypertension in neurosurgical patients by pretreatment with midazolam. Acta Anaesthesiol Scand 26:458, 1982.

247. Shapiro HM, Wyte SR, Harris AB: Ketamine anesthesia in patients with intracranial pathology. Br J Anaesth 44:1200, 1972.

248. Mayberg TS, Lam AM, Matta BF et al: Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. Anesth Analg 81:84, 1995.

249. Akeson J, Bjorkman S, Messeter K et al: Low-dose midazolam antagonizes cerebral metabolic stimulation by ketamine in the pig. Acta Anaesthesiol Scand 37:525, 1993.

250. Albanese J, Arnaud S, Rey M et al: Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. Anesthesiology 87:1328, 1997.

251. Sakabe T, Maekawa T, Ishikawa T et al: The effects of lidocaine on canine cerebral metabolism and circulation related to the electroencephalogram. Anesthesiology 40:433, 1974.

252. Lam AM, Donlon E, Eng CC et al: The effect of lidocaine on cerebral blood flow and metabolism during normocapnia and hypocapnia in humans (abstract). Anesthesiology 79:A202, 1993.

253. Bedford RF, Persing JA, Pobereskin L et al: Lidocaine or thiopental for rapid control of intracranial hypertension? Anesth Analg 59:435, 1980.

254. Donegan MF, Bedford RF: Intravenously administered lidocaine prevents intracranial hypertension during endotracheal suctioning. Anesthesiology 52:516, 1980.

255. Tommasino C, Maekawa T, Shapiro HM: Local cerebral blood flow during lidocaine-induced seizures in rats. Anesthesiology 64:771, 1986.

256. Stoelting RK: Pharmacology and Physiology in Anesthetic Practice, 2nd edition. Philadelphia, J.B. Lippincott Co., 1991.

257. Viegas O, Stoelting RK: Lidocaine in arterial blood after laryngotracheal administration. Anesthesiology 43:491, 1975.

258. Michenfelder JD, Theye RA: In vivo toxic effects of halothane on canine cerebral metabolic pathways. Am J Physiol 229:1050, 1975.

259. Michenfelder JD, Cucchiara RF: Canine cerebral oxygen consumption during enflurane anesthesia and its modification during induced seizures. Anesthesiology 40:575, 1974.

260. Todd MM, Drummond JC: A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 60:276, 1984.

261. Lutz LJ, Milde JH, Milde LN: The cerebral functional, metabolic, and hemodynamic effects of desflurane in dogs. Anesthesiology 73:125, 1990.

262. Scheller MS, Tateishi A, Drummond JC et al: The effects of sevoflurane on cerebral blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are similar to those of isoflurane in the rabbit. Anesthesiology 68:548, 1988.

263. Kuramoto T, Oshita S, Takeshita H et al: Modification of the relationship between cerebral metabolism, blood flow and electroencephalogram by stimulation during anesthesia in the dog. Anesthesiology 51:211, 1979.

264. Drummond JC, Todd MM, Scheller MS et al: A comparison of the direct cerebral vasodilating potencies of halothane and isoflurane in the New Zealand white rabbit. Anesthesiology 65:462, 1986.

265. Hansen TD, Warner DS, Todd MM et al: The role of cerebral metabolism in determining the local cerebral blood flow effects of volatile anesthetics: Evidence for persistent flow-metabolism coupling. J Cereb Blood Flow Metab 9:323, 1989.

266. Lam AM, Matta BF, Mayberg TS et al: Change in cerebral blood flow velocity with onset of EEG silence during inhalation anesthesia in humans: Evidence of flow-metabolism coupling? J Cereb Blood Flow Metab 15:714, 1995.

267. Kuroda Y, Murakami M, Tsuruta J et al: Blood flow velocity of middle cerebral artery during prolonged anesthesia with halothane, isoflurane, and sevoflurane in humans. Anesthesiology 87:527, 1997.

268. Sakabe T, Kuramoto T, Kumagae S et al: Cerebral responses to the addition of nitrous oxide to halothane in man. Br J Anaesth 48:957, 1976.

269. Heath KJ, Gupta S, Matta BF: The effects of sevoflurane on cerebral hemodynamics during propofol anesthesia. Anesth Analg 85:1284, 1997.

270. Murphy FL, Kennell EM, Johnstone RE et al: The effects of enflurane, isoflurane, and halothane on cerebral blood flow and metabolism in man. In Abstracts of the Annual Meeting of the American Society of Anesthesiologists, 1974, p 62.

271. Eintrei C, Leszneiwski W, Carlsson C: Local application of ^{133}xenon for measurement of regional cerebral blood flow (rCBF) during halothane, enflurane, and isoflurane anesthesia in humans. Anesthesiology 63:391, 1985.

272. Ornstein E, Young WL, Ostapkovich N et al: Comparative effects of desflurane and isoflurane on cerebral blood flow (abstract). Anesthesiology 75:A209, 1991.

273. Johnson J, Sperry RJ, Lam A et al: A phase III, randomized, open-label study to compare sevoflurane and isoflurane in neurosurgical patients. Anesth Analg 80:S214, 1995.

274. Drummond JC, Todd MM, Toutant SM et al: Brain surface protrusion during enflurane, halothane, and isoflurane anesthesia in cats. Anesthesiology 59:288, 1983.

275. Ornstein E, Young WL, Fleischer LH et al: Desflurane and isoflurane have similar effects on cerebral blood flow in patients with intracranial mass lesions. Anesthesiology 79:498, 1993.

276. Goadsby PJ, Kaube H, Hoskin KL: Nitric oxide synthesis couples cerebral blood flow and metabolism. Brain Res 595:167, 1992.

277. Todd MM, Drummond JC, Shapiro HM: Comparative cerebrovascular and metabolic effects of halothane, enflurane, and isoflurane. Anesthesiology 57:A332, 1982.

278. Rampil IJ, Lockhart SH, Eger EI et al: The electroencephalographic effects of desflurane in humans. Anesthesiology 74:434, 1991.

279. Boarini DJ, Kassell NF, Coester HC et al: Comparison of systemic and cerebrovascular effects of isoflurane and halothane. Neurosurgery 15:400, 1984.

280. Adams RW, Cucchiara RF, Gronert GA et al: Isoflurane and cerebrospinal fluid pressures in neurosurgical patients. Anesthesiology 54:97, 1981.

281. Grosslight K, Foster R, Colohan AR et al: Isoflurane for neuroanesthesia: Risk factors for increases in intracranial pressure. Anesthesiology 63:533, 1985.

282. Campkin TV, Flinn RM: Isoflurane and cerebrospinal fluid pressure: A study in neurosurgical patients undergoing intracranial shunt procedures. Anaesthesia 44:50, 1989.

283. Matta BF, Mayberg TS, Lam AM: Direct cerebrovasodilatory effects of halothane, isoflurane and desflurane during propofol-induced isoelectric electroencephalogram in humans. Anesthesiology 83:980, 1995.

284. Adams RW, Gronert GA, Sundt TM et al: Halothane, hypocapnia and cerebrospinal fluid pressure in neurosurgery. Anesthesiology 37:510, 1972.

285. Warner DS, Boarini DJ, Kassell NL: Cerebrovascular adaptation to prolonged halothane anesthesia is not related to cerebrospinal fluid pH. Anesthesiology 63:243, 1985.

286. Fleischer LH, Young WL, Ornstein E et al: Cerebral blood flow in humans does not decline over time during isoflurane or desflurane anesthesia (abstract). Anesthesiology 77:A167, 1992.

287. Madsen JB, Cold GE, Hansen ES et al: Cerebral blood flow, cerebral metabolic rate of oxygen and relative CO_2 -reactivity during craniotomy for supratentorial cerebral tumours in halothane anaesthesia: A dose-response study. Acta Anaesthesiol Scand 31:454, 1987.

288. Drummond JC, Todd MM: The response of the feline cerebral circulation to Pa CO_2 during anesthesia with isoflurane and halothane and during sedation with nitrous oxide. Anesthesiology 62:268, 1985.

289. Cho S, Fujigaki T, Uchiyama Y et al: Effects of sevoflurane with and without nitrous oxide on human cerebral circulation. Anesthesiology 85:755, 1996.

290. Morita H, Bleyaert AL, Stezoski SW et al: The effect of halothane anesthesia on cerebral blood flow, autoregulation and cerebral metabolism of oxygen and glucose. In Anesthesiology Abstracts presented at the Annual Meeting of the American Society of Anesthesiologists, 1974, p 63.

291. Strebel S, Lam AM, Matta B et al: Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. Anesthesiology 83:66, 1995.

292. Gupta S, Heath K, Matta BF: Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans. Br J Anaesth 79:469, 1997.

293. Neigh JL, Garman JK, Harp JR: The electroencephalographic pattern during anesthesia with Enthrane. Anesthesiology 35:482, 1971.

294. Wollman H, Smith AL, Hoffman JC: Cerebral blood flow and oxygen consumption in man during electroencephalographic seizure patterns induced by anesthesia with Ethrane (abstract). Fed Proc 28:356, 1967.

295. Fleming DC, Fitzpatrick J, Fariello RG et al: Diagnostic activation of epileptogenic foci by enflurane. Anesthesiology 52:431, 1980.

296. Opitz A, Brecht S, Stenyel E: Enflurane anesthesia in epileptics. Anaesthetist 26:329, 1977.

297. Kruczek M, Albin MS, Wolf S et al: Postoperative seizure activity following enflurane anesthesia. Anesthesiology 53:175, 1980.

298. Hymes JA: Seizure activity during isoflurane anesthesia. Anesth Analg 64:367, 1985.

299. Harrison JL: Postoperative seizures after isoflurane anesthesia. Anesth Analg 65:1235, 1986.

300. Kofke WA, Young RSK, Davis P et al: Isoflurane for refractory status epilepticus: A clinical series. Anesthesiology 71:653, 1989.

301. Komatsu H, Taie S, Endo S et al: Electrical seizures during sevoflurane anesthesia in two pediatric patients with epilepsy. Anesthesiology 81:1535, 1994.

302. Haga S, Shima T, Momose K et al: Anesthetic induction of children with high concentrations of sevoflurane (Japanese). Jpn J Anesthesiol 41:1951, 1992.

303. Osawa M, Shingu K, Murakawa M et al: Effects of sevoflurane on central nervous system electrical activity in cats. Anesth Analg 79:52, 1994.

304. Kofke WA, Hawkins RA, Davis DW et al: Comparison of the effects of volatile anesthetics on brain glucose metabolism in rats. Anesthesiology 66:810, 1987.

305. Stevens WC, Eger EI, Joas TA et al: Comparative toxicity of isoflurane, halothane, fluroxene, and diethyl ether in human volunteers. Can Anaesth Soc J 20:357, 1973.

306. Nakanishi O, Ishikawa T, Imamura Y et al: Inhibition of cerebral metabolic and circulatory responses to nitrous oxide by 6-hydroxydopamine in dogs. Can J Anaesth 44:1008, 1997.

307. Henriksen HT, Jorgensen PB: The effect of nitrous oxide on intracranial pressure in patients with intracranial disorders. Br J Anaesth 45:486, 1973.

308. Moss E, McDowall DG: I.C.P increases with 50% nitrous oxide in oxygen in severe head injuries during controlled ventilation. Br J Anaesth 51:757, 1979.

309. Pelligrino DA, Miletich DJ, Hoffman WE et al: Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. Anesthesiology 60:405, 1984.

310. Theye RA, Michenfelder JD: The effects of nitrous oxide on canine cerebral metabolism. Anesthesiology 29:1119, 1968.

311. Field LM, Dorrance DE, Krzeminska EK et al: Effect of nitrous oxide on cerebral blood flow in normal humans. Br J Anaesth 70:154, 1993.

312. Phirman JR, Shapiro HM: Modification of nitrous oxide-induced intracranial hypertension by prior induction of anesthesia. Anesthesiology 46:150, 1977.

313. Misfeldt BB, Jorgensen PL, Rishoj M: The effect of nitrous oxide and halothane upon the intracranial pressure in hypocapnic patients with intracranial disorders. Br J Anaesth 46:853, 1974.

314. Jung R, Reinsel R, Marx W et al: Isoflurane and nitrous oxide: Comparative impact on cerebrospinal fluid pressure in patients with brain tumors. Anesth Analg 75:724, 1992.

315. Hoffman WE, Miletich DJ, Albrecht RF: The effects of midazolam on cerebral blood flow and oxygen consumption and its interaction with nitrous oxide. Anesth Analg 65:729, 1986.

316. Knudsen L, Cold GE, Holdgard HO et al: The effects of midazolam on cerebral blood flow and oxygen consumption: Interaction with nitrous oxide in patients undergoing craniotomy for supratentorial tumors. Anaesthesia 45:1016, 1990.

317. Eng C, Lam AM, Mayberg TS et al: The influence of propofol with and without nitrous oxide on cerebral blood flow velocity and CO_2 reactivity in humans. Anesthesiology 77:872, 1992.

318. Manohar M, Parks C: Porcine regional brain and myocardial blood flows during halothane-O_2 and halothane-nitrous oxide anesthesia: Comparisons with equipotent isoflurane anesthesia. Am J Vet Res 45:465, 1984.

319. Manohar M, Parks CM: Porcine brain and myocardial perfusion during enflurane anesthesia without and with nitrous oxide. J Cardiovasc Pharmacol 6:1092, 1984.

320. Manohar M, Parks C: Regional distribution of brain and myocardial perfusion in swine while awake and during 1.0 and 1.5 MAC isoflurane anaesthesia produced without or with 50% nitrous oxide. Cardiovasc Res 18:344, 1984.

321. Drummond JC, Scheller MS, Todd MM: The effect of nitrous oxide on cortical cerebral blood flow during anesthesia with halothane and isoflurane, with and without morphine, in the rabbit. Anesth Analg 66:1083, 1987.

322. Todd MM: The effects of Pa CO_2 on the cerebrovascular response to nitrous oxide in the halothane-anesthetized rabbit. Anesth Analg 66:1090, 1987.

323. Kaieda R, Todd MM, Warner DS: The effects of anesthetics and Pa CO_2 on the cerebrovascular, metabolic, and electroencephalographic responses to nitrous oxide in the rabbit. Anesth Analg 68:135, 1989.

324. Lam AM, Mayberg TS, Eng CC et al: Nitrous oxide-isoflurane anesthesia causes more cerebral vasodilation than an equipotent dose of isoflurane in humans. Anesth Analg 78:462, 1994.

325. Strebel S, Kaufmann M, Anselmi L et al: Nitrous oxide is a potent cerebrovasodilator in humans when added to isoflurane. Acta Anesthesiol Scand 39:653, 1995.

326. Algotsson L, Messeter K, Rosen I et al: Effects of nitrous oxide on cerebral haemodynamics and metabolism during isoflurane anaesthesia in man. Acta Anaesthesiol Scand 36:46, 1992.

327. Reinstrup P, Ryding E, Algotsson L et al: Regional cerebral blood flow (SPECT) during anaesthesia with isoflurane and nitrous oxide in humans. Br J Anaesth 78:407, 1997.

328. Baughman VL, Hoffman WE, Miletich DJ et al: Cerebrovascular and cerebral metabolic effects of N_2O in unrestrained rats. Anesthesiology 73:269, 1990.

329. Roald OK, Forsman M, Heier MS et al: Cerebral effects of nitrous oxide when added to low and high concentrations of isoflurane in the dog. Anesth Analg 72:75, 1991.

330. Wollman H, Alexander SC, Cohen PJ et al: Cerebral circulation during general anesthesia and hyperventilation in man. Anesthesiology 26:329, 1965.

331. Tarkkanen L, Laitinen L, Johansson G: Effects of *α*-tubocurarine on intracranial pressure and thalamic electrical impedance. Anesthesiology 40:247, 1974.

332. Basta SJ, Savarese JJ, Ali HH et al: Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. Br J Anaesth 55:105S, 1983.

333. Basta SJ: Clinical pharmacology of mivacurium chloride: A review. J Clin Anesth 4:153, 1992.

334. Rosa G, Orfei P, Sanfilippo M et al: The effects of atracurium besylate (Tracrium) on intracranial pressure and cerebral perfusion pressure. Anesth Analg 65:381, 1986.

335. Schramm WM, Papousek A, Michalek-Sauberer A et al: The cerebral and cardiovascular effects of cisatracurium and atracurium in neurosurgical patients. Anesth Analg 86:123, 1998.

336. Rosa G, Sanfilippo M, Vilardi V et al: Effects of vecuronium bromide on intracranial pressure and cerebral perfusion pressure. Br J Anaesth 58:437, 1986.

337. Stirt JA, Maggio W, Haworth C et al: Vecuronium: Effect on intracranial pressure and hemodynamics in neurosurgical patients. Anesthesiology 67:570, 1987.

338. Benthuysen JL, Kien ND, Quam DD: Intracranial pressure increases during alfentanil-induced rigidity. Anesthesiology 68:438, 1988.

339. Lanier WL, Milde JH, Michenfelder JD: The cerebral effects of pancuromium and atracurium in halothane-anesthetized dogs. Anesthesiology 63:589, 1985.

340. Lanier WL, Sharbrough FW, Michenfelder JD: Effects of atracurium, vecuromium or pancuronium pretreatment on lignocaine seizure thresholds in cats. Br J Anaesth 60:74, 1988.

341. Tateishi A, Zornow MH, Scheller MS et al: Electroencephalographic effects of laudanosine in an animal model of epilepsy. Br J Anaesth 62:548, 1989.

342. Chapple DJ, Miller AA, Ward JB et al: Cardiovascular and neurological effects of laudanosine. Br J Anaesth 59:218, 1987.

343. Standaert FG: Magic bullets, science, and medicine. Anesthesiology 63:577, 1985.

344. Minton MD, Grosslight K, Stirt JA et al: Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. Anesthesiology 65:165, 1986.

345. Lanier WL, Milde JH, Michenfelder JD: Cerebral stimulation following succinylcholine in dogs. Anesthesiology 64:551, 1986.

346. Lanier WL, Iaizzo PA, Milde JH: Cerebral function and muscle afferent activity following intravenous succinylcholine in dogs anesthetized with halothane: The effects of pretreatment with a defasciculating dose of pancuronium. Anesthesiology 71:87, 1989.

347. Lanier WL, Iaizzo PA, Milde JH et al: The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Anesthesiology 80:392, 1994.

348. Stirt JA, Grosslight KR, Bedford RF et al: "Defasciculation" with metocurine prevents succinylcholine-induced increases in intracranial pressure. Anesthesiology 67:50, 1987.

349. Kovarik DW, Mayberg TS, Lam AM et al: Succinylcholine does not change intracranial pressure, cerebral blood flow velocity, or the electroencephalogram in patients with neurologic injury. Anesth Analg 78:469, 1994.

350. Cutler RWP, Spertell RB: Cerebrospinal fluid: A selective review. Ann Neurol 11:1, 1982.

351. Artru AA: Effects of halothane and fentanyl on the rate of CSF production in dogs. Anesth Analg 62:581, 1983.

352. Artru AA: Effects of halothane and fentanyl anesthesia on resistance to reabsorption of CSF. J Neurosurg 60:252, 1984.

353. Artru AA: Isoflurane does not increase the rate of CSF production in the dog. Anesthesiology 60:193, 1984.

354. Artru AA: Effects of enflurane and isoflurane on resistance to reabsorption of cerebrospinal fluid in dogs. Anesthesiology 61:529, 1984.

355. Artru AA, Nugent M, Michenfelder JD: Enflurane causes a prolonged and reversible increase in the rate of CSF production in the dog. Anesthesiology 57:255, 1982.

356. Maktabi MA, Elbokl FF, Faraci FM et al: Halothane decreases the rate of production of cerebrospinal fluid. Anesthesiology 78:72, 1993.

357. Artru AA: Rate of cerebrospinal fluid formation, resistance to reabsorption of cerebrospinal fluid, brain tissue water content, and electroencephalogram during desflurane anesthesia in dogs. J Neurosurg Anesthesiol 5:178, 1993.

358. Muzzi DA, Losasso TJ, Dietz NM et al: The effect of desflurane and isoflurane on cerebrospinal fluid pressure in humans with supratentorial mass lesions. Anesthesiology 76:720, 1992.

359. Muzzi D, Daltner C, Losasso T et al: The effect of desflurane and isoflurane with N_2O on cerebrospinal fluid pressure in patients with supratentorial mass lesions (abstract). Anesthesiology 75:A167, 1991.

360. Ebrahim ZY, Schubert A, Bloomfield E et al: The effect of desflurane and isoflurane on intracranial pressure in patients with small intracranial tumors (abstract). Anesthesiology 79:A182, 1993.

361. Talke P, Caldwell J, Richardson C et al: Effect of desflurane and isoflurane on lumbar CSF pressure (abstract). Anesth Analg 82:S443, 1996.

362. Young WL: Effects of desflurane on the central nervous system. Anesth Analg 75:S32, 1992.

363. Hatashita S, Hoff JT, Ishii S: Focal brain edema associated with acute arterial hypertension. J Neurosurg 64:643, 1986.

364. Sokrab T-EO, Johansson BB, Kalimo H et al: A transient hypertensive opening of the blood-brain barrier can lead to brain damage. Acta Neuropathol 75:557, 1988.

365. Mayhan WG: Disruption of blood-brain barrier during acute hypertension in adult and aged rats. Am J Physiol 258:H1735, 1990.

366. Johansson BB, Linder L-E: Do nitrous oxide and lidocaine modify the blood-brain barrier in acute hypertension in the rat? Acta Anaesthesiol Scand 24:65, 1980.

367. Johansson B: Blood-brain barrier dysfunction in acute arterial hypertension after papaverine-induced vasodilation. Acta Neurol Scand 50:573, 1974.

368. Smith AL, Marque JJ: Anesthetics and cerebral edema. Anesthesiology 45:64, 1976.

369. Modica PA, Tempelhoff R, White PF: Pro- and anticonvulsant effects of anesthetics. I. Anesth Analg 70:303, 1990.

370. Modica PA, Tempelhoff R, White PF: Pro- and anticonvulsant effects of anesthetics. II. Anesth Analg 70:433, 1990.

371. Kreisman NR, Magee JC, Brizzee BL: Relative hypoperfusion in rat cerebral cortex during recurrent seizures. J Cereb Blood Flow Metab 11:77, 1991.

372. Archer DP, McKenna JMA, Morin L et al: Conscious-sedation analgesia during craniotomy for intractable epilepsy: A review of 354 consecutive cases. Can J Anaesth 35:338, 1988.

373. Ford EW, Morrell F, Whisler WW: Methohexital anesthesia in the surgical treatment of uncontrollable epilepsy. Anesth Analg 61:997, 1982.

374. Rockoff MA, Goudsouzian NG: Seizures induced by methohexital. Anesthesiology 54:333, 1981.

375. Musella L, Wilder BJ, Schmidt RP: Electroencephalographic activation with intravenous methohexital in psychomotor epilepsy. Neurology 21:594, 1971.

376. Bennett DR, Madsen JA, Jordan WS et al: Ketamine anesthesia in brain-damaged epileptics. Neurology 23:449, 1973.

377. Steen P, Michenfelder JD: Neurotoxicity of anesthetics. Anesthesiology 50:437, 1979.

378. Hirshman CA, Krieger W, Littlejohn G et al: Ketamine-aminophylline-induced decrease in seizure threshold. Anesthesiology 56:464, 1982.

379. Ghoneim MM, Yamada T: Etomidate: A clinical and electroencephalographic comparison with thiopental. Anesth Analg 56:478, 1977.

380. Laughlin TP, Newberg LA: Prolonged myoclonus after etomidate anesthesia. Anesth Analg 64:80, 1985.

381. Ebrahim ZY, DeBoer GE, Luders H et al: Effect of etomidate on the electroencephalogram of patients with epilepsy. Anesth Analg 65:1004, 1986.

382. Gancher S, Laxer KD, Krieger W: Activation of epileptogenic activity by etomidate. Anesthesiology 61:616, 1984.

383. Avramov MN, Husain MM, White PF: The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. Anesth Analg 81:596, 1995.

384. Yeoman P, Hutchinson A, Byrne A et al: Etomidate infusions for the control of refractory status epilepticus. Intensive Care Med 15:255, 1989.

385. Maekawa T, Tommasino C, Shapiro HM: Local cerebral blood flow with fentanyl-induced seizures. J Cereb Blood Flow Metab 4:88, 1984.

386. DeCastro J, VanDeWater A, Wouters L et al: Comparative study of cardiovascular neurological and metabolic side-effects of eight narcotics in dogs. Acta Anaesthesiol Belg 30:5, 1979.

387. Kofke WA, Garman RH, Tom WC et al: Alfentanil-induced hypermetabolism, seizure, and histopathology in rat brain. Anesth Analg 75:953, 1992.

388. Kofke WA, Garman RH, Stiller RL et al: Opioid neurotoxicity: Fentanyl dose-response effects in rats. Anesth Analg 83:1298, 1996.

389. Rao TLK, Mummaneni N, El-Etr AA: Convulsions: An unusual response to intravenous fentanyl administration. Anesth Analg 61:1020, 1982.

390. Safwat AM, Daniel D: Grand mal seizure after fentanyl administration (letter). Anesthesiology 59:78, 1983.

391. Hoien A: Another case of grand mal seizure after fentanyl administration (letter). Anesthesiology 60:387, 1984.

392. Murkin JM, Moldenhauer CC, Hug CC et al: Absence of seizures during induction of anesthesia with high dose fentanyl. Anesth Analg 63:489, 1984.

393. Smith NT, Westover CJ, Quinn M et al: An electroencephalographic comparison of alfentanil with other narcotics and with thiopental. J Clin Monit 1:236, 1985.

394. Smith NT, Dec-Silver H, Sanford TJ et al: EEGs during high-dose fentanyl-, sufentanil-, or morphine-oxygen anesthesia. Anesth Analg 63:386, 1984.

395. Cascino GD, So EL, Sharbrough FW et al: Alfentanil-induced epileptiform activity in patients with partial epilepsy. J Clin Neurophysiology 10:520, 1993.

396. Choi DW: Cerebral hypoxia: Some new approaches and unanswered questions. J Neurosci 10:2493, 1990.

397. Siesjo BK: Pathophysiology and treatment of focal cerebral ischemia. I. Pathophysiology. J Neurosurg 77:169, 1992.

398. Siesjo BK: Pathophysiology and treatment of focal cerebral ischemia. II. Mechanisms of damage and treatment. J Neurosurg 77:337, 1992.

399. Siesjo BK, Katsura K, Zhao Q et al: Mechanisms of secondary brain damage in global and focal ischemia: A speculative synthesis. J Neurotrauma 12:943, 1995.

400. Kristian T, Siesjo BK: Calcium in ischemic cell death. Stroke 29:705, 1998.

401. Marsh WR, Anderson RE, Sundt TM: Effect of hyperglycemia on brain pH levels in areas of focal incomplete cerebral ischemia in monkeys. J Neurosurg 65:693, 1986.

402. Chopp M, Welch KMA, Tidwell CD et al: Global cerebral ischemia and intracellular pH during hyperglycemia and hypoglycemia in cats. Stroke 19:1383, 1988.

403. Smith M-L, vonHanwehr R, Seisjo BK: Changes in extra- and intracellular pH in the brain during and following ischemia in hyperglycemic and moderately hypoglycemic rats. J Cereb Blood Flow Metab 6:574, 1986.

404. Folbergrova J, Memezawa H, Smith M-L et al: Focal and perifocal changes in tissue energy state during middle cerebral artery occlusion in normo- and hyperglycemic rats. J Cereb Blood Flow Metab 12:25, 1992.

405. Dawson TM, Dawson VL, Snyder SH: A novel neuronal messenger molecule in brain: The free radical, nitric oxide. Ann Neurol 32:297, 1992.

406. Beckman JS: The double-edged role of nitric oxide in brain function and superoxide-mediated injury. J Dev Physiol 15:53, 1991.

407. Iadecola C: Bright and dark sides of nitric oxide in ischemic brain injury. Trends Neurosci 20:132, 1997.

408. Samdani AF, Dawson TM, Dawson VL: Nitric oxide synthase in models of focal ischemia. Stroke 28:1283, 1997.

409. Michenfelder JD, Sundt TM: Cerebral ATP and lactate levels in the squirrel monkey following occlusion of the middle cerebral artery. Stroke 2:319, 1971.

410. Michenfelder JD, Theye RA: The effects of anesthesia and hypothermia on canine cerebral ATP and lactate during anoxia produced by decapitation. Anesthesiology 33:430, 1970.

411. Astrup J, Symon L, Branston NM et al: Cortical evoked potential and extracellular K^+ and H^+ at critical levels of brain ischemia. Stroke 8:52, 1977.

412. Carter LP, Yamagata S, Erspamer R: Time limits on reversible cortical ischemia. Neurosurgery 12:620, 1983.

413. Jones TH, Morawetz RB, Crowell RM et al: Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 54:773, 1981.

414. Kaplan B, Brint S, Tanabe J et al: Temporal thresholds for neocortical infarction in rats subjected to reversible focal cerebral ischemia. Stroke 22:1032, 1991.

415. Hossmann KA: Viability thresholds and the penumbra of focal ischemia. Ann Neurol 36:557, 1994.

416. Branston NM, Symon L, Crockard HA et al: Relationship between the cortical evoked potential and local cortical blood flow following acute middle cerebral artery occlusion in the baboon. Exp Neurol 45:195, 1974.

417. Michenfelder JD, Sundt TM, Fode N et al: Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. Anesthesiology 67:336, 1987.

418. Perkins WJ, Lanier WL, Schroeder DR et al: Critical regional cerebral blood flow determined using logistic regression analysis (abstract). Anesthesiology 87:A173, 1997.

419. Sundt TM, Sharbrough FW, Piepgras DG et al: Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy. Mayo Clin Proc 56:533, 1981.

420. Busto R, Dietrich WD, Globus MY-T et al: Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7:729, 1987.

421. Busto R, Globus MY-T, Dietrich WD et al: Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20:904, 1989.

422. Minamisawa H, Smith M-L, Siesjo BK: The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. Ann Neurol 28:26, 1990.

423. Welsh FA, Sims RE, Harris VA: Mild hypothermia prevents ischemic injury in gerbil hippocampus. J Cereb Blood Flow Metab 10:557, 1990.

424. Sano T, Drummond JC, Patel PM et al: A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat. Anesthesiology 76:221, 1992.

425. Ridenour TR, Warner DS, Todd MM et al: Mild hypothermia reduces infarct size resulting from temporary but not permanent focal ischemia in rats. Stroke 23:733, 1992.

426. Boris-Moller F, Smith M-L, Siesjo BK: Effects of hypothermia on ischemic brain damage: A comparison between preischemic and postischemia cooling. Neurosci Res Comm 5:87, 1989.

427. Buchan A, Pulsinelli WA: Hypothermia but not the *N*-methyl- D- aspartate antagonist, MK-801, attenuates neuronal damage in gerbils subjected to transient global ischemia. J Neurosci 10:311, 1990.

428. Busto R, Dietrich WD, Globus MY-T et al: Post-ischemic moderate hypothermia inhibits CA1 hippocampal neuronal ischemic injury. Neurosci Lett 101:299, 1989.

429. Baker CJ, Onesti MT, Solomon RA: Reduction by delayed hypothermia of cerebral infarction following middle cerebral artery occlusion in the rat: A time-course study. J Neurosurg 77:438, 1992.

430. Coimbra C, Drake M, Boris-Moller F et al: Long-lasting neuroprotective effect of postischemic hypothermia and treatment with an antiinflammatory/antipyretic drug. Stroke 27:1578, 1996.

431. Ginsberg MD, Sternau LL, Globus MY-T et al: Therapeutic modulation of brain temperature: Relevance to ischemic brain injury. Cerebrovasc Brain Metab Rev 4:189, 1992.

432. Marion DW, Obrist WD, Carlier PM et al: The use of moderate therapeutic hypothermia for patients with severe head injuries: A preliminary report. J Neurosurg 79:354, 1993.

433. Shiozaki T, Sugimoto H, Taneda M et al: Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 79:363, 1993.

434. Clifton GL, Allen S, Barrodale P et al: A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 10:263, 1993.

435. Metz C, Holzschuh M, Bein T et al: Moderate hypothermia in patients with severe head injury: Cerebral and extracerebral effects. J Neurosurg 85:533, 1996.

436. Bouma GJ, Muizelaar JP, Choi SC et al: Cerebral circulation and metabolism after severe traumatic brain injury: The elusive role of ischemia. J Neurosurg 75:685, 1991.

437. Graham DI, Ford I, Adams JH et al: Ischaemic brain damage is still common in fatal nonmissile head injury. J Neurol Neurosurg Psychiatry 52:346, 1989.

438. Kuroiwa T, Bonnekoh P, Hossmann KA: Prevention of postischemic hyperthermia prevents ischemic injury of CA1 neurons in gerbils. J Cereb Blood Flow Metab 10:550, 1990.

439. Warner DS, Todd MM, McFarlane C et al: Sevoflurane and halothane reduce focal ischemic brain damage in the rat: Possible influence on thermoregulation. Anesthesiology 79:985, 1993.

440. Baena RC, Busto R, Dietrich WD et al: Hyperthermia delayed by 24 hours aggravates neuronal damage in rat hippocampus following global ischemia. Neurology 48:768, 1997.

441. Pulsinelli WA, Waldman S, Rawlinson D et al: Moderate hyperglycemia augments ischemic brain damage: A neuropathologic study in the rat. Neurology 32:1239, 1982.

442. Lanier WL, Stangland KJ, Scheithauer BW et al: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. Anesthesiology 66:39, 1987.

443. Drummond JC, Moore SS: The influence of dextrose administration on neurologic outcome after temporary spinal cord ischemia in the rabbit. Anesthesiology 70:64, 1989.

444. Nakakimura K, Fleischer JE, Drummond JC et al: Glucose administration prior to cardiac arrest significantly worsens neurologic outcome in cats. Anesthesiology 72:1005, 1990.

445. Vannucci RC, Brucklacher RM, Vannucci SJ: The effect of hyperglycemia on cerebral metabolism during hypoxia-ischemia in the immature rat. J Cereb Blood Flow Metab 16:1026, 1996.

446. Mullner M, Sterz F, Binder M et al: Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. J Cereb Blood Flow Metab 17:430, 1997.

447. Weir CJ, Murray GD, Dyker AG et al: Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. BMJ 314:1303, 1997.

448. Longstreth WT, Diehr P, Cobb LA et al: Neurologic outcome and blood glucose levels during out-of-hospital cardiopulmonary resuscitation. Neurology 36:1186, 1986.

449. Woo J, Lam CWK, Kay R et al: The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. Arch Neurol 47:1174, 1990.

450. Frasco P, Croughwell N, Blumenthal J et al: Association between blood glucose level during cardiopulmonary bypass and neuropsychiatric outcome (abstract). Anesthesiology 75:A55, 1991.

451. Toni D, Sacchetti ML, Argentino C et al: Does hyperglycaemia play a role on the outcome of acute ischaemic stroke patients? J Neurol 239:382, 1992.

452. Matchar DB, Divine GW, Heyman A et al: The influence of hyperglycemia on outcome of cerebral infarction. Ann Intern Med 117:449, 1992.

453. Hoffman WE, Cheng MA, Thomas C et al: Clonidine decreases plasma catecholamines and improves outcome from incomplete ischemia in the rat. Anesth Analg 73:460, 1991.

454. Hoffman WE, Thomas C, Albrecht RF: The effect of halothane and isoflurane on neurologic outcome following incomplete cerebral ischemia in the rat. Anesth Analg 76:279, 1993.

455. Smith AL, Hoff JT, Nielsen SL et al: Barbiturate protection in acute focal cerebral ischemia. Stroke 5:1, 1974.

456. Hoff JT, Smith AL, Hankinson HL et al: Barbiturate protection from cerebral infarction in primates. Stroke 6:28, 1975.

457. Michenfelder JD, Milde JH, Sundt TM: Cerebral protection by barbiturate anesthesia: Use after middle cerebral artery occlusion in Java monkeys. Arch Neurol 33:345, 1976.

458. Lawner PM, Laurent JP, Simeone FA et al: Effect of extracranial-intracranial bypass and pentobarbital on acute stroke in dogs. J Neurosurg 56:92, 1982.

459. Selman WR, Spetzler RF, Roski RA et al: Barbiturate coma in focal cerebral ischemia: Relationship of protection to timing of therapy. J Neurosurg 56:685, 1982.

460. Hoff JT, Nishimura M, Newfield P: Pentobarbital protection from cerebral infarction without suppression of edema. Stroke 13:623, 1982.

461. Nehls DG, Todd MM, Spetzler RF et al: A comparison of the cerebral protective effects of isoflurane and barbiturates during temporary focal ischemia in primates. Anesthesiology 66:453, 1987.

462. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. Anesthesiology 64:165, 1986.

463. Shapiro HM: Barbiturates in brain ischemia. Br J Anaesth 57:82, 1985.

464. Todd MM, Warner DS: A comfortable hypothesis re-evaluated: Cerebral metabolic rate depression and brain protection during ischemia (editorial). Anesthesiology 76:161, 1992.

465. Nakashima K, Todd MM, Warner DS: The relation between cerebral metabolic rate and ischemic depolarization. Anesthesiology 82:1199, 1995.

466. Warner DS, Takaoka S, Wu B et al: Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. Anesthesiology 84:1475, 1996.

467. Warner DS, Zhou J, Ramani R et al: Reversible focal ischemia in the rat: Effects of halothane, isoflurane, and methohexital anesthesia. J Cereb Blood Flow Metab 11:794, 1991.

468. Drummond JC, Cole DJ, Patel PM et al: Focal cerebral ischemia during anesthesia with etomidate, isoflurane or thiopental: A comparison of the extent of cerebral injury. Neurosurgery 37:742, 1995.

469. Gisvold SE, Safar P, Hendrickx HHL et al: Thiopental treatment after global ischemia in pig-tailed monkeys. Anesthesiology 60:88, 1984.

470. Abramson NA: Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med 314:397, 1986.

471. Warner DS, Desphande JK, Wieloch T: The effect of isoflurane on neuronal necrosis following near-complete forebrain ischemia in the rat. Anesthesiology 64:19, 1986.

472. Baughman VL, Hoffman WE, Miletich DJ et al: Neurologic outcome in rats following incomplete cerebral ischemia during halothane, isoflurane, or N_2O. Anesthesiology 69:192, 1988.

473. Milde LN, Milde JH, Lanier WL et al: Comparison of the effects of isoflurane and thiopental on neurologic outcome and neuropathology after temporary focal cerebral ischemia in primates. Anesthesiology 69:905, 1988.

474. Gelb AW, Boisvert DP, Tang C et al: Primate brain tolerance to temporary focal cerebral ischemia during isoflurane- or sodium nitroprusside-induced hypotension. Anesthesiology 70:678, 1989.

475. Ruta TS, Drummond JC, Cole DJ: A comparison of the area of histochemical dysfunction after focal cerebral ischaemia during anaesthesia with isoflurane and halothane in the rat. Can J Anaesth 38:129, 1991.

476. Ravussin P, deTribolet N: Total intravenous anesthesia with propofol for burst suppression in cerebral aneurysm surgery: Preliminary report of 42 patients. Neurosurgery 32:236, 1993.

477. Ridenour TR, Warner DS, Todd MM et al: Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. Anesthesiology 76:807, 1992.

478. Young Y, Menon DK, Tisavipat N et al: Propofol neuroprotection in a rat model of ischaemia reperfusion injury. Eur J Anaesthesiol 14:320, 1997.

479. Batjer HH, Frankfurt AI, Purdy PD et al: Use of etomidate, temporary arterial occlusion, and intraoperative angiography in surgical treatment of large and giant cerebral aneurysms. J Neurosurg 68:234, 1988.

480. Watson JC, Drummond JC, Patel PM et al: An assessment of the cerebral protective effects of etomidate in a model of incomplete forebrain ischemia in the rat. Neurosurgery 30:540, 1992.

481. Sano T, Patel PM, Drummond JC et al: A comparison of the cerebral protective effects of etomidate, thiopental and isoflurane in a model of forebrain ischemia in the rat. Anesth Analg 76:990, 1993.

482. McKay L, Drummond JC, Cole DJ et al: Effect of nitric oxide on focal cerebral ischemic injury during etomidate or halothane anesthesia in rats (abstract). Anesthesiology 85:A1181, 1996.

483. Nebauer AE, Doenicke A, Hoernecke R et al: Does etomidate cause haemolysis? Br J Anaesth 69:58, 1992.

484. Wolff DJ, Datto GA, Samatovicz RA et al: Calmodulin-dependent nitric-oxide synthase: Mechanism of inhibition by imidazole and phenylimidazoles. J Biol Chem 268:9425, 1993.

485. Samson D, Batjer HH, Bowman G et al: A clinical study of the parameters and effects of temporary arterial occlusion in the management of intracranial aneurysms. Neurosurgery 34:22, 1994.

486. Pickard JD, Murray GD, Illingworth R et al: Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British Aneurysm Nimodipine Trial. BMJ 298:636, 1989.

487. Gelmers HJ, Gorter K, DeWeerdt CJ et al: A controlled trial of nimodipine in acute ischemic stroke. N Engl J Med 318:203, 1988.

488. Rosenbaum D, Zabramski J, Frey J et al: Early treatment of ischemic stroke with a calcium antagonist. Stroke 22:437, 1991.

489. Trust: Trust Study Group. Randomised, double-blind, placebo-controlled trial of nimodipine in acute stroke. Lancet 336:1205, 1990.

490. Kassell NF, Haley EC, Apperson-Hansen C et al: Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: A cooperative study in Europe, Australia, and New Zealand. J Neurosurg 84:221, 1996.

491. Grotta J: Lubeluzole treatment of acute ischemic stroke. Stroke 28:2338, 1997.

492. Wise G, Sutter R, Burkholder J: The treatment of brain ischemia with vasopressor drugs. Stroke 3:135, 1972.

493. Cole DJ, Drummond JC, Osborne TN et al: Hypertension and hemodilution during cerebral ischemia reduce brain injury and edema. Am J Physiol 259:H211, 1990.

494. Young WL, Solomon RA, Pedley TA et al: Direct cortical EEG monitoring during temporary vascular occlusion for cerebral aneurysm surgery. Anesthesiology 71:794, 1989.

495. Soloway M, Nadel W, Albin MS et al: The effect of hyperventilation on subsequent cerebral infarction. Anesthesiology 29:975, 1968.

496. Artru AA, Merriman HG: Hypocapnia added to hypertension to reverse EEG changes during carotid endarterectomy. Anesthesiology 70:1016, 1989.

497. Waltz AG, Sundt TM, Michenfelder JD: Cerebral blood flow during carotid endarterectomy. Circulation 45:1091, 1972.

498. Christensen MS, Paulson OB, Olesen J et al: Cerebral apoplexy (stroke) treated with or without prolonged artificial hyperventilation. I: Cerebral circulation, clinical course, and cause of death. Stroke 4:568, 1973.

499. Michenfelder JD, Sundt TM: The effect of Pa CO_2 on the metabolism of ischemic brain in squirrel monkeys. Anesthesiology 38:445, 1973.

500. Michenfelder JD, Milde JH: Failure of prolonged hypocapnia, hypothermia, or hypertension to favorably alter acute stroke in primates. Stroke 8:87, 1977.

501. Ruta TS, Drummond JC, Cole DJ: The effect of acute hypocapnia on local cerebral blood flow during middle cerebral artery occlusion in isoflurane anesthetized rats. Anesthesiology 78:134, 1993.

502. Archer DP: The role of bloodletting in the prevention and treatment of asthenic apoplexy. J Neurosurg Anesthesiol 6:51, 1994.

503. Lenzi GL, Frackowiak RSJ, Jones T: Cerebral oxygen metabolism and blood flow in human cerebral ischemic infarction. J Cereb Blood Flow Metab 2:321, 1982.

504. Paulson OB: Regional cerebral blood flow in apoplexy due to occlusion of the middle cerebral artery. Neurology 20:63, 1970.

505. Agnoli A, Fieschi C, Bozzao L et al: Autoregulation of cerebral blood flow: Studies during drug-induced hypertension in normal subjects and in patients with cerebral vascular diseases. Circulation 38:800, 1968.

506. Fieschi C, Agnoli A, Prencipe M et al: Impairment of the regional vasomotor response of cerebral vessels to hypercarbia in vascular diseases. Eur Neurol 2:13, 1969.

507. Olsen TS: Regional cerebral blood flow after occlusion of the middle cerebral artery. Acta Neurol Scand 73:321, 1986.

508. Todd MM, Chadwich HC, Shapiro HM et al: The neurologic effects of thiopental therapy following cardiac arrest in cats. Anesthesiology 57:76, 1982.

509. Steen PA, Gisvold SE, Milde JH et al: Nimodipine improves outcome when given after complete cerebral ischemia in primates. Anesthesiology 62:406, 1985.

510. Tateishi A, Fleischer JE, Drummond JC et al: Nimodipine does not improve neurologic outcome after 14 minutes of cardiac arrest in cats. Stroke 20:1044, 1989.

511. Tateishi A, Scheller MS, Drummond JC et al: Failure of nimodipine to improve neurologic outcome after eighteen minutes of cardiac arrest in the cat. Resuscitation 211:191, 1991.

512. Steen PA, Newberg LA, Milde JH et al: Cerebral blood flow and neurologic outcome when nimodipine is given after complete cerebral ischemia in the dog. J Cereb Blood Flow Metab 4:82, 1984.

513. Forsman M, Aarseth HP, Nordby HK et al: Effects of nimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: Correlation with neurologic outcome. Anesth Analg 68:436, 1989.

514. Roine RO, Kaste M, Kinnunen A et al: Nimodipine after resuscitation from out-of-hospital ventricular fibrillation: A placebo-controlled, double-blind, randomized trial. JAMA 264:3171, 1990.

515. Brain Resuscitation Clinical Trial II Study Group: Lidoflazine: A randomized clinical study of a calcium-entry blocker (lidoflazine) in the treatment of comatose survivors of cardiac arrest. N Engl J Med 324:1225, 1991.

516. Finnerty FA, Witkin L, Fazekas JF: Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. J Clin Invest 33:1227, 1954.

517. Njemanze PC: Critical limits of pressure-flow relation in the human brain. Stroke 23:1743, 1992.

518. Vorstrup S, Barry DI, Jarden JO et al: Chronic antihypertensive treatment in the rat reverses hypertension-induced changes in cerebral blood flow autoregulation. Stroke 15:312, 1984.

519. Toyoda K, Fujii K, Ibayashi S et al: Attenuation and recovery of brain stem autoregulation in spontaneously hypertensive rats. J Cereb Blood Flow Metab 18:305, 1998.

520. Paulson OB, Vorstrup S, Anderson AR et al: Converting enzyme inhibition resets cerebral autoregulation at lower blood pressure. J Hypertens 3:S487, 1985.

521. Arbit E, DiResta GR, Bedford RF et al: Intraoperative measurement of cerebral and tumor blood flow with laser-Doppler flowmetry. Neurosurgery 24:166, 1989.

522. Schregel W, Geibler C, Winking M et al: Transcranial Doppler monitoring during induction of anesthesia: Effects of propofol, thiopental, and hyperventilation in patients with large malignant brain tumors. J Neurosurg Anesthesiol 5:86, 1993.

523. Bedford RF, Morris L, Jane JA: Intracranial hypertension during surgery for supratentorial tumor: Correlation with preoperative computed tomography scans. Anesth Analg 61:430, 1982.

524. Yeung WTI, Lee T-Y, Maestro RFD et al: Effect of steroids on iopamidol blood-brain transfer constant and plasma volume in brain tumors measured with x-ray computed tomography. J Neurooncol 18:53, 1994.

525. Jarden JO, Dhawan V, Moeller JR et al: The time course of steroid action on blood-to-brain and blood-to-tumor transport of ^{82}Rb: A positron emission tomographic study. Ann Neurol 25:239, 1989.

526. Wasterlain CG: Mortality and morbidity from serial seizures: An experimental study. Epilepsia 15:155, 1974.

527. Artru AA: Dose-related changes in the rate of cerebrospinal fluid formation and resistance to reabsorption of cerebrospinal fluid following administration of thiopental, midazolam, and etomidate in dogs. Anesthesiology 69:541, 1988.

528. Meyer FB, Anderson RE, Sundt TM et al: Treatment of experimental focal cerebral ischemia with mannitol. J Neurosurg 66:109, 1987.

529. Chiu D, Krieger D, Villar-Cordova C et al: Intravenous tissue plasminogen activator for acute ischemic stroke: Feasibility, safety, and efficacy in the first year of clinical practice. Stroke 29:18, 1998.

530. Kumura E, Yoshimine T, Takaoka M et al: Hypothermia suppresses nitric oxide elevation during reperfusion after focal cerebral ischemia in rats. Neurosci Lett 220:45, 1996.

531. Lubitz DK, Dambrosia JM, Kempski O et al: Cyclohexyl adenosine protects against neuronal death following ischemia in the CA1 region of gerbil hippocampus. Stroke 19:1133, 1988.

532. Kamisaki Y, Hamada T, Maeda K et al: Presynaptic alpha $_2$ adrenoceptors inhibit glutamate release from rat spinal cord synaptosomes. J Neurochem 60:522, 1993.

533. Doble A: The pharmacology and mechanism of action of riluzole. Neurology 47:S233, 1996.

534. Cross AJ, Jones JA, Baldwin HA et al: Neuroprotective activity of chlormethiazole following transient forebrain ischaemia in the gerbil. Br J Pharmacol 104:406, 1991.

535. Globus MY-T, Dietrich WD, Busto R et al: The combined treatment with a dopamine D $_1$ antagonist (SCH-23390) and NMDA receptor blocker (MK-801) dramatically protects against ischemia-induced hippocampal damage (abstract). J Cereb Blood Flow Metab 9:S5, 1989.

536. Nellgard B, Wieloch T: Postischemic blockade of AMPA but not NMDA receptors mitigates neuronal damage in the rat brain following transient severe cerebral ischemia. J Cereb Blood Flow Metab 12:2, 1992.

537. Davis SM, Albers GW, Diener H et al: Termination of acute stroke studies involving selfotel treatment. Lancet 349:32, 1997.

538. Tsuchida E, Bullock R: The effect of the glycine site-specific *N*-methyl- D-aspartate antagonist ACEA1021 on ischemic brain damage caused by acute subdural hematoma in the rat. J Neurotrauma 12:279, 1995.

539. Globus MY-T, Wester P, Busto R et al: Ischemia-induced extracellular release of serotonin plays a role in CA1 neuronal cell death in rats. Stroke 23:1595, 1992.

540. Umemura A, Mabe H, Nagai H: A phospholipase C inhibitor ameliorates postischemic neuronal damage in rats. Stroke 23:1163, 1992.

541. Park CK, Nehls DG, Graham DI et al: The glutamate antagonist MK-801 reduces focal ischemic brain damage in the rat. Ann Neurol 24:543, 1988.

542. Takaba H, Nagao T, Yao H et al: An ATP-sensitive potassium channel activator reduces infarct volume in focal cerebral ischemia in rats. Am J Physiol 273:R583, 1997.

543. Bartus RT, Baker KL, Heiser AD et al: Postischemic administration of AK275, a calpain inhibitor, provides substantial protection against focal ischemic brain damage. J Cereb Blood Flow Metab 14:537, 1994.

544. Hara K, Onodera H, Yoshidomi M et al: Staurosporine, a novel protein kinase C inhibitor, prevents postischemic neuronal damage in the gerbil and rat. J Cereb Blood Flow Metab 10:646, 1990.

545. Warner DS, Gionet TX, Todd MM et al: Insulin-induced normoglycemia improves ischemic outcome in hyperglycemic rats. Stroke 23:1775, 1992.

546. Soloniuk DS, Perkins E, Wilson JR: Use of allopurinol and deferox-amine in cellular protection during ischemia. Surg Neurol 38:110, 1992.

547. Nowicki JP, Duval D, Poignet H et al: Nitric oxide mediates neuronal death after focal cerebral ischemia in the mouse. Eur J Pharmacol 204:339, 1991.

548. Young B, Runge JW, Waxman KS et al: Effects of pegorgotein on neurologic outcome of patients with severe head injury: A multicenter, randomized controlled trial. JAMA 276:538, 1996.

549. Armstead WA, Mirro R, Thelin OP et al: Polyethylene glycol superoxide dismutase and catalase attenuate increased blood-brain barrier permeability after ischemia in piglets. Stroke 23:755, 1992.

550. Pahlmark K, Folbergrova J, Smith M-L et al: Effects of dimethyl-thiourea on selective neuronal vulnerability in forebrain ischemia in rats. Stroke 24:731, 1993.

551. Suzuki J, Akibo H, Mizoi K et al: Protective effect of phenytoin and its enhanced action by combined administration with mannitol and vitamin E in cerebral ischaemia. Acta Neurochir 88:56, 1987.

552. SASSInvestigators: Ganglioside GM_1 in acute ischemic stroke: The SASS trial. Stroke 25:1141, 1994.

553. Minamisawa H, Terashi A, Katayama Y et al: Brain eicosanoid levels in spontaneously hypertensive rats after ischemia with reperfusion: Leukotriene C4 as a possible cause of cerebral edema. Stroke 19:372, 1988.

554. Patel PM, Drummond JC, Sano T et al: Effect of ibuprofen on regional eicosanoid production and neuronal injury after forebrain ischemia in rats. Brain Res 614:315, 1993.

555. Pettigrew LC, Grotta JC, Rhoades HM et al: Effect of thromboxane synthase inhibition on eicosanoid levels and blood flow in ischemic rats. Stroke 20:627, 1989.

556. Adams HP, Woolson RF, Clarke WR et al: Design of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Control Clin Trials 18:358, 1997.

557. Bazan NG, Rodriguez deTurco EB, Allan G: Mediators of injury in neurotrauma: Intracellular signal transduction and gene expression. J Neurotrauma 12:791, 1995.

558. Zhang RL, Chopp M, Li Y et al: Anti-ICAM-1 antibody reduces ischemic cell damage after transient middle cerebral artery occlusion in the rat. Neurology 44:1747, 1994.

559. Du C, Hu R, Csernansky CA et al: Additive neuroprotective effects of dextrorphan and cycloheximide in rats subjected to transient focal cerebral ischemia. Brain Res 718:233, 1996.

560. Endres M, Namura S, Shimizu-Sasamata M et al: Attenuation of delayed neuronal death after mild focal ischemia in mice by inhibition of the caspase family. J Cereb Blood Flow Metab 18:238, 1998.

561. Colbourne F, Sutherland G, Corbett D: Postischemic hypothermia: A critical appraisal with implications for clinical treatment. Mol Neurobiol 14:171, 1997.

Chapter 20 - Neuromuscular Physiology and Pharmacology

J.A. Jeevendra Martyn
Frank G. Standaert
Ronald D. Miller

INTRODUCTION

The physiology of neuromuscular transmission could be analyzed and understood at the most simple level by using the classic model of nerve signaling to muscle via the acetylcholine receptor. Yet recent research has provided more detailed information on these processes, which, within the classic scheme, can modify neurotransmission or response to drugs, or both. One example of this would be the role of qualitative or quantitative changes in acetylcholine receptors modifying neurotransmission and response to drugs. [1] In myasthenia gravis, for example, the decrease in acetylcholine receptors results in decreased efficiency of neurotransmission (and therefore muscle weakness) and altered sensitivity to neuromuscular relaxants. [1] [2] At still another level is the evidence that muscle relaxants act in ways that are not encompassed by the classic scheme of unitary site of action: The observation that muscle relaxants can have prejunctional effects, [3] or that some nondepolarizers can also have agonist-like stimulatory actions on the receptor, [4] has provided new insights into some previously unexplained observations. Although this multifaceted action-response scheme makes the physiology and pharmacology of neurotransmission more complex, these added insights also bring experimentally derived knowledge much closer to clinical observations.

Crucial to the seminal concepts that have developed relative to neurotransmitter, acetylcholine, and its receptor systems have been the introduction of powerful and contemporary techniques in molecular biology, immunology, and electrophysiology. These have augmented the more traditional pharmacologic, protein chemical, and cytologic approaches. [5] Additionally, recent research has elucidated the manner in which the nerve ending regulates not only the synthesis and release of transmitter but also trophic factors, both of which control muscle function, and how these processes are influenced by exogenous and endogenous substances. [1] [6] [7] [8] Research continues into how receptors are synthesized and anchored at the end plate, the role of the nerve terminal in the maturation process, and the synthesis and control of acetylcholinesterase, the enzyme that breaks down acetylcholine. The reader is referred to several recent reviews that provide detailed insights into these areas. [7] [8] [9] [10]

NEUROMUSCULAR TRANSMISSION

Overview

Neuromuscular transmission occurs by a fairly simple and straightforward mechanism. The nerve synthesizes acetylcholine and stores it in small, uniformly sized packages called *vesicles.* Stimulation of the nerve causes these vesicles to migrate to the surface of the nerve, rupture, and discharge acetylcholine into the cleft separating nerve from muscle. Acetylcholine receptors in the end plate of the muscle

respond by opening its channels for influx of sodium ions into the muscle to depolarize the muscle. The end plate potential thus created is continued along the muscle membrane by the opening of the sodium channels present throughout the muscle membrane, initiating a contraction. [11] The acetylcholine immediately detaches from the receptor and is destroyed by acetylcholinesterase enzyme, which also is in the cleft. Drugs, notably depolarizing relaxants or carbachol, can also act on these receptors to mimic the effect of acetylcholine and cause depolarization of the end plate. These drugs are, therefore, called *agonists* of the receptor, since to a greater or lesser extent, at least initially, they stimulate the receptor. Nondepolarizing relaxants also act on the receptors, but they prevent acetylcholine from binding to the receptor and so prevent depolarization by agonists. Since these nondepolarizers prevent the action of agonists (e.g., acetylcholine, succinylcholine), the nondepolarizers are also referred to as *antagonists* of the acetylcholine receptor. Other compounds, frequently called *reversal agents* (e.g., neostigmine), inhibit acetylcholinesterase enzyme and therefore impair the hydrolysis of acetylcholine. The increased accumulation of undegraded acetylcholine can effectively compete with nondepolarizing relaxants, displacing the latter from the receptor (law of mass action), antagonizing the effects of nondepolarizers.

Morphology

The neuromuscular junction is specialized, both on the nerve side and on the muscle side, to transmit and receive chemical messages. [2] [3] [4] [5] [6] [7] Each motoneuron runs without interruption from the ventral horn of the spinal cord to the neuromuscular junction as a large myelinated axon. As it approaches the muscle, it branches repeatedly to contact many muscle cells and to gather them into a functional group known as a motor unit. The architecture of the nerve terminal is quite different from that of the rest of the axon. As the terminal reaches the muscle fiber, it loses its myelin to form a spray of terminal branches against the muscle surface and is covered by Schwann cells. [7] [9] This arrangement conforms to the architecture on the synaptic area of muscle membrane (Fig. 20-1). The nerve is separated from the surface of the muscle by an approximate 20 nm gap, *the junctional cleft.* The nerve and muscle are held in tight alignment by protein filaments, which span the cleft between nerve and end plate. The muscle surface is heavily corrugated, with deep invaginations of the junctional cleft--the primary and secondary clefts--between the folds in the muscle membrane; thus, the end plate's total surface area is very large. The shoulders of the folds are densely populated with acetylcholine receptors, about 5 million of them in each

Figure 20-1 Adult neuromuscular junction with the three cells that constitute the synapse: the motor neuron (nerve terminal), muscle fiber, and Schwann cell. The motor neuron from the ventral horn of the spinal cord innervates the muscle. Each fiber receives only one synapse. The motor nerve loses its myelin to terminate on the muscle fiber. The nerve terminal covered by a Schwann cell has vesicles clustered about the membrane thickenings, which are the active zones, toward its synaptic side, and mitochondria and microtubules toward its other side. A synaptic gutter, made up of a primary and many secondary clefts, separates the nerve from the muscle. The muscle surface is corrugated, and dense areas on the shoulders of each fold contain acetylcholine receptors. The sodium channels are present at the clefts and throughout muscle membrane.

junction. These receptors are sparse in the depths between the folds. Instead, these deep areas contain sodium channels.

The trophic function of the nerve is most vital for the development and maintenance of adequate neuromuscular function. Before birth, each muscle cell commonly has contacts with several nerves and thus has several neuromuscular junctions. At birth, all but one of the nerves retract and a single end plate remains. Once formed, however, the nerve-muscle contact, especially the end plate, is durable. Even if the original nerve dies, the one replacing it innervates exactly the same region of the muscle. The nerve endings on fast muscles are larger and more complicated than those on slow muscles. The reason for this is unclear. These differences in the nerve endings on the muscle surfaces may play a role in the differences in the response to muscle relaxants of fast and slow muscles.

Since all the muscle cells in a unit are excited by a single neuron, stimulation of the nerve either electrically or via an action potential originating from the ventral horn, or by any agonist, including depolarizing relaxants (e.g., succinylcholine), causes all muscle cells in the motor unit to contract synchronously. The synchronous contraction of the cells in a motor unit is fasciculation and often is vigorous enough to be observed through the skin. Although most adult human muscles have only one neuromuscular junction per cell, an important exception is some of the cells in the extraocular muscles. The extraocular muscles are "tonic" muscles, and, unlike other mammalian striated muscles, they are multiply innervated, with several neuromuscular junctions strung along the surface of each muscle cell. These muscles contract and relax slowly, rather than quickly as other striated muscles do; indeed, they can maintain a steady contraction, or contracture, whose strength is proportional to the stimulus received. Physiologically, this apparently is a specialization that holds the eye steadily in position. These muscles are important to an anesthetist because depolarizing relaxants affect them differently than they do most skeletal muscles. Instead of causing a brief contraction followed by paralysis, the drugs cause long-lasting contracture response, which pulls the eye against the orbit and contributes to a rise in the pressure of the intraocular fluid. [12]

The *perijunctional zone* is the area of muscle between and around the receptive area, and it is critical to the function of the neuromuscular junction. The perijunctional zone contains a mixture of the receptors, which include a smaller density of acetylcholine receptors and high-density sodium channels. The admixture enhances the capacity of the perijunctional zone to respond to the depolarization (end plate potential) produced by acetylcholine receptors and to transduce it into the wave of depolarization that travels along the muscle to initiate muscle contraction. The density of sodium channels in the perijunctional area is richer than in more distal parts of the muscle membrane. [13] The perijunctional zone is close enough to the nerve ending to be influenced by transmitter released from it. Moreover, special variants (isoforms) of receptors (see Biology of Prejunctional and Postjunctional Nicotinic Receptors) and sodium channels can appear in this area at different stages of life and in response to abnormal decreases in nerve activity. Congenital abnormalities in the acetylcholine receptor or the sodium channels (mutations) are also known. [11] [14] These variabilities seem to contribute to the differences in response to relaxants that are seen in patients of differing pathologic conditions and ages. [1] [15] These qualitative differences may also play a role in altered muscle function (see Myopathy of Critical Illness).

Quantal Theory

The contents of the ending are not homogeneous. As diagrammatically illustrated in Figure 20-1 , the vesicles are congregated in the portion toward the junctional

surface, whereas the microtubules, mitochondria, and other support structures are located toward the opposite side. The vesicles containing the transmitter are ordered in repeating clusters alongside small, thickened, electron-dense patches of membrane referred to as an *active zone.* This thickened area is a cross-section of a band running across the width of the synaptic surface of the nerve ending, believed to be the structure to which vesicles attach before they rupture into the junctional cleft. High-resolution scanning electron micrographs reveal small protein particles arranged alongside the active zone, between vesicles. These are believed to be special channels, the voltage calcium channels, that allow calcium to enter the nerve and cause the release of vesicles. [16]

When one observes the electrophysiologic activity of a skeletal muscle, small, spontaneous, depolarizing potentials at neuromuscular junctions can be seen. These potentials have only one-one hundredth the amplitude of the evoked end plate potential produced when the motor nerve is stimulated. Except for amplitude, these potentials resemble the end plate potential in time course and in the manner in which they are affected by drugs. Therefore, these small amplitude potentials are called miniature end plate potentials (MEPP). Statistical analysis led to the conclusion that they are unitary responses; that is, there is a minimum size for the MEPP, and the sizes of all MEPPs are either equal to or multiples of this minimum size. Because MEPPs are too big to be produced by a single molecule of acetylcholine, it was deduced that they are produced by uniformly sized packages, or quanta, of transmitter released from the nerve (in the absence of stimulation). The stimulus-evoked end plate potential is the additive depolarization produced by the synchronous discharge of quanta from several hundred vesicles. The action potential that is propagated to the nerve ending allows the entry of calcium in the nerve through voltage-gated calcium channels, and this causes vesicles to migrate to the active zone, fuse with the neural membrane, and discharge their acetylcholine into the junctional cleft. [16] [17] Since the release sites are located immediately opposite the receptors on the postjunctional surface, little transmitter is wasted, and the response of the muscle is coupled very directly with the signal from the nerve. The amount of acetylcholine released by each nerve impulse is large, at least 200 quanta of about 5,000 molecules each, and the number of acetylcholine receptors activated by the transmitter released by a nerve impulse also is large, about 500,000. The ions (mostly Na^+ and some Ca^{2+}) that flow through the channels of the activated receptors cause a maximum depolarization of the end plate, which in turn causes an end plate potential that is greater than the threshold for

stimulation of the muscle. This is a very vigorous system. The signal is carried by more molecules of transmitter than are needed, and these evoke a response that is greater than needed. At the same time, only a small fraction of the available vesicles and receptors/channels are used to send each signal. Consequently, transmission has a substantial margin of safety, and at the same time the system has substantial capacity in reserve.

THE NEUROMUSCULAR JUNCTION

Motor Nerve Endings

The axon of the motor nerve carries not only electrical signals from the spinal cord to the muscles but also all the biochemical apparatus needed to transform the electrical signal into a chemical one. All the ion channels, enzymes, other proteins, macromolecules, and membrane components needed by the nerve ending to synthesize, store, and release acetylcholine and other trophic factors are made in the cell body and are transmitted to the nerve ending by axonal transport (Fig. 20-2) . [7] [9] The simple molecules choline and acetate are obtained from the environment of the nerve ending, the former by a special system that transports it from the extracellular fluid to the cytoplasm and the latter in the form of acetylcoenzyme A from mitochondria. The enzyme choline acetyltransferase brings about the reaction of choline and acetate to form acetylcholine, which is stored in cytoplasm until it is transported into vesicles, which are more into position for release. During a nerve action potential, sodium flows across the membrane and the resulting depolarizing voltage opens calcium channels, which allow entry of the calcium ion into the nerve and cause the release of acetylcholine.

A nerve action potential is the normal activator that releases transmitter, acetylcholine. The number of quanta released by a stimulated nerve is greatly influenced by the concentration of ionized calcium in the extracellular fluid. If calcium is not present, depolarization of the nerve, even by electrical stimulation, will not produce release of transmitter. Doubling the extracellular calcium results in a 16-fold increase in the quantal content of an end plate potential. The calcium *current* persists until the membrane potential is returned to normal by outward fluxes of potassium from inside the nerve cell. Thus, the calcium current can be prolonged by potassium channel blockers (e.g., 4-aminopyridine, and tetraethylammonium), which slow or prevent potassium efflux out the nerve. The increase in quantal content produced in this way can reach astounding proportions. [18] An effect of increasing the calcium in the nerve ending is also seen clinically as the so-called *post-tetanic potentiation,* which occurs after a nerve of a patient paralyzed with a nondepolarizing relaxant is stimulated at high, tetanic frequencies. Calcium enters the nerve with every stimulus, but it cannot be excreted as quickly as the nerve is stimulated and so accumulates during the tetanic period. Since the nerve ending contains more than the normal amount of calcium for some time after the tetanus, a stimulus applied to the nerve during this time causes the release of more than the normal amount of acetylcholine. The abnormally large amount of acetylcholine antagonizes the relaxant

Figure 20-2 The working of a chemical synapse, the motor nerve ending, including some of the apparatus for transmitter synthesis. acetylCoA, acetyl coenzyme A; Ach, acetylcholine; CAT, choline acetyltransferase. Large intracellular structures are mitochondria. Acetylcholine, synthesized from choline and acetylcoenzyme A, is transported into coated vesicles, which are moved to release sites. A presynaptic action potential, which triggers calcium influx through specialized proteins (Ca^{2+} channels), causes the vesicles to fuse with the membrane and discharge transmitter. Membrane from the vesicle is retracted from the nerve membrane and recycled. The transmitter is inactivated by diffusion, catabolism, or reuptake.

and causes the characteristic increase in the size of the twitch.

Calcium enters the nerve via specialized proteins called *calcium channels.*[8] Of the several types of calcium channels, two seem to be important for transmitter release, the P channels and the slower L channels. The P channels, probably the type responsible for the normal release of transmitter, are found only in nerve terminals. [8] [19] In motor nerve endings they are located immediately adjacent to the active zones (see Fig. 20-2) . They are voltage-dependent (i.e., they are opened and closed by the changes in membrane voltage caused by the nerve action potential). Alterations in calcium entry into nerve ending can also alter release of transmitter. Eaton-Lambert myasthenic syndrome is an acquired autoimmune disease in which antibodies are directed against the voltage-gated calcium channel at nerve endings. [20] In this syndrome, the decreased function of the calcium channel causes decreased release of transmitter, resulting in inadequate depolarization and therefore muscle weakness. Patients with myasthenic syndrome exhibit increased sensitivity to depolarizing and nondepolarizing relaxants. [1]

Tiny concentrations of bivalent inorganic cations (e.g., magnesium, cadmium, manganese) can also block calcium entry through P channels and profoundly impair neuromuscular transmission. This is the mechanism for muscle weakness in the mother and fetus when magnesium sulfate is administered to treat preeclampsia. The P channels, however, are *not* affected by calcium entry-blocking drugs, such as verapamil, diltiazem, and nifedipine. These drugs have profound effects on the slower L channels present in the cardiovascular system. As a result, the L-type calcium channel blockers at *therapeutic* doses have no significant effect on the normal release of acetylcholine or on the strength of normal neuromuscular transmission. There have been a few reports, however, that calcium entry-blocking drugs may increase the block of neuromuscular transmission induced by nondepolarizing relaxants. The effect is small, and not all investigators have been able to observe it. The explanation may lie in the fact that nerve endings also contain L-type calcium channels.

There seem to be two pools of vesicles that release acetylcholine, a readily releasable store and a reserve store, sometimes called VP2 and VP1, respectively. [7] [21] The vesicles in the former are a bit smaller and are limited to an area very close to the nerve membrane, where they probably are bound to the active zones. These vesicles are the ones that ordinarily release transmitter. The release seems to occur when calcium ion enters the nerve via the P channels lined up on the sides of the active zones. [21] This calcium needs to move only a very short distance (i.e., a few atomic radii), to encounter a vesicle and to activate a protein, *synaptophysin,* in the vesicle wall. [22] The activated protein seems to react with the nerve membrane to form a pore, through which the vesicle discharges its acetylcholine into the junctional cleft.

The majority of the vesicles in the nerve ending are the larger "reserve" vesicles. These are firmly tethered to the *cytoskeleton* by proteins, the *synapsins.* From their position on the cytoskeleton, they may be moved to the readily releasable store to replace worn-out vesicles or to participate in transmission when the nerve is called upon to work especially hard (e.g., when it is stimulated at very high frequencies or for a very long time). Under such strenuous circumstances, calcium may penetrate more deeply than normal into the nerve or may enter via L channels to activate calcium-dependent enzymes, which cause breakage of the synapsin links that hold the vesicles to the cytoskeleton, thereby allowing the vesicles to be moved to the release sites. Repeated stimulation requires the nerve ending to replenish its stores of vesicles filled with transmitter, a process known as *mobilization.* The term commonly is applied to the aggregate of all steps involved in maintaining the nerve ending's capacity to release transmitter--everything from the acquisition of choline and the synthesis of acetate to the movement of filled vesicles to the release sites. The uptake of choline as well as the activity of choline acetyltransferase, the enzyme that synthesizes acetylcholine, probably are the a rate-limiting steps. [7] [8] [9] [16] [17] [18] [19]

Acetylcholinesterase

The acetylcholine released from the nerve diffuses across the junctional cleft and reacts with specialized receptor proteins in the end plate to initiate muscle contraction. Transmitter molecules that do not react immediately with a receptor or that are released after binding to the receptor are destroyed almost instantly by the acetylcholinesterase in the junctional cleft. Acetylcholinesterase is an asymmetric protein made in the muscle, under the end plate. It is secreted from the muscle but remains attached to it via thin stalks of collagen fastened to the basement membrane. [7] [10] Most of the molecules of acetylcholine released from the nerve initially

pass between the enzymes to reach the postjunctional receptors, but as they are released from the receptors, they invariably encounter acetylcholinesterase and are destroyed. Under normal circumstances, a molecule of acetylcholine reacts with only one receptor before it is hydrolyzed. Acetylcholine is a potent messenger, but its actions are very short-lived because it is destroyed in less than 1 millisecond after it is released.

Postjunctional Receptors

The similarity of the acetylcholine receptors among many species and the abundance of acetylcholine receptors from the *Torpedo* electric fish have greatly facilitated research in this area. The availability of the messenger ribonucleic acids (mRNAs) of humans and other species and of deoxyribonucleic acids (DNAs) has allowed the study of the receptor in artificial systems such as oocytes from frogs and mammalian cells that do not express the receptor (e.g., COS or fibroblast cells). It is also possible, by molecular techniques, to mutate receptors to simulate pathologic states and then study receptor function in these artificial systems. By using these and related techniques, a great deal has been learned about the synthesis, composition, and biologic function and the mechanisms that underlie physiologic and pharmacologic responses in the acetylcholine receptors. [4] [23] [24] [25] It is now evident that two isoforms of postjunctional receptors exist, a junctional or mature and an extrajunctional or immature receptor. [1] [7] (See Biology of Prejunctional and Postjunctional Nicotinic Receptors). The differences between receptor subtypes, however, can be neglected in a general discussion of the role of receptors in neuromuscular transmission.

Figure 20-3 Sketch of acetylcholine receptor channels (right) and tracings of cell patch records of receptor channel openings (left). The mature, or junctional, receptor consists of two alpha-subunits and one each of beta-, epsilon-, and delta- subunits. The immature, extrajunctional or fetal form consists of two alpha-subunits and one each of beta, gamma, and delta. The subunits are arranged around the central cation channel. The immature isoform containing the gamma-subunit shows long open times and low amplitude channel curents. The mature isoform containing the epsilon-subunit shows shorter open times and high amplitude channel currents. Substitution of the epsilon-subunit for the gamma-subunit gives rise to the fast-gated, high conductance channel type.

The acetylcholine receptors are synthesized in muscle cells and are anchored to the end plate membrane by a special protein known as the 43-Kd protein. The receptors, formed of five subunit proteins, are arranged like the staves of a barrel into a cylindrical receptor with a central pore for ion channeling. The key features are sketched in Fig. 20-3 . The receptor protein is about 250,000 d molecular weight. Each receptor has five subunits, which are designated alpha, beta, delta, and epsilon or gamma; there are two subunits of alpha and one of each of the others. [1] [7] Each of the subunits consists of approximately 400 to 500 amino acids. The receptor protein complex passes entirely through the membrane and protrudes both beyond the extracellular surface of the membrane and also into the cytoplasm. The binding site for acetylcholine is on each of the alpha-subunits, and these are the sites of competition between the receptor agonists and antagonists. Both agonists and antagonists are attracted to the binding site and either may occupy the site, which is located near cysteine residues (unique to the alpha-chain) at amino acid positions 192-193 of the alpha-subunit. [26] Radiolabeled alpha-bungarotoxin from the cobra is used to quantitate the receptor that binds to heptapeptide region 189-199 of the alpha-subunit. [27]

Progress in electrophysiologic techniques have moved *pari passu* with advances in molecular approaches to study the receptor. Patch clamping is a technique in which a glass micropipette is used to probe the membrane surface until a single functional receptor is encompassed. The tip of the pipette is pressed into the lipid of the membrane, and the electronic apparatus is arranged to keep the membrane potential clamped (fixed) and to measure the current that flows through the channel of the receptor. The solution in the pipette can contain acetylcholine, tubocurarine, another drug, or a mixture of drugs. By application of these drugs to the receptor via the micropipette, electrical changes could be monitored.

Figure 20-4 illustrates the results of the classical depolarizing action of acetylcholine on end plate receptors. Normally, the pore of the channel is closed by the approximation of the cylinders (subunits). When **both** alpha-subunit sites are occupied by an agonist, the protein molecule undergoes a conformation change that forms a channel in the center through which ions can flow along a concentration gradient (see Fig. 20-4). When the channel is open, there is a flow of sodium and calcium from the outside of the cell to the inside, and of potassium from the inside to the outside. The channel in the tube is large enough to accommodate many cations and electrically neutral molecules, but it excludes anions (e.g., chloride). The current carried by the ions depolarizes the adjacent membrane. The net current is depolarizing and creates the end plate potential that stimulates the muscle to contract. In this instance, downward-going (depolarizing) rectangular pulses (see Fig. 20-3) can be recorded by the electrophysiologic technique described previously.

The pulse stops when the channel closes and one or both agonist molecules detach from the receptor. The current that passes through each open channel is minuscule, only a few picoamperes (about 10^4 ions per millisecond). However, each burst of acetylcholine from the nerve normally opens about 500,000 channels simultaneously, and the total current is more than adequate to produce depolarization of the end plate and contraction of muscle. Thus, the opening of a channel causes the conversion of chemical signals from a

Figure 20-4 The actions of acetylcholine or curare on end plate receptors. (A) The ion channel is inactive and does not open in the absence of acetylcholine. (B) Even the binding of one acetylcholine **(** **)** to one of two binding sites does not open the channel. (C) When acetylcholine binds to recognition sites of *both* alpha-subunits simultaneously ( ), it triggers a conformation change that opens the channel and allows ions to flow across the membrane. (D) The action of antagonists (e.g., curare, bold square). Acetylcholine is in competition with tubocurarine for the receptor's recognition site but may also react with acetylcholinesterase. Inhibiting the enzyme increases the lifetime of acetylcholine and the probability that it will react with a receptor. When one of the two binding (recognition) sites is occupied by curare, the receptor will not open, even if the other binding site is occupied by acetylcholine.

nerve to current flows to end plate potentials, leading to muscle contraction. We are used to thinking of the end plate potential as a graded event, which may be reduced in magnitude or extended in time by drugs, but in reality the end plate potential is the summation of many all-or-nothing events occurring simultaneously at a myriad of individual ion channels. It is these tiny events that are affected by drugs.

Receptors that do not have two molecules of agonists bound, remain closed. Both alpha-subunits must be occupied simultaneously by agonist; if only one of them is occupied, the channel remains closed (see Fig. 20-4) . This is the basis for the prevention of depolarization by antagonists. Drugs such as tubocurarine act by binding to either, or both, alpha-subunits and in so doing preventing acetylcholine from binding and opening the channel. This interaction between agonists and antagonists is competitive, and the outcome--transmission or block--depends on the relative concentrations and binding characteristics of the drugs involved (see Drug Effects on Postjunctional Receptors).

Individual channels are also capable of a wide variety of conformations. [28] [29] Most simply, they may open or stay closed, thus affecting total current flow across the membrane. However, they can do more. They may open for a longer or shorter time than normal, open or close more gradually than usual, open briefly and repeatedly (chatter), or pass fewer or more ions per opening than they usually do. Also, their function is influenced by drugs, changes in the fluidity of the membrane, temperature, the electrolyte balance in the milieu, and other physical and chemical factors. [30] Thus, receptor-channels are dynamic structures that are capable of a wide variety of interactions with drugs and of entering a wide variety of current-passing states. All these influences on channel activity ultimately are reflected in the strength or weakness of neuromuscular transmission and the contraction of a muscle.

/das/book/view/29494766/875/212.html

DRUG EFFECTS ON POSTJUNCTIONAL RECEPTORS

Classical Actions of Nondepolarizing Muscle Relaxants

Neurotransmission occurs when the action potential releases acetylcholine and binds to the receptor. All nondepolarizing relaxants impair or block neurotransmission by competitively preventing the binding of acetylcholine to its receptor. The final outcome (block or transmission) is dependent on the relative concentrations of the chemicals and their comparative affinities for the receptor. Figure 20-4 shows a system exposed to acetylcholine and tubocurarine. One receptor has attracted two acetylcholine molecules and opened its channel where current will flow to depolarize that segment of membrane. Another has attracted one tubocurarine molecule; its channel will not open, and no current will flow, even if one acetylcholine molecule binds to the other site. The third receptor has acetylcholine on one alpha-subunit and nothing on the other. What will happen depends on which of the molecules binds. If acetylcholine binds, the channel will open and the membrane will be depolarized; if tubocurarine binds, the channel will stay closed and the membrane will not be depolarized. At other times, one or two tubocurarine molecules may attach to the receptor, in which case the receptor is not available to agonists; no current flow is recorded. In the presence of moderate concentrations

of tubocurarine, the amount flowing through the entire end plate at any instant is reduced from normal, which results in a smaller end plate potential and, if carried far enough, a blockade of transmission.

Normally, acetylcholinesterase enzyme destroys acetylcholine and removes it from the competition for a receptor, so that tubocurarine has a better chance of inhibiting transmission. If, however, an inhibitor such as neostigmine is added, the cholinesterase cannot destroy acetylcholine. The concentration of agonist in the cleft remains high, and this high concentration shifts the competition between acetylcholine and tubocurarine in favor of the former, thus improving the chance of two acetylcholine molecules binding to a receptor even though tubocurarine is still in the environment. This is the mechanism by which cholinesterase inhibitors overcome the neuromuscular paralysis produced by nondepolarizing relaxants. It must be noted, however, that the channel opens only when acetylcholine attaches to both the recognition sites. A single molecule of antagonist, however, is adequate to prevent the depolarization of that receptor. This modifies the competition by biasing it strongly in favor of the antagonist. Mathematically, if the concentration of tubocurarine is doubled, the concentration of acetylcholine must be increased 4-fold if acetylcholine is to remain competitive. This means that paralysis produced by high concentrations of antagonist is more difficult to reverse than those produced by low concentrations. Following large doses of nondepolarizing relaxants, reversal drugs may be ineffective until the concentration of the relaxant in the perijunctional area decreases to a lower level by either redistribution or elimination of the drug.

Classical Action of Depolarizing Muscle Relaxants

Depolarizing relaxants, at least initially, simulate the effect of acetylcholine and therefore can be considered agonists despite the fact that they block neurotransmission after initial stimulation. Structurally, succinylcholine is actually two molecules of acetylcholine bound together. It is, therefore, not surprising that it can mimic the effects of acetylcholine. Succinylcholine or decamethonium can bind to the receptor, open the channel, pass current, and depolarize the end plate. These agonists, similar to acetylcholine, attach only briefly; so each opening of a channel is of very short duration, 1 millisecond or less. The response to acetylcholine, however, is over in milliseconds because of its rapid degradation by acetylcholinesterase, and the end plate resets to its resting state long before another nerve impulse arrives. In contrast, the depolarizing relaxants characteristically have a biphasic action on muscle--an initial contraction, followed by relaxation lasting minutes to hours. The depolarizing relaxants, since they are not susceptible to hydrolysis by acetylcholinesterase, are not eliminated from the junctional cleft until after they are eliminated from the plasma. The time required to clear the drug from the body is the principal determinant of how long the drug effect lasts. Whole body clearance of the relaxant is very slow, as compared with the acetylcholine, even when the plasma cholinesterase is normal. Since relaxant molecules are not cleared from the cleft quickly, they react repeatedly with receptors, attaching to one almost immediately after separating from another, thereby repeatedly depolarizing the end plate and opening channels.

The quick shift from excitation of muscle contraction to blockade of transmission by depolarizing relaxants occurs even though--indeed because--the end plate is continuously depolarized. This comes about because of the juxtaposition at the edge of the end plate on the muscle membrane--a different kind of ion channel, the sodium channel that does not respond to chemicals but opens when they are exposed to a transmembrane voltage change. The sodium channel is also a cylindrical transmembrane protein, through which sodium ions can flow through. Two parts of its structure act as gates that allow or stop the flow of sodium ions. [31] Both gates must be open if sodium is to flow through the channel; the closing of either cuts off the flow. Because these two gates act sequentially, a sodium channel has three functional conformation states and can move progressively from one state to another (counterclockwise in Fig. 20-5) .

When the sodium channel is in its resting state, the lower gate (called the time-dependent or inactivation gate) is open, but the upper gate (the voltage-dependent gate) is closed, and sodium ions cannot pass. When the molecule is subject to a sudden change in voltage by depolarization of the adjacent membrane, the top gate opens and, since the bottom (time-dependent) gate is still open, sodium flows through the channel. The voltage-dependent gate stays open as long as the molecule is subject to a depolarizing influence from the membrane around it; it will not close until the depolarization disappears. However, shortly after the voltage-dependent gate opens, the bottom gate closes and again cuts off the flow of ions. It cannot open again until the voltage-dependent gate closes. When the depolarization of the end plate stops, the voltage-dependent gate closes, the

Figure 20-5 Sketch of sodium channel. The bars represent parts of the molecule that act as gates. The upper one is voltage dependent; the lower one is time dependent. The top drawing represents the resting state. Once activated by a voltage change, the molecule and its gates progress as illustrated but only in the counterclockwise direction (see text for details).

time-dependent one opens, and the sodium channel returns to its resting state. This whole process is short-lived when depolarization occurs with acetylcholine. The initial response of a depolarizing muscle relaxant resembles that of acetylcholine, but since the relaxant is not hydrolyzed rapidly, depolarization of the end plate is not brief.

The depolarization of the end plate by the relaxant initially causes the voltage gate in adjacent sodium channels to open, causing a wave of depolarization to sweep along the muscle, causing muscle contraction. Shortly after the voltage-dependent gate opens, the time-dependent inactivation gate closes. Since the relaxant is not removed from the cleft, the end plate continues to be depolarized. Since the sodium channels immediately adjacent to the end plate are influenced by the depolarization of the end plate, their voltage-dependent gates stay open and consequently their inactivation gates stay closed. Since sodium cannot flow through a channel that has a closed inactivation gate, the perijunctional muscle membrane does not depolarize. When the flow of ions though the sodium channels in the perijunctional zone stops because the inactivation gates have closed, the channels downstream (beyond the perijunctional zone) are freed of depolarizing influence. In effect, the perijunctional zone becomes a buffer that shields the rest of the muscle from events at the end plate. Consequently, the muscle membrane is separated into three zones: the end plate, which is depolarized by succinylcholine; the perijunctional muscle membrane, in which the sodium channels are frozen in an inactivated state; and the rest of the muscle membrane, in which the sodium channels are in the resting state. Since a burst of acetylcholine from the nerve cannot overcome the inactivated sodium channels in the perijunctional zone, neuromuscular transmission is blocked. This phenomenon is also called *accommodation.* During accommodation, when the synapse is inexcitable via the nerve (transmitter), direct electrical stimulation of muscle will cause muscle contraction, since the sodium channels beyond the junctional area are in the resting excitable state.

The extraocular muscles contain tonic muscle, which is multiply innervated and chemically excitable along most of its surface. Accommodation does not occur, and these muscles can undergo a sustained contracture in the presence of succinylcholine. The tension so developed forces the eye against the orbit and accounts for part of the rise in intraocular pressure produced by depolarizing relaxants. There is also evidence that the extraocular muscles contain a special type of receptor that does not become desensitized (see subsequent discussion) in the continued presence of acetylcholine or other agonists. [32]

Nonclassical and/or Noncompetitive Actions of Neuromuscular Drugs

Several drugs can interfere with the receptor, directly or via its lipid environment, to change transmission. These drugs react with the neuromuscular receptor to change its function and to impair transmission, but do not act via the acetylcholine binding site. These reactions cause druginduced changes in the dynamics of the receptor so that instead of opening and closing sharply, the modified channels are sluggish. They open more slowly and stay open longer or they close slowly and in several steps, or both. These effects on channels cause corresponding changes in the flow of ions and distortions of the end plate potential. The clinical effect depends on the molecular events. For example, procaine, ketamine, inhaled anesthetics, or other drugs that dissolve in the membrane lipid may change the opening or closing characteristics of the channel. [33] [34] If the channel is prevented from opening, transmission is weakened. If, on the other hand, the channel is prevented from or slowed in closing, transmission may be enhanced. They do not fit the classic model and the impaired neuromuscular function is not antagonized by increasing perijunctional acetylcholine concentrations with cholinesterase inhibitors. Such drugs can be involved in two clinically important reactions, receptor *desensitization* and *channel blockade.* The former occurs in the receptor molecule, while the latter occurs in the ion channel.

Desensitization Block

The acetylcholine receptor, because of its flexibility and the fluidity of the lipid around it, is capable of existing in a number of conformational states. [30] [33] [34] [35] The resting receptor is free of agonist, so its channel is closed. The second state is when two molecules of agonists are bound to the alpha-subunit of the receptor, and the receptor has undergone the conformation change that opens the channel and allows ions to flow. These reactions are the bases of normal neuromuscular transmission. Some receptors that bind to agonists, however, do not undergo the conformation change to open the channel. Receptors in these states are termed *desensitized* (i.e., they are not sensitive to the channel-opening actions of agonists). They bind agonists, indeed, with exceptional avidity, but the binding does not result in the opening of the channel. The mechanisms by which desensitization occurs are not known. The receptor macromolecule, 1,000 times larger by weight than most drugs or gases, provides many places at which the smaller molecules may act. The interface between lipid and receptor protein provides additional potential sites of reaction. Several different conformations of the protein are known, and because acetylcholine cannot cause the ion channel to open in any of them, they all are included in the functional term *desensitization.* Some evidence suggests that desensitization is accompanied by phosphorylation of a tyrosine unit in the receptor protein. [36]

Although agonists (e.g., succinylcholine) induce desensitization, the receptors are in a constant state of transition between resting and desensitized states whether or not agonists are present. Agonists do promote the transition to a desensitized state or, because they bind very tightly to desensitized receptors, trap a receptor in a desensitized state. Antagonists also bind tightly to desensitized receptors and can trap molecules in these states. This action of antagonists is not competitive with that of acetylcholine; in fact, it may be augmented by acetylcholine if the latter promotes the change to a desensitized state. Desensitization can lead to significant misinterpretations of data. Superficially, the preparation seems to be normal, but its responsiveness to agonists or antagonists is altered. One variety occurs very rapidly, within a few milliseconds after application of an agonist. This may explain the increased sensitivity to nondepolarizers

after prior administration of succinylcholine. There also is the phenomenon caused by prolonged administration of depolarizing relaxants and known as phase II block (see under Phase II Block). This frequently is referred to as a desensitization blockade but should not be, because desensitization of receptors is only one of many phenomena that contribute to the process.

Many other drugs used by anesthetists also promote the shift of receptors from a normal state to a desensitized state. [33] [34] [35] These drugs, some of which are listed in Table 20-1 , can weaken neuromuscular transmission by reducing the margin of safety that normally exists at the neuromuscular junction, or they can cause an apparent increase in the capacity of nondepolarizing agents to block transmission. These actions are independent of the classic effects based on competitive inhibition of acetylcholine. The presence of desensitized receptors means that fewer receptor-channels than usual are available to carry transmembrane current. Therefore, the production of desensitized receptors decreases

TABLE 20-1 -- Some Drugs That Can Cause or Promote Desensitization of Nicotinic Cholinergic Receptors

VOLATILE ANESTHETICS
Halothane
Methoxyflurane
Isoflurane
ANTIBIOTICS
Polymyxin B
COCAINE
ALCOHOLS
Ethanol
Butanol
Propanol
Octanol
BARBITURATES
Thiopental
Pentobarbital
AGONISTS
Acetylcholine
Decamethonium

Carbachol

Succinylcholine

AChE INHIBITORS

Neostigmine

Pyridostigmine

DFP

LOCAL ANESTHETICS

Dibucaine

Lidocaine

Prilocaine

Etidocaine

PHENOTHIAZINES

Chlorpromazine

Trifluperazine

Prochloperazine

PHENCYCLIDINE

CA^{2+} CHANNEL BLOCKERS

Verapamil

---

the efficacy of neuromuscular transmission. If many receptors are desensitized, insufficient normal ones are left to depolarize the motor end plate, and neuromuscular transmission will not occur. Even if only some receptors are desensitized, neuromuscular transmission will be impaired, and the system will be more susceptible to block by conventional antagonists such as tubocurarine or pancuronium.

Channel Block

Local anesthetics and calcium entry blockers block the flow of sodium or calcium through their respective channels. Thus, the term *channel-blocking drugs.* Similarly, a block to the flow of ions can occur at the acetylcholine receptor with concentrations of drugs used clinically and may contribute to some of the phenomena and drug interactions seen at the receptor. Two major types, closed channel and open channel block, can occur. [37] [38] In closed channel block, certain drugs can occupy the mouth of the channel and by their presence prevent physiologic ions from passing through the channel to depolarize the end plate. The process can take place even when the channel is not open. In open channel block, a drug molecule enters a channel that has been opened by reaction with acetylcholine but does not necessarily penetrate all the way through. Open channel blockade is use-dependent, which means that molecules can enter the channel only when it is open. In both open and closed channel block, the normal flow of ions through receptor is impaired, resulting in prevention depolarization of the end plate and a weaker or blocked neuromuscular transmission. However, since the action is not at the acetylcholine recognition site, it is not a competitive antagonism of acetylcholine and is not relieved by anticholinesterases that increase concentrations of acetylcholine. Indeed, increasing the concentration of acetylcholine may cause the channels to open more often and thereby become more susceptible to blockade by usedependent compounds. In this regard, there is evidence that neostigmine and related cholinesterase inhibitors themselves can act as channel-blocking drugs. [37] [38]

Channel blockade is believed to play a role in some of the antibiotics, cocaine, quinidine, piperocaine, tricyclic antidepressants, naltrexone, naloxone, and histrionicotoxininduced alterations in neuromuscular function. Muscle relaxants, in contrast, can bind to the acetylcholine recognition site of the receptor and also occupy the channel. Pancuronium preferentially binds to the recognition site. Gallamine seems to act equally at the two sites. Tubocurarine is in between: At low doses, those that produce minimal blockage of transmission clinically, the drug is essentially a pure antagonist at the recognition site; at larger doses, it also enters and blocks channels. Decamethonium and succinylcholine as agonists can open channels and as slender molecules also enter and block them. In fact, decamethonium and some other long, thin molecules can penetrate all the way through the open channel and enter the muscle cytoplasm. Whether prolonged administration of nondepolarizers, as in the intensive care situation, can result in entry of the relaxant, occupation of the channel, and finally entry of drug into the cytosol is unknown. This effect may partially explain the muscle weakness associated with relaxant therapy in the intensive care unit.

Phase II Block

Phase II block is a complex phenomenon that occurs slowly at junctions continuously exposed to depolarizing agents. The junction is depolarized by the initial application of a depolarizing relaxant, but then the membrane potential gradually recovers toward normal, even though the junction is still exposed to drug. Neuromuscular transmission usually remains blocked throughout the exposure. Several things seem to be involved. The repeated opening of channels allows a continuous efflux of potassium and influx of sodium, and the resulting abnormal electrolyte balance distorts the function of the junctional membrane. Calcium entering the muscle via the opened channels can cause disruption of receptors and sub-end plate elements themselves. On the other hand, the activity of a sodium-potassium adenosine triphosphatase pump in the membrane increases with increasing intracellular sodium and, by pumping sodium out of the cell and potassium into it, works to restore the ionic balance and membrane potential toward normal. As long as the depolarizing drug is present, the receptor channels remain open and ion flux through them remains high. [39]

Factors influencing the development phase II block include the duration of exposure to the drug, the particular drug used and its concentration, and even the type of muscle (i.e., fast or slow). Interactions with anesthetics and other agents also affect the process. All of these drugs may also have prejunctional effects on the rate and amount of transmitter release and mobilization. With so many variables involved in the interference with neuromuscular transmission, phase II block is a complex and ever-changing phenomenon. Thus, the reversal response of a phase II block produced by a depolarizing muscle relaxant to administration of cholinesterase inhibitors is difficult to predict. It is, therefore, best that reversal by cholinesterase inhibitors is not attempted, although the response to tetanus or train-of-four stimulation resembles that produced by nondepolarizers.

BIOLOGY OF PREJUNCTIONAL AND POSTJUNCTIONAL NICOTINIC RECEPTORS

Immature/Extrajunctional Versus Mature/Junctional Isoforms

As already indicated, there are two isoforms (variants) of the postjunctional acetylcholine receptors. The acetylcholine receptor isoform present in the innervated, adult neuromuscular junction is referred to as the adult, mature, or junctional receptor. When there is decreased activity in muscle, as seen in the fetus before innervation, following lower or upper motor neuron injury, after burns or sepsis, or after other events that cause increased muscle protein catabolism, another isoform is expressed. [40] To contrast with the mature, junctional receptors, the other isoform is referred to as the immature, extrajunctional, or fetal form of acetylcholine receptor. (Indirect evidence suggests that this immature isoform is not seen in muscle protein catabolism and wasting occurring with malnutrition.) [41] The differences in the protein structure of the isoforms cause significant qualitative variations among the responses of individual patients to relaxants and seem to be responsible for some of the anomalous results that are observed when administering relaxants to particular individuals. These qualitative differences in the isoforms can also cause variations in function of muscle. [14]

The structural composition and other characteristics differ between the two isoforms. [1] [7] [40] At the molecular level, both types of receptors consists of five subunits (see Fig. 20-3) . The mature junctional receptor is a pentamer of two alpha-subunits and one each of the beta-, delta-, and epsilon-subunits. The immature receptor consists of two alpha, and each of beta, delta and gamma-subunits. That is, in the immature receptor the gamma-subunit is present instead of the epsilon-subunit. The gamma- and epsilon-subunits differ from each other very little in amino acid homology, but the differences are great enough to affect the physiology and pharmacology of the receptor and its ion channel. Although the names junctional and extrajunctional imply that each is located in the junctional and extrajunctional areas, this is not strictly correct. Junctional receptors are always confined to the end plate (perijunctional) region of the muscle membrane. The immature, or extrajunctional, receptor may be expressed anywhere in the muscle membrane. Despite the name *extrajunctional,* they are not excluded from the end plate. During development and in certain pathologic states, the junctional and extrajunctional receptors can coexist in the perijunctional area of the muscle membrane (Fig. 20-6) .

Quite in contrast to other cells, muscle cells are unusual in that they have many, usually hundreds of, nuclei per cell. Each of these nuclei has the genes to make both types of receptors. Multiple factors, including electrical activity, growth factor signaling, and presence or absence of innervation, control the expression of the two types of receptor isoforms. [6] [7] [8] [42] This is most clearly seen in the developing embryo, as the neuromuscular junction is formed. Before they are innervated, the muscle cells of a fetus synthesize only the immature receptors, hence the term fetal isoform of receptor. The synthesis is directed by nearly all the nuclei in the cell, and the receptors are expressed throughout the membrane of the muscle cell (see Fig. 20-6) . As the fetus develops and the muscles become innervated, muscle cells begin to synthesize mature isoform of receptors, which are inserted exclusively into the developing (future) end plate area. The nerve releases several growth factors that influence the synthetic apparatus of the nearby nuclei. First, nerve-supplied factors induce the subsynaptic nuclei to increase synthesis of the acetylcholine receptors. Next the nerve-induced electrical activity results in repression of receptors in the extrajunctional area. Finally, the nervederived factors cause the clustering of the receptors in the subsynaptic area. [5] [7] [42] The innervation process progresses somewhat slowly during fetal life and infancy. [15] With time, the immature receptors diminish in concentration and disappear from the peripheral part of the muscle. A child is usually about 2 years old before nerve-muscle contacts are mature. Thus, in the active, adult, normal, innervated muscle, only the nuclei under and very near the end plate direct the synthesis of receptor; only the genes for expressing the mature receptors are active. The nuclei beyond the junctional area are not active and therefore no receptors are expressed anywhere in the muscle cells beyond the perijunctional area.

Figure 20-6 Distribution of acetylcholine receptors in developing adult, mature, and denervated muscle. (A and B) In the early fetal stage, mononucleated myoblasts, derived from the mesoderm, fuse to form multinucleated myotubes. The gamma-subunit containing immature acetylcholine receptors are scattered throughout the muscle membrane. (C) As the nerve makes contact with muscle, clustering of the receptors occurs at the synapse associated with some loss of extra synaptic receptors. (D) Maturation of the junction is said to occur when epsilon-subunit-containing receptors replace the gamma-subunit-containing receptors. Note that even mature muscle is multinucleated, but is devoid of extrasynaptic nuclei. (E) Denervation or some other pathologic states (burns, sepsis) leads to reexpression of the gamma-subunit receptor, at both the junctional and the extrajunctional areas. The latter changes are potentially reversible.

Proteins implicated in the linking of the mature receptors to the cytoskeleton include urotrophin, alpha- and beta-dystroglycan, and rapsyn. Several lines of evidence indicate that the clustering, expression, and stabilization of the mature receptors is triggered by at least three growth factors, agrin, acetylcholine receptor inducing activity, and calcitonin-gene related peptide. [6] [7] [42] Agrin is also released from the muscle, but muscle-derived agrin does not seem to be as important in the clustering and maturation of the receptor. The synapsins are made in the nerve and seem to play a role in the maturation of vesicular arrangement. All of these growth factors interact with distinct membrane and cytosolic receptor proteins causing phosphorylation, activation of nuclear (gene) transcriptional systems. These in turn control qualitative and quantitative changes at the junction. Once begun, the process is very stable; that is, these nuclei in the junctional area continue to express mature receptors.

The extrajunctional receptors can reappear soon after upper and lower motor denervation and in certain pathologic states (burns, immobilization, loss of electrical activity). The appearance of the immature receptors can be prevented by stimulating a denervated muscle with an external electrical stimulus. It has been suggested that the calcium that enters the muscle during activity is important to the suppression process. In the pathologic states just enumerated, if the process is severe and prolonged, extrajunctional receptors are inserted all over the surface of the muscle, including the perijunctional area. The junctional nuclei also continue to make mature receptors. The end plates thus will consist now of both mature and immature receptors. The synthesis of immature receptors is initiated within hours of inactivity, but it takes several days for the whole muscle membrane to be fully quoted with receptors. This upregulation of receptors has implications for the use of both depolarizing and nondepolarizing relaxants.

The changes in subunit composition (gamma versus epsilon) in the receptor confer certain changes in electrophysiologic (functional), pharmacologic, and metabolic characteristics. [1] [7] The mature receptors are metabolically stable, with half-life approximating 2 weeks, whereas the immature receptor has a metabolic half-life of less than 24 hours. Immature receptors have a smaller single-channel conductance and a 2- to 10-fold longer mean channel open time than mature receptors (see Fig. 20-3) . The changes in subunit composition may also alter the sensitivity or affinity, or both, of the receptor for specific ligands. Depolarizing or agonist drugs such as succinylcholine and acetylcholine depolarize immature receptors more easily, resulting in cation fluxes; one-tenth to one-hundredth doses, necessary for mature receptors, can effect depolarization. Potency of nondepolarizers is also reduced, demonstrated as resistance to nondepolarizers documented in burns, denervation, and immobilization. [1] This resistance may be related to decreased affinity of the receptor to nondepolarizers and to the upregulation of receptors. Indeed, recent data suggest that some nondepolarizers may also cause a partial agonist response in immature receptors, explaining the decreased potency. [4] The altered sensitivities for cholinergic ligands may also result from changes in composition of the lipid membrane surrounding the receptor that is known to occur with

some pathologic states. [30]

The sensitivity to muscle relaxants may occur in only certain parts of the body or certain muscles if only some muscles are affected by the diminution of nerve activity (e.g., after a stroke). The sensitivity to relaxants can begin to change between 24 and 72 hours after an injury or hospitalization. The most serious side effect with the use of succinylcholine in the presence of upregulated receptors in one or more muscle is hyperkalemia. [1] In these subjects, the receptors can be scattered over a large surface of the muscle. As indicated previously, the immature receptors are especially sensitive to succinylcholine. The channels opened by the agonist allow potassium to escape from the muscle and enter the blood. If a large part of the muscle surface consists of upregulated (immature) receptor-channels, each of which stays open for a longer time, the amount of potassium that moves from muscle to blood can be very large. The resulting hyperkalemia can cause dangerous disturbances in cardiac rhythm, including ventricular fibrillation. Moreover, it is difficult to prevent the hyperkalemia by the prior administration of nondepolarizers because extrajunctional receptors are not very sensitive to block by nondepolarizing relaxants. Larger than normal doses of nondepolarizers may attenuate the increase in blood potassium but will not completely prevent it.

Myopathy of Critical Illness

Critical illness (also see Chs. 12 and 72) such as sepsis, trauma, and burns induce functional and pharmacologic aberrations at the skeletal muscle, similar to that seen with upper or lower motor neuron injuries. As indicated previously, the aberrant *pharmacologic* responses consist of a hyperkalemic response to succinylcholine and resistance to nondepolarizers. The important *functional* change is muscle weakness resulting in hypoventilation, dependence on respirators, and decreased mobilization. [43] [44] The pathognomic biochemical feature in all of these conditions is the upregulation of acetylcholine receptors with expression of immature (gamma-subunit) isoform of receptors. [40]

The immature, as compared with the mature, isoform has different electrophysiologic characteristics, including prolonged open-channel time. In some clinical conditions, the presence of a prolonged open-channel time (due to congenital mutations in the receptor) is associated with muscle weakness. [14] [45] In the pathologic state of burns, sepsis, and trauma, in which muscle weakness is a concomitant finding, the expression of the immature isoform at the perijunctional membrane may have a role in muscle weakness. Additionally, the expression of the immature isoform may decrease the number of mature isoforms, a situation akin to myasthenia gravis, in which the mature receptor number at the junction is decreased. Furthermore, in mice, deletion of the mature epsilon-subunit-containing receptors causes muscle weakness despite the expression of immature receptors at the postjunctional membrane. [46] In all of these conditions in which the immature isoform is expressed, signaling via receptor tyrosine kinases or via growth factors seems to be impaired. [47] [48] Additional compounding effects related to deficient growth factor signaling include apoptosis in muscle with loss of contractile elements. Apoptosis, occurring in cardiac muscle, contributes significantly to myocardial dysfunction. [49] The loss of muscle mass, due to apoptosis, may compound the skeletal muscle weakness related to immature receptor expression. [50] Signaling via receptor kinases and its effects on acetylcholine expression and apoptosis seem to be an intense area of research by many groups. Correction of the altered signaling mechanism may therefore reverse the expression of the immature to mature isoform, attenuate the apoptosis in muscle, and correct the muscle weakness associated with critical illness.

Prejunctional Receptors

Compared with the postjunctional area, the prejunctional nerve ending is less well understood. Many drugs, with an abundance of potential targets for drug action, can affect the capacity of the nerve terminal to carry out its functions. The trophic function to maintain the nerve-muscle contact involves release and replenishment of acetylcholine together with trophic factors that require signaling through many receptors, of which the prejunctional nicotinic receptor is just one. Prejunctional or nerve terminal-associated cholinergic receptors have been demonstrated pharmacologically, but their form and functions are not well understood. Previously, it was observed that succinylcholine produces fasciculations and that these are prevented by nondepolarizing relaxants. Since a fasciculation is, by definition, the simultaneous contraction of the multitude of muscle cells in a single motor unit and since only the nerve can synchronize all the muscles in its motor unit, it was apparent that succinylcholine must also act on nerve endings. Also, since nondepolarizing relaxants prevent fasciculation, it was concluded that they acted on the same prejunctional receptor. Since then it has been shown many times that very small doses of cholinergic agonists (e.g., succinylcholine) and antagonists (e.g., curare) affect nicotinic receptors on the nerve ending, the former by depolarizing the ending and sometimes inducing

repetitive firing of the nerve, and the latter by preventing the action of agonists. [3]

Another clue to differences was the finding that although both pre- and postjunctional nicotinic receptors bind alpha- bungarotoxin, prejunctional binding was reversible whereas postjunctional binding was not. Additional clues were found in the many demonstrations of quantitative differences in the reaction of pre- and postjunctional nicotinic receptors to cholinergic agonists and antagonists. [51] For instance, it was known that tubocurarine and hexamethonium bind very poorly to the recognition sites of ganglionic nicotinic cholinoceptors and were not competitive antagonists of acetylcholine at this site. Instead, they blocked the opened channels of these receptors and owed their ability to block ganglionic transmission to this property. The functional characteristics of the receptor channels may also be different. For example, the depolarization of motor nerve endings initiated by administration of acetylcholine can be prevented by tetrodotoxin, a specific blocker of sodium flux with no effect on the end plate.

Specific information on the molecular organization of the neuronal nicotinic receptors on motoneuron terminal is lacking, but work on other parts of the nervous system (e.g., the brain and ganglia) indicate that they are structurally quite different from those found on the postjunctional muscle membrane. [52] [53] Some of the subunit composition is similar, but other subunits do not resemble that of the postjunctional receptor. At least ten different gene products (alpha $_2$ to alpha$_8$ and beta$_2$ to beta$_4$) are thought to contribute nicotinic receptors expressed in neurons. Most strikingly, nervous tissue does not contain genes for gamma-, delta- or epsilon-receptor subunits; it contains only the genes for alpha- and beta-subunits. Furthermore, the alpha- and beta-subunit genes in nerve and muscle are not exactly the same; they are variants. Muscle contains only one gene for each subunit, which are now termed alpha $_1$ and alpha$_1$ -subunit. By contrast, nervous tissue contains neither of these but rather contains a number of related genes termed alpha $_2$ through alpha$_8$. To emphasize the distinction between neural and muscle nicotinic receptors, the former are termed Nn and the latter Nm. With so many different subunits available, there are many possible combinations, and it is not known which combinations are found in motor nerves. Their physiologic roles have also not been completely characterized.

The nicotinic receptor in the nerve ending of the neuromuscular junction may serve the function of regulator of transmitter release, as shown in other parts of the nervous system. The nicotinic receptor on the junctional surface of the nerve senses transmitter in the cleft and, by a positive feedback system, causes the release of more transmitter. In other parts of the nervous system, this positive feedback is complemented by a negative one, which senses when the concentration of transmitter in the synaptic cleft has increased appropriately and shuts down the release system. Indirect evidence suggests that these receptors are muscarinic cholinergic receptors. Convincing data that motor nerve endings contain muscarinic receptors or a negative feedback system are not yet available for the motor neuron. The nerve ending is also known to bear several other receptors (e.g., opioid, adrenergic, dopamine, purine, and adenosine receptors, and receptors for endogenous hormones, neuropeptides, and a variety of proteins). The physiologic roles of these or of the effects of anesthetics on them are unknown.

The motor nerves take up choline, synthesize acetylcholine, store it in vesicles, and move the vesicles into position to be released by a nerve action potential, a series of processes known collectively as *mobilization.* Muscle relaxants to a greater or lesser extent, however, seem to influence this mobilization process. Tubocurarine and related muscle relaxants have a profound effect in decreasing the nerve's capacity to prepare more acetylcholine for release. Tubocurarine has no direct effect on the release process for acetylcholine; the amount of transmitter released is controlled by the availability of releasable acetylcholine and the amount of calcium that enters the nerve. Although it has frequently been observed that nondepolarizing relaxants do not diminish the transmitter released by a single nerve impulse or the first in a high-frequency train of impulses, they sharply decrease the release triggered by subsequent nerve pulses in the train. The most common manifestation of this is the so-called *tetanic fade* commonly seen after a nondepolarizing relaxant is administered. This effect is thought to be due to inhibition of the process that replenishes releasable acetylcholine. [3]

/das/book/view/29494766/875/214.html

ANTAGONISM OF NEUROMUSCULAR BLOCK

Mechanism of Antagonism

The nondepolarizing relaxants block (also see Ch. 12) neuromuscular transmission predominantly by competitive antagonism of acetylcholine at the postjunctional receptor. Therefore, the most straightforward way to overcome their effects is to increase the competitive position of acetylcholine. Two factors are important, the first of which is the concentration of acetylcholine. Increasing the number of molecules of acetylcholine in the junctional cleft changes the agonist/antagonist ratio and increases the probability that agonist molecules will occupy the recognition sites of the receptor. It also increases the probability that an unoccupied receptor will become occupied. It should be recalled that normally only about 500,000 of the 5 million available receptors are activated by a single nerve impulse, and so a large number of receptors are in "reserve" and could be occupied by an agonist. The second factor important to the competitive position of acetylcholine is the length of time acetylcholine is in the cleft. Acetylcholine must wait for the antagonist to dissociate spontaneously before it can compete for the freed site. The nondepolarizing relaxants bind to the receptor for slightly less than 1 millisecond, which is longer than the normal lifetime of acetylcholine. To put it another way, the destruction of acetylcholine normally takes place so quickly that most of it is destroyed before any significant number of antagonist molecules have dissociated from the receptor. Prolonging the time during which acetylcholine is in the junction allows time for the available acetylcholine to bind to receptor, when the antagonist dissociates from the receptors.

Classes of Drugs Used

Two classes of drugs, potassium channel-blocking drugs and acetylcholinesterase inhibitors, are used clinically to reverse

non-depolarizer-induced paralysis. The best known of the potassium blocking drugs is 4-aminopyridine. Its actions are predominantly prejunctional; it impedes the efflux of potassium from the nerve ending. Since the efflux of potassium is the event that normally ends the action potential of the nerve ending, this action prolongs the depolarization of the nerve. Because the flux of calcium into the nerve continues for as long as the depolarization lasts, drugs of this class indirectly increase the flux of calcium into the nerve ending. Therefore, the nerve releases more acetylcholine and for a longer time than usual, conditions described previously, which are effective in antagonizing nondepolarizing relaxants. Because they act prejunctionally, these drugs can antagonize a block produced by certain antibiotics that act on the nerve ending, notably the polymyxins. Although 4-aminopyridine and drugs like it can be used clinically, their use is severely restricted because they are not specific. They affect the release of transmitters by all nerve endings, including motor nerves, autonomic nerves, and central nervous system components. Accordingly, their use is accompanied by a variety of undesirable effects, and in practice they are used only in special circumstances. A most serious side effect of potassium channel blockers is seizures.

The more commonly used antagonists of neuromuscular block (e.g., neostigmine, pyridostigmine, and edrophonium) all inhibit acetylcholinesterase by mechanisms that are similar but not identical. [54] Neostigmine and pyridostigmine are attracted by an electrostatic interaction between the positively charged nitrogen in the molecules and the negatively charged catalytic site of the enzyme. This produces a carbamylated enzyme, which is not capable of further action (i.e., the catalytic site is blocked and the enzyme is inhibited). Edrophonium has neither an ester nor a carbamate group, but is attracted and bound to the catalytic site of the enzyme by the electrostatic attraction between the positively charged nitrogen in the drug and the negatively charged acetylcholinesterase site of the enzyme. Edrophoniuim also seems to have prejunctional effects, enhancing the release of acetylcholine from the nerve terminal. This effect is, therefore, useful when deep neuromuscular block needs reversal. Of the three commonly used anticholinesterases, edrophonium shows by far the greatest selectivity between acetylcholinesterase and butyrylcholinesterase, the serum esterase that hydrolyzes succinylcholine and mivacurium. It greatly favors the former enzyme and therefore would seem to be the most desirable agent to reverse mivacurium. However, assuming that the patient has normal serum esterase, pharmacokinetic factors are the principal determinants of the duration of blockade, and the activity of serum esterase or the lack of it plays only a minor role in the recovery. Therefore, there is little reason to prefer one or another reversal drug on these grounds.

The cholinesterase inhibitors do not only act preferentially at the neuromuscular junction but also act at other synapses that use the same transmitter, including muscarinic receptors. Thus, it is desirable to administer an atropine-like drug along with the cholinesterase inhibitor to counter the effects of the acetylcholine that accumulates in the muscarinic synapses of the gut, bronchi, and cardiovascular system. These three anticholinesterase inhibitors do not affect synapses in the central nervous system because all are quaternary ammonium ions, which do not easily penetrate the blood-brain barrier. Therefore, a quaternary ammonium derivative of atropine, such as glycopyrrolate, which does diffuse through the blood-brain barrier, frequently is used to limit the anticholinergic effects to the periphery. Other cholinesterase inhibitors, notably physostigmine and tacrine, are not quaternary ammonium compounds, and they have profound effects in the central nervous system. These may be antagonized by atropine but not by its quaternary ammonium analogue derivatives. Unlike the other cholinesterase inhibitors, physostigmine and tacrine are also potent inhibitors of the enzyme phosphodiesterase, which plays an important role in the regulation of transmitter release at many synapses in the central nervous system. This action may be related to the reported efficacy of these two in the treatment of Alzheimer's dementia.

Cholinesterase inhibitors also have actions at the postjunctional membrane, independent of its effects on the enzyme. Several of these compounds contain methyl groups on a positively charged nitrogen, and they can act as agonists on the receptor channels, initiating ion flow and enhancing neuromuscular transmission. It was noted long ago that neostigmine, physostigmine, and certain organophosphates can increase the frequency of MEPPs and increase the quantal content of end plate potentials, but the importance of the increased transmitter release to reversal of neuromuscular blockade is not known. Also, continuous exposure to the carbamate- or organophosphate-containing inhibitors causes degeneration of pre- and postjunctional structures, apparently because these structures accumulate toxic amounts of calcium. The neural actions of these drugs are prevented by calcium channel blockers such as verapamil. All the drugs of this class also act in or on receptors to influence the kinetics of the open-close cycle and to block the ion channel. [37] [38] The clinical significance of the drugs on reversal of nondepolarizers is not known.

SUMMARY

The neuromuscular junction provides a rich array of receptors and substrates for drug action. Several drugs used clinically have multiple sites of action. The muscle relaxants are not exceptions to the rule that most drugs have more than one site or mechanism of action. The major actions seem to occur by the mechanisms and at the sites described for decades, namely, agonistic and antagonistic actions at postjunctional receptors for depolarizing and nondepolarizing relaxants, respectively. This description of neuromuscular drug action is a simplistic one. Neuromuscular transmission is impeded by nondepolarizers because they prevent access of acetylcholine to its recognition site on the postjunctional receptor. If the concentration of nondepolarizer is increased, another, noncompetitive action, namely block of the ion channel, is superimposed. The paralysis is also potentiated by the prejunctional actions of the relaxant preventing the release of acetylcholine. The latter can be documented as fade that occurs with increased frequency of stimulation. Therefore, a more accurate description of the relaxant effects recognizes that the neuromuscular junction is a complex system and a dynamic one, in which the phenomena produced by drugs are composites of actions that vary with drug, dose, activity in the junction and muscle,

---

time after administration, the presence of anesthetics or other drugs, and the age and condition of the patient. Inhibition of the postjunctional acetylcholinesterase by anticholinesterases increases concentration of acetylcholine, which can compete and displace the nondepolarizerreversing paralysis. These anticholinesterases also have other effects, including those on nerve terminals and on the receptor, by an allosteric mechanism.

Depolarizing compounds initially react with the acetylcholine recognition site and, like the transmitter, open ion channels and depolarize the end plate membrane. Unlike the transmitter, they are not subject to hydrolysis by acetylcholinesterase and so remain in the junction. Soon after administration of the drug, some receptors are desensitized and, although occupied by an agonist, do not open to allow current to flow to depolarize the area. If the depolarizing relaxant is applied in high concentration and allowed to remain at the junction for a long time, other effects occur. These include entry of the drug into the channel to obstruct it or to pass through it into the cytoplasm. Depolarizing relaxants also have effects on prejunctional structures, and the combination of pre- and postjunctional effects plus secondary ones on muscle and nerve homeostasis results in the complicated phenomenon known as phase II blockade.

Intense research in the area of neuromuscular transmission continues at a rapid pace. The newer observations on receptors, ion channels, membranes, and prejunctional functions reveal a much broader range of sites and mechanisms of action for both agonists and antagonists and thereby allow a more complete understanding. In recognizing these sites and mechanisms we begin to bring our theoretical knowledge closer to explaining the phenomena observed when these drugs are administered to living humans. Most of the recent work seems to be focused on the postjunctional membrane and the control of acetylcholine receptor expression in normal and diseased states. The presence or absence of the mature and immature isoform seem to complicate matters further. In certain pathologic states (e.g., sepsis, burns, immobilization, and chronic use of relaxants), upregulation of acetylcholine receptors occurs, usually with expression of the immature isoform. The altered functional and pharmacologic characteristics of these receptors results in increased sensitivity with hyperkalemia to succinylcholine and resistance to nondepolarizers. An area of increasing attention is the control of the expression of mature versus immature receptors and the role of the immature isoform of the receptor in the muscle weakness associated with the critical illnesses enumerated previously. The immature isoform expression is probably related to aberrant growth factor signaling, which may also cause apoptosis in muscle. Loss of muscle mass due to apoptosis may contribute to the muscle weakness of critical illness. In the future, it may be possible to manipulate the signaling mechanism to alter the expression of the receptor isoforms, attenuate apoptosis, and possibly improve muscle functions. Alternately, these could be achieved by gene therapy.

References

1. Martyn JAJ, White DA, Gronert GA, et al: Up-and-down regulation of skeletal muscle acetylcholine receptors. Anesthesiology 76:822, 1992.

2. Drachman DB: Myasthenia gravis. N Engl J Med 330:1797, 1994.

3. Bowman WC, Prior C, Marshall IG: Presynaptic receptors in the neuromuscular junction. Ann N Y Acad Sci 604:69, 1990.

4. Fletcher GH, Steinbach JH: Ability of depolarizing neuromuscular blocking drugs to act as partial agonists at fetal and adult mouse muscle nicotinic receptors. Mol Pharmacol 49:938, 1996.

5. Lukas RJ, Bencherif M: Heterogeneity and regulation of nicotinic acetylcholine receptors. Int Rev Neurobiol 34:25, 1992.

6. Tansey MG, Chu GL, Merlie JP: Aria/HRG regulates AChR epsilon subunit gene expression at the neuromuscular synapse via activation of PI3Kinase and RAS/MAPK pathway. J Cell Biol 134:465, 1996.

7. Hall Z, Merlie JR: Synaptic structure and development: The neuromuscular junction. Cell 72:99-121, 1993.

8. Witzeman V, Brenner HR, Sakman B: Neural factors regulate AChR subunit mRNAs at rat neuromuscular synapses. J Cell Biol 114:125, 1991.

9. Kelly RB: The cell biology of the nerve terminal. Neuron 1:431, 1988.

10. Taylor P, Schumacher M, MacPhee-Quingley K, et al: The structure of acetylcholinesterase: Relationship to its function and cellular disposition. Trends Neurosci 10:93, 1987.

11. Catterall WA: Structure and functions of voltage-gated ion channels. Ann Rev Biochem 64:493, 1995.

12. Durant NN, Katz RL: Suxamethonium. Br J Anaesth 54:195, 1982.

13. Betz WJ, Caldwell JH, Kinnamon SC: Increased sodium conductance in the synaptic region of rat skeletal muscle fibres. J Physiol (Lond) 352:189, 1984.

14. Vincent A, Newland C, Croxen R, et al: Genes at the junction: Candidates for myasthenic syndrome. Trends Neurosci 20:15, 1997.

15. Goudsouzian NG, Standaert FG: The infant and the myoneural junction. Anesth Analg 65:1208, 1986.

16. Heuser JE, Reese TS: Structural changes after transmitter release at the frog neuromuscular junction. J Cell Biol 88:564, 1981.

17. Rash JE, Walrond JP, Morita M: Structural and functional correlates of synaptic transmission in the vertebrate neuromuscular junction. J Electron Microsc Tech 10:153, 1988.

18. Katz B, Miledi R: Estimates of quantal content during "chemical potentiation" of transmitter release. Proc R Soc Lond [Biol] 215:369, 1979.

19. Uchitel OD, Protti DA, Sanchez V, et al: P-type voltage dependent calcium channel mediates presynaptic calcium influx and transmitter release in mammalian synapses. Proc Natl Acad Sci U S A 89:3330, 1992.

20. Waterman S, Pinto A, Lang B, et al: The role of autoantibodies in Lambert-Eaton myasthenic syndrome. Ann N Y Acad Sci 84:596, 1998.

21. Llinas R, Sugimori M, Silver RB: Microdomains of high calcium concentration in a presynaptic terminal. Science 256:677, 1992.

22. Valtorta F, Jahn R, Fesce R, et al: Synaptophysin (p38) at the frog neuromuscular junction: Its incorporation into the axolemma and recycling after intense quantal secretion. J Cell Biol 107:2717, 1988.

23. Gu Y, Forsayeth JR, Verall S: Assembly of the mammalian muscle acetylcholine receptor in transfected COS cells. J Cell Biol 114:799, 1991.

24. Changeux J-P, Edelstein SJ: On allosteric transitions and acetylcholine receptors. Trends Biochem 19:399, 1994.

25. Kopta C, Steinbach JH: Comparison of mammalian adult and fetal nicotinic acetylcholinic receptors stably expressed in fibroblasts. J Neurosci 14:3922, 1994.

26. Pedersen SE, Cohen JB: d-tubocurarine binding sites are located at the alpha-gamma, alpha-delta interphases of the nicotinic acetylcholine receptor. Proc Natl Acad Sci U S A 87:2785, 1990.

27. Griesmann GE, McCormick DJ, De Aizpurua HJ, et al: alpha-bungarotoxin binds to human acetylcholine receptor alpha-subunit peptide 185-199. J Neurochem 54:1541, 1990.

28. Barrantes FJ: Muscle end plate cholinoceptors. Pharmacol Ther 38:331, 1988.

29. McCarthy MP, Stroud RM: Conformational states of the nicotinic acetylcholine receptor from *Torpedo californica* induced by the binding of agonist, antagonists, and local anesthetics. Equilibrium measurements using tritium-hydrogen exchange. Biochemistry 28:40, 1989.

30. Karlin A, DiPaola M, Kao PN, Lobel P: Functional sites and transient states of the nicotinic acetylcholine receptor. In Hille B, Fambrough DM (eds): Proteins of Excitable Membranes. Society of General Physiologists. New York, Wiley Interscience, 1987, p 43.

31. Marban E, Yamagishi T, Tomaselli GF: Structure and function of voltage-gated sodium channels. J Physiol 508:647, 1998.

---

32. Dionne VE: Two types of nicotinic acetylcholine receptors at slow fibre end-plates of the garden snake. J Physiol 409:313, 1989.

33. Raines DE: Anesthesia and nonanesthetic volatile compounds have dissimilar activities on nicotinic acetylcholine receptor desensitization kinetics. Anesthesiology 84:663, 1996.

34. Miller KW, Wood SC, Forman SA, et al: The nicotinic acetylcholine receptor in its membrane environment. Ann N Y Acad Sci 625:600, 1991.

35. Gage PW, Hammill OP: Effects of anesthetics on ion channels in synapses. Int Rev Neurophysiol 25:3, 1981.

36. Swope SL, Qu Z, Huganir RL: Phosphorylation of nicotinic acetylcholine receptor by protein tyrosine kinases. Ann N Y Acad Sci 757:197, 1995.

37. Albuquerque EX, Alkondon M, Pereira EF, et al: Properties of neuronal nicotinic acetylcholine receptors: Pharmacologic characterization and modulation of synaptic function. J Pharmacol Exp Ther 280:1117, 1997.

38. Maelicke A, Coban T, Storch A, et al: Allosteric modulation of Torpedo nicotinic acetylcholine receptor ion channel activity by noncompetitive agonists. J Receptor Signal Transduc Res 17:11, 1997.

39. Creese R, Head SD, Jenkinson DF: The role of the sodium pump during prolonged end-plate currents in guinea-pig diaphragm. J Physiol 384:377, 1987.

40. Martyn JAJ: Basic and clinical pharmacology of the acetylcholine receptor: Implications for the use of neuromuscular relaxants. Keio J Med 44:1, 1995.

41. Tomera JF, Martyn JAJ: Intraperitoneal endotoxin but not protein malnutrition shifts d-tubocurarine dose-response curves in mouse gastrocnemius. J Pharmacol Exp Ther 250:216-220, 1989.

42. Meier T, Hauser DM, Chiquet M, et al: Neural agrin induces ectopic synaptic specialization in innervated muscles. J Neurosci 17:6534, 1997.

43. Faragher MW, Day BJ, Dennett X: Critical care myopathy: An electrophysiological and histological study. Muscle Nerve 19:516, 1996.

44. Zifko UA, Zipko HT, Bolton CF: Clinical and electrophysiological findings in initial illness polyneuropathy. J Neurol Sci 159:186-193, 1998.

45. Beeson D, Newland C, Croxen R, et al: Congenital myasthenic syndromes: Studies of the AChR and candidate genes. Ann N Y Acad Sci 841:181, 1998.

46. Witzemann V, Schwartz H, Koenen M, et al: Acetylcholine receptor epsilon-subunit deletion causes muscle weakness and atrophy in juvenile and adult mice. Proc Nat Acad Sci U S A 93:13286, 1996.

47. Altiok N, Altiok S, Changeaux JP: Heregulin-stimulated acetylcholine receptor gene expression in muscle: Requirement for MAP kinase and evidence for a parallel inhibitory pathway independent of electrical activity. EMBO J 16:717, 1997.

48. Ikezu T, Okamoto T, Martyn JAJ: Analysis of thermal injury-induced insulin resistance in rodents: Implication of post-receptor mechanism. J Biol Chem 272:25289, 1997.

49. Olivetti G, Abbi R, Quaini F, et al: Apoptosis in the failing human heart. N Engl J Med 336:1131, 1997.

50. Yasuhara S, Ibebunjo C, Martyn JAJ: Loss of muscle mass in burns: Is apoptosis involved? J Burn Care Rehab 19:S241, 1998.

51. Deneris ES, Connolly J, Rogers SW: Pharmacological and functional diversity of neuronal nicotinic acetylcholine receptors. Trends Pharmacol Sci 12:34, 1991.

52. Galzi JL, Changeux JP: Neuronal nicotinic receptors: Molecular organization and regulation. Neuropharmacology 34:563, 1995.

53. Coggan JS, Paysan J, Conroy WG, et al: Direct recording of nicotinic responses in presynaptic nerve terminals. J Neurosci 17:5798, 1997.

54. Taylor P: Anticholinesterase agents. In Gilman AG, Goodna LS, Rall TW, Murad F, (eds): Pharmacological Basis of Therapeutics, 7th ed. New York, Macmillan, 1995, p 110.

Chapter 21 - Research Design and Statistics in Anesthesia

Dennis M. Fisher

INTRODUCTION

The process by which new information is acquired in anesthesia and in most medical specialties has changed. Traditionally, many issues of interest to anesthesiologists could be examined by descriptive, noncomparative studies such as one describing the physiologic effects of a new anesthetic. Although such studies provided valuable information to guide the clinician in the use of new anesthetics or devices, they often did not focus on comparisons with other drugs or techniques. In addition, outcomes research (which I define as the influence of an anesthetic practice on such outcomes as patient survival, satisfaction, or morbidity) was quite rare. In recent years and decades, the focus has changed so that the emphasis of many investigations is on a comparison among techniques. In addition, outcome studies examining such important issues as cardiovascular morbidity and mortality after surgery are now common. In this changing context of research, this chapter, formerly entitled "Statistics in Anesthesia," has been revised to examine a broader set of issues. In particular, a new section provides an overview of issues related to the design and conduct of research studies. This new material is not designed to be a comprehensive primer to guide researchers in research design. Rather, its intent is to provide an introduction to which "users" can refer, to assist in their critical assessment of published or unpublished materials. My assumption is that the critical reader of the medical literature will be better equipped to judge the quality of medical research if issues regarding research design and analysis are better understood. Although laboratory-based research now appears with greater frequency in the anesthesia literature than in past years, my efforts focus on clinically relevant research. In order to follow the logical approach that research design precedes analysis, the new section on research design precedes the section on analysis. However, the discussion of research design often requires some understanding of statistical techniques. Therefore, the reader may need to move between the two sections.

Mention of the word *statistics* evokes in many members of the medical community two responses: first, a recognition of its necessity for research, and second, distaste. This distaste results from a number of sources--the limited (and often incomprehensible) teaching provided in many courses, the inconsistent terminology used by different investigators, the frequency with which statistics is used to mislead rather than to clarify, and finally, a wariness of mathematics. Those who are not knowledgeable about the language and techniques of statistics may believe that journal editors ensure the appropriateness and accuracy of statistical techniques used in their publications. Unfortunately, this may not be true: several reviews have demonstrated a high incidence of statistical errors in reputable journals. [1] [2] In response to these criticisms, one journal, *Circulation Research,* adopted

the policy that articles accepted for publication must undergo review by a statistician. [3] This policy has not been widely accepted, probably because of potential delays in the editorial process and the additional costs of using a statistical advisor. However, one major anesthesia journal, *Anesthesiology,* added a statistical consultant to its editorial board.

In recent decades, emphasis on statistical analysis in research studies has increased. Readers tend to believe that any conclusion accompanied by the statement " $P < .05$" is true; conversely, all observations not supported by that statement are believed to be untrue. This emphasis on statistical significance has encouraged investigators to focus their analyses on statistical testing rather than on actually examining individual data points. When data have been collected, the investigator might call on one of several resources such as a hand-held calculator, a computer, or even a statistician (many of whom lack expertise in the statistical concerns relating to medicine). The raw data are entered, along with instructions on which test is desired, and the investigator is rewarded with a number of statistical results. For example, when data are analyzed by linear regression, the output from a computer program might state " $P < .001$." If the investigator does not understand terms such as *within-groups variance, residual mean square,* or *standard error of the estimate,* the statement " $P < .001$" suggests that the data show a strong statistical association. As examined later, for linear regression, the validity of the association is better supported by other statistical statements. However, the uninitiated researcher is usually pleased with the probability associated with this *P* value and may not devote additional time to interpreting or understanding the results. Of greater importance, he or she may not realize that these results do not ensure that a statistical difference exists, that the correct statistical test was employed, or even that the study was performed in a manner that permits any conclusions to be drawn. [4] Gaining a thorough knowledge of statistical techniques requires much time and energy. However, most statistical techniques used in medical research are simple. Emerson and Colditz [5] reviewed the statistical tests employed in original articles published in the *New England Journal of Medicine* from 1978 to 1979. These investigators found that seven statistical techniques (descriptive tests, *t*-tests, contingency tables, nonparametric tests, epidemiologic statistics, Pearson correlation, and simple linear regression) made up 82 percent of all the tests used in these studies. A compilation of the statistical tests used in manuscripts in *Pediatrics*[6] demonstrates similar findings, as does a review [7] of the two major U.S. anesthesia journals, *Anesthesiology* and *Anesthesia and Analgesia.*

This chapter introduces the reader to the principles governing these simple statistical tests. After the new section on research methodology and study design, descriptive statistics (how to examine and describe data) and the concept of probability are discussed. These concepts are then used to examine the principles of inferential statistics (i.e., using statistics to draw conclusions). For each statistical test, the mathematic derivation of that test and examples are provided.

The statistical techniques appropriate for most medical research have changed little in recent years. However, the techniques actually used by investigators have changed, a result of several factors. First, many investigators have learned the utility of nonparametric approaches. Second, particularly in anesthesia, investigators have become aware of the power of such techniques as repeated-measures analysis of variance (described later). Finally, the increasing number of outcome studies in anesthesia has required introduction of some epidemiologic methods previously rarely used in the anesthesia literature. In response, this chapter includes sections on power analysis (prospective determination of sample size), the Fisher exact test, nonlinear regression techniques (including logistic regression), and relative risks. With these additions, the investigator is offered an exposure to techniques useful for most statistical analyses.

RESEARCH METHODOLOGY AND STUDY DESIGN

On occasion, an investigation begins without a welldesigned plan regarding the design of the study and the sta-tistical analysis. After the study is under way or completed and the investigators have accumulated a large mass of data, they begin to contemplate its analysis. Unfortunately, in many instances, data are collected in an inappropriate manner, or the study was not designed to permit the question of interest to be answered. This chapter is not designed to address the many issues related to study design; instead, the reader is referred to other sources such as a recent monograph, *Medical Uses of Statistics,*[8] published by the *New England Journal of Medicine.* Unfortunately, much research effort has been wasted by not considering issues of study design or the type of statistical analysis prior to beginning the study.

Research interests in the anesthesia community have changed in recent years. Earlier research efforts focused on issues such as the physiologic effects of anesthetic techniques or pharmacologic agents. These studies were typically performed on small numbers of subjects, and statistical analysis was often descriptive or consisted of simple tests such as analysis of variance. As anesthetic and surgical techniques improved such that perioperative risk is now minimal, and as society has begun to question the cost-benefit ratio of medical therapy, the focus of medical research has shifted toward questions related to this cost-benefit ratio. Other medical specialties adopted these approaches a decade ago. For example, internists examined issues such as the cost-benefit ratio of a newer, expensive antibiotic or the efficacy of single versus multiple doses of antibiotics. In recent years, members of the anesthesia community, led by pioneers such as Dennis Mangano, have asked similar questions about anesthesia care.

One problem inherent to outcomes research in anesthesia results from our tremendous success in providing medical care without adverse outcomes. Consider a trial examining efficacy of a new antibiotic to treat a resistant infection. If the traditional therapy failed in 40 percent of patients, and we expected the new treatment to fail in fewer than 20 percent of patients (and its exorbitant cost could be justified only if its success rate attained this level or better), a power analysis reveals that a sample size of 128 patients (64 in each group) would be sufficient to "ensure" success of a clinical trial (Table 21-1) . One can readily imagine the drug's manufacturer sponsoring two or more clinical trials with this number of patients.

TABLE 21-1 -- Sample Sizes Needed to Detect a 50 Percent Decrease in the Incidence of an Adverse Event with a *P* Value of 5 Percent and 80 Percent Power

INCIDENCE IN CONTROL GROUP (%)	NUMBER PER GROUP (*n*)
40	64
10	342
1	3681

In contrast, the expected outcome of anesthesia and surgery is "success," and the expected "failure" rate, be it death, heart failure, or some other severe adverse outcome, is small. If the expected death rate after cardiac surgery were 1 percent, and we wanted to demonstrate that an intervention improved this to 0.5 percent (this is probably an unreasonable increment in successful outcome when one considers the multifactorial nature of severe adverse events during anesthesia), a sample size of 7,362 patients (3,681 in each group) would be necessary. This leads to an obvious problem. Who is willing to pay for one or more trials of this magnitude?

Selecting an Outcome or Surrogate Outcome

A clinically based profession such as anesthesia generates many questions of interest. For example, clinicians want to know whether a new antiemetic improves the patient's course relative to postoperative nausea and vomiting (PONV) or whether a drug given during cardiopulmonary bypass improves the perioperative course of patients undergoing coronary artery bypass grafting. Although these are but two of many questions important to clinical anesthesia, I use them as examples of statistical analyses.

The incidence of PONV in control (typically, placebo) groups ranges from 20 to 70 percent, and treatment with various drugs may decrease this incidence by 20 percent. In contrast, the incidence of perioperative myocardial infarction (MI) in control groups is much lower, probably 1 to 5 percent. This difference in the incidence of the adverse events in the control group has tremendous implications for study design. If the investigator expects that the "treatment" (i.e., the drug or monitoring device or any intervention that distinguishes a group from the control group) will improve outcome 2-fold, an expected incidence of vomiting of 50 percent in a control group might decrease to 25 percent with treatment; similarly, an incidence of MI may decrease from 1 percent in the control group to 0.5 percent with treatment. The sample size sufficient to demonstrate statistical significance differs between these two outcomes and might be prohibitive for the MI end point (see Table 21-1) but not for the PONV end point. Rather than discarding the MI issue as untestable, the investigator might choose to study a surrogate outcome measure instead. For MI, a surrogate outcome might be the incidence of electrocardiographic (ECG) changes consistent with ischemia. In certain instances, a surrogate marker may be desirable, not because it occurs more frequently, but because it can be measured more readily. For example, costs of medical care are often difficult to assess, but charges can be quantified more easily.

An ideal surrogate marker is one that is easy to measure and is sufficiently common to permit the study to be performed with a reasonable sample size. A second consideration is that changes in the incidence of surrogate measures must reflect changes in the incidence of the true measure. If it were known that under a variety of circumstances, 20 percent of patients who show ECG signs of ischemia develop MI, it might be reasonable to study the incidence of ECG changes rather than that of MI. However, if one anesthetic technique led to a frequent occurrence of ECG changes but not to MI, whereas another technique led to the same frequent occurrence of ECG signs and frequent MI, studies involving the surrogate outcome should not be extrapolated to predict the incidence of the true outcome.

It seems intuitive to assume that the percentage of patients free of PONV correlates well with patient satisfaction. Several factors militate against this correlation. [9] First, antiemetics may induce adverse effects that diminish their utility. An example is the demonstration by Tramer et al [10] that, although ondansetron decreases the incidence of PONV, it increases the incidence of headache and abnormalities in liver enzymes. Second, an analysis in which the occurrence of vomiting is treated dichotomously fails to distinguish between a patient with a single minor episode of vomiting 10 minutes after arrival in the postanesthetic care unit (to whom this episode is of no consequence) and another with persistent vomiting that delays discharge by 2 hours. If the true motivation to decrease the incidence of PONV is to improve patient satisfaction or to decrease the incidence of prolonged in-hospital recovery (e.g., rather than to decrease the soiling of linen), then the adverse effects of treatment might be sufficient to overcome or even overwhelm any potential benefits. However, if the intent is to measure costs (including the soiling of linen or

nursing activities related to cleaning patients), then all episodes of vomiting might be of equal importance.

A commonly used and problematic surrogate marker is hospital charges instead of costs. One such study examined whether (nonrandomized) extubation in the operating room versus the intensive care unit (ICU) decreased hospital charges. [11] In that the hospital's policy was to charge separately for ventilatory support provided before and after midnight, a patient who arrived in the ICU 1 hour before midnight and who was extubated 1.5 hours later would be charged for 2 days of support, whereas another patient ventilated for 12 hours but extubated before midnight would be charged for only 1 day. Even though the second patient used far fewer resources, the peculiarities of the accounting system resulted in larger charges for that patient. In that hospitals charge in a manner inconsistent with costs (a practice that insurance companies now recognize and reimburse hospitals accordingly), it seems imprudent to perform any analysis using charges rather than costs.

Perhaps most problematic in the use of surrogate outcomes is the failure of investigators to identify them as such. Many studies of PONV claim that a decreased incidence of PONV "should" lead to a decreased incidence of unanticipated hospital admission, fewer prolonged recovery room stays, and improved patient satisfaction. Yet, many of these studies do not measure these outcomes, but instead count

the incidence of patients free of PONV, despite the lack of studies that demonstrate the association of surrogate and true outcomes.

Despite my criticism of the use of surrogate outcomes in anesthesia research, [9] there are instances in which their use is inevitable. The most obvious of these is when the incidence of the true outcome is so small in the treatment group that no reasonable sample size would attain statistical significance. However, whenever a surrogate outcome is used, the investigator should acknowledge its use and the resulting limitations. Although the expected more frequent occurrence of the surrogate outcome makes it more likely that the investigator will demonstrate statistical significance, the investigator must be cautious not to extrapolate a positive finding with the surrogate outcomes to one regarding the true outcome.

Randomized Clinical Trials

Traditionally, most clinical studies in anesthesia were randomized clinical trials (RCT). There were several advantages to this approach. First, the investigator could control the design precisely, thereby ensuring that the data obtained would permit examination of the question of interest. Second, the study could be both randomized and blinded, both of which are important to minimize bias. Third, the investigator could perform a power analysis before the study to determine how many subjects should be studied to ensure sufficient power.

Randomization and Blinding

The hallmark of an RCT is that, if possible, both the investigator and the patient are blinded to the treatment to which each patient is assigned. In addition, treatments are assigned using some type of randomization procedure. Use of both of these approaches minimizes the opportunity for bias. Although investigators may claim that their nonrandomized, nonblinded studies are not biased, it is often difficult for them to demonstrate this convincingly. Bias can be introduced to studies in many subtle ways. In a well-publicized violation of the design of a multicenter trial of therapy for breast cancer, one investigator violated certain enrollment criteria because of a personal belief that treatment was effective. [12] [13] Had this violation not been identified by the study's coordinators, the results of the study might have been compromised. During the enrollment interview for an anesthesia study, a patient may report himself or herself to be at higher-than-average risk for a postoperative complication under investigation. An investigator who is aware of the group assignment may provide subtle clues that may influence the patient's willingness to participate. Unless there are compelling reasons that a trial cannot be both randomized and blinded, both should be demanded from investigators.

Single Center Versus Multicenter Trials

Occasionally, the investigator planning a study might determine that an RCT in his or her institution could not enroll sufficient subjects to demonstrate statistical significance, even if the trial were conducted for years. Demonstrating an improvement in adverse outcomes from 1.0 to 0.5 percent requires more than 7,000 patients, certainly a daunting task. In response, the investigator might invite 9 or 99 other investigators to participate, thus decreasing the number of subjects per center from 7,362 to 736 or 74. The last number is certainly closer to the range of sample sizes that one could obtain in a reasonable time frame, making the multicenter approach desirable. Although the multicenter approach presumably ensures that the study will be conducted more rapidly, it also incurs risks. Perhaps most significant of these risks (because of its subtlety) is the possibility that individual centers will deviate from the protocol in ways that influence outcome, but are not identified by the investigators.

Once the decision is made to involve more than a single center in a trial, several problems appear. An obvious one is that the results may differ among institutions, a function of differences in patient population, surgical technique, surgical skills, or other "covariates." For example, a new therapy (that we "know" to be effective) may be designed to decrease the quantity of blood lost perioperatively in patients undergoing cardiac surgery. Figure 21-1 displays simulated data from three centers in which this therapy was compared to a placebo group. Note that within each center, the effect of the treatment is evident and statistical significance is attained, despite a small sample size. However, a pooled analysis (as would be the statistical approach used to analyze this multicenter trial) fails to demonstrate statistical significance, a result of large intercenter differences in blood loss in both control and treatment groups. Thus, although the multicenter approach speeds collection of the data, it compromises the results. Fortunately, statistical techniques (in this instance, a linear data transform) exist to address this particular problem. The average value for blood loss at each center can be subtracted from the value for each subject. This approach, termed "centering the data," improves the statistical power of the analysis. However, statistical "manipulations" of this sort should be adopted a priori, that is, before the study is conducted.

Tight Versus Loose Control of Studies

The implications of tight versus loose control of experimental conditions should be considered. For example, one might conduct a study in which vigorous attempts are made to control blood pressure in both treatment and control groups versus one in which a significantly broader (yet still clinically acceptable) range of blood pressures was allowed in both groups. The incidence of adverse outcomes (the focus of this study) might be markedly lower in both treatment and control groups in which blood pressure was well controlled. Although this finding might lead to the conclusion that tight control of blood pressure is desirable to minimize adverse outcomes, that is not the stated goal of this study. However, adverse events might be so infrequent in the groups with tight control that one might not be able to demonstrate a benefit to the treatment under investigation. If "tight" control is realistic only in a research setting, then application of the results of this trial to the clinical environment might be limited.

Figure 21-1 Simulated data from a three-center clinical trial is shown. Each panel displays measured blood loss in two groups of ten patients. The control group at each center received a placebo, and the treatment group received a therapeutic agent designed to decrease blood loss. When data for the three centers are pooled, statistical significance is not attained. However, within each center, the data demonstrate statistical significance. This example illustrates how increasing sample size by increasing the number of sites included in a study may not necessarily improve (and, in this simulated instance, may actually worsen) statistical power.

Large Databases

In many instances, the opportunity to perform an RCT is limited. For example, the projected sample size might be so large as to make the cost of a study prohibitive, or the interested investigator might be someone who is unable to conduct a clinical trial but who has the ability to analyze data. In these instances, another source of data for analysis might be observational databases. With the advent of electronic data collection, organizations such as hospitals, health care systems, regulatory bodies, and governmental agencies compile massive quantities of data regarding health care outcomes that might be relevant to clinical research. For example, hospital or blood bank information systems might track all the blood that is administered to all patients, or governmental agencies might track all deaths that occur in each hospital and the reported cause of death. Frequently, these databases are available for research purposes.

The magnitude of these databases is seen by some investigators as providing unparalleled opportunities for research. Advocates of this approach note that the quantity of data available through existing databases probably cannot be matched, even at astronomic cost. In addition, these databases include information on actual clinical practice, rather than on the potentially altered practice used in research protocols (e.g., "tight" control).

However, critics note numerous problems. Foremost of these is that the information in these databases was not obtained in a prospective randomized manner. One example of such research is a study that examines the differences among medical centers in the likelihood of death after cardiac surgery. [14] Those hospitals with poor outcomes argue that their complications resulted from caring for higher-risk patients. Investigators who perform these analyses frequently attempt to control for risk (e.g., results can be stratified by age, accounting for possible differences in outcome for patients of different ages). Although these risk adjustments are claimed to be sufficient, it is doubtful whether they are. In contrast, the RCT design, one hopes, protects the investigator from introducing this problem.

Another example of the influence of lack of randomization can be seen in the comparison of two surgical approaches to the repair of coronary artery disease. In this fictitious example, investigators are unaware that the clinicians were interested in this same issue and that they provided all high-risk patients procedure A and lower-risk patients procedure B. The investigator obtained data from a hospital database, and the outcome measure is incidence of MI in the year after surgery. Even though procedure A is better (by definition), outcome is no different in the two groups because of differences in selection.

A second problem involves blinding, although I use the term differently here from when I refer to the RCT. It might be that the team caring for the patients is more interested in the outcome of patients undergoing procedure A than in those undergoing procedure B. So all patients undergoing procedure A are strongly encouraged to return for follow-up care (possibly even provided gratis). In turn, the percentage follow-up in the two groups differs markedly. This factor undoubtedly influences the results. Although issues of surveys are quite different, the analogy to return rates for surveys is important--investigators are often satisfied that 50 percent of individuals who were sent questionnaires returned them, yet they are unable to comment on what distinguishes the 50 percent who did from those who did not.

A third problem involves an unidentified influence of time. In some instances, investigators examine the incidence of an outcome before and after the introduction of a new clinical practice. For example, a trial mentioned earlier examined whether a new policy of extubating children in the operating room after cardiac surgery saved money compared with extubation in the ICU. [11] The authors of this study assumed that the only factor that changed costs during the period was the new extubation practice. The validity of this assumption is certainly questionable, even based on the data presented by these authors. In addition to the two groups already described (those patients "studied" before the change in practice who were not extubated in the operating room and those patients "studied" after the change in practice who were extubated in the operating room), the authors

obtained data on a third group, patients "studied" after the change in practice who were *not* extubated in the operating room. Of note, hospital charges for this group were markedly less than those for the group studied in the earlier time period. Thus, the decreased charges in the early extubation group could, at least partially, be attributed to practice changes that occurred over time, independent of the change in extubation practice.

One study demonstrates a similar phenomenon. Macario et al [15] found that institution of practice guidelines decreased costs of knee replacement by 19 percent. However, costs for a second procedure, prostatectomy, decreased 12 percent during the same time interval, although no practice guidelines were instituted. Thus, only a portion of the "savings" can be attributed to the guidelines, a finding that could be identified only because the investigators selected an appropriate control group. Lack of such a control group markedly diminishes the validity of other similar studies. For example, Lubarsky et al [16] reported that a pharmaceutical practice guideline in their institution decreased the cost of drugs used during anesthesia by $24. These authors dismissed a 7-minute increase in anesthesia time as being of no consequence. This increase in anesthesia time might have resulted from changes in surgical practice, such as a larger number of laparoscopies and a decrease in open procedures, and it might not have been a detrimental outcome from their pharmaceutical practice guidelines. However, the results of the practice guideline study of Macario et al and changes in practice in other university hospitals (e.g., the increased likelihood that an attending surgeon, rather than an undersupervised medical student, will perform skin closure) suggest that anesthesia time should have *decreased* rather than *increased* during the period of the study. Thus, the 7-minute increase in anesthesia time may represent the "tip of the iceberg." Lack of a control group prevents either the investigators or their critics from determining the answer.

A fourth problem with the use of retrospective databases involves the handling of missing data. When data are collected prospectively, investigators can define a priori how missing data will be handled in the ensuing analysis. In addition, investigators can make appropriate efforts to minimize the quantity of data that are missing. In contrast, databases often lack large quantities of critical information. Excluding these missing data from a retrospective analysis may lead to a bias. For example, if investigators are examining survival with different anesthetic techniques, it is possible that data missing at a 3-month follow-up visit might reflect either patients lost to follow-up (e.g., having moved to a new community or health care plan) or those who have died.

A fifth problem involves the quality of data. When investigators obtain data prospectively, they generally define criteria explicitly. For example, a study examining the influence of anesthetic technique on time to recovery room discharge might use strict criteria to define the time at which a patient is ready for discharge. In contrast, an existing database such as a recovery room log would provide information on when the patient was actually discharged, rather than when the patient attained the criteria for discharge. Thus, potentially irrelevant factors such as the availability of transportation might confound the results. In addition, the accuracy of the values entered for routine clinical purposes is often questionable.

Finally, the question of interest is probably not exactly answered by the database. For example, it is likely that the investigator has specific focused questions of interest, yet the people who created and implemented the database did not ask these specific questions. When this situation occurs, investigators might choose to use other measures such as surrogate outcomes. Compromise might be small or it might be large. Despite the marked cost savings associated with retrospective studies involving databases, few, in any, of these studies have been accepted into the anesthesia literature, presumably a result of these serious limitations.

Meta-Analysis: A Solution or a Problem

Frequently, as a clinical issue emerges, small clinical trials are conducted independently at a number of institutions. For example, numerous trials have examined the influence of antiemetics on the incidence of PONV. Some of these trials demonstrate statistical significance, whereas others suggest a trend, but their sample size is insufficient to demonstrate statistical significance. With the latter, investigators might conclude that the therapy was not beneficial. One prominent example in the anesthesia literature regards the influence of regional versus general anesthesia on outcomes in high-risk patients, an issue that has been examined in many small studies. The conflicting results of these multiple publications frustrates the clinician from applying the results of these analyses. Although the optimal solution might be to perform a large RCT that is sufficiently powered to demonstrate statistical significance, several factors militate against the likelihood of this new trial. First, the expense of such a trial might be prohibitive. Second, investigators may be concerned that efforts expended in the earlier trials will have been wasted. Finally, funding agencies may believe that the earlier trials provided sufficient evidence that the new trial is not warranted.

Under these circumstances, one approach that is currently popular is termed meta-analysis. With this technique, the investigator (henceforth identified as the meta-analyst) does not obtain data himself or herself. Rather, the metaanalyst carefully searches bibliographic databases to obtain a comprehensive list of relevant publications. Each study is then examined to determine its "quality" and suitability for inclusion in a pooled analysis. For example, studies in which the randomization procedure was not stated explicitly might be rejected. Statistical techniques specifically created for meta-analysis are then applied to the results of these studies, accounting for the different sample size in each study, to yield a pooled result, for example, an odds ratio. For example, a meta-analysis of the effects of regional versus general anesthesia for surgical repair of femoral neck fracture reported that general anesthesia was associated with a 4-fold higher incidence of deep vein thrombosis. [17]

Meta-analysis has polarized the medical research community. Its advocates claim that it is a legitimate means to resolve questions for which multiple inadequately powered studies have been performed, and its efficiency is appealing in that existing studies are used, and no additional patients need to be subjected to the "less desirable" therapy. In contrast, its critics claim that it is flawed.

First, meta-analysts typically do not have access to the original data, so that the published data become their new database. Unfortunately, editorial limitations often prevent publication of large quantities of data, so that the information available to the meta-analyst may be inadequate. In addition, issues that were well established and handled appropriately by the investigator may not be well defined in the manuscript, thus preventing the meta-analyst from using the information correctly. The meta-analyst typically deals with these issues by assigning a quality score to each study and using only those studies that meet certain criteria. However, the procedure by which studies are judged as acceptable or unacceptable for inclusion is questionable--well-designed studies might be rejected simply because the authors failed to specify certain criteria demanded by the meta-analyst (and such criteria might have been standard practice at the time the study was conducted but not routinely reported).

Second, the database from which the trials are identified may be incomplete and, possibly, biased. This "publication bias" (or "file drawer" problem) occurs because an underpowered study that fails to demonstrate statistical significance is likely not to be published, whereas a similarly sized study that attains statistical significance will be. Assuming that the former set of studies is inaccessible to the metaanalyst (and there are virtually no registries that collect these data), the meta-analysis will be biased toward studies with positive results. This problem is typically discounted by meta-analysts as unimportant, despite their inability to assess its prevalence. Finally, meta-analysis may include studies with different designs.

Ultimately, the test of meta-analysis is whether it yields the same results as a sufficiently powered, large RCT. Le Lorier et al [18] examined 40 primary and secondary outcomes for which such a comparison could be performed. In numerous instances, the large RCT yielded results different from those of the meta-analysis, despite effect size estimates that differed minimally (i.e., the magnitude of effect detected by the meta-analysis was similar to that detected by the large RCT, yet the results of the meta-analysis yielded a different conclusion than the RCT). In this case, one might question whether the meta-analysis or the large RCT yielded the more meaningful result. Of course, the design of each of the many small RCT and the large RCT must be compared. If there is no obvious difference between them, my bias would be toward the large RCT. In this context, many researchers are critical of meta-analysis.

Determining the Appropriate Sample Size

On some occasions, an investigator reports that the *P* value for a critical analysis was equal to .05. The implications of this *P* value should be considered. If one subject included in a study were replaced by another, it is likely that the results from these two subjects would differ. In turn, differences between the two groups would be either smaller or larger. If the difference were smaller, the *P* value would now be greater than .05, and the investigation would not attain statistical significance. In turn, the results of the study would diminish in importance.

To avert such problems, it is generally considered advisable for investigators to perform a power analysis before the study is initiated. This analysis permits the investigators to determine how many patients should be included to ensure the study's success. Unfortunately, many studies are performed without an appropriate power analysis, and investigators frequently submit manuscripts in which small sample sizes yield *P* values of .05 to .1 (5-10%). In some instances, the investigators claim that these results indicate a trend (i.e., they imply statistical significance); in others, they claim that this *P* value indicates no difference between groups. In either instance, the inadequate sample size prevents the reviewer and reader from arriving at a meaningful conclusion. In response, it is in vogue for reviewers to request a post hoc ("after the fact") power analysis, that is, to use the existing data to estimate how many patients *should* have been studied to attain statistical significance. If the *P* value is close to .05 (e.g., .06), then the results of this post hoc power analysis are obvious--the number of patients studied was inadequate, and a *small* increase in sample size (assuming the data from the new subjects followed a pattern identical to those of the patients already studied) would be sufficient to attain statistical significance. If the *P* value is much larger than .05, then a markedly larger sample size was needed. However, this post hoc power analysis does not provide any insights into the validity of the results or clinical implications of the present study. Thus, I remain skeptical of post hoc power analysis. Instead, power analyses should be performed *before* the study is initiated.

In planning an experiment, one presumably has some idea of the result. For example, the incidence of ECG changes consistent with ischemia might be 30 percent with a common anesthetic agent, and one might expect an incidence of only 12 percent with a new agent (therefore, an "effect size" of 18%). The number of eligible patients might be 100 per year, and the investigator might be constrained to performing the study within 1 year (e.g., during a fellowship). A statistical analysis (either a continuity-corrected chi^2 test or Fisher exact test) based on these expected results yields a *P* value lower than .05 (.049 and .048, respectively). So the investigator might embark on the experiment, confident that the results will turn out as expected and that statistical significance will be attained by the end of the experiment.

Luck may be with the investigator. After studying 100 patients, the incidence of adverse events may be exactly as planned, and statistical significance will have been attained. Or the situation may be even better--the incidence of ischemia may be only 10 percent in the treatment group and 30 percent in the control group (note that this results from only 1 less patient with ischemia in the treatment group), leading to a *P* value of .02. However, it is equally likely that the results could be unfavorable to the investigator's hypothesis. For example, the incidence of ischemia might be 14 percent in the treatment group and 30 percent in the control group (note again that this results from a change in outcome for only a single patient). Even though the effect size (16%) is still quite large, statistical significance is not attained (*P* = .09), and the investigator might conclude that the therapy was not efficacious (and might not even attempt to publicize the results). Conversely, the surgical team might vacation during the 12th month of the study, thus decreasing

the sample size to 46 per group, and a *P* value of .08. Thus, with an experiment designed to achieve a *P* value of .05, trivial changes in the samples size and/or results lead to either success or failure with nearly equal frequency.

This leads to the concept of the "power" of the trial. The trial described earlier, and any trial in which the expected results yield a *P* value of .05 exactly, has a power of 50 percent (meaning that 50 percent of the time, the "expected" variability leads to "success," and 50 percent of the time, it leads to "failure." Bettors might, or might not, consider 50 percent to be good odds, but most researchers would not consider them to be so. Therefore, before investing any resources (time, money, pride), an investigator should decide how much power a trial has. Typically, an investigator selects a sample size sufficient to ensure statistical significance with 80 percent power.

One of the more frustrating problems experienced by an investigator is to perform a study, then to determine that the anticipated trend in the data does not achieve statistical significance, such as *P* = .06. Although the investigator then may be tempted to increase the sample size slightly to achieve statistical significance, this approach is not considered appropriate. [19] This problem of inadequate sample size often can be eliminated by prospectively estimating the sample size necessary to achieve statistical significance. Many mathematic approaches exist to address this problem. However, a descriptive introduction to the techniques of *power analysis* is useful.

Two investigators (Dr. Goodluck and Dr. Badluck) are performing identical studies in identical populations. Both are examining whether the time to 100 percent twitch depression of a new muscle relaxant, "Faston," is faster than 4.0 minutes, the previous "gold standard" for a nondepolarizing muscle relaxant; both investigators plan to use a one-tailed, one-sample *t*-test to examine their results. Dr. Goodluck studies ten patients, finding a mean value of 3.0 minutes with a standard deviation (SD) of 1.6 minutes; his results achieve statistical significance (Table 21-2) . Dr. Badluck also studies ten patients, obtaining a mean value of 3.2 minutes with the same SD; however, although his mean value is minimally different from Goodluck's, Badluck's results yield a *P* of more than .05. How did this happen?

Unknown to these investigators is that their mentor previously determined the onset time for "Faston" in a large sample

TABLE 21-2 -- One-Sample *t*-Test for the Onset Time of "Faston," An Imaginary Anesthetic

[a]

[a] Read, "the one-tailed *t* value when alpha = 0.05 and degrees of freedom (df) = 9."

(*N* = 1,000); from that study, we know with reasonable assurance that the population mean is 3.0 minutes, with an SD of 1.6 minutes (and that the onset time is faster than that of the "gold standard"). Goodluck's sample mean is identical to the "true" value (merely a coincidence), and Badluck's value, although not identical, is close. Knowing that the population mean is 3.0 minutes, we can use the standard error (SE) to determine the distribution of sample means: with a sample size of ten, the SE is 0.5 minute (1.6/
10), and 95 percent of sample means lie between 2.1 and 3.9 minutes (mean ± *t* · SE). Thus, both Goodluck's and Badluck's mean values are likely estimates (i.e., not unusual events). Although Badluck's estimate is "correct," it lies in an unfortunate area (i.e., nonsignificant) of the distribution of possible mean values that he might have obtained (Fig. 21-2 , upper panel). Thus, Badluck's analysis succumbed to the laws of chance: in a large percentage of samples, by chance, differences between these groups would have achieved statistical significance with a sample size of ten, but his actual results did not. Had Badluck studied four times as many patients and obtained the same mean value and SD, his SE would have been smaller by a factor of two, and his results would have achieved statistical significance (Fig. 21-2 , lower panel): this larger sample size would have resulted in statistical significance in a larger percentage of studies.

Badluck could have avoided his misfortune by performing a power analysis. Prior to initiating the study, he might have realized (e.g., based on a pilot study or his impression from clinical use of "Faston") that the likely difference between groups was 1.0 minute and that the SD within a group was approximately 1.6 minutes. Assuming that the true (i.e., population) mean value for "Faston" is 3.0 minutes (and assuming that the distribution of possible sample means is symmetric), he would expect a 50 percent chance of obtaining a sample mean greater than 3.0 minutes and a 50 percent chance of obtaining one smaller than 3.0 minutes. With a sample size of ten and an expected SD of 1.6, his expected SE would be 1.6/
10 or 0.5 minute. Had he obtained a mean value greater than 3.1 minutes (determined as 4.0 min - *t* · SE, using the one-tailed *t* value for 9 *df* and alpha = 0.05), his *t* value would have been less than the critical value, and he would not have achieved statistical significance. Conversely, all experiments in which the mean value was less than 3.1 minutes would have resulted in statistical significance. Because the population mean for the onset of "Faston" is 3.0 minutes, * slightly more than half of all possible sample mean values would be equal to or less than 3.1 minutes. Thus, a statistician would conclude that this experiment had slightly better than a 50 percent power to detect a difference of 1.0 minute between groups. Once Badluck recognized that his experimental design had a power of only slightly greater than 50 percent, he likely would have increased the power of his analysis, most simply by increasing the sample size. An increased sample size accomplishes two goals. First, as the degrees of freedom increases, the critical value for *t* decreases (Table 21-3) ; this small decrease means that it is slightly more likely that his *t* value would exceed the critical value. Second, and of greater importance, is that an increase in the sample size decreases

*The population mean is rarely known; thus, power analyses are typically performed using the sample mean or an estimate of the sample mean.

Figure 21-2 Power analysis for onset time for subjects given the hypothetic muscle relaxant "Faston." The upper panel shows the distribution of possible sample mean values assuming a population mean value for "Faston" of 3.0 minutes, a standard deviation of 1.6 minutes, and a sample size of 10, resulting in a standard error of .51 minute. The population mean value for the standard is 4.0 minutes. Thus, any mean value for "Faston" greater than 3.1 minutes (determined as mean - *t* · SE = 4 - 1.833 · 0.51) will not result in statistical significance. In that 38 percent of sample means exceed 3.1 minutes, the likelihood of a type II error is 38 percent; conversely, 62 percent of sample mean values are less than 3.1 minutes, so the experiment has a power of 62 percent. The lower panel differs only by having a sample size of 40, resulting in a standard error of 0.25 minute. More than 98 percent of sample mean values are less than the new critical value (mean - *t* · SE = 4 - 1.685 · 0.25); thus, the power of this analysis exceeds 98 percent.

the SE of the sample (because the SE equals SD divided by the square root of the sample size). Had Badluck increased his sample size by a factor of four, his SE would have decreased by a factor of two, thereby increasing his value for *t* by a factor of two.

By estimating the expected difference between sample means and the expected SD within the groups, the investigator can prospectively determine the sample size necessary

TABLE 21-3 -- Critical Values of the *t* Distribution (Two-Tailed)

	alpha		
DEGREES OF FREEDOM	***0.05***	***0.01***	***0.001***
3	3.18	5.84	12.92
4	2.78	4.60	8.61
5	2.57	4.03	6.87
10	2.23	3.17	4.59
20	2.09	2.84	3.85
50	2.01	2.69	3.50
100	1.98	2.63	3.39
1,000	1.96	2.58	3.30
	1.96	2.58	3.29

for the analysis. Three approaches (the first two being mathematical, the third graphic) are commonly used, each of which requires the investigator to estimate the expected difference between mean values and the expected SD (or to perform a pilot study to obtain preliminary estimates). The first approach is to calculate Z_{beta}:

where $Z_{1-alpha}$ is the (1-alpha) percentile of the normal distribution (the area associated with the alpha tail of the normal distribution: 1.64 for the 5% tail or 1.96 for the 2.5% tail), mu_0 and mu_1 are the mean values for the null and alternate samples, and $sigma_0$ and $sigma_1$ are the SE of these respective samples (often assumed to be equal). The Z table is then consulted to determine the fractional area associated with this Z_{beta} value: this area represents the likelihood of a type II error. In turn, [1 - area(Z_{beta})] represents the power associated with the proposed analysis. For the Goodluck/Badluck analysis, a power of 62 percent is now demonstrated (Table 21-4) .

In the second approach, equation 1 is rewritten as

TABLE 21-4 -- Power Analysis for the Onset Time of "Faston," An Imaginary Muscle Relaxant

Using Equation 1 to determine the power of the analysis in Table 21-2 :
$mu_0 = 3.0$
$mu_1 = 4.0$
$sigma_0 = sigma_1 = 1.6$
Using the Z table, this value suggests a 38% likelihood of a type II error; alternately, this implies a 62% (100-38%) power to detect a 1.0-min difference with 10 subjects per group.

where $sigma_0$ and $sigma_1$ are the SD of the two samples. The investigator assumes that a power of 90 percent and a one-tailed type I error of 5 percent are desirable; the corresponding values of $Z_{1\text{ -beta}}$ (1.28) and $Z_{1\text{ -alpha}}$ (1.64) are used. Mean values and their SD are estimated (possibly based on a pilot study), usually assuming that SD for the groups are equal. Using this approach, a minimum sample size of 22 per group is now evident for the Goodluck/Badluck analysis (see Table 21-5) . Recognizing that the estimates for SD may be conservative, a prudent investigator might select a slightly larger sample size, such as 25 subjects per group. These two approaches to power analysis are explained in detail by Cohen. [20] The third approach to power analysis is graphic: the investigator examines a set of charts to estimate sample size. [21] [22]

If the data are nonparametric and require chi ^{2} analysis, other approaches are available to estimate sample size. For example, an investigator might be interested in whether a new anesthetic, "Nochuck," is associated with less PONV than the traditional anesthetic. Assume that the true incidence of vomiting is 10 percent in patients given "Nochuck" and 30 percent in patients given the traditional anesthetic. With a sample size of 40 patients in each group, these incidences would result in $P > .05$; a sample size of 50 patients in each group would achieve statistical significance ($P < .03$). With 50 patients in each group, the expected number of patients vomiting would be 5 with "Nochuck" and 15 with

TABLE 21-5 -- Estimating the Sample Size Necessary to Demonstrate that Onset of "Faston" (An Imaginary Muscle Relaxant) is Faster than that of the Gold Standard

Using Equation 2 to determine the sample size necessary to achieve 90% power for the experiment in Table 21-2 :
Using an alpha value of 0.05, $Z_{1\text{ -alpha}} = 1.645$
Using a beta value of 0.05, $Z_{1\text{ -beta}} = 1.282$
$mu_0 = 3.0$
$mu_1 = 4.0$
$sigma_0 = sigma_1 = 1.6$
Thus, 22 subjects per group are necessary to ensure a power of 90% of detecting a difference between groups.

the traditional anesthetic. However, as before, it is easy to imagine that 1 additional patient given "Nochuck" might vomit and 1 fewer given the traditional anesthetic might vomit, that is, 6 patients in the "Nochuck" group and 14 in the traditional anesthetic group. These new results would not achieve statistical significance ($P = .08$). Again, this problem can be addressed prospectively by a power analysis. For a 2 × 2 contingency table (also known as a two-sample test of proportions), the appropriate sample size in each group (n) can be determined as

where p_1 and p_2 are the expected proportions in the two groups, p equals ($p_1 + p_2$)/2, $Z_{1\text{ -alpha}}$ is the fractional area associated with a type I error of alpha (typically 5%), and $Z_{1\text{ -beta}}$ is the fractional area associated with a type II error of beta, or a power of (1 - beta), typically 90 percent. For example, if an investigator expected to find an incidence of perioperative ischemia of 10 percent for one anesthetic and 20 percent with a second, a total of 434 subjects (217 in each group) would be needed to ensure 90 percent power of detecting a difference. Without a prospective analysis, the investigator might well select a smaller sample size; conversely, the knowledge that such a large sample size is necessary might make the study prohibitive in expense.

A more serious problem occurs if the investigator attempts to extrapolate from a small sample size. For example, an investigator has developed a new technique to perform an axillary nerve block that he or she believes is less likely than the traditional technique to produce an intravascular injection. The nerve block is performed in 60 subjects in whom no intravascular injections occur. Can the investigator conclude that intravascular injections never occur? If the "true" incidence of intravascular injection in a large sample were 1 in 100, the likely incidence in 60 subjects would be 0.6. However, in that events occur in discrete individuals, the most likely value would be 1; however, 0 (or 2 or, possibly, 3) might be likely values. Hanley and Lippman-Hand [23] examined this issue in an interesting article entitled "If nothing goes wrong, is everything all right?" Briefly, an investigator who demonstrates no adverse events in N trials can conclude with 95 percent confidence that the "long run" rate is no higher than 3/ N. Thus, our investigator cannot claim that the experience of no adverse events in 60 subjects ensures no adverse events ever, but, rather, that adverse events are likely to occur in fewer than 5 percent of subjects (3/60). Finally, if sample size cannot be estimated prospectively, or if there may be a significant cost to prolonging the analysis once the earliest signs of statistical significance appear, the investigator may opt for the sequential analysis technique described later.

Statistical Errors

Many clinicians and investigators distrust statistical analysis. Sometimes this distrust is based, in part, on lack of

knowledge of the terms used by the investigator or on the inability of the investigator to communicate thoughts clearly. However, distrust also occurs when the data presented in a manuscript appear to contradict the statistical conclusions. For example, one study reported that theophylline's elimination half-life was 216 and 72 minutes in different groups, a 3-fold difference the authors claimed was not statistically significant. [24] In contrast, distribution half-lives for the same groups were 2.7 and 3.0 minutes, a 10 percent difference for which the authors claimed statistical significance ($P < .05$). Because neither individual data points nor SD were reported, the reader was unable to examine the data and draw his or her own conclusions; thus, the reader can only be suspicious regarding the conclusion.

Perhaps the most common error is presentation of descriptive data without indicating whether the values for variability represent the SD or the SE. Because there is no consensus or conventional practice regarding which of these should be reported, investigators may be tempted to report the smaller value (suggesting less variability in the data)--the SE--without identifying it as such. The reader may have insufficient information to determine which value is being reported. This problem occurs less frequently than in past years, probably because of the heightened interest in statistics in recent years. [25] [26] Another error is to use sample sizes that are

too small to detect expected differences. The denominator used in *t*-tests and analysis of variance is the variability within the groups, a value determined using sample size [see equation (19)]. If sample size is small, the denominator will be large, and the *t* or *F* will be smaller than they would be with a large sample size. Thus, the investigator may be unable to detect differences between groups. This problem might be prevented by the use of power analyses.

An additional reason for obtaining the wrong statistical conclusion is the use of the wrong statistical test. This error occurs most frequently when multiple *t*-tests are performed without applying the appropriate correction. The resulting type I errors can be avoided by using the appropriate statistical test, such as analysis of variance. Alternately, the investigator might select a test that is inappropriately strict. For example, if three or more measurements were obtained on the same subject, the investigator would be correct in avoiding multiple paired *t*-tests. Unless the investigator is knowledgeable of statistical techniques such as repeatedmeasures analysis of variance, he or she might erroneously use one-way analysis of variance, a test that ignores the information gained by obtaining repeated measurements on the same subject. Just as the two-sample *t*-test may be unable to find differences that can be detected with a paired *t*-test (assuming that paired measurements were obtained), a one-way analysis of variance may be unable to find differences that can be detected with the repeated-measures test. Frequently, investigators recognize the value of statistical tests that consider that paired measurements were obtained, but they are unaware that appropriate tests such as repeated-measures analysis of variance exist. In response, they analyze their data first with a one-way analysis of variance (a test that is inappropriately strict), then with paired *t*-tests with or without the Bonferroni correction. If the Bonferroni correction is applied, the analysis may be too strict; if it is not applied, the analysis is too lenient. Regardless, the analysis could have been performed more appropriately with a repeated-measures analysis of variance and one of the multiple comparison tests described later. Use of one-way analysis of variance instead of the more appropriate repeated-measures analysis of variance occurs frequently in the anesthesia literature. Using a statistical test with inadequate sensitivity often prevents investigators from detecting a difference when one really exists.

A final problem with statistical analyses results from collecting too much data. If the investigator fails to achieve statistical significance of the primary question, it is tempting to select a whole series of new questions, performing unintended statistical analyses, an approach known as "data torturing." [27] The legitimacy of this approach is certainly questionable.

Selecting the Appropriate Statistical Test

Most statistics courses focus their attention on the techniques necessary to perform statistical analysis and give the student examples of each statistical test. In contrast, when performing research, the investigator must decide which statistical test is appropriate for the data collected. Because statistics courses emphasize performance of the tests rather than study design and how to select the appropriate test, the investigator may have difficulty in selecting the appropriate test. Ironically, with the great availability of hand-held calculators, microcomputers, and even user-friendly mainframe computers, performing complicated statistical tests is now possible for almost all medical investigators. The greatest difficulty therefore lies in selecting the appropriate test.

The first question the investigator should ask is, "What type of data have I obtained?" If the data are on a nominal scale, the choice of analytic techniques is generally limited to chi^2 analysis. For data on an ordinal scale, the investigator is generally restricted to nonparametric analyses. For data on a ratio or interval scale, a large variety of tests, both parametric and nonparametric, is appropriate. To choose between parametric and nonparametric tests, the investigator should consider the sample size and whether the data are distributed normally. If the data are not distributed normally, a parametric test may not demonstrate statistical significance, because the distribution of critical values is based on the assumption of normality. Because of the small sample size frequently used in many medical studies, nonparametric techniques should probably be used more frequently. The major argument against their use is that, if the data are distributed normally, nonparametric tests are slightly less powerful and may not detect real differences. Typically, the advantage they yield with abnormal distributions significantly outweighs the minor lack of power compared with parametric analyses.

Once the investigator determines the type of data obtained, the data should be displayed in a readily understandable form, such as a histogram or scattergram. Appropriate visual presentation permits the investigator to learn whether the data are distributed normally and also to perform a quick and informal visual analysis. Many analyses can be terminated at this point--if no obvious difference exists between groups, statistical analysis will be fruitless, although an investigator might be able to find an obscure statistical test that suggests significance. For example, some statistical

packages perform the Bartlett test of equal variances with each analysis of variance. If mean values of each group do not differ but variances do, the Bartlett test (but not analysis of variance) will yield a statistically significant result.

The next step is to determine the descriptive statistics (including the mean, SD, and SE). These statistics describe the location and variability of the sample; in addition, they are prerequisites for subsequent analyses. Only after completing these preliminary steps should the investigator embark on inferential statistics. The choice of inferential test depends on the nature of the data. If the independent variable consists of only a single or paired measurement on one group, the one-sample *t*-test should be used. For two groups, the two-sample *t*-test should be used. For more than two groups, analysis of variance is the appropriate statistical test, although an investigator may choose the two-sample *t*-test with the Bonferroni correction. If measurements have been repeated on the same subject, repeated-measures analysis of variance should be used rather than the paired *t*-test. For each of these tests, the investigator may select the parametric or nonparametric version. Finally, if the independent variable is continuous and cannot be divided readily into discrete groups, analysis of linear regression is the appropriate test to apply.

For most of the research reported in the anesthesia literature, these statistical techniques are sufficient. As study design becomes more complicated, more sophisticated techniques may become necessary. Because a more detailed discussion of these tests is beyond the scope of this chapter, the investigator should turn to the resources described later. These resources permit the investigator to design a study for optimal data collection and analysis.

In some instances, the investigator performs a study for which a specific statistical approach has been developed and is appropriate. For example, an investigator may compare two techniques to estimate cardiac output, a noninvasive technique and the thermodilution technique. My previous experience suggests that the thermodilution technique is not a "gold standard," and therefore differences between the measured values do not necessarily indicate an error in the noninvasive technique (the error may be in the thermodilution technique); however, a linear regression comparing the two techniques would imply that all errors lay with one of the techniques, presumably the new technique. An alternate approach, suggested by Bland and Altman, [28] is to assume that the best estimate is the average of the values obtained by the two techniques; the investigator then examines the difference between the two techniques as a function of this best estimate. This scatterplot may permit the investigator to detect systematic errors in the new technique. Many other specific approaches for specific problems are available. Unfortunately, these approaches are not catalogued and are therefore not readily available to investigators. When these guidelines are used, the choice of statistical tests is often simple.

Statistical Resources

The techniques described in this chapter should permit the reader to examine a data set, to determine descriptive statistics, and to perform simple tests such as the onesample or two-sample *t*-test. More complicated tests such as analysis of variance or linear regression analysis, if done manually, are tedious and require mathematical precision beyond the ability and scope of many investigators. In addition, mathematical errors occur and, as the number of calculations increases, may be compounded. To avoid these problems, most investigators turn to a variety of resources. The simplest of these, a scientific calculator, permits accurate calculation of means, SD, and SE. More sophisticated programmable calculators can perform analysis of variance and linear regression analysis.

Microcomputers (e.g., PC and Macintosh) and minicomputers (e.g., Sun workstations) are commonplace in offices, laboratories, and homes. Various statistical packages that perform complicated analyses with minimal effort are available for these computers. Popular packages include Statvew (SAS Institute), BMDP (Biomedical Statistical Software, University of California Press), SPSS (Statistical Package for the Social Sciences), and SAS (SAS Institute). Regardless of the statistical package, the results must be examined by the investigator. I have found errors in several statistical software packages, one produced locally, and others, widely available. On occasion, errors are subtle and may escape notice; in some instances, the errors are obvious to even the casual user. Several steps are available to confirm the accuracy of the statistical package. First, the investigator can use a data set analyzed in a standard textbook; differences between the results offered in the textbook and those from the statistical package should alert the investigator to errors. Second, the investigator should always examine the entire output from the statistical package, not just the statistical results. If the mean values, SD, or other results differ from those predicted from the data, the investigator should be suspicious of the results.

Materials are readily available to guide the investigator toward more sophisticated statistical techniques. Glantz has written an excellent monograph, *Primer of Biostatistics*.[21] Textbooks by Zar, [29] Dixon and Massey, [30] and Colton [31] are also valuable resources, particularly if the investigator has selected a particular test and

needs guidance through the individual steps.

In addition, the number of statisticians who have biomedical expertise is increasing. These statisticians have knowledge of the particular problems associated with medical research, including small sample sizes and abnormal distri-butions. Biostatisticians can be valuable in directing the medical investigator toward the appropriate statistical test, in performing the analyses, and in interpreting the results.

Finally, a word of caution regarding study design is in order. Inexperienced investigators may accumulate a large amount of data before identifying the most appropriate statistical techniques to be used. When an attempt is made to select the appropriate statistical test, the investigator may learn that the data have been collected in a way that prohibits appropriate statistical analysis. This problem can usually be avoided if the investigator considers the issue of statistical analysis before data are collected, particularly if outside advice is necessary. With increasing awareness among anesthesia researchers, these problems should occur less frequently.

DESCRIPTIVE STATISTICS

The initial step in statistical analyses is to categorize and summarize the data, that is, to apply the techniques of descriptive statistics.

Types of Data

The most familiar type of data, data on a ratio scale, has two characteristics (Table 21-6) . First, the size interval between successive units on the measurement scale is constant. For example, the difference between cardiac outputs of 4 and 5 L/min is the same as the difference between cardiac outputs of 7 and 8 L/min. Second, the measurement scale must have a zero point, and this zero value must have physiologic significance. These characteristics permit statements about the ratio of different values on the measurement scale. For example, a drug effect lasting 30 minutes is twice as long as a drug effect lasting 15 minutes.

Data on an interval scale also have constant intervals but lack a true zero point. For example, most measurements of pressure are referenced to atmospheric pressure (
760 mm Hg) rather than to a true zero point. The pressure represented by 20 cm H_2O (14.7 mm Hg) is not twice as great as the pressure represented by 10 cm H_2O (7.4 mm Hg). To calculate the true ratio, we would have to convert the pressures to absolute measurements by adding the reference zero value, in this case 760 mm Hg. Similarly, the temperature represented by 36°C is not twice the temperature represented by 18°C.

For many physiologic variables, there are known numeric differences between subjects. However, the data may indicate only a relative, rather than a measurable, difference between subjects. For example, a patient whose American Society of Anesthesiologists (ASA) physical status is III is at greater risk of harm from undergoing anesthesia than is the patient having a physical status of I. However, the difference in terms of degree of illness between patients having a physical status of II and those having a status of III is not necessarily the same as the difference between patients having a status of I and those having a status of II. Similarly, an Apgar score of 8 is better than one of 5; however, the difference between these two scores, in terms of neurobehavioral well-being, is not necessarily the same as the difference between Apgar scores of 5 and 2. These scoring systems are examples of *data on an ordinal scale.* Ordinal scales have arbitrary intervals that describe relative, rather than absolute, relationships between the ranks. They convey less information than data on a ratio or interval scale, because only relative comparisons can be made (e.g., that an Apgar score of 10 is better than a score of 5). In medical literature, it is common to see data on an ordinal scale treated as if they were on a ratio or an interval scale. For example, the extent of sensory blockade produced by spinal or epidural anesthesia is often reported in units of dermatomes, although a segment in the sacral region may not be identical, in terms of the amount of anesthetic required to produce loss of sensation, to a segment in the thoracic region. The treatment of ordinal data with statistical techniques more appropriately applied to interval or ratio data is so common as to be widely accepted. [32] Nevertheless, special techniques are available that are often more appropriate for the analysis of these types of data.

On occasion, we choose to describe, that is, name, a variable in terms of a quality rather than a quantity. Variables described in this fashion are called *data on a nominal scale.* For example, genotypes of pseudocholinesterase are identified by names rather than by numeric measurements. [33] To permit mathematical comparisons, we can obtain ratio-scale measurements of pseudocholinesterase activity for each of the genotypes. Using these ratio-scale, rather than nominal-scale, measurements, we can compare the various groups. Finally, some variables have only two possible attributes. For example, after surgery, a patient is either alive or dead. The investigator must correctly identify the type of data collected. Only then can the appropriate statistical analysis be applied.

Significant Digits

For all measurements, there are limits to precision. For example, blood pressure is usually measured to the nearest millimeter of mercury, and arterial oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) partial pressures are measured to the nearest millimeter or, at best, to the nearest tenth of a millimeter of mercury. In neuromuscular studies, because the ulnar nerve is usually stimulated no more frequently than once every 10 seconds, onset times cannot be measured with a precision greater than that. Whenever data are reported, a greater degree of precision should not be suggested than really exists.

Populations and Samples

Inherent in statistical analysis of a measured variable is the desire to draw conclusions about that variable. To accomplish this goal, the investigator could measure the variable for the entire population. For example, if we were interested in knowing $P_{A}CO_2$ for all adult patients anesthetized with an end-tidal concentration of desflurane of 6.0 percent at the University of California, San Francisco, in 1998, we could measure that variable in all eligible subjects. The values for $P_{A}CO_2$ might then be presented in a histogram displaying the number of subjects having each value of $P_{A}CO_2$; the histogram might also display the percentage of subjects having each value of $P_{A}CO_2$ (Fig. 21-3) . Obtaining measurements for all eligible subjects would be cumbersome and expensive. To simplify the task, we might select a smaller sample of the original population and assume that

TABLE 21-6 -- Types of Data

TYPE OF DATA	CHARACTERISTIC	EXAMPLES
Data on a ratio scale	Measurement scale has constant intervals and a true zero point	Duration of drug effect, cardiac output
Data on an interval scale	Measurement scale has a constant interval, but no true zero point	Airway pressure, body temperature
Data on an ordinal scale	Data are ordered or ranked, not measured	ASA physical status, Apgar scores
Data on a nominal scale	Data are classified not by a numeric measurement but by some quality or attribute	Electroencephalographic patterns, survival, genotypes of pseudocholinesterase

Figure 21-3 Histogram showing hypothetic values for P $_{CO_2}$ for all patients undergoing desflurane anesthesia at the University of California, San Francisco during 1993. The X axis represents values for P $_{CO_2}$. There are two Y axes. The left-hand axis represents the actual number of patients with each value of P $_{CO_2}$; the right-hand axis shows these values as a percentage of the total population.

this sample represents the entire population. Values for P $_{ACO_2}$ for a hypothetic sample are shown in Figure 21-3 . Note that extreme values (>58 mm Hg and <36 mm Hg) are not represented, nor are certain intermediate values (e.g., 42, 44, 45 mm Hg). Using these data, we cannot conclude that P $_{A}CO_2$ is always somewhere between 36 and 58 mm Hg during light desflurane anesthesia, only that extreme values did not occur in this sample. The values obtained from this sample of 12 subjects suggest that during light desflurane anesthesia, P $_{A}CO_2$ is frequently between 40 and 52 mm Hg.

Although measurements have been made on 12 subjects, the purpose of our study was to make predictions about a larger group, the entire population of adults undergoing light desflurane anesthesia. In order for this prediction to be valid, we must assume that the sample represents the entire population. If this assumption is not true, the results may not apply to the entire population. For example, Stanley and Webster [34] found that fentanyl, in doses of 50 mug/kg, provided sufficient anesthesia for cardiac surgery; however, subsequent studies suggested that larger doses are necessary for most patients. The studies by Stanley and Webster were conducted in Salt Lake City, a community that is largely Mormon. Because Mormons abstain from alcohol and other drugs, the low dose requirement observed by Stanley and Webster may have resulted from the personal habits of the subjects; therefore, this sample may represent the population of Salt Lake City but not the population of the United States. Recognizing these types of bias is important. If possible, these biases should be avoided. If they cannot be avoided, they must be identified.

Central Tendency

After the investigator selects the sample population and obtains measurements, he or she must then describe the results. All the measured values could be displayed as in Figure 21-4 or in other formats, such as a table. Although these methods of data presentation permit the reader to make judgments about the individual data points, they limit communication about the general nature of the sample. To describe a variable for the entire population, the investigator would like to be able to select the single value from the sample

Figure 21-4 Histogram showing hypothetic values for P $_{CO_2}$ obtained from 12 patients undergoing desflurane anesthesia. These 12 values represent a sample taken from the values in Figure 21-3 .

that would represent the center of the entire population, a value known as the *index of central tendency.*[35] If all the values in the sample were identical, the investigator would report that single value. However, for most variables, the sample contains many different values for individual members.

Mean

The value most widely used to represent the population is the arithmetic mean, usually referred to as the mean. The mean is determined by adding all the values of the population and dividing by the number of values in the population. This is described mathematically as population mean equals the sum of observations/number of observations. When a large number of terms is being summed, a shorthand way of expressing the process, called *summation notation,* is used:

where mu is the *population mean,* X_i are the individual values, and upper case sigma (Sigma) means to sum these values. Therefore, this expression is read as follows: mu is equal to the sum of all individual values of X_i from X_1 to X_N , divided by *N.* Because we usually sum all the values of the population, it is conventional to omit several of these symbols and write

When the investigator is studying a sample rather than the entire population, another term, $\bar{X}$, is used to represent the *sample mean.* $\bar{X}$ is equal to the sum of all measurements in the sample divided by the number of measurements in the sample. The mean is expressed with the same units as the individual observations.

Median

Alternatively, central tendency might be expressed with the *median.* To determine the median, the individual values are ranked from smallest to largest (or from largest to smallest). The median is the middle measurement, that is, the value below which half the values lie and above which the

other half lie. Median values have rarely been reported in the anesthesia literature; however, the median, being less sensitive to extreme values than is the mean, is a sensitive indicator of central tendency and should probably be reported more frequently. In addition, most nonparametric analyses compare the median rather than the mean; therefore, when these analyses are performed, it is appropriate to report the median.

Mode

The *mode* is the value that occurs most frequently. With the small number of observations in many medical studies, there will be no mode if each observed value occurs only once.

The arithmetic mean is a valid description of the location of the population only when ratio or interval data are used; for ordinal data, the arithmetic mean has no meaning. For example, the arithmetic mean of 5 is not the appropriate value to describe a sample consisting of subjects having Apgar scores of 0 and 10. [36] Instead, the location of the sample is more accurately described with values such as the median or, in this case, with individual values.

For many sets of measurements, the arithmetic mean represents the population accurately. For the measurements of P $_{ACO_2}$ during desflurane anesthesia, the arithmetic mean is (37 + 38 + ... + 57)/12 or 47 mm Hg. Individual values range from 37 to 57 mm Hg, and most are between 40 and 52 mm Hg. Thus, the arithmetic mean of 47 mm Hg is close to each of the members of the sample and can be considered a fair representative of all the members of the sample. In contrast, two patients in this small sample (see Fig. 21-3) had values of 51 mm Hg, making this value the mode. Although the mode is theoretically a measure of central tendency, in this instance it lies near one extreme of the sample and therefore does not represent the population. Because the number of members of this sample is even, no value lies exactly in the middle. In such circumstances, the median is taken to be the average of the two values ranked nearest the middle of the population (47 and 48 mm Hg, respectively)--that is, 47.5 mm Hg. Therefore, of the three values describing the location of this population, the mean and median represent the population well, whereas the mode does not. In all statistical analyses, the investigator should examine the values in the sample to determine how the central tendency of the sample can best be described.

Finally, just because we have selected a value to represent the sample does not necessarily imply that this value represents the larger population from which the sample was drawn. For example, our sample might have been biased toward, or away from, certain members of the population; or by chance we might have selected highly unusual members of the population. We must always remember that the mean represents the sample, rather than the population. If we extrapolate conclusions to the population, we must also consider our sampling process and the ability of this sampling process to identify the mean of the population.

Data Transformation

Most samples can be well represented by one of these three indicators of central tendency, particularly the arithmetic mean or the median. However, some samples, particularly those that are not symmetrically distributed, are not well represented by the arithmetic mean. For example, Feinstein [37] determined that the arithmetic mean for four concentrations of hydrogen ion (0.03162, 0.0002512, 0.0000001995, 0.000000001259) was 0.00797. This value is close to the first member of the sample and far from the other three. Rather than using the arithmetic mean to locate the central tendency of the population, he suggested using another indicator, the geometric mean, which is equal to the *n*th root of the product of each of the observations.

Therefore, the geometric mean of these four concentrations would be $[(0.3162 \times 10^{-1}) \times (0.2512 \times 10^{-3}) \times (0.1995 \times 10^{-6}) \times (0.1259 \times 10^{-8})]^{1/4}$ or 0.6683×10^{-5}. In this instance, the geometric mean, being larger than two of the observations and smaller than the other two, is more representative than is the arithmetic mean. Alternatively, the hydrogen ion concentrations could be converted to pH values of 1.5, 3.6, 6.7, and 8.9, respectively. The arithmetic mean of these pH values is 5.2, which corresponds to a hydrogen ion concentration of 0.6683×10^{-5}. Thus, the central tendency of hydrogen ion concentration is best expressed using the geometric mean, whereas the central tendency for pH is best expressed using the arithmetic mean.

The foregoing example demonstrates how data might be converted to an easier-to-use form (transformed) by applying simple algebraic processes such as taking the logarithm or square root of each value. Data transformation permits easier manipulation of the data or changes the distribution, possibly making a skewed distribution normal (see next section). Before using a calculator or computer to determine the arithmetic mean, the investigator should examine the data to determine whether the arithmetic mean is representative of the sample and whether transformation may be necessary to improve statistical analysis.

Normal Distribution

The ability of the arithmetic mean to express the central tendency of the population is a function of the distribution of the values within the population. For many variables, such as P_{ACO_2} (shown earlier), values tend to cluster around a central value, with fewer values located toward the extremes. If one obtains a sufficiently large sample, for many biologic variables the histogram would assume the shape of a bell (Fig. 21-5 A). This distribution, known as the *normal distribution,* was first described by de Moivre, [29] but it is credited to Gauss, being called the gaussian distribution. Many statistical tests described in this chapter assume that the population under examination is distributed normally. Because medical studies often use a small sample size, the assumption that resulting data have a gaussian distribution frequently is not tested.

Populations that do not have a gaussian distribution may assume a number of different shapes (Fig. 21-5 B and C). For example, administration of an imaginary drug, histodrenaline, might result in the release of histamine in some individuals and in the release of catecholamines in others. Therefore, if we measured the change in blood pressure after administration of this drug, half the subjects might have

Figure 21-5 The distribution of values for a population may assume many shapes. One shape frequently encountered in biologic experiments is the normal distribution shown in A. On occasion, distributions may be bimodal (humped), as shown in B, or J-shaped, as shown in C.

an increase in blood pressure, whereas the other half could have an equal decrease (see Fig. 21-5 B). If the mean value were zero, we might be led to believe that histodrenaline had no cardiovascular effects. A more appropriate conclusion would be that the arithmetic mean did not represent the population. The importance of examining the distribution of the data points should now be readily apparent: on occasion, the investigator finds that the arithmetic mean should not be used to describe the population. In that case, alternate methods of describing the results of the study, such as a histogram or table, become essential.

Variability

Identifying the central location of the sample is necessary but not sufficient to describe the population. For example, had all P_{ACO_2} values during desflurane anesthesia ranged from 44 to 49 mm Hg, the mean might have been 47 mm Hg. Although the mean for this new sample would have been the same as that for the sample described earlier, these two samples probably describe different populations, one having a broad range of P_{ACO_2} values during desflurane anesthesia and the other having a narrow range. Thus, in addition to describing the central location of the sample, we need to describe how dispersed the data are, that is, the variability of the sample.

Range

The smallest and largest values within a sample define the *range* of the sample. Although a description of the range is often useful, it can also be misleading: outliers, whether they are small or large, may suggest a greater variability of the sample than is indicated by the remaining elements of the sample.

Mean Deviation, Mean Absolute Deviation

A second technique to describe variability might be to find the average deviation from the mean. However, because some deviations are positive and others are negative, their sum is always zero; hence, the average deviation has no value as an indicator of dispersion of the data. Alternatively, the investigator could sum the absolute values of these differences from the mean and divide by *n,* thus producing the *mean absolute deviation.* This technique is mathematically cumbersome and has not become popular.

Sum of Squares

Another approach to the problem of describing the dispersion of the data is to sum the square of the deviations from the mean, a method that eliminates the negative signs. Squaring the deviations has a second effect: it increases ("weights") the contribution of the values according to their distance from the mean. For example, if the deviations from the mean were -1, -5, +1, and +5, the sum of squared deviations would be 52. A sample containing deviations of -3, -3, +3, and +3 would produce a smaller sum of squared deviations, 36. Although the mean absolute deviation (3) is the same for both samples [(1 + 5 + 5 + 1)/4 or (3 + 3 + 3 + 3)/4], the sample containing values more distant from the mean has the larger sum of squares. This sum of the squared deviations from the mean, known as the *sum of squares* (SS), is a fundamental tool used repeatedly in statistics. It is expressed mathematically as

Calculating the value of this equation requires two passes through the data: the first pass, to sum the individual values to determine the mean value; and the second, to determine the difference between individual values and the mean. Calculators and computers reduce this to a single step, known as a *machine formula,* which is derived as follows:

This can be expanded to

The second part of this equation, 2Sigma X_i X, can be simplified to: 2 × X × Sigma X_i , which is equal to 2 × (Sigma X_i / n) × Sigma X_i , or [2 × (Sigma X_i)^2 / n]. Similarly, the third part of the equation, Sigma X^2 ,

can be simplified to n × X^2 , or [n × (Sigma X_i /n)^2] or (Sigma X_i)^2 / n. Equation (8) can then be simplified to

Using this machine formula, one can determine the sum of squares in a single pass through the data; this technique greatly simplifies data manipulation.

Variance

Dividing the sum of squares by the sample size yields the average squared deviation from the mean, also known as the *mean squared deviation* or *population variance,* sigma^2 :

This equation is read as follows: population variance is equal to the sum of the squared differences between individual values and the population mean, divided by the sample size. Usually we are dealing with samples rather than populations and, when we calculate the *sample variance,* we do not know the population (i.e., true) mean. Instead, we use the sample mean to estimate the population mean. If we represent the difference between the sample mean and the population mean as epsilon, equation 10 could be written as follows:

This can be rearranged to

The first term,

, is what we would obtain had we used the sample mean instead of the population mean to es- timate the sample variance. The second term,

always equals zero (it is equivalent to a sum of the average deviations from the mean). The third term,

, is equal to n × epsilon^2 / n, or epsilon^2 . Thus, when the sample mean (rather than population mean) is used to estimate sample variance, sample variance is underestimated by the amount epsilon^2 . We correct for this underestimate (bias) by decreasing the denominator by 1. This process produces a better estimate for sample variance (s^2):

If there are n values that are squared and summed to determine the sample variance (equation 13), after one determines the next-to-last [(n - 1)th] value, the last [n^{th}] difference has been predetermined [the sum of the individual deviations from the mean, Sigma(X_i - X), must equal zero]. Thus, the number of independent values used to calculate sample variance differs from the sample size and is known as the *degrees of freedom (df).* A more elaborate proof that using n - 1 as the denominator yields a less biased estimate is available elsewhere. [38]

Standard Deviation

Although it is possible to express variability of the sample or the population using the respective variances, this is impractical because the units for variance for a sample are different from those for the population. Because variance is determined by squaring the differences between individual values and the mean, the units for variance consist of the square of the original units. For example, for P $_A CO_2$ values, the units for variance would be (mm Hg)^2 . A more common approach is to obtain the square root of the variance, the *SD.* As before, the SD for the population (sigma) and the SD for the sample (s) differ depending on whether n or (n - 1) is used in the denominator. In most situations, the SD of the sample, rather than of the population, should be used, even though it is a larger number.

Now we have estimated the central tendency and the variability of the sample, two values that describe the location and dispersion of the entire sample. If the population has a gaussian distribution, approximately 68 percent of the values lie within the range from 1 SD above to 1 SD below the mean. Approximately 95 percent lie within 2 SD above or below the mean, and more than 99 percent of all values lie within 3 SD of the mean. [*] Returning to the values for P $_A CO_2$ during desflurane anesthesia, we find that the SD is 6.3 mm Hg. If we examine values ranging from 1 SD below the mean (approximately 47 - 6 = 41 mm Hg) to 1 SD above the mean (approximately 47 + 6 = 53 mm Hg), we find that two-thirds of the values in the sample lie in this range and that one-third lies outside this range. The range from 2 SD below the mean to 2 SD above the mean (
34 to 60 mm Hg) includes all the values in this sample. If P $_A CO_2$ for any subject had been higher than 65 mm Hg or lower than 29 mm Hg, 3 SD or more below or above the mean would have been necessary to include those values.

Coefficient of Variation

If the sole information communicated about a sample is that the SD is 6 mm Hg, we cannot assess whether variability is large or small. For a mean arterial pressure of

100 mm Hg, a SD of 6 mm Hg is small; however, for a pulmonary artery occlusion pressure of 12 mm Hg, an SD of 6 mm Hg suggests greater variability. The ratio of SD to the sample

*In a gaussian distribution, 95 percent of all values are actually found within 1.96 (rather than 2.0) SD of the mean, and the range of 2 SD from the mean actually includes 95.44 percent of all values. However, it is common practice to use 2.0, rather than 1.96, SD to describe the 95 percent variability of samples and populations.

mean is known as the *coefficient of variation* and is often expressed as a percentage. The coefficient of variation is valuable in describing the variability of the sample. The units of the numerator and denominator being the same, the coefficient of variation has no units.

Standard Error of the Mean

If we were to repeat our measurements of P_ACO_2 during desflurane anesthesia in another 12 subjects, we would probably obtain slightly different results. For example, P_ACO_2 values might be 34, 36, 40, 41, 44, 44, 47, 48, 48, 49, 54, and 55 mm Hg. The mean of this sample would be 45 mm Hg, and the SD 6.5 mm Hg. A third sample of 12 subjects might yield a mean of 44 mm Hg; additional samples might have mean values of 43, 44, 48, and 49 mm Hg. Which of these mean values best represents the population? Had we not divided these patients into 6 groups, we would have had a single sample containing 72 members. The mean value for such a sample would have been 46 mm Hg. This could be calculated by summing the values for all 72 subjects and dividing by 72 or by determining the weighted average of the means for the individual groups: [(12 × 43) + (12 × 44) + (12 × 45) + ... + (12 × 49)]/(12 + 12 + ... + 12) or 3,312/72 or 46 mm Hg. These different techniques yield identical results. Because this new mean value, the mean of mean values (also known as the *grand mean*), was obtained from a larger sample, it better represents the population than each of the other values. As sample size increases, so does the ability of the sample to represent the population from which it came.

Because the sample mean is only an estimate of the mean of the population, we would also like to describe how closely this value approximates the population mean. This is accomplished with the *SE of the mean* (SEM), more commonly called the SE. The SE is obtained by dividing the SD of the sample by the square root of the size of the sample. The term SEM is curious, because this value is neither standard nor an error. This phrase originated during the Industrial Revolution, at which time reproducibility of measurements was important. If one measured the length of an object repeatedly, successive measurements would differ slightly, and an individual measurement would be unlikely to represent the true length of the object. Repeating the measurement and determining the average of these measurements provides a better estimate. If we then calculate the SEM value, we determine the error with which our measurement was made or how far from the true length the measured values are.

Using our initial set of values for P_ACO_2 during desflurane anesthesia, we find that the SE is $6.3/12^{1/2}$, or 1.8 mm Hg. Just as approximately 68 percent of the sample lies within 1 SD deviation of the mean, there is a 68 percent likelihood that the population (i.e., true) mean lies within one SE of the sample mean. As before, increasing the range to 2 SE above and below the sample mean increases to approximately 95 percent the likelihood that the population mean is included. Expanding the range to 3 SE increases the likelihood to more than 99 percent. Note that doubling the sample size does not decrease the SE by a factor of two; to decrease the SE by half, one would have to increase the population by a factor of four.

Confidence Limits

These ranges, when used to describe the mean, are called confidence limits. The 68 percent confidence limits include all values from 1 SE below the mean to 1 SE above the mean (written as mean ± SEM or mean ± SE). More commonly reported are the 95 percent confidence limits, which include all values within 2 SE of the mean (mean ± 2 SEM). Because the likelihood is 95 percent that the population mean is included in these confidence limits, they are a valuable way to describe both the location and the variability of the mean.

What to Report: Standard Deviation or Standard Error?

When reporting data, investigators must decide whether to report the SD or SEM. This decision should follow from the purpose of the study, which is usually to describe the sample in order to predict values for the population. Because the SD describes the variability of the sample and, hence, is used to estimate values for the population, I contend that SD should usually be reported.

Why, then, are SE reported with such frequency? The answer to this question lies in the mathematical relationship between the two values, SE being SD divided by the square root of the sample size. Thus, the SE is always smaller than the SD (and the difference between the two increases as the sample size increases). When describing a sample, it is a too-frequent practice to provide the mean plus or minus a value describing variability without identifying whether that value is the SD or the SE. [39] Because the SE is the smaller of the two values, it suggests less variability than would the SD.

Two solutions may lessen the ambiguity. First, because it is usually more important to describe the variability of the population rather than the variability of the mean (and the SE can be calculated by the reader if sample size is reported), perhaps investigators should be required to report only SD rather than SE. A simpler solution would be to require that all values describing the sample be identified as SD or SE, a practice occurring with increasing frequency. Whenever SE is reported, the investigator should ensure that the reader can determine the sample size for that value and thus be able to calculate SD.

Z Transformations

If we select a single value from the population, it would be of value to know the location of that value within the population. For example, if we found that 30 minutes after administration of pancuronium, subject A had a serum drug concentration of 150 ng/mL, we might inquire how that subject compared in that regard with other subjects given the

same dose. If we knew that the average serum drug concentration for a number of other subjects was 200 ng/mL 30 minutes after drug administration, we could conclude that the value for subject A was lower than the mean. However, without knowing the distribution of data for the other subjects, we would not be able to conclude whether this subject had an unusual response. If we also knew the SD for the other subjects, we would be able to better estimate whether this subject differed from others. If the SD for the sample was 40 ng/mL, the value for subject A would be less than 2 SD from the mean. In contrast, if the SD were 5 ng/mL, the value for subject A would be 10 SD below the mean; such an occurrence would represent an unusual response.

The distance that a value lies from the mean can be expressed mathematically as the difference between that value and the mean divided by the SD (sigma). This statistic, known as the *Z transformation*, is calculated as

that is, how many SD the measured value is from the mean. If Z is large, the new value is far from the mean; if Z is small, the value is near to the mean.

Probability

If we measured P_ACO_2 in a single subject undergoing light desflurane anesthesia, we might obtain a value of 61 mm Hg, a value that occurred infrequently in our other subjects (see Fig. 21-3). If the population mean were 46 mm Hg and the SD 6 mm Hg, the Z score would be (61 - 46)/6 or 2.5, a value that indicates this subject had an unusual response to light desflurane anesthesia. Examining a table of Z scores reveals that values of 2.5 or greater occur less than 2 percent of the time. If we

established that this subject was healthy and that no other obvious reason existed for the greater degree of respiratory depression, we would be able to say that this response is unlikely. However, statistics does not permit us to conclude that the response is abnormal.

The concept of probability attaches a numeric likelihood to the occurrence of an event. Regarding the occurrence of a $P_{A}CO_2$ of 61 mm Hg during light desflurane anesthesia, we can conclude from our other measurements that this event occurs in fewer than 2 percent of all anesthetics; this degree of likelihood is expressed as $P < .02$. Is this a significant event? Instinct tells us that an event occurring less frequently than once in 50 times is unusual and therefore worthy of notice. Is an event occurring once in 10 times ($P = .10$) worthy of notice? By convention, statisticians accept as significant any event that occurs less frequently than once in 20 times ($P < .05$). However, no biologic or mathematical rationale exists for choosing 5 percent as the level of statistical significance. R.A. Fisher, a noted statistician, observed that "The value for which $P = .05$, or 1 in 20, is 1.96 or nearly 2 [SD]; it is convenient to take this point as a limit in judging whether a deviation is to be considered significant or not. Deviations exceeding twice the standard deviation are thus formally regarded as significant." [40] Later he wrote, "It is usual and convenient ... to take 5 per cent. as a standard level of significance ... [and] to ignore all results which fail to reach this standard ...." [41] Although a probability of 5 percent is the usual standard for statistical significance, one publication, the *Journal of Experimental Psychology,* has encouraged a significance level of 1 percent (i.e., $P < .01$). [42]

Type I and Type II Errors

The level of probability we select as representing significance, known as alpha, is also the frequency with which we erroneously conclude that a difference exists when there is no real difference. This is known as a *type I error,* or an a *error.* Alternatively, we could ask how often we can afford to be wrong. If an investigator repeats an experiment frequently, he or she will eventually select a sample whose mean differs significantly from the population mean. If we select a probability level of 5 percent (alpha = 0.05), we accept a 5 percent chance of being wrong. If the price for being wrong is very great, we may select a stricter criterion for statistical significance--for example, alpha = 0.01.

Thus far, we have focused on the issue of erroneously concluding that a difference exists when none exists in reality. A second issue involves whether we can truly state that no difference exists between 2 populations. For example, if we were to measure recovery of twitch tension 60 minutes after administration of a dose of pancuronium in a group of subjects and 90 minutes after administration of the same dose in another group, instinct would tell us that more recovery would have occurred in the group studied at 90 minutes. If the samples consisted of 3 patients each, the variability within each of the groups might be great enough to prevent us from detecting a difference; therefore, we might erroneously conclude that no recovery had occurred between 60 and 90 minutes. With samples of 20 subjects or more, we are more likely to detect a difference. The ability of a statistical test to detect a difference, known as its power, depends on the expected difference between groups, the variability within the groups, and the size of the samples. If the sample size is not sufficiently large, we will not be able to detect real differences between groups. This is known as a *type II* or beta *error.* Type II errors commonly occur when an investigator selects the sample size without considering the issues mentioned earlier. To avoid this type of error, the investigator should perform a *power analysis* prior to initiating any data collection. Several approaches to power analysis are described later in this chapter.

One-Tailed Versus Two-Tailed Comparisons

Thus far, we have considered the idea that a value located toward either extreme of the probability distribution is unlikely to occur. If alpha equals .05 and the distribution is symmetric, then the 5 percent of values considered unlikely to occur (and therefore worthy of note) would be found equally at both ends of the distribution; that is, the left-hand

tail of the curve would contain 2.5 percent of the values, and the right-hand tail of the curve would contain 2.5 percent of the values. An analysis that examines both tails of the curve is known as a *two-tailed comparison.*

An investigator often has a priori (i.e., "before the fact") assumptions that he or she is interested in testing. For example, in assessing the relationship between volume status and blood pressure, we would only be interested in assessing whether blood pressure was lower in hypovolemic patients, because we assume that hypovolemia would decrease, rather than increase, blood pressure. If we performed the two-tailed test, we would be able to answer two questions: First, does blood pressure differ between normovolemic and hypovolemic subjects? If so, is blood pressure higher or lower in hypovolemic patients? If we are interested in only one extreme, we can examine the 5 percent located at one end of the distribution, rather than the 2.5 percent located at each end of the distribution. This is known as a *one-tailed comparison.* If the investigator is able to make an a priori assessment as to the direction of the relationship between groups and is willing to limit statistical evaluation to that issue, a one-tailed test may be appropriate. The investigator must decide to perform a one-tailed comparison before the data are collected. It is inappropriate to examine the data, observe a difference between groups, and then test the significance of the difference using a one-tailed comparison.

Hypothesis Testing and Statistics

Statistics does not permit us to conclude whether or not an association is valid, only whether it is likely or unlikely to have occurred. For example, if we studied an adult with chronic lung disease whose P_{ACO_2} values were 59 mm Hg during desflurane anesthesia, we might ask whether this patient differed from the healthy adults mentioned previously whose $P_{A}CO_2$ was measured during desflurane anesthesia (i.e., does chronic lung disease affect ventilatory response during desflurane anesthesia?). A statistician would convert this question into a *null hypothesis;* that is, that there is no difference between this sample and the population. The likelihood of this hypothesis would then be tested. If the alpha were low, such as less than 5 percent, the statistician would reject the null hypothesis, stating that there is little probability that the sample was selected from the original population. In turn, we can conclude that there is likely to be a difference between these subjects and the original sample.

Before continuing to inferential statistics, we should define certain terms more specifically. The word *statistics* describes not only the name of the discipline that is the subject of this chapter, but also certain numeric entities calculated as part of that discipline. For example, mean, SD, and variance are all statistics. A statistic is an estimate, based on random sampling of the population, of parameters of the population. In addition, *t, F,* and a multitude of other symbols represent statistics. Tests employing these statistics are known as *parametric tests;* such tests are based on the actual magnitude of the values. In contrast, tests based on ranking of the values are known as *nonparametric tests.*

INFERENTIAL STATISTICS

After determining the descriptive statistics and noting differences between groups, the investigator would typically like to draw statistical conclusions regarding these differences. To draw these conclusions, the investigator employs a second area of statistics known as *inferential statistics.*

One- and Two-Sample t-Tests

The most widely used, and misused, statistical test is Student's *t*-test, a group of statistical tests designed for analysis of a single group or comparison of two groups. The name of this test refers to a pseudonym used by W.L. Gosset. Gosset's employer, the Guinness Brewing Company, did not permit its employees to publish their research under their own names; however, because of the importance of this work, Gosset was permitted to publish under the name Student. [43] Gosset's contribution was to develop the *t* distribution. The Z distribution (Z scores) described earlier is based on an infinite sample size. Gosset recognized that with smaller sample sizes (e.g., less than 30), the distributions differed from the exact bell-shape of the gaussian distribution. In particular, the presence of an extreme value (i.e., one far from the mean) was more likely to occur in a small sample. Gosset examined a variety of distributions of small samples and determined the frequency with which the more extreme values occurred.

Earlier we observed that in an infinitely large, normally distributed sample, 95 percent of all observations fell within 1.96 SD of the mean. Gosset found that with a sample size of 20, a slightly larger range, 2.09 SD, was necessary to include the same 95 percent of the observations. As the sample size decreased to 10, 2.26 SD were necessary; with a sample size of 5, an even larger range, 2.78 SD, was necessary to include 95 percent of all observations. These values (e.g., $t = 2.09$ for alpha = 0.05 and $N = 20$) comprise the *t* distribution. Every value in the *t* distribution is associated with a sample size and a value for alpha. As the sample size becomes large (e.g., >30), the values for the *t* distribution approach those for the Z distribution; with an infinite sample size, they are identical. Gosset's observations were then used to define three statistical tests: the one-sample, the twosample, and paired-sample *t*-tests.

Parametric t-Tests

One-Sample t-tests

If an investigator measures a variable in a single group of subjects, he or she may be interested in determining whether the mean for this sample differs from zero (or alternatively, from some other specific value). This analysis can be performed using the one-sample *t*-test. To examine the association between diuretic drugs and acid-base status, we might identify a group of patients taking diuretic drugs, obtain arterial blood samples, and determine base excess. A hypothetic set of values is shown in Table 21-7 . The mean of

TABLE 21-7 -- Hypothetic Set of Values for Base Excess for Subjects Given Diuretic Drugs

SUBJECT		BASE EXCESS (MEQ/L)
1		0
2		8
3		1
4		6
5		-3
6		7
7		9
8		2
9		1
10		0
11		-1
12		6
	N = 12	
	Mean = 3.0	
	Standard deviation = 3.98	
	Standard error = 1.15	
	Degrees of freedom = 11	

these values is 3.0, a fact that might suggest an association between diuretic drugs and alkalosis. However, two of the subjects have negative values and two have zero values. Because a quick and informal appraisal of the data (the "eye" test) cannot determine whether 3.0 differs significantly from zero, we must use statistical analysis--in this case, the one-sample *t*-test. If we assume that this sample represents the population and that the distribution of these values is normal, we can state with 95 percent confidence that the population mean lies between [mean - ($t \times SE$)] and [mean + ($t \times SE$)]. This statement is similar to an earlier one that the population mean lies between [mean - (1.96 × SE)] and [mean + (1.96 × SE)]. However, the value 1.96 (the Z value to include 95 percent of the population) must now be replaced by the value of *t* appropriate for the sample size, that is, 2.20. This value can be found on a table of *t* distribution by locating the row corresponding to the appropriate *df* (in this case, the value for *df* is one less than the sample size) and the desired value of alpha (typically, 0.05). Sample values for *t* distribution are shown in Table 21-3 ; a complete listing can be found in any statistical textbook. In this case, the 95 percent confidence limits for the mean are 0.47 and 5.53; these limits do not include the value zero. To determine the 99 percent confidence limits, we use the *t* value for alpha = 0.01 and 11 *df,* 3.11. This results in 99 percent confidence limits of -0.57 and 6.57, a range that does include zero. We can conclude with 95 percent, but not 99 percent, confidence that the use of diuretic drugs is associated with alkalosis. Note that our conclusion is limited to making an association between diuretic drugs and alkalosis rather than implying causality. Statistics

does not prove causality, only the likelihood of an association.

An alternate approach to this problem, more familiar to some readers, is shown in Table 21-8 . The division of the mean value by the SE produces a value for *t.* This value is compared with a value for *t* appropriate for the desired level of significance (usually, alpha = 0.05 or 5%) for the appropriate degrees of freedom. If the value for *t* exceeds the value from

TABLE 21-8 -- One-Sample Student's *t*-Test Applied to Hypothetic Data from Table 21-7

$t_{0.05(2),11}$ [a] = 2.20

$t_{0.01(2),11}$ [b] = 3.11

Therefore, .01 < *P* < .05

SE, standard error.

Notation from Zar [29]

[a] Read, "the two-tailed *t* value when alpha = 0.05 and degrees of freedom = 11."
[b] Read, "the two-tailed *t* value when alpha = 0.01 and degrees of freedom = 11."

the table (known as the *critical value*), the null hypothesis is rejected, and we would conclude that a difference exists (at the alpha level) between zero and the mean value for this population. In this instance, the value for *t* is 2.6. The critical value for *t* for alpha = 0.05 and 11 *df* is 2.20; the value for *t* for alpha = 0.01 and 11 *df* is 3.11. The value for *t* exceeds the critical value for alpha of 0.05, but not for alpha of 0.01. This fact also leads us to conclude (as we did earlier) that the mean for this sample differs from zero and that the likelihood is between 95 and 99 percent.

The one-sample *t*-test can also be applied to populations for which mean values are expected to be other than zero. For example, if we were interested in whether 90 mm Hg was the mean Pa_{O_2} of smokers, we would determine the difference between 90 mm Hg and the mean value for the sample population, divide this value by the SE of the sample to determine the *t* statistic, and then compare the resulting value with the critical value for *t.*

Two-Sample t-Tests

More commonly, we make measurements on two groups of subjects and compare the responses. Such a comparison requires use of the two-sample *t*-test. In this form of *t*-testing, two independent samples are being compared, that is, an individual datum in one sample is not associated with another datum in the second sample. For example, we might want to compare blood pressure in normovolemic and hypovolemic individuals. Hypothetic values are provided in Table 21-9 . In this instance, an informal appraisal of the data would establish that a significant difference exists between the mean values. This difference can be confirmed by using the two-sample *t*-test to evaluate the null hypothesis that there is no difference between these two samples; that is, they come from the same population.

Computation of the *t* statistic for the two-sample test is slightly more complicated than for the one-sample test. In the one-sample test, we divided the mean by its SE. With two samples, each sample has its own SE; we then determine the SE of the difference between the means. Although the derivation of the SE between the means is beyond the scope of this chapter, [44] the denominator of the equation is similar to that for the one-sample test:

TABLE 21-9 -- Application of the One-Tailed Two-Sample Student's *t*-Test to Hypothetic Sets of Mean Blood Pressure Values for Normovolemic and Hypovolemic Subjects

	NORMOVOLEMIC SUBJECTS	HYPOVOLEMIC SUBJECTS
	77	72
	91	62
	101	51
	81	81
	76	47
	68	74
	72	52
	82	65
N	8	8
Mean	81.0	63.0
SD	10.6	12.3
SE	3.76	4.33
$t_{0.05(1),14}$ [a] = 1.76		
$t_{0.01(1),14}$ [b] = 2.62		
Therefore, *P* < .01		

SD, standard deviation; SE, standard error.

[a] Read, "the one-tailed *t* value when alpha = 0.05 and degrees of freedom = 14."
[b] Read, "the one-tailed *t* value when alpha = 0.01 and degrees of freedom = 14."

Alternate methods are available to calculate the SE of the difference between means, one of which uses a pooled variance instead of the separate variances of equation (15). [44] Despite the different methods for calculation, the SE are similar.

Next, the difference between groups is divided by this SE; this process produces the now familiar *t* statistic, which is then compared with the critical value from the tables. If the value for *t* exceeds the critical value, the null hypothesis is rejected; if *t* is less than the critical value, the null hypothesis cannot be rejected. An instinctive approach to the comparison between the calculated value for *t* and the critical value is as follows: the numerator is the difference between the mean values, an estimate of the distance between the central location of the two samples. The denominator, shown in equation 15, is the SE of the difference between means, an estimate of the variability within the samples. The ratio of these values estimates how much of the difference between means can be explained by the variability within the samples. If the variability within each of the samples is small, only a small difference between mean values should be sufficient to suggest that a difference exists between the samples. In contrast, if the variability within one or both of the samples is great, the difference between the means of the samples must be larger if the investigator is to have confidence that a difference exists between groups.

Before using a table of *t* values to determine the critical value for this example, we should consider one special aspect. In our hypothetic situation, we have been comparing blood pressure in normovolemic and hypovolemic individuals. Our a priori assumption is that blood pressure will be lower, rather than higher, in the hypovolemic group. Therefore, rather than perform a two-tailed comparison that would permit us to assess all possible relationships among the data, it would be appropriate to perform a one-tailed test. Because the critical value for *t* (alpha = 0.05, *df* = 14) is lower for a one-tailed comparison (1.76) than for a two-tailed comparison (2.14), we have increased our chances of detecting a statistically significant difference by using the former.

In this example, the *t* statistic is markedly greater than the critical value; we conclude that it is unlikely (*P* < .05) that these two samples were selected from the same population. Therefore, the mean value for blood pressure is lower for these hypovolemic individuals than for normovolemic individuals. Because the *t* statistic is markedly greater than the critical value for alpha = 0.05, we can refer to the table to determine the critical values for higher levels of significance. With 14 *df,* the one-tailed *t* is 2.62 when alpha = 0.01 and 2.98 when alpha = 0.005. Because the *t* statistic exceeds both these values, we can conclude that the likelihood of these samples being from the same population is extremely small, less than 0.005 or 1 in 200.

Paired-Sample t-Tests

On occasion, an investigator obtains measurements before and after an intervention and then studies whether this intervention produced a significant effect. Under these circumstances, when the two samples being compared are paired, a *paired-sample* t- *test,* more commonly called a *paired* t *-test,* is used. For example, measuring cardiac output before and after the administration of pancuronium might produce the values shown in Table 21-10 . In this instance, an informal appraisal of the data suggests a strong difference between the "before" and "after" values, because five of six subjects had an increase in cardiac output. The paired *t*-test is used to confirm this observation. A new sample is created whose members are equal to the difference between the "before" and "after" values for each subject. This new sample is then analyzed by the one-sample *t*-test. The mean value for this sample is 0.80 L/min, and the SE is 0.30 L/min. Therefore, the *t* statistic is 2.69, a value that exceeds the critical value of 2.01 (again, we can use a one-tailed test because we assume that pancuronium will increase, not decrease, cardiac output). We would conclude that the "before" and "after" measurements are unlikely to be from the same population. This conclusion suggests that pancuronium increases cardiac output.

An alternate statistical approach to this hypothetic situation would be to use the two-sample *t*-test (Table 21-11) . This test produces a value for *t* of 1.69, which is less than the critical value of 1.81. Despite the greater degrees of freedom for the two-sample test (10) than for the one-sample test (5), the unpaired test does not support our belief that a difference exists between the "before" and "after" values. This lack of confirmation results because of the variability of the "before" and "after" values. The two-sample test assumes that the investigator obtained the "before" measurements in one group of subjects and the "after" measurements in another group. The paired test is more sensitive to small changes because it assumes that the "before" and "after"

TABLE 21-10 -- Application of the Paired *t*-Test to Hypothetic Values for Cardiac Output Before and After Administration of Pancuronium

SUBJECT	CARDIAC OUTPUT BEFORE PANCURONIUM (L/MIN)	CARDIAC OUTPUT AFTER PANCURONIUM (L/MIN)	CHANGE IN CARDIAC OUTPUT (L/MIN)
1	4.3	5.7	+1.4
2	5.6	5.4	-0.2
3	3.9	4.6	+0.7
4	5.7	7.3	+1.6
5	4.8	6.0	+1.2
6	5.2	5.3	+0.1
Mean	4.92	5.72	0.80
Standard deviation	0.72	0.91	0.73
Standard error	0.29	0.37	0.30
$t_{0.05(1),5}$ [a] = 2.01			
Therefore, *P* < .05			

[a] Read, "the one-tailed *t* value when alpha = 0.05 and degrees of freedom = 5."

TABLE 21-11 -- Inappropriate Application of the Two-Sample *t*-Test to the Hypothetic Analysis of Data of Table 21-10

$t_{0.05(1),10}$ [a] = 1.81	
Therefore, *P* > .05	
SE, standard error.	

[a] Read, "the one-tailed *t* value when alpha = 0.05 and degrees of freedom = 10."

values were measured in the same subject. For example, a change in cardiac output from 4 to 6 L/min in one subject means something entirely different than would the measurement of 4 L/min in one subject before pancuronium and the measurement of 6 L/min in a different subject after pancuronium.

Nonparametric t-Tests: the Mann-Whitney U-Test

Data on an ordinal scale require special treatment, because determining means and variances for this kind of data is usually inappropriate. In order to make statistical

comparisons on ordinal data, nonparametric tests, which assess the relative ranks rather than the magnitude of the data, are applied. Most parametric tests have a corresponding nonparametric test.

Nonparametric tests are also valuable for analyzing samples that deviate strongly from the normal distribution. Although parametric tests are based on the assumption that distribution is normal, they are sufficiently powerful (statisticians use the term *robust*) to detect differences even when samples are not distributed normally. However, as the samples stray significantly from a normal distribution, parametric tests lose their ability to detect differences. Because nonparametric tests analyze only the ranks rather than the individual values, they may detect differences not detected by parametric tests.

The nonparametric test corresponding to the two-sample *t*-test is the Mann-Whitney *U*-test. With this test, the values in each of the two groups are assigned ranks. The smallest (or largest) value is assigned the rank of 1; the next smallest (or next largest), the rank of 2. This process continues until the largest (or smallest) value has been assigned the rank equal to the sum of the two sample sizes. If values are tied in rank, they are assigned a value equal to the average of the corresponding ranks. For example, if two samples are tied for ranks 4 and 5, both are assigned the rank of 4.5. The statistics R_1 and R_2 are equal to the sum of the ranks for groups 1 and 2, respectively. The test statistic, *U,* is determined by the following equation:

where n_1 and n_2 are the sizes of the first and second groups, respectively. The value for *U* is then compared with critical values for *U* obtained from a table. The data comparing the blood pressures of normovolemic and hypovolemic subjects (see Table 21-9) can be analyzed using the Mann-Whitney *U*-test, as shown in Table 21-12 . As with the two-sample *t*-test, the results of the Mann-Whitney *U*-test suggest a difference between the two groups ($P < .05$). Nonparametric tests such as the Mann-Whitney *U*-test rarely appeared in the anesthesia literature until recent years; however, with increased sophistication in research, these tests are being used more frequently. The nonparametric version of the paired *t*-test is the Wilcoxon paired-sample test.

Comparing Three or More Groups

The critical values for *t* are calculated with the assumption that comparisons are being made between only two

TABLE 21-12 -- Nonparametric Comparison of Hypothetic Data from Table 21-9 Using the Mann-Whitney *U*-Test

BLOOD PRESSURE		RANKS	
NORMOVOLEMIC	***HYPOVOLEMIC***	***NORMOVOLEMIC***	***HYPOVOLEMIC***
77	72	11	7.5
91	62	15	4
101	51	16	2
81	81	12.5	12.5
76	47	10	1
68	74	6	9
72	52	7.5	3
82	65	14	5
$n_1 = 8$			
$n_2 = 8$			
$R_1 = (11 + 15 + ... + 14) = 92$			
$R_2 = (7.5 + 4 + ... + 5) = 44$			
$U = n_1 \times n_2 + n_1 \times (n_1 + 1)/2 - R_1 = 8 \times 8 + 8 \times 9/2 - 92 = 8$			
or			
$U = n_1 \times n_2 + n_2 \times (n_2 + 1)/2 - R_2 = 8 \times 8 + 8 \times 9/2 - 44 = 56$			
$U_{0.05(2),8,8}$ [a] = 51			
$U_{0.01(2),8,8}$ [b] = 57			
Therefore, $0.01 < P < .05$			

[a] Read, "the two-tailed *U* value when alpha = 0.05, $n_1 = 8$, and $n_2 = 8$."

[b] Read, "the two-tailed *U* value when alpha = 0.01, $n_1 = 8$, and $n_2 = 8$."

groups. If the investigator collected data on three groups of subjects, three comparisons would be possible: A versus B, A versus C, and B versus C. If each of these comparisons was made using the two sample *t*-test and alpha = 0.05, we would be accepting a 5 percent risk of committing a type I error for each comparison. For three comparisons, the chance of committing a type I error increases to approximately 3 × 5 percent, or 15 percent (actually closer to 14 percent [*]), a level that is usually considered unacceptable. As the number of groups increases, the number of possible comparisons increases such that, with enough groups, the investigator will eventually uncover a nonexistent difference.

Thus, the *t*-test is properly used for comparing two groups (or a single group to a predetermined value). When more than two groups are being compared, other tests, particularly analysis of variance, are more appropriate. If the investigator chooses to use the *t*-test to compare more than two groups, a correction must be made to prevent type I errors. When one such correction, the *Bonferroni inequality* (or *Bonferroni correction*), is applied, the alpha level for each comparison is divided by the number of comparisons to be performed. For example, if the investigator chooses a value of 0.05 for alpha and three comparisons are possible, a value of 0.05/3 or 0.0167 for alpha should be used for each of the comparisons. Then, the investigator is able to state that, overall, the chance of committing a type I error is less than 5 percent.

If the Bonferroni inequality is used, the investigator must decide in advance which of the comparisons will be made. For example, if there are four groups, the investigator may choose to compare group I with each of the other groups (e.g., if subjects in group I were given the placebo and subjects in groups II to IV were given one of three different drugs). In this case, only three of the six possible comparisons will be made. However, it is inappropriate to examine the data and then decide a posteriori which comparisons to make.

Multisample Tests: Analysis of Variance

Parametric Analysis of Variance

The *t*-test enabled examination of a single group or comparison of two groups. For comparison of three or more groups, another test, *analysis of variance* (also known as *single-factor analysis of variance* or *one-way analysis of variance*) is necessary. Analysis of variance is similar in principle to the two-sample *t*-test. Using analysis of variance, we determine two values, one value describing the variability between groups, and the other describing the variability within the groups. For the two-sample *t*-test, these values consisted of the difference between mean values and the SE of the difference between the means. For analysis of variance, the square of corresponding values is used. The variability between groups is called the *between-groups variance* (also the *groups variance*); variability within groups is called the *within-groups variance* (also the *error variance*). For the two-sample *t*-test, we divided the difference between the mean of each of the groups by the appropriate SE; similarly, for analysis of variance, we divide the between-groups

* For each comparison in which the investigator permits a type I error of alpha, he or she is (1 - alpha) confident that no error exists. For *n* comparisons, he or she is (1 - alpha) ^{n} confident that no error exists; conversely, the probability of a type I error is [1 - (1 - alpha) ^{n}].

variance by the within-groups variance. This process produces the statistic *F.* As with the *t*-test, this *F* value is compared with critical values from a table of *F* values: if *F* exceeds the critical value for the desired probability, we conclude that it is unlikely that the difference between the mean values occurred by chance, and we reject the null hypothesis. To determine the between-groups variance, we create a sample consisting of the mean values of the individual groups, determine its SS, and divide by the appropriate *df.* However, the resulting value estimates the variance of the mean rather than the variance of the population. Because we know that the variance of the mean is equal to the variance of the population divided by sample size (this is equivalent to saying that SEM is equal to SD divided by the square root of the sample size), we can estimate the between-groups SS by using the following:

where *k* is the number of groups, n_i is the number of subjects in each group, and *X* is the *grand mean* of the sample (the mean of values from all groups). The *between-groups variance* (also known as the *between-groups mean square* [MS]) is then estimated using this equation:

The within-groups sum of squares is obtained by calculating the SS for each individual group and adding these values. This SS is then divided by the appropriate *df* (the sum of *df* of the individual groups, i.e., one less than the size of each group) resulting in the *within-groups MS:*

where *N* is the total number of subjects in all groups. The Sigma within the brackets represents the SS for each of the groups; the outer Sigma means to sum these values. Having estimated the between-groups variance (the between-groups MS) and the within-groups variance (the within-groups MS), we calculate their ratio, *F:*

We then refer to a table of *F* values to learn whether this value exceeds the critical value. If *F* exceeds this value, we conclude that the difference between the mean values of the groups was not likely to occur as a result of the variability within groups. Thus, we can reject the null hypothesis and conclude that a difference exists between the groups.

In Table 21-13 , analysis of variance is used to compare volumes of distribution for histodrenaline (the imaginary drug causing release of either histamine or epinephrine) in

TABLE 21-13 -- Use of Single-Factor Analysis of Variance to Compare Hypothetic Values for Volume of Distribution (mL/kg) of "Histodrenaline" [a] in Three Age Groups

	INFANTS	CHILDREN	ADULTS
	465	291	192
	293	225	212
	371	287	270
	405	302	251
	451	210	290
N	5	5	5
Mean	397	263	243
Grand mean = (397 + 263 + 243)/3 = 301			
Between-group SS = $5(397 - 301)^2 + 5(263 - 301)^2 + (243 - 301)^2 = 70120$			
Between-group *df* = 3 - 1 = 2			
Between-group MS = 70120/2 = 35060			
Infant SS = $(465 - 397)^2 + (293 - 397)^2 +... = 19096$			
Child SS = $(291 - 263)^2 + (225 - 263)^2 + ... = 7134$			
Adult SS = $(192 - 243)^2 + (212 - 243)^2 +... 6564$			
Within-group SS = Infant SS + Child SS + Adult SS = 32794			
Within-group *df* = 3(5 - 1) = 12			
Within-group MS = 32794/12 = 2732.83			
$F_{0.05(1),2,12}$ [b] = 3.89			
$F_{0.0025(1),2,12}$ [c] = 10.3			

Therefore, $P < .0025$ that at least one group mean differs from the others

df, degrees of freedom; MS, mean square; SS, sum of squares.

[a] An imaginary drug causing release of either histamine or epinephrine.
[b] Read, "the one-tailed *F* value when alpha = 0.05, the between-groups *df* = 2, and the within-groups *df* = 12."
[c] Read, "the one-tailed *F* value when alpha = 0.0025, the between-groups *df* = 2, and the within-groups *df* = 12."

infants, children, and adults. The between-groups variance is 35,060, and the within-groups variance is 2,732.83; the resulting value for *F* is 12.83. Because this value exceeds the critical value for *F* for alpha = 0.05 and the appropriate degrees of freedom (note that we must now consider the number of degrees of freedom in both the numerator and the denominator), we can conclude that it is unlikely that the three samples were selected from the same population.

One-Way Analysis of Variance: Intragroup Comparisons

Using analysis of variance, we tested the null hypothesis that there is no difference in the mean value of any of the multiple groups. If we reject the null hypothesis, we can conclude that at least one of the mean values differs from at least one of the other mean values, not that each of the groups is different from each of the other groups. For example, in Table 21-13 , analysis of variance suggests that at least one group differs from the other groups. Examination of the data shows that the mean value for infants differs from the other mean values, and that no difference appears to exist between children and adults. To verify this observation, we need to apply a multiple comparison test. These tests fall into one of several categories, depending on whether the investigator is interested in all possible comparisons between

TABLE 21-14 -- Application of the Student-Newman-Keuls Test for Multiple Comparisons with the Hypothetic Data from Table 21-13

	INFANTS	CHILDREN	ADULTS
Mean	397	263	243
N	5	5	5

Error mean square = 2,732.83

COMPARISON	DIFFERENCE	SE	*q*	*p*[a]	$q_{0.05(2),12}$[b]	CONCLUSION
Infants versus Adults	154	23.4	6.58	3	3.77	$P < 0.05$
Infants versus Children	134	23.4	5.73	2	3.08	$P < 0.05$
Children versus Adults	20	23.4	0.85	2	3.08	$P > 0.05$

Therefore, the mean value for infants differs from that for children and adults; no difference exists between the mean values for children and adults.

SE, standard error.

[a] The number of mean values (groups) across which the comparison is made.
[b] Read, "the *q* value when alpha = 0.05 and degrees of freedom = 12."

pairs (the number of possible comparisons is equal to one-half the product of the number of groups and the number of groups minus one) or only specific ones.

All Possible Comparisons.

Numerous tests permit multiple comparisons, such as the Newman-Keuls test (also known as the Student-Newman-Keuls test), the Duncan test, the least significant difference test [*] , the Tukey test, and the Scheffe method. Although there is no consensus regarding the best multiple comparison test, the StudentNewman-Keuls test exemplifies the general procedure and is described here. To perform the Student-Newman-Keuls test, the investigator calculates the difference between the means of the largest and the smallest groups, followed by the next largest to the smallest, and so on, until all possible differences have been calculated. The SE is determined in a manner similar to that for the *t*-test, as the square root of the ratio of the within-groups MS (obtained from the analysis of variance) to the size of each of the groups [$SE = (s^2 / n)^{1/2}$].

The between-groups differences are then divided by the appropriate SE, much as with the two-sample *t*-test. This process produces the Student-Newman-Keuls statistic, *q;* critical values for *q* can be obtained from a table. In evaluating differences between the extreme means and differences between the less extreme means, the Student-Newman-Keuls test considers the number of ranks (*p*) between the means being compared. [45] As a result, the critical values for *q* are based on the number of groups being spanned in the comparison. In Table 21-14 , the Student-Newman-Keuls test is applied to the hypothetic data of Table 21-12 . Instructions regarding the use of other multiple comparison tests can be found in standard statistics textbooks.

Comparison to the Control Value.

The StudentNewman-Keuls test and other multiple comparison tests described previously are valuable when all possible comparisons must be made. However, the investigator pays a penalty for the opportunity to perform all possible comparisons between pairs, a penalty that may not be acceptable when the investigator is interested in a limited number of comparisons. For example, if subjects were given either placebo or one of four drugs, the investigator may be interested only in the comparison of each of the four drugs with the control state, rather than any comparisons among the four drugs. Although there are ten (i.e., 5 × 4/2) possible comparisons between the five groups, the investigator is interested in only four of these comparisons.

When an investigator is interested in only the comparisons between the control group and each of the test groups, the Dunnett test is most appropriate. First, the difference between the control mean and the mean of each of the other groups is determined. Then, the SE is determined: $SE = (2\ s^2 / n)^{1/2}$ where s^2 is the within-groups MS determined by analysis of variance, and *n* is the size of each of the groups. [*] The differences between the control value and each of the other means is then divided by the appropriate SE; the result is the test statistic, *q*
. As before, these values are compared with the appropriate critical value. Table 21-15 provides an example of how to apply the Dunnett test to compare systolic blood pressure for four hypothetic groups of subjects.

Specific Comparisons.

In certain instances, the investigator may desire to make only specific comparisons among

* Although the least significant difference test is reported by many statistical packages, its use is discouraged by at least one statistician. [29]

With the Student-Newman-Keuls test, if sample sizes are unequal, the SE is calculated as

where s^2 is the within-groups MS, and n_a and n_b are the sizes of each of the samples. Thus, SE may differ for each of the comparisons if sample sizes differ.

* With the Dunnett test, if group sizes are unequal, SE is calculated as

where n_a and n_b are sizes of each of the samples.

TABLE 21-15 -- Application of the Dunnett Test to Systolic Blood Pressure for Hypothetic Subjects Given Placebo or Premedications A, B, or C

	GROUP 1 (PLACEBO)	GROUP 2 (PREMEDICATION A)	GROUP 3 (PREMEDICATION B)	GROUP 4 (PREMEDICATION C)
	131	120	97	134
	127	117	105	147
	110	131	112	122
	125	110	121	138
	147	122	100	129
Mean	128	120	107	134
N	5	5	5	5

Error mean square (determined from analysis of variance) = 104.13

COMPARISON	DIFFERENCE	SE	*q*	*p*[a]	$q_{0.05(2),16}$[b]	CONCLUSION
1 versus 3	21	6.45	3.25	3	2.42	*P* < .05
1 versus 2	8	6.45	1.24	2	2.12	*P* > .05
1 versus 4	6	6.45	0.93	2	2.12	*P* > .05

Therefore, compared to placebo, premedication B (but not premedications A or C) decreases systolic blood pressure.

SE, standard error.

[a] The number of mean values (groups) across which the comparison is made.
[b] Read, "the *q* value when alpha = 0.05 and degrees of freedom = 16."

groups. For example, in comparing the values for desflurane minimum alveolar concentration (MAC) for 6 ethnic groups (e.g., Chinese, Japanese, German, French, Argentinian, and Peruvian), the investigator may be interested in only three (Chinese versus Japanese, German versus French, and Argentinian versus Peruvian) of the 15 (6 × 5/2) possible comparisons. The multiple comparison tests described earlier would be inappropriate for this purpose. If the investigator is interested in only a small number of comparisons, it is occasionally appropriate to perform multiple *t*-tests with the Bonferroni correction (Bonferroni inequality). As mentioned earlier, alpha values are adjusted to the number of comparisons to be performed. If the investigator is interested in performing 3 comparisons with an overall significance level of 0.05, the significance level is adjusted to 0.05/3 or 0.0167. For each of the comparisons, a level of 0.0167 must be achieved to permit the investigator to claim a difference between any of the groups. As the number of comparisons increases, the level of significance required by each (0.05 divided by the number of comparisons) is difficult to achieve, and the test becomes overly conservative (i.e., the investigator is unlikely to detect a difference even if one exists). To use *Bonferroni*' *s* t *-test* (the application of the Bonferroni inequality to the two-sample *t*-test), the investigator must make an a priori decision as to which comparisons will be made. In the example described earlier, the choice of comparisons was based on geographic considerations. It is not considered acceptable to perform multiple *t*-tests, to make an a posteriori decision as to which are the most significant, and then to use the Bonferroni inequality based on the number of comparisons that are likely to be significant.

Repeated-Measures (Two-Way) Analysis of Variance

Just as the paired *t*-test may detect differences not found with the two-sample *t*-test (when the study design has resulted in paired measurements), a paired test corresponding to analysis of variance *(repeated-measures analysis of variance)* may detect differences not found with single-factor analysis of variance. If the investigator obtains more than two measurements on each subject (each measurement on a subject is called a *treatment*), repeated-measures analysis of variance should be employed. Just as the SE for the paired *t*-test was calculated in a different manner than for the two-sample *t*-test, the denominator for repeated-measures analysis of variance is calculated differently than for single-factor analysis of variance. The within-subject variability results from two factors, that is, variability inherent to the subject (equivalent to the error variability for single-factor analysis of variance) and the variability resulting from the treatments. This can be stated as

The within-subject SS is determined by calculating the SS for each subject and determining the sum of these values. The between-treatments (treatment) SS (identical to the between-groups SS for analysis of variance) is calculated from the sample of means for the treatments. The difference between the within-subject SS and the treatment SS is the error SS (equation 20). The variances are determined by dividing the SS by the appropriate *df; F* is the ratio of the treatment variance to the error variance.

Repeated-measures analysis of variance, rather than single-factor analysis of variance, should be used whenever two or more measurements are obtained on the same subject.[*] For example, to assess the effects of neostigmine and

* If repeated-measures analysis of variance is used to compare two measurements, the results will be identical to those of the paired *t*-test, except the analysis of variance is a one-tailed test, whereas the paired *t*-test can be performed as either a one-tailed or a two-tailed test.

TABLE 21-16 -- Application of Repeated-Measures Analysis of Variance to Hypothetic Data for Heart Rate Before and After the Simultaneous Administration of Neostigmine and Atropine

SUBJECT	DRUG ADMINISTRATION			
	BEFORE (BEATS/MIN)	*1 MIN AFTER (BEATS/MIN)*	*5 MIN AFTER (BEATS/MIN)*	*15 MIN AFTER (BEATS/MIN)*
1	67	92	87	68
2	92	112	94	90

	3	58	71	69	62
	4	61	90	83	66
	5	72	85	72	69
Mean		70	90	81	71
N		5	5	5	5

Mean of individual subjects:

Subject 1 = 78.5

Subject 2 = 97.0

Subject 3 = 65.0

Subject 4 = 75.0

Subject 5 = 74.5

SS for individual subjects:

Subject 1 = $[(67 - 78.5)^2 + (92 - 78.5)^2 + (87 - 78.5)^2 + (68 - 78.5)^2] = 497$

Subject 2 = $[(92 - 97)^2 + (112 - 97)c + (94 - 97)^2 + (90 - 97)^2] = 308$

Subject 3 = $[(58 - 65)^2 + (71 - 65)^2 + (69 - 65)^2 + (62 - 65)^2] = 110$

Subject 4 = $[(61 - 75)^2 + (90 - 75)^2 + (83 - 75)^2 + (66 - 75)^2] = 566$

Subject 5 = $[(72 - 74.5)^2 + (85 - 74.5)^2 + (72 - 74.5)^2 + (69 - 74.5)^2] = 153$

Within-subject SS = 497 + 308 + 110 + 566 + 153 = 1634

Grand mean = (70 + 90 + 81 + 71)/4 = 78

Treatment SS = $5(70 - 78)^2 + 5(90 - 78)^2 + 5(81 - 78)^2 + 5(71 - 78)^2 = 1330$

Treatment *df* = 4 - 1 = 3

Treatment MS = 433.33

Error SS = Within-subject SS - Treatment SS = 1634 - 1330 = 304

Error *df* = 3(5 - 1) = 12

Error MS = 25.33

$F_{0.05(1),3,12}$ [a] = 3.49

$F_{0.0005(1),3,12}$ [b] = 12.7

Therefore, heart rate at one time interval differs from heart rate at another time interval. A multiple comparison test (such as the Student-Newman-Keuls test or Dunnett test) is necessary to determine which of these groups differs from the remainder.

df, degrees of freedom; MS, mean square; SS, sum of squares.

[a] Read, "the one-tailed *F* value when alpha = 0.05, the treatment *df* = 3, and the error *df* = 12."

[b] Read, "the one-tailed *F* value when alpha = 0.05, the treatment *df* = 3, and the error *df* = 12."

TABLE 21-17 -- Inappropriate Application of One-Way Analysis of Variance to the Hypothetic Data from Table 21-16

Grand mean = 78

Between-group SS = $5(70 - 78)^2 + 5(90 - 78)^2$ ... = 1330

Between-group *df* = 4 - 1 = 3

Between-group MS = 433.33

Within-group SS = [(67 - 70) + (92 - 70) + (58 - 70) ...] + [(92 - 90) + (112 - 90) + ...] + [(87 - 81) + (94 - 81) + ...] + [(68 - 71) + (90 - 71) + ...] = 2510

Within-group *df* = 4(5 - 1) = 16

Within-group MS = 156.88

$F_{0.05(1),3,16}$ [a] = 3.24

Therefore, when an inappropriate statistical test is used, *P* > .05

df, degrees of freedom; MS, mean square; SS, sum of squares.

[a] Read, "the one-tailed *F* value when alpha = 0.05, the between-groups *df* = 3, and the within-groups *df* = 16."

atropine on heart rate, we might measure heart rate before drug administration and 1, 5, and 15 minutes after drug administration (Table 21-16) . When repeated-measures analysis of variance is performed, *F* is 17.50, a value that markedly exceeds the critical value. In Table 21-17 , these same hypothetic data are analyzed inappropriately using analysis of variance. When this technique is applied, *F* is 2.83, a value less than the critical value, despite the greater *df.* This situation is analogous to that shown in Tables 21-5 and 21-6 , in which the paired *t*-test suggested differences not supported by the two-sample *t*-test.

As with analysis of variance, repeated-measures analysis of variance permits the conclusion that at least one group differs from the others regarding heart rate and the administration of neostigmine and atropine. In the example shown in Table 21-16 , we were able to conclude that at least one of the groups differs from the others. To determine which of the group means differs, we must apply the multiple comparison tests described earlier.

Nonparametric Analysis of Variance: The Kruskal-Wallis Test and the Friedman Test

A nonparametric version of analysis of variance, the Kruskal-Wallis test, can be used for ordinal data, or for ratio or interval data, particularly those data that are not distributed normally. The test is performed by ranking the values in much the same manner as for the Mann-Whitney *U*-test. The sums of ranks are determined, and a

test statistic, *H,* is calculated:

where n_i is the number of observations in the k^{th} group, *k* is the number of groups, *N* is the total number of observations, and R_i is the sum of ranks in each group. *H* is then compared with the critical value obtained from a table. Although a nonparametric version of the Student-Newman-Keuls test exists, it unfortunately requires equal sample sizes for each of the groups.

The Friedman test is a nonparametric version of repeated-measures analysis of variance. As with the Kruskal-Wallis test, ranks, rather than the individual values, are used in the analysis. The test is extremely powerful for the analysis of data in which repeated measures are obtained on the same subject. Nonparametric versions of tests to perform intragroup comparisons also exist.

Diagnostic Tests

When laboratory tests are used to diagnose the presence or absence of disease states, an ideal test is one for which a positive (i.e., abnormal) test is always associated with the presence of disease (termed *true positive* [TP]; Table 21-18) and a negative (i.e., normal) test is always associated with the absence of disease (*true negative* [TN]). Such a test would be both 100 percent "sensitive" and "specific." However, few laboratory tests meet these criteria.

There are four possible relationships between the result of a test and the presence of the disease. In addition to TP and TN, a test may be positive in the absence of the disease (*false positive* [FP]), or the test may be negative when the disease is present (*false negative* [FN]). The frequency of these latter relationships bears tremendous importance to the utility of the diagnostic test.

The terms sensitivity and specificity are typically used to describe the utility of a test. *Sensitivity* is defined as the fraction of patients with the disease who have a positive test, TP/(TP + FN); it indicates how well a test identifies the

TABLE 21-18 -- Terms Used to Define Sensitivity and Specificity

	DISEASE PRESENT	DISEASE ABSENT
Test Positive	True positive (TP)	False positive (FP)
Test Negative	False negative (FN)	True negative (TN)

presence of disease. *Specificity* is defined as the fraction of patients without the disease who have a negative test, TN/(TN + FP); it identifies how well a test identifies the absence of disease. Most tests yield FP and/or FN and are therefore less than 100 percent sensitive and specific.

If the laboratory test involves quantification (e.g., hyperkalemia may be diagnosed by the presence of a serum potassium value > 5.0 mmol/L), the value at which the disease is considered present ("cutoff") influences the reciprocal relationship between sensitivity and specificity, that is, increasing the cutoff increases sensitivity but decreases specificity. To determine the appropriate cutoff for a new diagnostic test, the investigator determines the sensitivity and specificity associated with different cutoff values. A *receiveroperator curve* (ROC) then displays values for sensitivity plotted against (1 - specificity). If the ROC has a slope of 45 degrees, each incremental gain in sensitivity is matched by an equal loss in specificity, and the test is considered worthless. In contrast, an ROC with a steep section indicates a worthwhile test, and the ideal cutoff is the point at which the ROC bends steeply; that is, a further increase in sensitivity decreases specificity. Reich et al [46] used this approach to develop an "expert system" to assess arterial blood pressure lability during anesthesia (Fig. 21-6) .

Equally important to sensitivity and specificity, but less frequently discussed, is the *positive predictive value* of a test. A test may be 90 percent specific and 90 percent sensitive and used to diagnose a disease that is prevalent in 20 percent of the population. If 100 individuals are selected randomly for testing, 20 should have the disease. Of these, 18 will have TP results. Of the 80 individuals who do not have the disease, 8 will have FP results. Thus, of 26 positive tests, only 18 are correct. The ratio of correct positive diagnoses to total positive diagnoses (69% in this instance) is termed the positive predictive value. With a test with a large positive predictive value (e.g., >95%), a positive result can be assumed to be TP, rather than FP.

The positive predictive value of a test varies with the incidence of the disease in the population being tested. If only one of 10,000 individuals is susceptible to malignant hyperthermia, a test with 99 percent sensitivity and 99 percent

Figure 21-6 A receiver-operator characteristics (ROC) curve is shown; values for sensitivity are plotted against (1 - specificity). Data represent the performance of an "expert system" to assess lability of arterial blood pressure during anesthesia. The labels indicate the "lability index criterion" associated with each pair of sensitivity/specificity values. *(Data from Reich et al [46])*

specificity (which would appear to be excellent characteristics for an assay) would have a positive predictive value of less than 1 percent; that is, fewer than 1 percent of subjects with an abnormal test would be diagnosed correctly. Thus, with rare diseases, an abnormal test does not necessarily indicate the presence of disease, even though the assay is quite sensitive and specific. A parallel statistic, the *negative predictive value,* assesses whether a negative result of the test indicates that the patient does not have the disease.

Contingency Tables, chi^2 Analysis, the Fisher Exact Test, Relative Risk, and Odds Ratios

For data on an ordinal or nominal scale, different techniques are available for the presentation and analysis of results. Histograms, which are valuable for presentation of ratio or interval data, are of limited value, because ordinal and nominal data can assume only a limited number of values. To present ordinal or nominal data collected for two or more variables simultaneously, the investigator might use a *contingency table,* that is, a table displaying the frequency of occurrence of events or characteristics. Contingency tables are described by the number of rows and columns they contain; for example, a 2 × 4 contingency table has two rows and four columns. Table 21-19 is an example of a 2 × 2 contingency table depicting the hypothetic incidences of succinylcholine-induced myalgias with "Antisore" (an imaginary defasciculating drug) or placebo. Examination of these data suggests that the incidence of myalgias is markedly lower after administration of "Antisore" than after administration of a placebo. Statistical confirmation of this observation requires varying the techniques described previously. This section describes analysis of ordinal data using a variation of the *Z* test, followed by an introduction to another variant of the *Z* test, chi^2 analysis. For the data presented in Table 21-19 , the incidence of myalgias in each group can be described as the number of patients having myalgias divided by the total number in that group (*N*). This ratio, the proportion (*p*), is analogous to the central location for ratio or interval data. To perform a statistical analysis, we need to determine the SD for these samples. If we assign the value 1 to subjects having the attribute (in this instance, myalgias), the value 0 to subjects not having the attribute, and the

TABLE 21-19 -- A "2 × 2" Contingency Table Depicting the Hypothetic Incidence of Succinylcholine-Induced Myalgias in Subjects Given "Antisore" (an Imaginary Defasciculating Drug) Versus Placebo

	NUMBER OF SUBJECTS		
AGENT	***MYALGIAS***	***NO MYALGIAS***	***TOTAL***
"Antisore"	8	22	30
Placebo	16	9	25
Total	24	31	55

mean equal to *p,* we can use equation (22) to determine the sample SD:

This equation can be simplified to

Because SE is equal to SD divided by the square root of the sample size, the SE is equal to

Table 21-20 shows the computation of SE for each of the hypothetic samples from Table 21-19 . Then, to compute the test statistic, we must determine the SE of the difference between the two proportions:

where *p* is the proportion determined by combining the groups (e.g., 24/55 for the values reported in Table 21-19) . This method of calculating the SE of the difference between two proportions is similar to that used to determine the SE

TABLE 21-20 -- Calculation of the Standard Error of a Proportion, the Standard Error of the Difference Between Proportions, and the *Z* Statistic for the Hypothetic Data from Table 21-19

S [a] [b]

SE, standard error.
[a] An imaginary defasciculating drug.
[b] Read, "the two-tailed Z value when alpha = 0.05."

of the difference between two means in the two-sample *t*-test. The test statistic *Z* is then calculated as:

This value for *Z* is then compared with the critical value obtained from a table. As before, if the value for *Z* exceeds the critical value, the null hypothesis (that the two samples were drawn from the same population) is rejected, and we conclude that a difference probably exists between the two samples.

This approach to determining statistical difference between proportions is mathematically cumbersome, because the investigator must determine several SD and SE. An alternate approach, chi^2 analysis, arrives at identical conclusions using many fewer mathematic calculations. To use chi^2 analysis, the investigator creates a second contingency table (Table 21-21) , the values of which correspond to the values expected to occur if no difference existed between the two treatments. For example, of the 55 subjects in Table 21-19 , 24 had myalgias, the overall incidence being 43.6 percent. Had there been no difference between treatments, we would expect 13 (actually 13.1) of the 30 subjects given "Antisore" and 11 (actually 10.9) of the subjects given a placebo to experience myalgias. The chi^2 statistic is determined as follows:

where O is the observed frequency and E is the expected frequency. If the observed frequencies are similar to the expected frequencies, the squared differences will be small relative to the expected values, and the value for chi^2 will be small. Conversely, large differences between expected and observed values will result in a large value for chi^2 . This value for chi^2 is then compared with the critical value. To determine the critical value, we must first determine the *df.* Unlike the previously discussed statistical techniques, in which the *df* was a function of the size of the samples, *df* for chi^2 analysis is a function of the dimension of the contingency table, the product of the number of rows minus one and the number of columns minus one. This contingency table includes two rows and two columns, resulting in (2 - 1) × (2 - 1), or 1 *df.* The critical

TABLE 21-21 -- A "2 × 2" Contingency Table of Hypothetic Expected Values for Succinylcholine-Induced Myalgias if No Difference Existed Between "Antisore" (an Imaginary Defasciculating Drug) and Placebo

	NUMBER OF SUBJECTS		
AGENT	***MYALGIAS***	***NO MYALGIAS***	***TOTAL***
Antisore	13.1	16.9	30
Placebo	10.9	14.1	25
Total	24	31	55

TABLE 21-22 -- Calculation of the chi^2 Statistic Using the Hypothetic Data from Table 21-19

$chi^2_{0.05(2),1}$ [a] = 3.84
Therefore, *P* < .05

[a] Read, "the two-tailed chi^2 value when alpha = 0.05 and degrees of freedom = 1."

value for chi^2 is determined from the chi^2 table using the appropriate *df.* chi^2 Analysis of the data from Table 21-19 is performed in Table 21-22 . Note that the value for chi^2 , 7.75, approximates the square of the value for *Z* obtained in Table 21-20 (differences are due to rounding errors). This is not a coincidence: chi ^{2} analysis is mathematically equivalent to *Z* analysis.

2 × 2 Tables

Yates Correction

As mentioned earlier, sample variance (Equation 11) underestimates population variability; therefore, a correction factor, a smaller denominator (usually *n* - 1, instead of *n*) must be applied to ensure reliable estimates for various statistics such as *t* and *F.* A similar problem exists with chi^2 analysis of 2 × 2 tables. This problem is usually resolved by using Yates (continuity) correction. Instead of using equation 27 to calculate chi ^{2} , the following equation is preferable:

where hO - Eh means the absolute value of the observed value minus the expected value. Yates correction reduces the numerator for each value and produces values for chi^2 that are smaller than those obtained with Equation 27. These values are less likely to result in a type I error and should always be used to analyze 2 × 2 tables. The data from Table 21-19 are reanalyzed using chi ^{2} analysis and Yates correction in Table 21-23 . There is no comparable correction procedure for larger contingency tables.

A Further Simplification

For a 2 × 2 table, Equation 28 can be further simplified to

where R_i and C_j are the sums of the values in the i^{th} rows and j^{th} columns, respectively, *n* is the total sample size, and n_{ij} are the values in each of the cells of the table. A further

TABLE 21-23 -- Use of Yates Correction to Determine the chi ^{2} Statistic for the Hypothetic Data from Table 21-19

$chi^2_{0.05(2),1}$ [a] = 3.84
Therefore, using the Yates correction, $P < .05$

[a] Read, "the two-tailed chi^2 value when alpha = 0.05 and degrees of freedom = 1."

simplification (but which is mathematically biased because it ignores Yates correction) is

I recommend this latter approach only for casual analysis of data, such as to confirm the accuracy of published data quickly.

Larger Contingency Tables

An investigator frequently obtains data involving more than two groups or possible outcomes. These data can also be presented in contingency tables and analyzed by chi^2 analysis. Table 21-24 displays a larger contingency table (2 × 4) for hypothetic incidences of vomiting associated with four doses of an imaginary antiemetic drug, "Calm." Determination of the chi ^{2} statistic is performed in a similar manner, by summing the squared differences between the observed and expected values and then dividing this value by the expected values. The resulting value is then compared with the critical value for chi ^{2} for three [(4 - 1) × (2 - 1)] degrees of freedom.

Limits of chi ^{2} Analysis

The assumptions of chi^2 analysis are valid only when certain conditions are met. For 2 × 2 tables, the expected value for each of the cells must be at least 5.0 or the resulting value for chi ^{2} will be biased (i.e., may suggest that a difference exists when, in fact, it does not); if the expected value for one or more cells is less than 5, the Fisher exact test (see next section) is recommended. [29] For larger tables, the expected value for each cell should be at least 1.0, and no more than 20 percent of the cells should have expected values of less than 5.0. Violating these conditions biases the estimates for chi ^{2} and should be avoided either by combining columns or rows to form a smaller contingency table or by collecting additional data.

Fisher Exact Test

The chi^2 test described earlier is a mathematically simple approach to examining significance of contingency tables; however, chi ^{2} analysis is biased when its assumptions are violated, particularly when the expected value of a cell is small. In this case, the *Fisher exact test,* a test of binomial distributions, is recommended. The data of Table 21-19 , previously used for a chi ^{2} analysis, can be analyzed using the Fisher exact test. Recognizing that 24 of the 55 total subjects developed myalgias, the chi^2 test assumed an expected value of 13 (actually 13.1) for myalgias in the "Antisore" group. Although 13 is the "most likely" value, we recognize that values of 12 or 14 also are likely. Similarly, values of 10, 11, 15, or 16 are possible, although each less likely than the value of 13. Using binomial distributions, we can calculate the likelihood of all possible distributions of myalgias (assuming an overall incidence of myalgias of 24 of 55). The probability associated with each of these distributions is shown in Table 21-24; these probabilities are determined as follows:

where R_i and C_j are the sums of the values in the ith rows and jth columns, respectively, n is the total sample size, n_{ij} are the values in each of the cells of the table, and the ! sign indicates factorial (e.g., 8! equals 8 · 7 · 6 · 5 · 4 · 3 · 2 · 1).

Of the 25 possible distributions shown on Table 21-25 , 1 equals the actual distribution observed by the investigators,

TABLE 21-24 -- Calculation of the chi^2 Statistic for a "4 × 2" Contingency Table Representing Hypothetic Incidences of Vomiting with "Calm" (an Imaginary Antiemetic)

	OBSERVED FREQUENCY		EXPECTED FREQUENCY	
	VOMITING	***NO VOMITING***	***VOMITING***	***NO VOMITING***
Placebo	9	11	8.5	11.5
Calm, 1 mg	10	10	8.5	11.5
Calm, 2 mg	8	12	8.5	11.5
Calm, 4 mg	7	13	8.5	11.5
Total	34	46	34	46
$chi^2_{0.05(2),3}$ [a] = 7.82				
Therefore, $P > .05$				

[a] Read, "the two-tailed chi^2 value when alpha = 0.05 and degrees of freedom = 3."

TABLE 21-25 -- Possible Distributions of Myalgias and No Myalgias with "Antisore" (an Imaginary Anesthetic) and Placebo (Based on the Data from Table 21-19) and the Probability of Each Distribution [a]

" ANTISORE"		PLACEBO		
MYALGIAS	***NO MYALGIAS***	***MYALGIAS***	***NO MYALGIAS***	***PROBABILITY (%)***
0	30	24	1	0.0000
1	29	23	2	0.0000
2	28	22	3	0.0000
3	27	21	4	0.0000
4	26	20	5	0.0001
5	25	19	6	0.0010
6	24	18	7	0.0115
7	23	17	8	0.0885
8	22	16	9	0.4805
9	21	15	10	1.8792
10	20	14	11	5.3815
11	19	13	12	11.4152
12	18	12	13	18.0741
13	17	11	14	21.4506
14	16	10	15	19.1013
15	15	9	16	12.7342
16	14	8	17	6.3203
17	13	7	18	2.3133
18	12	6	19	0.6155
19	11	5	20	0.1166
20	10	4	21	0.0153
21	9	3	22	0.0013
22	8	2	23	0.0001
23	7	1	24	0.0000
24	6	0	25	0.0000
Total				100.0000

[a] Of these distributions, the first nine and the final six are as, or more, unlikely (i.e., having the same or a lower probability) than the observed distribution. The cumulative probability of having the values shown in Table 21-14 or a more extreme set of values is therefore (0.0000% + 0.0000% + 0.0000% + 0.0000% + 0.0001% + 0.0010% + 0.0115% + 0.0885% + 0.4805% + 0.1166% + 0.0153% + 0.0013% + 0.0001% + 0.0000% + 0.0000%) or 0.7128%. This is equivalent to stating that $P = .007128$. In this example, the P value obtained with the Fisher exact test is similar to that obtained using chi^2 analysis.

and 14 are more extreme (i.e., less likely) than the actual distribution. The cumulative probability of these 15 "extreme" distributions is .0071 or 0.71 percent. Thus, we can conclude that there is a .71 percent probability ($P = .0071$) that the actual results occurred by chance. Note that the value obtained using the Fisher exact test is similar to that obtained using chi^2 analysis ($P = .0054$); however, when the assumptions of the chi^2 test are violated, the Fisher exact test is recommended.

Relative Risk and Odds Ratios

chi^2 Analysis or the Fisher exact test may be used by the investigator to determine the presence of differences in a 2 × 2 table. However, the resulting statistic and P value do not quantify the relative risks associated with two states. Relative risk is determined as the risk with one state divided by the risk with the other state where

risk is defined as the incidence of the outcome measure in the population. For example, if anesthetic technique A was associated with a 1 percent incidence of postoperative congestive heart failure and technique B was associated with a 0.5 percent incidence, the relative risk would be 2 (1%/0.5%). A confidence limit can be determined for this relative risk ratio.

Frequently, investigators report a minor variant, the odds ratio, instead of the relative risk ratio. The odds ratio is determined as the product of the number of subjects with technique A who develop congestive heart failure and the number of subjects with technique B who do not, divided by the product of the number of subjects with technique A who do not develop congestive heart failure and the number of subjects with technique B who do. Numerically, the values for relative risk and odds ratio are similar. However, ease of calculation appears to have promoted the use of the odds ratio.

Regression Techniques

Analysis of Linear Regression and Correlation Coefficient

Earlier in this chapter, statistics was used to compare values for different variables, such as blood pressure in hypo-volemic versus normovolemic patients, blood pressure before and after the administration of pancuronium, and the effects of placebo versus those of premedications. In these analyses, the independent variable was divided into discrete groups. In certain instances, dividing the independent variable into discrete groups may be undesirable or impossible. For example, the subjects in Table 21-9 were categorized as either normovolemic or hypovolemic, even though there are

Figure 21-7 This scattergram results from the plotting of a hypothetic set of values for two variables (in this instance, blood loss and systolic blood pressure) having a linear relationship.

various degrees of hypovolemia, each of which might be associated with differing amounts of hypotension. To investigate the association between the degree of hypovolemia and the extent of hypotension, the investigator might measure systolic blood pressure while inducing various degrees of hypovolemia by removing blood. These values might then be plotted on a scattergram (see Fig. 21-6) , which is similar to a two-dimensional histogram. The scattergram permits the investigator to examine the relationship between the independent variable (in this case, the amount of blood loss) and the dependent variable (blood pressure). Figure 21-7 shows that larger amounts of volume loss are associated with lower blood pressures.

This relationship also could be analyzed with the Student *t*-test by dividing the independent variable into two groups, mild hypovolemia (less than 10 mL/kg) and severe hypo-volemia (10-25 mL/kg). The investigator would find that blood pressure was lower during severe blood loss than during mild blood loss. Moreover, several smaller groups could be formed, depending on the amount of blood loss, thus permitting the use of analysis of variance.

The limitation of these analyses, however, is that they do not describe the apparently linear relationship existing between blood loss and blood pressure observed in Figure 21-7 . There is no discrete difference in blood pressure with blood loss of more than or less than 10 mL/kg; instead, the relationship between the two variables appears to be continuous. The slope and the position of the line that best describes that relationship are determined using analysis of lin-ear regression. The equation for this line is Y = alpha X + beta where alpha is the slope, and beta the Y intercept, of the line (Y is read Y-hat). The line that fits best is one that minimizes the sum of squared differences between the values of Y and Y. This accounts for the other name for linear regression analysis, *least-squares regression.* The distance between each point and the line is equal to (Y - Y), or [Y - (alpha X + beta)]; the sum of squared distances can be written as

The reader knowledgeable in calculus will realize that when the partial derivatives of the equation with respect to alpha and beta are equal to zero, the sum of squared distance is minimized. These simultaneous equations can be solved to yield the following equations for the slope and intercept of the least-squares regression line:

Table 21-26 demonstrates analysis of linear regression for the hypothetic data in Figure 21-7 . The line produced by this technique (Fig. 21-8) lies close to all the data points.

Just as the index of central tendency was a value near the center of the population, the least-squares regression line lies near the center of the values. Six of the data points are above the line and seven are below.

Using analysis of linear regression, we were able to minimize the sum of squared distances between this sample of points and the regression line. With a second sample, analysis of linear regression would identify a different (although possibly similar) best-fit line. Each different sample would result in a different line, resulting eventually in a family of best-fit lines.

Just as the SEM describes the variability with which the sample mean located the population mean, so do some statistical techniques assess the variability (goodness of fit) of this family of regression lines. The first test, an analysis of variance, evaluates whether the regression analysis suggests

TABLE 21-26 -- Analysis of Linear Regression for Data Shown in Figure 21-6

X = 14.2	
Y = 62.5	
Slope = -1.964	
Intercept = 90.26	
Total sum of squares = 2,927.3	
Regression sum of squares = 1,657.5	
Residual sum of squares = 1,269.8	
Regression mean square = 1,657.5	
Residual mean square = 115.4	
r = -0.75	

Standard error of the estimate = $115.4^{1/2}$ = 10.7

* In a scattergram, the independent variable is plotted on the X axis, the dependent variable on the Y axis. When one variable is used to predict another (e.g., when one assesses the accuracy of end-tidal P_{CO_2} to predict arterial P_{CO_2}), the predictor variable (in this case, end-tidal values) should be plotted on the X axis and the predicted variable (in this case, arterial values) on the Y axis. This permits one to assess the variability in the predicted variable for a given measured value. When there is no causal relationship between two variables (e.g., if one were to examine the relationship between heart rate and blood pressure in subjects who were hypovolemic), either variable can be plotted on the X axis.

Figure 21-8 The best-fit line for hypothetic data in Figure 21-6 using analysis of linear regression.

a trend between the independent and dependent variables. The investigator first determines the *regression SS,* which is equal to the variability resulting from the linear regression:

which has one *df.*

Combining equations 33, 34, and 35 yields

where Sigma *xy* is another notation for Sigma(X_i - X)(Y_i - Y), and Sigma x^2 is equivalent to Sigma(X_i - $X)^2$. As with analysis of variance, the total SS can be partitioned into two components:

where the *residual SS* is the variability not accounted for by the regression, that is, the sum of squared distance between Y_i and *Y:*

The residual SS has *N* - 2 *df.* The ratio between the regression MS and the residual MS,

is then compared with the critical value for *F* obtained from a table. If *F* exceeds the critical value, the regression is significant; that is, a relationship exists between the independent and dependent variables. If *F* is less than the critical value, the slope does not differ from zero, and the analysis does not support the hypothesis that an association exists between the independent and dependent variables.

The residual mean square (often noted as $s^2_{y \cdot x}$) has a second important role. Its square root, $s_{y \cdot x}$, called the *SE of the estimate* (or, occasionally, the *SE of the regression*) represents the average deviation of *Y* values from the regression line. The SE of the estimate provides an estimate for regression analysis in a manner similar to that in which SD describes variability of the sample (i.e., the SE of the estimate is actually the SD, not the SE, of the distance between the Y values and the regression line). For the sample described in Figure 21-7 , the SE of the estimate is 12.3, a value that represents the average distance of the points from the regression line.

The third method of describing fit to the regression line is by determining the correlation coefficient. The variability of the dependent variable, *Y,* has already been partitioned into two components, the component that is accounted for by the regression line (the regression SS) and the component that is not accounted for by the regression line (the residual SS). The sum of this SS, the total SS, can also be expressed as

The ratio of the regression SS to the total SS is equal to the percentage of the variability of one variable explained by the variability of the other variable. This ratio, r^2 , is known as the *coefficient of determination.* If the regression line fits the sample exactly, the error SS is equal to 0 and the regression SS is equal to the total SS. This results in a coefficient of determination equal to 1. The greater the distance between the values in the sample and the regression line, the larger the value of the error SS and the smaller the value of r^2 . The value for r^2 always lies between 0 and 1, with larger values implying a better fit between the regression line and the sample. More commonly reported than r^2 is its square root, *r,* known as the *correlation coefficient* or the *productmoment correlation coefficient.* Because r^2 is always between 0 and 1, its square root will always lie between -1 and +1, and its sign is identical to that of the slope. The advantage of using the coefficient of determination and the correlation coefficient is that they lack units, whereas the slope of the regression line depends on the magnitude of the units used to express the independent and dependent variables.

In addition to these techniques to evaluate the significance and goodness of fit of a regression line, some techniques compare the slopes and positions of two or more regression lines. These techniques can also be applied to two or more dose-response curves or to other data analyzed by linear regression.

The investigator who uses analysis of linear regression must decide which results to report to the reader. It is often tempting to search a computer output for a statement of probability such as *P* = .02. Reporting only this value limits the information provided to the reader, because it provides limited information as to the goodness of fit of the regression line. This is particularly important with large samples in which it is possible to obtain significant probabilities for the regression line (e.g., *P* = .05), despite large SE of the estimate and poor coefficients of determination. The variability of the regression analysis is better described by two statistics, the SE of the estimate and the coefficient of determination (or the correlation coefficient). The SE of the estimate describes the average distance of the points from the regression line, whereas the coefficient of determination describes the proportion of the variance that can be accounted for by the regression.

Figure 21-9 Data for a standard curve to estimate the concentration of a drug using optical density measurements are shown. There are four values at each concentration, and several of the values at low concentrations overlie. Note that the absolute variability is smaller at lower concentrations; in fact, variability is proportional to the concentration.

In the earlier description of analysis of linear regression, the goal was to minimize the sum of the squared distances between the observed points and those predicted by the regression analysis (Equation 32). This approach assumes that each residual distance should contribute equally to the *objective function* (the value to be minimized). For many analyses this is appropriate--this is because the "error" (variance) associated with each of the measurements is constant. However, in certain instances, this assumption is unquestionably violated. For example, an assay might use optical density to estimate the concentration of a drug over a large range of values. Repeated measurements of each of several known concentrations (Fig. 21-9) suggest that there is more variability at higher than at lower concentrations (i.e., variability is proportional to concentration). An unweighted least-squares linear regression might then fail to approximate all the data points, being particularly biased against low values (Fig. 21-10 , solid line). This problem can be addressed by *weighting* the contribution of each squared residual difference to the objective function. A typical

Figure 21-10 Using unweighted linear regression for data, a (solid line) fit to data from Figure 21-9 fails to approximate the values at a drug concentration of 1 ng/mL. A weighted linear regression (dashed line) approximates the data at all portions of the curve. Only values lower than 4 ng/mL and the corresponding regression lines are shown.

weighting scheme, assuming that variability is proportional to concentration (or that variance is proportional to the square of the concentration) might be to multiply each squared residual by the inverse of the square of the concentration; using this new objective function, the *weighted least-squares linear regression* may approximate all the data points better than its unweighted equivalent (see Fig. 21-10 , dashed line). Weighting of the objective function is necessary whenever the variance model is not constant (the case for many drug assays and certain other measurements). Another approach that would likely be successful in this situation is to perform a logarithmic trans-form of the data, then perform an unweighted linear regression.

Bias Analysis

A problem frequently encountered in medicine involves the comparison of two methods of analysis, such as two assays. Although regression analysis is intuitively appropriate for comparison, Bland and Altman [26] argue that a variant is more appropriate because the results of regression analysis might provide false confidence that two measurement methods differ minimally. For example, consider the data shown in Figure 21-11 comparing two fictitious assays for the blood concentrations of an inhaled anesthetic. Although values lie quite close to the regression line and the correlation coefficient approaches unity, the new assay is biased--it yields values consistently larger than the old assay at low concentrations and smaller than the old assay at high concentrations. Comparison of the regression line to the line of unity suggests the presence of this bias.

The variant proposed by Bland and Altman is termed *bias analysis.* Assuming that neither assay is known to be the "gold standard," the difference between the two measurements is plotted against the average of the two measurements.

Figure 21-11 Values for two fictitious assays for the measurement of the blood concentration of an inhaled anesthetic are displayed in a regression analysis. Values for the traditional assay are plotted on the Y axis; the new assay is plotted on the X axis. The best-fit regression line is solid; the line of identity is dashed.

Figure 21-12 Transformed values from Figure 21-11 are displayed. The X axis is the average of the measurements by the two assays; the Y axis is the difference between the two assays. Horizontal lines are displayed at the average difference, the average difference plus two standard deviations of that difference, and the average difference minus two standard deviations of that difference. Systematic bias is more evident in this plot than in the traditional regression analysis.

* The mean and SD of the differences is determined, and the mean is compared to zero (i.e., the average difference between the two assays is compared to zero); in addition, horizontal lines are plotted at the mean difference, the mean difference plus 2 SD, and the mean difference minus 2 SD. The plot is then examined for systematic trends and for individual differences larger than twice the SD. The data from Figure 21-11 , when examined in a bias analysis (Fig. 21-12) , reveal a systematic bias that is more evident than in the regression analysis.

Misuse of Linear Regression Analysis

One assumption of regression analysis is that the data points are selected independently from the population. This would occur if each point was from a separate experiment (e.g., different individuals) or all points were from a single individual but the independent variable changed during the course of the experiment. In some instances, investigators may obtain a small number of observations from each of a large number of individuals. A regression analysis based on this data set is flawed. Consider an investigator interested in determining whether cardiac output estimates obtained from echocardiographic measurements can replace those obtained by thermodilution. Four measurements (e.g., one after induction of anesthesia, a second before institution of cardiopulmonary bypass, a third after bypass, and the fourth during chest closure) are obtained from each of 5 individuals. The investigator plots these 20 values (Fig. 21-13) , recognizing that the thermodilution technique is not the gold standard, and determines that values from the two assays are highly correlated. In turn, the investigator extrapolates, incorrectly, that changes in cardiac output can be tracked by changes in the echocardiographic measure.

Figure 21-13 Values for cardiac output determined by thermodilution are plotted against values estimates determined using echocardiography. Four values were simulated for each of five subjects. Each subject is identified by a different symbol. The solid line is the best-fit linear regression line ($r^2 = .82$; $P < .0001$).

The flaw in this assessment can be seen by examining the data for each individual. Values for a representative subject are displayed in Figure 21-14 . These values fail to reveal a relationship between changes in the two measures. Had a single value from each subject (e.g., the initial measurement) been plotted, the resulting analysis would suggest that the new measurement technique provides a reasonable estimate of the magnitude of cardiac output for an individual. However, the new measurement technique cannot track changes within a given individual.

Regression analysis should not be performed when repeated measurements from individuals are pooled. In this instance, a specialized technique, mixed-effects modeling (which is beyond the scope of this chapter) is an appropriate technique.

Nonlinear and Logistic Regression

Certain types of data, such as the relationship between dose and effect, are appropriately analyzed using regression techniques. On occasion, effect is recorded in terms of a quantal response (e.g., yes or no) rather than discrete values; in this instance, analysis of linear regression may not be the appropriate statistical technique. For example, the relationship

Figure 21-14 Values for a single subject from Figure 21-13 are displayed. There is no relationship between the X and Y axes ($r^2 = .16$; $P > .61$).

* If one assay is known to be the "gold standard," the X axis can be the gold standard rather than the average of the two assays.

between the dose of thiopental and loss of the lid reflex is probably sigmoidal, rather than linear, in shape. Forcing a linear analysis onto nonlinear data may produce spurious results, particularly regarding nonlinear portions of the sigmoid curve. For example, because the middle portion of a sigmoid curve is linear, estimations of the ED_{50} (the dose producing 50% effect) may be accurate using analysis of linear regression; however, analysis of linear regression is likely to produce flawed estimates for ED_{95} (the dose producing 95% effect). The limitation of the linear approach becomes more evident as the value on the X axis (often dose) is extended beyond the ranges under investigation: a linear regression approach might suggest the impossible--effects greater than 100 percent or lower than 0 percent.

Special techniques are available for the analysis of these types of data. One simple technique that could be accomplished readily without a computer was the probit analysis technique popularized by Litchfield and Wilcoxon. [47] The Litchfield-Wilcoxon technique has been popular for the analysis of neuromuscular dose-response data. These data, in which the response versus dose relationship is typically sigmoidal (as are many biologic responses), are translated to probits. However, probit transforms are inappropriate for data at the extremes (e.g., a twitch response recorded as 100 percent depression translates to a probit value of infinity); therefore, extreme values are typically assigned an arbitrary value of eight probits. The transformed probit values, which bear a more linear relation to dose, are then analyzed using unweighted linear regression. This technique is flawed. One assumption of unweighted linear regression is that errors are uniform throughout the measurement scale (a statistician would state that the "variance model is constant"); for measurements of twitch tension, this is equivalent to assuming that measurement error is uniform throughout all levels of twitch depression (a reasonable assumption). However, when the data are translated into probits, the extremes of the response curve are "stretched"; that is, the sigmoidal curve is made linear by deforming the extremes, so that errors associated with these measurements are similarly "stretched." However, investigators typically analyze these probit versus dose data using unweighted linear regression, not accounting for the newly created nonhomogenous variance model. If an investigator were to use properly weighted linear regression, probit transforms would not compromise the analysis.

An alternative to the probit technique is *nonlinear regression.* For example, a sigmoidal curve can be described by the following equation:

where E_{max} and E_0 are maximal and initial responses of the system (e.g., 100% and 0% depression for twitch data), *e* is Euler's constant (2.718), and alpha and beta are parameters that describe the shape (sigmoidicity) and position (e.g., ED_{50}) of the curve. As with linear regression, the goal of this technique is to minimize the sum of the squared distances between the observed and the predicted values (i.e., the points on the fitted curve). Unlike linear regression, for which a

Figure 21-15 Values for a response (e.g., percentage of subjects moving at a certain end-tidal anesthetic concentration) are plotted against the end-tidal anesthetic concentration. Although a linear regression (solid line) approximates the data well, an extrapolation of the linear relationship to higher end-tidal concentrations suggests that fewer than 0 percent of subjects move, an unlikely possibility. In contrast, the sigmoid curve (dashed line) fit by the nonlinear regression technique approximates the data well, but it also suggests that the response asymptotes to the value 0 with increasing end-tidal concentrations. Thus, the nonlinear analysis yields more realistic results.

single "best-fit" solution exists for each data set, there is no unique solution to a nonlinear regression problem. Instead, the investigator approaches the best-fit iteratively, minimizing the sum of squares. Figure 21-15 shows this approach to the analysis of a dose-response relationship. As with linear regression, nonlinear regressions can be analyzed by weighting the contribution of each residual to the sum of squares.

If the data are strictly dichotomous (e.g., alive versus dead), a special case of nonlinear regression, *logistic regression,* is available. The fitted equation for logistic regression is similar to that shown in Equation 41; however, instead of minimizing the sum of squared residual distances, logistic regression uses an approach known as maximum likelihood. Logistic regression is a powerful tool for the analysis of epidemiologic data (e.g., data involving the effects of anesthetic techniques on outcome) and is seen with increasing frequency in the medical literature.

Other nonlinear regression techniques are commonly used in medical research. A familiar example for anesthesiologists is the fitting of compartmental models to pharmacokinetic data. For example, the plasma concentration versus time curve for many intravenous drugs appears to be well fit by a sum of exponentials

where C_p is plasma concentration at time *t* and *k* is the number of compartments. As with linear regression, the goal of this technique is to minimize the (weighted or unweighted) sum of the squared distances between the observed and the predicted values (i.e., the points on the fitted curve).

Sequential Analysis

To compare the results of two treatments, the investigator first estimates the difference in outcomes for each treatment

and uses this difference to estimate how many subjects will be required to demonstrate a statistical difference between treatments. Once the study has commenced, the investigator should not analyze the results until the predetermined number of studies have been performed. [19] In addition, should this number of subjects not yield statistically significant results, the investigator should not increase the number of subjects studied until statistical significance is achieved. These requirements are based on the same rationale as support the prohibition against multiple *t*-tests: the test statistic is based on the assumption that only one comparison is to be made between the two treatments.

In certain instances, it is vital to determine rapidly which treatment is more efficacious. For example, if the cost of conducting trials is excessive, or if knowledge of an improved therapy might greatly influence morbidity, the investigator might desire to learn the difference between treatments quickly. Sequential analysis is particularly suited for this purpose. [48] The investigator uses a chart similar to that shown in Figure 21-16 (Figure Not Available) . Paired subjects are given treatments (e.g., one subject is given an antiemetic drug; another subject a placebo), and their scores regarding some predetermined response (e.g., vomiting) are compared. If scores are the same (e.g., vomiting occurred in both trials), the results are ignored. If a difference exists that favors the antiemetic drug, a mark is made one unit upward and to the right; if a difference exists that favors the placebo, a mark is made one unit downward and to the right. Once the mark leaves the hatched area, the trial is complete. If the resulting line is above the enclosed area, the trial favors the antiemetic drug; if the resulting line is below the enclosed area, the trial favors the placebo. Completion of the trial beyond the right-hand border indicates that no statistical difference exists between the two treatments. Using sequential analysis, Abramowitz et al [49] demonstrated the antiemetic effect of droperidol using only 11 untied treatment pairs and a total of 42 subjects. In contrast, Cohen et al, [50] in a study of 87 subjects, found that the incidence of vomiting was lower in subjects given droperidol than in those given a placebo, but these investigators were unable to demonstrate a statistical difference using chi ^{2} analysis.

Figure 21-16 (Figure Not Available) Using sequential analysis, Abramowitz et al [49] demonstrated that droperidol decreased the incidence of postoperative vomiting. For each untied pair of subjects, the line is extended one box to the right and one box up or down, depending on which subject fared better. The trial is complete when the line exits the borders of the box. *(From Abramowitz et al [49])*

/das/book/view/29494766/875/222.html

OVERVIEW

This chapter has aimed to provide an introduction to the techniques used in many statistical analyses. Emphasis has been placed on descriptive statistics, particularly on identifying the location and distribution of data. This focus was chosen because of the increasing tendency of investigators to perform complicated analyses using sophisticated statistical techniques without spending sufficient time examining the data. The chapter also emphasized the more common abuses of statistics: reporting variability of the data without identifying whether SD or SE is being used, and the inappropriate use of multiple *t*-tests. Repeated-measures analysis of variance, a statistical technique that is appropriate for many of the studies performed in anesthesia, has been described, with the hope that it will be used with greater frequency.

Undoubtedly, many investigators will continue to view statistical analysis as a necessary evil in research. Despite increased awareness of the abuses of statistics, errors continue to appear in the anesthesia literature (as in all medical literature). However, with time, with improved editorial vigilance, with the availability of newer statistical resources for investigators, and with education for investigators, we are likely to see improvements in the future.

References

1. Gore SM, Jones IG, Rytter EC: Misuse of statistical methods: Critical assessment of articles in BMJ from January to March 1976. BMJ 1:85, 1977.

2. Glantz SA: Biostatistics: How to detect, correct and prevent errors in the medical literature. Circulation 61:1, 1980.

3. Rosen MR, Hoffman BF: Statistics, biomedical scientists, and circulation research (editorial). Circ Res 42:739, 1978.

4. Feinstein AR: Clinical biostatistics. XXXVII. Demeaned errors, confidence games, nonplussed minuses, inefficient coefficients, and other statistical disruptions of scientific communication. Clin Pharmacol Ther 20:617, 1973.

5. Emerson JD, Colditz GA: Use of statistical analysis in *The New England Journal of Medicine.* N Engl J Med 309:709, 1983.

6. Hayden GF: Biostatistical trends in *Pediatrics:* Implications for the future. Pediatrics 72:84, 1983.

7. Avram MJ, Shanks CA, Dykes MHM et al: Statistical methods in anesthesia articles: An evaluation of two American journals during two six-month periods. Anesth Analg 64:607, 1985.

8. Mosteller F, Bailar JC III (eds): Medical Uses of Statistics. Waltham, Mass, *New England Journal of Medicine* Books, 1986.

9. Fisher DM: Surrogate end points: Are they meaningful? [editorial]. Anesthesiology 81:795, 1994.

10. Tramer MR, Reynolds DJ, Moore RA et al: Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: A quantitative systematic review of randomized placebocontrolled trials. Anesthesiology 87:1277, 1997.

11. Laussen PC, Reid RW, Stene RA et al: Tracheal extubation of children in the operating room after atrial septal defect repair as part of a clinical practice guideline. Anesth Analg 82:988, 1996.

12. Fisher B, Redmond CK: Fraud in breast-cancer trials (letter). N Engl J Med 330:1458, 1994.

13. Poisson R: Fraud in breast-cancer trials (letter). N Engl J Med 330:1460, 1994.

14. Schneider EC, Epstein AM: Influence of cardiac-surgery performance reports on referral practices and access to care: A survey of cardiovascular specialists. N Engl J Med 335:251, 1996.

15. Macario A, Horne M, Goodman S et al: The effect of a perioperative clinical pathway for knee replacement surgery on hospital costs. Anesth Analg 86:978, 1998.

16. Lubarsky DA, Glass PS, Ginsberg B et al: The successful implementation of pharmaceutical practice guidelines: Analysis of associated outcomes and cost savings. Anesthesiology 86:1145, 1997.

17. Sorenson RM, Pace NL: Anesthetic techniques during surgical repair of femoral neck fractures: A meta-analysis. Anesthesiology 77:1095, 1992.

18. LeLorier J, Gregoire G, Benhaddad A et al: Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Engl J Med 337:536, 1997.

19. McPherson K: Statistics: The problem of examining accumulating data more than once. N Engl J Med 290:501, 1974.

20. Cohen J: Statistical power analysis for the behavioral sciences. Hillsdale, NJ, Lawrence Erlbaum Associates, 1988.

21. Glantz SA: Primer of Biostatistics, 3rd ed. New York, McGraw-Hill, 1992.

22. Selvin S: Statistical Analysis of Epidemiologic Data. New York, Oxford University Press, 1991, p 71.

23. Hanley JA, Lippman-Hand A: If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 249:1743, 1983.

24. Berger JM, Stirt JA, Sullivan SF: Enflurane, halothane, and aminophylline: Uptake and pharmacokinetics. Anesth Analg 62:733, 1983.

25. Longnecker DE: Support versus illumination: Trends in medical statistics (editorial). Anesthesiology 57:73, 1982.

26. Ford I: Can statistics cause brain damage? (editorial). J Cereb Blood Flow Metab 3:259, 1983.

27. Mills JL: Data torturing. N Engl J Med 329:1196, 1993.

28. Bland J, Altman D: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1:307, 1986.

29. Zar JH: Biostatistical Analysis, 2nd ed. Englewood Cliffs, NJ, Prentice-Hall, 1984.

30. Dixon WJ, Massey FJJ: Introduction to Statistical Analysis, 4th ed. New York, McGraw-Hill, 1983.

31. Colton T: Statistics in Medicine. Boston, Little, Brown, 1974.

32. Feinstein AR: Clinical biostatistics. XLIX. The basic data structures used in quantitative indexes. Clin Pharmacol Ther 26:525, 1979.

33. Viby-Mogensen J: Succinylcholine neuromuscular blockade in subjects heterozygous for abnormal plasma cholinesterase. Anesthesiology 55:231, 1981.

34. Stanley TH, Webster LR: Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 57:411, 1978.

35. Feinstein AR: Clinical biostatistics. L. On choosing a mean and other quantitative indexes to describe the location and dispersion of univariate data. Clin Pharmacol Ther 27:120, 1980.

36. Student: Illegal number crunching (letter). Pediatrics 71:864, 1983.

37. Feinstein AR: On central tendency and the meaning of mean for pH values (editorial). Anesth Analg 58:1, 1979.

38. Feinstein AR: Clinical biostatistics. LV. The *t*-test and the basic ethos of parmetric statistical inference. I. Clin Pharmacol Ther 29:548, 1981.

39. Brown GW: Standard deviation, standard error: Which "standard" should we use? Am J Dis Child 136:937, 1982.

40. Fisher RA: Statistical Methods for Research Workers. New York, Hafner Press, Macmillan, 1970, p 44.

41. Fisher RA: The Design of Experiments, 2nd ed. Edinburgh, Oliver and Boyd, 1937, p 15.

42. Melton AW: Editorial. J Exp Psychol 64:553, 1962.

43. Student: The probable error of a mean. Biometrika 6:1, 1908.

44. Feinstein AR: Clinical biostatistics. LVI. The *t*-test and the basic ethos of parametric statistical inference (conclusion). Clin Pharmacol Ther 30:133, 1981.

45. Schefler WC: Statistics for the Biological Sciences, 2nd ed. Reading, Mass, Addison-Wesley, 1979, p 136.

46. Reich DL, Osinski TK, Bodian C et al: An algorithm for assessing intraoperative mean arterial pressure lability. Anesthesiology 87:156, 1997.

47. Litchfield JT, Wilcoxon F: A simplified method of evaluating doseeffect experiments. J Pharmacol Exp Ther 96:99, 1949.

48. Armitage P: Sequential Medical Trials, 2nd ed. Oxford, Blackwell Scientific Publications, 1975.

49. Abramowitz MD, Oh TH, Epstein BS et al: The antiemetic effect of droperidol following outpatient strabismus surgery in children. Anesthesiology 59:579, 1983.

50. Cohen SE, Woods WA, Wyner J: Antiemetic efficacy of droperidol and metoclopramide. Anesthesiology 60:67, 1984.

Section 3 - Anesthesia Management

Chapter 22 - Risk of Anesthesia

Lee A. Fleisher

INTRODUCTION

A great deal of attention has focused on the risk of anesthesia, both from the perspective of providing patients with an accurate assessment of the probability of complications and as a means of quality assurance in order to improve outcome. Numerous studies have attempted to define the probability of morbidity and mortality, with wide variability of results. Additionally, risk indices have been developed to identify those patients who have a higher probability of developing complications. In all these studies, as well as in clinical discussions with patients, the key question is what risk are we attempting to define.

For the case of risk of anesthesia, there are multiple factors that enter into the equation. A myopic perspective could simply include morbidity and mortality that occur intraoperatively. From a quality assurance perspective, any death within 48 hours of an anesthetic regimen is evaluated for potential relevancy. Yet, other investigators have evaluated 30-day morbidity and mortality as part of their estimation of anesthetic risk. It is important to define the perspective when evaluating the studies (Table 22-1) (Table Not Available) .

It is also important to differentiate the potential risk solely attributable to administration of anesthesia from those risks that anesthesia may modify. For example, there has been a great deal of research and debate regarding the potential benefits of regional versus general anesthesia for patients undergoing infrainguinal arterial reconstruction. [1] [2] [3] One outcome that has been shown to benefit from regional anesthesia is the risk of graft thrombosis and of the need for reoperation or amputation. Despite two smaller studies demonstrating significant benefit of regional anesthesia, [1] [3] the largest study was unable to demonstrate any difference compared with general anesthesia. [2] Importantly, the two smaller studies had a much higher rate of reoperation than the larger study, a finding suggesting that the benefit may only manifest itself if the rate of complications is sufficiently large. Therefore, assessment of risk depends on the rate of complications.

Traditionally, anesthesiologists and investigators have focused on issues of death and major morbidity such as myo-cardial infarction, pneumonia, and renal failure. It is becoming increasingly important to include outcomes that affect economic issues, quality of life, or satisfaction for the patient (Table 22-2) . For example, nausea and vomiting, which delay or prevent discharge home, are important from an economic and quality of life perspective. Readmission to the hospital after outpatient surgery is now an important component of outcome studies. [4] Overall satisfaction with care is increasingly included as an outcome. [5] [6] [7] Further research will be required to assess the influence of anesthesia care for nonmorbid outcomes and the importance of these outcomes from a patient-oriented perspective.

Many studies have also looked at what some investigators describe as surrogate end points. [8] For example, nausea and vomiting that do not require treatment or do not delay discharge do not have the same impact as those episodes that do affect these outcomes. Myocardial ischemia on the electrocardiogram is another example of a surrogate outcome that may not directly lead to overt morbidity. [9] In determining the risk of anesthesia, it is important to define the outcome of greatest interest.

TABLE 22-1 -- Time Perspective of Anesthetic Morbidity and Mortality Studies

(Not Available)

Modified from Derrington MC, Smith G: A review of studies of anaesthetic risk, morbidity and mortality, Br J Anaesth 59:827, 1987.

TABLE 22-2 -- Examples of Common Outcome Measures

Mortality
Morbidity
Major
Myocardial infarction
Pneumonia
Pulmonary embolism
Minor
Nausea
Vomiting
Readmission
Patient satisfaction
Quality of life

Finally, it is imperative to realize that "perioperative" risk is multifactorial and depends on the interaction of factors specific to anesthesia, the patient, and surgery (Fig. 22-1) . With respect to anesthesia, both the effects of the agents and the skills of the practitioner are important. Similarly, both the surgical procedure itself and the surgeon's skills affect perioperative risk. From the patient's perspective, the question remains whether the coexisting disease raises the probability of complications to a level such that the benefit of the surgery is outweighed by the risk. As anesthesiologists, we frequently focus on perioperative risk, yet the patient is most concerned with management of the disease process. As the specialty focuses on its role in the 21st century, it is important to acknowledge the patient's perspective and desire to undergo procedures to prolong life or to improve quality of life. The ability of the anesthesiologist to affect the decision process and overall risk is the future challenge.

Given these varying goals, perspectives, and influences, this chapter attempts to define the current state of knowledge in this area. With the increasing interest in evidence-based medicine, it is important to define what is known and what is not known. Because it would be unethical to compare surgical procedures performed under an "ideal anesthetic" versus a less ideal regimen or no anesthesia, virtually all the studies looking at the factors that contribute to perioperative mortality involve evaluations of large cohorts of patients. However, over the past decade, there have been several well-designed randomized clinical trials to evaluate different anesthetic regimens that have advanced the field. This chapter reviews the literature, with an emphasis on the strength of the evidence for the conclusions.

/das/book/view/29494766/875/226.html

ISSUES RELATED TO STUDY DESIGN

Types of Studies

In order to interpret the literature, it is important to understand the strengths and limitations of the different study designs. Prospective cohort studies involve the identification of a group of patients who are followed over time for the occurrence of an outcome of interest. The goal is to determine those patients who develop the outcome. For studies of

Figure 22-1 Representation of the influences of different components related to perioperative poor outcomes. Surgical, anesthetic, and patient characteristics all contribute to outcome. Anesthetic contributions can include issues of judgment and mishaps and may relate to the provider. The surgical procedure itself affects outcome, as well as the location of intraoperative and postoperative care.

perioperative mortality, individual cases can be reviewed to determine the cause of mortality. Alternatively, data on all patients in the cohort can be obtained, and those factors that are associated with the development of morbidity or mortality can be discerned. An example of a prospective cohort study identifying factors associated with perioperative cardiac morbidity and mortality is that of Goldman and colleagues, [10] which led to the development of the cardiac risk index.

Another example of a prospective cohort study is one in which patients with a known disease are studied for the development of predefined outcomes. Such studies provide the natural history in patients with the disease. An example would be studies of patients who have sustained a myocardial infarction, the importance of which is that the optimal time between the infarct and surgery can be determined. [11] [12] [13]

Although prospective cohort studies have important value in identifying risk factors for the outcome of interest, there are significant limitations. The selection of the cohort of interest can significantly affect the results obtained. The larger the cohort, the more the results can be generalized. A second bias is that many patients may be lost to follow-up. In perioperative studies, this may not be an important issue for short-term outcomes. Finally, the importance of a risk factor depends on the completeness of the data. For example, if the presence of severe angina was not included in the database, then it could not be a risk factor, and other factors may appear to be more important. [10]

A specific example of a prospective cohort study is the randomized clinical trial. Randomized clinical trials represent the gold standard for evidence of causation. They have defined inclusion and exclusion criteria, treatment protocols, and outcomes of interest. They are usually either single or double blinded (both patient and physician) and are designed to test the effect of a new drug or intervention. They rarely are used as a means of identifying risk, but they may be used to determine if that risk factor is truly linked via a causal relationship or simply an association. In the perioperative period, hypothermia has been associated with an increased incidence of perioperative ischemia, a surrogate marker for morbidity. [14] In a subsequent randomized clinical trial, the use of forced-air warming to maintain normothermia was associated with a significantly lower incidence of perioperative morbid cardiac events. [15] Therefore, randomized clinical trials directed at interventions that reduce the frequency of a given risk factor in the population are often performed after the results of a prospective cohort study to confirm the findings of an association between poor outcome and that factor.

Randomized clinical trials derive their strength from an evidence-based perspective because of their high degree of internal validity; that is, the randomization scheme and the use of placebo (or accepted alternative treatments) provide strong evidence that the results are related to the intervention. Importantly, these trials have a lower degree of external validity because the intervention may not behave in the same manner as when it is diffused into a more heterogeneous population in whom treatment is not defined.

Retrospective studies involve identifying patients who have sustained an outcome and then defining risk factors associated with the outcome. An example of a retrospective design is a case-control study. Case-control studies identify patients with the outcome of interest. Frequently, these patients may be included as part of a prospective cohort study. The prevalence of a risk factor in the patients with the outcome (case) is compared with the prevalence of the risk factor in "matched" controls; the efficiency and power of the results can be maximized. The ratio of cases to controls can be varied, with greater power with an increasing number of controls.

Case-control studies are subject to a number of biases. The exact definitions of cases and controls can influence the analysis. Frequently, patients are matched by age and gender, but other factors may play an important role. It is also critical that the exposure precedes the outcome, and a dose-response gradient further confirms the relationship.

Problems Inherent in Studying Anesthetic Risk

There are several issues related to studying anesthetic risk that can affect findings. As described earlier, there are multiple definitions of perioperative mortality. In particular, the time frame in which a death can be attributed to the surgery and delivery of anesthesia varies. Because in-hospital stays have shortened, many events related to surgery may occur after discharge. This is particularly the case in ambulatory or short-stay surgery, in which recovery from anesthesia occurs at home. As anesthesiologists continue to monitor patients for safety, it will be important to include follow-up beyond the traditional hospital setting. Many recent studies have included such an approach.

A major problem in any study of risk is the actual rate of complications in the population of interest. There are multiple sources of data for studying perioperative risk. Although some of the original studies utilized data from only a single center or small group of institutions, such approaches may not be practical in the current era. As demonstrated throughout this chapter, risk related to anesthesia has decreased over time. For example, the rate of anesthetic-related mortality described in the Confidential Enquiry into Perioperative Deaths (CEPOD) was 1 in 185,000 patients compared to that reported by Beecher and Todd of 1 in 2,680 cases. [16] [17] Considering the current rate, any study would have to be enormous to detect anesthesia-related mortality. Such a study would require information from a large number of sites. Considering concerns in the United States regarding confidentiality and legal liability, such a study could not be undertaken. Such problems may not be inherent in other countries.

Another limitation relates to the issue of the effect of the actual act of studying outcome. As in any study of risk, the actual rate of complication is decreased by increased observation. This is frequently observed as a lower than expected rate of complications in the placebo arm of a randomized controlled trial.

An alternative approach is to identify bad outcomes and to study them for patterns of errors. For example, Cheney et al [18] developed the American Society of Anesthesiologists (ASA) Closed Claims Study. By obtaining the records of major events that led to litigation, these investigators were able

to identify factors that contributed to bad outcomes. Using such methodology, selected morbidity that leads to litigation can be identified. The limitation of this methodology is that the actual rates of complications are unknown, and only the number of closed legals claims is known. Additionally, those cases that do not result in litigation are not included in the database.

Several attempts have been made to establish large epidemiologic databases. The best example of such an approach has been the work of Mangano and the Multicenter Study of Perioperative Ischemia group [19] with regard to cardiac surgery. This group used their database to evaluate issues such as the rate and importance of atrial fibrillation after cardiac surgery. [19] Other approaches include the development of cardiac surgery databases by the Society of Thoracic Surgeons, the Veterans Administration, and the New England Collaborative Project. [20] [21] [22] [23] [24] These databases are used for defining risk factors for poor outcome, for benchmarking local to national complication rates, and as educational tools. Unfortunately, these databases do not include extensive or any information regarding anesthesia practice. Additionally, such databases include a predominance of patients from academic or major medical centers and do not include data from smaller or community hospitals, which may have very different patterns of care. Although these databases may provide extremely important information to improve care, the ability to generalize the results to the nonacademic centers is unknown.

This final issue of the site of surgery may have other implications related to the pattern of care at a particular hospital. Although most studies frequently categorize risk as related to anesthesia, surgery, or patient disease, postoperative care may have a profound impact on risk. For example, the risk of pulmonary embolism may relate to nursing care and the frequency with which a patient is ambulated after surgery. [25] Such variation in the total care provided by a hospital, including the anesthesiologists and surgeons, may significantly affect the results.

One advance in determining local complication rates is the development of hospital information systems. The use of computerized databases in the assessment of risk began with Marx et al. [26] Now, these information systems are almost a requirement of survival for the hospital. The ability to query these systems will make large-scale studies of institutional risk much less burdensome in the future.

When extremely large sample sizes are needed, administrative databases may be among the most cost-effective approaches to this issue. Examples of administrative databases include Medicare claims files, private insurance company claims, and hospital electronic records. These databases include a small number of data points on an extremely large number of subjects. For example, the Medicare database includes financial data, the ninth revision of the International Classification of Diseases codes (ICD-9), and Current Procedural Terminology (CPT) codes for each patient. They also include information regarding location of care and provider type. The Medicare claims files are now being extensively utilized to benchmark rates of mortality and major complications after coronary bypass surgery. [27] Hospitals can compare their rates with those of neighboring and competing hospitals and may use these data as surrogates for quality of hospital care. [28] [29]

MORTALITY RELATED TO ANESTHESIA

The first report of the delivery of anesthesia for an operative procedure was in 1846, using ether. Only 2 years after that report, there was a death attributable to anesthesia. [30] In that report, Hannah Greener died on induction with chloroform. Since that time, there have been numerous investigations into the cause of anesthetic death. The first formal published investigation of anesthetic deaths was by John Snow in 1858. [31] In that report, he analyzed 50 cases of death during chloroform anesthesia. At that time, mortality occurred principally in healthy patients undergoing minor procedures. This suggests that anesthesia was the principal cause of mortality. Subsequent studies report deaths in patients with significant comorbidities who were undergoing major surgical procedures. In these cases, the cause of mortality was frequently multifactorial.

Surgery Without Anesthesia

Surgical procedures were carried out prior to the introduction of anesthetics. The key to success was the speed of the procedure, with successful amputations lasting 30 seconds. Strong assistants and restraints were frequently required. Alternatively, decreased cerebral perfusion via bilateral carotid compression was used to decrease sensation during the procedure. Importantly, surgical procedures were associated with significant risk of death and, at a minimum, severe pain. The development of anesthesia was heralded as one of the great advances of modern medicine, in that it allowed surgery to advance.

Early Studies of Anesthetic Mortality

One of the earliest systematic approaches to anesthetic risk occurred in 1935, when Ruth helped to establish the first anesthesia study commission to analyze perioperative deaths [17] [26] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] (Table 22-3) (Table Not Available) . Ruth relied on voluntary submission of cases and determined the cause of death by majority vote. Both methodologies would be deemed inadequate in subsequent years.

From a pragmatic standpoint, determining the cause of anesthetic-related mortality is important if information from the analysis can be used to improve subsequent care. This concept was best voiced by Sir Robert Macintosh in 1948. [44] He stated that many anesthetic-related deaths were preventable and that improved education was the best means to avoid unnecessary mortality. He went so far as to suggest that all development of new drugs be halted for 5 years in order to direct more attention to training of young anesthetists. He attempted to focus attention on postoperative care and suggested that more deaths occur after the patient is returned to the ward than intraoperatively. His final comments related to a need for establishing a formal inquiry mechanism for determining the cause of all deaths, because such an analysis could lead to improved practice. In many ways, the CEPOD is the culmination of such a philosophy. [16]

TABLE 22-3 -- Estimates of the Incidence of Mortality Related to Anesthesia Before 1980

(Not Available)

From Ross AF, Tinker JH: Anesthesia risk. In Miller RD (ed): Anesthesia, 3rd ed. New York, Churchill Livingstone, 1990.

The major advance in the analysis of anesthetic risk was the report by Beecher and Todd [17] of anesthetic-related death in 10 institutions, published in 1954. Their study included 599,548 anesthetic regimens. The cause of mortality was determined at the local institution by consensus of a surgeon and the chief anesthetist of the institution. Each death was characterized as having one primary cause, and it may also have had multiple secondary causes. Overall, a patient had a chance of mortality of 1 in 75 cases from one cause or another. These investigators reported that anesthesia was the primary cause of mortality in 1 in 2,680 cases and was either the primary or contributory cause of mortality in 1 in 1,560 cases. Surgical error in diagnosis, judgment, or technique was the primary cause of death in 1 in 420 cases, and patient disease was the primary cause in 1 in 95 cases. Of note, these investigators placed these figures in the perspective of treating other causes of mortality:

> Data are present to show that death from anesthesia is of sufficient magnitude to constitute a public health problem. Anesthesia kills several times as many citizens each year out of the total population of the country as does poliomyelitis. Consideration of the millions of dollars rightly spent in attacking poliomyelitis and the next to nothing, comparatively, spent in anesthesia research makes clear an urgent need.
>
> [17]

Beecher and Todd [17] reported on a number of perioperative care issues that were associated with increased mortality. Mortality was greatest in the first decade of life and in the elderly. Use of curare was associated with a death rate six times higher than no use of curare in patients undergoing major operations (Table 22-4) (Table Not Available) . The proportion of "curare deaths" was similar in patients with and without coexisting disease. These authors suggested that muscle relaxants "be employed only when there are clear advantages to be gained by their use, that they not be employed for trivial purposes or as a corrective for generally inadequate anesthesia." [17]

Dornette and Orth [32] reported on deaths occurring in the operating room during a 12-year period from 1943 to 1954. During this period, 95 patients died on the operating table, 12 patients suffered intraoperative cardiac arrest and died postoperatively, and 1 patient died in the recovery room. This resulted in a total of 108 deaths in 63,105 anesthetic regimens. In 19 cases, the death was judged to be the result of the operation. In 13 patients, preexisting disease was judged to be the cause of death. The patient's condition plus operation was a cause of death in 29 instances. Anesthesia was the primary cause of death in 26 cases, 2 of which were the result of an overdose of local anesthetic by a surgeon, and it was partially the cause of mortality in an additional 21 patients. Therefore, the rate of mortality totally attributable to anesthesia was 1 in 2,427, and death was totally or partially attributable to anesthesia in 1 in 1,343 patients.

Dripps and colleagues [35] at the University of Pennsylvania in Philadelphia surveyed their experience during the

TABLE 22-4 -- Surgery and Associated Anesthesia Deaths with and Without "Curare"

(Not Available)

10-year period from 1947 to 1957. They noted 1,285 operative deaths, defined as death within 30 days, in approximately 120,000 anesthetic regimens, for a gross mortality rate of 1.1 percent. This definition includes late deaths, as opposed to many studies that focus on the intraoperative period or the first 48 postoperative hours. After review of the hospital records, these investigators determined whether anesthesia was definitely or possibly contributory to death. Patients were divided into those who underwent spinal anesthesia or those who had general anesthesia with or without muscle relaxants. In the group who underwent spinal anesthesia, mortality definitely related to anesthesia occurred in 1 in 1,560, and mortality definitely or possibly related to anesthesia occurred in 1 in 780. In the group who underwent general anesthesia, mortality definitely related to anesthesia was 1 in 536, and mortality definitely or possibly related to anesthesia was 1 in 259. Mortality was correlated with physical status, using the ASA physical status classification. The higher mortality compared with other reports may relate to the higher physical acuity at this hospital. Importantly, deaths attributable to anesthesia did not occur in any of the 16,000 ASA class I patients.

Dripps et al [35] compared their data with those of Beecher and Todd. In contrast to the earlier report, they did not find that muscle relaxants were the primary cause of death in their cohort. As noted earlier, there were no deaths in healthy individuals, many of whom had general anesthesia with muscle relaxants. Muscle relaxants contributed to death definitely in 1 of 1,210 patients and definitely or possibly in 1 of 520 patients. The principal intraoperative complications were hypotension and hypoxia. For patients who had spinal anesthesia, virtually all complications occurred intraoperatively, whereas postoperative complications were rare. These authors believed that anesthesia mortality had improved since the start of the study, mainly because of improvements in cardiac resuscitation, the use of more rational transfusion therapy, standard use of recovery rooms, and efficient use of mechanical ventilators.

There were numerous subsequent reports from individual or small groups of hospitals during the subsequent two decades. Gebbie [38] reported on the rate of mortality in an 800-bed general hospital in Ontario, Canada, during the period 1958 to 1964. There were 21 deaths within 10 days of surgery for which anesthesia was deemed totally or partially responsible. This results in a death rate of 1 in 6,158. The most common causes of death were respiratory failure, hypovolemia, and regurgitation. In only 1 case was the anesthesiologist totally responsible for the death, whereas a second death was related to an airway obstruction in the recovery room.

The Baltimore Anesthesia Study Committee reviewed 1,024 deaths on either the day of or the day after a surgical procedure in order to determine the potential contribution of anesthesia. [34] This short period of observation (48 h) compares to the 30-day period used by Dripps et al. [35] This cohort represented 87.5 percent of all such cases in Baltimore hospitals during the 5½-year period between 1953 and 1959. For each case reviewed, the committee determined whether anesthesia was the principal cause or one of several contributing factors. In 196 (19.2%) cases, the committee voted that anesthetic management contributed to the death of the patient. Anesthesia was the principal cause of death in approximately one-third of cases (64/196), with half of those (34/64) related to improper management of the anesthetic (see Table 22-6) (Table Not Available) . The authors estimated the rate of operative mortality as 4 in 10,000 operations using this data and applying rates of surgery from the National Health Survey. Mortality rates were higher in males (7.1/10,000) compared with females (2.7/10,000). The rates were estimated at 3 in 10,000 for patients younger than 15 years of age, decreasing to 1.1 in 10,000 for those 25 to 44 years old and increasing to 27.6 in 10,000 in those older than 75 years. Of all the patients studied, more than 50 percent died in their hospital rooms, a finding leading the authors to emphasize the need for routine utilization of postanesthesia care areas.

In an attempt to educate practitioners and to prevent duplication of preventable causes of death, each of the perioperative deaths in the foregoing study was discussed. The primary cause of death was overdosage of anesthesia in eight patients; four patients died following aspiration, and two patients died of chronic hypoxia from mismanagement of the airway. There were six deaths during transurethral resection of the prostate under spinal anesthesia, which the authors attribute to the spinal anesthesia or vasopressor use in patients with coronary disease. Importantly, this report attempts to define potentially preventable causes of mortality.

Schapira et al [33] reported on mortality within 24 hours of surgery between the years 1952 and 1956 at Montefiore Hospital in New York. They ascribed 27 deaths to anesthesia, 18 primarily related and 9 in which anesthesia was contributory. The overall rate in which death was partially or totally attributable to anesthesia was 1 in 1,232.

Clifton and Hotten [36] reported on 162 deaths associated with anesthesia in 205,640 operations performed in the Royal Prince Alfred Hospital in Sydney, Australia between 1952 and 1962. These investigators calculated that the incidence of mortality totally due to anesthesia was 1 in 3,955, that related to surgery was 1 in 2,311, and that caused by patient disease was 1 in 1,996. The incidence of death was lowest in those younger than the age of 20 and highest in the 21- to 49-year-old group, and it was more common in men. The time of death was most commonly postoperatively during the initial period of the study related to hypotension, which was much less frequent during the final years of the study. This change occurred simultaneously with the more common use of blood transfusion. An additional cause of postoperative mortality was respiratory insufficiency. These authors argued that many of these complications would have been prevented by the use of a recovery unit. The potential safety advantages of a postanesthesia care unit (PACU) was a general theme in these reports from the 1960s.

Dinnick [45] reported on 600 deaths associated with anesthesia as part of a series of investigations sponsored by the Association of Anaesthetists in London. This represents the second report from this group since a committee was established to collect clinical data in 1949. The first report included a review of 1,000 fatalities and concluded that "in the majority of the reports there were departures from accepted practice." [45] The initial report published in 1956 found that regurgitation and vomiting were the main factors in death, whereas the second report, published in 1964, found that low blood volume was more important. Underventilation was the second most common finding, comprising 25 percent of the cases.

Bodlander [41] provided a follow-up report of anesthetic mortality at the Royal Prince Alfred Hospital for the years 1963 to 1972. The incidence of mortality totally attributed to anesthesia decreased to 1 in 1,702, whereas anesthesia contributed to mortality in 1 in 502 cases compared with 1 in 1,208 for the years 1952 to 1962. The reduction in anesthesia-related death was attributed to the increase in the number of qualified staff members and the degree of supervision.

Marx et al [26] evaluated the incidence of death within 7 days of surgery in 34,145 consecutive patients at the Bronx Municipal Hospital Center in New York between 1965 and 1969. A total of 645 patients died, and a death report form was constructed based on one developed by a committee of the New York Academy of Medicine. The deaths were then analyzed in relation to perioperative data available from a computer system. The primary causes of death were patients' preexisting disease in 83 percent of cases, operation in 10 percent, and anesthesia in only 4 percent (1 in 1,265 cases). Several factors were shown to be associated with perioperative deaths. Three hundred eight-four deaths (59.5%) occurred in association with emergency cases, which was a significant difference. Mortality rose progressively with age; however, physical status correlated best with the incidence of mortality.

Marx et al [26] determined the relationship between the type of anesthesia and mortality. Regional anesthesia was associated with the lowest incidence of death and local with the highest, whereas general anesthesia was intermediate. Although this relationship was significantly different among groups, the difference appears to be related to the risk of the patient, a finding supported by a more recent study by Cohen et al. [46]

Farrow et al [47] [48] studied hospital mortality following 108,878 anesthetic regimens in Cardiff, Wales between 1972 and 1977. The crude mortality rate was 2.2 per 100 patients. Mortality was greatest in those patients older than 65 years. Mortality was greatest in men until they reached the age of 65 years. Mortality also increased with the severity of patient disease and with emergency operation.

Harrison [40] evaluated mortality associated with 240,483 anesthetic regimens performed between 1967 and 1976 at Groote Schuur Hospital in Cape Town, South Africa. Data were collected prospectively, beginning in 1956. Deaths for which anesthesia was the cause or a major contributory factor occurred in 0.22 cases per 1,000 anesthetics between 1967 and 1976, compared with 0.33 case per 1,000 operations in the 10 years earlier. Anesthesia contributed to 10 percent of all deaths associated with anesthesia. The most common causes of anesthetic-related mortality, in order of frequency, were hypovolemia, respiratory inadequacy following neuromuscular blockade, complications of tracheal intubation, and inadequate postoperative care. Although the improvement in anesthetic-related mortality could not be directly attributed to specific improvements in care, four specific changes did occur: continuing improvement in routine monitoring, an increase in the ratio of consultants to registrars, a decrease in the case load per anesthesiologist, and the introduction of recovery rooms and intensive care units.

In summary, studies prior to 1980 demonstrated steady improvements in anesthesia-related mortality. Studies performed throughout the world focused on identifying the causative factors for perioperative mortality. Several general themes emerged: anesthesia represents a small but significant cause of perioperative mortality; perioperative respiratory complications represent a major complication; and elucidation of the causes of perioperative mortality and education of these causes should lead to improved outcome.

Anesthetic Mortality Studies After 1980

Whereas studies conducted prior to 1980 focused on a single center or group of institutions, studies since that date have frequently been performed on a national basis. The improvements in anesthetic and overall mortality made the analysis of a single institution inadequate because of the small sample size. For example, Holland [49] reported on death within 24 hours of an anesthetic regimen in New South Wales, Australia. A committee of 6 anesthesiologists, 3 surgeons, an obstetrician, a general practitioner, and a medical administrator was established in 1960 and reviewed all such cases except during a 3-year period between mid-1980 and mid-1983. Four categories were established to define the relationship of anesthesia to operative morbidity and mortality (Table 22-5) (Table Not Available) . During the period from 1960 to 1985, information was obtainable on 92 to 96 percent of all cases. Twenty-five percent of the 5,262 deaths were deemed attributable in whole or part to the anesthetic regimen. The incidence of anesthesia-attributable deaths decreased from 1 in 5,500 anesthetics administered in 1960 to 1 in 10,250 in 1970 and to 1 in 26,000 anesthetics in 1984 (Table 22-6) (Table Not Available) .

TABLE 22-5 -- Edwards Classification of the Relation of Anesthesia to Operative Morbidity and Mortality *

(Not Available)

Modified from Holland [49]

*Within 24 hours of an anesthetic

TABLE 22-6 -- Estimated Risk of Anesthesia-Related Mortality in New South Wales, Australia

(Not Available)

From Holland [49]

Based on these estimates, the authors asserted that it was at least 5 times safer to undergo anesthesia in 1984 compared with 1960, particularly in healthy individuals. A subsequent follow-up report stated that factors under the control of the anesthesiologist caused or contributed to perioperative mortality at a rate of 1 in 20,000 operations. [50] The latest report on mortality demonstrated a preponderance of males over females (1.7:1). The reason for this finding is unclear, although it confirms other reports. Importantly, 64 percent of the deaths were inevitable, a finding suggesting that only one-third were preventable.

The New South Wales Committee determined the primary error in management that led to perioperative death mentioned in the previous paragraph. The primary cause was inadequate preparation of the patient, followed by a wrong choice of anesthetic agent. From the committee's standpoint, a wrong choice of agent would include administering a renally excreted agent to a patient with chronic renal failure. The third most common error was inadequate crisis management during the initial decade of the study, but this cause was much less important during the period from 1983 to 1985. In fact, inadequate postoperative management was the second most common cause of problems during the final years of the study.

The New South Wales study of anesthetic-related mortality evaluated the contribution of the "anesthetist" on perioperative mortality. Four groups of providers were identified: specialists, nonspecialists, registrars, and residents. The absolute number of anesthetic-related deaths decreased in all groups, but it was most pronounced in the nonspecialists. During the period from 1960 to 1969, the resident medical officer frequently provided anesthesia. During this same period, it was found that these physicians contributed significantly to the mortality observed among "good-risk" patients, a finding that led to a phasing out of the resident medical officer as a member of the anesthetic work force.

Tiret and colleagues [51] carried out a prospective survey of complications associated with anesthesia in France from 1978 to 1982 in a representative sample of 198,103 anesthetic regimens chosen at random from hospitals throughout the country in a study under the direction of the French Ministry of Health. The sample included a survey of 460 public and private hospitals. The investigators evaluated either deaths or coma within 24 hours of surgery. Both the opinion of the participating anesthesiologist and that of the National Committee of Assessors was determined, and the latter was accepted if there was no agreement. Major complications occurred in 268 patients, with death in 67 patients and persistent coma in 16 patients. Death was totally

TABLE 22-7 -- Incidence of Complications Partially or Totally Related to Anesthesia in 198,103 Anesthetic Regimens

(Not Available)

From Tiret et al [51]

related to anesthesia in 1 of 13,207 anesthetics and partially related in 1 of 3,810 (Table 22-7) (Table Not Available) . Coma occurred in 16 of 198,103 anesthetics, of which 62 percent were deemed totally attributable to anesthesia, with the remainder partially attributable. The French survey confirmed previous findings that major complications occurred more frequently in older patients, those undergoing emergency operations, and those with more extensive comorbidity, as measured by the ASA physical status classification.

One of the most important findings of the survey was that postanesthesia respiratory depression was the most frequent cause of death and coma that was totally attributable to anesthesia (Tables 22-8 (Table Not Available) and 22-9) (Table Not Available) . Almost all the patients who had respiratory depression leading to a major complication received narcotics and muscle relaxants that had not been reversed. These investigators also reported a high incidence of "anaphylactoid shock." The authors contended that this was primarily due to althesin and succinylcholine. Importantly, there was no category of drug overdose, which may have been a more appropriate label for some of these cases.

The study by Tiret and colleagues [51] had the advantage of collecting data prospectively, allowing more accurate estimation

TABLE 22-8 -- Timing of Complications and Mortality Occurrence in a French Survey

(Not Available)

From Tiret et al [51]

TABLE 22-9 -- Causes of Death or Coma Totally Attributable to Anesthesia in a French Survey

(Not Available)

From Tiret et al [51]

of overall mortality than many of the other studies completed. A major limitation of the study is that only death within 24 hours was included, thus ignoring late deaths

that were the direct result of intraoperative complications.

Tikkanen and Hovi-Viander [52] studied death associated with anesthesia and surgery in Finland and compared the results in 1986 with those collected in 1975. Mortality related to anesthesia decreased during the 9-year period, with an incidence of anesthesia-related mortality of 0.15 cases in 10,000 procedures in 1986.

Lunn and colleagues [53] [54] [55] published three reports concerning anesthesia-related surgical mortality in the United Kingdom. When a death occurred in a hospital within 6 days of surgery, a questionnaire was sent to the patient's anesthetist and surgeon. In 59.3 percent of 4,034 reported deaths, both the surgeon and the anesthetist returned the forms. The replies were reviewed anonymously by two assessors, and differences of opinion were determined by arbitration. After review, further details were obtained if the reply indicated that anesthesia was at least partly responsible for the death. Their second report was based on an analysis of 197 reports of deaths within 6 days of anesthesia during 1981. Forty-three percent were found by the assessors to have nothing to do with anesthesia, 41 percent were partly due to anesthesia, and 16 percent were totally due to anesthesia. Of the 32 cases in which death was totally due to anesthesia, most cases were due to either faulty anesthetic technique or postoperative respiratory failure.

The pioneering work of Lunn and others led to the development of the CEPOD, [16] [56] which assessed nearly a million cases of anesthesia during a 1-year period in 1987 in three large regions of the United Kingdom. Unique to this study was the establishment of "crown privilege" by the government to allow total confidentiality.

```
The Secretary of State is satisfied that the disclosure
of documents about individual cases prepared for the Enquiry into Perioperative
Deaths would be against the public interest and would undermine the whole basis
of a confidential study. Therefore, the data/information sent to the
confidential Enquiry into perioperative deaths is protected from subpoena.
```

Deaths within 30 days of surgery were included in the study. There were 4,034 deaths in an estimated 485,850 operations, resulting in a crude mortality rate of 0.7 to 0.8 percent. Surgery had contributed totally or partially to death in 30 percent of all patients. Progression of the presenting disease had contributed to death in 67.5 percent of all patients, with progress of an intercurrent disease relevant in 44.3 percent of patients. Anesthesia was considered the sole cause of death in only 3 individuals, for a rate of 1 in 185,000 cases, and anesthesia was contributory in 410 deaths, for a rate of 7 in 10,000 (Table 22-10) (Table Not Available) .

There are several potential causes for the improvement in mortality between the CEPOD study and previous studies, including improvements from the same group. One explanation is that improvement in care led to improvement in outcome. Importantly, many of the deaths in which anesthesia was previously considered totally contributory were now classified as deaths in which anesthesia was partially contributory.

An important aspect of the CEPOD study was that it established both anesthesia-related and surgery-related factors

TABLE 22-10 -- Death Totally Attributable to Each Component of Risk in the Confidential Enquiry into Perioperative Deaths

(Not Available)

Modified from Buck et al [16]

that contributed to mortality. The five most common causes of deaths are shown in Table 22-11 (Table Not Available) . Of the 410 perioperative deaths, there were 9 cases of aspiration or vomit and 18 cases of cardiac arrest. There was a large proportion of elderly women with fractures of the femoral neck, and the death rate was inversely related to the seniority of the operating surgeon and preoperative preparation. Specifically, the operating surgeon was a consultant in only 19 percent of the orthopedic cases compared to 47 percent overall.

The CEPOD study also provided important information regarding anesthetic practice. Patients were seen preoperatively in greater than 80 percent of the cases, but postoperatively in less than 50 percent. Although the electrocardiogram was monitored in 97 percent of the cases, core temperature was assessed in only 7 percent. Of note, muscle relaxants were used in more than 50 percent of the cases, but a nerve stimulator was used in only 14 percent.

The assessors concluded that avoidable factors were pres-ent in about 20 percent of the perioperative deaths. Contributing factors for anesthesiologists and surgeons tended to be failures to act appropriately with existing knowledge rather than a lack of knowledge, equipment malfunction, or fatigue. However, these authors suggested that inadequate supervision was a problem and suggested that no operation in a patient with an ASA physical status index of IV or V be performed without direct consultation with the appropriate anesthesia and/or surgical consultant (Table 22-12) (Table Not Available) .

There have been several large national studies published since the CEPOD. Pedersen and colleagues [57] in Denmark performed a series of studies in the late 1980s to look at the factors attributable to anesthesia that led to serious morbidity or mortality. They performed a prospective study of 7,306 anesthetic regimens. They used a similar approach to previous studies in that three anesthetists reviewed the records of complications and determined whether the cause

TABLE 22-11 -- Confidential Enquiry into Perioperative Deaths: The Five Most Common Clinical Causes of Death

(Not Available)

From Buck et al [16]

TABLE 22-12 -- Confidential Enquiry into Perioperative Deaths: Grade of Physician According to Hour of Operation [a]

(Not Available)

From Buck et al [16]

[a] Day represents Monday through Friday, 9 AM to 7 PM; night represents Monday through Friday, 7 PM to 9 AM, and Saturday and Sunday.

was attributable to anesthesia (no distinction was made between totally and partially contributable). Complications attributable to anesthesia occurred in 43 patients (1/170), with mortality in 3 patients (1/2,500). Complications, in order of incidence, included cardiovascular collapse (37%; 16/43), severe postoperative headache after regional anesthesia (21%; 9/43), and awareness during anesthesia (19%; 8/43). These investigators assessed that 37 percent of the anesthesia-related morbidity was preventable. The three deaths occurred in severely ill patients (ASA class III or greater), and two deaths were judged to be preventable.

Cohen et al [46] developed a methodology for studying anesthesia outcome in four teaching hospitals in Canada. These investigators developed a new anesthesia record to serve as a data collection instrument. Research nurses reviewed all inpatient records within 72 hours postoperatively, conducted interviews of patients using a standardized instrument, and conducted a telephone survey of the majority of outpatients. Assessment of the contribution of anesthesia to the complication was determined using the classification of the New South Wales Committee on Anaesthesia Mortality (see Table 22-5) (Table Not Available) . In a total of 6,914 adult anesthetics, no deaths were directly attributable to anesthesia.

Warner and colleagues [58] at the Mayo Clinic studied major morbidity and mortality within 1 month of ambulatory surgery in 38,598 patients. Four patients died, 2 of a myo-cardial infarction and 2 in an automobile accident (Fig. 22-2) (Figure Not Available) . The 2 deaths from a myocardial infarction occurred at least 1 week after surgery and were not directly attributable to anesthesia. Considering the rate of mortality directly related to anesthesia described in the CEPOD study, none would be expected in a study of this size.

Use of Computerized Analysis

Increasingly, the use of computerized databases has enhanced the ability of investigators to identify perioperative complications. One of the earliest uses of a computerized analysis of postanesthesia deaths was by Marx and colleagues. [26] They identified 645 individuals who died within 7 days of surgery from a total cohort of 34,145 consecutive surgical patients. The rate of mortality related to anesthesia was 1 in 1,265 cases and 1 in 1,707 cases related to postoperative management. The authors deemed two-thirds of all deaths preventable. Sanborn et al [59] used a computerized anesthesia record to identify intraoperative incidents with high sensitivity and specificity. These investigators were able to demonstrate that perioperative deaths occurred more frequently in those patients who sustained an intraoperative incident than in those who did not.

Figure 22-2 (Figure Not Available) Timing of perioperative events in patients undergoing ambulatory surgery. Many of the events occur within the first 48 hours and are likely related to the stress of surgery. A subset of events occurring after this period may relate to background event rates. The overall rate of morbidity was lower than expected for a similar cohort of age-matched nonsurgical patients. *(From Warner et al [56])*

Other Approaches to Discern the Root Cause of Morbidity and Mortality

Accumulating data clearly demonstrate that risk directly attributable to anesthesia has declined over time. The cause of this reduction in mortality is unclear. Numerous factors have been implicated in the improved outcome, including new monitoring modalities, new anesthetic drugs, and the changes in the anesthesia work force. However, it is difficult to document reduced risk related to any one factor. Issues related to manpower are addressed later in this chapter. Interestingly, although newer monitoring modalities, particularly pulse oximetry, would be expected to lead to improved outcomes, no randomized trial has been able to document such a conclusion. [60] This limitation supports the need to continue monitoring for complications and their root cause with studies such as the ASA Closed Claims Project.

Studies similar to the CEPOD study have not been performed in United States, most likely because of the legal system. Therefore, information related to perioperative mortality has had to be obtained from other sources. This basic concept led to the formation of the anesthesia Closed Claims Study. The Professional Liability Committee of the ASA conducted a nationwide survey of closed insurance claims for major anesthetic mishaps.

Both fatal and nonfatal outcomes were reviewed. Among the fatal events, cases involving unexpected cardiac arrest during spinal anesthesia were observed in 14 healthy patients from the initial 900 claims. [61] The cases were analyzed in detail in order to identify patterns of management that may have led to the event. Two patterns were identified: oversedation leading to respiratory insufficiency and inappropriate resuscitation of high spinal sympathetic blockade.

Tinker et al [62] queried the Closed Claims Study to determine the role of monitoring devices in the prevention of anesthetic mishaps. These investigators reviewed 1,097 anesthetic claims and determined that 31.5 percent of the negative outcomes could have been prevented by the use of additional monitors, primarily pulse oximetry and capnography. Those injuries that were deemed preventable with additional monitoring resulted in dramatically more severe injury and higher costs of settlement than those judged nonpreventable with additional monitoring. In almost 90 percent of the preventable cases (305/346), at least one clinical sign of abnormality had been present from the existing monitors.

Caplan et al [63] reviewed the Closed Claims Study for respiratory events (Table 22-13) (Table Not Available) . These claims represented the single largest class of injury (34%). Death or brain damage occurred in 85 percent of cases. These investigators identified inadequate ventilation, esophageal intubation, and difficult tracheal intubation as the primary causes of respiratory events. Most of the outcomes were thought by the investigators to be preventable with better monitoring (Fig. 22-3) (Figure Not Available) . Although no randomized trial has demonstrated the value of pulse oximetry or capnography, an analysis of claims supports the value of such monitoring. This analysis also formed part of the basis for the ASA Difficult Airway Guidelines and algorithm. [64]

Cooper and colleagues [65] [66] [67] [68] approached the problem of sample size for determining perioperative morbidity by identifying "critical incidences," defined as those that are preventable but that could lead to undesirable outcomes. Such a definition could include events that led to no or only transient effects for the patient. The investigation involved collecting anesthesia-related human errors and equipment failures from anesthesiologists, residents, and nurse anesthetists. In a series of reports, these investigators identified frequent incidences, such as disconnections in breathing circuits, and causes of discovery of errors, such as intraoperative relief. [65] [66] [67] [68] They confirmed that equipment failure was a minor cause of anesthesia mishaps (4%), whereas human error was dominant. They suggested that future studies of anesthesia mortality and morbidity should classify events according to a strategy for prevention, rather than outcome alone.

Buffington et al [69] studied the ability of attendees of an anesthesia meeting to identify five faults intentionally created

Figure 22-3 (Figure Not Available) Relationship between adverse events in the American Society of Anesthesiologists Closed Claims Study and preventable complications. Preventable events were significantly more common in relation to respiratory complications than all nonrespiratory complications. Of the respiratory complications, difficult intubation had the least number of preventable complications. *(From Caplan et al [63])*

TABLE 22-13 -- Distribution of Adverse Respiratory Events in the American Society of Anesthesiologists Closed Claims Study

(Not Available)

From Caplan et al [63]

in a standard anesthesia machine. A survey was distributed, and the answer sheets were scored with respect to the number of correct answers. Only 3.4 percent of the respondents found all 5 faults. On average, the number of faults detected was 2.2. The professional background of the participants did not influence the ability for finding the faults, with similar distributions between physicians and certified registered nurse anesthetists (CRNA). There was a small improvement in fault-finding ability in those with at least 10 years' experience compared with those with less experience. Studies such as these highlight the problem in the practitioner's ability to identify conditions that may lead to anesthetic mishaps. Whether improved technology or education will reduce some basal level of mishaps is unknown.

Analysis of Intraoperative Cardiac Arrests

As opposed to studying perioperative mortality and its association with anesthesia, several studies have evaluated intraoperative fatal and nonfatal cardiac arrests [70] [71] [72] [73] [74] [75] [76] [77] (Table 22-14) (Table Not Available) . In this manner, there are sufficient numbers of complications to perform an analysis at one institution. Keenan and Boyan [78] studied the incidence and causes of cardiac arrest due to anesthesia at the Medical College of Virginia, Richmond, during a 15-year period. There were 27 cardiac arrests during 163,240 anesthetic regimens, for an incidence of 1.7 per 10,000 cases. Death occurred in 14 patients, for an incidence of 0.9 per 10,000 cases. Pediatric patients had a 3-fold higher risk of cardiac arrest than adults. Emergency cases had a 6-fold greater risk. Specific errors in anesthetic management could be identified in 75 percent of cases, most commonly from inadequate ventilation and an absolute overdose of an inhalational agent. The time of day did not appear to influence the rate of anesthetic-related cardiac arrest. From an educational perspective, the authors identified progressive bradycardia preceding all but one cardiac arrest, a finding suggesting that early identification and treatment may prevent complications.

Olsson and Hallen [79] studied the incidence of intraoperative cardiac arrests at the Karolinska Hospital in Stockholm, Sweden from 1967 to 1984. A total of 170 cardiac arrests occurred in 250,543 anesthetic regimens performed. Sixty patients died, resulting in a mortality of 2.4 per 10,000 anesthetics. After elimination of cases of inevitable deaths (e.g., rupture of a cerebral aneurysm, trauma), the mortality caused by anesthesia was 0.3 deaths per 10,000 anesthetics. The most common causes of anesthetic-related cardiac arrest were inadequate ventilation (27 patients), asystole after succinylcholine (23 patients), and postinduction hypotension (14 patients). The incidence of cardiac arrest increased with increasing severity of comorbid disease, as assessed by the ASA physical status classification. In evaluating the incidence of intraoperative cardiac arrest over time, there was a considerable decline from 1967 to 1984 coincident with the increase

in the number of anesthesia specialists employed at the clinic.

The value of studying cardiac arrests may be related to issues of quality of care. The ability to resuscitate patients from an intraoperative cardiac arrest may reflect the skills of the care providers. Future research will be required to determine the validity of such an approach.

TABLE 22-14 -- Cardiac Arrest Series When the Denominator Is More Than 40,000 Anesthetics

(Not Available)

Modified from Brown DL: Risk and Outcome in Anesthesia: A Historical Perspective. Philadelphia. JB Lippincott.

Future Issues

Most of the studies to date have focused on in-hospital and short-term mortality, yet perioperative complication may be the event that directly leads to death. For example, a perioperative stroke or myocardial infarction may lead to death after the period of analysis. Even small myocardial infarctions or unstable angina during the perioperative period have been associated with worse long-term survival in several studies. Should these "late" deaths be attributed to anesthetic complications for the purpose of such analyses? From a theoretical standpoint, one study of perioperative beta-adrenergic blockade presents an even greater dilemma. Mangano and colleagues [80] performed a randomized clinical trial in which 7 days of perioperative beta-blockade was compared with placebo in high-risk patients undergoing noncardiac surgery. These investigators reported significantly improved 6-month survival, which remained significant up to the 2 years of follow-up. In a subsequent report regarding this trial, Wallace et al [81] demonstrated that the improved survival in the beta-blocker group was associated with a significantly lower incidence of perioperative myocardial ischemia. Although there have been several questions regarding study design and potential confounding issues related to the conclusions of the study, one guideline advocates the routine use of atenolol for all high-risk patients. The authors of the original study suggested that atenolol resulted in better plaque stabilization during the perioperative period, which improved long-term survival. If the hyperdynamic perioperative state is not well controlled, then this theory would suggest that more plaques become destabilized and progress to acute occlusion and sudden death. If atenolol is not used and patients die within 6 months of surgery, should this outcome be attributed to an error in anesthesia and perioperative management? Part of the answer relies on the strength of this study to support the conclusion that routine use of atenolol does result in improved long-term survival. Because the one study is small and questions remain regarding potential confounding factors, further studies appear warranted before the omission of prophylactic beta-blockade is considered less than the standard of care.

RISKS RELATED TO THE PATIENT

It is well known that perioperative morbidity and mortality increase with increasing patient comorbidity (Ch. 23) . The original ASA physical status scoring system was proposed in 1941 and included six categories. [82] It was originally intended to standardize terminology and to allow statistical analysis of outcomes between sites. [83] The original classification avoided the inclusion of surgical variables and was restricted to preoperative patient characteristics. It was revised in 1961 by Dripps and colleagues [35] to its present form of five categories, which were then adopted by the ASA and are still used today. The simplest example of such a relationship is the incidence of mortality by ASA physical status. In their original study of perioperative mortality, Dripps et al demonstrated that mortality increased as severity of comorbid disease increased, as assessed by the ASA physical status classification.

Several investigators have reevaluated the relationship between operative mortality and ASA physical status classification. The previously described study by Pedersen et al [57] and Tiret et al [51] demonstrated such relationships (Fig. 22-4) (Figure Not Available) . Vancanti et al [84] also demonstrated the relationship between increasing mortality and decreasing ASA physical status in 68,388 cases.

Cohen and colleagues [46] in Canada followed 100,000 anesthetic regimens and determined mortality within 7 days of operation using governmental vital statistics mortality data between the years 1975 and 1984. The investigators established a computerized database for each anesthetic regimen that included age, preoperative conditions, ASA physical status, anesthetic technique, and monitors, among other factors. The overall 7-day mortality rate was 71.04 deaths per 100,000 anesthetics. The mortality rate increased with advanced age and showed a marked increase in patients more than 80 years of age. Rates were low for normal, healthy individuals and for those undergoing minor procedures. The investigators developed a multiple logistic regression model to determine the independent predictors of mortality. Significant risk markers for increasing mortality were advanced age, male gender, increasing physical status score, major or intermediate surgery, emergency procedure, a complication in the operating room, narcotic anesthetic techniques, and administration of only one or two anesthetic drugs (Table 22-15) (Table Not Available) .

In an attempt to look at each of the categories of contributing factors independently, Cohen et al [46] constructed receiver-operator characteristic curves. There was no increment in prediction of mortality higher than that found by the patient plus surgical characteristics. Plots including "other" or anesthesia-related factors showed almost complete overlap with those curves including patient-specific and surgery-specific factors alone.

Figure 22-4 (Figure Not Available) Relationship between American Society of Anesthesiologists (ASA) physical status classification and mortality. Increasing physical status is associated with increasing mortality. Emergency surgery increases risk dramatically, especially in patients in ASA class IV and V. *(From Tiret et al [51])*

TABLE 22-15 -- Risk Factors Associated with Increased Odds of Dying Within 7 Days (All Cases)

(Not Available)

From Cohen et al [46] Copyright 1988, American Medical Association.

One of the limitations of the ASA physical status classification is that ranking is a subjective measure conferred by the practitioner rather than an objective measure determined by the presence of specific disease states. Owens et al [85] evaluated this hypothesis by asking 255 anesthesiologists to classify 10 hypothetic patients. In six of the cases, there was general agreement among the practitioners with regard to the classification of the patient, whereas there was divergence of opinion in the other four cases. The key finding of this study is that the ASA physical status classification is "useful but suffers from a lack of scientific precision." [85]

As opposed to evaluating the risk of overall mortality, many studies have attempted to define patient characteristics associated with morbidity and mortality related to a particular organ system. In evaluating the risk directly related to patient condition, it is important to understand the limitations of the methodology. All such studies evaluate the predictive value of a clinical or laboratory risk factor for a defined perioperative complication. In approaching such an evaluation, a cohort of individuals of interest is defined. In the most optimal state, the study is performed prospectively, and the outcome of interest is assessed in a rigorous, blinded fashion. Unfortunately, many of the studies focus on selected patients and include a retrospective design, features that greatly limit the studies' generalizability and validity. For example, many of the studies evaluating risk factors in patients undergoing vascular surgery only follow patients who are referred for diagnostic testing, not consecutive series.

Many of the studies have adopted the approach of defining a cohort of individuals, determining their clinical and laboratory risk factors, and using multivariate modeling to determine those factors associated with increased risk. Frequently, perioperative risk is used to define both intraoperative and postoperative complications. A major limitation in the use of multivariate modeling for this purpose is the assumption that the intraoperative period is a "black box" and that care is not modified by knowledge of the risk factor (Fig. 22-5) . However, anesthesiologists modify their intraoperative

Figure 22-5 The concept of the "black box" for risk indices. In developing a risk index, patients with a specific risk factor enter the operating room and have a complication at a rate *P.* If the anesthesiologist is aware of the importance of the risk factor and can modify care to reduce such risk (*P*/2), then the risk factor may no longer be significant. Importantly, if the risk factor is ignored, then complications may again occur in such patients.

care in high-risk patients in an attempt to reduce the risk. Therefore, changes in medical care over time and better knowledge of high-risk patients should result in reduction of risk related to specified clinical factors. Therefore, many of the indices developed previously may no longer hold clinical validity.

Finally, in designing a multivariate risk index for perioperative morbidity and mortality, only those factors included in the analysis and in the patient population of interest are included in the final model. For example, if the population studied represents a unique referral bias, then some risk factors may be overrepresented, whereas others may not be present in sufficient quantity to study. An example would be unstable angina in Goldman's original cardiac risk index. [10] Because such

patients would only present for emergency surgery, the risk factor would rarely be represented in many indices.

There are numerous specific disease states that increase perioperative risk. Cardiovascular disease is the most extensively studied, with the goal of identifying patients at greatest risk for fatal and nonfatal myocardial infarctions. One of the earliest attempts to define cardiac risk was performed by Goldman and colleagues [10] at the Massachusetts General Hospital. These investigators studied 1,001 patients older than 45 years of age who were undergoing noncardiac surgery, excluding those patients who underwent transurethral resection of the prostate under spinal anesthesia. Using multivariate logistic regression, these authors demonstrated nine clinical factors associated with increased morbidity and mortality (Table 22-16) (Table Not Available) . Each of these risk factors was associated with a given weight in the logistic regression equation, which was converted into points in the index. An increasing number of points was associated with increasing perioperative cardiac morbidity or mortality.

There have been several attempts to validate the Goldman cardiac risk index (Chs. 25 49 and 51) . Zeldin [86] pro-spectively determined the cardiac risk index in 1,140 surgical patients. They reported that the overall accuracy of the cardiac risk index was as high as in the original study, although the rate of complications in the highest-risk group was lower than originally reported. Larsen et al [87] also found that the cardiac risk index was accurate in 2,609 consecutive unselected patients older than 40 years. The validity of the cardiac risk index is more controversial in patients undergoing vascular surgery. Domaingue et al [88] studied patients undergoing various vascular surgery procedures and reported a higher probability of major cardiac complications than that reported by Goldman et al, but they also demonstrated a higher rate of complications with increasing cardiac risk class. Jeffrey et al [89] evaluated the rate of cardiac complications in 99 patients undergoing elective abdominal aortic surgery and demonstrated a similar pattern of increased overall complication rates with increasing cardiac risk. Importantly, a higher percentage (7%) of patients in the lowest category sustained a cardiac complication. White et al [90] demonstrated the value of the Goldman cardiac risk index for long-term survival after vascular surgery. Several other studies were unable to demonstrate any relationship between the cardiac risk index and perioperative cardiac complications and noted a high incidence of complications in patients with a cardiac risk index of I or II. [91] [92] Interestingly, when the ASA physical status classification was compared with the Goldman cardiac risk index in a cohort of 16,277 patients undergoing noncardiac surgery, [93] both indices demonstrated predictive value, although the objective Goldman cardiac risk index had little value over the more subjective ASA physical status classification.

Other investigators have attempted to develop risk indices. Cooperman et al studied perioperative cardiac risk in 566 patients undergoing major vascular surgery and developed a multivariate logistic regression model for predicting cardiac risk. [93A] Detsky et al [94] studied a cohort of individuals who were referred to an internal medicine service for preoperative evaluation, as opposed to an unselected group of

TABLE 22-16 -- Computation of the Cardiac Risk Index

(Not Available)

From Goldman et al [10]

surgical patients. Many of the factors identified by Goldman et al were confirmed or slightly modified in the Detsky index, although angina was added to the risk factors. Importantly, Detsky et al advocated the calculation of a pretest probability of complication based on the type of surgery, after which the modified risk index is applied using a nomogram. In this manner, the overall probability of complications can be determined as a function of both the surgical procedure and the patient's disease. The Detsky index has been advocated as the starting point for risk stratification for the American College of Physicians guideline on preoperative evaluation. [95]

There have been numerous risk indices developed for cardiac surgery. [96] [97] [98] [99] [100] [101] Again, the goal has been to define those patients at greatest risk for perioperative outcomes, not specific anesthesia-related risk. Many of these indices focus on anatomic considerations for perioperative risk. They are extremely useful in risk adjustment to assess rates of mortality. For example, New York State publishes annual mortality rates for surgeons and hospitals for coronary bypass grafting. [102] [103] [104] In order to be able to compare rates across institutions, it is important to adjust risk so that institutions that perform predominantly high-risk surgery are not penalized.

Vascular surgery represents a cohort of patients with very high perioperative complication rates. [105] Both clinical risk indices and noninvasive diagnostic testing have been used to identify the patients with the highest perioperative mortality and major morbidity. Numerous studies have demonstrated that the presence of a reversible defect on thallium imaging and of new regional wall motion abnormalities on dobutamine echocardiography predicts those patients with a high perioperative risk. [106] [107] [108] [109] [110] [111] [112] [113] [114] [115] As the technology became diffused, the tests lost much of their predictive value because they were used in lower-risk patients. [116] [117] Subsequent studies demonstrated that the tests should only be applied to those at moderate or high risk, and these studies identify a group of clinical patient characteristics that define those in whom the test will have the optimal predictive characteristics. Eagle and colleagues [118] determined the value of clinical risk factors for predicting perioperative cardiac events and the additive value of noninvasive testing based on the preoperative risk profile. Five clinical predictors were identified: age older than 70 years, diabetes mellitus, angina, ventricular ectopic activity under treatment, and Q waves on an electrocardiogram. In patients undergoing major vascular surgery, an increasing number of clinical variables was associated with an increasing perioperative risk. The presence of thallium redistribution after dipyridamole infusion further identified a high-risk cohort in those patients with one or two clinical risk factors. A subsequent multi-institutional report used a bayesian approach to define the additive value of these risk factors and thallium markers to identify high-risk patients. [119]

Vanzetto et al [120] performed a prospective evaluation in which an expanded number of clinical variables was identified in a cohort of patients undergoing major vascular surgery. Cardiovascular morbidity and mortality were determined prospectively in this population. Again, an increasing number of clinical variables was associated with an increasing perioperative risk. Most importantly, dipyridamole thallium imaging was only performed in the subset of patients with two or more clinical variables, and the results of the test were not made available to the clinicians caring for the patients. In this well-performed study, the presence of thallium redistribution again identified a cohort with an incrementally greater perioperative risk compared with patients with negative scans and a similar number of clinical variables.

As part of their study of anesthesia mortality, Pedersen and colleagues [57] also evaluated the occurrence of cardiovascular and pulmonary complications. In the total cohort of 7,306 anesthetic regimens, they reported a 6.3 percent incidence of intraoperative or postoperative cardiovascular complications and a 4.8 percent incidence of intraoperative or postoperative pulmonary complications. Acute myocardial infarction occurred in 0.16 percent of the patients. These investigators evaluated a number of characteristics, including gender, age, presence of ischemic heart disease, duration of anesthesia and type of surgery, and their relationship to cardiovascular and pulmonary complications, and overall mortality in the hospital (Table 22-17) (Table Not Available) . Cardiopulmonary complications were associated with advanced age (>70 y), preoperative signs of ischemic heart disease with recent myocardial infarction, chronic heart failure, chronic lung disease, and abdominal surgery, particularly of an emergency nature. Of interest, these workers noted that the use of pancuronium was associated with worse perioperative outcome, a finding reminiscent of the "curare deaths" of the 1940s and 1950s.

Numerous studies have evaluated the importance of single variables in perioperative risk. The presence of hypertension has been examined in several studies. Goldman and Caldera [121] evaluated a cohort undergoing noncardiac surgery with general anesthesia. Hypertension did not denote a group with increased perioperative risk, although the number of patients with a diastolic blood pressure greater than 110 mm Hg was insufficient to draw any conclusions. This study highlights the problems related to generalization of results, because many subsequent authors suggested that surgery be delayed in patients with a diastolic blood pressure higher than 110 mm Hg. In one of the few studies to demonstrate a relationship, Hollenberg et al [122] identified both hypertension and the presence of left ventricular hypertrophy as predictors of perioperative ischemia, but these investigators did not report on the independent relationship of these predictors with perioperative major morbidity.

The studies of the rate of perioperative reinfarction in patients who sustained a previous myocardial infarction are examples of prospective cohort studies to identify the risk of a particular clinical factor. Traditionally, risk assessment for noncardiac surgery was based on the time interval between the myocardial infarction and surgery. Multiple studies have demonstrated an increased incidence of reinfarction if the myocardial infarction was within 6 months of surgery [11] [12] [13] (Table 22-18) . With improvements in perioperative care, this difference has decreased.

However, this example of assessing risk illustrates the issue of changes in management over time. The importance of the intervening time interval may no longer be valid in the current era of thrombolytics, angioplasty, and risk stratification after an acute myocardial infarction. Although many patients with a myocardial infarction

may continue to have myocardium at risk for subsequent ischemia and infarction,

TABLE 22-17 -- Factors Associated with Increased Perioperative Complications

(Not Available)

From Pedersen et al [203]

other patients may have their critical coronary stenosis either totally occluded or widely patent. For example, the use of percutaneous transluminal coronary angioplasty (PTCA) is associated with a reduced incidence of death or reinfarction within 6 months. [123] Therefore, patients should be evaluated from the perspective of their risk for ongoing ischemia. The American Heart Association/American College of Cardiology Task Force on Perioperative Evaluation of the Cardiac Patient Undergoing Noncardiac Surgery [124] has advocated the use of a myocardial infarction within the past 30 days as the group at highest risk, whereas after that period, risk stratification is based on the presentation of disease and exercise tolerance.

SPECIAL PATIENT GROUPS

Obstetrics

Maternal mortality is very rare (Ch. 57) . The anesthesia-related component of maternal delivery represents only a small fraction of all maternal deaths, making the study of this problem difficult or impossible in any one institution. A series of studies was performed between 1974 and 1985 to determine the rate of complications in both the United States and England. One of the first reports was for the period 1974 to 1978. Kaunitz et al [125] reported an anesthetic death rate of 0.6 per 100,000 births using data from all 50

TABLE 22-18 -- Reinfarction Rates in Different Studies and Number of Patients Studied

TIME ELAPSED BETWEEN PRIOR MYOCARDIAL INFARCTION AND OPERATION (MO)	REFERENCE		
	TARHAN ET AL (1972)[11]	***RAO ET AL (1983)***[204]	***SHAH ET AL (1990)***[13]
0-3	37%, *n* = 18	5.8%, *n* = 52	4.3%, *n* = 23
4-6	16%, *n* = 19	2.3%, *n* = 86	0%, *n* = 18
>6	5.6%, *n* = 322	1.5%, *n* = 595	5.7%, *n* = 174
Time unknown	--	--	3.3%, *n* = 60

states. Endler et al [126] studied births in Michigan from 1972 to 1984 and reported 15 maternal deaths in which anesthesia was the primary cause and 4 deaths in which anesthesia was contributory. This resulted in a rate of 0.82 anesthetic deaths per 100,000 live births. Eleven of the 15 deaths were associated with cesarean section. Obesity and emergency surgery were risk factors in many patients. Complications related to regional anesthesia were problems during the early part of the study, whereas failure to secure a patent airway was the primary cause of mortality in later years. There was no anesthesia-related maternal mortality in the final 2 years of the study. The incidence of anesthetic death was markedly higher in black women, a finding that the authors suggest may be related to the inability to detect cyanosis. Rochat et al [127] studied 19 areas of the United States between 1980 and 1985 and reported 0.98 anesthetic deaths per 100,000 live births. Rochat et al noted that maternal mortality did not decrease over the time of the study.

The Confidential Enquiry into Maternal Deaths in England and Wales has been assessing maternal deaths since 1952. [128] All maternal deaths are sent to a district medical officer, who sends an inquiry form to all health practitioners who were involved in the care of these patients. These forms are then evaluated by a senior obstetrician and anesthetic assessor. Morgan [128] reported on the maternal deaths from anesthesia between 1952 and 1981 (Table 22-19) (Table Not Available) . The total maternal mortality has decreased over time, and the percentage of deaths related to anesthesia has increased, although the absolute number of deaths from anesthesia has decreased. During the early years of the study, endotracheal intubation was rarely performed during obstetric anesthesia. After reports advocated the use of endotracheal intubation after thiopental-succinylcholine administration, technical difficulties with intubation were noted. The other major finding is that the experience of the anesthetist in obstetric anesthesia was the most important factor in anesthetic maternal mortality.

There have been several studies that have attempted to define the cause of anesthetic-related maternal deaths. Insights into the cause of maternal mortality can also be elicited from the ASA Closed Claims Study. In 1989, Chadwick et al [129] published a report of closed malpractice claims related to 190 obstetric cases, representing 127 cases of cesarean section and 63 of vaginal delivery. The most frequent complications were maternal death and newborn brain damage. There were 15 maternal deaths in patients who had regional anesthesia and 26 maternal deaths in patients who had general anesthesia. Because the absolute number of patients who underwent each type of anesthesia was unknown, the risk attributable to anesthesia could not be determined, unlike the subsequent report by Hawkins et al. [130]

Hawkins et al [130] obtained data from the U.S. Centers for Disease Control and Prevention (CDC) ongoing National Pregnancy Mortality Surveillance System. Using state data on births and fetal deaths between 1979 and 1990, three obstetric anesthesiologists reviewed the record to determine the possible relation to anesthesia. A total of 129 women died of anesthesia-related causes during the study period, most of whom (82%) during cesarean section, with the incidence decreasing over time (Table 22-20) (Table Not Available) . Importantly, this decrease appears to be related to an increase in the use of regional anesthesia. The primary cause of mortality was related to the type of anesthesia. For general anesthesia, 73 percent of the deaths were related to airway problems. Unlike England, which has the Confidential Enquiry of Maternal Deaths, the United States study lacks the extensive detail for each event and therefore the absolute cause of mortality is somewhat in doubt. In particular, the authors acknowledge that general anesthesia may be used for patients with a higher acuity of disease, and that practice may account for the higher mortality rates. The availability of national databases should allow accurate tracking of mortality in order to ensure that appropriate quality assurance/quality improvement systems are in place.

Gibbs et al [131] surveyed 1,200 hospitals in 1981 and sent questionnaires to the chiefs of anesthesia and obstetrics. Anesthesiologists were available for obstetric anesthesia in only 21 percent of all hospitals, and at night and on the weekends, they were available in only 15 percent. Hospitals with less than 500 deliveries per year had the most striking deficiencies in anesthesia personnel. Even for cases in which general anesthesia was provided for cesarean section, an anesthesiologist was involved in the care 44 percent of the time, although hospitals with more than 1,500 deliveries had an anesthesiologist present 85 percent of the time. The authors did not evaluate the relationship between outcome

TABLE 22-19 -- Maternal Mortality Figures Obtained from the Confidential Enquiries into Maternal Deaths In England and Wales

(Not Available)

From Morgan [126]

TABLE 22-20 -- Numbers, Case Fatality Rates, and Risk Ratios of Anesthesia-Related Deaths During Cesarean Section Delivery by Type of Anesthesia: United States, 1979-1984 and 1985-1990

(Not Available)

From Hawkins et al [130]

and staffing models. The survey was performed again in 1992. [132] Compared with 1981, these investigators noted a marked increase in the availability of labor analgesia and a decrease in the use of general anesthesia. In more than one-half of anesthetic regimens for cesarean section, care was provided by nurse anesthetists without medical direction by an anesthesiologist. How these trends in staffing affect maternal mortality requires further evaluation.

Pediatrics

There are few studies of anesthetic risk in the pediatric population (Ch. 59) . Two themes emerge from these studies: very young infants are at increased risk; and anesthetic risk is reduced in centers with specialized pediatric anesthesia. In the report by Beecher and Todd, [17] there was a "disproportionate number" of anesthetic deaths in children less than 10 years of age.

Graff et al [133] from the Baltimore Anesthesia Study Committee reported on 335 operative deaths in the pediatric age group. Of these deaths, 58 were thought to be either primarily or partially attributable to anesthesia. The percentage of operative deaths attributable to anesthesia was relatively constant between age groups at 16.6 to 21.7 percent. The estimated anesthesia-associated mortality was 3.3 deaths per 10,000 operations for those younger than 15 years, compared with 0.6 for those between 15 and 24 years and 11.7 deaths per 10,000 operations for those older than 64 years of age. More than one-half of the patients were ASA physical status I or II, suggesting that the majority of the deaths occurred in children with good anesthetic risk. The majority of the deaths occurred in tonsillectomy, a finding that most likely reflects that this is the most common operation in this age group. In an attempt to determine the phase of the operation associated with the highest risk, improper management of the anesthetic accounted for approximately one-half of the cases. Respiratory complications were apparent in 82 percent of the anesthetic deaths due to underventilation and aspiration of vomitus or blood. Interestingly, the authors suggested that females are a better operative risk than males in all age groups.

Tiret et al [134] published a study of pediatric anesthesia risk in 1988. They prospectively studied major anesthetic complications in pediatric patients in 440 hospitals in France between 1978 and 1982. There were 27 major complications in 40,240 cases, which included 12 cardiac arrests and 1 death. The incidence of major complications and of cardiac arrest was significantly higher for infants than for children. The rate of cardiac arrests related to anesthesia was highest in infants (19/10,000) and lower in children (2.1/10,000) (Table 22-21) (Table Not Available) . The majority of the complications in infants involved the respiratory system, predominantly airway problems and aspiration. Older children experienced both respiratory and cardiac complications, which were most frequent during induction and recovery.

Cohen et al [135] studied 29,220 anesthetic regimens at the Winnipeg Children's Hospital in Manitoba, Canada. Data were collected from mid-1982 to 1987 and were stored in a databank. Data on patients' coexisting medical conditions and postoperative follow-up were obtained within 72 hours. Complications included death, cardiac arrest, drug incident, and airway obstruction, as well as minor complications including nausea and vomiting, arrhythmias, and sore throat. These investigators reported on the type of operation, with neonates undergoing a higher percentage of major vascular/ cardiac and intra-abdominal procedures, whereas older children had a higher incidence of extremity-related procedures. Intraoperative cardiac arrest occurred most frequently in infants (4/2,901 anesthetics in children <1 y old) compared with older children. Postoperatively, minor events such as nausea and vomiting were more common in older children, whereas respiratory events were more common in infants and younger children (Table 22-22) (Table Not Available) . When compared with adult patients, children experienced different complications

TABLE 22-21 -- Incidence (per 1,000) of Anesthetic Complications in Infants and Children Compared with Results in Adults

(Not Available)

From Tiret et al [51]

TABLE 22-22 -- Perioperative Events: Summary by Age Group (Percentage of Total Anesthetics)

(Not Available)

From Cohen et al [135]

that frequently extended well into the postoperative period. Comparing 2-year periods between 1982 and 1987, the rates of intraoperative events were stable, whereas the rate of postoperative complications decreased. These authors suggested that identification of these problems can lead to changes in management, thus resulting in improved outcomes.

Geriatrics

Numerous studies have documented the importance of advanced age on perioperative risk (Ch. 61) . In many of the original studies on the factors associated with perioperative mortality, both the youngest and oldest patients were shown to have the highest rates of death after surgery. Age has been implicated as one of the factors in the risk indices developed by Goldman, Detsky, and Pedersen and their colleagues. Age is predominantly analyzed as a dichotomous variable, with many studies focusing on age of more than 70 years.

One of the issues regarding the rate of mortality in the geriatric population is the definition of this group. Multiple definitions have been used for advanced age, including patients older than 65, 70, 80, and 90 years. Denney and Denson [136] evaluated risk of surgery in patients older than 90 years of age. They suggested that the prevailing philosophy in 1972 was that surgery may not be appropriate considering the high perioperative risk in this cohort, without objective data to support such a supposition. They reported on 272 patients undergoing 301 operations at the University of Southern California Medical Center in Los Angeles. Contrary to their expected belief, these investigators reported that in more than 70 percent of the nonagenarians, the benefit more than justified the risk they underwent. They reported that serious bowel obstruction was the only underlying comorbidity associated with prohibitive perioperative mortality (63%).

Djokovic and Hedley-Whyte [137] studied the outcome of surgery in 500 patients older than 80 years at the Harvard Medical System in Boston. They noted that mortality was predicted by ASA classification, with greater comorbidity associated with increasing risk. Myocardial infarction was the leading cause of postoperative death. Patients without significant comorbidities (ASA class I) had less than a 1 percent mortality. Their data suggest that surgery is safe in this cohort, and mortality is not a function of age but rather of coexisting disease.

Del Guercio and Cohn [138] evaluated the value of preoperative invasive monitoring in obtaining hemodynamic and cardiopulmonary variables for predicting operative risk in the elderly. Of the 148 consecutive patients older than 65 years studied preoperatively in an intensive care unit, only 13.5 percent had normal physiologic measurements. Advanced and uncorrectable functional deficits were found in 63 percent of outpatients; all those patients who underwent the planned operation died. This finding further supports the contention that age itself is not the risk factor, but rather it is the presence of coexisting disease.

The elderly patient represents a difficult issue for the anesthesiologist. Atherosclerosis increases with advancing age, and the heart muscle itself ages. Further preoperative evaluation in the elderly usually focuses on the identification of comorbidity. Based on the accumulating evidence, it is these factors that influence perioperative risk.

/das/book/view/29494766/875/230.html

RISK DIRECTLY RELATED TO THE ANESTHETIC DRUG

Numerous studies have evaluated the influence of choice of anesthesia on outcome, a question discussed throughout this book (Ch. 6) . From a global perspective, there does not appear to be one best anesthetic technique. In a study by Cohen et al [46] of 100,000 anesthetic regimens performed in Canada, the choice of anesthesia did not provide any additional prognostic information for predicting mortality beyond that of patient disease and the surgical procedure in multivariate analysis. In univariant analysis, monitored anesthesia

care did appear to be associated with a worse outcome, but this finding was attributable to the use of that technique in sicker patients (see Table 22-15) (Table Not Available) .

One question that has plagued the anesthesia literature is the issue of inherent toxicity of the anesthetic agents themselves. There are important distinctions between undesirable side effects of anesthesia and true toxicity. In the initial reports in the middle of this century, there was a great deal of concern about curare toxicity. In more recent times, the issue of anesthetic toxicity has been discussed in particular with respect to two drugs, halothane and sevoflurane. In the case of halothane, the issues were fulminant hepatic necrosis and death, whereas the issue with sevoflurane is whether its metabolite, compound A, is nephrotoxic. After several case reports of hepatic necrosis following halothane anesthesia, a retrospective study of 34 institutions and 856,500 anesthetics was undertaken. [139] [140] [141] In all but 9 cases, the cause of hepatic necrosis could be explained by other causes. Of the remaining 9 cases, only 7 of these patients received halothane. Therefore, halothane could be associated with hepatitis and hepatic failure, but the incidence was very low.

As of 1998, the issue of sevoflurane's renal toxicity remains, but the overall safety of this drug has been sufficiently established by the Food and Drug Administration to allow its continued sale in the United States. There have been laboratory studies to support the contention that sevoflurane reacts with sodalime to form compound A and that this metabolite can lead to renal toxicity. [142] [143] Yet, clinical studies have been unable to confirm this potentially detrimental effect. [144] [145]

There have been numerous studies attempting to define the "safest" anesthetic in high-risk patients. In the late 1980s, there was particular concern that isoflurane could cause coronary steal in patients with a coronary stenosis and collateral vessels and that this could result in myocardial ischemia. [146] [147] A series of studies was conducted to evaluate the rate of perioperative cardiac morbidity and mortality in patients undergoing coronary artery bypass grafting to determine the importance of the agent used for general anesthesia. [148] [149] [150] [151] [152] All these studies demonstrated no difference in outcome, supporting the contention that there is no one safest anesthetic technique.

There has been a series of randomized trials that demonstrate improved outcome with regional compared with general anesthesia. [2] [3] [153] [154] [155] [156] [157] For lower extremity and pelvic surgery, there is a lower incidence of graft thrombosis and of deep vein thrombosis and decreased bleeding. For patients undergoing vascular surgery, the primary finding was a lower incidence of graft thrombosis and of the need for reoperation in patients undergoing infrainguinal bypass surgery; however, the largest of these studies was unable to demonstrate any difference in outcome based on anesthetic technique. [2] [3] [156] As described earlier, the rate of this complication was low in the total cohort in the largest trial, making it impossible to detect any difference based on the actual technique.

RISK RELATED TO SURGERY

It is well recognized that the surgical procedure itself significantly influences perioperative risk. In virtually every study performed, emergency surgery was associated with additional risk. For example, in the study of Goldman and colleagues, [10] emergency surgery was associated with the second highest weight (number of points), behind active signs of congestive heart failure. In that same study, Goldman et al defined intrathoracic and abdominal procedures as having a higher risk.

In some cases, the risk related to surgery is a function of both the underlying disease processes and the stress related to the surgical procedure. Cardiovascular surgery is associated with the highest risk of any procedure. The risks related to cardiac surgery are reviewed in Chapter 49 . Vascular surgery is one of the highest-risk groups of noncardiac procedures. Although aortic reconstructive surgery has traditionally been considered the highest-risk procedure, infrainguinal procedures had a similar rate of cardiac morbidity in several studies. [158] [159] In attempting to analyze the origin of the high complication rate of a relatively peripheral procedure, L'Italien et al [159] demonstrated that the extent of coronary artery disease is higher in the infrainguinal patients, a finding that most likely accounts for the excess morbidity and mortality.

Ashton et al [160] evaluated perioperative morbidity and mortality in a cohort of patients at a Veterans Hospital in Houston, Texas. Although vascular surgery was among the highest-risk procedures, amputations were associated with the highest in-hospital cardiac complication rate within this subgroup. This finding most likely represents the severe nature of the cardiovascular disease of these patients and their prolonged hospitalization in order to facilitate recuperation. Similar to the study by Goldman et al, [10] intra-abdominal, thoracic, and orthopedic surgical procedures were associated with increased risk. In another report, Ashton [160a] evaluated the rate of perioperative myocardial infarction in patients undergoing transurethral resection of the prostate. Despite the high incidence of coronary artery disease in this population, the incidence of perioperative myocardial infarction was only 1 percent.

Numerous studies have evaluated the perioperative complication rate related to superficial procedures. Backer et al [161] evaluated the rate of perioperative myocardial reinfarction in patients undergoing ophthalmologic surgery. These investigators demonstrated that the rate of perioperative cardiac morbidity after ophthalmologic surgery was extremely low, even in patients with a recent myocardial infarction. Virtually all studies have confirmed that anesthesia in ophthalmologic surgery is very safe. Warner et al [58] studied patients undergoing ambulatory surgery and reported no anesthetic deaths in more than 45,000 cases.

Eagle and colleagues [162] evaluated the contribution of coronary artery disease and its treatment on perioperative cardiac morbidity and mortality by surgical procedure. They evaluated patients enrolled in the Coronary Artery Surgery Study who had documented coronary artery disease and who received either medical therapy or coronary revascularization and then underwent noncardiac surgery during the subsequent 10-year period. Their rates of perioperative myocardial infarction and death were determined, and the surgical procedures were divided into three broad categories. Major vascular surgery was again demonstrated to be associated with the highest risk, with a combined morbidity

and mortality of greater than 10 percent. Procedures associated with a combined complication rate of greater than or equal to 4 percent included intra-abdominal, thoracic, and head and neck operations. In all these cases, patients who had prior coronary artery bypass grafting had a significantly lower combined morbidity and mortality than the medically treated group. Low-risk procedures included breast, skin, urologic, and orthopedic surgery. These broad groups of surgical procedures were the basis for defining surgical risk in the American Heart Association/American College of Cardiology Task Force on Perioperative Evaluation of the Cardiac Patient Undergoing Noncardiac Surgery. [124]

RISK RELATED TO LOCATION OF SURGERY AND POSTOPERATIVE MONITORING

It has long been known that perioperative risk varies among hospitals for such major procedures as coronary artery bypass grafting and abdominal aortic aneurysm repair. [163] [164] Multiple studies have documented a relationship between surgical volume and mortality. Although surgical skill most certainly plays a role in the rate of complications and mortality, local factors may also play an important role. For example, low surgical volume may lead to less skilled anesthesia and postoperative care. The influence of each of these factors on overall morbidity and mortality is currently unknown.

Although the value of postoperative intensive care monitoring and care has not been documented in a randomized clinical trial, many investigators have suggested that such care is one of the primary reasons for improved morbidity and mortality in recent years. For the case of patients undergoing major vascular surgery, several investigators have suggested that more intense postoperative monitoring could obviate the need for preoperative cardiac testing and revascularization. [165] [166] One potential value of risk assessment is the identification of patients who would benefit from referral to centers with more extensive perioperative resources. In this manner, patients with a low probability of perioperative morbidity and mortality could have surgery performed locally, whereas those individuals at higher risk could receive the benefit of a larger center.

It is currently estimated that 60 percent of all surgical procedures are performed on an outpatient basis, with the percentage increasing annually (Ch. 65) . When reviewing the literature to determine the safety of this shift from the inpatient to the outpatient arena, there is a striking lack of good evidence to document such safety. As described earlier, Warner et al [58] studied the safety of surgery on an ambulatory basis in 38,598 patients. These investigators documented only 33 episodes of major morbidity or mortality within 1 month of surgery. Major morbidity included 14 myocardial infarctions, 7 central nervous system deficits, 5 pulmonary embolisms, and 5 cases of respiratory failure (see Fig. 22-2) (Figure Not Available) . When adjusted for the age and gender of the population, these rates of major morbidity and mortality were actually lower than expected in the nonsurgical population.

Importantly, Olmstead County, Minnesota, the site of the foregoing study, represents a unique population with high standards for health care. Facilities were immediately available to care for any unexpected emergency or admission. Additionally, the study was performed during an era in which the patient mix was primarily healthy individuals undergoing peripheral or superficial procedures. Importantly, the type or extent of surgical procedure performed in an outpatient setting is constantly changing, and procedures associated with greater perioperative risk are constantly being performed.

The value of overnight observation in a hospital setting as opposed to immediate discharge home has been studied for a number of surgical procedures. One of the first procedures advocated on an ambulatory basis was tonsillectomy. In 1968, a case series of 40,000 outpatient tonsillectomies was reported without 1 death. [167] Details on patient selection and length of postoperative monitoring were vague. Based on insurance company and state mandates, performance of tonsillectomy on an outpatient basis became routine. [168] Beginning in the mid-1980s and continuing in the 1990s, a number of articles evaluated the risk of early discharge. For example, Carithers and colleagues [169] at Ohio State University in Columbus analyzed 3,000 tonsillectomies and argued that early discharge may be both hazardous and economically unwarranted. The rate of readmission for active bleeding between 5 and 24 hours after surgery has been reported to be between 0.2 and 0.5 percent. [170] [171] [172] [173] [174] Although the absolute rate of readmission is low, it represents a substantial risk for children. Whether the benefits of early discharge outweigh the risks is a decision society will have to make.

Another procedure currently being performed on an outpatient basis is mastectomy. An analysis of Medicare claims demonstrated that the rate of outpatient mastectomy has increased from only 2 procedures reported to Medicare in 1986 to 10.8 percent of the mastectomies performed in this population in 1995. [175] The authors compared the rate of readmission within 7 days of surgery for those who had the procedure on an inpatient versus outpatient basis, adjusting for severity of disease. Patients with simple mastectomies performed as outpatients had a significantly higher rate of readmission compared with patients with 1-day stays, with an adjusted odds ratio of 1.84. There were 24.2 readmissions per 1,000 cases for the 1-day length of stay compared with 33.3 readmissions for the outpatients. There were significantly lower rates of readmission for 1-day lengths of stay for infections (4.1/1,000 versus 1.8/1,000 cases), nausea and vomiting (1.1/1,000 versus 0), and pulmonary embolism/ deep vein thrombosis (1.1/1,000 versus 0). Similarly, patients with modified radical mastectomies performed as outpatients had a significantly higher rate of readmission compared with patients who had 1-day stays, with an adjusted odds ratio of 1.72. These authors suggested that patients who have the procedure on an outpatient basis may wait longer at home until seeking medical care and may present with more advanced symptoms.

There is increasing interest in performing surgery and providing anesthesia in office-based settings. There are currently no good data to determine the safety of such practices, although there has been a flurry of high-profile cases

in which patients have died in plastic surgery and dental offices. Importantly, anesthesia and sedation are frequently provided by individuals other than anesthesiologists or nurse anesthetists in these settings. There are reports of office nurses or even clerical help administering anesthetic agents.

There has been one attempt to quantify the incidence of complications in an office-based setting. The American Association for Accreditation of Ambulatory Surgery Facilities mailed a survey to their members to determine the incidence of complications in an office. [176] The overall response rate was 57 percent. Of note, 0.47 percent of patients had at least 1 complication including bleeding, hypertension, infection, and hypotension, and 1 in 57,000 patients died. Assuming that only healthy individuals are seen or very minor procedures are performed in an office-based setting, a rate of mortality that is three times the current estimate for anesthetic-related complications is a concern. Further research and quality assurance mechanisms need to be in place before this practice is generalized. One of the problems inherent to an office-based setting is the inability to perform quality assurance reviews. For example, few, if any, surgeons or anesthesiologists would be willing to allow their "competitors" to review their complications unless they were mandated to perform such a review.

One of the current problems in evaluating the risk of outpatient surgery is the lack of any large database compiled from a diverse group of settings and the lack of uniform standards for quality assurance. Although the Joint Committee for the Accreditation of Heathcare Organizations has begun accrediting ambulatory surgery centers, and two other organizations also provide accreditation, it is still not widespread and remains voluntary. Finally, although ambulatory care centers have led the way in performing appropriate follow-up of their patients at home, it is not uniformly complete. With respect to office-based settings, only three states have regulations as of 1998, and these regulations vary greatly. The implications of a lack of regulation are currently unclear, but issues related to emergency plans and resuscitation equipment may be left to the discretion of the local setting, potentially placing patients at risk.

At the current time, the decision to perform a procedure in an ambulatory setting is based on the surgeon's preference and on insurance company mandates. Frequently, it follows a case series by a surgeon or a review by an in-surance company that demonstrates that healthy individuals can undergo a given procedure safely in an outpatient setting. The need for subsequent medical attention or the use of resources at home is not necessarily taken into account. This may lead to insurance company mandates that the procedure be performed in all patients in an ambulatory setting. This generalization from the healthy to the patient with comorbid disease may not be justified in the absence of data to demonstrate its safety. As an advocate for the patient, the anesthesiologist should continue to

evaluate the safety of such practices and should determine when the risks of ambulatory surgery outweigh any potential benefits. It is also important to determine whether the insurance companies are in essence transferring the risk of undergoing surgery from the medical system to the patient.

RISK RELATED TO THE ANESTHESIA PROVIDER

The issue of added risk associated with the provider of anesthesia is an emotionally charged issue, particularly in the United States. Over the history of the specialty, various individuals have provided anesthesia, including anesthesiologists, general medical officers, residents, and CRNAs.

The importance of the anesthesiologist in outcome is best illustrated by the work of Slogoff and Keats. [177] They studied the importance of perioperative myocardial ischemia as a predictor of cardiac morbidity in patients undergoing coronary artery bypass grafting. They found that a perioperative myocardial infarction occurred significantly more frequently in those patients with prebypass ischemia than in those without ischemia. They then reported the rate of ischemia and infarction by anesthesiologist (identified by number). Anesthesiologist no. 7 had a significantly higher rate of complications than the average for the rest of the group. Therefore, operator technique or experience may affect risk. This observation parallels similar findings that surgical volume (and therefore presumably experience) is associated with outcome.

There have been several studies that have attempted specifically to evaluate the complication rate and risk associated with different care provider models. Bechtoldt [178] on the North Carolina Anesthesia Study Committee evaluated 900 perioperative deaths from an estimated 2 million anesthetic regimens administered in North Carolina from 1969 to 1976. Data were obtained from the medical examiner's report, routine death certificate, and a questionnaire completed by the person who administered the anesthetic. The committee concluded 90 of these deaths were anesthesia related. About one-half of the anesthetic-related deaths occurred in the operating room, of which 19 occurred during induction. These investigators then determined the relationship between mortality and the anesthesia provider based on the total number of anesthetics given by each group attained from a survey of hospitals (Fig. 22-6) (Figure Not Available) .

The lowest rate (1/28,166) of anesthetic-related deaths was associated with the anesthesia care team (physician anesthesiologist/CRNA), and the highest rate occurred in patients who received anesthesia from a dentist (1/11,432) (see Fig. 22-6) (Figure Not Available) . The nurse anesthetist-only cohort was intermediate (1/20,723). The large number of cases in which the care provider was unknown and the reliance on hospital estimates of the number of cases performed by each group makes interpretation difficult.

The Stanford Center for Health Care Research [179] in California also evaluated the impact of provider on outcome of care. These investigators prospectively collected data from 8,593 patients undergoing 15 surgical procedures over a 10-month period from May 1973 to February 1974. Using a risk-adjustment methodology, the actual patient outcome was compared with that predicted based on the patient's health status and operative procedure. The investigators reported that death plus severe morbidity occurred 11 percent more frequently than predicted for patients who received their

Figure 22-6 (Figure Not Available) Relationship between anesthetic provider and anesthetic-related deaths in North Carolina. The actual number of cases performed by each group was estimated from a survey of hospitals. The certified registered nurse anesthetist/anesthesiologist care team was associated with the best outcomes, whereas the surgeon or dentist practicing anesthesia was associated with the worst. *(From Bechtoldt [176])*

care in a nurse-anesthetist setting only, 3 percent less frequently than predicted for patients who received their care in a physician-only model, and 20 percent less frequently than predicted for patients who received their care in an anesthesia care team environment. Because of the small sample size, these findings did not reach statistical significance among the groups. Whether such disparities would remain apparent more than 25 years later requires further evaluation.

The question regarding differences in outcome among providers is extremely difficult from a methodologic standpoint. In fact, specific provider types may make the most impact in specific situations. For example, there may be no difference in outcome for healthy individuals, particularly if no complications occur. In contrast, a patient with significant comorbidity or one who sustained a perioperative complication may benefit from specific skill sets. One method to study such issues is to evaluate the rate of survival from complications. Silber and colleagues [180] at the University of Pennsylvania advocated such an approach. They studied the medical records of 5,972 surgical patients randomly selected from 531 hospitals. They evaluated both patient and hospital characteristics, including the number and type of physicians, board certification status, and ratio of care providers. Thirty-day mortality correlated with patient characteristics. Failure to rescue (prevent death) after an adverse event was inversely associated with the proportion of board-certified anesthesiologists on staff in each facility. Improved perioperative survival was significantly associated with an increased number of board-certified anesthesiologists.

Parallel with the marked increase in the number of anesthesiologists has been a dramatic decrease in malpractice insurance premiums for anesthesiologists. [181] Because these premiums are based on the number and severity of claims, these data would suggest that anesthesia is becoming safer. Despite these findings, in 1998, the Health Care Finance Administration was considering changing the current regulations to allow CRNAs to practice independently. At the time of this writing, the issue remains unresolved. Further research into the importance of anesthesia provider to outcome will be required.

RISK TO THE ANESTHESIOLOGIST

There are several potential risks to the anesthesiologist related to provision of care. These include the medicolegal risk, the risk of an allergic reaction, and the risk of a needlestick injury with transmission of disease from the patient to the practitioner. The medicolegal risks are described in Chapter 85 .

It is becoming increasing apparent that anesthesiologists are at risk for a latex allergy, which could lead to a life-threatening reaction. Many anesthesiologists realize that they are sensitized to latex and take appropriate precautions. The problem is that many sensitized individuals are asymptomatic. Brown et al [182] studied 168 eligible anesthesiologists and nurse anesthetists working in the anesthesia department of the Johns Hopkins Hospital in Baltimore. The prevalence of latex allergy with clinical symptoms and latex sensitization without clinical symptoms was 2.4 and 10.1 percent, respectively. The prevalence of irritant or contact dermatitis was 24 percent. These data suggest that latex is an important problem to the anesthesiologist and that there is a need to transform the hospital to a latex-free environment.

There has always been concern that anesthesiologists are at risk of contracting a disease from a patient. In the past, the risk was primarily for hepatitis, but human immunodeficiency virus (HIV) is an even greater concern today. In a review of the literature, Berry and Greene [183] reported that at least 20 different pathogens have been transmitted through accidental needlestick injuries.

Hepatitis B seropositivity ranged from 12.7 to 48.6 percent of anesthesia personnel in several studies conducted in the United States, a rate at least four times greater than in the general population. [184] [185] [186] The risk of hepatitis B infection

following percutaneous exposure to antigen-positive blood is estimated to be 27 to 43 percent. [187] The development of the hepatitis B vaccine substantially reduced this risk. Hepatitis C virus has been identified as a major cause of post-transfusion hepatitis. There have been several reports of occupationally acquired hepatitis in health care workers. [188] Because up to 50 percent of infected individuals develop signs of chronic liver infection, this represents a potential serious problem.

Among the greatest fears of the health care worker is infection with HIV-1. The risk of acquiring HIV is approximately 0.4 percent from a single percutaneous exposure from blood or bloody fluid from an HIV-infected patient. [189] There has been at least one case report of an anesthesiologist who was infected with HIV from a needlestick during insertion of a central venous catheter into an HIV-positive patient. [190]

There have been several strategies to reduce transmission of communicable disease, which are reviewed in Chapter 84 . Although anesthesiologists traditionally think of the risk to their patients, they must now include the risk to themselves. The widespread adoption of universal precautions should reduce the rate of infection; however, anesthesiologists have not accepted these recommendations widely. In a study of nine hospitals, 59 percent of the contaminated percutaneous injuries were preventable. [191] In a theoretical model of risk of HIV, it was estimated that the 30-year occupational risk is 0.10 to 0.22 percent in low-prevalence areas and 8.26 to 13 percent in high-prevalence areas. [192] The authors of this report suggest that double gloving may reduce risk.

IMPROVING ANESTHESIA SAFETY

Over the past several decades, there have been major initiatives to improve the safety of anesthesia. In 1984, Cooper, Kitz, and Ellison hosted the first International Symposium on Preventable Anesthesia Mortality and Morbidity in Boston. Approximately 50 anesthesiologists attended the meeting from around the world and after much debate established a series of definitions of outcome, morbidity, and mortality (Table 22-23) (Table Not Available) . Such meetings have been held every 2 years since the first symposium.

The Anesthesia Patient Safety Foundation (APSF) was established as a result of the Boston meeting. The society has been active in publishing widely circulated newsletters and awarding annual grants. Similar societies have now been established in other countries, and a national patient safety society has also been created on the APSF model.

Starting with the ASA Closed Claims Study, there has been a great deal of interest in establishing guidelines for the best and safest practice. Practice policies or guidelines are the summation by clinicians of the available evidence about the benefits and risks of a treatment plan. Guidelines are a method of codifying recommendations regarding the use of a given technology. There are several types of recommendations that fall into the general category of a practice parameter. A standard implies that a therapy or practice should be performed on patients with a particular condition. Standards are only approved if an assessment of the probabilities and utilities of the group indicates that the decision

TABLE 22-23 -- Proposed Definitions from 1994 International Symposium on Preventable Anesthesia Morbidity and Mortality

(Not Available)

From Pierce et al [205]

to choose the treatment or a strategy would be virtually unanimous. If a particular therapy or strategy is considered a standard, it is cost-effective for those for whom it is recommended. Standards are intended to be applied rigidly. The ASA has established standards for intraoperative monitoring, which were developed from safety guidelines adopted at the Harvard hospital system. Guidelines are intended to be more flexible than standards, but they should be followed in most cases. Depending on the patient, setting, and other factors, guidelines can and should be tailored to fit individual needs. Like standards, guidelines should be cost-effective. Numerous guidelines have been adopted by the ASA for diverse issues such as the difficult airway, [193] use of pulmonary artery catheter, [194] and use of blood components. [195] The goal is to define the evidence on which optimal practice can be based.

Finally, there is a great deal of interest in the use of anesthesia simulators to train and test individuals and their ability to react to simulated crises. [196] [197] [198] [199] [200] Standardized simulations have been developed on which comparisons among individuals can be made. [201] [202] Further research will be required to determine how best to utilize this technology in anesthesia training and potentially in recertification.

SUMMARY

The risks related to anesthesia have dramatically decreased over the last several decades. It is now clear that death totally attributable to anesthesia is very rare. Both patient disease and the type and perhaps location of surgery have greater impact on overall outcome. With these changes in risk, the anesthesiologist must now focus on nonmorbid outcomes and must continue vigilance to maintain the high standards of hospital-based anesthesia in nonhospital settings.

References

1. Christopherson R, Beattie C, Frank SM et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery: The Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 79:422, 1993.

2. Bode RH Jr, Lewis KP, Zarich SW et al: Cardiac outcome after peripheral vascular surgery: Comparison of general and regional anesthesia. Anesthesiology 84:3, 1996.

3. Tuman KJ, McCarthy RJ, March RJ et al: Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 73:696, 1991.

4. Twersky R, Fishman D, Homel P: What happens after discharge? Return hospital visits after ambulatory surgery. Anesth Analg 84:319, 1997.

5. Cohn LH, Rosborough D, Fernandez J: Reducing costs and length of stay and improving efficiency and quality of care in cardiac surgery. Ann Thorac Surg 64:S58, 1997.

6. Fleisher LA, Metzger SE, Lam J et al: Perioperative cost-finding analysis of the routine use of intraoperative forced-air warming during general anesthesia. Anesthesiology 88:1357, 1998.

7. Klafta JM, Roizen MF: Current understanding of patients' attitudes toward and preparation for anesthesia: A review. Anesth Analg 83:1314, 1996.

8. Fisher DM: Surrogate end points: Are they meaningful? (editorial; comment) Anesthesiology 81:795, 1994.

9. Fleisher LA: . . . but, is suppression of postoperative ST segment depression an important outcome? (editorial; comment) Anesth Analg 84:709, 1997.

10. Goldman L, Caldera DL, Nussbaum SR et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845, 1977.

11. Tarhan S, Moffitt EA, Taylor WF et al: Myocardial infarction after general anesthesia. JAMA 220:1451, 1972.

12. Rao TLK, Jacobs KH, El-Etr AA: Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 59:499, 1983.

13. Shah KB, Kleinman BS, Sami H et al: Reevaluation of perioperative myocardial infarction in patients with prior myocardial infarction undergoing noncardiac operations. Anesth Analg 71:231, 1990.

14. Frank SM, Beattie C, Christopherson R et al: Unintentional hypothermia is associated with postoperative myocardial ischemia: The Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 78:468, 1993.

15. Frank SM, Fleisher LA, Breslow MJ et al: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. JAMA 277:1127, 1997.

16. Buck N, Devlin HB, Lunn JL: Report of a confidential enquiry into perioperative deaths: Nuffield Provincial Hospitals Trust. London, King's Fund Publishing House, 1987.

17. Beecher HK, Todd DP: A study of deaths associated with anesthesia and surgery. Ann Surg 140:2, 1954.

18. Cheney FW, Posner K, Caplan RA et al: Standard of care and anesthesia liability. JAMA 261:1599, 1989.

19. Mathew JP, Parks R, Savino JS et al: Atrial fibrillation following coronary artery bypass graft surgery: Predictors, outcomes, and resource utilization. Multicenter Study of Perioperative Ischemia Research Group. JAMA 276:300, 1996.

20. Nugent WC: Clinical applications of risk-assessment protocols in the management of individual patients. Ann Thorac Surg 64:S68, 1997.

21. Grover FL, Shroyer AL, Edwards FH et al: Data quality review program: The Society of Thoracic Surgeons Adult Cardiac National Database. Ann Thorac Surg 62:1229, 1996.

22. Grover FL, Shroyer AL, Hammermeister KE: Calculating risk and outcome: The Veterans Affairs database. Ann Thorac Surg 62:S6, 1996.

23. Clark RE: The development of The Society of Thoracic Surgeons voluntary national database system: Genesis, issues, growth, and status. Best Pract Benchmarking Healthcare 1:62, 1996.

24. Clark RE: The STS Cardiac Surgery National Database: An update. Ann Thorac Surg 59:1376, 1995.

25. Todd CJ, Freeman CJ, Camilleri-Ferrante C et al: Differences in mortality after fracture of hip: The East Anglian audit. BMJ 310:904, 1995.

26. Marx GF, Mateo CV, Orkin LR: Computer analysis of postanesthetic deaths. Anesthesiology 39:54, 1973.

27. Ghali WA, Ash AS, Hall RE et al: Statewide quality improvement initiatives and mortality after cardiac surgery. JAMA 277:379, 1997.

28. Mukamel DB, Mushlin AI: Quality of care information makes a difference: An analysis of market share and price changes after publication of the New York State Cardiac Surgery Mortality Reports. Med Care 36:945, 1998.

29. Hannan EL, Racz MJ, Jollis JG et al: Using Medicare claims data to assess provider quality for CABG surgery: Does it work well enough? Health Serv Res 31:659, 1997.

30. Beecher HK: The first anesthesia death with some remarks suggested by it on the fields of the laboratory and clinic in the appraisal of new anesthetic agents. Anesthesiology 2:443, 1941.

31. Snow J: On chloroform and other anesthetics. London, John Churchill, 1858, p. 107.

32. Dornette WHL, Orth OS: Death in the operating room. Anesth Analg 35:545, 1956.

33. Schapira M, Kepes ER, Hurwitt ES: An analysis of deaths in the operating room and within 24 hours of surgery. Anesth Analg 39:149, 1960.

34. Phillips OC, Frazier TM, Graff TD et al: The Baltimore Anesthesia Study Committee: Review of 1,024 postoperative deaths. JAMA 174:2015, 1960.

35. Dripps RD, Lamont A, Eckenhoff JE: The role of anesthesia in surgical mortality. JAMA 178:261, 1961.

36. Clifton BS, Hotten WIT: Deaths associated with anaesthesia. Br J Anaesth 35:250, 1963.

37. Memery HN: Anesthesia mortality in private practice. JAMA 194:127, 1965.

38. Gebbie D: Anaesthesia and death. Can Anaesth Soc J 13:390, 1966.

39. Minuck M: Death in the operating room. Can Anaesth Soc J 13:390, 1967.

40. Harrison GG: Death attributable to anaesthesia: A 10-year survey (1967-1976). Br J Anaesth 50:1041, 1978.

41. Bodlander FMS: Deaths associated with anaesthesia. Br J Anaesth 47:36, 1975.

42. Hovi-Viander M: Death associated with anaesthesia in Finland. Br J Anaesth 52:483, 1980.

43. Ruth HS: Anesthesia study commissions. JAMA 127:514, 1945.

44. Macintosh RR: Deaths under anaesthetics. Br J Anaesth 21:107, 1948.

45. Dinnick OP: Deaths associated with anaesthesia. Anaesthesia 19:536, 1964.

46. Cohen MM, Duncan PG, Tate RB: Does anesthesia contribute to operative mortality? JAMA 260:2859, 1988.

47. Farrow SC, Fowkes FG, Lunn JN et al: Epidemiology in anaesthesia: A method for predicting hospital mortality. Eur J Anaesthesiol 1:77, 1984.

48. Farrow SC, Fowkes FGR, Lunn JN et al: Epidemiology in anaesthesia. II. Factors affecting mortality in hospital. Br J Anaesth 54:811, 1982.

49. Holland R: Anaesthetic mortality in New South Wales. Br J Anaesth 59:834, 1987.

50. Warden JC, Horan BF: Deaths attributed to anaesthesia in New South Wales, 1984-1990. Anaesth Intensive Care 24:66, 1996.

51. Tiret L, Desmonts JM, Hatton F et al: Complications associated with anaesthesia: A prospective survey in France. Can Anaesth Soc J 33:336, 1986.

52. Tikkanen J, Hovi-Viander M: Death associated with anaesthesia and surgery in Finland in 1986 compared to 1975. Acta Anaesthesiol Scand 39:262, 1995.

53. Lunn JN: The study on anaesthetic-related mortality. Anaesthesia 35:617, 1980.

54. Lunn JN, Mushin WW: Mortality associated with anesthesia. Anaesthesia 37:856, 1982.

55. Lunn JN, Hunter AR, Scott DB: Anaesthesia-related surgical mortality. Anaesthesia 38:1090, 1983.

56. Lunn JN, Devlin HB: Lessons from the confidential enquiry into perioperative deaths in three NHS regions. Lancet 2:1384, 1987.

57. Pedersen T, Eliasen K, Henriksen E: A prospective study of mortality associated with anaesthesia and surgery: Risk indicators of mortality in hospital. Acta Anaesthesiol Scand 34:176, 1990.

58. Warner MA, Shields SE, Chute CG: Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. JAMA 270:1437, 1993.

59. Sanborn KV, Castro J, Kuroda M et al: Detection of intraoperative incidents by electronic scanning of computerized anesthesia records: Comparison with voluntary reporting. Anesthesiology 85:977, 1996.

60. Moller JT, Svennild I, Johannessen NW et al: Perioperative monitoring with pulse oximetry and late postoperative cognitive dysfunction. Br J Anaesth 71:340, 1993.

61. Caplan RA, Ward RJ, Posner K et al: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

62. Tinker JH, Dull DL, Caplan RA et al: Role of monitoring devices in prevention of anesthetic mishaps: A closed claims analysis. Anesthesiology 71:541, 1989.

63. Caplan RA, Posner KL, Ward RJ et al: Adverse respiratory events in anesthesia: A closed claims analysis. Anesthesiology 72:828, 1990.

64. Anonymous: Practice guidelines for management of the difficult airway: A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 78:597, 1993.

65. Cooper JB: Toward prevention of anesthetic mishaps. Int Anesthesiol Clin 22:167, 1984.

66. Cooper JB, Newbower RS, Kitz RJ: An analysis of major errors and equipment failures in anesthesia management: Considerations for prevention and detection. Anesthesiology 60:34, 1984.

67. Newbower RS, Cooper JB, Long CD: Learning from anesthesia mishaps: Analysis of critical incidents in anesthesia helps reduce patient risk. QRB Qual Rev Bull 7:10, 1981.

68. Cooper JB, Newbower RS, Long CD et al: Preventable anesthesia mishaps: A study of human factors. Anesthesiology 49:399, 1978.

69. Buffington CW, Ramanathan S, Turndorf H: Detection of anesthesia machine faults. Anesth Analg 63:79, 1984.

70. Hanks EC, Papper EM: Cardiac resuscitation. N Y State J Med 51:1801, 1951.

71. Ehrenhaft JL, Eastwood DW, Morris LE: Analysis of twenty-seven cases of acute cardiac arrest. J Thorac Surg 22:592, 1951.

72. Bonica JJ: Cardiac arrest. Northwest Med 52:719, 1953.

73. Blades B: Cardiac arrest. JAMA 155:709, 1954.

74. Hewlett TH, Gilpatrick CW, Bowers WF: Cardiac arrest. Surg Gynecol Obstet 102:607, 1956.

75. Briggs BD, Sheldon DB, Beecher HK: Cardiac arrest: A study of a thirty-year period of operating room deaths at Massachusetts General Hospital, 1925-1954. JAMA 160:1439, 1956.

76. Keenan RL, Boyan CP: Decreasing frequency of anesthetic cardiac arrest. J Clin Anesth 3:354, 1991.

77. Cohen MM, Duncan PG, Pope WDB et al: A survey of 112,000 anesthetics at one teaching hospital (1975-1983). Can Anaesth Soc J 33:22, 1986.

78. Keenan RL, Boyan CP: Cardiac arrest due to anesthesia. JAMA 253:2373, 1985.

79. Olsson GL, Hallen B: Cardiac arrest during anaesthesia: A computer-aided study in 250,543 anaesthetics. Acta Anaesthesiol Scand 32:653, 1988.

80. Mangano DT, Layug EL, Wallace A et al: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery: Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 335:1713, 1996.

81. Wallace A, Layug B, Tateo I et al: Prophylactic atenolol reduces postoperative myocardial ischemia: McSPI Research Group. Anesthesiology 88:7, 1998.

82. Saklad M: Grading of patients for surgical procedures. Anesthesiology 62:206, 1941.

83. Keats AS: The ASA classification of physical status: A recapitulation. Anesthesiology 49:233, 1978.

84. Vancanti CJ, VanHouten RJ, Hill RC: A statistical analysis of the relationship of physical status to postoperative mortality in 68,388 cases. Anesth Analg 49:564, 1970.

85. Owens WD, Felts JA, Spitznagel EL Jr: ASA physical status classifications. Anesthesiology 49:239, 1978.

86. Zeldin RA: Assessing cardiac risk in patients who undergo noncardiac surgical procedures. Can J Surg 27:402, 1984.

87. Larsen SF, Olesen KH, Jacobsen E et al: Prediction of cardiac risk in non-cardiac surgery. Eur Heart J 8:179, 1987.

88. Domaingue CM, Davies MJ, Cronin KD: Cardiovascular risk factors in patients for vascular surgery. Anaesth Intensive Care 10:324, 1982.

89. Jeffrey CC, Kunsman J, Cullen DJ et al: A prospective evaluation of cardiac risk index. Anesthesiology 58:462, 1983.

90. White GH, Advani SM, Williams RA et al: Cardiac risk index as a predictor of long-term survival after repair of abdominal aortic aneurysm. Am J Surg 156:103, 1988.

91. McEnroe CS, O'Donnell TF, Yeager A et al: Comparison of ejection fraction and Goldman risk factor analysis to dipyridamole-thallium imaging 201 studies in the evaluation of cardiac morbidity after aortic aneurysm surgery. J Vasc Surg 11:497, 1990.

92. Lette J, Waters D, Lassonde J et al: Postoperative myocardial infarction and cardiac death: Predictive value of dipyridamole-thallium imaging and five clinical scoring systems based on multifactorial analysis. Ann Surg 211:84, 1990.

93. Prause G, Ratzenhofer-Comenda B, Pierer G et al: Can ASA grade or Goldman's cardiac risk index predict peri-operative mortality? A study of 16,227 patients. Anaesthesia 52:203, 1997.

93A. Cooperman M, Pflug B, Martin EW, et al: Cardiovascular risk factors in patients with peripheral vascular disease. Surgery 84:505, 1978.

94. Detsky A, Abrams H, McLaughlin J et al: Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1:211, 1986.

95. Palda VA, Detsky AS: Perioperative assessment and management of risk from coronary artery disease. Ann Intern Med 127:313, 1997.

96. Magovern JA, Sakert T, Magovern GJ et al: A model that predicts morbidity and mortality after coronary artery bypass graft surgery. J Am Coll Cardiol 28:1147, 1996.

97. Newman MF, Wolman R, Kanchuger M et al: Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery: Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Circulation 94 (suppl II):II-74, 1996.

98. Jones RH, Hannan EL, Hammermeister KE et al: Identification of preoperative variables needed for risk adjustment of short-term mortality after coronary artery bypass graft surgery: The Working Group Panel on the Cooperative CABG Database Project. J Am Coll Cardiol 28:1478, 1996.

99. Weightman WM, Gibbs NM, Sheminant MR et al: Risk prediction in coronary artery surgery: A comparison of four risk scores. Med J Aust 166:408, 1997.

100. Higgins TL, Estafanous FG, Loop FD et al: ICU admission score for predicting morbidity and mortality risk after coronary artery bypass grafting. Ann Thorac Surg 64:1050, 1997.

101. Iezzoni LI, Ash AS, Shwartz M et al: Predicting in-hospital deaths from coronary artery bypass graft surgery: Do different severity measures give different predictions? Med Care 36:28, 1998.

102. Hannan EL, Kilburn H Jr, O'Donnell JF et al: Adult open heart surgery in New York State: An analysis of risk factors and hospital mortality rates. JAMA 264:2768, 1990.

103. Hannan EL, Kumar D, Racz M et al: New York State's Cardiac Surgery Reporting System: Four years later. Ann Thorac Surg 58:1852, 1994.

104. Hannan EL, Kilburn H Jr, Racz M et al: Improving the outcomes of coronary artery bypass surgery in New York State. JAMA 271:761, 1994.

105. Hertzer NR, Bevan EG, Young JR et al: Coronary artery disease in peripheral vascular patients: A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 199:223, 1984.

106. Boucher CA, Brewster DC, Darling RC et al: Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. N Engl J Med 312:389, 1985.

107. Cutler BS, Leppo JA: Dipyridamole thallium 201 scintigraphy to detect coronary artery disease before abdominal aortic surgery. J Vasc Surg 5:91, 1987.

108. Eagle KA, Singer DE, Brewster DC et al: Dipyridamole-thallium scanning in patients undergoing vascular surgery: Optimizing preoperative evaluation of cardiac risk. JAMA 257:2185, 1987.

109. Elliott BM, Robison JG, Zellner JL et al: Dobutamine-201T1 imaging: Assessing cardiac risks associated with vascular surgery. Circulation 84 (suppl III):54, 1991.

110. Lane RT, Sawada SG, Segar DS et al: Dobutamine stress echocardi-ography for assessment of cardiac risk before noncardiac surgery. Am J Cardiol 68:976, 1991.

111. Langan ER, Youkey JR, Franklin DP et al: Dobutamine stress echocardiography for cardiac risk assessment before aortic surgery. J Vasc Surg 18:905, 1993.

112. Lette J, Waters D, Lapointe J et al: Usefulness of the severity and extent of reversible perfusion defects during thallium-dipyridamole imaging for cardiac risk assessment before noncardiac surgery. Am J Cardiol 64:276, 1989.

113. Poldermans D, Fioretti PM, Forster T et al: Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular surgery. Circulation 87:1506, 1993.

114. Poldermans D, Fioretti PM, Boersma E et al: Dobutamine-atropine stress echocardiography and clinical data for predicting late cardiac events in patients with suspected coronary artery disease. Am J Med 97:119, 1994.

115. Poldermans D, Arnese M, Fioretti PM et al: Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol 26:648, 1995.

116. Baron JF, Mundler O, Bertrand M et al: Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. N Engl J Med 330:663,

1994.

117. Mangano DT, London MJ, Tubau JF et al: Dipyridamole thallium-201 scintigraphy as a preoperative screening test: A reexamination of its predictive potential. Study of Perioperative Ischemia Research Group. Circulation 84:493, 1991.

118. Eagle KA, Coley CM, Newell JB et al: Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 110:859, 1989.

119. L'Italien GJ, Paul SD, Hendel RC et al: Development and validation of a bayesian model for perioperative cardiac risk assessment in a cohort of 1,081 vascular surgical candidates. J Am Coll Cardiol 27:779, 1996.

120. Vanzetto G, Machecourt J, Blendea D et al: Additive value of thallium single-photon emission computed tomography myocardial imaging for prediction of perioperative events in clinically selected high cardiac risk patients having abdominal aortic surgery. Am J Cardiol 77:143, 1996.

121. Goldman L, Caldera DL: Risks of general anesthesia and elective operation in the hypertensive patient. Anesthesiology 50:285, 1979.

122. Hollenberg M, Mangano DT, Browner WS et al: Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery: The Study of Perioperative Ischemia Research. JAMA 268:205, 1992.

123. Stone GW, Grines CL, Browne KF et al: Predictors of in-hospital and 6-month outcome after acute myocardial infarction in the reperfusion era: The Primary Angioplasty in Myocardial Infarction (PAMI) trial. J Am Coll Cardiol 25:370, 1995.

124. Eagle K, Brundage B, Chaitman B et al: Guidelines for perioperative cardiovascular evaluation of noncardiac surgery: A report of the American Heart Association/American College of Cardiology Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. Circulation 93:1278, 1996.

125. Kaunitz AM, Hughes JM, Grimes DA et al: Causes of maternal mortality in the United States. Obstet Gynecol 65:605, 1985.

126. Endler GC, Mariona FG, Sokol RJ et al: Anesthesia-related maternal mortality in Michigan, 1972 to 1984. Am J Obstet Gynecol 159:187, 1988.

127. Rochat RW, Koonin LM, Atrash HK et al: Maternal mortality in the United States: Report from the Maternal Mortality Collaborative. Obstet Gynecol 72:91, 1988.

128. Morgan M: Anaesthetic contribution to maternal mortality. Br J Anaesth 59:842, 1987.

129. Chadwick HS, Posner K, Caplan RA et al: A comparison of obstetric and nonobstetric anesthesia malpractice claims. Anesthesiology 74:242, 1991.

130. Hawkins JL, Koonin LM, Palmer SK et al: Anesthesia-related deaths during obstetric delivery in the United States, 1979-1990. Anesthesiology 86:277, 1997.

131. Gibbs CP, Krischer J, Peckham BM et al: Obstetric anesthesia: A national survey. Anesthesiology 65:298, 1986.

132. Hawkins JL, Gibbs CP, Orleans M et al: Obstetric anesthesia work force survey, 1981 versus 1992. Anesthesiology 87:135, 1997.

133. Graff TD, Phillips OC, Benson DW et al: Baltimore Anesthesia Study Committee: Factors in pediatric anesthesia mortality. Anesth Analg 43:407, 1964.

134. Tiret L, Nivoche Y, Hatton F et al: Complications related to anaesthesia in infants and children: A prospective survey of 40,240 anaesthetics. Br J Anaesth 61:263, 1988.

135. Cohen MM, Cameron CB, Duncan PG: Pediatric anesthesia morbidity and mortality in the perioperative period. Anesth Analg 70:160, 1990.

136. Denney JL, Denson JS: Risk of surgery in patients over 90. Geriatrics 27:115, 1972.

137. Djokovic JL, Hedley-Whyte J: Prediction of outcome of surgery and anesthesia in patients over 80. JAMA 242:2301, 1979.

138. Del Guercio LR, Cohn JD: Monitoring operative risk in the elderly. JAMA 243:1350, 1980.

139. DeBacker LJ, Longnecker DS: Prospective and retrospective searches for liver necrosis following halothane anesthesia: Serum enzyme study and case report. JAMA 195:157, 1966.

140. Aach R: Halothane and liver failure. JAMA 211:2145, 1970.

141. Subcommittee of the National Halothane Study of the Committee on Anesthesia, National Academy of Sciences-National Research Council: Summary of the National Halothane Study: Possible association between halothane anesthesia and postoperative hepatic necrosis. JAMA 197:775, 1966.

142. Nishiyama T, Aibiki M, Hanaoka K: Inorganic fluoride kinetics and renal tubular function after sevoflurane anesthesia in chronic renal failure patients receiving hemodialysis. Anesth Analg 83:574, 1996.

143. Levine MF, Sarner J, Lerman J et al: Plasma inorganic fluoride concentrations after sevoflurane anesthesia in children. Anesthesiology 84:348, 1996.

144. Rooke GA, Ebert T, Muzi M et al: The hemodynamic and renal effects of sevoflurane and isoflurane in patients with coronary artery disease and chronic hypertension: Sevoflurane Ischemia Study Group. Anesth Analg 82:1159, 1996.

145. Conzen PF, Nuscheler M, Melotte A et al: Renal function and serum fluoride concentrations in patients with stable renal insufficiency after anesthesia with sevoflurane or enflurane. Anesth Analg 81:569, 1995.

146. Buffington CW, Romson JL, Levine A et al: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 66:280, 1987.

147. Becker LC: Is isoflurane dangerous for the patient with coronary artery disease? (editorial). Anesthesiology 66:259, 1987.

148. Slogoff S, Keats AS: Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. Anesthesiology 70:179, 1989.

149. Slogoff S, Keats AS, Dear WE et al: Steal-prone coronary anatomy and myocardial ischemia associated with four primary anesthetic agents in humans. Anesth Analg 72:22, 1991.

150. Leung JM, Hollenberg M, O'Kelly BF et al: Effects of steal-prone anatomy on intraoperative myocardial ischemia: The SPI Research Group. J Am Coll Cardiol 20:1205, 1992.

151. Leung JM, Goehner P, O'Kelly BF et al: Isoflurane anesthesia and myocardial ischemia: Comparative risk versus sufentanil anesthesia in patients undergoing coronary artery bypass graft surgery. The SPI (Study of Perioperative Ischemia) Research Group. Anesthesiology 74:838, 1991.

152. Inoue K, Reichelt W, el-Banayosy A et al: Does isoflurane lead to a higher incidence of myocardial infarction and perioperative death than enflurane in coronary artery surgery? A clinical study of 1178 patients. Anesth Analg 71:469, 1990.

153. Hjelmstedt A, Sahlstedt B, Maripuu E: Comparative influences of epidural and general anaesthesia on deep venous thrombosis and pulmonary embolism after total hip replacement. Acta Chir Scand 147:125, 1981.

154. Rivers SP, Scher LA, Sheehan E et al: Epidural versus general anesthesia for infrainguinal arterial reconstruction. J Vasc Surg 14:764, 1991.

155. Shir Y, Frank SM, Brendler CB, Raja SN: Postoperative morbidity is similar in patients anesthetized with epidural and general anesthesia for radical prostatectomy. Urology 44:232, 1994.

156. Christopherson R, Glavan NJ, Norris EJ et al: Control of blood pressure and heart rate in patients randomized to epidural or general anesthesia for lower extremity vascular surgery: Perioperative Ischemia Randomized Anesthesia Trial (PIRAT) Study Group. J Clin Anesth 8:578, 1996.

157. Norman JG, Fink GW: The effects of epidural anesthesia on the neuroendocrine response to major surgical stress: A randomized prospective trial. Am Surg 63:75, 1997.

158. Krupski WC, Layug EL, Reilly LM et al: Comparison of cardiac morbidity between aortic and infrainguinal operations: Study of Perioperative Ischemia (SPI) Research Group. J Vasc Surg 15:354, 1992.

159. L'Italien GL, Cambria RP, Cutler BS et al: Comparative early and late cardiac morbidity among patients requiring different vascular surgery procedures. J Vasc Surg 21:935, 1995.

160. Ashton CM, Petersen NJ, Wray NP et al: The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 118:504, 1993.

161. Backer CL, Tinker JH, Robertson DM et al: Myocardial reinfarction following local anesthesia for ophthalmic surgery. Anesth Analg 59:257, 1980.

162. Eagle KA, Rihal CS, Mickel MC et al: Cardiac risk of noncardiac surgery: Influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart

Care Program. Coronary Artery Surgery Study. Circulation 96:1882, 1997.

163. Kantonen I, Lepantalo M, Salenius JP et al: Mortality in abdominal aortic aneurysm surgery: The effect of hospital volume, patient mix and surgeon's case load. Eur J Vasc Endovasc Surg 14:375, 1997.

164. Luft HS, Bunker JP, Enthoven AC: Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 301:1364, 1979.

165. Rosenfeld BA, Breslow MJ, Dorman T: Postoperative management strategies may obviate the need for most preoperative cardiac testing (letter). Anesthesiology 84:1266, 1996.

166. D'Angelo AJ, Puppala D, Farber A et al: Is preoperative cardiac evaluation for abdominal aortic aneurysm repair necessary? J Vasc Surg 25:152, 1997.

167. Chaing TM, Sukis AE, Ross DE: Tonsillectomy performed on an out-patient basis: Report of a series of 40,000 cases without a death. Arch Otolaryngol 88:307, 1968.

168. Raymond CA: Study questions safety, economic benefits of outpatient tonsil/adenoid surgery (news). JAMA 256:311, 1986.

169. Carithers JS, Gebhart DE, Williams JA: Postoperative risks of pediatric tonsilloadenoidectomy. Laryngoscope 97:422, 1987.

170. Mitchell RB, Pereira KD, Friedman NR et al: Outpatient adenotonsillectomy. Is it safe in children younger than 3 years? Arch Otolaryngol Head Neck Surg 123:681, 1997.

171. Gabalski EC, Mattucci KF, Setzen M et al: Ambulatory tonsillectomy and adenoidectomy. Laryngoscope 106:77, 1996.

172. Gerber ME, O'Connor DM, Adler E et al: Selected risk factors in pediatric adenotonsillectomy. Arch Otolaryngol Head Neck Surg 122:811, 1996.

173. Schloss MD, Tan AK, Schloss B et al: Outpatient tonsillectomy and adenoidectomy: Complications and recommendations. Int J Pediatr Otorhinolaryngol 30:115, 1994.

174. Truy E, Merad F, Robin P et al: Failures in outpatient tonsillectomy policy in children: A retrospective study in 311 children. Int J Pediatr Otorhinolaryngol 29:33, 1994.

175. Warren JL, Riley GF, Potosky AL et al: Trends and outcomes of outpatient mastectomy in elderly women. J Natl Cancer Inst 90:833, 1998.

176. Morello DC, Colon GA, Fredricks S et al: Patient safety in accredited office surgical facilities. Plast Reconstr Surg 99:1496, 1997.

177. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107, 1985.

178. Bechtoldt AA: Committee on anesthesia study. Anesthetic-related deaths: 1969-1976. N C Med J 42:253, 1981.

179. Forrest WH: Outcome: The effect of the provider. In Hirsh RA, Forrest WH (eds): Health Care Delivery in Anesthesia. Philadelphia, George F. Stickley, 1980, p 137.

180. Silber JH, Williams SV, Krakauer H et al: Hospital and patient characteristics associated with death after surgery: A study of adverse occurrence and failure to rescue. Med Care 30:615, 1992.

181. Abenstein JP, Warner MA: Anesthesia providers, patient outcomes and costs. Anesth Analg 82:1273, 1996.

182. Brown RH, Schauble JF, Hamilton RG: Prevalence of latex allergy among anesthesiologists: Identification of sensitized but asymptomatic individuals. Anesthesiology 89:292, 1998.

183. Berry AJ, Greene ES: The risk of needlestick injuries and needlestick-transmitted diseases in the practice of anesthesiology. Anesthesiology 77:1007, 1992.

184. Denes AE, Smith JL, Maynard JE et al: Hepatitis B infection in physicians: Results of a nationwide seroepidemiologic survey. JAMA 239:210, 1978.

185. Berry AJ, Isaacson IJ, Hunt D et al: The prevalence of hepatitis B viral markers in anesthesia personnel. Anesthesiology 60:6, 1984.

186. Berry AJ, Isaacson IJ, Kane MA et al: A multicenter study of the prevalence of hepatitis B viral serologic markers in anesthesia personnel. Anesth Analg 63:738, 1984.

187. Henderson DK: HIV-1 in the health care setting. In Mandell GL, Douglas RG, Bennett JE (eds): Principles and Practice of Infectious Disease. New York, Churchill Livingstone, 1990, p 2221.

188. Kiyosawa K, Sodeyama T, Tanaka E et al: Hepatitis C in hospital employees with needlestick injuries. Ann Intern Med 115:367, 1991.

189. Marcus R: CDC Cooperative Needlestick Surveillance Group: Surveillance on health care workers exposed to blood from patients infected with the human immunodeficiency virus. N Engl J Med 319:1118, 1988.

190. Busby J: Through the valley of many shadows: HIV infected physicians. Texas Med 87:36, 1991.

191. Greene ES, Berry AJ, Arnold WP 3rd et al: Percutaneous injuries in anesthesia personnel. Anesth Analg 83:273, 1996.

192. Buergler JM, Kim R, Thisted RA et al: Risk of human immunodeficiency virus in surgeons, anesthesiologists, and medical students. Anesth Analg 75:118, 1992.

193. Anonymous: Practice guidelines for management of the difficult airway: A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 78:597, 1993.

194. Anonymous: Practice guidelines for pulmonary artery catheterization: A report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Anesthesiology 78:380, 1993.

195. Anonymous: Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 84:732, 1996.

196. Holzman RS, Cooper JB, Gaba DM et al: Anesthesia crisis resource management: Real-life simulation training in operating room crises. J Clin Anesth 7:675, 1995.

197. Howard SK, Gaba DM, Fish KJ et al: Anesthesia crisis resource management training: Teaching anesthesiologists to handle critical incidents. Aviat Space Environ Med 63:763, 1992.

198. Schwid HA, O'Donnell D: Anesthesiologists' management of simulated critical incidents. Anesthesiology 76:495, 1992.

199. Popp HJ, Schecke T, Rau G et al: An interactive computer simulator of the circulation for knowledge acquisition in cardio-anesthesia. Int J Clin Monit Comput 8:151, 1991.

200. Gaba DM, DeAnda A: A comprehensive anesthesia simulation environment: Re-creating the operating room for research and training. Anesthesiology 69:387, 1988.

201. Devitt JH, Kurrek MM, Cohen MM et al: Testing the raters: Inter-rater reliability of standardized anaesthesia simulator performance. Can J Anaesth 44:924, 1997.

202. Devitt JH, Kurrek MM, Cohen MM et al: Testing internal consistency and construct validity during evaluation of performance in a patient simulator. Anesth Analg 86:1160, 1998.

203. Pedersen T: Complications and death following anaesthesia: A prospective study with special reference to the influence of patient-, anaesthesia-, and surgery-related risk factors. Dan Med Bull 41:319, 1994.

204. Rao TLK, Jacobs KH, El-Etr AA: Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 59:499, 1983.

205. Pierce EC Jr: The 34th Rovenstein Lecture. 40 years behind the mask: Safety revisited. Anesthesiology 84:965, 1996.

Chapter 23 - Preoperative Evaluation *

Michael F. Roizen
Joseph F. Foss
Stephen P. Fischer

INTRODUCTION

The ultimate goals of preoperative medical assessment of patients are to reduce the morbidity of surgery, to increase the quality but decrease the cost of perioperative care, and to return the patient to desirable functioning as quickly as possible. Traditionally, these goals have been facilitated by a preoperative meeting between the patient and the anesthesiologist. The meeting has five specific purposes:

1. To obtain pertinent information about the patient's medical history and physical and mental conditions, in order to determine which tests and consultations are needed.
2. Guided by patient choices and the risk factors uncovered by medical history, to choose the care plans to be followed.
3. To obtain informed consent.
4. To educate the patient about anesthesia, perioperative care, and pain treatments in the hope of reducing anxiety and facilitating recovery.
5. To make perioperative care more efficient and less expensive.

Reducing anxiety and obtaining informed consent are discussed in other chapters. The importance of these goals should not be overlooked during preoperative evaluation. Most of the data indicate that recovery occurs more quickly when the anesthesiologist allays the patient's concerns, informs the patient about what is to come, and plans postoperative pain therapy with the patient [1] [2] [3] [4] [5] (Ch. 69).

The other functions of preoperative evaluation are closely related: the acquisition of a pertinent medical history and of information about physical and medical conditions. These functions affect all the decisions about testing, consultation, and discussion of care plans with the patient and lead to patient education, setting expectations for the patient's postoperative pain therapy and recovery plan, and cost reduction.

Thus, the first two functions of preoperative evaluation--optimizing patient health before surgery and/or planning the most appropriate perioperative management--not only improve perioperative outcome but also reduce costs. Data supporting this claim are substantial, but indirect; studies of perioperative morbidity over 4 decades repeatedly show that preoperative patient conditions are significant predictors of postoperative morbidity. [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] Specifically, less severe

---

* *See Practice Guidelines for Management of the Difficult Airway*

---

manifestations of adverse preoperative conditions are associated with lower perioperative morbidity and mortality (Table 23-1 (Table Not Available) and Fig. 23-1) (Figure Not Available) . The data imply (but do not prove) that preoperative treatment of conditions such as congestive heart failure and diabetes can reduce the severity of disease and thus perioperative morbidity and mortality. For this to occur, preoperative assessment must be accomplished far enough in advance to give the primary care physician a "second opinion" that guides therapy and consultations toward optimizing the preoperative health status of the patient. This step obliges the preoperative evaluator to take a thorough history and to determine the extent of consultation with the primary care physician that is needed to judge optimal health and the potential for improvement of preoperative status.

Preoperative evaluation produces other benefits as well. Patient education about perioperative care expectations can radically reduce the length of stay and costs (Table 23-2 (Table Not Available) [5]). Moreover, preoperative consultations may initiate additional risk-modification tactics such as reducing tachycardia [5] or the stress on plaque, [31] [32] [33] [34] [35] controlling hypertension, [36] [37] [38] perioperative cessation of smoking, [39] [40] [41] [42] nutritional fortification, [43] [44] immunization, [45] and stamina/strength training [46] [47] and in this way improve perioperative outcome.

Why can't this process of preoperative assessment be accomplished in isolation by a primary care physician or internist? Although much of the process probably could be, a condition considered "optimal for daily life" (e.g., some degree of prerenal azotemia in the patient with congestive heart failure) may not be "optimal preoperative status" (at which time vasodilation may cause hypotension or permanent renal impairment, or both). Furthermore, the process of preoperative evaluation and risk-factor modification requires a broad knowledge of the *content* of scientific perioperative care and a deep understanding of the *context* in which that knowledge is applied. Understanding the context--the environmental, sociologic, ethical, and team concepts and the economic influences--of perioperative care is almost as important as the technical knowledge on which the practice of perioperative care rests. Thus, compulsive attention to the effects of planned perioperative maneuvers on patient physiology would be desirable, perhaps even necessary, if the benefit of such pre-planning is deemed worth the cost. Preoperative evaluation by a physician is not inexpensive. However, later sections of this chapter show how preoperative planning can be much less expensive than current practices because of the

Figure 23-1 (Figure Not Available) Estimated risk of hospital mortality in relation to age, preoperative disease, and surgery. Elective surgery, top triangle; emergency surgery, bottom triangle. *(From Pedersen et al [22])*

TABLE 23-1 -- Mortality Risk for Elective Surgery, Determined for Various Degrees of Coexisting Disease

(Not Available)

Modified from Fowkes et al [16]

ability to order tests selectively and to use education and information tools to increase efficiency, to shorten the length of stay, to reduce the rate of cancellations, and to increase patient satisfaction. In addition, preoperative assessment can uncover hidden conditions that could cause problems both during and after surgery. In this way, the anesthesiologist is able to anticipate problems and to plan therapy intended to prevent or minimize the effects of such problems. [5] [18] [31] [32] [33] [34] [35]

A study at the University of Florida in Gainesville found that preanesthetic evaluations provided information leading to changes in care plans for more than 15 percent of all healthy patients (i.e., American Society of Anesthesiologists [ASA] physical status I and II patients) and for 20 percent of all patients in general. [24] Care plans were changed because of information from observation and history; the most common conditions causing changes were gastric reflux, insulin-dependent diabetes mellitus, asthma, and suspected difficult intubation (Table 23-3) (Table Not Available) . However, the data did not indicate that these changes improved patient outcome. Nevertheless, practitioners seem to believe that the discovery of these conditions calls for a change in plans, which is usually implemented in a way that

delays operating room (OR) schedules and increases costs.

Examples of such last-minute changes are as follows: administration of a histamine (H_2) blocker 1 to 2 hours before, and an oral antacid immediately before, entry to the operating room; the obtaining of equipment to measure blood glucose levels; the obtaining of a history of the patient's diabetic course and treatment from the primary care doctor as well as the patient; and the performance of fiberoptic laryngoscopy or additional procedures requiring skilled help. Thus, even if preoperative evaluation were not to alter outcome to any great degree, its ability to reduce costs by reducing laboratory tests and delays in obtaining equipment or treatments perceived to be beneficial (and medicolegally required) would be substantial and would warrant its use. Data from Stanford University, [25] [26] the University of Chicago, [5] [48] the University of South Florida, [27] the University of Rochester in New York State, [28] the University of Massachusetts, [29] and a community hospital in London, Ontario, [30] all confirm these cost advantages. Furthermore, a negative history and physical can lead to decreased resource utilization for healthy patients [23] and for those with comorbid conditions but without risk factors

TABLE 23-2 -- Benefits of Combining Changes in Pain Therapy With Preoperative Education of the Patient Regarding Perioperative Expectations, as Shown for Three Clinical Pathways[a]

(Not Available)

Modified from Worwag and Chodak [5]

[a] Preoperative education of the surgical patient about perioperative expectations, coupled with changes in pain therapy, can radically reduce the length of stay and costs without loss of patient satisfaction. Pathway 1, data collected before preoperative education and changes in pain therapy; pathway 2, after education and the first change in pain therapy; and pathway 3, after education and further refinement in pain therapy.

TABLE 23-3 -- Medical Problems Discovered on Preanesthetic Evaluations That Could Prompt a Change in Patient Management

(Not Available)

modified from data presented by Gibby et al. [24]

requiring high-intensity care. [49] In addition, preoperative evaluation gives practitioners confidence that they will not be surprised by unexpected patient conditions and gives the patients confidence that the health-care system is responding to their individual conditions.

In the beginning, the preoperative assessment described earlier relied only on accurate history-taking and physical examination. In the 1960s, multiphasic screening laboratory tests were added to the process. This chapter evaluates the goals of preoperative medical assessment and the *relative* importance of history-taking, physical examination, and laboratory testing regarding the improvement of perioperative outcome, but then it goes beyond these knowledge-based steps.

Since the first edition of *Anesthesia* in 1981, Roizen has attempted to describe not only current practice but also the need for innovative change. In the first edition, before the use of diagnosis-related groups (DRG) to establish fees, and before that cost-based push to reduce testing, he discussed the lack of benefit from nonselective laboratory testing. In the second edition, published in 1986, the chapter described how cost-benefit and benefit-risk analyses again pointed to the need to reduce the amount of laboratory testing. The third edition of this chapter, in 1991, also came to a nontraditional conclusion, that anesthesiologists needed to change the way they usually perform preoperative evaluation. The fourth edition of the chapter again suggested a major break with current practice, that unless anesthesiologists instituted a system of performing careful preoperative evaluations on all patients, these clinicians were in danger of doing too little assessment and even too little testing. In some areas of the United States, the pendulum may have swung too far to the "no-test" and only "cursory-assessment" side. Not surprisingly, in this fifth edition, the authors of this chapter accentuate the need to develop consensus in making a preoperative clinic effective for all and in implementing an effective electronic information system (informatics) process. However, we also emphasize the dramatic benefits of instituting a functional preoperative clinic that has gone through the stages of efficient patient evaluation, appropriate test selection, and effective prerequisite education of the patient and that is organized in a way that increases patient satisfaction. We highlight the importance and benefits of adding *patient education* to these processes.

We believe that just as the practice of anesthesia has changed during the past decade, the practice of preoperative evaluation also needs to change to ensure that the best cost-benefit and benefit-risk goals are attained. Specifically, data indicate that we can produce optimal cost-benefit and benefit-risk strategies for perioperative care only when we reduce testing to that indicated by history-taking and when we institute effective patient education informed by appropriate choices for pain therapy. Outcome can be improved, patient satisfaction increased, and hospital stays shortened appropriately when education about pain therapy and about recovery is taught intensively in the preoperative clinic. The difficulty is that we must obtain a thorough history far enough in advance to allow us to perform these selected tests and to implement the necessary therapies without disrupting surgical schedules and the patient's perioperative care plans. This must also be done far enough in advance to give the patient and his or her significant others time to plan for the options that have been selected.

CHANGING NATURE OF PREOPERATIVE EVALUATION

Preoperative evaluation strives to answer three questions: Is the patient in optimal health? Can, or should, the patient's physical or mental condition be improved before surgery? Does the patient have any health problems or use any medications that could unexpectedly influence perioperative events? Such an evaluation must include the long-accepted standard practices: review of hospital charts and prior anesthesia records, consultation with the primary care physician, history-taking, physical examination, evaluation of laboratory tests obtained, ordering of additional laboratory tests, and the discussion of perioperative anesthesia plans (including alternatives for intraoperative and postoperative analgesia) with the patient in a way that provides accurate information and reduces patient anxiety. However, the practice of medicine has changed. The cost-conscious environment of the 1990s has made it difficult for anesthesiologists to achieve these goals using the style of the 1970s and earlier.

For example, the increased need to minimize costs means fewer or no preoperative hospital days for the patient. More than 65 percent of all operations are performed on an outpatient basis; almost 5 percent are performed in the surgeon's office, and another 20 to 30 percent are done as morning admissions. Unfortunately, however, the increasing age of patients often means a greater likelihood of concurrent disease. Unlike the old days, when the entire evening before surgery could be spent learning about the medically complex patient, anesthesiologists are now being asked to perform preoperative evaluation as they "run" from case to case. They are being asked to deliver more for less, to do a more complete job, and to meet the continuing demand of administrators and surgeons to shorten turnover times. In such time-pressured situations, the anesthesiologist may be justifiably uncomfortable about the adequacy and comprehensiveness of the preoperative evaluation. "Did I ask the patient whether he or she had a drink during the past 72 hours, or whether he or she has ever had a problem with drinking?" (These are currently the two most sensitive and specific questions to ask when trying to determine the likelihood of alcoholism. [50] [51]) "Did I forget to ask other questions, for example, whether any family members had hepatitis?" *It is very difficult to make an adequate preoperative evaluation in 5 to 15 minutes, and it is impossible to change any therapy or to optimize any care that requires more than 10 minutes without increasing costs and inconveniencing all concerned.* Furthermore, the pressure to proceed, even when there may be increased or unknown risk, is much greater when time is short than when such evaluations are done in advance. Frequently, old records are not available. [52] In addition, the pressure to proceed quickly probably makes the consent process less informed and the discussion of anxiety relief and preoperative pain therapy plans less thorough. The patient and significant others also have little or no time to "digest" information about what to expect regarding the perioperative care plan.

Do we need to change the system? Clearly, a change is needed if preoperative assessment is to be adequate. To perform these assessments efficiently, the anesthesiologist needs to know about the patient. We also believe that preoperative evaluation is intrinsically valuable and that interacting with the patient in this way is an enjoyable and productive part of the practice of anesthesia. Moreover, for the practical-minded clinician, inadequate preoperative assessment is now one of the top three causes of lawsuits against anesthesiologists. Nevertheless, in the current atmosphere, there is not enough time to assess the patient preoperatively in the traditional method. Before solutions to this problem are suggested, the importance of preoperative assessment is evaluated, as well as the conditions that may be sought and determined from such assessment.

UNCOVERING PATIENT FACTORS THAT INCREASE THE RISK OF ANESTHESIA

This chapter provides information the anesthesiologist needs to know to ensure that the patient is asymptomatic from the standpoint of anesthetic risk. The management of patients found to be symptomatic is discussed in Chapter 25 . Ensuring that the patient is asymptomatic requires knowledge of the patient factors that increase the perioperative risk of anesthesia, because it is those factors that must be eliminated.

Major surgery usually represents a tremendous assault on the human organism. The body has an elaborate defense mechanism that alerts it to, and helps it escape from, trauma. The job of the anesthesiologist is *not* simply to put the patient to sleep and to wake him or her when surgery is over, but to maintain homeostasis during the assault of surgery and to provide pain relief to blunt the effects after the assault. To do this, the anesthesiologist must interfere with the stress response induced by pain, anticipate periods when the stress response will not be present, plan for the rare situations in which the patient's medical problems may occur acutely, and, at the same time, manage the patient's chronic medical conditions.

Even when the stress of surgery is not felt consciously, it evokes a complex physiologic response. Much of this response

---

is meant to allow the body to escape trauma. For example, blood flow is diverted from the kidney and liver to the heart and head, and blood pressure rises. Thus, the system most needed to be in a "good" state of health, the cardiovascular system, has first priority. [9] [18] [19] [20] [21] [22] Elaborate and simple tests and history-taking processes have evolved to evaluate the cardiovascular system, especially in aged patients or patients with comorbid disease. [53] [54] [55] We evaluate the process of history-taking first.

History

Illnesses in systems other than the cardiovascular also have an effect on perioperative risk. The following is a list of relatively common conditions that we ensure are not present before assuming that the patient is asymptomatic. [24] [56] [57] Chapters 22 and 25 discuss the increased risk posed by the problems discovered, and Chapter 25 describes optimization of the patient's physical condition, anticipation of potential problems, and possible therapies for the problems. The evaluation process that follows represents our initial screening procedure for disease. Although the process attempts to be relatively inclusive, it cannot cover all possible conditions that may be encountered when dealing with surgical patients.

First Areas of Concern

Included first in our history are general items, such as whether the patient has received recent medical care, has taken medication, or has allergies. Questions also are asked about prior exposure to anesthetics and subsequent problems:

1. When did you last have anesthesia?
2. Do you have any problems with anesthesia? Have any of your family members had any problems with anesthesia?
3. Do you have allergies?
4. What are you allergic to?
5. Have you had any blood tests in the last 6 months?
6. Have you had a chest x-ray in the last 2 months?
7. Have you had an electrocardiogram (ECG) in the last 2 months?
8. Has your stool been checked for blood in the last year?
9. Have you been a patient in a hospital, an emergency department, or an outpatient surgery center in the last 2 years? If so, why? What part of the hospital (for example, critical care unit)? How long were you there?
10. Do you take any medications?
11. What medications do you take?
12. Do you take any medications not prescribed by your doctor or that you just purchase off the shelf at a drugstore or grocery store?
13. Do you take any supplements or vitamins? (These can interact substantially with perioperative medications. [58])

Also included in this category of questions are items about artificial devices (e.g., hearing aids, false eyes) and use of alcohol:

1. Do you wear contact lenses?
2. Do you currently use eyedrops prescribed by a doctor?
3. When did you have your last alcoholic drink?
4. Have you ever had a drinking problem?

Because patients tend to give socially acceptable answers on sensitive subjects (Trigg DJ et al, unpublished data), [59] when probing in these types of areas, a checklist or computer-aided history may be more valid than an interview. Sensitive subjects include risk factors for use of illegal drugs and for human immunodeficiency virus (HIV) infection. Nevertheless, the personal interview is still essential for in-depth questioning.

Cardiovascular Disease

We try to ensure that the patient does not have the following cardiovascular conditions: congestive heart failure, cardiomyopathies, ischemic heart disease (stable or unstable), valvular or subvalvular heart disease, hypertension (diastolic or systolic [37]), disturbances in cardiac rhythm, pericarditis, arteritis, or other manifestations of atherosclerosis. These conditions require further evaluation to ensure that optimal treatment has been achieved before surgery (Ch. 25) . In the outcome studies described earlier, congestive heart failure incurred the highest risk. [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] Questions cannot be limited to the cardiovascular system. For example, to search for alcoholic cardiomyopathy, the following inquiries are made: Have you had a drink in the last 72 hours? Have you ever had a problem with drinking? As mentioned earlier, these two questions are the most sensitive and specific questions to ask when trying to determine the possibility of alcoholism. [50] Exercise tolerance is also checked, for example, the patient's ability to walk up stairs, play sports, and perform chores (mowing lawns, making beds, vacuuming), without becoming short of breath.

Typical questions regarding the cardiovascular system include the following:

1. What is the most vigorous activity you have done in the last 3 weeks?
2. How far have you walked in the last week without stopping?
3. Can you walk a block without stopping? When did you last do so?
4. Have you ever had a heart attack, or have you ever been treated for a possible heart attack?
5. Do you have heart problems such as skipped heart beats, angina, or chest pain?
6. Have you been told that you have a heart murmur or rheumatic fever?
7. Have you ever been told that you have mitral valve prolapse?
8. Have you ever had heart or lung surgery?
9. Have you ever awakened and felt short of breath?
10. Do you become short of breath after climbing a flight of stairs or after walking a short distance?
11. When did you last climb a flight of stairs? If not recently, when did you last walk two city blocks?
12. Are you able to walk up stairs at the same rate as 5 years ago?

13. Do your ankles ever swell?
14. Are you ever short of breath? When?
15. Do you ever have chest pains, angina, chest heaviness, or chest tightness?
16. Do you ever have indigestion that does *not* occur after overeating?
17. Have you ever been told by your doctor to exercise or diet to control high blood pressure?
18. Have you ever been a patient in a critical care unit (cardiac care unit, intensive coronary care unit)?
19. Have you passed out or nearly passed out in the last year? Why? [60]
20. Do you sleep with more than one pillow at night? (This question is useful only for men and women older than age 60, because 50 percent of women sleep with two pillows [Trigg DJ et al, unpublished data]. [59])
21. Do you currently take water pills or diuretics?
22. Do you currently take potassium pills or powder?
23. Do you currently take anticoagulants or blood thinning medicine?
24. Have you ever been told to take, or have you ever been given, antibiotics before routine dental work?

Some of these questions are asked in a different order, so that the patient is not startled or confused by them, as if they were a "pop quiz." To avoid surprising or confusing the patient, questions are asked in a "set." For instance, all questions related to medication are asked at the same time.

Respiratory and Airway Problems

Because airway problems cause substantial risk, the most important consideration regarding the respiratory system is securing the airway. Therefore, evidence of airway obstruction and of restriction of neck and jaw movement is sought. The end result of exposure to toxins (whether environmental or related to smoking) is also sought: emphysema, bronchitis, and chronic infections. We try to ensure that asthma is not present and that other conditions, such as obesity, have not progressed to the point of limiting respiratory function. The personal interview (no matter when performed) is usually quite efficient in revealing the condition of the airway, respiratory reserve, and the possible need for laboratory evaluation, such as pulmonary function testing with bronchodilators or blood gas analysis, or both (Chs. 15 and 39) . The personal interview may also be the best time to educate the patient and family members about the time needed for cessation of smoking to be beneficial (Ch. 25) . [39] [40]

Questions that usually elicit information about the general condition of the mouth and airway and possible reactions to anesthesia include the following:

1. Do you wear dentures, a crown, a partial plate, or a bridge?
2. Are any of your teeth loose, cracked, chipped, or capped?
3. Have you ever had anesthesia?
4. Have you or any blood relative ever had any problems with anesthesia? This question not only helps to reveal possible airway problems but also elicits information about some rarer diseases, such as malignant hyperthermia, glucose-6-phosphate dehydrogenase deficiency, acute porphyria, allergies, sickle cell disease, neurologic disorders, and hiatus hernia. It usually also elicits concerns about postoperative nausea and vomiting and thus provides an opportunity to reassure the patient, to plan the choice of anesthetic, to ask female patients about their last menstrual period, and to use preanesthetic suggestion, for those physicians believing in the value of this practice.
5. Can you open your mouth fully?
6. Do your joints ever click, pop, or hurt?
7. Have you ever been treated for a problem of the jaw joint (that is, a temporomandibular joint problem)?
8. Have you ever been hoarse for more than 1 month?
9. Do you snore, or do others say you snore? This question proved to be the best predictor of difficult intubation when our computer-based health history was compared with outcome studies, [48] but it was not very specific (four of five patients who answered yes to this question did not have a difficult intubation).
10. Have you ever had cancer?
11. Have you ever had, or been treated for, arthritis?
12. Do you have neck stiffness or problems moving your head?
13. Have you ever been told you had diphtheria? (Diphtheria can cause narrowing of the airway.)

The following questions search for lung disease:

1. Have you ever had pneumonia? When?
2. Have you ever undergone lung surgery?
3. Do you have shortness of breath, wheezing, chest pain, bronchitis, asthma, or emphysema?
4. Do you cough regularly or frequently?
5. Do you cough up mucus (sputum or phlegm)?
6. In the last 4 weeks, have you had a fever, chills, cold, or flu?
7. Have you ever smoked? When did you stop?
8. Have you ever smoked half a pack or more of cigarettes a day on a regular basis?
9. Have you ever smoked a pipe or cigars on a regular basis?

Hepatic or Gastrointestinal Disease

Past and present hepatic disease increases the risk of certain surgical procedures (Ch. 25) , sometimes contributes to abnormal clotting and pharmacokinetics, and may present medicolegal concerns (e.g., in the case of postanesthetic jaundice). Hepatic disease also increases the risk of surgery for nonhepatic problems (Ch. 25)

Gastrointestinal diseases may increase the potential for aspiration of gastric contents. For example, the gastroparesis of ulcer disease is often accompanied by solid food in the stomach, and inflammatory bowel disease may be accompanied by arthritis of the neck. Gastrointestinal disease also increases the potential for dehydration, electrolyte disturbances, and anemia. The presence of gastrointestinal or hepatic disease can give clues about possible endocrine, pulmonary, or cardiac disease (e.g., gastritis in the alcoholic patient could indicate the need to search for alcoholic cardiomyopathy).

Questions that screen for gastrointestinal or hepatic disease include the following:

1. Have you ever been diagnosed as having a hiatus hernia?
2. Have you ever had hepatitis, yellow jaundice, liver disease, or malaria?
3. Have you ever had gallstones or gallbladder disease?
4. Are your stools ever bloody or black and tarry?
5. Have you seen bright red blood on your stool or on toilet tissue after wiping?
6. Have your bowel habits changed this year?
7. Do you often have diarrhea?
8. Have you ever vomited blood, or material that looks like coffee grounds in the last 6 months?
9. Do you have frequent nausea or vomiting?
10. Have you lost weight this year without trying?
11. Has your appetite for food changed in the last year?
12. Are you eating the same foods you ate a year ago?
13. Have you had heartburn within the last month?
14. Are you now being treated, or have you been treated, for ulcer disease?
15. Are you currently taking antacids or Tagamet (cimetidine), Zantac (ranitidine), Pepcid (famotidine), Prilosec (omeprazole), or Axid (nizatidine)?

Bleeding Problems

Bleeding can occur because of a hereditary deficiency of clotting factors or because of abnormal platelet or vascular function caused by disease or drugs. The following questions search for such abnormalities:

1. Have you ever had a blood problem such as anemia or leukemia?
2. Have you ever had a problem with blood clotting?
3. Have you ever had a serious bleeding problem?
4. Have you received a blood transfusion since 1979?

These questions are often asked in two ways, because patients seem to need time to recall such events. For example:

1. Has a family member or blood relative ever had a serious bleeding problem?
2. Have you ever had prolonged or unusual bleeding from cuts, nosebleeds, minor bruises, tooth extractions, or surgery?
3. Have you ever had excessive bleeding that required blood transfusion?

Renal Disease

Renal disease can contribute to bleeding because of a functional platelet deficit associated with renal impairment (Ch. 25) . In addition, renal insufficiency can increase risk because it produces anemia (prior to, or in the absence of, optimal erythropoietin therapy), electrolyte disturbances, peripheral neuropathy, and abnormalities in drug metabolism and excretion. The following questions search for renal disease:

1. Have you ever had any kidney problem?
2. Have you ever had kidney failure, dialysis, or more than two kidney infections?
3. Have you ever had kidney stones?
4. Are you undergoing dialysis for kidney problems?
5. Have you had changes in bowel or bladder function in the last year?
6. Has your appetite for food changed in the last year? (Voluntary avoidance of foods having a high protein content is a subtle sign of renal disease.)

Endocrine Disturbances

Endocrine disturbances and the end-organ effects of diabetes or thyroid, parathyroid, pituitary, adrenal, and carcinoid disease can increase perioperative risk substantially. For instance, morbidity and mortality increase 5- to 10-fold because of the nephropathy and autonomic insufficiency of diabetes (Ch. 25) . The following questions help to ensure the patient does not have endocrine-related diseases:

1. Do you wake up at night to urinate? How often?
2. Have you ever been told that you have diabetes or sugar diabetes?
3. Do you take, or have you taken, steroids, cortisone, or adrenocorticotropic hormone (ACTH) in the last year?
4. Do you perspire (sweat) much more than others or a great deal every now and then?
5. Does your face flush or get red every now and then, even when you are not exercising?

These last two questions attempt to rule out the very hazardous perioperative situations of undiscovered pheochromocytoma and carcinoid syndromes. Both conditions can now be well managed if known in advance (Ch. 25) . Both, however, incur a mortality rate as high as 10 percent if undiscovered prior to operation. The following questions search for symptoms of thyroid and parathyroid disease:

1. Have you ever taken medicine (e.g., Synthroid [levothyroxine]) or had radioactive iodine (^{131}I) for thyroid disease?
2. Do you consistently like the room warmer or colder than your spouse?
3. Do you have muscle cramps or spasms in your legs more than three times a year?

Neurologic Disease

Physical examination can add significantly to one's impressions and can reduce the necessity for some questions, particularly regarding neurologic disease. Nevertheless, to exclude neurologic disease, the following questions are usually asked:

1. Have you ever had a seizure, convulsion, fit, stroke, or paralysis?
2. Have you ever been diagnosed as having a tremor?
3. Have you ever had migraine headaches?
4. Have you ever had nerve injury, multiple sclerosis, or any disorder of the nervous system?
5. Have you ever had numbness, tingling, or the feeling of "pins-and-needles" in your arm or leg that has lasted more than 2 hours?
6. Have you taken antidepressant, sedative, tranquilizing, or antiseizure medications in the last year?

Musculoskeletal Disease

Because arthritis affects the ease of securing the airway, we usually ask about potential musculoskeletal system disease during our search for airway and lung disease. Nevertheless, a brief review could include the following questions:

1. Have you ever had low back pain?
2. Have you been working at your usual job or doing your normal activities in the last week?

3. Have you taken pain pills or had pain shots in the last 6 months?

Sensitive Areas of Concern

One area not yet discussed concerns more difficult-to-manage subjects, such as the possibility of pregnancy in a minor, asymptomatic hemoglobinopathies when intense counseling and consultation service are not available, illicit drug use, and the potential for acquired immunodeficiency syndrome (AIDS). Much like Epstein, [61] Roizen believes that such matters should be handled in concert with hospital or facility policy. However, because this type of information can affect perioperative risk and plans, his usual procedure is to search for clues in the history. If one has taken the time to gain the patient's confidence so that the patient understands that these questions are being asked in order to provide better care, success is possible. If one tries to approach these sensitive areas in the 5 to 15 minutes usually allotted, the process ends up being awkward at best and usually does not succeed. In fact, patients seem to answer these questions more reliably on a checklist paper-and-pencil form or on a computer-based health history (Trigg DJ et al, unpublished data). [48] [59]

Under optimal conditions, the questions that can be asked include the following:

1. Within the last 2 years, have you taken nonprescription drugs, such as cocaine, crack, heroin, or LSD?
2. Have you been exposed to the body fluids (blood, semen, urine, or saliva) of anyone likely to have the AIDS virus?
3. Are you in any of the groups at high risk of AIDS (gays, bisexuals, hemophiliacs, and those who have had sex with a prostitute within the last 12 years)?
4. Would you like to undergo a test to find out whether you have been exposed to the AIDS virus?

It is our belief that AIDS testing will be an especially important consideration from an institutional point of view. In most states, testing requires patient consent. However, soon the decision not to test also may require patient consent. This requirement may arise because zidovudine (formerly known as azidothymidine [AZT]), in combination with other therapy, may delay the onset of AIDS in asymptomatic patients infected with HIV, and the use of triple therapy is now thought to be an issue of patient choice. [62] [63]

Physical Examination

The physical examination again looks for the same conditions sought by history. It consists of the following processes:

1. Determination of arterial blood pressure in both arms, and in at least one arm 2 minutes after the patient assumes the upright position after lying down, and examination of the pulses and of the chest, for heaves, thrusts, pulsations, murmurs, and gallops (third and fourth heart sounds). (Some clinicians believe that obtaining ankle blood pressure is useful in assessing the risk of cardiovascular disease, [64] [65] but this process is not routine.) The carotid and jugular pulses are also examined. Roizen has found that patients expect to be partially undressed for this examination and consider the examiner unprofessional if he or she does not auscultate blood pressure sounds using a bell or diaphragm held to the skin.)
2. Examination of the chest and auscultation of the bases of the heart for subtle rales suggestive of congestive heart failure, or for rhonchi, wheezes, and other sounds indicative of lung disease. (Although history-taking may detect these sounds as accurately as auscultation, the patient expects a "good" physician to auscultate the lungs preoperatively. Thus, this part of the physical examination also helps to increase patient confidence.)
3. Observation of the patient's walk for signs of neurologic disease or to assess back mobility and general health and a check of the eyes for abnormal movement and, along with the skin, for signs of jaundice, cyanosis, nutritional abnormalities, and dehydration. The skin is checked for clubbing. A functional evaluation of cardiovascular risk can be made by observing vigor and stamina in walking. Examination of the airway and mouth for neck mobility, tongue size, oral lesions, and ease of endotracheal intubation (Ch. 39)
4. Examination of the legs for edema, clubbing, mobility, sensation, and adequacy of hair growth (or skin texture) as signs of circulatory competence. Examination of the legs for bruising.

Although these portions of the history-taking and physical examination are routine, they are usually not recorded. Because the Health Care Financing Administration has insisted on recording of procedures as proof of their performance, the authors believe in using information system processes to document what has been done (see later).

DETECTING DISEASE: HISTORY, PHYSICAL EXAMINATION, AND CHART REVIEW VERSUS LABORATORY TESTS

Because more than 80 percent of patients receiving anesthesia are either outpatients or "come-and-stay" patients (i.e., patients admitted to the hospital after surgery), patients cannot be evaluated preoperatively as they were during the 1970s. A new system had to be devised. The resulting set of questions is extensive, consisting of more than 100 items. Roizen believes that use of either a written or an automated questionnaire to ask the screening questions, if coupled with a personal interview to pursue positive answers, does not decrease the accuracy or perceived personalization of the care given (see later) (Trigg DJ et al, unpublished data). [48] [59] [66] [67] [68] [69] [70] Gradually, Roizen began using this combination for inpatients as well (this process is described later in the chapter), especially for "come-and-stay" patients.

That means that *the anesthesiologist*' *s* task is to explore in depth any positive results on history-taking and to spend the rest of the time on issues the patient wants to discuss. Furthermore, storing this information electronically and securely (described later in this chapter) allows any anesthesiologist who is providing care to assess the patient's data the day or night before surgery. Most anesthesiologists have developed ways of putting the classic pattern (chart review; history-taking; physical examination; and discussion of risks, alternative anesthetic plans, and postoperative pain therapies) together so that all these questions are part of a compassionate flow of thought that helps the patient to recall information. A rigid, specific order for questioning is usually unnecessary.

The anesthesiologist must remember that older male patients tend to deny symptoms, often seeing disease as a sign of frailty. Some patients believe their symptoms indicate a life-threatening disease and therefore resist seeking medical help or answering questions until help is imperative. Despite such obstacles to the efficient discovery of pertinent information, seeing the patient before surgery does give the anesthesiologist one strong advantage: patients are usually willing and eager to share information. All surgery is a major event for both men and women; no patient really views any surgery as "minor." Thus, the preoperative interview can elicit vital information.

Some investigators have suggested that anesthesiologists forget the history and just use laboratory screening for disease. A review of the literature forces us to disagree strongly: the history (whether obtained personally, by questionnaire, or by telephone interview by person or computer screening device), and the investigation of positive answers by an in-person interview is many times more effective in screening for disease than use of laboratory tests alone. Moreover, the combination of history and personal interview can be a much less expensive process and avoids the medicolegal problems and inefficiency associated with too much testing.

In fact, the data presented later in this discussion led us to believe that the combination of history (from personal interview or questionnaire supplemented by personal interview) and physical examination is the best tool for optimal evaluation of patients and optimal selection of laboratory tests (i.e., selection of only those tests that have a greater chance of benefiting rather than harming the patient).

The primary problem with ordering batteries of laboratory tests for all patients is that laboratory tests are not very good screening devices for disease. In addition, the subsequent "extra" tests that physicians order as a follow-up to supposedly abnormal results are costly. More important, however, is that nonindicated tests often represent additional risk to the patient, increase medicolegal risk to the physician, and render ORs in outpatient centers and hospitals inefficient.

Laboratory Tests as Effective Screening Devices

In general, results of preoperative laboratory testing have been regarded as supplements to the patient's health history and physical examination. Collectively, this information has been the primary source of patient data available to the anesthesiologist. In the perioperative management of the patient, the anesthesiologist may alter the care of the patient based on preoperative laboratory test results. If a preoperative test suggests a change in the care of an individual such that the health of the patient is improved or a potential problem is avoided, then that test has been beneficial to the patient. *Other preoperative tests, the results of which are normal and merely borderline, may only distract the physician;* the results of these tests create no benefit but merely inconvenience, or worse, harm, through distraction. Finally, if a preoperative test suggests a change in the care of an individual so that the health of the patient suffers or a problem arises, that test decreases the overall quality of medical care and is harmful to the patient. One not uncommon example would be a situation in which abnormal results on a chest radiograph obtained for a 40-year-old man solely because he is scheduled for surgery leads to a computed tomographic needle biopsy that produces normal results but also a pneumothorax. This sequence shows how a "benign" test can result in harm. Thus, testing can incur a risk-benefit ratio that is higher than 1.

On the whole, not much benefit appears to arise from unindicated routine laboratory testing. Leonard and coworkers [71] reported that biochemical screening tests had no significant value in the preoperative screening of pediatric patients expected to be hospitalized for less than 1 week. When Korvin and associates [72] reviewed biochemical tests given routinely to 1,000 patients on hospital admission, none of the tests produced a new diagnosis that was unequivocally beneficial to the patient. In an ambitious, controlled trial of multiphasic screening of 1,500 patients, Olsen and coworkers [73] found no difference in morbidity between control groups and groups subjected to screening tests. Durbridge and colleagues [74] compared 1,500 patients randomly assigned to undergo or not to undergo screening tests on admission. With respect to length of hospital stay or patient outcome, no benefit resulted from the 8,363 extra tests performed for the group undergoing screening tests. Narr et al [23] [75] found that more than 3,000 ASA I or II patients failed to benefit from laboratory testing, and that absence of tests in more than 1,000 ASA I patients (average age, 21.4 y) did not adversely affect medical care.

Many studies have compared the yield from indicated (warranted based on history or risk group) versus unindicated (unwarranted) preoperative testing [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] [95] (Table 23-4) (Apfelbaum JL et al, unpublished data). Few unindicated tests have yielded beneficial changes in perioperative care: at most, only 16 patients of more than 16,000 who had unindicated preoperative tests benefited from such testing. Furthermore, this figure represents the most optimistic interpretation, because 4 patients in the study conducted by Kaplan et al [76] received no benefit, and for at least another 7 patients in the O'Connor and Drasner [81] study, the benefit of treating asymptomatic anemia prior to surgery not incurring blood loss was not clear.

Although laboratory tests can aid in ensuring that a patient's preoperative condition is optimal once a disease is suspected or diagnosed, such tests have several shortcomings as screening devices for the discovery of unknown disease. First, they frequently fail to uncover pathologic conditions. Second, they detect abnormalities the discovery of

TABLE 23-4 -- Reported Yields (Abnormal, Significantly Abnormal, Changes in Care) for Unindicated Versus Indicated Laboratory Testing

STUDY (POPULATION, *n*)	TOTAL NO. OF TESTS	PERCENTAGE OF ALL TESTS ABNORMAL (%)	UNINDICATED TESTS (NO. [%])	PERCENTAGE OF ABNORMAL RESULTS ACTED ON (%)	NO. OF UNINDICATED/INDICATED RESULTS THAT CHANGE MANAGEMENT	NO. OF UNINDICATED/INDICATED POTENTIAL BENEFITS	USED TO DEFINE ABNORMAL
Kaplan et al [76] (1985) (elect. surg., 1,000)	2,785	3.45	1,828 (65.6)	--	0/--	4/--	Action limits
Narr et al [75] (1991) (elect. surg., 3,782)	18,910	0.87	--	28.5	47 total	10 total	Substantially abnormal
McKee and Scott [77] (1987) (elect. surg., 397)	794 [a]	2.14	--	0	0 total	13 total	Reference range
Turnbull and Buck [78] (1987) (cholecystectomy, 1,010)	3,646 [a]	2.30 [b]	--	8.3	7 total	4/6	Reference range
Johnson et al [79] (1988) (ambul. surg., 212)	424 [a]	24.06 [b]	--	0.98	1 total	0/13	Reference range
Muskett and McGreevy [80] (1986) (consec. surg., [d] 200)	1,007 [a]	38.63 [b]	--	18.5	5/71 [c]	0/--	--
O'Connor and Drasner [81] (1990) (elect. surg., [e] 486)	937	12.9 [b]	--	15.7	24/--	7/--	Clinically significant
Hackmann et al [82] (1991) (day surg., [e] 2,649)	2,649	0.53	2,605 (98.3)	7.1	0/1	0/1	Hb <10 g/dL
Roy et al [83] (1991) (elect. surg., [e] 2,000)	2,000	0.55	--	27.3	3 total	3 total	Hb <10 g/dL
Nigam et al [84] (1990) (tonsillectomy, [e] 250)	250	0.80	--	0	0/0	0/2	Hb 10 g/dL
Baron et al [85] (1992) (elect. surg., [e] 1,863)	1,863	1.13	--	0	0/0	--	30% >Hct ?50%
Rohrer et al [86] (1988) (elect. surg., 282)	1,119	5.90	514 (45.9)	--	3/0000	0/21	Reference range
Lawrence and Kroenke [87] (1988)(orthop. surg., [f] 200)	200	17.00 [b]	180 (90.0)	29.4	6/4	0/3	Lawrence and Kroenke [87]
Apfelbaum et al [g] , [h] (elect. surg., 1,746)	21,318	16.1	10,899 (51.1)	18.4	13/121	1/91	Action limits

This table was coauthored with Dr. Raj Kim

[a] Electrocardiographic (ECG) and/or chest radiographic results excluded
[b] Urinalysis results included
[d] A high medical risk population at a Veterans Affairs Medical Center Hospital
[c] ECG and chest radiographic results included
[e] Pediatric population (<18 y)
[f] Clean-wound, nonprosthetic knee procedures
[g] Includes author of this manuscript
[h] Apfelbaum JL et al (unpublished data)

which does not necessarily improve patient care or outcome. In addition, laboratory tests are inefficient in screening for asymptomatic diseases. Finally, most abnormalities discovered on preoperative screening, or even on admission screening for nonsurgical purposes, are not recorded (other than on the laboratory report) or pursued appropriately.

By itself, the detection of abnormalities does not justify testing, because most abnormalities in asymptomatic patients do not reflect the presence of disease. For tests reported as continuous results, the distribution of results in a population of patients is gaussian (i.e., normal). The values defining "abnormal" are set arbitrarily, so that test results exceeding those of the highest 2.5 percent of healthy individuals, or falling below those of the lowest 2.5 percent of healthy individuals, are said to be abnormal. Test results between these two extremes are "within the reference range." Therefore, 5 percent of test results from patients without disease will be "outside the hospital reference range." If one were to order 100 hemoglobin determinations for a sample of healthy patients, 5 percent of the results would be expected to be "abnormal." Ordering multiple preoperative tests increases the chances of at least 1 abnormal result.

Assuming that results of tests are independent of one another, the more tests ordered, the higher the likelihood of an abnormal result. For example, if two tests are ordered for a patient without disease, the chance of both being normal is 0.95 × 0.95 or 0.90. For 20 tests, the chance that all would be normal would be only 36 percent. The chance that at least one result would be abnormal is 64 percent. Thus, if one chooses to use more than 13 tests to screen patients before surgery, one should expect at least one abnormal test result.

AIDS testing provides another example. More than 92 percent of the population at low risk of HIV infection who have positive (abnormal) results on two enzyme-linked immunosorbent assays (ELISA) and one Western blot test in reality do not have HIV infection. [94] Therefore, it is not surprising that the benefit from nonselective testing is so low or that so few abnormal results arising from unwarranted tests are cause for action (see Table 23-4) . Mammography is another example. If both mammograms and breast examinations were performed yearly starting at age 40, by age 50 more than 49 percent would have a false-positive test on examination, and more than 20 percent would have a breast biopsy for benign disease. [96]

Even for the very elderly, a patient group at higher risk of morbidity and mortality during surgery, the ultimate benefit of routine laboratory screening is doubtful. Domoto et al [97] examined the yield and benefit of a battery of 19 screening laboratory tests performed routinely in 70 functionally intact elderly patients (average age, 82.6 y) who resided at a chronic care facility. The 70 patients underwent 3,905 screening tests. "New abnormal" results occurred in 5 of the 19 screening tests. Most of these "new abnormalities" were only minimally outside the normal range. Only 4 discoveries (0.1% of all tests ordered) led to a change in patient management, none of which, Domoto and coworkers concluded, benefited any patient in any important way.

Wolf-Klein et al [98] retrospectively studied the results of annual laboratory screening on a population of 500 institutionalized and ambulatory elderly patients (average age, 80 y). From the 15,000 tests performed, 756 new abnormalities were discovered, 690 of which were ignored. Sixty-six of the new abnormalities were evaluated; the result was 20 new diagnoses, 12 of which were treated. Two patients of the 500 ultimately may have benefited from eradication of asymptomatic bacteriuria, although eradication of this condition has not been shown to improve the quality of life or to extend life. [99] [100]

Studies show that the history and physical examination are the best ways to screen for disease. Delahunt and Turnbull [101] evaluated 803 patients who were assessed preoperatively for varicose vein stripping or inguinal herniorrhaphy. A total of 1,972 tests produced only 63 abnormalities not indicated by history or physical findings. Furthermore, in no instance did the discovery of these abnormalities influence patient management. Another study retrospectively evaluated 690 admissions for elective pediatric surgical procedures. [102] Bates and colleagues [103] found that at least 40 percent of repeat tests were redundant in a large teaching hospital. The history and physical examination indicated the probability of abnormalities in all 12 patients for whom an abnormality was detected by laboratory testing. Clinical diagnosis, and not laboratory testing, was the apparent basis for any change in operative plans. Narr and colleagues [23] at the Mayo Clinic found no harm from omitting *all* laboratory testing for ASA I patients. The sample size of this study was large enough to indicate that more harm than benefit would probably occur by testing ASA I patients. One exception should be noted: the median age of these patients was 21.4 years, making the conclusion about testing of ASA I patients more than 40 years of age unclear.

Several studies have compared groups of hospitalized patients undergoing routine laboratory screening tests (to supplement the history and physical examination) with groups not undergoing routine screening tests. Would outcome differ? Wood and Hoekelman [104] found that abnormal results from the history, physical examination, or laboratory examination changed the preoperative clinical course (for all, surgery was postponed) for 28 of 1,924 children. For only 3 of those 28 patients did laboratory tests indicate an abnormality not suggested by the history or physical examination. Thus, the history and physical examination dictated the appropriate laboratory testing for all but 3 of 1,924 patients.

A more specific conclusion is also possible. The abnormalities discovered for these three patients were found on chest radiographs. (These children were part of a study comparing perioperative outcome at two hospitals, one that required chest radiograph as a screening test for elective surgery in children and one that did not.) There were no differences noted in anesthetic or perioperative complications between the two groups. Therefore, Wood and Hoekelman [104] recommended that chest radiographs not be obtained routinely for apparently healthy children.

Even in a referral population, history and physical examination determine more than 90 percent of the clinical course when a patient is referred for consultation about cardiovascular, neurologic, or respiratory disease. [105] Other studies also have demonstrated that the history and physical examination accurately indicate all areas in which subsequent laboratory testing proves beneficial to patients. For example, Rabkin and Horne [106] [107] examined the records of 165 patients having a "new" abnormality on ECG that was "surgically significant" (i.e., a change from a previous tracing

that represents a condition possibly affecting perioperative management or outcome). In only two instances were anesthetic or surgical plans altered by the discovery of "new abnormalities" found on ECG but not indicated by history. Thus, even for these 165 patients, for which the benefits of a laboratory test should have been maximal because abnormalities were detected before surgery, the history or physical examination determined case management most of the time. Furthermore, for one of the two instances of altered case management (a patient who had atrial fibrillation), physical examination should have indicated the need for an ECG. A history or physical examination was not available for the other patient.

Table 23-4 shows that patients who benefit from testing have risk factors, symptoms, or other conditions in their history that call forth testing. In our own study (Apfelbaum JL et al, unpublished data), for patients who were symptomatic with risk factors for disease or who only had risk factors for disease, 606 (5.8%) of 10,419 test results were significantly abnormal. Of these, 124 tests (1.2%) affected care. Of these patients, 6 tests resulted in harm (6 in 10,419, or 0.06%), whereas 91 patients (91 in 10,419, or 0.9%) benefited from a change in care. By contrast, for asymptomatic patients who had no risk factors for disease, only 121 (1.1%) of the 10,899 tests results were significantly abnormal. Of these, 10 tests (13 in 10,899, or 0.01%) affected care. During the study, every change in care that benefited or harmed a patient stemmed from a single test result. Therefore, the 13 "care-affecting" tests represented 13 "care-affected" patients. Of these 13 patients, 5 (in 10,899, or 0.05%) asymptomatic patients were harmed, whereas only 1 (in 10,899 tests results, or 0.009%) of the patients benefited from a change in care. Neither harm nor benefit was thought to result from the other 7 changes in care.

In summary, the studies cited point to the lack of benefit from routine laboratory tests as a method of assessing patients preoperatively. Many of these laboratory tests have been shown to be superfluous to patient care management. History and physical examination are considered the most effective ways of screening for disease. Laboratory tests can be used to screen for disease when the patient has appropriate risk factors and when such tests have proved effective. However, the better use of such tests is to confirm clinical diagnoses or to optimize the patient's condition prior to surgery.

Patient Risk

Unnecessary testing may lead physicians to pursue and to treat patients with borderline and false-positive laboratory abnormalities (Ch. 25) . This observation does not imply that all standard screening tests should be discontinued. Some are beneficial, such as the mammogram for all women older than 40 or 50 years of age, [96] [108] the test for occult blood in stool for all people more than 40 years of age, [88] [89] [90] [92] [93] and the Papanicolaou (Pap) smear for sexually active females. [88] [89] [90] [92] [93] However, few studies have examined whether increased testing and the follow-up on falsepositive test results adversely affect patients. In one study addressing this issue, Roizen et al [56] retrospectively examined the adverse effects of chest radiographs on patients. For 606 patients, 386 additional chest radiographs were ordered without indication of need. Among those 386 patients, the discovery of only one abnormality (an elevated hemidiaphragm probably caused by phrenic nerve palsy) may have resulted in improved care for that patient. On the other hand, the existence of three lung shadows on chest radiographs led to three sets of invasive tests, including a thoracotomy, but no discovery of disease. These procedures caused considerable morbidity, including one pneumothorax and 4 months of disability, for those three patients.

Tape and Mushlin [109] found a similar result when examining the benefits and risks of chest radiographs obtained preoperatively in Rochester, New York. Of 341 patients admitted for vascular surgery, 9 had radiographic findings that led to clinical action. Specifically, three patients (two with congestive heart failure and one with pulmonary fibrosis) may have benefited from the findings. However, all three patients were known by history to have the disease shown on chest radiographs. In addition, six patients were subjected to a potentially detrimental clinical response. Two had a false diagnosis of tuberculosis, with subsequent therapy for one patient; two others had false diagnosis of nodules, and the last two had falsely normal chest radiographic readings. All the beneficial effects attributed to preoperative chest radiographs accrued to patients who had obvious clinical history of pulmonary or cardiac disease. Orkin [110] further explained the basis of the risk of testing asymptomatic patients.

Similarly, in another study we participated in, even though few patients benefited by preoperative testing that was warranted by history or risk factors (91 of 1,746), even fewer were harmed by such testing (1 patient) (Apfelbaum JL et al, unpublished data). By contrast, testing of asymptomatic patients was more risky than beneficial to patient health. Specifically, 1 in every 2,000 preoperative tests (1 in 300 patients) led to patient harm because of the pursuit of abnormalities indicated by those tests; 1 in 10,000 tests (1 in 1,746 patients) led to benefit (Apfelbaum JL et al, unpublished data).

In another study, Turnbull and Buck [78] examined the charts of 2,570 patients undergoing cholecystectomy to determine the value of preoperative tests. With four possible exceptions, history and physical examinations successfully indicated the need for all tests that ultimately benefited the patients. Again, for those four patients, it is doubtful that any benefit actually occurred as a result of preoperative tests. Among them was a patient who had emphysema detected only by chest radiograph. This patient had preoperative physiotherapy without subsequent postoperative complication. Two patients had unsuspected hypokalemia (potassium levels of 3.2 and 3.4 mEq/L in blood) and received treatment prior to operation. Current data in the literature indicate that no harm occurs to patients undergoing

surgery with this degree of hypokalemia and that severe harm may be caused by treating such patients with oral or intravenous administration of potassium (Table 23-5) . [111] [112] [113] [114] [115] The fourth patient possibly benefiting from preoperative testing had an asymptomatic hemoglobin concentration of 9.9 g/dL and was given a blood transfusion prior to cholecystectomy. Because cholecystectomy is not normally associated with major blood loss, one could conclude that this patient also received no benefit from preoperative laboratory testing and its pursuit but was exposed to the risk of transfusion.

TABLE 23-5 -- Risk of Potassium Supplementation[a]

	ROUTE OF ADMINISTRATION			
	ORAL	***IV***	***ORAL AND IV***	***ALL ROUTES***
Patients (no.)	1,910	2,192	819	921
Death	3 (0.2%)	3 (0.15%)	1 (0.1%)	7 (0.14%)
Life-threatening reaction or death	6 (0.3%)	7 (0.35%)	14 (1.7%)	28 (0.57%)
Hyperkalemia	74 (3.9%)	34 (1.6%)	71 (8.7%)	179 (3.6%)
Other side effects	53 (2.8%)	18 (0.8%)	33 (4.0%)	283 (5.7%)

Data from Lawson [114] and Lawson et al [115]

[a] One in 200 patients given potassium supplementation dies or has a life-threatening reaction.

Thus, it is not clear that any patient in this study benefited from preoperative screening tests given without indication for need by history or physical examination.

In another study, only 2 patients at most (who had eradication of asymptomatic bacteriuria) benefited from the 9,720 screening tests that were obtained. [116] At least one patient was seriously harmed from pursuit and treatment of abnormalities on screening tests. For this patient, atrial fibrillation and congestive heart failure developed after institution of thyroid therapy for borderline low thyroxine and free thyroxine index tests. It is unclear whether these investigators examined other patients for potential harm arising from the pursuit and treatment of abnormalities on screening tests.

To determine benefits and risks, screening mammography was evaluated in a real-life practice setting. [96] Although yearly screening was beneficial, more than 20 percent of the women who did not have disease were subjected to a breast biopsy. Furthermore, more than 49 percent of these "normal" women would have been subjected to a breast biopsy if each had had a yearly mammogram and clinical breast examination. Thus, even when benefits exceed risk, there is substantial risk to routine testing.

TABLE 23-6 -- Unrecorded Abnormalities on Preoperative Tests

SERIES	TYPE TEST	UNEXPECTED ABNORMALITIES (*n*)	UNEXPECTED ABNORMALITIES NOTED ON CHART PREOPERATIVELY[a] (%)
Lorenzi and Cohen [b]	PT/PTT	20	5
Rabkin and Horne [106] [107]	ECG	157	31
Kaplan et al [76]	CBC/PTT		
	Glucose/SMA 6	12 [c]	17
Robbins and Rose [117]	PT	23	39
Wood and Hoekelman [104]	Hematocrit	15 [c]	27
Parkerson [118] [119] , [d]	Multiple	343	38
	Multiple; >10% abnormal	63?	60
Williamson et al [120] , [d]	Urinalysis	164	17
	FBS	63	32
	Hemoglobin	32	16
Huntley et al [121] , [d]	Multiple	343	67
Daughaday et al [122]	Multiple	167	60
Epstein et al [123]	T_4	111	60
Wheeler et al [124]	Hemoglobin	258	71
Kelley and Mamlin [125] , [d]	Multiple	852	64-85
Wolf-Klein et al [98] , [d]	Multiple	756	7-73 (avg. 50)
Lawrence and Kroenke [87]	Urinalysis	180	29
Umbach et al [126]	Chest radiographs	116	59
Narr et al [75]	Multiple	160	40
O'Connor and Drasner [81]	Hemoglobin and urinalysis	97	51

CBC, complete blood count; ECG, electrocardiogram; FBS, fasting blood sugar; PT, prothrombin time; PTT, partial thromboplastin time; SMA 6, simultaneous multichannel analyses of sodium, potassium, chloride, bicarbonate, urea nitrogen, and creatinine levels in blood; T_4, thyroxine

[a] Recording of an unexpected abnormality on the patient's chart, either preoperatively or at any time other than on the laboratory test report printout
[b] Personal communication
[c] Abnormalities potentially significant to perioperative management
[d] Test not obtained preoperatively.

Medicolegal Liability

"Extra testing"--testing not warranted by findings on a medical history--does not provide medicolegal protection against liability (Ch. 85) . Studies show that 30 to 95 percent of all unexpected abnormalities found on preoperative laboratory tests are not noted on the chart before surgery [76] [87] [98] [104] [106] [107] [117] [118] [119] [120] [121] [121] [122] [124] [125] [126] (Table 23-6) . This lack of notation occurs not only at university medical centers but at community hospitals as well.

Moreover, the failure to pursue an abnormality appropriately poses a greater risk of medicolegal liability than does failure to detect that abnormality. [127] In this way, extra testing increases the medicolegal risk to physicians. In addition, the Health Care Financing Administration is attempting to make failure to pursue abnormalities grounds for charging physicians with inadequate practice. However, such lack of attention to unexpected abnormalities is a completely reasonable response: the foregoing data [128] (Fig. 23-2) (Figure Not Available) indicate that most unexpected abnormalities in asymptomatic patients occur in patients who are actually healthy.

Furthermore, pursuit of unexpected abnormalities in asymptomatic patients is more likely to harm than to benefit such patients. For these reasons, we differ with Ross and Tinker, [129] who seem to believe that obtaining an unindicated test poses no liability if it is pursued. It is logical that pursuit of unindicated testing poses liability, because the tests were not warranted, and the statistics of testing theory and data in the literature indicate that the pursuit of such abnormalities is more likely to cause harm than to prove beneficial. Thus, the problems associated with nonselective batteries of tests include both direct and indirect risks to patients and society (Table 23-7) .

Operating Room Schedules

According to hospital administrators in the United States, surgeons say they order preoperative tests to satisfy anesthesiologists: surgeons find it easier just to order all the tests and let the anesthesiologist analyze them. Surgeons also believe that it is much more efficient to order batteries of tests than to have an anesthesiologist, who sees the patient the night before or the morning of surgery, obtain the tests on an emergency basis. This line of reasoning overlooks the fact that abnormalities arising from tests performed in the battery fashion are usually not discovered until the night before or the morning of surgery, if at all. Then, the discovery of abnormal results delays or postpones OR schedules, because effort and time are wasted to obtain consultant review of false-positive or slightly abnormal results. Moreover, data show clear cost reductions from delegating test selection to anesthesiologists, [26] [27] [28] [29] [30] as well as other benefits from educational practices that are discussed later in this chapter. [5] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [43] [44] [45] [46] [47] [130] [131] See also Chapter 82 .

PREOPERATIVE TESTING

Most hospitals, many anesthesia departments, many outpatient surgical centers, and now many office-based surgical facilities have rather arbitrary rules and recommendations regarding tests that should be performed before elective surgery. With good intentions, anesthesiologists tried to follow those rules, and problems began. The inexpensive multiphasic screening batteries of tests subsequently developed by the Kaiser Hospitals and Health Plan seemed to be the answer to this confusing and arbitrary process. [132] Physicians believed that they could now order inexpensive batteries of

Figure 23-2 (Figure Not Available) Probability of at least one abnormal result on multiple independent trials of tests, each with a probability (P_N) of a normal result, for selected values of P_N . *(From Berwick [126])*

TABLE 23-7 -- Consequences of Using Nonselective Batteries of Preoperative Tests

	CONSEQUENCES
Direct risks to patients	*False-positive* results (i.e., an erroneous "abnormality" on a radiograph or electrocardiogram) may initiate follow-up activities that are harmful to the patient.
	False-negative results encourage the overlooking of true problems or instill a false sense of security.
Indirect risk to patients	Diverts physician's attention to nonvital issues.
Cost to society	Reduces resources available to care for others.
Cost to physicians	Failure to pursue abnormalities increases medicolegal risks.

tests and thus efficiently screen for disease. However, physicians were still trying to determine which tests to order before surgery and what to do with the unexpectedly abnormal result on the morning of surgery. Kaiser found that this system of preoperative multiphasic screening was not practical. [133] The system produced so many false-positive and false-negative results that the subsequent harm vastly outweighed any possible benefit. Nevertheless, the notion of "the more testing, the better" still remains.

Low Predictive Value of an "Abnormal" Laboratory Test Result

Understanding what constitutes an "abnormal" laboratory test result requires an appreciation of the way "normal" values are determined. A normal range is based on the typical distribution of the gaussian curve. [134] For example, assuming a gaussian distribution and hemoglobin values of 13.5 to 16.7 g/dL ("reference range") for healthy men, one can expect 5 percent of "normal" men to have a test result outside that range.

Of prime importance in preoperative evaluation is knowing the percentage of abnormal laboratory test values that truly indicates disease. If the anesthetic management of a patient is altered because of test abnormality, that abnormality should indicate a condition (1) that poses a significant risk of preoperative morbidity that can be lessened by preoperative treatment, (2) that cannot be discovered through history-taking and physical examination, and (3) that is sufficiently prevalent in the population to justify the risk of performing the follow-up test. To be cost-efficient, the test should be sufficiently "sensitive" (have "positivity in disease") and sufficiently "specific" (have "negativity in health"); that is, test results should be positive if the patient has disease and negative if the patient is healthy. [133] [134] [135] [136] [137] In fact, what a clinician really wants to know is what a positive or negative test means for the individual patient. The values representing the predictive ability of a positive or negative test ("positive predictive values" and "negative predictive values") depend on the pretest population probability. [137] [138] [139]

We should now consider the significance of false-positive and false-negative results and the prevalence of disease in the test population in relation to abnormal laboratory test results. (We are indebted to Drs. Jorgen Hilden and Anders Hald, whose comments have helped to make this section clearer.) For example, patients with pneumonia would have the notation "pneumonia" (or some significant abnormality) written as the diagnosis on their chest radiograph reports. Let us also assume that the specificity of a test (its negativity in health) is 98.3 percent; that is, 983 of 1,000 people who actually do not have asymptomatic pneumonia have a comment such as "without evidence of pneumonia" or "normal" written on their chest radiograph reports. Let us further assume that 0.5 percent of the asymptomatic population younger than age 40 who are about to undergo routine elective surgery has pneumonia. Given the preceding assumptions, what is the likelihood that a person whose chest radiograph report reads "pneumonia" would actually have pneumonia?

If we test 100,000 asymptomatic persons, and 0.5 percent are assumed to be diseased, this means that 500 people would have undetected pneumonia. If the sensitivity of chest radiographs to pneumonia is assumed to be 75 percent, 375 of these people would have abnormal radiographs. Then, if specificity is assumed to be 98.3 percent, 97,809 of the 99,500 healthy people would have normal results on chest radiographs. This means that 1,691 (1.7%) would have abnormal radiographic results. Thus, of 2,066 patients having a diagnosis of pneumonia based on chest radiographs, 1,691 (82%) of the results would be falsely positive. Therefore, it is entirely possible that 82 percent of the chest radiographs indicating "infiltrate compatible with pneumonia" in otherwise asymptomatic persons would actually be describing totally healthy people. Expressed in another way, when the foregoing assumptions are applied, the likelihood that an asymptomatic person would actually have pneumonia when the chest radiograph contains that notation is only 18 percent; that is, for this patient group, the predictive value of a positive test (the "positive predictive value") is only 18 percent.

Only patients with abnormal test results who actually have disease ("true positives") benefit from laboratory testing. Let us assume that 2.2 percent of the chest radiographs in the population younger than age 40 are positive, and that for each true-positive, perioperative mortality decreases by 50 percent. If we use the 82 percent false-positive rate derived previously, the number of patients benefiting per 1,000 radiographs is 3.9 (true-positives per 1,000 = all positives - false positives, i.e., [2.2% × 1,000] - [82% × 2.2% × 1,000] = 3.9 patients). Therefore, a reduction in operative mortality of 50 percent, or 1 per 20,000 (i.e., 3.9 × 0.5 × 0.00005), gives 0.000095 fewer deaths per 1,000 operations when preoperative chest radiographs are obtained.

Hilden and Hald (personal communication) question whether this is a logical calculation. One study, for example, analyzed outcomes for asymptomatic patients. [140] The death rate for this group was 1 in 10,000. Of these deaths, more than 90 percent were caused by avoidable problems unrelated to unknown diseases. Therefore, at most, fewer than 10 percent of the deaths among asymptomatic individuals could be attributed to preoperative conditions, and probably fewer than 10 percent of those deaths (or <1% of the total, or 1 in 1,000,000) would be related to pneumonia. Thus, the intuitive value is similar to what we have estimated. Furthermore, from an examination of the data in Tables 23-4 and 23-8 , it is evident that few chest radiographs in the asymptomatic population younger than age 40 led to benefit. In

addition, the harm from these tests has not yet been considered.

TABLE 23-8 -- Screening Chest Radiographs: Incidence of Abnormal Test Results, the Discovery of Which May Change Management of Anesthesia

AGE (Y)	SERIES	PATIENTS EXAMINED (*n*)	ABNORMALITIES[a] (%)	NEW ABNORMALITIES[b] (%)
0-14	Farnsworth et al [145]	350	8.9	0.3
0-18	Brill et al [146]	1,000	1.9	0.7
0-19	Sagel et al [147]	521	0	0
0-19	Sane et al [148]	1,500	5.4	2.2
0-19	Wood and Hoekelman [104]	749	4.7	1.2
1-20	Rees et al [149]	46	0	0
20-29	Sagel et al [147]	894	1	--
21-30	Rees et al [149]	62	3	--
30	Loder [150]	437	10.1	0.2
30	Hubbell et al [151]	12	0	0
30	Maigaard et al [152]	1,256	4.5	0
0-39	Umbach et al [126]	305	3.0	--
30-39	Sagel et al [147]	942	2.3	--
40	Catchlove et al [153]	29	0	0
40	Collen et al [132]	15,978	2.1	--
40	Sagel et al [147]	2,357	1.3	1.3
40	McKee and Scott [77] , [c]	26	7.7	3.9
40	Combined [77] [126] [145] [146] [147] [148] [150] [151] [152] [153] , [d]	6,787	4.0	0.8
40-49	Sagel et al [147]	928	7.1	
<40	Velanovich [166]	--	3.1	--
40-49	Umbach et al [126]	290	6.2	--
40-59	Collen et al [132]	21,489	7.4	--
41-50	Hubbell et al [151]	28	17.9	0
41-50	Rees et al [149]	119	19	--
41-50	McKee and Scott [77] , [c]	53	17	0
30-69	Loder [150]	515	6.0	--
31-40	Rees et al [149]	93	13	--
31-40	Hubbell et al [151]	22	22.5	4.5
40-60	Velanovich [166]	NA	23.9	--
40	Sagel et al [147]	3,689	23.9	6.0
40	Catchlove et al [153]	50	0	0
40	Thomsen et al [154]	1,823	2.3	0.2
50-59	Umbach et al [126]	247	10.9	--
50-59	Sagel et al [147]	733	20.3	--
51-60	Hubbell et al [151]	87	36.8	4.4
51-60	Rees et al [149]	121	40.0	--
51-60	McKee and Scott [77] , [c]	85	40.0	0
>55	Gupta et al [155] , [c]	346	5.5	0.9
60-69	Umbach et al [126]	202	13.3	--
60-69	Sagel et al [147]	977	29.7	--
61-70	Boghosian and Mooradian [156]	78	49	--
>60	Boghosian and Mooradian [156]			
	Without risk factors [c]	44	34.0	--
	With risk factors	92	62.0	--
>60	Collen et al [132]	7,196	19.2	--
>60	Hubbell et al [151]	145	44.1	4.8 [e]
>60	McKee and Scott [77] , [c]	163	44.2	1.9
>60	Velanovich [166]	NA	31.9	--
61-70	Rees et al [149]	134	43.3	--

61-70	Hubbell et al [151]	94	36.2	5.4
>65	Sewell et al [157]	28	21	--
69	Loder [150]	48	72.9	--
?70	Wolf-Klein et al [98]	500	1.9	--
70	Sagel et al [147]	832	41.7	--
70	Tornebrandt and Fletcher [158]	100	37	8.1?
70	Boghosian and Mooradian [156]			
	Without risk factors [c]	58	59	--
	With risk factors	45	64	--
71	Levinstein et al [116]	121	84.4	0.9
70-79	Umbach et al [126]	110	27.2	--
71-80	Rees et al [149]	76	61.8	--
71-80	Hubbell et al [151]	28	57.1	0
>80	Umbach et al [126]	21	33.3	--
>80	Hubbell et al [151]	23	60.9	8.7
20-89	Fink et al [159]	127	46	--
74-97	Domoto et al [97]	69	72.5	33
>81	Rees et al [149]	16	68.8	--
?0-?90	Wiencek et al [160]	403	25.1	2.4
0-90	Delahunt and Turnbull [101]	860	--	0
24-90	Tape and Mushlin [109] , [f]	318	33	0
0-?90	Petterson and Janower [161]	1,530	9.8	1.3
0-?90	Turnbull and Buck [78] , [f]	691	5.5	--
0-?90	Royal College [162]	3,052	3.8	--
0-?90	Rucker et al [163] , [c]	371	0.3	--
0-?90	Blery et al [91]	2,765	0.7	0.1
0-90+	Weibman et al [164] , [f]	734	5.0	--
0-90+	Muskett and McGreevy [80]	119	29.4	5.0
0-90+	Gagner and Chiasson [165]	1,000	7.4	--

[a] These data constitute an edited summary of the date presented by various articles, edited to select abnormalaties that might change management of anesthesia.
[b] Abnormalities not already known or suspected by history or physical examination
[c] Patients were asymptomatic.
[d] Combined studies in younger-than-40 population excluding two studies, those by rees al [149] and Collen et al [132]
[e] 0% changed treatment.
[f] Tape amd Mushlin [109] studied vascular surgery patients; Turnbull and Buck, [78] chp;ecystectomy patients; abd weibman and colleagues, [164] cancer patients.

Translating this figure into the present value for years of life saved per 1,000 chest radiographs yields the following: 0.000095 fewer deaths per 1,000 operations × 22.62 years saved per life saved = 0.0022 years of life. The figure 22.62 is the present value of 60 more years of life for a 20-year-old, per Neuhauser. [134] At the University of Chicago, this 0.0022 years of life saved would cost $78,000 (anteroposterior and lateral chest radiographs cost $78, not including fees for consultations, repeated radiographs, or other laboratory tests or procedures). Therefore, each year of life saved by obtaining chest radiographs costs about $35,500,000 ($78,000 divided by 0.0022).

However, just as there are other costs (e.g., pursuing some false-positive chest shadows results in computed tomographic needle biopsies and lobectomies in totally healthy patients [74] [75] [76] [77]), there are other benefits (e.g., treatment of some patients having solitary nodules or mediastinal masses may prolong life). Let us arbitrarily assume that these costs and benefits are equal. One is forced to conclude that screening for an asymptomatic disease having a low prevalence rate is a very expensive and possibly risky procedure.

Simplified Benefit-Risk Analysis of Testing

The foregoing analysis is only a cost-benefit analysis and not a benefit-risk analysis and therefore disregards the possible harm of unwarranted testing, which in fact does incur risk (Fig. 23-3) . Let us assume that the chest radiograph in the population younger than age 40 has a sensitivity of 75 percent and a specificity of 95 percent. (These values are better than the best in the literature for readings referenced by a single radiologist.) Let us also assume that the prevalence of disease

detectable by the test is 0.5 percent, that the benefit from true-positives is 20 in 100 (better than the best in the literature) [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] (see Table 23-4) (Apfelbaum JL et al, unpublished data), and that harm from false-positive results is 6 in 100 (see earlier discussion) [56] [109] (Apfelbaum JL et al, unpublished data). For the asymptomatic population younger than age 40, the result would be harm to 3 individuals and benefit to only 0.8 individuals per 1,000 chest radiographs (Table 23-9) . Similar analyses are possible for other tests and situations (see Table 23-9).

Lead-Time and Length-Time Biases

Two important concepts related to the reported benefits and risks of screening tests deserve consideration: lead-time and length-time biases. [141] These two factors can indicate an apparent benefit of testing when there is none. Let us examine screening for lung cancer in smokers and screening for breast cancer. In a Czechoslovakian trial of screening of smokers, men at high risk were randomly assigned to either chest radiography twice a year or to no screening. [142] No difference in mortality from lung cancer occurred. However, the 5-year survival rate from the time of diagnosis was 23 percent for the screened group and 0 percent for the control group. Thus, this apparent improvement was entirely owing to earlier diagnosis ("lead-time bias"). In fact, mortality from lung cancer was actually higher in the

screened group, indicating that the real effect of screening and subsequent intervention was negative.

Black and Welch [141] reviewed the only other trial of screening strategies using diagnostic radiology evaluated in a randomized trial. In the only randomized trial of mammographic screening--the Malmo mammographic screening trial [143] --the benefits of this test also seem to disappear. Women older than 45 years of age were randomly assigned

Figure 23-3 Theory and actuality of what happens to well-being as testing increases. The straight line represents the common theory that "the more testing, the better," that is, that well-being increases with testing. The A-to-E curve shows what actually happens as testing increases. At a certain point (C), more harm than good may result. Therefore, point C represents the optimal point in the well-being versus testing relationship. The goal of using guidelines is to direct resources from point E to point C (to reduce testing and to increase well-being). Unless health-care providers allocate health resources in a cost-efficient manner, governmental restrictions will move testing from point C to point A, that is, will ration testing that improves well-being

to either regular mammography or no screening. Although survival from the time of diagnosis was 80 percent higher for the screened group, no difference existed in mortality from the time of randomization. Thus, the apparent increase in the survival rate for screened patients was entirely owing to lead-time bias (earlier diagnosis) and length-time bias (less severe cases diagnosed) associated with screening test detection, and not to any benefit from the screening strategy itself.

Before one concludes that no testing should occur preoperatively, let us remember that detection of subclinical conditions in high-risk groups and optimization of therapy for clinical conditions can result in less perioperative morbidity, fewer changes in perioperative plans, and better informed discussions of risk with the patient and significant others.

Laboratory Test Abnormalities in Asymptomatic Populations

Does Surgical Procedure Influence Laboratory Test Choice and Requirements?

A decade ago, the answer to this question was no. Today, the answer is yes. Some operations incur such low rates of morbidity and mortality that a test is not indicated unless it is necessary for "routine" preventive care of the patient. Examples are diagnostic knee arthroscopy and cataract extraction. [144] Table 23-10 divides procedures into three types. Type A procedures are minimally invasive operations that produce little tissue trauma and minimal blood loss. We believe that *no* laboratory testing is indicated for these operations, based on preoperative status alone (such a division was proposed in the ASA's draft guidelines for preanesthesia evaluation). Obviously, some laboratory testing may be required for patients undergoing such procedures, in order to provide preventive care for those patients or to optimize their medical condition (even a haircut can pose a risk for someone in severe congestive heart failure). On the other hand, type B and C procedures are progressively more risky and invasive. For these procedures, it becomes increasingly important to optimize any adverse conditions--even the less severe ones--that exist preoperatively. Therefore, type B and C procedures often require more preoperative testing.

TABLE 23-9 -- Hypothetic Benefit-Risk Analyses for Two Tests, Under Three Circumstances

TEST:	CHEST RADIOGRAPH	ELECTROCARDIOGRAM	
PATIENT:	**< 40-YEAR-OLD ASYMPTOMATIC PATIENT**	**30-YEAR-OLD ASYMPTOMATIC MAN, TO SEARCH FOR MI**	**47-YEAR-OLD ASYMPTOMATIC MAN, TO SEARCH FOR MI AND CONDUCTION DISTURBANCE**
Sensitivity of test	75%	33%	50%
Specificity of test	95%	90%	90%
Prevalence of disease detectable by test	0.5%	2.1%	15%
Benefit from true-positives	20%	20%	20%
Harm rate for false-positives	6%	6%	6%
Benefit per 1,000 patients			
Predicted true-positives	3.8	7	75
Benefited patients	0.8	1.4	15
Harm per 1,000 patients			
Predicted false-positives	49	97.9	85
Harmed patients	3	5.9	5.1
Conclusion:	*Harm greater than benefit: do not test!*		*Benefit greater than harm: test!*

MI, myocardial infarction

TABLE 23-10 -- Types of Surgical Procedures for Which Anesthesia May Be Administered

TYPE	GENERAL DEFINITION	SPECIFIC EXAMPLES
Type A	*Minimally invasive* procedures that have little potential to disrupt normal physiology and are associated with only rare periprocedural morbidity related to the anesthetic. These procedures rarely require blood administration, invasive monitoring, and/or postoperative management in a critical care setting.	Cataract extraction, diagnostic arthroscopy, postpartum interval tubal ligation
Type B	*Moderately invasive* procedures that have a modest or intermediate potential to disrupt normal physiology. These procedures may require blood administration, invasive monitoring, or postoperative management in a critical care setting.	Carotid endarterectomy, transurethral resection of the prostate, and laparoscopic cholecystectomy
Type C	*Highly invasive* procedures that typically produce significant disruption of normal physiology. These procedures commonly require blood administration, invasive monitoring, or postoperative management in a critical care setting.	Total hip replacement, open aortic aneurysm resection, aortic valve replacement, and posterior fossa craniotomy for aneurysm

Chest Radiographs

What abnormalities on chest radiographs would influence management of anesthesia? Certainly, it may be important to know about the existence of the following conditions before proceeding to anesthesia and surgery: tracheal deviation or compression; mediastinal masses; pulmonary nodules; a solitary lung mass; aortic aneurysm; pulmonary edema; pneumonia; atelectasis; new fractures of the vertebrae, ribs, and clavicles; dextrocardia; or cardiomegaly. However, a chest radiograph probably would not detect the degree of chronic lung disease requiring a change in anesthetic technique any better than would the history or physical examination. Table 23-8 [77] [78] [80] [91] [97] [98] [104] [132] [145] [146] [147] [148] [149] [150] [151] [152] [153] [154] [155] [156] [157] [158] [159] [160] [161] [162] [163] [164] [165] [166] shows the prevalence of conditions that a chest radiograph may detect. These data show that abnormalities are rare in the asymptomatic individual. In fact, the risks associated with chest radiographs probably exceed their possible benefit if the patient is asymptomatic and younger than 75 years. This analysis is predicated on maximizing benefit to all patients as a general

group, because one cannot say which individual patients will benefit and which will be harmed. Thus, chest radiographs are not warranted for any asymptomatic patient who is less than 75 years of age and free of risk factors. In fact, this conclusion may apply to patients older than 75 years of age as well.

Electrocardiograms

The incidence of ECG abnormalities has been determined by studies on patients (Hsu J et al, unpublished data) [78] [79] [132] [133] [167] [168] [169] [170] [171] [172] [173] and epidemiologic surveys of healthy people (Ch. 32) . [146] The abnormalities on ECG that have the potential to alter management of anesthesia are as follows: atrial flutter or fibrillation; first-, second-, and third-degree atrioventricular block; changes in ST segment suggesting myocardial ischemia or recent pulmonary embolism; premature ventricular and atrial contractions; left or right ventricular hypertrophy; short P-R interval; Wolff-Parkinson-White syndrome; myocardial infarction; prolonged QT segment; and tall peaked T waves. What is the incidence of finding these abnormalities on the 12-lead preoperative screening ECG but not on a standard monitor lead I or an MCL_5 lead applied immediately before induction of anesthesia in the OR?

Before answering that question, some qualifiers apply. First, few of the studies on the incidence of ECG abnormalities (Apfelbaum JL et al, unpublished data) [78] [79] [167] excluded patients having histories or physical examinations indicating cardiac problems. Second, the studies do not distinguish those findings evident on monitoring leads from findings evident on only 6-lead or 12-lead ECGs [77] [78] [79] [91] [98] [106] [107] [116] [132] [152] [166] [167] [168] [169] [170] [171] [172] [173] [174] [175] (Table 23-11) .

The data in Table 23-11 and elsewhere [175] [176] show that abnormalities on ECG are relatively common and increase exponentially with age. Averaging all those data indicates that the incidence of abnormal preoperative ECG results would exceed 10 percent at 40 years of age and would be 25 percent by 60 years of age. These estimates pool abnormalities for both sexes. Clearly, those studies that looked for abnormalities on ECG after first ensuring the patient was asymptomatic (McKee and Scott, [77] Yipintsoi et al, [167] and Blery et al [91]) found a much lower incidence of significant abnormalities. McKee and Scott [77] found no abnormalities significant to perioperative care for 160 individuals who had no cardiac symptoms and were less than 60 years of age, and only 2 abnormalities for 163 patients older than 60 years of age. Moorman and colleagues [172] found only 1 of 275 asymptomatic patients 45 years of age or younger who had abnormalities on preoperative ECG. In the study by Blery and coworkers, [91] only 0.6 percent of 2,256 patients younger than age 40 who had no cardiac or pulmonary symptoms had an abnormality on preoperative ECG. Our group found no abnormalities on ECG that were significant to, or altered, perioperative care among 510 patients judged to be asymptomatic

TABLE 23-11 -- Percentage of Patients Having Abnormalities Determined by Screening Electrocardiograms [a]

AGE (Y)	SEX	SERIES	PATIENTS EXAMINED (*n*)	TOTAL ABNORMALITIES [b] (%)	SPECIFIC ABNORMALITIES (%)			
					LVH	MI	ST CHANGES	AV BLOCK
16-19	M	Ostrander et al [169]	216	20.3	17.8	0.0	0.9	1.4
16-19	F	Ostrander et al [169]	24	5.9	1.3	0.0	4.2	0.4
20-29	M	Ostrander et al [169]	452	14.0	7.1	0.2	6.0	0.7
20-29	F	Ostrander et al [169]	577	11.3	0.2	0.2	9.9	1.0
20-29	M	Collen et al [132]	3,000	9.6	--	--	--	--
30-39	F	Collen et al [132]	4,000 [c]	9.3	--	--	--	--
>30	Either	Maigaard et al [152]	1,256	>4.5	--	0.1	--	--
30-39	M	Ostrander et al [169]	676	--	3.0	0.0	6.9	1.3
30-39	F	Ostrander et al [169]	699	--	0.4	0.1	11.6	1.6
30-39	M	Collen et al [132]	4,000 [c]	12.1	--	--	--	--
30-39	F	Collen et al [132]	5,000 [c]	11.7	--	--	--	--
35-44	M	Kannel et al [168] [170]	--	--	2.9	--	--	--
35-44	F	Kannel et al [168] [170]	--	--	0.9	--	--	--
<40	Either	Blery et al [91] , [d]	2,256	0.6	--	--	--	--
<40	Either	Apfelbaum et al [171] , [d] , [e]	510	0	--	--	--	--
<40	Either	McKee and Scott [77] , [d]	23	13 (0)	--	--	--	--
<40	Either	Gold et al [174]	94	37	--	--	--	--
<40	Either	Velanovich [166]	NA	15.8	--	--	--	--
>40	Either	Johnson et al [79]	212	66	2.8	13.2	23.1	2.8
40-49	M	Ostrander et al [169]	468	24 [a]	4.1	1.7	16.1	1.5
40-49	F	Ostrander et al [169]	474	21 [c]	0.6	0.8	17.2	0.6
40-49	M	Collen et al [132]	4,000 [c]	17.6	--	--	--	--
40-49	F	Collen et al [132]	5,000 [c]	15.6	--	--	--	--
40-49	Either	Gold et al [174]	260	36	--	--	--	--
41-50	Either	McKee and Scott [77] , [d]	53	1.9 (0)	--	--	--	--
<45	?	Moorman et al [172] , [d]	275	0.4	--	--	--	--
45-54	M	Kannel et al [168] [170]	--	--	4.8	--	--	--
45-54	F	Kannel et al [168] [170]	--	--	3.6	--	--	--
40-60	Either	Velanovich [166]	NA	47.5	--	--	--	--
>45	?	Moorman et al [172] , [d]	500	1.4	--	--	--	--
>50	Either	Yipintsoi et al [167]	424 [d]	14.4 [d]	--	--	--	--
50-59	M	Ostrander et al [169]	330	30 [c]	3.3	5.1	20.8	1.2
50-59	F	Ostrander et al [169]	327	40 [c]	3.4	0.9	32.4	2.1
50-59	M	Collen et al [132]	5,000 [c]	24.9	--	--	--	--
50-59	F	Collen et al [132]	6,000 [c]	20.7	--	--	--	--
50-59	Either	Gold et al [174]	163	44	--	--	--	--
51-60	Either	McKee and Scott [77] , [d]	84	23.8 (0)	--	--	--	--
55-64	M	Kannel et al [168] [170]	--	--	10.1	--	--	--
55-64	F	Kannel et al [168] [170]	--	--	4.1	--	--	--
<60	Either	Rabkin and Horne [106] [107]	309	13.5	2.5	1.6	11.0	1.0
>60	Either	Rabkin and Horne [106] [107]	503	24.4	2.2	1.9	13.0	0.6

			--	42.3	--	--	--	--
>60	Either	McKee and Scott [77] , [d]	163	(1.3)	--	--	--	--
>60	Either	Gold et al [174]	134	62	--	--	--	--
>60	Either	Velanovich [166]	--	61.5	--	--	--	--
>65	Either	Seymour et al [173]	222	52.7				
60-69	M	Ostrander et al [169]	177	--	8.4	9.0	37.1	4.5
60-69	F	Ostrander et al [169]	196	--	10.2	6.1	42.4	4.1
60-69	M	Collen et al [132]	2,000 [c]	35.1	--	--	--	--
60-69	F	Collen et al [132]	3,000 [c]	29.7	--	--	--	--
65-74	M	Kannel et al [168] [170]	--	--	7.1	--	--	--
65-74	F	Kannel et al [168] [170]	--	--	9.6	--	--	--
>?70	Either	Wolf-Klein et al [98]	500	11.9	--	--	--	--
>70	M	Collen et al [132]	1,000 [c]	52.2	--	--	--	--
>70	F	Collen et al [132]	1,000 [c]	41.2	--	--	--	--
71	Either	Levinstein et al [116]	121	24.4	0.7	13.8	6.3	3.6
70-79	M	Ostrander et al [169]	100	--	7.9	9.9	46.5	7.9
70-79	F	Ostrander et al [169]	119	--	11.8	2.5	43.8	6.7
74-97	Either	Domoto et al [97]	69	27.5	--	--	--	--
>80	M	Ostrander et al [169]	26	--	11.5	7.7	46.2	19.2
>80	F	Ostrander et al [169]	43	--	16.3	4.7	58.2	9.3
0-?90	Either	Blery et al [91] , [d]	2,256	0.6 (0.3)	--	--	--	--
0-?90	Either	Turnbull and Buck [41]	632	14.6	Combined: 0.67			
0-?90	Either	Muskett and McGreevy [8C] , [d]	145	1.3	--	--	--	--

AV, atrioventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction

[a] All studies are 12-lead studies, except for that of Collen et al, [132] which is a 6-lead study.
[b] These data constitute an edited summary of data given in several series, edited to select abnormalities that might change management of anesthesia. *Numbers in parentheses indicate abnormalities judged retrospectively by the authors of the paper to be significant to perioperative management.*
[c] Values are approximations that represent "best-guess" numbers from data not explicitly stated in the reports.
[d] Patients were asymptomatic
[e] Apfelbaum JL et al, unpublished data (patients were asymptomatic)

on the basis of results from a video questionnaire [171] (Apfelbaum JL et al, unpublished data). This study is discussed later in the chapter.

How useful is it to repeat an ECG if the patient has had an ECG within the past 2 years? Rabkin and Horne [106] [107] addressed this question. "New abnormalities" on a subsequent ECG occur with significant frequency, approximately 25 to 50 percent as frequently as all abnormalities occurring on the previous ECG (Table 23-12) . Thus, one would be justified in obtaining a screening ECG prior to elective surgery for all patients older than 40 years of age, even those who have recently had an ECG, if it is older than 2 months or was abnormal. (See Table 23-9 for an analysis of the risk versus benefit of obtaining an ECG for asymptomatic patients.)

Some physicians have questioned even that conclusion. Goldberger and O'Konski [176] believe that the most important potential benefit of the preoperative ECG is detection of previously unrecognized myocardial infarction. This risk increases with age. However, even for the highest-risk group, men 75 years of age or older, the estimated incidence of unrecognized Q-wave infarction within the preceding 6 months is relatively small (<0.5%). Goldberger and O'Konski concluded that the risk of obtaining a preoperative ECG and subsequent reactions probably exceeds its benefit if patients are asymptomatic, do not have important risk factors for coronary disease, and are less than 45 (men) or 55 (women) years of age. If the data in Table 23-11 are used and the benefit-risk analysis described in the section on chest radiographs is applied, an ECG is indicated for asymptomatic patients undergoing type B or C procedures who are more than 40 (men) or 50 (women) years of age.

These processes do not account for the differences in physiologic age that exist among patients of the same calendar age. We believe that those differences are important. Although we also believe that physiologic age ("RealAge" [177] [*]) should be the factor used to determine the need for testing, this hypothesis has not been widely tested. We know that conditions such as normal blood pressure, regular vigorous exercise, the absence of exposure to cigarette smoke, and

* Dr. Roizen is a scientific advisor to RealAge, Inc.; he has an equity interest in that company, and he has a book published by Harper Collins, entitled *RealAge: Are You As Young As You Can Be?*

TABLE 23-12 -- Patients Found to Have a New Abnormality on Electrocardiogram and a Previous Electrocardiogram [a]

	NEW ABNORMALITY WITH A PREVIOUSLY			
	NORMAL ECG		*ABNORMAL ECG*	
Age (y)	<60	60	<60	60
No. of patients/total no.	18/180	42/192	24/129	81/310
% new abnormalities	(10%)	(21.9%)	(18.6%)	(26%)
Abnormality				
T wave	11 (6.1%)	18 (9.4%)	10 (7.8%)	19 (6.1%)
ST segment	7 (3.9%)	9 (4.7%)	6 (4.7%)	20 (6.4%)
Arrhythmias				
SVT or PVC	3 (1.7%)	7 (3.6%)		8 (2.6%)
Others, including PAC	3 (1.7%)	6 (3.1%)	1 (0.8%)	1 (0.3%)
QRS duration		8 (4.2%)	2 (1.6%)	14 (4.5%)
LVH	3 (1.7%)	4 (2.1%)	5 (3.9%)	7 (2.3%)
Q wave	4 (2.2%)	3 (1.6%)	1 (0.8%)	7 (2.3%)
Ventricular conduction defects	5 (2.6%)	1 (0.8%)	7 (2.3%)	7 (2.3%)
AV block	2 (1.0%)	3 (2.3%)	1 (0.3%)	

AV, atrioventricular; ECG, electrocardiogram; LVH, left ventricular hypertrophy; PAC, premature atrial contractions; PVC, premature ventricular contractions; SVT, supraventricular tachycardia

Data from Rabkin and Horne [106] [107]

[a] Numbers in parentheses are percentages of patients; two-thirds of patients had a previous ECG within 2 years of their new ECG.

control of stress can all decrease physiologic age ("RealAge" [177]) by more than 8 years. Therefore, we delay routine ordering of ECGs for 10 calendar years for any male or female patient for whom these advantageous conditions apply.

Hemoglobin Level, Hematocrit Level, and White Blood Cell Counts

The classic references on hemoglobin level, hematocrit level, and white blood cell counts, and the inferences they allow, have stood the test of time. We describe them now, so that the reader will understand the rationale for decisions and practices used even today.

Wasserman and Gilbert [178] found that of 28 patients with uncontrolled polycythemia (hemoglobin level >16 g/dL) who underwent major surgery, 22 (79%) had complications and 10 (36%) died. This group was compared with 53 patients who had controlled polycythemia (hemoglobin level <16 g/dL) and major surgery; 15 (28%) had complications, and 3 (5%) died. For both groups, most of the complications were related to polycythemia (e.g., hemorrhage or thrombosis). Other data confirm that polycythemia is an independent risk factor for cardiovascular mortality. [179] Admittedly, the study of Wasserman and Gilbert [178] had deficiencies. It was a retrospective study, and no period of time was given. "Minor" surgery was excluded. Moreover, the study did not explain why polycythemia was controlled preoperatively for some patients but not for others. Nevertheless, knowledge and pretreatment of polycythemia decreased perioperative morbidity and mortality.

No such evidence exists for normovolemic anemia. Rothstein [180] concluded that a hemoglobin level of 9 g/dL is adequate for patients older than 3 months of age but should exceed 10 g/dL for younger patients (Chs. 46 and 47). As emphasized by Roy and colleagues, [83] the age of the patient at the time of discovery of anemia often points to its cause. Anemia in the neonatal period is often attributable to recent blood loss, isoimmunization, congenital hemolytic anemia, or congenital infection. Anemia first detected 3 to 6 months after birth suggests a congenital disorder of hemoglobin synthesis or structure. Therefore, assays of hemoglobin concentration in the first 6 months may represent the first opportunity for analysis. This use of the perioperative period for screening (or case finding) necessitates a proactive procedure for referring the patient/parents for counseling and/or treatment (ideally integrated through an automated information ["informatics"] system linking preoperative clinic and primary care physicians). Thus, preoperative evaluation can add to a patient's prior medical database.

This point--that preoperative evaluations and documentation of data from the history are often incomplete--was reiterated by Hackmann and colleagues [82] in their study of the prevalence of anemia. They pointed out that several patients whose anemia was not properly suspected had conditions (Hirschsprung disease, pyloric stenosis, or history of anemia accompanying juvenile rheumatoid arthritis) that should have alerted the anesthesiologist. These investigators also emphasized the importance of obtaining a thorough history.

Should asymptomatic anemia be treated prior to surgery that is associated with no blood loss, as O'Connor and Drasner [81] and others have done? Does this practice produce more benefit than harm? Does iron therapy at this early age contribute to late ischemic heart disease? Is this the function of preoperative testing, to spot chronic conditions? Although there are no definite answers to these questions, we agree with O'Connor and Drasner that these practices are indicated if one sets up the preoperative assessment to function in that role. This would mean that the anesthesiologist and the clinic would constitute second-opinion consultants to the primary care physician. It would also require that the preoperative assessment be performed sufficiently early (
1 wk before surgery) and be vested with enough authority to postpone surgery in a timely enough fashion to avoid any decrease in OR efficiency.

If the preoperative assessment is not done in advance or is not vested with sufficient authority, perhaps asymptomatic anemia prior to surgery not involving blood loss should not be treated preoperatively. These impressions seem to be confirmed by studies showing that patients survive anesthesia and type A surgery when hemoglobin levels are higher than 80 g/L. [181] [182] No data confirm the hypothesis that preoperative treatment of moderate or mild normovolemic anemia in such patients decreases perioperative morbidity or mortality. Similarly, no data exist regarding the possible harm from abnormal white blood cell counts found preoperatively. Therefore, the following ranges of "surgically acceptable values" are arbitrary: for hematocrit level, 29 to 57 percent for men and 27 to 54 percent for women; for white blood cell count, 2,400 to 16,000/mm^3 for both men and women. When values fall outside these ranges, we recommend seeking an alternative diagnosis before instituting anesthesia or surgery. [183]

How many healthy patients have this degree of abnormality in hematocrit level or white blood cell count? No such patient was found in either study among the 223 or 2,010 patients judged healthy by history (i.e., history indicated no need for tests). [76] [171] Table 23-13 provides the only other available data, which are limited. If we assume that 10 percent of all abnormalities are outside the "surgically acceptable" range [184] (see Table 23-13) , and if we apply the benefit-risk analysis described in the section on chest radiographs, we would conclude that either preoperative hematocrit or hemoglobin levels should be determined for all female surgical patients and for all male surgical patients more than 64 years of age who are undergoing type B or C surgical procedures. Red cell antigen screening would be warranted for all patients undergoing procedures involving possible blood loss of more than 2 U/70 kg body weight (type B and C surgical procedures). [185] [186] White blood cell counts appear to be rarely, if ever, justified for asymptomatic patients.

Blood Chemistries, Urinalysis, and Clotting Studies

What blood chemistries would have to be abnormal, and how abnormal would they have to be, to justify changing one's perioperative management? Abnormal hepatic or renal function may change the choice and dose of anesthetic or adjuvant drugs. Approximately 1 in 700 supposedly healthy patients actually harbors hepatitis, and 1 in 3 of

TABLE 23-13 -- Abnormalities Discovered by Screening Hemoglobin Tests and White Blood Cell Counts

AGE (Y)	SEX	SERIES	PATIENTS EXAMINED (*n*)	HEMOGLOBIN ABNORMALITIES (%)	WBC COUNT ABNORMALITIES (%)
<1	Either	Roy et al [83]	257	1.1	--
<1	Either	Hackmann et al [82]	269	2.6	--
1-5	Either	Roy et al [83]	1,113	0.7	--
3-12	Either	Nigam et al [84]	250	0.8	--
5-18	Either	Roy et al [83]	630	0	--
<18	Either	Hackmann et al [82]	2,649	0.5	--
<18	Either	Baron et al [85]	1,863	1.1	--
<18	Either	O'Connor and Drasner [81]	468	11.9	2.7
1-19	Either	Hackmann et al [82]	2,380	0.3	--
<19	Either	Wood and Hoekelman [104]	1,924	0.8	--

<40	M	Collen et al [132]	6,941	1.9	2.6
<40	F	Collen et al [132]	9,037	12.6	2.6
18	Either	Parkerson [119]	392	18.8	10.7
>19	Either	Johnson et al [79]	212	2.4 [a]	0
<40	Either	McKee and Scott [77] , [a]	96 [a]	0	0
<40	Either	Velanovich [166]	-- [b]	12	--
40-59	M	Collen et al [132]	11,832	3.1	2.2
40-59	F	Collen et al [132]	9,657	10.1	2.2
41-50	Either	McKee and Scott [77] , [a] a	53 [a]	5.7	?
40-60	Either	Velanovich [166]	-- [b]	15.5	--
51-60	Either	McKee and Scott [77] , [a]	85 [a]	0	0
60	M	Collen et al [132]	4,062	5.6	1.7
60	F	Collen et al [132]	3,134	5.5	1.7
>60	Either	McKee and Scott [77] , [a]	163 [a]	6.1	?
>60	Either	Velanovich [166]	-- [b]	31.6	--
>?70	Either	Wolf-Klein et al [98]	551	33.2	17.4
>71	Either	Levinstein et al [116]	121	27.8	4.0
74-97	Either	Domoto et al [97]	70	11.4	4.3
Unspecified	Either	Turnbull and Buck [78]	1,005 [a]	0.7	0.1
Unspecified	Either	Muskett and McGreevy [80]	199	60.8	34.8
				9.0 [c]	5.1 [c]
Unspecified	Either	Kaplan et al [76] , [a]	293	0 [c]	0 [c]
Unspecified	Either	Gold and Wolfersberger [191] , [a]	3,375	0.33	--
Unspecified	Either	Carmalt et al [184]	278	30.4 [d]	--
Unspecified	Either	Huntley et al [121]	119	23	--
Unspecified	Either	Williamson et al [120]	982	3.2	--
Unspecified	Either	Blery et al [91] , [a]	1,728	1.1	--

[a] Patients were asymptomatic.
[b] Five hundred twenty patients were examined, but no age distribution was presented.
[c] Abnormalities significant to perioperative management.
[d] Carmalt and coworkers found that 24.5% were new abnormalities; 2 patients had hemoglobin values of less than 8 g/dL, 17 had values of 8 to 10 g/dL, and 21 had values of 10 to 12 g/dL.

those patients will become jaundiced. [187] [188] However, our group found no asymptomatic patient who denied exposure to hepatitis who then became jaundiced after uneventful surgery [171] (Roizen MF, unpublished data for more than 11,500 patients in a prospective study of the "HealthQuiz," discussed later; Hsu J et al, unpublished data). These data suggest that either the screening history suffices or the incidence of asymptomatic hepatitis is decreasing.

Data from the National Veterans Affairs Surgical Risk Study [44] found that albumin level was an important predictor of perioperative morbidity and mortality in every surgical specialty. Therefore, one could argue for determining albumin levels, especially for all class C procedures.

Table 23-14 presents the available data regarding abnormalities found on screening blood chemistries. Unexpected abnormalities are reported for 2 to 10 percent of patients screened, and these abnormalities lead to many additional tests that usually (
80%) have no significance for the patient. In fact, as described in the section on laboratory tests as ineffective screening devices, if 20 chemistry tests were ordered for a healthy individual, there would be a 64 percent chance that results from at least 1 test would be abnormal (see Fig. 23-2 (Figure Not Available)). Unexpected abnormalities that are significant arise in 2 to 5 percent of patients studied. Of these abnormalities, approximately 70 percent are related to blood glucose [189] and blood urea nitrogen (BUN) levels. Note that the screen for diabetes may soon shift from random determinations of blood glucose levels to determination of the concentration of glycosylated hemoglobin (Hb A_{1c}) 2 hours after a glucose load or a meal. The 9 to 20 additional tests on the screening simultaneous multichannel analysis (SMA) of 12 to 20 variables lead to very few important discoveries affecting anesthesia. In fact, the falsepositive rate is so high (i.e., 96.5% for the test for calcium) that the value representing cost versus benefit for most of these tests (even when the tests are free) is negative, as is the

TABLE 23-14 -- Screening Blood Chemistries: Percentage of Patients Having Abnormalities

AGE (Y)	SERIES	PATIENTS EXAMINED (*n*)	BUN	Cr	GLUCOSE	AST OR SGOT	URIC ACID	CHOLESTEROL	ALBUMIN	TOTAL PROTEIN	Ca^{2+}	VDRL	ALK. PTAse	BILIRUBIN	K^{+}	PHOSPHATE
0-65	Narr et al [75]	3,782	--	--	1.9	0.3	--	--	--	--	--	--	--	--	0.2	--
10-54	Schemel [186]	7,620	--	--	--	0.144	--	--	--	--	--	--	--	--	--	--
15-85	Carmalt et al [184] , [a]	296	1.4	1.0	2.0	0	--	0.3	0	--	0.3	--	0	0	0.3	--
>18	Parkerson [119]	397	--	1.2	15.8	2.8	7.9	6.1	--	--	2.0	--	--	1.2	6.6	--
>18	Schneiderman et al [266]	547	--	9.3	--	1.3	--	--	--	--	--	--	9.7	3.7	--	--
>18	[Bryan data] [267] [268]	623	1.1	--	5.0	--	4.5	--	1.4	2.4	1.0	--	--	--	4.0	--
>25	Peery [269] , [a]	1,771	18	--	21	3.1	36	30	0.5	0.5	--	--	1.3	--	3.6	--
<40	McKee and Scott [77] , [b]	96	0	--	--	--	--	--	--	--	--	--	--	--	0	--
40-59	Collen et al [132]	21,489	--	1.4	5.6	4.6	4.8	2.7	0.3	4.4	1.3	1.9	--	--	--	--

41-50	McKee and Scott [77] , [b]	53	0	--	--	--	--	--	--	--	--	--	--	--	--	0	--
>40	Collen et al [132]	15,978	--	0.8	4.6	3.6	3.4	1.7	0.4	3.5	1.4	0.8	--	--	--	--
51-60	McKee and Scott [77] , [b]	85	0	--	--	--	--	--	--	--	--	--	--	--	--	0	--
>60	Collen et al [132]	7,196	--	2.7	8.3	4.5	6.0	3.0	0.4	3.9	1.5	2.3	--	--	--	--
>60	McKee and Scott [77] , [b]	163	2.5	--	--	--	--	--	--	--	--	--	--	--	--	0	--
>?70	Wolf-Klein et al [98]	500	24.6	14.5	24.6	9.4	7.7	13.8	20.4	9.9	7.2	--	23.2	1.7	5.4	--
71	Levinstein et al [116]	121	36	10.8	29.0	0.8	7.2	6.9	27.8	19.2	5.6	--	19.0	0.7	3.0	--
74-97	Domoto et al [97]	70	30	--	26.5	9.2	8.6	17.2	0	2.1	1.0	--	9.2	2.1	--	1.0
All	Wataneeyawech and Kelly [187]	6,540	--	--	--	0.234	--	--	--	--	--	--	--	--	--	--
All	Bryan et al [267]	2,846	1.4	--	5.6	--	--	--	1.4	0.7	0.3	--	--	--	0.3	--
All	Friedman et al [270]	8,446	3.4	3.3	5.9	2.7	2.7	3.8	1.5	2.5	5.4	--	3.9	2.4	1.4	--
All	Delahunt and Turnbull [101] , [b]	332	0	0	--	--	--	--	--	--	--	--	--	--	0.3	--
All	Young and Drake [271] , [a]	390	6.4	3.7	7.5	--	--	--	--	--	2.0	--	--	--	0	--
All	Berwick [128] , [c]	86,006 [c]	0.7	0.3	1.2	0.5	1.2	0.8	0.02	0.09	0.5	--	0.7	0.3	1.8	--
All	Berwick [128]	76,519	1.6	1.3	3.5	2.5	2.9	5.1	1.5	1.2	2.8	--	2.6	4.0	3.2	--
All	Boonstra and Jackson [272] , [a]	12,000	--	--	--	--	--	--	--	--	5.0 [a]	--	--	--	--	--
All	Apfelbaum et al [171] , [d]	1,784 [e]	2.0	1.8	3.4	1.8	--	--	0.3	1.3	1.0	--	1.3	--	2.6 [f]	0.3
All	Apfelbaum et al [171] , [d]	Variable (asymptom.) [e]	0.3	0.3	0.1	0.2	--	--	0.2	0.3	0.7	--	0.6	--	1.8 [f]	--
All	Whitehead [273]	2,871	3.4	--	10.0	1.8	9.2	9.3	2.9	--	9.2	--	8.3	6.0	4.7	--
All	Turnbull and Buck [78] , [b]	995	0.1	0.2	0.7	--	--	--	--	--	--	--	--	--	1.4	--
All	Blery et al [91] , [b]	~2,800	0.1	0.1	0.1	--	--	--	--	--	--	--	--	--	0.5	--

Alk. PTAse, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca^{2+}, calcium; Cr, creatinine; K^{+}, potassium; SGOT, serum glutamicoxaloacetic transaminase; VDRL, serologic test for syphilis, developed by the Venereal Disease Research Laboratory

[a] A high percentage of these findings were analyzed in more depth and were found to be clinically unimportant.
[b] Patients were asymptomatic.
[c] Significantly abnormal (outside action limits) [76]
[d] Also, Apfelbaum JL et al, unpublished data
[e] Symptomatic or asymptomatic patients
[f] Pertains to all abnormalities for all electrolytes measured, not just K^{+}

value representing benefit versus risk. Examination of the data reported by Berwick [128] in Table 23-14 helps to clarify the difficulty of screening. More than 75 percent of the abnormalities (see the line for the Berwick study, "76,519" in Table 23-14) were not even outside the range that caused the laboratories at these health screening fairs to notify the patient or physician of an abnormal value (see line containing 86,006 in Table 23-14) , let alone be judged significant to the patient's health.

If a screening test for hepatitis is desired, because the incidence of hepatitis is 0.14 percent and/or because one wishes to avoid the potential legal problems of postanesthetic jaundice, only three tests seem justified: determination of serum glutamic-oxaloacetic transaminase (SGOT) or its successor aspartate aminotransferase (AST), blood glucose (or its successor, Hb A_{1c}), and BUN. Even then, BUN is indicated only for patients more than 65 years of age, and glucose (or Hb A_{1c}) is indicated only for individuals more than 75 years of age. In fact, if the data from our group on asymptomatic liver disease can be generalized, no blood chemistry tests are warranted for patients less than 65 years of age. Furthermore, because the antibody test for hepatitis C is useful after infection has occurred, the medicolegal risk posed by postanesthetic jaundice should be even less. [190]

Abnormalities are commonly found on urinalysis [78] [79] [80] [81] [87] [97] [98] [103] [116] [120] [121] [132] [166] [191] [192] (Table 23-15) (Apfelbaum JL et al, unpublished data). The quality of urinalysis results obtained by dipstick technique has been variable at best. [193] In addition, these abnormal results usually do not lead to beneficial changes in management. Most of the results that do lead to beneficial changes could have been obtained by history or determination of BUN and glucose (or Hb A_{1c}) levels, tests that are already recommended for all patients more than 65 and 75 years of age, respectively. Thus, urinalysis, although initially inexpensive, becomes an expensive test to justify on a benefit-cost or benefit-risk basis.

Although partial thromboplastin time (PTT) and prothrombin time (PT) are useful tests with which to screen patients who have a history of bleeding, their value as screening tests for asymptomatic patients has never been

shown [75] [76] [78] [80] [86] [91] [95] [117] [194] [195] [196] [197] [198] [199] [200] [201] [202] [203] (Table 23-16) . Virtually no asymptomatic patient in the literature has had unequivocal benefit from clotting function studies performed preoperatively (see Table 23-16). Most patients show symptoms or have a medication history suggesting the possible need for clotting function tests. Suchman and Mushlin [199] and Macpherson [200] reviewed the data, as we did, [56] and came to the same conclusion: preoperative clotting function testing for asymptomatic patients who have no risk factors for coagulopathy is incapable of predicting perioperative bleeding.

TABLE 23-15 -- Abnormalities Discovered by Screening Urinalysis

AGE (Y)	SEX	SERIES	PATIENTS EXAMINED (*n*)	ABNORMALITIES (%)	SIGNIFICANT ABNORMALITIES (%)
<18	Either	O'Connor and Drasner [81]	453	15	0.4
<19	Either	Wood and Hoekelman [104]	1,859	11.7	0.5
Unspecified	Either	Huntley et al [121]	119	61	--
5-12	F	Cardiff-Oxford [192]	16,800	1.8	--

15-?	Either	Lawrence and Kroenke [87]	180	15	<1.6
Unspecified	Either	Gold and Wolfersberger [191]	3,375	2.7	--
Unspecified	Either	Williamson et al [120]	982	16.7	--
Unspecified	Either	Collen et al [132]	44,663	14.6	--
Unspecified	Either	Muskett and McGreevy [80]	144	22.4	--
Unspecified	Either	Berwick [128]	235	2.6	--
Unspecified	Either	Turnbull and Buck [78] , [a]	995	4.3	--
>19	Either	Johnson et al [79]	212	39	<1.9 (?0)
>?70	Either	Wolf-Klein et al [96]	550	12.9	--
71	Either	Levinstein et al [116]	121	25.8 [b]	--
74-97	Either	Domoto et al [97]	70	9.2	--

[a] Patients were asymptomatic.
[b] Was only 1.4% when a dipstick technique was used

TABLE 23-16 -- Percentage of Patients Having Coagulation Abnormalities, as Determined by Screening Prothrombin Time, Partial Thromboplastin Time, Platelet Count, or Bleeding Time Tests

AGE (Y)	SERIES	PATIENTS EXAMINED (N)	PERCENTAGE WITH ABNORMALITIES OF				PERCENTAGE WITH SURGICALLY SIGNIFICANT ABNORMALITIES OF			
			PT	PTT	PLT CNT	BT	PT	PTT	PLT CNT	BT
?0-90	Robbins and Rose [117]	1,025		14 (143/1,025)			0 (0/1,025)			
Unspecified	Baranetsky and Weinstein [194]	2,600	0.2 (5/2,600)				0 (0/2,600)			
Unspecified	Barber et al [195]	1,941 (including 141 with risk factors) 1,800				6(110/1,941) [a] 1.5(27/1,800) [a]			?2.2(43/1,941) [a] 0.19(2/1,800) [a]	
?0-90	Blery et al [91]	~2,900	0.1 (4/2,931)	0.1 (4/2,914)	0.3 (10/3,546)	0.4 (17/3,845)	0 (0/2,931)	0 (0/2,914)	?0.03 (1/3,576)	0 (0/3,845)
?0.25-65	Narr et al [75]	3,782			1.2 (40/3,782)				0 (0/3,782)	
0-93	Lorenzi and Cohen (personal communication)	578	3.5 (20/578)				0 (0/578)			
>18	Kaplan et al [76]	154					0 (0/154)			
?>18	Macpherson et al [196]	1,109	1.8 (12/668)	2.8 (29/1,008)	10.1 (108/1,022)		0 (0/668)	0 (0/1,008)	0 (0/1,022)	
>18	Rohrer et al [86] With risk factors	282	0.6 (1/159)	6.3 (10/159)	8.2 (20/117)	7.4 (14/170)	0.6 (1/154)	?1.4 (?3/159)	?2.6 (?3/117)	?
	Asymptomatic		0.8 (1/123)	2.4 (3/123)	8.0 (13/103)	3.8 (4/105)	0 (0/123)	0 (0/123)	0 (0/103)	0 (0/105)
71	Levinstein et al [116]	121			4.0		(0/154)			
Unspecified	Turnbull and Buck [78]	1,005	0 (0/213)	1.5 (3/210)	0 (0/1,005)		0 (0/213)	0 (0/210)	0 (0/1,005)	
Unspecified	Bushnick et al [197]	640	0.8 (5/591)	0.3 (2/640)						
Unspecified	Eisenberg et al [198]	750					0 (0/750)			
Unspecified	Muskett and McGreevy [80]	200	3.9 (5/128)	3.9 (5/126)			0 (0/128)	0 (0/126)		
Unspecified	Suchman and Mushlin [199] With known risk factors	1,004		10.4 (104/1,004)				4.6 (46/1,004)		
	Without known risk factors	11,334	13.3 (243/1,927)					0.71 [b] (13/1,827)		

BT, bleeding time; PLT CNT, platelet count; PT, prothrombin time; PTT, partial thromboplastin time.

[a] Number in parentheses represents number of patients.
[b] An abnormal PTT was not more likely to predict hemorrhage than was a normal PTT and was not helpful in preoperative management.

Figure 23-4 (Figure Not Available) Procedure for determining whether coagulation tests are needed. PT, prothrombin time; PTT, partial thromboplastin time. *(Modified from Roizen and Hurd [201])*

No information is gained from either an abnormal or a normal result on clotting studies in low-risk patients. Figure 23-4 (Figure Not Available) presents an algorithm that can be used to segregate high-risk and low-risk patients. [201]

One patient deserves special comment: the patient taking aspirin or aspirin-containing compounds. Aspirin at a dose of 3 to 10 mg/kg of body weight per day does not

seem to pose a risk of bleeding. However, data are not available for 300 mg or more administered within 12 hours of surgery. Because the pharmacokinetics of aspirin changes when more than 2 g/70 kg is consumed per day, a patient should be evaluated if he or she has not discontinued aspirin consumption sufficiently early to ensure no appreciable level of acetylsalicylic acid in the blood for 24 hours before surgery. (This is the period acetylsalicylic acid would have to be absent for the generation of the approximately 50,000 new platelets/mm^3 needed for normal platelet aggregation.) The patient should also be evaluated if surgical hemostasis cannot be ensured, or if a regional procedure into a closed space is planned. Nonsteroidal anti-inflammatory drugs present similar problems. [202] (For further explanation of these situations, see the section in Chapter 25 regarding interruption of a drug regimen prior to surgery.)

Tests for HIV, Pregnancy, Hemoglobinopathies, Malignant Hyperthermia, Magnesium Deficiency, and Low Albumin Levels

Tests for HIV infection, pregnancy, and screening for hemoglobinopathy and malignant hyperthermia raise ethical questions that may require close attention to institutional policy and the immediate availability of counseling services. Moreover, all these tests have risks. The physician may therefore decide to limit testing to only "at-risk" populations (e.g., for pregnancy testing, only female patients who believe they may be pregnant). Magnesium (Mg) testing is a special concern.

Testing of asymptomatic patients for AIDS is not likely to be the most effective way of uncovering the disease. Of the more than 700,000 people in the United States who have had AIDS, fewer than 200 have not been gay, had sex with a prostitute or engaged in other "at-risk" sexual behavior, used intravenously administered drugs or shared needles, had a "needlestick," been cared for by a family member with AIDS, or received a blood transfusion after 1979. One program

Figure 23-5 Suggested procedure for screening patients at high risk of malignant hyperthermia.

screening for HIV in asymptomatic individuals was able to produce an "acceptably low false-positive rate" by diagnosing HIV infection only after one sample of blood produced positive results on three different tests and after the second sample of blood had been used for verification. [94] Thus, for pregnancy, hemoglobinopathies, and HIV infection, the history is still the best tool for identifying those who should be tested or those who are at risk of the condition.

In the past, no screening test existed for susceptibility to malignant hyperthermia (MHS) other than a personal or family history of the condition (Ch. 27) . Several tests have become available, but none uses genetic testing. Despite previous studies suggesting a single localization of this disorder to chromosome 19q, Levitt and colleagues [204] [205] observed evidence for significant genetic heterogeneity in MHS. Nevertheless, they found seven MHS families in which the identified genetic aberrations appear linked to chromosome 17q11.2-24. Because the gene encoding the adult muscle sodium-channel alpha-subunit (SCN4A) has also been localized to this region of the long arm of chromosome 17, this area may be the site of a primary defect in MHS. However, because the specific site cannot yet be identified, linkage analysis for MHS coupled with polymerase chain amplification may be used in the future to screen for MHS in high-risk patients.

It is still too early to predict the usefulness of these tests as a screening procedure for MHS or even for other genetic diseases such as diabetes. Other screening tests for MHS have not been reliable enough to use for any but "at-risk" individuals (e.g., children with a history of myopathies who are undergoing surgery for strabismus; patients having a family history of problems with anesthesia; or patients with a history of abnormally red appearance, thermoregulation, and reactions to minor stresses) (Fig. 23-5) (Ch. 27) .

Mg deficiency represents another special situation. Putatively it is much more common than other ion deficiencies, and Mg treatment has been advocated as extremely beneficial. [206] However, because no data appear to link preoperative treatment of Mg deficiency with benefit, screening with tests appears superfluous. Let us expand on this concept.

Hypomagnesemia is a prevalent laboratory finding in hospitalized patients (11-16%; Table 23-17) (Table Not Available) . The total serum level of Mg represents the protein-bound (physiologically inactive) Mg, as well as the ionized (physiologically active) Mg. Total serum Mg constitutes less than 1 percent of total body Mg, there being no constant ratio between the two values.

Fanning and colleagues [207] showed that intravenous administration of Mg for 4 days after coronary artery bypass grafting decreased the incidence and severity of atrial fibrillation. Specifically, 14 patients in the control group had 42 episodes of fibrillation, 2 of whom required cardioversion. By contrast, 7 patients in the Mg-treated group had 12 episodes of atrial fibrillation, and none required cardioversion. In a similar study, intraoperative administration of Mg after cardiopulmonary bypass decreased the frequency of postoperative ventricular arrhythmias (8 of 50 [16%] in the Mg-treated group versus 17 of 50 [34%] in the placebo-treated group, $P < .04$). [208]

Some investigators believe that serum Mg should be measured routinely in hospitalized patients because of the high prevalence of hypomagnesemia coupled with the difficulty of diagnosing hypomagnesemia on clinical grounds alone. [206] [209] One investigator argues that common sense dictates that nonessential surgery be deferred until Mg depletion has been corrected, again with no data to support such an assertion. [210] Neither Dr. Jo (personal communication) nor we could find any data indicating better outcome

TABLE 23-17 -- Prevalence of Hypomagnesemia Among Hospitalized Patients

(Not Available)

Courtesy of Dr. Allan Jo et al

because of routine detection and correction of hypomagnesemia. The benefit of decreased frequency of cardiac dysrhythmias after cardiac surgery [207] [208] occurred with or without preoperative hypomagnesemia. If one is going to use Mg empirically, one probably should have a measure of renal function and should monitor Mg levels (or reflexes in the awake patient), but no data indicate that such levels should be routinely determined before surgery.

The Veterans Affairs cooperative studies found that albumin levels were an important predictor of outcome after surgery. [44] [186] Furthermore, changes in this level after enteral nutrition have been important predictors of perioperative outcome in malnourished or otherwise very sick patients (Ch. 25) . It may therefore be time to add this laboratory test for patients undergoing surgical class C procedures and for patients who have a physiologic age (a RealAge) of more than 85 years who are undergoing surgical class B procedures.

Even sophisticated laboratory tests have not been better in controlled trials than the history and physical examination in estimating the risk from a diagnosis. This lack of benefit from laboratory testing has applied to diagnoses as relatively amenable to laboratory diagnosis as the differential diagnosis of systolic murmurs [211] or assessment of nutritional status [212] or of cardiac or gastrointestinal disease. [60]

/das/book/view/29494766/875/244.html

IMPLEMENTING ACCURACY AND EFFICIENCY IN PREOPERATIVE EVALUATION

The ability of preoperative evaluation of even healthy patients (ASA physical status I or II) to detect important symptoms and medical history makes its benefit greater than its risk. Furthermore, preoperative evaluation done in advance is ultimately cost-efficient, because it minimizes expensive delays on the day of surgery. (Table 23-18 shows the laboratory tests recommended for asymptomatic patients by various investigators and institutions.) In addition, such assessment could be used to limit the amount of testing to only that warranted by symptoms or risk grouping (Table 23-19) . The protocol described in Table 23-19 (and the algorithms derived from it, Figs. 23-4 (Figure Not Available) to 23-12) do have certain requirements, if the patient's preoperative condition is to be optimized. A careful history and physical examination must be performed. In addition, any condition indicating the existence of one of the disease entities presented in Table 23-19 must be searched for, and that condition must be specifically tested for in patients undergoing type B or C surgical procedures. This protocol clearly places the burden of accuracy on the history-taker. Furthermore, use of the protocol does require that a system be in place so that the physician performing the assessment views the test results and communicates the readiness of the patient for surgery, or the need for further testing/consultation, to the primary care physician, surgeon, and scheduling system. *This step places an additional burden on the preoperative assessor: he or she must determine what degree of consultation with the primary care physician and surgeon is necessary to judge optimal health for perioperative care.*

Two possible objections by the assessor come immediately to mind:

1. Why can't the primary care physician do the evaluation and send it to me?
2. It is a time-consuming process for which I receive no compensation.

In their simplest forms, the answers to those objections are:

1. The primary care physician is not specifically trained in preoperative assessment.
2. Ultimately, preoperative evaluation is very costeffective for the institution, the health-care payers, and the patients. It would be justifiable to compensate the anesthesiologist for preoperative assessment at the same rate as for OR time.

With regard to the *first objection*, although the primary care physician can render a patient's condition optimal for daily life, he or she does not have the anesthesiologist's

TABLE 23-18 -- Recommended Test Guidelines for Asymptomatic Patients

AGE	ROIZEN[277] (1994) (SIMPLIFIED)	ROIZEN[277] (1994)		ROIZEN[57] (1990)		ROIZEN[278] (1986)		ROIZEN[279] (1981)		EISEMAN[280] [a] (1989)	VELANOVICH[281] (1991)	LARSON[234] (1992)	BLERY ET AL[91] (1986)		MCKEE AND SCOTT[77] (1987)		NARR ET AL[75] [b] (1991)
	1	2		3		4		5		6	7	8	9		10		11
<6 mo										CBC Elect. BUN/Glue Urin Protime PTT PLT Cnt CXR ECG FOBT		CBC Urin	Minor surg None	Major surg Hct or Hb	None		None
6 mo	Hb or Hct			None	Hb or Hct	None	Hct or Hb	?SGOT ?BUN ?Glue	Hb or Hct SGOT ?BUN ?Glue								
2 y																	
6 y		None	Hb or HCT ?Preg test								ECG						
18 y																	
30 y																	
40 y	Hct ECG	Hct ECG		BUN/ Glue ECG	Hb or Hct BUN/ Glue ECG	BUN/ Glue ECG	Hct or Hb BUN/ Glue ECG	?SGOT BUN/ Glue ECG	Hb or Hct ?SGOT BUN/ Glue ECG		Hct BUN/Glue/Creat Lymph Cnt ECG		ECG	Hct or Hb ECG	CBC		ECG Creat/Glue
50 y			Hct ECG									CBC Urin Elect BUN Creat Glue CXR ECG			CBC ECG		
60 y				Hb or Hct BUN/Glue CXR ECG		Hb or Hct BUN/Glue CXR ECG		Hb or Hct BUN/Glue CXR ECG ?SGOT							Minor surg CBC ECG	Major surg CBC BUN Elect ECG CXR	CBC Creat/Glue ECG CXR	
65 y	Hct ECG BUN/Glue	Hct BUN ECG											BUN/ Creat Elect ECG	Hct BUN/ Creat Elect ECG			
70 y																	
75 y and over		Hct BUN/Glue ECG															

Alb, albumin; BUN/Gluc, blood urea nitrogen and glucose; CBC, complete blood count; Creat, creatinine; ECG, electrocardiogram; Elect, electrolytes; CXR, chest radiograph; FOBT, glucose; Hb, hemoglobin; Hct, hematocrit; Lymph Cnt, lymphocyte count; PLT Cnt, platelet count; Preg test, pregnancy test; Protime, prothrombin time; PTT, partial thromboplastin ti glutamic-oxaloacetic transaminase; Tot Prot, total protein; Urin, urinalysis

[a] Recommendations of the American College of Surgeons
[b] Recommendations of the Mayo Clinic, Rochester, Minn
[c] Personal communication with JV Roth (Albert Einstein Hospital, NY)
[d] Personal communication with SL Kaplan (Westfall Surgery Center, Rochester, NY)

depth of understanding of the physiologic changes caused by surgery or the requirements that must be met to facilitate class B and C surgical procedures and to optimize perioperative outcome. One example is induction by the primary care physician of some degree of prerenal azotemia for the patient with congestive heart failure. Even though prerenal azotemia may make the patient more comfortable for the conditions of daily life, it would predispose the patient to hypovolemic disaster during surgery. Unfortunately, careful attention to optimizing of the perioperative condition is highly desirable, but it is just not compatible with the current state of knowledge and functioning of primary care physicians. Such education is more available and of better quality than in prior decades, [213] [214] [215] [216] [217] [218] [219] and many reports have highlighted the importance of this aspect of care. [9] [217] [219] Nevertheless, the training, knowledge, and ability of primary care physicians are still very deficient in this aspect of consultation.

In addition, the preoperative meeting of anesthesiologist and patient should serve other important functions: informing the patient about treatment options and educating the

TABLE 23-19 -- Simplified Strategy for Preoperative Testing [a]

PREOPERATIVE CONDITION[b]	Hb M	Hb F	WBC	PT/PTT	PLT, BT	ELECT	CREAT/BUN	BLOOD GLUCOSE OR Hb A_{1c}	SGOT/ALK PTAse	X-RAY	ECG	PREGTEST	ALBUMIN	T/S
Neonates	X	X												
Physiologic age 75 y	X	X					X	X		X	X			
Procedure type C	X	X					X	X			X		X	X
Cardiovascular disease							X			X	X			
Pulmonary disease										X	X			
Malignancy	X	X								X	X			
Radiation therapy			X							X	X			
Hepatic disease				X					X					
Exposure to hepatitis									X					
Renal disease	X	X				X	X							
Bleeding disorder				X	X									X
Diabetes						X	X	X			X			
Smoking 20 pack-y	X	X								X				
Possible pregnancy												X		
Use of:														
Diuretics						X	X							
Digoxin						X	X				X			
Steroids						X		X						
Anticoagulants	X	X		X										
Central nervous system disease			X			X	X	X			X			

X, obtain test;
, obtain test for leukemias only; BT, bleeding time; Creat/BUN, creatinine or blood urea nitrogen; ECG, electrocardiogram; Elect, electrolytes (i.e., sodium, potassium, chloride, carbon dioxide, and proteins); Hb, hemoglobin (obtain for male [M] or female [F] patients); Hb A_{1c}, glycosylated hemoglobin; pack-y, pack-years, i.e., the smoking of one pack of cigarettes per day for 1 year; PLT, platelet count; PT, prothrombin time; PTT, partial thromboplastin time; SGOT/Alk PTAse, serum glutamic-oxaloacetic transaminase and alkaline phosphatase; T/S, blood typing and screening for unexpected antibodies; WBC, white blood cell count

Data from Roizen, [57] Kaplan et al, [76] and Blery et al [91]

[a] For minimally invasive procedures (type A, e.g., cataracts, diagnostic arthroscopy), no tests are indicated. For moderately invasive surgery (type B procedures, in which blood loss or hemodynamic changes are rare), clinical judgment is needed when selecting tests.
[b] Not all diseases and pertinent conditions are included in this table. Therefore, the physician should use judgment regarding patients having diseases and conditions that are not listed.

Figure 23-6 Evaluating cardiovascular risk for patients undergoing noncardiac surgery: the procedure for determining which cardiovascular laboratory tests are necessary. The history is used to segregate patients into groups for testing and/or invasive monitoring. ICU, intensive care unit; PTCA, percutaneous transluminal coronary angioplasty.

patient about anesthesia, perioperative care, and pain treatment in the hope of reducing anxiety and facilitating recovery. [5] At this time, neither of these functions can be performed adequately by most primary care physicians, and there is no one better trained to do so than anesthesiologists.

With regard to the *second objection,* it is cost-efficient for both the institution and the health-care provider to have the anesthesiologist perform preoperative assessments, *provided a system is set up to make the process cost-efficient.* In the OR, the anesthesia service earns revenue only when a patient is undergoing surgery. Thus, the goals of the hospital in producing a cost-efficient OR environment and the goals of the anesthesia department are closely aligned. Long turnover times, unused OR time, and delays in the OR schedule have many disadvantages. They waste resources of the anesthesia department, reduce the cost-efficiency of hospitals, impede teaching, frustrate surgeons, and decrease harmonious teamwork among health-care providers. Such inefficiencies make

Figure 23-7 Procedure for determining when pulmonary function tests are warranted.

Figure 23-8 Procedure for determining when a chest radiograph should be obtained.

the hospital, surgical center, or office-based surgical facility less competitive when fees are determined on the basis of capitated care (payment of fixed fees), a DRG, or an ambulatory care group (ACG). Therefore, it is optimal to facilitate smooth transfer of the patient into the OR. In addition, if preoperative assessment by an anesthesiologist were supplemented by automated information systems linking primary care provider, surgeon, OR, and perioperative care site, more cost-efficiencies could be obtained. For example, a history would not be obtained by the internist, surgeon, surgical resident, anesthesiologist, anesthesia resident, and three teams of nurses--all with imperfect information transfer among them, much duplication of laboratory services, and many delays. Thus, even though the rules for payment have changed under capitated care (Fig. 23-13) , it is cost-efficient for the operative environment to have a system by which preoperative assessment occurs sufficiently early to minimize OR delays, to reduce unwarranted testing, to facilitate relief of patient anxiety, and to speed recovery.

For the anesthesiologist, several effective systems could be instituted. Supported by consultation 1 week or more before surgery, or by some other second-opinion mechanisms encouraged by appropriate "CPT" codes (i.e., the "current procedural terminology" of the American Medical Association) and fee schedules, such systems *could* pay for themselves (Fig. 23-14) . Initiating such a system would not be easy, but

Figure 23-9 Procedure for soliciting the signs and symptoms of significant liver disease that warrant the performance of liver function tests.

Figure 23-10 Procedure for determining when blood urea nitrogen (BUN) or creatinine levels should be obtained.

failure to do so will make the anesthesiologist and the practice site less efficient and more costly, less marketable and desirable to patients, and a continuing source of frustration to surgeons, OR administrators, and the anesthesiologist.

Danger of Underordering Tests

Inadequate preoperative evaluation leads to the missing of potential problems or to delays in the OR schedule for at least 15 percent of even healthy (ASA I) patients.[24] In addition, trying to reduce testing without such a system of assessment in place may not be beneficial. Since 1979, physicians at three university practices were found to decrease the ordering of unwarranted tests almost 1.5 times as fast as they decreased the ordering of indicated tests (19.6 and 12.9%, respectively). This would be good *if* the benefit from decreasing unjustified tests outweighed the benefit of ordering the truly useful ones. However, the possible benefit from a justified test is probably more than 1.5 times the possible

Figure 23-11 Procedure for determining when blood glucose levels should be obtained.

Figure 23-12 Procedure for determining when hemoglobin levels or a hematocrit should be obtained.

benefit from not ordering an unjustified test, at least regarding preoperative tests. Therefore, the net changes that have occurred in preoperative test selection since 1979 may not be beneficial. One is forced to conclude that a better system for obtaining the warranted tests and for eliminating the unwarranted tests may be a necessary supplement to education and to standard endorsements for the reduction of costs and errors if selective application of laboratory tests is to be beneficial.[220] This process calls forth use of information systems and an evaluative clinic. The need for an information system and clinic to make the idea work is accentuated by data on the errors we make when selecting tests without the availability of an information system.

Errors Made by Physicians When Ordering Tests

Selecting tests when there are no information systems to help has one major problem: it is a difficult procedure for

Figure 23-13 Rules for reimbursement of health-care costs have changed. In the former system of fee-for-service care, the more services given the patient, the greater the reimbursement. The present system of capitated care greatly reduces that incentive, and less care becomes the reality. As a result, the health-care provider is actually providing less care for relatively more reimbursement. Furthermore, the health-care provider now assumes the risks created by a reduced level of health care for the patient.

physicians to complete successfully. *Even when physicians agree to use specific, agreed-on criteria based on history and physical examination to order tests selectively and thereby to reduce routine testing, they still make a surprising number of mistakes when ordering tests.* Approximately 30 to 40 percent of patients who *should* have certain tests (based on agreed-on criteria such as those in Table 23-19) do not receive such tests, and 20 to 40 percent of patients who should *not* have certain tests are nevertheless subjected to them. For instance, Blery and coworkers [91] examined 3,866 surgical patients in France. Even after medical personnel had been educated regarding which criteria indicated a need for which tests, 30 percent of the tests were ordered without need; another 22 percent of tests should have been ordered but were not. Thus, surgeons and anesthesiologists not only increased costs but also failed to obtain possibly valuable information.

These mistakes occur mainly because integrating the history, physical examination, and indications for laboratory tests is not an easy process. Even when criteria for testing have been previously agreed on by surgeons and anesthesiologists, the number of variables one must remember makes arriving at the correct conclusions a complex task. As an example, let us consider how many mistakes are made regarding one commonly used preoperative test, the chest radiograph.

Charpak et al [221] examined the value of preoperative screening chest radiographs for 3,849 patients. Surgeons and anesthesiologists agreed that any of the following findings on history or physical examination would warrant ordering of a chest radiograph: any lung or cardiovascular disease; any malignant disease; current smoking for patients older than 50 years of age; major surgical emergencies; immunodepression; or, for immigrants, absence of prior health examination. Surgeons made their decision regarding ordering of chest radiographs after seeing the patient. Even with this agreement on criteria, of 1,426 chest radiographs that should have been ordered for this group of 3,849 patients, 271 were ordered but not warranted, and 596 were not ordered but should have been. Although clinical judgment may account for some of these discrepancies, most of these lapses appear simply to be errors. If so many errors occurred for a single test, even more errors would be likely if patients were subjected to multiple testing.

Data from studies performed by our group confirm this rate of error. [220] We tested the hypothesis that for the period 1979 through 1988, physicians voluntarily and

substantially reduced the ordering of preoperative tests not justified by history and physical examination. Reviewing 2,093 medical records from every other year of that period (and studying 4 operations at each of 3 cities), we investigated the indications for, and the performance of, preoperative tests. During this period, the incidence of unwarranted laboratory tests obtained preoperatively decreased from 32.2 to 25.8 percent. This decrease was irregular and varied from operation to operation, from test to test, and from city to city.

Furthermore, an unexpected 12 percent decrease (92.9-80.9%) in the ordering of *indicated* preoperative tests also occurred. Overall, 66.9 percent of tests obtained preoperatively in 1979 were not warranted, decreasing to 60.1 percent in 1987. If the possible benefit of ordering only appropriate tests outweighed the possible harm of not ordering a needed test, the net result would still be a benefit to society. Unfortunately, however, the possible benefit of performing a needed test is probably more than twice the possible harm of performing an unnecessary test.

We conclude that the pressures to order tests more optimally and to do assessments more quickly have not been accompanied by changes in practice patterns that ultimately benefit the patient. In order for the net benefit to accrue to the patient, a better *information* system is needed for obtaining the truly necessary tests and for not ordering the unwarranted ones. On the other hand, punitive measures to reduce testing may save money from testing but impair health care. That may be the approach the Health Care Financing Administration is attempting, now requiring the use of diagnosis-related codes (International Classification of Diseases, ninth edition [ICD-9]) for reimbursement of testing.

Can physicians do better at preoperative evaluation than the 5- to 15-minute history-taking prior to induction of anesthesia for outpatient or "come-and-stay" patients (those to be admitted after surgery)? They can, and should, for their patients' sake and their own sake. The British have reached the same conclusion. [222] [223] A change in the system of obtaining patient histories and ordering tests has been advocated even for internists. [224] [225] [226] [227] [228] [229] [230] [231] [232] [233]

Just as the need for a more effective *theoretical* system of preoperative evaluation became evident, the study just described reinforced our belief that the actual *information* system used for ordering tests also needed to change, in order to improve the efficiency of the process.

INFORMATION MANAGEMENT IN PREOPERATIVE EVALUATION

Being unaware of previously occurring in-hospital and perioperative events can lead to perioperative disaster in a subsequent surgical procedure. For example, an unanticipated difficult airway or allergic reaction that occurred earlier but is not known can (and has) contributed to disasters in subsequent anesthesia care. Avoiding such disasters

Figure 23-14 Billing form used to report preoperative second opinion or consultation activities to payers.

would seem to be a solvable problem in an age of records, paper or otherwise. Yet anyone who has practiced in a large modern-day American hospital (university or community) knows that past charts are often not available. Even when the patient is seen in a surgeon's office or a perioperative clinic, the transfer of records and consent forms can be a weak link in the chain. Enter the information age and the promise of making the chain perfect.

Information Systems and Preoperative Evaluation

Because we currently practice in an environment called the "Information Age," how is it possible that we still have trouble obtaining the information we need? As our health- care institutions switch to electronically stored patient records, this problem should vanish. However, these institutions

and a variety of vendors that now offer "solutions" for automating the preoperative assessment frequently fail to provide operational solutions. These "turnkey" products are often isolated implementations of paper records. Such preoperative systems have not achieved wide acceptance. [234] [235] [236] [237] However, planned with the overall goals of the preoperative evaluation in mind, information systems can be used successfully to improve patient care and the efficiency of the overall system.

Such a system requires an accurate and complete database on the patient's current health status and past anesthesia and surgical experiences. The sources for these data may be varied and collected at disparate locations and times. The ideal database would include the history of the current surgical problem and past medical, social, and surgical histories. It would also include review of organ systems, current physical examinations and perioperative plans, and notes on discussions with the patient and significant others. This database can also be used when providing ancillary services such as laboratory tests and consultations. Once the perioperative plan has been formulated, a record can be clearly communicated to the patient, the surgeon, and the anesthesiologist's colleagues. Finally, by establishing an accurate baseline status, the information that has been acquired can be used to initiate quality assurance procedures. This section provides an introduction to the use of information systems and identifies important issues for the clinician who is considering implementing such a system.

Collection of Data

Traditionally, the physician obtained needed information by talking with the patient, scanning the available paper chart, calling other physicians, and collecting reports from laboratories or consultants. These data were then recorded in a note. The information was often incomplete at the time the note was written (missing laboratory data or uncompleted consultation). Thus, the note that may have needed to be updated often was not.

To standardize the format and to help the physician obtain important information, many facilities use forms that range from simple headings placed on a page to detailed checklists. As physician contact time has become more limited, ancillary personnel have been recruited to help acquire and assemble the required data. Patients are also being asked to spend time completing checklists or questionnaires that cover many points in their history. Compared with the current procedure, automation should be able to improve many of these processes. For example, the use of electronic information systems ("informatics") could reduce or eliminate the redundant entry of information into a record, a situation that frequently creates discrepancies in that record.

The expense of obtaining these histories increases because we often rely on professionals to obtain the routine history rather than focus on the details that are abnormal or important to the planned care. The process could be less expensive if patients completed the screening process themselves. There are many ways the patient could do this. When patients are given a clear reason for their input and a clear and simple format for answering questions, the patient-completed questionnaire can be an accurate and powerful tool. [6] [237]

One of the first systems used for this purpose was originally called the HealthQuiz. [*] Now called the HealthQuiz Plus 2, this system has evolved in a way that parallels many other trends in information management. Developed in 1987, the system consisted of a laptop device that had a simple liquid crystal display and three buttons: the patient answered "yes," "no," or "not sure" to health-related questions. The HealthQuiz proved to be a simple enough system, not unlike many of the small electronic games becoming popular at the time, and it was readily accepted by patients. Its program consisted of a branching algorithm made up of 254 items. The wording of each question was carefully prepared and validated so that consistent answers were given whether the patient responded to a human or to a computer or was later asked the same question again. The initial questions were standard health-history items pertinent to anesthesia care and were based on health-maintenance guidelines. [59] [66] Subsequently, a variety of questionnaires were developed for general medicine, pediatrics, and preventive health.

Although compact and easy to use, the HealthQuiz required the use of a dedicated unit for producing the questionnaire. The unit, which produced a written report, was usually located only in preoperative clinics. In 1993, the rapid expansion of the Internet into health care and even the patient's home prompted the development of a networked version of the system, the HealthQuiz Plus 2, which could be accessed from any computer by means of an Internet browser. This Internet process enables any physician or patient who has a computer to complete the questionnaire at a wide variety of locations and at a convenient time. This concept has been extended, and now the patient can also complete the questionnaire from any touch-tone phone. Furthermore, the system allows for on-line viewing of the report and the ability to hone in on questions, suggested laboratory tests, or risk assessments to examine the underlying questions, answers, and logic. The data are also available at the point of care and are easily transferred into other medical information systems. For example, justification of laboratory tests by the assignment of diagnosis-related codes (ICD-9) is produced for each test suggested, and this information can be given to the laboratory to aid in reimbursement (Figs. 23-15 and 23-16) . Such procedures supersede the old but still often used paper-and-pencil check-off lists (Figs. 23-17 and 23-18) .

Although the value of the preoperative evaluation has been discussed, efforts to improve efficiency cause anesthesiologists to examine whether some patients may

still be just as effectively assessed immediately before surgery. To be

* Dr. Roizen developed this video preoperative health questionnaire at the University of Chicago to help ameliorate the problem of inefficient preoperative assessments and test selection methods. Consequently, the University of Chicago owns the rights to commercialize the product and has transferred the rights to the HealthQuiz to University Community Health Care, Inc., which developed it further and provided a telephone version. If this product is successful, the Department of Anesthesia and Critical Care at the University of Chicago may benefit financially. Both the University of Chicago and Johns Hopkins University in Baltimore may also benefit from commercialization of this technology and the applications described herein (see website www.Healthquiz.com for further explanations).

Figure 23-15 The HealthQuiz Plus 2 computer device uses the patient's answers to its questionnaire to produce this summary of the patient's health history and suggested laboratory tests, annotated with International Classification of Diseases (ICD-9) codes. BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CREAT, creatinine; CV, cardiovascular; DOB, date of birth; DOE, dyspnea on exertion; ECG, electrocardiogram; GI, gastrointestinal; HQASA 1-5; HR, heart rate; HT, height; Hx, history; IVDA, intravenous drug abuse; PSH, past surgical history; PULM, pulmonary; SOB, shortness of breath; S/P, status post; WT, weight.

successful, this plan should accomplish three key goals: (1) gain information about the planned procedure; (2) determine the patient's current health status; and (3) optimally allow for the patient to obtain information about the planned anesthetic before surgery. Surgical stress scales are being developed to stratify the need for evaluation and testing of patients. Tools such as the patient-completed health history, along with accessibility to previous information on perioperative care and other available data, can provide the second leg of the triad with minimal provider resources yet they can identify patients who need to come to a clinic for additional evaluation. Finally, on-line educational resources, perhaps in association with a brief call from the anesthesiologist, can complete the process of discussing the anesthesia plan with the patient. This plan could allow patients to present on the day of surgery yet minimize the potential for the discovery of unplanned conditions that would delay care, disrupt the OR schedule, or, worse, lead to adverse events.

Physician, hospital, and health-system methods for data gathering that include radiology reports, laboratory test reports, and prior operative notes and anesthetic records are just now becoming more widespread. They can use not only standard computer terminals but also handheld devices. These systems are able to decrease redundant data entry by communicating with other data sources, such as hospital billing systems (for demographic data), patient-completed questionnaires, and data from other providers. Such processes also allow more than one provider to record information for the evaluation and to communicate that information effectively to the anesthesiologist at different times or locations.

The provider systems are still evolving. Ease of use and ease of data entry are very important for acceptance by physicians, who seem to have a short tolerance time for clumsy system performance. Moreover, because typing on a computer can interfere with the physician-patient interaction,

Figure 23-16 Example of the summary sheet that gives the physician the rationale for each of the tests suggested for the patient. This sheet is generated by the HealthQuiz computer device, which uses the patient's answers to the HealthQuiz questionnaire, plus 480 algorithms programmed into the device, to make its decisions; it also provides International Classification of Diseases, ninth edition (ICD-9) codes for each choice.

a conscious effort must be made to move away from the computer and to address the patient directly, so that he or she does not "feel like a number."

Laboratory systems, pharmacies, and administrative billing systems have led the way in providing on-line data systems. [238] These data may be integrated into the collection process if suitable computer interfaces can be constructed. More problematic is the incorporation of notes or other nondigital data from outside sources. Unfortunately, manual transcription of these notes cannot capture certain kinds of data such as that on ECGs, or signatures. Although information systems are being adapted to transfer image-based data--perhaps by scanners or fax machines--at present there are few standard ways to facilitate exchange of these kinds of data.

A related problem is obtaining historical information and the past chart. Most institutions have large volumes of information on paper records that are available to varying degrees. As any system is developed and implemented, allowances must be made for the period in which the electronic and paper systems exist side by side until the paper records have been incorporated into the electronic system.

Collation of Data: Perioperative Database

Databases consist of an "engine" and an interface. The engine is the computer program that actually stores and retrieves information. Many commercial engines such as Dbase, Foxpro, Sybase, Access, and Filemaker, as well as proprietary programs written by vendors, are available. Although a full discussion of the different engines is beyond the scope of this chapter, several questions need to be addressed when evaluating any database system.

First, these systems range from intensely complex, requiring a full-time programmer available for maintenance and modifications, to relatively user-friendly, perhaps maintainable by a physician who has some background in database management. When selecting a system, the potential

Figure 23-17 Sample checklist for determining which preoperative laboratory tests should be obtained. CPK, creatine phosphokinase; ECG, electrocardiogram; HCT, hematocrit; Hgb, hemoglobin; PT, prothrombin time; PTT, partial thromboplastin time; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SMA 6 and SMA 12, simultaneous multichannel analyses of 6 and 12 blood components, respectively; WBC, white blood cells.

buyer must consider the resources necessary for maintenance. Second, these systems vary in their ability to exchange information with other database systems, such as a hospital-based information system. We believe that the ease of exchange, both now and in the future, should be considered in the selection of a system. Third, the hardware that implements the system also warrants some consideration, although to a lesser degree than the previous two criteria. Today, processor speed and storage on desktop systems are making the selection of hardware a less critical issue than before. Fourth and finally, thoughtful design of the interface system is very important, because this feature determines the everyday ease and usefulness of the system. Forty-five percent of medical information systems that are installed are not successful, even though they are technologically sound. Many of these failures arise from nonacceptance by users.

Clinicians want an easy way to specify how they move information in and out of the system (the interface) and to be able to modify that interface without being charged for each change in format of the report. Programs such as Filemaker and Access include so-called "drag-and-drop" designs that allow the user to create new input and report forms easily. Other systems may require programming assistance or, in the case of a proprietary system, a more formal process with the vendor, in order to change the system. With the rapid changes in health care, any system will need to be improved and changed on a regular basis in order to obtain maximum benefit from the system.

The hardware systems that run these programs have become more affordable and accessible. Again, a detailed discussion of specific hardware is beyond our scope, but some broad issues should be addressed. Many of these systems can run on personal computers. The clinical environment, however, is much more demanding than the office environment. The physician working in an office can tolerate a certain amount of instability and downtime on a computer. In a clinical environment, however, these conditions cannot be allowed without considerable consequences. For example, if a paper record is unavailable for one or two cases, the cases may be delayed 20 minutes. If the server or network is unavailable, 15 ORs will be delayed for 20 minutes. Clinical systems should have adequate back-up so that they

can meet the clinical demands of being available 24 hours a day. The cost of having adequate back-up and supporting personnel must be included in any planned installation. Maintenance

costs for information systems can be as high as 70 percent of the total system's cost over the life-span of the system. [239]

Integration of Information

If an electronic information system only collects information and duplicates the current paper system, the cost-benefit advantage is likely to be marginal. Furthermore, it is highly unlikely that merely automating the collection of data will produce significant time savings. The benefits become clear when data are analyzed and disseminated.

The first benefit concerns the reporting of data to facilitate evaluation, discussion, and subsequent care of the patient. By necessity, the paper record had to report data in the order recorded. Reexamination of the paper report may show that simple electronic reformatting of the displayed information, bringing key points to the top and emphasizing them, would benefit the person receiving the report. If the reports are available on-line, they no longer need a linear presentation at all. Only the key points may be initially presented, with additional details available through a mechanism that allows the user to select a statement or fact on the screen and to obtain additional details or information.

The computer can also help the physician clinically. It can provide reference material on unfamiliar conditions or drugs--sometimes even automatically, as in the case of warnings about possible drug interactions. In addition, when an institution wants to guide and track use of its resources, the computer can suggest preferred clinical pathways. The system may actually do an initial analysis of the data, based on algorithms, to assist in clinical decision-making. The ASA and other standard-setting organizations, including the state of Maine, recognize the importance of clinical judgment and the interaction between patient and physician (Fig. 23-19) (Figure Not Available) . An example of this assistance to the clinician is the HealthQuiz Plus 2 program, which not only collects patient-provided information, but also applies algorithms that include guidelines, facts about the performance of a variety of tests, and the prevalence of disease, based on the patient's information. The program then provides an initial assessment of risk and suggests appropriate laboratory tests. (All these processes facilitate reimbursement for test ordering.) The tests guide the physician in the assessment of the overall clinical situation and in the creation of a care plan. This system

Figure 23-18 Sample patient questionnaire for determining which preoperative laboratory tests should be obtained.

has been shown to reduce the ordering of tests without overlooking those that are medically warranted. Moreover, such systems have the advantages of always posing a comprehensive set of questions to the patient and of not forcing the clinician to compromise comprehensiveness because of time constraints. Beers and colleagues [240] showed that such a system did a better job of obtaining accurate and complete patient histories than time-pressed clinicians. Computer-assisted analysis of data will expand as we develop ways for computers to use all the data they have accumulated.

Research can be another opportunity for benefit. [241] [242] [243] [244] [245] [246] [247] However, as an initial warning, we emphasize that these systems build large data sets rapidly, and the temptation to search the data for a correlation is both strong and misguided. Correlations found in this manner are often misleading and, only if supported by logic, may at best provide the basis for asking more formal questions. Pursuit of these questions, in a prospective fashion, can be rewarding. If the interface is readily flexible, both the input and the analysis can be modified to address specific issues. In the future, the ability to connect the preoperative data with outcomes captured electronically will only increase the usefulness of these databases as tools.

Through improved coding and billing, the use of preoperative databases has been shown to improve economies and cost recovery. [26] [27] [247] These improvements in cost-recovery mechanisms, along with the improvements in laboratory utilization and reimbursement for medically indicated ICD-9-coded test ordering, may justify the cost of implementing a system in the context of a preoperative clinic (see later).

Dissemination of Information

One of the main reasons for instituting an electronic record is to ensure availability of the collected and analyzed data on the day of surgery. At one institution, as many as 20 percent of manually completed forms were being lost in the process. This loss would happen most frequently when either the date or location of surgery was changed after the preoperative visit. Many practitioners also find themselves working at multiple sites, either within the same institution, at different surgeons' offices or ambulatory care centers, or across the city or even across state lines. The ability to review information for any patient at any site the night before surgery allows the anesthesiologist to better plan and prepare

for the next day's cases, and to call the patient, with substantial knowledge about that patient. This process enhances both patient care and efficiency of the ORs.

The information has additional uses. Billing can be based on information about the planned procedure from the preoperative visit, a circumstance that enhances proper reimbursement. Other institutional forms that have redundant information, such as check-in sheets for the morning of surgery, can be replaced or eliminated, and this also increases OR efficiency.

Institutions will vary in the frequency with which patients return, but having the basic information for a patient from a previous procedure can be timesaving for subsequent elective operations. It can even be lifesaving in the event of an urgent procedure for which old records are unavailable and the patient cannot provide a history.

Every discussion of information systems should consider security and confidentiality. The same access that is necessary for efficient dissemination of information can have very negative effects on patient trust and a significant legal impact if improperly used. It is crucial that any system have both controlled access and accurate logging of use to minimize the opportunity for inappropriate use and to identify abuse. Users of the system must be informed of the significant and strictly applied penalties for improper use of the records. Additional protection of patient data is being provided by rapidly evolving legislation and frequent advances in technology, such as encryption. This area requires expert assistance, both technical and legal, that should be obtained by anyone who is implementing an information system containing patient data.

Improving Patient Satisfaction With Preoperative Evaluation

We have used our information system to increase patient satisfaction with preoperative evaluation in several ways (Foss JF et al, in preparation). We found that the most important factor in decreasing patient satisfaction was delay in

Figure 23-19 (Figure Not Available) Two standards published by the American Society of Anesthesiologists (ASA) in the *ASA Directory of Members 1994.* (A) Statement on routine preoperative laboratory and diagnostic screening. The routine use of laboratory or diagnostic screening tests is not an essential part of the preanesthetic evaluation of patients. (B) Basic standards for preanesthesia care. The history, physical examination, and chart review are essential when obtaining tests as part of preanesthesia care. *(From American Society of Anesthesiologists [282])*

seeing a physician. Therefore, we use our information system to decrease this time interval.

Our system logs the arrival time of the patient at the clinic. After the patient has completed the self-administered questionnaire on health matters, the computer system uses those answers to determine the risk status of that patient, categorized as HealthQuiz ASA status 1 through 5. A "triage nurse" then uses that risk status, definitions of the three levels of surgery (minimally invasive surgery, surgery of moderate intensity, or major surgery), and the functional age of the patient (i.e., *physiologic,* not chronologic, age [RealAge]) to determine what level of visit with the anesthesiologist is required. A comprehensive visit takes 20 minutes or more and assesses the patient who has a HealthQuiz ASA status of 1.75 or higher, *or* is undergoing major surgery, *or* has a RealAge of more than 65 years. The next category, the visit of intermediate intensity, takes 15 to 25 minutes. These patients have a HealthQuiz ASA status of 1.5 to 2, *or* are undergoing type B surgery, *or* have a RealAge of 61 to 65 years. Finally, the "expedited visit" takes 5 to 10 minutes and evaluates the patient who has a HealthQuiz ASA status of 1.74 or less, *and* is undergoing minimally invasive surgery, *and* has a RealAge of less than 61 years.

Once the appropriate level of visit has been determined, the patient is made ready to see the anesthesiologist. He or she is placed in an examination room and is dressed from

the waist up in a hospital gown. Blood pressure, heart rate, height, and weight are recorded, and a self-entered history is completed by the patient.

The patient's status is entered into the computer system, and the times to each room are tracked on the local area networked computer system. A red light signals when an "expedited patient" is ready to be seen. The anesthesiologist often excuses himself or herself from the comprehensive-visit patient and sees the expedited patient as soon as possible. (Comprehensive-visit patients seem not to object to the interruption, because they understand that they require, and will receive, extra physician time.) The total time for patients is not reduced, but the delay until the patient first sees the physician is decreased.

Another way we use our informatics system to improve patient satisfaction is to ask patients to complete another self-administered questionnaire after surgery. The questionnaire, which is given by phone or, if in-hospital, by computer or paper and pencil, assesses the patient's satisfaction with the anesthesia service's performance and pain therapy. Feedback for such results has improved performance of the physicians in satisfying patients' pain-relief requirements.

Thus, we use an informatics system to increase patient satisfaction directly, by shortening the time before the patient sees a physician, and by improving pain therapy. We also believe, however, that many other uses of informatics increase patient satisfaction indirectly. These uses fall broadly into the category of patient education. For example, in this stillexperimental role, our information system helps us to learn which patients desire video presentations about their anesthesia and surgery, which we are then able to provide.

Information systems are not a replacement for good care, nor is it likely that they will decrease the time spent with patients. If carefully designed and implemented, information systems can enhance the acquisition and management of data, so that physicians can spend more of the time they do have with patients attending to their care. Although such systems can decrease the risks of caring for a patient by providing a complete working database, they are also capable of introducing new risks regarding confidentiality of data and dependence on availability of the system. No matter how much automation, education, or informatics you decide to employ, the decision most important to success is to marshal the resources and consensus of department members and users (surgeons, obstetricians, radiologists, administrators) to compel such a considerable undertaking.

GAINING THE RESOURCES AND CONSENSUS TO INITIATE AND MAINTAIN AN ANESTHESIA PREOPERATIVE EVALUATION CLINIC

The anesthesiologist is the specialist most knowledgeable in evaluating and managing operative medical complexities as they relate to anesthesia and surgery. "The assessment of, consultation for and preparation of patients for anesthesia," is contained within the American Board of Anesthesiology's definition of the practice of anesthesiology in its *Booklet of Information* (Raleigh, NC, American Board of Anesthesiology, 1996, p 2). This assessment of the patient begins with the preoperative evaluation.

As changes in the health-care system decrease reimbursement and the length of stay in the hospital, more and more surgical patients are entering the hospital on an outpatient basis or as same-day admissions. [248] [249] This trend is expected to increase and reflects not only a national and even international cost-conscious environment but also the expanding market for managed care.

Same-day admissions present the anesthesiologist with a formidable challenge from both an organizational and a clinical perspective. The amount of time available to evaluate even medically complex patients has decreased. Providing quality, cost-effective preparation of patients before surgery is a central issue in the optimal perioperative management of the patient. This requirement and the consequent need to redefine and expand the traditional practice of anesthesia, especially outside the OR, have been accepted as necessary among anesthesiologists in both academic and community practices. [250] [251] [252]

The preoperative evaluation is often the first encounter a patient has with anesthesia and health-system-based or hospital-based services. Examination facilities, personalized services, and organizational efficiency during the evaluation often influence a patient's perception of the quality of health care at that institution. As mentioned, we have found that the rapidity with which a physician sees the patient is *the* most important factor in determining patient satisfaction with the preoperative process (Foss JF et al, in preparation). Facilitation of this process by an electronic medical record, coupled with "time-stamped" computer records, is discussed in the previous section.

The establishment of an anesthesia preoperative evaluation clinic (APEC) [25] [26] [253] [254] [255] [256] [257] [258] has become an important and formal process over the past several years at many private and academic institutions. A centralized APEC is a positive investment for the anesthesia group and the hospital, because it becomes a recognized center for decreasing perioperative costs, improving the efficiency of clinical services, implementing clinical pathways that educate and increase market share, and increasing patient and surgeon satisfaction with perioperative services.

Developmental and Organizational Changes

The goal of the APEC is to provide a comprehensive anesthesia service for physicians and their presurgical patients. One centralized location provides all anesthesia consultations, physical examinations, laboratory and ECG services, educational resources, and hospital registrations and insurance authorizations. The objective is effectiveness, efficiency, and equality of care for all patients. Modifying the existing clinical practice in order to provide cost-effective preoperative evaluation is within the ability of each anesthesiologist and can be approached from a variety of methods, educational tools, and uses of data (Table 23-20) .

The APEC may not be suitable in its entirety for all academic departments or private individuals and groups that administer anesthesia. However, many of the concepts and methods described can be adapted to smaller centers and to

TABLE 23-20 -- Key Areas to Consider in Promoting Cost-Effective Preoperative Preparation

1. Physician education and modification of physician practice (e.g., learn the cost of each diagnostic test ordered preoperatively, plan length of stay with pain therapy practitioners)
2. Practice guidelines
3. Clinical pathways (requires interdepartmental teamwork)
4. Information sharing (e.g., in areas of evaluative protocols and avoiding duplication of services)
5. Economic analysis (e.g., cost-identification, effectiveness, or cost-benefit studies)
6. Medical resource management (e.g., in the efficiency and effectiveness of the preoperative process)
7. Education about, and reassessment of, perioperative satisfaction and plans for perioperative pain therapy
8. Outcomes measurement and management

the private sector. Certain advantages do accrue when an APEC is established, but implementation may require stages of change and growth. (We advocate taking incremental steps up the organizational ladder to efficiency: improvement of preoperative testing, implementation of education about perioperative care, and then implementation of education about expectations on pain therapy.) Our collective experience is that instituting such a clinic requires a commitment from more than just the anesthesia department. Without the support of surgical services and without administrative, financial, and emotional commitment, the APEC will not meet its full potential and may even incur extra costs rather than savings. However, with such commitment, the health system will increase the quality of its care and will decrease costs. Nevertheless, logical as it is, such commitment will not come easily.

The development of the APEC represents a collaboration between hospital administration and the departments of anesthesia, surgery, gynecology, and nursing. Implementation of a successful APEC requires the commitment of money and time, defined organizational goals, changes in support resources, intradepartmental teamwork, and determination of the hospital and several departments to make effective changes in the existing operational procedures. Table 23-21 shows the operational goals for an APEC.

A timeline for the development of an APEC should be defined for hospital administration in a business plan. The plan would clearly describe not only reasonable and sustainable goals but also the financial, political, and emotional support necessary for success of the APEC. The plan would also include analysis of the existing method of providing preoperative evaluation, recommended changes, developmental strategies, descriptions of APEC management and organizational imperatives, and an evaluation of financial risk.

The development of an APEC begins with a departmental commitment to improve the current system. Even the simplest of changes can enhance the quality of patient care. For example, having a patient complete an anesthesia medical questionnaire at the surgeon's office and then having that information transmitted to the

anesthesiologist for review several days before surgery would greatly increase the anesthesiologist's awareness of the patient's medical status. The patient questionnaire could be completed by phone after the surgeon's nurse has entered some basic demographic data about the patient into the automated phone system (see previous section on informatics). The information could then be made available to the surgeon, OR, and anesthesiologists the day before the anticipated surgery. This practice could reduce the delays and cancellations that occur when unexpected medical problems are present or unresolved at the scheduled time of surgery.

Necessity for Teamwork

The APEC is an integrated partnership having visible alliances with the departments of anesthesia and nursing, often surgery and obstetrics, but always the hospital or health-system administration. Frequently, the existing system of preoperative assessment is beleaguered by the need for change in many of the time-honored traditions, structures, and processes.

Figure 23-20 shows the fundamental goals the APEC strives to accomplish. These goals recognize and encourage clinical responsibility in the portioning of services and, most important, in the sharing of financial costs and savings in the APEC enterprise; that is, because the department that bears the cost of making the APEC work is not always the department that enjoys the subsequent savings, transfers of funds are necessary to make the system really work fairly for all

TABLE 23-21 -- Operational Goals for an Anesthesia Preoperative Evaluation Clinic

1. To improve the patient's perception of the preoperative evaluation experience by increasing personalized patient care, comfort, and convenience.
2. To provide a centralized site for preoperative evaluation.
3. To institute an anesthesia scheduling system for timely patient access and flow.
4. To ensure the presence of an anesthesiologist on site when patients are present.
5. To appoint a medical director of the APEC to coordinate all activities.
6. To ensure the availability of medical records and surgical notes at the time of the preoperative evaluation.
7. To decrease logistical shuffling of patients to multiple hospital service areas.
8. To integrate and coordinate services through on-site facilities for admitting/registration, insurance authorization, laboratory tests, and electrocardiographic studies.
9. To improve the education of patients and families about the elements of their surgical procedure and the proposed anesthesia care, including postoperative pain-control options.
10. To educate patients about what to expect regarding postoperative feeding and discharge needs.
11. To ensure and coordinate cost-effective ordering of preoperative laboratory and diagnostic studies.
12. To provide an anesthesia medical consultation service for evaluation of medically complex inpatients and outpatients.
13. To decrease the number of cancellations and delays in the operative procedures on the day of surgery.
14. To enlist the skills of a nurse practitioner to assist in preoperative evaluations and patient/family education.
15. To develop protocols, policies, and clinical pathways.
16. To perform quality assurance reviews.
17. To maximize efficiency in operating room function and turnover time by coordinating all preoperative information at one location, the APEC.
18. To enhance patient and surgeon satisfaction.

APEC, anesthesia preoperative evaluation clinic

Figure 23-20 The anesthesia preoperative evaluation clinic is a constructive partnership working toward the achievement of common goals. The sharing of resources and budgetary costs is apportioned.

concerned. These transfers, plus agreement on the incentives and goals, should be considered *before* institution of the clinic.

To encourage the referral of patients to the APEC by surgeons, anesthesiologists should identify the clinical, and perhaps marketing, advantages. Interviewing surgeons regarding their concerns and problems with preoperative assessment helps to identify the changes that will be necessary. Likewise, administrators should be interviewed regarding their desires for efficiency of patient care, for increased patient education and satisfaction, and for marketing advantages. Such a process marks the anesthesiologist as an active partner and a resource for improving perioperative care.

In addition to the primary mandate of patient safety, our surgical colleagues are also concerned with avoiding cancellations and OR delays, and in reducing costs and improving patient satisfaction through education, in order to facilitate marketing. To enhance the anesthesiologist's commitment to the APEC and to increase the patient referral base, an "informal assurance" may be given that if the patient is deemed appropriate and remains medically stable, the patient's care will proceed to surgery without cancellation or delay. This process requires that the entire anesthesia group support the APEC program and protocols, and it means that not all physicians can give consultation in the APEC. It also means that this position requires an experienced clinician.

Economic Concerns and Benefits of Developing a Clinic

What are the costs and benefits of the APEC, and who ultimately supports the APEC financially? This last question is pertinent because the costs of an APEC are borne by one group, but the benefits accrue to another. One of the basic principles of economic analysis of a new venture is that comparison and choices must be made between the existing use of resources and the proposed alternative. An economic clinical analysis should evaluate both the cost and the outcome when comparing all the variables that would pertain to changing of the existing manner of preoperative assessment to that of an APEC.

Any financial support given to an APEC by a hospital would be based on price, quality, and value. Therefore, a cost analysis of the current system of preoperative evaluation would describe the problems, effectiveness, and cost of the traditional system and the subsequent surgical effectiveness of the new system. This document is more effective if it is comprehensive and focuses on opportunities for improvement. It could be supported by recent publications demonstrating cost-effectiveness and improved outcomes when an APEC has been established. An APEC that offers no improvement in outcome and an increase in cost is unsuitable and economically detrimental to the hospital or health system, as well as to the anesthesia department.

The strategic alliance and partnership with hospital/ health-system administration and the departments of nursing and surgery (obstetrics, gynecology, and radiology) toward the common goals of improvement in quality, cost reductions, and reduced length of stay through educational programs require that the financial support and gains of the APEC be delegated responsibly and fairly. For example, the facility and professional staff and the maintenance, equipment, registration, and phlebotomy personnel associated with an APEC would incur cost to the hospital/healthsystem administration. Nursing and educational resources would be supported through the department of nursing or anesthesia cost center. Similarly, benefits from reductions in length of stay and reduced OR times and cancellations should be shared among the parties.

The APEC staff can be cross-trained to provide services to other areas of the OR during periods of reduced patient volume. This sharing of resources would decrease APEC costs and increase APEC profits. An anesthesiologist would serve as medical director of the APEC. Financial support for the APEC would come from both the department of anesthesia and the hospital/health-system administration, because the APEC is a hospital-centered partnership. Similarly, in providing resources for the APEC, profits recovered from decreased costs elsewhere and increased market share should be shared among the departments, including surgery.

TABLE 23-22 -- Outline of a Business Plan for an Anesthesia Preoperative Evaluation Clinic

I. **Executive summary** (one-paragraph summary of the APEC program)

II. **Description** of an APEC
Objective or mission of the APEC (Fig. 23-20)
Names of the proposed APEC medical director, department chair
Location within the hospital designated for the APEC (define an area, even if currently occupied)
The development stage (is there an existing preoperative program?)
The services of an APEC (operational goals, Table 23-21)
Anesthesiology specialty information (i.e., anesthesiologists are the experts in operating room medicine and preoperative evaluation)

III. Analysis of general factors affecting **viability** of the APEC
Volume and medical condition of preoperative patients (present a graph for past years)
Anticipated growth trends
Vulnerability to economic factors (e.g., fee-for-service is decreasing, managed care is increasing, and hospitals need to decrease costs)
Technologic factors (e.g., anesthesia and surgical procedures are becoming increasingly complex)
Regulatory issues (the APEC conforms to all local, state, and federal policies)
Financial considerations

IV. Definition of **target markets**
All outpatient and same-day admissions (i.e., increased smooth flow of the healthy patient through the health-care system and educational processes, often starting in the surgical office)
Medically complex patients undergoing anesthesia and surgery

V. Discussion of factors relating to **competition**
Competitive position of the APEC (the anesthesiologist is the operating room and preoperative medicine expert)
Barriers to entry (primary care physicians/consultants believe they have sufficient specialty knowledge to clear patients for anesthesia and surgery)
Future competition (see earlier)

VI. Description of effective **marketing strategies**
Increased visibility, which increases viability of the APEC
Use of hospital/health-system news media to explain who anesthesiologists are and what they do
Formation of strategic partnerships with the departments of nursing, surgery, and gynecology, and with the hospital/health-system administration
Informal assurance that cases will be facilitated by anesthesia if seen in the APEC
Presentations at surgical, medical, gynecologic, pediatric, and administrative grand rounds and conferences

VII. Description of **operational aspects** of the APEC
Facilities (e.g., examination rooms, phlebotomy/ECG room)
Equipment and supplies
Variable labor requirements (e.g., nurse practitioner, anesthesiologist)
Daily anticipated operations and flow
Quality assurance and utilization review (Table 23-24)
Management information systems

VIII. Description of **management and organization** of the APEC
Clinical and administrative director
Inclusion of the department of nursing, and hospital administration
Organization management (presented in a flow chart)

IX. Description of the **developmental goals** of the APEC
Short-term goals (changes in clinical practice)
Long-term goals (e.g., renovation of facilities)
Time line (demonstrates a developmental plan)
Growth strategy (projection of 6-month, 1-year, and 5-year goals)
Evaluation of risk (as long as patients have surgical needs, risk is minimal)

X. Discussion of **financial matters**
Income statement (consider a facility fee, anesthesia medical consultation charge, projected hospital/health-system cost savings, and market share enrichment)
Variable expenditures (i.e., APEC personnel and resources: 90% of expenditures, facility housekeeping and supplies)
Balance sheet

APEC, anesthesia preoperative evaluation clinic

Development of an APEC and financial commitment in an era of cost containment require a business plan to secure support of the hospital or health-system administration. This plan should show an overall cost reduction that should be shared, because incentives determine the success of the process. Table 23-22 suggests the sequential elements of an APEC business plan.

Strategic Need to Market the Clinic

The concept of public relations and marketing of the APEC may be unfamiliar to the anesthesiologist. Increased visibility of the anesthesiologist in an APEC increases awareness of the clinical expertise of the anesthesiologist and his or her role in developing clinical pathways and pain therapy that decrease the patient's length of stay. For example, at one of our institutions, preoperative evaluation and postoperative pain-therapy groups are linked (i.e., provided by the same team of physicians, a subgroup of a department) in order to facilitate patient education and rapid discharge. The result has been superior satisfaction on the part of patients and other health-care providers.

Hospital/health-system publications, presentations at medical, surgical, and gynecologic grand rounds (and administrative grand rounds, if such exist at one's institution), and personal communication with physicians all increase the awareness of surgeons, hospitals, and health systems regarding

TABLE 23-23 -- Facilities of the Anesthesia Preoperative Evaluation Clinic at Stanford University Hospital and the University of Chicago [a]

The APEC at Stanford University consists of the following facilities (information for the University of Chicago is shown in brackets):

1. Five combination office and examination rooms [10]
2. A patient and family education room (preoperative teaching) [1]
3. A patient-centered media and video room [0]
4. A phlebotomy and electrocardiography room [8 are set up for this]
5. An on-site office for the APEC medical director [1]

6. A registration and reception area [1]
7. On-site restroom facilities [2]
8. A large, comfortable patient lounge [1]
9. An area for admitting and financial services [yes]
10. Approximately 2,200 square feet for facilities [2,600]
11. Conference room and shared chart and computer support room [University of Chicago only]

APEC, anesthesia preoperative evaluation clinic

[a] All areas are accessible to wheelchairs.

the direct influence of the APEC and anesthesiologist on cost-effective preoperative patient management. Many hospitals have an office of planning and development or a media center that can participate in marketing and educational strategies that would promote the APEC, its policies, and its educational programs.

Renovation of Facilities

The centralization and modernization of preoperative evaluation procedures represented by an APEC are long-term investments in the proper facilities, and they benefit the patient, anesthesia group, and hospital. Focusing all services into one area produces a center that is visible and efficient. Table 23-23 shows the facilities that constitute the APEC at Stanford University Hospital and at the University of Chicago.

Daily Operations and Procedures

The daily operations of an APEC vary according to patient volume, severity of the patient's medical conditions, availability of the facility, and employee resources. However, we are able to suggest a general operational structure that represents several APECs currently in existence.

A full-time APEC facility serves 40 to 60 patients a day. The full-time APEC requires availability of assessment from 8 AM to 6 PM Monday through Friday. The average time needed from check-in to discharge of ASA I patients is 40 minutes; for ASA II patients, it is 60 minutes; and for ASA III or IV patients, it is 80 minutes. Approximately one-third of that time is spent with a clinician. If fewer than 25 patients are seen a day, a half-day clinic may be appropriate. In this instance, physicians may rotate to the OR after 5-hour stints, because work in the APEC is intense.

To allow patients to be evaluated in a timely and efficient manner, the APEC appointment schedule is made available to the surgical specialty clinics. The surgeon's specific OR reservation can be linked to the requirement that a patient must also have an APEC appointment. This practice not only facilitates anesthesia appointments but also encourages the delivery of patient-centered care.

Previously, most patients ("drop-ins") would come to the APEC in large numbers in the midafternoon and would consequently experience long waits for anesthesia evaluation. Although this situation has been greatly improved by scheduling of appointments, some flexibility regarding "drop-ins" helps to accommodate patients requiring urgent surgical decisions and those from outside the hospital area.

After registration, the patient is processed through hospital/health-system admissions, utilization review, and financial services, located in the APEC. These processes are coordinated with the patient's completion of a preoperative questionnaire [259] (HealthQuiz Plus 2 or similar processes), which seeks information about pertinent medical history, previous surgeries, and medications. Processing of the patient through these services and completion of the questionnaire are scheduled with the goal of maximizing the efficient use of physician time. The patient's historical medical record is available at the time of the APEC appointment; the medical records department has received, by electronic communication and 24 to 72 hours in advance, a list of the patient's scheduled appointments for that day.

The anesthesia evaluator interviews and examines the patient and obtains (via facsimile and phone) whatever outside medical information is needed to complete the assessment. At one of our sites (the University of Chicago), all this information is directly entered into a patient database (see earlier). Appropriate laboratory, diagnostic, and ECG requirements are determined and are obtained on site in the APEC clinic. The centralization of services provides a significant convenience to patients, who no longer need to visit several hospital sites to complete preoperative requirements. ECGs are evaluated before the patient leaves the APEC. All laboratory tests are reviewed at the end of the clinic day.

A perioperative educator, usually a nurse, provides individualized education for the patient and family in the preoperative teaching center located in the APEC. Preoperative education increases the patient's understanding of what to expect regarding postoperative pain therapy and, by decreasing anxiety and fear, achieves its goal of increasing patient comfort. Additionally, preoperative patient education reduces pain and the length of stay in the phase II recovery area and inpatient facilities, and it sets the expectations regarding recovery and the needs of the patient on discharge from the hospital. The educational program is organized with the help of the specific surgical service and the office of hospital/health-system planning in order to provide patients with videotapes and descriptions of expectations and plans.

The personal interaction with a perioperative educator allows each patient to discuss concerns and to ask questions about his or her anesthesia and surgery, the rehabilitation process, pain-management options, and the expected hospital course. "Standardized care plans" written for each surgical procedure are used to focus on specific perioperative information and to provide an overview of the events on the day of, and after, surgery.

Previously, each surgical service had a nurse educator who provided perioperative education for patients. The

APEC program reduced use of this hospital resource significantly and currently coordinates all education through the centralized APEC location. The preoperative teaching center has a variety of anatomic models, brochures, charts, prostheses, specific videotapes made for this process, and other items to help patients understand their proposed anesthetic, surgical, and perioperative management. Some items can even focus on preventive long-term care, such as cessation of smoking, exercise programs, control of blood pressure, and medications. The anesthesia perioperative database program generates written instructions for the patient and significant others. These instructions specify where to go, when to be there, which medications to take, and what to expect in the perioperative period.

Staff members telephone patients on the evening before surgery [260] to confirm arrival time, to reinforce instructions, and to answer any questions. This contact by telephone helps to avoid delays and cancellations on the day of surgery.

Anesthesia Medical Consultation

The APEC provides another important service, the anesthesia medical consultation. This is not simply a routine preoperative examination but a conference requested by a primary care physician or surgeon who seeks advice on the suitability of the patient for anesthesia in light of the patient's medical condition. Obtaining these consultations 6 or more days before the planned day of surgery has many advantages. It facilitates the planning of intraoperative anesthesia and monitoring requirements, the obtaining of outside consultations and additional testing, and preparation for perioperative pain therapy and discharge. Although this system seems formidable, it is assembled in small steps by a team. The members of the team agree in advance not only to develop the plan, but also who has responsibility for each aspect of the plan.

An anesthesia medical consultation increases the awareness of surgeons and patients regarding the expertise of the anesthesiologist on perioperative medicine. For one thing, this type of consultation may initiate diagnostic and/or therapeutic actions for a specific medical problem. For example, instead of providing a general "clearance" for anesthesia and surgery, the APEC anesthesiologist may recommend referral of the patient to a specialist such as a cardiologist, for evaluation of a

specific intraoperative concern.

The expertise of the anesthesiologist is also evident when he or she is involved in the decision-making process regarding consultations. Fischer [25] reported a 73 percent reduction in unnecessary consultations to medical specialties when the anesthesiologist was involved in the consultation decision process. By reducing questionable consultations and further diagnostic studies, hospital costs decreased. Quality assurance data seemed to indicate no adverse patient outcome.

Regarding billings, APEC consultations are first coded using the CPT of the American Medical Association. Then a professional fee is submitted, and reimbursement is requested. Although routine visits (those usual in the past) are not billed for, the educational/evaluation process that differs from the past is billed for, and any savings that accrue from reduced length of stay are shared, in order to fund the clinic.

Perioperative Quality Assurance Indicators

The APEC is a multidisciplinary arrangement that requires changes in the existing clinical practices and hospital resources. Hospital/health-system administration, surgeons, and other physicians monitor its performance and outcome. A database system allows entry and analysis of quality assurance indicators for the APEC. This information can measure the effectiveness of activities that improve performance, cost and resource data, savings, and potential organizational inefficiencies and benefits.

System problems that cause costly surgical delays or cancellations, together with practices requiring improvement or enhancement, are easily identifiable. Figure 23-21 summarizes data from the previous section on preoperative informatics to suggest a database format that would allow evaluation of quality assurance indicators for an APEC.

Cost-Effectiveness of the APEC

To enhance market share and profitability, health-care institutions have focused heavily on cost reductions. [23] Several authors have reviewed the economic principles and issues associated with analysis of health-care costs.

In preparing a patient for surgery, physicians are directly responsible for providing and ordering virtually all the patient's evaluations, preoperative diagnostic tests, and referrals to specialists. The responsibilities of the anesthesiologist are unique in the preoperative process. The anesthesiologist is the final clinical pathway or "gatekeeper" for the patient entering the OR and for the facilitation of postoperative pain therapy. As such, the APEC anesthesiologist is a central figure in the review and implementation of practice guidelines [5] [261] [262] [263] [264] [265] and clinical pathways and also participates in sharing of information (such as patient evaluation protocols and consultations), avoiding duplication of services, identifying costs and benefits, and evaluating the management of medical resources and measurements of outcome.

Because the anesthesiologist is the specialist best able to evaluate intraoperative medical complexities as they relate to anesthesia and surgery, he or she is also best qualified to define and coordinate the appropriate preoperative studies needed for optimal intraoperative management of the patient.

Diagnostic Studies and the Clinic

Using guidelines and clinical judgment seems to be more cost-effective than using only clinical judgment or batteries of tests. Therefore, the APEC uses guidelines described earlier concerning the ability of preoperative diagnostic studies to determine which preoperative tests should be undertaken. These guidelines are provided to the surgeons for review and are based primarily on the patient's age, medical status, proposed surgical procedure, and judgment of the clinician.

Four studies reported a reduction in testing and hospital costs when preoperative diagnostic testing was coordinated

Figure 23-21 A quality assurance form used by an anesthesia preoperative evaluation clinic to assess the quality and efficiency of its service. H&P, history and physical examination; MUGA, multiple uptake gated analysis; PFT's, pulmonary function tests

through the anesthesiologist in the APEC. The reductions in testing and in average hospital costs per patient were, respectively, 55.1 percent and $112.09, [25] 28.6 percent and $20.89, [258] 55 percent and $137 [27] ; Roizen et al [259] reported a $100 decrease in costs.

Delays and Cancellations in the Surgery Schedule

Considerable hospital cost is incurred when an OR is vacant because of a cancellation or delay in surgery on the day

TABLE 23-24 -- Decrease in Surgical Cancellations for Patients Evaluated in the Anesthesia Preoperative Evaluation Clinic

INVESTIGATORS	DECREASE IN SURGICAL CANCELLATIONS
Fischer [25]	88%
Pollard et al [26]	20%
Boothe [257]	60%
Macarthur et al [254]	5 times lower

of surgery. These delays and cancellations can be a significant source of frustration for both the physician and patient, while multiple resources await the arrival of the next patient.

Day-of-surgery delays and cancellations, OR downtime, and loss of hospital revenue decrease when an unstable medical condition is determined *before* the day of surgery. Several authors have reported decreased day-of-surgery cancellations when patients were referred to an APEC prior to the day of surgery (Table 23-24) . Reductions in delays and cancellations increase revenue and produce a positive response from the surgeons and the hospital administration. The anesthesiologist becomes the primary physician identified with preoperative cost containment and improved quality of perioperative patient care. Furthermore, educating the patient about what to expect regarding postoperative pain therapy and feeding decreases the length of stay in the hospital.

Incentives for Cost Reductions

The contribution of the anesthesiologist to cost savings for the hospital or health system is often not obvious and is frequently difficult to quantify. However, the APEC provides several areas of identifiable cost reductions to the hospital or health system for which the anesthesiologist is directly responsible.

A contractual agreement negotiated with the hospital or health system could recognize that the department of anesthesia can influence hospital or health-system costs in the care of patients. The anesthesia department could enter into the hospital capitation risk pool and could share revenue linked to the APEC contribution to

cost-effective care.

Fischer [25] reported a 1-year hospital cost reduction of $1.01 million in unnecessary preoperative testing, and Starsnic et al [25a] noted a 1-year cost reduction of $643,056 when preoperative diagnostic studies were coordinated through the APEC.

Evolution of Anesthesiology

Health care is in an active state of transformation and reform. The next decade will be a transition-rich environment for consolidations, affiliations, and a wide range of strategic business relationships. The anesthesiologist-directed preoperative evaluation clinic represents a successful partnership between hospital and physician and a framework for growth in our specialty.

Anesthesiologists are being asked to provide optimal, efficient patient care within the limitation of finite resources. Current dynamic changes in the field of anesthesiology require a fundamental reassessment and restructuring of the manner in which clinical anesthesia care is provided.

The anesthesia preoperative evaluation is a medical assessment of the patient's current condition, integrated with the anesthesiologist's unique knowledge of the potential clinical and operative events that may occur. The expanding role of the anesthesiologist beyond the OR has redefined the specialty to the hospital, to our colleagues, and to the community regarding the anesthesiologist's clinical expertise, effectiveness, and contribution to quality patient care.

A successful APEC provides the foundation for preparation of the patient for surgery. It returns considerable advantage for the anesthesiologist, improves the quality of care and value for patients, and provides visible hospital leadership in responding to rapidly changing health-care demands.

Summary

Our primary goal has to be efficient delivery of quality care. Patients undergoing surgery move through a continuum of medical care to which a primary care physician, an internist, an anesthesiologist, and a surgeon work in partnership to ensure the best outcome possible. No aspects of medicine require greater cooperation than the performance of surgery and the perioperative care of a patient. For the anesthesiologist, this responsibility should start in a preoperative clinic. The importance of integrating practice is even greater because of the increasing life-span of our population. As the number of elderly patients increases, so does the need for preoperative consultation to plan for comorbidities and multiple drug regimens, knowledge of which is crucial to successful patient management.

At a time when medical information is encyclopedic, it is difficult for even the most conscientious anesthesiologist to keep abreast of medical issues relevant to perioperative patient management. Thus, the proposed preoperative assessment clinic facilitates those most sought-after goals: improved quality of care and reduced costs. We physicians can demonstrate to our constituency, the patients, and to their watchdog, the government, that the present system of preoperative evaluation can be changed to increase efficiency, to reduce costs substantially, and to improve the quality of care. At the same time, anesthesiologists would be able to lessen their own anxiety about performing the very best evaluation possible.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Dr. Raj Kim, who coauthored the analysis of benefit versus risk for laboratory tests, plus Table 23-4 ; and of Dr. Allan Jo, who provided the superb summary of testing for, and treatment of, magnesium deficiency.

References

1. Egbert LD, Battit GE, Turndorf H et al: The value of the preoperative visit by an anesthetist: A study of doctor-patient rapport. JAMA 185:553, 1963.

2. Egbert LD, Battit GE, Welch CE et al: Reduction of postoperative pain by encouragement and instruction of patients: A study of doctor-patient rapport. N Engl J Med 270:825, 1964.

3. Wolfer JA, Davis CE: Assessment of surgical patients' preoperative emotional condition and postoperative welfare. Nurs Res 19:402, 1970.

4. Anderson EA: Preoperative preparation for cardiac surgery facilitates recovery, reduces psychological distress, and reduces the incidence of acute postoperative hypertension. J Consult Clin Psychol 55:513, 1987.

5. Worwag E, Chodak GFW: Overnight hospitalization after radical prostatectomy: The impact of two clinical pathways on patient satisfaction, length of hospitalization, and morbidity. Anesth Analg 87:62, 1998.

6. Vacanti CJ, Van Houten RJ, Hill RC: A statistical analysis of the relationship of physical status to postoperative mortality in 68,388 cases. Anesth Analg 49:564, 1970.

7. Lewin I, Lerner AG, Green SH et al: Physical class and physiologic status in the prediction of operative mortality in the aged sick. Ann Surg 174:217, 1971.

8. Silber JH, Williams SV, Krakauer H et al: Hospital and patient characteristics associated with death after surgery: A study of adverse occurrence and failure to rescue. Med Care 30:615, 1992.

9. Goldman L, Caldera DL, Nussbaum SR et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845, 1977.

10. Keats AS: The ASA classification of physical recapitulation. Anesthesiology 49:233, 1978.

11. Olsson GL, Hallen B: Cardiac arrest during anaesthesia: A computer-aided study in 250 543 anaesthetics. Acta Anaesthesiol Scand 32:653, 1988.

12. Bechtoldt AA Jr: Committee on Anaesthesia Study. Anesthetic-related deaths: 1969-1976. N C Med J 42:253, 1981.

13. Rehder K: Clinical evaluation of isoflurane: Complications during and after anaesthesia. Can J Anaesth 29 (suppl):S44, 1982.

14. Cohen MM, Duncan PG: Physical status score and trends in anesthetic complications. J Clin Epidemiol 41:83, 1988.

15. Farrow SC, Fowkes FGR, Lunn JN et al: Epidemiology in anaesthesia. I. Factors affecting mortality in hospital. Br J Anaesth 54:811, 1982.

16. Fowkes FGR, Lunn JN, Farrow SC et al: Epidemiology in anaesthesia. III. Mortality risk in patients with coexisting physical disease. Br J Anaesth 54:819, 1982.

17. Tiret L, Hatton F, Desmonts JM et al: Prediction of outcome of anaesthesia in patients over 40 years: A multifactorial risk index. Stat Med 7:947, 1988.

18. Cohen MM, Duncan PG, Tate RB: Does anesthesia contribute to operative mortality? JAMA 260:2859, 1988.

19. Lunn JN, Farrow SC, Fowkes FGR et al: Epidemiology in anaesthesia. I. Anaesthetic practice over 20 years. Br J Anaesth 54:803, 1982.

20. Hosking MP, Warner MA, Lobdell CM et al: Outcomes of surgery in patients 90 years of age or older. JAMA 261:1909, 1989.

21. Duncan PG, Cohen MM, Tweed WA et al: The Canadian four-centre study of anaesthetic outcomes. III. Are anaesthetic complications predictable in day surgical practice? Can J Anaesth 39:440, 1992.

22. Pedersen T, Eliasen K, Henriksen E: A prospective study of mortality associated with anaesthesia and surgery: Risk indicators of mortality in hospital. Acta Anaesthesiol Scand 34:176, 1990.

23. Narr BJ, Warner ME, Schroeder DR et al: Outcomes of patients with no laboratory assessment before anesthesia and a surgical procedure. Mayo Clin Proc 72:505, 1997.

24. Gibby GL, Gravenstein JS, Layon AJ et al: How often does the preoperative interview change anesthetic management? (abstract) Anesthesiology 77:A1134, 1992.

25. Fischer SP: Development and effectiveness of an anesthesia preoperative evaluation clinic in a teaching hospital. Anesthesiology 85:196, 1996.

26. Pollard JB, Zboray AL, Mazze RI: Economic benefits attributed to opening a preoperative evaluation clinic for outpatients. Anesth Analg 83:407, 1996.

27. Fu ES, Scharf JE, Glodek J: Preoperative testing: A comparison between HealthQuiz recommendations and routine ordering. Am J Anesthesiol 24:237, 1997.

28. Vogt AW, Henson LC: Unindicated preoperative testing: ASA physical status and financial implications. J Clin Anesth 9:437, 1997.

29. Nardella A, Pechet L, Snyder LM: Continuous improvement, quality control, and cost containment in clinical laboratory testing: Effects of establishing and implementing guidelines for preoperative tests. Arch Pathol Lab Med 119:518, 1995.

30. Larocque BJ, Maykut RJ: Implementation of guidelines for preoperative laboratory investigations in patients scheduled to undergo elective surgery. Clin J Surg 37:397, 1994.

31. Stone JG, Foex P, Sear JW et al: Myocardial ischemia in untreated hypertensive patients: Effect of a single small oral dose of betaadrenergic blocking agent. Anesthesiology 68:495, 1988.

32. Slogoff S, Keats AS: Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 68:676, 1988.

33. Roizen MF: Should we all have a sympathectomy at birth? Or at least perioperatively? Anesthesiology 68:482, 1988.

34. Pasternack PF, Grossi EA, Baumann FG et al: Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. Am J Surg 158:113, 1989.

35. Mangano DT, Layug EL, Wallace A et al: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery: Multicenter Study of Perioperative Ischemia Research Group (McSPI). N Engl J Med 335:1713, 1996.

36. Stamler J, Stamler R, Neaton JD: Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. Arch Intern Med 153:598, 1993.

37. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of systolic hypertension in the elderly program (SHEP). JAMA 265:3255, 1991.

38. The fifth report on the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Ann Intern Med 153:154, 1993.

39. Skolnick ET, Vomvolakis MA, Buck KA et al: Exposure to environmental tobacco smoke and the risk of adverse respiratory events in children receiving general anesthesia. Anesthesiology 88:1144, 1998.

40. Warner MA, Offerd KP, Warner ME et al: Role of preoperative cessation of smoking and other factors in postoperative pulmonary complications: A blinded prospective study of coronary artery bypass patients. Mayo Clin Proc 64:609, 1989.

41. Fiore MC, Jorenby DE, Schensky AE et al: Smoking status as the new vital sign: Effect on assessment and intervention in patients who smoke. Mayo Clin Proc 70:209, 1995.

42. Munday IT, Desai PM, Marshall CA et al: The effectiveness of preoperative advice to stop smoking: A prospective controlled trial. Anaesthesia 48:816, 1993.

43. Starker PM, Group FE, Askanazi J et al: Serum albumin levels as an index of nutritional support. Surgery 91:194, 1982.

44. Khuri SF, Daley J, Henderson W et al: Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: Results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 185:315, 1997.

45. Brownstein AB, Roizen MF: A compelling rationale for using preoperative visits to complete adult immunizations. J Clin Anesth 10:338, 1998.

46. Tinetti ME, Williams CS: Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med 337:1279, 1997.

47. Kujala UM, Kaprio J, Sarna S et al: Relationship of leisure-time physical activity and mortality: The Finnish twin cohort. JAMA 279:440, 1998.

48. Apfelbaum J, Roizen MF, Robinson D et al: How frequently do asymptomatic patients benefit from the pursuit of abnormalities in their preoperative test results? (abstract) Anesthesiology 73:A1254, 1990.

49. Charlson ME, MacKenzie CR, Gold JP: Preoperative autonomic function abnormalities in patients with diabetes mellitus and patients with hypertension. J Am Coll Surg 179:1, 1994.

50. Cyr M, Wartman SA: The effectiveness of routine screening questions in the detection of alcoholism. JAMA 259:51, 1988.

51. Adams WL, Barry KL, Fleming MF: Screening for problem drinking in older primary care patients. JAMA 276:1964, 1996.

52. Gibby GL, Schwab WK: Availability of records in an outpatient preanesthetic evaluation clinic. J Clin Monit Comput 14:385, 1998.

53. Cahalin L, Pappagianopoulos P, Prevost S et al: The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. Chest 108:452, 1995.

54. Older P, Smith R, Courtney P et al: Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. Chest 104:701, 1993.

55. Older P, Hall A: The role of cardiopulmonary exercise testing for preoperative evaluation of the elderly. In Wasserman K (ed): Exercise Gas Exchange in Heart Disease. Armonk, NY, Futura Publishing, 1996, p 287.

56. Roizen MF, Kaplan EB, Schreider BD et al: The relative roles of the history and physical examination, and laboratory testing in preoperative evaluation for outpatient surgery: The "Starling" curve in preoperative laboratory testing. Anesthesiol Clin North Am 5:15, 1987.

57. Roizen MF: Preoperative evaluation. In Miller RD (ed): Anesthesia, vol 1, 3rd ed. New York, Churchill Livingstone, 1990, p 743.

58. Roizen MF: Is a patient's history of food supplement use simply supplementary? J Clin Anesth 10:89, 1998.

59. Lutner RE, Roizen MF, Stocking CB et al: The automated interview *versus* the personal interview: Do patient responses to preoperative health questions differ? Anesthesiology 75:394, 1991.

60. Mitchell TL, Tornelli JL, Fisher TD et al: Yield of the screening review of systems: A study on a general medical service. J Gen Intern Med 7:393, 1992.

61. Epstein B: Controversies in outpatient anesthesia. In White PF (ed): Outpatient Anesthesia. New York, Churchill Livingstone, 1990, p 473.

62. Deeks SG, Smith M, Holodniy M et al: HIV-1 protease inhibitors: A review for clinicians. JAMA 277:145, 1997.

63. Casarett DJ, Lantos JD: Have we treated AIDS too well? Rationing and the future of AIDS exceptionalism. Ann Intern Med 128:756, 1998.

64. Leng GC, Fowkes FGR, Lee AJ et al: Use of ankle brachial pressure index to predict cardiovascular events and death: A cohort study. BMJ 313:1440, 1996.

65. Kuller LH, Shemanski L, Psaty BM et al: Subclinical disease as an independent risk factor for cardiovascular disease. Circulation 92:720, 1995.

66. Roizen MF, Coalson D, Hayward RSA et al: Can patients use an automated questionnaire to define their current health status? Med Care 30 (suppl):MS74, 1992.

67. Badner NH, Craen RA, Paul TL et al: Anaesthesia preadmission assessment: A new approach through use of a screening questionnaire. Can J Anaesth 45:87, 1998.

68. Douglas E: Computerized preanesthetic records can lead to better DRG coding and more reimbursement. Anesthesiol News May:20, 1995.

69. Essin DJ, Dishakjian R, deCiutiis VL et al: Development and assessment of a computer-based preanesthetic patient evaluation system for obstetrical anesthesia. J Clin Monit 14:95, 1998.

70. Kobak KA, Taylor LV, Dottl SL et al: A computer-administered telephone interview to identify mental disorders. JAMA 278:905, 1997.

71. Leonard JV, Clayton BE, Colley JRT: Use of biochemical profile in Children's Hospital: Results of two controlled trials. BMJ 2:662, 1975.

72. Korvin CC, Pearce RH, Stanley J: Admissions screening: Clinical benefits. Ann Intern Med 83:197, 1975.

73. Olsen DM, Kane RL, Proctor PH: A controlled trial of multiphasic screening. N Engl J Med 294:925, 1976.

74. Durbridge TC, Edwards F, Edwards RG et al: Evaluation of benefits of screening tests done immediately on admission to hospital. Clin Chem 22:968, 1976.

75. Narr BJ, Hansen TR, Warner MA: Preoperative laboratory screening in healthy Mayo patients: Cost-effective elimination of tests and unchanged outcomes. Mayo Clin Proc 66:155, 1991.

76. Kaplan EB, Sheiner LB, Boeckmann AJ et al: The usefulness of preoperative laboratory screening. JAMA 253:3576, 1985.

77. McKee RF, Scott EM: The value of routine preoperative investigations. Ann R Coll Surg Engl 69:160, 1987.

78. Turnbull JM, Buck C: The value of preoperative screening investigations in otherwise healthy individuals. Arch Intern Med 147:1101, 1987.

79. Johnson H Jr, Knee-Ioli S, Butler TA et al: Are routine preoperative laboratory screening tests necessary to evaluate ambulatory surgical patients? Surgery 104:639, 1988.

80. Muskett AD, McGreevy JM: Rational preoperative evaluation. Postgrad Med J 62:925, 1986.

81. O'Connor ME, Drasner K: Preoperative laboratory testing of children undergoing elective surgery. Anesth Analg 70:176, 1990.

82. Hackmann T, Seward DJ, Sheps SB: Anemia in pediatric day-surgery patients: Prevalence and detection. Anesthesiology 75:27, 1991.

83. Roy WL, Lerman J, McIntyre BG: Is preoperative haemoglobin testing justified in children undergoing minor elective surgery? Can J Anaesth 38:700, 1991.

84. Nigam A, Ahmed K, Drake-Lee AB: The value of preoperative estimation of haemoglobin in children undergoing tonsillectomy. Clin Otolaryngol 15:549, 1990.

85. Baron MJ, Gunter J, White P: Is the pediatric preoperative hematocrit determination necessary? South Med J 85:1187, 1992.

86. Rohrer MJ, Michelotti MC, Nahrwold DL: A prospective evaluation of the efficacy of preoperative coagulation testing. Ann Surg 208:554, 1988.

87. Lawrence VA, Kroenke K: The unproven utility of preoperative urinalysis: Clinical use. Arch Intern Med 148:1370, 1988.

88. Canadian Task Force on the Periodic Health Examination: The periodic health examination. Can Med Assoc J 121:1193, 1979.

89. Sox HC Jr (ed): Common Diagnostic Tests: Use and Interpretation, 2nd ed. Philadelphia, American College of Physicians, 1990.

90. Hayward RSA, Steinberg EP, Ford DE et al: Preventive care guidelines: 1991. In Eddy DM (ed): Common Screening Tests. Philadelphia, American College of Physicians, 1991.

91. Blery C, Szatan M, Fourgeaux B et al: Evaluation of a protocol for selective ordering of preoperative tests. Lancet 1:139, 1986.

92. Lawrence RS: United States Task Force on Preventive Services Guide to Clinical Preventive Services: An Assessment of the Effectiveness of 169 Interventions. Baltimore, Williams & Wilkins, 1990.

93. Hayward RSA, Steinberg EP, Ford DE et al: Preventive care guidelines: 1991. Ann Intern Med 114:758, 1991.

94. Burke DS, Brundage JF, Redfield RR et al: Measurement of the false positive rate in a screening program for human immunodeficiency virus infections. N Engl J Med 319:961, 1988.

95. Houry S, Georgeac C, Hay JM et al: A prospective multicenter evaluation of preoperative hemostatic screening tests: The French Associations for Surgical Research. Am J Surg 170:19, 1995.

96. Elmore JG, Barton MB, Moceri VM et al: Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 338:1089, 1998.

97. Domoto K, Ben R, Wei JY et al: Yield of routine annual laboratory screening in the institutionalized elderly. Am J Public Health 75:243, 1985.

98. Wolf-Klein GP, Holt T, Silverstone FA et al: Efficacy of routine annual studies in the care of elderly patients. J Am Geriatr Soc 33:325, 1985.

99. Abrutyn E, Mossey J, Berlin JA et al: Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? Ann Intern Med 120:827, 1994.

100. Boscia JA, Kobasa WD, Knight RA et al: Therapy vs no therapy for bacteriuria in elderly ambulatory nonhospitalized women. JAMA 257:1067, 1987.

101. Delahunt B, Turnbull PRG: How cost-effective are routine preoperative investigations? N Z Med J 92:431, 1980.

102. Rossello PJ, Ramos Cruz A, Mayol PM: Routine laboratory tests for elective surgery in pediatric patients: Are they necessary? Bol Asoc Med P R 72:614, 1980.

103. Bates DW, Boyle DL, Rittenberg E et al: What proportion of common diagnostic tests appear redundant? Am J Med 104:361, 1998.

104. Wood RA, Hoekelman RA: Value of the chest x-ray as a screening test for elective surgery in children. Pediatrics 67:447, 1981.

105. Sandler G: Costs of unnecessary tests. BMJ 2:21, 1979.

106. Rabkin SW, Horne JM: Preoperative electrocardiography: Its costeffectiveness in detecting abnormalities when a previous tracing exists. Can Med Assoc J 121:301, 1979.

107. Rabkin SW, Horne JM: Preoperative electrocardiography: Effect of new abnormalities on clinical decisions. Can Med Assoc J 128:146, 1983.

108. Salzmann P, Kerlikowske K, Phillips K: Cost-effectiveness of extending screening mammography guidelines to include women 40 to 49 years of age. Ann Intern Med 127:955, 1997.

109. Tape TG, Mushlin AI: How useful are routine chest x-rays of preoperative patients at risk for postoperative chest disease? J Gen Intern Med 3:15, 1988.

110. Orkin FK: Practice standards: The Midas touch or the emperor's new clothes? Anesthesiology 70:567, 1989.

111. Hirsh IA, Tomlinson DL, Slogoff S et al: The overstated risk of preoperative hypokalemia. Anesth Analg 67:131, 1988.

112. Vitez TS, Soper LE, Wong KC et al: Chronic hypokalemia and intraoperative dysrhythmias. Anesthesiology 63:130, 1985.

113. Harrington JT, Isner JM, Kassirerr JP: Our national obsession with potassium. Am J Med 73:155, 1982.

114. Lawson DH: Adverse reactions to potassium chloride. Q J Med 43:433, 1974.

115. Lawson DH, Hutcheon AW, Jick H: Life threatening drug reactions amongst medical inpatients. Scott Med J 24:127, 1979.

116. Levinstein MR, Ouslander JG, Rubenstein LZ et al: Yield of routine annual laboratory tests in a skilled nursing home population. JAMA 258:1909, 1987.

117. Robbins JA, Rose SD: Partial thromboplastin time as a screening test. Ann Intern Med 90:796, 1979.

118. Parkerson GR Jr: Cost analysis of laboratory tests in ambulatory primary care. J Fam Pract 7:1001, 1978.

119. Parkerson GR Jr: Determinants of physician recognition and follow-up of abnormal laboratory values. J Fam Pract 7:341, 1978.

120. Williamson JW, Alexander M, Miller GE: Continuing education and patient care research: Physician response to screening test results. JAMA 201:938, 1967.

121. Huntley RR, Steinhauser R, White KL et al: The quality of medical care: Techniques and investigation in the outpatient clinic. J Chronic Dis 14:630, 1961.

122. Daughaday WH, Erickson MM, White W et al: Evaluation of routine 12-channel chemical profiles on patients admitted to a university general hospital. In Benson ES, Strandjord PE (eds): Multiple Laboratory Screening. San Diego, Academic Press, 1969, p 181.

123. Epstein KA, Schneiderman LJ, Bush JW et al: The "abnormal" screening serum thyroxine (T4): Analysis of physician response, outcome, cost and health effectiveness. J Chronic Dis 34:175, 1981.

124. Wheeler LA, Brecher G, Sheiner LB: Clinical laboratory use in the evaluation of anemia. JAMA 238:2709, 1977.

125. Kelley CR, Mamlin JJ: Ambulatory medical care quality: Determination by diagnostic outcome. JAMA 227:1155, 1974.

126. Umbach GE, Zubek S, Deck H-J et al: The value of preoperative chest x-rays in gynecological patients. Arch Gynecol Obstet 243:179, 1988.

127. Robertson WM: Medical Malpractice: A Preventive Approach. Seattle, University of Washington Press, 1985.

128. Berwick DM: Screening in health fairs: A critical review of benefits, risks, and costs. JAMA 254:1492, 1985.

129. Ross AF, Tinker JH: Preoperative evaluation of the healthy patient. In Rogers MC, Tinker JH, Covino BG et al (eds): Principles and Practice of Anesthesiology. St. Louis, Mosby-Year Book, 1993, p 20.

130. Blair SN, Kampert JB, Kohl HW et al: Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 276:205, 1996.

131. Singh NA: A randomized controlled trial of progressive resistance training in depressed elders. J Gerontol 52:M27, 1997.

132. Collen MF, Feldman R, Siegelaub AB et al: Dollar cost per positive test for automated multiphasic screening. N Engl J Med 283:459, 1970.

133. Collen MF (ed): Multiphasic Health Testing Services. New York, John Wiley & Sons, 1978.

134. Neuhauser D: Cost-effective clinical decision making. Pediatrics 60:756, 1977.

135. Robbins JA, Mushlin AI: Preoperative evaluation of the healthy patient. Med Clin North Am 63:1145, 1979.

136. Rembold CM, Watson D: Posttest probability calculation by weights: A simple form of Bayes' theorem. Ann Intern Med 108:115, 1988.

137. Pauker SG, Kopelman RI: Interpreting hoofbeats: Can Bayes help clear the haze? N Engl J Med 327:1009, 1992.

138. Foss JF, Ellis JE: Preoperative Considerations in the Vascular Surgery Patient. University of Chicago Vascular-Thoracic Anesthesia Manual, 1998. http://dacc.bsd.uchicago.edu/library/manuals/vtmanual/preop. html

139. Coley CM, Barry MJ, Fleming C et al: Early detection of prostate cancer. I. Prior probability and effectiveness of tests. Ann Intern Med 126:394, 1997.

140. Tinker JH, Dull DL, Caplan RA et al: Role of monitoring devices in prevention of anesthetic mishaps: A closed claims analysis. Anesthesiology 71:541, 1989.

141. Black WC, Welch HG: Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. N Engl J Med 328:1237, 1993.

142. Kubik A, Parkin DM, Khlat M et al: Lack of benefit from semi-annual screening for cancer of the lung: Follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. Int J Cancer 45:26, 1990.

143. Andersson I, Aspergren K, Janzon L et al: Mammographic screening and mortality from breast cancer: The Malmo mammographic screening trial. BMJ 297:943, 1988.

144. Obstbaum SA: An 82-year-old woman with cataracts. JAMA 275:1675, 1996.

145. Farnsworth PB, Steiner E, Klein RM et al: The value of routine preoperative chest roentgenograms in infants and children. JAMA 244:582, 1980.

146. Brill PW, Ewing ML, Dunn AA: The value (?) of routine chest radiography in children and adolescents. Pediatrics 52:125, 1973.

147. Sagel SS, Evens RG, Forrest JV et al: Efficacy of routine screening and lateral chest radiographs in a hospital-based population. N Engl J Med 29:1001, 1974.

148. Sane SM, Worsing RA Jr, Wiens CW et al: Value of preoperative chest x-ray examinations in children. Pediatrics 60:669, 1977.

149. Rees AM, Roberts CJ, Bligh AS et al: Routine preoperative chest radiography in non-cardiopulmonary surgery. BMJ 1:1333, 1976.

150. Loder RE: Routine pre-operative chest radiography: 1977 compared with 1955 at Peterborough District General Hospital. Anaesthesia 33:972, 1978.

151. Hubbell FA, Greenfield S, Tyler JL et al: The impact of routine admission chest x-ray films on patient care. N Engl J Med 312:209, 1985.

152. Maigaard S, Elkjaer P, Stefansson T: Vaerdien af praeoperativ rutinerontgenundersogelse af thorax og ekg. (English abstract: Value of routine preoperative radiographic examination of the thorax and ECG). Ugeskr Laeger 140:769, 1978.

153. Catchlove BR, Wilson RM, Spring S et al: Routine investigations in elective surgical patients: Their use and cost effectiveness in a teaching hospital. Med J Aust 2:107, 1979.

154. Thomsen HS, Gottlieb J, Madsen JK et al: Rutinemaessig rontgenundersogelse af thorax inden kirurgiske indgreg i universel anaestesi. (English abstract: Routine radiographic examination of the thorax prior to surgical intervention under general anesthesia.) Ugeskr Laeger 140:765, 1978.

155. Gupta SD, Gibbons FJ, Sen I: Routine chest radiography in the elderly. Age Ageing 14:11, 1985.

156. Boghosian SG, Mooradian AD: Usefulness of routine preoperative chest roentgenograms in elderly patients. J Am Geriatr Soc 35:142, 1987.

157. Sewell JMA, Spooner LLR, Dixon AK et al: Screening investigations in the elderly. Age Ageing 10:165, 1981.

158. Tornebrandt K, Fletcher R: Preoperative chest x-rays in elderly patients. Anaesthesia 37:901, 1982.

159. Fink DJ, Fang M, Wyle FA: Routine chest x-ray films in a Veterans Hospital. JAMA 245:1056, 1981.

160. Wiencek RG, Weaver DW, Bouwman DL et al: Usefulness of selective preoperative chest x-ray films: A prospective study. Am Surg 53:396, 1987.

161. Petterson SR, Janower ML: Is the routine preoperative chest film of value? Appl Radiol 6:70, 1977.

162. Royal College of Radiologists Working Party on the Effective Use of Diagnostic Radiology: Preoperative chest radiology: National study by the Royal College of Radiologists. Lancet 2:83, 1979.

163. Rucker L, Frye EB, Staten MA: Usefulness of screening chest roentgenograms in preoperative patients. JAMA 250:3209, 1983.

164. Weibman MD, Shah NK, Bedford RF: Influence of preoperative chest x-rays on the perioperative management of cancer patients (abstract). Anesthesiology 67:A332, 1987.

165. Gagner M, Chiasson A: Preoperative chest x-ray films in elective surgery: A valid screening tool. Can J Surg 33:271, 1990.

166. Velanovich V: Preoperative laboratory screening based on age, gender, and concomitant medical diseases. Surgery 115:56, 1994.

167. Yipintsoi T, Vasinanukorn P, Sanguanchua P: Is routine preoperative electrocardiogram necessary? J Med Assoc Thai 72:16, 1989.

168. Gordon T, Kannel WB: The Framingham Massachusetts study twenty years later. In Kessler II, Levin ML (eds): The Community as an Epidemiologic Laboratory: A Casebook of Community Studies. Baltimore, Johns Hopkins Press, 1970, p 123.

169. Ostrander LD Jr, Brandt RL, Kjelsberg MO et al: Electrocardiographic findings among the adult population of a total natural community, Tecumseh, Michigan. Circulation 31:888, 1965.

170. Kannel WB, McGee D, Gordon T: A general cardiovascular risk profile: The Framingham study. Am J Cardiol 38:46, 1976.

171. Apfelbaum J, Robinson D, Murray WJ et al: An automated method to validate preoperative test selection: First results of a multicenter study (abstract). Anesthesiology 71:A928, 1989.

172. Moorman JR, Hlatky MA, Eddy DM et al: The yield of the routine admission electrocardiogram: A study in a general medical service. Ann Intern Med 103:590, 1985.

173. Seymour DG, Pringle R, MacLennan WJ: The role of the routine preoperative electrocardiogram in the elderly surgical patient. Age Ageing 12:97, 1983.

174. Gold BS, Young ML, Kinman JL et al: The utility of preoperative electrocardiograms in the ambulatory surgery patient. Arch Intern Med 152:301, 1992.

175. Sox HC Jr, Garber AM, Littenberg B: The resting electrocardiogram as a screening test: A clinical analysis. Ann Intern Med 111:489, 1989.

176. Goldberger AL, O'Konski M: Utility of the routine electrocardiogram before surgery and on general hospital admission: Critical review and new guidelines. Ann Intern Med 105:552, 1986.

177. Roizen MF: RealAge: Are You As Young As You Can Be? New York, Harper Collins, 1999.

178. Wasserman LR, Gilbert HS: Surgical bleeding in polycythemia vera. Ann N Y Acad Sci 115:122, 1964.

179. Erikssen G, Thaulow E, Sandvik L et al: Haematocrit: A predictor of cardiovascular mortality? J Intern Med 234:493, 1993.

180. Rothstein P: What hemoglobin level is adequate in pediatric anesthesia? Anesthesiol Update 1:2, 1978.

181. Weiskopf RB, Viele MK, Feiner J et al: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 279:217, 1998.

182. Carson JL, Duff A, Berlin JA et al: Perioperative blood transfusion and postoperative mortality. JAMA 279:199, 1998.

183. Kowalyshyn TJ, Prager D, Young J: A review of the present status of preoperative hemoglobin requirements. Anesth Analg 51:75, 1972.

184. Carmalt MHB, Freeman P, Stephens AJH et al: Value of routine multiple blood tests in patients attending the general practitioner. BMJ 1:620, 1970.

185. Moore SB, Reisner RK, Offord KP: Morning admission for a same-day surgical procedure: Resolution of a blood bank problem. Mayo Clin Proc 64:406, 1989.

186. Daley J, Khuri SF, Henderson W et al: Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: Results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 185:328, 1997.

187. Wataneeyawech M, Kelly KA Jr: Hepatic diseases unsuspected before surgery. N Y State J Med 75:1278, 1975.

188. Schemel WH: Unexpected hepatic dysfunction found by multiple laboratory screening. Anesth Analg 55:810, 1976.

189. Singer DE, Samet JH, Coley CM et al: Screening for diabetes mellitus. Ann Intern Med 109:639, 1988.

190. Alter MJ: Non-A, non-B hepatitis: Sorting through a diagnosis of exclusion. Ann Intern Med 110:583, 1989.

191. Gold BD, Wolfersberger WH: Findings from routine urinalysis and hematocrit on ambulatory oral and maxillofacial surgery patients. J Oral Surg 38:677, 1980.

192. Cardiff-Oxford Bacteriuria Study Group: Sequelae of covert bacteriuria in schoolgirls: A four-year follow-up study. Lancet 1:889, 1978.

193. Challand GS: Is ward biochemical testing cheap and easy? Intensive Care World 4:9, 1987.

194. Baranetsky NG, Weinstein P: Partial thromboplastin time for screening. Ann Intern Med 91:498, 1979.

195. Barber A, Green D, Galluzzo T et al: The bleeding time as a preoperative screening test. Am J Med 78:761, 1985.

196. Macpherson DS, Snow R, Lofgren RP: Preoperative screening: Value of previous tests. Ann Intern Med 113:969, 1990.

197. Bushnick JB, Eisenberg JM, Kinman J et al: Pursuit of abnormal coagulation screening tests generates modest hidden preoperative costs. J Gen Intern Med 4:493, 1989.

198. Eisenberg JM, Clarke JR, Sussman SA: Prothrombin and partial thromboplastin times as preoperative screening tests. Arch Surg 117:48, 1982.

199. Suchman AL, Mushlin AI: How well does the activated partial thromboplastin time predict postoperative hemorrhage? JAMA 256:750, 1986.

200. Macpherson DS: Preoperative laboratory testing: Should any tests be "routine" before surgery? Med Clin North Am 77:289, 1993.

201. Roizen MF, Hurd MJ: Preoperative patient evaluation. In Rogers MC (ed): Current Practice in Anesthesiology, 2nd ed. St. Louis, Mosby-Year Book, 1990, p 14.

202. Souter AJ, Fredman B, White PF: Controversies in the perioperative use of nonsterodial (sic) antiinflammatory drugs. Anesth Analg 79:1178, 1994.

203. Ramsey G, Arvan DA, Steward S et al: Do preoperative laboratory tests predict blood transfusion needs in cardiac operations? J Thorac Cardiovasc Surg 85:564, 1983.

204. Levitt RC, Nouri N, Jedlicka AE et al: Evidence for genetic heterogeneity in malignant hyperthermia susceptibility. Genomics 11:543, 1991.

205. Levitt RC: Prospects for the diagnosis of malignant hyperthermia susceptibility using molecular genetic approaches. Anesthesiology 76:1039, 1992.

206. Wong ET, Rude RK, Singer FR et al: A high prevalence of hypomagnesemia and hypermagnesemia in hospitalized patients. Am J Clin Pathol 79:348, 1983.

207. Fanning WJ, Thomas CS Jr, Roach A et al: Prophylaxis in atrial fibrillation with magnesium sulfate after coronary bypass grafting. Ann Thorac Surg 52:529, 1991.

208. England MR, Gordon G, Salem M et al: Magnesium administration and dysrhythmias after cardiac surgery: A placebo-controlled, double-blind, randomized trial. JAMA 268:2395, 1992.

209. Reinhart RA, Desbiens NA: Hypomagnesemia in patients entering the ICU. Crit Care Med 13:506, 1985.

210. Gambling DR, Birmingham CL, Jenkins LC: Magnesium and the anaesthetist. Can J Anaesth 35:644, 1988.

211. Lembo NJ, Dell'Italia LJ, Crawford MH et al: Bedside diagnosis of systolic murmurs. N Engl J Med 318:1572, 1988.

212. Baker JP, Detsky AS, Wesson DE et al: Nutritional assessment: A comparison of clinical judgment and objective measurements. N Engl J Med 306:969, 1982.

213. Roizen MF: The preoperative cardiology consult: What the cardiologist should know about anesthesia. In Parmley WW, Chatterjee K (eds): Cardiology, vol 2: Cardiovascular Disease. Philadelphia, JB Lippincott, 1993, p 1.

214. Gluck R, Munoz E, Wise L: Preoperative and postoperative medical evaluation of surgical patients. Am J Surg 155:730, 1988.

215. Medical consultation. In Medical Knowledge Self-Assessment, program IX, part C, book 4. Philadelphia, American College of Physicians, 1992, p 939.

216. Merli GJ, Weitz HH, Lubin MF (eds): Medical Consultation. Med Clin North Am 77:289, 1993.

217. Mangano DT, Browner WS, Hollenberg M et al: Long-term cardiac prognosis following noncardiac surgery. JAMA 268:233, 1992.

218. Hollenberg M, Mangano DT, Browner WS et al: Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. JAMA 268:205, 1992.

219. Charlson ME, MacKenzie CR, Ales K et al: Surveillance for postoperative myocardial infarction after noncardiac operations. Surg Gynecol Obstet 167:407, 1988.

220. Macario A, Roizen MF, Thisted RA et al: Reassessment of preoperative laboratory testing has changed the test-ordering patterns of physicians. Surg Gynecol Obstet 75:539, 1992.

221. Charpak Y, Blery C, Chastang C et al: Usefulness of selectively ordered preoperative tests. Med Care 26:95, 1988.

222. Curran J, Chmielewski AT, White JB et al: Practice of preoperative assessment by anaesthetists. BMJ 291:391, 1985.

223. Leigh JM, Walker J, Janaganathan P: Effect of preoperative anaesthetic visit on anxiety. BMJ 285:987, 1977.

224. Finn AF Jr, Valenstein PN, Burke MD: Alteration of physicians' orders by nonphysicians. JAMA 259:2549, 1988.

225. Grady D: Going overboard on medical tests. Time, April 25, 1988, p 80.

226. Fischer AF, Stevenson DK: The consequences of uncertainty: An empirical approach to medical decision making in neonatal intensive care. JAMA 258:1929, 1987.

227. Wong ET, Nelson JM: Quality assurance and the clinical laboratory. JAMA 259:2584, 1988.

228. Tierney WM, McDonald CJ, Hui SL et al: Computer predictions of abnormal test results: Effects on outpatient testing. JAMA 259:1194, 1988.

229. Tierney WM, McDonald CJ, Martin DK et al: Computerized display of past test results: Effect on outpatient testing. Ann Intern Med 107:569, 1987.

230. Goldman L, Cook EF, Brand DA et al: A computer protocol to predict myocardial infarction in emergency department patients with chest pain. N Engl J Med 318:797, 1988.

231. Romm FJ, Fletcher SW, Hulka BS: The periodic health examination: Comparison of recommendations and internists' performance. South Med J 74:265, 1981.

232. Tierney WM, Miller ME, Overhage JM et al: Physician inpatient order writing on microcomputer workstations: Effects on resource utilization. JAMA 269:379, 1993.

233. Eddy DM: Three battles to watch in the 1990s. JAMA 270:520, 1993.

234. Larson CP Jr: Evaluation of the patient and preoperative preparation. In Barash PG, Cullen BF, Stoelting RK (eds): Clinical Anesthesia, 2nd ed. Philadelphia, JB Lippincott, 1992, p 545.

235. Chodoff P, Gianaris CD: A nurse-computer assisted preoperative anesthesia management system. Comput Biomed Res 6:371, 1973.

236. Prentice JW, Kenny GN: Microcomputer-based anaesthetic record system. Br J Anaesth 56:1433, 1984.

237. Tompkins BM, Tompkins WJ, Loder E et al: A computer-assisted preanesthesia interview: Value of a computer-generated summary of patient's historical information in the preanesthesia visit. Anesth Analg 59:3, 1980.

238. Freudenheim M: Hospitals increase use of computers. New York Times, September 11, 1990, p D2.

239. Lyytinen K, Hirschheim R: Information systems failures: A survey and classification of the empirical literature. Oxf Surv Information Technol 4:257, 1987.

240. Beers RA, O'Leary CE, Franklin PD: Comparing the history-taking methods used during a preanesthetic visit: The HealthQuiz versus the written questionnaire. Anesth Analg 86:134, 1998.

241. Forrest WJ, Bellville JW: The use of computers in clinical trials. Br J Anaesth 39:311, 1967.

242. Fournier L, Desmeules H, Tremblay PR et al: Use of computers IBM-360: Compilation of anesthetic data (in French). Can Anaesth Soc J 17:649, 1970.

243. Galla SJ, Schwarzbach R, Buccigrossi R: A computer program for analysis of anesthetic records. Anesthesiology 30:565, 1969.

244. Hallen B: Computerized anaesthetic record-keeping: A clinical study of the preanaesthetic data, the risk groups and the choice of anaesthetic method. Acta Anaesthesiol Scand Suppl 52:1, 1973.

245. Petersen J, Kochs E, Kochs HD: Expert systems in medicine: Possible uses in anesthesia (in German). Anasthesiol Intensivmed Notfallmed Schmerzther 29:74, 1994.

246. Weller L, Hartung HJ, Bender HJ et al: Development and practical use of a computerized anesthesia protocol. Acta Anaesthesiol Belg 35(suppl):331, 1984.

247. Gibby GL, Paulus DA, Sirota DJ et al: Computerized preanesthetic evaluation results in additional abstracted comorbidity diagnoses. J Clin Monit 13:35, 1997.

248. Twersky RS: Ambulatory Anesthesia. St. Louis, Mosby-Year Book, 1995.

249. White PF: Ambulatory anesthesia and surgery: Past, present and future. In White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 3.

250. Saidman LJ: The 33rd Rovenstine Lecture: What I have learned from 9 years and 9,000 papers. Anesthesiology 83:191, 1995.

251. Longnecker D: Planning the future of anesthesiology. Anesthesiology 84:495, 1996.

252. Deutschman CS, Traber KB: Evolution of anesthesiology. Anesthesiology 85:1, 1996.

253. Burk N, Mazzei W: The need for an anesthesia preoperative evaluation center (abstract). Anesth Analg 70:S44, 1990.

254. Macarthur AJ, Macarthur C, Bevan JC: Preoperative assessment clinic reduces day surgery cancellations (abstract). Anesthesiology 75:A1109, 1991.

255. Conway JB, Goldberg J, Chung F: Preadmission anaesthesia consultation clinic. Can J Anaesth 39:1051, 1992.

256. Finegan BA: Preadmission and outpatient consultation clinics. Can J Anaesth 39:1009, 1992.

257. Boothe P: Changing the admission process for elective surgery: An economic analysis. Can J Anaesth 42:391, 1995.

258. Starsnic MA, Guarnieri DM, Norris MC: Efficacy and financial benefit of an anesthesiologist-directed university preadmission evaluation clinic. J Clin Anesth 9:299, 1997.

259. Roizen MF, Kaplan EB, Sheiner LB et al: Elimination of unnecessary laboratory tests by preoperative questionnaire (abstract). Anesthesiology 61:A455, 1984.

260. Kleinfeldt AS: Preoperative phone calls: Reducing cancellation in paediatric day surgery. AORN J 51:559, 1990.

261. Eddy DM: Resolving conflicts in practice policies. JAMA 264:389, 1990.

262. Ginsburg WH: When does a guideline become a standard? The new American Society of Anesthesiologists guidelines give us a clue. Ann Emerg Med 22:121, 1993.

263. Roizen MF, Fleisher LA: Medical guidelines by other societies: Should we ignore or influence them? Anesth Analg 82:679, 1996.

264. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Executive summary of the ACC/AHA Task Force report: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Anesth Analg 82:854, 1996.

265. Pasternak LR: Preanesthesia evaluation of the surgical patient. ASA Refresher Courses in Anesthesiology 24:205, 1996.

266. Schneiderman LJ, DeSalvo L, Baylor S et al: The "abnormal" screening laboratory results: Its effect on physician and patient. Arch Intern Med 129:88, 1972.

267. Bryan DJ, Wearne JL, Viau A et al: Profile of admission chemical data by multichannel automation: An evaluative experiment. Clin Chem 12:137, 1966.

268. Schoen I: Clinical chemistry: A retrospective look at routine screening. Calif Med 108:430, 1968.

269. Peery TM: The role of the laboratory in health evaluation. Interim Report No. 77, from the 1964 Technicon International Symposium, New York, NY, as quoted in Schoen I: Clinical chemistry, a retrospective look at routine screening. Calif Med 108:430, 1968.

270. Friedman GD, Goldberg M, Ahuja JN et al: Biochemical screening tests: Effect of panel size on medical care. Arch Intern Med 129:91, 1972.

271. Young DM, Drake TGH: Unsolicited laboratory information presented to the College of American Pathologists, Chicago, 18 Oct 1965, as quoted in Schoen I: Clinical chemistry, a retrospective look at routine screening. Calif Med 108:430, 1968.

272. Boonstra CE, Jackson CE: The clinical value of routine serum calcium analysis. Ann Intern Med 57:963, 1962.

273. Whitehead TP: Multiple analyses and their use in the investigation of patients. Adv Clin Chem 14:389, 1971.

274. Whang R, Ryder KW: Frequency of hypomagnesemia and hypermagnesemia: Requested vs routine. JAMA 263:3063, 1990.

275. Lum G: Hypomagnesemia in acute and chronic care patient populations. Am J Clin Pathol 97:827, 1992.

276. Chernow B, Bamberger S, Stoiko M et al: Hypomagnesemia in patients in postoperative intensive care. Chest 95:391, 1989.

277. Roizen MF: Preoperative evaluation. In Miller RD (ed): Anesthesia, vol 1, 4th ed. New York, Churchill Livingstone, 1994, p 827.

278. Roizen MF: Routine preoperative evaluation. In Miller RD (ed): Anesthesia, vol 1, 2nd ed. New York, Churchill Livingstone, 1986, p 225.

279. Roizen MF: Routine preoperative evaluation. In Miller RD (ed): Anesthesia, vol 1. New York, Churchill Livingstone, 1981, p 3.

280. Eiseman B: Necessary preoperative tests. In Wilmore DW, Brennan MF, Harken AH et al (eds): Medicine: Care of the Surgical Patient, American College of Surgeons, vol 2. New York, Scientific American, 1989, p 1.

281. Velanovich V: The value of routine preoperative laboratory testing in predicting postoperative complications: A multivariate analysis. Surgery 109:236, 1991.

282. American Society of Anesthesiologists: The ASA Directory of Members 1998. Park Ridge, Ill, American Society of Anesthesiologists, 1998.

Chapter 24 - Pulmonary Function Testing

Thomas J. Gal

INTRODUCTION

Pulmonary function testing continues to play a role in traditional preoperative evaluation of patients undergoing major surgery. Although simple and risk free, such testing is often performed in reflex fashion without real indications because of limited physiologic and clinical insight on the part of many practicing physicians. As a result, they are often uncomfortable interpreting test data and are unsure of what the data mean or what was actually measured.

Such preoperative screening is aimed at identifying individuals with abnormal lung function in hopes of altering their outcome by reducing the risk of postoperative ventilatory impairment and other respiratory complications. The subjective information provided by the medical history and the findings on physical examination seldom identify the actual abnormalities of respiratory function and are often poor indicators of the severity of disease. In contrast, pulmonary function testing provides objective standardized measurements for assessing the presence and severity of respiratory dysfunction. Such measurements also enable the clinician to follow the progression of any impairment and to document the response to therapy such as bronchodilators. These tests fall into two major groups: those that detect abnormalities of gas exchange and those that relate to the mechanical ventilatory function of the lungs and chest wall. This discussion deals principally with the latter group.

The cornerstone of all pulmonary function testing is, of course, clinical spirometry. There are numerous other tests, including some that purport to indicate mild abnormalities of lung function. This presentation attempts to review the actual measurement techniques and to interpret the physiologic basis and significance of many of these tests. The aim is to provide a better understanding of the defects identified by each testing scheme. Such information does not merely serve to impress a board examiner or a colleague; it also enhances the anesthesiologist's role as a consultant in the ra-tional perioperative management of the patients evaluated. The actual management considerations include risk of postoperative morbidity, resectability of lung tissue, and management of the anesthetic.

CLINICAL SPIROMETRY

Vital Capacity

The most common measurement of lung function is the vital capacity (VC). John Hutchinson is given the credit for inventing the spirometer and for coining the term *vital capacity* in the mid-19th century. [1] The VC is simply the largest volume measured after an individual inspires deeply and maximally to total lung capacity (TLC) and then exhales completely to residual volume (RV) into a spirometer. The maneuver is performed without concern for rapidity of effort. Normal values for VC are lower in supine subjects than in sitting ones and vary directly with height and inversely with age. A given VC is generally suspected of being abnormal if it falls below 80 percent of the predicted value. Patients with abnormally low values for VC are said to have

restrictive disease. The decreased VC associated with restrictive disease may result from lung pathology, such as pneumonia, atelectasis, and pulmonary fibrosis. It may also occur with a loss of distensible lung tissue, such as that following surgical excision. Decreased VC is also seen in the absence of lung disease. In this case, muscle weakness, abdominal swelling, or pain may prevent the patient from obtaining either a full inspiration or a maximum expiratory effort.

Time-Expired Spirogram

If after a maximal inspiratory effort a subject exhales as forcefully and rapidly as possible, the maneuver is termed the forced VC (FVC), and the exhaled volume is recorded with respect to time. The rate of air flow during this rapid forceful exhalation indirectly reflects the flow resistance properties of the airways. In the presence of airway obstruction, FVC tends to be less than the standard VC because airways reach flow limitation early, and air trapping occurs. In healthy subjects, the two maneuvers usually result in nearly equal measured volumes. Because the FVC maneuver is an artificial one, patients must be instructed carefully and often require practice attempts before performing the test adequately. Generally, three acceptable tracings are required for analysis. These FVC maneuvers must be characterized by an initial full inspiration to TLC, followed by an abrupt onset of exhalation and continued maximum effort throughout exhalation to RV. The exhalation should take at least 4 seconds and should not be interrupted by coughing, glottic closure, or any mechanical obstruction. [2]

The FVC is reduced by the same conditions that reduce VC. Therefore, in order to identify airway obstruction, flow rates are determined by calculation of the volume exhaled during certain time intervals. Most commonly measured is the volume exhaled in the first second, or the forced expiratory volume in 1 second (FEV_1). The FEV_1 can be expressed as absolute volume in liters, and typical values for various patient groups are listed in Table 24-1 . The FEV_1 provides an even better perspective on the degree of airway obstruction when it is expressed as a percentage of the FVC (FEV_1/FVC%).

For the purposes of reporting and calculating values, the largest observed FVC and FEV_1 from any of the three acceptable spirograms are used, even if they are not obtained from the same curve. [2] Normal healthy subjects can exhale 75 to 80 percent of the FVC in the first second; the remaining volume is exhaled in two or three additional seconds

TABLE 24-1 -- Clinical Ranges for Forced 1 Second Expiratory Volume (FEV_1) in Liters

CLINICAL RANGE	PATIENT GROUP
3.0-4.5	Normal adult
1.5-2.5	Mild-to-moderate obstruction
<1.0	Qualifies as handicapped
0.8	Disability
0.5	Severe emphysema

Figure 24-1 Forced vital capacity (FVC) maneuver in a subject with a normal lung. Exhaled volume is plotted against time as the subject expires forcefully, rapidly, and completely to residual volume (RV) after a maximal deep inspiration to total lung capacity (TLC). (FEV_1, forced expired volume in 1 second; $FEF_{200-1200}$, forced expiratory flow between 200 and 1200 mL of expired volume; $FEF_{25\%-75\%}$, forced expiratory flow over the midportion of vital capacity, i.e., from 25 percent to 75 percent of expired volume.)

(Fig. 24-1) . Disease such as asthma and bronchitis, which obstruct the airway, reduce expiratory flow rates and, thus, reduce FEV_1 and FEV_1/FVC percent. An obstructive defect is essentially characterized by a disproportionate decrease in air flow rate relative to the actual volume exhaled (FVC) and indicates airway narrowing and flow limitation during expiration. Values for FEV_1/FVC that are less than 70 percent reflect mild obstruction, whereas those less than 60 percent suggest moderate obstruction and those less than 50 percent, severe obstruction. Because the FEV_1/FVC represents a ratio, it is important to realize that identical values, such as 50 percent, may not indicate equivalent degrees of lung dysfunction. For example, a patient with an FEV_1 of 1.5 L and an FVC of 3.0 L does not have the same degree of impairment as a similar-sized patient with an FEV_1 of 0.75 L and an FVC of 1.5 L. Nevertheless, in both, the FEV_1/FVC ratio is 50 percent.

Restrictive diseases are not usually associated with airway obstruction but do cause decreases in FVC. Although the absolute volume of FEV_1 may be reduced on a similar basis, the FEV_1 expressed as a percentage of FVC is usually normal (i.e., FEV_1/FVC >70 percent). The essential physiologic characteristic of a restrictive defect is a reduction in total lung volume, that is, TLC. However, the presence of such a defect is usually implied whenever FVC is reduced and the ratio of FEV_1/FVC is normal or increased. The impact of various mechanical abnormalities on VC and these dynamic lung volumes is summarized in Table 24-2 .

The maximal flow rate during an FVC maneuver occurs in the initial 0.1 second and is termed the peak flow measured in liters per second or liters per minute. Peak flow can be estimated by drawing a tangent to the steepest part of the FVC spirogram, but this method is subject to large errors. More commonly, maximal flow is measured as the average

TABLE 24-2 -- Forced Vital Capacity (FVC) and 1-Second Forced Expiratory Volumes (FEV_1) in Disease States

	FVC(L)	FEV_1 (L)	FEV_1 /FVC%
Airway obstruction (asthma, bronchitis)	Normal	Decreased	Decreased
Stiff lungs (pneumonia, pulmonary edema, pulmonary fibrosis)	Decreased	Decreased	Normal
Respiratory muscle weakness (myasthenia gravis, myopathies)	Decreased	Decreased	Normal

flow during the liter of gas expired after the initial 200 mL during an FVC maneuver (see Fig. 24-1) . This is usually designated as forced expiratory flow between 200 and 1200 mL of FVC ($FEF_{200-1200}$); however, the term maximal expiratory flow rate has also been used. This flow is slightly lower than the true peak flow, which can be measured conveniently with a hand-held flowmeter (Fig. 24-2) or more accurately with a pneumotachygraph. Peak flow is markedly affected by obstruction of large airways and is particularly responsive to bronchodilator therapy. Because repeat measurements are convenient to obtain, peak flow rates can be utilized to monitor therapeutic responses in acute asthma. Normal values in healthy males under 40 years of age are typically 500 L/min or more. Values less than 200 L/min in surgical candidates suggest impaired cough efficiency and the strong likelihood of postoperative complications. [3] The test is much less unpleasant and exhausting for patients than the FVC maneuver and thus provides a valuable tool to identify gross pulmonary disability at the bedside.

Although peak flow is largely a function of the caliber of the airways, it is also highly dependent on expiratory muscle strength, as well as on patient effort and coordination. As a result, the measurement can be variable. In contrast, high degrees of effort are not required to achieve maximal expiratory flow at intermediate and low lung volumes during forced expiration. Therefore, flow is often measured over the middle half of the FVC (i.e., between 25 and 75% of expired volume). This parameter, formerly called the maximal midexpiratory flow, is now referred to as the forced midexpiratory flow ($FEF_{25\%-75\%}$). Because the flow does not include the initial highly effort-dependent portion of forced expiration, $FEF_{25\%-75\%}$ is often referred to as "effort independent." This designation is not entirely appropriate, because $FEF_{25\%-75\%}$ can be decreased by marked reductions in expiratory effort and by a submaximal inspiration before the maneuver. The latter artificially reduces FVC and, along with it, the $FEF_{25\%-75\%}$. The same flow rates may also decrease with truly maximal effort, compared with slightly submaximal effort. [4] [5] This phenomenon has been termed "negative effort dependence" and appears to be an artifact of measuring volume changes at the mouth rather than actual changes in thoracic gas volume, which differ in the dynamic airway compression that occurs with truly maximal effort.

The $FEF_{25\%-75\%}$ is therefore a highly variable spirometric index, largely because of its dependence on the absolute volume of FVC, as well as on changes in expiratory time with varying degrees of airway obstruction. Values for $FEF_{25\%-75\%}$ in healthy young men average 4.5 to 5.0 L/sec, but because of wide variations even in normal subjects, the predicted limits of normal may be as low as 2 L/sec. The measurement has often been proposed as a sensitive indicator of early obstruction in the small distal airways. However, patients undergoing spirometry for suspected airway obstruction virtually always had normal values for $FEF_{25\%-75\%}$

Figure 24-2 Three hand-held peak flow meters. The classic Wright meter (Air Med Limited, Harlow, England) and the Assess peak flow meter (Health Scan Products, Cedar Grove, NJ) provide actual quantitation of peak flow rate, and the smaller Peak Flow Monitor (Biotrine Corp., Woburn, Mass) allows the patient to tape over the holes before blowing. If the flow rate indicated by the first uncovered hole is reached, a horn-like sound is produced by a metal reed-like device within the tube.

when FEV_1 /FEV was 75 percent or greater. [6] One exception to this may occur in patients with restrictive ventilatory defects. In these patients, the $FEF_{25\%-75\%}$ may be markedly reduced and the FEV/FVC percent normal. However, lung volumes, as reflected by TLC, FVC, and absolute volume of FEV_1, are all reduced. Therefore, $FEF_{25\%-75\%}$ does not appear to be any more sensitive than FEV_1 in detecting mild abnormalities of lung dysfunction.

Maximal Breathing Capacity

Dynamic lung function is also routinely evaluated in many pulmonary function laboratories by measuring the maximum breathing capacity or, more specifically, the maximal voluntary ventilation (MVV). This is the largest volume that can be breathed per minute by voluntary effort and reflects an estimate of the peak ventilation available to meet physiologic demands. The patient is instructed to breathe as hard and fast as possible for 12 seconds. The measured volume is extrapolated to 1 minute and is expressed as liters per minute. Because high rates of air flow are required for MVV, the measurement is significantly affected by changes in airway resistance. MVV is usually reduced in patients with obstructive airway disease and correlates reasonably well with FEV_1 measured in liters ($FEV_1 \times 35$ approximates MVV). Discrepancies between the measured MVV and that predicted by FEV_1 often indicate inconsistent or submaximal inspiratory effort. [7] The MVV as a comprehensive test of ventilatory function is altered by factors other than airway obstruction. These include the elastic properties of the lung and chest wall, respiratory muscle strength, learning, coordination, and motivation. In healthy male adults, MVV averages 150 to 175 L/min. This extremely high level of ventilatory effort cannot be maintained for much longer than 1 minute. However, approximately 80 percent of the MVV can be maintained by healthy subjects for as long as 15 minutes, and up to 60 percent of MVV can be sustained for even longer periods. Abnormally low values (<80 percent of those predicted) do not identify specific defects but do indicate gross impairment in respiratory function. The unique value of the test in the surgical candidate may lie in its dependence on intangible variables, such as cooperation, motivation, and stamina.

Respiratory Muscle Strength

All measurements of pulmonary function that require patient effort (e.g., FVC, FEV_1 peak flow, and MVV) are influenced by the strength of the respiratory muscles. The latter can be specifically evaluated by measurement of maximal static respiratory pressures. The pressures are generated against an occluded airway during a maximal forced inspiratory or expiratory effort and are usually measured with simple aneroid gauges. [8] Maximal static inspiratory pressure is measured when inspiratory muscles are at their optimal length near RV (Fig. 24-3) . Similarly, maximal static expiratory pressure ($P_{E}max$) is measured when expiratory muscles are optimally stretched after a full inspiration to near TLC. In young adult males, maximal static inspiratory pressure is about -125 cm H_2O, whereas $P_{E}max$ is about +200 cm H_2O.

The pressures measured at the mouth include that generated by the respiratory muscles and a portion resulting from the elastic recoil of the respiratory system. The latter is essentially zero at functional residual capacity (FRC). Pressures measured at FRC are simply less than at the extremes of lung volume (see Fig. 24-3) but unlike the other values reflect solely the pressure developed by the respiratory muscles.

A maximal static inspiratory pressure of -25 cm H_2O or less indicates severe inability to take a deep breath, whereas a $P_{E}max$ of less than +40 cm H_2O suggests severely impaired coughing ability. Although these pressures are not measured routinely in all pulmonary function laboratories, they are particularly useful in the evaluation of patients with neuromuscular disorders. In these patterns, the VC has long been used to indicate the severity of respiratory muscle weakness and to predict respiratory failure. Measurements of respiratory muscle strength have been shown to identify more readily the patients in whom respiratory muscle weakness is the prime cause of hypercapnic respiratory failure. [9]

Figure 24-3 Normal values for maximum static inspiratory ($P_{I}max$), and expiratory ($P_{E}max$) pressure measured at the mouth are plotted as a function of lung volume from residual volume (RV) to total lung capacity (TLC). (FRC, functional residual capacity.)

Figure 24-4 Elastic recoil pressures for the lung (PI), chest wall (Pcw), and total respiratory system (Prs) are plotted as a function of lung volume. (VC, vital capacity; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity.)

PHYSIOLOGIC DETERMINANTS OF MAXIMUM FLOW RATES

The maximal flow rates that can be achieved during pulmonary function testing maneuvers depend on three factors, each of which is highly influenced by the volume of the lung at the time. Foremost of these factors is the degree of effort, or the driving pressure generated by muscle contraction. The expiratory effort reflected by P_{Emax} is maximal at high lung volumes near TLC and decreases as lung volume decreases (see Fig. 24-3) . Maximal inspiratory effort (maximal static inspiratory pressure), conversely, is achieved at low lung volumes near RV and diminishes at higher lung volumes.

Another important determinant of maximal flow is the elastic recoil pressure of the lung (PI). At all lung volumes from RV to TLC, the lung has a tendency to recoil inward (Fig. 24-4) . The PI, therefore, is greater at TLC (25-30 cm H_2O) and lowest at RV (2-3 cm H_2O). The PI is opposed by the outward recoil of the chest wall (Pcw), except at very high lung volumes. The recoil pressure of the respiratory system (Prs) is the algebraic sum of PL + Pcw. Note that PI and Pcw are equal and opposite at a certain point (i.e., Prs = 0). This volume is the FRC that is the respiratory system's normal resting volume.

A third factor, which opposes these two driving pressures, is the resistance to flow provided by the airways. This airway resistance (Raw) is determined by the size of the airways. Because airways are largest at high lung volumes and smallest at RV, Raw is greatest at RV and least at TLC (Fig. 24-5A) . The inverse relationship between Raw and lung volume is not linear. Therefore, the reciprocal of Raw, conductance (Gaw), which is related to lung volume linearly (Fig. 24-5B) , is often utilized to identify bronchoconstriction or bronchodilation.

Flow-Volume Relationships

Because all of the determinants of maximal flow are dependent on lung volume, a useful format to assess the flow resistive properties of the airways is to plot flow as a function of volume during the FVC maneuver. At the beginning of the forced expiration, the rate of flow quickly rises to a maximal or peak value at a lung volume very near to TLC. As expiration continues, lung volume decreases, airways narrow, resistance increases, and flow rates progressively decrease. The impact of obstructive airway disease on such flow rates is emphasized in Figure 24-6 . In the patients with airway obstruction, flows are reduced over the full range of lung volume from TLC to RV.

The influence of expiratory effort on the flow-volume curves is very important. An individual can actually inscribe different flow-volume curves with differing efforts, although each may have the same FVC (Fig. 24-7) . At large lung volumes close to TLC, air flow rises with increasing effort (curve A). With decreasing effort, curves B and C exhibit decreased flows in this high range of lung volume, but all three curves merge at a point and continue together to RV. At these intermediate and low lung volumes, only moderate effort is needed to produce maximal flow. Because increased expiratory effort has little effect on increasing these flows, there is little difference between the three curves, and this portion of the curve is referred to as "effort independent."

Figure 24-5 The hyperbolic relationship of airway resistance (Raw) to lung volume (A) is contrasted with the linear relationship (B) of its reciprocal airway conductance (Gaw). (RV, residual volume; TLC, total lung capacity; FRC, functional residual capacity.)

Figure 24-6 Idealized maximum expiratory flow-volume curves in normal subjects are contrasted with those typically seen in patients with obstructive airway disease. Expiratory flow is plotted as a function of lung volume during maximal expiration from total lung capacity (TLC) to residual volume (RV).

At this point, flow is largely a function of the other two variables (PI and Raw). Once again, exaggerated effort may decrease these same flows as with $FEF_{25\%-75\%}$. [4] [5]

The rate of air flow during forced expiration is influenced not only by the effort expanded but also by the lung volume at which the expiratory maneuver is begun. True maximum flows occur only when expiration is begun at or near TLC.

Figure 24-7 Forced expiratory flow-volume curves in a normal subject. The exhalation from total lung capacity (TLC) to residual volume (RV) was performed at three levels of effort ranging from maximal (A) to minimal (C).

Figure 24-8 Forced expiratory flow-volume curves inscribed during maximal maneuvers performed by beginning at total lung capacity (TLC) and at 2 and 4 L below TLC.

When forced expirations are begun with maximal effort from volume below TLC (Fig. 24-8) , peak flow is not as high but flows quickly conform to the same performance envelope as if the maneuvers were begun at TLC. Even some healthy subjects can exhibit a decreased FEV_1/FVC ratio on the normal volume time spirogram when the forced expirations are started from such submaximal volumes. Therein lies some of the advantage of a flow-volume plot as opposed to the volume-time tracing with conventional spirometry.

Airway Compression and Flow Limitation

The failure of increasing effort to further augment flow over the lower two-thirds of the VC results from dynamic compression of the airways. This has been described in a model of flow limitation termed the equal pressure point (EPP) concept. The pressure head, which serves to move air from the alveoli to the mouth, is provided by the alveolar pressure (Palv). At any given lung volume, alveolar pressure is the sum of lung elastic recoil pressure (Pl) and pleural pressure (Ppl). At any lung volume when there is no flow, such as end-inspiration (Fig. 24-9A) , Ppl is subatmospheric and counterbalances Pl. Thus, this sum--Palv--is zero, as are pressures at the mouth and through the remaining airways. During forced expiration (Fig. 24-9B) , Ppl rises above atmospheric (becomes positive). The increased Palv again is the sum of Pl and Ppl. Pressure is dissipated along the airway to overcome resistance to flow and finally reaches zero at the mouth. At some point along the airway, the intraluminal pressure falls to a level that equals the surrounding pleural pressure. This site is referred to as the EPP. Toward the mouth (downstream), the lateral

pressure within the airway lumen is less than the compressing Ppl, and the airways

Figure 24-9 A model depicting the equal pressure point (EPP) concept of expiratory flow limitation (see text for explanation). (Pm, mouth pressure; Paw, intraluminal airway pressure; Pl, pleural pressure; Palv, alveolar pressure.)

tend to collapse. Once maximal flow is reached, further increases in Ppl from extra effort do not affect air flow in the upstream segment (from EPP toward the alveoli), because the driving pressure along this portion of the airway is equal to Pl. Therein lies the origin of the term "effort independent." The increased Ppl simply produces more compression of the downstream airways (from EPP to mouth). Thus, increasing effort produces more and more airway compression but fails to increase flow.

The principal value of this dynamic airway compression is in the production of an effective cough. Even though maximum flows may not be reached, the compressed downstream airway develops an increased linear velocity of air flow, which maximizes the removal of secretions along airway walls. At intermediate lung volumes, EPPs lie in segmental bronchi, but they may move farther upstream toward the alveoli at lower lung volumes. The dynamic compression involves primarily the lobar and mainstream bronchi and the intrathoracic trachea. Coughing is, therefore, most effective in removing material from these relatively large airways.

Sites and Mechanisms of Decreased Air Flow in Disease

Abnormal expiratory flow rates may be seen in many disease states and may result from alterations in any of the three major determinants of flow, ($P_{E}max$, Pl, and Raw), as seen in Table 24-3 . For example, the patients with neuromuscular disease who may exhibit decreased expiratory flows include those with myasthenia gravis, muscular dystrophy, Guillain-Barre syndrome, and spinal cord transection. Decreased ability to generate expiratory effort is the principal cause of low expiratory flows in these patients, who seldom exhibit increases in Raw or decreases in Pl. Other categories of restrictive disease, such as musculoskeletal deformities (kyphoscoliosis, ankylosing spondylitis, and interstitial lung disease), are often associated with near-normal muscle strength. In these situations, expiratory flows may actually be slightly increased because of an increased Pl associated with reductions in lung volume. Reduced lung volumes associated with long-term neuromuscular disease may likewise be associated with increases in Pl, which may result in more normal expiratory flow rates.

TABLE 24-3 -- Mechanisms for Decreased Expiratory Flow Rates

DISEASE	PHYSIOLOGIC VARIABLES		
	PEmax	***Raw***	***Pl***
Neuromuscular weakness		N	N
Emphysema	N	N	
Asthma, bronchitis	N		N
Peripheral airway disease	N	N	N

Symbols:
, increased;
, decreased

N, normal; $P_{E}max$, maximum static expiratory pressure; Raw, airway resistance; Pl, lung elastic recoil pressure

The classic example of decreased expiratory flow associated with decreased lung recoil (Pl) is emphysema. In this disease, expiratory muscle strength is usually adequate, and lung distention tends to increase airway size, such that Raw is also usually normal. In patients with bronchitis and asthma, conversely, airway narrowing is prominent. In these two variants of obstructive lung disease, the major factor reducing flow is an increased Raw. Early changes in these obstructive lung diseases may be confined to the smaller peripheral airways. Narrowing in these airways may reduce expiratory flows at middle and low lung volumes but does not appreciably affect measurements in Raw or the other determinants of air flow.

MEASUREMENT OF AIRWAY OBSTRUCTION

Airway Resistance

Of the standard techniques used to evaluate airway obstruction, Raw measurements appear to be the most direct. The technique is rapid and noninvasive and requires merely that a subject pant once or twice per second through a mouthpiece and with a nose clip in place. During normal breathing, a major fraction of the resistance to air flow resides in the nose, pharynx, and larynx and can mask changes taking place in the lungs. The use of a mouthpiece bypasses the nose in order to minimize the effects of the upper airway on the measurement. The panting maneuver is likewise utilized to keep the larynx dilated and to reduce its influence on the total resistance to air flow. The measurements of Raw requires the subject to sit in a constant volume body plethysmograph ("body box"), which also permits the recording of thoracic gas volume and thereby provides an accurate appraisal of the effects of lung volume on Raw. Lung volume is estimated by use of Boyle's law to relate changes in box pressure and mouth pressure, and Raw is calculated from changes in box pressure and flow. [10] The subjects initially pant against a closed mouthpiece, usually at end-expiration. Thus, thoracic gas volume (FRC) is calculated from relationship of box pressure to mouth pressure (Fig. 24-10) . The shutter in the mouthpiece is then opened, and continued panting inscribes the relationship between box pressure and flow at the mouth to derive Raw. The upper limit of normal Raw is usually considered to be 2 cm H_2O/1 second. In order to eliminate passive changes in Raw as a result of difference in lung volume, the reciprocal of Raw, Gaw, is calculated. The Gaw is usually divided by the lung volume at which the measurement is made (usually FRC) to obtain specific Gaw. The coefficient of variation (standard deviation/mean × 100) in normal baseline values for the same subject is usually small (<10 percent). Therefore, specific Gaw is a highly reproducible measurement that can identify changes in the caliber of the intrapulmonary airways. However, a significant portion of normal airway resistance resides in the upper airways. The latter can be significantly increased with head flexion, which reduces the caliber of the hypopharynx. [11] [12] Therefore, it is important that patients position themselves as erect as possible when attached to the mouthpiece in the body box.

Figure 24-10 Diagram of the constant volume body plethysmograph to measure airway resistance and lung volume. When subject pants against an obstructed mouthpiece (shutter closed), box pressure (Pb) is plotted against mouth pressure (Pm). Changes in Pb are converted in changes in lung volume by calibrating the box with known volumes of added gas and observing Pb changes. As subject pants through the open mouthpiece, flow (V) replaces Pm on the plot, and airway resistance is computed from the relationship between Pb and V.

Forced Expiratory Maneuvers

Despite the specificity and sensitivity of Raw measurements, airway obstruction is more commonly evaluated by measurements of maximal forced expiration. The indices obtained from forced expiration, unlike Raw, are determined by a complex interrelationship of flow-resistive properties of intrathoracic airways and elastic recoil of the lung. The simplest of such measurements is the peak expiratory flow, which is conveniently measured with a variable orifice flowmeter. Because the peak flow occurs early in a forced expiration, flow limitation has not occurred in the airways, and thus, flow is highly dependent on effort and subject cooperation. However, because the variation for the measurement in the same subject is surprisingly low, peak expiratory flow is a fairly reproducible test of airway function.

Another extensively used indirect measure of airway dimensions is the FEV_1 . Again, during the first 25 percent of an FVC maneuver, flow reflects dimensions of the airways between the alveoli and the mouth and is effort dependent. Although the physiologic parameters governing the remaining flow are complex, FEV_1 , like peak flow, is simple and reproducible and is thus a useful index of airway function. The measurement is subject to day-to-day variability, which is greater in patients with obstructive airway disease than in normal patients. [13] These changes in FEV_1 must exceed 15 percent in order to signify bronchodilation or constriction in patients. An even greater potential variability applies to $FEF_{25\%-75\%}$ measurements. In addition, one must account for the possibilities of negative effort dependence and, more importantly, the changes in FVC that might occur. For example, in bronchodilation, FVC may increase but may actually produce a misleading decrease in $FEF_{25\%-75\%}$. [14] Thus, the measurement should be adjusted to the same absolute lung volume, that is, the same segment of FVC below TLC (Fig. 24-11) .

Traditionally, the response to bronchodilators is expressed as the percentage change in FEV_1 from a baseline value. Healthy normal subjects and those with very mild obstruction typically exhibit a minimal increase in FEV_1 (<5%). Likewise, patients with severe baseline obstruction respond poorly because of accompanying secretions and airway edema. The most dramatic improvement occurs in patients with moderate obstruction such that response to bronchodilators follows a "bell-shaped" distribution. [15]

Additional assessment of the flow-resistive properties of the airways can be obtained from maximal expiratory flow volume (MEFV) curves, which illustrate the relationship between air flow and lung volume during an FVC maneuver (see Fig. 24-6) . A typical response when bronchoconstriction is induced consists of diminished flows throughout the sole MEFV curve envelope (Fig. 24-12) . Ventilatory flows and FVC usually decrease, and RV increases. Therefore, expiratory flows must be measured at the same reference lung volume. This is usually at a fixed percentage of the baseline or normal FVC and requires that all curves be superimposed at TLC.

In normal subjects, full inflation to TLC may remove the bronchoconstriction induced by mechanical stimuli or drugs, whereas in asthmatics, an increase in bronchomotor tone may accompany the same deep inspiration. To overcome these variable effects of a full inspiration on bronchial tone, flows can be measured with partial expiratory flow volume

Figure 24-11 Forced expiratory spirograms before (A) and after bronchodilator therapy (B). Note the increase in forced vital capacity in B, but flow over its midportion ($FEF_{25\%-75\%}$) is decreased unless adjusted to the same volume, i.e., the portion of FVC below total lung capacity (TLC). The artifact results from the increased FVC as a result of bronchodilation. Note: when $FEF_{25\%-75\%}$ is measured over the same actual volume segment as in A, the value increases.

curves. In this case, the maximal forced expiration is started at or slightly above the middle of FVC (Fig. 24-13) . In all cases, the partial expiratory flow volume curve is followed by a full inhalation to TLC and a maximal forced exhalation to RV to obtain a reference MEFV curve. Flows are usually measured between 20 and 40 percent of VC above RV. Because partial expiratory flow volume curves are unaffected by changes in upper airway resistance, they are sensitive to the change in the intrapulmonary airways and have been suggested as a useful alternative to Raw for detecting bronchoconstrictor and bronchodilator responses.

Flow-Volume Loops

The finding of reduced peak flow, MVV, and FEV_1 without additional clinical evidence of chronic obstructive lung disease may indicate the presence of an obstructing lesion of the upper airway, larynx, or trachea. In some cases, this obstruction may be suspected by a careful history and physical

Figure 24-12 Maximum expiratory flow-volume curves before (solid line) and after (broken line) induced bronchoconstriction. Flow is plotted against expired volume expressed in liters from total lung capacity (TLC) to residual volume (RV). Forced 1 second expiratory volumes (FEV_1) are indicated with arrows on each curve.

examination, but in many instances, it may stimulate diffuse airway obstruction and may suggest a marked degree of lung dysfunction. The latter is most likely to occur in patients who are going to undergo head and neck surgery who may present for operative procedures related to these lesions.

Figure 24-13 Partial expiratory flow-volume curves before (A) and after (B) bronchodilator treatment. Forced expiration is begun just above midpoint of vital capacity (VC). Flows are quantitated at 20 and 40% VC above residual volume (RV). A reference maximum expiratory curve (C) is also inscribed by beginning exhalation from total lung capacity (TLC).

Flow-volume loops provide a graphic analysis of flow at various lung volumes and have been utilized to discriminate between patients with upper obstructive lung lesions. Both flow and volume are plotted simultaneously on an X-Y recorder as subjects inhale fully to TLC and then perform an FVC maneuver. This is followed immediately by a maximal inspiration as quickly as possible back to TLC (Fig. 24-14) . Expiratory flow decreases over the latter half of the exhaled volume, despite the sustained expiratory effort indicated by the high positive pleural pressure. During maximal inspiration, airways do not undergo compression. Rather, with increasing inspiratory effort, airways become distended by the subatmospheric (negative) pleural pressure, and flow is increased. Thus, the entire inspiratory portion of the loop, as well as the expiratory curve near TLC, is highly dependent on effort. The ratio of expiratory flow to inspiratory flow at 50 percent of VC (mid-VC ratio) is normally about 1.0. This ratio is particularly useful in identifying the presence of upper airway obstruction, in which case inspiratory flow tends to be reduced more than expiratory flow, and the mid-VC ratio is increased (i.e., >1).

Flow-volume loops not only aid in suspecting upper airway obstruction but may also help to localize the site and the nature of the obstruction. Several characteristic patterns have been described. Perhaps the most common lesion is a fixed obstruction, such as a benign stricture resulting from tracheostomy or tracheal intubation. A tumor or mass such as a goiter may also produce a similar picture, as would breathing through a fixed external resistance. No significant change in airway diameter occurs during inspiration or expiration. As a result, expiratory flows show a plateau of constant flow over the effort-dependent portion of VC. Inspiratory flows show a similar plateau (Fig. 24-15A) . Because

Figure 24-14 Schematic representation of a maximum inspiratory ($\dot{V}_I$) and expiratory ($\dot{V}_E$) flow volume loop in a normal subject. The pleural pressure (ppl) associated with the maximal efforts are plotted as a function of lung volume from total lung capacity (TLC) to residual volume (RV). $\dot{V}_I$ and $\dot{V}_E$ at the midpoint (50%) of vital capacity are indicated by arrows.

Figure 24-15 Maximum inspiratory and expiratory flow-volume curves (flow- volume loops) in four types of airway obstruction.

both are reduced to nearly the same extent, the mid-VC ratio remains approximately 1.0.

A lesion whose influence varies with the phase of respiration is termed a variable obstruction. In order to understand the impact of such lesions on flow, it is necessary to characterize the behavior of the three basic partitions of the airway (Table 24-4) .

Variable extrathoracic obstructions (Fig. 24-15B) are most commonly associated with vocal cord paralysis, which is usually accompanied by inspiratory stridor. A similar pattern may be seen with marked pharyngeal muscle weakness in curarized volunteers [16] and in chronic neuromuscular disorders. [17] The flow pattern has also been noted occasionally in patients with severe obstructive sleep apnea. During forced inspiration, the negative transmural pressure inside the airway tends to collapse the airway with increasing effort and, thus, reduces inspiratory flow. During expiration, the positive pressure within the upper airway tends to decrease the obstruction so that expiratory flow is reduced far less and

TABLE 24-4 -- Airway Partitioning and Behavior

UPPER (EXTRATHORACIC)
Surrounding soft tissue unsupporting
Collapses during inspiration
Expands during expiration
INTRATHORACIC
Outer surface exposed to pleural pressure
Expands during inspiration
Collapses during expiration
DISTAL (PULMONARY)
Intimately related to lung tissue
Collapses as expiration proceeds

may even be normal. The mid-VC ratio of expiratory to inspiratory flow is often greater than 2.0.

The other form of variable obstruction occurs intrathoracically and is usually caused by tumors of the tracheal or major bronchi. During forced expiration, the high pleural pressures decrease airway diameter and may increase the obstruction. A plateau flow usually occurs during expiration when the compressed airway lumen assumes its minimal size at the area of the lesion (Fig. 24-15C) . During inspiration, the lowering of pleural pressure surrounding the airway tends to decrease the obstruction, such that the inspiratory portion of the flow-volume loop may be normal. The mid-VC ratio of expiratory flow is low as in the case of diffuse airway obstruction (Fig. 24-15D) . However, the shapes of the curves differ. Curve D, an example of diffuse or distal airway obstruction, exhibits abnormal decreased flow in the segment near RV. Curve C, conversely, demonstrates normal flow in this area.

The physiologic diagnosis of upper airway obstruction is sometimes difficult in the patients with diffuse airway obstruction, such as chronic bronchitis and asthma. These conditions themselves produce significant abnormalities of the flow-volume loop (see Fig. 24-15D). Therefore, flow-volume loops clearly identify upper airway

obstruction best in the absence of significant generalized airway disease.

/das/book/view/29494766/875/254.html

TESTS OF EARLY LUNG DYSFUNCTION

During the past 2 decades, there has been continued interest concerning disease in the peripheral airways. Several terms, such as "small airway disease," "early obstructive lung disease," and "minimal airway dysfunction," have been used to describe abnormalities of the small peripheral airways.

The basic concept has evolved that peripheral airway obstruction is a forerunner of chronic bronchitis and emphysema. These processes are thought to be moderately advanced and irreversible by the time routine indices of pulmonary function, such as FVC and FEV_1, become abnormal. Testing of such early lung dysfunction has included measurements of abnormal resting gas exchange, distribution of ventilation, airway instability, and variables derived from maximum expiratory flow-volume curves.

The initial enthusiasm with which these tests were greeted has been tempered somewhat by the complexity of the equipment required and their inherent variability because of technical and biologic factors. Furthermore, these test results did not always correlate with respiratory symptoms and, more importantly, with pathology in the small airways, that is, respiratory bronchioles <2 mm in diameter. [18] Despite this lack of specificity, these tests are sensitive indices of abnormal function of airways and lung parenchyma, and an understanding of their physiologic principles provides important perspective and insight into abnormalities of pulmonary function.

Alveolar-Arterial Oxygen Tension Difference

Abnormally high alveolar-arterial oxygen tension gradients during room air breathing are common in asymptomatic smokers and in patients with minimal signs of chronic bronchitis. Although the alveolar-arterial oxygen tension gradient appears to be a sensitive means of detecting regional ventilation-perfusion inequalities, the test is not widely used for screening purposes, because of the difficulty in measuring alveolar oxygen tension (P_{AO_2}), which must be estimated from the alveolar air equation. The oxygen tension of the warmed humidified inspired gas in the trachea is represented as P_{IO_2}. [19] The gas in the alveoli, however, also contains carbon dioxide. As a rule, less carbon dioxide is produced than oxygen consumed. This ratio of carbon dioxide production to oxygen consumption is the respiratory exchange ratio (R), which is usually assumed to be 0.8. A simple calculation of P_{AO_2} for bedside use may be derived by dividing Pa_{CO_2} by R, or simply multiplying the carbon dioxide value by 1.25, and then subtracting the value from P_{IO_2}. Therefore, the alveolar gas equation may be written simply as

$$P_{AO_2} = P_{IO_2} - Pa_{CO_2}/R$$

The normal alveolar-arterial oxygen tension gradient with subjects breathing room air averages 8 mm Hg in young persons and increases linearly with age. By the 8th decade, the typical values may reach 25 mm Hg. This widening of the alveolar-arterial oxygen tension gradient with age and in disease states results solely from decreases of Pa_{O_2}, not P_{AO_2}.

Frequency Dependence of Compliance

Another phenomenon demonstrable in asymptomatic smokers and attributed to small airway dysfunction is a decrease in dynamic compliance with increased rates of breathing. This was one of the first tests to be proposed as an indicator of small airway dysfunction and can still be regarded as somewhat of a standard. Compliance is considered frequency dependent if the dynamic compliance at any of the increased breathing rates falls to less than 80 percent of the static compliance. Most workers have measured dynamic compliance as the change in lung volume during a tidal breath divided by the maximal change in transpulmonary pressure. The static compliance is derived from the slope of an inspiratory static pressure-volume curve over the usual range of tidal volume. Both compliance measurements require the insertion of an esophageal balloon to estimate transpulmonary pressure (difference between esophageal pressure and mouth pressure). Because of the sophisticated equipment required and the discomfort associated with balloon insertion, the test is not technically suited for general screening purposes. Nevertheless, frequency dependence of compliance is commonly used as a reference for other tests in identifying peripheral airway dysfunction.

In normal lungs, alveoli fill and empty synchronously at all physiologic respiratory rates. Therefore, compliance is not commonly dependent on respiratory frequency. Frequency dependence of compliance, conversely, implies asynchronous behavior wherein some regions of the lung are moving out of phase with others. The rate at which alveoli respond to a given pressure change by a change in volume is determined by their time constant, the product of their resistance and compliance. The more restricted or more compliant a unit of lung is, the longer it takes for air to enter or leave.

When various areas of the lung have different time constants, they fill and empty at different rates. During slow breathing, air can still be so equally distributed that dynamic compliance is not altered appreciably. However, during rapid breathing, air moves less rapidly into areas with long time constants, especially those with a high resistance. There is insufficient time to expand these areas. As a result, greater transpulmonary pressure is required to move the same volume of air, and dynamic compliance falls.

This asynchronous behavior of lung units has been ascribed solely to obstruction in the small airways. However, other factors may cause time-constant discrepancies throughout the lung and must be eliminated before changes in dynamic compliance are attributed solely to small-airway obstruction. These may include abnormal lung elasticity, obstruction in the large central airways such as might occur with a bronchial tumor, and diffuse airway constriction. In the case of the former, static compliance would be abnormal, whereas abnormally increased airway resistance is likely in the latter two situations.

Multiple-Breath Nitrogen Washout

Measurements of the uneven distribution of ventilation are also sensitive to mild airway obstruction. If the resident nitrogen in the lung is washed out by breathing 100 percent oxygen, the concentration of nitrogen decreases as cumulative expired volume decreases. When the distribution of ventilation is normal and uniform, the lung appears to behave as a single compartment that produces a relatively fast single exponential washout curve for nitrogen (Fig. 24-16). In the abnormal patient with lung disease and nonuniform

Figure 24-16 Schematic representation of multiple breath nitrogen washout curves in a young healthy nonsmoker (normal) and an asymptomatic smoker (abnormal). Expired nitrogen concentration is plotted on a logarithmic scale against cumulative expired volume during pure oxygen breathing.

ventilation, the curve deviates from the single exponential and appears to contain more than one ventilatory compartment. Different lung units have their nitrogen diluted at different rates. The fast, well-ventilated alveoli cause a rapid decrease in expired nitrogen, whereas slow, poorly ventilated areas produce a prolonged tail on the washout curve. Ingram and Schilder [20] reported a direct relationship between nitrogen clearance and frequency dependence of compliance. Unequal time constants throughout the lung may explain both phenomena. Although multiple-breath nitrogen washout appears to be a sensitive test, appropriate analysis of the curve is tedious and requires computerization in order to be practical as a screening test.

Single-Breath Nitrogen Washout

Inequality of ventilation can also be measured by the single-breath nitrogen test, which has been used extensively since its original description by Fowler [21] in 1949. The expired nitrogen concentration was measured after inspiration of 1 L of oxygen from FRC. The change in nitrogen concentration between 750 and 1250 mL of expired volume was originally used as an index of uneven ventilation. Later, it was shown that this change in nitrogen concentration could also be measured from the plot of nitrogen versus lung volume in the resident gas technique as used to measure closing volume (CV). Instead of inspiring only 1 L, the patient makes a full inspiration from RV to TLC with pure oxygen. A line of best fit is drawn through the alveolar plateau (phase III, Fig. 24-17) , and the increase in nitrogen concentration per liter is quantitated. The alveolar nitrogen slope with this technique is less steep than the original Fowler technique. This results from the fact that oxygen is preferentially distributed to the lung bases when only 1 L is inspired from FRC. The nitrogen in lung apices is less diluted with oxygen, compared with when oxygen is inspired over the whole range of VC. This higher apexto-base nitrogen gradient (original standard technique) produces

Figure 24-17 Schematic representation of the plot of nitrogen (N_2) concentration versus expired volume during the closing volume (CV) measurement with resident gas technique. (CC, closing capacity, the sum of residual volume [RV] and CV; TLC, total lung capacity.)

a steeper rise in exhaled nitrogen than the new technique, in which less of an apex-to-base nitrogen gradient is established.

The slope of the alveolar nitrogen plateau ($^{Delta}N_{2\%}$ /L) is larger in old than in young subjects, reflecting the increasing uneven ventilation with age. Buist and Ross [22] found that $^{Delta}N_{2\%}$ /L was less than 2 percent in male nonsmokers regardless of age and as high as 10 percent in smokers. They also noted that nearly half of the asymptomatic smokers they tested had an abnormal alveolar nitrogen slope compared with their own predicted values. Therefore, quantitative analysis of the alveolar plateau (phase III) appears to be a sensitive test of early changes in the lungs of cigarette smokers. When found to be abnormal, there is a reasonable likelihood of structural abnormalities.

Closing Volume

One of the tests most frequently associated with the concept of small airway obstruction is the measurement of CV. The term describes the lung volume at which airways in dependent areas in the lung begin to close or, more precisely, cease contributing to the expired gas. This phenomenon presumably occurs because of gravity-dependent gradients in pleural pressure. At or near RV, the lower portions of the lungs are subjected to pleural pressures in excess of airway pressures. Hence, these airways are prone to close or, more precisely, contribute little to the expired gas.

The CV test attempts to detect the lung volume at which this phenomenon occurs. The basic technique is to tag these dependent lung areas by giving them a different concentration of a tracer gas than the ones that remain open near end-expiration. As a subject inspires from RV to TLC, a concentration difference for the tracer gas is created between the top and the bottom of the lung as a result of differences in distribution of ventilation. During the subsequent slow exhalation, the changing concentration of tracer gas is plotted against lung volume on an X-Y recorder. Two methods utilize

this principle to estimate CV: the bolus technique and the resident-gas technique.

The bolus technique employs a bolus of tracer gas. Although xenon and argon were originally used, the easier availability of helium has made it most popular. The technique depends on the principle that a bolus of gas inspired at RV is distributed preferentially to the apical lung areas because small airways in dependent lung zones are far less patent at these low lung volumes. Therefore, the preexpiratory concentration gradient created for the tracer gas results in the apical areas' containing most of the marker gas, whereas lower basilar areas contain very little.

The resident gas technique also depends on the creation of a preexpiratory concentration gradient of marker gas from top to bottom of the lung. However, it differs from bolus technique in two ways. First, the tracer gas is the nitrogen already present or resident in the lungs. Second, there is normally little difference in nitrogen concentration at TLC between the top and the bottom of the lung when a person is breathing air. Therefore, a preexpiratory concentration gradient is artificially created by the use of oxygen to dilute the nitrogen normally present in the lungs. The nitrogen in all alveoli is not diluted equally. At RV, the alveoli at the bottom of the lung are smaller than those at the top. At TLC, all alveoli reach essentially equal volumes. Thus, during inspiration from RV to TLC, the lower basal alveoli undergo almost one and a half times the volume change undergone by the upper or apical alveoli. As a result, the nitrogen in the lower zones is diluted more by the inspired oxygen than is the nitrogen in the upper zones. There is approximately a 2:1 concentration gradient for nitrogen between top and bottom of the lungs.

In normal subjects, the nitrogen concentration appearing at the mouth after inspiration of 100 percent oxygen changes gradually throughout the expiration. A typical trace displays four basic phases (see Fig. 24-16) . The first three are familiar from Fowler's original single-breath nitrogen test. Phase I contains expired gas essentially free of marker, representing emptying from the dead space of the apparatus as well as of the conducting airways (anatomic dead space). Phase II consists of a rapid rise in the concentration of marker gas, which mixes with dead space gas as alveolar emptying begins. Phase III, or the alveolar plateau, is produced by the mixing of expired air with marker gas from all lung regions, each with different concentrations. The "ripples" appearing during phase III are termed "cardiogenic oscillations" because they correspond to cardiac systole and are believed to rise as a result of interruptions in gas flow from the dependent lung zones during cardiac systole. The alveolar plateau exhibits a small positive slope even in normal lungs; the extent of this rise has been used as an index of abnormality, as discussed previously.

Near the end of expiration, another abrupt increase in tracer gas concentration occurs (phase IV). The point at which phase IV begins has been designated the CV because the dependent airways have presumably closed or, more correctly, have essentially ceased contributing to the expired gas. Now, the exhaled gas arises almost entirely from the upper lung zones, whose concentration of marker gas (in this case, nitrogen) was high. The CV is the difference in volume between the onset of phase IV and RV. Because it represents a portion of the VC maneuver, it is usually expressed as a percentage of VC (CV/VC percent). Most published values for CV in normal healthy subjects in the sitting position are between 15 and 20 percent of VC.

The terminology is confused by another term, "closing capacity" (CC). This term is used to designate the volume between the onset of phase IV and zero lung volume; it thus includes CV and RV. Because it is the absolute lung volume at which phase IV occurs, it is usually expressed as a percentage of TLC (CC/TLC percent).

Although the onset of phase IV is usually taken to represent a unique volume at which actual closure of the small airways occurs, Hyatt and Rodarte [23] suggested that rather than closing off, the small airways may merely be emptying more slowly because of dynamic compression and the resultant increased resistance to flow. This impression is based on the evidence that phase IV occurs at the time the lungs reach flow limitation and continue to empty at a decreased rate despite increasing transpulmonary pressures. This same phenomenon occurs during the later portions of the MEFV curve. In fact, high expiratory flow rates, such as those characterizing the MEFV curve, can actually increase the lung volume at which phase IV occurs, presumably because of some dynamic airway compression. Thus, in order to produce a satisfactory trace when measuring CV, one must ensure that expiration be performed slowly (about 0.5 L/s). This can be ensured by introducing mechanical resistance into the breathing circuit.

Whether the mechanism is closure or compression, most observers have noted significantly increased values for CC in cigarette smokers when compared with

nonsmokers of the same age. These findings have been cited as evidence of small airway disease. However, Hoeppner et al [24] suggested that these changes in CC in smokers reflect a loss of elastic recoil and not necessarily intrinsic small airway pathology. This same relationship between CC and lung elastic recoil is clearly demonstrated by the changes that occur with age. The progressive reduction in lung recoil and its associated tethering action on the bronchioles produce an increase in CC with advancing age; until age 65, CC exceeds the FRC (CC > FRC), even in seated individuals. [25] Young children who exhibit reduced values for lung elastic recoil likewise have increased closing capacities. [26] The smallest CC values occur in subjects during the late teens, when maximal values for static elastic recoil are observed.

Regardless of whether an increased CV represents intrinsic airway disease or parenchymal disease with loss of elastic recoil, the sensitivity of the measurement renders it a likely indicator of early functional abnormality that may represent lung disease. Perhaps the major obstacle to its application has been the difficulty of establishing well-defined limits of normality because of variability between measurements even under ideal conditions.

Maximum Expiratory Flow Rates

The frictional resistance of the small airways affects flows at low lung volumes, that is, after more than 50 percent of FVC has been expired. Reduced values for flow at the "foot" of the MEFV curve (see Fig. 24-6) have often been observed in smokers compared with nonsmokers, when no differentiations were possible on the basis of FEV_1 measurements. Unfortunately, normal variations sometimes make quantitation and interpretation of these flows at low lung volumes difficult.

Because of this difficulty in defining abnormal flows at low lung volumes, a modification of the maneuver has been devised to detect mild airway obstruction. The MEFV curves inscribed after inspiration of a gas mixture of low density (80 percent helium and 20 percent oxygen) are compared with those obtained during the breathing of air. Maximum flow in normal individuals is dependent on the density of the gases breathed and increases with gases of low density. However, this is true during the FVC maneuver only as long as the EPPs remain predominantly in the larger, more central, airways. In these airways, most of the resistance to air flow is due to connective acceleration and turbulence, both of which are density dependent.

In patients with obstructive lung disease, because of diminished elastic recoil and increased resistance of small upstream airways, the EPPs lie in the small airways, even at higher lung volumes. As a result of this peripheral airway obstruction, flow is less density dependent and does not increase with helium. Unfortunately, this response to breath-ing helium, although physiologically interesting, is too highly variable, even in normal subjects because of variations in lung recoil, airway geometry, performance, and interpretation, to lead to precise diagnosis concerning airway dysfunction.

Defining Normal Values

An important aspect of pulmonary function testing lies in defining what is normal and what indicates the presence of respiratory disease. The results are commonly interpreted in relation to reference values to determine whether or not they lie within a certain normal range. One statistically acceptable approach is to define as abnormal the lowest 5 percent of the reference population. For most tests, the results of large numbers of normal patients have been used to generate regression equations based on age, gender, race, and most importantly, height. [27] Although a number of clinical laboratories simply designate that values of FVC and FEV_1 less than 80 percent are predicted as abnormal, this arbitrary standard has no statistical basis and should be avoided. [28]

If one assumes a gaussian distribution, the 95 percent confidence limits can be derived as 1.65 times the coefficient of variation. The latter is the quotient of the standard deviation and the mean. For FVC and FEV_1, coefficients of variation are 12 to 13 percent in large groups of normal subjects. [29] Thus, a value 1.65 times these variations indicates that a measurement must be about 21 percent lower than the mean to be considered abnormal. Interestingly, the coefficient of variation for $FEF_{25\%-75\%}$ is about 25 percent in similar populations. Thus, values must be 40 percent below the population before they are truly considered abnormal.

PULMONARY FUNCTION TESTING IN SURGICAL PATIENTS

Significant postoperative changes in pulmonary function in many surgical patients include such phenomena as reduced lung volumes, rapid shallow breathing, and impaired gas exchange (Ch. 25) . These alterations in pulmonary function may occur as a result of the anesthetic, the surgical procedure, the associated body position, or the medications administered immediately after surgery. It has been suggested that the changes that occur in normal patients may be more severe in patients who undergo surgery with compromised pulmonary function and thus may produce significant postoperative pulmonary complications. Such complications usually include bronchospasm, bronchitis with purulent sputum, disabling cough pneumonia, and respiratory failure, as indicated by altered blood gases. Indeed, preexisting lung dysfunction is the major factor associated with postoperative pulmonary problems. Also important are incisional site and size, as well as possible surgical trauma to lung tissue. Both of these render the patient for thoracic surgery a prime candidate for evaluation.

The large body of literature suggests that preoperative pulmonary function testing provides the clinician with important information regarding the potential for postoperative respiratory morbidity. If pulmonary function data are of value, which patients are candidates for such testing? Although no general agreement exists as to which patients should be tested, the prime candidates are those in whom there is reasonable expectation of abnormal pulmonary function. This broad list has long included the following:

1. Patients with any evidence of chronic pulmonary disease
2. Heavy smokers with history of persistent cough
3. Patients with wheezing or dyspnea on exertion
4. Patients with chest wall and spinal deformities
5. Morbidly obese patients
6. Patients with thoracic surgery
7. Elderly patients (>70 years of age)
8. Patients who are to undergo upper abdominal surgery

Conflicting data abound regarding these broad criteria. This has led the American College of Chest Physicians to propose a more stringent set of guidelines. Adherence to these stricter American College of Chest Physicians guidelines has been recommended as a means of decreasing unnecessary and costly spirometric testing. [30] The American College of Chest Physicians criteria confine preoperative spirometry to patients who are to undergo lung resection, those who undergo cardiac and upper abdominal surgery in the presence of a history of smoking and dyspnea, and patients with pulmonary symptoms and uncharacterized disease who undergo prolonged lower abdominal surgery.

Initial identification of most of these patients is accomplished by history, physical examination, and chest x-ray studies. The chest film is a particularly valuable clinical marker for clinically severe disease, especially if lung hyperinflation is identified. The latter was associated with a 33 percent rate of significant postoperative pulmonary complications. [31]

The question then arises as to which pulmonary function studies are appropriate for preoperative evaluation. The objective of testing in the preoperative setting is not to detect mild early lung disease but rather to predict the likelihood of pulmonary complications. No single test appears to be the best predictor of risk, probably because none assesses all of the factors that are important regardless of whether complications will occur. The optimal scheme for evaluating patients preoperatively is by means of arterial blood gas analysis and the FEV_1, FVC, FEV_1/FVC percent, peak flow, and

forced midexpiratory flow, which can be obtained from a single spirometric study. Abnormalities on such spirometric tests seem to correlate with the incidence of postoperative pulmonary complications. [4]

Although the emphasis in evaluating preoperative pulmonary function is largely aimed at predicting the risk of postoperative complication, the identification of abnormal lung function and in particular obstructive airway disease is also important to reduce intraoperative morbidity. A reduced FEV_1/FVC, for example, not only documents the existence of airway obstruction but also suggests the likelihood of increased airway reactivity. The site and the nature of many surgical procedures often provide very little latitude for choosing between regional and general anesthesia. In patients with airway obstruction and heightened airway reactivity, airway instrumentation, such as laryngoscopy and tracheal intubation, is fraught with the hazard of provoking reflex bronchoconstriction, particularly under light planes of anesthesia. In many patients with obstructive airway disease, the deeper levels of inhalation anesthesia required to blunt such airway reflexes are difficult to achieve because of poor ventilation perfusion matching and, if achieved, are poorly tolerated by the cardiovascular system. Thus, it is important to utilize other prophylactic measures to minimize airway responses. These may include anticholinergics and beta agonists inhaled as aerosols before surgery and intravenous opioids and lidocaine administered before airway instrumentation.

Patients with abnormally low FEV_1 values before surgery are likely to experience severe hypercapnia if they are allowed to breathe spontaneously under general anesthesia. [32] The magnitude of the carbon dioxide increase is directly related to the degree of reduction in FEV_1 and develops largely because the rapid shallow breathing pattern characteristic of anesthetized patients worsens ventilation perfusion matching. It is therefore essential to control ventilation in such patients. With controlled ventilation, low respiratory rates (<10/min) are desirable to minimize ventilation/perfusion mismatch, which largely arises because of the prolonged time required to move air in and out of the obstructed airways. Because of this obstruction, low inspiratory flow rates have long been advocated to minimize peak airway pressure and presumably barotrauma and circulatory disturbances; however, evidence suggests the opposite. In patients with chronic obstructive pulmonary disease ventilated with customary tidal volumes (10 mL/kg), respiratory system resistance actually decreased as inspiratory flow rates were increased from 0.25 to 1.5 L/s. [33] The authors postulated that this effect was due to decreases in thoracic tissue resistance or was a reflection of time constant inequalities and or the visco-elastic behavior of the respiratory system. Other studies have shown that a high inspiratory flow rate in such patients produced improved gas exchange and was not complicated by barotrauma or circulatory depression. [34] [35] An important consequence of the increased inspiratory flow rate was a reduced inspiratory time, which then allowed increased time for exhalation. This increased expiratory time provides more complete emptying of alveoli, which must do so through high-resistance airways. Conversely, with a shorter expiratory time, which inevitably occurs with the increased inspiratory time needed with a lower inspiratory flow, alveoli are not allowed to empty completely. In addition, they actually receive less gas volume at the same distending pressures during inspiration.

/das/book/view/29494766/875/256.html

EVALUATION OF THE PATIENT FOR LUNG RESECTION

Resection of lung disease results in a greater impairment in postoperative lung function than most other types of surgery (Ch. 48) . Lung resection in patients with pulmonary dysfunction is associated, not surprisingly, with a high risk of postoperative complications, even the possibility of death. These patients require a more extensive pulmonary evaluation, particularly if removal of an entire lung is anticipated. A major aim of the evaluation is to decide whether the removal of lung tissue can be tolerated without compromising pulmonary function to a degree that the patient dies of pulmonary insufficiency or is severely disabled. The long-term ability to withstand such lung resection relates to the amount and the functional status of the lung parenchyma removed and more importantly to the function of the remaining lung tissue. Removal of lung from an already compromised patient may be followed by inadequate gas exchange, pulmonary hypertension, and incapacitating dyspnea.

Although much of the literature in this area emphasizes long-term disability in the pneumonectomy patient, in patients undergoing lobectomy, the immediate impact on pulmonary function may be as great because of surgical trauma to the remaining tissue of the same lung. The pulmonary function studies must be viewed in light of the patient's age, the status of the cardiovascular system, and the patient's cooperation and motivation. Data in pneumonectomy patients indicate that whole lung removal is likely to be tolerated if the preoperative pulmonary function meets the following criteria [36] : (1) FEV_1 greater than 2 L and FEV_1 /FVC ratio of at least 50 percent, (2) MVV greater than 50 percent of predicted, and (3) ratio of RV to TLC less than 50 percent.

If any of these criteria are not met, more sophisticated testing of split lung function is indicated in order to estimate the relative functional contribution of each lung. If, for example, the lung to be removed contributes less to ventilatory function than the other lung, low spirometric values are not as ominous. Usually, split function testing consists of xenon radiospirometry to assess ventilation and macroaggregates of iodine or technetium to scan perfusion. The relative contribution of each lung to either total ventilation or perfusion can be used to predict postoperative pulmonary function. A predicted postoperative FEV_1 of at least 800 mL is required before pneumonectomy should be performed. The risk of significant resting carbon dioxide retention and resting dyspnea appears to be high with FEV_1 values less than this. If surgery is still contemplated in the face of this low predicted FEV_1 , an invasive study is recommended. The pulmonary artery of the lung to be removed can be subjected to occlusion by a balloon. If pulmonary hypertension (mean pulmonary arterial pressure >35 mm Hg) and arterial hypoxemia (Pa_{O_2} <45 mm Hg) do not occur, it can be assumed that the remaining lung may be able to accommodate the entire cardiac output. Such a patient may be allowed to undergo surgery in spite of failure to fulfill the mechanical ventilatory criteria. The indications for performing this invasive procedure are not agreed on universally, but many physicians still heed the advice of Olsen et al [36] that balloon occlusion, if feasible, should be performed when the less invasive studies are inconclusive.

The past decade has seen an increased emphasis on preoperative evaluation of exercise capacity before lung resection.

Continued observations suggest that a patient's maximal oxygen uptake during exercise (V_{O_2} max) was an accurate preoperative means of identifying patients likely to experience postthoracotomy morbidity. [37] The V_{O_2} max is essentially a measure of physical fitness and thus reflects the ability to survive the stresses of the perioperative period and beyond. During exercise, the lung must accommodate the increased ventilation and blood flow, much like the remaining lung will experience after pneumonectomy. Patients with V_{O_2} max values of 20 mL/kg/min or more had minimal morbidity. Those with a V_{O_2} max of 15 mL/kg/min or less had increased cardiopulmonary complications, whereas those whose V_{O_2} max was less than 10 mL/kg/min appeared to have an unacceptably high risk and a mortality rate of greater than 30 percent in the short term. Insight into these V_{O_2} max values is provided by evidence that a two-flight stair climb (20 steps/min) without dyspnea approximates a V_{O_2} max of about 16 mL/kg/min. [38] The ability to walk 180 feet in 1 minute corresponds to about 12 mL/kg/min.

It appears that resting pulmonary function testing does not accurately predict exercise performance in patients with more severe lung disease. [39] Thus, cardiopulmonary exercise testing may be necessary to evaluate the degree of impairment. Exercise testing has become attractive because it reflects gas exchange, ventilation, tissue oxygenation, and cardiac output. When the latter is increased, blood flow to the pulmonary vascular bed increases, much like occurs when flow is diverted to the lung tissue remaining after resection. Thus, any patients who otherwise might have been considered inoperable on the basis of FEV_1 values might be considered to be operative candidates because of their performance and high V_{O_2} max during exercise. Conversely, patients with marked reductions in exercise oxygen consumption before surgery appear to be at high risk for postoperative morbidity, regardless of how well they performed on routine and split-function pulmonary testing.

PREOPERATIVE MEASURES TO IMPROVE LUNG FUNCTION

Aside from assessing operability in candidates for lung resection, the major goal of identifying preoperative pulmonary dysfunction is to alter outcome by reducing the morbidity and mortality associated with postoperative pulmonary complications (Chs. 23 and 25) . The assumption is that the patients identified as abnormal may benefit from the therapeutic measures to improve lung function, and thus the likelihood of postoperative complications may be reduced. Several groups have applied such therapy to poor-risk patients and have produced a decrease in the postoperative complications to levels approaching those found in patients with normal function. [40] [41] [42]

Usually, the therapy is carried out for 48 to 72 hours before surgery. However, it is equally important that some of the measures be continued after surgery as well. The treatment regimen is aimed largely at four modalities: (1) smoking cessation, (2) mobilization of secretions, (3) therapy for bronchospasm, and (4) improving motivation and stamina. Although it is generally assumed that smoking cessation is followed by a decrease in volume of airway secretions and airway reactivity as well as improved mucociliary transport, these beneficial effects take 2 to 4 weeks to develop. [43] The shorter-term (48-72 hours) effects may actually be associated with increased secretions and hyperactive airways. The major benefit from discontinuing smoking in the immediate preoperative period appears to be the decrease in carboxyhemoglobin content and thus better oxygen availability to the tissues. There is additional evidence that the sensitive upper airway reflexes of smokers are reduced by abstinence. [44] It is therefore reasonable to expect that adverse events so common during induction of anesthesia (cough, breath holding, and laryngospasm) would be reduced. [45]

The removal of secretions is an important component of preoperative preparation because their persistence increases the likelihood of infection and increased airway reactivity. Antibiotic therapy for patients with chronic bronchitis may be helpful, but the secretions are best loosened by adequate hydration, both systematically and by heating of aerosol therapy. The use of mucolytic agents and oral expectorants is at best of questionable benefit and is fraught with the hazards of increasing airway irritability and other side effects, such as gastrointestinal irritation. Mucociliary clearance is impaired in such patients, and cough is infestive because of an inability to generate sufficient air flow rates. Therefore, mechanical measures must be utilized to dislodge secretions and move them into the more proximal airways, where cough can more readily remove secretions. Such therapy is limited to percussion and vibration as well as postural drainage.

Reactive airways and reversible air flow obstruction are common features, especially in patients presenting for thoracic surgery. Thus, the use of medications to establish and sustain normal airway function is important in the perioperative period. beta $_2$ -Sympathomimetic aerosols are the mainstays for treatment and prevention of bronchospasm. The use of the quaternary anticholinergic compound ipra-tropium may also be helpful, particularly in patients in whom tachycardia is a concern with beta$_2$ -sympathetic drugs. [46] Theophylline is also often added to this regimen; however, there is considerable concern regarding toxicity and limited efficacy of intravenous theophylline when administered acutely.

The final preparative measure in thoracotomy patients concerns improving motivation and stamina. Education and practice with incentive spirometry devices are important in the maintenance of postoperative lung volume and coughing efficacy. Such preparation and continued postoperative use appears to be far more effective than intermittent positive-pressure breathing therapy. [47]

Utilization of the preparatory respiratory care maneuvers ultimately benefits the patient and contributes to reducing the incidence and the severity of postoperative respiratory complications. The question remains, however, of whether such an improved outcome actually reflects pulmonary function on spirometric testing. It may be unreasonable to expect a dramatic reversal in air flow obstruction and improved blood gases with such a brief (48-72 hour) regimen. Gracey et al [48] attempted to improve pulmonary function before surgery in patients with chronic obstructive pulmonary disease with such a standardized regimen. Although this therapy produced statistically significant changes in several tests of pulmonary function, the functional significance of the changes was doubtful. Nevertheless, the incidence of

complications in these improved patients was dramatically reduced, as in other studies. There are no definitive data that can identify whether this reduced complication rate results specifically from the preparation regimen, the use of specific agents or techniques, or just the added attention paid to patients in whom airway obstruction or other pulmonary dysfunction is identified.

It appears reasonably well established that patients whose clinical history and physical examination suggest the presence of pulmonary disease are at increased risk if spirometric results are abnormal. It is unclear exactly what should be done for such patients with abnormal test results short of an abbreviated regimen of preoperative preparation and concern intraoperatively for controlling airway reactivity. Equally uncertain is which test best predicts risk and what further testing is appropriate for patients with abnormal spirometric results. Nevertheless, in those about to undergo pulmonary resection, exercise testing seems to provide the best predictive insight.

References

1. Hess D: History of pulmonary function testing. Respir Care 34:427, 1989.

2. American Thoracic Society: Standardization of spirometry: Update. Am J Respir Crit Care Med 152:1107, 1995.

3. Stein M, Koota GM, Simon M et al: Pulmonary evaluation of surgical patients. JAMA 181:765, 1962.

4. Suratt PM, Hooe DM, Owens DA et al: Effect of maximal versus submaximal expiratory effort on spirometric values. Respiration 42:233, 1981.

5. Krowka MJ, Enright PL, Rodarte JR et al: Effect of effort on measurement of forced expiratory volume in one second. Am Rev Resp Dis 136:829, 1987.

6. Gelb AF, Williams AJ, Zamel N: Spirometry: FEV_1 vs FEF 25-75 percent. Chest 84:473, 1983.

7. Dillard TA, Oleh HW, McCumber TR: Maximum voluntary ventilation: Spirometric determinants in chronic obstructive pulmonary disease patients and normal subjects. Am Rev Respir Dis 147:870, 1993.

8. Black LF, Hyatt RE: Maximal respiratory pressures: Normal values and relationship to age and sex. Am Rev Respir Dis 103:641, 1971.

9. Braun NMT, Arora NS, Rochester DF: Respiratory muscle and pulmonary function in polymyositis and other proximal myopathies. Thorax 38:616, 1983.

10. Dubois AB, Botelho SY, Comroe JH: A new method for measuring airway resistance in man using a body plethysmograph: Values in normal subject and in patients with respiratory disease. J Clin Invest 35:327, 1956.

11. Suratt PM, Gal TJ, Hooe DM: Effect of head flexion on airway resistance measured in a body plethysmograph. Br J Dis Chest 75:204, 1981.

12. Siistro G, Stanescu D, Dooms G et al: Head position modifies upper airway resistance in men. J Appl Physiol 64:1285, 1988.

13. Rozas CJ, Goldman AL: Daily spirometric variability: Normal subjects and subjects with chronic bronchitis with and without airflow obstruction. Arch Intern Med 142:1287, 1982.

14. Cockroft DW, Berscheid BA: Volume adjustment of maximum mid-expiratory flow: Importance of changes in total lung capacity. Chest 78:585, 1980.

15. Enright PL, Lebowitz MD, Cockroft DW: Physiologic measures: Pulmonary function tests. Asthma outcome. Am J Respir Crit Care Med 149:59, 1994.

16. Gal TJ, Arora NS: Respiratory mechanics in supine subjects during progressive partial curarization. J Appl Physiol 52:57, 1982.

17. Vincken WG, Elleker MG, Cusio MG: Flow-volume loop changes reflecting respiratory muscle weakness in chronic neuromuscular disorders. Am J Med 83:673, 1987.

18. Matsuba K, Shirakusa T, Kuwand K et al: Small airways in patients with chronic airflow limitation. Am Rev Respir Dis 136:1106, 1987.

19. Snider GL: Interpretation of the arterial oxygen and carbon dioxide partial pressures. Chest 63:801, 1973.

20. Ingram RH, Schilder DP: Association of decrease in dynamic compliance with a change in gas distribution. J Appl Physiol 23:911, 1967.

21. Fowler WS: Lung function studies. III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. J Appl Physiol 2:283, 1949.

22. Buist AS, Ross BB: Quantitative analysis of the alveolar plateau in the diagnosis of early obstruction. Am Rev Respir Dis 108:1078, 1973.

23. Hyatt RE, Rodarte JR: "Closing volume": One man's noise--Other men's experiment. Mayo Clin Proc 50:17, 1975.

24. Hoeppner VH, Cooper DM, Samael N et al: Relationship between elastic recoil and closing volume in smokers and nonsmokers. Am Rev Respir Dis 109:81, 1974.

25. LeBlanc P, Ruff F, Milic-Emili J: Effects of age and body position on airway closure in man. J Appl Physiol 28:448, 1970.

26. Mansell A, Bryan C, Levision H: Airway closure in children. J Appl Physiol 33:711, 1972.

27. Morris JF, Koski A, Johnson LC: Spirometric standards for healthy non-smoking adults. Am Rev Respir Dis 102:57, 1971.

28. Clausen JL: Prediction of normal values. In Clausen JE (ed): Pulmonary Function Testing Guidelines and Controversies. Orlando, Grune & Stratton, 1984, pp 49-59.

29. Pennock BE, Rogers RM, McCaffree DR: Changes in measured spirometric indices: What is significant? Chest 80:97, 1981.

30. Hnatiuk OW, Dillard TA, Torrington KG: Adherence to established guidelines for preoperative pulmonary function. Chest 107:1294, 1995.

31. Kroenke K, Lawrence VA, Theroux JF et al: Postoperative complications after thoracic and major abdominal surgery in patients with and without obstructive lung disease. Chest 104:1445, 1993.

32. Pietak S, Weenig CS, Hickey RF et al: Anesthetic effects on ventilation in patients with chronic obstructive disease. Anesthesiology 42:160, 1975.

33. Tantucci C, Coreil C, Chasse M et al: Flow resistance in patients with chronic obstructive pulmonary disease in acute respiratory failure. Am Rev Respir Dis 144:384, 1991.

34. Connors AF, McAferee D, Gray BA: Effect of inspiratory flow rate on gas exchange during mechanical ventilation. Am Rev Respir Dis 124:537, 1981.

35. Tuxen DV, Lane S: The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 136:872, 1987.

36. Olsen GN, Block AJ, Swenson EW et al: Pulmonary function evaluation of the lung resection candidate: A prospective study. Am Rev Respir Dis 111:379, 1975.

37. Smith TP, Kinasawitz GT, Tucker WY et al: Exercise capacity as a predictor of post-thoracotomy morbidity. Am Rev Respir Dis 129:730, 1984.

38. Olsen GN: The evolving role of exercise testing prior to lung resection. Chest 95:218, 1989.

39. Ortega F, Montemayor T, Sanchez A et al: Role of cardiopulmonary exercise testing and the criteria used to determine disability in patients with severe chronic obstructive disease. Am J Respir Crit Care Med 150:747, 1994.

40. Stein M, Cassara EL: Preoperative pulmonary evaluation and therapy for surgery patients. JAMA 211:787, 1970.

41. Milledge JS, Nunn JF: Criteria of fitness for anaesthesia in patients with chronic obstructive lung disease. Br Med J 3:670, 1975.

42. Williams CD, Brenowitz JB: "Prohibitive" lung function and major surgical procedures. Am J Surg 132:703, 1976.

43. Pearce AC, Jones RM: Smoking and anesthesia: Preoperative abstinence and postoperative morbidity. Anesthesiology 61:576, 1984.

44. Erskine RJ, Murphy PJ, Langton JA: Sensitivity of upper airway reflexes in cigarette smokers: Effect of abstinence. Br J Anaesth 73:298, 1994.

45. Dennis A, Curran J, Sheriff J et al: Effects of passive and active smoking on induction of anaesthesia. Br J Anaesth 73:450, 1994.

46. Sackner MA, Friedman M, Silva G et al: The pulmonary and hemodynamic effects of aerosols of isoproterenol and ipratropium in normal subjects and patients with reversible airway obstruction. Am Rev Respir Dis 116:1013, 1977.

47. Dohi S, Gold MI: Comparison of two methods of postoperative respiratory care. Chest 73:592, 1978.

48. Gracey DR, Divertie MB, Didier EP: Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease: A prospective study. Chest 76:123, 1979.

Chapter 25 - Anesthetic Implications of Concurrent Diseases [*]

Michael F. Roizen

/das/book/view/29494766/875/260.html

INTRODUCTION

This chapter discusses conditions requiring special preoperative evaluation and intraoperative management. Patients undergoing surgery move through a continuum of medical care to which a primary care physician, an internist or pediatrician, an anesthesiologist, and a surgeon or radiologist or obstetrician-gynecologist contribute to ensure the best outcome possible. No aspect of medical care requires greater cooperation among physicians than does the performance of a surgical operation and the perioperative care of a patient. The importance of integrating physicians' expertise is even greater within the context of the increasing life span of our population. [1] As the number of the elderly and the very old (those >85 years of age) grows, so does the need of surgical patients for preoperative consultation that helps plan for comorbidity and multiple-drug regimens, knowledge of which is crucial to successful patient management. At a time when

* *See Appendix I, Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration*

medical information is encyclopedic, it is difficult for even the most conscientious anesthesiologist to keep abreast of the medical issues relevant to perioperative patient management. This chapter reviews such issues.

As with "healthy" patients (Ch. 23) , it is the history and physical examination of these patients that most accurately predict not only the associated risks but also the likelihood that a monitoring technique or change in therapy will be beneficial or necessary for survival. This chapter emphasizes those instances in which specific information should be sought in history-taking, physical examination, or laboratory evaluations. Although controlled studies designed to confirm that optimizing a patient's preoperative physical condition would result in lower morbidity have not been performed for most diseases, it is logical to assume that such is the case. Studies showing the benefits of optimizing specific preoperative conditions are highlighted. The fact that such preventive measures would cost less than treating the morbidity that would otherwise occur is an important consideration in a cost-conscious environment.

Recent data indicate that minimally invasive procedures such as cataract extraction, magnetic resonance imaging, or diagnostic arthroscopy (see Table 23-10) , performed in conjunction with the best current anesthetic practices, pose no greater risk than that of daily living and thus might not be considered an opportunity for special evaluation. Nonetheless, preanesthetic evaluations were found to provide information that led to changes in health-care plans for more than 15 percent of all American Society of Anesthesiologists (ASA) I and II patients (and for >20% of all patients in general) at the University of Florida (Gibby GL, et al, personal communication). Although these changes in care plans were attributable to data found on history and observation (the most common being gastric reflux, diabetes mellitus requiring insulin, asthma, and suspected difficult intubation), no data show that patient outcome was improved by such changes. Nevertheless, logic caused practitioners to alter plans for such patients in ways that would delay operating room schedules and increase costs. Examples would be administering a histamine type-2 antagonist 1 to 2 hours before and an oral antacid immediately before entry to the operating room, obtaining equipment to measure blood glucose levels, obtaining a history of the patient's diabetic course and treatment from the primary care doctor as well as from the patient, and obtaining a fiberoptic laryngoscopic examination or additional skilled attention. Thus, even if preoperative evaluation were not to alter outcome in an important way, its ability to reduce costs by reducing unwarranted laboratory testing and delays in obtaining treatment and equipment perceived to be beneficial (and medicolegally required) would be substantial and would warrant its use.

Examples of determining the costs of such benefits can be found in Chapter 23 or in this chapter in the section on preoperative preparation of the patient with cardiovascular disease. Conditions discussed in this chapter are:

1. Diseases involving the endocrine system and disorders of nutrition
2. Diseases involving the cardiovascular system
3. Disorders of the respiratory and immune system
4. Diseases of the central nervous system (CNS), neuromuscular diseases, and mental disorders
5. Diseases involving the kidney, infectious diseases, and disorders of electrolytes
6. Diseases involving the gastrointestinal (GI) tract or the liver
7. Diseases involving hematopoiesis and various forms of cancer
8. Diseases of aging or that occur more commonly in the aged, as well as chronic and acute medical conditions requiring drug therapy (Chs. 53 - 55 and 61) .

ROLE OF THE PRIMARY CARE PHYSICIAN OR CONSULTANT

The role of the primary care physician or consultant is not to select or suggest anesthetic or surgical methods but rather to optimize the patient's preoperative status regarding those conditions that increase the morbidity and mortality associated with surgery.

Quotations and a table in the Medical Knowledge Self-Assessment Program published in 1992 by the leading organization representing internists, the American College of Physicians, highlight this role for the consultant [2] :

Consultation practice is an important component of virtually every internist's professional activity and in some specialties accounts for up to 50 percent of patient care time. Effective interaction with colleagues in other specialties requires a thorough grounding in the language and science of these other disciplines as well as an awareness of basic guidelines for consultation [Table 25-1] (Table Not Available) .... The consulting internists' role in perioperative care is focused on the elucidation of medical factors that may increase the risks of anesthesia and surgery.... Selecting the anesthetic technique for a given patient, procedure, surgeon, and anesthetist is highly individualized and remains the responsibility of the anesthesiologist rather than the internist.

Optimizing a patient's preoperative condition is a cooperative venture between the anesthesiologist and the internist, pediatrician, surgeon, or family physician. If the primary care physician cannot affirm that the patient is in the very best physical state attainable (for that patient) by that physician and his or her consultants, the anesthesiologist and the physician should do what is necessary to optimize that condition. Failing to consult with the primary care physician preoperatively is as risky as not checking the oxygen in the spare tanks. In fact, statements that describe the preoperative physical

TABLE 25-1 -- Guidelines for Consultation Practice

(Not Available)

From the American college of Physicians [2]

condition of the patient (e.g., "This patient is in optimum shape" and "I believe the mitral stenosis is more severe than the slight degree of mitral insufficiency") are much more useful to the anesthesiologist than are statements that suggest overall clearance ("cleared for surgery") or perioperative procedures ("prevent hypoxia and hypotension").

Primary care physicians can prepare and treat a patient for optimal conditions for daily life. However, they do not have the depth of understanding of the anesthesiologist regarding the physiologic changes brought on by surgery and the manipulations of functioning that must be made to facilitate surgery and optimize perioperative outcome. One example would be the primary care physician's induction of some degree of prerenal azotemia for the patient with congestive heart failure. The volume depletion associated with prerenal azotemia may make the cardiac patient more comfortable in daily life but would predispose him or her to hypovolemic disaster during surgery. Thus, although it would be desirable for the primary care physician to start the process of preparing the patient for the needs of surgery, this activity would not be compatible with the current state of knowledge or functioning of the vast majority of primary care physicians. Although such education is more available and of better quality than in prior decades, [3] [4] [5] [6] [7] and although Mangano and colleagues, [7] Goldman and associates, [8] Charlson et al, [9] and even cardiologic organizations [10] have provided considerable data regarding the importance of this aspect of care, the training, knowledge, and ability of primary care physicians are still deficient in this aspect of consultation. Without understanding the physiologic changes that occur perioperatively, it is difficult to prescribe the appropriate therapy. It is therefore part of the anesthesiologist's job to educate the patient's consultants as to what information is needed from the preoperative consultation.

DISEASES INVOLVING THE ENDOCRINE SYSTEM AND DISORDERS OF NUTRITION

Pancreatic Disorders

Preoperative Diabetes Mellitus

This section makes nine major points regarding diabetes:

1. Diabetes itself may not be as important to perioperative outcome as its end-organ effects (see point 3 for exceptions). Although the presence of diabetes has long beenassumed to increase perioperative risk, results from epidemiologic studies may not support this assumption. These studies segregated the effects of diabetes per se on the organ system, from the effects of the complications of diabetes (e.g., cardiac, nervous system, renal, and vascular disease) and the effects of old age and the accelerated aging that diabetes causes. Surgical mortality rates for the diabetic population are on average five times higher than those for the nondiabetic population. [11] [12] However, in epidemiologic studies in which diabetes itself was segregated from the complications of diabetes (including cardiac and vascular disease) and old age, this finding was questioned. [12] [13] Similarly, if diabetics undergoing major vascular surgery are compared with nondiabetics who are matched for type of surgery, age, sex, weight, and complicating diseases, there is no difference in the mortality rate or the number of postoperative complications. [13]
2. Because diabetes represents at least two disease processes, its perioperative management may differ.
3. Chronic "tight" control of type I diabetes probably prevents, retards, or even ameliorates, to some degree, some of the chronic complications of diabetes. [14] However, current debate centers on the benefit associated with tight control and on the benefit-to-risk ratio. The evidence indicates that tight control of blood glucose might benefit the pregnant diabetic (and her future offspring) [15] (Ch. 57) , the diabetic undergoing cardiopulmonary bypass (Chs. 49 and 50) , and those undergoing (global) CNS ischemia [16] [17] (Chs. 19 and 52) . Little evidence indicates that tight control is of substantial benefit to any other group; the benefit-to-risk ratio of tight control has not been examined for any other group of patients. [3]
4. Different regimens permit almost any degree of perioperative control of blood glucose levels, but the tighter the control desired, the more frequently blood glucose levels must be monitored. Three treatment regimens are outlined later.
5. The major risk factors for diabetics undergoing surgery are the end-organ diseases associated with diabetes: cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities (limitations of neck extension, [18] poor wound healing), inadequate granulocyte production, and neuropathies. [11] [13] [19] Thus, a major focus of the anesthesiologist should be the preoperative evaluation and treatment of these diseases to ensure optimal preoperative conditions.
6. Regional anesthesia may be indicated to facilitate some procedures. The following considerations should be kept in mind regarding the use of regional anesthesia for diabetic patients. Local anesthetic requirements are lower and the risk of nerve injury is higher in diabetic patients. [20] [21] Also, combining local anesthetics with epinephrine may pose even greater risk of ischemic and/or edematous nerve injury in the diabetic.
7. Nosocomial infection rates can probably be decreased with outpatient surgery; complications may be decreased in those diabetics most at risk by either tight control of blood glucose or intense postoperative care, or both.
8. The United States has been experiencing a great and progressive growth in the number of people who are known to be diabetic. That growth parallels a gain in weight in the adult population that causes type II diabetes.
9. Both forms of diabetes cause accelerated aging. Thus, the risks involved in caring for someone with diabetes are similar to those for someone much older, i.e., someone who has a much higher physiologic age (or "RealAge" [22]).

More than 90 percent of the 16 million diabetics in the United States have non-insulin-dependent (type II) diabetes. Those with this type of disease tend to be elderly, overweight, and relatively resistant to ketoacidosis and susceptible to the development of a hyperglycemic-hyperosmolar nonketotic state. Plasma insulin levels are normal or elevated but are relatively low for the level of blood glucose. This hyperinsulinemia by itself is postulated to cause accelerated cardiovascular disease. [23] [24]

Insulin originates in the pancreas. Pancreatic islets are composed of at least three cells: alpha cells that secrete glucagon, beta cells that secrete insulin, and delta cells that contain secretory granules. Insulin is first synthesized as proinsulin, converted to insulin by proteolytic cleavage, and then packaged into granules within the beta cells. A large quantity of insulin, normally about 200 units, is stored in the pancreas; continued synthesis is stimulated by glucose. There is a basal, steady-state release of insulin from the beta granules and additional release controlled by stimuli external to the beta cell. Basal insulin secretion continues in the fasted state and is crucial to the inhibition of catabolism and ketoacidosis. Glucose and fructose are the primary regulators of insulin release. Other stimulators of insulin release include amino acids, glucagon, GI hormones (gastrin, secretin, cholecystokinin-pancreozymin, and enteroglucagon), and acetylcholine. Epinephrine and norepinephrine inhibit insulin release by stimulating alpha-adrenergic receptors and stimulate insulin release at beta-adrenergic receptors.

Diabetes mellitus is a heterogeneous group of disorders that have the common feature of a relative or absolute lack of insulin. The disease is characterized by a multitude of hormone-induced metabolic abnormalities, by a diffuse microvascular lesion, and by long-term end-organ complications. Diabetes can be divided into two very different diseases that share these end-organ abnormalities. Type I diabetes is associated with autoimmune diseases and has a concordance rate of 40 to 50 percent (i.e., if one of a pair of monozygotic twins had diabetes, the likelihood that the other twin would have diabetes is 40 to 50%). In type I, the patient is insulin deficient and is susceptible to ketoacidosis if insulin is withheld. For type II diabetes, the concordance rate is 100 percent (i.e., the genetic material is both necessary and sufficient for the development of type II diabetes). These patients are not susceptible to the development of ketoacidosis in the absence of insulin, and they have peripheral insulin resistance. Gestational diabetes develops in more than 2 percent of all pregnancies.

Type I and type II diabetes differ in other ways as well. Contrary to a long-standing belief, patient age does not allow a firm distinction between type I and type II diabetes; an older person can develop type I diabetes. A diabetesproducing variant of coxsackie B4 virus has been isolated from the pancreas of a patient who died of diabetic ketoacidosis (type I diabetes). This virus was also recovered from mice bred to be diabetes-prone after inoculation of the virus had produced hyperglycemia and pancreatic beta cell necrosis coincident with rising antibody titers. [25] Thus, the intrinsic genetic "vulnerability" in insulin-dependent type I diabetes mellitus may consist of diminished capacity of beta cells to survive exposure to potentially damaging extrinsic agents.

A recent series uncovered a genetic focus for some forms of diabetes, and another linked autoantibodies (some related to early-life exposure to cow's milk) to the glucose transporter in the pancreas as a major initiator of insulin deficiency in type I diabetes. Experimental treatment with cyclosporine to prevent diabetes after early discovery is based on suppressing the autoimmunity. Type I diabetes is associated with a 15 percent prevalence of other autoimmune diseases, including Graves disease, Hashimoto thyroiditis, Addison disease, and myasthenia gravis.

Currently, therapy for type II diabetes usually begins with exercise and dietary management. A 5- to 10-kg weight loss over 8 weeks, associated with a 20 percent reduction in calories and an increase in daily physical activity to 30 minutes, is often associated with normalization of fasting blood glucose. [26] However, this is a difficult task for many patients, who then progress to the use of oral hypoglycemic medications that act by stimulating release of insulin by pancreatic beta cells and by improving the tissue responsiveness to insulin by reversing the postbinding abnormality. The common orally administered drugs are tolazamide (Tolinase),

tolbutamine (Orinase), and the newer sulfonylureas glyburide (Micronase) and glipizide (Glucotrol). These latter drugs have a longer blood glucose-lowering effect, which persists for 24 hours or more, and fewer drug-drug interactions. Oral hypoglycemic drugs may produce hypoglycemia for as long as 50 hours after intake (chlorpropamide [Diabinese] has the longest half-life). Other drugs include metformin, which decreases hepatic glucose output and may increase peripheral responsiveness to glucose; acarbose, which decreases glucose absorption; and troglitazone, which increases peripheral responsiveness to insulin. [27] Progressively, physicians advocating tight control of blood sugar levels give insulin to "maturity onset" insulin-dependent diabetic patients twice a day or even more frequently. [28] [29]

Insulin-dependent diabetics tend to be young, nonobese, and susceptible to the development of ketoacidosis. Plasma insulin levels are low or nonmeasurable, and therapy requires insulin replacement. Patients with insulin-dependent diabetes experience an increase in their insulin requirements in the postmidnight hours; this may result in early-morning hyperglycemia (dawn phenomenon). This accelerated glucose production and impaired glucose utilization are the result of nocturnal surges in growth hormone secretion. [30] Diabetics taking insulin and nondiabetics have steady-state levels of insulin in their blood. (Unfortunately, traditional values for insulin pharmacokinetics derive from studies designed as though the diabetic received only one shot of insulin in a lifetime.) Absorption of insulin is highly variable and is dependent on the type and species of insulin, the site of administration, and subcutaneous blood flow. Nevertheless, the steady state is dependent on periodic administration of the preparations received by the patient. Thus, it seems logical to continue perioperatively the combinations of preparations the patient has been receiving chronically, after examining the patient's blood-glucose monitoring logbook for the degree of control. (In the author's clinical experience, erratic control can foreshadow perioperative hypoglycemia.)

Acute complications for the diabetic patient include hypoglycemia and diabetic ketoacidosis, as well as hyperglycemic, hyperosmolar, nonketotic coma. Diabetic patients are also subject to a series of long-term complications, including cataracts, neuropathies, retinopathy, and angiopathy involving peripheral and myocardial vessels, that lead to considerable morbidity and premature mortality. Many of these complications will bring the diabetic patient to surgery. The evidence that hyperglycemia itself accelerates these complications or that tight control of blood sugar levels decreases the rapidity of the progression of microangiopathic disease is becoming more definitive. [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38]

Glucose itself may be toxic: High levels can promote

nonenzymatic glycosylation reactions, leading to the formation of abnormal proteins that may decrease elastance and wound-healing tensile strength. The decrease in elastance is responsible for the stiff joint syndrome and for fixation of the atlanto-occipital joint that makes intubation difficult. [18] [33] [34] Furthermore, elevations in glucose may increase production of macroglobulins by the liver, thereby increasing blood viscosity, and may promote intracellular swelling by favoring the production of nondiffusible, large molecules (e.g., sorbitol). Newer drug therapies (e.g., aldose-reductase inhibitors) aim to decrease intracellular swelling by inhibiting formation of such large molecules.

A controversy now exists as to how tightly blood sugar levels should be controlled chronically. The controversy centers on whether attempts to attain normal blood sugar levels in diabetic patients are of greater benefit than risk. [35] Insulin itself may have toxicity for small blood vessels, and retinopathy initially worsens with tight control. However, accumulating data, much from the Diabetes Control and Complications Trials, clearly indicate that tight control of blood glucose levels reduces the risk of chronic complications in type I diabetics [14] (Table 25-2) (Table Not Available) . Similar studies relating to the long-term outcome for type II diabetics will be released by the United Kingdom group in the next two years.

Perioperative management of the diabetic patient may affect surgical outcome. Physicians advocating tight control of blood glucose levels point to the evidence of increased wound-healing tensile strength and decreased wound infections in animal models of diabetes (type I) under tight control. [36]

It has long been known that neuropathy, atherosclerosis, and small vessel disease may contribute to wound failure. Experimental studies suggest that hyperglycemia itself may cause deficient wound healing. Several investigators have shown that diabetic animals have delayed healing with poor collagen formation and poor tensile strength of deep surgical wounds. [38] These abnormalities can be corrected by the administration of insulin. Goodson and Hunt [36] reported that obesity, insulin resistance, hyperglycemia, and depressed leukocyte function interfere with collagen synthesis and lead to impaired wound healing. These investigators demonstrated slowing of granulocyte influx and retardation of early capillary ingrowth. Synthesis of protocollagen and collagen was decreased in the wounds of diabetic animals. In insulin-deficient animals, administration of insulin is crucial for early development of granulation tissue and for subsequent fibroblast growth and collagen synthesis. [38] Insulin is necessary in the early stages of the inflammatory response but seems to have no effect on collagen formation after the first 10 days.

In studies of corneal wounds, identical healing rates were observed in diabetic and nondiabetic animals and in human subjects. Healing epithelial wounds have minimal leukocyte infiltration; unlike deep wounds, they are not dependent on collagen synthesis for the integrity of the tissue. Thus, simple epithelial repair is not inhibited in the diabetic patient, whereas the repair of deeper wounds is impaired with respect to collagen formation and defense against bacterial growth.

Infections account for two-thirds of postoperative complications and about 20 percent of perioperative deaths in diabetic patients. Experimental data suggest many factors that can make the diabetic patient vulnerable to infection. Many alterations in leukocyte function have been demonstrated in hyperglycemic diabetics, including decreased chemotaxis and impaired phagocytic activity of granulocytes, as well as reduced intracellular killing of pneumococci and staphylococci. [39] [40] When diabetic patients are treated aggressively and blood glucose levels are kept below 250 mg/dL, the phagocytic function of granulocytes is improved and intracellular killing of bacteria is restored to near-normal levels. [41]

Diabetic patients have been thought to experience more infections in clean wounds than nondiabetics. In a review of 23,649 surgical patients, the rate of wound infection in clean incisions was 10.7 percent for diabetics versus 1.8 percent for nondiabetics. [42] However, when age is accounted for, the incidence of wound infection for diabetic surgical patients does not differ significantly from that for nondiabetic patients. In addition, hyperglycemia may worsen neurologic outcome after intraoperative cerebral ischemia.

Blood glucose levels may affect neurologic recovery after a global ischemic event. In a study of 430 consecutive patients resuscitated after out-of-hospital cardiac arrest, mean blood glucose levels were higher in patients who never awakened (341 ± 13 mg/dL) than in those who did awaken (262 ± 7 mg/dL). [43] Among patients who awakened, those

TABLE 25-2 -- Tight Control of Blood Glucose Levels Reduces Chronic Complications in Type I Diabetic Patients

(Not Available)

Modified from Reichard et al [14]

with persistent neurologic deficits had higher mean glucose levels (286 ± 15 mg/dL) than patients without deficits (251 ± 7 mg/dL). These results are consistent with the finding that hyperglycemia during a stroke is associated with poorer short- and long-term neurologic outcomes. Although several questions remain, the likelihood that blood glucose is a determinant of brain damage following global ischemia is supported by the vast majority of animal studies after *global* CNS ischemia, [16] and by most but not all studies after *focal* CNS ischemia. [17] The preponderance of data after CNS ischemia indicates that levels of glucose higher than 150 or 250 mg/dL have an adverse effect on CNS recovery. Until better data are available, many will argue that the diabetic patient about to undergo surgery in which hypotension or reduced cerebral flow may occur should have a blood glucose level below 200 mg/dL during a period of cerebral ischemia. Some special situations, such as surgery requiring cardiopulmonary bypass, surgery for pregnant patients, and emergency surgery on patients with diabetic ketoacidosis or hyperosmolar nonketotic coma, may also influence how tightly one should manage the patient's glucose level.

Diabetics undergoing coronary artery bypass graft (CABG) surgery in 1980 had a perioperative mortality rate of 5 percent, compared with 1.5 percent for nondiabetics. [44] In this study, and in most other studies of diabetic patients undergoing CABG surgery, important additional risk factors or confounding variables were not considered, including the incidence and extent of hypertension, ventricular dysfunction, congestive heart failure, or severity of coronary artery disease.

In this study of 340 diabetics and 2,522 nondiabetics undergoing CABG surgery, only a moderate increase in the operative mortality for diabetics (1.8% versus 0.6%) was demonstrated. [44] In the post-bypass phase, patients with diabetes were found to require inotropic therapy and intra-aortic balloon pump support five times more frequently than nondiabetics. There are several possible reasons. Diabetics with angina have more extensive coronary artery disease than do nondiabetic patients. They are also more likely to have hypertension, cardiomegaly, diffuse hypokinesis, and prior myocardial infarction. Insulin-dependent diabetics with coronary artery disease, impaired stress responses, and autonomic nerve dysfunction appear to have stiffer ventricles with greater elevation of left ventricular end-diastolic pressure than do matched nondiabetic controls. [45] [46] [47] During cardiopulmonary bypass, hypothermia and stress reactions decrease the response to insulin and result in marked hyperglycemia (even when the perfusate and intravenous solutions do not contain glucose). Administration of washed cells has been advocated for small individuals, as acid citrate dextrose or adenine-supplemented blood can result in significant hyperglycemia. These changes are exaggerated in the diabetic patient, and insulin administration may have little effect until rewarming is achieved. In a number of recently reported cases, inotropic agents were ineffective in maintaining cardiac contractility, although filling pressures, sinus rhythm, serum electrolytes, and arterial blood gases were adequate. Blood sugar levels were elevated in each case. After intravenous infusion of insulin, effective myocardial contractions returned, allowing easy and rapid bypass weaning. The effect of glucose levels during cardiopulmonary bypass on neurologic outcome is both unclear and controversial. [48] [49] A cautious prognosis should be given to the diabetic coronary bypass patient with poor ventricular function, as surgical mortality may be 10 to 15 percent. [44]

Many diabetics requiring emergency surgery for trauma or infection have significant metabolic decompensation, including ketoacidosis. Often, little time is available for stabilization of the patient, but even a few hours may be sufficient for correction of fluid and electrolyte disturbances that are potentially life-threatening. It is futile to delay surgery in an attempt to eliminate ketoacidosis completely if the underlying surgical condition will lead to further metabolic deterioration. The likelihood of intraoperative cardiac arrhythmias and hypotension resulting from ketoacidosis will be reduced if volume depletion and hypokalemia are at least partially treated.

Insulin therapy is initiated with a 10-unit intravenous bolus of regular insulin, followed by continuous insulin infusion. The rate of infusion is determined most easily if one divides the last serum glucose value by 150 (or 100 if the patient is receiving steroids, has an infection, or is considerably overweight). The actual amount of insulin administered is less important than regular monitoring of glucose, potassium, and pH level. Because the number of insulin-binding sites is limited, the maximum rate of glucose decline is fairly constant, averaging 75 to 100 mg/dL/h regardless of the dose of insulin. [50] During the first 1 to 2 hours of fluid resuscitation, the glucose level may fall more precipitously. When serum glucose reaches 250 mg/dL, the intravenous fluid should include 5 percent dextrose.

The volume of fluid required for therapy varies with overall deficits, ranging from 3 to 5 L to as high as 10 L. Despite losses of water in excess of losses of solute, sodium levels are generally normal or reduced. Factitious hyponatremia caused by hyperglycemia or hypertriglyceridemia may result in this seeming contradiction. The plasma sodium concentration decreases by about 1.6 mEq/L for every 100 mg/dL increase in plasma glucose above normal. Initially, normal saline is infused at the rate of 250 to 1,000 mL/h, depending on the degree of volume depletion and on cardiac status. Some measure of left ventricular volume should be monitored in diabetics who have a history of myocardial dysfunction. About one-third of the estimated fluid deficit is corrected during the first 6 to 8 hours, and the remaining two-thirds, over the next 24 hours.

The degree of acidosis present is determined by measurement of arterial blood gases and an increased anion gap:

Acidosis with an increased anion gap (
16 mEq/L) in the acutely ill diabetic may be caused by ketones in ketoacidosis, lactic acid in lactic acidosis, increased organic acids from renal insufficiency, or all three problems. In ketoacidosis, plasma levels of acetoacetate, beta-hydroxybutyrate, and acetone are increased. Plasma and urinary ketones are measured semiquantitatively with Ketostix and Acetest tablets. The role of bicarbonate therapy in diabetic ketoacidosis is controversial. Myocardial function and respiration are known to be depressed at a blood pH level below 7.0 to 7.10, yet rapid correction of acidosis with bicarbonate therapy may result in alterations in CNS function and structure. This may be caused by (1) paradoxical development of cerebrospinal

fluid and CNS acidosis resulting from rapid conversion of bicarbonate to carbon dioxide and diffusion of the acid across the blood-brain barrier, (2) altered CNS oxygenation with decreased cerebral blood flow, and (3) the development of unfavorable osmotic gradients. After treatment with fluids and insulin, beta-hydroxybutyrate levels decrease rapidly, whereas acetoacetate levels may remain stable or may even increase before declining. Plasma acetone levels remain elevated for 24 to 42 hours, long after blood glucose, beta-hydroxybutyrate, and acetoacetate levels have returned to normal; the result is continuing ketonuria. [50] Persistent ketosis, with a serum bicarbonate level of less than 20 mEq/L in the presence of a normal glucose level, represents a continued need for intracellular glucose and insulin for reversal of lipolysis.

The most important electrolyte disturbance in diabetic ketoacidosis is depletion of total body potassium. The deficits range from 3 to 10 mEq/kg body weight. Rapid declines in serum potassium level occur, reaching a nadir within 2 to 4 hours after the start of intravenous insulin administration. Aggressive replacement therapy is required. The potassium administered moves into the intracellular space with insulin as the acidosis is corrected. Potassium is also excreted in the urine with the increased delivery of sodium to the distal renal tubules that accompanies volume expansion. Phosphorus deficiency in ketoacidosis caused by tissue catabolism, impaired cellular uptake, and increased urinary losses may result in significant muscular weakness and organ dysfunction. The average phosphorus deficit is approximately 1 mmol/kg body weight. Replacement is needed if the plasma concentration falls below 1 mg/dL. [50]

Glucotoxicity

This idea has been alluded to previously, but the *chronic* tight control of blood glucose has been motivated by a theoretical concern about five potential glucotoxicities, plus the results from one major randomized outcome study on type I patients. (The Diabetes Control and Complications Trial has reported its 12-year follow-up data for type I patients and will soon have a report on type II patients.)

Glucose itself may be toxic: High levels can promote nonenzymatic glycosylation reactions that lead to the formation of abnormal proteins. These proteins may decrease elastance--which is responsible for the stiff joint syndrome (and the fixation of the atlanto-occipital joint that makes intubation difficult)--and wound-healing tensile strength. Furthermore, elevations in glucose may increase production of macroglobulins by the liver (which would increase blood viscosity) and promote intracellular swelling by favoring production of nondiffusible, large molecules (such as sorbitol). Newer drug therapies (e.g., aldose-reductase inhibitors) aim to decrease intracellular swelling by inhibiting formation of such large molecules.

Glycemia also disrupts autoregulation. Glucose-induced vasodilation prevents target organs from protecting against increases in systemic blood pressure. A glycosylated hemoglobin level of 8.1 percent is the threshold at which the risk of microalbuminuria increases logarithmically. A person with type I diabetes who has microalbuminuria of more than 29 mg/d has an 80 percent chance of experiencing renal insufficiency. The threshold for glycemic toxicity differs for various vascular beds. For example, the threshold for retinopathy is a glycosylated hemoglobin value of 8.5 to 9.0 percent (12.5 mmol/L or 225 mg/dL), and, for cardiovascular disease, an average blood glucose value of 5.4 mmol/L (96 mg/dL). Thus, different degrees of hyperglycemia may be required before different vascular beds are damaged, or certain degrees of glycemia are associated with other risk factors for vascular disease. Another view is that perhaps severe hyperglycemia and microalbuminuria are simply concomitant effects of a common underlying cause. Diabetics in whom microalbuminuria develops are more resistant to insulin, insulin resistance is associated with microalbuminuria in first-degree relatives of type II diabetics, and persons who are normoglycemic but subsequently have clinical diabetes have atherogenic risks before onset of disease.

Tight control may retard all of these glucotoxicities and may have other benefits in retarding the severity of diabetes itself. [51]

Thus, management of intraoperative glucose might be influenced by specific situations, such as type of operation, pregnancy, [52] [53] and expected global CNS insult; bias of the patient's primary care physician; or type of diabetes. Type I diabetic patients definitely need insulin and might be considered candidates for tight control of blood glucose levels. Type II diabetic patients have insulin, and current data indicate they do not benefit from tight perioperative control. [54]

The key to managing blood glucose levels in diabetic patients perioperatively is to set clear goals and then to monitor blood glucose levels frequently enough to adjust therapy to achieve those goals. Three regimens that afford various degrees of perioperative control of blood glucose levels are discussed in the following sections.

Classic"Nontight Control" Regimen

Aim

To prevent hypoglycemia. To prevent ketoacidosis and hyperosmolar states.

Protocol

1. Day before surgery: Patient should be given nothing by mouth after midnight; a 13-ounce glass of clear orange juice should be at the bedside or in the car for emergency use.
2. At 6 AM on day of surgery, institute intravenous fluids using plastic cannulae and a solution containing 5 percent dextrose, infused at the rate of 125 mL/h/70 kg body weight.
3. After institution of intravenous infusion, give one-half the usual morning insulin dose (and usual type of insulin) subcutaneously.
4. Continue 5 percent dextrose solutions through operative period, giving at least 125 mL/h/70 kg body weight.
5. In recovery room, monitor blood glucose concentrations and treat on a sliding scale. Such a regimen has been found to meet its goals. [55]

"Tight Control" Regimen 1

Aim

To keep plasma glucose levels at 79 to 120 mg/dL; this practice may improve wound healing and prevent wound infections, improve neurologic outcome after global or focal CNS ischemic insult, or improve weaning from cardiopulmonary bypass.

Protocol

1. Evening before operation, determine preprandial blood glucose level.
2. Through a plastic cannula, begin intravenous infusion of 5 percent dextrose in water at the rate of 50 mL/h/70 kg body weight.
3. "Piggyback" to the dextrose infusion an infusion of regular insulin (50 units in 250 mL or 0.9% sodium chloride) and an infusion pump (Fig. 25-1) . Before attaching this piggyback line to the dextrose infusion, flush the line with 60 mL of infusion mixture and discard the flushing solution. This approach saturates insulin-binding sites of the tubing. [56]
4. Set the infusion rate, using the following equation: Insulin (U/h) = plasma glucose (mg/dL)/150. (Note: This denominator should be 100 if patient is taking corticosteroids, e.g., 100 mg of prednisolone a day or its equivalent, not to include inhaled steroids.)
5. Repeat measurements of blood glucose levels every 4 hours as needed, and adjust insulin appropriately to obtain blood glucose levels of 100 to 200 mg/dL.
6. The day of surgery, intraoperative fluids and electrolytes are managed by continuing to administer non-dextrose-containing solutions, as described in steps 3 and 4.
7. Determine plasma glucose level at the start of operation and every 1 to 2 hours for the rest of the 24-hour period. Adjust insulin dosage appropriately.

Figure 25-1 Arrangement of intravenous lines for infusion of regular insulin in a regimen tightly controlling blood glucose levels in diabetic patients undergoing surgery.

Although I have not found the need to treat hypoglycemia (i.e., blood glucose levels of <50 mg/dL), I have been prepared to do so with 15 mL of 50 percent dextrose in water. Under such circumstances, the insulin infusion would be terminated. Such a regimen has been found to accomplish its goals, with the exception of such tight goals for blood glucose, even in very "brittle" diabetics (i.e., those extremely resistant to treatment) given high doses of steroids. [57]

"Tight Control" Regimen 2

Aim

Same as for "Tight Control" Regimen 1.

Pancreatic Disorders

Preoperative Diabetes Mellitus

"Tight Control" Regimen 2

Protocol

1. Obtain a "feedback mechanical pancreas" and set the controls for the desired plasma glucose regimen.
2. Institute two appropriate intravenous lines. This last regimen may well supersede all others if the cost of a mechanical pancreas can be reduced and if control of hyperglycemia is shown to make a meaningful difference perioperatively.

Despite the fact that hyperglycemic type I diabetic patients have a higher incidence of wound infections, a lower wound-healing tensile strength, and a higher incidence of renal transplant rejections than normal patients, [39] [42] it does not necessarily follow that short-term tight control of blood glucose levels perioperatively would reduce morbidity and mortality. For example, in one study, the incidence of perioperative mortality was 11 times higher for diabetic patients than for asymptomatic healthy patients. [58] However, in several other studies, [11] [12] [13] [59] no increase in wound or systemic infections or in any measure of perioperative morbidity or mortality could be attributable to diabetes itself. Also, when corrections were made for calendar age and endorgan disease (cardiovascular) in those studies, the increases in morbidity for diabetic patients seemed to disappear. [11] [12] [13] [59]

Diabetes and Accelerated Physiologic Aging

Adverse perioperative outcomes have repeatedly and substantially correlated with age of the patient, [7] [9] [12] [22] [58] [60] [61] and diabetes does cause physiologic aging. When the results of the Diabetes Control and Complications Trials are translated into age-induced physiologic changes, the type I diabetic who has poor control of blood sugar ages approximately 1.75 years physiologically for every chronologic year of the disease and 1.25 years if blood sugar has been controlled tightly. [22] The type II diabetic ages about 1.5 years for every chronologic year of the disease and about 1.20 years with tight control of blood sugar. [22] Thus, when providing

care for a diabetic patient, one must consider the associated risks to be those of a person who is much older physiologically. That is, the diabetic's physiologic age ("RealAge") is considerably higher than his or her calendar age just by virtue of having the disease. [1]

The increased prevalence of obesity and lack of physical exercise seem to be major contributors to the increased prevalence of type II diabetes. As with type I diabetes, tight control of blood sugar, increased physical activity, and reduction in weight appear to reduce the accelerated aging of type II diabetes and even to delay substantially the appearance of the disease. Although such a reduction in aging should reduce the perioperative risk for diabetic patients, no controlled trials have confirmed this theory.

Other Conditions Associated With Diabetes

Diabetes is associated with microangiopathy (in retinal and renal vessels), peripheral neuropathies, autonomic dysfunction, and infection. Diabetics are often treated with angiotensin-converting enzyme inhibitors even in the absence of gross hypertension in an effort to prevent the effects of disordered autoregulation, including renal failure. [62]

Before surgery, assessment and optimization of treatment of the potential and potent end-organ effects of diabetes are at least as important as an assessment of the diabetic's current overall metabolic status. Information about a diabetic patient that might merit special attention before surgery includes the therapeutic, dietary, and exercise regimens; adequacy of glucose control; prior surgical and anesthetic responses; and the presence of the end-organ effects of diabetes. In the author's experience, many diabetic patients pay extreme attention to glucose control, expect each physician to ask about it, and are annoyed (and probably rightly so) if the physicians treating them in the perioperative period are not at least as concerned about glucose level as the patient has had to be. Thus, if just to avoid making the patient angry (and, I believe, for more value than that), the anesthesiologist should inquire in some depth about the diabetic's control of blood glucose levels. Basic laboratory examinations might include determination of fasting blood sugar levels, electrolytes, blood urea nitrogen (BUN) or creatinine levels, and an electrocardiogram (ECG). Scheduling the operative procedure early in the day avoids prolonging the catabolic state and minimizes the risk of preoperative hypoglycemia.

Patients with diabetes and hypertension have a 50 percent incidence of autonomic neuropathy; those without hypertension have a 10 percent incidence. If one is to believe the few studies we have, the presence of autonomic neuropathy makes the operative period more hazardous and the postoperative period crucial to survival. Evidence of autonomic neuropathy might be routinely sought prior to surgery. Patients with diabetic autonomic neuropathy are at increased risk of gastroparesis (and consequent aspiration) and of intraoperative and postoperative cardiorespiratory arrest. Data indicate that diabetics who exhibit signs of autonomic neuropathy, such as early satiety, lack of sweating, lack of pulse rate change with inspiration or orthostatic maneuvers, and impotence, have a very high incidence of painless

Figure 25-2 Gastric emptying time (mean±SD) for a solid test meal for three groups of patients: diabetics (line 1); diabetics given metoclopramide (10 mg intravenously) 1.5 hours before the test meal (line 2); and nondiabetics (line 3). *(From Wright et al [886])*

myocardial ischemia [47] [55] [56] [57] [58] [59] [63] [64] and of gastroparesis. Some investigators have successfully used 10 mg of metoclopramide preoperatively to facilitate gastric emptying of solids (Fig. 25-2) . Interference with respiration or sinus automaticity by pneumonia or by anesthetics, pain medications, or sedative drugs appears to be the precipitating cause in most cases of sudden cardiorespiratory arrest. Measuring the degree of sinus arrhythmia or beat-to-beat variability provides a simple, accurate test for significant autonomic neuropathy. The difference between maximum and minimum heart rate on deep inspiration is normally 15 beats/min but was found to be 5 beats/min or less in all patients who sustained cardiorespiratory arrest. [63]

Other characteristics of patients with autonomic neuropathy include postural hypotension with a decrease in blood pressure of more than 30 mm Hg, resting tachycardia, nocturnal diarrhea, and dense peripheral neuropathy. Diabetics with significant autonomic neuropathy may have impaired respiratory responses to

hypoxia and are particularly susceptible to the action of drugs that have depressant effects. Such patients may warrant very close, continuous cardiac and respiratory monitoring for 24 to 72 hours postoperatively, although such logical treatment has not been tested in a rigorous, controlled trial. [65] In the absence of these conditions, the author favors outpatient surgery for the diabetic (Table 25-3) .

Perhaps most important, diabetic patients have an increased incidence of atherosclerosis and all its complications. These patients are particularly susceptible to episodes of painless myocardial ischemia and cardiovascular instability. [66] [67] [68] [69] In fact, over 80 percent of the ischemic episodes that occur in both patients who have myocardial ischemia and in those who are diabetic are "silent." However, a 65-year-old diabetic is as likely to die of a cardiovascular event in the next several years as is a person who has just had a

TABLE 25-3 -- Should a Diabetic Be an Outpatient or a Morning Admittance Patient?

OUTPATIENT IF	MORNING ADMITTANCE PATIENT IF
Can evaluate history in advance	Cannot evaluate history
End-organ disease does not require invasive monitoring	End-organ disease requires invasive monitoring
Prehydration is available or is unnecessary	Needs careful prehydration
No CNS ischemia or cardio-pulmonary bypass is planned	CNS ischemia is present or cardio-pulmonary bypass is planned
Not pregnant	Pregnant
Patient or vested home "mate" can determine blood glucose level	Patient cannot determine blood glucose level
Has vested home "mate"	No vested individual
Can take temperature or look for "red" wound	Cannot take temperature or look for "red" wound
Plan higher admit rate (no data)	Social care network is unsuitable

heart attack (Table 25-4) (Table Not Available) . [70] These data dramatically illustrate the increased risk of cardiovascular disease in the diabetic who does not have symptoms. As with other endocrinopathies, the cardiovascular system should be a focus for the anesthetist's attention for the diabetic patient.

Insulinoma and Other Causes of Hypoglycemia

Hypoglycemia can be caused by such diverse entities as a pancreatic islet cell adenoma or carcinoma, large hepatoma, large sarcoma, alcohol ingestion, hypopituitarism, adrenal insufficiency, altered physiology after gastric surgery, hereditary fructose intolerance, antidiabetic drug ingestions, galactosemia, or autoimmune hypoglycemia. [71] The last four entities cause postprandial reactive hypoglycemia. Because restriction of oral intake prevents severe hypoglycemia, the practice of giving the patient nothing by mouth and infusing small amounts of a solution containing 5 percent dextrose greatly lessens the possibility of postprandial reactive hypoglycemia. The other sources of hypoglycemia can cause serious problems during the perioperative period. [72]

The symptoms of hypoglycemia fall into two groups: adrenergic excess (tachycardia, palpitations, tremulousness, or diaphoresis) and neuroglycopenia (headache, confusion, mental sluggishness, seizures, or coma). Because all these symptoms may be masked by anesthesia, blood glucose levels should be determined frequently in such patients to ensure that hypoglycemia is not present. Because manipulation of an insulinoma can result in massive insulin release, this tumor should probably be operated on only at centers equipped with a mechanical pancreas; such machines have on-line blood glucose analysis and a glucose infusion setup.

A different point of view was expressed by Muir and colleagues, [73] who managed 38 patients undergoing insulinoma resection. Every 15 minutes, these investigators noted the plasma glucose concentration in these patients, in whom a mechanical pancreas produced no increase in plasma glucose. Although 9 of the 38 patients became significantly hypoglycemic (i.e., plasma glucose concentrations of <50 mg/dL), only 4 of 253 measurements taken before resection showed a decrease in glucose of more than 20 mg/dL in any 15-minute period. Muir et al [73] believe that intermittent sampling of plasma glucose (every 15 minutes) may be satisfactory as long as the plasma glucose concentration is kept at 60 mg/dL or above. In this series, the absence or presence of a hyperglycemic rebound after tumor resection was not of predictive value in determining completeness of insulinoma resection(s). Other causes of hypoglycemia do not involve the release of insulin in such vast quantities (or at all); therefore, less frequent (every 1 to 2 hours) intraoperative blood glucose determinations and continuous dextrose infusion appear to be sufficient.

The perioperative use of the somatostatin analogue octreotide, which suppresses insulin release from such tumors, appears to make the perioperative period a logarithm safer in anecdotal experience. Whether all tumors respond to this agent similarly and thus radically reduce hazard from insulinoma resection remains to be determined. [74]

Disorders of Nutrition

Hyperlipidemias and Hypolipidemias

Hyperlipidemia may result from obesity, estrogen or corticoid therapy, uremia, diabetes, hypothyroidism, acromegaly, alcohol ingestion, liver disease, inborn errors of metabolism, or pregnancy. Hyperlipidemia may cause premature coronary or peripheral vascular disease or pancreatitis. [75] Hypercholesterolemia,

TABLE 25-4 -- Seven-Year Risk of Cardiovascular Events in Type II Diabetics Without Prior Myocardial Infarctions [a]

(Not Available)

Modified from Haffner et al [76]

[a] The 7-year risk of cardiovascular events in type II diabetics who have *not* had a prior myocardial infarction (MI) is the same as for nondiabetics who *have* had a prior MI. Age- and sex-adjusted (median age at start, approximately 58 y).

a form of hyperlipidemia, appears to be associated with premature atherosclerosis. Most cholesterol is carried in serum by low-density lipoprotein (LDL), whereas approximately 30 percent of total serum cholesterol is carried by high-density lipoprotein (HDL). HDL cholesterol is carried in roughly equivalent amounts on two types of HDL: on a less dense HDL_2 subfraction that is negatively associated with coronary artery disease and on a more dense HDL_3 subfraction that is unrelated to coronary artery disease.

In regard to the production of atherosclerosis, LDL is distinguished from HDL by associating L with "lousy" and H with "healthy." That is, the oxidized form of LDL constitutes a risk factor for atherosclerosis, whereas HDL is believed to carry dangerous cholesterol away from the periphery to be metabolized by the liver and is therefore protective. Levels of HDL are 25 percent higher in women than in men; low levels of HDL in women are associated with premature atherosclerosis. Cigarette smoking lowers HDL levels, whereas regular exercise (particularly, strenuous exercise, but even nonstrenuous exercise) and small daily intake of alcohol raise HDL levels. However, alcohol increases HDL_3 , the HDL subfraction thought to be inert with respect to coronary artery disease. Octogenarians have high levels of HDL.

Data showing that coronary events can be reduced by treating individuals with even normal levels of LDL cholesterol with the "statins"--drugs that raise HDL and lower LDL cholesterol levels--have resulted from a decade of rapid progress in preventing reinfarction in high-risk patients. [76] [77] [78] [79] [80] Secondary prevention efforts

were successful when these high-risk patients stopped smoking; reduced blood pressure; controlled stress; increased physical activity; and used aspirin, vitamin E, beta-blocking drugs, angiotensin inhibitors, diet, and other drugs to reduce their levels of LDL and to increase their levels of HDL. [81] [82]

Although controlling diet remains a major treatment modality for all types of hyperlipidemia, [83] the drugs clofibrate (Atromid-S) and gemfibrozil, used to treat hypertriglyceridemia, can cause myopathy, especially in patients with hepatic or renal disease; clofibrate is also associated with an increased incidence of gallstones. Cholestyramine binds bile acids, as well as oral anticoagulants, digitalis drugs, and thyroid hormones. Nicotinic acid causes peripheral vasodilation and probably should not be continued through the morning of surgery. Probucol (Lorelco) decreases the synthesis of apoprotein A1; its use is associated on rare occasion with fetid perspiration and/or prolongation of the QT interval and with sudden death in animals.

The West of Scotland Coronary Prevention Study [77] [78] and its congeners produced convincing evidence that drugs in the "statin" class (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) prevent the morbidity and mortality related to arterial aging and vascular disease, as well as their consequences--coronary arterial disease, stroke, and peripheral vascular insufficiency. Thus, the statins--lovastatin (Mevacor), pravastatin (Pravachol), simvastatin, fluvastatin, and atorvastatin--are mainstays of therapy.

But the report of Downs et al [77] from the Air Force/Texas Coronary Atherosclerosis Prevention Study went farther. It showed a 37 percent reduction in the risk of first acute major coronary events in patients who had not only no risk factors for coronary artery aging but also normal (average) LDL cholesterol levels (Table 25-5) . In this study, lovastatin did not alter mortality rates; however, that had been true for many early short-term trials with the statins. Although much of the effect of the statins has been attributed to their lipid-lowering effects, statins have also been shown to modify endothelial function, inflammatory responses, plaque stability, and thrombogenicity. [84A] While the report of Downs and colleagues broadened the use of statins, they remain the mainstays of therapy for the hyperlipidemias. They are drugs that block HMG-CoA reductase, the rate-limiting enzyme of cholesterol synthesis. Their use is occasionally accompanied by liver dysfunction, CNS dysfunction, and severe depression not related to the high cost of each drug and its congeners.

Hypolipidemic conditions are rare diseases often associated with neuropathies, anemia, and renal failure. Although anesthetic experience with hypolipidemic conditions has been limited, some specific recommendations can be made: continuation of caloric intake and intravenous administration of protein hydrolysates and glucose throughout the perioperative period.

Obesity

Thirty percent of adults in the United States weigh more than 20 percent above what is considered the optimum body

TABLE 25-5 -- Acute Coronary Events in Patients With Average Cholesterol Levels Who Were Given Lovastatin: Results From the Air Force/Texas Coronary Atherosclerosis Prevention Study

	LOVASTATIN GROUP (20 - 40 mg/d)	PLACEBO GROUP	*P* VALUE
Patients (n)	3,304	3,301	NS
Men (%)	85%	85%	NS
Age (mean ± SD, y)			
Men	58±7	58±7	NS
Women	62±5	63±5	NS
First acute major coronary events	116	183	<.001
Unstable angina	60	87	.02
Myocardial infarction	57	95	.002
Revascularization	106	157	.001
Coronary events	163	215	.006

Data from Downs et al [77]

TABLE 25-6 -- Obesity as a Function of Body Mass Index[a]

HEIGHT[c]		AVERAGE WEIGHT (MEN AND WOMEN)[b]						*BMI 20% > IDEAL*
		19- 34 y			*35 Y*			
ft/in	*cm*	*lb*	*AVERAGE kg*	*AVERAGE BMI*	*lb*	*AVERAGE kg*	*AVERAGE BMI*	
5 0	152.4	97-128	51.1	22.0	108-138	55.9	24.1	27.5
5 1	154.9	101-132	53.0	22.0	111-143	57.7	24.8	27.5
5 2	157.5	104-137	54.7	22.0	115-148	59.5	23.9	27.5
5 3	160.0	107-141	56.4	22.0	119-152	61.5	24.0	27.5
5 4	162.6	111-146	58.4	22.0	122-157	63.4	24.0	27.5
5 5	165.1	114-150	60.0	22.0	126-162	65.5	24.0	27.5
5 6	167.6	118-155	62.0	22.1	130-167	67.5	24.0	27.5
5 7	170.2	121-160	63.9	22.0	134-172	69.5	24.0	27.5

58	172.7	125-164	65.7	22.0	138-178	71.5	24.0	27.5
59	175.3	129-169	67.7	22.0	142-183	73.8	24.0	27.5
510	177.8	132-174	69.6	22.0	146-188	75.9	24.0	27.5
511	180.3	136-179	71.6	22.0	151-194	78.4	24.1	27.5
60	182.9	140-184	73.6	22.0	155-199	80.4	24.0	27.5
61	185.4	144-189	75.7	22.0	159-205	82.7	24.0	27.5
62	188.0	148-195	77.9	22.0	164-210	85.0	24.0	27.5
63	190.5	152-200	80.0	22.0	168-216	87.2	24.0	27.5

Data from Roizen [265]

[a] Body mass index (BMI) = weight (in kilograms) ÷ height^2 (in meters)
[c] Without shoes
[b] Without clothes

weight for their height. One measure of obesity is body mass index, for which a value above 31 represents morbid obesity and its risks and a value above 27 for women and 28 for men corresponds to weight 25 percent above ideal (Table 25-6) . The pathophysiologic consequences of obesity involve every major organ system. Many of the metabolic, hormonal, and physiologic changes associated with obesity (e.g., insulin resistance, decreased number of insulin receptors, and subsequent diabetes mellitus) can be induced by overfeeding normal subjects and can be reversed by weight reduction. Obesity itself, its complications, and its treatment have significance for the anesthesiologist. A person who is 30 percent overweight has a 40 percent increased chance of dying from heart disease and a 50 percent increased chance of dying from a stroke. Obesity is also associated with higher resource utilization (more perioperative days in the hospital) and greater perioperative morbidity and mortality. [84B] [85]

Although many conditions associated with obesity (diabetes, cholelithiasis, cirrhosis) contribute to morbidity, the main concerns for the anesthesiologist are derangements of the cardiopulmonary system. [86] [87]

In the obese patient, gas exchange may be impaired by not only altered cardiopulmonary mechanisms but also management of a difficult airway. Obstruction of the airway by the abundant soft tissue in the upper airway frequently produces hypoxemia and hypercarbia, and obesity significantly increases the risk of difficult tracheal intubation. [88] [89] Functional residual capacity decreases because the weight of the torso and abdomen makes diaphragmatic excursions more difficult and more position-dependent, a problem made worse by mechanical ventilation. For many obese patients, this process causes functional residual capacity to be less than closing volume and decreases the time of safe apnea before hypoxia occurs (Amalraj S, personal communication) (Fig. 25-3) . Furthermore, obese patients have increased volume and acidity of gastric juices preoperatively (Fig. 25-4) , perhaps indicating the wisdom of premedicating such patients with cimetidine, ranitidine, Bicitra, or metoclopramide. (The simplest, least expensive scientifically tested regimen appears to be administration of cimetidine the night and morning before surgery [Fig. 25-5] (Figure Not Available) [Amalraj S, personal communication].) Others would conclude that awake intubation is indicated, but preference for this technique must be balanced by the realization that most episodes of gastroesophageal reflux and the greatest potential for pulmonary aspiration occur from and during "bucking" on an endotracheal tube. [90] [91] Obesity is also a significant risk factor for postoperative hypoxemia, [92] a situation partially remedied by placing the patient in the semirecumbent (rather than supine) position for the first 48 to 72 hours of recovery. [93]

Cardiac output must increase approximately 0.1 L/min to perfuse each kilogram of adipose tissue. As a result, obese patients often have hypertension, which can cause cardiomegaly and left ventricular failure. Care should be taken to use a blood pressure cuff of correct size when quantitating the degree of hypertension present.

The obese may have limited cardiac reserve and a poor tolerance for stress induced by hypotension, hypertension, tachycardia, or fluid overload associated with the preoperative period. Massively obese patients with carbon dioxide retention are called pickwickian, alveolar hypoventilation being the hallmark of this condition. Other components of the pickwickian syndrome are somnolence, hypoxemia, failure of the right side of the heart, and secondary polycythemia. Many of these patients have right ventricular failure (see Ch. 49 for monitoring considerations). Thus, preoperative assessment should include not only history-taking and physical examination accentuating drug therapy and cardiopulmonary problems but also an ECG examination (looking

Figure 25-3 Duration of safe apnea before hemoglobin desaturation in obese and normal weight patients (90% oxygen saturation), as reported by various studies. *(Amalraj S, personal communication)* BMI, body mass index.

specifically for left or right ventricular hypertrophy, ischemia, and conduction defects). If obesity is severe, arterial blood gases might also be analyzed to quantitate the degree of hypoventilation and to aid in assessing the most appropriate time to extubate the trachea. More extensive pulmonary function tests and preoperative treatment of any treatable abnormality (e.g., infectious and bronchospastic components of pulmonary disease) may be indicated for the obese patient who smokes or has pulmonary symptoms (e.g., chronic cough, sputum production, wheezing, shortness of breath at rest or on minor exertion).

Other features of obesity are of interest to the anesthesiologist as well. Because of excessive and extensive subcutaneous fat and large size of the extremities, proper positioning

Figure 25-4 Relationship between weight and risk factors for pulmonary aspiration, as reported by four studies. *(Amalraj S, personal communication)*

Figure 25-5 (Figure Not Available) Effect of drugs on the risk of pulmonary aspiration in obese patients, as reported by various studies. *(Amalraj S, personal communication)*

of the patient, placement of monitoring devices, and establishment of intravenous sites are more difficult to accomplish, and blood pressure (and cuff size choice) is less easy to ascertain than for patients of normal weight. Obese persons may metabolize lipophilic drugs to a greater degree (and for longer periods) than their thin counterparts. More fluorine is produced from enflurane given to obese patients than to thin ones. One would assume that responses to drugs stored in fat (e.g., narcotics, barbiturates, volatile anesthetics) would be prolonged in the obese. There is no evidence, however, that the use of the more soluble anesthetics delays recovery time in obese subjects. The dose requirements of pharmacologic agents used for analgesia and airway management are also altered by significant obesity (body mass index >27.5). Obesity increases the volume of distribution of sufentanil and slows its elimination. In one study, the elimination half-life of sufentanil was 208 minutes for eight obese patients (mean weight, 94 kg) versus 135 minutes for eight controls (mean weight, 70 kg). [94] Similarly, muscle relaxants that depend on hepatic blood flow for their elimination (i.e., pancuronium, vecuronium, and rocuronium) appear to have dosage requirements that are directly proportional to body surface area, as well as longer twitch recovery times. The 25 to 75 percent twitch recovery time for vecuronium was 38.4 minutes for obese patients (mean weight, 93 kg) versus 17.6 minutes for nonobese patients (mean weight, 61 kg) (Ch. 12) . [95] Furthermore, there is an increased incidence of wound infection, deep vein thrombosis, and pulmonary embolus; the latter two should probably be guarded against with subcutaneous heparin and early ambulation. [96]

The anesthesiologist should also be aware of conditions caused by remedies to obesity. [97] Drastic dieting can produce acidosis, hypokalemia, and hyperuricemia; protein hydrolysate liquid diets are associated with intractable ventricular arrhythmias. [98] These problems seem to have disappeared as the diets have changed from hydrolyzed collagen fasts to the currently used very-low-calorie diet. [99] Metabolic complications of jejunoileal bypass include hypokalemia, hypocalcemia, hypomagnesemia, anemia, renal stones, gout, and liver abnormalities. An attempt to reverse these abnormal conditions should be made before induction of anesthesia and may consist of infusing solutions containing amino acids. Because of the high morbidity associated with jejunoileal bypass, this procedure has been replaced by gastric plication or bypass surgery. However, long-term data concerning the chronic morbidity of these two procedures are not available.

Drug treatment for obesity also has implications for the anesthesiologist. Amphetamines (and probably mazindol) given *acutely* increase anesthetic requirements; by contrast, amphetamines administered *chronically* decrease anesthetic requirements. (See the section on chronic drug therapy.) Amphetamines may interfere with the action of vasoactive drugs given to treat hypotension or hypertension.

Since many obese patients have tried drug therapies, the anesthesiologist should consider asking questions about use of adjuvants. If such drugs have been used, the anesthesiologist might consider auscultation and echocardiography to search for mitral valve regurgitant lesions, as some dietary aids (notably "phen-fen") have been associated with these conditions. Because other dietary herbs are known to cause

liver dysfunction, determining whether these adjuvants have been used may be important. Fenfluramine (a drug that inhibits the serotonergic system) by itself may decrease both anesthetic requirement and blood pressure.

Anorexia Nervosa, Bulimia, and Starvation

Many endocrine and metabolic abnormalities occur in the patient with anorexia nervosa, a condition characterized by starvation to the point of 40 percent loss of normal weight, hyperactivity, and a psychiatrically distorted body image. Many anorectic patients exhibit impulsive behavior, including suicide attempts, and intravenous drug use is much more common than in the general population. Acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypothermia, diabetes insipidus, and severe endocrine abnormalities mimicking panhypopituitarism need attention before anesthesia and surgery. Similar problems occur in bulimia (bulimorexia), a condition that may affect as many as 50 percent of female college students. [100] As in severe protein deficiency (kwashiorkor), anorexia nervosa and bulimia may be accompanied by ECG alterations, including prolonged QT interval, atrioventricular (AV) block and other arrhythmias, sensitivity to epinephrine, and cardiomyopathy. [100] [101] Total depletion of body potassium makes the addition of potassium to glucose solutions useful; however, in these patients, fluid administration can precipitate pulmonary edema. Esophagitis, pancreatitis, and aspiration pneumonia are more frequent in these patients, as is delayed gastric emptying. Thus, invasive monitoring (radial artery and pulmonary artery catheterization) may be indicated for anorectic, bulimic, and malnurtured patients requiring emergency surgery. Elective surgery probably should be delayed until abnormalities are treated.

Hyperalimentation (Total Parenteral Nutrition)

Hyperalimentation (i.e., total parenteral nutrition [TPN]) consists of concentrating hypertonic glucose calories in the normal daily fluid requirements. The solutions contain protein hydrolysates, soybean emulsions (i.e., Intralipid), or synthetic amino acids. The major benefits of TPN or enteral nutrition have been fewer complications postoperatively and shorter hospital stays for patients scheduled to have no oral feeding for 7 days or who were malnourished preoperatively. [102] [103] Starker and colleagues [104] found that response to TPN, as monitored by serum albumin levels, predicted postoperative outcome. [105] The group having a rise in serum albumin with TPN had diuresis, weight loss, and fewer complications (1 of 15 patients) than the group that gained weight and had a decrease in serum albumin (8 of 16 patients had 15 complications) (Fig. 25-6) (Figure Not Available) . These data are echoed by those in the Veterans Affairs studies, which reported that serum albumin level was one of the most powerful predictors of perioperative outcome. [6] [61]

The major complications of hyperalimentation are sepsis and metabolic abnormalities. The central lines used for TPN require application of an absolutely aseptic technique

Figure 25-6 (Figure Not Available) (A-C) The response to administration of hyperalimentation (repletion), as measured by variations in serum albumin levels, predicted the outcome of surgery. Those patients who responded (B) to nutritional support with increased albumin levels had significantly better outcome than those whose albumin level did not increase (C). See text for a more complete explanation. *(Adapted from Starker et al [889])*

and should not be used routinely as an intravenous route for drug administration. Major metabolic complications of TPN relate to deficiencies and to development of hyperosmolar states. Complications of hypertonic dextrose can develop if the patient has insufficient insulin (diabetes mellitus) to metabolize the sugar or if insulin resistance occurs (e.g., because of uremia, burns, or sepsis). [102]

Gradual decrease in the infusion rate of TPN prevents the hypoglycemia that can occur on abrupt discontinuance. Thus, the infusion rate of TPN should be decreased the night before anesthesia and surgery or continued throughout the operation at its current rate. The main reason for slowing or discontinuing TPN before anesthesia is to avoid intraoperative hyperosmolarity secondary to accidental rapid infusion of the solution or hypoglycemia if the infusion is discontinued because of the high levels of endogenous insulin and lower levels of glucose present in usual crystalloid solutions. [102] Hypophosphatemia is a particularly serious complication that results from the administration of phosphate-free or phosphate-depleted solutions for hyperalimentation. The low serum phosphate level causes shifts of the oxygen dissociation curve to the left. The resulting low 2,3-diphosphoglycerate and adenosine triphosphatase levels mean that cardiac output must increase for oxygen delivery to remain the same. Hypophosphatemia of less than 1.0 mg/dL blood may cause hemolytic anemia, cardiac failure, tachypnea, neurologic symptoms, seizures, and death. In addition, long-term TPN is associated with deficiencies in trace metals such as copper (refractory anemia), zinc (impaired wound healing), and magnesium.

For these reasons, I have adopted the following practices. [102] The infusion of TPN or enteral nutrition is reduced beginning the night before surgery, substituting 5 or 10 percent dextrose solution preoperatively. If serum glucose phosphate and potassium concentrations (measured preoperatively) are abnormal, they are restored to within normal limits. Strict asepsis is maintained. Conversely, I often continue

infusing the TPN solution by using a pump system or enteral nutrition, strictly maintaining its normal rate and asepsis, administering all fluids through a different intravenous site, and performing a rapid-sequence induction of anesthesia (for those who received enteral nutrition).

Also see Chapter 74 .

Adrenocortical Malfunction *

Three major classes of hormones--androgens, glucocorticoids, and mineralocorticoids--are secreted by the adrenal cortex. [105] [106] For each class, an excess or a deficiency of hormone produces a characteristic clinical syndrome. The widespread use of steroids can also make the adrenal cortex unable to respond normally to the demands placed on it by surgical trauma and subsequent healing. [107] [108] [109] [110] [111] [112] [113] [114] [115] Unfortunately, the lack of a wide variety of abdominal imaging procedures, plus the underuse of those procedures that do exist, has meant that many adrenal masses have been discovered only incidentally. [116] [117] [118] Because etomidate is an anesthetic that profoundly limits adrenal reserves, it is often the anesthesiologist who comes into contact with abnormalities of adrenocortical function.

Controlled comparisons of perioperative management for patients who have disorders of adrenal function are lacking. [105] However, a review of the possible pathophysiologic changes in the adrenal cortex and techniques for their management should enable us to improve the perioperative care of patients with adrenal abnormalities.

Physiologic Properties of Adrenocortical Hormones

Androgens

Androstenedione and dehydroepiandrosterone, weak androgens arising from the adrenal cortex, [119] constitute major sources of androgens in women. Excess secretion of androgen causes masculinization, pseudopuberty, or female pseudohemaphroditism. With some tumors, androgen is converted to an estrogenic substance, in which case feminization results. [119] No special anesthetic evaluation is needed for such patients. Some congenital enzyme defects that cause androgen abnormalities also result in glucocorticoid and mineralocorticoid abnormalities that should be evaluated prior to surgery. [119] Most of these patients are treated with exogenous glucocorticoids and mineralocorticoids and consequently require supplementation of these hormones perioperatively (see later).

Glucocorticoids

The principal glucocorticoid, cortisol, is an essential regulator of carbohydrate, protein, lipid, and nucleic acid metabolism. Cortisol is believed to exert its biologic effects through a sequence of steps initiated by hormone binding to stereospecific intracellular cytoplasmic receptors. This bound complex stimulates nuclear transcription of specific messenger ribonucleic acids (mRNAs). These mRNAs are then translated to give rise to proteins that mediate the ultimate effects of hormones.

Most cortisol is bound to corticosterone-binding globulin (CBG, transcortin). It is the relatively small amounts of unbound cortisol that enter cells to induce actions or to be metabolized. Conditions that induce changes in the amount of CBG include liver disease and nephrotic syndrome, both of which result in decreased circulating levels of CBG, and estrogen administration and pregnancy, which result in increased CBG production. Total serum cortisol levels may become elevated or depressed under these conditions that alter the amount of bound cortisol, and yet the unbound, active form of cortisol is present in normal amounts. The most accurate measure of cortisol activity is the level of urinary cortisol--that is, the amount of unbound, active cortisol filtered by the kidney.

The serum half-life of cortisol is 80 to 110 minutes. [111] However, because cortisol acts through intracellular receptors, pharmacokinetic data based on serum levels are not good indicators of cortisol activity. After a single dose of glucocorticoid, serum glucose is elevated for 12 to 24 hours; improvements in pulmonary function in patients with bronchial asthma can still be measured 24 hours after glucocorticoid administration. [111] Treatment schedules for glucocorticoid replacement are based, therefore, not on the measured serum half-life, but on the well-documented prolonged end-organ effect of these steroids. Hospitalized patients requiring chronic glucocorticoid replacement therapy are usually treated twice daily, with a slightly higher dose given in the morning than in the evening, to stimulate the normal diurnal variations in cortisol levels. [105] For patients who require parenteral "steroid coverage" during and after surgery (see later paragraphs), administration of glucocorticoid every 12 hours is appropriate. [109] [110] Relative potencies of glucocorticoids are listed in Table 25-7 . Cortisol is inactivated primarily in the liver and is excreted as 17-hydroxycorticosteroid. Cortisol is also filtered and excreted unchanged into the urine.

The synthetic glucocorticoids vary in their binding specificity in a dose-related manner. When given in supraphysiologic doses (more than 30 mg/d), cortisol and cortisone bind to mineralocorticoid receptor sites and cause salt and water retention and loss of potassium and hydrogen ions. [111] When these steroids are administered in maintenance doses of 30 mg/d or less, patients require a specific mineralocorticoid for electrolyte and volume homeostasis. [111] Many other steroids do not bind to mineralocorticoid receptors, even at high doses, and have no mineralocorticoid effect [111] (see Table 25-7) .

Secretion of glucocorticoids is regulated by pituitary adrenocorticotropic hormone (ACTH). ACTH is synthesized from a precursor molecule (preopiomelanocortin) that breaks down to form an endorphin (beta-lipotropin) and ACTH. Episodic secretion of ACTH has a diurnal rhythm normally greatest during the early morning hours in men, later in women, and is regulated at least in part by light-dark cycles. Its secretion is stimulated by release of corticotropin-releasing factor from the hypothalamus. (An abnormality in the diurnal rhythm of corticoid secretion has been implicated

* Much of this section was modified from Lampe and Roizen. [105]

TABLE 25-7 -- Relative Potency and Equivalent Doses for Commonly Used Glucocorticoids

STEROIDS	RELATIVE GLUCOCORTICOID POTENCY	EQUIVALENT GLUCOCORTICOID DOSE (mg)
Short-acting		
Cortisol (hydrocortisone)	1.0	20.0
Cortisone	0.8	25.0
Prednisone	4.0	5.0
Prednisolone	4.0	5.0
Methylprednisolone	5.0	4.0
Intermediate-acting	5.0	4.0
Triamcinolone		
Long-acting		
Betamethasone	25.0	0.60
Dexamethasone	30.0	0.75

Data from Axelrod [111]

as a cause of so-called "jet lag.") Cortisol and other glucocorticoids exert negative feedback at both pituitary and hypothalamic levels to inhibit secretion of ACTH and corticotropin-releasing factor.

Mineralocorticoids

Aldosterone, the major mineralocorticoid secreted in humans, comes from the zona glomerulosa of the adrenal cortex and causes reabsorption of sodium and secretion of potassium and hydrogen ions, thereby contributing to electrolyte and volume homeostasis. [120] This action is most prominent in the distal renal tubule but

also occurs in salivary and sweat glands. The major regulator of aldosterone secretion is the renin-angiotensin system. Juxtaglomerular cells in the cuff of the renal arterioles are sensitive to decreased renal perfusion pressure or volume and, consequently, secrete renin. [120] Renin splits the precursor angiotensinogen (from the liver) into angiotensin I, which is further converted by a converting enzyme, primarily in lung, to angiotensin II. Angiotensin II binds to specific receptors to increase mineralocorticoid secretion, which is also stimulated by increased potassium concentration and, to a lesser degree, by ACTH. [120]

Adrenocortical Hormone Excess

Glucocorticoid Excess

Glucocorticoid excess (Cushing syndrome) resulting from either endogenous oversecretion or chronic treatment with high-dose glucocorticoids produces a moon-faced plethoric individual having a centripetal distribution of fat (truncal obesity and skinny extremities), thin skin, easy bruising, and striae. Muscle wasting is common, but the heart and diaphragm are usually spared. These patients often have osteopenia due to decreased formation of bone matrix and impaired absorption of calcium. Fluid retention and hypertension (because of increases in renin substrate and vascular reactivity caused by glucocorticoid) are common. Such patients may also have hyperglycemia and even diabetes mellitus resulting from inhibition of peripheral use of glucose, as well as anti-insulin action and concomitant stimulation of gluconeogenesis.

The most common cause of Cushing syndrome is the administration of glucocorticoids for such conditions as arthritis, asthma, and allergies. [105] In these conditions, the adrenal glands atrophy and cannot respond to stressful situations (e.g., the preoperative period) by secreting more steroid. Thus, additional glucocorticoids may be required perioperatively (see the later section, *The Patient Taking Steroids for Other Reasons*). Spontaneous Cushing syndrome may be caused by pituitary production of ACTH (60-70% of all spontaneous cases), which is usually associated with pituitary microadenoma, or nonendocrine ectopic ACTH production (principally by tumors of the lung, pancreas, or thymus). [121] Ten to twenty percent of cases of spontaneous Cushing syndrome are caused by an ACTH-independent process, either an adrenal adenoma or carcinoma.

Special preoperative considerations for patients having Cushing syndrome include regulating diabetes and hypertension and ensuring that intravascular fluid volume and electrolyte concentrations are normal. Ectopic ACTH production may cause marked hypokalemic alkalosis. [105] Treatment with the aldosterone antagonist spironolactone will stop the potassium loss and help mobilize excess fluid. Because of the high incidence of severe osteopenia and the risk of fractures, meticulous attention must be paid to positioning of the patient. [105] In addition, glucocorticoids are lympholytic and immunosuppressive, increasing the patient's susceptibility to infection. [122] [123] The tensile strength of healing wounds decreases in the presence of glucocorticoids, an effect that is at least partially reversed by topical administration of vitamin A. [122]

Specific considerations pertain to the surgical approach for each cause of Cushing syndrome. For example, nearly three-fourths of cases of spontaneous Cushing disease result from a pituitary adenoma that secretes ACTH. [121] Our perioperative treatment for patients who have Cushing disease and a pituitary microadenoma differs from that for patients who have a pituitary adenoma associated with amenorrhea and galactorrhea. [121] The patient with Cushing disease tends

to bleed more easily and (on the basis of anecdotal evidence) tends to have a higher central venous pressure. Thus, during trans-sphenoidal tumor resection in such patients, the author routinely monitors central venous pressure and maintain it in the low end of the normal range. In other cases of trans-sphenoidal resection of microadenoma, such monitoring is needed only infrequently.

Ten to fifteen percent of patients with Cushing syndrome have adrenal overproduction of glucocorticoids from an adrenal adenoma or carcinoma. [105] If either unilateral or bilateral adrenal resection is planned, the author normally begins administering glucocorticoids at the start of resectioning of the tumor. Although no definitive studies exist, I normally give 100 mg of hydrocortisone hemisuccinate or hydrocortisone phosphate every 12 hours intravenously. I reduce this amount over 3 to 6 days until a maintenance dose is reached. Beginning on day 3, I also give a mineralocorticoid, 9alpha-fluorocortisol (0.05-0.1 mg/d). For certain patients, both steroids may require several adjustments. This therapy continues if the patient has undergone bilateral resection. For the patient who has undergone unilateral adrenal resection, therapy is individualized according to the status of the remaining adrenal gland. At the University of California, San Francisco, the incidence of pneumothorax in adrenal resection approached 20 percent during the early 1980s; this rate is similar to the incidence at the University of Chicago at present. The diagnosis of pneumothorax is sought and treatment is begun before the wound is closed.

Bilateral adrenalectomy with Cushing syndrome has a high incidence of postoperative complications and a perioperative mortality rate of 5 to 10 percent; it often results in permanent mineralocorticoid and glucocorticoid deficiency. Ten percent of patients with Cushing syndrome who undergo adrenalectomy have an undiagnosed pituitary tumor. After reduction of high levels of cortisol by adrenalectomy, the pituitary tumor enlarges. [121] These pituitary tumors are potentially invasive and may produce large amounts of ACTH and melanocyte-stimulating hormone, thereby increasing pigmentation. [121]

Adrenal adenomas are generally treated surgically; often the contralateral gland resumes functioning after several months. Frequently, however, the effects of carcinomas are not cured by surgery. In such cases, administration of inhibitors of steroid synthesis, such as metyrapone or mitotane (*o,p* -DDD[2,2-bis(2-chlorophenyl-4-chlorophenyl)-1,1-dichloroethane]), may ameliorate some symptoms but may not improve survival. These drugs and the aldosterone antagonist spironolactone may aid in reducing symptoms in the case of ectopic ACTH secretion if the primary tumor proves unresectable. Patients given these adrenal suppressants are also prescribed chronic glucocorticoid replacement therapy (that is, the goal of therapy is complete adrenal suppression). These patients should be considered to have suppressed adrenal function, and glucocorticoid replacement should be increased perioperatively.

Mineralocorticoid Excess

Excess mineralocorticoid activity (common with glucocorticoid excess, since most glucocorticoids have some mineralocorticoid properties) leads to potassium depletion, sodium retention, muscle weakness, hypertension, tetany, polyuria, inability to concentrate urine, and hypokalemic alkalosis. [124] These symptoms constitute primary hyperaldosteronism, or Conn syndrome (a cause of low-renin hypertension, as renin secretion is inhibited by the effects of the high levels of aldosterone).

Primary hyperaldosteronism is present in 0.5 to 1.0 percent of hypertensive patients who have no other known cause of hypertension. [124] Primary hyperaldosteronism most often results from unilateral adenoma, although 25 to 40 percent of patients have been found to have bilateral adrenal hyperplasia. Intravascular fluid volume, electrolyte concentrations, and renal function should be restored to within normal limits preoperatively by administering the aldosterone antagonist spironolactone. The effects of spironolactone are slow in onset and increase for 1 to 2 weeks. [124] A patient who has a serum potassium level of 2.9 mEq/L may have a deficit of body potassium of as little as 40 mEq or as much as 400 mEq. Frequently, at least 24 hours is required to restore potassium equilibrium. [125] [126] [127] [128] A normal serum potassium level does not necessarily imply correction of a total body deficit of potassium. In addition, patients with Conn syndrome have a high incidence of hypertension and ischemic heart disease; hemodynamic monitoring should be appropriate for the degree of cardiovascular impairment. [129] A retrospective anecdotal study indicated that intraoperative hemodynamic status was more stable when blood pressure and electrolytes were controlled preoperatively with spironolactone than when other antihypertensive drugs were used. [106] However, the efficacy of optimizing the perioperative status of patients who have disorders of glucocorticoid or mineralocorticoid secretion has not been clearly established. The author has assumed that gradual restoration of a normal condition is good medicine and that it would decrease perioperative morbidity and mortality.

Adrenocortical Hormone Deficiency

Glucocorticoid Deficiency

Withdrawal of steroids or suppression of synthesis by steroid therapy is the leading cause of underproduction of corticosteroids. [105] The management of this type of glucocorticoid deficiency is discussed in the next section, *The Patient Taking Steroids for Other Reasons.* Other causes of adrenocortical insufficiency include defects in ACTH secretion and destruction of the adrenal gland by autoimmune disease, tuberculosis, hemorrhage, or cancer; some forms of congenital adrenal hyperplasia (see previous discussion); and administration of cytotoxic drugs.

Primary adrenal insufficiency (Addison disease) is associated with local destruction of all zones of the adrenal cortex and causes both glucocorticoid and mineralocorticoid deficiency if the insufficiency is bilateral. Autoimmune disease is the most common cause of primary (nonexogenous) bilateral ACTH deficiency in the United States, whereas tuberculosis is the most common cause worldwide.

Autoimmune destruction of the adrenals may be associated with other autoimmune disorders, such as Hashimoto thyroiditis. Enzymatic defects in cortisol synthesis also cause glucocorticoid insufficiency, compensatory elevations of

ACTH, and congenital adrenal hyperplasia. [119] Because adrenal insufficiency usually develops slowly, such patients develop marked pigmentation (from excess ACTH trying to stimulate an unproductive adrenal gland) and cardiopenia (apparently secondary to chronic hypotension). [105]

Secondary adrenal insufficiency occurs when ACTH secretion is deficient, often because of a pituitary or hypothalamic tumor. Treatment of pituitary tumors by surgery or radiation may result in hypopituitarism and consequent adrenal failure. [105]

If unstressed, glucocorticoid-deficient patients usually have no perioperative problems. However, acute adrenal crisis (addisonian crisis) can occur when even a minor stress (for example, upper respiratory infection) is present. [105] [130] Preparation of such a patient for anesthesia and surgery should include treatment for hypovolemia, hyperkalemia, and hyponatremia. [113] Because these patients cannot respond to stressful situations, it was traditionally recommended that they be given a stress dose of glucocorticoids (about 200 mg hydrocortisone/70 kg body weight/d) perioperatively. However, Symreng and colleagues [109] gave 25 mg of hydrocortisone phosphate intravenously to adults at the start of the operative procedure, followed by 100 mg intravenously over the next 24 hours. Because using the minimum drug dose that would produce an appropriate effect is desirable, this latter regimen seems attractive. Such a regimen has proved to be as successful as the regimen using maximum doses (about 300 mg hydrocortisone per 70 kg body weight/d--see *The Patient Taking Steroids for Other Reasons*). Thus, I now recommend giving 100 mg of hydrocortisone phosphate intravenously every 12 hours. [105] [109] [110]

Mineralocorticoid Deficiency

Hypoaldosteronism, a less common condition, [131] can be congenital or can occur after unilateral adrenalectomy or prolonged administration of heparin. It can also be a consequence of long-standing diabetes and renal failure. Nonsteroidal inhibitors of prostaglandin synthesis may also inhibit renin release and exacerbate this condition in patients who have renal insufficiency. [131] Plasma renin activity levels are below normal and fail to increase appropriately in response to sodium restriction or diuretic drugs. Most symptoms are caused by hyperkalemic acidosis rather than hypovolemia; in fact, some patients are hypertensive. These patients can have severe hyperkalemia, hyponatremia, and myocardial conduction defects. [131] These defects can be treated successfully by administering mineralocorticoids (9alpha-fluorocortisol, 0.05-0.1 mg/d) preoperatively. [131] Doses must be carefully titrated and monitored to avoid an increase in hypertension.

The Patient Taking Steroids for Other Reasons

Perioperative Stress and the Need for Corticoid Supplementation

Many experimental studies and other reports (mostly anecdotal) concerning the adrenal responses of normal patients to the perioperative period, and the responses of patients taking steroids for other diseases, indicate the following:

1. Perioperative stress relates to the degree of trauma and the depth of anesthesia. Deep general or regional anesthesia causes the usual intraoperative glucocorticoid surge to be postponed to the postoperative period. [132] [133]
2. Few patients who have suppressed adrenal function have perioperative cardiovascular problems if they do not receive supplemental steroids perioperatively. [108] [109] [110] [111] [112] [113] [114] [115]
3. Although a patient who chronically takes steroids occasionally becomes hypotensive perioperatively, only rarely has this event been documented sufficiently to implicate glucocorticoid or mineralocorticoid deficiency as the cause. [108] [109] [110] [111] [112] [113] [114] [115]
4. Acute adrenal insufficiency occurs only rarely but can be life-threatening. [108] [109] [110] [111] [112] [113] [114] [115]
5. There is little risk in giving these patients high-dose steroid coverage perioperatively. [109] [110] [130]

In a recent well-controlled study of glucocorticoid replacement in primates, the investigators clearly defined the life-threatening events that can be associated with inadequate perioperative corticosteroid replacement. [110] This study further defined the physiologic and hemodynamic consequences of inadequate cortisol replacement; an alternative dose regimen is suggested that has stood the test of a decade and has altered management methods to possibly improve patient safety. In this study, adrenalectomized primates and sham-operated controls were maintained on physiologic doses of steroids for 4 months. The animals were then randomly allocated to groups that received subphysiologic (one-tenth the normal cortisol production), physiologic, or supraphysiologic (ten times the normal cortisol production) doses of cortisol for 4 days preceding abdominal surgery (cholecystectomy). Hemodynamic variables were measured by means of arterial and pulmonary artery catheters. The animals were maintained on their randomized dosage schedules during and after surgery. The group given subphysiologic doses of steroid perioperatively had a significant increase in postoperative mortality. The death rates for the physiologic and supraphysiologic replacement groups were the same and did not differ from the rate for sham-operated controls. Death in the subphysiologic replacement group was related to severe hypotension associated with a significant decrease in systemic vascular resistance and a reduced left ventricular stroke work index. The filling pressures of the heart were unchanged compared with those in control animals. There was no evidence of hypovolemia or severe congestive heart failure. Despite low systemic vascular resistance, the animals did not become tachycardic. All these responses are compatible with the previously documented interaction of glucocorticoids and catecholamines, suggesting that glucocorticoids mediate catecholamine-induced increases in cardiac contractility and maintenance of vascular tone.

The investigators used a sensitive measure of wound healing by studying hydroxyproline accumulation. All treatment groups, including the group given supraphysiologic doses of glucocorticoids, had the same capacity for wound healing. Furthermore, perioperative administration of supraphysiologic doses of corticosteroids produced no adverse metabolic consequences.

This well-conducted study confirms several long-standing intuitive impressions concerning patients who have inadequate adrenal function, either resulting from underlying disease or secondary to administration of exogenous steroids. Inadequate replacement of corticosteroids perioperatively can lead to addisonian crisis and death. Administration of supraphysiologic doses of steroids for a short time perioperatively caused no discernible complications. However, there are at least theoretical negative consequences when large doses of steroids are given (see later). It is clear that inadequate corticosteroid coverage can cause death. What is not so clear is what dose of steroid for replacement therapy should be recommended. The authors of the previously discussed study on monkeys were reluctant to recommend simple physiologic steroid replacement doses for human patients perioperatively. [110] Our group agrees that a prospective, randomized double-blind trial in patients receiving physiologic doses of steroids is needed before current recommendations are modified. [109] [110] In any case, we never supplement perioperatively with a dose lower than what the patient has already been receiving. [111]

Which patients definitely need supplementation? If in doubt, how can a patient's need for supplementation with glucocorticoids be determined? Because the risk is low, the author normally provides supplementation for any patient who has received steroids within a year. [107] [108] [109] [110] [111] [112] [113] [114] [115] [119] [120] [121] [122] The data indicate that topical application of steroids (even without use of occlusive dressings) can suppress normal adrenal responses for as long as 9 months to 1 year [107] [111] (Table 25-8) .

How can one determine when adrenal responsiveness has returned to normal? The morning plasma cortisol level does not reveal whether the adrenal cortex has recovered sufficiently to ensure that cortisol secretion will increase adequately to meet the demands of stress. Inducing hypoglycemia with insulin has been advocated as a sensitive test of pituitary-adrenal competence but is impractical and probably a more dangerous practice than simply administering glucocorticoids. If the plasma cortisol concentration is measured during acute stress, a value of more than 25 mug/dL assuredly (and a value of >15 mug/dL probably) indicates normal

pituitary-adrenal responsiveness. In another test of pituitary-adrenal sufficiency, the baseline plasma cortisol level is determined. Then, 250 mug of synthetic ACTH (cosyntropin) is given, and plasma cortisol is measured 30 to 60 minutes later. [112] An increase in plasma cortisol of 6 to 20 mug/dL or more is normal. [134] A normal response indicates recovery of pituitary-adrenal axis function. A lesser response usually indicates pituitary-adrenal insufficiency, possibly requiring perioperative supplementation with steroids.

Usually laboratory data defining pituitary-adrenal adequacy are not available before surgery. However, rather than delay surgery or test most patients, the author assumes that any patient who has taken steroids at any time during the preceding year has suppressed pituitary-adrenal functioning and will require perioperative supplementation.

Under perioperative conditions, the adrenal glands secrete 116 to 185 mg of cortisol daily. Under maximum stress, they may secrete 200 to 500 mg/d. Good correlation exists between the severity and duration of the operation and the response of the adrenal gland. "Major surgery" would be represented by procedures such as colectomy, and "minor surgery," by procedures such as herniorrhaphy. In one study of 20 patients during major surgery, the mean maximal concentration of cortisol in plasma was 47 mug/dL (range, 22-75 mug/dL). Values remained above 26 mug/dL for a maximum of 72 hours after surgery. During minor surgery, the mean maximal concentration of cortisol in plasma was 28 mug/dL (range, 10-44 mug/dL).

Although the precise amount required has not been established, I usually administer intravenously the maximum amount of glucocorticoid that the body manufactures in response to a maximal stress (i.e., approximately 200 mg/d of hydrocortisone phosphate/70 kg body weight). [109] [110] [132] [133] For minor surgical procedures, I usually give hydrocortisone phosphate intravenously, 100 mg/70 kg body weight/d. Unless infection or some other perioperative complication develops, I decrease this dose by approximately 25 percent per day until oral intake can be resumed. At this point, the usual maintenance dose of glucocorticoids can be employed.

Risks of Supplementation

Rare complications of perioperative supplementation with steroids include aggravation of hypertension, fluid retention, inducement of stress ulcers, and psychiatric disturbance. Although data are not available to assess the incidences of the following risks, two common complications of short-term perioperative supplementation with glucocorticoids are described in the literature: abnormal wound healing and increased rate of infections. [108] [109] [110] [111] [112] [113] [114] [115] [120] [121] [122] [123] [124] [135] [136] This evidence is inconclusive, however, as it relates to acute glucocorticoid administration and not to chronic administration of glucocorticoids with increased doses at times of stress. Ehrlich and Hunt [122] found that moderate to large

TABLE 25-8 -- Recovery of Hypothalamic-Pituitary Adrenal Function After Withdrawal of Steroids

RECOVERY TIME (MO)	PLASMA 17-HYDROXYCORTICOID VALUES	PLASMA ACTH VALUES	ADRENAL RESPONSE TO EXOGENOUS ACTH	RESPONSE TO METYRAPONE
1	Low [a]	Low	Low	Low
2-5	Low	High [b]	Low	Low
6-9	Normal	Normal	Low	Low
>9	Normal	Normal	Normal	Normal

Data from Graber et al [112]

[a] Various subjective manifestations of mild adrenal insufficiency occur during this stage.
[b] The diurnal rhythm of the plasma concentrations is qualitatively normal during this stage.

doses of steroids exerted their morphologic effects best within 3 days of injury. They postulated that inhibition of the early inflammatory process by steroids after wounding was responsible for the delay in healing. Vitamin A was found to be somewhat protective against delayed healing, presumably because of its effect on stabilizing lysosomes. [122] In contrast to these studies that suggest a deleterious effect of perioperative glucocorticoid administration on wound healing in rats, a study on primates suggests that high doses of glucocorticoids, administered perioperatively, did not impair sensitive measures of wound healing. [110] Other data provide no better insight into these problems. [108] [109] [110] [111] [112] [113] [114] [115] [120] [121] [122] These data are not conclusive regarding a short-term increase in supplementation. However, an overall assessment of these results suggests that short-term perioperative supplementation with steroids has a small but definite deleterious effect on wound healing that is perhaps partially reversed by topical administration of vitamin A.

Information regarding the risk of infection from perioperative supplementation with glucocorticoids is also unclear. Winstone and Brooke [137] reported four cases of septicemia among 18 surgical patients given perioperative supplementation with glucocorticoids. No similar complications occurred in 17 others who were also taking glucocorticoids but who were not given perioperative supplementation. In a controlled study of 100 patients given perioperative supplementation with glucocorticoids, 11 wound infections occurred in the group treated with steroids, and only one occurred in the control group. [135] Test subjects and controls were not matched for underlying disease. By contrast, Jensen and Elb [136] found no change in the incidence of wound infections or of other infections in an uncontrolled series of 419 patients undergoing surgery and perioperative supplementation with glucocorticoids. Oh and Patterson [130] found only one minor suture abscess in 17 steroiddependent asthmatic patients undergoing 21 surgical procedures. Thus, although the data indicate that the risk of infection to the patient chronically taking steroids is real, these data are inadequate to conclude that perioperative supplementation with steroids increases that risk.

Adrenal Cortex Function in the Elderly

The adrenal gland shows a progressive decrease in production of androgens with age. [138] This decrease in androgen activity has no known implications for anesthesia. Plasma levels of cortisol are unaffected by increasing age. Levels of corticosterone-binding globulin are also unaffected by age; this suggests that a normal fraction of free cortisol (1-5%) is present in elderly patients. Several investigators have noted a progressively impaired ability of the aged patient to metabolize and excrete glucocorticoids. In normal individuals, the quantity of 17-hydroxycorticosteroids excreted is reduced by half by the seventh decade. This decreased excretion undoubtedly reflects reduced renal function that occurs with aging. When excretion of cortisol metabolites is expressed as a function of creatinine clearance, the age difference disappears. Further reductions in cortisol clearance may be due to impaired hepatic metabolism of circulating cortisol.

The rate of secretion of cortisol is 30 percent lower in the elderly. This reduced secretion is an appropriate compensatory mechanism for maintaining a normal level of cortisol in the face of its decreased hepatic and renal clearance. It is important to the anesthesiologist that the reduced cortisol production can be overcome during periods of stress and that the elderly display an entirely normal adrenal response to administration of ACTH and to stresses such as hypoglycemia.

Both underproduction and overproduction of glucocorticoids are generally considered diseases of younger individuals. The highest incidence of Cushing disease, of either pituitary or adrenal origin, occurs during the third decade of life. The most common cause of spontaneous Cushing disease is benign pituitary adenoma. [121] However, in patients older than 60 years in whom Cushing disease develops, the most likely cause is adrenal carcinoma or ectopic ACTH production from tumors usually located in the lung, pancreas, or thymus.

Also see Chapter 61 .

Effect of Etomidate on Adrenal Function

Even a single dose of etomidate used for induction of anesthesia suppresses adrenal function. [139] The clinical significance of adrenal suppression by etomidate is unknown, but there is justifiable concern over continued use of etomidate without steroid supplementation.

Etomidate is an imidazole sedative-hypnotic that induces rapid loss of consciousness with minimal cardiovascular depression even in compromised patients.

Etomidate has been administered in two clinical settings--as a bolus for induction of anesthesia and as a continuous infusion for prolonged sedation in the intensive care unit (ICU) setting. The pattern of adrenal suppression appears to be related to dose and time and differs with the duration of administration. [139]

Etomidate inhibits two essential adrenocortical enzymes, 11beta-hydroxylase and cholesterol side-chain cleavage enzyme, in rats and in humans. [139] I believe that it is important to clarify the difference between the adrenal suppression by etomidate and the stated goal of several anesthesiologists to provide stress-free anesthesia. It appears that providing a level of anesthesia that prevents grimacing, sweating, extreme elevations of blood pressure and heart rate, and an outpouring of the neurohumoral mediators of stress is evidence that we have adequately depressed CNS function and protected our patients from some of the unwanted side effects of surgery. This goal is different from the inhibition of peripheral adrenocortical enzymes of etomidate that occurs as an unwanted side effect of the drug.

Thus, it has been documented that adrenal reserve is compromised for at least 24 hours after a single induction dose of etomidate in most patients. [140] Should hypotension or electrolyte abnormalities associated with adrenal insufficiency (hyponatremia and hyperkalemia) occur in a patient who has recently received etomidate, I agree with previous suggestions [139] that corticosteroids should be administered in stress doses (e.g., cortisol, 100 mg bid) and be tapered as noted in the earlier section, *The Patient Taking Steroids for Other Reasons.*

Adrenal Incidentaloma

Adrenal tumors are found in as many as 9 percent of autopsies, and the increased use of imaging techniques brings many of these tumors to clinical attention before death. Previously, size was used as a discriminator: tumors larger than 6 cm were surgically removed because of the high probability of malignancy. Those smaller than 3 cm were followed up, and those 3 to 6 cm were investigated.

Recent data from three large series [116] [117] [118] and success from laparoscopic removal [141] [142] have called for a reevaluation. The three series found a significant number of adrenal carcinomas and pheochromocytomas (approximately 3% of each), an occasional aldosteronoma (approximately 1%), as well as a not insignificant number of metastases from as yet uncovered primary tumors (approximately 10%). These data may indicate the need for a more aggressive approach to adrenal incidentalomas that are smaller than 6 cm.

Also see Chapter 9 .

Adrenal Medullary Sympathetic Hormone Excess: Pheochromocytoma

Fewer than 0.1 percent of all cases of hypertension are caused by pheochromocytomas, catecholamine-producing tumors derived from chromaffin tissue. [143] Nevertheless, these tumors are clearly important to the anesthetist, as 25 to 50 percent of hospital deaths in patients with pheochromocytomas occur during induction of anesthesia or during operative procedures for other causes. [144] Although usually found in the adrenal medulla, these vascular tumors can occur anywhere, such as in the right atrium, the spleen, the broad ligament of the ovary, or the organs of Zuckerkandl at the bifurcation of the aorta. Malignant spread, which occurs in fewer than 15 percent of pheochromocytomas, usually proceeds to venous and lymphatic channels with a predisposition for the liver. This tumor is occasionally familial and/or part of the pluriglandular-neoplastic syndrome known as multiple endocrine adenoma type IIa or type IIb, manifesting as an autosomal dominant trait on chromosome 10. Type IIa consists of medullary carcinoma of the thyroid, and parathyroid adenoma or hyperplasia and pheochromocytomas. Often, bilateral tumors are found in the familial form. Localization of tumors can be done with magnetic resonance imaging (MRI) or computed tomography (CT) scans, metaiodobenzylguanidine nuclear scanning, ultrasonography, or intravenous pyelography studies (in decreasing order of combined sensitivity and specificity).

Symptoms and signs that may be solicited preoperatively and that are suggestive of pheochromocytoma are excessive sweating; headache; hypertension; orthostatic hypotension; previous hypertensive or arrhythmic response to induction of anesthesia or to abdominal examination; paroxysmal attacks of sweating, headache, tachycardia, and hypertension; glucose intolerance; polycythemia; weight loss; and psychological abnormalities. In fact, the occurrence of combined symptoms of paroxysmal headache, sweating, and hypertension is probably a more sensitive and specific indicator than any one biochemical test for pheochromocytoma [143] [145] [146] (Table 25-9) (Table Not Available) . Despite more than 2,000 articles in the literature about pheochromocytomas, little is known about what factors in care affect perioperative morbidity. [147] [148] [149]

Although no controlled, randomized, prospective clinical studies have studied the value of preoperative use of adrenergic receptor-blocking drugs, the use of such drugs is generally recommended before surgery. These drugs probably reduce the complications of hypertensive crisis, the wide blood pressure fluctuations during manipulation of the tumor (especially until venous drainage is obliterated), and the myocardial dysfunction that occur perioperatively. The reduction in mortality associated with resection of pheochromocytoma (from 40-60% to the current 0-6%) occurred when alpha-adrenergic receptor blockade was introduced as preoperative preparatory therapy for such patients [146] [147] [148] [149] [150] [151] (Table 25-10) .

alpha-Adrenergic receptor blockade with prazosin or phenoxybenzamine restores plasma volume by counteracting the vasoconstrictive effects of high levels of catecholamines. This re-expansion of fluid volume is often followed by a decrease in hematocrit. Because some patients may be very sensitive to the effects of phenoxybenzamine, it should initially be given in doses of 20 to 30 mg/70 kg orally once or twice a day. Most patients usually require 60 to 250 mg/d. Efficacy of therapy should be judged by a reduction in symptoms (especially sweating) and a stabilization of blood pressure. For patients who have carbohydrate intolerance because of inhibition

TABLE 25-9 -- Characteristics of Tests for Pheochromocytoma

(Not Available)

Modified from Pauker and Kopelman [145]

TABLE 25-10 -- Preoperative Mortality Associated With Resectioning of Pheochromocytoma [a]

YEAR OF SERIES	STUDY	MORTALITY (%)	PATIENTS IN SERIES (n)
1951	Apgar (review)	45.0	91
1951	Apgar	33.0	12
1963	Stackpole	13.0	100
Earlier than 1960	Mayo Clinic	0.0-26.0	101 (?)
Later than 1960	Mayo Clinic	2.9 (?)	44 (?)
Earlier than 1967	Modlin (without alpha blockade)	18.0	17
Later than 1967	Modlin (with;alpha blockade)	2.0	41
1976-1993	Scott	3.0	33
1976-1993	Roizen	0.0	56
1974-1994	Lucon	2.0	50

[a] *Data were abstracted from studies discussed in Roizen et al [149] and include more recent patient information.*

of insulin release mediated by alpha-adrenergic receptor stimulation, alpha-adrenergic receptor blockade may reduce fasting blood sugar levels. For patients who exhibit ST-T changes on ECG, long-term preoperative alpha-adrenergic receptor blockade (1-6 months) has produced ECG and clinical resolution of catecholamine-induced myocarditis. [147] [148] [149] [150] [151] [152]

beta-Adrenergic receptor blockade with propranolol is suggested for patients who have persistent arrhythmias or tachycardia, [147] [148] [149] [150] [151] [152] because these conditions can be precipitated or aggravated by alpha-adrenergic receptor blockade. beta-Adrenergic receptor blockade should not be used without concomitant alpha-adrenergic receptor blockade, lest the vasoconstrictive effects of the latter go unopposed, thereby increasing the risk of dangerous hypertension.

The optimal duration of preoperative therapy with phenoxybenzamine has not been studied. Most patients require 10 to 14 days, as judged by the time needed to stabilize blood pressure and to ameliorate symptoms. On the basis of my experience, this is a minimal period. [148] [149] [152] Because the tumor spreads slowly, little is lost by waiting until medical therapy has optimized the patient's preoperative condition. Accordingly, I recommend using the following criteria:

1. No in-hospital blood pressure reading higher than 165/90 mm Hg should be evident for 48 hours before surgery. We often measure arterial blood pressure every minute for 1 hour in a stressful environment (our postanesthesia care unit). If no blood pressure reading is greater than 165/90, this criterion is considered satisfied.
2. Orthostatic hypotension should be present, but blood pressure on standing should not be lower than 80/45mm Hg.
3. The ECG should be free of ST-T changes that are not permanent.
4. No more than one premature ventricular contraction should occur every 5 minutes.

Other drugs, including prazocin, calcium channel-blocking drugs, clonidine, and magnesium, have also been used to achieve suitable degrees of alpha-adrenergic blockade prior to surgery.

Although specific anesthetic drugs have been recommended, I believe that optimal preoperative preparation, a gentle induction of anesthesia, and good communication between surgeon and anesthesiologist are most important. Virtually all anesthetic agents and techniques (including isoflurane, sevoflurane, sufentanil, remifentanil, fentanyl, and regional anesthesia) have been used with success. In fact, all agents studied are associated with a high rate of transient intraoperative arrhythmias [148] (Table 25-11) . I have avoided halothane because it sensitizes the myocardium and may increase arrhythmogenic frequency, and desflurane, because it may precipitate nonneurogenic catecholamine release. No good data indicate these biases are appropriate.

Because of ease of use, the author prefers to give phenylephrine hydrochloride (Neo-Synephrine) or dopamine for hypotension and nitroprusside for hypertension. Phentolamine (Regitine) has too long an onset and duration of action. Occasionally (five times in >50 pheochromocytoma resections) I have used a beta-adrenergic blocking agent (esmolol is now the preferred one) for severe tachycardia without hypertension or volume depletion. Painful or stressful events such as intubation often cause an exaggerated stress response in less than perfectly anesthetized patients who have a pheochromocytoma. This response is caused by release of catecholamines from nerve endings that are "loaded" by the reuptake process. Such stresses may cause catecholamine levels of 200 to 2,000 pg/mL in normal patients. For the patient with pheochromocytoma, even simple stresses can lead to blood catecholamine levels of 2,000 to 20,000 pg/mL. However, infarction of a tumor, with release of products onto peritoneal surfaces, or surgical pressure causing release of products, can result in blood levels of 200,000 to 1,000,000 pg/mL--a situation that should be anticipated and avoided. (Ask for a temporary stay of surgery, if at all possible, while the rate of nitroprusside infusion is increased.) Once the venous supply is secured, and if intravascular volume is normal (as measured by pulmonary wedge pressure), normal blood pressure usually results. However, some patients become hypotensive, occasionally requiring massive infusions of catecholamines. On rare occasions, patients remain hypertensive intraoperatively. Postoperatively, about 50 percent remain hypertensive for 1 to 3 days--and initially have markedly elevated but declining plasma catecholamine levels--at which time all but 25 percent become normotensive. It is important to interview other family members and perhaps advise them to inform their future anesthetist about the potential for such familial disease.

Hypofunction or Aberration in Function of the Sympathetic Nervous System (Dysautonomia)

Disorders of the sympathetic nervous system include Shy-Drager syndrome, Riley-Day syndrome, Lesch-Nyhan syndrome, Gill familia dysautonomia, diabetic dysautonomia, and the dysautonomia of spinal cord transection.

Although individuals can function well without an adrenal medulla, a deficient peripheral sympathetic nervous system occurring late in life poses major problems for many facets of life [153] [154] [155] [156] [157] [158] [159] [160] [161] [162] [163] ; nevertheless, a perioperative sympathectomy or its equivalent has been recommended by some. [164] [165] [166] [167] [168] [169] [170] [171] [172] [173] [174] [175] [176] [177] [178] A

TABLE 25-11 -- Incidence of Perioperative Complications in a Randomized Study of Patients Undergoing Resectioning of Pheochromocytoma Under One of Four Anesthetic Techniques

	ANESTHETIC[a]			
	ENFLURANE (6)	***HALOTHANE (6)***	***DROPERIDOL AND FENTANYL (7)***	***REGIONAL (5)***
Ventricular tachycardia				
Needing no treatment	5	5	6	5
Needing treatment	0	1	1	0
Vasodilator needed				
Intraoperatively	6	6	7	5
Postoperatively	0	1 [b]	1 [b]	0
Vasopressor needed				
Intraoperatively	0	1	1	0
Postoperatively	0	0	0	0
Myocardial infarction [c]	0	0	0	0
Renal failure [c]	0	0	0	0
Congestive heart failure [c]	0	1	1	1
Stroke [c]	0	0	0	0
Death [c]	0	0	0	0

Data from Roizen et al [148]

[a] Number of patients shown in parentheses
[b] Not all the abnormally secreting tumor tissue was removed from the patient.
[c] Occurring postoperatively

primary function of the sympathetic nervous system appears to be the regulation of blood pressure and of intravascular fluid volume during changing of body position. Common features of all the syndromes of hypofunctioning of the sympathetic nervous system are orthostatic hypotension and decreased beat-to-beat variability in

heart rate. These conditions can be caused by deficient intravascular volume, deficient baroreceptor function (as also occurs in carotid artery disease [179]), abnormalities in CNS function (as in Wernicke or Shy-Drager syndrome), deficient neuronal stores of norepinephrine (as in idiopathic orthostatic hypotension [154] and diabetes [15]), or deficient release of norepinephrine (as in traumatic spinal cord injury [153]). Patients with these conditions may have an increased number of available adrenergic receptors (a compensatory response) and an exaggerated response to sympathomimetic drugs. [180] In addition to other abnormalities, such as retention of urine or feces and deficient heat exchange, hypofunctioning of the sympathetic nervous system is often accompanied by renal amyloidosis. Thus, electrolyte and intravascular fluid volume status should be evaluated preoperatively. Because many of these patients have cardiac abnormalities, intravascular fluid volume might be assessed preoperatively using a Swan-Ganz catheter or transesophageal echocardiograph rather than measurement of central venous pressure (Chs. 30 and 31) .

Because functioning of the sympathetic nervous system is not predictable in these patients, I usually employ slow, gentle induction of anesthesia and treat sympathetic excess or deficiency by infusing, with careful titration, drugs that directly constrict (phenylephrine) or dilate (nitroprusside) blood vessels or that stimulate (isoproterenol) or depress (esmolol) heart rate. I prefer these drugs to agonists or antagonists, which may indirectly release catecholamines. A 20 percent perioperative mortality rate for 2,600 patients with spinal cord transection has been reported, [161] indicating that such patients are difficult to manage and deserve particularly close attention.

After reviewing 300 patients with spinal cord injuries, Kendrick et al [181] concluded that autonomic hyperreflexia syndrome does not develop if the lesion is below spinal dermatome T7. If the lesion is above that level (the splanchnic outflow), 60 to 70 percent of patients experience extreme vascular instability. The trigger to this instability, or *mass reflex* involving noradrenergic and motor hypertonus, [155] can be a cutaneous, proprioceptive, or visceral stimulus (a full bladder is a common initiator). The sensation enters the spinal cord and causes a spinal reflex, which in normal persons is inhibited from above. Sudden increases in blood pressure are sensed in the pressure receptors of the aorta and carotid sinus. The resulting vagal hyperactivity produces bradycardia, ventricular ectopia, or various degrees of heart block. Reflex vasodilation may occur above the level of the lesion, resulting in flushing of the head and neck.

Depending on the length of time since spinal cord transection, other abnormalities may occur. Acutely (i.e., <3 wk from the time of spinal injury), retention of urine and feces is common and, by elevating the diaphragm, may impair respiration. Disimpaction of the intestine alleviates this respiratory problem. Hyperesthesia is present above the lesion; reflexes and flaccid paralysis are present below the lesion. The intermediate period (3 d-6 mo) is marked by a hyperkalemic response to depolarizing drugs. [160] The chronic phase is characterized by a return of muscle tone, positive Babinski sign, and frequently, the occurrence of hyperreflexia syndromes (e.g., mass reflex; see previous).

Thus, in addition to meticulous attention to perioperative intravascular volume and electrolyte status, the anesthesiologist should know--by history-taking, physical examination, and laboratory data--the status of the patient's myocardial conduction (as revealed by ECG), the status of renal functioning

TABLE 25-12 -- Biochemical Measurements of Thyroid Function That Account for Variation in Production of Thyroid-Binding Globulin

	EXAMPLES OF NORMAL THYROID STATUS					TSH
	FT_4 E	**=**	***T_4***	**×**	***THBR***	
Normal	0.19 (0.12-0.25)	=	0.6 (0.4-0.9)		31% (25-35%)	0.2 (0.2-0.8)
During use of oral contraceptives	0.19	=	1.3		15%	0.3
During use of corticosteroids	0.18	=	0.3		60%	0.3

Abbreviations: FT_4 E is the free T_4 (thyroxine) estimate. This is usually obtained by multiplying the total thyroxine (T_4) concentration (the free amount and the amount bound to protein) times the thyroid hormone binding ratio (THBR, formerly called the resin T_3 uptake). THBR is a measure of the bound thyroid hormone binding protein. TSH is the thyroid-stimulating hormone secreted by the pituitary in the negative feedback loop. (TSH increases when FT_4 E is low in hypothyroidism.)

(by noting the ratio of creatinine to blood urea nitrogen), and the condition of respiratory muscle (by determining the ratio of forced expiratory volume in 1 s to forced vital capacity [i.e., FEV_1/FVC]) (Ch. 24) . The anesthesiologist may also obtain a chest radiograph, if atelectasis or pneumonia is suspected on the basis of history-taking or physical examination. Temperature control, the presence of bone fractures or decubitus ulcers, and normal functioning of urination and defecation systems must be assessed. Confirmation of the latter prevents postoperative pneumonia or atelectasis caused by high positioning of the diaphragm.

Thyroid Dysfunction

The major thyroid hormones are thyroxine (T_4), a product of the thyroid gland, and the more potent 3,5,3-triiodothyronine (T_3), a product of both the thyroid and the extrathyroidal enzymatic deiodination of thyroxine. Approximately 80 to 85 percent of T_3 is produced outside the thyroid gland. Production of thyroid secretions is maintained by secretion of thyroid-stimulating hormone (TSH) in the pituitary, which in turn is regulated by secretion of thyrotropinreleasing hormone (TRH) in the hypothalamus. Secretion of TSH and TRH appears to be negatively regulated by T_4 and T_3. Whether all effects of thyroid hormones are mediated by T_3, or if T_4 has intrinsic biologic activity, remains unclear.

Thyroid hormones create their effects through several mechanisms. Binding of T_3 to high-affinity nuclear receptors (TR_{alpha} and TR_{beta}) and the subsequent activation of DNA-directed mRNA synthesis may account for the anabolic growth and developmental effects, plus some calorigenic effect, of thyroid hormones. Patients with the syndrome of thyroid hormone resistance have point mutations in the TR_{beta}. Thyroid hormone is also responsible for an increased concentration of adrenergic receptors, which may account for many of its cardiovascular effects.

Because T_3 has a greater biologic effect than does T_4, one would expect the diagnosis of thyroid disorders to be based on levels of T_3. However, this is not usually the case. The diagnosis of thyroid disease is confirmed by one of several biochemical measurements: levels of free T_4 or of total serum concentrations of T_4, and by the "free T_4 estimate." The estimate is obtained by multiplying total T_4 (free and bound) by the thyroid binding ratio (formerly called the resin T_3 uptake) (Table 25-12) . The T_3-binding ratio measures the extra quantity of serum protein binding sites. This measurement is necessary because thyroxine-binding globulin (TBG) is abnormally high during pregnancy, hepatic disease, and estrogen therapy (all of which would elevate the total T_4 level) (Table 25-13) . Reliable interpretation of measurements of the total hormone concentration in serum necessitates data on the percentage of bound hormone. The thyroid hormone-binding ratio test provides this information. In this test, iodine-131-labeled T_3 is added to a patient's serum and allowed to reach an equilibrium binding state. A resin is then added that binds the remaining radioactive T_3. The resin uptake is greater if the patient has fewer TBG binding sites. In normal patients, the resin T_3 uptake (the thyroid hormone-binding ratio) is 25 to 35 percent. When the serum TBG is elevated, the thyroid hormone-binding ratio is diminished (see Table 25-12) . When the serum TBG is diminished, as in the nephrotic syndrome, in conditions in which glucocorticoids are increased, or in chronic liver disease, the thyroid hormone-binding ratio is increased.

The free T_4 estimate and the free T_3 estimate are frequently used as measures of a patient's serum T_4 and T_3 hormone concentration. To obtain these estimates, the concentration of total serum T_4 or total serum T_3 is multiplied by the measured thyroid hormone-binding ratio. The values of these two indices are normal in the event of a primary alteration in binding, but not in secretion, of thyroid hormone.

Hyperthyroidism can be diagnosed by measuring the levels of TSH after administration of TRH. Although administering

TABLE 25-13 -- Factors Influencing Serum Levels of Thyroxine-Binding Globulin

CONDITIONS INCREASING SERUM LEVELS	CONDITIONS DECREASING SERUM LEVELS
Use of oral contraceptives	Testosterone
Pregnancy	Use of corticosteroids
Use of estrogen	Severe illness

Infectious hepatitis	Cirrhosis
Chronic active hepatitis	Nephrotic syndrome
Neonatal state	Inherited conditions
Acute intermittent porphyria	?Phenytoin
Inherited conditions	

TRH normally increases TSH levels in blood, even a small increase in the T_4 or T_3 level in blood abolishes this response. Thus, a subnormal or absent serum TSH response to TRH is a very sensitive indicator of hyperthyroidism. [182] In one group of disorders involving hyperthyroidism, serum TSH levels are elevated in the presence of elevated levels of free thyroid hormone.

Measurement of the alpha-subunit of TSH has been helpful in identifying the rare patients who have a pituitary neoplasm and who usually have increased alpha-subunit concentrations. Some patients are clinically euthyroid in the presence of elevated levels of total T_4 in serum. Certain drugs, notably gallbladder dyes, propranolol, glucocorticoids, and amiodarone, block the conversion to T_3 to T_4 , thereby elevating T_4 levels. Severe illness also slows this conversion. Levels of TSH are often high in situations where the rate of this conversion is decreased. In hyperthyroidism, cardiac function and responses to stress are abnormal; return of normal cardiac function parallels the return of TSH levels to normal values.

Hyperthyroidism

Although hyperthyroidism is usually caused by the multinodular diffuse enlargement in Graves disease (also associated with disorders of the skin and/or eyes), it can also occur with pregnancy, [183] thyroiditis (with or without neck pain), thyroid adenoma, choriocarcinoma, or TSH-secreting pituitary adenoma. Five percent of women have thyrotoxic effects 3 to 6 months postpartum and tend to have recurrences with subsequent pregnancies. Major manifestations of hyperthyroidism are weight loss, diarrhea, warm moist skin, weakness of large muscle groups, menstrual abnormalities, nervousness, jitteriness, intolerance to heat, tachycardia, cardiac arrhythmias, mitral valve prolapse, [184] and heart failure. When the thyroid is functioning abnormally, the entity most threatened is the cardiovascular system. When diarrhea is severe, dehydration should be corrected preoperatively. Mild anemia, thrombocytopenia, increased serum alkaline phosphatase, hypercalcemia, muscle wasting, and bone loss frequently occur in hyperthyroidism. Muscle disease usually involves proximal muscle groups; it has not been reported to cause respiratory muscle paralysis. In the apathetic form of hyperthyroidism (seen most commonly in persons older than 60 years), cardiac effects dominate the clinical picture. [185] These signs and symptoms include weight loss, anorexia, and cardiac effects such as tachycardia, irregular heart rhythm, atrial fibrillation (in 10%), heart failure, and occasionally papillary muscle dysfunction. [184] [185]

Although beta-adrenergic receptor blockade can control heart rate, its use is fraught with hazard in the patient already experiencing congestive heart failure (CHF). However, decreasing heart rate may improve heart pumping function. Thus, hyperthyroid patients who have fast ventricular rates, who are in CHF, and who require emergency surgery are given esmolol guided by changes in pulmonary artery wedge pressure and their condition. If slowing the heart rate with a small dose of esmolol (50 mug/kg) does not aggravate heart failure, the author administers more esmolol. I believe that we should aim to avoid imposing surgery on any patient whose thyroid function is clinically abnormal. Therefore, I believe only "life-or-death" emergency surgery should preclude making the patient pharmacologically euthyroid, a process that can take 2 to 6 weeks. Antithyroid medications include propylthiouracil or methimazole, both of which decrease the synthesis of thyroxine and may enhance remission by reducing TSH-receptor antibody levels (the primary pathologic mechanism in Graves disease). Propylthiouracil also decreases the conversion of T_4 into the more potent T_3 . However, the literature indicates a trend toward preoperative preparation with propranolol and iodides alone. [186] This approach is quicker (i.e., 7-14 d versus 2-6 wk); it shrinks the thyroid gland, as does the more traditional approach; and it treats symptoms but may not correct abnormalities in left ventricular function. [187] Regardless of approach, antithyroid drugs should be administered chronically and on the morning of surgery. If emergency surgery is necessary before the euthyroid state is achieved, if subclinical hyperthyroidism progresses without adequate treatment, [188] or if hyperthyroidism gets out of control during surgery, intravenous administration of esmolol, 50 to 500 mug/kg, should be titrated to restore normal heart rate (assuming the absence of congestive heart failure) (see previous). Also, intravascular fluid volume and electrolyte balance should be restored. However, administering propranolol or esmolol does not invariably prevent "thyroid storm." [189]

No controlled study has demonstrated clinical advantages of any anesthetic drug over another for surgical patients who are hyperthyroid. A review of cases performed at the University of California, San Francisco, from 1968 to 1982 reveals that virtually all anesthetic agents and techniques [190] have been employed without adverse effects being even remotely attributable to agent or technique. Furthermore, although some investigators have recommended that anticholinergic drugs (especially atropine) be avoided because they interfere with the sweating mechanism and cause tachycardia, atropine has been given as a test for adequacy of antithyroid treatment. Because patients are now subject to operative procedures only when euthyroid, the traditional "steal" of the heavily premedicated hyperthyroid patient (so commonly found in the iodine-deficient locales producing the Lahey, Mayo, and Cleveland Clinics) to the operating room has vanished.

The patient having a large goiter and an obstructed airway can be handled in the same way as any other patient having problematic airway management. Preoperative medication should avoid excessive sedation, and an airway should be established, often with the patient awake. A firm armored endotracheal tube is preferable and should be passed beyond the point of extrinsic compression. It is most useful to examine the CT scans of the neck preoperatively to determine the extent of compression. Maintenance of anesthesia usually presents little difficulty. Postoperatively, extubation should be performed under optimal circumstances for reintubation, in the event the tracheal rings have been weakened and the trachea collapses.

Of the many possible postoperative complications (nerve injuries, bleeding, and metabolic abnormalities), "thyroid storm" (discussed later), bilateral recurrent nerve trauma, and hypocalcemic tetany are the most feared. Bilateral recurrent laryngeal nerve injury (by trauma or edema) causes stridor and laryngeal obstruction due to unopposed adduction

of the vocal cords and closure of the glottic aperture. Immediate endotracheal intubation is required, usually followed by tracheostomy to ensure an adequate airway. This rare complication occurred only once in more than 30,000 thyroid operations at the Lahey Clinic. Unilateral recurrent nerve injury often goes unnoticed because of compensatory overadduction of the uninvolved cord. However, we often test vocal cord function before and after this surgery by asking the patient to say "E" or "moon." Unilateral nerve injury is characterized by hoarseness, and bilateral nerve injury, by aphonia. Selective injury of adductor fibers of both recurrent laryngeal nerves leaves the abductor muscles relatively unopposed, and pulmonary aspiration is a risk. Selective injury of abductor fibers leaves the adductor muscles relatively unopposed, and airway obstruction can occur. Bullous glottic edema, an additional cause of postoperative respiratory compromise, has no specific cause or known preventive measure.

The intimate involvement of the parathyroid gland with the thyroid gland can result in inadvertent hypocalcemia during surgery for thyroid disease. Complications relating to hypocalcemia are discussed in the later section, *Hypocalcemia*.

Because postoperative hematoma can compromise the airway, neck dressings and wound dressings are placed in a crossing fashion (rather than vertically or horizontally) and should be examined for evidence of bleeding before a patient is discharged from the recovery room.

Thyroid Storm

Thyroid storm is the name for the clinical diagnosis of a life-threatening illness in a patient whose hyperthyroidism has been severely exacerbated by illness or operation. Thyroid storm is manifested by hyperpyrexia, tachycardia, and striking alterations in consciousness. [191] Thyroid storm can thus present very similarly to malignant hyperthermia, pheochromocytoma, or the neuroleptic malignant syndrome. [150] No laboratory tests are diagnostic of thyroid storm, and the precipitating (nonthyroidal) cause is the major determinant of survival. Therapy can include blocking the synthesis of thyroid hormones by administering antithyroid drugs, blocking the release of preformed hormone with iodine, meticulous attention to hydration and supportive therapy, and correcting the precipitating cause. Blocking the

sympathetic nervous system with reserpine, guanethidine, or alpha- and beta-receptor antagonists may be exceedingly hazardous and requires skillful management and constant monitoring of the critically ill patient.

Hypothyroidism

Hypothyroidism is a common disease, occurring in 5 percent of a large population in Great Britain, in 3 to 6 percent of a healthy older population in Massachusetts, and in 4.5 percent of a medical clinic population in Switzerland. [192] [193] Usually hypothyroidism is subclinical, serum concentrations of thyroid hormones are in the normal range, and only serum TSH levels are elevated. The normal range of TSH being 0.3 to 4.5 mU/L, TSH values of 5 to 15 mU/L are characteristic of this entity. [193] In such cases, hypothyroidism may have little or no perioperative significance. However, a recent retrospective study of 59 mildly hypothyroid patients found that more hypothyroid patients than control subjects required prolonged postoperative intubation (9 of 59 versus 4 of 59) and had significant electrolyte imbalances (3 of 59 versus 1 of 59) and bleeding complications (4 of 59 versus 0 of 59). [194] Because only a small number of charts were examined, these differences did not reach statistical significance. In another study, a high percentage of patients with a history of subclinical hypothyroidism later developed overt hypothyroidism. [195] Thus, a prior history of subclinical hypothyroidism may indicate the need to search for, and be concerned about, the possibility of overt hypothyroidism.

In the less frequent occurrences of overt hypothyroidism, relative lack of thyroid hormone results in slow mental functioning, slow movement, dry skin, arthralgias, carpal tunnel syndrome, periorbital edema, intolerance to cold, depression of the ventilatory responses to hypoxia and hypercarbia, [196] impaired clearance of free water with or without hyponatremia, "hung-up reflexes," slow gastric emptying, and bradycardia. In extreme cases, cardiomegaly, heart failure, and pericardial pleural effusions manifest as fatigue, dyspnea, and orthopnea. [197] Hypothyroidism is often associated with amyloidosis, which may produce an enlarged tongue, abnormalities of the cardiac conduction system, and renal disease. Hypothyroidism decreases anesthetic requirement slightly. [198] The tongue may be enlarged in the hypothyroid patient even in the absence of amyloidosis, and this may hamper endotracheal intubation.

A rising TSH level is a most sensitive indicator of failing thyroid function. Ideal preoperative management of hypothyroidism consists of restoring normal thyroid status: I routinely administer the normal dose of T_3 or T_4 the morning of surgery, even though these drugs have long half-lives (1.4-10 d). Reduced gastrointestinal absorption of levothyroxine may occur with coadministration of cholestyramine or aluminum hydroxide, iron, a high-bran meal, or sucralfate or colestipol. For patients with myxedema coma requiring emergency surgery, T_3 can be given intravenously (with fear of precipitating myocardial ischemia, however) while supportive therapy is undertaken to restore normal intravascular fluid volume, body temperature, cardiac function, respiratory function, and electrolyte balance.

Treating hypothyroid patients having symptomatic coronary artery disease poses special problems and may require compromises in the general practice of preoperatively restoring euthyroidism with drugs. [197] Although both T_4 and esmolol may be given, adequate amelioration of both ischemic heart disease and hypothyroidism may be difficult to achieve. The need for thyroid therapy must be balanced against the risk of aggravating anginal symptoms. One review suggested early consideration for coronary artery revascularization. [199] It advocated initiating thyroid replacement therapy in the ICU soon after the patient's arrival from the operating room and myocardial revascularization surgery. However, several deaths due to arrhythmia and CHF as well as cardiogenic shock with infarction have occurred while patients who were not given thyroid therapy were awaiting surgery. Thus, there is need for consideration of true emergency coronary artery revascularization in patients having

both severe coronary artery disease and significant hypothyroidism.

In hypothyroidism, respiratory control mechanisms do not function normally. [196] However, the response to hypoxia and hypercarbia and the clearance of free water become normal with thyroid replacement therapy. [196] [197] Drug metabolism is anecdotally reported to be slowed, and awakening times from sedatives are reported to be prolonged during hypothyroidism. However, no formal study of the pharmacokinetics and pharmacodynamics of sedatives or anesthetic agents has been published. These concerns disappear when thyroid function is normalized preoperatively. Addison disease (with its relative steroid deficiency) is more common in hypothyroidism, and some endocrinologists routinely treat noniatrogenic hypothyroid patients with stress doses of steroids perioperatively, as both conditions are commonly caused by autoimmune responses. The possibility that this steroid deficiency exists should be considered if the patient becomes hypotensive perioperatively. Body heat mechanisms are inadequate in hypothyroid patients, and temperature should be monitored and maintained, especially in patients requiring emergency surgery. Because there is an increased incidence of myasthenia gravis in hypothyroid patients, it may be advisable to use a peripheral nerve stimulator to guide administration of muscle relaxants (Ch. 36) .

Thyroid Nodules and Carcinoma

Identifying malignancy in a solitary thyroid nodule is a difficult and important procedure. Male patients and patients with previous radiation to the head and neck have an increased likelihood of malignant disease in their nodules. Often, needle biopsy and scanning are sufficient for the diagnosis, but occasionally an excisional biopsy is needed. Papillary carcinoma accounts for more than 70 percent of all thyroid carcinomas. Simple excision of lymph node metastases appears to be as efficacious for patient survival as are radical neck procedures. Follicular carcinoma accounts for about 15 percent of thyroid carcinomas, is more aggressive, and has a less favorable prognosis.

Medullary carcinoma is the most aggressive form of thyroid carcinoma. It is associated with a familial incidence of pheochromocytoma, as are parathyroid adenomas. For this reason, a history might be obtained for patients who have a surgical scar in the thyroid region, so that the possibility of occult pheochromocytoma can be ruled out.

Disorders of Calcium Metabolism

The three substances that regulate the serum concentrations of calcium, phosphorus, and magnesium--parathyroid hormone (parathyrin, PTH), calcitonin, and vitamin D--act on bone, kidney, and gut. PTH stimulates bone resorption and inhibits renal excretion of calcium, two conditions that lead to hypercalcemia. Calcitonin can be considered an antagonist to PTH. Through its metabolites, vitamin D aids in the absorption of calcium, phosphate, and magnesium from the gut and facilitates the bone resorptive effects of PTH. [200]

Hyperparathyroidism and Hypercalcemia

Primary hyperparathyroidism most commonly begins in the third to fifth decades of life and occurs two to three times more frequently in women than in men. Primary hyperparathyroidism usually results from enlargement of a single gland, commonly an adenoma and very rarely a carcinoma. Hypercalcemia almost always occurs.

Calcium is the chief mineral component of the body, providing structure to the skeleton and performing key roles in neural transmission, intracellular signaling, blood coagulation, and neuromuscular functioning. Ninety-nine percent of the 1,000 g of calcium present in the average human body is stored in bone. The normal total serum calcium level is 8.6 to 10.4 mg/dL, as measured in most laboratories. Fifty to sixty percent is bound to plasma proteins or is complexed with phosphate or citrate. The value is dependent on the albumin level, declining 0.8 mg/dL for each 1-g/dL drop in albumin. Calcium binding to albumin is pH dependent: binding decreases with acidic pH and increases with alkaline pH. It should be noted that serum calcium and not ionized calcium decreases with decreases in albumin levels. Although ionized calcium is the clinically significant fraction, the cost and technical difficulties of stabilizing the electrodes used for measurement have limited the available assays. Nevertheless, parathyroid hormone and vitamin D_3 work to keep the level stable within 0.1 mg/dL in any individual.

Many of the prominent symptoms of hyperparathyroidism are a result of the hypercalcemia that accompanies it. Regardless of the cause, hypercalcemia can produce any of a number of symptoms, the most prominent involving the renal, skeletal, neuromuscular, and GI systems--anorexia, vomiting, constipation, polyuria, polydipsia, lethargy, confusion, formation of renal calculi, pancreatitis, bone pain, and psychiatric abnormalities. Free intracellular calcium initiates and/or regulates muscle contraction, release of neurotransmitters, secretion of hormones, enzyme action, and energy metabolism.

Nephrolithiasis occurs in 60 to 70 percent of patients with hyperparathyroidism. Sustained hypercalcemia can result in tubular and glomerular disorders, including proximal (type II) renal tubular acidosis. Polyuria and polydipsia are common complaints.

Skeletal disorders related to hyperparathyroidism are osteitis fibrosa cystica and simple diffuse osteopenia. The rate of bone turnover is five times higher for patients with hyperparathyroidism than for normal controls. Patients may have a history of frequent fractures or complain of bone pain, the latter especially in the anterior margin of the tibia.

Because free intracellular calcium initiates or regulates muscle contraction, neurotransmitter release, hormone secretion, enzyme action, and energy metabolism, abnormalities in these end organs are often symptoms of hyperparathyroidism. Patients may experience profound muscle weakness, especially in proximal muscle groups, as well as muscle atrophy. Depression, psychomotor retardation, and memory impairment may occur. Lethargy and confusion are frequent complaints.

Peptic ulcer disease is more common in these patients than in the rest of the population. Production of gastrin and

gastric acid is increased. Anorexia, vomiting, and constipation may also be present.

Approximately one-third of all hypercalcemic patients are hypertensive; the hypertension usually resolves with successful treatment of the primary disease. Long-standing hypercalcemia can lead to calcifications in the myocardium, blood vessels, brain, and kidney. Cerebral calcifications may cause seizures, whereas renal calcifications lead to polyuria that is unresponsive to vasopressin.

The most useful confirmatory test for hyperparathyroidism is a radioimmunoassay for PTH. In fact, some surgeons follow PTH levels intraoperatively to determine if they have resected the causative adenoma. [201] In hyperparathyroid patients, the hormone levels are abnormal for a given level of calcium. The level of inorganic phosphorus in serum is usually low, but it may be within normal limits. Alkaline phosphatase is elevated if considerable skeletal involvement is present.

Glucocorticoid administration reduces the level of calcium in the blood in many other conditions that cause hypercalcemia but usually not in primary hyperparathyroidism. In sarcoidosis, multiple myeloma, vitamin D intoxication, and some malignant diseases, all of which can cause hypercalcemia, administration of glucocorticoids may lower the serum calcium through an effect on gastrointestinal absorption. This effect occurs to a lesser degree in primary hyperparathyroidism.

Hypercalcemia may also occur as a consequence of secondary hyperparathyroidism in patients who have chronic renal disease. When phosphate excretion decreases as a result of a lower nephron mass, serum calcium levels fall because of deposition of calcium and phosphate in bone. Secretion of PTH subsequently increases, whereas the fraction of phosphate excreted by each nephron increases. Eventually, the chronic intermittent hypocalcemia of chronic renal failure leads to chronically high levels of serum PTH and hyperplasia of the parathyroid glands.

What should be done for asymptomatic patients with primary hyperparathyroidism? This question has become the subject of a major controversy, for which no definitive answer exists. *Symptomatic* primary hyperparathyroidism is usually treated surgically, as is hyperparathyroidism in young patients or in patients with azotemia, bone demineralization, or chronic total calcium elevations greater than 12 mg/dL. If the patient refuses surgery, or if other illnesses make surgery inadvisable, medical management can be difficult. This difficulty occurs when hyperfunctioning parathyroid glands secrete more hormone as the serum calcium is lowered, as if the calcium set point for feedback regulation of PTH secretion had been raised.

Patients with moderate hypercalcemia who have normal renal and cardiovascular function present no special preoperative problems. The electrocardiogram can be examined preoperatively and intraoperatively for shortened PR or QT intervals (Fig. 25-7) (Figure Not Available) . Because severe hypercalcemia can result in hypovolemia, normal intravascular volume and electrolyte status should be restored before anesthesia and surgery are begun.

Management of hypercalcemia can include increasing the urinary calcium excretion by means of hydration and diuresis. Restoration of intravascular volume, augmentation of urinary sodium, excretion, and administration of diuretics

Figure 25-7 (Figure Not Available) Measurement of the QT_c interval (properly termed $Q_E T_c$ to indicate that it begins with the start of the Q wave, lasts throughout the QT interval, ends with the end of the T wave, and is corrected for heart rate). RR is the RR interval in seconds. *(From Hensel and Roizen [200])*

(furosemide is commonly employed) usually increase urinary calcium excretion substantially. Complications of these interventions include hypomagnesemia and hypokalemia.

In emergency situations, vigorous expansion of intravascular volume usually reduces serum calcium to a safe level (<14 mg/dL); administration of furosemide is also often helpful in these situations. Phosphate should be given to correct hypophosphatemia, which decreases calcium uptake into bone, increases calcium, and stimulates breakdown of bone. Hydration and diuresis, accompanied by phosphate repletion, suffice in the management of most hypercalcemic patients. If additional intervention is needed, glucocorticoids, mithramycin, or calcitonin may be given. Corticosteroids inhibit further gastrointestinal absorption of calcium. Mithramycin lowers calcium levels by approximately 2 mg/dL in 36 to 48 hours through its effect on osteoclasts. Its toxic effects include thrombocytopenia, decreased levels of clotting factors, hepatotoxicity, azotemia, proteinuria, hypocalcemia, hypophosphatemia, and hypokalemia. Most of these side effects can be reversed simply by discontinuation of the drug. Consultation with an endocrinologist or oncologist is advisable before mithramycin is given, because it has a narrow therapeutic-to-toxic ratio.

Calcitonin lowers serum calcium levels through direct inhibition of bone resorption. It can decrease serum calcium levels within minutes after its intravenous administration. Calcitonin is less effective than phosphate or mithramycin, however, for patients with hypercalcemia caused by hyperparathyroidism. Side effects include urticaria and nausea.

It is especially important to know whether hypercalcemia has been chronic, because serious cardiac, renal, or CNS abnormalities may have resulted.

Hypocalcemia

Hypocalcemia (caused by hypoalbuminemia, hypoparathyroidism, hypomagnesemia, or chronic renal disease) is not usually accompanied by a clinically evident cardiovascular disorder. However, myocardial contractility does

vary directly with levels of blood ionized calcium, although contractility decreased only 20 percent when ionized calcium levels changed from 1.68 to 1.34 mmol/L. [202] The clinical signs of hypocalcemia are clumsiness; convulsions; laryngeal stridor; depression; muscle stiffness; paresthesia (oral and perioral); parkinsonism; tetany; Chvostek sign; dry, scaly skin, brittle nails, and coarse hair; low serum concentrations of calcium; prolonged QT intervals; soft tissue calcifications; and Trousseau sign.

Hypocalcemia delays ventricular repolarization, hence increasing the QT_c interval (normal, 0.35-0.44 seconds). With electrical systole prolonged, the ventricles may fail to respond to the next electrical impulse from the sinoatrial node, causing 2:1 heart block. Prolongation of the QT interval is a moderately reliable ECG sign of hypocalcemia, not for the population as a whole, but for the individual patient. [203] Thus, following the QT interval as corrected for heart rate (see Fig. 25-7) (Figure Not Available) is a useful but not always accurate means of monitoring hypocalcemia in any one patient. CHF may also occur with hypocalcemia, but this is rare. Because CHF in patients with coexisting heart disease is reduced in severity when calcium and magnesium ion levels are restored to normal, these levels might be normal before surgery in the patient with impaired exercise tolerance or signs of cardiovascular dysfunction. [200] [202] Sudden decreases in blood levels of ionized calcium (as with chelation therapy) can result in severe hypotension.

Patients with hypocalcemia may have seizures. These may be focal, jacksonian, petit mal, or grand mal in appearance, indistinguishable from such seizures in the

absence of hypocalcemia. Patients may also have a type of seizure called cerebral tetany, which consists of generalized tetany followed by tonic spasms. Therapy with standard anticonvulsants is ineffective and may even exacerbate these seizures (by an anti-vitamin D effect). In long-standing hypoparathyroidism, calcifications may appear above the sella, representing deposits of calcium in and around small blood vessels of the basal ganglia. These may be associated with a variety of extrapyramidal syndromes.

The most common cause of *acquired hypoparathyroidism* is surgery of the thyroid or parathyroid glands. Other causes include therapy with iodine-131, hemosiderosis, neoplasia, and granulomatous disease. *Idiopathic hypoparathyroidism* has been divided into three categories: an isolated persistent neonatal form, branchial dysembryogenesis, and multiple endocrine deficiency autoimmune candidiasis.

Pseudohypoparathyroidism and pseudopseudohypoparathyroidism are rare hereditary disorders characterized by short stature, obesity, rounded face, and shortened metacarpals. Patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia despite high serum levels of PTH. These patients have a deficient end-organ response to PTH because of abnormalities in G-protein function.

Because treatment of hypoparathyroidism is not surgical, hypoparathyroid patients who come to the operating room are those who require surgery for an unrelated condition. Their calcium, phosphate, and magnesium levels should be measured both preoperatively and postoperatively. Patients with symptomatic hypocalcemia might be treated with intravenous calcium gluconate before surgery. Initially, 10 to 20 mL of 10 percent calcium gluconate may be given at a rate of 10 mL/min. The effect on serum calcium levels is of short duration, but a continuous infusion with 10 mL/min of 10 percent calcium gluconate in 500 mL of solution over 6 hours helps keep serum calcium at adequate levels.

The objective of therapy is to bring the symptoms under control before surgery and anesthesia. For patients with chronic hypoparathyroidism, the objective is to keep the serum calcium level in the lower half of the normal range. A preoperative ECG is useful for maintaining the QT_c interval. The preoperative QT_c value may be used as a guide to the serum calcium level if rapid laboratory assessment is not possible.

The intimate involvement of the parathyroid gland with the thyroid gland can result in unintentional hypocalcemia during surgery for diseases of either organ. Because of the affinity of their bones for calcium, this relationship is crucial for patients having advanced osteitis. Internal redistribution of magnesium and/or calcium ions may occur (into "hungry bones") after parathyroidectomy, causing either hypomagnesemia or hypocalcemia, or both. Because the tendency to tetany increases with alkalosis, hyperventilation is usually assiduously avoided. The most prominent manifestations of acute hypocalcemia are distal paresthesias and muscle spasm (tetany). Potentially fatal complications of severe hypocalcemia include laryngeal spasm and hypocalcemic seizures. The clinical sequelae of magnesium deficiency include cardiac arrhythmias (principally ventricular tachyarrhythmias), hypocalcemic tetany, and neuromuscular irritability independent of hypocalcemia (tremors, twitching, asterixis, and seizures).

In addition to monitoring total serum calcium or ionized calcium postoperatively, one can test for Chvostek sign and Trousseau sign. (Note that serum calcium, and not ionized calcium, is dependent on albumin level, declining about 0.8 mg/dL for each 1-g/dL drop in serum albumin level.) Because Chvostek sign can be elicited in 10 to 15 percent of patients who are not hypocalcemic, an attempt should be made to elicit it preoperatively to ensure its appearance is meaningful. Chvostek sign is a contracture of the facial muscles produced by tapping the ipsilateral facial nerves at the angle of the jaw. Trousseau sign is elicited by applying a blood pressure cuff at a level slightly above the systolic level for a few minutes. The resulting carpopedal spasm, with contractions of the fingers and inability to open the hand, stems from the increased muscle irritability in hypocalcemic states, aggravated by ischemia produced by the blood pressure cuff.

Osteoporosis

Fifty percent of women older than 65 years suffer an osteoporotic fracture. (Because men are living longer, osteoporosis will probably become an increasing problem for them, too.) Osteoporosis is the thinning of bone that causes low bone mass and thus weakening of this living tissue to the point of breakage. Known risk factors include age, relative lifetime estrogen deficiency (late menarche, amenorrhea, early menopause, nulliparity), deficiency of dietary calcium, tobacco usage, increased aerobic exercise in combination with decreased weight-bearing exercise, decreased weight-bearing

exercise by itself, soft drink usage, and Asian or caucasian ancestry. Although therapy for osteoporosis (use of biphosphates, bone mineral depositors, weight-bearing exercises, calcium, vitamin D, estrogen--and now designer estrogens that may be useful for men, such as Evista) does not have major known implications for anesthesia care, bone fractures in such patients have occurred on movement to and from an operating table. Thus, the precautions mentioned earlier for hyperparathyroid patients relative to self-positioning and careful positioning may be useful.

Pituitary Abnormalities

Anterior Pituitary Hypersecretion

The anterior pituitary gland consists of five identifiable types of secretory cells (and the hormones they secrete): somatotrophs (growth hormone [GH]), corticotrophs (ACTH), lactotrophs (prolactin), gonadotrophs (luteinizing hormone [LH] and follicle-stimulating hormone), and thyrotrophs (TSH). The secretion of these pituitary hormones is regulated largely by a negative feedback loop by hypothalamic regulatory hormones and by signals that originate from the target site of pituitary action. Six hypothalamic hormones have been characterized: dopamine, the prolactin-inhibiting hormone; somatostatin, the GH release-inhibiting hormone; GH-releasing hormone; corticotropin-releasing hormone; gonadotropin-releasing hormone (or LH-releasing hormone); and thyrotropin-releasing hormone. Most pituitary tumors (>60 percent) are hypersecretory and are classified according to the excess production of a specific anterior pituitary hormone.

The three most common disorders of pituitary hypersecretion are those related to excesses of prolactin (amenorrhea, galactorrhea, and infertility), ACTH (Cushing syndrome), or GH (acromegaly). In addition to knowing the pathophysiologic processes of the disease involved, the anesthesiologist must determine whether the patient recently underwent air pneumoencephalography. If so, nitrous oxide should not be used; this practice lessens the risk of intracranial hypertension from gas collection. CT or MRI scanning of the sella has largely replaced neuroencephalography, but the latter is still performed.

Acromegaly is a syndrome that presents with characteristic facies, weakness, enlargement of the hands (often to the point of rendering the usual oximeter probes difficult to use) and feet, thickening of the tongue (often to the point of making endotracheal intubation difficult), and enlargement of the nose and mandible with spreading of the teeth (often to the point of requiring larger than normal laryngoscopic blades). [204] [20] The patient may even appear myxedematous. Other findings include abnormal glucose tolerance and osteoporosis. The most specific test for acromegaly is measurement of GH before and after glucose administration. The typical acromegalic has very elevated fasting levels of GH (usually >10 g/mL), and the levels do not change appreciably after oral administration of glucose. In the normal state, glucose markedly suppresses the GH level. A few patients with active acromegaly have normal levels of fasting GH, and GH levels are not suppressed by glucose. In addition, an elevated plasma insulin-like growth factor-I (IGF-I), also known as somatomedin-C, is pathognomonic of growth hormone excess. The drug L-dopa, which normally causes an elevation of GH in normal subjects, in the acromegalic either has no effect or lowers GH levels. More than 99 percent of cases of acromegaly are attributable to pituitary adenoma. Thus, the primary treatment of acromegaly is trans-sphenoidal surgery. If the pituitary tumor is not totally removed, patients are often offered external pituitary irradiation. In the case of suprasellar extension, conventional transfrontal hypophysectomy is often employed. The dopaminergic agonist bromocriptine can lower GH levels, but long-term follow-up with this drug is not favorable. Octreotide, a long-acting analogue of somatostatin, is an effective palliation in 50 percent of patients.

The effects of excessive GH stem from both direct actions of the hormone on tissue and stimulation of the production of somatomedins. Excessive GH often results in retention of sodium and potassium, inhibition of the peripheral action of insulin (which can result in diabetes mellitus), and premature atherosclerosis (often associated with cardiomegaly). Exertional dyspnea may be related to either heart failure or respiratory insufficiency due to kyphoscoliosis. Cardiac arrhythmias are common. The incidence of these problems in elderly men now being treated with or receiving GH (recombinant) for the possible improvement of functional status is not known. Preoperative evaluation of the patient who has acromegaly or who is receiving GH might begin by determining whether significant cardiac, hypertensive, pulmonary, or diabetic problems exist. If so, preoperative evaluation should proceed along the lines described in sections discussing those topics. In addition, difficulty with endotracheal intubation should be anticipated in the acromegalic patient; lateral neck films or CT scans of the neck and direct or indirect visualization can identify the patient who has subglottic stenosis or an enlarged tongue, mandibles, epiglottis, or vocal cords. [205] [206] If placement of an arterial line is necessary, a brachial or

femoral site may be preferable to a radial site. [207]

Prolactin has been one of the most interesting markers to identify patients with pituitary tumors. Elevated prolactin levels are often but not invariably associated with galactorrhea. Females commonly present with amenorrhea, and males present with impotence. Optimal therapy for prolactin-secreting tumors is now believed to be the dopamine agonist bromocriptine. This drug, which is extremely effective in controlling the prolactin level and restoring gonadotropin function, is used when fertility is desired. When normal menses, contraception, and skeletal integrity are desired, birth control pills are the treatment. [208] The side effects of bromocriptine include orthostatic hypotension, gastroparesis (possible increased risk of aspiration), constipation, and nasal congestion (possible need for oral intubation). [208] With large prolactin-secreting tumors (macroadenomas), loss of other pituitary function is common, and evaluation of thyroid and adrenocortical status is indicated. Preoperative preparation of patients with Cushing syndrome is discussed in the section on ACTH excess.

Anterior Pituitary Hypofunction

Anterior pituitary hypofunction results in deficiency of one or more of the following hormones: GH, TSH, ACTH,

prolactin, or gonadotropin. Preoperative preparation of those patients who are chronically deficient in ACTH and TSH was discussed previously. No special preoperative preparation is required for the patient deficient in prolactin or gonadotropin; deficiency in GH can result in atrophy of cardiac muscle, a condition that may necessitate preoperative cardiac evaluation. However, anesthetic problems have not been documented in patients with isolated GH deficiency. Acute deficiencies are another matter.

Acute pituitary deficiency is often caused by bleeding into a pituitary tumor. In surgical specimens of resected adenomas, as many as 25 percent show evidence of hemorrhage. Patients with this condition often present with acute headache, visual loss, nausea or vomiting, ocular palsies, disturbances of consciousness, fever, vertigo, or hemiparesis. In such patients, rapid transsphenoidal decompression should be accompanied by consideration of replacement therapy, including glucocorticoids and treatment for increased intracranial pressure.

The obstetrical anesthesiologist is often aware of these pituitary failure problems: Sheehan's syndrome is the clinical manifestation of pituitary infarction associated with hypotension after or during obstetric hemorrhage. Conditions that strongly suggest this diagnosis are failure to start postpartum lactation, increasing fatigue, cold intolerance, and especially hypotension unresponsive to volume replacement and pressors.

Posterior Pituitary Hormone Excess and Deficiency

The secretion of vasopressin, or antidiuretic hormone (ADH), is increased by increased serum osmolality or the presence of hypotension. Inappropriate secretion of vasopressin, without relation to serum osmolality, results in hyponatremia and fluid retention. This inappropriate secretion can result from a variety of CNS lesions; from drugs such as nicotine, narcotics, chlorpropamide, clofibrate, vincristine, vinblastine, and cyclophosphamide; and from pulmonary infections, hypothyroidism, adrenal insufficiency, and ectopic production from tumors. Preoperative management of the surgical patient with inappropriate secretion of vasopressin includes appropriate treatment of the causative disorders and restriction of water. Occasionally, drugs that inhibit the renal response to ADH (e.g., lithium or demeclocycline) should be administered preoperatively to restore normal intravascular volume and electrolyte status.

Most of the clinical features associated with the syndrome of inappropriate ADH (SIADH) secretion are related to hyponatremia and the resulting brain edema; these features include weight gain, weakness, lethargy, mental confusion, obtundation, and disordered reflexes and may progress, finally, to convulsions and coma. This form of edema rarely leads to hypertension.

SIADH should be suspected in any patient with hyponatremia who excretes urine that is hypertonic relative to plasma. The following laboratory findings further support the diagnosis:

1. Urinary sodium >20 mEq/L
2. Low serum levels of BUN, creatinine, uric acid, and albumin
3. Serum sodium <130 mEq/L
4. Plasma osmolality <270 mOsm/L
5. Urine hypertonic relative to plasma

Noting the response to water loading is a useful way of evaluating the patient with hyponatremia. Patients with SIADH are unable to excrete dilute urine even after water loading. Assay of ADH in blood can confirm the diagnosis. Too vigorous treatment of chronic hyponatremia can result in disabling demyelination. [209] [210] The increase in serum sodium should not be greater than 1 mEq/L/h. [209] [210] (See the discussion of hyponatremia in the later section, *Electrolyte Disorders*.)

Patients with mild to moderate symptoms of water intoxication can be treated with restriction of fluid intake to about 500 to 1,000 mL/d. Patients with severe water intoxication and CNS symptoms may need vigorous treatment, with intravenous administration of 200 to 300 mL of 5 percent saline solution over several hours, followed by fluid restriction.

Treatment should be directed at the underlying problem. If SIADH is drug induced, the drug should be withdrawn. Inflammation should be treated with appropriate measures, and neoplasms should be managed with surgical resection, irradiation, or chemotherapy, whichever is indicated.

No drugs are available that can suppress release of ADH from the neurohypophysis or from a tumor. Dilantin and narcotic antagonists such as naloxone and butorphanol have some inhibiting effect on physiologic ADH release but are clinically ineffective in patients with SIADH. Drugs blocking the effect of ADH on renal tubules include lithium, which is rarely used because its toxicity often outweighs its benefits, and demethylchlortetracycline in doses of 900 to 1,200 mg/d. The latter drug interferes with the ability of the renal tubules to concentrate urine, causing excretion of isotonic or hypotonic urine and thereby lessening hyponatremia. Demethylchlortetracycline can be used for ambulatory patients with SIADH when it is difficult to restrict fluids.

When a patient with SIADH comes to the operating room for any surgical procedure, fluids are managed by measuring the central volume status by central venous pressure, pulmonary artery lines, or cross-sectional left ventricular area at end-diastole on transesophageal echocardiography, and by frequent assays of urine osmolarity, plasma osmolarity, and serum sodium, including during the period immediately after surgery. Despite the common impression that SIADH is frequently seen in elderly patients in the postoperative period, studies have shown that the patient's age and the type of anesthetic used have no bearing on the postoperative development of SIADH. It is not unusual to see many patients in the neurosurgical intensive care unit suffering from this syndrome. The diagnosis is usually one of exclusion. Patients with SIADH usually require only fluid restriction; very rarely is hypertonic saline needed.

Lack of ADH, which results in diabetes insipidus, is caused by pituitary disease, brain tumors, infiltrative diseases such as sarcoidosis, head trauma (trauma after neurosurgery), or lack of renal response to ADH. The last can occur with such diverse causes as hypokalemia, hypercalcemia, sickle cell anemia, obstructive uropathy, or renal insufficiency. Preoperative treatment of diabetes insipidus consists of restoring normal intravascular volume by replacing urinary losses, by using nasal desmopressin, and by giving daily fluid requirements intravenously.

Perioperative management of patients with diabetes insipidus is based on the extent of the ADH deficiency. Management of a patient with complete diabetes insipidus and a total lack of ADH usually does not present any major problem as long as side effects of the drug are avoided and the presence of the condition is known before surgery. Just before surgery, the patient is given the usual dose of desmopressin acetate intranasally or an intravenous bolus of 100 mU of aqueous vasopressin, followed by constant infusion of 100 to 200 mU/h. [211] The dose is usually adjusted to permit daily breakthrough polyuria that avoids the iatrogenic syndrome of SIADH. We have found it useful to continue that dosing regimen perioperatively in all ambulatory patients who can take fluid orally in the postoperative period. All the

intravenous fluids given intraoperatively should be isotonic, to reduce the risk of water depletion and hypernatremia. Plasma osmolality should be measured every hour, both intraoperatively and immediately after surgery. If plasma osmolality rises well above 290 mOsm/L, hypotonic fluids can be administered; the rate of the intraoperative vasopressin infusion can be increased to more than 200 mU/h.

For patients who have a partial deficiency of ADH, it is not necessary to use aqueous vasopressin perioperatively unless plasma osmolality rises above 290 mOsm/L. Nonosmotic stimuli, for example, volume depletion, and stress of surgery usually cause the release of large quantities of ADH perioperatively. Consequently, these patients require only frequent monitoring of plasma osmolality during this period.

Because of side effects, the dose of vasopressin should be limited to that necessary for control of diuresis. [212] The oxytoxic and coronary artery-constricting properties of vasopressin make this limit especially applicable to patients who are pregnant or who have coronary artery disease. [210]

Another problem for anesthesiologists is the care of patients who come to the operating room with a vasopressin drip for treatment of bleeding from esophageal varices. This treatment is less common since the advent of laser therapy for varices. However, when vasopressin is given, the vasoconstrictive effect of vasopressin on the splanchnic vasculature is used to decrease bleeding. Such patients are often volume depleted and may have concomitant coronary artery disease. Because vasopressin has been shown to decrease oxygen availability markedly, primarily because of a decreased stroke volume and heart rate, monitoring of tissue oxygen delivery may be useful. In 1982, Nikolic and Singh [213] described a patient with a history of angina pectoris who received a combination of cimetidine and vasopressin for esophageal varices. Bradyarrhythmias and AV block occurred, necessitating placement of a pacemaker. On two occasions, discontinuation of either of these drugs alleviated the symptoms. This effect indicates that the combination of cimetidine and vasopressin could be deleterious to the heart because of the combined negative inotropic and arrhythmogenic effects of the two drugs.

DISEASES INVOLVING THE CARDIOVASCULAR SYSTEM

Hypertension

Analysis of the perioperative treatment of hypertension is important because of the prevalence of the condition (25% of the general population in the United States), the great risk in perioperative care of the hypertensive patient (Ch. 22) , and the high cost of unnecessary delays in surgery. The controversy centers around two issues. Does inadequate control of hypertension result in complications that could be prevented with some control? How much control of blood pressure is needed, and for how long? That is, does overzealous control just create unnecessary postponements of elective surgery or, worse, predispose the patient to exaggerated adverse drug reactions and greater hemodynamic instability than not-so-zealous control?

Because of the controversy regarding the appropriateness of preoperative treatment of hypertension, the original articles that stimulated this controversy are evaluated here. Smithwick and Thompson [214] and Brown [215] reported overall mortality rates of 2.5 to 3.6 percent, respectively, for hypertensive patients undergoing sympathectomy between 1935 and 1947. These values were five or six times higher than values for normotensive patients undergoing similar operations. Obviously, these patients were not randomly assigned to treatment or nontreatment groups, and no attempt was made to ensure that end-organ disease was equivalent for the two groups. In 1929, Sprague [216] analyzed the records of 75 patients with hypertensive cardiac disease and found that 24 (32%) died during or shortly after operations employing general anesthesia.

In the early 20th century, severely ill patients did not do well perioperatively; however, whether *pre*operative treatment would have improved surgical outcome is unknown. The evolution of drug therapy for hypertension was hampered in the late 1950s and early 1960s by the publication of case reports of severe hypotension and bradycardia in patients given antihypertensive drugs before surgery. The tailoring of anesthetic dose to patient condition and the realization that sympatholytic antihypertensive drugs decreased anesthetic requirement [217] caused such case reports to disappear from the literature.

A more recent prospective controlled double-blind study by the Department of Veterans Affairs provided a rationale for lifelong treatment of hypertension: Such treatment decreased the incidence of stroke, CHF, and progression to renal insufficiency and to accelerated (malignant) hypertension [218] [219] (Table 25-14) . Many other studies have confirmed the beneficial effect of treating hypertension, even for patients with diastolic pressures of 90 to 104 mm Hg. [220] [221] [222] One study has indicated caution in adding

TABLE 25-14 -- Effect on Morbidity of Treating Hypertension (Average Diastolic Blood Pressure 90-114 mm Hg)

	CONTROL GROUP	TREATMENT GROUP
5-y morbidity	55%	18%
Death	19/194	8/186
Terminating CHF	5	0
Terminating stroke	6	0
All CHF	11	0
All strokes	20	5

Abbreviation: CHF, congestive heart failure

Data from Veterans Affairs Cooperative Study Group on Antihypertensive Agents [219]

TABLE 25-15 -- Effect on Morbidity of Treating Isolated Systolic Hypertension [a]

(Not Available)

Modified from the Systolic Hypertension in the Elderly Program (SHEP) study [224]

[a] Systolic blood pressure >160 mm Hg

diuretics to therapeutic limits in therapy for the patient with an abnormal ECG whose blood pressure does not decrease after administration of the usual doses of diuretic drugs (see the section, *Hypokalemia,* which follows). [223] Substantial benefit has also been shown for treatment of isolated systolic hypertension (systolic blood pressure [BP] >160 mm Hg and diastolic BP <90 mm Hg) in the elderly [224] (Table 25-15) (Table Not Available) and in diabetics. [225] However, overvigorous treatment of hypertension can result in a "J curve" for morbidity, especially for patients with coronary artery stenosis (i.e., if BP is reduced too much, morbidity starts to increase again) [221] [226] (Fig. 25-8) (Figure Not Available) . Other studies in experimental models of hypertension and in humans indicate even more than prophylactic benefit: Treatment results in a regression of cardiac hypertrophy and in autonomic nerve alterations of hypertension. U.S. government statistics reveal significant decreases (>50%) in the death rate from stroke from 1969

Figure 25-8 (Figure Not Available) Studies that stratified cardiac events by treated diastolic blood pressure levels. Ischemic Heart Disease Events is a combination of morbidity and mortality. Summary curve was calculated using a systematic decrease of 10 mm Hg in diastolic blood pressure levels. Surrounding dashed curves show the 95 percent confidence intervals. *(From Farnett et al [226])*

to 1992 and a 40 percent overall decrease in age-adjusted cardiovascular mortality. Deaths related to hypertensive cardiovascular disease and to myocardial infarction have decreased dramatically since 1974, accounting for most of the decrease in cardiovascular death in this time period. This decrease (at least in localized communities) correlates with successful control of hypertension. This strong evidence from Veterans Affairs studies and the epidemiologic data have led to the belief that all patients with a diastolic blood pressure above 90 mm Hg should be treated, regardless of age.

Although the median blood pressure in the United States is 129/86 mm Hg, the ideal blood pressure for the prevention of arterial aging is 115/76 mm Hg. [22] Furthermore, as the Framingham studies have shown, we gain approximately 20 mm Hg in systolic BP and 10 mm Hg in diastolic BP as we age from 30 to 65. This is important because every 10-mm Hg increase in systolic BP and every 8-mm Hg increase in diastolic BP age the arteries the equivalent of 4 years. Therefore,

preventing these increases would make the average 65-year-old person only 52 years old physiologically. [22] If 115/76 mm Hg is the ideal, why, then, do we accept 130 or even 140/85 or 90 mm Hg before treatment? Arterial aging could be greatly mitigated if we advocated a more aggressive approach to treating blood pressure that exceeds 115/76 mm Hg.

The Framingham data also indicate that one should prevent elevations in both systolic and diastolic BP. [221] In fact, investigations of the Framingham study show there is nothing to suggest a greater impact of diastolic BP on aging of the arteries.

However, the question is, should elective surgery be postponed and patient and physician schedules disrupted so that treatment can be instituted and stabilized, even for systolic hypertension alone? Several schools of thought exist, the two oldest represented by the study conducted by Prys-Roberts et al [227] in 1971 and by Goldman and Caldera [228] in 1979. Several other studies (Bedford and Feinstein, [229] Asiddao et al, [230] Stone et al, [165] Flacke et al, [167] Ghignone et al, [168] Tuman et al, [172] Ellis et al, [231] Charlson et al, [8] Mangano et al, [166] [232] Stone et al, [233] Wolfsthal, [234] and Pasternack et al [235]) also have been cited. Unfortunately, each of these studies has deficiencies that prevent the establishment of a definitive answer to this question. However, I now believe that the weight of evidence from these studies taken together compels an answer.

Critical Analysis of the Data of Prys-Roberts and Colleagues

The followers of Prys-Roberts et al [227] believe that preoperative treatment of hypertension lowers the incidence of perioperative morbidity and mortality. This study compared three groups: a control group consisting of seven elderly normotensive patients having an average mean arterial BP of 89.5 mm Hg; a group of seven hypertensive patients whose high BP was not treated preoperatively (four were being treated not for high BP but for its complications) who had an average mean arterial BP (MABP) of 129.5 mm Hg; and a group of 15 hypertensive patients whose high BP was treated preoperatively and who had an average MABP of

129.9 mm Hg. The same doses of thiopental and halothane were given to all groups of patients, and measurements were made of absolute change in MABP, cardiac arrhythmias, and ECG evidence of ischemia. Patients with untreated hypertension had the greatest absolute fall in BP and the highest percentage of arrhythmias and ischemia.

Several flaws in study design create serious doubt as to whether the relationship between preoperative treatment of hypertension and perioperative morbidity has been evaluated objectively in this investigation. First, the wisdom of administering the same dose of anesthetic to both groups of patients should be questioned. If the anesthetic dose had been titrated to the anesthetic needs of the patient, would the results have been different? Second, BP did not differ between the treated and untreated groups. In addition, at least four of the seven hypertensive patients who were not treated for high BP were "sicker" than any of the hypertensive patients who were treated. Why some patients were treated for hypertension and others were not was not explained; selection definitely did not occur on a random basis. Finally, it was not stated whether surgery was similar for all groups.

This study does indicate that patients who are sick preoperatively have more problems perioperatively than do healthy patients. This has been shown many times. (See refs. [12] and [236] for reviews.) However, from these data, the efficacy of preoperative treatment of hypertension cannot be established. This study and others by the same group provide useful data regarding the hemodynamic consequences of anesthesia when a standard technique is used on patients who have untreated hypertension.

Critical Analysis of the Data of Goldman and Caldera

The school of thought represented by Goldman and Caldera [228] advocates that preoperative treatment of hypertension does not affect outcome. Goldman and Caldera state that their study is a prospective one. However, the only prospective aspect of their study appears to be that patients were examined preoperatively. These investigators compared surgical outcome for three groups: sick hypertensive patients whose high BP was treated preoperatively; less sick hypertensive patients whose high BP was "undertreated" preoperatively; and less sick, only moderately hypertensive patients who received no treatment preoperatively. No differences in outcome between groups were found.

This study has several flaws in design. Patients were not randomly assigned regarding preoperative treatment, undertreatment, or nontreatment of hypertension. Also, sicker patients were allocated to the treated hypertensive group (Table 25-16) , thus biasing study results toward favoring nontreatment of hypertension.

Other flaws concern statistical methods. Only 117 hypertensive patients were studied, and only 34 of the 117 patients who were hypertensive at surgery had diastolic BP of at least 100 mm Hg (see Table 25-14) . If morbid complications were assumed to be 20 percent in the untreated group, and if treatment was assumed to reduce morbidity 50 percent, then, by power analysis, [237] Goldman and Caldera [228] would have had to compare approximately 237 patients to have an 80 percent chance of finding a difference at a confidence level of 0.05 percent. If a lower rate of morbidity in the untreated group (e.g., 15%) and a lesser reduction in the rate of morbidity (e.g., 33%) were assumed, substantially more patients would have to be studied to be 80 percent sure no difference occurred, even at the 0.05 confidence level. For example, if morbid complications were assumed to be 15 percent in the untreated group, and if treatment were assumed to reduce morbidity 33 percent, 764 patients would have had to be studied in each group to be 80 percent certain no difference occurred, the confidence level being 0.05. These major flaws in study design make it impossible to ascertain whether preoperative treatment of hypertension decreased perioperative morbidity.

Critical Analysis of the Data of Bedford and Feinstein and of Wolfsthal

Bedford and Feinstein [229] and Wolfsthal [234] and their supporters believe that instability of BP is the condition most frequently predicting morbid perioperative complications. In the Bedford-Feinstein study, [229] the responses of three groups to rapid-sequence induction were compared prospectively. Patients were allocated to groups based on the initial admitting room BPs and the average presurgical

TABLE 25-16 -- Analysis of Treatment Groups Used by Goldman and Caldera [228] to Evaluate Effectiveness of Preoperative Treatment of Hypertension in Surgical Patients

PREOPERATIVELY HYPERTENSIVE PATIENTS	n	PREOPERATIVELY			
		DIASTOLIC BP > 100 MM HG (n)	*BUN > 30 MG % (n)*	*ANGINA OR CHF (%)*	*TIAS (%)*
Treated successfully [a]	79	0	8	47	13
Treated unsuccessfully	40	34	13	40	18
Not treated	77		1	26	4

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; CHF, congestive heart failure; TIAs, transient ischemic attacks

[a] These data demonstrate that the patients who were the sickest before surgery were allocated to this group, thereby biasing results toward nontreatment.

in-hospital BP: group I (30 patients) had a BP of less than 140/90 mm Hg during and after admission (normal BP group); group II (12 patients) had a BP of greater than 140/90 mm Hg on admission but less than 140/90 mm Hg during hospitalization (labile BP group); group III (eight patients) had a BP greater than 140/90 mm Hg during and after admission (hypertensive BP group). Whether any of the patients in the labile or hypertensive BP groups were under treatment for hypertension, had end-organ complications of hypertension (e.g., ischemic heart disease), or were told they were hypertensive was not stated. Patients were given standard (i.e., not tailored to the patient's condition) premedication (morphine, diazepam, and atropine) and a standard rapid-sequence induction (thiopental, 3-4 mg/kg intravenously;

succinylcholine, 1.5 mg/kg intravenously). After intubation, heart rate and BP increased significantly in all three groups. The increase was greatest in the labile BP group, rising from a mean BP of 102 ± 5 to 152 ± 4 mm Hg. Eight of 12 patients in that group required additional thiopental and/or vasodilating drugs to normalize BP, and 2 of 12 developed transient ST segment depression in lead II. No patient in either of the other two groups required similar treatment or had ST segment changes as seen on ECG.

Thus, this study does indicate that patients with labile BP may require more careful titration of anesthetic drugs than those whose BP is either normal or high but stable. However, whether the results would have been different if the anesthetic had been titrated to the anesthetic needs of the individual patient is not known. Nor do we know whether the groups had equivalent baseline end-organ disease. We do not even know how many patients were being treated for hypertension. Similar deficiencies are present in retrospective analyses of the effect of hypertension on perioperative hemodynamic lability (Wolfsthal [234]) and perioperative outcomes (Mangano studies [7] [232] and Charlson et al [8] [238] [239] [240]). Although such deficiencies mean that we do not know whether preoperative treatment lessened the perioperative risk for those particular hypertensive patients, the deficiencies do not decrease the importance of preoperative hypertension as a marker predicting increased perioperative cardiovascular and renal risk.

Critical Analysis of the Data of Asiddao and Colleagues

The study conducted by Asiddao et al [230] is cited by those advocating preoperative treatment of hypertension. In this study, records of 166 cases of unilateral carotid endarterectomy were reviewed to investigate the association of preoperative and intraoperative factors with perioperative complications. Asiddao and coworkers found that postoperative hypertension (i.e., systolic BP >200 mm Hg or diastolic BP >110 mm Hg) and transient postoperative neurologic deficits occurred more commonly in the 21 patients with poor preoperative control of BP (BP >170/95 mm Hg) (52 and 23.8%, respectively) than in the 79 patients with adequate BP control (BP <170/95 mm Hg) (35 and 2.5%, respectively) or in the 66 normotensive patients (17 and 1.5%, respectively). No statistically significant difference was found between the groups regarding permanent neurologic sequelae of surgery or the rate of myocardial ischemia.

The study by Asiddao et al [230] does not indicate whether postoperative hypertension caused the transient neurologic deficits or whether these deficits resulted in a compensation of postoperative hypertension. We also do not know whether the three groups were equivalent in end-organ manifestations of preoperative disease. Nor does the study indicate why BP was not controlled preoperatively in some patients or whether preoperative normalization of high BP would have reduced the rate of postoperative complications. This study does tell us that patients who have high BP before surgery are likely to have high BP after surgery.

Critical Analysis of the Data of Stone and Colleagues

Stone et al [165] [233] gave one of a variety of beta-adrenergic- blocking drugs or a placebo as preoperative medication to a group of mildly hypertensive patients, and, knowing to which group the patients were assigned, the investigators then looked for ischemic episodes. They observed a significantly greater incidence of brief ischemic episodes during induction and emergence in the untreated patients than in patients given a beta-adrenergic-blocking drug as premedication (Table 25-17) . Although, on the surface, the results seem to establish clearly the efficacy of beta-blocking drugs in reducing perioperative ischemic episodes in patients who are mildly hypertensive preoperatively, two limitations might temper enthusiasm. First, there seems to be a problem with the randomization. Although characteristics of the groups are not statistically different, they are numerically different. One wonders, therefore, whether bias was introduced by the fact that the control group underwent more vascular operations and had more pre-existing coronary artery disease than did the treatment groups. Second, the observers' awareness of which patients belonged to which treatment group could introduce insidious and subtle differences in management, such as provision of inadequate anesthesia, a closer search for myocardial ischemia, or a more lengthy sampling of ECG strips from the control group. Although one wishes one could perform a double-blind study in such a situation, and maybe it is possible to do so, the effect on heart rate induced by beta-adrenergic blockade may make this difficult. Stone et al [165] clearly note the limitations

TABLE 25-17 -- Myocardial Ischemia and Sympathectomy in "Mildly" Hypertensive Patients

	CONTROL GROUP	MILDLY HYPERTENSIVE PATIENTS RECEIVING beta -ADRENERGIC RECEPTOR - BLOCKING DRUG IMMEDIATELY PREOPERATIVELY
Developed myocar-dial ischemia	11	2
No evidence of myocardial ischemia	28	87

Data from Stone et al [165]

TABLE 25-18 -- Eligibility Criteria Used by the McSPI Group for Treatment With Atenolol on the Morning of Surgery and for Subsequent Two Weeks

(Not Available)

Modified from Mangano et al [166]

of their study and should be congratulated for not extrapolating or expanding their conclusions beyond that allowed by the data.

Some may comment that the tachycardia that was allowed to occur was severe, indicating inadequate anesthesia, and that the authors have merely demonstrated that betaadrenergic blockade takes the place of a skillful anesthesiologist. I hesitate to come to that conclusion, as I believe that these investigators really tried to provide the best anesthesia care possible. I doubt that even the subtle bias of an unblinded study could have caused this degree of inadequate anesthesia, but one must consider that possibility. Nevertheless, this study and several other published papers, [166] [167] [168] [172] [231] [234] demonstrating that clonidine or other techniques depressed sympathetic nervous system responses during anesthesia, all imply that modifying the response of the sympathetic nervous system, whether on the alpha-adrenergic side with clonidine or on the beta-adrenergic side with one of the beta-adrenergic-blocking drugs used by Stone et al, [165] or with deep general anesthesia [170] or with regional anesthesia, [169] may be all that is needed preoperatively in the mildly hypertensive patient. Data from the McSPI group (see following review) substantiate this point of view. [166]

Critical Analysis of the Data of the McSPI Group

Mangano and coworkers in the McSPI group [166] evaluated patients at risk of coronary artery disease who were undergoing

TABLE 25-19 -- Protocol for Administration of Atenolol in Patients at Risk of Coronary Artery Disease Who Were Undergoing Noncardiac Surgery: The McSPI Study

(Not Available)

Modified from Mangano et al [166]

noncardiac surgery. Those meeting the inclusion criteria listed in Table 25-18 (Table Not Available) were randomly assigned to receive atenolol or placebo for 7 days, as outlined in Table 25-19 (Table Not Available) . Although no difference in morbidity occurred in the first 2 weeks, atenolol produced significantly higher survival rates at 1 and 2 years (Table 25-20) . The difference was so great that administering atenolol was the equivalent of making the average 69-year-old man 3.7 years younger physiologically than the same patient not given atenolol. [22] Even though these data did not pertain solely to hypertensive patients (about 65% did relate to such patients), the results speak clearly about the benefit of controlling BP and "hemodynamic stress" in similar patients. Thus, the author believes the weight of evidence provides a clear answer to the question. The long-lasting benefit from even short-duration therapy indicates that prevention of plaque disruption may be the mechanism of benefit. [241]

Recommendations

Although preoperative systolic BP has been found to be a significant predictor of postoperative morbidity, [165] [197] [212] [213] [214] [215] [216] [217] [218] [219] [220] [222] [223] [224] [226] [227] [228] [229] [230] [231] [232] [233] [234] [238] [239] [240] [242] [249] [250] [251] no data establish definitively whether preoperative treatment of hypertension reduces perioperative risk. Until a definitive study is performed (and that would be, unfortunately, extremely difficult to do), I recommend letting the weight of evidence guide preoperative treatment of the patient with

TABLE 25-20 -- Benefits of Administration of Atenolol for 1 Week in Patients at Risk of Coronary Artery Disease Who Were Undergoing Noncardiac Surgery: The McSPI Study

	PLACEBO GROUP (n = 101; %)	ATENOLOL GROUP (n = 99; %)	*P* VALUE
6-mo survival rate	92	100	.001
1-y survival rate	86	97	.005
2-y survival rate	79	91	.019

Data from Mangano et al [166]

hypertension. Such treatment would be based on three general beliefs: (1) The patient should be educated as to the importance of the lifelong treatment of hypertension, [166] [218] [219] [221] [222] [223] [224] [225] [244] even isolated systolic hypertension; (2) perioperative hemodynamic fluctuations occur less frequently in treated than in untreated hypertensive patients (as demonstrated by Prys-Roberts et al [227] and confirmed by Goldman and Caldera, [228] Mangano et al, [232] and Wolfsthal [234]); and (3) hemodynamic fluctuations have some relationship to morbidity. The data of Stone et al, [165] Pasternack et al, [235] and the McSPI group [166] imply that rapid correction of BP or prevention of increases in heart rate may be all that is needed. However, data from animals that had declining renal function with acute reductions in arterial BP accentuate the risks of such reductions. [245] Even though other epidemiologic data confirm these risks, [226] the hazards of BP fluctuations and acute hypertension may be serious in the untreated hypertensive subject. [246] Modern drug therapy for hypertension appears to reduce these risks but does so with a decrement in quality of life that causes many patients to avoid such medications. [247] Specific racial differences need to be considered before treatment (African-Americans respond less well to beta-adrenergic receptor-blocking drugs and angiotensin-converting enzyme inhibitors but as well to calcium channel antagonists as do Caucasians). [248]

In addition to deciding whether a hypertensive patient needs treatment and ensuring that none of the complications of antihypertensive drugs is present, preoperative management should include a search for end-organ damage secondary to hypertension--that is, changes in the CNS and coronary arteries, myocardium, aorta, carotid arteries, kidneys, and peripheral blood vessels. This type of injury may affect perioperative management. For example, the presence of renal disease may alter the choice and dosage of anesthetic drugs. Similarly, recent myocardial ischemia may warrant a delay in elective surgery. Knowing the location of myocardial ischemia would indicate which ECG lead should be monitored intraoperatively (Ch. 32) . Also, to guide intraoperative regulation of BP and to judge the effects of therapy, I obtain multiple BP readings in both arms while the patient is in various positions. I do this even if these readings are obtained in the preoperative holding area, in the preprocedure evaluation clinic (Ch. 23) , or the operating room rather than on a ward the night before surgery. It is possible that patients admitted the morning of surgery do not receive as good care, but the difference in outcome is small. I try to minimize that difference by being especially careful.

I use such preoperative data to determine the individualized range of values I consider tolerable by a particular patient during and after surgery. That is, if BP is 180/100 mm Hg and heart rate 96 beats/min on admission with no signs or symptoms of myocardial ischemia, I feel confident that the patient can tolerate these levels during surgery. If during the night, BP decreases to 80/50 mm Hg and heart rate to 48 beats/min and the patient does not wake with signs of a new cerebral deficit, I believe he or she can tolerate safely such levels during anesthesia. Therefore, on the basis of preoperative data, I derive an individualized set of values for each patient. I then try to keep cardiovascular variables within that range and, in fact, plan prior to induction what therapies to use to accomplish that goal (e.g., administration of more or less anesthesia, nitroglycerin or nitroprusside/dopamine, dobutamine, phenylephrine, or propranolol/isoproterenol, atropine) (Fig. 25-9) . I believe this sort of planning is especially important for the patient with suspected cardiovascular disease and relatively unimportant for the totally healthy patient. I do not know for certain that keeping cardiovascular variables within an individualized

Figure 25-9 Window of acceptable values for cardiovascular variables during and after surgery. This hypothetical range of "safe" cardiovascular values for one patient illustrates possible therapies that might be employed if actual perioperative values approached the high or low end of that range. The range of safe values, variables treated, and therapies are tailored to the patient and surgical situation. SBP, systemic blood pressure; NTG, nitroglycerin; NTP, nitroprusside; HR, heart rate; PCWP, pulmonary capillary wedge pressure; NEO, Neo-Synephrine; DOPI ISUP, dopamine or Isuprel.

range of acceptable values improves surgical outcome, but I do believe that such a plan reduces morbidity. For example, in several studies, major intraoperative deviations in BP and/or heart rate from the preoperative level have correlated with the occurrence of myocardial ischemia. [227] [228] [229] [230] [239] [240] [249] [250] [251] [252] [253]

Preoperative Administration of All Antihypertensive Drugs

I routinely administer all antihypertensive drugs preoperatively, except angiotensin-converting enzyme (ACE) inhibitors. For these, I convert to intravenous preparations, which I administer after establishing hemodynamic stability. Coriat and colleagues [254] found that ACE inhibitors were associated with hypotension in 100 percent of patients during induction versus about 20 percent in whom ACE inhibitors were withheld on the morning of surgery. Although the long-term adverse effects from withholding therapy on the morning of surgery were not assessed, I withhold therapy until either oral fluid is able to be consumed (ambulatory patients), or until I can convert to intravenously or nasogastrically administered alternatives (patients who receive nothing by mouth postoperatively). I even administer the patient's chronic diuretics on the morning of surgery, as the major effect of diuretics after 1 week of therapy is arteriolar vasodilation, and assessment of urine output may be inaccurate if the diuretic is abruptly discontinued on the morning of surgery.

Ischemic Heart Disease

Identifying Ischemic Heart Disease

Any of the following conditions may indicate the presence of ischemic heart disease: a history of viselike chest pain, with or without radiation to the inner arm or neck; dyspnea on exertion, on exposure to cold, with defecation, or after eating (especially in postmenopausal women who do not take estrogen); orthopnea; paroxysmal nocturnal dyspnea; nocturnal coughing; nocturia; previous or current peripheral or pulmonary edema; history of myocardial infarction (MI); family history of coronary artery disease; diagnosis of MI by ECG or elevated levels of enzymes; and cardiomegaly. Other patients who should be suspected of having ischemic heart disease include those who have diabetes, hypertension (especially if they are cigarette smokers or hyperlipemic [Lichtor JL, et al, personal communication] [31] [32] [255]), left ventricular hypertrophy on ECG or echocardiogram, [79] [80] [256] [257] peripheral vascular disease (Lichtor JL, et al, personal communication), [257] [258] [259] [260] [261] [262] [263] [264] carotid bruits, [261] [262] [263] [264] [265] [266] [267] asymptomatic carotid artery occlusion, [261] [262] or unexplained tachycardia or fatigue.

The more difficult question to answer is, how common is ischemic heart disease in asymptomatic patients or in patients having a normal ECG but predisposing conditions? The history appears to be the best indicator of coronary artery disease. Tomatis et al [258] recorded coronary angiograms for "nearly all patients" who presented for aortoiliac reconstruction or resection of an abdominal aortic aneurysm. Of those having normal ECG results and histories not suggestive of coronary artery disease, 38 percent had stenosis of at least 50 percent in one or more coronary arteries, and 14 percent had stenosis of at least 75 percent in one or more coronary arteries. The percentages of patients with stenosis were the same for asymptomatic patients having abnormal ECG findings. However, a normal ECG result was not sensitive in ruling out significant stenosis when vascular disease was present: 44 percent of patients having normal ECGs and peripheral vascular disease had stenosis of at least 50 percent in one or more coronary arteries, and 30 percent had stenosis of at least 75 percent.

Hertzer et al [259] [260] found angina and a history of myocardial disease to be reliable indicators of coronary artery disease. These investigators studied 1,000 patients having peripheral vascular disease. Of the 500 patients having normal ECG results and no history of myocardial disease, 37 percent had narrowing of at least 70 percent in one or more coronary arteries. By contrast, of those suspected of coronary artery disease because of history and/or ECG results, 78 percent had narrowing of this same degree. Also, patients who currently had angina had a 66 percent incidence of either severe correctable or severe inoperable coronary artery disease, whereas those who had peripheral vascular disease but no angina had an incidence of only 22.5 percent. For women, knowing the estrogen status appears crucial to interpreting other aspects of their cardiovascular history. [268] Thus, in addition to the symptoms listed previously that are sought by routine questioning, [269] information about age, smoking, history of diabetes, cholesterol level, exercise tolerance, and estrogen status can all help predict the likelihood of coronary artery disease.

Are these data from 15 and 25 years ago still valid today? I believe so. Even though the average age of the typical surgical patient in America is now about 7 years higher than it was 20 years ago (Lichtor JL, et al, personal communication), the physiologic age (i.e., the RealAge) of the patients now being operated on is probably similar to that of patients 20 years ago. [22] Therefore, although the age-adjusted mortality rates for coronary artery disease have decreased by approximately 40 percent and the age-adjusted mortality rate for all in-hospital surgical procedures has fallen by over 40 percent, the aging of the surgical population has caused us to face the same risks we faced two decades ago.

Although more than 80 percent of all episodes of myocardial ischemia are "silent," [270] [271] patients with myocardial ischemia are *not* "silent." For example, although the episodes of myocardial ischemia may have been silent, for all 165 patients studied by Rabkin and Horne [269] [272] who had ECG evidence of coronary artery disease, the patient's history gave an indication of the risk of coronary artery disease. This has also been the finding of our own studies [269] [273] and several others when physiologic age of 74 years or older has been added to the factors in a clinical history that would indicate myocardial ischemia. These indicators consist of the following: chest pain, typical or atypical; dyspnea on exertion or exposure to cold, with defecation, or after eating; nocturnal coughing; nocturia; previous or current peripheral or pulmonary edema; history of myocardial infarction; a family history (especially sibling history) of coronary artery disease; cardiomegaly; abnormal ECG results; diabetes, hypertension; hyperlipemia; left ventricular hypertrophy; peripheral

vascular disease; cigarette smoking; carotid artery bruits; peripheral vascular surgery; and unexplained tachycardia.

Several studies of asymptomatic carotid artery disease have shown very high perioperative mortality rates and life risk from associated ischemic heart disease. [261] [265] [266] [267] Barnes and Marszalek [262] found perioperative mortality rates of 18.2 and 15 percent, respectively, for patients having an asymptomatic carotid bruit or occlusive disease but a rate of only 2.1 percent for patients undergoing similar peripheral vascular procedures who did not have a carotid bruit. Whereas the existence of asymptomatic carotid bruits did not predict the site of stroke or greatly influence the incidence of perioperative stroke, [212] [213] [214] it did predict mortality from ischemic heart disease (Table 25-21) . Another point of view is found in the retrospective case-controlled review of strokes after CABG surgery. [267] In that review, strokes after CABG surgery were 3.9 times more likely to occur if carotid bruit was present preoperatively than if such was not present. The group was too small to determine whether site of bruit predicted site of stroke. As few as 15 percent of patients with triple-vessel coronary artery disease have abnormal resting ECGs. [257] Transient ischemic attacks are even more predictive. The 5 to 6 percent annual mortality rate after transient ischemic attacks in a 60-year-old individual is due mainly to myocardial infarction; this rate is similar to the 4 percent annual mortality rate for the 60 year old with stable angina pectoris. [274]

The important point to remember is that the history is the best indicator of coronary artery disease. In most series, the sensitivity and specificity of the history in indicating coronary artery disease range from 80 to 91 percent (Lichtor JL, et al, personal communication). [255] [257] [258] [259] [267] [272] [273] [275] [276] The history has higher sensitivity and specificity than most tests in indicating such disease (also see Ch. 23 for the definition of sensitivity and specificity). However, one test is gaining in popularity, as it has been demonstrated to be easy to perform and to accurately predict perioperative morbidity.

One Easy Noninvasive Test and Two Easy Measures: But Does Preoperative Treatment Improve Outcome?

Fowkes and colleagues, [79] Leng et al, [277] and Kornitzer and associates [278] are testing a simple-to-measure index that would predict the degree of subclinical arterial aging that exists and the likelihood of subsequent cardiovascular events and death: the ratio of systolic BP in the posterior tibial artery of the ankle (as measured by Doppler) to systolic BP in the brachial artery (as measured by cuff). This index has predicted 8- and 10-year cardiovascular mortality in patients who did not undergo surgery: The incidence of cardiovascular death was 85 percent higher among those having an index of less than 0.7. The index is made even more powerful when combined with other historical factors. Patients who had an index of less than 0.9, were hypertensive, and currently smoked had a 43.8 percent risk of cardiovascular events in the next 5 years, as opposed to the 15.6 percent risk for those who had identical conditions but an index of 1.0 or higher.

TABLE 25-21 -- Carotid Artery Bruits and the Risk of Stroke in Elective Surgery

STUDY	INCIDENCE OF STROKE IN PATIENTS	
	WITH BRUITS	*WITHOUT BRUITS*
Ropper et al [265]	1/104	4/631
Of those having vascular surgery	1/37	4/130
Barnes et al [261]	5/85 [a]	0/364
Perioperative deaths	10.6%	0.3%
Reed et al [267]		
CABG; 54 strokes	13/54 [b]	4/54 [b]

Abbreviation: CABG, coronary artery bypass graft.

[a] All patients included in this study were undergoing vascular surgery. These 85 patients also had either a bruit or significant carotid artery obstruction or both.
[b] Case-control study. These investigators examined the incidence of carotid bruit in patients who had strokes after CABG surgery.

The exercise index of Older et al [279] [280] ("aerobic threshold") seems to have the same goal--to predict the degree of subclinical arterial aging. The RealAge system attempts to do the same thing with its measurements but uses a much broader range of modifiable factors. [22]

However, the key payoff would be the demonstration that using such tests would motivate patients to modify health-related habits, which would, in turn, improve their index values. This result would then have to be correlated with beneficial effects on perioperative cardiovascular events. (Examples of changes in health-related habits include food choices, smoking and smoke inhalation, increased physical activity, consumption of antioxidants, use of aspirin, use of beta-blocking drugs, weight reduction, BP control, and flossing of teeth.) Although an increasing body of data [22] [264] [281] [282] seems to predict that such changes would occur, they have not yet been confirmed. Such a study would be incredibly difficult to execute successfully, but would any study be more worthwhile?

Perioperative Morbidity

The presence of coronary artery disease, its severity, the time of most recent myocardial tissue death, the arteries affected, and the complications and treatment of the disease are important information to the anesthesiologist. These variables influence the manner in which anesthesia is given and, in fact, may determine whether anesthesia and surgery should be postponed.

Previous Myocardial Infarction

Numerous epidemiologic studies [129] [243] [251] [283] [284] [285] [286] [287] [288] [289] [290] [291] [292] (Table 25-22) (but none in the past 5 years) have shown that if a previous MI and subsequent surgery are separated by less than 6 months, the perioperative reinfarction rate is 5 to 86 percent (1.5-10 times higher than the value when previous MI

and subsequent surgery are separated by more than 6 months), and the mortality rate is 23 to 86 percent. After 6 months, the perioperative reinfarction rate seems to stabilize at 2 to 6

TABLE 25-22 -- Incidence of Perioperative Myocardial Infarction or Mortality in Patients With Previous Myocardial Infar

TIME FROM MI OPERATION	ARKINS ET AL[283] 1963	TOPKINS AND ARTUSIO[284] 1959 - 1963		FRASER ET AL[285] 1960 - 1964	TARHAN ET AL[286] 1967 - 1970		SAPALA ET AL[287] 1970 - 1974		STEEN ET AL[288] 1970		VON KNORRING[292] 1981		GOLDMAN ET AL[289] 1975 - 1976		EEROLA ET AL[250] 1970-1974		
(MO)	(MORT)	(REINF)	(MORT)	(MORT)	(REINF)	(MORT)	(REINF)	(MORT)	(REINF)	(MORT)	(REINF)	(MORT)	(REINF)	(MORT)	(REINF)	(MORT)	
0-3	40% 11/27	54.5% 12/22	a	38% 19/38	37% 3/8	a	86% 6/7	86% 6/7	27% 2/18		25% 4/16	a	4.5% 1/22	23% 5/22	8% 1/12	8% 1/12	
4-6	a		a	a	16% 3/19	a			11% 2/18					5.9% 1/12	5.9% 1/17	0% 0/1	
7-12	a	25.0% 9/36	a	a	5% 2/42	a					18% 2/11	a	0% 0/13	8% 1/13			
13-18	a	22.4% 11/49	a	a	4% 1/27	a								8-1/13			
19-24	a		a	a	4% 1/21	a	5.7% 9/159	1.9% 3/159	5.4% 30/544		11% 10/89				4.9% 4/82	12% 1/82	
25-36	a	5.9% 3/51	a	a	5% 11/232	a						a	3.3% 2/66	3.3% 2/66			
>36	a	1.0% 5/493	a	a													
Unknown	a	42.8% 3/7	a	a	5.6% 7/73	a					22% 9/41	a					
Total patients with MI	a	6.5% 43/658	4.7% 31/658	a	6.6% 28/422	3% 15/422	9% 15/166	5.4% 9/166	6.1% 36/587	4.2% 25/587	15.9% 25/157	4% 7/157		8.9% 9/109			

[a] Mortality was not stated.

Abbreviations: MI, myocardial infarction; Mort, mortality; Reinf, reinfarction

percent. An investigation by Schoeppel et al [290] studying a small number of patients produced a 0 percent mortality rate in the first year after infarction but a perioperative reinfarction rate of 16.7 percent and a mortality rate of 67 percent for patients experiencing perioperative reinfarction. Because the incidence and timing of perioperative reinfarction in the study by Schoeppel et al differ so much from those variables in the other studies listed in Table 25-22 , I have placed little emphasis on that study. However, for all 12 of the studies listed in Table 25-22 , the overall reinfarction rates are similar. [129] [238] [239] [240] [243] [249] [250] [251] [273] [275] [276] [283] [284] [285] [286] [287] [288] [289] [290] [291] [292] [293] These data do not include patients who have had immediate angiography, clot dissolution therapy, angioplasty, or stents therapy.

The study conducted by Rao et al [129] deserves special comment because it proposes to show a vast decrease in perioperative reinfarction rate attributable to the use of modern monitoring techniques. The rates of perioperative reinfarction and mortality were compared for two groups of patients who had previous MIs operated on at two different time periods: 364 patients between 1973 and 1976; and 733 patients between 1976 and 1982. Rao and coworkers attribute the reduction in overall perioperative reinfarction rate (from 7.7 to 1.9%) and in each time period (i.e., from 36 to 5.8% when surgery occurs within 3 months of a previous MI) to invasive monitoring and rapid treatment of cardiovascular variables when values deviated from normal values. These two practices apply to both the intraoperative period and the first 72 postoperative hours. (The 72-hour period may be critical, as virtually all 12 studies and others showed that reinfarction was most likely to occur 24-96 hours after surgery [129] [243] [251] [283] [284] [285] [286] [287] [288] [289] [290] [291] [292] [293] [294] [295] [296] [297] [298] [299] [Table 25-23].) Most of the reduction in the perioperative reinfarction rate applied to patients older than 65 years. (An MI makes the physiologic age or risk of death equivalent to that of someone 3-17 years older, depending on the location of the infarction and the decrease in the left ventricular ejection fraction. [22])

The editorial evaluating the study by Rao et al stated that the use of historical controls may have biased the conclusions. Also, a different patient mix, improved skills of the surgeon and anesthetist, and other unidentified or unmeasured changes over time may have contributed to the reduction in reinfarction rate.

Normalization of hemodynamics using pulmonary artery catheter monitoring and 3 days in an ICU also appears to reduce perioperative morbidity in vascular surgery patients, a group at high risk of postoperative cardiac morbidity. In a randomized controlled trial, Berlauk et al [299] examined that intervention scheme, which was similar to that investigated by Rao et al, [129] for patients undergoing vein graft bypass for limb salvage from 1986 to 1990. Forty-five patients were randomly assigned to group 1 (i.e., pulmonary artery catheterization performed 12 hours before surgery, followed by treatment for hemodynamic optimization). The 44 other patients were randomly assigned to either group 2 (23 patients; i.e., pulmonary artery catheterization within 3 hours of surgery, followed by a shorter treatment for hemodynamic optimization); or to group 3 (21 control patients; i.e., no preoperative catheterization or hemodynamic optimization, treatment via central venous pressure lines, and minimal or no stay in the ICU).

Berlauk and colleagues [299] reported that patients undergoing less intensive treatment (group 3) were significantly more likely to have intraoperative complications (tachycardia, hypotension, arrhythmia) than were patients in group 1. The overall incidence of postoperative complications (renal failure, CHF, myocardial infarction, graft thrombosis, death) was 18 percent for group 1, 13 percent for group 2, and 43 percent for group 3. One-half of the complications in group 3 were attributable to early graft thrombosis and accounted for most of the difference in complication rates. The authors conjectured that the increased incidence of thromboses was due to poor cardiac output. No significant difference in mortality existed between groups. Although Berlauk and coworkers reported a higher incidence of postoperative cardiac morbidity in the control group, this conclusion is difficult to follow, as discrepancies exist between their calculations and data provided elsewhere in the paper. For example, their Table 5 reports three postoperative cardiac complications for group 1, two for group 2, and five for group 3. However, their Table 4 says only three patients in group 3 (1, 7, and 8) experienced these complications. Simple explanations for these discrepancies may exist but were not evident to me or to the Task Force on Pulmonary Artery Catheterization of the ASA. [300]

This study had other deficiencies that preclude definitive advice on ways of reducing morbidity for the patient with a prior MI: outcome did not differ significantly between the groups undergoing "normalization" of hemodynamics more than 12 hours before surgery versus less than 3 hours before surgery. Furthermore, the rationale for group assignments in this study is unclear. Rather than randomly assign the 89 patients to three groups of equal size, the investigators created two randomly selected groups and then subdivided the second group in a separate randomization that created imbalanced sample sizes. Group assignments may not have been truly random, as there were significant preoperative

TABLE 25-23 -- When Do Myocardial Infarctions Occur After Vascular Surgery?

INVESTIGATORS	YEAR PUBLISHED	EXAMINED PROSPECTIVELY	POSTOPERATIVE				
			DAY 0	*DAY 1*	*DAY 2*	*DAY 3*	*DAY 4*
Plumlee and Boettner [294]	1972	No	11/24	3/24	1/24	2/24	
Tarhan et al [286]	1972	No		14/71	8/71	22/71	13/71
Rao et al [129]	1983	No		8/28	7/28	10/28	3/28
		No		3/14	4/14	7/14	
Becker and Underwood [295]	1987	?	11/28	6/28	9/28	0/28	1/28
Total (four studies)			22	34	29	41	17

differences between groups regarding the incidence of angina, CHF, and hemodynamic indices. Berlauk et al [299] explained that "although the randomization sequence was performed at the beginning of the study, actual patient entry into the study was finalized the evening before surgery. Bias of the chief surgical resident, who determined the operating room schedule, may account for the lack of patients with angina...." Furthermore, the role of pulmonary artery catheterization and hemodynamic control using aggressive management in reducing perioperative morbidity in a patient with a previous MI is unclear. [301] [302]

Other workers have pointed out that certain surgical procedures (e.g., ophthalmic operations) have low perioperative reinfarction rates, [288] [289] [290] [301] whereas others (e.g., vascular operations [289] [296] [297] [298] [299] [303] [304] [305] [306] [307] [308]) have high reinfarction rates. The study by Rao et al [129] does confirm that the perioperative reinfarction rate is higher in the first 6 months after a previous MI. Postponement of surgery for patients who have had an MI less than 6 months earlier should reduce mortality associated with anesthesia. Again, however, we are lacking data analyzing whether such risk changes with preoperative segregation by clinical criteria or provocative testing. The guidelines promulgated by the American College of Cardiology and the American Heart Association seem to indicate a liberalization of surgery to 6 weeks after infarction in "low risk patients." The less severe the coronary artery disease, the more similar the patient's anticipated survival curve to that of patients who do not have coronary artery disease [309] and probably the less the perioperative risk. [299] [310] [311]

Preoperative Testing: Analyses of Benefit Versus Risk and Versus Cost

Treadmill exercise testing, bicycle ergometer, dipyridamole-thallium imaging, dobutamine stress echocardiography, preoperative Holter monitoring, noninvasive imaging, ankle-brachial pressure index (see the earlier section, *One Easy Noninvasive Test* ....), and cardiac catheterization also add information to the history, increasing our knowledge about the likelihood of cardiac disease and perioperative cardiac function. [275] [296] [297] [298] [304] [305] [306] [307] [308] [312] Mantha et al [308] performed a meta-analysis to determine which preoperative noninvasive test was most predictive of the risk of adverse cardiovascular outcome after vascular surgery. They concluded that the search for wall-motion abnormalities during dobutamine stress echocardiography was not only successful in predicting risk but also the most cost-effective of the tests (Table 25-24 and Fig. 25-10) (Figure Not Available) .

The ECG criteria for myocardial ischemia during or after exercise consist of at least 1 mm of J-point depression with downsloping or horizontal ST segments; slowly upsloping ST-segment depression, defined as being 2 mm of ST depression, measured at 80 ms from the J point; and STsegment elevation [267] (Fig. 25-11) . Other responses to treadmill testing predictive of severe multivessel or of left main stem coronary artery disease include ST-segment depression exceeding 2.5 mm; serious ventricular arrhythmias at low heart rates, or early (first 3 minutes) onset of ischemic ST-segment depression; and/or prolonged duration of the ischemic ST-segment depression in the posttest recovery period (>8 minutes). [275]

TABLE 25-24 -- Adverse Cardiac Events After Abnormal Preoperative Tests: Relative Risks (Combined) and Costs of Tests

TEST	STUDIES (N)	RR (95% CI)	COST (U.S. $)
DTS	11	6.3 (3.0-13.1)	1,200-1,400
RNV	5	3.8 (1.5-9.4)	500-600
AECG	6	3.7 (2.0-7.1)	300-550
DSE	3	19.0 (5.9-60.8)	1,000-1,200

Abbreviations: RR, relative risks; CI, confidence intervals; DTS, dipyridamole-thallium scintigraphy; RNV, estimation of ejection fraction by radionuclide ventriculography; AECG, ambulatory electrocardiography; DSE, dobutamine stress echocardiography.

Data from Mantha et al [308]

Non-ECG responses to treadmill testing that predict severe coronary artery disease include low achieved heart rates (
120 beats/min), systolic hypotension (decrease of >10 mm Hg) in the absence of hypovolemia or antihypertensive medications, rise in diastolic BP to higher than 110 mm Hg, and inability to exercise beyond 3 minutes. The treadmill test responses predictive of severe multivessel and/or left main stem coronary artery disease are listed in Table 25-25 (Table Not Available) . Clearly, however, the response to the test must be interpreted in light of the patient's history and with knowledge that it is more predictive for men than for women [275] (Table 25-26) (Table Not Available) .

Inability to increase heart rate (cardiac risk index [CRI]) above 90 beats/min after supine bicycle exercise for 2 minutes at 50 rpm has been shown to predict perioperative myocardial infarction with 80 percent sensitivity. This test is claimed by its investigators to have better sensitivity (80%) with a small sacrifice in specificity (53%) than the Goldman CRI (sensitivity 60%, specificity 64%). This same group recommended this test for geriatric patients at low risk (according to the Goldman CRI) to identify the "false negatives" of the Goldman CRI or for geriatric patients at risk of perioperative MI. Limitations to this test, however, are recognized in patients with impaired joint mobility, dementia, muscle weakness, claudication, or exertional angina. [298] Ejection fractions of more than 50 percent (and normal left ventricular size on plain chest radiograph) predict good perioperative cardiac function and survival. [311] [312]

For dipyridamole-thallium scanning, patients received dipyridamole (0.56 mg/kg) intravenously over 4 minutes while their heart rate, BP, and ECG were monitored. After an additional 2 minutes, when the effect of dipyridamole was considered maximal, 2 mCi of thallium-201 was administered intravenously. Five minutes after administration of thallium, initial images were taken for 8 consecutive minutes. Delayed images were obtained 3 hours later. The anterior, 45-degree, and 70-degree left anterior oblique projections were taken each time. Dipyridamole causes vasodilation and increase in coronary blood flow. Because stenotic vessels cannot dilate normally, areas of myocardium supplied by them will take up less thallium during scanning than will areas supplied by normal vessels and will show up as filling defects on immediate image. On the late images, after vasodilation has resolved, thallium redistributes to these previously underperfused areas.

Dipyridamole infusion resulted in an increase in heart

Figure 25-10 (Figure Not Available) Relative risks and confidence intervals resulting from use of four preoperative tests to predict adverse outcome after vascular surgery, as reported by various studies. Names at left refer to first author of studies reviewed by Mantha et al. [308] Broken vertical lines represent combined relative risks, as assessed by each test. DTS, dipyridamole-thallium scintigraphy; RNV, estimate of ejection fraction by radionuclide ventriculography; AECG, ambulatory electrocardiography; and DSE, dobutamine stress echocardiography. *(Adapted from Mantha et al [308])*

Figure 25-11 Electrocardiographic criteria for myocardial ischemia consist of 1mm of J-point depression with downsloping or horizontal ST segments; slowly upsloping ST-segment depression, defined as 2 mm of ST depression measured 80 ms from the J point; and ST-segment elevation. Whereas STsegment depression indicates nontransmural ischemia, ST-segment elevation often connotes more severe degrees of ischemia reflecting transmural injury. The structure of the ST-segment slope is predictive of the severity of coronary disease shown angiographically, with downsloping ST depression indicating severe two- and three-vessel coronary artery disease more often than does either horizontal and slowly upsloping ST depression, and ST-segment elevation indicating high-grade, usually proximal, arterial obstruction in patients without previous myocardial infarction. *(From Goldschlager [275])*

TABLE 25-25 -- Treadmill Test Responses Predictive of Severe Multivessel and/or Left Main Coronary Artery Disease

(Not Available)

Modified from Goldschlager [275]

rate of 17 beats/min, a decrease in systolic BP of 17 mm Hg, and chest pain in 30 percent of patients, which was reversible with 125 mg of aminophylline intravenously. ECGs were examined for ischemic changes defined as 1-mm horizontal or downsloping ST-segment depression. Myocardial regions on initial and delayed images were graded as being normal, as showing fixed deficits (without redistribution), or as showing one or more segments with thallium redistribution (with or without evidence of fixed deficits). Initial studies [304] [305] [313] (reviewed by Mantha et al [308]) have shown this test to be valuable in further stratifying high risk, as assessed by five clinical factors (CHF, diabetes mellitus, history of ventricular ectopy, angina, and history of MI). Of patients with thallium redistribution, 45 percent had a perioperative MI, whereas 7 percent of patients without redistribution had a perioperative MI (*P* = .001). Dipyridamole-thallium scanning has been suggested to be valuable in stratifying patients with intermediate risk, as assessed by five clinical factors (Q waves on resting ECG, history of ventricular ectopy, diabetes, age >70 years, and angina) that were identified by logistic regression on several clinical findings and Goldman CRIs and Dripp classes. Fletcher et al [313] found the test superior to clinical assessment in identification of high-risk patients for further angiographic study, prophylactic CABG surgery, or intensive intraoperative and postoperative management. Dipyridamole-thallium scanning may reveal redistribution when coronary narrowing is only 40 to 60 percent. This process may aid in the management of higher-risk patients by initiating invasive monitoring, with prompt medication of hemodynamic changes. These actions may have artificially decreased the incidence of perioperative MI in the studies of thallium scanning cited. Because the results of thallium scans in all these studies were made known to the caretakers, those patients with positive scans may have received more invasive monitoring, as well as coronary angiography, angioplasty, medications, and CABG surgery. The discriminating capacities of this test may improve with further classification of redistribution segment by size and number and by additional projections (see Fig. 25-10 (Figure Not Available) . and Table 25-24)

Twenty-four to 48-hour Holter monitoring of intermediate-risk patients has recently been shown to be effective in detecting asymptomatic ischemia and has an excellent negative predictive value and a fair positive predictive value for postoperative cardiac complications (see Fig. 25-10 (Figure Not Available) and Table 25-24.) Preoperative ischemia increases the risk of intraoperative ischemia 3- to 4-fold. Raby and colleagues [306] studied 176 vascular surgery patients who were asymptomatic for ischemic cardiac disease and found preoperative ischemia on Holter monitoring to be an independent factor with high correlation for significant postoperative cardiac complications (e.g., infarction, unstable angina, and ischemic pulmonary edema). In this series, 24- to 48-hour Holter monitoring detected two of three patients with positive stress test results and four patients with postoperative cardiac complications who did not have a history suggestive of ischemic heart disease. With an overall sensitivity of 92 percent, specificity of 88 percent, positive predictive value of 38 percent, and negative predictive value of 99 percent, Holter monitoring may be the test of choice for evaluating intermediate-risk patients who have no suggestive history or for those patients who are unable to undergo an exercise stress test. Limitations of this method are seen in patients with left bundle branch block, left ventricular hypertrophy, with strain, and ST-T changes with digoxin because of the difficulties in analyzing ST-segment changes.

Studies of visual interpretation of the coronary angiogram suggest that the physiologic effects of most coronary artery obstruction cannot be determined accurately by conventional angiographic approaches.

Dobutamine stress echocardiography has also been tested recently for its ability to predict adverse cardiac outcome in patients undergoing vascular surgery. [308] [314] [315] [316] [317] For this test, an abnormal result or a positive result consists of new regional

TABLE 25-26 -- Electrocardiographic Response to Treadmill Exercise of Angiographically Demonstrated Coronary Artery Disease

(Not Available)

Modified from Goldschlager [275]

TABLE 25-27 -- Computation of the Cardiac Risk Index[a] [b]

(Not Available)

Modified from Goldman et al. [887] Risk calculation from Goldman et al, [289] Detsky et al [297] and Jeffrey et al [319]

[a] To calculate a patient's score, the number of points from all factors he or she possesses are summed.
[b] Patients are further segregated into class I (0-5 points), with a risk of 4-7% of major complications: class II 6 - 12 points), risk 7-11 % ;class III (13- 25 points), risk 14 -38 % and class IV (26 points), risk 30 -100 %.

wall motion abnormalities or worsening of existing regional wall motion abnormalities on echocardiography during infusion of dobutamine. A negative result consists of absence of any change on echocardiography during dobutamine infusion. This test has high predictive value for adverse cardiac events (although the findings of Mantha and coworkers [308] are limited to only three studies of dobutamine stress echocardiography for this purpose). The relative risk (95% confidence intervals) of adverse outcome predicted by the test was 19 (5.9-60.8) (see Fig. 25-10 (Figure Not Available) and Table 25-24) , which suggests that this test is very "effective." It is interesting to note that unlike the other studies, the Mantha et al [308] study found that the predictive value increased over the time period the test was available.

Recent studies have concentrated on the identification and stratification of risks in the intermediate-risk group of patients who would benefit most from a preoperative cardiac workup and risk assessment. Goldman et al [289] prospectively studied 1,001 patients older than 40 years undergoing a broad variety of emergency and elective surgery. Multiple regression analysis of the data showed that nine factors correlated independently with development of life-threatening or fatal cardiac complications: (1) the presence of an S_3 gallop, jugular vein distention, or CHF; (2) history of MI in the preceding 6 months; (3) a cardiac rhythm other than sinus; (4) the occurrence of more than five premature ventricular contractions (PVCs)/min; (5) performance of intraperitoneal, intrathoracic, or aortic surgery; (6) patient age above 70 years; (7) significant valvular aortic stenosis; (8) emergency surgery; and (9) poor general medical condition. On the basis of this study, the investigators developed a method of computing a CRI (Table 25-27) (Table Not Available) . This study suggests that history and physical examination account for 29 of 53 points in assessing cardiac risk of the general surgical population and that initial history and physical examination permit selection of intermediate-risk patients for further evaluation. Eagle and colleagues [304] studied 200 vascular surgery patients, a population with a high incidence of cardiovascular disease, and, using logistic regression, found independent risk factors to be as follows: Q waves on resting ECG, history of ventricular ectopy, diabetes, age above 70 years, angina, and CHF. Again, multiple regression studies suggest that initial clinical evaluation suffices for selecting patients for further evaluation.

The Cleveland Clinic group has established a clinical severity scoring system to characterize risk prior to coronary artery bypass surgery [318] (Table 25-28 (Table Not Available) and Fig. 25-12.) (Figure Not Available) This system predicts cardiovascular morbidity and gives stratification points for risk of adverse cardiovascular outcome for preoperative renal insufficiency, diabetes, age, anemia, chronic obstructive lung disease, mitral valve insufficiency, aortic valve stenosis, cerebrovascular disease, and surgery performed on an emergency basis--many factors found by Goldman and colleagues to affect outcome adversely. Therefore, diseases that

impinge on the cardiovascular system, such as renal insufficiency and diabetes, have important effects in predicting cardiovascular morbidity.

The American College of Cardiology/American Heart Association Task Force on Perioperative Cardiovascular Evaluation for Noncardiac Surgery used data such as that above, combined with expert opinion, to propose a series of algorithms for preoperative evaluation of such patients (Tables 25-29 (Table Not Available) 25-30 (Table Not Available) ; 25-31 (Table Not Available) ; . Fig. 25-13) (Figure Not Available) . [10]

TABLE 25-28 -- Use of Preoperative Factors to Predict Risk of Adverse Outcome After CABG: Clinical Severity Scoring System of the Cleveland Clinic

(Not Available)

Modified from Higgins et al. [318]

Figure 25-12 (Figure Not Available) The observed morbidity after coronary artery bypass surgery versus the morbidity predicted by a clinical severity scoring system that evaluated various pertinent preoperative conditions. Morbidity was lower than the predicted 99.4 percent confidence interval at scores 2, 5, 6, and 7 to 9. Model may not validate prospectively because of changes in clinical management resulting in complications. Vertical lines at top of bars indicate confidence intervals. *(From Higgins et al [318])*

They did this, realizing the importance of a surgical event to a patient's long-term prognosis and realizing that surgery may present the first opportunity for long-term evaluation, risk management, and motivation of the patient.

Thus, the major signposts of perioperative myocardial function that we can obtain before surgery are the risk factors for arterial aging and the history of ischemic pain (and its relationship to exercise), CHF, diabetes, and renal insufficiency. The value of this information is slightly enhanced by a 6-minute walk test, determination of the ankle-brachial pressure index, ECG and non-ECG responses to bicycle or treadmill exercise, determination of ejection fraction, and the use of an ECG, radionuclide imaging, radionuclide imaging after dipyridamole, wallmotion changes during dobutamine infusion, or angiogram. [232] [238] [239] [240] [275] [296] [297] [298] [304] [305] [306] [307] [308] [312] [313] [314] [315] [316] [317] [319] [320]

Relationship to Previous Coronary Artery Bypass Graft or to Percutaneous Transluminal Coronary Artery Angioplasty

Much of the information on which altered perioperative anesthetic management of ischemic heart disease is based derives from studies of patients undergoing aortic and CABG procedures. Although CABG relieves angina and increases exercise tolerance (as did many placebo operations and medications before it), [321] improved survival occurs only for patients having significant left main coronary artery disease [307] [322] and for those with mild to moderate impairment of left ventricular function. [323] However, a potential additional benefit of CABG surgery or percutaneous transluminal coronary angioplasty (PTCA) has been documented. Reduced perioperative morbidity during subsequent noncardiac surgical procedures may be an additional benefit of surviving CABG or PTCA. [10] [259] [260] [310] [323] [224] [325]

To provide definitive data for this hypothesis, a randomized controlled study would be necessary: CABG surgery may constitute a "survival test." That is, it may cause reinfarction or death, or both, in those patients who would have sustained an MI or who would have died after the noncardiac surgery. [310] This appears to be a likely conclusion, as those patients who do poorly during and after CABG surgery are those with poor left ventricular function and increased left ventricular end-diastolic pressure. [325] Patients with these same cardiovascular conditions also have increased perioperative risk after noncardiac surgery. [238] [240] [259] [260] [289] [296] [297] [298] [304] [305] [306] [307] [308] [311] [313] Therefore, one proposal to decrease perioperative risk in patients severely disabled with angina (or ischemic heart disease) is to study the coronary arteries and to perform PTCA or CABG, if indicated, prior to their noncardiac surgery.

Hertzer et al [259] [260] did just this. Knowing that survival after vascular surgery depends mainly on preserving myocardial function, these investigators obtained coronary angiograms from, and proposed CABG surgery (when appropriate) for, 1,001 consecutive patients needing peripheral vascular surgery (regardless of the degree of suspicion of coronary artery disease prior to angiogram). CABG was believed to be indicated in 251 patients, of whom 226 underwent CABG with 12 (5.13%) operative deaths; of those,

TABLE 25-29 -- Clinical Predictors of Increased Perioperative Cardiovascular Risk (Myocardial Infarction, Congestive Heart Failure, Death)

(Not Available)

From Eagle et al [10]

TABLE 25-30 -- Estimated Energy Requirements for Various Activities[a]

(Not Available)

From Eagle et al [10]

[a] *Adapted from the Duke Activity Status Index and the American Heart Association Exercise Standards*

TABLE 25-31 -- Stratification of Cardiac Risk for Noncardiac Surgical Procedures

(Not Available)

From Eagle et al. [10]

130 subsequently underwent peripheral vascular procedures with only one death.

Do these figures imply that mortality was decreased or increased by the CABG procedure? Did some patients not undergo their initially indicated vascular procedure because of morbidity associated with CABG? (The report did not indicate why 26 patients who initially were scheduled for peripheral vascular procedures did not undergo those procedures after CABG.) The long-term prognosis for the patients of Hertzer et al [259] [260] was better for those who underwent CABG prior to their noncardiac surgery than for those who did not: The 5-year cardiac survival rate was 82.5 versus 74 percent. In fact, in the Coronary Artery Surgery Study series, prior CABG or PTCA (versus medical therapy) reduced the risk to that of someone 4 years younger (Fig. 25-14) (Figure Not Available) . This was the equivalent risk reduction found by the McSPI group for beta-adrenergic receptor-blocking therapy for the day of surgery and seven subsequent days. [166] [326]

Are these therapies additive? We do not have an answer. Again, Hertzer and associates describe a nonrandomized series. [259] [260] Huber and colleagues [325] try to make the point that vascular surgery after PTCA is safer than without PTCA, but their series had a rate of serious complications (failed PTCA, MIs, death) from PTCA of more than 10 percent. Thus, perhaps these studies serve to reemphasize the point made by Goldman et al [9] and Higgins et al [318] in their risk indices (see Tables 25-27 (Table Not Available) and 25-28) (Table Not Available) that current vascular disease should call forth a warning about the risk of perioperative cardiovascular morbidity.

Therefore, the hypothesis that CABG or PTCA decreases morbidity and mortality in patients undergoing subsequent noncardiac surgery remains a hypothesis. (Although prior CABG or PTCA reduces risk, does the combination lead to better outcome?) This hypothesis warrants study in a randomized clinical trial.

Figure 25-13 (Figure Not Available) Coronary risk assessment. Risk stratification strategies for determining a patient's candidacy for preoperative noninvasive testing before elective surgery. CHF, congestive heart failure; MET, metabolic equivalent; MI, myocardial infarction. *(From Eagle et al [1C])*

Figure 25-14 (Figure Not Available) Long-term survival of 1,834 patients with peripheral vascular disease who were enrolled in the Coronary Artery Surgery Study (CASS) registry. Survival rates are shown for those undergoing coronary artery bypass grafting (CABG) versus medical therapy before their vascular sur-gery. *(From Rihal et al [89C])*

Summary of Preoperative and Intraoperative Factors That Correlate with Perioperative Morbidity

Summarizing a large number of studies, I list the following preoperative findings as conditions that correlate with perioperative morbidity and that can be corrected prior to operation: (1) recent MI (within 6 months), [129] [250] [283] [284] [285] [286] [287] [288] [289] [290] [291] [292] [293] (2) severe CHF (i.e., sufficiently severe to produce rales, an S_3 gallop, or distention of the jugular vein), [129] [232] [238] [240] [287] [289] [296] [297] [298] [299] [300] [302] [303] [304] [305] [306] [307] [311] [318] [327] (3) severe angina (see Table 25-32 for classification of the severity of angina), [289] [296] [307] [311] [327] (4) heart rhythm other than sinus, [287] [289] [296] [297] [298] (5) premature atrial contractions, [289] (6) more than five PVCs/min, [287] [289] and (7) blood urea nitrogen (BUN) levels higher than 50 mg/dL or potassium levels below 3.0 mEq/L. [289] [318]

Preoperative factors that correlate with perioperative risk but that cannot be altered include: (1) old physiologic or chronologic age (perioperative risk increases with age), [22] [236] [289] [296] [297] [298] [299] [308] [328] [329] (2) significant aortic stenosis, [289] [318] [330] (3) emergency operation, [129] [236] [283] [289] [296] [297] [298] [311] [318] (4) cardiomegaly, [240] [289] [296] [297] [298] [311] [318] (5) history of CHF, [129] [238] [240] [287] [289] [296] [297] [298] [299] [300] [302] [303] [304] [305] [306] [307] [311] [313] [318] (6) angina (or history of angina or ischemia) on ECG, [129] [232] [275] [287] [289] [296] [297] [298] [299] [300] [302] [303] [304] [305] [306] [307] [311] (7) abnormal ST-segment or inverted or flat T waves on ECG, [9] [289] [296] [298] abnormal QRS complex on ECG, [289] and (8) significant mitral regurgitant murmur. [289] [318]

Significant intraoperative factors that correlate with perioperative risk and that may be avoided or altered are as follows: (1) unnecessary use of vasopressors [331] [332] ; (2) unintentional hypotension [239] [251] [286] [289] (this point is controversial, however, as some investigators have found that unintentional hypotension does not correlate with perioperative morbidity [329] [332]); (3) hypothermia [333] ; (4) too low or too high a hematocrit level [334] [335] and (5) lengthy operations. [256] [283] [288] [289]

Significant intraoperative factors that correlate with perioperative morbidity and probably cannot be avoided are emergency surgery and thoracic or intraperitoneal surgery or above-the-knee amputations. [256] [287] [288] [289] [296] [297] [298] [299] [300] [302] [303] [304] [305] [306] [307] [308] [309] [310] [311] [313] [318] [328]

Although the evidence for these factors is fairly substantial, virtually no data are derived from prospective randomized studies indicating that treatment of the above conditions reduces the perioperative risk to patients with ischemic

TABLE 25-32 -- Classifications of Angina by the New York Heart Association and the Canadian Cardiovascular Society

NYHA	CCS
I. Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation or with sexual relations.	I. Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.
II. Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during a few hours after awakening. Walking more than two blocks on the level or more than one flight of stairsat a normal pace and under normal conditions.	II. Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after wakening. Walking more than two blocks on the level and climbing more than oneflight of ordinary stairs at a normal pace and under normal conditions.
III. Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs under normal conditions and at a normal pace. "Comfortable at rest."	III. Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight under normal conditions.
IV. Inability to carry on any physical activity without discomfort--anginal syndrome may be present at rest.	IV. Inability to carry on any physical activity without discomfort--anginal syndrome *may be* present at rest.

heart disease. Nevertheless, all logic dictates that such treatment does reduce risk. Thus, the goal in giving anesthesia to patients with ischemic heart disease is to achieve the best preoperative condition obtainable, by treating those conditions that correlate with perioperative risk. The next step is to monitor intraoperatively for those conditions that correlate with perioperative risk and, by careful attention to detail, avoid those circumstances that lead to perioperative risk. Although local anesthesia may reduce perioperative risk. [287] [301] epidemiologic studies do not indicate significant differences in perioperative morbidity for patients with ischemic heart disease who are given local anesthesia as opposed to general anesthesia.

Preoperative Evaluation

Preoperative evaluation of the patient with ischemic heart disease should include a review of the clinical course of any previous myocardial infarctions and a review of studies made subsequent to those events. Because the patients most likely to benefit are those who have severe coronary artery disease (i.e., multivessel left main stem coronary artery disease) and ejection fractions of 21 to 50 percent, some strategies have been devised to limit routine exercise testing, dipyridamole-thallium scanning, Holter monitoring, dobutamine stress echocardiography, and angiographic testing to only such patients (Figs. 25-15 25-16 (Figure Not Available) 25-17 (Figure Not Available)) [10] [336] That these studies have been or are being performed implies something about the patient's cardiac function.

The preoperative evaluation should also include a review of the results of exercise studies, Holter monitoring, other noninvasive tests such as dobutamine-stress echocardiography, and coronary angiography, to determine which ECG lead to monitor for ischemia. Although in theory the ECG lead that first indicates ischemia or best represents the stenosed artery on exercise should be the first to reveal ischemia in the operating room, no study has confirmed this

Figure 25-15 Assessment of cardiac risk in a patient about to undergo vascular surgery. If the clinical index is high, coronary arteriography (CATH) is recommended with subsequent coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA) for those with correctable lesions and patient (PT) consent. An equivocal history is followed by Holter monitoring and, if Holter monitoring is abnormal, by dobutamine stress echocardiography. *(See text and data of Fig. 25-9 for analyses by Mantha et al. [305])*

Figure 25-16 (Figure Not Available) Strategy for identifying patients who should undergo cardiac catheterization after acute myocardial infarction. This strategy is based on clinical assessment, evaluation of left ventricular (LV) function by radionuclide angiography (RNA) or echocardiography, analysis of arrhythmias, and stress testing. MI, acute myocardial infarction; CHF, overt congestive heart failure; EF, ejection fraction. *(From Epstein et al [891])*

assumption. If no exercise or coronary angiographic study has been performed, precordial lead V_5 is preferred. [8] [232] [337] [338]

The only known way to increase oxygen supply to the myocardium of patients with coronary artery stenosis is to maintain diastolic BP, hemoglobin concentration [318] [339] [340] (Fig. 25-18) , and oxygen saturation. The main goal of anesthesia practice for these patients has been to decrease the determinants of myocardial oxygen demand (Gibby GL, et al personal communication), heart rate, ventricular wall tension, and contractile performance. [233] [235] [303] [339] [340] [341] Thus, medical management designed to preserve all viable myocardial tissue may include (1) administration of beta-adrenergic receptor-blocking drugs (propranolol, atenolol, esmolol, or metoprolol) to decrease contractility and heart rate; and (2) vasodilation (with nitroglycerin [or its "long-acting" analogues nitroprusside, hydralazine, or prazosin]) to decrease ventricular wall tension. [165] [166] [167] [168] [231] [233] [235] The goal of anesthesia management should be the same, although only one prospective controlled study has documented a decrease in perioperative morbidity by reducing preload, afterload, or heart rate. [166] However, keeping cardiovascular variables within an acceptable range and the rate-pressure product below the threshold for angina appears to be an appropriate objective. [129] [166] [235] [252] [353] [341] [342] The use of Swan-Ganz catheters [300] [343] and transesophageal echocardiography for

Figure 25-17 (Figure Not Available) First-year mortality rates for patients with acute myocardial infarction, according to subgroup. Clear areas represent patients with ejection fractions of more than 30 percent; dotted area represents patients with ejection fractions of less than 30 percent. (The percentages are, by necessity, rough approximations.) MI, acute myocardial infarction; CHF, overt congestive heart failure. *(From Epstein et al [891])*

this type of patient is described in Chapters 30 and 31 , and the intraoperative management of ischemic heart disease patients is discussed in further detail in Chapters 49 through 51 .

Briefly, the author believes that drugs given chronically (e.g., antihypertensive medications and some ACE inhibitors) should be continued through the morning of surgery (see previous section). The topic of chronic drug therapy is discussed in more detail in the last section of this chapter. Finally, a patient with a subendocardial MI has been assumed to be at less perioperative risk than a patient with a transmural MI. This assumption is probably wrong. Thus, patients with a subendocardial MI should be treated no differently than those with a transmural MI.

Valvular Heart Disease

Major alterations in the preoperative management of patients with valvular heart disease have been made regarding the use of anticoagulant therapy and are now based on the causes of disease. Preoperative and intraoperative management of patients with valvular heart disease is discussed in Chapter 49 ; nevertheless, a few important points concerning preoperative care are emphasized here. Of prime importance is realizing that stenotic lesions are managed in a fashion exactly opposite that for regurgitant lesions. Therefore, the type of lesion that exists should be determined preoperatively.

Figure 25-18 Relationship of postoperative myocardial ischemia (solid bars) and morbid cardiac events (shaded bars) to hematocrit for 27 high-risk patients undergoing infrainguinal arterial bypass. *(Data from Nelson et al [340])*

Although the causes of various forms of valvular heart disease have not changed, the relative frequency has. Rheumatic valvulitis is much less common today than it was in the 1970s, and syphilitic aortitis has all but disappeared. Now common are congenital bicuspid aortic stenosis, mitral valve prolapse, hypertrophic cardiomyopathy (also called asymmetric septal hypertrophy or subvalvular aortic stenosis), and mitral valve insufficiency due to calcification, and to drug therapy.

The prognosis and, presumably, the perioperative risk for patients with valvular heart disease depend on the stage of the disease. [319] [330] Although stenotic lesions progress faster than regurgitant lesions, regurgitant lesions secondary to infective endocarditis, rupture of chordae tendineae, or ischemic heart disease can be rapidly fatal. Left ventricular dysfunction is common in the late stage of valvular heart disease. Once again history and physical examination appear to be the most sensitive and specific indicators of disease and disease stage [344] [345] (Table 25-33) (Table Not Available) .

Preoperative maintenance of drug therapy can be crucial: The patient with aortic stenosis can deteriorate rapidly with the onset of atrial fibrillation or flutter, as the atrial contribution to left ventricular filling can be critical in maintaining cardiac output. One of the most serious complications of valvular heart surgery and of valvular heart disease prior to surgery is cardiac arrhythmia. Conduction disorders and chronic therapy with antiarrhythmic and inotropic drugs are discussed elsewhere in this chapter. The reader is referred elsewhere in this book (Chs. 49 and 50) or to other sources [346] [347] for discussion of the management of the child with congenital heart disease who is undergoing noncardiac surgery.

Mitral Valve Prolapse

Mitral valve prolapse, perhaps the most frequent valvular abnormality, occurs in 5 to 17 percent of otherwise healthy people. It is associated with atrioseptal secundum defects, [348] [349] thoracic skeletal abnormality (due to time of development of these structures), and, for unknown reasons, migraine anxiety neurosis and autonomic dysfunction. Hereditary transmission has been proposed as occurring through autosomal dominance with reduced expressivity in humans. Mitral valve prolapse is also associated with von Willebrand syndrome and polycystic kidney disease, and the presence of one condition requires a search (by at least history and physical examination) for the other.

Mitral valve prolapse presents either asymptomatically or with palpitations, dyspnea, atypical chest pain, dizziness, syncope, or sudden death. Supraventricular arrhythmias (associated

TABLE 25-33 -- Bedside Diagnosis of Systolic Murmurs: Sensitivity, Specificity, and Predictive Value of Diagnostic Maneuvers

(Not Available)

Modified from Lembo et al. [344]

with atrioventricular bypass tracts and the preexcitation syndrome) occur in more than 50 percent of patients with mitral valve prolapse. Ventricular arrhythmias (usually in surgery) occur in 45 percent of such patients, bradyarrhythmias in 25 percent, and sudden death in 1.4 percent. [348] [349] The frequent occurrence of transient cerebral ischemia has resulted in the chronic use of aspirin or anticoagulants in patients with mitral valve prolapse, and the potential for endocarditis has led to the recommendation for prophylaxis with antibiotics prior to known bacteremic events, [348] [349] [350] and the avoidance of head-up positions and decreased afterload in such patients.

Valvular Heart Disease

Preoperative Antibiotic Prophylaxis for Endocarditis

Patients who have any form of valvular heart disease, as well as those with intracardiac (ventricular septal or atrial septal defects) or intravascular shunt, should be protected against endocarditis at the time of known bacteremic events. Endocarditis has occurred in a sufficiently significant number of patients with hypertrophic cardiomyopathy (subvalvular aortic stenosis, asymmetric septal hypertrophy) and mitral valve prolapse to warrant the inclusion of these two conditions in the prophylaxis regimen.

Is endotracheal intubation a bacteremic event? Bacteremia occurs after the following events at these rates: dental extraction, 30 to 80 percent; brushing of teeth, 20 to 24 percent; use of oral irrigation devices, 20 to 24 percent; barium enema, 11 percent; transurethral prostate resection, 10 to 57 percent; upper gastrointestinal endoscopy, 8 percent; nasotracheal intubation, 16 percent (4 of 25 patients); and orotracheal intubation, 0 percent (0 of 25 patients). [351] [352] Thus, although bacteremia from orotracheal intubation is rare, I believe that prophylaxis should be given to patients with valvular heart disease before instituting instrumentation of the gallbladder, GI tract, oropharynx, or genitourinary tract. The choice of antibiotic for prophylaxis should be aimed at the most commonly occurring (i.e., most numerous) pathogen [353] (Table 25-34) . Note that these prophylactic regimens should be altered to prevent sepsis after specific surgical procedures [354] (Table 25-35) (Table Not Available) . Guidelines of the American Heart Association state that all antimicrobial prophylaxis should be started 30 minutes to 1 hour, rather than 24 hours, before a known bacteremic event, so as to reach therapeutic levels without superinfecting the patient with unusual pathogens. [353] [354]

TABLE 25-34 -- Endocarditis Prophylaxis: Recommended Antibiotic Regimens[a]

	DOSAGE FOR ADULTS	DOOSAGE FOR CHILDREN (IN NO CASE TO EXCEED ADULT DOSE)
DENTAL AND UPPER RESPIRATORY PROCEDURES LIKELY TO PRODUCE BACTEREMIA (I.E., TONSILLOADENOIDECTOMY, BRONCHOSCOPY, NASAL INTUBATION, NASOGASTRIC TUBE PLACEMENT)		
Oral		
Amoxicillin	3 g 1 h before procedure and 1.5 g 6 h later	50 mg/kg
Amoxicillin, penicillin allergy:		
Erythromycin ethylsuccinate	800 mg	20 mg/kg 1 h before procedure and 10 mg/kg 6 h later
or		
Erythromycin sisarate	1 g PO 2 h before procedure and half the initial dose 6 h later	
or		
Clindamycin	300 mg orally 1 h before procedure and 150 mg 6 h after initial dose	10 mg/kg and 5 mg/kg 6 h later
Parenteral		
Ampicillin	2 g IM or IV 30 min before procedure	50 mg/kg IM or IV 30 min before procedure
Penicillin allergy: Clindamycin	300 mg IV 30 min before procedure	10 mg/kg IV 30 min before procedure
GASTROINTESTINAL AND GENITOURINARY PROCEDURES (I.E., GI OR GU SURGERY, OR INSTRUMENTATION OR SURGERY INVOLVING A TISSUE POSSIBLY CONTAMINATED WITH GI OR GU ORGANISMS)		
Parenteral		
Ampicillin	2 g IM or IV 30 min before procedure	50 mg/kg IM or IV 30 min before procedure
Plus gentamicin	1.5 mg/kg (not to exceed 80 mg) IM or IV 30 min before procedure	2.0 mg/kg IM or IV 30 min before procedure
Plus amoxicillin	1.5 g PO 6 h after ampicillin and gentamicin or repeat ampicillin and gentamicin after initial dose	50 mg/kg
Penicillin, amoxicillin allergy: Vancomycin	1 g IV infused slowly over 1 h beginning 1 h before procedure	20 mg/kg IV infused slowly over 1 h beginning 1 h before procedure
Plus gentamicin	1.5 mg/kg (not to exceed 80 mg) IM or IV 30 min before procedure	2.0 mg/kg IM or IV 30 min before procedure
Oral		
Amoxicillin	3 g 1 h before procedure and 1.5 g 6 h after initial dose	50 mg/kg 1 h before procedure and 25 mg/kg 6 h after initial dose

Data from Dajani et al [353]

[a] The frequently used cephalosporins are not recommended. A single dose of the parenteral drugs is probably adequate, because bacteremias after most oral cavity and diagnostic procedures are of short duration. However, one or two follow-up doses may be given at 8- to 12-h intervals in selected patients, such as hospitalized patients judged to be at higher risk.

TABLE 25-35 -- Prevention of Wound Infection and Sepsis in Surgical Patients

(Not Available)

Modified from Med Lett Drug et al Ther [354]

Cardiac Valve Prostheses and Anticoagulant Therapy, and Prophylaxis for Deep Venous Thrombosis

Prothrombin time (PT) or international ratio should be within 20 percent of control international ratio of time at the time of operation or an appreciable risk is incurred. [355] Therefore, to produce a normal PT on the day of surgery, chronic anticoagulant therapy should be suspended in surgical patients with cardiac valve prostheses. This can be done with safety several days before surgery if the prosthesis is an aortic valve. However, because the risk of thromboembolism is greater with mitral valve prostheses (5%) than with aortic valve prostheses (1-3%), patients having mitral valve prostheses should have rapid reversal of oral anticoagulation with vitamin K the day before surgery or fresh frozen plasma on the day of surgery. For resumption of anticoagulant therapy after surgery, rapid anticoagulation with heparin 12 hours postoperatively has proved successful in patients with mitral valve prostheses. [356] In patients with new aortic valve prostheses, resumption of anticoagulant therapy can start 2 days after surgery. Regional anesthetic techniques might be avoided, although controversy exists on this issue. [357] [358] [359] [360] [361] [362] [363] [364] [365] [366] [367] [368] [369] [370] [371] [372] Many practitioners do not hesitate to use regional anesthesia in the face of prophylaxis for deep venous thrombosis. [361] [364] [366] [368] However, many reports of epidural hematoma have been associated with anticoagulant therapy. Large retrospective reviews of outcome after epidural and/or spinal anesthesia during or shortly before initiation of anticoagulant therapy with heparin have not reported neurologic dysfunction relating to hematoma formation in any patient. [361] [362] [363] [364] This paucity of epidemiologic data, while reassuring, does not reduce the need for frequent evaluation of neurologic function and search for back pain in the perioperative period after regional anesthesia for any patient receiving any clotting function inhibitor, including aspirin. [369] [370] [371] [372] The risk of regional anesthesia concurrent with prophylaxis for deep venous thrombosis with heparin is greater with the use of the low-molecular-weight heparin. (Heparin-induced thrombocytopenia has been treated successfully with intravenous immunoglobulin. [366])

Deep venous thromboses are so common in postoperative patients that almost 1 percent of postsurgical patients die of fatal pulmonary embolism [373] (Table 25-36) . Because of this high mortality risk, prophylaxis against deep venous thrombosis has attained widespread acceptance; thus, prophylaxis often begins with 5,000 units of heparin given subcutaneously 2 hours prior to surgery. [373] [374] [375] Other trials have shown equal effect with external pneumatic compression. [374] [376] Persuading surgeons to use this technique may provide greater assurance in using regional anesthesia. Such an option, however, is not available for the patient with a prosthetic valve.

Another problem that can arise is managing the pregnant patient with a prosthetic valve during delivery. It is recommended that warfarin be replaced by subcutaneous heparin during the peripartum period. During labor and delivery, elective induction is advocated with discontinuance of all anticoagulant therapy, as indicated for the particular valve prosthesis (discussed previously). [377]

Auscultation of the prosthetic valve should be performed preoperatively to verify normal functioning [378] (Fig. 25-19) (Figure Not Available) . Abnormalities in such sounds warrant preoperative consultation and verification of functioning.

Cardiac Conduction Disturbances

Cardiac Arrhythmias

Bradyarrhythmias, especially if profound or associated with dizziness or syncope, are generally managed with pacemakers. However, on rare occasion, chronic bifascicular block (right bundle branch block with left anterior or posterior hemiblock or left bundle branch block with combined left anterior and posterior hemiblocks), even when only first-degree heart block is present, progresses to complete heart block and sudden perioperative death. This is a rare occurrence. In six studies, fewer than 2 percent of the approximately 266 patients with bifascicular block progressed to complete heart block perioperatively. [379] [380] [381] [382] [383] [384] On the other hand, these patients have a high 5-year mortality rate (160 of 554 patients, or 35%). Most of the deaths were related to tachyarrhythmias or MI--events usually not preventable by pacemakers. [385] Thus, the presence of bifascicular block on ECG should make the anesthesiologist more worried about associated coronary artery disease or left ventricular dysfunction. Nevertheless, these patients rarely have complete heart block perioperatively. Therefore, prophylactic preoperative insertion of temporary pacing wires for bifascicular block does not seem warranted. However, a central route can be established in advance in the event a temporary pacemaker needs to be inserted. (Most operating rooms do not rely on transthoracic pacing, although such might be attempted if available.) [386] The actual pacemaker equipment and appropriate personnel should be immediately available and tested regularly, because symptomatic heart block does occur perioperatively in more than 1 percent of patients. [379] [380] [381] [382] [383] One study appears to have confirmed this rate of at least 1 percent for patients undergoing cardiac surgery. [387] One percent of patients who had no preoperative insertion of a pacing pulmonary artery catheter subsequently required pacing prior to cardiopulmonary bypass. By contrast, 19 percent of patients who had such a catheter in place had cardiac pacing prior to cardiopulmonary bypass. Predictors of the need for pacing included prior symptomatic bradyarrhythmias, a history of transient complete atrioventricular block, and aortic valve disease.

Premature ventricular contractions (PVC) of more than five per minute on preoperative examination correlate with perioperative cardiac morbidity. [289] [297] [298] [311] To the classic criteria for treating PVCs (the presence of R-on-T couplets, the occurrence of more than three PVCs per minute, and multifocality of PVCs) must be added frequent (>10/h over a 24-h period) and repetitive ventricular beats. Electrophysiologic and programmed ventricular stimulation studies are being used to indicate and guide treatment for patients with ischemic heart disease or recurrent arrhythmias and for survivors of out-of-hospital cardiac arrest. [388] Although such patients are often treated with antiarrhythmic therapy, attention to their underlying condition should be a focus of our preoperative management. Chronic antiarrhythmic therapy

TABLE 25-36 -- Incidence of Deep Venous Thrombosis and Fatal Pulmonary Embolism, and Recommended Prophylaxis

TYPE OF SURGERY	INCIDENCE OF			RECOMMENDED PROPHYLAXIS
	DEEP VENOUS THROMBOSIS (%)	*PROXIMAL DEEP VENOUS THROMBOSIS* (%)	*FATAL PULMONARY EMBOLISM* (%)	
General				
Age > 40 y	10	<1	0.1	
Age > 60 y	10-40	3-15	0.8	
Malignancy	50-60			
Thoracic	30			
Vascular				Low-dose heparin with or without compression stockings
Aortic repair	26			or
Peripheral	12			
Urologic				External pneumatic compression
Open prostatectomy	40			
TURP	10			
Other urologic	30-40			
Major gynecologic				
With malignancy	40			
Without malignancy	10-20			
Neurosurgery				

Craniotomy	20-80			External pneumatic compression
Laminectomy	4-25		1.5-3.0	
Orthopedic				
Total hip replacement	40-80	10-20	1.0-5.0	Low-dose heparin and external pneumatic compression
Hip fracture	48-75		1.0-5.0	
Tibial fracture	45			or Warfarin or Adjusted-dose heparin or Low-molecular-weight heparin
Total knee	60-70	20	1.0-5.0	External pneumatic compression or Warfarin or Low-dose heparin
Head, neck, chest wall	11			
Medical				
Acute myocardial infarction	30	6		Ambulation
Stroke	60-75			or Low-dose heparin
Acute spinal injury	60-100			
Other bed bound	26			

Abbreviations: TURP, transurethral resection of the prostate

is discussed in the last section of this chapter. Torsades de pointes is an arrhythmia characterized by episodes of alternating electrical polarity such that the major vector of the QRS complex seems to alternate around an isoelectric line. The hallmark enabling differential diagnosis from ventricular tachycardia is the unusual response of this arrhythmia to commonly used antiarrhythmic drugs. That is, the use of drugs that prolong the QT interval (e.g., quinidine, procainamide, and disopyramide and the antipsychotic phenothiazines) may well make the arrhythmia more frequent or of longer duration. The report of the sudden occurrence of torsades de pointes during surgery has been rare in the anesthesia literature. Immediate therapy consists of administration of magnesium or electrical cardioversion, followed by overdrive cardiac pacing or administration of beta-adrenergic agonists and discontinuation of drugs that prolong the QT interval.

Premature atrial contractions and cardiac rhythm other than sinus also correlate with perioperative cardiac morbidity. [289] [297] These arrhythmias may be more a marker of poor cardiovascular reserve than a specific cause of perioperative cardiac complications.

Preexcitation syndrome is the name for supraventricular tachycardias associated with atrioventricular bypass tracts. [389] Successful treatment, which is predicated on an understanding of the clinical and electrophysiologic manifestations of the syndrome, consists of either catheter ablation techniques [385] or surgery using preoperative and intraoperative techniques that avoid release of sympathetic substances and other vasoactive substances and therefore

Figure 25-19 (Figure Not Available) Summary of the normal acoustic characteristics of valve prostheses according to type and location. SEM, systolic ejection murmur; DM, diastolic murmur; S_1, first heart sound; S_2, second heart sound; P_2, pulmonary second sound; A_2, aortic second sound; AO, aortic valve opening sound; AC, aortic valve closure sound; MO, mitral valve opening sound, MC, mitral valve closure sound. *(From Smith et al [376])*

tachyarrhythmias. [390] [391] [392] (Anesthesia for electrophysiologic procedures is discussed in Chs. 40, 49, and 66.)

Pacemakers (Control of Arrhythmias)

The types of pacemakers available and the indications for their use have changed significantly since 1980. More than 90 percent of pacemakers are inserted for the treatment of bradyarrhythmias occurring either after tachycardia (brady-tachy syndrome) or by themselves (that is, in sick sinus syndrome or AV conduction disorders). Physiologic pacing is an attempt to increase the patient's hemodynamic response to increased metabolic demands. An increase in heart rate provides greater augmentation of cardiac output than does maintenance of atrioventricular synchrony. The rate of pacemaker insertion has also declined by more than 50 percent since 1980; in 1984 a publication by the American College of Cardiology and the American Heart Association on the indications for pacemaker insertion codified these changes in practice patterns. The most common pacemaker for this type of dysfunction is the ventricular R-wave inhibited (demand) type (VVI). (Letter codes are described later and in Table 25-37.) More complex pacemakers are now being employed to provide better cardiac output in stressful situations and to decrease myocardial wall stress [393] or to treat ventricular or supraventricular tachyarrhythmias. Lithium batteries now give a pacemaker a 5- to 10-year life span. Programmable pacemakers are adjustable for sensitivity and rate. Currently available atrial pacemakers fired by an outside radiofrequency source permit termination of re-entrant or pre-excitation atrial arrhythmias; similarly, ventricular pacemakers can be used to terminate supraventricular tachycardia and recurrent ventricular tachycardia. [394] Thus, in addition to learning about the patient's underlying disease, current condition, and drug therapy, the anesthesiologist must learn, preoperatively, the following information about any implanted pacemaker [394]:

TABLE 25-37 -- The NASPE/BPEG Generic (NBG) Five-Letter Code for Pacemaker Systems

FIRST LETTER: CHAMBER PACED	SECOND LETTER: CHAMBER SENSED	THIRD LETTER: MODE OF RESPONSE	FOURTH LETTER (IF USED): PROGRAMMABLE FEATURES	FIFTH LETTER (IF USED): ARRHYTHMIA TREATMENT
A = atrium	A = atrium	T = triggered	P = programmable (single)	O = none
V = ventricle	V = ventricle	I = inhibited	M = multiprogrammable	P = Pacing (antitachyarrhythmia)
D = dual	D = dual	D = dual (T & I)	O = not programmable	S = shock
O = none	O = none	O = not applicable	R = rate modulated	D = dual (P & S)
			C = communicating	

Note: Positions I-III are used exclusively for antibradyarrhythmia function.

1. The indication for placement of the pacemaker and the default rhythm (i.e., what rhythm occurs if the pacemaker does not capture).
2. The type of pacemaker (demand, fixed, or radiofrequency), the chamber paced, and the chamber sensed. Pacemakers have traditionally been given a five-letter code (Table 25-37) . However, most pacemakers implanted since 1980 have codes consisting of only the first three letters. The *first* letter indicates the chamber paced (i.e., V = ventricle, A = atrium, D = dual or both). The *second* letter indicates the chamber sensed (i.e., V = ventricle, A = atrium, D = dual, 0 = none). The

third letter indicates the sensing pattern (i.e., 0 = no sensing, fixed mode; I = inhibited, demand pacer; T = triggered, meaning that the sensing of an electrical impulse triggers a pacemaker spike; D = dual, i.e., both T and I.). For example, a V00 pacemaker paces the ventricle, does not sense, and is in a fixed mode. In other words, it is a fixed-rate ventricular pacemaker. A VVI pacemaker paces the ventricle, senses the ventricle, and is inhibited. It is a ventricular-inhibited demand pacemaker. A DVI pacemaker

paces both atrium and ventricle, senses only the ventricle, and is inhibited. Thus, it is a sequential AV demand pacemaker that fires when it does not sense intrinsic ventricular activity. Rate-modulated pacemakers increase the heart rate in response to increased demand. They have special sensors and are placed in patients who may have abnormal sinus node function. These pacemakers have an R in the fourth position of the pacemaker letter code [393] (e.g., VVIR; see Table 25-37) . A DDDCP pacemaker has multiprogrammable "physiologic" dual chamber pacing, with telemetry and antitachyarrhythmia-pacing capability. An OOOPS is a simple, programmable cardioverter, defibrillator, or cardioverter-defribrillator. It cannot be overemphasized that no generic code can describe every antiarrhythmic device in a comprehensive and unambiguous fashion. It seems to me beneficial to consult with an electrophysiologist/cardiologist before anesthetizing any patient who has a pacemaker.

3. How to detect deterioration in battery function (increased rate or decreased rate).
4. How to change the mode or to fire the pacemaker if it is of the radiofrequency type. (These procedures should not only be learned by the anesthesiologist but also be demonstrated to him or her. Also, the magnet and/or programming device should be in or near the operating room at the time of surgery.)
5. The current rate and sensitivity settings of the pacemaker.
6. Whether the pacemaker is currently functioning and how well.

Because demand pacemakers can sense electrocautery, which sometimes inhibits pacemaker firing, asystole can occur in the pacemaker-dependent patient during electrocautery. Most pacemakers can be converted to a fixed rate, and the anesthesiologist should take the following precautions: (1) have the cardiologist demonstrate how this is done and (2) have the necessary magnet and/or programming device available in the operating room. In addition, the ground plate should be as far from the pulse generator and lead as possible, a bipolar form of electrocautery should be used, and, if possible, some measure of blood flow should be monitored (i.e., Doppler detector, pulse oximetry unaffected by electrocautery, or intra-arterial line). The rationale for the last measure is that electrocautery temporarily affects the accuracy of ECG results; because asystole could occur during this period, a measure of blood flow is necessary. Currently, at least eight manufacturers produce a total of more than 80 types of pacemakers, with a variety of default programs. A default program is the secondary program (i.e., the generator circuit) to which the primary program will revert if it senses problems in the initial circuit. Because default programs differ, pacemaker malfunction will present differently depending on the brand and model. Thus, it is necessary to learn before surgery how problems will manifest with each pacemaker during surgery. [394]

The most common cause of temporary pacemaker malfunction is lack of contact between the electrode wire and the endocardium. Pacemaker spikes continue to exist on the ECG oscilloscope, even when no myocardial contractions propel blood. This situation has occurred with muscular exertion, blunt trauma, cardioversion, and positive-pressure ventilation. [395] Treatment consists of advancing the electrode until it captures, administering isoproterenol (if that worked in the past), external pacing, or, failing that, cardiopulmonary resuscitation.

During the preoperative examination, the anesthesiologist can also assess the progression of underlying disease (e.g., CHF, electrolyte disorders, and the condition of all systems related to the underlying disease). Antiarrhythmic therapy and its implications are discussed in the last section of this chapter.

Also see Chapters 30 and 32 regarding detection and monitoring of cardiac arrhythmias.

DISORDERS OF THE RESPIRATORY AND IMMUNE SYSTEMS

General Preoperative Considerations

Although little may seem to have changed in preoperative preparation of the patient with respiratory disease, this impression is not true. Major changes in drug therapy have occurred, and appreciation has increased regarding the effects of smoking on perioperative and chronic care. [396] [397] [398] [399] [400] [401] [402] [403] [404] [405] [406] [407] [408] [409]

The main purpose of preoperative testing is to identify patients at risk of perioperative complications and to institute appropriate perioperative therapy. Preoperative assessment can also establish baseline function and the feasibility of surgical intervention. Whereas numerous investigators have used pulmonary function tests that define inoperability or high-risk versus low-risk groups for pulmonary complications, few have been able to demonstrate that the performance of any specific preoperative or intraoperative measure reliably decreases perioperative pulmonary morbidity or mortality. Because routine preoperative pulmonary testing and care are discussed extensively in Chapters 24 and 72 , the current discussion is limited to an assessment of the effectiveness of this type of care.

In fact, only four randomized prospective studies indicate an outcome benefit of preoperative preparation; a few more imply a benefit of intraoperative and postoperative pain therapy techniques [410] (usually planned preoperatively; see Ch. 23) . Stein and Cassara [411] randomly allocated 48 patients to undergo preoperative therapy (cessation of smoking, use of antibiotic treatment for purulent sputum, and use of bronchodilating drugs, postural drainage, chest physiotherapy, and ultrasonic nebulizer) or no preoperative therapy. The no-treatment group had mortality of 16 percent and morbidity of 60 percent, as opposed to the 0 and 20 percent rates, respectively, for the treatment group. In addition, the treatment group spent an average of 12 postoperative days in the hospital, compared with 24 days for the 21 survivors in the no-treatment group.

Collins et al [412] prospectively examined the benefits of preoperative antibiotics, perioperative chest physiotherapy and therapy with bronchodilating drugs, and routine postoperative analgesia (morphine) on postoperative respiratory complications in patients with chronic obstructive pulmonary disease (COPD). Of those therapies, only preoperative treatment with antibiotics had a beneficial effect.

Warner and colleagues [413] collected data retrospectively about smoking history and prospectively (concurrently) about pulmonary complications for 200 patients undergoing

CABG. These investigators documented that 8 weeks or more of smoking cessation was associated with a 66 percent reduction in postoperative pulmonary complications. Smokers who stopped for less than 8 weeks actually had an increase (from 33% for current smokers to 57.1% for recent quitters) in the rate of one or more of the six complications surveyed: purulent sputum with pyrexia; need for respiratory therapy care; bronchospasm requiring therapy; pleural effusion and/or pneumothorax necessitating drainage; segmental pulmonary collapse, as confirmed by radiograph; or pneumonia necessitating antibiotic therapy. Although others have found both shorter and longer periods of cessation of smoking prior to cardiovascular benefits [414] [415] [416] and hematologic benefits, [417] this is one of the few studies that show both harmful and beneficial outcomes for pulmonary status from the same maneuver--cessation of smoking. The fact that anesthesiologists rarely see their patients 8 weeks or more before surgery presents a dilemma: If one is unable to advise the patient to stop smoking 8 weeks or more before surgery, is it preferable for the patient to continue smoking? Perhaps these data will further support the implementation of preoperative assessment clinics in which anesthesiologists are able to advise and counsel patients about risk reduction. When Skolnick and coworkers [409] studied 602 children prospectively, exposure to passive smoking (as measured by urinary cotinine, the major metabolite of nicotine) correlated directly with airway complications. Children with the least exposure to passive smoke had the fewest complications.

Celli and coworkers [418] performed a randomized prospective controlled trial of intermittent positive-pressure breathing (IPPB) versus incentive spirometry and versus deep-breathing exercises in 81 patients undergoing abdominal surgery. The groups exposed to a respiratory therapist (regardless of treatment given) had both shorter hospital stays and an incidence of clinical complications that was more than 50 percent lower (30-33% versus 88%) than the control group. Thus, this third prospective study indicates that outcome improves when there is any concern about lung function on the part of someone knowledgeable in maneuvers designed to clear lung secretions.

Bartlett et al [419] randomly assigned 150 patients undergoing extensive laparotomy to one of two groups. One group received preoperative instruction in and postoperative use of (10 times/h) incentive spirometry. The other group received similar medical care but no incentive spirometry. Only 7 of 75 patients using incentive spirometry had postoperative pulmonary complications, as opposed to 19 of 75 in the control group. However, other studies have not shown a benefit for specific treatments or have been too contaminated with bias to have a clear result emerge. Lyager et al [420] randomly assigned 103 patients undergoing biliary or gastric surgery to receive either incentive spirometry with preoperative and postoperative chest physiotherapy or only preoperative and postoperative chest physiotherapy. No difference in postoperative course or pulmonary complications was found between the two groups. Other studies have shown a specific benefit (i.e., above that provided by routine care) for chest physiotherapy and IPPB. These studies are usually poorly controlled, not randomized, and/or retrospective in design; these deficiencies probably substantially bias the results toward finding a benefit in reducing postoperative pulmonary complications. [421] [422] [423] [424] Although randomized prospective studies showed no benefit or actual harm from chest physiotherapy and IPPB on the resolution of pneumonia, [425] [426] or postoperative pulmonary complications, [412] [418] [423] [426] [427] [428] [429] the four studies cited previously [411] [412] [418] [419] and numerous retrospective studies [413] [421] [422] [423] strongly suggest that preoperative evaluation and treatment of patients with pulmonary disease actually decrease perioperative respiratory complications, even if only by causing a change in anesthetic techniques. [410]

The evaluation of dyspnea is especially useful and so warrants discussion here. (For a review of the specific pulmonary function tests that identify high-risk groups, see Ch. 24) . Boushy et al [429] found that grades of preoperative dyspnea correlated with postoperative survival. (The grades of respiratory dyspnea are provided in Table 25-38.) (Table Not Available) Mittman [430] demonstrated an increased risk of death after thoracic surgery from 8 percent in patients without dyspnea to 56 percent in patients who were dyspneic. Similarly, Reichel [431] found that no patients died after pneumonectomy if they were able to complete a preoperative treadmill test for 4 minutes at the rate of 2 mph on level ground. Other studies have found that history and physical examination of the asthmatic subject can also predict the need for hospitalization. [398] [432] Wong and colleagues [433] found that the risk index (Table 25-39) (Table Not Available) correlated with postoperative pulmonary complications.

Other than dyspnea, what preoperative conditions make postoperative respiratory complications more likely [424] [433] [434] [435] (Ch. 72) ? The important information and conditions to search for during the history-taking and physical examination are as follows:

TABLE 25-38 -- Grade of Dyspnea Caused by Respiratory Problems (Assessed in Terms of Walking on the Level at a Normal Pace)

(Not Available)

Modified from Boushy et al. [429]

1. Dyspnea (see Table 25-38) (Table Not Available) .
2. Coughing and production of sputum. Sputum, if present, should undergo Gram staining and culturing, and appropriate antibiotic treatment should be instituted.
3. Recent respiratory infection. Viral respiratory infections affect respiratory function, giving rise to increased airflow obstruction that may persist for as long as 5 weeks. [436] [437] These infections also adversely affect respiratory mechanisms responding to bacteria. However, whether the incidence of complications in normal children is lessened by waiting 5 weeks until the symptoms of respiratory infections have disappeared is open to question. [438] [439] [440] [441] [442] [443] For all children (and possibly adults), it appears appropriate to

delay surgery that requires tracheal intubation for 5 weeks after the presence of an upper respiratory infection.
4. Hemoptysis.
5. Wheezing and prior use of bronchodilating drugs and corticosteroids (systemic or inhaled). Wheezing often suggests potentially reversible airway obstruction but is a notoriously poor indicator of the degree of obstruction. In addition, not all wheezing is caused by bronchospasm. Cardiac and other pulmonary causes must be differentiated from asthma. [444] Drug therapy for asthma should be ascertained and optimized if possible. Asthmatics have a 4-fold increase in perioperative respiratory complications. Holleman and Simel [398] found that auscultated audible wheezing on nonforced expiration (along with a 70-pack-year history of smoking and patient sensation of wheezing) was a reliable sign of severe airflow limitation.
6. Pulmonary complications from previous surgery. Prolonged endotracheal intubation after surgery can be required by many conditions, most probably respiratory and neuromuscular disorders.
7. A history of smoking. The incidence of respiratory complications is higher among tobacco smokers than among nonsmokers. [413] [421] [422] [445]
8. Age, general history of the patient, and any other significant physical findings. Although other disease conditions probably increase respiratory risk, the documentation on this hypothesis is barely adequate. [433] Old age definitely increases respiratory and cardiac risk. [413] [420] [445] [446] Cardiovascular history and examinations are obviously important in themselves but are also especially helpful in revealing signs of pulmonary hypertension, such as right ventricular lift (i.e., lift over the lower sternum), fixed and widely split second heart sound, and S_4 gallop at the left sternal border.
9. Breathing frequency and form. Pursed lips, cyanosis, and use of accessory muscles should be noted. Vocal cord dysfunction occurs commonly from both psychosocial illness and the attempt to increase end-expiratory pressure. [447]
10. Body habitus:
    a. Abnormalities of the chest wall, trauma, kyphoscoliosis with restrictive lung disease. Development of a barrel chest is a late manifestation of obstructive lung disease.
    b. Obesity. A weight 30 percent over ideal weight doubles the incidence of respiratory complications (Amalraj S, personal communication). [88] [89] [90] [91] [92] [93] [425] [445]
11. Adequacy of upper airway, presence of tracheal deviation, ease of face mask application, ease of endotracheal intubation.
12. Presence of rales, rhonchi, wheezing (especially on nonforced expiration), diaphragmatic excursion, and air movement and the ratio of expiratory to inspiratory times. [398]
13. Site of proposed surgery. Upper abdominal surgery increases the incidence of perioperative pulmonary complications. [410] [411] [422] [433] [434] [448]
14. Surgery performed on an emergency basis. Wong and colleagues [433] found that surgery performed on an emergency basis increased the risk of perioperative pneumonia 13-fold for patients with severe COPD.

TABLE 25-39 -- Classification of Risk of Pulmonary Complications for Thoracic and Abdominal Procedures

(Not Available)

Modified from Shapiro et al. [602]

Chapters 24 and 72 review the value of chest radiographs and pulmonary function tests in identifying patients with preoperative pulmonary disease as well as which tests should be ordered and for whom. Any patient who will require postoperative ventricular support should be considered for preoperative testing. Although we have yet to find the ideal pulmonary function test that guarantees success or that predicts a poor outcome that could be improved by therapy, the following conditions are relatively good predictors of complications associated with resection of a lung: a maximum breathing capacity of less than 40 or 50 L/min/70 kg, an FEV_1/FVC of less than 40 percent of predicted, an FEV_1 of less than 1.2 L, or a maximum midexpiratory flow rate of less than 50 L/min. [421] [424] [430] [431] [432] [433] [434] [449] [450] [451]

To these is now added the diffusing capacity of the lung for carbon monoxide (DLCO). [312] [450] [451] DLCO decreases with fixed obstructive lung disease (i.e., emphysema) but remains normal in bronchospastic disease. In one study, when preoperative DLCO was less than 60 percent of predicted, the mortality rate was 25 percent and pulmonary morbidity rate was 45 percent, whereas a DLCO of 100 percent or greater of predicted was associated with a 0 percent mortality rate and an 11 percent pulmonary morbidity rate. A subsequent study confirmed these findings. [451] Although I have always tried to reduce laboratory studies, these may prove useful in the patient with COPD who requires pulmonary surgery. Further analysis is necessary to determine whether the finding of a normal DLCO may allow expansion of the usual spirometric criteria to permit successful pulmonary resection in patients who are currently excluded as candidates for such operations. The author conducts such tests on any patient with dyspnea of grade II or higher or on any patient

who shows significant abnormalities or risk on the first 13 factors listed previously. Wong and colleagues [433] found that the Shapiro score (see Table 25-39) (Table Not Available) and ASA physical status independently predicted adverse outcome after surgery for patients with severe obstructive pulmonary disease. Although this score depends heavily on abnormal pulmonary function tests for grading risk, abnormalities in the cardiovascular, neuromuscular, and central nervous systems, plus restrictions in ambulation, can also increase the risk score. A Shapiro score of 5 points or more was associated with a 17-fold higher risk of perioperative death and a 14-fold higher risk of postoperative bronchospasm after nonthoracic surgery. [433]

Despite the lack of definitive data establishing the efficacy of preoperative pulmonary testing and therapy, I recommend the following approach:

1. Eradicate acute infections and suppress chronic infections by using appropriate diagnostic measures and antibiotic treatment.
2. Relieve bronchospasm by using inhaled corticosterodis and bronchodilating drugs and document such relief with measurements of FEV_1 (Chs. 24 and 72).
3. Institute measures to improve sputum clearance and to familiarize the patient with respiratory therapy equipment (incentive spirometry) and postural drainage maneuvers. Initiate practice coughing and deep-breathing exercises (Chs. 24 and 72) .
4. Treat uncompensated right ventricular heart failure with digoxin, diuretics, oxygen, and drugs that decrease pulmonary vascular resistance (e.g., hydralazine). [452]
5. Use low-dose heparin prophylactically to decrease the incidence of venous thrombosis (and pulmonary emboli). [373] [374] [375] [453]
6. Encourage reduction or cessation of smoking 8 weeks or more prior to surgery. [413] Although the debate about cessation of smoking includes more than pulmonary risk, cardiovascular, hematologic, and aspiration risks also have not been shown to be responsive to short-term cessation. [413] [414] [415] [416] [417] Perhaps the benefit of using a major life event--an operation--to promote cessation of smoking is worth the increased short-term risk that encouraging cessation within a day or two of surgery would entail; the latter hypothesis remains to be tested. Even young people who smoke only one-half to one pack of cigarettes per day exhibit abnormalities in respiratory function. [454] Avoiding passive smoking also appears beneficial. [409]

Specific Diseases

Pulmonary Vascular Diseases

Pulmonary vascular diseases include pulmonary hypertension secondary to heart disease (postcapillary disorders), parenchymal lung disease (pulmonary precapillary disorders), pulmonary embolism, and cor pulmonale from chronic obstructive pulmonary disease. [455] Optimal preoperative management of these conditions requires treatment of the underlying disease. [455] [456] Because pulmonary embolism can be especially difficult to diagnose, it is crucial to be especially alert to the possibility of this disease. The clinical findings of pulmonary emboli are not always present or specific for the diagnosis. The history may include tachypnea, dyspnea, palpitations, syncope, chest pain, or hemoptysis. Physical examination can reveal a pleural rub, wheezing, rales, a fixed and split second heart sound, right ventricular lift, or evidence of venous thromboses, none of which is present in most patients. If the ECG shows an S_1-Q_3 pattern, lung perfusion scans can be obtained to rule out the diagnosis of pulmonary emboli. A high degree of suspicion is necessary to warrant angiography and anticoagulation or fibrinolytic therapy. If possible, the reactivity of the pulmonary vasculature should be determined, for it may be enhanced or decreased by such agents as nifedipine, hydralazine, nitroglycerin, prazosin, tolazoline, phentolamine, and nitric oxide. Monitoring of pulmonary artery pressure is often required; preoperative measures should be undertaken to ensure that the patient is not exposed to conditions that elevate pulmonary vascular resistance (i.e., hypoxia, hypercarbia, acidosis, lung hyperinflation, hypothermia) [457] or that decrease blood volume (prolonged restriction of fluid intake) or systemic vascular resistance.

Infectious Diseases of the Lung

Preoperative evaluation and treatment should follow the basic guidelines outlined in the introduction to this section; treatment of the underlying disease should be completed before all but emergency surgery is performed. It bears repeating that viral respiratory infections do affect respiratory function, giving rise to increased airflow obstruction (especially in the small airways) that may persist for at least 5 weeks. Viral respiratory infections also adversely affect the respiratory mechanisms that defend against bacteria. Within 5 weeks of an upper respiratory tract infection, children may have an increased incidence of perioperative respiratory tract complications after intubation. [438] [439] [440] [441] [442] [443] It appears appropriate to delay surgery that requires tracheal intubation for all children (and possibly all adults) for 5 weeks after an upper respiratory infection. [438] [439] [440] [441] [442] [443]

Even though elective surgery should be postponed whenever infectious diseases of the lung are present, patients undergoing emergency surgery often have nosocomial infections and immunocompromised systems. The predominant pathogens for nosocomial pneumonia are gram-negative bacilli, *Staphylococcus aureus, Haemophilus influenzae,* anaerobes, and pneumococci. Furthermore, tuberculosis has been increasing since 1985, probably because of reactivation in patients infected with human immunodeficiency virus (HIV). Tuberculosis leads to chronic pulmonary and systemic symptoms. Affected patients may have malaise, headache, fever, hemoptysis, and extrapulmonary diseases affecting the skin, cervical lymph nodes, kidneys, pericardium, and meninges. Active disease is treated with isoniazid and rifampin for 9 months. Therapy should probably be started before surgery; for patients coming from countries having a high incidence of resistance to isoniazid, initial therapy might include more than two drugs. Administration of treatment before these emergency patients (many of whom have adult respiratory distress syndrome) are brought to the operating room might include initiation of antiinfective therapy, optimization of fluid status and gas exchange,

and therapy for the underlying pathophysiologic process. [456] [457] [458] [459] [460] [461]

Chronic Obstructive Pulmonary Disease

Treatment of COPD (reactive airways) may include the use of beta-adrenergic drugs, parasympatholytic agents (especially for exercise-induced asthma), systemic or inhaled corticosteroids, and leukotriene antagonists. [396] [397] [398] [399] [400] [401] [402] [403] [404] [405] [406] [407] [408] [462] An estimated 5 percent of the population has bronchospasm. Some investigators recommend using inhaled bronchodilators as first-line drugs and reducing the dose of inhaled steroids, such as beclomethasone dipropionate, budesonide, mometasone, or fluticasone, which are inactivated after absorption. However, in large doses, these "inhaled" steroids can suppress adrenal function, and supplemental systemic corticosteroids may be needed at times of stress. (See earlier discussion under the section on adrenocortical malfunction.) Preoperative assessment must include gaining knowledge of drug regimens and their effects and education of the patient regarding proper use of an inhaler (Table 25-40) , as these drugs can interact dangerously with anesthetic agents (see last section of this chapter) or can be used inappropriately and therefore produce side effects without maximum benefit. [396] [397] [398] [399] [400] [401] [402] [403] [404] [405] [406] [407] [408] No known interaction between the inhaled anticholinergic ipratropium bromide and muscle relaxants has been reported. It is important to note that patients can feel fine at rest but must be tested with exercise or spirometry to document the degree of current bronchospasm. Furthermore, symptomatic response to bronchodilators in the asymptomatic patient may not predict whether the patient responds to bronchodilator therapy. An estimated 10 percent of asthmatic patients exhibit sensitivity to aspirin and may react not only to compounds containing aspirin but also to tartrazine, yellow dye number 5, indomethacin, and aminopyrine. [463]

COPD takes several forms. Bronchial asthma, which occurs in 3 to 5 percent of the population, is characterized by reversible airway obstruction. When airway obstruction is partially reversible (by steroids or adrenergic mediators), it is often accompanied by chronic bronchitis. Some of the drugs may improve aspects of lung function other than bronchial muscle tone. [385] [441] Most patients with a history of chronic cough and production of sputum on most days for 3 months a year for at least 2 years have chronic bronchitis. These patients are (or almost always have been) smokers, although

TABLE 25-40 -- Procedures for Correct Use of a Metered-Dose Inhaler

Remove the cap and hold the inhaler upright.
Shake the inhaler.
Tilt the head back slightly and exhale steadily to functional residual capacity.
Position the inhaler using a spacer between the actuator and the mouth.
Press down on the inhaler while taking a slow, deep breath (3-5 s).
Hold the full inspiration for at least 5 s and up to 10 s, if possible, to allow medication to reach deeply into the lungs.
Repeat inhalations as directed; waiting 1 min after inhalations of the bronchodilator may permit subsequent inhalations to penetrate more deeply into the lungs and is necessary to ensure proper dose delivery.
Rinse the mouth and expectorate after using the inhaler.

environmental and occupational or genetic predisposition may contribute to hypertrophy of mucous glands in major airways, to hyperplasia of goblet cells, and to edema and inflammation of the airways. These patients will have a decreased DLCO, whereas patients with pure bronchospasm will have a normal DLCO. Hyperinflation of airspaces, abnormal dilation, and destruction of acinar units distal to the terminal bronchiole define emphysema. The destruction of alveolar membranes is believed to be related to an imbalance favoring destructive proteases (the most important of which are neutrophil-derived) over protective circulating antiproteases (the most important of which is $alpha_1$-antitrypsin). Cigarette smoking increases the protease-to-antiprotease ratio. The destruction of alveolar structures limits expiratory air flow by decreasing both elastic lung recoil and radial lung traction, and the loss of alveolar capillary blood volume results in a decreased DLCO. Cystic fibrosis is characterized by dilation and hypertrophy of bronchial glands, mucous plugging of peripheral airways, and often bronchitis, bronchiectasis, and bronchiolectasis. For all these conditions, the measures recommended earlier in this section, as well as appropriate hydration to allow for mobilization of secretions, should be followed.

Interstitial and Immune Lung Diseases

Included in this heterogeneous group of diseases are the hypersensitivity lung diseases, environmental exposure diseases, the inorganic dust diseases, radiation-induced lung disease, sarcoidosis, the collagen vascular disorders (systemic lupus erythematosus, polymyositis, dermatomyositis, Sjogren syndrome, rheumatoid arthritis, systemic sclerosis), Goodpasture syndrome, idiopathic pulmonary hemosiderosis, Wegener's granulomatosis, and the autoimmune diseases. [464] CT scans localize pulmonary inflammation and have become the primary decision-making tool in diagnosing infiltrative lung disease. [465] [466] Many of these disorders affect not only the lungs but also the blood vessels, the conduction system of the heart, the myocardium, the joints (including those of the upper airway and larynx), and the renal, hepatic, and/or central nervous systems. The reader is referred to a textbook of internal medicine to aid in understanding the pathophysiologic

processes and full preoperative assessment of these conditions. Therapy for these conditions includes the use of anti-inflammatory drugs, corticosteroids, and immunosuppressive drugs.

Neoplasms

Solitary nodules consist of tumors that are less than 6 cm in diameter, surrounded by lung parenchyma, and not associated with adenopathy or pleural effusion. The cure rate for bronchogenic carcinoma presenting as a solitary nodule is 50 percent--much better than the "cure" rate for other presentations. [467] (It should be remembered that tuberculosis can mimic cancer so closely that surgery has even been performed.) Blood studies including calcium and alkaline phosphatase levels and liver function studies help confirm that the neoplasm has not disseminated. If these studies and history and physical examination show no abnormal findings, it

is unlikely that bone, brain, or hepatic MRI or CT scanning techniques will indicate metastasis. Surgery need not await the results of these tests, as few patients not found to have metastatic disease by simple blood tests, history, and physical examination will prove to have such disease detected by these scans. Survival depends on stage of the tumor and age of the patient. [468]

Surgical resection is the primary therapy for non-small-cell carcinomas (e.g., adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma). These carcinomas constitute 75 percent of all lung carcinomas, 12 percent of all malignant tumors, and 20 percent of all cancer deaths in the United States. [468] Success of surgery can be predicted by stage of the tumor. The most widely accepted staging system for these carcinomas is the tumor-node-metastasis (TNM) classification. In this system, T1 lesions are smaller than 3 cm in diameter, T2 lesions are larger than 3 cm, T3 lesions invade chest wall mediastinum or diaphragm, and T4 lesions invade heart or great vessels. The designation N0 indicates no lymph node involvement; N1, tracheobronchial or hilar lymph node involvement; and N3, contralateral or supraclavicular lymph node involvement. M0 connotes no metastases; and M1, systemic metastases.

Patients in stage I who have small primary tumors (T1N0M0) usually undergo lobectomy and have a 5-year survival rate of 50 percent. Those surgical procedures that spare pulmonary parenchyma--wedge resection or bronchial sleeve resection--are reserved for patients with COPD and heart disease, although thoracoscopic resections may radically improve localization and tolerance of procedures. Patients in stage II (T1N1M0 or T2N1M0) also undergo total resection and have a 5-year survival rate of 30 percent. Patients in stage IIIa (T3N0M0, or T1 or T2N2M0) are resected for cure but currently have a 5-year survival rate of only 17 percent. [468] Postresection radiotherapy does not improve survival, and mass screening programs do not lead to better prognosis (see Ch. 23 sections on lead- and length-time biases). Diagnostic typing and staging often involve percutaneous transthoracic aspiration, which is associated with a 30 percent incidence of pneumothorax. [468]

The combination of chemotherapy and radiation therapy is the current treatment of choice for small-cell carcinomas of the lung. [469] Oat-cell (small-cell) carcinomas of the lung and bronchial adenomas are known for their secretion of endocrinologically active substances, such as ACTH-like hormones. Squamous cell cancers in the superior pulmonary sulcus produce Horner syndrome, as well as a characteristic pain in the areas served by the eighth cervical nerves and first and second thoracic nerves. These tumors are now treated with preoperative radiation; surgical resection leads to an almost 30 percent "cure" rate.

Anaphylaxis, Anaphylactoid Responses, and Allergic Disorders Other Than Those Related to Lung Diseases and Asthma

Anaphylactic and Anaphylactoid Reactions

Anaphylaxis is a severe life-threatening allergic reaction. *Allergic* applies to immunologically mediated reactions, as opposed to those caused by pharmacologic idiosyncrasy, by direct toxicity or drug overdosage, or by drug interaction. [466] [470] [471] Anaphylaxis is the typical immediate hypersensitivity reaction (type 1). Such reactions are produced by the immunoglobulin E (IgE)-mediated release of pharmacologically active substances. These mediators in turn produce specific end-organ responses in the skin (urticaria), the respiratory system (bronchospasm and upper airway edema), and the cardiovascular system (vasodilation, changes in inotropy, and increased capillary permeability). Vasodilation occurs at the level of the capillary and postcapillary venule, leading to erythema, edema, and smooth muscle contraction. This clinical syndrome is called *anaphylaxis.* By contrast, *anaphylactoid reaction* denotes an identical or very similar clinical response that is not mediated by IgE or (usually) an antigen-antibody process. [472]

In anaphylactic reactions, an injected substance can serve as the allergen itself. Low-molecular-weight agents are believed to act as haptens that form immunologic conjugates with host proteins. The offending substance, whether hapten or not, may be the parent compound, a nonenzymatically generated product, or a metabolic product formed in the patient's body. When an allergen binds immunospecific IgE antibodies on the surface of mast cells and basophils, histamine and eosinophilic chemotactic factors of anaphylaxis are released from the storage granules in a calcium- and energy-dependent process. [470] Other chemical mediators are rapidly synthesized and subsequently released in response to cellular activation. These mediators include slow-reacting substance of anaphylaxis, which is a combination of three leukotrienes; other leukotrienes [473] ; kinins; plateletactivating factors; adenosine; chemotactic factors; heparin tryptase; chymase; and prostaglandins, including the potent bronchoconstrictor prostaglandin D_2 , eosinophil growth and -activating factors, mast-cell growth factors, and proinflammatory and other factors that contribute to the IgE isotype switch.

The end-organ effects of the mediators produce the clinical syndrome of anaphylaxis. Usually a first wave of symptoms, including vasodilation and a feeling of impending doom, is quickly followed by the second wave as the cascade of mediators amplifies the reactions. In a sensitized patient, the onset of the signs and symptoms caused by these mediators is usually immediate but may be delayed 2 to 15 minutes or, in rare instances, as long as 2.5 hours after the parenteral injection of antigen. [473] [474] After oral administration, manifestations may occur at unpredictable times.

Mast-cell proliferation, together with severe progressive inflammation, contributes to the worsening of symptoms that occurs even after there is no longer an allergen load. Both activated mast cells and the antigen present in cells and lymphocytes start to make cytokines. These proinflammatory cytokines recruit more inflammatory cells, which promotes tissue edema and mediates a second wave of mast-cell degranulation. This second wave can promote recurrence of severe symptoms 6 to 8 hours later and necessitates, some believe, at least 8 hours of continued ICU-like observation.

In addition, there are multiple effector processes by which biologically active mediators can be generated to produce an anaphylactoid reaction. Activation of the blood coagulation and fibrinolytic systems, of the kinin-generating sequence, or of the complement cascade can produce the

same inflammatory substances that result in an anaphylactic reaction. The two mechanisms known to activate the complement system are called classic and alternate. The classic pathway can be initiated through IgG or IgM (transfusion reactions) or plasmin. The alternate pathway can be activated by lipopolysaccharides (endotoxin), drugs (Althesin [472]), radiographic contrast media, [475] membranes (nylon tricot membranes for bubble oxygenators [476]), cellophane membranes of dialyzers, [477] vascular graft material, [478] latex or latex-containing products, [479] and perfluorocarbon artificial blood. In addition, histamine can be liberated independent of immunologic reactions. [480] Mast cells and basophils release histamine in response to chemicals or drugs. Most narcotics can release histamine, [480] producing an anaphylactoid reaction, as can radiographic contrast media, [475] *d*-tubocurarine, [481] and thiopental. What makes some patients susceptible to histamine release in response to drugs is unknown, but hereditary and environmental factors may play a role.

Intravenous contrast material is probably the most frequently used agent causing anaphylactoid reactions. Because diagnostic (skin and other) tests are helpful only in IgE-mediated reactions, pretesting is not useful in contrast reactions. Pretreatment with diphenhydramine, cimetidine (or ranitidine), and corticosteroids has been reported to be useful in preventing or ameliorating anaphylactoid reactions to intravenous contrast material [475] [482] and perhaps to narcotics and chymopapain. [483] [484] Unfortunately, very large doses of steroids (1 g of methylprednisolone intravenously) may be necessary to obtain a beneficial effect. [485] The efficacy of large-dose steroid therapy has not been confirmed. Other common substances associated with anaphylactic or anaphylactoid reactions that might merit preoperative therapy include antibiotics, volume expanders, and blood products [470] [486] [487] (Table 25-41) (Table Not Available) . The anesthesiologist should be prepared preoperatively to treat an anaphylactic or anaphylactoid response.

In some cases, a patient with a history of anaphylactic or anaphylactoid reaction must receive a substance suspected of producing such a reaction (e.g., iodinated

contrast material). Also, some patients have a higher-than-average likelihood of having a reaction, warranting well-planned pretreatment and therapy for possible anaphylactic and anaphylactoid reactions. [470]

TABLE 25-41 -- Incidence of Anaphylactic or Anaphylactoid Reactions to Some Common Agents

(Not Available)

Data modified from Ring and Messmer. [486] Levy et al. [470] and Moss et al [483]

Minimizing the Risks Preoperatively

Although virtually all evidence on these subjects is merely anecdotal, enough consistent thought recurs through the literature to justify proposing an optimal approach to these problems. First, predisposing factors should be sought; the patient with a history of atopy or allergic rhinitis should be suspected as being at risk. Because anaphylactic and anaphylactoid reactions to contrast media occur five to ten times more frequently in patients with a previously suspected reaction, consideration should be given to administration of both H_1 - and H_2 -receptor antagonists for 16 to 24 hours before exposing these patients to a suspected allergen. The H_1 -receptor antagonist appears to require this much time to act on the receptor. Volume status should be optimized, [470] and perhaps large doses of steroids (2 g of hydrocortisone) should also be administered before exposing patients to agents associated with a high incidence of anaphylactic or anaphylactoid reactions. [485] [486] [488] Older patients and patients taking beta-adrenergic-blocking drugs present special problems; they are at higher risk of having complications from both pretreatment (especially vigorous hydration) and therapy for anaphylactic reactions and are less responsive to treatment regimens. [489] One approach is to avoid drugs likely to trigger anaphylactic or anaphylactoid reactions or to alter the treatment protocol for this group. Drawing blood for later analysis, especially of tryptase, can be useful in clarifying the diagnosis. [490]

Primary Immunodeficiency Diseases

The primary immunodeficiency diseases usually present early in life with recurrent infections. Along with survival achieved with antibiotic and antibody treatment have come new prominent features: cancer and allergic and autoimmune disorders. Heredity angioneurotic edema is an autosomal dominant genetic disease characterized by episodes of angioneurotic edema involving the subcutaneous tissues and submucosa of the GI tract and the airway and often presenting as abdominal pain. These patients have a functionally impotent inhibitor or a deficiency of an inhibitor to the complement component C1. Treatment of an acute attack is supportive because epinephrine, antihistamines, and corticosteroids often fail to work. Plasma transfusions have been reported to resolve attacks or to make them worse (theoretically by supplying either C1 esterase inhibitor or previously depleted complement components). The severity of attacks can be prevented or decreased by drugs that are either plasmin inhibitors (e.g., epsilon-aminocaproic acid and tranexamic acid) or androgens (e.g., danazol). Because trauma can precipitate acute attacks, prophylactic therapy with danazol, intravenous epsilon-aminocaproic acid, plasma, or all three, is recommended prior to elective surgery. Reports have also described the successful use of a partially purified C1esterase inhibitor in two patients. [491] [492]

Most of the 1 in 700 persons who have selective IgA deficiency (i.e., <5 mg/dL) have repeated serious infections or connective tissue disorders. [493] These infections commonly involve the respiratory tract (e.g., sinusitis, otitis) or GI tract (presenting as diarrhea, malabsorption, or both). If the patient has rheumatoid arthritis, Sjogren syndrome, or systemic

lupus erythematosus, the anesthetist should consider the possibility of isolated IgA deficiency. However, patients with this disorder can be otherwise healthy. Because these patients may develop antibodies to IgA if previously exposed to IgA (as might occur from a previous blood transfusion), subsequent blood transfusions can cause anaphylaxis, even when they contain washed erythrocytes. Transfusion should therefore consist of blood donated by another IgA-deficient patient.

Many immunomodulators are now being given to augment cancer treatments [494] ; no interactions between these modulators, or effects on the incidence of immune reactions during anesthesia, or interactions with anesthetic effects have been reported except regarding immune-suppressing agents. (See last section of this chapter.)

DISEASES OF THE CENTRAL NERVOUS SYSTEM, NEUROMUSCULAR DISEASES, AND PSYCHIATRIC DISORDERS

Taking the history and performing the physical examination suggested in Chapter 23 should help identify almost all significant neurologic or mental disease. Information gathered from the history that would warrant further investigation includes the previous need for postoperative ventilation in a patient without inordinate lung disease, indicating the possibility of metabolic neurologic disorders such as porphyria, alcoholic myopathy, other myopathies, neuropathies, and neuromuscular disorders such as myasthenia gravis. Other historical information warranting further investigation would be the use of drugs such as steroids; guanidine; anticonvulsant, anticoagulant, and antiplatelet drugs; lithium; tricyclic antidepressant drugs; phenothiazines; and butyrophenones.

Although preoperative treatment of most neurologic disorders has not been reported to lessen perioperative morbidity, knowledge of the pathophysiologic characteristics of these disorders is important in planning intraoperative and postoperative management. Thus, preoperative knowledge about these disorders and their associated conditions (e.g., cardiac arrhythmias with Duchenne muscular dystrophy or respiratory and cardiac muscle weakness in dermatomyositis) may reduce perioperative morbidity. A primary goal of neurologic evaluation is to determine the site of the lesion in the nervous system. Such localization is essential for accurate diagnosis and appropriate management. (Disorders accompanied by increased intracranial pressure and cerebrovascular disorders are discussed in Ch. 52 .)

Coma

Little is known about anesthesia for the comatose patient, but, as for all other conditions, it is imperative to know the cause of the coma, so as to avoid drugs that might worsen the condition or that might not be metabolized because of organ dysfunction. First, the patient should be observed. Yawning, swallowing, or licking of the lips implies a "light" coma with major brain stem function intact. If consciousness is depressed but respiration, pupillary reactivity to light, and eye movements are normal and no focal motor signs are present, metabolic depression is likely. Abnormal pupillary responses may indicate hypoxia, hypothermia, local eye disease, or drug intoxication with belladonna alkaloids, narcotics, or glutethimide; pupillary responses may also be abnormal, however, after the use of eyedrops. Other metabolic causes of coma include uremia, hypoglycemia, hepatic coma, alcohol ingestion, hypophosphatemia, myxedema, and hyperosmolar nonketotic coma. Except in extreme emergencies, such as uncontrolled bleeding or perforated viscus, care should be taken to render the patient as metabolically normal as possible before surgery. This practice and documenting the findings on the chart preoperatively lessen any confusion regarding the cause of intraoperative and postoperative problems. However, too-rapid correction of uremia or hyperosmolar nonketotic coma can lead to cerebral edema, a shift of water into the brain due to a reverse osmotic effect caused by the dysequilibrium of urea concentration.

The physical examination can be extremely helpful preoperatively in assessing the prognosis. [495] [496] [497] [498] [499] Flexion of the arms at the elbow (i.e., decorticate posture) implies bilateral hemisphere dysfunction but intact brain stem, whereas extension of legs and arms (bilateral decerebrate posture) implies bilateral damage to structures at the upper brain stem or deep hemisphere level. Seizures are often seen in uremia and in other metabolic encephalopathies. Hyperreflexia and upward-pointing toes suggest a structural CNS lesion or uremia, hypoglycemia, or hepatic coma; hyporeflexia and downward-pointing toes with no hemiplegia generally indicate no structural CNS lesion.

Epileptic Seizures

Epileptic seizures result from paroxysmal neuronal discharges of abnormally excitable neurons. Seizures can be generalized (arising from deep midline structures in the brain stem or thalamus, usually without aura or focal features during the seizure), partial focal motor, or sensory seizures (the initial discharge comes from a focal unilateral area of brain, often preceded by an aura). As with cerebrovascular accidents and coma, knowing the origin may be crucial to understanding the pathophysiologic processes of the disease and to managing the intraoperative and postoperative course.

Epileptic seizures can arise from discontinuation of sedative hypnotic drugs or alcohol, use of narcotics, uremia, traumatic injury, neoplasms, infection, congenital malformation, birth injury, drug usage (e.g., amphetamines, cocaine), hypercalcemia or hypocalcemia, blood in the ventricle or hypoxia, and vascular disease and vascular accidents. Thirty percent of epileptic seizures have no known cause. Most partial seizures are caused by structural brain abnormalities (secondary to tumor, trauma, stroke, infection, and other causes).

The epileptic patient requires no special anesthetic management other than that for the underlying disease. Most authorities believe anticonvulsant medications should be given in the therapeutic range [500] [501] [502] and continued through the morning of surgery; they should also be given postoperatively.

Appropriate treatment of status epilepticus may include general anesthesia. [502] In one controlled trial, phenobarbital was more rapidly effective at controlling status epilepticus than was diazepam followed by phenytoin. [502] The frequencies of side effects and required tracheal intubation were similar for both regimens. High concentrations of enflurane (especially with hyperventilation) can be associated with electroencephalographic evidence of epileptic activity and tonic-clonic movements. [503] [504] These seizures, however, do not appear to have serious sequelae. [505] Enflurane anesthesia does not appear to increase seizure activity in patients with a history of convulsive disorders and even suppresses seizures induced by electroshock, pentylene-tetrazole, strychnine, picrotoxin, or bemegride. [504] [505] [506] Thus, other than the use of current drug therapy and heeding precautions taken for the underlying disease, no known changes in perioperative management seem indicated.

Infectious Diseases and Degenerative Disorders of the Central Nervous System, and Headache

Many degenerative CNS disorders have been traced to slowly developing viral diseases or even the presence of certain proteins or viral particles ("prions"). No special perioperative anesthetic considerations appear to apply for infectious disorders of the CNS other than those for increased intracranial pressure and avoiding occupational exposures. (Also see Ch. 52 .) The appropriate prophylactic measures to take if one comes into contact with meningococcal disease or other infectious CNS disease are still not well established. The use of *H. influenzae* type b vaccine has made meningitis an adult disease. [507]

Parkinson disease is a degenerative disorder of the CNS that may or may not be caused by a virus. Clinically, Parkinson disease, chronic manganese intoxication, phenothiazine or butyrophenone toxicity, Wilson disease, Huntington chorea, traumatic boxing injury, the effects of street drug toxins such as methylphenyltetrahydropyridine, and carbon monoxide encephalopathy all present with similar features: bradykinesia, muscular rigidity, and tremor. The substantia nigra and nerve terminals in the striatum (caudate nucleus and putamen) degenerate, and the clinical signs presumably result from decreased production of dopamine in the neurons of the basal ganglia leading to the putamen and caudate nucleus. The effects of this dopaminergic deficiency may be compounded by the unopposed effects of cholinergic neurons bordering the basal ganglia. The resulting clinical syndrome (parkinsonism) includes tremor, rigidity, akinesia, and postural instability.

Newer therapies have been developed to arrest or even reverse the progression of this disease. Therapy is directed at (1) increasing the neuronal release of

dopamine or the receptor's response to dopamine, (2) stimulating the receptor directly with bromocryptine and lergotrile, (3) implanting dopaminergic tissue, or (4) decreasing cholinergic activity. The new therapies using the monoamine oxidase inhibitor deprenyl or adrenal medullary transplants to slow the progression of disease appear promising. [508] [509] There is insufficient experience with deprenyl in the perioperative milieu to make proscriptions about its use. Anticholinergic agents have been the initial drugs of choice, as they decrease tremor more than muscle rigidity. Because dopamine does not pass the blood-brain barrier, its precursor, L-dopa (levodopa) is used. Unfortunately, L-dopa is decarboxylated to dopamine in the periphery and can cause nausea, vomiting, and arrhythmia. These side effects are diminished by administration of alpha-methylhydrazine (Carbidopa), a decarboxylase inhibitor that does not pass the blood-brain barrier. Refractoriness to L-dopa develops; it is now debated if the drug should be used only when symptoms cannot be controlled with other anticholinergic medications. "Drug holidays" have been suggested as one means of restoring the effectiveness of these compounds, but cessation of such therapy may result in a marked deterioration of function and the need for hospitalization. Therapy for Parkinson's disease should be initiated before surgery and continued through the morning of surgery; such treatment seems to decrease drooling, the potential for aspiration, and ventilatory weakness. [510] [511] [512] [513] Reinstituting therapy promptly after surgery is crucial, [501] [508] [509] [510] [511] [512] [513] [514] as is avoiding such drugs as phenothiazines and butyrophenones (droperidol) that inhibit release of dopamine (and perhaps alfentanil) or that compete with dopamine at the receptor. [510] [514] Clonapine (a benzodiazepine) appears not to worsen the movement disorders of Parkinson disease and has been used postoperatively to stop levodopa-induced hallucinations.

Dementia, a progressive decline in intellectual function, can be caused by treatable infections (e.g., syphilis, cryptococcosis, coccidioidomycosis, Lyme disease, tuberculosis), myxedema, vitamin B_{12} deficiency, chronic drug or alcohol intoxication, metabolic causes (liver and renal failure), neoplasms, partially treatable infections (HIV), untreatable infections (Creutzfeldt-Jakob syndrome), or decreased acetylcholine in the cerebral cortex (Alzheimer disease). This last condition occurs in more than 0.5 percent of Americans. [498] [515] [516] [517] Although these patients are often given cholinergic agonists, controlled trials of these drugs have not as yet shown major significant benefits. [515] [516] [518] Gingko has been advertised and has improved the subjective symptoms in 37 percent of patients versus 23 percent of patients given placebos. However, the commonness of Alzheimer disease and the desperateness of the patients and their families have now widened such therapies. These families often desire surgery, but the interactions with perioperative analgesic and anesthetic drug therapies are not well established. Most reversible dementias are either drug-induced deliriums or depression. [515] [516] [519] Creutzfeldt-Jakob disease has been transmitted inadvertently by surgical instruments and corneal transplants; the causative virus is not inactivated by heat, disinfectants, or formaldehyde.

More than 90 percent of patients with chronic recurring headaches are diagnosed as having migraine, tension, or cluster headaches. The mechanism of tension or cluster headaches may not differ qualitatively from that for migraine headaches; all may be manifestations of labile vasomotor regulation. [520] A headache is said to be migraine if it is characterized by four of the following five " *POUND*ing" conditions: if it is *P*ulsating; if it lasts *O*ne day or more; if it is *U*nilateral; if there is *N*ausea; and if it *D*isturbs daily activities. [521]

Treatment for cluster and migraine headaches centers on the use of serotonin agents such as sumatriptan or ergotamine and its derivatives. [520] [521] [522] Other drugs that may be effective are propranolol, calcium-channel inhibitors, cyproheptadine, prednisone, antihistamines, tricyclic antidepressant drugs, phenytoin, and diuretic drugs, as well as biofeedback. Giant-cell arteritis, glaucoma, and all the meningitides, including Lyme disease, are other causes of headache that might benefit from treatment before surgery. [523] No other special treatment is indicated preoperatively for the patient who has a well-delineated cause for headaches. Acute migraine attacks can sometimes be terminated by ergotamine tartrate aerosol or by injection of sumatriptan or dihydroergotamine mesylate intravenously; general anesthesia has also been used. I normally continue all prophylactic headache medicine, except aspirin (because of the potential for bleeding), through the morning of surgery.

Back Pain, Neck Pain, and Spinal Canal Syndromes

Acute spinal cord injury is discussed earlier in the section on autonomic dysfunction. Although it is a common problem, little is written about the anesthetic management of syndromes related to herniated disc, spondylosis (usually of advancing age), and the congenital narrowing of the cervical and lumbar canal that gives rise to symptoms of nerve root compression. [524] [525] One report stresses the importance of the vascular component in the mechanism of damage to the spinal cord and, hence, the theoretical desirability of slight hypertension perioperatively. [526] Another report suggests the use of awake intubation, a fiberoptic bronchoscope, and evoked potential monitoring. [524] The preoperative management of the patient about to undergo chemonucleolysis is discussed earlier in the section on anaphylaxis. Other than the commonsense approach of seeking neurologic consultation or, if necessary, using awake positioning of patients in a comfortable position prior to emergency root-decompression procedures, no special procedures appear to be necessary.

Demyelinating Diseases

Demyelinating diseases constitute a diffuse group of diseases ranging from those with uncertain causes (e.g., multiple sclerosis, where genetic epidemiologic and immunologic factors are probably all involved and beta-interferon appears to be a promising treatment [527]) to those that follow infection, vaccination (e.g., Guillain-Barre syndrome), or antimetabolite treatment of cancer. Therefore, demyelinating disease can present with very diverse symptoms. Apparently, there is a risk of relapse of these diseases immediately after surgery. [528] Because relapse may occur because of rapid electrolyte changes in the perioperative period, such changes might be avoided. Also, perioperative administration of steroids has been advocated as a protective measure. [209] Thus far, no mode of treatment has been shown to alter most of these disease processes, although ACTH, steroids, beta-interferon, and plasmapheresis may ameliorate or abbreviate a relapse, especially of multiple sclerosis and (if started within 2 weeks of onset) of Guillain-Barre syndrome. [529] Such an effect is consonant with the hypothesis of an immunologic disorder as the cause of these diseases.

Sleep apnea may be considered a demyelinating or degenerative CNS disease or a peripheral disease of obesity, depending on etiology. Both types (central and peripheral etiologies) appear to be increasingly common and are present in more than 5 percent of elderly African-Americans. Because sleep apnea poses many problems for postoperative pain control, I now recommend using only nonsteroidal anti-inflammatory drugs for pain relief if I cannot monitor these patients in a second-stage recovery unit. [530] [531] [532]

Metabolic Diseases

Included in the category of metabolic diseases is nervous system dysfunction secondary to porphyrias, alcoholism, uremia, hepatic failure, and vitamin B_{12} deficiency. The periodic paralysis that can accompany thyroid disease is discussed under neuromuscular disorders (see later).

Alcoholism or heavy alcohol intake is associated with acute alcoholic hepatitis (Ch. 54) (the activity of which declines as alcohol is withdrawn), myopathy and cardiomyopathy that can be severe, and withdrawal syndromes. The best questions to ask in seeking a history of alcohol intake are, "Have you ever had a drinking problem?" and "Have you had a drink in the last 24 hours?" These questions have a higher sensitivity and specificity than many other longer series of questions about alcoholism [533] (Ch. 23) . Within 6 to 8 hours of withdrawal, the patient may become tremulous, a state that usually subsides within days or weeks. Alcoholic hallucinosis and withdrawal seizures generally occur within 24 to 36 hours. These seizures are generalized grand mal attacks; when focal seizures are manifest, other causes should be sought. Delirium tremens usually appears within 72 hours of withdrawal and is often preceded by tremulousness, hallucinations, or seizures. These three occurrences, combined with perceptual distortions, insomnia, psychomotor disturbances, autonomic hyperactivity, and, in a large percentage of cases, another potentially fatal illness (e.g., bowel infarction or subdural hematoma), comprise delirium tremens. This syndrome is now treated with benzodiazepines. Nutritional disorders of alcoholism include alcoholic hypoglycemia and hypothermia, alcoholic polyneuropathy, Wernicke-Korsakoff syndrome, and cerebellar degeneration. In alcoholic patients (i.e., those who drink at least two six-packs of beer, one pint of whiskey, or the equivalent per day), emergency surgery and anesthesia (despite alcoholic hepatitis) are not associated with worsening abnormalities of liver enzymes. [533] In addition, about 20 percent of alcoholic patients also have COPD. The patient who has a history of alcohol abuse therefore warrants careful examination of many systems for quantification of preoperative physical status.

Although hepatic failure can lead to coma with highoutput cardiac failure, unlike uremia, it does not lead to chronic polyneuropathy. Uremic polyneuropathy is a distal symmetric sensorimotor polyneuropathy that may be improved by dialysis. The use of depolarizing muscle relaxants has been questioned in polyneuropathies (Ch. 12) . I believe

that patients who have a neuropathy associated with uremia should not be given succinylcholine because of a possible exaggerated hyperkalemic response.

Pernicious anemia caused by vitamin B_{12} deficiency may result in subacute combined degeneration of the spinal cord; the signs are similar to those of chronic nitrous oxide toxicity. Both pernicious anemia and nitrous oxide toxicity are associated with peripheral neuropathy and disorders of the pyramidal tract and posterior column (which governs fine motor skills and the sense of body position). Combined system disease can also occur without anemia, as can nitrous oxide toxicity in dentists and nitrous oxide abusers. Patients with B_{12} deficiency and anemia, if treated with folate, improve hematologically but progress to dementia and severe neuropathy. It may thus be prudent to give an intramuscular administration of 100 mug of vitamin B_{12} before giving folate to the patient who has signs of combined system degeneration. [534]

The porphyrias are a constellation of metabolic diseases that result from an autosomally inherited lack of functional enzymes active in the synthesis of hemoglobin. Figure 25-20 depicts schematically the abnormalities that result from these enzyme deficits. It is important to note that types 1, 3, and 4 porphyrias can cause life-threatening neurologic abnormalities. These conditions are characterized by the presence of aminolevulinic acid (ALA) and/or porphobilinogen in urine, substances that do not occur in porphyria cutanea tarda, a disease that does not incur neurologic sequelae. [535] In acute intermittent porphyria, the typical pattern consists of acute attacks of colicky pain, nausea, vomiting, severe constipation, psychiatric disorders, and lesions of the lower motor neuron that can progress to bulbar paralysis. Certain drugs can induce the enzyme ALA synthetase, exacerbating the disease process. [536] [537] [538] These sensitizing drugs include barbiturates, meprobamate, chlordiazepoxide, glutethimide, diazepam, hydroxydione, phenytoin, imipramine, pentazocine, birth control pills, ethyl alcohol, sulfonamides, griseofulvin, and ergot preparations. Patients often have attacks during infection, fasting, or menstruation. Administration of glucose suppresses ALA synthetase activity and prevents or ablates acute attacks. Drugs used in anesthetic management that are reported to be safe for patients with porphyria include neostigmine (Prostigmin), atropine, gallamine, succinylcholine, *d*-tubocurarine, pancuronium, nitrous oxide, procaine, propofol, propanidid, etomidate, meperidine, fentanyl, morphine, droperidol, promazine, promethazine, and chlorpromazine. [536] [537] [538] Although ketamine has been used, postoperative psychoses attributed to the disease may be difficult to distinguish from those possibly caused by ketamine. In addition, although ketamine and etomidate are reported to be safe in humans, they seem to be porphyrinogenic in rats. Propofol has been used without provoking porphyria in at least two susceptible patients. [536] [537]

Figure 25-20 Schematic depiction of the functional enzyme deficits that occur in some of the porphyrias. ALA, aminolevulinic acid; PBG, porphobilinogen.

Neuromuscular Disorders

Neuromuscular disorders consist of conditions affecting any major component of the motor unit: motor neuron, peripheral nerve, neuromuscular junction, and muscle. Neuropathies may involve all components of the nerve, producing sensory, motor, and autonomic dysfunction, or only one component. Myopathies may involve only proximal or distal muscles, or both.

Myasthenia gravis (Ch. 12) is a disorder of the muscular system caused by partial blockade or destruction of nicotinic acetylcholine receptors by IgG antibodies. This syndrome is characterized by fluctuating ophthalmoplegia, ptosis, and bulbar, respiratory, or limb weakness and is confirmed by a beneficial response to cholinergic drugs. [539] [540] These patients often have other autoimmune diseases, including rheumatoid arthritis and hypothyroidism. Thirty-three percent of patients with myasthenia gravis have bulbar symptoms (and are therefore subject to problems with disposing of secretions) at presentation, and more than 60 percent of people with myasthenia gravis will have bulbar symptoms at some time during their life. This symptom should not be confused with respiratory muscle weakness, which occurs much less commonly.

The severity of the disease correlates with the ability of the antibodies to decrease the number of available acetylcholine receptors. [539] Treatment of myasthenia is usually begun with anticholinesterase agents but, in moderate and severe disease, progresses to steroids and thymectomy. [539] [540] Immunosuppressive drugs and plasmapheresis are begun if the more conservative measures fail. [539] [540]

One major problem for the anesthesiologist involves the use of muscle relaxants and their reversal. [541] [542] Because much of the care of myasthenia gravis patients involves tailoring the amount of anticholinesterase medication to the maximal muscle strength of the patient, derangement of the course of the patient during surgery could necessitate reassessment of the drug dosage. For that reason, several researchers recommend withholding all anticholinergic drugs for 6 hours before surgery and reinstituting medicine postoperatively with extreme caution, as the sensitivity of these patients to such drugs may have changed. In addition, there has been some concern that anticholinergic drugs may facilitate a high incidence of bowel anastomotic leaks in those patients who have undergone bowel anastomoses. Small doses of succinylcholine can be used to facilitate endotracheal intubation; tiny doses of nondepolarizing drugs can be used for intraoperative relaxation not obtained by regional anesthesia or volatile agents. Controlled ventilation is usually required for at least 24 to 48 hours postoperatively. [540] [541] [542] [543] This practice is especially important in cases involving myasthenia gravis of more than 6 years' duration, chronic obstructive lung disease, daily pyridostigmine requirement of 750 mg in association with significant bulbar weakness, and vital capacity of less than 40 mL/kg. [542] [543]

Eaton-Lambert syndrome (myasthenic syndrome) is characterized by proximal limb muscle weakness. Strength or reflexes may increase with repetitive effort. Affected patients have a decreased release of acetylcholine at the neuromuscular junction. Guanidine therapy enhances the release of acetylcholine from nerve terminals and improves strength. Men who have this syndrome generally have small-cell carcinoma of the lung or other malignancy, whereas women often have malignancy, sarcoidosis, thyroiditis, or a collagen-related vascular disease. In addition, these patients have increased sensitivity to both depolarizing and nondepolarizing muscle relaxants. [544] [545] Eaton-Lambert syndrome is also associated with an autonomic nervous system defect characterized by gastroparesis, orthostatic hypotension, and urinary retention. [544]

Dermatomyositis and polymyositis are characterized by proximal limb muscle weakness with dysphagia. These conditions are associated with malignancy or collagen-related vascular disease, often involving respiratory and cardiac muscle.

Periodic paralysis is another disease in which sensitivity to muscle relaxants increases. Periodic weakness starts in childhood or adolescence and is precipitated by rest after exercise, sleep, cold, surgery, or pregnancy. Hypokalemic and hyperkalemic forms exist and are associated with cardiac arrhythmias. Like thyrotoxic periodic paralysis, these hypokalemic and hyperkalemic forms usually spare the respiratory muscles. Anesthetic management consists of minimizing stress and maintaining normal fluid and electrolyte states and body temperature. [544] [545] [546] [547]

Muscular dystrophy patients now survive into their late 20s or early 30s. Complicating their disease are respiratory infections, kyphoscoliosis, muscle contractions, and cardiac abnormalities. Duchenne muscular dystrophy is a sex-linked recessive disease, at the Xp21 locus, the most common of the muscular dystrophies. [548] It occurs after 2 years of age, at which time patients experience a rapid progression of muscle disease that leads to incapacity in their teens. Cardiac involvement is common when the disease affects proximal and pelvic muscles, and respiratory failure is a common cause of death. Limb-girdle muscular dystrophy is not as severe as Duchenne muscular dystrophy; it occurs later in life, has cardiac involvement, and is transmitted as an autosomal recessive trait. Facioscapulohumeral muscular dystrophy is a disease of autosomal dominant inheritance that has a mild clinical form in adolescence. Patients with this disorder have a normal life-span without an increased risk of cardiac complications; however, postoperative respiratory deaths have been recorded. Myotonic dystrophy is a disease in which continued active contraction of the muscles persists after voluntary effort or stimulation has ceased. This autosomal dominant inherited disease begins at 20 to 40 years of age and is associated with cardiomyopathy, baldness, testicular atrophy, cataracts, intellectual and emotional abnormalities, and premature death in the 50- to 60-year age range. The facial, sternocleidomastoidal, distal, and pharyngeal muscles become weak and atrophy. Because the disease involves the muscles themselves and not their innervation, conduction anesthesia cannot produce adequate relaxation of tonic muscles. Gastric dilation has also been reported to be a problem, as has malignant hyperthermia. As with the other forms of muscular dystrophies, most problems in myotonic dystrophy arise from cardiac arrhythmias and inadequacies of the respiratory muscles. [549] For all the forms of muscular dystrophy, as for all the neuropathies (discussed earlier), there have been problems related to exaggerated serum potassium release after administration of depolarizing muscle relaxants (Ch. 12) .

Malignant hyperthermia (Ch. 27) in the patient or in a

relative of the patient merits careful history-taking and at least consideration of performing a test for susceptibility to the condition (Ch. 23) . Prophylaxis with intravenous dantrolene sodium (Dantrium) may also be warranted (Ch. 27) . In some cases, malignant hyperthermia has been associated with recognizable musculoskeletal abnormalities such as strabismus, ptosis, myotonic dystrophy, hernias, kyphoscoliosis, muscular dystrophy, central core disease, and marfanoid syndrome. The appropriate preparation for the patient with previous masseter spasm, or trismus, is a matter of considerable debate. I prepare for malignant hyperthermia (e.g., I ensure a contaminant-free machine, use nontriggering agents, and have a malignant hyperthermia cart in the room) but do not routinely perform muscle biopsy or prescribe dantrolene prophylaxis. [550] [551] Malignant hyperthermia occurs most frequently among children and adolescents, the incidence being 1 in 14,000 administrations of anesthetic. The incidence increases to 1 in 2,500 among patients requiring squint surgery. Questions to ask the parents during the preoperative evaluation include the following: Does your child become rigid when upset? Does your child sweat profusely when upset? However, the sensitivity and specificity of such questions in predicting malignant hyperthermia have not been confirmed. The reader is referred to Chapters 23 and 27 for a complete discussion of the screening procedure to use.

Down Syndrome

Down syndrome (trisomy 21) occurs 1.5 times in 1,000 live births. It is associated with congenital cardiac lesions, such as endocardial cushion defects (40%), ventricular septal defects (27%), patent ductus arteriosus (12%), and tetralogy of Fallot (8%), necessitating prophylactic antibiotics prior to predictable bacteremic events. Down syndrome is also associated with upper respiratory infections; with atlanto-occipital instability (in about 15% of patients, [552] [553] in which it is asymptomatic in most cases) and laxity of other joints; with thyroid hypofunction (50%); with an increased incidence of subglottic stenosis; and with enlargement of the tongue. [554] No abnormal responses to anesthetics or anesthetic adjuvants have been substantiated. A reported sensitivity to atropine has been disproved, although administration of atropine to any patient given digoxin for atrial fibrillation should be done with extreme care. [554] Examination for the conditions associated with Down syndrome should precede surgery.

Preoperative Prediction of Patients Having Increased Intracranial Pressure During Neurosurgery

Symptoms and signs of increased intracranial pressure include morning headache or headache made worse by coughing, nausea, vomiting, disturbances of consciousness, history of large tumors, tumors involving the brain stem, neck rigidity, and papilledema. Patients having theses signs, large ventricles (as seen on radiography or images of the brain), or edema surrounding supratentorial tumors should be considered at risk of intraoperative intracranial hypertension. These patients may benefit from preoperative treatment or anesthetic management that assumes this possibility [555] (Ch. 52) .

Other preoperative considerations for patients with neurologic disease that can cause intracranial hypertension are the associated hypoventilation and hypoxia in patients who have severe hemiplegia and the presence of subarachnoid bleeding or other forms of intracranial hemorrhage (especially likely in women given heparin who have two or more cerebral infarcts on CT scan). [556] Many strokes or transient ischemic attacks have a possible cardiac origin (59 of 184 patients). [557] [558] The drugs used to prevent cerebral arterial spasm, calcium channel blockers, are discussed in the last section of this chapter.

Mental Disorders

Perhaps the most important preoperative consideration for patients with mental disorders, in addition to developing rapport, is understanding their specific drug therapy and its effects and side effects. Lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors, phenothiazines, butyrophenones, and monoamine oxidase inhibitors are used in these patients. [559] These drugs have potent effects and side effects that are discussed in the last section of this chapter.

RENAL DISEASE, INFECTIOUS DISEASES, AND ELECTROLYTE DISORDERS

One may ask why preoperative preparation of the patient with renal disease is discussed in the same section as preoperative preparation of the patient with an infectious disease. Although it is commonly recommended that no surgery except emergency or curative (e.g., drainage of an abscess) be performed in patients with infectious disease, it has become evident that renal insufficiency can be caused by antimicrobial agents [560] and that sepsis, not shock, is probably the leading cause of acute postoperative renal failure. [561] The anesthesiologist has an important role to play in preventing the onset and consequences of renal failure and its initiators. [562] [563] The linking of renal failure to electrolyte disorders is more obvious: the kidney is the primary organ for regulating body osmolality and fluid volume and has a major role in the excretion of the end products of metabolism. In performing these functions, the kidney becomes intimately involved in the excretion of electrolytes.

The patient with renal insufficiency whose own kidneys are still functioning is distinct not only from the patient with end-stage renal disease whose renal functions are provided by a dialysis machine, but also from the patient who has a transplanted kidney. These three groups of patients require very different preoperative preparation. In addition, acute changes in renal function present quite a different problem than do chronic alterations in function. [562] [563] Certain renal diseases require different preoperative preparation than others, but generally renal disease of any origin presents the same preoperative problems (Chs. 18 , 34 , and 53) .

Renal Disease

Causes and Systemic Effects of Renal Disorders

The nephrotic syndrome may develop in patients with glomerular diseases without disturbing tubular function. The soundness of tubular function is an important consideration, as tubular dysfunction with attendant uremia presents quite different problems than does glomerular disease with only the nephrotic syndrome. This is not to minimize the adverse effects of glomerular disease; the nephrotic syndrome consists of massive proteinuria and consequent hypoalbuminemia. The resulting reduction in plasma oncotic pressure diminishes plasma volume; this calls forth compensatory mechanisms that result in retention of sodium and water. As a result, a common clinical finding in nephrotic syndrome is edema. Thus, patients with the nephrotic syndrome may have excess total body water and decreased intravascular volume. In addition, diuretics are often given in attempts to decrease edema. Although serum creatinine and creatinine clearance have limitations as indices of glomerular filtration rate (GFR) (inulin clearance is still the gold standard), these measurements are, for now, the most readily available to the anesthesiologist. [563] Plasma creatinine levels reflect endogenous muscle catabolism and dietary intake, as well as urinary excretion. Urinary excretion depends on both filtration and secretion by the kidney. Drugs that are commonly used in the preoperative and perioperative periods can distort this measure of glomerular filtration: Cimetidine and trimethoprim interfere with secretion, increasing plasma creatinine and decreasing creatinine clearance without altering filtration. [563] It should also be remembered that the commonly used methods for measuring creatinine have a 95 percent confidence limit of more than 20 percent for GFR greater than 30 mL/min. Thus, a normal creatinine level of 1.3 mg/dL might give a measured value ranging from 1.0 to 1.5 mg/dL. [563]

Furthermore, in patients with the nephrotic syndrome in whom renal tubular function has been preserved, hypovolemia appears to be a significant cause of deteriorating tubular renal function. [563] [564] [565] [566] [567] Consequently, I advocate the same intense preoperative, intraoperative, and postoperative fluid management for patients with the nephrotic syndrome as I do for patients with diminished tubular function. Admittedly, no randomized study shows that close control of intravascular volume status in these groups of patients preserves renal tubular function (or any other measure of perioperative morbidity) to a greater degree than does less rigid control.

Uremia, the end result of renal tubular failure (i.e., failure of the concentrating, diluting, acidifying, and filtering functions), presents in many ways. Changes occur in the cardiovascular, immunologic, hematologic, neuromuscular, pulmonary, and endocrine systems, as well as in bone. These alterations are ascribed either to the toxic end products of protein metabolism or to an imbalance in the functioning of the kidney. As the number of functioning nephrons diminishes, the still-functioning nephrons attempt to increase some solute and body composition preservation functions at the expense of other functions, such as the excretion of phosphate. The accumulation of phosphate increases parathormone levels, which in turn produces osteodystrophy. Osteodystrophy can be managed by (1) restriction of dietary phosphate, (2) the use of gels (e.g., aluminum hydroxide or carbonate) that bind with intestinal phosphate, (3) calcium supplementation, or (4) parathyroidectomy. [568]

Certain alterations in uremia, such as neuropathy, are most logically attributed to an accumulation of toxic metabolites. Peripheral neuropathy is most often sensory and of the lower extremities but may also be motor; peripheral neuropathies are often improved with hemodialysis and can be dramatically reversed with transplantation. The use of depolarizing muscle relaxants in patients with peripheral neuropathy is controversial; it is discussed in the section on neuropathies (Ch. 12) . Tubular function is commonly assessed by acidifying and concentrating capabilities. [569] Although these are crude tests, these capabilities are usually readily assessed by measuring urine pH level and specific gravity. Better assessment of renal blood flow, for the purpose of improving renal blood flow and its distribution, is promised by the use of contrast ultrasound in the operating room. [570] Along with the altered volume states and cardiac complications in uremic patients, autonomic neuropathy may contribute to hypotension during anesthesia. Atherosclerosis is often accelerated in uremic patients; hypertension, with its attendant consequences, is very common.

Cardiac failure (especially episodic) frequently occurs in uremic patients because of the presence of many adverse conditions: anemia with increasing myocardial work, hypertension, atherosclerosis, and altered volume states. Pericarditis can present with pericardial rub alone or with pain (with or without hemorrhage). Cardiac tamponade should be ruled out on the basis of clinical features and by echocardiography if this diagnosis is seriously suspected preoperatively. Also, cardiac tamponade should be treated or planned for preoperatively.

If anemia is present, its severity generally parallels the degree of uremia; chronically uremic patients seem to adapt well to anemia. No hard data substantiate the need to give a preoperative blood transfusion to a chronically uremic patient, even when preoperative hematocrit is as low as 16 or 18 vol percent. One of the major historical reasons for not transfusing blood in patients having end-stage renal disease has been disproved: Data show that the more blood transfusions a transplant recipient receives before transplant, the greater the chance that the transplant will function successfully. [571] This immunosuppressive effect of transfusions is now routinely used in transplantation. However, the development of recombinant human erythropoietin may obviate the need for transfusions in chronically uremic patients in the future. Administration of recombinant human erythropoietin to patients in chronic and progressive renal failure showed an average increase in hematocrit level of 10 percent above baseline within 3 weeks, with no serious side effects. [572] The balancing of the immunosuppressive uses of blood transfusions versus the benefits of erythropoietin and risks of transfusion remains to be determined. In uremic patients, coagulation and platelet adhesiveness may be abnormal and factor III activity decreased. Even those uremic patients not given corticosteroids or immunosuppressive drugs may demonstrate abnormal immunity, perhaps meriting increased attention regarding the procedures that lessen patient cross-contamination.

Uremic patients exhibit a wide variety of metabolic and endocrinologic disorders, in addition to hyperparathyroidism, [568] including impaired carbohydrate tolerance, insulin resistance, type IV hyperlipoproteinemia, autonomic insufficiency, hyperkalemia, and anion-gap acidosis (caused by the inability of the kidneys to reabsorb filtered bicarbonate and to excrete sufficient ammonium into the urine). [573] Also, the excretion and pharmacokinetics of drugs are different in uremic patients than in normal patients. In addition, the complications of hemodialysis include hepatitis B (and persistent hepatitis B antigenemia), nutritional deficiencies, electrolyte and fluid imbalances, and mental disorders. Because these conditions can lead to serious perioperative morbidity, they should be evaluated before surgery. No data, however, substantiate the hypothesis that preoperative optimization of these metabolic and endocrinologic disorders reduces perioperative risk in the uremic patient.

As with uremic patients, preoperative optimization of volume status is paramount in patients with kidney stones. [574] Seventy-five percent of all kidney stones are composed of calcium oxylate. Patients with these stones often take diuretic drugs, avoid calcium-rich foods, or restrict salt intake. Prevention of dehydration by institution of intravenous fluid therapy along with restricted oral intake of protein may be as important for these patients as it is for patients with struvate or uric acid stones. Struvate stones often result from urinary infection. Uric acid stones can be prevented by treatment with allopurinol, by preoperative hydration, or by alkalization of the urine. Acidosis may contribute to stone formation. Again, optimal intravascular volume status is important in preventing stones and preserving renal function. More thorough discussion of renal function and physiology is provided in Chapter 18 . Chapter 53 deals with the complexities of managing patients for renal surgery and other urologic procedures.

Creatinine clearance in conjunction with free water clearance appears to be the most accurate way of quantifying, for pharmacokinetic purposes, the degree of decreased renal function [575] [576] [577] (Ch. 34) . For the patient with stable renal function, creatinine clearance, which is a rough estimate of GFR, can be approximated by noting the serum creatinine levels: A doubling of creatinine level represents a halving of GFR. Thus, a patient with a stable serum creatinine level of 2 mg/dL would have a GFR of approximately 60 mL/min. A stable serum creatinine level of 4 mg/dL would accompany a GFR of approximately 30 mL/min, and a stable serum creatinine of 8 mg/dL would accompany a GFR of 15 mL/min or less. When pregnancy and considerable edema are not present and the serum creatinine level is stable, the following formulas can be used to estimate creatinine clearance and free water clearance [575] [576] [578]

Note that renal function must be stable. Unstable renal function often is associated with changes in serum creatinine levels that lag by several days. Although knowing the serum creatinine level is more useful than knowing the blood urea nitrogen level, the latter provides some information, as discussed in the next section.

Free water clearance is a measure of renal concentrating ability and is normally -25 to -100 mL/h, becoming more positive in renal insufficiency states. It may also become more positive in patients who have head injury or high blood alcohol levels, or who are undergoing aggressive fluid infusion or administration of diuretics. [577]

The Patient With Insufficient but Functioning Kidneys

One of the greatest challenges for the anesthesiologist is presented by patients with insufficient renal function whose renal function must be preserved during surgery. The many uremic symptoms and great perioperative morbidity associated with uremia can probably be avoided by attention to detail in the preoperative and perioperative management of patients with insufficient but still functioning kidneys. [561] [562] [563] [564] [565] [566] [567] [568] First, studies demonstrate that acute postoperative renal failure is associated with an extremely high mortality rate. Moreover, acute perioperative renal failure is most likely to occur in patients who have renal insufficiency before surgery, are older than 60 years, and have preoperative left ventricular dysfunction. [579] Proper hydration before surgery probably decreases mortality following acute renal failure due to radiocontrast agents. [566] [567] [568] Clues as to the presence of hypovolemia or hypervolemia should be sought from the history and physical examination (e.g., weight loss or gain, thirst, edema, orthostatic hypotension and tachycardia, flat neck veins, dry mucous membranes, decreased skin turgor). In seriously ill patients, insertion of a pulmonary arterial catheter will permit more precise monitoring of intravascular fluid volume. To preserve normal renal function, infusion of saline, mannitol, furosemide, or low-dose dopamine has been recommended. [580] [581] [582] [583] [584] [585] [586] These therapies should be initiated with caution because saline infusions and mannitol can lead to fluid overload and myocardial damage; also, diuretic drugs given intraoperatively can produce postoperative hypovolemia, which worsens renal function. Maintaining normal intravascular fluid volume can be guided by pulmonary capillary wedge pressure. Maintaining normal intravascular fluid volume has prevented impairment of renal function after abdominal aortic reconstruction, even when urinary volumes were low. [587] Other causes of deterioration in function in chronic renal insufficiency are low cardiac output or low renal blood flow (in prerenal azotemia, whether because of cardiac failure or because of fluid depletion from diuretic drugs, BUN often increases disproportionately to increases in creatinine), urinary tract infection, use of nephrotoxic drugs, hypercalcemia, and hyperuricemia. These conditions and drugs should be avoided; if any of these conditions exists, it should be treated preoperatively.

The Patient Undergoing Dialysis

Because the patient undergoing dialysis has already lost natural renal functioning, the emphasis in preoperative assessment

shifts toward protecting other organ systems and toward optimally maintaining vascular access sites for cannulation. Usually this does not require invasive monitoring. Emphasis is placed on intravascular fluid volume and electrolyte status, which can be ascertained by knowing when the patient last underwent dialysis, how much weight was normally gained or lost with dialysis, whether fluid loss was peritoneal or intravascular, and what electrolyte composition the blood was dialyzed against. Although preoperative dialysis may benefit patients who have hyperkalemia, hypercalcemia, acidosis, neuropathy, and fluid overload, the resulting dysequilibrium between fluid and electrolytes can cause problems. Because hypovolemia induced by dialysis can lead to intraoperative hypotension, I try to avoid weight and fluid reduction when giving preoperative dialysis. Also, hypopnea has been found to occur during and after dialysis when the dialysate contained acetate. [588] Avoiding an acetate bathing solution may prevent this cause of hypoventilation.

The Patient Who Has Had a Renal Transplant

More than 100,000 patients have received renal transplants (compared with 65,000 currently undergoing dialysis in the United States). Approximately 55 percent are still alive, although one-third must undergo dialysis. The advantages, in addition to increased survival, include improvement of the anemia, the endocrine and sexual functions, and the fatigue that inhibit employment and enjoyment for the dialysis patient. The disadvantages are the cost and risks of the transplant operation and of the chronic use of immunosuppressants. When these patients have subsequent surgery, the state of their renal function must be determined (i.e., whether they have normal renal function, insufficient but still functioning kidneys, or end-stage renal disease requiring hemodialysis). Descriptions of side effects from immunosuppressive drugs should also be sought. Drugs used preoperatively and intraoperatively to prevent acute rejection themselves have serious side effects that encourage close monitoring of blood glucose and cardiovascular function. [571] [589] [590] Because renal transplant greatly increases the risk of infection, it is very important to avoid invasive monitoring and prevent patient cross-contamination.

Drugs in Renal Failure

Patients with renal azotemia have a 3-fold or higher risk of an adverse drug reaction than do those with normal renal function. [591] [592] [593] [594] [595] Risk is increased by two conditions. (1) *Excessive pharmacologic effects* result from high levels of a drug or its metabolite (e.g., the metabolite of meperidine) in the blood because of physiologic changes in target tissues induced by the uremic state. An example would be excessive sedation in the uremic patient having standard blood levels of sedative hypnotic drugs. (2) *Excessive administration of electrolytes with drugs* also increases the risk of an adverse drug reaction. For example, the standard dose of

penicillin contains 1.7 mEq of potassium/1 million units. [591] [592] [593] [594] [595] Administration of standard doses of drugs that depend on renal excretion for their elimination can result in drug accumulation and enhanced pharmacologic effect. Bennett et al [591] and Gibson [594] have provided dosing guidelines for many drugs used by anesthesiologists for patients with and without renal failure.

Infectious Disease

Because it is commonly recommended that no surgery except emergency or essential surgery (e.g., drainage of an abscess) be performed when an acute infectious disease is present, and because renal insufficiency can be caused by antimicrobial agents, [560] [565] [566] renal function and organ damage due to renal insufficiency should be assessed preoperatively when infectious disease is present. Prophylactic administration of antibiotics (see Tables 25-34 and 25-35) (Table Not Available) helps prevent sepsis from bacteremic interventions. [596] [597] If therapeutic levels of an antibiotic are given and a reduction in fever occurs (presumably because of decreased levels of released interleukin-2, spinal anesthesia might be considered (using benefit-to-risk judgments) by the anesthesiologist when an acute infectious disease is present. [598]

Sepsis is a leading cause of postoperative morbidity, [561] [562] [566] [567] probably through a decrease in systemic vascular resistance related to activation of the complement system and other mediators. Thus, attention to the effects of antibiotic drugs must be supplemented by attention to intravascular volume status. [564] [565] [566] [567] [599] [600] The degree of impairment of the infected organ and its effect on anesthesia should be assessed. For instance, endocarditis merits examination of volume status; antibiotic and other drug therapy and side effects [601] ; myocardial function; and renal, pulmonary, neurologic, and hepatic function--those organ systems that can be affected by endocarditis.

Although all surgery except emergency or essential is proscribed when an acute infectious disease is present [436] [437] [438] [439] [440] [441] [442] [443] [444] [445] [446] [448] [449] [450] [451] [602] (also see section on upper respiratory infections in the pulmonary section of this chapter), many such diseases (e.g., influenza and pneumococcal pneumonia) are becoming less frequent because of successful immunization recommendations and programs. [603] [604] Whether the preoperative clinic can or should be used to increase use of preventive vaccines is currently being studied (Table 25-42) (Table Not Available) , but it is unclear whether vaccination during the 48 hours before surgery is effective or risky. [605] Furthermore, even though acute infections are less common, surgery for patients with chronic viral diseases such as hepatitis and HIV is more frequent. Many of these patients may also harbor opportunistic infections such as tuberculosis or may have other systemic problems. Whether anesthesia and/or surgery exacerbates these infections or their systemic manifestations is not clear. [606]

At least two other considerations merit preoperative consideration: patient isolation to prevent contamination of the patient and health-care providers. Both concerns are real and are the focus of at least several published volumes. Nosocomial infection is a major source of postsurgical morbidity. [607] [608] [609] [610] [611] [612] [613] Acquired immunodeficiency syndrome [614] and many forms of hepatitis (A, B, and C) appear to be due to viral infections but require direct contact with blood or body fluids. Screening for specific viruses or for the chronic end-organ effects of these viruses [615] [616] [617] is now being done to reduce

TABLE 25-42 -- Estimated Potential Benefit of Full Use of Vaccines Currently Advocated for Adults, in General, and if Immunization Were Encouraged During the Perioperative Period

(Not Available)

Modified from Gardner and Schaffner [604]

the risk of infection to both recipients and health-care personnel during blood transfusions. The usual precautions appear to be largely effective, [618] but the risk is considerable if these precautions are not followed meticulously. [619]

Electrolyte Disorders

Disorders of calcium, magnesium, and phosphate balance were discussed in the section on diseases involving the endocrine system and disorders of nutrition. (Also see Chs. 34 , 38 , and 45.)

Hyponatremia and Hypernatremia

Electrolyte disorders are usually detected by determining the levels of electrolytes in serum. These concentrations reflect the balance between water and electrolytes. The osmolality of all body fluids is normally maintained within the narrow physiologic range of 285 to 290 mOsm/kg H_2O by integration of three key processes: thirst, ADH release, and responsiveness of the medullary collecting ducts to ADH. Because of the permeability of biologic membranes, intracellular and extracellular osmolality are almost always equal and can be estimated by the following formula:

This formula will become easier to calculate when we convert fully to the Systeme International d'Unites (metric system), as millimoles (mmol) can be substituted for mg/(factor) in this formula to read

with concentrations expressed in millimoles per liter (mmol/L). Although secretion of ADH is tightly controlled by osmotic stimuli at 285 to 290 mOsm/kg, the osmotic threshold for thirst is high (300 mOsm/kg), making this sign an important guide to volume deficiency.

Hyponatremia is perhaps the third most common fluid-electrolyte abnormality in hospitalized patients. (Magnesium deficiency occurs in as many as 25% [Ch. 23] ; and potassium deficiency, discussed later in this section, in as many as 10%.) Hyponatremias can occur in isotonic, hypertonic, or hypotonic forms. For example, isotonic hyponatremia can occur in protein or liquid accumulation states such as myeloma. Hypertonic hyponatremia can be present with hyperglycemia or with infusions of glycine (as in the transurethral resection of the prostate syndrome [620]). Hypotonic hyponatremia is the largest classification and is subdivided according to the state of the extracellular fluid into hypovolemic, isovolemic, or hypervolemic hypotonic hyponatremia. All three types require that excretion of renal water be impaired despite continued intake of dilute fluid. Common causes of *hypovolemic* hypotonic hyponatremia (Table 25-43) are GI losses [621] (vomiting, diarrhea), third-space losses (diuretics or salt-wasting nephropathy), or

TABLE 25-43 -- Causes of Hypotonic Hyponatremias[a]

TYPE OF HYPOTONIC HYPONATREMIA, AND CAUSES
HYPOVOLEMIC
Gastrointestinal losses
Vomiting
Diarrhea
Skin losses
Third-space losses

Lung losses
Renal losses
  Diuretics
  Renal damage
  Urinary tract obstruction
Adrenal insufficiency
ISOVOLEMIC
Syndrome of inappropriate secretion of antidiuretic hormone
Renal failure
Water intoxication
Hypokalemia
Dysfunctional osmostat
HYPERVOLEMIC
Congestive heart failure
Nephrosis
Liver dysfunction
*Serum osmolality <280 mOsm/L

adrenal insufficiency. *Hypervolemic* hypotonic hyponatremic states complicate severe cardiac failure, [622] cirrhosis, nephrotic syndrome, or renal failure and are characterized by retention of sodium with disproportionately larger amounts of water.

The more common *isovolemic* hypotonic hyponatremia is caused by retention of water without sodium. Because edema is usually not clinically apparent, such patients appear isovolemic. Edema is most often caused by the syndrome of inappropriate ADH secretion. SIADH may be caused by CNS or pulmonary tumors or dysfunction. Secretion of ADH increases with age, rendering the elderly more prone to hyponatremia. Drugs that potentiate the secretion of ADH (tricyclic antidepressants and vincristine) or its effects on the medullary collecting duct system in the kidney (nonsteroidal anti-inflammatory drugs and chlorpropamide), or that have similar effects (oxytocin), may be more likely to cause hyponatremia in the elderly. To establish the diagnosis of SIADH, the physician should determine that the patient is free of renal and cardiac dysfunction, has normal adrenal and thyroid function, and is normovolemic. Urine osmolality would then be found to exceed 100 mOsm/kg, serum osmolality would be low, and urine sodium excretion would be higher than 20 mEq/L (20 mOsm/L).

Therefore, disturbances in serum sodium reflect alterations in glucose metabolism, renal function, or accumulation of body water. The last can be affected by disturbances in thirst, ADH release, and renal function. Thus, hyponatremia reflects a relative excess of free water and can occur when total body sodium increases (as in edematous disorders), when total body sodium is normal (as in excesses of free water because of SIADH), or when total body sodium decreases (as occurs with too-aggressive use of diuretic drugs). Definition of the cause defines treatment. For instance, water restriction is the mainstay of therapy for SIADH. Administration of demeclocycline is another option that corrects SIADH by inducing a reversible nephrogenic diabetes insipidus. The anesthesiologist is faced with the question: What levels of electrolytes require treatment prior to anesthesia? Although slowly developing hyponatremia usually produces few symptoms, the patient may be lethargic and apathetic. Chronic hyponatremia is better tolerated than acute hyponatremia because of mechanisms regulating intracellular fluid volume that alleviate brain edema; the loss of other solutes from the cell decreases the osmotic movement of water into cells. Despite this, severe chronic hyponatremia (i.e., serum sodium levels <123 mEq/L) can cause brain edema. [623] [624] By contrast, acute hyponatremia may manifest with severe symptoms requiring emergency treatment: profound cerebral edema with obtundation, coma, convulsions, and disordered reflexes and thermoregulatory control. [623] [624] Depending on the cause and relative total sodium and water content, treatment can range from administration of hypertonic saline or mannitol (with or without diuretic drugs) to restriction of fluids or administration of other drugs. [210] [623] [624] Because neurologic damage may develop if the serum sodium concentration is increased too rapidly, the rate of increase should not exceed 1 mEq/L/h. [209] [210] [624] After the serum sodium concentration has reached 125 mEq/L, therapy may consist of water restriction; more rapid correction may result in CNS demyelination. [209] [210] [624] In hyponatremic patients who have excess total body water secondary to SIADH, serum levels can be corrected by giving furosemide, 1 mg/kg, and hypertonic saline to replace loss of electrolytes in urine. [209] [623] [624] The diagnosis of SIADH is discussed earlier in this chapter *(Pituitary Abnormalities).*

Neither acute nor chronic hyponatremia necessitates the restoration of serum sodium levels to their normal levels; brain swelling usually disappears at a serum sodium level of 130 mEq/L. This leaves us with the question: What levels of serum sodium make anesthesia more risky? Because no data exist to answer this question, to allow for some error in caring for patients, I have arbitrarily chosen a flexible concentration of 131 mEq/L as the lower sodium limit for elective surgery. A discussion of intraoperative hyponatremia in patients undergoing transurethral prostatectomy [620] is in Chapter 53 .

Hypernatremia occurs much less commonly than hyponatremia. It is often iatrogenic in origin (e.g., it can be caused by failure to provide sufficient free water to the patient who is unconscious or who has had a recent stroke-induced deficit of the thirst mechanism) and can occur in the presence of low, normal, or excess total body sodium. The primary symptoms of hypernatremia relate to brain cell shrinking. Because too-rapid correction of hypernatremia can lead to cerebral edema and convulsions, correction should be made gradually. Again, with no data to support this stance, I believe that all patients undergoing surgery should have serum sodium concentrations of less than 150 mEq/L prior to anesthesia.

Hypokalemia and Hyperkalemia

Hypokalemia and hyperkalemia are also discussed in Chapters 34 , 36 , 38 , and 45 . The relationship between the measured potassium concentration in serum and the total body potassium stores can best be described using a scattergram. [126] [625] Only 2 percent of total body potassium is stored in plasma (4,200 mEq in cells and 60 mEq in extracellular fluid). In normal persons, 75 percent of the 50 to 60 mEq/L of total body potassium is stored in skeletal muscle, 6 percent in red blood cells, and 5 percent in the liver. Thus, a 20 to 25 percent change in potassium levels in plasma could represent a change in total body potassium of 1,000 mEq or more if the change were chronic, or as little as 10 to 20 mEq if the change were acute.

As with serum sodium levels, [623] [624] acute changes in serum potassium levels appear to be less well tolerated than chronic changes. Chronic changes are relatively well tolerated because of the equilibration of serum and intracellular stores that takes place over time to return the resting membrane potential of excitable cells to near-normal levels.

Hyperkalemia can result from factitious elevation of potassium (as in red blood cell hemolysis); excessive exogenous potassium from sources such as salt substitutes or, in large amounts, bananas; cellular shifts in potassium (owing to metabolic acidosis, tissue and muscle damage after burns, use of depolarizing muscle relaxants, or intense catabolism of protein); and decreased renal excretion (as occurs in renal failure, renal insufficiency with trauma, and therapy with potassium-sparing diuretic drugs, especially when combined with the angiotensin-converting inhibiting drugs or mineralocorticoid

deficiency). [625] [626] [627] [628] [629] [630] [631] Factitious hyperkalemia can occur when a tourniquet is left on for too long or even by simple fist clenching. [632]

The major danger in anesthetizing patients who have disorders of potassium balance appears to be abnormal cardiac function--that is, both electrical disturbance [626]

[627] [628] [629] and poor cardiac contractility. [627] [628] Hyperkalemia lowers the resting membrane potential of excitable cardiac cells and decreases the duration of the myocardial action potential and upstroke velocity. This decreased rate of ventricular depolarization, plus the beginning of repolarization in some areas of the myocardium while other areas are still undergoing depolarization, produces a progressively widening QRS complex that merges with the T wave into a sine wave on ECG.

Above a potassium level of 6.7 mEq/L, the degree of hyperkalemia and the duration of the QRS complex correlate well. [626] This correlation is even better than the correlation between the serum potassium level and T-wave changes. Nevertheless, the earliest manifestations of hyperkalemia are narrowing and peaking of the T wave. Although not diagnostic of hyperkalemia, T waves are almost invariably peaked and narrow when serum potassium levels are 7 to 9 mEq/L. When serum potassium levels exceed 7 mEq/L, atrial conduction disturbances appear, as manifested by a decrease in P-wave amplitude and by an increase in the PR interval. Supraventricular tachycardia, atrial fibrillation, PVCs, ventricular tachycardia, ventricular fibrillation, or sinus arrest may all occur.

The ECG and cardiac alterations of hyperkalemia are potentiated by low serum levels of calcium and sodium. Intravenous administration of saline, bicarbonate, glucose with insulin (1 U/2 g glucose), and calcium can reverse these changes by shifting some extracellular potassium into the cell.

beta-Adrenergic stimuli also cause redistribution of potassium into the cell. Indeed, the plasma potassium concentration measured in samples immediately before surgery is usually 0.2 to 0.8 mEq/L lower than that measured during the less stressful period 1 to 3 days before surgery. [633] beta-Adrenergic receptor-blocking drugs such as propranolol can be used to prevent such an effect preoperatively. A beta- adrenergic receptor-stimulating agent (20 mg of nebulized albuterol for a 70-kg patient) can be used to treat hyperkalemia when it occurs; it decreases potassium levels 1.0 mEq/L within 30 minutes, and its effect lasts 2 hours. [634] Although nebulized $beta_2$ -agonists effectively lower plasma potassium concentrations by stimulating sodium- and potassium-dependent adenosine triphosphatase, this therapy should be used as an adjunct to, rather than as a substitute for, more established measures. Kayexalate (sodium polystyrene sulfonate) enemas can be given to bind potassium in the gut in exchange for sodium. Dialysis against a hypokalemic solution will also decrease serum potassium levels. However, in the hyperkalemic patient, hypoventilation can be dangerous during anesthesia, [529] [533] [635] [636] because each 0.1 change in pH level can produce a 0.4 to 1.5 mEq/L change in serum potassium levels in the opposite direction. For example, if pH level decreases from 7.4 to 7.3, serum potassium levels could increase from 5.5 to 6.5 mEq/L. [629]

Hypokalemia can be caused by inadequate intake of potassium, excessive GI losses (through diarrhea, vomiting, nasopharyngeal suctioning; chronic use of laxatives; or ingestion of cation-exchange resins, as in certain wines), excessive renal losses (because of use of diuretic drugs, renal tubular acidosis, chronic chloride deficiency, metabolic alkalosis, mineralocorticoid excess, excessive ingestion of licorice, use of antibiotics, ureterosigmoidostomy, and diabetic ketoacidosis), and shifts of potassium from extracellular to intracellular compartments (as occur in alkalosis, insulin administration, beta-adrenergic agonist administration or stress, barium poisioning, and periodic paralysis). As with hyperkalemia, knowledge of the cause of potassium deficiency and the appropriate preoperative evaluation and treatment of that cause may be as important as treatment of the deficiency itself. Also like hyperkalemia, hypokalemia may reflect small or vast changes in total body potassium. Acute hypokalemia may be much less well tolerated than chronic hypokalemia. The major worrisome manifestations of hypokalemia pertain to the circulatory system, both the cardiac and peripheral components. In addition, chronic hypokalemia results in muscle weakness, hypoperistalsis, and nephropathy.

The cardiovascular manifestations of hypokalemia include autonomic neuropathy (which results in orthostatic hypotension and decreased sympathetic reserve), impaired myocardial contractility, and electrical conduction abnormalities that can result in sinus tachycardia, atrial and ventricular arrhythmias, and disturbances of intraventricular conduction that can progress to ventricular fibrillation. That these are real concerns for the hypokalemic patient has been shown far too often. [626] [627] [628] [634] [637] [638] [639] In addition to arrhythmias, the ECG shows widening of the QRS complex, ST-segment abnormalities, progressive diminution of the T-wave amplitude, and progressive increase in the U-wave amplitude. [640] Surawicz [626] found these changes to be present invariably when serum potassium levels decreased to below 2.3 mEq/L. Although U waves are not specific to hypokalemia, they are sensitive indicators of the condition. Replenishing the total body potassium deficit for a depletion reflected by a serum deficit of 1 mEq/L (e.g., from 3.3 to 4.3 mEq/L) may require 1,000 mEq of potassium. Even if this amount could be given instantaneously (and it should not be replenished at a rate exceeding 250 mEq/d), it would take 24 to 48 hours to equilibrate in all tissues. [127] [128] The potassium-depleted myocardium is unusually sensitive to digoxin, calcium, and, most important, potassium. Rapid potassium infusion in the hypokalemic patient can produce arrhythmias as severe as those produced by hypokalemia itself. [128] [641] [642] [643]

Thus, the decision to proceed with surgery and anesthesia in the face of acute or chronic depletions or excesses of potassium depends on many factors. [644] [645] [646] [647] [648] One must know the cause and treatment of the underlying condition creating the electrolyte imbalance and the effect of that imbalance on perioperative risk and physiologic processes. The urgency of the operation, the degree of electrolyte abnormality, the medications given, the acid-base balance, and the suddenness or persistence of the electrolyte disturbance are all considerations.

Retrospective epidemiologic studies attribute significant risk to administration of potassium (even chronic oral administration). [645] [646] In one study, 1,910 of 16,048 consecutive

hospitalized patients were given oral potassium supplements. Of these, hyperkalemia contributed to death in seven, making the incidence of complications of potassium therapy one in 250 patients. Armed with such data, many internists do not prescribe oral potassium therapy for patients given diuretic drugs. Yet these patients frequently become moderately hypokalemic. [649] [650] Modest hypokalemia occurs in 10 to 50 percent of patients given diuretic drugs. Should surgery be delayed to subject such patients to the risks of potassium therapy?

Two studies investigated whether modest hypokalemia was a problem by prospectively seeking arrhythmias on the ECGs of patients who had various preoperative levels of potassium. [647] [648] No difference in the incidence of arrhythmias occurred among 25 normokalemic (K >3.4 mEq/L) patients, 25 moderately hypokalemic (K = 3-3.4 mEq/L) patients, and 10 severely hypokalemic (K <2.9 mEq/L) patients. [647] The inability of the eye in picking up these changes--or of even Holter recordings for short periods [651] (which seem not to have been obtained in this study)--points to the need for confirming studies.

Other studies indicate that modest hypokalemia can have severe consequences. [650] [652] [653] Holland and coworkers [653] treated 21 patients with 50 mg of hydrochlorothiazide twice a day for 4 weeks. These patients had a history of becoming hypokalemic during diuretic therapy; none of them had cardiac disease or was taking other medication. Before and after diuretic therapy, 24-hour ambulatory ECGs were recorded. This study is also subject to the limitations of Holter monitoring. [651] Seven of the 21 patients (33%) developed ventricular ectopy, including complex ventricular ectopy (multifocal PVCs, ventricular couplets, ventricular tachycardia). Potassium repletion decreased the number of ectopic ventricular beats per patient from 71.2 to 5.4/h. Apparently, some patients are sensitive to even minor potassium depletion. In the Multiple Risk Factor Intervention Trial involving 361,662 patients, more than 2,000 of whom were treated for hypertension with diuretics, the reduction in serum potassium after diuretic therapy was greater for those with PVCs. [650] Although I recommend that hypokalemic patients be given potassium supplements, the merit of this practice is unclear.

My personal criteria for preoperative potassium therapy are as follows. As a rule, all patients undergoing elective surgery should have normal serum potassium levels. However, I do not recommend delaying surgery if the serum potassium level is above 2.8 mEq/L or below 5.9 mEq/L, if the cause of potassium imbalance is known, and if the patient is in otherwise optimal condition. This range of safe potassium levels is arbitrary and has changed from 3.3 in 1979, to 3.1 in 1986, to 2.9 in 1990 on the lower side and from 5.6 in 1979, to 5.7 in 1986, and to 5.9 in 1990 on the upper side as more data have become available on the safety of preoperative hypokalemia and the dangers of replacing potassium in a hospital environment. [645] [646] (See Table 23-5.) I subject all patients with end-stage renal failure to dialysis (using the same arbitrary safe range) before all surgical procedures except truly emergency ones (as in the instances of imminent exsanguination). In studies on dogs in 1978, Tanifuji and Eger [654] determined the relationships between electrolyte status and anesthetic requirement that may represent intraoperative considerations: Hyponatremia and hypo-osmolality decreased minimum alveolar concentration (MAC), hypernatremia increased MAC, and hyperkalemia did not affect anesthetic requirement.

/das/book/view/29494766/875/269.html

GASTROINTESTINAL AND LIVER DISEASES

The reader should also see the discussion of porphyrias in the section on neurologic disease; the discussion of nutritional deficiencies in the section on disorders of nutrition; and pediatric disorders, such as transesophageal fistula, in Chapters 58 , 59 , and 73 .

Gastrointestinal Disease

Preoperative Search for Diverse Associated Disorders in Gastrointestinal Disease

Although preoperative preparation of the GI tract is usually the responsibility of the surgeon, and although the GI tract frequently does not need to be extensively evaluated by the anesthesiologist, GI disease can, and often does, cause derangements in many or all other systems. Such disturbances can affect the safety of anesthesia for the patient. Thus, the anesthesiologist may need not only to optimize the patient's condition through extensive preoperative preparation but also to have knowledge of disease processes and their effects to guide the patient smoothly through the perioperative period. The major advances of correcting fluid and electrolyte disorders and of optimizing nutritional status before surgery now allow surgery to be performed in patients with GI disease previously deemed to be at too great a risk and may have lessened the risk for others. [101] [102] [103] [104] [655] [656] Still, in patients with GI disease, a thorough evaluation of intravascular fluid volume and electrolyte concentrations and nutrition is essential, including an evaluation of the supervening side effects of these therapies (e.g., hypophosphatemia from parenteral nutrition, hyperkalemia or cardiac arrhythmias from too-vigorous treatment of hypokalemia, and CHF from too-rapid or too-vigorous treatment of hypovolemia).

In addition to vast alterations in fluids, electrolytes, and nutrition that can occur with such diverse GI diseases as neoplasms and pancreatitis, patients with GI disorders can have reflux disease, [657] bowel obstruction, vomiting, or hypersecretion of acid. These effects may merit rapid induction of anesthesia with application of cricoid pressure or awake endotracheal intubation, preoperative nasogastric suctioning, or preoperative use of histamine receptor-blocking agents (Ch. 39) . Clotting abnormalities may need to be corrected, because the fat-soluble vitamin K (often malabsorbed) is necessary for synthesis of factors V, VII, IX, and X in the liver (Ch. 54) . Liver disease is often associated with GI disease and, if severe enough, can also result in deficiency of clotting factors synthesized by the liver.

Other factors should be remembered in any preoperative evaluation of the patient with GI disease. First, closed spaces containing gas expand by absorbing nitrous oxide.

This expansion can lead to ischemic injury and/or GI viscus rupture. [658] Second, GI surgery predisposes the patient to sepsis; sepsis and decreased peripheral vascular resistance can lead to massive fluid requirements, cardiac failure, and renal insufficiency. Recently, the wound infection rate has been declining. This decrease may be attributable to the use of better technique, to more appropriate prophylactic use of antibiotics, to better nutrition, to less invasive (laparoscopic and endoscopic) surgery, or to surgical resection of even solid tumors. [354] [658] [659] [660] [661] [662] Third, patients with GI disease may have many other associated disorders not directly related to the GI tract. For example, they may be anemic from deficiencies in iron, intrinsic factor, folate, or vitamin B_{12} . They may also manifest neurologic changes from combinedsystem disease. Respiration may be impaired because of heavy cigarette smoking, peritonitis, abscess, pulmonary obstruction, previous incisions, aspirations, or pulmonary embolism (as occurs with ulcerative colitis or with thrombophlebitis in the bedridden). [663] These patients may also have hepatitis, cholangitis, or side effects from antibiotic drugs or other medications, massive bleeding with anemia and shock, or psychologic derangements.

Because GI disease can be accompanied by so many diverse associated disorders, the clinician clearly must search for other system involvement and preoperatively assess and treat such disorders appropriately. Discussion of two specific diseases, ulcerative colitis and carcinoid tumors, will highlight the importance of involvement of other systems in GI disease.

Ulcerative Colitis and Carcinoid Tumors as Examples of Gastrointestinal Disease Affecting Other Systems

Patients with ulcerative colitis often have psychologic problems. They may also have phlebitis; deficiencies in iron, folate, or vitamin B_{12} ; anemia; or clotting disorders caused by malabsorption. They may be malnourished or dehydrated or have electrolyte abnormalities. In addition, ulcerative colitis can be accompanied by massive bleeding; bowel obstruction or perforation or toxic megacolon, causing respiratory compromise; hepatitis; arthritis; iritis; spondylitis; or diabetes; secondary to pancreatitis.

The site of origin of carcinoid tumors in more than 75 percent of patients is the GI tract. [664] Within the GI tract, carcinoid tumors have been documented to occur from the esophagus to the rectum. The most frequent site is the appendix, but carcinoids in this location rarely, if ever, metastasize or produce the carcinoid syndrome. Tumors arising in the ileocecal region have the highest incidence of metastases. Carcinoid tumors originating from other than the GI tract have been reported in other sites, such as the head and neck, lung, gonads, thymus, breast, and urinary tract. Cardiac involvement, although frequently reported, is usually limited to right-sided valvular and myocardial plaque formation.

Not all patients with carcinoid tumors have symptoms attributable to secretion of hormone by the tumor. The most comprehensive series in the literature indicates that only 7 percent of patients have the carcinoid syndrome, which consists of flushing, diarrhea, and valvular heart disease. Of those with the syndrome, approximately 74 percent have cutaneous flushing; 68 percent, intestinal hypermotility; 41 percent, cardiac symptoms; and 18 percent, wheezing. Factors influencing symptoms include location of the tumor and the specific hormones produced and secreted. Although it is generally believed that if patients do not exhibit the carcinoid syndrome, the tumors are not producing serotonin (5-hydroxytryptamine [5-HT]), this may not be the case. Approximately 50 percent of patients with carcinoid tumors of the GI tract demonstrate evidence of 5-HT production, as manifested by elevated levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolic product of 5-HT, in urine. The carcinoid syndrome is usually associated with ileal carcinoid tumors that have metastasized to the liver. Presumably, the liver clears mediators released from the tumor. Impairment of this clearing ability by the metastatic tumor results in the carcinoid syndrome.

Most patients with carcinoid tumors and increased urinary 5-HIAA have typical carcinoid tumors originating from the midgut (ileum or jejunum). These patients excrete only small amounts of 5-hydroxytryptophan (5-HTP). Patients with atypical carcinoid tumors that originate in the foregut (bronchus, stomach, and pancreas) excrete large amounts of 5-HT and 5-HTP as well as moderately higher amounts of 5-HIAA.

Although there is general agreement that 5-HT is responsible for the diarrhea experienced by patients with carcinoids, other neurohumoral agents may contribute to the flushing and hypotension. [664] [665] [666] These include dopamine, histamine, and some of the neuropeptides, such as substance P, neurotensin, vasoactive intestinal peptide, and somatostatin.

The net physiologic effect of circulating 5-HT represents a composite of both direct action (mediated by 5-HT receptors) and indirect action (mediated through the modulation of adrenergic neurotransmission). The existence of several subtypes of 5-HT receptors may account for the different effects of 5-HT on various serotonin-sensitive tissue beds. Indirect actions are effected through alterations in catecholamine release and depend on the level of circulating 5-HT.

5-HT has little, if any, direct effect on the heart. With elevated levels, however, positive chronotropic and inotropic myocardial effects may occur, mediated by the release of noradrenaline (norepinephrine). Effects of serotonin on the vasculature include both vasoconstriction and vasodilation.

Alterations in GI function attributed to 5-HT include increased motility and net secretion of water, sodium chloride, and potassium by intestine. 5-HT reportedly causes bronchoconstriction in many animals but rarely in humans. Asthmatics are a possible exception. Carcinoid tumors frequently present as diarrhea with fluid and electrolyte abnormalities. Because these tumors secrete vasoactive substances, patients can exhibit hypotension or hypertension with the flush of vasoactive substance release. Vasoactive substances can be released from the tumor by any number of substances, including catecholamines. Thus, the anesthesiologist must tread the fine line between avoiding substances known to release 5-HT (e.g., *d*-tubocurarine and morphine) and creating anesthesia so light that painful stimuli

activate a sympathetic stress response. [667] [668] The anesthesiologist must also be ready and able to treat hypotension, decreased peripheral vascular resistance, bronchospasm, and hypertension. alpha-Adrenergic receptor blockade with the phenothiazines, butyrophenones, or phenoxybenzamine and beta-adrenergic receptor blockade with propranolol have been advocated to prevent catecholaminemediated release of vasoactive substances. These practices, however, can lead to hypotension. In fact, somatostatin is now such a powerful inhibitor of release of peptides from carcinoid tumors and an inhibitor of peptic effects on receptor cells that it is the therapy of choice for preoperative, intraoperative, and postoperative management of carcinoid symptoms and crises. [664] [667]

If severe hypotension occurs that is not treatable with somatostatin, the drug of choice is either angiotensin or vasopressin. (Angiotensin is not commercially available in the United States but is an approved drug that is available by contacting CIBA-GEIGY.) However, the vasoactive substances released by carcinoid tumors cause fibrosis of heart valves, often resulting in pulmonic stenosis or tricuspid insufficiency. To increase cardiac output in the patient with tricuspid insufficiency, the anesthesiologist should avoid drugs or situations that increase pulmonary vascular resistance (e.g., angiotensin, vasopressin, acidosis, hypercarbia, hypothermia) (Chs. 49 and 50) . In addition, the production of large amounts of 5-HT (equal to 200 mg/d of 5-HIAA) can lead to the development of niacin deficiency with pellagra (as occurs with diarrhea, dermatitis, and dementia).

Acute elevation of plasma kinin activity in carcinoid patients has been postulated for many years as the explanation for the symptoms of carcinoid syndrome. Physiologic effects of kinins are known to include vasodilation of smaller resistance vessels and stimulation of release of histamine from mast cells. The latter action potentiates their own vasodilating properties and further reduces systolic and diastolic blood pressure. In addition, increases in vascular permeability may lead to edema. Kinins are not known to affect the myocardium directly.

Steroids have been effective in treating the symptoms of bronchial carcinoid tumors. Although prophylactic preoperative administration and intraoperative therapeutic uses have been described, controlled studies of beneficial effects are lacking. Aprotinin, like steroids, inhibits the kallikrein cascade. This agent is believed to be capable of blocking the proteinase activity of kallikrein. Some reports have described a dramatic clinical response.

A subset of patients with symptoms of the carcinoid syndrome excrete histamine at increased levels in their urine. Histamine causes vasodilation of small blood vessels, leading to flushing and decreased total peripheral resistance. Histamine is known to cause bronchoconstriction, particularly in patients with bronchial asthma and other pulmonary diseases. Its role in carcinoid bronchospasm, if any, is uncertain. Histamine receptor-blocking drugs have been used with some success in alleviating the flushing associated with carcinoid syndrome. H_2 -antagonism alone was found to be just as effective as combination therapy in preventing symptoms; pure H_1 -antagonism, however, was ineffective. These therapies have been relegated to a second-line defense since the use of somatostatin.

Catecholamines aggravate the symptoms of carcinoid syndrome, presumably by stimulating hormone release by the tumor. The mechanism by which this occurs remains obscure. Adrenergic receptors have not been demonstrated in carcinoid tumors, nor do these tumors usually have neural innervation. Perhaps adrenergic stimuli work through their mechanical effects on the gut and vessels to stimulate the release of tumor products. Treatment of patients with carcinoid tumors by means of alpha- and beta-adrenergic antagonists has been beneficial in ameliorating flushing in some instances but ineffective in others.

Results of prospective studies on somatostatin used to ameliorate symptoms of the carcinoid syndrome have been dramatic. In several case reports involving a total of 46 patients, all but two patients had rapid, dramatic improvement in flushing. [664] [665] [666] [667] [669] [670] [671] [672] Similar results have been obtained in patients with diarrhea. Somatostatin appears to be a major advancement in the treatment of carcinoid syndrome.

It might logically be concluded that preoperative preparation of the patient with carcinoid syndrome would be similar to that for the patient with pheochromocytoma, titrating adrenergic, histaminic, and serotonergic receptor-blocking drugs to maximum effect while monitoring intravascular volume status and adding somatostatin prior to surgery. Although this approach is logical, preoperative symptoms do not correlate with perioperative symptoms, and only the last two therapeutic options (optimization of intravascular fluid status and administration of somatostatin) are most effective.

Many patients also develop bronchospasm with or without flushing when vasoactive substances are released. Thus, a patient with a carcinoid tumor may be well or may be severely incapacitated by pulmonary, neurologic, nutritional, fluid, electrolytic, or cardiovascular disturbances. [664] [667] Therefore, although the GI system in itself may not require extensive preoperative preparation, GI disease can cause disturbances in any or all other systems that require both extensive preoperative preparation to optimize the patient's condition, plus preoperative knowledge of physiology and effects of diseases in order to guide patients through the perioperative period smoothly. In addition, the anesthesiologist's understanding of the nature of the surgery probably aids in determining the system involvement caused by GI disorder.

Another preoperative consideration is that patients with GI diseases (perhaps even more so than those with other diseases) have had to endure the psychosocial trauma of having to live with their disease for long periods or to face such a prospect. [673] They need emotional support and holistic kindnesses as much as, if not more, than others, without sacrificing scientific rigor in the treatment of their condition. Obtaining relevant psychologic data while gathering medical information, sitting (not standing) while taking the history, and empathizing with the patient as to how difficult it must be to accomplish tasks with this disease (stressing accomplishments, I have found) legitimize the physician's interests in, and support of, the patient's pain and other psychosocial issues. The time spent sitting and talking with the patient also allows the anesthesiologist to discuss options for pain therapy with the patient, why systemic morphine might be avoided in the patient with a fresh bowel anastomosis, [674] and other issues that show the anesthesiologist to be both a competent physician and particularly concerned with that

patient's well-being. In addition to an appreciation of the organic effects of their disease, attention to emotional support of these patients perioperatively presents opportunities to use one's full skills as a physician to bring about healing.

Liver Disease

What are the risks of giving anesthesia to patients with acute liver disease who require emergency surgery? What are the risks of giving anesthesia to patients with chronic impairment of liver function? What can be done to minimize these risks? Although one might think that the experiences gained from providing anesthesia for liver transplantation would answer many of these questions, there is a substantial difference between optimizing cardiovascular function to meet the needs of a new liver (e.g., supply of nutrients) and maintaining liver function in a diseased liver. Because hepatic function and physiology are discussed in Chapter 54 , I will mention only that the liver performs many functions: it synthesizes (e.g., proteins, clotting factors), detoxifies the body of both drugs and the products of normal human metabolism, excretes waste products, and stores and supplies energy. Tests of liver function assess synthesis (cholesterol levels, PT, albumin levels), cellular integrity (aspartate transaminase and alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase), the liver's ability to detoxify the body (e.g., ammonia,

direct bilirubin, or lidocaine levels), and the liver's ability to excrete certain substances (bromosulphthalein retention, total bilirubin levels).

In examining the effects of anesthesia (with or without surgery) on liver function, and in examining ways to reduce risk in patients with pre-existing liver disease, investigators have often looked at one or more of these tests or, more commonly, at major end points of morbidity (jaundice) or mortality. The evidence can be summarized as follows: Without anesthesia or surgery, approximately 1 in 700 to 800 patients who are otherwise healthy and scheduled for surgery will have abnormal preoperative results for liver function tests; of these patients, one in three will develop jaundice. [675] [676] (Also see Ch. 23 for these studies.) In our preliminary study, *every* patient with abnormal liver function tests was symptomatic preoperatively. [273] Therefore, the risk may be less than described (Ch. 23) .

All anesthetics tested (general, narcotic-nitrous oxide, and regional) have caused transient abnormalities in liver function tests. These abnormalities were magnified by upper intra-abdominal surgery and occurred regardless of preexisting liver disease. [635] [677] [678] [679] [680] [681] [682] [683] [684] [685] [686] Patients whose preoperative liver function tests are abnormal will obviously have a higher incidence of abnormal results on postoperative liver function tests. [635] [679] [680] [681] [683] [684] Lacking in the literature are investigations that studied patients with compromised hepatic function to determine how to decrease the risk of surgery and anesthesia. Also lacking are comparisons of outcome after various perioperative management strategies, based on the different causes of hepatic dysfunction (i.e., viral [or even one virus versus another virus], toxic, or drug induced). In addition to pre-existing hepatic disease and the operative site, hypokalemia, hypotension, sepsis, and the need for blood transfusion all contribute to postoperative hepatic dysfunction. Thus, anesthesia and surgery probably exacerbate hepatic disease, clearly increasing morbidity and mortality. [635] [678] [679] [680] [683] [684] Only one study, on alcoholic liver disease, has implied otherwise. [635]

The main goal of the anesthesiologist is to avoid making the hepatic disease (with perhaps its metabolic and CNS toxicity) worse and thereby increase the chance of renal failure, coma, and death. [687] Studies of portal hypertension have shown that mortality can be 50 percent when preoperative serum albumin concentrations are lower than 3 g/dL, preoperative serum bilirubin levels are greater than 3 mg/dL, and ascites and encephalopathy are present; mortality can be even higher when PT is grossly abnormal. By contrast, mortality decreases to 10 percent when preoperative serum albumin levels are 3 to 3.5 g/dL, preoperative serum bilirubin levels are 2 to 3 mg/dL, PT is normal, and encephalopathy is absent. The risks of anesthetizing a patient with chronic liver disease not requiring portacaval shunt are detailed only sporadically but appear to be greater than those associated with anesthetizing a healthy patient. [675] [676] [677] [678] [679] [680] [681] [682] [683] [684] [685] [686] [687] [688] [689] [690] [691]

Should halothane be given to patients with hepatitis or biliary tract disease? The National Halothane Study did not find halothane to cause massive hepatic necrosis or any other hepatic abnormality more frequently than any other anesthetic agent [574] and, in fact, demonstrated its safety in biliary tract surgery. Prospective studies have been contradictory at best as to whether repeat exposures to halothane within a short time elevate liver enzyme levels to a greater degree than do other anesthetic agents. [692] [693] [694] [695] Because the incidence of hepatitis attributable only to halothane would be very low, very large groups would have to be studied. The incidence of postoperative jaundice and hepatitis not attributable to halothane is much greater than the incidence of hepatitis attributable only to halothane, and the absence of differentiating pathologic features makes halothane hepatitis difficult to exclude as a possibility. Newer tests imply an immunologic basis to the continuation of either the hepatitis or liver dysfunction after the initial mechanism (e.g., if hypoxia begets the injury, the immune mechanism continues it) and are supported by resolution of the prolonged case of halothane hepatitis after treatment. [696] Although other cases that have resolved after steroid therapy have been presented, those cases did not, in fact, allow a long enough time before the beginning of their resolution when the disease was stable to conclude that the steroids made a difference and that this was not the natural course of the disease. One case is inconclusive but certainly implies that a controlled trial should be instituted. This subject is perhaps even more important now that several forms of viral hepatitis (acute and chronic) are now treatable: Left untreated, hepatitis C evolves to chronic type C hepatitis in 50 percent of patients and to cirrhosis in 20 percent of those developing chronic hepatitis. Treatment with alpha-(leukocyte) interferon appears to reduce the risk of these consequences substantially. [615] [616]

More sensitive tests of hepatocellular dysfunction after anesthesia and surgery, such as glutathione- *s*-transferase, reveal impairment more frequently. [697] One is left to conclude that both metabolic and immunologic mechanisms can contribute to hepatocellular dysfunction after anesthesia and surgery. Are these related to anesthesia or surgery? Internists almost always point to anesthesia and must be educated to shed light on their bias, although this need is reduced

with better diagnostic tests [615] [617] and with the possibility of treatment of some forms of hepatitis. [615] [616]

Thus, the strong bias of internists makes anestheticinduced hepatitis ("halothane hepatitis") a popular diagnosis, despite the higher incidence of viral and drug hepatitides. [635] [695] [696] [697] [698] [699] [700] [701] [702] [703] [704] [705] [706] [707] [708] [709] Another factor producing possible bias is the fact that animal models of halothane hepatitis incorporate liver hypoxia or pretreatment with polyvinylchlorides, conditions that can themselves adversely affect liver function. No irrefutable evidence exists implicating halothane as being better or worse than any other anesthetic for the patient with pre-existing liver disease. However, should liver disease worsen postoperatively, the tendency is to blame halothane. Anesthesia is certainly less likely than hypoxia, trauma, viral hepatitis, drug-induced hepatitis, or sepsis to cause serious hepatic injury. [675] [708] No one has yet determined whether a time limit exists within which repeat exposure to an anesthetic is more dangerous than exposure to various anesthetics, or after which repeat anesthesia is as safe as a first exposure to anesthetic. The common consistent feature of many forms of chronic liver disease is a vulnerability to decreased oxygen delivery to the hepatic artery. This vulnerability occurs because of increased resistance to portal vein blood flow. Many stimuli, including surgical palpation, appear to decrease oxygen delivery to the hepatic artery. Thus, anesthesia and surgery may affect hepatic well-being after surgery in the patient with an already compromised liver.

What should physicians do to prevent contracting hepatitis from patients--or giving it to them? It is cost-effective for anesthesia personnel to be given the vaccine. [709] [710] [711] How the physician with hepatitis B can prevent infecting patients is discussed in detail elsewhere. [712]

Liver disease severe enough to affect hepatic synthesis can impair the detoxification of many drugs, [696] [697] [708] [713] [714] [715] [716] including muscle relaxants [713] [714] [715] [716] (Ch. 12) , and can disturb coagulation (Ch. 46) but may or may not affect anesthetic requirements greatly. [717] [718] Administration of fresh-frozen plasma may be needed to correct coagulation disorders.

HEMATOLOGIC DISORDERS AND ONCOLOGIC DISEASE

Hematologic Disorders

Anemia and Polycythemia

Chapter 23 presents the evidence that normovolemic anemia or polycythemia increases perioperative morbidity. The results indicate that knowledge and pretreatment of polycythemia might decrease perioperative morbidity and mortality.

Except for patients with ischemic heart disease (see later), no such evidence exists for normovolemic anemia. [339] [340] (This is also reviewed in Chapter 23.) Thus, there are no specific preoperative routines for anemia itself, except regarding patients who have or are likely to have ischemic heart disease (as determined by risk factors). [719] [720] [721] [722] [723] [724] For these patients, hematocrit levels above or below 29 to 34 percent were found in two separate studies to be associated with increased episodes of myocardial ischemia after vascular surgery [339] [340] (see Fig. 25-18) . For patients at risk of current ischemic heart disease, the data indicate that transfusion to a hematocrit level of 29 to 34 percent may be appropriate. It should be remembered that anemia is the reduction in circulatory erythrocyte mass below the range of values considered normal for persons of the same gender at the same location. (Age over 6 months, race, and ethnic background do not explain anemia.) Each erythrocyte lives for approximately 120 days; therefore, replacement of 15 to 20 mL of senescent cells needs to be accomplished in the absence of diseases that destroy or cause loss of blood cells. Furthermore, the symptoms of anemia--headache, weakness, exertional dyspnea, and loss of endurance--do not provide much information about the severity, rapidity of onset, and cardiorespiratory effects of the underlying cause of anemia.

Furthermore, because anemia can be a hallmark of many other diseases possibly affecting perioperative anesthetic management, the preoperative presence of anemia requires a search for, and treatment of, the underlying cause. For instance, anemia could indicate renal insufficiency or a drug reaction, both of which could alter anesthetic management. For this reason, the cause of anemia should be known preoperatively. Similarly, polycythemia can be a primary disease (e.g., polycythemia vera) or it can be secondary to smoking, to the use of diuretic drugs, to chronic use of androgens, to hypoxia, or to other forms of chronic lung or heart disease. Phlebotomies are quite effective for patients with mild polycythemia. Cerebral blood flow improves when the hematocrit level is kept below 45 percent. [721] [722] No prospective controlled study has been performed on humans regarding a possible decrease in perioperative morbidity or wound healing [339] [340] [719] [720] [721] [722] [723] [724] from perioperative treatment of anemia or polycythemia. The time of most danger to the patient may be the early recovery room period, during which time oxygen delivery to the lungs is perhaps at its worst. [339] [340] (Also see Chs. 68 and 72.) When religious convictions prohibit blood transfusion and the patient is anemic or may become anemic, therapeutic options include autotransfusion with the salvaged or removed blood always connected to (or in contact with) the patient, and use of blood substitutes. Although perfluorocarbons have fallen into disrepute because of effects on reticuloendothelial function, other substitutes may become available, and synthetic erythropoietin will find greater use in preoperative prophylaxis and preoperative predeposit blood programs. [669] [725] This subject is discussed in greater detail in Chapters 46 and 47 .

Erythropoietin is one of the substances necessary for the normal production of red blood cells. The production and secretion of erythropoietin from the peritubular cells of the kidney are stimulated by tissue hypoxia. Signal transduction of this hypoxic stimulus depends on a heme-containing oxygen-sensing protein that mediates changes in the stability of mRNA from chromosome 7 in erythropoietinproducing cells. Erythropoietin triggers quiescent early erythroid progenitor cells into cycle, acting like a mitogen and facilitating differentiation into late committed erythroid progenitor cells. In normoxic individuals, erythropoietin synthesis is not stimulated until the concentration of hemoglobin falls below 10.5 g/dL. In severe anemia, erythropoietin levels can increase more than 1,000-fold. Iron, folic acid, and vitamin B_{12} are also needed for normal maturation of erythrocytes. Several forms of anemia present special situations,

such as sickle cell anemia, hereditary spherocytosis, and the autoimmune hemolytic anemias.

Sickle Cell Anemia and Related Hemoglobinopathies

The sickle cell syndromes comprise a family of hemoglobinopathies caused by abnormal genetic transformation of amino acids in the heme portion of the hemoglobin molecule. [726] The sickle cell syndromes arise from a mutation in the beta-globin gene that changes the sixth amino acid from valine to glutamic acid. A major pathologic feature of sickle cell disease is the aggregation of irreversibly sickled cells in blood vessels. The molecular basis of sickling is aggregation of deoxygenated hemoglobin B molecules along their longitudinal axis. [726] This abnormal aggregation distorts the cell membrane, producing a sickle shape. Irreversibly sickled cells become dehydrated and rigid and can cause tissue infarcts by impeding blood flow and oxygen to tissues. [726] [727] [728] [729] [730] Some other abnormal hemoglobins interact with hemoglobin S to various degrees, giving rise to symptomatic disease in patients heterozygous for hemoglobin S and one of the other hemoglobins such as the hemoglobin of thalassemia (hemoglobin C).

Three-tenths of 1 percent of the African-American population has sickle cell-thalassemia disease (hemoglobin SC); these patients also have end-organ disease and symptoms suggestive of organ infarction. For these patients, perioperative considerations should be similar to those for patients with sickle cell disease (hemoglobin SS), discussed later.

Whereas 8 to 10 percent of black Americans have the sickle cell trait (hemoglobin AS), 0.2 percent are homozygous for the sickle cell hemoglobin and have sickle cell anemia. Sickle cell trait is a heterozygous condition in which the individual has one betaS-globin gene and one betaA-globin gene, resulting in the production of both hemoglobin S and hemoglobin A, with a predominance of hemoglobin A. The sickle cell trait should not be considered a disease, because hemoglobin AS cells begin to sickle only when oxygen saturation of hemoglobin is below 20 percent. No difference has been found between normal persons (those with hemoglobin AA) and those with hemoglobin AS regarding survival rates or incidence of severe disease, with one exception: Patients with hemoglobin AS have a 50 percent increase in pulmonary infarction. However, single case reports of a perioperative death and a perioperative brain infarct in two patients with hemoglobin AS disease do exist, [730] [731] as does a report of death believed due to aortocaval compression during general anesthesia that resulted in a sickling crisis. [732] Frequent measurement of oxygen saturation (pulse oximetry) in multiple areas of the body is recommended, including ear and toe in pregnant patients. [732] A recent retrospective review of exercise in military recruits showed that soldiers with sickle cell trait had a higher risk of sudden death following extreme exertion during basic training than did black soldiers with only hemoglobin A--32 per 100,000 versus 1 per 1,000,000. [733] Although this magnitude of increase may not seem great, the vasoactive responses of the perioperative period can be similar to those of moderate to extreme exertion.

The pathologic end-organ damage that occurs in sickle cell states is attributable to three processes: the sickling of cells in blood vessels, which causes infarcts and consequent tissue destruction secondary to tissue ischemia; hemolytic crisis secondary to hemolysis; and aplastic crises that occur with bone marrow exhaustion, which can rapidly result in severe anemia. Logic dictates that patients currently in a crisis should not undergo surgery except for extreme emergencies and then only

after the performance of exchange transfusion. [728] [730] [731] [732] [733] [734]

Because sickling is increased with lowered oxygen tensions, acidosis, hypothermia, and the presence of more desaturated hemoglobin S, current therapy includes keeping the patient warm and well hydrated, giving supplemental oxygen, maintaining high cardiac output, and not creating areas of stasis with pressure or tourniquets. Meticulous attention to these practices in those periods when we usually do not pay most careful attention (i.e., waiting in the preinduction area) or when gas exchange may be most unmatched to cardiovascular-metabolic demands (early postoperative period) may be important in lessening morbidity. Even following these measures routinely, with no special emphasis placed on the periods described, researchers have succeeded in reducing mortality to 1 percent in several series of patients with sickle cell syndromes. [731] [732] [733] [734] [735] Retrospective review of patient charts led the authors of those studies to conclude that, at most, a 0.5 percent mortality rate could be attributed to the interaction between sickle cell anemia and anesthetic agent.

Can this rate be decreased? [727] [735] [736] [737] Several investigators have advocated using partial exchange transfusions perioperatively. In children with sickle cell anemia and acute lung syndromes, partial exchange transfusion improved clinical symptoms and blood oxygenation. Also, serum bilirubin levels decreased in patients with acute liver injury. Clinical improvement of pneumococcal meningitis and cessation of hematuria in papillary necrosis also accompanied exchange transfusion. [727] [738] The goal of exchange transfusion is to increase the concentration of hemoglobin A to 40 percent and the hematocrit to 35 percent. The 40 percent figure is an arbitrary one, as no controlled studies have established the threshold ratio of hemoglobin A to S that would render blood unable to sickle in vivo. To achieve the 40 percent ratio in a 70-kg adult, about 4 units of washed erythrocytes would have to be exchanged; the system is inexpensive but efficient.

The possible decrease in preoperative morbidity after partial exchange transfusion has not been compared with the risks of exchange, except in two studies, [729] [735] [739] in which the risks of exchange were found to exceed the benefits. In the first study, a retrospective review of 82 surgical procedures performed between 1978 and 1986 in 60 patients, no advantage was noted in preoperative exchange transfusion, as measured by a decrease in postoperative complications. [739] (However, only the sickest may have received exchange, as patients were not randomly allocated to exchange or nonexchange groups.) A slight increase in postoperative atelectasis requiring treatment was seen in those patients given preoperative transfusions. More than 50 percent of patients given transfusions had a postoperative complication. Patients who began with a hematocrit level of more than 36 percent had a lower rate of complications. [739] In the second study, a randomized comparison of aggressive

versus conservative transfusion practices in 551 patients (604 operations), perioperative sickling complications were *not* different between groups, and transfusion-related complications were substantially less in the conservative group. [729] Therefore, my recommendation is to pay meticulous attention to preventing conditions that increase sickling or that cause infection and to limit exchange transfusion to crisis situations. Perhaps giving higher concentrations of enriched oxygen to patients undergoing laparoscopic procedures should also become routine. Induction of hyponatremia has been shown to abort acute sickle cell crisis; however, this treatment has not gained widespread acceptance. Other conditions are common in sickle cell syndromes: pulmonary dysfunction with increased shunt, renal insufficiency, gallstones, small MIs, priapism, stroke, aseptic necrosis of bones and joints, ischemic ulcers, retinal detachments from neovascularization, and complications of repeated transfusions.

In thalassemia, globin structures are normal, but, because of gene deletion, the rate of synthesis of either the alpha- or beta-chains of hemoglobin (alpha- and beta-thalassemia, respectively) decreases. [740] [741] [742] Two copies of the gene that codes for the alpha-globin chain are located on chromosome 16. Deletion of all four of these genes causes cell death in utero, and three deletions cause severe chronic hemolysis and a shortened life span. "alpha-Thalassemia-1 [trait]" occurs when two genes have been deleted, leading to a mild anemia; "alphathalassemia-2 [silent]" occurs when the two genes have been deleted, but no mild anemia or microcytosis occurs. In alpha-thalassemia trait, the hemoglobin A_2 level is normal. beta-Thalassemia is associated with an excess of alpha-chains, which denature developing erythrocytes, leading to their premature death in the marrow or to shortened survival in the circulation. An elevated hemoglobin A_2 level is the hallmark of beta-thalassemia trait, a common cause of mild anemia and microcytosis. Bone marrow transplantation and pharmacologic manipulation of hemoglobin F synthesis are being tried in these hemoglobinopathies, as is direct gene replacement therapy. These syndromes are common in Southeast Asia, India, and the Middle East and in people of African descent.

In thalassemia, facial deformity from erythropoietinstimulated ineffective erythropoiesis (ineffective secondary to genetic inability to produce useful hemoglobin) has been reported to make endotracheal intubation difficult. [740] [741] [742] This one case report [741] has not been amplified, and there are no reports of this complication for patients with sickle cell anemia. However, the anemia associated with these syndromes often produces a compensatory hyperplasia of the erythroid marrow, which in turn is associated with severe skeletal abnormalities. [740] [741] [742]

Cytoskeletal Anemias (Hereditary Spherocytosis and Elliptocytosis), Enzyme-Deficient Anemias, and Autoimmune Hemolytic Anemias

Congenital abnormalities of the erythrocyte membrane are becoming better understood. In elliptocytosis and hereditary spherocytosis, the membrane is more permeable to cations and more susceptible to lipid loss when cell energy is depleted than is the membrane of the normal red blood cell. Both hereditary spherocytosis (present in 1 in 5,000 people) and hereditary elliptocytosis are inherited as autosomal dominant traits. In both disorders, defects in the membrane are thought to result from mutation of spectrin, a structural protein of the membrane cytoskeleton. [743] Although the therapeutic role of splenectomy in these diseases is not fully defined, in severe disease, splenectomy is known to improve the shortened life span of the red blood cell 100 percent (from 20-30 days to 40-70 days). Because splenectomy predisposes the patient to grampositive septicemia (particularly pneumococcal), perhaps patients should be given pneumococcal vaccine preoperatively prior to predictable bacteremic events. No specific problems relating to anesthesia have been reported for these disorders.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (a gender-linked recessive trait) is also reported to occur in approximately 8 percent of African-American men. [744] Young cells have normal activity, but older cells are grossly deficient compared with normal cells. A deficiency in this enzyme results in hemolysis of the erythrocyte and formation of Heinz bodies. Red cell hemolysis can also occur with intercurrent infections or after administration of drugs that produce substances requiring G6PD for detoxification (e.g., methemoglobin, gluthathione, and hydrogen peroxide). Drugs to be avoided are sulfa drugs, quinidine, prilocaine, lidocaine, antimalarial drugs, antipyretic drugs, non-narcotic analgesics, vitamin K analogues, and perhaps sodium nitroprusside.

The autoimmune hemolytic anemias include cold antibody anemia, warm antibody anemia (idiopathic), and drug-induced anemias. [745] [746] [747] The cold antibody hemolytic anemias are mediated by immunoglobulin M or G antibodies, which, at room temperature and below, cause red blood cells to clump. When these patients are given blood transfusions, the cells and all fluid infusions must be warm, and body temperature must be maintained meticulously at 37°C if hemolysis is to be prevented. Warm antibody (or "idiopathic") hemolytic anemia is a difficult management problem characterized by chronic anemia, the presence of antibodies active against red blood cells, positive Coombs test, and difficulty in cross-matching blood. For patients undergoing elective surgery, autologous transfusions, predeposit of blood with or without erythropoietin stimulation, [725] and blood from rare Rh-negative red blood cell donors and/or the patient's first-degree relatives can be used. In emergency situations, the possibility of autotransfusions, splenectomy, or corticosteroid treatment should be discussed with a hematologist knowledgeable in this area.

Drug-induced anemias have three mechanisms. In receptor-type hemolysis, a drug (e.g., penicillin) binds to the membrane of the red blood cell, and the complex stimulates formation of an antibody against the complex. In "innocent bystander" hemolysis, a drug (e.g., quinidine, sulfuramide) binds to a plasma protein, thereby stimulating an antibody (IgM) that cross-reacts with an erythrocyte. In autoimmune hemolysis, the drug stimulates production of an antibody (IgG) that cross-reacts with the erythrocyte. Drug-induced hemolytic anemias generally cease when drug therapy ends. In emergency situations, the least incompatible cells available should be used for blood transfusion.

Granulocytopenia

Granulocyte mechanisms have undergone experimental elaboration in the past decade, partly because of the molecular biologic revolution: In addition to erythropoietin (discussed previously), more than 14 hemolymphopoietic growth factors or cytokines have been characterized biochemically and cloned genetically. These growth factors interact with cell-surface receptors to produce their major actions [748] (Table 25-44) (Table Not Available) . The use of the colony-stimulating

factors has permitted more intense oncologic treatment. The few reports relating to their perioperative effects detail the adverse consequences such therapies can have on gas exchange when adverse immunologic effects occur. [749]

In patients who have fewer than 500 granulocytes/mL blood and established sepsis, use of growth factor and granulocyte transfusion has been shown to prolong life. [750] [751] [752] Although bone marrow transplantation is being used increasingly, complications usually occur after transplantation, not on harvesting of cells (at which time the anesthesiologist who is not involved in critical care is most frequently involved). Abnormal results on pulmonary function testing prior to bone marrow transplantation seem to predict complications after transplantation but not so strongly as to preclude transplantation. [753]

Platelet Disorders

Although *inherited* platelet disorders are rare, *acquired* disorders are quite common. Both conditions cause skin and mucosal bleeding, whereas defects in plasma coagulation produce deep-tissue bleeding or delayed bleeding. [754] Perioperative treatment of inherited platelet disorders (e.g., Glanzmann thrombasthenia, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome) consists of platelet transfusion. epsilon-Aminocaproic acid (EACA) has recently been used successfully (experimentally, 1 g/70 kg qid) to decrease perioperative bleeding in thrombocytopenic patients. The much more common acquired disorders may respond to one of several therapies. Immune thrombocytopenias, such as those associated with lupus erythematosus, idiopathic thrombocytopenic purpura, uremia, hemolytic-uremic syndrome, platelet transfusions, heparin, and thrombocytosis may respond to steroids, splenectomy, platelet pheresis, or alkylating agents or may require platelet transfusions, plasma exchange, whole blood exchange, or transfusion; sometimes these disorders do not respond to anything. [366] [754] [755] [756] [757]

Thrombotic thrombocytopenic purpura is a rare disorder of unknown cause. Despite various therapies, this disorder carries a very high mortality rate. However, the introduction of plasmapheresis has improved response rates dramatically for patients with this disease. One uncontrolled study implies that the benefit lies not only in improvement of the hematologic picture but also in the prevention of adult respiratory distress syndrome, a leading cause of death in these patients. [757] In that study, the early institution of plasmapheresis improved oxygenation.

By far, the largest number of platelet abnormalities consists of drug-related defects in the aggregation and release of platelets. Aspirin irreversibly acetylates platelet cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandin endoperoxidases. Because cyclo-oxygenase is not regenerated in the circulation within the life span of the platelet, and because this enzyme is essential for the aggregation of platelets, one aspirin may affect platelet function for a week. All other drugs that inhibit platelet function (e.g., vitamin E, indomethacin, sulfinpyrazone, dipyridamole, tricyclic antidepressant drugs, phenothiazines, furosemide, steroids) do not inhibit cyclo-oxygenase function irreversibly; these drugs disturb platelet function for only 24 to 48 hours. If emergency surgery is needed before the customary 8-day period for platelet regeneration after aspirin therapy, or if the 2-day period for other drugs has not elapsed, administration of 2 to 5 units of platelet concentrates will return platelet function to a 70-kg adult to an adequate level and platelet-induced clotting dysfunction to normal. [754] [758] Only 30,000 to 50,000 normally functioning platelets/mm^3 are needed for normal clotting. Because low-dose aspirin therapy (<650 mg/d) allows aspirin to be gone from the body 24 hours after the last dose, and because the body makes 70,000 platelets/mL blood per day, a 48-hour period after the last aspirin in minidose therapy should be sufficient time for platelet aggregation to become normal. This may be the time that must pass to avoid the need for platelet transfusions and their associated risks. One platelet transfusion will increase the platelet count from 4,000 to 20,000/mL blood; platelet half-life is about 8 hours. [754] [758] Although designer aspirin that affects only one part of the cyclo-oxygenase tree may soon be available, the form that is most likely to be used may cause clotting disturbances (without the GI effects, however) that are equal to those caused by the currently available form of aspirin.

Hemophilia and Related Clotting Disorders

Abnormalities in blood coagulation owing to defects in plasma coagulation factor are either inherited or acquired. Inherited disorders include X-linked hemophilia A (a defect in factor VIII activity), von Willebrand diseases (defect in von Willebrand component of factor VIII), hemophilia B (a sex-linked deficiency of factor IX activity), and other less common disorders. The sex-linked origin of some of these disorders means that hemophilia occurs almost exclusively in male offspring of female carriers; men do not transmit the disease to their male offspring.

In elective surgery, levels of the deficient coagulation factor should be assayed 48 hours before surgery and the level restored to 40 percent of normal before surgery. One unit of factor concentrate per kilogram of body weight normally increases the factor concentration by 2 percent. Thus, in the individual essentially devoid of activity, administration of 20 U/kg body weight would be required as an initial dose. Because the half-life is 6 to 10 hours for factor VIII and 8 to 16 hours for factor IX, approximately 1.5 U/h/kg of factor VIII or 1.5 U/2h/kg of factor IX should be given. Additional administration of factors VIII and IX should be guided by the activity of the clotting factors for about 6 to 10 days postoperatively. [759] [760] [761]

These factors are available in various preparations: The newer genetically engineered von Willebrand factor, cryoprecipitate,

TABLE 25-44 -- Major Effects of Hemolymphopoietic Growth Factors/Cytokines

(Not Available)

Modified from Quesenberg et al [745]

which contains 20 U/mL, is obtained from regular donors (the risk of hepatitis being 1:200 for 5-mL lots) or from fresh-frozen plasma (which contains 1 U/mL). Some risk of transmitting hepatitis and acquired immunodeficiency syndrome (AIDS) accompanies transfusion, but, with better testing, the risk is much lower than formerly. [762] [763] [764] [765] [766] Current screening of blood for aspartate transaminase or alanine aminotransferase levels is believed to result in a much lower risk of hepatitis C and even AIDS from transfusion. Theoretically, antigenic testing for the HIV viruses should further decrease the risk of their transmission by blood products. Heat treatment is also reported to reduce these risks substantially. Factor IX, but not factor VIII, is contained in prothrombin complex concentrates; however, these concentrates may contain activated clotting factors, leading to disseminated intravascular coagulation (DIC) and a high risk of hepatitis. In addition, although EACA or tranexamic acid (0.5 mg/kg) is sometimes administered as a fibrinolytic inhibitor, these substances carry with them a significant risk of DIC. Additional hazards of modern therapy include acute and chronic hepatitis, AIDS, hypersensitivity reactions, psychic trauma, chronic pain with narcotic addiction, and inhibition of factors, especially VIII.

Approximately 10 percent of patients with either hemophilia A or B develop an antibody that inactivates factor VIII or IX (fresh-frozen plasma fails to increase clotting factor activity after incubation with the patient's plasma). These acquired anticoagulants are usually composed of immunoglobulin G, are poorly removed by plasmapheresis, and are variably responsive to immunosuppressive drugs. The use of prothrombin complex concentrates can be life saving but carries the risk of DIC and hepatitis.

Vitamin K deficiency is discussed in the section on liver disease. To review, vitamin K-dependent clotting factors (II, VII, IX, and X) require vitamin K for the postsynthetic addition of gamma-carboxyl groups to glutamate residues; administration of vitamin K or fresh-frozen plasma can correct these deficiencies.

Patients who come to the operating room having received many units of blood (as in massive GI bleeding) may have deficient clotting. This impaired clotting is initially caused by depletion of platelets (which occurs after approximately 10-15 units of blood have been given) and later, by depletion of coagulation factors [767] [768] (Ch. 46) . Treatment of these deficiencies can be corrected with platelet concentrates--each concentrate is normally suspended in 50 mL of fresh plasma; thus, coagulation factors are also replaced.

Urokinase, streptokinase, and tissue plasminogen activator have been used to treat pulmonary embolism, deep venous thrombosis, stroke, and arterial occlusive disease. These drugs accelerate the lysis of thrombi and emboli, in contrast to heparin, which may prevent but not dissolve a thrombus. Bleeding complications associated with these fibrinolytic agents result from dissolution of hemostatic plugs and can be quickly reversed by discontinuing the medication and replenishing

plasma fibrinogen with cryoprecipitate or plasma. However, cryoprecipitate and plasma are seldom needed preoperatively because the fibrinolytic activity of urokinase and streptokinase usually dissipates within 1 hour of discontinuing their administration. However, insufficient data have accumulated to prescribe ideal preoperative preparation and intraoperative management of hemostasis in patients recently treated with urokinase, streptokinase, or tissue plasminogen activator. Postponing surgery for three half-lives of the drug (increases in plasmin activity in blood can be assayed for
4-8 hours) may not be possible, and observing the operative field for meticulous attention to hemostasis may not suffice. [769] [770] The process may be even more complex in the vascular or cardiac patient who requires heparin administration intraoperatively. To correct fibrinogen deficiency in these patients, some clinicians administer fibrinogen before surgery and EACA at heparin administration. I usually delay or avoid giving EACA until heparin is administered, in an effort to minimize the risk of thrombosis.

Desmopressin is now being tried in high-blood-loss operations as a routine measure to decrease bleeding and transfusion requirements. Desmopressin therapy began as a treatment for platelet dysfunction in von Willebrand disease but has since expanded to routine use in patients undergoing cardiovascular surgery and frequent use in other high-blood-loss operations. This increased use was prompted by the finding that desmopressin decreased bleeding and transfusion requirements. [771] Whether the side effects of desmopressin exceed the benefits remains to be determined and will probably influence how routine its administration becomes.

The problems of patients on oral anticoagulants are discussed in the cardiovascular section of this chapter. [358] [359] [360] [361] [362] [363] [364] [365] [366] [367] [368] [369] [370] [371] [373] [374] [375] [376] Regional anesthetic techniques might be avoided in patients given anticoagulant drugs. [358] [359] [360] [361] [362] [363] [364] [365] [366] [367] [368] [369] [370] [371] [373] [374] [375] [376] Whether these regional techniques should also be avoided in patients treated prophylactically with low-dose subcutaneous heparin has not been studied. The effects of heparin sulfate can be reversed by titrating protamine, using activated clotting time as a guide. Our group usually gives approximately 1 mg of protamine per 3 to 4 mg of heparin administered within the past 8 hours. Pharmacologic research is searching for specific molecular subtypes of heparin that have different anticoagulant potencies, binding affinities for antithrombin III, antithrombotic effects, and plateletaggregating effects. (See pulmonary section in this chapter on deep-venous thrombosis prophylaxis.) The search is for a "new" heparin preparation that will block thrombosis without causing clinical bleeding. (See previous.) Such a development might change our ways of monitoring clotting function. As of now, the new heparins appear to increase the risk of epidural hematoma. Determining bleeding time, platelet count, partial thromboplastin time, and PT will identify almost all problems in the patient with a suspected clotting or bleeding disorder (Ch. 46) . As explained in Chapter 23 , these screening tests probably should not be obtained for asymptomatic patients.

Oncologic Disease

Patients with malignant tumors may be otherwise healthy or may be desperately ill with nutritional, neurologic, metabolic, endocrinologic, electrolyte, cardiac, pulmonary, renal, hepatic, hematologic, or pharmacologic disabilities. Thus, determining the other disabilities accompanying malignant tumors requires evaluation of all systems. Abnormalities frequently accompanying such tumors include hypercalcemia

either by direct bone invasion or by ectopic elaboration of parathyroid hormone or other bone-dissolving substance, uric acid nephropathy, hyponatremia (especially with small-cell, or oat-cell, carcinoma of the lung), nausea, vomiting, anorexia and cachexia, fever, tumor-induced hypoglycemia, intracranial metastases (10-20% of all cancers), peripheral nerve or spinal cord disorders, meningeal carcinomatosis, toxic neuropathies secondary to anticancer therapy, and paraneoplastic neurologic syndromes (dermatomyositis, Eaton-Lambert syndrome, myopathies, and distal neuropathies).

Many patients with malignant tumors are given large doses of analgesics and should be kept comfortable during the perioperative period. Avoiding drug dependence is of no practical importance in terminally ill patients. [772] [773] Marijuana (tetrahydrocannabinol) depresses the CNS vomiting center and may be more effective than the phenothiazines or butyrophenones in suppressing nausea associated with cancer and its therapy; marijuana decreases anesthetic requirements 15 to 30 percent. [774] Immunomodulators, stimulating factors or cytokines, gene identification, [775] [776] and agents for treating side effects (e.g., midazolam or ondansetron) have given new hope for safer, more effective therapy, with fewer limiting side effects. The effect of ondansetron in preventing vomiting and the effect of midazolam in preventing "memory-stimulated vomiting" have been important additions.

The toxicity of cancer chemotherapy relates to the agents used and the dose. For radiation therapy, damage occurs when the following doses are exceeded: lungs, 1,500 rad; kidneys, 2,400 rad; heart, 3,000 rad; spinal cord, 4,000 rad; intestine, 5,500 rad; brain, 6,000 rad; and bone, 7,500 rad. The toxicities of biologic therapy and immunomodulating therapies relate to the change in immune function they cause. [494] [748] [749] [751] Alkylating agents cause bone marrow depression, including thrombocytopenia, alopecia, hemorrhagic cystitis, nausea, and vomiting. The alkylating agents including cyclophosphamide and mechlorethamine can act as anticholinesterase and prolong neuromuscular blockade. [777] The antineoplastic alkaloids vincristine and vinblastine produce, respectively, peripheral neuropathies and SIADH, and myelotoxicity. Cisplatin also produces peripheral neuropathies and severe nausea. Nitrosoureas can produce severe hepatic and renal damage, as well as bone marrow toxicity, myalgias, and paresthesia. Folic acid analogues such as methotrexate produce bone marrow depression, ulcerative stomatitis, pulmonary interstitial infiltrates, GI toxicity, and occasionally severe liver dysfunction. Fluorouracil and floxuridine, both pyrimidine analogues, cause bone marrow toxicity, megaloblastic anemia, nervous system dysfunction, and hepatic and GI alterations. Purine analogues (mercaptopurine, thioguanine) have bone marrow depression as their primary toxic effect. Anthracycline antibiotics (doxorubicin, daunorubicin, mithramycin, mitomycin C, bleomycin) can all cause pulmonary infiltrates; cardiomyopathies (especially doxorubicin and daunorubicin); myelotoxicity; and GI, hepatic, and renal disturbances.

The wisdom of anesthetizing patients given bleomycin has been questioned. A retrospective study by Goldiner et al [778] reported postoperative deaths in five consecutive patients given bleomycin. All five patients died of postoperative respiratory failure. Using the same anesthetic technique, Goldiner et al [778] then anesthetized 12 patients, limited the inspired oxygen concentration to 22 to 25 percent perioperatively, and replaced much of the blood loss with colloids, rather than crystalloids. None of the 12 patients died. These investigators postulated that bleomycin caused epithelial cell edema that progressed to necrosis of type I alveolar cells, fluid leakage into the alveolar space, and the formation of "hyaline membranes" similar to that associated with oxygen toxicity. [779] Goldiner et al [778] believe that this pathophysiologic similarity indicates a possible synergistic relationship between oxygen and bleomycin. However, LaMantia and coworkers [780] retrospectively analyzed the changes in 16 patients undergoing surgery after bleomycin therapy. Thirteen patients were given oxygen at inspired concentrations of 37 to 45 percent. No instances of postoperative respiratory failure occurred. Animal data do not support this effect of bleomycin in altering the toxicity of hyperoxia. [781] Thus, data are currently available to support all practices regarding oxygen administration to patients given bleomycin. I prefer to keep inspired oxygen concentrations at the lowest level providing adequate tissue oxygenation. When in doubt about side effects in patients undergoing cancer chemotherapy, my practice is to seek advice from two experts.

PATIENTS GIVEN DRUG THERAPY FOR CHRONIC AND ACUTE MEDICAL CONDITIONS

A steadily increasing number of potent drugs are being used to treat disease; the average hospitalized patient receives more than ten drugs. Many drugs have side effects that might make anesthesia more risky or patient management more difficult. Knowing the pharmacologic properties and potential side effects of commonly used drugs helps the anesthesiologist avoid pitfalls during anesthesia and surgery.

The first step in avoiding these pitfalls is to obtain a drug history (including vitamins, herbs, and supplements) [22] [782] from the patient. Then, for every drug, medicine, and over-the-counter preparation the patient is using, the anesthesiologist should know the name, classification of drug, diseases, conditions for which it is prescribed, and common side effects. Having this knowledge before surgery helps the anesthesiologist avoid making mistakes that might turn minor side effects into life-threatening situations. If necessary, the anesthesiologist should return to the patient's bedside to search for signs or symptoms of these effects. Unnecessary drugs should be discontinued for at least three and preferably five half-lives of the drugs. This period should be longer if metabolites of the drug have activity and longer half-lives. For essential or beneficial drugs, the optimal dose should be determined in consultation with the treating physician; the optimal dose is that maximizing the ratio of therapeutic value to risk of drug toxicity. Side effects should be sought and either corrected preoperatively or at least planned for in anesthetic management. For instance, if a patient is made hypokalemic with diuretic drugs, hypokalemia might be corrected before surgery; an even better approach would be to avoid hyperventilation during surgery. (See earlier section on hypokalemia.) This line of reasoning and planning is best

done at least 1 week before surgery. Ideally, the surgeon, internist, primary care practitioner, and anesthesiologist should communicate regarding these topics well in advance of surgery. Understanding the side effects of chronic drug therapy that affect the sympathetic nervous system requires some knowledge of the basic pharmacologic characteristics of the sympathetic nervous system. [669] [670]

Pharmacologic Processes in the Sympathetic Nervous System

The autonomic nervous system is discussed in detail in Chapter 14 . Although that review is comprehensive, it is important to remember several points related to the pharmacology of the sympathetic nervous system when considering chronic drug therapy.

Norepinephrine, dopamine, and epinephrine exert their physiologic effect by interacting with an appropriate receptor at the target tissue. The primary receptor acts through intermediary messenger systems (including cyclic 3
,5
-adenosine monophosphate and/or G-stimulatory or Ginhibitory proteins) and/or can change conformation (hence affinity for ligands) of bordering or neighboring receptors. These bordering or neighboring receptor effects may account for many of the multitude of effects associated with catecholamines. The three major kinds of catecholamine receptors are alpha-adrenergic, beta-adrenergic, and dopaminergic. These receptors are subdivided as follows:

1. alpha$_1$ -*Receptor:* Stimulation constricts vascular smooth muscle and thus increases peripheral vascular resistance.
2. alpha$_2$ -*Receptor:* Stimulation inhibits the release of norepinephrine itself (constituting negative feedback to the sympathetic neuron). These are largely presynaptic, although postsynaptic vasoconstricting alpha $_2$ -receptors exist on blood vessels.
3. beta$_1$ -*Receptor:* Stimulation increases heart rate and the strength of cardiac contractions.
4. beta$_2$ -*Receptor:* Stimulation causes dilation of smooth muscles of the blood vessels and airway, relaxation of uterine smooth muscle, and a variety of endocrine effects, including secretion of renin.
5. beta$_3$ -*Receptor:* Stimulation results in a greater release of norepinephrine from the sympathetic neuron (constituting positive feedback to the sympathetic neuron).
6. *Dopamine-1 receptor:* Stimulation causes dilation of vascular smooth muscle, notably of renal and mesenteric blood vessels.
7. *Dopamine-2 receptor:* Stimulation inhibits release of norepinephrine (presynaptic) and may also inhibit, via its ganglionic actions, the release of acetylcholine. The class of dopamine receptors involved in locomotion, inhibition of intestinal motility (the antagonism of which accounts for the increase in gastric emptying by metoclopramide), and vomiting is not known. These different effects may be caused by slight differences in receptor conformations.

The action of sympathomimetic substances is terminated through an unusual process: The nerve ending uses an active reuptake system to recapture most of the norepinephrine from the target tissue (Ch. 14) . Obviously, blockage of this system permits more norepinephrine to remain free to produce physiologic effects. In addition to this reuptake system, two enzymes transform catecholamines metabolically: monoamine oxidase (MAO) and catechol- *o*-methyltransferase (Ch. 14) .

Antihypertensive Drugs

Many antihypertensive agents and almost all mindaltering drugs affect sympathetic neuronal storage, uptake, metabolism, or release of neurotransmitters. For instance, the antihypertensive drug reserpine depletes the granules of norepinephrine, epinephrine, and dopamine in both the brain stem and the periphery. The depletion of transmitters in sympathetic nerve endings renders drugs such as ephedrine and metaraminol ineffective, as these drugs act primarily by releasing catecholamines (Fig. 25-21) . Guanethidine and guanadrel deplete granular norepinephrine and affect only the peripheral sympathetic system. In amounts used clinically, reserpine decreases the MAC by 20 to 30 percent, whereas guanethidine has no effect on anesthetic requirements. [217] In addition to causing a lack of response to indirect-acting vasopressors, reserpine can cause a denervation supersensitivity and hyperresponsiveness (with hypertension and/or tachycardia) to the usual doses of direct-acting sympathetic amines, such as phenylephrine (Neo-Synephrine), isoproterenol, norepinephrine, epinephrine, and dopamine. [781] [783] [784] [785] [786] Thus, in patients who have been treated with drugs that alter sympathetic neurotransmitter release, uptake, metabolism, or receptor function, some problems may occur: Hypotension, hypertension,

Figure 25-21 Antihypotensive drugs such as metaraminol (Aramine), tyramine, and ephedrine create their effect by releasing catecholamines from the granules of the nerve terminal. Therefore, when treatment with drugs such as methyldopa, reserpine, or guanethidine depletes the store of norepinephrine (NE) in the granules, little norepinephrine remains for release, and the antihypotensive drugs have been rendered ineffective.

and/or bradycardia should be treated by titrating doses of direct-acting vasoconstrictors, such as phenylephrine (Neo-Synephrine); vasodilators, such as nitroprusside; or chronotropic drugs, such as atropine, isoproterenol, or dopamine.

Another group of antihypertensive agents are the "false neurotransmitters." False neurotransmitters replace norepinephrine in the granules at the nerve ending. alpha-Methyldopa (Aldomet) becomes alpha-methyldopamine, which is further metabolized to alpha-methylnorepinephrine (Fig. 25-22) . In some nerve endings and for some receptors, alpha-methyldopamine or alpha-methylnorepinephrine is more potent than dopamine or norepinephrine as dopaminergic or alpha-adrenergic receptor stimulants. However, at most nerve endings, the false neurotransmitters are less potent stimulants; this lower degree of stimulation is one means by which their antihypertensive action is produced. Alternately, alpha-methyldopa may act by stimulating the brain-stem sympathetic nervous system. When this system antagonizes the peripheral sympathetic nervous system, the activity of the latter decreases and blood pressure is reduced. Through its central effect, alpha-methyldopa decreases anesthetic requirements 20 to 40 percent. [217]

In addition to altering the response to exogenously administered vasopressors, these neurotransmitter-depleting drugs can also produce side effects: psychic depression, nightmares, drowsiness, nasal stuffiness, diarrhea, bradycardia, and orthostatic hypotension with impotence (reserpine). [786] [787] Guanethidine and guanadrel can cause orthostatic hypotension, bradycardia, asthma, diarrhea, and inhibition of ejaculation. alpha-Methyldopa is associated with drowsiness, orthostatic hypotension, bradycardia, diarrhea, acute or chronic hepatitis, cirrhosis, and autoimmune hemolytic anemia (i.e., positive Coombs test result). [786] Because of these side effects, ACE inhibitors (captopril, enalapril, lisinopril, enalaprilat, and ramipril) are being used increasingly as first-line drugs and appear to improve the quality of life for the patient taking antihypertensive drugs. [247] However, ACE inhibitors may be associated with more peripheral vasodilation and hypotension on induction of anesthesia than are sympatholytics. [788] Added to this group are the ACE receptor-blocking agents. These last two

Figure 25-22 In the granules of the nerve terminal, alpha-methyldopa (Aldomet) is converted enzymatically to alpha-methyldopamine by the same enzyme that converts dopa to dopamine. alpha-Methyldopamine is converted to alpha-methylnorepinephrine by the same enzyme that converts dopamine to norepinephrine.

classes of drugs are associated with such severe hypotension with standard anesthetic induction that I discontinue those drugs preoperatively. [254] (See previous.)

Catecholamine or sympathetic receptor-blocking drugs affect the three major types of catecholamine receptors: alpha-adrenergic, beta-adrenergic, and dopaminergic. The existence of subdivisions (e.g., $beta_1$ and $beta_2$) suggested the possibility that some drugs would be found to affect only one set of receptors. For example, terbutaline is used more frequently than isoproterenol because terbutaline is said to exert a preferential effect on $beta_2$-receptors (i.e., to dilate bronchial smooth muscle), thereby avoiding the cardiac stimulation produced by drugs that stimulate $beta_1$-receptors. In fact, selectivity is dose-related. At a certain dose, a direct $beta_2$-receptor stimulating drug will affect only those receptors, but at a higher dose will stimulate both $beta_1$- and $beta_2$-receptors. The effect of a given dose varies with each patient. A certain dose may stimulate $beta_1$- and $beta_2$-receptors in one patient but neither receptor in another patient. More and more selective blocking drugs are being developed in hopes of widening the margin between $beta_1$- and $beta_2$- and alpha-adrenergic effects. Ultimately, however, more selectivity is desired than even this. It would be advantageous to be able to decrease heart rate without changing myocardial contractility or to increase contractility without changing heart rate. Such is the goal of much drug research and of the development of dobutamine (Chs. 14 and 16) . However, to date, all such selectivity appears to be dose-related, even for dobutamine. [789]

Metoprolol (Lopressor) and atenolol (Tenormin) (both $beta_1$-adrenergic receptor-blocking drugs) and propranolol, betaxolol, timolol, esmolol, pindolol, oxprenolol, acebutolol, carteolol, penbutolol, and nadolol are widely available beta-adrenergic receptor-blocking drugs used for chronic therapy in the United States. Because nadolol has poor lipid solubility, it has a long elimination half-life (17-24 hours) and does not cross the blood-brain barrier readily. Although nadolol should be associated with fewer CNS side effects, such as fatigue, nightmares, and depression, we do not know that definitely. The ability to use nadolol on a once-daily basis should increase patient compliance. Although selective beta-adrenergic receptor-blocking drugs should be more appropriate in patients with increased airway resistance or diabetes, this advantage is apparent only when low doses are used. The use of beta-adrenergic receptor-blocking drugs has become widespread, as these drugs treat everything from angina and hypertension to priapism and stage fright. These drugs appear to decrease morbidity and mortality in patients who have initially survived myocardial infarction [176] [790] [791] and to increase perioperative survival. [166] [235] [241]

Propranolol is the current standard for beta-adrenergic receptor-blocking drugs. Smulyan et al [792] studied the problems of long-term propranolol hydrochloride therapy on adult patients who must undergo abdominal surgery. Because these patients cannot take oral medications postoperatively for many days, they must be protected against perioperative sympathetic stimulation and the propranolol withdrawal syndrome. A continuous intravenous infusion of propranolol (3 mg/h, regardless of the patient's weight) given postoperatively accomplished these goals: Postoperative serum propranolol levels and beta-adrenergic receptor blockade returned to their "usual" preoperative levels. The hypotensive and bradycardic effects of propranolol and general

anesthesia appear to be additive. [793] Because of its shorter half-life (3-10 min), esmolol is quickly replacing propranolol in critical care (including anesthesia) settings, as errors in therapy or side effects, such as increased airway resistance, vanish much more quickly than if propranolol were administered. [794] Propranolol does not affect anesthetic requirements, [795] and one would expect the same lack of effect from other "pure" beta-adrenergic receptor-blocking drugs. The regimen for atenolol was presented earlier. (See Tables 25-18 (Table Not Available) and 25-19.) (Table Not Available)

alpha-Adrenergic receptor-blocking drugs include phentolamine, prazosin, terazosin, doxazosin, phenoxybenzamine, the phenothiazines, and the butyrophenones (e.g., droperidol). Dopaminergic receptor antagonists include the antischizophrenic drugs (phenothiazines and butyrophenones) and metoclopramide. The receptor-blocking drugs inhibit the action of sympathomimetic drugs at the receptor in a dose-related fashion. Thus, propranolol lowers blood pressure by blocking the tendency of norepinephrine and epinephrine to increase the rate and force of the contractions of the heart (and perhaps their tendency to increase the secretion of renin as well). To overcome this blockade, one need only provide more beta-receptor-stimulating drug. Thus, high doses of vasopressors may be needed to increase BP in a patient given large doses of propranolol.

When administration of beta-adrenergic receptor-blocking drugs is terminated, sympathetic stimulation often increases, as if the body had responded to the presence of these drugs by increasing sympathetic neuron activity. Thus, propranolol and nadolol (to name just two) withdrawal can be accompanied by the hyper-beta-adrenergic condition that increases myocardial oxygen demands. Administering propranolol or metoprolol can cause bradycardia, CHF, fatigue, dizziness, depression, psychoses, bronchospasm, and Peyronie disease. [786] [787] Side effects of the dopaminergic receptor-blocking drugs are discussed later in this chapter. Prazosin (Minipress), terazosin, and oxazocin are $alpha_1$-adrenergic receptor-blocking drugs used to treat both hypertension and ischemic cardiomyopathy because they dilate both veins and arteries. These agents are associated with vertigo, palpitations, depression, dizziness, weakness, and anticholinergic effects.

Brain-stem sympathomimetic drugs stimulate alpha-adrenergic receptors in the brain stem. Clonidine (Catapres), a drug with a half-life of 12 to 24 hours; guanabenz; and guanfacine (Tenex) are $alpha_2$-adrenergic receptor stimulants. Presumably, $alpha_2$-adrenergic agonists, including clonidine, guanabenz, and guanfacine, lower BP through the central brain-stem adrenergic stimulation referred to previously. They may also be used to treat opiate, cocaine, food, and tobacco withdrawal. Occasionally, withdrawal from clonidine can precipitate a sudden hypertensive crisis, analogous to that occurring on withdrawal from propranolol, causing a hyper-beta-adrenergic condition. The degree of hypertensive crisis following clonidine withdrawal is now being debated. (Although intravenous clonidine is not yet available in the United States, a skin patch of clonidine has been approved and is being used preoperatively to ablate sympathomimetic responses perioperatively.) Tricyclic antidepressant drugs and, presumably, phenothiazines and the butyrophenones interfere with the action of clonidine. Although administration of a butyrophenone (e.g., droperidol) to a patient given clonidine or guanabenz or guanfacine chronically could theoretically precipitate a hypertensive crisis, none has been reported. Clonidine administration can be accompanied by drowsiness, dry mouth, orthostatic hypotension, bradycardia, and impotence. In dogs, acute clonidine administration decreases anesthetic requirements by 40 to 60 percent; chronic administration decreases requirements by 10 to 20 percent. [167] [168] [231] [796] Because of the relative safety of these drugs and their ability to decrease anesthetic requirements, to block narcotic-induced muscle rigidity, and to provide pain relief, their popularity preoperatively is increasing. [167] [168] [231] [796] [797] [798] [799] [800] [801] [802]

Three other classes of antihypertensive drugs affect the sympathetic nervous system indirectly: diuretics, arteriolar dilators, and slow (calcium) channel-blocking agents. Thiazide diuretic drugs are associated with hypochloremic alkalosis, hypokalemia, hyperglycemia, hyperuricemia, and hypercalcemia. The potassium-sparing diuretic drug spironolactone is associated with hyperkalemia, hyponatremia, gynecomastia, and impotence. All diuretic drugs can cause dehydration. The thiazide

diuretics and furosemide appear to prolong neuromuscular blockade. [803] The arteriolar dilator hydralazine can cause a lupus-like condition (usually with renal involvement), nasal congestion, headache, dizziness, congestive heart failure, angina, and GI disturbances. Such a syndrome is nonexistent with the other direct vasodilator on the U.S. market, minoxidil.

The slow-channel calcium ion antagonists ("calcium channel-blocking drugs") inhibit the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. Such inhibition reduces heart rate (negative chronotropy); depresses contractility (negative inotropy); decreases conduction velocity (negative dromotropy); and dilates coronary, cerebral, and systemic arterioles [804] (Fig. 25-23) (Figure Not Available) . Verapamil, diltiazem, and nifedipine all produce such effects, but to varying degrees and apparently by similar but different mechanisms. [804] [805] These mechanisms relate to the three different classes of calcium channel antagonists they represent: the phenylalkylamines, the benzothiazepines, and the dihydropyridines, respectively. [804] [805] Nifedipine is the most potent of the three as a smooth-muscle dilator, whereas verapamil and diltiazem have negative dromotropic and inotropic effects and vasodilating properties. Diltiazem has weak vasodilating properties as compared with nifedipine and has less atrioventricular conduction effect than does verapamil. Thus, verapamil and diltiazem can increase the PR interval and produce AV block. In fact, reflex activation of the sympathetic nervous system may be necessary during administration of diltiazem and especially during verapamil therapy to maintain normal conduction. Clearly, verapamil and diltiazem must be titrated very carefully when a patient is already taking a beta-adrenergic receptor-blocking drug or when adding beta-blocking drugs to verapamil or diltiazem. Although the increased death rate among patients taking calcium channel-blocking drugs as antihypertensive treatment (versus other agents) has cast doubt on their utility, calcium channel-blocking drugs are still widely prescribed.

The use of calcium channel-blocking drugs has several important implications for anesthetic management. [804] [806] [807] [808] [809] [810] [811] [812] [813] [814] [815] [816] First, the effects of inhalational and narcotic anesthetic agents and of nifedipine in decreasing systemic vascular resistance,

Figure 25-23 (Figure Not Available) Schematic drawing of smooth muscle cell showing calcium flux and possible sites of interference by halothane and nifedipine. The concentration of calcium (Ca^{2+}) in the cytoplasm increases (black arrows) because of entry through the plasma membrane (PM) and release from surface vesicles (SV) or the sacroplasmic reticulum (SR). When the concentration of cytoplasmic Ca^{2+} is sufficiently high, adenosine triphosphate (ATP) is activated. The splitting of ATP by adenosinetriphosphatase (ATPase) into phosphatidylinositol (Pi) and ADP (adenosine diphosphate) provides the interaction and contraction of actin filaments and myosin particles constituting muscle fibers. The concentration of cytoplasmic Ca^{2+} decreases (white arrows) with the return of Ca^{2+} to cellular stores and the extracellular transport of Ca^{2+}. Both halothane and nifedipine probably (1) inhibit the entry of Ca^{2+} and (2) may also interfere with cytoplasmic Ca^{2+} flux by reducing the release of Ca^{2+} by the SR, by (3) reducing storage and reuptake, or by (4) blocking ATPase and/or the contractile mechanism. *(From Tosone et al [892])*

BP, and contractility may be additive. [804] [807] [808] [809] [810] Similarly, verapamil and anesthetics (inhalational anesthetics, nitrous oxide, and narcotics) increase atrioventricular conduction times and additively decrease blood pressure, systemic vascular resistance, and contractility. [808] [809] [810] [813] [816] Second, verapamil and presumably the other calcium channel-blocking drugs have been found to decrease anesthetic requirements by 25 percent. [806] These agents can produce neuromuscular blockade, potentiate both depolarizing and nondepolarizing neuromuscular blocking drugs, and in at least one type of myopathy (Duchenne muscular dystrophy) even precipitate respiratory failure. [811] [812] [814] Finally, because slow channel activation of calcium is necessary to cause spasms of cerebral and coronary vessels, bronchoconstriction, and normal platelet aggregation, these drugs may have a role in treating ischemia of the nervous system, bronchoconstriction, and unwanted clotting disorders perioperatively. [811] All three drugs are highly protein bound and may displace or be displaced by other drugs that are also highly protein bound (e.g., lidocaine, bupivacaine, diazepam, disopyramide, and propranolol). Adverse consequences can be minimized by titrating inhalational or narcotic agent to hemodynamic and anesthetic effects. By monitoring for side effects, the anesthetist can prevent side effects from becoming serious (Slogoff S, et al, personal communication). Hemodynamic, but not electrophysiologic, changes usually can be reversed by administering calcium. [815] Reversal of electrophysiologic effects may occur if "industrial" doses of beta-adrenergic agonists are given.

Mood-Altering Drugs

Mood-altering drugs are the most frequently prescribed medications in the United States. They include MAO inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), phenothiazines, tricyclic antidepressant drugs, and drugs of abuse such as cocaine. MAOIs, which include isocarboxazid (Marplan), phenelzine (Nardil), pargyline (Eutonyl), tranylcypromine (Parnate), and deprenyl, bind irreversibly to the enzyme MAO, thereby increasing intraneuronal levels of amine neurotransmitters (serotonin, norepinephrine, dopamine, epinephrine, octopamine). This increase is associated with an antidepressant effect, an antihypertensive effect, an antinarcoleptic effect, liver enzyme elevation, and delayed onset of Parkinson disease (deprenyl). [508] Because two forms of the enzyme (MAO-A and MAO-B) are selective in vitro for substrate (MAO-A is selective for serotonin, dopamine, and norepinephrine; MAO-B for tyramine and phenylethylamine), presumably MAOIs selective for MAO-A or MAO-B would have different effects. [817] This is not known for certain, as deprenyl (selegiline, Eldepryl), an MAOI-B-selective drug, improves a dopamine deficiency state, parkinsonism. [508]

Interactions between MAOIs and a variety of foods and drugs containing indirect-acting sympathomimetic substances such as ephedrine or tyramine (found especially in aged cheeses) can occur for as long as 2 weeks after the last dose of MAOI is given. The most serious effects of this interaction are convulsions and hyperpyrexic coma (particularly after narcotics).

Anesthetic management of a patient given an MAOI can be chaotic: For this reason it is widely accepted practice to discontinue MAOIs at least 2 to 3 weeks before any planned operation. [818] [819] [820] [821] [822] [823] [824] [825] [826] [827] [828] An alternate point of view has recently been expressed regarding severely psychotic patients or emergency surgery. [817] [829] [830] Clearly, the risk of discontinuing MAOIs must be weighed against the risk of suicidal tendencies in some patients deprived of MAOIs. There are no reported experiences of interactions between narcotics and deprenyl, so judgments about possible worsening of Parkinson disease and continuing MAOIs have no basis in data. It should be noted that severe reactions have occurred when too short an interval existed between administration of MAOIs and tricyclic antidepressants. [705] Emergency surgery on patients given MAOIs can be punctuated by hemodynamic instability. Regional block can be attempted as treatment for postoperative pain to avoid having to give narcotics. Case reports of hyperpyrexic coma following administration of most narcotics exist for humans, and animal studies document a 10 to 50 percent incidence of hyperpyrexic coma in animals pretreated with MAOIs and then given a variety of narcotics. [818] [819] [820] [821] [822] [823] [824] [825] [826] [827] [828] These reactions appear to be best treated using therapy supporting vital functions.

Alternate drugs for the treatment of severe depression include the tricyclic antidepressant drugs: amitriptyline (Elavil, Endep), imipramine (Imavate, Tofranil, Presamine), despiramine (Norpramine), doxepin (Adapin, Sinequan), nortriptyline (Aventyl), fluoxetine (Prozac), trazodone (Desyrel), and bupropion (Wellbutrin). [823] Tricyclic antidepressant drugs also block the reuptake of neurotransmitters and cause their acute release. Given chronically, these drugs decrease the stores of noradrenergic catecholamines. Tricyclic antidepressant drugs also produce side effects similar to those of atropine (dry mouth, tachycardia, delirium, urinary retention) and can cause changes on ECG (changes in T wave, prolongation of the QRS complex, bundle branch block or other conduction abnormalities, or premature ventricular contractions). Although arrhythmias induced by tricyclic antidepressants have been treated successfully with physostigmine, bradycardia has sometimes occurred. [823] Drug interactions with tricyclic antidepressants include those related to blockade of the reuptake of norepinephrine (such as interference with the action of guanethidine) and fatal arrhythmias after halothane and pancuronium. [831] [832] [833] Such interactions, although predictable for a population of patients, may not alter a patient's threshold for arrhythmias. The newer antidepressants (the SSRIs) also have serious side effects. Fluoxetine, a tricyclic that also has an SSRI effect, causes nausea, vomiting, headaches, nervousness, and possibly paranoia and ideas of suicide more commonly than do the other tricyclics [823] but is less likely to cause anticholinergic effects or orthostatic hypotension. Bupropion may cause nausea, vomiting, seizures, agitation, tremor, excitement, and increased motor activity but only rarely causes anticholinergic effects or orthostatic hypotension. Switching between drugs for depression can cause hyperpyrexia and coma. Thus, switching prior to surgery should not be requested casually. [823]

The effectiveness of phenothiazines and butyrophenones in schizophrenia suggests a dopamine receptor-blocking action. In addition, these drugs possess varying degrees of parasympathetic stimulation and ability to block alpha-adrenergic receptors. The phenothiazines include chlorpromazine (Thorazine, Chlor-PZ), promazine (Sparine), triflupromazine (Vesprin), fluphenazine (Prolixin), trifluoperazine, prochlorperazine (Compazine), and many others. The butyrophenones include droperidol and haloperidol (Haldol). Both phenothiazines and butyrophenones produce sedation, depression, and antihistaminic, antiemetic, and hypothermic responses. They are also associated with cholestatic jaundice, impotence, dystonia, and photosensitivity. Other side effects associated with phenothiazines include orthostatic hypotension (partly due to alpha-adrenergic blockade) and ECG abnormalities, such as prolongation of the QT or PR intervals, blunting of T waves, depression of the ST segment, and, on rare occasion, PVCs and torsades de pointes. [823] [832] [833] Although few data are available on the antidepressant drugs selective for serotonin (the SSRIs), occasional case reports of severe hypotension and cardiac arrest with severe bradycardia have been presented in abstract form.

Several important drug interactions are noteworthy for the phenothiazine derivatives. The effects of CNS depressants (especially narcotics and barbiturates) are enhanced by concomitant administration of phenothiazines. Also, CNS seizure threshold is lowered by administration of phenothiazines, which should be avoided in patients who are epileptic or withdrawing from any drug that depresses the CNS. The antihypertensive effects of guanethidine and guanadrel are blocked by tricyclic antidepressant drugs and phenothiazines. [786] Lithium carbonate is used to treat manic depression; it is more effective in preventing mania than in relieving depression. In excitable cells, lithium mimics sodium, decreasing the release of neurotransmitters both centrally and peripherally. Lithium prolongs neuromuscular blockade [834] and may decrease anesthetic requirements because it blocks brain-stem release of norepinephrine, epinephrine, and dopamine.

Psychoactive drugs such as amphetamines (including methamphetamines and their smokable derivative in crystal form, known as "ice") and cocaine acutely release norepinephrine, epinephrine, and dopamine and block their reuptake. Taken chronically, they deplete the nerve endings of these neurotransmitters.

Drugs that appear to increase central alpha-adrenergic release increase anesthetic requirement, whereas drugs that appear to decrease central alpha-adrenergic release decrease anesthetic requirements. (This may not be the mechanism by which they alter anesthetic requirement, but it is a convenient way of remembering the alteration.) Drugs that affect only the beta-adrenergic receptors do not alter anesthetic requirements. [167] [168] [217] [795] [796] [835] [836]

Sympathomimetic Drugs

Many antiasthmatic drugs (bronchodilators) such as terbutaline, aminophylline, and theophylline are sympathomimetic

drugs that can interact with the volatile anesthetics to cause cardiac arrhythmias. Halothane (and to some degree, most other volatile anesthetics) sensitizes the myocardium to exogenous catecholamines. [837] [838] [839] [840] Sensitization means that the minimum dose of exogenous epinephrine administered intravenously needed to produce premature ventricular contractions would be lower in patients anesthetized with halothane than in awake patients.

How much epinephrine is safe to give when halothane is the anesthetic? Katz and Bigger [837] reported that administration of 0.15 mL/kg of a 1/100,000 epinephrine solution per 10-min period (not to exceed 0.45 mL/kg of a 1/100,000 solution/h) was safe. Several studies have shown that lidocaine given with epinephrine affords extra protection and that enflurane and isoflurane are less sensitizing than halothane. [838] [839] [840] Because halothane is a potent bronchodilator, [841] it may be the best choice for anesthetizing patients with asthma. [842] However, this may not be the case; many asthmatic patients are already taking exogenous catecholamines such as xanthines as chronic bronchodilator therapy.

Xanthines are effective bronchodilators because they produce beta-adrenergic stimulation in two ways: They cause release of norepinephrine [843] [844] and also inhibit the breakdown of cyclic adenosine monophosphate (cAMP), [845] the mediator of many of the actions of beta-adrenergic receptor agonists. [434] Phosphodiesterase catalyzes the breakdown of cAMP. Thus, inhibition of phosphodiesterase by theophylline increases the concentration of cAMP. Marcus et al [843] and Westfall and Flemming [844] showed that at least 40 percent of the inotropic effects of aminophylline are due to its ability to release norepinephrine directly. Experimentally, aminophylline decreases the threshold for ventricular fibrillation. [846]

Plasma theophylline levels of 5 mg/L are needed to reduce abnormally high airway resistance. No further beneficial effects are obtained when levels exceed 20 mg/L; instead, toxic effects appear. [847] Theophylline (aminophylline is a combination of 85% theophylline and 15% ethylenediamine) is metabolized largely by the liver, less than 10 percent being excreted unchanged in the urine. The average half-life is 4.4±1.15 hours in adults, and clearance is 1.2 mL/min/kg. [847] Significant liver disease or pulmonary edema can decrease clearance of the drug by one-half and by one-third, respectively. [848] Cigarette smokers clear aminophylline more rapidly than do nonsmokers. [849]

An interaction between aminophylline and halothane appears to be a frequent, predictable occurrence: Of 16 dogs anesthetized with 1 percent halothane and given high-dose bolus injections of aminophylline, 12 had ventricular arrhythmias and 8 had ventricular tachycardia or fibrillation. [850] [851] [852] Thus, it is advisable to wait three drug half-lives after the last dose of aminophylline is given (i.e., approximately 13 hours in normal individuals) before using halothane to anesthetize an asthmatic patient. Using another anesthetic that is a bronchodilator [841] but that is less likely to predispose the patient to catecholamine-induced arrhythmias [838] [839] [840] (e.g., enflurane or isoflurane) or using inhaled or systemic steroids started several days in advance might be alternatives for patients requiring aminophylline or other exogenous sympathomimetic drugs before or during surgery. [853]

Also see Chapter 14 .

Other Drugs

Drugs other than those discussed earlier in this chapter have implications for anesthetic management. The therapies that have been discussed include anticoagulants and fibrinolytics (in hematologic section), endocrinologic preparations excluding birth control pills but including corticosteroids (in the section on endocrinologic disease), antihypertensive drugs (earlier in this section and in cardiovascular diseases), anticonvulsant drugs (in the section on neurologic disorders), and cancer chemotherapeutic agents (in the section on oncology).

Antiarrhythmic Drugs

Antiarrhythmic drugs include local anesthetics (lidocaine, procaine), anticonvulsant (phenytoin) or antihypertensive (propranolol) drugs, calcium channel-blocking agents, or primary antiarrhythmic drugs. These drugs are classified into five major categories: local anesthetics that alter phase 0 and phase 4 depolarization (quinidine, procainamide, and flecainide); local anesthetics that affect only phase 4 depolarization (lidocaine, tocainide, phenytoin, encainide); beta-adrenergic receptor antagonists; antiadrenergic drugs (bretylium, disopyramide, amiodarone); and calcium-entry blockers. These drugs are discussed elsewhere in this chapter and in Chapter 14 . A useful reference with suggestions about drug therapy for cardiac arrhythmias and monitoring of side effects was published by the *Medical Letter on Drugs and Therapeutics.* [854] Lack of adverse reports does not indicate that all these drugs should be continued through the time of surgery; pharmacokinetic studies have not yet determined whether anesthesia (or anesthesia with specific agents) alters the volume of distribution or clearance of these drugs to an extent sufficient to warrant changing the dosage or dosage schedule in the perioperative period. The dearth of reports on this subject may be due to a lack of significant drug interaction or to a lack of awareness that untoward events could be caused by such an interaction.

The pharmacologic characteristics of the various antiarrhythmic drugs can affect anesthetic management. Disopyramide is similar to quinidine and procainamide in its antiarrhythmic effectiveness. Disopyramide is mainly excreted by the kidneys, but hepatic disease increases its half-life. This drug often produces anticholinergic effects, including tachycardia, urinary retention, and psychosis. Hepatitis has also been reported to have occurred after its use. [854] Little is known of the interaction of bretylium with anesthetic agents. Because bretylium blocks the release of catecholamines, chronic therapy with this drug has been associated with hypersensitivity to vasopressors. [854] Quinidine is dependent on the kidneys for excretion, can have vagolytic effects that can decrease AV block, and is associated with blood dyscrasias and GI disturbances. [854] Most of the antiarrhythmic agents enhance a nondepolarizing neuromuscular blockade. Reports confirm this enhancement for quinidine, phenytoin, lidocaine, procainamide, and propranolol. [855] [856] [857] [858] [859] [860] [861] [862] [863] Amiodarone, an antiadrenergic drug used to treat recurrent supraventricular and ventricular tachycardias, causes a peripheral neuropathy and has been associated with hypertension, bradyarrhythmias, and reduced cardiac output during

anesthesia. [864] The drug has a half-life of 29 days, and pharmacologic effects persist for over 45 days after its discontinuance. [865] No data document such an effect for depolarizing muscle relaxants.

Antibiotics

Many antibacterial agents are nephrotoxic and/or neurotoxic, and many prolong neuromuscular blockade. [857] [858] [859] [860] [861] [862] [863] (Also see Ch. 12.) The only

antibiotics devoid of neuromuscular effects appear to be penicillin G and the cephalosporins. [862] Most enzyme-inducing drugs do not increase the metabolism of enflurane or isoflurane. However, isoniazid appears to induce the microsomal enzymes responsible for the metabolism of at least enflurane, increasing the possibility of fluorine-associated renal damage after enflurane. [866] Appropriate antibiotic prophylaxis for surgery (see Tables 25-34 and 25-35) (Table Not Available) requires a knowledge of the probability of infection for that type of surgical procedure and whether the incidence of infection warrants use of a drug regimen directed against the most likely infecting organisms. [354]

Digitalis

Digitalis preparations have a limited margin of safety, the risk of toxicity increasing with hypokalemia. [867] Although there is good rationale for administering digoxin prophylactically prior to surgery, [452] [868] I generally avoid doing so because potassium concentrations can fluctuate widely during anesthesia due to fluid shifts, ventilatory acid-base derangements, and adjuvant treatments, [596] [632] [633] [634] and because intraoperative arrhythmias caused by digitalis toxicity may be difficult to differentiate from those having other sources. Digitalis intoxication can present with such diverse cardiac arrhythmias as junctional escape rhythm, PVCs, ventricular bigeminy or trigeminy, junctional tachycardia, paroxysmal atrial tachycardia with or without block, sinus arrest, sinus exit block, Mobitz type I or II blocks, or ventricular tachycardia. [867] However, anesthetic agents appear to protect against digitalis toxicity, at least in animal studies. [869] [870] [871] [872] A titrated cardioversion technique, using at first 10-, and then 20-, 30-, 40-, 50-, 75-, 100-, 150-, and 200-joule doses, resulted in safe cardioversion in the presence of digitalis and propofol or midazolam hypnosis. [873] For patients in atrial fibrillation, the ventricular response should guide the choice of dose of digitalis.

Medications for Glaucoma

Medications for glaucoma include two organophosphates: echothiophate and isoflurophate. These drugs inhibit serum cholinesterase, which is responsible for hydrolysis and inactivation of succinylcholine and the ester-type local anesthetics, such as procaine, chloroprocaine, and tetracaine. [874] [875] These ester-type local anesthetics should be avoided in patients treated with eyedrops containing organophosphate. Table 25-45 lists other medications related to anesthesia and their side effects (from the National Registry for Drug-Induced Ocular Side Effects, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, Oregon 97201; 503-279-8456).

Also see Chapter 63 .

Magnesium, Cimetidine, and Oral Contraceptives

Magnesium is given to treat eclampsia; it can cause neuromuscular blockade by itself and potentiates neuromuscular blockade by both nondepolarizing and depolarizing muscle relaxants. [876] [877] Cimetidine reduces hepatic blood flow and inhibits enzymatic degradation of drugs by the liver. Thus, higher blood levels and prolonged elimination half-lives may result when drugs that are metabolized by the liver (e.g., lidocaine, procaine, some narcotics, and propranolol) are given to patients taking cimetidine chronically or acutely. [878] [879] The risk of postoperative venous thrombosis increases when oral contraceptives are used preoperatively. [880] [881] Although some authorities recommend changing from oral contraceptives to topical methods of birth control 2 to 4 weeks before surgery, [882] no controlled study has determined whether birth control pills should be discontinued before surgery, or the resulting incidence of pregnancy. Other authorities recommend preventing venous thromboembolism by using low-dose heparin, guided by a determination of efficacy and cost-effectiveness. [373] [374] [375] Because estrogens greatly decrease the incidence of cardiovascular disease and osteoporosis, their use in the elderly is being encouraged. [268] Thus, the uncertainty surrounding prophylaxis for heart disease (created by the dilemma of long-term benefit versus short-term risk of thromboembolism) makes necessary better data for resolution.

Interrupting a Drug Regimen Before Surgery

If a drug is needed for treatment preoperatively, it should be continued through surgery. It often must be specifically requested, as many patients and nurses perceive the nothing-by-mouth directive to include drugs. [883] [884] The only exception to this general rule of not altering preoperative drug therapy might pertain to (1) MAOIs; (2) anticoagulants and fibrinolytic agents if surgical hemostasis is needed; (3) nicotinic acid; (4) dosage adjustments for insulin and corticosteroids; and (5) ACE inhibitors and receptor antagonists. These recommendations require that the anesthesiologist be aware of the pharmacologic characteristics, interactions, and anesthetic implications of drugs described earlier in this chapter. [254] [512] [885] [886]

When in doubt about a disease or a drug, I consult the following textbooks: *Harrison' s Principles of Internal Medicine; Anesthesia and Uncommon Diseases; Pathophysiologic and Clinical Correlations; Anesthesia and Co-Existing Disease; To Make the Patient Ready for Anesthesia: Medical Care of the Surgical Patient; Anesthetic Implications of Congenital Anomalies in Children; Pharmacology and Physiology in Anesthetic Practice; Medical Care of the Surgical*

TABLE 25-45 -- Common Ophthalmologic Agents and Their Anesthetically Important Interactions

GLAUCOMA: PRIMARY GOAL IS TO REDUCE IOP BY-- MITOTICS AND EPINEPHRINE: INCREASE OUTFLOW OF AQUEOUS HUMOR beta -BLOCKADE AND CARBONIC ANHYDRASE INHIBITORS: REDUCE PRODUCTION OF AQUEOUS HUMOR OSMOTIC AGENTS: TRANSIENTLY DECREASE VOLUME	
AGENT (TRADE NAME)	***TOXICITIES AND SPECIFIC TREATMENTS***
Miotics	
Parasympathomimetics	
Pilocarpine (Adsorbocarpine, Isopto Carpine, Pilocar, Pilocel)	
Carbachol	
Acetylcholinesterase inhibitors	*Tox:* hypersalivation, sweating, N/V, bradycardia, hypotension, bronchospasm, CNS effects, coma, respiratory arrest, death
Physostigmine	
Demecarium	
Isoflurophate (Floropryl)	*Rx:* atropine, pralidoxime (Protopam)
Echothiophate (Echodide, Phospholine)	*Ix:* succinylcholine--prolonged apnea (agents must be discontinued 4 wk prior)
Epinephrine (Epitrate, Murocoll, Mytrate, Epifrin, Glaucon, Epinal, Eppy)	*Tox:* (rare) tachycardia, PVCs, hypertension, headache, tremors *Ix:* Avoid agents that sensitize to catecholamines, e.g., halothane.
beta -Blockers	
Timolol (Timoptic)	*Tox:* J-blockade with bradycardia, exacerbation of asthma, CNS depression, lethargy, confusion
Betaxolol (Betopic (?beta-1 selective))	
Levobunolol (Betagan)	Synergy noted with systemic agents
Carbonic anhydrase inhibitors	
Acetazolamide (Diamox)	*Tox:* Anorexia, GI disturbances,"general miserable feeling" and malaise, paresthesias, diuresis, hypokalemia (transient), renal colic and calculi, hyperuricemia, thrombo-cytopenia, aplastic anemia, acute respiratory failure in patients with COPD
Dichlorphenamide (Daranide, Oratrol)	

Ethoxzolamide (Cardrase, Ethamide)	
Methazolamide (Neptazane)	
Osmotic agents	
Glycerin (Glyrol, Osmoglyn)	*Tox:* Dehydration, hyperglycemia, nonketotic hyperosmolar coma (rare). Fatalities with mannitol secondary to CHF or intracranial bleeding
Isosorbide (Ismotic)	
Urea (Urevert, Ureaphil)	Urea may cause thrombosis
Mannitol (Osmitrol)	
Intraocular acetylcholine (Miochol)	*Tox:* hypotension, bradycardia *Rx:* atropine

MYDRIATICS AND CYCLOPLEGICS: PROVIDE PUPILLARY DILATATION AND PARALYSIS OF ACCOMMODATION-- ANTICHOLINERGICS BLOCK MUSCARINIC RECEPTORS; PARALYZING IN IRISalpha -ADRENERGICS CONTRACT THE DILATOR OF THE IRIS

AGENT (TRADE NAME)	***TOXICITIES AND SPECIFIC TREATMENTS***
Anticholinergics	
Atropine (Atropisol, Bufopto, Isopto Atropine)	*Tox:* dry mouth, flushing, thirst, tachycardia seizure, hyperactivity, transient psychosis, rare coma, and death
Cyclopentolate, alone (Cyclogyl) or with phenylephrine-homatropine (Cyclomydril)	*Rx:* physostigmine
Scopolamine tropicamide (Homatrocel, Isopto Homatropine, Isopto Hyoscine, Murocoll #19, Mydriacyl)	
alpha-Adrenergics	
Phenylephrine (Efricel, Mydfrin, Neo-Synephrine)	*Tox:* tachycardia, HTN, PVCs, myocardial ischemia, agitation
Hydroxyamphetamine (Paredrine)	

Abbreviations: IOP, intraocular pressure; Tox, toxicity; Rx, treatment; Ix, interaction; N/V, nausea and vomiting; PVCs, premature ventricular contractions; CNS, central nervous system; GI, gastrointestinal; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; HTN, hypertension

Patient: A Problem-Oriented Approach to Management; and *Goodman and Gilman*' *s The Pharmacologic Basis of Therapeutics.* It is then wise to consult two experts on the drug or disease and determine who is best able to care for the patient. The expert who is best qualified should be observed while he or she is attending to the patient, not only preoperatively and intraoperatively but also postoperatively. It is important to remember that few prospective controlled studies have shown that any preoperative technique, treatment, or management decreases perioperative risk. However, common sense and foreknowledge of potential pitfalls, as well as diligence in avoiding those pitfalls, should reduce avoidable perioperative complications.

References

1. Wei JY: Age and the cardiovascular system. N Engl J Med 327:1735, 1992.

2. Medical consultation. In Medical Knowledge Self-Assessment Program IX. Part C, Book 4. Philadelphia, American College of Physicians, 1992, p 939.

3. Hamilton WK: Do let the blood pressure drop and do use myocardial depressants! Anesthesiology 45:273, 1976.

4. Roizen M: The preoperative cardiology consult: What the cardiologist should know about anesthesia. In Parmley W, Chatterjee K (eds): Cardiology. Philadelphia, JB Lippincott, 1993, p 1.

5. Gluck R, Munoz E, Wise L: Preoperative and postoperative medical evaluation of surgical patients. Am J Surg 155:730, 1988.

6. Merli G, Weitz H, Lubin M (eds): Medical consultation. Med Clin North Am 77.

---

7. Mangano DT, Browner WS, Hollenberg M et al: Long-term cardiac prognosis following noncardiac surgery. JAMA 268:233, 1992.

8. Charlson ME, MacKenzie CR, Ales K et al: Surveillance for postoperative myocardial infarction after noncardiac operations. Surg Gynecol Obstet 167:407, 1988.

9. Goldman L, Caldera DL, Nussbaum SR et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845, 1977.

10. Eagle KA, Brundage BH, Chaitman BR et al: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. Circulation 93:1278, 1996.

11. Walsh DB, Eckhauser FE, Ramsburgh SR et al: Risk associated with diabetes mellitus in patients undergoing gall-bladder surgery. Surgery 91:254, 1982.

12. Fowkes FGR, Lunn JN, Farrow SC et al: Epidemiology in anesthesia. III. Mortality risk in patients with coexisting physical disease. Br J Anaesth 54:819, 1982.

13. Hjortrup A, Rasmussen BF, Kehlet H: Morbidity in diabetic and nondiabetic patients after major vascular surgery. Br Med J 287:1107, 1983.

14. Reichard P, Nilsson B-Y, Rosenqvist U: The effect of longterm intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 329:304, 1993.

15. Kenepp NB, Shelley WC, Gabbe SG et al: Fetal and neonatal hazards of maternal hydration with 5% dextrose before cesarean section. Lancet 1:1150, 1982.

16. Lanier WL, Stangland KJ, Scheithauer BW et al: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. Anesthesiology 66:39, 1987.

17. Zasslow MA, Pearl RG, Shuer LM et al: Hyperglycemia decreases acute neuronal ischemic changes after middle cerebral artery occlusion in cats. Stroke 20:519, 1989.

18. Reissell E, Orko R, Maunuksela E-L, Lindgren L: Predictability of difficult laryngoscopy in patients with long-term diabetes mellitus. Anaesthesia 45:1024, 1990.

19. Burgos LG, Ebert TJ, Asiddao C et al: Increased intraoperative cardiovascular morbidity in diabetes with autonomic neuropathy. Anesthesiology 70:591, 1989.

20. Kalichman MW, Calcutt NA: Local anesthetic-induced conduction block and nerve fiber injury in streptozotocin-diabetic rats. Anesthesiology 77:941, 1992.

21. Eastwood DW: Anterior spinal artery syndrome after epidural anesthesia in a pregnant diabetic patient with scleredema. Anesth Analg 73:90, 1991.

22. Roizen MF: RealAge: Are You As Young As You Can Be? New York, HarperCollins, 1999.

23. Wingard DL, Barrett-Connor EL, Ferrara A: Is insulin really a heart disease risk factor? Diabetes Care 18:1299, 1995.

24. Steward HL, Bethea MC, Andrews SS, Balant LA: Sugar Busters. New York, Ballantine Books, 1998.

25. Yoon J-W, Austin M, Onodera T et al: Virus-induced diabetes mellitus. N Engl J Med 300:1173, 1979.

26. Mayer-Davis EJ, D'Agostino R, Karter AJ et al, for the IRAS investigators: Intensity and amount of physical activity in relation to insulin sensitivity. The Insulin Resistance Atherosclerosis Study. JAMA 279:669, 1998.

27. Inzucchi SE, Maggs DG, Spollett GR et al: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med 338:867, 1998.

28. Hayward RA, Manning WG, Kaplan SH et al: Starting insulin therapy in patients with type 2 diabetes. Effectiveness, complications, and resource utilization. JAMA 278:1663, 1997.

29. Coldwell JA: Controlling type 2 diabetes. Are the benefits worth the costs? JAMA 278:1700, 1997.

30. Campbell PJ, Bolli GB, Cryer PE et al: Pathogenesis of the dawn phenomenon in patients with insulin-dependent diabetes mellitus. N Engl J Med 312:1473, 1985.

31. Stern MP, Rosenthal M, Haffner SM: A new concept of impaired glucose tolerance: Relation to cardiovascular risk. Atherosclerosis 5:311, 1985.

32. Brenner BM: Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int 23:647, 1983.

33. Grgic A, Rosenbloom AL, Weber FT et al: Joint contracture--common manifestation of childhood diabetes mellitus. J Pediatr 88:584, 1976.

34. Salzarulo HH, Taylor LA: Diabetic "stiff joint syndrome" as a cause of difficult endotracheal intubation. Anesthesiology 64:366, 1986.

35. Olson RL, Leichter S, Warram J et al: Deaths among patients using continuous subcutaneous insulin infusion pumps--United States. MMWR Morb Mortal Wkly Rep 31:80, 1982.

36. Goodson WH III, Hunt TK: Studies of wound healing in experimental diabetes mellitus. J Surg Res 22:221, 1977.

37. The DCCT Research Group: Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. Diabetes Care 18:1415, 1995.

38. Gottrup F, Andreassen TT: Healing of incisional wounds in stomach and duodenum: The influence of experimental diabetes. J Surg Res 31:61, 1981.

39. Bagdade JD: Phagocytic and microbiological function in diabetes mellitus. Acta Endocrinol (Copenh) 83(suppl 205):27, 1976.

40. Nolan CM, Beaty HN, Bagdade JD: Further characterization of the impaired bactericidal function of granulocytes in patients with poorly controlled diabetes. Diabetes 27:889, 1978.

41. McMurry JF: Wound healing with diabetes mellitus. Better glucose control for better wound healing in diabetics. Surg Clin North Am 64:769, 1984.

42. Cruse PJ, Foord R: A 5-year prospective study of 23,649 surgical wounds. Arch Surg 107:206, 1973.

43. Longstreth WT, Inui TS: High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. Ann Neurol 15:59, 1984.

44. Johnson WD, Pedraza PM, Kayser KL: Coronary artery surgery in diabetics: 261 consecutive patients followed four to seven years. Am Heart J 104:823, 1982.

45. Borow KM, Jaspan JB, Williams KA et al: Myocardial mechanics in young adult patients with diabetes mellitus: Effects of altered load, inotropic state and dynamic exercise. J Am Coll Cardiol 15:1508, 1990.

46. Croughwell N, Lyth M, Quill TJ et al: Diabetic patients have abnormal cerebral autoregulation during cardiopulmonary bypass. Circulation 82(suppl IV):IV-407, 1990.

47. Tsueda K, Huang KC, Dumont SW et al: Cardiac sympathetic tone in anaesthetized diabetics. Can J Anaesth 38:20, 1991.

48. Metz S, Keats AS: Benefits of a glucose-containing priming solution for cardiopulmonary bypass. Anesth Analg 72:428, 1991.

49. Lanier WL: Glucose management during cardiopulmonary bypass: Cardiovascular and neurologic implications. Anesth Analg 72:423, 1991.

50. Kitabchi AE, Wall BM: Diabetic ketoacidosis. Med Clin North Am 79:9, 1995.

51. The Diabetes Control and Complications Trial Research Group: Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the Diabetes Control and Complications Trial. A randomized, controlled trial. Ann Intern Med 128:517, 1998.

52. Ramanathan S, Khoo P, Arismendy J: Perioperative maternal and neonatal acid-base status and glucose metabolism in patients with insulin-dependent diabetes mellitus. Anesth Analg 73:105, 1991.

53. Kenepp NB, Shelley WC, Gabbe SG et al: Fetal and neonatal hazards of maternal hydration with 5 percent dextrose before cesarean section. Lancet 1:1150, 1982.

54. Daykin AP: Anesthetic and surgical stress in the diabetic patient: Carbohydrate homeostasis. Int Anesthesiol Clin 26:206, 1988.

55. Walts LF, Miller J, Davidson MB et al: Perioperative management of diabetes mellitus. Anesthesiology 55:104, 1981.

56. Peterson L, Caldwell J, Hoffman J: Insulin adsorbance to polyvinyl chloride surfaces with implications for constant-infusion therapy. Diabetes 25:72, 1976.

57. Meyer EJ, Lorenzi M, Bohannon NV et al: Diabetic management by insulin infusion during major surgery. Am J Surg 137:323, 1979.

58. Farrow SC, Fowkes FGR, Lunn JN et al: Epidemiology in anaesthesia. II: Factors affecting mortality in hospital. Br J Anaesth 54:811, 1982.

59. Galloway JA, Shuman CR: Diabetes and surgery. A study of 667 cases. Am J Med 34:177, 1963.

60. Glaser RB: Morbidity and mortality from major vascular surgery. In Roizen MF (ed): Anesthesia for Vascular Surgery. New York, Churchill Livingstone, 1990, p 8.

61. Khuri SF, Daley J, Henderson W et al: Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: Results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 185:315, 1997.

62. Ravid M, Brosh D, Levi Z et al: Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 128:982, 1998.

63. Page MM, Watkins PJ: Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet 1:14, 1978.

64. Thomas AN, Pollard BJ: Renal transplantation and diabetic autonomic neuropathy. Can J Anaesth 36:590, 1989.

65. Charlson ME, MacKenzie CR, Gold JP: Preoperative autonomic function abnormalities in patients with diabetes mellitus and patients with hypertension. J Am Coll Surg 179:1, 1994.

66. Garcia MJ, McNamara PM, Gordon T et al: Morbidity and mortality in diabetics in the Framingham population: Sixteen year follow-up study. Diabetes 23:105, 1974.

67. Heino A: Operative and postoperative nonsurgical complications in diabetic patients undergoing renal transplantation. Scand J Urol Nephrol 22:53, 1988.

68. Hirsch IB, McGill JB, Cryer PE, White PF: Perioperative management of surgical patients with diabetes mellitus. Anesthesiology 74:346, 1991.

69. Eldridge AJ, Sear JW: Peri-operative management of diabetic patients. Any changes for the better since 1985? Anaesthesia 51:45, 1996.

70. Haffner SM, Lehto S, Ronnemaa T et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229, 1998.

71. Service J: Hypoglycemias. J Clin Endocrinol Metab 76:269, 1993.

72. Schreider BD, Uitvlugt A, Roizen MF: Anesthesia for patients with insulinoma and other causes of hypoglycemia. Anesthesiol Clin North Am 5:357, 1987.

73. Muir JJ, Endres SM, Offord K et al: Glucose management in patients undergoing operation for insulinoma removal. Anesthesiology 59:371, 1983.

74. Reubi J-C, Laissue JA: Multiple actions of somatostatin in neoplastic disease. TiPS 16:110, 1995.

75. Schaefer EJ, Levy RI: Pathogenesis and management of lipoprotein disorders. N Engl J Med 312:1300, 1985.

76. Larsen ML, Illingworth DR: Drug treatment of dyslipoproteinemia. Med Clin North Am 78:225, 1994.

77. Downs JR, Clearfield M, Weis S et al: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA 279:1615, 1998.

78. Shepherd J, Cobbe SM, Ford I et al, for the West of Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 333:1301, 1995.

79. Fowkes FGR, Price JF, Leng GC: Targeting subclinical atherosclerosis. BMJ 316:1764, 1998.

80. Grundy SM, Balady GJ, Criqui MH et al, for the AHA Task Force on Risk Reduction: Primary prevention of coronary heart disease: Guidance from Framingham. A statement for healthcare professionals from the AHA Task Force on Risk Reduction. Circulation 97:1876, 1998.

81. Campbell NC, Thain J, Deans HG et al: Secondary prevention in coronary heart disease: Baseline survey of provision in general practice. BMJ 316:1430, 1998.

82. Weijden Tvd, Grol R: Preventing recurrent coronary heart disease. BMJ 316:1400, 1998.

83. Knopp RH, Walden CE, Retzlaff BM et al: Long-term cholesterol-lowering effects of 4 fat-restricted diets in hypercholesterolemic and combined hyperlipidemic men. The dietary alternatives study. JAMA 278:1509, 1997.

84A. Rosenson RS, Tangney CC: Antiatherothrombotic properties of statins. Implications for cardiovascular event reduction. JAMA 279:1643, 1998.

84B. Andres R: Effect of obesity on total mortality. Int J Obesity 4:381, 1980.

85. Quesenberry CP Jr, Caan B, Jacobson A: Obesity, health services use, and health care costs among members of a health maintenance organization. Arch Intern Med 158:466, 1998.

86. Fox GS, Whalley DG, Bevan DR: Anesthesia for the morbidly obese. Experience with 110 patients. Br J Anaesth 53:811, 1983.

87. Taylor RR, Kelly TM, Elliott CG et al: Hypoxemia after gastric bypass surgery for morbid obesity. Arch Surg 120:1298, 1985.

88. Wilson SL, Mantena NR, Halverson JD: Effects of atropine, glycopyrrolate, and cimetidine on gastric secretions in morbidly obese patients. Anesth Analg 60:37, 1981.

89. Rocke DA, Murray WB, Rout CC, Gouws E: Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 77:67, 1992.

90. Illing L, Duncan PG, Yip R: Gastroesophageal reflux during anaesthesia. Can J Anaesth 39:466, 1992.

91. Hardy J-F, Lepage Y, Bonneville-Chouinard N: Occurrence of gastroesophageal reflux on induction of anaesthesia does not correlate with the volume of gastric contents. Can J Anaesth 37:502, 1990.

92. Hudes ET, Marans HJ, Hirano GM et al: Recovery room oxygenation: A comparison of nasal catheters and 40 percent oxygen masks. Can J Anaesth 36:20, 1989.

93. Vaughan RW, Bauer S, Wise L: Effect of position (semirecumbent versus supine) on postoperative oxygenation in markedly obese subjects. Anesth Analg 55:37, 1976.

94. Schwartz AE, Matteo RS, Orstein E et al: Pharmacokinetics of sufentanil in obese patients. Anesth Analg 73:790, 1991.

95. Weinstein JA, Matteo RS, Orstein E et al: Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. Anesth Analg 67:1149, 1988.

96. Pasulka PS, Bistman BR, Benotti PN, Blackburn GL: The risk of surgery in obese patients. Ann Intern Med 104:540, 1986.

97. Rosenbaum M, Leibel RL, Hirsch J: Obesity. N Engl J Med 337:396, 1997.

98. Sours HE, Frattali VP, Brand CD et al: Sudden death associated with very low calorie weight reduction regimens. Am J Clin Nutr 34:453, 1981.

99. Wadden TA, Stunkard AJ, Brownell KD: Very low calorie diets: Their efficacy, safety and future. Ann Intern Med 99:675, 1983.

100. Goldbloom DS, Kennedy SH, Kaplan AS et al: Anorexia nervosa and bulimia nervosa. Can Med Assoc J 140:1149, 1989.

101. Arnold DE, Rose RJ, Stoddard P: Intraoperative cardiac dysrhythmias in a patient with bulimic anorexia nervosa. Anesthesiology 67:1003, 1987.

102. Veterans Administration Total Parenteral Nutrition Cooperative Study Group: Perioperative total parenteral nutrition in surgical patients. N Engl J Med 325:525, 1991.

103. Askanazi J, Hensle TW, Starker PM et al: Effect of immediate postoperative nutritional support on length of hospitalization. Ann Surg 203:236, 1986.

104. Starker PM, La Sala PA, Askanazi J et al: The responses to TPN, a form of nutritional assessment. Ann Surg 198:720, 1983.

105. Lampe GH, Roizen MF: Anesthesia for patients with abnormal function of the adrenal cortex. Anesthesiol Clin North Am 5:245, 1987.

106. Hanowell ST, Hittner KC, Kim YD et al: Anesthetic management of primary aldosteronism. Anesthesiol Rev 9:36, 1982.

107. Rabinowitz IN, Watson W, Farber EM: Topical steroid depression of the hypothalamic-pituitary-adrenal axis in psoriasis vulgaris. Dermatologica 154:321, 1977.

108. Knudsen L, Christiansen LA, Lorentzen JE: Hypotension during and after operation in glucocorticoid-treated patients. Br J Anaesth 53:295, 1981.

109. Symreng T, Karlberg BE, Kagedal B et al: Physiological cortisol substitution of long-term steroid-treated patients undergoing major surgery. Br J Anaesth 53:949, 1981.

110. Udelsman R, Ramp J, Gallucci WT et al: Adaptation during surgical stress: A reevaluation of the role of glucocorticoids. J Clin Invest 77:1377, 1986.

111. Axelrod L: Glucocorticoid therapy. Medicine (Baltimore) 55:39, 1976.

112. Graber AL, Ney RI, Nicholson WE et al: Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. J Clin Endocrinol Metab 25:11, 1965.

113. Ackerman GL, Nolan GM: Adrenocortical responsiveness after alternate-day corticosteroid therapy. N Engl J Med 278:405, 1968.

114. Sampson PA, Brooke BN, Winstone NE: Biochemical confirmation of collapse due to adrenal failure. Lancet 1:1377, 1961.

115. Streck WF, Lockwood DH: Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med 66:910, 1979.

116. Cook DM, Loriaux DL: The incidental adrenal mass. Am J Med 101:88, 1996.

117. Linos DA, Stylopoulos N, Raptis SA: Adrenaloma: A call for more aggressive management. World J Surg 20:788, 1996.

118. Mantero F, Masini AM, Opocher G et al, on behalf of the National Italian Study Group on Adrenal Tumors: Adrenal incidentaloma: An overview of hormonal data from the National Italian Study Group. Horm Res 47:284, 1997.

119. White PC, New MI, Dupont B: Congenital adrenal hyperplasia. N Engl J Med 316:1519, 1987.

120. Hollenberg NK, Williams GH: Hypertension, the adrenal and the kidney: Lessons from pharmacologic interruption of the reninangiotensin system. Adv Intern Med 25:327, 1980.

121. Tyrrell JB, Brooks RM, Fitzgerald PA et al: Cushing's disease. Selective trans-sphenoidal resection of pituitary microadenomas. N Engl J Med 298:753, 1978.

122. Ehrlich HP, Hunt TK: Effects of cortisone and vitamin A on wound healing. Ann Surg 167:324, 1968.

123. Dale DC, Fauci AS, Wolff SM: Alternate-day prednisone. Leukocyte kinetics and susceptibility to infections. N Engl J Med 291:1154, 1974.

124. Weinberger MH, Grim CE, Hollifield JW et al: Primary aldosteronism: diagnosis, localization, and treatment. Ann Intern Med 90:386, 1979.

125. Moore FD, Edelman IS, Olney JM et al: Body sodium and potassium. III: Inter-related trends in alimentary, renal and cardiovascular disease; lack of correlation between body stores and plasma concentration. Metabolism 3:334, 1954.

126. Jasani BM, Edmonds CJ: Kinetics of potassium distribution in man using isotope dilution and whole-body counting. Metabolism 20:1099, 1971.

127. Johnson JE, Hartsuck JM, Zollinger RM Jr et al: Radiopotassium equilibrium in total body potassium: Studies using ^{43} K and ^{42} K. Metabolism 18:663, 1969.

128. Surawicz B, Chlebus H, Mazzoleni A: Hemodynamic and electrocardiographic effects of hyperpotassemia: Differences in response to slow and rapid increases in concentration of plasma K. Am Heart J 73:647, 1967.

129. Rao TLK, Jacobs KH, El-Etr AA: Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 59:499, 1983.

130. Oh SH, Patterson R: Surgery in corticosteroid-dependent asthmatics. J Allergy Clin Immunol 53:345, 1974.

131. Schambelan M, Sebastian A: Hyporeninemic hypoaldosteronism. Adv Intern Med 24:385, 1979.

132. Oyama T, Taniguchi K, Jin T et al: Effects of anaesthesia and surgery on plasma aldosterone concentration and renin activity in man. Br J Anaesth 51:747, 1979.

133. Namba Y, Smith JB, Fox GS et al: Plasma cortisol concentrations during caesarean section. Br J Anaesth 52:1027, 1980.

134. Nieman LK, Oldfield EH, Wesley R et al: A simplified morning corticotrophin-releasing hormone stimulation test for the differential diagnosis of adrenocorticotrophin-dependent Cushing's syndrome. J Clin Endocrinol Metab 77:1308, 1993.

135. Engquist A, Backer OG, Jarnum S: Incidence of postoperative complications in patients subjected to surgery under steroid cover. Acta Chir Scand 140:343, 1974.

136. Jensen JK, Elb S: Per-og postoperative komplikationer hos tidligere kortikosteroidbehandlede patienter. Nord Med 76:975, 1966.

137. Winstone NE, Brooke BN: Effects of steroid treatment on patients undergoing operation. Lancet 1:973, 1961.

138. Migeon C, Keller A, Lawrence B, Shepard T: DHA and androsterone levels in human plasma. Effect of age and sex: Day-to-day and diurnal variations. J Clin Endocrinol Metab 17:1051, 1957.

139. Wagner RL, White PF, Kan PB et al: Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 310:1415, 1984.

140. Zurick AM, Sigurdsson H, Koehler LS et al: Magnitude and time course of perioperative adrenal suppression with single dose etomidate in male adult cardiac surgical patients. Anesthesiology 65:A248, 1986.

141. Gagner M, Breton G, Pharand D, Pomp A: Is laparoscopic adrenalectomy indicated for pheochromocytomas? Surgery 120:1076, 1996.

142. Linos DA, Stylopoulos N, Boukis M et al: Anterior, posterior, or laparoscopic approach for the management of adrenal diseases? Am J Surg 173:120, 1997.

143. Bravo EL: Evolving concepts in the pathophysiology, diagnosis and treatment of pheochromocytoma. Endocr Rev 15:356, 1994.

144. St John Sutton MG, Sheps SG, Lie JT: Prevalence of clinically unsuspected pheochromocytoma: Review of a 50-year autopsy series. Mayo Clin Proc 56:354, 1981.

145. Pauker SG, Kopelman RI: Interpreting hoofbeats: Can Bayes help clear the haze? N Engl J Med 327:1009, 1992.

146. Lucon AM, Pereira MAA, Mendonca BB et al: Pheochromocytoma: Study of 50 cases. J Urol 157:1208, 1997.

147. Desmonts JM, le Houelleur J, Remond P et al: Anaesthetic management of patients with pheochromocytoma: A review of 102 cases. Br J Anaesth 49:991, 1977.

148. Roizen MF, Horrigan RW, Koike M et al: A prospective randomized trial of four anesthetic techniques for resection of pheochromocytoma. Anesthesiology 57:A43, 1982.

149. Roizen MF, Hunt TK, Beaupre PN et al: The effect of alphaadrenergic blockade on cardiac performance and tissue oxygen delivery during excision of pheochromocytoma. Surgery 94:941, 1983.

150. Allen GC, Rosenberg H: Pheochromocytoma presenting as acute malignant hyperthermia--a diagnostic challenge. Can J Anaesth 37:593, 1990.

151. Zakowski M, Kaufman B, Berguson P et al: Esmolol use during resection of pheochromocytoma: Report of three cases. Anesthesiology 70:875, 1989.

152. Roizen MF, Schreider BD, Hassan SZ: Anesthetic for patients with pheochromocytoma. Anesthesiol Clin North Am 5:269, 1987.

153. Goldstein DS, Holmes C, Cannon RO III et al: Sympathetic cardioneuropathy in dysautonomias. N Engl J Med 336:696, 1997.

154. Ziegler MG, Lake CR, Kopin IJ: The sympathetic nervous system defect in primary orthostatic hypotension. N Engl J Med 296:293, 1977.

155. Naftchi NE, Wooten GF, Lowman EW et al: Relationship between serum dopamine-beta-hydroxylase activity, catecholamine metabolism, and hemodynamic changes during paroxysmal hypertension in quadriplegia. Circ Res 35:850, 1974.

156. Cohen CA: Anesthetic management of a patient with the Shy-Drager syndrome. Anesthesiology 35:95, 1971.

157. McCaughey TJ: Familial dysautonomia as an anaesthetic hazard. Can J Anaesth 12:558, 1965.

158. Meridy HW, Creighton RE: General anaesthesia in eight patients with familial dysautonomia. Can J Anaesth 18:563, 1971.

159. Stowe DF, Bernstein JS, Madsen KE et al: Autonomic hyperreflexia in spinal cord injured patients during extracorporeal shock wave lithotripsy. Anesth Analg 68:788, 1989.

160. Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 43:89, 1975.

161. Jousse AT, Wynne-Jones M, Breithaupt DJ: A follow-up study of life expectancy and mortality in traumatic transverse myelitis. Can Med Assoc J 98:770, 1968.

162. Bevan DR: Shy-Drager syndrome. A review and a description of the anaesthetic management. Anaesthesia 34:866, 1979.

163. Malan MD, Crago RR: Anaesthetic considerations in idiopathic orthostatic hypotension and the Shy-Drager syndrome. Can J Anaesth 26:322, 1979.

164. Roizen MF: Should we all have a sympathectomy at birth? Or at least preoperatively? Anesthesiology 68:482, 1988.

165. Stone JG, Foex P, Sear JW et al: Myocardial ischemia in untreated hypertensive patients. Effect of a single small oral dose of a betaadrenergic blocking agent. Anesthesiology 68:495, 1988.

166. Mangano DT, Layug EL, Wallace A, Tateo I, for the Multicenter Study of Perioperative Ischemia Research Group: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 335:1713, 1996.

167. Flacke JW, Bloor BC, Flacke WE et al: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 67:11, 1987.

168. Ghignone M, Calvillo O, Quintin L: Anesthesia and hypertension: The effect of clonidine on perioperative hemodynamics and isoflurane requirements. Anesthesiology 67:3, 1987.

169. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T: Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 66:729, 1987.

170. Roizen MF, Lampe GH, Benefiel DJ et al: Is increased operative stress associated with worse outcome? (abstract). Anesthesiology 67:A1, 1987.

171. Fleisher LA, Rosenbaum SH, Nelson AH, Barash PG: The predictive value of preoperative silent ischemia for postoperative ischemic cardiac

events in vascular and nonvascular surgery patients. Am Heart J 122:980, 1991.

172. Tuman KJ, McCarthy RJ, Spiess BD et al: Effect of pulmonary artery catheterization on outcome in patients undergoing coronary artery surgery. Anesthesiology 70:199, 1989.

173. Anand KJS, Hickey PR: Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. JAMA 326:1, 1992.

174. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 45:287, 1976.

175. Klassen GA, Bramwell RS, Bromage PR, Zborowska-Sluis DT: Effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. Anesthesiology 52:8, 1980.

176. Norris RM, Clarke ED, Sammel NL et al: Protective effect of propranolol in threatened myocardial infarction. Lancet 2:907, 1978.

177. Levine JD, Dardick SJ, Roizen MF et al: The contribution of sensory afferents and sympathetic efferents to joint injury in experimental arthritis. J Neurosci 6:3423, 1986.

178. Feigl EO: The paradox of adrenergic coronary vasoconstriction. Circulation 76:737, 1987.

179. Wade JG, Larson CP, Hickey RF et al: Carotid endarterectomy and carotid chemoreceptor and baroreceptor function in man. N Engl J Med 282:823, 1970.

180. Hui KKP, Conolly ME: Increased numbers of beta receptors in orthostatic hypotension due to autonomic dysfunction. N Engl J Med 304:1473, 1981.

181. Kendrick WW, Scott JW, Jousse AT et al: Reflex sweating and hypertension in traumatic transverse myelitis. Treat Serv Bull (Ottawa) 8:437, 1953.

182. Klee GG, Hay ID: Biochemical thyroid function testing. Mayo Clin Proc 69:469, 1994.

183. Amino N, Mori H, Iwatani Y et al: High prevalence of transient postpartum thyrotoxicosis and hypothyroidism. N Engl J Med 306:849, 1982.

184. Channick BJ, Adlin EV, Marks AD et al: Hyperthyroidism and mitral-valve prolapse. N Engl J Med 305:497, 1981.

185. Forfar JC, Miller HC, Toft AD: Occult thyrotoxicosis: A correctable cause of "idiopathic" atrial fibrillation. Am J Cardiol 44:9, 1979.

186. Feek CM, Sawers JSA, Irvine WJ et al: Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. N Engl J Med 302:883, 1980.

187. Forfar JC, Muir AL, Sawers SA, Toft AD: Abnormal left ventricular function in hyperthyroidism: Evidence for a possible reversible cardiomyopathy. N Engl J Med 307:1165, 1982.

188. Tenerz A, Forberg R, Jansson R: Is a more active attitude warranted in patients with subclinical thyrotoxicosis? J Intern Med 228:229, 1990.

189. Eriksson M, Rubenfeld S, Garber AJ et al: Propranolol does not prevent thyroid storm. N Engl J Med 296:263, 1977.

190. Saxe AW, Brown E, Hamburger SW: Thyroid and parathyroid surgery performed with patient under regional anesthesia. Surgery 103:415, 1988.

191. Roizen MF, Becker CE: Thyroid storm: A review of cases at University of California, San Francisco. Calif Med 115(4):5, 1971.

192. Murkin JM: Anesthesia and hypothyroidism: A review of thyroxine physiology, pharmacology, and anesthetic implications. Anesth Analg 61:371, 1982.

193. Sawin CT, Castelli WP, Hershman JM et al: The aging thyroid: Thyroid deficiency in the Framingham Study. Arch Intern Med 145:1386, 1985.

194. Weinberg AD, Brennan MD, Gorman CA et al: Outcome of anesthesia and surgery in hypothyroid patients. Arch Intern Med 143:893, 1983.

195. Vanderpump MPJ, Tunbridge WMG, French JM et al: The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham Survey. Clin Endocrinol 43:55, 1995.

196. Zwillich CW, Pierson DJ, Hofeldt FD et al: Ventilatory control in myxedema and hypothyroidism. N Engl J Med 292:662, 1975.

197. Bough EW, Crowley WF, Ridgway EC et al: Myocardial function in hypothyroidism. Relation to disease severity and response to treatment. Arch Intern Med 138:1476, 1978.

198. Babad AA, Eger EI II: The effects of hyperthyroidism and hypothyroidism on halothane and oxygen requirements in dogs. Anesthesiology 29:1087, 1968.

199. Levin HD: Compromise therapy in the patient with angina pectoris and hypothyroidism: A clinical assessment. Am J Med 69:411, 1980.

200. Hensel P, Roizen MF: Patients with disorders of parathyroid function. Anesthesiol Clin North Am 5:287, 1987.

201. Kao PC, van Heerden JA, Taylor RL: Intraoperative monitoring of parathyroid procedures by a 15-minute parathyroid hormone immunochemiluminometric assay. Mayo Clin Proc 69:532, 1994.

202. Lang RM, Fellner SK, Neumann A et al: Left ventricular contractility varies directly with blood ionized calcium. Ann Intern Med 108:524, 1988.

203. Rumancik WM, Denlinger JK, Nahrwold ML et al: The QT interval and serum ionized calcium. JAMA 240:366, 1978.

204. Melmed S, Ho K, Klibanski A et al: Clinical review 75: Recent advances in pathogenesis, diagnosis, and management of acromegaly. J Clin Endocrinol Metab 80:3395, 1995.

205. Southwick JP, Katz J: Unusual airway difficulty in the acromegalic patient: Indications for tracheostomy. Anesthesiology 51:72, 1979.

206. Hassan SZ, Matz G, Lawrence AM et al: Laryngeal stenosis in acromegaly: A possible cause of airway difficulties associated with anesthesia. Anesth Analg 55:57, 1976.

207. Campkin TV: Radial artery cannulation: Potential hazard in patients with acromegaly. Anaesthesia 35:1008, 1980.

208. Molitch EM: Pathologic hyperprolactinemia. Endocrinol Metab Clin North Am 21:877, 1992.

209. Rojiani AM, Prineas JW, Cho ES: Protective effect of steroids on electrolyte-induced demyelination. J Neuropathol Exp Neurol 46:495, 1987.

210. Ayus JC, Krothapalli RK, Arieff AI: Changing concepts in the treatment of severe symptomatic hyponatremia: Rapid correction and possible relation to central pontine myelinolysis. Am J Med 78:897, 1985.

211. Robertson GL: Diabetes insipidus. Endocrinol Metab Clin North Am 24:549, 1995.

212. Corliss RJ, McKenna DH, Sialers S et al: Systemic and coronary hemodynamic effects of vasopressin. Am J Med Sci 256:293, 1968.

213. Nikolic G, Singh JB: Cimetidine, vasopressin and chronotropic incompetence. Med J Aust 2:435, 1982.

214. Smithwick RH, Thompson JE: Splanchnicectomy for essential hypertension. JAMA 152:1501, 1953.

215. Brown BR: Anesthesia and essential hypertension. In Hershey SG (ed): ASA Refresher Courses in Anesthesiology. Vol. 7. Philadelphia, JB Lippincott, 1979, p 41.

216. Sprague HB: The heart in surgery. An analysis of results of surgery on cardiac patients during the past ten years at the Massachusetts General Hospital. Surg Gynecol Obstet 49:54, 1929.

217. Miller RD, Way WL, Eger EI II: The effects of alpha-methyldopa, reserpine, and guanethidine on minimum alveolar anesthetic requirement (MAC). Anesthesiology 29:1153, 1968.

218. Veterans Administration Study on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. JAMA 202:1028, 1967.

219. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. JAMA 213:1143, 1970.

220. Moser M, Hebert P, Hennekens CH: An overview of the metaanalyses of the hypertension treatment trials. Arch Intern Med 151:1277, 1991.

221. Kannel WB: Blood pressure as a cardiovascular risk factor. Prevention and treatment. JAMA 275:1571, 1996.

222. Hypertension Detection and Follow-up Program Cooperative Group: The effect of treatment on mortality in "mild" hypertension. N Engl J Med 307:976, 1982.

223. Multiple Risk Factor Intervention Trial Research Group: Multiple risk factor intervention trial. Risk factor changes and mortality results. JAMA 248:1465, 1982.

224. SHEP Cooperative Study Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). J Am Med Assoc 265:3255, 1991.

225. Curb JD, Pressel SL, Cutler JA et al, for the Systolic Hypertension in the Elderly Program Cooperative Research Group: Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. JAMA 276:1886, 1996.

226. Farnett L, Mulrow CD, Linn WD et al: The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? JAMA 265:489, 1991.

227. Prys-Roberts C, Meloche R, Foex P: Studies of anesthesia in relation to hypertension. I: Cardiovascular responses of treated and untreated patients. Br J Anaesth 43:122, 1971.

228. Goldman L, Caldera DL: Risks of general anesthesia and elective operation in the hypertensive patient. Anesthesiology 50:285, 1979.

229. Bedford RF, Feinstein B: Hospital admission blood pressure: A predictor for hypertension following endotracheal intubation. Anesth Analg 59:367, 1980.

230. Asiddao CB, Donegan JH, Whitesell RC et al: Factors associated with perioperative complications during carotid endarterectomy. Anesth Analg 61:631, 1982.

231. Ellis JE, Drijvers G, Shah MN et al: Topical clonidine fails to reduce postoperative stress response after noncardiac surgery. Anesth Analg 74:S85, 1992.

232. Mangano DT, Browner WS, Hollenberg M et al: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 323:1781, 1990.

233. Stone JG, Foex P, Sear JW et al: Risk of myocardial ischemia during anesthesia in treated and untreated hypertensive patients. Br J Anaesth 61:675, 1988.

234. Wolfsthal SD: The clinical characteristics and perioperative blood pressure lability in hypertensive patients referred for preoperative medical evaluation. Clin Res 37:8034A, 1989.

235. Pasternack PF, Grossi EA, Baumann FG et al: Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. Am J Surg 158:113, 1989.

236. Cohen MM, Duncan PG: Physical Status Score and trends in anesthetic complications. J Clin Epidemiol 41:83, 1988.

237. Fleiss JL: Statistical Methods for Rates and Proportions. New York, John Wiley & Sons, 1973, p 178.

238. Charlson ME, MacKenzie R, Gold JP et al: Postoperative renal dysfunction can be predicted. Surg Gynecol Obstet 169:303, 1989.

239. Charlson ME, MacKenzie CR, Gold JP et al: Preoperative characteristics predicting intraoperative hypotension and hypertension among hypertensives and diabetics undergoing noncardiac surgery. Ann Surg 212:66, 1990.

240. Charlson ME, MacKenzie CR, Gold JP et al: Risk for postoperative congestive heart failure. Surg Gynecol Obstet 172:95, 1991.

241. Burke AP, Farb A, Malcom GT et al: Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 336:1276, 1997.

242. Ayobe MH, Tarazi RC: Reversal of changes in myocardial beta-receptors and inotropic responsiveness with regression of cardiac hypertrophy in renal hypertensive rats (RHR). Circ Res 54:125, 1984.

243. Garraway WM, Whisnant JP: The changing pattern of hypertension and the declining incidence of stroke. JAMA 258:214, 1987.

244. Rutan GH, Kuller LH, Neaton JD et al: Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Intervention Trial. Circulation 77:504, 1988.

245. Okuda S, Onoyama K, Motomura K et al: Effect of acute reduction in blood pressure on renal function of rats with diseased kidneys. Nephron 45:311, 1987.

246. Mayhan WG, Faraci FM, Heistad DD: Disruption of the blood-brain barrier in cerebrum and brain stem during acute hypertension. Am J Physiol 251:H1171, 1986.

247. Croog SH, Levine S, Testa MA et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314:1657, 1986.

248. Materson BJ, Reda DJ, Cushman WC et al: Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. N Engl J Med 328:914, 1993.

249. Schneider AJL, Knoke JD, Zollinger RM Jr et al: Morbidity prediction using pre- and intraoperative data. Anesthesiology 51:4, 1979.

250. Eerola M, Eerola R, Kaukinen S et al: Risk factors in surgical patients with verified preoperative myocardial infarction. Acta Anaesthesiol Scand 24:219, 1980.

251. Mauney FM, Ebert PA, Sabiston DC: Postoperative myocardial infarction: A study of predisposing factors, diagnosis and mortality in a high risk group of surgical patients. Ann Surg 172:497, 1970.

252. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107, 1985.

253. Slogoff S, Keats AS: Further observations on perioperative myocardial ischemia. Anesthesiology 65:539, 1986.

254. Coriat P, Richer C, Douraki T et al: Influence of chronic angiotensin-converting enzyme inhibition in anesthetic induction. Anesthesiology 81:299, 1994.

255. Kuller LH, Shemanski L, Psaty BM et al: Subclinical disease as an independent risk factor for cardiovascular disease. Circulation 92:720, 1995.

256. Lichtor JL, Roizen MF, Lane B, Thisted R: Change in mortality rate for surgical procedures 1979 to 1994 (personal communication).

257. Benchimol A, Harris CL, Desser KB et al: Resting electrocardiogram in major coronary artery disease. JAMA 224:1489, 1973.

258. Tomatis LA, Fierens EE, Verbrugge GP: Evaluation of surgical risk in peripheral vascular disease by coronary angiography: A series of 100 cases. Surgery 71:429, 1972.

259. Hertzer NR, Beven EG, Young JR et al: Coronary artery disease in peripheral vascular patients. A classification of 1000 angiograms and results of surgical management. Ann Surg 199:223, 1984.

260. Hertzer NR, Young JR, Beven EG et al: Late results of coronary bypass in patients with infrarenal aortic aneurysms. The Cleveland Clinic Study. Ann Surg 205:360, 1987.

261. Barnes RW, Liebman PR, Marszalek PB et al: The natural history of asymptomatic carotid disease in patients undergoing cardiovascular surgery. Surgery 90:1075, 1981.

262. Barnes RW, Marszalek PB: Asymptomatic carotid disease in the cardiovascular surgical patient: Is prophylactic endarterectomy necessary? Stroke 12:497, 1981.

263. Operating to prevent stroke (editorial). Lancet 337:1255, 1991.

264. Markus RA, Mack WJ, Azen SP, Hodis HN: Influence of lifestyle modification on atherosclerotic progression determined by ultrasonographic change in the common carotid intima-media thickness. Am J Clin Nutr 65:1000, 1997.

265. Ropper AH, Wechsler LR, Wilson LS: Carotid bruit and the risk of stroke in elective surgery. N Engl J Med 307:1388, 1982.

266. Heyman A, Wilkinson WE, Heyden S et al: Risk of stroke in asymptomatic persons with cervical arterial bruits. A population study in Evans County, Georgia. N Engl J Med 302:838, 1980.

267. Reed GL, Singer DE, Picard EH, DeSanctis RW: Stroke following coronary-artery bypass surgery: A case-control estimate of the risk from carotid bruits. N Engl J Med 319:1246, 1988.

268. Morise AP, Dalal JN, Duval RD: Value of a simple measure of estrogen status for improving the diagnosis of coronary artery disease in women. Am J Med 94:491, 1993.

269. Roizen MF: Preoperative Test Selection Program. Software Manual of Version 2.15L. Pleasanton, CA, Nellcor, 1994.

270. Deanfield JE, Maseri A, Selwyn AP et al: Myocardial ischaemia during daily life in patients with stable angina: Its relation to symptoms and heart rate changes. Lancet 8353:753, 1983.

271. McCann RL, Clements FM: Silent myocardial ischemia in patients undergoing peripheral vascular surgery: Incidence and association with perioperative cardiac morbidity and mortality. J Vasc Surg 9:583, 1989.

272. Rabkin SE, Horne JM: Preoperative electrocardiography: Effect of new abnormalities on clinical decisions. Can Med Assoc J 128:146, 1983.

273. Apfelbaum J, Robinson D, Murray WJ et al: An automated method to validate preoperative test selection: First results of a multicenter study (abstract). Anesthesiology 71:A928, 1989.

274. Biller J, Saver JL: Transient ischemic attacks--populations and prognosis. Mayo Clin Proc 69:493, 1994.

275. Goldschlager N: Use of the treadmill test in the diagnosis of coronary artery disease in patients with chest pain. Ann Intern Med 97:383, 1982.

276. Weiner DA, Ryan TJ, McCabe CH et al: Exercise stress testing. Correlations among history of angina, ST-segment response and prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 301:230, 1979.

277. Leng GC, Fowkes FGR, Lee AJ et al: Use of ankle brachial pressure index to predict cardiovascular events and death: A cohort study. BMJ 313:1440, 1996.

278. Kornitzer M, Dramaix M, Sobolksi J et al: Ankle/arm pressure index in asymptomatic middle-aged males: An independent predictor of ten-year coronary heart disease mortality. Angiology 46:211, 1995.

279. Older P, Smith R, Courtney P, Hone R: Preoperative evaluation of cardiac failure and ischemia in elderldy patients by cardiopulmonary exercise testing. Chest 104:701, 1993.

280. Older P, Hall H: The role of cardiopulmonary exercise testing for preoperative evaluation of the elderly. In Wasserman K (ed): Exercise Gas Exchange in Heart Disease. Armonk, New York, Futura Publishing Co., 1996, p 421.

281. Russell LB, Carson JL, Taylor WC et al: Modeling all-cause mortality: Projections of the impact of smoking cessation based on the NHEFS. Am J Public Health 88:630, 1998.

282. Vita AJ, Terry RB, Hubert HB, Fries JF: Aging, health risks, and cumulative disability. N Engl J Med 338:1035, 1998.

283. Arkins R, Smessaert AA, Hicks RG: Mortality and morbidity in surgical patients with coronary artery disease. JAMA 190:485, 1964.

284. Topkins MJ, Artusio JF: Myocardial infarction and surgery: A five year study. Anesth Analg 43:715, 1964.

285. Fraser JG, Ramachandran PR, Davis HS: Anesthesia and recent myocardial infarction. JAMA 199:318, 1972.

286. Tarhan S, Moffitt EA, Taylor WF et al: Myocardial infarction after general anesthesia. JAMA 199:318, 1972.

287. Sapala JA, Ponka JL, Duvernow WFC: Operative and nonoperative risks in the cardiac patient. J Am Geriatr Soc 23:529, 1975.

288. Steen PA, Tinker JH, Tarhan S: Myocardial reinfarction after anesthesia and surgery. JAMA 239:2566, 1976.

289. Goldman L, Caldera DL, Southwick FS et al: Cardiac risk factors and complications in noncardiac surgery. Medicine (Baltimore) 57:357, 1978.

290. Schoeppel SL, Wilkinson C, Waters J et al: Effects of myocardial infarction on perioperative cardiac complications. Anesth Analg 62:493, 1983.

291. Knapp RB, Topkins MJ, Artusio JF Jr: The cerebrovascular accident and coronary occlusion in anesthesia. JAMA 182:332, 1962.

292. von Knorring J: Postoperative myocardial infarction: A prospective study in a risk group of surgical patients. Surgery 90:55, 1981.

293. Shah KB, Kleinman BS, Sami H et al: Reevaluation of perioperative myocardial infarction in patients with prior myocardial infarction undergoing noncardiac operations. Anesth Analg 71:231, 1990.

294. Plumlee JE, Boettner RB: Myocardial infarction during and following anesthesia and operation. South Med J 65:886, 1972.

295. Becker RC, Underwood DA: Myocardial infarction in patients undergoing noncardiac surgery. Cleve Clin J Med 54:25, 1987.

296. Eagle KA, Boucher CA: Cardiac risk of noncardiac surgery. N Engl J Med 321:1330, 1989.

297. Detsky AS, Abrams HB, McLaughlin JR et al: Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1:211, 1986.

298. Gerson MC, Hurst JM, Hertzberg VS et al: Cardiac prognosis in noncardiac surgery. Ann Intern Med 103:832, 1985.

299. Berlauk JF, Abrams JH, Gilmour IJ et al: Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: A prospective, randomized clinical trial. Ann Surg 214:289, 1991.

300. American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization: Practice guidelines for pulmonary catheterization. A report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Anesthesiology 78:380, 1993.

301. Backer CL, Tinker JH, Robertson DM et al: Myocardial reinfarction following local anesthesia for ophthalmic surgery. Anesth Analg 59:257, 1980.

302. Wolf GL, Lynch S, Berlin I: Intra-ocular surgery with general anesthesia. Arch Ophthalmol 93:323, 1975.

303. Roizen MF: Anesthesia goals for surgery to relieve or prevent visceral ischemia. In Roizen MF (ed): Anesthesia for Vascular Surgery. New York, Churchill Livingstone, 1990, p 171.

304. Eagle KA, Coley CM, Newell JB et al: Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 110:859, 1989.

305. Boucher CA, Brewster DC, Darling RC et al: Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. N Engl J Med 312:389, 1985.

306. Raby KE, Goldman L, Creager MA et al: Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. N Engl J Med 321:1296, 1989.

307. Lette J, Waters D, Lapointe J et al: Usefulness of the severity and extent of reversible perfusion defects during thallium-dipyridamole imaging for cardiac risk assessment before noncardiac surgery. Am J Cardiol 64:276, 1989.

308. Mantha S, Roizen MF, Barnard J et al: Relative effectiveness of preoperative noninvasive cardiac evaluation tests on predicting adverse cardiac outcomes following vascular surgery: A meta-analysis. Anesth Analg 79:422, 1994.

309. Bruschke AVG, Proudfit WL, Sones FM: Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5-9 years. Circulation 47:1147, 1973.

310. Mahar LJ, Steen PA, Tinker JH et al: Perioperative myocardial infarction in patients with coronary artery disease with and without aorta-coronary bypass grafts. J Thorac Cardiovasc Surg 76:533, 1978.

311. Kennedy JW, Kaiser GC, Fisher LD et al: Clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery (CASS). Circulation 63:793, 1981.

312. Mangano DT, Hedgcock MW, Wisneski JA: Noninvasive prediction of ventricular dysfunction: Coronary artery disease. Anesthesiology 57:A21, 1982.

313. Fletcher JP, Antico VF, Gruenwald S, Kershaw LZ: Dipyridamole-thallium scan for screening of coronary artery disease prior to vascular surgery. J Cardiovasc Surg 29:666, 1988.

314. Lane RT, Sawada SG, Segar DS et al: Dobutamine stress echocardiography for assessment of cardiac risk before noncardiac surgery. Am J Cardiol 68:976, 1991.

315. Lalka SG, Sawada SG, Dalsing MC et al: Dobutamine stress echocardiography as a predictor of cardiac events associated with aortic surgery. J Vasc Surg 15:831, 1992.

316. Davila-Roman VG, Waggoner AD, Sicard GA et al: Dobutamine stress echocardiography predicts surgical outcome in patients with aortic aneurysm and peripheral vascular disease. J Am Coll Cardiol 21:957, 1993.

317. Poldermans D, Fioretti PM, Forster T et al: Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular surgery. Circulation 87:1506, 1993.

318. Higgins TL, Estafanous FG, Loop FD et al: Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. JAMA 267:2344, 1992.

319. Jeffrey CC, Kunsman J, Cullen DJ, Brewster DC: A prospective evaluation of cardiac risk index. Anesthesiology 58:462, 1984.

320. Bittner V, Weiner DH, Yusuf S et al, for the SOLVD investigators: Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. JAMA 270:1702, 1993.

321. Benson H, McCallie DP: Angina pectoris and the placebo effect. N Engl J Med 300:1424, 1979.

322. Takaro T, Hultgren HN, Lipton MJ et al: The VA cooperative randomized study of surgery for coronary arterial occlusive disease. II: Subgroup with significant left main lesions. Circulation 54(suppl 3):III-107, 1976.

323. Reed RC, Murphy ML, Hultgren HN et al: Survival of men treated for chronic stable angina pectoris. A cooperative randomized study. J Thorac Cardiovasc Surg 75:1, 1978.

324. Crawford ES, Morris GC, Howell JF et al: Operative risk in patients with previous coronary artery bypass. Ann Thorac Surg 26:215, 1978.

325. Huber KC, Evans MA, Bresnahan JF et al: Outcome of noncardiac operations in patients with severe coronary artery disease successfully treated preoperatively with coronary angioplasty. Mayo Clin Proc 67:15, 1992.

326. Rihal CS, Eagle KA, Mickel MC et al: Surgical therapy for coronary artery disease among patients with combined coronary artery and peripheral vascular disease. Circulation 91:46, 1995.

327. Hultgren HN, Pfeifer JF, Angell WW et al: Unstable comparison of medical and surgical management. Am J Cardiol 39:734, 1977.

328. Santos AL, Gelperin A: Surgical mortality in the elderly. J Am Geriatr Soc 23:42, 1975.

329. Driscoll AC, Hobika JH, Etsten BE et al: Clinically unrecognized myocardial infarction following surgery. N Engl J Med 264:633, 1961.

330. O'Keefe JH, Shub C, Rettke SR: Risk of noncardiac surgical procedures in patients with aortic stenosis. Mayo Clin Proc 64:400, 1989.

331. Smith JS, Roizen MF, Cahalan MK, Benefiel DJ: Does anesthetic technique make a difference? Augmentation of systolic blood pressure during carotid endarterectomy: Effects of phenylephrine versus light anesthesia and of isoflurane versus halothane on the incidence of myocardial ischemia. Anesthesiology 69:846, 1988.

332. Riles TS, Kopelman I, Imparato AM: Myocardial infarction following carotid endarterectomy: A review of 683 operations. Surgery 85:249, 1979.

333. Frank SM, Fleisher LA, Breslow MJ et al: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. JAMA 277:1127, 1997.

334. Erikssen G, Thaulow E, Sandvik L et al: Haematocrit: A predictor of cardiovascular mortality? J Intern Med 234:493, 1993.

335. Nelson AH, Fleisher LA, Rosenbaum SH: Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. Crit Care Med 21:860, 1993.

336. Fleisher LA, Skolnick ED, Holyrod KJ, Lehmann HP: Coronary artery revascularization before abdominal aortic aneurysm surgery: A decision analytic approach. Anesth Analg 79:661, 1994.

337. Roy WL, Edelist G, Gilbert B: Myocardial ischemia during noncardiac surgical procedures in patients with coronary-artery disease. Anesthesiology 54:393, 1979.

338. Kaplan JA, King SB: The precordial electrocardiographic lead (V_5) in patients who have coronary-artery disease. Anesthesiology 45:570, 1976.

339. Christopherson R, Frank S, Norris E et al: Low postoperative hematocrit is associated with cardiac ischemia in high-risk patients (abstract). Anesthesiology 75(suppl 3A):A99, 1991.

340. Nelson AH, Fleisher LA, Rosenbaum SH: The relationship between postoperative anemia and cardiac morbidity in high risk vascular patients in the ICU. Crit Care Med 21:860, 1993.

341. Roizen MF, Beaupre PN, Alpert RA et al: Monitoring with twodimensional transesophageal echocardiography. J Vasc Surg 1:300, 1984.

342. Rehman A, Zalos G, Andrews NP et al: Blood pressure changes during transient myocardial ischemia: Insights into mechanisms. J Am Coll Cardiol 30:1249, 1997.

343. Naylor CD, Sibbald WJ, Sprung CL et al: Pulmonary artery catheterization: Can there be an integrated strategy for guideline development and research promotion? JAMA 269:2407, 1993.

344. Lembo NJ, Dell'Italia LJ, Crawford MH, O'Rourke RA: Bedside diagnosis of systolic murmurs. N Engl J Med 318:1572, 1988.

345. Etchells E, Bell C, Robb K: Does this patient have an abnormal systolic murmur? JAMA 277:564, 1997.

346. Hollinger I: Diseases of the cardiovascular system. In Katz R, Steward D (eds): Anesthesia and Uncommon Pediatric Diseases. Philadelphia, WB Saunders, 1993, p 93.

347. Noonan JA: Association of congenital heart disease with syndromes or other defects. Pediatr Clin North Am 25:797, 1978.

348. Devereux RB: Recent developments in the diagnosis and management of mitral valve prolapse. Curr Opin Cardiol 10:107, 1995.

349. Bor DH, Himmelstein DU: Endocarditis prophylaxis for patients with mitral valve prolapse: A quantitative analysis. Am J Med 76:711, 1984.

350. Clemens JD, Horwitz RI, Jaffe CC et al: A controlled evaluation of the risk of bacterial endocarditis in persons with mitral-valve prolapse. N Engl J Med 307:776, 1982.

351. Berry FA, Blanketbaker WL, Ball CG: A comparison of bacteremia occurring with nasotracheal and orotracheal intubation. Anesth Analg 52:873, 1973.

352. Shull HJ, Greene BM, Allen SD et al: Bacteremia with upper gastrointestinal endoscopy. Ann Intern Med 83:212, 1975.

353. Dajani AS, Bisno AL, Chung KJ et al: Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 264:2919, 1990.

354. Antimicrobial prophylaxis in surgery. Med Lett Drugs Ther 35:91, 1993.

355. Tinker JH, Tarhan S: Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses: Observations in 180 operations. JAMA 239:738, 1978.

356. Kearon C, Hirsh J: Management of anticoagulation before and after elective surgery. N Engl J Med 336:1506, 1997.

357. Edelson RN, Chernik NL, Posner JB: Spinal subdural hematomas complicating lumbar puncture. Arch Neurol 31:134, 1974.

358. Reddy NB, Rao TLK: Regional anesthesia for vascular surgery of the lower extremities: Considerations regarding anticoagulation. In Roizen MF (ed): Anesthesia for Vascular Surgery. New York, Churchill Livingstone, 1990, p 367.

359. Brem SS, Hafler DA, Van Uitert RL et al: Spinal subarachnoid hematoma: A hazard of lumbar puncture resulting in reversible paraplegia. N Engl J Med 303:1020, 1981.

360. Owens EL, Kasten GW, Hessel EA II: Spinal subarachnoid hematoma after lumbar puncture and heparinization: A case report, review of the literature, and discussion of anesthetic implications. Anesth Analg 65:1201, 1986.

361. Rao TLK, El-Etr AA: Anticoagulation following placement of epidural and subarachnoid catheters: An evaluation of neurologic sequelae. Anesthesiology 55:618, 1981.

362. Bargon HC, LaRaja RD, Rossi G, Atkinson D: Continuous epidural analgesia in the heparinized vascular surgical patient: A retrospective review of 912 patients. J Vasc Surg 6:144, 1987.

363. Onishchuk JL, Carlsson C: Epidural hematoma associated with epidural anesthesia: Complications of anticoagulant therapy. Anesthesiology 77:1221, 1992.

364. Odoom JA, Sih IL: Epidural analgesia and anticoagulant therapy: Experience with one thousand cases of continuous epidurals. Anaesthesia 38:254, 1983.

365. Locke GE, Giorgio AJ, Biggers SL Jr et al: Acute spinal epidural hematoma secondary to aspirin-induced prolonged bleeding. Surg Neurol 5:293, 1976.

366. Frame JN, Mulvey KP, Phares JC, Anderson MJ: Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. Ann Intern Med 111:946, 1989.

367. Tekkok IH, Cataltepe O, Tahta K, Bertan V: Extradural haematoma after continuous extradural anaesthesia. Br J Anaesth 67:112, 1991.

368. Waldman SD, Feldstein GS, Waldman HJ et al: Caudal administration of morphine sulphate in anticoagulated and thrombocytopenic patients. Anesth Analg 66:267, 1987.

369. Horlocker TT, Wedel DJ, Offord KP: Does preoperative antiplatelet therapy increase the risk of hemorrhagic complications associated with regional anesthesia? Anesth Analg 70:631, 1990.

370. Macdonald R: Aspirin and extradural blocks. Br J Anaesth 66:1, 1991.

371. Amrein PC, Ellman L, Harris WH: Aspirin-induced prolongation of bleeding and perioperative blood loss. JAMA 245:1825, 1981.

372. Vandermeulen EP, Van Aken H, Vermylen J: Anticoagulants and spinal-epidural anesthesia. Anesth Analg 79:1165, 1994.

373. International Multicentre Trial: Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Lancet 2:45, 1975.

374. Consensus Conference: Prevention of venous thrombosis and pulmonary embolism. JAMA 256:744, 1988.

375. Collins R, Scrimgeour A, Yusuf S, Peto R: Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. N Engl J Med 318:1162, 1988.

376. Gallus A, Raman K, Darby T: Venous thrombosis after elective hip replacement--the influence of preventive intermittent calf compression and on surgical technique. Br J Surg 70:17, 1983.

377. Lutz DJ, Noller KL, Spittell JA Jr et al: Pregnancy and its complications following cardiac valve prostheses. Am J Obstet Gynecol 131:460, 1978.

378. Smith ND, Raizada V, Abrams J: Auscultation of the normally functioning prosthetic valve. Ann Intern Med 95:594, 1981.

379. Pastore JO, Yurchak PM, Janis KM et al: The risk of advanced heart block in surgical patients with right bundle branch block and left axis deviation. Circulation 57:677, 1978.

380. Berg GR, Kotler MN: The significance of bilateral bundle branch block in the preoperative patient. A retrospective electrocardiographic and clinical study in 30 patients. Chest 59:62, 1971.

381. Rooney S-M, Goldiner PL, Muss E: Relationship of right bundle-branch block and marked left axis deviation to complete heart block during general anesthesia. Anesthesiology 44:64, 1976.

382. Kunstadt D, Punja M, Cagin N et al: Bifascicular block: A clinical and electrophysiologic study. Am Heart J 86:173, 1973.

383. Venkataraman K, Madias JE, Hood WB Jr: Indications for prophylactic preoperative insertion of pacemakers in patients with right bundle branch block and left anterior hemiblock. Chest 68:501, 1975.

384. Gauss A, Hubner C, Radermacher P et al: Perioperative risk of bradyarrhythmias in patients with asymptomatic chronic bifascicular block or left bundle branch block. Does an additional first-degree atrioventricular block make any difference? Anesthesiology 88:679, 1998.

385. Ruskin JN: Catheter ablation for supraventricular tachycardia. N Engl J Med 324:1660, 1991.

386. Kelly JS, Royster RL: Noninvasive transcutaneous cardiac pacing. Anesth Analg 69:229, 1989.

387. Risk SC, Brandon D, D'Ambra MN et al: Indications for the use of pacing pulmonary artery catheters in cardiac surgery. J Cardiothorac Vasc Anesth 6:275, 1992.

388. Ruskin JN, DiMarco JP, Garan H: Out-of-hospital cardiac arrest. Electrophysiologic observations and selection of long-term antiarrhythmic therapy. N Engl J Med 303:607, 1980.

389. Prystowsky EN: Diagnosis and management of the pre-excitation syndromes. Curr Probl Cardiol 13:225, 1988.

390. McAnulty JH, Rahimtoola SH, Murphy E et al: Natural history of "high-risk" bundle-branch block. Final report of a prospective study. N Engl J Med 307:137, 1982.

391. Rose MR, Koski G: Anesthesia in patients with Wolff-Parkinson-White syndrome (abstract). Anesthesiology 69:A146, 1988.

392. Sadowski AR, Moyers JR: Anesthetic management of the Wolff-Parkinson-White syndrome. Anesthesiology 51:553, 1979.

393. Furman S: Rate-modulated pacing. Circulation 82:1081, 1990.

394. Shapiro WA, Roizen MF, Singleton MA et al: Intraoperative pacemaker complications. Anesthesiology 63:319, 1985.

395. Thiagarajah S, Azar I, Agres M et al: Pacemaker malfunction associated with positive-pressure ventilation. Anesthesiology 58:565, 1983.

396. Anthonisen NR, Connet JE, Kiley JP et al: Effect of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The lung health study. JAMA 272:1497, 1994.

397. European Respiratory Society: Optimal assessment and management of chronic obstructive pulmonary disease (COPD). Eur Respir J 8:1398, 1995.

398. Holleman DR Jr, Simel DL: Does the clinical examination predict airflow limitation? JAMA 273:313, 1995.

399. Lacasse Y, Guyatt GH, Goldstein RS: The components of a respiratory rehabilitation program: A systematic overview. Chest 111:1077, 1997.

400. Saint S, Bent S, Vittinghoff E, Grady D: Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. JAMA 273:957, 1995.

401. Thompson WH, Nielson CP, Carvalho P et al: Controlled trial of oral prednisone in outpatients with acute COPD exacerbations. Am J Respir Crit Care Med 154:407, 1996.

402. NAEP Expert Panel Report 2: Guidelines for the diagnosis and management of asthma. Public Health Service. US Department of Health and Human Services Publication number 97-4051A, May 1997 (http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm).

403. Cockcroft DW: Management of acute severe asthma. Ann Allergy Asthma Immunol 75:83, 1995.

404. Tinkelman DG, Reed CE, Nelson HS, Offord KP: Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. Pediatrics 92:64, 1993.

405. Dompeling E, van Schayck CP, van Grunsven PM et al: Slowing the deterioration of asthma and chronic obstructive pulmonary disease observed during bronchodilator therapy by adding inhaled corticosteroids. A 4-year prospective study. Ann Intern Med 118:770, 1993.

406. Calligaro KD, Azurin DJ, Dougherty MJ et al: Pulmonary risk factors of elective abdominal aortic surgery. J Vasc Surg 18:914, 1993.

407. Homer CJ: Asthma disease management. N Engl J Med 337:1461, 1997.

408. Sur S, Hunt LW, Crotty TB, Gleich GJ: Sudden-onset fatal asthma. Mayo Clin Proc 69:495, 1994.

409. Skolnick ET, Vomvolakis MA, Buck KA et al: Exposure to environmental tobacco smoke and the risk of adverse respiratory events in children receiving general anesthesia. Anesthesiology 88:1144, 1998.

410. Ballantyne JC, Carr DB, deFerranti S et al: Comparative effects of postoperative analgesic therapies upon respiratory function: Meta-analysis of initial randomized control trials. Anesth Analg 86:598, 1998.

411. Stein M, Cassara EL: Preoperative pulmonary evaluation and therapy for surgery patients. JAMA 211:787, 1970.

412. Collins CD, Darke CS, Knowelden J: Chest complications after upper abdominal surgery: Their anticipation and prevention. Br Med J 1:401, 1968.

413. Warner MA, Offerd KP, Warner ME et al: Role of preoperative cessation of smoking and other factors in postoperative pulmonary complications: A blinded prospective study of coronary artery bypass patients. Mayo Clin Proc 64:609, 1989.

414. Robinson K, Conroy RM, Mulcahy R: When does the risk of acute coronary heart disease in ex-smokers fall to that in non-smokers? A retrospective study of patients admitted to hospital with a

first episode of myocardial infarction or unstable angina. Br Heart J 62:16, 1989.

415. Rosenberg L, Kaufman D, Helmrich S, Shapiro S: The risk of myocardial infarction after quitting smoking in men under 55 years of age. N Engl J Med 313:1511, 1985.

416. Gordon T, Kannell WB, McGee D: Death and coronary attacks in men after giving up smoking: A report from the Framingham Study. Lancet 2:1345, 1974.

417. Ernst E, Matrai A: Abstention from chronic cigarette smoking normalizes blood rheology. Atherosclerosis 64:75, 1987.

418. Celli BR, Rodriguez KS, Snider GL: A controlled trial of intermittent positive pressure breathing, incentive spirometry, and deep breathing exercises in preventing pulmonary complications after abdominal surgery. Am Rev Respir Dis 130:12, 1984.

419. Bartlett RH, Brennan ML, Gazzaniga AB et al: Studies on the pathogenesis and prevention of postoperative pulmonary complications. Surg Gynecol Obstet 137:925, 1973.

420. Lyager S, Wernberg M, Rajani N et al: Can postoperative pulmonary conditions be improved by treatment with the Bartlett-Edwards incentive spirometer after upper abdominal surgery? Acta Anaesthesiol Scand 23:312, 1979.

421. Tisi GM: Preoperative evaluation of pulmonary function validity, indications, benefits. Am Rev Respir Dis 119:293, 1979.

422. Hedley-Whyte J, Burgess GE, Feeley TW et al: Critical analysis of preventive measures. In Applied Physiology of Respiratory Care. Boston, Little, Brown, 1976, p 119.

423. Pontoppidan H: Mechanical aids to lung expansion in nonintubated surgical patients. Am Rev Respir Dis 122:109, 1980.

424. Celli BR: What is the value of preoperative pulmonary function testing? Med Clin North Am 77:309, 1993.

425. Graham WGB, Bradley DA: Efficacy of chest physiotherapy in the resolution of pneumonia. N Engl J Med 299:624, 1978.

426. Connors AF Jr, Hammon WE, Martin RJ et al: Chest physical therapy. The immediate effect on oxygenation in acutely ill patients. Chest 78:559, 1980.

427. Cottrell JE, Siker ES: Preoperative intermittent positive-pressure breathing therapy in patients with chronic obstructive lung disease: Effect on postoperative pulmonary complications. Anesth Analg 52:258, 1973.

428. Forthman HJ, Shepard A: Postoperative pulmonary complications. South Med J 62:1198, 1969.

429. Boushy SF, Billing DM, North LB et al: Clinical course related to preoperative pulmonary function in patients with bronchogenic carcinoma. Chest 59:383, 1971.

430. Mittman C: Assessment of operative risk in thoracic surgery. Am Rev Respir Dis 84:197, 1961.

431. Reichel J: Assessment of operative risk of pneumonectomy. Chest 62:570, 1972.

432. Fischl MA, Pitchenik A, Gardner LB: An index predicting relapse and need for hospitalization in patients with acute bronchial asthma. N Engl J Med 305:783, 1981.

433. Wong DH, Weber EC, Schell MJ et al: Factors associated with postoperative pulmonary complications in patients with severe COPD. Anesth Analg 80:276, 1995.

434. Wiener-Kronish JP, Matthay MA: Preoperative evaluation. In Murray J, Nadel J (eds): Textbook of Respiratory Medicine. Philadelphia, WB Saunders, 1988, p 683.

435. Roukema JA, Carol EJ, Prins JG: The prevention of pulmonary complications after upper abdominal surgery in patients with noncompromised pulmonary status. Arch Surg 123:30, 1988.

436. Hall WJ, Douglas RG, Hyde RW et al: Pulmonary mechanics after uncomplicated influenza A infection. Am Rev Respir Dis 113:141, 1976.

437. Green GM, Jakab GJ, Low RB et al: Defense mechanisms of the respiratory membrane. Am Rev Respir Dis 115:479, 1977.

438. Tait AR, Knight PR: The effects of general anesthesia on upper respiratory tract infections in children. Anesthesiology 67:930, 1987.

439. DeSoto H, Patel RI, Soliman IE, Hannallah RS: Changes in oxygen saturation following general anesthesia in children with upper respiratory infection signs and symptoms undergoing otolaryngological procedures. Anesthesiology 68:276, 1988.

440. Fennelly ME, Hall GM: Anaesthesia and upper respiratory tract infections--a non-existent hazard? Br J Anaesth 64:535, 1990.

441. Cohen MM, Cameron CB: Should you cancel the operation when a child has an upper respiratory tract infection? Anesth Analg 72:282, 1991.

442. Jacoby DB, Hirshman CA: General anesthesia in patients with viral respiratory infections: An unsound sleep? Anesthesiology 74:969, 1991.

443. Kinouchi K, Tanigami H, Tashiro C et al: Duration of apnea in anesthetized infants and children required for desaturation of hemoglobin to 95%. The influence of upper respiratory infection. Anesthesiology 77:1105, 1992.

444. Fishman AP: Cardiac asthma--a fresh look at an old wheeze. N Engl J Med 320:1346, 1989.

445. Latimer RG, Dickman M, Day WC et al: Ventilatory patterns and pulmonary complications after upper abdominal surgery determined by preoperative and postoperative computerized spirometry and blood gas analysis. Am J Surg 122:622, 1971.

446. Tarhan S, Moffitt EA, Sessler AD et al: Risk of anesthesia and surgery in patients with chronic bronchitis and chronic obstructive pulmonary disease. Surgery 74:720, 1973.

447. Newman KB, Mason UG III, Schmaling KB: Clinical features of vocal cord dysfunction. Am J Respir Crit Care Med 152:1382, 1995.

448. Knudson J: Duration of hypoxemia after uncomplicated upper abdominal and thoracoabdominal operations. Anaesthesia 25:372, 1970.

449. Boysen PG, Block AJ, Moulder PV: Relationship between preoperative pulmonary function tests and complications after thoracotomy. Surg Gynecol Obstet 152:813, 1981.

450. Furguson MK, Little L, Rizzo L et al: Diffusing capacity predicts morbidity and mortality after pulmonary resection. J Thorac Cardiovasc Surg 96:894, 1988.

451. Markos J, Mullan BP, Hillman DR et al: Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis 139:902, 1989.

452. Selzer A, Walter RM: Adequacy of preoperative digitalis therapy in controlling ventricular rate in postoperative atrial fibrillation. Circulation 34:119, 1966.

453. Ginsberg JS: Management of venous thromboembolism. N Engl J Med 335:1816, 1996.

454. Neiwoehner DE, Kleinerman J, Rice DB: Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 291:755, 1974.

455. Matthay RA, Niederman MS, Wiedemann HP: Cardiovascular pulmonary interaction in chronic obstructive pulmonary disease with special reference to pathogenesis and management of cor pulmonale. Med Clin North Am 74:571, 1990.

456. Dorinsky PM, Gadek JE: Mechanisms of non-pulmonary organ failure in ARDS. Chest 96:885, 1989.

457. Domino KB, Wetstein L, Glasser SA et al: Influence of mixed venous oxygen tension (PvO_2) on blood flow to atelectatic lung. Anesthesiology 59:428, 1983.

458. Combs DL, O'Brien RJ, Geiter LJ: USPHS tuberculosis short-course chemotherapy trial 21: Effectiveness, toxicity, and acceptability. The report of final results. Ann Intern Med 112:397, 1990.

459. Niederman MS, Craven DE, Fein AM, Schultz DE: Pneumonia in the critically ill hospitalized patient. Chest 97:170, 1990.

460. Murray JF, Mills J: Pulmonary infectious complications of human immunodeficiency virus infection: Parts 1 and 2. Am Rev Respir Dis 5:1356, 1582, 1990.

461. Skerrett SJ, Niederman MS, Fein AM: Respiratory infections and acute lung injury in systemic illness. Clin Chest Med 10:469, 1989.

462. Barnes PJ: A new approach to the treatment of asthma. N Engl J Med 321:1517, 1989.

463. Settipane GA, Dudupakkam RK: Aspirin intolerance. III: Subtypes, familial occurrence and cross reactivity with tartrazine. J Allergy Clin Immunol 56:215, 1975.

464. Crystal RG, Bitterman PB, Rennard SI et al: Interstitial lung disease of unknown cause: Disorders characterized by chronic inflammation of the lower respiratory tract. N Engl J Med 310:154, 1984.

465. Mathieson JR, Mayo JR, Staples CA, Muller NL: Chronic diffuse infiltrative lung disease: Comparison of diagnostic accuracy of CT and chest radiography. Radiology 171:111, 1989.

466. Cooper JAD (ed): Drug-induced pulmonary disease. Clin Chest Med 11:1, 1990.

467. Williams DE, Pairolero PC, Davis CS et al: Survival of patients surgically treated for stage I lung cancer. J Thorac Cardiovasc Surg 82:70, 1981.

468. Woodring JH: Lung cancer. Radiol Clin North Am 28:489, 1990.

469. Aisner J: Extensive-disease small-cell lung cancer: The thrill of victory; the agony of defeat. J Clin Oncol 14:658, 1996.

470. Levy JH, Roizen MF, Morris JM: Anaphylactic and anaphylactoid reactions: A review. Spine 11:282, 1986.

471. Kemp SF, Lockey RF, Wolf BL, Lieberman P: Anaphylaxis. A review of 266 cases. Arch Intern Med 155:1749, 1995.

472. Watkins J: Anaphylactoid reactions to I.V. substances. Br J Anaesth 51:51, 1979.

473. Smith PL, Kagey-Sobotka A, Bleecker ER et al: Physiologic manifestations of human anaphylaxis. J Clin Invest 66:1072, 1980.

474. Delage C, Irey NS: Anaphylactic deaths: A clinicopathologic study of 43 cases. J Forensic Sci 17:525, 1972.

475. Bettman MA: Radiographic contrast agents--a perspective. N Engl J Med 317:891, 1987.

476. Chenoweth DE, Cooper SW, Hugli TE et al: Complement activation during cardiopulmonary bypass. N Engl J Med 304:497, 1981.

477. Craddock PR, Fehr J, Brigham KL et al: Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. N Engl J Med 296:769, 1977.

478. Roizen MF, Rodgers GM, Valone FH et al: Anaphylactoid reactions to vascular graft material presenting with vasodilation and subsequent disseminated intravascular coagulation. Anesthesiology 71:331, 1989.

479. Swanson MC, Bubak ME, Hunt LW et al: Quantification of occupational latex aeroallergens in a medical center. J Allergy Clin Immunol 94:445, 1994.

480. Rosow CE, Moss J, Philbin DM et al: Histamine release during morphine and fentanyl anesthesia. Anesthesiology 56:93, 1982.

481. Moss J, Rosow CE, Savarese JJ et al: Role of histamine in the hypotensive action of *d*-tubocurarine in humans. Anesthesiology 55:19, 1981.

482. Millbern SM, Bell SD: Prevention of anaphylaxis to contrast media. Anesthesiology 50:56, 1979.

483. Moss J, McDermott DJ, Thisted RA et al: Anaphylactic/anaphylactoid reactions in response to Chymodiactin (chymopapain). Anesth Analg 63:253, 1984.

484. Philbin DM, Moss J, Akins CW et al: The use of H_1 and H_2 histamine antagonists with morphine anesthesia: A double-blind study. Anesthesiology 55:292, 1981.

485. Halevy S, Altura BT, Altura BM: Pathophysiological basis for the use of steroids in the treatment of shock and trauma. Klin Wochenschr 60:1021, 1982.

486. Ring J, Messmer K: Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1:466, 1977.

487. Milner LV, Butcher K: Transfusion reactions reported after transfusion of red blood cells and of whole blood. Transfusion 18:493, 1978.

488. Barach EM, Nowak RM, Lee TG et al: Epinephrine for treatment of anaphylactic shock. JAMA 251:2118, 1984.

489. Toogood JH: Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol 81:1, 1988.

490. Van Arsdel PP Jr, Larson EB: Diagnostic tests for patients with suspected allergic disease. Ann Intern Med 110:304, 1989.

491. Del Pizzo A: Hereditary angioneurotic edema. Anesthesiol Rev 5:41, 1978.

492. Hosea SW, Santaella ML, Brown EJ et al: Long-term therapy of hereditary angioedema with danazol. Ann Intern Med 93:809, 1982.

493. Oxelius V-A, Laurell A-B, Lindquist B et al: IgG subclasses in selective IgA deficiency. Importance of IgG2-IgA deficiency. N Engl J Med 304:1476, 1981.

494. Fauci AS, Rosenberg SA, Sherwin SA et al: Immunomodulators in clinical medicine. Ann Intern Med 106:421, 1987.

495. Levy DE, Caronna JJ, Singer BH et al: Predicting outcome from hypoxic-ischemic coma. JAMA 253:1420, 1985.

496. Plum F, Posner JB: The Diagnosis of Stupor and Coma, 3rd ed. Philadelphia, FA Davis, 1980.

497. Lowenstein DH, Massa SM, Rowbotham MC et al: Acute neurologic and psychiatric complications associated with cocaine abuse. Am J Med 83:841, 1987.

498. Barry PP, Moskowitz MA: The diagnosis of reversible dementia in the elderly: A critical review. Arch Intern Med 148:1914, 1988.

499. Boguosslavsky J, Meineberg O: Eye-movement disorders in brain-stem and cerebellar stoke. Arch Neurol 44:141, 1987.

500. Drugs for epilepsy. Med Lett Drugs Ther 37:37, 1995.

501. Montouris GD, Fenichel GM, McLain LW Jr: The pregnant epileptic: A review and recommendations. Arch Neurol 36:601, 1979.

502. Shaner DM, McCurdy SA, Herring MO et al: Treatment of status epilepticus: A prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. Neurology 38:202, 1988.

503. Joas TA, Stevens WC, Eger EI II: Electroencephalographic seizure activity in dogs during anesthesia. Br J Anaesth 43:739, 1971.

504. Buzello W, Jantzen K, Scholler KL: The influence of Ethrane on the electro- and pentylene-tetrazol-convulsions in mice. Anaesthesist 24:118, 1975.

505. Wollman H, Smith AL, Neigh JL et al: Cerebral blood flow and oxygen

consumption in man during electroencephalographic seizure patterns associated with Ethrane anesthesia. In Brock M, Fieschi C et al (eds): Cerebral Blood Flow. Berlin, Springer-Verlag, 1969, p 246.

506. Opitz A, Brechts B, Stenzel E: Enflurane anaesthesia for epileptic patients. Anaesthesist 26:329, 1977.

507. Schuchat A, Robinson K, Wenger JD et al: Bacterial meningitis in the United States in 1995. N Engl J Med 337:970, 1997.

508. Parkinson Study Group: Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATA TOP patients requiring levodopa. Ann Neurol 39:37, 1996.

509. Goetz CG, Olanow CW, Koller WC et al: Multicenter study of autologous adrenal medullary transplantation to the corpus striatum in patients with advanced Parkinson's disease. N Engl J Med 320:337, 1989.

510. Mets B: Acute dystonia after alfentanil in untreated Parkinson's disease. Anesth Analg 72:557, 1991.

511. Muzzi DA, Black S, Cucchiara RF: The lack of effect of succinylcholine on serum potassium in patients with Parkinson's disease. Anesthesiology 71:322, 1989.

512. Schwartz AJ, Wollman H: Anesthetic considerations for patients on chronic drug therapy: L-Dopa, monamine oxidase inhibitors, tricyclic antidepressants and propranolol. In Hershey SG (ed): ASA Refresh- er Courses in Anesthesiology. Vol. 4. Philadelphia, JB Lippincott, 1976, p 99.

513. Ngai SH: Parkinsonism, levodopa, and anesthesia. Anesthesiology 37:344, 1972.

514. Wiklund RA, Ngai SH: Rigidity, and pulmonary edema after Innovar in a patient on levodopa therapy: Report of a case. Anesthesiology 35:545, 1971.

515. Skoog I, Nilsson J, Palmertz B et al: A population-based study of dementia in 85-year-olds. N Engl J Med 328:153, 1993.

516. Clarfield AM: The reversible dementias: Do they reverse? Ann Intern Med 109:476, 1988.

517. Ross GW, Abbott RD, Petrovitch H et al: Frequency and characteristics of silent dementia among elderly Japanese-American men. The Honolulu-Asia Aging Study. JAMA 277:800, 1997.

518. Snowdon DA, Greiner LH, Mortimer JA et al: Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 277:813, 1997.

519. Hemmelgarn B, Suissa S, Huang A et al: Benzodiazepine use and the risk of motor vehicle crash in the elderly. JAMA 278:27, 1997.

520. Mozkowitz MA: Basic mechanisms in vascular headache. Neurol Clin 8:801, 1990.

521. Michel P, Henry P, Letenneur L et al: Diagnostic screen for assessment of IHS criteria for migraine by general practitioners. Cephalalgia 12:54, 1993.

522. MacIntyre PD, Bhargava B, Hogg KJ et al: Effect of subcutaneous sumatriptan, a selective 5HT-1 agonist, on the systemic, pulmonary, and coronary circulation. Circulation 87:401, 1993.

523. Shadick NA, Phillips CB, Logigian EL et al: The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Intern Med 121:560, 1994.

524. Ovassapian A, Land P, Schafer MF et al: Anesthetic management for surgical corrections of severe flexion deformity of the cervical spine. Anesthesiology 58:370, 1983.

525. Dahm LS, Dickson JH, Harrison GH: Perioperative and anesthetic management in the patient with scoliosis. Anesthesiol Rev 9:13, 1982.

526. Ferguson RJ, Caplan LR: Cervical spondylitic myelopathy. Neurol Clin 3:373, 1985.

527. Rudick RA, Cohen JA, Weinstock-Guttman B et al: Management of multiple sclerosis. N Engl J Med 337:1604, 1997.

528. Baskett PJF, Armstrong R: Anaesthetic problems in multiple sclerosis: Are certain agents contraindicated? Anaesthesia 25:397, 1970.

529. McKhann GM, Griffin JW, Cornblath DR et al: Plasmapheresis and Guillain-Barre syndrome: Analysis of prognostic factors and the effect of plasmapheresis. Ann Neurol 23:347, 1988.

530. Ancoli-Israel S, Klauber MR, Stepnowsky C et al: Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med 152:1946, 1995.

531. Ostermeier AM, Roizen MF, Hautkappe M et al: Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. Anesth Analg 85:452, 1997.

532. Aldrich MS: Narcolepsy. N Engl J Med 323:389, 1990.

533. Cyr MG, Wartman SA: The effectiveness of routine screening questions in the detection of alcoholism. JAMA 259:51, 1988.

534. Toh B-H, van Driel IR, Gleeson PA: Pernicious anemia. N Engl J Med 337:1441, 1997.

535. Jensen NF, Fiddler DS, Striepe V: Anesthetic considerations in porphyrias. Anesth Analg 80:591, 1995.

536. Kantor G, Rolbin SH: Acute intermittent porphyria and Caesarean delivery. Can J Anaesth 39:282, 1992.

537. Meissner PN, Harrison GG, Hift RJ: Propofol as an I.V. anaesthetic induction agent in variegate porphyria. Br J Anaesth 66:60, 1991.

538. McNeill MJ, Bennet A: Use of regional anaesthesia in a patient with acute porphyria. Br J Anaesth 64:371, 1990.

539. Drachman DB: Myasthenia gravis. N Engl J Med 330:1797, 1994.

540. d'Empaire G, Hoaglin DC, Perlo VP et al: Effect of prethymectomy plasma exchange on postoperative respiratory function in myasthenia gravis. J Thorac Cardiovasc Surg 89:592, 1985.

541. Eisenkraft JB, Book WJ, Mann SM et al: Resistance to succinylcholine in myasthenia gravis: A dose response study. Anesthesiology 69:760, 1988.

542. Miller RD: Myasthenia gravis. In Wilkinson PL, Ham J, Miller RD (eds): Clinical Anesthesia. Case Selections from the University of California, San Francisco. St Louis, CV Mosby, 1980, p 148.

543. Eisenkraft JB, Papatestas AE, Kahn CH et al: Predicting the need for postoperative mechanical ventilation in myasthenia gravis. Anesthesiology 65:79, 1986.

544. Miller J, Lee C: Muscle diseases. In Katz J, Benumof J, Kadis LB (eds): Anesthesia and Uncommon Diseases: Pathophysiologic and Clinical Correlations, 3rd ed. Philadelphia, WB Saunders,

1989, p 621.

545. Small S, Ali HH, Lennon VA et al: Anesthesia for unsuspected Lambert-Eaton myasthenic syndrome with autoantibodies and occult small cell lung carcinoma. Anesthesiology 76:142, 1992.

546. Lema G, Urzua J, Moran S, Canessa R: Successful anesthetic management of a patient with hypokalemic familial periodic paralysis undergoing cardiac surgery. Anesthesiology 74:373, 1991.

547. Ashwood EM, Russell WJ, Burrow DD: Hyperkalaemic periodic paralysis. Anaesthesia 47:579, 1992.

548. Gutmann DH, Fischbeck KH: Molecular biology of Duchenne and Becker's muscular dystrophy: Clinical applications. Ann Neurol 26:189, 1989.

549. Smith CL, Bush GH: Anesthesia and progressive muscular dystrophy. Br J Anaesth 57:1113, 1985.

550. Schwartz L, Rockoff MA, Koka BV: Masseter spasm with anesthesia: Incidence and implications. Anesthesiology 61:772, 1984.

551. Rosenberg H: Trismus is not trivial (editorial). Anesthesiology 67:453, 1987.

552. Pueschel SM, Scola FH: Atlantoaxial instability in individuals with Down syndrome: Epidemiologic, radiographic, and clinical studies. Pediatrics 80:55, 1987.

553. Morray JP, MacGillivray R, Duker G: Increased perioperative risk following repair of congenital heart disease in Down's syndrome. Anesthesiology 65:221, 1986.

554. Kobel M, Creighton RE, Steward DJ: Anaesthetic considerations in Down's syndrome: Experience with 100 patients and a review of the literature. Can J Anaesth 29:593, 1982.

555. Bedford RF, Morris L, Jane JA: Intracranial hypertension during surgery for supratentorial tumor: Correlation with preoperative computed tomography scans. Anesth Analg 61:430, 1982.

556. Allen GS, Ahn HS, Preziosi TJ et al: Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med 308:619, 1983.

557. Ramirez-Lassepas M, Quinones MR: Heparin therapy for stroke: Hemorrhagic complications and risk factors for intracerebral hemorrhage. Neurology 34:114, 1984.

558. Rem JA, Hachinski VC, Boughner DR, Barnett HJ: Value of cardiac monitoring and echocardiography in TIA and stroke patients. Stroke 16:950, 1985.

559. Drugs for psychiatric disorders. Med Lett Drugs Ther 39:33, 1997.

560. Appel GB, Neu HC: The nephrotoxicity of antimicrobial agents. N Engl J Med 296:663, 722, 784, 1977.

561. Fischer RP, Polk HC Jr: Changing etiologic patterns of renal insufficiency in surgical patients (editorial). Surg Gynecol Obstet 140:85, 1975.

562. Better OS, Stein JH: Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. N Engl J Med 322:825, 1990.

563. Levey AS, Perrone RD, Madias NE: Serum creatinine and renal function. Annu Rev Med 39:465, 1988.

564. Byrick RJ, Rose DK: Pathophysiology and prevention of acute renal failure: The role of the anaesthetist. Can J Anaesth 37:457, 1990.

565. Berns AS: Nephrotoxicity of contrast media. Kidney Int 36:730, 1989.

566. Myers BD, Moran SM: Hemodynamically mediated acute renal failure. N Engl J Med 314:97, 1986.

567. Shusterman N, Strom BL, Murray TG et al: Risk factors and outcome of hospital-acquired acute renal failure: A clinical epidemiologic study. Am J Med 83:65, 1987.

568. Bernard DB: Extrarenal complications of the nephrotic syndrome (clinical conference). Kidney Int 33:1184, 1988.

569. Thadhani R, Pascual M, Bonventre JV: Acute renal failure. N Engl J Med 334:1448, 1996.

570. Aronson S, Thisthelwaite RJ, Walker R et al: Safety and feasibility of renal blood flow determination during surgery with perfusion ultrasonography. Anesth Analg 80:353, 1995.

571. Rao KV, Anderson RC, O'Brien TJ: Factors contributing for improved graft survival in recipients of kidney transplants. Kidney Int 24:210, 1983.

572. Eschbach JW, Kelly MR, Haley NR et al: Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. N Engl J Med 321:158, 1989.

573. Burke GR, Gulyassy PF: Surgery in the patient with renal disease and related electrolyte disorders. Med Clin North Am 63:1191, 1979.

574. Coe FL, Parks JH, Asplin JR: The pathogenesis and treatment of kidney stones. N Engl J Med 327:1141, 1992.

575. Kellen M, Aronson S, Roizen MF et al: Predictive and diagnostic tests of renal failure: A review. Anesth Analg 78:134, 1994.

576. Novis BK, Roizen MF, Aronson S, Thisted RA: Association of preoperative risk factors with postoperative acute renal failure. Anesth Analg 78:143, 1994.

577. Shin B, Mackenzie CF, Helrich M: Creatinine clearance for early detection of posttraumatic renal dysfunction. Anesthesiology 64:605, 1986.

578. Rowe JW, Andres R, Tobin JD et al: The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. J Gerontol 31:155, 1976.

579. Koning HM, Koning AJ, Leusink JA: Serious acute renal failure following open heart surgery. Thorac Cardiovasc Surg 33:283, 1985.

580. Kleinknecht D, Ganeval D, Gonzalez-Duque LA et al: Furosemide in acute oliguric renal failure: A controlled trial. Nephron 17:51, 1976.

581. Flancbaum L, Choban PS, Dasta JF: Quantitative effects of low-dose dopamine on urine output in oliguric surgical intensive care unit patients. Crit Care Med 22:61, 1994.

582. Hanley MJ, Davidson K: Prior mannitol and furosemide infusion in a model of ischemic acute renal failure. Am J Physiol 241:F556, 1981.

583. Davis RF, Lappas DG, Kirklin JK et al: Acute oliguria after cardiopulmonary bypass: Renal functional improvement with low-dose dopamine infusion. Crit Care Med 10:852, 1982.

584. Polson RJ, Park GR, Lindop MJ et al: The prevention of renal impairment in patients undergoing orthotopic liver grafting by infusion of low dose dopamine. Anaesthesia 42:15, 1987.

585. Paul MD, Mazer CD, Byrick RJ et al: Influence of mannitol and dopamine on renal function during elective infrarenal aortic clamping in man. Am J Nephrol 6:427, 1986.

586. Crowley K, Clarkson K, Hannon V et al: Diuretics after transurethral prostatectomy: A double-blind controlled trial comparing furosemide and mannitol. Br J Anaesth 65:337, 1990.

587. Alpert RA, Roizen MF, Hamilton WK et al: Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery 95:707, 1984.

588. Dolan MJ, Whipp BJ, Davidson WD et al: Hypopnea associated with acetate hemodialysis: Carbon dioxide-flow-dependent ventilation. N Engl J Med 305:72, 1981.

589. Roth S, Kuperberg JP: Adverse responses following intraoperative administration of orthoclone OKT3. Anesth Analg 62:822, 1989.

590. Myers BD, Sibley R, Newton L et al: The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int 33:590, 1988.

591. Bennett WM, Aronoff GR, Morrison G et al: Drug prescribing in renal failure: Dosing guidelines for adults. Am J Kidney Dis 3:155, 1983.

592. Rubin AL, Stenzel KH, Reidenberg MM: Symposium on drug action and metabolism in renal failure. Am J Med 62:459, 1977.

593. Bennett WM, Aronoff GR, Golper TA et al: Drug Prescribing in Renal Failure. Dosing Guidelines for Adults, 2nd ed. Philadelphia, American College of Physicians, 1991.

594. Gibson TP: Renal disease and drug metabolism: An overview. Am J Kidney Dis 8:7, 1986.

595. Dawling S, Crome P: Clinical pharmacokinetic considerations in the elderly: An update. Clin Pharmacokinet 17:236, 1989.

596. Keighley MRB: Antibiotics in biliary disease: The relative importance of antibiotic considerations in the bile and serum. Gut 17:495, 1976.

597. Platt R, Zaleznik DF, Hopkins CC et al: Perioperative antibiotic prophylaxis for herniorrhaphy and breast surgery. N Engl J Med 322:153, 1990.

598. Chestnut DH: Spinal anesthesia in the febrile patient. Anesthesiology 76:667, 1992.

599. Rackow EC, Astiz ME: Pathophysiology and treatment of septic shock. JAMA 266:548, 1991.

600. Knaus WA, Wagner DP: Multiple systems organ failure: Epidemiology and prognosis. Crit Care Clin 5:522, 1989.

601. The choice of antibacterial drugs. Med Lett Drugs Ther 38:25, 1996.

602. Shapiro BA, Kacmarek RM, Cane RD, Peruzzi WT et al: Clinical Application of Respiratory Care, 4th ed. St. Louis, Mosby-Year Book, 1991.

603. Shapiro ED, Berg AT, Austrian R et al: The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 325:1453, 1991.

604. Gardner P, Schaffner W: Immunization of adults. N Engl J Med 328:1252, 1993.

605. Brownstein AB, Roizen MF: A compelling rationale for using preoperative visits to complete adult immunizations. J Clin Anesth 10:338, 1998.

606. Schwartz D, Schwartz T, Cooper E, Pullerits J: Anaesthesia and the child with HIV infection. Can J Anaesth 38:626, 1991.

607. Platt R, Polk BF, Murdock B et al: Mortality associated with nosocomial urinary-tract infection. N Engl J Med 307:637, 1982.

608. Albert RK, Condie F: Hand-washing patterns in medical intensive-care units. N Engl J Med 304:1465, 1981.

609. Farber BF, Kaiser DL, Wenzel RP: Relation between surgical volume and incidence of postoperative wound infection. N Engl J Med 305:200, 1981.

610. Gross PA, Neu HC, Aswapokee P et al: Deaths from nosocomial infections: Experience in a university hospital and a community hospital. Am J Med 68:219, 1980.

611. Bryan CS, Reynolds KL: Bacteremic nosocomial pneumonia: Analysis of 172 episodes from a single metropolitan area. Am Rev Respir Dis 129:668, 1984.

612. Maki DG, Botticelli JT, Le Roy ML, Thielke TS: Prospective study of replacing administration sets for intravenous therapy at 48- vs 72-hour intervals: 72 hours is safe and cost-effective. JAMA 258:1771, 1987.

613. Maki DG, Ringer M: Evaluation of dressing regimens for prevention of infection with peripheral intravenous catheters: Gauze, a transparent polyurethane dressing, and an iodophor-transparent dressing. JAMA 258:2396, 1987.

614. Popovic M, Sarngadharan MG, Read E et al: Detection isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 224:497, 1984.

615. Sharara AI, Hunt CM, Hamilton JD: Hepatitis C. Ann Intern Med 125:658, 1996.

616. Hoffnagle JH, Di Bisceglie AM: The treatment of chronic viral hepatitis. N Engl J Med 336:347, 1997.

617. Dodd RY: The risk of transfusion-transmitted infection. N Engl J Med 327:419, 1992.

618. Dworsky ME, Welch K, Cassady G et al: Occupational risk for primary cytomegalovirus infection among pediatric health-care workers. N Engl J Med 309:950, 1983.

619. Buergler JM, Kim R, Thisted RA et al: The risk of human immunodeficiency virus in surgeons, anesthesiologists, and medical students. Anesth Analg 75:118, 1992.

620. Jensen V: The TURP syndrome. Can J Anaesth 38:90, 1991.

621. Ostia JR: The binge-purge syndrome: A common albeit unappreciated cause of acid-base and fluid electrolyte disturbances. South Med J 80:58, 1987.

622. Schrier RW: Pathogenesis of sodium and water retention in highoutput and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (Parts 1 and 2). N Engl J Med 319:1065, 1127, 1988.

623. Arieff AI, Llacki F, Massry SG: Neurologic manifestations and morbidity of hyponatremia: Correlation with brain water and electrolytes. Medicine (Baltimore) 55:121, 1976.

624. Sterns RH: Severe symptomatic hyponatremia: Treatment and outcome. Ann Intern Med 107:656, 1987.

625. Muldowney FP, Williams RT: Clinical disturbances in serum sodium and potassium in relation to alteration in total exchangeable sodium, exchangeable potassium and total body water. Am J Med 35:768, 1963.

626. Surawicz B: Relationship between electrocardiogram and electrolytes. Am Heart J 73:814, 1967.

627. Sack D, Kim ND, Harrison CE Jr: Contractility and subcellular calcium metabolism in chronic potassium deficiency. Am J Physiol 226:756, 1974.

628. Wong KC, Vitez TS: Electrolyte imbalance. Semin Anesth 2:161, 1983.

629. Goggin MJ, Joekes AM: Gas exchange in renal failure. I: Dangers of hyperkalaemia during anaesthesia. Br Med J 2:244, 1971.

630. Busch EH, Ventura HO, Lavie CJ: Heparin-induced hyperkalemia. South Med J 80:1450, 1987.

631. Rimmer JM, Horn JF, Gennari FJ: Hyperkalemia as a complication of drug therapy. Arch Intern Med 147:867, 1987.

632. Don BR, Sebastian A, Cheitlin M et al: Pseudohyperkalemia caused by fist clenching during phlebotomy. N Engl J Med 322:1290, 1990.

633. Kharasch ED, Bowdle TA: Hypokalemia before induction of anesthesia and prevention by beta $_2$ adrenoceptor antagonism. Anesth Analg 72:216, 1991.

634. Allon M, Dunlay R, Copkney C: Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. Ann Intern Med 110:426, 1989.

635. Zinn SE, Fairley HB, Glenn JD: Liver function in patients with mild alcoholic hepatitis, after enflurane, nitrous oxide-narcotic, and spinal anesthesia. Anesth Analg 64:487, 1985.

636. Ellefson RD: Porphyrinogens, porphyrins, and the porphyrias. Mayo Clin Proc 57:454, 1982.

637. Edwards R, Winnie AP, Ramamurthy S: Acute hypocapneic hypokalemia: An iatrogenic anesthetic complication. Anesth Analg 56:786, 1977.

638. Lawson NW, Butler GH, Rat CT: Alkalosis and cardiac arrhythmias. Anesth Analg 52:951, 1973.

639. Adrogue HJ, Madias NE: Management of life-threatening acid-base disorders. First of two parts. N Engl J Med 338:26, 1998.

640. Aldinger KA, Samaan NA: Hypokalemia with hypercalcemia. Prevalence and significance in treatment. Ann Intern Med 87:571, 1977.

641. Wong KC, Kawamura R, Hodges MR et al: Acute intravenous administration of potassium chloride to furosemide pretreated dogs. Can J Anaesth 24:203, 1977.

642. Kawamura R, Wong KC, Hodges MR: Intravenous potassium chloride in hypokalemic dogs pretreated with digoxin. Anesth Analg 57:108, 1978.

643. Kunin AS, Surawicz B, Sims EAH: Decrease in serum potassium concentrations and appearance of cardiac arrhythmias during infusion of potassium with glucose in potassium-depleted patients. N Engl J Med 266:228, 1962.

644. Wilkinson PL, Ham J, Miller RD: Preoperative hyperkalemia and elective surgery. In Wilkinson PL, Ham J, Miller RD (eds): Clinical Anesthesia. Case Selections from the University of California, San Francisco. St Louis, CV Mosby, 1980, p 54.

645. Lawson DH: Adverse reactions to potassium chloride. Q J Med 43:433, 1974.

646. Lawson DH, Hutcheon AW, Jick H: Life threatening drug reactions amongst medical inpatients. Scott Med J 24:127, 1979.

647. Vitez TS, Soper LE, Wong KC, Soper P: Chronic hypokalemia and intraoperative dysrhythmias. Anesthesiology 63:130, 1985.

648. Hirsch IA, Tomlinson DL, Slogoff S, Keats AS: The overstated risk of preoperative hypokalemia. Anesth Analg 67:131, 1988.

649. Dyckner T, Wester PO: Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic treatment. Am Heart J 97:12, 1979.

650. Cohen JD, Neaton JD, Prineas RJ, Daniels KA: Diuretics, serum potassium and ventricular arrhythmias in the multiple risk factor intervention. Am J Cardiol 60:548, 1987.

651. Morganroth J, Michelson EL, Horowitz LN et al: Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 58:408, 1978.

652. Duke M: Thiazide-induced hypokalemia: Association with acute myocardial infarction and ventricular fibrillation. JAMA 239:43, 1978.

653. Holland OB, Nixon JV, Kuhnert L: Diuretic-induced ventricular ectopic activity. Am J Med 70:762, 1981.

654. Tanifuji Y, Eger EI II: Brain sodium, potassium and osmolality: Effect on anesthetic requirement. Anesth Analg 57:404, 1978.

655. Kornbluth A, Sachar DB: Ulcerative colitis practice guidelines in adults. American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 92:204, 1997.

656. Lindor KD, Fleming CR, Ilstrup DM: Preoperative nutritional status and other factors that influence surgical outcome in patients with Crohn's disease. Mayo Clin Proc 60:393, 1985.

657. Kahrilas PJ: Gastroesophageal reflux disease. JAMA 276:983, 1996.

658. Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 26:61, 1965.

659. Antimicrobial prophylaxis. Med Lett Drugs Ther 39:97, 1997.

660. Jain NK, Larson DE, Schroeder KW et al: Antibiotic prophylaxis for percutaneous endoscopic gastrostomy. Ann Intern Med 107:824, 1987.

661. Gorbach SL: Antimicrobial prophylaxis for appendectomy and colorectal surgery. Rev Infect Dis 13(suppl 10):S815, 1991.

662. Peterson WJ: Peptic ulcer--an infectious disease? West J Med 152:167, 1990.

663. Ross AHM, Smith MA, Anderson JR et al: Late mortality after surgery for peptic ulcer. N Engl J Med 307:519, 1982.

664. Longnecker M, Roizen MF: Patients with carcinoid syndrome. Anesthesiol Clin North Am 5:313, 1987.

665. Kvols LK, Moertel CG, O'Connell MJ et al: Treatment of the malignant carcinoid syndrome: Evaluation of a long-acting somatostatin analogue. N Engl J Med 315:663, 1986.

666. Quantrini M, Basilisco G, Conte D et al: Effects of somatostatin infusion in four patients with malignant carcinoid syndrome. Am J Gastroenterol 78:149, 1983.

667. Veall GRQ, Peacock JE, Bax NDS, Reilly CS: Review of the anaesthetic management of 21 patients undergoing laparotomy for carcinoid syndrome. Br J Anaesth 72:335, 1994.

668. Philbin DM, Coggins CH: Plasma antidiuretic hormone levels in cardiac surgical patients during morphine and halothane anesthesia. Anesthesiology 49:95, 1978.

669. Marsh HM, Martin JK Jr, Kvols LK et al: Carcinoid crisis during anesthesia: Successful treatment with a somatostatin analogue. Anesthesiology 66:89, 1987.

670. Watson JT, Badner NH, Ali MJ: The prophylactic use of octreotide in a patient with ovarian carcinoid and valvular heart disease. Can J Anaesth 37:798, 1990.

671. McCrirrick A, Hickman J: Octreotide for carcinoid syndrome. Can J Anaesth 38:339, 1991.

672. Quinlivan JK, Roberts WA: Intraoperative octreotide for refractory carcinoid-induced bronchospasm. Anesth Analg 78:400, 1994.

673. Drossman DA, McKee DC, Sandler RS et al: Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and non-patients with irritable bowel syndrome. Gastroenterology 95:701, 1988.

674. Aitkenhead AR, Robinson S: Influence of morphine and pethidine on the incidence of anastomotic dehiscence after colonic surgery. Br J Anaesth 63:230P, 1989.

675. Wataneeyawech M, Kelly KA Jr: Hepatic diseases, unsuspected before surgery. NY State J Med 75:1278, 1975.

676. Schemel WH: Unexpected hepatic dysfunction found by multiple laboratory screening. Anesth Analg 55:810, 1976.

677. Stevens WC, Eger EI II, Joas TA et al: Comparative toxicity of isoflurane, halothane, fluroxene, and diethyl ether in human volunteers. Can J Anaesth 20:357, 1973.

678. Gelman SI, Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 61:726, 1984.

679. Baden JM, Serra M, Fujinaga M, Mazze RI: Halothane metabolism in cirrhotic rats. Anesthesiology 67:660, 1987.

680. Harville DD, Summerskill WH: Surgery in acute hepatitis--cause and effects. J Am Med Assoc 184:257, 1963.

681. Viegas O, Stoelting RK: LDH_5 changes after cholecystectomy and hysterectomy in patients receiving halothane, enflurane or fentanyl. Anesthesiology 51:556, 1979.

682. Smith AA, Volpitto PP, Gramling ZW et al: Chloroform, halothane and regional anesthesia: A comparative study. Anesth Analg 52:1, 1973.

683. Ronk W: Liver function chemistries after enflurane and narcotic-N_2O anesthesia. AANA J 46:507, 1978.

684. The National Halothane Study, Bunker JP, Forrest WH, Mosteller F et al (eds): A Study of the Possible Association Between Halothane Anesthesia and Postoperative Hepatic Necrosis. Washington, DC, US Government Printing Office, 1969.

685. Shingu K, Eger EI II, Johnson BH et al: Effect of oxygen concentration, hyperthermia, and choice of vendor on anesthetic-induced hepatic injury in rats. Anesth Analg 62:146, 1983.

686. La Mont JT: Postoperative jaundice. Surg Clin North Am 54:637, 1974.

687. Black PM: Predicting the outcome from hypoxic-ischemic coma: Medical and ethical implications. JAMA 254:1215, 1985.

688. Resnick RH, Iber FL, Ishihara AM et al: A controlled study of the therapeutic portacaval shunt. Gastroenterology 67:843, 1974.

689. Green J, Beyar R, Sideman S et al: The "jaundiced heart": A possible explanation for postoperative shock in obstructive jaundice. Surgery 100:14, 1986.

690. Aranha GV, Sontag SJ, Greenlee HB: Cholecystectomy in cirrhotic patients: A formidable operation. Am J Surg 143:55, 1982.

691. Metcalf AMT, Dozois RR, Wolff BG, Beart RW Jr: The surgical risk of colectomy in patients with cirrhosis. Dis Colon Rectum 30:529, 1987.

692. Wright R, Eade OE, Chisholm M et al: Controlled prospective study of the effect on liver function of multiple exposures to halothane. Lancet 6:817, 1975.

693. Trowell J, Peto R, Smith AC: Controlled trial of repeated halothane anaesthetics in patients with carcinoma of the uterine cervix treated with radium. Lancet 1:821, 1975.

694. Allen PJ, Downing JW: A prospective study of hepatocellular function after repeated exposures to halothane or enflurane in women undergoing radium therapy for cervical cancer. Br J Anaesth 49:1035, 1977.

695. Fee JPH, Black GW, Dundee JW et al: A prospective study of liver enzyme and other changes following repeat administration of halothane and enflurane. Br J Anaesth 51:1133, 1979.

696. Moore DH, Benson GD: Prolonged halothane hepatitis: Prompt resolution of severe lesion with corticosteroid therapy. Dig Dis Sci 31:1269, 1986.

697. Hussey AJ, Howie J, Allan LG et al: Impaired hepatocellular integrity during general anaesthesia, as assessed by measurement of plasma glutathione S-transferase. Clin Chim Acta 161:19, 1986.

698. Dykes MHM: Is halothane hepatitis chronic active hepatitis? (editorial). Anesthesiology 46:233, 1977.

699. Brechot C, Nalpas B, Courouce A-M et al: Evidence that hepatitis B virus has a role in liver-cell carcinoma in alcoholic liver disease. N Engl J Med 306:1384, 1982.

700. Sipes I, Brown B: An animal model of hepatotoxicity associated with halothane anesthesia. Anesthesiology 45:622, 1976.

701. Klatskin G, Kimberg DV: Recurrent hepatitis attributable to halothane sensitization in an anesthetist. N Engl J Med 280:515, 1969.

702. Douglas HJ, Eger EI II, Biava CG et al: Hepatic necrosis associated with viral infection after enflurane anesthesia. N Engl J Med 296:553, 1977.

703. Gall EA: Report of the pathology panel: National Halothane Study. Anesthesiology 29:233, 1968.

704. Stoelting RK, Blitt CD, Cohen PJ, Merin RG: Hepatic dysfunction after isoflurane anesthesia. Anesth Analg 66:147, 1987.

705. Plummer JL, Hall PM, Jenner M et al: Effect of treatment with phenobarbitone or isoniazid on hepatotoxicity due to prolonged subanesthetic halothane inhalation. Pharmacol Toxicol 62:74, 1988.

706. Hubbard AK, Roth TP, Gandolfi AJ et al: Halothane hepatitis patients generate an antibody response toward a covalently bound metabolite of halothane. Anesthesiology 68:791, 1988.

707. Farrell G, Prendergast D, Murray M: Halothane hepatitis: detection of constitutional susceptibility factor. N Engl J Med 313:1310, 1985.

708. Lewis JH, Zimmerman HJ, Ishak KG, Mullick FG: Enflurane hepatotoxicity: A clinicopathologic study of 24 cases. Ann Intern Med 98:984, 1983.

709. Stevens CE, Taylor PE, Rubinstein P et al: Safety of the hepatitis B vaccine. N Engl J Med 312:375, 1985.

710. Berry AJ, Isaacson IJ, Hunt D et al: The prevalence of hepatitis B viral markers in anesthesia personnel. Anesthesiology 60:6, 1984.

711. Mulley AG, Silverstein MD, Dienstag JL: Indications for use of hepatitis B vaccine, based on cost-effectiveness analysis. N Engl J Med 307:644, 1982.

712. Naulty JS, Reves JG, Tobey RR et al: Hepatitis and operating room personnel: An approach to diagnosis and management. Anesth Analg 56:360, 1977.

713. Duvaldestin P, Agoston S, Henzel D et al: Pancuronium pharmacokinetics in patients with liver cirrhosis. Br J Anaesth 50:1131, 1978.

714. Orko R, Ailia A, Rosenberg PH: Effect of biliary obstruction on muscle relaxation with vecuronium. Eur J Anaesthesiol 5:9, 1988.

715. Arden JR, Lynam DP, Castagnoli KP et al: Vecuronium in alcoholic liver disease: A pharmacokinetic and pharmacodynamic analysis. Anesthesiology 68:771, 1988.

716. Parker CJR, Hunter JM: Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 62:177, 1989.

717. Swerdlow BN, Holley FO, Maitre PO, Stanski DR: Chronic alcohol intake does not change thiopental anesthetic requirement, pharmacokinetics, or pharmacodynamics. Anesthesiology 72:455, 1990.

718. Johnston RE, Kulp RA, Smith TC: Effects of acute and chronic ethanol administration on isoflurane requirement in mice. Anesth Analg 54:277, 1975.

719. Audet A-M, Goodnough LT: Practice strategies for elective red blood cell transfusion. American College of Physicians. Ann Intern Med 116:403, 1992.

720. Welch HG, Meehan KR, Goodnough LT: Prudent strategies for elective red blood cell transfusion. Ann Intern Med 116:393, 1992.

721. Thomas DJ, Du Boulay GH, Marshall J et al: Effect of hematocrit on cerebral blood flow in man. Lancet 2:941, 1977.

722. Thomas DJ: Whole blood viscosity and cerebral blood flow (editorial). Stroke 13:285, 1982.

723. Crystal GJ, Rooney MW, Salem MR: Myocardial blood flow and oxygen consumption during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. Anesth Analg 67:539, 1988.

724. Heughan C, Grislis G, Hunt TK: The effect of anemia on wound healing. Ann Surg 179:163, 1974.

725. Goodnough LT, Rudnick S, Price TH et al: Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. N Engl J Med 321:1163, 1989.

726. Bunn HF: Pathogenesis and treatment of a sickle cell disease. N Engl J Med 337:762, 1997.

727. Adams RJ, McKie VC, Hsu L et al: Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 339:5, 1998.

728. Platt OS, Thorington BD, Brambella DJ et al: Pain in sickle cell disease: Rates and risk factors. N Engl J Med 325:11, 1991.

729. Vichinsky EP, Haberkern CM, Neumayr L et al: A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. N Engl J Med 333:206, 1995.

730. Dalal FY, Schmidt GB, Bennett EJ et al: Sickle-cell trait: A report of a postoperative neurological complication. Br J Anaesth 46:387, 1974.

731. Oduro KA, Searle JF: Anaesthesia in sickle-cell states: A plea for simplicity. Br Med J 4:596, 1972.

732. Dunn A, Davies A, Eckert G et al: Intraoperative death during caesarean section in a patient with sickle-cell trait. Can J Anaesth 34:67, 1987.

733. Kark JA, Posey DM, Schumaeker IIR, Ruehle CJ: Sickle cell trait as a risk factor for sudden death in physical training. N Engl J Med 317:781, 1987.

734. Homi J, Reynolds J, Skinner A et al: General anesthesia in sickle-cell disease. Br Med J 1:1599, 1979.

735. Bischoff RJ, Williamson A III, Dalali MJ et al: Assessment of the use of transfusion therapy perioperatively in patients with sickle cell hemoglobinopathies. Ann Surg 207:434, 1988.

736. Morrison JC, Wiser WL: The use of prophylactic partial exchange transfusion in pregnancies associated with sickle cell hemoglobinopathy. Obstet Gynecol 48:516, 1976.

737. Morrison JC, Whybrew WD, Bucovaz ET: Use of partial exchange transfusion preoperatively in patients with sickle cell hemoglobinopathies. Am J Obstet Gynecol 132:59, 1978.

738. Lanzkowsky P, Shende A, Karayalcin G et al: Partial exchange transfusion in sickle cell anemia: Use in children with serious complications. Am J Dis Child 132:1206, 1978.

739. Tuck SM, James CE, Brewster EM et al: Prophylactic blood transfusion in maternal sickle cell syndromes. Br J Obstet Gynaecol 94:121, 1987.

740. Beutler E: The common anemias. JAMA 259:2433, 1988.

741. Orr D: Difficult intubation: A hazard in thalassemia. A case report. Br J Anaesth 39:585, 1967.

742. Pootrakul P, Hungsprenges S, Fucharoen S et al: Relation between erythropoiesis and bone metabolism in thalassemia. N Engl J Med 304:1470, 1981.

743. Lux SE, Wolfe LC: Inherited disorders of the red cell membrane skeleton. Pediatr Clin North Am 27:463, 1980.

744. Beutler E: Glucose-6-phosphate dehydrogenase deficiency. N Engl J Med 324:169, 1991.

745. Engelfriet CP, Overbeeke MA, van der Berne AE: Autoimmune hemolytic anemia. Semin Hematol 29:3, 1992.

746. Schilling RF: Is nitrous oxide a dangerous anesthetic for vitamin B_{12} -deficient subjects. JAMA 255:1605, 1986.

747. Beebe DS, Bergen L, Palahniuk RJ: Anesthesia utilizing plasmapheresis and forced air warming in a patient with severe cold agglutinin hemolytic anemia. Anesth Analg 76:1144, 1993.

748. Quesenberg PJ, Schafer AI, Schreiber AD et al: Hematology. In American College of Physicians: Medical Knowledge SelfAssessment. Philadelphia, American College of Physicians, 1991, p 374.

749. Tobias JD, Furman WL: Anesthetic considerations in patients receiving colony-stimulating factors (G-CSF and GM-CSF). Anesthesiology 75:536, 1991.

750. Alavi JB, Root RK, Djerassi I et al: A randomized clinical trial of granulocyte transfusion for infection in acute leukemia. N Engl J Med 296:706, 1977.

751. Gabrilove JL, Jakubowski A, Scher H et al: Effect of granulocyte colony stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. N Engl J Med 318:1414, 1988.

752. Quie PG: The white cells: Use of granulocyte transfusions. Rev Infect Dis 9:189, 1987.

753. Crawford SW, Fisher L: Predictive value of pulmonary function tests before marrow transplantation. Chest 101:1257, 1992.

754. Petrovitch CT: The bleeding patient. In Roizen MF (ed): Anesthesia for Vascular Surgery. New York, Churchill Livingstone, 1990, p 465.

755. Kelton JG: Management of the pregnant patient with idiopathic thrombocytopenic purpura. Ann Intern Med 99:796, 1983.

756. King DJ, Kelton JG: Heparin-associated thrombocytopenia. Ann Intern Med 100:535, 1984.

757. Douzinas EE, Markakis K, Karabinis A et al: Early plasmapheresis in patients with thrombotic thrombocytopenic purpura. Crit Care Med 20:57, 1992.

758. Majerus PW, Miletich JP: Relationships between platelets and coagulation factors in hemostasis. Annu Rev Med 29:41, 1978.

759. Evans BE: Dental treatment for hemophiliacs: Evaluation of dental program (1975-1976) at the Mount Sinai Hospital International Hemophilia Training Center. Mt Sinai J Med 44:409, 1977.

760. Zauber NP, Levin J: Factor IX levels in patients with hemophilia B (Christmas disease) following transfusion with concentrates of factor IX or fresh frozen plasma (FFP). Medicine (Baltimore) 56:213, 1977.

761. Brettler DB, Levine PH: Factor concentrates for treatment of hemophilia: Which one to choose? Blood 73:2067, 1989.

762. Curran JW, Lawrence DN, Jaffe H et al: Acquired immunodeficiency syndrome (AIDS) associated with transfusions. N Engl J Med 310:69, 1984.

763. Safety of therapeutic products used for hemophilia patients. MMWR Morb Mortal Wkly Rep 37:441, 1988.

764. Briere RO: Serum ALT levels: Effect of sex, race, and obesity on unit rejection rate. Transfusion 28:392, 1988.

765. Sloand EM, Pitt E, Klein HG: Safety of the blood supply. JAMA 274:1368, 1995.

766. Preparation of von Willebrand's factor. Med Lett Drugs Ther, June, 1993.

767. Miller RD: Complications of massive blood transfusions. Anesthesiology 39:82, 1973.

768. Sherman LA: Alterations in hemostasis during massive transfusion. In Nusbacher J (ed): Massive Transfusion. Washington, DC, American Association of Blood Banks, 1978, p 51.

769. Lee KF, Manchell J, Rankin JS et al: Immediate versus delayed coronary grafting after streptokinase treatment: Postoperative blood loss and clinical results. J Thorac Cardiovasc Surg 95:216, 1988.

770. Dickman CA, Shedd SA, Spetzler RF et al: Spinal epidural hematoma associated with epidural anesthesia: Complications of systemic heparinization in patients receiving peripheral vascular thrombolytic therapy. Anesthesiology 72:947, 1990.

771. Czer LS, Bateman TM, Gary RJ et al: Treatment of severe platelet dysfunction and hemorrhage after cardiopulmonary bypass: Reduction in blood product usage with desmopressin. J Am Coll Cardiol 9:1139, 1987.

772. Marks RM, Sachar EJ: Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med 78:173, 1973.

773. Brigden ML, Barnett JB: A practical approach to improving pain control in cancer patients. West J Med 146:580, 1987.

774. Vitez TS, Way WL, Miller RD et al: Effect of delta-9tetrahydrocannabinol on cyclopropane MAC in the rat. Anesthesiology 38:525, 1973.

775. Drugs of choice for cancer chemotherapy. Med Lett Drugs Ther 39:21, 1997.

776. Bishop JM: Molecular themes in oncogenesis. Cell 64:235, 1991.

777. Chung F: Cancer, chemotherapy, and anesthesia. Can J Anaesth 29:364, 1982.

778. Goldiner P, Carlon GC, Cvitkovic E et al: Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. Br Med J 1:1664, 1978.

779. Singer MM, Wright F, Stanley LK et al: Oxygen toxicity in man: A prospective study in patients after open-heart surgery. N Engl J Med 283:1473, 1970.

780. LaMantia KR, Glick JH, Marshall BE: Supplemental oxygen does not cause respiratory failure in bleomycin-treated surgical patients. Anesthesiology 60:65, 1984.

781. Matalon S, Harper WV, Nickerson PA, Olszowka J: Intravenous bleomycin does not alter the toxic effects of hyperoxia in rabbits. Anesthesiology 64:614, 1986.

782. Roizen MF: Is a patient's history of food supplement use simply supplementary? J Clin Anesth 10:89, 1998.

783. Weiner N, Taylor P: Neurohumoral transmission and the autonomic nervous system. In Gilman AG, Goodman LS, Rall TW et al (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th ed. New York, Macmillan, 1985, p 66.

784. Lake CR, Chernow B, Feuerstein G, et al: The sympathetic nervous system in man: Its evaluation and the measurement of plasma NE. In Ziegler MG, Lake CR (eds): Norepinephrine. Baltimore, Williams & Wilkins, 1984, p 1.

785. Burn JH, Rand MJ: Actions of sympathomimetic amines on animals treated with reserpine. J Physiol (Lond) 144:314, 1958.

786. Drugs for hypertension. Med Lett Drugs Ther 37:45, 1995.

787. Drugs that cause psychiatric symptoms. Med Lett Drugs Ther 35:65, 1993.

788. Woodside J Jr, Garner L, Bedford RJ et al: Captopril reduces the dose requirement for sodium nitroprusside induced hypotension. Anesthesiology 60:413, 1984.

789. Sethna DH, Gray RJ, Moffitt EA et al: Dobutamine and cardiac oxygen balance in patients following myocardial revascularization. Anesth Analg 61:917, 1982.

790. The Norwegian Multicenter Study Group: Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 304:801, 1981.

791. Frishman WH, Furberg CD, Friedewald WT: beta-Adrenergic blockade for survivors of acute myocardial infarction. N Engl J Med 310:830, 1984.

792. Smulyan H, Weinberg SE, Howanitz PJ: Continuous propranolol infusion following abdominal surgery. JAMA 247:2539, 1982.

793. Slogoff S, Keats AS, Hibbs CW et al: Failure of general anesthesia to potentiate propranolol activity. Anesthesiology 47:504, 1977.

794. Gold MR, Dec GW, Cocca-Spofford DC, Thompson BT: Esmolol and ventilatory function in cardiac patients with COPD. Chest 100:1215, 1991.

795. Tanifuji Y, Eger EI II: Effect of isoproterenol and propranolol on halothane MAC in dogs. Anesth Analg 55:383, 1976.

796. Bloor BC, Flacke WE: Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth Analg 61:741, 1982.

797. Weinger MB, Segal IS, Maze M: Dexmedetomidine, acting through central alpha-2 adrenoceptors, prevents opiate-induced muscle rigidity in the rat. Anesthesiology 71:242, 1989.

798. Ghignone M, Noe C, Calvillo O, Quintin L: Anesthesia for ophthalmic surgery in the elderly: The effects of clonidine on intraocular pressure, perioperative hemodynamics, and anesthetic requirement. Anesthesiology 68:707, 1988.

799. Engelman E, Lipszyc M, Gilbart E et al: Effects of clonidine on anesthetic drug requirements and hemodynamic response during aortic surgery. Anesthesiology 71:178, 1989.

800. Maze M, Tranquilli W: Alpha-2 adrenoreceptor agonists: defining the role in clinical anesthesia. Anesthesiology 74:581, 1991.

801. Segal IS, Jarvis DJ, Duncan SR et al: Clinical efficacy of oraltransdermal clonidine combinations during the perioperative period. Anesthesiology 74:220, 1991.

802. Muzi M, Goff DR, Kampine JP et al: Clonidine reduces sympathetic activity but maintains baroreflex responses in normotensive humans. Anesthesiology 77:864, 1992.

803. Miller RD, Sohn YJ, Matteo RS: Enhancement of *d*-tubocurarine neuromuscular blockade by diuretics in man. Anesthesiology 45:442, 1976.

804. Katz AM: Cardiac ion channels. N Engl J Med 328:1244, 1993.

805. Millard RW, Grupp G, Grupp IL et al: Chronotropic, inotropic, and vasodilator actions of diltiazem, nifedipine, and verapamil. Circ Res 52(suppl I):I-29, 1983.

806. Maze M, Mason DM: Verapamil decreases the MAC for halothane in dogs. Anesth Analg 62:274, 1983.

807. Reves JG, Kissin I, Lell WA et al: Calcium entry blockers: Uses and implications for anesthesiologists. Anesthesiology 57:504, 1982.

808. Hysing ES, Chelly JE, Doursout M-F: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. III: Nicardipine and isoflurane. Anesthesiology 65:385, 1986.

809. Merin RG, Chelly JE, Hysing ES et al: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. IV: Chronically administered oral verapamil and halothane, enflurane, and isoflurane. Anesthesiology 66:140, 1987.

810. Kapur PA, Matarazzo DA, Fung DM, Sullivan KB: The cardiovascular and adrenergic actions of verapamil and diltiazem in combination with propranolol during halothane anesthesia in the dog. Anesthesiology 66:122, 1987.

811. Dale J, Landmark KH, Myhre E: The effects of nifedipine, a calcium antagonist, on platelet function. Am Heart J 105:103, 1983.

812. Zalman F, Perloff JK, Durant NN et al: Acute respiratory failure following intravenous verapamil in Duchenne's muscular dystrophy. Am Heart J 105:510, 1983.

813. Zimpfer M, Fitzal S, Tonzcar L: Verapamil as a hypotensive agent during neuroleptanaesthesia. Br J Anaesth 53:885, 1981.

814. Durant NN, Nguyen N, Katz RL: Potentiation of neuromuscular blockade by verapamil. Anesthesiology 60:298, 1984.

815. Nugent M, Tinker JH, Moyer TP: Verapamil worsens rate of development and hemodynamic effects of acute hyperkalemia in halothane anesthetized dogs: Effects of calcium therapy. Anesthesiology 60:435, 1984.

816. Lalka SG, Rhodes RS, Lina AA et al: Effect of calcium entry and beta blockade during infrarenal aortic clamping. J Surg Res 46:246, 1989.

817. Michaels I, Serrins M, Shier NQ, Barash PG: Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. Anesth Analg 63:1014, 1984.

818. Evans-Prosser CDG: The use of pethidine and morphine in the presence of monoamine oxidase inhibitors. Br J Anaesth 40:279, 1968.

819. Campbell GD: Dangers of monamine oxidase inhibitors. Br Med J 1:750, 1963.

820. Rogers JK, Thornton JA: The interaction between monamine oxidase inhibitors and narcotic analgesics in mice. Br J Pharmacol 36:470, 1969.

821. Sjoqvist F: Psychotropic drugs. 2. Interaction between monoamine oxidase (MAO) inhibitors and other substances. Proc R Soc Med 58:967, 1965.

822. Monoamine oxidase inhibitors for depression. Med Lett Drugs Ther 31:11, 1989.

823. Drugs for psychiatric disorders. Med Lett Drugs Ther 33:43, 1991.

824. Roizen MF: Monoamine oxidase inhibitors: Are we condemned to relive history, or is history no longer relevant? J Clin Anesth 2:293, 1990.

825. Noble WH, Baker A: MAO inhibitors and coronary artery surgery: A patient death. Can J Anaesth 39:1061, 1992.

826. Wells DG, Bjorksten AR: Monoamine oxidase inhibitors revisited. Can J Anaesth 36:64, 1989.

827. Hirshman CA, Linderman KS: Anesthesia and monoamine oxidase inhibitors. JAMA 261:3407, 1989.

828. Stack CG, Rogers P, Linter SPK: Monoamine oxidase inhibitors and anaesthesia: A review. Br J Anaesth 60:222, 1988.

829. El-Ganzouri AR, Ivankovich AD, Braverman B, McCarthy R: Monoamine oxidase inhibitors: Should they be discontinued preoperatively? Anesth Analg 64:592, 1985.

830. Ebrahim ZY, O'Hara JF, Borden L, Tetzlaff J: Monoamine oxidase inhibitors and elective surgery. Cleve Clin J Med 60:129, 1993.

831. Edwards RE, Miller RD, Roizen MF et al: Cardiac effects of imipramine and pancuronium during halothane and enflurane anesthesia. Anesthesiology 50:421, 1979.

832. Veith RC, Raskind MA, Caldwell JH et al: Cardiovascular effects of tricyclic antidepressants in depressed patients with chronic heart disease. N Engl J Med 306:954, 1982.

833. Richelson E, El-Fakahany E: Changes in the sensitivity of receptors for neurotransmitters and the actions of some psychotherapeutic drugs. Mayo Clin Proc 57:576, 1982.

834. Martin BA, Kramer PM: Clinical significance of the interaction between lithium and a neuromuscular blocker. Am J Psychiatry 139:1326, 1982.

835. Johnston RR, Way WL, Miller RD: Alteration of anesthetic requirements by amphetamine. Anesthesiology 36:357, 1972.

836. Stoelting RK, Creasser CW, Martz RC: Effect of cocaine administration on halothane MAC in dogs. Anesth Analg 54:422, 1975.

837. Katz RL, Bigger JT: Cardiac arrhythmias during anesthesia and operation. Anesthesiology 33:193, 1970.

838. Joas TA, Stevens WC: Comparison of the arrhythmic doses of epinephrine during Forane, halothane and enflurane anesthesia in dogs. Anesthesiology 35:48, 1971.

839. Johnston RR, Eger EI II, Wilson C: A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man. Anesth Analg 55:709, 1976.

840. Horrigan RW, Eger EI II, Wilson CB: Epinephrine-induced arrhythmias during enflurane anesthesia in man: A nonlinear doseresponse relationship and dose-dependent protection from lidocaine. Anesth Analg 57:547, 1978.

841. Hirshman CA, Bergman NA: Halothane and enflurane protect against bronchospasm in an asthma dog model. Anesth Analg 57:629, 1978.

842. Shnider SM, Papper EM: Anesthesia for the asthmatic patient. Anesthesiology 22:886, 1961.

843. Marcus ML, Skelton CL, Graver LE et al: Effects of theophylline on myocardial mechanics. Am J Physiol 222:1361, 1972.

844. Westfall DP, Flemming WW: Sensitivity changes in the dog heart to norepinephrine, calcium and aminophylline resulting from pretreatment with reserpine. J Pharmacol Exp Ther 159:98, 1968.

845. Rall TW, West TC: The potentiation of cardiac inotropic responses to norepinephrine by theophylline. J Pharmacol Exp Ther 139:269, 1963.

846. Horwitz LN, Spear JF, Moore EN et al: Effect of aminophylline on the threshold for initiating ventricular fibrillation during respiratory failure. Am J Cardiol 35:376, 1975.

847. Mitenko PA, Ogilvie RI: Pharmacokinetics of intravenous theophylline. Clin Pharmacol Ther 14:509, 1973.

848. Piafsky KM, Ogilvie RI: Dosage of theophylline in bronchial asthma. N Engl J Med 292:1218, 1975.

849. Hunt SN, Jusko WJ, Yurchak AM: Effect of smoking on theophylline disposition. Clin Pharmacol Ther 19:546, 1975.

850. Takaori M, Loehning RW: Ventricular arrhythmias induced by aminophylline during halothane anaesthesia in dogs. Can J Anaesth 14:79, 1967.

851. Takaori M, Loehning RW: Ventricular arrhythmias during halothane anaesthesia: Effect of isoproterenol, aminophylline, and ephedrine. Can J Anaesth 12:275, 1965.

852. Roizen MF, Stevens WC: Multiform ventricular tachycardia due to the interaction of aminophylline and halothane. Anesth Analg 57:738, 1978.

853. Stirt JA, Berger JM, Sullivan SF: Lack of arrhythmogenicity of isoflurane following administration of aminophylline in dogs. Anesth Analg 62:568, 1983.

854. Drugs for cardiac arrhythmias. Med Lett Drugs Ther 38:75, 1996.

855. Harrah MD, Way WL, Katzung BG: The interaction of *d*tubocurarine with antiarrhythmic drugs. Anesthesiology 33:406, 1970.

856. Telivuo L, Katz RL: The effects of modern intravenous local anesthetics on respiration during partial neuromuscular block in man. Anaesthesia 25:30, 1970.

857. Miller RD, Way WL, Katzung BG: The potentiation of neuromuscular blocking agents by quinidine. Anesthesiology 28:1036, 1967.

858. Pittinger CB, Eryasa Y, Adamson R: Antibiotic-induced paralysis. Anesth Analg 49:487, 1970.

859. Singh YN, Harvey AL, Marshall IG: Antibiotic induced-paralysis of the mouse phrenic nerve-hemidiaphragm preparation, and reversibility by calcium and by neostigmine. Anesthesiology 48:418, 1978.

860. Pittinger CB, Adamson R: Antibiotic blockade of neuromuscular function. Annu Rev Pharmacol 12:169, 1972.

861. Becker LD, Miller RD: Clindamycin enhances a non-depolarizing neuromuscular blockade. Anesthesiology 45:84, 1976.

862. Snavely SR, Hodges GR: The neurotoxicity of antibacterial agents. Ann Intern Med 101:92, 1984.

863. McIndewar IC, Marshall RJ: Interactions between the neuromuscular blocking drug Org NC45 and some anaesthetic, analgesic and antimicrobial agents. Br J Anaesth 53:785, 1981.

864. Navalgund AA, Alifimoff JK, Jakymec AJ, Bleyaert AL: Amiodarone-induced sinus arrest successfully treated with ephedrine and isoproterenol. Anesth Analg 65:414, 1986.

865. Kannan R, Nademane K, Hendrickson JA et al: Amiodarone kinetics after oral doses. Clin Pharmacol Ther 31:438, 1982.

866. Rice SA, Sbordone L, Mazzo RI: Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following isoniazid administration. Anesthesiology 53:489, 1980.

867. Beller GA, Smith TW, Abelmann WH et al: Digitalis intoxication. N Engl J Med 284:989, 1971.

868. Ritchie AJ, Danton M, Gibbons JRP: Prophylactic digitalisation in pulmonary surgery. Thorax 47:41, 1992.

869. Morrow DH: Anesthesia and digitalis toxicity. VI. Effect of barbiturates and halothane on digoxin toxicity. Anesth Analg 49:305, 1970.

870. Pratila MG, Pratilas V: Anesthetic agents and cardiac electromechanical activity. Anesthesiology 49:338, 1978.

871. Logic JR, Morrow DH: The effect of halothane on ventricular automaticity. Anesthesiology 36:107, 1972.

872. Ivankovich AD, Miletich DJ, Grossman RK et al: The effect of enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether on ouabain tolerance in the dog. Anesth Analg 55:360, 1976.

873. Ali N, Dais K, Banks T, Sheikh M: Titrated electrical cardioversion in patients on digoxin. Clin Cardiol 5:417, 1982.

874. Adverse systemic effects from ophthalmic drugs. Med Lett Drugs Ther 24:53, 1982.

875. Pantuck EJ, Pantuck CB: Cholinesterases and anticholinesterases. In Katz RL (ed): Muscle Relaxants. Amsterdam, Excerpta Medica, 1975, p 143.

876. Ghonelm MM, Long JP: The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 32:23, 1970.

877. Del Castillo J, Engback L: The nature of neuromuscular block produced by magnesium. J Physiol (Lond) 124:370, 1954.

878. Feely J, Wilkinson GR, McAllister CB et al: Increased toxicity and reduced clearance of lidocaine by cimetidine. Ann Intern Med 96:592, 1982.

879. Lam AM, Parkin JA: Cimetidine and prolonged post-operative somnolence. Can J Anaesth 28:450, 1981.

880. Vessey MD, Doll R, Fairbairn AS et al: Postoperative thromboembolism and the use of oral contraceptives. Br Med J 3:123, 1970.

881. Greene GR, Sartwell PE: Oral contraceptive use in patients with thromboembolism following surgery, trauma, or infection. Am J Public Health 62:680, 1972.

882. Interruption of a drug regimen before anesthesia. Med Lett Drugs Ther 16:19, 1974.

883. Wyld R, Nimmo WS: Do patients fasting before and after surgery receive their prescribed drug treatment? Br Med J 296:744, 1988.

884. Lesar TS, Briceland LL, Delcoure K et al: Medication prescribing errors in a teaching hospital. JAMA 263:2329, 1990.

885. Halsey MJ: Drug interactions in anaesthesia. Br J Anaesth 59:112, 1987.

886. Update: Drugs in breast milk. Med Lett Drugs Ther 21:21, 1979.

887. Goldman L, Caldera DL, Nussbaum SR et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845, 1977.

888. Wright RA, Clemente R, Wathen R: Diabetic gastroparesis: An abnormality of gastric emptying of solids. Am J Med Sci 289:240, 1985.

889. Starker PM, Group FE, Askanazi J et al: Serum albumin levels as an index of nutritional support. Surgery 91:194, 1982.

890. Rihal CS, Eagle KA, Mickel MC et al: Surgical therapy for coronary artery disease among patients with combined coronary artery disease and peripheral vascular disease. Circulation 91:46, 1995.

891. Epstein SE, Palmeri ST, Patterson RE: Evaluation of patients after acute myocardial infarction. Indications for cardiac catheterization and surgical intervention. N Engl J Med 307:1487, 1982.

892. Tosone SR, Reves JG, Kissin I et al: Hemodynamic responses to nifedipine in dogs anesthetized with halothane. Anesth Analg 62:903, 1983.

/das/book/view/29494766/875/273.html

Chapter 26 - Patient Positioning

Roy F. Cucchiara
Ronald J. Faust

INTRODUCTION: GOALS OF POSITIONING FOR THE SURGICAL PATIENT

In general, the goal of surgical positioning is to facilitate the surgeon's technical approach while balancing risk factors. Surgical techniques have been expanded by the flexibility provided by anesthesia methodology, so that new areas of the body have become accessible and new positions have been developed. All surgical positions carry some degree of position-related risk; these risks are increased in the anesthetized patient, who cannot make the clinician aware of compromised positions. The goal of providing the best surgical exposure is always balanced by the need to minimize the risk to the patient.

PHYSIOLOGIC EFFECTS OF CHANGE IN POSITION FROM VERTICAL TO HORIZONTAL IN HUMANS

Body responses to alterations in position are in response to gravity. Most of the changes are related to gravitational effects on blood and its distribution within the venous, pulmonary, and arterial systems. There are also important effects on pulmonary mechanics and perfusion, again related to gravity.

Cardiovascular System

There is evidence that changes in blood volume occur as we change from erect to supine. Some of these are demonstrable within minutes, [1] whereas others are associated with long-term bed rest. For most purposes, the redistribution of blood volume within the vascular system that is caused by position changes is more important. In the erect position, there is opportunity for considerable increase in transmural vascular pressure in the lower extremities because of the hydrostatic effects of the columns of blood. This increase is limited by increased pressure in the tissue surrounding the vessels, which is due to muscle tone and contraction required to maintain the erect position, and by venous valves. Even with this compensation, clinically there is considerable blood volume or capacity within the lower-extremity vascular bed. [2]

A complex system of reflexes in both the venous and the arterial systems maintains blood pressure during changes in position. Although these reflexes work in concert, anesthesia can blunt the response of selected limbs of the system, thereby altering the final response in either direction. The venous atrial reflexes are responses both to stretching of the atrial wall and to autonomic nervous influences. Arterial pressor reflexes are more directly related to autonomic response to baroreceptors in the aortic arch and the carotid sinus. Changes in position alone do not alter the responsiveness of these reflexes, but other factors, including drugs and age, are important in this alteration of response.

Cardiac output tends to increase immediately on assumption of the supine position. Venous blood from the lower body flows back to the heart, stretching the atrial wall, and stroke volume increases. If contractility and arterial tone remained constant, arterial pressure would rise. Baroreceptor impulses travel afferently from the aorta via the vagus nerve and from the carotid sinus via the glossopharyngeal nerve to the medulla. Increased efferent parasympathetic and decreased efferent sympathetic activity change the parasympathetic/sympathetic balance, which causes decreased heart rate, stroke volume, and contractility and thereby results in little change in blood pressure. [3]

Pulmonary System

During spontaneous ventilation in the erect position, the primary force of inspiration is the downward movement of the diaphragm. In the supine position, the diaphragm shifts upward and outward and contributes only about two-thirds of the ventilatory force. In the erect position, the abdominal contents and the diaphragm shift downward, allowing functional residual capacity and total lung capacity to increase. When supine, the abdominal contents move cephalad, stretching the posterior portion of the diaphragm more cephalad. The resulting diaphragmatic contraction provides greater movement of the posterior portion of the diaphragm, with increased ventilation of the dependent portions of the lung. This aids in matching ventilation to perfusion because the dependent portions of the lung are also preferentially perfused. However, total lung capacity and functional residual capacity decrease in the supine position. In the anesthetized, mechanically ventilated, supine patient, the position of the diaphragm and its subsequent function change slightly. The diaphragm shifts still more cephalad, reducing functional residual capacity even more from the awake value. Intermittent positive-pressure ventilation (IPPV) does not restore the diaphragm to the awake position. Differential ventilation occurs within the lung during IPPV, and those areas that are gravitationally lower receive proportionately more ventilation. In the supine position, ventilation is more nearly uniform throughout, with a smaller gradient anterior to posterior. [4] [5]

HORIZONTAL POSITIONS

The transition from supine to lateral to prone is a continuum, with various procedures placing the torso at all points of the circle. The usual and common supine position is generally considered to be safer than modifications. The most common serious positional injuries are peripheral nerve injuries.

Supine

The lithotomy position is most used in gynecologic and urologic surgery. The simultaneous elevation of the legs while the person is in the supine position provides the advantages of reducing torsion on the pelvis and lower back and promotes translocation of vascular volume centrally (Fig. 26-1) (Figure Not Available) . However, the areas that support the weight of the legs provide points of potential nerve and muscle injury. The goal is to suspend or support the legs so that they are flexed at the hips perpendicular to the torso and spread far enough apart to allow appropriate access to the abdomen (Fig. 26-2) (Figure Not Available) . Sometimes, less or more flexion is required (Figs. 26-3 (Figure Not Available) , 26-4 (Figure Not Available)). There are several devices to support the legs, the vertical bars being common to all of these. The support from the bar may be by built-in concave metal supports (see Figs. 26-2 (Figure Not Available) , 26-3 (Figure Not Available)) or by straps (see Fig. 26-4 (Figure Not Available) ; Fig. 26-5) (Figure Not Available) Both of these positions usually require additional padding.

There is risk of injury to the peroneal nerve if it is compressed between the head of the fibula and the bar or the support structures. Pressure over the medial tibial condyle may result in saphenous nerve injury. There is no obvious sign that such compression is occurring, and it can apparently be prevented by proper padding of the leg. Femoral nerve injury is probably due to angulation of the thigh such that the inguinal ligament is stretched tightly and compresses the femoral nerve. Obturator nerve injury is also related to greater degrees of thigh flexion, perhaps by stretching the nerve as it exits the obturator foramen. Bilateral lower compartment syndrome can occur in the lithotomy position and is perhaps related to the duration of the case, the tightening of the leg straps, the dorsiflexion of the ankle, or the surgeon leaning on the suspended leg for long periods of time. [6] [7] The pathogenesis of the compartment syndrome probably involves direct local muscle pressure as the initiating event. [8] [9]

A devastating injury in this position, which is fortunately uncommon, is hand and finger injury. As the foot of the bed is being rolled to a vertical position, care must be taken that

Figure 26-1 (Figure Not Available) (A) Flexing, then raising of the legs for the lithotomy position. (B) Holding the legs and stirrups for final positioning. *(Adapted from Goldstein [55])*

Figure 26-2 (Figure Not Available) Final lithotomy position showing leg placement. See text for potential risks. *(Adapted from Goldstein [55])*

the fingers are not caught in the gap and crushed (see Fig. 26-5) (Figure Not Available) . Compartment syndrome of the hand can occur if it is compressed between the buttocks and the operating table. [10] Extension of the arms perpendicular to the body prevents such an occurrence but introduces the possibility that the arms will be pushed too far cephalad. This stretches the brachial plexus and can result in nerve injury. The general practical rule is that the arms should be at an angle no greater than 90 degrees when extended on fixed arm boards. In the lithotomy position, pooling of the preparation solution at the buttocks and lower back can result in a chemical burn; it is wise to remove all drapes in this area after preparation so that puddles of residual solution can be removed.

Lateral

As the torso is tilted slightly laterally, usually a pad is placed under the shoulder so that the head and neck can be turned without tension. Such turning of the shoulder area alone may place torque on the lower back. It may be useful to place a pad under the hip so that it can follow the tilt of the shoulder and prevent the torque on the spine. Extreme lateral neck flexion has been reported to cause transient Horner syndrome. [11]

Thoracotomy patients are usually placed in the full lateral position. The arm is placed perpendicular to the torso, either on a pillow or on an overarm rest to support its weight (Fig. 26-6) (Figure Not Available) ; the arm is usually taped in this position. Care must be taken that the tape does not impinge on the ulnar nerve at the elbow or on the radial nerve as it wraps around the radial groove in the upper third of the humerus. For some thoracotomy procedures, a higher chest exposure is needed, and the arm is placed above the shoulder plane. Special care must be taken to avoid plexus injury in these situations (Fig. 26-7) (Figure Not Available) . Tension on the brachial plexus can be reduced by bringing the arm into a more anterior plane with the body. The lower chest is generally supported with an axillary roll. This places the weight of the chest on the rib cage and prevents the shoulder and axilla from being compressed; such compression of the axilla can lead to brachial plexus injury in the down arm. Palpation of the arterial pulse in the down arm is sometimes used as a measure of the adequacy of decompression. However, because the axillary brachial plexus can be substantially compressed well before pulses are lost, this method is probably insufficient evidence of safety. If the peripheral arm pulse is absent, substantial compression must have already occurred, and the patient and roll should be repositioned.

Figure 26-3 (Figure Not Available) Lithotomy position with less hip flexion for endoscopic procedures such as transurethral resection of the prostate. *(Adapted from Kropp [56])*

Figure 26-4 (Figure Not Available) Lithotomy with hip flexion slightly greater than 90 degrees. Legs do not touch support poles (inset). *(Adapted from Kropp [56])*

Figure 26-5 (Figure Not Available) Lithotomy position with straps instead of stirrups for leg support. Inset shows the risk to fingers when the lower portion of the operating table is lowered. *(Adapted from Welborn [57])*

Figure 26-6 (Figure Not Available) The lateral position showing upper arm rest in position; axillary roll, which supports the chest to free the axilla; and one type of leg positioning. *(Adapted from Day [58])*

Figure 26-7 (Figure Not Available) The lateral decubitus position for thoracotomy, showing a more headward position of the arms to facilitate surgical exposure. *(Adapted from Lawson [59])*

Lateral Oblique

The lateral oblique (sometimes called the three-quarters prone) position is used primarily for exposure of the posterior fossa in neurosurgery but may be used for other procedures on the back and upper neck. In this position, the torso is rotated from supine to lateral (Fig. 26-8) (Figure Not Available) . [12] The upper leg is brought forward and flexed slightly, and the lower leg is left straight. The head-holder pins may be placed before or after the patient is turned. An axillary roll is placed under the chest to support the weight of the body and thus prevent the down axilla from being compressed. This is done at an angle, slightly higher posteriorly and slightly more caudad anteriorly. It should be possible to get part of a hand in the space between the chest wall and the axilla. The lower shoulder is brought to the forward edge of the bed or just slightly over it (Fig. 26-9) . The patient is then rotated to three-quarters prone so that the lateral occipital skull is accessible to the surgeon or so that the patient is looking directly at the floor. The upper arm is placed downward near the side wherever it falls comfortably. The upper shoulder must not be so high that it interferes with surgical access.

Figure 26-8 (Figure Not Available) Movement of the patient from the supine to the lateral oblique position. *(From Tew and Scodary [12])*

Figure 26-9 The lateral oblique (three-quarters prone) position. The axillary roll is placed under the chest, and the lower shoulder is brought forward to the edge of the bed or just slightly over the edge.

In obese patients, especially women, it may not be possible to fit the lower arm below the torso; it may have to be placed posteriorly and parallel to the torso. This position places considerable weight on the head of the humerus and acromion, and these areas should be padded carefully without excessive bulk. Attention must be paid to the lower breast to prevent pressure on the nipple and areola. Extreme flexion of the head might compromise cervical spinal cord perfusion; quadriplegia can occur in the prone position despite this precaution. [13]

Monitoring such a patient requires special attention. The electrocardiograph (ECG) electrodes must not be placed in the dependent areas, where pressure necrosis can develop under the metal connections or wires. An arterial catheter is helpful in obtaining an accurate assessment of pressure. The incidence of Doppler-detected venous air embolism (VAE) during craniectomy in this position is about 10 percent. Consideration should be given to the use of the precordial Doppler and a central access line. However, positioning the precordial Doppler in this position is difficult and may not be effective for monitoring for VAE. Opinions vary regarding the value of an atrial catheter for air retrieval in this situation.

There are several difficulties in placing a patient in this position. Pressure on the dependent axilla and its contents and breast tissue are appropriate concerns, but there are no real guidelines for how much pressure is acceptable. The ability to place one's own hand into the axilla and feel for compression there is a good starting point, as is observation to be sure that the areola is free. Clinical experience must ultimately be the guide.

Trendelenburg

The Trendelenburg modification of the supine position places the head down, often with the knees flexed, so that the patient does not slide headward on the table. Shoulder braces may be used to restrict patient movement, but the weight of the torso can put considerable tension and stretch on the brachial plexus, with resultant injury.

The position moves the viscera cephalad and is used to improve exposure during lower abdominal surgery, to increase venous return after spinal anesthesia, or to increase central blood volume to facilitate jugular or subclavian cannulation, as well as to minimize aspiration during regurgitation by facilitating removal of material from the pharynx.

This position causes an increase in central venous pressure, intracranial and intraocular pressure, myocardial work, and pulmonary venous pressure and a decrease in pulmonary compliance and functional residual capacity. [14] [15] If longer operations are planned, we believe that endotracheal intubation is clearly indicated. There are no data demonstrating a higher incidence of unexpected neurologic events in patients placed in the steep Trendelenburg position for long operations, but there is one case report of a patient who had a cerebral hemorrhage during such a procedure and emerged with a significant neurologic deficit. [16] Clinical swelling of the face, eyelids and conjunctiva, and tongue has been observed, along with a plethoric color of venous stasis in the head and neck. Lingual and buccal nerve neuropathy can occur. [17] In patients with substantial swelling, it may be prudent to delay removal of the endotracheal tube until that situation has improved.

UNUSUAL POSITIONS

Positions for Orthopedic Surgery

Total hip arthroplasty, femoral neck fractures, and midfemur fractures for open reduction and internal fixation require different positions because of the need for surgical access and roentgenographic and fluoroscopic guidance (Figs. 26-10 (Figure Not Available) , 26-11) (Figure Not Available) Ch. 60) The lateral decubitus position is usually used for total hip arthroplasty. Patients having total hip arthroplasty often have concomitant degenerative cervical spine disease or at best some limitation of motion of the neck, which causes pain if exceeded. Careful alignment of the neck and head with the thoracic spine is usually not difficult. The down hip and leg are at risk during total hip arthroplasty in the lateral decubitus position. Rhabdomyolysis, much like that in a crush injury (five of the six patients reported were obese), [18] arterial insufficiency resulting in below-the-knee amputation, massive swelling of the thigh, and renal failure associated with myoglobinuria have been reported. Use of the pulse oximeter to detect excessive pressure on the femoral triangle has been suggested. [19]

The orthopedic fracture table consists of a body section to support the head and thorax, a sacral plate for the pelvis with a perineal post, and adjustable foot plates. The most important features of the table are the ability to maintain traction on the extremity and to obtain surgical and fluoroscopic access. Because the patients requiring this table are often in pain, anesthesia is usually induced before the patient is moved to the table. If regional anesthesia is used, the fracture side should be placed up. Once the patient has been transferred, the arm on the fracture side should be placed so that it does not interfere with surgical access to the

---

Figure 26-10 (Figure Not Available) Femoral neck fractures can be managed in the supine position on the fracture table. *(Adapted from Day [15])*

fracture; placing it across the chest directly or on an overarm board is effective.

Complications from this position include brachial plexus injury, lower-extremity compartment syndrome, and pudendal nerve injury related to the post. [20] [21]

Position for Shoulder Surgery

The use of the "beach chair," "barber's chair," or semirecumbent position is increasing in popularity in parallel with surgical procedures on the shoulder. The key element of the position is that it provides both anterior and posterior access to the shoulder, with the upper extremity freely mobile. Extreme rotation of the head away from the operative side can result in stretching of the brachial plexus during surgical manipulation. Figure 26-12 shows one method of securing the endotracheal tube and head to prevent movement and accidental extubation. [22] Although the head is not elevated as much as is required for neurosurgical procedures, the surgical field is clearly higher than the heart. An impressive complication of shoulder arthroscopy is rapid, progressive, and complete airway obstruction, caused by extravasation of the fluid used during visualization out of the capsule and into the tissues of the neck. [23]

Figure 26-11 (Figure Not Available) For midfemoral fractures, the patient is placed on the fracture table in the lateral position, with the legs spaced and positioned to allow roentgenography at an angle in several planes. *(Adapted from Day [15])*

Figure 26-12 Lateral view of upright shoulder position. The endotracheal tube and head are secured to prevent movement and accidental extubation.

SITTING POSITION

The sitting position is said to offer some surgical advantages (Table 26-1) . Surgeons might weigh these advantages differently, but most would agree that ease of surgical exposure, amount of blood pooling in the operative field, and operative position of the surgeon are different among the sitting, lateral, supine, and prone positions. Some anesthesiologists believe that access to the endotracheal tube, reduction of facial swelling, and ability to observe facial nerve function are notable advantages of the sitting position in anesthetic management. One workable

TABLE 26-1 -- Practical Reasons for Selective Use of Sitting Position

Better surgical exposure
Less tissue retraction and damage
Less bleeding
Less cranial nerve damage
More complete resection of the lesion
Ready access to airway, chest, extremities
Modern monitoring gives early warning of venous air embolism
Serious problems due to venous air embolism are uncommon

arrangement of equipment and operating table for procedures using the sitting position (and performed by a right-handed surgeon) is shown in Figure 26-13 . The two most common procedures performed in the sitting position are cervical laminectomy and posterior fossa exploration. Hazards to the patient undergoing posterior fossa craniectomy in the sitting position include VAE, hypotension, vital sign changes resulting from brain-stem manipulation, specific cranial nerve stimulation, airway obstruction, and position-related brain-stem ischemia. These are not unique to the sitting position and may occur in other positions as well. Management should be directed at the prevention, early detection, and treatment of these problems.

There is much concern about the use of the sitting position, and some even suggest that it constitutes malpractice for today's surgery. These intimidating statements may have some basis in fact but in general do not consider the large body of information about the safety of the sitting position.

Safety

Several large published series show a remarkably similar and favorable safety record for operations using the sitting

Figure 26-13 Arrangement for surgery in the sitting position. The scrub nurse is to the right of the surgeon to place instruments into the surgeon's right hand. The entire left side of the patient is available for the anesthesiologist's care.

position. [24] [25] [26] [27] The sitting position is being used less, and more posterior fossa procedures are being performed in horizontal positions. The sitting position is becoming a conscious selection rather than an automatic response for any posterior fossa lesion. There are risks and benefits for each position, and these must be weighed in the overall care of the patient.

A study by Black et al [24] put the problem into perspective, and its results are consistent with those of other studies. These authors retrospectively reviewed 579 posterior fossa craniectomies (333 sitting and 246 horizontal) performed concurrently from 1981 through 1984. It is the only study in the literature comparing the sitting and horizontal positions; no prospective randomized comparative study has been performed to date. Intraoperatively, the incidence of hypotension did not differ between the two groups either from induction of anesthesia to incision or from incision to closure. About 20 percent of the patients in each group became hypotensive during each of these periods; all responded to vasopressors and/or fluids. The incidence of VAE in patients monitored by Doppler ultrasound was significantly greater in the sitting position (45%) than in the horizontal position (12%).

Another important difference between the two groups was the need for blood transfusion, confirming the traditional surgical impression that upright patients bleed less. More than 2 units of blood were required in 13 percent of the patients in the horizontal position and in only 3 percent of those in the sitting position. Average blood volume transfused was also lower for the patients in the sitting position.

After surgery, no differences were found in cardiac or respiratory complications. The perioperative myocardial infarction rate was less than 1 percent overall and was not different in the two groups. Respiratory complications were found in 2.5 percent of patients and did not differ between groups or in comparison with other studies. [26] Thus, the data do not support the general selection of either the sitting or the horizontal position based on outcome. There are certain risks and advantages to each, and selection of position should be made with these in mind as they relate to the specific patient.

There are some conditions that seem prudent to consider as relative contraindications to the sitting position (Table 26-2) . However, there are few objective data to support our approach. If a shunt tube is in place from the cerebral ventricular system to the right atrium, air may enter the end of the shunt as cerebrospinal fluid drains out and may be pulled into the heart. The noncollapsible tubing acts as a noncollapsible vein and allows air to pass unimpeded into the heart. This is not a potential problem with a ventriculoperitoneal shunt, because the air would have no venous access. We recommend that a patient with a ventriculoatrial

TABLE 26-2 -- Relative Contraindications to Operative Sitting Position

Ventriculoatrial shunt in place and open
Cerebral ischemia upright awake
Left atrial pressure < right atrial pressure
Platypnea-orthodeoxia
Preoperative demonstration of patent foramen ovale or right-to-left shunt

? Cardiac instability ? Age extremes	Chest compression and resuscitation not really better in prone or lateral position

shunt in place have the shunt tied off before the patient undergoes an intracranial procedure in the sitting position. Some patients experience cerebral ischemia whenever they assume the upright position. Their cardiovascular and cerebrovascular systems may both be implicated in this situation. These patients may present for an extracranial-intracranial bypass for the posterior cerebral circulation; some surgeons believe that the sitting position gives the best exposure for this procedure. We cannot be sure that cerebral circulation will be maintained in the sitting position, because we must not only place the patient upright but must also provide an anesthetic. It seems a reasonable balance of risks and benefits to place such a patient in the horizontal position.

There has been a suggestion that if the left atrial pressure, as measured by pulmonary artery occlusion pressure, is less than the right atrial pressure in the sitting position, the patient should be placed horizontally because of an increased risk of paradoxical embolism. [28] This is based on two important assumptions: first, the left atrial pressure will be greater than the right atrial pressure in the horizontal position; second, the atrial pressure gradient and its direction constitute a prognostic indicator of whether VAE will become paradoxical air embolism (PAE). Some work suggests that these assumptions may not be applicable. In a pig model with an iatrogenic atrial septal defect, the atrial pressure gradient before air embolism was unrelated to the occurrence of PAE. [29] Thus, we believe that decisions regarding the use of the sitting position based on estimates of preoperative atrial pressure gradients are not well founded. Some patients demonstrate a potential right-to-left shunt before surgery. Platypnea-orthodeoxia is an unusual cardiovascular illness in which the atrial gradients apparently reverse when the upright position is assumed [30] ; patients with this condition are well oxygenated in the supine position but become desaturated in the upright position because of unsaturated blood passing from right to left at the atrial level. Other patients demonstrate a patent foramen ovale before surgery during a cardiac work-up, and still others may have a known right-to-left shunt. These patients might be at greater risk for PAE should VAE occur, and therefore it seems prudent to give these findings appropriate consideration before using the sitting position for such patients.

Some suggest that the sitting position should be avoided in patients with cardiac instability or at extremes of age because of a possible need to resuscitate intraoperatively. We believe that it is no easier to provide chest compression in the prone or lateral position than in the sitting position; all are equally undesirable. The rare need to resuscitate probably does not justify giving up whatever surgical advantage is thought to be gained by the use of the sitting position. Thus, in our opinion, these last considerations are not relative contraindications.

There are several details that should be considered when a patient is placed into a sitting or semirecumbent position (Fig. 26-14) (Figure Not Available) . Attention to detail in these matters probably only rarely prevents complications, but some of the complications can be major and are long remembered. Strict attention should be paid to the flexion of the head on the neck. We usually position the awake patient for up to 1 minute to see how much flexion can be tolerated, and that degree of flexion is not exceeded after the patient has been anesthetized. In general, we try to place two fingers between the chin and the sternum when positioning is complete as a possible way to

Figure 26-14 (Figure Not Available) The patient is in a semisitting position with the knees flexed slightly. The headrest support is fastened to the upper part of the table so that the head can be lowered without changing the relationship of the pinion head holder to the torso. The arms must be supported (not shown) so that the weight of the arm does not stretch the brachial plexus. The buttock area is padded. *(Adapted from Martin [60])*

prevent spinal cord ischemia with postoperative quadriparesis or quadriplegia. We have accepted one fingerbreadth, but only in selected circumstances. Although there is no study to show that this approach is effective, we have had no cases of quadriplegia attributable to cervical flexion in our practice.

In the sitting position, the arms tend to hang by the side. When muscle relaxants are used, the downward force caused by the weight of the arms is sufficient to stretch the brachial plexus and cause unilateral arm paralysis or weakness. This is not a theoretical consideration in our practice. This situation can be prevented by the placement of blankets under the elbow and forearm to support the weight of the arm so that there is no downward stretch on the arm, and the arm is actually pushed up slightly, giving the appearance of a slight shoulder shrug.

The hips are often flexed for two reasons: (1) this position tends to place the buttocks at an angle to support the weight of the body, and (2) it is thought to aid venous return. The legs must not be outstretched, however, because this places considerable tension on the sciatic nerve and can result in postoperative weakness. Bending the legs at the knees removes this tension, and placing an artificial fat pad under the buttocks to include the sciatic notch of the pelvis may reduce the chances of pressure ischemia of the nerve. Venous return may be aided and thromboembolism may be prevented by the use of elastic leg wrapping or alternating inflatable leg wraps (e.g., sequential TEDS).

Monitoring

The data from many studies indicate that the sitting position seems relatively safe, provided that adequate monitoring is used (Chs. 28 to 38).

Central Nervous System

Central nervous system monitoring techniques for patients in the sitting position are directed not only at minimizing the hazards of the position but also at providing positive information to the surgeon, particularly during posterior fossa exploration. The same central nervous system monitoring is required for any infratentorial procedure, regardless of surgical position. The response of the vital signs to brain-stem manipulation and the response of the cranial nerves to stimulation can provide pathophysiologic data that the surgeon can use in real time during dissection (Table 26-3) .

The ECG is an effective monitor of brain-stem compression. Spontaneous respiration has been advocated as a means of detecting transgression of the respiratory centers during posterior fossa exploration. However, a large series has indicated that monitoring the ECG provides adequate warning of brain-stem compromise during light anesthesia while mechanical ventilation is used to maintain reduced arterial carbon dioxide tension levels. [31] Brain-stem auditory evoked responses and somatosensory evoked potentials can provide an electrophysiologic monitor for early detection of brain-stem compromise. Stimulation of the seventh cranial nerve results in a facial twitch that is visible in the seated patient. Electromyography over the distribution of this nerve can aid in the detection of stimulation of the facial nerve if

TABLE 26-3 -- Cranial Nerve Stimulation During Posterior Fossa Surgery

CLASSIC ACTIVITY DESCRIPTION -- PHYSICAL SIGNS	ELECTRONIC TECHNIQUE
V. Motor: jaw jerk	EMG
Sensory: hypertension	Arterial line
bradycardia	ECG
VII. Facial twitch	EMG
X. Hypotension	Arterial line
Bradycardia	ECG
XI. Shoulder jerk	EMG
Pons, brain-stem compression	BAER, SEP
Ectopic cardiac foci	ECG
Hypertension and hypotension	Arterial line
Tachycardia and bradycardia	ECG
Gasp, irregular respirations	Respirator "trigger"

EMG, electromyography; ECG, electrocardiography; BAER, brain-stem auditory evoked responses; SEP, sensory evoked potentials

the face is not accessible to palpation or visual assessment. This is especially true in the prone patient because it is not appropriate to have the anesthesiologist under drapes with a flashlight looking for facial twitch. The observation period can be protracted and can result in failure to properly monitor other parameters of anesthesia response because of unavoidable diversion of field of view and attention.

Cerebral Perfusion Pressure

Blood pressure and pulse rate are measured to monitor several interrelated systems and factors. Some operations performed in the sitting position might result in sudden and extreme changes in pulse rate and blood pressure either because of the surgery or because of VAE. Intra-arterial blood pressure measurements yield instantaneous information, particularly with regard to cerebral perfusion pressure. They can be easily obtained when the strain gauge is zeroed to the base of the skull, which can be accomplished by use of the routine zero at the heart level with the patient supine and by placement of the strain gauge at the level of the external auditory meatus once the patient is placed in the sitting position.

Venous Air Embolism

Let us examine the most troublesome complications of the sitting position as well as those that are common but not very troublesome. The most feared complication of surgery in the sitting position is VAE with subsequent PAE to the brain. This complication not only places the patient at risk from the air itself but also can cause a surgeon who lacks confidence in the ability of the anesthesia team to take care of the problem to become distracted and concerned; this takes the focus away from the job at hand, namely performing the surgery. Thus, we believe that open communication between the anesthesiologist and the surgeon about air before and during the surgery improves the level of awareness and the confidence that the situation can be managed appropriately. That is not to say that disasters cannot happen even with the best of management; however, early detection of such problems usually prevents their progression to disastrous consequences. We also believe that it is an oversimplification to place all patients in the horizontal position because of the risk of air without regard for the increased surgical risk of compromised exposure in certain patients.

Monitoring for VAE can be approached from several aspects. Monitors include a precordial Doppler device, a right-sided heart catheter, a capnograph or mass spectrometer, an esophageal stethoscope, a transcutaneous oxygen monitor, and a transesophageal echocardiogram. The most sensitive of these methods are transesophageal echocardiography and Doppler ultrasound, followed by expired nitrogen fraction, end-tidal carbon dioxide, transcutaneous oxygen, right-sided heart catheterization, and, least sensitive, esophageal stethoscope measurements. None of these monitoring methods is totally reliable; we believe that it is generally necessary to use at least three of them to ensure that VAE can be detected (Fig. 26-15) (Figure Not Available) .

The risk of VAE is not eliminated by placing the patient horizontal, but it is reduced. A 12 percent incidence of Doppler-detected air occurs in supine infratentorial craniectomy cases. [24] Once VAE has occurred, about 20 percent of patients will have hypotension, regardless of their position. Except in the unusual situation of massive VAE, these episodes can be expected to respond promptly to vasopressor therapy.

The precordial Doppler device is advocated as the basic monitor for reducing complications caused by VAE. It is reasonably priced, relatively easy to use, noninvasive, and sensitive; its position over the right side of the heart can be verified by rapid injection of agitated saline into the central venous circulation, and its sounds can be heard by both surgeon and anesthesiologist. Its sensitivity has led some to criticize its use because it may indicate "insignificant air" before hemodynamic consequences ensue. Protagonists argue that such sensitivity is precisely the early warning needed to identify the occurrence of VAE and to stop its entry surgically to prevent further secondary complications.

The use of the right-sided heart catheter has evolved and has been improved to an extent such that air can frequently be aspirated when it is detected by Doppler monitoring. But what are the real functions of the right-sided heart catheter? [32] Rapid injection of agitated saline through the catheter can help to confirm that the Doppler probe is properly

Figure 26-15 (Figure Not Available) Changes in detection parameters for venous air embolism with increasing air volume. Data are aggregated from human and animal studies under a wide variety of circumstances. *(Modified from Cucchiara et al [61])*

placed over the right side of the heart. The aspiration of air confirms or establishes the diagnosis of VAE. The role of the catheter in the treatment of VAE is more anecdotal and less solidly founded. The aspiration of air from the right atrium during VAE is occasionally life saving; this is limited to the rare situation of massive VAE. Whether routine aspiration of smaller or medium quantities of air from the heart can prevent PAE or cardiopulmonary complications is not known. Right atrial multiorifice catheters allow a larger amount of air to be aspirated than single-orifice catheters. Proper placement of the right atrial catheter high in the right atrium can increase its effectiveness because this is where the air tends to localize (Fig. 26-16) (Figure Not Available) . [33]

The right-sided heart catheter may be positioned by ECG control, roentgenography, or pressure recordings. It is likely that the ECG trace from a multiorifice catheter comes from the proximal hole, usually 2 cm from the tip. [34] [35] Thus, the tracing sought is slightly different with these catheters. The standard concept of a progressively more negative P wave as the catheter is advanced still applies, but the proximal orifice should be placed in the superior vena cava, allowing the

Figure 26-16 (Figure Not Available) The air tends to localize at the atrial superior vena caval (SVC) junction, moving through the tricuspid valve or into upright portions of the atrium. The multiorifice catheter placement most likely to aspirate air is shown. The ECG tracing from the catheter in this position is described in Fig. 30-17 (Figure Not Available) . The conceptualization of localization of air embolism in the upright heart is based on a human cardiac model and human echocardiographic findings. *(From Cucchiara et al [61])*

Figure 26-17 (Figure Not Available) The intracardiac ECG for each position is shown. With a single-orifice catheter, tracing 4 indicates mid-right atrial position. Since the ECG trace originates from the proximal orifice of a multiorifice catheter and since placement as shown in Fig. 30-15 (Figure Not Available) is desirable, tracing 2 should be sought. *(From Cucchiara et al [37])*

portion of the catheter that has the holes to float at the superior vena cava/high right atrial level. The P wave should be large and negative, with no positive component (Fig. 26-17) (Figure Not Available) . This indicates that the proximal orifice is not in the atrium. In practice, one can usually obtain an increasingly negative P wave that finally develops a small positive deflection and then withdraw slightly to an all-negative P wave. Care must be taken when the arm is returned to the side because the catheter will likely migrate a little more centrally and may need to be withdrawn slightly. [36] Placement of the right atrial catheter through an arm vein by ECG control can be performed in 5 minutes or less in 53 percent of patients and in 15 minutes or less in 92 percent of patients. The overall success rate in several studies was greater than 90 percent. [37]

The use of a pulmonary artery catheter for the aspiration of a VAE has generally been unsatisfactory because of the small lumen size and slow speed of blood return. However, other information can be obtained from the pulmonary artery catheter. The entry of air into the pulmonary circulation causes pulmonary artery pressures to rise. One can use this information to evaluate when the VAE has cleared the pulmonary circulation. If pulmonary artery pressure rises during the VAE and the Doppler recording clears, a return of pulmonary artery pressure to previous levels suggests that the air obstructing the pulmonary circulation has been moved more distally and has probably been excreted through the lungs. [38]

Capnography and mass spectrometry demonstrate a decrease in end-tidal carbon dioxide during VAE with intermediate sensitivity. One can expect to see changes in end-tidal carbon dioxide after Doppler changes occur but before hemodynamic changes occur. When enough air has been entrained to cause hemodynamic changes, the end-tidal carbon dioxide usually decreases within a few breaths after the Doppler change. Sensitive mass spectrometry can show increases in expired nitrogen fraction as the VAE is excreted through the lung. Transcutaneous oxygen tension monitoring is also intermediate in sensitivity but has more practical and technical problems, making its use in the operating room somewhat less popular. [39]

Figure 26-18 (Figure Not Available) Paradoxical air as noted by transesophageal echocardiography. (A) Normal; (B) air in right atrium; (C) air in left atrium, right atrium nearly opacified; (D) more air in left and right atrium. *(From Cucchiara et al [40])*

Transesophageal echocardiography is still a research tool but holds considerable promise in the diagnosis of VAE. It is very sensitive and allows visualization of air in the cardiac chambers themselves, thus providing the unique opportunity to identify the occurrence of air in the left side of the heart [40] (Fig. 26-18) (Figure Not Available) . Transcranial Doppler monitoring may identify air in the arteries of the brain. The only other clinical way to identify PAE during surgery in the sitting position is for the surgeon to visualize air in the small arteries of the brain or spinal cord. This implies that it is already late because the air is already in the vessels to the brain in amounts large enough to be readily seen and is likely to cause focal cerebral ischemia.

PERIPHERAL NERVE INJURY

Mechanism of Peripheral Nerve Injuries

In position-related nerve injuries, there are two basic forces that impair nerve function and, if severe or prolonged, impair axonal structure. Nerves that course superficially for long distances between two points of fixation are particularly vulnerable to stretch injury. Neural structures that are adjacent to or pass over bony surfaces in a small area are subject to compression between internal and ex-ternal structures, with resultant injury. The final result is likely the same--nerve ischemia resulting from reduction of blood flow through the intraneural vasa nervorum. The combination of stretch and ischemia makes the nerve more vulnerable to injury. [41] Compression injury usually occurs at a point along the nerve course; the smaller the contact point, the greater the focus of the force in compressing the nerve. Awake patients usually move when pain and paresthesia associated with nerve ischemia occur. Ischemia that persists for over 30 minutes can result in nerve palsy. [41]

Intraoperative diagnosis of nerve impairment during general anesthesia is usually clinical. The distal pulse should be checked where nerves and blood vessels pass together. Pulse oximetry and capillary refill are measures of impaired blood flow. If there is sufficient external pressure on the axilla, for example, to decrease these parameters from prepositioning values, there is certainly enough pressure to reduce blood flow to the nerve through the small vessels supplying the adjacent nerves. Conversely, intact perfusion by these clinical measures does not guarantee normal nerve perfusion and function. Somatosensory evoked potentials from medial nerve stimulation can be lost despite preservation of peripheral pulse, capillary refill, and pulse oximetry saturation and plethysmography. [42]

There are three types of nerve injury based on structure and function. Neurapraxic injury occurs with a loss of function (or occurrence of dysfunction) in the nerve without demonstrable anatomic injury. This is the type of injury related to positioning that is most likely to occur during anesthesia. Recovery is complete within 6 weeks, and no long-term treatment is indicated or needed. Axonotmesis occurs with anatomic disruption of the axon but preservation of the nerve sheath and connective tissue. The axon degenerates distal to the lesion and regenerates at a rate of about 1 mm/day. Function gradually returns, but in longer

nerves, such as those of the upper extremity, this may take a year. Surgery is not usually indicated, but physical therapy is helpful to prevent degeneration of the joints and muscles and to reintroduce those structures to load bearing when they are reinnervated. Neurotmesis results in axon, sheath, and connective tissue disruption. This leads to degeneration of the axon distal to the injury, but regeneration usually does not occur. Neurosurgical, rehabilitation, and pain services intervention may be helpful in these types of injuries. [43]

Ulnar Nerve Injury During Anesthesia

Although the true frequency of nerve injuries during anesthesia and surgery is not known, some pieces of information help to place the problem in perspective. A 1990 analysis of the American Society of Anesthesiologists Closed Claims Project database showed that 15 percent of the claims were for nerve injuries. Three distributions accounted for 73 percent of those cases: ulnar (34%), brachial plexus (23%), and lumbosacral nerve root (16%). The mechanism of ulnar nerve injury during anesthesia is unclear. In most cases, the injury seems to have occurred despite all the precautions of padding and careful placement of the elbow to protect the nerve. Some have questioned whether the injury is even preventable. [44]

The so-called cubital tunnel external compression syndrome has been advanced as a possible mechanism for postoperative ulnar nerve injury. [44] The ulnar nerve passes through the cubital tunnel of the elbow as it courses to the forearm. The anatomic boundaries of the cubital tunnel are the floor (the medial ligament of the elbow) and the roof (the arcuate ligament, which extends from the medial epicondyle of the humerus to the medial aspect of the olecranon process of the ulna). The nerve lies superficially in the tunnel and thus is vulnerable to injury. Perhaps when the arm is fixed at the patient's side or to an abducted arm board with the forearm pronated, the cubital tunnel is placed in contact with the surface of the cushion, and the nerve is externally compressed within the tunnel. Supination of the forearm places the olecranon process of the ulna in contact with the flat surface and might reduce its vulnerability. Importantly, flexion of the elbow to more than 90 degrees tenses the arcuate ligament and reduces the volume of the tunnel containing the ulnar nerve, possibly compressing it. Although this is a theoretical consideration, there is no evidence that altering the position of the arms in the supine patient during anesthesia and surgery decreases the likelihood of ulnar nerve injury. Ulnar nerve injury is more common in men (5:1, male/female ratio), which suggests some anatomic predisposition of the tunnel [45] or hypermobility of the nerve. [46] Preexisting medical diseases, such as diabetes and vitamin deficiency, and chronic subclinical compression of the ulnar nerve at this level have also been implicated as possible causes of this postoperative complication. Warner et al [47] retrospectively reviewed the records of 1,129,692 consecutive procedures on patients undergoing diagnostic or noncardiac surgical procedures at the Mayo Clinic over a 35-year period. Persistent (>3 months) ulnar neuropathies occurred at a rate of 1:2,729 patients. Nine percent were bilateral, and most were not noted until at least 24 hours after the procedure.

A particularly high incidence of postoperative ulnar nerve palsy has been noted in patients having cardiac surgical sternal retraction (60%). [48] [49] [50] Intraoperative somatosensory evoked potentials have been shown to identify those patients in whom persistent peripheral nerve deficits have occurred. [51] The mechanism is again unclear, but wide retraction of the sternum and first rib fractures may play a role. Placement of the arms at the side or abducted 90 degrees on padded arm boards did not eliminate the problem of ulnar nerve injury. There is a separate clinical entity of chronic compression of the ulnar nerve by focal constriction under the aponeurosis connecting the heads of the flexor carpi ulnaris muscle (Fig. 26-19) . [52] [53] Perhaps the effects of the blood pressure cuff, decreased neural vascular flow during cardiac bypass, and external pressure of positioning and/or central line placement produce additive effects on a more vulnerable nerve. [44] Evidence supports the conclusion that ulnar nerve palsy is not always a preventable complication despite the best efforts at careful positioning and padding.

EYE INJURY

The frequency of eye injury during anesthesia and surgery is low. If the pressure on the eye exceeds venous pressure, the veins may collapse, arterial inflow may continue, and arterial hemorrhage may occur. If pressure on the eye exceeds arterial pressure, arterial inflow may be dramatically reduced, resulting in ischemia of the retina. The use of the horseshoe headrest (Fig. 26-20) (Figure Not Available) carries the risk of such pressure injury to the eye because the head may shift during the procedure, even if the head is properly positioned at the beginning of the case. Corneal abrasion during neurosurgical procedures has been shown to be largely preventable by the application of eye tape but has not been shown to be influenced by the use of eye ointment. In patients undergoing lumbar laminectomy, the abrasions usually occur in the down eye. [54]

Figure 26-19 Anatomic compression of the ulnar nerve.

Figure 26-20 (Figure Not Available) The head can slip while in the horseshoe headrest, and pressure may develop in the eye owing to the weight of the head. *(Adapted from Reid and Grundy [62])*

References

1. Ekelund LG, Eklund B, Kaijser L: Time course for the change in hemoglobin concentration with change in posture. Acta Med Scand 190:335, 1971.

2. Waterfield RL: The effect of posture on the volume of the leg. J Physiol 72:121, 1931.

3. Ward RJ, Danziger F, Bonica JJ et al: Cardiovascular effects of change of posture. Aviat Space Environ Med 37:257, 1966.

4. Smith BL: Physiologic changes in normal conscious human subject on changing from the erect to supine position. In Martin JT (ed): Positioning in Anesthesia and Surgery. 2nd ed. Philadelphia, WB Saunders, 1987, p 13.

5. Barnas GM, Green MD, Mackenzie CF et al: Effect of posture on lung and regional chest wall mechanics. Anesthesiology 78:251, 1993.

6. Lydon JC, Spielman FJ: Bilateral compartment syndrome following prolonged surgery in the lithotomy position. Anesthesiology 60:236, 1984.

7. Adler LM, Loughlin JS, Morin CJ et al: Bilateral compartment syndrome after a long gynecologic operation in the lithotomy position. Am J Obstet Gynecol 162:1271, 1990.

8. Matsen FA: Compartment syndrome: A unified concept. Clin Orthop 113:8, 1975.

9. Rorabeck CH, MacNab I: The pathophysiology of the anterior tibial compartmental syndrome. Clin Orthop 113:52, 1975.

10. Parkes AR: Traumatic ischemia of peripheral nerves with some observations on Volkmann's ischemic contracture. Br J Surg 32:403, 1945.

11. Jaffe TB, McLeskey CH: Position-induced Horner's syndrome. Anesthesiology 56:49, 1982.

12. Tew JM, Scodary DJ: Surgical positioning. In Apuzzo MJ (ed): Brain Surgery: Complication Avoidance and Management. New York, Churchill Livingstone, 1993, p 1609.

13. Deem S, Shapiro HM, Marshall LF: Quadriplegia in a patient with cervical spondylosis after thoracolumbar surgery in the prone position. Anesthesiology 75:527, 1991.

14. Sibbald WJ, Paterson NA, Holliday RL et al: The Trendelenburg position: Hemodynamic effects in hypotensive and normotensive patients. Crit Care Med 7:218, 1979.

15. Wilcox S, Vandam LD: Alas, poor Trendelenburg and his position! A critique of its uses and effectiveness. Anesth Analg 67:574, 1988.

16. Oliver SB, Cucchiara RF, Warner MA et al: Unexpected focal neurologic deficit on emergence from anesthesia: A report of three cases. Anesthesiology 67:823, 1987.

17. Winter R, Munro M: Lingual and buccal nerve neuropathy in a patient in the prone position: A case report. Anesthesiology 71:452, 1989.

18. Lachiewicz PF, Latimer HA: Rhabdomyolysis following total hip arthroplasty. J Bone Joint Surg Br 73:576, 1991.

19. Smith JW, Pellicci PM, Sharrock N et al: Complications after total hip replacement. The contralateral limb. J Bone Joint Surg Am 71:528, 1989.

20. Hofmann A, Jones RE, Schoenvogel R: Pudendal-nerve neurapraxia as a result of traction on the fracture table. J Bone Joint Surg Am 64:136, 1982.

21. Lindenbaum SD, Fleming LL, Smith DW: Pudendal-nerve palsies associated with closed intramedullary femoral fixation: A report of two cases and a study of the mechanism of injury. J Bone Joint Surg Am 64:934, 1982.

22. Elliott BA: Positioning and monitoring. In Wedel DJ (ed): Orthopedic Anesthesia. New York, Churchill Livingstone, 1993, p 99.

23. Hynson JM, Tung A, Guevara JE et al: Complete airway obstruction during arthroscopic shoulder surgery. Anesth Analg 76:875, 1993.

24. Black S, Ockert DB, Oliver WC et al: Outcome following posterior fossa craniectomy in patients in the sitting or horizontal position. Anesthesiology 69:49, 1988.

25. Matjasko J, Petrozza P, Cohen M et al: Anesthesia and surgery in the seated position: Analysis of 554 cases. Neurosurgery 17:695, 1985.

26. Standefer M, Bay JW, Trusso R: The sitting position in neurosurgery: A retrospective analysis of 488 cases. Neurosurgery 14:649, 1984.

27. Young ML, Smith DS, Murtagh F et al: Comparison of surgical and anesthetic complications in neurosurgical patients experiencing venous air embolism in the sitting position. Neurosurgery 18:157, 1986.

28. Perkins-Pearson NAK, Marshall WK, Bedford RF: Atrial pressures in the seated position: Implication of paradoxical air embolism. Anesthesiology 57:493, 1982.

29. Black S, Cucchiara RF, Nishimura RA et al: Parameters affecting occurrence of paradoxical air embolism. Anesthesiology 71:235, 1989.

30. Seward JB, Hayes DL, Smith HC et al: Platypnea-orthodeoxia: Clinical profile, diagnostic workup, management, and report of seven cases. Mayo Clin Proc 59:221, 1984.

31. Michenfelder JD, Gronert GA, Rehder K: Neuroanesthesia. Anesthesiology 30:65, 1969.

32. Michenfelder JD: Central venous catheters in the management of air embolism: Whether as well as where. Anesthesiology 55:339, 1981.

33. Bunegin L, Albin MS, Helsel PF et al: Positioning the right atrial catheter: A model for reappraisal. Anesthesiology 55:343, 1981.

34. Artru AA, Colley PS: The site of origin of the intravascular electrocardiogram recorded from multiorificed intravascular catheters. Anesthesiology 69:44, 1988.

35. Warner DO, Cucchiara RF: Position of proximal orifice determines electrocardiogram recorded from multiorificed catheter. Anesthesiology 65:235, 1986.

36. Lee DS, Kuhn J, Shaffer MJ et al: Migration of tips of central venous catheters in seated patients. Anesth Analg 63:949, 1984.

37. Cucchiara RF, Messick JM, Gronert GA et al: Time required and success rate of percutaneous right atrial catheterization: Description of a technique. Can J Anaesth 27:572, 1980.

38. Perkins-Pearson NAK, Marshall WK, Bedford RF: Atrial pressures in the seated position: Implication for paradoxical air embolism. Anesthesiology 57:493, 1982.

39. Glenski JA, Cucchiara RF: Transcutaneous O_2 and CO_2 monitoring of neurosurgical patients: Detection of air embolism. Anesthesiology 64:546, 1986.

40. Cucchiara RF, Nugent M, Seward JB et al: Air embolism in upright neurosurgical patients: Detection and localization by two-dimensional transesophageal echocardiography. Anesthesiology 60:353, 1984.

41. Britt BA, Gordon RA: Peripheral nerve injuries associated with anaesthesia. Can J Anaesth 11:514, 1964.

42. Mahla ME, Long DM, McKennett J et al: Detection of brachial plexus dysfunction by somatosensory evoked potential monitoring: A report of two cases. Anesthesiology 60:248, 1984.

43. Mahla ME: Nervous system. In Gravenstein N (ed): Manual of Complications During Anesthesia. Philadelphia, JB Lippincott, 1991, p 383.

44. Stoelting RK: Postoperative ulnar nerve palsy: Is it a preventable complication? Anesth Analg 76:7, 1993.

45. Aita JF: Postoperative ulnar neuropathy. JAMA 245:2295, 1981.

46. Cameron MG, Stewart OJ: Ulnar nerve injury associated with anaesthesia. Can J Anaesth 22:253, 1975.

47. Warner MA, Warner ME, Martin JT: Ulnar neuropathy: Incidence, outcome, and risk factors in sedated or anesthetized patients. Anesthesiology 81:1332, 1994.

48. Seyfer AE, Grammer NY, Bogumill GP et al: Upper extremity neuropathies after cardiac surgery. J Hand Surg [Am] 10:16, 1985.

49. Roy RC, Stafford MA, Charlton JE: Nerve injury and musculoskeletal complaints after cardiac surgery: Influence of internal mammary artery dissection and left arm position. Anesth Analg 67:277, 1988.

50. Wey JM, Guinn GA: Ulnar nerve injury with open-heart surgery. Ann Thorac Surg 39:358, 1985.

51. Hickey C, Gugino LD, Agilo LS et al: Intraoperative somatosensory evoked potential monitoring predicts peripheral nerve injury during cardiac surgery. Anesthesiology 78:29, 1993.

52. Miller RG: The cubital tunnel syndrome: Diagnosis and precise localization. Ann Neurol 6:56, 1979.

53. Eisen A: Early diagnosis of ulnar nerve palsy: An electrophysiologic study. Neurology 24:256, 1974.

54. Cucchiara RF, Black S: Corneal abrasion during anesthesia and surgery. Anesthesiology 69:978, 1988.

55. Goldstein PJ: The lithotomy position. Surgical aspects: Obstetrics and gynecology. In Martin JT (ed): Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1987, p 41.

56. Kropp KK: The lithotomy position. Surgical aspects: Urology. In Martin JT (ed): Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1987, p 53.

57. Welborn SG: The lithotomy position: Anesthetic considerations. In Martin JT (ed): Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1987, p 58.

58. Day LJ: Unusual positions. Orthopedics: Surgical aspects. In Martin JT (ed): Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1987, p 226.

59. Lawson NW: The lateral decubitus position: Anesthesiologic considerations. In Martin JT (ed): Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1987, p 161.

60. Martin JT: The head-elevated positions: Anesthesiologic considerations. In Martin JT (ed): Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1987, p 81.

61. Cucchiara RF, Black S, Layon AJ, Stachniak J: Anesthesia and intensive care management of patients with brain tumors. In Kaye AH, Laws ER (eds): Encyclopedia of Brain Tumors. Edinburgh, Churchill Livingstone, 1995, p 263.

62. Reid SA, Grundy BL: The head-elevated positions. Surgical aspects: The neurosurgical skull clamp. In Martin JT (ed): Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1987, p 71.

Chapter 27 - Malignant Hyperthermia

Gerald A. Gronert
Joseph F. Antognini
Isaac N. Pessah

INTRODUCTION

Malignant hyperthermia (MH) identifies a clinical syndrome classically observed during general anesthesia--rapidly increasing temperature (as great as 1°C/5 min) and high mortality rate. This results from acute uncontrolled increases in skeletal muscle metabolism that may proceed to severe rhabdomyolysis. The early mortality rate reached 70 percent, but with earlier diagnosis and the advent of dantrolene, it has dropped to less than 5 percent. Wilson et al's [1] group apparently first used the term malignant hyperthermia in print in 1966. A Danish survey [2] indicates an incidence of fulminant MH of one in 250,000 anesthetics. However, when only the potent anesthetics and succinylcholine (SCh) are considered, fulminant MH occurred in one in 62,000 anesthetics. A suspicion of MH occurred in one of 16,000 anesthetics overall, and in one of 4,200 anesthetics involving potent volatile agents in combination with SCh.

A layman's organization provides public education and communication among affected families (Malignant Hyperthermia Association of the United States [MHAUS], 32 S. Main St., PO Box 1069, Sherburne, New York 13460-1069) and a 24-hour 7-day telephone service for emergency consultation (MH Hotline: 1-800-MH-HYPER). The routine telephone number of MHAUS for information purposes is 800-98MHAUS; fax: 800-440-9990; e-mail: mhaus@ norwich.net; website: www.mhaus.org. The professional subsidiary of MHAUS, the North American MH Registry, collates findings from biopsy centers in Canada and the United States and provides access to specific patient data, via either the hotline or its Director, Dr. Greg Allen, Department of Anesthesiology, Pennsylvania State University, Hershey, Pennsylvania, 17033-0850, telephone 717-531-5437.

This review focuses on new developments: the concept that disorders of the ion channels that control skeletal muscle may be grouped as channelopathies, that is, disorders of sodium, potassium, chloride, and calcium, and that their various mutations are associated with specific neuromuscular disorders. Of the three forms of the ryanodine receptor (Ry), Ry_1 , Ry_2 , and Ry_3 , only mutations in Ry_1 have been linked to MH. The genetics of MH and its related abnormal function of Ry_1 are now investigated at the level of molecular biology, with the porcine model providing intricate detail. Equivalent parallels in humans are limited by scarcer material for scientific study and difficulty in identifying underlying sources of abnormal responses, complicated by the fact that phenotypes vary within a genotype. Dantrolene remains the key in therapy, but its precise mechanism of action continues to be elusive. Standardization of MH testing with two protocols, the European and the North American, has resulted in sufficiently large databases to confirm acceptable sensitivity and specificity. However, minor differences in these protocols create problems in interpretation

among test center results, and it is time to focus standardization into one international protocol, admittedly a challenge in cooperation. Fulminant MH is now seldom seen because of greater awareness and consistent use of more sophis-ticated monitoring, especially of expired carbon dioxide. Diagnostic challenges are now provided by intraanesthetic changes that mimic MH, especially in its earlier manifestations.

HISTORY

Between 1915 and 1925, one family experienced three anesthetic MH deaths featuring rigidity and hyperthermia and was puzzled for decades regarding their cause. Susceptibility was eventually confirmed in three descendants. [3] In 1929, Ombredanne [4] described anesthesia-induced postoperative hyperthermia and pallor in children with significant mortality (Ombredanne's syndrome) but did not detect familial relationships. Critical worldwide insight into MH began in 1960, when Denborough and Lovell [5] described a 21-year-old Australian with an open leg fracture who was more anxious about anesthesia than about surgery because 10 of his relatives had died during or after anesthesia. Lovell initially anesthetized him with the then-new agent halothane, halted it when signs of MH appeared, and subsequently used a spinal anesthetic. Further evaluations of affected families came from Locher in Wausau, Wisconsin, in conjunction with Britt in Toronto, Canada. Direct skeletal muscle involvement rather than central loss of temperature control was established by recognition of increased muscle metabolism or muscle rigidity early in the syndrome, low-threshold contracture responses by Kalow et al, [6] and elevated values for creatine kinase (CK).

The pig, when inbred for muscle development (e.g., Landrace, Pietrain, and Poland China), provides an excellent animal model. The ubiquitous single-point mutation of porcine MH is likely due to the random occurrence of the altered Ry_1 allele, followed by deliberate inbreeding for desirable traits. International sharing of breeding stock probably spread the mutation worldwide. The experimental model evolved from earlier reports describing unsuitable pork [7] ; the stresses of the abattoir resulted in accelerated metabolism and rapid deterioration of the muscle, resulting in pale soft exudative pork. [8] Its incidence increased with breeding patterns designed to produce rapid growth rate, superior muscling, and hybrid vigor, although the drawback is a link with stress susceptibility. This increased incidence led to the term porcine stress syndrome. [9] Any stresses, such as separation, shipping, weaning, fighting, coitus, or preparation for slaughter, could lead to increased metabolism, acidosis, rigidity, fever, and death.

In 1966, Hall et al [10] reported on MH induced by halothane and SCh in stress-susceptible swine. The human and porcine forms are virtually identical, in comparisons of the clinical and laboratory changes of anesthesia-induced MH. [11] In 1975, Harrison [12] described the efficacy of dantrolene in preventing and treating porcine MH, which was confirmed in humans by a multihospital evaluation of dantrolene used to treat unanticipated episodes that occurred during anesthesia. [13]

There is now little doubt that MH in swine is a manifestation of a generalized susceptibility to stress. The sympathetic nervous system undoubtedly exaggerates skeletal muscle responses during stress, but its role in MH appears to be secondary (see Sympathetic Nervous System). Stress-induced awake triggering is common in MH swine but uncommon in MH-susceptible humans (see Awake Triggering).

Malignant hyperthermia presents several paradoxes. Anesthetics are inconsistent in their ability to trigger MH and are therefore frequently ineffective in triggering episodes in affected humans [14] ; this may be related to delay of the response by various depressants and nondepolarizing muscle relaxants. [15] Conversely, "safe" anesthetics, which are more aptly described as those less likely to trigger MH, can still be associated with apparent MH episodes. [16] Generally, susceptible individuals appear normal in regard to structure and function until they are stressed, thereby complicating detection of the condition. Detection requires either an anesthetic challenge or an invasive destructive muscle biopsy with contracture responses to caffeine or halothane. Testing in the pig is possible solely by genetic tracing of the single-point mutation in Ry_1 , but this test is weakened in humans by heterogeneity.

PATHOPHYSIOLOGY, MOLECULAR BIOLOGY, GENETICS, DANTROLENE

Malignant hyperthermia is a myopathy, usually subclinical, that features an acute loss of control of intracellular calcium (Ca^{2+}). Normally, the wave of depolarization from end plate to transverse tubule (T tubule) is transferred to the sarcoplasmic reticulum (SR), resulting in release of Ca^{2+}. The dihydropyridine receptor (DHPR), which is located in the wall of the transverse tubule, functionally couples the T tubule membrane to the SR membrane. A physical link between DHPR and Ry_1 is thought to transmit a signal across the triadic junction to promote the release of Ca^{2+} necessary to activate the contractile apparatus. The free ionized unbound intracellular Ca^{2+} concentration within the muscle cell increases from the relaxed level of 10^{-7} M to about 5×10^{-5} M. This increase in Ca^{2+} removes the troponin inhibition from the contractile proteins, resulting in muscle contraction. The intracellular Ca^{2+} pumps rapidly transfer Ca^{2+} back into the SR, and relaxation occurs when the concentration is restored to less than mechanical threshold. Both contraction and relaxation require adenosine triphosphate (ATP) (i.e., both are energy-related processes that consume ATP) (Fig. 27-1) (Figure Not Available) .

The clinical and laboratory data in swine and humans indicate decreased control of intracellular Ca^{2+}, resulting in a release of free unbound ionized Ca^{2+} from storage sites that normally maintain muscle relaxation. Aerobic and anaerobic metabolism increases to provide more ATP to drive the Ca^{2+} pumps that maintain Ca^{2+} homeostasis across the sarcolemma into extracellular fluid and into the SR and mitochondria. Virtually all of these reactions are exothermic, that is, they produce heat. Rigidity occurs when unbound myofibrillar Ca^{2+} approaches the contractile threshold.

Figure 27-1 (Figure Not Available) The key ion channels involved in neuromuscular transmission and excitation contraction coupling. Nerve impulses arriving at the nerve terminal activate voltage-gated Ca^{2+} channels (1). The resulting increase in cytoplasmic Ca^{2+} is essential in exocytosis of acetylcholine. Binding of acetylcholine to postsynaptic nicotinic cholinergic receptors activates an integral nonselective cation channel, which depolarizes the sarcolemmal membrane (2). Depolarizing the sarcolemma to threshold activates voltage-gated Na^{+} channels (3), which propagate action potential impulses deep into the muscle via the transverse tubule system. Within the transverse tubule system, L-type voltage-gated Ca^{2+} channels sense membrane depolarization and undergo a conformational change (4). A physical link between the $alpha_1$-subunit and the ryanodine receptor is thought to transfer the signal to sarcoplasmic reticulum to induce the release of stored Ca^{2+} (5). *(Modified from Alberts et al [144])*

Dantrolene is therapeutic because it reduces Ca^{2+} release from the SR without altering Ca^{2+} reuptake.

A more comprehensive description follows; several excellent reviews have been published. [17] [18] [19] [20] [21]

Molecular Events in Excitation-Contraction Coupling

Understanding the mechanisms underlying MH requires brief review of the process of excitation-contraction (EC) coupling, the process by which skeletal muscle transforms a chemical signal in the form of a neurotransmitter at the surface of the fiber into muscle contraction. Figure 27-1 (Figure Not Available) depicts a neuromuscular junction in which an efferent motoneuron synapses with muscle fibers to form a motor endplate. Membrane depolarization at the nerve terminal activates voltage-dependent Ca^{2+} channels on the presynaptic membrane. Rise of cytosolic Ca^{2+} within the nerve terminals initiates a process of vesicle migration and fusion that leads to exocytosis of acetylcholine (ACh) stored within the synaptic vesicles. Simultaneous release of thousands of quanta of ACh results in excitatory postsynaptic potentials. ACh binds to nicotinic ACh receptors, which are nonselective cation channels, and activates inward current (primarily carried by the sodium ion [Na^{+}]), thereby depolarizing the muscle cells. When excitatory postsynaptic potentials sum to threshold, action potentials are propagated from the sarcolemma to the T tubule. Acetylcholinesterase present in the synaptic cleft catalyzes rapid breakdown of ACh; rapid removal of ACh from the synaptic cleft enables the motor unit to be ready for another stimulus within a few milliseconds.

Within the T tubule of skeletal muscle, L-type voltage-gated Ca^{2+} channels, that is, DHPR, are clustered in tetrads and are in close proximity to the terminal cisternae, or junctional SR (Fig. 27-2) (Figure Not Available) . The $alpha_1$-subunit of DHPR functions as a voltage sensor within the T tubule membrane. Membrane depolarization induces a discrete movement of charge within the S4 segment of the DHPR $alpha_1$-subunit. A mechanical signal, thought to be in the form of a conformational transition, is transmitted to the cytoplasmic loop between repeats II and III of the $alpha_1$-subunit. Some evidence suggests a direct physical coupling between the II-III loop of DHPR $alpha_1$ and an as-yet unidentified region within the large hydrophilic cytoplasmic domain of Ry_1. Such a link could transmit a signal across the narrow gap of the triadic junction and could lead to SR Ca^{2+} channel activation. These results are consistent with the nature of skeletal muscle EC coupling, which is independent of extracellular Ca^{2+}. However, after the initial signal, which activates Ca^{2+} release from SR, Ca^{2+}-induced Ca^{2+} release appears to play a role in regulating the temporal and quantitative characteristics of Ry_1 activation. Cytosolic Ca^{2+} is rapidly removed through active transport by sarcoplasmic endoplasmic reticulum Ca^{2+} adenosine triphosphatase ATPase pumps located on junctional and longitudinal SR. Calsequestrin inside the lumen of SR binds to Ca^{2+} and further enhances Ca^{2+} loading within SR. Cytosolic Ca^{2+} is typically brought back to basal nanomolar concentration within 30 ms of muscle contraction. The rapid removal of cytosolic Ca^{2+} is essential for normal muscle relaxation and requires rapid termination of Ca^{2+} efflux from SR. Aberrant termination of Ry_1 activity has emerged as a key underlying mechanism in the etiology of MH susceptibility.

Structure of Ryanodine Receptor

The toxic plant alkaloid ryanodine was first purified and characterized from the powdered stemwood and roots of *Ryania speciosa* Vahl by Rogers and coworkers in 1948. The

---

Figure 27-2 (Figure Not Available) Schematic representation of the triad junction of skeletal muscle showing the junctional foot protein (ryanodine receptor) and its associated proteins. See text for details. *(Modified from Pessah et al [145])*

alkaloid produces profound rigidity in skeletal muscle. Isolation of 9,21-dehydroryanodine from *Ryania* has facilitated the synthesis of radiolabeled ryanodine ([^{3}H]ryanodine) and has permitted direct studies aimed at understanding the mechanism of this muscle poison. The availability of [^{3}H]ryanodine led to identification of a Ry receptor, which in fact is synonymous with the junctional foot protein and possesses Ca^{2+} release channel activity. Ry receptors bind [^{3}H]ryanodine with selectivity and the high-affinity binding interaction is sensitive to the conformational state of the channel (see Fig. 27-2 (Figure Not Available) Fig. 27-3 (Figure Not Available)). High-affinity and low-affinity ryanodine binding sites appear to be located within a 76-kd tryptic fragment from the C-terminus of Ry_1 of rabbit skeletal muscle. The hydrophobic segments within residues 3985-4362 are thought to form the M1-M4 transmembrane domains, enabling Ry_1 to span the SR membrane four times.

However, based on the criteria of MacLennan for structure elucidation of the SR Ca^{2+} -ATPase, Zorzato and coworkers have proposed the presence of an additional eight transmembrane domains. The M1-M4 domains of Ry_1 have high sequence homology to the analogous domains of inositol trisphosphate receptors, suggesting a possible role in forming the SR/ER Ca^{2+} channel pore.

Skeletal (Ry_1), cardiac (Ry_2), and "brain" (Ry_3) isoforms are encoded by three genes located on human chromosomes 19q13.1, 1q42.1-q43, and 15q14-q15, respectively. Based on sedimentation analysis and channel reconstitution studies in bilayer lipid membranes, each functional Ry consists of four identical subunits. Complementary DNA sequence analysis reveals that each Ry protomer is composed of 5032-5037, 4968-4976, and 4872 amino residues with calculated molecular weights of 564-565, 565, and 552 kd for Ry_1, Ry_2, and Ry_3 isoforms, respectively. Typically, a sequence homology of 66 to 70 percent is observed between any two conspecific isoforms. Ry receptors are also highly conserved in the same tissue among different species (>95% sequence homology of Ry_1 found in mammalian skeletal muscle of human, pig, and rabbit). The tetrameric organization of the Ry_1 from skeletal muscle has been corroborated by electron microscopy of cryosections of purified Ry_1 protein. Threedimensional reconstruction of Ry_1 cryosections have revealed the quatrefoil appearance of each homooligomer with four radial channels on the cytoplasmic face, which may converge into a single common transmembrane pore on the luminal face. Direct coupling of alpha $_1$ -subunit of DHPR and Ry_1 has been suggested to be involved in the initial steps of EC coupling in skeletal muscle. In addition, channel gating of Ry_1 has been shown to be modulated by several accessory proteins.

Calmodulin interacts directly with Ry_1 of skeletal muscle with a stoichiometry of two to three calmodulin molecules per subunit. The calmodulin sites with greatest affinity have been localized to the foot region of Ry_1 (see Fig. 27-3 (Figure Not Available)). Through a mechanism independent of kinase activity, calmodulin enhances channel activity at low cytoplasmic Ca^{2+}, whereas it inhibits channel activity at optimal Ca^{2+} (10-100 muM).

Calsequestrin, the major Ca^{2+} binding protein within SR lumen, links indirectly to a luminal domain of Ry_1. The conformational change in Ry_1 also conveys information to the SR lumen through calsequestrin and may be essential in regulating the Ca^{2+} release process. Functional interactions between Ry_1 and calsequestrin have been suggested to play an important role in regulating excitability of the Ca^{2+} channel in response to different filling states of SR.

Triadin, a 95-kd highly basic glycoprotein, was initially suggested to couple Ry_1 and the alpha$_1$ -subunit of DHPR; however, amino acid analysis of triadin indicates but a single pass

---

Figure 27-3 (Figure Not Available) Image reconstruction using cryoelectron microscopy of skeletal muscle ryanodine receptors showing the positions of FKBP12 (FK506 binding protein 12kDa) and calmodulin (CaM). See text for details. *(Modified from Wagenknecht et al [146])*

through the SR membrane, which thus contradicts its hypothesized role in coupling. The extremely high density of basic residues in the luminal terminus of triadin may be critical in interacting with the acidic moiety of Ry_1. The linkage between Ry_1 and triadin is also thought to provide an anchorage site for calsequestrin within the SR lumen.

FKBP12, the major T-cell immunophilin, tightly associates with Ry_1 in skeletal muscle with a stoichiometry of four per channel oligomer. The site on Ry_1 that recognizes FKBP12 is distinct from that which binds calmodulin (see Fig. 27-3) (Figure Not Available) . Binding of FKBP12 appears to stabilize both the closed conformation of the Ca^{2+} channel complex and its full conductance transitions. The immunosuppressant FK506 promotes dissociation of FKBP12 from Ry_1 by competing with a common binding site essential for proteinprotein interaction of the heterocomplex. The resulting FKBP12-deficient channel conducts current with multiple subconductance states. In the presence of channel activators like Ca^{2+} and caffeine, activity of the FKBP12-deficient channel is further enhanced by increasing the mean open time and open probability. Association of FKBP12 to Ry_1 may promote cooperativity among subunits. Dissociation of FKBP12 with FK506 increases maximal binding capacity of [^{3} H]ryanodine with lowered binding affinity, suggesting loss of negative allosteric interaction between high-affinity and low-affinity [^{3} H]ryanodine binding sites. Furthermore, the association of FKBP12 to Ry_1 complex may be involved in promoting cooperativity between neighboring channels. The "coupled gating" behavior of multiple channels has been reported in measurements with multiple channels reconstituted in membrane lipid bilayer by use of recombinant Ry_1 (coexpressed with FKBP12), as well as native SR. Introduction of FK506 dissociates FKBP12 from the recombinant Ry_1 complex and eliminates the coupled gating behavior of multiple channels. The cooperativity between neighboring Ry_1 channels may contribute significantly to the robust release of Ca^{2+} from SR during EC coupling.

Two novel proteins, 60 kd and 90 kd, whose function is unknown, are also found to be associated with the Ry_1 complex; one possesses kinase activity, and the other is the substrate of this kinase. Finally, another 150/160-kd protein is found to be associated with Ry_1. Phosphorylation of the 150/160-kd protein by casein II kinase inhibits Ry_1 channel activity.

The Ry_1 Mutation in Malignant Hyperthermia

Fujii et al first reported MH susceptibility in swine as an autosomal dominant trait that cosegregates with a mutation (Arg615Cys) within the Ry_1 locus on chromosome 6. A homologous mutation occurs within the Ry_1 receptor

---

(Arg614Cys) in humans at q13.1 on chromosome 19, although segregation of this mutation with MH syndrome occurs in less than 5 percent of susceptible individuals. At least 15 additional mutations within the Ry_1 locus have been associated with human MH susceptibility, [22] including Arg163Cys, Gly248Arg, Gly341Arg, Ile403Met, Tyr522Ser, Arg552Trp, Gly2433Arg, and Arg2434His. Association of chromosome 19-linked mutations with MH has been demonstrated in fewer than 50 percent of the families examined. Many of these MH studies are based on *in vitro* contracture tests; the threshold chosen to define a positive diagnosis for MH susceptibility greatly influences the outcome of linkage studies. [22] [23]

Mutations that do not cosegregate on chromosome 19 may be associated with MH. These include region q11.2-24 on chromosome 17 coding for the alpha-subunit of the sodium channel and for the beta- and gamma-subunits of the L-type Ca^{2+} channel; a mutation on chromosome 7 near the gene encoding the alpha$_2$ /delta-subunit of the L-type Ca^{2+} channel; region q31-32 of chromosome 1 coding for the alpha $_1$ -subunit of DHPR. Monnier et al [24] showed a high logarithm of the odds score (LOD = 4.38) between an Arg1086His mutation within the CACNL1A3 gene encoding the alpha $_1$ -subunit of the human skeletal muscle, DHPR-sensitive, L-type, voltagedependent Ca^{2+} channel and susceptibility to MH in a large French family. The mutation is localized in a different part of the alpha $_1$ -subunit than that in previously reported mutations found in patients with hyperkalemic periodic paralysis. If these results are confirmed as MH associated, then human MH is a genetically heterogeneous disorder in which one of several abnormalities occurring in proteins involved in the regulation of EC coupling could render a person susceptible, that is, an MH episode may be the result of abnormalities leading to a final common path.

Functional Changes in Ry_1 Associated with Malignant Hyperthermia Mutations

Altered SR Ca^{2+} channel gating kinetics are thought to underlie the uncontrolled skeletal muscle metabolism associated with administration of halogenated anesthetics or depolarizing agents. The sustained elevation of Ca^{2+} level in the sarcoplasm results in abusive stimulation of both aerobic and glycolytic metabolism, which accounts for a combined acidosis, rigidity, altered permeability, and hyperkalemia. Although studies using Ca^{2+} -selective microelectrodes have indicated that MH-affected muscle has a higher level of resting Ca^{2+}, this has not been confirmed by ratiometric fluorescent Ca^{2+} dyes. Study of the chronologic relationship of the biochemical and clinical development of porcine MH demonstrates that the increase in $[Ca^{2+}]_i$ precedes the increase in expired carbon dioxide and the classic first

sign, tachycardia. [25]

The porcine model has been extensively studied to determine the biochemical and functional changes in SR Ca^{2+} transport and Ry_1 function underlying the MH syndrome. The validity of the single-point porcine Ry_1 mutation for studying the cause of MH has been affirmed by use of the fluorescence calcium indicator indo-1 to determine the concentration of Ca^{2+} in myoblastic cells transfected with either wild-type or mutated Ry_1 complementary DNA. The cells expressing the porcine Ry_1 mutation showed higher sensitivity to caffeine. Further, clinical doses of halothane resulted in a rapid increase of $[Ca^{2+}]_i$ in cells expressing the mutated Ry_1, whereas no changes in $[Ca^{2+}]_i$ were observed in cells expressing the wild-type receptor. These results provide definitive evidence that a single amino acid mutation, namely Arg615Cys, in Ry_1 is causative of porcine MH.

Although active SR Ca^{2+} accumulation appears to be normal in MH-affected pig muscle, significant abnormalities in the Ca^{2+} release process have been documented in several types of *in vitro* bioassays. In skinned muscle fiber preparations, the rate and the extent of Ca^{2+} release from SR were higher in fibers with MH abnormalities than in normal fibers. These results in skinned fibers correlate well with those obtained from isolated SR membrane preparations enriched in Ry_1 protein. Although initial studies revealed a difference in the Ca^{2+} threshold for activation for SR Ca^{2+} release, later studies using rapid quench methods found no apparent difference in the sensitivity of SR Ca^{2+} release with respect to Ca^{2+}. O'Brien and Li [26] developed a microassay that reveals functional differences in Ca^{2+} transport in SR membranes isolated from normal pigs and those with MH susceptibility. They found that SR from swine with MH susceptibility had normal maximal Ca^{2+}-ATPase pumping but that the activity of Ry_1 after addition of a bolus of Ca^{2+} was 50 percent greater in heterozygotes and 100 percent greater in homozygotes for the MH mutation. Hypersensitivity to receptor agonists, such as caffeine, and an associated hyposensitivity to inhibition with Mg^{2+} were also demonstrated. There has been some controversy about whether changes exist in the sensitivity of MH-affected muscles to inhibition by Mg^{2+} compared with normal fibers. [16] Owen et al [27] demonstrated that fibers from pigs heterozygous or homozygous for the Ry_1 MH allele needed only a smaller reduction in free $[Mg^{2+}]$ to induce Ca^{2+} release from SR. Dantrolene counteracted the effect of reduced Mg^{2+} inhibition in MH-affected muscle. Thus, the abnormal responsiveness of MH-affected muscle to various stimuli may and perhaps in large part result from the reduced ability of myoplasmic Mg^{2+} to inhibit Ca^{2+} release from SR.

Reconstitution of channels isolated from MH-susceptible pigs studied in bilayer lipid membranes has revealed significantly reduced sensitivity to inactivating concentrations of Ca^{2+}, whereas the sensitivity of channels to activating Ca^{2+} remains unchanged. [28] Interestingly, Ca^{2+} channels from pigs with MH susceptibility exhibit a significantly higher open probability compared with wild-type channels across a broad range of Ca^{2+} (7muM-10mM) on the cytoplasmic face when measured at pH 6.8. Whether Ca^{2+} channels reconstituted in bilayer lipid membranes from pigs with MH susceptibility exhibit an altered response to inhibition by Mg^{2+} remains controversial. In porcine MH, Mg^{2+} inhibition of Ry_1 channels was not altered, whereas Laver et al [28] found a threefold lower potency for Mg^{2+} inhibition of MHaffected Ca^{2+} channels. The underlying cause of these different experimental results is unclear, but the concentration of monovalent ions used in measuring channel activity may have influenced the inhibitory potency of Mg^{2+}. Channels isolated from pigs heterozygous for the MH mutation suggest that the heterozygous porcine Ca^{2+} release channel population contains heterotetramers with properties distinct

from those of either MH homozygote or normal channels. The data also imply that the Ca^{2+} release channel population in humans with MH syndrome who are heterozygous for a dominant mutation in this protein also contains heterotetrameric channels. In contrast to Ca^{2+} uptake and release studies with isolated SR, single-channel measurements have failed to reveal an altered sensitivity of channels to activation by caffeine.

Radioligand-receptor binding studies with nM [^{3}H]ryanodine have been utilized to determine whether differences exist between SR isolated from normal humans and pigs and those with MH susceptibility. [^{3}H]Ryanodine binding assays represent a sensitive means of assessing functional anomalies regulating the channel pore by use of a simple tube assay. This is possible because [^{3}H]ryanodine binds to a conformationally sensitive site within or near the channel pore. Mickelson et al first demonstrated that the binding of [^{3}H]ryanodine to MH homozygotic porcine heavy SR exhibits an altered Ca^{2+} dependence at the low-affinity (inhibitory) Ca^{2+} site as well as a lower affinity for ryanodine when compared with normal porcine SR. However, the maximum capacity of SR to bind [^{3}H]ryanodine was the same in both tissues, indicating an altered structure and/or function of the receptor rather than a change in expression associated with the disease. Studies performed with Ry_1 isolated from human biopsies revealed a higher affinity for [^{3}H]ryanodine and a higher sensitivity to activation by caffeine with MH syndrome preparations. Surprisingly, it was the activation, not the inactivation, of the binding of [^{3}H]ryanodine by Ca^{2+} that was abnormal in human MH SR.

Dantrolene

Dantrolene is the drug of choice for preventing and reversing the symptoms of MH. Dantrolene sodium is a hydantoin derivative (1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]imino]-2,4-imidazolidinedione) that relaxes but does not totally paralyze skeletal muscle. These properties of dantrolene have been closely correlated with its ability to reduce Ca^{2+} efflux from SR *in vitro.* Using mechanically skinned skeletal muscle fibers from pigs of different Ry_1 genotypes, Owen and coworkers [27] showed that for fibers from pigs homozygous for normal Ry_1, the free Mg^{2+} concentration had to be lowered from the normal resting level of 1 mM to approximately 0.1 mM to induce Ca^{2+} release and a force response. Fibers from pigs heterozygous or homozygous for the MH Ry_1 needed only a smaller reduction in free Mg^{2+} to induce Ca^{2+} release (reduction to 0.1-0.2 and 0.2 mM, respectively). Dantrolene (20 muM) counteracted the effect of this reduced Mg^{2+} inhibition in MH affected muscle. Caffeine contractures induced after K^+ conditioning of skeletal muscles from pigs and mice were found to render muscles refractory to brief electrical stimulation, but there was still an enhancement of contracture tension elicited by subsequent direct caffeine stimulation of SR calcium release. This enhanced sensitivity to caffeine was inhibited by dantrolene (20 muM) and its water-soluble analogue azumolene (150 muM).

Preparations of skeletal SR membrane vesicles have been utilized to examine the ability of dantrolene to alter Ca^{2+} fluxes. Dantrolene (10-90 muM) was shown to inhibit SR Ca^{2+} release, especially when assayed in the presence of caffeine and adenine nucleotide. Later, depolarizationinduced Ca^{2+} release measured from triadic vesicles by use of a stopped-flow apparatus and fura-2 was shown to be inhibited by dantrolene. [29] However, the exact mechanism by which dantrolene induces muscle relaxation is unclear, and some results have been conflicting. For example, halothane-activated Ry_1 from frog skeletal muscle was unaffected by as much as 100 muM of dantrolene, whereas single-channel studies with porcine and human Ry_1 revealed a biphasic action of dantrolene; channel activation at low (0.5-2 nM) concentrations and channel inhibition at a higher (5 muM) concentration. Species differences may in part account for this difference in response.

Radioligand receptor-binding experiments performed with [^{3}H]ryanodine have shown that under certain assay conditions, muM dantrolene or its water-soluble derivative azumolene could inhibit the binding of ryanodine to its conformationally sensitive site. In this respect, doxorubicin-stimulated binding was much more inhibited by dantrolene than by either caffeine or Ca^{2+}-stimulated binding. These results are in agreement with Ca^{2+} transport studies with skeletal SR, in which azumolene was shown to block doxorubicin-induced Ca^{2+} release. However, a later investigation found little pharmacologic overlap between the modulation of [^{3}H]ryanodine and [^{3}H]dantrolene binding sites in porcine skeletal muscle. For example, the binding of [^{3}H]dantrolene was insensitive to ryanodine and Ca^{2+} and adenine nucleotides. Experiments performed with [^{3}H]dantrolene have revealed that specific binding sites for the drug colocalize to junctional SR membranes with [^{3}H]ryanodine-binding sites. [^{3}H]Dantrolene-binding sites were not detected in either T tubule membranes or sarcolemmal membranes. There is still controversy as to whether dantrolene binds directly to the Ry_1 protein or to an accessory protein. Using differential solubilization techniques, Palnitkar and Parness separated specific binding sites for [^{3}H]ryanodine and [^{3}H]dantrolene, suggesting a distinct effector protein for the latter.

Potential Factors in Malignant Hyperthermia Other Than Ry_1 Abnormalities

Other cellular processes affect MH episodes; this impact may be due to their own inherited abnormalities, especially in heterogeneic humans, or to secondary changes prompted by the altered Ry_1. These other processes include DHPR, inositol trisphosphate, lipase and fatty acids, catechol-amines, oxidation-reduction activity, altered ionic reactivity, and the mechanical threshold of muscle.

/das/book/view/29494766/875/286.html

SPECIFIC ORGAN/TISSUE ABNORMALITIES

Skeletal Muscle

Affected human muscle frequently has no histologic defect or else has protean nonspecific pathology so variable that none can be directly attributed to MH. These include

central cores, internal nuclei, target fibers, supercontracted fibrils, and marked variation in fiber diameter. A histologic study found various myopathic and neurologic abnormalities in 58 of 75 patients suspected of having MH; 20 of these 58 patients were MH susceptible. [30]

Metabolism, Enzymatic Considerations, and Heat Production

Affected muscle has greater responses to potent volatile anesthetics, classically halothane, and the depolarizing muscle relaxants, such as SCh, than does normal muscle, whether pig [11] or human. [31] Aerobic metabolism (oxygen consumption, V_{O_2}) and glycolytic metabolism increase dramatically. There is an approximate threefold increase in V_{O_2} and a 15- to 20 fold increase in blood lactate level, with related acid-base imbalances. The earliest changes appear as an increase in muscle intracellular Ca^{2+} concentration [25] and in the venous effluent from skeletal muscle, as decreases in pH or partial pressure of oxygen (Po_2), or as increases in partial pressure of carbon dioxide (Pco_2), lactate, potassium, or temperature. [31] These changes occur before the increases in heart rate, temperature, and circulating catecholamine levels. The most sensitive early sign during anesthesia is an increase in expired carbon dioxide (during constant ventilation), but it can be misleading (see Diagnosis). Heat production during acute MH derives from aerobic metabolism, glycolysis, neutralization of hydrogen ions, and hydrolysis of high-energy phosphate compounds involved in ion transport and contraction-relaxation. [32] Precise calculations of the expended energy are difficult because of unsteady metabolic and circulatory states, variable and uncontrolled heat loss, and production of heat by neutralization of acid.

Contractures

The muscle rigidity that occurs during MH episodes is a contracture rather than a contraction. A contracture is similar to a muscle cramp; it is nonpropagated and prolonged and can be irreversible. A contraction is due to a propagated wave of depolarization that is brief and reversible. Contractures are used in tissue baths in the laboratory to study various aspects of MH. Unfortunately, satisfactory samples of tissue are difficult to obtain; an intact muscle fiber undamaged from tendon to tendon is preferred. Most contracture studies use cut muscle excised from quadriceps; these specimens function satisfactorily in a bath but progressively deteriorate as a result of injury currents from the cut ends. A further modification is the skinned fiber, in which the sarcolemma and portions of the T tubules are either stripped away mechanically or "eaten away" chemically. The tissue bath now becomes the intracellular environment, and laboratory manipulations directly affect function of intracellular organelles. Responses of all these preparations are qualitatively similar; the cut muscle preparation develops much less tension.

Although tension can vary as a result of amounts of Ca^{2+} available to the fibrils, in general, they are exposed to contracture-producing drugs acting via the SR, either directly or indirectly. These drugs include caffeine, [6] halothane [6] [33] or other potent volatile anesthetics, potassium, ryanodine, [34] and 4-chloro-m-cresol. [35] Standardized protocols use either the European or the North American guidelines (see Evaluation of Susceptibility). Whatever the method or drug used, MH syndrome bundles produce low threshold responses.

Intrafibrillar Proteins

The lack of consistent correlation of fiber-type or fiber proteins with abnormal function underscores the difficulties in analyzing this disorder--stress is necessary to detect the abnormality. The altered Ry_1 is expressed in both fast and slow fibers.

Calcium

The SR is the intracellular organelle primarily responsible for control of intracellular Ca^{2+} transients, and mitochondria serve a secondary reserve function in binding Ca^{2+}. When intracellular Ca^{2+} levels increase beyond the capabilities of the SR, the mitochondria begin to bind it. The mitochondrion provides the greatest supply of ATP via aerobic metabolism; only secondarily does it bind and store Ca^{2+}. There is evidence of muscle mitochondrial binding and accumulation of Ca^{2+} during acute MH. [36] In these studies, pigs were evaluated by biopsy before and during MH and after treatment with dantrolene, and mitochondrial functions analyzed elegantly.

Mitochondrial deficiencies do not explain the diminished aerobic responses in MH. V_{O_2} consistently increases about threefold during MH, in contrast to the 10-fold increase possible during severe exercise. In view of the serious acid-base imbalances and depletion of muscle energy stores, this increase seems paradoxically low. Perhaps V_{O_2} and hence ATP production by mitochondria are limited during MH by several factors, including ATP translocation, mitochondrial Ca^{2+} binding, intracellular acid-base, and electrolyte aberrations.

Ca^{2+} antagonists generally affect smooth or cardiac muscle more than skeletal muscle and have contradictory effects in MH: they can block contractures in affected human muscle *in vitro* and are associated with hyperkalemia and potentially increased mortality *in vivo* when used in conjunction with dantrolene. [37] [38] [39] They do not prevent or effectively treat MH in susceptible pigs. [40] [41] Furthermore, in addition to the risk of hyperkalemia with Ca^{2+} antagonists and dantrolene, there is the added hazard that the hyperkalemia could trigger MH in susceptible skeletal muscle. [42]

Electrophysiologic Measurements

The Ca^{2+} control abnormalities of MH are reflected in altered electrophysiology. Multiple pulse stimulation of porcine muscle (six pulses with 5-ms spacing) demonstrated an increase in tension and an increased rate of rise of tension in susceptible pigs; this difference was accentuated after

dantrolene was given, as the susceptible pig muscle recovered much more effectively from the effects of dantrolene than did that of the normal animals. [43] This again suggests abnormally increased Ca^{2+} transients via intracellular organelles. Similar studies in humans disclosed parallel significant differences, but not striking enough

to use in MH testing. [44] During slaughter, affected swine are found to have a lower (and rapidly declining) resting membrane potential than that of normal swine. [45] [46] This may contribute to the rapid decline of muscle pH and energy stores as this is prevented or attenuated by curarization and ventilation to maintain oxygenation. [45] Halothane lowers mechanical threshold in both susceptible and normal muscle, predis-posing susceptible muscle toward the development of a contracture. [47]

Channelopathies

One of the considerations regarding MH and disorders of EC coupling in general is the existence of channelopathies, disorders of the voltage-gated ion channels that control fluxes of ions across membranes. [48] These channels are ion-conducting proteins with a membrane spanning pore, gates, and voltage sensors, equipping them for passage of sodium, calcium, and chloride ions. Chloride channels provide 75 to 80 percent of membrane conductance at rest, thus contributing to the fast repolarization phase of the action potential. These channels are present in the surface and inner membranes of all excitable and most nonexcitable cells. There are naturally occurring mutations that alter their function, with specific pathologic consequences. Abnormalities relating to skeletal muscle pathology include the sodium channel (hyperkalemic periodic paralysis, paramyotonia congenita, and some others, known collectively as potassium-aggravated myotonias), potassium channel (myo-kymias, e.g., episodic ataxia), calcium channel (e.g., DPH receptor (hypokalemic periodic paralysis, muscular dysgenic mouse), and the chloride channel (myotonia congenita in humans, mice, and goats). Channel abnormalities of other tissues are not a part of this chapter, nor are considerations of ligand-gated channels, such as those involving the ACh receptor. The Ry_1 is not a voltage-gated channel per se.

Implications of Findings in Skeletal Muscle

The single-point mutation of Ry_1 in all susceptible pig breeds strongly suggests that this is the major cause of porcine MH [49] and that other abnormalities are secondary or occurring in parallel. Inositol trisphosphate is a major physiologic second messenger mobilizing Ca^{2+} from endoplasmic reticulum, but it does not seem likely to be involved in MH, because it lacks the surface membrane interactions possessed by the Ry_1 for SR. [21] Because human MH does not correlate as strongly genetically with the Ry_1 abnormality, it may be that other inherited abnormalities are important factors. Altered lipase, fatty acids, and triglycerides could then play a more important role. [50] Free-radical peroxidation likely occurs during porcine MH as an adaptive response to sustained stress that contributes to abnormal calcium homeostasis and fatty acid metabolism. [51] Volatile anesthetics and SCh represent a stress for skeletal muscle because they perturb membranes and disturb Ca^{2+} homeostasis. In general, normal muscle can withstand and compensate for these stresses. However, in susceptible muscle, the membrane perturbation induced by halothane or the depolarization induced by SCh may cause an earlier Ca^{2+} release that itself strikingly stimulates greater Ca^{2+} release. Coupled with the lower mechanical contractile threshold, an early MH response may result. Although MH-susceptible muscle may briefly tolerate these stresses, a cascading cycle of increasing metabolism, temperature, and acidosis eventually results. Skeletal muscle represents a "sleeping giant" in regard to metabolism, and, once aroused, it dominates whole body responses. Furthermore, the resting concentration of intracellular Ca^{2+} may be increased in susceptible subjects, apparently without an associated stimulation of metabolism. Thus, MH affected muscle may always be closer to "loss of control" than normal muscle. Normal muscle can respond abnormally with extreme prolonged effort, such as the overstraining disease or capture myopathy of wild animals after prolonged chase. [52]

Heart

Myocardial function is severely altered in human and porcine MH. Initially, tachycardia and arrhythmias occur and are followed by hypotension, decreased cardiac output, and eventual cardiac arrest. The controversy is whether the heart is primarily abnormal, as a consequence of dysfunction directly related to MH, as in skeletal muscle, or whether the heart is affected secondarily by the hyperthermia, acidosis, hyperkalemia, and increased membrane permeability.

Porcine data suggest a secondary involvement: increased myocardial oxygen consumption during MH is related to beta-agonist stimulation of sympathetic activation without the lactate production or potassium efflux that would be suggestive of a primary MH response. [53] Porcine MH myocardium does not respond abnormally to exaggerated concentrations of calcium, digoxin, potassium, or carbon dioxide. [42] Much work has been done on cardiac responses during MH. Overall, it appears to be affected primarily by the tremendous potentially ischemic demands placed on it by exaggerated whole-body metabolism. [54] The Ry defect is expressed in fast and slow skeletal muscle fibers but not in porcine cardiac muscle. [55]

Human myocardial abnormalities were inferred by the higher incidence of sudden death in members of susceptible families and by the occurrence of nonspecific cardiomyopathies and abnormal thallium scans in some affected patients. [31] One might expect that pigs, with their recognized greater frequency of awake MH episodes and MH homogeneity, would provide evidence for primary myocardial abnormalities, if they indeed exist.

Central Nervous System

Central nervous system involvement during fulminant human MH appears to be secondary to increased temperature,

acidosis, hyperkalemia, and hypoxia. With the involved ionic and fluid shifts, changes in plasma osmolality may be factors that in part induce cerebral edema. The extreme picture of coma, areflexia, unresponsiveness, and fixed, dilated pupils suggests acute cerebral edema and intracranial hypertension. Recovery is variable and is related to the duration and severity of the MH episode. Severe fever itself, to 42.5°C, may result in a virtually flat electroencephalogram and coma, but recovery is still possible. [56]

An MH episode is not likely related to the central nervous system, because a limb tourniquet prevented rigidity in the isolated limb when whole-body rigidity existed dur-ing acute episodes. [57] Cerebral oxygen consumption and lactate production are not increased in swine during MH. [58] Kochs et al [59] observed early profound electroencephalographic depression during porcine MH and improvement with dantrolene, and these investigators suggested primary brain involvement. Hofer et al [60] contradicted this opinion by correlating alteration of electroencephalographic and cerebral metabolites with beginning whole-body MH episodes.

Sympathetic Nervous System

Activation of the sympathetic nervous system during MH occurs early. In addition, "fight, fright, or flight" can initiate an MH episode in susceptible swine without anesthetic agents. [9] This is rarely observed in humans (see Awake Triggering). During MH, circulating levels of epinephrine and norepinephrine increase markedly (e.g., from less than 1 ng/mL to 30 ng/mL). Sympathetic responses appear secondary in porcine MH, although the physiologic effects of sympathetic excitation would be expected to magnify the changes of an MH episode. For example, metabolic responses precede altered sympathetic activity [31] ; the MH response is unaltered despite acute sympathetic denervation (total spinal anesthesia) [61] ; infusion of norepinephrine to blood levels greater than those associated with MH does not trigger MH [62] [63] and norepinephrine does not potentiate halothane-induced porcine MH, although triggering is delayed when blood flow to muscle is reduced. [63] beta-Agonist effects result in pronounced myocardial stimulation. [53] alpha- Agonists and beta-agonists do not result in increased metabolism in susceptible porcine muscle. [62] [64]

Sympathetic antagonists may protect from or ameliorate episodes of MH by lowering body temperature and modifying acid-base changes. [65] This protection has been found to be variable and, when demonstrated, has been attributed to an effect on sympathetic-induced MH. It seems more likely that alpha-antagonists merely increase heat loss and potentially increase muscle perfusion. beta-Antagonists attenuate metabolism and fever during MH, yet do not improve survival. [65] In large doses, they completely block the myocardial stimulation that occurs during porcine MH, but this stimulation of metabolism is secondary to beta-agonist effects without evidence of active myocardial MH. [53] Thus, although Wingard's theory resulted in a variety of investigations and counterinvestigations over the ensuing years, there is still no direct evidence that the sympathetic nervous system initiates or plays an important primary role in MH. [31]

Miscellaneous

Disseminated intravascular coagulation frequently occurs during MH, with varying severity. Although a number of causes have been proposed, the most likely appear to be release of tissue thromboplastin during fever, acidosis, hypoxia, hypoperfusion, and gross alterations in membrane permeability of various body tissues. [31] Porcine MH erythrocytes show greater fragility [66] and peroxidation. [67] These findings directly support MH alteration of porcine tissue other than skeletal muscle.

Liver from normal swine transplanted into MHsusceptible swine remains normal, whereas liver from swine with homozygous MH transplanted into normal swine

functions as normal. [68] Pulmonary changes during MH appear to be secondary to systemic manifestations. These include tachypnea, hyperventilation, V/Q abnormalities, increased blood and expired carbon dioxide, decreased blood Po_2, and ultimately pulmonary edema. The increase in whole-body carbon dioxide stores during MH is better reflected by measurements of expired carbon dioxide or mixed venous carbon dioxide than arterial measurements. Renal function during active MH is altered indirectly (i.e., oliguria and anuria secondary to shock, ischemia, cardiac failure, myoglobinuria, and myoglobinemia).

CLINICAL SYNDROME

The onset of MH can be acute and rapid, particularly during induction of anesthesia with an inhaled anesthetic or with the use of SCh. On rare occasions, the onset can be delayed for some hours and may not become overt until the patient is in the recovery room. Regardless of the time of onset, once initiated, the course of MH can be extraordinarily rapid. When clinical signs, such as increased expired carbon dioxide, muscle rigidity, tachycardia, and fever, suggest the presence of MH, the association is not strong unless more than one abnormal sign is noted. When there is but a single suggestive adverse sign, the diagnosis is usually not MH.

The volatile anesthetics and SCh cause affected subjects to undergo a striking increase in metabolism, both aerobic and anaerobic, resulting in intense production of heat, carbon dioxide, and lactate and an associated respiratory and metabolic acidosis. [11] [31] These reactions markedly alter whole-body acid-base balance and temperature because of the large proportion of skeletal muscle to body weight (40-50%) and are magnified as temperature increases. Whole-body rigidity occurs in almost all pigs and in most humans. Temperature may exceed 43°C (109.4°F), Pa CO_2 may exceed 100 mm Hg, and pHa may be less than 7.00. Associated with this is increased permeability of muscle with increased serum levels of potassium, ionized calcium, CK (although MH-related changes do not differ overall from CK changes observed during surgery [69]), myoglobin, and serum sodium. [31] Later, serum potassium and calcium levels decrease; muscle edema may occur. Sympathetic hyperactivity occurs early as a sign of increased metabolism (tachycardia, sweating, hypertension). With metabolic exhaustion, cellular permeability in general may increase, with whole-body

edema, including acute cerebral edema. As MH progresses, disseminated intravascular coagulation and cardiac or renal failure may develop. MH is a disorder of increased metabolism--it need not involve increased temperature, for example, if heat loss is greater than production, or if cardiac output plummets early.

The clinical MH syndrome can occur as a "final common path" in situations that may not involve susceptibility to MH. This is somewhat analogous to observing Raynaud's phenomenon in the absence of Raynaud syndrome. Examples (Table 27-1) include exaggerated heat stroke, the neuroleptic malignant syndrome (NMS), thyroid storm, [70] diabetic coma, [71] alcohol therapy for limb arteriovenous malformation, [72] free blood in cerebrospinal fluid, [73] [74] hypokalemic periodic paralysis, [75] and various myopathies involving constantly and precariously altered permeability of cellular membranes and intracellular organelles, such as Duchenne's muscular dystrophy. [76]

Trismus-Masseter Spasm

Trismus-masseter spasm is defined as jaw muscle rigidity in association with limb muscle flaccidity after administration of SCh. Trismus occurs as a unique property of jaw muscle in normal people.

Masseter and lateral pterygoid muscles contain slow tonic fibers that can respond to depolarizers with a contracture. [77] [78] This is manifested clinically on exposure to SCh as an increase in jaw muscle tone, which was well defined by van der Spek et al. [79] When this increase in jaw muscle tone becomes exaggerated, prolonged, and tight--the so-called jaws of steel--the risk of MH increases greatly. Thus, there

TABLE 27-1 -- Mimics of Malignant Hyperthermia

DISORDER	REFERENCE
Alcohol therapy for limb arteriovenous malformation	[72]
Contrast dye	[136]
Cystinosis	[137]
Diabetic coma	[71]
Drug toxicity or abuse	[31]
Environmental heat gain > loss	[56]
Equipment malfunction and increased carbon dioxide	[103]
Exercise hyperthermia	[98] [138]
Familial hyperthermia, benign	[102]
Freeman-Sheldon syndrome	[143]
Heat stroke	[125]
Hyperthyroidism	[70]
Hypokalemic periodic paralysis	[48] [75]
Intracranial free blood	[73] [74]
Muscular dystrophies--Duchenne, Becker	[76]
Myotonias	[48]
Neuroleptic malignant syndrome	[107]
Osteogenesis imperfecta	[139]
Pheochromocytoma	[138] [140]
Prader-Willi syndrome	[141]
Rhabdomyolysis	[31] [82] [83]
Sepsis	[31]
Ventilation problems	[103]
Wolf-Hirschhorn syndrome	[142]

Figure 27-4 Succinylcholine usually increases jaw muscle tone slightly. In some patients, this increase is moderate, and, in very few, extreme, i.e., "jaws of steel." As much as 50% of this latter group may be MH susceptible. See text for details.

is a spectrum of normal responses: a tight jaw that blends into a rigid jaw and then to a very rigid jaw (Fig. 27-4) . Somewhere in the area of the curve is the boundary for the MH population--the difficulty is in defining it. Trismus may still occur after pretreatment with a defasciculating dose of a nondepolarizing relaxant. If there is rigidity of other muscles in addition to trismus, the association with MH is absolute; anesthesia should be halted as soon as possible and treatment of MH begun. The following considerations involve trismus without rigidity in other muscles.

When trismus occurs, should administration of the anesthetic be halted? Should the patient be given dantrolene? Once trismus occurs, proper monitoring should include end-expired carbon dioxide, examination for cola-colored urine, and arterial or venous blood sampling for CK acid-base status, and electrolyte levels, particularly potassium. The initial degree of tightness of the jaw and its duration should dictate the response of the anesthesiologist. With jaws of steel, the procedure should be halted, especially if the condition persists for more than several minutes. If the jaw is slightly resistant to opening, the anesthesiologist should continue anesthesia while observing the patient. If the jaw is modestly tight and distinctly a problem, then there are two choices: (1) halt the procedure, and (2) continue with nontriggering agents. Any suggestion of MH should prompt MH therapy, including the use of dantrolene. The patient with a fever may have an exaggerated response to SCh's effect in increasing jaw muscle tension. Patients who experience trismus should undergo testing for MH susceptibility to help further our understanding of MH and to provide the means whereby we can determine the relationship of masseter spasm to MH. Trisumus that occurs after use of nondepolarizing muscle relaxants is not apparently related to MH or to hyperkalemia. [80]

Sudden Unexpected Pediatric Cardiac Arrest

MH rarely begins as an abrupt cardiac arrest after the use of SCh during the induction of anesthesia. In the absence of upregulation of nicotinic skeletal muscle ACh receptors, [81]

such a response appears to be due to an occult myopathy that responds to SCh with abrupt massive rhabdomyolysis and an associated acute rapid massive hyperkalemia. [82] [83] Many of these patients are subsequently found to have a myopathy, usually Duchenne. For these reasons, there should be definite indications for using SCh in young children. Case reports available to the MH hotline suggest that this response occurs on five to six occasions in the United States per year, or perhaps in one in every 1 million pediatric anesthesias. It is a devastating response to the caregivers and the family because a previously healthy child can scarcely be resuscitated because of the difficulties during cardiopulmonary resuscitation in redistributing potassium from levels greater than 10 mEq/L to the normal range. With these young patients, heroic efforts in care, including cardiopulmonary bypass, may be successful. [84] These cases may respond acutely to the use of dantrolene because of its effect in stabilizing muscle membrane permeability, and to calcium because it aids in counteracting hyperkalemia by reestablishing the ionic membrane balance in the heart. Because of potential cerebral ischemia, glucose should be administered with caution. A regional survey [85] of 280 British anesthetists (180 responded) noted that 84 percent use SCh routinely and that there were 13 cardiac arrests (with two additional cases of hyperkalemia without accompanying arrest). They concluded that "life-threatening reactions were rare." We wonder how they define "life-threatening reactions."

Rhabdomyolysis

Rhabdomyolysis (see preceding section) may occur during an MH episode or trismus, but milder forms of rhabdomyolysis occur more often than realized. In a study of 11 normal children, those given SCh had a serum myoglobin level of 1,187 ± 615 ng/mL, in contrast to 30 ± 9 ng/mL in those not given SCh. [86] Myoglobinuria with rhabdomyolysis can occur in various muscle disorders and without exposure to SCh. Because of the virtual identity of myoglobin and hemoglobin, myoglobinuria can be misdiagnosed as hemolysis if massive fluid shifts occur during an MH episode. Any unusual anesthetic incident--muscle response, arrhythmia, trismus, fever--should prompt examination of urine color and plasma electrolytes, especially potassium.

TRIGGERING OF MALIGNANT HYPERTHERMIA

Acute episodes depend on three variables: (1) a genetic (perhaps rarely acquired) predisposition, (2) the absence of inhibiting factors, and (3) the presence of a sufficiently potent anesthetic or nonanesthetic trigger.

Anesthetic Triggering

Anesthetic drugs that trigger MH include halothane, enflurane, isoflurane, desflurane, and sevoflurane, as well as SCh. The onset may be explosive if SCh is used. [31] Inbred susceptible swine are identified predictably during an inhalation induction with a potent volatile anesthetic; they develop pronounced hindlimb rigidity within 5 minutes. [31] Prior exercise even an hour before induction of anesthesia increases the severity and hastens the onset of these attacks in swine. [31] Mild hypothermia, depressants such as barbiturates and tranquilizers, and nondepolarizing relaxants delay the onset of MH. [15] [87] [88]

Susceptible humans respond less predictably than swine to these triggers. Many affected humans have previously tolerated potent triggers without visible difficulty. [14] This unpredictability might in part be related to the delaying effects described earlier, as well as to the brevity of short-duration anesthetics. Some patients have experienced MH episodes during anesthesia that did not involve recognized triggering agents [16] ; fortunately, all have responded appropriately to dantrolene. Obviously, the mechanism of anesthetic triggering in humans is unsolved.

Succinylcholine has several variant responses that can occur singly or in combination: (1) a muscle contracture, also noted in muscle that is myotonic or denervated [81] ; (2) a change in muscle membrane permeability without contracture, resulting in the release of CK and myoglobin from muscle (even in normal patients, SCh releases CK and myoglobin from muscle in small amounts; this is exaggerated in the presence of halothane and attenuated by curare, [31] and myoglobin release can be fairly marked even in the absence of obviously discolored urine [86]); and (3) an increase in metabolism, as in MH, usually associated with both muscle contracture and increased membrane permeability. [31]

Nitrous oxide has been proposed as a weak trigger of human MH. [31] This is most unlikely because it has been used repeatedly as the basic anesthetic in MH-susceptible humans and swine without triggering MH. Hyperbaric nitrous oxide does not produce MH in susceptible swine, even in concentrations causing apnea. [89]

Nondepolarizing muscle relaxants block the effects of SCh in triggering MH. They attenuate the effects of the volatile anesthetics. [15] [87] *d*-Tubocurarine has been incriminated as an MH trigger because it produced fever in two susceptible children. [31] *d*-Tubocurarine has been associated with greater lactate production in susceptible pigs exposed to environmental stress, [31] but it has not been shown to be a trigger of MH in susceptible swine; it does produce a contracture in denervated muscle, suggesting that it may have a mild depolarizing action that is not apparent under usual conditions. [90] Reversal of a nondepolarizing neuromuscular blockade has been performed without untoward events in humans with MH susceptibility.

Episodes of MH have been reported during various operative procedures, with general or regional anesthesia, and in extremes of ages. Although rare, prolonged and recurrent MH can still occur despite the absence of triggering agents. [16] Prior fever or SCh-induced trismus should not be ignored, even if the patient survived without obvious mishap. [91] The youngest probable case of MH involved an episode of SCh-related muscle rigidity occurring in utero just before birth. [92] Presumably, the fetus inherited susceptibility from his father that was triggered by anesthetic agents given to his mother.

Volatile agents reportedly stimulate MH Ca^{2+} release in site-specific channel gating actions that occur at lower concentrations than in normal muscle, and perhaps even at subclinical

---

concentrations (see Pathophysiology). It was previously believed that amide local anesthetics, such as lidocaine, could trigger MH. However, the evidence for this effect is weak. Animal data demonstrating Ca^{2+} release from the SR by amide anesthetics involve millimolar concentrations, which can only be achieved clinically by doses of about 2 g. [31] MH is not triggered in the most susceptible species, inbred swine, even if enormous doses of lidocaine are administered intravenously. It is ironic that Kalow et al [6] first commented about the possible efficacy of intravenous local anesthetics in treating MH, when one of the two cases the investigators were referring to involved treatment with intravenous lidocaine. Finally, amide anesthetics are now routinely used without untoward events for nerve block anesthesia in susceptible patients undergoing muscle biopsy.

It has been suggested that long-term propofol infusions in pediatric intensive care may induce MH-type reactions. [93] However, propofol has been demonstrated as safe in patients with MH syndrome, [94] and its effects on membranes of MH-affected skeletal muscle are stabilizing and opposite to those of volatile triggers. [95]

Awake Triggering

Malignant hyperthermia episodes can be triggered with environmental stress in swine (see History). Specific factors include exercise, heat stress, anoxia, apprehension, and excitement. [31] That these responses may be related to muscle movement or to increased temperature is suggested by the following findings: (1) susceptible swine *in vitro* or *in vivo* react with abnormally increased oxygen consumption and lactate production to carbachol or heat (41 to 42°C) but not to alpha-sympathetic and/or beta-sympathetic agonists, [64] [96] and (2) abnormal responses can be blocked or delayed by nondepolarizing relaxants. [15] [31] [45] [87]

Several findings suggest that human MH unrelated to anesthesia may occur. Anxiety reactions may precipitate an apparent MH response. [97] Susceptible families may have an increased incidence of unexplained sudden deaths and may tend to have a nonspecific cardiomyopathy. [31] We cite four case reports as examples of unusual events relating heat stroke, sudden and unexpected death, unusual stress and fatigue, or myalgias to possible awake MH episodes. [98] [99] [100] [101] Two of these involved environmental exposure to highly volatile vapors, and two were related to exercise. Although it is difficult to be certain how many of these types of cases represent human MH episodes in the absence of the anesthetic environment, some of these situations undoubtedly reflect that. The incidence of awake episodes in humans is undoubtedly low, and the less than 100 percent specificity in MH testing will result in some false-positive diagnoses (see Evaluation of Susceptibility). In general, susceptible patients should be advised that it is safe to live their everyday lives. Finally, proposed mechanisms explaining porcine awake MH may not be applicable to human awake MH.

/das/book/view/29494766/875/289.html

DIAGNOSIS

Malignant hyperthermia is a disorder of increased metabolism, the early signs of which may be subtle or masked. Its onset may be delayed until the patient is emerging from the anesthetic. Fulminant MH is now rarely seen because of greater awareness and sophistication in monitoring, and the more subtle onsets must be distinguished from other disorders with similar signs (see Table 27-1) . Some rare families manifest repeated hyperthermia during or after anesthesia, despite pretreatment with dantrolene and other various precautions. [102] These episodes do not feature clinical or laboratory evidence of MH and appear to be familial fever. Postoperative fever in the absence of other signs of MH is unlikely to represent MH.

When the diagnosis is obvious, that is, fulminant MH or SCh-induced rigidity with rapid metabolic changes, there is marked hypermetabolism and heat production, and there may be little time left for specific therapy to prevent death or irreversible sequelae. One could make the diagnosis directly with measurements of increased expired carbon dioxide during constant ventilation. However, other causes must first be ruled out, such as increased temperature with increased V_{O_2}/V_{CO_2} and unchanged controlled ventilation, and a stuck valve with increased inspired carbon dioxide (see Table 27-1 for an exhaustive list). Further, if end-tidal carbon dioxide increases and ventilation is then increased to maintain normal end-tidal values, diagnosis of MH may be delayed. [103] CK values aid in MH diagnosis if they acutely increase to greater than 10,000 U/L, but changes in CK during MH, especially if dantrolene is involved, overlap with changes observed in patients undergoing ordinary surgical procedures, particularly if the surgery is major. [69] A clinical grading scale aids in establishing the likelihood of MH in specific problem cases. It is based on weighted scores for muscle tone, muscle breakdown, acid-base parameters, temperature, tachycardia or other arrhythmias, and response to dantrolene. This scale is hampered if clinical laboratory evaluation has been minimal. [104]

In general, MH would not be expected to occur in any patient given barbiturate/nitrous oxide/opiate/tranquilizer/ nondepolarizing relaxant anesthesia, although there are rare exceptions. [16] When volatile anesthetics or SCh is used, MH should be suspected if there is undue tachycardia, tachypnea, arrhythmias, mottling of the skin, cyanosis, increased temperature, muscle rigidity, sweating, or unstable blood pressure. If any of the preceding abnormalities occurs, signs of increased metabolism, acidosis, or hyperkalemia must be sought. Analysis of arterial blood gases demonstrates metabolic acidosis and may show respiratory acidosis if the patient is unable to increase ventilation as metabolism increases. Central venous oxygen and carbon dioxide levels change more markedly than do those in arterial blood; therefore, end-expired carbon dioxide or central venous carbon dioxide levels are a more accurate reflection of whole-body carbon dioxide stores. Venous carbon dioxide, unless the blood drains an area of increased metabolic activity, should have P_{CO_2} levels only about 5 mm Hg greater than that of expected or measured Pa_{CO_2}. Suggested limits for venous blood include 55 mm Hg for P_{CO_2} and 35 mm Hg for P_{O_2}, assuming that Pa_{O_2} is greater than 100 mm Hg. If Pa_{CO_2} is greater than 60 mm Hg and base deficit is 5 to 7 mEq/L or more, the diagnosis is established (again assuming that other factors have been ruled out). In small children, particularly those who have had no oral food or fluid for a prolonged period, base deficit may be 5 mEq/L because of their smaller energy stores.

ASSOCIATION WITH OTHER DISORDERS

The King-Denborough syndrome, characterized by short stature, musculoskeletal abnormalities, and mental retardation, is associated with susceptibility to MH, as is central core disease (CCD). CCD was present in the family of Denborough's original patient, [5] as was discovered during later evaluations. Phenotypic expression of the Ry_1 mutation is variable; CCD appears to result when more deleterious mutant effects impose greater channel alterations. [105] This may be in part because although MH and CCD can share a locus, CCD must also have an additional locus. [106] Duchenne dystrophy is an X-linked myopathy; the associated deterioration of muscle membranes can result in a clinical MH episode on exposure to membrane perturbors such as MH triggers, despite normal contracture testing results. [76] Patients with Duchenne dystrophy can respond to anesthesia with sudden acute difficult-to-resuscitate cardiac arrest or sudden acute rhabdomyolysis, even without the use of SCh. [76] [82] Patients with occult myopathies of any type, and not necessarily related to MH or to the use of SCh, may experience these potentially and rapidly disastrous anesthetic events [82] (see Sudden Unexpected Pediatric Cardiac Arrest).

Neuroleptic malignant syndrome is caused by central effects of long-term administration of psychoactive drugs (e.g., butyrophenones, phenothiazines, monoamine oxidase inhibitors, lithium, or a combination of these drugs). These result in a slow-onset MH with varied symptoms. There are three key elements of pathophysiology: (1) the patient usually experiences an impairment of motor function with generalized rigidity, akinesis, and/or extrapyramidal disturbances; (2) deterioration in mental status occurs, with coma, stupor, and/or delirium; and (3) hyperpyrexia develops, with deterioration and lability of other "vegetative" functions, resulting in diaphoresis, dehydration, fluctuations in blood pressure and heart rate, and tachypnea. The picture may be similar to that of acute MH, but the onset generally requires several days to several weeks. Treatment involves discontinuation of the drugs and symptomatic control of temperature, acid-base balance, intravenous fluid balance, and muscle tone. Recovery is slow because the drug effects dissipate slowly. Dantrolene aids in therapy of NMS because it lowers muscle heat production and therefore body temperature, and in addition, it eases rigidity without the need for tracheal intubation. NMS and MH are different. [107] NMS responds favorably to electroshock therapy, and MH triggers are safe. Some NMS patients have positive MH muscle biopsy results, and some results are normal.

The relationship of isolated CK elevations and MH susceptibility in otherwise normal asymptomatic individuals remains unclear. In a study of 49 patients, 36 of whom were male, with CK level greater than twice normal on three occasions during a 3-month period, the Mayo group found 19 males and five females with MH susceptibility on contracture testing. This finding may represent another point on the MH spectrum, confirming heterogeneity, or it could include some false-positive results. [108] Some of these patients had received triggers uneventfully.

Other disorders are less convincing in their possible association with MH: crib death, or the sudden infant death syndrome; Smith-Lemli-Opitz syndrome [109] ; Charcot-Marie-Tooth syndrome [110] ; and heat stroke. Exertional heat stroke likely occurs more easily in MH-susceptible individuals. SCh induces contractures in myotonic muscle, which could be confused with MH. Myotonic goats develop brief rigidity after SCh administration but, even with the concomitant use of halothane, show no evidence of MH. In myotonia, there appears to be rigidity in the absence of serious metabolic abnormalities; infrequent positive biopsy results appear to relate to non-MH factors.

TREATMENT

Discontinuation of the trigger may be adequate treatment for acute MH if the onset is slow or if there was a brief administration of the trigger. However, if MH is fulminant (i.e., Pa CO_2 greater than 60 mm Hg and increasing, mixed venous P CO_2 greater than 90 mm Hg and increasing, base deficit greater than 5 mEq/L and falling, and temperature increasing 1°C/15 min), then adequate therapy is urgently needed for survival. In some patients, cardiac output falls rapidly, and there are minor metabolic and acid-base changes because of minimal tissue perfusion. This can result in rapid demise.

Dantrolene is the specific therapeutic drug, but it must be given while adequate muscle perfusion is present. [13] [31] It is also important to use symptomatic therapy to control body temperature, acid-base balance, and renal function. Adjunctive drugs are seldom necessary if proper treatment is begun soon enough. Dantrolene rapidly halts the increases in metabolism and secondarily results in a return to normal levels of catecholamines and potassium. [12] [13] The homeostatic mechanisms of the body then rapidly restore arterial blood pressure, heart rate, and sympathetic hyperactivity back toward normal.

For clinical use, dantrolene is packaged in 20-mg bottles with sodium hydroxide with pH 9 to 10 (otherwise it will not dissolve) and mannitol (for isotonicity). Dantrolene must be dissolved in sterile water rather than solutions such as 5 percent dextrose in water or bicarbonate because the extra molecules in solution lead to a salting-out effect with greater difficulty in dissolving dantrolene. If it does not dissolve immediately, producing a clear yellow to yellow-orange color, it should be heated under tap water or autoclaved for a few minutes. In a dire emergency, it should be administered through a blood filter without concern for crystals. In a fulminant episode in a large adult, as many as 10 bottles may be required to provide the therapeutic dose of 2 mg/kg. This requires the full-time efforts of three or four people. Preoccupation with facets of therapy other than dantrolene can accomplish control of symptomatic factors but can lead to the patient's death as a result of uncontrolled metabolic mayhem within the cells, leading to cell destruction. Dantrolene administration is the key therapy.

Dantrolene cardiac effects are complex and include interactions with calcium antagonists (see Calcium). Intravenous dantrolene, 2 mg/kg, provides therapeutic blood levels with a half-life of at least 10 hours in children and adults. [111] [112] Dantrolene in high doses does not paralyze because the effect plateaus. Peak effects include moderate muscle weakness with adequate strength for deep breathing and coughing. Weakness is accentuated in myopathic patients. The

therapeutic dose may be repeated every 5 minutes for a total dose of 10 mg/kg. Aside from cholestasis during long-term (more than 3 weeks) therapy for spasticity, dantrolene has no serious side effects.

Acute therapy for MH can be summarized as follows:

1. Discontinue all anesthetic agents and hyperventilate with 100 percent oxygen. Normal ventilation is that required to remove metabolic carbon dioxide. Therefore, with increased aerobic metabolism, normal ventilation, by definition, must increase. However, carbon dioxide production is also increased because of neutralization of fixed acid by bicarbonate. Therefore, hyperventilation is needed to remove this additional carbon dioxide.
2. Repeat dantrolene, 2 mg/kg, every 5 minutes to a total dose of 10 mg/kg, if needed.
3. Administer bicarbonate, approximately 2 to 4 mEq/kg. Continued efflux of lactate from skeletal muscle may result in recurrent acidosis [113] because lactate, being ionized, slowly crosses the muscle cell membrane to extracellular fluid.
4. Control fever by whatever means are available, including use of iced fluids, surface cooling, cooling of body cavities with sterile iced fluids, and heat exchanger with a pump oxygenator. [84] One should not become so preoccupied with cooling techniques and other busy work that he or she neglects the prime factor in therapy: intravenous administration of dantrolene. Cooling should be halted at 38 to 39°C to prevent inadvertent hypothermia.
5. Monitor urinary output to prevent shock to kidneys or acute tubular necrosis, as well as to examine for myoglobinuria.
6. Further therapy is guided by blood gases, electrolytes, temperature, arrhythmia, muscle tone, and urinary output.
7. Some clinicians recommend steroids.
8. Perform blood studies (electrolytes, CK, liver profile, blood urea nitrogen, lactate, glucose), coagulation studies (prothrombin time, fibrinogen, activited partial thromboplastin time, fibrinolytic split products, platelet count), and serum hemoglobin and myoglobin and urine hemoglobin and myoglobin studies.

Repetition of the drugs or laboratory studies depends on the clinical course. Dantrolene should probably be repeated at least every 10 to 15 hours (because this is its half-life) for several doses. [111] [112] If there are no signs of recurrence, dantrolene administration may be discontinued.

Treatment of the hyperkalemia should be performed slowly. Plasma K^+ level must be serially monitored because it may be an important factor in treatment (e.g., persistently elevated K^+ level may prevent defibrillation). The most effective way to lower serum potassium is reversal of MH by effective doses of dantrolene. Calcium administration is indicated only for related arrhythmias or for poor cardiac function. However, when indicated, calcium and cardiac glycosides may be used because their administration to the susceptible pig does not trigger MH. [42] They can be life saving during persistent hyperkalemia. [82] Arrhythmias may be treated with either procainamide or lidocaine.

Permanent neurologic sequelae, coma or paralysis, may occur in advanced cases, probably secondary to inadequate cerebral oxygenation and perfusion for the increased metabolism and, because of the fever, acidosis and potassium release. Even satisfactory care during anesthesia may not prevent neurologic complications. Measurements of intracranial pressure may help in the evaluation of cerebral edema.

Disseminated intravascular coagulation or consumptive coagulopathy may be caused by hemolysis, release of tissue thromboplastins, overt tissue damage, or shock. The best treatment is adequate therapy for MH to prevent stagnation of peripheral blood flow and to lower temperature.

Among the ineffective therapeutic adjuncts are calcium antagonists, drugs such as nimodipine, verapamil, nifedi-pine, and diltiazem, and sympathetic antagonists, such as propranolol. Calcium antagonists do not increase porcine survival. [40] [41] Further, they may interact with dantrolene to produce hyperkalemia; this can result in retriggering of MH [42] or in profound myocardial depression. [37] [38] [39] Magnesium reduces the increase in intracellular calcium during porcine MH but does not prevent the increase in metabolism. Although it may play a role in MH mechanisms (see Pathophysiology, Molecular Biology, Genetics, Dantrolene), [27] [28] its therapeutic value appears to be minimal.

Early diagnosis and treatment of MH are essential. The complications that may arise are all difficult to treat and may lead to serious and permanent sequelae. Finally, retriggering may occur even with dantrolene therapy, as the initial dose of the drug is redistributed, metabolized, or excreted.

/das/book/view/29494766/875/292.html

ANESTHESIA FOR SUSCEPTIBLE PATIENTS

Anesthesia should consist of nitrous oxide, barbiturates, etomidate, propofol, opiates, tranquilizers, and/or nondepolarizing muscle relaxants (Table 27-2) . Potent volatile agents, such as halothane, enflurane, sevoflurane, desflurane, and isoflurane, and the depolarizing muscle relaxants, such as SCh, must be avoided, even in the presence of dantrolene. Some human patients have experienced a hypermetabolic state despite these precautions; however, these patients have always responded favorably to intravenous

TABLE 27-2 -- Drugs in Patients Susceptible to Malignant Hyperthermia

UNSAFE	SAFE
Volatile anesthetics [31]	Amide anesthetics
Desflurane	Barbiturates [15] [31]
Enflurane	Calcium [42]
Halothane	Dantrolene [12] [13]
Isoflurane	Digitalis drugs [42]
Sevoflurane [110]	Epinephrine [64]
	Ester anesthetics
Cyclopropane [91]	Etomidate
Ether [3]	Ketamine [31]
Relaxants	Nitrous oxide [31] [89]
Succinylcholine [10] [82] [83]	Nondepolarizing relaxants [87] (except curare, a weak depolarizer [90])
Cautious use:	Norepinephrine [62] [63] [64]
Dantrolene in combination with calcium antagonist [37] [38] [39] [40] [41]	Opiates [31]
	Propofol [94] [95]
	Tranquilizers in general (except chlorpromazine)

dantrolene. [16] The consensus is that in most instances, preoperative dantrolene is not needed in susceptible patients because the use of nontriggering agents is almost always associated with uneventful anesthesia. If used, the dose is 1 to 2 mg/kg given intravenously just before induction. This approach avoids the side effects of lengthy pretreatment. If used in obstetrics, it is best given after the cord is clamped, to avoid the problems of a floppy child because cord blood levels may approach 65 percent of maternal levels. [114] Dantrolene has been used in a heart transplant patient without evident problems. [115]

Regional anesthesia is safe and may be preferred for certain procedures in susceptible patients. Amide anesthetics had been considered dangerous in susceptible patients because they induce or worsen contractures *in vitro* as a result of their effect in increasing calcium efflux from the SR. However, these effects require millimolar concentrations of these drugs, far greater than the plasma values achieved in clinical use. Because of these theoretical considerations, procaine was proposed as a therapeutic drug for MH, and lidocaine was condemned as dangerous. Eventually, porcine and human studies demonstrated the lack of danger of amide anesthetics, and, at present, ester or amide anesthetics may be used safely. Further, intravenous lidocaine was used as long ago as 1970 to treat acute MH without apparent harm and with apparent good results. [6]

It is no longer necessary to clean the anesthetic machine by flushing with oxygen and/or air for many hours. Removal or sealing of the vaporizers, change of soda lime, perhaps replacement of the fresh gas outlet hose, and use of a disposable circle with a flow of 10 L/min for 5 minutes suffice. [116] Use of an expired gas analyzer aids in demonstrating that volatile vapors have been removed from the anesthetic system.

One should discuss the anesthetic care with the patient with the confidence that all will be done to avoid difficulties with MH, and should any problems occur, the appropriate drugs, knowledge, and skills are immediately at hand. Some physicians are overly cautious in handling patients with MH to the point that medical precautions and apprehension are magnified to an exaggerated degree. Many of these patients have undergone certain procedures, such as dental analgesia and obstetric anesthesia, without problems before the diagnosis of susceptibility was made. With such a confident approach, the patient enters the therapeutic environment in a relaxed and comfortable state of mind. Anxiety and stress are minimal, and the patient is reassured by confidence in the doctor's ability to monitor appropriately and to provide proper treatment for any difficulties. Outpatient procedures are feasible in patients with MH in most environments; the time of discharge depends on the usual outpatient criteria.

STRESS-RELATED DISORDERS IN OTHER SPECIES

Several species, such as dogs, cats, and horses, have MH episodes with anesthesia. [31] The pig is well known to have stressed awake MH as well as anesthetic-related MH. Continuing study of the capture myopathy of wild animals, more recently in feral deer, suggests that this is "overstraining" during the chase of normal animals rather than a genetic disorder similar to MH. [117] Broiler chickens, which are inbred to grow faster and develop heftier breast muscles, have a greater incidence of sudden cardiovascular-related death than do ordinary chickens. [118] A strain of laboratory rats has an increased incidence of sudden death during acute respiratory alkalosis. [119] This does not appear to be related to the cardiac potassium shifts observed with rapid reversal of severe hypercarbia. [120]

EVALUATION OF SUSCEPTIBILITY

Evaluation includes a history and physical examination for the detection of subclinical abnormality. A genealogy going back two generations with specific information about anesthetic exposure and agents estimates the likelihood of adequate exposure to triggering agents.

Measurements of blood CK values provide a basic screening tool. CK values, when determined in a resting, fasting state without recent trauma, reflect muscle membrane stability. When CK level is elevated in a close relative of a person with known MH susceptibility, then this relative may be considered to have MH susceptibility without further testing. If the CK level is normal on several occasions, there is no predictive value, and a muscle biopsy with contracture studies is necessary.

Muscle biopsy contracture studies, performed at some 30 centers around the world, use exposures to halothane, caffeine, halothane plus caffeine, ryanodine, [34] [121] or 4-chloro-m-cresol. [35] Contracture responses are sometimes positive in patients with myopathies that bear no direct relationship to MH; one cannot be certain in these cases that the positive biopsy result indicates susceptibility. Patients must not be given dantrolene before the biopsy, because this could mask the response of abnormal muscle to contracture producing drugs. Other drugs might alter contracture responses. For example, Ca^{2+} antagonists *in vitro* decrease halothane contractures, and propranolol *in vitro* decreases caffeine contractures in MH-susceptible humans. However, it is not known whether these drugs are washed out in the muscle bath, with little effect on the results. Contracture testing also evaluates susceptibility in other species, such as pigs and dogs. Nelson [122] observed abnormal animal contracture responses in association with altered Ry_1 but recognized that association does not confirm causality. Cosgrove et al [123] examined contractures in Greyhounds in conjunction with a triggering anesthetic challenge and were unable to confirm that anesthetic-related problems were MH.

For the student of anesthesia, it is only important to remember that susceptible individuals have a lower threshold to the contracture-producing drugs than do normal individuals. However, the muscle specimen must be viable (i.e., must twitch when stimulated electrically) because the contracture threshold may vary if the fiber is degenerating or deteriorating. Bath kinetics are stable with experienced laboratories, and variations in temperature have less effect than anticipated on contracture thresholds. [124]

Once a patient is diagnosed with MH susceptibility, professional advice should include the following: precautions are necessary as regards general anesthesia, and for little else; triggers include all potent volatile agents and SCh;

awake episodes are uncommon, and, if not experienced before the diagnosis is established, are not a worry; military personnel may have restrictions because of the necessary avoidance of combat trauma and the possible mandatory use of triggers, and soldiers with MH susceptibility may be less desirable because some believe that they may fatigue sooner with harsh military conditioning because of their subclinical myopathy. [125] [126]

The predictive value (percentage of positive results that are true positives) or efficiency (percentage of all results that are true, whether positive or negative) of contracture testing in determining susceptibility cannot be estimated. False-positive results resulting from cautious interpretation or decreased specificity are masked because the patient will never be exposed to triggering agents. Both the European and the North American contracture protocols have yielded sufficient multicenter data to confirm acceptable test results. [127] [128] For separation of control patients and those with MH susceptibility based on clinical information that is entirely separate from contracture testing results, both groups used the clinical grading scale [104] to establish the strong likelihood of MH during a specific clinical episode. They used patients with a very low risk of MH susceptibility as controls. The European data include 202 low-risk control patients and 105 patients suspected of having MH, [127] and the North American include 120 low-risk controls and 32 patients suspected of having MH. [128] Both have 97 to 99 percent sensitivity (frequency of positive results in the patients with clinically established MH) and acceptable (78-94%) specificity (frequency of negative results in low-risk controls). Threshold values attempt to provide 100 percent sensitivity so as not to miss any patients with MH susceptibility; this restriction limits specificity.

Thus, the protocols of the North American MH Registry and European MH Group provide uniform contracture testing and acceptable specificity and sensitivity within their own geographic areas. However, minor differences in protocol lead to major difficulties in interpretation of results. [127] The North American protocol uses incremental caffeine concentrations of 0.5, 1, 2, 4, 8, and 32 mM, and halothane 3 percent as a bolus application. The European protocol uses additional steps in its increments, caffeine 0.5, 1, 1.5, 2, 3, 4, and 32 mM, and halothane 0.5, 1, 2, and sometimes 3 percent. Greater fractionation of caffeine and halothane increments in the European protocol results in lower diagnostic thresholds, that is, 0.2 g for both drugs. The lesser fractionation of increments in the North American protocol leads to greater thresholds, 0.3 g for caffeine, and a relatively large gray area for halothane, about 0.5 to 0.8 g. [128] Some investigators urge the use of the combination of halothane and caffeine in testing and believe that some false-negative diagnoses will otherwise occur. [129]

It is now time to standardize the two protocols into a single worldwide test. This would ease interpretation and aid other countries that plan to begin MH testing in selection of a protocol. At present, European test centers, and likely Canadian centers, are performing many more biopsies than American centers because of limitations in care with modern American medicine. Thus, genetic data collection is becoming more comprehensive in these other countries. Uniformity would benefit all and would aid in collating results. Delay in achieving uniformity will slow growth in worldwide recognition of the various mutations in humans with heterogeneic MH susceptibility and will complicate efforts in determining various aspects of human MH. People generally resist efforts at standardization, and delays can restrict development in a field. As an example, about 46 years ago, the pediatric anesthesiologist M. Digby Leigh had the foresight to attempt to establish standard monitoring of expired carbon dioxide; his efforts "... were rebuffed by incredulous scoffers," [130] thus delaying the routine use of one of our more valued standard monitors by about 2 decades.

What is needed in MH testing is an accurate noninvasive or nondestructive measure of susceptibility. Nuclear magnetic resonance probably has the greatest promise. [131] [132] The difficulty is to standardize a stress, such as forearm ischemia, that will differentiate susceptible tissue from normal. As with so many tests, a major problem is establishing conditions whereby no overlap exists between the ranges of normal and susceptible responses. Although ultrasound was recommended as possibly promising, a careful study of skeletal muscle ultrasound was unsuccessful in humans with MH susceptibility. [133] Adnet et al [134] examined masseter muscle in a skinned fiber *in vitro* preparation in attempts to explain its propensity for contracture (see Trismus-Masseter Spasm). They observed greater sensitivity to Ca^{2+} and caffeine than that noted in quadriceps muscle. However, their findings were contradicted in a contracture study of masseter biopsy specimens taken during major craniofacial cancer surgery. [135] Responses of masseter muscle contractures examined in intact cut muscle bundles were similar to those of quadriceps contractures. The response of masseter muscle remains an incompletely explained phenomenon that is fascinating but unlikely to add to innovative probes for MH testing.

/das/book/view/29494766/875/295.html

FINAL COMMENTS

Malignant hyperthermia is a subclinical myopathy that is unmasked on exposure to the potent vaporous anesthetics or SCh; skeletal muscle acutely and unexpectedly increases its oxygen consumption and lactate production, resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation, and increased cellular permeability. MH is caused by a loss of control of Ca^{2+} concentration within the muscle fiber, and it can involve a generalized alteration in cellular or subcellular membrane permeability. This is an EC coupling defect resulting from an alteration in Ry_1. It is a homozygous single-point mutation of Ry_1 in swine and a heterozygous disorder in humans, in whom there might also be a modification of Ry_1 function by interacting structures, membranes, or enzymes; that is, MH may occur as a final common path phenomenon. The study of channelopathies is an aid in defining this area. Diagnosis is made on the basis of extraordinary temperature and acid-base and muscle aberrations. Specific treatment is the action of dantrolene on muscle Ca^{2+} movements; symptomatic treatment is by reversal of acid-base and temperature changes. Evaluation of affected families is guided by measurements of circulating CK and by analysis of druginduced contractures in muscle biopsy specimens. Either general or regional anesthesia is safe for patients susceptible to MH, provided that if a general technique is chosen, care

is taken to specially prepare the anesthesia machine and to avoid all potent volatile anesthetics and SCh.

Research in MH has yielded new insights into the physiology of metabolism and into the molecular biology of genetic muscle disorders. Remaining challenges include identification of the genes responsible for human MH, elucidation of the mechanism that links exposure to the subsequent loss of Ca^{2+} control, development of noninvasive nondestructive testing for susceptibility, and determination of the mode of action of dantrolene.

References

1. Wilson RD, Nichols RJ Jr, Dent TE et al: Disturbances of the oxidative-phosphorylation mechanism as a possible etiological factor in sudden unexplained hyperthermia occurring during anesthesia. Anesthesiology 27:231, 1966.

2. Ording H: Investigation of malignant hyperthermia susceptibility in Denmark. Dan Med Bull 43:111, 1996.

3. Harrison GG, Issacs H: Malignant hyperthermia: An historical vignette. Anaesthesia 47:54, 1992.

4. Ombredanne L: De l'influence de l'anesthesique-employe dans la genese des accidents post-operatoires de paleur-hyperthermie observes chez les nourrissons. Rev Med Fr 10:617, 1929.

5. Denborough MA, Lovell RRH: Anaesthetic deaths in a family. Lancet 2:45, 1960.

6. Kalow W, Britt BA, Terreau ME et al: Metabolic error of muscle metabolism after recovery from malignant hyperthermia. Lancet 2:89, 1970.

7. Herter M, Wilsdorf G: Die Bedeutung des Schweines fur die Fleischversorgung, vol 270. Berlin, Arbeiten der Deutscher Landwirtschaft-Gesellschaft, 1914.

8. Briskey EJ: Etiological status and associated studies of pale, soft, exudative porcine musculature. Adv Food Res 13:89, 1964.

9. Topel DG, Bicknell EJ, Preston KS et al: Porcine stress syndrome. Mod Vet Pract 49:40, 1968.

10. Hall LW, Woolf N, Bradley JWP et al: Unusual reaction to suxamethonium chloride. Br Med J 2:1305, 1966.

11. Berman MC, Harrison GG, Bull AB et al: Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. Nature 225:653, 1970.

12. Harrison GG: Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. Br J Anaesth 47:62, 1975.

13. Kolb ME, Horne ML, Martz R: Dantrolene in human malignant hyperthermia: A multicenter study. Anesthesiology 56:254, 1982.

14. Bendixen D, Skovgaard LT, Ording H: Analysis of anaesthesia in patients susceptible to malignant hyperthermia before diagnostic in vitro contracture test. Acta Anaesth Scand 41:480, 1997.

15. Gronert GA, Milde JH: Variations in onset of porcine malignant hyperthermia. Anesth Analg 60:499, 1981.

16. Pollock N, Hodges M, Sendall J: Prolonged malignant hyperthermia in the absence of triggering agents. Anaesth Intensive Care 20:520, 1992.

17. Zucchi R, Ronca-Testoni S: The sarcoplasmic reticulum Ca^{2+} channel/ryanodine receptor: Modulation by endogenous effectors, drugs and disease states. Pharmacol Rev 49:1, 1997.

18. Mickelson JR, Louis CF: Excitation-contraction coupling, Ca^{2+} release channel, and cell Ca^{2+} regulation defects. Physiol Rev 76:538, 1996.

19. Coronado R, Morrissette J, Sukhareva M et al: Structure and function of ryanodine receptors. Am J Physiol 266:C1485, 1994.

20. Zimanyi I, Pessah IN: Pharmacology of ryanodine-sensitive Ca^{2+} - release channels. In Peracchia C (ed): Handbook of Membrane Channels: Molecular and Cellular Physiology. San Diego, Academic Press, 1994, p 475.

21. Franzini-Armstrong C, Potasi F: Ryanodine receptors of striated muscles: A complex channel capable of multiple interactions. Physiol Rev 77:699, 1997.

22. Tong J, Oyamada H, Demaurex N et al: Caffeine and halothane sensitivity of intracellular Ca^{2+} release is altered by 15 calcium release channel (ryanodine receptor) mutations associated with malignant hyperthermia and/or central core disease. J Biol Chem 272:26332, 1997.

23. Healy JMS, Quane KA, Keating KE et al: Diagnosis of malignant hyperthermia: A comparison of the in vitro contracture test with the molecular genetic diagnosis in a large pedigree. J Med Genet 33:18, 1996.

24. Monnier N, Procaccio V, Stieglitz P et al: Malignant hyperthermia susceptibility is associated with a mutation of the alpha $_1$ -subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. Am J Hum Genet 60:1316, 1997.

25. Ryan JF, Lopez JR, Sanchez VB et al: Myoplasmic calcium changes precede metabolic and clinical signs of porcine malignant hyperthermia. Anesth Analg 79:1007, 1994.

26. O'Brien PJ, Li G: Rapid, simple and sensitive microassay for skeletal muscle homogenates in the functional assessment of the Ca^{2+} -release channel of sarcoplasmic reticulum: Application to diagnosis of susceptibility to malignant hyperthermia. Mol Cell Biochem 167:61, 1997.

27. Owen VJ, Taske NL, Lamb GD: Reduced Mg^{2+} inhibition of Ca^{2+} release in muscle fibers of pigs susceptible to malignant hyperthermia. Am J Physiol 272:C203, 1997.

28. Laver DR, Owen VJ, Junankar PR et al: Reduced inhibitory effect of Mg^{2+} on ryanodine receptor-Ca^{2+} release channels in malignant hyperthermia. Biophys J 73:1913, 1997.

29. Yamaguchi N, Igami K, Kasai M: Kinetics of depolarization-induced calcium release from skeletal muscle triads in vitro. J Biochem 121:432, 1997.

30. Fricker R, Kress HG, Bittner R: Malignant hyperthermia (MH) and morphological references to neuromuscular diseases (NMD). Anesth Analg 84:S188, 1997.

31. Gronert GA: Malignant hyperthermia. Anesthesiology 53:395, 1980.

32. Hall GM, Bendall JR, Lucke JN et al: Porcine malignant hyperthermia. II: Heat production. Br J Anaesth 48:305, 1976.

33. Ellis FR, Harriman DGF, Keaney NP et al: Halothane-induced muscle contracture as a cause of hyperpyrexia. Br J Anaesth 43:721, 1971.

34. Hopkins PM, Ellis FR, Halsall PJ et al: An analysis of the predictive probability of the in vitro contracture test for determining susceptibility to malignant hyperthermia. Anesth Analg 84:648, 1997.

35. Ording H, Glahn K, Gardi T et al: 4-chloro-m-cresol test: A possible supplementary test for diagnosis of malignant hyperthermia susceptibility. Acta Anaesthesiol Scand 41:967, 1997.

36. Stadhouders AM, Viering WAL, Verburg MP et al: In vivo induced malignant hyperthermia in pigs. III: Localization of calcium in skeletal muscle mitochondria by means of electronmicroscopy and microprobe analysis. Acta Anaesthesiol Scand 28:14, 1984.

37. Saltzman LS, Kates RA, Corke BC et al: Hyperkalemia and cardiovascular collapse after verapamil and dantrolene administration in swine. Anesth Analg 63:272, 1984.

38. Rubin AS, Zablocki AD: Hyperkalemia, verapamil, and dantrolene. Anesthesiology 66:246, 1987.

39. Yoganathan T, Casthely PA, Lamprou M: Dantrolene-induced hyperkalemia in a patient treated with diltiazem and metoprolol. J Cardiothor Anesth 2:363, 1988.

40. Harrison GG, Wright IG, Morrell DF: The effects of calcium channel blocking drugs on halothane initiation of malignant hyperthermia in MHS swine and on the established syndrome. Anaesth Intensive Care 16:197, 1988.

41. Gallant EM, Foldes FF, Rempel WE et al: Verapamil is not a therapeutic adjunct to dantrolene in porcine malignant hyperthermia. Anesth Analg 64:601, 1985.

42. Gronert GA, Ahern CP, Milde JH et al: Effect of CO_2, calcium, digoxin, and potassium on cardiac and skeletal muscle metabolism in malignant hyperthermia susceptible swine. Anesthesiology 64:24, 1986.

43. Quinlan JG, Iaizzo PA, Gronert GA et al: Use of dantrolene plus multiple pulses to detect stress-susceptible porcine muscles. J Appl Physiol 60:1313, 1986.

44. Quinlan JG, Wedel DJ, Iaizzo PA: Multiple-pulse stimulation and dantrolene in malignant hyperthermia. Muscle Nerve 13:904, 1990.

45. Bendall JR: The effect of pre-treatment of pigs with curare on the postmortem rate of pH fall and onset of rigor mortis in the musculature. J Sci Food Agric 17:333, 1966.

46. Schmidt GR, Goldspink G, Roberts T et al: Electromyography and resting membrane potential in longissimus muscle of stresssusceptible and stress-resistant pigs. J Anim Sci 34:379, 1972.

47. Gallant EM, Gronert GA, Taylor SR: Cellular membrane potential and contractile threshold in mammalian skeletal muscle susceptible to malignant hyperthermia. Neurosci Lett 28:181, 1982.

48. Lehmann-Horn F, Rudel R: Molecular pathophysiology of voltage-gated channels. Rev Physiol Biochem Pharmacol 128:195, 1996.

49. Fujii J, Otsu K, Zorzato F et al: Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. Science 253:448, 1991.

50. Wieland SJ, Gong Q-H, Fletcher JE et al: Altered sodium current response to intracellular fatty acids in halothane-sensitive skeletal muscle. Am J Physiol 271:C347, 1996.

51. Duthie GG, Arthur JR: Free radicals and calcium homeostasis: Relevance to MH? Free Radic Biol Med 14:435, 1993.

52. Martucci RW, Jessup DA, Gronert GA et al: Blood gases and catecholamine levels in capture stressed desert bighorn sheep. J Wildl Dis 28:250, 1992.

53. Gronert GA, Theye RA, Milde JH et al: Catecholamine stimulation of myocardial oxygen consumption in porcine malignant hyperthermia. Anesthesiology 49:330, 1978.

54. Roewer N, Dziadzka A, Greim CA et al: Cardiovascular and metabolic responses to anesthetic-induced malignant hyperthermia in swine. Anesthesiology 83:141, 1995.

55. Ervasti JM, Strand MA, Hanson TP et al: Ryanodine receptor in different malignant hyperthermia-susceptible porcine muscles. Am J Physiol 260:C58, 1991.

56. Cabral R, Prior PF, Scott DF et al: Reversible profound depression of cerebral electrical activity in hyperthermia. Electroencephalogr Clin Neurophysiol 42:697, 1977.

57. Satnick JH: Hyperthermia under anesthesia with regional muscle flaccidity. Anesthesiology 30:472, 1969.

58. Artru AA, Gronert GA: Cerebral metabolism during porcine malignant hyperthermia. Anesthesiology 53:121, 1980.

59. Kochs E, Roewer N, Schulte am Esch J: Improvement of brain electrical activity during treatment of porcine malignant hyperthermia with dantrolene. Br J Anaesth 71:881, 1993.

60. Hofer RE, Wedel DJ, Sharbrough FW: The effects of malignant hyperthermia on cerebral metabolites and the electroencephalogram in Pietrain swine. Anesthesiology 79:A435, 1993.

61. Gronert GA, Milde JH, Theye RA: Role of sympathetic activity in porcine malignant hyperthermia. Anesthesiology 47:411, 1977.

62. Gronert GA, White DA: Failure of norepinephrine to initiate porcine malignant hyperthermia. Pflugers Arch 411:226, 1988.

63. Maccani RM, Wedel DJ, Hofer RE: Norepinephrine does not potentiate porcine malignant hyperthermia. Anesth Analg 82:790, 1996.

64. Gronert GA, Milde JH, Taylor SR: Porcine muscle responses to carbachol, alpha- and beta-adrenoceptor agonists, halothane or hyperthermia. J Physiol (Lond) 307:319, 1980.

65. Lister D, Hall GM, Lucke JN: Porcine malignant hyperthermia. III: Adrenergic blockade. Br J Anaesth 48:831, 1976.

66. Reiner G, Dzapo V: Erythrocyte osmotic fragility in porcine malignant hyperthermia and effects of halothane. J Vet Med A36:269, 1989.

67. Duthie GG, Arthur JR, Bremner P et al: Increased peroxidation of erythrocytes of stress-susceptible pigs: An improved diagnostic test for porcine stress syndrome. Am J Vet Res 50:84, 1989.

68. Carr RJ, Belani KG, Iaizzo PA et al: Porcine malignant hyperthermia and liver transplantation: Further insight into systemic pathophysiology. Anesth Analg 80:S68, 1995.

69. Antognini JF: Creatine kinase alterations after acute malignant hyperthermia episodes and common surgical procedures. Anesth Analg 81:1039, 1995.

70. Yamamoto Y, Tanaka H, Ikeda K: A case in which it was difficult to differentiate between malignant hyperthermia and thyroid storm. Anesth Resuscitation 32(suppl):85, 1996.

71. Wappler F, Roewer N, Kochling A et al: Fulminant malignant hyperthermia associated with ketoacidotic coma. Intensive Care Med 22:809, 1996.

72. Behnia R: Systemic effects of absolute alcohol embolization in a patient with a congenital arteriovenous malformation of the lower extremity. Anesth Analg 80:415, 1995.

73. DeRuyter ML, Wedel DJ, Berge KH: Hyperthermia requiring prolonged administration of high-dose dantrolene in the postoperative period. Anesth Analg 80:834, 1995.

74. Kitanaka C, Inoh Y, Toyoda T et al: Malignant brain stem hyperthermia caused by brain stem hemorrhage. Stroke 25:518, 1994.

75. Lambert C, Blanloeil Y, Krivosic-Horber R et al: Malignant hyperthermia in a patient with hypokalemic periodic paralysis. Anesth Analg 79:1012, 1994.

76. Gronert GA, Fowler W, Cardinet GH III et al: Absence of malignant hyperthermia contractures in Becker-Duchenne dystrophy at age 2. Muscle Nerve 15:52, 1992.

77. Butler-Browne GS, Eriksson P-O, Laurent C et al: Adult human masseter muscle fibers express myosin isozymes characteristic of development. Muscle Nerve 11:610, 1988.

78. Morgan DL, Proske U: Vertebrate slow muscle: Its structure, pattern of innervation, and mechanical properties. Physiol Rev 64:103, 1984.

79. van der Spek AFL, Reynolds PI, Fang WB et al: Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants. Br J Anaesth 64:21, 1990.

80. Albrecht A, Wedel DJ, Gronert GA: Masseter muscle rigidity and non-depolarizing neuromuscular blocking agents. Mayo Clin Proc 72:329, 1997.

81. Martyn JAJ, White DA, Gronert GA et al: Up-and-down regulation of skeletal muscle acetylcholine receptors: Effects on neuromuscular blockers. Anesthesiology 76:822, 1992.

82. Larach MG, Rosenberg H, Gronert GA et al: Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathy. Clin Pediatr (Phila) 36:9, 1997.

83. Schulte-Sasse U, Eberlein HJ, Schmucker I: Sollte die Verwendung von Succinylcholin in der Kinderanasthesie neu uberdacht werden? Anaesthol Reanimat 18:13, 1993.

84. Lee G, Antogninin JF, Gronert GA: Complete recovery after prolonged resuscitation and cardiopulmonary bypass for hyperkalemic cardiac arrest. Anesth Analg 79:172, 1994.

85. Robinson AL, Jerwood DC, Stokes MA: Routine suxamethonium in children: A regional survey of current usage. Anaesthesia 51:874, 1996.

86. Brustowicz RM, Moncorge C, Koka BV: Metabolic responses to tourniquet release in children. Anesthesiology 67:792, 1987.

87. Hall GM, Lucke JN, Lister D: Porcine malignant hyperthermia. IV: Neuromuscular blockade. Br J Anaesth 48:1135, 1976.

88. Iaizzo PA, Kehler CH, Carr RJ et al: Prior hypothermia attenuates malignant hyperthermia in susceptible swine. Anesth Analg 82:803, 1996.

89. Gronert GA: Hyperbaric nitrous oxide and malignant hyperpyrexia. Br J Anaesth 53:1238, 1981.

90. McIntyre AR, King RE, Dunn AI: Electrical activity of denervated mammalian skeletal muscle as influenced by d-tubocurarine. J Neurophysiol 8:297, 1945.

91. Lips FJ, Newland M, Dutton G: Malignant hyperthermia triggered by cyclopropane during cesarean section. Anesthesiology 56:144, 1982.

92. Sewall K, Flowerdew RMM, Bromberger P: Severe muscular rigidity at birth: Malignant hyperthermia syndrome? Can Anaesth Soc J 27:279, 1980.

93. Plotz FB, Waalkens HJ, Verkade HJ et al: Fatal side-effects of continuous propofol infusion in children may be related to MH. Anaesth Intensive Care 24:724, 1996.

94. McKenzie AJ, Couchman KG, Pollock N: Propofol is a "safe" anaesthetic agent in malignant hyperthermia susceptible patients. Anaesth Intensive Care 20:165, 1992.

95. Fruen BR, Mickelson JR, Roghair TJ et al: Effects of propofol on Ca^{2+} regulation by malignant hyperthermia-susceptible muscle membranes. Anesthesiology 82:1274, 1995.

96. Ording H, Hald A, Sjontoft E: Malignant hyperthermia triggered by heating in anaesthetized pigs. Acta Anaesth Scand 29:698, 1985.

97. Fletcher R, Ranklev E, Olsson AK et al: Malignant hyperthermia syndrome in an anxious patient. Br J Anaesth 53:993, 1981.

98. Ogletree JW, Antognini JF, Gronert GA: Postexercise muscle cramping associated with positive malignant hyperthermia contracture testing. Am J Sports Med 24:49, 1996.

99. Ryan JF, Tedeschi LG: Sudden unexplained death in a patient with a family history of malignant hyperthermia. J Clin Anesth 9:66, 1997.

100. Anetseder M, Hartung E, Klepper S et al: Gasoline vapors induce severe rhabdomyolysis. Neurology 44:2393, 1994.

101. Denborough MA, Hopkinson KC, Banney DG: Firefighting and malignant hyperthermia. Br Med J 296:1442, 1988.

102. Lee DS, Adams JP, Zimmerman JE: Malignant hyperthermia: A possible new variant. Can Anaesth Soc J 32:268, 1985.

103. Karan SM, Crowl F, Muldoon SM: Malignant hyperthermia masked by capnographic monitoring. Anesth Analg 78:590, 1994.

104. Larach MG, Localio AR, Allen GC et al: A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 80:771, 1994.

105. Lynch PJ, Krivosic-Horber R, Reyford H et al: Identification of heterozygous and homozygous individuals with the novel RYR1 mutation Cys35Arg in a large kindred. Anesthesiology 86:620, 1997.

106. Fagerlund TH, Islander G, Ranklev-Twetman E et al: Recombination between the postulated CCD/MHE/MHS locus and RYR1 gene markers. Clin Genet 50:455, 1996.

107. Keck PE Jr, Caroff SN, McElroy SL: Neuroleptic malignant syndrome and malignant hyperthermia: End of a controversy? J Neuropsychiatry Clin Neurosci 7:135, 1995.

108. Weglinski MR, Wedel DJ, Engel AG: Malignant hyperthermia testing in patients with persistently increased serum CK levels. Anesth Analg 84:1038, 1997.

109. Haji-Michael PG, Hatch DL: Smith-Lemli-Opitz syndrome and malignant hyperthermia. Anesth Analg 83:200, 1996.

110. Ducart A, Adnet P, Renaud B et al: Malignant hyperthermia during sevoflurane anesthesia. Anesth Analg 80:609, 1995.

111. Lerman J, McLeod ME, Strong HA: Pharmacokinetics of intravenous dantrolene in children. Anesthesiology 70:625, 1989.

112. Flewellen EH, Nelson TE, Jones WP et al: Dantrolene dose response in awake man: Implications for management of malignant hyperthermia. Anesthesiology 59:275, 1983.

113. Gronert GA, Ahern CP, Milde JH: Treatment of porcine malignant hyperthermia: Lactate gradient from muscle to blood. Can Anaesth J 33:729, 1986.

114. Shime J, Gare D, Andrews J et al: Dantrolene in pregnancy: Lack of adverse effects on the fetus and newborn infant. Am J Obstet Gynecol 159:831, 1988.

115. Koehntop DE, Beebe DS, Belani KG: The safety of dantrolene in a patient with a severe cardiomyopathy requiring a heart transplant. Anesth Analg 85:229, 1997.

116. Beebe JJ, Sessler DI: Preparation of anesthesia machines for patients susceptible to malignant hyperthermia. Anesthesiology 69:395, 1988.

117. Antognini JF, Eisele PH, Gronert GA: Evaluation for malignant hyperthermia susceptibility in black-tailed deer. J Wildl Dis 32:678, 1996.

118. Reiner G, Hartmann J, Dzapo V: Skeletal muscle sarcoplasmic calcium regulation and sudden death syndrome in chickens. Br Poultr Sci 36:667, 1995.

119. Belonje PC, Wilson GR, Berman PA et al: Sudden death in laboratory rats induced by acute respiratory alkalosis: Biochemical similarities to malignant hyperthermia in pigs. South Afr J Sci 91:18, 1995.

120. Brown EB, Mowlem A: Potassium loss from the heart during the immediate posthypercapnic period. Am J Physiol 198:962, 1960.

121. Hartung E, Koob M, Anetseder M et al: Malignant hyperthermia (MH) diagnostics: A comparison between the halothane-caffeine- and the ryanodine-contracture-test results in MH susceptible, normal and control muscle. Acta Anaesthesiol Scand 40:437, 1996.

122. Nelson TE: Do ryanodine contractures in skeletal muscle from malignant hyperthermia susceptible humans, pigs and dogs equate to MH mutations? Anesthesiology 79:441, 1993.

123. Cosgrove SB, Eisele PH, Martucci RW et al: Evaluation of Greyhound susceptibility to malignant hyperthermia using halothanesuccinylcholine anesthesia and caffeine-halothane contractures. Lab Anim Sci 42:482, 1992.

124. Antognini JF, Gronert GA: Effect of temperature variation (22C-44C) on halothane and caffeine contracture testing in humans. Acta Anaesthesiol Scand 41:639, 1997.

125. Bourdon L, Canini F: On the nature of the link between malignant hyperthermia and exertional heatstroke. Med Hypotheses 45:268, 1995.

126. Ben Abraham R, Cahana A, Krivosic-Horber RM et al: Malignant hyperthermia susceptibility: Anaesthetic implications and risk stratification. Review. Q J Med 90:13, 1997.

127. Ording H, Brancadoro V, Cozzolino S et al: In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH group: Results of testing patients surviving fulminant MH and unrelated low-risk subjects. Acta Anaesthesiol Scand 41:955, 1997.

128. Allen GC, Larach MH, Kunselman AR: The sensitivity and specificity of the caffeine halothane contracture test: A report from the North American malignant hyperthermia registry. Anesthesiology 88:579, 1998.

129. Wedel DJ, Nelson TE: Malignant hyperthermia--Diagnostic dilemma: False negative contracture responses with halothane and caffeine alone. Anesth Analg 78:787, 1994.

130. Smith RM: History of pediatric anesthesia. In Motoyama EK, Davis PJ (eds): Smith's Anesthesia for Infants and Children. 6th ed. St. Louis, Mosby, 1996, p 909.

131. Payen J-F, Fouilhe N, Sam-Lai E et al: In vitro 31P-magnetic resonance spectroscopy of muscle extracts in malignant hyperthermiasusceptible patients. Anesthesiology 84:1077, 1996.

132. Bendahan D, Kozak-Ribbens G, Confort-Gouny S et al: Definition d'un score diagnostique de l'hyperthermie maligne par spectroscopie de resonance magnetique du P-31. Ann Fr Anesth Reanim 15:583, 1996.

133. Antognini JF, Anderson M, Cronan M et al: Ultrasonagraphy: Not useful in detecting susceptibility to malignant hyperthermia. J Ultrasound Med 13:371, 1994.

134. Adnet PJ, Reyford H, Tavernier BM et al: In vitro human masseter muscle hypersensitivity: A possible explanation for increase in muscle tone. J Appl Physiol 80:1547, 1996.

135. Melton AT, Antognini JF, Gronert GA: In vitro contracture tests on normal human masseter muscle. Anesth Analg 84:S368, 1997.

136. Mozley PD: Malignant hyperthermia following intravenous iodinated contrast media. Diagn Gynecol Obstet 3:81, 1981.

137. Purday JP, Montgomery CJ, Blackstock D: Intraoperative hyperthermia in a paediatric patient with cystinosis. Paediatr Anaesth 5:389, 1995.

138. Scully RE (ed): Case records of the Mass General Hospital. N Engl J Med 331:259, 1994.

139. Peluso A, Cerullo M: Malignant hyperthermia susceptibility in patients with osteogenesis imperfecta. Paediatr Anaesth 5:398, 1995.

140. Allen GC, Rosenberg H: Phaeochromocytoma presenting as acute malignant hyperthermia: A diagnostic challenge. Can J Anaesth 37:595, 1990.

141. Arakura K, Narita M, Nisimura C et al: Malignant hyperthermia in a child with Prader-Willi syndrome. Anesth Resuscitation 32(suppl):53, 1996.

142. Ginsburg R, Purcell-Jones GMH: Malignant hyperthermia in the Wolf-Hirschhorn syndrome. Anaesthesia 43:386, 1988.

143. Jones R, Dolcourt J: Muscle rigidity following halothane anesthesia in two patients with Freeman-Sheldon syndrome. Anesthesiology 77:599, 1992.

144. Alberts B, Bray D, Lewis J et al: Molecular Biology of the Cell. 3d ed. New York, Garland Press, 1994.

145. Pessah IN, Lynch C III, Gronert GA: Complex pharmacology of malignant hyperthermia. Anesthesiology 84:1275, 1996.

146. Wagenknecht T, Radermacher M, Grassucci R et al: Locations of calmodulin and FK506-binding protein on the three-dimensional architecture of the skeletal muscle ryanodine receptor. J Biol Chem 272:32463, 1997.

Chapter 28 - Fundamental Principles of Monitoring Instrumentation

James F. Szocik
Steven J. Barker
Kevin K. Tremper

INTRODUCTION

Patient monitoring has been a key aspect of anesthesiology since its beginnings as a medical specialty. As anesthesiology has grown more sophisticated and complex, so have the monitors and the data they produce. The anesthesiologist's senses of sight, hearing, and touch, at first expanded with the stethoscope, sphygmomanometer, and electrocardiograph, are now supplemented by the pulse oximeter, expired gas analyzer, evoked potential monitor, and transesophageal echocardiograph, to name a few. The complexity of some of these devices can be intimidating, and we are tempted to regard them as incomprehensible "black boxes" that provide us with clinical data. However, to do so would be to shirk an important part of our clinical responsibility. We must be able not only to understand and interpret the data from our monitors but also to anticipate and recognize errors associated with their use. We cannot accomplish this without understanding how these devices work.

The purpose of this chapter is to provide an understanding of the scientific principles underlying the design and function of our most commonly used monitors. An introduction defining some concepts of basic physics is followed by more detailed descriptions of the principles. The text and figures explain these principles predominantly in a qualitative manner. For those desiring a more quantitative explanation, the relevant equations are provided in the appendices to this chapter.

BASIC PRINCIPLES

Nature of Physics and Measurement

What is monitoring? The verb *monitor* (derived from the Latin *monere,* "to warn") means to check systematically or to keep watch over. In the context of anesthesiology, monitoring means using both our senses and electronic devices to

repeatedly or continuously measure important variables in the anesthetized patient.

Physics is the science of matter and energy and of the interactions between the two, that is, it is the study of everything in the physical universe. Physics encompasses everything from the motions and inner workings of the atom to those of galaxies. Physics is quantitative, and mathematics is the language of physics. In fact, Isaac Newton invented "the calculus" as a tool for expressing and studying the laws of physics. Our monitors are also quantitative. Before we can discuss and understand the complexity of modern anesthetic monitors, we must quantitatively define that which we are attempting to measure.

We measure and monitor mass and energy: how much of a substance is present and in what energy state. Much of what we desire to monitor is outside of the range of the human physical senses. Therefore, we must measure in this insensible realm using devices that enhance or extend our senses. Just as the senses have limitations and can be "fooled" under certain circumstances (Fig. 28-1) , our physiologic monitors are limited by their design and can also be fooled under some conditions. The intelligent user of these devices must understand their basic design assumptions in order to predict when they are likely to produce erroneous data.

As we make measurements of mass, space, time, and other physical variables, we often encounter confusion between the terms *units* and *dimensions.* A dimension describes

Figure 28-1 Optical illusions. We perceive the circles to be different sizes because we infer the size by relative dimension. The closeness of the smaller circles makes the inner circle appear smaller, and vice versa. The lines appear to be different sizes because we use straight-line perspective to estimate size and distance. This illusion reportedly does not work in cultures where straight lines are not used. Therefore, our internal perceptions lead us to err in estimating size and length. In the same way, the internal programming of our monitors can lead us to misinterpret results.

the measure by which a physical variable is expressed quantitatively. For example, length (l) is the dimension used to describe distance, height, or width. Units are specific ways of measuring a given dimension: meters, feet, furlongs, and light-years are all units of length. In basic mechanics, all dimensions can be expressed in terms of the three *fundamental dimensions* of mass (m), length (l), and time (t). In problems of energy transport, a additional dimension of temperature or heat content must be added. In electricity and magnetism, the dimension of charge is also required.

As stated earlier, *units* are specific ways of measuring a particular dimension. Although there are many units of mass, length, and time, the scientific community has standardized to the *Systeme International d' Unites,* or SI units: length in meters, mass in kilograms, time in seconds. To understand how all quantities in basic mechanics can be expressed in terms of mass (m), length (l), and time (t), we must introduce one (and *only* one) equation: Newton's second law of motion, the basis of all classical physics:

Stated in English, force equals mass times acceleration. Force and acceleration are *vectors;* that is, they have both a magnitude and a direction. Mass is a *scalar;* it has only a magnitude. From this simple equation, we can see that the dimensions of force must be the dimensions of mass times those of acceleration. Acceleration is the rate of change of velocity, and velocity is the rate of change of distance. Thus, velocity has dimensions of length divided by time, l/t, and acceleration has dimensions of l/t/t, or l/t^2 The SI units of acceleration are meters per second per second, or m/s^2 . Because the SI unit of mass is the kilogram, Equation 1 tells us that the unit of *force* must be $kg\text{-}m/s^2$ (kilogram-meters per second squared). This unit is called the *newton,* after Sir Isaac, so that one newton equals one $kg\text{-}m/s^2$.

Other dimensions and units can be derived in the same way. For example, kinetic energy is proportional to mass times velocity squared (Mv^2), so its dimensions are $M(L/t)^2$, and its SI unit is the $kg\text{-}m^2/s^2$. Because "kilogram-meter squared per second squared" is quite a mouthful, we define this unit of energy as the *joule.* The term *power* refers to the time derivative of energy, that is, the change in energy per unit time. The unit of power is thus the joule per second, which we call the *watt.* One watt equals one joule per second. Throughout physics, there are many other "practical units," which can always be related to SI units. For example, we are all familiar with *horsepower* as a unit of the power of an engine. One horsepower equals 746 watts.

Measurement is the determination of a physical quantity (e.g., mass, length, time, energy, and any of their derivatives). Measuring depends on a physical interaction. If a mass or energy does not interact with anything, it cannot be perceived to exist. As we have stated, physics uses the second, meter, and kilogram to measure time, space, and matter. How do we define the size of these standard units? Historically, the second was defined as a fraction (1/60 of 1/60 of 1/24) of a day. However, because of tidal forces on the earth, the days are becoming longer, and the second is now defined as the interval required for 9,192,631,770 vibrations of the cesium-133 atom measured via atomic beam clock. The meter

was originally one ten-millionth of the distance from the North Pole to the Equator. In 1960, the meter was redefined to be 1,650,763.73 wavelengths of orange-red light from a krypton-86 lamp. Today, the meter is defined as the distance light travels in a vacuum during a time of 1/299,792,458 second because time can be measured with better accuracy and precision than the wavelengths of the krypton lamp. The gram was originally defined as the weight of that volume of pure water at 4°C, which occupies a cube that is onehundredth of a meter on all sides. Today, the kilogram is defined as a unit of mass based on a physical standard (a platinum-iridium cylinder).

Temperature is related to the energy per unit mass of a substance in the form of motions on an atomic level. When an object of higher temperature is brought in contact with one of lower temperature, thermal energy, or *heat,* spontaneously passes from the "hot" to the "cold" object until the two reach equilibrium at a temperature between the two original temperatures. In gases, temperature is a quantitative measure of the kinetic energy of molecular motion per unit mass. In 1742, Celsius proposed a temperature scale of *degrees* using the freezing point of water as 0°C and the boiling point of water at one atmospheric pressure as 100°C. A temperature of absolute zero is defined as the point at which the molecules in a substance are in their lowest possible energy state. This condition occurs at -273.15°C or, in SI units, 0° *Kelvin* (K).

Physical measurements can be either continuous or discrete. That is, we can measure a distance of 3.1416 m, but we cannot measure out 3.1416 eggs. We consider most numerically defined quantities to be continuous. However, when we measure very tiny quantities (wavelengths of light, energies of photons, masses of atoms), we find that our measurements are not continuous; they change in small jumps, or *quanta.* Continuous measurement is thus an illusion, but a practical one for most purposes.

Accuracy

All measurements have errors. Error is usually determined by the comparison of a measurement to a "gold standard" of that measure. Unfortunately, all measurements, even the so-called gold standards, are subject to errors with respect to reproducibility. From a clinician's perspective, we can depend on a physiologic measurement only if it is accurate to the degree required for clinical decision making. For example, there are several ways to measure systemic blood pressure. We can listen to Korotkoff sounds by use of a sphygmomanometer cuff and stethoscope; we can rely on an oscillometric automated noninvasive blood pressure device, or if we need continuous measurement, we may place an arterial cannula. [1] Unfortunately, each of these techniques provides a slightly different arterial blood pressure value, and each has different sources of error. Our choice of method may be determined by accuracy or by our needs for the frequency of the data and the ease of retrieving these data. An automatic oscillometric device is usually chosen over manual auscultatory measurements for ease of acquisition and reproducibility. Two people taking auscultatory blood pressure may hear the Korotkoff sounds at slightly different points and record different blood pressures. The required accuracy of a clinical monitor is determined by the smallest change in the measured variable that could affect a clinical decision. The requirements for "absolute accuracy" (is the measured value correct?) may be different from the requirements for "relative accuracy" (does the measured value follow trends?).

For example, a pulse oximeter estimates arterial hemoglobin oxygen saturation by measuring light absorbance. The pulse oximeter saturation estimate, Sp_{O_2}, is compared with the hemoglobin saturation determined from the analysis

Figure 28-2 Accuracy and precision. The bias plot is a way to compare two different methods of measuring the same variable. Examples are plotted above on the right for saturation values, blood analysis versus pulse oximetry. It is a plot of the difference between the two measurements being compared versus the average of those two measurements. If one method constantly measures slightly higher than the other by a consistent value, it has a positive bias. If it has only slight variation around that bias, it is said to have very low random error (or precision, which equals the standard deviation of the differences) (A). (B) The values are randomly scattered, such that the average difference is near zero, but the precision value is very large. This large random error makes the device unusable because calibration will not improve this random error. Figure 28-2 (C) This is the optimal device, that is a bias near zero and a very small precision (standard deviation of the differences). No amount of calibrating or "sighting in" could cause Figure 28-2 (B) to become more accurate because the error is randomly scattered.

of an arterial blood sample by a laboratory co-oximeter, Sa_{O_2}. There are errors associated with arterial blood sampling and *in vitro* analysis of the sample by the co-oximeter. Nevertheless, the co-oximeter is considered to be the gold standard in this comparison of methods.

The pulse oximeter's saturation value can be compared with that of the co-oximeter by the determination of *bias* and *precision* (Fig. 28-2). The bias is the average difference between simultaneous values from the two methods, or the systematic error. If a pulse oximeter reads an average of 5 percent higher than the co-oximeter analysis, it has a bias of 5 percent, and we can adjust for that systematic error by recalibrating the device. The precision is the standard deviation of the differences between the two measurements, and it quantifies the random error, or "scatter." A higher value of the precision indicates a larger random error. (This statistic may be more appropriately called the "imprecision.") If the random error is too large, the device may not be clinically useful. We can adjust for systematic error (bias) by recalibration, but there is no way to adjust for random error. [2]

Signal Processing

Some physiologic values are constant over time; others vary. When a measured value changes over time, it constitutes a signal. Many physiologic processes generate signals that cannot be perceived by our senses or are too small to measure directly. We must process and amplify these signals, a situation that introduces new problems. The first step in processing is to convert the raw physiologic variable (pressure, temperature, velocity, etc.) into another form of energy, usually electrical. This conversion is accomplished by a *transducer* (Fig. 28-3) (Figure Not Available) For example, a pressure transducer converts pressure (force/area) into an electrical signal, which can then be amplified and processed. The processed output is usually transmitted to a display device.

When an analog signal (e.g., voltage versus time) is amplified, both the background noise and the desired signal are amplified (Fig. 28-4) Various techniques can be used to enhance the signal-to-noise ratio. For example, most pulse oximeters assume that a patient's pulse rate is between 30 and 300 beats per minute. Therefore, the instrument filters out any pulsations that occur at frequencies below 30 or above 300 (see the section on alternating current, capacitors, and impedance). In some cases, a desired signal can be repeated and summated, and the accompanying random noise becomes a smaller fraction of the signal. Evoked potentials are an excellent example of this process. The evoked response signal for a single stimulus is actually much smaller than the random noise, but this signal is nearly identical after each stimulus. Therefore, by summing the potentials after many stimuli, we reinforce the evoked response signal but not the noise (Fig. 28-5)

Finally, the waveform of any periodic signal can be represented by a summation of sinusoidal waves, called a "Fourier series" [3] (Fig. 28-6) . The component sine waves can be described by their frequency and amplitude (or power, which is proportional to the square of amplitude). Thus, a waveform originally expressed as amplitude versus time is *transformed* into a plot of power versus frequency (Fig. 28-7) . The resulting plot, called the "power spectrum," is a common form for displaying and interpreting some types of waveform data, for example, the electroencephalogram (Ch. 35)

When we monitor a patient, we measure physical quantities in a physiologic setting, and these measurements are

Figure 28-3 (Figure Not Available) Transducer. A transducer changes a signal from one form of energy to another. A common transducer in anesthesia changes mechanical energy, e.g., an arterial pulse, into electrical energy. Microphones and speakers are also examples of transducers. *(Modified from Tremper and Barker [20])*

Figure 28-4 Digital and analogue signal processing. The analogue signal shows distortion and loss of fidelity as it is reduced and then amplified. The digital signal shows no such loss. To create the analogue example, a copying machine was used to shrink the text and then enlarge it. For the digital signal, the font size was reduced, the text copied, and the process reversed.

subject to error and uncertainty. Our task as anesthesiologists is to understand both the physiologic and the physical limitations of these measurements, judge the potential for error, and make clinical decisions in the face of these uncertainties.

Figure 28-5 Somatosensory evoked potentials. A background signal can be separated from random noise by repeatedly adding the signals. The noise (random) is equally likely to be positive or negative; hence, adding positive and negative yields zero with multiple summations.

/das/book/view/29494766/875/300.html

PRESSURE MEASUREMENT

Principles of Pressure (Mass, Force, and Energy)

Many of our monitors are based on fundamental principles of the mechanics of solids and fluids, usually a derivation from F = ma. We discuss a few of these principles in this section, providing common examples of each one.

Many of our monitors measure force, which is related to mass and acceleration as described by Equation 1, Newton's second law. The force may be generated by gravity, a beating heart, a compressed gas, or a contracting muscle. When we weigh a patient, we are determining the force exerted by gravity at the earth's surface on the patient's mass (m). This gravitational force (F_g) is related to mass by the formula

where g, the gravitational constant for acceleration, equals 9.8 N/kg (Fig. 28-8) . Many anesthetic monitors measure pressure, which is force divided by the area of the surface on which that force is exerted. Pressure thus has dimensions of force/area, and its SI unit is the newton/(meter)^2, which is called the *pascal.* Because the pascal is a very small unit of pressure, we usually choose to use *kilopascals,* which equal 1,000 pascals.

As noted earlier, kinetic energy is proportional to mass times velocity squared and is measured in kg-m^2/s^2 or joules.

Figure 28-6 Fourier series. This pseudoarterial waveform was generated by adding the three sine waves with the following characteristics, y = 50 sinx, y = 25 sin2x, y = 12 sin4x.

If a force (F) acts on a mass (m) over a distance (d), we define *work* as the product of the force and distance: W = Fd. It can be shown from Equation 1 (using a little calculus; see Appendix 1 at the end of this chapter) that the work performed on a mass equals the change in its kinetic energy:

Work has dimensions of force times distance, and SI units of newton-meters. Because work and energy change are equivalent, one newton-meter must equal 1 kg-m^2/s^2 = 1 joule (J). This equivalence of units can be verified by Equation 1.

The relationship of work and energy leads to the concept of *potential energy.* If we lift mass (m) by a height (z) above the floor and let it fall, the force of gravity (F_g = mg)

Figure 28-7 Spectral arrays. A compressed spectral array can display the frequency on the x axis and power on the y axis. A number of these can be aligned with time as a third axis, giving an indication of changes in power over time.

acts on the mass through the distance (z), thus doing work, given by:

At the end of its fall, the mass has a kinetic energy equal to the work performed, mgz (Equation 3). Therefore, we say that when the mass is raised to the height (z) above the floor, we have given it a potential energy equal to mgz. A 1-kg mass lifted 1 meter off the floor has a potential energy of 9.8 J. This potential energy can be converted into kinetic energy of motion simply by letting the mass fall. Potential energy can be stored in many other forms besides height (called "gravitational potential"), for example, a compressed spring, gas at high pressure in a tank, or the electrical potential of a battery (Fig. 28-9) .

Energy is related to matter in one additional way through Einstein's famous equation: E = mc^2 . That is to say, matter and energy are the same "stuff." In the absolute sense, usually reserved for thermonuclear weapons, atomic reactors, and the sun, matter can be converted into energy, and vice versa. If a 1-kg mass were completely converted to energy via E = mc^2 , it would yield 8.987 × 10^{16} J (Table 28-1) (Table Not Available) .

We have already defined power as the rate of change of energy per unit time. With the additional relationship between work and energy (Equation 3), it is clear that power is also the "rate of work," or amount of work performed per unit time. Thus, the unit of power (1 watt = 1 J/s) can also be expressed as the newton-meter/s.

Static Pressure Measurement (Manometer)

We have defined pressure as the force acting on a surface per unit area. A *fluid* is defined as matter that continuously deforms (changes shape) as long as any stress

(surface force) is applied to it. Fluids are subdivided into liquids, which are relatively incompressible, and gases, which are compressible.

Figure 28-8 Balance. A scale is in balance when the forces are equal and in opposite directions. The force of gravity on the unknown mass of fruit is balanced by the known standard masses on the opposite side of the balance. $F_1 = F_2$, hence $m_1 a_g = m_2 a_g$; because $a_g = a_g$, m1 = m2. (a_g = acceleration due to gravity).

Pressure exists and can be measured everywhere within a fluid, even where it is not in contact with a rigid surface. Although the SI unit of pressure is the pascal (or newton per meter squared), in medicine, we more commonly use units such as millimeters of mercury (mm Hg) and centimeters of water (cm $H_2 O$). How does a unit of length become a unit of pressure? This is the principle of the liquid manometer, the oldest method of pressure measurement. The manometer *balances* the pressure to be measured against the pressure exerted by a vertical column of liquid of known density, for example, mercury and water. The density of a fluid is its mass per unit volume,

Figure 28-9 Potential energy and kinetic energy. Potential energy is stored energy that can be released or converted into kinetic energy, the energy of motion. Energy can be stored as gravitational, chemical, electrical, and other forms of potential energy.

TABLE 28-1 -- Comparison of Energy Levels of Common and Uncommon Events

(Not Available)

(Modified from Hecht. [19] *)*

---

which has SI units of kilograms per cubic meter (kg/m^3) or commonly, grams per milliliter. The pressure exerted by a liquid column of height (z) and density (rho) is simply rhogz (see Appendix 2 at the end of this chapter for derivation). If the manometer liquid is mercury, which has a density of 13,600 kg/m^3 , then the manometer pressure in pascals is

Because these large numbers are rather awkward, we express p in kilopascals (kPa) and z in millimeters of mercury (mm Hg):

A useful reference for the various pressure units in use today is the pressure of the earth's atmosphere at sea level, called "one atmosphere" or 1 atm:

= 760 millimeters of mercury (mm Hg)

= 14.7 pounds/square inch (psi)

= 988 cm $H_2 O$

For slowly changing pressures, a water or mercury manometer is simple and dependable (Fig. 28-10) . The manometer cannot respond quickly to rapid changes in pressure because of its inertia; that is, the mass of the liquid column resists rapid changes in height. If a fluid-filled catheter is connected to a patient, the height of the fluid in the manometer determines the mean pressure at the tip of the catheter. If the pressure measured is the central venous pressure, we can use these data to infer right ventricular preload. Because this manometer is in direct continuity with the patient's circulation, the manometer fluid must be compatible with blood, that is, it must be iso-osmolar, as well as nontoxic.

Figure 28-10 Manometer. A water manometer uses a balance of forces. In this case, the downward pressure of the fluid, as determined by its density and height, balances the upward pressure of the central venous system, caused by hydrostatic and elastic recoil forces.

Dynamic Pressure Measurement (Transducer)

The accurate measurement of a rapidly changing pressure, such as arterial blood pressure, is more difficult and complex. There are many characteristics of the pressure versus time waveform that we might wish to determine. The systolic, diastolic, and mean arterial pressures are given by the maximum, minimum, and average pressure values during the cardiac cycle (Fig. 28-11) . In addition, we can measure the maximum upward slope of the waveform during systole, which is related to the speed of ventricular ejection. An abnormally rapid downslope after aortic valve closure (indicated by the dicrotic notch) suggests possible aortic insufficiency. Thus, the details of the pressure-time waveform as well as its maxima and minima are potentially important to the clinician.

The modern pressure transducer is a device that changes either electrical resistance or capacitance in response to changes in pressure on a solid-state device. The variable transducer resistance is placed in an electrical circuit involving three known resistances (Wheatstone bridge; see Appendix 3 at the end of this chapter), which converts the resistance change into an electrical voltage. The moving part of the transducer itself is very small and has little mass. However, it is not clinically or commercially practical to place the transducer in contact with the arterial blood, so we use a liquid-filled tube to connect the intra-arterial catheter to the pressure transducer. This system of a fluctuating driving pressure (i.e., the arterial pressure being measured), a liquid-filled tube, and a pressure transducer is mechanically equivalent to the mass-spring harmonic oscillator shown in Figure 28-12 . The mass (m) represents the mass of the fluid in the tubing. The spring represents the elasticity of the tubing. The damper, shown schematically as a piston moving in oil, represents the friction generated by the fluid moving to and fro in the tubing.

A more commonly encountered harmonic oscillator is that of a car driving down a bumpy dirt road (see Fig. 28-12) .

Figure 28-11 Arterial waveform. Systolic pressure is defined as the instantaneous maximal pressure; diastolic, the instantaneous minimum pressure; and mean, the average pressure over a cycle. DP/dT refers to the upstroke of the arterial pressure, i.e., the rate of pressure generation. The mean pressure is estimated as the diastolic plus 1/3 the pulse pressure (systolic-diastolic) when only the

systolic and diastolic are known.

In this case, the oscillating driving pressure is provided by the bumps in the road, which force the car wheel to oscillate up and down. The car springs are analogous to the compliance of the arterial pressure tubing, and the car's shock absorbers, which oppose motion of the wheel in either direction are analogous to the friction of the fluid moving back and forth in the fluid-filled tube. Depending on the frequency of the bumps (i.e., driving pressure frequency) the system can either suppress the bumpy road or may initiate dramatically increased oscillations. The frequency of the driving force that causes maximal amplification of the signal is called the natural resonant frequency (Fig. 28-13) (Figure Not Available) . The degree of amplification is directly related to the mass and is inversely related to the amount of friction present; for large amounts of friction, there is attenuation rather than amplification (see Appendix 4 at the end of this chapter).

To visualize this intuitively, hang a weight on the end of a rubber band, holding the upper end of the band in your hand. If you move your hand up and down slowly, the weight follows your hand movements almost exactly. As you increase the frequency of your hand oscillations, the weight begins to "lag" behind your hand, and the amplitude of the weight movement begins to increase. As you approach the natural frequency of this simple system, you will observe the phenomenon of "resonance" when the amplitude of the weight motion becomes very large. If you try different rubber bands and weights, you will find that stiffer bands or smaller weights yield higher natural frequencies. The same is true of our fluid-couple pressure transducer system. A stiffer (i.e., less compliant) tubing or a shorter length of tubing (less mass) produces higher natural frequencies in this system, that is, it requires a much higher pulse rate before amplification.

To minimize the potential of an amplification of the real arterial pressure, the system should have very noncompliant (i.e., stiff) tubing and the total mass of liquid in the system

Figure 28-12 Damping and resonance. Pressure measured in an invasive arterial catheter can actually overshoot or amplify the real blood pressure. This phenomenon is referred to as the dynamic frequency response of the fluid-filled arterial line and transducer system. This phenomenon has a physical model, which can generate an equation to predict the output pressure response, depending on the frequency of the input pressure and several physical parameters of the system. In the physical model on the right, the driving pressure (the arterial blood pressure) acts on a mass (the fluid within the arterial pressure tubing), pushing it up and down against a spring, which stores energy (the compliant pressure tubing), and a dash pot, which opposes motion in either direction (the resistance of the fluid as it moves to and fro within the pressure tubing). Depending on the input frequency, the output may go through an amplification as it reaches a specific frequency, known as the resonant frequency of the system. On the left side of the figure, there is a common phenomenon noted when a car drives along a bumpy dirt road. In this situation, the driving force is the bumps in the road, which act on the tire. The car spring is equivalent to the compliance to the pressure tubing, and the shock absorber corresponds to the resistance of fluid moving back and forth in the arterial line. The mass of the fluid is analogous to the mass of the front of the car. You may have experienced the phenomenon in which you reach a certain speed as you are driving along a bumpy road when the front of the car starts to oscillate with increasing amplitude. If you speed up or slow down, this phenomenon disappears. The car bounces highest when you have reached the resonant frequency of this harmonic oscillator. See Appendix 4 for detailed mathematical description of this process.

Figure 28-13 (Figure Not Available) Amplitude and frequency. As the frequency increases, the amplification can increase to a maximum, and then the signal becomes attenuated. *(Adapted from Sykes et al [5])*

should also be minimized. This can be accomplished by having small-diameter tubing and as short a length as possible. In most clinical systems, the natural resonant frequency is 10 to 15 Hz, which is much higher than the primary frequency of the arterial wave form (the heart rate, 60-120 beats/min or 1-2 Hz). Unfortunately, the arterial waveform is not a sine wave but is the more complex shape shown in Figure 28-6 and is made up of a summation of sine waves, a Fourier series. The higher-frequency components of the arterial waveform (higher harmonics) are the ones that are closer to the natural frequency and are therefore amplified. This is why we see a "whip" in the waveform where the peak systolic pressure and the initial upstroke are amplified significantly above the true systolic pressure, even if the heart rate itself is not in the range of the resonant frequency. In theory, the mean arterial pressure should be the same because this amplification of systolic pressure also produces a reduction in diastolic pressure (Appendix 4)

Signal-Processed Pressure Measurement (Noninvasive Blood Pressure Monitor)

Systolic pressure can be estimated by noting the return to flow pulse after occlusion of the artery by a cuff. The return to flow can be detected by (1) simple palpation of the radial artery, (2) recording with a Doppler device over the radial artery, or (3) use of a pulse oximeter. Most anesthesiologists are familiar with the loss of pulse oximeter signal when the noninvasive blood pressure monitor is cycling.

Automated noninvasive blood pressure monitoring devices used in most operating rooms employ a more sophisticated application of this principle. These devices monitor the oscillating signal generated in the cuff by the arterial pressure changes. The cuff first inflates to above systolic pressure, at which point the signal and oscillations are abolished. Then the cuff slowly deflates in a stepwise fashion. The pressure at which the signal first appears is interpreted as the systolic pressure. The signal increases in amplitude as the cuff pressure decreases. When the signal is at maximal amplitude, this is interpreted as mean arterial pressure. As

Figure 28-14 (Figure Not Available) Noninvasive blood pressure measurement. Using the signal from the arterial pulse, oscillometric blood pressure measurements are obtained by determining the point at which the signal is first detected, its maximal amplitude, and the signal decay rate. [4] *(Adapted from Ehrenwerth and Eisenkraft [21])*

the cuff pressure decreases further, the oscillations drop off rapidly. Diastolic pressure is mathematically inferred from the systolic and mean values (Fig. 28-14) (Figure Not Available) . [4] Errors can be introduced in the same manner as for manual ausculation of Korotkoff sounds: too small or too large a cuff requires a higher or a lower pressure to occlude the arterial flow, and stiff atherosclerotic arteries are resistant to compression. External compression by a patient's motion or a surgeon's leaning on the noninvasive blood pressure monitoring cuff can cause oscillations in the cuff pressure that are not related to the arterial pressure and may result in erroneous reading, most commonly a high diastolic pressure.

FLOW MEASUREMENT

Principles of Flow

Pressure in fluids can be thought of as a form of potential energy, as described earlier. Kinetic energy in fluids is expressed in terms of *flow,* the bulk movement of fluid with a given direction and speed. We must carefully distinguish between fluid *flow* and fluid *velocity,* which are often confused. Flow (Q) refers to the volume of fluid passing a particular location per unit of time; its SI units are meter cubed per second, but it is more commonly measured in milliliters per second or liters per minute. Fluid velocity (U) is simply the speed of the fluid at a particular point in space, measured in meters per second. By analogy, imagine a multilane freeway: the speed (velocity) of individual cars may vary depending on the lane; the flow is the number of cars passing a point per minute. The potential energy of pressure can be converted into the kinetic energy of flow: for example, the hydrostatic pressure generated by gravity acting on a vertical column of liquid can be transformed into flow by opening a valve at the bottom of the column. Pressure and flow can also change independently. With the human circulatory system used as an example, a healthy young trauma patient can have relatively high blood pressure but low blood flow (hypovolemic shock) with high systemic resistance. On the

TABLE 28-2 -- Comparison of Hydronamic and Electrical Energy Commonly Encountered

WATER	ELECTRICITY	ENERGY
Squirt gun	Static electric spark	High pressure, low flow, low energy
Garden hose	House current	Moderate pressure, moderate flow, moderate energy
	Car battery	Low pressure, moderate flow, moderate energy
River flood		Low pressure, huge flow, huge energy
Fire hose	High-tension wires	High pressure, high flow
	Lightning	High pressure, high flow

other hand, a septic patient can have very low blood pressure accompanied by high blood flow (high-output septic shock). The total mechanical energy of a moving fluid is the sum of the kinetic (flow) energy and the potential (pressure) energy (Table 28-2) .

A pressure gradient exerts a force on the fluid, tending to accelerate the fluid in the direction of *decreasing* pressure. Pressure gradient is only one of the forces that commonly act on fluids; other forces include gravity (discussed earlier) and viscous force or friction. If these other forces are negligible and if the fluid is incompressible (i.e., a liquid with constant density), then the equation of motion (F = ma) can be integrated to yield

where P is pressure, rho is fluid density, U is the magnitude of the fluid velocity, and P_o is a constant called the *stagnation pressure* (see Appendix 5 at the end of this chapter). This form of the *Bernoulli equation* tells us that as velocity increases in a frictionless flow, pressure decreases, and vice versa. This concept resolves the common misconception that pressure always decreases in the direction of flow. For example, in the flow inside a tube (a pipe or a large vein) of gradually increasing diameter, the fluid velocity (U) decreases in the downstream direction as the diameter and cross-sectional area of the tube increase. As U decreases, Equation 5 tells us that p actually increases in the direction of flow. This example again shows the relationship of potential and kinetic energy in fluids: as the kinetic energy of this tube flow decreases (U^2 falls) in the flow direction, the potential energy increases (p rises) by equal amount. The total energy remains constant because we have assumed no friction.

Flow can be determined from knowing the average velocity of the across the tube. In laminar flow, Figure 28-15 A, the velocity profile is distributed such that the highest velocity is in the center and the fluid at the edges is virtually stationary. In turbulent flow, the velocity profile is "flattened" (Fig. 28-15 B) Some monitors measure flow directly, but most measure flow indirectly, by either pressure or velocity measurements.

The Bernoulli equation applies to a specific subset of flow parameters as listed earlier. Many flows important to anesthesiologists do not follow the Bernoulli equation. Most commonly, the flow that we desire to measure is not laminar but is turbulent. The transition from laminar to turbulent flow depends on the type of fluid and the shape of flow. The fluid factors are summarized in the Reynold's number:

where rho is the density of the fluid, U is the mean flow velocity, D is the diameter of tube, and mu is the viscosity of fluid. Thus, as the average speed of flow increases, the flow becomes more turbulent. In straight tubes, the change from laminar to turbulent flows occurs at Re >2100 (Appendix 5). Many flowmeters require laminar flow for their measured values (pressure or velocity) to be accurately transformed into a flow measurement (e.g., Pitot tube; see later section).

Mass/Volume Flowmeters (Urometer, Volumeter, Dilutional Measurements)

We can actually measure the mass or volume of fluid flowing per unit time by catching fluid in a container and either weighing it or measuring its volume. The common urometer for measuring urine volume is an example. The volumeter used in North American Drager anesthesia machines also

Figure 28-15 Laminar and turbulent flow. In a smooth-walled tube at low flow rates, i.e., small pressure gradients, the flow rate is laminar, i.e., flow moves smoothly in concentric circles, with the

centermost area having the greatest flow velocity and the area nearest the wall of the tube being virtually stationary. As flow rate (and pressure gradient) increases, the flow transitions from laminar to turbulent. Instead of a neatly ordered flow, the velocities are more randomly distributed, energy is dissipated as heat, and the energy needed for a given flow rate increases. Many factors govern this transition, including size of the tube, viscosity of the fluid, flow rate and pressure gradient. These are combined in the determination of the Reynold's number (Appendix 5).

Figure 28-16 (Figure Not Available) Volumeter. Flow can be described as volume over time. This design of flowmeter allows gas to pass in only little aliquots, each of which turns a counter to measure the amount flowing past. When divided by time, this results in a flow measurement. *(Adapted from Ehrenwerth and Eisenkraft [21])*

measures aliquots of volume, integrated over time to measure tidal and minute volumes (Fig. 28-16) (Figure Not Available) . [5]

Both volume and mass flow can be measured by dilutional techniques. If some measurable indicator (a bolus of dye, a thermal pulse) is injected into a flow and its concentration is measured downstream, then the volume flow (Q) can be calculated by integration. The most common medical application is the determination of cardiac output by the pulmonary artery thermodilution method (see Appendix 6 at the end of this chapter). Errors associated with these methods involve using the wrong injectate volume (too small a volume, resulting in too large a flow) or an error in temperature measurement (see the section on temperature).

Velocity/Flow Measurements (Venturi, Pitot, Doppler)

A Venturi tube is a very gradual contraction and expansion in a tube, in contrast to the sudden contraction of an orifice flowmeter (Fig. 28-17) . Because the contraction is smooth and gradual, the Bernoulli equation (Equation 5) applies to this geometry. If we measure the pressure difference between the widest and the narrowest parts of the Venturi tube, we can solve the Bernoulli equation for the velocity (Appendix 5) The Venturi tube derives fluid velocity (U) from the pressure difference, not volume flow (Q). In laminar flow, fluid velocity is proportional to flow. The Venturi tube is used in many industrial applications and is also used on some aircraft to measure speed.

A Pitot tube is a cylindrical tube whose open end is pointed directly into the flow, that is, "upstream" (Fig. 28-18) (Figure Not Available) . The pressure measured in the pitot tube is the *stagnation pressure,* given earlier by Equation 5. If we also measure the static pressure (p) (the p_1 side port in the figure) and we know the fluid density rho, then we can easily solve Equation 5 for the fluid velocity (U). Note again that the Pitot tube derives velocity (U), not volume flow (Q). The Pitot tube is simple and reliable and is almost universally used on aircraft to measure their speed. In anesthesia, the Pitot tube is used in Datex Ultima monitors. In order to measure gas flow in two directions, the Datex monitor incorporates two pitot tubes, one facing in each direction. Additionally, the monitor samples gas composition to correct for the density and the viscosity of the gas mixture.

Balance-of-Pressure Flowmeters (Bourdon Tube, Thorpe Tube)

If flow in a tube passes through a sudden restriction, such as an orifice, the volume flow (Q) is proportional to the area of the orifice and the square root of the pressure drop through the orifice. (The Bernoulli Equation 5 does not apply to this flow geometry.) This is the principle of all orifice flowmeters, including the floating bobbin rotameter of an anesthesia machine, described later (Appendix 5).

The most common flowmeter seen by anesthesiologists is the rotameter on the anesthesia machine (Fig. 28-19) . This is a variable-orifice flowmeter that uses a balance of forces to determine pressure change. When the flowmeter valve is opened, the flow of gases through the annular orifice between the bobbin and the tapered glass tube provides a force to raise the bobbin. As the bobbin rises, the area of the annular gap between the bobbin and the tube increases as a result of the taper of the tube. As the area of this gap (orifice) increases, the pressure change across the bobbin decreases because the pressure change across an orifice is inversely

Figure 28-17 Venturi tube. By measuring the pressure difference between two points in a laminar flow, the average flow velocity can be determined because the mass flow must be the same (Appendix 5).

Figure 28-18 (Figure Not Available) Pitot tube. As flows increase, wall pressure decreases as a result of the Bernoulli principle. The Pitot tube measures the difference in pressure from the middle of the flow to the wall and converts this to a flow measurement (Appendix 5). *(Adapted from Ehrenwerth and Eisenkraft [21])*

proportional to the square of the orifice area. The bobbin ceases its upward motion at an equilibrium point when the downward force of gravity is balanced by the upward pressure forces. Thus, the height of the bobbin in the tube is proportional to the gas flow. Although this flowmeter is simple in principle, its application becomes more complex when the flow in the tube changes from laminar to turbulent as velocity and diameter increase. For mathematical derivations, see Appendix 5.

Another flowmeter (Bourdon tube, Fig. 28-20 (Figure Not Available)) keeps the orifice constant and allows the pressure to vary. As flow (Q) increases, the gradient of P1 to P2 increases, causing the flattened metal tube to uncoil and move the pointer.

Vane Spirometer Flowmeters (Wright Spirometer)

Vanes or propellers placed in a confined flow turn at a rate proportional to the volume flow if there is no friction in the propeller bearings. Various vane spirometers (Fig. 28-21) (Figure Not Available) (e.g., Wright spirometer) work by this principle. These tend to be less accurate at both very high and low flow rates because of frictional forces.

Figure 28-19 Thorpe tube flowmeter. At low flows, density of gas predominates, and the flows balance when the gravitational attraction equals the pressure gradient across the equivalent orifice. At higher flows, viscosity takes over, and the balance is the same, except for the formula determining pressure (Appendix 5).

Figure 28-20 (Figure Not Available) Bourdon tube flowmeter. Unlike the Thorpe tube, which has a constant pressure but a variable orifice, the Bourdon tube has a constant orifice but a variable pressure. The tube uncoils under the high back pressure. This drawback makes it unsuitable for use in low-pressure respiratory systems. However, it receives much use in portable oxygen tanks. Of note, if the orifice is increased in radius, the flowmeter will underread actual flow. If dirty (i.e., decreased radius), the flow will be overestimated. *(From Mushin and Jones [22])*

Summary of Flow Measurement

There are problems associated with every method of measuring flow. Because not all gases are pure, with a known, constant density, flowmeters based on the Bernoulli equation 5 are subject to errors. Furthermore, any device inserted into a fluid flow can disturb the flow by its presence. For example, a rotating vane spirometer may reduce the gas flow at high flow rates because of friction. Several methods of flow or fluid velocity measurement are dependent on a pressure measurement (Pitot tube, Venturi tube, orifice flowmeter); hence, the flow measurement is no more accurate than the pressure measurement.

Figure 28-21 (Figure Not Available) Vane spirometer. Moving gases contain kinetic energy. This can be sampled by a rotating "windmill" in the gas stream. [4] *(Adapted from Ehrenwerth and Eisenkraft [21])*

/das/book/view/29494766/875/302.html

MEASUREMENT UTILIZING SOUND

Principles of Sound

Sound waves are small fluctuations in pressure, density, and velocity that can propagate through matter of any form: solid, liquid, or gas. Unlike electromagnetic waves, such as light (see the section on light), sound cannot propagate through a vacuum. Sound is called a *longitudinal wave* because the motion of the particles occurs in the same direction as wave propagation. In contrast, waves on the surface of the ocean are *transverse waves* because the motion of the particles is mainly perpendicular to the direction of wave propagation (Fig. 28-22) .

In 1842, Christian Johann Doppler first described the apparent change in pitch of a sound that occurred when either the source of the sound or the listener was moving. [6] This Doppler effect now has several applications in patient monitoring, including precordial and esophageal Doppler ultrasound monitoring of local blood velocities or cardiac output.

When a sound source is moving toward the listener, the apparent pitch increases, and vice versa. The amount of frequency shift depends on whether the listener or the sound source is moving (Fig. 28-23 (Figure Not Available) ; see Appendix 7 at the end of this chapter). Because changes in the frequency of sine waves can be measured precisely, the Doppler principle provides a very accurate method of measuring the velocities of moving sound reflectors. At the high frequencies often used (
5 MHz), objects as small as red corpuscles can scatter enough sound for detection.

Sound has been used for many years in medical diagnosis and monitoring. It can be used as a diagnostic method in two ways: passive and active. In a passive examination, the sounds generated by the patient are studied. The basic examination of this type uses the stethoscope. In an "active" examination, acoustic energy is transmitted into the patient, and the resulting interaction of this energy with the patient is analyzed for information. Both types of examination employ the same physics principles.

Passive Sound Examination (Stethoscope)

Vibrations, such as those caused by the closing and opening of heart valves or air traveling through the respiratory passages, travel through the body as sound waves. Sound is generally conducted better and more rapidly in liquids than in gases. Thus, bronchial breath sounds are heard better when the bronchi are surrounded by lung consolidation. When sound waves reach a sudden change in density, some of the energy is reflected.

Some simple facts about sound waves can facilitate an understanding of the reflection and scattering process in the body. First, all sound waves can be represented as a summation of sinusoidal waves of various frequencies and amplitudes. This process of Fourier or power spectral analysis has been discussed earlier in this chapter. A note from a musical instrument thus consists of a sine wave at the "fundamental frequency" plus many "harmonics." The fundamental is the frequency that describes the pitch of the tone: middle C is standardized at 256 Hz, for example. Harmonics are sine waves at frequencies that are multiples of the fundamental frequency.

Fortunately for our ears, all of these many frequencies propagate at the same speed, the speed of sound (called "a"). For ideal gases, the speed of sound is proportional to the square root of temperature. The speed of sound in room temperature air is 344 m/s, or 1,129 ft/s, or 770 miles/hr (mph). At an altitude of 13,000 m (40,000 ft), where the standard temperature is -57°C, the speed of sound is only 295 m/s, or 661 mph. The speed of sound is much higher in liquids than in gases. For example, the speed of sound through water at 15°C is 1,450 m/s. This value approximates the speed of sound through most of the solid parts of the body. In solids, the speed of sound varies greatly, ranging from 54 m/s in rubber to 6,000 m/s in granite. Reflection of sound occurs at interfaces where the product of the tissue density and the speed of sound (rho × a) changes suddenly. Larger changes in this "acoustic impedance" result in

Figure 28-22 Transverse and longitudinal waves. In transverse waves (e.g., ocean waves), the particles move perpendicular to the motion of the wave. In longitudinal waves (e.g., sound waves), the particles move back and forth in the direction of the wave. The actual matter in either wave does not move much. The energy transfers without mass transfer.

Figure 28-23 (Figure Not Available) Doppler effect. (A) When a listener is moving toward a stationary sound source, the frequency increases because the listener transverses more waves per unit time than a stationary listener. (B) When a sound source is moving toward a stationary listener, the wave fronts "stack up," causing an apparent increased frequency. *(Modified from Tremper and Barker [20])*

greater reflection and less transmission. In the human body, the largest changes in acoustic impedance occur at gas-tissue boundaries: the lungs and the gastrointestinal tract. Reflection of sound thus makes it difficult to auscultate heart tones through an air-filled, emphysematous chest. For the same reason, a transthoracic echocardiograph provides less detail than the transesophageal technique; in the former case, the lungs are in the way.

First attempts to gather information about the inside of the patient using sound involved placing one's ear directly to the patient. Although this procedure had many limitations, it led to the development of the modern stethoscope, which is based on the physical principles of sound transmission. The stethoscope uses a large diaphragm to transmit and concentrate the sound energy. The bell acts as both an amplifier and a low-pass filter to transmit low-frequency dia-stolic rumbles. The physics of stethoscopy were described in depth by Rappaport and Sprague. [7]

Active Sound Examination (Percussion, Echo, Doppler)

The earliest "active" acoustic diagnostic technique was percussion of the chest wall. A skilled clinician can use this method to detect consolidation of the lungs, pleural effusion, and a few other chest pathologies. Although based on transmission and reflection of sound, percussion is purely qualitative and is unable to accurately localize pathologic changes. Modern ultrasound improves on percussion by using shorter-wavelength sound waves and quantitative detection of their reflections (echoes). The resolution of an examination is limited by the wavelength of the sound used (Fig. 28-24) . Using ultrasound at frequencies in the MHz (10^6 cycles/s) range allows resolution of much smaller objects. The wavelength of 1.0-MHz sound waves in solid tissue is about 1.5 mm, whereas the wavelength of a

256-Hz tone (middle C) in tissue is 5.7 m.

By use of esophageal transducers, echocardiography has become a popular intraoperative monitoring technique. [8] [9] Sound waves in the 2- to 10-MHz range are transmitted toward the heart in short bursts or pulses. After each pulse, the transducer passively listens to the reflected echoes from various tissues. The ability to place the transducer in the esophagus is advantageous because sound does not then have to pass through air spaces or bone on its way to and from the heart. The speed of sound through the heart and surrounding soft tissues is a nearly constant 1540 m/s. Thus, the elapsed time between transmission of the pulse and receipt of the echo provides the distance to the reflecting structure. The sound beam from the transducer is projected in a narrow "searchlight" pattern, so that the exact direction of reflecting structures is also known.

Doppler effect is used in echocardiography to determine the presence and the degree of valvular regurgitation by converting the Doppler shift of sound waves reflecting from the erythrocytes into a color display (Appendix 7; Ch. 31).

MEASUREMENT UTILIZING ELECTRICITY

Principles of Electricity

Most of our monitors and other anesthesiology apparatus involve basic principles of electricity and magnetism. Nearly all of our transducers use some form of electrical energy as their output, and the subsequent data processing and display are entirely electrical. We review some of the principles in this section, using examples from medical equipment.

Static Electricity.

Electricity is a manifestation of a property called *charge* that is inherent in matter. The charge can be negative, positive, or neutral. Static electricity involves charges at rest: like charges repel one another, whereas opposite charges attract. What we usually mean by the word "electricity" involves the flow of charges, or the electrical *current.* Current flows in one direction in "direct-current" (DC) electronic devices and alternates back and forth in "alternating-current" (AC) devices.

The SI unit of charge is the *coulomb,* and the smallest quantum of charge is the charge of an electron, which is equal but opposite to the charge of a proton. An *electrostatic* force is exerted between two charged objects and is directly proportional to the product of the two charges and inversely proportional to the square of the distance between them

This force is attractive when the charges are of opposite sign, repulsive when they are of the same sign. In a Nobel Prize-winning experiment, Robert Millikan determined the charge of an electron by suspending charged oil drops between two horizontal charged plates such that the electrostatic force balanced the gravitational force and the drops were held in mid-air (Fig. 28-25) Approximately 20 years

Figure 28-24 Wave size and resolution. Wave reflection depends on the relative size of waves and objects. For small objects, small waves are needed for good reflection and resolution. (A) The object size is small relative to the wave size, causing the waves to be scattered, resulting in poor spatial resolution. (B) The object size is large relative to the wavelength, leading to a clear reflection and better resolution. This principle applies to light waves also. Hence, electron microscopes can resolve smaller objects than light microscopes because the wavelengths emitted are smaller.

later, his son, Glen Allen Millikan, developed one of the earliest infrared ear oximeters, the forerunner of the pulse oximeter (see the section on Pulse Oximeter).

Direct Current.

Just as mechanical energy may be stored as potential energy, electrical energy can be stored as a *potential difference.* A common analogy is to compare electrical potential difference to water pressure (Fig. 28-26; Table 2) . The potential difference (V) between points A and B is defined as the work required to move a unit charge from A to B (see the discussion of the relationship of work and energy, earlier in this chapter). The SI unit of potential difference is the *volt;* hence, the term voltage is often used for potential difference. Charges can move easily through *conductors;* they do not move well through *insulators,* also called *dielectrics.* If there is a potential (V) between A and B and these two points are connected by a conductor, then charges will flow between them, producing a current (I).

Figure 28-25 Electric force. The quantity of charge on an electron was determined by balancing the electric force on an oil drop against the gravitational force on the same drop. $F_1 = kq_1 q_2 / r^2 = F_2 = m_1 a_g$.

Figure 28-26 Water and electricity. The pressure drop over the water wheel (A to B) is analogous to the voltage drop over the resistance (A to B) (e.g., light bulb). The amount of flow (Q) is analogous to the current (I). Both falling water and electrical potential can do work.

The SI unit of current is the coulomb per second, called the *ampere.* If A and B are separated by an insulator, no current will flow until the potential difference becomes so great that a breakdown of the insulator occurs. For example, if A and B are separated by dry air, no current will flow until the potential difference reaches 3,000 volts/mm. At this potential gradient, air suddenly becomes a conductor, and a current flows in the form of a visible (and audible) spark. To generate a spark between two electrodes 1 cm apart, one must create a potential difference of 30,000 volts. Lightning is a larger manifestation of the same phenomenon.

A battery is a chemical cell that produces a constant potential difference between two electrodes, which is called *electromotive force* (EMF). The battery can provide a continuous source of electrons, or current, to flow through any conducting circuit connected between its electrodes. Flow of electricity is opposed by *resistance,* analogous to resistance in water pipes. In most materials, the resistance (R) is related to the voltage (V) and current flow (I), in the following way:

This relationship is called Ohm's law, and materials that follow this behavior are called ohmic materials. This is analogous to hemodynamic flow, in which the pressure drop (mean arterial pressure - central venous pressure) equals cardiac output times systemic vascular resistance.

The power (i.e., rate of work, see discussion earlier in this chapter) required to drive an electric current is the product of voltage and current: P = VI. Combining this formula with Ohm's law (V = IR), we have $P = I^2 R = V^2/R$. Thus, if we double the current through a fixed resistance (R), we use four times the original power. This power loss in resistors is dissipated as heat, which is the reason why nearly all electrical devices become warm during use.

A *capacitor* is a device that stores charge (Q) in direct proportion to the potential difference (V) between its two electrodes: Q = CV. The proportionality constant (C) is called *capacitance,* which is measured in SI units of *farads.* When a capacitor is connected to a battery, current flows until the capacitor is charged to the point that the potential across the capacitor equals the EMF of the battery: V = Q/C = EMF (Fig. 28-27) . When we push the "charge" button of a defibrillator, this kind of circuit is activated to charge a capacitor to the desired level. As shown in (Fig. 28-27) B, time is required to charge a capacitor. For a large capacitor, more time is required. Hence, it takes longer to charge a defibrillator to 200 joules than to 50 joules.

Alternating Current.

In an AC circuit, the current and the voltage fluctuate rapidly (Fig. 28-28) . There are many important differences between AC and DC. The voltage in common AC house power fluctuates sinusoidally at a frequency of 60 Hz (50 Hz in Europe). We characterize the amplitude of such a fluctuating voltage by calculating its root mean square (RMS), that is, the square root of the time average of V^2 . Thus, for AC house power, V_{RMS} = 115 volts (230 V in Europe). Current in an AC system is also constantly changing and is also measured as an RMS value.

In AC circuits, there are three forms of *impedance:* resistance (R), capacitance (C) and the *inductance* (L). An inductor is a circuit element whose impedance increases with the frequency (f) of the current fluctuations (R = 2pifL). Conversely, the impedance of a capacitor decreases with increasing frequency (R = ½ pifC). Inductors thus tend to block high frequencies, whereas capacitors tend to block low frequencies (Fig. 28-29) (Figure Not Available) . This is used in stereo systems to direct the signal to either the woofer (low-frequency) speaker or the tweeter (high-frequency) speaker. In medical instruments, inductance and capacitance circuits can be used to "filter" the signal, for example, decreasing the amount of 60-Hz interference from AC wiring.

Passive Electrical Examination (Electrocardiograph, Electroencephalograph)

Electrocardiograph.

Now that some of the basics of electricity have been described, we can discuss the electrocardiograph (ECG) and the electroencephalograph (EEG), where the sources of EMF are the heart and the brain.

Figure 28-27 Resistance and capacitance in a direct-current circuit. (A), Under direct current, the resistance impedes flow, developing a voltage drop across the resistance. The capacitor allows current to flow until the charge builds on the capacitor (B). Under direct current, the voltage is constant over time, and the current flow decreases as the charge on the capacitor increases. This type of circuit is used to charge a defibrillator.

Electrical potentials on biologic surfaces are too small to observe directly and must be amplified and processed before display. ECG potentials on the skin are in the 1-mV range, and EEG potentials are near 0.1 mV.

Figure 28-30 (Figure Not Available) illustrates why electrical potentials on biologic surfaces are so small. The heart generates an electrical signal as a result of the synchronous depolarization and repolarization of multiple cells. The electrical potentials generated by the heart are measured by two skin electrodes, A and B. As the figure shows, there are multiple effective resistances and capacitances in the tissues between the EMF source and the measuring electrodes. These impedances lower the magnitude of the voltage signal at the skin. The "shunt" resistors R_3 , R_4 , and R_5 combined with the "series" resistors R_1 , R_2 , and R_3 form what is called a *voltage divider network.* Lower values of shunt resistance or higher values of series resistance result in smaller voltages at the skin. The skin capacitance (C_s) also acts to attenuate the low-frequency components, distorting the waveform. The skin resistance,

Figure 28-28 Resistance and capacitance in an alternating-current (AC) circuit. In an AC circuit (A), unlike a direct-current circuit, the capacitor does not block current flow. The capacitor and resistance act to shift the phase of the AC current. Current changes lag voltage changes.

which may be a megaohm (10^6 ohms) for dry skin, can be reduced to a few hundred ohms by conductive gels.

If a DC voltage is applied between two body-surface electrodes, current flows through the tissues between them. Although the electrical current in metals consists entirely of electron flow, in tissues, both positive and negative ions migrate. Negative ions tend to accumulate at the positive electrode (the anode), and positive ions accumulate at the negative electrode (the cathode). This collection of anions and cations near each electrode creates its own EMF, and this force opposes the EMF that set up the original current. The current therefore decreases, so that the effective impedance between the electrodes increases. This phenomenon, called *polarization of electrodes,* has two harmful effects. First, the increased impedance from polarization can attenuate the ECG signal for several seconds after defibrillation or direct-current cardioversion. Such attenuation could be misinterpreted as a lack of electrical activity, resulting in inappropriate administration of a second shock. The second consequence of prolonged application of DC voltage is accumulation

Figure 28-29 (Figure Not Available) Woofer and tweeter. Stereo speakers use resistors to act as an impedance to high-frequency components of sound, allowing only the bass frequencies to pass on to the woofer speaker. Capacitors are used as a high-pass filter to allow only the high frequencies to get to the tweeter. 60-Hz interference from electrical appliances can be decreased by a similar process. *(From Hecht [16])*

of a local concentration of toxic ions near electrode sites, a condition that can cause burns or tissue necrosis. A partial solution to the problem is use of a nonpolarizable electrode, such as a silver and silver chloride combination. This electrode can act as a source of, or "sink," for both anions and cations, thereby minimizing accumulation of ions. Most disposable ECG electrodes now use such materials. Even these electrodes, however, are nonpolarizable for only a limited time, and application of prolonged DC voltages between any tissue electrodes must be avoided.

Electroencephalograph.

Similar problems complicate measurements of the EEG, but in this case, the signal is only 1/10 the amplitude: 100 muV, as compared with 1 mV for the ECG. The spontaneous surface EEG provides eight or more channels of amplitude (surface voltage) versus time data, which is of limited use for monitoring in the operating room. For rapid interpretation and diagnosis, the amplitude versus time data are usually transformed into plots of amplitude versus frequency. This process of power spectral analysis has been discussed in the section on signal processing. The EEG power spectrum facilitates rapid diagnosis of

Figure 28-30 (Figure Not Available) Why the ECG is so small. Multiple resistances and capacitances in the body decrease the potential and distort the waveform before the EMF reaches the surface. *(From Tremper and Barker [20])*

hemisphere asymmetries and changes in frequency content that accompany either deep anesthesia or cerebral hypoxia. The "bispectral density" is a newer method of analyzing the EEG that determines levels of correlation between various frequency components in the power spectrum. This type of analysis may provide improved determination of depth of anesthesia in some settings.

Active Electrical Examination (Somatosensory Evoked Potentials)

A muscle twitch is elicited by generating a 0.2- to 0.3-ms pulse of current in order to depolarize a motor nerve. This motor nerve then conducts the impulse to the muscle, where a twitch is generated. We can understand the "in-use" failings of this device by following the path of the signal. Clearly, we must start with an adequate power source (no power = no twitch). Aside from intrinsic mechanical failure, if the coupling of the electrodes to the patient is poor, that is, if the electrodes are dry and/or good skin contact is not made, the circuit has a high resistance, and very little current will flow (see earlier discussion and Equation 8), resulting in a diminished twitch. In summary, the simplest way to be certain that this monitor is functioning properly is to perform both a positive (see the desired response, i.e., thumb twitch, before the chosen drug is given) control and a negative control (see the twitch disappear in response to administered drug) (Ch. 36) .

Evoked potential (evoked response) monitors can determine the status of multiple parts of the sensory nervous system by measuring the central nervous system response to a discrete sensory stimulus. The stimulus can be auditory, optical, or peripheral sensory. The amplitude of the evoked response measured at the skin can be very small: 5 muV, in the case of some cortical potentials. This very small signal is in a "sea" of spontaneous EEG (100-muV amplitude) signals. We therefore resort to a signal-enhancement technique called "ensemble averaging." Rather than trying to measure the response to a single stimulus, we average the responses from hundreds (or thousands) of stimuli. Because the evoked responses occur consistently at the same time after the stimulus, this averaging process reinforces the signal from the evoked response, and the random "noise" cancels itself. In this way, we commonly measure signals whose amplitude is perhaps 1/20 the amplitude of the background noise (see Fig. 28-5) .

MEASUREMENT UTILIZING LIGHT

Principles of Light

What we commonly refer to as light is electromagnetic radiation in the visible range. Every substance having a temperature above absolute zero emits electromagnetic radiation. This radiation is characterized by a frequency and wavelength that are related by the speed of light: fre quency = speed of light ÷ wave length. (C = speed of light = 3×10^8 m/s or 186,400 miles/s or 7.5 times around the earth's circumference in 1 second.) High energies are associated with high frequencies and short wavelengths, such as those of gamma rays and x-rays. As wavelength increases to the micron range, ultraviolet radiation proceeds to visible light, and at larger wavelengths, infrared is then followed by microwaves and radio waves with wavelengths in the kilometer range.

There are some important differences between electromagnetic waves and sound waves. The particles in motion in sound waves are in the same direction as the propagation (longitudinal waves), where the electromagnetic waves are perpendicular to the direction of propagation (transverse waves). Sound waves can only propagate through matter, whereas electromagnetic waves propagate through a vacuum without attenuation. The speed of light is about 1 million times faster than the speed of sound in air. If an observer is moving relative to a sound source, he or she can measure a speed of sound that depends on the observer's own motion, but the speed of light is the same to any observer and any frame of reference. This statement is a basic premise of Einstein's special theory of relativity. At the high-frequency end of the electromagnetic spectrum, there are two forms of ionizing radiation: x-rays and gamma rays. These high-frequency waves are capable of knocking electrons out of their orbits and thereby can cause cell injury and cell death or ontogenesis. Gamma rays are commonly emitted by decaying radioactive nuclei.

Visible and infrared light demonstrate several properties common to all electromagnetic radiation. Light represents a form of energy that when passing through matter, may be reflected, transmitted, or absorbed. Although light itself cannot be stored, it can be converted into some other form of energy, such as electricity, chemical energy, and heat. In addition, light can be generated from other forms of energy, including heat (incandescent), electrical (gas discharge), and chemical (photoluminescent) energies.

Light as a Multifunctional Tool: Beer-Lambert Law

When light passes through matter, it is transmitted, absorbed, or reflected. The relative absorption or reflection of light is used in several monitoring devices to estimate the concentrations of dissolved substances, for example, carbon dioxide respiratory gas and hemoglobin dissolved in plasma. The field of absorption spectrophotometry is based on the Beer-Lambert law. This law states that if a known intensity of light illuminates a chamber of known dimensions, the concentration of the dissolved substance can be determined if the incident and transmitted light intensity are measured.

Solved for C,

where C is the concentration of the dissolved substance, d is the path length of the light a, and alpha is an absorption constant for the substance C at the wavelength used. I_i and I_t are the

incident and transient light intensity, respectively. The unknown concentration (C) is inversely proportional to the path length (d) of light and is directly proportional to the log of the ratio of light incident to transmitted light intensity (Fig. 28-31) (Figure Not Available) . Red and infrared light are generally used because the constituents of interest to anesthesiologists (anesthetic agents, CO_2 , Hb) absorb light in that range. It is also fortunate that red and infrared light can penetrate tissue and therefore may be used to measure the concentration of hemoglobin species in living tissue (see the section on pulse oximeters). Infrared light is absorbed by small molecules only if they have bonds and are asymmetric. Therefore, nitrogen, oxygen, and helium cannot be measured by infrared light. Another limitation of infrared light is that it is absorbed by ordinary glass; therefore, the measurement chambers for these devices must be made of sapphire, which is permeable to red and infrared light.

Light Monitors (Capnometer, Agent Analyzer)

Capnographs and agent analyzers both utilize the Beer law by analyzing the constituents of the respiratory gas stream. The physical design of most capnometers is divided into two categories: mainstream and sidestream. In mainstream capnometers, the light-absorption chamber is placed directly in the airway, and the light source shines throughout the chamber, measuring CO_2 during inspiration and expiration directly. The advantages of this technique are very fast response time and no problems with clogging of the sampling of tubes, which is a disadvantage of sidestream capnometers. Disadvantages include the necessity of having a potentially heavy, expensive infrared measurement device placed directly in the endotracheal tube and that devices are not available that can measure both anesthetic agents and CO_2 . The most commonly used devices in the operating

Figure 28-31 (Figure Not Available) Cuvette. Light entering the cuvette is reflected and absorbed. The concentration of substances absorbing and reflecting light can be determined by measuring the amount of light entering and exiting the system. *(Modified from Tremper and Barker [23])*

room are sidestream capnometers, which use a small capillary sampling tube attached to the airway, aspirating a sample at 200 to 300 mL/min into the measurement chamber, which is within the monitor. The advantages of this method are just the opposite of the disadvantages of the mainstream capnometers, that is, the sampling tube is lightweight, and the device can be used to measure carbon dioxide and anesthetic agents. The disadvantages relate mostly to the delayed response time and the potential clogging of the aspiration tubing. [10]

Agent analyzers and capnography function via the same physical principles, using different wavelengths of light (Fig. 28-32) (Figure Not Available) . The mixture of

gases can interfere with each other, so compensations are built into current devices.

Pulse Oximeters

Oximeters are devices that use light-absorbance measurements to determine the concentrations of various species of hemoglobin. One of the first *in vivo* oximeters was a noninvasive monitor employed in aviation research during World War II. This device transilluminated tissue (the earlobe) with light of two wavelengths. One wavelength was sensitive to changes in oxyhemoglobin, and the other was not. In effect, the earlobe acted as a test tube containing the suspended hemoglobin. For a review of the development of pulse oximetry, the reader is referred to Severinghaus and Astrup. [11]

Before specific engineering problems are discussed, we need to define what we wish to measure. Adult blood usually contains four species of hemoglobin: oxyhemoglobin (Hb o_2), reduced hemoglobin (Hb), methemoglobin (metHb), and carboxyhemoglobin (COHb) Each of these hemoglobin species has a different light absorption profile. Figure 28-33 (Figure Not Available) illustrates the different absorption constants for each hemoglobin over a range of light from red to infrared. Except in

Figure 28-32 (Figure Not Available) Absorption spectra. Absorption spectra of some gases and materials important to anesthesia. Note that the absorption is not constant over wavelengths. Therefore it is important to choose the proper wavelength to measure. Also, when multiple substances are present, it is still possible to measure their concentrations, provided enough wavelengths are available. (The solution becomes one of multiple equations with multiple unknowns.) *(From Gravenstein et al [10])*

Figure 28-33 (Figure Not Available) Hemoglobin extinction curves. Pulse oximetry uses the wavelengths of 660 and 940 nm because these are available in solid state emitters (not all wavelengths are able to be emitted from diodes). Unfortunately, HbCO and HbO_2 absorb equally at 660 nm. Therefore HbCO and HbO_2 both read as Sa o_2 to a conventional pulse oximeter. Also, Hbmet and Hb reduced share absorption at 660 nm and interfere with correct Sa o_2 measurement. *(Courtesy of Susan Manson, Biox/Ohmeda, Boulder, Colorado, 1986.)*

pathologic conditions, metHb and COHb occur in low concentrations. Fractional hemoglobin saturation (O_2 Hb%) is defined as the ratio of oxyhemoglobin to total hemoglobin:

Measuring this quantity requires four wavelengths of light, producing four simultaneous Beer-Lambert law equations to solve for the four hemoglobin species. Because metHb and COHb do not contribute to oxygen transport, *functional saturation* is defined as the ratio of oxyhemoglobin to oxyhemoglobin plus reduced hemoglobin:

Although functional saturation depends explicitly on only HbO_2 and Hb, four light wavelengths are still required to measure it in the presence of significant concentrations of COHb and metHb. [12] [13] If the concentrations of metHb and COHb are both zero, then O_2 Hb% and Sa o_2 become identical.

The pulse oximeter performs substantial signal processing of the optically transduced physiologic data. Although the principle governing pulse oximetry is straightforward, the application of this principle to produce a clinically useful device involves significant engineering problems. [12] [14] The remainder of this section describes the physical and physiologic problems of pulse oximeter design and the engineering solutions to these problems. The discussion is divided into (1) basic design, and (2) management of signal artifacts.

Basic Design of Pulse Oximeters.

Noninvasive in vivooximeters measure red and infrared light transmitted through, and reflected by, a tissue bed. Accurate estimation of Sa o_2 by this method entails several technical problems. First, there are many light absorbers in the transmitted light path other than arterial hemoglobin (e.g., skin, soft tissue, and venous and capillary blood). The pulse oximeter accounts for the effects of absorption of light by tissue and venous blood by assuming that only arterial blood pulsates. Figure 28-34 (Figure Not Available) illustrates schematically the series of absorbers in a typical sample of living tissue. At the top of the figure is the AC component, which represents absorption of light by the pulsating arterial blood. The DC (baseline) component represents absorption of light by the tissue bed, including venous, capillary, and nonpulsatile arterial blood. The pulsatile expansion of the arteriolar bed increases the light path length (Equations 10 and 11), thereby increasing absorbency. Pulse oximeters use only two wavelengths of light: 660 nm (red light) and 940 nm (near-infrared light). The pulse oximeter first determines the AC component of absorbance at each wavelength and then divides this value by the corresponding

Figure 28-34 (Figure Not Available) Pulse oximetry signals. A primary difficulty with pulse oximetry is that the pulsatile signal is small compared with the total absorbance of the ear or finger being examined. Pulsatile flow is needed to determine the Sa o_2 . *(Adapted from Ohmeda Pulse Oximeter model 3700 Service Manual)*

DC component to obtain a "pulse-added" absorbance, which is independent of the incident light intensity. The oximeter then calculates the ratio R of the two pulse-added absorbances (one for each wavelength): [12]

Finally, the value of R is related to the displayed saturation estimate SpO_2 by a "look-up table" programmed into the oximeter's software. The tables used in all commercial pulse oximeters are based on experimental studies in healthy human volunteers. Although each manufacturer's exact calibration curve is proprietary, these curves are very similar. For instance, when the ratio of red to infrared pulse-added absorbance is 1.0, the displayed SpO_2 is approximately 85 percent. This fact has clinical implications, which are discussed below.

Signal Artifact Management.

Probably the most difficult engineering problem in pulse oximetry is the identification of the fluctuating absorbance pattern of the arterial blood in a sea of electromagnetic and other artifacts. Artifacts have three major sources: ambient light, low perfusion (weak pulse, low AC-to-DC signal ratio), and motion (high AC-to-DC signal ratio). All of these sources of artifacts produce a low signal-to-noise ratio.

The photodiodes used in the sensor to detect light cannot differentiate one wavelength of light from another. Therefore, the detector does not know whether received light originates from the red light-emitting diode (LED), the infrared LED, or the room lights. This problem is solved in most pulse oximeters by alternating the red and infrared LED sources. The red LED is turned on first, and the photodiode detector produces a current resulting from the red LED plus the room lights. Next, the red LED is turned off, and the infrared LED is turned on. The photodiode signal then represents the infrared LED plus the room lights. Finally, both LEDs are turned off, and the photodiode generates a signal from the room lights alone. This sequence is repeated hundreds of times per second. In this way, the oximeter attempts to eliminate light interference even in a quickly changing background of room light. [12] Some sources of fluctuating light can cause problems despite this clever design.

Artifact from ambient light can be minimized simply by covering the sensor with an opaque shield.

Another engineering problem is that of low AC-to-DC signal ratio, or low perfusion. When a small pulsatile absorbance signal is detected, the pulse oximeter amplifies the signal and estimates saturation from the ratio of the amplified absorbances. In this way, the pulse oximeter can estimate saturation values of Sp o_2 for a wide range of patients who generate different amplitudes for pulsatile absorbance. Unfortunately, as with a radio receiver, when a weak signal is amplified, the background noise, or "static," is also amplified. At the highest amplifications (which can be up to a million times), some pulse oximeters may analyze this noise signal and generate an Sp o_2 value from it. Because the noise is usually equal in the red and the infrared signals, the ratio of the two is often near unity (1.0), which yields a displayed saturation of approximately 85 percent. This problem could be demonstrated in early pulse oximeters by placing a piece of paper in the sensor between the photodiode and the LED. Many early models amplified the background noise while searching for a pulse until they eventually displayed a pulse and saturation value derived from the noise. To prevent this type of artifact, manufacturers have now incorporated minimum values for signal-to-noise ratio, below which the device displays no value for Sp o_2 . Some oximeters also display a low-signal-strength error message; many also display a plethysmographic wave for visual identification of noise.

Patient motion (high AC-to-DC signal ratio) may be the most difficult artifact to eliminate. Engineers have tried several approaches to this problem, beginning with increasing the signal-averaging time. If the device averages its measurements over a longer time period, the effect of an intermittent artifact is usually less. However, this longer averaging period also slows the response time to any acute change in Sa o_2 . Most pulse oximeters now allow the user to select one of several time-averaging modes. In addition, the designer can use sophisticated algorithms to identify and reject spurious signals.

One innovation aimed at reducing motion artifact is based on the premise that motion causes pulsations of the venous blood within the tissue bed. Conventional pulse oximetry cannot distinguish these venous pulsations from those of the arterial blood; hence, large errors or loss of signal can result. In the new signal processing algorithm developed by Masimo, the oximeter actually computes a venous "noise reference signal," which is common to both light wavelengths. The noise reference is then subtracted from the total signal, leaving a "true" arterial signal. Tests in human volunteers as well as preliminary clinical studies indicate that this new technology represents an improvement in pulse oximeter performance in low signal-to-noise ratio situations. [15] [16]

Over the past decade, other *in vivo* oximeters have been developed to measure light reflected by living tissue, in an attempt to determine tissue hemoglobin saturation in specific organs. Using reflected rather than transmitted light adds complexity because the path length of the light through the tissue may be tortuous, making calibration difficult. Nevertheless, a signal reflected from living tissue may produce useful information regarding the average saturation of the hemoglobin within the tissue illuminated by the reflectance oximeter. [17] For example, a cerebral oximeter may be able to measure mean brain hemoglobin saturation, reflecting the intracerebral balance between venous and arterial blood as well as the oxygenation of both.

Raman Scattering

As stated earlier, light of a specific energy can be absorbed by, or emitted from, a substance, depending on its allowable levels of vibrational, rotational, and electronic energy. Another absorption and reemission phenomenon of light scattering occurs in a very small percentage of interactions. In this process, called Raman scattering, light in the visible and ultraviolet range is absorbed by molecules of a substance, thereby producing unstable vibrational or rotational energy states. Because these excited states are unstable, some of the absorbed energy is immediately re-emitted, allowing the molecule to relax into a stable state. This Raman scattering signal occurs very infrequently; therefore, most photons pass through the gas sample without taking part in this particular absorption-re-emission phenomenon.

If the intensity of the transmitted light is sufficiently great, the Raman-scattered signal can be measured and used to identify the molecules within the gas sample. Because the signal is scattered light, it is emitted in all directions relative to the incident beam. [10] [18] The Raman light is of low intensity, so it is best to measure it at right angles to the high-intensity exciting beam.

An advantage of Raman scattering over gas analysis based on absorption of infrared light is that a spectrum of Raman scattering lines can be used to identify all types of molecules in the gas phase (e.g., O_2 and N_2). Because it involves only vibrational and rotational energy states, Raman scattering cannot be used to identify single atoms. As discussed earlier, infrared absorption can be used to analyze molecules having a dipole moment and, therefore, cannot be used to identify oxygen or nitrogen. A disadvantage of Raman scattering as a clinical tool is the requirement for a very high-intensity laser light source to produce the small Raman-scattered signal. [10] [18]

TEMPERATURE MEASUREMENT

Principles of Temperature

Moving matter contains energy. Even stationary objects are moving at the atomic level. This kinetic energy of the molecules and atoms is described as temperature. When all atomic motion ceases, the substance is said to be at absolute zero. This provides a reference point for all temperature measurements. Heat has been defined as a form of internal kinetic energy that flows between two contacting bodies at different temperatures. When all atomic motion ceases, the substance is said to be at absolute zero. This provides a reference point for all temperature measurements.

The amount of heat required to raise the temperature of 1 g of a given substance by 1°C is called the *specific heat* of that substance. The calorie, a common heat unit, is the amount of heat required to raise the temperature of 1 g of water from 14.5 to 15.5°C. One calorie is equal to 4.184 joules. When we refer to calories in terms of the calories in the food we eat or the calories we expend exercising, we are actually referring to kilocalories, or thousands of calories. The total amount of heat energy in an object thus depends on its specific heat, its temperature, and its mass. For example, although a cup of 60°C coffee is much "hotter" than a 30°C swimming pool, the coffee contains much less total thermal energy than the pool. The same is true for potential energy stored as pressure potential or electrical potential. A small container at high pressure may have less potential energy than a larger container at a lower pressure.

Temperature Monitors (Thermometer, Thermistor, Thermocouple)

There are three general techniques for measuring temperature: those based on expansion of a material as the temperature of the material increases, those based on changes in electrical properties with temperature, and those based on optical properties of a material. As heat is added to most substances (gases, liquids, or solids), the motion of the molecules increases, causing the volume of the material to expand at constant pressure. Depending on the material, this expansion can be calibrated linearly to changes in temperature. Liquids are most commonly used, specifically, mercury, because its effective range extends from its freezing point of -39°C to approximately 250°C. Mercury thermometers have two general disadvantages. They require 2 to 3 minutes for complete thermal equilibration (mercury has a high specific heat). Also, they are enclosed in a glass tube, which may break and injure the patient. Thermometers based on the expansion of gas (the Borden tube) or metal (the bimetallic strip) are frequently used as thermostats because they respond slowly to transient changes in temperature.

Electrical techniques for measuring temperature can be subdivided into three categories: resistance thermometers, thermistors, and thermocouples. Resistance thermometers operate on the principle that the electrical resistance of metals increases with temperature. These devices most frequently use a platinum wire as the temperature-sensitive resistor; a battery; and a galvanometer to measure current, which can be calibrated to temperature. The platinum wire is incorporated into a Wheatstone bridge circuit, which accurately measures very small changes in resistance (Fig. 28-35) .

Compared with a platinum thermometer, a thermistor is a semiconductor that displays the opposite behavior with regard to electrical resistance. Specifically, as the thermistor is heated, its resistance decreases. Thermistors, being solid- state devices, can be manufactured as extremely small devices and therefore have a fast response to change in temperature (i.e., little heat is needed to increase their temperature). Most of the temperature probes used in anesthesia, from the ones at the end of Swan-Ganz catheters to esophageal probes, are thermistors.

Figure 28-35 Wheatstone bridge. A Wheatstone bridge is an electronic circuit designed so that an unknown resistance can be calculated by knowing two sets of variables: (1) the voltage drop across the bridge and (2) the other resistances in the circuit (Appendix 3).

References

1. DeGowin EL, DeGowin RL: Bedside Diagnostic Examination, 5th ed. New York, Macmillan Publishing Company, 1987.

2. Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1:307, 1986.

3. Sykes MK, Vickers MD, Hull CJ: Ultrasound. In Principles of Measurement and Monitoring in Anaesthesia and Intensive Care, 3rd ed. Oxford, Blackwell Scientific Publications, 1979.

4. Raemer DB: Monitoring ventilation. In Ehrenwerth J, Eisenkraft JB (eds): Anesthesia Equipment Principles and Applications. St. Louis, Mosby-Year Book, 1993, p 221.

5. Cicman JH, Gotzon J, Himmelwright C et al: Operating Principles of Narkomed Anesthesia Systems, 2nd ed. Telford, Pennsylvania, WE Andrews Company, 1998.

6. Resnick R, Halliday D: Physics for Students of Science and Engineering. New York, John Wiley & Sons, 1960.

7. Rappaport MB, Sprague HB: Physiologic and physical laws that govern auscultation, and their clinical application. Am Heart J 21:257, 1941.

8. Cahalan MK, Litt L, Botvinick EH et al: Advances in noninvasive cardiovascular imaging: Implications for the anesthesiologist. Anesthesiol 66:356, 1987.

9. Clements FM, deBruijn NP: Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. Anesth Analg 66:249, 1987.

10. Gravenstein JS, Paulus DA, Hayes TJ: Capnography in Clinical Practice. Boston, Butterworths, 1989.

11. Severinghaus JW, Astrup PB: History of blood gas analysis. Int Anesthesiol Clin 25:205, 1987.

12. Tremper KK, Barker SJ: Pulse oximetry. Anesthesiol 70:98, 1989.

13. Barker SJ, Tremper KK, Hyatt J: Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. Anesthesiol 70:112, 1989.

14. Pologe JA: Pulse oximetry: Technical aspects of machine design. Int Anesthesiol Clin 25:137, 1987.

15. Dumas C, Wahr JA, Tremper KK: Clinical evaluation of a prototype motion artifact resistant pulse oximeter in the recovery room. Anesth Analg 83:269, 1996.

16. Barker SJ, Shah NK: The effects of motion on the performance of pulse oximeters in volunteers (revised publication). Anesthesiol 86:101, 1997.

17. Wahr JA, Tremper KK, Samra S, et al: Near-infrared spectroscopy: Theory and applications. J Cardiovasc Anesth 10:406, 1996.

18. Westenskow DR, Smith KW, Coleman DL: Clinical evaluation of a Raman scattering multiple gas analyzer for the operating room. Anesthesiol 70:350, 1989.

19. Hecht E: Physics: Algebra/Trig. Pacific Grove, California, Brooks/Cole Publishing Company, 1994.

20. Tremper KK, Barker SJ: Fundamental principles of monitoring and instrumentation. In Miller RD (ed): Anesthesia, 4th ed. Edinburgh, Churchill Livingstone, 1994.

21. Ehrenwerth J, Eisenkraft JB: Anesthesia Equipment: Principles and Applications. St. Louis, Mosby-Year Book, 1993.

22. Mushin WW, Jones PL: Flow of fluids through orifices: Flowmeters. In Physics for the Anaesthetist. Oxford, Blackwell Scientific Publications, 1987.

23. Tremper KK, Barker SJ: Pulse oximetry and oxygen transport pulse oximetry. In Payne PJ, Severinghaus JW (eds): Pulse Oximetry. London, Springer-Verlag, 1986.

Appendix *1*-Distance Versus Time Under Constant Acceleration: Equivalence of Potential and Kinetic Energy

Velocity **v** is the rate at which distance is changing, i.e., it is the time derivative of distance:

v = d **x**/dt (1)

v is written in boldface type to indicate that it is a vector: it has both magnitude and direction. Distance **x** is a vector pointing from the origin to the present location of the particle or object; this is called the "position vector." Time (t) is a scalar: it has magnitude but no direction and is therefore written in plain type.

Acceleration **a** is the time rate of change of velocity. Thus, it is the time derivative of the velocity vector, or the second derivative of distance with respect to time.

a = d **v**/dt = (d/dt)(d **x**/dt) = d^2 **x**/dt^2 (2)

If an object starts with zero velocity (**v** = 0) at time zero (t = 0), and then accelerates with constant acceleration (**a**), then its velocity at time t will be simply **v** = **a**t. To calculate the distance traveled by the object at between time t = 0 and time t, we must divide the time interval 0 to t into a series of very small intervals, each of time length dt. The distance traveled during the interval dt is simply the velocity at that time multiplied by the time interval:

d **x** = **v**dt = (**a**t)dt (3)

In the second step, we have substituted the constant acceleration relation **v** = **a**t from above. Now to compute the total distance traveled, we must sum the distance from all of the small dt time intervals that occur between 0 and t.

x = Sigma(**a**t)dt (4)

If we allow the length of the time interval dt to approach zero, the summation process becomes the *integral* with respect to time, from time zero to time t.

x =
vdt =
(**a**t)dt = (½) **a**t^2 (5)

Thus, an object starting from rest at t = 0 and moving with constant acceleration (**a**) will move a distance (½) **a**t^2 in time t. If this is a falling object (in a vacuum, where there is no air resistance) then a = g = 9.8 m/s^2 , and the distance formula becomes:

x = (½)gt^2 = (4.9)t^2 (6)

In the first second the object falls 4.9 ms; at the end of 2 seconds, it has fallen 19.6 meters; after 3 seconds, 44.1 meters, and so on.

The kinetic energy (KE) of a moving object is

KE = (½)mv^2 (7)

where m is the mass of the object and v is the magnitude of its velocity (also called *speed*). Note that v used in this sense is in plain type, not boldface. Consider again the falling object that started at position x = 0 at time t = 0 and falls a distance h:

Because velocity v = at = gt, we have by substitution from Equation 8:

The kinetic energy is given by

KE = (½)mv^2 = (½)m(2gh) = mgh(10)

Now let us consider the *work* required to lift the fallen object back to its original height of h. Recall that work is defined as the force exerted times the distance over which the force acts: W = Fd. The force of gravity acting on our object is F_g = mg, so the work required to lift it the distance (h) back to x = 0 is

W = Fd = (mg)d = mgh(11)

Thus, the work required to restore the object equals the kinetic energy possessed by the object at the bottom of its fall, KE = W = mgh. When we lift the object from x = h back to x = 0, we have increased its *potential energy* (PE) by an amount (mgh). This potential energy can be converted to kinetic energy by allowing the object to fall the distance h. This type of potential energy, called *gravitational potential,* has a value that clearly depends on where we locate the origin of our coordinates, x = 0. However, it is the *changes* in potential energy, not its absolute value, that the potential energy/kinetic energy balance:

DeltaKE = -DeltaPE(12)

The change in kinetic energy is equal to, and of opposite sign of, the change in potential energy.

/das/book/view/29494766/875/308.html

Appendix *2*-Physics of Hydrostatic Pressure

The liquid manometer is a simple and reliable means of monitoring pressures that do not change rapidly. It simply uses the weight of a measured vertical column of liquid to balance the pressure exerted against the bottom of the column. We have defined weight as the force exerted by gravity on a mass (m): ($F_g = mg$). To determine the weight of a column of liquid of known dimensions (the manometer in Fig. 28-10) , we must first know the density (mass per unit volume) of the liquid. Density has dimensions of M/L^3 , and the SI units are kilograms per cubic meter (kg/m^3). Because liquids are almost incompressible, their density is little influenced by pressure (but is affected by temperature). The density of water at room temperature is 997.8 kg/m^3 , or 1.0 g/cm^3 .

The pressure (p) exerted by the bottom of the vertical column of liquid in the manometer (see Fig. 28-10) is determined as follows. If the cross-sectional area of the liquid cylinder is A and the height of the cylinder is z, then its volume is V = Az. If the liquid has a density of rho, then the mass of the column is

m = rhoV = rhoAz (1)

and its weight is

W = mg = rhoAzg (2)

The liquid column exerts a force equal to its weight on its base, whose surface area is A, thus creating the following pressure on the surface:

p = force/area = rhoAzg/A = rhogz (3)

The pressure exerted by the manometer is therefore independent of its cross-sectional area (A); it depends on only the density of the working fluid and the vertical height of the column. If we know the liquid density, then measurement of the column height (z) allows us the calculate the pressure (p). For example, if the working fluid is mercury (e.g., sphygmomanometers), the density is 13,680 kg/m^3 (13.68 g/cm^3 , or 13.68 times the density of water). The relationship of pressure to height of the column is then

p = rhogz = (13,600 kg/m^3)(9.8 N/kg)(z) p [N/m^2] = 133,300(z) (4)

The unit of pressure newton/$meter^2$ is called the pascal (Pa). Because a pascal is a small unit of pressure, we usually use kilopascals (10^3 pascals) or kPa. If we express p in kPa and z in millimeters of mercury (rather than meters), Equation 4 becomes

p [kPa] = 0.1333 (z) [millimeters] (5)

Appendix *3*-Wheatstone Bridge

The Wheatstone bridge is a network of four resistors connected as shown in Figure 28-35 , with a battery or direct-current voltage source (electromotive force) connected between A and C, and a voltmeter (V) connected between B and D. The bridge is said to be "balanced" when the voltmeter reads zero potential difference between points B and D. From Ohm's law (V = IR), it is easy to show that balance occurs when $R_x = R_s \times (R_2 / R_1)$. If Rs is an adjustable standard resistor and R_1 and R_2 are fixed known resistors, then the balanced bridge provides a very precise means of determining R_x, the unknown resistance. This principle has many applications in biomedical engineering, including strain-gauge pressure transducer measurements. In this case, the transducer itself is the unknown resistance R_x.

Appendix *4*-Amplification Artifact of a Fluid Tube/Transducer Pressure Wave

The amplification artifact of a fluid/transducer pressure waveform can be calculated if a few properties of the system are known. The most relevant part of this solution is the response amplitude, which is plotted against the driving frequency (f) in Figure 28-13 (Figure Not Available) . This figure shows some important properties of fluid-coupled transducers and other harmonic oscillators. One of these is the existence of a resonant frequency, f_0, which is defined as follows:

Remember, m is the mass of the system and k is the elasticity, or spring constant.

As we increase the amount of damping (i.e., friction; c is the friction constant), we observe a decrease in the peak amplitude at resonance, and the frequency at which the peak occurs decreases slightly, the damping coefficient (z), is defined as follows:

Even though the arterial pressure waveform is not actually sinusoidal, Figure 28-13 (Figure Not Available) shows the most important characteristics of the pressure transducer response. Any combination of catheter, tubing, and transducer can be characterized by two quantities: a resonant frequency (f_0) and a damping coefficient (z). Gardner measured these quantities for many transducer and tubing systems; most systems have resonant frequencies of 10 to 20 cycles/s, or hertz (Hz), and damping coefficients of 0.2 to 0.3. For clinical systems, the maximum amplification factor (the ratio of transducer output to input waveform amplitude) at resonance is near 2.5.

If the resonant frequency is 10 Hz (600 cycles/min), one might conclude that amplification plays little role in the clinical range of pulse rates, which are five to 10 times smaller. However, the arterial pressure waveform is not a sine wave. It can be represented as a summation of sine waves (a Fourier series) of frequencies up to many times the pulse rate. It is these higher harmonic frequencies that are amplified most and that yield the spiked appearance of the poorly processed arterial waveform. Depending on the shape of the actual arterial pressure wave, this distortion can introduce a 20 to 40 percent "overshoot" error in systolic blood pressure readings. Even worse, this error is dependent on pulse rate, so that an error determined for a particular patient at the beginning of an anesthetic may not remain constant.

From this discussion, we can easily predict how to optimize the performance of a pressure transducer system. First, the resonant frequency (f_0) should be as high as possible. Therefore, the value for k in Equation 1 should be large (i.e., the spring should be "stiff"), and the value for m should be small. That is, the cannula and pressure tubing should be as stiff and inelastic as possible. To minimize the mass of the moving fluid, the tubing should be short in length and small in diameter. Judging from plots of amplitude versus frequency/resonant frequency at different damping coefficients, the optimal damping coefficient would be 0.4 to 0.5. One should also carefully eliminate air bubbles from the system because these add elasticity and friction, thereby lowering the resonant frequency. In a clinical system, one can determine the approximate f_0 and z of a transducer system if graphic output is available. If the high-pressure flush is turned on and then quickly off at a high chart speed (50 mm/s), the tracing oscillates through several cycles at a frequency near f_0. The damping coefficient can be found by determining the ratio of amplitudes of successive peaks on the tracing.

This is a practical example of how fundamental principles of mechanics can be used to predict and optimize the performance of monitoring systems. These concepts of mechanics will recur in later sections of this chapter.

Appendix 5-Flowmeters, Bernoulli's Principle, Laminar and Turbulent Flow

The equations governing the motion of fluids are expressions of Newton's second law, F = ma. Forces associated with fluids fall into three major categories: (1) gravity, (2) pressure, and (3) friction. In the example using manometers, the gravitational force per unit volume of fluid is simply rg, acting in the vertical direction. Pressure forces are actually the result of differences in pressure from one point to another and are expressed mathematically as the negative of the pressure gradient. (The pressure gradient is a vector in the direction of maximum rate of pressure increase, having magnitude equal to the pressure derivative in that direction.) Friction is proportional to viscosity, the physical property of a fluid that relates shear stress to rate of strain.

$P_0 = p + (½)rhoU^2 + rhogz$(1)

Equation 1 shows the relationship between velocity and pressure of a fluid in a flow that meets the conditions described. For flows in tubes, the manometer technique provides an easy method of measuring mean pressure. Therefore, the simplest flowmeters apply a combination of these two principles to a tube of changing cross-sectional diameter. For example, the Venturi flowmeter shown in Figure 28-17 consists of a tube of varying cross-sectional area that has two ports for measurement of pressure. The Bernoulli equation for points 1 and 2 in the figure becomes

Here, the gravity terms have canceled out because the tube is horizontal, but these terms are usually negligible for gas flows in any direction.

The volume of the fluid flow (Q), (also called flux) at both locations must be the same because no fluid is entering or leaving through the tube walls. The dimensions and SI units for the volume of fluid flow are L^3/T and m^3/s, respectively. This volume is determined at each cross-section of the tube by multiplying the average velocity (U) by the cross-sectional area (A):

$Q = U_1 A_1 = U_2 A_2$ (3)

Assuming that A_1, A_2, P_1, and P_2 are known, we now have two equations for the two unknowns U_1 and U_2. Solving these for the velocity U_1 produces

To find the volume of the flow (Q), we merely multiply this result by A_1. Note that velocity is proportional to the square root of the pressure drop or that the pressure change varies as velocity squared. For a given U_1, magnitude of flow velocity, the pressure drop varies as the square of the ratio of the areas, or the fourth power of the ratio of the diameters. If we choose A_2 greater than A_1, Equation 4 implies that P_2 is greater than P_1. In this case, the pressure increases in the direction of flow, a change that initially seems contrary to intuition.

The bobbin flowmeters (also called variable-orifice flowmeters) in anesthesia machines use a similar principle. These devices consist of a slightly tapered vertical tube and a bobbin or ball that fits inside the tube (Fig. 28-19) . The cross-sectional area of the ring-shaped gap between the bobbin and the tube wall is proportional to the height of the bobbin. Because changes in the cross-sectional area of flow are abrupt rather than gradual (as in Figure 17), the Bernoulli equation does not accurately describe this type of flow. The flow above the bobbin (i.e., downstream) is highly turbulent, and turbulence is a condition that dissipates kinetic energy into heat. However, introduction of an empirical constant C_d enables one to use the same formulation as in Equation 4:

and

$P_1 - P_2 = (½\ rhoQ^2)/(C_d^2 A^2)$(6)

where C_d is a dimensionless constant called the discharge coefficient. This constant varies with the shape of the orifice and with the value for another dimensionless parameter, the Reynolds number (Re). The Reynolds number, the overall ratio of inertial forces to viscous forces in a particular flow, is determined as follows:

Re = rhoUL/mu(7)

where U is mean flow velocity, L is a characteristic length for the flow (in our flowmeter, L is the diameter of the tube), and mu is the viscosity of the fluid. The dimension for viscosity is M/LT. The value for the Reynolds number is important to any fluid flow because it determines some of the most important characteristics of the flow. For example, the transition from laminar, or "smooth," flow to turbulent flow is determined by the shape of the flow and the Reynolds number. Flow in a long, straight, smooth-walled tube becomes turbulent at an Re value of approximately 2,100. On the other hand, flow through an abrupt orifice, such as that of the flowmeter in Figure 28-19 , becomes turbulent at a Reynolds number of less than 100

Returning now to the function of the flowmeter, one can see that as gas flows upward through the tapered tube, the bobbin begins to rise. As the bobbin rises, the cross-sectional area of the orifice A increases because of the taper of the tube; therefore, the drop in pressure ($P_1 - P_2$) decreases. The bobbin reaches an equilibrium position for a given volume of flow (Q) when the pressure lifting the bobbin is exactly equal to the weight of the bobbin. In this type of flowmeter, the pressure difference is fixed by the bobbin weight, and the area of the orifice varies with the volume of the flow, hence the name variable-orifice flowmeter. Equations 5 and 6 show that calibration of these flowmeters depends on both the density and the viscosity of the gas: density (rho) appears explicitly, and viscosity (mu) appears in the dependence of C_d on the Reynolds number. If we use the wrong gas in a particular flowmeter, equations 5 and 6 and the viscosity and density of the new gas

enable us to predict the change in calibration.

Appendix *6*-Thermal Dilution Cardiac Output

A commonly used method of measuring blood flow is dilutional calculations, i.e., dye or thermal dilution. These methods are simply mass or energy balances that determine the volume of fluid that has diluted by giving a volume of dye or given thermal energy. If you have a bucket of water at room temperature (25°C) and you want to determine the volume of water within the bucket, you could add a known volume of water and a known temperature. If 100 mL of water at 35°C is added to the bucket and the final temperature is 27°C, then the unknown volume can be calculated by balancing the heat energy associated with the dilutional process. This assumes that no heat is lost to the environment. This dilutional process can be used to measure blood flow by completing this same heat balance measured over time. Thermodilution cardiac output measurements can have significant error as a result of the many assumptions associated with the technique, i.e., rapid injection of the thermodilution injectate; accurate temperature and volume of the injected fluid; constant known heat capacity of blood, which in reality is a function of hematocrit value; little heat loss to the lung; and so on.

Thermistor probes are most commonly used in clinical monitoring of patient temperature because they are inexpensive, small, and flexible. For these reasons, the thermistor probe is also used to measure cardiac output determined by the thermodilution technique. Computation of cardiac output performed in this manner is, in effect, a heat balance for the right side of the heart. (A heat balance is a method of accounting for all heat in a process or change involving transfer of heat.) The technique consists of quick injection of a known volume of a sterile solution (usually 10 mL of 5% dextrose in water) into the right side of the heart while a sensor notes the temperature of the blood in the pulmonary artery. It is assumed that the cold injected solution equilibrates thermally with the blood as it perfuses the pulmonary artery but that the solution does not acquire heat from other tissues. The following equation is the solution of this heat balance:

where CO is cardiac output (liters per minute); rhoi and rhob are the densities of the injectate and blood, respectively; C_i and C_b are the heat capacities of the injectate and the blood, respectively; V_i is the volume of the injectate; T_b and T_i are the temperature of the blood and the injectate, respectively; Cr is a computational constant that corrects for the rising temperature of the injectate; and is the area under the thermo-dilution curve. Because the injectate warms as it is injected through the catheter before mixing with the blood, the correction factor Cr is applied to the equation.

Appendix 7-Ultrasound

The simplest sound wave to represent mathematically is a sinusoidal wave propagating in one dimension:

$$p = p_0 \sin [(2\pi/\lambda)(x - at)] \quad (1)$$

where p is the pressure fluctuation, λ is the wavelength (distance between waves), x is the coordinate in the direction of propagation, and a is the speed of propagation, or the speed of sound.

The amplitude of a sound wave is measured by the root mean square value of the pressure fluctuations. This value is called the sound pressure level (SPL). Because the range of SPL values is often very wide, a logarithmic scale is used:

$$SPL = 20 \log (p^*/P_0) \quad (2)$$

where p^* is the root mean square pressure fluctuation and P_0 is a reference pressure, chosen as the lowest sound pressure detectable by the human ear. This pressure representing the threshold of hearing is 2×10^{-8} kPa at a sound frequency of 2 kHz (2,000 cycles/s). The units in this SPL scale are called decibels. Thus, a sound pressure of 2×10^{-8} kPa corresponds to an SPL of zero decibels (0 dB), the lowest audible sound level [$(p^*/P_0 = 1; \log (1) = 0)$]. Quiet conversation has an SPL of approximately 40 to 50 dB, or a pressure of 10 to 300 times that of the threshold of hearing.

When sound waves encounter a sudden change in the properties of the conducting medium, some of the sound is transmitted through the new medium, and some of it is reflected, or "scattered," in many directions. Although the mathematics of this process are complex, one conclusion is readily apparent: the greater the mismatch in density and compressibility between the two media, the more sound is reflected. The quantity that best determines the degree of reflection at an interface between two media is the ratio (R) of the products of density (ρ) and the speed of sound (a) through the two media:

$$R = (\rho_1 a_1)/(\rho_2 a_2) \quad (3)$$

We can easily see that the greatest acoustic mismatch in the body occurs between the solid tissues and the lungs. Both the density and the speed of sound are much lower in the air-filled lungs than in solid tissues. Therefore, ultrasonography cannot "look" through the lungs to tissues or organs on the other side. The second greatest mismatch occurs between soft tissues and bone, the latter having a much higher rhoa than the former. In 1842, Christian Johann Doppler first described the apparent change in pitch of a sound that occurred when either the source of the sound or the listener was moving. This Doppler effect now has several applications in patient monitoring, including precordial and esophageal Doppler ultrasound devices that measure local blood velocities or cardiac output. If a sound source radiating a frequency (f) is stationary and the listener is moving (Fig. 28-23 (Figure Not Available) A) , the wavelength of the waves can be determined by the equation

$$\lambda = a/f \quad (4)$$

because the time between wavefronts is $1/f$, and the waves are moving at the speed of sound (a). If the listener moves toward the source at speed V_0, his velocity relative to the moving wavefronts is $(a + V_0)$. The number of wavefronts the listener encounters per unit time is therefore

$$f = \text{velocity/distance between waves} = (a + V_0)/\lambda \quad (5)$$

Because the sound frequency for a stationary listener is $f = a/\lambda$ (Equation 4), the frequency f heard by the moving listener becomes

$$f = (a + V_0)/\lambda = f + (V_0/\lambda) = f + (V_0 f/a) = f[1 + (V_0/a)] \quad (6)$$

The apparent frequency of the listener is thus increased by the factor $[1 + (V_0/a)]$. A listener moving toward the source at half the speed of sound hears a frequency 1.5 times that of a stationary listener.

Now consider a stationary listener and a source moving at speed V_0, as shown in Figure 28-23 (Figure Not Available) B. The wavefronts are no longer concentric circles; they are more closely spaced in the direction that the source is moving. If the frequency of the sound emitted at the source is f, then during each vibration, the source moves a distance V_0/f. The wavelength in the direction of motion is thus shortened by V_0/f, becoming $\lambda = (a - V_0)/f$. The waves themselves are traveling at speed a, so that the frequency heard by the stationary listener is

$$f = a/\lambda = af/(a - V_0) = f[1/(1 - V_0/a)] \quad (7)$$

Now, if the source is moving at half the speed of sound toward the listener, the apparent frequency doubles. Compare this with the preceding situation, in which the listener is moving and the apparent frequency increases by only 50 percent. Doppler ultrasound systems combine the two situations shown in Figure 28-23 (Figure Not Available) . The initial acoustic source is a stationary transducer, and the sound from this device is scattered from a moving target (e.g., red blood cells). The scattered sound then returns to a stationary listener: the receiving transducer. In effect, the target is a moving listener hearing a stationary source; the target then reradiates the sound as a moving source toward a stationary listener. The

frequency heard by the receiving transducer is obtained by combining equations 6 and 7:

In this example, we have assumed that the target is moving toward the ultrasound transducers at speed V. If the target is moving at half the speed of sound, the observed frequency is increased by a factor of 3! Because changes in the frequency of sine waves can be measured precisely, the Doppler principle provides a very accurate method of measuring the velocities of moving sound reflectors. At the high frequencies often used (
5 MHz), objects as small as red corpuscles can scatter enough sound for detection.

Chapter 29 - Monitoring Depth of Anesthesia

Donald R. Stanski

INTRODUCTION

The conceptual approaches to defining depth of anesthesia are extremely varied, ranging from in-depth scientific discussions of the minimum alveolar concentration of anesthetic necessary to eliminate movement in 50 percent of subjects (MAC) [1] to clinical, anecdotal descriptions of "light," "moderate," or "deep" anesthesia. [2] The range of these approaches indicates the complexity of conceptualizing depth of anesthesia.

The chapter is divided into three general sections. The first discusses two related topics: the evolving definitions of depth of anesthesia and the problem of recall (memory) and awareness. The many attempts to define "depth of anesthesia" make one realize that our knowledge of the specific attributes of the drugs used in clinical practice has to be incorporated into our understanding of this phrase. Currently, the diverse nature of anesthetic drugs makes it difficult to define depth of anesthesia in a unifying manner. Although modern techniques and drugs have increased the intraoperative and postoperative safety of anesthesia care, the unfortunate consequence of this otherwise advantageous effect is the occasional occurrence of intraoperative recall and awareness during surgery.

The second section of this chapter involves basic pharmacologic concepts relevant to the scientific investigation of depth of anesthesia. This brief review prepares the reader for the third section, which discusses specific drugs and clinical situations in two subsections. The first subsection discusses clinical measures of anesthetic depth that derive directly from the patient. Each discussion begins with a review of the scientific approaches available for individual drugs and culminates in the more subjective clinical approaches used in anesthetic practice. The second subsection discusses several electrophysiologic approaches to assessing depth of anesthesia. This represents the application of technology to the issue of quantitation of anesthetic drug effect and depth of anesthesia.

DEPTH OF ANESTHESIA: INTRAOPERATIVE MEMORY AND AWARENESS

The word *anesthesia* was first used by the Greek philosopher Dioscorides in the first century of the current era to describe the narcotic effect of the plant *Mandragora.* The word reappeared in the 1771 *Encyclopaedia Britannica,* where it was defined as a "privation of the senses." [3] After the introduction of ether anesthesia by Morton in 1846, Oliver Wendell Holmes used the word to describe the new phenomenon that made surgical procedures possible.

Defining Depth of Anesthesia

Plomley [4] was the first, in 1847, to define depth of anesthesia. He described three stages: intoxication, excitement (both conscious and unconscious), and the deeper levels of narcosis. In that same year, John Snow [5] described "five degrees of narcotism" for ether anesthesia. The first three stages encompassed induction of anesthesia, and the last two represented surgical anesthesia. Eleven years later, Snow [6] turned his attention to chloroform. Snow's excellent characterizations of ether and chloroform anesthesia described the following signs: conjunctival reflex; regular, deep, automatic breathing; movement of the eyeballs; and

inhibition of the intercostal muscles. Many of these clinical signs were later "rediscovered." [7] Because oxygen was not readily available until the early 1900s, Snow and his successors tried to minimize the use of deep anesthesia to decrease morbidity and mortality.

The early 1900s saw the introduction of premedication with sedatives or opioids. In addition, anesthetics with more rapid onset, such as nitrous oxide and ethylene, became available. Therefore, the anesthetic excitement phase could be traversed more rapidly with the use of preanesthetic medication and rapid-onset inhaled anesthetics.

In 1937, Guedel [8] published his classic description of the clinical signs of ether anesthesia. He used clear physical signs involving somatic muscle tone, respiratory patterns, and ocular signs (Fig. 29-1) (Figure Not Available) to define four stages. In the first stage, analgesia, characterized by slow, regular breathing with the diaphragm and intercostal muscles and the presence of the lid reflex, the subject experiences complete amnesia, analgesia, and sedation. In the second stage (delirium), the subject experiences excitement, unconsciousness, and a dream state with uninhibited activity. Ventilation is irregular and unpredictable. Reflex dilatation of the pupils occurs, the lid reflex is intact, and the risk of clinically important reflex activity (e.g., vomiting, laryngospasm, or arrhythmias) increases. The third stage (surgical anesthesia) consists of four progressive planes. Plane 1 is characterized by slight somatic relaxation, regular periodic breathing, and active ocular muscles. During plane 2, breathing changes, inhalation becomes briefer than exhalation, and a slight pause separates inhalation and exhalation. The eyes become immobile. In plane 3, the abdominal muscles are completely relaxed, and diaphragmatic breathing is very prominent. The eyelid reflex is absent. In plane 4, the intercostal muscles are completely paralyzed, and paradoxic rib cage movement occurs. Breathing is irregular, and pupils are dilated. In Guedel's fourth stage (respiratory paralysis), muscles become flaccid, and eyes widely dilate. Cardiovascular and respiratory arrest occurs, as does cardiovascular collapse.

In 1954, Artusio [9] expanded Guedel's description of ether analgesia (stage 1) into three planes. In plane 1, the patient has no amnesia or analgesia. In plane 2, the patient has total amnesia and partial analgesia. In plane 3, the patient has complete analgesia and amnesia, but is comfortable and responsive to verbal stimulation; there is little depression of reflexes. Artusio observed that once patients were anesthetized past stage II (delirium) to the deeper anesthesia of stage III, they could be brought back and forth between stage III and plane 3 of stage II without ever exhibiting stage II. The clinical signs of depth of anesthesia defined by Guedel and others had significant practical utility for the administration of ether, cyclopropane, and chloroform anesthesia.

Beginning in 1942, small doses of the muscle relaxant *d*-tubocurarine were used with the deep levels of ether anesthesia that produced plane 2 or 3 of Guedel's stage III. Respiration was assisted when necessary. Over time, the dose of *d*-tubocurarine began to increase as fully controlled ventilation became commonplace. Anesthesiologists soon realized that they could combine controlled ventilation and large doses of muscle relaxants with low concentrations of inhaled anesthetics to reduce the risk of toxicity (cardiovascular and respiratory depression) and to increase the speed of emergence from anesthesia. However, the use of muscle relaxants eliminated two valuable types of clinical signs of depth of anesthesia: the rate and volume of respiration and the degree of muscle relaxation induced by the anesthetic. [10] Seven of the nine components of Guedel's classification system involved skeletal muscle activity. When muscle relaxants are used with ether anesthesia, only pupil size and lacrimation are left as clinical signs. These signs are inadequate to judge anesthetic depth clinically. [11] A 1945 editorial in the *Lancet* discussed the clinical problems that muscle relaxants would

Figure 29-1 (Figure Not Available) Guedel's classic text described the stages and planes of ether anesthesia (A) and then related them to clinical signs or relevant reflexes (B). *(From Guedel [6])*

create, [12] and descriptions of patient awareness during surgery later began to appear in the literature. [13]

In 1957, Woodbridge [14] examined the diverse use of anesthetic drugs at that time. He defined anesthesia as having four components: (1) sensory blockade of afferent nerve impulses; (2) motor blockade of efferent impulses; (3) reflex blockade of the respiratory, cardiovascular, or gastrointestinal tract; and (4) mental block, sleep, or unconsciousness. Different drugs could be used to achieve each effect. However, Woodbridge made no effort to define methods of assessing each of these components.

In a 1986 letter to the editor, Pinsker [15] described his conceptualization of "anesthesia" as a broad, descriptive term, comparable to the idea of "sickness," in that the source is not one mechanism, but rather, several components. Anesthesia has three components: paralysis, unconsciousness, and attenuation of the stress response. Any drug or combination of drugs that reversibly provides these three conditions could be used in anesthesia. Paralysis or the absence of movement or skeletal muscle tone in the operative field could be achieved by neural blockade or nondepolarizing muscle relaxants. Attenuation of the stress response could be defined only poorly because of limited knowledge regarding the nature of stress. By contrast, heart rate and blood pressure are clinically measurable components of stress. Unconsciousness, which consists of amnesia and hypnosis, is also a parameter that could not be well defined. No universal end point serves as the basis for the rational administration of drugs to achieve unconsciousness. At present, an absence of recall is the only objective criterion for unconsciousness (hypnosis or amnesia).

In a 1987 editorial, Prys-Roberts [16] made a meaningful contribution to the concept of depth of anesthesia by redefining which elements are truly relevant to anesthesia. He began by observing that depth of anesthesia is difficult to define because anesthetists have approached the issue in terms of the drugs available to them rather than the patient's needs during surgery. Prys-Roberts believed that the noxious stimulation of surgery induces a variety of reflex responses that may be independently modified to the benefit of the patient. One important premise is that pain is the conscious perception of noxious stimuli. Thus, he defined anesthesia as

the state in which, as a result of drug-induced unconsciousness, the patient neither perceives nor recalls noxious stimuli. The loss of consciousness is considered a threshold or all-or-none (quantal) phenomenon. By this definition, there can be no degrees of anesthesia or any variable depth of anesthesia. Prys-Roberts defined anesthesia in terms of the drugs producing unconsciousness and modification of noxious stimuli, classifying them by pharmacologic properties of the drugs and not by their ability to produce components of the state of anesthesia.

Prys-Roberts focused his concepts on the body's response to noxious stimuli, which he defined as factors causing potential or actual cell damage--mechanical, chemical, thermal, or induced by radiation. Figure 29-2 (Figure Not Available) shows the somatic and autonomic responses to noxious stimuli. In this scheme, one reads from left to right and from top to bottom to see the order in which reflex responses are suppressed by anesthetic drugs. For example, somatic responses include both sensory and motor activity. Sensory input obtained through the central nervous system (CNS) can originate from somatic or visceral tissue. The subject must be conscious to perceive pain. Low concentrations of inhaled or intravenously administered anesthetics can eliminate recall of pain, but they allow a motor response. The motor response to noxious stimuli is typically an all-or-none reflex withdrawal of the stimulated part. Eger et al [17] used this movement response as a clinical end point in developing the concept of MAC; MAC was used to quantitate the potency of inhaled anesthetics. The concentrations of anesthetics required to eliminate somatic motor response are higher than those necessary to induce unconsciousness and to eliminate perception of pain.

The response of the respiratory system is part of the autonomic response described by Prys-Roberts. The motor response to noxious stimuli can involve an increase in tidal volume or the frequency of breathing. This ventilatory response may occur even if there is no somatic motor response to surgical stimulation. A higher concentration is required to suppress the breathing response than is required to suppress the somatic response to noxious stimuli.

Prys-Roberts divided autonomic responses into three categories. The hemodynamic response consists of autonomic responses to noxious stimuli, namely, increased sympatho-adrenal activity that elevates arterial blood pressure and

Figure 29-2 (Figure Not Available) Depth of anesthesia can be defined by the suppression of clinically relevant responses to noxious stimul, as proposed by Prys-Roberts. *(Modified from Prys-Roberts [16])*

heart rate. The sudomotor response consists of sweating. Release of hormones is an extremely difficult response to eliminate completely.

Prys-Roberts considered pain relief, muscle relaxation, and suppression of autonomic activity as discrete pharmacologic events. These events may be engendered by specific drugs. Some drugs can produce all these end points; others can achieve only one or two. The only feature common to most anesthetics is the suppression of sensory perception and the production of unconsciousness. Prys-Roberts considered the inclusion of muscle relaxation in the definition of the anesthetic state illogical and confusing. Although muscle relaxation is necessary for laryngoscopy and surgical access, it is neither a component of anesthesia nor an alternative to adequate anesthesia.

Kissin, [18] in a 1993 editorial, expanded, refined, and further contributed to the definition of anesthesia. He began by indicating that a wide spectrum of pharmacologic actions via different drugs can be used to create the general anesthetic state. These pharmacologic actions include analgesia, anxiolysis, amnesia, unconsciousness, and suppression of somatic motor, cardiovascular, and hormonal responses to the stimulation of surgery. Kissin stated that the spectrum of effects that constitutes the state of general anesthesia should not be regarded as several components of anesthesia resulting from one anesthetic action, but rather, it represents separate pharmacologic actions, even if the anesthesia is produced by one drug. Kissin then reviewed a series of investigative studies and concepts that supported his hypothesis:

1. Several groups of drugs (benzodiazepines, opiates, alpha $_2$ -agonists) that induce anesthesia by acting on specific receptors can have their anesthetic effects reversed by administration of a specific receptor antagonist.
2. There is growing understanding that the molecular mechanisms of general anesthesia are more specific than was suggested by the previous unitary hypothesis of anesthesia.
3. The rank order of effects for two important goals of anesthesia (hypnotic effect and blockade of somatic motor response to noxious stimuli) can be different for different classes of anesthetics. Opiates induce blockade of movement response to noxious stimulation before hypnosis occurs. For intravenous anesthetics, the opposite occurs.
4. When studies of anesthetic interactions are undertaken, the type of interaction (synergism, antagonism, summation) for one component of anesthesia may differ from that of another component.
5. Classic theories of anesthesia, based on the unitary nonspecific mechanisms of anesthetic action, suggest that one anesthetic may be replaceable freely by another, and anesthetic effects of anesthetic combinations should be additive. Many combinations of anesthetic drugs prove to be supra-additive for the hypnotic effects, a finding that suggests that the mechanisms of hypnotic actions of different components of a combination are different.

If one understands general anesthesia as a spectrum of separate pharmacologic actions that vary according to the goals of anesthesia, certain conclusions can be made regarding the measurement of anesthetic potency and depth of anesthesia. Kissin stated that "Diversity of pharmacological actions that in combination provide anesthesia make[s] it almost impossible to determine the potency of different actions with one measure." [18] The accuracy of this statement will become apparent in the remainder of this chapter.

The definitions of anesthesia depth have evolved with the drugs used in clinical practice. With ether, the clinical signs described by Guedel [8] were clinically relevant, and depth of anesthesia was well defined. The use of potent inhaled anesthetics, opioids, and intravenous anesthetics in modern clinical practice has precluded simple unifying definitions of anesthetic depth. In this author's view, the editorials of Prys-Roberts [16] and Kissin, [18] which emphasize the type of noxious stimuli and the specific class of drug that eliminates that response, represent concepts most appropriate for current clinical practice.

Memory and Awareness

Before the introduction of anesthesia in 1846, surgical operations were uncommon. Robertson [19] unearthed two descriptions of the torture suffered by victims of surgical operations performed before the introduction of anesthesia. In spite of the introduction of surgical anesthesia, however, the vivid descriptions of pain during surgery have not been eliminated completely. Reports of awareness, recall, and memory under anesthesia still occur in clinical practice.

Vickers [20] described two degrees of inadequate depth of anesthesia. The first degree involves the recall or retention of memory of an event that occurred while under anesthesia. Conscious or explicit memory refers to intentional or conscious recollection of prior experiences as assessed by tests of recall or recognition. The second degree of inadequate anesthesia involves the responsiveness to auditory input, also called "wakefulness." Wakefulness has been described as the responding of a patient to a verbal command during or after surgery without recall of the stimuli. Unconscious or implicit memory refers to changes in performance or behavior that are produced by prior experiences on tests that do not require any intentional or conscious recollection of those experiences. [21]

Recall, Conscious or Explicit Memory

In some clinical situations, the risk of intraoperative recall is high. Bogetz and Katz [22] examined the incidence of recall in 51 patients having surgical procedures after major trauma. Thirty-seven patients with stable hemodynamic status were able to receive drugs for induction and maintenance of anesthesia. In this group, 4 had intraoperative recall. Two of the 4 patients considered this awareness their worst hospital experience. Fourteen of the 51 subjects were so severely injured and hemodynamically unstable that no anesthetic was administered for at least 20 minutes of surgery. Six of 14 of these patients (43%) recalled events from their surgery. Two of the latter subjects considered this intraoperative awareness the worst aspect of their hospital experience. Bogetz and Katz could not identify factors predicting which patients would have recall.

Intraoperative recall has been well described in patients given general anesthesia for cesarean section. [23] A prospective

study of 150 obstetric patients reported a 2 percent incidence of intraoperative recall, a 17 percent incidence of unpleasant dreams, and 7 percent incidence of recall of pain. [24] Anesthetic technique was not consistent in this study. Major literature reviews of awareness in anesthesia for the general surgical population have cited a 0.2 to 2 percent incidence of intraoperative recall. [25] [26] [27] Wilson et al [28] reported a 1 percent incidence of awareness, a 2 percent incidence of dreaming, and an 8 percent incidence of hallucinations in 490 adult patients. No correlation existed between the incidence of mental aberrations and anesthetic agent, sex, or length or type of surgery. Liu et al [27] reported a 0.2 percent incidence of recall of events and 0.9 percent of dreaming in a cohort of 1,000 patients evaluated over a 4-month period. Hutchinson's [29] prospective study of 656 patients reported only 6 patients who had recall or intraoperative dreams. All 6 had been given nitrous oxide, oxygen, and muscle relaxants. No recall occurred in patients given potent inhaled anesthetics. However, the use of potent inhaled anesthetics does not guarantee lack of recall. [30] [31]

Intraoperative awareness or recall has occurred with high-dose opioid anesthesia. In one case report, the patient had intraoperative awareness and hypertensive crises after fentanyl (96 mug/kg) and diazepam (0.28 mg/kg) following morphine and scopolamine preanesthetic medication. [32] Previous case reports using high-dose opioid anesthesia had not documented a significant hemodynamic response associated with intraoperative awareness. [33] [34] Two clinical signs possibly predicting the occurrence of recall are movement and autonomic response. The use of muscle relaxants can eliminate the movement response, leaving only autonomic activity as a measure of intraoperative awareness. To circumvent the problem of complete muscle paralysis, Tunstall [35] [36] proposed using the isolated forearm technique to allow the possibility of movement during and after administration of muscle relaxants. This procedure involves application of a tourniquet to an extremity before the administration of muscle relaxants. Because the muscles do not receive the relaxant, the extremity is not paralyzed and can be monitored for movement.

This technique has been used to study the relationship of purposeful muscle movement to intraoperative recall. Schultetus et al [37] used the isolated arm technique to compare the incidence of movement and recall in patients given ketamine, thiopental, or a combination of the 2 induction drugs for cesarean section. For 11 of 24 subjects given thiopental (2 mg/kg) or the combination of ketamine (0.5 mg/kg) and thiopental (2 mg/kg), movement occurred in the isolated arm. Four of the 24 patients had dreams, whereas 3 of the 24 had intraoperative recall. In 12 subjects given only ketamine (1 mg/kg), 1 had a movement response, and none had recall.

Russell [38] [39] showed that the incidence of movement with the isolated arm technique can vary markedly with the choice of anesthetic. The incidence of intraoperative movement was 44 percent after nitrous oxide and fentanyl anesthesia, but it was only 7 percent after a continuous infusion of etomidate with fentanyl. The high incidence of wakefulness (as judged by movement) in the nitrous oxide/fentanyl group caused the investigators to terminate the study. Although the incidence of purposeful movement in the isolated arm was high, the incidence of actual intraoperative recall was low (only one subject).

Other investigators have not been able to correlate other clinical signs of light anesthesia or postoperative recall to the isolated arm movement response. [40] [41] [42] Moreover, the effects of ischemia from prolonged inflation of the tourniquet at pressures higher than arterial blood pressure on this methodology are unknown. Abouleish and Taylor [43] could not correlate movement, size of pupils, or changes in blood pressure with awareness or dreams in patients given morphine (0.2 mg/kg) and diazepam (0.1 mg/kg) after cesarean section. The foregoing studies suggest that the occurrence of purposeful movement in an isolated extremity is not a good predictor of intraoperative recall.

Detection of Auditory Input, Unconscious or Implicit Memory

Although the patient may not overtly recall a stimulus or an event, auditory input can register in the brain during apparently adequate surgical anesthesia. Auditory and verbal input must be "meaningful"; however, for input to "register," frequently hypnosis or other cues may be needed to elicit recall.

Levinson [44] performed the classic study of detection of meaningful auditory input under anesthesia. Ten volunteers undergoing dental surgery were given thiopental followed by nitrous oxide and diethyl ether. Monitoring the electroencephalogram (EEG) for an irregular slow-wave high-voltage pattern allowed the anesthetist to maintain a similar depth of anesthesia in all patients. This EEG pattern was considered equivalent to moderate to deep ether anesthesia. During surgery, the anesthetist provided verbal stimulation for the patient in the form of intraoperative crisis, verbally stating that cyanosis was present and then treated appropriately. All ten patients had no spontaneous recall of the simulated intraoperative crisis. Under hypnosis, however, four patients could remember the frightening words in exact detail. An additional four remembered someone speaking to them. All eight became anxious and either emerged spontaneously from their hypnotic trance or refused to continue exploring the event. One subject had activation of the EEG pattern when the intraoperative crisis occurred, but no recall of the event.

Blacher [45] described his efforts to duplicate Levinson's experiment using noxious, threatening verbal stimuli and hypnosis for subsequent recall. He reported similar findings, but he did not complete the project, considering it too inhumane. Benign verbal stimuli did not produce significant evidence of auditory recall. He postulated that a noxious or crisis event was required. Bennett et al [46] randomly assigned 33 subjects to receive either no intraoperative verbal stimuli or a personalized but nonthreatening instruction to pull on their ear during a postoperative interview. Anesthesia was maintained with nitrous oxide, halothane, or enflurane. All subjects given the intraoperative suggestion did not recall the event. The incidence of pulling of the ear during the postoperative interview was significantly higher for patients given the intraoperative message than for those not given the message. This and other studies [47] [48] suggest that unconscious memory may occur during general anesthesia, as shown by the effect of intraoperative suggestion on postoperative

---

behavior. Other studies with similar methodology, however, demonstrate no unconscious memory. [49] [50] [51]

In a volunteer study examining subanesthetic concentrations of nitrous oxide and isoflurane on memory and responsiveness, Dwyer and colleagues [52] demonstrated that memory was decreased by increasing concentrations of each anesthetic. Both conscious and unconscious memories of the information presented during anesthetic administration were prevented by 0.45 MAC isoflurane, but they were not completely prevented by 0.6 MAC nitrous oxide. Although this volunteer study had significant methodologic rigor, it did not address the impact that surgical stimulation could have on anesthetic concentrations required to prevent conscious and unconscious memory. The stimuli in this study involved only verbal and visual input, stimuli less intense than surgical manipulation.

Little information exists regarding the postoperative consequences of intraoperative recall. Blacher [53] described a traumatic postcardiac surgery neurosis involving anxiety and irritability, repeated nightmares, preoccupation with death, and a reluctance to discuss these symptoms. He attributed this postoperative state to patients' being awake and paralyzed during open heart surgery. These patients responded favorably to assurances that their postoperative difficulties may have been caused by awareness during surgery. Ghoneim and Block [54] reviewed the consequences of intraoperative or explicit recall. The two most frequent complaints were ability to hear events during surgery and the sensation of weakness/paralysis, with some patients experiencing pain. Patients particularly recall conversations that are of a negative nature concerning themselves or their medical condition. The most frequent reported postoperative effects were sleep disturbances, dreams, nightmares, flashbacks, and daytime anxiety. For many patients, the experience of awareness may not leave prolonged aftereffects; some, however, can develop a post-traumatic stress disorder, marked by repetitive nightmares, anxiety, irritability, a preoccupation with death, and a concern with sanity. It is unclear why some patients develop a post-traumatic distress syndrome and others do not.

Although extensive literature exists regarding intraoperative recall and wakefulness, much of it is anecdotal. As a result, our understanding of the factors relevant to patient recall or wakefulness is limited. There are several reasons for this situation. The incidence of intraoperative recall is low (0.2-2%). Therefore, extremely large numbers of patients would have to be studied to identify the factors that predispose a patient to recall. Most investigators cannot or will not have the large group sizes needed for rigorous research on recall. In addition, the ethical implications of this research are significant. Ethically, one cannot subject patients to an anesthetic regimen that imposes a moderate or high risk of intraoperative recall. Finally, the measurement tools tend to be subjective. Frequently, one relies on the patient's verbal interpretation of the occurrence of intraoperative recall. The clinical implications of complex psychometric testing such as that performed by Eich et al [50] are unknown. Bonke et al [55] summarized in a textbook the multiple presentations of a symposium held in 1995 that was dedicated to memory and awareness in anesthesia. This symposium clearly demonstrated the need for postoperative recognition and appropriate management of any episode of intraoperative awareness and conscious recall in a surgical patient. Although the area of unconscious memory during anesthesia has attracted a great deal of attention and investigation, it remains unproven in clinical relevance.

Veselis and colleagues [56] used the best current clinical pharmacology methodology to characterize the pharmacodynamics of anesthetic drugs used during sedation when the patient is still awake and cooperative, but amnestic. The authors evaluated the effects of midazolam, propofol, thiopental, and fentanyl on volunteer

participants' memory of words and pictures at equi-sedative plasma concentrations. Controlling for sedation was essential in this research, because sedation itself can produce amnesia resulting from inattention to the stimuli presented for later recall. Equi-sedative concentrations were as follows: midazolam, 64.5 ng/mL; propofol, 0.7 mug/mL; thiopental, 2.9 mug/mL; and fentanyl, 0.9 ng/mL. The plasma concentrations of drugs that result in 50 percent of maximal effect (Cp_{50}) for loss of memory to words were midazolam (56 ng/mL), propofol (0.62 mug/mL), thiopental (4.5 mug/mL), and fentanyl (3.2 ng/mL). Large effects on memory were produced only by propofol and midazolam. Thiopental had mild memory effects, whereas fentanyl had none. These findings have relevance to examine the choice of drug for sedation, but they cannot be translated into an anesthetic situation with general anesthesia, surgical stimulation, and prevention of intraoperative recall. Although certain drugs used in anesthesia have very specific effects in combating recall (e.g., scopolamine, benzodiazepines), we still do not know whether routine use of these drugs will guarantee lack of intraoperative recall. [57]

PHARMACOLOGIC PRINCIPLES OF MEASURING DEPTH OF ANESTHESIA

Before discussing the clinical and electrophysiologic methods of measuring depth of anesthesia, one must understand the pharmacologic concepts governing the relationship among the dose of an anesthetic agent, its concentration in the blood biophase, and the pharmacologic response it produces. [58] Figure 29-3 depicts a situation in which a dose of drug is given to obtain a desired anesthetic response. Pharmacokinetic and pharmacodynamic concepts govern the relationship between drug dose and response. The body's interaction with the drug, through distribution and elimination processes, governs the concentration that is ultimately available at the site of action or biophase. Figure 29-3 shows that the dose-response relationship is the interaction between its pharmacokinetic and pharmacodynamic components. To quantitate a change in anesthetic dose requirement, one must be able to distinguish these components. Depth of anesthesia is a pharmacodynamic measurement.

Measurement of the pharmacologic effect of an anesthetic drug, which is the essence of measurement of depth of anesthesia, depends primarily on three factors: (1) the equilibration of the concentrations of the drug in plasma with the concentration at the drug's site of action, and with the measured drug effect; (2) the appropriate characterization of the relationship between drug concentration and drug effect; and (3) the influence of noxious stimuli. To understand

Figure 29-3 Pharmacokinetic and pharmacodynamic components of the dose-response relationship.

these issues, one must address the following questions: (1) When assessing depth of anesthesia, what methods of drug administration are important, and what site does one use to measure the concentration of the drug? (2) How does one model the relationship between concentration of drug and depth of anesthesia? (3) What pharmacokinetic and pharmacodynamic characteristics must be considered when measuring depth of anesthesia?

Equilibration of Drug Concentration and Effect

The ideal body site for measurement of a drug concentration consists of the biologic fluids immediately surrounding the site of drug action (i.e., the receptor or CNS membrane). Because such measurement is impossible in an intact organism, one must sample at sites that are less than ideal. One is left with the measurement of drug concentration in blood or plasma for intravenously administered drugs or inspired end-tidal gas concentrations for inhaled anesthetics. The most important principle in sampling for measurement of plasma or end-tidal concentrations of a drug is to obtain a representative sample of blood that is in equilibrium with the biologic fluids at the site of action or biophase. Because slow administration of a drug allows time for equilibration with the effect site, the direct measurement of drug concentrations in plasma can be related to the drug concentrations at the site of effect.

In the case of rapid intravenous administration of drugs, the disequilibrium between the concentration of the drug in plasma and the concentration at the effect site means that a plasma sample cannot be used directly to determine the relationship between concentration and response. However, once this lag has been recognized, it is possible to use mathematic modeling concepts to estimate its magnitude. [59] [60] Specifically, a first-order rate constant, K_{ec}, can be estimated from plasma concentration and effect data. This rate constant can be used to estimate the half-time of equilibration between drug concentrations in blood and at the site of effect, half-life ($t_{½}$) K_{ec}. The $t_{½}$ K_{ec} is governed by physiologic and physicochemical properties, such as the perfusion of blood at the site of action, the diffusion of blood at the site of action, the solubility of the drug at the site of action, and the time required to initiate and translate drug receptor interactions into measurable pharmacologic effect. Jacobs and Reves [61] reviewed the application of effect-site equilibration times to anesthetic drugs, specifically thiopental, and concluded that this concept is an inescapable determinant of both the temporal characteristics of acute drug effects and the appropriateness of experimental designs used to study drug effects.

The choice of arterial versus venous sites for blood sampling also can become a relevant issue when obtaining representative samples of plasma. Venous blood samples can reflect local tissue uptake of drug (i.e., muscle and skin uptake if sampled in an extremity) and are therefore less than ideal. Sampling of biologic fluids from the site of action of anesthetic drugs is not physically possible under most circumstances. Arterial blood sampling reflects the concentration of drug being delivered to all tissues and thus may be the most representative sampling site. Appropriate modeling must be undertaken to eliminate disequilibrium between arterial concentration and effect.

A similar concept also applies to potent inhaled anesthetics. Eger and Bahlman [62] showed that the concentration and partial pressure of anesthetic in arterial blood, in the alveoli, and in the brain are approximately equal after 15 minutes of administration of an anesthetic inhaled at a constant expired concentration. The easy measurement of the alveolar concentration of anesthetic in expired gas provides a convenient way of assessing the concentrations of potent inhaled anesthetics for subsequent evaluation of depth of anesthesia. The alveolar concentration of anesthetic in expired gas is in equilibration with the concentration in arterial blood, which has equilibrated with the concentration of the drug in the brain.

Characterizing the Relationship Between Drug Concentration and Effect

The ideal measurement of drug effect has several basic characteristics. A stable baseline effect that has minimal variability must occur. In addition, as the drug concentration increases, the effect should increase in a continuous fashion that is measurable with high resolution. Finally, the effect should reach some maximal plateau, after which an increase in drug concentration does not further increase effect.

Figure 29-4 (A) Sigmoidal relationship between plasma concentration of a drug (Cp) and drug effect has the following characteristics: E_{max}, the maximal drug effect; Cp_{50}, the plasma concentration of the drug that produces 50 percent of maximal effect; and the slope of the curve (or rate of change). (B) Two concentration-response curves for two anesthetics having different maximal effects.

Figure 29-4 A shows the concentration-effect relationship one expects to see under these ideal conditions. This sigmoid curve has four characteristics that can be quantitated. The baseline effect and maximal effect are the extremes of drug response. The midpoint between baseline and maximal effect is commonly referred to as the Cp_{50} . This parameter indicates the potency of the drug and the sensitivity of the individual to that drug. Finally, one can also measure the slope, or rate of change, of the curve. Although generation of the drug concentration versus effect curve is a powerful tool in assessing depth of anesthesia, it is important to understand some of the limitations of this methodology. Figure 29-4 B provides such curves for two drugs having different maximal effects. If the maximal effects differ, then the Cp_{50} values cannot be used to compare drug potency or individual sensitivity to the drugs. [63]

Many drug effects do not increase in a continuous fashion. Frequently, drug effect is an all-or-none ("quantal") response (i.e., the organism responded in some way or not at all). Therefore, when the response is quantal, only the presence or absence of a defined drug effect can be noted. However, one can construct concentration versus response curves using quantal data. Although data would include only the two extremes of "response" or "no response," it is possible to use mathematic techniques such as logistic regression, probit, or logit analysis to construct the probability of no response. [64] Figure 29-5 provides an example of the curve that results when drug concentration is plotted against the percentage probability of no drug response. The Cp_{50} now represents the midpoint of the probability curve or the concentration that has a 50 percent probability of producing no response. The drug concentrations that result in both responses and no responses define the Cp_{50} . If the drug concentrations causing both response and no response are large, then the variability of the estimated value for Cp_{50} will increase. The slope of the curve can also change. When examining drug concentration versus quantal response data, it is important to examine the raw data used to generate the fitted function, as well as the variability associated with the estimated Cp_{50} . Quantal response data are more limiting than continuous data regarding interpretation of data. A quantal response represents only a single point in a theoretic

Figure 29-5 By means of logistic regression, one can use response/no-response data ("quantal" data) to construct the probability of no response. The solid dot represents the Cp_{50} value, that is, the plasma concentration of a drug producing a 50 percent probability of no response.

continuous relationship between drug concentration and effect. [64]

Study Design, Choice and Application of Stimuli

To measure depth of anesthesia, one must apply some appropriate form of stimulus to the CNS and then observe the clinical response. This is the essence of Prys-Roberts's definition of depth of anesthesia. [16] The stimulus should have several characteristics: (1) it should be measurable and reproducible; (2) if it cannot be measured accurately, it should be supramaximal, so that variations in the degree of stimulation do not change the nature of the response; and (3) the time between initiation of stimulation and the occurrence of peak response must be known reasonably well. Ideally, the response to stimulation should occur rapidly. Given the usually finite period of time between the initiation of the stimulation and the occurrence of the clinical response, it is critically

important for the concentration of anesthetic drug to be relatively stable during this time. If the concentrations fluctuate markedly, meaningful information cannot be gathered.

Good methodology in the assessment of depth of anesthesia attempts to achieve pharmacokinetic equilibrium in which drug concentrations in plasma do not change rapidly. This condition is desired because drug concentrations would then be relatively constant. This state of affairs "freezes" the pharmacokinetic component. The appropriate stimulus can then be applied, and a finite period of time may be allowed to measure other drug responses. The ideal situation would allow the effective separation of pharmacokinetic and pharmacodynamic components of the doseresponse relationship.

SPECIFIC DRUGS AND CLINICAL SITUATIONS

This section describes the scientific approaches used for potent inhalational anesthetics, opioids, and intravenously administered hypnotics used to induce anesthesia. Following the scientific approaches, a discussion of more subjective approaches relevant to the clinical practice of anesthesia is presented.

Clinical Measures of Depth of Anesthesia

The clinical measures of depth of anesthesia to be discussed derive directly from the patient. The measures of anesthetic effect represent normal physiologic responses that can be quantitated and are used in clinical practice. Electrophysiologic techniques are discussed in a later section.

Inhaled Anesthetics

Movement Response and the MAC Concept

The purposeful movement of a body part in response to noxious perioperative stimuli is one of the most useful clinical signs of depth of anesthesia. Using this movement to quantitate depth of anesthesia induced by potent inhaled anesthetics, Eger and Merkel and their colleagues [17] [65] defined MAC as the minimum alveolar concentration of inhaled anesthetic required to prevent 50 percent of subjects from responding to a painful stimulus with "gross purposeful movement." Readers are referred to the excellent review articles that document the development of the MAC concept and its many applications in anesthesia. [66] [67] The MAC concept has four basic components: (1) an all-or-none (quantal) movement response must occur after applications of supramaximal noxious stimulus; (2) end-tidal concentrations of anesthetic in the alveoli, considered an equilibrated sample site, are used as an indication of the concentration of anesthetic in the brain; (3) appropriate mathematic quantitation of the relationship between the alveolar concentration of anesthetic and the quantal response is used to estimate MAC; and (4) MAC can be quantitated for altered physiologic and pharmacologic states.

For determination of MAC in humans, the standard noxious stimulus has been the initial surgical skin incision. [17] Skin incision represents a reproducible form of supramaximal surgical stimulation. There has been no systematic examination of other perioperative surgical stimuli (e.g., peritoneal traction) representing more profound surgical manipulation than skin incision or endotracheal intubation. For determination of MAC in animals, the standard stimulus has been application of a surgical clamp to the base of the tail. After examining other noxious stimuli in dogs, Eger et al [17] concluded that tail clamping represented the most noxious stimulation that was clinically reproducible and not excessively traumatic. Response to stimulation must entail a positive, gross, purposeful muscular movement, usually of the head or extremities. Twisting or jerking of the head is considered a movement response, but twitching or grimacing is not. Coughing, rigidity, swallowing, and chewing are not considered positive movement responses, nor is movement of an incised extremity.

The MAC concept has been expanded by evaluating other clinical end points or stimuli. Stoelting et al [68] determined the MAC of anesthetic that would allow opening of the eyes on verbal command during emergence from anesthesia ("MAC awake"). This stimulation is less intense than surgical skin incision, and response occurs at lower concentrations of anesthetic than movement to skin incision. Yakaitis et al [69] determined the MAC of anesthetic that would inhibit movement and coughing during endotracheal intubation ("MAC intubation"). This event is significantly more stimulating than skin incision; therefore, elimination of the subsequent response requires higher concentrations of anesthetic than does elimination of the movement response. Finally, Roizen et al [70] investigated the MAC of anesthetic necessary to prevent adrenergic response to skin incision ("MAC BAR"), as measured by the concentration of catecholamine in venous blood. When one examines the values for (1) MAC awake, (2) MAC skin incision, (3) MAC intubation, and (4) MAC BAR, one sees a family of concentrationresponse curves, the separation of which depends on the noxious stimuli used to elicit the response.

Zbinden and colleagues [71] undertook a comprehensive examination of the effects of different noxious stimuli on the purposeful movement response with isoflurane. Twenty-six healthy surgical patients were administered isoflurane only with adequate inspired/end-tidal equilibration. Multiple noxious stimuli were applied at varying end-tidal isoflurane concentrations. From the resulting data, the authors were able to define a family of concentration versus response curves for different noxious stimuli, as displayed in Figure 29-6 (Figure Not Available) . The end-tidal isoflurane concentrations that resulted in a 50 percent probability of no movement response for different stimuli were as follows: verbal responsiveness, 0.37 percent; trapezius muscle squeeze, 0.84 percent; 50-Hz electrical tetanus, 1.03 percent; laryngoscopy, 1.0 percent; skin incision, 1.16 percent; and laryngoscopy with intubation, 1.76 percent. This study demonstrates how varying stimuli require different isoflurane concentrations to prevent

Figure 29-6 (Figure Not Available) Logistic regression analysis of the end-tidal isoflurane concentration relative to the predicted probability of no movement response for different noxious stimuli. Bars indicate the 95 percent confidence bounds to the end-tidal concentration with a 50 percent probability of response. I, laryngoscopy/intubation; L, laryngoscopy; S, trapezius muscle squeeze; SI, skin incision; T, tetatic nerve stimulation. *(Modified from Zbinden et al [71])*

a clinical response and can be used to define isoflurane anesthetic depth.

A second component of the MAC concept involves the use of the alveolar concentration of an anesthetic as an indication of drug concentration. Because the concentration of gas is defined as a percentage of one atmosphere, it is independent of barometric pressure and elevation. Additionally, partial pressures of inhaled anesthetics at equilibrium should be similar in all body parts, such as alveolus, blood, and brain. Thus, the measured end-tidal concentration of anesthetic (representative of the alveolar concentration) is in direct proportion to the underlying concentration in the brain. Because cerebral blood perfusion is large, it is possible to achieve an equilibration among end-tidal, alveolar, arterial, and brain anesthetic partial pressures within 15 minutes of exposure to a constant end-tidal anesthetic concentration.

Eger and Bahlman [62] quantitated the difference between arterial concentrations of halothane and the end-tidal expired concentrations of halothane. If the difference between the inspired and end-tidal anesthetic concentrations was less than 10 percent, the difference between the end-tidal and arterial concentrations would be minimal. In the early literature on MAC, the end-tidal concentration of anesthetic was frequently called the "anesthetic dose," and the MAC relationship was referred to as a "dose-response curve." However, Waud and Waud [63] pointed out that this terminology was incorrect, because the MAC concept really describes a concentration versus response relationship. These investigators also believed that a major contribution of the MAC concept was to turn attention from the inspired concentration of an anesthetic to the equilibrated alveolar concentration of the anesthetic, a more accurate and precise reflection of the concentration of the drug in the brain.

A third component of the MAC concept involves the use of appropriate mathematic approaches to quantitate the relationship between dose and response. The original MAC concept of Eger and colleagues [17] used a "bracketing approach" in humans and animals. In an individual patient, a fixed end-tidal concentration of anesthetic was achieved, and the response to a single skin incision was observed. Depending on the patient's response or lack of response, the next patient received a higher or

lower concentration. A single measurement was obtained per patient. Patients were studied over a range of end-tidal concentrations. They were placed in groups of four; the subject having the lowest end-tidal (alveolar) concentration of anesthetic was the first to be studied. For each group, the percentage of patients moving in response to stimulation was plotted against the average end-tidal concentration for that group. A visual line of "best fit" through these points yielded the concentration at which 50 percent of patients would respond (i.e., the MAC). Figure 29-7 (Figure Not Available) is an example of this analysis, using the concentration versus response data gathered for halothane alone, for halothane with morphine premedication, and for halothane with 70 percent nitrous oxide. Both morphine premedication and 70 percent nitrous oxide decreased the MAC value for halothane. [72]

In animal studies, it was possible to manipulate the end-tidal concentration of anesthetic and to apply the tail-clamp stimuli on multiple occasions. A MAC value can be obtained for each animal by sequentially increasing or decreasing the end-tidal concentrations to bracket the value between movement and no movement. de Jong and Eger [73] extended the analysis of MAC data by using more appropriate mathematic/statistical techniques to quantitate the relationship between alveolar anesthetic concentration and response/no response data. A nonlinear logistic regression analysis was used to estimate the probability of no movement at any given end-tidal concentration. [64] The logistic regression analysis produced values for MAC comparable to those produced by the bracketing technique. Logistic regression allowed estimation of the variance associated with the estimate of MAC. It was also possible to extrapolate the

Figure 29-7 (Figure Not Available) Minimal alveolar concentration (MAC) necessary to prevent movement in 50 percent of subjects subjected to a noxious stimulus (MAC) was determined for three combinations of halothane: (1) with oxygen only; (2) with oxygen and a morphine premedication (0.15 mg/kg IM), and (3) with 70 percent nitrous oxide (N_2O). The anesthetic requirement for halothane is greatly decreased by nitrous oxide, and less so by premedication with nitrous oxide. *(Modified from Saidman and Eger [72])*

probability of movement from 50 percent to any given probability within the curve. Thus evolved the concept of end-tidal concentration of anesthetic that inhibited response in 95 percent of patients. Waud and Waud [63] argued that MAC defines only one point on a hypothetic curve that plots the concentration of anesthetic against one index of depth of anesthesia. Because there are no other experimentally defined points on this curve, one cannot be certain that such curves are indeed parallel for different anesthetics or stimuli. This lack of certainty theoretically limits one's ability to infer that multiples or fractions of MAC represent equal levels of CNS depression for different anesthetics. To address this issue properly and to define the complete curve for anesthetic concentration versus response adequately, one would need a continuous measure of anesthetic effect. In the absence of such a clinical measure, indirect reasoning must be applied to the question of the soundness of adding MAC multiples or of combining MAC values for different anesthetics. Investigators have examined the relationship between MAC skin incision and a more noxious stimulus, MAC intubation [69] or a less noxious stimulus, MAC awake. [68] When different inhaled anesthetics are compared, the ratio of MAC skin incision to MAC intubation or MAC awake is relatively constant. When the possible relationship between synergism and antagonism of four different potent inhaled anesthetics was examined relative to nitrous oxide, no evidence of a relationship could be demonstrated. [74] Thus, there is only indirect evidence that MAC values can be added.

A fourth feature of MAC is that it has served as a sensitive tool to determine the interaction of other anesthetics and CNS drugs with the inhaled anesthetics. Other drugs used in anesthesia decrease anesthetic requirement, as measured by a reduction in MAC. In addition, numerous altered physiologic states (e.g., aging) change the requirements for inhaled anesthetics. Several review articles have described the many studies applying the MAC concept to the clinical practice and science of anesthesia. [66] [67] Table 29-1 summarizes the results of these studies regarding the factors that affect the MAC.

TABLE 29-1 -- Factors That Affect Minimum Alveolar Concentration

EFFECT ON MAC	FACTORS (STUDY SUBJECTS)
Decrease	Hypothermia (animals)
	Severe hypotension (animals)
	Age (humans)
	Narcotics, ketamine (humans, animals)
	Benzodiazepines, barbiturates (humans, animals)
	Chronic administration of amphetamine (animals)
	Reserpine, alpha-methyldopa (animals)
	Cholinesterase inhibitors (animals)
	Intravenous local anesthetics (humans, animals)
	Pregnancy (animals)
	Hypoxemia (Pa_{O_2} < 40 mm Hg) (animals)
	Anemia (<4.3 mL of O_2 /dL blood) (animals)
	$alpha_2$ -Agonists (animals)
Increase	Hyperthermia (animals)
	Hyperthyroidism (animals)
	Alcoholism (humans)
	Acute administration of dextroamphetamine (animals)
No effect	Duration of anesthesia (humans, animals)
	Sex (humans, animals)
	Metabolic acid-base status (animals)
	Hypercarbia and hypocarbia (humans, animals)
	Isovolemic anemia (animals)
	Hypertension (animals)

MAC, minimum alveolar concentration of an anesthetic required to abolish movement in 50 percent of patients, in response to a noxious stimulus

Data from Quasha et al [66] and Cullen [67]

Much of the previous research on MAC assumed that the lack of movement response from inhaled anesthetics was due to the anesthetic effects on the central, cortical brain tissues. Rampil et al [75] suggested that the spinal cord may represent a major site of action for inhaled anesthetics. Their studies demonstrated that the MAC of isoflurane in rodents was identical in value for intact animals to that of rodents who have been decorticate or decerebrate, a finding suggesting that the main ability of inhaled anesthetics in

preventing purposeful movement occurs at the spinal cord level. [75] [76] Antognini and Schwartz [77] also drew the same conclusions from experiments whereby they determined MAC in the goat by having the animal's brain isolated from the remainder of the body using a complex cardiopulmonary bypass procedure. These investigators demonstrated that the MAC value for the goat was approximately twice as large when the brain only was exposed to isoflurane relative to when both the brain and spinal cord were exposed to the anesthetic. These series of studies strongly suggest that the response to purposeful movement is achieved by the inhaled anesthetic at both cortical and subcortical anatomic levels.

Other Clinical Responses

The movement response to noxious stimuli is not commonly used in clinical practice. The extensive use of muscle relaxants makes interpretation of movement both difficult and imprecise in most clinical circumstances. In certain clinical situations, movement of the patient would interfere with the surgical procedure. Therefore, other signs have been investigated as possible clinical measures of depth of anesthesia: the rate and volume of ventilation in spontaneously breathing subjects, eye movement, the diameter and reactivity of pupils to light, heart rate, arterial blood pressure, and autonomic signs such as sweating.

It has not been possible to use these clinical signs to generate uniform measures of depth of anesthesia for inhaled anesthetics. Although some clinical signs do correlate with depth of anesthesia for certain inhaled anesthetics, the same cannot be said for other inhaled anesthetics. In a study of clinical signs and inhaled anesthetics, Cullen et al [78] examined the relationship between alveolar concentration of inhaled anesthetics and clinical signs of depth of anesthesia in both volunteers and surgical patients. Clinical signs were found to change in usefulness over time. For example, during the first hour of halothane anesthesia, decreasing mean arterial blood pressure was the only useful clinical sign of depth of anesthesia; that is, increasing concentrations of halothane caused a progressive decrease in arterial blood pressure, whereas heart rate remained constant. Moreover, the pupils were constricted and nonreactive, and there was no eye movement or tearing. However, after 5 hours of halothane anesthesia, further increases in concentration no longer caused a decrease in arterial blood pressure. This previously useful sign of depth of anesthesia had been eliminated. For cyclopropane, diethyl ether, and fluroxene, only pupillary dilation and reduced pupillary activity correlated with changes in the concentration of anesthetic. Mean arterial blood pressure did not change as the concentration of anesthetic increased.

Cullen and coworkers [78] also found that skin incision modified most clinical signs of drug effect. For example, during anesthesia with halothane and oxygen, heart rate, respiratory tidal volume, and pupil diameter increased after skin incision. Systolic and diastolic blood pressures and respiratory rate did not change. After 12 minutes of surgical incision and manipulation (and unchanged concentrations of halothane), heart rate, tidal volume, and pupil diameter decreased to preincision levels. The clinical response during isoflurane/oxygen anesthesia was different. After skin incision, systolic and diastolic blood pressures and heart rate increased. The pupils dilated in some subjects. No patient moved in response to incision. In general, the increases in blood pressure and heart rate persisted throughout the first hour of surgery, even though higher concentrations of isoflurane were being given.

Zbinden and colleagues [79] systematically examined the interaction of isoflurane concentrations with the hemodynamic response to different noxious stimuli. In 26 healthy surgical patients receiving different equilibrated end-tidal concentrations of isoflurane, the following noxious stimuli were applied, several of them on multiple occasions: trapezius muscle squeeze, 50-Hz electrical tetanus, laryngoscopy, laryngoscopy with intubation, and skin incision. With the continuous recording of intra-arterial hemodynamics, acute increases of heart rate and systolic blood pressure were recorded and were related to the isoflurane concentration and presence or absence of purposeful movement. Table 29-2 (Table Not Available) presents the absolute increase of systolic blood pressure and heart rate at the isoflurane end-tidal concentration that had a 50 percent probability of no purposeful movement for that specific stimulus. Different noxious stimuli result in different degrees of hemodynamic response. There is a relative rank order of the degree of hemodynamic response, with laryngoscopy and intubation being the most intense stimuli. Multiple regression analysis demonstrated that the type of stimulation had the highest influence on the blood pressure increase, with the isoflurane concentration the least important. Figure 29-8 (Figure Not Available) presents the baseline systolic blood pressure and subsequent increase in systolic

TABLE 29-2 -- Hemodynamic Response to Defined Noxious Stimuli Under Isoflurane Anesthesia

(Not Available)

Modified from Zbinden et al [79]

Figure 29-8 (Figure Not Available) Response of systolic blood pressure (BP, in mm Hg) to skin incision as a function of end-tidal isoflurane concentration.
, systolic blood pressure values before stimulation.
, systolic blood pressure values after stimulation. Single oblique lines: The lower line is the regression line to the systolic blood pressure before stimulation (using all values of all preoperative stimuli, *r* = -.46). The upper line is the regression line to the blood pressure after skin incision (using only the values of the stimulation pattern under consideration). The correlation coefficient *r* to these lines is indicated in the figure. Shaded area, 95 percent confidence interval for regression lines; vertical arrow, median effective (ED_{50}) isoflurane concentration for the motor response of the stimulation pattern under consideration. *(From Zbinden et al [79])*

pressure at a measured isoflurane concentration for the subjects receiving a skin incision. The shaded areas represent the linear regression relationship of isoflurane concentration versus prestimulus and poststimulus systolic blood pressure. Increasing isoflurane concentration did not prevent the increase of systolic blood pressure, even at very high end-tidal concentrations. Rather, increasing isoflurane concentration only decreased the prestimulation systolic pressure such that the noxious stimuli returned systolic pressure closer to the normal, awake values. Similar results were found with the other noxious stimuli on both heart rate and systolic blood pressure response, with the degree of hemodynamic response determined by the nature of the noxious stimuli.

The clinical implications of these data relative to judging anesthetic depth from hemodynamic response for inhalational anesthetics are significant. When used as a sole agent, even at high concentrations, isoflurane is unable to suppress hemodynamic responses to noxious stimuli. Rather, the hemodynamic control seen with high isoflurane concentrations occurs from a decrease of the prestimulation hemodynamic baseline. Thus, although hemodynamic responses are the most commonly used clinical measures to judge inhalational anesthetic depth of anesthesia, the scientific basis for this certainly is not obvious. In clinical practice, additional anesthetic drugs are commonly used with inhalational anesthetics. Daniel et al [80] examined how fentanyl (0-3 mug/kg) and 60 percent nitrous oxide alter the heart rate, mean arterial blood pressure, and catecholamine response (components of MAC BAR) during desflurane and isoflurane anesthesia. Fentanyl, 1.5 mug/kg, reduced MAC BAR for desflurane from 1.3 to 0.4 MAC and for isoflurane from 1.3 to 0.55 MAC. Increasing the fentanyl dose to 3 mug/kg did not cause further change of the MAC BAR values for both inhalational anesthetics. This study suggests that the addition of analgesic components, such as nitrous oxide and fentanyl, can prevent the sympathetic stimulation and hemodynamic responses seen with noxious surgical stimuli when inhalational anesthetics are used.

Eger's [81] review of the subjective interpretation of clinical signs of depth of anesthesia found increasing pupil diameter to be of limited value during halothane, enflurane, isoflurane, or methoxyflurane anesthesia. Premedication with opioids eliminates the usefulness of this clinical end point. Pupillary response to light is rapid and brisk with small amounts of the inhaled anesthetic; however, the response becomes sluggish, and the pupils do not respond at deeper levels. Eye movements may suggest a light level of anesthesia. Eyelash and corneal reflexes disappear once a surgical level of anesthesia has been achieved and normally do not return at useful surgical depths of anesthesia.

Decreasing arterial blood pressure is the most commonly used sign of increasing depth of anesthesia for halothane or enflurane anesthesia. However, many factors modify the balance between the increase in autonomic cardiovascular activity caused by surgical stimulation and the depression in cardiovascular function caused by potent inhaled anesthetics. These factors include blood volume, cardiac contractility, sympathetic tone, age, and acid-base status. Surgical stimulation also increases blood pressure to a variable degree. Change in blood pressure is also not a useful clinical sign for inhaled anesthetics that cause sympathetic stimulation, such as cyclopropane, diethyl ether, and fluroxene. Pulse rate is a relatively poor sign, because it can be influenced by many factors. Pulse rate is modulated by baroreceptor

function, which is sensitive to arterial pressure and its changes. Some anesthetics, such as enflurane and isoflurane, can actually increase pulse rate independent of the surgical stimulation or changes in blood pressure. Such an increase could lead to incorrect decisions regarding dosage.

All inhaled anesthetics depress ventilation and can ultimately cause apnea. This clinical sign is useful only during spontaneous ventilation. Inhaled anesthetics decrease tidal volume in a dose-related fashion, whereas respiratory rate increases in an amount that may sustain minute ventilation (but not necessarily alveolar minute ventilation) at normal levels. Surgical stimulation modifies respiratory depression, frequently returning alveolar minute ventilation to normal values. At light levels of anesthesia with inhaled anesthetics, adverse respiratory events such as breath-holding, coughing, and laryngospasm may occur. These respiratory events are very sensitive to the nature and degree of noxious stimulation. Normally, deeper levels of anesthesia eliminate these reflex responses.

For potent inhaled anesthetics, the MAC concept has provided clinical anesthesia with an abundant body of knowledge regarding factors that affect depth of

anesthesia and the requirement for anesthetic agents. It is unfortunate, however, that the movement response is not used extensively in clinical practice. The many clinical measures that have poor or unpredictable utility when evaluated scientifically (blood pressure or pulse) have become the mainstay of clinical assessment of depth of anesthesia in routine clinical practice. [78]

Opioids

Opioid analgesics are used extensively for premedication, as a supplement to regional and general anesthesia, as the primary anesthetic agent, and as an analgesic for postoperative pain (Ch. 10) . The narcosis produced by these drugs through specific receptor systems within the CNS decreases autonomic, endocrine, and somatic responses to noxious stimulation. However, efficient use of opioids that maximizes benefit and limits toxicity can be challenging. The difficulty arises when one attempts to monitor opioid drug effects rapidly and carefully during their intraoperative application.

Opioids as Complete Anesthetics

In 1947, Neff et al [82] used meperidine as an intravenous supplement to nitrous oxide/oxygen anesthesia in what is now known as a "balanced anesthesia" technique. The later use of opioids as complete anesthetics coincided with the development of cardiac surgery and intensive care during the early 1960s. Providing anesthesia for patients with severe valvular or congenital heart disease without causing cardiovascular collapse was problematic prior to the use of the opiates. These early cardiac surgery patients were extremely ill and had little or no circulatory reserve. During the late 1960s, Lowenstein et al [83] noted the hemodynamic stability of patients undergoing mechanical ventilation who were given frequently large doses of intravenous morphine to suppress respiration in the intensive care units. This observation encouraged Lowenstein and coworkers to become the first to administer morphine (0.5-3.0 mg/kg) as a complete anesthetic. The resulting cardiovascular stability in acutely ill patients with acquired valvular heart disease was impressive. As cardiac surgery advanced in methodology, patients with ischemic heart disease began to undergo surgical anesthesia. Unfortunately, morphine anesthesia was less satisfactory for these patients, who developed hypertension, tachycardia, and awareness during surgery, in contrast to those patients with valvular heart disease. [83]

In 1978, Stanley and Webster [84] introduced the concept of high-dose fentanyl for cardiac anesthesia. This technique minimized the undesirable effects of morphine on induction (hypotension) and provided better hemodynamic stability in patients with good ventricular function and ischemic heart disease. As clinical experience with fentanyl increased, however, investigators found that even increasingly large doses of fentanyl could not always produce a complete anesthetic state in all subjects. [85] This discovery raised the important issue of whether opioids are complete anesthetics.

Human and animal studies show that opioids are not complete anesthetics. Wynands et al [86] used moderate to large doses of fentanyl (50-150 mug/mL) and measured plasma concentrations at defined surgical stimuli (intubation, skin incision, sternotomy, aortic root dissection) in patients with good ventricular function who were undergoing coronary surgery. Figure 29-9 (Figure Not Available) shows the relationship among drug concentrations, stimulation, and hemodynamic response. In approximately 20 percent of patients, extremely high plasma concentrations of fentanyl (15 ng/mL) did not eliminate hemodynamic responses, defined as a 20 percent increase in systolic blood pressure. These results have been confirmed by Hynynen and colleagues [87] and Philbin et al. [88]

The investigations conducted by Murphy and Hug [89] in measuring depth of opioid anesthesia in animals (dogs) also address the issue of whether opioids are complete anesthetics. These investigators examined the ability of fentanyl to decrease enflurane MAC. They first anesthetized the dog with enflurane and determined MAC. Several infusions of fentanyl at progressively higher rates were used to obtain a constant steady-state plasma concentration of fentanyl in each animal. After each increase in infusion rate, enflurane MAC was determined again. Measurement of opioid concentrations in blood samples ensured that several different steady-state plasma concentrations of fentanyl were obtained in each animal. Murphy and Hug found that even high plasma concentrations of fentanyl (20 ng/mL) did not decrease enflurane MAC beyond 60 to 70 percent of its initial value (Fig. 29-10) (Figure Not Available) . That is, there was a ceiling to the enflurane-sparing effect. Morphine, sufentanil, and alfentanil also decrease enflurane MAC and have a similar ceiling effect in dogs. [90] [91] [92]

Stimulation by tail clamping in dogs anesthetized with sufentanil and enflurane produces nearly equivalent increases in heart rate and blood pressure, whether the animals move or not. [90] This observation suggests that hemodynamic and somatic signs are not equally good indicators of depth of anesthesia. When the agonist-antagonist analgesics butorphanol and nalbuphine were examined using this model, enflurane MAC could only be decreased by 11 and 8 percent, respectively. [92] Therefore, the agonist-antagonist analgesics have markedly lower maximal anesthetic effects

Figure 29-9 (Figure Not Available) Plasma concentration of fentanyl at the time of certain clinical stimuli, along with the presence or absence of hypertension. During sternotomy and aortic dissection, even high plasma concentrations of fentanyl (>15 ng/mL) do not always prevent hypertension. *(Modified from Wynands et al [86])*

Figure 29-10 (Figure Not Available) Percentage reduction in enflurane minimum alveolar concentration (MAC) as a function of the logarithm of the plasma concentrations of fentanyl. Each point represents the mean concentration (±SEM) for fentanyl in plasma and the average percentage (±SEM) reduction in enflurane MAC. Numbers of dogs below the vertical standard-error bars indicate the number per data point. *(From Murphy and Hug [86])*

than the pure opioid agonists. Even massive doses of fentanyl (3,000 mug/kg with no use of supplemental analgesics) produce a very temporary and transient anesthetic state, as judged by absence of response to tail clamping. [93]

Ardnt et al [94] [95] attempted to develop a trained, unanesthetized, spontaneously breathing dog model to examine the relationship between plasma concentration of fentanyl or alfentanil and clinical signs of depth of anesthesia. They measured hemodynamic and movement responses at low opioid doses that resulted in moderate ventilatory depression. Interpretation of their data is confounded by their use of increasingly large intravenous administered bolus doses of each opioid. Thus, all plasma concentrations of opioids were measured in a non-steady-state environment, and an unknown degree of disequilibrium existed between drug concentration and clinical responses. However, their data appear to confirm the observation of Hug and colleagues that the plasma concentration of fentanyl and alfentanil at which maximal anesthetic effects occur in dogs are very similar to those for humans. McEwan and colleagues [96] undertook similar studies in humans, thus characterizing the decrease of isoflurane MAC with varying constant fentanyl plasma concentrations achieved with a computer-driven infusion pump. Movement response to initial skin incision was examined relative to end-tidal isoflurane concentrations. McEwan and coworkers [96] found very similar results in humans to those observed by Hug's group in dogs (see earlier). Isoflurane MAC decreased 39 percent at a steady-state fentanyl plasma concentration of 1 ng/mL and 63 percent at a fentanyl plasma concentration of 3 ng/mL. Increasing fentanyl plasma concentrations to more than 3 ng/mL produced a minimal further reduction of isoflurane MAC. The maximal MAC reduction was 82 percent at a steady-state fentanyl plasma concentration of 10.6 ng/mL. Similar MAC reduction results have been obtained with other inhaled

anesthetics (desflurane, sevoflurane) and other opiates (alfentamil, sufentanil, remifentanil). [97] [98]

As mentioned earlier, different investigations show that high-dose opioid anesthesia does not induce complete anesthesia. It has not been possible to identify why or which 30 to 40 percent of patients undergoing coronary artery bypass will have a hemodynamic response to noxious stimuli during even high plasma concentrations of fentanyl. Therefore, it has not been possible to use autonomic responses to noxious stimuli as reliable and predictable measures of depth of anesthesia. If a patient shows clinical signs of responsiveness, the administration of additional opioid may or may not result in hemodynamic control. If it does not, the extra opioid will certainly prolong postoperative respiratory depression and may delay emergence from anesthesia. Thus, no consistent and reliable clinical signs exist that can be used to quantitate depth of anesthesia induced by opioids. Current clinical practice supplements high-dose opioids with amnestic drugs (benzodiazepines) or low concentrations of potent inhaled anesthetics. Profound hypertensive or tachycardic responses are treated with vasodilating and cardiovascular depressant drugs. Empirically, additional opioid may be given, and, if no response occurs, vasodilating drugs are administered.

Whereas opioids are used alone for cardiovascular procedures, these drugs are usually accompanied by nitrous oxide for surgical procedures involving no postoperative mechanical ventilation. By itself, 70 percent nitrous oxide provides approximately 0.7 MAC anesthesia. Nitrous oxide also interacts profoundly with opioids, markedly decreasing the amount of opioid necessary to provide surgical anesthesia. When alfentanil is used with oxygen, plasma concentrations of approximately 1,500 to 2,000 ng/mL are needed to suppress hemodynamic response in most patients. [99] The addition of 70 percent nitrous oxide decreases this

plasma concentration to approximately 300 ng/mL. [100] A similar degree of potentiation occurs with fentanyl.

Clinical Signs of Inadequate Anesthesia and Plasma Concentration of Opioids

Ausems and colleagues [100] used pharmacodynamic modeling concepts to relate clinical signs of inadequate opioid anesthesia to plasma concentrations of the drug. In their study paradigm, patients were premedicated with a benzodiazepine, anesthesia was induced with alfentanil (150 mug/kg), and the trachea was intubated with the aid of succinylcholine. Anesthesia was maintained with 70 percent nitrous oxide and a variable-rate infusion of alfentanil. The infusion was titrated to the following clinical end points: (1) increased systemic arterial blood pressure greater than 15 mm Hg higher than the patient's normal value; (2) heart rate exceeding 90 beats/min in the absence of hypovolemia; (3) somatic responses, such as body movements (minimal muscle paralysis allowed physical movement), swallowing, coughing, grimacing, or opening of the eyes; and (4) autonomic signs of inadequate anesthesia (e.g., lacrimation, flushing, or sweating). If any clinical signs occurred, the infusion rate was increased 25 to 50 mug/kg/h, and a small bolus dose (7 mug/kg) was given. Good hemodynamic control was possible in all subjects. If no clinical signs occurred, however, the infusion rate was decreased at regular 15-minute intervals.

Table 29-3 shows the incidence of response to intraoperative noxious stimuli in 37 patients; 3 different types of surgical procedures are represented. Although hypertension was the most common clinical response, the other 3 clinical measures occurred a significant number of times. The authors could not predict which patients would have somatic responses, tachycardia, or hypertension. Measurement of plasma concentrations made it possible to describe the concentration versus response relationship for different perioperative stimuli. Figure 29-11 (Figure Not Available) A shows the relationship between the plasma concentration of alfentanil and response/no response for 3 clinical end points: intubation,

TABLE 29-3 -- Response of 37 Patients to Noxious Intraoperative Stimulation During Anesthesia With Alfentanil and Nitrous Oxide [a]

	SURGICAL PROCEDURE		
	BREAST	***LOWER ABDOMINAL***	***UPPER ABDOMINAL***
No. of patients	12	14	11
Hemodynamic responses	4	4	5
Hypertension	(1-7)	(1-7)	(1-7)
Tachycardia	0	1	3
	(0-1)	(0-4)	(1-7)
Somatic responses	2	5	2
Body movement, swallowing, coughing, grimacing, eye opening	(0-4)	(0-9)	(0-6)
Other autonomic signs of inadequate anesthesia	0	0	1
Lacrimation, flushing, sweating	(0-1)	(0-3)	(0-2)

Data from Ausems et al [100]

[a] Data are presented as the median number of response episodes per patient. Numbers in parentheses represent the range of number of episodes among the patients in each group. Hypertension is an increase in systemic arterial systolic blood pressure of more than 15 mm Hg above the patient's normal value; tachycardia is a heart rate higher than 90 beats/min in the absence of hypovolemia.

Figure 29-11 (Figure Not Available) (A) Relationship between the plasma concentration of alfentanil and response/no response at three specific events of short duration. The quantal data are characterized with logistic regression in the lower panel. -, ±SE for the Cp_{50}, which is the plasma concentration of alfentanil producing a 50 percent probability of no response. (B) Plasma concentration of alfentanil versus the probability of no response for each of 34 patients during the intra-abdominal phase of lower abdominal surgery. Dots represent the Cp_{50} values, and the heavy dark line represents the average response of the 34 patients. *(A from Ausems et al [100] ; B from Ausems et al [101])*

skin incision, and skin closure. Regarding elimination of response to noxious stimulation, intubation required significantly higher plasma concentrations of alfentanil than skin incision, and skin closure required significantly lower concentrations than skin incision.

Use of logistic regression made it possible to define Cp_{50} values for these clinical events (Table 29-4) . The plasma concentrations of alfentanil were varied in the individual subject during surgery to obtain multiple response/no response data points, after which a curve plotting plasma concentration against response was constructed for each subject [101] (Fig. 29-11 (Figure Not Available) B). Especially noteworthy are the steep slope of the individual curves and the moderate pharmacodynamic variability among individuals. Table 29-3 demonstrates that upper abdominal surgery required significantly higher plasma concentrations of alfentanil than lower abdominal or breast surgery. The foregoing pharmacodynamic modeling concept has been used to examine the alfentanil dose requirement, pharmacokinetics, and pharmacodynamics in heavy alcohol consumption. Lemmens et al [102] showed that moderate consumers of alcohol (20-40 g/d) have an increased requirement for alfentanil because of decreased CNS sensitivity to alfentanil. The Cp_{50} of alfentanil in patients with alcohol consumption was 522 ± 104 ng/mL compared with 208 ± 26 ng/mL in a control group. This finding suggests that there may be a cross-tolerance between opiates and ethanol. Lemmens et al [103] also defined the role of plasma protein binding in determining the clinical effects of alfentanil anesthesia. By examining the alfentanil plasma concentration versus clinical response relationship both total bound and free, and the degree of alfentanil plasma protein binding, they determined there was a significant negative correlation ($r = .67$) between Cp_{50} (total drug) and the free fraction of alfentanil. These data suggest that 45 percent of the variability in alfentanil CNS response, as estimated by the Cp_{50} , could be explained by variability in the plasma protein binding of alfentanil.

Remifentanil is a newer opioid, related to the fentanyl family of short-acting, 4-aniliopiperidine derivatives; however, it is unique in having ester linkages that are susceptible to hydrolysis by nonspecific blood and tissue esterases, resulting in very rapid metabolism. Egan and colleagues [104] described the comparative clinical pharmacology of remifentanil to alfentanil. Both opioids have a similar, small volume of distribution, because of limited tissue solubility; however, remifentanil has a significantly higher metabolic clearance, 2.9 L/min versus 0.36 L/min for alfentanil. Remifenanil has

TABLE 29-4 -- Cp_{50} Values for Perioperative Events and Intraoperative Manipulation Associated With Three Types of Surgical Procedures During Alfentanil Anesthesia

EVENT	CP_{50} (ng/mL)
Single events	
Intubation	475 ± 28 [a]
Skin incision	279 ± 20
Skin closure	150 ± 23
Spontaneous ventilation	233 ± 13
Intraoperative manipulation	
Breast surgery ($n = 12$)	270 ± 63 [b]
Lower abdominal ($n = 14$)	309 ± 44
Upper abdominal ($n = 11$)	412 ± 135

Cp_{50} , the plasma concentration of a drug producing a 50 percent chance of suppressing response to a certain stimulus

Data from Ausems et al [101]

[a] Standard error of estimated value for parameter
[b] Values are presented as mean ± SD

a similar rate of blood-brain equilibration, with a $t_{½}$ K_{e0} value of 1.6 minutes versus 0.96 minute for alfentanil. Remifentanil, however, is significantly more potent than alfentanil, with an EEG Cp_{50} value of 19.9 ng/mL versus 375.9 ng/mL for alfentanil. Minto and colleagues [105] [106] quantitated the population pharmacokinetics and dynamics of this opioid, using simulation techniques to develop dosing guidelines. Drover and colleagues [107] applied the opioid anesthetic depth concepts developed by Ausems et al [100] to define therapeutic plasma concentrations of remifentanil in surgical patients.

The rapid blood-brain equilibration of alfentanil and remifentanil means that a given plasma concentration has a close relation to the CNS concentration, hence to drug effect. [108] Drugs having a slower rate of blood-brain equilibration (e.g., fentanyl, sufentanil, morphine) would be less amenable to the type of pharmacodynamic analysis of the plasma concentration versus clinical effect relationship used by Ausems and coworkers. [100] Glass and colleagues [109] applied the fundamental concepts proposed by Ausems et al to fentanyl, using a computer-driven infusion pump to obtain constant fentanyl plasma concentrations from induction of anesthesia to skin incision. Because of the long equilibration delay between plasma and the effect site in the CNS ($t_{½}$ K_{e0} of 6.4 minutes), a significant period of time was allowed between establishing the constant plasma concentration and application of the noxious stimuli. Only fentanyl and 70 percent nitrous oxide were used, no premedication or induction sedative was given, and fentanyl plasma concentrations were also measured. Following skin incision, patients were observed for purposeful somatic movement. The fentanyl plasma concentration that had a 50 percent probability of no movement (Cp_{50}), with 70 percent nitrous oxide, was 3.26 ng/mL.

The approach to opioid administration presented by Ausems and colleagues [100] provides useful insight into the clinical assessment of depth of anesthesia. Overdosage with opioids cannot be judged intraoperatively. Only at the end of anesthesia, when spontaneous ventilation should occur, does one know whether administration of opioids has been excessive. To prevent overdosage, Ausems and coworkers [100] proposed using a viable rate of infusion in which one titrates plasma concentrations to clinical effect to find the lowest possible effective rate of opioid administration. To achieve this end point, one must look for clinical signs of inadequate anesthesia. Once the infusion rate just causing inadequate anesthesia has been determined, one increases the rate slightly, thus providing adequate anesthesia. The steep slope of the concentration versus response curve for alfentanil (see Fig. 29-11) (Figure Not Available) demonstrates that a small increase in the plasma concentration of the drug rapidly converts inadequate anesthesia (100% probability of response to stimuli) to adequate anesthesia. Because of the moderate variability in the pharmacokinetics of alfentanil, this process of titrating dose (infusion rate) against clinical effect and pharmacodynamics is necessary for each patient. This concept is most applicable to alfentanil, which has rapid blood-brain equilibration, [108] and it is ideal with remifentanil, which has extremely rapid pharmacokinetics along with rapid blood-brain equilibration. [104] Intermittent intravenous bolus administration of opioids is not as efficient as variable-rate infusion when titrating plasma concentrations of opioids to clinical effects. [101]

Intravenously Administered (Nonopioid) Anesthetics

Traditionally, these intravenous anesthetics were used only for induction of anesthesia as a single intravenous bolus. Only with the clinical introduction of propofol have these agents been infused for maintenance of anesthesia, in which assessment of depth of anesthesia becomes more relevant.

Assessing Depth During Induction of Anesthesia

Induction of anesthesia consists of a rapid intravenous bolus injection of a hypnotic anesthetic (i.e., thiopental, etomidate). Plasma concentrations peak within ½ to 1 minute and decline rapidly on redistribution of the drug. The rapidly changing plasma concentrations cause a corresponding fluctuation in the degree of CNS depression. Depth of anesthesia increases rapidly (causing loss of consciousness), peaks, and then decreases as plasma concentrations decline. CNS depression lags behind the plasma concentrations, manifesting as hysteresis on curves plotting effect against plasma concentration. All the concepts discussed earlier regarding non-steady-state conditions produced by rapid administration of a drug make assessment of the relationship of plasma concentration and depth of anesthesia difficult, if not impossible, during bolus intravenous administration.

Clinical end points useful in assessing depth of anesthesia during induction include loss of verbal responsiveness, loss of eyelid reflex, and loss of corneal reflex. Typical stimulation occurring during induction of anesthesia include laryngoscopy and intubation, which constitute profoundly noxious stimuli. Frequently, response to these two procedures cannot be eliminated completely with just the intravenously administered anesthetic. In one study, administration of thiopental (6 mg/kg) was followed by an average increase in systolic blood pressure of 53 mm Hg on laryngoscopy and intubation. [110] In another study, administration of thiamylal (4 mg/kg) was followed by an increase in mean arterial blood pressure from 92 mm Hg (control) to 136 mm Hg on laryngoscopy. [111] Because most intravenous anesthetics do not provide a significant analgesia, the hemodynamic response to major noxious stimuli is great, even when large doses are given. Thus, assessment of depth of anesthesia using clinically relevant noxious stimuli such as laryngoscopy and intubation requires the concurrent administration of other analgesic drugs (opioids or nitrous oxide) to provide reasonable and clinically acceptable hemodynamic control.

Most research on estimating depth of anesthesia induced by intravenous anesthetics has focused on the relationship between dose and response. For example, Brett and Fisher [112] reported that the dose of thiopental associated with a 50 percent probability of no movement in response to a firm squeeze of the trapezius muscle was 3 to 7 mg/kg for

adults and more than 7 mg/kg for infants 1 to 11 months of age. It is possible that a larger initial volume of distribution or a more rapid redistribution (both pharmacokinetic mechanisms) in infants accounts for the difference in dose requirement. It is also possible that brain sensitivity to thiopental differs for infants and adults. Dose-response studies cannot differentiate between these two very different mechanisms.

Dose-response studies can have meaningful scientific and clinical value if they are performed with multiple measures of drug effect, concomitant variables, and appropriate statistical data analysis. Avram et al [113] demonstrated this point by successfully examining the thiopental induction dose requirement using an EEG end point (3-5 s of isoelectric signal), clinical end points (dropping of a syringe), and measurement of multiple covariates (age, gender, lean body mass, cardiac output). Avram's group [113] concluded that age and either lean or total body weight are the most important predictors of thiopental dose requirement, with gender and cardiac output less important. Jacobs and Reves [61] provided editorial comment on this article and used computer simulations to confirm and extend the findings of the study by Avram et al.

Assessing Depth During Maintenance of Anesthesia

Becker [114] presented one of the first studies to quantitate the relationship between plasma concentrations of an intravenous anesthetic (in this case, thiopental) and clinical measures of depth of anesthesia. First studying patients anesthetized with 67 percent nitrous oxide and thiopental, Becker found that the corneal reflex and movement response to a firm squeeze of the trapezius muscle correlated highly with the movement response to surgical stimulation (cervical dilation or skin incision). He then related the plasma concentration of thiopental to three clinical signs (loss of eyelid reflex, loss of the corneal reflex, and absence of movement in response to squeezing the trapezius muscle) in another group of patients given thiopental/oxygen anesthesia. Anesthesia was induced with thiopental, 2 to 2.5 mg/kg, followed by an intravenous infusion of 1 to 1.5 mg/kg/min. Patients were observed for the three clinical signs. Arterial blood samples drawn at these clinical end points were analyzed for both total plasma concentration and free (or unbound) plasma concentrations of thiopental. Plasma levels of thiopental gathered under these pseudo-steady-state conditions, especially free or unbound plasma levels, are believed to be accurate predictors of brain levels of the drug and are therefore good indicators of depth of anesthesia. The eyelid reflex was lost at significantly lower levels of thiopental than corneal reflex or the movement response. Similar plasma concentrations of thiopental were needed for loss of corneal reflex and loss of movement response to squeeze of the trapezius muscle, both of which had been found to correlate highly with loss of movement in response to skin incision. Becker did not report hemodynamic responses to the corneal or trapezius stimuli. For the patients given 67 percent nitrous oxide, the plasma concentrations of thiopental necessary to achieve the same surgical end points were as much as 71 percent lower

than those in patients given only thiopental.

Hung et al [115] proposed a conceptual approach to examining intravenous anesthetic pharmacodynamics using clinical measures. A computer-driven infusion pump using a pharmacokinetics model of thiopental disposition was used to achieve rapidly and then maintain constant thiopental plasma concentrations in 26 surgical patients. A low (10-40 mug/mL) and then high (40-90 mug/mL) constant thiopental plasma concentration was achieved and then maintained for 10 minutes. After allowing 5 minutes for blood-brain equilibration, the following sequential clinical stimuli were applied to the patient at 1-minute intervals: verbal command, 50-Hz electrical tetanus, trapezius muscle squeeze, laryngoscopy, and laryngoscopy followed by intubation. Purposeful movement response was used as the measure of clinical response. Logistic regression was used to relate the measured constant thiopental plasma concentration to the presence or absence of movement and to estimate the Cp_{50} value. Figure 29-12 (Figure Not Available) displays the thiopental plasma concentration versus response/no response in the data, along with the logistic regression characterization. Prevention of movement for intubation required significantly higher thiopental concentrations (78.8 mug/mL) relative to laryngoscopy (50.7 mug/mL), trapezius muscle squeeze (39.8 mug/mL), electrical tetanus (30.3 mug/mL), and verbal responsiveness (15.6 mug/mL). These data confirm the utility of purposeful movement as a measure of depth of anesthesia for intravenous anesthetics and demonstrate that different noxious stimuli can be statistically separated with this methodology. The conceptual approach developed by Hung et al [115] can be used to examine how altered physiologic states and diseases alter intravenous anesthetic requirement.

Kazama and colleagues [116] examined the pharmacodynamics of propofol alone and then of propofol with fentanyl using the defined noxious stimuli/movement responses that Hung et al [115] used for thiopental and the hemodynamic methodology developed by Zbinden et al [79] for isoflurane. Kazama et al found propofol Cp_{50} values for the following defined stimuli: loss of verbal responsiveness, 4.4 mug/mL; electrical tetanus, 9.3 mug/mL; laryngoscopy, 9.8 mug/mL; skin incision, 10.0 mug/mL; and intubation, 17.4 mug/mL. With the addition of a steady-state fentanyl plasma concentration of 1 or 3 ng/mL, there was only a minimal decrease of the loss of verbal responsiveness Cp_{50} of 11 percent for 1 ng/mL and 17 percent for 3 ng/mL. For the other, more intense noxious stimuli (tetanus, laryngoscopy, skin incision, and intubation), a much greater decrease of propofol Cp_{50} occurred. Fentanyl, 1 ng/mL decreased the Cp_{50} values 31 to 34 percent, whereas fentanyl, 3 ng/mL, decreased the Cp_{50} values 50 to 55 percent. Further increases of fentanyl plasma concentrations did not further decrease propofol Cp_{50} values. Kazama et al found that systolic blood pressure response to propofol alone was profound, similar to what Zbinden et al described. The addition of fentanyl to propofol attenuated the systolic blood pressure increases in a dose-dependent manner. The conceptual methodology used by Kazama et al allows for characterization of anesthetic depth, using multiple, defined noxious stimuli. The combination of the hypnotic anesthetic, propofol, with the analgesic effects of fentanyl allows a clinically successful anesthetic to be given to patients with quantitative methodology.

Figure 29-12 (Figure Not Available) (A) Move/no move versus serum thiopental concentration for five different clinical stimuli. Each bar indicates the serum thiopental concentration and response for stimuli applied to an individual patient. (B) Predicted probability of no movement versus serum thiopental concentrations, obtained using logistic regression of the data indicated in A. The bars indicate the 95 percent confidence bounds of the estimate of the serum thiopental concentration producing a 50 percent probability of no movement response. I, laryngoscopy and intubation; L, laryngoscopy; S, trapezius muscle squeeze; T, tetanic nerve stimulation; V, verbal. *(From Hung et al [115])*

The quantitation of clinical depth of anesthesia for the combination of opioid and intravenous anesthetic was reported by Vuyk et al. [117] Using the pharmacodynamic methodology developed by Ausems et al, [100] the interaction of a constant plasma concentration of propofol (in place of nitrous oxide) was examined as the alfentanil was titrated to clinical responses. Propofol had a significant interaction with alfentanil, thus decreasing the total dose of alfentanil and the alfentanil plasma concentrations needed for adequate anesthesia. Table 29-5 (Table Not Available) indicates how the total dose of alfentanil needed decreased from 22.8 mg with 66 percent nitrous oxide to 10.3 mg with a steady-state propofol plasma concentration of 4 mug/mL. The mechanism of this decreased dose requirement was a marked potentiation of alfentanil, such that alfentanil plasma concentrations needed to achieve the same degree of pharmacologic effect were two to four times lower with propofol.

TABLE 29-5 -- Interaction of Propofol and Nitrous Oxide With Alfentanil in Lower Abdominal Surgery

(Not Available)

Modified from Vuyk et al [117]

In a subsequent study, Vuyk et al [118] used this same methodology, but they randomized the surgical subjects into a range of constant propofol blood concentrations. With blood propofol concentrations increasing from 2 to 10 mug/mL, the alfentanil Cp_{50} for laryngoscopy decreased from 170 to 25 ng/mL, from 280 to 23 ng/mL for intubation, from 259 to 9 ng/mL for opening of the peritoneum, and from 209 to 16 ng/mL for the intra-abdominal surgical stimulus. With plasma alfentanil concentrations increasing from 10 to 150 ng/mL, the Cp_{50} for propofol to the regaining of consciousness decreased from 3.8 to 0.8 mug/mL. This study confirms the profound, synergistic interaction of propofol with alfentanil. Vuyk and colleagues used computer simulations of their gathered data to suggest that the optimal blood propofol and plasma alfentanil concentrations that allow the most rapid recovery from intraoperative anesthesia occur at 3.5 and 85 ng/mL, respectively. An editorial [119] comment on this study provided more general guidelines for using the quantitative interaction of propofol and alfentanil to design dosing regimens for total intravenous anesthesia.

In clinical practice, intravenously administered anesthetic drugs are frequently combined with other drugs that provide additional analgesia (opiates, nitrous oxide, potent inhaled anesthetics). As indicated earlier, large intravenously administered doses of thiopental or propol are less than effective in eliminating hemodynamic response to relevant clinical stimuli such as laryngoscopy and intubation. [110] [111] [116] Fentanyl decreases the anesthetic requirement for thiopental or propolol by providing antinociceptive effects that thiopental does not provide. [116] [120] Clinically, the hemodynamic response to laryngoscopy, intubation, or skin incision is most commonly used to assess depth of anesthesia. The use of muscle relaxants to ease endotracheal intubation precludes use of the movement response. Because laryngoscopy and intubation are single events, if clinical depth is inadequate (e.g., in the event of profound hemodynamic

response), additional intravenous anesthetics, opioids, or maintenance anesthetic agents are rapidly administered. When precise hemodynamic control becomes important (as in coronary artery disease), larger doses of opioids are used instead of intravenously administered anesthetics. The scientific basis for the clinical use of intravenously administered anesthetics is rapidly developing to approach knowledge of potent inhaled anesthetics or opioids.

Electrophysiologic Approaches to Measuring Depth of Anesthesia

Spontaneous Electroencephalogram

The realization that anesthetic drugs alter the EEG dates back to the discovery that the brain produces electrical activity [121] (Ch. 35) . In 1875, Caton [122] used chloroform to convince himself that the electrical oscillations from the brain were indeed biologic in origin. During the 1920s and 1930s, when electronic amplifiers allowed the recording of these small voltages through the skull, Berger [123] measured the influence of chloroform on the EEG. In 1937, Gibbs et al [124] reported that anesthetics changed EEG activity from low-voltage fast waves to high-voltage slow waves and postulated that the EEG could be used to measure the effects of anesthesia. In 1952, Faulconer [125] demonstrated with ether that the depth of anesthesia, based on recognition of EEG patterns, correlated with the arterial concentration of ether. He also demonstrated that the presence of nitrous oxide lowered the arterial concentration of ether necessary to produce a given EEG effect.

The EEG can be considered a measure of depth of anesthesia for several reasons. It represents cortical electrical activity derived from summated excitatory and inhibitory postsynaptic activity, which are controlled and paced by subcortical thalamic nuclei. This electrical activity has direct physiologic correlates relevant to depth of anesthesia. Cerebral blood flow and cerebral metabolism are related to the degree of EEG activity. [126] Anesthetic drugs affect both cerebral physiology and EEG patterns. The EEG is a noninvasive indicator of cerebral function when the patient is unconscious and unresponsive. Although recording of the raw EEG involves accumulating a large amount of information and EEG tracing, new computer analysis techniques can summarize and distill the EEG into a condensed, descriptive format (the "processed" EEG). [127] [128] Rampil [129] reviewed the value of the processed EEG in the clinical practice of anesthesia.

Inadequate anesthesia generally causes EEG activation. Peripheral noxious stimuli reach the brain via afferent systems that pass through the ascending reticular activating systems of the brain stem. These systems regulate corticocerebral function and thus affect the underlying EEG pattern. Noxious stimuli can cause three types of changes on the electroencephalogram: (1) desynchronization with the appearance of 20- to 60-Hz fast rhythms (EEG activation); (2) the appearance of 6- to 10-Hz spindles; and (3) bursts of 1- to 3-Hz slow waves. [130] These patterns vary with individual anesthetics and with the nature of stimulation. [131] For example, during light levels of thiopental anesthesia in dogs (steady-state plasma concentrations of 15-27 mug/mL), supramaximal stimulation of the sciatic nerve caused EEG activation and increased cerebral metabolic oxygen requirement and blood flow by 15 percent. [132] During deep levels of thiopental anesthesia (37-49 mug/mL), stimulation produced no change in these variables. A distinct threshold concentration of thiopental seems to block the response to noxious stimuli during anesthesia in animals.

All anesthetics change the underlying raw EEG signal. [133] Figure 29-13 indicates the raw EEG changes that occur with administration of thiopental or fentanyl, including changes in the voltage and frequency of the signals. Techniques such as the use of fast Fourier transform and aperiodic waveform analysis are being used to extract univariate (single-value) parameters that can be related to drug concentration and clinical depth of anesthesia. [127] [128] In Figure 29-14 , aperiodic waveform analysis was used to process the signal and extract the number of waves per second for thiopental, whereas for fentanyl, the fast Fourier transform was used to derive the spectral edge, which is the frequency below which 95 percent of the EEG power is located. Using the processed EEG requires that one choose EEG parameters that can be appropriately used as measures of drug effect or depth of anesthesia.

The EEG is a valuable tool because it reflects cerebral physiology, it is a continuous and noninvasive measure, and

Figure 29-13 Increasing plasma concentrations of thiopental or fentanyl produce a characteristic progression of changes on the electroencephalogram (EEG). In stage 1, the frequency and amplitude of waveforms increase (thiopental). In stage 2, both drugs produce a decrease in frequency and an increase in amplitude. In stage 3, thiopental produces a burst-suppression pattern and, finally, an isoelectric EEG. Fentanyl has its maximal effect in stage 3, that is, large, slow delta waves.

Figure 29-14 (A and B) Relationships between (1) the plasma concentration (Cp) of thiopental or fentanyl and time and (2) the response on the processed electroencephalogram (EEG) and time. The two drugs were characterized in different ways. A periodic waveform analysis provided the number of waves per second produced by thiopental. The fast Fourier transform was used to estimate the spectral edge produced by fentanyl. Note the biphasic effect of thiopental on the EEG: the number of waves first increases and then decreases as the plasma concentration of thiopental increases. Note also the lag or hysteresis between plasma concentration and EEG effect for each drug.

it changes markedly on administration of anesthetic drugs. However, early studies concluded that the EEG was not a meaningful measure of depth of anesthesia. Galla et al [134] examined raw EEG signals for 43 patients and correlated EEG patterns with clinical signs of anesthesia. A discrepancy seemed to exist between the clinical signs and EEG patterns, especially during emergence from, and induction of, anesthesia. During induction, clinical signs indicated that the patients were more lightly anesthetized than EEG patterns suggested, whereas on emergence, clinical signs indicated greater anesthetic depth. Levy [135] examined processed EEG signals during induction and before bypass in patients undergoing cardiac surgery who were given potent inhaled anesthetics and opioids. He examined a series of univariate descriptors, including median frequency (the frequency below which 50% of the EEG power is located) and spectral edge (the frequency below which 95% of the EEG power is located). He concluded that the multimodal EEG activity observed in 64 percent of the cases precluded the use of single univariate parameters to describe the anesthetic state. Berezowskyj et al [136] had similar findings using power spectral analysis of patients given nitrous oxide, opioid, and halothane for anesthesia. Clinical assessment of depth of anesthesia did not correlate well with EEG patterns.

Two studies attempted to correlate univariate EEG parameters to the clinical end point of awakening from anesthesia. Drummond et al [137] examined five numeric descriptors derived from the processed EEG during imminent arousal (spontaneous movement, coughing, or eye opening) from isoflurane/nitrous oxide anesthesia. Drummond and colleagues determined the threshold value for each parameter that best served to predict imminent arousal. Although several parameters (median frequency, spectral edge 90% frequency, total power, and frequency band ratio) thresholds predicted imminent arousal with sensitivities of 90 percent and specificities of 82 to 90 percent, none of the EEG descriptors could serve as a completely reliable, sole predictor of imminent arousal. Long et al [138] undertook a similar analysis, using either isoflurane or fentanyl anesthesia. For isoflurane anesthesia, these investigators found that awakening was always presaged by an abrupt decrease in power in the 1- to 4-Hz frequency range (decrease of delta power). During emergence from fentanyl/nitrous oxide anesthesia, there was no obvious change in the overall EEG power spectrum; however, the same numeric EEG descriptors that were predictive of awakening from isoflurane also occurred during emergence from fentanyl. These two studies concluded that consistent trends in the EEG can be expected to occur with changing depth of anesthesia, with the available EEG descriptors providing potentially useful trend information regarding changing depth of anesthesia. However, sensitivity and specificity of the available parameters are such that none can serve as the sole indicator of anesthetic depth.

Dwyer and colleagues [139] examined the power spectrum of the EEG in surgical patients receiving 0.6 to 1.4 MAC isoflurane-only anesthesia with skin incision. A second group of volunteers received 0.15 to 0.45 MAC isoflurane with memory testing. Different time-dependent, frequency EEG parameters (e.g., spectral edge, median frequency) were examined relative to the clinical measures. The authors found that isoflurane caused some decrease of EEG activity; however, there was no difference in EEG parameters between subjects who moved and those who did not move with skin incision. In volunteers receiving lower-dose isoflurane, memory of the information presented did not correlate with values of any EEG parameter. The authors concluded that the examined EEG parameters did not predict depth of anesthesia as defined by response to surgical skin incision, response to verbal command, or development of memory.

The previously described clinical research attempting to relate EEG effects to clinical anesthetic depth has resulted in inconclusive findings. When single anesthetic drugs are examined under defined conditions, it has been possible to demonstrate scientifically valid relationships between EEG parameters and anesthetic drug concentrations and to use pharmacokinetic and pharmacodynamic modeling concepts to link the drug concentrations to the EEG drug effects. [140] Different EEG waveform data analysis approaches have

been used to define different univariate EEG parameters as measures of anesthetic drug effect. The most powerful application has been to understand further the fundamental clinical pharmacokinetics of the anesthetic drugs.

The application of the EEG to measure clinical depth of anesthesia failed previously for several reasons. There has been a lack of understanding of the effects of interactions of several concurrently administered anesthetic drugs on the EEG. There has not been a standard approach to choosing an optimal EEG parameter, and finally, a "gold standard" for the measurement and assessment of clinical depth of anesthesia has been lacking. Only recently has an integrated research effort been undertaken to develop the EEG as a measure of anesthetic depth, directed by Aspect Medical Systems, a medical device company in Natick, Massachusetts. This company has developed a medical device that quantitates the anesthetic effects on the brain, specifically the hypnotic component of anesthesia. The device presents a continuous, EEG parameter, the Bispectral Index (BIS), which ranges from an awake, no-drug-effect value of 95 to 100 to zero with no detectable EEG activity.

Bispectral EEG Monitoring

The successful development of the Aspect Bispectral (BIS) EEG monitoring system can be identified with the following concepts:

1. The use of a more advanced EEG signal processing approach that allows for incremental information compared with the traditional fast Fourier transformation methodology.
2. The concurrent collection of clinically relevant (movement, hemodynamics, drug concentrations) data in patients/volunteers with EEG data, followed by the use of advanced multivariate statistical data analysis techniques to correlate the components of the EEG bispectrum with the clinical data to create the BIS

parameter.

3. The recognition that the BIS measured the hypnotic components of the anesthetic and was less sensitive to the analgesic/opiate components of an anesthetic.
4. The development of relevant clinical outcome data to demonstrate that BIS EEG monitoring can improve the quality of an anesthetic regimen.
5. The development of optimal hardware/signal processing technology adapted to the noisy electrical environment of the operating room.

Bispectral EEG Signal Processing

Bispectral EEG signal processing has been elegantly reviewed by Ramil [141] and Sig and Chamoun. [142] To date, most EEG signal processing has involved a form of time domain analysis, which examines the EEG signal as a function of frequency. The frequency analysis involves characterizing the EEG signal into sine waves with Fourier analysis, with the sine waves being described relative to amplitude, frequency, and phase angle. The sine wave amplitude is one-half the peak-to-peak voltage, the frequency is the number of complete cycles per second, and the phase angle is the way to describe the starting point (angle) of the waveform. Fourier analysis is a mathematical technique that takes a time varying waveform and decomposes it into the sum of simple sine or cosine waves. For a short, defined period of EEG signal, the Fourier analysis generates a frequency spectrum that is a histogram of the amplitudes and phase angles as a function of frequency. Traditional power (Fourier) spectral analysis assumes that the amplitudes of the EEG are normally (gaussian) distributed, the statistical properties do not change over time (stationary), and the frequency constituents are uncorrelated (linear). In Fourier analysis, only frequency and amplitude (power) estimates are used; the phase information is ignored.

Bispectral analysis is a higher-order statistical approach, relative to Fourier analysis, that was first applied to geophysics in the early 1960s to study wave motion, atmospheric pressure changes, seismic activity, and sunspots. [142] Bispectral analysis can characterize the correlation of the phase among different frequencies of the Fourier transform (phase coupling). The meaning of EEG phase relationships is not yet clear, but one simplistic approach holds that strong phase relationships relate inversely to the number of independent EEG pacemakers in the brain. In addition, bispectral analysis can identify nonlinearities in the EEG that may be important in the EEG signal-generation process and that allow for suppression of gaussian sources of noise that can enhance the signal/noise ratio of the nongaussian EEG. [141] Bispectral analysis, along with estimation of the Fourier transform of data, can also quantitate the relationship among the underlying sinusoidal components of the EEG to calculate a phase parameter termed the bicoherence. Thus, use of the bispectrum allows for a more comprehensive description of the information available from Fourier analysis to be used in determining an EEG parameter.

Developing the Bispectral Index

The BIS is a complex, proprietary EEG parameter that has been under development since 1985 by Aspect Medical Systems. The commercially available version of this EEG parameter was approved by the U.S. Food and Drug Administration (FDA) in 1996 as a monitor of anesthetic effect on the brain and is the only FDA-approved device for this indication. Figure 29-15 (Figure Not Available) displays the conceptual process whereby Aspect took EEG and clinical data from approximately 1,500 anesthetic regimens and 5,000 hours of EEG signal gathered under a broad range of anesthetic regimens. The approach involved taking EEG data, removing artifacts, and then performing spectral calculations, both Fourier and bispectral. Additionally, clinical data such as movement or no movement to skin incision along with equilibrated anesthetic concentration data were gathered. Statistical data analysis techniques were used to identify the components of the EEG that appeared to correlate best with the clinical and pharmacologic end points. As prototype versions of the BIS were developed over several years, subsequent clinical testing was used to improve and to refine the algorithms and components of the EEG parameter. The BIS algorithm was adapted to handle burst-suppression EEG, to minimize the initial activation of the EEG seen with some anesthetic drugs, and optimally to utilize components of Fourier analysis

Figure 29-15 (Figure Not Available) Algorithm for the development of the bispectral index. A library of high-quality, artifact-free electroencephalogram (EEG) were first accumulated. Different prospective subparameters were calculated, and their correlation to clinical measures of anesthetic response and drug concentrations was tested. The EEG parameters with the best performance were used in a multivariate analysis for the creation of the final composite parameter. This process was repeated with at least three major sets of data at different times. *(Modified from Rampil [141])*

and bispectral analysis. Thus, the BIS is a complex parameter composed of a combination of time domain, frequency domain, and higher-order spectral subparameters derived from clinical data. [141]

Clinical Development and Validation of the Bispectral Index

The initial studies with early versions of the BIS algorithm demonstrated, in a retrospective manner, that the BIS could be used to predict movement in response to skin incision using isoflurane/oxygen, [143] propofol/nitrous oxide [144] or propofol/alfentanil anesthesia. [145] In the first major clinical evaluation, a large, multicenter study by Sebel et al [146] randomized 300 patients into 2 groups. One group had the BIS continuously monitored and drug dosing adjusted to create a BIS value whereby 50 percent of the subjects would respond. In the second group, while BIS was recorded, no drug dosage adjustment occurred. In the control group, the mean BIS was a mean of 66 + 19 (SD) with a 43 percent movement rate. In the BIS-adjusted group, the BIS was lower, a mean 51 ± 19 (SD) with a significantly lower movement rate of 13 percent. This study was the first suggestion that the utility of BIS depends on the anesthetic technique. When hypnotic drugs such as propofol or isoflurane are used as the primary anesthetic, changes in BIS correlate with the probability of movement response to skin incision. When opiate analgesics are used at higher doses, the correlation to patient movement becomes much less significant.

A subsequent study by Glass et al [147] was designed to examine further the relationship among BIS, measured drug concentrations, and increasing levels of sedation when the anesthetic drugs propofol, midazolam, isoflurane, and alfentanil were given to volunteers in a controlled manner. The data from this study were used to provide greater optimization of the currently available BIS algorithm. Seventy-two volunteers received a single drug at 4 or 5 defined, increasing target concentrations that ultimately created an unconscious subject. The BIS EEG, arterial drug, or end-tidal concentrations and subjective sedation score and memory were measured. The BIS score correlated significantly with measured drug concentrations and had effective correlation with the clinical measures of sedation. None of the alfentanil patients lost consciousness and had minimal change of BIS, a finding confirming that the BIS EEG is not sensitive to low concentrations of opiate analgesics. The pooled BIS values at which 50 and 95 percent of volunteers were unconscious were 67 and 50, respectively.

Liu, Singh, and White [148] demonstrated in 26 surgical subjects that the BIS index accurately tracked the degree of clinical sedation with intermediate (4-mg) to large (20-mg) doses of midazolam given during regional anesthesia. When midazolam created an unresponsive subject, the mean BIS value was 69.2 + 13.9 (SD). Katoh, Suzuki, and Ikeda [149] found similar results with low, sedating doses of sevoflurane and also with higher, anesthetic concentrations in sixty-nine surgical patients. The BIS and sevoflurane end-tidal concentrations correlated closely with the clinical sedation scores of the patients. With end-tidal sevoflurane concentration increasing from 0.2 to 1.4 percent, BIS values decreased almost linearly from a median value of 95.3 to 45.5. Sevoflurane concentrations greater than 1.4 percent produced a limited further reduction of the BIS. Figure 29-16 (Figure Not Available) indicates the relationship between BIS, spectral edge, sevoflurane end-tidal concentration, and clinical response to defined stimuli. One can see the clear activation of the spectral edge parameter at low sevoflurane concentrations, whereas this is not seen with BIS. Flaishon et al [150] examined the behavior of BIS when surgical patients were given a single, intravenous bolus of propofol, 2 mg/kg or thiopental, 4 mg/kg with concurrent muscle relaxants. The isolated arm technique was used to identify loss then return of consciousness. No patient with a BIS of less than 58 was conscious; a BIS of less than 65 signified a less than 5 percent probability of return of consciousness within 50 seconds.

Kearse et al [151] undertook a more detailed examination of memory and command performance during propofol/ nitrous oxide sedation and BIS monitoring. These investigators

Figure 29-16 (Figure Not Available) Comparison of the cumulative probability of patients remaining unconscious after the discontinuation of propofol. The light hatched area is the bispectral index (BIS)-titrated group, and dark area is standard clinical practice (SP), without BIS monitoring. *(From Gan et al [152])*

found that there was a strong association between BIS and command scores, whether the command consisted simply of a uniform voice asking a volunteer to move a hand or foot or incorporated graded, then varied, stimuli. The relationship between BIS and responsiveness scores remained consistent over time and with increases or decreases of propofol concentrations. No subject was responsive when BIS was less than 57.

Several studies examined the clinical and economic outcome benefits of BIS monitoring in routine surgery. Gan and colleagues [152] studied 302 subjects in 4 different institutions using a propofol/alfentanil/nitrous oxide anesthetic regimen. Half the subjects were randomized to a "standard practice" whereby the propofol and alfentanil were infused and were adjusted to provide a stable anesthetic with the fastest possible recovery. The remaining subjects received a "standard-practice plus BIS monitoring." BIS was recorded in the standard-practice group, but it was not displayed to the practitioner. In the BIS group, propofol infusions were adjusted to achieve a target BIS between 45 and 60 and then were increased to 60 to 75 during the final 15 minutes of the anesthetic regimen. In the standard-practice group only, propofol adjustments were made using clinical signs and judgment, without BIS information. Patients in the BIS group required significantly lower normalized propofol infusion rates (134 versus 116 mug/kg/min), were extubated significantly sooner (11.2 versus 7.3 min), had a higher percentage of patients oriented on arrival in the recovery room (43 versus 23%), and had more rapid discharge from the recovery room. Figure 29-17 (Figure Not Available) displays the cumulative probability of patients' remaining unconscious after the discontinuation of propofol in the two study groups. This study demonstrated that titrating propofol with BIS monitoring during balanced anesthesia decreased propofol use and significantly improved recovery with no difference in intraoperative conditions.

Similar findings were presented by Song and colleagues [153] using inhalational anesthetics. Sixty surgical patients were randomized to desflurane or sevoflurane with 65 percent nitrous oxide and low doses of fentanyl. Half the patients

Figure 29-17 (Figure Not Available) Scatter diagram showing the relation among bispectral index (A), 95 percent spectral edge (B), end-tidal sevoflurane concentration, and response to different defined stimuli. Open symbols denote either responders or movers, whereas filled symbols denote either nonresponders or nonmovers. *(From Kaoh et al [149].)*

were randomized to standard practice whereby the inhalational anesthetic was titrated according to clinical end points and judgment. The second group had the volatile anesthetic titrated to a BIS value of 60. During the maintenance period, the BIS values were significantly lower in the standard-treatment group (mean, 42), a finding suggesting a deeper anesthetic compared with the BIS-titrated group with a mean of 60. The volatile anesthetic usage in the BIS-titrated group was 30 to 38 percent lower compared with the control group. Similarly, the times to verbal responsiveness were 30 to 55 percent shorter in the BIS-titrated group. This study demonstrated that titrating desflurane and sevoflurane using the BIS monitor decreased the utilization of the drugs and contributed to faster emergence from anesthesia.

The role of BIS monitoring in many other aspects of anesthesia care remains to be examined with clinical research. This includes the role of BIS monitoring in special patient populations, (pediatrics, pregnancy, disease states) and other clinical situations such as sedation in the intensive care unit.

The previously described development of the BIS and its application to patient care monitoring represents the first scientifically validated and commercially supported monitor of anesthetic drug effect on the CNS that has clinical applicability and relevance. The utility of the BIS is maximal when the anesthetic is a combination of a low or moderate dose of opiate analgesic and a hypnotic drug (volatile inhalational anesthetic, intravenous anesthetic) that is titrated to the bispectral response. For the BIS to reflect the pharmacodynamics of the hypnotic drugs on the CNS maximally, lower doses of opiates are needed. High-dose opiates result in significant synergistic interaction with the hypnotic drugs, as demonstrated by Glass and colleagues, [97] [98] such that minimal amounts of hypnotic drug are required to obtain adequate anesthesia. The reduced amounts of hypnotic drug present result in less profound hypnotic EEG drug effects on the CNS and therefore a less sensitive BIS response. It appears that the synergistic interaction of opiates with volatile anesthetics or intravenous anesthetics on clinical end points (hemodynamics, movement responses), does not occur with the EEG effects of the hypnotics. Stated another way, the pharmacodynamic relationship of the BIS to hypnotic drug concentrations (decrease of BIS with increasing hypnotic drug concentrations) is unchanged as opiates are added to the anesthetic. There is not an equal synergistic interaction of the EEG and clinical end points.

The clinical use of BIS monitoring involves separating the hypnotic and analgesic components of an anesthetic regimen. The concept involves increasing the hypnotic component dosage (isoflurane, desflurane, sevoflurane, propofol, midazolam) to lower the BIS to a range of 50 to 60. This appears to be the therapeutic window associated with a high probability of unconsciousness. A small to moderate amount of analgesic drug (opiate) is also given with the hypnotic drug. The anesthesiologist then evaluates the clinical and BIS responses to the surgical procedure over time. During times of intense surgical stimulation, if the BIS increases and the patient exhibits movement and hemodynamic responses, the anesthesiologist should respond by increasing the hypnotic component to lower the BIS value to the 50 to 60 range. If the BIS is lowered, but movement and hemodynamic responses continue, incremental opiate should be added to increase the analgesic component of the anesthetic until movement and hemodynamics are controlled. If the patient has a BIS in the 50 to 60 range, but movement and hemodynamic responses occur, then the analgesic component of the anesthetic should be increased. As the end of the anesthetic regimen approaches, the hypnotic component should be decreased to allow the BIS value to begin to increase. BIS monitoring provides an important, new dimension to the ability to adjust the components of an anesthetic in a logical manner.

Other Measures of Anesthetic Depth

Two other electrophysiologic measurement techniques have been studied as potential monitors of anesthetic depth: sensory evoked potentials and esophageal motility.

Evoked Responses

Sensory or nerve stimulation produces a low-amplitude signal, or evoked response, within the CNS. This evoked response can be separated by means of special computer signal-averaging techniques, from the underlying, spontaneous EEG. The ability to evoke a response is a measure of the functional integrity of the sensory receptors and the pathways between the sensory receptor and neural generator of peaks in the evoked response waveform. The evoked responses are used primarily to monitor the functional integrity of the neural structures, to identify neural structures, and to diagnose neurophysiologic conditions. Because evoked responses are sensitive to anesthetic drugs, they have been investigated as possible measures of anesthetic drug effect and depth of anesthesia. [133] The sensory stimulation most commonly used in recording of evoked responses consists of the following: somatosensory (electrical) stimulation of peripheral nerves; auditory stimulation, in which noises (clicks) are applied to the auditory canal; visual stimulation using flashing lights; or electrical stimulation of the tooth pulp.

Recording of evoked responses involves recording of EEG epochs and time-referencing them to sensory stimuli that have been applied in a repeated fashion. Computer techniques for processing EEG signals extract the evoked potential from the underlying EEG after repetitive stimuli; the evoked potential represents 100 to 1,000 stimuli. Therefore, the evoked response represents a time versus voltage relationship that can be quantitated by measuring the poststimulus latency and interpeak amplitudes in the waveform. Evoked response methodology has been reviewed by Grundy. [154] [155]

Many investigations have been performed with evoked potentials, with special emphasis on auditory evoked potentials. [156] [157] [158] [159] [160] [161] [162] [163] Relationships between anesthetic concentrations and changes of evoked potential parameters have been demonstrated. However, no consistent systematic relationships with clinical depth of anesthesia have been demonstrated.

Contractility of the Lower Esophagus

Measuring lower esophageal contractility is a novel method of assessing depth of anesthesia. The human esophagus is composed of striated muscle in the upper quarter, smooth muscle in the lower quarter, and both types of muscle in the middle portion. The striated portion of the esophagus is innervated by the reticular formation of the brain stem. Three different types of esophageal contraction have been identified: (1) primary contractions initiated by swallowing; (2) secondary propulsive contractions that occur in response to esophageal dilatation; and (3) tertiary or spontaneous nonpropulsive contractions that occur only in the lower quarter of the esophagus. As with the evoked potentials, no consistent, systematic relationship of lower esophageal contractility has been demonstrated relative to anesthetic depth.

/das/book/view/29494766/875/319.html

SUMMARY

The definitions of "anesthesia" and "depth of anesthesia" are among the most controversial, emotional, and subjective aspects of our discipline, frequently becoming philosophic exchanges instead of thoughtful scientific analysis. With the inhalational anesthetic diethyl ether and spontaneous ventilation, judging and quantitating the presence or absence and depth of anesthesia were relatively easy. With the introduction of the muscle relaxants in the 1940s and the subsequent evolution of the modern anesthetic pharmacologic armamentarium in the next 50 years, progress in defining, measuring, and understanding anesthetic depth has moved forward at a very slow pace compared with other aspects of the science of anesthesia. In the opinion of this author, the two most useful conceptual contributions to the topic of anesthetic depth have been the editorial comments by Prys-Roberts in 1987 [16] and by Kissin in 1992. [18]

Prys-Roberts [16] pointed out that "anesthesia" and "depth of anesthesia" are two different entities that are frequently confused because of the sharing of a common word. Anesthesia can be defined as the lack of response and recall to noxious stimuli. Anesthesia does not include paralysis, nor does it include analgesia when consciousness is present. He defined anesthesia in terms of the drugs that produce unconsciousness and modification of the responses to noxious stimuli, classifying them by pharmacologic properties of the drugs and not by their ability to produce components of the state of anesthesia. Kissin [18] extended these concepts by stating his view that the spectrum of effects that constitutes the state of general anesthesia should not be regarded as several components of anesthesia resulting from one anesthetic action, but rather as separate pharmacologic actions, even if produced by a single drug.

Depth of anesthesia can only be defined by examining specific noxious stimuli and defined clinical responses under specific pharmacologic conditions, that is, one versus two drugs at defined plasma concentrations. Moreover, for both hypnotic anesthetic drugs (i.e., propofol, inhalational anesthetics) and opiate analgesic anesthetics, different types of noxious stimuli require different concentrations of anesthetic agent to suppress somatic, autonomic, and hemodynamic responses. [164] Suppression of sympathetically mediated hemodynamic responses does not guarantee suppression of somatic responses and vice versa. Anesthesia using the currently available drugs involves using the combination of at least two different classes of anesthetic drugs to obtain adequate clinical anesthesia, a hypnotic anesthetic (intravenous anesthetic, inhalational anesthetic) and an analgesic opiate. Thus, to define anesthetic depth fundamentally, it is essential to understand in a quantitated manner the interaction of these two classes of anesthetic drugs. Finally, in recent years, the BIS, as developed by Aspect Medical Systems, has been established as an objective electrophysiologic measure of the hypnotic component of an anesthetic regimen. This CNS monitoring device, coupled with observation of surgical stimuli and clinical responses, can be used to adjust the amount of hypnotic versus analgesic drug in patients.

References

1. Cullen DJ: Anesthetic depth and MAC. In Miller RD (ed): Anesthesia, vol 1, 2nd ed. New York, Churchill Livingstone, 1986, p 553.

2. Cullen SC, Larson CP: Evaluation of anesthetic depth. In Cullen SC, Larson CP (eds): Essentials of Anesthetic Practice. Chicago, Year Book, 1974, p 77.

3. White DC: Anaesthesia: A privation of the senses. An historical introduction and some definitions. In Rosen M, Lunn JN (eds): Consciousness, Awareness, and Pain in General Anaesthesia. London, Butterworths, 1987, p 1.

4. Plomley F: Operations upon the eye (letter). Lancet 1:134, 1847.

5. Snow J: On the Inhalation of the Vapors of Ether in Surgical Operations: Containing a Description of the Various Stages of Etherization, and a Statement of the Result of Nearly Eighty Operations in Which Ether has been Employed in St. George's and University College Hospitals. London, John Churchill, 1847. Reproduced by Lea & Febiger, Philadelphia, 1959.

6. Snow J: On chloroform and other anesthetics. London, John Churchill, 1858.

7. Gillespie NA: The signs of anaesthesia. Anesth Analg 22:275, 1943.

8. Guedel AE: Inhalational Anesthesia: A Fundamental Guide. New York, Macmillan, 1937.

9. Artusio JF Jr: Di-ethyl ether analgesia: A detailed description of the first stage of ether analgesia in man. J Pharmacol Exp Ther 111:343, 1954.

10. Robson JG: Measurement of depth of anaesthesia. Br J Anaesth 41:785, 1969.

11. Tomas DW, Runciman WB: Monitoring depth of anesthesia. Anaesth Intensive Care 16:69, 1988.

12. Curare in anaesthesia (editorial). Lancet 2:81, 1945.

13. Winterbottom EH: Insufficient anaesthesia (letter). Br Med J 1:247, 1950.

14. Woodbridge PD: Changing concepts concerning depth of anesthesia. Anesthesiology 18:536, 1957.

15. Pinsker MC: Anesthesia: a pragmatic construct (letter). Anesth Analg 65:819, 1986.

16. Prys-Roberts C: Anaesthesia: A practical or impossible construct? (editorial) Br J Anaesth 59:1341, 1987.

17. Eger EL II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. Anesthesiology 26:756, 1965.

18. Kissin I: General anesthetic action: An obsolete notion? Anesth Analg 76:215, 1993.

19. Robertson HR: Without benefit of anesthesia: George Wilson's amputation and Fanny Burney's mastectomy. Ann R Coll Physicians Surg Can 22:27, 1989.

20. Vickers MD: Detecting consciousness by clinical means. In Rosen M, Lund NJ (eds): Consciousness, Awareness, and Pain in General Anesthesia. London, Butterworths, 1987, p 12.

21. Schacter DL: Implicit knowledge: New perspectives on unconscious processes. Proc Natl Acad Sci USA 89:11,113, 1992.

---

22. Bogetz MS, Katz JA: Recall of surgery for major trauma. Anesthesiology 61:6, 1984.

23. On being aware (editorial). Br J Anaesth 51:711, 1979.

24. Wilson J, Turner DJ: Awareness during caesarean section under general anaesthesia. Br Med J 1:280, 1969.

25. Mainzer J Jr: Awareness, muscle relaxants and balanced anaesthesia. Can Anaesth Soc J 26:386, 1979.

26. Breckenridge JL, Aitkenhead AR: Awareness during anaesthesia: A review. Ann R Coll Surg Engl 65:93, 1983.

27. Liu WHD, Thorp AS, Graham SG et al: Incidence of awareness and recall during general anesthesia. Anaesthesia 46:437, 1991.

28. Wilson SL, Vaughan RW, Stephen CR: Awareness, dreams, and hallucinations associated with general anesthesia. Anesth Analg 54:609, 1975.

29. Hutchinson R: Awareness during surgery: A study of its incidence. Br J Anaesth 33:463, 1961.

30. Saucier N, Walts LF, Moreland JR: Patient awareness during nitrous oxide, oxygen, and halothane anesthesia. Anesth Analg 62:239, 1983.

31. Bahl CP, Wadwa S: Consciousness during apparent surgical anaesthesia: A case report. Br J Anaesth 40:289, 1968.

32. Mark JB, Greenberg LM: Intraoperative awareness and hypertensive crisis during high-dose fentanyl-diazepam-oxygen anesthesia. Anesth Analg 62:698, 1983.

33. Mummaneni N, Rao TLK, Montoya A: Awareness and recall with high-dose fentanyl-oxygen anesthesia. Anesth Analg 59:948, 1980.

34. Hilgenberg JC: Intraoperative awareness during high dose fentanyl-oxygen anaesthesia. Anesthesiology 54:341, 1981.

35. Tunstall ME: Detecting wakefulness during general anaesthesia for caesarean section. Br Med J 1:1321, 1977.

36. Tunstall ME: The reduction of amnesic wakefulness during caesarean section. Anaesthesia 34:316, 1979.

37. Schultetus RR, Hill CR, Dharmaraj CM et al: Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined. Anesth Analg 65:723, 1986.

38. Russell IF: Balanced anesthesia: Does it anesthetize? (letter) Anesth Analg 64:941, 1985.

39. Russell IF: Comparison of wakefulness with two anaesthetic regimens: Total I.V. balanced anaesthesia. Br J Anaesth 58:965, 1986.

40. Breckenridge J, Aitkenhead AR: Isolated forearm technique for detection of wakefulness during general anaesthesia (abstract). Br J Anaesth 53:665P, 1981.

41. Bogod DG, Orton JK, Yau HM et al: Detecting awareness during general anesthetic caesarean section: An evaluation of two methods. Anaesthesia 45:279, 1990.

42. Russell IF: Midazolam-alfentanil: An anesthetic? An investigation using the isolated forearm technique. Br J Anaesth 70:42, 1993.

43. Abouleish E, Taylor FH: Effect of morphine-diazepam on signs of anesthesia, awareness, and dreams of patients under NO for cesarean section. Anesth Analg 55:702, 1976.

44. Levinson BW: States of awareness during general anaesthesia: Preliminary communication. Br J Anaesth 37:544, 1965.

45. Blacher RS: Awareness during surgery (editorial). Anesthesiology 61:1, 1984.

46. Bennett HL, Davis HS, Giannini JA: Non-verbal response to intraoperative conversation. Br J Anaesth 57:174, 1985.

47. Block RI, Ghoneim MM, Sum Ping ST et al: Human learning during general anesthesia and surgery. Br J Anaesth 66:170, 1991.

48. McLintock TT, Aitken H, Downie CF et al: Postoperative analgesic requirements in patients exposed to positive intraoperative suggestions. BMJ 301:788, 1990.

49. Woo R, Seltzer JL, Marr A: The lack of response to suggestion under controlled surgical anesthesia. Acta Anaesthesiol Scand 31:567, 1987.

50. Eich E, Reeves JL, Katz RL: Anesthesia, amnesia, and memory/awareness distinction. Anesth Analg 64:1143, 1985.

51. Block RI, Ghoneim MM, Sum Ping ST et al: Efficacy of therapeutic suggestions for improved postoperative recovery presented during general anesthesia. Anesthesiology 75:746, 1991.

52. Dwyer R, Bennett HL, Eger EI et al: Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. Anesthesiology 77:888, 1992.

53. Blacher RS: On awakening paralyzed during surgery: A syndrome of traumatic neurosis. JAMA 234:67, 1975.

54. Ghoneim MM, Block RI: Learning and memory during general anesthesia, an update. Anesthesiology 87:387, 1997.

55. Bonke B, Bovill JG, Moermon N: Memory and Awareness in Anaesthesia, vol 3. Assen, Netherlands, Van Gorcum, 1996.

56. Veselis RA, Reinsel RA, Feschenko VA et al: The comparative amnestic effects of midazolam, propofol, thiopental and fentanyl at equisedative concentrations. Anesthesiology 87:49, 1997.

57. Pandit SK, Heisterkamp DV, Cohen PJ: Further studies on the anti-recall effect of lorazepam: A dose-time-effect relationship. Anesthesiology 45:495, 1976.

58. Holford NHG, Sheiner LB: Understanding the dose-effect relationship: Clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet 6:429, 1981.

59. Sheiner LB, Stanski DR, Vozeh S et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application of *d*-tubocurarine. Clin Pharmacol Ther 25:358, 1979.

60. Stanski DR, Sheiner LB: Pharmacokinetics and dynamics of muscle relaxants (editorial). Anesthesiology 51:103, 1979.

61. Jacobs RJ, Reves JG: Effect site equibration time is a determinant of induction dose requirement. Anesth Analg 76:1, 1993.

62. Eger EI II, Bahlman SH: Is the end-tidal anesthetic partial pressure an accurate measure of the arterial anesthetic partial pressure? Anesthesiology 35:301, 1971.

63. Waud BE, Waud DR: On dose-response curves and anesthetics (editorial). Anesthesiology 33:1, 1970.

64. Waud DR: On biological assays involving quantal responses. J Pharmacol Exp Ther 183:577, 1972.

65. Merkel G, Eger EI II: A comparative study of halothane and halopropane anesthesia: Including the method for determining equipotency. Anesthesiology 24:346, 1963.

66. Quasha AL, Eger EI II, Tinker JH: Determination and applications of MAC. Anesthesiology 53:315, 1980.

67. Cullen DJ: Drugs and anesthetic depth. In Smith NT, Miller RD, Corbascio AN (eds): Drug Interactions in Anesthesia. Philadelphia, Lea & Febiger, 1981, p 287.

68. Stoelting RK, Longnecker DE, Eger EI II: Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluroxene anesthesia: MAC awake. Anesthesiology 33:5, 1970.

69. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal halothane concentration for endotracheal intubation. Anesthesiology 47:386, 1977.

70. Roizen MF, Horrigan RW, Frazer BM: Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision: MAC BAR. Anesthesiology 54:390, 1981.

71. Zbinden AM, Maggiorini M, Petersen-Felix S et al: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. Anesthesiology 80:253, 1994.

72. Saidman LJ, Eger EI II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 25:302, 1964.

73. de Jong RH, Eger EI II: MAC expanded: AD_{50} and AD_{95} values of common inhalation anesthetics in man. Anesthesiology 42:384, 1975.

74. Torri G, Damia G, Fabiani ML: Effect of nitrous oxide on the anaesthetic requirement of enflurane. Br J Anaesth 46:468, 1974.

75. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. Anesthesiology 78:707, 1993.

76. Rampil IJ: Anesthetic potency is not altered after hypothermic spinal cord transactions in rats. Anesthesiology 80:606, 1994.

77. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. Anesthesiology 79:1244, 1993.

78. Cullen DJ, Eger EI II, Stevens WC et al: Clinical signs of anesthesia. Anesthesiology 36:21, 1972.

79. Zbinden AM, Petersen-Felix S, Thomson DA: Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. II. Hemodynamic responses. Anesthesiology 80:261,

1994.

80. Daniel M, Weiskopf RB, Noorani BA et al: Fentanyl augments the blockade of the sympathetic response to incision (MAC-BAR) produced by desflurane and isoflurane. Anesthesiology 88:43, 1998.

81. Eger EI II: Monitoring the depth of anesthesia. In Saidman LJ, Smith NT (eds): Monitoring in Anesthesia, 2nd ed. New York, John Wiley & Sons, 1983, p 1.

82. Neff W, Mayer EC, de la Luz Percales M: Nitrous oxide and oxygen anesthesia with curare relaxation. Calif Med 66:67, 1947.

83. Lowenstein E, Hallowell P, Levine FH et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389, 1969.

84. Stanley TH, Webster LR: Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 57:411, 1978.

85. Waller JL, Hug CC Jr, Nagle DM et al: Hemodynamic changes during fentanyl-oxygen anesthesia for aortocoronary bypass operation. Anesthesiology 55:212, 1981.

86. Wynands JE, Wong P, Townsend GE et al: Narcotic requirements for intravenous anesthesia. Anesth Analg 63:101, 1984.

87. Hynynen M, Takkunen O, Salmenpera M et al: Continuous infusion of fentanyl or alfentanil for coronary artery surgery: Plasma opiate concentrations, haemodynamics and postoperative course. Br J Anaesth 58:1252, 1986.

88. Philbin DM, Rosow CE, Schneider RC et al: Fentanyl and sufentanil anesthesia revisited: How much is enough? Anesthesiology 73:5, 1990.

89. Murphy MR, Hug CC Jr: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 57:485, 1982.

90. Hall RI, Murphy MR, Hug CC Jr: The enflurane sparing effect of sufentanil in dogs. Anesthesiology 67:518, 1987.

91. Hall RI, Szlam F, Hug CC Jr: The enflurane-sparing effect of alfentanil in dogs. Anesth Analg 66:1287, 1987.

92. Murphy MR, Hug CC Jr: The enflurane sparing effect of morphine, butorphanol, and nalbuphine. Anesthesiology 57:489, 1982.

93. Bailey PL, Port JD, McJames S et al: Is fentanyl an anesthetic in the dog? Anesth Analg 66:542, 1987.

94. Ardnt JO, Bednarski B, Parasher C: Alfentanil's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. Anesthesiology 64:345, 1986.

95. Ardnt JO, Mikat M, Parasher C: Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. Anesthesiology 61:355, 1984.

96. McEwan AI, Smith C, Dyar O et al: Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology 78:864, 1993.

97. Glass PAS: Anesthetic drug interactions: An insight into general anesthesia--its mechanisms and dosing strategies. Anesthesiology 88:5, 1998.

98. Glass PSA, Gan TJ, Howell S et al: Drug interactions: Volatile anesthetics and opiates. J Clin Anesth 9:18S, 1997.

99. de Lange S, de Bruijn NP: Alfentanil-oxygen anaesthesia: Plasma concentrations and clinical effects during variable-rate continuous infusion for coronary artery surgery. Br J Anaesth 55:183S, 1983.

100. Ausems ME, Hug CC Jr, Stanski DR et al: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. Anesthesiology 65:362, 1986.

101. Ausems ME, Vuyk J, Hug CC Jr et al: Comparison of computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 68:851, 1988.

102. Lemmens HJM, Bovill JG, Hennis PJ et al: Alcohol consumption alters the pharmacodynamics of alfentanil. Anesthesiology 71:669, 1989.

103. Lemmens HJM, Burm AGL, Bovill JG et al: Pharmacodynamics of alfentanil: The role of protein binding. Anesthesiology 76:65, 1992.

104. Egan TD, Minto CF, Hermann DJ et al: Remifentanil vs alfentanil, comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. Anesthesiology 84:821, 1996.

105. Minto CF, Schnider TW, Egan TD et al: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 86:10, 1997.

106. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil. II. Model development. Anesthesiology 86:24, 1997.

107. Drover DR, Lemmens HJM: Population pharmacodynamics and pharmacokinetics of remitentanil as a supplement to nitrous oxide anesthesia for elective abdominal surgery. Anesthesiology 89:869, 1998.

108. Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234, 1985.

109. Glass PS, Doherty M, Jacobs JR et al: Plasma concentration of fentanyl, with 70% nitrous oxide, to prevent movement at skin incision. Anesthesiology 78:842, 1993.

110. King BD, Harris LC Jr, Greifenstein FE et al: Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 12:556, 1951.

111. Stoelting RK: Circulatory changes during direct laryngoscopy and tracheal intubation: Influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology 47:381, 1977.

112. Brett CM, Fisher DM: Thiopental dose-response relations in unpremedicated infants, children, and adults. Anesth Analg 66:1024, 1987.

113. Avram MJ, Sanghvi R, Henthorn TK et al: Determinants of thiopental induction dose requirements. Anesth Analg 76:10, 1993.

114. Becker KE Jr: Plasma levels of thiopental necessary for anesthesia. Anesthesiology 49:192, 1978.

115. Hung OR, Varvel JR, Shafer SL et al: Thiopental pharmacodynamics. II. Quantitation of clinical and electroencephalographic depth of anesthesia. Anesthesiology 77:237, 1992.

116. Kazama T, Ikeda K, Morita K: Reduction of fentanyl of the Cp_{50} values of propofol and hemodynamic responses to various noxious stimuli. Anesthesiology 87:213, 1997.

117. Vuyk J, Lim T, Engbers FHM et al: Pharmacodynamics of alfentanil as a supplement to propofol or nitrous oxide for lower abdominal surgery in female patients. Anesthesiology 78:1036, 1993.

118. Vuyk J, Lim T, Engbers FHM et al: The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. Anesthesiology 83:8, 1995.

119. Stanski DR, Shafer SL: Quantifying anesthetic drug interaction: Implications for drug dosing. Anesthesiology 83:1, 1995.

120. Tammisto T, Aromaa U, Korttila K: The role of thiopental and fentanyl in the production of balanced anaesthesia. Acta Anaesthesiol Scand 24:31, 1980.

121. Brazier MAB: The effect of drugs on the electroencephalogram of man. Clin Pharmacol Ther 5:102, 1964.

122. Caton R: The electrical currents of the brain (abstract). BMJ 2:278, 1875.

123. Berger H: Uber das Elektrenkaphalogramm des Menschen. Arch Psychiatry 101:452, 1933.

124. Gibbs FA, Gibbs EL, Lennox WG: Effect on the electro-encephalogram of certain drugs which influence nervous activity. Arch Intern Med 60:154, 1937.

125. Faulconer A Jr: Correlation of concentrations of ether in arterial blood with electro-encephalographic patterns occurring during ether-oxygen and during nitrous oxide, oxygen and ether anesthesia of human surgical patients. Anesthesiology 13:361, 1952.

126. Kuramoto T, Oshita S, Takeshita H et al: Modification of the relationship between cerebral metabolism, blood flow, and electroencephalogram by stimulation during anesthesia in the dog. Anesthesiology 51:211, 1979.

127. Levy WJ, Shapiro HM, Maruchak G et al: Automated EEG processing for intraoperative monitoring: A comparison of techniques. Anesthesiology 53:223, 1980.

128. Gregory TK, Pettus DC: An electroencephalographic processing algorithm specifically intended for analysis of cerebral electrical activity. J Clin Monit 2:190, 1986.

129. Rampil IJ: What every neuroanesthesiologist should know about electroencephalograms and computerized monitors. Anesthesiol Clin North Am 10:683, 1992.

130. Prior PF: The EEG and detection of responsiveness during anaesthesia and coma. In Rosen M, Lunn JN (eds): Consciousness, Awareness, and Pain in General Anesthesia. London, Butterworths, 1987, p 34.

131. Bimar J, Bellville JW: Arousal reactions during anesthesia in man. Anesthesiology 47:449, 1977.

132. Miyauchi Y, Sakabe T, Maekawa T et al: Responses of EEG, cerebral oxygen consumption and blood flow to peripheral nerve stimulation during thiopentone anaesthesia in the dog. Can Anaesth Soc J 32:491, 1985.

133. Clark DL, Rosner BS: Neurophysiologic effects of general anesthetics. I. The electroencephalogram and sensory evoked responses in man. Anesthesiology 38:564, 1973.

134. Galla SJ, Rocco AG, Vandam LD: Evaluation of the traditional signs and stages of anesthesia: An electroencephalographic and clinical study. Anesthesiology 19:328, 1958.

135. Levy WJ: Intraoperative EEG patterns: Implications for EEG monitoring. Anesthesiology 60:430, 1984.

136. Berezowskyj JL, McEwen JA, Anderson GB et al: A study of anaesthesia depth by power spectral analysis of the electroencephalogram (EEG). Can Anaesth Soc J 23:1, 1976.

137. Drummond JC, Brann CA, Perkins DE et al: A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power and dominance shift in the determination of depth of anesthesia. Acta Anaesthesiol Scand 35:693, 1991.

138. Long CW, Shah NK, Lounghlin C et al: A comparison of EEG determinants of near awakening from isoflurane and fentanyl anesthesia. Anesth Analg 69:169, 1989.

139. Dwyer RC, Rampil IJ, Eger EI et al: The electroencephalogram does not predict depth of isoflurane anesthesia. Anesthesiology 81:403, 1994.

140. Stanski DR: Pharmacodynamic modeling of anesthetic EEG drug effects. Annu Rev Pharmacol Toxicol 32:421, 1992.

141. Rampil IJ: A primer for EEG signal processing in anesthesia. Anesthesiology 89:980, 1998.

142. Sigl JC, Chamoun NG: An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 10:392, 1994.

143. Sebel PS, Bowles SM, Saini V et al: EEG bispectrum predicts movement during thiopental isoflurane anesthesia. J Clin Monit 11:83, 1995.

144. Kearse LA, Manberg P, Chamoun N et al: Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. Anesthesiology 81:1365, 1994.

145. Vernon JM, Lang E, Sebel PS et al: Prediction of movement using bi-spectral EEG during propofol/alfentanil or isoflurane/alfentanil anesthesia. Anesth Analg 80:780, 1995.

146. Sebel PS, Lang E, Rampil IJ et al: A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg 84:891, 1997.

147. Glass PS, Bloom M, Kearse L et al: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. Anesthesiology 86:836, 1997.

148. Liu J, Singh H, White PF: Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. Anesthesiology 84:64, 1996.

149. Kaoh T, Suzuki A, Ikeda K: Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. Anesthesiology 88:642, 1998.

150. Flishon R, Windsor A, Sigl J et al: Recovery of consciousness after thiopental or propofol: Bispectral index and the isolated forarm technique. Anesthesiology 86:613, 1997.

151. Kearse LA, Rosow C, Zaslavsky A et al: Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. Anesthesiology 88:25, 1998.

152. Gan TJ, Glass PS, Windsor A et al: Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil and nitrous oxide anesthesia. Anesthesiology 87:808, 1997.

153. Song D, Joshi GP, White PF: Titration of volatile anesthetics using bi-spectral index facilitates recovery after ambulatory anesthesia. Anesthesiology 87:842, 1997.

154. Grundy BL: Evoked potential monitoring. In Blitt ED (ed): Monitoring in Anesthesia and Critical Care Medicine. New York, Churchill Livingstone, 1985, p 345.

155. Grundy BL: Intraoperative monitoring of sensory-evoked potentials. Anesthesiology 58:72, 1983.

156. Thornton C, Catley DM, Jordan C et al: Enflurane anaesthesia causes graded changes in the brainstem and early cortical auditory evoked response in man. Br J Anaesth 55:479, 1983.

157. Thornton C, Heneghan CPH, James MFM et al: Effects of halothane or enflurane with controlled ventilation on auditory evoked potentials. Br J Anaesth 56:315, 1984.

158. Thornton C, Heneghan CPH, Navaratnarajah M et al: Effect of etomidate on the auditory evoked response in man. Br J Anaesth 57:554, 1985.

159. Thornton C, Heneghan CPH, Navaratnarajah M et al: Selective effect of Althesin on the auditory evoked response in man. Br J Anaesth 58:422, 1986.

160. Heneghan CPH, Thornton C, Navaratnarajah M et al: Effect of isoflurane on the auditory evoked response in man. Br J Anaesth 59:277, 1987.

161. Thornton C, Konieczko K, Jones JG et al: Effect of surgical stimulation on the auditory evoked response. Br J Anaesth 60:372, 1988.

162. Thornton C, Barrowcliffe MP, Konieczko KM et al: The auditory evoked response as an indicator of awareness. Br J Anaesth 63:113, 1989.

163. Newton DEF, Thornton C, Konieczko K et al: Auditory evoked response and awareness: A study in volunteers at sub-MAC concentrations of isoflurane. Br J Anaesth 69:122, 1992.

164. Hug CC Jr: Propofol requirements versus stimulus intensity. Anesthesiology 87:201, 1997.

Chapter 30 - Cardiovascular Monitoring *

Jonathan B. Mark
Thomas F. Slaughter
J. Gerald Reves

/das/book/view/29494766/875/322.html

INTRODUCTION: EXTENDING THE PHYSICAL EXAMINATION

Although some might consider electronic devices as the only cardiovascular monitors, the fundamental basis for circulatory monitoring remains in the eyes, hands, and ears of the anesthesiologist. Just as inspection, palpation, and auscultation are the cornerstones for standard physical examination of the cardiovascular system, these procedures remain the critical elements of perioperative cardiovascular monitoring. These procedures must be adapted and focused on the unique requirements of surgical and critically ill patients. Furthermore, their limitations must be recognized.

Many standard physical means of assessing circulation are employed throughout an operation. For many healthy patients undergoing minor procedures, these physical signs

* *See Appendix 1, Practice Guidelines for Perioperative Transesophageal Echocardiography and Practice Guidelines for Pulmonary Artery Catheterization*

may provide a considerable fraction of the total cardiovascular monitoring. When the operation becomes more complex or the patient comes to surgery with more advanced or unstable cardiovascular disease, the extent of supplemental electronic monitoring grows accordingly. However, careful physical assessment still provides the clinician with an all-important back-up system used to confirm or refute information derived from other monitoring devices. The most obvious, perhaps trivial, example is the patient whose electrocardiogram (ECG) shows asystole. Detection of a normal pulse by direct palpation directs the anesthesiologist back to correct the monitoring artifact rather than to initiate cardiopulmonary resuscitation. In a sense, the clinical examination here is an example of redundant monitoring. Heart rate is monitored continuously by the ECG, but checking the heart rate by intermittently palpating the pulse provides the most important supplemental safety monitor.

Early advances in cardiovascular assessment beyond the methods of basic physical examination were not accepted readily into medical practice. Around 1900, introduction of sphygmomanometry to measure blood pressure was criticized because it would weaken clinical acuity by blunting the senses and acute perceptions of the clinician. Even chest stethoscopy had its critics, simply on the basis that it placed the physician at greater distance from the patient. [1] Today, these concerns might appear somewhat ludicrous, given our patient care responsibilities in unusual environments, as in the use of magnetic resonance scanners, where clinicians must monitor patients from a remote site. Nonetheless, there can be little doubt that increased reliance on electronic monitoring devices has diminished our fundamental clinical skills of physical assessment.

Palpation of the pulse, its rate and character, should not be forgotten in the perioperative setting. Unique constraints in the operating room may dictate which pulses are accessible for monitoring. The anesthetist standing at the patient's head during induction of anesthesia can easily palpate the carotid artery, the superficial temporal artery anterior to the ear, or the facial artery at the mandible. When only an arm is accessible, the axillary, brachial, radial, and ulnar pulses may be examined. Even procedures necessitating that the anesthetist be positioned near the patient's feet permit palpation of femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Many of these vessels also serve as suitable sites for sampling arterial blood or direct arterial cannulation for pressure monitoring (see later in chapter). Perhaps most important, one should consider the unique opportunities for pulse monitoring during surgery, rather than just the constraints of this environment. During cardiac surgery, the beating heart may be observed directly and palpation of the ascending aorta by the surgeon provides a useful estimate of central blood pressure. In fact, the surgeon's evaluation of any arterial pulse within the surgical field should be considered whenever severe hemodynamic instability develops.

Clinical evaluation of venous pressure is often technically difficult perioperatively. Factors hindering the anesthesiologist include unusual patient positions, positive pressure mechanical ventilation, and lack of access to observe the neck veins. However, early recognition of venous obstruction in an extremity or the head and neck may have important clinical consequences. Not only might this observation herald hemodynamic problems for the patient, but communicating these observations to the operating surgeon should allow timely correction of associated technical problems, such as a malpositioned venous cannula during cardiopulmonary bypass.

Given that the cardiovascular system is responsible for transport of substrates and byproducts to and from all organ systems, monitoring end-organ function reflects the adequacy of cardiovascular system performance. Inspection of mucous membranes, skin color, and skin turgor can reveal pertinent clues about hydration, oxygenation, and perfusion. Additional simple clinical techniques include empiric estimation of fluid deficits and measurement of intraoperative blood loss. Decreased urine output may indicate hypo-volemia or reduced cardiac output, and altered mental status may be a sign of inadequate cerebral perfusion. Unfortunately, preexisting end-organ dysfunction may confound interpretation of these simple physical signs and measurements. Furthermore, drugs may alter organ function directly. For example, general anesthesia makes it impossible to monitor mental status or sensory or motor function using physical examination; diuretic therapy obviates urine output monitoring as an indicator of overall systemic perfusion. As a result, simple clinical assessment of end-organ function is of limited value in many anesthetized or critically ill patients, so that additional cardiovascular monitoring techniques are required.

Stethoscopy

Although Laennec is credited with introducing the stethoscope into general medical practice in 1818, nearly a century elapsed before Harvey Cushing proposed in 1908 that the stethoscope be used as a routine continuous cardiopulmonary monitoring device during surgery. [2] Today, intraoperative monitoring with either a precordial or esophageal stethoscope has become a fundamental extension of the physical examination for all anesthetized patients. [3] [4]

Stethoscopy provides a simple and reliable means of listening to heart and breath sounds continuously throughout an operation. The most common equipment used for precordial stethoscopy consists of a heavy metal bell or accumulator attached to a length of rubber or plastic extension tubing and a custom-molded monaural plastic earpiece. Electronically amplified stethoscopes have been designed in an attempt to improve the quality and clarity of heart and breath sounds, and wireless systems, using radiotransmitted signals, allow continuous monitoring without the anesthetist being tethered to the patient by the stethoscope extension tubing. [5] [6] [7] However, stethoscopes with these electronic modifications have not supplanted the standard inexpensive mechanical device in everyday practice.

Although minimally invasive and practical only for the patient who is undergoing general endotracheal anesthesia, the esophageal stethoscope provides monitoring benefits not available with its precordial cousin. Clear breath sounds and distinct heart sounds are audible in most patients with the stethoscope tip positioned 28 to 30 cm from the incisors. [8] Core body temperature can be measured via a thermistor incorporated in the tip of the stethoscope. Specially configured stethoscopes permit recording of a transesophageal ECG, which may be useful to diagnose atrial

arrhythmias, right ventricular ischemia, or posterior left ventricular ischemia. [9] [10] The esophageal stethoscope may also be a valuable therapeutic tool for treating intraoperative sinus bradycardia or junctional rhythm. For this special application, transesophageal atrial pacing can be accomplished with a stethoscope equipped

with bipolar pacing electrodes on its outer surface. [11] [12] Use of the esophageal stethoscope is safe in most patients, but it has been associated with occasional complications including hypoxemia from unintended tracheobronchial placement or compression of the membranous posterior trachea in small infants, loss down the esophagus, detachment of the acoustic cuff, and distortion of surgical anatomy in the neck. [13] [14] [15] Placement of the esophageal stethoscope may also cause pharyngeal or esophageal trauma and interfere with nasogastric tube positioning or transesophageal echocardiography.

Despite the apparent value of the precordial or esophageal stethoscope for basic patient safety monitoring, its widespread application in clinical practice has diminished in recent years. [15] [16] This may be driven by the routine use of pulse oximetry, capnography, and other electronic safety monitors that have become ubiquitous and even required by law in some locations. As a practical matter, clinicians may not recognize the loss of heart or breath sounds as readily as might be expected, owing to reliance on the more modern electronic devices or distractions and noise pollution inherent in the operating room. [2] [13] These practice patterns appear to be borne out by the 1993 Australian Incident Monitoring Study, which noted that a stethoscope was employed in only 5 percent of the 1,256 critical incidents reported. Furthermore, it was the first monitor to detect the morbid incident--cardiac arrest--in only one instance. [16]

The current role of intraoperative stethoscopy may be summarized as follows: [2] [13] [16]

1. Use of the stethoscope as a continuous monitor has become limited to enthusiasts (mainly pediatric anesthetists) and to institutions with insufficient resources to purchase electronic monitors.
2. A stethoscope should be immediately available in all locations where anesthesia is administered. Its role in diagnosing important respiratory problems (e.g., bronchospasm) probably exceeds its value as a continuous circulatory monitor.
3. Monitors like the oximeter, capnograph, and ECG detect untoward incidents more often than the stethoscope, in part because it is difficult to concentrate continuously on listening to both heart and breath sounds.
4. The stethoscope thus remains a valuable additional safety monitor, but only as a supplement to standard disconnect alarms, pulse oximetry, capnography, and direct observation of the patient.

Heart Rate Monitoring

The simplest and least invasive form of cardiac monitoring remains the measurement of heart rate. This vital sign provides an important guide to the baseline condition of the circulation as well as the influence of anesthetics and surgical stimuli. Ability to estimate heart rate quickly using a "finger on the pulse" is a skill as important as this expression is common. However, under most circumstances in modern anesthesia practice, electronic monitoring devices are used to provide a continuous, numeric display of heart rate.

Although any monitor that senses the period of the cardiac cycle can be used to determine heart rate, the most common technique applied in the operating room is electrocardiography. Current monitors use multiple ECG leads to sense cardiac electrical activity. [17] This redundancy aids detection of the R wave and improves the accuracy of heart rate measurement. As a result, a single noisy lead, or one in which the R waves are of very low amplitude, will not prevent the monitor for calculating heart rate properly.

Electrocardiographic measurement of heart rate begins with accurate detection of the R wave and measurement of the R-R interval. The digital value displayed for heart rate is generated from an algorithm designed to count and average a certain number of beats and then display a number that is updated every 5 to 15 seconds. [18] As a result, acute but transient changes in heart rate may have little impact on the displayed digital value. For example, consider an episode of complete heart block, which interrupts slow sinus rhythm. Depending on the algorithms employed by the monitor, the digital value for heart rate may show only a slight reduction from the baseline value. In this instance, the heart rate of 49 beats/min displayed by the monitor fails to alert the clinician of the dangerous transient bradyarrhythmia (Fig. 30-1) (Figure Not Available) . Although the monitor could update the digital value for heart rate after each beat by reporting an instantaneous R-R interval, this would result in numbers flashing on the display screen, changing with each heart beat, owing to the normal physiologic beat-to-beat variability in heart rate. Instead, the displayed digital value for heart rate (and for all the direct pressure measurements as well) is derived by the monitor using a *moving average filter.* In more sophisticated monitors, this filter weights the most recent values more heavily than older values in deriving the average value for the digital display.

Occasionally, the clinician must check electrode attachment, increase ECG signal gain, or select alternate ECG leads to facilitate heart rate monitoring. Some monitors allow manual adjustment of threshold or sensitivity for R-wave detection. Despite these measures, the monitor may display inaccurate heart rates when the ECG trace is distorted by patient movement or other electrical interference. In the operating room, this frequently occurs when the electrosurgical unit is in use. Visual inspection of the ECG trace always should be used to confirm the numeric value for heart rate displayed on the monitor. Spurious values are recognized quickly, and true heart rate can be estimated by noting the R-R interval when the ECG trace reappears briefly on the monitor screen. In addition, the arterial pressure trace or the pulse oximeter plethysmograph confirms the pulse rate in these instances.

Electrical interference in the ECG trace may arise from sources other than the electrosurgical unit. Power line noise appears as a 60-Hz artifact and may be eliminated by selecting narrower bandpass ECG filters, including a 60-Hz notch filter. Fortunately, this type of power line electrical artifact rarely prevents accurate ECG measurement of heart rate. Other artifacts result from muscle twitching and fasciculations, as well as various medical devices, including litho-tripsy machines, cardiopulmonary bypass equipment, and fluid warmers. [19]

Figure 30-1 (Figure Not Available) Digital heart (HR) displays may fail to warn of dangerous bradyarrhythmias. Direct observation of the electrocardiogram (ECG) and the arterial blood pressure traces reveals complete heart block and a 4-sec period of asystole, while the digital display reports an HR of 49 beats/min. Note that the ECG filter (arrow) corrects the baseline drift so that the trace remains on the recording screen. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 13-2.) (Figure Not Available)*

Paced rhythms often produce problems for ECG measurement of heart rate. When tall pacing spikes are present, the monitor may misinterpret these high amplitude signals as R waves and miscalculate heart rate. Tall T waves may produce the same artifact when the monitor mistakenly double counts these T waves along with the R waves. These problems may be lessened by decreasing ECG gain, adjusting R-wave detection sensitivity, or changing the ECG lead to one with a reduced pacing spike or T-wave amplitude.

Pulse Rate Monitoring

Although the preceding discussion has focused on methods to estimate heart rate from the ECG trace, it might be argued that monitoring pulse rate is more important than monitoring heart rate, in terms of perioperative hemodynamic assessment. By definition, the distinction centers on whether a given electrical depolarization and systolic contraction of the heart (heart rate) generates a palpable peripheral arterial pulsation (pulse rate). Pulse deficit describes the extent to which the pulse rate is less than the heart rate. This is typically seen in patients with atrial fibrillation, in which short R-R intervals compromise cardiac filling during diastole, resulting in reduced stroke volume and imperceptible arterial pulse. The most extreme example of a pulse deficit is electrical-mechanical dissociation or pulseless electrical activity, seen in patients with cardiac tamponade, extreme hypovolemia, and other conditions in which cardiac contraction does not generate a palpable peripheral pulse.

Most monitors report heart rate and pulse rate separately. The former is measured from the ECG trace, and the latter is determined by a pulse source, which is generally selectable by the user. For example, the pulse oximeter plethysmograph trace will provide a suitable pulse measurement source for most patients except those with severe arterial occlusive disease or those with marked peripheral vasoconstriction. Automatic noninvasive blood pressure devices determine the pulse rate by counting oscillations in pressure sensed by the surrounding cuff. When direct arterial pressure measurement is in place, the pressure waveform provides a reliable pulse source. As already emphasized, this is particularly useful in distinguishing artifactual ECG signals and erroneous heart rates from important real cardiac events. Beware, however, that even the arterial pressure trace may be misleading when nonsystolic arterial pulsations are detected by the monitor and counted separately. In patients treated with intraaortic balloon counterpulsation, the pressure pulse resulting from balloon inflation during diastole may be detected and produce a factitiously high pulse rate. [19] Other arterial pressure waveforms that have a bisferiens, double-peaked morphology, such as those arising in patients with aortic valve regurgitation, may produce a similar artifactually increased pulse rate measurement. In contrast, patients with pulsus alternans may have inappropriately low pulse rates measured, owing to the diminished magnitude of every other arterial pulsation. In these cases, selection of an alternative pulse source, such as the pulmonary artery pressure waveform, can provide a reliable pulse rate.

In summary, pulse rate monitoring and heart rate monitoring complement one another. Even though monitoring both pulse rate and heart rate may seem redundant in many cases, such intentional redundancy is being applied to modern computerized monitoring algorithms. One example is termed robust fusion sensor technology, which fuses heart rate and pulse rate data from multiple sources--ECG, pulse oximeter plethysmogram, and arterial pressure waveform. [20] This approach improves the accuracy of heart and pulse rate monitoring and reduces the frequency of distracting false alarms. [21] In the end, however, as with all numeric information displayed on the bedside monitor, it is the clinician's ultimate responsibility to scrutinize the analog ECG and pressure waveforms to ensure the veracity of all digital values displayed by bedside monitors.

ARTERIAL BLOOD PRESSURE MONITORING

As with heart rate, blood pressure is a fundamental cardiovascular vital sign, which reflects the force that derives perfusion of the body. In addition, blood pressure is the most important determinant of left ventricular afterload, the workload of the heart. Consequently, frequent measurement of arterial blood pressure is a critical part of monitoring anesthetized or seriously ill patients. The importance of

monitoring this vital sign is underscored by the fact that standards for basic anesthetic monitoring mandate measurement of arterial blood pressure at least every 5 minutes in all anesthetized patients. [3]

Techniques for measuring blood pressure fall into two major categories: indirect Riva-Rocci cuff devices and direct arterial cannulation and pressure transduction. These methods differ in nearly every respect, notably in terms of the physical process being monitored and in the level of invasiveness of their application. In clinical practice, blood pressures measured by different techniques often yield significantly different values. [22] So common are these inconsistencies that some investigators have declared: "Blood pressure is a function of the way it is measured." [23]

Studies comparing different blood pressure monitoring techniques usually use direct arterial pressure measurement as the reference standard against which another method is judged. However, there are many ways in which direct arterial pressure measurement can yield spurious results (see the section *Technical Aspects of Direct Blood Pressure Measurement*). In view of these considerations, Gorback's [24] comments provide a valuable guide: "It is preferable to understand the strengths and weaknesses of the various techniques and expected relative values, since they do not measure the same event." In the end, the clinician must acquire sufficient understanding of the performance characteristics of these monitors to become the arbiter of measurement discrepancies by integrating all available data.

Indirect Measurement of Arterial Blood Pressure

Manual Intermittent Techniques

Most indirect methods of blood pressure measurement rely on a Riva-Rocci sphygmomanometer. As described by Riva-Rocci in 1896, [25] this apparatus included an armencircling inflatable elastic cuff, a rubber bulb to inflate the cuff, and a mercury manometer to measure cuff pressure. [26] Riva-Rocci described the measurement of systolic arterial blood pressure by determining the pressure at which the palpated radial arterial pulse disappeared as the cuff was inflated. The scientific rigor and attention to detail of Riva-Rocci's work are chronicled in a translation celebrating his original publications. [26]

A variation of the Riva-Rocci method commonly employed today is generally termed the *return-to-flow technique.* Whereas the Riva-Rocci technique recorded the pressure during *cuff inflation* at which the pulse completely disappeared, the return-to-flow method records the pressure during *cuff deflation* at which the pulse reappears. Using this technique, systolic blood pressure can be estimated without a stethoscope using only a cuff and manometer. When the patient has a finger pulse oximeter or indwelling arterial catheter in the ipsilateral arm, the return to flow can be determined visually by the reappearance of the plethysmographic or arterial pressure waveforms.

Although return-to-flow methods provide a simple, rapid means to estimate systolic blood pressure, they do not allow measurement of diastolic blood pressure. Undoubtedly, the most widely used intermittent manual method for blood pressure determination is the auscultation of sounds originally described by Korotkoff in 1905. [27] [28] Using a Riva-Rocci sphygmomanometer and cuff, Korotkoff applied a stethoscope to the artery directly below the cuff to auscultate the sounds generated as the cuff was slowly deflated. These sounds are a complex series of audible frequencies produced by turbulent flow, instability of the arterial wall, and shock wave formation created as external occluding pressure on a major artery is reduced. [24] The pressure at which the first Korotkoff sound is auscultated is generally accepted as the systolic pressure (phase I). The sound character progressively changes (phases II and III), becomes muffled (phase IV), and finally absent (phase V). Diastolic pressure is recorded at phase IV or V. However, phase V may never occur in certain pathophysiologic states, such as aortic regurgitation. [29]

The auscultatory method for blood pressure determination is limited by excessively long or loose stethoscope tubing, which impairs sound transmission, or by poor hearing sensitivity of the observer. Aneroid manometers are subject to calibration errors and should be checked periodically. A more basic shortcoming of auscultation is the reliance on blood flow to generate Korotkoff sounds. Pathologic or iatrogenic causes for decreased peripheral blood flow, such as cardiogenic shock or high-dose vasopressor infusion, can attenuate or obliterate sound generation and result in significant underestimation of blood pressure. [30] In contrast, low compliance of the tissues underlying the cuff, as encountered in a shivering patient, will require an excessively high cuff-occluding pressure and produce "pseudohypertension." [24] Patients with severe calcific arteriosclerosis may have relatively noncompressible arteries, another circumstance wherein cuff blood pressures will yield spuriously elevated results compared with true intra-arterial blood pressure. [31]

Other common sources of error during intermittent manual blood pressure measurement include selection of an inappropriate cuff size or excessively rapid cuff deflation. Blood pressure cuff width should be 20 percent greater than arm diameter, and the cuff should be applied snugly after any residual air has been squeezed out. The pneumatic bladder inside the cuff should span at least half the circumference of the arm and be centered over the artery. Although too large a cuff generally will work well and produce little error, cuffs that are too narrow yield erroneously elevated values for blood pressure (Fig. 30-2) . [32] [33] Cuff deflation rate is another important variable that influences accurate blood pressure measurement, especially when deflation is performed manually. The decrease in cuff pressure should proceed slowly enough for the Korotkoff sounds to be auscultated and assigned properly to the current pressure in the cuff. Failure to identify the initial Korotkoff sounds will result in a falsely low measure of blood pressure. A deflation rate of 3 mm Hg/s limits this source of error, and coupling deflation rate to heart rate--2 mm Hg/beat--has been found to improve accuracy further. [34]

Automated Intermittent Techniques

Many limitations of manual intermittent blood pressure measurement have been overcome by automated noninvasive blood pressure (NIBP) devices, which are now used widely in medical care. By applying a single algorithm or

Figure 30-2 Effect of cuff size on manual blood pressure measurement. An inappropriately small blood pressure cuff yields erroneously high values for blood pressure because the pressure within the cuff is incompletely transmitted to the underlying artery. See text for greater detail.

method of data interpretation, NIBP devices provide consistent, reliable values for systolic, diastolic, and mean arterial pressure (MAP). In addition, automated NIBP devices provide alarm systems to draw attention to extreme blood pressure values and have the capacity to transfer data to an automated trending device or information system. However, the greatest advantage of automated NIBP devices compared with manual methods of blood pressure measurement is that they free the operator to perform other vital clinical duties while simultaneously ensuring frequent, repetitive blood pressure measurements.

Most automated NIBP devices are based on the technique termed oscillometry, a technique first described by von Recklinghausen in 1931. [35] In this method, variations in cuff pressure resulting from arterial pulsations during cuff deflation are sensed by the monitor and used to determine arterial blood pressure values. Peak amplitude of arterial pulsations corresponds closely to true MAP. [36] [37] (Interestingly, the reason many clinicians still refer to an automated NIBP device as a "Dinamap" is that the original clinically available monitors provided only this single, easily measured pressure value--MAP.) Values for systolic and diastolic pressure are derived using proprietary formulas that examine the rate of change of the pressure pulsations (Fig. 30-3). Systolic pressure is generally chosen as the pressure at which pulsations are increasing and are at 25 to 50 percent of maximum. Diastolic pressure is more difficult to determine but is commonly placed at the point where the pulse amplitude has declined by 80 (Figure Not Available) percent. [24]

Although oscillometry is used primarily in automated NIBP measurement, the same principles may be applied to determine blood pressure manually using a standard cuff and aneroid manometer. If the cuff is deflated slowly until the needle on the aneroid gauge begins to flicker or oscillate, this pressure value will provide a close estimate for systolic blood pressure. The primary advantage of this technique is that it can be performed quickly, using only one hand on the inflation bulb and pressure relief valve, thereby leaving the anesthesiologist's other hand free to maintain the patient's airway.

In clinical practice, oscillometric automated NIBP measurement has focused largely on pressures measured from

Figure 30-3 (Figure Not Available) Comparison of blood pressure measurements using Korotkoff sounds and oscillometry. Oscillometric systolic blood pressure is recorded at the point where cuff pressure oscillations begin to increase, mean pressure corresponds to the point of maximal oscillations, and diastolic pressure is measured where the oscillations become attenuated. Note the correspondence between these measurements and the Korotkoff sounds that determine auscultatory systolic and diastolic pressures. *(From Geddes LA: Cardiovascular Devices and Their Applications. New York; John Wiley, 1984: Fig. 34-2 . Reprinted by permission of John Wiley & Sons, Inc.)*

the upper arm. Sometimes the patient's surgical procedure or medical condition requires that the cuff be applied to the calf, ankle, or thigh. These are all acceptable alternatives, keeping in mind that an appropriate size cuff must be employed. Because the oscillometric NIBP technique provides accurate pressure measurements in pediatric patients, [38] [39] [40] several investigators have proposed using neonatal sized cuffs placed around a finger or thumb of an adult patient. [41] [42] [43] Although these alternatives may be appropriate in certain circumstances, their overall accuracy has not been widely validated and may not conform to accepted industry standards. [44]

Many other techniques have been described for automated NIBP measurement, but none have supplanted the standard oscillometric technique. One device uses the Doppler principle to determine blood flow distal to the cuff [45] and another senses motion of the arterial wall. [46] Although these have been found to record blood pressure with acceptable accuracy, they require extra efforts to place and stabilize additional sensing transducers. Supraorbital artery oscillometry has been studied as an alternative site for blood pressure measurement but appears inaccurate compared with direct radial artery pressure values, perhaps owing to the peripheral location and vasoreactive sensitivity of the supraorbital artery. [47] Photo-oscillometry to detect brachial artery movement has also been described, but awaits broader validation in clinical practice. [48]

Under controlled clinical conditions, numerous investigators have demonstrated that automated NIBP measurements closely approximate directly measured arterial pressure. [22] [32] [37] [49] However, other studies underscore the fact that marked disagreement occurs when direct and indirect pressure measurements are compared, [50] particularly when radial artery pressure is used as the direct measurement standard [23] [51] or when techniques are compared under changing clinical conditions. When direct brachial artery pressures have been compared with various indirect methods, (including manual auscultation, automated oscillometry, aneroid manometer visual onset of needle oscillations, and return to flow), the relation between the indirect and direct pressures varied between patients, within patients over time, and with changing hemodynamic conditions. [52]

As noted, some authors have emphasized the lack of exact agreement between different measurements of blood pressure. [23] [24] [48] [53] Standards for performance of automated NIBP devices have been advanced by organizations such as the American Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society. AAMI standards require a monitor to record blood pressure to within 5±8 mm Hg (mean ± standard deviation) prediction error compared with the reference method. [48] However, clinical performance of an NIBP monitor should be evaluated by other criteria as well. These include the number of outlier values, duration of discrepancies, magnitude of individual errors, and performance under variable clinical conditions. [48]

Although automated blood pressure measurement techniques are considered noninvasive and relatively safe, complications have been reported. These include pain, petechiae and ecchymoses, limb edema, venous stasis and thrombophlebitis, peripheral neuropathy, and even compartment syndromes. [48] [54] [55] [56] These morbid events occur more often following prolonged periods of excessively frequent cuff inflation/deflation cycling, resulting in local trauma or impaired distal limb perfusion. Other factors that may contribute include cuff misplacement across a joint or repeated attempts to determine blood pressure in the presence of an artifact-producing condition, such as involuntary muscle tremors. [57] Caution should be exercised when using these monitors in patients with depressed consciousness, preexisting peripheral neuropathies, arterial or venous insufficiency, or irregular cardiac rhythms. [54]

Automated Continuous Techniques

In the past, continuous blood pressure monitoring required direct arterial cannulation. Advances in microprocessor and servomechanical control technology have enabled noninvasive techniques to provide a reasonable representation of the arterial pressure waveform and a nearly continuous assessment of blood pressure. The most widely investigated of these devices measures finger blood pressure using a servoplethysmomanometer, designed and first reported by Penaz in 1973. [58]

In essence, the finger blood pressure device uses an *arterial volume-clamp* method. It consists of a small cuff secured around the middle phalanx of a finger or the base of the thumb. The inflatable, flexible cuff contains an infrared photoplethysmograph. The cuff and photoplethysmograph are linked through a sophisticated servocontrolled mechanism housed within a small box that is strapped to the wrist. The plethysmograph continually measures the size (i.e., diameter) of the digital arteries using transillumination. To begin monitoring, a "locking" calibration procedure is performed by varying cuff pressure to establish the vessel size at which oscillometric pressure variation is maximal. As noted, this corresponds to MAP. An electromechanical feedback loop is then established, and external pressure applied to the cuff is varied continuously to keep the measured vessel size constant at the set-point. Thus, cuff pressure tracks arterial pressure throughout the cardiac cycle and is displayed on the monitor screen as a continuous waveform. More detailed descriptions of this technology are readily available. [59] [60] [61] [62] [63]

Over the past 15 years, continuous noninvasive finger blood pressure measurement devices have undergone numerous clinical evaluations comparing their performance with direct arterial pressure measurements. [59] [60] [61] [62] [63] Many of these investigations have demonstrated small overall mean differences between finger and intra-arterial pressure meas-urements. However, as noted earlier, small overall mean pressure differences do not necessarily indicate good meas-urement agreement. In clinical practice, the frequency of major measurement errors may be the more relevant and important issue. For example, Smith et al [63] found that finger arterial spasm precluded accurate pressure measurement in 5 percent of patients. Gibbs et al [64] studied 20 patients during anesthesia for major surgery and reported that MAP measured from a finger cuff differed from direct arterial pressure values by more than 10 mm Hg in 30 percent of patients and more than 20 mm Hg in 5 percent of patients. Other investigations in patients undergoing thoracic [65] and vascular [66] surgery similarly have shown small

average pressure differences overall but large discrepancies in a significant number of individual patients.

In addition to the questionable accuracy of finger blood pressure measurement, other factors undoubtedly have limited more widespread application of this technology. Unlike direct invasive arterial blood pressure monitoring, indirect noninvasive pressure measurement does not provide access for blood sampling, which is a frequent requirement in the setting of continuous pressure monitoring. By definition, finger blood pressure monitoring records a distal arterial pressure, which tends to be lower than brachial arterial pressure in elderly patients with atherosclerosis and to be higher than brachial pressure in young patients, because of peripheral pulse wave amplification. Using sophisticated electronic processing techniques, Bos et al [67] demonstrated that the pulse wave shape and pressure values of the finger blood pressure signal could be corrected to resemble direct brachial artery pressure waveforms within the limits of accuracy described by the AAMI. However, these sophisticated algorithms have not yet been integrated into commercially available monitors. Because the "transducer" recording blood pressure with this method is the finger, the vertical height of the finger becomes an important determinant of the pressure recorded, just as transducer height is important with direct arterial pressure measurement (see later discussion). [63] Finally, the potential for circulatory impairment of the distal finger caused by the constantly inflated cuff has been a cause for concern. Gravenstein et al [68] demonstrated mild hypoxemia in the capillary blood of the fingertip during finger blood pressure monitoring. No adverse outcomes were noted in these study patients or in others in whom finger blood pressure measurement was performed for as long as 7 hours. [63] Despite the apparent safety of these devices for short-term use, it is not surprising that these considerations have limited more widespread clinical application of continuous finger blood pressure monitoring.

Other automatic and continuous techniques have been used to measure blood pressure noninvasively. One such device reconstructs an arterial pressure waveform from *arterial wall displacement* measurements, following an oscillometric calibration. Unfortunately, changes in arterial compliance affect the clinical performance of this instrument. [69] Because arterial pulse wave velocity depends on arterial blood pressure, another device uses *pulse transit time* as recorded from dual pulse oximeter probes placed on the ear and finger following oscillometric calibration from the contralateral arm. [70] This device has also performed poorly in clinical settings, with indirectly monitored blood pressures changing in an opposite direction from the direct intraarterial pressure more than 30 percent of the time. [70] A third method used for continuous noninvasive pressure monitoring is *arterial tonometry,* a version of applanation tonometry. [71] [72] [73] In brief, a superficial artery (usually the radial) is compressed and partially flattened against the underlying bone. This flattened arterial surface serves as a "transducer" for intravascular pressures acting perpendicularly against the vessel wall. An array of piezoelectric crystals positioned on the skin overlying this flattened portion of artery senses arterial pressure changes and translates them into a continuous arterial pressure waveform. The device is calibrated at intervals by cuff oscillometry from the upper arm. Early investigations suggested that the clinical performance of this device was better than other forms of continuous noninvasive pressure monitoring. [71] [72] Unfortunately, more recent clinical studies have identified limitations of this device in pediatric patients [74] and in patients receiving vasodilating drugs. [48] Like other automated, continuous noninvasive blood pressure techniques, arterial tonometry holds promise as a means of rapidly detecting changes in blood pressure. However, in terms of absolute accuracy of blood pressure measurement, intermittent oscillometry appears to be superior to radial artery tonometry. It remains unclear whether any noninvasive technique will significantly reduce the need for direct arterial pressure monitoring or whether these methods will replace automated intermittent oscillometry as the standard noninvasive blood pressure monitoring method in anesthesia and critical care.

Direct Measurement of Arterial Blood Pressure

Arterial cannulation with continuous pressure transduction and waveform display remains the accepted standard for blood pressure monitoring. Although direct blood pressure measurement is more costly, has the potential for more complications, and requires more technical expertise to initiate and maintain compared with noninvasive monitoring, this technique is selected in many patients undergoing anesthesia. Indications for and advantages of direct arterial blood pressure measurement can be considered to fall into five major categories:

1. *Arterial blood sampling.* When frequent samples ofarterial blood are required, an arterial catheter provides reliable vascular access and obviates the need for multiplearterial punctures. New clinical devices allow continuous monitoring of arterial blood gas values using fiberoptic sensors placed directly into the artery through the vascular catheter. [75] [76] An alternative newer technology uses an automated, in-line sampling method for point of care *ex vivo* analysis of blood gases and chemistries. [77]
2. *Continuous real-time monitoring.* Direct arterial catheterization is chosen when rapid, moment-to-moment blood pressure changes are anticipated, and their immediate detection is considered to be a high priority. These changes in blood pressure might be expected when the patient has circulatory instability caused by an underlying medical condition, or when the planned operative procedure will cause large, sudden cardiovascular changes. Direct arterial monitoring is employed for many operative procedures in which major blood loss or fluid shifts are anticipated. The Australian Incident Monitoring Study of 1993 confirmed the superiority of direct arterial pressure monitoring over indirect monitoring techniques for the early detection of intraoperative hypotension. [78]
3. *Intentional pharmacologic or mechanical cardiovascular manipulation.* Direct arterial pressure monitoring is vital whenever the clinician expects to employ therapies that will cause major circulatory changes. Familiar examples include cardiac surgery with cardiopulmonary bypass, intra-aortic balloon counterpulsation, deliberate induced hypotension, major vascular surgery, and administration of vasoactive drug infusions.

4. *Failure of indirect blood pressure measurement.* The limitations of indirect blood pressure measurement are reviewed earlier in this chapter. Any cuff-based measurement techniques may prove impossible in some morbidly obese patients or those with burned extremities.
5. *Supplementary diagnostic clues.* Many diagnostic clues about the patient's condition may be derived from a critical analysis of the arterial pressure waveform. Fifty years ago, Eather et al [79] emphasized these diagnostic insights in a paper that introduced and promoted direct monitoring of "arterial pressure and pressure pulse contours" in anesthetized patients. Some of these diagnostic insights are readily apparent and commonly sought, such as identification of the arterial pressure dicrotic notch to guide proper timing for intra-aortic balloon counterpulsation. Careful analysis of the arterial pressure waveform can provide many additional subtle pathophysiologic insights. [80] Some important examples appear at the end of this section.

Percutaneous Radial Artery Cannulation

Several peripheral arteries are available for percutaneous cannulation, but radial artery pressure monitoring is most common in anesthesia and critical care. It is technically easy to perform and rarely associated with complications, owing to good collateral circulation of the hand. [81] Slogoff et al [82] described 1,700 cardiovascular surgical patients who underwent radial artery cannulation without ischemic complications, despite evidence of radial artery occlusion after decannulation in more than 25 percent of patients. Serious complications after radial artery cannulation are extremely rare in the absence of contributing factors, such as preexisting vasospastic arterial disease, previous arterial injury, protracted shock, high-dose vasopressor administration, prolonged cannulation, or infection. [83] [84] Like any procedural skill, percutaneous arterial cannulation is best learned by observing and emulating the methods of more experienced professionals. From the various elements of this collected array of techniques, the clinician should settle on a method that produces greatest overall personal success.

Before attempting radial artery cannulation, many clinicians assess the adequacy of collateral flow to the hand by performing a modified Allen test. This bedside examination, originally described by E.V. Allen in 1929, [85] provided a technique to assess arterial stenosis in the hands of patients with thromboangiitis obliterans. To perform the Allen test, the examiner compresses the radial and ulnar arteries and asks the patient to make a tight fist to exsanguinate the palm. As the ulnar occlusion is released, the color of the open palm is observed. Normally the palm will have a striking flush in several seconds; severely reduced ulnar collateral flow is present when the palm remains pale for more than 10 seconds.

Although the Allen test is meant to identify patients at high risk for ischemic complications from radial artery catheterization, the predictive value of this test has been questioned. Many reports reviewing permanent ischemic sequelae noted normal Allen tests prior to catheterization. [83] [86] [87] [88] In contrast, numerous radial cannulations performed despite abnormal Allen test results have not produced ischemic complications. [82] [89] [90] Allen tests of radial artery patency bore no relationship to distal blood flow assessment by fluorescein dye injection [91] or photoplethysmography. [92] Although it is obviously of great importance that the clinician minimize the chances of significant distal ischemia from arterial pressure monitoring, it appears that the Allen test cannot be relied on to predict this adverse outcome.

The following technique is offered as one method for consistent, successful radial artery cannulation (Fig. 30-4) . The wrist and hand are immobilized in mild dorsiflexion and secured with the wrist resting across a soft pad, folded towel, or stack of sponges. The course of the radial artery at the wrist is identified by gentle palpation. After sterile preparation of the skin, local anesthetic solution (typically 1% lidocaine) is injected intradermally and subcutaneously alongside the artery, using a 25- or 26-gauge needle. Generous local anesthetic infiltration not only ensures that the procedure is pain free, but it may also reduce vessel spasm at the time of arterial puncture. A small nick is placed in the skin at the intended puncture site with a #11 surgical blade or large hypodermic needle. This serves to prevent "burring" of the catheter tip as it passes through tough skin.

Next, the arterial catheter is checked for frictionless movement over the needle. Many catheters come encased in a plastic sleeve that should be inserted into the needle hub to serve as a reservoir for the blood that pulses out when the artery is entered. Alternatively, a 3-mL syringe with the plunger removed should be used as a blood reservoir. Although a 20-gauge Teflon catheter is the most common one used for radial artery cannulation, the size (20- or 18-gauge) and composition (Teflon or polypropylene) of the catheter seem to have little influence on the frequency of complications. [82] The catheter is advanced toward the palpated artery at a comfortable angle for the operator, generally 30 to 45 degrees. The needle tip is often perceived to be piercing the artery, but successful puncture is confirmed by identifying a "flash" of arterial blood flow into the needle hub and reservoir.

Because the needle always protrudes slightly beyond the tip of the catheter, the needle tip is the only portion of the needle-catheter assembly that is certainly within the arterial lumen when the flash of blood is first identified. To ensure that the catheter enters the vessel lumen, the clinician must lower the angle and advance the entire needle-catheter assembly a few millimeters (see Fig. 30-4) . If blood continues to flow into the needle reservoir, it is certain that the needle and catheter are both within the lumen of the radial artery, and the catheter alone can now be advanced gently its full length into the artery. Failure to recognize that the needle is the leading edge of the needle-catheter assembly is responsible for most technical failures by inexperienced operators. The novice often attempts to advance the catheter into the radial artery when only the needle tip has entered the lumen. The catheter then "fails to thread" because it has not yet entered the radial artery. One should never try to advance the catheter unless blood is flowing into the collecting reservoir, thereby confirming that the catheter tip is within the arterial lumen.

Once the catheter is fully advanced into the vessel lumen, occlusive pressure is held transiently on the proximal artery

Figure 30-4 Percutaneous radial artery cannulation. (A) The wrist is positioned and the artery identified by palpation. (B) The catheter-over-needle assembly is introduced through the skin and advanced toward the artery. (C) Entry of the needle tip into the artery is identified by the flash of arterial blood in the needle hub reservoir. (D) Needle-catheter assembly is advanced at a lower angle to assure entry of the catheter tip into the vessel. (E) If blood flow continues into the needle reservoir, the catheter is advanced gently over the needle into the artery. (F) The catheter is attached to pressure monitoring tubing while maintaining proximal occlusive pressure on the artery. See text for greater detail.

to limit blood loss, and the needle is removed. A narrow bore, low compliance pressure tubing is then fastened to the catheter, an appropriate sterile dressing is applied, and the apparatus is taped securely or sutured to the wrist.

If the needle punctures the back wall of the artery, it is not a grievous error as long as the operator recognizes this by observing that blood no longer enters the needle reservoir (Fig. 30-5) . In fact, some clinicians choose the "transfixion" technique, in which both the front and back walls of the artery are punctured intentionally, the needle is removed from the catheter, and the catheter is pulled back into the vessel lumen. Although it is unnecessary to place an additional hole in the back wall of the radial artery for successful cannulation, technique per se does not appear to influence the incidence of postcannulation arterial thrombosis. [90] [93] [94]

When blood flow into the needle reservoir ceases, it is

Figure 30-5 Salvaging arterial cannulation (I). (A) When blood flow into the needle reservoir ceases, the needle tip has exited the vessel lumen. (B) The needle tip is withdrawn several millimeters so that the catheter tip becomes the leading edge of the needle-catheter assembly and arterial blood flow reappears in the collection reservoir. (C) When arterial blood flow is reestablished, the catheter is advanced into the arterial lumen.

easy to salvage the procedure if one considers the two most likely explanations and acts accordingly. Either the needle tip alone or both the needle and catheter tips have pierced the back wall of the artery, and one can easily determine which has occurred. At this point, even though blood flow into the collection reservoir has stopped, one should not withdraw the entire needle-catheter assembly. Instead, the needle alone should be retracted several millimeters into the catheter, thereby making the catheter tip the "leading edge." If arterial blood flow reappears in the collection reservoir, the catheter tip evidently has remained in the vessel lumen, and the catheter now may be advanced fully (see Fig. 30-5) . Conversely, if retraction of the needle into the catheter fails to restore blood flow into the collection reservoir, the catheter is pulled back slowly until pulsatile blood flow reappears, and then the catheter is advanced into the artery (Fig. 30-6) . The key point is for the operator to note at all times whether the needle tip or the catheter tip is the leading edge of the assembly.

If one is unsuccessful in passing the catheter, repeated attempts can be made, but excessive punctures of the artery will increase the risk of hematoma, damage to the vessel wall, and loss of radial artery flow. If the catheter appears to be in the lumen of the artery, but there is difficulty in advancing further into the vessel, a sterile guide wire may be passed through the catheter into the artery to aid insertion (Fig. 30-7) . Some arterial cannulation kits have integrated needle-guide-wire-catheter assemblies for this purpose. When these devices are employed, the needle tip is introduced into the artery, the wire is inserted through the needle, and then the catheter is inserted over the guide wire (Fig. 30-8) . Although some authors have suggested that guide-wire-based techniques will improve arterial cannulation success rate in some patients, [95] it appears that success is more a function of operator experience and personal preference. [96]

Alternative Arterial Pressure Monitoring Sites

If the radial arteries are unsuitable for pressure monitoring, several alternative cannulation sites are available. The *ulnar artery* is cannulated using a technique much like that described for the radial artery. Even in circumstances in which previous attempts to cannulate the ipsilateral radial artery have failed, the ulnar artery may be cannulated safely. [82] However, adequacy of collateral flow from the radial artery to the hand should be established prior to this procedure with a modified Allen test in which one releases radial artery occlusion, maintains ulnar artery compression, and observes restoration of flow to the hand. Although *brachial artery* cannulation does not have the anatomic benefit of the collateral circulation present at the wrist, some investigators have confirmed the safety of this cannulation site. [97] [98] Bazaral et al [99] reported the use of more than 3,000 brachial artery catheters in patients undergoing cardiac surgery over a 3-year period, with only one patient requiring a postoperative thrombectomy and no untoward sequelae. A slightly longer catheter is preferred for the brachial site, owing to the need for the catheter to traverse the elbow joint. Other small peripheral arteries occasionally chosen for pressure monitoring include the *dorsalis pedis, posterior tibial,* and *superficial temporal arteries.* The dorsalis pedis and posterior tibial arteries form the same collateral circulation to the foot that the radial and ulnar arteries provide to the hand. However, this anatomic safety feature is more theoretical than real in older adults because of the high incidence of lower extremity vascular

Figure 30-6 Salvaging arterial cannulation (II). (A) When blood flow into the needle reservoir ceases, both the needle tip and catheter tip may have exited the vessel lumen. (B) The needle tip is withdrawn several millimeters so that the catheter tip becomes the leading edge of the needle-catheter assembly. (C) If arterial blood flow does not reappear in the collection reservoir, the entire needle catheter assembly is now withdrawn, allowing the catheter tip to reenter the vessel as the leading edge. This is confirmed by the reappearance of arterial blood flow in the collection reservoir. (D) When arterial blood flow has been reestablished, the catheter is advanced into the arterial lumen.

disease in many of these same patients who require direct arterial pressure monitoring. Consequently, successful clinical experience using these smaller peripheral arteries for pressure monitoring has been reported predominantly in children. [100]

Axillary artery monitoring provides another site for long-term pressure monitoring. Advantages include patient comfort and mobility and access to a central arterial pressure waveform. Complications appear to be infrequent. [101] [102] A wire-guided catheterization technique and a longer indwelling catheter may improve the success rate of axillary cannulation. Clinicians should be aware, however, that the risk of cerebral embolization is increased when using more centrally located catheters. The *femoral artery* is the largest artery commonly selected for pressure monitoring and appears to have a safety record comparable with that of other sites. [103] As with axillary arterial pressure monitoring, the femoral artery waveform more closely resembles aortic pressure than waveforms recorded from peripheral sites. Although the risk of distal ischemia may be reduced because of the large luminal diameter of the artery, infectious complications may occur more often with femoral than with radial artery catheters. [102] [104] Catheterization of the femoral artery is best achieved with a guide-wire technique, much like the procedure for central venous cannulation. The operator must be careful to puncture the femoral artery below the inguinal ligament, thereby limiting the risk of catastrophic complications, such as uncontained hemorrhage, into the pelvis or peritoneum. [105] [106]

Choosing the Site for Arterial Pressure Monitoring

Several factors influence the choice of site for arterial pressure monitoring, even though the radial artery of the nondominant hand is usually preferred for most applications. One important consideration is whether significant regional differences in blood pressure exist. Frank et al [107] demonstrated that 21 percent of patients undergoing peripheral vascular surgery had a blood pressure difference between the two arms that exceeded 20 mm Hg. In view of the prevalence of this problem, when the blood pressure is lower in one arm than the other, or when the pulses are weaker on one side, one should never select the side with the weaker pulse, because the blood pressure from this site will likely underestimate aortic pressure. [107] Clearly, evidence for abnormal collateral

Figure 30-7 Using a guide wire to aid arterial cannulation. (A) A catheter may not thread into a tortuous artery. (B) The needle is removed from the catheter, and a guide wire is advanced through the catheter into the artery. (C) The catheter is advanced over the guide wire into the arte-rial lumen.

flow in one hand but not the other would be another important reason to select the more normal side.

Several surgical and anatomic considerations also influence the site of arterial pressure monitoring. Regional arte-rial pressure gradients caused by atherosclerosis, arterial dissection, and embolism preclude monitoring from the affected sites, because the true central aortic pressure may be underestimated significantly. Unusual patient positions during surgery may produce regional arterial compression, and surgical retraction, particularly during cardiothoracic operations,

Figure 30-8 Arterial cannulation using an integrated needle-guide-wire-catheter assembly. (A) The artery is identified by a flash of arterial blood into the collection reservoir as the needle tip enters the vessel. (B) The guide wire is advanced through the needle into the vessel lumen. (C) The catheter is advanced over the guide wire.

can produce local vascular compression. [53] [108] The nature of the operative procedure is another important determinant of the appropriate site for arterial pressure monitoring. Operations requiring placement of a proximal thoracic aortic cross-clamp may interrupt arterial flow to the left subclavian artery and its tributaries in the left arm, as well as branches of the aorta beyond the clamp. In these cases, blood pressure monitored from the right arm best estimates aortic root pressure and carotid arterial pressure and is used to

guide anesthetic management. In addition, pressure may be monitored simultaneously from a femoral artery in an attempt to estimate perfusion pressure to vital organs distal to the aortic cross-clamp.

Various pathophysiologic disturbances will produce generalized arterial pressure gradients in the body and thus should be considered when choosing a site for arterial pressure monitoring. Large differences between peripheral and central arterial pressures may be seen in patients with shock. [30] Femoral artery systolic pressure may exceed radial artery systolic pressure by more than 50 mm Hg in septic patients receiving high-dose norepinephrine infusions, an observation that has significant therapeutic implications for the management of critically ill patients. [109] Other vasoactive drugs, anesthetics (particularly neuraxial block), and changes in patient temperature produce pressure gradients that alter the relation between central and peripheral arterial pressure measurements. [48] During hypothermia, thermoregulatory vasoconstriction causes radial arterial systolic pressure to exceed femoral artery systolic pressure. [110] Conversely, during rewarming, vasodilation reverses this gradient and causes radial artery pressure to underestimate femoral artery pressure. [110] This phenomenon is observed daily in cardiac surgical patients who are rewarmed rapidly at the termination of cardiopulmonary bypass (Fig. 30-9) . Numerous investigations have documented that the radial arterial pressure underestimates central aortic pressure in these patients, often by more than 20 mm Hg. [48] [111] [112] [113] [114] [115] [116] These pressure differences persist after bypass for several minutes in most patients, usually resolve within an hour, and should be considered when one uses the radial artery pressure to guide treatment in this setting. Its mechanism is still unresolved. [48] [117] Some investigators believe that the lower radial arterial than central arterial pressure results from vasodilation and decreased resistance in the forearm and hand vasculature during rewarming. [111] [113] [114] [115] [116] Others have demonstrated that the gradient arises because of radial artery

Figure 30-9 Arterial pressure gradients following cardiopulmonary bypass. (A) Femoral and radial artery pressure traces recorded 2 minutes after bypass (2 min postbypass), when radial artery pressure underestimates the more centrally measured femoral artery pressure and 30 minutes later (30 min postbypass), when radial and femoral arterial pressures have been equalized and radial pressure has assumed a more typical morphology. Note that dicrotic notch (arrows) is visible in the femoral pressure trace after bypass, but not initially in the radial pressure trace. (B) Femoral and radial artery pressure traces recorded before cardiopulmonary bypass (prebypass), two minutes following bypass (2 min postbypass), and 30 minutes following bypass (30 min postbypass). Note changing relationship between femoral and radial artery pressure measurements at these different times. See text for greater detail.

vasoconstriction, which begins shortly after aortic cross-clamping. [48] [118] Finally, one must recognize that even under normal circumstances, the arterial pressure waveform changes its morphology as it is transmitted through the vascular tree, resulting in a wider pulse pressure recorded from a peripheral artery than from a more central location. [119] [120] These normal physiologic differences in arterial pressure recorded from different sites should be considered whenever direct arterial pressure monitoring is performed.

Complications of Direct Arterial Pressure Monitoring

The widespread application of invasive arterial pressure monitoring in anesthesia and intensive care is related, no doubt, to the extremely good safety record of this technique. Large clinical investigations confirm the low incidence of long-term complications following radial artery cannulation, in particular, the small risk of distal ischemia, which is likely in the range of 0.1 percent or less. [81] [82] Despite suggestions in the literature that catheter size and composition influence the frequency of arterial thrombosis, it is unlikely that these factors are important determinants of clinical complications. [82]

The Australian Incident Monitoring Study provides some noteworthy recent observational data describing the incidence and types of complications of blood pressure monitoring. [78] [121] Of 2,000 untoward clinical events reported in this investigation, only 13 related to peripheral arterial cannulation, fewer than the number associated with central venous or peripheral venous cannulation (18 and 33 incidents, respectively). [121] Five of these 13 cases involved equipment faults or misassembly; in three cases, the arterial line was mistaken for an intravenous line and used for drug injection; in three cases, the arterial line was either disrupted or kinked; in one case, a fragment of guide wire was broken off inside the patient; and in only one instance did transient vasospasm follow radial artery cannulation. [121] A second report from this study, which focused entirely on blood pressure monitoring, noted that direct pressure monitoring failed or gave misleading results in ten instances, including five in which there was either incorrect calibration, incorrect interpretation of the pressure display, or unrecognized subclavian artery stenosis. [78]

Certain clinically relevant conclusions can be drawn from these data. First, it is striking that many if not most of the complications from direct arterial pressure monitoring can be attributed to equipment misuse. This serves to highlight the importance of proper operator knowledge, training, and experience in ensuring patient safety. Second, it is vital to have a system for the manual determination of blood pressure readily available at all times. The clinician should have a low threshold to measure the blood pressure manually and from a different site, particularly when the results of invasive pressure monitoring do not match the patient's general clinical appearance.

In summary, serious complications, although rare, do occur following arterial cannulation. Reports describe retained guide wires requiring surgical extraction, [122] fatal hemorrhage following difficult femoral artery cannulation, [105] and upper extremity compartment syndrome following brachial artery cannulation. [123] In almost all cases, however, there were technical problems during catheter placement or confounding medical problems, such as shock or coagulopathy. Infectious complications are increasingly rare now that disposable transducers have replaced reusable ones. Because retrograde arterial embolism is possible whenever forceful flushing of a peripheral arterial catheter is performed, [124] special care should be exercised whenever more centrally located arterial catheters are used, including those in the superficial temporal artery, axillary artery, or aorta, when monitoring from the central lumen of an intra-aortic balloon pump.

Technical Aspects of Direct Blood Pressure Measurement

Direct measurement of arterial blood pressure requires that the original pressure waveform from the cannulated artery be reproduced accurately on the bedside monitor. Not surprisingly, the displayed pressure signal is influenced by the system plumbing, including the arterial catheter, extension tubing, stopcocks, flush devices, transducer, amplifier, and recorder. Consequently, it is very important to appreciate how the monitoring system may influence the contour of the pressure waveform, as well as the displayed values for systolic and diastolic blood pressure. [55] [125] [126]

Direct pressure monitoring systems used in the operating room and intensive care units are described as *underdamped second-order dynamic systems.* [125] [127] Other authors have provided detailed technical descriptions of the underlying physical principles. [125] [128] [129] [130] Briefly, fluid-filled, catheter-transducer monitoring systems may be modeled after simple mass-spring systems. [128] Intuitively, when the mass at the end of a spring is displaced and then released, a characteristic simple harmonic motion is observed. Clinical pressure monitoring systems exhibit similar physical behavior. This behavior depends on three characteristic physical properties: elasticity, mass, and friction. These three properties determine the system operating characteristics, termed the *frequency response* or *dynamic response,* which in turn is characterized by two important system parameters, *natural frequency* (f_n, omega) and *damping coefficient* (zeta , *Z,* alpha , *D).* Natural frequency describes how rapidly the system oscillates, and the damping coefficient describes how rapidly it comes to rest. Natural frequency and damping coefficient are relatively easy to measure and dramatically influence the appearance of the recorded pressure waveform. Before describing how these parameters can be measured in clinical practice, it is useful to consider why they are important.

Frequency Content of the Arterial Pressure Waveform

The arterial blood pressure waveform is a periodic complex wave, which can be reproduced by Fourier analysis, a technique that recreates the original complex pressure wave by summing a series of simpler sine waves of various amplitudes and frequencies. [126] [131] The original pressure wave has

Figure 30-10 (Figure Not Available) Arterial blood pressure waveform produced by summation of sine waves. The fundamental wave (top) added to 63% of the second harmonic wave (middle) results in a pressure wave (bottom) that resembles an arterial blood pressure waveform (box). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 9-1.)*

a characteristic periodicity termed the *fundamental frequency,* which is equal to the pulse rate. Note that the pulse rate is reported in beats per minute, whereas the fundamental frequency is reported in cycles per second or Hertz (Hz). For example, a pulse rate of 60 beats/min equals 1 beat/s or 1 cycle/s or 1 Hz.

The sine waves that sum to produce the complex wave have frequencies that are multiples or *harmonics* of the fundamental frequency. A crude arterial waveform, which displays a systolic upstroke, systolic peak, dicrotic notch, and so forth, can be reconstructed with reasonable accuracy from two sine waves, the fundamental frequency and the second harmonic (Fig. 30-10) (Figure Not Available) . If the original arterial pressure waveform contains high-frequency components such as a steep systolic upstroke or other sharp details, higher frequency sine waves (and more harmonics) are needed to provide a faithful reconstruction of the original pressure waveform. As a general rule, six to ten harmonics are required to provide adequate reproduction of most arterial pressure waveforms, [131] [132] Hence, accurate blood pressure measurement in a patient with a pulse rate of 120 beats/min (2 cycles/s or 2 Hz) requires a monitoring system dynamic response of 12 to 20 Hz. Clearly, the faster the heart rate and the steeper the systolic pressure upstroke, the greater will be the dynamic response that is required from the monitoring system. As a corollary, venous pressure waveforms, which generally do not have steep waves or high frequency components, do not require monitoring systems with such high frequency responses.

Natural Frequency and Damping Coefficient

If the monitoring system has a natural frequency that is too low, frequencies in the monitored pressure waveform will approach the natural frequency of the measurement system. As a result, the system will resonate, and pressure waveforms recorded on the monitor will be exaggerated or amplified versions of true intra-arterial pressures (Fig. 30-11) (Figure Not Available) .

Figure 30-11 (Figure Not Available) Underdamped arterial pressure waveform. Systolic pressure overshoot and additional small, nonphysiologic pressure waves (arrows) distort the waveform and make it hard to discern the dicrotic notch (boxes). Digital values displayed for direct arterial blood pressure (ART 166/56, mean 82 mm Hg) and noninvasive blood pressure (NIBP 126/63, mean 84

mm Hg) show the differences in pressure measurement that arise because of an underdamped arterial pressure waveform. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 9-4.)*

This phenomenon is the familiar arterial pressure waveform that displays *overshoot, ringing,* or *resonance.* Tachycardia and steep systolic pressure upstrokes present the greatest challenge for clinical monitoring, because the higher frequency contents of these waveforms more likely approach the resonant frequency of the measurement system.

The bedside monitoring system must not only have a sufficiently high natural frequency, but it must also have an adequate damping coefficient. The *overdamped* arterial pressure waveform has a slurred upstroke, absent dicrotic notch, and loss of fine detail. Severely overdamped pressure waves display a falsely narrowed pulse pressure, although the MAP value may remain reasonably accurate (Fig. 30-12) (Figure Not Available) . In contrast, *underdamped* pressure waveforms display systolic pressure overshoot and contain additional artifacts that are produced by the measurement system but not part of the original intravascular pressure waveform (see Fig. 30-11) (Figure Not Available) . It is a mistake to attach physiologic significance to these small waves or artifacts, because they are produced by an underdamped monitoring system that continues to ring or oscillate abnormally in response to the input pressure signal.

Adequate Dynamic Response

With a basic understanding of natural frequency and damping, the way in which these two parameters interact in a monitoring system to produce the observed waveforms can be considered. Most catheter-tubing transducer systems are underdamped but have an acceptable natural frequency that exceeds 12 Hz. If the system natural frequency is lower than 7.5 Hz, the pressure waveform may be distorted, and damping adjustment cannot make the monitored waveform resemble the original waveform adequately. [55] [125] Conversely, if

Figure 30-12 (Figure Not Available) Overdamped arterial pressure waveform. The overdamped pressure waveform (A) shows a diminished pulse pressure compared to the normal waveform (B). The slow speed recording below demonstrates a 3-minute period of damped arterial pressure. Despite the damped pressure waveform, mean arterial pressure remains unchanged during this period. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 9-3.)*

natural frequency can be increased sufficiently (e.g., 24 Hz), damping will have minimal effect on the monitored waveform, and faithful reproduction of intravascular pressure is achieved more easily (Figs. 30-13 (Figure Not Available) and 30-14) (Figure Not Available) . In other words, *the lower the natural frequency of the monitoring system, the more narrow will be the range of damping coefficients that can be tolerated to ensure faithful pressure wave reproduction or adequate dynamic response.* For example, if the monitoring system natural frequency is 10 Hz, the damping coefficient must be between 0.45 and 0.6 for accurate pressure waveform reproduction. In this situation, too low a damping coefficient causes the system to be underdamped, to resonate, and to produce a factitiously elevated systolic blood pressure. In contrast, too high a damping coefficient produces an overdamped system, in which systolic pressure is falsely decreased and fine detail in the pressure trace is lost.

In summary, a pressure monitoring system will have optimal dynamic response if its natural frequency is as high as possible. In theory, this is achieved best by limiting the length of tubing and using only stiff tubing that is designed for pressure monitoring. Normal intravenous extension tubing should not be used because it is too compliant and will cause the monitoring system to have too low a natural frequency and be excessively damped. Blood clots and air bubbles contained within the tubing-stopcock transducer plumbing will adversely affect the dynamic frequency response in a similar fashion. These clots and bubbles are often trapped and concealed in stopcocks and other connection points, so it is best to keep the monitoring system simple with the fewest components necessary.

Because clinical pressure monitoring systems are typically underdamped and display some degree of systolic pressure overshoot, some clinicians may attempt to increase the damping in the system by introducing a small air bubble into the monitoring tubing line. There are several problems with this approach. First, placing an air bubble in the line exposes

Figure 30-13 (Figure Not Available) Interaction between damping coefficient (D) and natural frequency (f_n) in pressure waveform recordings. (A) Underdamped pressure waveform (f_n 10 Hz, D 0.1) displays small artifactual waves and systolic pressure overshoot. (B) A small increase in D (0.2) diminishes these artifacts. (C) Critical damping (D 0.4) provides an accurate pressure waveform, even though f_n remains low. (D) Overdamping results in loss of fine detail and precludes determination of f_n or D. (E) Increased f_n (20 Hz) allows a low D (0.1) to have minimal impact on waveform morphology. Notice the similarities between waveforms (C) and (E). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 9-7.) (Figure Not Available)*

the patient to the risk of arterial air embolism and the potential for retrograde flushing of the air bubble into the cerebral circulation. [124] Second, the "proper" size for the air bubble is not known. Too large a bubble will overdamp the system, distort the pressure waveform, and decrease systolic blood pressure artifactually. The third reason for avoiding air bubbles is somewhat counterintuitive but equally important. A small air bubble not only increases system damping, but it simultaneously lowers natural frequency. Consequently, resonance in the system may increase paradoxically, and systolic pressure overshoot may worsen. In this example (Fig. 30-15) (Figure Not Available) , a 0.1-mL air bubble markedly dampens the system but lowers natural frequency and causes an artifactual 25 mm Hg increase in systolic pressure.

As an alternative to placing air bubbles in the monitoring system, devices can be added to increase damping without lowering natural frequency (see Fig. 30-13) (Figure Not Available) . [125] To be more precise, these devices actually work through *impedance matching,* which eliminates wave reflections and prevents resonance in the monitoring system. The theoretical basis by which these devices work is beyond the scope of this chapter but is well described by other authors. [125] [128] [130] Although use of these devices in monitoring systems has been advocated by some, [125] others have highlighted the limitations of

Figure 30-14 (Figure Not Available) Interaction between damping coefficient and natural frequency. Depending on these two system parameters, catheter tubing- transducer systems fall into one of five different dynamic response ranges. Systems with an optimal dynamic response will record faithfully the most demanding pressure waveforms, whereas those with adequate dynamic response will record accurately most pressure waveforms seen in clinical practice. Overdamped and underdamped systems introduce artifacts characteristic of these technical limitations. Systems with a natural frequency less than 7 Hz are considered unacceptable. The rectangular cross-hatched box indicates the ranges of damping coefficients and natural frequencies commonly encountered in clinical pressure measurement systems. The point within the box shows the mean values of 30 such systems recorded by Schwid. [134] See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 9-6 (Figure Not Available) , 9-8 (Figure Not Available) , and 9-11.)*

these devices, including the inability to adjust or tune the monitoring system to provide the most accurate *in vivo* pressure recordings. [48] [130]

Clinical Measurement of Natural Frequency and Damping Coefficient

Although it may be preferable to limit the length of pressure monitoring tubing to optimize the system's dynamic response, this may not be possible in clinical practice. Thus, it becomes important to be able to assess the amount of distortion existing in the monitoring system in clinical use. The method used most often to evaluate the dynamic response of the monitoring system is the *fast flush test.*[125] [127] Under most conditions, this method yields results that are essentially identical to those from the standard laboratory square-wave testing. [133] The fast flush method has several practical advantages. It can be performed at the bedside without additional equipment beyond the normal monitors and recorders, and it tests the entire monitoring system, from catheter tip to transducer. [55] [125] [127]

To perform this test, the fast flush valve is opened briefly several times, and the resulting flush artifact is examined. Monitoring system natural frequency is related to the time period or distance between two successive oscillation cycles. An example is illustrated (Fig. 30-16) (Figure Not Available) , where the distance between two cycles is 1.7 mm at a recorder speed of 25 mm/s (standard ECG speed). Natural frequency is then easily calculated: 1 cycle/1.7 mm × 25 mm/s = 14.7 cycles/s or 14.7 Hz. Note that the distance between successive oscillation

Figure 30-15 (Figure Not Available) Effect of small air bubbles within arterial pressure monitoring systems. Arterial pressure waveforms are displayed, along with superimposed fast flush square-wave artifacts. (A) Original monitoring system has an adequate dynamic response (natural frequency 17 Hz, damping coefficient 0.2). (B) A small 0.1-mL air bubble added to the monitoring system produces a paradoxic increase in arterial blood pressure. Note decreased natural frequency of the system. (C) A larger 0.5-mL air bubble further degrades dynamic response and produces spurious

arterial hypotension. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 9-14.)*

cycles (i.e., cycles 1 to 2, 2 to 3) should be identical, because this is a fundamental characteristic of the measurement system--its natural frequency. Furthermore, *the tighter the oscillation cycles, the higher the natural frequency will be.* To measure natural frequency most accurately, a fast recording speed should be chosen (e.g., 50 mm/s), several flush cycles should be examined, and an average value calculated.

The damping coefficient is determined from the flush artifact by measuring the amplitudes of successive oscillation cycles. The amplitude ratio so derived indicates how quickly the measuring system comes to rest. *A low amplitude ratio corresponds to a high damping coefficient, or a system that comes to rest quickly. Conversely, a high amplitude ratio corresponds to a low damping coefficient, or a system that tends to resonate.* The damping coefficient can be calculated mathematically, but it is usually determined graphically from the measured amplitude ratio. [125] [129] In this example,

Figure 30-16 (Figure Not Available) Clinical measurement of natural frequency and damping coefficient. (A) Two square-wave fast flush artifacts interrupt an arterial pressure waveform recorded on standard 1-mm grid paper at a speed of 25 mm/sec. Natural frequency is determined by measuring the period of one cycle of adjacent oscillation peaks (1.7 mm). Damping coefficient is determined by measuring the heights of adjacent oscillation peaks (17 and 24 mm). From these measurements, a natural frequency of 14.7 Hz and an amplitude ratio of 0.71 may be calculated. See text for greater detail. (B) Relation between amplitude ratio and damping coefficient. The amplitude ratio determined in the fast flush test in (A) corresponds to a damping coefficient of 0.11. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 9-9 (Figure Not Available) and 9-10.) (Figure Not Available)*

the amplitudes of two successive oscillation cycles are 24 and 17 mm, respectively, giving an amplitude ratio of 17/24 or 0.71, which corresponds to a damping coefficient of 0.11 using the graphic solution shown (see Fig. 30-16) (Figure Not Available) . As in the case for measuring natural frequency, any two adjacent peaks may be used to determine the amplitude ratio, because the ratio of successive peaks should be relatively constant. Again, this is a fundamental characteristic of the measurement system--the damping coefficient.

Note that the monitoring system illustrated here has an adequate natural frequency of approximately 15 Hz but is notably underdamped, with a damping coefficient of 0.11. Consequently, this catheter-tubing-transducer system falls into the underdamped region illustrated in Figure 30-14 (Figure Not Available) , and one would expect to find systolic pressure overshoot in such a system.

Although the technical requirements for accurate blood pressure measurement are evident from the preceding considerations, it appears that these conditions are often unmet in routine clinical practice. Schwid [134] examined the frequency response of 30 radial artery catheter-transducer systems used in routine intensive care monitoring. Mean values (± standard deviation) for natural frequency (14.7 ± 3.7 Hz) and damping coefficient (0.24 ± 0.07) were worse than values typically reported for measurements made under laboratory conditions, falling instead in the underdamped response region reported by Gardner. [125] Furthermore, the range of frequency responses (10.2-25.3 Hz) and damping coefficients (0.15-0.44) measured in this setting suggests that distortion of the arterial waveform is common in clinical practice, with systolic arterial pressure overshoot resulting from a relatively underdamped system the most common problem. Figure 30-14 (Figure Not Available) shows these data from Schwid [134] in the format suggested by Gardner [125] and graphically highlights this situation.

Several practical points for direct pressure monitoring in daily clinical practice emerge from these technical considerations. First, in an attempt to optimize the dynamic response of the monitoring system, one should attempt to keep the catheter-tubing-transducer system as simple as possible, using the minimum length of tubing and number of stopcocks required for patient-care purposes. Second, one should know how the natural frequency and damping coefficient might be calculated using the fast flush method. One practical application is that this testing allows the clinician to distinguish true hypotension from an artifact that results from an overly damped system caused by a large air bubble or blood clot in the catheter or tubing (see Fig. 30-15) (Figure Not Available) . A third practical point regarding these technical considerations relates to the clinical interpretation of systolic arterial hypertension. Owing to the dynamic response limitations of most clinical pressure-monitoring systems, direct measurement of systolic arterial pressure often exceeds indirect noninvasive measurement, simply because of underdamping and resonance (see Fig. 30-11) (Figure Not Available) . [130]

Pressure Monitoring Systems

Arterial pressure monitoring systems have a number of components beginning with the intra-arterial catheter and including extension tubing, stopcocks, continuous flush device, pressure transducer, and bedside monitor with a waveform display screen. The flush device provides a continuous, slow (1-3 mL/h) infusion of saline to purge the monitoring system, which thereby prevents thrombus formation within the arterial catheter. Historically, a dilute concentration of heparin (1-2 units/mL saline) has been added to this flush solution to reduce further the incidence of thrombosis. [135] However, this practice may unnecessarily expose the patient to heparin and increase the risk of immune-mediated thrombocytopenia. [136] [137] The monitoring system also includes a spring-loaded valve that allows periodic, highpressure flushing to purge the extension line of blood after an arterial sample has been taken. The stopcocks in the system provide sites

for blood sampling and allow the transducer to be exposed to atmospheric pressure to establish a zero reference value.

Newer systems include "needle-less" sampling ports and in-line aspiration systems. These permit blood sampling without the use of sharp needles and allow the aspirated waste blood to be returned to the patient within a convenient closed system. Modifications such as these are intended to reduce the risk of needle injury and blood exposure to health-care workers, as well as to decrease waste of the patient's blood during sampling. However, these additional features may degrade the dynamic response of the monitoring system.

Transducer Setup: Zeroing, Calibrating, and Leveling

Prior to initiating patient monitoring, the pressure transducer must be zeroed, calibrated, and leveled to the appropriate position on the patient. The initial step in this process is to expose the transducer to atmospheric pressure by opening the adjacent stopcock to air, pressing the zero pressure button on the monitor, and thus establishing the zero pressure reference value. The transducer now has a reference--ambient atmospheric pressure--against which all intravascular pressures are measured. This process underscores the fact that all pressures displayed on the monitor are referenced to atmospheric pressure, outside the body. Although clinicians generally refer to "zeroing the transducer," actually the transducer is exposed to atmospheric pressure via an open stopcock affixed to the transducer. To be precise, it is this air-fluid interface at the level of the stopcock that is the zero pressure locus. This point must be aligned with a specific position on the patient to ensure the correct transducer level.

When a significant change in pressure occurs, the zero reference value should be rechecked prior to initiating therapy. [55] This can be accomplished quickly, by opening the stopcock and exposing the transducer to atmospheric pressure. The monitor should be inspected to ensure that the pressure trace overlies the zero pressure line on the display screen and the digital pressure value equals zero. Note that checking the zero value is different from establishing the zero reference, which is done at the beginning of the monitoring procedure. [138] If the stopcock is exposed to atmospheric pressure and pressure is not equal to zero, baseline drift of the transducer's electrical circuit may have occurred. This transducer drift is caused by problems with membrane dome coupling to the electronic pressure transducing elements, as well as other technical problems with the transducer, the attached electrical cable, or the monitor itself. [55] [139] [140] These technical problems appear to be uncommon now that high-quality disposable transducers are widely available. [141]

Historically, transducer calibration was the next step following the zeroing procedure. Calibration is an adjustment of system gain to ensure the proper response to a known reference pressure value. Traditionally, this has been performed using a mercury manometer as the standard. [55] Currently, however, disposable pressure transducers meet or exceed accuracy standards established by the AAMI and the American National Standards Institute. [141] Transducer calibration at the bedside thus appears to be unnecessary. By avoiding daily calibration, attendant serious risks of arterial air embolism and infection may be reduced. [141] In general, if a pressure transducer or monitoring cable is faulty, the initial zero value cannot be established, and the monitoring system must be changed. Rarely, despite successful zeroing, the recorded pressure values appear erroneous, and a malfunctioning pressure transducer, cable, or monitor must be suspected and replaced. [139] [140] [142]

The final step in transducer setup is leveling the pressure monitoring zero point to the appropriate position on the patient. In general, zeroing and leveling the

transducer are accomplished at the same time, prior to initiating patient monitoring. However, these are two distinct procedures. Zeroing exposes the transducer to ambient, atmospheric pressure via an open stopcock. Leveling assigns this zero reference point to a specific position on the patient's body.

In the supine patient, pressure transducers are leveled most often to the midchest position in the midaxillary line, [55] a site chosen because it is easy to estimate by eye and provides a reasonable approximation for the midpoint of the heart in the chest. Although precise location for the zero reference level is important for all pressure monitoring, it is critical for measurement of cardiac filling pressures. An error in arterial blood pressure measurement of 10 mm Hg is generally of minor clinical importance, but the same error in central venous pressure (CVP) or pulmonary artery wedge pressure (PAWP) may have major diagnostic implications.

Some investigators have questioned the use of the midchest position as an appropriate zero reference level. In addition, they suggest that experienced clinicians and researchers do not understand how hydrostatic pressure influences the measurement of pressure with fluid-filled catheter-transducer systems. [143] *The only factor that contributes to measured hydrostatic pressure with a fluid-filled catheter-transducer system is the level of the transducer relative to the uppermost fluid level in the chamber in which pressure is being measured.*[143] *It follows that to remove all such hydrostatic pressure influences, transducers should be leveled to the top of the fluid column in the chamber or vessel being measured.* For example, errors in measurement of left ventricular filling pressure up to 7 mm Hg occur when transducers are leveled to the midchest rather than to the top of the left ventricle. [143] Consequently, transducers used to measure pressures in the cardiac chambers or pulmonary artery are best positioned 5 cm below the left sternal border at the fourth intercostal space, to obviate the confounding influence of hydrostatic pressure. Because many critically ill or anesthetized patients have direct arterial pressure meas-ured along with other direct intravascular cardiac filling pressures, it seems prudent to use the same zero reference level for all direct pressure measurements.

In some circumstances, the clinician may choose to level the arterial pressure transducer at a different position on the body. During neurosurgical operations, performed with the patient in a seated position, the pressure transducer is often aligned with the patient's ear to approximate the level of the circle of Willis and better estimate cerebral perfusion pressure. The transducer should not need to be rezeroed by pushing the zero pressure button on the monitor, in that only the reference level has been altered. In fact, if zero is

Figure 30-17 (Figure Not Available) Effect of pressure transducer level on measurement of blood pressure. (A) In the supine patient, the same arterial blood pressure (ART) is measured at the level of the heart or the brain. (B) With the patient in the sitting position, blood pressure recorded from a transducer that remains at heart level (#1) will be unchanged, but blood pressure recorded from a transducer adjusted to the level of the brain (#2) will be lower by an amount equal to the hydrostatic pressure difference between these two transducer positions (20 cm H_2O, or approximately 15 mm Hg). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 9-19.)*

rechecked, it should be unchanged, regardless of transducer location, because atmospheric pressure changes little over the few inches of height alteration being considered in this situation. Arterial blood pressure now recorded at the level of the head will be lower than that recorded at the heart, the difference being precisely equal to the hydrostatic pressure difference between the head and the heart (Fig. 30-17) (Figure Not Available) . [138]

Often, pressure transducers are attached to an intravenous (IV) pole, and patient position is altered by adjusting the height of the operating room table or intensive care bed. A sudden change in blood pressure is noted and is attributable entirely to the change in transducer level in relation to patient position. Raising the patient above the transducer will produce spuriously high pressures, whereas lowering the patient below the transducer will produce spuriously low pressures. Again, the error introduced is exactly equal to the hydrostatic pressure difference between patient and transducer. Although these leveling artifacts are generally small relative to arterial blood pressure, they are of critical importance when measuring CVP or pulmonary artery pressure (PAP). However, on occasion, a pressure transducer will fall from its normal position and come to rest near the floor. In this instance, the blood pressure may be falsely elevated by nearly 80 mm Hg. Taping pressure transducers directly to the patient can obviate these types of level artifacts. Without question, the most common major mistakes in pressure monitoring involve failure to establish zero, failure to recheck the zero value for transducer drift, and failure to relevel the transducer appropriately when changes in patient position occur. [55]

A final example may help to understand the distinction between zeroing and leveling pressure transducers. Consider the difference between invasive blood pressure and NIBP measurement in a patient in the lateral position (Fig. 30-18) (Figure Not Available) . While the patient is supine, blood pressure is 120/80 mm Hg in both arms, as measured by noninvasive cuffs and direct indwelling radial artery catheters. The patient is now placed in the right lateral decubitus position, the left arm is 20 cm above the heart, and the right arm is 20 cm below the heart. The invasive blood pressure transducers remain leveled to the heart at the midthoracic position. Blood pressure measured in the left arm by cuff will be lower, that is, 105/65 mm Hg, because the left arm is 20 cm above the level of the heart, whereas blood pressure measured in the right arm by cuff will be higher, 135/95 mm Hg. However, blood pressure measured from either the left or right radial catheters will remain unchanged, 120/80 mm Hg, given that the reference level for zero pressure remains fixed at the midchest position. Indeed, if the arterial pressure transducers were attached to the arms, the zero reference levels for the transducers would have changed as the patient assumed the lateral position, and pressures recorded from right and left radial artery catheters would equal those recorded by the ipsilateral noninvasive cuffs.

Arterial Pressure Waveforms

Direct arterial pressure monitoring in anesthetized patients began more than 50 years ago. [79] In that early era, arterial pulse waveform analysis was noted to provide useful diagnostic information, but somewhat surprisingly, modern physicians pay little attention to the morphology and detail of the arterial pressure waveform. O'Rourke and Gallagher [144] attribute this change in practice to the reliance on cuff sphygmomanometry, which provides "numbers which came to be linked in a simplistic way to cardiac strength (systolic pressure) and arteriolar tone (diastolic pressure). Pseudoscience had arrived with (these) numbers.... Even when monitored directly in operating theatres and critical care areas, anesthetists and intensivists show little interest in the waveform and base their judgments on values of systolic, diastolic and mean pressure."

Because clinicians today benefit from the widespread availability of high resolution, multicolored monitor displays,

Figure 30-18 (Figure Not Available) Effect of patient position on the relation between direct arterial blood pressure (ART) and indirect noninvasive blood pressure (NIBP) measurements. (A) In the supine patient, pressures measured from the right (R) or left (L) arms by either technique will be the same. (B) In the right lateral decubitus position, ART pressures recorded directly from the right and left radial arteries will remain unchanged so long as the respective pressure transducers remain at heart level. However, NIBP will be higher in the dependent right arm and lower in the nondependent left arm. Differences in NIBP are determined by the positions of the arms above and below the level of the heart and are equal to the hydrostatic pressure differences between the level of the heart and the respective arm. A 20-cm difference in height produces a 15-mm Hg difference in pressure. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 9-22.) (Figure Not Available)*

renewed interest in waveform analysis should expand clinical monitoring capabilities. [80] Appreciation of the diagnostic clues provided by the direct arterial pressure waveform requires full understanding of normal waveform components, their relation to the cardiac cycle, and differences in waveforms recorded from different sites in the body.

The systemic arterial pressure waveform results from ejection of blood from the left ventricle into the aorta during systole, followed by peripheral arterial runoff of this stroke volume during diastole (Fig. 30-19) (Figure Not Available) . The systolic components follow the ECG R wave and consist of a steep pressure upstroke, peak, and decline and correspond to the period of left ventricular systolic ejection. The downslope of the arterial pressure waveform is interrupted by the dicrotic notch, then continues its decline during diastole following the ECG T wave, reaching its nadir at end-diastole. The dicrotic notch recorded directly from the central aorta is termed the *incisura* (from the Latin, *a cutting into*). The incisura is sharply defined and undoubtedly is related to aortic valve closure. [145] In contrast, the peripheral arterial waveform generally displays a later, smoother dicrotic notch that only approximates timing of aortic valve closure and depends more on arterial wall properties. [146] Note that the systolic upstroke of the radial artery pressure trace does not appear for 120 to 180 milliseconds after inscription of the ECG R wave (see Fig. 30-19) (Figure Not Available) . This interval reflects the sum of times required for spread of electrical depolarization through the ventricular myocardium, isovolumic left ventricular contraction, aortic valve opening, left ventricular ejection, transmission of the aortic pressure wave to the radial artery, and finally, transmission of the pressure signal from the arterial catheter to the pressure transducer.

The bedside monitor displays numeric values for the systolic peak and end-diastolic trough pressures. Measurement of mean pressure is more complicated and depends on the algorithm employed by the monitor. [147] In simplest terms, MAP is equal to the area beneath the arterial pressure curve divided by the beat period and

averaged over a series of consecutive heartbeats. Although MAP is often estimated as diastolic pressure plus one-third times the pulse pressure, this estimation can be misleading. At equivalent heart rates, narrow or thin arterial pressure waveforms spend more time at lower pressures, resulting in a low MAP, whereas wide or full arterial pressure waveforms spend more time at higher pressures, resulting in a higher MAP.

One of the most important features of the arterial pressure waveform is the phenomenon of distal pulse amplification. Pressure waveforms recorded simultaneously from different

Figure 30-19 (Figure Not Available) Normal arterial blood pressure waveform and its relation to the electrocardiographic R wave. (1) Systolic upstroke, (2) systolic peak pressure, (3) systolic decline, (4) dicrotic notch, (5) diastolic runoff, and (6) end-diastolic pressure. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 8-1.)*

Figure 30-20 (Figure Not Available) Distal pulse wave amplification of the arterial pressure waveform. Compared with pressure in the aortic arch, the more peripherally recorded femoral artery pressure waveform demonstrates a wider pulse pressure (compare 1 and 2), a delayed upstroke (3), a delayed, slurred dicrotic notch (compare arrows), and a more prominent diastolic wave. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 8-4.) (Figure Not Available)*

arterial sites will have different morphologies owing to the physical characteristics of the vascular tree, namely impedance and harmonic resonance (Fig. 30-20) (Figure Not Available) . [48] [109] [119] [144] [148] As the arterial pressure wave travels from the central aorta to the periphery, several characteristic changes occur. The arterial upstroke becomes steeper, the systolic peak becomes higher, the dicrotic notch appears later, the diastolic wave becomes more prominent, and the end-diastolic pressure becomes lower. Thus, compared with central aortic pressure, peripheral arterial waveforms have higher systolic pressure, lower diastolic pressure, and wider pulse pressure. Furthermore, there is a delay in the arrival of the pressure pulse at peripheral sites, so that the systolic pressure upstroke begins approximately 60 milliseconds later in the radial artery than in the aorta. Despite morphologic and temporal differences between peripheral and central arterial waveforms, the MAP in the aorta is just slightly greater than that in the radial artery. [119] [148]

Pressure wave reflection is the predominant factor that influences the shape of the arterial pressure waveform as it travels peripherally. [119] [144] [149] [150] [151] As blood flows from aorta to radial artery, mean pressure only decreases slightly, because there is little resistance to flow, but then falls markedly in the arterioles, owing to the dramatic increase in vascular resistance at this site. This high resistance to flow diminishes pressure pulsations in small downstream vessels but acts to augment upstream arterial pressure pulses owing to pressure wave reflection. [119] [152] Murgo et al [150] [151] and O'Rourke et al [119] [144] provide detailed explanations of the arterial pressure wave, along with models of the circulation that provide more complete insight into these phenomena. These studies underscore the importance of wave reflection in determining the shape of the arterial pulse recorded from all sites in the body, in health and disease. For example, elderly patients have reduced arterial distensibility, which results in early return of reflected pressure waves, an increased pulse pressure, a late systolic pressure peak, and disappearance of the diastolic pressure wave (Fig. 30-21) (Figure Not Available) . [119] [144] [152]

From these considerations, it becomes evident that the morphology of the arterial waveform and the precise values for systolic and diastolic blood pressure vary throughout the body under normal conditions in otherwise healthy individuals.

Figure 30-21 (Figure Not Available) Impact of pressure wave reflection on arterial pressure waveforms. In elderly individuals with reduced arterial distensibility, early return of reflected waves increases pulse pressure, produces a late systolic pressure peak (arrow), and attenuates the diastolic pressure wave. Myocardial oxygen balance is more tenuous in the elderly because these changes in blood pressure cause an increased myocardial oxygen demand during systole and a reduced myocardial oxygen supply during diastole. See text for greater detail.

Perhaps of even greater importance, the relation between central and peripheral arterial pressure varies with age and is altered by various physiologic changes, pathologic conditions, and pharmacologic interventions. (See the section *Choosing the Site for Arterial Pressure Monitoring* for more detail.)

Morphologic features of individual arterial pressure waveforms provide diagnostic clues to various pathologic conditions. *Aortic stenosis* produces a fixed obstruction to left ventricular ejection, resulting in a reduced stroke volume and an arterial pressure waveform that rises slowly *(pulsus tardus)* and peaks late in systole (Fig. 30-22) (Figure Not Available) . A distinct shoulder, termed the *anacrotic notch,* often distorts the pressure upstroke. [153] In addition, the dicrotic notch may not be discernible and the arterial pressure is small in amplitude *(pulsus parvus).* All of these features make the arterial pressure waveform appear overdamped, in contrast to the normal arterial pressure waveform, which has a sharp upstroke and distinct dicrotic notch.

In *aortic regurgitation,* the arterial pressure wave rises rapidly, pulse pressure increases, and diastolic pressure is low, owing to the runoff of blood into the left ventricle as well as the periphery during diastole. Because of the large stroke volume ejected from the left ventricle in this condition, the arterial pressure pulse may have two systolic peaks *(bisferiens pulse)* (see Fig. 30-22) (Figure Not Available) . These two peaks represent separate percussion and tidal waves, with the former resulting from left ventricular ejection and the latter arising from the periphery as a reflected wave. [153] The bisferiens pulse is also described in patients with mixed aortic regurgitation and stenosis and in patients with hypertrophic cardiomyopathy, although the physiologic basis is different in the latter condition. In *hypertrophic cardiomyopathy,* the arterial pressure waveform assumes a peculiar bifid shape, termed a "spike-and-dome" configuration. After an initial sharp pressure upstroke that results from rapid left ventricular ejection in early systole, arterial pressure falls rapidly as

---

Figure 30-22 (Figure Not Available) Influence of pathologic conditions on arterial pressure (ART) waveform morphology. (A) Normal ART and pulmonary artery pressure (PAP) waveform morphologies demonstrating the similar timing of these waveforms relative to the electrocardiographic R wave. (B) In aortic stenosis, the ART waveform is distorted and demonstrates a slurred upstroke and delayed systolic peak. These changes are particularly striking in comparison with the normal PAP waveform. Note the beat-to-beat respiratory variation in the PAP waveform. See text for greater detail. For (A) and (B), the ART scale is on the left and the PAP scale is on the right. (C) Aortic regurgitation produces a bisferiens pulse and a wide pulse pressure. See text for greater detail. (D) Arterial pressure waveform in hypertrophic cardiomyopathy shows a peculiar "spike-and-dome" configuration. Pressure waveform assumes a more normal morphology following surgical correction of this condition. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 3-3 (Figure Not Available) , 17-21, and 17-24.)*

dynamic left ventricular outflow obstruction develops during midsystole, and a late systolic reflected wave follows, thereby creating the characteristic double-peaked waveform (see Fig. 30-22) (Figure Not Available) . [153] [154]

Observation of arterial waveform patterns over consecutive heartbeats provides an additional set of diagnostic clues. *Pulsus alternans* is recognized by the alternating beats of larger and smaller pulse pressures (Fig. 30-23) (Figure Not Available) . In general, it is considered to be a sign of severe left ventricular systolic dysfunction, often noted in patients with advanced aortic stenosis. It may be seen occasionally during general anesthesia, presumably as a consequence of the anesthetic-induced reduction in sympathetic nervous system activity in patients with underlying impairment of left ventricular contractility. [155] Pulsus alternans should be distinguished from the bigeminal pulse that arises from a bigeminal rhythm, usually ventricular bigeminy. Both abnormalities create an alternating pulse pressure in the arterial pressure waveform, but the rhythm is regular in pulsus alternans.

Pulsus paradoxus is an exaggerated inspiratory fall in systolic arterial pressure, exceeding 10 to 12 mm Hg during quiet breathing (see Fig. 30-23) (Figure Not Available) . [153] [156] [157] [158] The term may be confusing because a small inspiratory reduction in blood pressure is a normal phenomenon, and pulsus paradoxus is not truly paradoxic, but rather an exaggeration of this normal inspiratory decline in blood pressure. Pulsus paradoxus is a characteristic, almost universal finding in cardiac tamponade and occurs in many patients with pericardial constriction. It is said to occur in patients with airway obstruction, bronchospasm, dyspnea, or any condition in which there are large swings in intrathoracic pressure. [153] However, in cardiac tamponade, the pulse pressure and left ventricular stroke volume fall during inspiration, in contrast to the blood pressure changes observed in patients with forced breathing patterns and exaggerated changes in intrathoracic pressure in which pulse pressure is relatively unchanged. [156]

Pulsus paradoxus is a phenomenon described during spontaneous ventilation, not during positive-pressure mechanical ventilation in which large cyclic changes in systolic blood pressure occur in many patients. [156] [159] [160] These large arterial pressure changes during mechanical ventilation have been noted as an incidental observation on the bedside monitor for a long time, but only recently have they been shown to have clear diagnostic implications. [160] [161] [162] [163] [164] [165] [166] [167] *Systolic pressure variation* is the difference between maximal and minimal values of systolic arterial pressure recorded over the mechanical positive-pressure respiratory cycle. [164] [168] Using end-expiration as the equilibrium period for pressure measurement, the total systolic pressure variation is divided into an early inspiratory increase in pressure, Delta up, and a later decrease in pressure, Delta down (see Fig. 30-23) (Figure Not Available) . Delta up reflects the inspiratory augmentation in left

ventricular

Figure 30-23 (Figure Not Available) Beat-to-beat variability in arterial pressure waveform morphologies. (A) Pulsus alternans. (B) Pulsus paradoxus. The marked decline in systolic arterial pressure and pulse pressure during spontaneous inspiration (arrows) is characteristic of this condition. (C) Systolic pressure variation. Compared with systolic blood pressure recorded at end expiration (1) a small increase occurs during positive pressure inspiration (2, Delta up) followed by a decrease (3, Delta down). Normally, total systolic pressure variation does not exceed 10 mm Hg. In this instance, the large Delta down indicates hypovolemia even though systolic arterial pressure and heart rate are relatively normal. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 18-10C , and 16-16.)*

output, and Delta down reflects the impairment in systemic venous return that becomes manifest in the arterial pressure trace shortly thereafter. Normally, mechanically ventilated patients will have Delta up and Delta down of about 5 mm Hg each and total systolic pressure variation of approximately 10 mm Hg. [160]

The greatest clinical use of systolic pressure variation has been in the early diagnosis of hypovolemia. [161] [163] [164] [168] Both in experimental animals and patients, hypovolemia causes a dramatic increase in systolic pressure variation, particularly Delta down. Some authors have suggested that the increase in systolic pressure variation and Delta down may herald hypovolemia, even in patients in whom the arterial blood pressure is maintained near normal by compensatory arterial vasoconstriction. [168] In a heterogeneous group of intensive care patients, Marik [162] demonstrated that a large systolic pressure variation (>15 mm Hg) was highly predictive of a low PAWP (<10 mm Hg). Using echocardiography to measure left ventricular cross-sectional area as a surrogate for preload, Coriat et al [161] found Delta down to be an even better predictor of left ventricular preload than wedge pressure. Other uses of systolic pressure variation focus on changes in the Delta up portion of the arterial pressure trace. Just as Delta down may reveal changes in cardiac preload, the Delta up portion of the arterial pressure trace may provide clues to the afterload dependence of the left ventricle. Preliminary evidence suggests that a marked increase in Delta up during positive-pressure inspiration occurs when the increased pleural pressure reduces transmural left ventricular pressure sufficiently that left ventricular stroke output increases in the failing, afterload-dependent left ventricle. [164] [166] [168] [169]

The arterial pressure waveform provides diagnostic clues in other more unusual physiologic states. Proper time of *intra-aortic balloon counterpulsation* mandates a detailed interpretation of the arterial waveform (Fig. 30-24) (Figure Not Available) . [170] Even during nonpulsatile cardiopulmonary bypass, the minor variations in

Figure 30-24 (Figure Not Available) Unusual arterial pressure waveforms. (A) Intraaortic balloon counterpulsation with a 1:2 balloon-assist ratio produces a characteristic change in the arterial pressure waveform. Four cardiac cycles are shown, two with balloon assistance and two without. (0) Unassisted enddiastolic pressure, (1) unassisted systolic pressure, (2) dicrotic notch, (3) assisted or augmented diastolic pressure, (4) end-diastolic or presystolic dip, (5) assisted systolic pressure. Effective afterload reduction by the intraaortic balloon is evidenced by the presystolic dip pressure (4) lower than the unassisted end-diastolic pressure (0) and the assisted systolic pressure peak (5) lower than the unassisted systolic pressure peak (1). (B) Arterial pressure waveform during cardiopulmonary bypass. Small phasic pressure variations (arrows) result from the mechanical action of the bypass roller pump. Bypass pump flow rate may be estimated by measuring these pulsations. Nineteen pulsations are recorded in a 3-sec time interval. In this case, the pump configured with 3/8-in tubing has an effective stroke volume of 27 mL. Pump flow rate may be calculated as follows: (19 pulsations/3 sec) × (1 pump revolution/two pulsations) × (27 mL/revolution) × (60 sec/min) = 5130 mL/minute. This calculated pump flow rate should equal the flow rate displayed on the pump console (i.e., 5.2 L/minute). *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 20-3 and 19-8.)*

blood pressure created by the arterial roller head allow calculation and confirmation of the adequacy of systemic blood flow (see Fig. 30-24) (Figure Not Available) . [171]

CARDIAC FILLING PRESSURE MONITORING

Physiologic Considerations: Diastolic Pressure-Volume Relations and Transmural Pressure

Cardiac filling pressures are monitored to estimate cardiac filling volumes, which, in turn, determine the stroke outputs of the left and right ventricles. According to the Frank-Starling principle, the force of cardiac contraction is directly proportional to end-diastolic muscle fiber length at any given level of intrinsic contractility or inotropy. [131] [135] This muscle fiber length or preload is proportional to end-diastolic chamber volume. Even though it would be ideal to monitor cardiac chamber volumes continuously in critically ill patients, this remains an elusive goal in clinical practice. Transesophageal echocardiography has brought continuous

Figure 30-25 (Figure Not Available) Ventricular diastolic pressure-volume relation. Along the flat portion of the curve, a 20-mL increase in ventricular volume causes a small increase in ventricular pressure (A to B). In contrast, the same increase in volume along the steep portion of the ventricular filling curve causes a marked increase in filling pressure (C to D). Another problem associated with the use of filling pressure as a surrogate for filling volume arises when shifts in the pressure-volume relation occur. At point C, ventricular volume is 100 mL and ventricular pressure is 8 mm Hg. An increase in filling pressure to 15 mm Hg may accompany either an increased volume (D) or decreased volume (E). The latter occurs when ventricular compliance changes and shifts the ventricular diastolic pressure-volume relation up and to the left. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 15-2.)*

monitoring of left ventricular volume or cross sectional area a step closer, [172] but the accuracy of this technique applied in real time remains suboptimal. [173]

When a cardiac filling pressure is measured as a surrogate for estimating cardiac volume, one must not assume that these two variables always change in direct proportion or even in the same direction. In fact, the diastolic pressure-volume relation in cardiac muscle is not linear, but rather curvilinear, with a progressively steeper slope at higher volumes (Fig. 30-25)) (Figure Not Available) . [174] [175] [176] [177] This diastolic pressure-volume relation is one limb of a pressure-volume loop, which describes the relation between pressure and volume for the left or right ventricle during an entire cardiac cycle. When a ventricle is operating along the flat portion of its diastolic filling curve, a significant increase in filling volume or preload results in a small increase in filling pressure. In contrast, the same increase in filling volume causes a significant increase in filling pressure when the ventricle is operating on the steep portion of its curve (see Fig. 30-25) (Figure Not Available) . [178] An even more confusing situation arises when the diastolic pressure-volume relation of the ventricle changes, for example with the onset of myocardial ischemia. [176] [179] [180] [181] [182] Rather than moving along the same diastolic pressure-volume curve, the ventricle now shifts to a different, steeper curve where--somewhat paradoxically--an increase in filling pressure may accompany a decrease in filling volume (see Fig. 30-25) (Figure Not Available) . [183] [184] As a result, one cannot assume that a given measured change in cardiac filling pressure reflects a proportional change in ventricular preload, and on occasion, diastolic pressure and volume can change in opposite directions. [177] [183] [184] [185] [186] [187]

The relation between ventricular volume and filling pressure depends on the portion of the pressure-volume curve over which the patient's heart is operating and the shape or slope of the curve. Commonly termed *ventricular compliance,* [131] [135] [188] [189] this change in pressure for a given change

in volume (DeltaP/DeltaV) is actually the reciprocal of compliance and is more accurately termed *ventricular elastance, distensibility,* or *stiffness.* A patient with an abnormally stiff ventricle will have a greater change in end-diastolic pressure for any given change in end-diastolic volume, and the converse is true for a patient with an abnormally compliant ventricle. By definition, *diastolic dysfunction* is present when ventricular pressure is abnormally elevated for any given ventricular volume.

The ventricular diastolic pressure-volume relation is influenced by intrinsic properties of the ventricle, such as the passive mechanical characteristics of cardiac muscle, chamber geometry, and relaxation. In addition, external forces exerted by the pericardium, the adjacent ventricle, coronary vasculature, and pleural pressure will further influence ventricular pressure-volume relations. [174] [175] [180] [182] [188] [189] [190] [191] One should not equate cardiac filling pressures with filling volumes when patients are functioning over wide ranges of their diastolic pressure-volume curve or under conditions in which diastolic stiffness is abnormal or changing rapidly.

In general, all intravascular pressures measured in clinical practice are referenced to ambient atmospheric pressure. (Indeed, the first step in pressure transducer setup is to zero the transducer by exposing it to atmospheric pressure and assigning this pressure a value of zero by pressing the zero pressure button on the attached monitor. See the earlier section *Technical Aspects of Direct Blood Pressure Monitoring.)* Thus, a cardiac filling pressure of 10 mm Hg is 10 mm Hg higher than ambient atmospheric pressure. Does this pressure value accurately represent the distending force across the cardiac chamber wall at end-diastole?

To answer this question, one needs to consider *transmural pressure.* The cardiac chambers are all contained within the pericardium and thorax. Clearly, changes in pressure in the structures surrounding the heart will influence pressures recorded within the heart. Transmural pressure is the difference between chamber pressure and juxtacardiac or pericardial pressure. This transmural pressure determines ventricular preload, end-diastolic volume, or fiber length. [131] [177] The same measured filling pressure, referenced to atmospheric pressure, can be associated with markedly different transmural pressures and chamber volumes, depending on whether juxtacardiac pressure is high or low. Although juxtacardiac pressure can be ignored under some circumstances, marked alterations in pleural and pericardial pressures occur commonly and must be considered when any cardiac filling pressure is interpreted. Transmural pressure is always the pressure of physiologic interest. Because juxtacardiac pressure is not measured routinely, one always must consider that the measured central vascular pressure, referenced to the ambient atmosphere, may be a poor estimate of transmural pressure. [160] [178]

Cardiac filling pressures are measured directly from a number of sites in the vascular system. CVP monitoring is the least invasive method, followed by PAP monitoring and left atrial pressure (LAP) monitoring. Proper interpretation of all cardiac filling pressures requires knowledge of normal values for these pressures, as well as pressures in the cardiac chambers and great vessels, and other measured and derived hemodynamic variables (Tables 30-1 and 30-2) . Methods for measuring CVP, PAP, and LAP will be described, along with indications, complications, and physiologic

TABLE 30-1 -- Normal Cardiovascular Pressures

PRESSURES	AVERAGE (MM HG)	RANGE (MM HG)
Right atrium		
a wave	6	2-7
v wave	5	2-7
mean	3	1-5
Right ventricle		
peak systolic	25	15-30

end-diastolic	6	1-7
Pulmonary artery		
peak systolic	25	15-30
end-diastolic	9	4-12
mean	15	9-19
Pulmonary artery wedge		
mean	9	4-12
Left atrium		
a wave	10	4-16
v wave	12	6-21
mean	8	2-12
Left ventricle		
peak systolic	130	90-140
end-diastolic	8	5-12
Central aorta		
peak systolic	130	90-140
end-diastolic	70	60-90
mean	90	70-105

interpretations of normal and pathologic waveforms encountered during monitoring.

Central Venous Cannulation

Indirect assessment of CVP, through physical examination of the neck veins, is a fundamental aspect of cardiovascular assessment but one that has many shortcomings. One real anatomic limitation to the physical assessment of jugular venous pulsations rests with the recent observation that competent venous valves exist in the internal jugular veins of most individuals. These valves are located approximately 0.5 to 2.0 cm above the junction of the internal jugular and subclavian veins bilaterally and withstand back pressures of 50 to 100 cm H_2O. [192] [193] [194] In addition, the jugular veins may be impossible to identify in 20 percent of patients, and the bedside diagnosis of low, normal, or high CVP may be inaccurate almost 50 percent of the time. [195] These general problems are compounded in the perioperative period, when

TABLE 30-2 -- Normal Hemodynamic Values

Cardiac output (L/min)	5.0	4.0-6.5
Stroke volume (mL)	75	60-90
Systemic vascular resistance		
(Wood units)	15	10-20
(Dynes-sec-cm^{-5})	1,200	800-1,600
Pulmonary vascular resistance		
(Wood units)	1	0.5-3
(Dynes-sec-cm^{-5})	80	40-180
Arterial oxygen content (mL/dL)	18	16-20
Mixed venous oxygen content (mL/dL)	14	13-15
Arteriovenous oxygen difference (mL/dL)	4	3-5
Oxygen consumption (mL/min)	225	200-250

visualization of the neck veins is further obscured and acute, large changes in CVP occur in many patients. As a result, direct measurement of CVP is performed frequently in patients with advanced cardiovascular diseases and those undergoing major operations.

Cannulation of a large vein is the standard clinical method for monitoring CVP. In addition, central venous cannulation is performed to provide secure vascular access for administration of vasoactive drugs or to initiate rapid fluid resuscitation. Often the central venous location is the only site available for intravenous access of any kind. Patients at risk for venous air emboli may have central venous catheters placed for aspiration of entrained air. Central venous access is required to initiate transvenous cardiac pacing, temporary hemodialysis, or pulmonary artery catheterization for more comprehensive cardiac monitoring (Table 30-3) .

In certain patients, such as those with ischemic heart disease, the cardiovascular consequences of pain or anxiety during central venous or arterial cannulation may produce untoward hemodynamic changes. [196] Although some authors advocate postponing central venous catheterization until general anesthesia is established, [197] this is not a practical option in critically ill patients in intensive care, or in surgical patients who will not receive general anesthesia. Furthermore, safe vascular cannulation before induction of anesthesia is achieved easily through use of adequate local anesthesia, intravenous sedatives, and careful patient observation. [198] [199] In the end, the decision to perform central venous cannulation before or after induction of anesthesia is guided most often by individual patient and physician preferences or institutional practices. [197] [198] Perhaps of greatest importance, one should consider abandoning attempts at preoperative central venous cannulation in any patient who becomes overly sedated or uncooperative during the procedure. In most cases, the prudent course is to proceed with anesthetic induction and tracheal intubation as planned, then gain central vascular access under more controlled circumstances.

Among the numerous potential sites for central venous cannulation, the most popular are the right internal jugular vein and the subclavian veins. A common theme in many texts and articles describing cannulation techniques is the apparent preference of most anesthesiologists for the internal

TABLE 30-3 -- Indications for Central Venous Cannulation

Central venous pressure monitoring
Pulmonary artery catheterization and monitoring
Transvenous cardiac pacing
Temporary hemodialysis
Drug administration
Concentrated vasoactive drugs
Hyperalimentation

Chemotherapy
Agents irritating to peripheral veins
Prolonged antibiotic therapy (e.g., endocarditis)
Rapid infusion of fluids (via large cannulas)
Trauma
Major surgery
Aspiration of air emboli
Inadequate peripheral intravenous access
Sampling site for repeated blood testing

jugular vein and of most surgeons for the subclavian vein. The advantages and disadvantages of each approach are considered next, along with a description of techniques to accomplish these procedures safely and successfully.

Right Internal Jugular Vein Cannulation

Many different techniques for internal jugular vein cannulation have been described, although the "central" approach described by Daily et al [200] is among the most popular and is described with minor modifications here. Careful positioning will make the patient comfortable, improve identification of surface landmarks, and increase the likelihood of successful venipuncture. The patient is placed in the supine position, with the head turned slightly to the left to expose the right side of the neck and keep the chin from interfering with the procedure. Pillows that cause the neck to be flexed should be removed, but forceful neck extension or extreme leftward rotation of the head should be avoided, because this may alter cervical vascular anatomy, cause the internal jugular vein to overlie the carotid artery, and increase the risk of carotid arterial puncture. [201]

Anatomic landmarks, including the sternal notch, clavicle, and sternocleidomastoid muscle, should be assessed before preparation and draping for the sterile procedure because these landmarks are appreciated better before they are covered by the sterile drape (Fig. 30-26) . The carotid artery should be palpated and its course determined as it lies lateral to the trachea, usually under the more medial sternal head of the sternocleidomastoid muscle. The internal jugular vein lies in the groove between the sternal and clavicular heads of the sternocleidomastoid muscle, lateral and slightly anterior to the carotid artery. In many patients, venous pulsations from the internal jugular vein are observed directly within this groove and further identify the approximate site for venipuncture.

The patient should be calm, sedated, and receiving supplemental oxygen if necessary, and monitored with an ECG, blood pressure monitor, and pulse oximeter. Owing to the frequency and potential morbidity of infectious complications from central venous catheterization, strict aseptic technique is required. Guidelines to reduce these complications, published by the U.S. Centers for Disease Control and Prevention, have been updated recently by the American Society of Anesthesiologists Task Force on Infection Control and provide prudent recommendations that should be followed during all but emergency basis catheterizations. [202]

1. Wash hands before the procedure.
2. Use a mask and sterile gloves and gown, even when placing the catheter in the operating room.
3. Cleanse the skin widely from earlobe to clavicle to sternal notch, using an appropriate antiseptic, such as 10 percent povidone-iodine.
4. Apply a sterile drape for maximal barrier precautions. A large drape that covers the entire patient is preferred when the central venous catheterization is intended for long-term catheter placement, although a smaller, disposable, fenestrated drape is generally used for more routine perioperative catheterizations.

Figure 30-26 Technique for right internal jugular vein central venous cannulation. (A) Important surface landmarks are identified. (B) The course of the internal carotid artery is palpated. (C) The internal jugular vein is punctured at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle with the needle tip directed toward the ipsilateral nipple. (D) A guide wire is introduced through the thin-wall needle into the vein. (E) The central venous cannula is inserted over the guide wire, making sure that the proximal end of the guide wire protrudes beyond the catheter and is controlled by the operator. See text for greater detail.

Under these sterile conditions, the relevant anatomy is again identified, particularly the course of the carotid artery in the neck. An assistant then places the patient in a slight head-down (Trendelenburg) position to increase central venous pressure and jugular vein diameter in the neck. This step is omitted when physical examination indicates high venous pressure, and occasionally venipuncture must even be performed with the head slightly elevated in a patient who has markedly elevated CVP and cannot lie flat in bed. The intended venipuncture site is anesthetized by subcutaneous infiltration with a local anesthetic solution (typically 1% lidocaine), using a 25- or 26-gauge needle. The local anesthetic wheal should be generous enough to allow pain-free suturing of the catheter at the end of the procedure.

With the fingers of the left hand gently resting on the carotid artery pulse as a valuable anatomic landmark, venipuncture then proceeds using a 22-gauge, 1-1/2-in (3.8-cm) *finger needle* mounted on a 5-mL syringe (see Fig. 30-26) . The needle is inserted at the apex of the triangle formed by the two heads of the sternocleidomastoid muscle, at an angle of approximately 30v degrees from the plane of the skin, and directed at the ipsilateral nipple. Gentle aspiration will identify the jugular vein when dark venous blood enters the syringe. Although use of the small finder needle is an extra step in this procedure, it presumably increases the margin of safety, [203] because unintentional puncture of the carotid artery with this small needle is less likely to result in significant bleeding and hematoma formation. Although blood may have been aspirated earlier during injection of the local anesthetic, the color of the blood may not be appreciated when it mixes with the local anesthetic solution, thereby making it difficult to distinguish venous from arte-rial blood. Thus, it is important that the finder needle be attached to an empty syringe during this step.

If the blood is not aspirated as the finder needle is advanced and then withdrawn, additional needle passes may locate the internal jugular vein by fanning laterally in a small arc from the point where the needle enters the skin. As long as the carotid artery remains palpable medially, exploring in an orderly fashion with the finder needle directed slightly more laterally will often identify the vein, with little risk of carotid artery puncture. If the vein is not located after several needle passes, the finder needle is withdrawn completely and checked for patency, the anatomy is reassessed, and the puncture may then proceed with the needle entering the skin several millimeters closer to the palpated

carotid pulse but still directed in a sagittal or slightly lateral direction. Because of the normal anatomic relation between the carotid artery and the internal jugular vein, one should resist the temptation to explore with a medial or leftward direction of the finder needle when this technique for venipuncture is being used.

When the internal jugular vein is located with the finder needle, the needle is gently withdrawn, while the skin and surface anatomy remain fixed by the left hand. The vein is then repunctured with an 18-gauge 2-½-inch (6.4 cm) *thin-wall needle* attached to a 5-mL syringe, following the same track used with the finder needle, keeping in mind the location and depth of the identified internal jugular vein (see Fig. 30-26) . It is common that the lumen of the jugular vein is compressed as this

larger thin-wall needle is advanced, which causes the needle to pierce both front and back walls almost simultaneously. [204] [205] Consequently, the thin-wall needle should be inserted only slightly beyond the expected depth, then slowly withdrawn, maintaining gentle aspiration on the syringe. Frequently, a sudden gush of free-flowing venous blood is identified during needle withdrawal.

Successful puncture of the internal jugular vein is confirmed by the easy aspiration of dark venous blood into the 5-mL syringe. The hub of the thin-wall needle is fixed with the fingers of the left hand, the syringe is detached, and venous blood should slowly drip from the needle. A 0.035-inch (0.89-mm) guide wire is inserted through the needle, using either the J-shaped tip or the soft, flexible straight end (see Fig. 30-26) . The wire should advance easily into the vein with little resistance. The ECG is monitored continuously to observe arrhythmias, which are common, if the wire tip contacts the walls of the right atrium or ventricle. [206] From this point in the procedure, it is critical that the clinician maintain control over the guide wire and pay attention to its depth of insertion and continued sterility.

In preparation for placing the central venous catheter over the guide wire, the puncture site is enlarged, using a #11 scalpel blade, to the size required for the intended catheter. A firm, tapered-tip, vessel dilator may be inserted to dilate the subcutaneous tissues around the guide wire and allow a larger catheter to pass more smoothly. (When an introducer sheath is to be used for internal jugular vein cannulation, the dilator and sheath form one unit, and this separate dilation step usually is omitted.) The vessel dilator is removed, and the central venous catheter is inserted over the guide wire while traction on the skin is maintained. Again, the clinician must be attentive to the guide wire and ensure that a sufficient length protrudes from the catheter hub so that the wire may be extracted easily (see Fig. 30-26) . The catheter is inserted to an appropriate depth that will place the tip in the superior vena cava, above its junction with the right atrium. This depth is typically 15 to 18 cm if the catheter is placed using the technique described. However, the position of the catheter tip always must be confirmed radiographically, because catheter tips located within the heart increase the risk of cardiac perforation and tamponade, an often fatal complication. [207] [208] [209] [210] [211] Ideally, the catheter tip should lie within the superior vena cava, parallel to the vessel walls, and be positioned below the inferior border of the clavicles and above the level of the third rib, the T4 to T5 interspace, the azygos vein, or the tracheal carina. [209]

Finally, the guide wire is withdrawn, the catheter is attached by a Luer-Lok connector to the monitoring or infusion tubing and sutured in place, and a sterile gauze or transparent dressing is applied. Antibiotic ointment should not be applied to the insertion site, because this may increase the risk of catheter colonization with multidrug-resistant bacteria or *Candida.* [202] [212] Before monitoring or infusion commences, aspiration of blood should confirm intravenous location of the catheter and remove any residual air from the catheter-tubing system. Even in circumstances when the central venous cannulation is intended primarily for infusion, the venous pressure should be measured before infusion to document that the catheter is located in the jugular vein and not the carotid artery.

Choosing the Method, Catheter, and Site for Central Venous Cannulation

Since its introduction into clinical practice in the late 1960s, [200] [213] [214] , percutaneous venipuncture of the right internal jugular vein has been the method preferred by anesthesiologists for central venous cannulation. [215] Reasons for this preference include the following:

1. Consistent, predictable anatomic location.
2. Readily identified, palpable landmarks.
3. Short, straight course to the superior vena cava (which facilitates right heart catheterization).
4. Position at the patient's head, providing intraoperative accessibility to the anesthesiologist.
5. High success rate (90-99%). [200] [213] [215] [216] [217]

Numerous techniques have been described for percutaneous internal jugular vein cannulation. [218] [219] [220] Although it is unlikely that one single method will lead to the greatest success rate in the hands of all clinicians, it appears that certain techniques may result in a higher incidence of unintentional carotid artery puncture. [219] It seems prudent, therefore, to determine the location of the carotid pulse prior to attempted jugular vein cannulation and, when possible, to continue to palpate the pulse gently during the initial steps of venipuncture. This is easily done by a right-handed operator, but continued palpation of the carotid artery during jugular venipuncture is awkward when a left-handed individual is performing the procedure. In this instance, it is best to evaluate the course of the carotid artery prior to, but not during, the venipuncture.

Other adjunctive methods have been proposed to limit complications during central venous cannulation, particularly the frequency of carotid arterial puncture during attempted internal jugular cannulation. (Also see the later section, *Ultrasound-Guided Central Venous Cannulation.*) Many individuals substitute a 2-in, 18-gauge intravenous catheter for the 18-gauge thin-wall needle for venipuncture and guide wire placement. Although this catheter can be advanced completely into the vein, it is kinked more easily than a needle, thereby making it more difficult to recognize pulsatile arterial blood flow from unintentional arterial puncture. To confirm intravenous location of this catheter, several things may be done. The color of the aspirated blood is examined, and it may be compared with a simultaneously obtained arterial sample, or even sent for quantitative blood gas analysis. A quicker, simpler method is to transduce the pressure from the 18-gauge catheter, [221] or attach a sterile

intravenous extension tubing set to create a simple vertical fluid manometer to estimate the pressure and distinguish arterial from venous catheterization. [222] Although none of these safety measures are foolproof, they may provide a margin of safety and reduce the serious complications resulting from unintentional cannulation of the carotid artery with a large-bore catheter. Continuous pressure transduction of the thin-wall needle has been advocated as an even better method to detect arterial puncture and prevent arte-rial cannulation, because the needle will not kink and thereby provide a misleading pressure waveform. [217] [223]

Widespread adoption of guide wire-based vascular cannulation methods undoubtedly has increased the safety of central venous cannulation. These techniques, originally described by Seldinger, [224] allow initial vascular puncture with a smaller gauge needle, followed by guide-wire placement and subsequent vessel dilation and cannulation with a large-bore catheter. [225] This method has virtually replaced the "catheter through the needle" method, which requires vascular puncture with a needle larger than the catheter and results in more complications from cannulation site hemorrhage and shearing of the catheter if it is withdrawn inappropriately through the insertion needle. Some newer central venous catheter insertion kits contain a modified syringe that allows the guide wire to be placed directly through the syringe plunger, without disconnecting the syringe from the thin wall needle. However, when this technique is used, one of the most valuable signs of unintentional arterial puncture is virtually impossible to recognize--namely, the pulsatile return of bright red blood through the thin-wall needle. This may lead to erroneous arterial placement of a central venous catheter. [226]

Numerous types of central venous catheters are available. [227] [228] These vary according to the purpose of catheterization, whether for CVP monitoring or other therapeutic needs, and whether intended for short- or long-term use. [228] Catheters come in a variety of lengths, gauge, composition, and lumen number. This makes it critical for the physician to choose the best catheter for any given application and thereby reduce risk to the patient caused by improper catheter selection. Although multilumen catheters are very popular because they allow simultaneous continuous pressure monitoring and fluid or drug infusion, their use has been associated with a greater risk of infection than single-lumen catheters. [202] Furthermore, multilumen catheters may have a greater propensity to cause vascular perforation than single lumen catheters, because more septations and a stiffer plastic are required in the manufacturing process of a multilumen catheter. [227] A popular alternative method for multilumen central venous access uses a side-arm introducer sheath attached to a series of stopcocks for multiple drug infusions, with a single-lumen catheter inserted through the hemostasis valve for simultaneous continuous CVP monitoring. Although use of these larger introducer sheaths is not free from complications, [229] their use allows rapid placement of a pacing wire or pulmonary artery catheter for more intensive monitoring, without the need for additional central venipunctures or catheter exchanges over a guide wire.

In patients at risk for major intraoperative blood loss and hemodynamic instability, two central venous catheters frequently are inserted. Some physicians advocate double cannulation of the same central vein (usually the right internal jugular) with two catheters in close proximity. [230] With this technique, a guide wire is introduced into the internal jugular vein using the standard method. Then, before catheter placement, a second jugular venipuncture is performed, approximately 1 to 2 cm cephalad or caudad, and a second guide wire is introduced into the vein. Placing appropriate catheters over each guide wire and securing them at the skin in the normal fashion completes the procedure. Limited evidence suggests that the incidence of major complications with this double cannulation technique is no greater than with single central venous catheterization, although arrhythmias may be more common because of unintentional intracardiac placement of the guide wires. [230] However, it is not clear whether this approach is safer than central venous cannulation in two separate central veins. Serious reported complications of the double cannulation technique include facial vein avulsion, catheter entanglement, and catheter fracture. [230] [231] [232] Double central venous cannulation must be reserved for patients whose needs for venous access and hemodynamic monitoring cannot be met through single cannulation.

Selecting the best site for safe and effective central venous cannulation ultimately requires that the physician consider several important medical issues. These include the purpose of catheterization (pressure monitoring versus drug or fluid infusion), the patient's underlying medical condition, the intended operation, and the skill and experience of the physician performing the procedure. In patients with severe bleeding diatheses, it is best to choose a puncture site where bleeding from the vein or adjacent artery is easily detected and controlled with local compression. In this instance, an external jugular approach would be preferred to an infraclavicular subclavian catheterization. Patients with severe emphysema, or other patients who would be severely compromised by pneumothorax would be better candidates for right internal jugular cannulation than subclavian cannulation, owing to the higher risk of pneumothorax with the latter approach. If transvenous cardiac pacing were required in an emergency situation, catheterization of the right internal jugular vein is recommended, in that it provides the most direct course to the right ventricle. Trauma patients, with their necks immobilized in a hard cervical collar, are best resuscitated using femoral or subclavian cannulas; the latter may be placed even more safely if the risk of pneumothorax is obviated by prior placement of thoracostomy tubes. The physician must recognize that the length of catheter inserted to position the catheter tip properly in the superior vena cava will vary according to puncture site, being slightly (3-5 cm) longer when the left internal or external jugular veins are chosen, compared with the right internal jugular vein. [233] Finally, a physician's personal experience undoubtedly plays a significant role in determining the safest site for central venous cannulation, particularly when the procedure is performed under urgent or emergent circumstances.

Ultrasound-Guided Central Venous Cannulation

To increase the success and decrease the complications of central venous cannulation, different ultrasound-guided techniques have been described for cannulating the internal

jugular vein, [234] [235] [236] [237] [238] subclavian vein [239] [240] [241] [242] and femoral vein. [243] Some methods use dedicated devices, which are incorporated into the sterile field, to provide real-time twodimensional ultrasound images of the pertinent vascular anatomy, particularly the relation between the target vein and its adjacent artery. [234] [235] [238] [239] [243] Another approach employs the sophisticated ultrasound equipment that may already be available in the operating room to provide anatomic images immediately prior to the procedure and allow the surface anatomy to be marked appropriately. [237] [242] Finally, Doppler-based, nonimaging techniques provide a real-time, audible Doppler signal to guide venous cannulation, based on distinguishing the continuous audible hum of the vein from the pulsatile signal of the artery. [236] [241]

In general, these ultrasound-guided techniques appear to have several advantages. Invariably, with ultrasound assistance, fewer needle passes are required for successful venous cannulation. In addition, most investigators have shown that ultrasound guidance reduces the time required for catheterization, increases overall success rates, and results in fewer complications. In one of the largest controlled trials, Denys et al [235] used dedicated two-dimensional real-time imaging to cannulate the internal jugular vein in more than 900 patients and found that ultrasound-guided cannulation was successful in all patients and reduced the risk of carotid artery puncture (1.7 versus 8.3%), brachial plexus irritation (0.4 versus 1.7%), and hematoma (0.2 versus 3.3%) compared with landmark-guided techniques.

Although most published studies support the use of ultrasound guidance during central venous cannulation, most of these procedures are still performed with landmark-based techniques. This may be explained by the relatively high success rate and low morbidity of this procedure when performed by experienced individuals, as well as the additional cost and perceived inconvenience of acquiring or using an ultrasound device. However, increased use of ultrasound-guided venous cannulation has disclosed several pertinent technical insights that should lead to improved central venous cannulation in all patients, regardless of the technique employed.

The large central veins are distinguished readily from their accompanying arteries by their lack of pulsatility, marked enlargement during a Valsalva maneuver, and easy compressibility with the ultrasound probe. This provides several lessons for landmark-based venipuncture. When the internal jugular vein is not located easily with the finder needle, the clinician can increase the venous target size markedly by asking the patient to perform a Valsalva maneuver. In contrast, jugular venipuncture will be much more difficult if the vein is compressed during overzealous attempts to palpate and localize the carotid artery. Ultrasound imaging has demonstrated that both the subclavian [239] and internal jugular [235] veins are actually compressed, before vessel entry, by the cannulating needle as it advances. This observation explains the common clinical finding that venipuncture is recognized as often during needle withdrawal as during needle advancement. [204] [205] [235] Furthermore, in a significant number of patients, ultrasonography demonstrates that the internal jugular vein lies directly over the carotid artery, thereby increasing the risk of carotid artery puncture, unless the needle is directed more laterally [235] or lower in the neck where the internal jugular vein assumes a more lateral location. [238] Ultrasound-guided techniques may be particularly useful for increasing the success rate and decreasing complications when less experienced individuals and trainees perform central venous cannulation. [235] [239] Perhaps of greatest importance, ultrasound-guided central venous cannulation provides a method to salvage the procedure when landmark-based methods are unsuccessful, [235] [238] [239] making its use particularly attractive in high-risk patients in whom the clinician anticipates difficulties with vascular access.

Alternative Central Venous Cannulation Sites

Left Internal Jugular Vein

Left internal jugular vein cannulation may be accomplished using a technique similar to the one described earlier for the right internal jugular vein, although several anatomic details make the left side a less popular site for cannulation than the right. The cupola of the pleura is higher on the left than on the right, theoretically increasing the risk of pneumothorax. The thoracic duct may be injured during venipuncture, because it enters the venous system at the junction of the left internal jugular and subclavian veins. [244] The left internal jugular vein is often smaller than the right and demonstrates a greater degree of overlap of the adjacent carotid artery during head rotation. Catheters inserted from the left side of the patient must traverse the innominate (i.e., left brachiocephalic) vein and enter the superior vena cava perpendicularly, and their distal tips may impinge on the right lateral wall of the superior vena cava, thereby increasing the risk of vascular injury. (This anatomic disadvantage pertains to all left-sided catheterization sites and highlights the need for radiographic confirmation of proper catheter location.) In addition, because clinicians cannulate the left internal jugular vein much less often than the right, it is not surprising that cannulation of the left internal jugular vein is more difficult, more time-consuming, and associated with more complications than right internal jugular cannulation. [201] [245]

Subclavian Vein

The subclavian vein is an important site for central venous cannulation and is particularly popular among surgeons and other physicians who place central venous catheters for emergency volume resuscitation and long-term intravenous therapy, rather than for shorter-term monitoring purposes. [242] [246] [247] The advantages of subclavian venous cannulation include the following:

1. Lower risk of infection than jugular or femoral sites. [204] [247]
2. Ease of insertion in trauma patients who may be immobilized in a cervical collar.
3. Increased patient comfort, especially for long-term intravenous therapy, such as hyperalimentation and chemotherapy.

The most common technique used for subclavian vein cannulation is the infraclavicular approach. [247] The patient is placed in a slight head-down position with the arms kept to the side, the head is turned slightly away from the side of venipuncture, and a small bedroll is placed between the shoulder blades to expose the infraclavicular area fully. The skin is punctured 2 to 3 cm caudad to the midpoint of the clavicle, far enough from its inferior edge to avoid a downward angulation of the needle as it is walked under the posterior surface of the clavicle. The needle tip is directed toward the suprasternal notch, which may be constantly identified by the fingers of the operator's other hand. If the subclavian vein is not entered in the first pass, the needle may be withdrawn and a second pass attempted in a slightly more cephalad direction, while ensuring that the needle continues to hug the undersurface of the clavicle as it is advanced. Once the subclavian vein is punctured, catheterization proceeds in a similar manner to that described for jugular vein catheterization.

Several important technical details must be followed to ensure successful subclavian vein cannulation and avoid complications, particularly pneumothorax.

Venipuncture generally proceeds without first identifying the vein with a smaller gauge finder needle, because the depth of the subclavian vein is often beyond the reach of the standard 1-½-in 22-gauge needle. A thin-wall needle is preferred over an 18-gauge catheter for venipuncture and guide-wire placement because the 18-gauge catheter is easily kinked as it courses under the clavicle. Of greatest importance, however, the clinician should resist the temptation to make multiple needle thrusts if the subclavian vein is not punctured on the second or third attempt. It is clear that complications from this procedure, particularly the incidence of pneumothorax and subclavian arterial puncture, are directly related to the number of attempts at venipuncture and are more common when venipuncture is unsuccessful. [242] [247] [248] Bilateral attempts at subclavian venipuncture rarely should be undertaken, owing to the potential serious morbidity of bilateral pneumothoraces. Perhaps even more than in the case of internal jugular vein cannulation, the safety of subclavian venipuncture rests in the experience of the operator. In more practiced hands, the incidence of complications should be lower, with pneumothorax in fewer than 2 per-cent and arterial puncture in fewer than 5 percent of cases. [242] [247] [248]

External Jugular Vein

Both the right and left external jugular veins provide a safe alternative to internal jugular or subclavian vein cannulation. Because the external jugular veins are superficial structures, they allow central venous cannulation with essentially no risk of pneumothorax or unintended arterial puncture. [221] In most instances, it is best to use an 18-gauge catheter, rather than the thin-wall needle, to introduce the guide wire because of the tortuous course of the external jugular vein and the frequent need to manipulate the guide wire repeatedly to guide it into the superior vena cava. A J-tip guide wire should always be used, because it may be advanced under the clavicle into the central circulation more successfully than a straight-tip wire. [249] [250] When the guide wire does not advance as desired and appears to be moving peripherally into the subclavian vein, central venous passage may be facilitated by abducting the ipsilateral shoulder beyond 90 degrees prior to advancing the wire. Alternatively, the patient's ipsilateral arm is placed at the side, and an assistant applies mild caudad traction on the shoulder to straighten the course of the external jugular vein while the wire is advanced. Essentially the only factors that preclude use of the external jugular veins for CVP monitoring are an inability to visualize and cannulate the vessel in the neck and to advance a catheter into the central circulation. Unfortunately, these problems occur in approximately 20 percent of patients, thus limiting more widespread application of this technique. [221] [251]

Femoral Vein

Femoral vein cannulation provides a useful site for CVP monitoring when the more common jugular and subclavian sites are not accessible, as in patients with burns, trauma, or surgical procedures that involve the head, neck, and upper thorax. Use of the femoral venous site obviates many of the common complications of central venous catheterization, particularly pneumothorax and carotid or subclavian arterial injury. Femoral venipuncture is performed below the inguinal ligament just medial to the palpated femoral arterial pulse in a manner similar to that used for femoral arterial cannulation. Either a long (40-70 cm) catheter is positioned, using ECG guidance, in the inferior vena cava close to the cavoatrial junction, [252] or a shorter (15-20 cm) catheter is inserted from the femoral vein into the common iliac vein. [253] Both techniques provide intra-abdominal venous pressure measurements that agree closely with simultaneously obtained superior vena caval CVPs when these pressures are measured in mechanically ventilated, critically ill adults. [252] [253] However, it is unclear whether or not intra-abdominal venous pressure will reflect intrathoracic CVP in spontaneously breathing patients, those who are not supine, or in individuals with marked elevations in intrathoracic or intra-abdominal pressure. Potential disadvantages of the femoral venous route include increased risks of thromboembolic and infectious complications, although the magnitude of these risks has not been established. In addition, femoral arterial or venous injury during attempted cannulation may result in intra-abdominal hemorrhage.

Axillary and Other Peripheral Veins

In patients with extensive, severe burn injuries, the axillary region often is spared and provides a useful site for either arterial or venous pressure monitoring. [254] Standard 20-cm CVP catheters placed in the axillary veins, approximately 1 cm medial to the palpated axillary artery, will allow pressure measurement from the superior vena cava. Even more distal pressures measured from peripheral veins in the hand and forearm may provide a reasonably accurate estimate of CVP in selected surgical patients. [255] [256] Modified volumetric infusion pumps can measure in-line peripheral venous pressures without the need for additional transducers and monitoring equipment. [257] Although this method of measuring CVP

incurs no risk beyond that associated with placing any standard peripheral intravenous catheter, it has not been validated widely and clearly is no replacement for central venous cannulation in most circumstances when the latter is needed.

Peripherally inserted central venous catheters (PICC) have become a popular alternative to centrally inserted catheters in patients requiring long-term intravenous therapy. Advantages of the PICC include bedside placement under local anesthesia, extremely low risk of major insertion-related complications, and safe placement by nonphysicians (i.e., registered nurses and physician assistants). This technique may be particularly cost-effective, because it eliminates the need for a minor operative procedure in those patients who require a Hickman or Broviac central venous catheter. [258] Venous access for a PICC is obtained through an antecubital vein. Central catheter placement from the basilic vein is generally more successful than from the cephalic vein, in that the course of the latter is more tortuous, particularly at the clavipectoral fascia. Early reports described only modest success positioning PICCs in an appropriate central location as well as a considerable risk of venous thrombosis, [259] [260] [261] but improvements in catheter design and insertion technique now result in successful placement and few complications in most patients. [258] In current medical practice, most PICCs are placed for long-term therapeutic indications (chemotherapy or parenteral nutrition), using very flexible, nonthrombogenic silicone catheters. [258] Less commonly, a standard polyurethane 40-cm intravenous catheter is inserted peripherally and advanced to a central location for short-term infusion of vasoactive drugs or monitoring CVP or PAP. When these standard long venous catheters are inserted from an antecubital vein, the catheter tip may advance into the heart as the arm is abducted, thereby increasing the risk of cardiac perforation or arrhythmias. [208] [262] Whenever a PICC line is in place, the clinician should exercise caution when placing any additional central venous catheters because of the risk of shearing the PICC line within the central venous circulation.

Complications of Central Venous Cannulation and Pressure Monitoring

Complications of central venous cannulation have been recognized since this technique was introduced into clinical practice nearly 40 years ago. Although serious complications are infrequent when these procedures are performed by well-trained, experienced clinicians, significant morbidity and even fatal complications have been reported. [210] [211] Complications may be divided into those occurring during attempted venipuncture to gain central venous access, those occurring during placement of the venous catheter, those late complications associated with catheter residence in the body, and those associated with misuse of equipment and misinterpretation of data (Table 30-4) . This categorization is, however, somewhat arbitrary. Some complications, like nerve injury, may go unnoticed at the time of venipuncture but be clinically recognized days following the procedure. In contrast, cardiac perforation and tamponade usually occur in the days following successful central venous cannulation but may occur shortly after the initial catheterization procedure.

Clearly, the incidence of complications depends on various factors, including the site and techniques chosen for venipuncture and the patient's medical condition. Large retrospective and observational studies provide the best estimates of the most frequent complications. In general, unintended *arterial puncture* leads this list of adverse events. Shah et al [263] reported more than 6,000 central venous catheterizations over a 5-year period, with more than 95 percent performed via the internal jugular vein. In this series, the most common complication was carotid artery puncture, which occurred in 120 patients (1.9%) but did not result in any serious morbidity. Authors of other large studies report a somewhat higher incidence of arterial puncture during central venous catheterization, ranging from approximately 3 to 9 percent. [216] [217] [242] In all likelihood, the frequency of arterial puncture with a small-gauge finding needle is even higher. Although usually benign, on rare occasions even small-gauge-needle arterial punctures may lead to serious complications. [264]

If arterial puncture occurs during central venous cannulation, the needle is removed and external pressure is applied to the puncture site for at least 5 minutes or for as long as necessary to prevent hematoma formation. The most efficacious clinical management of unintentional cannulation of the carotid artery with a large-gauge catheter is less clear. In the large series of Shah and coworkers [263] arterial cannulation with a 7.5-French introducer sheath occurred in four patients. The sheath was removed immediately when its intra-arterial location was recognized by the high-pressure backflow of blood. External compression was applied for 5 minutes; there was no hematoma formation requiring further treatment in any patient. Other reports, however, emphasize that unintentional arterial cannulation may result in hematoma formation after catheter removal, with significant risk of airway compromise that may require urgent tracheal intubation and surgical exploration for hematoma evacuation or arterial repair. [121] [216] In summary, when unintentional carotid artery cannulation occurs, it can usually be managed conservatively by removing the catheter, applying local compression to the puncture site, and monitoring the patient's airway and neurologic status. Ideally, a vascular surgeon should be consulted promptly to help manage the complication. Under no circumstances should prolonged cannulation of the carotid artery be tolerated, because arteritis,

thrombus formation, and cerebral embolization may result. [265]

Pneumothorax is often cited as the most common complication of subclavian central venous cannulation, although it appears that unintended arterial puncture occurs more often than pneumothorax, even with the subclavian site of venipuncture. [121] [242] Mansfield et al [242] reported 821 patients who underwent attempted subclavian venous cannulation, with a 1.5 percent incidence of pneumothorax and a 3.7 percent incidence of subclavian arterial puncture. Pneumothorax occurs even less frequently with the internal jugular approach. Shah et al [263] reported an incidence of pneumothorax of 0.5 percent in their series of nearly 6,000 internal jugular catheterizations. This is likely a conservative overestimate, because most patients in this series underwent median sternotomy for cardiac surgery, a procedure that may

TABLE 30-4 -- Complications of Central Venous Pressure Monitoring

VENIPUNCTURE AND GAINING CENTRAL VENOUS ACCESS
Arterial puncture
Hematoma
Hemothorax
Hemomediastinum [1]
Arterial thromboembolism [2]
Airway compromise [3]
Pneumothorax
Subcutaneous, mediastinal emphysema
Chylothorax [4]
Nerve injury
Brachial plexus
Stellate ganglion
Phrenic nerve [5]
Vocal cord paralysis [6]
Chronic pain syndrome [7]
Tracheal puncture
Endotracheal tube cuff perforation [8]
CATHETERIZATION
Arterial cannulation [9] [1]
Venous injury, right facial vein avulsion [1]
Venous valve injury [1] [1]
Catheter shearing and embolization [1]
Guide-wire embolization [1]
Guide-wire-induced arrhythmias, heart block [1] [1]
Chlorhexidine hypersensitivity, anaphylaxis [1] [1]
Air embolism [2] [2] [2] [2]
CATHETER RESIDENCE (LATE COMPLICATIONS)
Delayed vascular injury
Aortoatrial fistula [2]
Venobronchial fistula [2] [2]
Pseudoaneurysm
Right atrial, right ventricular, superior vena caval perforation
Cardiac tamponade [2] [2] [2] [3] [3] [3] [3]
Venous thrombosis [3] [3]
Pulmonary embolism
Superior vena caval syndrome
Impaired venous drainage
Hydrothorax [3] [3]
Hydromediastinum [3]
Infection [3] [3] [4] [4] [4]
Phlebitis [4]
Cellulitis
Bacteremia, fungemia, sepsis
Catheter fracture, embolism
Catheter migration, malposition [4] [4]
Catheter-induced arrhythmias [1]
MISINTERPRETATION AND MISUSE [1] [3] [4] [4] [4]

1. Bernard RW, Stahl WM: Mediastinal hematoma: Complication of subclavian vein catheterization. N Y State J Med January Part I:83, 1974.
2. Heath KJ, Woulfe J, Lownie S et al: A devastating complication of inadvertent carotid artery puncture. Anesthesiology 89:1273, 1998.
3. Goldfarb G, Lebrec D: Percutaneous cannulation of the internal jugular vein in patients with coagulopathies: An experience based on 1,000 attempts. Anesthesiology 56:321, 1982.
4. Khalil KG, Parker FB, Mukherjee N et al: Thoracic duct injury: A complication of jugular vein catheterization. JAMA 221:908, 1972.
5. Drachler DH, Koepke GH, Weg JG: Phrenic nerve injury from subclavian vein catheterization. JAMA 236:2880, 1976.
6. Butsch JL, Butsch WL, Da Rosa JFT: Bilateral vocal cord paralysis. Arch Surg 111:828, 1976.
7. Burton AW, Controy BP, Sims S et al: Complex regional pain syndrome type II as a complication of subclavian catheter insertion. Anesthesiology 89:804, 1998.
8. Klipper WS, Waite HD, Tomlinson CO: Endotracheal cuff perforation complicating subclavian venipuncture. JAMA 228:693, 1974.
9. Brown CQ: Inadvertent prolonged cannulation of the carotid artery. Anesth Analg 61:150, 1982.
10. Oishi AJ, Zietlow SP, Sarr MG: Erroneous arterial placement of a central venous catheter. Mayo Clin Proc 69:287, 1994.
11. Reeves ST, Baliga P, Conroy JM et al: Avulsion of the right vacial vein during double cannulation of the internal jugular vein. J Cardiothroac Vasc Anesth 9:429, 1995.
12. Imai M, Hanaoka Y, Kemmotsu O: Valve injury: A new complication of internal jugular vein cannulation. Anesth Analg 78:1041, 1994.
13. Sum-Ping ST: Internal jugular valves: competent or incompetent. Anesth Analg 78:1039, 1994.

14. Inoue S, Ohnishi Y, Kuro M: Accidental penetration of an indwelling retrograde introducer sheath by an introducer needle during right internal jugular vein cannulation. J Cardiothoracic Vasc Anesth 12:67, 1998.
15. Reynen K: 14-year follow-up of central embolization by a guide wire. N Engl J Med 329:970, 1993.
16. Eissa NT, Kvetan V: Guide wire as a cause of complete heart block in patients with preexisting left bundle branch block. Anesthesiology 73:772, 1990.
17. Kasten GW, Owens E, Kennedy D: Ventricular tachycardia resulting from central venous catheter tip migration due to arm position changes: Report of two cases. Anesthesiology 62:185, 1985.
18. Kessler LG: FDA alert: Hypersensitivity reactions to central venous catheters. Am Soc Anesthesiol Newslett 62:24, 1998.
19. Terazawa E, Shimonaka H, Nagase K et al: Severe anaphylactic reaction due to a chlorhexidine-impregnated central venous catheter. Anesthesiology 89:1296, 1998.
20. Grace DM: Air embolism with neurologic complications: A potential hazard of central venous catheters. Can J Surg 20:51, 1977.
21. Levinsky WJ: Fatal air embolism during insertion of CVP monitoring apparatus. JAMA 209:1721, 1969.
22. Schachner SM, Rahn G, Kampine JP: Atrial catheter malfunction and venous air embolism: A clinical report. Anesthesiol Rev 8:34, 1981.
23. Tahir AH: Prevention of air embolism during subclavian venipuncture. JAMA 223:79, 1973.
24. Danenberg HD, Hasin Y, Milgalter E et al: Aorto-atrial fistula following internal jugular vein catheterization. Eur Heart J 16:279, 1995.
25. Brennan MF, Sugarbaker PH, Moore FD: Venobronchial fistula: A rare complication of central venous catheterization for parenteral hyperalimentation. Arch Surg 106:871, 1973.
26. Caron NR, Demmy TL, Curtis JJ: Bronchial erosion by an indwelling central venous catheter. Chest 106:1917, 1994.
27. Bone DK, Maddrey WC, Eagan J et al: Cardiac tamponade: A fatal complication of central venous catheterization. Arch Surg 106:868, 1973.
28. Bowdle TA: Central line complications from the ASA Closed Claims Project. Am Soc Anesthesiol Newslett 60:22, 1996.
29. Kapadia CB, Heard SO, Yeston NS: Delayed recognition of vascular complications caused by central venous catheters. J Clin Monit 4:267, 1988.
30. Kline IK, Hofman WI: Cardiac tamponade from CVP catheter perforation. JAMA 206:1794, 1968.
31. Kuiper DH: Cardiac tamponade and death in a patient receiving total pa-renteral nutrition. JAMA 230:877, 1974.
32. Mitchell MR, Wood DG, Naraghi M et al: Fatal cardiac perforation caused by the dilator of a central venous catheterization kit. J Clin Monit 9:288, 1993.
33. Pierce EC: Complications associated with the use of central venous venous catheters. Am Soc Anesthesiol Newslett, January 1989.
34. Qureshi GD, Lilly EL: Complications of CVP catheter insertion in cubital vein. JAMA 209:1906, 1969.
35. Seeberger M, Wu X, Skarvan K et al: Does short-term central venous catheterization of the internal jugular vein cause the thrombi of pathologic relevance. Anesthesiology 89:A1203, 1998.
36. Naguib M, Farag H, Joshi RN: Bilateral hydrothorax and hydromediastinum after a subclavian line insertion. Can Anaesth Soc J 32:412, 1985.
37. Rudge CJ, Bewick M, McColl I: Hydrothorax after central venous catheterization. BMJ 3:23, 1973.
38. American Society of Anesthesiologists: Recommendations for Infection Control for the Practice of Anesthesiology, 2nd ed. Park Ridge, IL, American Society of Anesthesiologists, 1998, p 15.
39. Badley AD, Steckelberg JM, Wollan PC et al: Infectious rates of central venous pressure catheters: Comparison between newly placed catheters and those that have been changed. Mayo Clin Proc 71:838, 1996.
40. Corona ML, Peters SG, Narr BJ et al: Infections related to central venous catheters. Mayo Clin Proc 65:979, 1990.
41. Darouiche RO, Raad II, Heard SO et al: A comparison of two antimicrobial-impregnated central venous catheters. N Engl J Med 340:1, 1999.
42. Wenzel RP, Edmond MB: The evolving technology of venous access. N Engl J Med 340:48, 1999.
43. Walters MB, Stanger HAD, Rotem CE: Complications with percutaneous central venous catheters. JAMA 220:1455, 1972.
44. Oakes DD, Wilson RE: Malposition of a subclavian line. Resultant pleural effusions, interstitial pulmonary edema, and chest wall abscess during total pa-renteral nutrition. JAMA 233:532, 1975.
45. Roblin D, Porter JC, Knight RK: Spontaneous migration of totally implanted venous catheter systems from subclavian into jugular veins. Thorax 49:281, 1994.
46. Gilron I, Magder S: Monitoring complication due to a pulsatile femoral vein from tricuspid regurgitation. Can J Anaesth 42:141, 1995.
47. Schapira M, Stern WZ: Hazards of subclavian vein cannulation for central venous pressure monitoring. JAMA 201:111, 1967.
48. Singleton RJ, Webb RK, Ludbrook GL et al: Problems associated with vascular access: An analysis of 2000 incident reports. Anaesth intensive Care 21:664, 1993.

have been responsible for the pneumothorax in many of these patients. Small pneumothoraces may be managed by radiographic observation, with or without needle aspiration, assuming the patient remains clinically stable. Tube thoracostomy is the best treatment, however, for larger pneumothoraces or pneumothorax in the patient receiving positive pressure mechanical ventilation or scheduled for major surgery. The physician must always be prepared for the possibility of tension pneumothorax and its adverse hemodynamic sequelae.

By far, the most common major late complication of central venous cannulation is *infection.* Bloodstream infections occur in approximately 5 percent of patients with standard central venous catheters, leading to an estimated 150,000 cases of catheter-related bacteremia or fungemia annually. [266] Given that the crude mortality of nosocomial bloodstream infections is nearly 35 percent, most simple efforts to reduce this complication appear to be both cost-effective and life saving. [266] [267] As previously noted, the starting point is meticulous attention to aseptic technique. [202] When more long-term central venous cannulation is anticipated, the subclavian site is preferred, because use of the jugular or femoral veins carries a higher risk of infection. [202] [266] Multilumen catheters carry a higher risk than single-lumen catheters, although the added clinical functionality of such catheters may mandate their use. [202] [268] Clearly, the type of catheter inserted influences the rate of catheter colonization and subsequent sepsis. Catheters are made from materials such as silicone, polyvinyl chloride, Teflon, and polyurethane. Furthermore, catheters of the same material may be manufactured differently, which influences their surfaces and the frequency of bacterial adherence to the surface. [269] One recent improvement in catheter design has been incorporation of an antimicrobial treatment onto the catheter surface. Combinations of either chlorhexidine and silver sulfadiazine or monocycline and rifampin have been shown to reduce the rates of catheter colonization and sepsis, although the latter treatment may be the more efficacious. [266] [267] Other effective catheter modifications include the use of a silver-impregnated subcutaneous cuff with catheters intended for long-term use. [212] Despite these improvements, several important issues pertaining to catheter-related infection remain controversial and unresolved. When patients require central venous catheterization for more than 3 to 4 days, some clinicians recommend catheter replacement at a new site, others suggest exchanging the catheter over a guide wire, and still others believe that catheters should not be changed unless there are signs of infection or other clinical indications. [202] [212] [268] [270] Clearly, the risks of infection must be weighed against the alternative risks of establishing a new site for central venous catheterization.

Many other adverse sequelae of central venous cannulation have been reported (see Table 30-4) . Although their incidence is not clearly known, most appear to be uncommon. They should be recognized, however, by all physicians performing these procedures, to limit the morbidity of central venous cannulation. Although some complications may be unavoidable, such as catheter-related infection in an immunocompromised host, many complications result from operator error. [121] [211] [271] [272] Several deserve special emphasis. *Cardiac tamponade* from perforation of the superior vena cava, right atrium, or right ventricle was the single most common fatal complication of central venous cannulation among 3,533 cases in the American Society of Anesthesiologists Closed Claims Project. [211] Most reports document the avoidable nature of this catastrophic event and highlight that patients are predisposed to this complication when central venous catheter tips are malpositioned within the right atrium, right ventricle, or abutting the wall of the superior vena cava. These observations emphasize that radiographic confirmation of proper catheter tip location is mandatory, regardless of whether the catheter is inserted from a central or peripheral site. In fact, many early reports of catheter-related cardiovascular perforation suggest that peripheral catheters may present unusually high risk for this complication, because arm abduction may cause the catheter tip to advance into a dangerous location within the heart. [207] [208] When cardiac tamponade is caused by catheter-induced cardiac perforation, symptoms develop suddenly, requiring the physician to have a high index of suspicion if severe hypotension occurs in any patient with a central venous catheter in place. Cardiac arrhythmias may provide an early clue to the intracardiac location of the catheter tip. [262] [273] Occasionally, both posteroanterior and lateral chest radio-graphs and injection of radiopaque contrast are required to locate the catheter tip precisely. [227] [274] The life-threatening nature of catheter-associated cardiac tamponade has been recognized for several years by the Food and Drug Administration and equipment manufacturers. [210] [211] Package inserts in central venous catheterization kits clearly and explicitly warn the user to avoid intracardiac catheter tip locations, except in the rare circumstance when this is needed, as for aspiration of venous air emboli.

Use of *guide wires, vessel dilators,* and *large-bore catheters* carries certain additional risks that mandate meticulous attention to technique. The proximal tip of the guide wire must remain under the physician's control at all times to avoid inserting the wire too far into the heart, thus causing arrhythmias or heart block [273] or potentially losing the guide wire within the circulation. [121] [275] By design, vessel dilators are stiffer than central venous catheters and may cause significant trauma if inserted forcefully or further than necessary to dilate the subcutaneous tissue track from skin to vein. [272] Large-bore introducer sheaths and multilumen catheters have become popular because of their clinical usefulness, yet their size may increase the risk of cannulation-associated trauma, hemorrhage from unrecognized line disconnections, and major *venous air embolism.* Not only may air be entrained during initial cannulation, [276] but improperly connected large-bore cannulas may pose an additional risk because of the large site for air entry directly into the central venous circulation. [229] [277] [278]

Unusual complications of central venous cannulation continue to be reported as new catheter modifications are designed. To reduce the risk of infection, catheters are being manufactured with an exterior antiseptic surface treatment containing silver sulfadiazine and chlorhexidine. Although more than 2.5 million of these catheters have been used in the United States without incident, [279] rare but severe anaphylactoid reactions have been reported in Japanese patients. [279] [280] A new double-lumen 15.5-French catheter has been designed for use in immunocompromised patients to provide long-term central venous access and an introducer

lumen to accommodate a standard pulmonary artery catheter for hemodynamic monitoring. It remains to be seen whether this type of extremely large catheter will create more problems than it solves. [281]

Although many complications of CVP monitoring relate to equipment misuse, the frequency of complications caused by data misinterpretation remains unknown. It is extremely likely, however, that clinicians misinterpret CVP measurements and have suboptimal understanding of CVP monitoring, just as has been demonstrated repeatedly for PAP monitoring by both physicians and nurses (see later discussion). Safe and effective use of CVP monitoring requires a detailed understanding of normal CVP waveforms and common pathologic changes in these measurements.

Central Venous Pressure Waveforms

Strictly speaking, CVP is the pressure at the junction of the vena cavae and the right atrium and reflects the driving force for filling the right atrium and ventricle. Because the large veins of the thorax, abdomen, and proximal extremities form a compliant reservoir for a sizable percentage of the total blood volume, CVP is highly dependent on intravascular blood volume and intrinsic vascular tone of these capacitance vessels. In other words, the CVP or right atrial pressure reflects the appropriateness of the blood volume to the capacity of the venous system. [282] In addition to providing a measure of the circulating blood volume, CVP reflects the functional capacity of the right ventricle. Based on the Frank-Starling mechanism, higher right heart filling pressures are required to maintain the ventricular stroke output when right ventricular contractility is impaired. Thus, in clinical practice, CVP monitoring is used for assessment of blood volume and right heart function.

CVP monitoring is performed using the same fluid-filled pressure tubing-transducer setup described earlier for direct arterial pressure monitoring (see the earlier section *Technical Aspects of Direct Blood Pressure Measurement*). Although a simple fluid-filled mechanical manometer may be used to estimate CVP, this method is not preferred for routine monitoring. First, manometric measurements are not as accurate as electronically transduced pressures and

TABLE 30-5 -- Central Venous Pressure Waveform Components

WAVEFORM COMPONENT	PHASE OF CARDIAC CYCLE	MECHANICAL EVENT
a wave	End-diastole	Atrial contraction
c wave	Early systole	Isovolumic ventricular contraction, tricuspid motion toward right atrium
v wave	Late systole	Systolic filling of atrium
h wave	Mid- to late diastole	Diastolic plateau
x descent	Mid-systole	Atrial relaxation, descent of the base, systolic collapse
y descent	Early diastole	Early ventricular filling, diastolic collapse

Figure 30-27 (Figure Not Available) Normal central venous pressure (CVP) waveform. The diastolic components (y descent, end-diastolic a wave) and the systolic components (c wave, x descent, end-systolic v wave) are all clearly delineated. A mid-diastolic plateau wave, the h wave, is also seen because heart rate is slow. Waveform identification is aided by timing the relation between individual waveform components and the electrocardiographic R wave, which is highlighted. Waveform timing using the arterial (ART) pressure trace is more confusing, owing to the relative delay in the systolic arterial pressure upstroke. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 2-5.)*

can only be measured intermittently, not displayed continuously. [283] [284] [285] Second, the use of an open manometer system may expose the patient to unnecessary risk of infection and venous air embolism. Finally, a wealth of information exists in the CVP waveform, which can be observed only by electronic transduction and display on a bedside monitor. [80]

The normal mechanical events of the cardiac cycle are responsible for the sequence of waves seen in a typical CVP trace. The CVP waveform consists of five phasic events, three peaks (a, c, v) and two descents (x, y) (Table 30-5 , Fig. 30-27) (Figure Not Available) . [286] [287] [288] The most prominent wave is the *a wave* of atrial contraction, which occurs at end-diastole following the ECG P wave. The a wave increases atrial pressure and provides the "atrial kick" to fill the right ventricle through the open tricuspid valve. Atrial pressure decreases following the a wave, as the atrium relaxes. This smooth decline in pressure is interrupted by the *c wave.* This wave is a transient increase in atrial pressure produced by isovolumic ventricular contraction, which closes the tricuspid valve and displaces it toward the atrium. The c wave always follows the ECG R wave, because it is generated by the beginning of ventricular systole. *

* The c wave observed in a jugular venous pressure trace may have a slightly more complex origin. This wave has been attributed to early systolic pressure transmission from the adjacent carotid artery and may be termed a *carotid impact wave.*[289] Because the jugular venous pressure also reflects right atrial pressure, however, this c wave likely represents both arterial (carotid impact) and venous (tricuspid motion) origins.

Atrial pressure continues its decline during ventricular systole, owing to continued atrial relaxation and changes in atrial geometry produced by ventricular contraction and ejection. This is the *x descent* or systolic collapse in atrial pressure. The x descent can be divided into two portions, x and x
, corresponding to the segments before and after the c wave. The last atrial pressure peak is the *v wave,* caused by venous filling of the atrium during late systole, while the tricuspid valve remains closed. The v wave usually peaks just after the ECG T wave. Atrial pressure then decreases, inscribing the *y descent* or diastolic collapse, as the tricuspid valve opens and blood flows from atrium to ventricle. (A final component of the CVP waveform, the *h wave,* occasionally appears as a pressure plateau in mid- to late diastole. The h wave is not normally seen unless the heart rate is slow and venous pressure is elevated. [289] [290]) In summary, the normal venous waveform components may be remembered as follows: the a wave results from atrial contraction; the c wave from tricuspid valve closure and isovolumic right ventricular contraction; and the v wave from ventricular ejection, which drives venous filling of the atrium.

Thus, in relation to the cardiac cycle and ventricular mechanical actions, the CVP waveform can be considered to have three systolic components (c wave, x descent, v wave) and two diastolic components (y descent, a wave). By recalling the mechanical actions that generate the pressure peaks and troughs, it is easy to identify these waveform components properly by aligning the CVP waveform and the ECG trace and using the ECG R wave to mark end-diastole and the onset of systole. When the radial artery pressure trace is used for CVP waveform timing instead of the ECG, confusion may arise because the arterial pressure upstroke occurs nearly 200 milliseconds after the ECG R wave (see Fig. 30-27) (Figure Not Available) . This normal physiologic delay reflects the times required for the spread of the electrical depolarization through the ventricle (
60 milliseconds), isovolumic left ventricular contraction (
60 milliseconds), transmission of aortic pressure rise to the radial artery (
50 milliseconds), and transmission of the radial artery pressure rise through fluid-filled tubing to the transducer (
10 milliseconds). [126] [145]

The normal CVP peaks have been designated systolic (c, v) or diastolic (a) according to the phase of the cardiac cycle in which the wave begins. However, one generally identifies these waves not by their onset or upstroke, but rather by the location of their peaks. For instance, the a wave generally begins and peaks in end-diastole, but the peak may appear delayed to coincide with the ECG R wave, especially in a patient with a short PR interval. In this instance, a and c waves merge, and this composite wave is termed an *a-c wave.* Designation of the CVP v wave as a systolic event may be even more confusing. Although the ascent of the v wave begins during late systole, the peak of the v wave occurs during isovolumic ventricular relaxation, immediately prior to atrio-ventricular valve opening and the y descent. Consequently, the most precise description would be that the v wave begins in late systole, but peaks during isovolumic ventricular relaxation, the earliest portion of diastole. For clinical purposes, it is simplest to consider the v wave to be a systolic wave, and most authors have adopted this approach. [286] [289]

Although three distinct CVP peaks (a, c, v) and two troughs (x, y) are discernible in the normal venous pressure trace, heart rate changes and conduction abnormalities alter this pattern. A short ECG PR interval causes fusion of a and c waves, and tachycardia reduces the length of diastole and the duration of the y descent, causing v and a waves to merge. In contrast, bradycardia causes each wave to become more distinct, with separate x and x
descents visible and a more prominent h wave. Although there are circumstances in which other pathologic waves may be evident in the CVP trace, one should resist the temptation to assign physiologic significance to each small pressure peak, as many will arise as artifacts of fluid-filled tubing-transducer monitoring systems. Instead, search for the expected waveform components, including those waveforms that are characteristic of the pathologic conditions suspected.

Various pathophysiologic conditions may be diagnosed or confirmed by examination of the CVP waveform. One of the most common applications is the rapid diagnosis of cardiac arrhythmias. [291] In *atrial fibrillation* (Fig. 30-28A) (Figure Not Available) , the a wave disappears and the c wave becomes more prominent, because atrial volume is greater at end-diastole and onset of systole, owing to the absence of effective atrial contraction. Occasionally, atrial fibrillation or flutter

waves may be seen in the CVP trace, when the ventricular rate is slow. *Isorhythmic atrioventricular dissociation* or *junctional (nodal) rhythm* (Fig. 30-28B) (Figure Not Available) alters the normal sequence of atrial contraction prior to ventricular contraction. Instead, atrial contraction now occurs during ventricular systole, when the tricuspid valve is closed, thereby inscribing a tall *cannon a wave* in the CVP waveform. Absence of normal atrioventricular synchrony during *ventricular pacing* (Fig. 30-28C) (Figure Not Available) can be identified in a similar fashion by searching for cannon waves in the venous pressure trace. In these instances, the CVP helps diagnosis the cause of arterial hypotension; loss of the normal end-diastolic atrial kick may not be as evident in the ECG trace as it is in the CVP waveform.

Right-sided valvular heart diseases alter the CVP waveform in different ways. [292] *Tricuspid regurgitation* (Fig. 30-29A) (Figure Not Available) produces abnormal systolic filling of the right atrium through the incompetent valve. A broad, tall systolic c-v wave is inscribed, which begins in early systole and obliterates the systolic x descent in atrial pressure. The CVP trace is said to be ventricularized, resembling right ventricular pressure. Note that this regurgitant wave differs in onset, duration, and magnitude from a normal CVP v wave caused by end-systolic atrial filling from the vena cavae. In patients with tricuspid regurgitation, right ventricular end-diastolic pressure is overestimated by the numeric display on the bedside monitor, which reports a single mean value for CVP. Instead, right ventricular end-diastolic pressure is estimated best by measuring the CVP value at the time of the ECG R wave, prior to the regurgitant systolic wave (see Fig. 30-29A) (Figure Not Available) . Unlike tricuspid regurgitation, *tricuspid stenosis* (Fig. 30-29B) (Figure Not Available) is a diastolic defect in atrial emptying and ventricular filling. Mean CVP is elevated, and a pressure gradient exists throughout diastole between right atrium and ventricle. The a wave is unusually prominent and the y descent is slurred, owing to the impaired diastolic egress of blood from the atrium. Other conditions that reduce right ventricular compliance, such as right ventricular ischemia, pulmonary hypertension, or pulmonic valve stenosis, may produce a prominent end-diastolic a wave in the CVP trace but do not attenuate the early diastolic y descent. CVP waveform morphology changes in other characteristic ways in the presence of pericardial diseases and right ventricular

Figure 30-28 (Figure Not Available) Central venous pressure (CVP) changes caused by cardiac arrhythmias. (A) Atrial fibrillation obliterates the a wave, increases the c wave and preserves the v wave and y descent. This arrhythmia also causes variation in the electrocardiographic (ECG) R-R interval and left ventricular stroke volume, which can be seen in the ECG and arterial (ART) pressure traces. (B) Isorhythmic atrioventricular dissociation. In contrast to the normal end-diastolic a wave in the CVP trace (left panel), an early systolic cannon wave is inscribed (*, right panel). Reduced ventricular filling accompanying this arrhythmia causes a decreased arterial blood pressure. (C) Ventricular pacing. Systolic cannon waves are evident in the CVP trace during ventricular pacing (left panel). Atrioventricular sequential pacing restores the normal venous waveform and increases arterial blood pressure (right panel). ART scale left, CVP scale right. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 14-1 , 14-5 (Figure Not Available) , and 14-16.) (Figure Not Available)*

Figure 30-29 (Figure Not Available) Central venous pressure (CVP) changes in tricuspid valve disease. (A) Tricuspid regurgitation increases CVP and the waveform displays a tall systolic c-v wave that obliterates the x descent. In this example, the a wave is not seen because of atrial fibrillation. Right ventricular enddiastolic pressure is estimated best at the time of the electrocardiographic R wave (arrows) and is lower than mean CVP. See text for greater detail. (B) Tricuspid stenosis also increases mean CVP, but the characteristic venous waveform is different from the one seen in tricuspid regurgitation. The diastolic y descent is attenuated and the end-diastolic a wave is prominent. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 17-3 (Figure Not Available) and 17-15.)*

infarction. These patterns are interpreted best in conjunction with PAP monitoring, which is discussed later.

Perhaps the most important application of CVP monitoring is to provide an estimate of the adequacy of the circulating blood volume and right ventricular preload. As noted earlier, for this purpose, transmural CVP is always the pressure of physiologic interest. In clinical practice, however, we measure and record pressures referenced to ambient atmospheric pressure. Consequently, accurate interpretation of CVP requires the physician to consider alterations in intrathoracic or juxtacardiac pressure that occur during the respiratory cycle. [160] [178] During spontaneous breathing

Figure 30-30 (Figure Not Available) Respiratory influences on the measurement of central venous pressure (CVP). (A) During spontaneous ventilation, onset of inspiration (arrows) causes a reduction in intrathoracic pressure, which is transmitted to both the CVP and the pulmonary artery pressure (PAP) waveforms. CVP should be recorded at end-expiration (mean CVP 14 mmHg). (B) During positive pressure ventilation, onset of inspiration (arrows) causes an increase in intrathoracic pressure. CVP is still recorded at end-expiration (mean CVP 8 mmHg). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Figs. 16-1 (Figure Not Available) and 16-2.) (Figure Not Available)*

(Fig. 30-30A) (Figure Not Available) , inspiration causes a decrease in pleural and juxta-cardiac pressures, which is transmitted, in part, to the right atrium and lowers CVP. This same decrease in pleural pressure will influence other measured central vascular pressures in a similar fashion (see Fig. 30-30A) (Figure Not Available) . Note a subtle but critically important observation about the measurement of central vascular pressures. Although CVP measured relative to atmospheric pressure decreases during the inspiratory phase of spontaneous ventilation, transmural CVP, the difference between right atrial pressure and juxtacardiac pressure may actually increase slightly as more blood is drawn into the right atrium. The opposite pattern is observed during positive-pressure ventilation, in which inspiration increases intrathoracic pressure, raises the measured CVP, but decreases transmural CVP, because venous return is reduced by the elevated intrathoracic pressure. In clinical practice, transmural pressures are rarely measured, owing to difficulties in assessing juxtacardiac or intrathoracic pressure. Instead, *end-expiratory* values for cardiac filling pressures should be recorded in all patients, to provide the best estimate of transmural pressure. At the end of expiration, intrathoracic and juxtacardiac pressures approach atmospheric pressure, whether the patient is breathing spontaneously or receiving positive-pressure mechanical ventilation (Fig. 30-30B) (Figure Not Available) . Proper pressure values can be determined by visual inspection of the CVP waveform on a calibrated monitor screen or paper recording. Under most circumstances, the transmural CVP and the end-expiratory value for CVP will be close to one another. This facilitates comparison of CVP values (and other cardiac filling pressures) obtained from the same patient under varying patterns of ventilation, a common situation in anesthesia and critical care.

Not only can individual CVP waveforms provide unique diagnostic clues about the circulation, but trends in CVP during anesthesia and surgery also are useful in estimating fluid or blood loss and guiding replacement therapy. It is important to remember that there is a significant range for normal values and that small changes in CVP may reflect significant changes in the circulating blood volume and right ventricular preload. Additional useful information may be derived from examining how a fluid bolus simultaneously alters CVP and other variables of clinical interest, such as the blood pressure, urine output, and so forth.

PULMONARY ARTERY PRESSURE MONITORING

Swan, Ganz, and colleagues [293] introduced pulmonary artery catheterization for hemodynamic monitoring into clinical practice in 1970. In fact, many clinicians still refer to balloon-tipped, flow-directed pulmonary artery catheters (PAC) as Swan-Ganz catheters, in reference to the two cardiologists who originally popularized this diagnostic tool for management of patients with acute myocardial infarction. [293] [294] [295] [296] [297] These catheters allowed accurate measurement of important cardiovascular physiologic variables at the bedside, and their popularity soared over the next two decades as they were used in an increasing number of critically ill and surgical patients. By the middle 1990s, estimated annual PAC sales in the United States approached 2 million catheters, [298] [299] with an estimated cost associated with their use in excess of 2 billion dollars each year. [300]

Clearly, proper use of the PAC discloses a wide range of pertinent cardiovascular data that many clinicians, including experts in intensive care, cannot accurately predict from standard clinical signs and symptoms. [301] [302] [303] However, despite this evidence that PACs provide accurate cardiovascular measurements, it is not known, with any measure of certainty, whether PAC monitoring leads to improved patient outcome. [299] [300] [304] [305] [306] [307] [308] [309] [310] [311] Before considering this issue, we will review the physiologic basis for PAC monitoring, techniques for catheterization, complications associated with PAC use, and interpretation of normal and pathologic PAP waveforms. With these important concepts in mind, we will return to consider the PAC monitoring controversy, including the evidence for and against use of the catheter, as well as the current indications for this technique.

Physiologic Considerations: Prediction of Left Ventricular Filling Pressure

PAC is performed to measure hemodynamic variables in critical patients, including cardiac output, mixed venous oxygen saturation, and most importantly, pulmonary artery diastolic pressure (PADP) and PAWP. These pressure

Figure 30-31 (Figure Not Available) Pulmonary artery wedge pressure measurement creates a static column of blood connecting the catheter tip to a junction point where flow resumes in the pulmonary veins (PV) near the left atrium (LA). RA, right atrium; RV, right ventricle, PA, pulmonary artery; and LV, left ventricle. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 4-1.) (Figure Not Available)*

measurements are used to estimate left ventricular filling pressure and help guide fluid and vasoactive drug administration when clinical signs, symptoms, or other monitored variables are felt to be inadequate or unreliable. [299]

When a PAC floats to the wedge position, the inflated balloon at its tip isolates the distal pressure-monitoring orifice from upstream PAP. Blood flow ceases between the catheter tip and a junction point where pulmonary veins draining the occluded pulmonary vascular region join other veins in which blood still flows toward the left atrium (Fig. 30-31) (Figure Not Available) . A continuous static column of blood now connects the wedged PAC tip to this junction point in the pulmonary veins near the left atrium. Thus, wedging the PAC functionally extends the catheter tip to measure the pressure at the point at which blood flow resumes on the venous side of the pulmonary circuit. [312] Because resistance to flow in the large pulmonary veins is negligible, PAWP provides an accurate, indirect measurement of both pulmonary venous pressure and LAP. [131] [313]

PADP is used often as an alternative to the wedge pressure to estimate left ventricular filling pressure. Under normal circumstances, resistance to pulmonary blood flow is low, and the pressure in the pulmonary artery at end of diastole equilibrates with downstream pressure in the pulmonary veins and left atrium. [314] [315] [316] [317] From a monitoring standpoint, PADP has the added advantage of being available for continuous monitoring, in contrast to PAWP, which can be measured only intermittently when the PAC balloon is inflated.

For PADP or PAWP to be a valid estimate of left ventricular filling pressure, a continuous, static column of blood must exist between the tip of the wedged catheter and the draining pulmonary venous radicle. At the microcirculatory levels, this connecting channel consists of thin pulmonary capillaries, which are subject to extramural compressive forces exerted by surrounding alveoli. West et al [318] described a physiologic model of the pulmonary vasculature consisting of three zones that are based on the gravitationally determined relations between PAP, pulmonary venous pressure, and alveolar pressure. This lung zone model provides useful insights into conditions when the PAC may not provide accurate estimates of left ventricular filling pressures.

In lung physiologic zones 1 and 2, alveolar pressure can exceed pulmonary venous pressure (zone 2) or both PAP and pulmonary venous pressure (zone 1) (Fig. 30-32) (Figure Not Available) . A PAC positioned in these lung zones will be influenced by alveolar pressure and bear little relationship to the downstream pulmonary venous pressure or left ventricular filling pressure. Under these circumstances, alveolar or airway pressures are being monitored, rather than the intended vascular pressure in the left atrium or ventricle. Fortunately, in most clinical settings in which a PAC is used, patients are supine, which favors creation of zone 3 conditions. However, patients nursed in the lateral or semisitting position may have considerable nondependent portions of their lungs exhibit zone 2 behavior. In general, zones 1 and 2 become more extensive when LAP is low, when the PAC tip is located vertically above the left atrium, or when alveolar

Figure 30-32 (Figure Not Available) The pulmonary artery catheter tip must be wedged in lung Zone 3 to provide an accurate measure of pulmonary venous (P_v) or left atrial (LA) pressure. When alveolar pressure (P_A) rises above P_v in lung zone 2, or above pulmonary arterial pressure (P_a) in lung zone 1, wedge pressure will reflect alveolar pressure rather than intravascular pressure. RA, right atrium; RV, right ventricle; PA, pulmonary artery; and LV, left ventricle. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 6-10.)*

pressure is high. Catheters that are wedged outside zone 3 may be suspected when the normal phasic PAWP a and v waves are absent, when wedge pressure varies markedly with the respiratory cycle, and when mean wedge pressure exceeds PADP, because this should never occur unless tall a or v waves are present in the wedge-pressure trace [131] (see section on *Pulmonary Artery Pressure and Pulmonary Artery Wedge Pressure Waveforms*).

Pulmonary Artery Catheterization

PACs can be placed from any of the central venous cannulation sites described earlier, but the right internal jugular vein is preferred because it provides the most direct route to the right heart chambers and thereby usually leads to successful catheterization. [263] The procedure is conducted as already described for central venous cannulation, until the step where the venous catheter is to be inserted. At this point, a slightly larger skin nick is made to accommodate the large-bore (7.5-9.0 French) introducer sheath. This introducer has a hemostasis valve at its outer end, through which the PAC will be inserted, and a side-arm extension that allows

continuous central venous access for fluid and drug administration. A tapered-tip, stiff, dilator stylet is placed into the introducer sheath to facilitate passage of this large cannula over the guide wire from the skin, through the subcutaneous tissues, into the vein. Utmost care must be exercised when introducing this large dilator-cannula assembly, advancing it only to the depth required to enter the vein, then threading the introducer cannula completely into the vein over the guide wire and dilator. Finally, the guide wire and dilator are removed, the side-arm extension is secured to an intravenous infusion set using a Luer-lock connector, and the introducer sheath is sutured in place.

The standard PAC has a 7.0-, 7.5-, or 8.0-French circumference and is 110 cm in length, with these distances marked at 10-cm intervals. It contains four separate internal lumens. One leads to the distal port at the catheter tip and is used for PAP monitoring. The second leads to a proximal port, located approximately 30 cm from the catheter tip, and it is intended for CVP monitoring, as well as intravenous fluid and drug administration. The third lumen leads to a balloon near the catheter tip, and the fourth contains fine wires leading to a temperature thermistor, just proximal to the balloon. This thermistor is used to monitor pulmonary artery blood temperature as part of the thermodilution method for cardiac output monitoring (see later discussion).

The final steps in placing a PAC require the aid of a skilled assistant to help prepare the catheter and attach it properly to pressure monitoring transducers. The physician performing the catheterization removes the PAC from its package and inserts it through a sterile plastic sheath, being careful not to damage the balloon in this process. [319] This sheath or sleeve covers a length of the PAC residing outside the patient and thereby allows minor manipulations of PAC position during the monitoring period, while attempting to maintain catheter sterility. The assistant then attaches the distal (PAP) and proximal (CVP) ports to the standard pressure transducing system that will allow these waveforms to be displayed on the bedside monitor. These ports are flushed to ensure their proper function and to expel the air from these catheter lumina. [320] The balloon is inflated with the special syringe packaged with the PAC. This syringe is volume-limited to 1.5 mL, the standard volume used for balloon inflation. The balloon is tested by filling it with 1.5 mL of air to make certain that there are no leaks and that the balloon inflates symmetrically, without obstructing the opening of the distal lumen. [321]

The balloon should always be inflated with air, *not* liquid. The air-filled balloon at the tip of the catheter serves to carry the catheter forward with the blood flow through the right heart chambers and helps "float" the catheter to its proper position in the pulmonary artery, much like the spinnaker on a sailboat is driven by the trailing wind. Some authors have suggested that the balloon may be inflated with sterile saline to aid catheter passage when difficulties, such as severe tricuspid valve regurgitation, are present. [322] However, this is a fairly dangerous practice because saline, unlike air, is a noncompressible fluid, and using it to inflate the PAC balloon may increase the risk of pulmonary artery rupture. To reduce the risk of unintentional balloon inflation with liquid, the special balloon-inflation system should remain attached to the PAC at all times. [323]

A simple maneuver may now be performed to check for proper assembly and function of the PAC and monitoring system (Fig. 30-33) (Figure Not Available) . [324] [325] When the tip of the PAC is held near heart level, the recorded pressure should be 0 mm Hg, confirming that the transducer was correctly adjusted to the level of the heart at the beginning of the procedure. The catheter tip is then raised up straight to create a 30-cm tall vertical fluid column, which should produce a pressure of 22 mm Hg (equivalent to 30 cm H_2O), on the bedside monitor (see Fig. 30-33) (Figure Not Available) . This quick, simple step ensures that the pressure recorded from the distal lumen during PAC flotation is correct, because it checks the integrity of the entire monitoring system from the tip of the catheter to the waveform display on the screen.

The PAC is inserted through the hemostasis valve of the introducer to a depth of 20 cm, or approximately 5 cm beyond the tip of the introducer sheath. A characteristic CVP waveform must be identified to confirm that the PAC tip is in the vena cava or right atrium. The gentle curvature

Figure 30-33 (Figure Not Available) Bedside testing of the pulmonary artery catheter- pressure transducer system. With the tip of the catheter held at the level of the transducer and the heart, a pressure of 0 mm Hg is recorded. The catheter tip is raised to create a 30-cm vertical fluid column, and the resulting pressure display should equal 22 mm Hg (equivalent to 30 cm H_2O). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 3-4.)*

Figure 30-34 (Figure Not Available) Characteristic waveforms recorded during passage of the pulmonary artery catheter. The right atrial pressure resembles a central venous pressure waveform and displays a, c, and v waves. Right ventricular pressure shows a higher systolic pressure than seen in the right atrium, although the end-diastolic pressures are equal in these two chambers. Pulmonary artery pressure shows a diastolic step-up compared with RVP. Note also that RVP increases during diastole, whereas pulmonary artery pressure decreases during diastole (shaded boxes). Pulmonary artery wedge pressure has a similar morphology to right atrial pressure, although the a-c and v waves appear later in the cardiac cycle relative to the electrocardiogram. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 3-1.)*

of the PAC should be oriented to point just leftward of the saggital plane (the 11-o'clock position as viewed from the patient's head). This orientation will facilitate catheter passage through the anteromedially located tricuspid valve. The balloon now is inflated, and the catheter is advanced into the right atrium, through the tricuspid valve into the right ventricle, through the pulmonic valve into the pulmonary artery, and finally into the wedge position. Characteristic waveforms from each of these positions confirm proper catheter passage and placement. These waveforms are later reviewed in detail (Fig. 30-34) (Figure Not Available) .

After PAWP is measured, the balloon is deflated, and the PAP waveform should reappear. During the monitoring period, wedge pressure may be obtained as needed by reinflating the balloon with 1.5 mL air, so that pulmonary blood flow can help float the catheter distally until pulmonary artery occlusion again occurs. The clinician must recognize that the PAC tip advances to a smaller pulmonary artery each time the balloon is inflated to measure PAWP. Similarly, the PAC should return to its monitoring position in the proximal pulmonary artery after the balloon is deflated. In some patients, the PAC may migrate distally even without balloon inflation. This problem is more common during cardiopulmonary bypass, owing to the repeated cardiac manipulations and temperature changes that alter the stiffness of the catheter. [326] Consequently, proper catheter position must be ensured throughout the monitoring period by observing the PAP waveform continuously. If a PAWP trace appears without balloon inflation, or during only partial balloon inflation, the balloon should be deflated and the catheter withdrawn several centimeters to reduce the risk of pulmonary vascular injury. If necessary, the PAC may be readvanced subsequently to achieve proper position and obtain the wedge pressure. Although the external protective sleeve covering the PAC is intended to maintain sterility during these minor adjustments in catheter position, the sleeve does not preclude contamination. Therefore, PACs should be manipulated only as necessary to maintain a proper safe location. [327]

Guidelines for Catheter Placement

From a right internal jugular vein puncture site, the right atrium should be reached when the PAC is inserted 20 to 25 cm, the right ventricle at 30 to 35 cm, the pulmonary artery at 40 to 45 cm, and the wedge position at 45 to 55 cm. When other vascular puncture sites are chosen for catheter placement, additional distance is required, typically an additional 5 to 10 cm from the left internal jugular and left and right external jugular veins, an additional 15 cm from the femoral veins, and an additional 30 to 35 cm from the antecubital veins. [325] These distances serve only as a guide. Waveform morphology must be verified from the monitor display, and catheter position must be confirmed with a chest radio-graph. The tip of the PAC should be within 2 cm of the cardiac silhouette on a standard anteroposterior chest film. [328]

Keeping in mind these typical distances aids proper waveform identification and helps avoid complications caused by unintended catheter loops and knots. If a right ventricular waveform is not observed after inserting the catheter 40 cm, coiling in the right atrium is likely. Similarly, if a pulmonary artery waveform is not observed after inserting the catheter 50 cm, coiling in the right ventricle has probably occurred. The balloon should be deflated, the catheter withdrawn to 20 cm, and then the PAC floating sequence is repeated.

Although the right internal jugular vein is the primary site for pulmonary artery catheterization, failure to achieve venous cannulation or other medical and surgical considerations may require use of alternative sites. For cardiac surgery, the left internal jugular vein is often the second choice because use of the subclavian veins poses a problem unique to this setting. After sternotomy and sternal retraction, a PAC inserted by the subclavian route may be compressed and kinked under the clavicle, making it impossible to withdraw or advance the catheter, should this be required during the course of surgery. [329]

Regardless of the intended surgical procedure, whenever one plans to insert a PAC through the left internal jugular, subclavian, and particularly the external jugular veins, the more tortuous course of these vessels may make it difficult to advance the large-bore introducer sheath fully into the vessel. This is not a problem, so long as the introducer cannula is withdrawn slightly to maintain a position in the vein that allows unimpeded intravenous infusion and free aspiration of venous blood. Often the introducer cannula needs to remain in this partially inserted position, while the PAC is introduced through its hemostasis valve. Owing to the more flexible, smaller tip of the PAC compared with that of the introducer, the PAC may advance easily and completely into the central vein and right atrium. The PAC balloon then

may be inflated and the procedure completed in the normal fashion. With the PAC in proper position, the introducer sheath usually can be guided fully into the central vein and sutured in place because the PAC has served, in essence, as a more effective "guide wire." Occasionally, the introducer sheath must remain partially or completely withdrawn to avoid acute angulation and kinking of the PAC as it leaves the sheath and enters the central vein. [329] [330] [331]

After successful venous cannulation, when attempts to advance the PAC to the right ventricle prove difficult, the physician should consider whether this results from abnormal venous anatomy. The most common abnormality of the systemic veins is *persistence of the left superior vena cava,* which is present in approximately 0.5 percent of the general population and 2 to 5 percent of patients with other forms of congenital heart disease. [332] [333] [334] [335] [336] The persistent left superior vena cava descends along the left mediastinum and empties into the coronary sinus, which is dilated as a consequence of the abnormal venous drainage pattern. Occasionally, the condition is recognized radiographically by an abnormal appearance of the left side of the mediastinum and cardiac border, or an abnormal pulsation of the left internal jugular vein. [335] [336] However, because there are no physiologic consequences of this abnormal venous anatomy, virtually all cases are asymptomatic and discovered incidentally at the time of attempted central venous or pulmonary artery catheterization. In patients with this anomaly, PAC placement may be difficult or impossible, owing to the tortuous course the catheter must follow from the vena cava, through the coronary sinus, to reach the right heart chambers. Because a normal right superior vena cava is present in most of these patients, the anomaly is recognized only when attempted PAC placement proceeds from a left-sided vein. More rarely, difficult PAC placement is encountered during attempted right-sided venous cannulation because the right superior vena cava is absent as well. In these cases, the right internal jugular vein joins the persistent left superior vena cava by a bridging innominate vein. A rare form of atrial septal defect, termed *unroofed coronary sinus,* may also be encountered in patients with these venous abnormalities. This congenital defect provides a site for coronary sinus-left atrial communication, with the potential for a PAC to enter the left atrium and systemic circulation through this defect. [336] With any of these venous anomalies, PAC advancement into the coronary sinus may disclose an unexpected pressure waveform, coronary sinus pressure. This waveform has characteristics of both the downstream right atrial pressure and an indirectly transmitted, dampened left ventricular pressure waveform. Its recognition requires that the physician have a clear appreciation for the expected waveforms encountered by the PAC as right heart catheterization proceeds.

A few additional points might aid successful positioning of the PAC. The air-filled balloon tends to float to nondependent regions as it passes through the heart into the pulmonary vasculature. Consequently, positioning a patient head down will aid flotation past the tricuspid valve, and tilting the patient onto the right side and placing the head up will aid flotation out of the right ventricle and may reduce the frequency of malignant ventricular arrhythmias during catheterization. [337] Owing to gravitational and anatomic factors, most catheters float to the right pulmonary artery. [338] Thus, to catheterize the left pulmonary artery selectively, the patient should be positioned with the right side down. [339] Deep inspiration during spontaneous ventilation will increase venous return and right ventricular output transiently. This may facilitate catheter flotation in a patient with low cardiac output. On occasion, a catheter may be floated to proper position when stiffened by injecting, through the distal lumen, 10 to 20 mL of the iced solution prepared for cardiac output measurement. Finally, a catheter that is initially difficult to place may be positioned easily when hemodynamic conditions change, as commonly occurs after induction of general anesthesia and initiation of positive-pressure ventilation.

Complications of Pulmonary Artery Catheterization and Pressure Monitoring

Use of PACs has been associated with various adverse effects. As in the case of CVP monitoring, PAC monitoring complications may be divided into: (1) those that occur during initial attempts to gain venous access, (2) those occurring during pulmonary artery catheterization, (3) those late complications associated with catheter residence in the body, and (4) those associated with misuse of equipment and misinterpretation of data. For the most part, problems during attempts to gain central venous access are similar for PAC or CVP monitoring (see Table 30-4) . However, catheterization of the right heart chambers beyond the cavoatrial junction may cause complications uniquely associated with PACs and rarely, if ever, seen with CVP monitoring alone (Table 30-6) .

Although many complications have been described over the past 25 years, their incidence is not clearly known because they are described, for the most part, in isolated case reports or small case series. [340] When all adverse effects are considered, including self-limited arrhythmias observed during catheter insertion, it appears that minor complications occur in more than 50 percent of patients. [299] [341] However, of much greater clinical relevance, major morbidity specifically associated with PAC use is uncommon. [342] In 1993, the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization [299] reviewed 860 publications in the medical literature in an attempt to delineate the risks and benefits of PAC. This group discovered that the reported incidence of complications from PAC monitoring varied widely. Based on this literature review and their collective expert opinions, the task force suggested that serious complications due specifically to pulmonary artery catheterization occur in 0.1 to 0.5 percent of PAC-monitored surgical patients. [299] Two large prospective observational studies of more than 5,000 patients each provide good support for this contention. In 1984, Shah et al [263] reported use of PACs in 6,245 patients undergoing cardiac and noncardiac operations. [263] Quite remarkably, only 10 patients (0.16%) had serious complications resulting in morbidity and only 1 patient (0.016%) died as a result of pulmonary artery catheterization. More recently, a preliminary European report of PAC use in 5,306 patients undergoing cardiac operations confirms a similar low incidence of major morbidity, with injury

TABLE 30-6 -- Complications of Pulmonary Artery Pressure Monitoring

CATHETERIZATION
Arrhythmias
Supraventricular arrhythmias, atrial fibrillation
Ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation [1] [2] [3]
Right bundle branch block [4] [5] [6]
Complete heart block
Misplaced catheter tip
Air embolism
CATHETER RESIDENCE (LATE COMPLICATIONS)
Mechanical problems
Catheter entrapment [7] [8] [9] [1] [1] [1]
Catheter coiling, knotting [1] [1] [1]
Catheter tip migration [1]
Introducer sheath problems [1] [1] [1] [1]
Balloon rupture
Thrombosis, pulmonary embolism [2] [2] [2] [2] [2]
Thrombocytopenia [2]
Pulmonary infarction
Infection [2] [2] [2]
Endocarditis [2] [3]
Structural damage
Endocardium, tricuspid valve, pulmonic valve [3] [3]
Pulmonary artery

Rupture [3] [3] [3] [3] [3]

Pseudoaneurysm [3] [3] [3] [4] [4] [4]

MISINTERPRETATION AND MISUSE [4] [4] [4] [4] [4] [4]

1. Salmenpera M, Peltola K, Rosenberg P: Does prophylactic lidocaine control cardiac arrhythmias associated with pulmonary artery catheterization? Anesthesiology 56:210, 1982.
2. Shaw TJI: The Swan-Ganz pulmonary artery catheter. Anaesthesia 34:651, 1979.
3. Voukydis PC, Cohen SI: Catheter-induced arrhythmias. Am Heart J 88:588, 1974.
4. Morris D, Mulvihill D, Lew WYW: Risk of developing complete heart block during bedside pulmonary artery catheterization in patients with left bundle-branch block. Arch Intern Med 147:2005, 1987.
5. Sprung CL, Elser B, Schein RMH et al: Risk of right bundle-branch block and complete heart block during pulmonary artery catheterization. Crit Care Med 17:1, 1989.
6. Thompson IR, Dalton BC, Lappas DG et al: Right bundle-branch block and complete heart block caused by the Swan-Ganz catheter. Anesthesiology 51:359, 1979.
7. Cooper SC, Desai M, Alpern JB: Beware the pulsating Swan. J Cardiothorac Anesth 4:474, 1990.
8. Daccache G, Depoix J-P, Provenchere S et al: Pulmonary artery catheter during cardiac surgery: A rare but severe adverse effect. J Cardiothorac Vasc Anesth 12:125, 1998.
9. Eguaras MG, Lluch M, Valdivia J et al: An unusual complication of Swan-Ganz catheter use. Texas Heart Inst J 19:149, 1992.
10. Klockgether-Radke A, Rathgeber J, Lange H: Unbeabsichtigte intrakardiale Fixierung eines Swan-Ganz-Katheters. Anaesthesist 44:116, 1995.
11. Shah KB, Rao TLK, Laughlin S et al: A review of pulmonary artery catheterization in 6,245 patients. Anesthesiology 61:271, 1984.
12. Troianos CA, Stypula RW: Transesophageal echocardiographic diagnosis of pulmonary artery catheter entrapment and coiling. Anesthesiology 79:602, 1993.
13. Fibuch EE, Tuohy GF: Intracardiac knotting of a flow-directed balloon-tipped catheter. Anesth Analg 59:217, 1980.
14. Lipp H: Intra-cardiac knotting of a flow-directed balloon catheter. N Engl J Med 284:220, 1971.
15. Shin B, Ayella RJ, McAslan TC: Pitfalls of Swan-Ganz catheterization. Crit Care Med 5:125, 1977.
16. Bromley JL, Moorthy SS: Acute angulation of a pulmonary artery catheter. Anesthesiology 59:367, 1983.
17. Campbell FW, Schwartz AJ: Pulmonary artery catheter malfunction? Anesthesiology 60:513, 1984.
18. Guntupalli RM: Mechanical aberrations with pulmonary-artery catheters. Anesthesiology 50:374, 1979.
19. Noel TA: Pulmonary artery catheter sheath malfunction with sternotomy. Anesthesiology 61:633, 1984.
20. Chastre J, Cornud F, Bouchama A et al: Thrombosis as a complication of pulmonary-artery catheterization via the internal jugular vein. N Engl J Med 306:278, 1982.
21. Foote GA, Schabel SI, Hodges M: Pulmonary complications of the flowdirected balloon-tipped catheter. N Engl J Med 290:927, 1974.
22. Hoar PF, Stone JG, Wicks AE et al: Thrombogenesis associated with Swan-Ganz catheters. Anesthesiology 48:445, 1978.
23. Hoar PF, Wilson RM, Mangano DT et al: Heparin bonding reduces thrombogenicity of pulmonary-artery catheters. N Engl J Med 305:993, 1981.
24. Yorra FH, Oblath R, Jaffe H et al: Massive thrombosis associated with use of the Swan-Ganz catheter. Chest 65:682, 1974.
25. Vincent J-L, Dhainaut J-F, Perret C et al: Is the pulmonary artery catheter misused? A European view. Crit Care Med 26:1283, 1998.
26. Applefield JJ, Caruthers TE, Reno DJ: Assessment of the sterility of long-term cardiac catheterization using the thermodilution Swan-Ganz catheter. Chest 74:377, 1978.
27. Cobb DK, High KP, Sawyer R et al: A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. N Engl J Med 327:1062, 1992.
28. Mermel LA, McCormick RD, Springman SR et al: The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: A prospective study utilizing molecular subtyping. Am J Med 91:197S, 1991.
29. Bernardin G, Milhaud D, Roger PM et al: Swan-Ganz catheter-related pulmonary valve infective endocarditis: A case report. Intensive Care Med 20:142, 1994.
30. Rowley KM, Clubb KS, Smith GJW et al: Right-sided infective endocarditis as a consequence of flow-directed pulmonary-artery catheterization. N Engl J Med 311:1152, 1984.
31. Connors AF, Castele RJ, Farhat NZ et al: Complications of right heart catheterization: A prospective autopsy study. Chest 88:567, 1985.
32. Barash PG, Nardi D, Hammond G et al: Catheter-induced pulmonary artery perforation. J Thorac Cardiovasc Surg 82:5, 1981.
33. Kelly TF, Morris GC, Crawford ES et al: Perforation of the pulmonary artery with Swan-Ganz catheters: Diagnosis and surgical management. Ann Surg 193:686, 1981.
34. Klafta JM, Olson JP: Emergent lung separation for management of pulmonary artery rupture. Anesthesiology 87:1248, 1997.
35. Lemen R, Jones JG, Cowan G: A mechanism of pulmonary-artery perforation by Swan-Ganz catheters. N Engl J Med 292:211, 1975.
36. McDaniel DD, Stone JG, Faltas AN et al: Catheter-induced pulmonary artery hemorrhage: Diagnosis and management in cardiac operations. J Thorac Cardiovasc Surg 82:1, 1981.
37. Bartter T, Irwin RS, Phillips DA et al: Pulmonary artery pseudoaneurysm. Arch Intern Med 148:471, 1988.
38. Carlson TA, Goldenberg IF, Murray PD et al: Catheter-induced delayed recurrent pulmonary artery hemorrhage. JAMA 261:1943, 1989.
39. Karak P, Dimick R, Hamrick KM et al: Immediate transcatheter embolization of Swan-Ganz catheter-induced pulmonary artery pseudoaneurysm. Chest 111:1450, 1997.
40. Roberts LC, Ramsay MAE, Alivizatos PA et al: Successfully treated pulmonary artery rupture complicated by aneurysm formation. J Cardiothorac Vasc Anesth 6:70, 1992.
41. Sprung J, Schoenwald PK, Hayden J et al: Contained pulmonary artery perforation by pulmonary artery catheter. J Clin Monit 14:195, 1998.
42. Urschel JD, Myerowitz PD: Catheter-induced pulmonary artery rupture in the setting of cardiopulmonary bypass. Ann Thorac Surg 56:585, 1993.
43. Ginosar Y, Thijs LG, Sprung CL: Raising the standard of hemodynamic monitoring: Targeting the practice or the practitioner? Crit Care Med 25:209, 1997.
44. Gnaegi A, Feihl F, Perret C: Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: Time to act? Crit Care Med 25:213, 1997.
45. Iberti TJ, Fischer EP, Leibowitz AB et al: A multicenter study of physicians' knowledge of the pulmonary artery catheter. JAMA 264:2928, 1990.
46. Iberti TJ, Daily EK, Leibowitz AB et al: Assessment of critical care nurses' knowledge of the pulmonary artery catheter. Crit Care Med 22:1674, 1994.
47. Komadina KH, Schenk DA, LaVeau P et al: Interobserver variability in the interpretation of pulmonary artery catheter pressure tracings. Chest 100:1647, 1991.
48. Trottier SJ, Taylor RW: Physicians' attitudes toward and knowledge of the pulmonary artery catheter: Society of Critical Care Medicine Membership Survey. New Horiz 5:201, 1997.

of the right ventricle or PA occurring in only 4 patients (0.07%). [343] Finally, only 1 of 2,000 adverse events reported in the Australian Incident Monitoring Study of 1993 involved use of a PAC, in contrast to 64 other adverse events involving access to the arterial or venous systems. [121] Although these large studies suggest that there is a low incidence of serious complications attributable to the use of PAC, the frequency of complications in a particular clinical setting or patient group remains unknown. However, clinicians who use PAC must be familiar with all the potential complications associated with catheter use in an attempt to avoid these problems, or at least recognize these problems early and treat them successfully.

Arrhythmias are the primary complication observed during pulmonary artery catheterization (PAC-PA catheter). In fact, minor atrial or ventricular arrhythmias are so common during PAC passage through the heart that most clinicians do not consider this a complication, but rather a confirmation that the PAC is traversing the cardiac chambers en route to the pulmonary artery. Shah et al [263] observed transient premature ventricular contractions in 68 percent and atrial dysrhythmias in 1.3 percent of their catheterized patients. Of greater clinical significance, *persistent ventricular arrhythmias* requiring treatment with lidocaine occurred in only 3.1 percent of patients, none of whom suffered prolonged hemodynamic instability. Although the balloon-tipped PAC is less arrhythmogenic when it strikes the endocardium than a standard intravenous catheter or transvenous pacing wire, [344] PACs have been reported to cause atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. [337] [343] [344] [345] As rare as these arrhythmias may be, the physician must always consider them as a risk factor when placing a PAC. For example, in a patient with critical aortic stenosis scheduled for valve replacement, one may choose to withhold a PAC or to delay flotation of the catheter until the heart is exposed and cardiopulmonary bypass support is immediately available. Prophylactic use of IV lidocaine prior to pulmonary artery catheterization has not been shown to reduce consistently the incidence of ventricular arrhythmias, [346] [347] and most clinicians reserve this drug for treatment of sustained arrhythmias. When ventricular tachycardia or frequent ventricular premature beats occur during the catheterization procedure, the balloon should be deflated and the catheter withdrawn to the right atrium. This terminates the arrhythmia in nearly all cases, and the pulmonary artery may be catheterized using standard procedures once the arrhythmia has ceased.

A more difficult clinical question arises when hemodynamically significant arrhythmias develop later in the monitoring period, after the PAC has been in place for hours or days. Although it is unlikely that the PAC is responsible for these new arrhythmias, the position of the catheter tip should always be checked by observation of the pressure waveform and chest radiograph. A catheter tip that is malpositioned within the right ventricle is significantly more arrhythmogenic than a catheter tip, cushioned by the inflated balloon, that is floating through the heart during initial catheterization. Once proper PAC position is confirmed and other causes of ventricular arrhythmia, such as myocardial ischemia, are excluded, several clues may point toward the PAC as the cause of the rhythm disturbance. These include left bundle branch block morphology of the ventricular premature beats, their resistance to medical therapy, and their response to withdrawal of the catheter into the right atrium. [344]

As the PAC passes through the right ventricle and strikes the interventricular septum, transient *right bundle branch block* occurs in up to 5 percent of patients. [348] [349] [350] This complication presumably results from the minor trauma of catheter passage through the heart. It occurs less frequently with balloon-tipped catheters than with standard stiff cardiac catheters, which are known to cause right or left bundle branch block, depending on which ventricular chamber is catheterized. [349] [351] Right bundle branch block is of no real clinical consequence except in patients with preexisting left bundle branch block, in whom *complete heart block* may be precipitated. [350] Despite this theoretical concern, complete heart block from pulmonary artery catheterization is uncommon. Shah et al [263] catheterized 113 patients with preexisting left bundle branch block with only one patient developing complete heart block (0.9%). In a different population of 47 high-risk patients with left bundle branch block, many of whom had acute myocardial infarction or heart failure, Morris et al [348] employed 82 PACs without a single episode of complete heart block during the catheterization or for 24 hours thereafter. Thus, prophylactic placement of a transvenous ventricular pacing wire is not necessary in patients with preexisting left bundle branch block who require PAC monitoring. Instead, transcutaneous pacing equipment, an external pulse generator, and a temporary transvenous pacing wire or pacing PAC (see later discussion) should be readily available to treat severe bradycardia. It is important for the anesthesiologist to recognize that onset of heart block from pulmonary artery catheterization may be delayed and only fully manifest following administration of anesthetic drugs. For example, incomplete right bundle branch block following PAC insertion has been reported to progress to complete right bundle branch block and bradycardia following induction of anesthesia. [350] Thus, the anesthesiologist must be prepared to treat this complication whenever it arises.

Various *mechanical problems* with PACs or introducer sheaths have been reported, and a physician who is familiar with these potential problems should be able to

avoid most of them. In the setting of cardiac surgery, PACs may become entrapped by sutures placed in the heart or by the cannulas used for these operations. [263] [352] [353] [354] [355] [356] Sternal retraction during cardiac surgery poses another mechanical problem with PACs, particularly when they are inserted through the external jugular or subclavian routes. The PAC may kink as it exits the introducer sheath and makes an acute angle between the sheath and vessel wall. [329] [330] [331] This problem may be resolved by withdrawing the introducer sheath slightly or limiting the amount of surgical retraction. These mechanical difficulties may be recognized by a damped appearance of the monitored pressure traces or by difficulty infusing fluid or withdrawing blood through one of the catheter lumens. [263] They serve to remind the anesthesiologist and heart surgeon that the PAC should be checked for free movement during the surgical procedure and following any cardiac repair in which sutures have been placed near the course of the PAC. Although gross structural defects in PAC should be recognized by inspection prior to catheter insertion, more subtle manufacturing problems may escape

detection. [319] [320] Some of these, such as interluminal communications between the PAP, CVP, and balloon inflation lumens, may be suspected only when information derived from the catheters is inconsistent with other clinical data. [321] [357]

PACs may become entangled with other cardiac structures or catheters or dislodge temporary transvenous pacing wires. Knotting of PACs has also been reported. [358] [359] Knots or kinks in the catheter should be suspected if there is any difficulty withdrawing a PAC, and the diagnosis may be confirmed by chest radiography. Knots may be untied *in vivo* by radiologists using intravascular snares and fluoroscopic guidance. [360] If the knot has already been drawn tight, removal under direct surgical exposure of the venous cannulation site may be required. [361] These problems are more likely when the PAC is inserted an excessive distance leading to looping or coiling of the catheter within the cardiac chambers. Prevention is the best treatment.

Like any prosthetic intravascular device, PACs may serve as a nidus for intravascular *thrombosis.* [362] Although the incidence of thromboembolic complications is increased in patients who require PAC monitoring for longer periods of time, thrombi have been noted to be attached to a PAC within 1 to 2 hours of their insertion. [363] [364] When drugs such as aprotinin and epsilon aminocaproic acid are used to reduce perioperative bleeding, the risk of thrombus formation on the PAC may be even greater. [365] [366] Although external surface heparin bonding unquestionably has reduced thrombogenicity of PACs, [364] [367] it does not entirely remove this complication. [366] This predisposition to intravascular thrombosis in patients with PAC monitoring arises in part from the prosthetic catheter itself and in part from the subclinical endothelial injury produced by the catheter. Through autopsy examination of 32 patients who died with PACs in place, Connors et al [368] demonstrated that venous thrombi, fibrin strands, mural ecchymoses, or intimal petechiae were evident in 90 percent of patients. Rowley et al [369] performed autopsies on 55 previously catheterized patients and found that 53 percent had right-sided endocardial lesions. Although the general clinical implications of these autopsy findings are unclear, they serve as a warning of the potential risks of pulmonary artery catheterization.

Although minor venous thrombi [362] and pulmonary ischemic lesions [370] are fairly common in patients with PAC monitoring, major pulmonary embolism arising from use of a PAC is a rare occurrence. [371] Rather than thromboembolism, the most common cause of *pulmonary infarction* in patients with PACs is occlusion of pulmonary blood flow by a malpositioned catheter that occludes a branch of the pulmonary artery. [370] The radiographic hallmark of this condition is a wedge-shaped infiltrate radiating from the tip of a peripherally located PAC. This iatrogenic complication may be prevented by diligent monitoring of the PAP waveform recorded from the catheter tip, allowing early recognition of a catheter that migrated distally, became wedged within a small pulmonary artery, and obstructed distal blood flow.

PAC-related *infections* occur more commonly in patients who require monitoring for more than 3 days and those with preexisting sepsis. [372] Using sophisticated microbiologic techniques in 297 critically ill medical and surgical patients, Mermel et al [373] demonstrated a 22 percent incidence of local infection of the introducer sheath, but a low 0.7 percent incidence of bacteremia caused by the PAC. Although PACs may be colonized from multiple sources, the patient's skin is the most important source of organisms, and it is the introducer sheath, rather than the PAC itself, that is usually the infected device. In view of these findings, it is not surprising that scheduled changes of PACs do not reduce the risk of bloodstream infection, particularly when the catheter is changed over a guide wire through the original venipuncture site. [374] When clinical factors mandate changing the PAC, placement through a new vascular access site will reduce the risk of infection compared with guide wire- assisted exchange. However, cannulation at a new puncture site carries a greater risk of mechanical complications, and these risks and benefits must be balanced in each individual patient. [374]

The most serious infection related to PACs is *endocarditis.* The pulmonic and tricuspid valves are the most likely sites, but right atrial endocarditis has also been reported. [369] [375] Although these catastrophic infections appear to be rare, they represent part of the continuum of endocardial damage, thrombosis, and infection that has been documented to be associated with use of PACs. [369] Immunocompromised, debilitated, bacteremic patients may be at particular risk for these complications.

Perhaps the most life-threatening complication of pulmonary artery catheterization is one that is uncommon and often avoidable through meticulous attention to insertion and monitoring techniques. *Pulmonary artery rupture* occurs in approximately 0.02 to 0.2 percent of catheterized patients and appears to be a fatal complication in nearly 50 percent of cases. [263] [433] [376] [378] Although it may occur in a variety of monitoring situations, [379] many reported cases have involved patients undergoing heart surgery requiring cardiopulmonary bypass. [378] [380] Several patient factors common to this clinical setting have been proposed to increase the risk of this complication, including hypothermia, anticoagulation, advanced age, and pulmonary hypertension. [380] [381] [382] [383] Pulmonary hypertension may predispose patients to arterial injury during balloon inflation owing to the increased pressure gradient between the proximal PAP and the distal wedge pressure or because pulmonary hypertension distends the pulmonary vasculature and causes the PAC to wedge in a distal, less compliant vessel. Even though both factors may result in eccentric balloon inflation that tends to drive the exposed catheter tip into the vessel wall, [383] [384] experimental evidence that pulmonary hypertension increases risk of pulmonary artery rupture remains controversial. [382] [383]

Several mechanisms for pulmonary artery injury have been proposed and investigated. Hardy et al, [382] studying cadaveric specimens, determined that the pressure required to rupture the pulmonary artery of patients older than 60 years was well within the range of pressures normally exerted during balloon inflation, suggesting that a balloon forcefully inflated in a pulmonary artery smaller than the balloon diameter may rupture the vessel wall. Other proposed mechanisms for pulmonary artery rupture include chronic erosion by a catheter tip abutting the vessel wall or eccentric balloon inflation that forces the uncushioned catheter tip through the vessel wall. [381] [385] Regardless of the precise mechanism by which pulmonary arterial injury occurs in an individual patient, many case reports highlight

that this complication often results from suboptimal catheter insertion and monitoring techniques. These procedural errors include unnecessary catheter manipulation, excessive insertion distances predisposing to catheter tips located in distal small pulmonary arteries, unrecognized persistent wedge pressure, prolonged balloon inflation, or improper balloon inflation with liquid rather than air. [323] [378] [381] [384] [385] It is critical that the clinician recognize artifactual "overwedged" pressure recordings that indicate peripheral location of the PAC tip or impaction against the vessel wall and correct this problem immediately by withdrawing the catheter into the proximal pulmonary artery (see later discussion).

The hallmark of catheter-induced pulmonary artery rupture is hemoptysis, which may cause life-threatening exsanguination or hypoxemia. Less commonly, this complication presents as occult hypotension or respiratory compromise. If the visceral pleura fails to contain the bleeding, free rupture into the pleural space produces a large hemothorax. When time allows, a chest radiograph helps make the diagnosis by revealing the hemothorax or a new infiltrate near the tip of a distally positioned PAC. This infiltrate may be confused with catheter-related pulmonary infarction, but its pattern of resolution and other clinical signs and symptoms help distinguish these diagnoses. [377] In confusing cases, the diagnosis may be made by performing a wedge angiogram, in which radiopaque dye injected through the wedged PAC will extravasate into the pulmonary parenchyma to identify the site of arterial disruption. [381]

Treatment focuses on cardiorespiratory stabilization, maintaining adequate gas exchange, and arresting the hemorrhage. Specific therapeutic steps depend on the setting in which the complication occurs and may be quite different when pulmonary artery rupture is suspected in a debilitated patient in the intensive care unit compared with a relatively fit patient undergoing cardiopulmonary bypass. The first priority is ensuring adequate pulmonary ventilation and may require endobronchial intubation with either a single- or double-lumen endotracheal tube to allow selective unilateral lung ventilation and protect the unaffected lung. [386] Positive end-expiratory pressure (PEEP) applied to the affected lung may help control hemorrhage. [380] Anticoagulation, if present, should be reversed unless the patient must remain on cardiopulmonary bypass. Bronchoscopy is performed for tracheobroncheal toilet and to localize the site of bleeding. Other maneuvers may be performed at the bedside to provide temporary control of hemorrhage. A Fogarty catheter may be guided into the involved bronchus to tamponade the bleeding and prevent continued contamination of the uninvolved lung. [376] Management of the PAC itself in these circumstances is more controversial. Some authors recommend removing the catheter, [377] but others suggest leaving the PAC in place to monitor PAP and guide antihypertensive therapy targeted at lowering this pressure and reducing

bleeding. [378] Others have suggested that the PAC balloon may be carefully reinflated and the catheter floated into the involved pulmonary artery to occlude the bleeding arterial segment as a temporizing measure. [376]

Although these conservative medical treatments may be effective in many cases, some patients will require defini-tive surgical therapy, such as oversewing the involved pulmonary artery or resecting the involved segment, lobe, or lung. [376] [377] [380] [381] Patients who have this complication and are managed with conservative medical therapy alone are at risk for *pseudoaneurysm* formation and secondary hemorrhage. [376] [380] [384] [387] [388] Because of these delayed risks and the high mortality associated with rebleeding, some authors have recommended followup pulmonary arteriography and possible coil embolization or elective surgical resection in patients who were initially managed medically. [376] [380] [387] [389]

All the already described complications of PAC have been validated by published case reports or large case series, and the causal link between PAC use and these complications has been well established. A more insidious complication of PAC monitoring, and perhaps the most common serious adverse effect from the use of this technology is *misinterpretation of data,* leading to inappropriate, harmful therapy. [298] Although it is not clear what role this factor plays in creating complications in an individual patient, there is reason to believe that there are widespread knowledge deficits among practitioners who use PACs in clinical care. In 1990, Iberti et al [390] reported the results of a 31-question multiple-choice examination that tested knowledge of the PAC. The test was administered to 496 resident and staff physicians in medicine, surgery, and anesthesiology departments, who practiced in 13 North American medical centers. The authors found a poor overall level of knowledge of PACs, as evidenced by a mean test score of only 67 percent correct answers, and they concluded, "there is reason to be concerned about the effective use of the PAC." [390] Although higher scores were demonstrated by individuals with more training and more experience inserting and using catheter-derived information in patient management, none of these factors ensured a high level of knowledge. Similarly disappointing results were obtained subsequently when this examination was administered to 216 critical care nurses, [391] 535 European intensive care physicians, [392] and 1,095 members of the United States Society of Critical Care Medicine. [393] The authors of these reports seemed particularly concerned that wedge pressure measurement from a strip-chart recording was performed incorrectly by 30 to 50 percent of the clinicians reported in these studies. Other authors have also noted the large interobserver variability in interpretation of PAC pressure tracings. [394] These observations highlight the fact that effective use of PACs require a great deal of expertise and clinical experience, and even measuring the most fundamental PAC-derived variable, namely PAWP, may prove to be a complicated exercise. [395] [396] [397] With these issues in mind, normal and pathologic PAC waveforms are next reviewed, with an emphasis on the physiologic mechanisms that produce them.

Pulmonary Artery Pressure and Pulmonary Artery Wedge Pressure Waveforms

Normal Waveforms

As the flow-directed, balloon-tipped PAC is floated from a central vein to its proper position in the pulmonary artery, characteristic pressure waveforms are recorded (see Fig. 30-34) (Figure Not Available) . When the catheter tip reaches the superior vena

---

Figure 30-35 (Figure Not Available) Temporal relations between normal systemic arterial pressure (ART), pulmonary artery pressure (PAP), central venous pressure (CVP), and pulmonary artery wedge pressure (PAWP). Note that the PAWP a-c and v waves appear to occur later in the cardiac cycle compared with their counterparts on the right side of the heart seen in the CVP trace. ART pressure scale on the left; PAP, CVP, and PAWP pressure scales on the right. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 3-3.) (Figure Not Available)*

cava or right atrium, a CVP waveform should be observed, with its a, c, and v waves and low mean pressure value (see Table 30-1) . At this point, the PAC balloon is inflated, and the catheter is advanced until it crosses the tricuspid valve to record *right ventricular pressure.* This waveform is recognized by the sudden increase in systolic pressure, the wide pulse pressure, and the low diastolic pressure that approximates CVP. The PAC next enters the right ventricular outflow tract and floats across the pulmonic valve into the main pulmonary artery. Often, this passage is heralded by arrhythmias, especially premature ventricular beats, as the balloon-tipped catheter strikes the right ventricular infundibulum. *Pulmonary artery pressure* is characterized by the step-up in diastolic pressure recorded as the catheter crosses the pulmonic valve. In the absence of pulmonic valve stenosis, systolic PAP closely approximates right ventricular systolic pressure, but PADP generally exceeds right ventricular dia-stolic pressure. On occasion, it may be difficult to distinguish right ventricular pressure from PAP, particularly if only digital values for these pressures are reported. However, by examining the diastolic pressure contours, the distinction between right ventricular pressure and PAP becomes clear. PAP decreases steadily during diastole, as blood flows from the pulmonary artery toward the left atrium. In contrast, right ventricular pressure increases steadily during diastole as blood flows into the right ventricle through the open tricuspid valve (see Fig. 30-34) (Figure Not Available) . [325]

Under normal conditions, the PAP upstroke slightly precedes the radial artery pressure upstroke (Fig. 30-35) (Figure Not Available) . This reflects the longer duration of left ventricular isovolumic contraction, as well as the transmission time of the central aortic pressure upstroke to the downstream radial artery recording site. [145] Although the PAP upstroke precedes the radial artery pressure upstroke by 50 milliseconds, peak PAP precedes peak radial artery pressure by only 10 milliseconds. [398] As a practical matter, PAP and systemic arterial pressure contours appear to overlap on the bedside monitor, with these pressures rising, peaking, and falling at approximately the same points in time (see Fig. 30-35) (Figure Not Available) . [325] Understanding these temporal relations is critically important if one is to properly interpret abnormal PAP and PAWP waveforms, particularly when tall v waves are present in these traces (see later discussion).

The PAC, with balloon inflated, finally reaches the wedge position. As noted above, the PAWP is an indirect measurement of pulmonary venous pressure and LAP and should therefore resemble these pressure waveforms. Consequently, the PAWP waveform may be identified as a venous pressure trace that displays characteristic a and v waves and x and y descents. However, owing to the pulmonary vascular bed interposed between the PAC tip and left atrium, PAWP is a delayed representation of LAP. [313] [399] On average, 160 milliseconds are required for the LAP pulse to traverse the pulmonary veins, capillaries, arterioles, and arteries. As a consequence of this delay, the wedge-pressure a wave appears to follow the ECG R wave in early ventricular systole (see Fig. 30-35) (Figure Not Available) . However, the a wave is an end-diastolic pressure event, produced by left atrial contraction. This time delay in phasic wedge pressure waves must be appreciated for proper waveform interpretation.

Not only is PAWP a delayed representation of LAP, but it is also a damped reflection of phasic atrial pressure waves. The amount of damping is variable, but when LAP waves are prominent, the pressure peaks may be significantly underestimated and the pressure nadirs significantly overestimated by the wedge trace (Fig. 30-36) (Figure Not Available) . Even though the PAWP waveform will always appear to be a damped, delayed version of LAP, the mean pressure recorded from these two sites should be similar under most circumstances. [287]

To recognize prominent a or v waves in the PAWP trace, it is not always necessary to inflate the PAC balloon and obtain wedge position (Fig. 30-37) (Figure Not Available) . Because the wedge pressure records LAP waves transmitted in retrograde fashion from the left atrium, these waves will normally sum with the antegrade PAP waves produced by right ventricular ejection. The PAP trace thus becomes a composite wave, reflecting both retrograde and antegrade components. Consequently, tall left atrial a and v waves distort the normal PAP contour,

---

Figure 30-36 (Figure Not Available) Pulmonary artery wedge pressure (PAWP) is a damped, delayed reflection of left atrial pressure (LAP). The tall regurgitant v waves (v) caused by severe mitral regurgitation are seen clearly in the LAP trace but appear delayed and smaller in magnitude in the PAWP trace. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 4-4.) (Figure Not Available)*

with the a wave inscribed at the onset of the systolic upstroke and the v wave distorting the dicrotic notch (see Fig. 30-37) (Figure Not Available) . [313] [400] Once these waves are identified by observing the wedge pressure and comparing it with the PAP trace, it is convenient, and perhaps more prudent, to follow the wedge-pressure a and v waves in the PAP trace, without repeatedly inflating the balloon to measure wedge pressure. However, marked changes in PAP values or wave morphology should initiate balloon inflation and wedge-pressure measurement, because artifacts occasionally mimic these observations (see later discussion).

In summary, PAWP measured with a balloon-tipped PAC provides a delayed, damped estimate of LAP, by measuring the pressure where flow resumes at a pulmonary venous junction point near the left atrium. Mean PAWP will always be lower than mean PAP; otherwise, blood would not flow in an antegrade direction.

The PAWP waveform should display small a and v waves just as the LAP waveform, and these phasic components should be identifiable if the pressure

Figure 30-37 (Figure Not Available) Tall left atrial pressure (LAP) a and v waves transmitted in a retrograde direction through the pulmonary vasculature distort the antegrade pulmonary artery pressure (PAP) waveform. The LAP a wave distorts the systolic upstroke, and the v wave distorts the dicrotic notch. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 4-10.) (Figure Not Available)*

trace is displayed with sufficient gain and resolution on the monitor screen.

Left Atrial Pressure, Pulmonary Artery Wedge Pressure, and Pulmonary Capillary Pressure

Because of its method of placement, direct *left arterial pressure* (*LAP)* monitoring is usually restricted to patients undergoing cardiac surgery. The most common technique for monitoring LAP involves catheterization of the left atrium with a thin catheter introduced through the right superior pulmonary vein and secured with a purse-string suture. The catheter is brought out through the skin beneath the xiphoid process and attached to a closed pressure monitoring tubing-transducer system. Because LAP monitoring is discontinued in the postoperative period simply by withdrawing the left atrial catheter through the skin, transseptal methods for LAP monitoring during surgery have been proposed to reduce the risk of bleeding following catheter removal. [213] [401] [402] LAP measurement has also been performed for diagnostic cardiac catheterization by a retrograde arterial approach, transseptal venous catheterization, and even percutaneous direct left atrial puncture from a right paravertebral insertion site. [403]

LAP monitoring is less widely practiced today than in the past, largely because it has been supplanted by PAC monitoring. This has occurred, no doubt, because the PAC simultaneously provides an estimation of left ventricular filling pressure as well as additional useful monitoring information, including CVP and cardiac output. Although some authors have shown modest discrepancies between the LAP and PAWP in the period immediately following cardiopulmonary bypass, [404] the PAWP generally provides an excellent estimate of LAP for cardiac surgical patients in the postoperative period. [316] [404] [405] Furthermore, the pathophysiologic conditions that alter the relationships among the PADP, PAWP, and LAP have been well described and should be recognized by the physician to avoid misinterpretation of the data provided by these monitors (see later discussion).

Direct LAP monitoring continues to be particularly useful in pediatric patients undergoing complex congenital heart surgery, because of the difficulties using some of the standard percutaneous techniques in this patient population. Gold et al [406] reported use of more than 6,000 transthoracic left atrial and right atrial pressure monitoring catheters, with complications from LAP monitoring occurring in only 0.68 percent of 2,393 left atrial catheters. [407] However, the physician must recognize that direct access to the left heart chambers always carries the risk of air and particulate embolization to the systemic circulation. LAP monitoring therefore requires close attention to proper management by the entire team of caregivers to ensure that line patency is maintained and flushing is performed with care. The most common complications of LAP monitoring actually result from catheter removal. Because of the risk of bleeding from the cardiac site of catheter entry, the left atrial catheter must be removed before mediastinal chest drains. When the catheter cannot be withdrawn through the skin, surgical reexploration is needed to remove the retained

catheter. Other rare complications of LAP monitoring include entrapment of the catheter in mechanical aortic or mitral valve prostheses, [406] [408] fistula formation between the right superior pulmonary vein and the right mainstem bronchus, [406] and unrecognized retained catheter fragments that serve as a source of systemic embolization. [409]

Normal LAP waveforms resemble CVP or right atrial pressure waveforms, although there are few subtle morphologic distinctions. Because atrial depolarization originates in the sinoatrial node located at the junction of the superior vena cava and the right atrium, the right-sided a wave appears slightly earlier than the left-sided a wave (Fig. 30-38) (Figure Not Available) . Although the a wave is the most prominent pressure peak in a normal CVP trace, the v wave is often taller than the a wave in a normal LAP waveform. These observations suggest that right atrial contraction is generally more forceful than left atrial contraction, and that the left atrium is less distensible than the right atrium during passive systolic filling. [145] Finally, the interval between right atrial contraction and right ventricular contraction is longer by approximately 40 milliseconds than the interval between left atrial contraction and left ventricular contraction. [145] Consequently, a and c waves are seen more often as separate waves in a right atrial pressure trace than in a LAP trace. In normal LAP waveforms, the a and c waves merge into a composite a-c wave, although most clinicians simply describe this pressure peak as the a wave. Similarly, the PAWP waveform generally displays only a and v waves, because the PAWP c wave is obscured further by the transpulmonary damping effect of the lung vasculature.

The terms PAWP and pulmonary artery occlusion pressure (PAOP) are used interchangeably and refer to the same measurement obtained from the tip of a PAC following balloon inflation and flotation to the wedged position. As already discussed, PAWP and PAOP are used as indirect estimates of mean LAP. In contrast, the hydrostatic pressure in the pulmonary capillaries is a different pressure that must exceed LAP to maintain antegrade blood flow through the lungs. This pulmonary capillary pressure must not be confused with PAWP or LAP, nor should these terms be used interchangeably. [410] Continued use of the phrase "pulmonary capillary wedge pressure" to mean PAWP or PAOP has perpetuated misconceptions about these measurements.

Figure 30-38 (Figure Not Available) Normal temporal relations between the electrocardiographic, central venous pressure (CVP), and left atrial pressure (LAP) traces. The LAP and CVP waveforms have nearly identical morphologies, although the CVP a wave slightly precedes the LAP a wave. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 2-9.)*

Although the magnitude of the difference between pulmonary capillary pressure and PAWP is generally small, it can increase markedly when resistance to flow in the pulmonary veins is elevated. In most situations, the major component of pulmonary vascular resistance occurs at the precapillary, pulmonary arteriolar level. However, rare conditions like pulmonary veno-occlusive disease may cause a marked increase in postcapillary resistance to flow within the pulmonary veins. A similar situation arises in other conditions that disproportionately increase pulmonary venous resistance, such as central nervous system injury, acute lung injury, hypovolemic shock, endotoxemia, and norepinephrine infusion. [410] [411] Under these conditions, measurement of PAWP will underestimate pulmonary capillary pressure substantially and thereby underestimate the risk of hydrostatic pulmonary edema. Although pulmonary capillary pressure may be measured at the bedside by analyzing the decay in PAP following PAC balloon inflation, these techniques have not been adopted widely in clinical practice. [412] [413] [414] [415] [416] [417] To avoid confusion, the phrase "pulmonary capillary wedge pressure" should be abandoned because it is imprecise and misleading. [410]

Abnormal Waveforms

PAC catheter monitoring is subject to the same technical artifacts inherent in all invasive pressure monitoring techniques, as well as some additional problems unique to this method. [385] [418] [419] [420] Because the PAC is longer than other intravascular catheters, greater attention must be paid to ensure that the lumens are free from clot or air bubbles that will distort the pressure waveforms. In addition, the PAC passes through the heart and is subject to pressure recording artifacts resulting from cardiac-induced catheter motion. These artifactual pressure spikes may be distinguished from the underlying physiologic pressure waveform by their unique morphology and timing.

The most common prominent pressure spike artifact observed in a PAC trace is seen immediately following the ECG R wave at the onset of systole (Fig. 30-39) (Figure Not Available) . [418] [421] At this point in the cardiac cycle, tricuspid valve closure and right ventricular contraction and ejection set the PAC in motion and inscribe a spurious, nonphysiologic pressure wave. Note that this artifactual PAP wave occurs at the same time as the CVP c wave and may appear as an artifactual pressure trough, as well as artifactual pressure peak. If this artifactual trough pressure is detected inappropriately by the bedside monitor, it may be reported as a spuriously low value for PADP. Repositioning the PAC by advancing or withdrawing it a few centimeters often helps it assume a slightly different position in the heart and ameliorates this problem. [418]

Another common artifact in PAP measurement occurs when attempts to inflate the balloon cause the catheter tip to become obstructed and thus fail to measure intravascular pressure. This phenomenon is generally termed *overwedging* and usually is caused by distal catheter migration, with subsequent eccentric balloon inflation that forces the catheter tip against the pulmonary artery wall. Rather than recording intravascular pressure, the catheter now records the gradually rising pressure produced by the continuous flush system as it builds up pressure against the obstructed

Figure 30-39 (Figure Not Available) Artifactual pressure peaks and troughs in the pulmonary artery pressure (PAP) waveform caused by catheter motion. The correct value for pulmonary artery end-diastolic pressure is 8 mm Hg (A) although the monitor digital display erroneously reports the PAP as 28/0 mm Hg (B). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 5-6.) (Figure Not Available)*

Figure 30-40 (Figure Not Available) Overwedging of the pulmonary artery (PA) catheter causes artifactual waveform recordings. The first two attempts to inflate the PA catheter balloon (first two arrows) produce a nonpulsatile increasing pressure caused by an occluded catheter tip. After the catheter is withdrawn slightly, balloon inflation allows proper wedge-pressure measurement (third arrow). Prior to the third attempt at balloon inflation, the PA pressure lumen is flushed. This restores the appropriate pulsatile detailed to the PA and wedge-pressure waveforms on the right side of the trace. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 5-7.) (Figure Not Available)*

distal opening. (Fig. 30-40) (Figure Not Available) Note that the overwedged pressure is devoid of pulsatile detail, much higher than PADP, and is continuously rising toward the flush pressure level. These observations all suggest that this cannot be an accurate measurement of PAWP.

As emphasized earlier, each PAC balloon inflation allows the catheter tip to migrate distally several centimeters to reach the wedge position. This flotation process generally occurs over several cardiac cycles. "Instant wedge pressure" occurring before full balloon inflation suggests that the PAC is located inappropriately in a smaller, distal branch of the pulmonary artery. The catheter should be withdrawn before overwedging results in vascular injury or pulmonary infarction. A distally positioned catheter may overwedge itself without balloon inflation. This must be recognized immediately by observing the waveform, and the PAC must be withdrawn until a normal PAP tracing is restored.

Pathophysiologic conditions involving the left-sided cardiac chambers or valves produce characteristic changes in the PAP or PAWP waveforms. [422] One of the most widely recognized abnormalities is the tall v wave of *mitral regurgitation* (Fig. 30-41) (Figure Not Available) . Unlike a normal wedge pressure v wave produced by late systolic pulmonary venous inflow, which fills the left atrium while the mitral valve is closed, the prominent v wave of mitral regurgitation begins in early systole and might be more precisely designated a regurgitant c-v wave. Mitral regurgitation causes fusion of c and v waves and obliteration of the systolic x descent, as the isovolumic phase of left ventricular systole is eliminated owing to the retrograde ejection of blood into the left atrium. [292] Because the prominent v wave of mitral regurgitation is generated during ventricular systole, measurement of mean PAWP will result in overestimation of left ventricular filling pressure, just as measurement of mean CVP in patients with severe tricuspid regurgitation will result in overestimation of right ventricular filling pressure (see Fig. 30-29) (Figure Not Available) . In patients with severe mitral regurgitation, left ventricular end-diastolic pressure (LVEDP) is estimated best by measuring PAWP prior to onset of the regurgitant v wave (Fig. 30-42 (Figure Not Available) ; see Fig. 30-41) (Figure Not Available) . Although mean wedge pressure exceeds LVEDP in

Figure 30-41 (Figure Not Available) Mitral regurgitation. A tall regurgitant v wave (v) is seen in the pulmonary artery wedge pressure (PAWP) trace and also may be noted in the unwedged pulmonary artery pressure (PAP) waveform (arrow). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 17-5.)*

Figure 30-42 (Figure Not Available) Severe mitral regurgitation. A tall systolic v wave (v) is inscribed in the pulmonary artery wedge pressure (PAWP) trace and also distorts the pulmonary artery pressure (PAP) trace, giving it a bifid appearance. The electrocardiogram (ECG) is abnormal owing to ventricular pacing. Left ventricular end-diastolic pressure is estimated best by measuring PAWP at the time of the electrocardiographic R wave, prior to onset of the regurgitant v wave. Note that mean PAWP exceeds left ventricular enddiastolic pressure in this condition. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 17-11.)*

patients with mitral regurgitation, it remains a good approximation of mean LAP. Consequently, the regurgitant v wave contributes to left atrial hypertension and the subsequent risk of hydrostatic pulmonary edema.

When large v waves are present in the PAWP trace, it is critically important to recognize them and be able to distinguish the PAWP waveform from the unwedged PAP waveform. At first glance, a wedge trace with a tall systolic v wave resembles a typical unwedged PAP trace, but closer observation reveals a number of discriminating morphologic details. The PAP upstroke is steeper and slightly precedes the systemic arterial pressure upstroke, whereas a PAWP with a prominent v wave has a more gradual upstroke that begins after the radial artery pressure upstroke. Although the PAP peak occurs at about the same time as the systemic arterial pressure peak and the ECG T wave, the wedge pressure v wave reaches its peak later in the cardiac cycle, after the ECG T wave (see Figs. 30-41 (Figure Not Available) and 30-42) (Figure Not Available) . [292] [398] This so-called "rightward shift" in the PAP waveform should be recognized by careful scrutiny and comparison of the ECG, systemic arterial, pulmonary artery, and wedge pressure traces. Another feature that distinguishes PAP and PAWP traces in patients with severe mitral regurgitation is the unusual morphology of the PAP waveform itself. The prominent regurgitant v wave distorts the PAP waveform, giving it a bifid appearance in systole and obscuring the normal end-systolic dicrotic notch (see Figs. 30-41 (Figure Not Available) and 30-42) (Figure Not Available) . This is most evident in patients with the tallest wedge pressure v waves. [400] [423] By recognizing these subtle but important diagnostic details, a clinician may monitor the wedge pressure v wave by observing the unwedged PAP trace and obviate the need for repeated balloon inflation. Of greater importance, one should hope to avoid the disastrous situation in which a PAC migrates distally, becomes wedged unintentionally without balloon inflation, and the clinician, not recognizing the wedge tracing, attempts to inflate the balloon and thus causes pulmonary artery rupture.

Although some clinicians use the height of the PAWP v wave as an indicator of mitral regurgitation severity, this practice is fraught with problems and has some fundamental physiologic limitations. [292] [424] [425] [426] [427] [428] Because wedge pressure is a damped reflection of LAP, there may be some instances in which a prominent v wave is present in the LAP trace but is obscured in the wedge pressure trace. [429] More important, the PAWP v wave is a pressure surrogate for a volume event, namely regurgitant systolic flow, across the mitral valve. A closer look at left atrial pressure-volume relations helps to elucidate the apparently paradoxic coexistence of severe mitral regurgitation and a normal PAWP trace. [425] [430] Three factors determine whether mitral regurgitation produces a prominent v wave in the left atrial or wedge pressure traces: left atrial volume (often termed the patient's volume status), left atrial compliance, and volume of regurgitation (Fig. 30-43) (Figure Not Available) . Given that the left atrial pressure-volume relation is curvilinear, the same volume of regurgitation will result in a small increment in systolic pressure or a large increment in pressure, depending on the preexisting atrial volume at onset of systole. Similarly, the shape of the left atrial pressurevolume curve, which reflects atrial stiffness or compliance, will determine the height of the pressure wave for any given regurgitant volume. This may explain why patients with acute mitral regurgitation tend to have prominent PAWP v waves, in that they have smaller, stiffer left atria than

Figure 30-43 (Figure Not Available) V wave height as an indicator of mitral regurgitation severity. Left atrial pressure-volume curves describe the three factors that determine v wave height. (A) Influence of left atrial volume. For the same regurgitant volume (x), the left atrial v wave will be taller if baseline atrial volume is greater (point B versus point A) (B) Influence of left atrial compliance. For the same regurgitant volume (x), the left atrial v wave will be taller if baseline atrial compliance is reduced (point B versus point A). (C) Influence of regurgitant volume. Beginning at the same baseline left atrial volume (points A and B), if regurgitant volume increases (X versus x), the left atrial pressure v wave will increase (V versus v). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 17-13.)*

patients with chronic valvular regurgitation. [426] [430] Although the total regurgitant volume of blood entering the left atrium will influence the height of v wave, this clearly is not the only determinant of v wave magnitude. Therefore, it is not surprising that wedge-pressure v waves are neither sensitive nor specific indicators of mitral regurgitation severity. [425] [426] [427] [428] Prominent PAWP v waves may exist in the absence of mitral regurgitation when LAP is elevated, which might occur when the left atrium is compressed, [431] and they also are seen commonly in patients with hypervolemia, congestive heart failure, and ventricular septal defect. [425] Note that the giant v waves seen in patients with ventricular septal defect have a different cause. They result from exaggerated antegrade systolic flow into the left atrium, caused by the left-to-right shunt, which increases pulmonary blood flow and systolic atrial filling through the pulmonary veins. [424]

In contrast to mitral regurgitation, which distorts the systolic portion of the PAWP waveform, *mitral stenosis* alters the morphology of the diastolic portions of this waveform. In this condition, the holodiastolic pressure gradient across the mitral valve results in an increased mean PAWP, a slurred early diastolic y descent, and a tall end-diastolic a wave. Similar hemodynamic abnormalities are seen in patients with left atrial myxoma or whenever there is obstruction to mitral flow. Diseases that increase left ventricular stiffness (e.g., left ventricular infarction, pericardial constriction, aortic stenosis, and systemic hypertension) produce changes in PAWP that resemble in part those seen in mitral stenosis. In these conditions, mean wedge pressure is increased and the trace displays a prominent a wave, but the y descent remains steep, because there is no obstruction to flow across the mitral valve during diastole. Because patients with advanced mitral stenosis often have coexisting atrial fibrillation, the prominent PAWP a wave will not be present in many of these cases, although the other hemodynamic features persist (Fig. 30-44) (Figure Not

Available) . [292]

Myocardial ischemia is accompanied by a number of physiologic abnormalities that are detectable with the PAC. Ischemia impairs or delays left ventricular relaxation and produces diastolic dysfunction. This pattern of ischemia is particularly characteristic of demand ischemia associated with tachycardia or induced by rapid atrial pacing. [183] [432] [433] [434] [435] [436] [437] Impaired ventricular relaxation results in a stiffer, less compliant left ventricle in diastole, causing LVEDP to rise. Not only does this, in turn, increase LAP and PAWP, but the morphology of these waveforms changes as well, with the phasic a and v wave components becoming more prominent as diastolic filling pressure increases. [435] [438] [439] [440] [441] [442] [443] [444] Although myocardial ischemia will often be detectable as a rise in PAP, (diastolic, mean, or even systolic pressure), these changes are generally less striking than the accompanying change in wedge pressure and the appearance of tall a and v waves in the PAWP trace (Fig. 30-45) (Figure Not Available) . In patients with left ventricular ischemia, the tall PAWP a wave is produced by end-dia-stolic atrial contraction into a stiff, incompletely relaxed left ventricle, and underscores the fact that the atrial kick provides a greater than normal contribution to ventricular filling under these conditions. [315] [442] [445] Although the hallmark of left ventricular diastolic dysfunction is an elevated LVEDP, this pressure elevation often coexists with a reduced left ventricular end-diastolic volume. [183] [433] The astute clinician must recognize that an elevated diastolic PAP

Figure 30-44 (Figure Not Available) Mitral stenosis. Mean pulmonary artery wedge pressure (PAWP) is increased (35 mm Hg), and the diastolic y descent is markedly attenuated. Compare the slope of the y descent in the PAWP trace with the y descent in the central venous pressure (CVP) trace. In addition, compare this PAWP y descent with the PAWP y descent in mitral regurgitation (see Figs. 30-41 (Figure Not Available) and 30-42) (Figure Not Available) . A waves are not seen in the PAWP or CVP traces owing to atrial fibrillation. Arterial blood pressure (ART). See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 17-19.)*

or wedge pressure in patients with myocardial ischemia may not indicate increased left ventricular preload.

Myocardial ischemia produces a characteristic pattern of left ventricular systolic dysfunction in addition to the dia-stolic abnormalities noted earlier. Systolic dysfunction is the hallmark of supply ischemia, caused by a sudden reduction or cessation of coronary blood flow to a region of the myo-cardium. [434] [446] With severe systolic dysfunction, changes in global left ventricular pump performance may be detected with hemodynamic monitoring. As ejection fraction falls and

Figure 30-45 (Figure Not Available) Myocardial ischemia. Pulmonary artery pressure (PAP) is relatively normal and mean pulmonary artery wedge pressure (PAWP) is only slightly elevated (15 mm Hg). However, PAWP morphology is markedly abnormal with tall a waves (21 mm Hg) resulting from the diastolic dysfunction seen in this condition. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 12-4.)*

left ventricular end-diastolic volume and LVEDP rise, hemodynamic monitoring will show systemic arterial hypotension and elevated diastolic PAP and wedge pressures. This hemodynamic pattern is uncommon during anesthesia and surgery and suggests severe systolic myocardial dysfunction. [447] [448] [449] A more common hemodynamic manifestation of myocardial ischemia occurs when left ventricular geometry is distorted or when the region of ischemic myocardium overlies a papillary muscle. [450] Acute mitral valve regurgitation may result, not because of any inherent abnormality of the mitral valve leaflets, but rather because of critical alterations in the supporting structures of the mitral valve, including the mitral annulus, chordae tendineae, papillary muscles, and underlying left ventricular myocardium. [450] [451] This form of mitral regurgitation is often termed "papillary muscle ischemia" or "functional mitral regurgitation." As noted earlier, PAC monitoring is particularly well suited to detect this event by revealing the onset of new regurgitant v waves in the PAWP or PAP traces (see Figs. 30-41 (Figure Not Available) and 30-42) (Figure Not Available) .

Whether the PAC should be used in all high-risk patients as a supplemental monitor for detection of myocardial ischemia remains debatable. [299] [452] [453] [454] [455] However, if physicians choose this form of monitoring, they should have a clear understanding of the mechanism by which ischemia alters PAP and PAWP, as well as an appreciation for the characteristic pressure waveform changes that will be produced. None of the current methods for detecting perioperative myocardial ischemia is perfectly sensitive or specific. Although patients with left ventricular ischemia are likely to have a higher mean PAWP than those without ischemia, these differences are small and may be difficult to detect clinically. [444] Furthermore, clear quantitative threshold values for mean wedge pressure or a and v wave peak pressures that are diagnostic of ischemic have not been identified, perhaps owing to the wide variation in these pressures in healthy individuals. [438] [439] [440] [441] [444] Consequently, the best approach is to integrate the PAC data with other monitored values and use changes in the PAWP or PAP as valuable parts of the diagnostic puzzle. [435] [456]

Right ventricular ischemia produces characteristic hemodynamic patterns that may be recognized with PAC monitoring. Just as left ventricular ischemia increases PAWP, right ventricular ischemia increases CVP and is one of the situations in which CVP may be higher than PAWP. In addition, CVP waveform morphology changes in a characteristic manner and displays a prominent a wave, resulting from right ventricular diastolic dysfunction, and a prominent v wave, resulting from ischemia-induced tricuspid regurgitation. [10] [287] [435] [457] [458] The CVP waveform in this condition is described as having an M or W configuration, referring to the tall a and v waves and steep x and y descents. [435] Severe pulmonary artery hypertension also may result in secondary right ventricular ischemia and dysfunction and increase CVP, but this condition is distinguished from primary right ventricular dysfunction because the PAP and pulmonary vascular resistance will be normal in the latter condition.

The CVP waveform in right ventricular infarction shares many morphologic features with that recorded from patients with restrictive cardiomyopathy or pericardial constriction, including elevated mean pressure, prominent a and v waves, and steep x and y descents. [458] [459] The pathophysiologic feature common to these conditions is impaired right ventricular diastolic compliance and is often termed "restrictive physiology." In *pericardial constriction,* this arises from the restraining effect of the diseased pericardium, whereas in restrictive cardiomyopathy and right ventricular infarction, diastolic dysfunction impairs ventricular relaxation and increases intrinsic ventricular stiffness. Pericardial constriction, also termed constrictive pericarditis or pericardial restriction, limits cardiac filling because of the rigid, often calcified pericardial shell. Impaired venous return decreases end-diastolic volume, stroke volume, and cardiac output. Despite reduced cardiac volumes, cardiac filling pressures are markedly elevated and equal in all four chambers of the heart at end-diastole (Fig. 30-46) (Figure Not Available) . Although PAC monitoring reveals this pressure equalization, the characteristic M or W configuration is more apparent in the CVP trace than in the PAWP trace, most likely because of the damping effect of the pulmonary vasculature on the left-sided filling pressure as recorded by the PAC. [156] [158] [287] [460] [461] [462]

Figure 30-46 (Figure Not Available) Pericardial constriction. This condition causes elevation and equalization of diastolic filling pressures in the pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and central venous pressure (CVP) traces. The CVP waveform reveals tall a and v waves with steep x and y descents and a mid-diastolic plateau wave (*) or h wave. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 18-1.) (Figure Not Available)*

Another hemodynamic hallmark of pericardial constriction is observed in the right and left ventricular pressure traces. These demonstrate rapid but short-lived early dia-stolic ventricular filling, which produces a diastolic "dip-and-plateau" pattern or "square root sign" (Fig. 30-47) (Figure Not Available) . [158] [463] In some cases, particularly when heart rate is slow, a similar waveform pattern may be noted in the CVP trace: a steep y descent (the diastolic dip) produced by rapid early diastolic flow from atrium to ventricle, followed by a mid-diastolic h wave (the plateau) from the interruption in flow imposed by the restrictive pericardial shell (see Figs. 30-46 (Figure Not Available) and 30-47) (Figure Not Available) .

Like pericardial constriction, *cardiac tamponade* impairs cardiac filling, but in the case of tamponade, a compressive pericardial fluid collection produces this effect. This results in a marked increase in CVP and a reduced cardiac diastolic volume, stroke volume, and cardiac output. Despite many similar hemodynamic features, tamponade and constriction may be distinguished by the different CVP waveforms seen in these two conditions. In tamponade, the venous pressure waveform appears more monophasic and is dominated by the systolic x pressure descent. The diastolic y pressure descent is attenuated or absent, because early diastolic flow from right atrium to right ventricle is impaired by the surrounding compressive pericardial fluid collection (Fig. 30-48) (Figure Not Available) . [156] [158] [287] [458] [460] [464] [465] [466] Clearly, other clinical and hemodynamic clues help distinguish these diagnoses, such as the presence of pulsus paradoxus, which is an almost invariable finding in cardiac tamponade (see Fig. 30-23) (Figure Not Available) . [467] CVP traces in pericardial constriction and cardiac tamponade thus have many similarities but also important distinguishing features. As a general rule, the CVP waveform in

Figure 30-47 (Figure Not Available) Pericardial constriction. The diastolic filling abnormality in this condition inscribes a "dip-and-plateau pattern" or "square root sign" in both the right ventricular (RV) and right atrial (RA) pressure traces. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 18-3.) (Figure Not Available)*

pericardial constriction has prominent x and y descents or a predominant y descent, whereas in cardiac tamponade, the venous pressure waveform shows attenuation

or obliteration of the y descent. Coexisting abnormalities such as tachycardia, arrhythmias, and atrial contractile failure may complicate interpretation of these waveforms. [460] [461] [462] [464] On occasion, localized pericardial constriction may simulate valvular stenosis, and hypovolemia may lower cardiac filling pressures to within the normal range and confound the diagnosis. [158] [461] [462] In some instances, patients may show features

Figure 30-48 (Figure Not Available) Cardiac tamponade. The central venous pressure waveform shows an increased mean pressure (16 mm Hg) and attenuation of the y descent. Compare with Figures 30-46 (Figure Not Available) and 30-47 (Figure Not Available) . See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 18-5.) (Figure Not Available)*

Figure 30-49 (Figure Not Available) Influence of positive pressure mechanical ventilation on pulmonary artery pressure. Pulmonary artery pressure should be measured at end expiration (#1, 15 mm Hg) in order to obviate the artifact caused by positive pressure inspiration (#2, 22 mm Hg). Compare with Figure 30-30 (Figure Not Available) . See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 16-3.) (Figure Not Available)*

of more than one condition, such as seen in patients with *effusive-constrictive pericarditis* who have constriction of the heart by the visceral pericardium in addition to a pericardial effusion that compresses the heart. [468]

Probably the single most important waveform abnormality or interpretive problem in PAC monitoring is discerning the correct pressure measurement in patients receiving positive pressure ventilation. When any PAP or PAWP recording is used to estimate ventricular preload, the physician must consider the confounding effects of changes in intrathoracic pressure that occur during the respiratory cycle. Just as in the case of CVP monitoring, transmural cardiac filling pressures are estimated best when end-expiratory pressure values are recorded. (See previous sections discussing *Cardiac Filling Pressure Monitoring; Physiologic Considerations: Diastolic Pressure-Volume Relations and Transmural Pressure,* and *Central Venous Pressure Waveforms.*) During positive pressure mechanical ventilation, inspiration increases PAP and PAWP. By measuring these pressures at end-expiration, the confounding effect of this inspiratory increase in intrathoracic pressure is obviated (Fig. 30-49) (Figure Not Available) . [160] Forceful inspiration during spontaneous ventilation has the opposite impact on measured PAP and PAWP, but again, measurement of these pressures at end-expiration eliminates this confounding factor (see Fig. 30-30) (Figure Not Available) . Bedside monitors are designed with algorithms that aim to identify and report the numeric values for endexpiratory pressures. [469] [470] [471] [472] Unfortunately, these are notoriously inaccurate. The most reliable method for measuring central vascular pressures at end-expiration is examination of the waveforms on a calibrated monitor screen or paper recording. [472] [473]

Use of Central Vascular Pressure to Estimate Left Ventricular Preload

It is clear that accurate, clinically meaningful interpretation of PAC-derived cardiac filling pressures requires a detailed understanding of the underlying physiologic principles and an awareness of the clinical conditions under which the measurements have been performed. By way of illustration, there are several different ways to interpret a PAWP measurement of 20 mm Hg (Fig. 30-50) (Figure Not Available) . This pressure is somewhat higher than the normal value, but depending on how this measured PAWP is interpreted, the therapeutic response that it generates may be quite different. These interpretations all depend on two factors, juxtacardiac pressure and ventricular compliance. The most common interpretation of a PAWP of 20 mm Hg assumes that the juxtacardiac pressure and ventricular compliance are normal and leads to the diagnosis of hypervolemia, with an increased left ventricular end-diastolic volume causing the increased PAWP. One arrives at a different interpretation of this PAWP if juxtacardiac pressure is increased for any reasons just reviewed, including cardiac tamponade, pericardial constriction, or positive pressure inspiration. Under these conditions, the same elevated PAWP may be associated with normal or reduced left ventricular end-diastolic volume. Finally, a PAWP of 20 mm Hg has a third interpretation if ventricular compliance is decreased, such as might occur with diastolic dysfunction from myocardial ischemia, hypertrophy, or cardiomyopathy. Under these conditions, as in the case of increased juxtacardiac pressure, left ventricular volume may be normal or reduced, despite elevated PAWP (see. Fig. 30-50) (Figure Not Available) .

Deciding whether any given central vascular pressure is ideal for a particular patient may be a clinical challenge. When the wedge pressure is extremely high or low, it is easy to recognize that this value must be adjusted to avoid pulmonary edema or improve cardiac output. However, things are rarely so clear-cut in critically ill patients, and the target value for optimal wedge pressure is uncertain and often decided empirically. Under these circumstances, a rapid *fluid challenge* may be a useful method to determine whether the PAWP is optimal for the patient in that setting. An intravenous bolus of crystalloid solution (250 mL) is given rapidly over 15 minutes, and the change in PAWP is measured, along with other pertinent hemodynamic variables. If the baseline wedge pressure is high or if a severe pulmonary capillary injury is present, a reduced volume may be used. Small increases in PAWP following the fluid challenge (e.g., less than 3 mm Hg) suggest that the ventricle is operating on the flat portion of its diastolic filling curve, whereas large increases in wedge pressure (e.g., 7 mm Hg or greater) suggest that the steep portion of the curve has been reached and that little further increase in stroke volume and cardiac output can be achieved without a substantial risk of producing hydrostatic pulmonary edema. [131] [177] [472]

As difficult as it may be to decide whether the PAWP is optimal for a particular patient, even greater uncertainty confronts the physician who uses CVP to determine whether cardiac preload is adequate or optimal. Clinicians

---

Figure 30-50 (Figure Not Available) Influence of juxtacardiac pressure and ventricular compliance on left ventricular (LV) preload. There are three interpretations of an increased transduced pulmonary artery wedge pressure (PAWP, 20 mm Hg). (A) Juxtacardiac pressure (-5 mm Hg) and LV compliance are normal, transmural PAWP is increased (25 mm Hg), and LV volume is increased. (B) Juxtacardiac pressure is increased (+10 mm Hg), LV compliance is normal, transmural PAWP is decreased (10 mm Hg), and LV volume is normal or decreased. (C) Juxtacardiac pressure is normal, LV compliance is decreased, transmural PAWP is increased (25 mm Hg), and LV volume is normal or decreased. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 15-8.)*

have recognized for years that in many patients, CVP may be misleading. [474] [475] [476] [477] It is now evident, however, that there are several anatomic and physiologic reasons to explain why this occurs. [178] The diastolic pressure-volume curves for the left and right ventricles are different even in healthy individuals, with the left ventricle being stiffer or less compliant. As a result, the issue is not whether there is a correlation between a change in CVP and PAWP, because in most cases, changes in CVP, PAWP, and PADP all occur in the same direction. [478] Instead, a more clinically relevant question might be whether small changes in CVP are clinically detectable, because they often coexist with larger changes in PAWP simply because the right and left ventricles have different dia-stolic pressure-volume curves. [479]

Use of CVP to estimate left ventricular preload is associated with additional interpretive problems, owing to the fact that the right and left ventricles share a common septal wall and are both surrounded by the pericardium. These confounding influences, termed *ventricular interdependence* and *pericardial constraint,* couple changes in right and left ventricular function, such that a primary change in right ventricular filling may produce a secondary change in left ventricular filling by altering its diastolic pressure-volume relation. [175] [177] [178] [185] [191] For example, acute pulmonary artery hypertension may increase right ventricular enddiastolic volume and pressure, shift the ventricular septum leftward, and increase LVEDP while decreasing left ven-tricular end-diastolic volume, owing to a shift in the left ventricular pressure-volume relation to a steeper, stiffer curve. Finally, numerous additional anatomic, physiologic, and pathophysiologic factors may alter the relationship between CVP and left ventricular preload (Fig. 30-51) (Figure Not Available) . [178] The further upstream from the left ventricle one records the "filling pressure," the greater the number of these factors that may conspire to alter the relation between the monitored pressure and left ventricular preload. In view of these considerations, it should be no surprise that reliance on CVP to estimate left ventricular preload is often misleading in critically ill patients. Furthermore, many of these factors may even alter the relation between pulmonary artery diastolic and wedge pressures as estimates for LVEDP, and these are considered later in this chapter.

Predicting Left Ventricular End-Diastolic Pressure

PAWP measurement has two somewhat distinct purposes. [480] First, knowledge of the pulmonary venous pressure provides an estimate of the hydrostatic pressure within the pulmonary capillaries, which is a major determinant of the vascular backpressure favoring formation of pulmonary edema. For this purpose, the *mean* PAWP averaged over the cardiac cycle is the pressure of interest. Note that wedge and capillary pressures are not identical, but in general, increases in wedge pressure lead to increases in capillary pressure. [411]

The second purpose for measuring left ventricular filling pressure is to estimate the preload of the left ventricle. In this instance, the *end-diastolic* wedge pressure following atrial contraction best predicts the end-diastolic filling pressure or preload of the left ventricle. [472] Measurement of LVEDP is performed at the Z-point,

identified on the left ventricular pressure trace as the point at which the slope of the ventricular pressure upstroke changes, approximately 50 milliseconds after the ECG Q wave, and generally coinciding with the ECG R wave (Fig. 30-52) (Figure Not Available) . [145] Most important, this is a phasic pressure point measured at end-diastole, not

Figure 30-51 (Figure Not Available) Anatomic and physiologic factors that influence the relations between various measures of left ventricular (LV) filling and true LV preload. The further upstream filling pressure is measured, the more confounding factors may influence the relation between this measurement and LV preload. RA, right atrium, RV, right ventricle, PA, pulmonary artery; LA, left atrium; CVP, central venous pressure; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure; LAP, left atrial pressure; LVEDP, left ventricular end-diastolic pressure; and P-V, pressure-volume. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 15-5.) (Figure Not Available)*

a mean diastolic pressure in the left ventricle. Although PAWP is generally reported as mean pressure, an enddiastolic component of wedge pressure can be identified in its phasic pressure trace as well. In the presence of normal sinus rhythm, atrial contraction provides this end-diastolic mechanical event. Thus, measurement of the PAWP a wave pressure peak provides a more accurate estimate of LVEDP than that provided by mean PAWP (see Fig. 30-52) (Figure Not Available) . The important distinction is that average or mean wedge pressure estimates the hydrostatic pressure on the lungs, whereas the phasic or end-diastolic wedge pressure recorded after the a wave estimates LVEDP. Put more eloquently, "While the ventricular end diastolic pressure may be considered to be the hemodynamic 'stimulus' which determines the force of ventricular contraction, the mean atrial pressure may be considered the hemodynamic 'price' which the organism must pay for this stimulus to be provided." [481]

Pressure tracings from two patients, one with aortic stenosis and one with mitral regurgitation, help illustrate this point (Fig. 30-53) (Figure Not Available) . LVEDP is elevated (25 mm Hg) in both patients and well approximated by the left atrial (or wedge) pressure a wave peak. In both patients, this pressure provides the best single pressure estimate of left ventricular preload. Although both patients have the same LVEDP, mean left atrial (or wedge) pressure is much higher in the patient with mitral regurgitation (30 mm Hg) than in the patient with aortic stenosis (15 mm Hg). The patient with aortic stenosis produces an LVEDP of 25 mm Hg with a strong left atrial contraction, as evidenced by the tall left atrial a wave. This effective booster pump mechanism provides adequate LVEDP with a reasonable mean LAP that does not place the patient at risk for pulmonary edema. In contrast, the patient with mitral regurgitation has a very high mean LAP (30 mm Hg) caused by the tall regurgitant c-v wave. Clearly, mean PAWP is not always equal to the end-diastolic PAWP value, and the taller the pulsatile a and v wave components,

Figure 30-52 (Figure Not Available) Relationship between left atrial pressure (LAP) and left ventricular end-diastolic pressure (LVEDP). LVEDP is measured at the Z-point on the left ventricular pressure (LVP) trace, at the time of the electrocardiographic R wave. Mean LAP (9 mm Hg) underestimates LVEDP (15 mm Hg), but the LAP a wave pressure peak closely estimates LVEDP. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 6-1.)*

Figure 30-53 (Figure Not Available) Relationship between left atrial pressure (LAP) and left ventricular end-diastolic pressure (LVEDP) in aortic stenosis and mitral regurgitation. LVEDP is elevated in both conditions (25 mm Hg), but mean LAP (LAP-bar) remains low in aortic stenosis (15 mm Hg) but high in mitral regurgitation (30 mm Hg), owing to the regurgitant c-v wave inscribed during systole. LVP, left ventricular pressure. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 6-2.)*

the greater the discrepancy may be. This distinction is important and has been obscured in daily clinical practice by our emphasis on single numeric values for wedge pressure.

When a PAC is used in clinical practice, there are various situations in which the LVEDP is either underestimated or overestimated by the PAWP or PADP measurement (Tables 30-7 (Table Not Available) and 30-8) (Table Not Available) . [480] *Decreased left ventricular compliance* is the most common cause of underestimation of LVEDP. [482] Atrial contribution to left ventricular end-diastolic volume and LVEDP is normally less than 20 percent, but with dia-stolic dysfunction, this atrial contribution may approach 50 percent. [442] [445] Under these conditions, the PAWP a wave will be unusually prominent and will provide a close estimate for LVEDP, even though the mean wedge pressure underestimates LVEDP (see Fig. 30-45) (Figure Not Available) . [315] In patients with *aortic regurgitation,* abnormal diastolic left ventricular filling occurs from the aorta as soon as left ventricular pressure falls below aortic pressure and continues after left atrial contraction and closure of the mitral valve. Left ventricular diastolic pressure continues to rise until LVEDP is reached at the onset of mechanical systole, which reestablishes antegrade flow from left ventricle to aorta. Because mitral valve closure occurs prior to end-diastole, mean PAWP as well as the wedge-pressure a wave both underestimate LVEDP. [315] In the presence of *pulmonic regurgitation,* diastolic flow from the proximal pulmonary artery becomes bidirectional, antegrade into the left atrium, and retrograde into the right ventricle. When the right ventricular diastolic pressure is lower than LAP, pulmonary artery

TABLE 30-7 -- Underestimation of Left Ventricular End-Diastolic Pressure

(Not Available)

Modified from Mark JB: Predicting left ventricular end-diastolic pressure. In Mark JB: (ed): Atlas of Cardiovascular Monitoring New York, Churchill Livingstone, 1998, p 59.

TABLE 30-8 -- Overestimation of Left Ventricular End-Diastolic Pressure

(Not Available)

Modified from Mark JB: Predicting left ventricular end-diastolic pressure. In Mark JB: (ed): Atlas of Cardiovascular Monitoring New York, Churchill Livingstone, 1998, p 59.

diastolic flow seeks the lower pressure pathway toward the right ventricle, and PADP will underestimate PAWP, LAP, and LVEDP. [480] When pulmonary vascular resistance is normal, there is no pressure gradient across the pulmonary vascular bed at end of diastole, and PADP equilibrates with the downstream LAP. When right ventricular systole is delayed because of *right bundle branch block,* PAP continues to fall with the x or systolic descent in LAP. Under such conditions, PADP will underestimate LVEDP by as much as 7 mm Hg. [483]

A final condition that causes underestimation of LVEDP with the PAC is different from the pathophysiologic states noted earlier because, in this condition, the process of meas-uring PAWP alters circulation and produces a change in cardiac filling. Under normal conditions, inflation of the PAC balloon to measure PAWP interrupts antegrade blood flow through a small section of the lung and has no measurable effect on total pulmonary blood flow or left atrial filling. However, after *pneumonectomy,* and possibly other conditions that markedly reduce the pulmonary vascular bed, balloon inflation may occlude a significant portion of the remaining pulmonary vascular cross-sectional area. Mechanical obstruction of pulmonary blood flow results, causing increased CVP, and decreased LAP, cardiac output, and systemic blood pressure. [484] [485] Therefore, because the PAWP measurement itself obstructs pulmonary blood flow, the measured PAWP underestimates the LVEDP that existed prior to balloon inflation. This artifact should be suspected in the appropriate clinical setting, when a sudden reduction in systemic arterial pressure occurs coincident with PAC balloon inflation.

Respiratory influences on the PAP or PAWP traces are the most common cause of overestimation of LVEDP. In this regard, use of PEEP may pose a particular problem, because it may create zone 1 or zone 2 lung conditions and cause PAWP to be influenced by alveolar pressure. [486] Formulas have been derived to adjust for the effects of PEEP on wedge-pressure measurement. In general, mechanical ventilation with PEEP increases wedge pressure by an amount less than one-half the value of PEEP applied (i.e., 10 cm H_2O PEEP will raise wedge pressure less than 5 cm H_2O or 4 mm Hg). [131] [487] However, the ratio of chest wall compliance to lung compliance has a significant impact on the relation between the level of PEEP and its effect on PAWP, and simple mathematical methods to adjust for this effect are not entirely reliable. [131] [177] [488] [489] Alternative methods to correct for PEEP, such as measuring pleural pressure using an esophageal balloon, are cumbersome and not generally used. Prolonged discontinuation of PEEP before measuring wedge pressure is to be discouraged. Not only will circulatory dynamics change dramatically owing to rebound central hypervolemia caused by translocation of blood from the periphery, but respiratory gas exchange may deteriorate and be slow to recover. [131] As an alternative, Pinsky et al [489] found that transient airway disconnection for 2 to 3 seconds in patients receiving mechanical ventilation with PEEP

allowed measurement of nadir wedge pressure, which proved to be a better and safer way to estimate left ventricular filling pressure at higher levels of PEEP. When wedge pressure measurement did not change after abrupt airway disconnection, the on-PEEP wedge-pressure measurement accurately reflected left ventricular filling pressure. However, when wedge pressure decreased after airway disconnection, the nadir wedge pressure reached within 3 seconds provided a more accurate measurement. Fortunately, most patients who require high levels of PEEP may not manifest these artifactual wedge-pressure measurement problems. In patients with the adult respiratory distress syndrome, pulmonary artery wedge pressure closely estimates LVEDP at all levels of PEEP up to 20 cm H_2O owing to the relative microvascular protection from the effects of PEEP created by this condition. [490]

When the pulmonary vasculature is normal, pulmonary blood flow ceases at end-diastole, and PADP equals LAP. [491] However, if pulmonary vascular resistance increases, PAP equilibration with downstream pressure does not occur. Under these conditions, the pulmonary vascular bed begins to resemble the systemic vasculature, where a large pressure gradient between the systemic arterial pressure and the right atrial pressure persists at end-diastole. Therefore, in the presence of *pulmonary hypertension* caused by elevated pulmonary vascular resistance, PADP overestimates PAWP, LAP, and LVEDP (Fig. 30-54) (Figure Not Available) .

In contrast to the precapillary pulmonary vasoconstriction that exists in patients with pulmonary arterial hypertension, postcapillary obstruction to flow in the pulmonary veins may occur in the rare condition *pulmonary veno-occlusive disease.* Patients with this condition have normal LAP, but some disagreement exists as to whether these patients have normal or elevated PAWP. [131] [410] [492] [493] In part, these different observations may relate to whether the PAC has been wedged successfully, because the wedge position may be difficult to obtain in these patients or wedge pressure may be recorded from a vascular channel that is totally occluded. The most important factor, however, is whether the patient has predominantly small vein occlusion or large vein occlusion. Obstruction to flow in the small pulmonary veins narrows the static column of blood connecting the wedged PAC tip with the flowing column in the larger pulmonary veins. Given that the partial obstruction involves only the static column, wedge pressure will measure normal pulmonary venous and left atrial pressures because there is no pressure drop across the stenotic segment in the absence of flow. Conversely, large vein obstruction creates a gradient in the column of blood flowing from these veins toward the left atrium. In this instance, wedge pressure will detect an increased pulmonary venous pressure and overestimate LAP. [131] [410] [492] [493]

Figure 30-54 (Figure Not Available) Pulmonary hypertension. The increased gradient across the pulmonary vasculature causes pulmonary artery diastolic pressure to exceed pulmonary artery wedge pressure (PAWP). PAP, pulmonary artery pressure. See text for greater detail. *(From Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998: Fig. 6-11.)*

This model of pulmonary vein obstruction is consistent with the observations of Zidulka and Hakim, [312] who measured PAWP from both large and small pulmonary arteries. Other conditions may mimic the hemodynamic features of pulmonary veno-occlusive disease, including mediastinal fibrosis and intrathoracic or atrial tumors that obstruct pulmonary venous flow near the left atrium.

Mitral stenosis causes obstruction to blood flow from left atrium to left ventricle, and consequently, LAP will exceed left ventricular pressure throughout diastole. Furthermore, all upstream pressures recorded by the PAC will overestimate LVEDP owing to the valvular obstruction. [494] Because the pressure gradient across the mitral valve is directly related to the flow across it, PADP and PAWP will overestimate left ventricular filling pressures even more when transmitral flow is increased by tachycardia or elevated cardiac output.

LAP is increased in *mitral regurgitation* owing to the abnormal leakage of blood across the incompetent valve during systole, and LVEDP is better approximated by measuring wedge pressure prior to the onset of the regurgitant c-v wave (see Figs. 30-41 (Figure Not Available) and 30-42) (Figure Not Available) . [426] In contrast to the patient with mitral stenosis in whom LAP exceeds left ventricular pressure throughout diastole, the patient with mitral regurgitation has appropriate diastolic equilibration of atrial and ventricular pressures. The problem in mitral regurgitation is choosing the appropriate end-diastolic, pre-v wave pressure to use as an estimate for LVEDP. Mean PAWP will overestimate LVEDP in any patient whose PAWP has tall systolic v waves, including patients with *ventricular septal defect* and left ventricular failure. [424] [425]

When *tachycardia* develops, the duration of diastole is shortened, and there is less time for egress of blood from pulmonary vasculature to left atrium and from left atrium to left ventricle. [314] [481] [495] At both mitral valve and pulmonary vascular levels, pressure gradients develop as the duration of diastole progressively decreases during tachycardia. Consequently, PADP overestimates mean PAWP, which in turn overestimates LVEDP. Patients in atrial fibrillation will have more complete equilibration of PADP and LVEDP during longer R-R intervals. Consequently, these beats should be chosen to provide the best estimate of LVEDP.

In summary, there are many circumstances under which PAWP or PADP may underestimate or overestimate LVEDP. Some conditions are relatively common, whereas others are extremely rare, and often several conditions coexist, further complicating the measurement problem. For example, a patient with mitral stenosis resulting in pulmonary hypertension who develops tachycardia has three reasons for PADP to overestimate LVEDP. Major clinical errors would result if the high PADP is presumed to indicate increased left ventricular preload in this patient.

Pulmonary Artery Catheterization and Outcome: Controversies and Indications for Catheterization

Pulmonary artery catheterization has evoked more controversy than any other widely adopted cardiovascular monitoring practice, because it is an expensive, invasive technique that is widely used but still not rigorously proven to result in improved patient outcome. The PAC controversy has been fueled in part by strongly worded editorials, written by prominent physicians, debating whether PAC use should be suspended, pending better scientific proof of the efficacy of this monitoring practice. [300] [310] [496] [497] [498] [499] The titles of these editorials convey the emotional nature of these issues--"Death by pulmonary artery flow-directed catheter (editorial). Time for a Moratorium?"; [498] "Use and abuse of the balloon tip pulmonary artery (Swan Ganz) catheter: Are patients getting their money's worth?"; [500] and "Swan song for the Swan-Ganz catheter? The use of pulmonary artery catheters probably need re-evaluation--but they should not be banned." [310] Although some may take solace in the fact that similar controversies surround the use of other widely adopted, high-technology, clinical monitoring techniques, such as electronic fetal monitoring, [501] [502] [503] physicians who use PAC must remain well informed about the evidence for efficacy of this practice, because this evidence must guide selection of patients for PAC monitoring. [504]

In reviewing the scientific evidence for efficacy of PAC monitoring, one discovers many studies both supporting [505] [506] [507] [508] [509] [510] and refuting [304] [511] [512] [513] the benefits of this technique, but the small numbers of patients reported invariably limit the validity and applicability of these investigations. [299] Unfortunately, even larger studies currently available have had similar mixed results and marked limitations in study design. One observational study involving more than 1,000 general surgical patients reported lower perioperative mortality and reinfarction rates in patients monitored with PAC compared with historical controls, [514] but other large studies have not found a similar outcome benefit. One reason for these divergent results may be that these studies focused on different patient populations: patients with acute myocardial infarction, [515] [516] those undergoing cardiac surgery, [517] [518] and those critically ill with diverse medical and surgical diseases. [306] [309] Despite the large numbers of patients in some of these reports, many experts have questioned these studies because they were observational in design, rather than randomized controlled trials. [299] [308] [342] [519] Nonetheless, several of these studies have raised serious concerns among physicians because they suggested that the PAC was not only ineffective, but that patients who received PAC monitoring suffered increased morbidity and mortality compared with patients who did not receive such monitoring. [306] [515] [516]

Perhaps the most controversial of all these PAC outcome studies is the most recent, published in 1996, in which Connors et al [306] examined the association between PAC use during the first 24 hours of intensive care and subsequent survival. This prospective cohort study included 5,735 patients in 5 teaching hospitals, as part of a larger 9,000 patient study entitled "The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT)." [520] [521] [522] [523] The patients in this study were desperately ill; entry into the study required a predicted 6-month mortality in excess of 50 percent. Patients who received PAC were judged to be sicker by every measurement analyzed, but the authors used case-matching analyses and applied a propensity score to adjust for these confounding medical covariates. To the extent that these statistical adjustments were successful, the results of the study were very worrisome. PAC-monitored patients had increased mortality, increased

lengths of hospital stay, and increased costs. Moreover, there was no subgroup of patients who appeared to benefit from PAC monitoring. The publication of this study was accompanied by a strongly worded editorial calling for a moratorium on PAC use or a randomized controlled trial to define its efficacy. [300]

The controversies surrounding PAC use have helped identify several key issues that remain unanswered but are intimately related to the basic question of PAC monitoring and patient outcome. These points may be summarized as follows:

1. There is tremendous variability in the level of skill and knowledge among clinicians who use PACs [390] [391] (see earlier discussion). Many experts believe that failure to control for this factor has been responsible for the poor performance of the PAC in most of the studies in the literature. [308] [311] [522] [524] Because previous studies have not provided an explicit description of how the PAC was used to guide care, the question of PAC efficacy remains uncertain. [299] [311]
2. Use of PAC varies widely between individual physicians, institutions, and different geographic locations. [309] [525] As in other parts of modern medicine, this begs the question whether PAC is overused in many settings or perhaps underused in others. Some have even raised the issue that PAC use has been driven in part by the variation in regionalmedical-care payment structures. [342]
3. Learning bias may be another important confounding factor. [311] [342] This is a well-recognized phenomenon in clinical medicine. In brief, it suggests that we now take better care of patients in general because we have learned such a great deal about cardiovascular pathophysiology and patterns of disease by using PACs that we now apply this knowledge effectively in the care of patients who do not have PAC monitoring.
4. Early use of PAC monitoring in the care of surgical patients, [526] [527] trauma patients, [509] or elderly patients who are at high risk [506] has been touted by some authors to be the real benefit of this procedure. The studies of Shoemaker et al [500] [526] [527] in particular have emphasized the importance of early monitoring and treatment to optimize tissue perfusion before irreversible organ damage occurs.
5. The role of PAC monitoring in improving patient outcome is inextricably tied to the therapies that it guides. As several authors have noted, "if there is no good treatment for the pathophysiologic state that is identified, there is no expectation of therapeutic benefit from the diagnostic procedure." [328] [342] This may be one of the key issues in our current conundrum, namely our inability to treat effectively many serious illnesses, like sepsis, even when the cardiovascular problems are clearly identified through PAC monitoring. In terms of PAC-guided therapies, one of the mostcontroversial is one in which the physician measures hemodynamic variables with the catheter, then attempts to increase oxygen delivery to some empiric goal. This treatment algorithm has been termed "maximizing oxygen delivery," "goal-oriented therapy," or "supraphysiologic goaldriven treatment." In essence, these therapies involve PAC monitoring to guide fluid and inotropic drug administration with various supranormal circulatory goals as end points: oxygen delivery greater than 600 mL/min/m ^{2} , oxygen consumption greater than 170 mL/min/m^2 , or cardiac index higher than 4.5 L/min/m^2 . Although some investigations have shown outcome benefit with this therapeutic approach, [510] [526] [528] others have shown either no effect of such therapy [529] or even increased mortality. [530] The questionable efficacy of this therapeutic approach has been cited as a significant reason why PAC monitoring has not proven effective. [306] [306] A complete consideration of this treatment strategy is beyond the scope of this discussion, but it remains an extremely controversial aspect of PAC monitoring. [531] [532] Although most experts agree that PACs allow more accurate titration of traditional therapy in critically ill patients, some of the most "aggressive" therapies that it guides remain unproven. [533]

In summary, the practice guidelines and consensus statements that have been generated over the past several years best summarize current indications for PAC monitoring. [299] [308] [534] [535] [536] The most recent of these practice guidelines is the Pulmonary Artery Consensus Conference, published in 1997. [308] [537] [538] [539] Conference participants addressed the question: Does management with the PAC improve patient outcomes in each of 21 different medical and surgical conditions? In 3 conditions, the answer was "no;" in 11, the answer was "uncertain;" and in 7, the answer was "yes." The panel further suggested that there was no basis for a moratorium on PAC use and that randomized controlled trials should be performed to resolve remaining questions regarding PAC effectiveness.

Randomized controlled trials of PAC monitoring remain very difficult to perform, owing to problems in gaining informed consent from critically ill patients, difficulties ensuring that physicians remain committed to trial guidelines, and obstacles encountered in patient selection bias and crossover from non-PAC monitoring to PAC monitoring. [513] [540] [541] [542] Although many believe that randomized clinical trials are the only way to resolve these issues, [299] [308] [524] [541] [542] [543] [544] [545] [546] [547] others believe that it would be better to spend our efforts improving the level of knowledge of PAC use, [298] or focusing on alternative technology like echocardiography. [342]

Rather than offer a long list of indications for PAC, a better approach to this clinical thought process is the one offered by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. [299] Three factors must guide the physician's decision to employ PAC monitoring:

1. The patient is at high risk because of severe underlying cardiopulmonary disease.
2. The intended operation places the patient at risk because of the magnitude or extent of the procedure.
3. The environment or practice setting is propitious for PAC monitoring.

Many high-risk patients undergo low-risk operations that have little physiologic impact, and these individuals should not need PAC monitoring. One example would be the patient with advanced ischemic cardiomyopathy who needs cataract surgery under monitored anesthesia care. In contrast, a relatively low-risk patient undergoing a very high-risk procedure may benefit from PAC monitoring in the perioperative period. An example might be a patient with stable ischemic heart disease scheduled to undergo extensive abdominal cancer surgery. Finally, the third factor that

determines whether PAC monitoring is appropriate relates to the individual practice setting. [299] Clearly, all physicians and nurses using the PAC must have the requisite knowledge and skills to use it safely and effectively. However, there is something that, at the present time, still defies objective assessment. Keats [548] has termed this feature "the role of environment in the outcome of operation," by which he meant all the important unmeasurable aspects of each clinical setting, including, among other things, surgical skills and experience.

Additional Features of Pulmonary Artery Catheters

The popularity of PAC monitoring relates in large part to the fact that these catheters are multipurpose and provide a wide range of supplementary features for therapeutic and diagnostic applications. In addition to the standard lumens that allow measurement of PAP and CVP, catheters may have an additional venous infusion lumen, opening either 20 or 30 cm from the catheter tip. Special PACs are available that allow temporary endocardial pacing or intracardiac ECG recording. One such catheter has five small electrodes embedded in its outer wall, two located approximately 20 cm from the catheter tip, and three located approximately 30 cm from the catheter tip. Combinations of these electrodes allow bipolar endocardial ventricular, atrial, or atrioventricular pacing. [549] Other pacing PACs do not have the pacing electrodes permanently attached but instead have a special lumen that opens in the right ventricle, through which a thin bipolar wire may be introduced for endocardial ventricular pacing. [550] Another type of pacing PAC has special atrial and ventricular lumens that accommodate two separate wires to allow atrioventricular sequential pacing. [551] Although successful endocardial pacing is achieved in most patients with these catheters, reliable catheter positioning is more problematic than with standard PACs. Patient movement or PAC balloon inflation to measure PAWP may alter the position of the catheter or dislodge the wires within the heart and thereby interrupt pacing.

CARDIAC OUTPUT MONITORING

Aside from its pressure monitoring capabilities, undoubtedly the most important feature of the PAC is its ability to measure cardiac output using the thermodilution method. Cardiac output is the total blood flow generated by the heart, and in a normal adult at rest, it ranges from 4.0 to 6.5 L/min (see Table 30-2) . To the extent that the body regulates cardiac output to meet tissue metabolic requirements, measurement of cardiac output provides a global assessment of the circulation, including the neurohumoral influences on it. Cardiac output measurements are usually combined with other hemodynamic measurements (heart rate, arterial blood pressure, CVP, PAP, and PAWP) to allow calculation of additional important circulatory variables, such as systemic and pulmonary vascular resistance (see later discussion). Thus, the PAC provides a large fraction of the data that the critical care physician or anesthesiologist uses for comprehensive cardiovascular assessment.

Thermodilution Cardiac Output Monitoring

The *thermodilution* technique has become the *de facto* clinical standard for measuring cardiac output because of its ease of implementation and the long clinical experience using it in various settings. It is a variant of the *indicator dilution* method, in which a known amount of a substance is injected into the blood stream and its concentration change measured over time at a downstream site. As its name implies, the thermodilution method uses a thermal indicator, whereas other indicator dilution methods use various substances, such as indocyanine green dye. The fundamental physical basis for the indicator dilution method is given by the Stewart-Hamilton equation, named after the two investigators who were instrumental in the development of this technique. [552] [553]

The dye dilution method has not maintained widespread clinical popularity because it requires continuous withdrawal of arterial blood to plot the dye concentration curve, and the indicator, indocyanine green, can gradually build up with repeated injections. However, this method has been used to diagnose intracardiac shunts, by observing the altered shape of the dye dilution curve that is produced by the abnormal recirculation of dye under these conditions.

Two developments have had significant impact on the routine measurement of cardiac output in clinical practice. The first was the introduction of thermal indicators by Feg-ler, [554] and the second was the incorporation of a temperature measuring thermistor in the tip of a PAC. [555] [556] [557] Several unique features of the thermodilution cardiac output monitoring technique have led to its widespread popularity and rapid clinical acceptance. It can be performed quickly and repeatedly, the measurement does not require advanced diagnostic or technical skills, and it employs a nontoxic, nonaccumulating, and nonrecirculating indicator.

When a thermal indicator is used to measure cardiac output, the Stewart-Hamilton equation must be modified.

Blood temperature is measured continuously by the thermistor at the tip of the PAC and injectate temperature is measured by a second thermistor at the injectate port. [558] The computation constant (K) is provided in each PAC package insert, and it must be entered manually into the cardiac output computer prior to cardiac output measurement. This constant adjusts for the amount of thermal signal that will be introduced with each measurement, and it depends on the physical characteristics of the catheter (i.e., size and composition) and the intended injectate that will be used (i.e., specific heat, specific gravity, and volume). [557] The integral of temperature change over time is equal to the area under the thermodilution curve and is calculated electronically by the cardiac output computer.

To perform a thermodilution cardiac output measurement, a fixed volume of cold fluid is injected as a bolus into the proximal CVP lumen of the PAC, and the resulting change in the pulmonary artery blood temperature is recorded by the thermistor at the catheter tip. As in all other forms of cardiovascular monitoring, it is important to have a real-time display of the thermodilution curve resulting from each cardiac output measurement. [422] [529] This allows the clinician to discern artifacts that would invalidate the cardiac output measurement, such as unstable blood temperature or incomplete bolus injection. Usually a series of three cardiac output measurements performed in rapid succession are averaged to provide a more reliable result. [560] When carefully performed, thermodilution cardiac output measurements appear to provide results that are within 5 to 10 percent of other reference methods. [556] [561] [562] [563] Few complications are directly attributable to the technique itself, although tachyarrhythmias and bradyarrhythmias have been reported. [557] [564]

Several important technical issues must be considered to interpret thermodilution cardiac output measurements properly. The thermodilution technique measures right ventricular output and pulmonary artery blood flow. In the face of a large left-to-right or right-to-left shunt, right ventricular and left ventricular outputs will not be equal. The validity of the technique also requires that the thermal indicator be injected as a rapid bolus into the right atrium and that there is complete mixing of the indicator in the right ventricle, prior to its delivery to the pulmonary artery. These fundamental methodologic assumptions of the thermodilution technique are not valid in patients with right-sided valvular regurgitation. For example, patients with severe tricuspid regurgitation have recirculation of the thermal signal between the right atrium and right ventricle. The resulting thermodilution curves have an abnormally prolonged decay time, and the measured cardiac output may be inaccurate. [422] [565] [566] Unfortunately, there is no simple method to correct for this problem. In the presence of severe tricuspid regurgitation, cardiac output usually is underestimated by the thermodilution method, but it may be overestimated, depending on the severity of valvular regurgitation and the magnitude of the cardiac output. [567]

Other technical problems with thermodilution cardiac output measurement occur when the proximal CVP injectate port is not fully within the right atrium but rather contained within the introducer sheath. In this case, the thermal bolus will not be delivered properly and an abnormal cardiac output curve will be produced. [568] [569] This problem should be recognized when there is difficulty making the bolus injection in a patient whose PAC is inserted a relatively short distance: for instance, 40 cm. Similarly, a blood clot on the PAC that covers the thermistor at the tip may make temperature measurements inaccurate and produce spurious cardiac output values.

Because this measurement method is a thermal-based technique, there are many circumstances when an unrecognized change in blood temperature may alter the cardiac output measurement and cause it to be spuriously increased or decreased. In most patients, pulmonary artery blood temperature falls rapidly in the initial minutes following cardiopulmonary bypass. By progressively lowering the baseline blood temperature, these post-bypass temperature changes cause the

thermodilution method to underestimate significantly the true cardiac output at this time. [570] Other inaccuracies in thermodilution cardiac output measurement occur when pulmonary artery blood temperature changes because of rapid fluid infusion through a peripheral intravenous site, through the PAC introducer sheath, or through one of the proximal PAC ports. [571] [572] Either overestimation or underestimation of cardiac output occurs, depending on the timing of the additional fluid bolus.

The clinician can understand and predict all of these measurement artifacts by recalling the Stewart-Hamilton equation and recognizing that cardiac output is inversely proportional to the area under the thermodilution curve. Any factor that causes a factitious reduction in this area will result in an erroneous increase in measured cardiac output. For example, if the constant entered in the cardiac output computer was the value for a 10-mL injectate, but only a 5-mL injectate was used, the injected thermal indicator would be one-half the intended amount. As a result, the area under the thermodilution curve would be approximately one-half the expected value, and the computed cardiac output would overestimate the true cardiac output by a factor of two.

The choice of iced (0°C) or room temperature injectate has been examined in detail to determine the preferred method for accurate cardiac output measurement. Although the size of the thermal bolus signal is increased when an iced injectate is employed, this indicator is more time-consuming, expensive, and cumbersome to prepare, compared with a room temperature injectate. In addition, if the injection port thermistor becomes disconnected during use of iced injectate, the injectate temperature will be measured erroneously as room temperature, resulting in artifactually decreased cardiac output values because the $T_B - T_I$ term will be too small. Because several groups have demonstrated equivalent accuracy in cardiac output determinations when iced and room temperature injectates are compared, it appears that room temperature injectate is preferred for almost all clinical applications. [573] [574] However, an injectate volume of 10 mL should be used in all adults, because the measurements will be more accurate with this volume, compared with a smaller 3- or 5-mL volume. [574]

One of the more controversial issues in standard bolus thermodilution cardiac output monitoring is the proper timing of measurement in relation to the respiratory cycle,

particularly in patients receiving positive pressure mechanical ventilation. By the nature of its measurement and mathematical expression, cardiac output is reported as flow per minute, even though it is measured by a thermodilution curve that is generated over several seconds. The computer usually measures the first 60 to 70 percent of this curve, then extrapolates the remainder to the expected baseline. [571] Not surprisingly, the stroke output of the right ventricle varies considerably throughout the respiratory cycle, and measurements of right ventricular cardiac output will vary by as much as 50 percent, depending on the point during the respiratory cycle when the measurements are performed. [575] [576] Although reproducibility of consecutive measurements improves markedly when the bolus injections are synchronized to the same phase of the respiratory cycle, [577] true cardiac output is estimated better by making numerous injections throughout all phases of the respiratory cycle and then averaging the results. [576] Because the variation in pulmonary blood flow during respiration depends on many factors including the respiratory rate, tidal volume, airway pressure, and so forth, there is no simple way to know whether timing measurements at end-expiration will always provide the highest, lowest, or an intermediate value for cardiac output. [576] In the end, the clinician is faced with a tradeoff--accuracy versus reproducibility. [577] Recent studies with continuous cardiac output techniques highlight these issues and are discussed later.

Continuous Thermodilution Cardiac Output Monitoring

Over the past decade, new technologies were applied to PAC monitoring to allow nearly continuous cardiac output (CCO) monitoring using either hot [578] [579] [580] [581] [582] [583] or cold [584] thermal indicators. The hot thermal techniques are the ones more widely accepted in clinical practice. In brief, these methods involve the release of small quantities of heat from a 10-cm thermal filament incorporated into the right ventricular portion of a PAC. [581] [585] Commercially available CCO PACs use different proprietary algorithms to analyze the thermal signal measured by the thermistor at the tip of the catheter to arrive at an average cardiac output value. Typically, the displayed value for cardiac output is updated every 30 seconds and represents the average cardiac output over the previous 3 to 6 minutes. [586] Consequently, current thermal signal-based CCO methods should not really be considered continuous, real-time monitors, but rather techniques that provide continual, frequently updated cardiac output values.

In general, the CCO methods appear to have good agreement with standard bolus thermodilution cardiac output measurements or electromagnetic flow probe techniques. [579] [582] [583] [587] In a small, multicenter study, Mihm et al [579] found that CCO provided a clinically reliable measurement for a group of 47 intensive care unit patients. The device performed well in patients with a wide range of cardiac outputs (1.6-10.6 L/min) and core temperatures (33.2°C-39.8°C), and the method showed no deterioration in performance over the 72-hour monitoring period. In addition, CCO monitoring appears to be more reproducible or precise than standard bolus thermodilution techniques, although this may simply be a function of the fact that the continuous methods display a time-weighted, average cardiac output value, as opposed to a single instantaneous measurement. [578] [579] [588] [589]

Despite the fairly rapid clinical acceptance of the thermal CCO techniques, there are several issues that the user should appreciate. As already noted, CCO monitors have an inherent 5 to 15 minute delay in responding to abrupt changes in cardiac output, and the magnitude of this delay depends on the computer algorithm and measurement technique used in the monitor. [585] Although modifications of CCO algorithms to allow a more rapid response time have improved this aspect of monitor performance, acute changes in blood flow are still detected more slowly by CCO monitoring than by other methods, such as direct arterial pressure or mixed venous oximetry. [578] Claims that CCO monitoring provides the best early warning of important circulatory changes remain anecdotal at present. [590]

Because the thermal signal sensed by the CCO PAC is very small, sophisticated computer algorithms are needed to distinguish this signal from extraneous thermal noise. These same algorithms are employed to derive a displayed CCO value that represents a running, time-weighted average measured over the previous several minutes. Clearly, this CCO value will represent a cardiac output that is an average value recorded over the respiratory cycle. In contrast, bolus thermodilution cardiac output measurements will show quite different cardiac output values, depending on the phase of respiration during which they are recorded (see earlier discussion). Thus, the CCO-averaging algorithm obviates this physiologic effect that confounds bolus thermodilution cardiac output techniques. As a result, cardiac output measured by the CCO method may provide a more accurate measurement for patients receiving positive pressure mechanical ventilation. Although electronic smoothing or filtering is standard for all hemodynamic values displayed on the bedside monitor, such as heart rate (see Fig. 30-1) (Figure Not Available) , blood pressure, and so forth, the delay inherent in thermal CCO monitoring is much longer--minutes rather than seconds. In effect, the CCO technique involves a fundamental tradeoff between rapid response time and overall accuracy of measurement. The standards for these performance characteristics have not been defined, but must balance the response time against the stability of the displayed value and its immunity from thermal noise. [586]

In summary, the CCO PAC monitoring technique is growing in clinical popularity. It is more reproducible and precise than bolus thermodilution cardiac output measurement, but time delays inherent in the CCO technique require the clinician to rely on other monitored variables to detect acute circulatory changes. Because an external system for cold fluid injection is not required, the CCO technique requires less nursing time and may result in fewer measurement errors, less risk of fluid overload, and less risk of infection. This new method requires a significant warm-up time and may work poorly in an environment where there is a great deal of thermal noise, such as the cardiac operating room.

Fick Cardiac Output Measurement

The *Fick method* for cardiac output determination is a form of indicator dilution in which exogenous indicators are not required, but instead, transported oxygen serves this purpose. This method was first proposed in 1870 by the

German physiologist Adolph Fick, [591] who described a means to determine blood flow by measuring overall oxygen uptake and content in the blood. [592] The Fick equation relates cardiac output to oxygen consumption and blood oxygen content and is recognizable as a special form of the generalized indicator dilution equation:

And 10 converts deciliters to liters (dL = 100 mL)

The denominator of the Fick equation is the arteriovenous oxygen content difference.

This difference is calculated from the arterial and mixed venous oxygen contents.

In general, the contribution of dissolved oxygen is ignored in these calculations because it is small (0.003 × arterial or mixed venous partial pressure of oxygen).

To calculate cardiac output by the Fick method, arterial and mixed venous blood must be drawn for blood gas analysis. The latter requires pulmonary artery catheterization to collect a true mixed venous sample. In addition, oxygen consumption must be measured; traditionally, this required collecting the patient's exhaled air over several minutes with cumbersome equipment. In an attempt to simplify and automate the Fick technique, newer approaches have used pulse oximetry, pulmonary artery oximetry, and on-line respiratory gas analysis or indirect calorimetry to measure oxygen consumption. [593] [594] [595] Although clinicians sometimes estimate the Fick cardiac output by assuming a constant basal value for oxygen consumption of approximately 200 to 250 mL/min, this approach is likely to be inaccurate in critically ill patients. [559] Normal values for all of these variables are given in Table 30-2 .

/das/book/view/29494766/875/327.html

CONTINUOUS MIXED VENOUS OXIMETRY PULMONARY ARTERY CATHETERS

Although the formal Fick cardiac output method is not applied widely in clinical practice, the physiologic relations described by the Fick equation form the basis for another PAC-based monitoring technique termed continuous mixed venous oximetry. Rearrangement of the Fick equation reveals the four determinants of mixed venous oxygen saturation ($S_{v\text{--}O}$ 2):

To the extent that arterial oxygen saturation, oxygen consumption, and hemoglobin concentration remain stable, mixed venous oxygen saturation may be used as an indirect indicator of cardiac output. For example, when cardiac output falls, tissue oxygen extraction increases and the mixed venous blood will become more desaturated. However, as noted in this equation, mixed venous oxygen saturation also varies directly with arterial oxygen saturation and hemoglobin concentration and varies inversely with oxygen consumption. When any of these other variables change significantly, one cannot assume that a change in mixed venous oxygen saturation results solely from a change in cardiac output. Although these considerations may confound the use of mixed venous oxygen saturation as an indicator of cardiac output, monitoring this variable provides more comprehensive information about the balance of oxygen delivery and consumption by the body--not just cardiac output, but also the adequacy of cardiac output. [586]

Although mixed venous oxygen saturation may be determined by intermittent blood sampling from the pulmonary artery, a specially designed PAC can provide this information reliably and continuously. Fiberoptic bundles incorporated into the PAC determine the hemoglobin saturation in pulmonary artery blood based on the principles of reflectance oximetry. A special computer connected to this PAC displays mixed venous oxygen saturation continuously and allows standard thermodilution cardiac output measurements. Technical problems with continuous mixed venous oximetry are generally limited to improper PAC tip positioning or inaccurate calibration. [586] Multiwavelength fiberoptic technology and reflection intensity algorithms help to reduce wall artifacts caused by spurious reflections from a PAC thrombus or the pulmonary arterial walls. These catheters are calibrated at the bedside prior to use but may also be calibrated *in vivo* from a pulmonary artery blood gas sample if mixed venous saturation values are questionable. [596]

The continuous mixed venous oximetry PAC may be used to measure thermodilution cardiac output and arterial and mixed venous oxygen content values and thereby calculate oxygen consumption using a rearrangement of the Fick equation. However, values for oxygen consumption derived using these measurements generally underestimate direct oxygen consumption measured by mass spectrometry, metabolic

cart, or water-sealed spirometry. [531] Oxygen delivery also may be calculated from these PAC-derived values:

Many physicians have used these derived measures of oxygen consumption and oxygen delivery to guide treatment of critically ill patients. Unfortunately, as noted in the earlier discussions of pulmonary artery catheterization, this "goal-oriented therapy" has not been shown to result in improved patient outcomes in most instances. In summary, continuous mixed venous oximetry is an appealing, wellestablished technology, but these catheters are more ex-pensive than standard PAC, and clinical studies to date have not yet defined appropriate clinical indications for their use. [308] [513] [531] [586]

RIGHT VENTRICULAR EJECTION FRACTION PULMONARY ARTERY CATHETERS

Although cardiovascular monitoring has focused predominantly on left ventricular performance, in some instances, right ventricular dysfunction may be the more important factor limiting the circulation. [597] [598] [599] [600] Patient populations at increased risk for right ventricular dysfunction include those with chronic obstructive pulmonary disease, adult respiratory distress syndrome, pulmonary hypertension, and right ventricular ischemia and infarction. [458] [597] [598] [599] [600] [601]

Standard techniques are available for monitoring right ventricular performance in patients with acute myocardial infarction involving the right ventricle. Electrocardiographic monitoring using the V_4R lead has proved to be a sensitive and specific indicator of right ventricular ischemia and infarction. [602] [603] [604] PAC monitoring in patients with right ventricular infarction often reveals the characteristic hemodynamic patterns described earlier. [457] [458] [601] [605] However, accurate evaluation of right ventricular performance in patients with other causes of right ventricular dysfunction has proved more complicated. In patients with severe respiratory failure, the confounding effects of mechanical ventilation with high levels of PEEP have made interpretation of cardiac filling pressures difficult and, in some cases, misleading. [586] [606] [609]

In intraoperative and critical care environments, measurement of right ventricular ejection fraction (RVEF) with a specially designed PAC offers another method for evaluating right ventricular function. [610] This method uses a standard PAC equipped with a rapid response thermistor that detects and quantifies changes in pulmonary artery blood temperature with each heartbeat. [610] [611] The thermistor measures these small temperature changes following bolus administration of an iced or room temperature injectate, and the cardiac output computer determines the residual fraction of thermal signal following each heart beat and calculates the RVEF as 1 minus this average residual fraction. [611] Clearly, all factors that confound standard thermo-dilution cardiac output measurement will also interfere with accurate determination of RVEF. In addition, because the temperature changes measured by the RVEF PAC are small, beat-to-beat changes, the method will not work if the ECG R waves cannot be detected accurately, the R-R interval is short owing to tachycardia, or the cardiac rhythm is irregular. [586] Comparison of PAC-based RVEF measurements with angiographic or nuclear techniques has yielded mixed results in terms of accuracy, but this may reflect, in part, the absence of a widely accepted reference standard for this measurement. [611] [612] [613]

Intraoperative use of the RVEF PAC has focused primarily on detection of right ventricular dysfunction in patients with coronary artery disease undergoing surgical revascularization. Reduced RVEF has been noted following cardiopulmonary bypass, [614] particularly in patients with preexisting right coronary artery obstruction. [615] [616] Anecdotally, an acute reduction in RVEF from its normal value of approximately 40 percent may provide an early sign of right ventricular ischemia. [617] However, RVEF is an extremely loaddependent measurement of right ventricular performance, and the clinician must keep this fact in mind to interpret this measurement properly. [586] [607] [608]

Clinical use of the RVEF PAC appears to have found its greatest application to date in critically ill patients, especially in those with respiratory failure. [586] [607] [608] [609] [618] In these applications, the measurement of greatest interest has been the right ventricular end-diastolic volume (RVEDV), which is derived mathematically from RVEF:

Various authors have demonstrated that the RVEDV correlates better with cardiac output than standard preload measurements, such as CVP or PAWP. [586] [608] [609] These findings are not surprising given all the interpretive problems associated with cardiac filling pressure monitoring previously discussed. The better correlation between RVEDV and cardiac output may result, however, from the mathematical coupling of measurements, because both are derivatives of stroke volume determined with the PAC. [586] [609] Furthermore, as in the case of standard PAC monitoring, the benefit of RVEF PAC monitoring in terms of patient outcome remains unproven. [308]

PULMONARY ARTERY CATHETER-DERIVED HEMODYNAMIC VARIABLES

The cardiovascular system often is modeled as an electrical circuit, with the relationship between cardiac output, blood pressure, and resistance to flow related in a manner similar to Ohm's law. The electrical version of this relation is familiar as

The analogous formulas for determining systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR)

rearrange Ohm's law and replace voltage with blood pressure and current with blood flow:

Multiplying by 80 corrects SVR and PVR values from Wood units (mm Hg/L/min) to standard metric units (dynesseccm^{-5}).

Normal values for SVR and PVR are given in Table 30-2 . Note that these calculations of systemic and pulmonary vascular resistance are based on a hydraulic fluid model that assumes continuous, laminar flow through a series of rigid pipes. [619] [620] These calculations also use atrial pressure as the downstream pressure for systemic or pulmonary flow, with CVP used for right atrial pressure in the SVR calculation and PAWP used for LAP in the PVR calculation. Alternative methods to calculate resistance ignore the effect of these downstream pressures. For the systemic circulation, total resistance may be calculated from MAP and cardiac output alone, and for the pulmonary circulation, total pulmonary resistance describes the ratio of mean pulmonary arterial pressure and cardiac output.

Clearly, all these resistance formulas oversimplify the behavior of the cardiovascular system. A more physiologic model of the systemic circulation considers the vasculature to be a series of collapsible vessels with intrinsic tone. This model, also called the *vascular waterfall,* describes a critical closing pressure in the downstream end of the circuit that exceeds right atrial pressure and serves to limit flow--an effective downstream pressure that is higher than the right atrial pressure used in the SVR formula. A detailed consideration of these issues is beyond the scope of this discussion and is available in other sources. [621] [622] The important issue for clinicians is that therapy focused on the fine adjustment of SVR may be very misleading and should be avoided.

Additional problems arise in considering the pulmonary vasculature and using PVR as a measure of resistance to flow across the lung. Pulmonary vasculature is more compliant than systemic vasculature, and marked increases in pulmonary blood flow may not produce any significant increase in PAP. In addition, flow usually ceases at end-diastole in the low resistance pulmonary circuit. [411] [623] Thus, changes in PVR may result from intrinsic alterations in pulmonary vascular tone (constriction or dilation), vascular recruitment, or rheologic changes. [620] [623] [624] For the pulmonary circuit, a better approach to evaluating the changes in pulmonary vascular resistance may be to examine the end-diastolic gradient between PADP and PAWP (see Fig. 30-54) (Figure Not Available) . [624] Alternatively, more complex calculations of impedance rather than resistance will better describe this property of the pulmonary circuit. [625]

Another set of common calculations derived from standard hemodynamic variables adjusts these measurements for the patient's body surface area (BSA) in an attempt to normalize these measurements for patients of different sizes. The BSA is generally determined from standard nomograms based on height and weight. The most commonly indexed variables are the cardiac index (CI = CO/BSA) and stroke volume index (SVI = SV/BSA), although the SVR and PVR are sometimes indexed as well (SVRI and PVRI). Note that indexed resistances are higher than nonindexed values, because the cardiac index term is in the denominator of these equations. The appropriate formulas are: SVRI = SVR × BSA and PVRI = PVR × BSA.

In theory, normalizing hemodynamic values through "indexing" should help clinicians determine appropriate normal physiologic ranges to help guide therapy. Unfortunately, there is little evidence that these additional calculations provide valid normalizing adjustments. BSA is a biometric measurement with an obscure relationship to blood flow, and it does not adjust for variations between individuals based on age, sex, body habitus, or metabolic rate. [626] Although it is important to be aware of a patient's size and medical history in interpreting and treating changes in any of the measured or calculated hemodynamic variables, it is not appropriate to target therapy solely at achieving normal indexed values.

ULTRASOUND-BASED METHODS OF CARDIAC OUTPUT MONITORING

The popularity and safety of diagnostic Doppler echocardiography in clinical medicine have driven the application of these techniques for measuring cardiac output. All of the ultrasound-based methods for cardiac output monitoring employ the Doppler principle. When ultrasound waves strike moving objects, these waves are reflected back to their source at a different frequency, termed the Doppler shift frequency, that is directly related to the velocity of the moving objects and the angle at which the ultrasound beam strikes these objects. For blood flow measurements, the red blood cells flowing through a major artery serve as the moving objects targeted by the ultrasound beam:

To measure blood flow velocity, the Doppler shift equation is rearranged to solve for velocity. In general, this method requires measurement only of the Doppler shift frequency, because the velocity of ultrasound in blood and the transmitted ultrasound frequency are known, and Costheta is assumed to equal 1 as long as the angle of insonation is small. This assumption requires that the ultrasound beam be oriented as much as possible in a direction that is parallel to the blood flow. For example, for angles less than 20 degrees, Costheta will be greater than 0.94, thereby introducing an error of less than 6 percent in the cardiac output calculation. Once the Doppler shift frequency is measured and blood flow velocity is calculated, stroke volume is derived as follows:

Finally, the cardiac output is derived from the product of the calculated stroke volume and heart rate.

Several different methods for measuring cardiac output use these basic principles of Doppler ultrasonography. Each technique employs slightly different equipment and meas-ures blood flow from a different site in the body. One method uses a Doppler probe mounted on the tip of an endotracheal tube to measure cardiac output using *transtracheal Doppler* insonation of aortic blood flow. [627] [628] The transtracheal Doppler method uses pulsed wave Doppler ultrasound to measure the flow velocity in the ascending aorta. In addition, the aortic cross-sectional area is determined by range-gating the Doppler signal in small 1-mm increments to measure aortic diameter and then calculate aortic cross-sectional area, assuming the aorta to be a circular vessel. [628] Although the method reportedly tracked directional changes in cardiac output accurately, it did not have wide clinical acceptance owing to problems with its implementation, including the requirement for tracheal intubation, a high failure rate, and marked operator-related dependency for success because of a difficult user interface and poor signal stability. [629] [630]

Another Doppler method uses a PAC equipped with three 1-mm ultrasound transducers mounted on the front and rear surfaces of the catheter tip. [631] [632] [633] The theoretical advantages of *Doppler PAC* cardiac output monitoring are that the technique determines a space-averaged measurement of blood flow velocity in the pulmonary artery and an instantaneous measurement of vessel diameter throughout the cardiac cycle. [633] [634] However, the modest accuracy of the technique and its requirement for pulmonary artery catheterization have limited wider clinical acceptance. The Doppler principle has also been applied to measure cutaneous blood flow by *laser Doppler velocimetry.* [635] Because this method detects only changes in skin blood flow rather than absolute cardiac output, its use is confined mainly to determining adequacy of graft tissue flow following microvascular anastomoses of major tissue flaps.

Other clinical methods to measure cardiac output using Doppler ultrasound have focused on less invasive approaches than the transtracheal or PAC techniques. Nearly 25 years ago, methods were developed to measure the blood flow velocity in the distal aortic arch with an ultrasound transducer applied to the suprasternal notch. [636] Further refinements of the technique used continuous wave Doppler to measure the systolic velocity integral and to estimate stroke volume in the ascending aorta. [637] By the 1980s, successful noninvasive measurement of cardiac output was reported in patients, using commercially available equipment to determine the velocities in the ascending aorta with continuous wave Doppler and the aortic cross-sectional area with A-mode pulsed echocardiography. [638] [639] [640] Although these *suprasternal Doppler* cardiac output techniques showed reasonable agreement with thermodilution methods, [638] [640] [641] they were relatively labor intensive, required a fair degree of experience and expertise, and could not be accomplished in a significant number of critically ill medical and surgical patients. [640] Because they provided only intermittent measurements at best, clinical acceptance of this method was limited.

The evolution of Doppler techniques into practical clinical monitoring tools required an ultrasound transducer that could be positioned and left in place for continuous monitoring without the need for repeated adjustments or time-consuming measurements by the physician. Such a transducer was incorporated into the tip of a standard esophageal stethoscope to allow continuous monitoring of cardiac output by interrogating the blood flow profile in the descending thoracic aorta. This technique, *esophageal Doppler* cardiac output monitoring, is the most widely applied method of noninvasive (or minimally invasive) cardiac output monitoring performed currently in surgical and critically ill patients. [642] In brief, the Doppler probe is inserted into the esophagus to a depth of approximately 35 cm from the incisors in a tracheally intubated patient. Probe position is adjusted to optimize the audible Doppler flow sound from the descending aorta. Because the esophagus and the descending aorta lie in close proximity and run essentially parallel to one another, the ultrasound transducer is mounted at a fixed angle that is known by the cardiac output computer and is used to correct the resulting Doppler shift frequency to provide an accurate velocity measurement (see earlier discussion).

The esophageal Doppler monitoring method interrogates blood flow in the descending thoracic aorta and therefore only measures a fraction of the total cardiac output. Consequently, the esophageal Doppler probe must be "calibrated" by some method. Most early investigators performed this initial calibration with a suprasternal Doppler measurement of cardiac output in the ascending aorta. [639] [643] [644] [645] [646] [647] In some instances, ascending aortic diameter was also measured using A-mode ultrasound, [639] [643] whereas later versions of these monitors employed a nomogram to estimate aortic diameter based on the patient's age, sex, height, and weight. [644] [645] [646] [647]

Early studies comparing cardiac outputs measured with the esophageal Doppler device to measurements using

other methods showed variable performance of the new technique. [648] [649] Although several investigators showed that the esophageal Doppler method accurately tracked changes in cardiac output measured by thermodilution, there were significant absolute differences in cardiac output between methods, with the Doppler technique both underestimating and overestimating simultaneous thermodilution values. [639] [644] Other investigations were less favorable, suggesting that the

esophageal Doppler method could not even be relied on as a trend monitor. [646] [647] [650] It appeared that the suprasternal Doppler measurements and the aortic diameter measurements were often in error and did not provide suitable initial calibration of the esophageal Doppler probe. Furthermore, these initial calibration methods were cumbersome, time consuming, and required significant operator expertise. [639] [646]

In recent years, the esophageal Doppler method for cardiac output monitoring has seen a certain amount of renewed enthusiasm, not so much as an accurate measure of absolute cardiac output, but as an indicator or estimate of systemic flow. [642] Singer et al [651] have popularized this technique in the United Kingdom, applying it to the care of critically ill patients and using newer features of the Doppler technique to discern additional hemodynamic information. [652] [653] [654] Improvements in instrument design have made it more informative to the clinician and much simpler to use. Current devices provide a clear visual display of the spectral Doppler waveform and calculate and display additional, albeit somewhat less conventional, hemodynamic variables. These derived variables include the peak blood flow velocity and acceleration and the heart rate-corrected flow time. Some studies have shown that these derived variables provide additional useful information about left ventricular preload, contractility, and systemic vascular resistance. [642] [651] [652] [653] [654] [655]

The newer esophageal Doppler monitoring devices are much simpler to operate because they do not require any of the ultrasound-based calibration procedures demanded by earlier devices. The emphasis in developing these devices has been more toward providing a continuous trend of cardiac output rather than an accurate continuous absolute measurement of blood flow. For this trending purpose, certain assumptions must still remain valid: the angle between the esophageal Doppler probe and the descending aorta is known and remains constant throughout the monitoring period; the aortic cross-sectional area remains constant throughout the monitoring period; and the fraction of cardiac output flowing down the descending aorta remains constant throughout the monitoring period. As could be predicted from all of these assumptions, newer esophageal Doppler monitors still do not provide cardiac output measurements that agree closely with thermodilution values. [656] [657]

The advantages and limitations of esophageal Doppler monitoring should be recognized to apply this method optimally in clinical practice. The technique is easy to use, minimally invasive, and inherently safe. This monitoring can be initiated rapidly, even in patients in whom pulmonary artery catheterization cannot be achieved or is contraindicated. [652] Esophageal Doppler monitoring provides a continuous, beat-to-beat waveform that is proportional to the left ventricular stroke volume. In addition, it derives other hemodynamic variables that may help guide clinical management. Limitations of the technique must also be appreciated by the physician to avoid pitfalls in data interpretation. First and foremost, as currently designed, the technique provides only an estimate of the true cardiac output. Furthermore, for changes in cardiac output to be properly detected, the previously mentioned assumptions must hold. It is not surprising that aortic cross-clamping and flow redistribution following cardiopulmonary bypass provide conditions when these assumptions are invalid. [639] [645] The esophageal Dop-pler technique cannot be used in non-tracheally intubated patients or in individuals with esophageal pathology, and the method is likely to be unreliable in patients with diseases of the aortic valve or thoracic aorta. Finally, like all ultrasound techniques, the acoustic window to acquire the Doppler signal may not be adequate in some individuals, thereby precluding use of this method.

The current clinical role for esophageal Doppler cardiac output monitoring is not to serve as a replacement for the PAC, but rather as an additional circulatory monitor in higher risk patients who do not warrant invasive monitoring. [642] [658] The popularity of this technique in the United Kingdom may reflect in part the much more restricted use of PACs in that country compared with use in the United States. [642] Preliminary studies have suggested that perioperative esophageal Doppler-guided volume resuscitation of moderate risk surgical patients reduces perioperative morbidity and shortens hospital stay. [659] [660] If these results can be duplicated in other settings and with larger groups of patients, this technique may find a role as a more routine monitor in patients who are at increased risk for perioperative circulatory complications.

NONPULMONARY ARTERY CATHETER-BASED CARDIAC OUTPUT AND PERFUSION MONITORING

An interest in studying cardiovascular function during space flight initially prompted investigations of impedance plethysmography as a noninvasive method of determining cardiac output. This technique of *bioimpedance* cardiac output monitoring was first described by Kubicek et al [661] and is based on changes in electrical impedance of the thoracic cavity occurring with ejection of blood during cardiac systole. [661] Their original formula relates these bioimpedance measurements to stroke volume:

Cardiac output is computed from the product of the derived stroke volume and heart rate. Over the years, this formula for deriving stroke volume has been modified based on refined models of the behavior of the thoracic resistivity. [642] [662] [663]

Various devices have been marketed commercially that measure cardiac output using the bioimpedance method. Each requires application of disposable electrodes to the skin surface along the sides of the neck and lateral aspect of the lower thorax. Impedance measurements are made by applying a continuous small electrical current across the chest. Patient height, weight, and gender are entered into the monitor by the operator to allow an accurate computation of the volume of the thoracic cavity. Bioimpedance cardiac output is computed for each cardiac cycle and continuously displayed as an average value over several heart beats.

Validation studies comparing the bioimpedance cardiac output measurement with other methods have produced inconsistent results. [642] [647] [648] [663] [664] [665] [666] [667] [668] [669] Although many studies suggest that the bioimpedence method is accurate in healthy volunteers, its reliability deteriorates in critically ill patients, including those with sepsis, increased lung water, aortic regurgitation, and electronic cardiac pacing. [663] [664] [669] Because the bioimpedance method is an indirect measure of cardiac output with a complex mathematical derivation, it is not surprising that this monitoring method has not proved to be as reliable as some other techniques. Despite recent claims of improved performance of newer devices with refined algorithms, [670] [671] bioimpedance cardiac out-put monitoring has not found broad clinical acceptance to date.

Other methods for cardiac output monitoring are available that do not require pulmonary artery catheterization. One such totally noninvasive technique is the *partial CO_2 rebreathing Fick technique.*[672] This method uses the change in CO_2 production and end-tidal CO_2 in response to a brief, sudden change in ventilation. A computer-controlled pneumatic valve intermittently increases dead space, thereby causing partial rebreathing of exhaled gases. Changes in CO_2 production and end-tidal CO_2 in response to the rebreathing are used to calculate cardiac output by a differential version of the Fick equation. The attractive features of this method are that it is entirely noninvasive, it can be performed every few minutes, and the brief episodes of rebreathing pose no substantial risk to most patients. [673] [674] [675] [676] As with all Fick-based techniques, the partial CO_2 rebreathing method does not account for pulmonary shunt. In effect, it measures pulmonary capillary blood flow as an indicator of total cardiac output and thus may require correction for this factor. [677] [678]

The *lithium dilution* technique is another cardiac output monitoring method that derives its fundamental basis from indicator dilution principles. [679] [680] [681] In brief, following a central venous bolus injection of a small dose of lithium chloride, an ion-selective electrode attached to a peripheral arterial catheter measures the lithium dilution curve, from which the cardiac output is derived. Preliminary investigations suggest that this is an accurate technique compared with standard thermodilution methods or electromagnetic flowmetry and may be even more precise than thermal indicator techniques. [682] [683] Although the lithium dilution method appears to be scientifically robust, it is not known how frequently small doses of lithium chloride (e.g., 0.15-0.6 mmol) may be injected in the typical clinical setting. Furthermore, the present method requires both central venous and arterial cannulation and thus carries all standard risks inherent in these invasive procedures.

Attempts to derive cardiac output from the systemic arterial pressure trace have met with limited success. These methods, generally termed *pulse contour* cardiac output, determine the cardiac output from computerized analysis of the aortic pressure waveform, [684] the radial artery pressure waveform, [685] or even a continuous noninvasive finger blood pressure waveform. [686] [687] In general, agreement between these methods and clinical standards, such as thermodilution cardiac output, have been poor, particularly when there are large changes in systemic vascular resistance. [684] This is not surprising in view of the complex nature of the morphology of the peripheral arterial pressure waveform.

The clinical role for these alternative methods of cardiac output monitoring remains in evolution. Advocates of flow monitoring argue that early preemptive therapy guided by these devices is more likely to improve patient outcome, compared with delayed therapy in critically ill patients who already have evidence of end-organ failure. [642] In the acute care setting, noninvasive cardiac output monitoring methods that are easily applied during surgery or on initial pres-entation to the emergency department or intensive care unit may have a unique role in providing a bridge to more comprehensive, invasive monitoring with a PAC. Inasmuch as several of these techniques have been found to be useful in detecting occult hypovolemia, [654] [660] other methods of detecting the adequacy of the circulating blood volume or end-organ perfusion have received attention recently.

The *double indicator dilution* method is one new technique for blood volume assessment at the bedside. It appears to provide measures of intravascular volume that may be superior to those of traditional preload measurements derived from pulmonary artery catheterization. [688] [689] *Pulse dye densitometry* is another new method that may provide a bedside indication of the circulating blood volume that was previously only measured with complex radioactive isotope techniques. This method involves the intravenous injection of indocyanine green dye, and its detection with a peripheral pulse dye densitometer that uses two-wavelength light absorption, similar to a pulse oximeter. [690] [691] [692] [693]

Other monitoring techniques aimed at detecting inadequate tissue perfusion have focused on the splanchnic circulation as a site that may provide an early indication of hypoperfusion. *Gastric tonometry* is a recently automated technique that allows measurement of gastric intramucosal P_{CO_2} and calculation of intramuscosal pH with a semicontinuous air tonometer. [694] [695] [696] Some investigations have already noted the superiority of this end-organ monitor as an indicator of the adequacy of tissue perfusion and a predictor of perioperative complications [659] [696] and death in critically ill patients. [697] Unfortunately, it is not known whether therapy directed at correcting such splanchnic hypoperfusion will confer clinical benefit. [698] [699] Newer cardiovascular monitoring techniques, such as measurement of circulating blood volume and gastric intramucosal pH, offer new variables for cardiovascular monitoring, that may augment or even supplant some current monitors.

/das/book/view/29494766/875/332.html

AUTOMATED ANESTHESIA DATA MANAGEMENT SYSTEMS AND DATA RECORDERS

Use of numerous supplementary cardiac monitors in patients with cardiovascular disease results in the generation of huge amounts of data during the course of an anesthetic. One of the responsibilities of the anesthesiologist is to create a record that chronicles the anesthetic management and clinical course of the patient in the perioperative period. However, transcribing all data produced in complex, highly monitored cases can become a burdensome clerical task that can actually detract from patient care by diverting the anesthesiologist's attention. Use of automated data acquisition and anesthesia record-keeping devices addresses this problem. Obviously, the recording of hemodynamic data from monitors is only a part of the anesthetic record. Patient demographics, a history of operative events, fluid and anesthetic drug administration, and various text notes are all important additional components of this document. The automated device performs all of these functions efficiently, completely, and reliably, and thus can replace the traditional manual anesthesia record. [700]

Another significant and unique benefit of automated systems is the ability to collect anesthesia-related data in a unified format across all cases in an institution or in a number of linked institutions. Analysis of this database of comprehensive information allows efficient use of operating room resources, [701] facilitates quality assurance management, and offers valuable data for clinical research. The data from many centers can be merged to identify expected clinical outcomes across large patient populations and determine variances from the expected.

Use of computerized devices for intraoperative anesthesia data gathering purposes is not new, but only recently has there been a proliferation of commercially available devices. Implementation of an anesthesia information system is relatively easy and has high acceptance by clinicians, especially for complicated cases such as those involving cardiothoracic anesthesia. [700] In addition, the accuracy and precision of data recorded automatically are likely to be superior to the manually kept record. [702] [703]

The great advances made since the early 1980s in the power and miniaturization of microcomputers allow the recording system to perform with a suitable user interface. These computers are small, yet powerful enough to be designed as individual stand-alone units for each anesthetizing location, thus improving reliability and sustaining communication with larger systems over well-established hospital networks. Connection to a hospital network system provides an opportunity for remote printing of completed anesthesia records and downloading of vital data from other information systems. Another benefit of these systems is the opportunity for long-term data storage that allows future analysis. The potential value of such databases both within and among institutions is essentially limitless.

COAGULATION MONITORING

In contrast to hemodynamic monitoring, assessment of perioperative coagulation remains, at present, entirely an *ex vivo* process. Traditionally, coagulation monitoring in the surgical patient has focused on preoperative testing to identify patients at increased risk for perioperative bleeding and intraoperative monitoring of heparin therapy during cardiac and vascular surgery. More recently, availability of increasingly sensitive and specific point-of-care coagulation monitors has provided an opportunity to guide administration of blood components and hemostatic drugs more specifically, without the delays inherent in standard laboratory testing.

Monitoring heparin anticoagulation during cardiac and vascular surgery is widely recognized as essential for the safe performance of these operations. Heparin is a biopharmaceutical derived from bovine lung or porcine intestinal mucosa, composed of a heterogeneous mixture of compounds with diverse anticoagulant activities. [704] Consequently, variability of heparin activity and pharmacodynamic response are well documented. Various patient-specific factors also affect pharmacodynamic response to heparin, including age, intravascular volume, and plasma/membrane concentrations of antithrombin III, heparin cofactor II, platelet factor 4, and other heparin-binding proteins. [704] Not surprisingly, therefore, patients exhibit widely different anticoagulant responses to the same standard dose of heparin. [705] Finally, heparin anticoagulation monitoring must be performed if only to prevent the rare, but potentially lethal, complication resulting from a failure to administer heparin as intended prior to cardiopulmonary bypass or arterial clamping. [706]

The ideal test of perioperative coagulation would be simple to perform, accurate, reproducible, diagnostically specific, and cost-effective. Although no single monitoring device available to date has all these ideal operating characteristics, many provide useful information to guide patient management. Particularly when combinations of these devices are used, they provide valuable diagnostic insights into the mechanism of a patient's perioperative coagulopathy. The importance of integrated monitoring described earlier for hemodynamic assessment is equally applicable to coagulation monitoring.

Commercially available point-of-care coagulation monitors used in the perioperative setting may be divided into four categories:

1. Functional measures of coagulation or assays that measure the intrinsic ability of the blood to clot

    Activated coagulation time (ACT)

    Heparin management test (HMT)

    High-dose thrombin time (HiTT)

    Prothrombin time (PT)

    Activated partial thromboplastin time (aPTT)

2. Monitors of heparin concentration

    Protamine titration

    Ion-selective electrodes

3. Viscoelastic measures of coagulation

    Thromboelastogram (TEG)

    Sonoclot

4. Platelet function analyzers

Functional Measures of Coagulation

The ACT, described by Hattersley in 1966, [707] is a version of the Lee-White whole blood clotting time that is modified

to include an initiator for contact activation of the coagulation system. This activator, frequently diatomaceous earth, is used to accelerate clot formation and reduce the time to assay completion.

Hattersley's original assay required manual mixing of a blood sample with the contact activator followed by repeated visual assessment of the tube to determine time-to-visible-clot formation. More recent commercial ACT monitors simplify testing by automating clot detection. One of the more widely available ACT monitors employs a glass test tube that contains a small magnet at the bottom (Hemochron; International Technidyne, Inc., Edison, N.J.). After adding a sample of blood, the tube is placed into the analyzer, where a constant temperature of 37°C is maintained, and the tube is rotated slowly while the magnet maintains contact with a proximity detection switch. As fibrin clot forms, the magnet becomes enmeshed and is pulled away from the detection switch, thereby triggering an alarm and providing an end-time for the ACT measurement. Another ACT device uses a "plumb-bob" flag assembly that is raised and dropped repeatedly through the sample vial containing blood and contact activator (Hepcon and ACT II; Medtronic Blood Management, Parker, Colo.). As clot forms, the rate of descent of the flag through the blood slows, triggers an optical detector, and alarms to signify the end-time for the ACT.

Because each patient's baseline ACT measurement serves as a control for subsequent determinations, the method selected for ACT testing might appear to be unimportant. However, drugs used in the perioperative period, such as the antifibrinolytic drug aprotinin, may dramatically alter the times measured using different ACT monitoring systems. Aprotinin inhibits contact activation by celite (dia-tomaceous earth) [708] and produces an artifactual elevation of the celite ACT. If this interaction is not considered, an insufficient dose of heparin may be administered. Kaolin, an alternative contact activator, should be used to measure ACT in patients

receiving aprotinin, because it will bind the aprotinin and remove it from the plasma. [708] It is not clear whether excess concentrations of aprotinin will overwhelm the kaolin-binding capacity and thereby affect the kaolinactivated ACT.

The ACT in normal individuals is approximately 107 ± 13 sec (mean ± standard deviation). [707] However, the time at which a patient's "baseline" ACT is measured can influence the result. Following surgical incision, the baseline ACT decreases by more than two standard deviations in patients undergoing cardiac surgery, perhaps because of tissue factor release with tissue injury. [709] Heparin clearly prolongs the ACT, because this test measures the clotting potential of the intrinsic and common pathways of coagulation. In addition to ACT prolongation by heparin, a prolonged ACT signifies impaired ability of the blood sample to generate clot, for whatever reason. However, the ACT is relatively resistant to platelet dysfunction and is affected only by severe thrombocytopenia and platelet inhibitors such as prostacyclin or monoclonal antibodies directed against GPIIb/IIIa surface receptors. [710] [711] [712]

ACT testing is probably the most widely used perioperative coagulation monitor because of its simplicity, low-cost, and ability to monitor anticoagulation when large doses of heparin are used as required for cardiac surgical procedures. However, there are limitations associated with this method of monitoring. ACT is relatively insensitive to low concentrations of heparin, and ACT measurements are not particularly reproducible. [713] These deficiencies are especially important when ACT monitoring is used to verify hep-arin neutralization with protamine. ACT monitoring also may be influenced by phospholipid-bound microparticles extruded from the platelet surface during activation. These platelet microparticles artifactually shorten the ACT even in the presence of residual heparin. [714] In addition to artifactually low ACT values, high ACT values greater than 600 sec do not represent a linear dose-response relationship to high-dose heparin administration. [713] Furthermore, both hypothermia and hemodilution prolong the time to ACT clot formation. In some instances, these artifactual effects on measurement of the ACT may lead to false assumptions regarding the extent of anticoagulation. Reproducibility of the ACT may be improved by averaging duplicate ACT determinations. [715] In one study, ACT tubes containing either heparinase or protamine have been employed in conjunction with unmodified ACT tubes to improve the sensitivity for detecting low heparin concentrations that persist in the blood. [716]

The HMT (Cardiovascular Diagnostics, Inc., Raleigh, N.C.) offers promise as a solution to many problems associated with use of the ACT for monitoring during cardiac surgery. This method employs recent advances in dry reagent chemistry analysis of coagulation. It uses a microprocessor-controlled analyzer and disposable test cards to provide a rapid, reproducible measure of functional anticoagulation when large doses of heparin are employed. A reaction chamber within each test card contains paramagnetic iron oxide beads and the dry chemical reagents necessary to activate coagulation in the blood sample. [717] After a drop of blood is added to the card, capillary action draws a small portion of this blood sample into the reaction chamber. An oscillating magnetic field is applied to the solution of blood, chemical reactants, and beads. A light beam passed through the test chamber detects oscillations in the amplitude of transmitted light coincident with bead movement in the test chamber. As clot formation occurs, the beads become enmeshed within the clot, reducing the amplitude of light oscillations to trigger the end-time for the HMT measurement. The minute sample of blood drawn into the test chamber and the extreme sensitivity of the clot detection method used in this system minimize confounding effects from hypothermia and hemodilution. Preliminary evaluation of this monitor during cardiac surgery suggests that the HMT provides a more accurate and more reproducible measure of heparin activity than the ACT. [718] [719]

A third measure of heparin anticoagulation, also used primarily during cardiac surgery, is the HiTT (International Technidyne, Edison, N.J.). The HiTT assay contains high reagent concentrations of thrombin to cleave fibrinogen directly and generate a fibrin clot. In the presence of these excess thrombin concentrations, clot formation occurs independently of plasma coagulation factors other than fibrinogen. As a result, the HiTT is prolonged by heparin (or other thrombin inhibitors), extreme degrees of hypofibrinogenemia or dysfibrinogenemia, and high concentrations of fibrin split products. [720] [721] During most surgical procedures when heparin is being used, HiTT prolongation will correlate with the heparin anticoagulant effect. The major limitation to

more widespread use of the HiTT has been the limited shelf-life of the thrombin reagent, which must be mixed just prior to performing the assay.

Standard laboratory-based coagulation testing remains a common practice in patients with a preexisting coagulopathy and those scheduled to undergo surgical procedures commonly associated with postoperative coagulopathy, such as cardiac or hepatic surgery. Most often, the PT and aPTT are measured to provide baseline values for the patient, although the dose-response curves for these assays limit their usefulness when high-dose heparin anticoagulation is employed. As point-of-care coagulation monitors that measure the PT and aPTT become increasingly available, it is important to recognize that the test results from these monitors will not necessarily match the results reported by the hospital-based laboratory. These different methods of coagulation monitoring may differ from laboratory testing because reagent sensitivities vary considerably from manufacturer to manufacturer and from one lot of reagent to another. In addition, laboratory-based testing relies on plasma, as opposed to point-of-care monitors that use whole blood. [722] Indeed, some of the delay inherent in laboratory-based testing results from the time required to process the plasma sample from the patient's whole blood. Because values obtained with point-of-care monitors are unlikely to agree with laboratory-based testing, their successful use in clinical practice will often require that baseline measurement values be determined for each individual patient.

Heparin Concentration Measurement

Protamine titration is at present the most widely used method for determining heparin concentration in the perioperative setting. Protamine is a strongly basic polycationic protein, which directly inhibits heparin in a stoichiometric manner. In other words, 1 mg of protamine will inhibit 1 mg (approximately 100 units) of heparin. This reaction forms the basis for the protamine titration method of heparin concentration measurement. As increasing concentrations of protamine are added to a sample of heparin-containing blood, time-to-clot formation decreases until the point at which protamine concentration exceeds the heparin concentration in the blood sample, and then the time-to-clot formation increases. If a series of blood samples with incremental doses of protamine are analyzed, the sample in which the protamine and heparin concentrations are most closely matched will be the first one to generate clot. Thus, using protamine titration methodology, it is possible to estimate the heparin concentration present in a given sample of blood. [723] Assuming that the heparin-protamine titration curve of an individual patient remains constant throughout the operative period, it is possible to use the protamine titration method to estimate the dose of heparin required to achieve a desired plasma heparin concentration. In a similar manner, determination of heparin concentration at the conclusion of surgery allows a more precise estimate of the amount of protamine required to neutralize the circulating heparin. More precise administration of heparin and protamine may have a number of clinical advantages. Some investigations have suggested that thrombin activity during cardiopulmonary bypass may be reduced when stable heparin concentrations are maintained. [724] More effective thrombin inhibition during bypass should benefit patients by decreasing consumption of coagulation factors and thereby reducing postoperative bleeding. [725] Although protamine titration initially was performed manually, automated methods currently are available (Hepcon; Medtronic Blood Management, Parker, Colo.). These monitors employ cassettes of 4 to 6 vials containing protamine to perform the titration assay. Different measurement cassettes are chosen, depending on the expected range of heparin concentration.

Protamine titration methodology is relatively sensitive to low concentrations of heparin and is limited only by the range of protamine concentrations provided for testing. For this reason, protamine titration has proved particularly useful for verifying heparin neutralization following protamine administration. This method for determining heparin concentration is relatively resistant to the influences of hypothermia and hemodilution. Furthermore, heparin concentration monitoring by protamine titration is not altered during aprotinin therapy, in contrast to celite ACT measurements. The major limitation of heparin concentration monitoring is failure to assess functional coagulation or the intrinsic clotting potential of the blood. To use an extreme example, consider a patient with a homozygous deficiency for antithrombin III. Although functional measures of coagulation, such as the ACT, would clearly identify these patients by failure to achieve the desired prolongation of the ACT after heparin administration, measures of heparin concentration alone would demonstrate the expected blood heparin level but would fail to identify the lack of anticoagulant effect.

Preliminary reports have described another method for measuring heparin concentration in whole blood using electrochemical sensors. These heparin sensors use a polyvi-nylchloride membrane impregnated with triiododecylmethyl-ammonium chloride (TDMAC) to produce an electric potential in response to heparin, which correlates well with laboratory-based measures of heparin concentration. [726] The heparin sensor offers several advantages over protamine titration methods for determination of heparin concentration. First, the heparin sensor is not dependent on clot for-mation. This allows determination of heparin concentrations in patients with underlying coagulopathies as well as with blood samples containing anticoagulants in addition to heparin, such as citrate or ethylenediaminetetra-acetic acid (EDTA). In addition, the heparin sensor produces a linear response over a greater heparin concentration range than current protamine titration methods. Rather than reporting heparin concentration discontinuously, as necessitated by protamine titration cartridges, heparin concentrations de-termined with ion-selective membranes are reported over a continuous range. Despite the apparent advantages of these electrochemical sensors, their accuracy may be altered by high plasma concentrations of salicylate, nitrate, iodide, or bromide. [727] The clinical usefulness of these ion-selective electrodes awaits further development of these sensors into commercially applicable forms.

Viscoelastic Measures of Coagulation

Initially developed in the 1940s, viscoelastic measures of coagulation have undergone a resurgence in popularity

---

during the past decade. The unique aspect of viscoelastic measures lies in their ability to measure the entire spectrum of clot formation from early fibrin strand generation through clot retraction and eventual fibrinolysis. The Thromboelastograph (TEG) (Haemoscope; Morton Grove, Ill), developed by Hartert in 1948, [728] uses a small 0.35-mL blood sample placed into a disposable cuvette within the instrument. The cuvette is maintained at a temperature of 37°C and continuously rotates around an axis of approximately 5 degrees. A metal piston attached by a torsion wire to an electronic recorder is lowered into the blood within the cuvette. As clot formation occurs, the piston becomes enmeshed within the clot, and rotation of the cuvette is transferred to the piston and electronic recorder.

Although variables derived from the TEG tracing do not coincide directly with laboratory-based tests of coagulation, the TEG is capable of detecting characteristic abnormalities of clot formation and fibrinolysis. [729] Various parameters that describe characteristics of clot formation and lysis are inscribed by the TEG recorder. The *R* value (reaction time) measures time to initial clot formation (normal: 7.5-15 min). It is considered comparable to the whole blood clotting time and may be accelerated by adding celite to the TEG sample cuvette. The R value is prolonged by a deficiency of one or more plasma coagulation factors. Maximum amplitude *(MA)* provides a measure of clot strength and may be decreased by either qualitative or quantitative platelet dysfunction or decreased fibrinogen concentration. Normal MA is 50 to 60 mm. The *alpha angle* and *K* (BiKoatugulierung or coagulation) values measure the rate of clot formation and may be prolonged by any factor slowing clot generation, such as

Figure 30-55 (Figure Not Available) The functional components of the thromboelastograph consist of a rotating cuvette, a suspended piston attached to a torsion wire, and a recorder. As the blood sample clots, rotation of the curvette is transferred to the torsion wire and translated by the recorder as a characteristic tracing. Quantitative parameters derived from the thromboelastograph trace are the reaction time (R), BiKoatugulierung value or coagulation time (K), alpha angle (alpha), and maximum amplitude (MA). See text for greater detail. *(From Tuman K, Speiss B, McCarthy R et al: Effects of progressive blood loss on coagulation as measured by thromboelastography. Anesth Analg 66:856, 1987.)*

Figure 30-56 Characteristic thromboelastograph tracings.

plama coagulation factor deficiency or heparin anticoagulation (Figs. 30-55 (Figure Not Available) and 30-56) .

The Sonoclot (Sienco, Inc; Morrison, Colo.) provides an alternative viscoelastic measure of coagulation. Compared with TEG, the Sonoclot immerses a rapidly vibrating probe into a 0.4-mL sample of blood. As clot formation occurs, impedance to probe movement through the blood increases and generates an altered electrical signal and characteristic clot "signature." The Sonoclot may be used to derive the ACT as well as provide information regarding clot strength and clot lysis. [730]

Both the TEG and Sonoclot generate characteristic diagrams by translating the mechanical resistance encountered by the sensor as it moves through the clotting blood sample. Measurements derived from these diagrams have been related to more traditional measures of coagulation, such as the ACT. [731] In addition, abnormal patterns have been associated with deficiencies of coagulation factors and functional platelet abnormalities. [732] [733] One of the more common applications of the TEG analyzer is the real-time detection of excessive fibrinolysis during liver transplantation. The TEG also may be used to differentiate surgical bleeding from coagulopathy following cardiac surgery. [734] More widespread application of viscoelastic coagulation monitoring has been hindered by the lack of specificity associated with abnormal findings and the qualitative nature of assay interpretation. Recent computerization and automation of these instruments have improved the reproducibility of the measurements and have made the results more quantitative. However, additional investigations are required to define further the usefulness of viscoelastic coagulation monitoring in the perioperative setting.

Platelet Function Monitors

Despite tremendous advances in point-of-care monitoring of plasma coagulation, bedside assessment of platelet function has remained problematic. Although platelet function

---

influences many point-of-care coagulation monitoring methods currently in use, these platelet-mediated effects are often nonspecific and unpredictable. The ACT is influenced only by profound platelet dysfunction, [710] and whereas the TEG and Sonoclot are capable of detecting platelet abnormalities, their sensitivity and specificity are limited in terms of defining the platelet problem in the context of a complex perioperative coagulopathy. The standard method for identifying qualitative platelet dysfunction is laboratory-based optical aggregometry, performed with specific platelet agonists in platelet-rich plasma. Unfortunately, this form of testing is technically demanding and cannot be performed at the bedside. Furthermore, alteration of platelet function by the method of sample preparation may affect the results. [735] Flow cytometry, using fluorescent-labeled antibodies, provides a sensitive method for quantitating platelet activation and platelet surface receptor availability. A further advantage of this form of platelet function analysis is the ability to use whole blood, thereby eliminating the potential for blood sampling and processing artifacts. However, as with platelet aggregation studies, flow cytometry requires substantial technical expertise and laboratory-based support.

Several platelet function assays, specifically designed for use at the bedside, have entered clinical trials. The HemoSTATUS (Medtronic Blood Systems; Parker, Colo.) platelet function test exploits the ability of platelet-activating factor (PAF) to accelerate clot formation of a kaolin-activated ACT. HemoSTATUS testing is performed on the Medtronic HMS coagulation analyzer using a six-channel kaolin ACT cartridge preloaded with increasing concentrations of PAF. A clot ratio is determined for each individual patient assay based on the ratio of the PAF-accelerated ACT compared with the standard ACT. An individual patient's clot ratio is compared with a maximal clot ratio derived from normal volunteers and provides a measure of the patient's platelet function. In the presence of platelet dysfunction, higher concentrations of PAF are required to achieve a comparable PAF-activated ACT. When the HemoSTATUS monitor has been used following cardiac surgery, investigators have demonstrated a relationship between platelet function and postoperative bleeding. [736] Furthermore, maximal clot ratio as determined by the HemoSTATUS has been demonstrated to improve following administration of either DDAVP or platelet concentrates. However, other investigators have failed to corroborate these results, and thus, further investigations are needed. [737] [738]

Currently undergoing clinical trials, the Rapid Platelet Function Analyzer (RPFA; Accumetrix, San Diego, Calif.) is an automated turbidimetric whole blood assay of platelet function, which assesses the ability of activated platelets to bind fibrinogen-coated polystyrene beads. [739] On addition of the test blood sample, thrombin receptor activating peptide directly activates platelets within the sample, thereby stimulating the expression of GPIIb/IIIa platelet surface receptors. As activated platelets bind and aggregate fibrinogen-coated beads, light transmission through the sample increases and generates a measurable signal. Although the RPFA is simple to operate and provides a rapid bedside measure of platelet function, a baseline measurement is required for each patient to calculate the extent of subsequent changes in platelet function.

The PFA-100 (Platelet Function Analyzer; Dade International Inc; Miami, Fla.) is unique among both laboratory-based and point-of-care platelet function monitors. It incorporates high-shear conditions to simulate primary hemostasis following injury to a small vessel. Citratecontaining blood, added to a disposable test cartridge, is aspirated through a 200-mum capillary and then forced through a 150-mm aperture in a membrane containing collagen and either adenosine diphosphate or epinephrine. [740] Exposure of platelets within the blood sample to activating agents within the membrane under high-shear conditions stimulates platelet adherence and aggregation. As the platelet plug forms, blood flow through the aperture decreases and the time to aperture occlusion is displayed as the "closure time." Although clinical trials with this instrument remain in progress, preliminary findings have demonstrated that the PFA-100 detects both congenital and acquired disorders of platelet function with a high degree of sensitivity and specificity. [741] [742]

Advances in our understanding of hemostasis and thrombosis at the molecular level have contributed directly to recent biotechnologic innovations in the assessment of perioperative hemostasis. Further advances in point-of-care coagulation monitoring offer the opportunity for clinicians to make more informed decisions about

transfusion therapy and hemostatic drug administration to minimize bleeding in the perioperative setting.

/das/book/view/29494766/875/334.html

References

1. Vandam LD: The senses as monitors. In Blitt CD (ed): Monitoring in Anesthesia and Critical Care Medicine. New York, Churchill Livingstone, 1985, p 5.

2. McIntyre JWR: Stethoscopy during anaesthesia. Can J Anaesth 44:535, 1997.

3. American Society of Anesthesiologists: Standards for basic anesthetic monitoring. Park Ridge, IL, American Society of Anesthesiologists, 1993, p 5.

4. Blitt CD: Precordial and esophageal stethoscopes. In Blitt CD (ed): Monitoring in Anesthesia and Critical Care Medicine. New York, Churchill Livingstone, 1985, p 25.

5. Philip JH, Raemer DB: An electronic stethoscope is judged better than conventional stethoscopes for anesthesia monitoring. J Clin Monit 2:151, 1986.

6. Barthram CN, Taylor L: The oesophageal and precordial stethoscope transducer as a monitoring and teaching aid. Anaesthesia 49:713, 1994.

7. Biro P: Electrically amplified precordial stethoscope. J Clin Monit 10:410, 1994.

8. Manecke GR, Poppers PJ: Esophageal stethoscope placement depth: Its effect on heart and lung sound monitoring during general anesthesia. Anesth Analg 86:1276, 1998.

9. Kates RA, Zaidan JR, Kaplan JA: Esophageal lead for intraoperative electrocardiographic monitoring. Anesth Analg 61:781, 1982.

10. Trager MA, Feinberg BI, Kaplan JA: Right ventricular ischemia diagnosed by an esophageal electrocardiogram and right atrial pressure tracing. J Cardiothorac Anesth 1:123, 1987.

11. Pattison CZ, Atlee III JL, Matthews EL et al: Atrial pacing thresholds measured in anesthetized patients with the use of an esophageal stethoscope modified for pacing. Anesthesiology 74:854, 1991.

12. Smith I, Monk TG, White PF: Comparison of transesophageal atrial pacing with anticholinergic drugs for the treatment of intraoperative bradycardia. Anesth Analg 78:245, 1994.

13. Cooper JO, Cullen BF: Observer reliability in detecting surreptitious random occlusions of the monaural esophageal stethoscope. J Clin Monit 6:271, 1990.

14. Reitan JA, Barash PG: Noninvasive monitoring. In Saidman LJ, Smith NT (eds): Monitoring in anesthesia. Boston, Butterworth, 1984, p 117.

15. Prielipp RC, Kelly JS, Roy RC: Use of esophageal or precordial stethoscopes by anesthesia providers: Are we listening to our patients? J Clin Anesth 7:367, 1995.

16. Klepper ID, Webb RK, Van Der Walt JH et al: The stethoscope: Applications and limitations--an analysis of 2000 incident reports. Anaesth Intensive Care 21:575, 1993.

17. Weinfurt PT: Electrocardiographic monitoring: An overview. J Clin Monit 6:132, 1990.

18. Block FE: What is heart rate, anyway? J Clin Monit 10:366, 1994.

19. Mark JB: Monitoring heart rate. In Mark JB (ed): Atlas of cardiovascular monitoring. New York, Churchill Livingstone, 1998, p 205.

20. Ebrahim MH, Feldman JM, Bar-Kana I: A robust sensor fusion method for heart rate estimation. J Clin Monit 13:385, 1997.

21. Feldman JM, Ebrahim MH, Bar-Kana I: Robust sensor fusion improves heart rate estimation: Clinical evaluation. J Clin Monit 13:379, 1997.

22. Davis RF: Clinical comparison of automated auscultatory and oscillometric and catheter-transducer measurements of arterial pressure. J Clin Monit 1:114, 1985.

23. Bruner JMR, Krenis LJ, Kunsman JM et al: Comparison of direct and indirect methods of measuring arterial blood pressure. Med Instrum 15:11, 1981.

24. Gorback MS: Considerations in the interpretation of systemic pressure monitoring. In Lumb PD, Bryan-Brown CW (eds): Complications in Critical Care Medicine. Chicago, Year Book Medical Publishers, 1988, p 296.

25. Riva-Rocci S: Un nuovo sfigmomanometro. Gaz Med Torino 47:981, 1896.

26. Zanchetti A, Mancia G: The centenary of blood pressure measurement: A tribute to Scipione Riva-Rocci. Hypertens 14:1, 1996.

27. Korotkoff NS: On the subject of methods of determining blood pressure. Bull Imp Med Acad St Petersburg 11:365, 1905.

28. Shevchenko YL, Tsitlik JE: 90th anniversary of the development of Nikolai S. Korotkoff of the auscultatory method of measuring blood pressure. Circulation 94:116, 1996.

29. Goldstein S, Killip T: Comparison of direct and indirect arterial pressures in aortic regurgitation. N Engl J Med 267:1121, 1962.

30. Cohn JN: Blood pressure measurement in shock: Mechanism of inaccuracy in auscultatory and palpatory methods. JAMA 199:972, 1967.

31. Messerli FH, Ventura HO, Amodeo C: Osler's maneuver and pseudohypertension. N Engl J Med 312:1548, 1985.

32. Ramsey M: Blood pressure monitoring: Automated oscillometric devices. J Clin Monit 7:56, 1991.

33. Iyriboz Y, Hearon CM, Edwards K: Agreement between large and small cuffs in sphygmomanometry: A quantitative assessment. J Clin Monit 10:127, 1994.

34. Yong PG, Geddes LA: The effect of cuff pressure deflation rate on accuracy in indirect measurement of blood pressure with the auscultatory method. J Clin Monit 3:155, 1987.

35. von Recklinghausen H: Neue Wege zur Blutdruckmessung. Berlin, Springer-Verlag, 1931.

36. Posey JA, Geddes LA, Williams H et al: The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure. Part 1. Cardiovasc Res Ctr Bull 8:15, 1969.

37. Yelderman M, Ream AK: Indirect measurement of mean blood pressure in the anesthetized patient. Anesthesiology 50:253, 1979.

38. Cullen PM, Dye J, Hughes DG: Clinical assessment of the neonatal Dinamap 847 during anesthesia in neonates and infants. J Clin Monit 3:229, 1987.

39. Friesen RH, Lichtor JL: Indirect measurement of blood pressure in neonates and infants utilizing an automatic noninvasive oscillometric monitor. Anesth Analg 60:742, 1981.

40. Kimble KJ, Darnall RA, Yelderman M: An automated oscillometric technique for estimating mean arterial pressure in critically ill newborns. Anesthesiology 54:423, 1981.

41. Khan SQ, Wardlaw JM, Davenport R et al: Use of a neonatal blood pressure cuff to monitor blood pressure in the adult finger: Comparison with a standard adult arm cuff. J Clin Monit 14:233, 1998.

42. Lyew MA, Jamieson JW: Blood pressure measurement using oscillometric finger cuffs in children and young adults. Anaesthesia 49:895, 1994.

43. Green DW: Use of a neonatal noninvasive blood pressure module on adult patients. Anaesthesia 51:1129, 1996.

44. O'Brien E, Atkins W: Blood pressure measurement using oscillometric finger cuffs. Anaesthesia 50:743, 1995.

45. Kazamias TM, Gander MP, Franklin DL: Blood pressure measurement with Doppler ultrasonic flowmeter. J Appl Physiol 30:585, 1971.

46. Zahed B, Sadove MS, Hatano S: Comparison of automated Doppler ultrasound and Korotkoff measurements of blood pressure. Anesth Analg 50:699, 1971.

47. Lee TK, Westenkow DR: Comparison of blood pressure measured by oscillometry from the supraorbital artery and invasively from the radial artery. J Clin Monit 14:113, 1998.

48. Weiss BM, Pasch T: Measurement of systemic arterial pressure. Curr Opin Anaesthesiol 10:459, 1997.

49. Borow KM, Newburger JW: Noninvasive estimation of central aortic pressure using the oscillometric method for analyzing systemic artery pulsatile blood flow: Comparative study of indirect systolic, diastolic, and mean brachial artery pressure with simultaneous direct ascending aortic pressure measurements. Am Heart J 103:879, 1982.

50. Van Bergen FH, Weatherhead DS, Treloar AE et al: Comparison of indirect and direct methods of measuring arterial blood pressure. Circulation 10:481, 1954.

51. Nystrom E, Reid KH, Bennett R et al: A comparison of two automated indirect arterial blood pressure meters: With recordings from a radial arterial catheter in anesthetized surgical patients. Anesthesiology 62:526, 1985.

52. Gravlee GP, Brockschmidt JK: Accuracy of four indirect methods of blood pressure measurement, with hemodynamic correlations. J Clin Monit 6:284, 1990.

53. Mark JB: Arterial blood pressure. Direct vs. indirect measurement. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 81.

54. Sutin KM, Longaker MT, Wahlander S et al: Acute biceps compartment syndrome associated with the use of a noninvasive blood pressure monitor. Anesth Analg 83:1345, 1996.

55. Gardner RM, Hollingsworth KW: Optimizing the electrocardiogram and pressure monitoring. Crit Care Med 14:651, 1986.

56. Bickler PE, Schapera A, Bainton CR: Acute radial nerve injury from use of an automatic blood pressure monitor. Anesthesiology 73:186, 1990.

57. Celoria G, Dawson JA, Teres D: Compartment syndrome in a patient monitored with an automated blood pressure cuff. J Clin Monit 3:139, 1987.

58. Penaz J: Photoelectric measurement of blood pressure, volume, and flow in the finger. Digest of the 10th International Conference on Medical and Biological Engineering 1973, p 104.

59. Boehmer RD: Continuous, real-time, non-invasive monitor of blood pressure: Penaz methodology applied to the finger. J Clin Monit 3:282, 1987.

60. Hirschl MM, Binder M, Herkner H et al: Accuracy and reliability of noninvasive continuous finger blood pressure measurement in critically ill patients. Crit Care Med 24:1684, 1996.

61. Kurki T, Smith NT, Head N et al: Noninvasive continuous blood pressure measurement from the finger: Optimal measurement conditions and factors affecting reliability. J Clin Monit 3:6, 1987.

62. Molhoek GP, Wesseling KH, Settels JJM: Evaluation of the Penaz servoplethysmomanometer for continuous, non-invasive measurement of finger blood pressure. Basic Res Cardiol 79:598, 1984.

63. Smith NT, Wesseling KH, de Wit B: Evaluation of two prototype devices producing noninvasive, pulsatile, calibrated blood pressure measurement from a finger. J Clin Monit 1:17, 1985.

64. Gibbs NM, Larach DR, Derr JA: The accuracy of Finapress noninvasive mean arterial pressure measurements in anesthetized patients. Anesthesiology 74:647, 1991.

65. Bardoczky GI, Levarlet M, Engelman E et al: Continuous noninvasive blood pressure monitoring during thoracic surgery. J Cardiothorac Vasc Anesth 6:51, 1992.

66. Pace NL, East TD: Simultaneous comparison of intraarterial, oscillometric, and Finapres monitoring during anesthesia. Anesth Analg 73:213, 1991.

67. Bos WJW, van Goudoever J, van Montfrans GA et al: Reconstruction of brachial artery pressure from noninvasive finger pressure measurements. Circulation 94:1870, 1996.

68. Gravenstein JS, Paulus DA, Feldman J et al: Tissue hypoxia distal to a Penaz finger blood pressure cuff. J Clin Monit 1:120, 1985.

69. de Jong JR, Tepaske R, Scheffer G-J et al: Noninvasive continuous blood pressure measurement: A clinical evaluation of the Cortronic APM 770. J Clin Monit 9:18, 1993.

70. Young CC, Mark JB, White W et al: Clinical evaluation of continuous noninvasive blood pressure monitoring: Accuracy and tracking capabilities. J Clin Monit 11:245, 1995.

71. Kemmotsu O, Ueda M, Otsuka H et al: Blood pressure measurement by arterial tonometry in controlled hypotension. Anesth Analg 73:54, 1991.

72. Kemmotsu O, Ueda M, Otsuka H et al: Arterial tonometry for noninvasive, continuous blood pressure monitoring during anesthesia. Anesthesiology 75:333, 1991.

73. Weiss BM, Spahn DR, Rahmig H et al: Radial artery tonometry: Moderately accurate but unpredictable technique of continuous noninvasive arterial pressure measurement. Br J Anaesth 76:405, 1996.

74. Kemmotsu O, Ohno M, Takita K et al: Noninvasive, continuous blood pressure measurement by arterial tonometry during anesthesia in children. Anesthesiology 81:1162, 1994.

75. Lumsden T, Marshall WR, Divers GA et al: The PB3300 intraarterial blood gas monitoring system. J Clin Monit 10:59, 1994.

76. Wahr JA, Tremper KK: Continuous intravascular blood gas monitoring. J Cardiothorac Vasc Anesth 8:342, 1994.

77. Bailey PL, Lu JK, Cluff ML et al: Evaluation of a new automated bedside blood gas and chemistry analyzer. Anesthesiology 87:A432, 1997.

78. Cockings JGL, Webb RK, Klepper ID et al: Blood pressure monitoring--Applications and limitations: An analysis of 2000 incident reports. Anaesth Intensive Care 21:565, 1993.

79. Eather KF, Peterson LH, Dripps RD: Studies of the circulation of anesthetized patients by a new method for recording arterial pressure and pressure pulse contours. Anesthesiology 10:125, 1949.

80. Mark JB: Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998.

81. Mandel MA, Dauchot PJ: Radial artery cannulation in 1000 patients: Precautions and complications. J Hand Surg 2:482, 1977.

82. Slogoff S, Keats AS, Arlund C: On the safety of radial artery cannulation. Anesthesiology 59:42, 1983.

83. Mangano DT, Hickey RF: Ischemic injury following uncomplicated radial artery catheterization. Anesth Analg 58:55, 1979.

84. Rose SH: Ischemic complications of radial artery cannulation: An association with a calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia variant of scleroderma. Anesthesiology 78:587, 1993.

85. Allen EV: Thromboangiitis obliterans: Methods of diagnosis of chronic obstructive lesions distal to the wrist with illustrative cases. Am J Med Sci 178:237, 1929.

86. Baker RJ, Chunprapaph B, Nyhus LM: Severe ischaemia of the hand following radial artery catheterization. Surgery 80:449, 1976.

87. Thompson SR, Hirschberg A: Allen's test re-examined. Crit Care Med 16:915, 1988.

88. Wilkins RG: Radial artery cannulation and ischaemic damage: A review. Anaesthesia 40:896, 1985.

89. Bedford RF, Wollman H: Complications of percutaneous radial artery cannulation: An objective prospective study in man. Anesthesiology 38:228, 1973.

90. Davis FM, Stewart JM: Radial artery cannulation: A prospective study in patients undergoing cardiothoracic surgery. Br J Anaesth 52:42, 1980.

91. McGregor AD: The Allen test--An investigation of its accuracy by fluorescein dye. J Hand Surg 12:82, 1987.

92. Stead SW, Stirt JA: Assessment of digital blood flow and palmar collateral circulation. Int J Clin Monit Comput 2:29, 1985.

93. Cederholm I, Sorensen J, Carlsson C: Thrombosis following percutaneous radial artery cannulation. Acta Anaesthesiol Scand 30:227, 1986.

94. Jones RM, Hill AB, Nahrwold ML: The effect of method of radial artery cannulation on post-canulation blood flow and thrombus formation. Anesthesiology 55:76, 1981.

95. Mangar D, Thrush DN, Connell GR et al: Direct or modified Seldinger guide wire-directed technique for arterial catheter insertion. Anesth Analg 76:714, 1993.

96. Gerber DR, Zeifman WE, Khouli HI et al: Comparison of wire-guided and nonwire-guided radial artery catheters. Chest 109:761, 1996.

97. Barnes RW, Foster EJ, Jansen GA: Safety of brachial arterial catheterization as monitors in the intensive care unit: Prospective evaluation with the Doppler ultrasonic velocity detector. Anesthesiology 44:260, 1976.

98. Moran KT, Halpin DP, Zide RS et al: Long-term brachial artery catheterization: Ischemic complications. J Vasc Surg 8:76, 1988.

99. Bazaral MG, Welch M, Golding LAR et al: Comparison of brachial and radial arterial pressure monitoring in patients undergoing coronary artery bypass surgery. Anesthesiology 73:38, 1990.

100. Randel SN, Tsang BH, Wung JT: Experience with percutaneous indwelling peripheral arterial catheterization in neonates. Am J Dis Child 141:848, 1987.

101. Brown M, Gordon LH, Brown OW: Intravascular monitoring via the axillary artery. Anaesth Intensive Care 13:38, 1985.

102. Gurman GM, Kriemerman S: Cannulation of big arteries in critically ill patients. Crit Care Med 13:217, 1985.

103. Ersoz CJ, Hedden M, Lain L: Prolonged femoral arterial catheterization for intensive care. Anesth Analg 49:160, 1973.

104. Singh S, Nelson N, Acosta I et al: Catheter colonization and bacteremia with pulmonary and arterial catheters. Crit Care Med 10:736, 1982.

105. Muralidhar K: Complication of femoral artery pressure monitoring. J Cardiothorac Vasc Anesth 12:128, 1998.

106. Sim EKW, Beynen FA, Danielson GK: Intraperitoneal hemorrhage following femoral artery cannulation for intraoperative monitoring: an unusual complication. J Clin Monit 9:295, 1993.

107. Frank SM, Norris EJ, Christopherson R et al: Right- and left-arm blood pressure discrepancies in vascular surgery patients. Anesthesiology 75:457, 1991.

108. Kinzer JB, Lichtentrhal PR, Wade LD: Loss of radial artery pressure trace during internal mammary artery dissection for coronary artery bypass graft surgery. Anesth Analg 64:1134, 1985.

109. Dorman T, Breslow MJ, Lipsett PA et al: Radial artery pressure monitoring underestimates central arterial pressure during vasopressor therapy in critically ill surgical patients. Crit Care Med 26:1646, 1998.

110. Urzua J, Sessler DI, Meneses G et al: Thermoregulatory vasoconstriction increases the difference between femoral and radial arterial pressures. J Clin Monit 10:229, 1994.

111. Stern DH, Gerson JI, Allen FB et al: Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass? Anesthesiology 62:557, 1985.

112. Mohr R, Lavee J, Goor DA: Inaccuracy of radial artery pressure measurement after cardiac operations. J Thorac Cardiovasc Surg 94:286, 1987.

113. Gravlee GP, Wong AB, Adkins TG et al: A comparison of radial, brachial, and aortic pressures after cardiopulmonary bypass. J Cardiothorac Anesth 3:20, 1989.

114. Pauca AL, Hudspeth AS, Wallenhaupt SL et al: Radial artery-to-aorta pressure difference after discontinuation of cardiopulmonary bypass. Anesthesiology 70:935, 1989.

115. Urzua J: Aortic-to-radial arterial pressure gradient after bypass. Anesthesiology 73:191, 1990.

116. Maruyama K, Horiguchi R, Hashimoto H et al: Effect of combined infusion of nitroglycerin and nicardipine on femoral-to-radial arterial pressure gradient after cardiopulmonary bypass. Anesth Analg 70:428, 1990.

117. Hynson JM, Katz JA, Mangano DT: On the accuracy of intra-arterial pressure measurement: The pressure gradient effect. Crit Care Med 26:1623, 1998.

118. Baba T, Goto T, Yoshitake A, Shibata Y: Radial artery diameter decreases with increased femoral to radial arterial pressure gradient during cardiopulmonary bypass. Anesth Analg 85:252, 1997.

119. O'Rourke MF, Yaginuma T: Wave reflections and the arterial pulse. Arch Intern Med 144:366, 1984.

120. Mark JB: Direct arterial blood pressure monitoring. Normal waveforms. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 91.

121. Singleton RJ, Webb RK, Ludbrook GL et al: Problems associated with vascular access: An analysis of 2000 incident reports. Anaesth Intens Care 21:664, 1993.

122. Garey C, Sprung J, Thomas P: Unusual complication of arterial catheterization. Anesth Analg 76:668, 1993.

123. Horlocker TT, Bishop AT: Compartment syndrome of the forearm and hand after brachial artery cannulation. Anesth Analg 81:1092, 1995.

124. Lowenstein E, Little JW, Lo HH: Prevention of cerebral embolization from flushing radial-artery cannulas. N Engl J Med 285:1414, 1971.

125. Gardner RM: Direct blood pressure measurement: Dynamic response requirements. Anesthesiology 54:227, 1981.

126. Shinozaki T, Deane RS, Mazuzan JE: The dynamic responses of liquid-filled catheter systems for direct measurements of blood pressure. Anesthesiology 53:498, 1980.

127. Kleinman B, Powell S, Kumar P et al: The fast flush test measures the dynamic response of the entire blood pressure monitoring system. Anesthesiology 77:1215, 1992.

128. Kleinman B: Understanding natural frequency and damping and how they relate to the measurement of blood pressure. J Clin Monit 5:137, 1989.

129. Geddes LA, Bourland JD: Technical note: Estimation of the damping coefficient of fluid-filled, catheter-transducer pressure-measuring systems. J Clin Engineering 13:59, 1988.

130. Hipkins SF, Rutten AJ, Runciman WB: Experimental analysis of catheter-manometer systems *in vitro* and *in vivo.* Anesthesiology 71:893, 1989.

131. O'Quin R, Marini JJ: Pulmonary artery occlusion pressure: Clinical physiology, measurement, and interpretation. Am Rev Respir Dis 128:319, 1983.

132. Geddes LA: Handbook of blood pressure measurement. Clifton, NJ, Humana Press, 1991.

133. Kleinman B, Powell S, Gardner RM: Equivalence of fast flush and square wave testing of blood pressure monitoring systems. J Clin Monit 12:149, 1996.

134. Schwid HA: Frequency response evaluation of radial artery catheter-manometer systems: Sinusoidal frequency analysis versus flush method. J Clin Monit 4:181, 1988.

135. Wiedemann HP, Matthay MA, Matthay RA: Cardiovascularpulmonary monitoring in the intensive care unit. Part 1. Chest 85:537, 1984.

136. Heeger PS, Backstrom JT: Heparin flushes and thrombocytopenia. Ann Intern Med 105:143, 1985.

137. Slaughter TF, Greenberg CS: Heparin-associated thrombocytopenia and thrombosis. Implications for perioperative management. Anesthesiology 87:667, 1997.

138. Mark JB: Technical requirements for direct blood pressure measurement. In Mark JB (ed): Atlas of cardiovascular monitoring. New York, Churchill Livingstone, 1998, p 99.

139. Meyer RM, Kimovec MA, Hefner GG: Cable-testing device fails to indicate that hypertension is artifactual. J Clin Monit 9:54, 1993.

140. McDermott M, Dearlove OR: Nasogastric contents short-circuit pressure transducer. Anaesthesia 52:719, 1997.

141. Gardner RM: Accuracy and reliability of disposable pressure transducers coupled with modern pressure monitors. Crit Care Med 24:879, 1996.

142. Barbieri LT, Kaplan JA: Artifactual hypotension secondary to intraoperative transducer failure. Anesth Analg 62:112, 1983.

143. Courtois M, Fattal PG, Kovacs SJ et al: Anatomically and physiologically based reference level for measurement of intracardiac pressures. Circulation 92:1994, 1995.

144. O'Rourke MF, Gallagher DE: Pulse wave analysis. J Hypertens 14:S147, 1996.

145. Braunwald E, Fishman AP, Cournand A: Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. Circ Res 4:100, 1956.

146. Schwid HA, Taylor LA, Smith NT: Computer model analysis of the radial artery pressure waveform. J Clin Monit 3:220, 1987.

147. Ream AK: Mean blood pressure algorithms. J Clin Monit 1:138, 1985.

148. Abrams JH, Cerra F, Holcroft JW: Cardiopulmonary monitoring. In Wilmore DW (ed): Care of the Surgical Patient. New York, Scientific American Medicine, 1989.

149. Hettrick DA, Warltier DC: Ventriculoarterial coupling. In Warltier DC (ed): Ventricular Function. Baltimore, Williams & Wilkins, 1995, p 153.

150. Murgo JP, Westerhof N, Giolma JP et al: Aortic input impedance in normal man: relationship to pressure wave forms. Circulation 62:105, 1980.

151. Murgo JP, Westerhof N, Giolma JP et al: Manipulation of ascending aortic pressure and flow wave reflections with the valsalva maneuver: Relationship to input impedance. Circulation 63:122, 1981.

152. Franklin SS, Weber MA: Measuring hypertensive cardiovascular risk: The vascular overload concept. Am Heart J 128:793, 1994.

153. Braunwald E: The physical examination. In Braunwald E (ed): Heart Disease. A Textbook of Cardiovascular Medicine. Philadelphia, WB Saunders Company, 1992, p 13.

154. Wynne J, Braunwald E: The cardiomyopathies and myocarditides: Toxic, chemical, and physical damage to the heart. In Braunwald E (ed): Heart Disease. A Textbook of Cardiovascular Medicine. Philadelphia, WB Saunders Company, 1992, p 1398.

155. Freeman AB, Steinbrook RA: Recurrence of pulsus alternans after fentanyl injection in a patient with aortic stenosis and congestive heart failure. Can Anaesth Soc J 32:654, 1985.

156. Mark JB: Pericardial constriction and cardiac tamponade. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 313.

157. McGregor M: Pulsus paradoxus. N Engl J Med 480, 1979.

158. Shabetai R, Fowler NO, Guntheroth WG: The hemodynamics of cardiac tamponade and constrictive pericarditis. Am J Cardiol 26:480, 1970.

159. Fowler NO: Clinical problem-solving: A broken heart. N Engl J Med 334:1474, 1996.

160. Mark JB: Respiratory-circulatory interactions. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 261.

161. Coriat P, Vrillon M, Perel A et al: A comparison of systolic blood pressure variations and echocardiographic estimates of end-diastolic left ventricular size in patients after aortic surgery. Anesth Analg 78:46, 1994.

162. Marik PE: The systolic blood pressure variation as an indicator of pulmonary capillary wedge pressure in ventilated patients. Anaesth Intensive Care 21:405, 1993.

163. Pizov R, Segal E, Kaplan L et al: The use of systolic pressure variation in hemodynamic monitoring during deliberate hypotension in spine surgery. J Clin Anesth 2:96, 1990.

164. Rooke GA: Systolic pressure variation as an indicator of hypovolemia. Curr Opin Anaesthesiol 8:511, 1995.

165. Robotham JL, Lixfeld W, Holland L et al: Effects of respiration on cardiac performance. J Appl Physiol 44:703, 1978.

166. Robotham JL, Cherry D, Mitzner W et al: A re-evaluation of the hemodynamic consequences of intermittent positive pressure ventilation. Crit Care Med 11:783, 1983.

167. Robotham JL, Scharf SM: Effects of positive and negative pressure ventilation on cardiac performance. Clin Chest Med 4:161, 1983.

168. Perel A, Pizov R: Cardiovascular effects of mechanical ventilation. In Perel A, Stock MC (eds): Handbook of Mechanical Ventilatory Support. Baltimore, Williams & Wilkins, 1992, p 51.

169. Rasanen J, Howie MB: Mitral regurgitation during withdrawal of mechanical ventilatory support. J Cardiothorac Anesth 2:60, 1988.

170. Mark JB: Intraaortic balloon counterpulsation. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 343.

171. Mark JB: Hemodynamic observations during cardiopulmonary bypass. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 327.

172. Bergquist BD, Bellows WH, Leung JM: Transesophageal echocardi-ography in myocardial revascularization: II. Influence on intraoperative decision making. Anesth Analg 82:1139, 1996.

173. Bergquist BD, Leung JM, Bellows WH: Transesophageal echocardi-ography in myocardial revascularization: I. Accuracy of intraoperative real-time interpretation. Anesth Analg 82:1132, 1996.

174. Nishimura RA, Housmans PR, Hatle LK et al: Assessment of diastolic function of the heart: Background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. Mayo Clin Proc 64:71, 1989.

175. Pagel PS, Grossman W, Haering JM et al: Left ventricular diastolic function in the normal and diseased heart: Perspectives for the anesthesiologist (first of two parts). Anesthesiology 79:836, 1993.

176. Pantely GA, Bristow JD: Ischemic cardiomyopathy. Prog Cardiovasc Dis 27:95, 1984.

177. Tuman KJ, Carroll GC, Ivankovich AD: Pitfalls in interpretation of pulmonary artery catheter data. J Cardiothorac Anesth 3:625, 1989.

178. Mark JB: Pressure-volume relations, transmural pressure, and preload. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 247.

179. Kramer DC, Oka Y, Yellin EL: Post-ischemic diastolic function: Pursuing a cautious path from laboratory to operating room. J Cardiothorac Vasc Anesth 8:609, 1994.

180. Labovitz AJ, Pearson AC: Evaluation of left ventricular diastolic function: Clinical relevance and recent Doppler echocardiographic insights. Am Heart J 114:836, 1987.

181. Marsch SCU, Dalmas S, Philbin DM et al: Post-ischemic diastolic dysfunction. J Cardiothorac Vasc Anesth 8:611, 1994.

182. Pagel PS, Grossman W, Haering JM et al: Left ventricular diastolic function in the normal and diseased heart: Perspectives for the anesthesiologist (second of two parts). Anesthesiology 79:1104, 1993.

183. Dwyer EM: Left ventricular pressure-volume alterations and regional disorders of contraction during myocardial ischemia induced by atrial pacing. Circulation 42:1111, 1970.

184. Hansen RM, Viquerat CE, Matthay MA et al: Poor correlation between pulmonary arterial wedge pressure and left ventricular enddiastolic volume after coronary artery bypass graft surgery. Anesthesiology 64:764, 1986.

185. Alderman EL, Glantz SA: Acute hemodynamic interventions shift the diastolic pressure-volume curve in man. Circulation 54:662, 1976.

186. Calvin JE, Driedger AA, Sibbald WJ: Does the pulmonary capillary wedge pressure predict left ventricular preload in critically ill patients? Crit Care Med 9:437, 1981.

187. Ellis RJ, Mangano DT, VanDyke DC: Relationship of wedge pressure to end-diastolic volume in patients undergoing myocardial revascularization. J Thorac Cardiovasc Surg 78:605, 1979.

188. Gaasch WH, Levine HJ, Quinones MA et al: Left ventricular compliance: Mechanisms and clinical implications. Am J Cardiol 38:645, 1976.

189. Grossman W, McLaurin LP: Diastolic properties of the left ventricle. Ann Intern Med 84:316, 1976.

190. Brutsaert DL, Sys SU: Relaxation and diastole of the heart. Physiol Rev 69:1228, 1989.

191. Shah PM, Pai RG: Diastolic heart failure. Curr Probl Cardiol 787, 1992.

192. Dresser LP, McKiney WM: Anatomic and pathophysiologic studies of the human internal jugular valve. Am J Surg 154:220, 1987.

193. Imai M, Hanaoka Y, Kemmotsu O: Valve injury: A new complication of internal jugular vein cannulation. Anesth Analg 78:1041, 1994.

194. Sum-Ping ST: Internal jugular valves: Competent or incompetent. Anesth Analg 78:1039, 1994.

195. McGee SR: Physical examination of venous pressure: A critical review. Am Heart J 136:10, 1998.

196. Lunn JK, Stanley TH, Webster LR et al: Arterial blood-pressure and pulse-rate responses to pulmonary and radial arterial catheterization prior to cardiac and major vascular operations. Anesthesiology 51:265, 1979.

197. Dzelzkalns R, Stanley TH: Placement of the pulmonary arterial catheter before anesthesia for cardiac surgery: A stressful, painful, unnecessary crutch. J Clin Monit 1:197, 1985.

198. Streisand JB, Clark NJ, Pace NL: Placement of the pulmonary arterial catheter before anesthesia for cardiac surgery: Safe, intelligent, and appropriate use of invasive hemodynamic monitoring. J Clin Monit 1:193, 1985.

199. Waller JL, Zaidan JR, Kaplan JA et al: Hemodynamic responses to preoperative vascular cannulation in patients with coronary artery disease. Anesthesiology 56:219, 1982.

200. Daily PO, Griepp RB, Shumway NE: Percutaneous internal jugular vein cannulation. Arch Surg 101:534, 1970.

201. Sulek CA, Gravenstein N, Blackshear RH et al: Head rotation during internal jugular vein cannulation and the risk of carotid artery puncture. Anesth Analg 82:125, 1996.

202. American Society of Anesthesiologists: Recommendations for infection control for the practice of anesthesiology, 2nd ed. Park Ridge, IL, American Society of Anesthesiologists, 1998, p 15.

203. Civetta JM, Gabel JC, Gemer M: Internal-jugular-vein puncture with a margin of safety. Anesthesiology 36:622, 1972.

204. Ellison N, Jobes DR, Troianos CA: Internal jugular vein cannulation. Anesth Analg 78:198, 1994.

205. Mangar D, Turnage WS, Mohamed SA: Is the internal jugular vein cannulated during insertion or withdrawal of the needle during central venous cannulation? Anesth Analg 76:1375, 1993.

206. Royster RL, Johnston WE, Gravelee GP: Arrhythmias during venous cannulation prior to pulmonary artery catheter insertion. Anesth Analg 64:1214, 1985.

207. Bone DK, Maddrey WC, Eagan J et al: Cardiac tamponade: A fatal complication of central venous catheterization. Arch Surg 106:868, 1973.

208. Kuiper DH: Cardiac tamponade and death in a patient receiving total parenteral nutrition. JAMA 230:877, 1974.

209. Kapadia CB, Heard SO, Yeston NS: Delayed recognition of vascular complications caused by central venous catheters. J Clin Monit 4:267, 1988.

210. Pierce EC: Complications associated with the use of central venous venous catheters. Am Soc Anesthesiol Newsletter January *1989,* p 3.

211. Bowdle TA: Central line complications from the ASA Closed Claims Project. Am Soc Anesthesiol Newsletter 60:22, 1996.

212. Maki DG, Cobb L, Garman JK et al: An attachable silver-impregnated cuff for prevention of infection with central venous catheters: A prospective randomized multicenter trial. Am J Med 85:307, 1988.

213. English IC, Frew RM, Pigott JF et al: Percutaneous catheterisation of the internal jugular vein 1969 (classical article). Anaesthesia 50:1071, 1995.

214. Jernigan WR, Gardner WC, Mahr MM et al: The internal jugular vein for access to the central venous system. JAMA 218:97, 1971.

215. Sanford TJ: Internal jugular vein cannulation versus subclavian vein cannulation. An anesthesiologist's view: The right internal jugular vein. J Clin Monit 1:58, 1985.

216. Goldfarb G, Lebrec D: Percutaneous cannulation of the internal jugular vein in patients with coagulopathies: An experience based on 1,000 attempts. Anesthesiology 565:1982.

217. Oliver WC, Jr., Nuttall GA, Beynen FM et al: The incidence of artery puncture with central venous cannulation using a modified technique for detection and prevention of arterial cannulation. J Cardiothorac Vasc Anesth 11:851, 1997.

218. Rosen M, Latto IP, Shang W: The internal jugular vein. In Handbook of Percutaneous Vein Catherizations. London, WB Saunders, 1981.

219. Metz S, Horrow JC, Balcar I: A controlled comparison of techniques for locating the internal jugular vein using ultrasonography. Anesth Analg 63:673, 1984.

220. Willeford KL, Reitan JA: Neutral head position for placement of internal jugular vein catheters. Anaesthesia 49:202, 1994.

221. Jobes DR, Schwartz AJ, Greenhow DE et al: Safer jugular vein cannulation: Recognition of arterial puncture and preferential use of the external jugular route. Anesthesiology 59:353, 1983.

222. Fabian JA, Jesudian MC: A simple method of improving the safety of percutaneous cannulation of the internal jugular vein. Anesth Analg 64:1032, 1985.

223. Alexander R: Using continuous pressure monitoring to aid central vein cannulation. Can J Anaesth 44:99, 1997.

224. Seldinger SI: Catheter replacement of the needle in percutaneous arteriography. Acta Radiol 39:368, 1953.

225. Conahan TJI, Schwartz AJ, Geer RT: Percutaneous catheter introduction: The Seldinger technique. JAMA 237:446, 1977.

226. Oishi AJ, Zietlow SP, Sarr MG: Erroneous arterial placement of a central venous catheter. Mayo Clin Proc 69:287, 1994.

227. Gravenstein N, Blackshear RH: In vitro evaluation of relative perforating potential of central venous catheters: Comparison of materials, selected models, number of lumens, and angles of incidence to simulated membrane. J Clin Monit 7:1, 1991.

228. Fisher KL, Leung AN: Radiographic appearance of central veous catheters. Am J Roentgenol 166:329, 1996.

229. Cohen MB, Mark JB, Morris RW et al: Introducer sheath malfunction producing insidious air embolism. Anesthesiology 67:573, 1987.

230. Reeves ST, Roy RC, Dorman BH et al: The incidence of complications after the double-catheter technique for cannulation of the right internal jugular vein in a university teaching hospital. Anesth Analg 81:1073, 1995.

231. Reeves ST, Baliga P, Conroy JM et al: Avulsion of the right facial vein during double cannulation of the internal jugular vein. J Cardiothorac Vasc Anesth 9:429, 1995.

232. Inoue S, Ohnishi Y, Kuro M: Accidental penetration of an indwelling retrograde introducer sheath by an introducer needle during right internal jugular vein cannulation. J Cardiothorac Vasc Anesth 12:67, 1998.

233. Peres PW: Positioning central venous catheters--A prospective study. Anaesth Intensive Care 18:536, 1990.

234. Denys BG, Uretsky BF, Reddy PS et al: An ultrasound method for safe and rapid central venous access. N Engl J Med 324:566, 1991.

235. Denys BG, Uretsky BF, Reddy PS: Ultrasound-assisted cannulation of the internal jugular vein: A prospective comparison to the external landmark-guided technique. Circulation 87:1557, 1993.

236. Gratz I, Afshar M, Kidwell P et al: Doppler-guided cannulation of the internal jugular vein: A prospective, randomized trial. J Clin Monit 10:185, 1994.

237. Hayashi H, Tsuzuku M, Amano M: Simplified echo-guided internal jugular vein puncture: A comparison to the landmark-guided technique. Anesth Analg 86:SCA89, 1998.

238. Troianos CA, Jobes DR, Ellison N: Ultrasound-guided cannulation of the internal jugular vein: A prospective, randomized study. Anesth Analg 72:823, 1991.

239. Gualtieri E, Deppe S, Sipperly ME et al: Subclavian venous catheterization: Greater success rate for less experienced operators using ultrasound guidance. Crit Care Med 23:692, 1995.

240. Lane P, Waldron RJ: Real-time ultrasound-guided central venous access via the subclavian approach. Anaesth Intensive Care 23:728, 1995.

241. Lefrant J-Y, Cuvillon P, Benezet J-F et al: Pulsed Doppler ultrasonography guidance for catheterization of the subclavian vein. Anesthesiology 88:1195, 1998.

242. Mansfield PF, Hohn DC, Fornage BD et al: Complications and failures of subclavian-vein catheterization. N Engl J Med 331:1735, 1994.

243. Sato S, Ueno E, Toyooka H: Central venous access via the distal femoral vein using ultrasound guidance. Anesthesiology 88:838, 1998.

244. Khalil KG, Parker FB, Mukherjee N et al: Thoracic duct injury: A complication of jugular vein catheterization. JAMA 221:908, 1972.

245. Lobato EB, Myers JA, Sulek CA et al: A randomized study of right versus left internal jugular venous cannulation in adults. Anesthesiology 89:A1189, 1998.

246. Haire WD, Lieberman RP: Defining the risks of subclavian-vein catheterization. N Engl J Med 331:1769, 1994.

247. Hoyt DB: Internal jugular vein cannulation versus subclavian vein cannulation. A surgeon's view: The subclavian vein. J Clin Monit 1:61, 1985.

248. Lefrant J-Y, Muller L, Nouvellon E et al: When subclavian vein cannulation attempts must be stopped. Anesthesiology 89:B11, 1998.

249. Blitt CD, Wright WA, Petty WC et al: Central venous catheterization via the external jugular vein: A technique employing the J-wire. JAMA 229:817, 1974.

250. Blitt CD, Carlson GL, Wright WA: J-wire versus straight wire for central venous system cannulation via the external jugular vein. Anesth Analg 61:536, 1982.

251. Schwartz AJ, Jobes DR, Levy WJ et al: Intrathoracic vascular catheterization via the external jugular vein. Anesthesiology 56:400, 1982.

252. Joynt GM, Comersall CD, Buckley TA et al: Comparison of intrathoracic and intra-abdominal measurements of central venous pressure. Lancet 347:1155, 1996.

253. Ho KM, Joynt GM, Tan P: A comparison of central venous pressure and common iliac venous pressure in critically ill mechanically ventilated patients. Crit Care Med 26:461, 1998.

254. Andel H, Koller R, Andel D et al: Central venous approach via vena axillaris in critically burned patients. Anesthesiology 89:B26, 1998.

255. Joseph DM, Philip BK, Philip JH: Peripheral venous pressure can be an accurate estimate of central venous pressure. Anesthesiology 65:A166, 1986.

256. Amar D, Melendez JA, Zhang H et al: Peripheral venous pressure predicts intraoperative central venous pressure. Anesthesiology 89:A946, 1998.

257. Philip JH, Philip BK: Hydrostatic and central venous pressure meas-urement by the IVAC 560 Infusion Pump. Med Instrument 19:232, 1985.

258. Ng PK, Ault MJ, Ellrodt AG et al: Peripherally inserted central catheters in general medicine. Mayo Clin Proc 72:225, 1997.

259. Kellner GA, Smart JF: Percutaneous placement of catheters to monitor "central venous pressure." Anesthesiology 36:515, 1972.

260. Nichols PKT, Major E: Central venous cannulation. Curr Anaesth Crit Care 1:54, 1989.

261. Webre DR, Arens JF: Use of cephalic and basilic veins for introduction of central venous catheters. Anesthesiology 38:389, 1973.

262. Kasten GW, Owens E, Kennedy D: Ventricular tachycardia resulting from central venous catheter tip migration due to arm position changes: Report of two cases. Anesthesiology 62:185, 1985.

263. Shah KB, Rao TLK, Laughlin S et al: A review of pulmonary artery catheterization in 6,245 patients. Anesthesiology 61:271, 1984.

264. Heath KJ, Woulfe J, Lownie S et al: A devastating complication of inadvertent carotid artery puncture. Anesthesiology 89:1273, 1998.

265. Brown CQ: Inadvertent prolonged cannulation of the carotid artery. Anesth Analg 61:150, 1982.

266. Darouiche RO, Raad II, Heard SO et al: A comparison of two antimicrobial-impregnated central venous catheters. N Engl J Med 340:1, 1999.

267. Wenzel RP, Edmond MB: The evolving technology of venous access. N Engl J Med 340:48, 1999.

268. Corona ML, Peters SG, Narr BJ et al: Infections related to central venous catheters. Mayo Clin Proc 65:979, 1990.

269. Tebbs SE, Sawyer A, Elliott TS: Influence of surface morphology on invitro bacterial adherence to central venous catheters. Br J Anaesth 72:587, 1994.

270. Badley AD, Steckelberg JM, Wollan PC et al: Infectious rates of central venous pressure catheters: Comparison between newly placed catheters and those that have been changed. Mayo Clin Proc 71:838, 1996.

271. Gilron I, Magder S: Monitoring complication due to a pulsatile femoral vein from tricuspid regurgitation. Can J Anaesth 42:141, 1995.

272. Mitchell MR, Wood DG, Naraghi M et al: Fatal cardiac perforation caused by the dilator of a central venous catheterization kit. J Clin Monit 9:288, 1993.

273. Eissa NT, Kvetan V: Guide wire as a cause of complete heart block in patients with preexisting left bundle branch block. Anesthesiology 73:772, 1990.

274. Oakes DD, Wilson RE: Malposition of a subclavian line: Resultant pleural effusions, interstitial pulmonary edema, and chest wall abscess during total parenteral nutrition. JAMA 233:532, 1975.

275. Reynen K: 14-year follow-up of central emobilization by a guide wire. N Engl J Med 329:970, 1993.

276. Levinsky WJ: Fatal air embolism during insertion of CVP monitoring apparatus. JAMA 209:1721, 1969.

277. Grace DM: Air embolism with neurologic complications: A potential hazard of central venous catheters. Can J Surg 20:51, 1977.

278. Tahir AH: Prevention of air embolism during subclavian venipuncture. JAMA 223:79, 1973.

279. Kessler LG: FDA alert: Hypersensitivity reactions to central venous catheters. Am Soc Anesthesiol Newsletter 62:24, 1998.

280. Terazawa E, Shimonaka H, Nagase K et al: Severe anaphylactic reaction due to a chlorhexidine-impregnated central venous catheter. Anesthesiology 89:1296, 1998.

281. Pomfret EA, Blackburn GL: Central venous access risk factors. Crit Care Med 22:196, 1994.

282. Kelman GR: Interpretation of CVP measurements. Anaesthesia 26:209, 1971.

283. Clayton DG: Inaccuracies in manometric central venous pressure measurement. Resuscitation 16:221, 1988.

284. Mark JB: Monitoring philosophy, displays, and recorders. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 1.

285. Verweij J, Kester A, Stroes W et al: Comparison of three methods for measuring central venous pressure. Crit Care Med 14:288, 1986.

286. Mark JB: Central venous pressure monitoring: Clinical insights beyond the numbers. J Cardiothorac Vasc Anesth 5:163, 1991.

287. Mark JB: Getting the most from your central venous pressure catheter. In Barash PG (ed): ASA Refresher Courses in Anesthesiology. Philadelphia, Lippincott-Raven, 1995, p 157.

288. Mark JB: Central venous pressure, left atrial pressure. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 15.

289. O'Rourke RA, Silverman ME, Schlant RC: General examination of the patient. In Schlant RC, Alexander RW (eds): The Heart Arteries and Veins. New York, McGraw-Hill, 1994, p 238.

290. Mackay IFS, Walker RL: An experimental examination of factors responsible for the 'h' (d
) wave of the jugular phlebogram in human beings. Am Heart J 71:228, 1966.

291. Mark JB: Arrhythmias. An integrated ECG and hemodynamic approach. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 219.

292. Mark JB: Patterns of valvular heart disease. In Mark JB (ed): Atlas of cardiovascular monitoring. New York, Churchill Livingstone, 1998, p 287.

293. Swan HJC, Ganz W, Forrester J et al: Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med 283:447, 1970.

294. Crexells C, Chatterjee K, Forrester JS et al: Optimal level of filling pressure in the left side of the heart in acute myocardial infarction. N Engl J Med 289:1263, 1973.

295. Forrester JS, Diamond G, McHugh TJ et al: Filling pressures in the right and left sides of the heart in acute myocardial infarction: A reappraisal of central-venous-pressure monitoring. N Engl J Med :190, 1971.

296. Forrester JS, Diamond G, Chatterjee K et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets (first of two parts). N Engl J Med 295:1356, 1976.

297. Forrester JS, Diamond G, Chatterjee K et al: Medical therapy of acute myocardial infarction by application of hemodynamic subsets (second of two parts). N Engl J Med 295:1404, 1976.

298. Ginosar Y, Thijs LG, Sprung CL: Raising the standard of hemodynamic monitoring: Targeting the practice or the practitioner? Crit Care Med 25:209, 1997.

299. Roizen MF, Berger DL, Gabel RA et al: Practice guidelines for pulmonary artery catheterization: A report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Anesthesiology 78:380, 1993.

300. Dalen JE, Bone RC: Is it time to pull the pulmonary artery catheter? JAMA 276:916, 1996.

301. Connors AF, McCaffree DR, Gray BA: Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. N Engl J Med 308:263, 1983.

302. Eisenberg PR, Jaffe AS, Schuster DP: Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. Crit Care Med 12:549, 1984.

303. Staudinger T, Locker GJ, Laczika K et al: Diagnostic validity of pulmonary artery catheterization for residents at an intensive care unit. J Trauma Injury Infect Crit Care 44:902, 1998.

304. Bender JS, Smith-Meek MA, Jones CE: Routine pulmonary artery catheterization does not reduce morbidity and mortality of elective vascular surgery. Ann Surg 226:229, 1997.

305. Bone RC: High-tech predicament: Pulmonary artery catheter. JAMA 264:2933, 1990.

306. Connors AF, Speroff T, Dawson NV et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 276:889, 1996.

307. Fink MP: The flow-directed, pulmonary artery catheter and outcome in critically ill patients: Have we heard the last word? Crit Care Med 25:902, 1997.

308. Pulmonary Artery Catheter Consensus Conference Participants: Pulmonary artery catheter consensus conference: Consensus statement. Crit Care Med 25:910, 1997.

309. Saarela E, Kari A, Nikki P et al: Current practice regarding invasive monitoring in intensive care units in Finland. Intensive Care Med 17:264, 1991.

310. Soni N: Swan song for the Swan-Ganz catheter? The use of pulmonary artery catheters probably needs re-evaluation--but they should not be banned. BMJ 313:763, 1996.

311. Tuman KJ, Roizen MF: Outcome assessment and pulmonary artery catheterization: Why does the debate continue? Anesth Analg 84:1, 1997.

312. Zidulka A, Hakim TS: Wedge pressure in large vs. small pulmonary arteries to detect pulmonary venoconstriction. J Appl Physiol 59:1329, 1985.

313. Mark JB: Pulmonary artery wedge pressure. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 39.

314. Bouchard RJ, Gault JH, Ross J: Evaluation of pulmonary arterial end-diastolic pressure as an estimate of left ventricular end-diastolic pressure in patients with normal and abnormal left ventricular performance. Circulation 44:1072, 1971.

315. Falicov RE, Resnekov L: Relationship of the pulmonary artery enddiastolic pressure to the left ventricular end-diastolic and mean filling pressures in patients with and without left ventricular dysfunction. Circulation 42:65, 1970.

316. Lappas D, Lell WA, Gabel JC et al: Indirect measurement of left-atrial pressure in surgical patients: Pulmonary-capillary wedge and pulmonary-artery diastolic pressures compared with left-atrial pressure. Anesthesiology 38:394, 1973.

317. Scheinman M, Evans GT, Weiss A et al: Relationship between pulmonary artery end-diastolic pressure and left ventricular filling pressure in patients in shock. Circulation 47:317, 1973.

318. West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung: Relation to vascular and alveolar pressures. J Appl Physiol 19:713, 1964.

319. Erb J, Ramsay JG: Is your pulmonary artery catheter shedding? Anesthesiology 89:543, 1998.

320. Fitch JCK, Fang X-E, Dewar ML: Preinsertion pulmonary artery catheter flushing. Anesthesiology 88:1690, 1998.

321. Mark JB, Spillane R: Interluminal communication in a pulmonary artery catheter causing artifactual pressure measurement. Anesth Analg 78:1184, 1994.

322. Baraka A, Nawfal M, Dahdah S: Difficult pulmonary artery catheterization in the patient with tricuspid regurgitation. Anesthesiology 74:393, 1991.

323. Swan HJC, Ganz W: Guidelines for use of balloon-tipped catheter. Am J Cardiol 34:119, 1974.

324. Donahue PJ, Satwicz PR: A method for ensuring proper function of multiorifice catheters. Anesthesiology 76:148, 1992.

325. Mark JB: Pulmonary artery pressure. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 27.

326. Johnston WE, Royster RL, Choplin RH: Pulmonary artery catheter migration during cardiac surgery. Anesthesiology 64:258, 1986.

327. Heard SO, Davis R, Sheretz RJ: Influence of sterile protective sleeves on the sterility of pulmonary artery catheters. Crit Care Med 15:499, 1987.

328. Bennett D, Boldt J, Brochard L et al: Expert panel: The use of the pulmonary artery catheter. Intensive Care Med 17:I, 1991.

329. Noel TA: Pulmonary artery catheter sheath malfunction with sternotomy. Anesthesiology 61:633, 1984.

330. Bromley JL, Moorthy SS: Acute angulation of a pulmonary artery catheter. Anesthesiology 59:367, 1983.

331. Campbell FW, Schwartz AJ: Pulmonary artery catheter malfunction? Anesthesiology 60:513, 1984.

332. Dhar P, Kaufman B, Doerfler M et al: Unusual course of pulmonary artery catheter. J Cardiothorac Vasc Anesth 12:487, 1998.

333. Hanson EW, Hannan RL, Baum VC: Pulmonary artery catheter in the coronary sinus: implications of a persistent left superior vena cava for retrograde cardioplegia. J Cardiothorac Vasc Anesth 12:448, 1998.

334. Hara Y, Ota K, Fujita M et al: Absence of right superior vena cava that was not detected by insertion of a pulmonary arterial catheter via the right internal jugular vein. J Clin Monit 10:210, 1994.

335. Schelling G, Briegel J, Eichinger K et al: Pulmonary artery catheter placement and temporary cardiac pacing in a patient with a persistent left superior vena cava. Intensive Care Med 17:507, 1991.

336. Sweitzer BJ, Hoffman WJ, Allyn JW et al: Diagnosis of a left-sided superior vena cava during placement of a pulmonary artery catheter. J Clin Anesth 5:500, 1993.

337. Keusch DJ, Winters S, Thys DM: The patient's position influences the incidence of dysrhythmias during pulmonary artery catheterization. Anesthesiology 70:582, 1989.

338. Benumof JL, Saidman LJ, Arkin DB et al: Where pulmonary arterial catheters go: Intrathoracic distribution. Anesthesiology 46:336, 1977.

339. Parlow JL, Milne B, Cervenko FW: Balloon flotation is more important than flow direction in determining the position of flow-directed pulmonary artery catheters. J Cardiothorac Vasc Anesth 6:20, 1992.

340. Kelso LA: Complications associated with pulmonary artery catheterization. New Horiz 5:259, 1997.

341. Horst HM, Obeid FN, Vij D: The risks of pulmonary artery catheterization. Surg Gynecol Obstet 159:229, 1984.

342. Weil MH: The assault on the Swan-Ganz catheter: A case history of constrained technology, constrained bedside clinicians, and constrained monetary expenditures. Chest 113:1379, 1998.

343. Procaccini B, Clementi G, Miletti E et al: A review of pulmonary artery catheterization in 5,306 consecutive patients undergoing cardiac surgery. Br J Anaesth 80:A26, 1998.

344. Voukydis PC, Cohen SI: Catheter-induced arrhythmias. Am Heart J 88:588, 1974.

345. Sise CJ, Hollingsworth P, Brimm JE et al: Complications of the flow-directed pulmonary-artery catheter: A prospective analysis in 219 patients. Crit Care Med 9:315, 1981.

346. Salmenpera M, Peltola K, Rosenberg P: Does prophylactic lidocaine control cardiac arrhythmias associated with pulmonary artery catheterization? Anesthesiology 56:210, 1982.

347. Shaw TJI: The Swan-Ganz pulmonary artery catheter. Anaesthesia 34:651, 1979.

348. Morris D, Mulvihill D, Lew WYW: Risk of developing complete heart block during bedside pulmonary artery catheterization in patients with left bundle-branch block. Arch Intern Med 147:2005, 1987.

349. Sprung CL, Elser B, Schein RMH et al: Risk of right bundle-branch block and complete heart block during pulmonary artery catheterization. Crit Care Med 17:1, 1989.

350. Thompson IR, Dalton BC, Lappas DG et al: Right bundle-branch block and complete heart block caused by the Swan-Ganz catheter. Anesthesiology 51:359, 1979.

351. Ezeugwu CO, Graham S: Evaluation of a hemodynamic tracing. J Cardiothorac Vasc Anesth 12:365, 1998.

352. Cooper SC, Desai M, Alpern JB: Beware the pulsating Swan. J Cardiothorac Anesth 4:474, 1990.

353. Daccache G, Depoix J-P, Provenchere S et al: Pulmonary artery catheter during cardiac surgery: A rare but severe adverse effect. J Cardiothorac Vasc Anesth 12:125, 1998.

354. Eguaras MG, Lluch M, Valdivia J et al: An unusual complication of Swan-Ganz catheter use. Texas Heart Inst J 19:149, 1992.

355. Klockgether-Radke A, Rathgeber J, Lange H: Unbeabsichtigte intrakardiale fixierung eines Swan-Ganz-Katheters. Anaesthesist 44:116, 1995.

356. Troianos CA, Stypula RW: Transesophageal echocardiographic diagnosis of pulmonary artery catheter entrapment and coiling. Anesthesiology 79:602, 1993.

357. Paulsen AW: Artifactually low cardiac outputs resulting from a communication between the proximal and distal lumens of an Edwards pacing thermodilution Swan-Ganz Catheter. Anesthesiology 68:308, 1988.

358. Fibuch EE, Tuohy GF: Intracardiac knotting of a flow-directed balloon-tipped catheter. Anesth Analg 59:217, 1980.

359. Lipp H: Intra-cardiac knotting of a flow-directed balloon catheter. N Engl J Med 284:220, 1971.

360. Dumensil JG, Proulx G: A new nonsurgical technique for untying tight knots in flow-directed balloon catheters. Am J Cardiol 53:395, 1984.

361. Michel L, Installe E, Joucken K: Knotting of intracardiac flowdirected balloon catheter. Chest 83:147, 1983.

362. Chastre J, Cornud F, Bouchama A et al: Thrombosis as a complication of pulmonary-artery catheterization via the internal jugular vein. N Engl J Med 306:278, 1982.

363. Hoar PF, Stone JG, Wicks AE et al: Thrombogenesis associated with Swan-Ganz catheters. Anesthesiology 48:445, 1978.

364. Hoar PF, Wilson RM, Mangano DT et al: Heparin bonding reduces thrombogenicity of pulmonary-artery catheters. N Engl J Med 305:993, 1981.

365. Bohrer H, Fleischer F, Lang J et al: Early formation of thrombi on pulmonary artery catheters in cardiac surgical patients receiving high-dose aprotinin. J Cardiothorac Anesth 4:222, 1990.

366. Dentz ME, Slaughter TF, Mark JB: Early thrombus formation on heparin bonded pulmonary artery catheters in patients receiving epsilon aminocaproic acid. Anesthesiology 82:583, 1995.

367. Randolph AG, Cook DJ, Gonzales CA et al: Benefit of heparin in central venous and pulmonary artery catheters. Chest 113:165, 1998.

368. Connors AF, Castele RJ, Farhat NZ et al: Complications of right heart catheterization: A prospective autopsy study. Chest 88:567, 1985.

369. Rowley KM, Clubb KS, Smith GJW et al: Right-sided infective endocarditis as a consequence of flow-directed pulmonary-artery catheterization. N Engl J Med 311:1152, 1984.

370. Foote GA, Schabel SI, Hodges M: Pulmonary complications of the flow-directed balloon-tipped catheter. N Engl J Med 290:927, 1974.

371. Yorra FH, Oblath R, Jaffe H et al: Massive thrombosis associated with use of the Swan-Ganz catheter. Chest 65:682, 1974.

372. Applefield JJ, Caruthers TE, Reno DJ: Assessment of the sterility of long-term cardiac catheterization using the thermodilution Swan-Ganz catheter. Chest 74:377, 1978.

373. Mermel LA, McCormick RD, Springman SR et al: The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: A prospective study utilizing molecular subtyping. Am J Med 91:197S, 1991.

374. Cobb DK, High KP, Sawyer R et al: A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. N Engl J Med 327:1062, 1992.

375. Bernardin G, Milhaud D, Roger PM et al: Swan-Ganz catheterrelated pulmonary valve infective endocarditis: A case report. Intensive Care Med 20:142, 1994.

376. Carlson TA, Goldenberg IF, Murray PD et al: Catheter-induced delayed recurrent pulmonary artery hemorrhage. JAMA 261:1943, 1989.

377. Kelly TF, Morris GC, Crawford ES et al: Perforation of the pulmonary artery with Swan-Ganz catheters: Diagnosis and surgical management. Ann Surg 193:686, 1981.

378. McDaniel DD, Stone JG, Faltas AN et al: Catheter-induced pulmonary artery hemorrhage: Diagnosis and management in cardiac operations. J Thorac Cardiovasc Surg 82:1, 1981.

379. Mangar D, Connell GR, Lessin JL et al: Catheter-induced pulmonary artery haemorrhage resulting from a pneumothorax. Can J Anaesth 40:1069, 1993.

380. Urschel JD, Myerowitz PD: Catheter-induced pulmonary artery rupture in the setting of cardiopulmonary bypass. Ann Thorac Surg 56:585, 1993.

381. Barash PG, Nardi D, Hammond G et al: Catheter-induced pulmonary artery perforation. J Thorac Cardiovasc Surg 82:5, 1981.

382. Hardy J-F, Morissette M, Taillefer J et al: Pathophysiology of rupture of the pulmonary artery by pulmonary artery balloon-tipped catheters. Anesth Analg 62:925, 1983.

383. Lemen R, Jones JG, Cowan G: A mechanism of pulmonary-artery perforation by Swan-Ganz catheters. N Engl J Med 292:211, 1975.

384. Roberts LC, Ramsay MAE, Alivizatos PA et al: Successfully treated pulmonary artery rupture complicated by aneurysm formation. J Cardiothorac Vasc Anesth 6:70, 1992.

385. Shin B, Ayella RJ, McAslan TC: Pitfalls of Swan-Ganz catheterization. Crit Care Med 5:125, 1977.

386. Klafta JM, Olson JP: Emergent lung separation for management of pulmonary artery rupture. Anesthesiology 87:1248, 1997.

387. Bartter T, Irwin RS, Phillips DA et al: Pulmonary artery pseudoaneurysm. Arch Intern Med 148:471, 1988.

388. Sprung J, Schoenwald PK, Hayden J et al: Contained pulmonary artery perforation by pulmonary artery catheter. J Clin Monit 14:195, 1998.

389. Karak P, Dimick R, Hamrick KM et al: Immediate transcatheter embolization of Swan-Ganz catheter-induced pulmonary artery pseudoaneurysm. Chest 111:1450, 1997.

390. Iberti TJ, Fischer EP, Leibowitz AB et al: A multicenter study of physicians' knowledge of the pulmonary artery catheter. JAMA 264:2928, 1990.

391. Iberti TJ, Daily EK, Leibowitz AB et al: Assessment of critical care nurses' knowledge of the pulmonary artery catheter. Crit Care Med 22:1674, 1994.

392. Gnaegi A, Feihl F, Perret C: Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: Time to act? Crit Care Med 25:213, 1997.

393. Trottier SJ, Taylor RW: Physicians' attitudes toward and knowledge of the pulmonary artery catheter: Society of Critical Care Medicine Memebership Survey. New Horiz 5:201, 1997.

394. Komadina KH, Schenk DA, LaVeau P et al: Interobserver variability in the interpretation of pulmonary artery catheter pressure tracings. Chest 100:1647, 1991.

395. Feihl F, Gnaegi A, Perret C: Interpretation of the pulmonary artery occlusion (wedge) pressure: Physicians' knowledge versus the experts' knowledge. Crit Care Med 26:1763, 1998.

396. Marik P, Heard SO, Varon J: Interpretation of the pulmonary artery occlusion (wedge) pressure: Physicians' knowledge versus the experts' knowledge. Crit Care Med 26:1761, 1998.

397. Trottier SJ, Taylor RW: Interpretation of the pulmonary artery occlusion (wedge) pressure: physicians' knowledge versus the experts' knowledge. Crit Care Med 26:1763, 1998.

398. Moore RA, Neary MJ, Gallagher JD et al: Determination of the pulmonary capillary wedge position in patients with giant left atrial V waves. J Cardiothorac Anesth 1:108, 1987.

399. Kern MJ, Deligonul U: The left-sided V wave. In Kern MJ (ed): Hemodynamic Rounds. Interpretation of Cardiac Pathophysiology from Pressure Waveform Analysis. New York, Wiley-Liss, 1993, p 49.

400. Mark JB, Chetham PM: Ventricular pacing can induce hemodynamically significant mitral valve regurgitation. Anesthesiology 74:375, 1991.

401. Rao PS, Sathyanarayana PV: Transseptal insertion of left atrial line: A simple and safe technique. Ann Thorac Surg 55:785, 1993.

402. Zahorec R, Holoman M: Transatrial access for left atrial pressure monitoring in cardiac surgery patients. Eur J Cardiothorac Surg 11:379, 1997.

403. Leach JK, Friedlich AL, Myers GS et al: Usefulness and limitations on left heart catheterization in mitral disease. Am J Cardiol 6:57, 1962.

404. Entress JJ, Dhamee S, Olund T et al: Pulmonary artery occlusion pressure is not accurate immediately after cardiopulmonary bypass. J Cardiothorac Anesth 4:558, 1990.

405. Humphrey CB, Oury JH, Virgilio RW et al: An analysis of direct and indirect measurements of left atrial filling pressure. J Thorac Cardiovasc Surg 71:643, 1976.

406. Gold JP, Jonas RA, Lang P et al: Transthoracic intracardiac monitoring lines in pediatric surgical patients: A ten-year experience. Ann Thorac Surg 42:185, 1986.

407. Donahue PJ, Hansen DD, Mayer JE: A new complication of left atrial catheters. J Cardiothorac Anesth 3:757, 1989.

408. Porter EJ, Norfleet EA, Boone FD et al: Entrapment of a mitral valve prosthesis with a left atrial catheter. Anesthesiology 60:246, 1984.

409. Yeo TC, Miller FA, Oh JK et al: Retained left atrial catheter: An unusual cardiac source of embolism identified by transesophageal echocardiography. J Am Soc Echocardiogr 11:66, 1998.

410. Wiedemann HP: Wedge pressure in pulmonary veno-occlusive disease. N Engl J Med 315:1233, 1986.

411. Fang K, Krahmer RL, Rypins EB et al: Starling resistor effects on pulmonary artery occlusion pressure in endotoxin shock provide inaccuracies in left ventricular compliance assessments. Crit Care Med 24:1618, 1996.

412. Collee GG, Lynch KE, Hill RD et al: Bedside measurement of pulmonary capillary pressure in patients with acute respiratory failure. Anesthesiology 66:614, 1987.

413. Cope DK, Allison RC, Parmentier JL et al: Measurement of effective pulmonary capillary pressure using the pressure profile after pulmonary artery occlusion. Crit Care Med 14:16, 1986.

414. Gilbert E, Hakim TS: Derivation of pulmonary capillary pressure from arterial occlusion in intact conditions. Crit Care Med 22:986, 1994.

415. Hakim TS, Maarek JI, Chang HK: Estimation of pulmonary capillary pressure in intact dog lungs using the arterial occlusion technique. Am Rev Respir Dis 140:217, 1989.

416. Holloway H, Perry M, Downey J et al: Estimation of effective pulmonary capillary pressure in intact lungs. J Appl Physiol 54:846, 1983.

417. Yamada Y, Komatsu K, Suzukawa M et al: Pulmonary capillary pressure measured with a pulmonary arterial double port catheter in surgical patients. Anesth Analg 77:1130, 1993.

418. Mark JB: Pulmonary artery and wedge pressure artifacts. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 49.

419. Morris AH, Chapman RH, Gardner RM: Frequency of technical problems encountered in the measurement of pulmonary artery wedge pressure. Crit Care Med 12:164, 1984.

420. Schmitt EA, Brantigan CO: Common artifacts of pulmonary artery and pulmonary artery wedge pressures: Recognition and interpretation. J Clin Monit 2:44, 1986.

421. Bashein G: Another source of artifact in the pulmonary artery pressure waveform. Anesthesiology 68:310, 1988.

422. Sharkey SW: Beyond the wedge: Clinical physiology and the Swan-Ganz catheter. Am J Med 83:111, 1987.

423. Dobson GM, Horan BF, Bradburn NT: Significance of diastolic pulmonary artery pressure peaks. J Clin Monit 8:62, 1992.

424. Bethea CF, Peter RH, Behar VS et al: The hemodynamic simulation of mitral regurgitation in ventricular septal defect after myocardial infarction. Cathet Cardiovasc Diag 2:97, 1976.

425. Fuchs RM, Heuser RR, Yin FCP et al: Limitations of pulmonary wedge V waves in diagnosing mitral regurgitation. Am J Cardiol 49:849, 1982.

426. Grossman W: Profiles in valvular heart disease. In Grossman W, Baim DS (ed): Cardiac Catheterization, Angiography, and Intervention. Philadelphia, Lea & Febiger, 1991, p 557.

427. Pichard AD, Kay R, Smith H et al: Large V waves in the pulmonary wedge pressure tracing in the absence of mitral regurgitation. Am J Cardiol 50:1044, 1982.

428. Snyder RW, Glamann DB, Lange RA et al: Predictive value of prominent pulmonary arterial wedge V waves in assessing the presence and severity of mitral regurgitation. Am J Cardiol 73:568, 1994.

429. Royster RL, Johnson JC, Prough DS et al: Differences in pulmonary artery wedge pressures obtained by balloon inflation versus impaction techniques. Anesthesiology 61:339, 1984.

430. Braunwald E, Awe WC: The syndrome of severe mitral regurgitation with normal left atrial pressure. Circulation 27:29, 1963.

431. Velky PJ, Harte FA: The appearance of large "V" waves in association with sternal retraction during coronary artery surgery. J Cardiothorac Vasc Anesth 6:453, 1992.

432. Bourdillon PD, Lorell BH, Mirsky I et al: Increased regional myocardial stiffness of the left ventricle during pacing-induced angina in man. Circulation 67:316, 1983.

433. Dodek A, Kassebaum DG, Bristow JD: Pulmonary edema in coronary-artery disease without cardiomegaly: Paradox of the stiff heart. N Engl J Med 286:1347, 1972.

434. Grossman W: Diastolic dysfunction in congestive heart failure. N Engl J Med 325:1557, 1991.

435. Mark JB: Myocardial ischemia. Hemodynamic detection. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 181.

436. McLaurin LP, Rolett EL, Grossman W: Impaired left ventricular relaxation during pacing-induced ischemia. Am J Cardiol 32:751, 1973.

437. Waters DD, da Luz, P., Wyatt HL et al: Early changes in regional and global left ventricular function induced by graded reductions in regional coronary perfusion. Am J Cardiol 39:537, 1977.

438. Attia RR, Murphy JD, Snider M et al: Myocardial ischemia due to infrarenal aortic cross-clamping during aortic surgery in patients with severe coronary artery disease. Circulation 53:961, 1976.

439. Haggmark S, Hohner P, Ostman M et al: Comparison of hemodynamic, electrocardiographic, mechanical, and metabolic indicators of intraoperative myocardial ischemia in vascular surgical patients with coronary artery disease. Anesthesiology 70:19, 1989.

440. Kaplan JA, Wells PH: Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 60:789, 1981.

441. Kaplan JA: Indications for pulmonary arterial catheterization. Anesth Analg 61:477, 1982.

442. Rahimtoola SH, Loeb HS, Ehsani A et al: Relationship of pulmonary artery to left ventricular diastolic pressures in acute myocardial infarction. Circulation 46:283, 1972.

443. Sanchez R, Wee M: Perioperative myocardial ischemia: Early diagnosis using the pulmonary artery catheter. J Cardiothorac Vasc Anesth 5:604, 1991.

444. van Daele MERM, Sutherland GR, Mitchell MM et al: Do changes in pulmonary capillary wedge pressure adequately reflect myocardial ischemia during anesthesia: A correlative preoperative hemodynamic, electrocardiographic, and transesophageal echocardiographic study. Circulation 81:865, 1990.

445. Stott DK, Marpole DGF, Bristow JD et al: The role of left atrial transport in aortic and mitral stenosis. Circulation 41:1031, 1970.

446. Wohlgelernter D, Jaffe CC, Cabin HS et al: Silent ischemia during coronary occlusion produced by balloon inflation: relation to regional myocardial dysfunction. J Am Coll Cardiol 10:491, 1978.

447. Leung JM, O'Kelly BF, Mangano DT et al: Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand in patients undergoing CABG surgery. Anesthesiology 73:802, 1990.

448. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107, 1985.

449. Slogoff S, Keats AS: Further observations on perioperative myocardial ischemia. Anesthesiology 65:539, 1986.

450. Sabbah HN, Rosman H, Kono T et al: On the mechanism of functional mitral regurgitation. Am J Cardiol 72:1074, 1993.

451. Longabaugh JP, Sheikh KH, Bengtson JR et al: Diagnosis and management of ischemic mitral regurgitation with the use of transesophageal echocardiography. Coron Artery Dis 3:377, 1992.

452. Bashein G, Ivey TD: Con: A pulmonary artery catheter is not indicated for all coronary artery surgery. J Cardiothorac Anesth 1:362, 1987.

453. Keats AS: Adventures in perioperative myocardial ischemia. Tex Heart Institute J 20:5, 1993.

454. Lieberman RW, Orkin FK, Jobes DR, Schwartz AJ: Hemodynamic predictors of myocardial ischemia during halothane anesthesia for coronary-artery revascularization. Anesthesiology 59:36, 1983.

455. Weintraub AC, Barash PG: A pulmonary artery catheter is indicated in all ptaients for coronary artery surgery. J Cardiothorac Anesth 1:358, 1987.

456. Wickey GS, Larach DR, Keifer JC et al: Combined interpretation of transesophageal echocardiography, electrocardiography, and pulmonary artery wedge waveform to detect myocardial ischemia. J Cardiothorac Anesth 4:102, 1990.

457. Goldstein JA, Barzilai B, Rosamond TL et al: Determinants of hemodynamic compromise with severe right ventricular infarction. Circulation 82:359, 1990.

458. Lorell B, Leinbach RC, Pohost GM et al: Right ventricular infarction. Clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction. Am J Cardiol 43:465, 1979.

459. Kushwaha SS, Fallon JT, Fuster V: Restrictive cardiomyopathy. N Engl J Med 336:267, 1997.

460. Kern MJ, Aguirre F: Interpretation of cardiac pathophysiology from pressure waveform analysis: Pericardial compressive hemodynamics. I. Cathet Cardiovasc Diagn 25:336, 1992.

461. Kern MJ, Aguirre F: Interpretation of cardiac pathophysiology from pressure waveform analysis: Pericardial compressive hemodynamics. II. Cathet Cardiovasc Diagn 26:34, 1992.

462. Kern MJ, Aguirre F: Interpretation of cardiac pathophysiology from pressure waveform analysis: Pericardial compressive hemodynamics. III. Cathet Cardiovasc Diagn 26:152, 1992.

463. Hirschmann JV: Pericardial constriction. Am Heart J 96:110, 1978.

464. Beloucif S, Takata M, Shimada M et al: Influence of pericardial constraint on atrioventricular interactions. Am J Physiol 263:H125, 1992.

465. Greenberg MA, Gitler B: Left ventricular rupture in a patient with coexisting right ventricular infarction. N Engl J Med 309:539, 1983.

466. Lorell BH, Braunwald E: Pericardial disease. In Braunwald E (ed): Heart Disease. A Textbook of Cardiovascular Medicine. Philadelphia, WB Saunders, 1992, p 1465.

467. Fowler NO: Cardiac tamponade: A clinical or an echocardiographic diagnosis? Circulation 87:1738, 1993.

468. Hancock EW: Subacute effusive-constrictive pericarditis. Circulation 43:183, 1971.

469. Ellis DM: Interpretation of beat-to-beat blood pressure values in the presence of ventilatory changes. J Clin Monit 1:65, 1985.

470. Hoeksel SAAP, Blom JA, Jansen JRC et al: Correction for respiration artifact in pulmonary blood pressure signals of ventilated patients. J Clin Monit 12:397, 1996.

471. Mitchell MM, Meathe EA, Jones BR et al: Accurate, automated, continuously displayed pulmonary artery pressure measurement. Anesthesiology 67:294, 1987.

472. Teplick RS: Measuring central vascular pressures: A surprisingly complex problem. Anesthesiology 67:289, 1987.

473. Cengiz M, Crapo RO, Gardner RM: The effect of ventilation on the accuracy of pulmonary artery and wedge pressure measurements. Crit Care Med 11:502, 1983.

474. Bell H, Stubbs D, Pugh D: Reliability of central venous pressure as an indicator of left atrial pressure. A study in patients with mitral valve disease. Chest 59:169, 1971.

475. Buchbinder N, Ganz W: Hemodynamic monitoring: Invasive techniques. Anesthesiology 45:146, 1976.

476. Cohn JN, Tristani FE, Khatri IM: Relationship between left and right ventricular function. J Clin Invest 48:2008, 1969.

477. Toussaint GPM, Burgess JH, Hampson LG: Central venous pressure and pulmonary wedge pressure in critical surgical illness: A comparison. Arch Surg 109:265, 1974.

478. Mangano DT: Monitoring pulmonary arterial pressure in coronary-artery disease. Anesthesiology 53:364, 1980.

479. Lowenstein E, Teplick R: To (PA) catheterize or not to (PA) catheterize: that is the question. Anesthesiology 53:361, 1980.

480. Mark JB: Predicting left ventricular end-diastolic pressure. In Mark JB (ed): Atlas of Cardiovascular Monitoring. New York, Churchill Livingstone, 1998, p 59.

481. Mitchell JH, Gilmore JP, Sarnoff SJ: The transport function of the atrium: Factors influencing the relation between mean left atrial pressure and left ventricular end diastolic pressure. Am J Cardiol 9:237, 1962.

482. Herbert WH: Left ventricular compliance and pulmonary artery end-diastolic pressure. N Y State J Med 77:344, 1977.

483. Herbert WH: Pulmonary artery and left heart end-diastolic pressure relations. Br Heart J 32:774, 1970.

484. Berry AJ, Geer RT, Marshall BE: Alteration of pulmonary blood flow by pulmonary-artery occluded pressure measurement. Anesthesiology 51:164, 1979.

485. Wittnich C, Trudel J, Zidulka A et al: Misleading "pulmonary wedge pressure" after penumonectomy: its importance in postoperative fluid therapy. Ann Thorac Surg 42:192, 1986.

486. Berryhill RE, Benumof JL: PEEP-induced discrepancy between pulmonary arterial wedge pressure and left atrial pressure: The effects of controlled vs. spontaneous ventilation and compliant vs. noncompliant lungs in the dog. Anesthesiology 51:303, 1979.

487. Guyton RA, Chiavarelli M, Padgett CA et al: The influence of positive end-expiratory pressure on intrapericardial pressure and cardiac function after coronary artery bypass surgery. J Cardiothorac Anesth 1:98, 1987.

488. Nadeau S, Noble WH: Misinterpretation of pressure measurements from the pulmonary artery catheter. Can Anaesth Soc J 33:352, 1986.

489. Pinsky M, Vincent J-L, De Smet J-M: Estimating left ventricular filling pressure during positive end-expiratory pressure in humans. Am Rev Respir Dis 143:25, 1991.

490. Teboul JL, Zapol WM, Brun-Buisson C et al: A comparison of pulmonary artery occlusion pressure and left ventricular end-diastolic pressure during mechanical ventilation with PEEP in patients with severe ARDS. Anesthesiology 70:261, 1989.

491. Cozzi PJ, Hall JB, Schmidt GA: Pulmonary artery diastolic-occlusion pressure gradient is increased in acute pulmonary embolism. Crit Care Med 23:1481, 1995.

492. Case Records of the Massachusetts General Hospital (Case 21-1986). N Engl J Med 314:1435, 1986.

493. Case records of the Massachusetts General Hospital (Case 48-1993). N Engl J Med 329:1720, 1993.

494. Kern MJ, Aguirre FV: Mitral valve gradients: Part I. In Kern MJ (ed): Hemodynamic Rounds. Interpretation of Cardiac Pathophysiology from Pressure Waveform Analysis. New York, Wiley-Liss, 1993, p 35.

495. Enson Y, Wood JA, Mantaras NB et al: The influence of heart rate on pulmonary arterial-left ventricular pressure relationships at enddiastole. Circulation 56:533, 1977.

496. Prielipp RC, Morell R: Con: Swan song for the Swan-Ganz? J Clin Monit 313:339, 1997.

497. Robin ED: The cult of the Swan-Ganz catheter. Intensive Crit Care Digest 5:18, 1986.

498. Robin ED: Death by pulmonary artery flow-directed catheter: Time for a moratorium? (editorial). Chest 92:727, 1987.

499. Tuman KJ: Pro: A moratorium on PAC is unjustified. J Clin Monit 13:337, 1997.

500. Shoemaker WC: Use and abuse of the balloon tip pulmonary artery (Swan-Ganz) catheter: Are patients getting their money's worth? Crit Care Med 18:1294, 1990.

501. MacDonald D: Cerebral palsy and intrapartum fetal monitoring. N Engl J Med 334:659, 1996.

502. Nelson KB, Dambrosia JM, Ting TY et al: Uncertain value of electronic fetal monitoring in predicting cerebral palsy. N Engl J Med 334:613, 1996.

503. Shy KK, Luthy DA, Bennett FC et al: Effects of electronic fetal-heart-rate monitoring, as compared with periodic auscultation, on the neurologic development of premature infants. N Engl J Med 322:588, 1990.

504. Cooper AB, Doig GS, Sibbald WJ: Pulmonary artery catheters in the critically ill. An overview using the methodology of evidence-based medicine. Crit Care Clin 12:777, 1996.

505. Berlauk JF, Abrams J, Gilmour IJ et al: Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: A prospective, randomized clinical trial. Ann Surg 214:289, 1991.

506. Del Guercio LRM, Cohn JD: Monitoring operative risk in the elderly. JAMA 243:1350, 1980.

507. Flancbaum L, Ziegler DW, Choban PS: Preoperative intensive care unit admission and hemodynamic monitoring in patients scheduled for major elective noncardiac surgery: A retrospective review of 95 patients. J Cardiothorac Vasc Anesth 12:3, 1998.

508. Moore CH, Lombardo R, Allums JA et al: Left main coronary artery stenosis: Hemodynamic monitoring to reduce mortality. Ann Thorac Surg 26:445, 1978.

509. Scalea TM, Simon HM, Duncan AO et al: Geriatric blunt multiple trauma: Improved survival with early invasive monitoring. J Trauma 30:129, 1990.

510. Tuchschmidt J, Fried J, Astiz M et al: Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 102:216, 1992.

511. Afessa B, Tefferi A, Hoagland HC et al: Outcome of recipients of bone marrow transplants who require intensive-care unit support. Mayo Clin Proc 67:117, 1992.

512. Isaacson IJ, Lowdon JD, Berry AJ et al: The value of pulmonary artery and central venous monitoring in patients undergoing abdominal aortic reconstructive surgery: A comparative study of two selected, randomized groups. J Vasc Surg 12:754, 1991.

513. Pearson KS, Gomez MN, Moyers JR et al: A cost/benefit analysis of randomized invasive monitoring for patients undergoing cardiac surgery. Anesth Analg 69:336, 1989.

514. Rao TLK, Jacobs KH, El-Etr AA: Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 59:499, 1983.

515. Gore JM, Goldberg RJ, Spodick DH et al: A community-wide assessment of the use of pulmonary artery catheters in patients with myocardial infarction. Chest 92:721, 1987.

516. Zion MM, Balkin J, Rosenmann D et al: Use of pulmonary artery catheters in patients with acute myocardial infarction: Analysis of experience in 5,841 patients in the SPRINT Registry. Chest 98:1331, 1990.

517. Bashein G, Johnson PW, Davis KB et al: Elective coronary bypass surgery without pulmonary artery catheter monitoring. Anesthesiology 63:451, 1985.

518. Tuman KJ, McCarthy RJ, Spiess BD et al: Effect of pulmonary artery catheterization on outcome in patients undergoing coronary artery surgery. Anesthesiology 70:199, 1989.

519. Sibbald WJ, Keenan SP: Show me the evidence: A critical appraisal of the pulmonary artery catheter consensus conference and other musings on how critical care practitioners need to improve the way we conduct business. Crit Care Med 25:2060, 1997.

520. Knaus WA, Harrell FEJ, Lynn J et al: The SUPPORT prognostic model: Objective estimates of survival for seriously ill hospitalized adults. Ann Intern Med 122:191, 1995.

521. Lo B: Improving care near the end of life: Why is it so hard? JAMA 274:1634, 1995.

522. Mark JB: Pulmonary artery catheterization wither. Cardiovasc Thorac Anesth J Club J 2:8, 1997.

523. SUPPORT Principal Investigators: A controlled trial to improve care for seriously ill hospitalized patients. JAMA 274:1591, 1995.

524. Chernow B: Pulmonary artery flotation catheters. Chest 111:261, 1997.

525. Vincent J-L, Dhainaut J-F, Perret C et al: Is the pulmonary artery catheter misused? A European view. Crit Care Med 26:1283, 1998.

526. Shoemaker WC, Kram HB, Appel PL et al: The efficacy of central venous and pulmonary artery catheters and therapy based upon them in reducing mortality and morbidity. Arch Surg 125:1332, 1990.

527. Shoemaker WC, Belzberg H: Pulmonary artery catheter consensus conference. Crit Care Med 26:1760, 1998.

528. Boyd O, Grounds RM, Bennett ED: A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 270:2699, 1993.

529. Gattinoni L, Brazzi L, Pelosi P et al: A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025, 1995.

530. Hayes MA, Timmins AC, Yau EHS et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717, 1994.

531. Gasman JD, Ruoss SJ, Fishman RS et al: Hazards with both determining and utilizing oxygen consumption measurements in the management of critically ill patients. Crit Care Med 24:6, 1996.

532. Heyland DK, Cook DJ, King D et al: Maximizing oxygen delivery in critically ill patients: A methodologic appraisal of the evidence. Crit Care Med 24:517, 1996.

533. Hinds C, Watson D: Manipulating hemodynamics and oxygen transport in critically ill patients. N Engl J Med 333:1074, 1995.

534. American College of Physicians/American College of Cardiology/ American Heart Association Task Force on Clinical Privileges in Cardiology: Clinical competence in hemodynamic monitoring. J Am Coll Cardiol 15:1460, 1990.

535. Naylor CD, Sibbald WJ, Sprung CL et al: Pulmonary artery catheter-ization: can there be an integrated strategy for guideline development and research promotion? JAMA 269:2407, 1993.

536. Technology Subcommittee of the Working Group on Critical Care: Hemodynamic monitoring: A technology assessment. Can Med Assoc J 145:114, 1991.

537. Taylor RW, Calvin JE, Matuschak GM: Pulmonary artery catheter consensus conference: The first step. Crit Care Med 25:2064, 1997.

538. Taylor RW: Controversies in pulmonary artery catheterization. New Horiz 5:173, 1997.

539. Taylor RT: Pulmonary artery catheter consensus conference. Crit Care Med 26:1761, 1998.

540. Guyatt G and the Ontario Intensive Care Study Group: A randomized control trial of right-heart catheterization in critically ill patients. J Intensive Care Med 6:91, 1991.

541. Sandham JD, Hull RD, Brant RF: Ethics of technology assessment: Pulmonary artery flow directed catheter revisited. Am J Respir Crit Care Med 153:A422, 1996.

542. Sandham JD, Hull RD, Branta RF: Effect of the pulmonary artery catheter on morbidity and mortality, a multicenter trial. Am J Respir Crit Care Med 153:A601, 1996.

543. Leibowitz AB: Perioperative pulmonary artery catheterization: What is the evidence that it improves outcome? J Cardiothorac Vasc Anesth 12:1, 1998.

544. Sandham JD, Hull RD, Brant RF: Pulmonary artery flow directed catheter: The evidence. Lancet 348:1324, 1996.

545. Sandham JD, Hull RD, Brant RF: The pulmonary artery catheter takes a great fall. Crit Care Med 26:1288, 1998.

546. Spodick DH: Analysis of flow-directed pulmonary artery catheterization. JAMA 261:1946, 1989.

547. Spodick DH: Effectiveness of right heart catheterization: Time for a randomized trial. JAMA 277:113, 1997.

548. Keats AS: The Rovenstine lecture, 1983: Cardiovascular anesthesia: Perceptions and perspectives. Anesthesiology 60:467, 1984.

549. Zaidan JR, Freniere S: Use of a pacing pulmonary artery catheter during cardiac surgery. Ann Thorac Surg 35:633, 1983.

550. Mora CT, Seltzer JL, McNulty SE: Evaluation of a new design pulmonary artery catheter for intraoperative ventricular pacing. J Cardiothorac Anesth 2:303, 1988.

551. Trankina MF, White RD: Perioperative cardiac pacing using an atrioventricular pacing pulmonary artery catheter. J Cardiothorac Anesth 3:154, 1989.

552. Hamilton WF, Moore JW, Kinsman JM: Studies on the circulation. IV. Further analysis of the injection method, and changes in hemodynamics under physiologic and pathological conditions. Am J Physiol 99:534, 1932.

553. Stewart GN: Researches on the circulation time and on the influences which affect it. IV. The output of the heart. J Physiol 22:159, 1897.

554. Fegler G: Measurement of cardiac output in anesthetized animals by a thermodilution method. Q J Exp Physiol 39:153, 1954.

555. Berger RL, Weisel RD, Vito L et al: Cardiac output measurement by thermodilution during cardiac operations. Ann Thorac Surg 21:43, 1976.

556. Ganz W, Donoso R, Marcus HS et al: A new technique for measurement of cardiac output by thermodilution in man. Am J Cardiol 27:392, 1971.

557. Weisel RD, Berger RL, Hechtman HB: Measurement of cardiac output by thermodilution. N Engl J Med 292:682, 1975.

558. Wong M, Skulsky A, Moon E: Loss of indicator in the thermodilution technique. Cathet Cardiovasc Diag 4:103, 1978.

559. Sharkey SW: A Guide to Interpretation of Hemodynamic Data in the Coronary Care Unit. Philadelphia, Lippincott-Raven, 1997.

560. Stetz CW, Miller RG, Kelly GE et al: Reliability of the thermodilution method in the determination of cardiac output in clinical practice. Am Rev Respir Dis 126:1001, 1982.

561. Bilfinger TV, Lin CY, Anagnostopoulos CE: In vitro determination of accuracy of cardiac output measurements by thermal dilution. J Surg Res 33:409, 1982.

562. Levett JM, Replogle RL: Thermodilution cardiac output: A critical analysis and review of the literature. J Surg Res 27:392, 1979.

563. Powner DJ, Snyder JV: In vitro comparison of six commercially available thermodilution cardiac output systems. Med Instrumentation 12:122, 1978.

564. Nishikawa T, Dohi S: Slowing of the heart during cardiac output measurement by thermodilution. Anesthesiology 57:538, 1982.

565. Boerboom LE, Kinney TE, Olinger GN et al: Validity of cardiac output measurement by the thermodilution method in the presence of acute tricuspid regurgitation. J Thorac Cardiovasc Surg 106:636, 1993.

566. Cigarroa RG, Lange RA, Williams RH et al: Underestimation of cardiac output by thermodilution in patients with tricuspid regurgitation. Am J Med 86:417, 1989.

567. Heerdt PM, Pleimann BE, Hogue CW: Flow-dependency of error in thermodilution cardiac output during tricuspid regurgitation in dogs. Anesthesiology 83:A614, 1995.

568. Bearss MG, Yonutas DN, Allen WT: A complication with thermodilution cardiac outputs in centrally-placed pulmonary artery catheters. Chest 81:527, 1982.

569. Stoller JK, Herbst TJ, Hurford W et al: Spuriously high cardiac output from injecting thermal indiator through an ensheathed port. Crit Care Med 14:1064, 1986.

570. Bazaral MG, Petre J, Novoa R: Errors in thermodilution cardiac output measurements caused by rapid pulmonary artery temperature decreases after cardiopulmonary bypass. Anesthesiology 77:31, 1992.

571. Griffin K, Benjamin E, DelGiudice R et al: Thermodilution cardiac output measurement during simultaneous volume infusion through the venous infusion port of the pulmonary artery catheter. J Cardiothorac Vasc Anesth 11:437, 1997.

572. Wetzel RC, Latson TW: Major errors in thermodilution cardiac output measurement during rapid volume infusion. Anesthesiology 62:684, 1985.

573. Nelson LD, Anderson HB: Patient selection for iced versus room temperature injectate for thermodilution cardiac output determinations. Crit Care Med 13:182, 1985.

574. Pearl RG, Rosenthal MH, Nielson L et al: Effect of injectate volume and temperature on thermodilution cardiac output determination. Anesthesiology 64:798, 1986.

575. Okamoto K, Komatsu T, Kumar V et al: Effects of intermittent positive-pressure ventilation on cardiac output measurements by thermodilution. Crit Care Med 14:977, 1986.

576. Snyder JV, Powner DJ: Effects of mechanical ventilation on the measurement of cardiac output by thermodilution. Crit Care Med 10:677, 1982.

577. Stevens JH, Raffin TA, Mihm FG et al: Thermodilution cardiac output measurement. JAMA 253:2240, 1985.

578. Lazor MA, Pierce ET, Stanley GD et al: Evaluation of the accuracy and response time of STAT-Mode continuous cardiac output. J Cardiothorac Vasc Anesth 11:432, 1997.

579. Mihm FG, Gettinger A, Hanson CW et al: A multicenter evaluation of a new continuous cardiac output pulmonary artery catheter system. Crit Care Med 26:1346, 1998.

580. Philip JH, Long MC, Quinn MD et al: Continuous thermal measurement of cardiac output. IEEE Trans Biomed Eng 31:393, 1984.

581. Yelderman M: Continuous measurement of cardiac output with the use of stochastic system identification techniques. J Clin Monit 6:322, 1990.

582. Yelderman ML, Ramsay MA, Quinn MD et al: Continuous thermodilution cardiac output measurement in ICU patients. J Cardiothorac Vasc Anesth 6:270, 1992.

583. Yelderman M, Quinn MD, McKown RC: Continuous thermodilution cardiac output measurement in sheep. J Thorac Cardiovasc Surg 104:315, 1992.

584. Jansen JRC, Johnson RW, Yan JY et al: Near continuous cardiac output by thermodilution. J Clin Monit 13:233, 1997.

585. Aranda M, Mihm F, Garrett S et al: Continuous cardiac output catheters. Anesthesiology 89:1592, 1998.

586. Nelson LD: The new pulmonary artery catheters: continuous venous oximetry, right ventricular ejection fraction, and continuous cardiac output. New Horiz 5:251, 1997.

587. Hogue CW, Rosenbloom M, McCawley C et al: Comparison of cardiac output measurement by continuous thermodilution with electromagnetometry in adult cardiac surgical patients. J Cardiothorac Vasc Anesth 8:631, 1994.

588. Gardner RM: Continuous cardiac output: how accurate and how timely? Crit Care Med 26:1302, 1998.

589. Le Tulzo Y, Belghith M, Seguin P et al: Reproducibility of thermodilution cardiac output determination in critically ill patients: Comparison between bolus and continuous method. J Clin Monit 12:379, 1996.

590. Lichtenthal PR, Wade LD: Continuous cardiac output measurements. J Cardiothorac Vasc Anesth 8:668, 1994.

591. Hoff HE, Scott HJ: Physiology. N Engl J Med 239:120, 1948.

592. Fick A: Uber die Messung des Blutquantums in den Herzventrikeln. Verh Phys Med Ges Wurzburg 2:16, 1870.

593. Carpenter JP, Nair S, Staw I: Cardiac output determination: thermodilution versus a new computerized Fick method. Crit Care Med 13:576, 1985.

594. Davies GG, Jebson PJR, Glasgow BM et al: Continuous Fick cardiac output compared to thermodilution cardiac output. Crit Care Med 14:881, 1986.

595. Doi M, Morita K, Ikeda K: Frequently repeated Fick cardiac output measurements during anesthesia. J Clin Monit 6:107, 1990.

596. Norfleet EA, Watson CB: Continuous mixed venous oxygen saturation measurement: A significant advance in hemodynamic monitoring? J Clin Monit 1:245, 1985.

597. Prewitt RM, Ghignone M: Treatment of right ventricular dysfunction in acute respiratory failure. Crit Care Med 11:346, 1983.

598. Sibbald WJ, Driedger AA: Right ventricular function in acute disease states: Pathophysiologic considerations. Crit Care Med 5:339, 1983.

599. Vlahakes GJ, Turley K, Hoffman JIE: The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. Circulation 63:87, 1981.

600. Weber KT, Janicki JS, Shroff SG et al: The right ventricle: Physiologic and pathophysiologic considerations. Crit Care Med 11:323, 1983.

601. Cohn JN, Guiha NH, Broder M et al: Right ventricular infarction: Clinical and hemodynamic features. Am J Cardiol 33:209, 1974.

602. Kinch JW, Ryan TJ: Right ventricular infarction. N Engl J Med 330:1211, 1994.

603. Klein HO, Tordjman T, Ninio R et al: The early recognition of right ventricular infarction: Diagnostic accuracy of the electrocardiographic V_4R lead. Circulation 67:558, 1983.

604. Zehender M, Kasper W, Kauder E et al: Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. N Engl J Med 328:981, 1993.

605. Isner JM: Right ventricular myocardial infarction. JAMA 259:712, 1988.

606. Biondi JW, Schulman DS, Soufer R et al: The effect of incremental positive end-expiratory pressure on right ventricular hemodynamics and ejection fraction. Anesth Analg 67:144, 1988.

607. Her C, Lees DE: Accurate assessment of right ventricular function in acute respiratory failure. Crit Care Med 21:1665, 1993.

608. Nelson LD: Hemodynamic monitoring: A new day dawning. Crit Care Med 21:1626, 1993.

609. Reuse C, Vincent J-L, Pinsky MR: Measurements of right ventricular volumes during fluid challenge. Chest 98:1450, 1990.

610. Kay H, Afshan M, Barash PG: Measurement of ejection fraction by thermal dilution techniques. J Surg Res 34:337, 1983.

611. Dhainaut J-F, Brunet F, Monsallier JF et al: Bedside evaluation of right ventricular performance using a rapid computerized thermodilution method. Crit Care Med 15:148, 1987.

612. Morrison DA, Stovall R, Sensecqua J: Thermodilution measurement of the right ventricular ejection fraction. Cathet Cardiovasc Diagn 13:167, 1987.

613. Urban P, Scheidegger D, Gabathuler J: Thermodilution determination of right ventricular volume and ejection fraction. Crit Care Med 15:652, 1987.

614. Stein KL, Breisblatt W, Wolfe C et al: Depression and recovery of right ventricular function after cardiopulmonary bypass. Crit Care Med 18:1197, 1990.

615. Boldt J, Kling D, Thiel A et al: Revascularization of the right coronary artery: Influence on thermodilution right ventricular ejection fraction. J Cardiothorac Anesth 2:140, 1988.

616. Boldt J, Kling D, Moosdorf R et al: Influence of acute volume loading on right ventricular function after cardiopulmonary bypass. Crit Care Med 17:518, 1989.

617. Hines R, Barash PG: Intraoperative right ventricular dysfunction detected with a right ventricular ejection fraction catheter. J Clin Monit 2:206, 1986.

618. Chang MC, Mondy JS, Meredith JW et al: Clinical application of ventricular end-systolic elastance and the ventricular pressure-volume diagram. Shock 7:413, 1997.

619. Harvey RM, Enson Y: Pulmonary vascular resistance. Adv Intern Med 15:73, 1969.

620. McGregor M, Sniderman A: On pulmonary vascular resistance: The need for more precise definition. Am J Cardiol 55:217, 1985.

621. Permutt S, Riley RL: Hemodynamics of collapsible vessels with tone: The vascular waterfall. J Appl Phys 34:924, 1963.

622. Rouby J-J, Andreev A, Leger P et al: Peripheral vascular effects of thiopental and propofol in humans with artificial hearts. Anesthesiology 75:32, 1991.

623. Gorback MS: Problems associated with the determination of pulmonary vascular resistance. J Clin Monit 6:118, 1990.

624. Hilgenberg JC: Pulmonary vascular impedance: Resistance versus pulmonary artery diastolic-pulmonary artery occluded pressure gradient. Anesthesiology 58:484, 1983.

625. Schulte-Sasse U, Hess W, Tarnow J: Pulmonary vascular impedance: Resistance versus pulmonary artery diastolic-pulmonary artery occluded pressure gradient. Anesthesiology 58:485, 1983.

626. Reeves JT, Grover RF, Filley GF: Cardiac output in normal resting man. J Appl Physiol 16:276, 1961.

627. Abrams JH, Weber RE, Holmen KD: Continuous cardiac output determination using transtracheal Doppler: Initial results in humans. Anesthesiology 71:11, 1989.

628. Abrams JH, Weber RE, Holmen KD: Transtracheal Doppler: a new procedure for continuous cardiac output measurement. Anesthesiology 70:134, 1989.

629. Hausen B, Schafers H, Rohde R et al: Clinical evaluation of transtracheal Doppler for continuous cardiac output estimation. Anesth Analg 74:800, 1992.

630. Perrino AC, O'Connor T, Luther M: Transtracheal Doppler cardiac output monitoring: comparison to thermodilution during noncardiac surgery. Anesth Analg 78:1060, 1994.

631. Segal J, Pearl RG, Ford AJ et al: Instantaneous and continuous cardiac output obtained with a Doppler pulmonary artery catheter. J Am Coll Cardiol 13:1382, 1989.

632. Segal J, Nassi M, Ford AJ et al: Instantaneous and continuous cardiac output in humans obtained with a Doppler pulmonary artery catheter. J Am Coll Cardiol 16:1398, 1990.

633. Segal J, Gaudiani V, Nishimura T: Continuous determination of cardiac output using a flow-directed Doppler pulmonary artery catheter. J Cardiothorac Vasc Anesth 5:309, 1991.

634. Reich DL: Has continuous perioperative cardiac output monitoring finally arrived? J Cardiothorac Vasc Anesth 5:307, 1991.

635. Waxman K, Police AM, Cheung CK et al: Laser Doppler velocimetry as a monitor of cardiac output changes in dogs. Crit Care Med 13:194, 1985.

636. Huntsman LL, Gams E, Johnson CC et al: Transcutaneous determination of aortic blood-flow velocities in man. Am Heart J 89:605, 1975.

637. Colocousis JS, Huntsman LL, Curreri PW: Estimation of stroke volume changes by ultrasonic Doppler. Circulation 56:914, 1977.

638. Huntsman LL, Stewart DK, Barnes SR et al: Noninvasive Doppler determination of cardiac output in man: Clinical validation. Circulation 67:593, 1983.

639. Mark JB, Steinbrook RA, Gugino LD et al: Continuous noninvasive monitoring of cardiac output with esophageal Doppler ultrasound during cardiac surgery. Anesth Analg 65:1013, 1986.

640. Nishimura RA, Callahan MJ, Schaff HV et al: Noninvasive measurement of cardiac output by continuous-wave Doppler echocardiography: Initial experience and review of the literature. Mayo Clin Proc 59:484, 1984.

641. Chandraratna PA, Nanna M, McKay C et al: Determination of cardiac output by transcutaneous continuous-wave ultrasonic Doppler computer. Am J Cardiol 53:234, 1984.

642. Singer M: Cardiac output in 1998. Heart 79:425, 1998.

643. Freund PR: Transesophageal Doppler scanning versus thermodilution during general anesthesia. Am J Surg 153:490, 1987.

644. Perrino AC, Fleming J, LaMantia KR: Transesophageal Doppler ultrasonography: Evidence for improved cardiac output monitoring. Anesth Analg 71:651, 1990.

645. Perrino AC, Fleming J, LaMantia KR: Transesophageal Doppler cardiac output monitoring: Performance during aortic reconstructive surgery. Anesth Analg 73:705, 1991.

646. Schmid ER, Spahn DR, Tornic M: Reliability of a new generation transesophageal Doppler device for cardiac output monitoring. Anesth Analg 77:971, 1993.

647. Siegel LC, Shafer SL, Martinez GM et al: Simultaneous measurements of cardiac output by thermodilution, esophageal Doppler, and electrical impedance in anesthetized patients. J Cardiothorac Anesth 2:590, 1988.

648. Wong DH, Tremper KK, Stemmer EA et al: Noninvasive cardiac output: Simultaneous comparison of two different methods with thermodilution. Anesthesiology 72:784, 1990.

649. Wong DH, Watson T, Gordon I et al: Comparison of changes in transit time ultrasound, esophageal Doppler, and thermodilution cardiac output after changes in preload, afterload, and contractility in pigs. Anesth Analg 72:584, 1991.

650. Kamal GD, Symreng T, Starr J: Inconsistent esophageal Doppler cardiac output during acute blood loss. Anesthesiology 72:95, 1990.

651. Singer M, Clarke J, Bennett ED: Continuous hemodynamic monitoring by esophageal Doppler. Crit Care Med 17:447, 1989.

652. Singer M, Bennett D: Pitfalls of pulmonary artery catheterization highlighted by Doppler ultrasound. Crit Care Med 17:1060, 1989.

653. Singer M, Allen MJ, Webb AR et al: Effects of alterations in left ventricular filling, contractility, and systemic vascular resistance on the ascending aortic blood velocity waveform of normal subjects. Crit Care Med 19:1138, 1991.

654. Singer M, Bennett ED: Noninvasive optimization of left ventricular filling using esophageal Doppler. Crit Care Med 19:1132, 1991.

655. Thys DM, Hillel Z: Left ventricular performance indices by transesophageal Doppler. Anesthesiology 69:728, 1988.

656. Guzzetta NA, Ramsay JG, Bailey JM et al: Clinical evaluation of the esophageal Doppler monitor for continuous cardiac output monitoring. Anesth Analg 86:SCA82, 1998.

657. Kuck K, Fine PG, Westenskow DR: Evaluation of a new esophageal Doppler cardiac output monitor. J Clin Monit 13:424, 1997.

658. Gan TJ, Arrowsmith JE: The oesophageal Doppler monitor. BMJ 315:893, 1997.

659. Gan TJ, Wakeling H, Hardman D et al: Intraoperative volume expansion guided by esophageal Doppler reduces the incidence of gastric mucosal hypoperfusion and may be associated with improved outcome following major surgery. Anesthesiology 87:A391, 1997.

660. Sinclair S, James S, Singer M: Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 315:909, 1997.

661. Kubicek WG, Karnegis JN, Patterson RP: Development and evaluation of an impedance cardiac output system. Aviat Space Environ Med 37:1208, 1966.

662. Bernstein DP: A new stroke volume equation for thoracic electrical bioimpedance: Theory and rationale. Crit Care Med 14:904, 1986.

663. Mattar JA: Noninvasive cardiac output determination by thoracic electrical bioimpedance. Intensive Crit Care Dig 7:14, 1988.

664. Appel PL, Kram HB, MacKabee J: Comparison of measurements of cardiac output by bioimpedance and thermodilution in severely ill surgical patients. Crit Care Med 14:933, 1986.

665. Bernstein DP: Continuous noninvasive real-time monitoring of stroke volume and cardiac output by thoracic electrical bioimpedance. Crit Care Med 14:898, 1986.

666. Donovan KD, Dobb GJ, Woods WPD et al: Comparison of transthoracic electrical impedance and thermodilution methods for measuring cardiac output. Crit Care Med 14:1038, 1986.

667. Thomas AN, Ryan J, Doran BR et al: Bioimpedance versus thermodilution cardiac output measurement: The Bomed NCCOM3 after coronary bypass surgery. Intensive Care Med 17:383, 1991.

668. Tremper KK, Hufstedler SM, Barker SJ et al: Continuous noninvasive estimation of cardiac output by electrical bioimpedance: An experimental study in dogs. Crit Care Med 14:231, 1986.

669. Young JD, McQuillan P: Comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis. Br J Anaesth 70:58, 1993.

670. Shoemaker WC, Wo CCJ, Bishop MH et al: Multicenter trial of a new thoracic electrical bioimpedance device for cardiac output estimation. Crit Care Med 22:1907, 1994.

671. Thangathurai D, Charbonnet C, Roessler P et al: Continuous intraoperative noninvasive cardiac output monitoring using a new thoracic bioimpedance device. J Cardiothorac Vasc Anesth 11:440, 1997.

672. Orr J, Westenskow D, Kofoed S et al: A non-invasive cardiac output system using the partial re-breathing Fick method. J Clin Monit 12:464, 1996.

673. Bailey PL, Haryadi DG, Orr JA, et al: Partial CO_2 rebreathing Fick technique for noninvasive measurement of cardiac output. Anesth Analg 86:SCA53, 1998.

674. Guzzi L, Jaffe MB, Orr JA: Clinical evaluation of a new noninvasive method of cardiac output measurement: Preliminary results in CABG patients. Anesthesiology 89:A543, 1998.

675. Jopling MW: Noninvasive cardiac output determination utilizing the method of partial CO_2 rebreathing: A comparison with continuous and bolus thermodilution cardiac output. Anesthesiology 89:A544, 1998.

676. Kuck K, Haryadi DG, Orr JA et al: Evaluation of partial re-breathing cardiac output measurement during surgery. Anesthesiology 89:A542, 1998.

677. Haryadi DG, Orr JA, Kuck K et al: Evaluation of a partial CO_2 breathing Fick technique for measurement of cardiac output. Anesthesiology 89:A534, 1998.

678. Johnson KB, Haryadi DG, Orr JA et al: Influence of pulmonary edema on noninvasive measurements of cardiac output using partial CO_2 rebreathing in a canine model. Anesthesiology 89:A535, 1998.

679. Band DM, Linton RAF, O'Brien TK et al: The shape of indicator dilution curves used for cardiac output measurement in man. J Physiol 498:225, 1997.

680. Linton RAF, Band DM, Haire KM: A new method of measuring cardiac output in man using lithium dilution. Br J Anaesth 71:262, 1993.

681. Linton RAF, Linton NWF, Band DM: A new method of analysing indicator dilution curves. Cardiovasc Res 30:930, 1995.

682. Kurita T, Morita K, Kato S et al: Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output. Br J Anaesth 79:770, 1997.

683. Linton R, Band D, O'Brien T et al: Lithium dilution cardiac output measurement: A comparison with thermodilution. Crit Care Med 25:1796, 1997.

684. English JB, Hodges MR, Sentker C et al: Comparison of aortic pulse-wave contour analysis and thermodilution methods of measuring cardiac output during anesthesia in the dog. Anesthesiology 52:56, 1980.

685. Tannenbaum GA, Mathews D, Weissman C: Pulse contour cardiac output in surgical intensive care unit patients. J Clin Anesth 5:471, 1993.

686. Gratz I, Kraidin J, Jacobi AG et al: Continuous noninvasive cardiac output as estimated from the pulse contour curve. J Clin Monit 8:20, 1992.

687. Hirschl MM, Binder M, Gwechenberger M et al: Noninvasive assessment of cardiac output in critically ill patients by analysis of the finger blood pressure waveform. Crit Care Med 25:1909, 1997.

688. Godje O, Peyerl M, Seebauer T et al: Central venous pressure, pulmonary capillary wedge pressure and intrathoracic blood volumes as preload indicators in cardiac surgery patients. Eur J Cardiothoracic Surg 13:533, 1998.

689. Hoeft A, Schorn B, Weyland A et al: Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. Anesthesiology 81:76, 1994.

690. Barker SJ: Blood volume measurement: The next intraoperative monitor? Anesthesiology 89:1310, 1998.

691. Haruna M, Kumon K, Yahagi N et al: Blood volume measurement at the bedside using ICG pulse spectrophotometry. Anesthesiology 89:1322, 1998.

692. Iijima T, Aoyagi T, Iwao Y et al: Cardiac output and circulating blood volume analysis by pulse dye-densitometry. J Clin Monit 13:81, 1997.

693. Iijima T, Iwao Y, Sankawa H: Circulating blood volume measured by pulse dye-densitometry. Anesthesiology 89:1329, 1998.

694. Knichwitz G, Van Aken H, Brussel T: Gastrointestinal monitoring using measurement of intramucosal P_{CO_2}. Anesth Analg 87:134, 1998.

695. Kolkman JJ, Zwaarekant LJ, Boshuizen K et al: *In vitro* evaluation of intragastric P_{CO_2} measurement by air tonometry. J Clin Monit 13:115, 1997.

696. Welsby I, Mythen MG: Gut perfusion during cardiac surgery. Curr Opin Anaesth 10:34, 1997.

697. Marik PE: Gastric intramucosal pH: A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. Chest 104:225, 1993.

698. Marshall JC: An intensivist's dilemma: Support of the splanchnic circulation in critical illness. Crit Care Med 26:1637, 1998.

699. Silva E, DeBacker D, Creteur J et al: Effects of vasoactive drugs on gastric intramucosal pH. Crit Care Med 26:1749, 1998.

700. Coleman RL, Stanley T, Gilbert WC et al: The implementation and acceptance of an intra-operative anesthesia information management system. J Clin Monit 13:121, 1997.

701. Lubarsky DA, Sanderson IC, Gilbert WC et al: Using an anesthesia information management system as a cost containment tool. Anesthesiology 86:1161, 1997.

702. Richardson C, Stafford M, Warren J et al: Accuracy, precision and availability of hemodynamic data in the anesthesia record, a study of 226 patients at 19 sites in Europe and North America. Anesthesiology 89:A967, 1998.

703. Richardson C, Stafford M, Warren J et al: Using Bland-Altman plots and linear regression to detect bias in hemodynamic data in the anesthesia record, a study of 226 patients at 19 sites in Europe and North America. Anesthesiology 89:A966, 1998.

704. Hirsh J: Heparin. N Engl J Med 324:1565, 1991.

705. Bull BS, Korpman RA, Huse WM et al: Heparin therapy during extracorporeal circulation. I. Problems inherent in existing protocols. J Thorac Cardiovasc Surg 69:674, 1975.

706. Metz S: Administration of protamine rather than heparin in a patient undergoing normothermic cardiopulmonary bypass. Anesthesiology 80:691, 1994.

707. Hattersley PG: Activated coagulation time of whole blood. JAMA 196:150, 1966.

708. Dietrich W, Jochum M: Effect of celite and kaolin on activated clotting time in the presence of aprotinin: Activated clotting time is reduced by binding of aprotinin to kaolin. J Thorac Cardiovasc Surg 109:177, 1995.

709. Gravlee GP, Whitaker CL, Mark LJ et al: Baseline activated coagulation time should be measured after surgical incision. Anesth Analg 71:549, 1990.

710. Ammar T, Fisher CF, Sarier K et al: The effects of thrombocytopenia on the activated coagulation time. Anesth Analg 83:1185, 1996.

711. Moliterno DJ, Califf RM, Aguirre FV et al: Effect of platelet glycoprotein IIb/IIIa integrin blockade on activated clotting time during percutaneous transluminal coronary angioplasty or directional atherectomy (The EPIC Trial). Am J Cardiol 75:559, 1995.

712. Moorehead MT, Westengard JC, Bull BS: Platelet involvement in the activated clotting time of heparinized blood. Anesth Analg 63:394, 1984.

713. Gravlee GP, Case LD, Angert KC et al: Variability of the activated coagulation time. Anesth Analg 67:469, 1988.

714. Bode AP, Eick L: Lysed platelets shorten the activated coagulation time (ACT) of heparinized blood. Am J Clin Pathol 91:430, 1989.

715. Bennett JA, Horrow JC: Activated coagulation time: One tube or two? J Cardiothorac Vasc Anesth 10:471, 1996.

716. Baugh RF, Deemar KA, Zimmermann JJ: Heparinase in the activated clotting time assay: Monitoring heparin-independent alteration in coagulation function. Anesth Analg 74:201, 1992.

717. Oberhardt BJ, Dermott SC, Taylor M et al: Dry reagent technology for rapid, convenient measurements of blood coagulation and fibrinolysis. Clin Chem 37:520, 1991.

718. Mertzlufft FO, Risch A, Koster A et al: Heparin monitoring during CPB: A comparison of methods. Anesthesiology 89:A961, 1998.

719. Watke CM, Kern FH, Schulman SR et al: The heparin management test (HMT): An improved method for monitoring anticoagulation during pediatric cardiac surgery. Anesthesiology 89:A910, 1998.

720. Huyzen RJ, van Oeveren W, Wei F et al: In vitro effect of hemodilution on activated clotting time and high-dose thrombin time during cardiopulmonary bypass. Ann Thorac Surg 62:533, 1996.

721. Wang JS, Lin CY, Karp RB: Comparison of high-dose thrombin time with activated clotting time for monitoring of anticoagulant effects of heparin in cardiac surgical patients. Anesth Analg 79:9, 1994.

722. Macik GB: Designing a point-of-care program for coagulation testing. Arch Pathol Lab Med 119:929, 1995.

723. Despotis GJ, Summerfield AL, Joist JH: Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg 108:1076, 1994.

724. Despotis GJ, Joist HJ, Hogue Jr CW et al: More effective suppression of hemostatic system activation in patients undergoing cardiac surgery by heparin dosing based on heparin blood concentrations rather than ACT. Thromb Haemost 76:902, 1996.

725. Despotis GJ, Joist JH, Hogue CW et al: The impact on heparin concentration and activated clotting time monitoring on blood conservation. J Thorac Cardiovasc Surg 110:46, 1995.

726. Wahr JA, Yun J-H, Yang VC et al: A new method of measuring heparin levels in whole blood by protamine titration using a heparin-responsive electrochemical sensor. J Cardiothorac Vasc Anesth 10:447, 1996.

727. Yang VC, Ma SC, Liu D et al: A novel electrochemical heparin sensor. ASAIO J 39:M195, 1993.

728. Hartert H: Blutgerninnungstudien mit der Thrombelastographic, einen neuen untersuchings verfahren. Klin Wochensch 16:257, 1948.

729. Mallett SV, Cox DJA: Thromboelastography. Br J Anaesth 69:307, 1992.

730. Shenaq SA, Saleem A: Viscoelastic measurement of clot formation: The Sonoclot. In Ellison N, Jobes DR (eds): Effective Hemostasis in Cardiac Surgery. Philadelphia, WB Saunders Company, 1988, p 183.

731. Tuman KJ, Spiess BD, McCarthy RJ et al: Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass. Anesth Analg 69:69, 1989.

732. Saleem A, Blifeld C, Saleh SA et al: Viscoelastic measurement of clot formation: A new test of platelet function. Ann Clin Lab Sci 13:115, 1983.

733. Zuckerman L, Cohen E, Vagher JP et al: Comparison of thromboelastography with common coagulation tests. Thromb Haemost 46:752, 1981.

734. Spiess BD, Tuman KJ, McCarthy RJ et al: Thromboelastography as an indicator of post-cardiopulmonary bypass coagulopathies. J Clin Monit 3:25, 1987.

735. Nicholson NS, Panzer-Knodle SG, Haas NF et al: Assessment of platelet function assays. Am Heart J 135:S170, 1998.

736. Despotis GJ, Levine V, Filos KS et al: Evaluation of a new point-of-care test that measures PAF-mediated acceleration of coagulation in cardiac surgical patients. Anesthesiology 85:1311, 1996.

737. Ereth MH, Nuttall GA, Klindworth JT et al: Does the plateletactivated clotting test (HemoSTATUS) predict blood loss and platelet dysfunction associated with cardiopulmonary bypass? Anesth Analg 85:259, 1997.

738. Ereth MH, Nuttall GA, Santrach PJ et al: The relation between the platelet-activated clotting test (HemoSTATUS) and blood loss after cardiopulmonary bypass. Anesthesiology 88:962, 1998.

739. Coller BS, Lang D, Scudder LE: Rapid and simple platelet function assay to assess GPIIb/IIIa receptor blockade. Circulation 95:860, 1997.

740. Kundu SK, Heilmann EJ, Sio R et al: Description of an in vitro platelet function analyzer: PFA-100. Semin Thromb Hemost 21:106, 1995.

741. Fressinaud E, Veyradier A, Truchaud F et al: Screening for von Willebrand disease with a new analyzer using high shear stress: A study of 60 cases. Blood 91:1325, 1998.

742. Mammen EF, Koets MH, Washington BC et al: Hemostasis changes during cardiopulmonary bypass surgery. Semin Thromb Hemost 11:281, 1985.

Chapter 31 - Transesophageal Echocardiography *

Michael K. Cahalan

INTRODUCTION

In 1976, Dr. Leon Frazin and associates [1] published the results of studies using an esophageal M-mode transducer and thereby introduced the technique of transesophageal echocardiography (TEE). Subsequently, Matsumoto et al [2] used M-mode TEE to study left ventricular (LV) function during cardiovascular surgery, but M-mode echocardiography provides too limited a view of spatial relationships to be practical for intraoperative monitoring. In the early 1980s, Hanrath et al [3] introduced a two-dimensional (2-D), phased-array transducer mounted on the tip of a flexible gastroscope, and TEE's intraoperative potential became apparent. In the mid-1980s, color flow Doppler technology became commercially available, making it possible for TEE to provide not only high-resolution, real-time images of cardiac structure and function, but also simultaneous, superimposed maps of intracardiac blood flow. With these technical advances, TEE's role was ensured in the perioperative assessment of patients with a wide variety of cardiovascular diseases.

In this chapter, the perioperative applications of TEE most important for the anesthesiologist are emphasized. The tools and techniques for exploiting TEE are presented, including basic ultrasound modalities, probe operation, and techniques to diagnose the causes of common hemodynamic problems. TEE assessment of global and regional LV function is described in detail, because standard textbooks of echocardiography tend to ignore or gloss over such applications. TEE evaluation of valvular function and surgical repairs is well covered elsewhere, so it is given more limited coverage here. [4] [5] [6] [7] [8] [9] [10] [11] For the practitioner who plans extensive use of TEE, one or more of the standard texts on echocardiography should prove invaluable. [12] [13] [14]

ULTRASOUND IMAGING MODALITIES

Physical Principles

Echocardiography typically involves intermittent pulses of ultrasound waves with a frequency of 2.5 to 7.5 million cycles per second (MHz). Frequencies greater than 7.5 MHz are not routinely used in echocardiography because penetration of the sound waves into tissues is too limited (penetration is inversely related to frequency). Frequencies less than 2.5 MHz are not routinely used, because resolution of small objects is too limited (resolution is directly related to frequency). Ultrasound waves in the range of 2.5 to 7.5

* *Also see Appendix 1, Practice Guidelines for Perioperative Transesophageal Echocardiography*

MHz provide tissue penetration of 10 to 25 cm and resolve objects 1 mm or less in size. When ultrasound waves strike an interface of tissues of differing densities, such as the pericardium and the heart, a portion is reflected. The amount reflected depends on the difference in the tissue densities; that is, the greater the difference, the greater the portion reflected. For example, air in the LV reflects a much greater portion of the transmitted ultrasound than blood and is translated as a brighter signal on the display screen. Tissue is localized by the time a sound wave takes to bounce back to the transducer; that is, the longer a sound wave takes to bounce back, the greater is its distance from the transducer. (Sound is assumed to travel at 1,540 m/s in all tissues of the body at 37°C.) No ionizing radiation of any type is used in echocardiography, and no adverse effects of ultrasound have been demonstrated in humans.

M-Mode and Two-Dimensional Echocardiography

The first echocardiograms, "motion" or "M-mode" studies, were one-dimensional views of cardiac structures produced by single crystal transducers with the results traced on moving photosensitive paper. Today, M-mode echocardiography is used principally to view rapidly moving structures, such as valve leaflets, because M-mode transducers can produce up to 1,000 images per second (Fig. 31-1) (Figure Not Available) . However, M-mode images reveal only a small portion of the heart at one time, making orientation and interpretation of spatial relationships difficult.

Figure 31-1 (Figure Not Available) An M-mode transesophageal echocardiogram of a normal aortic valve. For reference, a single frame (stop action) of the two-dimensional cross-section is shown at the top right of the figure. The dotted vertical line through the two-dimensional echocardiogram depicts the single line of sampling provided by the M-mode echocardiogram over time (the horizontal axis for the lower two-thirds of the figure). The electrocardiogram defines systole and diastole. Note in the middle of the M-mode image the three tilted rectangles connected by the slightly undulating line. These rectangles and lines are formed by the motion of the leaflets of the aortic valve as they open and close during the cardiac cycles shown. From top to bottom in this M-mode echocardiogram, the structures indicated by the white lines are the posterior wall of the left atrium (just under the electrocardiogram), the posterior wall of the aortic annulus, the aortic valve (as already described), the anterior wall of the aortic annulus, a pulmonary artery catheter, and the myocardium of the right ventricular outflow tract. *(From Cahalan [21])*

Figure 31-2 (Figure Not Available) A short-axis two-dimensional cross-section of a normal aortic valve (AV). This basal two-dimensional short-axis view reveals the morphology of the three cusps of this normal valve. LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract; TV, tricuspid valve. *(From Cahalan [21])*

By using multiple crystals (linear or phased-array transducers) or by rapidly moving a single crystal (mechanical transducer), multiple views can be obtained and collated into a 2-D image. Although 2-D techniques produce only about 30 images per second, definition in two dimensions provides an enormous advantage in recognizing anatomic and pathologic landmarks (Fig. 31-2) (Figure Not Available) . Images are displayed in "real time" on a monitor screen and are recorded on videotape or digital format for later review. By altering the position or angle of the ultrasound beam, the operator produces multiple cross-sectional (tomographic) images revealing the external and internal anatomy and function of the heart and great vessels.

Pulsed-Wave Doppler

By measuring the Doppler shift, modern ultrasonographs quantify blood flow velocities. The Doppler shift is the shift in frequency of a wave when the source of the wave is moving (in this case, the wave reflected by moving red cells). When pulses of sound are used (pulsed-wave or PW Doppler), the operator defines a small area (termed "sample volume") anywhere in the 2-D sector scan, and the ultrasonograph automatically converts the Doppler data in that sample volume to a display of the real-time blood flow velocities (Fig. 31-3) (Figure Not Available) . Thus, PW Doppler defines blood flow velocities and their location within the heart and great vessels.

However, two important limitations apply. First, the Doppler shift is proportional to the cosine of the angle theta between the ultrasound beam and the direction of the blood cells. Thus, if the cells are moving directly parallel to the ultrasound beam, the angle is zero and the cosine of zero is one, providing a true estimate of blood flow velocity. At all other angles, the cosine is less than one, resulting in less Doppler shift and an underestimation of flow velocity. Clinically,

Figure 31-3 (Figure Not Available) Pulsed-wave Doppler echocardiogram of the main pulmonary artery (MPA). At the top of the echocardiogram is a still-frame image of the two-dimensional cross-section used to position the Doppler sample volume (white sphere). On the bottom two-thirds of the echocardiogram is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electro-cardiogram (ECG) is shown for timing purposes. The horizontal line through the base of the Doppler tracing is the baseline (zero flow) for the flow velocities. Flow velocities above this line are positive (i.e., toward the transducer) to a maximum of 68 cm/s. Flow below the line is negative (i.e., away from the transducer) to a maximum of -14 cm/s. *(From Cahalan [21])*

angles of less than 15 degrees (the cosine is almost one) are insignificant to velocity estimation, whereas angles exceeding 20 degrees markedly attenuate the Doppler shift, necessitating caution in interpreting such data. This relationship is best stated in the Doppler equation:

where V is the velocity to be measured, F_d is the Doppler shift in ultrasound frequency measured by the ultrasound machine, C is the speed of sound in tissue (a constant), and F_0 is the frequency of the transducer. Second, the maximum velocity of blood flow that can be unambiguously measured is inherently limited ("Nyquist limit"). The Nyquist limit is determined by the pulse repetition frequency, which, in turn, depends directly on the depth of the ultrasound scan and inversely on the ultrasound frequency. If the Nyquist limit is exceeded, sudden apparent flow reversal ("aliasing") will be depicted (Fig. 31-4) (Figure Not Available) . "Aliasing" is

analogous to the sudden apparent reversal of direction in stagecoach wheels visible in old Westerns when the velocity of the wheel spokes exceeds the frame rate of the movie camera. Typically, aliasing of PW Doppler occurs at blood flow velocities of 0.4 to 0.6 m/s. Normal flow within the heart may reach 1.4 m/s, and pathologic flows may be up to 6 m/s. To measure these velocities, continuous-wave (CW) Doppler is needed.

Continuous-Wave Doppler

CW Doppler uses two separate crystals: one to emit ultrasound continuously and one to receive it continuously. CW Doppler is basically PW Doppler with an infinite pulse repetition frequency that eliminates the problem of aliasing (Fig. 31-5) (Figure Not Available) . However, this infinite pulse repetition rate allows insufficient time for the first pulse to return to the transducer before the next is emitted. Consequently, the ultrasonograph cannot determine which pulse of sound was frequency shifted and, therefore, cannot precisely define the location of the moving target. Nonetheless, the maximum velocity can prove to be vital information: by simplification of the Bernoulli equation, Hatle et al [15] and Holen et al [16] proved that the peak gradient across a stenotic valve equals $4V^2$, where V is the velocity determined by CW Doppler in meters per second. Thus, CW Doppler defines higher blood flow velocities than PW, but, unlike the latter, CW Doppler cannot precisely define the location of the velocities.

Color Doppler

Point-by-point determination of blood flow velocities often is too time-consuming and does not reveal the instantaneous distribution of flow velocities within the cross-sectional image that is required for many diagnostic decisions. Color Doppler imaging was developed for this purpose: to permit sampling of the Doppler shift simultaneously in many areas of the sector scan. In color Doppler, a form of PW Doppler, a color code is used to depict flow toward (red) and away (blue) from the transducer; lighter and darker shades of red and blue, respectively, denote relatively faster and slower velocities. Continuous color maps of flow are superimposed on gray-scale cross-sectional echocardiograms. However, color Doppler generally is a semiquantitative technique and, like PW Doppler, will alias (color reversal) when the Nyquist limit is exceeded. Two aliasing patterns are easily recognized: the first is "normal" aliasing in which the area of apparent flow reversal forms one or more broad, relatively homogenous color surfaces (Color Plate 31-1).

Figure 31-4 (Figure Not Available) Pulsed-wave Doppler echocardiogram with aliasing at the high-velocity point. Pulsed-wave Doppler measurement of blood flow velocities in a mitral valve (MV) orifice during four cardiac cycles is shown. At the top of the figure is a still-frame image of the two-dimensional cross-section used to position the Doppler sample volume (white sphere). On the bottom two-thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electrocardiogram is shown for timing purposes. The horizontal line through the base of the Doppler tracing is the baseline (zero flow) for the flow velocities. Flow velocities above the line are positive (i.e., toward the transducer) to a maximum of 183 cm/s. Flow velocities below the line are negative (i.e., away from the transducer) to a maximum of -77 cm/s. This tracing documents significant mitral regurgitation (the positive systolic velocities), but it does not measure the peak velocity of regurgitant flow because it is beyond the Nyquist limit--the systolic velocities off the top of the scale are said to alias, that is, they go off scale and wrap around into the domain of negative velocities. LA, left atrium; LV, left ventricle. *(From Cahalan [21])*

Blood flow velocities within a normal heart (0.6-1.4 m/s) often produce this type of aliasing because they exceed the Nyquist limit for color Doppler (0.4-0.6 m/s). The second type of aliasing results from disturbed or turbulent flow within the heart (e.g., mitral regurgitation) and is not normal (Color Plate 31-2). When the ultrasonograph detects two different velocities within the same small sample volume (from disturbed flow), it displays a mixture or mosaic of colors. These mosaics often form jet-like configurations and are commonly called "color jets." Because color Doppler presents the spatial relationships between structure and blood flow, it greatly enhances the recognition of valvular abnormalities and intracardiac shunts.

EQUIPMENT DESIGN AND OPERATION

Probes

The simplest TEE probe has one phased-array transducer with 64 piezoelectric elements. The transducer is about 40 mm long, 13 mm wide, and 11 mm thick; operates at 5 or 7.5 MHz; and is mounted on the tip of a 9-mm-diameter gastroscope. The ultrasound beam is oriented at right angles to the gastroscope to produce transverse imaging planes of the heart. As with standard gastroscopes, two rotary knobs ("wheels") control the movement of the tip of the scope. One of the wheels flexes and retroflexes the transducer (i.e., moves the transducer toward and away from the heart). The other wheel angulates the transducer rightward and leftward.

Biplane transducers incorporate a second transducer mounted immediately proximal and at right angles to the first to add a longitudinal imaging plane. These probes have a significantly longer inflexible tip than single-transducer probes, but this feature rarely prevents esophageal passage in the unconscious patient.

Multiplane transducers use a single transducer mounted on a rotating device that allows the transducer to spin on its axis from 0 to 180 degrees within the tip of the gastroscope (transducer housing). Because cardiac structures and blood flow are not always aligned precisely with the transverse or longitudinal plane, this design has significantly refined imaging capability. Although a few millimeters wider and thicker than single-plane transducers, multiplane probes are easily passed through the esophagus of the unconscious patient.

By reducing the number of crystals and by further miniaturizing transducers, manufacturers have produced single-plane and biplane transducers small enough (6 to 7-mmdiameter gastroscopes) for use in infants and neonates (Fig. 31-6) (Figure Not Available) .

Figure 31-5 (Figure Not Available) Continuous-wave Doppler measures high-velocity flows without aliasing. Continuous-wave Doppler measurement of blood flow velocities in a mitral valve orifice during four cardiac cycles is shown. At the top of the figure is a still-frame image of the two-dimensional cross-section used to position the Doppler sample cursor (diagonal white line). On the bottom two-thirds of the figure is the display in white of all the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor. The electrocardiogram (ECG) is shown for timing purposes. The horizontal line through the base of the Doppler tracing is the baseline (zero flow) for the flow velocities. Flow velocities above the line are positive (i.e., toward the transducer) to a maximum of 753 cm/s. Flow velocities below the line are negative (i.e., away from the transducer) to a maximum of -316 cm/s. This tracing documents significant mitral regurgitation (the positive systolic velocities) with a peak blood flow velocity of approximately 5 m/s (each white dot on the vertical axis equals 100 cm/s or 1 m/s). LA, left atrium; LV, left ventricle. *(From Cahalan [21])*

Figure 31-6 (Figure Not Available) Four transesophageal echocardiography probes are compared. From left to right, the probes are single plane, pediatric single plane, multiplane, and biplane. The probe tips are viewed in their maximum dimension. *(From Cahalan [21])*

Ultrasonographs

Ultrasonographs contain high-powered computers capable of initiating the ultrasound signal and processing the returning data. A series of electronic transforms (some guarded commercial secrets) produces the real-time images displayed on the video screen. All ultrasonographs share common technical aspects including gain, depth, and Doppler controls. However, the differences in technical aspects among manufacturers and even among models from the same manufacturer are sufficiently great to prevent the formulation of any universal operating instructions. Fortunately, detailed instructions for each model are available in the operator's manual supplied with each ultrasonograph. Alternatively, cardiac sonographers are often excellent sources of instruction in the operation of these machines.

BASIC EXAMINATION TECHNIQUE AND CROSS-SECTIONS

Overview

Unless specific diagnostic questions require the assistance of a cardiologist, anesthesiologists usually perform intraoperative TEE. Because of time constraints and relatively narrow

TABLE 31-1 -- The Four Basic Transverse Cross-Sections [a]

(Not Available)

From Cahalan [21]

[a] The four basic transverse-plane cross-sections are listed along with the depth from the incisors at which they are most commonly found, their anatomic level, the transducer angle for optimal viewing in most patients (multiplane probes only), and their principal use

diagnostic goals, the anesthesiologist performs a more limited examination than often described in the cardiology literature. [17] [18] [19] [20] However, an absolute minimum of four cross-sections should be attempted even when only a single-plane transducer is available (Table 31-1) (Table Not Available) . Without these cross-sections, common cardiac pathologic features may be missed, and correct interpretation of subsequent hemodynamic alterations may be impossible. Therefore, a standardized intraoperative examination is recommended as the foundation for monitoring and for detailed diagnostic imaging when indicated.

Probe Introduction

Once the patient is anesthetized and the trachea is securely intubated, the contents of the patient's stomach are suctioned. Gentle massage of the left upper quadrant of the abdomen during suctioning may help to remove air that otherwise can degrade imaging. Then the patient's neck is extended, and the well-lubricated TEE probe is introduced into the midline of the hypopharynx with the transducer side facing anteriorly. Usually, with minimal force, the probe will pass blindly into the esophagus, especially if the patient's neck is extended. If the probe does not pass blindly, a laryngoscope is used to lift the larynx anteriorly, and the probe is placed into the patient's esophagus under direct vision. During transducer insertion or withdrawal, the controls of the gastroscope must be in the neutral or relaxed position to allow the transducer to follow the natural course of the esophagus, thereby potentially minimizing the risk of injury.

Basic Transverse Plane Examination

With the transducer at 28 to 32 cm (measured at the upper incisors), the basal short-axis cross-section of the aortic valve is easily obtained by turning the shaft of the gastroscope and adjusting its depth in the esophagus until the transducer is directly behind the aortic valve (see Fig. 31-2 (Figure Not Available) ; Color Plate 31-3). "Basal" specifies the position of the transducer behind the base of the heart. This cross-section is ideal for detection of aortic valve abnormalities, including aortic stenosis. With a single or biplane probe, the best view of the aortic valve is obtained by using the appropriate wheel of the gastroscope to angulate the tip of the probe leftward 15 to 30 degrees. This angulation better aligns the transverse imaging plane with the annulus of the aortic valve, thereby achieving a true short-axis cross-section. With a multiplane transducer, angulation of the tip of the gastroscope is unnecessary. Instead, the transducer can be rotated 15 to 30 degrees within the tip of the gastroscope to accomplish the same effect.

Advancing the transducer 3 to 5 mm from this position, turning it slightly leftward (by rotating the shaft of the gastroscope) and retroflexing it (with the appropriate wheel of the gastroscope) to direct the ultrasound beam downward (10-30 degrees caudally) provides a view of the LV outflow tract (the "five-chamber" cross-section): left atrium and ventricle, right atrium and ventricle, and LV outflow tract (Fig. 31-7 (Figure Not Available) ; Color Plate 31-4). With color Doppler, this cross-section permits detection of mitral stenosis, mitral regurgitation, and aortic insufficiency. When examining valves and other three-dimensional (3-D) structures with 2-D imaging and Doppler techniques, the operator must use multiple, closely spaced 2-D "slices" of the 3-D structures to be certain that localized abnormalities have not been missed. Fortunately, this is easily accomplished with the mitral valve and LV outflow tract: after the five-chamber cross-section has

Figure 31-7 (Figure Not Available) Five-chamber echocardiogram. This image was obtained with a multiplane transducer positioned at 0 degrees as indicated by the semicircular icon positioned to the right of the sector scan. This cross-section is commonly called the five-chamber view because all four cardiac chambers and the left ventricular outflow tract (LVOT) can be seen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *(From Cahalan [21])*

been achieved, the operator relaxes the retroflexion of the gastroscope, centers the mitral valve in the sector scan, and slowly withdraws and then advances the transducer until the entire mitral valve surface has been sliced like a loaf of bread. This slicing procedure is first performed with 2-D imaging and then with color Doppler. Thereafter, the operator centers the LV outflow tract in the sector scan and repeats the 2-D and color Doppler examinations.

Advancing the transducer 3 to 5 mm deeper into the esophagus below the level at which the five-chamber cross-section was achieved and again retroflexing it to direct the ultrasound beam 10 to 30 degrees caudally provides the four-chamber cross-section (Fig. 31-8 (Figure Not Available) ; Color Plate 31-5). This cross-section is best for evaluation of relative LV and right ventricular size and function. A normal right ventricle appears smaller than the LV (intracavitary area roughly two-thirds of the LV cavity area) because it is crescent shaped and partially wrapped around the LV. With color Doppler, this cross-section permits detection of tricuspid stenosis and regurgitation.

Finally, advancing the transducer 2 to 7 cm further and then flexing it anteriorly 20 to 40 degrees reveals the short-axis cross-section of the LV at the level of the papillary muscles (Fig. 31-9 (Figure Not Available) ; Color Plate 31-6). This short-axis cross-section is ideal for monitoring LV filling and ejection, because all major coronary arteries supply myocardium viewed in this cross-section, changes in preload cause greater changes in the LV short-axis than in the long-axis dimension, and movement of the probe from this cross-section is readily apparent because of the prominent landmarks the papillary muscles provide.

Figure 31-8 (Figure Not Available) Four-chamber echocardiogram. Because this cross-section, like the five-chamber cross-section, rarely reveals the apex of the left ventricle (LV), estimates of filling

and ejection derived from these cross-sections usually underestimate LV end-diastolic volume and overestimate ejection fraction. However, the relative size and function of the two ventricles are apparent in the four-chamber cross-section, and, as a result, this cross-section is often the best for detection of right ventricular (RV) dysfunction. Although RV function appears normal in this image, the leftward bulging of the intra-atrial septum is abnormal and suggests high right-sided pressures. LA, left atrium; RA, right atrium. *(From Cahalan [21])*

Figure 31-9 (Figure Not Available) Midpapillary short-axis echocardiogram. This echocardiogram was obtained with a single-plane probe. ALPM, anterior lateral papillary muscle; IVS, intraventricular septum; LV, left ventricle; PMPM, posterior medial papillary muscle. *(From Cahalan [21])*

Biplane and Multiplane Examination

Five additional, longitudinal cross-sections are added to the basic examination when using a biplane or multiplane probe--three basal cross-sections at the aortic valve level, one midesophageal cross-section at the mitral valve level, and one transgastric cross-section at the mid-LV level (Table 31-2) (Table Not Available) . Thus, the basic biplane or multiplane examination requires nine cross-sections. To appreciate the relationship between transverse and longitudinal cross-sections requires some 3-D conceptualization. At the aortic valve level, transverse plane, short-axis cross-section, one needs to imagine the ascending aorta coming out of the page and the LV outflow tract behind it (see Fig. 31-2 (Figure Not Available) and Color Plate 31-3). When the imaging plane is reoriented from transverse to longitudinal (accomplished by switching to the second transducer in a biplane system or rotating the transducer to 90 degrees in a multiplane system), the heart appears to have rotated 90 degrees so that the ascending aorta is positioned on the right side of the image and the LV outflow tract is on the left (Fig. 31-10 (Figure Not Available) ; Color Plate 31-7). This cross-section (longitudinal plane, ascending aorta) is excellent for detection of ascending aortic abnormalities, including aortic dissections. With a biplane probe, the best view of the ascending aorta is obtained by using the appropriate wheel of the gastroscope to angulate the transducer leftward 20 to 30 degrees. With a multiplane transducer, the best view of the ascending aorta is achieved at 110 to 120 degrees of transducer rotation.

Next, the gastroscope is turned to the right until the longitudinal imaging plane reveals a long-axis cross-section of the superior vena cava and right atrium, an optimal cross-section for locating central venous catheters and sinus venous atrial septal defects (Fig. 31-11 (Figure Not Available) ; Color Plate 31-8). With a biplane probe, the best view of the superior vena cava is obtained by using the appropriate wheel of the gastroscope to angulate the transducer leftward 20 to 30 degrees. With a multiplane transducer, this cross-section is best achieved at 110 to 120 degrees of transducer rotation.

TABLE 31-2 -- Longitudinal Imaging Planes[a]

(Not Available)

From Cahalan [21]

[a] The five basic longitudinal-plane cross-sections are listed along with the depth from the incisors at which they are most commonly found, their anatomic level, the transducer angle for optimal viewing in most patients (multiplane probes only), and their principal use.

Then the gastroscope is turned to the left past the view of the ascending aorta until the longitudinal imaging plane reveals the right ventricular outflow tract and pulmonary artery (Fig. 31-12 (Figure Not Available) ; Color Plate 31-9 (Figure Not Available)). This cross-section is ideal for guiding pulmonary artery catheterization and for detecting pulmonary valvular disorders and some ventricular septal defects. With a biplane probe, the best view of the right ventricular outflow tract and pulmonary artery is obtained by using the appropriate wheel of the gastroscope to angulate the transducer rightward 10 to 30 degrees. With a multiplane transducer, this cross-section is best achieved at 60 to 80 degrees of transducer rotation.

The next longitudinal cross-section is obtained with the transducer at the mid esophageal level (i.e., behind the mitral valve). The operator positions the transducer for either the transverse plane, four-chamber, or five-chamber cross-section (whichever affords the best view of the LV) (see Figs. 31-7 (Figure Not Available) and 31-8; (Figure Not Available) Color Plates 31-4 (Figure Not Available) and 31-5 (Figure Not Available)). Then, one imagines the anterior wall of the LV coming out of the page and the inferior wall behind it. When the imaging

Figure 31-10 (Figure Not Available) Ascending aorta (AsAo) long-axis echocardiogram. This image was obtained with a multiplane transducer rotated to 120 degrees (as indicated by the semicircular icon positioned to the right of the sector scan) to align the ultrasound beam optimally with the ascending aorta. This degree of optimal alignment can usually be attained with a biplane probe as well by angulating the tip of the probe leftward. LA, left atrium; LV, left ventricle; LVOT, LV outflow tract; MV, mitral valve; RVOT, right ventricular outflow tract. *(From Cahalan [21])*

Figure 31-11 (Figure Not Available) Superior vena cava long-axis echocardiogram. This image was obtained with a multiplane transducer rotated to 110 degrees (as indicated by the semicircular icon positioned to the right of the sector scan) to align the ultrasound beam optimally with the superior vena cava. This degree of optimal alignment can usually be attained with a biplane probe as well by angulating the tip of the probe leftward. LA, left atrium; RA right atrium; SVC, superior vena cava. *(From Cahalan [21])*

plane is reoriented from transverse to longitudinal, the heart appears to have rotated 90 degrees, placing the LV anterior wall on the right side of the image and the inferior wall on the left (two-chamber cross-section) (Fig. 31-13 (Figure Not Available) ; Color Plate 31-10 (Figure Not Available)). Often, this cross-section provides the best TEE image of the LV apex. With a biplane probe, the view of the apex is optimized by using the appropriate wheel of the gastroscope to angulate the transducer leftward 10 to 20 degrees. With a multiplane transducer, this view is optimized at 110 to 120 degrees of transducer rotation. Because the LV apex is the furthest cardiac structure from the TEE transducer, it is rarely visualized in sufficient resolution to exclude the presence of a thrombus.

The last longitudinal cross-section in the standard examination is obtained with the transducer in the transgastric position (i.e., mid-LV level). The operator positions the transducer for the transverse plane, midpapillary short-axis cross-section and imagines the mitral valve and left atrium in front of the page and the LV apex behind it (see Fig. 31-9 (Figure Not Available) and Color Plate 31-6 (Figure Not Available)). When the imaging plane is reoriented

Figure 31-12 (Figure Not Available) Right ventricular outflow tract (RVOT) echocardiogram. This image was obtained with a multiplane transducer rotated to 80 degrees (as indicated by the semicircular icon positioned to the right of the sector scan) to align the ultrasound beam optimally with the RVOT and main pulmonary artery (MPA). This degree of optimal alignment can usually be attained with a biplane probe as well by angulating the tip of the probe rightward. AV, aortic valve; LA, left atrium; PV, pulmonary vein; TV, tricuspid valve. *(From Cahalan [21])*

from transverse to longitudinal, the heart appears to have rotated 90 degrees, and the mitral valve and left atrium appear on the right side of the image and part of the LV apex on the left (Fig. 31-14 (Figure Not Available) ; Color Plate 31-11 (Figure Not Available)). This midpapillary long-axis cross-section shows less of the apex than the two-chamber cross-section, but it does not require repositioning of the probe from its usual monitoring position in the midpapillary short-axis cross-section (where changes in LV filling and ejection are most easily detected). Moreover, the midpapillary long-axis cross-section may reveal basal and sometimes apical segmental dysfunction missed if only the midpapillary short axis is monitored.

Although the basic TEE examination outlined earlier reveals most of the essential information available from TEE,

Figure 31-13 (Figure Not Available) Two-chamber echocardiogram. This image was obtained with a multiplane transducer rotated to 90 degrees (as indicated by the semicircular icon positioned to the right of the sector scan). Note the left atrial appendage (LAA). It overhangs the anterior wall of the left ventricle (LV). The other ventricular wall seen in this cross-section is the inferior wall. LA, left atrium; MV, mitral valve. *(From Cahalan [21])*

Figure 31-14 (Figure Not Available) Midpapillary long-axis echocardiogram. This image was obtained with a biplane probe. Part of the left ventricular inferior (top of image) and anterior (opposite wall) walls are seen. The apex is not seen. The posterior medial papillary muscle (PMPM) gives rise to the chordae tendineae supporting the anterior leaflet of the mitral valve (MV). Between the posterior leaflet and the anterior ventricular wall, the left ventricular outflow tract is particularly well seen in this patient. Often it is not seen in this cross-section, but it can be well evaluated in other cross-sections such as the five-chamber view. The anterior lateral papillary muscle is not seen in this patient, because it lies posterior to the midline of this ventricle. In fact, in this cross-section, both papillary muscles are usually not seen, because they are usually not located exactly opposite each other on the anterior and inferior ventricular walls. LA, left atrium; LV, left ventricle. *(From Cahalan*

[21])

additional cross-sections often are required to resolve specific questions. For example, withdrawing the transverse plane transducer approximately 2 to 3 cm above the aortic valve level reveals the main pulmonary artery and its bifurcation. At this level, pulmonary artery flow is almost directly parallel to the ultrasound beam, permitting Doppler estimates of true blood flow velocity for evaluation of pulmonic stenosis or regurgitation and for calculation of cardiac output (see later). Midway between this cross-section and the aortic valve short-axis cross-section, the entrance of the left superior pulmonary vein can be imaged by rotating the probe approximately 45 degrees to the left. PW Doppler measurements of blood flow velocities in this vein provide estimates of left atrial filling pressure or of the severity of mitral regurgitation (see later). Rotation of the probe further leftward reveals the descending aorta. By insertion and withdrawal of the probe from this position, the descending aorta and parts of the transverse arch can be imaged using both transverse and longitudinal transducer orientations. The presence and extent of dissection, atheroma, and thrombi in the descending aorta can be evaluated reliably. The last of the most commonly useful additional crosssections is achieved by advancing the transversely oriented transducer well into the patient's stomach and then flexing the tip of the gastroscope to its maximum extent. If the probe is well into the stomach, maximum flexion will require very little force on the wheel of the gastroscope. Then the operator gently withdraws the probe until feeling resistance at the gastroesophageal junction, where an inverted five-chamber cross-section is achieved (deep gastric five-chamber).

In this cross-section, the ultrasound beam is parallel to the blood flow through the LV outflow tract and aortic valve facilitating Doppler estimation of cardiac output or of the degree of aortic stenosis (see later). Further details on TEE cross-sections can be found in standard echocardiography texts or multimedia CD-ROM. [11] [12] [13] [14] [21]

Essential Precautions

TEE poses very little risk if it is properly performed. Although anesthesiologists are highly skilled in instrumentation of the airway and esophagus, some special precautions need to be observed to minimize the chances of injury caused by TEE. First, if the history and physical examination suggest esophageal disease, the potential benefits of TEE must clearly outweigh the apparent risks, or TEE should be abandoned. Second, the TEE probe should be inspected prior to each use, and if defects are detected (i.e., cracks in the transducer housing or shaft of the gastroscope), the probe must not be used, but instead sent for repairs. Each manufacturer supplies maintenance and service recommendations that should be incorporated into the departmental quality assurance program. Third, when the TEE probe is advanced or withdrawn in the patient's esophagus, the control wheels of the gastroscope should be in their neutral positions and left unrestrained. These wheels have locking devices that must be unlocked during probe movements. Fourth, if the probe meets resistance in the esophagus, it should not be forced to advance further. Rarely, repositioning of an abdominal or thoracic retractor relieves the resistance. Otherwise, the operator should suspect esophageal disease and should abandon the TEE examination. Alternatively, esophagoscopy can be performed to determine the safety of persisting in efforts to pass the TEE probe. Last, when the TEE probe is to remain in one position for an extended period, the ultrasound energy (transmitting power of the transducer) and mechanical deflection of the probe tip (i.e., flexion, retroflexion, and angulation) should be minimized. Ideally, the wheels of the gastroscope should not be locked for extended periods, in order to prevent extremes of mechanical deflections from inadvertently persisting.

HEMODYNAMIC DETERMINATIONS

Preload

TEE provides high-resolution images that depict the extent of LV filling. For instance, in 30 patients scheduled for cardiac surgery, Cheung et al [22] removed 15 percent of each patient's blood volume (in 6 equal aliquots) prior to cardiopulmonary bypass while monitoring the midpapillary short-axis cross-section with TEE. A significant decrease in LV end-diastolic area was detected after removal of the first aliquot (2.5% of the estimated blood volume or about 200 mL). With subsequent aliquots, end-diastolic area decreased linearly (0.3 cm^2 /1.0% of blood volume removed), such that, after removal of all 6 aliquots, the end-diastolic area had decreased by 27 percent in patients with normal LV function and by 21 percent in patients with depressed LV function. Although the pulmonary artery occlusion pressure and central venous pressure also declined during the study, the correlation with end-diastolic area was very weak or nonexistent, indicating marked differences in LV compliance.

In settings in which LV compliance changes, TEE may be the only practical method to assess preload adequately. For instance, Harpole et al [23] studied patients undergoing resection of abdominal aortic aneurysm in whom intraoperative echocardiograms, pulmonary artery pressures, and first-pass radionuclide data were recorded simultaneously. The correlation between echocardiographic and radionuclide estimates of preload and ejection was excellent. Virtually no correlation was found between estimates from either of these techniques and pulmonary artery pressures. Thus, TEE, but not pulmonary artery catheterization, provides a direct, quantitative method to assess changes in LV preload in patients with changing LV compliance.

However, absolute measurement of LV volumes is more difficult with TEE, because TEE rarely reveals the true apex of the LV. Without this landmark, the LV long-axis dimension must be empirically assigned, or foreshortened estimates must be accepted. For instance, Smith et al [24] studied 36 patients undergoing LV angiography and TEE. These investigators used the LV long-axis dimension measured in the 4-chamber cross-section. Although they found good correlation between the estimates of LV volumes from angiography and TEE, TEE consistently underestimated absolute volumes, because it underestimated the long-axis dimension. Use of the longitudinal plane, 2-chamber cross-section should improve TEE estimates of the LV long-axis dimension and thereby should improve absolute estimates of LV volumes, but, to date, no study has definitely proven this assertion.

Hypotension

When a sudden, severe change in hemodynamics occurs, qualitative estimates of LV filling and ejection serve as the practical guide for administration of fluids and inotropes. With some ultrasonographs, computer technology converts the echocardiographic images from one cardiac cycle into digital code and then plays this cycle repetitively to allow side-by-side comparison with other cardiac cycles captured at other times during surgery. With this technology, an experienced observer consistently can detect decreases in preload before they result in greater than a 10 percent decrease in blood pressure. [25] This technology also facilitates qualitative assessment of changes in LV ejection and prompts differential diagnosis of the cause of hypotension. For example, severe hypovolemia is easily recognized as a marked decrease in LV end-diastolic area with a marked increase in LV ejection fraction, and LV failure is seen as a marked increase in LV end-diastolic area and marked decrease in LV ejection fraction. During hypotension, arterial vasodilatation, aortic regurgitation, mitral regurgitation, and ventricular septal defect can manifest the same LV filling and ejection pattern at the midpapillary short-axis cross-section: adequate LV end-diastolic filling area with increased LV ejection fraction. Fortunately, distinguishing among these causes of hypotension is not difficult using other cross-sections and color Doppler (see subsequent sections). Table 31-3 (Table Not Available) summarizes the most

TABLE 31-3 -- Origin of Hypotension[a]

(Not Available)

From Cahalan [21]

[a] Obviously, other problems can cause hypotension, but the ones listed here include the most common occurring in the operating room. Two important caveats need to be mentioned. First, low systemic vascular resistance and hypovolemia sometimes occur simultaneously (for instance, in sepsis), and until hypovolemia is treated, low systemic vascular resistance will not be apparent. Second, one cannot assume that just because the papillary muscles meet during systole (i.e., LV cavity obliteration) the patient is hypovolemic. This finding can occur in either low systemic vascular resistance or hypovolemia. To make this differential diagnosis correctly, one must determine whether diastolic filling is adequate.

common causes of hypotension and their echocardiographic characteristics at the midpapillary short-axis cross-section.

Consider two dramatic examples of the value of TEE in hypotensive patients. First, Reichert et al [26] used TEE in 60 consecutive patients with severe, persistent hypotension following cardiac surgery. In one-half of these patients, TEE demonstrated that the presumed cause of the hypotension was incorrect. Indeed, in 5 patients, unnecessary reoperations were prevented because TEE correctly revealed that tamponade was not present despite hemodynamic data suggesting it. Second, Heidenreich et al [27] compared transthoracic echocardiography and TEE in 61 consecutive patients who experienced more than 1 hour of severe hypotension during their care in a combined surgical and medical intensive care unit. The echocardiographic results were immediately revealed to the attending physician, who determined whether any change in therapy was indicated. Based on these results, the cause of each patient's hypotension was classified as nonventricular (i.e., valvular or pericardial), ventricular (i.e., failure), or noncardiac (i.e., hypovolemia or low systemic vascular resistance). Transthoracic echocardiography and TEE were diagnostically adequate in 36 and 97 percent of the patients, respectively. When nonventricular conditions were diagnosed as the cause of the hypotension, patient survival (81%) was almost twice as likely as when ventricular (41%) or noncardiac causes (44%) were revealed. Moreover, TEE revealed clinically significant new findings missed by transthoracic echocardiography in 28 percent of patients leading to surgery in 20 percent of the patients. These two prospective studies and other retrospective studies confirm the diagnostic and prognostic value of TEE in patients with severe, persistent hypotension. [26] [27] [28] [29]

Cardiac Output

Real-time images of LV filling and ejection permit qualitative, immediate assessment of marked changes in cardiac output. However, with PW and CW Doppler, TEE can quantify cardiac output. A Doppler measurement of blood flow velocity is combined with a 2-D measurement of cross-sectional area:

Cardiac output = VTI × CSA × costheta × heart rate

where VTI is the velocity time integral (the area under the Doppler-derived velocity versus time curve per systole), CSA is the cross-sectional area through which the velocity passes, and costheta is the cosine of the angle between the ultrasound beam and the blood flow (usually the angle is assumed to be zero degrees so that this factor equals unity and can be disregarded). Initial studies of flow in the main pulmonary artery and across the mitral valve compared with thermodilution-derived estimates yielded somewhat disappointing results. [30] Subsequent comparisons, when patients with tricuspid regurgitation were excluded (tricuspid regurgitation confounds thermodilution measurements), when CW Doppler was used from a deep gastric five-chamber cross-section, and when multiplane or biplane capabilities were exploited, suggest that TEE should have a bias of near zero and limits of agreement of less than 1 L/min for measurement of cardiac output. [31] [32] [33] [34]

Left Ventricular Filling Pressure

Surprisingly, TEE provides practical ways to estimate LV filling pressure. Placing the Doppler cursor at the junction of the left atrium and the left superior pulmonary vein, Kuecherer et al [35] demonstrated that a systolic fraction of flow of less than 55 percent was a specific and sensitive sign of left atrial pressure greater than 15 mm Hg. This sign is easily detected as predominance of flow during diastole [36] (Figs. 31-15 (Figure Not Available) and 31-16) (Figure Not Available) . Significant mitral regurgitation, the presence of nonsinus rhythm, and extremes of cardiac output affect pulmonary venous flow and therefore limit this application of TEE. [37] Alternative methods have been described that obviate these limitations. [38] [39] Accordingly, TEE cannot estimate left atrial pressure precisely, but it can reliably identify clinically significant elevations.

Left Ventricular Contractility

Measuring LV contractility is much more difficult. The LV fractional area change measured at the midpapillary short-axis cross-section is a reasonable approximation of LV ejection fraction, but the ejection fraction is clearly afterload dependent and should be viewed cautiously as an index of overall ventricular performance. However, LV ejection fraction is an excellent predictor of survival in patients with coronary artery disease and is widely used in the perioperative assessment of high-risk patients.

Left Ventricular Afterload

TEE provides a better estimate of LV afterload, endsystolic wall stress (which incorporates LV systolic dimension, pressure, and wall thickness) than is possible with other intraoperative monitors. Moreover, TEE-determined wall stress and intraoperative myocardial ischemia are strongly associated. In a study of patients undergoing carotid endarterectomy, systolic blood pressure and heart rate were maintained at ward level in all patients using phenylephrine

---

Figure 31-15 (Figure Not Available) Normal pulmonary venous flow pattern. Pulsed-wave Doppler measurement of normal blood flow velocities in the left upper pulmonary vein (LUPV) is shown. At the top of the figure is a still-frame image of the two-dimensional cross-section used to position the Doppler sample volume (white sphere). On the bottom two-thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electrocardiogram (ECG) is shown for timing purposes. The horizontal line through the base of the Doppler tracing is the baseline (zero flow) for the flow velocities. Flow velocities above the line are positive (i.e., toward the transducer) to a maximum of 69 cm/s. Flow below the line is negative (i.e., away from the transducer) to a maximum of -32 cm/s. In this patient with normal left atrial pressure, systolic predominance of flow is evident; that is, more flow enters the atrium during the period of ventricular systole than during ventricular diastole, as evidenced by the greater peak and average flow velocities during systole than during diastole. LA, left atrium. *(From Cahalan [21])*

in one group and "light" anesthesia in the other. [40] Endsystolic wall stress was 40 percent greater and the incidence of ischemia was 2.5-fold higher in the phenylephrine group (because of LV distention and wall thinning), findings indicating the importance of afterload as a determinant of oxygen demand and myocardial ischemia.

DETECTION OF MYOCARDIAL ISCHEMIA

Intraoperative Transesophageal Echocardiography Versus Electrocardiography

Since Tennant and Wiggers [41] first described the association of segmental wall-motion abnormalities (SWMA) and ischemia, many other investigators have demonstrated that ischemic segments of human and animal heart do not exhibit normal inward wall motion or thickening during systole (Chs. 32 and 49) . During acute myocardial ischemia, SWMA precede and may occur in the absence of electrocardiographic (ECG) changes. [42] [43] [44] [45] In 50 patients undergoing coronary artery or major vascular surgery, echocardiographic and 7-lead ECG (3 limb leads, 3 augmented leads, and V_5) studies revealed new intraoperative SWMA diagnostic of myocardial ischemia (marked decrement in LV segmental motion and thickening) in 24 patients, compared with ischemia-indicative ST-segment changes (>0.1 mV deviation) in only 6 patients. [45] SWMA occurred minutes before the ECG change in 3 of these 6 patients, and no ST-segment change occurred before or without new SWMA. Similarly, 3 of 50 patients who sustained intraoperative myocardial infarctions developed SWMA that persisted until the end of surgery in the corresponding area of myocardium, but only 1 of 3 had ischemic ST-segment changes. Four of 5 patients with double-vessel disease developed SWMA in regions of myocardium supplied by the diseased coronary arteries, not in the "risk-free" myocardium. Of 10 study patients without coronary disease, none had ST-segment changes or SWMA. Subsequent studies in similar patients confirmed these results. [46] [47]

However, in noncardiac surgical patients at risk for coronary artery disease, investigators comparing TEE, 2-lead Holter monitoring, and 12-lead continuous ECG monitoring found that 2-lead Holter monitoring detected almost twice as many episodes of ischemia as the 12-lead ECG or TEE. [48] The apparently superior sensitivity of 2-lead Holter monitoring likely is due to differences between the TEE and ECG protocols and the patient population; that is, the 2-lead Holter and 12-lead ECG were monitored continuously, whereas TEE was evaluated only intermittently, and TEE images were analyzed by review of videotape recordings, not by the more reliable technique of cine loop analysis. Additionally, only about one-half of these patients had proven coronary artery disease, a factor critical in interpreting the results, because as the prevalence of a disease decreases

Figure 31-16 (Figure Not Available) High left atrial (LA) pressure produces diastolic predominance in the pulmonary venous flow pattern. Pulsed-wave Doppler measurement of blood flow velocities in the left upper pulmonary vein (LUPV) in a patient with abnormally high LA pressure is shown. At the top of the figure is a still-frame image of the two-dimensional cross-section used to position the Doppler sample volume (white sphere). On the bottom two-thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in that sample volume. The electrocardiogram (ECG) is shown for timing purposes. The horizontal line through the base of the Doppler tracing is the baseline (zero flow) for the flow velocities. Flow velocities above the line are positive (i.e., toward the transducer) to a maximum of 80 cm/s. Flow below the line is negative (i.e., away from the transducer) to a maximum of -44 cm/s. In this patient with abnormally high LA pressure, diastolic predominance of flow is evident; that is, more flow enters the atrium during the period of ventricular diastole than during ventricular systole as evidenced by the greater peak and average flow velocities during diastole than during systole. The negative flow velocities are due to atrial contraction pushing blood back into the pulmonary vein. *(From Cahalan [21])*

in a population, the risk of false-positive findings increases. For example, 2-lead Holter monitoring reveals ST-segment changes diagnostic of ischemia in 7 percent of healthy young adults and in 26 percent of healthy young adults given digitalis. [49] [50] Thirteen percent of patients in the study just described were receiving digitalis.

Limitations of Transesophageal Echocardiography for Ischemia Detection

Even when an area of myocardium is clearly in view, segmental contraction can be difficult to evaluate if the entire heart rotates or translates markedly during systole or if discoordinated contraction results from bundle branch block or ventricular pacing. Consequently, a valid system for SWMA assessment first must compensate for global motion of the heart (typically by using a "floating" frame of reference), then evaluate both regional endocardial motion and myocardial thickening. A worsening of segmental wall motion and wall thickening (in the absence of similar global changes) of at least two classes (Table 31-4) (Table Not Available) is required to make the diagnosis of ischemia; less pronounced changes are not interpreted consistently, even by experts.

Interpretation of septal motion is the most problematic because septal motion is often confounded by discoordinated contraction patterns. However, a simple rule applies: when the septum is viable and nonischemic, it thickens appreciably during systole, although its inward motion may begin slightly before or after inward motion of the other ventricular segments. Thus, new SWMA can be detected

TABLE 31-4 -- Classes of Segmental Wall Motion and Thickening [a]

(Not Available)

From Cahalan [21]

[a] Assessment of segmental wall motion is subjective, but this grading system helps to limit the variability among readers by defining categories of inward endocardial motion and myocardial thickening. "Change in radius" refers to the percentage of change during systole in the radius from the endocardium to the imaginary center of the left ventricle. Because normal myocardial thickening is 2 to 5 mm and inward endocardial motion is 5 to 10 mm, thickening is more difficult to assess than endocardial motion. Nevertheless, thickening is the more reliable guide to myocardial function, because it is unaffected by variables that confound assessment of endocardial motion: translational motion of the heart, conduction abnormalities, and ventricular pacing. In the absence of these variables, endocardial motion usually is an adequate indicator of the function of the underlying myocardium.

during bundle branch block, ventricular pacing, and marked global movements of the heart, but not by assessment of endocardial motion alone.

Owing to biologic differences in healthy patients, not all hearts contract normally, and not all parts of the same heart contract to the same degree. [51] Consequently, not all SWMA are indicative of myocardial ischemia. For example, myocardial infarction and myocarditis can cause SWMA. However, an acute decrease or cessation of segmental contraction, such as new intraoperative SWMA, is almost always due to myocardial ischemia. The few exceptions to this rule are noted in the next few paragraphs.

One exception to this rule is myocardial stunning, or prolonged, postischemic ventricular dysfunction. [52] When ischemia has been prolonged, full restoration of blood flow may occur minutes to hours before return of normal segmental contraction. Does a new SWMA detected immediately after bypass represent inadequate revascularization and ongoing ischemia, or is it stunned myocardium from inadequate cooling during bypass? Differentiating this cause is important: inadequate revascularization may require placement of additional grafts, whereas stunned myocardium requires only supportive measures until its function returns.

Echocardiographic contrast agents can delineate myocardial blood flow, [53] but, to date, they have not been proven to do so reliably in stunned myocardium. Fortunately, stress echocardiography may be an alternative approach: moderate to high doses (
40 mug/kg) of dobutamine may improve segmental function in chronically stunned but not infarcted myocardium. [54] [55] [56] Intraoperative studies confirming these findings in acutely stunned myocardium are needed. In the meantime, when stunned myocardium is suspected following cardiopulmonary bypass, graft status should be reevaluated, and segmental myocardial function should be closely monitored for signs of improvement. If worsening occurs, if graft status is questionable, or if the patient's hemodynamic status is tenuous, additional revascularization should be considered.

Acute SWMA also may be due to unmasking areas of scarring by changes in LV afterload; that is, a marked increase in blood pressure may retard contraction more in an already damaged segment of myocardium than in a normal segment. However, this is an unlikely explanation for the acute SWMA reported in intraoperative studies to date. First, most new SWMA have occurred in segments of myocardium with normal contraction at baseline (after induction of anesthesia). Second, only marked changes in segmental contraction are judged indicative of ischemia. It is difficult to imagine that a sudden increase in afterload would cause one segment to cease or nearly cease contracting in the absence of changes in the other segments. Buffington and Coyle and others [57] [58] used an animal model to test the effects of extreme increases in afterload and demonstrated changes so minimal that they are unlikely to be detected with TEE. Third, with one exception (see next paragraph), there is no consistent correlation between hemodynamics and new SWMA.

The one exception was noted by Seeberger et al [59] during an experimental intraoperative stress-testing protocol. They observed new SWMA during marked preload reduction resulting from rapid atrial pacing in patients with baseline SWMA (presumably from prior infarction). Although some of the new SWMA induced in this protocol were due to myocardial ischemia (they had associated ST-segment changes and/or they persisted briefly after restoration of normal preload), others appeared not to be due to ischemia (no ST-segment changes and immediate resolution with restoration of preload). In a follow-up study using rapid phlebotomy, these investigators confirmed that sudden preload reduction can induce acute, nonischemic SWMA in patients with existing SWMA. [60] Thus, when a new SWMA is suspected and preload is markedly reduced, restoration of preload should be attempted prior to definitive assessment of segmental function.

DETECTION OF CARDIOVASCULAR DISORDERS

Aortic Pathology

Unlike most other sophisticated diagnostic tests, TEE can be performed rapidly at the patient's bedside or during surgery (Ch. 49) . As a result, TEE may be the diagnostic test of choice in patients with suspected aortic injury or aortic dissection. In 160 consecutive victims of blunt chest trauma, TEE correctly identified aortic injury in 14 patients and suggested it in 2 others, while producing no false-positive diagnoses. [61] In contrast, aortography required more time and produced one false-positive and four false-negative diagnoses. Moreover, TEE reliably differentiates two distinct patterns of injury: subadventitial disruptions, which require emergency surgery; and intimal tears, which do not. [62] However, TEE's diagnostic value in this clinical setting may depend on the operator or the patient population. [63] [64] [65]

For the detection of aortic dissection, TEE has proven superior to aortography and computed tomography. [66] [67] Although marginally less specific than magnetic resonance imaging for some dissections (those originating in the aortic arch), TEE requires less time and expense. [68] In patients with aortic dissection, delays in treatment can be fatal. However, TEE does not consistently image the origins of the innominate and left carotid arteries. Because of this limitation, TEE has only a 60 percent sensitivity for detection of arch vessel involvement in dissection, compared with 94 percent sensitivity for spiral computed tomography. [69]

In 130 patients older than 65 years who were undergoing coronary artery bypass grafting, TEE detection of protruding atheroma of the ascending aorta proved the only independent predictor of stroke--not age, previous stroke, carotid bruit, transient ischemic attacks, or surgical palpation of the ascending aorta. [70] In a related study, TEE detected protruding atheroma of the ascending aorta in ten patients scheduled for cardiopulmonary bypass: three of the six patients undergoing customary cardiopulmonary bypass sustained strokes, in contrast to none of the remaining four patients in whom surgical management was altered to circulatory arrest and aortic debridement. [71] Less aggressive approaches to this problem include alteration of the cannulation site to avoid "sand blasting" of the atheroma and raising the patient's blood pressure (50-90 mm Hg) during cardiopulmonary bypass to supply better collateral flow should cerebral embolus occur. [72] [73] Although one study indicated that TEE is not as sensitive as epiaortic scanning for detection

of atheromas of the aortic arch, it is an excellent screening tool: if TEE reveals no significant atheromas in the ascending or descending aorta, none are likely to be present in the aortic arch. [74] [75] Moreover, TEE-detected atheromatous disease of the descending aorta is a better predictor of significant coronary artery disease than conventional risk factors. [76]

Valvular Pathology

Intraoperatively, TEE commonly refines the preoperative diagnosis and reveals new findings with major implications. In 5 of 182 patients scheduled for coronary artery surgery, intraoperative TEE detected unsuspected mitral regurgitation so severe that it required unscheduled mitral valve repair. [77] Conversely, TEE performed before cardiopulmonary bypass revealed so little mitral valve dysfunction that mitral repair was omitted in 22 of 51 patients scheduled for combined coronary artery and mitral valve surgery. However, detailed assessment of valvular function can be very challenging, even for the most experienced echocardiographers. Nevertheless, with a modest degree of training, severe abnormalities are recognized readily with the help of color Doppler (see later). Comprehensive coverage of this topic is included in standard textbooks of echocardiography. [12] [13] [14] [78] [79] [80]

The degree of aortic stenosis is easily appreciated in the transverse plane, aortic valve short-axis cross-section in which the extent of leaflet opening sometimes can be directly measured with planimetry. [81] [82] [83] Multiplane TEE provides marginally more accurate assessment of anatomy and valve area than single-plane TEE, because with multiplane TEE the ultrasound beam can be more precisely aligned with the short axis of the aortic annulus than can be done with single-plane TEE, [84] but both reliably detect severe stenosis. [85] [86] Doppler studies in this cross-section reveal turbulence above the valve and in the sinuses of Valsalva, but they cannot quantify severity because blood flow is perpendicular to the ultrasound beam. In contrast, the transgastric five-chamber cross-section allows excellent alignment of the beam with blood flow for determination of the gradient across the valve [87] (Fig. 31-17) (Figure Not Available) . Additional information on the morphology of the aortic valve can be garnered from the longitudinal plane, ascending aorta cross-section.

Even modest degrees of aortic regurgitation can be clinically significant during cardiac surgery, producing LV distention during cardiopulmonary bypass and diminishing the effectiveness of antegrade cardioplegia. [88] With color Doppler, aortic regurgitation is easily recognized using the transverse plane, five-chamber cross-section (Table 31-5) (Table Not Available) . Mild regurgitation is characterized by a narrow-based, diastolic color jet (<2 mm at its origin in the valve) that occupies less than one-third of the cross-sectional area of the LV

Figure 31-17 (Figure Not Available) Continuous-wave Doppler estimation of aortic valve (AV) gradient. Continuous-wave Doppler measurement of blood flow velocities immediately above the AV during seven cardiac cycles is shown. At the top of the figure is a still-frame image of the two-dimensional cross-section used to position the Doppler sample cursor (diagonal white line). On the bottom two-thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor. The electrocardiogram is shown for timing purposes, and the gray horizontal line running through the Doppler tracing is the baseline (zero flow) for the flow velocities. With this Doppler alignment, all flow velocities are negative (i.e., away from the transducer). The Doppler scale has been set to a maximum of -629 cm/s, and this tracing documents significant aortic stenosis: a peak blood flow velocity of approximately 4 m/s (each white dot on the vertical axis equals 100 cm/s or 1 m/s) corresponding to a peak gradient across the AV of 64 mm Hg. LV, left ventricle. *(From Cahalan [21])*

TABLE 31-5 -- Simplified Grading Criteria for Aortic Insufficiency [a]

(Not Available)

From Cahalan [21]

[a] Diastolic jet width is assessed with color Doppler in the five-chamber view at the closure point of the aortic valve (the origin of the regurgitant jet). The transducer should be repositioned until the origin of the jet is clearly imaged. Failure to image the origin of the jet may lead to overestimation of its severity. Diastolic jet area is assessed with color Doppler in the five-chamber view. % of LVOT is the percentage of the LVOT occupied by the plume of the color jet (the area of turbulent flow depicted by the mosaic of color pixels). This parameter is markedly affected by aortic diastolic pressure. Failure to adjust color or two-dimensional gains correctly may lead to underestimation or overestimation of the severity of the regurgitation. Color gain should be set just below the level that results in random color sparkle, and two-dimensional gains should be set at the minimum levels allowing adequate visualization of cardiac structures. Diastolic jet depth is assessed with color Doppler in the 5-chamber view. The length of penetration of the jet from the LVOT into the LV is estimated in centimeters. This parameter is also markedly affected by aortic diastolic pressure and gain settings.

outflow tract and extends minimally into the LV (1-2 cm). Moderate regurgitation is a broader-based, diastolic color jet (3-5 mm) occupying less than two-thirds of the cross-sectional area of the LV outflow tract and extending moderately into the LV (3-5 cm). Severe regurgitation is a broad-based, diastolic color jet (>5 mm) occupying all the LV outflow tract and extending well into the LV (Color Plate 31-12 (Figure Not Available)). If the LV outflow tract is not visible in the five-chamber view because of an intervening mitral prosthesis, the longitudinal cross-section of the ascending aorta or the transgastric five-chamber cross-section may be excellent alternative views for the evaluation of aortic regurgitation.

The presence and severity of mitral stenosis are easily determined with TEE using the transverse plane, four- or five-chamber cross-sections and the longitudinal plane, two-chamber and midpapillary long-axis cross-sections. 2-D imaging reveals thickened leaflets that dome toward the LV and open poorly. Color Doppler reveals laminar flow acceleration into the stenotic orifice and a turbulent jet emerging into the ventricle (Color Plate 31-13 (Figure Not Available)). PW and CW Doppler traces display a characteristic flow pattern with increased peak and mean velocities (Fig. 31-18) (Figure Not Available) . Although mathematical evaluation of these traces is the most precise method to

Figure 31-18 (Figure Not Available) Continuous-wave Doppler evaluation of mitral stenosis. Continuous-wave Doppler measurement of blood flow velocities through a stenotic mitral valve is shown. At the top of the figure is a still-frame image of the four-chamber cross-section used to position the Doppler cursor. On the bottom two-thirds of the figure is the display in white of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring anywhere along that cursor. The electrocardiogram (ECG) is shown for timing purposes. The horizontal line through the base of the Doppler tracing is the baseline (zero flow) for the flow velocities. Velocities displayed above the baseline are positive and represent flow toward the transducer. These velocities are due to mitral regurgitation and are so high they exceed the scale used in this example. Velocities displayed below the baseline are negative and represent flow away from the transducer. These velocities are due to severe mitral stenosis and average about 2 m/s indicating a gradient across the mitral valve of 16 mm Hg. Also note how slowly the flow velocity decreases after the peak of the E wave (indicated in the figure by "Slope"). The pressure half-time can be calculated from this slope and is markedly increased in the presence of severe mitral stenosis. *(From Cahalan [21])*

assess the severity of mitral stenosis, [15] [16] [89] no mathematics is required to recognize severe mitral stenosis. In addition to the signs noted earlier, severe mitral stenosis always causes marked left atrial enlargement and left atrial spontaneous contrast. Spontaneous contrast is a swirling, smoke-like appearance of 1- to 2-mm densities not due to exogenously administered contrast agents, but to aggregation of red cells in areas of low flow. Whenever left atrial enlargement and spontaneous contrast are noted, thrombus in the left atrium and, in particular, in the left atrial appendage should be suspected and excluded. [90] [91] [92] [93] [94]

The presence and severity of mitral regurgitation are evaluated from the same cross-sections used for evaluation of mitral stenosis and with the same grading strategy used for aortic regurgitation (Table 31-6) (Table Not Available) . Mild regurgitation is characterized by a narrow-based, systolic color jet (<2 mm at its origin in the valve) that occupies less than 25 percent of the left atrial cross-sectional area and extends less than half of the distance to the posterior wall of the left atrium. Moderate regurgitation is a broader-based, systolic color jet (3-5 mm at its origin in the valve) occupying less than 50 percent of the left atrial cross-sectional area and extending 50 to 90 percent of the distance to the posterior wall of the left atrium. Severe regurgitation is a broad-based, systolic color jet (>5 mm) occupying most of the left atrium and extending into the pulmonary veins and left atrial appendage [95] [96] [97] [98] (Fig. 31-19) (Figure Not Available) .

TABLE 31-6 -- Simplified Grading Criteria for Mitral Regurgitation [a]

(Not Available)

From Cahalan [21]

[a] Systolic jet width is assessed with color Doppler in the five- or four-chamber view at the closure point of the mitral valve (the origin of the regurgitant jet). The transducer should be repositioned until the origin of the jet is clearly imaged. Failure to image the origin of the jet may lead to overestimation of its severity. Systolic jet area is assessed with color Doppler in the five- or four-chamber view. $\%LA_a$ is the percentage of the LA_a occupied by the plume of the color jet (the area of turbulent flow depicted by the mosaic of color pixels). This parameter is markedly affected by left ventricular systolic pressure. Failure to adjust color or two-dimensional gains correctly may lead to underestimation or overestimation. Color gain should be set just below the level that results in random color sparkle, and two-dimensional gains should be set at the minimum levels allowing adequate visualization of cardiac structures. Systolic jet depth is assessed with color Doppler in the five- or four-chamber view. $\%LA_d$ is the depth of the penetration of the jet into the LA expressed as a percentage of the distance from the mitral annulus to the posterior wall of the left atrium. This parameter is also markedly affected by left ventricular systolic pressure. In severe mitral regurgitation, the regurgitant jet may extend into one or more pulmonary veins and may cause transient reversal of pulmonary venous blood flow.

Figure 31-19 (Figure Not Available) Pulmonary vein flow reversal and severe mitral regurgitation. Pulsed-wave Doppler measurement of blood flow velocities in the left upper pulmonary vein (LUPV) is shown. At the top of the figure is a still-frame image of the two-dimensional cross-section used to position the Doppler sampling volume (white circle). On the bottom two-thirds of the figure is the display of the instantaneous blood flow velocities (vertical axis) versus time (horizontal axis) occurring in the LUPV. The electrocardiogram (ECG) is shown for timing purposes, and the horizontal line running through the Doppler tracing is the baseline (zero flow) for the flow velocities. Velocities displayed above the baseline are positive and represent flow toward the transducer (in this case, into the left atrium [LA]). Velocities displayed below the baseline are negative and represent flow away from the transducer (in this case, into the LUPV). This Doppler tracing documents systolic flow reversal (normally it is positive, that is, toward the LA in systole) and confirms the presence of severe mitral regurgitation. *(From Cahalan [21])*

Figure 31-20 (Figure Not Available) Severe mitral regurgitation with wall-hugging jet. This honed-down five-chamber echocardiogram reveals severe mitral regurgitation. The long color jet (depicted in gray in this image) has a fairly broad base and an eccentric direction indicating severe mitral regurgitation. Wall-hugging jets such as this one have a small cross-sectional area because much of their energy is absorbed by the wall of the atrium. The mechanism of the regurgitation is apparent: the anterior leaflet (on the left side of the video screen) is prolapsing, allowing blood to escape beneath it and to jet over the surface of the posterior leaflet into the left atrium (LA). LV, left ventricle; MV, mitral valve. *(From Cahalan [21])*

Eccentrically directed jets of mitral regurgitation that hug the wall of the atrium generally are associated with more severe valvular regurgitation than their cross-sectional area may suggest [99] (Fig. 31-20) (Figure Not Available) . Moreover, eccentrically directed jets usually point away from the defective leaflet (i.e., laterally directed jets usually are associated with anterior leaflet defects, and medially directed jets are associated with posterior leaflet defects). [100]

The general guidelines listed earlier are widely used, but at least 20 more criteria have been described for assessment of mitral regurgitation. [101] Most important, the degree of regurgitation may be exquisitely dependent on LV loading conditions and papillary muscle perfusion. For practical purposes, quantitative measures of the regurgitant orifice area, for example, calculations based on the theory of proximal isovelocity surface area (PISA) are rarely used in most operating rooms, because they are too time-consuming and require meticulous technique. [102] Fortunately, simply using the width of the base of the regurgitant jet (as described earlier) may be more accurate in estimating mitral regurgitation severity and may be less susceptible to alterations in loading conditions than other more complicated methods. [103] [104] Pulmonary and tricuspid valve disorders are assessed in a fashion analogous to that just described for the aortic and mitral valves.

ASSESSMENT OF SURGICAL REPAIRS

Adults

TEE has profoundly affected valvular heart surgery (Chs. 49 and 50) . It provides the surgical team with a definitive evaluation of valvular function immediately before and after the surgical intervention, thereby allowing surgery to be revised if necessary and flawed repairs to be corrected before leaving the operating room. Morbidity and mortality are reduced if the patient leaves the operating room with the most appropriate and properly functioning repair. In a study of 154 patients undergoing valve surgery at Duke University in Durham, North Carolina, [105] TEE detected new findings that changed the surgical plan prior to cardiopulmonary bypass in 29 patients (19%). The most common new finding of major importance was detection of unsuspected valvular insufficiency in seven patients (5%) resulting in unscheduled surgery of the affected valves. Other findings with major surgical implications included unsuspected left atrial thrombi (three patients), unsuspected atrial septal defects (two patients), and unsuspected ascending aortic dissection (one patient). In one other patient, TEE revealed adequate mitral function, and the scheduled mitral operation was canceled. Following cardiopulmonary bypass, TEE documented unsatisfactory repairs in ten patients (6%) resulting in immediate further surgery. Although six of these patients had abnormal V waves or elevated pulmonary capillary wedge pressures, four patients had normal hemodynamics, and their defective repair was detected only by TEE. At the conclusion of surgery, TEE revealed adequate valvular function in 123 patients (80%): 18 of these patients (15%) suffered a major postoperative complication, and 6 died (5%). In contrast, TEE revealed moderate valve dysfunction in seven (5%) patients: six of these patients suffered major complications (86%), and three died (50%).

In a similar study at the Mayo Clinic in Rochester, Minnesota, [106] TEE detected 3+ mitral regurgitation after the first attempt at mitral valve repair in 11 (8%) of 143 patients and severe systolic anterior motion of the mitral leaflet in 13 (9%) patients. This motion of the mitral leaflet refers to an abnormal, septally directed motion of the anterior mitral leaflet during systole (best seen in the 5-chamber cross-section) which partially opens the mitral valve and obstructs the LV outflow tract. TEE verified that the systolic anterior motion resolved with restoration of normal hemodynamics in 8 of these 13 patients, without surgical intervention. Although traditional methods of assessing mitral valve function during surgery may detect some failed repairs, [107] they are not highly reliable and do not reveal the mechanism of failure, a key factor in the decision to repeat the repair or replace the valve. [108] [109] [110]

TEE may change the course of coronary artery surgery. In a study of 88 patients deemed to be at high risk for perioperative complications, Savage et al [111] reported that TEE had a major effect on anesthetic management in 51 percent of patients and on surgical management in 33 percent of patients including revised or unplanned coronary grafts in 15 percent of the patients and unplanned valve procedures in 20 percent. In this high-risk study group, the incidence of myocardial infarction (1.2%) and death (1.2%) was less than in a comparable group of patients in whom TEE was not used (3.8 and 3.5%, respectively). This difference did not reach statistical significance. In infants and children, TEE reliably detects congenital heart defects including residual defects that require immediate reoperation. [112] [113] [114]

COMPLICATIONS

Most of the reported complications of TEE have occurred in outpatients and have been associated with the stress response that awake or minimally sedated patients experience while swallowing the probe. However, a low incidence of oral and pharyngeal injuries (0.1-0.3%) has been reported, [115] but in other studies, the incidence of postoperative gastrointestinal complaints did not differ significantly from that in comparable patients who had not undergone TEE. [116] [117] [118] One early report described two patients who suffered temporary unilateral vocal cord paralysis after TEE monitoring during "sitting" craniotomies. [119] Both patients were positioned with nearly full neck flexion, likely resulting in injury to the recurrent laryngeal nerve when the larynx, endotracheal tube, and shaft of the gastroscope were compressed between the chin and vertebral column. Subsequent, uncontrolled studies reported a 0.1 to 12 percent incidence of transient hoarseness after TEE. [116]

Serious pharyngeal or esophageal injury following TEE has been reported, but it is rare. [120] [121] [122] [123] [124] [125] [126] [127] Among 10,218 patients (European multicenter study) undergoing TEE (primarily outpatients), esophageal perforation occurred in 1 patient, who subsequently died; autopsy revealed a malignant tumor invading the esophagus. [128] Although bacteremia during TEE is uncommon, [129] [130] endocarditis has been reported in outpatients. [131] [132] Endocarditis from intraoperative TEE has not been reported, and the risk is probably near zero because antibiotics are usually administered. In infants, even an appropriate-sized TEE probe may occasionally obstruct the airway distal to the endotracheal tube or may compress the descending aorta. [133] [143] In our experience in neonates, TEE may be associated with inadvertent extubation.

INDICATIONS

In 4 to 33 percent of patients undergoing cardiac surgery, information provided by TEE has a major effect on surgical management. [71] [77] [105] [106] [109] [111] [112] [135] [136] [137] [138] [139] Because the patients who will benefit from TEE cannot be reliably identified prior to cardiac surgery, because TEE is an exceedingly low-risk procedure, and because surgical complications and reoperations potentially avoidable with TEE are extremely expensive, TEE is likely to be quite cost-effective for cardiac surgical programs to employ routinely. [114] [140] Some types of minimally invasive cardiac surgery cannot be performed without it. [141]

In other patient populations, the indications for TEE are less clear. In patients with thoracic trauma or suspected aortic dissection, TEE may be the diagnostic test of choice prior to surgery because TEE is diagnostically reliable and faster than alternative techniques. [62] [66] [67] [68] [142] [143] [144] If a pulmonary artery catheter is planned principally for intraoperative monitoring, TEE should be considered as a potentially more informative and lower-risk alternative. Whenever marked intraoperative hemodynamic changes are anticipated in patients unlikely to tolerate such changes, TEE should be considered. In persistently hypotensive patients and those with low output syndromes who fail to respond to initial therapy, TEE should be used--the presumed diagnosis may be wrong. In one study, TEE corrected erroneous diagnoses (based on standard hemodynamic measurements) in one-half of patients with persistent hypotension following cardiac surgery. [26] TEE also should be considered for monitoring neurosurgical patients at special risk for air embolism, because TEE is more sensitive than alternative monitors for detection of intravascular air and readily reveals paradoxic transit of air. [145] Finally, TEE should be considered whenever it is likely to reveal information that will alter care significantly and comparable information cannot be obtained with less costly or less invasive procedures.

The perioperative guidelines for TEE published by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force go beyond the foregoing recommendations by delineating three categories of TEE applications. [146] Category I applications are supported by the strongest evidence, are frequently useful in improving outcome, and are often indicated depending on individual circumstances. Examples of category I applications include TEE in patients undergoing valvular heart surgery and in patients with persistent, severe hypotension of unknown origin. Category II applications are supported by weaker evidence, may be useful in improving outcome, and may be indicated depending on individual circumstances. Examples of category II applications include monitoring hemodynamics and detection of myocardial ischemia in high-risk patients. Category III applications are supported by little evidence and are infrequently useful in improving outcome. The indications for category III applications are uncertain. Examples of category III applications include assessment of myocardial perfusion (contrast echocardiography) and detection of embolic events during orthopedic surgery.

Three important caveats apply to these guidelines. First, these guidelines are for anesthesiologists who practice TEE, not for all anesthesiologists. Second, these guidelines do not state that TEE must be used in any clinical setting, because they recognize that variations in medical needs, resources, and expertise may dictate better alternatives. Third, these guidelines state that deviations from them are expected, and the individual anesthesiologist should have great latitude in determining when TEE is appropriate for a particular patient. Expert opinion was used in the formulation of the guidelines, but only when objective evidence was lacking, and never as the sole reason for classifying an application as category I. In addition, the Task Force report defines two levels of TEE training and practice: a basic level in which TEE is used for indications that lie within the customary practice of anesthesiology (i.e., assessment of ventricular filling and function); and an advanced level in which TEE is utilized to its full perioperative diagnostic potential (i.e., evaluation of surgical repairs and other complex diagnostic applications). Cognitive and technical skills required to achieve these levels are delineated, but no arbitrary number of cases is specified. These guidelines are intended for anesthesiologists who practice TEE and not for others who use alternative diagnostic techniques. Moreover, these guidelines should prove more applicable and appropriate for anesthesiology than guidelines published by other specialties. [147]

Figure 31- (Figure Not Available) **Color Plate 31-1.** "Normal" color Doppler aliasing. In this five-chamber echocardiogram, "normal" color Doppler aliasing is seen because laminar flow of blood through the mitral valve and into the left ventricle (LV) exceeds the Nyquist limit (68 cm/s in this example--see color reference icon at upper right of figure) resulting in reversal of the color coding of flow direction. Notice that this color reversal occurs across fairly broad, regular areas, and not in a random or point-by-point fashion, as occurs with turbulent flows (always abnormal). In this example, follow the blue flow from high in the left atrium (LA) as it accelerates into the mitral orifice and notice how color Doppler depicts the increasing flow velocities: the blue color becomes lighter and lighter until the Nyquist limit is reached. Then, color reversal occurs with light blue becoming yellow. Just at that reversal point, the velocity equals the Nyquist limit, in this example 68 cm/s. Subsequent reversals may occur at that limit or at multiples of that limit. RA, right atrium; RV, right ventricle. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-2.** Color Doppler aliasing depicting turbulent flow. In this five-chamber echocardiogram, color Doppler reveals aliasing due to severe mitral regurgitation: a broad-based systolic color jet emanating from the mitral valve and extending far into the left atrium (LA). This jet is composed of a mosaic of colors mixed in a seemingly random, point-by-point fashion, because the jet results from the turbulent flow of mitral regurgitation. Turbulence is never normal in the heart, and thus mosaic jets such as the one shown here are highly valuable diagnostic signs of underlying pathology. LV, left ventricle; LVOT, LV outflow tract. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-3.** Transversely oriented ultrasound beam directed through the aortic valve. The left side of this illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the short-axis cross-section of the aortic valve. The right side of the illustration depicts the two-dimensional image that results. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-4.** Transversely oriented ultrasound beam directed through the mitral valve, left ventricular outflow tract, and left ventricle. The left side of this illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the five-chamber cross-section. The right side of the illustration depicts the two-dimensional image that results. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-5.** Transversely oriented ultrasound beam directed through the four cardiac chambers. The left side of this illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the four-chamber cross-section. The right side of the illustration depicts the two-dimensional image that results. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-6.** Transversely oriented ultrasound beam directed through the short axis of the left ventricle at the level of the papillary muscles. The left side of this illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the midpapillary short-axis cross-section. The right side of the illustration depicts the two-dimensional image that results. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-7.** Longitudinally oriented ultrasound beam directed through the ascending aorta, aortic valve, and left ventricular outflow tract. The left side of this illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the long-axis cross-section of the ascending aorta. The right side of the illustration depicts the twodimensional image that results. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-8.** Longitudinally oriented ultrasound beam directed through the superior vena cava and atria. The left side of this illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the superior vena cava cross-section. The right side of the illustration depicts the two-dimensional image that results. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-9.** Longitudinally oriented ultrasound beam directed through the right ventricular outflow tract (RVOT) and pulmonary artery (PA). The left side of this illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the RVOT cross-section. The right side of the illustration depicts the two-dimensional image that results. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-10.** Longitudinally oriented ultrasound beam directed through the left atrium and ventricle. This illustration depicts the spatial relationships between

the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the two-chamber cross-section. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-11.** Longitudinally oriented ultrasound beam directed through the left ventricle at the level of the papillary muscles. This illustration depicts the spatial relationships between the probe, ultrasound beam, and anatomic structures when the beam is directed to produce the midpapillary long-axis cross-section. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-12.** Severe aortic insufficiency. This five-chamber echocardiogram reveals a broad-based diastolic jet filling the left ventricular outflow tract and extending well into the left ventricle indicating severe aortic regurgitation. LA, left atrium; RA, right atrium; RV, right ventricle; LV, left ventricle; AI, aortic insufficiency. (From Cahalan [21])

Figure 31- (Figure Not Available) **Color Plate 31-13.** Color Doppler imaging of severe mitral stenosis. This four-chamber echocardiogram reveals a thickened and narrowed mitral valve indicating mitral stenosis. Color Doppler demonstrates the following: (1) acceleration of blood flow into the stenotic valve (a light blue semicircular area immediately above the valve called "PISA"--proximal isovelocity surface area), (2) a narrow color jet across the valve itself; and (3) a 1 by 4 cm color jet extending from the undersurface of the valve into the left ventricle. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; MV, mitral valve; MS, mitral stenosis. (From Cahalan [21])

References

1. Frazin L, Talano JV, Stephanides L et al: Esophageal echocardiography. Circulation 54:102, 1976.

2. Matsumoto M, Oka Y, Strom J et al: Application of transesophageal echocardiography to continuous intraoperative monitoring of left ventricular performance. Am J Cardiol 46:95, 1980.

3. Schluter M, Langenstein BA, Polster J et al: Transoesophageal cross-sectional echocardiography with a phased array transducer system: Technique and initial clinical results. Br Heart J 48:67, 1982.

4. Dittrich HC: Clinical Transesophageal Echocardiography. St. Louis, Mosby-Year Book, 1992.

5. Freeman WK: Transesophageal Echocardiography. Boston, Little, Brown, 1994.

6. Labovitz A, Pearson AC: Transesophageal Echocardiography: Basic Principles and Clinical Applications. Philadelphia, Lea & Febiger, 1993.

7. Maurer G: Transesophageal Echocardiography. New York, McGraw-Hill, 1994.

8. Missri J: Transesophageal Echocardiography. New York, Churchill Livingstone, 1993.

9. Oka Y, Goldine PL: Transesophageal Echocardiography. Philadelphia, JB Lippincott, 1992.

10. Silverman NH: Pediatric Echocardiography. Baltimore, Williams & Wilkins, 1993.

11. Oka YA, Konstadt SN: Clinical Transesophageal Echocardiography: A Problem-Oriented Approach. Hagerstown, Md, Lippincott-Raven, 1995.

12. Feigenbaum H: Echocardiography. Philadelphia, Lea & Febiger, 1994.

13. Weyman AE: Principles and Practice of Echocardiography. Philadelphia, Lea & Febiger, 1994.

14. Otto CM, Pearlman AS: Textbook of Clinical Echocardiography. Philadelphia, WB Saunders, 1995.

15. Hatle L, Brubakk A, Tromsdal A et al: Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. Br Heart J 40:131, 1978.

16. Holen J, Simonsen S: Determination of pressure gradient in mitral stenosis with Doppler echocardiography. Br Heart J 41:529, 1979.

17. Seward JB, Khandheria BK, Freeman WK et al: Multiplane transesophageal echocardiography: Image orientation, examination technique, anatomic correlations, and clinical applications. Mayo Clin Proc 68:523, 1993.

18. Fehske W, Grayburn PA, Omran H et al: Morphology of the mitral valve as displayed by multiplane transesophageal echocardiography. J Am Soc Echocardiogr 7:472, 1994.

19. Bansal RC, Shakudo M, Shah PM et al: Biplane transesophageal echocardiography: Technique, image orientation, and preliminary experience in 131 patients. J Am Soc Echocardiogr 3:348, 1990.

20. Schneider AT, Hsu TL, Schwartz SL et al: Single, biplane, multiplane, and three-dimensional transesophageal echocardiography: Echocardiographic-anatomic correlations. Cardiol Clin 11:361, 1993.

21. Cahalan MK: Intraoperative Transesophageal Echocardiography: An Interactive Text and Atlas. New York, Churchill Livingstone, 1996.

22. Cheung AT, Savino JS, Weiss SJ et al: Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. Anesthesiology 81:376, 1994.

23. Harpole DH, Clements FM, Quill T et al: Right and left ventricular performance during and after abdominal aortic aneurysm repair. Ann Surg 209:356, 1989.

24. Smith MD, MacPhail B, Harrison MR et al: Value and limitations of transesophageal echocardiography in determination of left ventricular volumes and ejection fraction. J Am Coll Cardiol 19:1213, 1992.

25. Reich DL, Konstadt SN, Nejat M et al: Intraoperative transesophageal echocardiography for the detection of cardiac preload changes induced by transfusion and phlebotomy in pediatric patients. Anesthesiology 79:10, 1993.

26. Reichert CL, Visser CA, Koolen JJ et al: Transesophageal echocardiography in hypotensive patients after cardiac operations: Comparison with hemodynamic parameters. J Thorac Cardiovasc Surg 104:321, 1992.

27. Heidenreich PA, Stainback RF, Redberg RF et al: Transesophageal echocardiography predicts mortality in critically ill patients with unexplained hypotension. J Am Coll Cardiol 26:152, 1995.

28. Sohn DW, Shin GJ, Oh JK et al: Role of transesophageal echocardiography in hemodynamically unstable patients. Mayo Clin Proc 70:925, 1995.

29. Poelaert JI, Trouerbach J, De BM et al: Evaluation of transesophageal echocardiography as a diagnostic and therapeutic aid in a critical care setting. Chest 107:774, 1995.

30. Muhiudeen IA, Kuecherer HF, Lee E et al: Intraoperative estimation of cardiac output by transesophageal pulsed Doppler echocardiography. Anesthesiology 74:9, 1991.

31. Savino JS, Troianos CA, Aukburg S et al: Measurement of pulmonary blood flow with transesophageal two-dimensional and Doppler echocardiography. Anesthesiology 75:445, 1991.

32. Darmon PL, Hillel Z, Mogtader A et al: Cardiac output by transesophageal echocardiography using continuous-wave Doppler across the aortic valve. Anesthesiology 80:796, 1994.

33. Pu M, Griffin BP, Vandervoort PM et al: Intraoperative validation of mitral inflow determination by transesophageal echocardiography: Comparison of single-plane, biplane and thermodilution techniques. J Am Coll Cardiol 26:1047, 1995.

34. Feinberg MS, Hopkins WE, Davila RV et al: Multiplane transesophageal echocardiographic Doppler imaging accurately determines cardiac output measurements in critically ill patients. Chest 107:769, 1995.

35. Kuecherer HF, Muhiudeen IA, Kusumoto FM et al: Estimation of mean left atrial pressure from transesophageal pulsed Doppler echocardiography of pulmonary venous flow. Circulation 82:1127, 1990.

36. Hofmann T, Keck A, van Ingen G et al: Simultaneous measurement of pulmonary venous flow by intravascular catheter Doppler velocimetry and transesophageal Doppler echocardiography: Relation to left atrial pressure and left atrial and left ventricular function. J Am Coll Cardiol 26:239, 1995.

37. Castello R, Vaughn M, Dressler FA et al: Relation between pulmonary venous flow and pulmonary wedge pressure: Influence of cardiac output. Am Heart J 130:127, 1995.

38. Kusumoto FM, Muhiudeen IA, Kuecherer HF et al: Response of the interatrial septum to transatrial pressure gradients and its potential for predicting pulmonary capillary wedge pressure: An intraoperative study using transesophageal echocardiography in patients during mechanical ventilation. J Am Coll Cardiol 21:721, 1993.

39. Nomura M, Hillel Z, Shih H et al: The association between Doppler transmitral flow variables measured by transesophageal echocardiography and pulmonary capillary wedge pressure. Anesth Analg 84:491, 1997.

40. Smith JS, Roizen MF, Cahalan MK et al: Does anesthetic technique make a difference? Augmentation of systolic blood pressure during carotid endarterectomy: Effects of phenylephrine versus light anesthesia and of isoflurane versus halothane on the incidence of myocardial ischemia. Anesthesiology 69:846, 1988.

41. Tennant R, Wiggers C: The effect of coronary occlusion on myocardial contraction. Am J Physiol 112:351, 1935.

42. Wohlgelernter D, Jaffe CC, Cabin HS et al: Silent ischemia during coronary occlusion produced by balloon inflation: Relation to regional myocardial dysfunction. J Am Coll Cardiol 10:491, 1987.

43. Hauser AM, Gangadharan V, Ramos RG et al: Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: Echocardiographic observations during coronary angioplasty. J Am Coll Cardiol 5:193, 1985.

44. Battler A, Froelicher VF, Gallagher KP et al: Dissociation between regional myocardial dysfunction and ECG changes during ischemia in the conscious dog. Circulation 62:735, 1980.

45. Smith JS, Cahalan MK, Benefiel DJ et al: Intraoperative detection of myocardial ischemia in high-risk patients: Electrocardiography versus two-dimensional transesophageal echocardiography. Circulation 72:1015, 1985.

46. Leung JM, O'Kelly B, Browner WS et al: Prognostic importance of postbypass regional wall-motion abnormalities in patients undergoing coronary artery bypass graft surgery. Anesthesiology 71:16, 1989.

47. van Daele ME, Sutherland GR, Mitchell MM et al: Do changes in pulmonary capillary wedge pressure adequately reflect myocardial ischemia during anesthesia? A correlative preoperative hemodynamic, electrocardiographic, and transesophageal echocardiographic study. Circulation 81:865, 1990.

48. Eisenberg MJ, London MJ, Leung JM et al: Monitoring for myocardial ischemia during noncardiac surgery: A technology assessment of transesophageal echocardiography and 12-lead electrocardiography. The Study of Perioperative Ischemia Research Group. JAMA 268:210, 1992.

49. Voller H, Andresen D, Bruggemann T et al: Transient ST segment depression during Holter monitoring: How to avoid false positive findings. Am Heart J 124:622, 1992.

50. Mooss AN, Prevedel JA, Mohiuddin SM et al: Effect of digoxin on ST-segment changes detected by ambulatory electrocardiographic monitoring in healthy subjects. Am J Cardiol 68:1503, 1991.

51. Pandian NG, Skorton DJ, Collins SM et al: Heterogeneity of left ventricular segmental wall thickening and excursion in 2-dimensional echocardiograms of normal human subjects. Am J Cardiol 51:1667, 1983.

52. Braunwald E, Kloner RA: The stunned myocardium: Prolonged, postischemic ventricular dysfunction. Circulation 66:1146, 1982.

53. Aronson S, Lee BK, Wiencek JG et al: Assessment of myocardial perfusion during CABG surgery with two-dimensional transesophageal contrast echocardiography. Anesthesiology 75:433, 1991.

54. Voci P, Bilotta F, Caretta Q et al: Low-dose dobutamine echocardiography predicts the early response of dysfunctioning myocardial segments to coronary artery bypass grafting. Am Heart J 129:521, 1995.

55. Panza JA, Dilsizian V, Laurienzo JM et al: Relation between thallium uptake and contractile response to dobutamine: Implications regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction. Circulation 91:990, 1995.

56. Baer FM, Voth E, Deutsch HJ et al: Assessment of viable myocardium by dobutamine transesophageal echocardiography and comparison with fluorine-18 fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol 24:343, 1994.

57. Lowenstein E, Haering JM, Douglas PS: Acute ventricular wall motion heterogeneity: A valuable but imperfect index of myocardial ischemia. Anesthesiology 75:385, 1991.

58. Buffington CW, Coyle RJ: Altered load dependence of postischemic myocardium. Anesthesiology 75:464, 1991.

59. Seeberger MD, Cahalan MK, Chu E et al: Rapid atrial pacing for detecting provokable demand ischemia in anesthetized patients. Anesth Analg 84:1180, 1997.

60. Seeberger MD, Cahalan MK, Chu E et al: Severe loading reductions may induce new segmental wall motion abnormalities in the absence of myocardial ischemia. Anesth Analg 85:1252, 1997.

61. Buckmaster MJ, Kearney PA, Johnson SB et al: Further experience with transesophageal echocardiography in the evaluation of thoracic aortic injury. J Trauma 37:989, 1994.

62. Vignon P, Gueret P, Vedrinne JM et al: Role of transesophageal echocardiography in the diagnosis and management of traumatic aortic disruption. Circulation 92:2959, 1995.

63. Minard G, Schurr MJ, Croce MA et al: A prospective analysis of transesophageal echocardiography in the diagnosis of traumatic disruption of the aorta. J Trauma 40:225, 1996.

64. Swenson JD, Lu J: Kommerell's diverticulum: A potential cause for false diagnosis of aortic disruption by transesophageal echocardiography. Anesth Analg 84:220, 1997.

65. Ducart AR, Broka SM, Collard EL: Linear reverberation in the ascending aorta: A cause of multiplane transesophageal echocardiographic artifact. Anesthesiology 85:1497, 1996.

66. Erbel R, Engberding R, Daniel W et al: Echocardiography in diagnosis of aortic dissection. Lancet 1:457, 1989.

67. Bansal RC, Chandrasekaran K, Ayala K et al: Frequency and explanation of false negative diagnosis of aortic dissection by aortography and transesophageal echocardiography. J Am Coll Cardiol 25:1393, 1995.

68. Nienaber CA, von Kodolitsch Y, Nicolas V et al: The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. N Engl J Med 328:1, 1993.

69. Sommer T, Fehske W, Holzknecht N et al: Aortic dissection: A comparative study of diagnosis with spiral CT, multiplanar transesophageal echocardiography, and MR imaging. Radiology 199:347, 1996.

70. Katz ES, Tunick PA, Rusinek H et al: Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: Experience with intraoperative transesophageal

echocardiography. J Am Coll Cardiol 20:70, 1992.

71. Ribakove GH, Katz ES, Galloway AC et al: Surgical implications of transesophageal echocardiography to grade the atheromatous aortic arch. Ann Thorac Surg 53:758, 1992.

72. Grossi EA, Kanchuger MS, Schwartz DS et al: Effect of cannula length on aortic arch flow: Protection of the atheromatous aortic arch. Ann Thorac Surg 59:710, 1995.

73. Hartman GS, Yao FS, Bruefach MR et al: Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: A prospective study. Anesth Analg 83:701, 1996.

74. Davila RV, Phillips KJ, Daily BB et al: Intraoperative transesophageal echocardiography and epiaortic ultrasound for assessment of atherosclerosis of the thoracic aorta. J Am Coll Cardiol 28:942, 1996.

75. Konstadt SN, Reich DL, Kahn R et al: Transesophageal echocardiography can be used to screen for ascending aortic atherosclerosis. Anesth Analg 81:225, 1995.

76. Khoury Z, Gottlieb S, Stern S et al: Frequency and distribution of atherosclerotic plaques in the thoracic aorta as determined by transesophageal echocardiography in patients with coronary artery disease. Am J Cardiol 79:23, 1997.

77. Sheikh KH, Bengtson JR, Rankin JS et al: Intraoperative transesophageal Doppler color flow imaging used to guide patient selection and operative treatment of ischemic mitral regurgitation. Circulation 84:594, 1991.

78. Nanda NC: Doppler Echocardiography. Philadelphia, Lea & Febiger, 1993.

79. Labovitz AJ, Williams GA: Doppler Echocardiography: The Quantitative Approach. Lippincott, Philadelphia, 1992.

80. Felner JM: Echocardiography. In Hurst JW (ed): The Heart. New York, McGraw-Hill, 1990, p 2010.

81. Stoddard MF, Arce J, Liddell NE et al: Two-dimensional transesophageal echocardiographic determination of aortic valve area in adults with aortic stenosis. Am Heart J 122:1415, 1991.

82. Hofmann T, Kasper W, Meinertz T et al: Determination of aortic valve orifice area in aortic valve stenosis by two-dimensional transesophageal echocardiography. Am J Cardiol 59:330, 1987.

83. Tardif JC, Miller DS, Pandian NG et al: Effects of variations in flow on aortic valve area in aortic stenosis based on in vivo planimetry of aortic valve area by multiplane transesophageal echocardiography. Am J Cardiol 76:193, 1995.

84. Kim KS, Maxted W, Nanda NC et al: Comparison of multiplane and biplane transesophageal echocardiography in the assessment of aortic stenosis. Am J Cardiol 79:436, 1997.

85. Hoffmann R, Flachskampf FA, Hanrath P: Planimetry of orifice area in aortic stenosis using multiplane transesophageal echocardiography. J Am Coll Cardiol 22:529, 1993.

86. Tribouilloy C, Shen WF, Peltier M et al: Quantitation of aortic valve area in aortic stenosis with multiplane transesophageal echocardiography: Comparison with monoplane transesophageal approach. Am Heart J 128:526, 1994.

87. Blumberg FC, Pfeifer M, Holmer SR et al: Transgastric Doppler echocardiographic assessment of the severity of aortic stenosis using multiplane transesophageal echocardiography. Am J Cardiol 79:1273, 1997.

88. Moisa RB, Zeldis SM, Alper SA et al: Aortic regurgitation in coronary artery bypass grafting: Implications for cardioplegia administration. Ann Thorac Surg 60:665, 1995.

89. Stoddard MF, Prince CR, Tuman WL et al: Angle of incidence does not affect accuracy of mitral stenosis area calculation by pressure half-time: Application to Doppler transesophageal echocardiography. Am Heart J 127:1562, 1994.

90. Black IW, Hopkins AP, Lee LC et al: Left atrial spontaneous echo contrast: A clinical and echocardiographic analysis. J Am Coll Cardiol 18:398, 1991.

91. Chimowitz MI, DeGeorgia MA, Poole RM et al: Left atrial spontaneous echo contrast is highly associated with previous stroke in patients with atrial fibrillation or mitral stenosis. Stroke 24:1015, 1993.

92. Shah PM: Significance of spontaneous echo contrast, or, does "smoke" indicate "fire"? J Heart Valve Dis 2:257, 1993.

93. Kranidis A, Koulouris S, Anthopoulos L: Clinical implications of left atrial spontaneous echo contrast in mitral valve disease. J Heart Valve Dis 2:267, 1993.

94. Hwang JJ, Kuan P, Chen JJ et al: Significance of left atrial spontaneous echo contrast in rheumatic mitral valve disease as a predictor of systemic arterial embolization: A transesophageal echocardiographic study. Am Heart J 127:880, 1994.

95. Sadoshima J, Koyanagi S, Sugimachi M et al: Evaluation of the severity of mitral regurgitation by transesophageal Doppler flow echocardiography. Am Heart J 123:1245, 1992.

96.

Klein AL, Obarski TP, Stewart WJ et al: Transesophageal Doppler echocardiography of pulmonary venous flow: A new marker of mitral regurgitation severity. J Am Coll Cardiol 18:518, 1991.

97. Klein AL, Stewart WJ, Bartlett J et al: Effects of mitral regurgitation on pulmonary venous flow and left atrial pressure: An intraoperative transesophageal echocardiographic study. J Am Coll Cardiol 20:1345, 1992.

98. Klein AL, Bailey AS, Cohen GI et al: Importance of sampling both pulmonary veins in grading mitral regurgitation by transesophageal echocardiography. J Am Soc Echocardiogr 6:115, 1993.

99. Thomas JD, Liu CM, Flachskampf FA et al: Quantification of jet flow by momentum analysis: An *in vitro* color Doppler flow study. Circulation 81:247, 1990.

100. Himelman RB, Kusumoto F, Oken K et al: The flail mitral valve: Echocardiographic findings by precordial and transesophageal imaging and Doppler color flow mapping. J Am Coll Cardiol 17:272, 1991.

101. Schiller NB, Foster E, Redberg RF: Transesophageal echocardiography in the evaluation of mitral regurgitation. Cardiol Clin 11:339, 1993.

102. Pu M, Vandervoort PM, Griffin BP et al: Quantification of mitral regurgitation by the proximal convergence method using transesophageal echocardiography: Clinical validation of a geometric correction for proximal flow constraint. Circulation 92:2169, 1995.

103. Baumgartner H, Schima H, Kuhn P: Value and limitations of proximal jet dimensions for the quantitation of valvular regurgitation: An *in vitro* study using Doppler flow imaging. J Am Soc Echocardiogr 4:57, 1991.

104. Tribouilloy C, Shen WF, Quere JP et al: Assessment of severity of mitral regurgitation by measuring regurgitant jet width at its origin with transesophageal Doppler color flow imaging. Circulation 85:1248, 1992.

105. Sheikh KH, de Bruijn NP, Rankin JS et al: The utility of transesophageal echocardiography and Doppler color flow imaging in patients undergoing cardiac valve surgery. J Am Coll Cardiol 15:363, 1990.

106. Freeman WK, Schaff HV, Khandheria BK et al: Intraoperative evaluation of mitral valve regurgitation and repair by transesophageal echocardiography: Incidence and significance of systolic anterior motion. J Am Coll Cardiol 20:599, 1992.

107. Moulijn AC, Smulders YM, Koolen JJ et al: Intraoperative assessment of the mitral valve: Transesophageal Doppler echocardiography vs. left ventricular filling of the flaccid heart. Eur J Cardiothorac Surg 6:122, 1992.

108. Lee KS, Stewart WJ, Lever HM et al: Mechanism of outflow tract obstruction causing failed mitral valve repair: Anterior displacement of leaflet coaptation. Circulation 88:1124, 1993.

109. Marwick TH, Stewart WJ, Lever HM et al: Benefits of intraoperative echocardiography in the surgical management of hypertrophic cardiomyopathy. J Am Coll Cardiol 20:1066, 1992.

110. Kalman JM, Jones EF, Lubicz S et al: Evaluation of mitral valve repair by intraoperative transoesophageal echocardiography. Aust N Z J Med 23:463, 1993.

111. Savage RM, Lytle BW, Aronson S et al: Intraoperative echocardiography is indicated in high-risk coronary artery bypass grafting. Ann Thorac Surg 64:368, 1997.

112. Stevenson JG, Sorensen GK, Gartman DM et al: Transesophageal echocardiography during repair of congenital cardiac defects: Identification of residual problems necessitating reoperation. J Am Soc Echocardiogr 6:356, 1993.

113. O'Leary PW, Hagler DJ, Seward JB et al: Biplane intraoperative transesophageal echocardiography in congenital heart disease. Mayo Clin Proc 70:317, 1995.

114. Ungerleider RM, Kisslo JA, Greeley WJ et al: Intraoperative echocardiography during congenital heart operations: Experience from 1,000 cases. Ann Thorac Surg S539, 1995.

115. Rafferty T, LaMantia KR, Davis E et al: Quality assurance for intraoperative transesophageal echocardiography monitoring: A report of 846 procedures. Anesth Analg 76:228, 1993.

116. Messina AG, Paranicas M, Fiamengo S et al: Risk of dysphagia after transesophageal echocardiography. Am J Cardiol 67:313, 1991.

117. Hulyalkar AR, Ayd JD: Low risk of gastroesophageal injury associated with transesophageal echocardiography during cardiac surgery. J Cardiothorac Vasc Anesth 7:175, 1993.

118. Owall A, Stahl L, Settergren G: Incidence of sore throat and patient complaints after intraoperative transesophageal echocardiography during cardiac surgery. J Cardiothorac Vasc Anesth 6:15, 1992.

119. Cucchiara RF, Seward JB, Nishimura RA et al: Identification of patent foramen ovale during sitting position craniotomy by transesophageal echocardiography with positive airway pressure. Anesthesiology 63:107, 1985.

120. Dewhirst WE, Stragand JJ, Fleming BM: Mallory-Weiss tear complicating intraoperative transesophageal echocardiography in a patient undergoing aortic valve replacement. Anesthesiology 73:777, 1990.

121. Polhamus CD, Werth TE, Clement DJ et al: Gastrointestinal bleeding complicating transesophageal echocardiography. Endoscopy 25:198, 1993.

122. Savino JS, Hanson CW 3rd, Bigelow DC et al: Oropharyngeal injury after transesophageal echocardiography. J Cardiothorac Vasc Anesth 8:76, 1994.

123. Spahn DR, Schmid S, Carrel T et al: Hypopharynx perforation by a transesophageal echocardiography probe. Anesthesiology 82:581, 1995.

124. Badaoui R, Choufane S, Riboulot M et al: Esophageal perforation after transesophageal echocardiography (in French). Ann Fr Anesth Reanim 13:850, 1994.

125. Latham P, Hodgins LR: A gastric laceration after transesophageal echocardiography in a patient undergoing aortic valve replacement. Anesth Analg 81:641, 1995.

126. Kharasch ED, Sivarajan M: Gastroesophageal perforation after intraoperative transesophageal echocardiography. Anesthesiology 85:426, 1996.

127. Tam JW, Burwash IG, Ascah KJ et al: Feasibility and complications of single-plane and biplane versus multiplane transesophageal imaging: A review of 2947 consecutive studies. Can J Cardiol 13:81, 1997.

128. Daniel WG, Erbel R, Kasper W et al: Safety of transesophageal echocardiography: A multicenter survey of 10,419 examinations. Circulation 83:817, 1991.

129. Mentec H, Vignon P, Terre S et al: Frequency of bacteremia associated with transesophageal echocardiography in intensive care unit patients: A prospective study of 139 patients. Crit Care Med 23:1194, 1995.

130. Nikutta P, Mantey SF, Becht I et al: Risk of bacteremia induced by transesophageal echocardiography: Analysis of 100 consecutive procedures. J Am Soc Echocardiogr 5:168, 1992.

131. Foster E, Schiller NB: The role of transesophageal echocardiography in critical care: UCSF experience. J Am Soc Echocardiogr 5:368, 1992.

132. Read RC, Finch RG, Donald FE et al: Infective endocarditis after transesophageal echocardiography. Circulation 87:1426, 1993.

133. Gilbert TB, Panico FG, McGill WA et al: Bronchial obstruction by transesophageal echocardiography probe in a pediatric cardiac patient. Anesth Analg 74:156, 1992.

134. Lunn RJ, Oliver WJ, Hagler DJ et al: Aortic compression by transesophageal echocardiographic probe in infants and children undergoing cardiac surgery. Anesthesiology 77:587, 1992.

135. Deutsch HJ, Curtius JM, Leischik R et al: Diagnostic value of transesophageal echocardiography in cardiac surgery. Thorac Cardiovasc Surg 39:199, 1991.

136. Guyton SW, Paull DL, Anderson RP: Mitral valve reconstruction. Am J Surg 163:497, 1992.

137. Stumper O, Kaulitz R, Elzenga NJ et al: The value of transesophageal echocardiography in children with congenital heart disease. J Am Soc Echocardiogr 4:164, 1991.

138. Stewart WJ, Salcedo EE, Cosgrove DM: The value of echocardiography in mitral valve repair. Cleve Clin J Med 58:177, 1991.

139. Kalman PG, Wellwood MR, Weisel RD et al: Cardiac dysfunction during abdominal aortic operation: The limitations of pulmonary wedge pressures. J Vasc Surg 3:773, 1986.

140. Benson M, Cahalan MK: Cost effectiveness of transesophageal echocardiography during cardiac surgery. Echocardiography 12:171, 1995.

141. Siegel LC, St. Goar FG, Stevens JH et al: Monitoring considerations for port-access cardiac surgery. Circulation 96:562, 1997.

142. Oxorn D, Towers M: Traumatic aortic disruption: False positive diagnosis on transesophageal echocardiography. J Trauma 39:386, 1995.

143. Saletta S, Lederman E, Fein S et al: Transesophageal echocardiography for the initial evaluation of the widened mediastinum in trauma patients. J Trauma 39:137, 1995.

144. Catoire P, Orliaguet G, Liu N et al: Systematic transesophageal echocardiography for detection of mediastinal lesions in patients with multiple injuries. J Trauma 38:96, 1995.

145.

Glenski JA, Cucchiara RF, Michenfelder JD: Transesophageal echocardiography and transcutaneous O_2 and CO_2 monitoring for detection of venous air embolism. Anesthesiology 64:541, 1986.

146. Practice guidelines for perioperative transesophageal echocardiography: A report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. Anesthesiology 84:986, 1996.

147. Pearlman AS, Gardin JM, Martin RP et al: Guidelines for physician training in transesophageal echocardiography: Recommendations of the American Society of Echocardiography Committee for Physician Training in Echocardiography. J Am Soc Echocardiogr 5:187, 1992.

/das/book/view/29494766/875/347.html

Chapter 32 - Electrocardiography

Zaharia Hillel
Daniel M. Thys

INTRODUCTION

The intraoperative use of the electrocardiogram (ECG) has markedly developed over the past several decades. [1] Originally, this monitor was used during anesthesia for the detection of arrhythmias in high-risk patients. [2] At that time, standard limb lead II was displayed, because its electrical axis parallels the electrical axis of the heart and the P wave is usually easily observed. In recent years, the importance of ECG as a standard monitor has been recognized, and its use during the conduct of any anesthetic regimen is now recommended. [3] Beyond the usefulness of ECG for the recognition of intraoperative arrhythmias, one of the major indications for ECG monitoring is the intraoperative diagnosis of myocardial ischemia. [4] Despite widespread attempts at prevention, coronary artery disease continues to be a major health problem in the United States. Patients undergoing different types of surgical procedures have significant coronary artery disease, and in these patients, the ECG should be used to identify myocardial ischemia as well as to recognize arrhythmias. With many patients now coming to surgery with pacemakers in place, the ECG also enables the physician to follow the function of the device during the surgical procedure. Since the first utilization of the ECG during anesthesia, the technology available to the anesthesiologist has become considerably more sophisticated. The aim of this chapter is to familiarize the reader with some of the newer developments in the use and interpretation of the ECG.

NORMAL ELECTRICAL ACTIVITY

P Wave

A complete ECG cycle, intervals, and segments are shown in Figure 32-1 . Under normal circumstances, the sinoatrial (SA) node has the most rapid spontaneous depolarization rate and is therefore the dominant cardiac pacemaker (Table 32-1) . From the SA node, the impulse spreads through the right and left atria. Specialized tracts conduct the impulse to the atrioventricular (AV) node, but they are not essential. The three selective inputs to the AV node are (1) the right superior "fast" pathway, (2) the right superior "slow" pathway, and (3) a left-sided, less well-characterized pathway. On the ECG, depolarization of the atria is represented by the P wave. The initial depolarization involves primarily the right atrium and occurs predominantly in an anterior, inferior, and leftward direction. Subsequently, it proceeds to the left atrium, located in a more posterior position.

P- R Interval

Once the depolarization has reached the AV node, a delay is observed. The delay permits contraction of the atria and supplemental filling of the ventricular chambers. On the ECG, it is represented by the P-R interval.

QRS Complex

After passage through the AV node, the electrical impulse is conducted along the ventricular conduction pathways

Figure 32-1 A single normal ECG cycle with waves, segments, and intervals identified.

consisting of the common bundle of His, the left and right bundle branches, the distal bundle branches, and the Pur-kinje fibers. The QRS complex represents the progress of the depolarization wave through this conduction system. After terminal depolarization, the ECG should normally return to baseline.

ST Segment and T Wave

Repolarization of the ventricles begins at the end of the QRS complex and consists of the ST segment and T wave. Whereas ventricular depolarization occurs along established conduction pathways, ventricular repolarization is a prolonged process that occurs independently in every cell. The T wave represents the uncanceled potential differences of ventricular repolarization. The junction of the QRS and the ST segment is called the J junction. The T wave is sometimes followed by a small U wave, the origin of which is unclear. An inverted U wave has been associated with several clinically significant conditions, such as hypertension, coronary artery disease, valvular heart disease, and certain metabolic disorders. There may be an association between exercise- or rest-related U-wave inversion and significant stenosis of the left anterior descending artery or the left main coronary artery.

TABLE 32-1 -- Spontaneous Electrical Activity of Cardiac Tissues

TISSUE	INTRINSIC DEPOLARIZATION RATE (BEATS/MIN)
Sinoatrial node	>60
Atrioventricular node	40-60
Purkinje fibers	<40

Figure 32-2 (Figure Not Available) Einthoven triangle. *(From Thys and Kaplan [1])*

LEAD SYSTEMS

Standard Limb and Precordial Leads

The small electric currents produced by the electrical activity of the heart spread throughout the body, which behaves as a volume conductor, allowing the surface ECG to be recorded at any site. The standard leads are bipolar leads, because they measure differences in potential between pairs of electrodes. The electrodes are placed on the right arm, the left arm, and the left leg. The leads are formed by the imaginary lines connecting the electrodes, and the polarities correspond to the conventions of the Einthoven triangle (Fig. 32-2) (Figure Not Available) . They are labeled leads I, II, and III. If the 3 electrodes of the standard leads are connected through resistances of 5,000 ohms each, a common central terminal with zero potential is obtained. When this common electrode is used with another exploring electrode, the potential difference between them represents the actual potential (Fig. 32-3) (Figure Not Available) . On a standard 12-lead ECG, 3 unipolar limb

Figure 32-3 (Figure Not Available) Unipolar limb lead circuit (VR). *(From Thys and Kaplan [1])*

Figure 32-4 (Figure Not Available) Goldberger modification to the unipolar lead aVR. *(From Thys and Kaplan [1])*

leads are usually recorded: aVR, aVL, and aVF. The "a" indicates that they are augmented limb leads and were obtained using the Goldberger modification (Fig. 32-4) (Figure Not Available) . In this modification, the resistors are removed from the circuit, and the exploring electrode is disconnected from the central terminal. This modification produces larger ECG deflections.

Additional information on the heart's electrical activity is obtained by placing electrodes closer to the heart or around the thorax. In the precordial lead system, the neutral electrode is formed by the standard leads, and an exploring electrode is placed on the chest wall. The ECG is normally recorded with the exploring electrode in one, or more, of six precordial positions. They are indicated by the letter V, followed by a numeral from 1 to 6 indicating the location of the electrode on the chest wall (Fig. 32-5) (Figure Not Available) .

ECG Monitoring Systems

Three-Electrode System

As the name implies, the three-electrode system uses only three electrodes to record the ECG. In such a system, the ECG is observed along one bipolar lead between two of the electrodes while the third electrode serves as a ground. A selector switch allows the user to alter the designation of the electrodes. Three ECG leads can be examined in sequence without changing the location of the electrodes. Although the three-electrode system has the advantage of simplicity, its use is limited in myocardial ischemia because it provides a narrow picture of myocardial electrical activity.

Modified Three-Electrode System

Numerous modifications of the standard bipolar limb lead system have been developed. Some of these are displayed in Figure 32-6 (Figure Not Available) . They are used in an attempt to maximize P-wave height for the diagnosis of atrial arrhythmias or to increase

Figure 32-5 (Figure Not Available) Anatomic location of the precordial unipolar leads V_1-V_6. *(From Thys and Kaplan [1])*

the sensitivity of the ECG for the detection of anterior myocardial ischemia. In clinical studies, these modified three-electrode systems have been shown to be as sensitive as or more sensitive than the standard V_5 lead system for the intraoperative diagnosis of ischemia. [5]

Central Subclavicular Lead

The central subclavicular (CS_5) lead is particularly well suited for the detection of anterior myocardial wall isch-emia. The right arm (RA) electrode is placed under the right clavicle, the left arm (LA) electrode is placed in the V_5 position, and the left leg electrode is in its usual position to serve as a ground. Lead I is selected for detection of anterior wall ischemia, and lead II can be selected for monitoring inferior wall ischemia or for the detection of arrhythmias. If a unipolar precordial electrode is unavailable, this CS_5 bipolar lead is the best and easiest alternative to a true V_5 lead for monitoring myocardial ischemia.

Central Back Lead

The central back (CB_5) lead is good for the detection of ischemia and supraventricular arrhythmias as demonstrated in a study comparing CB_5 and V_5 in patients with closed and open chests. [6] The P wave was 90 percent larger than in lead V_5, whereas a good correlation between ventricular deflections of CB_5 and V_5 leads was noted. CB_5 is obtained by placing the RA electrode over the center of the right scapula and the LA electrode in the V_5 position. The lead selector switch should be on lead I. The CB_5 lead may be useful in patients with ischemic heart disease, who are susceptible to the development of arrhythmias during the perioperative period.

Figure 32-6 (Figure Not Available) Modified bipolar standard limb lead system: MCL_1, CS_5, CM_5, CB_5, CC_5. *(From Thys and Kaplan [1])*

When modified bipolar limb leads are used, monitoring personnel should be aware that in certain aspects these leads differ significantly from true unipolar precordial leads. The modified precordial leads usually show a greater R-wave amplitude than standard precordial leads, and this feature can result in amplification of the ST-segment response.

The criteria for diagnosing myocardial ischemia (see later) may therefore need to be adjusted when modified bipolar leads are used. It has been shown during exercise stress testing that normalization of the degree of ST-segment depression to the height of the R wave increases the sensitivity and specificity of ECG for the

recognition of myocardial ischemia. [7] In an intraoperative study, Mark et al [8] noted that during cardiac surgery, placement of a Canadian sternal retractor was associated with a reduction in V_5 R-wave amplitude from 15 ± 1 to 10 ± 1 mm. Simultaneously, V_5 S-wave amplitude and absolute ST-segment deviation were reduced from 3.5 ± 0.4 to 1.7 ± 0.3 mm and from 0.50 ± 0.04 to 0.39 ± 0.05 mm, respectively (Table 32-2) (Table Not Available) . Mark et al concluded that their results support the proposal

TABLE 32-2 -- Electrocardiographic Changes During Sternal Retractor Placement in 83 Patients

(Not Available)

(Modified from Mark et al [8])

that inclusion of an R-wave gain factor may improve perioperative ECG monitoring.

Five-Electrode System

The use of five electrodes allows the recording of the six standard limb leads (I, II, III, aVR, aVL, aVF), as well as one precordial unipolar lead. Generally, the unipolar lead is placed in the V_5 position, along the anterior axillary line in the fifth intercostal space (Fig. 32-7) (Figure Not Available) . With the addition of only two electrodes to the ECG system, up to seven different leads can be monitored simultaneously. This allows one to monitor several areas of the myocardium for ischemia or to establish a differential diagnosis between atrial and ventricular arrhythmias.

In 1976, Kaplan and King [9] suggested monitoring lead V_5 as the best choice for the detection of intraoperative isch-emia. Using a single lead, London et al [10] demonstrated that, in high-risk patients undergoing noncardiac surgery, the greatest sensitivity was obtained with lead V_5 (75%), followed by lead V_4 (61%). Combining leads V_4 and V_5 increased the sensitivity to 90 percent, whereas with the standard lead II and V_5 combination, the sensitivity was only 80 percent. London and colleagues also suggested that if three leads (II, V_4 , and V_5) could be examined simultaneously, the sensitivity would rise to 98 percent. Most modern ECG monitors, however, do not readily allow the simultaneous display of more than one precordial lead. Some investigators have also suggested that the monitoring of a right-sided precordial lead (V_{4R}) may be of benefit in patients with occlusive disease of the right coronary artery. [11]

Great individual variability in the placement of precordial leads is a problem that has been recognized. In an attempt to reduce the error, Herman et al [12] studied a device that facilitates precordial lead placement. ECG obtained after device-guided electrode placement showed variations with those obtained without it in 60 percent of patients. Significant Q-wave appearance/disappearance and/or significant

Figure 32-7 (Figure Not Available) Multiple lead ECG system consisting of four extremity electrodes and the V_5 lead. RA = right arm, LA = left arm, RL = right leg, LL = left leg. *(From Narang and Thys [3])*

ST-segment elevation/depression occurred in 19 percent of patients.

Invasive Electrocardiographic Monitoring

The electrical potentials of the heart can be measured not only from a surface ECG but also from body cavities adjacent to the heart (esophagus or trachea) or from within the heart itself.

Esophageal ECG

The concept of esophageal ECG is not new; numerous studies have demonstrated the usefulness of this approach in the diagnosis of complicated arrhythmias. The esophageal electrodes are incorporated into an esophageal stethoscope and are welded to conventional ECG wires (Fig. 32-8) (Figure Not Available) . A prominent P wave is usually displayed in the presence of atrial depolarization, and its relation to the ventricular electrical activity can be examined (Fig. 32-9) (Figure Not Available) . To observe a bipolar esophageal ECG, the electrodes are connected to the right and left arm terminals and lead I is selected on the monitor.

Figure 32-8 (Figure Not Available) The Cardioesophagoscope. The esophageal leads are made of plastic. The ECG wires are connected to the right and left arms, with lead I selected on the ECG monitor. *(From Narang and Thys [3])*

Figure 32-9 (Figure Not Available) Enhanced detection of atrial electrical activity using the esophageal ECG (EsECG). EsECG demonstrates arrhythmia progression from normal sinus rhythm (NSR), with one premature contraction (PAC), to atrial flutter (A flutter) and atrial fibrillation (A fibrillation). Lack of information about atrial activity from lead V_5 made definitive diagnosis impossible. *(From Thys and Kaplan [1])*

In a study of 20 cardiac patients, 100 percent of atrial arrhythmias were correctly diagnosed with the esophageal lead (using intracavitary ECG as the standard), whereas lead II led to a correct diagnosis in 54 percent of the cases and V_5 in 42 percent of cases (Table 32-3) (Table Not Available) . [13] Additionally, the esophageal ECG may be helpful in the detection of posterior wall ischemia because of its proximity to the posterior aspect of the left ventricle (Fig. 32-10) (Figure Not Available) . To minimize the risk of esophageal burn injury, an electrocautery protection filter capable of filtering radiofrequencies greater than 20 kHz should be inserted between the ECG cable and the esophageal lead.

Several investigators have described devices that allow both ECG recording from the esophagus and pacing of the heart using the same device. [14] Esophageal electrodes have been found particularly useful in patients with emphysema or in critically ill patients in whom satisfactory surface ECG cannot be obtained. [15] [16]

Intracardiac ECG

For many years, long saline-filled central venous catheters have been used to record intracardiac ECG. More recently, Chatterjee et al [17] described the use of a modified balloon-tipped flotation catheter for recording intracavitary ECG (Fig. 32-11) (Figure Not Available) . The multipurpose pulmonary artery catheter that is currently available has all the features of a standard pulmonary artery catheter. In addition, three atrial and two ventricular electrodes have been incorporated into the catheter. These electrodes permit recording of intracavitary ECG and the establishment of atrial or AV pacing. The diagnostic capabilities with this catheter are great because atrial, ventricular, or AV nodal arrhythmias and conduction blocks can be demonstrated. The large voltages obtained from the intracardiac electrodes are relatively insensitive to electrocautery interference, thus making them useful for intraaortic balloon pump triggering. [18] Other pulmonary artery catheters have ventricular and atrial ports that allow passage of pacing wires. These catheters can also be used for diagnostic purposes, as well as for therapeutic interventions (pacing).

Endotracheal ECG

The endotracheal ECG allows monitoring of the ECG when it is impractical or impossible to monitor the surface ECG. The endotracheal ECG consists of a standard endotracheal tube in which two electrodes have been embedded (Fig. 32-12) (Figure Not Available) . This device may be most useful in pediatric patients for the diagnosis of atrial arrhythmias. [19] The same safety precautions as for esophageal ECG (see earlier) should be followed.

Intracoronary ECG

The clinical use, during angioplasty, of a coronary guide wire for the recording of intracoronary ECG was first reported during 1985. [20] The major advantage was perceived to be a greater detection of acute ischemia than with surface ECG.

TABLE 32-3 -- Comparison of Esophageal and Standard Electrocardiography for Correct Arrhythmia Diagnosis in 20 Patients

(Not Available)

(Modified from Kates et al [13])

Figure 32-10 (Figure Not Available) Tracing of EsECG, II, and V_5 showing posterior ischemia. *(From Kates et al [13])*

In a study of 300 consecutive patients, intracoronary ECG detected ST-segment changes in 83 percent of lesions, versus 67 percent on surface ECG. [21] Maeda et al [22] noted a more rapid shortening of the Q-T interval with intracoronary ECG than with surface ECG after angioplasty balloon inflation.

DISPLAY, RECORDING, AND INTERPRETATION

The American Heart Association (AHA) has published instrumentation and practice standards for ECG monitoring in special care units. [23] They consist of performance standards, performance requirements, and disclosure requirements. Some of the recommendations include that monitors be able simultaneously to display and to analyze multiple leads and that users be informed of minimally acceptable accuracy in a standardized manner. Many of the principles detailed in these standards are also applicable to intraoperative monitoring.

Basic Requirements

The function of the ECG monitor is to detect, amplify, display, and record the ECG signal. The ECG is usually displayed on an oscilloscope. Several monitors now offer nonfade storage oscilloscopes to facilitate wave recognition. All ECG monitors for use in patients with cardiac disease should also have paper recording capabilities. The recorder is needed to make accurate diagnoses of complex arrhythmias, as well as to allow careful analysis of all the ECG waveforms. In addition, the recorder allows one to differentiate real ECG changes from artifacts.

Oscilloscope Displays

Most modern oscilloscopes are high-resolution monochrome or color monitors, similar to those used in computer technology. They frequently allow considerable flexibility in screen configuration, including waveform positions, colors, and sweep speeds. The norm in modern technology is to display three ECG channels simultaneously. These usually consist of two limb leads and one unipolar precordial lead. In addition to the waveforms, average heart rates and optional arrhythmia and ST-segment information are displayed in alphanumeric format (see later).

Standard ECG Recordings

The ECG is normally recorded on special paper consisting of grids of horizontal and vertical lines. Distances between vertical lines represent time intervals, whereas distances between horizontal lines represent voltages. The

Figure 32-11 (Figure Not Available) The multipurpose pacing pulmonary artery catheter. Three atrial and two ventricular electrodes can be seen. *(From Narang and Thys [5])*

Figure 32-12 (Figure Not Available) Diagram of tracheal tube ECG system. *(From Narang and Thys [5])*

lines are 1 mm apart, with every fifth line intensified. The speed of the paper is standardized to 25 mm/s. Therefore, on the horizontal axis, 1 mm represents 0.04 second and 0.5 cm represents 0.20 second. On the vertical axis, 10 mm represents 1 mV. On every recording, a 1-cm (1-mV) calibration mark should indicate that the ECG is appropriately calibrated. The user should follow the manufacturer's recommended calibration procedure for each monitoring episode. Strip chart recorders that are part of an ECG monitoring system should meet all the standards of time base accuracy, frequency response, linearity, and so forth, proposed for conventional ECG recording systems. [24] [25]

Artifacts

The Patient

The electrical signal generated by the heart and monitored by the ECG is very weak, amounting to only 0.5 to 2 mV at the skin surface. It is therefore imperative that the skin be prepared optimally, to avoid signal loss at the skin-electrode interface. Hair should be removed from the electrode sites with scissors and shavers. The skin should be cleaned with alcohol and should be free of any dirt. It is best to abrade the skin lightly to remove part of the stratum corneum, which can be a source of high resistance to the measured voltages. To avoid the problem of muscle artifact, electrodes should be placed over bony prominences, whenever possible. Muscle movement, in the form of shivering, can produce significant ECG artifact.

Electrodes and Leads

Loose electrodes and broken leads may produce a variety of artifacts that may stimulate arrhythmias, Q waves, or inverted T waves. Pregelled disposable silver/silver chloride electrodes are generally used in the operating room. The technical standards for such electrodes have been published by the American Association for the Advancement of Medical Instrumentation. [26] It is important that all the electrodes be moist, uniform, and not out of date. Needle electrodes should be avoided because of the risk of thermal injury. Some ECG monitors have built-in cable testers that enable a lead to be tested by connecting the cable's distal end into the monitor. A high resistance causes a large voltage drop, indicating that the lead is faulty. The main source of artifact from ECG leads is loss of the integrity of the lead insulation. This subsequently leads to pickup of other electric fields in the operating room, such as the 60-Hz alternating current (AC) from lights and also currents from the electrocautery device. Any damaged ECG lead should be discarded for this reason. Lead movement can also lead to artifact.

Operating Room Environment

Many pieces of equipment found in the operating room emit electric fields that can interfere with the ECG: 60-Hz power lines for lights, electrosurgical equipment, cardiopulmonary equipment, and defibrillator discharges. Most of this interference can be minimized by proper shielding of the cables and leads of the ECG, although the interference created by the electrosurgical equipment cannot be reliably filtered without distortion of the ECG. Electrocautery is the most important source of interference on the ECG in the operating room; it usually completely obliterates the ECG tracing. Analysis of the electrocautery has identified three component frequencies. The radiofrequency between 800 and 2,000 kHz comprises most of the interference, coupled with 60-Hz AC frequency and 0.1- to 10-Hz low-frequency noise from intermittent contact of the electrosurgical unit with the patient's tissues. Preamplifiers may be modified to suppress radiofrequency interference, but these filter circuits are still not widely available in the operating room.

Other causes of ECG artifacts in the operating room environment have been reported. Intraoperative monitoring of somatosensory-evoked potentials has been known to simulate pacemaker spikes. [27] They are caused by incorporation in certain monitors of a "pacer enhancement circuit." This problem can be eliminated by disabling the circuit. Artifactual spikes have been noted to coincide with the drip rate in the drip chamber of a warming unit. [28] The spikes were probably related to the generation of static electricity from water droplets. The use of an automated percutaneous lumbar diskectomy nucleotome has been reported to simulate

supraventricular tachycardia (SVT), related to a mechanical interference. [29]

Monitoring System

All ECG monitors use filters to narrow the bandwidth in an attempt to reduce environmental artifacts. The highfrequency filters reduce distortions from muscle movement, 60-Hz electrical current, and electromagnetic interference from other electrical equipment. [30] The low-frequency filters ensure a more stable baseline by reducing respiratory

---

and body movement artifacts, as well as those resulting from poor electrode contact. The AHA recommends that a flat frequency response be obtained at a bandwidth of 0.05 to 100 Hz. [25] The 100-Hz high-frequency limit ensures that tracings are of sufficient fidelity to assess QRS morphology and to evaluate rapid rhythms such as atrial flutter accurately. The low-frequency limit of 0.05 Hz allows accurate representation of slower events such as P-wave and T-wave morphology and ST-segment excursion. Most modern ECG monitors allow the operator a choice among several bandwidths. The actual filter frequencies tend to vary among manufacturers. One manufacturer (Hewlett Packard, Andover, Mass) allows a choice among a "diagnostic mode" with a bandwidth of 0.05 to 130 Hz for adults and 0.5 to 130 Hz for neonates, a "monitoring mode" with a bandwidth of 0.5 to 40 Hz for adults and 0.5 to 60 Hz for neonates, and a "filter mode" with a bandwidth of 0.5 to 20 Hz. The importance of bandwidth selection on the detection of perioperative myocardial ischemia was evaluated by Slogoff et al. [31] These investigators simultaneously used five ECG systems: a Spacelabs (Redmond, Wash) Alpha 14 model series 3200 Cardule with bandwidths of 0.05 to 125 Hz or 0.5 to 30 Hz, a Marquette Electronics (Milwaukee, Wisc) MAC II ECG with 0.05 to 40 Hz or 0.05 to 100 Hz, and a Del Mar (Cincinatti, Ohio) Holter recorder at 0.1 to 100 Hz. The ST-segment positions with the three systems using the lower filter limit (0.05 Hz) recommended by the AHA were similar, whereas on the Spacelabs (0.5 to 30 Hz), they were consistently more negative. The ST-segment displacement on the Holter recorder was consistently less negative and less positive. In at least one automatic ST-segment analysis system (Hewlett Packard, Andover, Mass), the lower frequency filter (0.05 Hz) is automatically activated when the ST analyzer is in use.

INDICATIONS

Diagnosis of Arrhythmias

Arrhythmias are common during surgery, and their causes are numerous. Using continuous electromagnetic tape recordings, Bertrand et al [32] reported an 84 percent incidence of supraventricular and ventricular arrhythmias in 100 patients during surgery. These arrhythmias were most common during endotracheal intubation or extubation and occurred more frequently in patients with preexisting cardiac disease (60% versus 37%). In a study of patients undergoing cardiac surgery, Angelini et al [33] reported that in 29 of 50 patients (58%) having valve surgery and in 35 of 78 patients (45%) undergoing coronary revascularization, significant postoperative arrhythmias developed. There are several major factors contributing to the development of perioperative arrhythmias:

1. *General anesthetics:* Halogenated hydrocarbons, such as halothane or enflurane, produce arrhythmias, probably by a reentrant mechanism. [34] Halothane also sensitizes the myocardium to endogenous and exogenous catecholamines. Drugs that block the reuptake of norepinephrine, such as cocaine and ketamine, can facilitate the development of epinephrine-induced arrhythmias (Ch. 3).
2. *Local anesthetics:* Regional anesthesia by central neuraxial blockade, the goal of spinal or epidural anesthesia, may be associated with a profound albeit transient pharmacologic sympathectomy. This phenomenon may cause parasympathetic nervous system dominance leading to bradyarrhythmias from mild to very severe. This is especially true when the blockade extends to very high thoracic levels (Ch. 39).
3. *Abnormal arterial blood gases or electrolytes:* Edwards et al [35] showed that hyperventilation to a Pa CO_2 of 30 or 20 mm Hg lowered a normal serum potassium to 3.64 or 3.12 mEq/L, respectively. If serum potassium and total body potassium start at low levels, it is possible to decrease the serum potassium to the 2-mEq/L range by hyperventilation and thus precipitate severe cardiac arrhythmias. Alterations of blood gases or electrolytes may lead to arrhythmias either by producing reentrant mechanisms or by altering phase 4 depolarization of conduction fibers. Electrolyte disturbances associated with cardiopulmonary bypass can also lead to intraoperative arrhythmias (Ch. 38) .
4. *Endotracheal intubation:* This maneuver may be the most common cause of arrhythmias during surgery and is often associated with hemodynamic disturbances (Ch. 39) .
5. *Reflexes:* Vagal stimulation may produce sinus bradycardia and may allow ventricular escape mechanisms to occur. It may also produce AV block or even asystole. In vascular surgery, these reflexes may be related to traction on the peritoneum or to direct pressure on the vagus nerve during carotid surgery (Ch. 51) . During jugular vein cannulation, stimulation of the carotid sinus may occur due to pressure from fingers and can lead to bradyarrhythmias. Specific reflexes, such as the oculocardiac reflex, can produce severe bradycardia or asystole.
6. *Central nervous system stimulation and dysfunction of the autonomic nervous system:* Many ECG abnormalities can occur in patients with intracranial disease, especially subarachnoid hemorrhage. These abnormalities include changes in Q-T intervals, development of Q waves, ST-segment changes, and the occurrence of U waves (Ch. 52) . [36] The mechanism of these arrhythmias appears to be related to changes in autonomic nervous system tone.
7. *Preexisting cardiac disease:* Angelini et al [33] showed that patients with known cardiac disease have a much higher incidence of arrhythmias during anesthesia than do patients without known disease.
8. *Central venous cannulation:* The insertion of catheters or wires into the central circulation often leads to arrhythmias (Ch. 30).
9. *Surgical manipulation of the cardiac structures:* Arrhythmias are often noted during insertion of atrial sutures or placement of venous bypass cannulas (Chs. 49 and 50) .
10. *Location of surgery:* Dental surgery is often associated with arrhythmias, because profound stimulation of both sympathetic and parasympathetic nervous systems often occurs. [37] Junctional rhythms are often seen and may be due to stimulation of the autonomic nervous system via the fifth cranial nerve.

Once an arrhythmia is recognized, it is important to determine whether it produces a hemodynamic disturbance, what type of treatment is required, and how urgently therapy should be instituted. Treatment should be initiated promptly if the arrhythmia results in marked hemodynamic

---

impairment. Additionally, treatment should be instituted if the arrhythmia is a precursor of a more severe arrhythmia (e.g., frequent multifocal ventricular premature beats [VPB] with R-on-T phenomenon can lead to ventricular fibrillation), or the arrhythmia may be detrimental to the patient's underlying cardiac disease (e.g., tachycardia in a patient with mitral stenosis). For the detection of rhythm disturbances, the standard limb lead II is preferred because it usually displays large P waves.

Treatment of Arrhythmias

The diagnosis and treatment of arrhythmias can be simplified by using the following six questions as a checklist when looking at an ECG display and attempting to decide whether treatment is necessary:

1. What is the heart rate?
2. Is the rhythm regular?
3. Is there one P wave for each QRS complex?
4. Is the QRS complex normal?
5. Is the rhythm dangerous?
6. Does the rhythm require treatment?

Following are some common intraoperative arrhythmias to which the six questions should be applied.

Sinus Bradycardia

The pacemaker site is in the sinus node, but the rate is slower than normal. Etiologic factors include drug effects, acute inferior myocardial infarction, hypoxia, vagal stimulation, and high sympathetic blockade. Sinus bradycardia accounts for 11 percent of intraoperative arrhythmias:

1. *Heart rate:* 40 to 60 beats/min. In patients on chronic beta blocker therapy, it is defined as a heart rate of less than 50 beats/min.
2. *Rhythm:* The rhythm is regular, except for occasional escape beats from other pacemaker sites.
3. *P*: *QRS:* There is 1:1 relationship between the P waves and the QRS complexes.
4. *QRS complex:* Normal.
5. *Significance:* Heart rates lower than 40 beats/min are poorly tolerated even in healthy patients and should be evaluated on the basis of their effect on cardiac output. Treatment is recommended if hypotension, ventricular arrhythmias, or signs of poor peripheral perfusion are observed. Sinus bradycardia may be part of the sick sinus syndrome in which sinus node dysfunction can precipitate bradycardias, heart block, tachyarrhythmias, or alternating bradytachyarrhythmias [38]

(Fig. 32-13) (Figure Not Available) .

6. *Treatment:* Usually none is necessary, but a progression from atropine (0.5-1.0 mg intravenous [IV] bolus, repeated every 3-5 min up to 0.04 mg/kg or approximately 3.0 mg total dose for the average 75-kg male), to ephedrine (5-25 mg IV bolus), dopamine (5-20 mug/kg/min IV infusion), epinephrine (1-10 mug/min IV infusion), or isoproterenol (1-4 mug/min IV infusion) to temporary transcutaneous pacing or transvenous pacemaker insertion may be necessary for severe or refractory sinus bradycardia.

Sinus Tachycardia

The pacemaker site is in the sinus node, but the rate is faster than normal. Sinus tachycardia is the most commonly occurring arrhythmia in the perioperative period. It occurs with such frequency that it is not included in most incidence studies. Common causes include pain, inadequate anesthesia, hypovolemia, fever, hypoxia, hypercarbia, heart failure, and drug effects. [4]

1. *Heart rate:* The rate is faster than 100 beats/min in the adult patient and can go up to 170 beats/min, which may be seen during a severe episode of hyperpyrexia.
2. *Rhythm:* Regular.
3. *P*: *QRS:* 1:1.
4. *QRS complex:* Normal. There may be associated ST-segment depression with severe increases in heart rate and resulting myocardial ischemia.
5. *Significance:* Prolonged tachycardias in patients with underlying heart disease can precipitate congestive heart failure owing to the increased myocardial work required. The tachycardia decreases coronary perfusion time, which can cause secondary ST-T-wave changes and can precipitate angina pectoris in patients with coronary artery disease. A major diagnostic problem is encountered when the heart rate is 150 beats/min, because this is a common rate for sinus tachycardia, paroxysmal atrial tachycardia (PAT), or atrial flutter with a 2:1 block. These three arrhythmias can

sometimes be separated by the use of carotid sinus massage, intravenous administration of edrophonium, or atrial or esophageal ECG leads to identify the P waves on the ECG more accurately.

6. *Treatment:* The underlying disorder should be treated. If necessary, while determining the cause, esmolol or propranolol should be used in patients with ischemic heart disease who develop ST-segment changes, to prevent further myocardial ischemia.

Figure 32-13 (Figure Not Available) Sick sinus syndrome. *(From Marriott [81])*

Sinus Arrhythmia

The pacemaker impulse arises from the SA node, but the arrhythmia is manifested by alternating periods of slower and faster heart rates. The P-R interval is normal, as is the QRS complex. Most commonly, but not invariably, the rate increases with inspiration and decreases with expiration. This arrhythmia occurs more often in children than in adults. [4]

1. *Heart rate:* 60 to 100 beats/min.
2. *Rhythm:* Irregular.
3. *P*: *QRS:* 1:1.
4. *QRS complex:* Normal.
5. *Significance:* Normal finding.
6. *Treatment:* None.

Atrial Premature Beats

An ectopic pacemaker site in either the left or the right atrium initiates the atrial premature beat (APB). The shape of the P wave is different from the usual SA node P wave and may be inverted. The P-R interval may be shorter or longer than normal, depending on the site of the ectopic focus and on the refractoriness of the AV nodal pathway. The APB spreads not only through the AV node and ventricular conduction system, but also in retrograde fashion reaches the SA node, thus resetting the sinus pacemaker. The interval from the APB to the next sinus beat is therefore a normal sinus cycle (i.e., no compensatory pause). The absence of a compensatory pause is an important distinguishing feature between APB and VPB. Occasionally, APB may find part of the ventricular conduction system refractory. In that case, they travel down an aberrant pathway and create an abnormal QRS complex. They are then called APB with aberrant ventricular conduction and can easily be confused with VPB. Because the recovery period of the right ventricular conduction system outlasts that of the left, the most common form of aberration appears as a right bundle branch block (RBBB). Helpful points in separating APB with aberrant ventricular conduction from VPB include (1) the presence of a preceding P wave, usually abnormally shaped, (2) an RBBB configuration of the QRS complex, (3) the presence of an rsR
ventricular complex in V_1 , and (4) the finding that the initial vector forces are identical to the preceding beat but are usually the opposite with a VPB. Other characteristics of APB are as follows:

1. *Heart rate:* Variable, depending on the frequency of APB.
2. *Rhythm:* Irregular.
3. *P*: *QRS:* Usually 1:1. The P waves have various shapes and may even be lost in the QRS or T waves. Occasionally, the P wave is so early as to find the ventricle refractory, and a nonconducted beat occurs.
4. *QRS complex:* Usually normal unless there is ventricular aberration.
5. *Significance:* In one study, APB represented 10 percent of all intraoperative arrhythmias. They have little clinical significance, but frequent APB may lead to other more serious supraventricular arrhythmias or may be a sign of digitalis intoxication.
6. *Treatment:* Rarely necessary, but digitalis, beta blockers, or verapamil may be considered if hemodynamic function is impaired.

Paroxysmal Supraventricular Tachycardia

Paroxysmal SVT (PSVT) is characterized by a rapid regular rhythm usually with a narrow QRS complex and lacking the normal SA node P wave. The inclusion of tachycardias involving the AV node (Fig. 32-14) (Figure Not Available) allows for their useful classification as due to reentry in the AV node, apparent or concealed accessory AV pathways, or, less often, SA node reentry (Table 32-4) (Table Not Available) . Ectopic atrial or ectopic nodal tachycardias are also among the less frequent SVT. Inappropriate or persistent sinus tachycardia is another variant. PSVT rhythms are usually abrupt in both onset and termination. PSVT is easily distinguished from rapid atrial fibrillation, which is an irregular rhythm, or rapid atrial flutter, which has flutter waves.

1. *Heart rate:* 130 to 270 beats/min.
2. *Rhythm:* Usually regular unless the impulse originates from multiple atrial foci.
3. *P*: *QRS:* There is a 1:1 relationship, although the P wave may often be hidden in the QRS complex or T wave.
4. *QRS complex:* Generally normal, but ST-T changes indicative of ischemia may be noted. Aberration of ventricular conduction may occur, complicating the differential diagnosis with ventricular tachycardia. SVT may also be confused with sinus tachycardia, atrial flutter, and atrial fibrillation. In differentiating these rhythms, carotid sinus massage or edrophonium (5-10 mg IV) traditionally was used. More recently, adenosine, 6 to 12 mg by IV bolus, has been used to slow the rate by transiently enhancing the normal degree of AV block or terminate the arrhythmia. [39] Esophageal ECG leads may also be helpful to better define atrial activity. [40]

5. *Significance:* PSVT can be seen in 5 percent of normal young adults and in patients with Wolff-Parkinson-White syndrome or other preexcitation syndromes. During anesthesia, PSVT accounts for up to 2.5 percent of all arrhythmias, and the arrhythmia has been associated with intrinsic heart disease, systemic illness, thyrotoxicosis, digitalis toxicity, pulmonary embolism, and pregnancy. When a patient is under anesthesia, PSVT can be precipitated by changes in the autonomic nervous system tone, by drug effects, or by intravascular volume shifts and can produce severe hemodynamic deterioration. At times, the PSVT may

be associated with AV block, owing to the fast atrial rate and slow AV conduction. PSVT with 2:1 block represents digitalis intoxication in many patients.

6. *Treatment:* This arrhythmia often must be treated because of its rapid rate and associated poor hemodynamic function. Several steps can be taken to treat this arrhythmia:
   a. Vagal maneuvers such as carotid sinus massage, which should only be applied to one side. [41] [42] [43]
   b. Adenosine, which is the drug of choice: 6-mg rapid IV bolus, preferably via an antecubital or more central vein. If no response is elicited, second and third doses of 12 to 18 mg adenosine may be administered by rapid IV bolus. [44]
   c. Verapamil (2.5-10 mg IV), which terminates AV nodal reentry successfully in about 90 percent of cases (was the drug of choice and is now second choice). [45]
   d. Esmolol (1-mg/kg bolus and 50-200-g/kg/min infusion), which has been shown effective. [46]
   e. Propranolol, in 0.5-mg IV bolus doses.
   f. Edrophonium, in 5- to 10-mg IV bolus doses. [47]
   g. Phenylephrine (100-mug IV bolus) if the patient is hypotensive. [47]
   h. Intravenous digitalization with one of the short-acting digitalis preparations: ouabain (0.25-0.5 mg IV) or digoxin (0.5-1.0 mg IV). [48]
   i. Rapid overdrive pacing, in an effort to capture the ectopic focus. [49]
   j. Synchronized cardioversion with incremental doses of energy of 100, 200, 300, and 360 J, preferably after light sedative premedication with a benzodiazepine. [50]
   k. Procainamide, in addition to cardioversion or antitachycardia pacing. Procainamide may be useful to treat SVT when antegrade conduction across an accessory AV path is the suspected mechanism.

TABLE 32-4 -- Classification of Supraventricular Tachycardia

(Not Available)

(From Marriott [81])

Figure 32-14 (Figure Not Available) Diagrammatic representation of various mechanisms of supraventricular tachycardia. S-AN = sinus node, BP = bypass tract, A-VN = A-V node. *(Modified from Marriott [81])*

Electrode catheter ablation using radiofrequency energy has evolved as the definitive, long-term treatment for most persistent AV reentrant or focal atrial SVT. [51]

Atrial Flutter

Atrial flutter most commonly represents a macro-reentrant arrhythmia that circulates in a specific manner in the right atrium (counterclockwise rotation as viewed in the angiographic left anterior oblique view). Because it is associated with very fast heart rates, it is usually accompanied by AV block. Classic sawtooth flutter waves (F waves) are usually present. The characteristics of atrial flutter are as follows:

1. *Heart rate:* The atrial heart rate is 250 to 350 beats/min with a ventricular rate of about 150 beats/min (2:1 or 3:1 AV conduction block).

2. *Rhythm:* The atrial rhythm is regular. The ventricular rhythm may be regular if a fixed AV block is present or irregular if a variable block exists.
3. *P*: *QRS:* Usually, there is a 2:1 block with an atrial rate of 300 beats/min and a ventricular rate of 150 beats/min, but it may vary between 2:1 and 8:1. F waves are best seen in leads V_1 , II, and the esophageal lead.
4. *QRS complex:* Normal. T waves are lost in the F waves.
5. *Significance:* It usually indicates the presence of severe heart disease. It is seen with increased incidence in patients with coronary artery disease, mitral valve disease, pulmonary embolism, hyperthyroidism, cardiac trauma, cancers of the heart, and myocarditis.
6. *Treatment:* The initial treatment should be control of the ventricular response rate with agents that slow AV node conduction:
   a. Beta blockers such as IV esmolol, 1-mg/kg IV bolus (or propranolol).
   b. Calcium channel blockers such as verapamil, 5 to 10 mg IV (or diltiazem). [52]
   If the ventricular response is excessively rapid and/or secondary hemodynamic instability is present:
   c. Synchronized direct current (DC) cardioversion starting with a relatively high energy of 100 J and gradually increasing to 360 J is indicated. [53]
   d. The class III antiarrhythmic agent ibutilide (Corvert, 1 mg in 10 mL saline or D_5W, infused IV slowly over 10 min) has been documented to convert atrial flutter to sinus rhythm in a majority of patients with relatively new-onset atrial flutter. [54] This may be repeated once, [55] and although it is highly effective, life-threatening torsades de pointes (see later) may occur hours after ibutilide administration, thus making 4- to 8-hour monitoring after treatment highly desirable.
   e. Procainamide (5-10-mg/kg IV loading dose infused no faster than 0.5 mg/kg/min) may rarely be used in attempt to restore sinus rhythm after the ventricular response has been adequately controlled. [56]
   f. Rapid atrial pacing from within the atrium enhanced by ibutilide or procainamide also effectively terminates atrial flutter. [57]

Atrial Fibrillation

Atrial fibrillation is an excessively rapid and irregular atrial focus with no P waves appearing on the ECG, but, instead, a fine fibrillatory activity called f waves. This is the most irregular rhythm: it is called irregularly irregular and may be associated with a pulse deficit. The characteristics are as follows:

1. *Heart rate:* The atrial rate is 350 to 500 beats/min, and the ventricular rate is 60 to 170 beats/min.
2. *Rhythm:* Irregularly irregular.
3. *P*: *QRS:* The P wave is absent and is replaced by f waves or no obvious atrial activity at all.
4. *QRS complex:* Normal.
5. *Significance:* The causes of atrial fibrillation are similar to those of atrial flutter. This rhythm is often associated with significant cardiac disease; however, idiopathic, lone paroxysmal atrial fibrillation has become increasingly recognized. The clinical significance and treatment of atrial fibrillation are also similar to those of atrial flutter, except for two important considerations. The loss of an atrial "kick" secondary to inefficient contraction of the atria may reduce ventricular filling and may significantly compromise cardiac output. In addition, after 24 hours, atrial fibrillation may be associated with the development of atrial thrombi, with resultant pulmonary and systemic embolization.
6. *Treatment*
   a. *Acute atrial fibrillation:* Treatment of acute atrial fi-brillation is very similar to that for atrial flutter. More attention should be focused on ventricular response, especially with the administration of IV diltiazem or esmolol. Ibutilide may restore sinus rhythm, but it is less effective than in the treatment of flutter. [54] [55] Synchronized DC cardioversion should be relied on in patients with pronounced hemodynamic instability. However, if fibrillation is present for longer than 48 hours, attempts to restore sinus rhythm may be associated with a heightened risk of embolization. In this setting, in a patient with normal coagulation function, adequate anticoagulation for 3 to 4 weeks should be considered prior to attempting to restore sinus rhythm.
   b. *Long-term therapy:* Long-term therapy of atrial fibrillation varies and depends on factors such as whether the arrhythmia is constant or paroxysmal, the nature of the underlying heart disease, and the state of ventricular function or hemodynamic stability/reserve. In the older individual or in the setting of specific risk factors (e.g., hypertension, diabetes mellitus, severe left-ventricular systolic dysfunction), anticoagulation with warfarin should be strongly considered. When control of ventricular response is difficult with standard agents (e.g., beta blockers, calcium channel blockers, digitalis), electrode catheter ablation of the AV junction and permanent pacemaker insertion have seen increased use. These are definitive, curative, not merely rate-control procedures. In the absence of coronary artery disease or significant left-ventricular systolic dysfunction, class 1c antiarrhythmic agents (flecainide or propafenone) have become the agents of choice. [58] Use of class 1a drugs (quinidine, procainamide, disopyramide) has sharply diminished because of concerns about their significant proarrhythmic function, as well as their systemic and organ side effects. Off-label use of antiarrhythmic drugs that block repolarizing potassium currents (e.g., sotalol [59] and amiodarone [60] [61] has gained popularity for the suppression of atrial fibrillation in individuals with significant structural heart disease; however, controlled trials that document efficacy are still lacking.

Junctional Rhythms

The AV node itself shows no intrinsic phase 4 depolarization. Therefore, cells in the node cannot act as pacemakers. Ectopic activity, however, may be initiated from sites just above and below the AV node. It makes sense to consider these arrhythmias as AV junctional in nature. The resultant P wave is abnormal and, depending on the position of the ectopic pacemaker, may be very close to, buried in, or following the QRS complex. Depending on the rate of fire of the ectopic pacemaker, the resultant rhythm is nodal premature,

---

nodal quadrigeminy, trigeminy, or bigeminy, nodal rhythm, or nodal tachycardia.

1. *Heart rate:* Variable, 40 to 180 beats/min (nodal bradycardia to junctional tachycardia).
2. *Rhythm:* Regular.
3. *P*: *QRS:* 1:1 but, there are three varieties:
   a. *High-nodal rhythm:* The impulse reaches the atrium before the ventricle; therefore, the P wave precedes the QRS but has a shortened P-R interval (0.1 s).
   b. *Mid-nodal rhythm:* The impulse reaches the atrium and the ventricle at the same time. The P wave is lost in the QRS.
   c. *Low-nodal rhythm:* The impulse reaches the ventricle first and then the atrium, so that the P wave follows the QRS complex.
4. *QRS complex:* Normal, unless altered by the P wave.
5. *Significance:* Junctional rhythms are common in patients under anesthesia (20%) especially with halogenated anesthetic agents. The junctional rhythms frequently decrease blood pressure and cardiac output by about 15 percent, but they can decrease it up to 30 percent in patients with heart disease. [62]
6. *Treatment:* Usually, no treatment is required, and the rhythm reverts spontaneously. If hypotension and poor perfusion are associated with the rhythm, treatment is indicated. Atropine, ephedrine, or isoproterenol can be used in an effort to increase the activity of the SA node so it will take over as the pacemaker. A small dose of succinylcholine (10 mg IV) may revert a nodal rhythm to a sinus rhythm during anesthesia with halothane or enflurane. This probably works as a result of the effect of succinylcholine as a sympathetic ganglionic stimulator. In some cases, propran-olol may correct the rhythm disturbance if it is due to sympathetic stimulation. Dual-chamber electrical pacing at a rate faster than a slow nodal rhythm is another option. For a comparative description of different physical methods to terminate junctional tachycardia, the reader is referred to a review. [63]

Ventricular Premature Beats

VPBs result from ectopic pacemaker activity arising below the AV junction. The VPB originates in and spreads through the myocardium or ventricular conducting system, resulting in a wide (>0.12-s), bizarre QRS complex. The ST segment usually slopes in the direction opposite to that of the main deflection of the QRS complex. There is no P wave associated with a VPB, but retrograde depolarization of the atria or blocked sinus beats may obscure the diagnosis.

The most important entity in the differential diagnosis is APB with aberrant ventricular conduction. The distinction should be made whenever possible.

Although an APB normally reaches the SA node and resets the sinus rhythm, such an occurrence is rare when the ectopic pacemaker is in the ventricle. Therefore, a VPB often blocks the next depolarization from the SA node, but the following sinus beat occurs on time. The result is a compensatory pause, consisting of the interval from the VPB to the expected normal QRS, which is blocked at the AV node, plus a normal sinus interval.

VPBs are common during anesthesia, accounting for 15 percent of observed arrhythmias. They are much more common in anesthetized patients with preexisting cardiac disease. Other than heart disease, known etiologic factors include electrolyte and blood gas abnormalities, drug interactions, brain-stem stimulation, and trauma to the heart.

1. *Heart rate:* Depends on the underlying sinus rate and frequency of the VPBs.
2. *Rhythm:* Irregular.
3. *P*: *QRS:* No P wave with the VPB.
4. *QRS complex:* Wide and bizarre with a width of more than 0.12 second. If it is of an RBBB nature, prominent R forces are present in V_1. If left bundle branch block (LBBB) in appearance, notching of the S wave and less acute downslopes are common.
5. *Significance:* The new onset of VPBs must be considered life-threatening because, in certain clinical situations, the arrhythmia may progress to ventricular tachycardia or fibrillation. These situations include coronary artery insufficiency, myocardial infarction, digitalis toxicity with hypokalemia, and hypoxemia. VPBs are more likely to lead to fibrillation if they are multiple, multifocal, or bigeminal, occur near the vulnerable period of the preceding ventricular repolarization (the so-called R-on-T phenomenon), [64] or appear in short-long-short coupling sequences.
6. *Treatment:* The first step is to correct any underlying abnormalities such as decreased serum potassium or low arterial oxygen tension. If the arrhythmia is of hemodynamic significance or if it is believed to be a harbinger of worse arrhythmias, lidocaine is usually the treatment of choice, with an initial bolus dose of 1.5 mg/kg. Recurrent VPBs can be treated with a lidocaine infusion of 1 to 4 mg/min; additional therapy can be supplied with esmolol, propranolol, procainamide, quinidine, disopyramide, atropine, verapamil, or overdrive pacing.

Ventricular Tachycardia

The presence of three or more sequential VPBs defines ventricular tachycardia. Diagnostic criteria include the presence of fusion beats, capture beats, and AV dissociation. The specific morphologic appearance of the QRS complex may also be helpful in distinguishing ventricular tachycardia from other arrhythmias. The characteristics of ventricular tachycardia are as follows:

1. *Heart rate:* 100 to 200 beats/min.
2. *Rhythm:* Usually regular, but may be irregular if the ventricular tachycardia is paroxysmal.
3. *P*: *QRS:* No fixed relationship, because ventricular tachycardia is a form of AV dissociation in which the P waves can be seen marching through the QRS complex.
4. *QRS complex:* Wide, more than 0.12 second in width, with similar morphologic criteria in lead V_1 as for VPB.
5. *Significance:* Acute onset is life-threatening and requires immediate treatment.
6. *Treatment:* Lidocaine IV bolus followed by infusion is indicated, and immediate cardioversion may also be needed. Recurrent episodes may require therapy with procainamide, amiodarone, bretylium, or any of the drugs used in the treatment

---

of VPB. IV amiodarone has been shown to be as effective as bretylium. [65] Amiodarone is administered as one or more doses of 150 mg IV in 100 mL saline or D_5 W over 10 minutes followed by an IV infusion of 1 mg/min for 6 hours and 0.5 mg/min thereafter. Although amiodarone is associated with substantially less hypotension compared with bretylium, hypotension and bradycardia are its main side effects. Its pharmacologic effects persist for more than 45 days.

Ventricular Fibrillation

Ventricular fibrillation is an irregular rhythm resulting either from a rapid discharge of impulses from one or more ventricular foci or from multiple wandering reentrant circuits in the ventricles. The ventricular contractions are erratic and are represented on the ECG by bizarre patterns of various sizes and configurations. P waves are not seen. Important causes of the arrhythmia include myocardial isch-emia, hypoxia, hypothermia, electric shock, electrolyte imbalance, and drug effects. The characteristics are as follows:

1. *Heart rate:* Rapid and grossly disorganized.

2. *Rhythm:* Totally irregular.
3. *P*: *QRS:* None seen.
4. *QRS complex:* Not present.
5. *Significance:* There is no effective cardiac output, and life must be sustained by artificial means, such as external cardiac massage.
6. *Treatment:* Cardiopulmonary resuscitation must be initiated immediately, and then defibrillation must be performed as rapidly as possible. Asynchronous external defi-brillation should be performed with a DC defibrillator, using 200 to 400 J. In extreme situations, the use of two defibrillators in tandem across the chest, one applied in the anteroposterior direction and the second applied in the left midaxillary to right midaxillary direction, has been suggested. The two devices are discharged simultaneously to increase the likelihood of successful defibrillation. Animal studies have failed to demonstrate the superiority of dual-pathway simultaneous shocks over single-pathway shock. [66] Early administration of repeated doses of 1 mg of magnesium sulfate may facilitate defibrillation. Supportive pharmacologic therapy may include lidocaine, amiodarone, bretylium, procainamide, phenytoin, or esmolol. In some instances, epinephrine is used to coarsen the fibrillation in an attempt to defibrillate the patient. Torsades de pointes, which may mimic ventricular fibrillation or ventricular tachycardia, is a life-threatening arrhythmia that occurs in the presence of disturbed repolarization (hence its association with prolonged Q-T intervals). [67] Discontinuation of drugs that predispose to Q-T-interval prolongation and correction of electrolyte abnormalities are essential in the treatment of torsades de pointes. Acute therapy may include defibrillation, IV magnesium sulfate, IV isoproterenol, overdrive pacing, and IV amiodarone. [68]

Diagnosis of Ischemia

Perioperative myocardial ischemia is predictive of adverse cardiac outcomes [69] (Chs. 30 and 49) . Factors that predispose to the development of perioperative ischemia include the presence of preexisting coronary artery disease and perioperative events that affect the myocardial oxygen balance. Perioperative clinical studies have found a high incidence of ECG evidence of ischemia (20-80%) in patients with coronary artery disease who are undergoing cardiac or noncardiac surgery. [70] [71] The incidence of perioperative myocardial infarction in patients with coronary artery disease with or without previous coronary artery bypass grafting (CABG) has been studied. [72] Most patients without prior CABG in whom perioperative infarction developed had three-vessel disease. The infarction rate in the CABG group was very low, supporting the protective effect of prior CABG before noncardiac surgery. In the anesthetized patient, the detection of ischemia by ECG becomes even more important because the hallmark symptom, angina, is not available.

It has also become evident that a significant number of patients suffer from asymptomatic or "silent ischemia." [73] Silent ischemia is manifested by characteristic ECG signs of ischemia in the absence of angina and is not necessarily associated with changes in hemodynamics or heart rate. Among patients with chronic stable angina who have ST-segment depression during exercise, ambulatory ECG monitoring during daily life identifies transient ambulant ischemic episodes in approximately 40 to 50 percent of patients. In these patients, silent ischemic episodes account for about 75 percent of all ambulant ischemic episodes. [74]

The ECG changes occurring during myocardial ischemia are often characteristic and are detected with careful ECG monitoring. Although the ECG criteria for ischemia were established in patients undergoing exercise stress testing, they may also be applied to anesthetized patients (Table 32-5) . These criteria are (1) horizontal or downsloping ST-segment depression of 0.1 mV, (2) ST-segment elevation of 0.1 mV in a non-Q-wave lead, and (3) slowly upsloping ST-segment depression of 0.2 mV (all measured from 60 to 80 ms after the J point) [75] (Fig. 32-15) (Figure Not Available) . Okin et al [76] studied the relation of the time after the J point at which ST depression is measured to the magnitude of ST-segment depression during peak exercise. These investigators found that a positive exercise ECG (0.1 mV or more of additional horizontal or downsloping ST depression at end-exercise) had a specificity of 96 percent for coronary artery disease when ST-segment depression was measured at either the J point or J + 60 milliseconds. There was no difference in sensitivity of ECG criteria at the J point or at J + 60 ms. However, at J + 60 milliseconds there were significant differences in ST-segment depression at peak exercise among healthy persons, patients with clinical angina, and patients with documented coronary artery disease.

It is commonly believed that monitoring for intraoperative myocardial ischemia is unnecessary in neonates.

TABLE 32-5 -- Electrocardiographic Criteria for Ischemia in Anesthetized Patients

Upsloping ST segment: 2-mm depression, 80 ms after J point
Horizontal ST segment: 1-mm depression, 60-80 ms after J point
Downsloping ST segment: >1 mm from top of curve to PQ junction
ST elevation
T-wave inversion

Figure 32-15 (Figure Not Available) Assessment of ST-segment abnormality in the diagnosis of ischemia. *(From Ellestad [97])*

Whereas ECG lead systems for adults are concerned with the detection of ischemia as well as arrhythmias, neonatal ECG monitoring has focused on arrhythmia recognition alone. Results of some studies, however, suggest that the neonatal heart is more susceptible to ischemia than the adult heart. [77] These studies have demonstrated the importance of calibrated ECG monitoring in neonates with congenital heart disease (Ch. 50) .

Although ST-segment analysis provides sensitive information about myocardial ischemia, it should, nonetheless, be remembered that in about 10 percent of patients, underlying ECG abnormalities hinder the analysis. Such abnormalities include hypokalemia, digitalis administration, LBBB, Wolff-Parkinson-White syndrome, left ventricular hypertrophy with strain, and acute pericarditis (Fig. 32-16) (Figure Not Available) . In these patients, other diagnostic modalities, such as transesophageal echocardiography, should be considered.

Diagnosis of Conduction Defects

Conduction defects can be observed during surgery. They can result from the passage of the pulmonary artery catheter through the right ventricle, or they can be a manifestation of myocardial ischemia. Because high-grade (second- and third-degree AV blocks) conduction defects often have deleterious effects on hemodynamic performance, their intraoperative recognition is important.

Three types of conduction system blocks are possible: SA block, AV heart block, and intraventricular conduction block (Table 32-6) (Table Not Available) . His bundle ECG has greatly improved the understanding of conduction through the heart. [78] In SA block, the block occurs at the sinus node. Because atrial excitation is not initiated, P waves are not found on the ECG. The next

Figure 32-16 (Figure Not Available) Digitalis effect on ST segments and T waves (ectopic atrial rhythm, 2:1 AV block, type 1 second degree AV block, left ventricular hypertrophy with strain). *(From Marriott [81])*

beat can be a normal sinus beat, a nodal escape beat, or a ventricular escape beat.

The second type of heart block is an AV heart block, or AV block, which may be either incomplete or complete. [79] First- and second-degree AV blocks are usually considered incomplete, whereas a third-degree AV block is considered to be complete heart block. First-degree AV block is often found in healthy hearts, but it is also associated with coronary artery disease or digitalis administration. It is characterized by a P-R interval longer than 0.21 second. All atrial impulses progress through the AV node to the Purkinje system. This form of heart block ordinarily requires no treatment (Fig. 32-17) (Figure Not Available) . Second-degree AV block is associated with the conduction of some, but not all, of the atrial impulses to the AV node and into the Purkinje system. It is further subdivided into two specific types. [80] Mobitz type 1, or Wenckebach, block is characterized by progressive lengthening of

TABLE 32-6 -- Conduction Defects

(Not Available)

(From Thys and Kaplan [1])

the P-R interval until an impulse is not conducted and the beat is dropped (Fig. 32-18) (Figure Not Available) . This form of block is relatively benign and often reversible and does not require a pacemaker. It may be caused by digitalis toxicity or myocardial infarction and is usually transient. Mobitz type 1 block reflects disease of the AV node. The other form of second-degree heart block is Mobitz type 2 block, which may reflect disease of the bundle of His and Purkinje tissues, especially when the QRS complex is broad. In this, the less common and more serious form of second-degree heart block, dropped beats occur without any progressive lengthening of the P-R interval (Fig. 32-19). (Figure Not Available) This type of block has a serious prognosis, because it frequently progresses to complete heart block and may require pacemaker insertion prior to major surgical procedures. Third-degree AV block, also called complete heart block, occurs when all electrical activity from the atria fails to progress into the Purkinje system. The atrial and ventricular contractions have no relationship with each other, although each chamber contracts regularly. The ventricular rate is approximately 40 beats/min. The QRS complex may be normal if the pacemaker site is in the AV node, but it is usually widened to longer than 0.12 second when the pacemaker site is located in the ventricle (Fig. 32-20). (Figure Not Available) The heart rate is usually too slow to maintain adequate cardiac output, and syncope or Adams-Stokes syndrome may occur, as well as heart failure. These patients usually require insertion of a transvenous endocardial or epicardial pacemaker to increase their heart rate and cardiac output. The third type of block is an intraventricular conduction disturbance, which is usually classified as LBBB, RBBB, or hemiblock. LBBB is the most serious of these conduction disturbances. Impulses reach the ventricles exclusively through the right bundle branch, hence the wide QRS complex of more than 0.12 second and a wide-notched R wave in leads I, aVL, and V_6 (Fig. 32-21) (Figure Not Available) . The most important leads to study in bundle branch blocks are I, V_1 , and V_6 . The pattern of LBBB in V_6 is similar to that of left ventricular hypertrophy, but exaggerated. An LBBB pattern is always associated with significant cardiac disease. In an RBBB, the QRS complex exceeds 0.11 second and leads V_1 to V_3 have broad rSR
complexes, whereas leads I and V_6 have wide S waves (Fig. 32-22) (Figure Not Available) . RBBB may be of no clinical significance, as opposed to LBBB. However, it is frequently associated with chronic lung disease or atrial septal defects.

Hemiblock is a term used when one of two divisions of the left bundle is blocked, because if both divisions are blocked, complete LBBB exists. Even though hemiblocks are a form of intraventricular block, the QRS complex is not prolonged. Marriott's [81] criteria for left anterior hemiblock are as follows (Fig. 32-23) (Figure Not Available) : (1) left axis deviation (usually -60 degrees); (2) small Q in leads I and aVL and small R in leads II, III, and aVF; (3) a normal QRS duration; (4) a late intrinsicoid deflection in lead aVL (0.045 s); and (5) an increased QRS voltage in limb leads. By contrast, the criteria for a left posterior hemiblock are as follows (Fig. 32-24): (Figure Not Available) (1) right axis deviation (usually +120 degrees); (2) small R in leads I and aVL and small Q in leads II, III, and aVF; (3) a normal QRS duration; (4) a late intrinsicoid deflection in lead aVF (>0.045 s); (5) an increased QRS voltage in limb leads; and (6) no evidence of right ventricular hypertrophy. The hemiblocks can occur by themselves but are often associated with an RBBB to form a bilateral bundle branch block. Patients with an RBBB and a left anterior hemiblock (Fig. 32-25) (Figure Not Available) progress to complete heart block only 10 percent of the time, whereas patients with RBBB and a left posterior hemiblock (Fig. 32-26) (Figure Not Available) often do proceed to complete heart block.

Figure 32-17 (Figure Not Available) First-degree AV block is diagnosed by the presence of a P-R interval onger than 0.21 second. *(From Thys and Kaplan [1])*

Figure 32-18 (Figure Not Available) Mobitz type 1 (or Wenckebach) is diagnosed by the progressive lengthening of the P-R interval until an impulse is not conducted and a dropped beat occurs. *(From Thys and Kaplan [1])*

Trifascicular blocks are usually said to consist of one of the foregoing bilateral bundle branch blocks (i.e., RBBB plus a left fascicular block) in addition to a prolonged PR interval (Fig. 32-27) (Figure Not Available) . Bundle of His ECGs are necessary to determine whether the AV conduction disturbance is, in fact, localized in the AV node or whether it is distal, possibly representing an incomplete fascicular block in the last remaining fascicle.

AUTOMATIC RECORDING

Holter monitoring has been used by a number of anesthesiologists to document the perioperative incidence of arrhythmias and ischemia. In Holter monitoring, ECG information from one or two bipolar leads is recorded by a miniature magnetic tape recorder. Up to 48 hours of ECG signals can be collected. Subsequently, the tape is processed by a playback system, and the ECG signals are analyzed. On most modern systems, the playback unit includes a dedicated computer for rapid analysis of the data and automatic recognition of arrhythmias.

A significant early obstacle to the widespread use of conventional Holter monitoring in the perioperative period was the delayed, retrospective analysis and interpretation. This limitation was overcome by real-time Holter monitors. They record specific ECG segments for later playback, as well as analyze the rhythm and ST segment in real time and alert the user to acute perturbations. [82] A report on validation testing of the SEER real-time digital Holter device (Marquette Electronics, Milwaukee, Wisc) found it highly accurate in detecting ST-segment deviations. [83] These results were obtained with digitally simulated ECG data, and accuracy in the clinical setting remains yet to be validated. A different device, the Q-Med (Q-Med, Inc, Clark, NJ), is a small, continuous ECG recording device that has been used in patients undergoing cardiac and noncardiac surgery. [84] [85] The device not only records the ECG signals, but also it performs an automatic analysis of the ECG tracing and sounds an alarm when ischemic changes are recognized. Abnormal events are selectively stored and are subsequently retrievable. In spite of significant technical progress, however, Holter monitoring continues to be limited primarily to clinical investigations.

COMPUTER-ASSISTED INTERPRETATION

Computer programs for the interpretation of ECG are now widely used. In a large study, the ECG of 1,200 adult patients with known clinical conditions were interpreted by cardiologists and by nine different computer programs. [86] The results demonstrated that, in some cases, computer interpretations

Figure 32-19 (Figure Not Available) Mobitz type 2 second-degree heart block is demonstrated when dropped beats occur without progressive lengthening of the P-R interval. *(From Thys and Kaplan [1])*

Figure 32-20 (Figure Not Available) Complete, or third-degree, heart block is demonstrated by the total dissociation between atrial and ventricular complexes with a ventricular rate about 40 beats/min. *(From Thys and Kaplan [1])*

Figure 32-21 (Figure Not Available) Left bundle branch block. Note the rS pattern in V_1 and the notched rR pattern in V_6 . In V_5 and V_6 a moderate depression of the ST segment is noted. *(From Thys and Kaplan [1])*

of ECG were correct and cardiologists were incorrect when their diagnoses were tested against the clinical evidence. The opposite was twice as likely when the average computer program and the average cardiologist were compared. The computer programs with the best performance were almost as accurate as the best cardiologists in classifying the ECG of patients in seven common diagnostic groups. The study did not the test the computers' abilities, however, in two critical areas: acute myocardial ischemia and arrhythmia recognition. Modern monitoring equipment is highly computerized, and most of the physiologic information is manipulated, analyzed, and stored in the digital format. An early step in data collection therefore involves the conversion of analogue signals (time-variable voltages or amplitudes) into digital format with an analogue-to-digital converter. Once in the digital format, the physiologic information can readily be

Figure 32-22 (Figure Not Available) Right bundle branch block. Note the rSR pattern in lead V_1 with slurring of R reflecting late right ventricular depolarization. *(From Thys and Kaplan [1])*

Figure 32-23 (Figure Not Available) Left anterior hemiblock. Note the left axis deviation and the terminal S in the inferior leads. *(From Thys and Kaplan [1])*

subjected to a variety of analyses. In ECG, the most common analyses, besides rate calculations, are related to arrhythmia recognition and the detection of myocardial ischemia.

Arrhythmias

There is little doubt that, during prolonged visual observation of the ECG on the oscilloscope, certain arrhythmias go undetected. This was clearly demonstrated by Romhilt et al, [87] who showed that coronary care unit nurses failed to detect serious ventricular arrhythmias in 84 percent of their patients. Computers have therefore been designed for the automatic detection of arrhythmias in an attempt to increase the detection of abnormal rhythms. Using an early preproc-essing algorithm called AZTEC, a computer accurately detected 78 percent of ventricular ectopic beats. It measured QRS width, offset, amplitude, and area to classify complexes into morphologic families. [88] In a prospective evaluation of such a system, it was found that the computer accurately detected 95.4 percent of VPB, but only 82.4 percent of supraventricular premature beats.

Other systems have depended on QRS recognition and cross-correlation with stored QRS complexes. [89] In cross-correlation, each detected QRS complex is compared with a list of previously detected complexes. If a complex does not correlate better than 0.9 with a previously stored complex, it is considered to have a new configuration and is added to the list (Fig. 32-28) (Figure Not Available) . Certain points of the complex, such as the P-R interval and ST segment, are stored as a template for future comparison. Whenever a new complex matches an existing template, it is averaged into that template, so that each template represents a running average of all complexes of a particular configuration. [90] Each template is defined as normal, abnormal, or questionable according to previously defined criteria. The AHA has published several parameters that need to be tested to permit a meaningful understanding of a system's values and limitations and to permit reasonable comparison among systems. [25]

Figure 32-24 (Figure Not Available) Left posterior hemiblock in association with biatrial enlargement and nonspecific ST- and T-wave abnormalities. *(From Thys and Kaplan [1])*

Myocardial Ischemia

One method of detecting intraoperative myocardial ischemia is automated ST-segment monitoring. [91] Several computer programs for on-line detection of ischemia and

Figure 32-25 (Figure Not Available) Right bundle branch block in association with left anterior hemiblock. Note the RsR pattern in V_1 and the wide S in the lateral leads. The axis of the initial QRS vector is -88 degrees. *(From Thys and Kaplan [1])*

analysis of ST segments are available commercially. Each manufacturer uses different analysis techniques, and not all the algorithms are in the public domain. In one system (Marquette Electronics, Milwaukee, Wisc), an ST learning phase begins by looking at the first 16 beats, in all leads, for the dominant normal or paced shape. The shapes are correlated using a selected number of points on each of the active valid lead waveforms. An algorithm looks for leads in the fail or artifact mode to determine the number of valid leads used in the analysis. The algorithm also makes all leads positive to enable totaling the sum of the points on the valid

Figure 32-26 (Figure Not Available) Right bundle branch block with left posterior hemiblock. Note the wide S in the lateral leads and the rR pattern in V_1 . The axis of the initial QRS vector is +166 degrees. *(From Thys and Kaplan [1])*

Figure 32-27 (Figure Not Available) Trifascicular block. The P-R interval is 232 milliseconds, and a right bundle branch block is noted. The axis of the QRS vector is -85 degrees, indicating a left anterior hemiblock. *(From Thys and Kaplan [1])*

leads. This sum is used in determining a peak or fiducial point. The fiducial point is used as a point of reference on the QRS. A template is formed from selected points around the fiducial point for each ECG lead. As each beat is analyzed, its template is compared with templates of previous beats. If the templates correlate within 75 percent of a previously stored shape, it is deemed a match and is classified as an existing shape. If there is no match, it becomes a new

Figure 32-28 (Figure Not Available) Computerized "template" of the underlying normal QRS complex (X) and an ectopic complex termed a "test beat" (Y). Beat Y is matched to beat X by the computer during the region of comparison by cross-correlation algorithms. *(Modified from Morganroth [90])*

shape. On the 17th beat, the dominant normal QRS shape or paced shape is determined. The algorithm then searches for an additional 16 beats that correlate with the dominant template. With the 18th beat, a process called incremental averaging is initiated. The incremental averaging is a method of tracking positive or negative changes occurring on the waveform. These changes are tracked for each of the valid leads. The changes may be physiologic, such as ST-segment changes resulting from ischemia or related to artifact caused by high-frequency noise. The tracking of the changes is achieved by only allowing a 0.1-mm adjustment, either positive or negative, from the prior shape of each beat. On the 32nd beat, the product of the incrementally averaged templates become the learned ST templates. Until ST is relearned, all changes in the QRS shape are tracked against this learned template. The isoelectric point and ST points are determined during the learning phase and are based on the width of the QRS shape. The isoelectric point is placed 40 milliseconds prior to the onset of the QRS and the ST point is placed 60 milliseconds past the offset of the QRS measurement. The isoelectric point provides the point of reference for determining the ST-segment measurement. The technique of incremental averaging is well suited to a continuous input with slow changes. It, however, links the speed at which changes occur in the template to the heart rate. [92]

This system was evaluated in the intraoperative setting in patients undergoing cardiac surgery. [93] The device monitored three selected leads and displayed the absolute values of the ST segment as a line. Upward deflection of the trend line indicated worsening ischemia, whereas a downward trend reflected a return of the ST segment toward the isoelectric line. It was concluded that once the device was clinically accepted, the awareness for ischemic changes was heightened among the participating anesthesiologists and therapeutic interventions were more rapidly instituted, possibly leading to improved outcome.

A second ST-segment analysis system (Hewlett Packard, Andover, Mass) differs from the foregoing in several ways. A period of 15 seconds is analyzed first, and the ST displacement is determined on the basis of five "good" beats. These displacements are ranked, and the median value is determined. This technique eliminates the influence of occasional VPBs and ensures that a representative beat is selected. The objective of this procedure is to obtain a representative beat, rather than an average template. The measurement point for the ST segment can be selected as the R wave + 108 milliseconds (default) or the J point + 60 or 80 milliseconds. ST values and representative complexes are stored at 1-minute resolution for the most recent 30-minute trend and at 5-minute resolution for the preceding 7.5-hour trend.

In a third system (Spacelabs, Redmond, Wash), a composite ST-segment waveform is developed every 30 seconds and is compared with a reference tracing acquired during an initial learning period. The isoelectric and ST-segment points can be manually adjusted to any location on the ECG tracing, or they may be automatically set to predetermined values. Using selective ST-segment displacement on seven different types of digitally simulated ECGs, London and Ahlstrom [94] "bench tested" a version of a Spacelabs automated ST-analysis device, the PC2 Bedside monitor. The device performed very well with five of the

---

simulated ECGs, but it had some difficulty with two because of improper placement of the isoelectric point. Visual confirmation of ST-segment analyzer results was therefore advised.

The relative merits and shortcomings of the different ST-segment analysis systems in the clinical setting have not been fully elucidated. The ability of two automated ST-segment analysis systems to detect myocardial ischemia during noncardiac surgery was compared with 8-lead printed ECG and transesophageal echocardiography as reference standards. [95] In this study of 44 patients, the automated ST-analysis systems showed only fair agreement with transesophageal echocardiography or ECG in detecting ischemia. A different, brief cautionary report mentions a case in which automated ST-segment monitoring falsely signaled the presence of intraoperative ischemia. [96]

CONCLUSIONS

The ECG should be monitored in all patients undergoing anesthesia. Although it does not provide information on the mechanical function of the heart, it permits detection of electrical disturbances that can profoundly affect this function. Today, with the judicious use of selected lead combinations, most arrhythmias and ischemic events can be precisely diagnosed in the intraoperative setting. This diagnostic activity is time consuming, however, and there is considerable evidence that many intraoperative ECG changes go undetected. There is little doubt that future technologic developments will facilitate the intraoperative recognition of ECG disturbances and, one hopes, will lead to better patient outcome.

ACKNOWLEDGMENT

The authors acknowledge the contribution of Professor JA Kaplan to this chapter, as well as his continuing inspiration.

References

1. Thys DM, Kaplan JA: The ECG in Anesthesia and Critical Care. New York, Churchill Livingstone, 1987.

2. Cannard TH, Dripps RD, Helwig J et al: The ECG during anesthesia and surgery. Anesthesiology 21:194, 1960.

3. Narang J, Thys DM: Electrocardiographic monitoring. In Ehrenwerth J, Eisenkraft JB, (eds): Anesthesia Equipment: Principles and Applications. St. Louis, CV Mosby-Year Book, 1992, p 284.

4. Skeehan TM, Thys DM: Monitoring the cardiac surgical patient. In Hensley FA, Martin DE (eds): The Practice of Cardiac Anesthesia. Boston, Little, Brown, 1990, p 123.

5. Griffin RM, Kaplan JA: Comparison of ECG V, CS, CB, and II by computerized ST segment analysis (abstract). Anesth Analg 65:S1, 1986.

6. Bazaral MG, Norfleet EA: Comparison of CB and V leads for intraoperative electrocardiographic monitoring. Anesth Analg 60:849, 1981.

7. Hollenberg M, Mateo G, Massie BM et al: Influence of the R-wave amplitude on exercise-induced ST depression: Need for a "gain factor" correction when interpreting a stress electrocardiogram. Am J Cardiol 56:13, 1985.

8. Mark JB, Chien GL, Steinbrook RA et al: Electrocardiographic R-wave changes during cardiac surgery. Anesth Analg 74:26, 1992.

9. Kaplan JA, King SB: The precordial electrocardiographic lead (V) in patients who have coronary artery disease. Anesthesiology 45:570, 1976.

10. London MJ, Hollenberg M, Wong MG et al: Intraoperative myocardial ischemia: Localization by continuous 12 lead electrocardiography. Anesthesiology 69:232, 1988.

11. De Hert SG, De Jongh RF, Van den Bossche AO et al: The detection of intraoperative myocardial ischaemia: Preliminary experience with the right-sided precordial lead. Anaesthesia 44:881, 1989.

12. Herman MV, Ingram DA, Levy JA et al: Variability of electrocardiographic precordial lead placement: A method to improve accuracy and reliability. Clin Cardiol 14:469, 1991.

13. Kates RA, Zaidan JR, Kaplan JA: Esophageal lead for intraoperative electrocardiographic monitoring. Anesth Analg 61:781, 1982.

14. Heinke M, Volkmann H: Balloon electrode catheter for transesophageal atrial pacing and transesophageal ECG recording. PACE 15:1953, 1992.

15. Srivastava P, Mittal SR, Srivastava N: Role of oesophageal electrocardiograms in differentiation of old anteroseptal myocardial infarction from emphysema in cases with poor R wave progression in precordial leads. J Assoc Physicians India 39:249, 1991.

16. Katz A, Guetta V, Ovsyshcher IA: Transesophageal electrocardiography using a temporary pacing balloon-tipped electrode in acute cardiac care. Ann Emerg Med 20:961, 1991.

17. Chatterjee K, Swan HJC, Ganz W et al: Use of a balloon-tipped flotation electrode catheter for cardiac monitoring. Am J Cardiol 36:56, 1975.

18. Lichtenthal PR: Multipurpose pulmonary artery catheter. Ann Thorac Surg 36:493, 1983.

19. Mylrea KC, Calkins JM, Carlson J et al: ECG lead with the endotracheal tube. Crit Care Med 11:199, 1983.

20. Meier B, Killisch JP, Adatte JJ et al: Intrakoronares Elektrokardiogramm wahrend transluminaler Koronarangioplasty. Schweiz Med Wochenschr 115:1590, 1985.

21. Pande AK, Meier B, Urban P et al: Intracoronary electrocardiogram during coronary angioplasy. Am Heart J 124:337, 1992.

22. Maeda T, Saikawa T, Niwa H et al: QT interval shortening and ST elevation in intracoronary ECG during PTCA. Clin Cardiol 15:525, 1992.

23. Mirvis DM, Berson AS, Goldberger AL et al: Instrumentation and practice standards for electrocardiographic monitoring in special care units. Circulation 79:464, 1989.

24. Pipberger HV, Arzbaecher RC, Berson AS et al: Report of the Committee on Electrocardiography, American Heart Association: Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation 52:11, 1975.

25. Sheffield LT, Berson AS, Bragg-Remschel D et al: Recommendations for standards of instrumentation and practice in the use of ambulatory electrocardiography: The task force of the committee on electrocardiography and cardiac electrophysiology of the council on clinical cardiology. Circulation 71:626A, 1985.

26. Association for the Advancement of Medical Instrumentation (AAMI): American National Standards for Pregelled Disposable Electrodes (EC12-1983). Arlington, Va, American National Standards Institute/ AAMI, 1984.

27. Legatt AD, Frost EAM: ECG artifacts during intraoperative evoked potential monitoring. Anesthesiology 70:559, 1989.

28. Paulsen AW, Pritchard DG: ECG artifact produced by crystalloid administration through blood/fluid warmer sets. Anesthesiology 69:803, 1988.

29. Lampert BA, Sundstrom FD: ECG artifacts simulating supraventricular tachycardia during automated percutaneous lumbar discectomy. Anesth Analg 67:1096, 1988.

30. Arbeit SR, Rubin IL, Gross H: Dangers in interpreting the electrocardiogram from the oscilloscope monitor. JAMA 211:453, 1970.

31. Slogoff S, Keats ASS, David Y et al: Incidence of perioperative myocardial ischemia detected by different electrocardiographic systems. Anesthesiology 73:1074, 1990.

32. Bertrand CA, Steiner NV, Jameson AG et al: Disturbances of cardiac rhythm during anesthesia and surgery. JAMA 216:1615, 1971.

33. Angelini L, Feldman MI, Lufschonowski R et al: Cardiac arrhythmias during and after heart surgery: Diagnosis and management. Prog Cardiovasc Dis 16:469, 1974.

34. Atlee JL, Rusy BF: Ventricular conduction times and AV nodal conductivity during enflurane anesthesia in dogs. Anesthesiology 47:498, 1977.

35. Edwards R, Winnie AP, Ramamurthy S: Acute hypocapneic hypokalemia: An iatrogenic anesthetic complication. Anesth Analg 56:786, 1977.

36. Smith M, Ray CT: Cardiac arrhythmias, increased intracranial pressure, and the autonomic nervous system. Chest 61:125, 1972.

37. Alexander JP: Dysrhythmia and oral surgery. Br J Anesth 43:773, 1971.

38. Slapa WJ: The sick sinus syndrome. Am Heart J 92:648, 1976.

39. DiMarco JP, Sellers TD, Lerman BB et al: Daiagnostic and therapeutic use of adenosine in patients with supraventricular tachyarrhythmias. J Am Coll Cardiol 6:417, 1985.

40. Bushman GA: Clinical correlates of dysrhythmias requiring an esophageal ECG for accurate diagnosis in patients with congenital heart disease. J Cardiothorac Anesth 3:290, 1989.

41. Lim SH, Anantharaman V, Teo WS et al: Comparison of treatment of supraventricular tachycardia by Valsalva maneuver and carotid sinus massage. Ann Emerg Med 31:30, 1998.

42. Hess DS, Hanlon T, Scheinman M et al: Termination of ventricular tachycardia by carotid sinus massage. Circulation 65:627, 1982.

43. Aydin M, Baysal K, Kucukoduk S et al: Application of ice water to the face in initial treatment of supraventricular tachycardia. Turk J Pediatr 37:15, 1995.

44. Camm AJ, Garratt CJ: Adenosine and supraventricular tachycardia. N Engl J Med 325:1621, 1991.

45. Di Marco JP, Miles W, Akhtar M et al: Adenosine for paroxysmal supraventricular tachycardia: Dose ranging and comparison with ver-apamil. Assessment in placebo-controlled, multicenter trials: The Adenosine for PSVT Study Group. Ann Intern Med 113:104, 1990.

46. The Esmolol Research Group: Intravenous esmolol for the treatment of supraventricular tachyarrhythmia: Results of a multicenter, baseline-controlled safety and efficacy study in 160 patients. Am Heart J 112:498, 1986.

47. Waxman MB, Wald RW, Sharma AD et al: Vagal techniques for termination of paroxysmal supraventricular tachycardia. Am J Cardiol 46:655, 1980.

48. Basta M, Klein GJ, Yee R et al: Current role of pharmacologic therapy for patients with paroxysmal supraventricular tachycardia. Cardiol Clin 15:587, 1997.

49. Altamura G, Bianconi L, Toscano S et al: Transcutaneous cardiac pacing for termination of tachyarrhythmias. Pacing Clin Electrophysiol 13:2026, 1990.

50. Kerber RE: Electrical treatment of cardiac arrhythmias: Defibrillation and cardioversion. Ann Emerg Med 22:296, 1993.

51. Kay GN, Epstein AE, Daily SM et al: Role of radiofrequency ablation in the management of supraventricular arrhythmias: Experience in 760 consecutive patients. J Cardiovasc Electrophysiol 4:371, 1993.

52. Ellenbogen KA, Dias VC, Cardello FP et al: Safety and efficacy of intravenous diltiazem in atrial fibrillation or atrial flutter. Am J Cardiol 75:45, 1995.

53. Cummins RO (ed): Advanced Cardiac Life Support. Dallas, Tex, American Heart Association, 1997.

54. Ellenbogen KA, Stambler BS, Wood MA et al: Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: A dose-response study. J Am Coll Cardiol 28:130, 1996.

55. Stambler BS, Wood MA, Ellenbogen KA et al: Efficacy and safety of repeated doses of ibutilide for rapid conversion of atrial flutter or fibrillation: Ibutilide Repeat Dose Study Investigators. Circulation 94:1613, 1996.

56. Chapman MJ, Moran JL, O'Fathartaigh MS et al: Management of atrial tachyarrhythmias in the critically ill: A comparison of intravenous procainamide and amiodarone. Intensive Care Med 19:48, 1993.

57. Stambler BS, Wood MA, Ellenbogen KA: Comparative efficacy of intravenous ibutilide versus procainamide for enhancing termination of atrial flutter by atrial overdrive pacing. Am J Cardiol 77:960, 1996.

58. Naccarelli GV, Dorian P, Hohnloser SH et al: Prospective comparison of flecainide versus quinidine for the treatment of paroxysmal atrial fibrillation/flutter: The Flecainide Multicenter Atrial Fibrillation Study Group. Am J Cardiol 77:53A, 1996.

59. Gallik DM, Kim SG, Ferrick KJ et al: Efficacy and safety of sotalol in patients with refractory atrial fibrillation or flutter. Am Heart J 134:155, 1997.

60. Opolski G, Stanislawska J, Gorecki A et al: Amiodarone in restoration and maintenance of sinus rhythm in patients with chronic atrial fibrillation after unsuccessful direct-current cardioversion. Clin Cardiol 20:337, 1997.

61. Daoud EG, Strickberger SA, Man KC et al: Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. N Engl J Med 337:1785, 1997.

62. Haldemann G, Sehaer H: Haemodynamic effects of transient atrioventricular dissociation in general anesthesia. Br J Anaesth 44:159, 1972.

63. Mehta D, Wafa S, Ward DE et al: Relative efficacy of various physical manoeuvers in the termination of junctional tachycardia. Lancet 1:1181, 1988.

64. Cranefeld PF: Ventricular fibrillation. N Engl J Med 289:732, 1973.

65. Kowey PR, Levine JH, Herre JM et al: Randomized double blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent ventricular tachycardia or fibrillation: The Intravenous Amiodarone Multicenter Investigators Group. Circulation 92:3255, 1995.

66. Kerber RE, Bourland JD, Kallok MJ et al: Transthoracic defibrillation using sequential and simultaneous dual shock pathways: Experimental studies. Pacing Clin Electrophysiol 13:207, 1990.

67. Roden DM: Torsade de pointes. Clin Cardiol 16:683, 1993.

68. Roden DM: A practical approach to torsade de pointes. Clin Cardiol 20:285, 1997.

69. Slogoff S, Keats A: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107, 1985.

70. Sonntag H, Larsen R, Hilfiker O et al: Myocardial blood flow and oxygen consumption during high-dose fentanyl anesthesia in patients with coronary artery disease. Anesthesiology 56:416, 1982.

71. Coriat P, Harari A, Daloz M et al: Clinical predictors of intraoperative myocardial ischemia in patients with coronary artery disease undergoing non-cardiac surgery. Acta Anaesthesiol Scand 26:287, 1982.

72. Crutchley P, Kaplan JA, Hug CC et al: Non-cardiac surgery in patients with prior myocardial revascularization. Can Anaesth Soc J 30:629, 1983.

73. Coy KM, Imperi GA, Lambert CR et al: Silent myocardial ischemia during daily activities in asymptomatic men with positive exercise response. Am J Cardiol 59:45, 1987.

74. Pepine CJ: Is silent ischemia a treatable risk factor in patients with angina pectoris? Circulation 82(suppl II):135, 1990.

75. Chaitman BR, Hanson JS: Comparative sensitivity and specificity of exercise electrocardiographic lead systems. Am J Cardiol 47:1335, 1981.

76. Okin PM, Bergman G, Kligfield P: Effect of ST segment measurement point on performance of standard heart rate-adjusted ST segment criteria for the identification of coronary artery disease. Circulation 84:57, 1991.

77. Bell C, Rimar S, Barash P: Intraoperative ST segment changes consistent with myocardial ischemia in the neonate: A report of three cases. Anesthesiology 71:601, 1989.

78. Hecht HH, Kossman EC, Childers RW et al: Atrioventricular and intraventricular conduction: Revised nomenclature and concepts. Am J Cardiol 31:232, 1973.

79. Kastor JA: Atrioventricular block. N Engl J Med 292:462, 1976.

80. Wynands JE: Anesthesia for patients with heart block and artificial cardiac pacemakers. Anesth Analg 55:626, 1976.

81. Marriott HJL: Practical Electrocardiography, 7th ed. Baltimore, William & Wilkins, 1983.

82. Dodds TM, Delphin E, Stone G et al: Detection of perioperative myocardial ischemia using Holter with real-time ST segment analysis. Anesth Analg 67:890, 1988.

83. London MJ: Validation testing of the SEER real-time digital Holter monitor. J Cardiothorac Vasc Anesth 10:497, 1996.

84. Levin RI, Cohen D, Frisbie W et al: Potential for real-time processing of the continuously monitored electrocardiogram in the detection, quantitation, and intervention of silent myocardial ischemia. Cardiol Clin 4:735, 1986.

85. Clements FM, McCann RL, Levin RI: Continuous ST-segment analysis for the detection of perioperative myocardial ischemia. Crit Care Med 16:710, 1988.

86. Willems JL, Abreu-Lima C, Arnaud P et al: The diagnostic performance of computer programs for the interpretation of electrocardiograms. N Engl J Med 325:1767, 1991.

87. Romhilt DW, Bloomfield SS, Chai TC et al: Unreliability of conventional electrocardiographic monitoring of arrhythmia detection in coronary care units. Am J Cardiol 31:457, 1973.

88. Oliver GE, Nolle FM, Wolff GA et al: Detection of premature ventricular contractions with a clinical system for monitoring electrocardiographic rhythms. Comput Biomed Res 4:523, 1971.

89. Shah PM, Arnold JM, Haberen NA et al: Automatic real-time arrhythmia monitoring in the intensive coronary care unit. Am J Cardiol 39:701, 1977.

90. Morganroth J: Ambulatory Holter electrocardiography: Choice of technique and clinical uses. Ann Intern Med 102:73, 1985.

91. Kortly K, Kotter G, Mortara D et al: Intraoperative detection of myocardial ischemia with an ST segment trend monitoring system. Anesth Analg 63:343, 1984.

92. London MJ: Monitoring for myocardial ischemia. In Kaplan JA (ed): Vascular Anesthesia. New York, Churchill Livingstone, 1991, p 249.

93. Kotter GS, Kotrly KJ, Kalbfleisch JH et al: Myocardial ischemia during cardiovascular surgery as detected by an ST segment trend monitoring system. J Cardiothorac Anesth 1:190, 1987.

94. London MJ, Ahlstrom LD: Validation testing of the Spacelabs PC2 ST-segment analyzer. J Cardiothorac Vasc Anesth 9:684, 1995.

95. Ellis JE, Shah MN, Briller JE et al: A comparison of methods for the detection of myocardial ischemia during noncardiac surgery: Automated ST-segment analysis systems, electrocardiography and transesophageal echocardiography. Anesth Analg 75:764, 1992.

96. Brooker S, Lowenstein E: Spurious ST segment depression by automated ST segment analysis. J Clin Monit 11:186, 1995.

97. Ellestad MH: Stress Testing: Principles and Practice. Philadelphia, FA Davis, 1975.

Chapter 33 - Respiratory Monitoring

Richard E. Moon
Enrico M. Camporesi

/das/book/view/29494766/875/359.html

INTRODUCTION

The Oxford English Dictionary defines a monitor as "something that reminds or gives warning." [1] Another defini-tion is "an instrument used to measure continuously or at intervals a condition that must be kept within prescribed limits." [2] If the discussion of monitors were to be confined to the latter definition, perhaps only self-contained instruments (e.g., pulse oximeters) should be discussed in this chapter; however, a wider view is more appropriate. For example, intermittent, although not necessarily at fixed intervals, analysis of arterial blood gases is often an important monitor of a patient's condition and can be considered as a "monitor." We discuss respiratory physiology as it applies to assessment of patient well-being and the appropriate measures that may be obtained either continuously or intermittently.

There is general agreement that patient safety has been enhanced by the development of technologies that permit accurate physiologic monitoring; basic studies to elucidate the causes of mishaps, including incident monitoring; educational efforts by national patient safety organizations such as the Anesthesia Patient Safety Foundation and the Australian Patient Safety Foundation; and the promulga-tion of monitoring standards that have become widely accepted. Eichhorn et al [3] outlined minimal recommended standards for patient monitoring during anesthesia at hos-pitals within the Harvard Medical School system, com-monly referred to as the "Harvard Standards." In addition to monitors of cardiovascular function and patient temperature, these authors suggested that mandatory respiratory monitors include methods of continuous monitoring of patient ventilation (including a breathing system disconnection monitor) and a monitor of oxygen concentration within the patient breathing system. A strong recommendation was made for monitoring end-tidal CO_2 concentrations. Since then, the American Society of Anesthesiologists has also promulgated basic monitoring standards. [4] *

* ASA address: 520 N. Northwest Highway, Park Ridge, IL 60068-2573 USA. ASA standards can be obtained from the World Wide Web at http://www.asahq.org/Standards/SG 03.html.

Figure 33-1 (Figure Not Available) Oxygen transport cascade. A schematic view of the steps in oxygen transport from the atmosphere to the site of utilization in the mitochondrion is shown here. Approximate P_{O_2} values are shown for each step in the cascade, and factors determining those partial pressures are shown within the square brackets. There is a distribution of tissue P_{O_2} values depending on local capillary blood flow, tissue oxygen consumption, and diffusion distances. Mitochondrial P_{O_2} values are depicted as a range because reported levels vary widely. *(Adapted from Nunn. [286]) Reprinted by permission of Butterworth Heinemann, a division of Reed Educational & Professional Publishing Ltd.*

Included in the ASA standards are a requirement for measurement of both inspired oxygen concentration and quantitative assessment of blood oxygenation, such as pulse oximetry. Adequate illumination and exposure of the patient are necessary to assess color. Adequacy of ventilation must be continually evaluated, and quantitative monitoring of carbon dioxide or volume of expired gas is strongly encouraged. When an endotracheal tube is inserted, correct placement of the tube must be verified by clinical assessment and by identification of carbon dioxide in the expired gas. Continual end-tidal carbon dioxide analysis shall be performed from the time of endotracheal tube placement until extubation or initiation of transport to a postoperative care location, using a quantitative method such as capnography. During mechanical ventilation a device capable of detecting airway disconnects shall be in continuous use. *Continual* is defined as *repeated regularly and frequently in steady rapid succession; continuous* is defined as *prolonged without any interruption at any time.*

The limited ability of human organ systems to function anaerobically dictates a transport system that can maintain O_2 delivery to peripheral tissues. The monitoring of one component of this system, the cardiovascular system, is discussed in Chapter 30 . This chapter discusses the other component, the respiratory system, and the appropriate monitoring necessary to detect malfunction in its gas exchange function.

GAS EXCHANGE

The major function of the lung is gas exchange: addition of O_2 to blood and the elimination of CO_2 from blood (Ch. 15) . Because of the close relationship between the partial pressure of CO_2 in blood (P_{CO_2}) and arterial (and hence tissue) pH, it is important to ensure that arterial CO_2 remain within an appropriate physiologic range. Adequate O_2 delivery must also be maintained. Figure 33-1 (Figure Not Available) shows the O_2 cascade from atmospheric gas to the intracellular site of utilization. Assessment of the adequacy of this delivery system may theoretically be made at any step of the cascade. For example, common clinical practice dictates that arterial O_2 content (Pa_{O_2}) should be sufficient. It is common practice to attempt to maintain arterial hemoglobin Hb-O_2 saturation (Sa_{O_2}) above 90 percent. This level is reasonable for two reasons. First, clinical experience supports the notion that maintenance of hemoglobin at 90 percent saturation with O_2 in the presence of adequate cardiac output will provide sufficient O_2 delivery to the tissues. Second, because the Hb-O_2 dissociation curve becomes abruptly steeper at O_2 saturation levels below 90 percent, further decreases in Pa_{O_2} may result in sharp diminution of O_2 content and, hence, O_2 delivery. In addition to Sa_{O_2}, however, O_2 delivery is a function of blood flow and Hb concentration. A target value for Sa_{O_2} of 90 percent or greater should not become a sacrosanct standard for all conditions. Acute altitude hypoxia with Sa_{O_2} values at 80 to 89 percent is well tolerated by normal individuals, even during exercise, at least for periods of several hours, with no evidence of permanent sequelae. [5] [6] [7] It is conceivable that individuals with acute anemia may not tolerate hypoxia as well because of the enhanced reduction in arterial O_2 content.

Alveolar Gases

Before attempting to understand respiratory gas exchange monitoring it is imperative to understand the basis of gas exchange physiology. The lung consists of a heterogeneous collection of gas exchange units (alveoli), with a range of O_2 and CO_2 gas tensions. It is therefore erroneous to speak of "the" alveolar P_{O_2} or P_{CO_2}; however, the concept of a homogeneous lung, in which all alveoli have the same gas tensions, is a useful one. The alveolar partial pressures calculated by using such a model may be thought of as averages for the O_2 and CO_2 partial pressures in the real (nonhomogeneous) lung. The following equations exemplify alveolar P_{O_2} and P_{CO_2} (P_{AO_2} and P_{ACO_2}), or alveolar gas equations.

where V_{CO_2} = CO_2 production rate; V_{O_2} = O_2 consumption rate; V_A = alveolar ventilation rate; k = constant; F_{IO_2} = fractional inspired O_2 concentration; P_{IO_2} = inspired P_{O_2} after humidification = (P barometric - PH_2O) · F_{IO_2}; and R = respiratory quotient = V_{CO_2}/V_{O_2} (usually 0.8).

The equation for P_{ACO_2} is a function of only two variables. In clinical medicine, V_{CO_2} is relatively constant, and P_{ACO_2} is mainly a function of alveolar ventilation V_A, to which it is inversely proportional.

Because

where V_E = respiratory minute ventilation; and V_D = dead-space ventilation, and because alveolar ventilation is usually a constant fraction of minute ventilation:

The alveolar gas equation for CO_2 may be rewritten as

where c is a constant derived from k and k
.

This approximation may not hold if CO_2 production is substantially elevated, for example, during a major motor seizure, shivering, or fever. CO_2 may decrease as a result of general anesthesia or hypothermia. It is altered by approximately 7 percent for each degree (Celsius) change in body temperature, and in the young has been observed to increase up to 3-fold during violent shivering, [8] although in elderly patients (>60 years) the observed increase is only about one-third. [9]

The alveolar gas equation for O_2 (Equation 2) can be used to delineate the following major factors that result in low P_{AO_2}:

1. Low P_{IO_2} (decreased barometric pressure [altitude] or breathing a gas mixture with inspired O_2 fraction [F_{IO_2}] less than 0.21)
2. Elevated P_{ACO_2} (either due to hypoventilation or increased CO_2 production)
3. Reduced respiratory quotient (R); this is usually a minor effect because the physiologic range of R is on the order of 0.7 to 1.2, the latter seen during metabolic acidosis or excessive feeding

Figure 33-2 CO_2 content of arterial blood as a function of P_{CO_2}. For a given P_{CO_2} deoxygenated blood has a higher CO_2 content than oxygenated blood (Haldane effect). Unlike the Hb-O_2 saturation curve, the CO_2 content curve has no plateau and in the clinically useful range can be approximated by a straight line. *(Data from Christiensen et al [289])*

Arterial Blood Gases

The variables that determine alveolar gas tension have been described. The following additional factors also determine the gas tensions in arterial blood:

1. Ventilation/perfusion (V_A/Q) mismatching
2. Right-to-left shunting
3. Diffusion nonequilibrium

To understand fully the role of V_A/Q in determining arterial gas tensions, it is necessary to discard the homogeneous lung model and consider a model with multiple parallel units of gas exchange and blood flow, in which the resulting arterial gas tension is determined by the mixing of different proportions of blood from each gas exchange unit. The gas tensions in each unit depend upon the regional ventilation, perfusion, and diffusion.

Gas exchange units with low or zero V_A/Q ratios have low end-capillary P_{O_2}. The O_2-blood dissociation curve has a plateau at the point at which Hb is fully saturated (see Fig. 33-9), and there is a maximum to which gas exchange units with normal ventilation and perfusion can raise their end-capillary O_2 content. Arterial oxygen content (and hence P_{O_2}) is a flow-weighted average of all gas exchange units. Therefore, under usual conditions, V_A/Q mismatching always results in arterial hypoxemia.*

The effect of V_A/Q mismatching on Pa_{CO_2} is often erroneously assumed to be negligible because Pa_{CO_2} usually can be maintained within the normal range even in the face of severe pulmonary pathology. However, the reason this occurs is that the CO_2-blood dissociation curve (Fig. 33-2) is a

* The only circumstance in which V_A/Q mismatch results in an increase in arterial P_{O_2} is during uptake of nitrous oxide.

Figure 33-3 (Figure Not Available) Arterial P_{O_2} as a function of F_{IO_2} and shunt fraction (Q_S/Q_T). Assumptions are shown on the upper left. The presence of shunt decreases arterial P_{O_2} for a given F_{IO_2}. As Q_S/Q_T increases, supplemental O_2 has progressively less effect on arterial P_{O_2}. *(Modified from Lawler and Nunn [291])*

monotonically increasing one. Moreover, the degree to which Pc_{CO_2} can be increased by units with abnormal V_A/Q is relatively small. The venoarterial P_{CO_2} difference is usually only 5 mm Hg under resting conditions and rarely exceeds 10 mm Hg. Therefore, it is usually possible for lung units with low P_{CO_2} (and hence Pc_{CO_2}) to "compensate" for units with high P_{CO_2}, producing a normal Pa_{CO_2} even in the face of significant V_A/Q abnormality. Although V_A/Q mismatching affects CO_2 exchange to the same degree as it does O_2 exchange, this is often not reflected in the blood gases because, as pointed out previously, compensatory hyperventilation can maintain Pa_{CO_2} within the normal range.

Right-to-left shunting is a special case of V_A/Q mismatch, with a V_A/Q ratio of zero. Blood flowing through a right-to-left shunt, whether intrapulmonary or intracardiac, will have gas tensions equal to mixed venous values. The net effect on arterial P_{O_2} and P_{CO_2} depends on the magnitude of the shunt (Fig. 33-3) (Figure Not Available) and the mixed venous and pulmonary capillary gas tensions. Because a major determinant of mixed venous P_{O_2} (and to a lesser extent mixed venous P_{CO_2}) is cardiac output (Q), changes in Q may modify the degree to which arterial P_{O_2} is determined by pulmonary gas exchange (Fig. 33-4).

Diffusion nonequilibrium is the situation that would exist if the gas tensions in the pulmonary capillary erythrocyte (Pc_{O_2}, Pc_{CO_2}) are not equal to the alveolar gas tensions. This situation can occur under two physiologic conditions: (1) increased pulmonary blood flow such that the erythrocyte does not have sufficient time in the alveolar capillary to enable gas tensions to reach equilibrium, or (2) a thickening of the alveolar-capillary membrane such that the rate of diffusion of gas from alveolus to capillary or vice versa is slowed. For CO_2 diffusion, nonequilibrium would result in arterial P_{CO_2} (Pa_{CO_2}) higher than P_{ACO_2}. For O_2 it would mean that Pa_{O_2} would be less than P_{AO_2}. In practice, there has never been any evidence for failure of diffusion equilibrium of CO_2. Despite much discussion of O_2 diffusion nonequilibrium, it probably rarely exists in clinical medicine. There is evidence for its existence during moderate exercise in patients with interstitial fibrosis and during severe exercise in normal individuals, particularly at high altitudes. [5] In anesthesia or critical care, O_2 diffusion nonequilibrium would probably occur only under very unusual circumstances

Figure 33-4 Effect of cardiac output on P_{O_2}. (A) Arterial and mixed venous O_2 tension and content are shown at a cardiac output of 5 L/min. Assuming a constant V_{O_2}, it can be seen that an increase in cardiac output to 8 L/min (B) will increase the Pa_{O_2} from 78 to 85 mm Hg. The reason for this is that at higher cardiac output Sv_{O_2} increases. The resulting increase in O_2 content of the shunted blood (here assumed to be 10% of cardiac output) then raises arterial O_2 content and hence Pa_{O_2}. P_{O_2} is in mm Hg; O_2 content is in mL/dL.

(e.g., a septic patient with high cardiac output breathing air at the top of Pike's Peak--altitude 4,301 m, barometric pressure 444 mm Hg).

It follows that the most likely causes of low Pa_{O_2} are low inspired P_{O_2}, hypoventilation, and V_A/Q mismatching, including right-to-left shunt (effect modulated by mixed venous P_{O_2}).

A common measurement used to assess the adequacy of pulmonary gas exchange is the A-a gradient:

Calculation of the A-a gradient takes into account any degree of hypoventilation or low inspired P_{O_2} such that an abnormally high A-a gradient reflects either V_A/Q mismatch (more specifically, low V_A/Q units) or shunt. The normal value for a child or young adult is less than 10 mm Hg. The A-a gradient has been related to age in years [10] according to the following formula:

There is considerable scatter of the data around the mean values predicted by this relationship, with individual values for the A-a gradient exceeding 30 mm Hg. The A-a gradient also increases with abnormalities of pulmonary gas exchange. The utility of the A-a gradient may be demonstrated by an example. The interpretation of the following arterial blood gases in an unconscious individual in an emergency room (breathing room air) may be aided by calculating the A-a gradient:

Assuming that barometric pressure equals 760 mm Hg, body temperature is 37°C (therefore P_{H_2O} = 47 mm Hg), and R equals 0.8 (in this case using Equation 2), then P_{AO_2} equals 59 mm Hg. Therefore, the A-a gradient equals 9 mm Hg (59 - 50), a normal value. Because the impairment of arterial oxygenation is associated with a normal A-a gradient, there is no intrinsic abnormality of pulmonary gas exchange. The diagnosis is most likely central respiratory depression.

One problem with the clinical use of the A-a gradient is that the normal value is highly dependent on inspired O_2 concentration. As F_{IO_2} increases, the A-a gradient becomes larger. In a normal individual breathing 100 percent O_2, the A-a gradient can exceed 70 mmHg; therefore, the interpretation of the A-a gradient in a patient breathing supplemental O_2 can be difficult. A more useful parameter is the a/A ratio (Pa_{O_2}/P_{AO_2}). Empirically, the a/A ratio was shown by Gilbert and Keighley [11] to be relatively invariant with F_{IO_2}. This observation of constant a/A ratio is also valid in a hyperbaric chamber up to an ambient pressure of 3 atm abs (Ch. 67). The normal a/A ratio is 0.85; lower values indicate impaired pulmonary gas exchange.

If mixed venous blood is available for analysis, a solution can be found for a simplified but clinically useful compartmental model of the lung. This three-compartment model assumes the following division of gas exchange units within the lung:

1. A compartment with V_A/Q = 1 (optimal matching of ventilation and perfusion).
2. A compartment with V_A/Q = 0 (shunt compartment).
3. A compartment with V_A/Q =
   (dead space compartment).

Shunt fraction (venous admixture) is the proportion of total blood flow perfusing the shunt compartment and can be calculated from the following equation:

where Q_S = shunt blood flow; and Q_T = cardiac output. Cc
O_2, CaO_2, CvO_2 = O_2 content in end-capillary, arterial and mixed venous blood, respectively.

CaO_2 and CvO_2 can be calculated directly. Cc
O_2 must be calculated from P_{AO_2} and the Hb-O_2 dissociation curve.

O_2 content is in mL/dL; P_{O_2} is in mm Hg; Hb concentration is in g/dL.

If P_{AO_2} is sufficiently high that end-capillary blood has Hb-O_2 saturation close to 100 percent, then by dividing numerator and denominator by the O_2 capacity (i.e., O_2 content at 100 percent saturation), Equation 8 can be rewritten as the following approximation:

Q_S/Q_T calculated using either equation (i.e., using oxygen as the "marker gas") includes units of low V_A/Q in addition to pure shunt. Breathing 100 percent O_2, however, eliminates the contribution of low V_A/Q units to Q_S/Q_T because any lung unit with nonzero V_A/Q will fully saturate with O_2 the capillary blood perfusing it. Some clinicians measure blood gases in patients breathing 100 percent O_2 in order to estimate the shunt. Unfortunately, the measurement is complicated by the fact that 100 percent O_2 breathing results in the progressive development of resorption atelectasis and a parallel increase in shunt. [12]

Whereas normal a/A ratio and hence Pa_{O_2} must imply the absence of low V_A/Q ratios or shunt, a normal Pa_{CO_2} does not. Regional hypercapnia may occur in pulmonary capillaries perfusing lung units that are relatively underventilated. A unit may be underventilated because of local airway obstruction or because of a high proportion of underperfused or nonperfused units (dead space) that consume a disproportionate amount of total ventilation. In either case, Pa_{CO_2} can be restored to normal by increasing total ventilation. V_A/Q abnormalities that affect pulmonary CO_2 exchange may not be detectable simply by inspection of the arterial blood gases. A method of assessing the most likely type of abnormality to affect CO_2 exchange is to determine physiologic dead space (V_D) using the Bohr equation:

where P_{ECO_2} = mixed expired P_{CO_2}; and V_T = tidal volume.

Frequently it is assumed that P_{ACO_2} = Pa_{CO_2} (Enghoff modification). To measure P_{ECO_2}, expired gas must be analyzed in a mixing box, or a bag must be used to collect several expired breaths. The dead space calculated using this equation includes anatomic and physiologic dead space as well as external dead space such as in the breathing circuit. Dead space can also be measured on a breath-by-breath basis if a volume capnogram is used. Dead space measured using this formula (total physiologic dead space) includes airway dead space (anatomic or series dead space) and alveolar dead space (intrapulmonary or parallel dead space).

Mixed expired gas analysis is often not clinically available, but an assessment of dead space ventilation may be made by examining the relationship between minute ventilation (V_E) and Pa_{CO_2}. V_E is continuously displayed by modern ventilators and can also be measured in spontaneously breathing individuals by using a spirometer. Assuming normal V_{CO_2}, the following equation describes an empirical relationship [13]:

where W = body weight (kg).

In other words, if V_E (L/min) multiplied by Pa_{CO_2} (mm Hg) exceeds eight times body weight (kg), an increase in dead space exists, indicating that to maintain a normal Pa_{CO_2}, higher than usual ventilation is required. This product may also be elevated by increased CO_2 production (shivering, fever, or metabolic acidosis).

Using the respiratory gases to assess pulmonary gas exchange has some drawbacks. First, the relationship between partial pressure and gas content is nonlinear for both O_2 and CO_2. Alterations in cardiac output, hemoglobin concentration (resulting in altered venous blood gas tensions), or inspired gas composition may lead to different calculated values of Q_S/Q_T or V_D/V_T even if actual V_A/Q ratios in the lung are unchanged. [14] Second, changes in O_2 or CO_2 exchange can only provide information on a limited portion of the spectrum of V_A/Q ratios. Furthermore, an increase in calculated Q_S/Q_T (Equation 8) cannot distinguish between a shift to lower

V A/Q ratios and an increase in true shunt.

In a more sophisticated technique described by Wagner et al, [12] [15] a dilute mixture of several "inert" (not metabolically active) tracer gases is infused intravenously. The ratio of partial pressures Pc
/Pv or P A/Pv at a gas exchange unit is described by the following equation

where Pc
, Pv, P A = partial pressures of the gas in end-capillary blood, venous blood, and alveolar gas, respectively; lambda = blood/gas partition coefficient of the gas; and V A/Q = ventilation/perfusion ratio of the gas exchange unit.

In this technique (multiple inert gas elimination, MIG), the six gases generally used are sulfur hexafluoride, ethane, cyclopropane, enflurane, diethyl ether, and acetone, spanning a range of lambda around 70,000. Each gas provides information about a particular region in the spectrum of V A/Q, permitting a multi-compartment model to be calculated. The MIG method has been used to demonstrate the development of both V A/Q mismatching and shunt during general anesthesia. [16] Figure 33-5 (Figure Not Available) demonstrates the use of MIG to calculate a 50 compartment model of V A/Q. Using this model, shunt fraction assessed by using MIG has been correlated with atelectatic areas in dependent lung regions visible on chest computed tomography (CT) scan (see Fig. 33-5) (Figure Not Available) . [17] [18] MIG has been used to demonstrate improved V A/Q matching during continuous axial rotation in patients with acute lung injury. [19] Although this technique cannot yet be used as an on-line monitor, future development of rapid, inexpensive gas analyzers could conceivably allow continuous monitoring of V A/Q using this principle.

MEASUREMENT OF BLOOD GAS TENSIONS

The most straightforward method of ascertaining Pa O_2 is to measure it directly from a blood sample (Ch. 38) , usually by using a Clark electrode, which incorporates platinum and reference electrodes in an electrolyte bath. When a negative polarizing voltage is applied to the platinum electrode, O_2 molecules in solution are reduced by electrons from the electrode. The electrons from the cathode react as follows:

Each molecule of O_2 is reduced to two hydroxyl ions by four electrons. In the Clark electrode, the electrolyte solution is separated from the fluid being measured (e.g., blood) by a thin O_2 permeable membrane. The current generated is proportional to P O_2 within the sample. When CO_2 is equilibrated with an aqueous solution the concentration of carbonic acid is proportional to the P CO_2 .

P CO_2 electrodes work by measuring the change in pH induced when blood equilibrates with a potassium chloride/sodium bicarbonate solution. [20]

The history of the development of blood gas analysis has been described in Severinghaus and Astrup, [21] and that of oxygen monitoring in general by Severinghaus. [22] An excellent treatment of the electrochemistry and mathematics of blood gas electrodes can be found in Cobbold. [23]

To obviate the need to withdraw blood samples for P O_2 analysis, intra-arterial P O_2 monitors are being developed. Initial attempts to use a Clark-type electrode were confounded by problems of drift and blood coagulation, problems that have largely been overcome. A fiberoptic technique has also been used, based on the property of O_2 to absorb energy from excited electrons in a fluorescent dye. Incident light is used to elevate electrons in the dye to a higher energy state. These excited electrons may then return to a lower energy level, emitting a photon in the process. Molecular O_2 , by absorbing the energy, inhibits the photon emission. This process, fluorescence quenching, is related to the P O_2 . [24]

In situations in which arterial puncture cannot be achieved or may be technically difficult (for example, in

Figure 33-5 (Figure Not Available) Effect of anesthesia on pulmonary atelectasis and gas exchange. (A) CT scan through the chest of an awake patient. Adjacent to it is the distribution of ventilation (open circles) and perfusion (solid circles) in a 50-compartment lung model, determined by using the multiple inert gas method. A unimodal distribution is shown for the awake individual with a shunt-fraction ($\dot{Q}_S/\dot{Q}_T$) of 0.8 percent. (B) After a period of general anesthesia with positive-pressure ventilation, crescent-shaped areas of increased tissue density (arrows) appear in posterior lung regions. Corresponding to these changes are a widening of both V_A and Q distributions and an increase in $\dot{Q}_S/\dot{Q}_T$ to 7.4 percent. (C) The same individual after the application of 10 cm H_2O PEEP. Very little change is observed in the areas of atelectasis, and V_A/Q matching is further worsened, with the development of a bimodal ventilation distribution and a further increase in $\dot{Q}_S/\dot{Q}_T$ to 11.1 percent. These changes are accompanied by a drop in Pa O_2 from 162 to 137 mmHg. *(From Tokics et al [17])*

neonates), capillary P O_2 may approximate the arterial value. This is particularly true if the sampling site (e.g., heel) is prewarmed, causing an abundance of local blood flow relative to local tissue O_2 consumption. Although capillary P O_2 tends to be significantly lower than the arterial value, capillary O_2 saturation approximates arterial O_2 saturation (Sa O_2) (capillary value is usually slightly lower) because of the shallow slope of the upper part of the Hb-O_2 dissociation curve.

Temperature Correction of Blood Gases

Conventionally, blood gas electrode temperature is maintained at 37°C in most hospital laboratories. Rarely is a patient's body temperature exactly 37°C. Obtaining a blood gas sample at any other temperature and then either warming or cooling the sample to 37°C will cause a change in the blood gas tensions inside the syringe. Heating a sample of blood causes decreased gas solubility in plasma as well as reduced O_2 affinity for hemoglobin. Therefore, if a syringe of blood is gas-tight and no bubbles are present, heating of the syringe will elevate blood gas tension. The reverse is true for cooling a blood sample. Therefore, P O_2 (and P CO_2) values obtained from a hypothermic patient will be artifactually elevated. Several algorithms exist for temperature correction, such that the true partial pressure, predictive of physical and chemical activity at the tissue, can be calculated (Table 33-1) . The algorithms approved by the National Committee for Clinical Laboratory Standards [25] and most commonly used in clinical instruments sold in the United States are indicated in Table 33-1 .

The application of this equation for P O_2 is shown in Figure 33-6 (Figure Not Available) . The P O_2 derived from a 37°C electrode is overestimated if the patient is hypothermic and underestimated if the patient is febrile. At high P O_2 values (>400 mm Hg) the effect is small because hemoglobin is fully saturated in this region. At P O_2 values below 100 mm Hg, however, the degree of overestimation may be severe. For example, at a patient temperature of 30°C and a P O_2 below 80 mm Hg, the

TABLE 33-1 -- Algorithms for Correction to Body Temperature of Blood Gas Tensions Measured at 37°C
Data from a collective review by Ashwood et al [275] and Siggaard-Andersen et al [276]

[a]

[a] NCCLS-approved standard [25]

true P O_2 is overestimated by about 60 percent unless temperature correction is applied.

Presently available evidence indicates that, during hypothermia, corrected arterial pH should be maintained in the alkalotic range (i.e., maintain uncorrected pH close to 7.4 (Ch. 38) . In contradistinction, the analysis presented previously suggests that P O_2 values should be corrected for temperature. [26]

Figure 33-6 (Figure Not Available) Temperature correction of blood P O_2 : percentage error of P O_2 measurement at various body temperatures, with blood gas electrode at 37°C. If patient temperature is 20°C, a P O_2 measurement performed at 37°C would overestimate the true value by more than 200 percent. The curves demonstrate that the percentage of error is greater for venous values (P O_2 < 100 mm Hg) than for arterial measurements (P O_2 > 300 mm Hg). *(From Camporesi and Moon [26])*

Artifactual Effects on Gas Tension Measurement

Handling of arterial blood samples for measurement in a laboratory removed from the patient is important to maintain stability of gas tensions. Gas bubbles in the syringe will allow diffusion of O_2 and CO_2 between the blood sample and the bubbles, usually lowering the values in the blood. This is particularly true for O_2 at high P O_2 values because in this region, O_2 is less soluble in blood than is CO_2 . Removal of all air bubbles before capping the syringe and placing it in ice water can maintain stability of blood gas samples for several hours. Erythrocytes do not contain mitochondria, and therefore, do not consume oxygen. Both leukocytes and platelets do contain mitochondria, and in the presence of extreme leukocytosis or thrombocytosis, significant O_2 consumption by the blood sample may occur. [27] This may be suspected when P O_2 values are inexplicably low in the presence of high leukocyte or platelet counts. Inhibition of cellular O_2 consumption may be accomplished by adding to the sample sodium fluoride [28] (available in evacuated tubes used for collection of blood for glucose measurement) or cyanide.

TRANSCUTANEOUS GAS TENSION MEASUREMENT

In areas of the skin where local blood flow exceeds the amount required for local O_2 consumption, as mentioned previously, capillary P_{O_2} may approximate Pa_{O_2}, which may be particularly true if the local area is warmed. This principle has been exploited by manufacturers of transcutaneous P_{O_2} (P_{TCO_2}) measuring devices, which usually consist of a small electrode that is attached with adhesive to the skin. The skin is locally warmed to 40 or 41°C. O_2 from capillaries diffuses through the intact skin into a Clark-type electrode that measures P_{O_2} directly. This value usually correlates well with Pa_{O_2}; however, in the presence of peripheral vasoconstriction [29] or with thick (adult) skin, the measurement may be erroneous. A reduction in cardiac output tends to result in an artifactual decrease in P_{TCO_2} because of the ensuing cutaneous hypoxia. Peripheral vascular disease also reduces P_{TCO_2}, and the technique has been demonstrated to predict the success or failure of wound healing. [30]

Transcutaneous gas monitoring is particularly useful in infants, in whom local skin blood flow tends to be high and in whom repeated withdrawals of arterial blood may cause anemia. These instruments require frequent calibration. Furthermore, the time constant of measurement is relatively long, and a sudden decrease in Pa_{O_2} may not be detectable quickly enough so that a therapeutic response can be made. Also, skin burns have sometimes resulted from prolonged application of these devices.

Using a miniaturized Clark electrode embedded in a polymethylmethacrylate eyepiece, transconjunctival P_{O_2} monitoring devices are well tolerated and provide a P_{O_2} reading that is approximately half the arterial P_{O_2}. [31] Although it is highly correlated with Pa_{O_2} in hemodynamically stable patients, it is significantly affected by degree of hydration. [32] [33]

P_{TCCO_2} monitoring devices are also available, [34] although because of the ease with which end-tidal P_{CO_2} can be measured, particularly in intubated patients, P_{TCCO_2} measurement has been less popular. Because the changes in transcutaneous gas tensions that occur during apnea are relatively slow to monitor for airway disconnects, other techniques are preferable.

MEASUREMENT OF OXYGEN SATURATION

Several species of Hb may exist in blood: oxyhemoglobin (O_2Hb), deoxygenated Hb (HHb), carboxyhemoglobin (COHb), and methemoglobin (MetHb). To avoid ambiguity, the following definitions have been proposed [35]:

S_{O_2} is most commonly reported as a percentage obtained by multiplying the value obtained from Equations 17 and 18 by 100.

Measurement of Sa_{O_2} is an alternative method to PO_2 of assessing arterial blood oxygenation. The fact that absorption and reflectance spectra of Hb are affected by its oxygenation allows for convenient optical methods of measurement. The traditional method for monitoring Sa_{O_2} is to observe the skin and mucous membranes for cyanosis (Ch. 28) . In 1947 a systematic comparison of the clinical detection of a cyanosis by medical staff and blood O_2 saturation measurement with an ear oximeter in normal volunteers demonstrated the poor accuracy of cyanosis as an indicator of hypoxemia. [36] In this study a total of 7,204 observations of skin and mucous membrane color were made in normal volunteers breathing air or hypoxic gas over a measured Sa_{O_2} range of 71 to 100 percent. False-positive diagnosis of cyanosis was common; cyanosis was diagnosed in 37 percent of 4,587 observations despite a measured Sa_{O_2} of 91 to 100 percent. On the other hand, in 1,723 observations of hypoxic volunteers with a measured Sa_{O_2} between 71 and 80 percent, normal color was said to be present 12 percent of the time. Lundsgaard and Van Slyke [37] had suggested that in order for cyanosis to be detectable, 5 g/dL of deoxygenated Hb must be present in the arterial blood, although Stadie [38] found that cyanosis could be detected at lower arterial concentrations of deoxygenated Hb (Fig. 33-7) . If the threshold for visual detection of cyanosis is assumed to be at an arterial concentration of desaturated blood = 5 g/dL, then at a total Hb concentration of 16 g/dL cyanosis would not occur until Sa_{O_2} decreased to less than 70 percent. At a total Hb concentration of 10 g/dL, cyanosis would only occur when Sa_{O_2} reached 50 percent. The evident inaccuracy and uncertainty inherent in attempts to assess oxygenation by visual inspection have led to highly successful quantitative methods.

CO-Oximetry

Simultaneous measurement of several Hb species with different absorption spectra can be accomplished by using

Figure 33-7 Quantity of deoxygenated Hb in arterial blood as a function of degree of cyanosis. Although traditionally it has been assumed that 5 g/dL of deoxygenated hemoglobin is required for the detection of cyanosis, mild cyanosis can clearly be observed at lower values. *(Data plotted from Stadie [38])*

multi-wavelength absorption with at least one wavelength for each component Hb. [39] This principle has been incorporated into clinical instruments capable of measurement of a blood sample in a cuvette within 1 to 2 minutes. Commonly available devices measure Hb, O_2Hb, COHb, and MetHb and, except when the patient has been administered a dye (e.g., methylene blue [40] [41]) they are susceptible to few artifacts.

Transcutaneous Oximetry

The fact that different hemoglobin species, particularly Hb and oxyhemoglobin (OHb) have different absorption spectra suggests the possibility of using absorption of light *in vivo* to calculate arterial Hb-O_2 saturation (Sa_{O_2}). A dual-wavelength system can be used to estimate Sa_{O_2} if the following conditions are met: (1) the light is transilluminating arterial blood, (2) there are no significant quantities of other hemoglobin species, for example, methemoglobin (MetHb) or carboxyhemoglobin (COHb), and (3) the absorption of light by tissue is negligible.

The first condition may be met, for example, by transilluminating the earlobe if the tissue is kept warm. Under these circumstances the ratio of blood flow to tissue O_2 consumption is relatively high and the capillary blood is predominantly arterial. The second condition is met under most clinical circumstances, in which the total of other Hb species is usually less than 5 percent of the total. The third condition can be ensured by appropriate choice of wavelength.

Dual-wavelength oximeters became available in the 1940s, but because of their rather cumbersome size and the need to calibrate them for each individual patient, they never attained widespread use. An eight-wavelength ear oximeter was produced by Hewlett-Packard, [42] in which active heating of the earlobe by the sensor maintained a high proportion of arterial blood in the capillary bed.

Principles of Pulse Oximetry

One of the major objections to the use of ear oximeters is that one can never be totally sure that the earlobe contains predominantly arterial blood because this instrument has no means of differentiating between arterial and venous hemoglobin. The pulse oximeter is able to make this differentiation by assuming that the pulsatile portion of the signal is entirely arterial blood. This assumption is almost always true except under unusual clinical circumstances, such as when there are prominent venous pulsations as in tricuspid regurgitation. [43]

The principle of pulse oximetry is shown schematically in Figure 33-8 (Figure Not Available) . The light passing through tissue is absorbed by tissue, as well as by venous and arterial blood. The ratio S is calculated at two wavelengths of light, usually around 660 nm and 940 nm.

where AC_{660} , AC_{940} = pulsatile components of absorbance at 660 and 940 nm wavelengths; and DC_{660} , DC_{940} = corresponding steady-state components.

S is then empirically related to O_2 saturation and incorporated into the design of the instrument. It has been proposed that the assessment of Sa_{O_2} by pulse oximetry be abbreviated as Sp_{O_2} . [35]

In practice, pulse oximeters use two light-emitting diodes (LED) and one photo diode as transmitting and sensing transducers, usually placed on opposite sides of a digit. The two LEDs are activated alternately. The ratio S is calculated electronically; from it Sp_{O_2} is derived by an internally stored algorithm. Although in principle the light absorbance technology for monitoring oxyhemoglobin (O_2Hb) saturation has been in existence for almost 50 years, the use of the pulse principle has increased substantially the reliability of such monitors and resulted in their widespread use.

Figure 33-8 (Figure Not Available) Principle of pulse oximetry. Light passing through tissue containing blood is absorbed by tissue as well as arterial, capillary, and venous blood. Usually only the arterial blood is pulsatile, however. Light absorption may therefore be split into a pulsatile component (AC) and a constant or nonpulsatile component (DC). Hb-O_2 saturation may be obtained by application of equation (19) in text. *(From Tremper and Barker [86])*

To assess arterial oxygenation in instances in which it is impossible to provide a transmission path, reflectance oximetry has been exploited. Probes have been developed to monitor fetal oxygenation during labor, [44] [45] [46] and an esophageal probe has been used for monitoring Sp_{O_2} in situations when extremities are unavailable or have a pulse of insufficient amplitude. [47]

One drawback of oximetry is that it is rather insensitive to large changes in arterial P_{O_2} at the high end of the Hb-O_2 dissociation curve, where large changes in P_{O_2} are associated with small changes in Sp_{O_2} . Another problem with it is that because only two wavelengths are used, only two species of Hb can be resolved (assumed to be oxyhemoglobin and reduced hemoglobin). Depending on their absorption spectrum, significant quantities of other Hb species may not be readily detected (see later). Other disadvantages of pulse oximetry include inability to obtain a signal of sufficient amplitude during hypothermia or low cardiac output, interference by electrocautery and a variety of artifacts described later. Finally, as a monitor of the adequacy of ventilation and because Sp_{O_2} is only minimally affected by P_{CO_2} (via the Bohr effect), pulse oximetry may fail to warn when circumstances permit an open airway and availability of 100 percent inspired O_2 . [48]

Use of Pulse Oximetry

Although oximetry has been available since the 1940s, the development of pulse oximetry triggered its wide acceptance because of the latter's reliability and convenience. Pulse oximetry has become a standard component of anesthesia monitoring, and it has also gained wide acceptance in postanesthesia care units and ICUs, as well as for patients undergoing a variety of diagnostic procedures such as gastrointestinal endoscopy. The wide application of pulse oximetry attests to the clinical utility of this major advance in monitoring.

Intraoperative Monitoring

In a trial in which 20,802 patients scheduled for surgery were randomly assigned to receive monitoring with pulse oximetry or not, hypoxemia was detected during anesthesia 20 times and hypoventilation 3 times as frequently in the pulse oximetry group. [49] [50] These differences persisted in the postanesthesia care unit, and in addition bronchospasm, atelectasis, and bradycardia were detected more frequently in the group monitored with oximetry. There were no differences, however, between groups in the incidence of cardiovascular, neurologic, or infectious complications or death. One might incorrectly conclude that the use of pulse oximetry has made no measurable improvement in the practice of anesthesia. In the closely monitored setting of the operating room, however, the incidence of catastrophic events attributable to undetected hypoxemia is predictably low. It is likely that pulse oximetry can detect and possibly avoid some catastrophic perioperative complications, but a trial likely to have sufficient statistical power to demonstrate such an outcome difference would be impossibly large. On the basis of favorable clinical experience with this technology, pulse oximetry will undoubtedly remain a standard monitoring technique during anesthesia. [51]

Postoperative Monitoring

Bierman et al [52] reported that the use of pulse oximetry may reduce the number of arterial blood gas analyses by approximately 50 percent in a group of patients followed through their ICU course after elective cardiac surgery (Ch. 68) . In addition, several clinically unrecognized hypoxemic episodes were detected in the group of patients monitored with pulse oximetry. In 1985 Catley et al [53] continuously monitored patients in the early postoperative period and observed frequent episodes of arterial desaturation. Since then there have been numerous studies in which continuous recording of pulse oximetry was used to monitor patients for up to several days after surgery. [54] [55] [56] [57] [58] [59] [60] [61] [62] [63] [64] [65] [66] [67] [68] However, a significant number of the low readings can be due to motion artifact, the elimination of which requires appropriate methodology. [69]

These studies indicate that significant desaturation (Sp_{O_2} , 80-85%) is relatively common. Desaturation also occurs in some patients prior to surgery, [60] [61] [63] [64] and there is evidence that the existence of preoperative hypoxemic episodes may predict desaturation postoperatively. Hypoxemia is often correlated with peak effects of analgesia, and supplemental O_2 administration appears to be effective in prevention. [58] [65]

Desaturation is often correlated with an increase in heart rate [57] [59] and electrocardiographic (ECG) evidence of myocardial ischemia. [59] [62] Rosenberg and Kehlet [67] also observed that patients who experienced postoperative desaturation tended to have lower scores on cognitive tests.

The demonstration of hypoxemic episodes by continuous pulse oximetry and the evidence suggesting that they may cause important central nervous system and cardiovascular morbidity points to other clinical situations in which similar studies are warranted. For example, studies in pregnant experimental animals have shown that moderate reduction in inspired P_{O_2} of the mother can cause significant reduction in umbilical artery and venous P_{O_2} , alteration of fetal heart rate, and reduced fetal O_2 consumption. [70] [71] [72] [73] Therefore, postoperative hypoxemic episodes in pregnant women might be detrimental to the fetus. However, in a human study in which 10% inspired O_2 was administered for 10 minutes to women in the third trimester of pregnancy there was no measurable change in baseline fetal heart rate, heart rate variability, or Doppler velocimetry in the umbilical or middle cerebral arteries, [74] despite Sp_{O_2} values as low as 80 percent. These observations suggest that during short-term periods of maternal hypoxemia in humans, compensation mechanisms such as increased uterine blood flow prevent significant fetal hypoxia.

Errors in Pulse Oximetry

Because pulse oximeters are dual-wavelength devices, the presence of Hb species other than Hb and O_2Hb must result in erroneous readings.

Carboxyhemoglobin

The effect of carboxyhemoglobin may be discerned by examining its absorption spectrum. At 920 nm, COHb has an

extremely low absorbance and does not contribute to total absorbance. At 660 nm, however, COHb has an absorbance very similar to that of O_2Hb; therefore, Sp_{O_2} will be falsely high. This effect has been measured in a canine study in which the actual pulse oximeter reading of Nellcor and Ohmeda pulse oximeters was approximated by the following formula [75] :

where Sp O_2 * = pulse oximeter reading.

A falsely high pulse oximeter reading occurs in the presence of COHb. In that study, when COHb was 50 percent, Sp O_2 was approximately 95 percent. In human cases of carbon monoxide poisoning, a similar error has been observed. [76] [77] [78] [79] [80] In 30 patients with COHb levels ranging from 25.2 to 54 percent (mean 36.9%) Hampson [80] observed that each percent increase in COHb resulted in only a 1 percent decrease in Sp O_2 reading.

Methemoglobin

Methemoglobin (MetHb) has a larger absorbance than either of the two major species of Hb at 940 nm but simulates Hb at 660 nm. Therefore, at high Sa O_2 levels (>85%) the reading underestimates the true value; at low Sa O_2 levels (<85%) the value is falsely high. [81] [82] In the presence of high MetHb concentrations, the measured Sa O_2 approaches 85 percent, independently of the actual arterial oxygenation.

Other Toxic Alterations in Hemoglobin

Sulfhemoglobin, which can form after exposure to certain drugs and chemicals, and cyanmethemoglobin, a product of the pharmacologic induction of methemoglobinemia for treatment of cyanide poisoning, are nonfunctional hemoglobins. Although sufhemoglobinemia is known to produce errors in CO-oximetry, [83] [84] [85] usually with a false reading of methemoglobin, the effects of these species on pulse oximetry has not been reported.

Structural Hemoglobinopathies

In neonates there is a large proportion of hemoglobin F. Because hemoglobin F has almost the same absorption spectrum as hemoglobin A, it has almost no measurable effect on Sp O_2 . [86]

Sp O_2 has been reported to be accurate in patients with hemoglobin S disease when Sa O_2 determined by this method was compared with Sa O_2 obtained by using *in vitro* oximetry, [87] [88] [89] although it is possible that the presence of Hb S produces a similar artifact in both types of instrument. During sickle cell crisis it has been reported that Sp O_2 overestimates Sa O_2 measured by CO-oximetry [90] by an average of 6.9 percent. Patients with sickle cell disease have a rightward shift of the Hb-O_2 dissociation curve (increased P_{50}), and therefore at any given Pa O_2 value, the Sp O_2 is lower than the normal Hb-O_2 dissociation curve would predict.

Jay and Renzi [91] reported pulse oximetry in a patient with hemoglobin H anemia. They reported that two different pulse oximeters read 93 and 95 percent (artifactually high), respectively, in a patient who had a hematocrit of 9 percent; however, they did not report independent measurements of Sa O_2 with which to compare the pulse oximeter readings.

Hemoglobin Koln, an unstable hemoglobin, has been associated with an artifactual reduction of 8 to 10 percent in Sp O_2 reading. [92] [93]

Artificial hemoglobin solutions, such as diaspirin-cross-linked hemoglobin [94] and bovine polymerized hemoglobin (oxygen carrier 201), [95] [96] have no apparent effect on Sp O_2 , at least after infusion of relatively low doses and under normoxic conditions (Ch. 45) .

Hemoglobin Concentration

At normal oxygenation levels in humans, over a range of hemoglobin levels from 2.3 to 8.7 g/dL, Sp O_2 accurately reflects Sa O_2 . [97] During hypoxia, however, Sp O_2 tends to underestimate Sa O_2 to a degree that increases linearly as Hb concentration falls. In a study by Severinghaus and Koh, [98] at an actual Sa O_2 of 53 percent and an Hb concentration of 8.2 g/dL, the average measured Sp O_2 was approximately 15 percent low, of which 8 percent was attributed to anemia (the remaining error was due to oximeter measurement errors unrelated to Hb concentration).

Polycythemia has no apparent effect upon pulse oximeter reading. In studies of children with cyanotic congenital heart disease, many of whom were polycythemic, there was no systematic error in Sa O_2 reading that could be attributed to high Hb concentration. [99] [100]

Dyes

Clinically used dyes may also have an effect on pulse oximetry. Methylene blue results in a severe decrease in measured Sp O_2 . [101] [102] [103] [104] [105] Its administration can also cause alterations in cardiac output (an increase, then a decrease). Therefore, in the presence of V_A/Q mismatch, this may result in a transient increase and then a decrease in actual Sa O_2 . The presence of high concentrations of methylene blue in blood can also alter CO-oximeter readings such that an artifactual decrease in measured O_2 saturation may result. Quantitative information, however, is lacking.

Indocyanine green causes less artifactual decrease than methylene blue, [102] and a still smaller decrease is noted with indigo carmine. [102] [106] Fluorescein injection has no measurable effect. [102] [106]

Isosulfan blue (sulfan blue, Patent blue V), a dye used to visualize lymphatic vessels for surgical procedures, has a peak absorption at 640 nm [107] and increased absorbance at 660 nm. Its administration has been associated with prolonged artifactual reduction in Sp O_2 . [108] [109] [110] It tends to affect CO-oximetry by producing an artifactual increase in methemoglobin and a negative carboxyhemoglobin reading. This phenomenon is not observed with subcutaneous injection of up to 100 mg into adults.

Nail Polish and Other Nail Pigments

Effects of nail polish have also been measured. Blue nail polish, with absorbance near 660 nm, has the greatest effect on Sp O_2 reading, an artifactual decrease. Other colors have smaller effects. [111] Red henna, a pigment used for hand and nail decoration in some tropical countries, has no significant effect on Sp O_2 , although black henna can block enough light to prevent a satisfactory reading. [112]

Bilirubin

High levels of bilirubin have no significant effect on pulse oximeter readings, [113] [114] although older types of ear oximeters may measure a falsely low value. [42] In the presence of jaundice, multi-wavelength laboratory oximeters may also register a falsely low Sa O_2 and a falsely high COHb and MetHb. [115] [116]

Skin Pigment

Deeply pigmented skin can result in inability to pick up arterial pulsations by a pulse oximeter. Small errors in Sp O_2 readings from black individuals have been reported by some investigators, with others finding no significant effect. [106]

Tape

Four varieties of transparent tape have been shown not to alter Sp O_2 measurements between 85 and 100 percent [117] ; however, smeared adhesive caused by

reusing a disposable oximeter probe has been reported to cause falsely low Sp o_2 readings. [118]

Low Oxygen Saturation

There are obvious practical difficulties associated with *in vivo* calibration of pulse oximeters in humans at low Sa o_2 . Using normal volunteers and direct measurement of Sa o_2 in arterial blood, Severinghaus et al [119] compared the results of Sp o_2 obtained from a variety of pulse oximeters during brief periods of profound hypoxemia. The mean nadir of arterial Hb-O_2 saturation was 56 percent. Within the pulse oximeters tested at that time, there was considerable variation. At 75 percent Sa o_2 the bias (systematic error) was scattered uniformly around zero, with individual units either overestimating or underestimating the true Sa o_2 by as much as 7 percent. Below 60 percent Sa o_2 most units underestimated the actual Sa o_2 (false low measurement).

Other

Ambient light, particularly fluorescent light, can falsely elevate Sp o_2 reading, [120] [121] which occurs especially if the flicker frequency of the light is close to a harmonic of the diode switching frequency. Poor contact of the sensor with the skin can result in direct "optical shunting" of light from source to detector, either directly or by reflection from the skin, resulting in a falsely low Sp o_2 reading. [122] Reduced blood flow to the extremity results in a diminished signal and can cause inability to obtain an Sp o_2 reading [123] or a falsely low reading, [123] [124] possibly in part due to greater fractional tissue consumption of arterial oxygen. This results in a lower saturation in the pulsatile blood component that is measured. There may be a slight reduction (approximately 1%) in measured Sp o_2 during the reactive hyperemia that occurs after ischemia in the arms. [125] The authors hypothesized that venous pulsations may have been responsible for the decrease.

Vasoconstriction or hypotension can cause loss of Sp o_2 signal. Topical application of nitroglycerin ointment has been used to restore the signal, although this can worsen hypotension. Digital block is often successful. Topical application of Emla cream (lidocaine 2.5%, prilocaine 2.5%, Astra Pharmaceuticals, Westborough, Mass) to the earlobe covered by an occlusive plastic dressing for 30 minutes has been reported to facilitate a reliable signal. [126]

The reported errors in pulse oximetry are summarized in Table 33-2 . Pulse oximetry has been well reviewed by Alexander et al, [127] Kelleher, [106] Tremper and Barker, [86] Severinghaus and Kelleher, [121] and Wahr et al. [128]

MIXED VENOUS OXYGEN MONITORING

Mixed venous O_2 saturation (Sv $_{O_2}$) is affected by several factors:

where [Hb] = hemoglobin concentration (g/dL); 13.9 = constant (O_2 combining power of Hb [mL/10 g]); and Q= cardiac output.

Low Sa $_{O_2}$ or low cardiac output, low [Hb], or elevated V $_{O_2}$ may result in a decrease in Sv $_{O_2}$. All these conditions could produce impairment of O_2 delivery to the tissues. Therefore, this single measurement (Sv $_{O_2}$) may be uniquely helpful in detecting any condition that might result in impaired tissue oxygenation. Sv $_{O_2}$ can be monitored by intermittent measurement of blood withdrawn through a pulmonary artery catheter or may be continuously monitored by using a pulmonary artery catheter equipped with fiberoptic bundles. These catheters have two fiberoptic bundles carrying an incident light beam and a reflected light beam. Using the fact that the reflected spectrum of Hb is dependent on the degree of oxygenation, the appropriate calculations can be performed by the instrument and a continuous display of Sv $_{O_2}$ provided. Low Sv $_{O_2}$ (usually < 60%) may sensitively reflect an abnormality of one or more of the factors on the right-hand side of Equation 21. Several factors may artifactually elevate Sv $_{O_2}$, however. These include wedging of the catheter and mitral regurgitation (which tend to bring the catheter tip into contact with arterialized blood), as well as sepsis and left-to-right shunts (either intracardiac or peripheral).

Monitoring of P $_{vO_2}$ instead of Sv $_{O_2}$ requires additional considerations. Although Sv $_{O_2}$ is a function of four variables (Equation 21), other factors acting on the Hb-O_2 binding curve may alter P $_{vO_2}$ independently. In Figure 33-9 a normal

TABLE 33-2 -- Artifacts in Pulse Oximetry

FACTOR	EFFECT	REFERENCES
TOXIC ALTERATIONS IN HEMOGLOBIN		
Carboxyhemoglobin (COHb)	Slight reduction in Sp $_{O_2}$ reading (i.e. overestimates fraction of Hb available for O_2 transport)	[76] [77] [78] [79] [80]
Cyanmethemoglobin	Not reported	
Methemoglobin (MetHb)	At high levels of MetHb, Sp $_{O_2}$ approaches 85%, independent of actual Sa $_{O_2}$.	[81] [82]
Sulfhemoglobin	Not reported (affects CO-oximetry by producing a falsely high reading of MetHb [83] [84] [85]).	
STRUCTURAL HEMOGLOBINOPATHIES		
Hemoglobin F	No significant effect	[86]
Hemoglobin H	No significant effect (i.e., overestimates fraction of Hb available for O_2 transport)	[91]
Hemoglobin Koln	Artifactual reduction in Sp $_{O_2}$ of 8-10%	[92] [93]
Hemoglobin S	No significant effect	
HEMOGLOBIN REPLACEMENT SOLUTIONS		
Diaspirin cross-linked Hb	No significant effect	[94]
Bovine polymerized Hb (oxygen carrier-201)	No significant effect	[95] [96]
DYES		
Fluorescein	No significant effect	[102] [106]
Indigo carmine	Transient decrease	
Indocyanine green	Transient decrease	[102] [106]
Isosulfan blue (Patent Blue V)	No significant effect at low dose; prolonged decrease at high dose.	[108] [109] [110]
Methylene blue	Transient, marked decrease in Sp $_{O_2}$, lasting up to several minutes. Possible secondary effects due to effects on hemodynamics (see text)	[101] [102] [103] [104] [105]
HEMOGLOBIN CONCENTRATION		
Anemia	If Sa $_{O_2}$ normal: no effect. During hypoxemia, at Hb values less than 14.5 g/dL: progressive underestimation of actual Sa $_{O_2}$	[97] [98]
Polycythemia	No significant effect	[99] [100]
OTHER		
Ambient light interference	Bright light, particularly if flicker frequency is close to a harmonic of light-emitting diode switching frequency, can falsely elevate Sp $_{O_2}$ reading.	[120] [121]
Arterial O_2 saturation	Dependent on manufacturer. During hypoxemia Sp $_{O_2}$ tends to be artifactually low.	[119] [268] [277] [278]
Blood flow	Reduced amplitude of pulsations can cause difficulty in obtaining a reading and a falsely low reading.	[123] [124]

Henna	Red henna: no effect; black henna: may block light sufficiently to preclude measurement.	[112]
Jaundice	No effect. Multi-wavelength laboratory oximeters may register a falsely low Sa O_2 and a falsely high COHb and MetHb. [115] [116]	[113] [114]
Motion	Movement, especially shivering, may depress Sp O_2 reading.	[121]
Nail polish	Slight decrease in Sp O_2 reading; greatest effect is with blue nail polish.	[111]
Sensor contact	"Optical shunting" of light from source to detector either directly or by reflection from skin results in falsely low Sp O_2 reading.	[122]
Skin pigmentation	Small errors or no significant effect reported. Deep pigmentation can result in reduced signal.	[106]
Tape	Transparent tape between sensor and skin has little effect. Falsely low Sp O_2 has been reported when smeared adhesive is in the optical path.	[117] [118]
Vasodilatation	Slight decrease	[125]
Venous pulsation (e.g., tricuspid insufficiency)	Artifactual decrease in Sp O_2	[43]

curve is shown adjacent to curves depicting both increased and decreased Hb-O_2 affinity. For the same Sa O_2 and Sv O_2 (and hence arteriovenous O_2 content difference) substantially different values for P vO_2 will occur under the three conditions. Correct interpretation of P vO_2 values must depend on the position of the Hb-O_2 dissociation curve, as dictated by pH, P CO_2, body temperature, and erythrocyte 2,3-diphosphoglycerate (DPG) concentration.

Sv O_2 measurement has been carried one step further by Rasanen et al, [129] who have used this instrument (to measure Sv O_2) and a pulse oximeter (to measure Sa O_2) to calculate shunt fraction continuously according to Equation 10.

Rasanen et al demonstrated that continuous reading of Q_S/Q_T using this principle could be used as a guide to providing an optimum level of continuous positive airway pressure (CPAP) in a group of patients whose tracheas were intubated and in whom lowest Q_S/Q_T was desired. [129] The authors found that the on-line method was cost-effective and concluded that CPAP therapy could be accurately titrated in the majority of patients with acute respiratory failure by using this method to calculate shunt fraction.

TISSUE OXYGENATION

Arterial oxygenation as an indicator of respiratory function may be controversial because an acceptable arterial O_2 content may not necessarily be associated with adequate tissue

Figure 33-9 Hb-O_2 saturation curves. Dotted lines indicate common arterial and venous values: Sa O_2 = 90 percent and Sv O_2 = 70 percent. The middle curve (A_0 , V_0) represents the relationship with pH 7.40, body temperature 37°C. The right-hand curve (A_1 , V_1) would occur if pH were 7.20 or T = 41°C. The left-hand curve (A_2 , V_2) represents the relationship when T = 33°C. Increased levels of any of the four factors shown (temperature, $[H^+]$, erythrocyte 2,3-diphosphoglycerate, P CO_2) will decrease Hb-O_2 affinity (rightward shift); decreased levels will raise Hb-O_2 affinity (leftward shift). The same arterial and venous Hb-O_2 saturation under different conditions can therefore result in a wide range of arterial and venous gas tension values.

oxygenation because of abnormalities of blood flow. A more appropriate monitor of oxygen delivery would in fact measure tissue oxygenation. Tissue P O_2 electrodes have been designed and implemented but have associated problems of sampling bias and tissue destruction. In addition, because of heterogeneity of local tissue blood flow and O_2 consumption, there exists a distribution of tissue P O_2 values, rather than a single value as in blood P O_2 . Nevertheless, changes in tissue oxygenation have been demonstrated under varying clinical conditions (Fig. 33-10) (Figure Not Available) . [130]

Another approach is the noninvasive monitoring of O_2 saturation of blood within the tissue, which can be accomplished by transilluminating the tissue with at least two appropriately chosen wavelengths of light. [131] Light within the near infrared band (wavelengths 650-1100 nm) can penetrate tissue reasonably well. Incident light is applied to the scalp, where it enters the tissue; a small proportion is scattered by the tissue and returned to the analyzer via a fiberoptic bundle. Instruments capable of monitoring blood O_2 saturation *in vivo* within brain tissue have been commercially available for some years. Measured saturation within the illuminated volume includes arterial, capillary, and venous blood but is heavily weighted toward venous values, [132] which under normal circumstances reflect adequacy of tissue oxygenation. [133]

Reduction of O_2 to water occurs at the terminal end of the cytochrome chain, and therefore, monitoring of the cytochrome redox state is more likely to provide a better estimate of O_2 availability at the cellular level than currently available clinical monitoring parameters. By using a similar technique with four wavelengths, it is possible to obtain information about the state of oxygenation of intracellular chromophores, including myoglobin and cytochrome a,a $_3$. [134] [135] This technology has been used to monitor intracellular changes in muscle and brain because of respiratory acidosis in anesthetized cats [132] (Fig. 33-11) (Figure Not Available) , in canine hearts

Figure 33-10 (Figure Not Available) Changes in muscle P O_2 during dopamine infusion. Displayed values represent the mean of seven septic patients treated in an intensive care unit. Dopamine infusion results in an increase in tissue P O_2 of about 12 mm Hg after 100 minutes. *(From Kersting et al [130])*

during and after coronary occlusion, [136] in human forearm ischemia, [137] and in human brain during hypoxia [138] and cardiopulmonary bypass. [139]

EXPIRED GAS ANALYSIS

Mass Spectrometry

Mass spectrometers are devices that measure concentrations of gases largely on the basis of their molecular weight. Gas samples are passed through an ionizer, typically an electron beam, which strips the individual molecules of one or more electrons, giving them a positive charge. The ionizing beam also splits some molecules, creating molecular fragments. After ionization the gas mixture to be measured is accelerated through a magnetic field. In the sector type the ionized gas molecules are passed through magnetic and electric fields at right angles to each other. The paths of the ions become curved by the action of these two fields, in a manner dependent upon the charge/mass ratio. Detectors placed at specific locations allow individual gas concentrations to be measured proportionally to the counts per minute. The quadrupole type of mass spectrometer uses both radio frequency and constant electric fields to force ions of a fixed charge/mass ratio to pass through selectors into a detector, usually a photomultiplier tube. After ionization the gas molecules can then be accelerated by an electric field toward a target after first being focused into a narrow beam. On the way to the target the ion beam passes through an arrangement of rods, the quadrupole. The quadrupole's electrostatic field is changed in a stepwise fashion so only

Figure 33-11 (Figure Not Available) Change in cytochrome a,a $_3$ redox level in brain and muscle of anesthetized cat as a function of arterial P $_{CO_2}$ determined with a three-wavelength differential spectrophotometer. Near-infrared light (wavelengths 775, 815, and 904 nm) was applied to the skin overlying hindlimb muscles and the intact skull via fiberoptic bundles. Transmitted light from the muscles and reflected light (at approximately 60 degrees to the incident beam) from the brain was collected via a second fiberoptic bundle. Processing of the signals allowed independent assessment of cytochrome a,a$_3$ redox level. Changes in density are shown as mean ± SEM. Arterial P $_{O_2}$ was between 100 and 125 mm Hg. The cerebral vasodilation accompanying hypercapnia resulted in increased oxidation of cytochrome a,a $_3$, indicating greater oxygen availability to mitochondria in the brain. In skeletal muscle there was a simultaneous change in cytochrome a,a $_3$ redox state consistent with reduced oxygen availability. This technique may eventually allow continuous monitoring of tissue oxygenation in patients under anesthesia or in the intensive care unit. *(From Hampson and Piantadosi. [132] With permission from Elsevier Science.)*

ions of a single charge/mass ratio may reach the target area (Fig. 33-12) (Figure Not Available) . The rate at which ions hit the target is proportional to the concentration of that particular gas in the original mixture. The electrostatic field settings appropriate for a given charge/mass ratio are alternated in order to measure in turn each of the gases of interest in the mixture (multiplexing). These instruments are reliable and relatively rugged, with delay time typically on the order of 100 to 200 ms.

The ability of the mass spectrometer to measure individually different concentrations of gases depends upon charge/mass ratio. Because most of the ions created by the ionizer are singly charged (missing a single electron), the most important variable is the molecular weight. Two different molecules of the same molecular weight (for example, CO_2 and N_2O) are not ordinarily distinguishable by a mass spectrometer using the principles outlined. In order to surmount this difficulty, empirical algorithms that distinguish particular pairs of molecules by analyzing molecular fragments created by the ionizing beam have been designed.

Because mass spectrometers have traditionally been large and expensive instruments, the original implementation of their use in anesthesia placed them in a remote location. Samples were conveyed to the instrument from a large number of operating rooms, and analysis was performed on a time-sharing basis. [140] This time-sharing approach increased the delay time because of the necessary length of tubing necessary between the patient and the instrument. Another disadvantage was that each patient could only be analyzed for a fraction of the total time available. Presently, a number of portable instruments are available for individual operating room use. These instruments typically can measure CO_2 , O_2 , N_2 , Ar, N_2O, and volatile anesthetic agents simultaneously.

Raman Gas Analysis

When a photon from a light source collides with a molecule of gas, it may be re-emitted (scattered light) with no loss of energy (Rayleigh scattering). Alternatively, there may be absorption of some of the kinetic energy from the photon, resulting in the scattered photon's having a lower energy level and hence longer wavelength (Raman scattering). In Raman scattering the degree of energy absorption by a

Figure 33-12 (Figure Not Available) Quadrupole mass spectrometer. The gas sample passes through the ionization chamber and focusing electrode. Ions then pass through the quadrupole. Rapid changes in the applied electric fields cause all ions except those with the chosen charge to mass ratio to hit the sides of the instrument. Only the ions of interest will strike the target and be detected. *(Modified from Datex-Ohmeda [292])*

molecule from incident photons depends upon molecular weight and structure; therefore, spectral analysis of the scattered light may be used to measure simultaneously the individual concentrations of a mixture of gases. The light source is usually an argon laser with a wavelength of 488 nm. Samples of gas are conducted through a cell, and the scattered light is passed through a spectrometer. The peaks are then detected with a photomultiplier tube. Anesthetic gases and respiratory gases can be simultaneously measured. [141] A clinical instrument based upon the Raman principle has been tested on patients undergoing general anesthesia with accuracy comparable to a mass spectrometer. [142]

Infrared Absorption

In the infrared absorption method an infrared light beam is projected through the gas sample and the intensity of the transmitted light is measured. CO_2 absorbs light with a characteristic peak at a wavelength close to 4,300 nm. Several other molecules, such as anesthetic gases (especially nitrous oxide), water vapor, carbon monoxide, and O_2 also absorb light in this area of the spectrum, interfering with CO_2 measurement, especially if the incident light composition includes wavelengths other than those in a very narrow region around the CO_2 absorption peak. In practical use, the fixed geometry of the gas-sampling cell, a narrow-band infrared light source, and compensating electronic circuits can often automatically correct for interference by other gases.

Colorimetric CO_2 Analysis

Colorimetric detectors make use of the fact that CO_2 forms acidic solutions in water. Paper impregnated with an aqueous solution of a pH sensitive dye (e.g., metacresol purple) can be maintained inside a hydrophobic filter. When CO_2 -containing gas comes into contact with the test paper, the pH drops, and the indicator changes color. Disposable devices can be manufactured to analyze CO_2 semiquantitatively (e.g., Easy Cap, manufactured by Nellcor Puritan Bennett, Pleasanton,

Calif) and used to confirm tracheal intubation in the field. [143]

Polarographic Analysis

Because in the Clark electrode the electrolyte solution is contained within a gas permeable membrane, the electrode can be used for P_{O_2} measurement in gaseous oxygen mixtures. This method is commonly used for on-line gas analysis in anesthesia or intensive care ventilator circuits.

Paramagnetic Analysis

Oxygen has the property of *paramagnetism,* which means it is attracted toward a magnetic field. Several types of instruments have been designed to use this property of O_2 to measure the P_{O_2} in a mixture of gases (Fig. 33-13) (Figure Not Available) .

Figure 33-13 (Figure Not Available) Paramagnetic oxygen analyzer. Two sealed spheres filled with nitrogen are suspended in a magnetic field. N_2 is slightly diamagnetic, and the resting position of the beam is such that the spheres are displaced away from the strongest portion of the field. If the surrounding gas contains oxygen, the spheres are pushed further out of the field by the relatively paramagnetic oxygen. The magnitude of the torque is related to the paramagnetism of the gas mixture and is proportional to the P_{O_2} . Movement of the dumbbell is detected by photocells, and a feedback current is applied to the coil encircling the spheres, returning the dumbbell to the zero position. The restoring current, and hence the output voltage, are proportional to the P_{O_2} . *(Courtesy of Servomex Co., Norwood, Mass.)*

Nitric Oxide (NO) Analysis

Nitric oxide (Ch. 72) has been administered therapeutically in concentrations of 1 to 100 parts per million (ppm) as a pulmonary vasodilator. Continuous monitoring of the inhaled concentration can be accomplished using relatively inexpensive but specific and stable electrochemical detectors. [144] [145] Recently, there has been interest in monitoring endogenously produced NO in exhaled gas. [146] Analysis of exhaled NO waveforms, in which end-tidal NO concentrations are typically on the order of 1 to 100 parts per billion (ppb), can only be satisfactorily performed using mass spectrometry or rapid response chemiluminescence analyzers, [147] which typically have a resolution of 0.1 ppb or less. Gaseous chemiluminescence analyzers usually rely upon the chemical reaction of NO with ozone (O_3) to produce nitrogen dioxide (NO_2). Some NO_2 molecules are produced in an excited state (NO_2*). [148] When NO_2* then spontaneously reverts to its ground state, a photon is emitted. This emitted chemiluminescence signal, which has a wavelength at maximum intensity of approximately 1,200 nm, can be detected using a photomultiplier. NO_2 in the original gas sample reacts slowly with O_3 , even if it is present in high concentration. Chemiluminescence analyzers measure NO_2 concentration by first converting it to NO in a high temperature reactor chamber.

WAVEFORM ANALYSIS OF EXPIRED RESPIRATORY GASES

Capnography, the measurement of CO_2 in expired gases, has evolved in the last few years into a commonly used procedure. Whereas a variety of techniques can be used for CO_2 measurement (mass spectrometry, Raman analysis), the majority of capnographs rely on infrared absorption. [149] Use of this technique can reliably and quantitatively provide vital respiratory monitoring information in the operating room and in all critical care areas.

End-tidal P_{O_2} (PET_{O_2}) may be used as an estimate of P_{AO_2} and hence Pa_{O_2}. End-tidal CO_2 (PET_{CO_2}) analysis has achieved a high degree of popularity, which has not occurred for P_{O_2} monitoring because of unpredictable variability of the A-a gradient. In normal individuals this gradient may be less than 10 mm Hg; however, in patients with severe V_A/Q mismatching, the gradient may be substantially increased. Furthermore, the A-a gradient is increased at high-inspired O_2 concentration even with normal lungs. Therefore, PET_{O_2} almost always overestimates Pa_{O_2}. For example, the PET_{O_2} of a dead person being ventilated with 100 percent O_2 would be approximately 700 mm Hg (P barometric - P_{H_2O})! An example of a continuous tracing of expired P_{O_2} in an anesthetized patient is shown in Figure 33-14.

According to the gas sampling technique, infrared CO_2 monitors can be separated into two categories: sidestream monitors, which draw a continuous sample of the gas from the respiratory circuit into the measuring cell, and mainstream monitors, which directly straddle the airway with a reading cell placed at the attachment between respiratory circuit and endotracheal tube or breathing mask. The key difference in use between the two types of capnographs depends

Figure 33-14 Simultaneous measurement of expired P_{CO_2} and P_{O_2}. These tracings were obtained with Pa_{O_2} = 153 mm Hg and Pa_{CO_2} = 32 mm Hg. Whereas PET_{CO_2} is close to Pa_{CO_2}, PET_{O_2} substantially overestimates the arterial value.

on details of practical importance and on the type and duration of the monitoring environment.

Sidestream Capnographs

An important concept is that sidestream capnographs depend crucially on a sampling flow that continuously aspirates from the "side" of the main respiratory gas flow a fixed amount of gas. The rate of gas sampling can usually be adjusted from 50 to 500 mL per minute and at times up to 2 L per minute. This continuous bias flow can be the source of significant methodologic error. If the sampling flow ever exceeds the expired gas flow, contamination from the fresh gas flow source will occur. The sampling gas pump, flow regulator, sampling system (including the connector to the sampling port), and water trap or water separator constitute multiple sites for gas leak or breakage. Additionally, depending upon the size and length of the sampling tube and the rate of gas flow, a certain delay in gas detection is introduced (CO_2 flight time), which can amount to several seconds when the sampling rate is low and the sampling dead space is high (e.g., long tubes). After measurement in the gas cell, the sampled gas can be exhausted into the atmosphere or retrieved and reinjected through a second tube into the breathing circuit to restore breathing circuit volume. This variable may be of great importance in closed-circuit and precise metabolic gas volume measurements. The analytic core of the instrument, the infrared measuring cell, must be carefully protected so that liquids and particulate matter do not enter it and cause erroneous readings of CO_2 because of their high infrared absorbance. The major problem is caused by water vapor, which is invariably present in expired air (at 37°C) with a saturated vapor pressure of 47 mm Hg. This condenses at lower (room) temperature on sampling tube walls. In critical care settings and often in the operating room, the inspired gas is kept warm and humid during long cases. This increases the load on water separation systems applied to capnographs. Water traps and filters have been

designed to protect the measuring chamber. Several clever designs have been tested, but all work best when cleaned and maintained periodically.

Monitoring of end-tidal carbon dioxide concentration ($E_{t\,CO_2}$) in the spontaneously breathing patient whose trachea is not intubated requires some improvisation. Nasotracheal cannulas connected to a sidestream monitor usually provide a usable waveform but frequently become obstructed with saliva or mucus and are uncomfortable. A convenient method to obviate this problem is to thread an intravenous catheter into the common lumen of a pair of nasal O_2 cannulas so that the tip lies midway between the two nasal prongs. The extension tube normally connected to the O_2 source is tied off, and the intravenous catheter is then connected to a sidestream capnometer. [150] A commercially available version allows O_2 administration while $E_{t\,CO_2}$ is continuously monitored (Divided Canula, Salter Labs, Arvin, Calif).

Mainstream Capnometers

In a mainstream capnometer, with the measuring head placed in close proximity to the endotracheal tube, the measuring chamber is usually heated to about 40°C to prevent water condensation on the chamber window. The heating sensing head must be kept away from direct contact with the patient's skin; it is relatively heavy and must be supported to prevent endotracheal tube kinking. In addition, the sensor's window must be kept clean of mucus and particles to prevent false reading; calibration may be problematic. Despite all these problems, the response time is faster: no gas is subtracted from the breathing circuit, no sampling pumps or other suction devices add complexities to the mechanical system, and there is no uncertainty caused by the rate of gas sampling.

Capnographs must be calibrated periodically, at different intervals in various models but usually at least daily. Equipment drift is most often due to accumulation of saliva or other extraneous materials accumulating in the light path of the analyzer. Calibration can usually be performed by periodic use of calibrated gases. Mainstream capnometers are often equipped with calibration sample cells sealed with mixtures of CO_2 and N_2. In some instruments, room air is sampled in the mainstream cuvette to "zero" the CO_2 level automatically.

A useful analysis range varies from 0 to 10 percent (76 mm Hg) for $E_{t\,CO_2}$ to an extended range up to 100 mm Hg, which may be useful in rare cases of hypoventilation or malignant hyperthermia. The inspired CO_2 range must include 0 and extend up to 15 mm Hg for cases in which rebreathing must be detected and peak values determined.

Time Delays and Other Errors

A capnogram is produced by the sequential analysis of inspired and expired gas, either flowing by the mainstream window, which is usually positioned just proximal to the endotracheal tube or breathing mask, or sampled from a sidestream sampling site connected to the breathing circuit. In the case of sidestream sampling, a definite time delay is introduced by the length and volume of the tubing carrying the sampled gas to the detector. This holds equally true for a capnogram produced by an

infrared sensing device, a respiratory mass spectrometer, or other gas-sensing devices based on a different principle. This delay time caused by the transfer of the sampled gas into the reading cell can be minimized by using high-flow rates for the sampling flow and narrow, short tubing assemblies compatible with the position of the equipment with respect to the patient breathing circuit. Once the sampled gas reaches the sensing cell, an additional delay is introduced by the rise time of the instrument. The rise time is a characteristic delay induced by the exponential response to a square front of changing gas concentration, in which CO_2 concentration changes instantaneously from zero to a new steady-state level ($CO_{2\,SS}$). This can be described by the following exponential equation:

where S = signal at time t; e = base of natural logarithms
2.718); and tau = time constant.

When t = tau (one time constant), it is possible to calculate that S = 0.63 · I. This is frequently used to measure the response of the circuitry. It is often presented in clinical instruments as a different fraction of the response, such as the 10 to 90 percent response time (
2 tau).

If we assume, for argument's sake only, a square-wave capnogram is the most difficult for an instrument to follow, and a time constant of 100 ms (a frequent value for a clinical instrument), it is usually theoretically possible to follow respiratory profiles of CO_2 within 5 percent of the real value (accuracy better than 5 percent) up to respiratory rates of 100 breaths per minute. In practice, most clinical capnographs display this accuracy up to 60 breaths per minute. [149] A shared mass-spectrometer, with the usually longer sampling line used in the share configuration, may display significant inaccuracy at respiratory rates around 40 breaths per minute. [151] The relative duration of inspiration and expiration (I/E ratio) can also affect the accuracy of the recording instrument. Standardized respiratory cycle profiles have been used to compare the most commonly employed clinical instruments. [152]

When quantitative results are expected from sidestream capnographs, the solubility of CO_2 in the tubing materials used must be taken into account: polyethylene and Teflon tubing are much more permeable to CO_2 than is nylon. The composition of sampling lines has been shown to significantly affect mass spectrometry readings for CO_2 . [153] Whereas radial diffusion of CO_2 out of the sampling line is mainly affected by the tubing material and the length of exposure of the sample inside the tubing (related to the flow rate of sampling), axial diffusion across the fronts of CO_2 -rich boluses traveling along sampling lines can also smear both the upstrokes and the downstrokes of waveforms. This type of diffusion has a significant effect on the interpretation of $E_{t\,CO_2}$ at higher respiratory frequencies.

The Capnographic Waveform

Time Capnogram

The most commonly used display mode is P_{CO_2} versus time.

Traditionally, several phases are distinguished in the capnograph trace. During inspiration and the first portion of

Figure 33-15 Time and volume capnographs. (Left): Expired P_{CO_2} versus time (standard time capnogram). The waveform is conventionally subdivided into phases. During phase I exhaled gas from the large airways has $P_{CO_2} = 0$. Phase II is the transition between airway and alveolar gas. Phase III (alveolar plateau) is normally flat, but in the presence of V_A/Q mismatching has a positive slope. The down slope of the capnogram at the onset of inspiration is usually referred to as phase IV; however, there is sometimes a terminal increase in slope associated with the onset of airway closure (dashed line, labeled phase IV
in the figure. This corresponds to the terminal upstroke seen in single inert gas washout curves, referred to in that setting as phase IV. [293] The P_{CO_2} value at the end of exhalation is referred to as the end-tidal P_{CO_2} (PET_{CO_2}). Also shown are exhaled gas flow rate and volume. (Right): Volume capnogram. In this form of the capnogram, exhaled P_{CO_2} is plotted versus exhaled volume. Mixed expired P_{CO_2} can be measured for each breath, as the area under the capnogram. Total physiologic dead space ($V_{D\,PHYS}$) can be measured, therefore, using arterial P_{CO_2} and Equation 11 (Bohr equation, assuming $P_{ACO_2} = Pa_{CO_2}$). Line AC is drawn tangent to the terminal portion of the alveolar plateau. Vertical line BE is constructed such that the two shaded areas (EFG and BCG) are equal in area. FE represents anatomic dead space ($V_{D\,ANAT}$), [294] which includes not only the volume in the trachea and large airways but also any volume within a breathing circuit in which exhaled gas is rebreathed, such as the endotracheal tube, passive humidification device, or Y-piece. Alveolar dead space ($V_{D\,ALV}$) can therefore be calculated as the difference between $V_{D\,PHYS}$ and $V_{D\,ANAT}$. [295] Because the area of trapezoid BCDE is equal to the volume of CO_2 exhaled per breath, mean (or average) alveolar P_{CO_2} is the value at the midpoint of segment BC (point M). [295]

expiration during which dead space gas is exhaled, there is no CO_2 (phase I). As expiration continues, a short phase of the capnograph is recognized (phase II), with a rapid upstroke toward the alveolar plateau, representing the rising front of CO_2 (Fig. 33-15 left). The boundary of this front can be smeared by a variety of causes but most notably by uneven mixing of the alveolar CO_2 bolus in the airways. Phase III, also called the alveolar plateau, represents the constant or slowly upsloping part of the capnogram.

In the time capnogram the alveolar plateau lasts for the greater part of the trace (Fig. 33-16A1) , although the expiratory flow is highest at the beginning of the expiration and tapers off in exponential fashion during the last third of expiratory time. Most of the exhaled volume of a passive expiration,

Figure 33-16 Examples of capnograph waveforms. (A1) A normal tracing. (A2) An increased slope of phase III, usually representing uneven gas mixing within the lung. (B1) Spontaneous ventilation with added dead space demonstrated by nonzero-inspired P_{CO_2} . After removal of dead space (B2), inspired P_{CO_2} decreases to zero, and the upstroke and downstroke of the waveforms become sharper because of reduced mixing. (C1) Rapid oscillations of expired P_{CO_2} due to cardiac action, producing "mini-breaths." (C2) Bifid waveform in patient undergoing elective surgery after unilateral lung transplantation for emphysema. The initial upstroke represents gas from the normal (transplanted) lung. This is followed by gas exhaled from the remaining (emphysematous) lung, which has a steep slope of its individual alveolar plateau (phase III).

therefore, exits the trachea (and the tracheal tube or the anesthetic mask) during the first half of exhalation time.

Several effects are responsible for the frequent appearance of the gentle upslope observed in the alveolar plateau. Most can be traced to uneven emptying of different alveolar regions with different time constants and varying V_A/Q ratios. An additional important cause is that the alveolar gas that is sampled later in expiration is, in fact, richer in CO_2 than the early fraction because CO_2 excretion from pulmonary capillaries into the alveoli continues at a nearly constant rate during expiration, but CO_2 molecules are diluted into a lung volume made progressively smaller by the exhalation process. Slow exhalation, as during an acute asthmatic attack or in patients with chronic obstructive pulmonary disease (COPD), with reduced lung recoil, usually induces a steeper alveolar plateau (see Fig. 33-16A2) . Phase III reaches a peak, usually attained only during the final phase of exhalation, and is called the end-tidal partial pressure of CO_2 (PET_{CO_2}). PET_{CO_2} in the normal individual is usually 2 to 3 mm Hg lower than Pa_{CO_2} . Chronic pulmonary disease and acute disturbances in V_A/Q usually widen this difference to several millimeters of mercury. Occasionally $PETCO_2$ may exceed $PaCO_2$. [154] [155] [156] [157] Other than calibration error, the most common cause is slow respiratory rate or high mixed venous P_{CO_2} . In these situations the cyclic variations in alveolar P_{CO_2} (which oscillates between arterial and mixed venous values) may be relatively large, causing the PET_{CO_2} to rise above the arterial value.

When patients are anesthetized in the lateral position (Ch. 26) uneven ventilation of the dependent lung and lesser perfusion of the nondependent lung increase the range of alveolar gas disparity and hence the upslope of the alveolar plateau. This can be verified by alternating sampling sites between the two lungs when ventilating a patient in the lateral position with separate endobronchial tubes.

Sometimes, when expiration is prolonged and progresses to a lung volume below closing capacity, expired CO_2 concentration may rise sharply at the end of the alveolar plateau, in a fashion analogous to that of N_2 concentration after washout with 100 percent O_2. [158] One possible reason for this is that if lung units subtended by airways predisposed to closure, at least in the spontaneously breathing patient, contain alveolar gas with lower P_{CO_2}, closure of these airways would allow a greater proportion of CO_2-rich gas to reach the upper airway, producing the sharp upswing in CO_2 concentration. An alternative hypothesis is that during the course of expiration, well-ventilated lung units have a progressive, nonlinear, upsloping increase in P_{CO_2}, whereas that of poorly ventilated (closure prone) units increases in a linear fashion. Therefore, when airway closure occurs, the rate of rise in well-ventilated units predominates, and slope of the capnogram abruptly increases. [159] Using the terminology of the single breath washout curve, this portion of the capnogram is occasionally referred to as phase IV (see Fig. 33-15 left).

The last segment of a capnograph is represented by the beginning of inspiration, when the CO_2 concentration rapidly decreases toward the inspired value (most commonly referred to as Phase IV). The capnogram value during inspiration represents the concentration of CO_2 in the inspirate and is dependent mostly on the breathing circuit used and inspiratory flow and fresh gas flow values. Rebreathing of dead space volume is often the cause of an inspired level above baseline (see Fig. 33-16B1), but this can be promptly corrected by removing the dead space (see Fig. 33-16B2). Exhaustion of the CO_2 absorber may also result in elevated inspired P_{CO_2}. The sampling flow rate of sidestream monitors must be taken into account when interpreting many features of the capnogram profile. Usually, sampling flow rates vary, and they can be set between 50 and 400 mL per minute, with an average optimal value for an adult patient of about 200 mL per minute. As soon as the respiratory gas flows decrease below the sidestream gas sampling rate, the characteristics of the sampling vary: Instead of sampling a portion of the mainstream flow, the equipment contributes significantly to bulk flow out of the respiratory circuit, which is important in the pediatric setting, during low-flow anesthesia, and when interpreting capnograms obtained during very low respiratory rates. For example, during a prolonged expiration or an end-expiratory pause, while the gas flow exiting the trachea approaches zero, the sampling of the monitor may aspirate gas alternately from the trachea and the inspiratory limb. A profile that illustrates this effect is shown in Figure 33-15C1 ; it is called *cardiogenic oscillation,* referring to the cause of the alteration. Synchronous changes in pulmonary blood flow during slow expiration and mechanical agitation of different lung regions induced by cardiac activity and pulmonary blood flow contribute to the creation of ripples, often observed in a repetitive pattern during the alveolar plateau in synchrony with the heartbeat. The usual interpretation of cardiogenic oscillatory ripples is mechanical agitation of deep lung regions that expel CO_2-rich gas in synchrony with the heartbeat. Waveforms caused by cardiogenic oscillation are more pronounced when sampling of gas is obtained from deeper tracheal and bronchial areas. Such fluctuations are often smoothed over when the sampling port is more distal to the airways or when lung volume is increased by application of positive end-expiratory pressure (PEEP) (see Fig. 33-16C2) .

Inspection of the whole curve rather than measurement only of peak expired and peak inhalation values, which may be reported digitally, improves the scope and interpretation of the trace. When a capnographic trace is displayed so that all characteristics of the various stages of the waveform are visible, on a rapidly scrolling oscilloscope or on fast-moving paper, it is possible to recognize several features that may be of diagnostic value. When capnograms are plotted on slow-moving paper or trends of only inspired and $E_{t\,CO_2}$ values are produced, it is still possible to recognize important clinical information regarding rising or falling concentrations of both inspired and expired CO_2. Examples of capnograph waveforms are shown in Figure 33-16 .

Normal end-expiratory CO_2 partial pressure ranges between 35 and 45 mm Hg. An increase above this level (hypercapnia) must be interpreted in the light of additional information because it depends on a variety of factors: (1) increased CO_2 production, as during an acute attack of malignant hyperpyrexia or developing fever, (2) depression of the respiratory center, with concomitant reduction of total ventilation and elevation of $E_{t\,CO_2}$, and (3) reduction of effective ventilation induced by partial paralysis, neurologic disease, high spinal anesthesia, weakened respiratory muscle, or respiratory disease.

If ventilation is controlled, inadequate mechanical ventilation must be the first interpretation of increased $E_{t\,CO_2}$. If an increasing trend in $E_{t\,CO_2}$ is observed while total ventilation remains constant, it is essential to verify the patient's temperature to exclude the diagnosis of hyperpyrexia. Additional frequently observed causes of transient increases in $E_{t\,CO_2}$ are release of tourniquets with reperfusion of isch-emic areas, release of aortic clamps, intravenous administration of bicarbonate (Fig. 33-17) , insufflation of CO_2 into the peritoneal cavity as during laparoscopy, and acute defects in mechanical ventilation systems.

Abnormally low end-tidal values (below 35 mm Hg) most often reflect hyperventilation but may also be caused by increased dead space with normal Pa_{CO_2}. For example, alveolar gas emanating from a lung region with no blood flow (and hence no local CO_2 transfer) dilutes exhaled gas and decreases PET_{CO_2} relative to Pa_{CO_2}. Hypocapnia may also be artifactually induced by high sampling rate of the sidestream monitor in the face of an elevated fresh gas flow rate. In addition, low $E_{t\,CO_2}$ may reflect decreased V_{CO_2} ($E_{t\,CO_2}$ during cardiac arrest may equal zero).

Similarly, areas of lung that are perfused but unventilated (e.g., in atelectasis), due to shunting of mixed venous blood, will have high regional Pa_{CO_2} and hence high arterial minus end-tidal CO_2 (Pa_{CO_2} - PET_{CO_2}), which has been used as a criterion for optimizing PEEP in ventilated patients. [160] Increasing levels of PEEP would be expected to resolve atelectasis and decrease Pa_{CO_2} - PET_{CO_2} in these areas. In normal areas, overdistension will impair perfusion and therefore increase regional $PaCO_2$ - $E_{t\,CO_2}$. Optimum PEEP can be defined as when a balance is reached.

Irregularities in the alveolar plateau are often observed when mechanical factors acutely alter the pattern of alveolar emptying, such as when the arm of a surgeon compresses the chest at midexpiration. A cleft or a dip may indicate a spontaneous breath of small tidal volume, able to move just a small bolus of inspired gas past the sampling site. This has been often interpreted as indicating activation of respiratory

Figure 33-17 The effect of sodium bicarbonate administration on $E_{T\,CO_2}$. A continuous tracing of $E_{T\,CO_2}$ is shown as a function of time. Intravenous administration of 50 mEq followed by 30 mEq of $NaHCO_3$ results in an abrupt increase in expired CO_2 due to neutralization of bicarbonate by hydrogen ion.

centers by a patient recovering from anesthesia or activation of respiration induced by sudden increasing stimulation in the surgical field. It may also indicate inadequate inspiratory power during switching from mechanical to spontaneous ventilation and can be the first sign of the need for reversal of neuromuscular blockade; however, it may indicate just the opposite, the need for increased total ventilation to induce apnea in the patient. The dip in the plateau of the capnogram must be interpreted with care, therefore, depending on the surgical stage, the drug exposure history of the patient, and the anesthetic plan.

The main use of the capnographic signal in anesthesia is the immediate verification of tracheal intubation beyond doubt by the immediate and continuous presence of metabolic CO_2 in the expired gas. Esophageal intubation may produce one or a few breaths containing CO_2 during expiration, but the concentration of this gas in exhalations from the stomach cavity rapidly decreases to zero. In this fashion, the continuous appearance of expired CO_2 is rapidly being adopted as a criterion for correct tracheal intubation.

Another major use of this signal has been to determine the correct ventilatory needs (minute ventilation) during controlled ventilation. This use is easily extended to continuous monitoring of spontaneous ventilation and to monitoring of appropriate ventilation during titration of anesthetic agents that depress ventilation. In partial rebreathing circuits and in low-flow anesthesia, capnometry facilitates the adjustment of fresh gas flow, which is a major determinant of CO_2 levels insofar as it may increase minute ventilation. The shape of a partial rebreathing capnogram may vary greatly, depending on the ventilatory frequency and tidal volume. In all these utilization modes, the sensing head of the capnograph or the site of gas sampling is best kept close to the tracheal tube, connected with the minimal dead space assembly. In this mode, for instance, it is easy to reveal disconnection of the breathing system or inappropriate functioning of mechanical ventilators. Partial rebreathing circuit systems include a CO_2 absorber, whose exhaustion is manifested by hypercarbia. Clinical signs of hypercarbia may be only slowly recognized, whereas increase in inspired CO_2 is immediately observable with a capnograph. Rapid alterations in $E_{t\,CO_2}$ can be recognized within a single exhalation. In a different

setting, capnography has been used on the exhaust side of a cardiopulmonary bypass oxygenator to track CO_2 excretion at different body temperatures.

Volume Capnogram

If exhaled volume and P_{CO_2} are measured simultaneously, exhaled P_{CO_2} can be displayed versus exhaled gas volume (see Fig. 33-15 right). Volume capnography has several advantages over time capnography. First, the CO_2 signal can be integrated to obtain the volume of CO_2 exhaled per breath, thus obtaining an on-line, breath-by-breath measurement of V_{CO_2}. Second, significant changes in the morphology of the expired waveform can be detected in the volume capnogram (e.g., secondary to PEEP) that are not seen in the traditional time capnogram. [161]

Third, dead space can be partitioned into components of interest. Total physiologic dead space ($V_{D\,PHYS}$) can therefore be measured, using arterial P_{CO_2} and Equation 11

(Bohr equation, assuming $P_{ACO_2} = Pa_{CO_2}$). Anatomic dead space ($V_{D\,ANAT}$, including gas volume within a breathing circuit in which exhaled gas is rebreathed, such as the endotracheal tube, passive humidification device, or Y-piece) can be calculated directly from the volume capnogram (see Fig. 33-15) . Alveolar dead space ($V_{D\,ALV}$) is the difference between $V_{D\,PHYS}$ and $V_{D\,ANAT}$, and is related to the difference between alveolar and arterial P_{CO_2}, according to Equation 23. [295]

Normally, one can estimate alveolar P_{CO_2} using PET CO_2 obtained from the time capnogram as a measure of P_{ACO_2}. When the alveolar plateau has a significant slope, however, PET CO_2 can exceed Pa_{CO_2} [154] [155] [156] [157] , and average alveolar P_{CO_2} ($P_{AE}CO_2$; see Fig. 33-15) obtained from the volume capnogram may be a more appropriate measure. [161]

Effect of Water Vapor

Because water vapor is often the major source of error, several "water trap" devices or heated suction tubes are used to deliver moisture-free gas to the reading cell.

The effect of gas temperature is as follows. Assume body temperature is 37°C and Pa_{CO_2} = PET CO_2 = 40 mm Hg. If the sampling tube and detector are maintained at a temperature above 37°C, there will be no condensation or "rain out" of water, and the measured P_{CO_2} will be 40 mm Hg. On the other hand, if the expired gas is allowed to cool to room temperature (say 20°C), water will condense in the tubing and the new water vapor pressure (P_{H_2O}) will decrease to the saturated P_{H_2O} at room temperature. If a drying agent is used in the sample line, P_{H_2O} will drop to zero. In either case, the measured P_{CO_2} will change, as shown in Table 33-3 .

TABLE 33-3 -- Effect of Water Condensation or Gas Sample Drying on End-Tidal CO_2 Measurement at Sea Level and 15,000 Ft Altitude [a]

	MOUTH	CELL (20°C)	CELL (ACTIVE DRYING)
Sea level (P_B 760 mm Hg)			
PH_2O	47.0	17.5	0
$ETFCO_2$	0.053	0.055	0.056
$ETPCO_2$	40.0	41.7	42.6
15,000 ft altitude (P_B = 429 mm Hg)			
PH_2O	47.0	17.5	0
$ETFCO_2$	0.093	0.100	0.105
$E_{T\,CO_2}$	40.0	43.1	44.9

Abbreviations: P_B , barometric pressure; PH_2O, water vapor pressure; $ETFCO_2$, end-tidal fractional concentration of CO_2 ; $E_{T\,CO_2}$, end-tidal CO_2 pressure

[a] Since barometric pressure remains constant throughout the system, the removal of water vapor either partially (tubing and cell at room temperature) or completely (active drying) will elevate the fractional concentration and hence the partial pressure of remaining gases. The magnitude of the effect is greater at high altitude, where PH_2O is a larger fraction of barometric pressure. Note that the fractional concentration of CO_2 in end-tidal gas is considerably higher at 15,000 ft than at sea level despite a constant $E_{T\,CO_2}$.

OXYGEN AND CARBON DIOXIDE EXCHANGE MONITORING

The most direct method of measuring oxygen uptake (V_{O_2}) and CO_2 elimination (V_{CO_2}) is by analysis of inspired and expired gas concentrations. If one can measure the minute volume along with inspired and expired O_2 and CO_2 concentrations, V_{CO_2} can be calculated by the following equation:

where V_E, V_I = expired and inspired respiratory minute volumes, respectively; and F_{ECO_2}, F_{ICO_2} = mixed expired and inspired CO_2 concentrations, respectively.

Because the quantities of oxygen consumed and carbon dioxide eliminated are rarely exactly equal, V_E and V_I differ slightly. Because F_{ICO_2} is usually zero, Equation 24 can be simplified:

Similarly, an equation can be written for the calculation of oxygen consumption:

In practice, it is difficult to measure minute ventilation with the necessary degree of accuracy to be able to distinguish small differences between V_I and V_E. Because exchange of inert gas (i.e., gas in the breathing mixture that is neither CO_2 nor O_2) generally equals zero, V_I can be calculated as follows:

where

Therefore, Equation 26 can be rewritten as

V_{O_2} measurement using this equation becomes progressively less accurate as inspired O_2 fraction is increased above 50 percent. At high F_{IO_2} values, because F_I inert becomes small, errors in the measurement of F_I inert result in correspondingly large errors in V_{O_2}. At $F_{IO_2} = 1$, this equation breaks down completely.

Open-circuit measurement of V_{O_2} and V_{CO_2} under anesthesia using this method has been described by Viale et al. [162] Self-contained analyzers have been designed. [163] [164] These instruments have proved to be extremely satisfactory for gas exchange monitoring in patients in the critical care environment. One practical problem with systems incorporating a zirconium oxide O_2 sensor is extreme sensitivity to

small concentrations of fluorinated anesthetic gases, which may cause severe malfunction.

Another method of measuring O_2 consumption is to monitor the arteriovenous O_2 content difference and multiply by cardiac output:

where CaO_2, CvO_2 = arterial and mixed venous O_2 contents, respectively (mL/L); and Q_T = cardiac output.

Blood O_2 content may be calculated using Equation 9 (note: when using Equation 31, the O_2 content values calculated using Equation 9 must be multiplied by 10 to obtain the VO_2 in the correct units).

This method of calculation of V_{O_2} (reversed Fick technique) is reasonably satisfactory for clinical purposes, although it becomes less accurate in the setting of high

cardiac output and low arteriovenous O_2 content differences. It tends to underestimate the V_{O_2} measured directly, as described previously, by 30 to 60 mL per minute. [165] [166] [167] This difference has been attributed to pulmonary O_2 consumption, which is not measured by the reversed Fick method. Direct measurement is closer to the reversed Fick technique when continuous thermodilution cardiac output is used, suggesting that a bias in thermodilution cardiac output measurement may also be partly responsible for the difference. [168]

RESPIRATORY CENTER DRIVE

Measurement of the respiratory drive (Ch. 15) is particularly important in assessment of the effects of anesthetics on the respiratory system and in particular in the process of weaning patients from mechanical ventilation. Of the various causes of respiratory failure, including pulmonary mechanical abnormalities and impairment of respiratory gas exchange, depressed ventilatory drive is probably the most common cause of failure to wean immediately after general anesthesia. Experimentally, the drive to breathe has been measured as the ventilatory output (minute ventilation, V_E) as a function of varying levels of elevated Pa CO_2 or decreased levels of Pa O_2. Formal assessment of respiratory drive in the traditional manner is difficult to obtain in the clinical environment, and various measures of neural respiratory center output have been sought.

Partitioning the respiratory waveform into inspiratory and expiratory components can provide further information. Mean inspiratory flow (tidal volume/inspiratory time) is an index of respiratory drive. [169] It is possible, however, for a patient to have a high respiratory drive but not be able to translate that drive into respiratory output because of impaired ventilatory mechanics.

A low ventilation rate is considered to be a reasonably accurate indicator of respiratory depression caused by anesthetic agents, particularly narcotics. Although parenteral narcotics usually produce a slowing of ventilation rate, there are pitfalls in the reliance on bradypnea as a sign of respiratory depression. Camporesi et al [170] demonstrated that the predominant mode of ventilatory depression in normal volunteers given epidural morphine was a reduction in tidal volume, with little change in respiratory rate. Rawal and Wattwil [171] showed in both normal volunteers and postoperative cholecystectomy patients no change or increase in ventilation rate after epidural morphine despite a significant reduction in minute ventilation. Sandler and Chovaz [172] monitored six patients receiving epidural morphine after elective thoractomy. Two of the six experienced periods of apnea that were not preceded by slow respirations. Ready et al [173] described four cases of marked respiratory depression after epidural morphine. All had Pa CO_2 values of 63 mm Hg or higher; one patient developed a Pa CO_2 of 95 mm Hg. Respiratory rates in all four patients were 8 per minute or faster. The patient with a Pa CO_2 of 95 mmHg had a respiratory rate of 12 per minute. Clearly, bradypnea does not predict apnea, and severe respiratory depression can exist in patients with acceptable respiratory rates.

A more sophisticated measure is the maximum negative inspiratory airway pressure obtained 100 ms after a temporary occlusion of the airway (P_{100} or $P_{0.1}$) in a spontaneously breathing patient. Periodic transient airway occlusion that occurs in this way is not appreciably noticed by the patient. Furthermore, chemosensitivity, determined in volunteers by CO_2 responsiveness, is not significantly affected by intermittent (every 30 seconds) P_{100} maneuvers. [174] The normal value for P_{100} during resting ventilation is 1 to 2 cm H_2O. P_{100} is a useful index of respiratory drive, requiring no voluntary effort on the part of the subject and being minimally affected by changes in respiratory mechanics. The technique is well described by Milic-Emili et al. [175] Under anesthesia, P_{100} is depressed [176]; however, the effect of anesthesia is highly dependent upon Pa CO_2 so that P_{100} at high Pa CO_2 is actually increased, even under anesthesia. Conceivably one could use P_{100} as a guide to the discontinuation of mechanical ventilation after general anesthesia. In acute respiratory failure due to other causes, P_{100} is generally elevated; Herrera et al [177] and Sassoon et al [178] observed values of P_{100} above 6 cm H_2O and 4.2 cm H_2O, respectively, during T-tube trials to be correlated to lack of success in weaning. Montgomery et al [179] found a similar relationship but reported a better prediction of weaning successes using the P_{100} response after breathing of 3 percent CO_2 (P_{100} H). The mean P_{100} H/P_{100} ratio was 2.04 in seven successful weaning attempts and 1.17 in seven failures.

PULMONARY AND CHEST WALL MECHANICAL FUNCTION

Principles of Gas Flow Measurement

Monitoring of inspiratory and expiratory flow can be useful for a variety of reasons. First, measures of resistance (discussed later) require both pressure and flow measurement. Second, flow may be integrated to provide a monitor of inspired or expired volume. Several types of flow meter exist. Possibly the most commonly used flow meter in anesthesia is the rotameter, in which gas flow imparts movement to a series of vanes connected to a wheel. The Wright spirometer integrates this movement, providing the user with a measure of volume. The Fleisch pneumotachograph consists of a bundle of small-diameter tubes in parallel. Flow within these capillary tubes is laminar, and pressure drop is therefore

linearly related to gas flow. [180] Screen-type pneumotachographs work by measurement of the pressure drop across a mesh screen. These devices are usually smaller and lighter than Fleisch-type pneumotachographs; however, they are inherently nonlinear. Moreover, their practical implementation is often limited by their tendency to collect moisture and debris, which changes their operating characteristics. Modern mechanical ventilators often incorporate vortex-type pneumotachographs, which work by measurement of interruptions in an ultrasonic beam placed across a tube in which struts disrupt the laminar flow, resulting in vortices. [180] Ultrasonic flow meters measure the speed of ultrasonic waves propagated parallel to the direction of flow. [181] Hot-wire anemometers consist of electrically heated wires placed in the gas stream, which tend to cool the wire and change the electric conductivity. Flow is measured by the amount of additional electric current generated by a feedback circuit that is necessary to maintain the wire at constant temperature. These devices characteristically have an extremely high frequency response, but their behavior is highly dependent on gas temperature and contamination of the gas stream with mucus and water droplets. [180]

Respiratory Output

The mechanical output of the respiratory system may be assessed by measuring respiratory muscle activity and resulting gas flow.

The electric activity of the diaphragm, the most important inspiratory muscle, has been measured in adults with needle electrodes inserted into the eighth or ninth intercostal spaces in the midaxillary line [182] and in neonates with surface electrodes applied subcostally at the nipple line. [183] Diaphragmatic electromyograms (EMGs) can be obtained in this manner in neonates but in adults is frequently contaminated by the simultaneous electric activity of the overlying intercostals. A cleaner diaphragmatic EMG signal may be obtained by using an esophageal electrode. [184] Electric gating of the much larger electrocardiographic (ECG) signal may allow relatively pure diaphragmatic EMG signals to be recorded. [185] Fatiguing muscle tends to produce EMG potentials at lower frequencies, allowing diaphragmatic fatigue in a variety of situations to be diagnosed by frequency analysis of the signal obtained in this way. [184] Mechanical activity of the diaphragm cannot be assessed directly; however, because of its shape (approximately hemiellipsoidal) contraction of the diaphragm must result in a transdiaphragmatic pressure. Esophageal and gastric pressure simultaneously measured may be used to calculate transdiaphragmatic pressure. A nasogastric tube with esophageal and gastric balloons is specifically manufactured for this purpose (Bicore Monitoring Systems, Irvine, Calif). Transdiaphragmatic pressure measurement has been used to assess diaphragmatic function [186] and loss of diaphragmatic contraction demonstrated in the early postoperative period after upper abdominal surgery. [187] Loss of transdiaphragmatic pressure generation implies lack of diaphragmatic contraction (Fig. 33-18) (Figure Not Available) . [188]

Diaphragm motion can be assessed somewhat more indirectly by observing or monitoring thoracic and abdominal movements during inspiration. The normal outward movement of both chest and abdomen during inspiration is replaced by paradoxic inward movement of the abdomen in the presence of diaphragmatic inaction, [189] which may be due to phrenic nerve paresis or diaphragmatic fatigue. [190] [191] External movement of the thorax and abdomen can be monitored in this way by using magnetometers, which can monitor anteroposterior and lateral thoracic and abdominal dimensions [189] [192] or strain gauge displacement transducers. [193] Another method uses two coils of wire that encircle the torso at the thorax and abdomen. The selfinductances of the coils change in proportion to the encircled areas and can be calibrated to provide continuous monitoring of ventilation. [194] Unfortunately, these methods are rather sensitive to changes in posture or body position [195] and cannot be used during surgery on the thorax or abdomen.

The final mechanical output of the respiratory system (gas flow) can be assessed by monitoring minute ventilation directly or monitoring its components, ventilation rate, and tidal volume.

Monitoring of breath sounds provides a low-cost, high-reliability, semiquantitative measure of gas flow into and out of the lung. Continuous monitoring of breath sounds using an earpiece connected to a precordial or esophageal stethoscope allows immediate detection of breathing circuit disconnection in mechanically ventilated patients. It facilitates early detection of decreased tidal volume, changes in respiration rate, and endotracheal tube cuff leaks. It also provides qualitative data that may indicate changes in pulmonary mechanics. Wheezes (rhonchi) are produced when gas flow and

Figure 33-18 (Figure Not Available) Examples of transdiaphragmatic pressure monitoring. (A) Simultaneous esophageal and gastric pressure waveforms during tidal breathing in the normal individual. Negative esophageal (and hence pleural) pressure swings are accompanied by positive gastric pressure waves, indicating the development of transdiaphragmatic pressure during inspiration. (B) The same waveforms in a patient with phrenic nerve palsy (and hence absent diaphragmatic contraction). Negative intrathoracic pressure swings (arrows) are accompanied by gastric pressure swings in the same direction. Intrathoracic pressure changes are therefore being directly transmitted through a passive diaphragm. These changes can also be observed in the early postoperative period in patients who have had upper abdominal surgery. *(From Brown et al [185])*

airways interact so that airway walls become apposed. Oscillation of the airways between open and nearly closed causes airway vibration, which results in sound production detected as wheezing. Wheezes may occur when airway diameter is narrowed as a result of smooth muscle contraction (bronchospasm), mucosal thickening or edema, buildup of secretions, extrinsic compression, or an endobronchial mass such as a tumor or foreign body. Although severe generalized airways obstruction may occur without wheezing, for example, in emphysema, the presence of wheezes correlates with reversibility of airways obstruction. [196] Crackles (rales) are discontinuous sounds produced by the sudden opening of small airways during inspiration. These are indicative of airway closure and subsequent reopening, which may occur in interstitial fibrosis or in any situation resulting in premature closure of small airways (pneumonia, pulmonary edema, low lung volumes). In patients with large amounts of airway secretions, particularly in the large airways, coarse crackles may also be caused by gas bubbling through airway secretions. The origin of lung sounds has been reviewed. [197] [198] [199]

Minute ventilation and tidal volume are easy to measure directly in patients whose tracheas are intubated, and these parameters are routinely measured by modern mechanical ventilators. In the patient whose trachea is not intubated, however, these parameters can only be obtained somewhat inaccurately by monitoring external dimensions of the thorax and abdomen either "clinically" by direct observation or by using one of the techniques noted. Subjective assessment in particular is

extremely inaccurate, [200] commonly with overestimation of tidal volume by up to 60 percent. Alternatively, V_E can be monitored directly by using a head tent. [201] These methods are difficult to apply for routine clinical use. Therefore, measurement of ventilation rate remains the mainstay of respiratory output monitoring. Mechanical measures of gas flow, such as these, provide combined assessments of both respiratory drive and mechanical function of the respiratory system. In the presence of relatively normal thoracic mechanics, however, respiratory gas movement is considered to be a reasonable monitor of respiratory output.

Measurement of Respiratory Mechanics

Principles

Mechanical properties of the respiratory system include the passive mechanical properties of resistance, elastance, and inertance, in addition to the motor properties of the muscles of respiration (Ch. 24) . Resistance (R), in pulmonary mechanical terms, is the increment in pressure (DeltaP) applied to the system divided by the increment in flow or rate of change of volume (DeltaV):

Normal resistance is 1.5 $cm/H_2O.L^{-1}.s$, but under anesthesia it may be as high as 9 $cm/H_2O.L^{-1}.s$. Most of the resistance of the respiratory system is due to the flow resistance of the major conducting airways. A small portion of the resistance is due to the tissue viscosity.

Conductance (G) is the reciprocal of resistance:

Elastance (E) is the applied pressure divided by the resulting static change in volume:

A more commonly used variable is compliance (C), the reciprocal of elastance:

A commonly used unit for compliance is $mL/cm\ H_2O$. Because the lung and chest wall are mechanically in series,

where C_{TH}, C_L and C_{CW} are the thoracic, lung, and chest- wall compliances, respectively.

Inertance (I) is the applied pressure divided by the gas acceleration or the second derivative of volume with respect to time:

Inertance is analogous to the mass of tissue and gas within the lung. Normal thoracic inertance is .02 to .04 $cmH_2O.L^{-1}.s^2$. Ordinarily, because acceleration of gas flow and mass of gas and tissue are low, inertance plays a minor part in the mechanical behavior of the respiratory system. Under conditions of high-frequency ventilation or high-inspired gas density (e.g., in deep diving), however, inertance may play a major role in determining gas flow.

Practical Measurement of Passive Respiratory Mechanical Properties

Estimates of compliance and resistance in the respiratory system may be obtained by inspection of the airway pressure-volume (or time) relationships. Thoracic compliance may be obtained by inflating the lungs with known increments of volume and measuring the static pressure at each point. Under normal circumstances, the lung and chest wall have approximately equal compliance of approximately 200 mL/cmH_2O^{-1} , resulting in a total thoracic compliance of 100 $mL/cm\ H_2O^{-1}$. Individual measurements of chest wall and lung components of the total respiratory compliance cannot be made without some estimate of pleural pressure. Conventionally, pleural pressure is measured by inserting a pressure-monitoring balloon within the esophagus. Unfortunately,

in the supine patient the weight of the mediastinum results in a falsely high estimate of pleural pressure when using this technique. Direct pleural pressure measurement must therefore be obtained to measure lung and chest wall compliance accurately in this position. A noninvasive method of pleural pressure measurement, using a flat loop of Teflon-insulated wire attached to the skin of the suprasternal fossa, has been described. [202] The skin movement that accompanies changes in intrapleural pressure is transduced by the coil of wire by continuous measurement of its self-inductance. Measurements of pulmonary compliance using this technique correlated well with similar measurements using an esophageal balloon to estimate intrapleural pressure. The technique is time-consuming, however, and measurements cannot be obtained in some individuals.

Thoracic compliance can be estimated on a breath-by-breath basis by monitoring the inspiratory pressure-time curve. If a constant tidal volume is being used to ventilate a patient, the thoracic compliance will be inversely related to the inspiratory pressure. It is important that the pressure used to calculate thoracic compliance be at end inspiration (plateau pressure) because during the period of inspiratory gas flow there is an additional component of pressure due to airways resistance. The changes in peak airway pressure (related to both airways resistance and thoracic compliance) and the plateau pressure (related only to compliance) may quickly identify pulmonary mechanical abnormalities in ventilated patients (Fig. 33-19) . An empirically defined measurement, tidal volume divided by peak inspiratory pressure change, is defined as dynamic compliance (Cdyn):

where V_T = tidal volume; P_{pk} = peak airway pressure; PEEP = positive end-expiratory pressure; and the normal value is 40 to 80 $mL/cm\ H_2O$.

Static compliance (Cstat) can be calculated by measuring the "plateau" pressure and using the following equation:

The normal value is 50 to 100 mL/cm H_2O.

In order to make these compliance calculations, the end-expiratory pressure (if any) must be subtracted from the peak pressure or plateau pressure. The PEEP value can usually be read directly from the airway pressure monitor at end-expiration. However, when insufficient expiratory time prevents complete emptying of the lungs, significant end-expiratory elevation of alveolar pressure that is not detected at the airway pressure monitor (auto-PEEP) may occur. [203] [204] Auto-PEEP is most likely to exist when elevation of airway resistance or compliance causes prolongation of expiratory time or when high ventilation rates are required. [203] Auto-PEEP can result in decreased cardiac output, hypotension, and electromechanical dissociation in mechanically ventilated patients. It also affects compliance measurements. Detection of auto-PEEP can be accomplished by occluding the exhalation port of the ventilator while delaying the onset of the next ventilator breath. Alveolar pressure will then equilibrate with the ventilator circuit, and auto-PEEP can be read on the airway pressure monitor (Fig. 33-20) (Figure Not Available) . During this temporary occlusion maneuver, it is important to prevent supplementary gas flow (e.g., fresh gas flow) from entering the circuit and falsely elevating the auto-PEEP value.

An increase in static compliance may be caused by atelectasis, pulmonary edema, pneumothorax, external compression

Figure 33-19 Examples of airway pressure waveforms. Airway pressure is plotted versus time. Decreased static thoracic compliance results in an increase in *plateau* pressure; increases in airway resistance cause increased *peak* airway pressure and hence decreased dynamic compliance. (See text for details.)

Figure 33-20 (Figure Not Available) Auto-PEEP. Severe airway obstruction may result in high alveolar gas pressure at end expiration, which can exert the same effect on hemodynamics as externally applied PEEP. This is not usually detectable unless the expiratory port of the ventilator circuit is occluded. Auto-PEEP may then be read directly from the airway pressure monitor. *(Modified from Pepe and Marini [203])*

of the chest (e.g., intra-abdominal hemorrhage or in the operating room, abdominal packing, or the surgeon's leaning on the torso), or accumulation of pleural fluid. Increases in dynamic compliance may be caused by elevated airways resistance (e.g., due to bronchospasm, mucus accumulation) or obstruction or kinking of the endotracheal tube.

It is important to realize that in parallel with the patient's thoracic compliance are the internal compliances of the breathing circuit and any associated humidification or gas warming systems. Circuit compliance may be as high as 10 mL/cm H_2O and must be accounted for if an accurate measurement of thoracic compliance is required.

During spontaneous breathing decreased thoracic compliance places an additional load on the patient's respiratory muscles. Thoracic compliance less than 25 mL/cm H_2O is unlikely to result in successful weaning from mechanical ventilation. [205]

Thoracic resistance (Rth) can be measured in the intubated patient by oscillating the airway with a sinusoidal or randomly varying flow with simultaneous measurement of flow and pressure. Significant increases in Rth have been observed in anesthetized patients after reversal of neuromuscular blockade with edrophonium 0.43 mg/kg. [206] An indirect estimate of airways resistance may also be obtained by monitoring the flow-time or volume-time relationship of a passive exhalation after manual inflation of a lung. [207] If a constant thoracic compliance is assumed, the time constant of exhalation is related to airways resistance.

A commercially available instrument (Datex-Ohmeda, Tewksbury, Mass) is capable of providing continuous displays

Figure 33-21 (Figure Not Available) Intraoperative spirometry (Side Stream Spirometry, Datex Medical Instrumentation, Tewksbury, Mass). Labels have been added for clarification. (A) Volume-pressure loop. Peak (Ppk) and plateau (Pplat) inspiratory pressures are shown. The slopes of the solid and dashed lines represent dynamic compliance (C_{dyn}) and static compliance (C_{stat}), respectively. (B) Flow-volume loop from the same breath as in Fig. A. Inspiratory flow is primarily regulated by the ventilator and therefore in the midportion of inspiration is relatively constant. Expiratory flow is determined by passive emptying of the lungs, which in turn is dependent upon recoil pressure and airways resistance, resulting in a different configuration of the expiratory portion of the loop. The expiratory loop is most sensitive to changes in airways resistance; increased expiratory flow resistance results in a flattening of the expiratory curve (see Fig. 33-22D) (Figure Not Available) . *(Patient record courtesy of Dr. R. Sladen)*

of inspired volume versus airways pressure and flow versus inspired volume (Figs. 33-21 (Figure Not Available) and 33-22). (Figure Not Available) [208] This instrument has been used to monitor changes in pulmonary compliance due to intraoperative pulmonary edema, [208] during laparoscopic instillation of gas into the peritoneal cavity, [209] and to detect malpositioning of double-lumen endotracheal tubes. [210]

APNEA MONITORING

Most of the principles of apnea monitoring have already been discussed. In practice, the appropriateness of a particular apnea monitor depends on the situation in which it is to be used. For example, a head canopy monitor of ventilation [201]

Figure 33-22 (Figure Not Available) Pressure-volume loops (A, C) and flow-volume loops (B, D) recorded during two-lung ventilation (1) and one-lung ventilation (2). (A, B) Double-lumen tube placed correctly; (C, D) double-lumen tube malpositioned. Ventilator settings were identical (tidal volume 10 mL/kg, rate 10-12 breaths/min) during all recordings. When changing from double- to single-lung ventilation, compliance is reduced (A) and expiratory airways resistance slightly increased (flattening of the expiratory flow-volume curve (B). Malpositioning of the tube resulted in increased flow resistance and reduced compliance to a significantly greater degree than when the tube was correctly positioned. The flattening of the expiratory portion of the flow-volume curve is most evident in Fig. D. *(From Bardoczky [210])*

may be appropriate in an ICU but is entirely inappropriate for use at home in a young child. Apnea monitors are usually based on one of three general principles: detection of gas flow, chest-wall movement, and gas exchange (monitors of either Pa CO_2 or Sa O_2). Guyatt et al [211] described a method in which a pressure transducer was connected to a nasal O_2 cannula. Periodic fluctuations of around 1 cm H_2O because of cyclical respiratory flow were observed during nose breathing. Respiratory rates could easily be obtained with this technique even when O_2 was flowing through the cannula. Direct monitoring of ventilation can be obtained easily in a patient whose trachea is intubated. Use of a rigid air-tight canopy that encases the subject's head with a neck seal has been described by Sorkin et al. [201] The canopy is continuously flushed with fresh gas. The subject's respiration produces a net flow in and out of the canopy, which is unaffected by the fresh gas flow. The system could comfortably be worn while either awake or asleep. Another method of airflow detection was described by Werthammer et al [212] ; in it an acoustic monitor encapsulated in silicone rubber was taped 0.25 cm inside a nostril. Eight premature infants were continuously monitored for 1 to 2 hours; 26 episodes of apnea lasting 15 seconds or more were detected and confirmed by direct observation. An impedance monitor detected only seven of these episodes. Hok et al [213] have described an acoustic method that was demonstrated to detect hypoventilation and apnea with greater sensitivity than pulse oximetry. An extremely unobtrusive method is to use a tiny, rapid response hygrometer taped close to a nostril. This type of sensor can monitor respiratory rates at least up to 60 per minute as effectively as capnometry, in either infants or adults. [214]

Chest-wall movement may be detected in several ways. One method is inductive plethysmography (e.g., Respitrace and Respigraph [Non-Invasive Monitoring Systems, Miami, Fla]). [194] The abdomen and thorax are each encircled by a coil, in which respiratory movements are detected as changes in the self-inductance. A more commonly used approach is transthoracic impedance, a technique that is commonly implemented in commercially available ECG monitors. In this method, a small alternating current (typically 100 microamps) at around 100 kHz is passed through a pair of ECG leads, allowing transthoracic electrical impedance to be continuously measured by a change in the induced 100 kHz voltage. Low-frequency changes in respiratory impedance can easily be demodulated from the signal. [69] [212] EMG of the respiratory muscles can also be used to monitor respiration, [183] although it is more difficult because of contamination of the EMG signal with a much higher voltage ECG potential. Another monitor of chest-wall movement makes use of a detector placed under the bed mattress (RE-134 Apnea/Respiration Monitor, Electronics Monitors, Inc., Euless, Tex). This monitor detects changes in the patient's center of gravity that occur because of respiration. Algorithms

are used to exclude ballistocardiographic artifacts that may otherwise be interpreted as respiratory movements. The main disadvantage of patient movement monitors is that they may fail to detect obstructive apnea, in which ventilatory effort or movement can occur without gas flow.

Because apnea per se may not result in any physiologic abnormality, a measure of its possible adverse effects (hypoxia or hypercapnia) may be preferable. Continuous measurement of E_tCO_2 , although easy in an intubated patient, is more difficult in a patient whose trachea is not intubated because of discomfort from the catheter placement and clogging with mucus and saliva. This problem frequently accompanies direct placement of a cannula into the nasopharynx. Some improvements may be obtained if a catheter is placed inside a nasal airway. A more satisfactory solution is to use specially designed nasal cannulas in which one prong is used to sample exhaled gas and the other can be used to deliver oxygen.

Another approach is to use O_2 saturation. George et al [215] compared arterial desaturation with manually detected events using a variety of monitors, including chin EMG, airflow measurement, and respiratory movement measured by inductance plethysmography. Apnea was defined as cessation of respiration for more than 10 seconds. Nine overnight records from six patients with sleep apnea were analyzed and compared with Sa O_2 measurement using an ear oximeter. Decreases in Sa O_2 of more than 3 percent from baseline were considered significant. Using this criterion only 1.32 percent of 4,008 apneic episodes were undetected. Catley et al [53] used ear oximetry and respiratory inductive plethysmography to monitor patients postoperatively and demonstrated that morphine analgesia, compared with regional analgesia with local anesthetic, was associated with a high incidence of hypoxemia and associated obstructive apnea, central apnea, paradoxic breathing, and slow respiratory rate.

Given the proven reliability of pulse oximetry, it would seem that this method, perhaps in association with capnography, may provide an excellent method of apnea monitoring. Principles of apnea monitoring have been reviewed in detail by Sackner and Krieger. [216]

LUNG WATER

The frequent occurrence of pulmonary edema in clinical medicine has led to a variety of techniques for the early detection of increased lung water. Bedside estimation of lung water would be clinically useful. A variety of techniques exist presently.

Chest Radiography

The most commonly used technique clinically is the standard chest radiograph, in which signs of pulmonary edema are well described. An animal study demonstrated that approximately a 35 percent increase in extravascular lung water is required for the diagnosis of "definite pulmonary edema." The absence of radiographic evidence of pulmonary edema, however, virtually rules out significant increases in lung water. [217]

Computed tomography (CT) of the lung may provide more detailed information about regional lung density changes that correlate with localized edema. [218] As in plain radiography, the changes seen on CT are not specific. Moreover, the radiation dose is higher and the cost is significantly greater than for plain radiography.

Compton scattering has also been used for lung water measurement. Rather than using the attenuation of transmitted x-ray photons as the monitor, the Compton technique measures photons scattered at 90 degrees to the incident beam. As lung water increases, the number of scattered photons increases. A portable instrument based on this technology has been described, [219] and the technique has been used in humans to compare physiologic and radiographic effects of intravenous saline infusion. [220]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has significant theoretical advantages over radiographic techniques. Clinical devices operate by measurement of protons in water, with no interference from other molecules. [221] [222] It requires no radiation and it has resolution at least as good as that of CT scanning. Disadvantages are cost and long image acquisition time. Extravascular water cannot be distinguished from intravascular water, although the blood contained in large vessels can be subtracted.

Positron Emission Tomography

Positron emission tomography (PET) can be used to provide tomographic images of the lung by use of radioactive tracers. [223] Intravenous administration of radioactive tracer (^{15} O-labeled water) provides a marker for lung water. Extravascular water can be separated from total water by subtracting the intravascular signal for ^{15} O-labeled carbon monoxide administered by inhalation. An advantage is the ability to examine lung water by lung region. Disadvantages include high cost and the necessity for an on-site cyclotron to produce the necessary short-lived isotopes.

Double Indicator Dilution

Injection of an ice-cold indocyanine green dye solution into the pulmonary artery and simultaneous thermal and green dye densitometry by constant withdrawal of blood from the femoral artery constitute another technique for measurement of lung water. [224] Green dye passes undisturbed through the lung, whereas heat diffuses into the bolus, tending to warm it to a degree that is dependent upon the thermal mass within the lung (primarily lung water). Using this technique in human organ donors, the thermal dye technique consistently overestimated gravimetric measurement of extravascular lung water postmortem. [225] The error is probably due to warming of the bolus by the heart and blood vessels and to differences in the time constants of the thermal and green dye detectors. Use of a thermal indicator alone has been shown to have approximately the same sensitivity as double dilution. [226]

A method has been described in which heat is replaced as the diffusible indicator by heavy water (deuterium oxide,

---

D_2O), which can be assayed in arterial blood by infrared absorption. After an aqueous mixture of indocyanine green dye and heavy water is injected into a central vein, continuous withdrawal of arterial blood through an optical cell allows for simultaneous measurement of D_2O and green dye. Thus, time constant errors, which occur with thermal dilution, are eliminated. This technique has been used in animals to assay lung water in experimentally produced pulmonary edema [227] and in humans during general anesthesia for abdominal surgery [228] and during hemodialysis. [229] Direct comparisons with gravimetric determination of lung water in experimental animals reveal that this method tends to underestimate lung water. Possible reasons include a slow diffusion constant for D_2O into lung water and inaccessibility of some lung water to the pulmonary vascular bed. [230] All indicator dilution techniques depend on physical contiguity of the lung water to the pulmonary vessels; nonperfused areas of edema are not measured.

Multiple Gas Technique

Inhalation of a mixture of an insoluble gas (e.g., helium) with a gas that is soluble in water (e.g., acetylene) allows another method of lung water estimation. [231] [232] In one application of this method a mixture of gases is rebreathed. The rate of disappearance of the soluble gas is related to lung water and pulmonary blood flow. Corrections can be made for blood flow by adding to the gas mixture carbon monoxide (which is highly soluble in blood but has low solubility in extravascular lung water not containing hemoglobin). This method is noninvasive and relatively inexpensive. Like thermal measurement of lung water, however, the method of gas dilution measures only lung water that is accessible to the airways.

Impedance Plethysmography

Electric impedance of the chest is inversely related to the amount of lung water. Four band-shaped electrodes are applied. One pair of excitation electrodes (placed at the neck and lower thorax) is used to pass an alternating current of approximately 0.5 mA longitudinally through the thorax. Two inner electrodes (at the base of the neck and at the diaphragm, cephalad to the lower excitation electrode) detect the induced voltage, which is proportional to the thoracic electric impedance (Z). Increases in air volume or intrathoracic fluid accumulation cause a decrease in impedance. Absolute water measurement cannot be obtained; however, patients can each serve as their own controls. Moreover, the technique is sensitive to changes in any intrathoracic water. Van De Water et al [233] have reported an experience using this technique in over 200 patients. In cases in which a decrease in intrathoracic water could be observed (radiographic clearance of pulmonary edema, thoracentesis, and pericardiocentesis), the expected increase in Z occurred.

None of these methods has attained routine clinical use, although the value of lung water measurements has been demonstrated by a number of studies, for example

measurement of the effect on lung water of perioperative administration of crystalloid versus colloid to patients undergoing aortic surgery. [234] Future developments will undoubtedly result in clinical applicability for lung water measurement.

MONITORING HIGH-FREQUENCY VENTILATION

High-frequency ventilation (Ch. 72) has been variously defined but in general represents mechanical ventilation at high rates (usually 160 breaths/min). Several means of ventilating in this manner have been used experimentally and clinically. The use of conventional positive-pressure ventilators at high rates and small tidal volumes is called high-frequency positive pressure ventilation (HFPV). Tidal volumes are usually on the order of 3 to 4 mL/kg body weight, with a frequency of 60 to 100 per minute. The use of an oscillator, providing both positive and negative pressure fluctuations (e.g., a loudspeaker), is called high-frequency oscillatory ventilation (HFOV). Higher frequencies, upward of 3,000 per minute, have been used with this modality. A "bias flow" of fresh gas at the level of the oscillator provides the source of the respiratory gas and washes out CO_2. Injection of a high-velocity pulse of gas into the airway through a narrow cannula, entraining with it fresh gas, is termed *high-frequency jet ventilation* (HFJV).

In all of these forms of high-frequency ventilation, instantaneous gas flows and pressure fluctuations cannot usually be monitored with conventional transducers. Because the system is basically open, a portion of the gas flow directed into the airway may leak out and not participate in intrapulmonary gas exchange. High-frequency ventilatory fluctuations generated by these ventilators may also in part do nothing more than compress and decompress the compliance of the ventilatory circuit and large conducting airways. Conventional mechanical monitoring is therefore difficult. Furthermore, capnography is difficult to apply because dilution of expired gas may render end-tidal measurements, even assuming a high-fidelity, high-frequency capnograph, artificially low.

Monitoring of patients receiving high-frequency ventilation requires the ability to monitor O_2 and CO_2 exchange, as well as mechanical safety, including airway disconnection and obstruction. Hoskyns et al [235] measured tidal volumes in 0.8- to 1.9-kg infants ventilated at 2 to 25 Hz using an external respiratory jacket. A side port of the jacket was used to monitor pressure changes, which correlated linearly with tidal volume.

Whereas patient oxygenation can readily be monitored with pulse oximetry, there is no reliable noninvasive monitor of CO_2 exchange. One way of monitoring CO_2 is to measure the mean waste gas CO_2 concentration by placing a capnograph in the expired circuit. If any condition that interferes with CO_2 exchange develops, the mean expired CO_2 decreases. Although this method provides a fairly gross measure of adequacy of CO_2 exchange, the expired CO_2 concentration is highly dependent upon fresh gas flow rate. A more satisfactory monitor might multiply fresh gas flow by expired CO_2 fraction to obtain V_{CO_2}. Changes in CO_2 could then reflect a mechanical problem with the ventilator. Unfortunately, there are other factors that may alter V_{CO_2}, such as anesthesia or hypothermia. One cannot obtain a measure of

P_{ACO_2} or Pa_{CO_2} by this method. The most commonly used currently available method is to interject a conventional breath periodically in order to measure $E_{t\,CO_2}$. Capnometry can be used to measure $E_{t\,CO_2}$ during HFJV without such a maneuver, provided that gas is sampled from a port situated at the tip of the endotracheal tube. [236]

Monitoring of airway pressure is extremely important in high-frequency ventilation. HFJV, in particular, uses high pressures and gas flows. Expiratory port occlusion can therefore result in extremely high airway pressures. Commonly, gas pressures are measured on both sides of the jet valve (drive pressure and jet pressure), along with an independent pressure measurement in the airway (Fig. 33-23). An automated feedback loop is required to interrupt the jet ventilation by closing the solenoid valve in the event of excessively high pressures either in the airway or on the jet side of the valve. Low pressures can be used as indications of airway disconnection or ventilator malfunction.

In addition to safety concerns, airway pressure in a number of studies has been shown to correlate with gas exchange efficiency during HFJV. [237] Increasing peak airway pressures result in lower Pa_{CO_2}. A superior indicator of Pa_{CO_2} is actually the difference between peak airway pressure and end-expiratory airway pressure. [238] There is no unique relationship, however, and the actual Pa_{CO_2} obtained for a given patient depends on properties of the lung. Position of the monitoring transducer may be critical because proximal airway pressures may be artifactually low. [238]

Jet ventilation for prolonged periods of time ideally should be performed on patients with the ability to monitor arterial blood gases directly. Periodic measurement of Pa_{CO_2} may provide greater assurance of adequate pulmonary gas exchange than simple reliance on noninvasive measures.

Figure 33-23 High-frequency jet ventilation. The jet is created when a high-pressure air-O_2 supply is rapidly modulated by the solenoid valve. Fresh inspired gas is from a low-pressure source, typically an anesthesia circuit. Drive pressure (P_D) and jet pressure (P_J) are customarily monitored in order to detect solenoid or jet malfunction. An independent monitor of airway pressure (P_{AW}), which will reliably detect overpressurization of the airway, circuit disconnection, or ventilator malfunction, should also be available.

WEANING FROM MECHANICAL VENTILATION AND TRACHEAL EXTUBATION

Mechanical ventilation may be instituted for a variety of reasons, including impaired respiratory drive, increased mechanical load, impaired respiratory motor function, and impaired pulmonary gas exchange. Endotracheal intubation is usually performed to facilitate mechanical ventilation but may also be instituted for maintenance of a patent upper airway, to enable suctioning of secretions, bronchoscopy, and to provide airway protection. Liberation of a patient from mechanical ventilation and successful extubation may be separate clinical issues.

When considering the challenge of weaning from mechanical ventilation (Ch. 72) it is useful to examine the reason for its initiation. The most common reason for mechanical ventilation during and after anesthesia is impaired respiratory drive; however, components of increased mechanical load and impaired neuromuscular function may contribute to an abnormally low ventilatory function. Patients with severe COPD usually are mechanically ventilated because of transient increases in mechanical load superimposed upon a chronic increase in airways resistance. Impaired respiratory drive and abnormal respiratory muscle mechanics may also play a role, however. Abnormal arterial oxygenation may exist despite what would appear to be adequate ventilatory effort. Therefore, ventilatory support may be required mainly to support arterial oxygenation or CO_2 elimination. Assessment of the patient with regard to possible discontinuation of mechanical ventilation may vary somewhat, depending on the reason for mechanical ventilatory support. Weaning ventilatory support from a patient whose only reason for mechanical ventilation is residual anesthesia is generally straightforward. A different approach is often required for a patient who has had prolonged ventilatory support for chronic respiratory disease. [239] After surgery, patients may have components of both impaired respiratory drive (residual anesthesia) and abnormal pulmonary mechanics (stiff lungs because edema or surgical trauma to respiratory muscles). Some criteria that have been used are shown in Table 33-4 . The most commonly used weaning criteria have included a vital capacity not below 10 mL/kg, maximum inspiratory pressure (MIP) not above 25 cm/H_2O, respiratory rate not above 20 per minute and V_E not above 10 to 20 L per minute in the face of normal Pa_{CO_2} . Arterial oxygenation should also be maintained with an inspired O_2 concentration not above 50 percent, with 5 cm/H_2O or less of PEEP.

The success or failure of a weaning criterion often depends upon the clinical situation. Many of the criteria that were originally derived from patients being weaned from mechanical ventilation in the postoperative period are not applicable to patients who have been ventilator-dependent for several days or weeks, in whom respiratory muscle atrophy, malnutrition, and peripheral neuropathy have often supervened. In the latter situation it is unlikely that a single weaning criterion will be adequate to predict success.

Frequently, a trial of spontaneous ventilation is instituted (T-tube trial). T-tube trials often result in reduced functional residual capacity, which may further add to an increased respiratory

TABLE 33-4 -- Possible Criteria for Ventilator Weaning

TEST	CRITERION FOR WEANING
MECHANICAL FUNCTION	
Vital capacity (FVC)	>10-15 mL/kg
FEV_1	>10 mL/kg
Tidal volume (V_T)	>5 mL/kg
Maximum inspiratory pressure (MIP)	<-20 cm H_2O
Maximum voluntary ventilation (MVV)	>2 times resting V_E
Respiratory rate (V_F)	>25/min
Respiratory minute volume (V_E)	<10 L/min
V_F/V_T	<100 bpm/l
$V_F/(V_T/kg)$ [a]	<11 bpm/mL/kg
Thoracic compliance	
Static	33 mL/cm H_2O
Dynamic	22 mL/cm H_2O
Work of breathing	
Per minute	1.6 kg · m/min
Per L/min V_E	0.14 kg · m/min
$(0.75V_T/C\ dyn) \cdot (T_I/T_{TOT})/(MIP)$ [b]	<0.15
Functional residual capacity (FRC)	>50% predicted
GAS EXCHANGE FUNCTION	
A-a gradient (F_{IO_2} = 1.0)	<350 mm Hg
Pa_{O_2}/P_{AO_2} ratio	0.35
Shunt fraction (Q_S/Q_T)	<0.2
Dead space/tidal volume ratio (V_D/V_T)	<0.6

Minute ventilation (V_E) with normal Pa CO_2	<180 mL · kg^{-1} · min^{-1}
Respiratory quotient (R)	<0.9
Pa O_2 /F IO_2	>200
RESPIRATORY DRIVE	
P_{100}	<6 cm H_2O
P_{100} /MIP	<0.09
OTHER	
Urine output	500 mL/6 h
Arterial pH	>7.30
Gastric intramural pHi during pressure support trial	>7.30 or a change <0.09
[C dyn · MIP · (Pa O_2 /P AO_2)]/V F[c]	13 mL/bpm
[(C dyn/kg) · MIP · (Pa O_2 /P AO_2)]/V F[a]	0.1 mL/kg per bpm

Abbreviations: C dyn, dynamic thoracic compliance; T_I, inspiratory time; T_{TOT}, respiratory cycle length; bpm, breaths per minute

Data from [3] [176] [179] [239] [240] [241] [242] [244] [280] [281] [282] [283] [284] [285] [286] [287]

[a] Pediatric use [279]

[b] Inspiratory effort quotient (IEQ). If intrinsic PEEP (PEEPi) present, IEQ = (PEEPi + 0.75V_T/C dyn) · (T_I/T_{TOT})/(MIP · PEEPi) [280]

[c] CROP index (compliance, rate, oxygenation, pressure) [242]

load after extubation. Therefore, some clinicians advocate extubation while the patient is being supported with intermittent mandatory ventilation. For example, Gorback and Kantor [240] evaluated general surgical patients postoperatively for extubation when the synchronized intermittent mandatory ventilation (SIMV) rate was 4 per minute, Pa O_2 was not below 60 mm Hg with F IO_2 not above 0.4, PEEP was not above 5 cm H_2O, and no inotropic support was required. The investigators then proceeded to extubate patients if they matched three of the following five criteria: maximum inspiratory pressure 30 cm H_2O or less, arterial pH 7.30 or more, respiratory rate 30 per minute or more (including IMV breaths), vital capacity 10 mL/kg or more, and tidal volume 5 mL/kg or more. These criteria were used for 120 consecutive extubations; only 1 of the 120 patients required reintubation.

The individual approach used depends on the clinical situation. Whereas the approach suggested previously may be successful in patients mechanically ventilated after general surgical procedures, other criteria may be required after prolonged ventilation for respiratory failure due to pulmonary or neuromuscular disease. Indeed, a combination of measures that will assess respiratory mechanical function as well as gas exchange is generally implemented. Excellent reviews of weaning criteria and techniques have been published by Tobin and Yang, [241] Yang and Tobin, [242] Goldstone and Moxham, [243] Esteban, [244] and Mancebo. [245]

TRACHEAL EXTUBATION AFTER COMPROMISE OF AIRWAY

Protection of the airway with potential encroachment by hemorrhage, edema, infection, or tumor using an endotracheal tube (Ch. 39) often engenders uncertainty at the time of extubation. Airway patency after extubation may not be ensured, and sudden loss of airway may occur. Reintubation may then be difficult or impossible.

Useful measures that can be taken at the time of extubation include the following: inspection of the upper airway, either directly or with a fiberoptic instrument to detect residual swelling of the oropharynx or nasopharynx, or occlusion of the endotracheal tube with cuff deflated. If the patient is able to breathe around the tube in this way, it is less likely that critical airway compromise will occur after extubation. It is possible that if the endotracheal tube is large with respect to the patient's airway, the patient may not be able to breathe around it even in the presence of a normal airway. Replacement of the tube with a smaller one may be accomplished over a rigid introducer, which allows abrupt loss of the airway to be treated immediately with reinsertion. A nasogastric tube with the bulbous end cut off may be used, but a more rigid plastic introducer is preferable. Alternatively, a fiberoptic bronchoscope may be introduced into the endotracheal tube. If the patient is able to breathe after removal of the tube from the larynx and lower pharynx, direct inspection of the airway may be accomplished during removal of the fiberoptic instrument.

These measures should be undertaken while someone with the necessary skills to perform an emergency tracheotomy is available. Before removal of the endotracheal tube, the patient should be preoxygenated with 100 percent O_2, providing a margin of safety in the event of loss of airway patency.

TRANSPORTATION OF THE PATIENT

Movement of the patient between various critical care units (operating room, ICU, or postanesthesia care unit) or between the ICU and diagnostic radiology presents special problems (Ch. 66) . Planning for such a move should include preparing for a worst-case scenario. Movement of the patient from the operating room to the postanesthesia care unit may engender problems of hypoxemia, loss of airway, hemodynamic instability or vomiting, and aspiration. After an uncomplicated anesthetic, the most likely untoward event is arterial hypoxemia and loss of airway. Because the patient is at risk for hypoxemia due to a variety of causes, including hypoventilation, atelectasis, impaired V_A/Q matching, residual second gas effect (N_2O), shivering, and resulting decrease in mixed venous P_{O_2} and airway obstruction, it would appear safest to transport the patient with supplemental O_2 unless the distance between operating room and postanesthesia care unit is short. Respiration can be continuously monitored using one of the following: a tightly fitting mask and observing movements of a breathing bag, a hand held under the chin to feel exhalations, a precordial stethoscope or, if the patient is still intubated, an esophageal stethoscope. Patients at higher risk of hypoxemia during transport include children, patients with baseline gas exchange abnormality, and obese individuals. Particularly in these types of patients relatively rapid desaturation may occur, even if the patient has been ventilated with 100 percent O_2 immediately before transport. [246] [247] Continuous monitoring of Sp_{O_2} is an additional option.

A worst-case scenario for a patient undergoing transportation over a long distance, particularly in an elevator, would include accidental extubation or inability to ventilate. Therefore, in addition to the monitoring techniques described, long-distance transportation within the hospital should always occur with the ability to provide emergency positive-pressure ventilation and emergency endotracheal intubation. Several manufacturers produce portable pulse oximeters, which can be very useful in this setting.

EPIDURAL AND INTRATHECAL OPIATES

A large number of clinical reports suggest that spinal (epidural or intrathecal) opiate administration may provide prolonged superior analgesia after surgery as compared with parenteral administration in the traditional fashion (Ch. 69) . Moreover, clinical investigation suggested that respiratory function, particularly after upper abdominal surgery, [248] may be improved with epidural administration of morphine, compared with intravenous administration. However, early reports of delayed respiratory depression after epidural and intrathecal morphine administration have led to tremendous scrutiny of the respiratory depressant effect of narcotics given by this route. [249] Several detailed clinical investigations of blood gases, ventilation, and respiratory drive have shown acceptable degrees of depression after spinal narcotic administration. However, assessment of the mean response in small numbers of individuals may not predict the likelihood of an extreme response, which may occur infrequently. Few large-scale surveys are available. Rawal et al [250] reported on a survey in 1984 of 93 departments of anesthesia in Sweden, in which approximately 12,000 patients received epidural narcotics perioperatively, and 1,000 patients received intrathecal narcotics. The vast majority of these patients received morphine; 0.04 percent of patients showed clinical signs of ventilatory depression within 1 hour of epidural morphine injection, and 0.09 percent demonstrated delayed ventilatory depression. Delayed ventilatory depression occurred in 0.36 percent of patients who received intrathecal morphine, which occurred within 7 to 9 hours after injection. Stuart-Taylor et al [251] reported that 7 of 800 patients receiving epidural diamorphine experienced respiratory depression to less than 10 breaths per minute. Ready et al [252] reported that 2 of 1,106 consecutive patients treated with epidural morphine after surgery required medication for respiratory depression. Scherer et al [253] reported that 1 of 1,071 patients receiving thoracic epidural buprenorphine experienced respiratory depression. Lubenow [254] reported six incidents of respiratory depression in 5,172 patients receiving epidural narcotics. All patients with ventilatory depression were successfully treated, and there were no deaths from this complication.

Respiratory depression and consequent hypoxemia is not confined to patients who have received epidural narcotics. Periodic desaturation has also been reported after intravenous or intramuscular opiate administration. [53] [54] [59] [60] [63] [64] [66] [67] [255] [256] [257] [258] [259] Reeder [63] reported that one patient after abdominal vascular surgery experienced 229 episodes of desaturation to Sp O_2 less than 70%, representing 43 percent of the third postoperative night. Etches [260] reported eight cases of serious respiratory depression out of approximately 1,600 patients who had received intravenous opioids via patient-controlled infusion pumps.

Some studies have compared traditional and epidural routes of administration. Wheatley et al [60] reported that hypoxemia occurred in patients receiving narcotics intravenously and intramuscularly as well as via the epidural route, although most commonly in the latter. Jayr et al [261] observed that 13 percent of patients receiving a subcutaneous 2.5-mg-per-hour infusion of morphine after abdominal surgery experienced at least one episode of arterial desaturation (Sp O_2 below 85%) during the first postoperative night; only 6 percent of patients receiving an epidural infusion of morphine and bupivacaine experienced similar desaturation. Small series reported by other investigators suggest that mild desaturation is equally likely with either technique. [56] [262] [263] In the study of Pan and James 1 of 15 patients in the epidural group, who had earlier received 37.5 mg of promethazine for nausea and vomiting, required naloxone treatment for somnolence and hypoxemia. [263] Brose and Cohen [55] observed that episodes of desaturation (Sp O_2 < 85%) were more frequent in patients who received epidural narcotics compared with intravenous narcotics but not different from those who received narcotics intramuscularly. A randomized, controlled study of PCA versus epidural infusion of bupivacaine in 60 patients who had undergone major abdominal surgery for cancer indicated that mild decreases in Sp O_2 (85-89%) were more common in patients receiving epidural analgesia, but there was no difference between groups in frequency of Sp O_2 in the range 80 to 84 percent. [264]

These observations suggest that narcotic administration via the epidural or intravenous route carries a similar risk of mild or moderate episodic hypoxemia. Notwithstanding the hypothesis that these phenomenona produce morbidity, [67] [259] [265] [266] [267] the clinical significance of such episodes presently, if any, must be considered unproven. Temporal association of transient hypoxemia with clinical events such as myocardial ischemia and confusion does not prove causation. Normal volunteers can be safely exposed to repetitive periods of hypoxemia (Sa O_2 as low as 40%) for 30 to 45 seconds. [119] [268] Although there is evidence that exposure to extreme hypoxia (mean lowest Sa O_2 68%) for prolonged periods can cause minor psychomotor deficits, [269] there is little evidence that exposure to moderate altitude hypoxia for hours (for example astronomers commuting daily from sea level to the Mauna Kea observatories at barometric pressure = 468 mmHg; mean arterial P O_2 = 39.7 mm Hg, P CO_2 = 27.7 mm Hg[7]) or even days results in permanent sequelae. [7] [270] [271] Therefore, in terms of assessing the risks of various forms of postoperative analgesia, mild postoperative reduction in Sp O_2 is only a surrogate end point, which may not reflect the risk of the most feared complication: major respiratory depression resulting in respiratory arrest or death.

Earlier reports recommended the routine use of apnea monitoring on patients given spinal narcotics, but apnea monitors are often associated with false alarms and are frequently ignored. Furthermore, significant respiratory depression can occur with a normal respiratory rate. [170] [171] [173] Significant respiratory depression is almost invariably associated with sedation, however. Thus, a periodic check of mental status may be more sensitive than mechanical monitors in detecting clinical respiratory depression and is an essential component of monitoring patients who have received epidural narcotics.

Several years of clinical experience with epidural opiates has suggested that monitoring beyond clinical assessment is not necessary, particularly in low-risk patients [173] [251] [252] [253] [254] [272] [273] and has led to the implementation of less stringent policies in most institutions. [274] Standards of care after epidural opioid administration in the United States are illustrated by a survey of 197 institutions, including teaching and community hospitals, published by Muir et al. [273] Patients are monitored in a general care ward after opioid administration via a thoracic epidural catheter in 88.6 percent of institutions and after lumbar administration in 96.8 percent. Pulse oximetry and electronic apnea monitoring are each routinely utilized in 28 percent of institutions after thoracic opioid administration, and in 27 percent and 5 percent, respectively, after lumbar administration. The frequency with which respiration rate and sedation are monitored is shown in Table 33-5 .

There is a fairly widespread consensus that, in addition to regular monitoring of respiration rate and level of sedation, monitoring equipment and resuscitative drugs should be readily available. Naloxone and a syringe with which to administer it should be stored at the bedside. Dosage adjustment or more intensive monitoring may be suitable for individuals with cardiorespiratory disease or other risk factors

TABLE 33-5 -- Frequency of Respiratory Rate and Sedation Monitoring following Epidural Narcotic Analgesia in a Survey of 197 Institutions

FREQUENCY	THORACIC		LUMBAR	
	CONTINUOUS	BOLUS	CONTINUOUS	BOLUS
Q 1 h	28	17	31	19
Q 1 h × 24 h then Q 2 h	25	14	27	17
Q 1 h × 12 h then Q 2 h	19	9	19	9
Q 1 h × 4 h then Q 2 h	12	3	13	5
Q 1 h × 4 h then Q 4 h	25	13	31	16

Q 2 h	2	1	3	1
Q 2 h × 24 h then Q 4 h	9	1	9	1
Q 2 h × 12 h then Q 4 h	6	2	4	1
Q 4 h	7	3	7	3
TOTALS	133	63	144	72

Data from Muir et al [273]

TABLE 33-6 -- Factors Predisposing to the Development of Respiratory Depression Following Epidural Opioids

(Not Available)

From Etches et al [245]

for respiratory depression (Table 33-6) (Table Not Available) . Because delayed respiratory depression can occur particularly after morphine administration, it is prudent to continue the monitoring algorithm for several hours after the final dose has been administered.

In conclusion, the widespread clinical use of epidural narcotics, particularly morphine, suggests that this technique is safe for most patients without the need for monitoring beyond simple clinical observation.

REFERENCES

1. The Shorter Oxford Dictionary. Oxford, Oxford University Press, 1987.

2. McGraw-Hill Dictionary of Scientific and Technical Terms. New York, McGraw-Hill, 1989.

3. Eichhorn JH, Cooper JB, Cullen DJ, et al: Standards for patient monitoring during anesthesia at Harvard Medical School. JAMA 256:1017, 1986.

4. American Society of Anesthesiologists: Standards for basic anesthetic monitoring. 1998 Directory of Members. Park Ridge, IL, American Society of Anesthesiologists, 1998.

5. Wagner PD, Gale GE, Moon RE, et al: Pulmonary gas exchange in humans exercising at sea level and simulated altitude. J Appl Physiol 61:260, 1986.

6. Rock PB, Johnson TS, Cymerman A, et al: Effect of dexamethasone on symptoms of acute mountain sickness at Pikes Peak, Colorado (4,300 m). Aviat Space Environ Med 58:668, 1987.

7. Heath D, Williams DR: High-Altitude Medicine and Pathology. Oxford, Oxford University Press, 1995.

8. Ciofolo MJ, Clergue F, Devilliers C, et al: Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. Anesthesiology 70:737, 1989.

9. Frank SM, Fleisher LA, Olson KF, et al: Multivariate determinants of early postoperative oxygen consumption in elderly patients. Effects of shivering, body temperature, and gender. Anesthesiology 83:241, 1995.

10. Mellemgaard K: The alveolar-arterial oxygen difference: Its size and components in normal man. Acta Physiol Scand 67:10, 1966.

11. Gilbert R, Keighley JF: The arterial-alveolar oxygen tension ratio: An index of gas exchange applicable to varying inspired oxygen concentrations. Am Rev Respir Dis 109:142, 1974.

12. Wagner PD, Laravuso RB, Uhl R, et al: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100 percent O_2. J Clin Invest 54:54, 1974.

13. Sahn SA, Lakshminarayan S, Petty TL: Weaning from mechanical ventilation. JAMA 235:2208, 1976.

14. West JB: Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. Respir Physiol 7:88, 1969.

15. Wagner PD, Saltzman HA, West JB: Measurement of continuous distributions of ventilation-perfusion ratios: Theory. J Appl Physiol 36:588, 1974.

16. Dueck R, Young I, Clausen J, et al: Altered distribution of pulmonary ventilation and blood flow following induction of inhalation anesthesia. Anesthesiology 52:113, 1980.

17. Tokics L, Hedenstierna G, Strandberg A, et al: Lung collapse and gas exchange during general anesthesia: Effects of spontaneous breathing, muscle paralysis and positive end-expiratory pressure. Anesthesiology 66:157, 1987.

18. Tokics L, Hedenstierna G, Svensson L, et al: V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. J Appl Physiol 81:1822, 1996.

19. Bein T, Reber A, Metz C, et al: Acute effects of continuous rotational therapy on ventilation-perfusion inequality in lung injury. Intensive Care Med 24:132, 1998.

20. Severinghaus JW: Blood gas concentrations. In Fenn WO, Rahn H (eds): Handbook of Physiology, section 3: Respiration. Washington, DC, American Physiological Society, 1965.

21. Severinghaus JW, Astrup PB: History of blood gas analysis. Int Anesthesiol Clin 25:1, 1987.

22. Severinghaus JW: Historical development of oxygenation monitoring. In Payne JP, Severinghaus JW (eds): Pulse Oximetry. New York, Springer-Verlag, 1986.

23. Cobbold RSC: Transducers for Biomedical Measurements: Principles and Applications. New York, John Wiley & Sons, 1974.

24. Barker SJ, Tremper KK, Hyatt J, et al: Continuous fiberoptic arterial oxygen tension measurements in dogs. J Clin Monit 3:48, 1987.

25. National Committee for Clinical Laboratory Standards: Definitions of Quantities and Conventions Related to Blood pH and Gas Analysis; Approved Standard. NCCLS Document C12-A, vol. 14. Villanova, PA, 1994.

26. Camporesi EM, Moon RE: Arterial blood gas values should be corrected for body temperature during hypothermia. In Fyman PH, Gotta AW (eds): Controversies in Cardiovascular Anesthesia. Boston, Kluwer Academic Publishers, 1988.

27. Hess CE, Nichols AB, Hunt WB, et al: Pseudohypoxemia secondary to leukemia and thrombocytosis. New Engl J Med 301:361, 1979.

28. Schmaier AH: Pseudohypoxemia due to leukemia and thrombocytosis. New Engl J Med 302:584, 1980.

29. Barker SJ, Hyatt J, Clarke C, et al: Hyperventilation reduces transcutaneous oxygen tension and skin blood flow. Anesthesiology 75:619, 1991.

30. Mathieu D, Neviere R, Pellerin P, et al: Pedicle musculocutaneous flap transplantation: Prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. Plast Reconstr Surg 91:329, 1993.

31. Asmussen J, Gellett S, Pilegaard H, et al: Conjunctival oxygen tension measurements for assessment of tissue oxygen tension during pulmonary surgery. Eur Surg Res 26:372, 1994.

32. Heyworth J: Conjunctival oxygen monitoring in the initial assessment of trauma. Arch Emerg Med 9:274, 1992.

33. Sjostrom P, Wiklund L, Odlind B: Conjunctival oxygen tension is influenced by plasma and blood volume, and flow through the external carotid artery. Int J Clin Monit Comput 11:99, 1994.

34. Janssens JP, Howarth-Frey C, Chevrolet JC, et al: Transcutaneous PCO_2 to monitor noninvasive mechanical ventilation in adults: Assessment of a new transcutaneous PCO_2 device. Chest 113:768, 1998.

35. Severinghaus JW: Nomenclature of oxygen saturation. Adv Exp Med Biol 345:921, 1994.

36. Comroe JH Jr, Botelho S: The unreliability of cyanosis in the recognition of arterial hypoxemia. Am J Med Sci 214:1, 1947.

37. Lunsgaard C, Van Slyke DD: Cyanosis. Medicine (Baltimore) 2:1, 1923.

38. Stadie WC: The oxygen of the arterial and venous blood in pneumonia and its relation to sepsis. J Exp Med 30:215, 1919.

39. Severinghaus JW, Astrup PB: History of blood gas analysis, VI: Oximetry. J Clin Monit 2:270, 1986.

40. Kirlangitis JJ, Middaugh RE, Zablocki A, et al: False indication of arterial oxygen desaturation and methemoglobinemia following injection of methylene blue in urological surgery. Mil Med 155:260, 1990.

41. Gourlain H, Buneaux F, Borron SW, et al: Interference of methylene blue with CO-oximetry of hemoglobin derivatives. Clin Chem 43:1078, 1997.

42. Chaudhary BA, Burki NK: Ear oximetry in clinical practice. Am Rev Respir Dis 117:173, 1978.

43. Skacel M, O'Hare E, Harrison D: Invalid information from the ear probe of a pulse oximeter in tricuspid incompetence. Anaesth Intensive Care 18:270, 1990.

44. Faisst K, Kirkinen P, Konig V, et al: Intrapartum reflectance pulse oximetry--effects of sensor location and fixation duration on oxygen saturation. J Clin Monit 13:299, 1997.

45. Izumi A, Minakami H, Sato I: Accuracy and utility of a new reflectance pulse oximeter for fetal monitoring during labor. J Clin Monit 13:103, 1997.

46. Kuhnert M, Seelbachgoebel B, Butterwegge M: Predictive agreement between the fetal arterial oxygen saturation and fetal scalp pH--results of the German multicenter study. Am J Obstet Gynecol 178:330, 1998.

47. Borum SE: The successful use of transesophageal pulse oximetry in a patient in whom peripheral pulse oximetry was unobtainable. Anesth Analg 85:514, 1997.

48. Ayas N, Bergstrom LR, Schwab TR, et al: Unrecognized severe postoperative hypercapnia--a case of apneic oxygenation. Mayo Clin Proc 73:51, 1998.

49. Moller JT, Pedersen T, Rasmussen LS, et al: Randomized evaluation of pulse oximetry in 20,802 patients: I. Design, demography, pulse oximetry failure rate, and overall complication rate. Anesthesiology 78:436, 1993.

50. Moller JT, Johannessen NW, Espersen K, et al: Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. Anesthesiology 78:445, 1993.

51. Eichhorn JH: Pulse oximetry as a standard of practice in anesthesia. Anesthesiology 78:423, 1993.

52. Bierman MI, Stein KL, Snyder JV: Pulse oximetry in the postoperative care of cardiac surgical patients. A randomized controlled trial. Chest 102:1367, 1992.

53. Catley DM, Thornton C, Jordan C, et al: Pronounced, episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. Anesthesiology 63:20, 1985.

54. Morris RW, Buschman A, Warren DL, et al: The prevalence of hypoxemia detected by pulse oximetry during recovery from anesthesia. J Clin Monit 4:16, 1988.

55. Brose WG, Cohen SE: Oxyhemoglobin saturation following cesarean section in patients receiving epidural morphine, PCA, or IM meperidine analgesia. Anesthesiology 70:948, 1989.

56. Choi HJ, Little MS, Garber SZ, et al: Pulse oximetry for monitoring during ward analgesia: Epidural morphine versus parenteral narcotics. J Clin Monit 5:87, 1989.

57. Rosenberg J, Dirkes WE, Kehlet H: Episodic arterial oxygen desaturation and heart rate variations following major abdominal surgery. Br J Anaesth 63:651, 1989.

58. Rosenberg J, Ullstad T, Larsen PN, et al: Continuous assessment of oxygen saturation and subcutaneous oxygen tension after abdominal operations. Acta Chir Scand 156:585, 1990.

59. Rosenberg J, Rasmussen V, von Jessen F et al: Late postoperative episodic and constant hypoxaemia and associated ECG abnormalities. Br J Anaesth 65:684, 1990.

60. Wheatley RG, Somerville ID, Sapsford DJ, et al: Postoperative hypoxaemia: Comparison of extradural, i.m. and patient-controlled opioid analgesia. Br J Anaesth 64:267, 1990.

61. Entwistle MD, Roe PG, Sapsford DJ, et al: Patterns of oxygenation after thoracotomy. Br J Anaesth 67:704, 1991.

62. Gill NP, Wright B, Reilly CS: Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. Br J Anaesth 68:471, 1992.

63. Reeder MK, Goldman MD, Loh L, et al: Late postoperative nocturnal dips in oxygen saturation in patients undergoing major abdominal vascular surgery. Predictive value of pre-operative overnight pulse oximetry. Anaesthesia 47:110, 1992.

64. Reeder MK, Goldman MD, Loh L, et al: Postoperative hypoxaemia after major abdominal vascular surgery. Br J Anaesth 68:23, 1992.

65. Rosenberg J, Pedersen MH, Gebuhr P, et al: Effect of oxygen therapy on late postoperative episodic and constant hypoxaemia. Br J Anaesth 68:18, 1992.

66. Wheatley RG, Shepherd D, Jackson IJ, et al: Hypoxaemia and pain relief after upper abdominal surgery: Comparison of i.m. and patient-controlled analgesia. Br J Anaesth 69:558, 1992.

67. Rosenberg J, Kehlet H: Postoperative mental confusion--association with postoperative hypoxemia. Surgery 114:76, 1993.

68. Rosenberg J, Oturai P, Erichsen CJ, et al: Effect of general anesthesia and major versus minor surgery on late postoperative episodic and constant hypoxemia. J Clin Anesth 6:212, 1994.

69. Lewer BMF, Larsen PD, Torrance JM, et al: Artifactual episodic hypoxaemia during postoperative respiratory monitoring. Can J Anaesth 45:182, 1998.

70. Parker HR, Purves MJ: Some effects of maternal hyperoxia and hypoxia on the blood gas tensions and vascular pressures in the foetal sheep. Q J Exp Physiol Cogn Med Sci 52:205, 1967.

71. Brinkman CR 3d, Weston P, Kirschbaum TH, et al: Effects of maternal hypoxia on fetal cardiovascular hemodynamics. Am J Obstet Gynecol 108:288, 1970.

72. Parer JT: The effect of acute maternal hypoxia on fetal oxygenation and the umbilical circulation in the sheep. Eur J Obstet Gynecol Reprod Biol 10:125, 1980.

73. Jackson BT, Piasecki GJ, Novy MJ: Fetal responses to altered maternal oxygenation in rhesus monkey. Am J Physiol 252:R94, 1987.

74. Polvi HJ, Pirhonen JP, Erkkola RU: The hemodynamic effects of maternal hypo- and hyperoxygenation in healthy term pregnancies. Obstet Gynecol 86:795, 1995.

75. Barker SJ, Tremper KK: The effect of carbon monoxide inhalation on pulse oximetry and transcutaneous PO_2. Anesthesiology 66:677, 1987.

76. Gonzalez A, Gomez-Arnau J, Pensado A: Carboxyhemoglobin and pulse oximetry. Anesthesiology 73:573, 1990.

77. Buckley RG, Aks SE, Eshom JL, et al: The pulse oximetry gap in carbon monoxide intoxication. Ann Emerg Med 24:252, 1994.

78. Nijland R, Jongsma HW, Nijhuis JG, et al: Notes on the apparent discordance of pulse oximetry and multi-wavelength haemoglobin photometry. Acta Anaesthesiol Scand Suppl 107:49, 1995.

79. Bozeman WP, Myers RAM, Barish RA: Confirmation of the pulse oximetry gap in carbon monoxide poisoning. Ann Emerg Med 30:608, 1997.

80. Hampson NB: Pulse oximetry in severe carbon monoxide poisoning. Chest 114:1036, 1998.

81. Eisenkraft JB: Pulse oximeter desaturation due to methemoglobin-emia. Anesthesiology 68:279, 1988.

82. Barker SJ, Tremper KK, Hyatt J: Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. Anesthesiology 70:112, 1989.

83. Kouides PA, Abboud CN, Fairbanks VF: Flutamide-induced cyanosis refractory to methylene blue therapy. Br J Haematol 94:73, 1996.

84. Zijlstra WG, Maas AH, Moran RF: Definition, significance and measurement of quantities pertaining to the oxygen carrying properties of human blood. Scand J Clin Lab Invest Suppl 224:27, 1996.

85. Wu C, Kenny MA: A case of sulfhemoglobinemia and emergency measurement of sulfhemoglobin with an OSM3 CO-oximeter. Clin Chem 43:162, 1997.

86. Tremper KK, Barker SJ: Pulse oximetry. Anesthesiology 70:98, 1989.

87. Weston Smith SG, Glass UH, Acharya J, et al: Pulse oximetry in sickle cell disease. Clin Lab Haematol 11:185, 1989.

88. Pianosi P, Charge TD, Esseltine DW, et al: Pulse oximetry in sickle cell disease. Arch Dis Child 68:735, 1993.

89. Rackoff WR, Kunkel N, Silber JH, et al: Pulse oximetry and factors associated with hemoglobin oxygen desaturation in children with sickle cell disease. Blood 81:3422, 1993.

90. Craft JA, Alessandrini E, Kenney LB, et al: Comparison of oxygenation measurements in pediatric patients during sickle cell crises. J Pediatr 124:93, 1994.

91. Jay GD, Renzi FP: Evaluation of pulse oximetry in anemia from hemoglobin-H disease. Ann Emerg Med 21:572, 1992.

92. Katoh R, Miyake T, Arai T: Unexpectedly low pulse oximeter readings in a boy with unstable hemoglobin Koln. Anesthesiology 80:472, 1994.

93. Gottschalk A, Silverberg M: An unexpected finding with pulse oximetry in a patient with hemoglobin Koln. Anesthesiology 80:474, 1994.

94. Przybelski RJ, Daily EK, Kisicki JC, et al: Phase I study of the safety and pharmacologic effects of diaspirin cross-linked hemoglobin solution. Crit Care Med 24:1993, 1996.

95. Hughes GS Jr, Francome SF, Antal EJ, et al: Hematologic effects of a novel hemoglobin-based oxygen carrier in normal male and female subjects. J Lab Clin Med 126:444, 1995.

96. Hughes GS, Francom SF, Antal EJ, et al: Effects of a novel hemoglobin-based oxygen carrier on percent oxygen saturation as determined with arterial blood gas analysis and pulse oximetry. Ann Emerg Med 27:164, 1996.

97. Jay GD, Hughes L, Renzi FP: Pulse oximetry is accurate in acute anemia from hemorrhage. Ann Emerg Med 24:32, 1994.

98. Severinghaus JW, Koh SO: Effect of anemia on pulse oximeter accuracy at low saturation. J Clin Monit 6:85, 1990.

99. Boxer RA, Gottesfeld I, Singh S, et al: Noninvasive pulse oximetry in children with cyanotic congenital heart disease. Crit Care Med 15:1062, 1987.

100. Schmitt HJ, Schuetz WH, Proeschel PA, et al: Accuracy of pulse oximetry in children with cyanotic congenital heart disease. J Cardiothorac Vasc Anesth 7:61, 1993.

101. Kessler MR, Eide T, Humayun B, et al: Spurious pulse oximeter desaturation with methylene blue injection. Anesthesiology 65:435, 1986.

102. Sidi A, Paulus DA, Rush W, et al: Methylene blue and indocyanine green artifactually lower pulse oximetry readings of oxygen saturation: Studies in dogs. J Clin Monit 3:249, 1987.

103. Barker SJ, Tremper KK: Pulse oximetry: Applications and limitations. Int Anesthesiol Clin 25:155, 1987.

104. Gorman ES, Shnider MR: Effect of methylene blue on the absorbance of solutions of haemoglobin. Br J Anaesth 60:439, 1988.

105. Scott DM, Cooper MG: Spurious pulse oximetry with intrauterine methylene blue injection. Anaesth Intensive Care 19:267, 1991.

106. Kelleher JF: Pulse oximetry. J Clin Monit 5:37, 1989.

107. Larsen VH, Freudendal-Pedersen A, Fogh-Andersen N: The influence of patent blue V on pulse oximetry and haemoximetry. Acta Anaesthesiol Scand Suppl 107:53, 1995.

108. Morell RC, Heyneker T, Kashtan HI, et al: False desaturation due to intradermal patent blue dye. Anesthesiology 78:363, 1993.

109. Saito S, Fukura H, Shimada H, et al: Prolonged interference of blue dye "patent blue" with pulse oximetry readings. Acta Anaesth Scand 39:268, 1995.

110. McEwan D, Lam K: Oximetry and patent blue five dye. Anaesth Intensive Care 25:587, 1997.

111. Cote CJ, Goldstein EA, Fuchsman WH, et al: The effect of nail polish on pulse oximetry. Anesth Analg 67:683, 1988.

112. al-Majed SA, Harakati MS: The effect of henna paste on oxygen saturation reading obtained by pulse oximetry. Trop Geogr Med 46:38, 1994.

113. Veyckemans F, Baele P, Guillaume JE, et al: Hyperbilirubinemia does not interfere with hemoglobin saturation measured by pulse oximetry. Anesthesiology 70:118, 1989.

114. Lebecque P, Shango P, Stijns M, et al: Pulse oximetry versus measured arterial oxygen saturation: A comparison of the Nellcor N100 and the Biox III. Pediatr Pulmonol 10:132, 1991.

115. Beall SN, Moorthy SS: Jaundice, oximetry, and spurious hemoglobin desaturation. Anesth Analg 68:806, 1989.

116. Veyckemans F, Baele PL: More about jaundice and oximetry. Anesth Analg 70:335, 1990.

117. Read MS: Effect of transparent adhesive tape on pulse oximetry. Anesth Analg 68:701, 1989.

118. Racys V, Nahrwold ML: Reusing the Nellcor pulse oximeter probe: Is it worth the savings? Anesthesiology 66:713, 1987.

119. Severinghaus JW, Naifeh KH: Accuracy of response of six pulse oximeters to profound hypoxia. Anesthesiology 67:551, 1987.

120. Costarino AT, Davis DA, Keon TP: Falsely normal saturation reading with the pulse oximeter. Anesthesiology 67:830, 1987.

121. Severinghaus JW, Kelleher JF: Recent developments in pulse oximetry. Anesthesiology 76:1018, 1992.

122. Gardosi JO, Damianou D, Schram CM: Inappropriate sensor application in pulse oximetry. Lancet 340:920, 1992.

123. Severinghaus JW, Spellman MJ Jr: Pulse oximeter failure thresholds in hypotension and vasoconstriction. Anesthesiology 73:532, 1990.

124. Vegfors M, Lindberg LG, Lennmarken C: The influence of changes in blood flow on the accuracy of pulse oximetry in humans. Acta Anaesth Scand 36:346, 1992.

125. Broome IJ, Mills GH, Spiers P, et al: An evaluation of the effect of vasodilatation on oxygen saturations measured by pulse oximetry and venous blood gas analysis. Anaesthesia 48:415, 1993.

126. Bhargava M, Pothula SNM: Improvement of pulse oximetry signal by Emla cream. Anesth Analg 86:915, 1998.

127. Alexander CM, Teller LE, Gross JB: Principles of pulse oximetry: Theoretical and practical considerations. Anesth Analg 68:368, 1989.

128. Wahr JA, Tremper KK, Diab M: Pulse oximetry. Respir Care Clin N Am 1:77, 1995.

129. Rasanen J, Downs JB, DeHaven B: Titration of continuous positive airway pressure by real-time dual oximetry. Chest 92:853, 1987.

130. Kersting T, Reinhart K, Fleckenstein W, et al: Tissue PO_2 measurements in critical care: The effects of dopamine on muscular oxygen pressure fields. In Ehrly AM, Hauss J, Hach R (eds): Clinical Oxygen Pressure Measurement. New York, Springer-Verlag, 1985, p 109.

131. McCormick PW, Stewart M, Goetting MG, et al: Noninvasive cerebral optical spectroscopy for monitoring cerebral oxygen delivery and hemodynamics. Crit Care Med 19:89, 1991.

132. Hampson NB, Piantadosi CA: Near-infrared optical responses in feline brain and skeletal muscle tissues during respiratory acid-base imbalance. Brain Res 519:249, 1990.

133. Tenney SM: A theoretical analysis of the relationship between ve-nous blood and mean tissue oxygen pressures. Respir Physiol 20:283, 1974.

134. Jobsis FF: Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198:1264, 1977.

135. Piantadosi CA, Comfort BJ: Development and validation of multiwavelength algorithms for *in vivo* near infrared spectroscopy. In Chance B, Blumberg WE (eds): Photon Migration in Tissue. New York, Plenum, 1989, p 69.

136. Parsons WJ, Rembert JC, Bauman RP, et al: Myocardial oxygenation in dogs during reactive hyperemia. J Biomed Opt 3:191, 1998.

137. Hampson NB, Piantadosi CA: Near-infrared monitoring of human skeletal muscle oxygenation during forearm ischemia. J Appl Physiol 64:2449, 1988.

138. Hampson NB, Camporesi EM, Stolp BW, et al: Cerebral oxygen availability by NIR spectroscopy during transient hypoxia in humans. J Appl Physiol 69:907, 1990.

139. Greeley WJ, Kern FH, Ungerleider RM, et al: The effect of hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral metabolism in neonates, infants, and children. J Thorac Cardiovasc Surg 101:783, 1991.

140. Gillbe CE, Heneghan CP, Branthwaite MA: Respiratory mass spectrometry during general anaesthesia. Br J Anaesth 53:103, 1981.

141. Van Wagenen RA, Westenskow DR, Benner RE, et al: Dedicated monitoring of anesthetic and respiratory gases by Raman scattering. J Clin Monit 2:215, 1986.

142. Westenskow DR, Smith KW, Coleman DL, et al: Clinical evaluation of a Raman scattering multiple gas analyzer for the operating room. Anesthesiology 70:350, 1989.

143. Ornato JP, Shipley JB, Racht EM, et al: Multicenter study of a portable, hand-size, colorimetric end-tidal carbon dioxide detection device. Ann Emerg Med 21:55, 1992.

144. Malinski T, Czuchajowski L: Nitric oxide measurement by electrochemical methods. In Feelisch M, Stamler JS (eds): Methods in Nitric Oxide Research. New York, John Wiley & Sons, 1996, p 319.

145. Purtz EP, Hess D, Kacmarek RM: Evaluation of electrochemical nitric oxide and nitrogen dioxide analyzers suitable for use during mechanical ventilation. J Clin Monit 13:25, 1997.

146. Brett SJ, Evans TW: Measurement of endogenous nitric oxide in the lungs of patients with the acute respiratory distress syndrome. Am J Respir Crit Care Med 157:993, 1998.

147. Nishimura M, Imanaka H, Uchiyama A, et al: Nitric oxide (NO) measurement accuracy. J Clin Monit 13:241, 1997.

148. Hampl V, Walters CL, Archer SL: Determination of nitric oxide by the chemiluminescence reaction with ozone. In Feelisch M, Stamler JS (eds): Methods in Nitric Oxide Research. New York, John Wiley & Sons, 1996, p 309.

149. Gravenstein JS, Paulus DA, Hayes TJ: Gas Monitoring in Clinical Practice. 2nd ed. Boston, Butterworth-Heinemann, 1995, p 202.

150. Turner KE, Sandler AN, Vosu HA: End-tidal CO_2 monitoring in spontaneously breathing adults. Can J Anaesth 36:248, 1989.

151. Meny RG, Bhat AM, Aranas E: Mass spectrometer monitoring of expired carbon dioxide in critically ill neonates. Crit Care Med 13:1064, 1985.

152. Brunner JX, Westenskow DR: How the rise time of carbon dioxide analysers influences the accuracy of carbon dioxide measurements. Br J Anaesth 61:628, 1988.

153. Scamman FL, Fishbaugh JK: Frequency response of long mass-spectrometer sampling catheters. Anesthesiology 65:422, 1986.

154. Fletcher R, Veintemilla F: Changes in the arterial to end-tidal PCO_2 differences during coronary artery bypass grafting. Acta Anaesth Scand 33:656, 1989.

155. Russell GB, Graybeal JM, Strout JC: Stability of arterial to end-tidal carbon dioxide gradients during postoperative cardiorespiratory support. Can J Anaesth 37:560, 1990.

156. Russell GB, Graybeal JM: Reliability of the arterial to end-tidal carbon dioxide gradient in mechanically ventilated patients with multisystem trauma. J Trauma 36:317, 1994.

157. Russell GB, Graybeal JM: The arterial to end-tidal carbon dioxide difference in neurosurgical patients during craniotomy. Anesth Analg 81:806, 1995.

158. Bindslev L, Hedenstierna G, Santesson J, et al: Airway closure during anaesthesia, and its prevention by positive end expiratory pressure. Acta Anaesth Scand 24:199, 1980.

159. Bhavani-Shankar K, Kumar AY, Moseley HSL, et al: Terminology and the current limitations of time capnography: A brief review. J Clin Monit 11:175, 1995.

160. Murray IP, Modell JH, Gallagher TJ, et al: Titration of PEEP by the arterial minus end-tidal carbon dioxide gradient. Chest 85:100, 1984.

161. Breen PH, Mazumdar B, Skinner SC: Comparison of end-tidal PCO_2 and average alveolar expired PCO_2 during positive end-expiratory pressure. Anesth Analg 82:368, 1996.

162. Viale JP, Annat G, Bertrand O, et al: Continuous measurement of pulmonary gas exchange during general anaesthesia in man. Acta Anaesth Scand 32:691, 1988.

163. Westenskow DR, Cutler CA, Wallace WD: Instrumentation for monitoring gas exchange and metabolic rate in critically ill patients. Crit Care Med 12:183, 1984.

164. Lewis WD, Chwals W, Benotti PN, et al: Bedside assessment of the work of breathing. Crit Care Med 16:117, 1988.

165. Smithies MN, Royston B, Makita K, et al: Comparison of oxygen consumption measurements: Indirect calorimetry versus the reversed Fick method. Crit Care Med 19:1401, 1991.

166. Bizouarn P, Soulard D, Blanloeil Y, et al: Oxygen consumption after cardiac surgery--a comparison between calculation by Fick's principle and measurement by indirect calorimetry. Intensive Care Med 18:206, 1992.

167. Oudemans-van Straaten HM, Scheffer GJ, Eysman L, et al: Oxygen consumption after cardiopulmonary bypass--implications of different measuring methods. Intensive Care Med 19:105, 1993.

168. Bizouarn P, Blanloeil Y, Pinaud M: Comparison between oxygen consumption calculated by Fick's principle using a continuous thermodilution technique and measured by indirect calorimetry. Br J Anaesth 75:719, 1995.

169. Schoene RB: The control of ventilation in clinical medicine: To breathe or not to breathe. Respir Care 34:500, 1989.

170. Camporesi EM, Nielsen CH, Bromage PR, et al: Ventilatory CO_2 sensitivity after intravenous and epidural morphine in volunteers. Anesth Analg 62:633, 1983.

171. Rawal N, Wattwil M: Respiratory depression after epidural morphine--an experimental and clinical study. Anesth Analg 63:8, 1984.

172. Sandler AN, Chovaz P, Whiting W: Respiratory depression following epidural morphine: A clinical study. Can Anaesth Soc J 33:542, 1986.

173. Ready LB, Oden R, Chadwick HS, et al: Development of an anesthesiology-based postoperative pain management service. Anesthesiology 68:100, 1988.

174. Camporesi EM, Feezor M, Fortune J, et al: An electromagnetic valve for inspiratory occlusion pressures. J Appl Physiol 45:481, 1978.

175. Milic-Emili J, Whitelaw WA, Grassino AE: Measurement and testing of respiratory drive. In Hornbein TF (ed): Regulation of Breathing, Part II. New York, Marcel Dekker, 1981, p 675.

176. Derenne JP, Couture J, Iscoe S, et al: Occlusion pressures in men rebreathing CO_2 under methoxyflurane anesthesia. J Appl Physiol 40:805, 1976.

177. Herrera M, Blasco J, Venegas J, et al: Mouth occlusion pressure (P0.1) in acute respiratory failure. Intensive Care Med 11:134, 1985.

178. Sassoon CS, Te TT, Mahutte CK, et al: Airway occlusion pressure. An important indicator for successful weaning in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 135:107, 1987.

179. Montgomery AB, Holle RH, Neagley SR, et al: Prediction of successful ventilator weaning using airway occlusion pressure and hypercapnic challenge. Chest 91:496, 1987.

180. Sullivan WJ, Peters GM, Enright PL: Pneumotachographs: Theory and clinical application. Respir Care 29:736, 1984.

181. Blumenfeld W, Turney SZ, Denman RJ: A coaxial ultrasonic pneumotachometer. Med Biol Eng 13:855, 1975.

182. de Troyer A, Bastenier J, Delhez L: Function of respiratory muscles during partial curarization in humans. J Appl Physiol 49:1049, 1980.

183. O'Brien MJ, Van Eykern LA, Oetomo SB, et al: Transcutaneous respiratory electromyographic monitoring. Crit Care Med 15:294, 1987.

184. Schweitzer TW, Fitzgerald JW, Bowden JA, et al: Spectral analysis of human inspiratory diaphragmatic electromyograms. J Appl Physiol 46:152, 1979.

185. Bloch R: Subtraction of electrocardiographic signal from respiratory electromyogram. J Appl Physiol 55:619, 1983.

186. Rochester DF: Tests of respiratory muscle function. Clin Chest Med 9:249, 1988.

187. Ford GT, Whitelaw WA, Rosenal TW, et al: Diaphragm function after upper abdominal surgery in humans. Am Rev Respir Dis 127:431, 1983.

188. Brown KA, Hoffstein V, Byrick RJ: Bedside diagnosis of bilateral diaphragmatic paralysis in a ventilator-dependent patient after open-heart surgery. Anesth Analg 64:1208, 1985.

189. Stagg D, Goldman M, Newsom-Davis JN: Computer-aided measurement of breath volume and time components using magnetometers. J Appl Physiol 44:623, 1978.

190. Roussos C, Fixley M, Gross D, et al: Fatigue of inspiratory muscles and their synergic behavior. J Appl Physiol 46:897, 1979.

191. Roussos C, Zakynthinos S: Fatigue of the respiratory muscles. Intensive Care Med 22:134, 1996.

192. Mead J, Peterson N, Grimby G, et al: Pulmonary ventilation measured from body surface movements. Science 156:1383, 1967.

193. Faithfull D, Jones JG, Jordan C: Measurement of the relative contributions of rib cage and abdomen/diaphragm to tidal breathing in man. Br J Anaesth 51:391, 1979.

194. Cohn MA, Rao AS, Broudy M, et al: The respiratory inductive plethysmograph: A new non-invasive monitor of respiration. Bull Eur Physiopathol Respir 18:643, 1982.

195. Stradling JR, Chadwick GA, Quirk C, et al: Respiratory inductance plethysmography: Calibration techniques, their validation and the effects of posture. Bull Eur Physiopathol Respir 21:317, 1985.

196. Marini JJ, Pierson DJ, Hudson LD, et al: The significance of wheezing in chronic airflow obstruction. Am Rev Respir Dis 120:1069, 1979.

197. Forgacs P: The functional basis of pulmonary sounds. Chest 73:399, 1978.

198. Forgacs P: Lung Sounds. London, Bailliere Tindall, 1978.

199. Loudon R, Murphy RL Jr: Lung sounds. Am Rev Respir Dis 130:663, 1984.

200. Semmes BJ, Tobin MJ, Snyder JV, et al: Subjective and objective measurement of tidal volume in critically ill patients. Chest 87:577, 1985.

201. Sorkin B, Rapoport DM, Falk DB, et al: Canopy ventilation monitor for quantitative measurement of ventilation during sleep. J Appl Physiol 48:724, 1980.

202. Tobin MJ, Jenouri GA, Watson H, et al: Noninvasive measurement of pleural pressure by surface inductive plethysmography. J Appl Physiol 55:267, 1983.

203. Pepe PE, Marini JJ: Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: The auto-PEEP effect. Am Rev Respir Dis 126:166, 1982.

204. Bardoczky GI, Yernault JC, Engelman EE, et al: Intrinsic positive end-expiratory pressure during one-lung ventilation for thoracic surgery. The influence of preoperative pulmonary function. Chest 110:180, 1996.

205. Tobin MJ: Respiratory monitoring in the intensive care unit. Am Rev Respir Dis 138:1625, 1988.

206. Carle KA, Camporesi EM, Moon RE: Edrophonium-induced bronchoconstriction during reversal of muscle relaxants. Anesthesiology 65(Suppl):A495, 1986.

207. Wakakuri H, Camporesi EM: Peak expiratory flow during a passive exhalation: An index of expiratory resistance during anesthesia. Acta Anaesth Scand 23:207, 1979.

208. Bardoczky GI, deFrancquen P, Engelman E, et al: Continuous monitoring of pulmonary mechanics with the sidestream spirometer during lung transplantation. J Cardiothorac Vasc Anesth 6:731, 1992.

209. Bardoczky GI, Engelman E, Levarlet M, et al: Ventilatory effects of pneumoperitoneum monitored with continuous spirometry. Anaesthesia 48:309, 1993.

210. Bardoczky GI, Levarlet M, Engelman E, et al: Continuous spirometry for detection of double-lumen endobronchial tube displacement. Br J Anaesth 70:499, 1993.

211. Guyatt AR, Parker SP, McBride MJ: Measurement of human nasal ventilation using an oxygen cannula as a pitot tube. Am Rev Respir Dis 126:434, 1982.

212. Werthammer J, Krasner J, DiBenedetto J, et al: Apnea monitoring by acoustic detection of airflow. Pediatrics 71:53, 1983.

213. Hok B, Wiklund L, Henneberg S: A new respiratory rate monitor: Development and initial clinical experience. Int J Clin Monit Comput 10:101, 1993.

214. Tatara T, Tsuzaki K: An apnea monitor using a rapid-response hygrometer. J Clin Monit 13:5, 1997.

215. George CF, Millar TW, Kryger MH: Identification and quantification of apneas by computer-based analysis of oxygen saturation. Am Rev Respir Dis 137:1238, 1988.

216. Sackner MA, Krieger BP: Noninvasive respiratory monitoring. In Scharf SM, Cassidy SS (eds): Heart-Lung Interactions in Health and Disease. New York, Marcel Dekker, 1989.

217. Laggner A, Kleinberger G, Haller J, et al: Bedside estimation of extravascular lung water in critically ill patients: Comparison of the chest radiograph and the thermal dye technique. Intensive Care Med 10:309, 1984.

218. Hedlund LW, Vock P, Effmann EL, et al: Hydrostatic pulmonary edema: An analysis of lung density changes by computed tomography. Invest Radiol 19:254, 1984.

219. Webber CE, Coates G: A clinical system for the in vivo measurement of lung density. Med Phys 9:473, 1982.

220. Coates G, Powles AC, Morrison SC, et al: The effects of intravenous infusion of saline on lung density, lung volumes, nitrogen washout, computed tomographic scans, and chest radiographs in humans. Am Rev Respir Dis 127:91, 1983.

221. Cutillo AG, Morris AH, Ailion DC, et al: Determination of lung water content and distribution by nuclear magnetic resonance imaging. J Thorac Imaging 1:39, 1986.

222. Mayo JR, MacKay AL, Whittall KP, et al: Measurement of lung water content and pleural pressure gradient with magnetic resonance imaging. J Thorac Imaging 10:73, 1995.

223. Serizawa S, Suzuki T, Niino H, et al: Using $H_2{}^{15}O$ and $C^{15}O$ in noninvasive pulmonary measurements. Chest 106:1145, 1994.

224. Sivak ED, Wiedemann HP: Clinical measurement of extravascular lung water. Crit Care Clin 2:511, 1986.

225. Mihm FG, Feeley TW, Jamieson SW: Thermal dye double indicator dilution measurement of lung water in man: Comparison with gravimetric measurements. Thorax 42:72, 1987.

226. Baudendistel LJ, Kaminski DL, Dahms TE: Evaluation of extravascular lung water by single thermal indicator. Crit Care Med 14:52, 1986.

227. Leksell LG, Schreiner MS, Sylvestro A, et al: Commercial double-indicator-dilution densitometer using heavy water: Evaluation in oleic-acid pulmonary edema. J Clin Monit 6:99, 1990.

228. Wallin CJ, Leksell LG: Estimation of extravascular lung water in humans with use of $^{2}H_2O$: Effect of blood flow and central blood volume. J Appl Physiol 76:1868, 1994.

229. Wallin CJ, Jacobson SH, Leksell LG: Subclinical pulmonary oedema and intermittent haemodialysis. Nephrol Dial Transplant 11:2269, 1996.

230. Leksell LG: Measurement of extravascular lung water--methods and clinical implications. Acta Anaesthesiol Scand Suppl 95:81, 1991.

231. Overland ES, Gupta RN, Huchon GJ, et al: Measurement of pulmonary tissue volume and blood flow in persons with normal and edematous lungs. J Appl Physiol 51:1375, 1981.

232. Petrini MF, Norman JR: Soluble gas uptake from alveolar gas. Respir Care 34:470, 1989.

233. Van de Water JM, Mount BE, Barela JR, et al: Monitoring the chest with impedance. Chest 64:597, 1973.

234. Shires GTD, Peitzman AB, Albert SA, et al: Response of extravascular lung water to intraoperative fluids. Ann Surg 197:515, 1983.

235. Hoskyns EW, Milner AD, Hopkin IE: Measurement of tidal lung volumes in neonates during high-frequency oscillation. J Biomed Eng 14:16, 1992.

236. Nishimura M, Imanaka H, Tashiro C, et al: Capnometry during high-frequency oscillatory ventilation. Chest 101:1681, 1992.

237. Waterson CK, Quan SF: Delivery equipment and monitoring techniques for high frequency ventilation. In Hamilton LH, Neu J, Calkins JM (eds): High Frequency Ventilation. Boca Raton, CRC Press, 1986, p 90.

238. Waterson CK, Militzer HW, Quan SF, et al: Airway pressure as a measure of gas exchange during high-frequency jet ventilation. Crit Care Med 12:742, 1984.

239. Hall JB, Wood LD: Liberation of the patient from mechanical ventilation. JAMA 257:1621, 1987.

240. Gorback MS, Kantor K: Extubation without a trial of spontaneous ventilation in the general surgical population. Respir Care 32:178, 1987.

241. Tobin MJ, Yang K: Weaning from mechanical ventilation. Crit Care Clin 6:725, 1990.

242. Yang KL, Tobin MJ: A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. New Engl J Med 324:1445, 1991.

243. Goldstone J, Moxham J: Assisted ventilation, 4. Weaning from mechanical ventilation. Thorax 46:56, 1991.

244. Esteban A, Frutos F, Tobin MJ, et al: A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. New Engl J Med 332:345, 1995.

245. Mancebo J: Weaning from mechanical ventilation. Eur Respir J 9:1923, 1996.

246. Chripko D, Bevan JC, Archer DP, et al: Decreases in arterial oxygen saturation in paediatric outpatients during transfer to the postanaesthetic recovery room. Can J Anaesth 36:128, 1989.

247. Tait AR, Kyff JV, Crider B, et al: Changes in arterial oxygen saturation in cigarette smokers following general anaesthesia. Can J Anaesth 37:423, 1990.

248. Bromage PR, Camporesi E, Chestnut D: Epidural narcotics for postoperative analgesia. Anesth Analg 59:473, 1980.

249. Etches RC, Sandler AN, Daley MD: Respiratory depression and spinal opioids. Can J Anaesth 36:165, 1989.

250. Rawal N, Arner S, Gustafsson LL, et al: Present state of extradural and intrathecal opioid analgesia in Sweden: A nationwide follow-up survey. Br J Anaesth 59:791, 1987.

251. Stuart-Taylor ME, Billingham IS, Barrett RF, et al: Extradural diamorphine for postoperative analgesia: Audit of a nurse-administered service to 800 patients in a district general hospital. Br J Anaesth 68:429, 1992.

252. Ready LB, Loper KA, Nessly M, et al: Postoperative epidural morphine is safe on surgical wards. Anesthesiology 75:452, 1991.

253. Scherer R, Schmutzler M, Giebler R, et al: Complications related to thoracic epidural analgesia: A prospective study in 1071 surgical patients. Acta Anaesth Scand 37:370, 1993.

254. Lubenow TR: Epidural analgesia: Considerations and delivery methods. In Sinatra RS, Hord AH, Ginsberg B,et al (eds): Acute Pain. Mechanisms and Management. St. Louis, CV Mosby, 1992, p 233.

255. Russell GB, Graybeal JM: Hypoxemic episodes of patients in a postanesthesia care unit. Chest 104:899, 1993.

256. Russell AW, Owen H, Ilsley AH, et al: Background infusion with patient-controlled analgesia: Effect on postoperative oxyhaemoglobin saturation and pain control. Anaesth Intensive Care 21:174, 1993.

257. Moller JT: Anesthesia related hypoxemia: The effect of pulse oximetry monitoring on perioperative events and postoperative complications. Dan Med Bull 41:489, 1994.

258. Rosenberg J, Wildschiodtz G, Pedersen MH, et al: Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. Br J Anaesth 72:145, 1994.

259. Rosenberg J, Ullstad T, Rasmussen J, et al: Time course of postoperative hypoxaemia. Eur J Surg 160:137, 1994.

260. Etches RC: Respiratory depression associated with patient-controlled analgesia: A review of eight cases. Can J Anaesth 41:125, 1994.

261. Jayr C, Thomas H, Rey A, et al: Postoperative pulmonary complications. Epidural analgesia using bupivacaine and opioids versus parenteral opioids. Anesthesiology 78:666, 1993.

262. Madej TH, Wheatley RG, Jackson IJ, et al: Hypoxaemia and pain relief after lower abdominal surgery: Comparison of extradural and patient-controlled analgesia. Br J Anaesth 69:554, 1992.

263. Pan PH, James CF: Anesthetic-postoperative morphine regimens for cesarean section and postoperative oxygen saturation monitored by a telemetric pulse oximetry network for 24 continuous hours. J Clin Anesth 6:124, 1994.

264. Motamed C, Spencer A, Farhat F, et al: Postoperative hypoxaemia--continuous extradural infusion of bupivacaine and morphine vs patient-controlled analgesia with intravenous morphine. Br J Anaesth 80:742, 1998.

265. Reeder MK, Muir AD, Foex P, et al: Postoperative myocardial isch-aemia: Temporal association with nocturnal hypoxaemia. Br J Anaesth 67:626, 1991.

266. Kehlet H, Rosenberg J: Late post-operative hypoxaemia and organ dysfunction. Eur J Anaesthesiol Suppl 10:31, 1995.

267. Eichhorn JH: Pulse oximetry monitoring and late postoperative hypoxemia on the general care floor. J Clin Monit 14:49, 1998.

268. Severinghaus JW, Naifeh KH, Koh SO: Errors in 14 pulse oximeters during profound hypoxia. J Clin Monit 5:72, 1989.

269. Hornbein TF, Townes BD, Schoene RB, et al: The cost to the central nervous system of climbing to extremely high altitude. N Engl J Med 321:1714, 1989.

270. Clark CF, Heaton RK, Wiens AN: Neuropsychological functioning after prolonged high altitude exposure in mountaineering. Aviat Space Environ Med 54:202, 1983.

271. Jason GW, Pajurkova EM, Lee RG: High-altitude mountaineering and brain function: Neuropsychological testing of members of a Mount Everest expedition. Aviat Space Environ Med 60:170, 1989.

272. Brodsky JB, Brose WG, Vivenzo K: A postoperative pain management service. Anesthesiology 70:719, 1989.

273. Muir MR, Sullivan FL, Dear G, et al: Monitoring practices following epidural analgesics for pain management: A follow-up survey. J Pain Symptom Manage 14:36, 1997.

274. Grichnik K, Ginsberg B: Epidural analgesia for patients recovering from surgery. In Sinatra RS, Hord AH, Ginsberg B, et al (eds): Acute Pain. Mechanisms and Management. St. Louis, CV Mosby, 1992, p 243.

275. Ashwood ER, Kost G, Kenny M: Temperature correction of blood-gas and pH measurements. Clin Chem 29:1877, 1983.

276. Siggaard-Andersen O, Wimberley PD, Gothgen I, et al: A mathematical model of the hemoglobin-oxygen dissociation curve of human blood and of the oxygen partial pressure as a function of temperature. Clin Chem 30:1646, 1984.

277. Trivedi NS, Ghouri AF, Lai E, et al: Pulse oximeter performance during desaturation and resaturation: A comparison of seven models. J Clin Anesthes 9:184, 1997.

278. Carter BG, Carlin JB, Tibballs J, et al: Accuracy of two pulse oximeters at low arterial hemoglobin-oxygen-saturation. Crit Care Med 26:1128, 1998.

279. Baumeister BL, el-Khatib M, Smith PG, et al: Evaluation of predictors of weaning from mechanical ventilation in pediatric patients. Pediatr Pulmonol 24:344, 1997.

280. Milic-Emili J: Is weaning an art or a science? Am Rev Respir Dis 134:1107, 1986.

281. Hodgkin JE, Bowser MA, Burton GG: Respirator weaning. Crit Care Med 2:96, 1974.

282. Tahvanainen J, Salmenpera M, Nikki P: Extubation criteria after weaning from intermittent mandatory ventilation and continuous positive airway pressure. Crit Care Med 11:702, 1983.

283. Karpel JP, Aldrich TK: Respiratory failure and mechanical ventilation: Pathophysiology and methods of promoting weaning. Lung 164:309, 1986.

284. Tobin MJ, Perez W, Guenther SM, et al: The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 134:1111, 1986.

285. Sporn PH, Morganroth ML: Discontinuation of mechanical ventilation. Clin Chest Med 9:113, 1988.

286. Mohsenifar Z, Hay A, Hay J, et al: Gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation. Ann Intern Med 119:794, 1993.

287. Capdevila XJ, Perrigault PF, Perey PJ, et al: Occlusion pressure and its ratio to maximum inspiratory pressure are useful predictors for successful extubation following T-piece weaning trial. Chest 108:482, 1995.

288. Nunn JF: Nunn's Applied Respiratory Physiology. 4th ed. Boston, Butterworth-Heinemann, 1993.

289. Christiansen J, Douglas CG, Haldane JS: The absorption and dissociation of carbon dioxide by human blood. J Physiol (Lond) 48:244, 1914.

290. Benumof JL: Anesthesia for Thoracic Surgery. 2nd ed. Philadelphia, WB Saunders, 1995.

291. Lawler PGP, Nunn JF: A reassessment of the validity of the iso-shunt graph. Br J Anaesth 56:1325, 1984.

292. Ohmeda 6000 Multi-Gas Monitor Service Manual. Ref #0178-0174-000. Ohmeda, Madison, Wisc. 1988.

293. Gilmour I, Burnham M, Craig DB: Closing capacity measurement during general anesthesia. Anesthesiology 45:477, 1976.

294. Fowler WS: Lung function studies, II: The respiratory dead space. Am J Physiol 154:405, 1948.

295. Fletcher R, Jonson B, Cumming G, et al: The concept of dead space with special reference to the single breath test for carbon dioxide. Br J Anaesth 53:77, 1981.

Chapter 34 - Renal Function Monitoring

Solomon Aronson

INTRODUCTION

Renal dysfunction remains a serious complication during the perioperative period in critically ill patients undergoing major surgery. The onset of acute perioperative renal failure portends a poor prognosis not solely from the loss of renal function but also from associated life-threatening complications, including sepsis, gastrointestinal hemorrhage, and central nervous system dysfunction. In high-risk patients undergoing high-risk surgery, the mortality rate from perioperative acute renal failure (ARF) has changed little during the past 3 decades. [1] [2] [3] [4] [5] [6] The reported mortality from ARF, once diagnosed, remains between 20 and 90 percent. [1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11] Perioperative renal failure continues to account for half of all patients requiring acute dialysis. [12] Perhaps one reason for our inability to prevent renal failure is a shift in medical populations to older and more critically ill patients. An unfortunate consequence of the use of sophisticated support mechanisms and a willingness to expend considerable resources is that critically ill patients now survive high-risk surgery that was previously not offered, only to die later of ARF. The persistently high incidence of perioperative renal failure observed may also be due to our inability to adequately monitor renal function changes and to predict the onset of ARF in the operative and critical care setting.

An understanding of how to interpret information derived from monitoring presumes an understanding of terms used to describe the observations made. In the case of renal function monitoring, these assumptions may not always be warranted. Perioperative renal failure, for example, has been defined clinically as the need for postoperative dialysis or, in some cases, as a postoperative serum creatinine level exceeding a predetermined preoperative value (e.g., an increase of 0.5 mg/dL or of 50% or more). In one review, no two studies of 26 defined ARF the same way. [13] The overall reported frequency of ARF among all patients admitted to the hospital is 1 percent [14] and may increase to 2 to 5 percent [4] [15] during hospitalization; however, there is no universally accepted standard for detecting renal insufficiency or failure. Reporting on the cause, incidence, and management of renal dysfunction also varies greatly because of wide variations in the definition of terms used to describe degrees of renal dysfunction in the literature. It is not surprising, therefore, that an estimated 5 percent of the general population has renal disease (however defined) that is severe enough to adversely affect surgical outcome. [16]

Several mechanisms involving a renal tubule, a tubulointerstitial process, and a reduction in filtering capacity of the glomerulus have been implicated in renal dysfunction. Prerenal causes are responsible for most cases of perioperative ARF. Since the second World War, it has become clear that ARF can result from decreased renal blood flow from a myriad of causes. Prerenal azotemia accounts for 70 percent of general community-acquired ARF [14] [15] and for more than 90 percent of perioperative ARF. [13] [17] Typically, an early compensatory phase of normal renal adaptation (e.g. pre- prerenal failure) progresses to become decompensatory as prerenal failure ensues. [18] ARF may simply be characterized as an abrupt decline in renal function at this transitional stage. Depending on preexisting reserve capacity, this stage may persist from a period of hours to days. At this point, the key decline in renal function is sufficient to result in retention of nitrogenous end products of metabolism and cessation of fluid and electrolyte homeostasis. These events are not reversible by modifying nonrenal factors and are difficult to predict. Prerenal azotemia and tubular ischemic injury represent extreme examples of the same problem (i.e., insufficient renal blood flow). When prerenal azotemia progresses

to renal failure, the terms acute tubular necrosis, vasomotor nephropathy, and ischemic tubular injury are often used interchangeably in the literature.

Although most causes of ischemic renal failure are reversible, after a critical point of prolonged severe ischemia, necrosis may be irreversible. [19] In patients with inadequate renal blood flow, this irreversible injury is commonly caused by the added risk of drugs that alter the intrarenal distribution of blood flow by abnormal hemodynamics or by preexisting disease (Chs. 51 , 53 , and 55). [20] These predisposing variables, as well as the onset and pathogenesis of perioperative renal failure, are often difficult to determine, however, because direct assessment of renal hemodynamics and renal tubular function is typically not possible. Therefore, renal function must often be indirectly assessed. An understanding of normal renal physiology and of the pathophysiology of ARF is thus critical. Furthermore, because perioperative treatment strategies depend on differentiating normal from abnormal renal function, understanding the limitations of commonly used renal function monitoring techniques is also important.

THE BASIS OF RENAL FUNCTION MONITORING

In general, the renal response to any specific condition or insult is primarily determined by associated physiologic and hemodynamic conditions prevailing at the time (Ch. 18). In patients with renal disease, the challenge of optimal perioperative management is demanding because recognition of subtle change is difficult. As our understanding of renal disease evolves, traditional answers have turned into new questions. In the past decade, we have gained great insight into intrarenal actions of intrinsically produced substances and extrinsically administered agents. Overall, however, renal failure symptoms typically are not detected until less than 40 percent of normal functioning nephrons remain, and uremic symptoms occur when less than 5 percent of normal functioning nephrons remain. [18]

The three general functions of the kidneys are (1) to excrete potentially toxic metabolic end products, (2) to regulate water and tonicity, and (3) to produce hormones. The kidney excretes a majority of the waste products metabolized from dietary intake, chiefly urea formed from ammonia released in protein metabolism, creatinine from muscle metabolism, and uric acid from purine metabolism. Serum creatinine levels and blood urea nitrogen (BUN) levels are used to measure the efficiency of metabolic waste removal. The levels of these end products rise slightly with increased dietary intake or increased catabolism. With normal renal function, an increase in concentration of waste products in blood results in rapid excretion of the increased load. The waste products are filtered in the glomeruli and tend to remain in the tubular fluid because they cannot permeate the nephron wall. In contrast, more than 98 percent of the filtered water and solute is reabsorbed back into the body. Some degradation products, like uric acid, are reabsorbed in the proximal tubule, secreted back into the tubule fluid, and then eliminated in urine. Cells and proteins with molecular masses greater than 70,000 daltons do not cross the glomerular capillary wall. However, smaller proteins, peptides, amino acids, and glucose are filtered to a variable degree. The proximal tubule reabsorbs these substances, thus minimizing their loss in urine. Other substances that cannot be filtered are excreted primarily by active secretion into the tubular fluid (Fig. 34-1) . Thus, the kidney is able to clear metabolic waste from the blood efficiently while conserving cells, proteins, and nutrients. When the glomerular membrane is damaged, red blood cells and large amounts of protein may enter the filtrate and later appear in urine.

The kidney regulates extracellular volume (approximately one-third of total body water) primarily by manipulating sodium to maintain normal tonicity. The body senses intravascular volume losses through receptors in the left atrium, the afferent arteriole of the kidney, and the carotid sinus. Increased sympathetic neural tone to the kidney, decreased sodium delivery to the macula densa of the distal convoluted tubule, or reduced perfusion pressure stimulates renin release. The renin-angiotensin-aldosterone system then acts to conserve sodium and water (Figs. 34-2 , 34-3). Normally, daily sodium intake is excreted in the urine (150 mEq/d). With changes in water intake, sodium excretion in urine changes to maintain normal extracellular volume. The homeostatic range for the sodium intake/urinary excretion balance is great: less than 1 to more than 1,000 mEq/d. Urinary excretion of sodium begins with filtration. The tubules then reabsorb almost all (99%) of the filtered sodium. Seventy percent is reabsorbed in the proximal tubule, 20 percent in the thick ascending limb of the loop of Henle and distal convoluted tubule, and 9 percent in the collecting ducts. The mechanisms regulating the urine excretion of sodium include systemic changes in circulating volume, causing decreased filtration and consequently decreased filtered sodium load. Less circulating volume also decreases levels of atrial natriuretic factor and increases aldosterone levels.

The second part of the tonicity function that the kidney serves is maintaining osmolarity within normal limits through regulation of water excretion. Reduced water intake with continued urinary water excretion leads to a rise in plasma osmolarity, and vice versa. The major effector in the regulation of water excretion is the antidiuretic hormone (ADH) vasopressin. Vasopressin is secreted into the peripheral plasma by the posterior pituitary gland. The kidney is capable of wide variations in water excretion (urine flow) in

Figure 34-1 The glomerular permeability (e.g., filtration to plasma ratio) is represented on the Y axis compared to the molecular weight of the filtered substance represented on the X axis. *(Data from Renkin and Robinson [14])*

Figure 34-2 Renin released into the circulation interacts with angiotensinogen to cleave off the decapeptide angiotensin I; through converting enzymatic activity this becomes the active octapeptide angiotensin II. Angiotensin II is a potent vasopressor and has a direct effect on the adrenals to stimulate aldosterone. By its vasoconstrictive action angiotensin II increases salt retention.

response to changing levels of vasopressin in the peripheral plasma. Water excretion can be 100-fold lower in extreme antidiuresis (high vasopressin) than in extreme diuresis. These changes are achieved without substantial changes in steady-state rate of total solute excretion (osmolar excretion). This ability depends on the kidneys' ability to concentrate or dilute the urine. Water output from the kidneys of a 70-kg person normally ranges from 500 mL to 12 L/d. The kidney maintains a normal range of urinary concentrations and volumes first by producing a large amount of dilute fluid in the loop of Henle and the distal convoluted tubule. When the fluid passes through the highly concentrated solutes in the medulla in the presence of ADH, most of the water is reabsorbed. In the absence of ADH, only about half the water is reabsorbed. An acute (transient) effect of altered levels of circulating vasopressin (or ADH) or solute excretion is different from a steady-state response. When vasopressin is begun in water-loaded rats, an almost immediate decrease in water excretion occurs, and the excretion rates eventually return to control levels (consistent with steady-state behavior).

Figure 34-3 Mechanism for renal sodium and volume regulation. ANF, atrial natriuretic factor; GFR, glomerular filtration rate; C.O., cardiac output; B.P., blood pressure; NaCl, sodium chloride.

Such transient behavior is observed not only in response to altered levels of circulating vasopressin but also following induction of anesthesia.

The medullary concentration of solutes is high (1,400 mOsm/L) because (1) the ascending limb of the loop of Henle actively reabsorbs sodium and chloride without water into the medullary interstitium, and (2) large amounts of urea enter the inner medulla from the collecting tubule. The cortical and outer medullary collecting tubules are sites of passive water reabsorption that are impermeable to urea. Urea becomes concentrated in the collecting ducts of the inner medulla, which are permeable to urea moving passively down its concentration gradient. The high concentrations of sodium, chloride, and urea are not washed out of the medulla because medullary blood flow is low and the configuration of the capillaries of the vasa recta permits a countercurrent exchange. Of the 140 to 180 L/d of fluid filtered at glomeruli, approximately 70 percent (100 L/d) is reabsorbed isosmotically in the proximal tubule, and 15 percent (20 L/d) is reabsorbed passively in the medulla in

the descending loop of Henle. The remaining 15 percent (20 L/d) of highly concentrated tubular fluid reaches the papillary tip of the loop of Henle. As the fluid ascends the loop of Henle, sodium is reabsorbed (passively in the medulla and actively in the thick ascending limb in the outer medulla and cortex). Tubular fluid thus becomes hypotonic to plasma. Sodium reabsorption without water continues in the distal tubule. The collecting ducts may receive tubular fluid with concentrations below 100 mOsm/L. Tubular permeability to water increases or decreases, depending on the amount of ADH present, and may vary from 8 to 20 L, with subsequent urine volumes varying from 0.5 to 12 L/d in the normal 70-kg person.

The kidney functions as an endocrine gland in the renin-angiotensin system. Renin is secreted into the body by the granular cells of the juxtaglomerular apparatus of the kidney. Once in the blood stream, renin catalyzes the splitting of angiotensin I from angiotensinogen, which is secreted from the liver and is always present in the plasma in high concentrations. The kidneys also secrete renal erythropoietic factor, which is involved in the control of erythrocyte production by the bone marrow. In response to decreased oxygen delivery to the kidney, renal erythropoietic factor is secreted and acts enzymatically in the plasma on a globulin secreted by the liver to form erythropoietin, which then acts to stimulate the bone marrow to increase its production of erythrocytes. The kidneys produce the active form of vitamin D and are linked to calcium metabolism; during times of prolonged fasting, the kidneys synthesize glucose from amino acids and other precursors and thus have the potential to be gluconeogenic organs.

Physiology of Urine Formation

Urine formation is dependent on a number of factors: hydraulic and oncotic pressures within the glomerular capillary, local and systemic neurohumoral influences, and an intact kidney-ureter-bladder feedback loop (Ch. 18). The formation of urine begins with glomerular ultrafiltration and progresses to selective tubular reabsorption and tubular secretion. General anesthesia and surgery influence renal function primarily by affecting filtration and reabsorp-tion. [21] [22] [23] [24] [25] All anesthetic agents, whether volatile or intravenous, have the potential to alter renal function by altering blood pressure and cardiac output so that renal blood flow is redistributed. This redistribution is accompanied by sodium and water conservation and decreased urine formation. Commonly used premedications can also influence urine output. [26] Narcotics and barbiturates, for example, can produce a small decrease in glomerular filtration rate (GFR) and, consequently, urine volume.

Regional anesthesia above level T4 reduces sympathetic tone to the kidney and makes renal blood flow and filtration directly dependent on perfusion pressure during sympathectomy. [27] Renal function and urine formation during regional anesthesia depend on the overall sum of the different homeostatic responses evoked, not just the sympathectomy. The combined effect of multiple factors, such as level of the block, preservation of autoregulatory mechanisms to preserve renal blood flow, circulating catecholamines, reninangiotensin, ADH, steroids, and prostaglandins, all determine the degree of urine formation.

Anesthetic drugs may increase or decrease catecholamines, alter renal vascular resistance, depress myocardium, and decrease renal blood flow, or they may have a direct nephrotoxic effect on renal tubular function. Surgery in general, aortic cross-clamping and declamping in particular; trauma; and stress also may indirectly influence urine formation by changing myocardial function, sympathetic activity, neuronal or hormonal activity (e.g., renin and angiotensin production), intravascular volume, or systemic vascular resistance. [28] [29] [30]

Starling Forces

Glomerular filtration is governed by the equation

where GFR is the glomerular filtration rate or the rate at which fluid is filtered through the glomerular capillaries into the Bowman capsule, K_f is the glomerular filtration coefficient or the factor that considers the permeability and surface area of the glomerular basement membrane, P_{GC} is the glomerular capillary pressure, P_{BC} is the pressure in the Bowman capsule, and P_{PO} is the plasma oncotic pressure.

The last three factors represent the Starling forces that govern the hydrostatic forces through the glomerular membrane. Acute changes in GFR, and consequently in urine formation, are commonly caused by changes in glomerular capillary pressure. For example, events that reduce plasma flow rates reduce the hydraulic pressure of glomerular capillaries and favor decreased ultrafiltration, whereas events that increase plasma flow rate have the opposite effect. Theoretically, the effects of varying concentrations of plasma proteins may influence urine formation and GFR. As the concentration of proteins in plasma decreases, the oncotic pressure and the oncotic force opposing ultrafiltration also decrease. Conversely, a rise in oncotic pressure reduces the rate of glomerular filtration. This effect is most likely offset by the oncotic force of plasma proteins (albumin), which enables adequate intravascular volume to be maintained. The

precise role in preserving renal function of oncotic pressure versus maintenance of adequate renal blood flow or other variables influencing glomerular filtration has never been studied. It is interesting to note, however, that in one reported series, patients resuscitated with albumin after massive transfusion had more renal dysfunction than those resuscitated with saline. [31]

Neurohumoral Influences

Because the tubules and the collecting ducts of the kidney reabsorb almost 99 percent of the filtered solute, the daily filtration volume (approximately 180 L) greatly exceeds the typical daily urinary volume of 1 to 2 L. To clear nitrogenous wastes daily, 400 to 500 mL of urine is required. The countercurrent multiplier system in the loop of Henle is a critical component of the kidney's ability to excrete or conserve salt and water. Sodium and water reabsorption depend on the hypertonicity of the medullary interstitium, which is dependent on the maintenance of normal renal blood flow. The major hormonal influences determining conservation or loss of filtered sodium and water are aldosterone, ADH, atrial natriuretic factor, and the renal prostaglandins.

High concentrations of aldosterone stimulate reabsorption of sodium and water, primarily in the distal tubule and the collecting ducts. Aldosterone is produced by the adrenal cortex in response to the feedback from the renin-angiotensinaldosterone system, simplified as follows: reduced delivery of sodium to the macula densa causes release of renin from the granular cells of the juxtaglomerular apparatus. Renin, in turn, catalyzes the release of angiotensin I from angiotensinogen. Angiotensin I is then transformed to angiotensin II in the lungs, catalyzed by angiotensin-converting enzyme. Finally, angiotensin II stimulates the production of aldosterone.

Antidiuretic hormone acts primarily on the collecting ducts to increase water reabsorption. ADH is released from the posterior pituitary gland in response to increased blood osmolarity, which stimulates osmoreceptors in the hypothalamus. ADH is inhibited by stimulation of atrial baroreceptors or increased atrial volume. [32] ADH release is also influenced by stress and increased partial pressure of arterial carbon dioxide. [33] A high level of ADH thus results in the excretion of small volumes of concentrated urine.

Atrial natriuretic peptide causes systemic vasodilation and promotes renal excretion of sodium and water by increasing glomerular filtration. [34] Atrial natriuretic peptide is secreted by the cardiac atria and other organs in response to increased intravascular volume. It decreases systemic blood pressure by relaxing vascular smooth muscle, reducing sympathetic stimulation, and inhibiting the renin-angiotensin-aldosterone system.

The kidney also synthesizes prostaglandins, which regulate the influence of other hormones. During hemodynamic instability and increased adrenergic stimulation, for example, prostaglandin E_2 decreases the vasoconstrictive effect of angiotensin II on the afferent arterioles and preserves renal blood flow. Inhibition of prostaglandin synthesis during normal states of hydration, renal perfusion, and sodium balance does not affect renal function. When the kidney is confronted with a vasoconstricted state, such as hypotension and hypovolemia, however, the presence of renal prostaglandins is essential for preserving adequate renal blood flow. Patients taking nonsteroidal anti-inflammatory drugs are at risk during conditions of impaired circulatory status because these agents inhibit cyclooxygenase activity, an important enzyme in the prostaglandin synthesis pathway, thereby rendering the kidney (afferent arteriole) susceptible to the systemic vasoconstrictive effect of angiotensin II and other catecholamines normally secreted to preserve intravascular volume and perfusion pressure.

Ureteral Peristalsis

Ureteral peristalsis influences urine formation. Interaction between the urinary bladder, the kidney, and the ureters regulates urine production by the kidney and urine transport to the bladder by the ureter. [35] During general anesthesia, ureteral peristalsis may influence the rate of urine output measured with a Foley catheter. Young et al [36] demonstrated in an experimental model of ureteral peristalsis that general anesthesia decreases the rate of ureteral contractility (Fig. 34-4) (Figure Not Available) . Normally, ureteral peristalsis originates with electrical activity at pacemaker sites located in the proximal portion of the urinary collecting system. The electrical activity is then propagated, giving rise to the mechanical event peristalsis and ureteral contraction, which propels the bolus of urine distally. Basal peristalsis within the ureter is influenced by pressures within the renal pelvis, the ureter, and the ureteral-vesical junction. The autonomic nervous system also plays an important role in ureteral function and consequently in urine formation. [37] Cholinergic agonists generally increase the frequency and the force of ureteral contraction. Agents that act primarily on adrenergic receptors tend to stimulate ureteral activity, whereas agents that primarily activate adrenergic receptors tend to inhibit ureteral activity. Histamine stimulates ureteral activity. In a variety of preparations, morphine has been reported to increase ureteral tone. Infections within the urinary tract may impair urine transport. In humans, irregular peristaltic contractions have been recorded with retroperitoneal inflammation secondary to appendicitis, regional enteritis, ulcerative colitis, and peritonitis. [38] Clinically, the response of the ureter to pathologic conditions seems to vary with age. More marked degrees of ureteral dilation are observed in the neonate and the young child than in the adult. [39] Aging brings both a decrease in the effectiveness of beta-adrenergic agonists to relax the ureter and a progressive increase in smooth muscle cell mass, producing the overall effect of no apparent change in the ureteral contractile process in the geriatric patient.

Monitoring of Glomerular Filtration Rate

Structure of the Glomerulus

In general, the GFR is determined by the rate of glomerular plasma flow (as it influences ultrafiltration pressure), systemic oncotic pressure, glomerular hydraulic pressure

Figure 34-4 (Figure Not Available) Effect of general anesthesia on the rate of ureteral contractility. *(From Young et al [36])*

differences, and an ultrafiltration coefficient. The ultrafiltration coefficient is the product of glomerular capillary hydraulic permeability and total surface area available for filtration. The filtration rate across a capillary bed is therefore the product of surface area, pressure gradients, and permeability. In the glomerulus, the capillaries are configured in tufts, which increases their surface area. Hydrostatic pressures are normally maintained higher in glomerular capillaries than in other capillary beds by a delicate balance of preglomerular and postglomerular vascular tone in arterioles. The permeability of the glomerular capillary wall is equal for substances with molecular masses up to 5,000 to 6,000 daltons and falls to almost zero at 60,000 to 70,000 daltons. [40] Thus, metabolic wastes and essential nutrients are filtered freely, and larger proteins, such as albumin and immunoglobulin G, are filtered in trace amounts, if at all. The glomerulopathic process in diabetes, [41] for example, most likely derives from all of the factors that cause sustained increase in glomerular pressure and flow. Hyperglycemia induces a state of extracellular fluid volume expansion, structural hypertrophy of the kidney, and altered glucoregulatory and vasoregulatory hormone action. These hemodynamic consequences of hyperglycemia lead to renal vasodilation and increased plasma flow rate. The increase of plasma flow in turn causes increased glomerular transcapillary flux of plasma proteins. The elevation in glomerular flow (pressure) also alters the permeability and selectivity of the glomerular basement membrane, resulting in increased protein filtration. The increased transglomerular flux of plasma proteins leads to their accumulation in the mesangium, which serves further as a stimulus to proliferate glomerulosclerosis.

Inulin Clearance

GFR, the rate at which plasma water is filtered across the glomerulus, is an important index of renal function. Because the tubule reabsorbs most of the water filtered through the glomerulus, urine volume cannot be used to measure GFR. For measurement, a substance is required that is filtered through the glomerulus at the same rate as water and is excreted in the urine (i.e., neither reabsorbed or secreted). The amount of such a substance filtered is then equal to the amount eliminated in the urine and can be determined from the product of the substance's concentration in plasma and the amount of plasma water filtered.

Inulin, an exogenous polysaccharide with a molecular mass of 5,200 daltons, is an ideal substance to measure GFR because it is filtered freely in the glomerulus, is not reabsorbed or secreted, and is excreted in the urine. Since its introduction into clinical practice in 1934, inulin clearance has been considered the standard for measurement of GFR. [42] To assess inulin clearance, one administers a priming dose of inulin intravenously, followed by a continuous infusion calculated to maintain constant blood concentrations. After an equilibration period (generally 1 hour), clearance measurements are obtained. Urine is collected (typically with a Foley catheter), and venous blood samples are obtained at the

midpoint of each clearance period. The longer the clearance period, the less likely the introduction of error from incomplete voiding. The standard formula for calculation of clearance is as follows:

where U_I and P_I are the urine and plasma concentrations of inulin, C_I is its clearance, and V is the urine flow rate.

Creatinine Clearance

In clinical practice, the endogenous substance creatinine is used to measure clearance. Creatinine (molecular mass 133 daltons) is a smaller substance than inulin and is produced from muscle metabolism. Creatinine is not an ideal substance for measuring clearance, because a small amount is secreted under normal conditions. Although creatinine clearance may exceed inulin clearance, the clearance of endogenous creatinine approximates that of inulin and has proved an excellent measure of GFR. [43] The creatinine to inulin clearance ratio is almost identical in normal infants, children, and adults. In subjects with moderate-to-severe renal insufficiency, however, the creatinine to inulin clearance ratio is increased. [44] Increased secretion and clearance of creatinine in patients with renal insufficiency may result in overestimates of true GFR. Urea (molecular mass 60 daltons), on the other hand, cannot be used to estimate GFR because under normal conditions, it is filtered and reabsorbed. More importantly, urea clearance changes with the state of hydration; for example, under conditions of dehydration, urea clearance would be significantly less than inulin clearance.

UNDERSTANDING CHANGES IN PERIOPERATIVE RENAL FUNCTION

The precise mechanisms heralding the transition from compensated preserved renal function to uncompensated renal failure during the perioperative period remain poorly understood, in part because the methods used to assess renal function changes are insensitive and nonspecific. All anesthetic techniques and perioperative events that decrease blood pressure and cardiac output have the potential to alter renal function because of blood flow redistribution within the kidney and decreased glomerular filtration.

Effects of Regional Anesthesia

Regional anesthetics and the kidneys interact in a complex manner that varies according to the underlying cardiovascular, renal, fluid, and electrolyte status of the patient (Ch. 42). [45] The combined effect of multiple factors (e.g., catecholamines, renin-angiotensin, ADH, steroids, prosta-glandin) determines the consequences for renal function. The effect of sympathetic blockade depends on the level of the block and the presence of underlying disease. In a patient with global systolic ventricular dysfunction or dilated cardiomyopathy, regional anesthesia may exert the beneficial effects of an afterload-reducing and preload-reducing agent. However, the same anesthesia in a patient with hypovolemia may exacerbate hypotension and decrease renal perfusion. Thus, the interactions between regional anesthesia and renal function are different in patients with different underlying disease. In patients with ischemic heart disease, regional anesthesia may exacerbate regional myocardial dysfunction through vasodilation, hypotension, and decreased coronary perfusion pressure [46] and may thereby decrease renal perfusion.

Recall that spinal cord segments T4 through L1 contribute to the sympathetic innervation of the renal vasculature, which is innervated via sympathetic fibers from the celiac and renal plexus. [27] [47] Therefore, as long as flow is maintained and perfusion pressure does not fall below the autoregulatory range during spinal and epidural anesthesia, there will be little change in GFR or renal vascular resistance. Sulerman et al [48] demonstrated in healthy volunteers that renal blood flow is unchanged during epidural anesthesia with a T6 sensory block. In their study, mean arterial pressure remained above 70 mm Hg and never decreased below 6 percent of the baseline level. The sympathetic innervation of the kidney affects multiple aspects of renal function, including hemodynamics, electrolyte and water reabsorption, and renin secretion. [45] Urine volume and free water clearance may decrease during spinal anesthesia as a result of increased ADH secretion. Increased renal sympathomimetic activity decreases renal blood flow through alpha-adrenergic mediation and increases renin release via beta-adrenergic innervation directly or by interaction with the renal tubular macula densa and the baroreceptor reflex mechanism. [49]

Effects of Inhaled Anesthetics

There is a well-recognized renal nephrotoxic effect of the older fluorinated inhalation anesthetics that is attributed to serum inorganic fluoride concentration (Chs. 4 and 6). Increased levels of serum inorganic fluoride caused polyuric renal insufficiency. [50] Methoxyflurane, which is no longer used clinically, and enflurane, when used for prolonged periods (9.6 MAC hours), cause an increase in serum inorganic fluoride. [50] [51] [52] After enflurane anesthesia, maximal urinary osmolality decreases in response to vasopressin for 5 days. These changes are of little consequence in patients with normal renal function. However, in patients with preexisting renal dysfunction, enflurane may cause further renal deterioration.

Sevoflurane appears to act as does enflurane with regard to the generation of inorganic fluoride (F-) as a result of metabolism. [53] [54] [55] [56] Sevoflurane undergoes approximately 5 percent metabolism, and the primary metabolites are fluoride and hexafluoroisopropanol. Once formed, hexafluoroisopropanol is conjugated in the liver with glucuronic acid and excreted. The oxidative defluorination of sevoflurane in the liver causes liberation of free fluoride ions. Concerns that sevoflurane might have the potential (as does methoxyflurane) to impair the ability of the kidneys to concentrate urine have been raised. [54] Earlier research had indicated that renal dysfunction from methoxyflurane was likely

---

to occur when dose or duration of administration resulted in serum fluoride concentrations that exceeded 50 muM/L. [51] This presumed threshold for toxicity has been extrapolated for other halogenated anesthetic agents, including enflurane and sevoflurane. However, because sevoflurane is defluorinated by the cytochrome P-450 enzyme system, renal defluorination of sevoflurane is not clinically significant. In American Society of Anesthesiologists class I and II patients, it was shown that serum fluoride levels averaged 36.6±4.3 muM/L after 9 MAC hours of sevoflurane anesthesia. [53] [57] These fluoride levels peaked 2 hours after the end of anesthesia and decreased by 50 percent within 8 hours. The rapid decline of plasma fluoride was attributed to the insolubility and rapid pulmonary elimination of sevoflurane. Desmopressin was used to test urine concentrating ability before anesthesia and on days 1 and 5 after 9.5 MAC hours of sevoflurane and enflurane anesthesia. [57] Mean plasma fluoride levels were approximately twice as high in volunteers receiving sevoflurane than in those receiving enflurane, and 43 percent of volunteers receiving sevoflurane had plasma fluoride levels that exceeded 50 muM/L. Despite these results, the kidneys of the volunteers receiving sevoflurane were not impaired in their ability to concentrate urine, whereas 20 percent of volunteers receiving enflurane had transient concentrating deficits on day 1. The investigators postulated that intrarenal production of fluoride ion was a more important factor in the pathogenesis of nephrotoxicity than the association between plasma fluoride levels and nephrotoxicity. [56] The intrarenal metabolism of methoxyflurane is 4-fold greater than the intrarenal metabolism of sevoflurane.

All inhaled anesthetic agents interact with carbon dioxide absorbents to produce toxic compounds. A controversy has arisen concerning the relationship between sevoflurane, nephrotoxicity, and compound A. In circuit systems under conditions of high temperature and low flow rates, carbon dioxide absorbents degrade sevoflurane, resulting in detectable concentrations of vinyl ether compound A (fluoromethyl-2,2-difluoro-1-{trifluoromethyl} vinyl ether). These degradation products are conjugated in the liver with glutathione. Cysteine conjugates formed in the bile ducts and kidney by the conjugates are metabolized in the kidney by an enzyme (cysteine-conjugate beta-lyase) to form end products that result in renal injury, which is characterized by diuresis, glycosuria, proteinuria, and elevated serum BUN and creatinine levels. The renal injury in experimental rat models was a function of the concentration and the duration of exposure of compound A. [58] The threshold for injury was exposure to compound A at 50 to 114 parts per million (ppm) for 3 hours while the lethal dose of compound A, from which 50 percent of rats died, was 331 ppm over 3 hours; 203 ppm over 6 hours; or 127 ppm over 12 hours. [59] It has been proposed that the disparity between the results in humans and those in rats is due to differences in the metabolic pathway of compound A in the species. Of the four recognized metabolic pathways for compound A, three do not involve renal beta-lyase and do not result in organ toxicity. Humans have a 10-fold to 30-fold relative absence of the renal beta-lyase enzyme pathway compared with rats, which may account for the apparent absence of renal injury from sevoflurane in humans. One study [60] evaluated the safety of low-flow sevoflurane anesthesia compared with low-flow isoflurane anesthesia in patients scheduled to have prolonged surgery (i.e., >6 hours). The average MAC hours in the sevoflurane group and in the isoflurane group were similar. The soda lime temperature averaged 45±1.6°C. The average compound A concentration in the sevoflurane group was 20±7 ppm. Markers of renal injury, including BUN, creatinine, *N*-acetyl-beta- D-glucosaminidase (NAG), and alanine aminopeptidase were increased similarly in all groups during the prolonged exposure to the volatile anesthetics.

Eger et al [61] evaluated the highest concentrations of compound A possible during anesthesia (mean arterial pressure, 56 mm Hg) with sevoflurane in human volunteers. Fresh carbon dioxide absorbent was used and sevoflurane was given (without nitrous oxide) at 1.25 MAC, while esophageal temperature was maintained at 37°C. Volunteers were exposed to the anesthetic gas for 8 hours. In that study, compound A levels approached 50 ppm in the inspired limb of the breathing circuit, and the volunteers were asked to bring in 24-hour urine collections for 3 consecutive days after the anesthetic exposure. In most subjects, there were transient

elevations of urinary protein, albumin, glucose, alpha- glutathione S-transferase , and pi-glutathione S-transferase. No such increases were observed after a similar exposure to desflurane.

Subsequently, [62] another study evaluating the safety and efficacy of sevoflurane versus isoflurane in patients during conditions of flow of less than 2 L/min was conducted. In that study, patients from multiple institutions undergoing elective surgery lasting from 2 to 8 hours were evaluated. Fresh Baralyme was used for all cases, and nitrous oxide was not permitted. The use of sevoflurane averaged 1 MAC hour. No differences were found in urine albumin, glucose, protein, or osmolality between treatment groups. Moreover, within the sevoflurane group, there were no significant correlations between compound A levels and BUN, creatinine or urinary excretion of protein, glucose, NAG, proximal tubule alpha-GST, or distal tubule pi-GST. [62]

Effects of Hemodynamic Changes

Both prerenal and renal factors can cause or lead to ischemic renal dysfunction. There appears to be an early phase of renal adaptation or pre-prerenal failure to the decreased delivery of blood to the glomerulus. [18] When these compensatory mechanisms become decompensatory, prerenal failure ensues. Renal clearance is determined by the delivery of waste products to the kidney (renal blood flow) and by the kidney's ability to extract them (GFR).

A variety of experimental models have been devised to simulate hemodynamically mediated human ARF. [63] [64] [65] [66] In these models, renal blood flow is commonly interrupted mechanically or pharmacologically. A reduction of flow by more than 50 percent is the rule during the initial phase of the experiment. After transient but total renal ischemia for 40 to 60 minutes in a dog, rat, or rabbit, a lesion appears whose clinical manifestations, laboratory features, and pathologic features closely resemble those in humans with ARF. [35] During the established phase, GFR is disproportionately depressed, compared with a moderate decline in renal blood flow. Micropuncture studies *in vivo* and perfusion of isolated

renal tubules *in vitro* have revealed that the ensuing oliguria can be attributed to reduced GFR, sequestration of tubule fluid within obstructed tubules, and backleak of tubule fluid across necrotic epithelium into the interstitium. [66] The maintenance of adequate blood supply to the kidneys therefore is critical; however, determining what constitutes adequate blood supply (oxygen) is difficult. The exact role and the timing of changes in renal blood flow in the initiation and the maintenance of ARF continue to be studied.

A number of theories have been proposed to explain the pathogenesis of hemodynamically mediated ARF. Although a reduction in renal blood blow is clearly the initiating cause (Fig. 34-5) (Figure Not Available) , [67] [68] the occurrence of ARF after hypotension is unpredictable. The precise circumstances precipitating a change from an underperfused healthy kidney to a damaged organ are difficult to define. Even with decreased delivery of blood to the glomerulus, a series of compensatory mechanisms may still preserve renal filtration function (Fig. 34-6) (Figure Not Available) . [18] Salt and water are retained to restore intravascular volume and fractional tubular reabsorption. The distribution of cardiac output to the kidneys is also regulated. At a given level of cardiac output, intrarenal factors affect the ratio of renal to systemic vascular resistance, thereby influencing the percentage of cardiac output received by the kidneys. Another critical component in the intrinsic modulation of renal filtration function is the regulation of filtration fraction. At the glomerular capillary, plasma is separated into a protein-free ultrafiltrate and a nonfiltered portion. Normally, the filtration fraction (the relationship of GFR to renal plasma flow) is about 0.2. Initially, filtration fraction is maintained by efferent arteriolar constriction. Unabated, the mechanisms that influence efferent arteriolar vasoconstriction ultimately may influence afferent arteriolar vasoconstriction. The resulting decrease in filtration fraction is the hallmark of postischemic ARF. [18] Ischemic tubular damage may be exacerbated further by an imbalance between oxygen supply and demand. Most vulnerable to the imbalance are the thick ascending tubular cells of the loop of Henle in the medulla. [68] [69] [70] [71]

Figure 34-5 (Figure Not Available) Schematic representation of the mechanisms that initiate and maintain decreased glomerular filtration seen in experimental-induced acute renal failure. K_f, glomerular capillary ultrafiltration coefficient; RBF, renal blood flow. *(Modified from Hostetter et al [185])*

Figure 34-6 (Figure Not Available) The regulatory mechanisms through which glomerular filtration is modulated include (1) fractional regional blood flow (renal blood flow/cardiac output; (2) filtration fraction (glomerular filtration rate/glomerular plasma flow rate; and (3) fractional tubular fluid reabsorption (tubular reabsorption/glomerular filtration rate). *(Modified from Badr et al [18] . Copyright 1988, Massachusetts Medical Society. All rights reserved.)*

Intrarenal distribution of blood flow as well as total renal blood flow can be assessed with radioactive gases or radiolabeled microspheres. Microsphere, xenon washout, and angiographic techniques have shown that outer cortical blood flow decreases in ischemic models of ARF. [72] [73] [74] Because 85 to 90 percent of renal blood flow is distributed to cortical glomeruli, the finding of cortical pallor and redistribution of renal blood flow away from the cortex means that redistribution may be responsible for the functional lesions of ARF. In some cases, the return of perfusion to the cortex has correlated with a return of renal function. [73] The theory that intrarenal distribution of blood flow away from the outer cortex to the inner medulla decreases oxygen supply while increased tubular reabsorption of solute increases oxygen demand is further supported by studies of renal energetics during ARF. [75] [76] When biochemical changes were monitored in the hypotensive rat kidney with phosphorus 31 nuclear magnetic resonance imaging, [77] oli-guria preceded decreases in cellular adenosine triphosphate and tissue acidosis. It has been postulated that a decrease in GFR and, consequently, energy requirement for tubular reabsorption may be a mechanism by which the kidney reduces energy demands before energy supply is critically limited. Both increased demand and decreased supply are precipitated during states of inadequate perfusion, such as those resulting from depleted intravascular volume, maldistribution of systemic flow away from the renal vascular bed, cardiogenic shock, and destructive vascular conditions.

PREOPERATIVE EVALUATION OF RENAL FUNCTION

The greater the magnitude and duration of the surgical insult and the number of acute and chronic risk factors, the greater the likelihood of perioperative renal compromise and the need for preoperative identification of renal function (Chs. 23 and 25). In patients with inadequate blood flow, injury is commonly caused by the added risk of drugs, by abnormal hemodynamics, or by preexisting disease. [20] Acute risk factors, such as volume depletion, aminoglycoside use, radiocontrast dye exposure, use of nonsteroidal anti-inflammatory drugs, septic shock, and pigmenturia, augment the risk of ARF rather than induce it. It appears that the combined interaction of these multiple acute risk factors is central in the pathogenesis of ARF (Table 34-1) . [15] Patients with preexisting renal insufficiency, for example, are especially prone to develop ARF as a result of cardiovascular surgery. Patients with diabetes mellitus and renal insufficiency are especially vulnerable to radiocontrast agents. A review of the literature suggests that the most critical determinants of postoperative renal function are preoperative renal function, maintenance of appropriate intravascular volume, and normal myocardial function.13 Acute elevations of BUN and serum creatinine levels occur in approximately 5 percent of all hospital admissions and in up to 20 percent of intensive care patients.16 The incidence increases directly with the severity of trauma and the degree of injury or disease.

Under normal physiologic conditions, homeostasis may be maintained despite substantially reduced renal function. Impaired functional reserve capacity becomes evident only when operative stress imposes severe demands on renal function; therefore, a comprehensive evaluation of renal function reserve should be sought before surgery. In addition to intrinsic renal disease, several extrinsic variables influence the outcome of renal function tests: intracellular and extracellular volume, cardiovascular function, and neuroendocrine factors. [78] [79] [80] Advanced age also markedly decreases renal function reserve. GFR, normally about 125 mL/min in a young adult, decreases to about 80 mL/min at 60 years of age and to 60 mL/min at 80 years. Although not necessarily

TABLE 34-1 -- Risk Factors Associated With the Development of Acute Renal Failure

ACUTE
Volume depletion
Use of aminoglycosides
Radiocontrast dye exposure
Use of nonsteroidal anti-inflammatory drugs
Septic shock
Pigmenturia
CHRONIC
Preexisting renal disease
Hypertension
Congestive heart failure
Diabetes mellitus
Advanced age
Cirrhosis of the liver

the primary cause for end-stage renal disease, hypertension in up to 85 percent of patients with renal failure is a major risk factor for the high cardiovascular morbidity that occurs. [81] In addition to its contribution to renal failure in hypertensive nephrosclerosis, secondary to essential hypertension and hyperfiltration in diabetic nephropathy, hypertension also contributes to the loss of renal function associated with aging. Mild hypertensive disease that is associated with renal disease therefore implies that renal disease may be primary. Reliable evaluation requires not only a knowledge of various renal function tests but also an awareness of their diagnostic limitations. For appropriate management, ischemic causes (prerenal azotemia) should ideally be distinguished from those factors that maintain the intrinsic state of renal failure (acute tubular necrosis). Prerenal azotemia and acute tubular necrosis, however, may not necessarily be mutually exclusive.

Unfortunately, there is no simple, inexpensive test that adequately quantifies renal function. The readily available tests fail to accurately reflect the status of the kidneys in a large percentage of patients, especially the elderly, the malnourished, and the dehydrated. Commonly obtained tests of renal function are urinalysis, BUN determination, serum creatinine determination, and creatinine clearance.

Urinalysis provides qualitative information that must be interpreted cautiously. Hematuria (more than one to two red blood cells per high-power field in a concentrated sediment) suggests glomerular disease or, in a trauma patient, injury to the kidneys or the lower urinary tract. A urine test result that is positive for blood in the absence of red blood cells suggests the presence of free hemoglobin or myoglobin in the urine. Pyuria (more than four white blood cells per high-power field) suggests urinary tract infection. Although urine may normally contain hyaline and granular casts, cellular casts represent a pathologic condition. Red blood cell casts suggest interstitial nephritis, including pyelonephritis. Urinary pH, although difficult to interpret on a spot urine sample, may assist in the diagnosis of some acid-base disturbances. The pH of urine tends to be more acidic when factors that initiate failure are prerenal rather than postrenal. The presence of proteinuria on a routine dipstick examination may be "normal" or it may suggest severe renal disease. In a concentrated urine sample, trace or 1+ proteinuria is a nonspecific finding, whereas 3+ or 4+ proteinuria suggests glomerular disease. The existence of glucosuria without hyperglycemia indicates proximal tubular damage. Lysozymuria, the increase of the enzymatic protein lysozyme in urine, occurs if serum level is elevated above the normal renal threshold (45 mg/mL) or when renal tubular function is impaired. [82] Normal urinary lysozyme level is less than 1.9 mg/mL, with a level greater than 5 mg/mL regarded as evidence for significant renal tubular damage. Elevated serum levels of lysozyme may be a consequence of renal failure as well as a marker for it. Because white blood cells have a high concentration of lysozyme, urinary tract infections may also lead to elevated serum levels.

Both BUN and serum creatinine levels offer rapid but inexact estimates of creatinine clearance. The incidence and severity of ARF usually is greater when preoperative serum creatinine level is greater than 2 mg/dL [4] ; however, an isolated serum creatinine measurement is an unreliable indicator

Figure 34-7 The inverse logarithmic relationship between serum creatinine concentration (Y axis) and glomerular filtration rate (X axis). Note that serum creatinine is not markedly increased until

there is a reduction in glomerular filtration rate to about one-fourth of normal (120 to 30).

of GFR when renal function is changing. There is an inverse logarithmic relationship between GFR and serum creatinine concentration (Fig. 34-7) . Decreasing the rate by half results in twice the serum creatinine level. For example, a patient with a preoperative serum creatinine level of 0.6 mg/dL whose filtration rate was reduced by half (after a large preoperative contrast dye load) would have a serum creatinine of 1.2 mg/dL, still in the normal range. Therefore, a single serum creatinine measurement is not a very sensitive test for preoperative renal function reserve. However, it is relatively specific and useful in considering significant renal disease; that is, it would be rare for someone who is not emaciated to have a creatinine level of 1.5 mg/dL and to have a creatinine clearance of less than 40 mL/min. The actual measurement of creatinine clearance constitutes the best overall indicator of GFR. In one study, more than half of 131 critically ill patients had normal urine output, BUN level, and serum creatinine level but reduced creatinine clearance. Creatinine clearance was the best predictor of mortality in these patients compared with the other measures of renal function. [83] Although serum creatinine level may be a more reliable measure of glomerular function than is BUN level, the simultaneous determination of BUN and serum creatinine levels offers a more complete evaluation of renal function than either determination alone. Ordinarily, the BUN-to-serum creatinine ratio is approximately 10; that is, if the BUN level is approximately 10 times as great as the serum creatinine level, one may conclude that the measurements are probably correct. Conversely, if the ratio deviates significantly from 10, one should consider the nonrenal factors influencing BUN level, or serum creatinine level, or both. All three measurements (BUN, serum creatinine level, and creatinine clearance) require careful interpretation.

DIRECT AND INDIRECT MONITORS OF RENAL FUNCTION

Means for direct, on-line evaluation of renal function are limited. We can monitor indirectly, however, the several factors that may contribute to the failure of compensatory mechanisms supporting renal function perioperatively. To maintain the normal excretory functions of the kidney (filtration,

TABLE 34-2 -- Direct and Indirect Monitors of Renal Function

Preload
Ventricular function
Distribution of cardiac output to the kidneys
Intrarenal blood flow distribution
Regional renal utilization of substrate and oxygen delivery

reabsorption, and secretion), adequate perfusion is essential. Among obstructive causes that may initiate ARF, an occluded or kinked urinary catheter can cause perioperative oliguria and must be eliminated as a source of obstruction. Toxic causes precipitated by antibiotics (aminoglycosides, amphotericin B) and radiocontrast agents also may be responsible for the development of ARF. For example, with aminoglycosides, nephrotoxicity is poorly correlated with either kidney tissue or plasma levels of the drug but is markedly augmented by concomitant volume depletion or liver cirrhosis. [15] Similarly, ARF loosely correlates with the amount of radiocontrast material injected unless the patient has preexisting diabetic nephropathy or low cardiac output syndrome. Thus, the vigilance of the anesthesiologist is the first monitor required for preserving renal function.

Unlike the nephrologist, who can evaluate a patient's renal function under stable conditions over long periods, an anesthesiologist caring for hemodynamically unstable patients in the operating room is unable to use standard tests of renal function, such as creatinine clearance. The anesthesiologist must rely on indirect variables, such as urine volume, to assess renal perfusion. Unfortunately, urine output may not reliably reflect glomerular filtration and renal function under intraoperative conditions. Toward the ideal goal of monitoring renal perfusion directly, we have monitors to ensure adequate intravascular volume (preload) and adequate cardiac performance or systemic perfusion. Serum chemistries and urinary indices may enable the assessment of adequate distribution of cardiac output to the kidneys themselves. However, only direct assessment of renal blood flow (and its regional distribution) can tell us whether a kidney is adequately perfused. Evidence of local renal tissue metabolism ensures that oxygen use is adequate. The combination of blood flow (oxygen delivery) and oxygen utilization should reflect normal function (Table 34-2) .

Intravascular Volume

Central Venous Pressure Versus Pulmonary Capillary Wedge Pressure

Monitoring techniques to ensure adequate intravascular volume should be selected after a consideration of the physiologic condition of the patient in each specific situation (Ch. 30). Epidemiologic studies have shown that renal failure commonly develops when dehydration acts in synergy with other chronic conditions. Diabetes mellitus and volume depletion together, for example, increase the chance of developing ARF 100-fold. [15] Monitoring central venous pressure to assess adequate preload is contingent on normal

left and right ventricular function; normal pulmonary vascular resistance; and normal mitral, pulmonary, and tricuspid valve function. Monitoring pulmonary artery pressure or pulmonary capillary wedge pressure to assess preload assumes normal left ventricular compliance, normal mitral valve function, and normal airway pressure.

Left Atrial Pressure

Directly measuring left atrial pressure may offer insights for understanding the kidney pressure-flow relationship because left atrial hypotension has been shown to be a powerful stimulus for renal vasoconstriction. [84] Despite similar reductions in cardiac output and arterial blood pressure, renal blood flow appears to decrease much less during experimental conditions of cardiogenic shock, in which left atrial pressures are increased, compared with conditions of hemorrhagic shock, in which left atrial pressures are decreased. [84] It is postulated that when a decrease in cardiac output is accompanied by left atrial hypotension, reduction in systemic arterial pressure is followed by the normal response of renal vasoconstriction. The left atrial receptors are connected to the renal circulation by atrial natriuretic peptide, a hormone secreted by the cardiac atria in response to intravascular volume expansion. [85] Atrial natriuretic hormone acts on the arterial and venous systems, the adrenals, and the kidneys to reduce intravascular volume and decrease blood pressure. [34] Within the kidney, the hormone increases hydraulic pressure in the glomerular capillaries via afferent arteriolar dilation and efferent arteriolar vasoconstriction. Atrial natriuretic peptide reduces blood pressure by relaxing smooth muscle and reducing sympathetic vascular stimulation. It also inhibits renin and aldosterone secretion, thus producing renal vasodilation, natriuresis, and diuresis. [34] [86]

Left Ventricular End-Diastolic Area

Although the most direct way to clinically monitor for adequate intravascular volume or preload may be during surgery by assessment of the left ventricular end-diastolic area with echocardiography, [87] [88] the most practical method is by obtaining preoperative history and physical examination and by maintaining changes in systemic blood pressure to changing conditions. An awake patient may be observed for orthostatic changes in blood pressure, whereas an anesthetized patient may be observed for paradoxical arterial pulse changes with positive-pressure inspiration. [89] The clinician must decide which modality will most accurately reflect intravascular volume for a patient in a particular situation.

Cardiopulmonary Function

The next step in the logical sequence of renal function monitoring is the assessment of adequate cardiac function through determination of systemic perfusion, pulse oximetry, acid-base assessment, cardiac output monitoring, or left ventricular fractional area of change as a surrogate for ejection fraction (Chs. 16 and 30). [90]

Systemic Perfusion and Acid-Base Balance

Severe arterial hypoxemia to a partial pressure of arterial oxygen (Pa O_2) value of less than 40 mm Hg is associated with decreased renal blood flow and renal vasoconstriction. [91] [92] There is no consensus on the mechanism that underlies the antidiuresis response to hypoxia. It appears that systemic hypoxia can produce antidiuresis and antinatriuresis independent of renal nerve innervation. [93] Capnometry may be a useful monitor because hypercarbia has been associated with decreased renal blood flow in patients requiring mechanical ventilation. [94]

Cardiac Output

The electrocardiogram is essential not only to detect the depolarization-repolarization changes consistent with the electrolyte abnormalities of renal dysfunction but also to monitor for normal rate and rhythm. The synchronized atrial kick preceding ventricular contraction may contribute significantly to cardiac output in the patient with a noncompliant left ventricle. The clinician can assess cardiac function by using the thermodilution technique for measuring cardiac output with the pulmonary artery catheter and can assess global and regional myocardial function with echocardiography.

Perfusion Pressure

Stone and Stahl [95] studied the effect of renal hemorrhage in otherwise healthy patients and concluded that a decrease in mean perfusion pressure from 80 to 60 mm Hg reduced renal blood flow about 30 percent without an autoregulatory response of the renal vasculature. Others have suggested that renal blood flow decreases precipitously when mean blood pressure drops below 80 mm Hg, [35] a theory that has not been adequately tested in patients under general anesthesia with cardiac output maintained. In chronically hypertensive patients with altered vascular autoregulation, the minimum perfusion pressure may be higher. The lowest level of acceptable perfusion pressure during cardiopulmonary bypass remains a subject for debate. It has been suggested that low renal perfusion during extracorporeal circulation may be a cause of renal failure because of the physiologic alterations, such as hypotension, inherent in the technique. [96] In a study by Yao et al, [97] mean arterial pressure during cardiopulmonary bypass was maintained with vasoactive drugs at 80 to 100 mm Hg in one group of patients and at 50 to 60 mm Hg in another group during moderate hypothermic conditions. It was found that renal circulation was maintained as long as mean arterial pressure was maintained above 50 mm Hg. Other studies challenge evidence that demonstrates decreased perfusion pressure as a cause of renal failure. [98] [99] Because renal function in the perioperative period is influenced by a number of hemodynamic and hormonal factors, attempting to generalize an optimal perfusion pressure for every patient is difficult.

The decision to use an arterial line, a pulmonary artery catheter, or transesophageal echocardiography should depend

on the patient's functional cardiac reserve status, the extent of the proposed surgical insult, and the capabilities of the anesthesiologist, the perioperative team, and the hospital. Differentiation between hypovolemic hypotension and cardiogenic hypotension, for example, is critical if one is to properly tailor management and prevent exacerbation of renal ischemia. The best way to prevent intraoperative renal ischemia is to maintain renal blood flow. Although maintaining adequate cardiac output is necessary for maintaining adequate renal blood flow, it may not guarantee adequate flow. Monitoring with invasive devices, such as pulmonary artery catheters, arterial cannulas, and transesophageal echocardiography, has never been demonstrated to reduce the incidence of ARF.

Distribution of Cardiac Output to the Kidneys

Although the kidneys constitute less than 0.5 percent of body mass, they receive 20 to 25 percent of the total cardiac output in the normal adult. The distribution of cardiac output to the kidneys may be influenced by a number of factors, including hypovolemia, activation of the sympathetic nervous system or the renin-angiotensin system, extrinsically administered vasopressors and vasodilators, and local neurohumoral factors.

The fraction of cardiac output perfusing the kidneys depends on the ratio of renal vascular resistance to systemic vascular resistance. [18] In general, the response to renal hypoperfusion involves three major regulatory mechanisms that support renal function: (1) afferent arteriolar dilation increases the proportion of cardiac output that perfuses the kidney; (2) efferent arteriolar resistance increases the filtration fraction; and (3) hormonal and neural responses improve renal perfusion by increasing intravascular volume, thereby indirectly increasing cardiac output. The afferent arterioles react to reductions in perfusion pressure by relaxing their smooth muscle elements to decrease renal vascular resistance. This property represents a relaxation response or myogenic reflex to reduced transmural pressure across the arteriolar wall. The kidney also possesses a tubuloglomerular feedback system, which is designed to maintain the homeostasis of salt and water excretion. Decreased solute delivery to the macula densa in the cortical portion of the thick ascending loop of Henle results in relaxation of the juxtaposed afferent arteriolar smooth muscle cells, thus improving glomerular perfusion and filtration.

The kidney produces vasodilator prostaglandins to counteract the effects of systemic vasoconstrictor hormones such as angiotensin II. [100] In a state of low cardiac output when systemic blood pressure is preserved by the action of systemic vasopressors, renal blood flow is not depressed because the effect of the vasopressors is blunted within the kidney.

A selective increase in efferent arteriolar resistance decreases glomerular plasma flow, thereby preserving GFR. Glomerular filtration is augmented because capillary pressure upstream from the site of vasoconstriction tends to rise. This mechanism enables the kidney to offer high organ vascular resistance to contribute to the maintenance of systemic blood pressure without compromising its function of filtration. Studies using specific inhibitors of angiotensin II have shown that efferent arteriolar resistance is due largely to the action of angiotensin II. [101] At low concentrations, norepinephrine has a vasoconstricting effect on efferent arterioles, indicating that the adrenergic system may also be important for maintaining the renal compensatory response. [102]

There is abundant evidence to support the notion that reductions in cardiac output are accompanied by the release of vasopressin and by increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system. These regulatory mechanisms to preserve renal blood flow conserve salt and water. The control of blood delivery to the kidney, the fraction of plasma filtered, and the amount of volume returned to the systemic circulation are determined by regulatory mechanisms within the kidney that attempt to preserve filtration function during compromised circulation. These compensatory mechanisms, however, have limits. Excessive vasoconstrictive forces may eventually induce a decrease in filtration function. This shift from compensation to decompensation may be exacerbated by pharmacologic interventions. Thus, oliguria is both a symptom of ARF and a consequence of the normal compensatory mechanisms to prevent it. Differentiating between the two is critical for outcome and therapeutic strategies.

Clinical investigators have expended considerable effort to evaluate laboratory tests of serum and urinary indexes that attempt to differentiate the cause of oliguric states, to predict outcome, and to direct therapy for the prevention of ARF. Unfortunately, none of the tests is sensitive or specific enough to predict which patients will and which will not respond to therapy. Among the tests commonly obtained are urine volume, urine specific gravity, urine osmolality, serum creatinine level, serum GFR level, urine/plasma creatinine ratio, urine/plasma urea ratio, urine sodium level, fractional excretion of sodium, free rate clearance, and creatinine clearance.

Urine Volume

Monitoring urinary output as a sign of the adequacy of renal perfusion is easy and is based on the assumption that patients with diminished renal perfusion excrete a low volume of concentrated urine. Urinary flow rate is, however, an indirect parameter of renal function because many nonrenal factors may directly and profoundly affect urine output. Oliguria (anuria) during hypotensive anesthesia on one hand and polyuria on the other make it obvious that low urine output does not specifically reflect inadequate renal perfusion and that normal urine output does not guarantee a normally functioning kidney. The presence of urine flow (regardless of the amount) indicates that there is blood flow to the kidney, because without perfusion, glomerular filtration and generation of urine cease. The level of nitrogenous wastes in the blood depends on systemic production and renal clearance. Renal clearance depends on renal blood flow and glomerular filtration. The kidney concentrates the ultrafiltrate so that at maximal concentration, 400 to 500 mL of urine is required to clear the daily obligatory nitrogenous wastes. [103] Traditionally, inadequate urinary volume, or oli-guria, is defined as urinary output of less than 0.5 mL/kg/h.

Multiple studies, however, have shown no correlation between urine volume and histologic evidence of acute tubular necrosis, GFR, creatinine clearance, or changes

from preoperative to postoperative levels of BUN and creatinine levels in patients with burn injury, [104] trauma, [105] [106] or shock status, or those undergoing cardiovascular surgery. [107] [108] [109] Moreover, measurement of mean and lowest hourly urinary output during aortic vascular surgery has not been predictive of postoperative renal insufficiency. [107]

Oliguria may reflect a variety of factors independent of GFR, and a normal hourly urine output does not rule out renal failure. Among these factors is tubular excretion of solute and water, which is determined by local and systemic levels of renin, aldosterone, and ADH. In the operating room, patients are often hemodynamically unstable; decreased blood volume or cardiac output, fluctuating hormone levels (aldosterone, renin, ADH), nervous system reflexes, and increased catecholamine concentrations, added to the effects of general anesthesia, can alter GFR. The data do not support oliguria as a reliable sign of pending renal dysfunction. [103] [104] [105] [106] [107] [108] [109]

Urine Indexes and Serum Chemistries

Urine Specific Gravity

The specific gravity of urine is also easy to measure. In this test, the mass of 1 mL of urine is compared to the mass of 1 mL of distilled water to reflect renal concentrating ability. With poor perfusion or prerenal azotemia, urine specific gravity should be 1.030, reflecting the kidney's conservation of sodium and water. With acute tubular necrosis, the loss of concentrating ability moves urine specific gravity toward 1.010. Because urine specific gravity is a measure of mass and the renal concentrating system responds to osmolality, [110] [111] many substances and conditions can change the specific gravity of urine. The factors that make the test nonspecific appear in Table 34-3 . For example, in patients of advanced age, distal renal tubular function is often impaired, whereas proximal tubular function is spared. The ability of their kidneys to concentrate urine after water deprivation is impaired in these patients, making urine specific gravity an unreliable test. Because the pathophysiology of acute tubular necrosis often reveals significant heterogeneity

TABLE 34-3 -- Substances and Conditions Affecting Urine Specific Gravity and Urine Osmolality

Proteins
Glucose
Mannitol
Dextran
Diuretics
Advanced age
Extremes of age
X-ray contrast media
Antibiotics (e.g., carbenicillin)
Hydrometer calibration
Detergents
Temperature
Hormonal imbalances

of tubular damage and the value of urine specific gravity depends on the extent of that damage, the test is unreliable unless the significance of the tubular damage has previously been assessed.

Urine Osmolality

Osmolality is a measure of the number of osmotically active particles in solution in the solvent phase. It is one of the major forces that move fluid throughout the body, especially in the kidney. Theoretically, then, urine osmolality is physiologically superior to urine specific gravity as a test of renal function; however, the same substances and conditions that render urine specific gravity a nonspecific test can also affect the reliability of urine osmolality (see Table 34-3) . Since the late 1940s, physicians have recognized the inability of the kidneys to produce concentrated urine during acute tubular necrosis and have used as a guideline urine osmolality of greater than 500 mOsm/kg H_2O to identify prerenal azotemia and urine osmolality of less than 350 mOsm/kg H_2O to indicate acute tubular necrosis. Indeed, a defective urinary concentrating mechanism tends to be one of the most consistent and lasting tubular defects of ARF.

The sensitivity and specificity of urine osmolality as a test for predicting or distinguishing acute tubular necrosis from prerenal azotemia are clinically inadequate. [109] [112] [113] [114] [115] [116] [117] With greater than 500 mOsm, the positive predictive value for diagnosing prerenal azotemia ranges from 60 to 100 percent. With less than 350 mOsm, the positive predictive value for diagnosing acute tubular necrosis ranges from 69 to 95 percent. Thus, the measure of urine osmolality appears to be helpful at extreme values but is, unfortunately, a nonspecific test most of the time.

Serum Creatinine and Blood Urea Nitrogen

The relationship between serum creatinine and BUN levels to GFR seems to make the determination of either one an ideal indicator of filtration rate. However, there are two important points to remember about elevations of serum creatinine and BUN levels: they are late signs of renal dysfunction because GFR must often be reduced as much as 75 percent before elevations reach abnormal levels, [118] and many nonrenal variables affect serum creatinine and BUN levels (Table 34-4) . A product of protein metabolism, BUN level is increased by high protein intake, blood in the gastrointestinal tract, and accelerated catabolism (e.g., as occurs in traumatized or septic patients). The normal range is 8 to 20 mg/dL. Because urea is synthesized in the liver, hepatic dysfunction decreases urea production and therefore BUN concentration. Most important, BUN concentration fails a key criterion as a reliable estimate of GFR. Although urea is freely filtered at the glomerulus, it is reabsorbed to a large and variable extent. The reabsorption of urea is greater, approximately 60 percent of the filtered load, when urinary flow is low; only about 40 percent is reabsorbed when flow is high.

Creatinine, a product of skeletal muscle protein catabolism, is produced at a lower rate in elderly than in young adults and in women than in men. Consequently, serum creatinine

TABLE 34-4 -- Nonrenal Variables Affecting Serum Creatinine and Blood Urea Nitrogen Levels

Increased nitrogen absorption
Tissue breakdown
Body mass
Diet
Activity
Hepatic disease
Diabetic ketoacidosis
Large hematoma

levels may fail to accurately reflect the magnitude of nephron loss. Because creatinine production is proportional to muscle mass, many chronically ill, wasted, elderly patients have serum creatinine values in the normal range, despite reduced renal concentrating ability and GFR. Conversely, many critically ill patients at risk for developing ARF may have high metabolic rates secondary to hyperalimentation, sepsis, or posttraumatic states. Higher metabolic rates mean higher nitrogenous waste production requiring greater-than-average renal blood flow and urine flow rates to maintain normal serum creatinine concentration. Postoperative serial serum creatinine measurements are predictive of renal dysfunction in only 33 percent of cases following noncardiac surgery [16] and are equally unreliable following cardiovascular surgery. [118] It was believed that combining BUN and serum creatinine levels would provide more reliable information than either alone: if ratios of BUN to serum creatinine exceeded 20:1: for example, dehydration was suspected. However, the same factors that render the individual tests nonspecific and insensitive remain true when their ratios are considered.

Urine/Plasma Creatinine

The urine/plasma creatinine index was first introduced in 1950 by Bull et al [119] as a method of evaluating patients with acute tubular necrosis. It was determined retrospectively that patients whose urine/plasma creatinine levels rose above 10 after having been below 10 were no longer at serious risk for "uncontrolled mineral and water loss." Thus, this index was introduced primarily as a prognostic aid and not as a diagnostic one.

The sensitivity and specificity of the urine/plasma creatinine index are unfortunately clinically unreliable for diagnosing acute tubular necrosis and prerenal azotemia. [120] Miller et al [113] concluded that the index was not useful, except in extreme situations, because of significant overlap between groups. Espinel and Gregory [114] prospectively studied 87 patients (61 with acute tubular necrosis or pre-renal azotemia) and concluded that urine/plasma creatinine ratio may be a useful indicator of acute tubular necrosis if the ratio is less than 10 and that it may be an indicator of prerenal azotemia if the ratio is less than 40. However, significant overlap in values was noted for 33 percent of patients.

Urine/Plasma Urea

In 1959, Perlmutter et al [121] proposed that the ratio between urine and serum urea nitrogen levels would differentiate prerenal azotemia from acute tubular necrosis. These investigators proposed that a ratio of greater than 14 is associated with transient oliguria and that a ratio of less than 10 is associated with acute tubular necrosis. In 1965, Eliahou and Bata [112] reported that the urine/blood urea ratio may not be useful for diagnosis in all cases. Subsequently, Chisholm et al [122] confirmed that the urine/plasma urea ratio was often misleading in the diagnosis of uremia.

Urea production is not constant and is affected by many nonrenal variables (see Table 34-4) . [123] These variables include sudden increases or decreases in protein intake, states of increased protein catabolism (trauma, infections, hyperthermia, or steroid therapy), gastrointestinal bleeding, and liver dysfunction. Because urea levels can vary tremendously independent of renal function, it is not surprising that knowing the urine/plasma urea ratio does not make it possible to differentiate between prerenal azotemia and acute tubular necrosis.

Urinary Sodium

With decreasing perfusion, the normally functioning kidney conserves sodium and water. The factors affecting this phenomenon are numerous and include heterogenicity of nephrons, secretion of aldosterone, secretion of ADH, diuretic therapy, saline content of intravenous infusion solutions, sympathetic neural tone, and sodium-avid states (congestive heart failure, cirrhosis). It is traditionally accepted that a urinary sodium level of less than 20 mEq suggests prerenal azotemia and a level of greater than 40 mEq, acute tubular necrosis.

The reported sensitivity and specificity of urinary sodium levels for diagnosis of acute tubular necrosis and prerenal azotemia suggest that the levels can be used for diagnosis of approximately half of the patients with acute tubular necrosis. [109] [113] [114] [115] [119] [124] [125] Considering the complex physiology of sodium homeostasis, it is not surprising that levels of urinary sodium are unreliable indicators of prerenal azotemia or acute tubular necrosis. The test is nonspecific because a significant overlap exists between the diagnostic categories, and urinary sodium measurement tends to correlate more with volume and type of resuscitation fluid than with renal function. [106]

Fractional Excretion of Sodium

The fractional excretion of sodium was first described by Espinel [124] and represents the fraction of sodium excreted of that filtered. Handa and Morrin [120] had previously described the renal failure ratio, which is also derived from the excreted fraction of filtered sodium. The only difference between the two is that in determining renal failure ratio, it is assumed that plasma sodium level is controlled within fairly

narrow limits and is constant. The fractional excretion of sodium (FeNa) is calculated as follows:

where P_{cr} is plasma creatinine, P_{Na} is plasma sodium, U_{cr} is urinary creatinine, and U_{Na} is urinary sodium, and all variables are easy to obtain.

At first investigators had reported that the fractional excretion of sodium clearly differentiated prerenal azotemia from acute tubular necrosis. [113] [114] [115] [124] Subsequently, case reports have demonstrated that the fractional excretion of sodium is a nonspecific indicator and is not as sensitive as initially believed. [124] [125] [126] [127] [128] [129] [130] Brown [126] suggested that the fractional excretion of sodium was diagnostic of acute tubular necrosis but was of little or no value for the early prediction of renal failure. Brosius and Lau [127] showed that early determinations of the fractional excretion of sodium were more apt to be misleading than later determinations, indicating that the measurement is unlikely to be helpful in the early diagnosis of acute tubular necrosis. Shin et al [105] concluded that knowing the fractional excretion of sodium was useful only when oliguria was already present. A sodium excretion value of less than 1 versus greater than 1 percent enables differentiation between prerenal azotemia and acute tubular necrosis in most cases. However, because this indicator is usually noted later in the course of renal disease than are changes in creatinine or free water clearance, the fractional excretion of sodium is less beneficial for predicting imminent renal failure. [131] [132]

Free Water Clearance

Free water clearance is a measure of the kidney's ability to dilute or concentrate urine as necessary to maintain homeostasis. It is determined by the following equation:

where UV is urine volume, U_{osm} is urinary osmolality, and P_{osm} is plasma osmolality.

After an initial retrospective analysis, Jones and Weil [133] prospectively assessed the sensitivity of free water clearance and concluded that serial measurements predicted the patients who would experience progressive renal dysfunction. [109] In a prospective study, however, Rosenberg et al [106] found no significant correlation between renal function and free water clearance in 69 patients with trauma or sepsis. After studying 38 patients in an intensive care unit, Baek et al [134] concluded that

the diagnosis of ARF was evident 1 to 3 days sooner with free water clearance than with other clinical and laboratory diagnostic criteria (creatinine clearance was not measured). These investigators recommended that sequential measurements of free water clearance could be used as an early indicator of pending ARF. A free water clearance of -15 to +15 mL/h is a sign of incipient renal dysfunction. The normal range for free water clearance is -25 to -20 mL/h. After retrospectively reviewing the records of 675 trauma victims, Shin et al [135] concluded that free water clearance alone was not sufficient for the early detection of renal dysfunction. They suggested that the combination of free water clearance greater than 20 mL/h and creatinine clearance less than 25 mL/min predicted a high-risk group. When they prospectively monitored free water clearance in patients after surgery, [105] they concluded that this measure was not as sensitive as creatinine clearance for predicting ARF in trauma patients. The same substances and conditions that decrease the usefulness of urine osmolality for indicating renal failure can similarly decrease the usefulness of free water clearance (see Table 34-3) . [136]

Creatinine Clearance

Creatinine clearance measures the ability of the glomeruli to filter creatinine from the plasma and approximates the rate of glomerular filtration. Measurements of creatinine clearance are most useful to quantify renal reserve. Creatinine clearance often is estimated in the stable patient by use of the following equation:

where wt is weight in kilograms. However, that estimate is subject to the same limitations as the measurement of serum creatinine. Precise measurements of creatinine clearance require collection of timed urine samples, by use of the following formula:

where U is the urinary concentration of creatinine (mg/dL), V is the volume of urine (mL/min), and P is the plasma concentration (mg/dL).

When Shin et al [135] retrospectively reviewed the records of 26 patients who had acute tubular necrosis, they concluded that the diagnosis was likely to be made in patients who had both a creatinine clearance of less than 25 mL/min and a free water clearance of greater than 15 mL/h. In a follow-up study of 40 trauma patients who underwent surgery, Shin et al [105] concluded that creatinine clearance of less than 25 mL/min alone permitted the early detection of renal dysfunction in patients with the potential for development of renal failure, and free water clearance was not as sensitive.

The major limitation in the determination of creatinine clearance is the necessity of collecting urine accurately. Although reasonable correlation between 2-hour and 24-hour creatinine clearance (R=0.85) has been reported in intensive care patients (Fig. 34-8) (Figure Not Available) , [137] [138] it remains true that the longer the urine collection period, the more accurate the calculation of creatinine clearance. Changing hydration of the patient invalidates short-term determinations of GFR, as does failure to record urine volume accurately. The error in calculation of creatinine clearance can vary from 10 to 27 percent, depending on the accuracy of urine collection, [139] body weight, surface area, and normal day-to-day variation. Another significant drawback is that for the patient with ARF, a test that requires 24-hour urine collection is often impractical. Nevertheless, it appears that creatinine clearance

Figure 34-8 (Figure Not Available) Correlation between the 2-hour creatinine clearance (CC02) and the 22-hour creatinine clearance (CC22) *(From Sladen et al [137])*

is the most efficient test available to assess glomerular filtration.

Biochemical Markers of Renal Function

The kidney contains many different cell types with its primary roles concerned with glomerular filtration, tubular reabsorption and secretion, and concentration of metabolites. Although complex, the kidney may be able to respond to disease in only a limited number of ways at the cellular level. Noninvasive tests have been developed that reflect the morphologic, functional, and biochemical regional specialization.

NAG is a widely used urinary enzyme assay for the assessment of renal disease and the detection of nephrotoxicity. Unlike a number of unstable enzymes excreted into the urine, NAG remains suitable for clinical diagnosis of renal disease. An increase in NAG activity in urine is a sensitive test for renal tubular damage. [140] Its molecular mass precludes filtration by the glomerulus and it is also the most active glycosidase found in the proximal tubule lysosomes. The value of NAG as a diagnostic test is further enhanced by its presence in a number of isoenzyme forms. The relative amount of each isoenzyme varies at different stages of renal disease.

A number of analytical methods are available for the determination of urinary NAG, including fluorometric, colorimetric, spectrophotometric, and dipstick tests. Each of these methods is tedious and is associated with limitations that prevent widespread clinical adaptation. Low levels of NAG are excreted by normal individuals; therefore, assay procedures must be sensitive enough to overcome the endogenous inhibitor urea. [141] Another variable to overcome is variation from urine collection that occurs over time. Factoring the enzyme activity with creatinine concentration over the same urine flow collection period is a reasonable approach for this latter problem. [142] In general, sensitivity and reproducibility of the fluorometric method, when it is performed correctly, is excellent; however, the equipment necessary is not commonly available in laboratories.

The colorimetric technique overcomes the limitations of the fluorometric technique, by the incorporation of a calibrant for easy interlaboratory comparison and access in most clinical chemistry laboratories with modification for use with spectrophotometric analysis. [143] The latest development is a dipstick method (RENAG, Boehringer-Mannheim) for detection of NAG in the urine. [144] The NAG strip incorporates a biochemical derivative that releases a blue-violet color on hydrolysis. The test requires up to 30 minutes after the addition of reagents; however, problems can arise if the sample is contaminated with blood or bilirubin. Besides pigmented material in urine, a concentrated urine specimen that is high in urea also renders the test inaccurate.

Perhaps the most interesting discovery regarding urinary NAG for detection of renal disease is that there appears to be isoenzyme specificity for various types of pathology. [145] NAG is the most active lysosomal hydrolase and is normally found in tissues as two major forms: A and B. These major forms differ in their subunit composition. Traditionally, the main clinical interest in these isoenzymes had been their use in the detection of two autosomal recessive disorders, Tay-Sachs disease and Sandhoff disease. In 1970, Price et al [146] reported that the B form increased in a urinary pattern of NAG following surgical trauma. Since that time, it has been

appreciated that the relative amount of the B form increased (i.e., the ratio of A to B forms decreased) compared with urine in the normal population. The development of automated methods for separation of NAG isoenzymes allows the pattern of excretion to be compared in various disease states (Table 34-5) (Table Not Available) . Of interest to the anesthesiologist is that evidence suggests that following major surgery, the percentage of an intermediate form (I) increases in the urine. [147] Smaller increases in the I form were also observed in rejection of renal transplants. Rejection was more strongly associated with a decrease in the A/B ratio in a cohort of renal transplant patients. No change in the isoenzyme profile was found in stable transplant patients, whereas reversible rejection was characterized by an increase in the intermediate form and a decrease in the relative amount of the A form present. When a patient did not respond to treatment, both the I and the B forms were elevated, but the A form decreased. [148]

In addition, different nephrotoxic drugs or conditions appear to produce characteristic urinary isoenzyme profiles. There is elevation of the B and I forms following administration of aminoglycosides, for example. Total urinary and serum NAG activity also has been reported to increase in diabetic patients. Overall, NAG activity in the urine reflects the activity of the disease or severity of the damage. Serial monitoring is therefore most useful because trending is the most appropriate method to

interpret the results. The lack of sensitive, simple, inexpensive and efficient methods is the limiting factor for widespread clinical use. Another urinary enzyme, clusterin, may prove to be more specific than NAG [149] for nephrotoxicity caused by aminoglycoside use while remaining equally sensitive.

A number of other urinary constituents have been identified to detect cytotoxic and abnormal processes in specific regions of the kidney (Table 34-6) (Table Not Available) . alpha-Glutathione S-transferase is found principally in the proximal convoluted tubules, and pi-glutathione S-transferase is found principally in the distal convoluted tubule. beta$_2$ -Microglobulin is a subunit of the class 1 antigen of the major histocompatibility complex and is structurally homologous to immunoglobulins. [150] Its mass is 11,600, it is freely filtered from plasma by the renal glomerulus, and more than 99.9 percent is reabsorbed in the proximal tubule. beta $_2$ -Microglobulin is measured by radioimmunoassay and immunodiffusion techniques. [151] Its secretion in urine is a sensitive indicator of tubular damage or disease. Limitations to its use include its unstable nature in urine of pH 5.5 or below, thereby precluding

TABLE 34-5 -- Variation of Urinary *N*-Acetyl-beta-d-Glucosaminidase

(Not Available)

From Campbell et al [186]

TABLE 34-6 -- Urinary Constituents Used to Measure Renal Function

(Not Available)

From Baines [189]

its use when concomitant urinary tract infection or pyuria is present. There is also a temperature lability of its degradation by proteolysis, and its measurement requires a sophisticated laboratory that precludes widespread clinical use. Alanine aminopeptidase excretion has been identified as a specific marker for proximal tubular brush border dysfunction, as has gamma-glutamyl transpeptidase excretion. In general, a concern for these sensitive markers of renal function is the lack of essential gold standardization for discriminating disease process from normal variant. The enhanced excretion of biochemical markers, tubular enzymes, or antigens might be the consequence of an exfoliated damaged tubular cell, an increased turnover of tubular cells, or some other metabolic disturbance. The biologic variability of the sensitive analytes in response to physiologic stress is large compared with anticipated changes observed in early disease. Therefore, the signals of early irreversible disease may not always be distinguished from the noise of biologic variability, and their use should be applied with appropriate caution.

Renal Blood Flow

Normally, the kidneys receive 1,000 to 1,250 mL/min of blood in the average adult. This amount far exceeds that needed to provide the kidney's intrinsic oxygen requirement but ensures optimal clearance of all wastes and drugs. Essentially, all blood passes through glomeruli, and about 10 percent of renal blood flow is filtered (a GFR of 125 mL/min in the normal adult). The basal normal blood flow is 3 to 5 mL/min/g of tissue, greater than in most other organs (i.e., seven to eight times as much as basal coronary blood flow and 400 times as much as skeletal muscle blood flow). This average primarily reflects blood flow in the cortical glomeruli because perfusion to the inner medulla and papilla is only about one-tenth of total flow.

The vascular structure of the renal cortex is complex, and intracortical blood flow may not be evenly distributed (Fig. 34-9) (Figure Not Available) . [152] The renal artery enters the kidney at the hilum, where it divides into five interlobar arteries, each an end artery. At the junction of the renal medulla and cortex, the interlobar branches divide into arcuate arteries, which

Figure 34-9 (Figure Not Available) Diagram demonstrating the complex vascular and tubule organization of the kidney. The pattern of glomeruli (G) arising from afferent arterioles (AA) is demonstrated in the left-hand portion of the figure. Proximal convoluted tubules (PCT) are perfused by a peritubular capillary network derived from efferent vessels (EV). Loops of Henle are grouped together with collecting ducts (CD). Only thin limbs of Henle extend with collecting ducts to the papillary tip. These are accompanied by vasa recta extending from the cores of the vascular bundles. C, cortex; OM, outer medulla; IM, inner medulla. *(From Beeuwkes and Bonventre [186])*

course at right angles to the interlobar arteries. The interlobular arteries arise at right angles to the arcuate arteries and penetrate through the renal cortex. The afferent arterioles, which arise from the interlobular arteries, divide within the cortical tissue to form the glomerular capillary network. The capillaries then reunite to form the efferent arterioles. The subsequent course of the efferent arterioles varies, depending on whether they are located superficially in the cortex or are situated in the juxtamedullary cortex. Superficial efferent arterioles feed a plexus of peritubular venous capillary vessels. These vessels supply the proximal and distal tubules and portions of the loops of Henle and the collecting ducts before joining the interlobular veins and returning to the inferior vena cava through the arcuate, interlobar, and renal veins. Juxtamedullary efferent arterioles also supply the venous capillary network and give rise to the vasa recta, small-diameter vessels that penetrate deep into the medulla. These vessels provide most of the oxygen supply to the loop of Henle and join together to form the arcuate veins. The juxtaglomerular apparatus is between the afferent and efferent arterioles and the macula densa, a specialized group of cells in the distal convoluted tubule.

Because the renal cortex contains most of the glomeruli and depends on oxidative metabolism for energy, ischemic hypoxia injures the renal cortical structures, particularly the pars recta of the proximal tubules. As ischemia persists, the supply of glucose and substrates continues to decrease; glycogen is consumed, and the medulla, which depends to a greater extent on glycolysis for its energy sources, becomes more adversely affected. Interruption of blood flow to kidneys for more than 30 to 60 minutes results in ARF and irreversible cell damage. Early cell changes are reversible, such as the swelling of cell organelles, especially in the mitochondria. As ischemia progresses, lack of adenosine triphosphate interferes with the sodium pump mechanism, water and sodium accumulate in the endoplasmic reticulum of tubular cells, and the cells begin to swell. In experimental models of ARF, the following pathologic changes occur: (1) swelling of tubular epithelial cells leads to formation of bullae, which protrude into the tubular lumen distal to the cell; (2) necrosis of tubular cells results in abnormal membrane permeability; (3) structural changes in the glomerular epithelium may decrease glomerular filtration; and (4) constriction of intrarenal arteries and arterioles may further reduce glomerular blood flow.

The time of onset for tubular damage in experimental models of ARF is usually within 25 minutes of ischemia as the microvilli of the proximal tubular cell brush borders begin to change. Within an hour, they slough off into the tubular lumen, and membrane bullae protrude into the straight portion of the proximal tubule. After a few hours, intratubular pressure rises, and tubular fluid backflows passively. Within 24 hours, obstructing casts appear in the distal tubular lumen. Even if renal blood flow is completely restored after 60 to 120 minutes of ischemia, GFR may not immediately improve. [64]

In ischemia-induced ARF, lesions are unevenly distributed among nephrons, probably reflecting variability in blood flow. In contrast, in nephrotoxin-induced failure, the necrosis of proximal tubular cells obstructs the tubular lumen with cast-like material, and lesions are more evenly distributed among all nephrons. [153] After restoration of blood flow, intrarenal vascular resistance is high because of cell swelling and ischemic damage, and flow is as much as 50 percent below control values. [154] Renal hypoperfusion in the setting of a toxic insult may act in synergy to increase the risk of ARF. As blood flow becomes inadequate to support glomerular filtration, urine flow ceases, and toxic substances accumulate in the urine and renal parenchyma. Other factors contributing to increase the risk of renal failure include the interference of certain drugs (e.g., nonsteroidal antiinflammatory drugs) with autoregulation and preservation of blood flow to strategic regions of the kidney, drug-induced membrane damage, or mitochondrial uncoupling causing an insufficient utilization of oxygen. Finally, toxic substances

and oxygen deprivation (because of low blood flow) produce depletion of adenosine triphosphate (aminoglycosides).

Distribution

Renal function reflects, and is reflected by, regional nephron heterogenicity and changes in regional renal blood flow. The vascular pattern of the kidney is complex, and the distribution of renal blood flow is nonhomogeneous (see Fig. 34-9) (Figure Not Available) . In the clinical setting of hypotension, the kidney appears to have a distinct susceptibility to injury. The reason for this susceptibility is not readily apparent, because renal blood flow is normally high and oxygen supply exceeds by far

the requirements for oxygen utilization. This overall balance, however, may conceal regional hypoxia, predominately in the outer medulla.

The interest in renal blood flow as a predictor of renal function was first stimulated in 1947, when Trueta et al [155] introduced the concept of cortical ischemia and attributed the pathogenesis of ARF to increased blood flow through the medulla. Supporting evidence for this view has since been confirmed by many investigators who measured renal blood flow distribution with various methods. [156] [157] [158] [159] [160] [161] Monitoring regional renal blood flow patterns may help us understand the physiology of renal salt and water excretion and the comparative pharmacologic effects on the "redistribution" of blood flow within the cortex. Perhaps nephrons in the outer cortex are "salt losers," and those in the inner cortex, the "salt retainers." If this is true, salt-retaining states should occur with the selective reduction of renal blood flow to the superficial cortex, and these states may or may not be accompanied by a rise in renal blood flow to the deep cortex. [30] [161]

Because oliguria most commonly results from reduced cardiac output secondary to hypovolemia, it is essential to understand how hypovolemia affects distribution of renal blood flow. Activation of the sympathetic nervous system and possibly the renin-angiotensin system reduces renal blood flow and GFR. Despite well-maintained arterial blood pressure, blood flow may decrease to one-third its normal level. Constriction of afferent arterioles becomes sufficient to reduce the hydrostatic pressure in glomerular capillaries to levels inadequate for maintenance of normal filtration. Thus, oliguria is initially caused by a decrease in filtration rate from reduced renal blood flow. This condition occurs before the metabolic function of the kidney itself becomes inadequate. As renal blood flow continues to decrease, arteriolar vasoconstriction leads to ischemia and morphologic damage.

Renal arteriographic and xenon washout studies in patients with ARF have shown selected profound reduction in renal blood flow. [157] [159] [160] Arteriography revealed severe attenuation of the intrarenal arterial tree, inability to visualize cortical vessels, absence of a normal cortical nephrogram, and striking reduction in the velocity of contrast dye as it passed through the kidney. These same patients had no bleeding from the cortex during open renal biopsy. Also, xenon washout studies show that the usual rapid transit of xenon through the cortex (indicating cortical perfusion) in the normal kidney is absent in acute oliguria. Renal cortical perfusion at one-third its normal level, involving constriction of the afferent arterioles, is a condition that is more than sufficient to stop renal functioning.

Assessment

The understanding that distribution of renal blood flow is nonhomogeneous, the recognition of nephron structure and functional heterogenicity, and the suggestion that changes in the zonal distribution of renal blood flow affect renal salt and water homeostasis have led investigators to focus on developing new techniques to measure intrarenal blood flow. [161] Methods to measure distribution of renal blood flow in humans include the extraction para-aminohippurate, indicator dilution, radiolabeled tracers, Doppler ultrasonography, and external gas washout techniques. The risks and limitations associated with these techniques limit their usefulness.

Any nontoxic substance cleared by the kidney and not metabolized may be used to measure renal blood flow by application of the Fick principle, whereby renal plasma flow is calculated as follows:

where U is urinary concentration, V is urine flow rate, A is arterial plasma concentration, and RV is renal venous plasma concentration. Renal blood flow is then calculated from the formula

The volume of plasma from which the kidney can extract and excrete a specific substance in a given time is, by definition, the renal clearance of the substance. If a substance is completely eliminated from the plasma in one pass through the renal circulation, is filtered at the glomerulus, is not synthesized or destroyed, and is physiologically inert, then it would be ideal for measuring renal plasma flow. Paraaminohippurate is a substance that almost meets these criteria. The practical advantage of measuring the extraction of para-aminohippurate is that its renal extraction is approximately 90 percent in humans after one passage. Measurement of renal blood flow is based on the assumption that cortical extraction is 100 percent and that extraction in the medulla is zero percent; therefore, it has been assumed that the nonextracted fraction (10 %) should reflect the fraction of blood flowing through the medulla. There is, however, experimental evidence that cortical extraction is not 100 percent, [162] casting doubt on the accuracy of intrarenal blood flow assessment with extraction techniques. Other limitations of the extraction technique include the requirement for a high rate of urine flow, a steady state for 15 to 30 minutes, and the sampling of systemic arterial and renal venous blood.

Indocyanine green, which is bound to albumin in plasma, has been used in the indicator dilution method with densi-tometry. The indicator dilution method necessitates catheterization of a renal artery and vein. Although attempts have been made to measure renocortical (fast) and medullar (slow) blood flows separately from dye dilution curves, no convincing results have been produced. [163] Measurement of

renal blood flow by a continuous thermodilution technique, which requires renal venous cannulation and continuous injection of normal saline, has been proposed. [164] Measurements have correlated with calculated renal blood flows derived from clearance techniques in patients after cardiac catheterization; however, only total renal blood flow is measured with the thermodilution technique.

External krypton 85 and xenon 133 clearance techniques estimate local blood flow per gram of tissue from local gas clearance. [157] The gas washout technique requires selective catheterization of the renal artery and is usually performed in conjunction with arteriography. The renal artery also may be punctured intraoperatively for injection. After intra-arterial injection, the gas diffuses rapidly into the renal tissue, theoretically equilibrating in tissue and blood. The renal washout curve is then assessed by external counting (Fig. 34-10) (Figure Not Available) . The reliability of washout methods has been questioned, and absolute flow rates cannot be determined with this method. In anuric subjects, various causes for unreliability of the method may be suspected. For example, the disappearance rate of the gas decreases when kidney volume increases, and kidney volume typically increases during ARF. The partition coefficient of 133 Xe may be less than 1.0 when the water content of the kidney is increased, as in ARF. If equilibrium of gas between tissue and capillaries is not achieved, actual flow rates may be underestimated. Hemodynamics must remain constant during washout curve recordings. The analysis is further complicated by the problem of resolving "external" summation curves into appropriate components representing flow through anatomic regions of the kidney. Theoretically, the desaturation curve after rapid injection of the radioactive isotope (recorded with a gamma counter placed over the kidney) is a summation of different desaturation curves. Each of the component curves represents a different region of the kidney, thereby allowing flow rate per gram of tissue and relative volume of each region to be calculated. [165] [166] What remains to be shown, however, is whether these calculated components really correspond to well-defined anatomic regions in the kidney. Until now, little evidence supports such a conclusion, beyond agreement that the first rapid washout component curve corresponds to flow in the renal cortex. The limitations of the gas washout method should be kept in mind when clinical measurements are made; another limitation of this gas washout technique occurs because areas without perfusion cannot be demonstrated. The component representing an ischemic area is fused with components corresponding to regions that are normally perfused at a slow rate. This procedure results in lack of detection of renal infarctions or segmental ischemic zones if the surrounding unaffected tissue is perfused normally.

Qualitative and semiquantitative evaluation of renal perfusion can be obtained with a gamma camera recording of the transit of a radiopharmaceutical tracer through the kidney.

Figure 34-10 (Figure Not Available) Analysis of an externally monitored radioactive krypton washout curve for the kidney in a dog. (Note the logarithmic vertical scale.) The rapid component (component I) represents cortical blood flow. Half-times for each component together with estimated flow rates and compartment sizes are shown in the table above the plotted curves. *(From Thorburn et al [165])*

Qualitative evaluation of renal perfusion consists of the visual assessment of the serial images. Quantitative evaluation consists of the comparative evaluation of the first transit of tracer from the aorta (or iliac-renal artery) to the kidney. Among the problems and limitations associated with the renogram is movement of the radiopharmaceutical (injected intravenously as a bolus) before it reaches the kidney, necessitating that the pharmacokinetic model contain all the possible exchange compartments between the kidney and the plasma for accurate analysis of the tissue radioactivity curve. The presence of low urine flow rates, dilated pelvic caliceal cavities, or severely reduced renal function may also cause difficulties for test interpretation. In general, the information that can be derived from the renogram includes renal clearance (as a fraction of the radioisotope to blood volume) and comparative blood flow of the two kidneys relative to each other. [167] Because the results obtained are comparative, lesions are revealed only when they have asymmetric distribution.

The development of duplex ultrasound has enabled the evaluation of changes in renovascular resistance and intrarenal blood flow in patients. The technique is noninvasive and may be repeated as often as required. Typically, an interlobar artery is selected for evaluation for these reasons: the anatomic course and relations of the vessel allow easy recognition on subsequent serial scans in the same patient; the vessel is large enough to assume laminar flow throughout its length; and the angle of the ultrasound beam can generally be minimized to assume maximum Doppler frequency shift. Renal vascular resistance can be assessed by the pulsatility index. [168] The lower the pulsatile index, the less the resistance to flow. The value is derived by dividing the difference between systolic maximum height and dia-stolic minimum height of the waveform by its mean height (Fig. 34-11) (Figure Not Available) . Change in flow velocity can be assessed from change in mean frequency shift. The frequency shift is proportional to the mean velocity of blood flow within the vessel multiplied by the cosine of the angle between the ultrasound beam and the direction of flow. The angle is assumed to be close to zero. With this method, only blood flow velocity in large interlobar arteries and resistance can be assessed. The duplex Doppler ultrasound technique may provide a unique opportunity to demonstrate the effects of drugs on the renal vasculature as well as to predict the onset of pending renal failure or transplanted kidney rejection. Overall, this technique should provide an opportunity for measuring relative changes in large vessel flow velocity but not in absolute renal blood flow.

Contrast ultrasonography is a clinical diagnostic tool for assessing tissue perfusion with contrast agents, typically nontoxic solutions containing gaseous microbubbles, which reflect the ultrasonic beam emitted by an echo transducer. [169] Contrast ultrasonography has been used to image renal blood flow. [170] [171] The microbubbles produced by ultrasonic cavitation (sonication) are smaller than red blood cells and, in passing with them through the microcapillary vascular bed, reflect an echo beam to permit direct ultrasonic imaging of tissue perfusion (Fig. 34-12) (Figure Not Available) . Sonicated microbubbles have been shown to exhibit intracavitary velocities comparable to those of red blood cells, as observed by Doppler. Numerous investigators have postulated that by controlling the size and stability of the microbubbles, quantitative measurements could be accomplished. With contrast ultrasonography, absolute blood flow and volume *in vitro* can be calculated; with contrast ultrasound and a mathematical model based on indicator dye-dilution theory, cortical blood flow in the canine kidney has been assessed. [171] Modest correlations have been found between calculated renal blood flow assessed by contrast ultrasonography and flow assessed with an electromagnetic flow probe. The pharmacologic effects of fenoldopam and dopamine on distribution of blood flow in the renal cortex also have been

Figure 34-11 (Figure Not Available) Renal duplex scan showing sample volume superimposed over B-scan image in typical normal velocity flow pattern, from the main renal artery at the hilum. vS, systolic velocity; vd, diastolic velocity; theta, angle of incidence between transmitted ultrasound signal and received ultrasound signal.

Figure 34-12 (Figure Not Available) Serial recordings of a single intra-arterial bolus injection of Renografin-76. Baseline image (before contrast injection) is represented in frame 1. After the bolus injection, contrast material is seen in the interlobar arteries (frames 2 and 3) before being seen in the renal cortex (frame 4). Frames 5 and 6 represent contrast washout. *(From Lang et al [187])*

assessed with contrast ultrasonography. [172] With anticipated improvements in the sensitivity of commercial ultrasound imaging devices and in the stability of contrast agents, contrast ultrasound may allow absolute quantitation of renal blood flow in an intraoperative setting for the early recognition of ARF. Clinical trials are under way to test the safety and efficacy of commercially prepared ultrasound contrast agents for assessing renal perfusion patterns in surgical patients.

Utilization of Renal Blood Flow

Although the kidneys receive nearly a quarter of the cardiac output and extract relatively little oxygen, there is a marked discrepancy between cortical and medullary blood flow and oxygen delivery and consumption. The apparent overabundance of blood flow to the cortex is designed to maximize flow-dependent functions, such as glomerular filtration and tubular reabsorption. In the medulla, blood flow and oxygen supply are restricted by a tubulovascular anatomy specifically designed for urinary concentration. Hypoxic perfusion of an isolated kidney preparation has demonstrated that the cells of the thick ascending limb of the loop of Henle in the medulla are extremely vulnerable to hypoxic damage. [69] This damage is patchy and is most evident in tubules farthest from a vessel. The selective vulnerability of the cells in the thick ascending loop of Henle is thought to result from their high oxygen consumption. Blood flow is approximately 90 to 95 percent to the cortex, compared with 5 to 10 percent to the medulla. Average blood flow is 5.0 mL/g/min and 0.03 mL/g/min for the cortex and medulla, respectively, and the oxygen extraction ratio (i.e., oxygen consumption over oxygen delivery) is 0.18 and 0.79 for the cortex and medulla, respectively. Normally, the partial pressure of oxygen is about 50 mm Hg in the cortex and 8 to 15 mm Hg in the medulla, making the thick ascending loop of Henle most vulnerable to tissue hypoxia. Severe hypoxia may therefore easily develop in the medulla if total renal blood flow is inadequate.

The initial response to decreased renal blood flow is an increase in sodium absorption in the ascending loop of Henle, which increases oxygen demand in the regions most vulnerable to decreased oxygen delivery. Ischemic renal damage may reflect hypoxic injury deep in the medulla to the metabolically active cells of the ascending loop of Henle. The normal response to systemic hypoperfusion is active sodium and water reabsorption, a metabolic response that demands oxygen at the time of greatest hypoxic vulnerability. To compensate, sympathoadrenal mechanisms cause cortical vasoconstriction and oliguria, which redistributes blood flow away from the outer cortex to the inner cortex and medulla. Another compensatory mechanism, increased sodium delivery to the macula densa, results in afferent arteriolar constriction. With afferent arteriolar vasoconstriction, glomerular filtration decreases, after which solute reabsorption in the loop of Henle and oxygen consumption are reduced. In a hypoperfused kidney preparation, oxygen-enriched perfusion reduced cellular damage, hypoxic perfusion increased it, and complete cessation of perfusion (glomerular filtration zero, preventing ultrafiltration) was associated with less cellular injury than hypoxic

perfusion. [68] Thus, the severity of cellular injury appears related to the degree of imbalance between cellular oxygen supply and demand. Afferent arteriolar vasoconstriction may be a normal protective response to acute tubular injury. By reducing ultrafiltration, further energy expenditure by already ischemic medullary tubular cells is prevented, even at the cost of retaining nitrogenous waste.

Theoretically, therapeutic intervention designed to prevent renal insufficiency should be focused on preserving renal blood flow and oxygen delivery. Continuous monitoring of urinary oxygen tension has been examined as a method for assessing renal function during the perioperative period. [173] [174] [175] Urinary oxygen tension (Pu_{O_2}) decreases with clinical shock and dehydration. It has been demonstrated that Pu_{O_2} decreased when renal blood flow decreased and/or when Pa_{O_2} decreased and that Pu_{O_2} increased when Pa_{O_2} increased. Changes in Pu_{O_2}, however, are relatively insensitive to oxygen content compared with changes in Pa_{O_2}. Because urinary oxygen tension is dependent on renal perfusion and renal oxygenation, it may be a useful tool for predicting renal cell injury, yet it is not now clinically practical to measure Pu_{O_2}. Urine samples obtained from bladder catheters provide artificially high Pu_{O_2} values because samples are easily contaminated with oxygen present in room air. Another problem with measuring urinary oxygen tension or saturation is that bladder measurements may be different from ureteral measurements. Ureteral measurements also may not reflect accurately the regional use of oxygen in the renal cortex versus the renal medulla or the renal pelvis. Thus, interpreting the physiologic significance of changes in urine oxygen tension or saturation requires knowledge of where the oxygen comes from and its relationship to other physiologic variables.

Regional Oxygen Supply and Demand in the Kidney

Total renal blood flow to the kidney is extremely high when compared with its weight and arteriovenous oxygen difference. Greater than 90 percent of the blood flow is directed to the outer cortex, and relatively little goes to the renal medulla. There appears to be a physiologically important reason for the paucity of blood flow and, consequently, the oxygenation in the medulla. [176] The tubules carrying blood to the medulla are arranged in a "hairpin loop" pattern to allow a countercurrent exchange of solute between the ascending and the descending limbs of the hairpin loop. In this way, urine in the tubule becomes highly concentrated. The osmotic gradient in the deeper portions of the medulla requires active transport of sodium in the thick ascending loop of Henle and limited blood flow through the medullary vessels to prevent washout of the solutes in those deeper tubules. To maintain this concentration gradient in the thick ascending limb, high energy demand (active

sodium transport) must be coupled with low oxygen delivery. The ambient partial pressure of oxygen in the medulla ranges from 10 to 15 mm Hg. The high metabolic requirement of the thick ascending loop of Henle in a hypoxic environment makes it especially vulnerable to injury associated with an imbalance in oxygen supply and demand. [177] [178] [179]

Influence of Renal Blood Flow on Glomerular Filtration Rate

Decreased renal perfusion initiates a series of systemic and renal compensatory responses that act to preserve ultrafiltration. [35] At this stage, glomerular filtration and renal blood flow are maintained by increased distribution of cardiac output to the kidney, selective afferent vasodilation and efferent vasoconstriction, and increased sodium and water conservation. If these protective mechanisms fail, the response progresses from compensation to decompensation and renal blood flow decreases. Then, a positive feedback loop is stimulated, heralded by afferent arteriolar vasoconstriction that decreases capillary hydrostatic pressure and ultrafiltration.

Cortical and medullary nephrons have a unique relationship to their respective vascular bundles in the kidney: cortical nephrons have their thick ascending limbs far from vascular bundles, and medullary nephrons have their thick ascending limbs adjacent to vascular bundles. During hypoxia, the cortical nephrons suffer the most. [180] When renal blood flow is compromised, blood flow and glomerular filtration in the superficial outer cortical nephrons decline first. Corticomedullary redistribution of renal blood flow protects the vulnerable medullary oxygen balance. Decreased glomerular filtration during compromised flow appears to be protective because decreased urine delivery to the tubules requires less reabsorptive work of them and prevents further imbalance of oxygen supply and demand. Medullary hypoxia can be modulated by a variety of pharmacologic or physiologic maneuvers. Reduction of tubular work load by furosemide (Lasix) administration is effective in preventing medullary hypoxic cellular injury. [176] [181] In addition to maneuvers that reduce tubular transport or glomerular filtration, adenosine [182] and nitric oxide [183] have been proposed as pharmacologic options that can modify medullary hypoxia.

MONITORING RENAL FUNCTION DURING RENAL TRANSPLANT SURGERY

During renal transplant surgery (Ch. 55), maintaining renal perfusion is the obvious goal when the "donor" kidney is removed. If the donor is brain dead, every effort should be focused on augmenting oxygen supply and reducing oxygen consumption. Supportive means, such as maintaining intravascular volume (even blood administration) and cardiac performance with inotropic agents if needed, should be considered. Theoretically, reduction in medullary thick ascending loop tubular transport (an energy-consuming and oxygen-consuming mechanism) may be inhibited before removal of the kidneys; however, improved renal function after transplantation remains to be demonstrated. Methods for tubular preservation by decreasing sodium transport in the thick ascending loop of Henle include administration of diuretics, hemodilution, and complete cessation of renal blood flow via renal artery clamping, which effectively prevents ultrafiltration. [181]

The number of patients receiving kidney transplants as therapy for end-stage renal disease should continue to increase

---

because transplantation both is cost effective and improves quality of life when compared with dialysis. Unavailability of donor organs is often the limiting variable when transplantation is considered. Other than incurable disease (e.g., human immunodeficiency virus positivity or disseminated malignancy) or active infection, there may be no absolute contraindications for transplantation. A patient's systemic disease and ability to tolerate the operative procedure, both of which can be influenced by the anesthesiologist, are relative contraindications for transplantation. When patients are monitored during renal transplant surgery, venous and arterial access should be used cautiously because they may be limited when shunts or fistula sites are required. Monitoring for arrhythmias with an electrocardiogram is also useful. Electrolyte disturbances that may require treatment as a result of renal dysfunction may thus be detected.

Posttransplant delayed function (the need for more than one hemodialysis treatment during the first week after transplant) is associated with significantly worse morbidity and mortality in transplant patients than is immediate function. [184] One measure that facilitates immediate function is intraoperative fluid and drug management. Segmental renal perfusion following transplantation and augmentation of blood flow after drug administration can be safely assessed with intraoperative contrast echocardiography [170] during renal transplant surgery. The technique offers promise for monitoring regional renal blood flow changes following hemodynamic or pharmacologic perturbations during surgery. Aggressive intraoperative blood volume expansion (central venous pressure, 15 to 18 mm Hg) has improved function after cadaver renal transplantation. The decision to monitor intravascular volume and tolerance for blood volume expansion during transplantation with a central venous catheter, pulmonary artery catheter, or transesophageal echocardiography depends on a patient's cardiac reserve function.

SUMMARY

In patients with real or potential renal dysfunction, the perioperative management continues to be challenging. The causes of perioperative ARF vary but typically have a common mechanism of insufficient renal blood flow delivery, or acute tubular necrosis, or both.

As our understanding of renal function continues to evolve, traditional answers turn into new questions. The introduction of new agents and the reexploration of old techniques and their respective influence and reliance on renal function should become clearer with advances in renal function monitoring. That this information will modify the prognosis of renal dysfunction remains untested at this time, however. Meanwhile, we are limited to relying on indirect variables of renal function that may or may not bear a reliable relationship to GFR and renal blood flow, and therefore renal function, during the perioperative period.

References

1. McCarty JT: Prognosis of patients with acute renal failure in the intensive care unit: A tale of two eras. Mayo Clin Proc 71:117-126, 1996.

2. Drumk RN, Lax F, Grimn G et al: Acute renal failure in the elderly 1975-1990. Clin Nephrol 41:342-349, 1994.

3. Butkus DE: Persistent high mortality in acute renal failure: Are we asking the right questions. Arch Intern Med 143:209-212, 1983.

4. Hou SH, Bushinsky DA, Wish JB et al: Hospital-acquired renal insufficiency: A prospective study. Am J Med 74:243, 1983.

5. Beanan M, Turney JH, Rodgers RS et al: Changing pattern of acute renal failure. Q J Med 62:15-23, 1987.

6. Wilkes BM, Mailloux LU: Acute renal failure: Pathogenesis and prevention. Am J Med 80:1129, 1986.

7. Maher ER, Robinson KN, Scoble JE et al: Prognosis of critically ill patients with acute renal failure: Apache II score and other predictive factors. Q J Med 72:857-866, 1989.

8. Abreo K, Moorthy AV, Osborne M: Changing patterns and outcome of acute renal failure requiring hemodialysis. Arch Intern Med 146:1338, 1986.

9. Ostri P, Mouritsen L, Jorgensen B et al: Renal function following aneurysmectomy of the abdominal aorta. J Cardiovasc Surg 27:714, 1986.

10. Sturm JT, Billiar TR, Luxenberg MG et al: Risk factors for the development of renal failure following the surgical treatment of traumatic aortic rupture. Ann Thorac Surg 43:425, 1987.

11. Wait RB, Kahng KU: Renal failure complicating obstructive jaundice. Am J Surg 157:256, 1989.

12. Kasiske BL, Kjellstrand CM: Perioperative management of patients with chronic renal failure and postoperative acute renal failure. Urol Clin North Am 10:35, 1983.

13. Novis BK, Roizen MF, Aronson S et al: Association of perioperative risk factors with postoperative acute renal failure. Anesth Analg 78:143-149, 1994.

14. Kaufman J, Dhakal M, Patel B et al: Community-acquired acute renal failure. Am J Kidney Dis 17:191-198, 1991.

15. Shusterman N, Strom BL, Murray TG et al: Risk factors and outcome of hospital acquired acute renal failure: Clinical epidemiology study. Am J Med 83:65-71, 1987.

16. Charlson ME, MacKenzie CR, Gold JP et al: Postoperative changes in serum creatinine: When do they occur and how much is important? Ann Surg 209:328-333, 1989.

17. Thadhani R, Pascual M, Bonventre JV: Acute renal failure. N Engl J Med 334:1448-1460, 1996.

18. Badr KF, Ichikawa I: Prerenal failure: A deleterious shift from renal compensation to decompensation. N Engl J Med 319:623, 1988.

19. Kellen M, Aronson S, Roizen MF et al: Predictive and diagnostic tests of acute renal failure: A review. Anesth Analg 78:134-142, 1994.

20. Davidman M, Olson P, Kohen J et al: Iatrogenic renal disease. Arch Intern Med 151:1809-1812, 1991.

21. Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. Anesthesiology 40:536, 1974.

22. Mazze RI, Calverley RK, Smith NT: Inorganic fluoride nephrotoxicity: Prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46:265, 1977.

23. Bastron RD, Pyne JL, Inagaki M: Halothane-induced renal vasodilation. Anesthesiology 50:126, 1979.

24. Seyde WC, Ellis JE, Longnecker DE: The addition of nitrous oxide to halothane decreases renal and splanchnic flow and increases cerebral blood flow in rats. Br J Anaesth 58:63, 1986.

25. Davidkova TI, Fujii K, Kikuchi H et al: Urinary excretion of inorganic and organic fluoride after inhalation of sevoflurane. Hiroshima J Med Sci 36:99, 1987.

26. Papper S, Papper EM: The effects of preanesthetic, anesthetic and postoperative drugs on renal function. Clin Pharmacol Ther 5:205, 1964.

27. Kennedy WF, Sawyer TK, Gerbershagen HU et al: Systemic cardiovascular and renal hemodynamic alterations during peridural anesthesia in normal men. Anesthesiology 31:414, 1969.

28. Gamulin Z, Forster A, Morel D et al: Effects of infrarenal aortic cross-clamping on renal hemodynamics in humans. Anesthesiology 61:394, 1984.

29. Gamulin Z, Forster A, Simonet F et al: Effects of renal sympathetic blockade on renal hemodynamics in patients undergoing major aortic abdominal surgery. Anesthesiology 65:688, 1986.

30. Sladen RN: Effects of anesthesia and surgery on renal function. Crit Care Clin 3:373, 1987.

31. Lucas CE, Weaver D, Higgins RF et al: Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function. J Trauma 18:564, 1978.

---

32. Brennan LA Jr, Malvin RL, Jochim KE et al: Influence of right and left atrial receptors on plasma concentrations of ADH and renin. Am J Physiol 221:273, 1971.

33. Philbin DM, Baratz RA, Patterson RW: The effect of carbon dioxide on plasma antidiuretic hormone levels during intermittent positive-pressure breathing. Anesthesiology 33:345, 1970.

34. Cogan MG: Renal effects of atrial natriuretic factor. Annu Rev Physiol 52:699, 1990.

35. Weiss RM: Ureteral function. Urology 12:114, 1978.

36. Young CJ, Attele A, Toledano A et al: Volatile anesthetics decrease peristalsis in the guinea pig ureter. Anesthesiology 81:452-458, 1994.

37. Morita T, Wada I, Saeki H et al: Ureteral urine transport changes in bolus volume, peristaltic frequency, intraluminal pressure and volume of flow resulting from autonomic drugs. J Urol 137:132, 1987.

38. Makker SP, Tucker AS, Izant RJ Jr et al: Nonobstructive hydronephrosis and hydroureter associated with peritonitis. N Engl J Med 287:535, 1972.

39. Wheeler MA, Cho YH, Hong KW et al: Age-dependent alterations in beta-adrenergic receptor function in guinea pig ureter. Prog Clin Biol Res 327:711-715, 1990.

40. Renkin EM, Robinson RR: Glomerular filtration. N Engl J Med 290:785, 1974.

41. Mauer MS, Steffes MW, Ellis EN et al: Structural-functional relationships in diabetic nephropathy. J Clin Invest 74:1143-1155, 1984.

42. Richards AN, Westfall BB, Bott PA: Renal excretion of inulin, creatinine, and xylose in normal dogs. Proc Soc Exp Biol 32:73, 1934.

43. Miller BF, Winkler AW: The renal excretion of endogenous creatinine in man, comparison with exogenous creatinine and inulin. J Clin Invest 17:31, 1938.

44. Skov PE: Glomerular filtration rate in patients with severe and very severe renal insufficiency. Acta Med Scand 187:419, 1970.

45. Mark JB, Steel SM: Cardiovascular effects of spinal anesthesia. Int Anesthesiol Clin 27:31-39, 1989.

46. Saada M, Duval AM, Bounet F et al: Abnormalities in myocardial segmented wall motion during lumbar epidural anesthesia. Anesthesiology 71:26-32, 1989.

47. Kennedy WF, Sawyer TK, Gerbershagen HV: Simultaneous systemic cardiovascular and renal hemodynamic measurements during high spinal anesthesia in normal man. Acta Anaesthesiol Scand 37:163-171, 1970.

48. Sulerman MY, Passannante AN, Onder RL et al: Alterations of renal blood flow during epidural anesthesia in normal subjects. Anesth Analg 84:1076-1080, 1997.

49. Halperin BD, Feeley TW: The effect of anesthesia and surgery on renal function. Int Anesthesiol Clin 22:157-168, 1984.

50. Mazze RI, Calverley RK, Smith NT: Inorganic fluoride nephrotoxicity: Prolonged enflurane and halothane anesthesia in volunteers. Anesthesiology 46:265-271, 1977.

51. Cousins MJ, Mazze RI: Methoxyflurane nephrotoxicity: A study of dose response in man. JAMA 225:1611-1616, 1973.

52. Mazze RI, Cousins MJ, Kosek JC: Dose-related methoxyflurane nephrotoxicity in rats: A biochemical and pathologic correlation. Anesthesiology 36:571-587, 1972.

53. Manday IT, Stoddart PA, Jones RM et al: Serum fluoride concentration and urine osmolality after enflurane and sevoflurane anesthesia in male volunteers. Anesth Analg 81:353-359, 1995.

54. Kharasch ED, Armstrong AS, Gunn et al: Clinical sevoflurane metabolism and disposition II. The role of cytochrome P450 2E1 in fluoride and hexafluoroisopropanol formation. Anesthesiology 82:1379-1388, 1995.

55. Conzen PF, Nuscheler M, Melotte A et al: Renal function and serum fluoride concentration in patients with stable renal insufficiency after anesthesia with sevoflurane or enflurane. Anesth Analg 81:569-575, 1995.

56. Kharasch ED, Hawkins DC, Thummel KE: Human kidney methoxyflurane and sevoflurane metabolism: Intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. Anesthesiology 82:689-699, 1995.

57. Frink E, Malan T, Isner RJ et al: Renal concentrating function with prolonged sevoflurane or enflurane anesthesia in volunteers. Anesthesiology 80:1019-1025, 1994.

58. Morio M, Fujii K, Satoh N et al: Reaction of sevoflurane and its degradation products with soda lime: Toxicity of the byproducts. Anesthesiology 77:1155-1164, 1992.

59. Gonsowski CT, Laster MJ, Eger EI et al: Toxicity of compound A in rats: Effects of increasing duration of administration. Anesthesiology 80:566-573, 1994.

60. Bito H, Ikewchi Y, Ikeda K: Effects of low-flow sevoflurane anesthesia on renal function. Anesthesiology 86:1231-1237, 1997.

61. Eger EI, Koblin DD, Bowland T et al: Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 84:160-168, 1997.

62. Kharasch ED, Frink EJ, Zager R et al: Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular function. Anesthesiology 86:1238-1253, 1997.

63. Schrier RW: Acute renal failure JAMA 247:2518, 1982.

64. Donohoe JF, Venkatachalam MA, Bernard DB et al: Tubular leakage and obstruction after renal ischemia: Structural-functional correlations. Kidney Int 13:208, 1978.

65. Cronin RE, Erickson AM, De Torrente A et al: Norepinephrine-induced acute renal failure: A reversible ischemic model of acute renal failure. Kidney Int 14:187, 1978.

66. Tanner GA, Sophasan S: Kidney pressures after temporary renal artery occlusion in the rat. Am J Physiol 230:1173, 1976.

67. Myers BD, Moran SM: Hemodynamically mediated acute renal failure. N Engl J Med 314:97, 1986.

68. Brezis M, Rosen S, Silva P et al: Renal ischemia: A new perspective. Kidney Int 26:375, 1984.

69. Brezis M, Rosen S, Silva P et al: Selective vulnerability of the medullary thick ascending limb to anoxia in the isolated perfused rat kidney. J Clin Invest 73:182, 1984.

70. Byrick RJ, Rose DK: Pathophysiology and prevention of acute renal failure: The role of the anaesthetist. Can J Anaesth 37:457, 1990.

71. Zimmerhackl B, Robertson CR, Jamison RL: The microcirculation of the renal medulla. Circ Res 57:657, 1985.

72. Flamenbaum W: Pathophysiology of acute renal failure. Arch Intern Med 131:911, 1973.

73. Chedru M-F, Baethke R, Oken DE: Renal cortical blood flow and glomerular filtration in myohemoglobinuric acute renal failure. Kidney Int 1:232, 1972.

74. Knapp R, Hollenberg NK, Busch GJ et al: Prolonged unilateral acute renal failure induced by intra-arterial norepinephrine infusion in the dog. Invest Radiol 7:164, 1972.

75. Ross B, Freeman D, Chan L: Contributions of nuclear magnetic resonance to renal biochemistry. Kidney Int 29:131, 1986.

76. Ratcliffe PJ, Moonen CTW, Halloway PAH et al: Acute renal failure in hemorrhagic hypotension: Cellular energetics and renal function. Kidney Int 30:355, 1986.

77. Ratcliffe PJ, Moonen CTW, Ledingham JGG et al: Timing of the onset of changes in renal energetics in relation to blood pressure and glomerular filtration in hemorrhagic hypotension in the rat. Nephron 51:225, 1989.

78. Diehl JT, Cali RF, Hertzer NR et al: Complications of abdominal aortic reconstruction: An analysis of perioperative risk factors in 557 patients. Ann Surg 197:49, 1983.

79. Crawford ES, Crawford JL, Safi HJ et al: Thoracoabdominal aortic aneurysms: Preoperative and intraoperative factors determining immediate and long-term results of operations in 605 patients. J Vasc Surg 3:389, 1986.

80. MacKenzie CR, Charlson ME: Assessment of perioperative risk in the patient with diabetes mellitus. Surg Gynecol Obstet 167:293, 1988.

81. Luke RG: Can renal function due to hypertension be prevented? Hypertension 3:139-142, 1991.

82. Harrison JF, Parker RW, De Silva KL: Lysozymuria and acute disorders of renal function. J Clin Pathol 26:278, 1973.

83. Wilson RF, Soullier G, Antonenko D: Creatinine clearance in critically ill surgical patients. Arch Surg 114:461, 1979.

84. Gorfinkel HJ, Szidon JP, Hirsch LJ et al: Renal performance in experimental cardiogenic shock. Am J Physiol 222:1260, 1972.

85. Kahl FR, Flint JF, Szidon JP: Influence of left atrial distension on renal vasomotor tone. Am J Physiol 226:240, 1974.

86. Zeidel ML: Renal actions of atrial natriuretic peptide: Regulation of collecting duct sodium and water transport. Annu Rev Physiol 52:747, 1990.

87. Smith MD, MacPhail B, Harrison MR et al: Value and limitations of transesophageal echocardiography in determination of left ventricular volumes and ejection fraction. J Am Coll Cardiol 19:1213, 1992.

88. Helak JW, Reichek N: Quantitation of human left ventricular mass and volume by two-dimensional echocardiography: In vitro anatomic validation. Circulation 63:1398, 1981.

89. Perel A, Pizov R, Cotev S: Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 67:498, 1987.

90. Folland ED, Parisi AF, Moynihan PF et al: Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography: A comparison of cineangiographic and radionuclide techniques. Circulation 60:760, 1979.

91. Kilburn KH, Dowell AR: Renal function in respiratory failure: Effects of hypoxia, hyperoxia and hypercapnia. Arch Intern Med 127:754, 1971.

92. Pelletier CL, Shepherd JT: Effects of hypoxia on vascular responses to the carotid baroreflex. Am J Physiol 228:331, 1975.

93. Neylon M, Johns EJ, Marshall JM: The renal response to systemic hypoxia in the anesthetized rat. J Physiol (Lond) 452:88P, 1992.

94. Sladen A, Laver MB, Pontoppidan H: Pulmonary complications and water retention in prolonged mechanical ventilation. N Engl J Med 279:448, 1968.

95. Stone AM, Stahl WM: Renal effects of hemorrhage in normal man. Ann Surg 172:825, 1970.

96. Hilberman M, Derby GC, Spencer RJ et al: Sequential pathophysiological changes characterizing the progression from renal dysfunction to acute renal failure following cardiac operations. J Thorac Cardiovasc Surg 79:838, 1990.

97. Yao FS, Hartman GS, Thomas SI et al: Does arterial pressure during cardiopulmonary bypass effect renal and pulmonary complications following coronary artery surgery? Anesth Analg 80:SCA 113, 1995.

98. Slogoff S, Reul GJ, Keats AS et al: Role of perfusion pressure and flow in major organ dysfunction after cardiopulmonary bypass. Ann Thorac Surg 50:911, 1990.

99. Urzua J, Troncoso S, Bigedo G et al: Renal function and cardiopulmonary bypass: Effects of perfusion pressure. J Cardiothorac Vasc Anesth 6:299, 1992.

100. Makhoul RG, Gewertz BL: Renal prostaglandins. J Surg Res 40:181, 1986.

101. Packer M, Lee WH, Kessler PD: Preservation of glomerular filtration rate in human heart failure by activation of the renin-angiotensin system. Circulation 74:766, 1986.

102. Edwards RM: Segmental effects of norepinephrine and angiotensin II on isolated renal microvessels. Am J Physiol 244:F526, 1983.

103. Goldstein MB: Acute renal failure. Med Clin North Am 67:1325, 1983.

104. Vertel RM, Knochel JP: Nonoliguric acute renal failure. JAMA 200:118, 1967.

105. Shin B, Mackenzie CF, Helrich M: Creatinine clearance for early detection of posttraumatic renal dysfunction. Anesthesiology 64:605, 1986.

106. Rosenberg IK, Gupta SL, Lucas CE et al: Renal insufficiency after trauma and sepsis. Arch Surg 103:175, 1971.

107. Alpert RA, Roizen MF, Hamilton WK et al: Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery 95:707, 1984.

108. Knos GB, Berry AJ, Isaacson IJ et al: Intraoperative urinary output and postoperative blood urea nitrogen and creatinine levels in patients undergoing aortic reconstructive surgery. J Clin Anesth 1:181, 1989.

109. Jones LW, Weil MH: Water, creatinine, and sodium excretion following circulatory shock with renal failure. Am J Med 51:314, 1971.

110. Pru C, Kjellstrand C: Urinary indices and chemistries in the differential diagnosis of prerenal failure and acute tubular necrosis. Semin Nephrol 5:224, 1985.

111. Haskell JP, Tannenberg AM: Elevated urinary specific gravity in acute oliguric renal failure due to hetastarch administration. NY State J Med 88:387, 1988.

112. Eliahou HE, Bata A: The diagnosis of acute renal failure. Nephron 2:287, 1965.

113. Miller TR, Anderson RJ, Linas SL et al: Urinary diagnostic indices in acute renal failure: A prospective study. Ann Intern Med 89:47, 1978.

114. Espinel CH, Gregory AW: Differential diagnosis of acute renal failure. Clin Nephrol 13:73, 1980.

115. Zager RA, Rubin NT, Ebert T et al: Rapid radioimmunoassay for diagnosing acute tubular necrosis. Nephron 26:7, 1980.

116. Miller PD, Krebs RA, Neal BJ et al: Polyuric prerenal failure. Arch Intern Med 140:907, 1980.

117. Heimann T, Brau S, Sakurai H et al: Urinary osmolal changes in renal dysfunction following open-heart operations. Ann Thorac Surg 22:44, 1976.

118. Doolan PD, Alpen EL, Theil GB: A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 32:65, 1962.

119. Bull GM, Joekes AM, Lowe KG: Renal function studies in acute tubular necrosis. Clin Sci 9:379, 1950.

120. Handa SP, Morrin PAF: Diagnostic indices in acute renal failure. Can Med Assoc J 96:78, 1967.

121. Perlmutter M, Grossman SL, Rothenberg S et al: Urine-serum urea nitrogen ratio: Simple test of renal function in acute azotemia and oliguria. JAMA 170:1533, 1959.

122. Chisholm GD, Charlton CAC, Orr WM: Urine-urea/blood-urea ratios in renal failure. Lancet 1:20, 1966.

123. Luke RG, Briggs JD, Allison MEM et al: Factors determining response to mannitol in acute renal failure. Am J Med Sci 259:168, 1970.

124. Espinel CH: The FE Na test: Use in the differential diagnosis of acute renal failure. JAMA 236:579, 1976.

125. Diamond JR, Yoburn DC: Nonoliguric acute renal failure associated with a low fractional excretion of sodium. Ann Intern Med 96:597, 1982.

126. Brown RS: Renal dysfunction in the surgical patient: Maintenance of the high output state with furosemide. Crit Care Med 7:63, 1979.

127. Brosius FC, Lau K: Low fractional excretion of sodium in acute renal failure: Role of timing of the test and ischemia. Am J Nephrol 6:450, 1986.

128. Fang LST, Sirota RA, Ebert TH et al: Low fractional excretion of sodium with contrast media-induced acute renal failure. Arch Intern Med 140:531, 1980.

129. Saha H, Mustonen J, Helin H et al: Limited value of the fractional excretion of sodium test in the diagnosis of acute renal failure. Nephrol Dial Transplant 2:79, 1987.

130. Vaz AJ: Low fractional excretion of urine sodium in acute renal failure due to sepsis. Arch Intern Med 143:738, 1983.

131. Steiner RW: Interpreting the fractional excretion of sodium. Am J Med 77:699, 1984.

132. Zarich S, Fang LST, Diamond JR: Fractional excretion of sodium: Exceptions to its diagnostic value. Arch Intern Med 145:108, 1985.

133. Jones LW, Weil MH: Changes in urinary output and free water clearance in patients with acute circulatory failure (shock). J Urol 102:121, 1969.

134. Baek SM, Brown RS, Shoemaker WC: Early prediction of acute renal failure and recovery. I. Sequential measurements of free water clearance. Ann Surg 177:253, 1973.

135. Shin B, Isenhower NN, McAslan TC et al: Early recognition of renal insufficiency in post-anesthetic trauma victims. Anesthesiology 50:262, 1979.

136. Kosinski JP, Lucas CE, Ledgerwood AM: Meaning and value of free water clearance in injured patients. J Surg Res 33:184, 1982.

137. Sladen RN, Endo E, Harrison T: Two-hour versus 22-hour creatinine clearance in critically ill patients. Anesthesiology 67:1013, 1987.

138. Wheeler LA, Sheiner LB: Clinical estimation of creatinine clearance. Am J Clin Pathol 72:27, 1979.

139. Greenblatt DJ, Ransil BJ, Harmatz JS et al: Variability of 24-hour urinary creatinine excretion by normal subjects. J Clin Pharmacol 16:321, 1976.

140. Price RG: Urinary enzymes: Nephrotoxicity and renal disease. Toxicology 23:99-134, 1982.

141. Mueller PW, MacNeal ML, Steinberg KK: N-acetyl-beta- D-glucosamini-dase assay in urine urea inhibition. J Anal Toxicol 13:188-190, 1989.

142. Stolarek I, Howey JE, Frazer CG: Biological variation of urinary NAG: Practical and clinical implications. Clin Chem 35:560-563, 1989.

143. Yeun CT, Price RG, Chattagoon L et al: Colorimetric assays for N-acetyl-beta- D-glucosaminidase in human urine using newly developed nitrostyryl substrates. Clin Chim Acta 124:195-204, 1982.

144. Hofmann W, Guder WG: A diagnostic program for quantitative analysis of proteinuria. J Clin Chem Clin Biochem 27:589-600, 1989.

145. Robinson D, Sterling S: N-acetyl-beta-glucosaminidases in human spleen. Biochem J 107:321-327, 1968.

146. Price RG, Dance N, Richards B et al: The excretion of N-acetyl-beta-glucosaminidase and beta-galactosidase following surgery to the kidney. Clin Chim Acta 27:65-72, 1970.

147. Tucker SM, Pierce RJ, Price RG et al: Characteristics of human NAG isoenzymes as an indicator of tissue damage and disease. Clin Chim Acta 102:29-40, 1980.

148. Whiting PH, Peterson J, Power DA et al: Diagnostic value of urinary N-acetyl-beta- D-glucosaminidase, its isoenzymes and the fractional excretion of sodium following renal transplantation. Clin Chim Acta 130:369-376, 1983.

149. Eti S, Cheng CY, Marshall A et al: Urinary clusterin in chronic nephrotoxicity in the rat. Proc Soc Exp Biol Med 202:487-490, 1992.

150. Karlsson FA, Wibell L, Evrin PE: Beta-2-microglobulin in clinical medicine. Scan J Clin Lab Invest 154:27-37, 1980.

151. Norden AGW, Flynn FV: Degredation of beta2-microglobulin in infected urine by leukocyte elastase activity. Clin Chim Acta 134:167-176, 1983.

152. Barger AC, Herd JA: Renal vascular anatomy and distribution of blood flow. In Orlaff J, Berliner RW (eds): Handbook of Physiology. Section 8. Baltimore, Williams & Wilkins, 1973, p 249.

153. Kreisberg JI, Venkatachalam MA: Morphologic factors in acute renal failure. In Brenner BM, Lazarus JM (eds): Acute Renal Failure. 2nd ed. New York, Churchill Livingstone, 1988, p 45.

154. Arendshorst WJ, Finn WF, Gottschalk CW: Pathogenesis of acute renal failure following temporary renal ischemia in the rat. Circ Res 37:558, 1975.

155. Trueta J, Barclay AE, Daniel PM et al: Studies on the Renal Circulation. Oxford, Blackwell Scientific Publications, 1947.

156. Carriere S, Thorburn GD, O'Morchoe CCC et al: Intrarenal distribution of blood flow in dogs during hemorrhagic hypotension. Circ Res 19:167, 1966.

157. Hollenberg NK, Epstein M, Rosen SM et al: Acute oliguric renal failure in man: Evidence for preferential renal cortical ischemia. Medicine (Baltimore) 47:455, 1968.

158. Barger AC, Herd JA: The renal circulation. N Engl J Med 284:482, 1971.

159. Logan A, Jose P, Eisner G et al: Intracortical distribution of renal blood flow in hemorrhagic shock in dogs. Circ Res 29:257, 1971.

160. Rector JB, Stein JH, Bay WH et al: Effect of hemorrhage and vasopressor agents on distribution of renal blood flow. Am J Physiol 222:1125, 1972.

161. Auckland K: Intrarenal distribution of blood flow: Are reliable methods available for measurements in man? Scand J Clin Lab Invest 34:481, 1975.

162. Aukland K, Loyning EW: Intrarenal blood flow and para-aminohippurate (PAH) extraction. Acta Physiol Scand 79:95, 1970.

163. Reubi FC, Gossweiler N, Gurtler R: Renal circulation in man studied by means of a dye-dilution method. Circulation 33:426, 1966.

164. Haywood GA, Stewart JT, Counihan PJ et al: Validation of bedside measurements of absolute human renal blood flow by a continuous thermodilution technique. Crit Care Med 20:659, 1992.

165. Thorburn GD, Kopald HH, Herd A et al: Intrarenal distribution of nutrient blood flow determined by krypton 85 in the unanesthetized dog. Circ Res 13:290, 1963.

166. Grunfeld J-P, Sabto J, Bankir L et al: Methods for measurement of renal blood flow in man. Semin Nucl Med 4:39, 1974.

167. Farmelaut MH, Burrows BA: The renogram: Physiologic basis and current clinical use. Semin Nucl Med 4:61, 1974.

168. Stevens PE, Gwyther SJ, Hanson ME et al: Noninvasive monitoring of renal blood flow characteristics during acute renal failure in man. Intensive Care Med 16:153, 1990.

169. Heidenreich P, Wiencek JG, Zaroff JG et al: In vitro flow calculation using contrast echocardiography. J Am Soc Echocardiogr 6:51-61, 1993.

170. Aronson S, Feinstein SB, Wiencek JG et al: Assessment of renal blood flow with contrast ultrasonography. Anesth Analg 76:964-970, 1993.

171. Aronson S, Thisthelwaite R, Walker R et al: Determination of renal blood flow during surgery with perfusion ultrasonography. Anesth Analg 80:353-359, 1995.

172. Aronson S, Bilotta F, Wiencek JG et al: Assessment of renal blood flow distribution in dogs with contrast ultrasound following dopamine infusion. Anesth Analg 74:S11, 1992.

173. Kainuma M, Kimura N, Shimada Y: Effect of acute changes in renal arterial blood flow on urine oxygen tension in dogs. Crit Care Med 18:309, 1990.

174. Rennie DW, Reeves RB, Pappenheimer JR: Oxygen pressure in urine and its relation to intrarenal blood flow. Am J Physiol 195:120, 1958.

175. Hong SK, Boylan JW, Tannenberg AM et al: Total and partial gas tensions of human bladder urine. J Appl Physiol 15:115, 1960.

176. Brezis M, Rosen SN, Epstein FH: The pathophysiological implications of medullary hypoxia. Am J Kidney Dis 13:253, 1989.

177. Brezis M, Rosen S, Spokes K et al: Transport-dependent anoxic cell injury in the isolated perfused rat kidney. Am J Pathol 116:327, 1984.

178. Brezis M, Rosen S, Silva P et al: Transport activity modifies thick ascending limb damage in the insulated perfused kidney. Kidney Int 25:65, 1984.

179. Brezis M, Rosen S, Silva P et al: Polyene toxicity in renal medulla: Injury mediated by transport activity. Science 224:66, 1984.

180. Brezis M, Greenfeld Z, Shina A et al: Angiotensin II (AII) augments medullary hypoxia and predisposes to acute renal failure. Kidney Int 33:354, 1988.

181. Heyman S, Brezis M, Greenfeld Z et al: Protective role of furosemide and saline in radiocontrast-induced acute renal failure. Clin Res 36:520A, 1988.

182. Dinour D, Brezis M: Effects of adenosine upon intrarenal oxygenation. Am J Physiol 261:787, 1991.

183. Brezis M, Heghan SN, Dinour D et al: Role of nitric oxide in renal medullary oxygenation. J Clin Invest 88:390, 1991.

184. Williams CD, Dawidson IJA, Dickerman R et al: Intraoperative blood volume expansion induces primary function after renal transplantation: A study of 96 paired cadaver kidneys. Transplant Proc 23:1338, 1991.

185. Hostetter TH, Wilkes BM, Brenner BM: Mechanisms of impaired glomerular filtration in acute renal failure. In Brenner BM, Stein JH (eds): Acute Renal Failure. New York, Churchill Livingstone, 1980, p 52.

186. Beeuwkes R, Bonventre JV: Tubular organization and vascular tubular relations in the dog kidney. Am J Physiol 229:695, 1975.

187. Lang RM, Feinstein SB, Powsner SM et al: Contrast ultrasonography: A new method for evaluation of renal perfusion in vivo. Circulation 75:229, 1987.

188. Campbell JAH, Conigall AV, Guy A et al: Immunohistologic localization of alpha, mu, and pi class glutathione S-transferases in human tissue. Cancer 67:1608-1613, 1991.

189. Baines AD: Strategies and criteria for developing new urinalysis tests. Kidney Int Suppl 47:S137-S141, 1994.

Chapter 35 - Neurologic Monitoring

Susan Black
Michael E. Mahla
Roy F. Cucchiara

INTRODUCTION

The evaluation of neurologic signs was one of the earliest scientific approaches to judging the effects of anesthetics on the brain. In the 1940s Guedel proposed the use of pupillary signs as a guide to determining the depth of anesthesia. As the patient passes through the stages of anesthesia, the pupils change from normal when awake to dilated during the excitement phase of stage II. In early stage III the pupils constrict secondary to the loss of cortical inhibitory effects on the Edinger-Westphal nucleus. In deeper planes of stage III the pupils progressively dilate as paralysis of the fibers of the pupiloconstrictor muscles ensues.

Modern anesthetic techniques usually combine inhaled anesthetics with intravenously administered drugs or supplemental drugs (e.g., opioids); therefore, eye signs are no longer as helpful in determining anesthetic depth as they once were. The development of modern electronics and microprocessors has made possible the rapid evaluation of electrical data from the body to permit nearly real-time evaluation of nervous system function.

This chapter focuses on monitoring the intact nervous system using electronic instruments, examines some of the electroneurophysiologic and pathologic changes that occur acutely in the operating room, and shows how these signals are altered by commonly used anesthetics.

MONITORING MODALITIES

The technology that is most available in sophisticated operating rooms today is the electroencephalogram (EEG), evoked potentials (EP), and electromyogram (EMG). The EEG is used to help identify pathologic brain findings, define clinical problems, and predict outcome of brain insults. These uses are the result of correlation of pattern recognition with clinical states of over nearly half a century of experience. The encephalographer can accurately identify consciousness, unconsciousness, epilepsy, sleep, and coma. The correlation between EEG pattern and anesthetic depth is less clear, perhaps because of the variety and types of drugs used in anesthesia and the subtle loss of awareness. The electrode records activity from the brain tissue nearest to it, and all areas of the brain do not respond identically to the same anesthetic drug level. Precise assessment of anesthetic depth by EEG is possible with certain specific drugs at specific levels of anesthesia. The steps in the continuum from awake to deeply anesthetized are not all equally clear, but some general patterns are described. Computer advances have made possible high-speed mathematic manipulation of the EEG signal to present it in a more readable fashion. Interpretation of the raw EEG is still largely dependent on the experience of the reader.

Evoked potentials are measurements of electrical potential changes that pass along stimulated nervous tissue. The voltages generated in this process are quite small and are obscured by the higher voltages produced by the EEG. Repeated sampling and sophisticated electronic summation and averaging techniques are needed to extract the evoked potential signal from the background EEG.

Sensory evoked potentials are by far the most common type of evoked potentials monitored intraoperatively. During the last decade much research has been carried out regarding the use of intraoperative motor evoked potentials; however, motor evoked potentials are used routinely only in a very few centers currently. There are three basic types of sensory evoked potentials: somatosensory (SSEP), auditory (BAEP), and visual (VEP). The SSEP is used to assess a peripheral nerve to central nervous system pathway. The BAEP is a measure of conduction along cranial nerve VIII, through brain-stem structures, and out to the cortex. The VEP utilizes stimulation of the light receptors of the retina to evaluate pathways from the optic nerve to the occipital cortex.

THE STANDARD EEG

The Signal

The technical goal of the EEG is to provide a clear signal free of electrical noise and permit anatomic localization of the various signals generated. The recording electrode impedance should be about 5 kOmega to permit clear EEG signals in the 10- to 50-muV range. As electrode impedance increases, the signal to noise ratio decreases, which permits the background electrical "noise" to obscure the EEG signal. Impedance is kept low by using silver electrodes with electrolyte gel between the scalp and electrode and holding the electrode tightly to the scalp with colloidin. When wick electrodes are applied directly to the brain surface, impedance is decreased by saturation of the wick with an electrolyte solution.

The recording montage permits anatomic localization of the signal. The standard EEG montage is the 10-20 system (Fig. 35-1) (Figure Not Available) . This system is a symmetric array of scalp electrodes 10 percent of the circumferential distance above the inion and external auditory meatus and 20 percent of the circumferential distance apart. Twenty recording electrodes are used with one or more reference electrodes placed outside the recording field. This set-up permits the encephalographer to select a pair of electrodes with a discrete anatomic location from which to record. The standard is a 16-channel recording. [1]

Recordings of electrical activity of the brain may be made directly from microelectrodes to measure activity from an individual unit or from larger electrodes to record from the brain surface or from the scalp. The conventional EEG is recorded from the scalp; the recording from the surface of the brain is the electrocorticogram (ECoG). The generators of these waveforms are not clearly defined, although the patterns have been well described and correlated with clinical and pathologic conditions.

The EEG signal contains three basic parameters: amplitude, frequency, and time. Amplitude is the electrical height of the wave in V. Frequency can be thought of simply as the number of times per second the wave crosses the zero voltage line. Time is the duration of the sampling of the signal; this is continuous and is real time in the standard EEG but is a sample epoch in the processed EEG.

The Normal EEG

The patterns seen on the EEG vary somewhat among individuals but are consistent enough to allow for accurate recognition. The usual base frequency in the awake patient is the beta range (>13 Hz). This high-frequency and usually low-amplitude signal is common from the alert attentive brain. With the action of closing the eyes, the tracing immediately adds signals from the alpha range (8-13 Hz) with a slightly higher amplitude (Fig. 35-2) (Figure Not Available) . This range is usually used as a reference signal during anesthesia. When events that lead the brain to produce higher frequencies occur, the EEG is described as "activated," and when slower frequencies are produced (theta at 4-7 Hz and delta at 4 Hz) the EEG is "depressed." The sleep EEG may contain all of these frequencies at various times. The slower frequencies occur during deep natural sleep with sleep spindles (Fig. 35-3) (Figure Not Available) , but during light sleep (rapid eye movement [REM] sleep) the EEG becomes activated and the eye muscle EMG appears on the EEG.

General characteristics of the normal EEG are that it is symmetric, the patterns are predictable, spike waveforms are absent, and it cannot be used to predict normal brain function.

The Abnormal EEG

General characteristics of the "abnormal" EEG are asymmetry and patterns of amplitude and frequency that are not predictable or expected in the usual recording. These reflect either anatomic or metabolic alteration in the underlying brain. Regional asymmetry can be seen with tumor, epilepsy, and cerebral infarction. Epilepsy may be recognized by high-voltage spike waves, whereas cerebral infarction may appear as a low voltage and low frequency pattern, as compared to the rest of the brain tracing. Global distortions of the EEG are not asymmetric because there is no normal side with which to compare the tracing. Identifying "abnormality" in global EEG patterns that deviate from normal is very important in the clinical situation. Epilepsy, hypoxia, and anesthetic effects are examples.

PROCESSED EEG

The interpretation of the standard written EEG record is both a science and an art. The waveforms are the data base for the interpretation; qualitative overall impression of the record is the experience. Both are important in arriving at a diagnosis. Until recent years the latter approach was dominant simply because the waveforms could not be described mathematically in a time frame that would make such a data base of any use. Mainframe computers then began to convert the analogue signal of the EEG to a digital signal and

---

Figure 35-1 (Figure Not Available) International 10-20 system of electrode placement for recording EEG as well as SEP. *(From Hughes [1])*

mathematically manipulate the data. The process was complex, expensive, and still had little relevance to the clinician. Early techniques took 1 hour to digitize and analyze 1 second of EEG data. The hardware capability of computers has exploded during the past decade and has caught up with the mathematic potential available in analysis of complex waveforms. Real-time on-line processing that previously required mainframe computer capability began to appear as the EEG processor "black box" developed.

A number of assumptions must be made when moving to the processed EEG. First, as the processed EEG signal becomes more electronically remote (more processed), there is a point where it will be increasingly difficult or even impossible to relate what we know about the raw EEG data to

Figure 35-2 (Figure Not Available) The loss and return of alpha-activity as the eyes open and close can be seen. The large spikes are muscle artifact. *(By permission of the Mayo Foundation)*

Figure 35-3 (Figure Not Available) Characteristic "sleep spindles" in normal sleep are shown in the center. *(By permission of the Mayo Foundation)*

comprehension of the processed signal; this is true of many of the processed EEG displays utilized today. Increasingly, clinicians with no experience in interpreting raw EEG data are utilizing processed EEG with little ability to understand how it relates to the original raw data. Second, the standard 16-channel EEG montage provides more information than can be consistently utilized in processed EEG and more than is needed for routine intraoperative use. Third, because the processed EEG is derived from the raw EEG, it will not contain information that is not in the original signal. Derivations of the original signal may include computational displays and algorithms, but the data base can only be the original signal. Fourth, some of the diagnostic changes will be unilateral and some bilateral. Display of the activity of both hemispheres is necessary to delineate unilateral from bilateral changes. An appropriate number of leads is needed. The gold standard for EEG analysis is the continuous visual inspection of a 16- to 20-channel ink-on-paper EEG by an experienced electroencephalographer. [2] [3]

Devices

There are specific frequency and amplitude ranges that seem to be important in the EEG under anesthesia. The simplest way to remove artifact and accentuate the waves of interest is to use a system of filters and amplifiers so that frequencies above 20 Hz are filtered out, and waves between 4 and 10 Hz are selectively amplified. There are two basic forms of EEG processing utilized currently: power analysis and bispectral analysis. Power analysis utilizes Fourier transformation to convert the raw EEG signal into its component sine waves of an identifiable frequency and amplitude. The raw EEG data, which is a plot of amplitude over time can then be converted to plot amplitude of EEG activity at each frequency at a given point in time. Many commercially available processed EEG machines display power that is amplitude squared as function of frequency. These monitors may then display the data in two general forms, either compressed spectral array (CSA) or density spectral array (DSA). In CSA, frequency is displayed along the x axis and power along the y axis with height of the waveform equal to the power at that frequency. Time is displayed along the z axis with the tracings overlapping each other, with the most recent in front (Fig. 35-4) (Figure Not Available) . DSA displays frequency along the x axis, time along the y axis, and power is reflected by the density of the dot at each frequency. Each display format provides the same data, and choice depends simply on the preference of the user. Many changes that occur under anesthesia are reflected as changes in amplitude, frequency, or both. These changes can be clearly seen in these displays if adequate and appropriate channels are monitored. Power analysis has been utilized clinically for many years as a diagnostic tool during procedures with risk for intraoperative cerebral ischemia such as carotid endarterectomy and cardiopulmonary bypass. Power analysis has proven to be a sensitive and reliable monitor in the hands of experienced operators utilizing an adequate number of channels. In addition, parameters obtained from power analysis have been investigated as monitors for depth of anesthesia. [4] This application has not yet found widespread use.

On the other hand, bispectral analysis also takes into account the phase relationships between the individual components of the raw EEG signal. The phase relationships are not included in power analysis. Bispectral analysis is a more recent modality and, currently, the primary use is as a monitor of anesthetic depth. Although the bispectral analysis may also yield components indicative of cerebral pathologic states developing

Figure 35-4 (Figure Not Available) Diagram of technique used to generate compressed spectral array. Example below shows compressed spectra of the alpha-rhythm from a normal subject. *(From Stockard and Bickford [27])*

---

intraoperatively, such as cerebral ischemia, monitors utilizing this technology in a diagnostic mode are not available. [5]

Data Acquisition Period

An important consideration in the processed EEG is the element of time. The standard EEG is continuous in real time. The processed EEG usually obtains its data over a given time period (epoch), processes the data, and then displays them. There is a relationship between epoch length and spectral resolution. If an infinite epoch length is chosen, the waveform can be described precisely. If a short length is selected, three main factors mitigate against mathematic precision: the epoch sampled may not be representative of the overall activity, the nature of the data window becomes increasingly important, and there may be insufficient data points for Fourier transformation. This issue, as related to the intraoperative EEG for anesthetic depth, has been studied by Levy. [6] A longer epoch may produce less epoch-to-epoch variability and allow more precise description of frequency and power; however, the longer epoch increases the delay before new information is processed and displayed, thereby reducing the amount of information available for clinical decision making. In studying EEG epochs of 2 to 32 seconds, Levy

concluded that 2-second epochs are appropriate during general anesthesia. Burst suppression is an exception, however, because of the possibility of sampling primarily during burst or suppression periods. This shortcoming is not a major one because this pattern is easily identified on raw EEG and is expected with use of barbiturates in anesthesia.

ANESTHESIA AND THE EEG

With the advent of the then "high-tech" EEG in 1950, Courtin et al [7] sought to monitor the brain and devise a servo-controlled system that could adjust the anesthetic concentration administered on the basis of the EEG pattern. It was an ingenious idea, but despite descriptions of the EEG during anesthesia, knowledge and technology were not adequate at that time. In addition, because all anesthetic drugs do not produce exactly the same changes in EEG pattern as anesthesia deepens, generic correlation of the EEG with depth of anesthesia remains an elusive goal. One of the major reasons that EEG is difficult to use for assessing anesthetic depth is that most modern anesthetics utilize many different classes of drugs for premedication, induction, and maintenance of anesthesia, all of which have significant EEG effects. In addition, other intraoperative factors may affect the EEG (Table 35-1) , further adding to the difficulty of interpreting the EEG.

In recent years much research has been directed at developing a processed EEG parameter that is indicative of depth of anesthesia. These processed parameters fall into two broad categories: parameters derived from power analysis of the raw EEG data and parameters derived from bispectral analysis of the EEG. Power analysis processes data from the raw EEG related to frequency and amplitude

TABLE 35-1 -- Nonanesthetic Factors Affecting the EEG During Anesthesia

SURGICAL FACTORS	PATHOPHYSIOLOGIC FACTORS
Cardiopulmonary bypass	Hypoxemia
Occlusion of major cerebral vessel (carotid endarterectomy, aneurysm clipping)	Hypotension Hypothermia Hypercarbia and hypocarbia
	Untoward events
	Brain death

of the waveforms over time but does not consider phase relationships between the component waves. Bispectral analysis is a somewhat more complex process that includes phase relationship data. Processed parameters from power analysis investigated as indicators for depth of anesthesia include Spectral Edge Frequency 95% (SEF95), which is the frequency below which 95% of the EEG activity falls; Median Frequency (frequency at the midpoint of the power spectrum); and Relative Delta Power (percent of the EEG power in the delta band). Some authors have had success in utilizing one or more of these parameters to predict depth of anesthesia. [4] Other authors have found that although these parameters change with changes in depth of anesthesia, they were not consistently predictive of depth of anesthesia as assessed by response to stimuli or return of consciousness during emergence from anesthesia. [8] [9] In particular it has been noted that these parameters are very dependent on the type of anesthetic agent or combination of agents utilized. Whereas one parameter might correlate well with a primarily volatile anesthetic technique, it might perform less consistently during a narcotic-based anesthetic.

Most recently, encouraging results have been obtained using the bispectral index (BIS) to monitor anesthetic depth (Ch. 29) . The bispectral index is a processed parameter derived from multiple features generated by bispectral analysis of the EEG. Through clinical trials, features of the bispectral analysis that were predictive of response to stimuli under the effects of a variety of anesthetic agents were identified. These features were combined to a multivariate index using discriminant analysis. [5] [10] Once the BIS was developed, it was further tested and refined to improve the predictive ability. [10] The BIS is displayed as a numeric value from 0 to 100 and can be trended over time. Many clinical trials have investigated the ability of BIS to monitor anesthetic depth and predict response to stimuli. Trials have been directed at determining values of BIS predictive of loss of consciousness, loss of recall, and prevention of movement in response to surgical stimulation. The BIS value indicative of a certain level of consciousness varies somewhat between different anesthetic techniques [10] ; however, the ability of the BIS to predict loss of consciousness and lack of recall during sedation has been consistently demonstrated by a number of authors using a variety of drugs and drug combinations. [4] [10] On the other hand, the ability of BIS to predict hemodynamic response to surgical stimulation or movement in response to surgical stimulation has been less consistently demonstrated and may be more dependent on the anesthetic technique. [11] [12] These results

Figure 35-5 BIS tracings from an awake craniotomy with intraoperative cortical mapping. Propofol infusion was titrated against BIS value to provide adequate sedation during the operative procedure. Termination of the propofol infusion during the cortical mapping is followed by a prompt increase in BIS value and recovery of the patient to fully alert.

have suggested to some that the anesthetic state involves at least two different components. One is a reflection of hypnosis and consists of loss of consciousness and recall; BIS is indicative of this state. However, the obtundation of response to noxious stimuli is less well predicted by BIS. [10] BIS monitoring of level of sedation during an awake craniotomy with cortical mapping is shown in Figure 35-5 .

Anesthetic drugs affect both the frequency and amplitude of EEG waveforms. Although each drug class and each specific drug has some specific, dose-related EEG effects (Table 35-2) , some generalizations (basic anesthesia-related EEG pattern) are possible. Subanesthetic doses of both intravenous and inhaled anesthetics usually produce an increase in frontal beta activity and abolish the alpha activity normally seen in the occipital leads in the awake, relaxed patient with the eyes closed. As the patient actually goes to sleep with general anesthesia, the brain waves become larger in amplitude and slower in frequency. In addition, under general anesthesia, the alpha EEG frequencies are primarily seen in the frontal EEG leads rather than in the occipital leads. Further increases in the dose of the inhalation or intravenous agent produce further slowing of the EEG, and some agents have the capability to totally suppress EEG activity (see Table 35-2) . Other agents never produce burst suppression or an isoelectric EEG, despite increasing dose either because they are incapable of suppressing the EEG (e.g., opioids) or because cardiovascular toxicity of the drug (e.g., halothane) prevents administration of a large enough dose.

Intravenous Anesthetic Drugs

Barbiturates, Propofol, and Etomidate

Despite widely varying potencies and durations of action, all of these drugs produce similar EEG patterns (Fig. 35-6 (Figure Not Available) shows EEG effects of thiopental). These drugs all follow the basic anesthesia-related EEG pattern described previously with initial EEG activation (see Fig. 35-6 (Figure Not Available) A), followed by dose-related depression. As the patient loses consciousness, characteristic frontal spindles are seen (see Fig. 35-6 (Figure Not Available) B), which are

replaced by polymorphic 1- to 3-Hz activity (see Fig. 35-6 (Figure Not Available) C) as the drug is further administered. Increases in dose result in lengthening periods of suppression interspersed with periods of activity (burst suppression). With a very high dose, EEG silence results. All these drugs have been reported to cause epileptiform activity in humans, but epileptiform activity is clinically significant only following methohexital and etomidate.

Ketamine

Ketamine does not follow the basic anesthesia-related EEG pattern. Anesthesia with ketamine is characterized by frontally dominant rhythmic theta activity with increased amplitude. Increased doses produce intermittent polymorphic delta activity of very large amplitude interspersed with

TABLE 35-2 -- Anesthetic Drugs and the EEG

DRUG	EFFECT ON EEG FREQUENCY	EFFECT ON EEG AMPLITUDE	BURST SUPPRESSION?
Isoflurane			Yes, >1.5 MAC
Subanesthetic	Loss of alpha, frontal beta		
Anesthetic	Frontal 4-8 Hz activity		
Increasing dose >1.5 MAC	Diffuse theta and delta burst suppression silence	0	
Desflurane	Similar to equi-MAC dose of isoflurane	Similar to equi-MAC dose of isoflurane	Yes, >1.2 MAC
Sevoflurane	Similar to equi-MAC dose of isoflurane	Similar to equi-MAC dose of isoflurane	Yes, >1.2 MAC
Nitrous oxide (alone)	Frontal fast oscillatory activity (>30 Hz)	, especially with inspired concentration >50%	No
Enflurane			Yes, >1.5 MAC
Subanesthetic	Loss of alpha, frontal beta		
Anesthetic	Frontal 7-12 Hz activity		
Increasing dose >1.5 MAC	Spikes/spike and slow waves burst suppression; hypocapnia seizures		
Halothane			Not seen in clinically useful dosage range
Low dose	Frontal 10-20 Hz activity		
Moderate dose	Frontal 10-15 Hz activity		
Increasing dose >1.5 MAC	Diffuse theta, slowing with increasing dose		
Barbiturates			Yes, with high doses
Low dose	Fast frontal beta-activity	Slight	
Moderate dose	Frontal alpha-frequency spindles		
Increasing high dose	Diffuse delta burst suppression silence	0	
Etomidate			Yes, with high doses
Low dose	Fast frontal beta-activity		
Moderate dose	Frontal alpha-frequency		
Increasing high dose	Diffuse delta burst suppression silence	0	
Propofol			Yes, with high doses
Low dose	Loss of alpha, frontal beta		
Moderate dose	Frontal delta, waxing/waning alpha		
Increasing high dose	Diffuse delta burst suppression silence	0	
Ketamine			No
Low dose	Loss of alpha, variability		
Moderate dose	Frontal rhythmic theta		
High dose	Polymorphic delta, some beta	(beta is low amplitude)	
Benzodiazepines			No

Low dose	Loss of alpha, increased frontal beta-activity		
High dose	Frontally dominant delta and theta		
Opiates			No
Low dose	Loss of beta, alpha slows		
Moderate dose	Diffuse theta, some delta		
High dose	delta, often synchronized		

delta-<4 Hz frequency; theta-4-7 Hz frequency; alpha-8-13 Hz frequency; beta->13 Hz frequency; MAC-minimum alveolar concentration

low-amplitude beta activity. [13] Electrocortical silence cannot be produced with ketamine. EEG activity may be very disorganized and variable at all doses. Recovery of EEG activity even after a single bolus dose of ketamine is relatively slow compared to barbiturates. There is no information available about the relationship between emergence reactions following ketamine and the EEG. Ketamine has also been associated with increased epileptiform activity. [13]

Benzodiazepines

Despite varying potencies and durations of actions, benzodiazepines also follow the basic anesthesia-related EEG pattern. As a class, however, these drugs are incapable of producing burst suppression or an isoelectric EEG.

Opioids

Opioids do not, as a class, follow the basic anesthesiarelated EEG pattern. In general, opioids produce a doserelated decrease in frequency and increase in amplitude of the EEG. If further doses of opiates are not given, alpha and beta activity will eventually return. The rapidity of return depends on the initial dose and on the drug. Remifentanil is associated with the most rapid return to normal. [14] Complete suppression of the EEG cannot be obtained with the opioids.

Figure 35-6 (Figure Not Available) EEG effects of intravenous administration of thiopental in humans. (A) Rapid activity; (B) barbiturate spindles; (C) slow waves; (D) burst suppression. *(From Clark and Rosner [138])*

Epileptiform activity occurs both in humans and in animals receiving large to supraclinical doses of opioids. For example, sharp wave activity is relatively common after induction of anesthesia with fentanyl with 20 percent of patients showing this phenomenon after 30 mug/kg, 60 percent at 50 mug/kg, 58 percent at 60 mug/kg, and 80 percent at 70 mug/kg. This activity is mainly noted in the frontotemporal region. [15]

Inhaled Anesthetics

Nitrous Oxide

Used alone, nitrous oxide causes a decrease in amplitude and frequency of the dominant alpha rhythm. With the onset of analgesia and depressed consciousness, frontally dominant fast oscillatory activity (>30 Hz) is frequently seen. [16] This activity may persist to some extent for up to 50 minutes after discontinuation of nitrous oxide. When nitrous oxide is used in combination with other agents, it increases the depth of anesthesia that would be associated with the agent alone, both clinically and with respect to the EEG pattern seen.

Isoflurane, Sevoflurane, Enflurane, Halothane, and Desflurane

Potent inhaled anesthetics follow the basic anesthesiarelated EEG pattern. Isoflurane causes a slowing of the EEG activity that increases with increasing depth of anesthesia. Isoflurane begins to produce periods of EEG suppression at 1.5 minimum alveolar concentration (MAC), which become longer with increasing dose until electrical silence is produced at 2 to 2.5 MAC. At times, an isolated spike wave can be seen during intersuppression activity at 1.5 to 2.0 MAC isoflurane. [17] Sevoflurane causes similar dose-dependent EEG effects as does isoflurane with equi-MAC concentrations of sevoflurane and isoflurane, causing similar EEG changes. [18] Epileptiform activity has not been

induced by administration of sevoflurane in patients without epilepsy; however, seizure activity on EEG, but not clinical seizure activity, has been reported in pediatric patients with a history of epilepsy during induction of anesthesia with sevoflurane. [19] The enflurane pattern is similar to that of isoflurane except that epileptiform activity is considerably more prominent. At 2 to 3 MAC, burst suppression is seen, but virtually all intersuppression activity consists of large spike and wave discharges. Hyperventilation with these high concentrations of enflurane increases the length of suppression, decreases the duration of bursts but increases the amplitude and main frequency component of the intersuppression activity. Frank EEG seizures may also occur that produce the same cerebral metabolic effects as pentylenetet-razol, a known convulsant. Halothane follows a pattern similar to that of isoflurane, but the greater degrees of EEG suppression seen with isoflurane are not seen with halothane until dosages associated with profound cardiovascular depression (3-4 MAC) are used. Desflurane produces EEG changes similar in nature to equi-MAC concentrations of isoflurane. In limited clinical studies, there has been no evidence of epileptiform activity with desflurane, despite hyperventilation and 1.6 MAC dosage. [20] Clinical studies have demonstrated that the EEG effects of inhalational anesthetic agents are influenced by age and baseline EEG characteristics. Older patients and those with EEG slowing at baseline were more sensitive to the EEG effects of isoflurane and desflurane. Similar changes were noted but at lower anesthetic concentrations. [21]

SURGERY AND THE EEG

Although EEG has not yet seen widespread use as a measure of depth of anesthesia, it has found much greater success as a monitor of the adequacy of cerebral blood flow, especially during carotid endarterectomy. Because anesthetic drugs do affect the EEG (see Table 35-2) , and many of these EEG changes may mimic EEG changes associated with inadequate cerebral blood flow, some guidelines about anesthetic management during EEG monitoring for cerebral ischemia might be helpful (Table 35-3) .

Cardiopulmonary Bypass

In humans there are always several circumstances that occur with the institution of cardiopulmonary bypass (CPB)

TABLE 35-3 -- Anesthetic Guidelines for Intraoperative Monitoring for Ischemia

1. No changes in anesthetic technique should be made during critical periods of monitoring (e.g., induced hypotension, carotid clamping, or aneurysm clipping).
2. Specifically avoid major changes in anesthetic gas levels or boluses of opiates, barbiturates, or benzodiazepines near times of increased ischemic risk.
3. If drugs must be given that create extreme EEG showing or an isoelectric pattern, it is sometimes possible to monitor SSEPs, which may remain relatively unaffected.

(Ch. 49) . For example, the level of anesthesia may be altered by CPB, alterations in arterial carbon dioxide tension and blood pressure may occur, and hemodilution with hypothermic perfusate may be used. These possible outcomes make it difficult to isolate the effects of CPB, brain perfusion, and anesthetic level on EEG. Profound EEG changes occur, sometimes asymmetrically, and interpretation is difficult at best. Levy has tried to distinguish the effects of hypothermia from other events occurring at the institution of bypass. [22] Assessment of anesthetic level during narcotic-based anesthesia suggests a shift to lower frequencies with production of an anesthetic state without recall. [23] Much work remains to be done in utilization of the processed EEG to provide information for clinical management of patients during CPB.

Carotid Endarterectomy

Of all the uses of the processed EEG, those events that are linked to a known event at a specific time and are unilateral, involving a large part of the hemisphere, are the easiest to interpret. These are the fortunate circumstances that are present when monitoring the brain of a patient undergoing carotid endarterectomy (Ch. 51) . The primary reason to monitor the brain during carotid endarterectomy is to acquire data to use as a basis for therapeutic intervention (e.g., placement of a shunt). We may fortuitously see changes in the processed EEG when a shunt becomes kinked or displaced or when cerebral emboli occur during dissection of the plaque, during hypotension, or even after the repair should a patient suffer intracerebral hemorrhage. But these are uncommon events. The main thrust of brain monitoring in carotid procedures is to aid in identifying the patient who needs a shunt. The concept of selective shunting is not agreed upon by all surgeons. Some never place a shunt and claim results that are nearly flawless. Others always place a shunt with similar results. If the processed EEG is not utilized to provide information for selective shunting, its usefulness is drastically reduced. If the processed EEG is to be used as a guide for shunting, then it must accurately identify those patients who are made critically ischemic by temporary unilateral occlusion of their carotid system.

Two issues impact the efficacy and reliability of processed EEG as a monitor for cerebral ischemia during carotid endarterectomy. First, what are the minimum number of channels (or areas of the brain) to be monitored? The 16-channel unprocessed EEG is clearly a reliable and sensitive monitor for intraoperative cerebral ischemia during carotid endarterectomy. In a series of over 2,000 patients monitored with 16-channel EEG at the Mayo Clinic, there were no false-negatives. [24] In other words, no patient had undetected intraoperative cerebral injury; however, 16-channel EEG monitored by a dedicated technician is not possible in the majority of operating rooms. Therefore, processed EEG using fewer than 16 channels is utilized much more commonly. Clinical experience as well as clinical investigations suggest that the minimum number of channels for adequate sensitivity and specificity are four channels (two per side). When a limited number of channels was compared to 16-channel EEG monitoring, 100 percent sensitivity and specificity were obtained utilizing 2 channels per hemisphere,

Figure 35-7 (Figure Not Available) This Lifescan printout was obtained approximately 3 minutes after occlusion (XC) of the left carotid artery. It shows attenuation of activity on the left with occlusion. The EEG showed a similar change. The rCBF with occlusion was 9 mL/100 g/min. *(From Spackman et al [26])*

provided those channels monitored the middle cerebral artery territory. These results were obtained with the combination of a frontoparietal channel with a frontotemporal channel. [25] The second issue is the experience level of the observer monitoring the processed EEG. Is a dedicated, experienced technician or electroencephalographer needed? In a study addressing this question, the 16-channel unprocessed EEG monitored by a dedicated technician was compared to a processed EEG reviewed by three anesthesiologists of differing levels of experience with processed EEG. Fifty patients undergoing carotid endarterectomy were studied to compare the processed EEG to the full 16-channel EEG and regional cerebral blood flow measurements as indicators of cerebral ischemia. [26] The three anesthesiologists interpreted the tracings without knowledge of the case. They were presented only with the written trace with an indication of the point at which the carotid was clamped (Fig. 35-7) (Figure Not Available) . The accuracy of interpretation hinges on the false-negative result. If a false-negative finding is read, the surgeon might fail to shunt an ischemic patient. A false-positive result is less of a problem because that patient is not ischemic but is given a shunt anyway.

The predictive value of the anesthesiologist being correct in interpreting the trace as unchanged after clamping was 91 to 98 percent, which indicates that the device can be used by relatively novice interpreters with fair accuracy to determine the presence of cerebral ischemia at the time of carotid occlusion. In this study, the review by the anesthesiologist was not carried out during the course of the procedure but rather "off line." As such it does not address the issue of whether an anesthesiologist providing the intraoperative anesthetic management of the patient can provide adequate monitoring of the processed EEG simultaneously.

Surgery for Epileptic Foci

It has long been recognized that seizures can begin with a focus of electrical synchrony that spreads to include the remainder of the cortex. Localization of such a focus at the operating table is an important part of present-day surgery for drug-resistant seizures. This localization is performed by electrocorticography in either the awake patient or by provocation during general anesthesia. At some centers, the electrocorticography leads are placed in the awake patient, and mapping is done in the EEG laboratory. The patient then returns another day for resection of the excitable focus under either local or general anesthesia. The anesthetic level is minimized, and a provocative technique such as hyperventilation or small-dose barbiturate administration can be employed to trigger the focus so as to aid in its localization. If the cortex is excessively depressed pharmacologically, seizure activity cannot be provoked. Intraoperative seizure mapping requires the involvement of

an electroencephalographer familiar with this technique. Rarely would an anesthesiologist possess the expertise required for intraoperative seizure focus localization.

/das/book/view/29494766/875/395.html

PATHOPHYSIOLOGIC EFFECTS ON THE EEG

Hypoxia

"Slowing" of the EEG during hypoxia is a nonspecific global effect. Fast frequencies are lost, and low frequencies dominate. Eventually, the EEG is abolished as cerebral metabolic activity is severely reduced, depending upon the severity of the hypoxic event.

Hypotension

Significant levels of hypotension seem to be needed to cause the earliest of central nervous system (CNS) signs, as measured by discrimination tests such as the flicker-fusion test. This test examines the flicker rate at which the observer

Figure 35-8 (Figure Not Available) Changes in the compressed spectral array during hypotension. *(From Stockard and Bickford [27])*

perceives the light to be continuous. In the early days of deliberate hypotension this test was part of the preoperative evaluation to judge how far the pressure could be reduced for operation. Clear signs of confusion and inability to concentrate or respond properly to simple commands must represent very low levels of cerebral perfusion when caused by hypotension because the cerebral vasculature is maximally dilated at that time. The EEG changes associated with even this level of hypotension are not dramatic, although they are clear by comparison with a previously active recording. Herein lies the problem with using the processed EEG to determine whether the level of hypotension has resulted in brain ischemia. The changes on processed EEG are not very pronounced and are bilateral. Such changes can be detected, but when the hypotension is induced slowly the changes are gradual and harder to read. Changes associated with acute hypotension as caused by sudden arrhythmia and are easier to read. A tracing of the effect of hypotension on the compressed spectral array is shown in Figure 35-8 (Figure Not Available) . [27] In our opinion, EEG changes due to hypotension really do represent cerebral ischemia of a significant degree and should be considered an important finding.

Hypothermia

During cooling on CPB, the total power and peak power frequency of the high-frequency band were highly correlated with temperature using Fourier analysis and spectral edge data; however, there was significant variability between subjects, especially during cooling. [27] Complete EEG suppression usually develops at 15 to 18°C.

Hypercarbia and Hypocarbia

Hyperventilation is known to activate excitable seizure foci. Hypoventilation with accumulation of carbon dioxide has subtle effects similar to increasing end-tidal tension of the volatile anesthesia. [28]

Untoward Events

One of the suggested reasons for monitoring the brain is to enable us to detect "untoward events" during anesthesia, which suggests that there are CNS insults that, if detected early, could be rapidly reversed or treated to prevent permanent injury. We have already considered hypoxia, hypotension, and cerebral ischemia caused by carotid artery occlusion. What "untoward event" may have occurred when a patient awakens from general anesthesia with an unexpected neurologic deficit? Most such problems are caused by peripheral nerve injuries and with a sufficiently detailed neurologic examination can be identified as such. It is unlikely that any routine brain monitor is going to help identify such injuries. Although SSEPs measured from the distribution of the nerve at risk might very well do so, this level of monitoring is not routine and would probably be used only when one expects a nerve injury to occur.

We had an opportunity to describe three patients who demonstrated an unexpected focal neurologic deficit on emergence from anesthesia. [29] On the basis of what we know about the processed EEG, we can speculate on whether it would have been useful in these cases. An older man with chronic atrial fibrillation underwent percutaneous ultrasonic lithotripsy under general anesthesia. He awakened slowly and was found to have right hemiplegia and aphasia. The diagnosis was thromboembolism of cardiac origin to the distribution of middle cerebral artery. This intraoperative event probably would have been detected on the processed EEG because it would have been acute and unilateral. Recent studies utilizing fibrinolytic agents (tissue plasminogen activator) within 3 hours of onset of thromboembolic strokes have demonstrated improvements in outcome. Delay of treatment beyond 3 hours is associated with increasing complications. [30] Use of this treatment in the immediate postoperative period has not been studied and could be expected to be associated with increased bleeding complications. Therefore, as yet it is unclear whether diagnosing the intraoperative event in this patient would have resulted in a therapeutic intervention. Another patient was a middle-aged woman undergoing vaginal hysterectomy also under general anesthesia. She was lethargic in the recovery room for some time before it was realized that she was hemiplegic. She had suffered an intracerebral bleed intraoperatively. Again the processed EEG would be expected to show a fairly definitive picture in this kind of case because the changes would be hemispheric and rather acute. That information might have raised the level of suspicion and could have led to earlier diagnosis. Treatment consisted of evacuation of the hematoma. The sooner this therapy could be implemented the better the result expected. Perhaps

this patient's residual deficit would have been reduced if such monitoring had been used. Finally, a young woman was undergoing laparoscopic tubal ligation. During the procedure she had multifocal ventricular ectopy and elevated airway pressures. She entered the recovery room unusually lethargic, and hemiplegia was noted shortly thereafter. She probably sustained paradoxical carbon dioxide embolism to her coronary and cerebral circulation. This type of global cerebral event probably would not be evident on the processed EEG because even though it is acute, the changes would have to be very dramatic to be noticed because they would be bilateral. These cases occurred in a surgical case load of nearly 60,000 general anesthetics. Similar series of rare catastrophic intraoperative neurologic events have been reported from other centers. [31] The routine use of the processed EEG could have been expected to contribute rarely to the overall care of this patient group. It is for the reader to decide whether this information applies to his or her practice.

Brain Death

The clinical diagnosis of brain death (Ch. 76) is made when there is demonstration of the absence of all cerebral and brain stem function (Table 35-4) (Table Not

Available) . Various clinical tests have been devised to diagnose brain death (Table 35-5) (Table Not Available) . Apnea testing is accepted as an essential component of the evaluation; however, electrocerebral silence on the EEG, when not confounded by the presence of high-dose barbiturates, metabolic encephalopathy, or very young age, supports the diagnosis of brain death. [32] [33]

TABLE 35-4 -- Criteria for Determination of Brain Death

(Not Available)

From Darby et al. [33] Copyright 1989, American Medical Association

TABLE 35-5 -- Clinical Tests of Brain Death

(Not Available)

From Darby et al. [33] Copyright 1989, American Medical Association

INTRAOPERATIVE MONITORING OF SENSORY EVOKED POTENTIALS

Intraoperative monitoring of sensory evoked potential (SEP) has gained increasing popularity over the last several years because it provides the ability to monitor the functional integrity of sensory pathways in the anesthetized patient undergoing surgical procedures placing these pathways at risk. EPs are electrical manifestations of the CNS response to external stimuli. SEPs are recorded by stimulating a peripheral sensory nerve and recording the resulting electrical potential at various sites along the sensory pathway to the cerebral cortex. Because of the very low amplitude of EP (0.1-20 muV), it is not possible to distinguish them from background brain wave activity and artifacts in the routine EEG. To extract the EP from the background EEG activity, computer signal averaging or summation is used. With this technique the electrical activity, both evoked and spontaneous, after a repetitive sensory stimulus is averaged. The SEP occurs at a constant time after the sensory stimulus; the spontaneous brain activity (the EEG) occurs at random intervals after the sensory stimulus. The sum of the nonrandom evoked response increases directly with the number of responses added. The sum of the random EEG activity increases by the square root of the number of samples obtained. The averaged response of two electrical activities, SEP and spontaneous EEG, increases at different rates, and the SEP is revealed above the spontaneous electrical activity of the brain. [34] The resolution of the EPs increases as the square root of the responses recorded.

SEPs are of two general types determined by the distance of the recording electrode from the neural generator of the evoked response. EPs recorded from electrodes close to the neural generators (within approximately 3-4 cm in the average adult) are termed near-field potentials. [35] Near-field potentials are transmitted to the recording electrode by propagated conduction along a discrete length of nerve, [36] and the morphology is directly affected by electrode location. [35] Far-field potentials are recorded from electrodes located a greater distance from the neural generator and are conducted to the recording electrode through a volume conductor (brain, cerebrospinal fluid, and membranes). As a result, it is more difficult to locate the source of the active tissue (the current spreads diffusely throughout the conducting medium), and the electrode position has little effect on the morphology of the recorded EP. [35] [36] As the distance between the recording electrode and the neural generator increases, the recorded SEP becomes smaller and slower. More signals have to be averaged to record far-field potentials (up to several thousand) than near-field potentials (as few as 50 to 100). [35] [36] EPs are also defined as cortical or subcortical (which arise from the spinal cord and brain stem). With EPs recorded from scalp electrodes (standard 10-20 system for EEG) (see Fig. 35-1) (Figure Not Available) , cortical evoked responses are near-field potentials, and brain-stem responses are far-field potentials.

In evaluating EPs, the latency and amplitude of the generated waveforms are measured. Deflections below the baseline are labeled positive (P) and those above the baseline negative (N). Standard identification of waveforms is by letter designating the direction of the deflection followed by

a number representing the latency of that waveform (e.g., N14). Because amplitude and latency change with recording circumstances, normal values must be established for each neurologic monitoring laboratory and differ somewhat from values recorded in other labs. SEPs utilized for diagnostic evaluation of patients with suspected neurologic abnormalities as well as those monitored intraoperatively are SSEPs, brain-stem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs). For all these modalities, recording electrodes are placed on the scalp, using the same standard 10-20 system as for recording the EEG.

Intraoperative changes in EPs, such as decreased amplitude, increased latency, or complete loss of the waveform, are considered to be indications of surgical trespass or ischemia, or they may reflect systemic changes. When these changes are detected and considered to be significant, the anesthesiologist or surgeon can make changes to relieve or lessen the insult to the monitored pathway. Interventions by the anesthesiologist are directed at improving perfusion to the nervous tissue at risk and include increasing arterial blood pressure, especially if induced hypotension is used or if the patient's pressure has fallen to below the preoperative level; transfusion if significant anemia is present; volume expansion; and normalization of arterial blood gas tensions if indicated. Alterations in EPs may warn the surgeon of direct injury of nervous tissue in the operative field often due to retractor pressure or ischemia caused by compromise of blood supply either through placement of vascular clips or cross-clamps or due to distortion of the vasculature (i.e. during correction of scoliosis, or with use of retractors). Appropriate changes in the operative procedure may result in avoidance or lessening of postoperative neurologic dysfunction. Tolerance limits for degree of change in EPs or duration of complete loss of waveform before permanent neurologic dysfunction occurs are not clearly defined. Many centers utilizing intraoperative SEP monitoring define decreases in amplitude of 50 percent or more from baseline associated with a prolongation in latency as clinically significant SEP changes, in need of intervention or explanation. In practice, often any SEP changes associated with a surgical event are considered clinically significant. Changes in SEP that do not progress to complete loss of the waveform are less likely to indicate a new postoperative neurologic deficit. Complete loss of the SEP waveform intraoperatively without recovery is highly likely to be associated with a new deficit. If the SEP recovers either spontaneously or by interventions intraoperatively, the likelihood of neurologic injury depends on the procedure and the duration of the SEP loss. Some studies suggest that loss of the SEP waveform for less than 15 minutes is associated with no new permanent neurologic deficit, whereas complete loss for longer periods is highly likely to reflect permanent neurologic injury. [37]

The operating room is a "hostile" environment for recording SEP. Because these potentials are very small in amplitude, electrical noise, which is quite common in most operating rooms, will often interfere with recording of good quality EPs. "Biologic noise" such as the cardiac electrical activity (ECG) and muscle movement (EMG activity) may obscure the desired evoked response. To successfully record SEP in the operating room environment, these sources of noise must be recognized and the appropriate action taken to allow recording of the desired evoked response (i.e., unnecessary electrical equipment unplugged, and small doses of muscle relaxant given to minimize EMG). A number of physiologic changes as well as drugs administered intraoperatively can result in changes in the SEP unrelated to potential injury to nervous tissue. These factors must be recognized, minimized if possible, and included in the differential diagnosis as changes in SEP are detected intraoperatively. One of the most important principles of recording SEP intraoperatively is that reproducible, reliable tracings must be obtained at baseline prior to any intervention likely to cause changes in the evoked response. If good quality tracing with identifiable waveforms cannot be recorded and reproduced at baseline, then SEP monitoring will be of little use in monitoring integrity of the CNS intraoperatively. If significant variability exists or waveforms are difficult to identify, then it will not be possible intraoperatively to distinguish SEP changes that are clinically significant from the preexisting variability of waveforms.

SOMATOSENSORY EVOKED POTENTIALS

SSEPs are recorded after stimulation of a peripheral sensory nerve, usually with electrical stimulation via a surface electrode on the skin or fine needle electrodes. A square wave stimulus of 0.2- to 2-ms duration is delivered to the peripheral nerve, and the intensity is adjusted to produce a minimal muscle contraction. Increasing the stimulus intensity beyond the sum of the motor and sensory threshold does not influence the amplitude or latency of the recorded EP. [28] Rate of stimulation varies from 1 to 2 Hz. [35] The common sites of stimulation include median nerve at the wrist, common peroneal nerve at the knee, and posterior tibial nerve at the ankle. [38] The tongue, trigeminal nerve, pudendal nerve, and ulnar nerve have also been studied. [38]

SSEPs consist of both short- and long-latency EPs. The short-latency SSEPs are the EPs most commonly studied intraoperatively because they are less influenced by factors that may vary during the perioperative period, such as anesthetic depth. The pathways involved in the generation of short-latency SSEPs include large-fiber sensory nerves with their cell bodies in the dorsal root ganglia and central processes traveling rostrally in the ipsilateral posterior column of the spinal cord synapsing in the dorsal column nuclei at the cervicomedullary junction (first-order fibers), second-order fibers crossing and traveling to the contralateral thalamus via the medial lemniscus, and third-order fibers from the thalamus to the frontoparietal sensorimotor cortex. [26] Primary cortical evoked responses result from the earliest electrical activity generated by the cortical neurons and are thought to arise from the postcentral sulcus parietal neurons. The secondary cortical potentials (longer-latency) are thought to arise in the association cortex, are less stable, have greater variability of waveform than primary cortical responses, [36] and habituate rapidly on repetitive stimulation. [35] Nonspecific cortical responses occur widely across the frontal and temporal cortex regardless of the sensory stimulation, show marked habituation with repetitive stimulation, but are enhanced when the stimulation is meaningful or when the subject concentrates. [35] Cortical EPs other than the primary cortical response

TABLE 35-6 -- Generators of SSEPs After Median Nerve Stimulation

PEAK	GENERATORS
N9 (EP)	Brachial plexus
N11	Posterior columns or spinal roots
N13/P13	Dorsal column nuclei
N14,15	Brain stem or thalamus
N19/P22	Parietal sensory cortex

are not recorded intraoperatively because they are severely altered by general anesthesia or are extremely difficult to record in the operating room environment. [35]

For recording SSEPs after upper limb stimulation, recording electrodes are placed at the Erb point above the clavicle overlying the brachial plexus, at the posterior midline of the neck at the second cervical vertebra (over the gracile and cuneate nuclei), and on the scalp overlying the sensory (parietal) cortex contralateral to the stimulated limb. For recording EPs after lower limb stimulation, electrodes are placed over the lower lumbar spine. [38] Intraoperatively, cortical SSEPs may also be recorded from electrodes placed directly on the cerebral cortex and subcortical potentials with electrodes placed invasively into bone, ligament, or the epidural space in the operative site. [35] Purported generators for short-latency SSEPs are listed in Table 35-6 and Figure 35-9 (Figure Not Available) . [35] [38] After lower-limb stimulation, absolute latencies are increased because of the greater distance the

Figure 35-9 (Figure Not Available) Short-latency SEPs produced by stimulation of the median nerve at the wrist. *(From Chiappa and Ropper [38])*

stimulation must travel along the peripheral sensory nerve. The first cortical response occurs at approximately 27 ms after stimulation. Interpeak latencies are also evaluated to assess specific conduction times such as N9 to N14 conduction time, reflecting transmission in the proximal brachial plexus, the cervical roots, and the dorsal columns; the N14 to N19 conduction represents pure central conduction time between the dorsal column nuclei and the primary sensory cortex. [39]

Intraoperative recording of SSEPs has been used to assess the functional integrity of the sensory pathways during operative procedures that place these pathways at risk as a result of surgical trespass either along the course of the peripheral nerve, within the spinal canal, or in the brain or when there is potential for compromise of the vascular supply to the sensory pathways. SSEP monitoring has also been used to assess the integrity of adjacent structures that are more difficult to monitor directly, such as the motor tracts. Intraoperative SSEP monitoring has been described for a wide variety of procedures, including correction of scoliosis with instrumentation [40] [41] ; spinal cord decompression and stabilization after acute spinal cord injury [42] [43] ; spinal fusion [44] ; brachial plexus exploration after injury to the plexus [45] ; resection of spinal cord tumor, cyst, or vascular lesion [46] ; correction of cervical spondylosis [46] ; resection of fourth ventricular cyst [46] ; release of a tethered cord [46] ; resection of intracranial vascular lesions involving the sensory cortex [46] ; clipping of intracranial aneurysms [37] ; carotid endarterectomy [47] ; resection of thalamic tumor [48] ; surgical correction after thoracic spine fracture [49] ; abdominal and thoracic aortic aneurysm repair [28] ; and repair of coarctation of the aorta. [50] Intraoperative monitoring of SSEPs has been used most extensively in patients undergoing surgical procedures involving the spinal column or spinal cord, or both. Extensive experience has been gained in patients who have decompressive laminectomies or who have undergone corrective procedures for scoliosis. Intraoperative changes in SSEPs have been noted in 2.5 to 65 percent of patients undergoing surgical procedures on the spine or spinal cord. [41] [44] [49] [51] When these changes are promptly reversed either spontaneously or with interventions by the surgeon or anesthesiologist (such as lessening the degree of spine straightening in scoliosis surgery or increasing arterial blood pressure), the patients most often have preserved neurologic function postoperatively. When these changes persisted, however, the patients most often awakened with worsened neurologic deficit. Both false-negative and false-positive results have been reported with SSEP monitoring during spine surgery. Patients with intact SSEPs throughout the procedure have awakened with a new significant neurologic deficit. On the other hand, patients with significant changes in intraoperative SSEPs have suffered no change in neurologic function postoperatively. [51] Overall, the reliability of adequate SSEP monitoring to predict the postoperative somatic sensory function has been reported to be excellent. [35] [46] [49] However, because the motor tracts are not monitored and the blood supply to the dorsal columns of the somatosensory tracts monitored is primarily from the poste- rior spinal arteries and that to the motor tracts is primarily from the anterior spinal artery, it is possible for a significant motor deficit to develop postoperatively in patients with intact SSEPs throughout the operative course. Indeed, such

events have been reported. [42] [52] In operations on the spine and after acute spinal cord injury the sensory and motor changes usually follow closely [35] ; however, in patients suffering neurologic dysfunction after thoracic aortic aneurysm repair, frequently proprioception is intact when motor and other sensory functions are impaired. This result occurred in 32 percent of patients with neurologic injury after aortic aneurysm repair in one series. [53] Clearly, intraoperative SSEP monitoring in

these patients carries a significant risk for false-negative results. In addition, significant difficulties in intraoperative recording of SSEPs have been reported. Technically inadequate intraoperative SSEP recordings are reported to occur in 0 to 41 percent of patients monitored. [46] [48] [49] [54] These difficulties arise from the electrically hostile environment of the operating room, a high incidence of artifact, abnormal preoperative SSEPs in patients with abnormal neurologic function, inaccessible electrodes during the operative procedure, and sensitivity of the EP, especially the cortical components, to factors that may fluctuate in the intraoperative period, such as temperature, blood gas tensions, anesthetic depth, and blood pressure. Indeed, one author found the SSEPs to be the most difficult of SEPs to monitor intraoperatively. [49] In order for SSEP monitoring to benefit a patient, the neurologic pathway monitored must be potentially at risk during the procedure, and if SSEP changes occur, an option for intervention must exist. If both of these are not true, then monitoring is likely to offer little benefit to the patient. To optimize conditions for SSEP monitoring, the anesthesiologist should choose an anesthetic technique that does not markedly depress the SSEP and the anesthetic depth and physiologic state of the patient should remain as constant as possible during periods of potential surgical injury to the monitored pathway. In addition, reliable tracings should be obtained before any intervention.

Evaluation of central conduction time during SSEP monitoring has also been used in acute settings other than the perioperative period. Prolongation of central conduction in comatose patients has been associated with a worse long-term prognosis. [55] Prolongation of central conduction time in patients after subarachnoid hemorrhage is associated with transient neurologic deficits and precedes the development of these deficits. The changes in central conduction time are likely related to cerebral ischemia. [56]

BRAIN-STEM AUDITORY EVOKED POTENTIALS

BAEPs are recorded by delivering clicks repeatedly to one ear. Stimulus intensity is usually set at 60 to 70 dB above the patient's click-hearing threshold. The duration of the click is approximately 100 sec and the frequency 10 Hz. Use of different click polarity (the direction of the initial movement of the tympanic membrane) to cause either rarefaction or condensation produces different waveforms, amplitudes, and latencies. BAEP may be recorded with one or the other click polarity but not both usually. Intraoperatively, clicks of alternating polarity may be used to decrease stimulus artifact, but the waveforms produced are an average of those produced by either one alone. Rate and intensity of stimulus delivery affect the BAEP. [35] [57] Monaural stimulation is used because responses from a normal ear stimulated simultaneously obscure any abnormal responses from the contralateral ear. The stimuli are delivered by acoustically shielded headphones when not used in the operation room. Intraoperatively, inserted earphones on molded earpieces are used. Although they admit more extraneous noise, they do not interfere with access to the surgical field and are preferable for intraoperative monitoring. [35] [57] Recording electrodes are placed on the lobe of the stimulated ear and on the top of the head (vertex). [57] White noise is delivered to the contralateral ear. Five hundred to 2,000 repetitions are required on average because BAEPs recorded from the scalp are far-field potentials. [35] [57]

Peaks in recordings of BAEP are labeled I through VII, and the purported neural generators for these peaks are shown in Figure 35-10 . As with SSEP, amplitude, absolute latencies, and interpeak latencies are evaluated to assess integrity of the auditory system, localize the functional defect, and assess peripheral and central conduction times. Because waves VI and VII are inconsistent, they are not routinely studied, [57] and most papers reporting use of BAEP in the operating room use waves up to wave V. [58] [59] [60]

BAEPs have been monitored intraoperatively during procedures involving or near the auditory pathway as well as in posterior fossa procedures when brain-stem function might be compromised. Cases in which BAEPs are commonly monitored include microvascular decompression of cranial nerves (especially V and VII), resection of acoustic neuroma, posterior fossa exploration for vascular or neoplastic lesions, clipping of basilar artery aneurysm, and section of nerve VIII for intractable tinnitus. [46] [58] [59] During microvascular decompression of the facial nerve in patients with hemifacial spasm, hearing loss has been reported in up to 15 percent of cases, and this incidence can be greatly decreased with BAEP monitoring. [61] [62] Intraoperative changes noted included transient or permanent latency increases on the operative side, obliteration of waveform distal to the operative site that was either transient or permanent, and, rarely, obliteration of BAEP contralateral to the operative side. [48] [49] [58] [59] These changes were associated with a variety of perioperative events, including section of nerve VIII (deliberate or unintentional); retraction of nerve VIII, cerebellum, or brain stem; operative manipulation of nerve VIII; hypotension and hypocarbia; drilling around the internal auditory canal; irrigation of nerve VIII; severe cerebellar edema; and positioning of the head for retromastoid cra-niotomy (Table 35-7) . [48] [58] [59] Patients with transient or persistent increases in latency or decreases in amplitude can be expected to have unchanged or only slight worsening of hearing postoperatively. Patients with complete but reversible loss of BAEP will also have unchanged or mild worsening of hearing postoperatively. Patients with complete irreversible loss of BAEP will most likely have complete or near complete loss of hearing in the ipsilateral ear postoperatively. [46] [48] [49] [59] One series had a single false-positive result. One patient had complete loss of BAEP with intact hearing postoperatively. [48] False-negative results are extremely rare. In one series, BAEPs were monitored in a patient undergoing resection of a meningioma in the lateral ventricle and were unchanged intraoperatively and postoperatively; however, this patient did not regain consciousness postoperatively. [49] This case illustrates the lack of cortical

Figure 35-10 Schematic of auditory neural pathway. The BAEP is initiated by stimulation of the cochlea with a broadband click stimulus given via an ear insert in the external auditory canal. Neural generators of the BAEP peaks are shown.

function monitoring with intraoperative monitoring of BAEP through wave V. Acoustic neuroma resection and posterior fossa craniotomy for microvascular decompression of the V and VII nerves are the most common cases in which BAEPs are monitored. Changes observed are commonly increased in I-V interpeak latency and loss of amplitude of wave V. These changes are usually due to intraoperative stretch of the VIII nerve by retractor placement during cerebellar retraction. Such changes are usually reversed with repositioning of the retractor. Complete loss of wave V may be caused by injury of the VIII nerve in the operative field. During acoustic neuroma resection, occasionally waves I-V are lost. Generally, this is due to interruption of the cochlear blood supply and is associated with complete deafness in the affected side. [63] BAEPs are considered the easiest of the SEPs to monitor intraoperatively and are least

TABLE 35-7 -- Correlation Between BAEP Changes and Associated Clinical Events

BAEP CHANGE	ASSOCIATED EVENTS
Transient latency increase	Drilling, irrigation, retraction, surgical irritation, hypocarbia and hypotension, positioning
Persistent latency increases	Retraction or pressure on auditory tract
Transient loss of EP	Retraction, pressure, surgical dissection
Permanent loss of ipsilateral EP	Surgical interruption of auditory pathway or interruption of cochlear blood supply
Loss of contralateral EP	Cerebellar edema

sensitive to changes in perioperative variables. Ability to record technically adequate BAEP has been reported in 90 to 100 percent of cases in which monitoring was attempted. [46] [48] [58] [59] Preoperative deafness on the operative side eliminates the possibility of recording intraoperative BAEPs. Preservation of BAEP intraoperatively indicates preserved hearing postoperatively, and persistent changes indicate significant risk of injury.

VISUAL EVOKED POTENTIALS

VEPs are recorded after monocular stimulation with recording electrodes over the occipital, parietal, and central scalp. [59] Shift reversal of a checkerboard pattern with constant luminance is the preferred stimulus because the generated EPs have a narrower range of normal variation and are more sensitive to conduction defects. However, it is currently not possible to deliver this type of stimulation intraoperatively. Instead flash stimulation with a change in luminance is utilized. The stimuli are produced by light-emitting diodes placed in a goggle over a closed lid. The flash rate is 1 to 3 Hz with a duration of 3 to 5 ms. The sample time is 250 to 500 ms, and 64 to 128 samples are averaged per recording. [35] [48] [49] [57] For some operative procedures, such as operations on the anterior cranial fossa, the goggles interfere with approach to the operative field. Light-emitting diodes mounted on a contact lens have been used in these situations. [46] VEPs are cortical EPs, which vary with the type of stimulus, part of the retina stimulated, degree of pupil dilation, and patient's attention level. [35] Two positive peaks at approximately 100 and 200 ms are observed (Fig. 35-11) (Figure Not Available) . [35]

Figure 35-11 (Figure Not Available) Pattern-shift VEPs. *(From Chiappa and Ropper [57])*

Intraoperative VEP monitoring has been advocated for procedures placing the visual system at risk, especially for those in the area of the optic chiasm. Procedures in which VEP monitoring has been used include resection of pituitary tumors, craniopharyngioma, optic glioma, orbital pseudotumor, occipital arteriovenous malformation, meningioma impinging on the optic chiasm, chondrosarcoma of the sphenoid wing, drainage of pituitary abscess, clipping of internal carotid artery and basilar artery aneurysms, surgical correction of CSF rhinorrhea, and treatment of orbital fracture. [46] [48] [49] Changes in EP latency and amplitude were used to guide operative manipulations or to indicate adequate systemic blood pressure in patients in whom induced hypotension was being used. [35] [49] Satisfactory intraoperative recordings can be recorded in 88 to 100 percent of patients. [46] [48] [49] However, intraoperative variability unrelated to changes in neurologic function may be as high as 68 to 81 percent. [48] [49] In addition, in one large series there was a relatively high incidence of both false-positive and false-negative results. Thirteen percent of patients with intraoperative loss of VEPs had unchanged vision postoperatively, and 7 percent had intact VEPs with significant visual defects. [49] VEPs are sensitive to a number of factors that cannot be controlled intraoperatively, such as luminance because the flash must pass through the closed eyelid; pupil size and direction; and attention to the stimulus. In addition, improved systems to deliver the stimulus intraoperatively have to be developed. [49] In the opinion of the author of one of the largest series of patients studied with intraoperative VEP monitoring with current techniques, VEPs cannot be reliably interpreted intraoperatively. [49] VEPs have enjoyed the least popularity of all forms of intraoperative EP monitoring.

Pharmacologic Factors Influencing Sensory Evoked Potentials

There are multiple drugs used in the perioperative period that can influence the intraoperative monitoring of SEPs (Table 35-8) . Different classes of drugs have differing effects. In addition, the sensitivity of evoked responses to drug effects varies with the sensory modality monitored. In general, VEPs are the most sensitive, and BAEPs are the most resistant to drug effects. In addition, early waves (brain-stem) are less affected by drugs than are late potentials (cortical).

The volatile anesthetics isoflurane, sevoflurane, desflurane, enflurane, and halothane have similar effects in differing degrees on the SEPs. As with most drugs, VEPs are the most sensitive to the effects of volatile anesthetics, and the BAEPs are the most resistant to anesthetic-induced changes. The spinal and subcortical waves are less affected than the cortical potentials. [64] [65] [66]

The effects of the currently used volatile agents on SSEPs are dose-dependent increases in latency and conduction times and a decrease in amplitude. [64] [65] [66] [67] [68] The relative effects of different volatile agents on SSEPs are somewhat controversial: Some evidence suggests that halothane has a greater

TABLE 35-8 -- Drug Effects on Sensory and Motor Evoked Potentials

DRUG	SSEPS		BAEPS		VEPS		TRANSCRANIAL MEPS	
	LAT	*AMP*	*LAT*	*AMP*	*LAT*	*AMP*	*LAT*	*AMP*
Isoflurane				0				P
Enflurane				0				
Halothane				0		0		
Nitrous oxide	0		0	0				
Barbiturates				0			P [b]	P [a] [b]
Etomidate								0
Propofol							P	P [b]
Droperidol								
Diazepam			0	0				[c]
Midazolam	0						P	P
Ketamine	0							0

Fentanyl			0	0			0				0
Morphine											
Meperidine		/									

Lat-latency; Amp-amplitude; P-prohibitive in clinically useful doses

[a] P if inspired concentration > 50%
[b] Following bolus administration; low dose infusions may be acceptable in some cases
[c] Drug not given during general anesthesia; volunteers awake following administration dose

Figure 35-12 (Figure Not Available) Representative SSEP cortical responses (C-3, C-4-FPz) at various MAC levels of isoflurane. *(From Peterson et al [64])*

impact on SSEPs than either isoflurane or enflurane [66] other evidence supports a greater effect by enflurane and isoflurane than halothane. [64] Both desflurane and sevoflurane appear to have qualitatively and quantitatively similar effects of SEPs as isoflurane. [69] [70] Up to 0.5 to 1 MAC isoflurane in the presence of nitrous oxide is compatible with adequate monitoring of cortical SSEPs (Fig. 35-12) (Figure Not Available) . [64] [68] Preservation of the ability to monitor cortical SSEPs has been reported with similar levels (0.5-1 MAC) of both halothane and enflurane in nitrous oxide [64] [68] (Figs. 35-13 (Figure Not Available) . and 35-14 (Figure Not Available))

The volatile anesthetics result in increases in latency of BAEPs without affecting the amplitude. [68] [71] [72] [73] However, volatile anesthetics cause both increases in latency and decreases in amplitude in the early cortical responses after auditory stimulation. [72] Adequate monitoring of BAEPs is possible with the volatile anesthetics in concentrations up to

Figure 35-13 (Figure Not Available) Representative SSEP cortical responses (C-3, or C-4-FPz) at various MAC levels of enflurane. *(From Peterson et al [64])*

Figure 35-14 (Figure Not Available) Representative SSEP cortical responses (C-3, C-4-FPz) at various MAC levels of halothane. *(From Peterson et al [64])*

and exceeding 1 MAC (with and without nitrous oxide) (Figs. 35-15 (Figure Not Available) and 35-16 (Figure Not Available)). [68] [71] [72] [73] [74]

Use of the volatile agents during monitoring of VEPs results in dose-dependent increases in latency with or without changes in amplitude. [68] [75] [76] [77] [78] Isoflurane results in dose-dependent increases in latency and decreases in amplitude up to 1.8 percent in 100 percent oxygen, at which time the waveform is lost. [68] [75] Enflurane in the absence of hypocarbia also leads to decrease in amplitude. [75] Halothane causes

Figure 35-15 (Figure Not Available) Influence of isoflurane alone on BAEP in a typical subject. Latency of peaks III and IV to V increased at 1.0 percent but stabilized with increasing anesthetic depth. *(From Manninen et al [71])*

Figure 35-16 (Figure Not Available) BAEP recording obtained in one patient at different enflurane-inspired concentrations. *(From Dubois et al [73])*

increases in latency without changes in amplitude (Fig. 35-17) (Figure Not Available) . [76] [77]

Although volatile anesthetics cause significant changes in the waveforms of sensory evoked potential, it is possible to provide adequate monitoring intraoperatively in the presence of volatile anesthetics. Doses of agents causing obliteration of the response to be monitored must be prevented. Equally important, anesthetic concentration should not be changed during the critical periods of intraoperative monitoring, those in which surgical interventions are most likely to result in damage to neurologic tissue and changes in the SEPs. Because the volatile anesthetic-induced changes in SEPs are dose-dependent, increasing anesthetic depth at a crucial point in the operative procedure can result in confusing changes in the SEPs that may be due to either the anesthetic or the surgical procedure. The appropriate intervention is then difficult to determine.

As with the volatile anesthetics, nitrous oxide causes differing effects on the SEPs depending on the sensory system monitored. It causes decreases in amplitude without changes in latency in SSEPs when used alone or when added to a narcotic-based or volatile anesthetic. [64] [65] [79] Addition of 50 percent nitrous oxide to a fentanyl-based anesthetic results in greater decreases in amplitude than administration

Figure 35-17 (Figure Not Available) Waveforms of visual evoked responses from one patient elicited when awake and anesthetized at three end-expired levels of halothane. Four separate tracings obtained during each condition have been superimposed. *(From Uhl et al [76])*

of up to 1 percent isoflurane or enflurane, especially in patients with abnormal preoperative SSEPs. [65] The addition of nitrous oxide to a maintenance volatile anesthetic during the monitoring of BAEPs causes no further change. [71] Likewise use of nitrous oxide alone causes no change in BAEPs. [79] Use of nitrous oxide alone results in an increase in latency and a decrease in amplitude in VEPs, but when it is added to a volatile anesthetic technique it causes no further changes in VEPs. [75] [79]

The effects of barbiturates on EPs have been studied both in animal models and in humans. Increasing doses of thiopental in patients result in progressive dose-dependent increases in latency, decreases in amplitude in median nerve SSEPs, and progressive increases in latency in BAEPs. The changes in SSEPs are more pronounced than are the changes in BAEPs, and changes in later waveforms exceeded those in the earlier waveforms. This finding is consistent with the theories that barbiturates affect synaptic transmission more than axonal conduction, that the early waveforms in SEPs are to axonal transmission, and that later waves are dependent on multisynaptic pathways. At doses of thiopental far in excess of

those producing an isoelectric EEG, adequate monitoring of SSEPs and BAEPs was preserved. [80] The effects of pentobarbital in cats have also been evaluated. The effects on SSEPs and BAEPs observed are similar to those of thiopental in humans. Increases in latency of both BAEPs and SSEPs were seen. The waveforms were never obliterated even at doses above those causing complete suppression of spontaneous EEG activity. VEPs were more sensitive in that at low doses all except the earliest waveforms were obliterated. The early potentials persisted with increases in latency even to very high pentobarbital doses. [81] Similar increases in latency and decreases in amplitude of both spinal and cortical SSEPs were seen in humans with thiamylal sodium. [82] Preserved ability to monitor SSEPs in head-injured patients receiving therapeutic thiopental infusions has been demonstrated. [83] Adequate perioperative monitoring of SEPs is possible even in the presence of high-dose barbiturate therapy as long as the effects of the drug (increased latency with or without decreased amplitude) are considered.

After both bolus administration and intravenous infusions etomidate causes increases in latency of all waves and prolongation of central conduction time in SSEPs as well as increases in amplitude of the cortical waves but slight decreases in amplitude of cervical potentials. [84] This effect may be due to an alteration in the balance of inhibitory and excitatory influences or an increase in the irritability of the CNS. The effects seem to be present in the cortex but not in the spinal cord. [85] Etomidate infusions have been used to enhance SSEP recording in patients when it was not possible to obtain reproducible responses at the beginning of intraoperative

monitoring because of the patients' pathology. The infusions provided adequate monitoring and detection of intraoperative events leading to compromise of the spinal cord. [85] The effects of etomidate on BAEPs are dose-dependent increases in latency and decreases in amplitude. [86]

Droperidol in premedicant doses has been demonstrated to have varying effects on SSEPs. In most patients, decreases in amplitude were noted as well as loss of late waves. However, in a few patients increases in amplitude were noted. In all patients, conduction time was prolonged. [87] The benzodiazepines also can cause changes in SEPs. [88] [89] Diazepam causes increases in latency and decreases in amplitude of SSEPs, increases in latency in the cortical response after auditory stimulation, and no change in BAEPs. [88] [89] Midazolam causes decreases in amplitude without changes in latency of SSEPs. [84] Phenothiazines, diphenylhydantoin, phenobarbital, and ethosuximide in therapeutic doses do not result in consistent changes in BAEPs. [90] Acute alcohol ingestion results in dose-dependent increases in latency and decreases in amplitude in VEPs in healthy patients. [91]

In general, opioids cause dose-dependent increases in latency and decreases in amplitude of SSEPs. Fentanyl causes dose-dependent increases in latency of all waves, with the cortical or late waves affected more than earlier waves. It also causes a decrease in amplitude. The amplitude changes are more variable than the latency increases. [92] [93] Even at large doses of fentanyl (up to 60 mug/kg) reproducible SSEPs can be recorded. [93] Morphine causes similar dosedependent changes in SSEPs to fentanyl. [92] Meperidine causes increases in latency but may also result in increases in amplitude of SSEPs. [94] Even in relatively high doses, opioids can be used in patients requiring intraoperative SSEP monitoring without impairment of ability to monitor neurologic function adequately. However, opioid-induced changes must be taken into account when evaluating the recordings. Large intravenous bolus administration of opioids should be avoided at times of potential surgical compromise to neurologic function to prevent confusing the interpretation of SEP changes if they develop. BAEPs were resistant to doses of fentanyl up to 50 g/kg with no changes observed in absolute latency, interpeak latency, or amplitude. [95]

Physiologic Factors Influencing Sensory Evoked Potentials

A number of physiologic variables, including systemic blood pressure, temperature, and blood gas tensions can influence SEP recordings. With decreases in mean arterial blood pressure to below levels of cerebral autoregulation due to either blood loss or vasoactive agents, progressive changes in SEPs have been noted. SSEP changes observed are progressive decreases in amplitude until loss of the waveform with no changes in latency. [96] [97] BAEPs are relatively resistant to even profound levels of hypotension (mean arterial pressure of 20 mm Hg in dogs). [96] Cortical (synaptic) function appears to be more sensitive to ischemia than spinal cord transmission. [97] Rapid decreases in blood pressure to levels above the lower limit of autoregulation have also been associated with transient SSEP changes of decreased amplitude that resolve after several minutes of continued hypotension at the same level. [98] Reversible SSEP changes at systemic pressures within the normal range have been observed in patients undergoing Harrington rod placement after spinal distraction. These changes resolved with increases of systemic blood pressure to slightly above the patient's normal pressure, suggesting that the combination of surgical manipulation with levels of hypotension generally considered "safe" could result in spinal cord ischemia. [99] Changes in temperature also affect SEPs. Hypothermia causes increases in latency and decreases in amplitude with loss of the waves at 25 to 27°C in VEPs, [100] increases in latency, and alterations in morphology of BAEPs with late waves more affected than early ones. [101] Hyperthermia also alters SEPs, with increases in temperature leading to decreases in amplitude in SSEPs and loss of EPs at 42°C during induced hyperthermia. [102] Changes in arterial blood gas tensions have been reported to alter SEPs, probably in relation to changes in blood flow or oxygen delivery to neural structures. [103] [104] SSEP changes (decreased amplitude) resulting from hypoxia have been reported. [104] Isovolemic hemodilution results in progressive increases in latency of SSEPs and VEPs that become significant at hematocrits below 15 percent. Changes in amplitude were variable until very low hematocrits (<7%) were reached when amplitude of all waveforms decreased. [105]

MONITORING OF MOTOR TRACTS AND NERVES

Intraoperative monitoring of cranial and peripheral motor nerves is used in a number of operative procedures to allow

early detection of surgical trespass of the nerve and to assess level of nerve function intraoperatively. Intraoperative electromyographic monitoring of motor nerve function can include evaluation of three types of motor nerve and muscle activity. Neurotonic discharges are recorded from fine wires placed in muscles innervated by the motor nerve and are spontaneous bursts of activity resulting from operative stimulation of the nerve by either irrigating fluids or operative instruments. [106] Occurrence of neurotonic discharges warns the surgeon of the presence of the nerve within the operative area and can help prevent unintentional damage to the nerve during the procedure. Density and frequency of neurotonic discharges are correlated with degree of postoperative nerve dysfunction. [107] Compound muscle action potential (CMAP) is the muscle activity recorded from either fine wires within muscles innervated by the motor nerve or surface electrodes over the muscle after direct stimulation of the nerve within the operative field by the surgeon using a hand-held stimulating electrode. Stimulation of the nerve proximal to the operative area or tumor can be used to assess functional integrity of the nerve. [106] Nerve action potential (NAP) is recorded after direct stimulation of the nerve either within or outside the operative field, and a recording of the summated activity of the axons within the operative field is made. NAP monitoring allows for localization of slowing or block of nerve impulse conduction within the operative field. [106]

Intraoperative monitoring of facial nerve function has been used in patients undergoing surgical procedures placing the facial nerve at risk, such as acoustic neuroma resection, microvascular decompression for hemifacial spasm, resection of cerebellopontine angle meningiomas, removal of temporal bone neoplasms and cerebellar hemangioblastoma, and surgical treatment of glomus tympanicum and traumatic facial nerve paralysis. [106] [108] Much of the experience with intraoperative facial nerve monitoring is during acoustic neuroma resection. Improved preservation of facial nerve function after acoustic neuroma resection by intraoperative facial nerve EMG monitoring has been demonstrated, especially in patients with medium- to large-size tumors. [107] The National Institutes of Health consensus conference on acoustic neuroma therapy has recommended that facial nerve monitoring be used in patients undergoing resection of acoustic neuroma, based on the clinical experience and research indicating that its use results in improved neurologic outcome.

In patients with hemifacial spasm, two abnormal responses are seen during EMG monitoring: autoexcitation and lateral spread response. Autoexcitation refers to late responses lasting 50 to 100 ms that follow the normal motor response to facial nerve stimulation. Electrical stimulation of one branch of the facial nerve results in muscle response not only in the muscle innervated by that branch but also in those innervated by other branches of the facial nerve; this is termed the lateral spread response. Both of these responses are abnormal and have been demonstrated to disappear intraoperatively when the facial nerve is adequately decompressed. During microvascular decompression for hemifacial spasm, intraoperative monitoring of the facial nerve provides both warning of surgical encroachment on the nerve and information on the adequacy of the operative procedure to relieve the patient's symptoms intraoperatively. [109]

Intraoperative monitoring of the motor component of other cranial nerves has been performed. EMG monitoring of the trigeminal nerve can be accomplished with wires placed in the temporalis or masseter muscles or surface electrodes over these muscles. Cranial nerve V monitoring has been used during nerve section for tic douloureux to ensure preservation of the motor branch of the trigeminal nerve. It is also used in conjunction with facial nerve monitoring during resection of large posterior fossa lesions. [106] The spinal accessory nerve can be monitored with recording electrodes in the trapezius or sternocleidomastoid muscles, for example, during resection of large meningiomas, glomus jugular tumors, and neck carcinomas. [106] EMG monitoring of the hypoglossal nerve with electrodes in the tongue has been infrequently used for large posterior fossa lesions and clivus tumors. [106] Although EMG monitoring of the eye muscles can be performed, it is rarely used.

Monitoring of peripheral motor nerves has been performed in a number of operative procedures by placing wire electrodes in the muscles innervated by nerves that may traverse the operative area. EMG monitoring can warn the surgeon of unexpected surgical trespass of the nerve, help locate a nerve within the field, and localize the level of conduction block or delay. EMG of peripheral nerves has been used in patients undergoing spine surgery to decrease the risk of nerve root injury during the procedure because radiculopathies have been reported to occur after these procedures. [106] Monitoring of peripheral nerves has also been performed in patients undergoing nerve plexus or single-nerve explorations to locate areas of injury and assess axonal continuity to help guide the operative procedure. [106]

In patients undergoing EMG monitoring of cranial or peripheral motor nerves, anesthetic management is not influenced, except that muscle relaxants should be avoided or limited during the period of monitoring. Although the most common approach is to avoid neuromuscular blocking agents completely during the period of monitoring, adequate monitoring of the facial nerve is possible during partial neuromuscular blockade (decrease of the CMAP by 50%). This level of blockade is associated with clinical weakness [110] however, the most commonly used monitors of neuromuscular paralysis are not adequate to accurately monitor this level of relaxation. The trials in which partial neuromuscular paralysis were utilized are small-, and large-scale trials evaluating outcome have not been performed. As a result, most neuroanesthesiologists continue to recommend avoidance of neuromuscular blocking agents. In patients undergoing selective dorsal rhizotomy for relief of spasticity, the EMG is monitored to determine which rootlets to section. These patients have abnormal muscle responses, and in some volatile anesthetics and nitrous oxide may impair the ability to monitor adequately, and narcotics tend to have less impact on the ability to monitor. [111] [112]

MOTOR EVOKED POTENTIALS

Monitoring of the integrity of the motor tracts within the spinal cord is a technique with great potential benefit. Loss of motor function during spinal or vascular surgery without loss of sensory function or change in SSEPs can occur. SSEPs monitor the ascending proprioception fibers of the

fasciculus gracilis and cuneatus in the dorsal columns of the spinal cord, which differ in blood supply from the lateral corticospinal tracks in the anterior columns of the spinal cord where the descending motor tracks are located. Trans-cranial stimulation of the motor tract with monitoring of nerve impulse in the spinal cord and peripheral nerve as well as muscle response has been performed (motor evoked potential [MEP]) and loss of motor transmission without loss of SSEP demonstrated. [113] This technique has potential applications in spinal surgery in which transmission across the operative field can be assessed as well as in aortic surgery with the potential for impairment of the blood supply to the anterior cord. To monitor muscle function, neuromuscular blocking agents should be avoided. However, these agents can be used if only nerve transmission in the cord or peripheral nerves is monitored.

MEP monitoring was developed specifically to assess function of motor pathways and overcome one of the limitations of SEP monitoring. There are many variants of MEP monitoring. The first method involves transcranial stimulation, either electrical or magnetic. For electrical stimulation, electrodes placed on the scalp overlying the motor cortex are used to activate the motor cortex and produce the MEP. For magnetic stimulation, a powerful magnetic stimulator is placed on the scalp over the motor cortex. Brief repetitive applications of a strong magnetic field induce current in the motor cortex and produce an MEP. These transcranial stimulating methods may also activate surrounding cortical structures as well as subcortical white matter pathways (both sensory and motor). Distal antidromic propagation of the transcranially applied stimulus is blocked by synapses in all of the ascending sensory pathways. The stimulus is propagated easily orthodromically via descending motor pathways. The evoked responses may be recorded over the spinal cord, the peripheral nerve, and the muscle itself. In order to enhance the MEP, these responses may be averaged in the same manner as sensory EPs, but averaging is often unnecessary. A third method of producing the MEP involves electrical stimulation of the spinal cord itself above the area of the cord at risk during surgery. Responses are recorded over the distal spinal cord, peripheral nerve, and muscle.

This monitoring modality, while promising in some aspects, has many problems associated with it that remain to be resolved. The exact pathways and generators involved with MEP production have not been completely determined, and intraoperative experience with MEPs is relatively limited. Multiple anecdotal reports suggest that MEP monitoring during surgery on the spine or its blood supply may be very useful, but whether this monitor can be used to guide management and predict postoperative neurologic function in a large series of patients is unclear. [114] [115] [116] [117] For example, it is hoped that MEPs would be able to better predict postoperative motor function than SEPs following occlusion of the blood supply to the spinal cord during operations on the thoracic aorta. Two studies suggest that MEPs may not be as effective as hoped. The first study recorded MEPs from the lumbar spinal cord in dogs produced by transcranial electrical stimulation. [115] Elmore et al [118] found that these spinally recorded potentials did not accurately predict postoperative motor function. A second study recorded MEPs at both the spinal cord and peripheral nerve level in dogs produced by transcranial electrical stimulation. [119] Reuter et al [119] also found that the spinally recorded responses were inaccurate in predicting motor function postoperatively. The peripheral nerve responses disappeared in all animals and were not present 24 hours later regardless of whether the animal could move its lower extremities. These studies suggest that the spinally recorded MEP is likely representing a response generated by the descending corticospinal tract. This white matter pathway is relatively resistant to ischemia when compared to the more metabolically active anterior horn cells (gray matter). Recovery of this white matter-generated MEP response could occur following reperfusion of the cord while the gray matter might not recover. Responses recorded from the peripheral nerve would reflect postsynaptic anterior horn cell function, but lower extremity ischemia occurring following aortic cross-clamping often precludes recording this or the response from muscles during surgery. Much more experimental and clinical work is needed before MEP monitoring becomes widely accepted.

Effects of anesthetics are surprisingly profound, particularly on MEP recordings from muscle produced by either transcranial electrical or especially magnetic stimulation (see Table 35-8) . [111] [120] [121] [122] [123] [124] Anesthetic effects on MEP responses recorded at spinal levels appear to be much less profound. Anesthetic effects on MEPs produced by spinal stimulation are also relatively minor. When responses are recorded from muscle, neuromuscular blocking agents should be avoided or monitored quantitatively, maintaining T1 at or greater than 30 percent of control values. [116] [120] Otherwise, muscle relaxants are desirable because they will reduce gross muscle movement produced by MEP stimulation and facilitate the surgical procedure. There are only limited data regarding short- or long-term safety of either magnetic or electrical transcranial stimulation of the cortex. Although some centers have had consistent success utilizing transcranial MEP monitoring, its use is not widespread and should be considered promising but experimental.

TRANSCRANIAL DOPPLER MONITORING

An easy to apply, direct noninvasive measurement of cerebral blood flow (CBF) is the transcranial Doppler (TCD). The TCD is a diagnostic tool that has found application as a monitor in the operating room relatively recently. [124] The TCD uses sound waves to measure the velocity of blood flowing in the basal arteries of the brain. Sound waves are transmitted through the relatively thin temporal bone (Fig. 35-18) . When these sound waves come in contact with blood, they are reflected off the red blood cells back through the brain and skull to a detector. The velocity of the sound waves reflected back to the surface will be changed because the blood cells themselves are in motion either toward or away from the sound wave detector. This phenomenon is known as the Doppler shift and is directly related to the velocity and flow direction of the blood cells. The velocity of the blood cells will be faster during systole and slower during diastole. The blood in the center of the lumen will move faster than the blood near the vessel wall. Thus, a spectrum

Figure 35-18 Schematic of TCD. Sound waves are transmitted through the relatively thin temporal bone and reflected from red blood cells moving in the basal arteries of the brain.

of flow velocities is produced. This spectrum resembles the shape of the waveform produced by the pulse oximeter or an arterial pressure transducer (Fig. 35-19A) . TCD flow velocity measurements are most commonly and easily made in the middle cerebral artery (MCAv) but may also be measured in other arteries, including the anterior cerebral, anterior communicating, posterior cerebral, posterior communicating, and basilar arteries.

Two assumptions must be made in order for TCDmeasured blood flow velocity to have a direct relationship to CBF. First, flow and flow velocity will only be directly related if the diameter of the artery where the flow velocity is measured and the measurement angle of the Doppler probe remain constant. Second, CBF in the basal arteries of the brain must be directly related to cortical CBF. Neither of these assumptions has been scientifically proven. The TCD has not been validated in a large series of intraoperative cases against either established monitors of cerebral flow such as the EEG or against direct cortical CBF measurements.

The major reported intraoperative use of the TCD involves testing adequacy of CBF, while the carotid is cross-clamped during carotid endarterectomy. Studies comparing measured CBF with MCAv have not shown a good correlation between the two measurements. [125] In addition, the period of carotid cross-clamping is only a relatively small portion of the time that the patient with carotid disease is at risk for ischemia, and most strokes occur at other times during or after surgery. Few data are available about the nature and degree of acceptable TCD changes during the remainder of the operation. Normal variations in blood flow velocities during surgery in patients without cerebrovascular disease appear to be large (Pashayan AG and Mahla ME, unpublished data). With increasing clinical experience with TCD during carotid endarterectomy, it has become one of the accepted monitors of CBF during carotid surgery.

TCD is also used during CPB to detect air or particulate emboli during cannulation, during bypass, when weaning from bypass, and during decannulation. [126] TCD can detect

Figure 35-19 (A) Normal TCD tracing from the middle cerebral artery at a depth of 55 mm. (B) TCD tracing from a patient with cerebral vasospasm. Note very high flow velocities beyond the ability of the machine to quantify. (C) TCD pattern from middle cerebral artery in brain death. Note brief systolic inflow of blood followed by flow reversal in diastole.

these emboli quite easily. Several small clinical studies have suggested that TCD monitoring is useful in identifying portions of the procedure with highest risk for microemboli, allowing potential for alterations in the procedure to decrease

microembolic events. In addition, the number of microemboli has been suggested to be predictive of postoperative neurologic dysfunction; however, the majority of these studies are relatively small and the clinical utility is still undefined. [127] [128] Ease of application and interpretation of the characteristic spectra produced by emboli make this a very attractive monitor for cardiac surgery.

TCD has been used in the ICU to document both the presence and severity of cerebral vasospasm following subarachnoid hemorrhage. As the major cerebral arteries narrow, flow velocity within the lumen must increase if blood flow is to be maintained (Fig. 35-19B). Mean flow velocities over 120 cm per second seem to correlate well to angiographic vasospasm. [129] [130]

The TCD has also been used in the intensive care unit as an aid to the diagnosis of brain death. Studies have demonstrated a characteristic blood flow velocity pattern in patients who are clinically brain dead [131] (Fig. 35-19C) . TCD studies are easily performed at the bedside and can be used to determine whether definitive studies documenting brain death (which may require transporting the patient) need to be performed. Further studies documenting the sensitivity and specificity of this test in the diagnosis of brain death are needed before this test can be used as a sole criterion for brain death.

JUGULAR BULB VENOUS OXYGEN SATURATION

Jugular bulb venous oxygen saturation (SjvO2) can be measured by placing a fiberoptic catheter via the internal jugular vein retrograde into the jugular bulb. It is a measure of the global balance between oxygen supply and demand. In most clinical studies, SjvO2 measurements of below 50 percent have been considered to be indicative of cerebral ischemia. Because it is a measure of global cerebral oxygenation, focal areas of cerebral ischemia may go undetected. SjvO2 monitoring has been used most extensively in the intensive care unit to monitor patients with severe head injury. In addition, its use to guide intraoperative treatment has been described during carotid endarterectomy, crani-otomy for neoplasms and vascular anomalies, and car-diopulmonary bypass procedures. [132] [133] [134] [135] [136] [137] Although it is used routinely in some neurosurgical centers, it has not yet gained widespread clinical acceptance as a routine monitor of neurologic well-being during procedures placing the CNS at risk.

SUMMARY

Regardless of the type of intraoperative neurologic monitor, several principles must be true in order for the utilization of neurologic monitoring to provide potential benefit to the patient. First, the pathway at risk during the surgical procedure must be amenable to monitoring. Second, if evidence of injury to the pathway is detected, there must be some intervention possible. If changes in the neurologic monitor are detected and no intervention is made, then although the monitor may be of prognostic value, it does not have the potential to benefit the patient by avoiding neurologic injury. Third, the monitor must provide reliable and reproducible data. If the data have a high degree of variability in the absence of clinical interventions, then their utility for detecting clinically significant events is limited.

TABLE 35-9 -- Current Practice in Neurologic Monitoring

PROCEDURE	MONITORS	CURRENT PRACTICE
Carotid endarterectomy	Awake patient/neurologic exam EEG SSEP TCD	NIH recommends use of one of the available monitors
Scoliosis surgery	SSEP Wake-up test	Monitoring recommended
Acoustic neuroma	Facial nerve monitor BAEP	VIIth nerve monitoring recommended; BAEP shows some clinical evidence of improved outcome
Intracranial aneurysm clipping	SSEP EEG	Used routinely in some centers; limited clinical data on outcome
Vth nerve decompression	BAEP	Used in some centers
VIIth nerve decompression	BAEP	Data from small series shows improved hearing preservation
Supratentorial mass lesions	SSEP	Used in some centers in selected high risk procedures
Infratentorial mass lesions	BAEP/SSEP	BAEP to detect retractor-related VIII nerve injury, SSEP in rare, high-risk lesions adjacent to ascending sensory pathways
Decompression of spinal stenosis	SSEP	Used in some centers in high-risk procedures (more often cervical)
Spinal cord trauma	SSEP	Used in some centers in high-risk procedures
Cardiopulmonary bypass	EEG TCD SjvO2	Used routinely in some centers, actively studied, but no outcome data as of yet
Aortic coarctation	SSEP	Used routinely in a few centers
Aortic aneurysm repair	SSEP	Used routinely in a few centers

In this chapter, we have discussed the current clinically utilized intraoperative neurologic monitors. Ideally, clinical studies would provide outcome data on the efficacy of a neurologic monitor in a given procedure to improve neurologic outcome. Unfortunately, although there is a wealth of clinical experience with many monitoring modalities, there is little in the way of randomized prospective studies evaluating the efficacy of neurologic monitoring. Based on clinical experience with neurologic monitoring as well as nonrandomized clinical studies in which neurologic monitoring is utilized and generally compared to historical controls, practice patterns for use of neurologic monitoring have developed. In certain procedures, neurologic monitoring is recommended and used by the majority of centers; it is used almost routinely in some centers but not in others, and there is no clear evidence that it should be recommended for all. Finally, there are procedures in which monitoring is used selectively for patients believed to be at higher-than-usual risk for intraoperative neurologic injury. Table 35-9 provides a summary of current clinical practice.

References

1. Hughes JR: EEG in Clinical Practice, 2nd ed. Newton, ME, Butterworth-Heinemann, 1994.

2. Martin JT, Faulconer A Jr, Bickford RG: Electroencephalography in anesthesiology. Anesthesiology 20:359, 1959.

3. Sharbrough FW, Messick JM Jr, Sundt TM: Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. Stroke 4:674, 1973.

4. Billard V, Gambus PL, Chamoun N et al: A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol, and midazolam drug effect. Clin Pharmacol Ther 61:45, 1997.

5. Sigl JC, Chamoun NG: An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 10:392, 1994.

6. Levy WJ: Effect of epoch length on power spectrum analysis of the EEG. Anesthesiology 66:489, 1987.

7. Courtin RF, Bickford RG, Faulconer A Jr: The classification and significance of electroencephalographic patterns produced by NO/ether anesthesia during surgical operations. Proc Staff Meeting Mayo Clin 25:197, 1950.

8. Ghouri AF, Monk TG, White PF: Electroencephalogram spectral edge frequency, lower esophageal contractility, and autonomic responsiveness during general anesthesia. J Clin Monit 9:176, 1993.

9. Long CW, Shah NK, Loughlin C et al: A comparison of EEG determinants of near-awakening from isoflurane and fentanyl anesthesia. Anesth Analg 69:169, 1989.

10. Glass PS, Bloom M, Kearse L et al: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 86:836, 1997.

11. Vernon JM, Lang E, Sebel PS et al: Prediction of movement using bispectral electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. Anesth Analg 80:780, 1995.

12. Kearse LA, Manberg P, DeBros F et al: Bispectral analysis of the electroencephalogram during induction of anesthesia may predict hemodynamic responses to laryngoscopy and intubation. Electroencephogr Clin Neurophysiol 90:194, 1994.

13. Rosen I, Hagerdal: Electroencephalographic study of children during ketamine anesthesia. Acta Anaesthesiol Scand 20:32, 1976.

14. La Marca S, Lozito RJ, Dunn RW: Cognitive and EEG recovery following bolus intravenous administration of anesthetic agents. Psychopharmacol (Berl) 120:426, 1995.

15. Sebel PS, Bovill JG, Wauquier A et al: Effects of high dose fentanyl anesthesia on the electroencephalogram. Anesthesiology 55:203, 1981.

16. Yamamura T, Fukuda M, Takeya H et al: Fast oscillatory EEG activity induced by analgesic concentrations of nitrous oxide in man. Anesth Analg 60:283, 1981.

17. Clark DL, Hosick EC, Neigh JL: Neurophysiologic effects of isoflurane in man. Anesthesiology 39:261, 1973.

18. Artru AA, Lam AM, Johnson JO et al: Intracranial pressure, middle cerebral artery flow velocity, and plasma inorganic fluoride concentrations in neurosurgical patients receiving sevoflurane or isoflurane. Anesth Analg 85:587, 1997.

19. Komatsu H, Taie S, Endo S et al: Electrical seizures during sevoflurane anesthesia in two pediatric patients with epilepsy. Anesthesiology 81:1535, 1994.

20. Rampil IJ, Lockhart SH, Eger EI et al: The electroencephalographic effects of desflurane in humans. Anesthesiology 74:434, 1991.

21. Hoffman WE, Edelman G: Comparison of isoflurane and desflurane anesthetic depth using burst suppression of the electroencephalogram in neurosurgical patients. Anesth Analg 81:811, 1995.

22. Levy WJ: Quantitative analysis of EEG changes during hypothermia. Anesthesiology 60:291, 1984.

23. Smith NT, Dec-Silver H, Sanford TJ Jr et al: EEGs during high-dose fentanyl-, sufentanil-, or morphine-oxygen anesthesia. Anesth Analg 63:386, 1984.

24. Michenfelder JD, Sundt TM, Fode N et al: Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. Anesthesiology 67:336, 1987.

25. Craft RM, Losasso TJ, Perkins WJ et al: EEG monitoring for cerebral ischemia during carotid endarterectomy (CEA): How much is enough? J Neurosurg Anesthesiol 6:301, 1994.

26. Spackman TN, Faust RJ, Cucchiara RF et al: A comparison of a periodic analysis of the EEG with standard EEG and cerebral blood flow for detection of ischemia. Anesthesiology 66:229, 1987.

27. Stockard JJ, Bickford RG: The neurophysiology of anaesthesia. In Gordon E (ed): A Basis and Practice of Neuroanesthesia. New York, Elsevier, 1981, p 3.

28. Clowes GHA Jr, Kretchmer HE, McBurney RW et al: The electroencephalogram in the evaluation of the effects of anesthetic agents and carbon dioxide accumulation during surgery. Ann Surg 138:558, 1953.

29. Oliver SB, Cucchiara RF, Warner MA et al: Unexpected focal neurologic deficit on emergence from anesthesia. Anesthesiology 67:823, 1987.

30. The National Institute of Neurological Disorders and Stroke--PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 333:1581, 1995.

31. Black S, Enneking FK, Cucchiara RF: Failure to awaken after general anesthesia due to cerebrovascular events: J Neurosurg Anesthesiol 10:10, 1998.

32. Report of the Medical Consultants on the Diagnosis of Death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Guidelines for the determination of death. JAMA 246:2184, 1981.

33. Darby JM, Stein K, Grenvik A et al: Approach to management of the heart beating "brain dead" organ donor. JAMA 261:2222, 1989.

34. Kelly DL, Goldring S, O'Leary JL: Averaged evoked somatosensory responses from exposed cortex of man. Arch Neurol 13:1, 1965.

35. Grundy BL: Monitoring of sensory evoked potentials during neurosurgical operation: Methods and applications. Neurosurgery 11:556, 1982.

36. Greenberg RP, Ducker TB: Evoked potentials in the clinical neurosciences. J Neurosurg 56:1, 1982.

37. Freedman WA, Chadwick GM, Verhoeven JS et al: Monitoring of somatosensory evoked potentials during surgery of middle cerebral artery aneurysms. Neurosurgery 29:98, 1991.

38. Chiappa KH, Ropper AH: Evoked potentials in clinical medicine. N Engl J Med 306:1205, 1982.

39. Ganes T: A study of peripheral, cervical, and cortical evoked potentials and afferent conduction times in the somatosensory pathway. Electroencephalogr Clin Neurophysiol 49:446, 1980.

40. Engler GL, Spielholz NI, Bernhard WN et al: Somatosensory evoked potentials during Harrington instrumentation for scoliosis. J Bone Joint Surg 60A:528, 1978.

41. Maccabee PJ, Pinkhasov EI, Tsairis P et al: Spinal and short latency scalp derived somatosensory evoked potentials during corrective spinal column surgery. Electroencephalogr Clin Neurophysiol 53:P32, 1982.

42. Spielholz NI, Benjamin MV, Engler GL et al: Somatosensory evoked potentials during decompression and stabilization of the spine: Methods and findings. Spine 4:500, 1979.

43. Spielholz NI, Benjamin MV, Engler G et al: Somatosensory evoked potentials and clinical outcome in spinal cord injury. In Popp AJ,

Bourke RS, Nelson LR et al (eds): Neural Trauma. New York, Raven Press, 1979, p 217.

44. Luederes H, Gurd A, Hahn J et al: A new technique for intraoperative monitoring of spinal cord function: Multichannel recording of spinal cord and subcortical evoked potentials. Spine 7:110, 1982.

45. Landi A, Copeland SA, Wynn-Parry CB et al: The role of somatosensory evoked potentials and nerve conduction studies in the surgical man-agement of brachial plexus injuries. J Bone Joint Surg 62B:492, 1980.

46. Grundy BL: Intraoperative monitoring of sensory evoked potentials. In Nodar RH, Barber C (eds): Evoked Potentials II. Boston, Butterworth, 1984, p 624.

47. Markand ON, Dilley RS, Moorthy SS et al: Monitoring of somatosensory evoked responses during carotid endarterectomy. Arch Neurol 41:375, 1994.

48. Allen A, Starr A, Nudleman K: Assessment of sensory function in the operating room utilizing cerebral evoked potentials: A study of fifty-six surgically anesthetized patients. Clin Neurosurg 28:457, 1981.

49. Raudzens PA: Intraoperative monitoring of evoked potentials. Ann NY Acad Sci 388:308, 1982.

50. Kaplan BJ, Friedman WA, Alexander JA et al: Somatosensory evoked potential monitoring of spinal cord ischemia during aortic operations. Neurosurgery 19:82, 1986.

51. McCallum JE, Bennett MH: Electrophysiologic monitoring of spinal cord function during intraspinal surgery. Surg Forum 26:469, 1975.

52. Halliday AM, Wakefield GS: Cerebral evoked potentials in patients with dissociated sensory loss. J Neurol Neurosurg Psychiatry 26:211, 1963.

53. Szilagyi DE, Hageman JH, Smith RF et al: Spinal cord damage in surgery of the abdominal aorta. Surgery 83:38, 1978.

54. Grundy BL: Intraoperative monitoring of sensory-evoked potentials. Anesthesiology 58:72, 1983.

55. Hume Al, Cant BR, Shaw NA: Central somatosensory conduction time in comatose patients. Ann Neurol 5:379, 1979.

56. Symon L, Hargadine J, Zawirshi M et al: Central conduction time as an index of ischemia in subarachnoid hemorrhage. J Neurol Sci 44:95, 1979.

57. Chiappa KH, Ropper AH: Evoked potentials in clinical medicine. N Engl J Med 306:1140, 1982.

58. Grundy BL, Jannetta PJ, Procopio PT et al: Intraoperative monitoring of brain-stem auditory evoked potentials. J Neurosurg 57:674, 1982.

59. Raudzens PA, Shetter AG: Intraoperative monitoring of brain-stem auditory evoked potentials. J Neurosurg 57:341, 1982.

60. Duncan PG, Sanders RA, McCollough DW: Preservation of auditory-evoked responses in anaesthetized children. Can Anaesth Soc J 26:492, 1979.

61. Auger RG, Piepgras DG, Laws ER: Hemifacial spasm: Results of microvascular decompression of the facial nerve in 54 patients. Mayo Clin Proc 61:640, 1986.

62. Miller AR, Jannetta PJ: Monitoring auditory functions during cranial nerve microvascular decompression operations by direct recording from the eighth nerve. J Neurosurg 59:493, 1983.

63. Glascock III ME, Hays JW, Minor LB et al: Preservation of hearing in surgery for acoustic neuromas. J Neurosurg 78:864, 1993.

64. Peterson DO, Drummond JC, Todd MM: Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. Anesthesiology 65:35, 1986.

65. McPherson RW, Mahla M, Johnson R et al: Effects of enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials during fentanyl anesthesia. Anesthesiology 62:626, 1985.

66. Pathak KS, Amaddio BS, Scoles PV et al: Effects of halothane, enflurane, and isoflurane in nitrous oxide on multilevel somatosensory evoked potentials. Anesthesiology 70:207, 1989.

67. Samra SK, Vanderzant CW, Domer PA et al: Differential effects of isoflurane on human median nerve somatosensory evoked potentials. Anesthesiology 66:29, 1987.

68. Sebel PS, Ingram DA, Flynn PJ: Evoked potentials during isoflurane anaesthesia. Br J Anaesth 58:580, 1986.

69. Scholz J, Bischoff P, Szafarczyk W et al: Comparison of sevoflurane and isoflurane in ambulatory surgery. Results of a multicenter study. Anaesthesist 45:S63, 1996.

70. Haghighi SS, Sirintrapun SJ, Johnson JC et al: Suppression of spinal and cortical somatosensory evoked potentials by desflurane anesthesia. J Neurosurg Anesthesiol 8:148, 1996.

71. Manninen PH, Lam AM, Nicholas JF: The effects of isofluranenitrous oxide anesthesia on brainstem auditory evoked potentials in humans. Anesth Analg 64:43, 1985.

72. Thornton C, Catley DM, Jordan C et al: Enflurane anaesthesia causes graded changes in the brainstem and early cortical auditory evoked response in man. Br J Anaesth 55:479, 1983.

73. Dubois MY, Sato S, Chassy J et al: Effects of enflurane on brainstem auditory evoked responses in humans. Anesth Analg 61:898, 1982.

74. Cohen MS, Britt RH: Effects of sodium pentobarbital, ketamine, halothane, chloralose on brainstem auditory evoked responses. Anesth Analg 61:338, 1982.

75. Chi OZ, Field C: Effects of isoflurane on visual evoked potentials in humans. Anesthesiology 65:328, 1986.

76. Uhl RR, Squires KC, Bruce DL et al: Effect of halothane anesthesia on the human cortical visual evoked response. Anesthesiology 53:273, 1980.

77. Domino EF, Corssen G, Sweet RB: Effects of various general anesthetics on the visually evoked response in man. Anesth Analg 42:735, 1963.

78. Burchiel KG, Stockard JJ, Myers RR et al: Visual and auditory evoked responses during enflurane anesthesia in man and cats. Electroencephalogr Clin Neurophysiol 39:434P, 1973.

79. Sebel PS, Flynn PJ, Ingram DA: Effect of nitrous oxide on visual, auditory, and somatosensory evoked potentials. Br J Anaesth 56:1403, 1984.

80. Drummond JC, Todd MM, Sang H: The effect of high dose sodium thiopental on brain stem auditory and median nerve somatosensory evoked responses in humans. Anesthesiology 63:249, 1985.

81. Sutton LN, Frewen T, Marsh R et al: The effects of deep barbiturate coma on multimodality evoked potentials. J Neurosurg 57:178, 1982.

82. Shimoji K, Kano T, Nakashima H et al: The effects of thiamyl sodium on electrical activities of the central and peripheral nervous systems in man. Anesthesiology 40:234, 1974.

83. Ganes T, Lundar T: The effect of thiopentone on somatosensory evoked responses and EEGs in comatose patients. J Neurol Neurosurg Psychiatry 46:509, 1983.

84. Koht A, Schutz W, Schmidt G et al: Effects of etomidate, midazolam, and thiopental on median nerve somatosensory evoked potentials and the additive effects of fentanyl and nitrous oxide. Anesth Analg 67:435, 1988.

85. Sloan TB, Ronai AK, Toleikis JR et al: Improvement of intraoperative somatosensory evoked potentials by etomidate. Anesth Analg 67:582, 1988.

86. Navaratnarajah M, Thornton C, Heneghan CPH et al: Effect of etom-idate on the auditory evoked response in man. Proceedings of the Anaesthetic Research Society 55:1157P, 1983.

87. Grundy BL, Brown RH, Clifton PC: Effect of droperidol on somatosensory cortical evoked potentials. Electroencephalogr Clin Neurophysiol 50:158, 1980.

88. Doring WH, Daub D: Akustisch evozierte Hirstamm und Rindepotentiale bei sedierung mit diazepam. Arch Otorhinolaryngol 227:522, 1980.

89. Grundy BL, Brown RH, Greenbergh BA: Diazepam alters cortical potentials. Anesthesiology 51:538, 1979.

90. Stockard JJ, Rossiter VS, Jones TA et al: Effects of centrally acting drugs on brainstem auditory responses. Electroencephalogr Clin Neurophysiol 43:550, 1977.

91. Erwin CW, Linnoila M: Effect of ethyl alcohol on visual evoked potentials. Alcoholism 5:49, 1981.

92. Pathak KS, Brown RH, Cascorbi HF et al: Effects of fentanyl and morphine on intraoperative somatosensory cortical-evoked potentials. Anesth Analg 63:833, 1984.

93. Schubert A, Peterson DO, Drummond JC et al: The effect of high-dose fentanyl on human median nerve somatosensory evoked responses. Anesth Analg 65:S136, 1986.

94. Grundy BL, Brown RH: Meperidine enhances somatosensory cortical evoked potentials. Electroencephalogr Clin Neurophysiol 50:177, 1980.

95. Samra SK, Lilly DJ, Rush NL et al: Fentanyl anesthesia and human brain-stem auditory evoked potentials. Anesthesiology 61:261, 1984.

96. Eng DY, Dong WK, Bledsoe SW et al: Electrical and pathological correlates of brain hypoxia during hypotension. Anesthesiology 53:S92, 1980.

97. Kobrine AI, Evans DE, Rizzoli HV: Relative vulnerability of the brain and spinal cord to ischemia. J Neurol Sci 45:65, 1980.

98. Bunegin L, Albin MS, Helsel P et al: Evoked responses during trimethaphan hypotension. Anesthesiology 55:A232, 1981.

99. Grundy BL, Nash CL, Brown RH: Arterial pressure manipulation alters spinal cord function during correction of scoliosis. Anesthesiology 54:249, 1981.

100. Russ W, Kling D, Loesevitz A et al: Effect of hypothermia on visual evoked potential (VEP) in humans. Anesthesiology 61:207, 1984.

101. Stockard JJ, Sharbrough FW, Tinker JA: Effects of hypothermia on the human brainstem auditory response. Ann Neurol 3:368, 1978.

102. Dubois M, Loppola R, Buchsbaum MS et al: Somatosensory evoked potentials during whole body hyperthermia in humans. Electroencephalogr Clin Neurophysiol 52:157, 1981.

103. Nakagawa Y, Ohtsuka T, Tsura M et al: Effects of mild hypercapnia on somatosensory evoked potentials in experimental cerebral ischemia. Stroke 25:275, 1984.

104. Grundy BL, Heros RC, Tung AS et al: Intraoperative hypoxia detected by evoked potential monitoring. Anesth Analg 60:437, 1981.

105. Nagao S, Roccaforte P, Moody RA: The effects of isovolemic hemodilution and reinfusion of packed erythrocytes on somatosensory and visual evoked potentials. J Surg Res 25:S30, 1978.

106. Harper CM, Daube RJ: Surgical monitoring with evoked potentials: The Mayo Clinic experience. In Desmedt JE (ed): Neuromonitoring in Surgery. New York, Elsevier Science, 1989, p 275.

107. Harner SG, Daube JR, Beatty CW: Improved preservation of facial nerve function with use of electrical monitoring during removal of acoustic neuromas. Mayo Clin Proc 62:92, 1987.

108. Harner SG, Daube JR, Ebersold MJ: Electrophysiologic monitoring of facial nerve during temporal bone surgery. Laryngoscope 96:65, 1986.

109. Miller AR, Jannetta PJ: Microvascular decompression in hemifacial spasm: Intraoperative electrophysiological observations. Neurosurgery 16:612, 1985.

110. Lennon RL, Hosking MP, Daube JR et al: Effect of partial neuromuscular blockade on intraoperative electromyography in patients undergoing resection of acoustic neuroma. Anesth Analg 75:729, 1992.

111. Zentner J, Kiss I, Ebner A: Influence of anesthetics--nitrous oxide in particular--on electromyographic response evoked by transcranial electrical stimulation of the cortex. Neurosurgery 24:253, 1989.

112. Zentner J, Abner A: Nitrous oxide suppresses the electromyographic response evoked by electrical stimulation of the motor cortex. Neurosurgery 24:60, 1989.

113. Levy WJ, York DH, McCaffrey M et al: Motor evoked potentials from transcranial stimulation of the motor cortex in humans. Neurosurgery 15:287, 1984.

114. Zentner J: Motor evoked potential monitoring during neurosurgical operations on the spinal cord. Neurosurg Rev 14:29, 1991.

115. Owen JH, Laschinger J, Bridwell K et al: Sensitivity and specificity of somatosensory and neurogenic-motor evoked potentials in animals and humans. Spine 13:1111, 1988.

116. Edmonds HL, Paloheimo MPJ, Backman MH et al: Transcranial magnetic motor evoked potentials for functional monitoring of motor pathways during scoliosis surgery. Spine 14:683, 1989.

117. Boyd SG, Rothwell JC, Cowan JMA et al: A method of monitoring function in corticospinal pathways during scoliosis surgery with a note on motor conduction velocities. J Neurol Neurosurg Psychiatry 49:251, 1986.

118. Elmore JR, Gloviczki P, Harper CM et al: Failure of motor evoked potentials to predict neurologic outcome in experimental thoracic aortic occlusion. J Vasc Surg 14:131, 1991.

119. Reuter DG, Tacker WA, Badylak SF et al: Correlation of motor-evoked potential response to ischemic spinal cord damage. J Thorac Cardiovasc Surg 104:262, 1992.

120. Jellinek D, Jewkes D, Symon L: Noninvasive intraoperative monitoring of motor evoked potentials under propofol anesthesia: Effects of spinal surgery on the amplitude and latency of motor evoked potentials. Neurosurgery 29:551, 1991.

121. Nadstawek J, Taniguchi M, Langenbach U et al: Effects of four intravenous anesthetic agents on motor evoked potentials elicited by magnetic transcranial stimulation. Anesthesiology 77:A500, 1992.

122. Ghaly R, Stone J, Kartha R et al: The effect of etomidate anesthesia on magnetic spinal motor and sensory potentials in monkeys: A dose response study. Anesthesiology 77:A717, 1992.

123. Kalkman CJ, Drummond JC, Patel PM et al: Effects of droperidol, pentobarbital and ketamine on myogenic motor evoked responses in humans. Anesthesiology 77:A163, 1992.

124. DeWitt LD, Wechsler LR: Transcranial doppler. Stroke 19:915, 1988.

125. Halsey JH, McDowell HA, Gelman S: Transcranial doppler and rCBF compared in carotid endarterectomy. Stroke 17:1206, 1986.

126. van der Linden J, Casimir AH: When do cerebral emboli occur during open heart operations? A transcranial Doppler study. Ann Thoracic Surg 51:237, 1991.

127. Pugsley W, Klinger L, Paschalis C et al: The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 25:1393, 1994.

128. Clark RE, Brillman J, Davis DA et al: Microemboli during coronary artery bypass grafting. J Thorac Cardiovasc Surg 109:249, 1995.

129. Sloan MA, Haley EC, Kassell NF et al: Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. Neurology 39:1514, 1989.

130. Sekhar LN, Wechsler LR, Yonas H et al: Value of transcranial Doppler examination in the diagnosis of cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery 22:813, 1988.

131. Petty GW, Mohr JP, Pedley T et al: The role of transcranial Doppler in confirming brain death. Neurology 40:300, 1990.

132. Williams IM, Picton A, Farrell A et al: Light-reflective cerebral oximetry and jugular bulb venous oxygen saturation during carotid endarterectomy. Br J Surgery 81:1291, 1994.

133. Gopinath SP, Cormio M, Ziegler J et al: Intraoperative jugular desaturation during surgery for traumatic intracranial hematomas. Anesth Analg 83:1014, 1996.

134. Unterberg AW, Kiening KL, Hartl R et al: Multimodal monitoring in patients with head injury: Evaluation of the effects of treatment on cerebral oxygenation. J Trauma 42:S32, 1997.

135. Matta BF, Lam AM: The rate of blood withdrawal affects the accuracy of jugular venous bulb oxygen saturation measurements. Anesthesiology 86:806, 1997.

136. Moss E, Dearden NM, Berridge JC: Effects of changes in mean arterial pressure on SjO_2 during cerebral aneurysm surgery. Br J Anaesthesia 75:527, 1995.

137. Croughwell ND, White WD, Smith LR et al: Jugular bulb saturation and mixed venous saturation during cardiopulmonary bypass. J Card Surg 10:503, 1995.

138. Clark DL, Rosner BS: Neurophysiologic effects of general anesthetics. Anesthesiology 38:564, 1973.

Chapter 36 - Neuromuscular Monitoring

Jorgen Viby-Mogensen

INTRODUCTION

In 1958, Christie and Churchill-Davidson [1] described how nerve stimulators could be used to assess neuromuscular function objectively during anesthesia. For many years, however, only a few anesthesiologists used nerve stimulators routinely. Instead, the degree of neuromuscular block during and after anesthesia was evaluated with clinical criteria alone. Nevertheless, I believe that the interest in monitoring neuromuscular function during anesthesia has been growing over the past few years: New short- and intermediate-acting nondepolarizing neuromuscular blocking drugs have become available and awareness of the problems of postoperative residual neuromuscular blockade has been increasing. [2] [3]

In awake patients, muscle power can be evaluated through tests of voluntary muscle strength, but during anesthesia and recovery from anesthesia this is not possible. Instead, the clinician uses clinical tests to assess muscle power directly and to estimate neuromuscular function indirectly (muscle tone, the feel of the anesthesia bag, an indirect measure of pulmonary compliance, tidal volume, and inspiratory force). All of these tests, however, are influenced by factors other than the degree of neuromuscular blockade. Therefore, whenever more precise information regarding the status of neuromuscular functioning is desired, the response of muscle to nerve stimulation should be assessed. This procedure also takes into account the considerable variation in individual response to muscle relaxants. [4]

This chapter reviews the basic principles of peripheral nerve stimulation, the requirements for effective use of nerve stimulators, and the clinical conditions warranting their use. It also describes the response to nerve stimulation during depolarizing (phase I and phase II) and nondepolarizing neuromuscular blocks. Finally, the chapter discusses methods of evaluating evoked neuromuscular responses both with and without the availability of recording equipment.

PRINCIPLES OF PERIPHERAL NERVE STIMULATION

Neuromuscular function is monitored by evaluating the muscular response of muscle to supramaximal electrical stimulation of a peripheral motor nerve. The reaction of a single muscle fiber to a stimulus follows an all-or-none pattern. By contrast, the response of the whole muscle depends on the number of muscle fibers activated. If a nerve is stimulated with sufficient intensity, all muscle fibers supplied by the nerve will react, and the maximum response will be triggered. After administration of a neuromuscular blocking drug, the response of the muscle decreases in parallel with the number of fibers blocked. The reduction, in response during constant stimulation, reflects the degree of neuromuscular blockade.

For the preceding principles to be in effect, the stimulus must be truly maximal throughout the period of monitoring;

---

therefore, the electrical stimulus applied is usually at least 20 to 25 percent above that necessary for a maximal response. For this reason, the stimulus is said to be supramaximal; however, supramaximal stimulation hurts, which is not a concern during anesthesia, but during recovery the patient may be awake enough to experience the discomfort of nerve stimulation. Therefore, some researchers advocate stimulation with submaximal current during recovery. Although several investigations indicate that testing of neuromuscular function can be reliably performed postoperatively using submaximal stimulation, [5] [6] [7] the accuracy of the monitoring is unacceptable at low current. [8] As a result, supramaximal stimulation should be used when possible. The character of the waveform produced by the electrical impulse and the length of the stimulus are also important. [9] The impulse should be monophasic and rectangular (i.e., it should be a square wave) because a biphasic pulse may cause a burst of action potentials in the nerve (repetitive firing), increasing the response to the stimulation. The optimal pulse duration is 0.2 to 0.3 ms. A pulse exceeding 0.5 ms may stimulate the muscle directly or cause repetitive firing.

PATTERNS OF NERVE STIMULATION

Traditionally, evaluation of neuromuscular function has used three patterns of electrical stimulation: single-twitch, train-of-four (TOF), and tetanic nerve stimulation. Two newer modes are also available: post-tetanic count (PTC) stimulation and double-burst stimulation (DBS).

Single-Twitch Stimulation

In the single-twitch mode of stimulation, single supramaximal electrical stimuli are applied to a peripheral motor nerve at frequencies ranging from 1.0 Hz (once every second) to 0.1 (once every 10 seconds) (Fig. 36-1) (Figure Not Available) . The response to single-twitch stimulation depends on the frequency with which the individual stimuli are applied. If the rate of delivery is increased to more than 0.15 Hz, the evoked response will gradually decrease and settle at a lower level. [10] As a result, a frequency of 0.1 Hz is generally used. Because 1-Hz stimulation shortens the time necessary to determine supramaximal stimulation, this frequency is sometimes employed during induction of anesthesia; however, the apparent time of onset and length of neuromuscular blockade depend on the pattern and duration of stimulation. Therefore, results obtained using 1-Hz single-twitch stimulation cannot be compared with results obtained by using, for instance, 0.1-Hz single-twitch stimulation or TOF stimulation. [11]

Train-of-Four Stimulation

In TOF nerve stimulation, introduced by Ali et al [12] during the early 1970s, four supramaximal stimuli are given every 0.5 seconds (2 Hz) (Fig. 36-2) (Figure Not Available) . When used continuously, each set (train) of stimuli normally is repeated every 10th to 12th second. Each stimulus in the train causes the muscle to contract, and "fade" in the response provides the

Figure 36-1 (Figure Not Available) Pattern of electrical stimulation and evoked muscle responses to single-twitch nerve stimulation (at frequencies of 0.1 to 1.0 Hz) after injection of nondepolarizing *(Non-dep)* and depolarizing *(Dep)* neuromuscular blocking drugs *(arrows).* Note that except for the difference in time factors, no differences in the strength of the evoked responses exist between the two types of block. *(From Viby-Mogensen J [10C])*

basis for evaluation. That is, dividing the amplitude of the fourth response by the amplitude of the first response provides the TOF ratio. In the control response (the response obtained before administration of muscle relaxant), all four responses are ideally the same: The TOF ratio is 1.0. During a partial nondepolarizing block, the ratio decreases ("fades") and is inversely proportional to the degree of blockade. During a partial depolarizing block, no fade occurs in the TOF response; ideally, the TOF ratio is approximately 1.0. Fade in the TOF response after injection of succinylcholine signifies the development of a phase II block (discussed later in the *Depolarizing Neuromuscular Blockade* section).

The advantages of TOF stimulation are greatest during nondepolarizing blockade, as the degree of block can be

Figure 36-2 (Figure Not Available) Pattern of electrical stimulation and evoked muscle responses to TOF nerve stimulation before and after injection of nondepolarizing *(Non-dep)* and depolarizing *(Dep)* neuromuscular blocking drugs *(arrows). (From Viby-Mogensen J [10C])*

read directly from the TOF response, even though a preoperative value is lacking. [13] [14] [15] In addition, TOF stimulation has some advantages over tetanic stimulation: It is less painful and, unlike tetanic stimulation, generally does not affect the degree of neuromuscular blockade. However, onset and recovery of neuromuscular blockade after succinylcholine and atracurium were different with 0.08-Hz single-twitch stimulation and TOF stimulation. Although statistically significant, these differences were too small to be clinically important. [11] Also, it has been found that increasing periods of control TOF stimulations before injection of a nondepolarizing muscle relaxant may decrease the onset time and increase the duration of clinical relaxation. [16] [17]

Tetanic Stimulation

Tetanic stimulation consists of very rapid (e.g., 30-, 50-, or 100-Hz) delivery of electrical stimuli. The most commonly used pattern in clinical practice is 50-Hz stimulation given for 5 seconds, although some investigators have advocated the use of 50-, 100-, and even 200-Hz stimulation for 1 second. [18] During normal neuromuscular transmission and a pure depolarizing block, the muscle response to 50-Hz tetanic stimulation for 5 seconds is sustained. During a nondepolarizing block and a phase II block after succinylcholine, the response will not be sustained (i.e., fade occurs) (Fig. 36-3) (Figure Not Available) .

Figure 36-3 (Figure Not Available) Pattern of stimulation and evoked muscle responses to tetanic (50-Hz) nerve stimulation for 5 seconds (Te) and post-tetanic stimulation (1.0-Hz) twitch. Stimulation was applied before injection of neuromuscular blocking drugs and during moderate nondepolarizing and depolarizing blocks. Note fade in the response to tetanic stimulation, plus post-tetanic facilitation of transmission during nondepolarizing blockade. During depolarizing blockade, the tetanic response is well sustained and no post-tetanic facilitation of transmission occurs. *(From Viby-Mogensen J [10C])*

Fade in response to tetanic stimulation is normally considered a presynaptic event, and the traditional explanation is that at the start of tetanic stimulation, large amounts of acetylcholine are released from immediately available stores in the nerve terminal. As these stores become depleted, the rate of acetylcholine release decreases until equilibrium between mobilization and synthesis of acetylcholine is achieved. Despite this equilibrium, the muscle response caused by tetanic stimulation of the nerve at, for example, 50 Hz, is maintained (given normal neuromuscular transmission) simply because the release of acetylcholine is many times greater than the amount necessary to evoke a response. When the "margin of safety" of the postsynaptic membrane (i.e., the number of free cholinergic receptors) is reduced by a nondepolarizing neuromuscular blocking agent, the decrease in release of acetylcholine during tetanic stimulation produces "fade." [19] In addition to blocking the postsynaptic receptors, nondepolarizing neuromuscular blocking drugs may also impair the mobilization of acetylcholine within the nerve terminal. This effect may contribute to the fade in the response to tetanic (and TOF) stimulation. The degree of fade depends primarily on the degree of neuromuscular blockade. Fade also depends on the frequency (Hz) and the length (seconds) of stimulation and on how often tetanic stimuli are applied. Unless these variables are kept constant, results from different studies using tetanic stimulation cannot be compared.

During partial nondepolarizing blockade, tetanic nerve stimulation is followed by a post-tetanic increase in twitch tension (i.e., post-tetanic facilitation of transmission [PTF]) (see Fig. 36-3) (Figure Not Available) . This event occurs because the increase in mobilization and synthesis of acetylcholine caused by tetanic stimulation continues for some time after discontinuation of stimulation. The degree and duration of PTF depend on the degree of neuromuscular blockade, with PTF usually disappearing within 60 seconds of tetanic stimulation. PTF is evident in electromyographic (EMG), acceleromyographic, and mechanical recordings during a partial nondepolarizing neuromuscular blockade. By contrast, post-tetanic twitch potentiation, which sometimes occurs in mechanical recordings before any neuromuscular blocking drug has been given, is a muscular phenomenon that is not accompanied by an increase in the compound muscle action potential. [20] [21]

Tetanic stimulation has several disadvantages. It is very painful and therefore normally not acceptable to the unanesthetized patient. Furthermore, especially in the late phase of neuromuscular recovery, tetanic stimulations may produce a lasting antagonism of neuromuscular blockade in the stimulated muscle, such that the response of the tested site may no longer be representative of other muscle groups. [22] [23]

Traditionally, tetanic stimulation has been used to evaluate residual neuromuscular blockade. Except in connection with the technique of post-tetanic count, however, tetanic stimulation has very little place in everyday clinical anesthesia. If the response to nerve stimulation is recorded, all the information required can be obtained from the response to TOF nerve stimulation. By contrast, if the response to nerve stimulation is evaluated only by feel [24] or by eye (VibyMogensen et al, unpublished observation), even experienced observers are unable to judge the response of tetanic

stimulation with sufficient certainty to exclude residual neuromuscular blockade.

Post-Tetanic Count Stimulation

Injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient to ensure smooth tracheal intubation causes intense neuromuscular blockade of the peripheral muscles. Because no response to TOF and single-twitch stimulation occurs under these conditions, those modes of stimulation cannot be used to determine the degree of blockade. It is possible, however, to quantify intense neuromuscular blockade of the peripheral muscles by applying tetanic stimulation (50 Hz for 5 sec) and observing the post-tetanic response to single-twitch stimulation given at 1 Hz starting 3 seconds after the end of tetanic stimulation. [25] During very intense blockade, there is no response to either tetanic or post-tetanic stimulation (Fig. 36-4) . However, when the very intense neuromuscular blockade dissipates and before the first response to TOF stimulation reappears, the first response to post-tetanic twitch stimulation occurs. For example, after injection of pancuronium (0.1 mg/kg) for tracheal intubation, the response to post-tetanic twitch stimulation appears approximately 37 minutes before the first reaction to TOF stimulation. [25] The corresponding figures for atracurium (0.5 mg/kg) and vecuronium (0.1 mg/kg) vary from 7 to 8 minutes. [26] [27] As the intense block dissipates, more and more responses to post-tetanic twitch stimulation appear. For a given neuromuscular blocking drug, the time until return of the first response to TOF stimulation is related to the number of post-tetanic twitch responses present at a given time (the post-tetanic count) (Fig. 36-5) (Figure Not Available) .

The main application of the PTC method is in evaluating the degree of neuromuscular blockade when there is no reaction to single twitch or TOF nerve stimulation, as may be the case after injection of a large dose of a nondepolarizing neuromuscular

Figure 36-4 Pattern of electrical stimulation and evoked muscle responses to TOF nerve stimulation, 50 Hz tetanic nerve stimulation for 5 seconds (TE), and 1.0 Hz post-tetanic twitch stimulation (PTS) during four different levels of nondepolarizing neuromuscular blockade. During very intense blockade of the peripheral muscles (A), no response to any of the forms of stimulation occurs. During less pronounced blockade (B and C), there is still no response to stimulation, but post-tetanic facilitation of transmission is present. During surgical block (D), the first response to TOF appears and post-tetanic facilitation increases further. The post-tetanic count (see text) is 1 during intense block (B), 3 during less intense block (C), and 8 during surgical block (D).

Figure 36-5 (Figure Not Available) Relationship between time to the first reaction to TOF nerve stimulation and the number of post-tetanic twitches (i.e., the post-tetanic count) during intense blockade caused by pancuronium, atracurium, and vecuronium. Mean curves and 95 percent prediction regions are shown. *(From Viby-Mogensen J [10C])*

blocking drug. However, PTC can also be used whenever sudden movements must be eliminated (e.g., during ophthalmic surgery). The necessary level of block of the adductor pollicis muscle to ensure paralysis of the diaphragm depends on the type of anesthesia and, in the intensive care unit (ICU), on the level of sedation. [28] [29] To ensure elimination

Figure 36-6 (Figure Not Available) Relationship between the rate of muscle response to stimulation of the tracheal carina and the degree of neuromuscular blockade of peripheral muscles, as evaluated by using post-tetanic count. The subjects were 25 patients anesthetized with thiopental, nitrous oxide, and fentanyl who were given vecuronium (0.1 mg/kg) for tracheal intubation. For comparison, the first response to TOF stimulation usually occurs when PTC is approximately 10 (range, 6 to 16). The carina was stimulated with a soft sterile rubber suction catheter introduced via the endotracheal tube. The total response consisted of mild responses plus severe response. A mild response was said to occur if stimulation of the carina induced only slight bucking that did not interfere with surgery. A severe response was said to occur if stimulation elicited bucking that interfered with surgery and required intervention. Elimination of severe responses requires an intense neuromuscular blockade; PTC must be less than 2 to 3, and elimination of all reactions requires that PTC be 0. *(From Fernando PUE et al. [26] Copyright 1987, Munksgaard International Publishers, Ltd. Copenhagen, Denmark)*

of any bucking or coughing in response to tracheobronchial stimulation, neuromuscular blockade of the peripheral muscles must be so intense that no response to post-tetanic twitch stimulation can be elicited (PTC-0) (Fig. 36-6) (Figure Not Available) . [28]

The response to PTC stimulation depends primarily on the degree of neuromuscular blockade. It also depends on the frequency and duration of tetanic stimulation, the length of time between the end of tetanic stimulation and the first post-tetanic stimulus, the frequency of the single-twitch stimulation, and also (probably) the length of single-twitch stimulation before tetanic stimulation. When the PTC method is used, these variables should therefore be kept constant. Also, because of possible antagonism of neuromuscular blockade in the hand, tetanic stimulation should not be given more often than every 6 minutes. [30] If the hand muscles undergo antagonism of neuromuscular blockade while the rest of the body is still paralyzed, the hand muscles are no longer useful for monitoring.

Double-Burst Stimulation

DBS was developed with the specific aim of allowing manual (tactile) detection of small amounts of residual neuromuscular blockade under clinical conditions. [31] During recovery from neuromuscular blockade, the degree of residual block can be evaluated from recorded responses to TOF nerve stimulation. Without recording equipment, however, it is not possible by visual or tactile means to evaluate the TOF response with certainty to exclude shallow degrees of residual neuromuscular blockade. [32] With DBS (as opposed to TOF stimulation), it is easier to "feel" fade in the response. [33]

DBS consists of two short bursts of 50-Hz tetanic stimulation separated by 750 ms. The duration of each square wave impulse in the burst is 0.2 ms (Fig. 36-7) . Although the number of impulses in each burst can vary, initial studies indicate that DBS with three impulses in each of the two tetanic bursts ($DBS_{3,3}$) is suitable for clinical use. Studies are currently evaluating the suitability of other types of DBS. [34] [35] [36]

Figure 36-7 Pattern of electrical stimulation and evoked muscle responses to TOF nerve stimulation and double-burst nerve stimulation (i.e., three impulses in each of two tetanic bursts, $DBS_{3,3}$) before injection of muscle relaxants (control) and during recovery from nondepolarizing neuromuscular blockade. TOF ratio = the amplitude of the fourth response to TOF divided by the amplitude of the first response. $DBS_{3,3}$ ratio = the amplitude of the second response to $DBS_{3,3}$ divided by the amplitude of the first response. (See text for further explanation.)

Figure 36-8 Fade detectable by feel in the response to TOF and double-burst stimulation ($DBS_{3,3}$) in relation to the true TOF ratio, as measured mechanically. The axis indicates the percentage of instances in which fade can be felt at a given true TOF ratio. [32] [33] A TOF ratio of 0.70 to 0.75 is normally taken to reflect adequate recovery of neuromuscular function, [86] so that ideally fade should be felt in all patients with a TOF ratio below 0.7 and in no patients with a ratio above 0.7 (the "ideal curve"). (This figure was based on an idea originating with N. Ueda, Kurume University, Japan).

In nonparalyzed muscle, the response to $DBS_{3,3}$ is two short muscle contractions of equal strength. In the partly paralyzed muscle, the second response is weaker

than the first (i.e., the response fades) (see Fig. 36-7) . Measured mechanically, the TOF ratio correlates closely with the $DBS_{3,3}$ ratio. During recovery and immediately after surgery, tactile evaluation of the response to $DBS_{3,3}$ is superior to tactile evaluation of the response to TOF stimulation. [33] [37] [38] However, as appears from Figure 36-8 , absence of fade in the manually evaluated response to $DBS_{3,3}$ does not exclude residual neuromuscular blockade. [39]

THE NERVE STIMULATOR

Although many nerve stimulators are commercially available, not all meet the basic requirements for clinical use. The stimulus should produce a monophasic and rectangular waveform, and the length of the pulse should not exceed 0.2 to 0.3 ms. Stimulation at a constant current is preferable to stimulation at a constant voltage because current is the determinant of nerve stimulation. Also, for safety reasons, the nerve stimulator should be battery operated, include a battery check, and be able to generate 60 to 70 mA, but not more than 80 mA. Many commercially available stimulators can deliver only 25 to 50 mA and a constant current only when skin resistance ranges from 0 to 2.5 k. This deficiency is a disadvantage; during cooling, skin resistance may increase to approximately 5 k, which may cause the current delivered to the nerve to fall below the supramaximal level, leading to a decrease in the response to stimulation. As a result, the anesthesiologist may misjudge the degree of neuromuscular blockade. Ideally, the nerve stimulator should have a built-in warning system or a current level display that alerts the user when the current selected is not delivered to the nerve.

The ideal nerve stimulator should have other features as well. The polarity of the electrodes should be indicated. Also, the apparatus should be capable of delivering the following modes of stimulation: TOF (as both a single train and in a repetitive mode, with TOF stimulation being given every 10-20 sec); single-twitch stimulations at 0.1 and 1.0 Hz; and tetanic stimulation at 50 Hz. In addition, the stimulator should have a built-in time constant system to facilitate post-tetanic count. Tetanic stimulus should last 5 seconds and be followed 3 seconds later by the first post-tetanic stimulus. At least one DBS mode should be available, preferably DBS $_{3,3}$. Single-twitch stimulation at 1 Hz is useful during initiation of monitoring because it shortens the time necessary to determine supramaximal stimulation. Most investigators agree that there is no need for tetanus at 100 or 200 Hz because 50-Hz tetanic stimulation stresses neuromuscular function to the same extent as does a maximal voluntary effort. [40] Furthermore, in contrast to 100- and 200-Hz stimulation, 50-Hz tetanic stim-ulation does not cause fatigue (fade) in nonparalyzed muscle. [20] [21]

THE STIMULATING ELECTRODES

Electrical impulses are transmitted from stimulator to nerve by means of surface or needle electrodes, the former being the more commonly used in clinical anesthesia. Two basic types of surface electrodes exist: rubber electrodes and disposable pregelled silver or silver chloride electrodes. Both types can be used equally well, provided the actual conducting area is small, approximately 7 to 8 mm in diameter. Otherwise, the current produced in the underlying nerve may not be adequate. Rubber electrodes should not be allowed to become old because impedance of the electrodes increases with time. The skin should always be cleansed properly and preferably rubbed with an abrasive before application of the electrodes. When a supramaximal response cannot be obtained by using surface electrodes, needle electrodes should be used. Although specially coated needle electrodes are commercially available, ordinary steel injection needles can be used as well. The needles should be placed subcutaneously but never in a nerve.

SITES OF NERVE STIMULATION AND DIFFERENT MUSCLE RESPONSES

In principle, any superficially located peripheral motor nerve may be stimulated. In clinical anesthesia, the ulnar nerve is the most popular site; the median, the posterior tibial, common peroneal, and facial nerves are also sometimes used. For stimulation of the ulnar nerve, the electrodes are best applied at the volar side of the wrist (Fig. 36-9) (Figure Not Available) . The distal electrode should be placed about 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the radial side of the tendon to the flexor carpi ulnaris muscle. The proximal electrode preferably should be placed 2 to 5 cm proximal to the distal electrode. With this placement of the electrodes, electrical stimulation normally elicits only finger flexion and thumb adduction. If the one electrode is placed over the ulnar groove at the elbow, thumb adduction is often pronounced because of stimulation of the flexor carpi ulnaris muscle. When this latter placement of electrodes (sometimes preferred in small children) is used, the active negative electrode should be at the wrist to ensure a maximal response. [41] [42] Polarity of the electrodes is less crucial when both electrodes are close to each other at the volar side of the wrist; however, placement of the negative electrode distally normally elicits the greatest neuromuscular response. [43] When the temporal branch of the facial nerve is stimulated, the negative electrode should be placed over the nerve, and the positive electrode should be placed somewhere else over the forehead.

Because different muscle groups have different sensitivities to neuromuscular blocking agents, [44] results obtained for one muscle cannot be extrapolated automatically to other muscles. The diaphragm is among the most resistant of all muscles to both depolarizing [45] and nondepolarizing [46] neuromuscular blocking drugs. In general, the diaphragm requires 1.4 to 2.0 times as much muscle relaxant as the adductor pollicis muscle for an identical degree of blockade (Fig. 36-10) (Figure Not Available) . [46] Also of clinical significance are the facts that onset time is normally shorter for the diaphragm than for

Figure 36-9 (Figure Not Available) Evaluation of neuromuscular blockade by feeling the response of the thumb to stimulation of the ulnar nerve. *(Courtesy of Organon Teknika, Boxtel, Holland).*

Figure 36-10 (Figure Not Available) Mean cumulative dose-response curve for pancuronium in two muscles shows that the diaphragm requires approximately twice as much pancuronium as does the adductor pollicis muscle for the same amount of neuromuscular blockade. The depression in muscle response to the first stimulus in TOF nerve stimulation (probit scale) was plotted against dose (log scale). Force of contraction of the adductor pollicis was measured on a force-displacement transducer; response of the diaphragm was measured electromyographically. *(From Donati F [46])*

the adductor pollicis muscle and that the diaphragm recovers from paralysis more quickly than do the peripheral muscles (Fig. 36-11) (Figure Not Available) . [47] Less resistant than the diaphragm are the other respiratory muscles, as well as the larynx and the orbicularis oculi muscle. [48] [49] [50] [51] Most sensitive are the abdominal muscles, the peripheral muscles of the limbs, the geniohyoid muscle, the masseter, and the upper airway muscles. [52] [53] [54] [55] [56] From a practical clinical point of view, it is worth noting that (1) the orbicularis oculi response to facial nerve stimulation reflects the extent of neuromuscular blockade of the diaphragm better than does the response of the adductor pollicis to ulnar nerve stimulation, [38] and (2) the upper airway muscles seem to be more sensitive than peripheral muscles, at least to pancuronium. [53] [54] Although three recent investigations using acceleromyography have indicated small differences in the response to TOF nerve stimulation in the arm (adductor pollicis muscle) and the leg (flexor hallucis brevis muscle), these differences are probably of little clinical significance. [58] [59] [60]

The precise source of these differences is unknown. Possible causes may be differences in the margin of safety of the neuromuscular junction of different muscle groups, fiber composition, innervation ratio (number of neuromuscular junctions), blood flow, and muscle temperature.

In assessing neuromuscular function, the use of a relatively sensitive muscle such as the adductor pollicis of the hand has both disadvantages and advantages. Obviously, during surgery it is a disadvantage that even total elimination

Figure 36-11 (Figure Not Available) Evolution of twitch height (mean ± SD) of the diaphragm *(closed circles)* and of the adductor pollicis muscle (open circles) in 10 anesthetized patients after administration of atracurium 0.6 mg/kg. *(From Pansard J-L [47])*

of the response to single-twitch and TOF stimulation does not exclude the possibility of movement of the diaphragm, such as hiccuping and coughing. With the introduction of PTC, however, which allows for evaluation of the very intense blockade necessary to ensure total paralysis of the diaphragm, this problem has diminished. On the positive side, the chance of overdosing the patient decreases if the response of a relatively sensitive muscle is used as a guide to the administration of muscle relaxants during surgery. Also, during recovery, when the adductor pollicis has recovered sufficiently, it can be assumed that no residual neuromuscular blockade exists in the diaphragm.

RECORDING OF EVOKED RESPONSES

The choice of recording method is a practical decision. Three methods are available: measurement of evoked mechanical responses (mechanomyography), measurement of evoked electrical responses (EMG), and measurement of acceleration of the muscle response.

Mechanomyography

A requirement for correct and reproducible measurements of evoked tension is that the muscle contraction be isometric. In clinical anesthesia, this condition is most easily achieved by measuring thumb movement after application of a resting tension of 200 to 300 g (a preload) to the thumb. When the ulnar nerve is stimulated, the thumb (the adductor pollicis muscle) acts on a force-displacement transducer. The force of contraction is then converted into an electrical signal, which is amplified, displayed, and recorded. The arm and hand should be fixed rigidly, and care should be taken to prevent overloading of the transducer. [20] Also, the transducer should be placed in correct relationship to the thumb (i.e., the thumb should always apply tension precisely along the length of the transducer). It is important to remember that the response to nerve stimulation depends on the frequency with which the individual stimuli are applied and that the time used to achieve a stable control response may influence the subsequent determination of onset time and duration of block. [16] [17] [61] [62] Generally, the reaction to supramaximal stimulation increases during the first 8 to 12 minutes after commencement of the stimulation. Therefore, in clinical studies, control measurements (before injection of muscle relaxant) should not be made before the response has stabilized for 8 to 12 minutes or a 2-second or 5-second 50-Hz tetanic stimulation has been given. [62] Even then, twitch response often recovers to 110 to 150 percent of the control response after paralysis with succinylcholine. This increase in response, thought to be caused by a change in the contractile response of the muscle, normally disappears within 15 to 25 minutes.

Although numerous methods for mechanical recording of evoked mechanical responses exist, [15] [63] [64] not all meet the criteria outlined.

Electromyography

Evoked EMG records the compound action potentials produced by stimulation of a peripheral nerve. The compound action potential is a high-speed event that for many years could only be picked up by means of a preamplifier and a storage oscilloscope. Modern neuromuscular transmission analyzers are able to make on-line electronic analyses and graphic presentations of the EMG response.

The evoked EMG response is most often obtained from muscles innervated by the ulnar or the median nerves. Stimulating electrodes are applied as in force measurements. Although both surface and needle electrodes may be used for recording, no advantage is obtained by using the latter. Most often, the evoked EMG is obtained from the thenar or hypothenar eminence of the hand or from the first dorsal interosseous muscle of the hand, preferably with the active electrode over the motor point of the muscle (Fig. 36-12) (Figure Not Available) . The signal picked up by the analyzer is processed by an amplifier, a rectifier, and an electronic integrator. The results are displayed either as a percentage of control or as a TOF ratio.

Evoked electrical and mechanical responses represent different physiologic events. Evoked EMG records changes

---

Figure 36-12 (Figure Not Available) Electrode placement for stimulation of the ulnar nerve and for recording of the compound action potential from three sites of the hand. (A), Abductor digiti minimi muscle (in the hypothenar eminence). (B), Adductor pollicis muscle (in the thenar eminence). (C), First dorsal interosseus muscle. *(Courtesy of Datex-Ohmeda, Helsinki, Finland).*

in electrical activity of one or more muscles, whereas evoked mechanomyography records changes associated with excitation-contraction coupling and the contraction of the muscle as well. For these reasons, the results obtained with these methods may differ. [65] [66] [67] Although evoked EMG responses generally correlate well with evoked mechanical responses, [68] marked differences may occur, especially in the response to succinylcholine and in the TOF ratio during recovery from a nondepolarizing block. [65] [66] [67] [68]

So far, only one study has correlated the evoked EMG response with clinical criteria of adequate recovery of neuromuscular function. [68] This study compared clinical recovery from atracurium-induced blockade with TOF ratios meas-ured simultaneously by evoked electrical and mechanical responses. These two types of evoked responses were very similar in their relationship to clinical recovery. More studies are needed to correlate the evoked EMG responses with clinical criteria of surgical relaxation and adequacy of recovery from neuromuscular blockade.

In theory, recording of evoked EMG has several advantages over recording of evoked mechanical responses. Equipment for measuring evoked EMG responses is easier to set up, the response reflects only those factors influencing neuromuscular transmission, and the response can be obtained from muscles not accessible to mechanical recording. However, evoked EMG does entail some difficulties. Although good recordings are possible in most patients, results are not always reliable. For one thing, improper placement of electrodes may result in inadequate pickup of the compound EMG signal. If the neuromuscular transmission analyzer does not allow observation of the actual waveform of the compound EMG, determining the optimal placement of the electrodes is difficult. Another source of unreliable results may be that fixation of the hand with a preload on the thumb may be more important than generally appreciated, [68] [69] as changes in the position of the electrodes in relationship to the muscle may affect the EMG response. In addition, direct muscle stimulation sometimes occurs. If muscles close to the stimulating electrodes are stimulated directly, the recording electrodes may pick up an electrical signal even though neuromuscular transmission is completely blocked. Another difficulty is that the EMG response often does not return to control value. Whether this situation is the result of technical problems, inadequate fixation of the hand or changes in temperature is unknown (Fig. 36-13) (Figure Not Available) . Finally, the evoked EMG response is very sensitive

---

Figure 36-13 (Figure Not Available) Evoked electromyographic printout from a Relaxograph. Initially, single-twitch stimulation was given at 0.1 Hz, and vecuronium (70 mug/kg) was given intravenously for tracheal intubation. After approximately 5 minutes, the mode of stimulation was changed to TOF stimulation every 60 seconds. At a twitch height (first twitch in TOF response) of approximately 30 percent of control (marker 1), 1 mg of vecuronium was given intravenously. At marker 2, 1 mg of neostigmine was given intravenously, preceded by 2 mg of glycopyrrolate. The printout also illustrates the common problem of failure of the electromyographic response to return to control level. *(Courtesy of Datex-Ohmeda, Helsinki, Finland).*

to electrical interference, such as that caused by diathermy.

Acceleromyography

The technique of acceleromyography is based on Newton's second law: force equals mass times acceleration. [70] If mass is constant, acceleration is directly proportional to force. Accordingly, after nerve stimulation, one can measure not only the evoked force but also the acceleration of the thumb.

Acceleromyography uses a piezoelectric ceramic wafer with electrodes on both sides (Fig. 36-14) . Exposure of the electrode to a force generates an electrical voltage proportional to the acceleration of the thumb in response to nerve stimulation. When the accelerometer is fixed to the thumb and the ulnar nerve is stimulated, an electrical signal is produced whenever the thumb moves. This signal is then analyzed in a specially designed analyzer [71] or perhaps displayed on a recording system. At least three detached monitors based on measurement of acceleration are commercially available: The TOF-Guard, the TOF-Watch (both from Organon Teknika, Boxtel, Holland), and the ParaGraph Neuromuscular Blockade Monitor (Vital Signs Inc., Totowa, NJ). Furthermore, a unit, the Neuromuscular Transmission Module, M-NMT, based on the same principle, is part of the Datex AS/3 monitoring system (Datex-Ohmeda, Helsinki, Finland).

Acceleromyography is a simple method of analyzing neuromuscular function, both in the operating room and in the intensive care unit. [72] [73] One requirement is that the muscle be able to move freely. During a nondepolarizing neuromuscular blockade, good correlation exists between the TOF ratio measured by this method and TOF ratio measured with

Figure 36-14 TOF-Watch (Organon Teknika, Boxtel, Holland). This neuromuscular transmission monitor is based on measurement of acceleration using a piezo-electric transducer. [46] [47] Note the transducer fastened to the thumb and the stimulating electrodes. At the display of the TOF-Watch, note the TOF ratio given in percentage.

a force-displacement transducer [70] [71] [74] or using electromyography. [75] Also, the precision of acceleromyography seems to be comparable to that of mechanical measurements. [76]

Some questions still exist, however, regarding the use of this method of measurement that was primarily introduced for clinical use. [70] [71] The control TOF ratio is consistently higher than when measured using a force-displacement transducer. Therefore, measurements made with an accelerometer for scientific purposes are not directly comparable with results obtained with a force-displacement transducer [77] [78] [79] or with electromyography. [75]

For further information on recording evoked responses, the reader is referred to guidelines for Good Clinical Research Practice in pharmacodynamic studies of neuromuscular blocking agents, published in *Acta Anaesthesiologica Scandinavica* 40:59-74, 1996. [61]

EVALUATION OF RECORDED EVOKED RESPONSES

Nerve stimulation in clinical anesthesia is usually synonymous with TOF nerve stimulation. Therefore, the recorded response to this form of stimulation is used to explain how to evaluate the degree of neuromuscular blockade during clinical anesthesia.

Nondepolarizing Neuromuscular Blockade

After injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient for smooth tracheal intubation, TOF recording demonstrates three phases or levels

---

Figure 36-15 (Figure Not Available) Diagram of the changes in response to TOF nerve stimulation during nondepolarizing neuromuscular blockade. *(From Viby-Mogensen J [101])*

of neuromuscular blockade: intense blockade, moderate or surgical blockade, and recovery (Fig. 36-15) (Figure Not Available) .

Intense Neuromuscular Blockade

Intense neuromuscular blockade occurs within 3 to 6 minutes of injection of an intubating dose of a nondepolarizing muscle relaxant, depending on the drug and the dose given. This phase is also called the "period of no response" because no response to TOF or single-twitch stimulation occurs. The length of this period varies, again depending primarily on the duration of action of the muscle relaxant and the dose given. The sensitivity of the patient to the drug also affects the period of no response. Although during this phase, it is not possible to determine exactly how long intense neuromuscular blockade will last, correlation does exist between PTC and time to reappearance of the first response to TOF stimulation (see Fig. 36-5) (Figure Not Available) .

Moderate or Surgical Blockade

Moderate or surgical blockade begins when the first response to TOF stimulation appears. This phase is characterized by a gradual return of the four responses to TOF stimulation. Furthermore, good correlation exists between the degree of neuromuscular blockade and the number of responses to TOF stimulation. When only one response is detectable, the degree of neuromuscular blockade (the depression in twitch tension) is 90 to 95 percent. When the fourth response reappears, neuromuscular blockade is usually 60 to 85 percent. [14] [80] [81] The presence of one or two responses in the TOF pattern normally indicates sufficient relaxation for most surgical procedures. During light anesthesia, however, patients may move, buck, or cough. Therefore, when elimination of sudden movements is crucial, a more intense block (or a deeper level of anesthesia) may be necessary. The more intense block can then be evaluated by using the post-tetanic count (see Fig. 36-6) (Figure Not Available) .

Antagonism of neuromuscular blockade should normally not be attempted when blockade is intense because reversal will often be inadequate, regardless of the dose of antagonist administered. [82] Also, after the administration of large doses of muscle relaxants, reversal of the block to clinically normal activity is not always possible if only one response in the TOF is present. In general, antagonism should not be initiated before at least two, or preferably three, responses in the TOF are observed.

Recovery

The return of the fourth response in the TOF heralds the recovery phase. During neuromuscular recovery, a reasonably good correlation exists between the actual TOF ratio and clinical observations, but the relationship between TOF ratio and signs and symptoms of residual blockade varies greatly among patients. [83] When the TOF ratio is 0.4 or less, the patient is generally unable to lift the head or arm. Tidal volume may be normal, but vital capacity and inspiratory force will be reduced. When the ratio is 0.6, most patients are able to lift the head for 3 seconds, open the eyes widely, and stick out the tongue, but vital capacity and inspiratory force are often still reduced. At a TOF ratio of 0.7 to 0.75, the patient can normally cough sufficiently, and lift the head for at least 5 seconds, but the grip strength may still be as low as about 60% of control. [83] When the ratio is 0.8 and more, vital capacity and inspiratory force are normal. [13] [84] [85] [86] The patient may, however, still have diplopia and facial weakness (Table 36-1) . [83]

In clinical anesthesia, a TOF ratio of 0.70 to 0.75 or even 0.50, has been thought to reflect adequate recovery of neuromuscular function. [86] [87] However, recent studies have shown that the TOF ratio, whether recorded mechanically or by EMG, must exceed 0.80 or even 0.90 to exclude clinically important residual neuromuscular blockade. [56] [68] [88] [89] [90] Eriksson et al have shown that moderate degrees of neuromuscular block decrease the chemoreceptor sensitivity to hypoxia, leading to insufficient response to a decrease in oxygen tension in blood. [88] [89] They also showed that residual block (TOF < 0.90) is associated with functional impairment of the muscles of the pharynx and upper esophagus, most probably predisposing to regurgitations and aspiration. [56]

TABLE 36-1 -- Clinical Signs and Symptoms of Residual Paralysis in Awake Volunteers After Mivacurium-Induced Neuromuscular Block [83]

TOF ratio	Diplopia and visual disturbances
0.70-0.75	Decreased hand-grip strength
	Inability to maintain incisor teeth apposition
	"Tongue depressor test" negative
	Inability to sit up without assistance
	Severe facial weakness
	Speaking a major effort
	Overall weakness and tiredness
TOF ratio	Diplopia and visual disturbances

0.85-0.90	Generalized fatigue

In accordance with this, it has recently been documented that residual block (TOF < 0.70) caused by the long-acting muscle relaxant, pancuronium, is a significant risk factor for the development of postoperative pulmonary complications (Table 36-2 and Fig. 36-16) . [90] Available evidence indicates that adequate recovery of neuromuscular function requires return of the TOF ratio to
0.90, which cannot be guaranteed without the use of mechano-, electro, or acceleromyography. [91] [92] [93]

Depolarizing Neuromuscular Blockade (Phase I and II Blocks)

Patients with normal plasma cholinesterase activity who are given a normal dose of succinylcholine (0.5-1.5 mg/kg) undergo a typical depolarizing neuromuscular block (phase I block) (i.e., the response to TOF or tetanic stimulation does not fade, and no post-tetanic facilitation of transmission occurs). By contrast, some patients with genetically determined abnormal plasma cholinesterase activity who are given the same dose of succinylcholine undergo a nondepolarizing-like block characterized by fade in the response to TOF and tetanic stimulation and occurrence of post-tetanic facilitation of transmission (Fig. 36-17) (Figure Not Available) . This type of block is called a phase II block (or dual, mixed, or desensitizing block). Also, phase II blocks sometimes occur in genetically normal patients after prolonged infusion of succinylcholine.

Figure 36-16 Predicted probabilities of postoperative pulmonary complications in different age groups in orthopedic, gynecologic, and major abdominal surgery with a duration of anesthesia of less than 200 minutes. The full lines represent patients having residual neuromuscular block (TOF < 0.70) following the use of pancuronium; the broken lines represent patients with TOF 0.70 following pancuronium and all atracurium and vecuronium patients, independent of the TOF ratio at the end of anesthesia. [90]

TABLE 36-2 -- Relationship Between Train-of-Four Ratio at First Postoperative Recording and Postoperative Pulmonary Complications (POPC) [a]

	PANCURONIUM (n = 226)			ATRACURIUM OR VECURONIUM (N = 450)		
	NO. OF PATIENTS	PATIENTS WITH POPC		*NO. OF PATIENTS*	PATIENTS WITH POPC	
		n	%		*n*	%
TOF 0.70	167	8	4.8	426	23	5.4
TOF < 0.70	59	10	16.9 [b]	24	1	4.2

[a] Results from a prospective, randomized, and blinded study of postoperative POPC in a total of 691 adult patients undergoing abdominal, gynecologic, or orthopedic surgery, receiving either pancuronium, atracurium, or vecuronium. [90] In 4 of the 46 patients with POPC (1 in the pancuronium group and 3 in the atracurium-vecuronium groups) the TOF ratio was not available. Because there were no significant differences in the two groups of patients given the intermediate-acting muscle relaxants, the data from these groups are pooled.
[b] $P < 0.02$ compared with patients in the same group with TOF ratio 0.70.

Figure 36-17 (Figure Not Available) Typical recording of the mechanical response (Myograph 2000) to TOF nerve stimulation of the ulnar nerve after injection of succinylcholine, 1 mg/kg *(arrow)* in a patient with genetically determined abnormal plasma cholinesterase activity. The prolonged duration of action and the pronounced fade in the response indicate a phase II block. *(From Viby-Mogensen J [94])*

From a therapeutic point of view, a phase II block in normal patients must be differentiated from a phase II block in patients with abnormal cholinesterase activity. In normal patients, a phase II block can be antagonized by administering a cholinesterase inhibitor a few minutes after discontinuation of succinylcholine. [94] In patients with abnormal genotypes, the effect of intravenous injection of an acetylcholinesterase inhibitor (e.g., neostigmine) is unpredictable. For example, neostigmine can potentiate the block dramatically, temporarily improve neuromuscular transmission, and then potentiate the block or partially reverse the block, all depending on the time elapsed since administration of succinylcholine and the dose of neostigmine given. [94] Therefore, unless the cholinesterase genotype is known to be normal, antagonism of a phase II block with a cholinesterase inhibitor should be undertaken with extreme caution. Even if the neuromuscular function improves promptly, patient surveillance should continue for at least 1 hour.

USE OF NERVE STIMULATORS WITHOUT RECORDING EQUIPMENT

Although the interest in recording the evoked responses to nerve stimulation during clinical anesthesia is growing, muscle response is usually still evaluated by eye or by feel. Therefore, the anesthesiologist must know how to use a nerve stimulator when recording equipment is unavailable and must be aware of the possible pitfalls of this method. Otherwise, the information obtained from nerve stimulation may not be clinically useful.

First, for supramaximal stimulation, careful cleansing of the skin and proper placement and fixation of electrodes are essential. Second, every effort should be taken to prevent central cooling as well as cooling of the extremity being evaluated. Both central and local surface cooling of the adductor pollicis muscle may reduce the twitch tension and the TOF ratio. [95] [96] Peripheral cooling may affect nerve conduction, decrease the rate of release of acetylcholine [97] and muscle contractility, increase skin impedance, and reduce blood flow to the muscles, thus decreasing the rate of removal of muscle relaxant from the neuromuscular junction. These factors may account for the occasional very pronounced difference in muscle response between a cold extremity and the contralateral warm extremity. [98] Third, when possible, the response to nerve stimulation should be evaluated by feel and not by eye, and the response of the thumb (rather than that of the fifth finger) should be evaluated. Direct stimulation of the muscle often causes subtle movements of the fifth finger when no response is present at the thumb. Finally, the different sensitivities of various muscle groups to neuromuscular blocking agents should always be kept in mind.

Figure 36-18 shows which modes of nerve stimulation can be used at various perioperative times.

Figure 36-18 This diagram shows when the different modes of electrical nerve stimulation can be used during clinical anesthesia. Dark dotted areas indicate appropriate use; light dotted areas, less effective use. Modes of nerve stimulation: TOF = train-of-four stimulation; PTC = post-tetanic count; DBS = double-burst stimulation; and ? = TOF is less useful in the recovery room unless measured using mechano-, electro-, or acceleromyography. (See text for further explanation.)

Use of a Peripheral Nerve Stimulator During Induction of Anesthesia

The nerve stimulator should be attached to the patient before induction of anesthesia but should not be turned on until after the patient is unconscious. Single-twitch stimulation at 1 Hz may be used initially when seeking supramaximal stimulation. However, after supramaximal stimulation has been ensured and before muscle relaxant is injected, the mode of stimulation should be changed to TOF (or 0.1-Hz twitch stimulation). Then, after the response to this stimulation has been observed (the control response), the neuromuscular blocking agent is injected. Although the trachea is often intubated when the response of TOF stimulation disappears, postponement of this procedure for 30 to 90 seconds, depending upon the muscle relaxant used, usually produces better conditions.

Use of a Peripheral Nerve Stimulator During Surgery

If tracheal intubation is facilitated by the administration of succinylcholine (1 mg/kg), no more muscle relaxant should be given until the response to nerve stimulation reappears or until the patient shows other signs of returning neuromuscular function. If the plasma cholinesterase activity is normal, the muscle response to TOF nerve stimulation reappears within 4 to 8 minutes.

When a nondepolarizing neuromuscular drug is used for tracheal intubation, a longer-lasting period of intense blockade usually follows. During this period of no response to TOF and single-twitch stimulation, the time until return of response to TOF stimulation may be evaluated by using post-tetanic count (see Fig. 36-5) (Figure Not Available) .

For most surgical procedures requiring muscle relaxation, a twitch depression of approximately 90 percent will be sufficient, provided the patient is properly anesthetized. If a nondepolarizing relaxant is used, one or two of the responses in TOF can be felt. However, because the respiratory muscles (including the diaphragm) are less sensitive to neuromuscular blocking agents than are the peripheral muscles, the patient may breathe, hiccup, or even cough at this depth of block. To ensure paralysis of the diaphragm, neuromuscular blockade of the peripheral muscles must be so intense that PTC is zero in the thumb.

An added advantage of keeping the neuromuscular blockade at a level of one or two responses to TOF stimulation is that antagonism of the block is facilitated at the end of surgery.

Use of a Peripheral Nerve Stimulator During Reversal of Neuromuscular Blockade

Antagonism of a nondepolarizing neuromuscular block should not be initiated before at least two, and preferably three or four, responses to TOF stimulation can be felt or before obvious clinical signs of returning neuromuscular function are present. If all four responses to TOF stimulation can be felt before injection of the cholinesterase inhibitor, reversal is normally sufficient in less than 10 minutes, even when a long-lasting muscle relaxant has been given.

During recovery of neuromuscular function, when all four responses to TOF stimulation can be felt, an estimation of the TOF ratio may be attempted. However, manual (tactile) evaluation of the response to TOF stimulation (see Fig. 36-9) (Figure Not Available) is not sensitive enough to exclude the possibility of residual neuromuscular blockade. [33] [93] [95] Greater sensitivity is achieved with double-burst stimulation ($DBS_{3,3}$), but even absence of manual fade in the $DBS_{3,3}$ response does not exclude clinically significant residual blockade. [39] Therefore, manual evaluation of responses to nerve stimulation should always be considered in relation to clinical signs and symptoms of residual neuromuscular blockade, such as the ability of the patient to lift the head for 5 seconds, to open the eyes, to stick out the tongue, and to cough sufficiently. [44] [54]

/das/book/view/29494766/875/416.html

CONDITIONS WARRANTING THE USE OF PERIPHERAL NERVE STIMULATORS

At some institutions, nerve stimulators are used routinely whenever a neuromuscular blocking drug is given. In most cases, the response is evaluated by touch, and only in selected cases are the responses recorded. Many anesthesiologists do not agree with this extensive use of nerve stimulators and argue that they manage quite well without these devices. As stated elsewhere, however, [64] the question is not how little an experienced anesthetist can manage with, but rather, how to ensure that all patients receive optimal treatment. In my opinion, a nerve stimulator should be used in at least the following situations [4] : (1) whenever a long-acting muscle relaxant is used, (2) when the pharmacokinetics of a muscle relaxant are abnormal--in severe liver or kidney disease, severe illness, or the extremes of age, (3) during pharmacodynamics change--as in neuromuscular diseases such as myasthenia gravis and myasthenic syndrome, (4) when one wishes to avoid drug-induced reversal (with, for example, neostigmine) of neuromuscular blockade--as in severe heart disease or bronchial asthma, (5) when it is important that postoperative muscle power be maximal--as in severe pulmonary disease and marked obesity, (6) when surgery will be lengthy, and (7) when neuromuscular blockade is produced by continuous infusion of a neuromuscular blocking drug. [60] [91]

In some instances, tactile evaluation of the response to nerve stimulation is sufficient, when considered in relation to clinical signs and symptoms of residual neuromuscular blockade. However, it should be kept in mind that absence of manually and visually detectable fade in TOF and DBS $_{3,3}$ responses does not exclude clinically significant residual neuromuscular blockade. [39] [92] [93] [99] Only by measuring the response to nerve stimulation by more objective methods can this be achieved. [91] Thus every anesthesia department and every recovery room should have at least one apparatus for recording evoked responses. Whether the functioning of such a neuromuscular transmission analyzer is based on electromyography, mechanomyography, or measurement of acceleration is not crucial, as long as the physician knows how to use the apparatus in question.

References

1. Christie TH, Churchill-Davidson HC: The St. Thomas's Hospital nerve stimulator in the diagnosis of prolonged apnea. Lancet 1:776, 1958.

2. Viby-Mogensen J, Chraemmer-Jorgensen B, Ording H: Residual curarization in the recovery room. Anesthesiology 50:539, 1979.

3. Lennmarken C, Lofstrom JB: Partial curarization in the postoperative period. Acta Anesthesiol Scand 28:260, 1984.

4. Katz RL: Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 28:327, 1967.

5. Brull SJ, Ehrenwerth J, Silverman DG: Stimulation with submaximal current for train-of-four monitoring. Anesthesiology 72:629, 1990.

6. Brull SJ, Ehrenwerth J, Connelly NR, et al: Assessment of residual curarization using low-current stimulation. Can J Anaesth 38:164, 1991.

7. Silverman DG, Brull SJ: Assessment of double-burst monitoring at 10 mA above threshold current. Can J Anaesth 40:502, 1993.

8. Helbo-Hansen HS, Bang U, Nielsen HK, et al: The accuracy of train-of-four monitoring at varying stimulating currents. Anesthesiology 76:199, 1992.

9. Maclagan J: Competitive neuromuscular blocking drugs. In Zaimis E (ed): Neuromuscular Junction. Berlin, Springer-Verlag, 1976, p 426.

10. Ali HH, Savarese JJ: Stimulus frequency and dose response to d-tubocurarine in man. Anesthesiology 52:36, 1980.

11. Curran MJ, Donati F, Bevan DR: Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. Br J Anaesth 59:989, 1987.

12. Ali HH, Utting JE, Gray C: Stimulus frequency in the detection of neuromuscular blocks in humans. Br J Anaesth 42:967, 1970.

13. Ali HH, Utting JE, Gray C: Quantitative assessment of residual antidepolarizing block (part II). Br J Anaesth 43:478, 1971.

14. Lee C-M: Train-of-4 quantitation of competitive neuromuscular block. Anesth Analg 54:649, 1975.

15. Ali HH, Savarese JJ: Monitoring of neuromuscular function. Anesthesiology 45:216, 1976.

16. Meretoja OA, Taivanen T, Brandom BW, et al: Frequency of train-of-four stimulation influences neuromuscular response. Br J Anaesth 72:686, 1994.

17. McCoy EP, Mirakhur RK, Connolly FM, et al: The influence of the duration of control stimulation on the onset and recovery of neuromuscular block. Anesth Analg 80:364, 1995.

18. Gissen AJ, Katz RL: Twitch, tetanus and post-tetanic potentiation as indices of nerve-muscle block in man. Anesthesiology 30:484, 1969.

19. Paton WDM, Waud DR: The margin of safety of neuromuscular transmission. J Physiol 191:59, 1967.

20. Epstein RA, Epstein RM: The electromyograph and the mechanical response of indirectly stimulated muscle in anesthetized man following curarization. Anesthesiology 38:212, 1973.

21. Stanec A, Heyduk J, Stanec G, et al: Tetanic fade and post-tetanic tension in the absence of neuromuscular blocking agents in anesthetized man. Anesth Analg 57:102, 1978.

22. Brull SJ, Silverman DG: Tetanus-induced changes in apparent recovery after bolus doses of atracurium or vecuronium. Anesthesiology 77:642, 1992.

23. Saitoh Y, Masuda A, Toyooka H, et al: Effect of tetanic stimulation on subsequent train-of-four responses at various levels of vecuronium-induced neuromuscular block. Br J Anaesth 73:416, 1994.

24. Dupuis JY, Martin R, Tessonnier JM, et al: Clinical assessment of the muscular response to tetanic nerve stimulation. Can J Anaesth 37:397, 1990.

25. Viby-Mogensen J, Howardy-Hansen P, Chraemmer-Jorgensen B, et al: Post-tetanic count (PTC). A new method of evaluating an intense nondepolarizing neuromuscular blockade. Anesthesiology 55:458, 1981.

26. Bonsu AK, Viby-Mogensen J, Fernando PUE, et al: Relationship of post-tetanic count and train-of-four response during intense neuromuscular blockade caused by atracurium. Br J Anaesth 59:1089, 1987.

27. Muchhal KK, Viby-Mogensen J, Fernando PUE, et al: Evaluation of intense neuromuscular blockade caused by vecuronium using post-tetanic count (PTC). Anesthesiology 66:846, 1987.

28. Fernando PUE, Viby-Mogensen J, Bonsu AK, et al: Relationship between post-tetanic count and response to carinal stimulation during vecuronium-induced neuromuscular blockade. Acta Anaesthesiol Scand 31:593, 1987.

29. Werba A, Klezl M, Schramm W, et al: The level of neuromuscular block needed to suppress diaphragmatic movement during tracheal suction in patients with raised intracranial pressure: A study with vecuronium and atracurium. Anaesthesia 48:301, 1993.

30. Howardy-Hansen P, Viby-Mogensen J, Gottschau A, et al: Tactile evaluation of the post-tetanic count (PTC). Anesthesiology 60:372, 1984.

31. Engbaek J, Ostergaard D, Viby-Mogensen J: Double burst stimulation (DBS). A new pattern of nerve stimulation to identify residual curarization. Br J Anaesth 62:274, 1989.

32. Viby-Mogensen J, Jensen NH, Engbaek J, et al: Tactile and visual evaluation of the response to train-of-four nerve stimulation. Anesthesiology 63:440, 1985.

33. Drenck NE, Olsen NV, Ueda N, et al: Clinical assessment of residual curarization. A comparison of train-of-four stimulation and double burst stimulation. Anesthesiology 70:578, 1989.

34. Ueda N, Muteki T, Tsuda H, et al: Is the diagnosis of significant residual neuromuscular blockade improved by using double-burst nerve stimulation? Eur J Anaesth 8:213, 1991.

35. Saitoh Y, Nakazawa K, Tanaka H, et al: Double burst stimulation $_{2,3}$: A new stimulating pattern for residual neuromuscular block. Can J Anaesth 43:1001, 1996.

36. Saitoh Y, Nakazawa K, Makita K, et al: Evaluation of residual neuromuscular blockade using modified double burst stimulation. Acta Anaesthesiol Scand 41:741, 1997.

37. Saddler JM, Bevan JC, Donati F, et al: Comparison of double-burst and train-of-four stimulation to assess neuromuscular blockade in children. Anesthesiology 73:401, 1990.

38. Gill SS, Donati F, Bevan DR: Clinical evaluation of double-burst stimulation. Its relationship to train-of-four stimulation. Anaesthesia 45:543, 1990.

39. Fruergaard K, Viby-Mogensen J, Berg H, et al: Tactile evaluation of the response to double burst stimulation decreases, but does not eliminate the problem of postoperative residual paralysis. Acta Anaesthesiol Scand, 42:1168, 1998.

40. Merton PA: Voluntary strength and fatigue. J Physiol 123:553, 1954.

41. Berger JJ, Gravenstein JS, Munson ES: Electrode polarity and peripheral nerve stimulation. Anesthesiology 56:402, 1982.

42. Rosenberg H, Greenhow DE: Peripheral nerve stimulator performance: The influence of output polarity and electrode placement. Can J Anaesth 25:424, 1978.

43. Brull SJ, Silverman DG: Pulse width, stimulus intensity, electrode placement, and polarity during assessment of neuromuscular block. Anesthesiology 83:702, 1995.

44. Johansen SH, Jorgensen M, Molbeck S: Effect of tubocurarine on respiratory and non-respiratory muscle power in man. J Appl Physiol 19:990, 1964.

45. Smith CE, Donati F, Bevan DR: Potency of succinylcholine at the diaphragm and the adductor pollicis muscle. Anesth Analg 67:625, 1988.

46. Donati F, Antzaka C, Bevan DR: Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 65:1, 1986.

47. Pansard J-L, Chauvin M, Lebrault C, et al: Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 67:326, 1987.

48. Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. Anesthesiology 73:870, 1990.

49. Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. Anesthesiology 74:833, 1991.

50. Ungureanu D, Meistelman C, Frossard J, et al: The orbicularis oculi and the adductor pollicis muscles as monitors of atracurium block of laryngeal muscles. Anesth Analg 77:775, 1993.

51. Rimaniol JM, Dhonneur G, Sperry L, et al: A comparison of the neuromuscular blocking effects of atracurium, mivacurium, and vecuronium on the adductor pollicis and the orbicularis oculi mucle in humans. Anesth Analg 83:808, 1996.

52. Smith CE, Donati F, Bevan DR: Differential effects of pancuronium on masseter and adductor pollicis muscles in humans. Anesthesiology 71:57, 1989.

53. Isono S, Ide T, Kochi T, et al: Effects of partial paralysis on the swallowing reflex in conscious humans. Anesthesiology 75:980, 1991.

54. Pavlin EG, Holle R, Schone R: Recovery of airway protection compared with ventilation in humans after paralysis with curare. Anesthesiology 70:381, 1989.

55.

D'Honneur G, Guignard B, Slavov V, et al: Comparison of the neuromuscular blocking effect of atracurium and vecuronium on the adductor pollicis and the geniohyoid muscle in humans. Anesthesiology 82:649, 1995.

56. Eriksson LI, Sundman E, Olsson R, et al: Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans. Anesthesiology 87:1035, 1997.

57. Sopher MJ, Sears DH, Walts LF: Neuromuscular function monitoring comparing the flexor hallucis brevis and adductor pollicis muscles. Anesthesiology 69:129, 1988.

58. Suzuki T, Suzuki H, Katsumata N, et al: Evaluation of twitch responses obtained from abductor hallucis muscle as a monitor of neuromuscular blockade: Comparison with the results from adductor pollicis muscle. J Anesth 8:44, 1994.

59. Kern SE, Johnson JO, Orr JA, et al: Clinical analysis of the flexor hallucis brevis as an alternative site for monitoring neuromuscular block from mivacurium. J Clin Anesth 9:383, 1997.

60. Saitoh Y, Fujii Y, Takahashi K, et al: Recovery of post-tetanic count and train-of-four responses at the great toe and thumb. Anaesthesia 53:244, 1998.

61. Viby-Mogensen J, Engbaek J, Gramstad L, et al: Good Clinical Research Practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand 40:59, 1996.

62. Lee GC, Iyengar S, Szenohradszky J, et al: Improving the design of muscle relaxant studies. Anesthesiology 86:48, 1997.

63. Stanec A, Stanec G: The adductor pollicis monitor--apparatus and method for the quantitative measurement of isometric contraction of the adductor pollicis muscle. Anesth Analg 62:602, 1983.

64. Viby-Mogensen J: Clinical assessment of neuromuscular transmission. Br J Anesth 54:209, 1982.

65. Donati F, Bevan DR: Muscle electromechanical correlation during succinylcholine infusion. Anesth Analg 63:891, 1984.

66. Engbaek J, Skovgaard LT, Fries B, et al: Monitoring of neuromuscular transmission by electromyography (II). Evoked compound EMG area, amplitude and duration compared to mechanical twitch recording during onset and recovery of pancuronium-induced blockade in the cat. Acta Anaesthesiol Scand 37:788, 1993.

67. Kopman AF: The relationship of evoked electromyographic and mechanical responses following atracurium in humans. Anesthesiology 63:208, 1985.

68. Engbaek J, Ostergaard D, Viby-Mogensen J: Clinical recovery and train-of-four ratio measured mechanically and electromyographically following atracurium. Anesthesiology 71:391, 1989.

69. Kosek PS, Sears DHJ, Rubinstein EH: Minimizing movementinduced changes in twitch response during integrated electromyography, [letter]. Anesthesiology 69:142, 1988.

70. Viby-Mogensen J, Jensen E, Werner M, et al: Measurement of acceleration: A new method of monitoring neuromuscular function. Acta Anaesthesiol Scand 32:45, 1988.

71. Jensen E, Viby-Mogensen J, Bang U: The Accelograph: A new neuromuscular transmission monitor. Acta Anaesthesiol Scand 32:49, 1988.

72. Viby-Mogensen J: Monitoring neuromuscular function in the Intensive Care Unit. Intensive Care Med 19:S74, 1993.

73. Hodges UM: Vecuronium infusion requirements in paediatric patients in intensive care units: The use of acceleromyography. Br J Anaesth 76:23, 1996.

74. Werner MU, Kirkegaard Nielsen H, et al: Assessment of neuromuscular transmission by the evoked acceleration response. An evaluation of the accuracy of the acceleration transducer in comparison with a force displacement transducer. Acta Anaesthesiol Scand 32:395, 1988.

75. Ansermino JM, Sanderson PM, Bevan DR: Acceleromyography improves detection of residual neuromuscular blockade in children. Can J Anaesth 43:589, 1996.

76. May O, Kirkegaard Nielsen H, Werner MU: The acceleration transducer--an assessment of its precision in comparison with a force displacement transducer. Acta Anaesthesiol Scand 32:239, 1988.

77. Harper NJN, Martlew R, Strang T, et al: Monitoring neuromuscular block by acceleromyography: Comparison of the Mini-Accelograph with the Myograph 2000. Br J Anaesth 72:411, 1994.

78. Kern SE, Johnson JO, Westenkow DR, et al: An effectiveness study of a new piezoelectric sensor for train-of-four measurement. Anesth Analg 78:978, 1994.

79. McCluskey A, Meakin G, Hopkinson JM, et al: A comparison of acceleromyography and mechanomyography for determination of the dose-response curve of rocuronium in children. Anaesthesia 52:345, 1997.

80. Gibson FM, Mirakhur RK, Clarke RSJ, et al: Quantification of train-of-four responses during recovery of block from non-depolarizing muscle relaxants. Acta Anaesthesiol Scand 31:655, 1987.

81. O'Hara DA, Fragen RJ, Shanks CA: Comparison of visual and meas-ured train-of-four recovery after vecuronium-induced neuromuscular blockade using two anaesthetic techniques. Br J Anaesth 58:1300, 1986.

82. Engbaek J, Ostergaard D, Theil Skovgaard L, et al: Reversal of intense neuromuscular blockade following infusion of atracurium. Anesthesiology 72:803, 1990.

83. Kopman AF, Yee PS, Neuman GG: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 86:765, 1997.

84. Ali HH, Wilson RS, Savarese JJ, et al: The effect of tubocurarine in indirectly elicited train-of-four muscle response and respiratory meas-urements in humans. Br J Anaesth 47:570, 1975.

85. Ali HH, Utting JE, Gray C: Quantitative assessment of residual antidepolarizing block (part I). Br J Anaesth 43:473, 1971.

86. Brand JB, Cullen DJ, Wilson NE, et al: Spontaneous recovery from non-depolarizing neuromuscular blockade: Correlation between clinical and evoked responses. Anesth Analg 56:55, 1977.

87. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453, 1984.

88. Eriksson LI, Lennmarken C, Wyon N, et al: Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. Acta Anaesthesiol Scand 36:710, 1992.

89. Eriksson LI, Sato M, Severinghaus JW: Effect of a vecuroniuminduced partial neuromuscular block on hypoxic ventilatory response. Anesthesiology 78:693, 1993.

90. Berg H, Viby-Mogensen J, Roed J, et al: Residual neuromuscular block is a risk factor for postoperative pulmonary complications. Acta Anaesthesiol Scand 41:1095, 1997.

91. Mortensen CR, Berg H, El-Mahdy A, et al: Perioperative monitoring of neuromuscular transmission using acceleromyography prevents residual neuromuscular block following pancuronium. Acta Anaesthesiol Scand 39:797, 1995.

92. Shorten GD, Merk H: Perioperative train-of-four monitoring and residual curarization. Can J Anaesth 42:711, 1995.

93. Kopman AF, Ng J, Zank LM, et al: Residual postoperative paralysis. Pancuronium versus mivacurium, does it matter? Anesthesiology 85:1253, 1996.

94. Viby-Mogensen J: Cholinesterase and succinylcholine. Dan Med Bull 30:129, 1983.

95. Heier T, Caldwell JE, Sessler DI, et al: The effect of local surface and central cooling on adductor pollicis twitch tension during nitrous oxide/isoflurane and nitrous oxide/fentanyl anesthesia in humans. Anesthesiology 72:807, 1990.

96. Eriksson LI, Lennmarken C, Jensen E, et al: Twitch tension and train-of-four ratio during prolonged neuromuscular monitoring at different peripheral temperatures. Acta Anaesthesiol Scand 35:247, 1991.

97. Thornton RL, Blakeney C, Feldman SA: The effect of hypothermia on neuromuscular conduction. Br J Anaesth 48:264, 1976.

98. Thornberry EA, Mazumdar B: The effect of changes in arm temperature on neuromuscular monitoring in the presence of atracurium blockade. Anaesthesia 43:447, 1988.

99. Pedersen T, Viby-Mogensen J, Bang U, et al: Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative residual neuromuscular blockade? Anesthesiology 73:835, 1990.

100. Viby-Mogensen J: Monitoring of neuromuscular block. In Swen J, et al (eds): New Developments in Neuromuscular Relaxant Drugs. Leiden, Boerhave Committee for Postgraduate Medical Education, 1984, p 71.

101. Viby-Mogensen J: Clinical measurement of neuromuscular function: An update. Clin Anaesthesiol 3:467, 1985.

Chapter 37 - Temperature Monitoring

Daniel I. Sessler

INTRODUCTION

Mammals and birds are homeothermic, requiring a nearly constant internal body temperature. When internal temperature deviates significantly from normal, metabolic functions usually deteriorate, and death may result. The thermoregulatory system usually maintains core body temperature within 0.2°C of "normal," which is about 37°C in humans. Anesthetic-induced inhibition of thermoregulation combines with exposure to a cold operating room environment to make most unwarmed patients hypothermic.

In recent years, major outcome studies have shown that mild hypothermia (
1-2°C) (1) triples the incidence of morbid cardiac outcomes, (2) triples the incidence of surgical wound infections and prolongs hospitalization 20 percent, and (3) significantly increases surgical blood loss and the need for allogeneic transfusions. An understanding of normal and anesthetic-influenced thermoregulation facilitates prevention and management of these and numerous other temperature-related complications.

NORMAL THERMOREGULATION

Thermoregulation is similar to many other physiologic control systems in that the brain uses negative and positive feedback to minimize perturbations from preset, "normal" values. Since 1912, investigators have known that animals regulate body temperature poorly when the hypothalamus is destroyed. The importance of thermal input from the skin surface was recognized in the late 1950s, when it was observed that mice placed in a cold environment shivered *without decreasing* their hypothalamic temperatures.

In the early 1960s, physiologists reported active thermoregulation in response to isolated warming and cooling at sites other than hypothalamus or skin surface, including extrahypothalamic portions of the brain, deep abdominal tissues, and the spinal cord. [1] Thus, thermoregulation is now known to be based on multiple, redundant signals from nearly every type of tissue. The processing of thermoregulatory information occurs in three phases: *afferent thermal sensing, central regulation,* and *efferent responses.*

Afferent Input

Temperature information is obtained from thermally sensitive cells throughout the body. Cold-sensitive cells are anatomically and physiologically distinct from those that detect warmth. Warm receptors increase their firing rates when temperature increases, and cold receptors increase their firing rates when temperature decreases. Cutaneous warm receptors rarely depolarize at normal skin temperatures and probably are important only during heat stress. The hypothalamus, other parts of the brain, the spinal cord, the deep abdominal and thoracic tissues, and the skin surface each contribute roughly 20 percent of the total thermal input to the central regulatory system. [2] [3]

Cold signals travel primarily via Adelta nerve fibers, and warm information travels by unmyelinated C fibers, although there is some overlap. [4] The C fibers also detect and convey pain sensation, which is why intense heat cannot be distinguished from sharp pain. Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. Consequently, the entire anterior spinal cord must be destroyed to ablate thermoregulatory responses.

Central Control

Temperature is regulated by central structures (primarily the hypothalamus) that compare integrated thermal inputs from the skin surface, neuroaxis, and deep tissues with *threshold* temperatures for each thermoregulatory response. Although integrated by the hypothalamus, most thermal information is "preprocessed" in the spinal cord and other parts of the central nervous system. This hierarchical arrangement presumably developed when the evolving thermoregulatory control system co-opted previously existing mechanisms (e.g., shivering from muscles previously used for posture and locomotion). [1] It is likely that some thermoregulatory responses can be mounted by the spinal cord alone. [3] For example, animals and patients with high spinal-cord transections regulate temperature better than expected.

The slope of response intensity versus core temperature defines the *gain* of a thermoregulatory response. Response intensity no longer increasing with further deviation in core temperature identifies the *maximum intensity.* This system of thresholds and gains is a model for a thermoregulatory system that is further complicated by interactions between other regulatory responses (i.e., vascular volume control) and time-dependent effects.

How the body determines absolute threshold temperatures is unknown, but the mechanism appears to be mediated by norepinephrine, dopamine, 5-hydroxytryptamine, acetylcholine, prostaglandin E_1, and neuropeptides. The thresholds vary daily in both sexes (circadian rhythm) and monthly in women by 0.5°C. Exercise, food intake, infection, hypothyroidism and hyperthyroidism, anesthetic and other drugs (including alcohol, sedatives, and nicotine), and cold and warm adaptation alter threshold temperatures. Central regulation is intact in infants, but it frequently is impaired in elderly or extremely ill patients.

Figure 37-1 (Figure Not Available) There is a linear relation between mean skin temperature and the core temperature triggering vasoconstriction and shivering. Skin temperature contributes about 20 percent to control of each thermoregulatory defense. *(From Cheng et al [5])*

Control of autonomic responses is approximately 80 percent determined by thermal input from core structures (Fig. 37-1) (Figure Not Available) . [5] [6] In contrast, a large fraction of the input controlling behavioral responses is derived from the skin surface. The *interthreshold range* (core temperatures *not* triggering autonomic thermoregulatory responses) is only 0.2°C. [7] This range is bounded by the sweating threshold at its upper end and by vasoconstriction at the lower end. Because energy cost and nutrients are conserved without excessive autonomic control within this range, some animals, such as camels and desert rats, use this strategy extensively, allowing core temperature changes up to 10°C each day.

Both sweating and vasoconstriction thresholds are 0.3 to 0.5°C higher in women than in men, even during the follicular phase of the monthly cycle (first 10 days). [8] Differences are even greater during the luteal phase. [9] Central thermoregulatory control is apparently intact even in somewhat premature infants. [10] In contrast, thermoregulatory failure is common in the elderly. [11]

Efferent Responses

The body responds to thermal perturbations (body temperatures differing from the appropriate threshold) via effector mechanisms that increase metabolic heat production or alter environmental heat loss. Each thermoregulatory effector has its own threshold and gain, so there is an orderly progression of responses and response intensities in proportion to need. In general, energy-efficient effectors such as vasoconstriction are maximized before metabolically costly responses such as shivering are initiated. The interaction among thermal input, central control, and effector responses

---

Figure 37-2 (Figure Not Available) Schematic illustration of thermoregulatory control mechanisms. Mean body temperature is the integrated thermal input from a variety of tissues including the brain, skin surface, spinal cord, and deep core structures. These are shown entering the hypothalamus (large square) from the left. However, thresholds usually are expressed in terms of core temperature. A core temperature below the thresholds for response to cold provokes vasoconstriction, nonshivering thermogenesis, and shivering. Core temperature exceeding the hyperthermic thresholds produces active vasodilation and sweating. No thermoregulatory responses are initiated when core temperature is between these thresholds; these temperatures identify the interthreshold range. The interthreshold range in humans is usually only about 0.2°C. (Threshold data from Lopez et al [7] ; figure from Sessler DI: Perioperative hypothermia. N Engl J Med 336:1730, 1997.)

is shown in Figure 37-2; this figure also shows the normal values for the major autonomic response thresholds.

Effectors determine the ambient temperature range that the body will tolerate while maintaining core temperature normal. When specific effector mechanisms are inhibited (e.g., shivering prevented by administration of muscle relaxants), the tolerable range is decreased. Still, temperature remains normal unless other effectors cannot compensate for the imposed stress. Quantitatively, *behavioral regulation* (e.g., dressing appropriately, modifying environmental temperature, assuming positions that oppose skin surfaces, and voluntary movement) is the most important effector mechanism.

Infants regulate their temperatures remarkably well. In contrast, advanced age, infirmity, or medications can diminish the efficacy of thermoregulatory responses and can increase the risk of hypothermia. For example, decreased muscle mass, neuromuscular diseases, and muscle relaxants all inhibit shivering and thereby increase the minimum tolerable ambient temperature. Similarly, anticholinergic drugs inhibit sweating, thus decreasing the maximum tolerable temperature.

Cutaneous vasoconstriction is the most consistently used autonomic effector mechanism. Metabolic heat is lost primarily via convection and radiation from the skin surface, and vasoconstriction reduces this loss. Total digital skin blood flow is divided into nutritional (mostly capillary) and thermoregulatory (mostly arteriovenous shunt) components. [12] The arteriovenous shunts are anatomically and functionally distinct from the capillaries supplying nutritional blood to the skin; thus, vasoconstriction does not compromise the needs of peripheral tissues. Shunts are typically 100 mum in diameter, which means that one can convey 10,000-fold as much blood as a comparable length of capillary 10 mum in diameter.

Control of blood flow through the arteriovenous shunts tends to be "on" or "off." In other words, the gain of this response is high. Local alpha-adrenergic sympathetic nerves mediate constriction in the thermoregulatory arteriovenous shunts; flow is minimally affected by *circulating* catecholamines. Systemic hemodynamic changes usually are not observed during thermoregulatory vasoconstriction because only about 10 percent of cardiac output traverses these vessels; larger arterioles that control blood pressure are not influenced.

Nonshivering thermogenesis increases metabolic heat production (measured as whole-body oxygen consumption) without producing mechanical work. It doubles heat production in infants, [13] but it increases it only slightly in adults. [14] The intensity of nonshivering thermogenesis increases in linear proportion to the difference between mean body temperature and its threshold. Skeletal muscle and brown fat are the major sources of nonshivering heat in adults. The metabolic rate in both tissues is controlled primarily by norepinephrine release from adrenergic nerve terminals, and it is further mediated locally by an uncoupling protein. [15]

Sustained shivering increases metabolic heat production only 50 to 100 percent in adults. This augmentation is small compared with that produced by exercise (which can at least briefly increase metabolism 5-fold) and is thus surprisingly ineffective. Shivering does not occur in newborn infants, and probably it is not fully effective until children are several years old. The rapid tremor (
250 Hz) and unsynchronized muscular activity of thermogenic shivering suggest no central oscillator. However, superimposed on the fast activity, there usually is a slow (4-8 cycle/min), synchronous "waxing-and-waning" pattern that presumably is centrally mediated. [16]

Sweating is mediated by postganglionic, cholinergic nerves. [17] It thus is an active process that is prevented by nerve block or atropine administration. [18] Even untrained individuals can sweat up to 1 L/hr, and athletes can sweat at twice that rate. Sweating is the only mechanism by which the body can dissipate heat in an environment exceeding core temperature. Fortunately, the process is remarkably effective, dissipating 0.58 kcal/g of evaporated sweat.

Active vasodilation is mediated by a yet-to-be-identified factor released from sweat glands; the mediator may be a protein because it is not blocked by any standard drugs. [19] Because active vasodilation requires intact sweat gland function, it also is largely inhibited by nerve block. During extreme heat stress, blood flow through the top millimeter of skin can reach 7.5 L/min, equaling the entire resting cardiac output. [20] The threshold for active vasodilation usually is similar to the sweating threshold, but the gain may be less. Consequently, maximum cutaneous vasodilation usually is delayed until core temperature is well above that provoking maximum sweating intensity.

THERMOREGULATION DURING GENERAL ANESTHESIA

Behavioral regulation is not relevant during general anesthesia because patients are unconscious and frequently paralyzed. All general anesthetics so far tested markedly impair

normal autonomic thermoregulatory control. Anestheticinduced impairment has a specific form: warm-response thresholds are elevated slightly, whereas cold-response thresholds are markedly reduced. Consequently, the interthreshold range is increased from its normal values near 0.2°C to 2 to 4°C. [21] [22] [23] [24] [25] The gain and maximum intensity of some responses remain normal, [8] whereas others are reduced by general anesthesia. [26] [27]

Response Thresholds

Propofol, [21] alfentanil, [22] and dexmedetomidine [23] all produce a slight, linear increase in the sweating threshold combined with a marked and linear decrease in the vasoconstriction and shivering thresholds. Isoflurane [25] and desflurane [24] similarly slightly increase the sweating threshold; however, they decrease the cold-response thresholds nonlinearly. Consequently, the volatile anesthetics inhibit vasoconstriction and shivering less than propofol at low concentrations, but more than propofol at typical anesthetic doses. In all cases (except during meperidine administration [28]), vasoconstriction and shivering decrease synchronously, thus maintaining their normal
1°C difference.

The dose-dependent response thresholds for four anesthetic drugs are shown in Figure 37-3. The combination of increased sweating thresholds and reduced vasoconstriction thresholds increases the interthreshold range
20-fold, from its normal value near 0.2°C to
2 to 4°C. Temperatures within this range do *not* trigger thermoregulatory defenses; by definition, patients are thus poikilothermic within this temperature range.

Halothane, [29] enflurane, [30] and the combination of nitrous oxide and fentanyl [31] decrease the vasoconstriction threshold 2 to 4°C from its normal value near 37°C. However, the effects of these drugs on sweating or shivering remain unknown. Clonidine synchronously decreases cold-response thresholds, [32] while slightly increasing the shivering threshold. [33] Nitrous oxide decreases the vasoconstriction threshold less than equipotent concentrations of volatile anesthetics. [34] It also decreases the shivering threshold. [35] The only sedative or anesthetic drug so far tested that minimally influences thermoregulatory control is midazolam. [36]

Thresholds in Infants and the Elderly

Thermoregulatory vasoconstriction is comparably impaired in infants, children, and adults given isoflurane [37] or halothane [38] (Fig. 37-4). In contrast, the vasoconstriction threshold is about 1°C less in patients aged 60 to 80 years than in those between 30 and 50 years old (Fig. 37-5) (Figure Not Available) . [39] [40] Painful stimulation slightly increases vasoconstriction thresholds [30] ; Consequently, thresholds are somewhat lower when surgical pain is prevented by simultaneous local or regional anesthesia.

Nonshivering thermogenesis does not occur in anesthetized adults, [41] a finding that is not surprising because this response is not particularly important in unanesthetized adults. [14] Nonshivering thermogenesis in animals is inhibited peripherally by volatile anesthetics. [42] However, this thermoregulatory defense also fails to increase metabolic rate in infants anesthetized with propofol. [43]

Figure 37-3 The major autonomic thermoregulatory response thresholds in volunteers given desflurane, alfentanil, dexmedetomidine, and propofol. All slightly increase the sweating threshold (triggering core temperature) while markedly and synchronously decreasing the vasoconstriction and shivering thresholds. Standard deviation bars smaller than the data markers have been deleted. *(Data from Annadata et al [24] ; Kurz et al [22] ; Talke et al [25] ; and Matsukawa et al [21])*

Figure 37-4 (Figure Not Available) The core thermoregulatory threshold in 23 healthy children and infants undergoing abdominal surgery with halothane anesthesia. Differences among the groups are not statistically significant. Results are presented as means ± standard deviation. *(From Bissonnette and Sessler [36])*

Gain and Maximum Response Intensity

Both the gain and maximum intensity of sweating remain normal during isoflurane [8] and enflurane anesthesia. [44] The gain of arteriovenous shunt vasoconstriction is reduced 3-fold during desflurane anesthesia (Fig. 37-6) (Figure Not Available) . [26] Maximum vasoconstriction intensity, however, remains normal during general anesthesia. [45]

Shivering is rare during surgical doses of general anesthesia, a finding consistent with its threshold of roughly 1°C less than the vasoconstriction threshold. [21] [22] [23] [24] [25] (Vasoconstriction usually prevents additional hypothermia, [46] so even unwarmed patients rarely become cold enough to shiver.)

Figure 37-5 (Figure Not Available) The vasoconstriction threshold was significantly less in elderly patients (33.9 ± 0.6°C) than in younger patients (35.1 ± 0.3°C) during 60 percent nitrous oxide and isoflurane (0.75% end-tidal concentration). Filled squares indicate the vasoconstriction threshold in each patient; open circles show the mean and standard deviations in each group. *(From Kurz et al [39])*

Figure 37-6 (Figure Not Available) Finger blood flow without (open circles) and with (filled squares) desflurane administration. Values were computed relative to the thresholds (finger flow, 1.0 mL/min) in each subject. Flows of exactly 1.0 mL/min are not shown because flows in each individual were averaged over 0.1 or 0.05°C increments; each data point thus includes both higher and lower flows. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although errors bars are shown only at a flow near 1.0 mL/min, the same temperature variability applies to each data point. The slopes of the flow versus core temperature relationships (1.0-
0.15 mL/min) were determined using linear regression. These slopes defined the gain of vasoconstriction with and without desflurane anesthesia. Gain was reduced by a factor of 3, from 2.4 to 0.8 $mL \cdot min^{-1} \cdot °C^{-1}$ ($P < .01$). *(From Kurz et al [26])*

Nonetheless, shivering can be induced by sufficient active cooling.

Gain and maximum shivering intensity remain normal during both meperidine and alfentanil administration. [47] Gain also remains nearly intact during nitrous oxide administration, although maximum intensity is reduced. [35] Isoflurane changes the macroscopic pattern of shivering to such an extent that is no longer possible to determine gain easily. The drug does, however, reduce maximum shivering intensity. [27]

Sweating thus appears to be the thermoregulatory defense that is best preserved during anesthesia. Not only is the threshold only slightly increased, but also the gain and maximum intensity are well preserved. In contrast, the thresholds for vasoconstriction and shivering are markedly reduced. Furthermore, these responses are less effective than normal, even after being activated.

DEVELOPMENT OF HYPOTHERMIA DURING GENERAL ANESTHESIA

Inadvertent hypothermia during anesthesia is by far the most common perioperative thermal disturbance. Hypothermia results from a combination of anesthetic-impaired thermoregulation and exposure to a cold operating room environment.

Heat Transfer

Heat can be transferred from a patient to the environment four ways: (1) radiation, (2) conduction, (3) convection, and (4) evaporation. Among these, radiation and convection contribute most to perioperative heat loss.

All surfaces at temperatures higher than absolute zero radiate heat; similarly, all surfaces absorb radiative heat from surrounding surfaces. Heat transfer via this mechanism is proportional to the difference of the fourth power of the absolute temperature difference between the surfaces. It is likely that radiation is the major type of heat loss in most surgical patients. [48]

Conductive heat loss is proportional to the temperature difference between two adjacent surfaces and the strength of the thermal insulation separating them. In general, conductive losses are negligible during surgery because patients usually only directly contact the foam pad (an excellent thermal insulator) covering most operating room tables.

Conductive loss of heat directly to air molecules is limited by the development of a layer of still air adjacent to the skin that serves as an insulator. When this layer is disturbed by air currents, the insulative properties diminish substantially, and heat loss therefore increases. This increase is termed convection, and it is proportional to the square root of air speed; this is the correction used in the familiar "wind chill" factor. Air speed in operating rooms--even those with fairly high rates of air turnover--typically is only
20 cm/s, a speed that only slightly increases loss compared with that in still air. Nonetheless, convective loss usually is the second most important mechanism by which heat is transferred from patients to the environment. Convective loss presumably increases substantially in operating rooms equipped to provide laminar flow. However, the actual augmentation has not been quantified and may be less than expected from the increase in air speed because surgical draping provides considerable thermal insulation.

Sweating increases cutaneous evaporative loss enormously, but it is rare during anesthesia. In the absence of sweating, evaporative loss from the skin surface is limited to less than 10 percent of metabolic heat production in adults. In contrast, infants lose a higher fraction of their metabolic heat from transpiration of water through thin skin. The problem becomes especially acute in premature infants, who may lose one-fifth of their metabolic heat production via transcutaneous evaporation. [49] [50] Simple thermodynamic calculations and clinical measurements indicate that only trivial amounts of heat are lost from the respiratory system. [51] However, evaporation inside surgical wounds can contribute substantially to total heat loss. [52]

Patterns of Intraoperative Hypothermia

Hypothermia during general anesthesia develops with a characteristic pattern. An initial rapid decrease in core temperature is followed by a slow, linear reduction in core temperature. Finally, core temperature stabilizes and subsequently remains virtually unchanged (Fig. 37-7) . Each component of this typical pattern has a different cause.

Figure 37-7 Hypothermia during general anesthesia develops with a characteristic pattern. An initial rapid decrease in core temperature results from a core-to-peripheral redistribution of body heat. This is followed by a slow, linear reduction in core temperature that results simply from heat loss exceeding heat production. Finally, core temperature stabilizes and subsequently remains virtually unchanged. This plateau phase may be a passive thermal steady state, or it may result when sufficient hypothermia triggers thermoregulatory vasoconstriction. Results are presented as means ± standard deviation.

Volatile anesthetics cause vasodilation via a direct peripheral action. [53] More importantly, they also inhibit tonic thermoregulatory vasoconstriction, resulting in arteriovenous shunt dilation. [21] [22] [23] [24] [25] Nonetheless, anesthetic-induced vasodilation increases cutaneous heat loss only slightly. [54] Anesthetics reduce metabolic rate 20 to 30 percent. [55] However, even the combination of increased heat loss and reduced heat production is insufficient to explain the 0.5 to 1.5°C decrease in core temperature usually observed during the first hour of anesthesia.

The key to understanding the initial decrease in core temperature is to appreciate that body heat is not evenly distributed. Core temperature represents only about half the body mass (mostly the trunk and head); the remaining mass is considerably cooler, typically 2 to 4°C less than core temperature. This core-to-peripheral tissue temperature gradient is normally maintained by tonic thermoregulatory vasoconstriction. Anesthetic-induced vasodilation, however, allows core heat to flow peripherally. This warms the arms and legs, but it does so at the expense of the core (Figs. 37-8, 37-9) . [56]

Following initial redistribution hypothermia, core temperature usually decreases in a slow, linear fashion for 2 to 4 hours. This reduction results simply from heat loss exceeding metabolic heat production. [57] After 3 to 4 hours of anesthesia, core temperature usually reaches a plateau and remains virtually constant for the duration of surgery. [31] The core temperature plateau may simply represent a thermal steady state (heat production equaling heat loss) in patients remaining relatively warm. [58] In others, however, the plateau phase is associated with peripheral thermoregulatory vasoconstriction triggered by core temperatures 33 to 35°C. [59]

Thermoregulatory vasoconstriction during anesthesia significantly decreases cutaneous heat loss, [45] but this decrease alone is usually insufficient to produce a thermal steady state. Furthermore, neither adults [41] nor infants [43] appear able to increase intraoperative heat production in response to hypothermia. An additional mechanism must therefore

Figure 37-8 A cartoon illustrating internal redistribution of body heat following induction of general anesthesia. Hypothermia following induction of spinal or epidural anesthesia results similarly, but

redistribution is restricted to the legs.

contribute to the core temperature plateau. Evidence suggests that a primary factor is constraint of metabolic heat to the core thermal compartment. In this situation, distribution of metabolic heat (which largely is produced centrally) is restricted to the core compartment, thus maintaining its temperature. Peripheral temperature, in contrast, continues to decrease because the tissue is no longer being supplied

Figure 37-9 (Figure Not Available) Changes in body heat content and distribution of heat within the body during induction of general anesthesia (at elapsed time zero). The change in mean body temperature was subtracted from the change in core (tympanic membrane) temperature, leaving the core hypothermia specifically resulting from redistribution. Redistribution hypothermia was thus not a measured value; instead, it is defined by the decrease in core temperature not explained by the relatively small decrease in systemic heat content. After 1 hour of anesthesia, core temperature had decreased 1.6 ± 0.3°C, with redistribution contributing 81 percent to the decrease. Even after 3 hours of anesthesia, redistribution contributed 65 percent to the entire 2.8 ± 0.5°C decrease in core temperature. Results are presented as means ± standard deviation. *(Modified from Matsukawa et al [56])*

Figure 37-10 (Figure Not Available) Changes in body heat content and distribution of heat within the body during the core temperature plateau. Elapsed time zero indicates the onset of arteriovenous shunt vasoconstriction, which causes the plateau. Core temperature decreased 1.3°C in 2 hours before constriction, then remained constant. The difference between core temperature and mean body temperature (which continued to decrease) indicates how much heat was retained in the core thermal compartment by thermoregulatory vasoconstriction. In this case, 22 ± 8 kcal was constrained to the core. Results are presented as means ± standard deviation. *(Modified from Kurz et al [46])*

with sufficient heat from the core (Fig. 37-10) (Figure Not Available) . [46] A core temperature plateau resulting from thermoregulatory vasoconstriction thus is not a thermal steady state, and body heat content continues to decrease even though core temperature remains nearly constant.

NEUROAXIAL ANESTHESIA

Autonomic thermoregulation is impaired during regional anesthesia, and the result typically is intraoperative core hypothermia. Interestingly, this hypothermia often is not consciously perceived by patients, but it nonetheless triggers shivering. The result frequently is a potentially dangerous clinical paradox: a shivering patient who denies feeling cold.

Thermoregulation

Epidural [60] [61] and spinal [61] [62] anesthesia each decreases the thresholds triggering vasoconstriction and shivering (above the level of the block) about 0.6°C (Fig. 37-11) (Figure Not Available) . Presumably, this decrease does not result from recirculation of neuroaxially administered local anesthetic because impairment is similar during epidural and spinal anesthesia, [60] [61] [62] although the amount and location of administered local anesthetic differ substantially. Furthermore, lidocaine administered intravenously (IV) in doses producing plasma

Figure 37-11 (Figure Not Available) Spinal anesthesia increased the sweating threshold but reduced the thresholds for vasoconstriction and shivering. Consequently, the interthreshold range increased substantially. The vasoconstriction-to-shivering range, however, remained normal during spinal anesthesia. Results are presented as means ± standard deviation. *(From Kurz et al [62])*

concentrations similar to those occurring during epidural anesthesia has no thermoregulatory effect. [63] Finally, neuroaxial administration of 2-choloprocaine, which has a plasma half-life near 20 seconds, also impairs thermoregulatory control. [64]

The vasoconstriction and shivering thresholds are comparably decreased during regional anesthesia, [62] suggesting an alteration in central, rather than peripheral, control. Peripheral administration of local anesthesia appears to impair centrally mediated thermoregulation by altering afferent thermal input from the legs. The key factor here is that tonic cold signals dominate thermal input at leg skin temperatures in typical operating room environments. [4] [65] Regional anesthesia blocks all thermal input from blocked regions, but in the typical case this is mostly cold information. The brain then seems to interpret decreased cold information as relative leg warming. Because skin temperature is an important input to the thermoregulatory control system, leg warming proportionately reduces the vasoconstriction and shivering thresholds. Consistent with this theory, a leg skin temperature near 38°C is required to reduce cold-response thresholds as much as regional anesthesia. [66] Furthermore, reduction in the thresholds is proportional to the number of spinal segments blocked (Fig. 37-12) (Figure Not Available) . [67] Major conduction anesthesia thus appears to reduce the vasoconstriction and shivering thresholds by producing an abnormal elevation of *apparent* (as opposed to actual) leg temperature.

Because neuroaxial anesthesia prevents vasoconstriction and shivering in blocked regions, it should not be surprising that epidural anesthesia decreases the maximum intensity of shivering. However, epidural anesthesia also reduces the gain of shivering, which suggests that the regulatory system is unable to compensate for lower body paralysis (Fig. 37-13) (Figure Not Available) . [68] Thermoregulatory defenses, once triggered, are thus less effective than usual during regional anesthesia.

Neuroaxial anesthesia is frequently supplemented with sedative and analgesic medications. With the exception of midazolam, [36] most such agents significantly impair thermoregulatory control. Alfentanil [22] and meperidine, [28] for example, decrease the vasoconstriction and shivering thresholds. Similarly, propofol impairs cold responses during epidural anesthesia. [69] Such inhibition may be severe when combined with the intrinsic impairment produced by regional

Figure 37-12 (Figure Not Available) The number of dermatomes blocked (sacral segments, 5; lumbar segments, 5; thoracic segments, 12) versus reduction in the shivering threshold (difference between the control shivering threshold and spinal shivering threshold). The shivering threshold was reduced more by extensive spinal blocks than by less extensive ones (Delta threshold = 0.74 - 0.06 (dermatomes blocked); r^2 = .58, P < .006). The curved lines indicate the 95 percent confidence intervals for the slope. *(Modified from Leslie and Sessler [67])*

anesthesia and other factors, including advanced age or preexisting illness (Fig. 37-14) (Figure Not Available) . [11]

Interestingly, core hypothermia during regional anesthesia may not trigger a perception of cold. [60] [70] The reason is

Figure 37-13 (Figure Not Available) Systemic oxygen consumption without (circles) and with (squares) epidural anesthesia. The horizontal standard deviation bars indicate variability in the thresholds among the volunteers; although errors bars are shown only once in each series, the same temperature variability applies to each data point. The slopes of the oxygen consumption versus core temperature relationships (solid lines) were determined using linear regression. These slopes defined the gain of shivering with and without epidural anesthesia. Gain was reduced 3.7-fold, from -412 $mL \cdot min^{-1} \cdot °C^{-1}$ (r^2 = .99) to -112 $mL \cdot min^{-1} \cdot °C^{-1}$ (r^2 = .96). *(From Kim et al [66])*

Figure 37-14 (Figure Not Available) Fifteen patients aged less than 80 years (58 ± 10 y) (mean ± SD) shivered at 36.1 ± 0.6°C during spinal anesthesia; in contrast, 8 patients aged 80 years (89 ± 7 y) or more shivered at a significantly lower mean temperature, 35.2 ± 0.8°C. The shivering thresholds in 7 of the 10 patients aged more than 80 years was less than 35.5°C, whereas the threshold equaled or exceeded this value in all the younger patients. *(From Vassilieff et al [11])*

that thermal perception (behavioral regulation) is largely determined by skin rather than by core temperature. During regional anesthesia, core hypothermia is accompanied by real and apparent increases in skin temperature. The result typically is a perception of continued or increased warmth accompanied by autonomic thermoregulatory responses including shivering (Fig. 37-15) (Figure Not Available) . [60] [70]

Taken together, these data indicate that neuroaxial blocks inhibit numerous aspects of thermoregulatory control. The vasoconstriction and shivering thresholds are reduced by regional anesthesia, [60] [61] [62] [66] [67] and they are further reduced by adjuvant drugs [22] [28] [69] and advanced age. [11] Even once triggered, the gain and maximum response intensity of shivering

Figure 37-15 (Figure Not Available) Induction of epidural anesthesia at elapsed time 15 minutes decreased core temperature and increased thermal comfort as determined by a 100-mm visual-analogue scale (VAS). However, maximal thermal comfort coincided with *minimum* core temperature. Results are presented as means ± standard deviation. *(Modified from Sessler and Ponte [60])*

are about half normal. [68] Finally, behavioral thermoregulation is impaired. [70] The result is that cold defenses are triggered at a lower temperature than normal during regional anesthesia, defenses are less effective once triggered, and patients frequently do not recognize that they are hypothermic. Because core temperature monitoring remains rare during regional anesthesia, substantial hypothermia often goes undetected in these patients.

Heat Balance

Hypothermia is common during regional anesthesia and may be nearly as severe as during general anesthesia. [71] [72] [73] Core temperature typically decreases 0.5 to 1.0°C shortly after induction of anesthesia. However, vasodilation induced by regional anesthesia only slightly increases cutaneous heat loss. Furthermore, metabolic heat production remains constant, or it increases because of shivering thermogenesis. This rapid decrease in core temperature, similar to the one that follows induction of general anesthesia, also results from an internal core-to-peripheral redistribution of body heat (Fig. 37-16) (Figure Not Available) . [74] As during general anesthesia, redistri-bution hypothermia during regional anesthesia can be minimized by cutaneous warming before induction. [75]

Subsequent hypothermia results simply from heat loss that exceeds metabolic heat production. Unlike in patients given general anesthesia, however, core temperature does

Figure 37-16 (Figure Not Available) Overall heat balance was only slightly negative (loss exceeding production) before induction of anesthesia, and subsequently changed little. To separate the contributions of decreased overall heat balance and internal redistribution of body heat to the decrease in core temperature, the change in overall heat balance was divided by body weight and the specific heat of humans. The resulting change in mean body temperature ("mean body") was subtracted from the change in core temperature ("core"), leaving the core hypothermia specifically resulting from redistribution ("redistribution"). After 1 hour of anesthesia, core temperature had decreased 0.8 ± 0.3°C, with redistribution contributing 89 percent to the decrease. During the subsequent 2 hours of anesthesia, core temperature decreased an additional 0.4 ± 0.3°C, with redistribution contributing 62 percent. Redistribution thus contributed 80 percent to the entire 1.2 ± 0.3°C decrease in core temperature during the 3 hours of anesthesia. The increase in the "redistribution" curve before induction of anesthesia indicates that thermoregulatory vasoconstriction was constraining metabolic heat to the core thermal compartment. Such constraint is, of course, the only way in which core temperature could increase while body heat content decreased. Induction of epidural anesthesia is identified as elapsed time zero. Results are presented as means ± standard deviation. *(Modified from Matsukawa et al [74])*

not necessary plateau after several hours of surgery. Not only is the vasoconstriction threshold centrally impaired by regional anesthesia, [61] [62] but more importantly, vasoconstriction in the legs is directly prevented by nerve block. [76] [77] Because the legs constitute the bulk of the thermal compartment, an effective plateau cannot develop without vasoconstriction in the legs and the resulting decrease in cutaneous heat loss and constraint of metabolic heat to the core.

The importance of intraoperative leg vasoconstriction is illustrated during combined regional/general anesthesia. Consistent with the impairment of thermoregulatory responses with regional anesthesia alone, [61] [62] vasoconstriction during combined regional/general anesthesia is triggered at a core temperature approximately 1°C less than during general anesthesia alone. Furthermore, vasoconstriction, once triggered, produces a core temperature plateau during general anesthesia alone but not during combined regional/general anesthesia. The result is that core temperature during combined regional/general anesthesia continues to decrease throughout surgery. [78] Consequently, core temperature monitoring and thermal management are particularly important in patients given simultaneous regional and general anesthesia.

Shivering

Shivering-like tremor in volunteers given regional anesthesia always is preceded by core hypothermia and vasoconstriction (above the level of the block). [60] Furthermore, electromyographic analysis indicates that the tremor has the 4- to 8-cycle/min waxing-and-waning pattern characterizing normal shivering. [64] The tremor thus apparently is normal thermoregulatory shivering, triggered when redistribution hypothermia decreases core temperature. It remains probable, however, that tremor during regional anesthesia in pregnant women has a different cause. Similarly, the shivering-like tremor so often observed during labor without regional anesthesia has yet to be adequately characterized. In both cases, there appears to be a significant incidence of shivering-like tremor in normothermic and vasodilated patients. This observation suggests that some tremor is nonthermoregulatory because shivering should always be preceded by hypothermia and arteriovenous shunt vasoconstriction.

Spinal thermal receptors have been detected in every mammal and bird so far tested. Experimental stimulation of these receptors reliably produces shivering in animals. Stimulation in humans of these putative receptors by epidural anesthetic injection theoretically could initiate thermoregulatory responses including shivering. Consistent with this possibility, the incidence of shivering in pregnant women is greater when they are given refrigerated epidural anesthetic than when the anesthetic is warmed before injection. [79] However, epidural administration of large amounts of ice-cold saline does not trigger shivering in nonpregnant volunteers. [80] Furthermore, the incidence of shivering is comparable in volunteers [60] and nonpregnant patients [81] given warm or cold epidural anesthetic injections. These data indicate that, at least in nonpregnant individuals, temperature of injected local anesthetic does not influence the incidence of shivering during major conduction anesthesia.

Most shivering during regional anesthesia can be prevented by maintaining strict normothermia. [60] However, it may be difficult to prevent redistribution from decreasing core temperature the relatively small amount necessary to trigger shivering. Alternatively, shivering can be treated in most cases by warming sentient skin to increase cutaneous thermal input to the central regulatory system, thus increasing the degree of tolerated core hypothermia. [82] Because the entire skin surface contributes 20 percent to thermoregulatory control [5] and the lower body contributes about 10 percent, [66] sentient skin warming is likely only to compensate for small reductions in core temperature. The same drugs that are effective for postanesthetic tremor also are useful for shivering during regional anesthesia: these include meperidine (25 mg IV or epidurally), [83] clonidine (75 mug IV), [84] ketanserin (10 mg IV), [84] and magnesium sulfate (30 mg/kg). [85]

CONSEQUENCES OF MILD INTRAOPERATIVE HYPOTHERMIA

Perianesthetic hypothermia produces potentially severe complications as well as distinct benefits. Thermal management thus deserves the same thoughtful analysis of potential risks and benefits as other therapeutic decisions.

Benefits

Substantial protection against ischemia and hypoxia is provided by just 1 to 3°C of hypothermia. [86] [87] [88] Protection initially was thought to result from the 8 percent/°C reduction in tissue metabolic rate. However, the efficacy of mild hypothermia far exceeds that of treatments, such as high-dose isoflurane or barbiturate coma, that comparably reduce metabolic rate. [89] These data suggest that other actions (e.g., decreased release of excitatory amino acids) explain the protective action of hypothermia.

The protection afforded by mild hypothermia is so great that reduced core temperature (i.e., 34°C) is probably indicated during carotid artery surgery, neurosurgery, and other procedures in which tissue ischemia can be anticipated. However, there are currently no outcome data in humans substantiating this extrapolation from animal data. Mild hypothermia does, however, appear beneficial in patients with traumatic brain injury. [90] It similarly appears beneficial in patients with acute respiratory distress syndrome. [91]

Acute malignant hyperthermia is more difficult to trigger in mildly hypothermic swine than in those kept normothermic. Furthermore, once triggered, the syndrome is less severe. [92] [93] These data suggest that active warming should be avoided in patients known to be susceptible to malignant hyperthermia; instead, they should be allowed to become slightly hypothermic during surgery.

Complications

Coagulation is impaired by mild hypothermia. The most important factor appears to be a cold-induced defect in platelet function. [94] Interestingly, the defect in platelet function

is related to local temperature, not core temperature. [95] Wound temperature, however, is largely determined by core temperature and is distinctly higher in normothermic patients. Perhaps as important, hypothermia directly impairs enzymes of the coagulation cascade. This is not apparent during routine coagulation screening because the tests are performed at 37°C. When these tests are performed at hypothermic temperatures, however, the defect becomes apparent. [96] [97] Consistent with these *in vitro* defects, a prospective, randomized clinical trial indicates that mild hypothermia significantly increases blood loss during hip arthroplasty and increases allogeneic transfusion requirements. [98]

Wound infections are among the most common serious complications of anesthesia and surgery, probably causing more morbidity than all anesthetic complications combined. [99] [100] Hypothermia can contribute to wound infections both by directly impairing immune function [101] and by triggering thermoregulatory vasoconstriction that, in turn, decreases wound oxygen delivery. [102] It is well established that fever is protective and that infections are aggravated when naturally occurring fever is prevented. [103] [104] Similarly, mild hypothermia, maintained only during anesthesia, impairs subsequent resistance to the both *Escherichia coli* and *Staphylococcus aureus* dermal infections in guinea pigs. [105] [106] As may be expected from these *in vitro* and animal data, a prospective, randomized clinical trial indicated that mild intraoperative hypothermia tripled the incidence of surgical wound infection in patients undergoing colon surgery. Furthermore, hypothermia delayed wound healing and prolonged duration of hospitalization 20 percent even in patients without infection. [107] Consistent with poor wound healing, urinary nitrogen excretion remains elevated for several postoperative days in patients allowed to become hypothermic during surgery. [108]

Thermal comfort is markedly impaired by postoperative hypothermia. [109] Patients, asked years after surgery, often identify feeling cold in the immediate postoperative period as the worst part of their hospitalization--sometimes rating it worse than surgical pain. Postoperative thermal discomfort is also physiologically stressful, by elevating blood pressure, heart rates, and plasma catecholamine concentrations. [110] [111] These factors presumably contribute to what may be the most important consequence of mild perioperative hypothermia: morbid myocardial outcomes. [112] Given that myocardial ischemia is among the leading causes of unanticipated perioperative death, the results of this prospective, randomized trial must be taken extremely seriously.

Drug metabolism is markedly decreased by perioperative hypothermia. The duration of action of vecuronium is more than doubled by 2°C of core hypothermia, and the prolongation is a pharmacokinetic effect, not a pharmacodynamic one. [113] Atracurium duration is less dependent on core temperature: a 3°C reduction in core temperature increases the duration of muscle relaxation only by 60 percent. [114] With each drug, the recovery index (time for 25-75% twitch recovery) remains normal during hypothermia. Interestingly, core hypothermia per se decreases twitch strength 10 to 15 percent, even without muscle relaxants. [115]

During a constant infusion of propofol, plasma concentration is 30 percent greater than normal when individuals are 3°C hypothermic. [114] The effects of mild hypothermia on the metabolism and pharmacodynamics of most other drugs have yet to be reported. However, the results for muscle relaxants and propofol suggest that the effects likely are substantial. Hypothermia also alters the pharmacodynamics of the volatile anesthetics, reducing the minimum alveolar concentration (MAC) about 5%/°C. [116] [117] Consequently, no anesthesia whatsoever is required to prevent movement in response to skin incision at core temperatures lower than 20°C. [118] As may be expected from the pharmacokinetic and pharmacodynamic effects of hypothermia, duration of postanesthetic recovery is significantly prolonged, even when temperature is not a discharge criterion. When "fitness for discharge" and a core temperature exceeding 36°C are required (as in many postanesthesia care units), recovery duration is prolonged by several hours. [119] Table 37-1 (Table Not Available) lists proven consequences of mild perioperative hypothermia.

Postanesthetic Shivering

The incidence of postoperative shivering-like tremor reportedly is 40 percent, but it now appears to be less because

TABLE 37-1 -- Major *In Vivo* Consequences of Mild Perioperative Hypothermia in Humans[a]

(Not Available)

From Sessler DI: Perioperative hypothermia. N Engl J Med 336:1730, 1997. Copyright 1997 Massachusetts Medical Society. All rights reserved.

[a] Only prospective, randomized human trials are included; subjective responses were evaluated by observers blinded to treatment group and core temperature.

more patients are kept normothermic, and opioids are administered more frequently and in larger doses than previously. It is a potentially serious complication, increasing oxygen consumption roughly 100 percent, in proportion to intraoperative heat loss. [120] Interestingly, however, myocardial ischemia is poorly correlated with shivering, a finding suggesting that increased metabolic rate is not the primary cause of this complication. [112] In addition to increasing intraocular and intracranial pressures, postoperative shivering likely aggravates wound pain by stretching incisions.

Over the years, postanesthetic tremor has been attributed to uninhibited spinal reflexes, pain, decreased sympathetic activity, pyrogen release, adrenal suppression, respiratory alkalosis, and, most commonly, simple thermoregulatory shivering in response to intraoperative hypothermia. Unfortunately, the causes of postanesthetic shivering-like tremor remain unclear. Certainly, much postoperative tremor is simply normal shivering. As early as 1972, however, investigators recognized the existence of at least two distinct tremor patterns. [121] That perceptive observation subsequently was confirmed in a study that used electromyography to demonstrate (1) a tonic pattern resembling normal shivering, typically having a 4- to 8-cycle/min waxing-and-waning component, and (2) a phasic, 5- to 7-Hz bursting pattern resembling pathologic clonus. [122] The clonic pattern was consistent with the previous observation that pathologic spinal cord responses, including clonus, nystagmus, and exaggerated deep tendon reflexes, were common during recovery from general anesthesia. [123]

It was not until 1991 that a triple crossover study in volunteers established that the tonic and clonic patterns were both thermoregulatory, that is, always preceded by core hypothermia and arteriovenous shunt vasoconstriction. [124] The tonic pattern consistently demonstrated the 4- to 8-cycle/min waxing-and-waning pattern of normal shivering, [16] and apparently it is a simple thermoregulatory response to intraoperative hypothermia. In contrast, the clonic pattern is not a normal component of thermoregulatory shivering and appears specific to recovery from volatile anesthetics. Although the precise cause of this tremor pattern remains unknown, it may result from anesthetic-induced disinhibition of normal descending control over spinal reflexes. Data in surgical patients, however, belie the simple conclusion from the volunteer study [124] that all postanesthetic tremor is thermoregulatory. Instead, there appears to be a distinct incidence of nonthermoregulatory tremor in normothermic postoperative patients [125] ; similar nonthermoregulatory tremor has been observed in women during labor. The cause of this tremor and the reason that volunteers and patients should respond differently remain unknown; however, preliminary data suggest that pain contributes.

Postanesthetic shivering can be treated by skin surface warming [82] because the regulatory system tolerates more core hypothermia when cutaneous warm input is augmented. [5] The degree to which clinically available skin surface warmers can compensate for core hypothermia remains to be quantified, but the technique probably is effective in most patients with core temperatures exceeding 35°C. Postanesthetic shivering also can be treated using a variety of drugs, including clonidine (75 mug IV), [84] [126] ketanserin (10 mg IV), [84] physostigmine (0.04 mg/kg), [127] and magnesium sulfate (30 mg/kg). [85] The specific mechanisms by which ketanserin, physostigmine, and magnesium sulfate stop shivering remain unknown. Similarly, how clonidine arrests shivering also remains unknown, but the drug comparably reduces the vasoconstriction and shivering thresholds, [32] suggesting it acts on the central thermoregulatory system, rather than by peripherally preventing shivering.

Alfentanil, a pure mu-receptor agonist, significantly impairs thermoregulatory control. [22] However, meperidine reportedly is considerably more effective in treating shivering than equi-analgesic doses of other mu-agonists. [128] Clinically, this efficacy is manifested as a shivering threshold that is reduced twice as much as the vasoconstriction threshold [28] without a decrease in the gain or maximum intensity of shivering. [47] The efficacy of meperidine is largely preserved during administration of moderate doses of naloxone (0.5 mug·kg$^{-[1]}$·min$^{-[1]}$) but it is virtually obliterated by enormous doses (5.0 mug·kg$^{-[1]}$·min$^{-[1]}$). [129] These data suggest that action of this drug is, in part, mediated by non-mu-opioid receptors. The most likely target is the kappa receptor, and meperidine possesses considerable kappa activity. [130]

PERIOPERATIVE THERMAL MANIPULATIONS

Intraoperative thermoregulatory vasoconstriction, once triggered, is remarkably effective in preventing further core hypothermia. [38] [46] Nonetheless, most patients are poikilothermic during surgery because they do not become sufficiently hypothermic to trigger thermoregulatory responses. [21] [22] [24] [25] Therefore, intraoperative hypothermia can be minimized by any technique that limits cutaneous heat loss to the environment resulting from cold operating rooms, evaporation from surgical incisions, and conductive cooling produced by administration of cold IV fluids.

Mean body temperature decreases when heat loss to the environment exceeds metabolic heat production. Heat production during anesthesia is approximately 0.8 $kcal \cdot kg^{-1} \cdot hr^{-1}$ [1] . Because the specific heat of the human body is about 0.83 kcal/kg, [131] body temperature decreases approximately 1°C/h when heat lost to the environment exceeds metabolic production by a factor of 2. Normally, about 90 percent of metabolic heat is lost through the skin surface. During anesthesia, additional heat is lost directly from surgical incisions and by administration of cold IV fluids.

Effects of Vasomotor Tone on Heat Transfer

Thermoregulatory vasodilation causes the initial core-to-peripheral redistribution of body heat [56] ; similarly, reemergence of vasoconstriction in patients becoming sufficiently hypothermic produces a core temperature plateau. [46] It is thus evident that vasomotor tone alters intercompartmental heat transfer. In addition to thermoregulatory arteriovenous shunt status, arteriolar tone is directly modulated by anesthetics per se. [132] Both factors potentially influence the speed with which peripherally applied heat reaches the core thermal compartment.

Thermoregulatory vasoconstriction slightly impairs induction of therapeutic hypothermia during neurosurgery. [133] Similarly, nitroprusside administration facilitates even distribution of heat during rewarming on cardiopulmonary bypass. [134] However, arteriovenous shunt tone has little effect on intraoperative cooling [135] or heating. [136] It thus seems that intraoperative vasoconstriction impedes peripheral-to-core transfer of cutaneous heating and cooling, but the effect is relatively small. Little clinical effect presumably results because intraoperative thermoregulatory vasoconstriction is opposed by direct anesthetic-induced peripheral vasodilation.

During postanesthetic recovery, however, the situation differs markedly. Here, anesthetic-induced peripheral dilation [132] dissipates, leaving unopposed thermoregulatory vasoconstriction. As may be expected, this vasoconstriction then becomes an important factor and significantly impairs transfer of peripherally applied heat to the core thermal compartment. Patients having a residual spinal anesthetic block thus warm considerably faster than those recovering from general anesthesia alone (Fig. 37-17) (Figure Not Available) . [137] Heat balance studies indicate that core warming is slowed because vasoconstriction constrains up to 30 kcal in peripheral tissues. [138]

Because postoperative thermoregulatory vasoconstriction decreases peripheral-to-core transfer of heat, applied warming is most effective during surgery when patients are vasodilated. From a practical point of view, this means that it is easier to maintain intraoperative normothermia (when most patients are vasodilated) than to rewarm them postoperatively (when virtually all hypothermic patients are vasoconstricted). In addition to being more effective, intraoperative warming is more appropriate than postoperative treatment of hypothermia because it prevents the complications resulting from hypothermia. [98] [107] [112] Patients who unavoidably

Figure 37-17 (Figure Not Available) Intraoperative and postoperative core temperatures in patients assigned to general anesthesia (*n* = 20) and spinal anesthesia (*n* = 20). All patients were warmed with forced air during the postoperative period. Core temperature did not differ significantly during surgery, but it increased significantly faster postoperatively in patients given spinal anesthesia (1.2 ± 0.1°C/h versus 0.7 ± 0.2°C/h, means ± standard deviations). *(From Szmuk et al [137])*

become hypothermic during surgery nonetheless should be actively heated postoperatively to increase thermal comfort, to decrease shivering, and to hasten rewarming.

Preventing Redistribution Hypothermia

The initial 0.5 to 1.5°C reduction in core temperature is difficult to prevent because it results from redistribution of heat from the central thermal compartment to cooler peripheral tissues. [56] Consequently, even the most effective clinical warmers do not prevent hypothermia during the first hour of anesthesia. [57] [107] Lack of efficacy during this period results both because the central-to-peripheral flow of heat is massive and because transfer of applied cutaneous heat to the core requires nearly an hour, even in vasodilated patients.

Although redistribution cannot effectively be treat-ed, [57] [107] it can be prevented. Redistribution results when anesthetic-induced vasodilation allows heat to flow peripherally down the normal temperature gradient. Skin surface warming before induction of anesthesia does not significantly alter core temperature (which remains well regulated), but it does increase body heat content. Most of the increase is in the legs, the most important component of the peripheral thermal compartment. When peripheral tissue temperature is sufficiently increased, subsequent inhibition of normal tonic thermoregulatory vasoconstriction produces little redistribution hypothermia because heat only can flow down a temperature gradient (Fig. 37-18) (Figure Not Available) . [139] [140] Although substantial amounts of heat must be transferred across the skin surface, active prewarming for as little as 30 minutes likely prevents considerable redistribution. [141]

Figure 37-18 (Figure Not Available) During the preinduction period (-120-0 min), volunteers were either actively warmed or passively cooled (no warming). At induction of anesthesia (time, 0 minutes), active warming was discontinued and volunteers were exposed to the ambient environment. Initial tympanic membrane temperatures were similar before each preinduction treatment. During the 60 minutes following induction of anesthesia, core temperature decreased less when volunteers were prewarmed. (DeltaT = -1.1 ± 0.3°C) compared with when the same volunteers were not warmed (DeltaT = -1.9 ± 0.3°C). Data presented as means ± standard deviations. *(From Hynson et al [139])*

Airway Heating and Humidification

Simple thermodynamic calculations indicate that less than 10 percent of metabolic heat production is lost via the respiratory tract. The loss results from both heating and humidifying inspiratory gases, but humidification requires two-thirds of the heat. [51] Because little heat is lost via respiration, even active airway heating and humidification minimally influence core temperature. [57] [142] The *apparent* clinical efficacy of these devices probably results from artifactual warming of proximally positioned esophageal stethoscopes. [143]

Because respiratory heat loss remains virtually constant during anesthesia, the fraction of total heat lost via the respiratory tract decreases dramatically during large operations in which substantial heat is lost from evaporation within surgical incisions. [52] Consequently, airway heating and humidification are even less effective than usual in patients most in need of effective warming. Cutaneous warming maintains normothermia so much better than respiratory gas conditioning that intraoperative active airway heating and humidification are rarely, if ever, indicated. Airway heating and humidification are more effective in infants and children than in adults, [144] but cutaneous warming also is more effective in these patients and transfers more than ten times as much heat. Hygroscopic condenser humidifiers and heat-and-moisture exchanging filters ("artificial noses") retain substantial amounts of moisture and heat within the respiratory system. In terms of preventing heat loss, these passive devices are about half as good as active systems [144] ; however, they cost only a fraction as much. Heat retention is comparable in all clinically available heat-and-moisture exchangers. [51]

Intravenous Fluids

It is not possible to warm patients by administering heated fluids because the fluids cannot (much) exceed body temperature. On the other hand, heat loss resulting from cold IV fluids becomes significant when large amounts of crystalloid solution or blood are administered. One unit of refrigerated blood or 1 L of crystalloid solution administered at room temperature decreases mean body temperature
0.25°C. Fluid warmers minimize these losses and should be used when large amounts of IV fluid or blood are administered.

For routine cases, there are no clinically important differences among the available warmers. Although most warmers allow fluid to cool in the tubing between the heater and the patient, this cooling is of little consequence in adults: at high flows, there is little cooling, and at low flows, the amount of fluid given is trivial. [145] Special high-volume systems with powerful heaters and little resistance to flow facilitate care of trauma victims and are useful in other cases in which large amounts of fluid must be administered quickly.

Cutaneous Warming

Operating room temperature is the most critical factor influencing heat loss because it determines the rate at which metabolic heat is lost by radiation and convection from the skin and by evaporation from within surgical incisions. Consequently, increasing room temperature is one way to minimize heat loss. However, room temperatures exceeding 23°C generally are required to maintain normothermia in patients undergoing all but the smallest procedures [146] ; most operating room personnel find such temperatures uncomfortably warm. Infants may require ambient temperatures exceeding 26°C to maintain normothermia. Such temperatures are sufficiently high to impair performance of operating room personnel and to decrease their vigilance.

The easiest method of decreasing cutaneous heat loss is to apply passive insulation to the skin surface. Insulators readily available in most operating rooms include cotton blankets, surgical drapes, plastic sheeting, and reflective composites ("space blankets"). A single layer of each reduces heat loss approximately 30 percent, and there are no clinically important differences among the insulation types (Fig. 37-19) (Figure Not Available) . [147] Insulators, therefore, should be chosen strictly on the basis of cost; paying a premium to purchase reflective composites, for example, is not justified.

The reduction in heat loss from all the commonly used passive insulators is similar because most of the insulation is provided by the layer of still air trapping beneath the covering. Consequently, adding additional layers of insulation further reduces heat loss only slightly. For example, one cotton blanket reduces heat loss about 30 percent, but three cotton blankets reduce heat loss only by 50 percent. Furthermore, warming the cotton blankets provides little benefit, and the benefit is short-lived (Fig. 37-20) (Figure Not Available) . [148] These data indicate that simply adding additional layers of passive insulation or warming the insulation before application usually is insufficient in patients who become hypothermic while covered with a single layer of insulation.

Cutaneous heat loss is roughly proportional to surface area throughout the body. [149] (The popular perception that a large fraction of metabolic heat is lost from the head is false in adults. Loss from the head can be substantial in small infants, [150] [151] but loss is high mostly because the head represents a large fraction of the total surface area.) Consequently, the amount of skin covered is more important than which surfaces are insulated. It does not make sense, for example, to cover the head and to leave the arms exposed: the arms have more surface area than the head and account for more heat loss.

Figure 37-19 (Figure Not Available) Insulators readily available in most operating rooms include cotton blankets, surgical drapes, plastic sheeting, and reflective composites ("space blankets"). A single layer of each reduces total cutaneous heat loss approximately 30 percent, and there are no clinically important differences among the insulation types. Data presented as means ± standard deviations. *(From Sessler et al [147])*

Figure 37-20 (Figure Not Available) Total cutaneous heat loss when the volunteers were covered with a single warmed or unwarmed blanket ("1 warm" or "1 unwarmed") or three warmed or unwarmed blankets ("3 warm" or "3 unwarmed"). These data indicate that warming cotton blankets is of little benefit, and adding additional blankets only slightly decreases cutaneous heat loss. Data presented as means ± standard deviations. *(From Sessler and Schroeder [148])*

Passive insulation alone rarely is sufficient to maintain normothermia in patients undergoing large operations: active warming is required in those cases. Because about 90 percent of metabolic heat is lost via the skin surface, only cutaneous warming transfers sufficient heat to prevent hypothermia. Most infrared systems are little more effective than passive insulation. [147] [152] Consequently, for intraoperative use, circulating-water and forced-air devices are the two major systems requiring consideration.

Studies consistently report that circulating-water mattresses are nearly ineffective. [153] Presumably, they are unable

Figure 37-21 (Figure Not Available) Rectal temperatures increased in adults given forced-air warming and decreased in those warmed with circulating water during maxillofacial surgery. Temperature of the warmer was decreased from "high" to "medium" (
37°C) in all patients assigned to forced-air warming
7 hours after induction of anesthesia when their rectal temperatures exceeded 36.5°C. After 15 hours of anesthesia, core temperatures were 3.4°C higher in the patients given forced-air warming. There was no initial redistribution hypothermia because these patients were maintained in a warm environment before induction of anesthesia. *(From Kurz et al [158])*

to maintain normothermia because little heat is lost from the back into the 5 cm of foam insulation covering most operating room tables. Furthermore, the combination of heat and decreased local perfusion (resulting when the patient's weight reduces capillary blood flow) increases the propensity for pressure/heat necrosis ("burns"). [154] Such tissue injury can occur even when water temperature does not exceed 40°C. [155] Circulating water is more effective, and safer, when placed *over* patients rather than *under* them, and in that position, it can almost completely eliminate metabolic heat loss. [152] Metabolic heat production increases mean body temperature approximately 1°C/h when cutaneous heat loss is eliminated.

The most effective perianesthetic warming system is forced air. The best forced-air systems transfer more than 50 watts across the skin surface, rapidly increasing mean body temperature. [152] [156] Forced air has been shown to maintain normothermia even during the largest operations [57] [107] [157] and is superior to circulating water (Fig. 37-21) (Figure Not Available) . [158] Figure 37-22 shows the relative effect of common patient warming methods and the changes in mean body temperature resulting from infusion of unwarmed crystalloid or blood.

Figure 37-22 Relative effects of warming methods on mean body temperature (DeltaMBT) as a function of time (upper portion) or administered fluid (lower portion). Mean body temperature is the average temperature of body tissues and is usually somewhat less than core temperature. The calculations assume an undressed 70-kg patient with a metabolic rate of 80 kcal/h, in thermal steady state with a typical 21°C operating room environment. Only changes resulting from specific treatments are shown; changes from combined interventions are additive. (A-D) Changes in MBT per liter of administered blood or crystalloid at various fluid temperatures. (E) Inspiring warmed, humidified gas. (F, G) Warmed or unwarmed blankets, with all skin below the neck covered. Savings are similar with a single layer of other passive insulators. (H) Full-length circulating-water mattress. (I) Full-length forced-air warmer. *(From Sessler DI: Consequences and treatment of perioperative hypothermia. Anesthesiol Clin North Am 12:425, 1994.)*

/das/book/view/29494766/875/426.html

DELIBERATE SEVERE INTRAOPERATIVE HYPOTHERMIA

Severe hypothermia may be induced deliberately to confer protection against tissue ischemia, specifically during cardiac and, occasionally, neurosurgery. Drugs such as barbiturates and volatile anesthetics provide considerably less protection than even mild hypothermia. [89] Because many organs compensate poorly for hypothermia, temperatures as low as those deliberately induced are usually lethal when unintentional. Deliberate hypothermia is safe only because anesthesiologists understand and treat the physiologic changes caused by core temperatures 10 to 15°C lower than normal.

Organ Function

Ischemia damages tissues because oxygen deprivation forces cells to obtain energy anaerobically. Because this mechanism is inefficient, it may not provide adequate energy. Anaerobic metabolism also produces more toxic metabolic waste products (e.g., lactate and superoxide radicals) than does the Krebs cycle, a situation that is particularly serious when these products are not removed by circulating blood.

Hypothermia decreases the whole-body metabolic rate by
8 percent/°C, to approximately half the normal rate at 28°C. Whole-body oxygen demand diminishes, and oxygen consumption in tissues that have higher than normal metabolic rates, such as the brain, is especially reduced. Low metabolic rates allow aerobic metabolism to continue during periods of compromised oxygen supply; toxic waste production declines in proportion to the metabolic rate. Although decreased metabolic rate certainly contributes to the observed protection against tissue ischemia, other specific actions of hypothermia (including "membrane stabilization" and decreased release of toxic metabolites) may be most important.

Cerebral blood flow also decreases in proportion to metabolic rate during hypothermia because of an autoregulatory increase in cerebrovascular resistance. The arteriovenous partial pressure of oxygen (P_{O_2}) difference thus remains constant, and venous lactate concentration does not increase. Cerebral function is well maintained until core temperatures reach
33°C, but consciousness is lost at temperatures lower than 28°C. Primitive reflexes such as gag, pupillary constriction, and monosynaptic spinal reflexes remain intact until
25°C. Nerve conduction decreases, but peripheral muscle tone increases, resulting in rigidity and myoclonus at temperatures near 26°C. Somatosensory- and audio-evoked potentials are temperature-dependent, but they are not significantly modified at core temperatures of 33°C or higher.

Hypothermic effects on the heart include a decrease in heart rate, increased contractility, and well-maintained stroke volume. Cardiac output and blood pressure both decrease. At temperatures lower than 28°C, sinoatrial pacing becomes erratic, and ventricular irritability increases. Fibrillation usually occurs between 25 and 30°C, and electrical defibrillation is usually ineffective at these temperatures. Because coronary artery blood flow decreases in proportion to cardiac work, hypothermia per se does not cause myocardial ischemia.

Hypothermia decreases blood flow to the kidneys by increasing renal vascular resistance. Inhibition of tubular absorption maintains normal urinary volume. As temperature decreases, reabsorption of sodium and potassium is progressively inhibited, causing an antidiuretic hormone-mediated "cold diuresis." Despite increased excretion of these ions, plasma electrolyte concentrations usually remain normal. Kidney functions return to normal when patients are rewarmed. Respiratory strength is diminished at core temperatures less than 33°C, but the ventilatory carbon dioxide response is minimally affected. Hepatic blood flow and function also decrease, significantly inhibiting metabolism of some drugs.

Acid-Base Changes

The pH of neutral water ($[OH^-] = [H^+]$) increases 0.017 units for each 1°C reduction in temperature; pH of blood in a closed system (e.g., test tube or artery) changes similarly (Ch. 38). Cold-blooded animals allow pH to vary with body temperature as it would *in vitro* (i.e., blood becomes more alkalotic as temperature decreases), whereas homeotherms who decrease body temperature during hibernation maintain an arterial pH (pH_a) near 7.4. Interpretation of pH_a in hypothermic humans is difficult because it is unclear which strategy is optimal. [159] To mimic the compensatory mechanisms used by hibernating homeotherms, blood pH (which is measured by electrodes at 37°C) traditionally has been "corrected" to the patient's actual body temperature. Without correction, tissue oxygen availability decreases because hemoglobin's affinity for oxygen increases
1.7 percent/°C. This effect is small compared with the 5.7 percent/°C increase in oxyhemoglobin affinity caused by hypothermia itself. Fortunately, the combined increases in affinity are offset by the 8 percent/°C reduction in metabolic rate caused by hypothermia. Tissue hypoxia is thus unlikely, with or without correction, and it has not been demonstrated experimentally.

Ectothermic strategy also is known as "alphastat" because the dissociation constant of the alpha-imidazole group in histidine changes in parallel with that of water. Maintaining constant imidazole ionization results in optimal enzyme function as temperature changes. In contrast, homeothermic dynamics significantly decrease metabolic function, and animals are essentially anesthetized by cold. Constant relative alkalinity also maintains a stable intracellular to extracellular gradient that promotes removal of acidic products of intracellular metabolism.

There are no convincing studies indicating that ectothermic strategy is better than that adopted by hibernating homeotherms. However, many anesthesiologists now use "uncorrected" values. This technique facilitates comparison among serial blood gas values because "normal" pH_a remains
7.4, and "normal" partial arterial pressure of carbon dioxide (Pa_{CO_2}) remains
40 mm Hg at any temperature. However, both techniques work well, and physiologic differences between them appear to be subtle and have minimal effect on patient outcome.

HYPERTHERMIA AND FEVER

Hypothermia is by far the most common perianesthetic thermal perturbation. However, hyperthermia is more dangerous than a comparable degree of hypothermia. Hyperthermia is a generic term simply indicating a core body temperature exceeding normal values. In contrast, fever is a regulated increase in the core temperature targeted by the thermoregulatory system. Hyperthermia can result from a variety of causes, and it usually indicates a problem of sufficient severity that physician intervention is required.

Passive Hyperthermia and Malignant Hyperthermia

Passive intraoperative hyperthermia results from excessive patient heating and is most common in infants and children (Ch. 27). It is especially frequent when effective active warming is used without adequate core temperature monitoring. Passive hyperthermia, by definition, does not result from thermoregulatory intervention. Consequently, it can easily be treated by discontinuing active warming and removing excessive insulation.

The increase in body temperature during malignant hyperthermia results from an enormous increase in metabolic heat produced by both internal organs and skeletal muscles. Central thermoregulation presumably remains intact during acute crises, but efferent heat loss mechanisms may be compromised by intense peripheral vasoconstriction resulting from circulating catecholamine concentrations 20 times normal. [160]

Fever

Normal body temperature is neither set nor maintained by circulating factors. In contrast, fever results when endogenous pyrogens increase the thermoregulatory target temperature ("set point"). Identified endogenous pyrogens include interleukin-1, tumor necrosis factor, interferon-alpha, and macrophage inflammatory protein-1. [161] Although it was initially believed that these factors acted directly on hypothalamic thermoregulatory centers, [162] there is increasing evidence for a more complicated system involving vagal afferents. [163] Most endogenous pyrogens have peripheral actions (e.g., immune system activation) in addition to their central generating capabilities.

Fever usually results from infection. Such fevers may reflect preexisting infection, or they may result, for example, from urologic manipulations. However, perioperative fever also occurs in response to mismatched blood transfusions, blood in the fourth cerebral ventricle, and allergic reactions. [164] The causes of fever are sufficiently diverse, and potentially serious, that a search for a specific cause usually is warranted.

Fever is relatively rare during general anesthesia, considering how often febrile stimuli are likely to be present. Fever is rare because volatile anesthetics per se inhibit expression of fever (Fig. 37-23) (Figure Not Available) . Clinical management of fever should primarily be directed at identifying and treating the

Figure 37-23 (Figure Not Available) Change in core temperature after administration of 50,000 IU/kg of interleukin-2 (IL-2) followed by a second dose of 100,000 IU/kg 2 hours later. The first dose of IL-2 defined elapsed time zero; anesthesia was started after 3 elapsed hours and was continued for 5 hours. Data are presented as means ± standard deviations. *(From Negishi C, Lenhardt R, Sessler DI et al: Desflurane reduces the febrile response to interleukin-2 administration. Anesthesiology 88:1162, 1998.)*

underlying cause. A secondary approach is to administer antipyretic medications such acetaminophen, centrally reducing the thermoregulatory drive to maintain an abnormally high core temperature. In contrast, simple cooling measures are rarely effective, but they do decrease thermal comfort and increase shivering.

TEMPERATURE MONITORING

Core temperature measurements (e.g., tympanic membrane, pulmonary artery, distal esophagus, and nasopharynx) are used to monitor intraoperative hypothermia, to prevent overheating, and to facilitate detection of malignant hyperthermia. Muscle or skin surface temperatures may be used to evaluate vasomotion [165] and ensure validity of peripheral neuromuscular monitoring. [166] Both core and skin surface temperature measurements are required to determine the thermoregulatory effects of different anesthetic drugs. Temperatures are not uniform within the body; consequently, temperatures measured at each site have different physiologic and practical significance.

Thermometers

Traditionally, the medical community has used mercury-in-glass thermometers. These slow and cumbersome thermometers have largely been replaced by electronic systems. The most common electronic thermometers are thermistors and thermocouples. Both devices are sufficiently accurate for clinical use and are inexpensive enough to be disposable. Also sufficiently accurate for clinical use are "deep tissue" thermometers that are based on actively reducing cutaneous

---

heat flux to zero [167] [168] unfortunately, these monitors are not currently available in Europe or the United States. True infrared tympanic membrane thermometers are another alternative. [169] [170] However, the more common infrared monitors that extrapolate tympanic membrane temperature from outer ear temperature are often unreliable. [171]

When Temperature Monitoring is Required

Local anesthetics (including amides) administered to produce regional blocks and sedatives used during monitored anesthesia care do not trigger malignant hyperthermia. [172] Nonetheless, core hypothermia is as common during epidural and spinal anesthesia as during general anesthesia, and it can be nearly as severe. [71] Core temperature should therefore be measured during regional anesthesia in patients likely to become hypothermic (e.g., those undergoing body cavity surgery).

Core temperature monitoring is appropriate during most cases of general anesthesia, both to facilitate detection of malignant hyperthermia and to quantify hyperthermia and hypothermia. Malignant hyperthermia is best detected by tachycardia and an increase in end-tidal P_{CO_2} out of proportion to minute ventilation. [173] Although increasing core temperature is not the first sign of acute malignant hyperthermia, it certainly helps confirm the diagnosis. More common than malignant hyperthermia is intraoperative hyperthermia, which has other causes including excessive warming, infectious fever, blood in the fourth cerebral ventricle, and mismatched blood transfusions.

By far the most common perioperative thermal disturbance is inadvertent hypothermia. Core temperature usually decreases 0.5 to 1.5°C in the first 30 minutes following induction of anesthesia. Hypothermia results from internal redistribution of heat and a variety of other factors whose importance in individual patients is hard to predict. [56] [74] Core temperature perturbations during the first 30 minutes of anesthesia thus are difficult to interpret, and measurements are not usually required. Body temperature should, however, be monitored in patients undergoing general anesthesia exceeding 30 minutes in duration and in all patients whose surgery lasts longer than 1 hour.

Temperature Monitoring Sites

The core thermal compartment is composed of highly perfused tissues whose temperature is uniform and high compared with the rest of the body. Temperature in this compartment can be evaluated in the pulmonary artery, distal esophagus, tympanic membrane, or nasopharynx. [174] [175] Temperature probes incorporated into esophageal stethoscopes must be positioned at the point of maximal heart sounds, or even more distally, to provide accurate readings. [143] Even during rapid thermal perturbations (e.g., cardiopulmonary bypass), these temperature monitoring sites remain reliable. Core temperature can be estimated with

Figure 37-24 (Figure Not Available) Axillary and esophageal temperatures correlated well during acute malignant hyperthermia in swine, but forehead and neck skin temperatures did not. Rectal temperature also failed to identify onset of malignant hyperthermia promptly. Elapsed time zero indicates an end-tidal P_{CO_2} of 70 mm Hg. These data indicate that forehead and neck skin surface temperatures do not adequately confirm other clinical signs of malignant hyperthermia. Valid core temperature monitoring sites include the distal esophagus, pulmonary artery, nasopharynx, and tympanic membrane. Except during cardiopulmonary bypass, body temperature also can be measured in the mouth, axilla, and bladder. Data presented as means ± standard deviations. *(Modified from Iaizzo PA, Zink RS, Kehler CH et al: Skin and central temperature during malignant hyperthermia in swine. Anesthesiology 77:A569, 1992.)*

reasonable accuracy using oral, axillary, rectal, and bladder temperatures except during extreme thermal perturba-tions. [174] [175]

Skin surface temperatures are considerably lower than core temperature. [176] Skin surface temperatures, even when adjusted with an appropriate offset, sometimes reflect core temperature reasonably well. [177] In other cases, though, they are insufficiently accurate and precise for perioperative use. Skin temperatures fail to confirm the clinical signs of malignant hyperthermia (tachycardia and hypercarbia) reliably in swine [178] and have not been evaluated for this purpose in humans (Fig. 37-24) (Figure Not Available) . Rectal temperatures also normally correlate well with core temperature, [174] [175] but they fail to increase appropriately during malignant hyperthermia crises [178] and under other documented situations. [179] [180] Consequently, rectal and skin surface temperatures must be used with some caution.

Even during cardiopulmonary bypass, the core temperature monitoring sites (e.g., tympanic membrane, nasopharynx, pulmonary artery, and esophagus) remain useful. In contrast, rectal temperatures lag behind those measured in core sites. Consequently, rectal temperature is considered an "intermediate" temperature in deliberately cooled patients. During cardiac surgery, bladder temperature is equal to rectal temperature (and therefore intermediate) when urine flow is low, but it is equal to pulmonary artery temperature (and thus core) when flow is high. [181] Because bladder temperature is strongly influenced by urine flow, it may be difficult to interpret in these patients. The adequacy of rewarming is best evaluated by considering both "core" and "intermediate" temperatures.

Temperature Monitoring and Thermal Management Guidelines

The objective of temperature monitoring and perioperative thermal management is to detect thermal disturbances and to maintain appropriate body temperature during anesthesia. Available data suggest the following guidelines:

1. Core body temperature should be measured in most patients given general anesthesia for more than 30 minutes.
2. Temperature should also be measured during regional anesthesia when changes in body temperature are intended, anticipated, or suspected. This at the very least includes body cavity surgery and other large and long operations.
3. Unless hypothermia is specifically indicated (e.g., for protection against ischemia), efforts should be made to maintain the intraoperative core temperature higher than 36°C.

/das/book/view/29494766/875/429.html

ACKNOWLEDGMENTS

Many of the studies described in this chapter were supported by the National Institutes of Health, the Fonds zur Forderung der Wissenschaftlichen Forschung (Vienna, Austria), and the Joseph Drown (Los Angeles), Anesthesia Patient Safety (Ermire, Penna), Max Kade (New York, NY), and Erwin Schroedinger (Vienna, Austria) Foundations. Major corporate funding for the Outcomes Research Laboratory is provided by Augustine Medical, Inc. Mallinckrodt Anesthesiology Products, Inc. (St. Louis, Mo) donated the thermocouples used in many of the described studies. The authors do not consult for, accept honoraria from, or own stock or stock options in any anesthesia-related company.

SUMMARY

Body temperature normally is controlled by a negative feedback system in the hypothalamus that integrates thermal information from most tissues. Approximately 80 percent of this thermal input is derived from core body temperature, which can be measured using distal esophageal, nasopharyngeal, or tympanic membrane thermometer probes. The hypothalamus coordinates increases in heat production (nonshivering thermogenesis and shivering), increases in environmental heat loss (sweating), and/or decreases in heat loss (vasoconstriction) as needed to maintain normothermia.

Thermal steady state requires that heat loss to the environment equal metabolic heat production; hypothermia occurs when heat loss exceeds production. Mild core hypothermia is common during surgery and anesthesia and results initially from redistribution of body heat from the core to peripheral tissues and subsequently from heat loss exceeding metabolic heat production. Clinical doses of all tested general anesthetics decrease the threshold for response to hypothermia from approximately 37°C (normal) to 33 to 35°C. Thus, anesthetized patients with core temperatures exceeding these temperatures usually are poikilothermic and do not actively respond to thermal perturbations. Patients who become sufficiently hypothermic do trigger thermoregulatory vasoconstriction, and the vasoconstriction is remarkably effective in minimizing further core hypothermia.

Mild intraoperative hypothermia provides significant protection against tissue ischemia and hypoxia. It also decreases triggering of malignant hyperthermia and reduces the severity of the syndrome, once triggered. However, most consequences of inadvertent hypothermia are harmful. Major adverse effects include morbid myocardial outcomes, reduced resistance to surgical wound infections, impaired coagulation, prolonged duration of drug action, shivering, and decreased postoperative thermal comfort.

Little metabolic heat is lost via the respiratory tract. Consequently, even active airway heating and humidification are of little benefit and are rarely indicated. Administration of sufficient volumes of cold IV fluid can produce substantial hypothermia. Fluids therefore should be warmed in patients requiring IV administration of more than several liters per hour. Among the clinically available active systems, forced air is the most effective and can usually maintain normo-thermia even during the largest operations.

Regional anesthesia produces both peripheral and central inhibition of thermoregulatory control. Peripheral inhibition results when local anesthetics block nerves that are required for thermoregulatory defenses. In contrast, central impairment apparently results when the regulatory system incorrectly concludes that leg skin temperature has markedly increased. Hypothermia during neuroaxial anesthesia results initially from core-to-peripheral redistribution of body heat and subsequently from heat loss exceeding heat production. Hypothermia during major conduction anesthesia may be as severe as that during general anesthesia.

Increased core temperature can result from augmented thermogenesis (malignant hyperthermia), excessive heating (passive hyperthermia), or a specific increase in the thermoregulatory target temperature (fever). Because the causes of hyperthermia are varied and often serious, the cause of observed increases in core temperature should be sought, and appropriate treatments should be instituted.

A reasonable strategy for detecting and preventing thermal disturbances is to monitor core temperature in patients having general anesthesia lasting longer than 30 minutes and in those undergoing major surgery with regional anesthesia. Unless hypothermia is specifically indicated (i.e., for protection against cerebral ischemia), core temperature should be maintained at more than 36°C.

References

1. Satinoff E: Neural organization and evolution of thermal regulation in mammals: Several hierarchically arranged integrating systems may have evolved to achieve precise thermoregulation. Science 201:16, 1978.

2. Jessen C, Feistkorn G: Some characteristics of core temperature signals in the conscious goat. Am J Physiol 247:R456, 1984.

3. Simon E: Temperature regulation: The spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev Physiol Biochem Pharmacol 71:1, 1974.

4. Poulos DA: Central processing of cutaneous temperature information. Fed Proc 40:2825, 1981.

5. Cheng C, Matsukawa T, Sessler DI et al: Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. Anesthesiology 82:1160, 1995.

6. Wyss CR, Brengelmann GL, Johnson JM et al: Altered control of skin blood flow at high skin and core temperatures. J Appl Physiol 38:839, 1975.

7. Lopez M, Sessler DI, Walter K et al: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. Anesthesiology 80:780, 1994.

8. Washington D, Sessler DI, Moayeri A et al: Thermoregulatory responses to hyperthermia during isoflurane anesthesia in humans. J Appl Physiol 74:82, 1993.

9. Hessemer V, Bruck K: Influence of menstrual cycle on thermoregulatory, metabolic, and heart rate responses to exercise at night. J Appl Physiol 59:1911, 1985.

10. Mestyan J, Jarai I, Bata G et al: The significance of facial skin temperature in the chemical heat regulation of premature infants. Biol Neonate 7:243, 1964.

11. Vassilieff N, Rosencher N, Sessler DI et al: The shivering threshold during spinal anesthesia is reduced in the elderly. Anesthesiology 83:1162, 1995.

12. Hales JRS: Skin arteriovenous anastomoses: Their control and role in thermoregulation. In Johansen K, Burggren W (eds): Cardiovascular Shunts: Phylogenetic, Ontogenetic and Clinical Aspects. Copenhagen, Munksgaard, 1985, p 433.

13. Dawkins MJR, Scopes JW: Non-shivering thermogenesis and brown adipose tissue in the human newborn infant. Nature 206:201, 1965.

14. Jessen K: An assessment of human regulatory nonshivering thermogenesis. Acta Anaesthesiol Scand 24:138, 1980.

15. Nedergaard J, Cannon B: The uncoupling protein thermogenin and mitochondrial thermogenesis. New Comp Biochem 23:385, 1992.

16. Israel DJ, Pozos RS: Synchronized slow-amplitude modulations in the electromyograms of shivering muscles. J Appl Physiol 66:2358, 1989.

17. Hemingway A, Price WM: The autonomic nervous system and regulation of body temperature. Anesthesiology 29:693, 1968.

18. Boudet J, Qing W, Boyer-Chammard A et al: Dose-response effects of atropine in human volunteers. Fund Am Clin Pharmacol 5:635, 1991.

19. Rowell LB: Active neurogenic vasodilation in man. In Vanhoutte P, Leusen I (eds): Vasodilatation. New York, Raven Press, 1981, p 1.

20. Detry J-MR, Brengelmann GL, Rowell LB et al: Skin and muscle components of forearm blood flow in directly heated resting man. J Appl Physiol 32:506, 1972.

21. Matsukawa T, Kurz A, Sessler DI et al: Propofol linearly reduces the vasoconstriction and shivering thresholds. Anesthesiology 82:1169, 1995.

22. Kurz A, Go JC, Sessler DI et al: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. Anesthesiology 83:293, 1995.

23. Talke P, Tayefeh F, Sessler DI et al: Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. Anesthesiology 87:835, 1997.

24. Annadata RS, Sessler DI, Tayefeh F et al: Desflurane slightly increases the sweating threshold, but produces marked, non-linear decreases in the vasoconstriction and shivering thresholds. Anesthesiology 83:1205, 1995.

25. Xiong J, Kurz A, Sessler DI et al: Isoflurane produces marked and non-linear decreases in the vasoconstriction and shivering thresholds. Anesthesiology 85:240, 1996.

26. Kurz A, Xiong J, Sessler DI et al: Desflurane reduces the gain of thermoregulatory arterio-venous shunt vasoconstriction in humans. Anesthesiology 83:1212, 1995.

27. Ikeda T, Kim J-S, Sessler DI et al: Isoflurane alters shivering patterns and reduces maximum shivering intensity. Anesthesiology 88:866, 1998.

28. Kurz A, Ikeda T, Sessler DI et al: Meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold. Anesthesiology 86:1046, 1997.

29. Sessler DI, Olofsson CI, Rubinstein EH et al: The thermoregulatory threshold in humans during halothane anesthesia. Anesthesiology 68:836, 1988.

30. Washington DE, Sessler DI, McGuire J et al: Painful stimulation minimally increases the thermoregulatory threshold for vasoconstriction during enflurane anesthesia in humans. Anesthesiology 77:286, 1992.

31. Sessler DI, Olofsson CI, Rubinstein EH: The thermoregulatory threshold in humans during nitrous oxide-fentanyl anesthesia. Anesthesiology 69:357, 1988.

32. Delaunay L, Bonnet F, Liu N et al: Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. Anesthesiology 79:470, 1993.

33. Delaunay L, Herail T, Sessler DI et al: Clonidine increases the sweating threshold, but does not reduce the gain of sweating. Anesth Analg 83:844, 1996.

34. Ozaki M, Sessler DI, Suzuki H et al: Nitrous oxide decreases the threshold for vasoconstriction less than sevoflurane or isoflurane. Anesth Analg 80:1212, 1995.

35. Passias TC, Mekjavic IB, Eiken O: The effect of 30% nitrous oxide on thermoregulatory responses in humans during hypothermia. Anesthesiology 76:550, 1992.

36. Kurz A, Sessler DI, Annadata R et al: Midazolam minimally impairs thermoregulatory control. Anesth Analg 81:393, 1995.

37. Bissonnette B, Sessler DI: The thermoregulatory threshold in infants and children anesthetized with isoflurane and caudal bupivacaine. Anesthesiology 73:1114, 1990.

38. Bissonnette B, Sessler DI: Thermoregulatory thresholds for vasoconstriction in pediatric patients anesthetized with halothane or halothane and caudal bupivacaine. Anesthesiology 76:387, 1992.

39. Kurz A, Plattner O, Sessler DI et al: The threshold for thermoregulatory vasoconstriction during nitrous oxide/isoflurane anesthesia is lower in elderly than young patients. Anesthesiology 79:465, 1993.

40. Ozaki M, Sessler DI, Suzuki H et al: The threshold for thermoregulatory vasoconstriction during nitrous oxide/sevoflurane anesthesia is reduced in elderly patients. Anesth Analg 84:1029, 1997.

41. Hynson JM, Sessler DI, Moayeri A et al: Absence of nonshivering thermogenesis in anesthetized humans. Anesthesiology 79:695, 1993.

42. Dicker A, Ohlson KB, Johnson L et al: Halothane selectively inhibits nonshivering thermogenesis. Anesthesiology 82:491, 1995.

43. Plattner O, Semsroth M, Sessler DI et al: Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. Anesthesiology 86:772, 1997.

44. Lopez M, Ozaki M, Sessler DI et al: Physiological responses to hyperthermia during epidural anesthesia and combined epidural/enflurane anesthesia in women. Anesthesiology 78:1046, 1993.

45. Sessler DI, Hynson J, McGuire J et al: Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases heat loss. Anesthesiology 76:670, 1992.

46. Kurz A, Sessler DI, Christensen R et al: Heat balance and distribution during the core-temperature plateau in anesthetized humans. Anesthesiology 83:491, 1995.

47. Ikeda T, Sessler DI, Tayefeh F et al: Meperidine and alftentanil do not reduce the gain or maximum intensity of shivering. Anesthesiology 88:858, 1998.

48. Hardy JD, Milhorat AT, DuBois EF: Basal metabolism and heat loss of young women at temperatures from 22 degrees C to 35 degrees C. J Nutr 21:383, 1941.

49. Hammarlund K, Sedin G: Transepidermal water loss in newborn infants. III. Relation to gestational age. Acta Paediatr Scand 68:795, 1979.

50. Maurer A, Micheli JL, Schutz Y et al: Transepidermal water loss and resting energy expenditure in preterm infants. Helv Paediatr Acta 39:405, 1984.

51. Bickler P, Sessler DI: Efficiency of airway heat and moisture exchangers in anesthetized humans. Anesth Analg 71:415, 1990.

52. Roe CF: Effect of bowel exposure on body temperature during surgical operations. Am J Surg 122:13, 1971.

53. Robinson BJ, Ebert TJ, O'Brien TJ et al: Mechanisms whereby propofol mediates peripheral vasodilation in humans. Anesthesiology 86:64, 1997.

54. Sessler DI, McGuire J, Moayeri A et al: Isoflurane-induced vasodilation minimally increases cutaneous heat loss. Anesthesiology 74:226, 1991.

55. Stevens WC, Cromwell TH, Halsey MJ et al: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 35:8, 1971.

56. Matsukawa T, Sessler DI, Sessler AM et al: Heat flow and distribution during induction of general anesthesia. Anesthesiology 82:662, 1995.

57. Hynson J, Sessler DI: Intraoperative warming therapies: A comparison of three devices. J Clin Anesth 4:194, 1992.

58. Sessler DI, Rubinstein EH, Eger EI II: Core temperature changes during N_2 O fentanyl and halothane/O_2 anesthesia. Anesthesiology 67:137, 1987.

59. Belani K, Sessler DI, Sessler AM et al: Leg heat content continues to decrease during the core temperature plateau in humans. Anesthesiology 78:856, 1993.

60. Sessler DI, Ponte J: Shivering during epidural anesthesia. Anesthesiology 72:816, 1990.

61. Ozaki M, Kurz A, Sessler DI et al: Thermoregulatory thresholds during spinal and epidural anesthesia. Anesthesiology 81:282, 1994.

62. Kurz A, Sessler DI, Schroeder M et al: Thermoregulatory response thresholds during spinal anesthesia. Anesth Analg 77:721, 1993.

63. Glosten B, Sessler DI, Ostman LG et al: Intravenous lidocaine does not cause tremor or alter thermoregulation. Reg Anesth 16:218, 1991.

64. Hynson J, Sessler DI, Glosten B et al: Thermal balance and tremor patterns during epidural anesthesia. Anesthesiology 74:680, 1991.

65. Pierau F-K, Wurster RD: Primary afferent input from cutaneous thermoreceptors. Fed Proc 40:2819, 1981.

66. Emerick TH, Ozaki M, Sessler DI et al: Epidural anesthesia increases apparent leg temperature and decreases the shivering threshold. Anesthesiology 81:289, 1994.

67. Leslie K, Sessler DI: Reduction in the shivering threshold is proportional to spinal block height. Anesthesiology 84:1327, 1996.

68. Kim J-S, Ikeda T, Sessler D et al: Epidural anesthesia reduces the gain and maximum intensity of shivering. Anesthesiology 88:851, 1998.

69. Leslie K, Sessler DI, Bjorksten A et al: Propofol causes a dosedependent decrease in the thermoregulatory threshold for vasoconstriction, but has little effect on sweating. Anesthesiology 81:353, 1994.

70. Glosten B, Sessler DI, Faure EAM et al: Central temperature changes are not perceived during epidural anesthesia. Anesthesiology 77:10, 1992.

71. Frank SM, Beattie C, Christopherson R et al: Epidural versus general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothermia. Anesthesiology 77:252, 1992.

72. Jenkins J, Fox J, Sharwood-Smith G: Changes in body heat during transvesical prostatectomy: A comparison of general and epidural anesthesia. Anaesthesia 38:748, 1983.

73. Hendolin H, Lansimies E: Skin and central temperatures during continuous epidural analgesia and general anaesthesia in patients subjected to open prostatectomy. Ann Clin Res 14:181, 1982.

74. Matsukawa T, Sessler DI, Christensen R et al: Heat flow and distribution during epidural anesthesia. Anesthesiology 83:961, 1995.

75. Glosten B, Hynson J, Sessler DI et al: Preanesthetic skin-surface warming reduces redistribution hypothermia caused by epidural block. Anesth Analg 77:488, 1993.

76. Valley MA, Bourke DL, Hamill MP et al: Time course of sympathetic blockade during epidural anesthesia: Laser doppler flowmetry studies of regional skin perfusion. Anesth Analg 76:289, 1993.

77. Modig J, Malmberg P, Karlstrom G: Effect of epidural versus general anesthesia on calf blood flow. Acta Anaesthesiol Scand 24:305, 1980.

78. Joris H, Ozaki M, Sessler DI et al: Epidural anesthesia impairs both central and peripheral thermoregulatory control during general anesthesia. Anesthesiology 80:268, 1994.

79. Ponte J, Collett BJ, Walmsley A: Anaesthetic temperature and shivering in epidural anaesthesia. Acta Anaesthesiol Scand 30:584, 1986.

80. Ponte J, Sessler DI: Extradurals and shivering: Effects of cold and warm extradural saline injections in volunteers. Br J Anaesth 64:731, 1990.

81. Harris MM, Lawson D, Cooper CM et al: Treatment of shivering after epidural lidocaine. Reg Anesth 14:13, 1989.

82. Sharkey A, Lipton JM, Murphy MT et al: Inhibition of postanesthetic shivering with radiant heat. Anesthesiology 66:249, 1987.

83. Brownbridge P: Shivering related to epidural blockade with bupivacaine in labour, and the influence of epidural pethidine. Anaesth Intensive Care 14:412, 1986.

84. Joris J, Banache M, Bonnet F et al: Clonidine and ketanserin both are effective treatments for postanesthetic shivering. Anesthesiology 79:532, 1993.

85. Kizilirmak S, Karakas SE, Akca O et al: Magnesium sulphate stops postanesthetic shivering. Proc Natl Acad Sci U S A 813:799, 1997.

86. Busto R, Globus MY-T, Dietrich WD et al: Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 20:904, 1989.

87. Minamisawa H, Smith M-L, Siesjo BK: The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. Ann Neurol 28:26, 1990.

88. Wass CT, Lanier WL, Hofer RE et al: Temperture changes of
1°C alter functional neurologic outcome and histopathology in a canine model of a complete cerebral ischemia. Anesthesiology 83:325, 1995.

89. Todd MM, Warner DS: A comfortable hypothesis reevaluated: Cerebral metabolic depression and brain protection during ischemia (editorial). Anesthesiology 76:161, 1992.

90. Marion DW, Penrod LE, Kelsey SF et al: Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540, 1997.

91. Villar J, Slutsky AS: Effects of induced hypothermia in patients with septic adult respiratory distress syndrome. Resuscitation 26:183, 1993.

92. Nelson TE: Porcine malignant hyperthermia: Critical temperatures for *in vivo* and *in vitro* responses. Anesthesiology 73:449, 1990.

93. Iaizzo PA, Kehler CH, Carr RJ et al: Prior hypothermia attenuates malignant hyperthermia in susceptible swine. Anesth Analg 82:782, 1996.

94. Michelson AD, MacGregor H, Barnard MR et al: Reversible inhibition of human platelet activation by hypothermia *in vivo* and *in vitro.* Thromb Haemostasis 71:633, 1994.

95. Valeri CR, Khabbaz K, Khuri SF et al: Effect of skin temperature on platelet function in patients undergoing extracorporeal bypass. J Thorac Cardiovasc Surg 104:108, 1992.

96. Reed L, Johnston TD, Hudson JD et al: The disparity between hypothermic coagulopathy and clotting studies. J Trauma 33:465, 1992.

97. Staab DB, Sorensen VJ, Fath JJ et al: Coagulation defects resulting from ambient temperature-induced hypothermia. J Trauma 36:634, 1994.

98. Schmied H, Kurz A, Sessler DI et al: Mild intraoperative hypothermia increases blood loss and allogeneic transfusion requirements during total hip arthroplasty. Lancet 347:289, 1996.

99. Bremmelgaard A, Raahave D, Beir-Holgersen R et al: Computer-aided surveillance of surgical infections and identification of risk factors. J Hosp Infect 13:1, 1989.

100. Polk HC, Simpson CJ, Simmons BP et al: Guidelines for prevention of surgical wound infection. Arch Surg 118:S1213, 1983.

101. Van Oss CJ, Absolam DR, Moore LL et al: Effect of temperature on the chemotaxis, phagocytic engulfment, digestion and O_2 consumption of human polymorphonuclear leukocytes. J Reticuloendothel Soc 27:561, 1980.

102. Sheffield CW, Sessler DI, Hopf HW et al: Centrally and locally mediated thermoregulatory responses alter subcutaneous oxygen tension. Wound Rep Reg 4:339, 1997.

103. Kluger MJ: Is fever beneficial? Yale J Biol Med 59:89, 1986.

104. Kluger MJ, Ringler DH, Anver MR: Fever and survival. Science 188:166, 1975.

105. Sheffield CW, Sessler DI, Hunt TK: Mild hypothermia during isoflurane anesthesia decreases resistance to *E. coli* dermal infection in guinea pigs. Acta Anaesthesiol Scand 38:201, 1994.

106. Sheffield CW, Sessler DI, Hunt TK et al: Mild hypothermia during halothane anesthesia decreases resistance to *S. aureus* dermal infection in guinea pigs. Wound Rep Reg 2:48, 1994.

107. Kurz A, Sessler DI, Lenhardt RA et al: Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 334:1209, 1996.

108. Carli F, Emery PW, Freemantle CAJ: Effect of peroperative normo-thermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. Br J Anaesth 63:276, 1989.

109. Kurz A, Sessler DI, Narzt E et al: Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia. J Clin Anesth 7:359, 1995.

110. Frank SM, Fleisher LA, Olson KF et al: Multivariate determinants of early postoperative oxygen consumption in elderly patients. Anesthesiology 83:241, 1995.

111. Frank SM, Higgins MS, Breslow MJ et al: The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. Anesthesiology 82:83, 1995.

112. Frank SM, Fleisher LA, Breslow MJ et al: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. JAMA 277:1127, 1997.

113. Heier T, Caldwell JE, Sessler DI et al: Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 74:815, 1991.

114. Leslie K, Sessler DI, Bjorksten AR et al: Mild hypothermia alters propofol pharmacokinetics and increases the duration of action of atracurium. Anesth Analg 80:1007, 1995.

115. Heier T, Caldwell JE, Eriksson LI et al: The effect of hypothermia on adductor pollicis twitch tension during continuous infusion of vecuronium in isoflurane-anesthetized humans. Anesth Analg 788:312, 1994.

116. Eger EI II, Johnson BH: MAC of I-653 in rats, including a test of the effect of body temperature and anesthetic duration. Anesth Analg 66:974, 1987.

117. Vitez TS, White PF, Eger EI II: Effects of hypothermia on halothane MAC and isoflurane MAC in the rat. Anesthesiology 41:80, 1974.

118. Antognini JF: Hypothermia eliminates isoflurane requirements at 20°C. Anesthesiology 78:1152, 1993.

119. Lenhardt R, Marker E, Goll V et al: Mild intraoperative hypothermia prolongs postoperative recovery. Anesthesiology 87:1318, 1997.

120. Lienhart A, Fiez N, Deriaz H: Frisson postoperatoire: Analyse des principaux facteurs associes. Ann Fr Anesth Reanim 11:488, 1992.

121. Soliman MG, Gillies DMM: Muscular hyperactivity after general anaesthesia. Can Anaesth Soc J 19:529, 1972.

122. Sessler DI, Israel D, Pozos RS et al: Spontaneous post-anesthetic tremor does not resemble thermoregulatory shivering. Anesthesiology 68:843, 1988.

123. Rosenberg H, Clofine R, Bialik O: Neurologic changes during awakening from anesthesia. Anesthesiology 54:125, 1981.

124. Sessler DI, Rubinstein EH, Moayeri A: Physiological responses to mild perianesthetic hypothermia in humans. Anesthesiology 75:594, 1991.

125. Horn E-P, Ramsperger K, Sessler DI et al: Shivering following normothermic desflurane or isoflurance anesthesia (abstract). Anesthesiology 87:A321, 1997.

126. Delaunay L, Bonnet F, Duvaldestin P: Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia. Br J Anaesth 67:397, 1991.

127. Horn E-P, Standl T, Sessler DI et al: Physostigmine prevents postanesthetic shivering as does meperidine or clonidine. Anesthesiology 89:108, 1998.

128. Guffin A, Girard D, Kaplan JA: Shivering following cardiac surgery: Hemodynamic changes and reversal. J Cardiothorac Vasc Anesth 1:24, 1987.

129. Kurz M, Belani K, Sessler DI et al: Naloxone, meperidine, and shivering. Anesthesiology 79:1193, 1993.

130. Magnan J, Paterson SJ, Tavani A et al: The binding spectrum of narcotic analgesic drugs with different agonist and antagonist properties. Naunyn Schmiedebergs Arch Pharmacol 319:197, 1982.

131. Burton AC: Human calorimetry: The average temperature of the tissues of the body. J Nutr 9:261, 1935.

132. Weiskopf RB: Cardiovascular effects of desflurane in experimental animals and volunteers. Anaesthesia 50:S14, 1995.

133. Kurz A, Sessler DI, Birnbauer F et al: Thermoregulatory vasoconstriction impairs active core cooling. Anesthesiology 82:870, 1995.

134. Noback CR, Tinker JH: Hypothermia after cardiopulmonary bypass in man: Amelioration by nitroprusside-induced vasodilation during rewarming. Anesthesiology 53:277, 1980.

135. Plattner O, Xiong J, Sessler DI et al: Rapid core-to-peripheral tissue heat transfer during cutaneous cooling. Anesth Analg 82:925, 1996.

136. Clough D, Kurz A, Sessler DI et al: Thermoregulatory vasoconstriction does not impede core warming during cutaneous heating. Anesthesiology 85:281, 1996.

137. Szmuk P, Ezri T, Sessler DI et al: Spinal anethesia only minimally increases the efficacy of postoperative forced-air rewarming. Anesthesiology 87:1050, 1997.

138. Plattner O, Ikeda T, Sessler DI et al: Postanesthetic vasoconstriction slows postanesthetic peripheral-to-core transfer of cutaneous heat, thereby isolating the core thermal compartment. Anesth Analg 85:899, 1997.

139. Hynson JM, Sessler DI, Moayeri A et al: The effects of pre-induction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia. Anesthesiology 79:219, 1993.

140. Just B, Trevien V, Delva E et al: Prevention of intraoperative hypothermia by preoperative skin-surface warming. Anesthesiology 79:214, 1993.

141. Sessler DI, Schroeder M, Merrifield B et al: Optimal duration and temperature of prewarming. Anesthesiology 82:674, 1995.

142. Deriaz H, Fiez N, Lienhart A: Influence d'un filtre hygrophobe ou d'un humidificateur-rechauffeur sur l'hypothermie peroperatoire. Ann Fr Anesth Reanim 11:145, 1992.

143. Kaufman RD: Relationship between esophageal temperature gradient and heart and lung sounds heard by esophageal stethoscope. Anesth Analg 66:1046, 1987.

144. Bissonnette B, Sessler DI: Passive or active inspired gas humidification increases thermal steady-state temperatures in anesthetized infants. Anesth Analg 69:783, 1989.

145. Faries G, Johnston C, Pruitt KM et al: Temperature relationship to distance and flow rate of warmed IV fluids. Ann Emerg Med 20:1198, 1991.

146. Morris RH: Operating room temperature and the anesthetized, paralyzed patient. Surgery 102:95, 1971.

147. Sessler DI, McGuire J, Sessler AM: Perioperative thermal insulation. Anesthesiology 74:875, 1991.

148. Sessler DI, Schroeder M: Heat loss in humans covered with cotton hospital blankets. Anesth Analg 77:73, 1993.

149. Sessler DI, Moayeri A, Stoen R et al: Thermoregulatory vasoconstriction decreases cutaneous heat loss. Anesthesiology 73:656, 1990.

150. Simbruner G, Weninge RM, Popow C et al: Regional heat loss in newborn infants. I. Heat loss in healthy newborns at various environmental temperatures. S Afr Med J 68:940, 1985.

151. Simbruner G, Weninger W, Popow C et al: Regional heat loss in newborn infants. II. Heat loss in newborns with various diseases: A method of assessing local metabolism and perfusion. S Afr Med J 68:945, 1985.

152. Sessler DI, Moayeri A: Skin-surface warming: Heat flux and central temperature. Anesthesiology 73:218, 1990.

153. Morris RH, Kumar A: The effect of warming blankets on maintenance of body temperature of the anesthetized, paralyzed adult patient. Anesthesiology 36:408, 1972.

154. Kokate JY, Leland KJ, Held AM et al: Temperature-modulated pressure ulcers: A porcine model. Arch Phys Med Rehabil 76:666, 1995.

155. Crino MH, Nagel EL: Thermal burns caused by warming blankets in the operating room. Anesthesiology 29:149, 1968.

156. Giesbrecht GG, Ducharme MB, McGuire JP: Comparison of forced-air patient warming systems for perioperative use. Anesthesiology 80:671, 1994.

157. Camus Y, Delva E, Just B et al: Leg warming minimizes core hypothermia during abdominal surgery. Anesth Analg 77:995, 1993.

158. Kurz A, Kurz M, Poeschl G et al: Forced-air warming maintains intraoperative normothermia better than circulating-water mattresses. Anesth Analg 77:89, 1993.

159. White FN: A comparative physiological approach to hypothermia. J Thorac Cardiovasc Surg 82:821, 1981.

160. Gronert GA, Theye RA, Milde JH et al: Catecholamine stimulation of myocardial oxygen consumption in porcine malignant hyperthermia. Anesthesiology 49:330, 1978.

161. Davatelis G, Wolpe SD, Sherry B et al: Macrophage inflammatory protein-1: A prostaglandin-independent endogenous pyrogen. Science 243:1066, 1989.

162. Blatteis C: Role of the OVLT in the febrile response to circulating pyrogens. Prog Brain Res 91:409, 1992.

163. Blatteis C, Sehic E: Fever: How may circulating pyrogens signal the brain? News Physiol Sci 12:1, 1997.

164. Kotani N, Kushikata T, Matsukawa T et al: A rapid increase in foot tissue temperature predicts cardiovascular collapse during anaphylactic and anaphylactoid reactions. Anesthesiology 87:559, 1997.

165. Rubinstein EH, Sessler DI: Skin-surface temperature gradients correlate with fingertip blood flow in humans. Anesthesiology 73:541, 1990.

166. Heier T, Caldwell JE, Sessler DI et al: The relationship between adductor pollicis twitch tension and core, skin and muscle temperature during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 71:381, 1989.

167. Togawa T, Nemoto T, Yamazaki T et al: A modified internal temperature measurement device. Med Biol Eng 14:361, 1976.

168. Matsukawa T, Sessler DI, Ozaki M et al: Comparison of distal oesophageal temperature with "deep" and tracheal temperatures. Can J Anaesth 44:433, 1997.

169. Lopez M, Ozaki M, Sessler DI et al: Mild core hyperthermia does not alter electroencephalographic responses during epidural/enflurane anesthesia in humans. J Clin Anesth 5:425, 1993.

170. Matsukawa T, Kashimoto S, Miyaji T et al: A new infrared tympanic thermometer in surgery and anesthesia. J Anesth 7:33, 1993.

171. Matsukawa T, Imamura M, Ozaki M et al: The accuracy and precision of four infrared tympanic membrane thermometers during cardiopulmonary bypass (abstract). Anesthesiology 87:A492, 1997.

172. Wingard DW, Bobko S: Failure of lidocaine to trigger porcine malignant hyperthermia. Anesth Analg 58:99, 1979.

173. Baudendistel L, Goudsouzian N, Cote C et al: End-tidal CO_2 monitoring. Its use in the diagnosis and management of malignant hyperthermia. Anaesthesia 39:1000, 1984.

174. Bissonnette B, Sessler DI, LaFlamme P: Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. Anesth Analg 69:192, 1989.

175. Cork RC, Vaughan RW, Humphrey LS: Precision and accuracy of intraoperative temperature monitoring. Anesth Analg 62:211, 1983.

176. Burgess GE III, Cooper JR, Marino RJ et al: Continuous monitoring of skin temperature using a liquid-crystal thermometer during anesthesia. South Med J 71:516, 1978.

177. Ikeda T, Sessler DI, Marder D et al: The influence of thermoregulatory vasomotion and ambient temperature variation on the accuracy of core-temperature estimates by cutaneous liquid-crystal thermometers. Anesthesiology 86:603, 1997.

178. Iaizzo PA, Kehler CH, Zink RS et al: Thermal response in acute porcine malignant hyperthermia. Anesth Analg 82:803, 1996.

179. Ash CJ, Cook JR, McMurry TA et al: The use of rectal temperature to monitor heat stroke. Mo Med 89:283, 1992.

180. Buck SH, Zaritsky AL: Occult core hyperthermia complicating cardiogenic shock. Pediatrics 83:782, 1989.

181. Horrow JC, Rosenberg H: Does urinary catheter temperature reflect core temperature during cardiac surgery? Anesthesiology 69:986, 1988.

182. Just B, Delva E, Camus Y et al: Oxygen uptake during recovery following naloxone. Anesthesiology 76:60, 1992.

Chapter 38 - Acid-Base Balance

Robert E. Shangraw

INTRODUCTION

A thorough understanding of acid-base balance is important for the anesthesiologist because changes in acid-base balance can occur quickly in the patient undergoing surgery or otherwise requiring critical care. Further, these rapid changes may exert a profound influence on the body's physiologic functions, including compatibility with life. [1] [2] The purposes of this chapter are to present the dynamics of acid-base homeostasis and to facilitate recognition and treatment of acid-base disturbances encountered in clinical anesthesiology. The principal determinants for assessing acid-base balance are pH and CO_2 partial pressure (P_{CO_2}), from which are derived bicarbonate [HCO_3^-] and base excess (BE). Briefly, the goals are to

1. Use arterial blood P_{CO_2} (Pa_{CO_2}) to quantify a respiratory abnormality.
2. Use arterial [HCO_3^-] and BE to quantify a metabolic abnormality.
3. Diagnose a general acid-base derangement (respiratory acidosis, respiratory alkalosis, metabolic acidosis, or metabolic alkalosis).
4. Make a differential diagnosis of a metabolic disturbance using anion gap (AG), or unidentified anions (UA^-) calculated from the strong ion difference (SID).
5. Determine the extent to which compensatory mechanisms have been activated.
6. Synthesize a treatment plan, based on correcting the proximate cause and mechanism of the disturbance.

The chapter is organized to define clinical terms for acid, base, and buffer, to present the action of the HCO_3^- and other buffers, to discriminate among different causes of acid-base disturbance and their respective consequences, to show physiologic compensatory mechanisms, and to outline mechanisms for and treatment of the four basic types of acid-base disturbance.

OVERVIEW: ACID GENERATION AND ELIMINATION

Acid-base balance is regulation of hydrogen ion activity ($[H^+]$), in solution. Arterial blood $[H^+]$ is normally maintained at 40 ± 4 nmol/L, which is one-millionth of that for other common cations. In the circulation, $[H^+]$ may change by an order of magnitude, which makes it unique among ions. H^+ competes for protein binding space, and by displacing protein-bound hormones and drugs, it affects their bioavailable free concentrations.

Complex mechanisms control H^+ movement across plasma membranes to determine its intracellular versus extracellular concentrations, details of which are only beginning to be elucidated. Intracellular $[H^+]$ varies among tissues and, as a general rule, is slightly higher and less variable than that of the blood. [3] [4] [5] [6] Because of its small size and charge density, it exerts a powerful regulatory action on cellular function. [5] [6] Intracellular $[H^+]$, however, cannot be evaluated with equipment routinely available in the operating room, thus making direct assessment impractical. Fortunately, intracellular acid-base status can be reasonably, if indirectly, evaluated by analysis of blood. Ease of accessibility has made arterial blood the most common sampling source for assessment of acid-base balance, reflecting the extracellular compartment and serving as a window of whole-body acid-base balance. The intracellular compartment, however, contains a large reservoir of H^+ that may not change in lock step with extracellular fluid (ECF), but it can exchange with it.

Either $[H^+]$ or its negative logarithm, pH, is the central indicator of acid-base balance. The relationship between $[H^+]$ and pH is shown in Figure 38-1. (Figure Not Available) Note that pH 7.40 is equivalent to an $[H^+]$ of 40 nmol/L. Most of this chapter is devoted to control of blood acid-base balance *in vivo,* the processes of H^+ production into and removal from the blood that maintain H^+ homeostasis.

Endogenous H^+ is produced intracellularly by turnover of high-energy phosphates (adenosine triphosphate [ATP]), metabolism of sulfur-containing or cationic amino acids, incomplete or nonoxidative metabolism of carbohydrates, and ingested or administered metabolic acids such as salicylate. Oxidative catabolism of protein in general yields 1,000 mmol each of HCO_3^- and ammonium (NH_4^+) daily. The kidney excretes about 80 mmol H^+ per day, mostly as NH_4^+.

Cellular oxidative metabolism produces at least 20,000 mmol of CO_2 per day in adults, which is matched by alveolar ventilation (V_A) such that Pa_{CO_2} is normally maintained at 40 ± 4 mm Hg. The relationship between CO_2 and ventilation is described by the V_A equation:

where V_A (mL/min) is the difference between minute ventilation (V_E) and dead space (V_D); V_{CO_2} is tissue CO_2 pro-duction (mL/min); and K is a patient-specific constant (mm Hg · min/L). Rearrangement of the equation as:

Figure 38-1 (Figure Not Available) Relationship between $[H^+]$ and pH. Note an approximately linear relationship near pH 7.40, but that $[H^+]$ increases more than pH at pH less than 7.20. *(From Narins and Emmett [141])*

demonstrates that Pa_{CO_2} is directly proportional to V_{CO_2} and is inversely proportional to V_A.

V_{CO_2} and H^+ production are linked by carbonic acid (H_2CO_3), which enables H^+ to interconvert with CO_2. This interaction is known as the HCO_3^- buffer system:

The relationship between H^+ and CO_2 is important for three reasons. First, it indicates that the largest single H^+ source under physiologic conditions is tissue CO_2 production. Second, it allows flexibility in $[H^+]$ regulation because H^+ can be more quickly and efficiently removed from the body as CO_2 than as the H^+ with which it equilibrates. Renal excretion alone cannot effectively remove a H^+ challenge. Third, it permits CO_2 removal from the body to keep pace with its tissue production by allowing interconversion of CO_2 and HCO_3^-.

CO_2 produced by oxidative metabolism ultimately leaves the body as CO_2 by alveolar ventilation. However, most CO_2 (~80%) is transported in blood to the lungs in the form of HCO_3^-, because of the poor water solubility of CO_2. Carbamino compounds, including carbaminohemoglobin, account for another 15 percent of blood CO_2 content, and dissolved CO_2 represents only ~5 percent of total blood CO_2 content. CO_2 is converted to HCO_3^- in the nonpulmonary microcirculation and back to CO_2 in the pulmonary circulation. [7] These important relationships illustrate that acid-base regulation is intimately linked to body CO_2 transport.

ACIDS, BASES, AND BUFFERS

An *acid,* as defined by Bronsted and Lowry, is a substance that donates H^+ at a given pH. A *base* accepts H^+ at a given

pH, and a *buffer pair* is a weak acid (HA) in equilibrium with a weak conjugate base (A^-):

The relative strength of the acid and base components of the buffer pair determines the balance of the equation to either the right or left, according to an equililibrium constant (K):

which rearranges to form the Henderson equation:

Acidity of a solution, or $[H^+]$, is determined by the degree of dissociation of an acid into its free H^+ and conjugate base. Mineral acids, such as hydrochloric acid (HCl), dissociate completely in solution and have infinitely high K values.

The Henderson relationship is better recognized when expressed in the logarithmic form of the Henderson-Hasselbalch equation:

where pK is the negative logarithm of K, the dissociation constant. A low pK indicates a strong acid, and a high pK represents a weak acid or strong base. When pH equals pK, an acid is 50 percent dissociated. Common organic acid pK values are shown in Table 38-1 .

A *buffer* minimizes changes in $[H^+]$ from the baseline value, which for arterial blood is 40 nmol/L (pH 7.4). It must be capable of either binding free H^+ during an H^+ challenge or donating free H^+ during an OH^- challenge, to defend the baseline $[H^+]$. A buffer thus acts as a weak base during an H^+ challenge or a weak acid during an OH^- challenge. Because a buffer must be able to either donate or accept H^+, its best buffering capacity occurs at a pH that approximates its pK, where it is 50 percent dissociated. Greater than 90 percent of buffering capacity occurs when the pH is within ±1 units relative to the pK of a buffer.

Let us first consider the buffering capacity of lactic acid, which has a pK of 3.86. Lactic acid (HL) equilibrates with

TABLE 38-1 -- Strength of Common Organic Acids

ORGANIC ACID	pK_a
Acetoacetate	3.58
Formate	3.75
Carbonic acid	3.77
Lactate	3.86
beta-Hydroxybutyrate	4.70
Acetate	4.76
Phosphate	6.80

pK_a , negative logarithm of the acid ionization dissociation constant

lactate (L^-) as HL
$H^+ + L^-$. Substitution of lactic acid values into the Henderson-Hasselbalch equation at pH 7.40 yields:

rearranging:

Lactic acid (or lactate) is a poor buffer at physiologic pH because it exists steadfastly in the dissociated state and cannot bind free H^+ ions. Similarly, most common organic acids are poor buffers in the physiologic pH range for both intracellular and extracellular fluids (see Table 38-1) . These organic acids are overwhelmingly ionized within the relatively small $[H^+]$ range that is compatible with life.

In contrast, phosphate (HPO_4^{2-}), with a pK of 6.80, yields the following values at pH 7.40:

rearranging:

During an H^+ challenge, HPO_4^{2-} readily accepts H^+ to form $H_2PO_4^-$, minimizing free H^+ accumulation in solution and the change in $[H^+]$ from the baseline 40 nmol/L. HPO_4^{2-} is an effective buffer when present at the concentration found in urine and intracellular fluid. Its concentration in extracellular fluid, however, is normally too low for it to play a major role in acid-base balance.

Protein can be an effective buffer, largely dependent on the imidazole ring of its histidine (His) moiety, which has a nominal pK of 6.00. At pH 7.4:

rearranging:

Histidine's imidazole ring buffers within the physiologic pH range, especially in intracellular fluid where the pH is closer to 7.0, and the imidazole ring ionized/unionized ratio becomes 10:1. A high histidine content of hemoglobin (Hb) is important for its buffering capacity. Protein conformation may alter the effective pK of imidazole. For example, at least 13 histidine residues in albumin can buffer, with individual pK values ranging from 5.15 to 7.82. [8] Buffers play an important role in acid-base homeostasis by preventing wide $[H^+]$ oscillations during the course of diurnal H^+ or CO_2 challenges.

COMPONENTS OF BODY ACID-BASE BUFFERING

Carbon Dioxide - Bicarbonate Buffer System

The most important buffer in blood is the CO_2 -HCO_3^- system, where HCO_3^- acts as a weak base:

CO_2 -HCO_3^- is not a true, or closed, buffer because its ability to maintain a pH of 7.4 depends on free movement of CO_2 out of the system, rather than HCO_3^- absorbing H^+ and remaining in solution. Hydration of CO_2 to form carbonic acid (H_2CO_3) is relatively slow unless the reaction is catalyzed by *carbonic anhydrase* (CA). CA is widely distributed in tissues throughout the body in the form of different isoenzymes. [9]

H_2CO_3 is a strong organic acid with a pK of 3.77. H_2CO_3 quickly and almost completely dissociates into H^+ and HCO_3^- at physiologic pH. Therefore, H_2CO_3 represents less than 0.5 percent of the CO_2 -HCO_3^- system mass. Because of rapid overall equilibration in the presence of CA, the reaction between CO_2 and HCO_3^- is considered collectively. Substituting CO_2 -HCO_3^- buffer values in the Henderson equation yields:

where the equilibrium constant for the overall CO_2 -HCO_3^- reaction (K
) is 24 nmol H^+ · mmol HCO_3^- /mm Hg at 37°C. Alternatively, substituting CO_2 -HCO_3^- buffer values into the Henderson-Hasselbalch equation yields:

where pK_a
is the dissociation constant for the overall CO_2 -HCO_3^- reaction, and alpha is the solubility coefficient for CO_2 in plasma. At 37°C, pK_a
is 6.1 and alpha is 0.03 mmol/L/mm Hg, yielding the equation:

Note that by the Henderson or the Henderson-Hasselbalch equation, acidity of a solution is determined by the ratio of P_{CO_2} to [HCO_3^-], not by the absolute value of either. Substituting the normal values Pa_{CO_2} = 40 mm Hg and [HCO_3^-] = 24.0 mmol/L:

Let us first perturb the system by increasing Pa_{CO_2} to 80 mm Hg and assume that the change in [HCO_3^-] (nmol/L) is too small to affect the result:

At pH 7.10, [H^+] is 80 nmol/L, or 40 nmol/L greater than the baseline 40 nmol/L (see Fig. 38-1) (Figure Not Available) . For electroneutrality, [HCO_3^-] must also increase by 40 nmol/L accompanying the H^+ increase, but the change (to 24.000040 mmol/L) is negligible. From a practical standpoint, [HCO_3^-] is insensitive to changes in P_{CO_2} in an isolated system, and the change in [H^+] is directly proportional to the change in P_{CO_2}. Of course, the body is normally an open system that can rapidly eliminate CO_2 via the lungs, and [HCO_3^-] does increase modestly *in vivo* with increases in P_{CO_2}. [10]

Consider next a 5-mmol/L nonvolatile H^+ challenge in the form of HCl. An equal quantity of HCO_3^- will be consumed, decreasing its concentration from 24 to 19 mmol/L. The effect on pH is:

At pH 7.30, [H^+] is 50 nmol/L, or 10 nmol above the baseline 40 nmol/L (see Fig. 38-1). Thus, addition of 5 (Figure Not Available) million nmol H^+ to a solution containing 24 mmol/L HCO_3^- increases free [H^+] by only 10 nmol/L. This relationship is also demonstrated by using the Siggaard-Andersen nomogram (Fig. 38-2) (Figure Not Available) .

Body *total* CO_2 content includes HCO_3^-, carbonate, carbamino compounds, dissolved CO_2, and H_2CO_3. The whole body total CO_2 pool, at 13 to 18 mmol/kg body weight, is very large. From the standpoint of acid-base balance, it is not easily exhausted. However, it is compartmentalized into at least three distinct functional pools, only one of which (central compartment) turns over rapidly (Fig. 38-3) (Figure Not Available) . [11] [12] Body fluid HCO_3^- accounts for about 9 mmol/kg, and most of the

remaining 4 to 9 mmol/kg exists as carbonate in bone. The relative size of the total CO_2 compartments may change with acid-base status, such that the fast turnover central pool can increase 3-fold when [H^+] is increased. [13] Another consequence of the large but compartmentalized total CO_2 pool is some functional separation of CO_2 and HCO_3^- fluxes *in vivo.*[14]

The CO_2 -HCO_3^- buffer system exerts a powerful effect on acid-base balance. Further, when presented in graphic form (Fig. 38-4) (Figure Not Available) , it is used to differentiate the various types of acid-base disturbances. It an ideal buffer for the following reasons:

1. The system is open, allowing volatile CO_2 produced from reaction of H^+ and HCO_3^- to be easily removed from the body by V_A. Ventilatory adjustment can quickly correct acid-base disturbances.
2. It has an extraordinary apparent molar buffer value, roughly four times that of most other buffer species, such as HPO_4^{2-}. (See the discussion on quantitation of buffer content later.)
3. Its other physiologic functions are uncompromised when it is consumed for H^+ homeostasis, although a protracted

H^+ load depleting HCO_3^- will ultimately demineralize and weaken bone over a period of months to years. In contrast, acute dependence on albumin as the principal H^+ buffer system would, by displacing hormones and drugs from their binding sites, lead to endocrine dysfunction or convert an appropriate drug dose into a lethal one. Similarly, excessive dependence on hemoglobin for H^+ buffering would decrease its ability to bind and carry oxygen (O_2) to tissues.

Figure 38-2 (Figure Not Available) Siggaard-Andersen alignment nomogram. This is used for determination of HCO_3^- and base excess (BE) from measured values of pH and P_{CO_2}. See text for details. *(From Astrup and Severinghaus [22])*

Two principal measures of the CO_2 -HCO_3^- system, pH and P_{CO_2}, can be rapidly and directly measured with substrate-specific electrodes. These values are part of the *blood gas analysis* routinely performed in clinical laboratories. The third component, HCO_3^-, is calculated as the difference between total CO_2 and dissolved P_{CO_2} ($0.03 \cdot P_{CO_2}$), or a by using a nomogram (see Fig. 38-2) (Figure Not Available) .

Carbonate and carbamino compounds, although a major fraction of whole body total CO_2 content, are absent from plasma. HCO_3^- accounts for 95 percent of plasma total CO_2, with the remaining 5 percent due to dissolved CO_2. [7] Therefore, venous plasma total CO_2 content is commonly used as a surrogate measure of [HCO_3^-], to approximate acid-base status in patients without a respiratory abnormality.

Weak Acid Plasma Buffers: Proteins and Phosphate

Despite its great importance, the CO_2 -HCO_3^- system is not the only buffer in the body, or even in the intravascular compartment. The next buffers to consider are plasma proteins

Figure 38-3 (Figure Not Available) Distribution of the HCO_3^-/CO_2 pool in humans. Note that most of the pool is located in slow-turnover compartments. *(Modified from Irving et al [11])*

and HPO_4^{2-}. Plasma proteins are heterogenous, with different pK values and buffering capacities. *Albumin* is the only important buffering plasma protein, and its buffering capacity can be modified when other substrates, including Ca^{2+}, bind to it. [8] *Phosphate* (HPO_4^{2-}) can usually be ignored as a buffer unless its plasma concentration becomes pathologically increased, for example, by renal failure. Even in renal failure, the added buffering of hyperphosphatemia plays a relatively minor role in clinical acid-base homeostasis.

Whole Blood: The Importance of Erythrocytes

Although erythrocytes are cells, they are in practice considered part of the ECF when assessing acid-base balance. Erythrocytes supply CA within blood, a process that facilitates the CO_2 -HCO_3^- buffer system by catalyzing rapid interconversion of CO_2 and HCO_3^-. [9] As mentioned earlier, CO_2 -HCO_3^- interconversion is critically important for efficient removal of CO_2 produced by the tissues.

Erythrocytes also contain a Cl^-/HCO_3^- anion-exchange transporter (AE-1), which mediates isoelectric exchange of HCO_3^- for Cl^- across its plasma membrane *(chloride shift).*[7] Tissue CO_2 production increases venous P_{CO_2}, and V_A decreases P_{CO_2} in pulmonary capillaries. AE-1 mediates erythrocyte HCO_3^- release in peripheral tissues (in exchange for Cl^- uptake), maintaining a stable P_{CO_2}/HCO_3^- ratio and minimizing the increase in venous blood acidity. HCO_3^- in venous plasma also reacts with H^+ released by tissues. An opposite Cl^-/HCO_3^- exchange occurs in the pulmonary microcirculation, where AE-1 mediates erythrocyte uptake of HCO_3^- in exchange for intracellular Cl^-. Erythrocyte HCO_3^- uptake from plasma in the lung coincides with CO_2 movement from the blood into the alveoli, again maintaining a constant P_{CO_2}/HCO_3^- ratio and minimizing the alkalinity that would occur in the pulmonary capillary. Furthermore, because the Cl^- shift in peripheral tissues promotes HCO_3^- movement from the erythrocyte into the plasma, it speeds the CA reaction by dispersing intracellular [HCO_3^-] and facilitates CO_2 transport.

Erythrocyte-bound Hb buffers in two ways. First, Hb has a high histidine content (8% of total amino acid content) with an average pK of ~6.8. Several histidine residues participate in each chain of the Hb molecule, increasing its effective buffering. The molecular mechanism of H^+ buffering by Hb depends on the Hb O_2 saturation state. Hb deoxygenation in peripheral tissues increases its H^+ binding according to the equation: $HbO_2 + H^+$ $HHb + O_2$ (the *Bohr effect*). The effect of H^+ binding by Hb on the free [H^+] is mitigated by the HCO_3^- system ($CO_2 + H_2O$ $H^+ + HCO_3^-$), making the overall equation: $HbO_2 + CO_2 + H_2O$ $HHb + HCO_3^- + O_2$ (the *Haldane effect*). The

Figure 38-4 (Figure Not Available) Siggaard-Andersen acid-base chart. This is used to determine the appropriate compensation for a primary acid base disturbance. Chronic metabolic adaptation to respiratory disturbances requires days to weeks. *(From Astrup and Severinghaus [22])*

process reverses in the lung: Hb oxygenation releases CO_2 and H_2O as HCO_3^- is consumed. The Haldane effect represents coordination of Hb with the CA and AE-1 systems. It minimizes the pH decrease in nonpulmonary tissues and the venous system, where Hb is desaturated, maintaining acid-base homeostasis.

The second Hb buffering mechanism is direct Hb binding of CO_2 to form *carbaminohemoglobin,* which accounts for ~10 percent of peripheral CO_2 uptake by the blood. [7] Non-Hb proteins in the erythrocyte also form carbamino compounds to buffer a CO_2 challenge. Both non-Hb proteins and intracellular HPO_4^{2-} serve as direct H^+ buffers.

Extracellular Fluid Buffering

ECF includes plasma, erythrocytes, and interstitial fluid. Total ECF volume is three to five times that of blood because of a large interstitial space that, unfortunately, is

difficult to sample. Interstitial fluid [HCO_3^-] and [HPO_4^{2-}] resemble those of plasma, but [albumin] is normally about onethirtieth of that in plasma and [Hb] is negligible. Further, the relationship between plasma and interstitial albumin and Hb concentrations may change during acute hemodilution.

Despite the distance of interstitial fluid from erythrocytes, its close juxtaposition to tissues containing CA facilitates local HCO_3^- formation from CO_2 diffusing from the tissues. This augments CO_2 transport to the lungs. A side effect of the CA reaction is that H^+ is produced along with the HCO_3^-, thereby decreasing the local pH. Skeletal muscle contains a CA isoenzyme (CA-3) with low catalytic activity, which minimizes local H^+ production in skeletal muscle because of CO_2 hydration. [9]

QUANTITATION OF EXTRACELLULAR FLUID BUFFER CONTENT AND ACID-BASE BALANCE

Buffer power (beta) quantitates the effectiveness of buffers in solution. It is defined as the negative of the slope of the acid titration curve at a given pH, usually 7.40 (Fig. 38-5) . Buffer power is expressed as millimoles of H^+ removed (or

Figure 38-5 Quantitation of buffering capacity (beta) in extracellular or intracellular fluid. This model depicts a hypothetic buffer solution, with point A on the X axis representing the baseline pH. The Y axis is the change in OH^- removed (or H^+ added) and X axis it the consequent change in pH. beta is defined as the slope of -DeltaH^+ added/DeltapH. A better buffer, which requires either more H^+ or OH^- added for a given pH change, would have a larger beta value.

base added) per liter/DeltapH unit. In the presence of CO_2 -HCO_3^-, non-HCO_3^- buffering power is defined in units called *slykes* (Delta[HCO_3^-]/DeltapH unit). [15] *Molar buffer power* is the defined as buffer power/mole buffer. For example, at pH 7.40, the molar buffer power is 2.3 for HCO_3^-, 0.575 for HPO_4^{2-}, ~3 for Hb, and 8 for albumin. [8] [15]

Understanding buffer power requires knowledge of the conditions of analysis. First, a CO_2 challenge should be distinguished from a nonvolatile acid (H^+) challenge. Second, the buffer components present during the challenge must be identified. Third, it is important to determine whether the data were generated *in vitro* or *in vivo.* Most buffer power data have been generated from *in vitro* samples.

For CO_2 titration, the buffer power of plasma separated from blood cells before CO_2 equilibration ("separated" plasma) is proportional to its protein content (Table 38-2) . Much greater buffer power is obtained from plasma that has been equilibrated with CO_2 *before* separation from cells ("true" plasma). The added buffering is due to erythrocyte-contained Hb, which converts CO_2 to plasma HCO_3^- before separation. Erythrocytes and other cells have a buffer power of ~50 slykes. [7] [15] [16] Buffer power of human whole blood is intermediate between that of plasma and red cells, whereas that of overall normal ECF resembles that of dilute "true" plasma.

ECF buffering power *in vivo* is more time-dependent than that determined *in vitro,* because of the influences of cellular buffering mechanisms (discussed later), mobilization of carbonate from bone, and the extent to which [H^+] or [HCO_3^-] is altered by renal function. In dogs breathing CO_2, *in vivo* buffer power almost doubles within 2 hours from that predicted on the basis of ECF buffering capacity, and it further increases to 5-fold by 24 hours. [17] Similar findings have been made in rats. [7] Comparable data in humans are not available, other than to demonstrate that the apparent HCO_3^- volume of distribution *(HCO_3^- space)* increases over time. [11] [14] One implication of this progressive increase in buffer power is that an unexpected overshoot is possible during acute therapy of acid-base disturbances as intrinsic buffer power increases. Conservative initial treatment and frequent reassessments of acid-base status are prudent. There are few nontheoretic descriptions of the effect of changes in the individual factors controlling acid-base balance. [18] [19]

Different clinical methods have been developed to quantify the buffer content, or to assess acid-base status, in body solutions. An important, and widely used, method to assess buffer content is *base excess* (BE) , developed by Siggaard-Andersen and colleagues using blood samples *in vitro.*[20] [21] [22] BE is popular because it is easy to calculate or determine using a nomogram (see Fig. 38-2) (Figure Not Available) . It is also automatically reported by many commercially available blood gas machines. BE is defined as the deviation of the patient's [HCO_3^-] from 24 mmol/L after the pH is corrected to 7.40. This could be determined by adjusting the patient's arterial blood pH to 7.40 by altering minute ventilation (V_E) to change Pa_{CO_2}. At

TABLE 38-2 -- Buffer Power of Body Constituents

BUFFER	BUFFER POWER (beta)	INVESTIGATORS
Phosphate solution		
2.5 mmol/L	1.0	Klocke [7]
10 mmol/L	4.0	Klocke [7]
Separated plasma		
[Protein] 0 g/dL	0.7	Klocke [7]
[Protein] 7-8 g/dL	4-6	Klocke [7] and Woodbury [15]
"Normal" extracellular fluid	10-12	Woodbury [15]
True plasma		
[Hemoglobin] 5 g/dL	15	Klocke [7]
[Hemoglobin] 10 g/dL	23	Klocke [7]
[Hemoglobin] 15 g/dL	32	Klocke [7]
"Normal" whole blood (human)	31-34	Klocke [7] and Woodbury [15]
Erythrocytes	~50	Woodbury [15]
Liver	~50	Benedetti et al [16]
Muscle	~50	Woodbury [15]

pH 7.40, all non-HCO_3^- buffers are in their resting distribution; that is, they are neither accepting nor donating H^+ to compensate for a pH deviation from 7.40. All buffering is then produced by the CO_2 -HCO_3^- system.

Alternatively, BE can be calculated by multiplying the pH deviation from 7.40 by the apparent ECF buffer power, then adding this value to the "measured" [HCO_3^-] value, and subtracting these from the expected "normal" [HCO_3^-] value of 24 mmol/L at 7.40. ECF buffer power, assuming normal concentrations of Hb, albumin, and HPO_4^{2-}, is ~10 to 12 slykes (= Delta[HCO_3^-](mmol/L)/DeltapH). [15] An ECF buffer power of 10 slykes is often used to simplify the mathematics. The equation for BE can be written as follows:

where both [HCO_3^-] and Delta[HCO_3^-] are expressed in millimoles per liter and

Substituting blood gas values of pH 7.20, Pa CO_2 32 mm Hg, and [HCO_3^-] 20 mmol/L, the DeltapH is 7.20 - 7.40 = -0.20, and:

Combining this with the [HCO_3^-] determined from the blood gas analysis and subtracting from the normal [HCO_3^-] of 24 mmol/L:

Normal ECF volume is approximately three times that of the intravascular compartment. For this reason, determination of ECF base excess using the Siggaard-Andersen nomogram (see Fig. 38-2) (Figure Not Available) is most accurate using the isobar for a Hb concentration of 5 mg/dL or less. The single charge on HCO_3^- permits BE to be expressed as either millimoles per liter or milliequivalents per liter. A negative BE value is referred to as a "base deficit."

The numeric value for BE has clinical importance. A normal BE is 0 ± 2 mmol/L. If the base deficit, in millimoles per liter, is multiplied by the HCO_3^- space, in liters per kilogram of body weight, an appropriate dose of sodium HCO_3^- ($NaHCO_3$) to reverse the base (HCO_3^-) deficit can be calculated. Alternatively, if a BE has an appreciable value, this can be used to determine the HCO_3^- excess to be neutralized by HCl infusion. HCO_3^- space is often used interchangeably with ECF, although the functional HCO_3^- space is in practice more variable than ECF. Commonly, the HCO_3^- space is taken to be 0.2 to 0.3 L/kg (40-50% total body water), but it can double (to 100% of total body water) when [H^+] is markedly increased. [13] Almost 30 percent of the HCO_3^- space can be accounted for by CO_2 loss in the breath. [23] The space also increases slowly over time (hours) as administered HCO_3^- distributes progressively into slower turnover compartments *in vivo.* [11] [12] [14]

The BE concept, as presented, has three shortcomings. First, it does not elucidate the mechanism for a pH disturbance other than to eliminate the contribution of CO_2. Second, because it assumes "normal" ECF concentrations of Hb, albumin, and HPO_4^{2-}, it is insensitive to the change in buffering power consequent to abnormal concentrations of these factors. Specifically, hypoalbuminemia can mask an acidosis because the BE equivalent of albumin is 3.7 mEq/g. [18] Third, because the Siggaard-Andersen nomogram was generated from blood *in vitro,* it is insensitive to *in vivo* processes that increase buffering power over time. [7] [17] Nevertheless, it provides a useful, if imperfect, assessment of clinical acid-base balance.

An alternative approach to assessing acid-base balance utilizes the terms "acid" and "base" to refer to anions and cations, respectively. Singer and Hastings introduced the term "buffer base" (B_B) using whole blood *in vitro.* [24] They defined B_B as the sum of charges on all strong "bases" (nonbuffering cations) minus the sum of charges on all strong "acids" (nonbuffering anions), according to the equation:

where [SI] is the concentration of a strong ion (e.g., Na^+, Cl^-), and *z*SI is its charge. To satisfy the requirement for electroneutrality, B_B must be balanced by the charge sum of buffer ions such that:

where [BI] is buffer ion concentration and zBI is its charge. The weakness of B_B is that the distinction between strong and buffer ions is arbitrary, and it depends on the prevailing pH. A nomogram has been created using pH, P CO_2, and Hb concentration to determine B_B. [24]

Stewart's "physicochemical" approach to acid-base is a modification of B_B, although it was developed using plasma rather than whole blood. [25] It defines "strong ion difference" (SID) as the net charge sum of strong electrolytes:

It is important to account for the double charge on Ca^{2+}, although magnesium (Mg^{2+}) is typically reported as milliequivalents per liter. As originally developed, acid-base problem solving required simultaneous iterative approximations of six polynomial equations, which limited its appeal to bedside clinicians. Fencl and Leith experimentally simplified the Stewart approach. [26] Actual SID cannot be determined directly because "other strong anions" are not quantified. The "other strong anions" are ignored to calculate an *apparent SID* ($SID_{apparent}$), defined as the charge sum:

An example of normal $SID_{apparent}$ is 140 + 4 + (2 · 2.5) + 2 - 105 = 46 mEq/L.

For electroneutrality, $SID_{apparent}$ is balanced in part by the sum of charges on buffers, that is, HCO_3^- and all weak nonvolatile acids, which Fencl and Leith [26] termed *effective SID* ($SID_{effective}$). Plasma weak nonvolatile acids are proteins (albumin) and inorganic phosphate. Albumin has a net

charge of -2.6 mEq/g at pH 7.4. [8] Phosphate has a net charge of -1.8 at pH 7.4, based on its equilibrium between HPO_4^{2-} and $H_2PO_4^-$. Therefore:

A normal plasma albumin concentration of 3.6 to 5.2 g/dL produces a negative charge range of 9 to 14 mEq/L, whereas phosphate, with a normal plasma concentration of 0.8 to 1.5 mmol/L, yields a negative charge range of 1.5 to 2.2 mEq/L. An example of normal $SID_{effective}$ at pH 7.4 is:

The charge difference between $SID_{apparent}$ and $SID_{effective}$ is accounted for by unidentified anions (UA^-). Thus a normal UA^- value is 46 minus 36 = -10 mEq/L. A UA^- value of substantially greater magnitude than -10 mEq/L indicates an increased plasma content of anions, possibly pathogenic.

The SID physicochemical approach, by accounting for plasma albumin and HPO_4^{2-} concentrations, has the potential to provide insight into the mechanism of an acid-base disturbance. $SID_{effective}$ may become an important adjuvant to evaluate acid-base status during marked hypoalbuminemia or when plasma [HPO_4^{2-}] is pathologically increased. However, the clinical utility of $SID_{effective}$ and UA^- remains to be tested in widespread application. A database of normal population values is lacking.

An analogue of SID used in clinical medicine is the "anion gap" (AG), which is defined as

For simplicity, potassium ([K^+]) is often ignored, and total CO_2 is substituted for [HCO_3^-] because 95 percent of plasma total CO_2 is due to HCO_3^-. [7] [27] AG allows gross assessment of acid-base balance, even using peripheral venous plasma. The AG is due to the presence of unmeasured anions, similar to the UA^- for the SID approach. [25] [26] An altered AG is sometimes the first indication of an acid-base disturbance in a patient, most commonly resulting from a change in [HCO_3^-]. [28]

Calculated as [Na^+] - ([Cl^-] + [total CO_2]), the normal AG has historically been 12 mEq/L (range, 8-16). However, a change in laboratory equipment over the past 15 years to an ion-specific electrode for the [Cl^-] assay has resulted in higher reported [Cl^-] values, without a commensurate decrease in the expected normal AG range. As a result, AG has been criticized as an insensitive gauge for acid-base disturbances. [29] An update (decrease) of institutional AG normal values to reflect the equipment change would allow true AG increases to be better appreciated.

A limitation of the AG, besides the technical matter regarding normal [Cl^-] values, is that it also cannot distinguish plasma concentration changes of negatively charged proteins (albumin) or HPO_4^{2-} from that of other anions. Hypoalbuminemia masks an increased AG caused by pathogenic organic acids. [18] [19] [30] Alternatively, hyperphosphatemia increases AG without being diagnosed specifically because it is not part of the defining equation for AG.

INTRACELLULAR FLUID BUFFERS AND PUMPS

Acid-base balance within cells is very important because many cellular functions are exquisitely sensitive to pH changes. Further, endogenous H^+ or CO_2 production usually originates within the intracellular space. Intracellular pH (pH_i) regulation has recently been reviewed. [5] [6] However, it remains poorly understood in clinical acid-base balance, especially *in vivo.* Tissue cells contain high buffer content in the form of proteins, HPO_4^{2-}, and HCO_3^-. Intracellular concentrations of both protein and HPO_4^{2-} are approximately three times greater than those in plasma. [15] [31] [32] [33] [34] [35] Cells also actively transport H^+ or HCO_3^- across the plasma membrane. [16] [36] Although not true buffering, this transport contributes to maintaining a stable pH_i. Both true buffering and active ion transport are included in the term *cellular buffering power* (beta), also defined as millimoles H^+ added per liter intracellular fluid/DeltapH unit, similar to that for ECF (Fig. 38-6) (Figure Not Available). Intracellular fluid has a buffer power approximately five times greater per liter than the ECF (see Table 38-2).

Although pH_i is generally lower than in the ECF, it is still higher than that predicted by Nernst electrochemical equilibrium, which would be about pH 6.8. Measured pH_i is 7.30 in liver, 7.00 in resting skeletal muscle, and 7.20 to 7.30 in different regions of the kidney. [3] [16] [37] Relatively high pH_i is maintained by active H^+ extrusion and/or importation. Mechanisms involved in cellular acid-base regulation have recently been described. [5] [6] [16]

Liver cells maintain low intracellular $[H^+]$ at plasma pH 7.4 in part by taking up plasma HCO_3^- via the Na^+:HCO_3^- cotransporter (Fig. 38-7) (Figure Not Available). [16] [36] Although not directly energy driven, the Na^+:HCO_3^- cotransporter is linked to membrane Na^+/K^+-ATPase because the Na^+ must be subsequently extruded to prevent intracellular Na^+ accumulation. With extracellular H^+ challenge, HCO_3^- uptake is

Figure 38-6 (Figure Not Available) Intracellular buffering capacity as a function of intracellular pH. Filled circles indicate buffering, which includes active ion pumps, and open circles indicate passive buffering alone. *(From Benedetti et al [16])*

Figure 38-7 (Figure Not Available) Schematic mechanisms of cellular ion pumps that regulate intracellular acid-base homeostasis. *(Modified from Strazzabosco et al [36])*

decreased by diminished availability of extracellular HCO_3^- because the HCO_3^- is consumed directly as it reacts with H^+. There is still a tendency for pH_i to decrease, which activates a normally dormant H^+ extruder, the amiloridesensitive Na^+-H^+ *e*xchanger (NHE-1), which is also linked to the Na^+/K^+ ATPase to maintain constant intracellular $[Na^+]$. The net result is a modest but sustained increase in intracellular $[H^+]$. Extracellular H^+ challenge also activates a separate mechanism involving the plasma membrane, whereby extracellular H^+ is, in effect, exchanged for intracellular K^+. Increased intracellular H^+, in turn, activates the NHE-1:Na^+/K^+-ATPase system to moderate the effect, by passively extruding H^+ and actively importing K^+, but net result is cellular H^+ influx and K^+ efflux.

Increased extracellular $[HCO_3^-]$ has the exact opposite effect on the liver Na^+:HCO_3^- transporter, but intracellular HCO_3^- accumulation is mollified by a Cl^-/HCO_3^- exchanger (AE-2), similar to that in the erythrocyte, which is normally inactive at resting pH_i but increases its activity markedly with alkalization of pH_i. [16] [36] Increased extracellular P_{CO_2} decreases pH_i acutely, with a gradual but incomplete return to baseline. The opposite effect is observed with a decrease in P_{CO_2}. The pH_i moves in the direction of the extracellular pH, reducing but not eliminating the changes in the plasma by availing more passive buffer and redistributing H^+, HCO_3^-, or both. The $DeltapH_i/DeltapH_o$ for liver cells is 0.2 to 0.5 in response to changes in extracellular pH, regardless of whether the primary event is an alteration of $[H^+]$ or P_{CO_2}.

Skeletal muscle has a lower resting pH_i than liver. Muscle contains the NHE-1 transporter ("acid-extruder") and the AE-2 isoform of a Na^+-driven, Cl^-/HCO_3^- exchanger ("acid-loader"). Both transporters resist a change in pH from occurring in the same direction as that produced in plasma. [6] However, skeletal muscle pH_i still decreases in the setting of decreased extracellular pH, with a $DeltapH_i/DeltapH_o$ of 0.2 to 0.5, comparable to liver. [15] The importance of this relationship is that change in pH_i occurs despite the large buffering capacity of the concentrated intracellular HPO_4^{2-} and protein (including myoglobin), and the larger intracellular volume in comparison to the ECF.

Brain tissue has an overall pH_i of 7.2 to 7.5, depending on the region evaluated. It contains the NHE-1 exchanger like liver and skeletal muscle. [6] [38] [39] When studied *in vitro,* brain pH_i changes in response to extracellular $[H^+]$ alterations in a manner comparable to other tissues. *In vivo,* however, brain pH_i is unusually resistant to changes in blood $[H^+]$. [38] [39] Although the brain pH_i *in vivo* is resistant to fixed H^+ challenge compared with other tissues, its sensitivity to P_{CO_2} changes is similar to that for liver and muscle. [38] [39] Resistance of brain pH_i to a blood H^+ challenge may be a function of the blood-brain barrier, which excludes H^+ and/or the accompanying anion.

Overall, the intracellular compartment limits changes in H^+ presented to the ECF by absorbing or releasing H^+. Quantitation of intracellular buffering in various clinical circumstances remains difficult. Nevertheless, half of the total body acid-base buffering capacity to either a CO_2 or exogenous H^+ challenge resides within cells. [40] [41]

RENAL ACID SECRETION AND HCO_3^- KINETICS

In kidney, intracellular "buffering" of ECF pH acquires another dimension because H^+ is secreted by the kidney into the urine and is lost from the body. First, the proximal tubule reabsorbs 90 percent of filtered HCO_3^-, mostly by virtue of a specialized electrogenic 1:3 *Na^+ / bicarbonate cotransporter* (NBC) that is unique to kidney (Fig. 38-8) (Figure Not Available) . [42] NBC differs from most Na^+/HCO_3^- cotransporters by its reverse polarity; that is, it extrudes HCO_3^- into the plasma instead of importing it. The NBC acts in concert with a Na^+/H^+ exchanger (NHE-3) located on the luminal surface, and luminal (CA-4) and cytosolic (CA-2) isoforms of

Figure 38-8 (Figure Not Available) Major mechanism of kidney proximal tubule HCO_3^- reabsorption. See text for details. *(From Boron et al [42])*

carbonic anhydrase. HCO_3^- absorption in the proximal tubule, although large in volume, does not create new HCO_3^- to replace that consumed in neutralizing H^+, and its function is not greatly altered by changes in acid-base balance. A "vacuolar" H^+-AT-Pase located on the urine luminal surface actively secretes H^+ into the urine and accounts for 30 to 40 percent of proximal tubule H^+ secretion. [43]

The distal tubule and collecting duct, in contrast to the proximal tubule, actively synthesize HCO_3^- in addition to secreting H^+. CO_2 produced from substrate oxidation rapidly yields H^+ and HCO_3^-, facilitated by CA. The "vacuolar" H^+-ATPase also secretes H^+ into the urine in the distal tubule (Fig. 38-9A) (Figure Not Available) . [43] Simultaneously, HCO_3^- is exported to plasma by a Cl^-/HCO_3^- exchanger, which takes up plasma Cl^-. In addition, H^+ is actively secreted into urine in exchange for K^+ uptake, against steep [H^+] and [K^+] gradients, by a "colonic" H^+,K^+-ATPase (cHKA). [44] Distal tubule and collecting duct cHKA responds to acid-base disturbances within hours, increasing H^+ secretion in exchange for cellular K^+ uptake in response to a systemic H^+ challenge. [45]

NH_4^+ secretion is the most important mechanism for direct H^+ elimination from the body. (Fig. 38-9B) (Figure Not Available) . [46] [47] The source of the NH_4^+ is glutamine synthesized by the liver and other tissues. Renal glutamine metabolism forms NH_4^+ in the net reaction: glutamine $3CO_2 + 2NH_4^+ + 2HCO_3^-$. Ammonium (pK 9.0) equilibrates as:

Because of the high pK, 99.7 percent of intracellular NH_4^+ is ionized NH_4^+ at a renal pH_i of 7.23. Proximal tubule NH_4^+ is excreted into urine by the NHE-3 exchanger, with NH_4^+ substituting for H^+, as Na^+ moves into the cell. NH_4^+ is subsequently reabsorbed into the interstitial fluid

Figure 38-9 (Figure Not Available) Important mechanisms for kidney distal tubule H^+ secretion. (A) Direct H^+ secretion by H^+-ATPase, which has two types. (B) The role of renal glutamine in H^+ elimination as NH_4^+. See text for details. *(From Halperin and Goldstein [142])*

at the loop of Henle, then resecreted into urine by collecting duct cells. Mechanisms of urinary NH_4^+ elimination in the collecting duct are poorly understood, although an exchange of interstitial NH_4^+ for intracellular K^+ is involved. [48] Imported NH_4^+ then passively moves into the acidic urinary lumen. The role of Na^+/K^+-ATPase in renal NH_4^+ transport is uncertain. NH_3 also diffuses into the urine space, where it is trapped as NH_4^+ because of the lower urinary pH.

HPO_4^{2-} (pK 6.8) excretion in the urine is another mechanism for H^+ elimination. H^+ is trapped in the urine as the acid $H_2PO_4^-$, the major component of the so-called urinary *titratable acid.* Failure of glomerular HPO_4^{2-} filtration and its consequent paucity in urine with accumulation in plasma contribute to the acidosis of renal failure. HPO_4^{2-} excretion is controlled, in part, by the prevailing plasma acid-base status; that is, tubular HPO_4^{2-} reabsorption is increased in the setting of increased plasma or pH_i and decreased by low pH. [49] Renal H^+ secretion and HCO_3^- reabsorption or synthesis are important in long-term acid-base regulation, as evidenced in chronic renal failure.

Renal mechanisms are less important in acute acid-base disturbances because they are either completely insensitive to acute disturbances (i.e., they do not alter), or they respond slowly over a period of several hours to days. Renal

function, unlike pulmonary function controlling Pa CO_2 or the various buffering mechanisms, cannot quickly moderate acid-base derangements that may develop in the operating room.

HEPATIC HCO_3^- "PRODUCTION" AND CONSUMPTION

The liver has a central role in substrate metabolism that may influence acid-base balance. First, the liver is the principal organ that clears lactic acid produced by different tissues of the body. [50] Each mole of lactic acid is accompanied by a mole of H^+ . Lactic acid taken up can be metabolized by two pathways; either oxidation to CO_2 , or gluconeogenesis to form glucose and glycogen (Fig. 38-10) . Regardless of the pathway, lactate disposal is accompanied by a stoichiometric 1:1 consumption of H^+ . Removal of free H^+ during lactate metabolism in effect increases the available HCO_3^- pool by diminishing its consumption. Normally, each pathway accounts for ~50 percent of lactate uptake. During a lactic acid challenge, however, most lactate follows the oxidative pathway, and glucose production remains unchanged. [51] [52] Decreased ECF pH stimulates hepatic lactate uptake unless the liver itself is ischemic or hypoxic.

Countering H^+ consumption during lactate metabolism is HCO_3^- consumption during synthesis of urea from protein and amino acid catabolism. Urea synthesis, which occurs only in the liver, can be written empirically as

where each mole of urea synthesis consumes two moles of HCO_3^- . Urea produced by the liver is excreted in the urine. A normal daily excretion of 30 g urea in the urine translates

Figure 38-10 Schematic representation of hepatic lactate metabolism. Normally 50 percent of lactate uptake traverses the pathway to oxidation via the TCA cycle, and the remaining lactate is converted to glucose by gluconeogenesis. During a lactate challenge, the TCA cycle oxidative pathway is preferentially employed. PDH, pyruvate dehydrogenase, the rate-limiting enzyme for pyruvate and lactate oxidation; DCA, dichloroacetate. See text for details.

to the equivalent of 1,000 mmol of HCO_3^- . [53] In perfused liver, an *in vitro* H^+ challenge markedly decreases urea synthesis and hepatic HCO_3^- consumption. [54]

Hepatic nitrogen disposal also involves synthesis of glutamine from glutamate and NH_4^+ liberated from other amino acid catabolism. Hepatic glutamine synthesis, in contrast to urea synthesis, does not affect HCO_3^- consumption. It does, however, provide glutamine for renal NH_4^+ excretion. Haussinger proposed a model whereby the liver controls acid-base balance by altering the balance of urea or glutamine synthesis rates to dispose of nitrogen at a constant rate (Fig. 38-11) (Figure Not Available) . [55] Accordingly, an H^+ surfeit inhibits urea synthesis and stimulates hepatic glutamine synthesis, whereas the balance is reversed during plasma HCO_3^- excess. [55] However, the extent to which liver function regulates acid-base balance in humans remains to be tested.

HOMEOSTASIS

All the individual components presented separately in the previous discussion coordinate to maintain H^+ homeostasis. A primary disturbance of acid-base balance prompts a response among one or more of the other factors, to minimize the change in pH. These responses are collectively called *compensation.* Acid-base compensation, however vital for life, complicates assessment of acid-base status. Nevertheless, compensation is never complete with a continued primary disturbance. A deviation in arterial pH from 7.4 persists in the direction of the precipitating event. This permits diagnosis of the primary problem, enabling one to distinguish between primary and compensatory mechanisms.

In Vivo Compensation for Ventilatory Derangements

Primary ventilatory disturbances, which either increase or decrease Pa CO_2, prompt certain responses that return pH back toward 7.4. Increased Pa CO_2, along with the consequent decrease in pH, stimulates ventilatory drive in the spontaneously breathing patient. Augmented ventilatory drive occurs via feedback to the brain and the medullary respiratory control center, mediated by central and carotid body chemoreceptors (Ch. 15). The ultimate result is increased V_A, returning Pa CO_2 back toward 40 mm Hg.

Increased Pa CO_2 does not directly alter plasma [HCO_3^-], as demonstrated by the Henderson-Hasselbalch equation. However, decreased plasma pH decreases hepatic HCO_3^- uptake and stimulates HCO_3^- transfer into plasma from erythrocytes. Carbonate (CO_3^{-2}) is mobilized from bone to form free $HCO_3^- \cdot (CO_3^{-2} + H^+ \; HCO_3^-)$. Together, these increase plasma [HCO_3^-]. Further, decreased pH inhibits phosphofructokinase (PFK), an enzyme that controls glycolysis in liver, erythrocytes, and other tissues. PFK inhibition, in turn, decreases tissue lactic acid production with a consequent decrease in plasma HCO_3^- consumption. Urea production, which consumes plasma HCO_3^-, may also be inhibited by the decreased pH. Respiratory acidosis acutely increases arterial [HCO_3^-] by 0.8 mmol/L for each 10 mm

Figure 38-11 (Figure Not Available) Putative role for hepatic urea and glutamine synthesis in whole body acid-base regulation. *(Modified from Haussinger, [55] with permission from Elsevier Science.)*

Hg of CO_2 greater than 40. [10] During respiratory alkalosis, the acute decrease in [HCO_3^-] is 2.5 mmol/L for each 10 mm Hg of CO_2 less than 40. [56] About 50 percent of an acute CO_2 challenge is buffered by intracellular mechanisms, and another 30 percent by the erythrocyte-mediated Cl^- shift. [7] [40] Acute compensatory responses occur within minutes and persist for hours. In general, however, ventilatory derangements prompt a weak acute compensation.

A long-term increase in Pa CO_2 will, over a period of days to weeks, prompt renal compensation in the form of decreased Cl^- and HPO_4^{2-} reabsorption, increased HCO_3^- reabsorption, and increased active H^+ secretion. Chronic adaptation by the kidney can effectively return arterial pH close to normal, by increasing arterial [HCO_3^-] to reestablish a normal plasma Pa CO_2 /HCO_3^- ratio. In chronic respiratory acidosis, arterial [HCO_3^-] increases by 5 mmol/L for each 10 mm Hg of Pa CO_2 greater than 40. [57] [58] Wellcompensated respiratory acidosis is often observed in the patient with significant chronic obstructive lung disease (COPD), in whom a [HCO_3^-] of greater than 30 mmol/L may accompany an arterial pH only slightly less than 7.40. Opposite effects occur in the setting of chronic hypocapnia. Chronic respiratory alkalosis decreases arterial [HCO_3^-] by 5 mmol/L for each 10-mm Hg decrease in Pa CO_2 less than 40. [59]

In Vivo Compensation for Metabolic Derangements

A nonvolatile acid H^+ challenge is first buffered to minimize free H^+ accumulation. Free H^+ is neutralized by reacting with body HCO_3^- to form CO_2, which is removed from the body by alveolar ventilation (V_A). V_A is stimulated by increased Pa CO_2 and also directly by plasma H^+ (Ch. 15). The ventilatory response decreases Pa CO_2 by 1.1 mm Hg less than 40 for each mmol/L HCO_3^- less than 24. [60] Increased ventilation is the most important compensation to a nonvolatile H^+ load, and it occurs over a period of minutes. However, there are also "metabolic" responses that attenuate H^+ accumulation. The actual nature of the metabolic response depends on the underlying cause of the H^+ challenge.

Decreased pH secondary to a nonvolatile H^+ challenge inhibits PFK, decreasing endogenous lactic acid production. Together with stimulated lactic acid uptake by the liver, the result is decrease plasma lactic acid concentration. Urea synthesis is also inhibited, which decreases physiologic HCO_3^- utilization. In addition, CO_3^{-2} is mobilized from bone to form plasma HCO_3^-, according to the reaction: $CO_3^{-2} + H^+ \; HCO_3^-$. [61] These responses increase HCO_3^- availability in the ECF. In addition, cellular H^+ uptake and intracellular buffering account for ~50 percent of an exogenous H^+ challenge. [41] Renal responses to a nonvolatile H^+ challenge require hours to days for full expression, but ultimately they include decreased Cl^- and HPO_4^{2-} reabsorption, increased H^+ and NH_4^+ secretion, and increased HCO_3^- reabsorption.

Opposite compensatory mechanisms, in general, occur in response to decreased ECF [H^+], including deposition of HCO_3^- into bone as Na_2CO_3. [61] HCO_3^- accumulation, by decreasing [H^+], inhibits respiratory drive such that Pa CO_2 increases above 40 mm Hg by 0.4 to 1.2 mm Hg for each mmol/L HCO_3^- greater than 24. [60] [62] [63] However, ECF volume depletion with or without hypochloremia hampers renal compensation for decreased ECF [H^+]. This is partly because hypovolemia increases aldosterone-mediated Na^+ reabsorption. Na^+ must be accompanied by Cl^- or HCO_3^- reabsorption for electroneutrality, and Na^+ uptake outstrips Cl^- supply. In addition, decreased glomerular filtration leads to increased efficiency of proximal tubule HCO_3^- reabsorption. [64] Thus, despite negligible urinary Cl^- excretion, HCO_3^- reabsorption is inappropriately increased, perpetuating the ECF [H^+] depletion. Only Cl^- replacement reverses H^+ deficiency coupled with hypo-volemia.

/das/book/view/29494766/875/442.html

TERMINOLOGY OF ACID-BASE DISTURBANCES

Clinical acid-base disturbances are usually defined on the basis of changes in arterial blood. Arterial blood pH is normally regulated such that the pH is between 7.35 and 7.45, corresponding to a [H^+] of 45 to 36 nmol/L, respectively (see Fig. 38-1) (Figure Not Available) . *Acidemia* is clinically defined as blood pH less than 7.35, and *alkalemia* is defined as blood pH greater than 7.45, although less marked deviations from 7.40 could technically be included. *Acidosis* is a process leading toward acidemia, whereas *alkalosis* is a process leading toward alkalemia.

When arterial pH falls below 7.35, or exceeds 7.45, as a result of an overwhelming primary event or impaired compensation, physiologic tissue consequences begin to appear. There are four fundamental acid-base disturbances: respiratory acidosis, respiratory alkalosis, metabolic alkalosis, and metabolic acidosis. The defining variables (pH, P_{CO_2}, [HCO_3^-], and BE) are all available on, or calculated from, a commercially available blood gas analysis. Alternatively, [HCO_3^-] and BE can also be determined from pH and P_{CO_2} using a Siggaard-Andersen alignment nomogram (see Fig. 38-2) (Figure Not Available) . It is nevertheless important to understand the limitations of these calculations, as outlined earlier.

A single acid-base disturbance can be present, or more than one disturbance may be superimposed. Compensation is a second disturbance that physiologically attenuates the effect of the primary disturbance. Alternatively, a more complex picture occurs when two acid-base disturbances alter the pH in the same direction (mixed disturbance). This chapter limits the presentation to uncomplicated disturbances, listing the definition, pathophysiology, consequences, and fundamental treatment of each.

Respiratory Acidosis

Definition

Respiratory acidosis is concomitant arterial pH less than 7.35 and Pa_{CO_2} greater than 45 mm Hg (see Fig. 38-4; (Figure Not Available) . Ch. 72)

Mechanism and Compensation

Respiratory acidosis results when CO_2 production exceeds V_A (hypoventilation). This is most commonly the result of decreased V_E. Most anesthetic drugs decrease V_E in the spontaneously breathing patient by impairing ventilatory drive (Ch. 12) . Other causes for decreased V_E include airway obstruction, obstructive or restrictive lung disease, obesity, marked ascites, or neuromuscular disease. Pulmonary edema can lead to CO_2 retention by increasing pulmonary dead space, thus compromising V_A even with a well-maintained V_E. Alternatively, tissue and mixed venous (but not arterial) P_{CO_2} is retained during low cardiac output states with normal respiratory function because blood CO_2 transport to the alveoli is impaired. In the paralyzed, mechanically ventilated patient, increased Pa_{CO_2} can result from inappropriately low ventilator settings or interrupted communication between alveoli and fresh gas inflow (e.g., extubation, endotrachial tube obstruction, circuit disconnection, or ventilator failure).

Less frequently, respiratory acidosis can be caused by increased V_{CO_2} . Mechanisms of increased V_{CO_2} include marked fever, extensive burn injury (which increases V_{CO_2} by as much as 80-100%), and malignant hyperthermia. It is noteworthy that malignant hyperthermia is often heralded not by temperature change, but by a failure to contain the end-tidal CO_2 concentration despite a high V_E.

Acute metabolic compensation to respiratory acidosis has very limited effectiveness. Renally mediated metabolic compensation can return arterial pH close to normal, but it requires days to months for a full effect.

Consequences

Acute respiratory acidosis is associated with dysfunction of the central nervous system (CNS) and cardiovascular system. In the patient breathing room air, hypercapnia is commonly accompanied by hypoxemia, sometimes making it difficult to differentiate between the two causes. However, *CNS effects* of acute hypercapnia are anxiety, disorientation, incoherence, confusion, and dyspnea. Very high Pa_{CO_2} (>70 mm Hg) can produce a *CO_2 narcosis* syndrome of drowsiness progressing to stupor or coma. CO_2 -induced cerebrovascular dilation presents a clinical picture consistent with intracranial hypertension (pseudotumor cerebri), with headache and diminished mental status accompanied by papilledema.

Cardiovascular effects of acute hypercarbia are hypertension, tachycardia, and increased cardiac output mediated by increased sympathoadrenal tone. This hyperdynamic cardiovascular response occurs despite a direct negative inotropic effect of increased P_{CO_2} . [65] Increased catecholamine concentration with high Pa_{CO_2} may mediate supraventricular or ventricular dysrhythmias other than tachycardia. Cardiovascular effects may be altered in the presence of hypoxia, drugs, or preexisting cardiac disease, such that hypotension supplants hypertension. Increased P_{CO_2} increases pulmonary vascular tone in patients with preexisting pulmonary hypertension, to induce or exacerbate extrapulmonary shunting of blood flow. Acute cor pulmonale may result. Respiratory acidemia causes hyperkalemia as intracellular K^+ is released in exchange for cellular uptake of H^+ by liver and skeletal muscle. [66] Hyperkalemia can contribute to dysrhythmias, including cardiac arrest. In the patient receiving beta-adrenergic blockade, diaphoresis and peripheral vasodilation with warm, flushed skin may be evident. Respiratory acidosis potentiates the neuromuscular blockade produced by several nondepolarizing muscle relaxants, including pancuronium, vecuronium, pipecuronium, and atracurium. [67] Chronic hypercapnia differs from acute hypercapnia because, given adequate time for renal compensation, it is well tolerated. However, pulmonary hypertension is likely to persist in the patient with COPD and chronic respiratory acidosis.

Treatment

The goal of treatment is to remove the underlying cause and return the Pa_{CO_2} to baseline, usually 40 mm Hg. Decreasing Pa_{CO_2} is accomplished by increasing V_A. Even if increased Pa_{CO_2} is due to increased V_{CO_2} , such as in malig-nant hyperthermia, it is still appropriate to temporize by increasing V_E to return the Pa_{CO_2} to baseline. In the spontaneously breathing patient with respiratory insufficiency, assisted mask ventilation or controlled mechanical ventilation may be required. Residual neuromuscular blockade, or inappropriately high plasma levels of opioids or benzodiazepines, should be reversed. Supplemental O_2 , in addition to ventilatory support, is appropriate therapy for accompanying hypoxemia. Alternatively, cardiac output should be optimized if low cardiac output underlies respiratory acidosis.

Coexisting metabolic acidosis, such as lactic acidosis secondary to hypoxemia, should be treated according to the section on metabolic acidosis. Metabolic alkalosis leading to hypoventilation should be rectified according to the section on metabolic alkalosis.

In the patient with well-compensated CO_2 retention, the goal of therapy is to return Pa $_{CO_2}$ to the patient's baseline, which may exceed 40 mm Hg. Caution should be used in O_2 therapy for patients with well-compensated respiratory acidosis because of their dependence on hypoxic O $_2$ drive for ventilation.

Respiratory Alkalosis

Definition

Respiratory alkalosis is concomitant arterial pH greater than 7.45 and Pa $_{CO_2}$ less than 35 mm Hg.

Mechanism and Compensation

Respiratory alkalosis occurs when alveolar ventilation outstrips V $\cdot$ $_{CO_2}$. The most common cause is frank hyperventilation (increased V $_E$), resulting either from the patient's action or from that of the anesthesiologist. Common patient-related causes are fear, anxiety, and pain, all of which can occur in the perioperative setting. Hypoxemia from a variety of causes (e.g., pulmonary embolism), brain injury, and chronic cirrhosis, also lead to respiratory alkalosis. In the mechanically ventilated patient, inappropriately high ventilator settings may underlie respiratory alkalosis. Hyperventilation may be intentional during craniotomy or in the patient with intracranial hypertension, in an effort to decrease intracranial volume. However, the decrease in cerebral blood flow in response to hyperventilation is transient, lasting less than 24 hours.

Alkalosis can also result from decreased V $_{CO_2}$ if V $_E$ is not decreased to match. Decreased V $_{CO_2}$ during surgery results from an anesthetic drug-induced decrease in metabolic rate, especially in the CNS and skeletal muscle. Second, hypothermia reduces metabolic rate by 9 percent/°C decrease in anesthetized humans. [68] In the patient undergoing general anesthesia, the net result is decreased whole-body V $_{CO_2}$, with relative preservation of splanchnic V $_{CO_2}$. [69] As with respiratory acidosis, there is no clinically significant compen- sation for acute respiratory alkalosis. Effective renal com-pensation for chronic respiratory alkalosis, as HCO_3^- reabsorption decreases to match the decreased Pa $_{CO_2}$, requires days to occur.

Consequences

Respiratory alkalosis produces CNS and cardiovascular dysfunction. Acute hypocapnia causes lightheadedness, impaired judgment, confusion, or coma. Neuromuscular irritability may be due to decreased free Ca^{2+} availability resulting from increased albumin binding. The condition is hallmarked by parasthesias, tetany, or seizures. Although hypocapnia-induced cerebral vasoconstriction is useful to decrease intracranial volume during craniotomy or with intracranial hypertension, it can cause regional cerebral ischemia in patients with a preexisting limitation of cerebral blood flow. Increased brain lactate production during respiratory alkalosis has been interpreted as a sign of cerebral ischemia. However, increased lactic acid production is a widespread physiologic response to alkalemia, which also occurs in well-perfused tissues. [70]

Respiratory alkalosis is associated with a propensity to ventricular dysrhythmias. During anesthesia with positive-pressure ventilation, decreased cardiac output and hypotension can occur. However, it is difficult to determine whether these hemodynamic effects are caused by alkalosis per se or whether they are the mechanical effect of decreased venous return secondary to increased intrathoracic pressure. No hemodynamic effects of respiratory alkalosis have been reported in spontaneously breathing patients.

Hypokalemia is a frequent consequence, especially when mannitol or furosemide is concomitantly administered during neurosurgery. Hypokalemia results from the confluence of increased K^+ uptake by liver and skeletal muscle, and diuretic-induced kaliuresis. [66] Hypokalemia can cause ventricular dysrhythmias, including increased sensitivity to those mediated by digitalis. Finally, alkalemia shifts the hemoglobin O $_2$ dissociation curve to the left, impairing O_2 delivery by compromising off-loading to the tissues.

Treatment

The only effective therapy in the spontaneously breathing patient is to remove the underlying cause, such as O $_2$ therapy for hypoxemia or analgesia for pain. In the mechanically ventilated patient, V $_E$ can be decreased to allow return of Pa $_{CO_2}$ to baseline, usually 40 mm Hg.

Metabolic Alkalosis

Definition

Metabolic alkalosis is arterial pH greater than 7.45, concomitant with [HCO_3^-] greater than 30 mmol/L, or BE greater than 2 mEq/L.

Mechanism and Compensation

Potential mechanisms underlying an increased [HCO_3^-] are, at the most basic level, due to increased H^+ losses, decreased H^+ production, increased HCO_3^- production, or decreased HCO_3^- elimination. In most circumstances, metabolic alkalosis is an iatrogenic disease.

Increased H^+ loss can result from metabolism of an excessive intake of lactate, citrate, or acetate. Lactate administration, such as with lactated Ringer's solution, has been shown to increase arterial pH in volunteers. [71] [72] Packed erythrocytes contain a high lactic acid content that is directly proportional to the age of the blood unit. Alkalemia occurs because H^+ is consumed as the lactate is metabolized (see the discussion of hepatic HCO_3^- "production" and consumption). Citrate is contained in banked blood products, particularly plasma. Massive transfusion, for example during liver transplantation, can increase plasma citrate concentration 10-fold. This citrate challenge is ultimately cleared and metabolized. Three moles of H^+ is consumed with each mole of citrate metabolized. Patients receiving a large intraoperative transfusion generally clear the accumulated lactate and citrate within the first 2 postoperative days. During this time, a characteristic metabolic alkalosis develops. [73] Acetate metabolism results in net consumption of one H^+ for each acetate. Acetate infusion during hemodialysis or hyperalimentation has been reported to produce acetate intoxication and consequent metabolic alkalosis. [74] [75]

Other causes of excessive H^+ loss are nasogastric tube suctioning and diuretic therapy. Nasogastric suctioning depletes H^+ and Cl^- directly. Thiazide and loop diuretics increase urinary H^+ loss because they augment Cl^- excretion more than Na^+ loss and induce hypovolemia. Cl^- loss is an important factor initiating metabolic alkalosis. [76] Hypo-volemia stimulates mineralocorticoid secretion, retaining plasma Na^+ at the expense of plasma K^+ and, as hypokalemia ensues, plasma H^+ . Rarely, excessive H^+ loss is caused by a primary mineralocorticoid excess (primary hyperaldosteronism or Cushing disease).

Metabolic alkalosis is maintained, regardless of the initiating cause, by a hypovolemia-induced decrease in glomerular filtration, with or without hypochloremia, because renal HCO_3^- reabsorption is inappropriately increased. [64] Increased HCO_3^- retention occurs regardless of the precipitating cause of the alkalosis. The major difference between alkalosis resulting from diuretics and that of other metabolic causes is that urinary [Cl^-] is increased by diuretic therapy, but it is markedly decreased in other settings. Decreased hepatic HCO_3^- elimination as a mechanism underlying metabolic alkalosis has been reported in patients with urea synthesis impaired by cirrhosis, but this is very unusual. [77] Excessive $NaHCO_3$ intake in antacid therapy has been reported to cause metabolic alkalosis, with a [HCO_3^-] of 64

mmol/L. [63]

Major compensation for metabolic alkalosis is decreased ventilation leading to increased Pa $_{CO_2}$. Hypoventilation is often the initial sign of underlying metabolic alkalosis. It can cause hypoxemia in the patient with marginal pulmonary function who is breathing room air. Chronic metabolic alkalosis decreases renal NH_4^+ elimination by inhibiting proximal tubule NH_4^+ secretion. [78] Alkalemia stimulates PFK, increasing lactic acid release, with the concomitant H^+ reacting with HCO_3^- to decrease plasma [HCO_3^-]. [70] [79] Metabolic alkalosis may also increase urea synthesis and hepatic HCO_3^- consumption. [54]

Consequences

The most serious consequence of metabolic alkalosis is decreased ventilatory drive, resulting in hypoventilation. In the postoperative patient receiving opioid analgesia, decreased CO_2 ventilatory drive coupled with a pharmacologically ablated O_2 drive can cause frank apnea. Alkalemiamediated hypoventilation complicates weaning of some patients from mechanical ventilation. Compensatory hypercapnia causes confusion, lethargy, and stupor, even with increased arterial pH because CO_2 , unlike HCO_3^- , readily penetrates the blood-brain barrier. [38] [39]

Neuromuscular irritability, marked by agitation, twitching, or seizure activity occurs uncommonly. It is thought to be caused by increased binding of Ca^{2+} by albumin, causing a functional free hypocalcemia. The relationship between metabolic alkalosis and plasma [K^+] is not straightforward. [66] Early studies with a small number of patients indicated that metabolic alkalosis produced by $NaHCO_3$ infusion causes hypokalemia. [66] However, $NaHCO_3$ -induced metabolic alkalosis does not alter plasma [K^+] in patients with renal failure and normal baseline plasma [K^+]. [80] [81] In the unusual case in which metabolic alkalosis occurs without hypo-volemia or Cl^- depletion (for example, with excessive HCO_3^- intake) there is increased urinary HCO_3^- loss. This can lead, eventually, to hypokalemia as the distal tubule secretes K^+ to accompany the urinary HCO_3^- . On the other hand, thiazide diuretic therapy causes both hypokalemia and metabolic alkalosis, with hypokalemia exacerbating metabolic alkalosis. Hypokalemia causes cardiac dysrhythmias, notably those associated with digitalis therapy, and muscle weakness. Hyperlactatemia may be misinterpreted as an indication of tissue disease or hypoperfusion, but it is usually a benign response that disappears with correction of the alkalemia. [70] [82]

Treatment

Two treatment modalities may be appropriate as the underlying cause is identified. The first is to reverse the Cl^- deficit resulting from nasogastric suction or diuretic therapy. The easiest method of Cl^- replacement is intravenous 0.9 percent NaCl infusion, although KCl or $CaCl_2$ can be substituted in the patient in whom aggressive volume replacement is contraindicated. KCl administration also corrects coincident hypokalemia. A more aggressive replacement therapy is HCl infusion, which in addition to Cl^- provided H^+ directly to react with HCO_3^- , forming CO_2 and H_2O. HCl therapy is usually reserved for severe metabolic alkalosis, with [HCO_3^-] greater than 50 mmol/L.

The second approach is to decrease renal proximal tubule HCO_3^- reabsorption by inhibiting CA with acetazolamide. Acetazolamide effectiveness may be limited, however, in part because it also inhibits the hepatic CA that facilitates hepatic HCO_3^- uptake for urea synthesis. [9] Moreover, by increasing proximal tubule HCO_3^- loss, acetazolamide may

exacerbate hypokalemia. Rarely, for example in primary hyperaldosteronism or Cushing disease, metabolic alkalosis is refractory to Cl^- replacement and acetazolamide therapy. In these cases, removing the steroid-secreting neoplasm is the only effective treatment.

Metabolic Acidosis

Definition

Metabolic acidosis is arterial pH less than 7.35, concomitant with [HCO_3^-] less than 20 mmol/L, or BE less than -2 mEq/L.

Mechanism and Compensation

Metabolic acidosis is the most complex and potentially most ominous acid-base disturbance encountered. There are multiple possible causes, unlike respiratory acidosis, which is a pure CO_2 phenomenon. At the simplest level, the initiating event increases [H^+], decreases [HCO_3^-], or both. A host of different diseases could be responsible for metabolic acidosis, each one stimulating a slightly different compensatory response.

Ventilatory compensation is reasonably consistent, because H^+ stimulates carotid body chemoreceptors, a process that, in turn, leads to increased V_E and decreased Pa $_{CO_2}$ (Ch. 10) . Many patients with metabolic acidosis are debilitated by their underlying disease, and the compensatory Pa $_{CO_2}$ decrease could falter as the patient fatigues. The acute "metabolic" response to metabolic acidosis involves tissues not affected by the primary event. For example, lactic acidosis of acute liver failure is not compensated by increased lactic acid uptake by the liver, and acute renal failure is not ameliorated by renal compensation. A renal response to lactic acidosis of acute liver failure occurs, but it has a latency of hours to days. Therefore, the most common causes of metabolic acidosis are presented separately.

Differential Diagnosis

The magnitude of acidosis is first quantitated by the base deficit. To determine the cause, the next step is to calculate the AG (Table 38-3) . An increased AG reflects increased presence of one or more unmeasured anions and is referred to as *increased AG acidosis.* In contrast, acidosis without an increased AG *(non- AG acidosis)* reflects a pathologic failure of Cl^-/HCO_3^- exchange leading to hyperchloremia. Non-AG acidosis is usually due to gastrointestinal or renal tubular dysfunction, although there are other causes (see Table 38-3). In addition, plasma albumin and HPO_4^{2-} concentrations should be evaluated. Hypoalbuminemia masks the severity and alters the AG of metabolic acidosis: A decrease in plasma [albumin] of 1 g/dL increases apparent BE by 3.7 mEq/L and decreases the AG by 2.4 to 3 mEq/L. [18] Rarely, a very elevated HPO_4^{2-} alone can be responsible for an increased AG, but more often it is part of the acidosis of renal failure. A potentially more discriminating index is the UA^- , using the SID (see the earlier discussion of quantitation

TABLE 38-3 -- Anion Gap in Assessment of Metabolic Acidosis

INCREASED ANION GAP (> 16 mEq/L)	
DISEASE	***ANION RESPONSIBLE***
Lactic acidosis (e.g., shock, ischemia)	Lactate
Diabetic ketoacidosis	Acetoacetate, beta-hydroxybutyrate
Starvation	Acetoacetate, beta-hydroxybutyrate
Alcohol intoxication	beta-Hydroxybutyrate, acetoacetate, lactate
Salicylate intoxication	Salicylate
Methanol intoxication	Formate
Rhabdomyolysis	Phosphate, others (?)
Acute renal failure	Sulfate, phosphate, others (?)
Chronic renal failure	Unknown

NORMAL ANION GAP (16 mEq/L)
DISEASE
Protracted diarrhea
Potassium-sparing diuretics
Carbonic anhydrase inhibition
Renal tubular acidosis
Copious sodium chloride fluid administration
Pancreatic fistula
Biliary drainage
Ammonium chloride administration
Hypoaldosteronism

of buffers). UA^- has only recently been introduced into clinical practice, but it may be less prone to the criticism of insensitivity to lactic acidosis that has been directed toward the AG because it corrects for hypoalbuminemia, a common occurrence in the critically ill patient. [30]

Consequences

Metabolic acidosis induces widespread system dysfunction. *CNS effects* are fatigue, somnolence, confusion, and possibly coma. The initial respiratory response is increased ventilation. However, decreased systemic pH impairs muscle strength and endurance. As a result, respiratory function may be compromised, especially in the debilitated patient, and complicating *respiratory failure* can ensue. The *cardiovascular system* is affected at many points. First, H^+ progressively impairs cardiac contractility with decreasing pH below 7.2. [83] H^+ dilates both capacitance and resistance vasculature, decreasing both preload (functional hypovolemia) and afterload. Hypotension commonly occurs. If tissue O_2 delivery is compromised by hypotension, tissues commence anaerobic production of lactic acid, exacerbating the acidemia. To some extent, the negative direct hemodynamic effects are moderated by increased sympathoadrenal activity, which maintains cardiac output and blood pressure. However, concomitantly increased [catecholamines] and $[H^+]$ irritate the myocardium and conduction system, sensitizing them to ventricular fibrillation and other dysrhythmias. [84] Although patients receiving beta-adrenergic blockers are theoretically less susceptible to epinephrine-induced cardiac dysrhythmias, they are at increased risk for hypotension.

Acute hyperkalemia secondary to metabolic acidemia per se is unusual, possibly because organic anions (lactate, acetoacetate,

beta-hydroxybutyrate) may accompany H^+ into cells and may minimize the electrochemical charge effect of the H^+, and the modest K^+ efflux can be offset by increased urinary K^+ excretion. [66] However, massive blood transfusion presents a concomitant lactic acid and K^+ challenge. Under this circumstance, K^+ is poorly tolerated because it does not redistribute normally into acidotic cells, and urinary K^+ excretion alone cannot match its rate of appearance in the plasma. Hyperkalemia is potentially life-threatening because of its arrhythmogenicity, including cardiac arrest. Protracted metabolic acidosis depletes total body K^+ stores, despite normal or slightly increased plasma $[K^+]$. Body K^+ depletion eventually manifests as hypokalemia once the acidemia is corrected and K^+ redistributes into its normal compartments.

Acute acidosis impairs O_2 uptake by Hb, compromising O_2 carrying capacity and delivery. Decreased protein binding of anesthetic drugs, such as thiopental, increases their bioavailability in the acidemic patient. This causes an otherwise appropriate thiopental dose, for example, to become an overdose in the acidemic patient. A direct action of acidemia on local anesthetics, which are weak bases, is to increase their ionization, which decreases their effectiveness. On the other hand, acute acidemia potentiates the action of several nondepolarizing neuromuscular blockers, pancuronium, vecuronium, pipecuronium, and atracurium. [67] Finally, protracted metabolic acidosis eventually depletes bone structural calcium carbonate as CO_3^{-2} is mobilized to replenish free plasma HCO_3^-. [61] Demineralized bone can develop pathologic fractures.

Treatment

The underlying cause should be corrected. General temporizing measures include mechanical ventilation to facilitate respiratory compensation. Additional supportive care measures are O_2 therapy for hypoxemia and pharmacologic reversal of low cardiac output or inappropriate systemic vasodilation. HCO_3^- replacement therapy may be indicated, depending on the severity and nature of the disturbance. [85] [86] Specific therapy depends upon the etiology of the acidosis. [1] [13] [87]

Lactic Acidosis

Lactic acid flux is rapid in healthy persons, on the order of 55 to 66 mmol/h. [50] Tissues (muscle, brain, skin, erythrocytes) produce and release lactic acid into the blood. Erythrocytes lack mitochondria, rendering them completely dependent on glycolysis, which yields lactic acid for energy production. Lactic acid is taken up by the liver (and kidney), where it is converted to glucose to complete the Cori cycle (see Fig. 38-10 mmol/L.). These processes yield a normal arterial [lactate] of ~1

Plasma lactic acid accumulates when production outstrips clearance, and the change occurs quickly because of the rapid turnover. *Lactic acidosis* is concomitantly increased [lactate] and decreased pH. It is generally associated with high mortality. Lactic acidosis is perhaps the most common, and worrisome, cause of metabolic acidosis encountered by the anesthesiologist. It is divided clinically into *type A,* associated with tissue hypoxia, and *type B,* resulting from other causes. [50]

Increased lactic acid production occurs during hypoxia, tissue ischemia, exercise, seizures, sepsis, burn injury, biguanide intoxication, and liver disease. Hypoxia, ischemia, and nitroprusside intoxication inhibit oxidative metabolism, causing tissues to rely on anaerobic glycolysis for ATP production. [88] O_2 metabolism is normal in sepsis, burn injury, or biguanide (metformin) intoxication. However, excessive pyruvate production from stimulated glycolysis overwhelms its oxidative capacity. Pyruvate then "spills over" to produce lactic acid. Patients with liver disease exhibit normal peripheral lactate production, but they have an exaggerated lactate output in response to a glucose challenge. [89] An exogenous source of lactic acid is packed erythrocytes, which have a high lactic acid content directly proportional to the age of banked blood. Plasma lactate clearance is impaired in cirrhosis, even in patients without baseline hyperlactatemia. [90] Hepatic ischemia alters the role of the liver in lactate metabolism such that it will produce, rather than clear, plasma lactic acid.

Treatment is based on correcting the cause and replenishing HCO_3^- to return the pH toward 7.4. $NaHCO_3$, the mainstay of HCO_3^- replacement therapy, has been criticized on four grounds. First, in a closed system in which circulation or ventilation is compromised, $NaHCO_3$ causes paradoxic intracellular acidosis as the increased CO_2 generated by the CA reaction accumulates and crosses into cells. [91] [92] [93] [94] [95] This is especially true in brain, which most effectively excludes HCO_3^- because of the blood-brain barrier. [39] [93] Second, the high Na^+ load of $NaHCO_3$ therapy (1,000 mmol/L) is associated with rapid-onset hypernatremia and brain injury (central pontine myelinolysis). [96] [97] Third, a Na^+ -induced intravascular volume overload may worsen hemodynamics and may cause pulmonary edema in a patient with congestive heart failure. Fourth, $NaHCO_3$ therapy either does not change or occasionally compromises myocardial performance even in the absence of volume overload. [92] [98] [99] [100] [101] Incidentally, $NaHCO_3$ may further increase plasma [lactate] as the PFK inhibition is reversed by the eventually increased pH_i. [79] [82]

Carbicarb, a mixture of $NaHCO_3$ and sodium carbonate (Na_2CO_3) was recently introduced as an experimental alternative to $NaHCO_3$. [102] Carbicarb administration avoids a marked increase in P_{CO_2} because Na_2CO_3 dissociates to form two Na^+ and CO_3^{2-}. CO_3^{2-} reacts with H^+ as:

In effect, one Na_2CO_3 neutralizes two H^+ because the produced HCO_3^- can then react with H^+ to form CO_2. Consumption of 2 mmol H^+ with Na_2CO_3 results in production of only 1 mmol of CO_2, half of that by $NaHCO_3$. Carbicarb is referred to as a "CO_2-consuming" buffer, which is a misnomer because it still generates CO_2, but less than $NaHCO_3$ of equal effectiveness. Carbicarb increases P_{CO_2} less and decreases intracellular pH less than an equimolar treatment with $NaHCO_3$ alone. [93] [94] [103] This could be valuable in a clinical setting of compromised CO_2 elimination. Despite the theoretic advantage, Carbicarb has not been shown to be superior to $NaHCO_3$ in treatment of lactic acidosis.

THAM (*T*ris *h*ydroxymethyl *a*mino *m*ethane) is a less potent alkalinizing agent than $NaHCO_3$. [104] It does not increase Pa_{CO_2} or $[Na^+]$. However its negative side effects, including local vascular irritation, tissue necrosis, and hyperkalemia, have caused its virtual disappearance from clinical practice. [104] An experimental tris buffer combined with $NaHCO_3$ is being evaluated in preclinical trials. [105]

A different experimental approach is to activate pyruvate dehydrogenase (PDH), rather than to alkalinize plasma directly. PDH is a regulatory enzyme that controls pyruvate entry into the Krebs cycle. PDH activity varies among tissues, being high in cardiac tissue (60-80% active), intermediate in skeletal muscle, and low in liver (10-20% active). Dichloroacetate (DCA) stimulates PDH activity, increasing fractional PDH activity to 100 percent of the total enzyme content. [106] As a result, whole-body lactate production decreases and hepatic lactate clearance is stimulated. [107] DCA decreases circulating [lactate] by 50 percent in healthy volunteers, burned patients, septic patients, and in patients undergoing liver transplantation. [106] [108] It remains to be demonstrated whether DCA can affect outcome of lactic acidosis of a specific etiology, although it does not alter the course of profound hypodynamic sepsis. [109] DCA is a specific therapy for lactic acidosis, because its mechanism directly affects lactate metabolism. With a pK of 3, it is neither a buffer nor an alkalinizing agent.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) occurs in the insulindependent, type 1, diabetic patients (Chs. 25 and 55). It results from plasma accumulation of the ketone bodies, acetoacetate and beta-hydroxybutyrate. Ketone bodies are formed by the liver from lipolysis-generated free fatty acid metabolism. If lipolysis is accelerated, because of a lack of insulin, ketone body accumulation occurs because hepatic synthesis outstrips clearance by, mostly, kidney and brain. Ketone bodies are strong acids like lactate (see Table 38-1). Perioperative DKA occurs because of the combination of preoperative fasting, inappropriate withholding of insulin therapy, and the stress response to infection or surgical trauma. These factors all decrease plasma insulin concentration. The plasma insulin concentration required to suppress lipolysis and ketone body formation is less than one-tenth of that necessary for plasma glucose regulation. Patients with type 2 diabetes, with insulin resistance and a generally increased circulating insulin concentration, are therefore not at risk for DKA.

A detailed treatment protocol for DKA can be found elsewhere. [1] [13] [59] [87] In short, the essential treatment is insulin infusion, to inhibit ketone body production, and intravenous fluid resuscitation. Care must be taken to monitor plasma potassium concentration during insulin therapy, because the insulin promotes intracellular uptake of plasma K^+, particularly by the liver. The term "insulin resistance," which applies to glucose regulation, does not extend its hypokalemic effect. Hypokalemia occurs during insulin therapy for DKA unless a prophylactic KCl infusion is begun with the insulin, even if the initial plasma K^+ concentration is normal or modestly elevated. $NaHCO_3$ therapy may be required for marked acidemia to return the arterial pH toward normal, restoring physiologic stability until the ketone bodies excess is cleared.

Renal Failure

Metabolic acidosis resulting from renal failure can have more than one component (Chs. 53 and 55). Glomerular diseases limit filtration of phosphates and sulfates, which normally serve to trap H^+ in the urine. Proximal tubule injury compromises its HCO_3^- reabsorption. Because the distal tubule cannot handle the added urinary HCO_3^- load, HCO_3^- is excreted. Primary distal tubule disease inhibits active H^+ secretory function as well as *de novo* HCO_3^- synthesis. Renal failure thus results in decreased plasma HCO_3^- and increased plasma H^+ concentrations. AG may or may not be increased, depending on the extent of proximal tubule involvement, because proximal tubule dysfunction retains Cl^- and minimizes the increase in AG associated with HCO_3^- depletion. Less well known is the importance of the kidney in handling a HCO_3^- challenge, making the patient with chronic renal dysfunction more prone to alkalemia from aggressive $NaHCO_3$ intake. [63]

Conservative treatment of acute renal failure includes stimulation of diuresis with furosemide, mannitol, or low-dose dopamine infusion. A more aggressive treatment, also utilized in chronic renal failure, is dialysis or continuous arteriovenous hemofiltration (which usually includes HCO_3^- replacement in the dialysate). The definitive treatment is renal transplantation.

SPECIAL CIRCUMSTANCES IN ACID-BASE MANAGEMENT

Hypothermia and Cardiopulmonary Bypass

Acid-base management during hypothermic cardiac surgery is controversial, with two distinct schools of thought regarding the ideal blood pH at low body temperature, during which CO_2 solubility in blood is increased (Chs. 49 and 50) . [110] The traditional strategy, *pH-stat,* holds that Pa $_{CO_2}$ must be maintained to preserve pH. Under pH-stat management, arterial blood gas analysis measured with electrodes at 37°C is corrected to the patient temperature, and blood Pa $_{CO_2}$ maintained constant by addition of CO_2 to the blood during hypothermic cardiopulmonary bypass (CPB).

The rival management concept, alpha *-stat,* proposes that what must be maintained during hypothermia is not Pa $_{CO_2}$ but the ratio of ionized to un-ionized alpha-imidazole ring on the histidine moiety of proteins, as occurs naturally in poi-kilotherms. [111] Imidazole ionization, unlike Pa $_{CO_2}$, does not change with temperature in the setting of constant total CO_2 content. Under alpha-stat management, no correction is made for patient temperature during interpretation of arterial blood gases determined with electrodes at 37°C. A characteristic "corrected" arterial blood gas during CPB at 28°C with pH-stat management is pH 7.34 to 7.38 and Pa $_{CO_2}$ 40 to 41 mm Hg; corresponding values for alpha-stat management are pH 7.51 to 7.55 and Pa $_{CO_2}$ 25 to 27 mm Hg. [112]

Neither management strategy appreciably alters *in vivo* pH_i in animal heart or brain. [113] The alpha-stat method has been reported to limit myocardial damage and better preserve sensitivity to adrenergic stimulation during CPB, but this has not been universally observed. [114] [115] [116] [117] One consistent major difference is greater cerebral blood flow during CPB with pH-stat management. [112] [115] [118] [119] Neuropsychiatric outcome studies reveal little immediate postoperative effect of acid-base management strategy. [116] [120] [121] However, a lower incidence of cognitive dysfunction may be apparent later (7 days or 6 weeks postoperatively) in patients managed by the alpha-stat technique. [112] [122] On the other hand, in the special circumstance of deep hypothermia with cardiac arrest, pH-stat management may be more beneficial, as assessed by recovery of cerebral energy metabolism in animals and attainment of postoperative developmental milestones in children. [123] Currently, slightly over half of cardiac surgery centers in the United States and the United Kingdom utilize alpha-stat acid-base management, and debate continues regarding which strategy is better. [124] [125]

Cardiopulmonary Resuscitation

Ischemia and hypoxemia after cardiac arrest quickly lead to metabolic (lactic) acidosis, and metabolic acidosis is often a precipitating factor for the cardiac arrest (Ch. 75) . [126] During cardiopulmonary resuscitation (CPR), an acid-base environment of arterial respiratory alkalosis, tissue respiratory acidosis, and metabolic acidosis coincides. [127] Although metabolic acidosis sensitizes the myocardium to fibrillation, it does not appear to affect the defibrillation threshold. [84] [128] $NaHCO_3$ has historically been a component of CPR because it increases arterial HCO_3^- and pH. $NaHCO_3$ therapy, however, fails to increase intracellular pH during CPR, and may instead decrease it, at least transiently. [105] [129] $NaHCO_3$ also induces hypernatremia and hyperosmolarity, because it has an Na^+ concentration of 1,000 mEq/L. [96] $NaHCO_3$ -induced metabolic alkalemia is associated with a worse outcome from CPR. [130] Carbicarb causes less transient intramyocardial acidosis than $NaHCO_3$. [105] The Na^+ load of carbicarb, however, does not differ from that of $NaHCO_3$ alone. An experimental mixture of tris and $NaHCO_3$ causes less CO_2 production than $NaHCO_3$, and also it does not increase serum Na^+ concentration. [105] However, despite these theoretic advantages, neither carbicarb nor tris demonstrably improves outcome in animal CPR studies. [105] [131] [132] This may be due, in part, to the failure of buffer agents to reverse intramyocardial acidosis despite alkalinizing the blood. [129] In addition, buffer agents may reduce effective coronary perfusion pressure during CPR. [133] Alkalinizing therapy in general during CPR remains controversial. [127]

Laparoscopic Surgery

Laparoscopy-assisted gynecologic and general surgery can expose the patient to potential acid-base disturbances because of systemic absorption of insufflated CO_2 (Ch. 56) . Insufflated CO_2 diffusing into the circulation increases effective CO_2 "production" and causes respiratory acidosis unless V_E is increased to maintain a normal Pa $_{CO_2}$ and to return

Figure 38-12 (Figure Not Available) Decay curve for $^{13}CO_2$ release after equilibration with body HCO_3^- stores. *(From Irving et al [111])*

pH to 7.40. Depending on the abdominal pressure achieved with CO_2 insufflation, V_E must be increased 35 to 50 percent to restore normal Pa $_{CO_2}$. [134] [135] Steady-state apparent CO_2 "production" during laparoscopy may be delayed by up to 2 hours because the insufflated CO_2 equilibrates with the large reservoir of slow turnover HCO_3^- in extravascular compartments (Fig. 38-12) (Figure Not Available) . Increased Pa $_{CO_2}$ persists during postoperative recovery because the absorbed excess CO_2 must be eliminated by V_A. [134] A patient with poor respiratory mechanics and function is at risk for respiratory acidosis during and after laparoscopic procedures.

There is also a tendency to *metabolic* acidosis during laparoscopy, because of compromised splanchnic blood flow as abdominal pressure is increased. [134] [136] An additional factor underlying intraoperative metabolic acidosis is the impairment of renal function associated with increased abdominal pressure. [134] Whether metabolic acidosis persists into the postoperative setting is unknown.

UTILITY OF VENOUS BLOOD GAS

Peripheral venous blood is more readily available for sampling than arterial blood. However, because venous blood is collected downstream from the microcirculation, it differs from the arterial sample in that P $_{O_2}$ is decreased and P $_{CO_2}$ is increased relative to that of arterial blood. Normally, the peripheral venous P $_{CO_2}$ is only ~5 mm Hg greater than that in arterial blood. Peripheral venous P $_{CO_2}$ can be used to roughly approximate systemic acid-base balance, provided cardiac output is within normal limits and blood flow through the dependent tissue is unimpeded.

Mixed venous P $_{CO_2}$, sampled at the right atrium or pulmonary artery, normally differs from Pa $_{CO_2}$ by less than 6 mm Hg. In the setting of increased muscle V $_{CO_2}$ (e.g., severe exercise) or decreased cardiac output, mixed venous P $_{CO_2}$ may be markedly increased relative to arterial P $_{CO_2}$. Mixed venous P $_{CO_2}$ has special diagnostic value with decreased cardiac output, such as occurs during CPR, because tissue respiratory acidosis may be reflected only in mixed venous

blood, whereas it is not apparent in arterial blood. [137] [138] An increased P $_{CO_2}$ gradient between mixed venous and arterial blood may indicate suboptimal cardiac output in the immediate postoperative environment.

GASTRIC TONOMETRY

Gastric tonometry has been introduced as a technique to assess splanchnic acid-base balance, and splanchnic perfusion (Ch. 71) . [139] A nasogastric probe is used to indirectly measure [H^+] in the gastric mucosa, determining intraluminal pH rather than pH_i . A decrease in mucosal pH without a commensurate change in arterial blood pH is evidence of a local acidosis, usually resulting from lactic acid production, in the splanchnic bed. Gastric tonometry may therefore be especially useful during surgical procedures that potentially compromise splanchnic oxygenation or perfusion. The intraoperative and postoperative potential for gastric tonometry has recently been reviewed. [140]

ACKNOWLEDGMENT

The author thanks Drs. Thomas Hornbein, Vladimir Fenel, Wendell Stevens, and Per-Olaf Jarnberg for their advice and critical review of the manuscript.

References

1. Adrogue HJ, Madias NE: Management of life-threatening acid-base disorders (first of two parts). N Engl J Med 338:26, 1998.

2. Adrogue HJ, Madias NE: Management of life-threatening acid-base disorders (second of two parts. N Engl J Med 338:107, 1998.

3. Spriet LL, Lindinger MI, McKelvie RS et al: Muscle glycogenolysis and H^+ exchange concentration during maximal intermittent cycling. J Appl Physiol 66:8, 1989.

4. Lin C-W, Kalaria RN, Kroon SN et al: The amiloride-sensitive Na^+/K^+ exchange antiporter and control of intracellular pH in hippocampal brain slices. Brain Res 731:108, 1996.

5. Madshus IH: Regulation of intracellular pH in eukaryotic cells. Biochem J 250:1, 1988.

6. Putnam RW, Roos A: Intracellular pH. In Hoffman JF, Jamieson JD (eds): Handbook of Physiology, sect 14: Cell Physiology. New York, Oxford University Press, 1997, p 389.

7. Klocke RA: Carbon dioxide transport. In Fishman AP (ed): Handbook of Physiology, sect 3: The Respiratory System. Bethesda, Md, American Physiological Society, 1987, p 173.

8. Figge J, Mydosh T, Fencl V: Serum proteins and acid-base equilibria: A follow-up. J Lab Clin Med 120:713, 1992.

9. Sly WS, Hu PK: Human carbonic anhydrases and carbonic anhydrase deficiencies. Annu Rev Biochem 64:375, 1995.

10. Brackett NC Jr, Cohen JJ, Schwartz WB: Carbon dioxide titration curve of normal man: Effect of increasing degrees of acute hypercapnia on acid-base equilibrium. N Engl J Med 272:6, 1965.

11. Irving CS, Wong WW, Shulman RJ et al: [^{13}C]bicarbonate kinetics in humans: Intra- vs interindividual variations. Am J Physiol 245:R190, 1983.

12. Saccomani MP, Bonadonna RC, Caveggion E et al: Bicarbonate kinetics in humans: Identification and validation of a three-compartment model. Am J Physiol 269:E183, 1995.

13. Kassirer JP, Hrick DE, Cohen JJ: Repairing Body Fluids: Principles and Practices. Philadelphia, WB Saunders, 1989.

14. Leese GP, Nicoll AE, Varnier M et al: Kinetics of $^{13}CO_2$ elimination after ingestion of ^{13}C bicarbonate: The effects of exercise and acid-base balance. Eur J Clin Invest 24:818, 1994.

15. Woodbury JW: Body acid-base state and its regulation. In Ruch TC, Patton HD (eds): Physiology and Biophysics, 20th ed, vol 2. Philadelphia, WB Saunders, 1974, p 480.

16. Benedetti A, Strazzabosco M, Corasanti JG et al: Cl^--HCO_3^- exchanger in isolated rat hepatocytes: Role in regulation of intracellular pH. Am J Physiol 261:G512, 1991.

17. Cohen JJ, Brackett NC Jr, Schwartz WB: The nature of the carbon dioxide titration curve in the normal dog. J Clin Invest 43:777, 1964.

18. McAuliffe JJ, Lind LJ, Leith DE et al: Hypoproteinemic alkalosis. Am J Med 81:86, 1986.

19. Rossing TH, Maffeo N, Fencl V: Acid-base effects of altering plasma protein concentration in human blood *in vitro.* J Appl Physiol 61:2260, 1986.

20. Siggaard-Andersen O: The Acid-Base Status of the Blood, 4th ed. Baltimore, Williams & Wilkins, 1976.

21. Siggaard-Andersen O, Fogh-Andersen N: Base excess or buffer base (strong ion difference) as a measure of a non-respiratory acid-base disturbance. Acta Anaesthesiol Scand 39 (Suppl 107):123, 1995.

22. Astrup P, Severinghaus JW: The History of Blood Gases, Acids and Bases. Copenhagen, Munksgard, 1986.

23. Kindig NB, Sherrill DS, Shapiro JI et al: Extracorporeal bicarbonate space after bicarbonate or a bicarbonate-carbonate mixture in acidotic dogs. J Appl Physiol 67:2331, 1989.

24. Singer RB, Hastings AB: An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. Medicine 27:223, 1948.

25. Stewart PA: Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 61:1444, 1983.

26. Fencl V, Leith DE: Stewart's quantitative acid-base chemistry: Applications in biology and medicine. Respir Physiol 91:1, 1993.

27. Emmett M, Narins RG: Clinical use of the anion gap. Medicine 56:38, 1977.

28. Gabow PA: Disorders associated with an altered anion gap. Kidney Int 27:472, 1985.

29. Winter SD, Pearson JR, Gabow PA et al: The fall of the serum anion gap. Arch Intern Med 150:311, 1990.

30. Iberti TJ, Leibowitz AB, Papadakos PJ et al: Low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. Crit Care Med 18:275, 1990.

31. Humphrey SM, Garlick PB: NMR-visible ATP and P_i in normoxic and reperfused rat hearts: A quantitative study. Am J Physiol 260:H6, 1991.

32. Kemp GJ, Polgreen KE, Radda GK: Skeletal muscle P_i transport and cellular [P_i] studied in L6 myoblasts and rabbit muscle-membrane vesicles. Biochim Biophys Acta 1137:10, 1992.

33. Kushmerick MJ, Moerland TS, Wiseman RW: Mammalian skeletal muscle fibers distinguished by contents of phosphocreatine, ATP, and P_i. Proc Natl Acad Sci U S A 89:7521, 1992.

34. Barac-Nieto M, Spitzer A: NMR-visible intracellular Pi and phosphoesters during regulation of Na^+-Pi cotransport in opossum kidney cells. Am J Physiol 267:C915, 1994.

35. Fitzpatrick JH Jr, Kintner D, Anderson M et al: NMR studies of P_i-containing extracellular and cytoplasmic compartments in brain. J Neurochem 66:2612, 1996.

36. Strazzabosco M, Okolicsanyi L, Boyer JL: Acid/base transport system in isolated rat bile ductular epithelial cells. In Gentilini P, Dianzani MU (eds): Experimental and Clinical Hepatology.

Amsterdam, Elsevier Science, 1991, p 133.

37. Schoolwerth AC, Culpepper RM: Measurement of intracellular pH in suspensions of renal tubules from potassium-depleted rats. Miner Electrolyte Metab 16:191, 1990.

38. Behar KL: Cerebral metabolic studies *in vivo* by combined $^{1}H/^{31}P$ and $^{1}H/^{13}C$ NMR spectroscopic methods. Acta Neurochir 57(suppl): 9, 1993.

39. Nakashima K, Yamashita T, Kashiwagi S et al: The effect pf sodium bicarbonate on CBF and intracellular pH in man: Stable Xe-CT and ^{31}P-MRS. Acta Neurol Scand Suppl 166:96, 1996.

40. Giebisch G, Berger L, Pitts RF: The extrarenal response to acute acid-base disturbances of respiratory origin. J Clin Invest 34:231, 1955.

41. Swan RC, Pitts RF: Neutralization of infused acid by nephrectomized dogs. J Clin Invest 34:205, 1955.

42. Boron WF, Fong P, Hediger MA et al: The electrogenic Na/HCO_3 cotransporter. Wien Klin Wochenschr 109:445, 1997.

43. Bastani B: Immunocytochemical localization of the vacuolar H^+ - ATPase pump in the kidney. Histol Histopathol 12:769, 1997.

44. Wang Z, Rabb H, Craig T et al: Ischemic reperfusion injury in the kidney-overexpression of colonic H^+/K^+ ATPase and suppression of NHE-3. Kidney Int 51:1106, 1997.

45. Kone BC: Renal H,K-ATPase-structure, function and regulation. Miner Electrolyte Metab 22:349, 1996.

46. Hanna JD, Scheinman JI, Chan JCM: The kidney in acid-base balance. Pediatr Nephrol 42:1365, 1995.

47. Wall SM: Ammonium transport and the role of the Na,K-ATPase. Miner Electrolyte Metab 22:311, 1996.

48. Amlal H, Soleimani M: $K^+/NH4^+$ antiporter- a unique ammonium carrying transporter in the kidney inner medulla. Biochim Biophys Acta 1323:319, 1997.

49. Yanagawa N, Jo OD: Intracellular acidification inhibits opossum kidney cell phosphate uptake. Am J Physiol 272:R1904, 1997.

50. Kreisberg RA: Pathogenesis and management of lactic acidosis. Annu Rev Med 35:181, 1984.

51. Naylor JM, Kronfeld DS, Freeman DE et al: Hepatic and extrahe-patic lactate metabolism in sheep: Effects of lactate loading and pH. Am J Physiol 247:E747, 1984.

52. Phillips JW, Clark DG, Henly DC et al: The contribution of glucose cycling to the maintenance of steady-state levels of lactate by hepatocytes during glycolysis and gluconeogenesis. Eur J Biochem 227:352, 1995.

53. Haussisnger D: pH Homeostasis. New York, Academic Press, 1988.

54. Haussinger D, Gerok W: Hepatic urea synthesis and pH regulation: Role of CO_2 , HCO_3^- , pH, and the activity of carbonic anhydrase. Eur J Biochem 152:381, 1985.

55. Haussinger D: Regulation of hepatic ammonia metabolism: The intercellular glutamine cycle. Adv Enzyme Regul 25:159, 1986.

56. Arbus GS, Hebert LA, Levesque PR et al: Characterization and clinical application of the "significance band" for acute respiratory alkalosis. N Engl J Med 280:117, 1969.

57. Dulfano MJ, Ishikawa S: Quantitative acid-base relationships in chronic pulmonary patients during the stable state. Am Rev Respir Dis 93:251, 1966.

58. Goldring RM, Turino GM, Heinemann HO: Respiratory-renal adjustments in chronic hypercapnia in man. Am J Med 51:772, 1971.

59. Krapf R, Beller I, Hertner D, Hultner HN: Chronic respiratory alkalosis. The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med 324:1394, 1991.

60. Javaheri S, Shore NS, Rose B et al: Compensatory hypoventilation in metabolic alkalosis. Chest 81:296, 1982.

61. Burnell JM, Teubner EJ: Changes in bone sodium and carbonate in metabolic acidosis and alkalosis in the dog. J Clin Invest 50:327, 1971.

62. Tuller MA, Mehdi F: Compensatory hypoventilation and hypercapnia in primary metabolic alkalosis. Am J Med 50:281, 1971.

63. Perrone J, Hoffman RS: Compensatory hypoventilation in severe metabolic alkalosis. Acad Emerg Med 3:981, 1996.

64. Berger BE, Cogan MG, Sebastian A: Reduced glomerular filtration and enhanced bicarbonate reabsorption maintain metabolic alkalosis in humans. Kidney Int 26:205, 1983.

65. Ng ML, Levy MN, Zieske HA: Effects of changes of pH and of carbon dioxide tension on left ventricular performance. Am J Physiol 213:115, 1967.

66. Adrogue HJ, Madias NE: Changes in plasma potassium concentration during acute acid-base disturbances. Am J Med 71:456, 1981.

67. Biro K: Effects of respiratory and metabolic alkalosis and acidosis on pipecuronium neuromuscular block. Eur J Pharmacol 154:329, 1988.

68. Hynson JM, Sessler DI, Moayeri A et al: Absence of nonshivering thermogenesis in anesthetized adult humans. Anesthesiology 79:695, 1993.

69. Sellden E, Branstrom R, Brundin T: Augmented thermic effect of amino acids under general anaesthesia occurs predominantly in extrasplanchnic tissues. Clin Sci 91:431, 1996.

70. Eichenholz A, Mulhausen RO, Anderson WE et al: Primary hypocapnia: A cause of metabolic acidosis. J Appl Physiol 17:283, 1962.

71. Kuze S, Naruse T, Yamazaki M et al: Effects of sodium L-lactate and sodium racemic lactate on intraoperative acid-base status. Anesth Analg 75:702, 1992.

72. Tappy L, Cayeux M-C, Chiolero R: Effects of sodium lactate on ventilation and acid-base balance in healthy humans. Clin Physiol 16:393, 1996.

73. Litwin MS, Smith LL, Moore FD: Metabolic alkalosis following massive transfusion. Surgery 45:805, 1959.

74. Dolan MJ, Whipp BJ, Davidson WD et al: Hypopnea associated with acetate hemodialysis: Carbon dioxide-flow-dependent ventilation. N Engl J Med 305:72, 1981.

75. Burnier P, Tappy L, Jequier E et al: Metabolic and respiratory effects of infused sodium acetate in healthy humans. Am J Physiol 263:R1271, 1992.

76. Schwartz WB, van Ypersele de Strihou C, Kassirer JP: Role of anions in metabolic alkalosis and potassium deficiency. N Engl J Med 279:630, 1968.

77. Haussinger D, Steeb R, Gerok W: Ammonium and bicarbonate ho-meostasis in chronic liver disease. Klin Wochenschr 68:175, 1990.

78. DuBose TD Jr, Good DW: Effects of chronic Cl depletion alkalosis on proximal tubule transport and renal production of ammonium. Am J Physiol 269:F508, 1995.

79. Bersin RM, Arieff AI: Primary lactic alkalosis. Am J Med 85:867, 1988.

80. Allon M, Shanklin N: Effect of bicarbonate administration on plasma potassium in dialysis patients: Interactions with insulin and albuterol. Am J Kidney Dis 28:508, 1996.

81. Kim H-J: Combined effect of bicarbonate and insulin with glucose in acute therapy of hyperkalemia in end-stage renal disease patients. Nephron 72:476, 1996.

82. Pichette C, Bercovici M, Goldstein M et al: Elevation of the blood lactate concentration by alkali therapy without requiring additional lactic acid accumulation: Theoretical considerations. Crit Care Med 10:323, 1982.

83. Teplinsky K, O'Toole M, Olman M et al: Effect of lactic acidosis on canine hemodynamics and left ventricular function. Am J Physiol 258:H1193, 1990.

84. Gerst PH, Fleming WH, Malm JR: Increased susceptibility of the heart to ventricular fibrillation during metabolic acidosis. Circ Res 19:63, 1966.

85. Morris LR, Murphy MB, Kitabchi AE: Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med 105:836, 1986.

86. Narins RG, Cohen JJ: Bicarbonate therapy for organic acidosis: The case for its continued use. Ann Intern Med 106:615, 1987.

87. Effros RM, Widell JL: Acid-Base Balance. In Murray JF, Nadel JA (eds): Textbook of Respiratory Medicine, 2nd ed. Philadelphia, WB Saunders, 1994, p 175.

88. Arieff AI: Pathogenesis of metabolic acidosis with hypoxia. In Arieff AI (ed): Hypoxia, Metabolic Acidosis, and the Circulation. New York, Oxford University Press, 1992, p 116.

89. Leatherdale BA, Chase RA, Rogers J et al: Forearm glucose uptake in cirrhosis and its relationship to glucose tolerance. Clin Sci 59:191, 1980.

90. Woll PJ, Record CO: Lactate elimination in man: Effects of lactate concentration and hepatic dysfunction. Eur J Clin Invest 9:397, 1979.

91. Ostrea EM Jr, Odell GB: The influences of bicarbonate administration on blood pH in a "closed system": Clinical implications. J Pediatr 80:671, 1972.

92. Graf H, Leach W, Arieff AI: Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 227:754, 1985.

93. Shapiro JI, Whalen M, Kucera R et al: Brain pH responses to sodium bicarbonate and Carbicarb during system acidosis. Am J Physiol 256:H1316, 1989.

94. Shapiro JI, Whalen M, Chan L: Hemodynamic and hepatic pH responses to sodium bicarbonate and Carbicarb during systemic acidosis. Magn Reson Med 16:403, 1990.

95. Thompson CH, Syme PD, Williams EM et al: Effect of bicarbonate administration on skeletal muscle intracellular pH in the rat: Implications for acute administration of bicarbonate in man. Clin Sci 82:559, 1992.

96. Bishop RL, Weisfeldt ML: Sodium bicarbonate administration during cardiac arrest: Effect on arterial pH, P_{CO_2}, and osmolality. JAMA 235:506, 1976.

97. Norenberg MD, Leslie KO, Robertson AS: Association between rise in serum sodium and central pontine myelinolysis. Ann Neurol 11:128, 1982.

98. Cooper DJ, Worthley LIG: Adverse haemodynamic effects of sodium bicarbonate in metabolic acidosis. Intensive Care Med 13:425, 1987.

99. Cooper DJ, Walley KR, Wiggs BR et al: Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. Ann Intern Med 112:492, 1990.

100. Mathieu D, Neviere R, Billard V et al: Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: A prospective, controlled clinical study. Crit Care Med 19:1352, 1991.

101. Zahler R, Barrett E, Majumdar S et al: Lactic acidosis: Effect of treatment on intracellular pH and energetics in living rat heart. Am J Physiol 262:H1572, 1992.

102. Filley GF, Kindig NB: Carbicarb, an alkalinizing ion-generating agent of possible clinical usefulness. Trans Am Clin Climatol Assoc 96:141, 1984.

103. Bersin RM, Arieff AI: Improved hemodynamic function during hypoxia with Carbicarb, a new agent for the management of acidosis. Circulation 77:227, 1988.

104. Bleich HL, Schwartz WB: Tris buffer (THAM). N Engl J Med 274:782, 1966.

105. Li Y-C, Wiklund L, Tarkkila P et al: Influence of alkaline buffers on cytoplasmic pH in myocardial cells exposed to metabolic acidosis. Resuscitation 32:33, 1996.

106. Shangraw RE, Rabkin JM, Lopaschuk GD: Hepatic pyruvate dehydrogenase activity in humans: Effect of liver disease, transplantation and dichloroacetate. Am J Physiol 274:G569, 1998.

107. Graf H, Leach W, Arieff AI: Effects of dichloroacetate in the treatment of hypoxic lactic acidosis in dogs. J Clin Invest 76:919, 1985.

108. Shangraw RE, Winter R, Hromco J et al: Amelioration of lactic acidosis with dichloroacetate during liver transplantation in humans. Anesthesiology 81:1127, 1994.

109. Stacpoole PW, Wright EC, Baumgartner TG et al: A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. N Engl J Med 327:1564, 1992.

110. Severinghaus JW: Respiration and hypothermia. Ann N Y Acad Sci 80:384, 1959.

111. Rahn H, Reeves RB, Howell BJ: Hydrogen ion regulation, temperature and evolution. Am Rev Respir Dis 112:165, 1975.

112. Patel RL, Turtle MR, Chambers DJ et al: Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuropsychologic outcome in patients undergoing coronary artery bypass grafting. J Thoracic Cardiovasc Surg 111:1267, 1996.

113. Swain JA, McDonald TJ Jr, Robbins RC et al: Relationship between cerebral and myocardial intracellular pH to blood pH during hypothermia. Am J Physiol 260:H1640, 1991.

114. Becker H, Vinten-Johansen J, Buckberg GD et al: Myocardial damage caused by keeping pH 7.40 during systemic deep hypothermia. J Thorac Cardiovasc Surg 82:810, 1981.

115. Rogers AT, Stump DA, Gravlee GP et al: Response of cerebral blood flow to phenylephrine infusion during hypothermic cardiopulmonary bypass. Anesthesiology 69:547, 1988.

116. Bashein G, Townes BD, Nessly ML et al: A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. Anesthesiology 72:7, 1990.

117. Hering JP, Schroder T, Singer D et al: Influence of pH management on hemodynamics and metabolism in moderate hypothermia. J Thorac Cardiovasc Surg 104:1388, 1992.

118. Murkin JM, Farrar JK, Tweed WA et al: Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: The influence of Pa_{CO_2}. Anesth Analg 66:825, 1987.

119. Johnston WE, Vinten-Johansen J, DeWitt DS et al: Cerebral perfusion during canine hypothermic cardiopulmonary bypass: Effect of arterial carbon dioxide tension. Ann Thorac Surg 52:479, 1991.

120. Englehardt W, Dierks T, Pause M et al: Early cerebral functional outcome after coronary artery bypass surgery using different acid-base management during hypothermic cardiopulmonary bypass. Acta Anaesthesiol Scand 40:457, 1996.

121. Tallman RD Jr: Acid-base regulation, alpha-stat and the emperors' new clothes. J Cardiothorac Vasc Anesth 11:282, 1997.

122. Stephan H, Weyland A, Kazmaier S et al: Acid-base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome. Br J Anaesth 69:51, 1992.

123. Jonas RA, Bellinger DC, Rappaport LA et al: Relation of pH strategy and developmental outcome after hypothermic circulatory arrest. J Thorac Cardiovasc Surg 106:362, 1993.

124. Murkin JM: Con: Blood gases should not be corrected for temperature during hypothermic cardiopulmonary bypass: Alpha-stat mode. J Cardiothorac Anesth 2:705, 1988.

125. Tinker JH, Campos JH: Pro: Blood gases should be corrected for temperature during hypothermic cardiopulmonary bypass: pH-Stat mode. J Cardiothorac Anesth 2:701, 1988.

126. Fillmore SJ, Shapiro M, Killip T: Serial blood gas studies during cardiopulmonary resuscitation. Ann Intern Med 72:465, 1970.

127. Cummins RO (ed): Advanced Cardiac Life Support. Dallas, Tex, Am Heart Association, 1997.

128. Yakaitis RW, Thomas JD, Mahaffey JE: Influence of pH and hypoxia on the success of defibrillation. Crit Care Med 3:139, 1975.

129. Kette F, Weil MH, von Planta M et al: Buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation. Circulation 81:1660, 1990.

130. Weil MH, Ruiz CE, Michaels S et al: Acid-base determinants of survival after cardiopulmonary resuscitation. Crit Care Med 13:888, 1985.

131. Gazmuri RJ, von Planta M, Weil MH et al: Cardiac effects of carbon dioxide-consuming and carbon dioxide-generating buffers during cardiopulmonary resuscitation. J Am Coll Cardiol 15:482, 1990.

132. Blecic S, De Backer D, Deleuze M et al: Correction of metabolic acidosis in experimental CPR: A comparative study of sodium bicarbonate, carbicarb, and dextrose. Ann Emerg Med 20:235, 1991.

133. Kette F, Weil MH, Gazmuri RJ: Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure. JAMA 266:2121, 1991.

134. Koivusalo A-M, Kellokumpu I, Ristkari S et al: Splanchnic and renal deterioration during and after laparoscopic cholecystectomy: A comparison of the carbon dioxide pneumoperitoneum and the abdominal wall lift method. Anesth Analg 85:886, 1997.

135. Makinen MT: Comparison of body temperature changes during laparoscopic and open cholecystectomy. Acta Anaesthesiol Scand 41:736, 1997.

136. Gandara V, deVega DS, Escriu N et al: Acid-base balance alterations in laparoscopic cholecystectomy. Surg Endosc 11:707, 1997.

137. Adrogue HJ, Rashad MN, Gorin AB et al: Assessing acid-base status in circulatory failure. N Engl J Med 320:1312, 1989.

138. Weil MH, Rackow EC, Trevino RF et al: Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 315:153, 1986.

139. Fiddian-Green RG, Pittenger G, Whitehouse WM Jr: Back-diffusion of CO_2 and its influence on the intramural pH in gastric mucosa. J Surg Res 33:39, 1982.

140. Garrett SA, Pearl RG: Improved gastric tonometry for monitoring tissue perfusion: The canary sings louder. Anesth Analg 83:1, 1996.

141. Narins RG, Emmett M: Simple and mixed acid-base disorders: A practical approach. Medicine 59:161, 1980.

142. Halperin ML, Goldstein MB: Fluid, Electrolyte, and Acid-Base Emergencies. Philadelphia, WB Saunders, 1988.

Chapter 39 - Airway Management *

David J. Stone
Thomas J. Gal

INTRODUCTION

The major responsibility of the anesthesiologist is to provide adequate respiration for the patient. The most vital element in providing functional respiration is the airway. No anesthetic is safe unless diligent efforts are devoted to maintaining an intact functional airway. Furthermore, the same principles of airway management outlined in this chapter are equally applicable to all clinical situations in which respiratory inadequacy may develop.

STRUCTURE AND FUNCTION OF THE UPPER AIRWAYS

Nose

The normal airway begins functionally at the nares. As air passes through the nose, the important functions of warming and humidification occur. The nose is the primary pathway for normal breathing unless obstruction by polyps or upper respiratory infection is present. During quiet breathing the resistance to air flow through the nasal passages accounts for nearly two-thirds of the total airway resistance. [1] The resistance through the nose is nearly twice that associated with mouth breathing. This explains why mouth breathing is utilized when high flow rates are necessary as with exercise.

The sensory innervation of the nasal mucosa arises from two divisions of the trigeminal nerve. The anterior ethmoidal nerve supplies the anterior septum and lateral wall whereas the posterior areas are innervated by nasopalatine nerves from the sphenopalatine ganglion. Local anesthesia can be produced by blocking anterior ethmoidal and maxillary nerves bilaterally; however, simple topical anesthesia is usually quite effective.

Pharynx

The pharyngeal airway extends from the posterior aspect of the nose down to the cricoid cartilage, where the passage continues as the esophagus. An upper area, the nasopharynx, is separated from the lower oropharynx by the tissue of the soft palate. The principal impediments to air passage through the nasopharynx are the prominent tonsillar lymphoid structures. The tongue is the principal source of oropharyngeal obstruction, usually because of decreased tone of the genioglossus muscle. The latter contracts to move the tongue forward during inspiration and thus acts as a pharyngeal dilator.

Larynx

The larynx, which lies at the level of the third through sixth cervical vertebrae, serves as the organ of phonation and as a valve to protect the lower airways from the contents of the alimentary tract. The structure consists of muscles, ligaments,

* *See Appendix 1, Practice Guidelines for Management of the Difficult Airway*

and a framework of cartilages. These include the thyroid, cricoid, arytenoids, corniculates, and the epiglottis. The latter, a fibrous cartilage, has a mucous membrane covering that reflects as the glossoepiglottic fold onto the pharyngeal surface of the tongue. On either side of this fold are depressions called valleculae. These areas provide the site for placement of the curved MacIntosh laryngoscope blade. The epiglottis projects into the pharynx and overhangs the laryngeal inlet. However, it is not absolutely essential for sealing off the airway during swallowing. [2]

The laryngeal cavity extends from the epiglottis to the lower level of the cricoid cartilage. The inlet is formed by the epiglottis, which joins to the apex of the arytenoid cartilages on each side by the aryepiglottic folds. Inside the laryngeal cavity one first encounters the vestibular folds, which are narrow bands of fibrous tissue on each side. These extend from the anterolateral surface of each arytenoid to the angle of the thyroid where the latter attaches to the epiglottis. These folds are referred to as the false vocal cords and are separated from the true vocal cords by the laryngeal sinus or ventricle. The true vocal cords are pale white ligamentous structures that attach to the angles of the thyroid anteriorly and to the arytenoids posteriorly. The triangular fissure between these vocal cords is termed the glottic opening, which represents the narrowest segment of the laryngeal opening in adults. In young children (<10 years old), the narrowest segment lies just below the cords at the level of the cricoid ring. The mean length of the relaxed open glottis is about 23 mm in males and 17 mm in females. The glottic width is 6 to 9 mm but can be stretched to 12 mm. Thus, the cross-sectional area of the relaxed glottis may be 60 to 100 mm^2 .

The scope of this chapter does not permit a detailed description of the actions of the laryngeal muscles; however, these muscles may be classified into three basic groups relative to their actions on the cords: (1) abductors, (2) adductors, and (3) regulators of tension. The entire motor innervation to these muscles as well as the sensory supply to the larynx is supplied by two branches of the vagus nerve: the superior and recurrent laryngeal nerves. This motor and sensory innervation is summarized in Table 39-1 .

Trachea

The trachea is a tubular structure that begins opposite the sixth cervical vertebra at the level of the thyroid cartilage. It is flattened posteriorly and supported along its 10- to 15-cm length by 16 to 20 horseshoe-shaped cartilaginous rings until bifurcating into right and left main bronchi at the level of the fifth thoracic vertebra. The cross-sectional area of the trachea is considerably larger than that of the glottis and may be more than 150 mm^2 and as high as 300 mm^2 .

There are a number of receptors in the trachea that are sensitive to mechanical and chemical stimuli. Slowly adapting stretch receptors are located in the trachealis muscle of the posterior tracheal wall. These are involved in regulating the rate and depth of breathing, but they also produce dilation of upper airways and the bronchi by decreasing vagal efferent activity. Other rapidly adapting irritant receptors lie all around the tracheal circumference. These are usually considered to be cough receptors, although their other reflex actions consist of bronchoconstriction. Studies of topical anesthesia in dogs suggest that the latter receptors are more readily blocked by local anesthetics than are the slowly adapting stretch receptors. [2]

Upper Airway Obstruction

Airway obstruction may be total or partial. Total obstruction is characterized by the lack of any air movement or breath sounds. Confronted with ineffective breathing efforts, it is important that inexperienced persons not interpret any retractive movements of the rib cage and the diaphragmatic tugging motions as respiration. Actual air movement must be perceived by feeling with the hand or placing the ear over the mouth. Recognition of obstruction depends on close observation and a high index of suspicion.

The patient with partial obstruction exhibits diminished tidal exchange that is associated with retraction of the upper chest and accompanied by a snoring sound if the obstruction is nasopharyngeal or inspiratory stridor if obstruction is near the area of the larynx. If inspiratory efforts are severe, the upper airway may undergo a dynamic inspiratory compression because of the marked pressure gradient in the upper airway.

Treatment of upper airway obstruction depends for the most part on whether it is due to soft tissue obstruction, tumor, foreign body, or laryngospasm. Most often, upper airway obstruction is due to reduction of the space between the pharyngeal wall and the base of the tongue by relaxation of the tongue and jaw. The same

obstruction may occur with foreign bodies or even dentures. In the absence of a foreign body, air flow may be restored by preventing the mandible from falling back. Forward motion is applied by placing the forefinger and second finger behind the angle of the

TABLE 39-1 -- Laryngeal Innervation

NERVE	SENSORY	MOTOR
Superior laryngeal (internal division)	Epiglottis, base of tongue	None
	Supraglottic mucosa	
	Thyroepiglottic joint	
	Cricothyroid joint	
Superior laryngeal (external division)	Anterior subglottic mucosa	Cricothyroid (adductor, tensor)
Recurrent laryngeal	Subglottic mucosa	Thyroarytenoid
	Muscle spindles	Lateral cricoarytenoid
		Interarytenoid (adductors)
		Posterior cricoarytenoid (abductor)

mandible. The patient's neck can also be slightly extended to provide an optimal airway. The resultant changes in head position have been shown to modify upper airway resistance significantly. [3]

Oropharyngeal obstruction can also be overcome to some extent by increased oropharyngeal pressure from manual inflations with a breathing bag. One of the major concerns with such manual inflation of the lungs without tracheal intubation is the potential for gastric insufflation with high inflation pressures. The relationship between pressure and gas entry into the stomach has been examined in unconscious paralyzed patients. [4] The authors reported that gastric inflation rarely occurred when pressures less than 15 to 20 cm H_2O were utilized. In general such pressures were associated with tidal volumes well in excess of 1 L.

One of the primary skills required of anesthesiologists is the ability to correct upper airway obstruction in the unconscious or anesthetized patient. This obstruction is commonly attributed to occlusion of the pharynx by the tongue, which falls back. Correction of such a problem would be expected by insertion of devices termed oropharyngeal or nasopharyngeal airways (insertion is described later in the chapter). The nasopharyngeal airway is a soft rubber tube that is less traumatic and better tolerated in lighter stages of anesthesia or unconsciousness. The airway itself extends sufficiently into the pharynx to pass behind the base of the tongue. In situations in which the nares do not permit passage, bleeding occurs, or obstruction is not received, an oropharyngeal airway may be used. The latter is designed for insertion along the tongue until teeth or gums prevent further passage. The placement of these devices that provide an artificial passage behind the tongue does not in many cases provide unobstructed airflow. This suggests that the tongue is not the principal cause of upper airway obstruction in the anesthetized patient.

This is further borne out by daily experience of the frequent need to utilize head tilt and maintain head extension, even in patients with an oral airway in place. It is difficult to understand how this means of establishing airway patency produces any forward pull on the tongue. Observations in anesthetized patients indicate that this maneuver actually elevates the hyoid bone and epiglottis and appears to relieve the major cause of upper airway obstruction. [5] The angle of the extension or retroflexion required to achieve airway patency was reduced as the occiput was elevated. The latter to some extent pushes the mandible forward. Further support of the mandible may be provided by forward traction or pressing forward at the mandibular angles. When these simple maneuvers and the use of artificial airways do not provide adequate relief of upper airway obstruction, the insertion of an endotracheal tube to bypass the upper airway must be contemplated.

Physiology of Airway Protection

The pharynx, epiglottis, and vocal cords play a role in protecting the lower airway from aspiration of foreign bodies and secretions. Although the epiglottis covers the laryngeal inlet, it is not absolutely essential for airway protection. Most vital in this protective function is the glottic closure reflex, which produces protective laryngeal closure during deglutition. The physiologic exaggeration of this reflex, laryngospasm, is counterproductive to respiration. Laryngospasm consists of prolonged intense glottic closure in response to direct glottic or supraglottic stimulation from inhaled agents, secretions, or foreign bodies. Stimulation from the periosteum or celiac plexus or dilation of the rectum may also precipitate the problem on a reflex basis.

Varying degrees of laryngospasm produce sounds that range from a high-pitched squeaky sound to total absence of sound. The latter indicates complete closure of the cords and must be diagnosed and treated immediately. Treatment of severe spasm may require use of muscle relaxants such as succinylcholine. However, forward displacement of the mandible together with oxygen administered by a mask under pressure is often effective. Strong intermittent pressure applied manually to a bag full of oxygen can force gas effectively through the upper airway and the adducted cords. The traditional concerns about limiting airway pressure to avoid pulmonary barotrauma are not important in this case. However, the stomach contour should be watched closely should an inordinate amount of air be forced into the esophagus. In many cases when laryngospasm is less severe, slight amounts of positive pressure alleviate the difficulty. In any case, one should certainly utilize these simple maneuvers before resorting to tracheal intubation.

An indispensable mechanism for expelling secretions and foreign bodies from the lower respiratory tract is the act of coughing. The major stages of a cough are characterized by three events. First, there is a deep inspiration to attain a high lung volume, which allows attainment of maximum expiratory flow rates. Second, a tight closure of glottis occurs along with contraction of the expiratory muscles. Intrapleural pressure rises to above 100 cm H_2O such that during the third, or expiratory phase, a sudden expulsion of air occurs as the glottis opens. Glottic opening at the onset of the phase is associated with oscillation of tissue and gas that results in the characteristic noise of a cough.

Various physiologic aspects of cough have been observed with radiologic and endoscopic techniques. None is more important than the dramatic narrowing of the airway lumen. The physiologic significance of this reduced airway caliber is the fact that the decreased cross-sectional area increases linear velocity of gas flow and improves cough effectiveness. Various estimates suggest that this dynamic compression decreases the cross-sectional area of the trachea and main bronchi to about 40 percent of their caliber during normal breathing and thus increases linear velocity two and a half times. [6]

Neuromuscular weakness may decrease cough flow rates by limiting the inspired volume prior to cough if inspiratory muscles are weakened. Expiratory weakness, on the other hand, does not appreciably diminish flow rates. [7] The major effect appears to be a reduction in cough-induced dynamic airway compression, which results in decreased linear velocity of flow.

Glottic closure is the one phase of cough that differentiates it from other forced expiratory maneuvers and that allows for greater development of pressures. Closure of the glottis is not crucial, however, to the development of high pressures and flow rates of a normal cough. This is well illustrated in tracheotomized and intubated patients. The presence of the endotracheal tube, for example, does not lessen

the build-up of peak pressure during coughing. However, by preventing normal glottic closure, the tube allows flow to begin as soon as pressure begins to increase, and, in most cases, the tube allows flow to continue between cough bursts. [8] The normal timing of pressure and flow is altered such that cough resembles a normal forced expiration. Also, because the tube is noncollapsible, it does not permit the high velocities through the tracheal segment that it occupies. Secretions therefore are likely to accumulate in the area at the end of the tube unless subsequent coughs are begun from high lung volumes to allow high flow rates to be achieved.

/das/book/view/29494766/875/451.html

EVALUATION OF THE AIRWAY

History

A documented history of difficulties with general anesthesia or, more specifically, mask ventilation or endotracheal intubation should immediately arouse concern regarding a patient's airway, and the information should not be lightly dismissed. If one encounters a difficult airway, it is important to specifically inform the patient of the problems encountered so that this information can be transmitted to the next anesthesia caregiver. Until a searchable national database is available, the patient can be provided with a form letter providing information on the airway problem. [9] Even a brief note on the back of a business card provides a handy mobile source of information to future caregivers: e.g., "difficult mask ventilation and intubation." The best means of communication may be the use of a MedicAlert bracelet labeled "difficult airway/intubation." [10] The MedicAlert System can be reached at 1-800-344-3226. Previous anesthesia records are extremely useful, especially when the problem is clearly defined. Remember also that some diseases, such as rheumatoid arthritis and morbid obesity, may have progressed in the interim and now may present a more difficult airway than suggested by the previous anesthetic record.

TABLE 39-2 -- Selected Congenital Syndromes Associated With Difficult Endotracheal Intubation

SYNDROME	DESCRIPTION
Down	Large tongue, small mouth make laryngoscopy difficult; small subglottic diameter possible
	Laryngospasm frequent
Goldenhar (oculoauriculovertebral anomalies)	Mandibular hypoplasia and cervical spine abnormality make laryngoscopy difficult
Klippel-Feil	Neck rigidity because of cervical vertebral fusion
Pierre Robin	Small mouth, large tongue, mandibular anomaly; awake intubation essential in neonate
Treacher Collins (mandibulofacial dysostosis)	Laryngoscopy difficult
Turner	High likelihood of difficult intubation

Many congenital syndromes that involve the airway may make mask ventilation or endotracheal intubation difficult. Several excellent sources provide an extensive listing of these. [11] It may be prudent to keep one of these lists in a readily available place. The more common congenital syndromes and their airway implications are listed in Table 39-2 .

Other diseases of infectious, traumatic, neoplastic, or inflammatory cause may also profoundly affect airway management. Table 39-3 lists many that should be considered while eliciting a patient history.

Physical Examination

The patient must be initially subjected to simple inspection from front and side to identify obvious problems such as massive obesity, cervical collars or traction devices, external trauma, or any indications of respiratory difficulty such as stridor. The presence of ear and hand anomalies often suggests the presence of a difficult airway. Nostril size and patency are essential to establish before considering nasal intubation. A large beard may make physical examination, mask ventilation, and direct laryngoscopy more difficult. Consideration to trimming or removing the beard should be made when the airway is judged difficult or when the surgery prevents circumferential securement of the tracheal tube (e.g., cervical or intracranial surgery).

Edentulous patients are seldom difficult to intubate unless other associated problems are severe. Protuberant upper incisors, on the other hand, can make laryngoscopy difficult and expose the teeth to damage. Isolated loose teeth are particularly prone to damage. These should be noted as well as the location of crowns, bridges, braces, and other significant dental work. Bridges and dentures should be removed if possible unless dentures significantly improve mask fit. Very loose teeth are best removed prior to laryngoscopy to avoid aspiration of a tooth. Most important, patients should be warned of likely damage to teeth both in person and in the preoperative note.

Mouth opening, which is largely a function of the temporomandibular joint, is of prime importance to allow the insertion of a laryngoscope blade and subsequent glottic visualization. [12] Adults should be able to open their mouths so that there is a 30- to 40-mm distance between upper and lower incisors (about two large fingerbreadths). [13] A problem with mouth opening should not be underestimated as it can make visualization of any laryngeal structures impossible. It may be risky to assume that limited mouth opening is due to spasm that will reverse after neuromuscular blockade. Conversely, in some patients able to open the mouth widely in the awake state, adequate mouth opening in the anesthetized state was only possible when the mandible was pulled forward. [14] Previous transtemporal neurosurgery may produce severe limitation in mouth opening that was not present during the original anesthetic. [15]

The oral cavity examination is aimed at identifying a long narrow mouth with a high arched palate that is associated with difficult intubation. A large tongue in relation to oral cavity size may make laryngoscopy more difficult. Mallampati et al [16] emphasized the importance of the base of the tongue in determining the difficulty of laryngoscopy. If the faucial pillars (palatoglossal and palatopharyngeal arches)

TABLE 39-3 -- Selected Pathologic States That Influence Airway Management

PATHOLOGIC STATE	DIFFICULTY
Infectious epiglottitis	Laryngoscopy may worsen obstruction
Abscess (submandibular, retropharyngeal, Ludwig's angina)	Distortion of airway renders mask ventilation or intubation extremely difficult
Croup, bronchitis, pneumonia (current or recent)	Airway irritability with tendency for cough, laryngospasm, bronchospasm
Papillomatosis	Airway obstruction
Tetanus	Trismus renders oral intubation impossible

Traumatic foreign body	Airway obstruction
Cervical spine injury	Neck manipulation may traumatize spinal cord
Basilar skull fracture	Nasal intubation attempts may result in intracranial tube placement
Maxillary/mandibular injury	Airway obstruction, difficult mask ventilation, and intubation; cricothyroidotomy may be necessary with combined injuries
Laryngeal fracture	Airway obstruction may worsen during instrumentation
	Endotracheal tube may be misplaced outside larynx and may worsen the injury
Laryngeal edema (postintubation)	Irritable airway, narrowed laryngeal inlet
Soft tissue, neck injury (edema, bleeding, emphysema)	Anatomic distortion of airway
	Airway obstruction
Neoplastic upper airway tumors (pharynx, larynx)	Inspiratory obstruction with spontaneous ventilation
Lower airway tumors (trachea, bronchi, mediastinum)	Airway obstruction may not be relieved by tracheal intubation
	Lower airway distorted
Radiation therapy	Fibrosis may distort airway or make manipulations difficult
Inflammatory rheumatoid arthritis	Mandibular hypoplasia, temporomandibular joint arthritis, immobile cervical spine, laryngeal rotation, cricoarytenoid arthritis all make intubation difficult and hazardous
Ankylosing spondylitis	Fusion of cervical spine may render direct laryngoscopy impossible
Temporomandibular joint syndrome	Severe impairment of mouth opening
True ankylosis	
"False" ankylosis (burn, trauma, radiation, temporal craniotomy)	
Scleroderma	Tight skin and temporomandibular joint involvement make mouth opening difficult
Sarcoidosis	Airway obstruction (lymphoid tissue)
Angioedema	Obstructive swelling renders ventilation and intubation difficult
Endocrine/metabolic acromegaly	Large tongue, bony overgrowths
Diabetes mellitus	May have reduced mobility of atlanto-occipital joint
Hypothyroidism	Large tongue, abnormal soft tissue (myxedema) make ventilation and intubation difficult
Thyromegaly	Goiter may produce extrinsic airway compression or deviation
Obesity	Upper airway obstruction with loss of consciousness
	Tissue mass makes successful mask ventilation unlikely

and uvula cannot be seen in a seated, vocalizing patient with the tongue protruding (Figs. 39-1 (Figure Not Available) , 39-2) (Figure Not Available) , then visualization of the glottis is likely to be more difficult than in patients in whom these structures are readily visible. An increase in Mallampati score may be noted during pregnancy and correlates with the slightly higher rate of difficult laryngoscopy in this population. [17]

The distance from the inner surface of the mandible to the hyoid bone during neck extension should be at least two large fingerbreadths in adults. If the thyromental space is examined, the comparable distance is 50 mm or about three large fingerbreadths. There appears to be no difference in the results of using the hyomental versus thyromental distances, except that the thyroid cartilage may be easier to locate. [18] These areas are important because the laryngoscope displaces the tongue into this space, and exposure of the glottis may be inadequate if the space is narrowed or noncompliant. [19] A receding or hypoplastic mandible results in a situation often referred to as an "anterior larynx" or "high larynx" by clinicians. An inability to bring the lower incisors edge to edge with the upper incisors, i.e., impaired mandibular protrusion, is an important warning that laryngoscopy may be difficult. [20]

The neck is examined for masses, fixation of the trachea, and mobility, particularly with extension. A patient with a short, thick, muscular neck (such as the classic football lineman)

Figure 39-1 (Figure Not Available) Illustration of patient in whom faucial pillars, soft palate, and uvula are visible. *(From Mallampati et al [16])*

with a full set of teeth may pose difficult mask ventilation as well as very difficult laryngoscopy. Exposure of the larynx requires some degree of flexion (
35 degrees) in the lower cervical spine and extension (
80 degrees) in the upper

Figure 39-2 (Figure Not Available) Illustration of patient in whom none of the three pharyngeal structures is visible. *(From Mallampati et al [16])*

cervical spine (especially at the atlanto-occipital joint) (Fig. 39-3) . [21] Consequently, the patient should be asked to flex and extend the neck maximally, provided there are no contraindications such as suspected or known cervical spine fracture, severe cervical spondylosis with cord or vertebral artery symptoms on motion, or rheumatoid arthritis with atlantoaxial subluxation. Extension of the head can be quantitated by determining the angle of head extension, with the lower neck flexed about 30 to 40 degrees in the "sniff position." Normal extension is 80 degrees, with lesser degrees representing increasing limitation and increased potential for difficult laryngoscopy. [22] The presence of a hoarse voice or previous prolonged intubation or tracheostomy should alert the clinician to the possibility of a stenotic airway at some level. Note that the combination of several minor physical anomalies may result in a difficult intubation even when no one single factor is severely abnormal. [22] [23] A number of studies have attempted to combine physical factors to predict difficult intubation with mixed results, but it is not clear to the authors that these indices represent an improvement over the clinical evaluation of a seasoned clinician. [24] [25] Additional problems with preoperative airway assessment tests are that they have only moderate interobserver reliability and depend on the definitions of airway difficulties. [26] [27] Difficult intubations also occur occasionally for reasons that are currently unexplained, and none of the available indices predicts all difficult intubations. The truly life-threatening problem is the inability to ventilate when intubation is difficult or impossible. [28]

Further Evaluation

If there is suspicion of undetected disease, such as an airway tumor or if the impact of such a tumor or an infection on airway management is not clear, consultation should be obtained for indirect or fiberoptic laryngoscopy. [29] These may be the only methods to detect occult but life-threatening

Figure 39-3 Schematic diagram demonstrating head position for endotracheal intubation. (A) Successful direct laryngoscopy for exposure of the glottic opening requires alignment of the oral, pharyngeal, and laryngeal axes. (B) Elevation of the head about 10 cm with pads below to occiput with the shoulders remaining on the table aligns the laryngeal and pharyngeal axes. (C) Subsequent head extension at the atlanto-occipital joint serves to create the shortest distance and most nearly straight line from the incisor teeth to glottic opening.

problems such as lingual tonsillar hyperplasia. [30] Serious doubt about an airway may justify the presence of an otolaryngologist during induction to establish an airway surgically, if necessary.

The chest x-ray may reveal problems undetected by the history and physical examination. Lateral and anteroposterior cervical spine films should be obtained if the bony spine or joints may be a source of difficulty or if there is suspected encroachment on the airway. CT scanning has been employed to evaluate the involvement of the trachea, bronchi, and cardiovascular structures in mediastinal tumors. [31] [32] Other means of airway assessment with magnetic resonance

imaging have been reported. [33] However, flow-volume loops provide detection and assessment of the physiologic importance of such obstructive lesions, be they extra- or intrathoracic.

MASK: VENTILATION EQUIPMENT AND TECHNIQUE

Anesthesia face masks of rubber or plastic are employed to administer oxygen and anesthetic gases as well as to ventilate the nonintubated patient. Masks come in a large variety of shapes, but the anatomic mask is most commonly used in adults. [34] Adult masks come in small, medium, and large sizes (#3, 4, and 5). Most adults can be ventilated with a small or medium mask, but the occasional patient with a long or wide face or large nose will need a large mask. Children's masks come in newborn, infant, and children sizes. In addition to the anatomic mask, the relatively flat Rendell-Baker-Soucek mask is often used as it conforms to the child's flatter face and has minimal dead space. Transparent masks are being used more often for adults as well as for children. They are less frightening than a black opaque mask, and the patient can be better observed for cyanosis and vomiting.

The mask is held with one hand as shown in Figure 39-4 . The fingers should be kept on the bone rather than soft tissues because the latter can cause discomfort in the awake patient and can cause airway obstruction if such pressure sufficiently raises the base of the tongue. Ventilation with a mask requires a tight fit that involves downward displacement of the mask with the thumb and first finger and upward displacement of the mandible with the other three fingers. Mandibular displacement along with upper cervical extension and chin lift all tend to pull the tongue and soft tissues up off the posterior pharyngeal wall and relieve the upper airway obstruction that occurs in the anesthetized or unconscious patient (Fig. 39-5) (Figure Not Available) . This may require holding the mask with two hands and vigorously pulling the mandible upward ("jaw thrust") (Fig. 39-6) . A two-handed mask grip will require an assistant to provide manual ventilation. If no such help is available, the anesthesia ventilator can be used to supply positive-pressure breaths. If necessary, the anesthetist's chin can exert downward pressure on the elbow connector to achieve a tight mask fit. Alternatively, the second person can provide jaw thrust while the first seals the mask and ventilates by anesthesia bag. [35]

As noted in the previous section, mask ventilation may be extremely difficult for patients with problems such as obesity, tumors, infections, and inflammatory disorders. The pediatric patient usually presents less of a problem than the adult as the pediatric airway can usually be managed by mask ventilation unless laryngospasm ensues. Providing a leak-free seal with the mask may be particularly difficult in the older, edentulous patient, and this may be helped by leaving dentures in place, using packing, or employing a mask strap or assistant to pull up the sagging cheeks. In addition to the inability to ventilate, other serious problems with mask ventilation include pulmonary aspiration and pressure damage to the eyes.

When airway integrity cannot be maintained with manipulation of the mask, mandible, or neck, a mechanical airway may restore airway patency. Both oral and nasal airways serve to separate the tongue from the posterior pharyngeal wall (Figs. 39-7 (Figure Not Available) , 39-8) (Figure Not Available) . The rigid oral airway may provoke a gag reflex or be followed by cough, vomiting, laryngospasm, or even bronchospasm if the patient is not adequately anesthetized. The airway may be inserted right side up or upside down and then rotated 180 degrees into the position of function. In either case, trauma to the teeth must be avoided as well as a misplacement in which the airway (especially if too short) pushes the tongue back into the pharynx and actually increases airway obstruction. After intubation, an airway is often inserted to prevent the patient from biting down on the tube. However, it is advisable to avoid the use of oral airways in prone cases that require extensive

Figure 39-4 Technique for holding the mask with one hand. An effort should be made to avoid excessive pressure on the soft tissues of the neck.

Figure 39-5 (Figure Not Available) (A) The normal airway. The tongue and other soft tissue are forward, allowing an unobstructed air passage. (B) Obstructed airway. The tongue and epiglottis fall back to the posterior pharyngeal wall, occluding the airway. *(From Dorsch and Dorsch [34])*

neck flexion as severe swelling of the tongue may result. [36] A 4 × 4-inch piece of gauze can be placed between the teeth to avoid active or passive biting with occlusion of the airway. Oral airways are generally made of plastic and in adults range in size from 80 to 90 to 100 mm (#3, 4, and 5, respectively). Children's airways range from 50 to 60 to 70 mm (#0, 1 and 2, respectively), with special small airways (#00, 000) for premature and newborn babies.

Soft nasal airways are useful in patients who are not deeply anesthetized because such airways tend to provoke less of a gag reflex. Relative contraindications to such airways include coagulopathy, basilar skull fracture, and nasal infections or deformities. If possible, vasoconstriction with phenylephrine nose drops (and topical anesthesia with lidocaine if the patient is awake) should precede any nasal instrumentation. However, in the acute situation, the lubricating qualities of lidocaine ointment may suffice. The tip of the airway should be inserted perpendicularly to the face and not upwards toward the cribriform plate. It has been suggested that the length of the airway should be roughly the distance from the tip of the nose to the meatus of the ear. [34] Adult nasal airways are measured in French numbers, which relate to their outer diameter and hence reflect circumferences that range in size from 28, 30, and 32 to 34. If the nasal airway does not have a sizable flange at the nasal end, the placement of a safety pin (taped to the face) in the airway tip will prevent loss of the nasal airway into the patient's lower airway. Both adequately large oral and nasal airways should be employed together if mask ventilation cannot be otherwise accomplished. [35]

Figure 39-6 Technique for holding the mask with two hands.

Figure 39-7 (Figure Not Available) Oropharyngeal airway in place. The airway follows the curvature of the tongue, pulling it and the epiglottis away from the posterior pharyngeal wall and providing a channel for air passage. *(From Dorsch and Dorsch [34])*

Figure 39-8 (Figure Not Available) The nasopharyngeal airway in place. The airway passes through the nose and ends at a point just above the epiglottis. *(From Dorsch and Dorsch [34])*

/das/book/view/29494766/875/453.html

LARYNGEAL MASK AIRWAY

The laryngeal mask airway (LMA) is an ingenious supraglottic airway device that is designed to provide and maintain a seal around the laryngeal inlet for spontaneous ventilation and allow controlled ventilation at modest levels (up to 15 cm H_2O) of positive pressure. [37] This device is currently available in seven sizes for neonates, infants, young children, older children, and small, normal, and large adults (Fig. 39-9) (Figure Not Available) . After establishing an adequate depth of anesthesia and lubrication of the cuff, the appropriately sized LMA is inserted into the mouth, with the aperture facing the base of the tongue and the cuff tip pressed against the posterior pharyngeal wall. While the standard method involves total cuff deflation, other clinicians prefer to insert the LMA with the cuff partially inflated. An excellent instruction manual is available from the manufacturer (Gensia Automedics Inc, 9360 Towne Centre Drive, San Diego, Calif 92121). The requirement for adequate anesthesia makes the LMA generally unsuitable for use in the conscious emergency room patient. The index finger of the dominant hand is used to guide the LMA into the hypopharynx until resistance is felt, and the cuff is inflated with the appropriate volume of air (Fig. 39-10) (Figure Not Available) . The resistance indicates that the cuff tip has reached the upper esophageal sphincter (Fig. 39-11) (Figure Not Available) . A bite block, usually a folded 4 × 4- inch gauze, is inserted in the mouth to protect the LMA before both gauze and LMA are secured with tape. It is important to check by capnography as well as by auscultation and visualization of air movement that the cuff is correctly positioned and has not produced obstruction from downward displacement of the epiglottis. Because of the limited ability of the LMA to seal off the laryngeal inlet, the elective use of the device is contraindicated in any of the conditions associated with an increased risk for aspiration. [38] In patients without these predisposing factors, the risk for pharyngeal regurgitation appears to be low. [39]

The LMA may be used as a substitute for the classic mask airway to eliminate the presence of a relatively large mask and practitioner's hand that may interfere with surgical access. [40] A new, flexible LMA (LMA-Flexible, Gensia Medtronics) may allow for easier connection at any angle from the mouth while resisting kinking and displacement. The LMA may be inserted to establish an emergency airway in awkward settings for intubation such as the lateral or prone positions. The device may also be employed to establish an airway in the patient in whom either mask ventilation or tracheal intubation is difficult. [36] This role is discussed in a later section of this chapter. In addition, the LMA may be used to provide a conduit to facilitate fiberoptic, gum bougie-guided or blind oral tracheal intubation (Fig. 39-12) (Figure Not Available) . The size of the LMA dictates the size of endotracheal tubes that can be employed; cuffed 6.0 mm internal diameter (ID) for the size 3 and 4 and 7.0 mm ID for the recently introduced size 5 [42] Problems include inadequate endotracheal tube length as dictated by the presence of the LMA, limitation on endotracheal tube size, and inability to remove the LMA without risking extubation. [43] The use of the fiberoptic scope to assist in placing a gum elastic bougie rather than direct placement of the endotracheal tube is one possible approach to this situation. Benumof [43] has suggested a number of alternative solutions to the LMA/ fiberoptic intubation dilemma. A laryngeal mask specifically designed to facilitate tracheal intubation is now available (LMA-Fastrach, Gensia Automedics, San Diego, Calif.)

With increasing use, problems have been reported with the LMA; they include pulmonary aspiration, laryngospasm, need for neck extension in the patient with cervical spine disorder, and failure to function properly in the presence of local pharyngeal or laryngeal disease. [41] [44] [45] In patients with diminished pulmonary compliance or increased airway resistance,

Figure 39-9 (Figure Not Available) Range of patient laryngeal mask airway sizes. From upper left to lower right: Size 1: neonates/infants up to 5 kg (4); Size 1.5: infants 5-10 kg (7); Size 2: infants/children 10-20 kg (10); Size 2.5: children 20-30 kg (14); Size 3: children/small adults over 30 kg (20); Size 4: normal and large adults (30); Size 5: large adults (40). Maximum cuff inflation volumes in mL are given in parentheses for each size LMA. *(Gensia Automedics, San Diego, Calif)*

Figure 39-10 (Figure Not Available) Insertion of the LMA. (A) The tip of the cuff is pressed upward against the hard palate by the index finger while the middle finger opens the mouth. (B) The LMA is pressed backward in a smooth movement; note that the nondominant hand is used to extend the head. (C) The LMA is advanced until a definite resistance is felt. (D) Before the index finger is removed, the nondominant hand presses down on the LMA to prevent dislodgement during removal of the index finger; the cuff is subsequently inflated; an outward movement of the tube is often noted during this inflation. *(Gensia Automedics, San Diego, Calif)*

Figure 39-11 (Figure Not Available) The laryngeal mask in position. *(From Brain [37])*

adequate ventilation may not be possible because of the high inflation pressures required and the resultant leaks. The overall role of the LMA in clinical anesthesia would appear to lie somewhat between that of the face mask and that of the endotracheal tube as it provides more airway security (when properly positioned) than the former but not the reliable airway protection and maintenance of the latter. The LMA can be used to access the glottis for intubation as described; this is likely to become a more common use as the LMA becomes more generally available and clinicians gain experience with it. More important, it has become a nearly essential back-up airway device to provide emergency ventilation when conventional mask ventilation and intubation attempts fail.

THE COMBITUBE

The Combitube (Sheridan Catheter, Argyle, NY) is another supraglottic airway device that can provide an emergency airway when conventional means are not effective or possible. The Combitube has two lumens so that it can function appropriately whether placed in the trachea or, much more commonly, in the esophagus (Fig. 39-13) (Figure Not Available) . It also possesses an esophageal balloon to provide for protection from aspiration, which may represent an advantage over the LMA in obstetric anesthesia. The Combitube has been used successfully in cardiopulmonary resuscitation and probably presents a lower risk of esophageal rupture than the older esophageal obturator airway. [46] Care must also be taken to avoid excessively deep placement in the esophagus, which obstructs the glottic openings. [47] The Combitube is contraindicated for patients less than 5 feet tall and those with intact gag, esophageal disease, or caustic ingestion. A redesigned Combitube with a larger pharyngeal orifice has been found effective in providing a conduit for tracheal suctioning, fiberoptic bronchoscopy, and the use of a guide wire for tube exchange. [48] The practicing clinician can probably

Figure 39-12 (Figure Not Available) The use of the LMA as a conduit for fiberoptic intubation. (A) After loading an appropriately sized endotracheal tube, the fiberoptic scope is placed through the LMA into the glottis. (B) The endotracheal tube is threaded into the trachea. (C) The fiberoptic scope is removed. *(Gensia Medtronics, San Diego, Calif)*

Figure 39-13 (Figure Not Available) Insertion of the Combitube. (A) The tongue and mandible are lifted with one hand and the Combitube is inserted in the direction of the natural curvature of the pharynx with the other hand. The printed ring is aligned with the teeth. (B) The blue pharyngeal cuff is inflated with 100 mL of air while the white distal cuff is inflated with 15 mL. (C) Ventilation is begun through the longer blue tube as placement is usually in the esophagus. (D) If ventilation is absent and the stomach is being insufflated, begin ventilation through the clear connecting tube *(Sheridan Catheter, Argyle, NY)*

anticipate continued modifications in the present supraglottic devices as well as the introduction of new modalities to maintain and protect the airway without tracheal intubation.

ENDOTRACHEAL INTUBATION

Indications

The basic indications for endotracheal intubation in the operating room and intensive care unit are summarized in Table 39-4 . Before attempting tracheal intubation, the clinician should clearly establish the basis for the decision.

Equipment

In addition to endotracheal tubes and laryngoscopes, other essential items include an oxygen source, bag and

TABLE 39-4 -- Indications for Tracheal Intubation

Airway protection
Maintenance of patent airway
Pulmonary toilet
Application of positive-pressure ventilation
Maintenance of adequate oxygenation
Predictable F_{IO_2}
Positive end-expiratory pressure

mask, airways, stylet, lubricant, tape, and reliable suction. Other devices that may be utilized in special situations are also discussed.

Endotracheal Tubes

The endotracheal tube that is most commonly utilized in current practice is a polyvinylchloride tube that has a low-pressure,

Figure 39-14 Various types of endotracheal tubes. (A) An armored or anode tube with a built-in spiral wire to minimize the opportunity of collapse or kinking. (B-D) Tubes made of smooth plastic and recommended for single use. Tube B is uncuffed and is a size appropriate for a child. Tubes C and D are appropriate for adult patients. Tube C is equipped with a built-in high-pressure low-residual-volume cuff. Tube D is constructed to incorporate a low-pressure high-residual-volume cuff. Numbers and letters visible on tubes B, C, and D denote tube diameter, length from tracheal end, and confirmation that the tubes have been tested for tissue compatibility (I.T. or Z-79).

high-volume cuff. This type of tube is illustrated in Figure 39-14 . Clinical use of the tube is generally dictated by the internal diameter that limits air flow. The external diameter of the tube depends on the internal diameter and on the thickness of the tube's wall, which varies among manufacturers. In adults, external diameter is limited at the level of the glottic aperture, whereas in children the subglottic (cricoid cartilage) area is the limiting factor in external diameter. Tubes are manufactured in 0.5 mm ID increments from 2.5 to 9.0 mm (Table 39-5) . French size reflects the circumference, the product of external diameter and pi, and is therefore higher for thicker-walled tubes than for thinner-walled tubes with the same ID. The table also gives recommended distance of insertion for the tube tip to be placed in the midtrachea. This distance must be evaluated in each individual patient. A small percentage of patients will require a shorter or longer distance of insertion, depending on the highly variable tracheal length.

TABLE 39-5 -- Endotracheal Tube Size and Position Based on Patient Age

AGE	INTERNAL DIAMETER (mm)	EXTERNAL DIAMETER (mm) (APPROXIMATE, VARYING AMONG MANUFACTURERS)	FRENCH UNIT	DISTANCE INSERTED FROM LIPS FOR TIP PLACEMENT IN MID-TRACHEA[a] (cm)
Premature	2.5	3.3	10	10
Full-term newborn	3.0	4.0-4.2	12	11
1-6 mo	3.5	4.7-4.8	14	11
6-12 mo	4.0	5.3-5.6	16	12
2 y	4.5	6.0-6.3	18	13
4 y	5.0	6.7-7.0	20	14
6 y	5.5	7.3-7.6	22	15-16
8 y	6.0	8.0-8.2	24	16-17
10 y	6.5	8.7-9.3	26	17-18
12 y	7.0	9.3-10	28-30	18-22
14 y	7.0 (females)	9.3-10	28-30	20-24
	8.0 (males)	10.7-11.3	32-34	

[a] Add 2 to 3 cm for nasal tubes.

The tube material itself is stamped Z-79 (Committee Z-79 on Anesthesia Equipment of the USA Standards Institute) or IT (implantation tested), indicating that the tube is free of toxic or irritant properties so far as testing can indicate. A line of x-ray opaque material is manufactured into the wall of the tube to aid in placement. Most tubes have a hole cut in the wall opposite to the bevel. This hole is known as the Murphy eye and is designed to allow gas passage if the bevel lumen is occluded. The tube is manufactured to be sterile, and most present-day tubes are disposable. It is wise to check the free flow of air through the tube as part of the pre-case checkout. The interface between the plastic tube and 15 mm connector should be tightened snugly.

The cuffs of present-day plastic tubes are so-called high-volume, low-pressure cuffs. These compliant cuffs are designed to accommodate a relatively large volume of inflation before pressure rises. High pressure in the cuff lumen is transmitted to the tracheal mucosa where it can cause ischemic injury. This is generally not an important issue during an anesthetic and is addressed further in the section on complications of intubation. Before the use of the tube, the cuff should be inflated to check for symmetry and leaks. The syringe must be removed from the one-way valve to test the sealing function of the valve. After insertion, the cuff should be inflated so that there is no air leak on positive-pressure inspiration. This will allow for reasonable airway protection from aspiration without excessive lateral wall pressure. Cuff pressures that afford good (but not perfect) protection (20-25 mm Hg) are just below the perfusion pressure of the tracheal mucosa (25-35 mm Hg). [49] [50] During the case, nitrous oxide may diffuse into the cuff and increase its pressure. [51] With high-volume cuffs and cases of reasonable duration (<24 hours), this is probably not an important issue as even high-pressure cuffs are acceptable for such cases. Although the tension of the pilot balloon is not an exact indication of pressure, a small amount of gas can be released from the cuff in this setting if the balloon becomes very tense, and the clinician is concerned about mucosal ischemia. Alternatively, nitrous oxide can be avoided or even used in the clinical concentration to inflate the cuff. Uncuffed endotracheal tubes have generally been used in children younger than age 8 years. The narrow subglottic area is believed to limit the use of cuffed tubes in these young children. An uncuffed tube is shown in Figure 39-14 . Endotracheal tube leak pressure is a clinically useful way to fit to confirm proper selection of uncuffed tube size in children. [52] Leak should occur at 15 to 20 cm H_2O pressure. The use of cuffed tubes in neonates, infants, and children has undergone renewed scrutiny and has the advantages of reducing waste gas exposure, allowing for lower fresh gas flows, and avoiding repeat laryngoscopy without an increased incidence of croup. [53] These authors used a new formula (cuffed endotracheal tube internal diameter = age/4 + 3) to successfully predict the required cuffed tube size in 99 percent of 488 children younger than 8 years of age.

The top tube shown in Figure 39-14 is reinforced with a spiral wire to reduce kinking or collapse. These tubes are known as armored, anode, spiral embedded, or reinforced tubes, among other names. [34] They are useful when an endotracheal tube is placed in a tracheostomy or laryngectomy stoma to provide an airway. They may also be used in head and neck or neurosurgical procedures when kinking of the tube is a strong possibility. However, care must then be taken to avoid an excessive degree of neck flexion by overenthusiastic surgeons as increased peak airway pressures during positioning will not be available as a monitor for excessive flexion or head turning. The RAE tube is made in oral and nasal versions and is bent to keep the tube out of the respective surgical fields (Fig. 39-15) . It may be somewhat difficult to secure the tube tip at an appropriate tracheal level if the patient has an unusually long or short lip to midtracheal distance. The Endotrol tracheal tube (Mallinckrodt Critical Care, Glens Falls, NY) has a mechanism that allows for anterior tip displacement when an operator end loop is pulled. This is particularly useful when a nasally placed tube repeatedly enters the esophagus, and cervical movement is contraindicated. Further information on the equipment employed in airway management can be found in the monograph by Dorsch and Dorsch. [34]

Tube Size Versus Age and Sex

In adult males, an 8.0 mm ID endotracheal tube is appropriate, whereas in adult females a 7.0 mm endotracheal tube is usually suitable. Given the variation between individuals, a tube of 1 mm ID size smaller or larger may be best for an individual patient. In general, the larynx is smaller in women, and it is the glottic aperture that limits the size of endotracheal tubes in adults. As noted, uncuffed tubes have traditionally been used in young children. The sizes of uncuffed endotracheal tubes for use in children is given in Table 39-5 . Tubes of 0.5 mm ID smaller and larger sizes must be immediately available. Tube size on children can be estimated from the formula (16+ age) ÷ 4, but variation between individuals requires the availability of multiple tube sizes. If there is a suspicion of laryngeal or tracheal disease in any age group, smaller tubes should be available. A small tube (such as 6 mm ID in adults) may facilitate an otherwise difficult intubation.

Laryngoscopes

The standard rigid laryngoscope consists of a detachable blade with removable bulb that connects to a battery-containing handle. Each of the standard blades has a flange for displacing the tongue to the side and an open side for visualization of the larynx (Fig. 39-16) . Sizes range from 0 (Miller) to 1 (MacIntosh), which are the smallest blades, to 4 (Miller or MacIntosh), which are the largest. The No. 3 blades are most frequently employed for adult use, with the No. 4 blades reserved for unusual or difficult patients. The smaller blades are used in pediatric patients.

The curved blade introduced by MacIntosh is probably most popular for adult use. [54] The commonly used straight blades are the Miller, which has a curved tip, and the Wisconsin blade (and its modified forms) which has a straight tip. [55] Although straight blades may be advantageous in young children, the choice of blade in older children and adults is really a matter of familiarity and taste. The practitioner should be trained in the use of curved and straight blades, because when laryngoscopy is difficult with one type of blade, use of the other type may permit adequate laryngeal

Figure 39-15 Preformed RAE endotracheal tubes: bottom, oral; top, nasal.

visualization. For example, the straight blade may be advantageous when mouth opening is vertically limited or the larynx is anterior. It has been reported that less force and head extension is required with the Miller blade. [56] The curved blade may be advantageous when mouth opening is horizontally limited or when more room is needed to perform the instrumentation desired (e.g., use of Magill forceps, changing tubes, intubation with esophageal obturator in place). Many other types of blades have been designed but their use is too limited to warrant additional discussion.

Figure 39-16 Examples of the most frequently used detachable laryngoscope blades, which can be used interchangeably on the same handle. The uppermost blade is the straight or Jackson-Wisconsin design. The middle blade incorporates a curved distal tip (Miller). The lowermost blade is the curved or MacIntosh blade. All three blades are available in lengths appropriate for neonates and adults.

Other Equipment for Routine Use

A stylet is a rigid implement usually made of a flexible metal, which is inserted into the endotracheal tube in order to maintain a chosen shape. This will facilitate intubation when the glottis is visualized, but the tube tip cannot be directed through the glottis or when glottic visualization is minimal or absent and a semiblind or blind technique is required. The usual shape used is that of a hockey stick, but more of a curve may be required for blind or difficult intubations. A stylet is used during rapid sequence intubations or whenever the hemodynamically stressful time of laryngoscopy is best minimized (e.g., cardiac anesthesia or neuroanesthesia). The stylet should be lightly lubricated to facilitate removal and advanced into the tube without its tip protruding past the end of the tube. The stylet should be removed as the endotracheal tube tip enters the larynx to avoid undue trauma.

The Eschmann introducer (Connell Neurosurgical, Exton, Pa) is a 60-cm stylet-like device that is 5 mm in external diameter and has a 35-degree bend 2.5 cm from the end that is inserted into the trachea. Its structure is designed to provide a combination of stiffness and flexibility. It is more commonly known as the gum elastic bougie although it is neither gum, elastic, nor bougie. It is an extremely useful instrument when laryngoscopic view is poor or the tube cannot be otherwise guided into the glottis. It is also useful in limiting the degree of necessary neck movement during intubation with potential cervical spine injuries and to lessen the risk of dental damage. [57] The bent tip is directed blindly or under reduced vision into the glottic inlet and passed about 30 cm into the trachea (the "bougie" has distance markings).

Tracheal entry is marked by the sensation of clicking over the tracheal cartilages as well as the hold-up by the reduction in luminal size near the carina. [58] While keeping the laryngoscope in place, the endotracheal tube is slid over the bougie into the trachea--a 90-degree counterclockwise turn facilitates glottic passage by presenting the bevel posteriorly. A smaller tube may also be required for passage. The bougie can also be used as tube changer, although it is a bit short for this purpose. It is reasonable to practice use of the bougie in a simulated difficult laryngoscopy in which a good glottic view is progressively reduced by lessening the force on the laryngoscope. This device is an indispensable part of practice in the United Kingdom and clearly allows for a significant number of direct laryngoscopic intubations that cannot be otherwise accomplished. It is a relatively expensive piece of equipment, and care must be taken that it is not inadvertently thrown out in the course of a difficult airway situation.

Some clinicians lubricate the tip of the endotracheal tube with local anesthetic ointment. This is not necessary, and the ointment may actually increase the incidence of sore throat. [59] Furthermore, the greasy ointment may interfere with handling of the endotracheal tube. The ointment is useful for placing nasal instruments (airways, endotracheal tubes, nasogastric tubes) with oral airways and for lubricating the stylet. Some kind of adhesive tape is necessary for securing the tube after placement. Taping methods that avoid splitting the tape and that include additional reinforcing segments over the tape applied directly to the tube are most effective in preventing dislodgement. [60] Particular care in securing the tracheal tube is indicated for surgical positions in which later access is difficult (e.g., prone neurosurgical patient in head pins with table turned away from the anesthesiologist), when dislodgement is likely (e.g., cleft palate repair), and when intubation is difficult. Cloth (twill) tape is useful in trauma where blood makes adhesive tape less effective and in patients with heavy beards. It cannot be overemphasized that oxygen, bag and mask, and suction should be available for all but the most emergent intubations. An additional oxygen source connected to a manual ventilation bag should be available in the operating room to back-up and supplement the oxygen supply available from the anesthesia machine.

Techniques

In every case, the anesthesiologist must attempt to determine whether mask ventilation and intubation will be possible if the patient is anesthetized and paralyzed. The usual intubation sequence includes the administration of a rapidly acting induction agent (e.g., thiopental), the demonstration of adequate mask ventilation, and the administration of a rapidly acting neuromuscular blocking agent (e.g., succinylcholine). The introduction of sevoflurane has made inhalational induction and intubation a reasonable alternative for selected adults as well as children. [61] Preoxygenation of such routine patients is optional but strongly recommended as it provides an added margin of safety. Preoxygenation is essential when a "rapid-sequence" intubation is chosen because of a "full-stomach" situation or other propensity to aspiration (e.g., esophageal disease). In this situation, the neuromuscular blocker is administered with the induction agent, cricoid pressure (Sellick maneuver) is applied, and mask ventilation is not provided unless unsuccessful intubation necessitates it. [62]

Before routine or rapid-sequence intravenous induction, the clinician must determine whether this is the best and safest way to intubate the patient. This determination is aided by the history and physical examination, as noted previously in this chapter, in conjunction with a knowledge of those factors and syndromes that affect the airway. The critical point in the decision tree is the administration of muscle relaxants: the clinician must decide whether difficulties in ventilation are due to factors that will be improved by the advent of paralysis or if the patient should be awakened and intubated with a conscious technique. If there is sufficient doubt before induction with regard to the patient's airway, a conscious intubation with sedation and topicalization is indicated. Other clinical factors may influence the decision, including hemodynamic instability and severe intestinal obstruction, for example. In children, such an awake intubation is not generally possible except in newborns. However, a mask airway can usually be maintained in most difficult pediatric intubations.

Endotracheal Intubation During Anesthesia

Once the decision has been made that the patient can be safely anesthetized for intubation, a variety of methods can be used to achieve acceptable intubating conditions.

For intravenous induction, a rapidly acting anesthetic is first administered (Ch. 12) . This is usually thiopental or propofol, but induction drugs include other rapidly acting barbiturates (methohexital, thiamylal), ketamine, benzodiazepines, narcotics (large doses if given alone), and etomidate. The details of the pharmacology of these drugs are described in the chapters on narcotics and nonnarcotic intravenous anesthetic agents. The choice of drug depends mainly on the status of the cardiovascular system but is also influenced by central nervous system effects, effects on bronchomotor tone, presence of an allergy, pharmacokinetic differences, side effects, and the experience of the clinician. Intubation may be accomplished with intravenous or inhalational anesthetics without relaxant, but this approach also possesses difficulties such as the potential for laryngospasm and a lesser degree of muscle relaxation to improve laryngoscopic conditions. In practice, the majority of clinicians employ muscle relaxants to facilitate intubation.

The most commonly employed relaxant for intubation is succinylcholine, but the nondepolarizing relaxants in appropriate doses may be used as well. The popularity of succinylcholine has been questioned, mainly in reference to its association with masseter spasm and malignant hyperthermia. Succinylcholine may also produce the severe side effect of hyperkalemia after burns, neurologic injury, and trauma as well as increases in intraocular and intracranial pressure. The great advantage of succinylcholine is that it produces excellent intubating conditions usually within a minute, or slightly longer if pretreatment with a small (about 1/10 intubating dose) amount of nondepolarizing relaxant is employed to diminish fasciculations and postoperative throat and skeletal muscle soreness. [63] However, others believe that with this pretreatment the quality of intubating conditions is worsened. In sensitive individuals, frightening paralysis and even aspiration may occur. The rapid onset of adequate paralysis for intubation can now be duplicated with rocuronium. [64] However, succinylcholine maintains the advantage of rapid offset of action by ester hydrolysis. If the airway cannot be secured, the patient's own ventilation and airway maintenance will return much more quickly than with any of the currently available nondepolarizing relaxants. Succinylcholine is still the only relaxant with a duration of action (assuming normal pseudocholinesterase activity) that may provide for the resumption of spontaneous ventilation within a time sufficiently short that cerebral integrity can be maintained in the properly preoxygenated patient. When a muscle relaxant is to be employed in a difficult or potentially difficult airway, succinylcholine appears to be the relaxant of choice unless there are contradictions to its use, such as a risk of hyperkalemia.

The use of nondepolarizing relaxants for intubation has increased with the availability of short-acting compounds such as rocuronium. Atracurium, vecuronium and cisatracurium are alternatives that are not quite as rapid in onset as is rocuronium. [64] The effects of these agents can generally be reversed in a shorter time than those of the older, nondepolarizing relaxants. Intubating doses of curare, metocurine, and pancuronium may result in histamine release or undesirable autonomic effects. However, the pancuronium-induced tachycardia that is disadvantageous with certain cardiac disorders may be advantageous in children, with bradycardia, or in massive trauma. In addition, an intubating dose of pancuronium may be cost-effective when relaxation will be required for several hours after intubation.

Nasal Versus Oral Route

In the operating room, nasal intubation is performed when surgery in the oral cavity or on the mandible is facilitated by an unobstructed view. If the mouth is to be wired or banded shut after surgery, a nasal tube must be used. Contraindications to nasal intubation include coagulopathy, severe intranasal disorder, basilar skull fracture, and presence of a cerebrospinal fluid leak. There is at least one report of an endotracheal tube entering the cranium through a nasal fracture. [65] If an oral tube is surgically unacceptable, and nasal intubation is contraindicated, the anesthesiologist must discuss the relative risks of tracheostomy and oral and nasal intubation in that patient with the surgeon to arrive at an acceptable compromise.

Nasal intubation is also used in the operating room in difficult airway situations. These include blind or fiberoptic intubation in the topicalized, sedated patient. Nasal intubation may be chosen because direct laryngoscopy is impossible; it may be quicker and more comfortable than oral intubation in the topicalized, sedated patient. Details on nasal intubations follow in the appropriate sections. Nasal intubation (unlike oral intubation) may produce a bacteremia, and appropriate endocarditis prophylaxis should therefore precede it. [66] [67]

Oral Endotracheal Intubation

This is the usual method of intubation in the operating room. In adults, a rapidly acting anesthetic is usually given intravenously, mask ventilation is ensured, and a muscle relaxant is administered to facilitate laryngoscopy. In children, mask, rectal, and intramuscular inductions are frequently employed. Intubation may be performed with anesthesia and no relaxant, but a deep level of anesthesia must be achieved to avoid unforgiving reflexes such as laryngospasm. Unless there is a

contraindication, the head is maintained in the classic "sniffing position" to align the oral, pharyngeal, and laryngeal axes (see Fig. 39-3) . In adults, a small foam pillow or several folded sheets are often employed to maintain flexion in the lower cervical spine. The Popitz "sniffing position" pillow is an excellent way to establish a satisfactory position for both mask ventilation and endotracheal intubation in the adult patient (Fig. 39-17) . It is important to use a head support that, unlike a big, soft pillow, does not allow the head to sink down into it. The laryngoscope is held in the left hand while the fingers of the right hand are used to gently open the mouth. The clinician should wear gloves because of the likely entry of fingers into the patient's mouth. The laryngoscope blade is gently inserted into the right side of the patient's mouth to avoid the incisor teeth and to enable the flange of the blade to keep the tongue to the left. Pressure on the teeth, gums, or lips is avoided. A mouth piece or maxillary teeth protector may be employed to lessen the likelihood of injury to those teeth. A full-fingered grip on the laryngoscope handle rather than a two-fingered hold at the junction of the handle and blade may provide a mechanical advantage that helps in difficult adult exposures.

Figure 39-17 A volunteer positioned on the Popitz pillow demonstrating cervical flexion and a small degree of atlanto-occipital extension (Dermacare, Louisville, Ky). The flexion serves to align the laryngeal and pharyngeal axes. Further extension of the head results in the true "sniffing" position.

After visualization of the epiglottis, the curved blade (e.g., MacIntosh) is inserted into the vallecula (the space between the tongue and epiglottis), and the laryngoscope is pulled forward and upward (Fig. 39-18) to expose the glottis. It is important to recognize structures sequentially as the blade is inserted and not just to insert deeply, pull, and hope for the best. The endotracheal tube is inserted into the right side of the mouth and inserted between the open vocal cords under direct vision (Fig. 39-19) (Figure Not Available) . An assistant may help by pulling the right side of the mouth open to improve vision (especially with the Miller blade). Difficulties in visualization may be due to head position, a blade that is too far advanced or not far enough advanced, or a reluctance on the part of the novice laryngoscopist to apply adequate (but gentle) upward force.

A straight blade is used in somewhat similar fashion except that it is usually advanced beyond the epiglottis, so that

Figure 39-18 Schematic diagram depicting proper position of the laryngoscope blade during direct laryngoscopy for exposure of the glottic opening. (A) The distal end of the curved blade is advanced into the space between the base of the tongue and pharyngeal surface of the epiglottis (vallecula). (B) The distal end of the straight blade (Jackson-Wisconsin or Miller) is advanced beneath the laryngeal surface of the epiglottis. Regardless of blade design, forward and upward movement exerted along the axis of the laryngoscope blade (arrows) serves to elevate the epiglottis and expose the glottic opening.

Figure 39-19 (Figure Not Available) Schematic view of glottic opening during direct laryngoscopy when the epiglottis is elevated with a curved or straight laryngoscope blade. The glottic opening is recognized by its triangular shape and the pale white vocal cords. *(From Stoelting RK and Miller RD: Basics of Anesthesia, 3rd ed. New York, Churchill Livingstone, 1994)*

the epiglottis is included in the structures lifted up by the blade (see Fig. 39-18) . Gentle dorsad pressure on the cricoid or thyroid cartilage may bring a nonvisualized larynx into view. The BURP maneuver, which includes backward, upward, and right lateral displacement of the thyroid cartilage, has been shown to be effective in improving the grade of glottic exposure. [68] As noted, the choice of blade is a matter of the clinician's preference. It is not established that one or the other blade causes less of a stimulus to airway reflexes and cardiovascular response. It is traditional but in no way mandatory for the novice to start with a curved blade. Because the peculiar anatomy of an individual patient may allow successful laryngoscopy with one blade but not the other, skill should be developed in the use of both blade types. Turning the head to the left and inserting a straight blade lateral to the molars may improve visualization on occasion by displacing the tongue and affording a more direct line of sight to the larynx. A common cause of inadequate visualization is insufficient flexion of the lower cervical spine that can be augmented while mask ventilation is continued.

In adult males, the tube is generally inserted to about 23 cm at the lips to position the tube, with the tip an appropriate

Figure 39-20 (Figure Not Available) Diagrammatic representation of key distances relating to endotracheal tube position *(From Stone and Bogdonoff [171])*

4 cm above the carina. For adult females, the distance is about 21 cm. Tubes inserted too far will cause endobronchial (usually right) intubation whereas tubes that are not in far enough may be difficult to seal because of cuff protrusion through the larynx and will be more at risk for accidental extubation (Fig. 39-20) (Figure Not Available) . Exact placement of the tube requires a fiberoptic bronchoscope, but this is not usually necessary. Endobronchial intubation is easier to remedy than accidental extubation. In children, the distance (cm) at the lips can be estimated from the formula: 12 + (age/2). In this age of laparoscopic surgery, be aware that abdominal insufflation can shift the carina cephalad and convert an acceptable location to an endobronchial one. [69]

A rapid-sequence induction is employed when the patient is at particular risk for aspiration and there is reasonable certainty that intubation should not be difficult (Table 39-6) . If there is sufficient doubt about the ability to intubate the patient in this setting, an intubation in the conscious patient with judicious use of topical anesthesia with or without sedation should be strongly considered. Before a rapid-sequence induction, the patient is preoxygenated. Although healthy lungs may be largely denitrogenated with four vital capacity breaths, the longer time constants of diseased or aged lungs require a longer period of preoxygenation to ensure adequate

TABLE 39-6 -- Patients at Risk of Aspiration of Gastric Contents

Full stomach (<8-h fast)
Trauma
Intra-abdominal pathology
Intestinal obstruction, inflammation
Gastric paresis (drugs, diabetes, uremia, infection)
Esophageal disease
Symptomatic reflux
Motility disorders
Pregnancy
Obesity
Uncertainty about intake of food or drink

nitrogen washout. [70] End-tidal nitrogen concentration, if available, can be used to assess nitrogen washout more precisely if a tight mask seal can be established. When time is critical, as in emergency cesarean section, four vital capacity breaths are adequate. [71] After preoxygenation, an intravenous anesthetic and muscle relaxant are administered together. It is the authors' practice to locate the cricoid cartilage in the conscious patient but not apply pressure until the patient is unconscious. This is because the proper amount of cricoid pressure is very uncomfortable in the awake patient, may provoke vomiting and obstruct the airway, is less likely to be effective in the patient before paralysis inhibits active vomiting, and has been shown to lower esophageal sphincter tone. [72] The downward force on the cricoid cartilage required to occlude the esophagus appears to be approximately 30 to 40 N, about the force of an 8- to 9-lb weight. [73] This may prevent regurgitation if applied properly, and because the force of vomiting is blunted by the muscle relaxant, the force should greatly decrease the risk of aspiration. [74] Interestingly, there have been no studies proving that cricoid pressure is truly beneficial. [73] Incorrectly applied pressure will not protect the patient from aspiration because only the

cricoid forms a complete ring that will occlude the esophagus. [75] When intubation is difficult, cephalad (in conjunction with dorsal) cricoid pressure may aid visualization. [76] Laryngoscopy and intubation in this setting are generally performed without any preceding manual ventilation, if possible. If intubation is not possible, mask ventilation should be provided while cricoid pressure continues. It is critical that the cricoid pressure be applied correctly so that it does not actually impede visualization of the glottis or passage of the tube. If glottic visualization or endotracheal tube passage is impaired, pressure may need to be let up or entirely released to see if it is contributing to the problem. In addition to preventing regurgitation, cricoid pressure decreases the flow of gas to the stomach, minimizing gastric distention that can impede ventilation as well as predisposing to regurgitation. Pretreatment with an anticholinergic is recommended to minimize secretions that may impair visualization during a rapid-sequence intubation. Pharmacologic approaches to the patient at risk from aspiration are discussed in Chapters 12 and 57 .

Special Considerations

Laryngoscopy and intubation are powerful noxious stimuli, and the response may have deleterious respiratory, neurologic, or cardiovascular effects. Furthermore, deeper levels of anesthesia are required to blunt the response to laryngoscopy and intubation than the response to surgical incision. [77] [78] When planning the anesthetic induction, these effects must be blunted to whatever degree is possible, especially if the patient falls into a high-risk population (e.g., with coronary artery disease, asthma, elevated intracranial pressure, cerebral aneurysm, and so on).

Nasal Endotracheal Intubation

When nasal intubation is chosen solely for purposes of surgical convenience, anesthesia may be induced before intubation. A vasoconstrictor should be applied before nasal

instrumentation. Cocaine (4% up to 1.5 mg/kg) can be used but phenylephrine (¼-1% nose drops) is more readily available and less toxic. After anesthesia is induced and mask ventilation is established, the endotracheal tube is introduced into the nose in a plane that is roughly perpendicular to the face. The patient may be allowed to breathe spontaneously to facilitate blind intubation. In this case, the tube is inserted until maximum breath sounds are heard (usually about 14-16 cm in adults), implying that the tube tip is just above the glottis. The tube is then inserted into the glottis during inspiration. Some clinicians choose to administer CO_2 or doxapram to induce hyperpnea and facilitate intubation during spontaneous ventilation, but this is not commonly done currently. Because entry into the glottis is not seen directly, it is essential to have capnographic or bronchoscopic confirmation of endotracheal placement because, at times, all the indirect signs of intubation may be misleading. Anesthetized blind nasal intubation may also be attempted in the apneic, paralyzed patient, but in this case there are no spontaneous breath sounds to aid placement, which is guided by external observation for tip location in the neck.

If the tube does not enter the glottis, the patient's head may be extended, flexed, or turned to guide the tip (if not contraindicated by spinal bony disease). If the tube tip is felt anteriorly, flexion may help; if the tip is felt beside the larynx (in the pyriform sinus), turning the tube tip away from that side may help. Most of the time, the tube enters the esophagus, and extension of the head will help. If the trachea cannot be blindly intubated, the patient can be intubated with guidance under direct vision (after appropriate mask ventilation). In this situation, a curved laryngoscope blade appears to provide the greatest amount of space for maneuvering. The tube is inserted into the nose, and direct laryngoscopy is performed in the usual fashion. Under such direct vision, the laryngoscopist may be able to direct the tip into the glottis. If not, Magill forceps may be used to carefully grasp the tube while avoiding trauma to the cuff. The tube can then be directed into the glottis, often with the help of an assistant who can push on the nasal end of the tube. If the glottis cannot be visualized by direct laryngoscopy, the Magill forceps can still be used to attempt to guide the tip blindly into the area of the glottis. Excessive force on the tube should be avoided as delicate laryngeal structures can be damaged or false passages created.

An anterior curve in the endotracheal tube may help in blind nasotracheal intubation. This can be accomplished by putting a stylet in the tube (removed before use) with the desired C-shape or by placing the tube tip in the 15-mm connector to form a circle. The time that the tube holds the curve can be lengthened by placing the curved tube in a refrigerator or freezer for some time before the case. An Endotrol endotracheal tube, which has an operator-end loop that directs the tube tip anteriorly when pulled, may be used. Another technique that utilizes cuff inflation has been described to further aid blind intubation. [79] Breath sounds must be audible, so breathing must be spontaneous. When breath sounds are of maximal intensity, the endotracheal tube cuff is inflated with 15 mL of air, which tends to direct the tip anteriorly. The air is released from the cuff as the tube is passed (2 cm) through the glottis to avoid damage to the cords. The use of a stylet has also been suggested in difficult nasal intubations. [80] After the endotracheal tube is placed so that its tip should be just above the glottis, a stylet in a C-shape is carefully inserted into the endotracheal tube. The tube is then slid off the stylet, which directs it more anteriorly and (ideally) into the glottis.

When Intubation Fails

Every practitioner, no matter how skilled, will encounter patients who are unexpectedly difficult to intubate. The induction of anesthesia should be approached with this possibility in mind so that a clear plan of action can be pursued. The prevalence of difficult laryngoscopy appears to be approximately 1 to 4 percent and is higher in the obstetric than the nonobstetric population. [23] The degree of glottic exposure as described by Cormack and Lehane allows interobserver comparison of the difficulty of laryngoscopy (Fig. 39-21) (Figure Not Available) . Patients of grade 4 difficulty and many patients of grade 3 view are likely to present difficulties and may even be impossible to intubate. In addition to difficult visualization,

Figure 39-21 (Figure Not Available) Grades of difficulty in laryngoscopy ranging from grade 1, no difficulty; grade 2, only posterior extremity of glottis visible; grade 3, only epiglottis seen; grade 4, no recognizable structures. *(From Cormack RS, Lehane J: Difficult tracheal intubation in obstetrics. Anaesthesia 39:1105, 1984)*

Figure 39-22 (Figure Not Available) Difficult airway algorithm developed by ASA Task Force on Guidelines for Difficult Airway Management *(Modified from American Society of Anesthesiologists Task Force on Management of the Difficult Airway: Practice guidelines for the management of the difficult airway. Anesthesiology 78:597, 1993)*

other pathologies, including epiglottitis, laryngeal or tracheal stenosis, and luminal tumors, may make translaryngeal passage of the endotracheal tube difficult.

When an initial attempt at intubation fails, mask ventilation should be resumed while the situation is reassessed. As long as mask ventilation can be maintained, the problem is not emergent. Cricoid pressure should be maintained when a full stomach is suspected. Head position and laryngoscopy technique need to be reexamined. The laryngoscopist may wish to exchange a curved for a straight blade (or vice versa). A longer MacIntosh blade (#4) can be useful in this situation. The Miller No. 4 blade is wider but not much longer than the No. 3 model. This width may help keep the tongue out of the visual field and provide a more effective fulcrum for displacement of the tongue muscle. If repeated laryngoscopy by an experienced practitioner is unsuccessful, a decision-branch point is reached if short-acting drugs (thiopental, inhalational anesthetic, succinylcholine) have been used: the patient may be allowed to awaken for an attempt at intubation with topical anesthesia, or the case may even be postponed if nonemergent. If long-acting drugs have been used (high-dose narcotic, nondepolarizing relaxant), mask ventilation must obviously be maintained until reversal is possible. A task force of the American Society of Anesthesiologists has developed an algorithm for the difficult airway, which is a useful guide in this setting (Fig. 39-22) (Figure Not Available) . Benumof has incorporated previously approved ideas and concepts into one flow diagram that some readers may find preferable (Fig. 39-23) (Figure Not Available) . He has defined a best attempt at laryngoscopy as being performed by a laryngoscopist with at least 3 years' experience, optimal positioning, use of external laryngeal manipulation, and change of blade type and length one time each. [35] As he also points out, a difficult laryngoscopy will likely be readily apparent to a skilled practitioner on the first attempt.

If intubation cannot be accomplished, and the decision has been made to keep the patient anesthetized for intubation (or long-acting drugs have been used), a variety of other techniques can be utilized. First, help should be obtained, if possible. The assistant may provide laryngeal displacement such as a BURP maneuver, which is likely to improve glottic exposure. The assistant also provides a fresh pair of hands for mask ventilation and laryngoscopy and an objective viewpoint in what may be a rapidly deteriorating situation. An anticholinergic should be administered to reduce the secretions that often accumulate in this situation. If the arytenoids or epiglottis

can be visualized, the gum elastic bougie represents an effective approach to intubation. [81] Currently, this is

Figure 39-23 (Figure Not Available) Single-flow diagram version of the ASA Difficult Airway Algorithm. +Always consider calling for help (e.g., technical, medical, surgical) when difficulty with mask ventilation and/or tracheal intubation is encountered. ++Consider the need to preserve spontaneous ventilation. *Nonsurgical tracheal intubation choices consist of laryngoscopy with a rigid laryngoscope blade (many types), blind orotracheal or nasotracheal intubation, fiberoptic/stylet technique, retrograde technique, illuminating stylet, rigid bronchoscope, and percutaneous dilational treacheal entry. See Benumof [38] for a complete discussion of these TI choices. *(Modified from Benumof [43])*

the next approach to this situation at the authors' institution. The elastic gum bougie is less effective in grade 4 views, but an attempt at entering the glottis can still be made. If a skilled bronchoscopist is available and mask ventilation is possible, fiberoptic bronchoscopy is probably best attempted immediately, before the field is obscured with blood and edema. However, this is not an ideal setting for the novice bronchoscopist. Other options include blind nasotracheal intubation or blind orotracheal intubation employing direct laryngoscopy with a curved blade and an endotracheal tube directed anteriorly with a stylet. The use of a lighted stylet or retrograde intubation may be appropriate and are described later. The use of the LMA as a conduit for blind, bougie-guided, or fiberoptic intubation has been discussed. [43] Selected cases can proceed with an LMA or Combitube as airways. An LMA can also be inserted simply to facilitate ventilation until the effects of relaxants and other agents wear off. Other clinicians have suggested the Bullard laryngoscope (Circon ACMI, Stamford, Conn) or the Augustine introducer (Augustine Medical, Eden Prairie, Minn). [82] [83] If multiple attempts fail and the case is not of an emergent nature, it is best to simply ventilate the patient until drugs can be reversed, because edema and blood may produce serious airway obstruction, preventing even mask ventilation. A patient for elective surgery who experiences intermittent laryngospasm and serious dysrhythmias is also a poor candidate for continued attempts at intubation.

When Mask Ventilation and Intubation Are Impossible

The patient who is truly impossible to mask-ventilate (two-handed mask ventilation with oral and nasal airways, complete forward mandibular dislocation, and bag ventilation by an assistant) or intubate presents a brain- and life-threatening emergency that has been estimated to occur 1 in 10,000 anesthetics. [84] As in so many instances in medicine, the best treatment is prevention: the clinician must always carefully evaluate the airway to determine the safest plan for intubation and extubation. [85] In the patient who has been thoroughly denitrogenated, there should be sufficient time to institute one of the following interventions before serious oxygen desaturation and consequent hemodynamic deterioration occur. In reality, one is often dealing with a severely hypoxic patient who has suffered or is near to cardiac arrest. It is critical to institute one of the following interventions *before* irreversible cardiac arrest or brain damage has occurred. If only short-acting drugs have been used (succinylcholine, thiopental, lidocaine, etc.) and the patient has been adequately preoxygenated, adequate spontaneous ventilation may resume before further intervention is required.

The LMA has become the next intervention in this situation; the Combitube is a reasonable alternative, particularly if aspiration is a major concern (Fig. 39-24) (Figure Not Available) . If one of these supraglottic devices does not produce adequate gas exchange quickly, transtracheal jet ventilation (TTJV) should be instituted. In TTJV, a 14- or 16-g cannula is inserted through the cricothyroid membrane and attached to a high-pressure oxygen source via a low-compliance circuit (Fig. 39-25) (Figure Not Available) . The review of Benumof and Scheller [84] demonstrates that TTJV can provide adequate ventilation as well as oxygenation and serves as a valuable source for those planning to assemble an acceptable TTJV system. Perhaps the most readily available (and least expensive) system employs the fresh gas outlet and oxygen flush valve of the anesthesia machine as the high pressure oxygen source. A 5-mm ID endotracheal tube adapter attached to oxygen supply tubing is

Figure 39-24 (Figure Not Available) Role of the LMA in the ASA Difficult Airway Algorithm. *(Modified from Benumof [43])*

Figure 39-25 (Figure Not Available) Anatomy of the cricothyroid membrane *(Courtesy of Cook Critical Care, Bloomington, In.)*

inserted into the fresh gas outlet. A three-way stopcock (of large bore, if possible) is attached to the other end of the tubing and then connected to the translaryngeal cannula (Fig. 39-26) . The three-way stopcock may help in preventing excessive pressure build-up by releasing the aperture to air between jet inspirations. A much less effective but more readily available system includes use of the standard anesthesia circuit or a self-inflating reservoir bag attached to the translaryngeal cannula (via a 3-mm ID endotracheal tube adapter placed directly into the cannula or an 8-mm ID endotracheal tube adapter placed into the wide end of a 3-mL plungerless syringe, then connected to the cannula). [84] Successful TTJV should be followed up with provision of a definitive airway by tracheostomy, endotracheal intubation, or wake-up and resumption of the normal airway. The most serious complications of TTJV involve some form of hyperinflation due to inadequate venting of inspired gases in the presence of complete or nearly complete upper airway obstruction. This may result in barotrauma and/or diminished

Figure 39-26 Transtracheal jet ventilation apparatus assembled from components generally available in the operating room (5.0-mm ID endotracheal tube adapter, oxygen tubing, three-way stopcock). The connections can be banded for further security.

cardiac output in the context of an immediately life-threatening problem.

Although a classic tracheostomy can, in general, not be performed quickly enough in the "cannot ventilate/intubate" situation, cricothyroidotomy can be employed to insert a small endotracheal or tracheostomy tube. A surgical blade (such as #11) on a handle and a Kelly clamp for spreading the incision are required. Kits with all the required materials are commercially available (Melker emergency cricothyrotomy catheter set, Cook Critical Care, Bloomington, Ind). Although an experienced surgeon is the best choice to perform a cricothyroidotomy, the anesthesiologist must be prepared to do so if TTJV is unavailable or unsuccessful. Neither therapy, however, will relieve obstruction that occurs below the first few tracheal rings. Complications of cricothyroidotomy include misplaced tubes early and hoarseness and subglottic stenosis as later problems. [86]

Difficult-Airway Cart

The ASA Task Force on Difficult Airway Management has made the reasonable suggestion that a portable storage unit for a variety of intubation aids be readily available. Suggested equipment for this is listed in Table 39-7 (Table Not Available) . The bronchoscope cart itself is a practical choice for storage of these additional devices, which may be needed urgently on rare occasions.

Conscious ("Awake") Intubation

While emergency nonanesthetized intubations outside the operating room may be performed with minimal topical anesthesia and no sedation, the term "awake" intubation applied to nonanesthetized intubations in the operating room is usually something of a misnomer. After appropriate sedation, topical anesthesia, and nerve blocks, such intubations can be performed with minimal discomfort in the conscious patient. Conscious intubation is performed when the clinician

TABLE 39-7 -- Suggested Contents of the Portable Storage Unit for Difficult Airway Management

(Not Available)

Modified from Caplan RA (Task Force Chairman): Ameriacn society of Anesthesiologists Guidelines for Difficulty Airway Management, 1992

believes that it is the safest way to insert an endotracheal tube. Indications include a history of difficult intubation, findings on history or physical examination that can

make intubation difficult, and severe risk for aspiration or hemodynamic instability. The reasons for conscious intubation should be explained to the patient as time allows and documented in the chart. The primary consideration of safety should be emphasized. At times, surgeons (and other physicians) may be unhappy about their patients being subjected to such procedures because of unwarranted fear of patient discomfort and the time required. If the anesthesiologist has concluded that such intubation is indicated, the demands of such individuals must not take precedence over patient safety. The reasons for conscious intubation should be emphasized to the surgeon as well as to the patient because airway disaster, poor outcome, and litigation may follow airway mismanagement. In the American Society of Anesthesiologists' closed claims study, adverse respiratory events including inadequate ventilation, esophageal intubation, and difficult tracheal intubation form the largest single class of injury. [87] [88]

Drugs for Sedation

Narcotic analgesics are the key to facilitating conscious intubation. They afford mild sedation, analgesia, and reduction of airway reactivity that may result in cough and bronchospasm. Any narcotic may be used, but the overall characteristics of fentanyl have made it the most useful in such procedures. A lag in onset (hysteresis) of about 5 minutes for the full effect of fentanyl should be kept in mind as incremental doses of the drug are administered. [89] Dose requirements also vary greatly between individuals (25-500 mug), and thus the drug should be administered slowly in small increments. The effect (or lack thereof) may not be apparent until the laryngoscope is inserted. Perhaps the greatest advantage of narcotics, especially fentanyl, is the ease of reversibility by naloxone should an undesired degree of respiratory depression result. Such patients may simply need to be reminded to breathe in order to ventilate adequately. If awake intubation is being performed because of a severe risk of aspiration, narcotics (and other intravenous sedatives) must be used sparingly.

In order to afford more sedation than a moderate dose of narcotics provides, a second drug is usually given. Droperidol (Inapsine) is a butyrophenone that supplies adequate sedation without adding to narcotic-induced respiratory depression. [90] The drug is contraindicated in patients with Parkinson's disease because it blocks dopamine receptors and may produce a dystonic reaction. Doses of 1.25-5.0 mg intravenously are usually adequate, although doses up to 10 mg can be used. The latter doses may be associated with bizarre side effects such as akathisia and dysphoria and a prolonged state of sedation (up to 24 hours). To maximize patient comfort, it is best to administer a small dose of fentanyl before droperidol is given.

Other clinicians prefer to add a benzodiazepine to the narcotic effect. Midazolam (Versed), diazepam (Valium), or lorazepam (Ativan) may all be used, but midazolam is probably the most popular at present because of its relatively rapid onset and offset of action as well as the production of anterograde amnesia. The benzodiazepines should be administered slowly in small doses because their effect on consciousness, respiration, and cardiovascular status in individuals is unpredictable. Even 0.5 mg may produce adequate amnesia in some adults. Unlike droperidol, benzodiazepines result in increased respiratory depression in the presence of narcotics, which is usually manifest by apneic spells. [91] Flumazenil, a specific reversal agent, is now available clinically. The principal disadvantage of using benzodiazepines may be the profound decreased level of consciousness that results in loss of verbal contact with the patient, who in such situations must be able to respond to commands, especially to breathe. In the frail elderly patient, intravenous diphenhydramine (Benadryl) in doses of 12.5 mg may provide good supplemental sedation to narcotics without excessive respiratory depression or adverse mental effects.

Anticholinergicsical Anesthesia

Before any anticipated difficult intubation, a dose of anticholinergic, such as glycopyrrolate (Robinul) 0.2 mg intravenously, is strongly advised. If bronchospasm is anticipated, larger doses (0.4-1.0 mg IV) are recommended to blunt the response to airway instrumentation. Besides improving visualization during laryngoscopy by reducing secretions, topical solutions of local anesthetics will be less diluted and less likely to be washed off the desired site of application. The use of anticholinergics is reasonable for general anesthesia in any smoker, for surgical positions in which suctioning will be difficult, for surgical positions in which secretions could loosen securing tape and predispose to tube dislodgement, and for surgery that involves the airway. For patients in whom succinylcholine is contraindicated, the decreased production of secretions occurring after prophylactic anticholinergics may lessen the chance of severe postextubation laryngospasm, which is especially difficult to treat without succinylcholine.

Anesthesia of the nares and nasopharynx should be accompanied by vasoconstriction to widen the available passage and decrease bleeding. Cocaine (4%) may be used up to 1.5 mg/kg. It is far more convenient and reasonably effective to use a lidocaine/phenylephrine combination. The phenylephrine may be applied first as 1/4 to 1 percent nose drops or the solutions may be mixed and applied together (4 percent lidocaine and 1 percent phenylephrine in a 3:1 combination to yield a 3 percent lidocaine/0.25 percent phenylephrine solution). [92] To anesthetize the sensitive nasopharynx, the solution may be instilled through a 16- or 18-gauge plastic catheter inserted deeply into the nose or on long cotton-tipped applicators that are slowly inserted until they reach the posterior wall of the nasopharynx. If three such applicators can be inserted, a 7.0-mm ID endotracheal tube will usually pass through that nostril. The applicators can be gently moved anteriorly and posteriorly to contact the entire mucosa, and additional solution can be dripped in along the wooden sticks as necessary. The total dose of lidocaine should be carefully controlled to avoid toxicity, particularly if additional lidocaine application is planned. Other practitioners topicalize the nares using progressively larger-sized soft nasal airways coated with 2 percent lidocaine ointment. Finally, the nasal endotracheal tube can be coated

with 2 percent lidocaine ointment to facilitate passage and give further analgesia.

The tongue and oropharynx can be anesthetized with 10 percent lidocaine spray, which is placed progressively further into the pharynx using the laryngoscope blade or a tongue depressor to keep the tongue out of the way. The cooperative patient can also gargle and expectorate viscous lidocaine to produce topical anesthesia of the tongue and pharynx. Once there is sufficient topicalization to allow the insertion of an oral airway, the long applicator adaptor for 10 percent lidocaine spray can be blindly placed through the airway to spray local anesthetic directly onto the supraglottic and glottic structures. Nebulization of 5 mL of 4 percent lidocaine can also be employed. [93]

The larynx can be sprayed with additional lidocaine directly onto the visualized glottis. If a laryngotracheal applicator (LTA) kit is to be used, it can be inserted with some holes below the vocal cords and some above. This will anesthetize the supraglottic area (including epiglottis) as well as the trachea when the lidocaine is injected. The LTA kit has also been used as an intubation guide with the applicator inserted through the Murphy eye and the endotracheal tube oriented with the concavity to the left. [94] The trachea can also be anesthetized with a transtracheal (or more correctly, translaryngeal) application of 2 to 3 mL of 2 percent lidocaine. A 23-gauge needle is inserted perpendicularly through the cricothyroid membrane in the midline, air is aspirated to ascertain the location of the needle tip, the lidocaine is quickly injected, and the needle is removed (see Fig. 39-25) (Figure Not Available) . This may cause vigorous coughing in some patients, but coughing provides excellent spread of the anesthetic in the larynx below the vocal cords. Other practitioners insert a 14-gauge or 16-gauge intravenous catheter through the cricoid membrane and remove the metal inner cannula before injecting local anesthesia. The catheter can be left in place to provide TTJV or access for retrograde intubation. The topicalization produced in the larynx and trachea is suitable for the use of the elastic gum bougie as well as a direct attempt at intubation. Contraindications to such injections include coagulopathy and local disorders such as tumor masses.

The use of topical anesthesia of the airway in the presence of a full stomach should be approached with common sense. The nose, tongue, and oropharynx can be safely anesthetized, but similar anesthesia in the larynx and trachea may diminish airway protection to unacceptable levels. When the cords are visualized, some clinicians may choose to spray the laryngotracheal structures with an LTA kit and then immediately follow with insertion of the tube. Others believe that even such a brief period of susceptibility to aspiration is unacceptable.

Nerve Blocks

The glossopharyngeal block blocks the sensory input from the areas of the posterior tongue innervated by that cranial nerve (Ch. 43) . A 22-gauge spinal needle is used to inject 5 mL of 1 percent lidocaine with epinephrine into the area where the base of the tongue apposes the palatoglossal fold (Fig. 39-27) (Figure Not Available) . The needle should be aspirated to avoid intravascular injections. The block is acceptable with a full stomach and does not appear to affect airway integrity when performed bilaterally. The block is intended to provide more comfortable laryngoscopy with lower doses of injective drugs. However, a study reported that viscous lidocaine

Figure 39-27 (Figure Not Available) Area of needle insertion for glossopharyngeal block. *(Courtesy of Andrew Woods, M.D., and Christopher Lander, M.D.)*

swish and gargle folowed by spray application of 10 percent lidocaine is as effective as glossopharyngeal block without producing the prolonged local discomfort seen in some individuals after the block. [95]

The superior laryngeal nerve innervates the epiglottis, aryepiglottic folds, and the laryngeal structures down to the false cords. The superior laryngeal nerve (SLN) may be blocked by an external approach using a 23-gauge needle and 3-mL syringe to inject 2 to 3 mL of 1 percent lidocaine between the greater cornu of the hyoid bone and the thyroid cartilage. This block is contraindicated by coagulopathy, a local pathologic problem, or full stomach. The SLN may also be blocked by the application (for about a minute per side) of lidocaine-soaked gauze pads with Krause forceps held in the pyriform fossa. This latter technique is frequently performed by otolaryngologists prior to laryngoscopy.

Choice of Technique

The choice of technique for conscious intubation depends on preference for oral or nasal tube placement, experience, and availability of equipment. If one technique fails, another is usually tried. All anesthesiologists should develop skill with conscious oral intubation with direct laryngoscopy. Blind nasal intubation that avoids the discomfort of laryngoscopy is equally important to learn. If fiberoptic bronchoscopy is an option, it should be performed reasonably early in the sequence because blood, secretions, and edema can make its use extremely difficult.

Conscious Oral Intubation with Direct Laryngoscopy

Preparation for conscious oral intubation involves use of the drying agents, sedation, topical anesthesia, and/or nerve blocks previously discussed. Topical application of anesthesia to oropharynx and tongue without glossopharyngeal nerve blocks may allow for laryngoscopic visualization and further anesthesia of the glottis and the trachea via an LTA kit or similar device. The laryngoscope must be inserted gently but with firm manipulation when required. The requirement for sedation, topicalization, and nerve blocks varies greatly among patients so that care must be taken to avoid excessive doses while providing acceptable comfort levels. The use of the elastic gum bougie may improve comfort by reducing the force required to produce acceptable glottic exposure. Superior laryngeal blocks and transtracheal anesthesia are not generally used if there is a concern for aspiration of gastric contents.

To supplement the commonly used laryngoscope blades, a variety of ingenious blades have been devised to cope with the difficult intubation. In addition to a variety of shapes, mirrors (Siker blade) and prisms (Huffman, Bellhouse) have been adapted for looking literally "around the corner." [96] [97] The Howland lock fits between the blade and handle, changing the angle of their relationship. In very obese patients, the laryngoscope may need to be inserted by turning the handle to the right, inserting the blade and then attaching the handle, or by using a short laryngoscope handle. [98] While some clinicians take an "awake look" and then anesthetize the patient for intubation, visualization of the glottis in the conscious patient does not guarantee similar visualization after anesthesia and/or paralysis as muscle relaxation causes the larynx to shift anteriorly. [99]

Conscious Oral Intubation with Indirect Laryngoscopy

Unlike the flexible fiberoptics to be discussed, a rigid stylet fiberoptic laryngoscope is available for oral intubation only. The device is used to locate the glottis, but the stylet tip does not actually enter the larynx. [34] The Bullard laryngoscope, an instrument for indirect laryngoscopy, is inserted much like a routine laryngoscope. The handle is then rotated from horizontal to vertical as the blade slides around the tongue. The endotracheal tube may be passed from the intubating attachment of the laryngoscope, or a tube containing a stylet in the shape of the laryngoscope may be used. [83]

Blind Oral Intubation

When there is minimal visualization of laryngeal structures during direct laryngoscopy, a blind or semiblind technique for intubation may be attempted in the conscious or anesthetized patient. A MacIntosh blade is helpful to pull up the tongue and thereby open up and maintain the airway. An endotracheal tube with a curved stylet is then guided in the presumed direction of the glottis where the tube is then slid off, ideally, into the trachea. Spontaneous ventilation is helpful as breath sounds will guide the way to the larynx. After a blind intubation, confirmation of endotracheal intubation with capnometry and/or bronchoscopy is advisable. The use of the elastic gum bougie has already been discussed. [100] In order to change the direction of the tube tip, stylets with a tip-moving device have been designed [101] (Flexguide, Scientific Sales International, Kalamazoo, Mich). The Magill forceps may also be used to guide the tube tip in the desired direction. Even the clinician's fingers may be used in a blind, tactile technique. The first and second fingers of the nondominant hand are placed on either side of the tip of the epiglottis to guide the tube. The patient must be cooperative lest the anesthetist risk getting bitten. The Augustine guide includes a curved positioning blade with a guide channel that fits in the vallecula. The tip is then moved anteriorly to expose the vocal cords, and an endotracheal tube is slid over a flexible stylet that has been passed into the trachea after confirmation of easy air aspiration. [82]

Stylets with lights at the tip ("lightwand" stylet) are advantageous in that the stylet tip can be guided by observation of the light's movement under the skin (Flexilum, Concept Corp., Clearwater Fla; Tubestat, Xomed-treace, Jacksonville, Fla). These are useful when mouth opening or neck movement is limited. The room must usually be quite dark to see the light adequately. When the tube tip is correctly positioned just above the vocal cords in the midline, a distinct glow is seen in the anterior neck, and the tube is slid off into the trachea. [102] [103] To avoid the reported complication of disruption of the light bulb, the stylet should be well lubricated,

---

removed gently, used a single time, and not used nasally (unless manufactured for nasal use). [104] A new lightwand device (Trachlight, Laerdal Medical, Armonk, NY) has been studied and has the potential advantages of a brighter light source and a flexible wand to facilitate tracheal entry. [105]

Nasal Intubation in a Conscious Patient

Conscious nasal intubation is useful for urgent intubations outside the operating room when mouth opening or neck movement is limited or prohibited and whenever a nasal endotracheal tube is required but anesthesia and/or paralysis are thought to be too risky. Topical anesthesia of the nose and oropharynx as described is important as well as an appropriate amount of sedation. The supraglottic area can be anesthetized with superior laryngeal blocks or local anesthetic sprayed through the tube during its passage. Translaryngeal anesthesia is especially useful for blind, conscious nasal intubation. The lubricated, curved endotracheal tube is inserted perpendicularly into the nose and gently passed into the hypopharynx. If breath sounds disappear, the tube has passed into the esophagus or a pyriform sinus and must be withdrawn above the level of the glottis. A variety of devices have been employed to amplify the breath sounds, but the ear over the end of the tube is usually adequate. On occasion, vomiting or bronchial secretions will make this unpleasant. Capnography may be used to assist in the process of placement in addition to confirmation of proper position. [106] The tube is passed into the larynx during inspiration, which tends to be deepest immediately following a cough. Some clinicians ask the patient to "pant" to maintain an open glottis with plenty of air movement. The section on anesthetized nasal intubation describes several techniques for facilitating passage of the recalcitrant endotracheal tube. If the mouth can be opened, direct laryngoscopy and Magill forceps can be used to guide the tube into the glottis. If direct laryngoscopy is necessary, further airway anesthesia, heavier sedation, or glossopharyngeal blocks are likely to be required.

Retrograde Endotracheal Intubation

Retrograde intubation involves passage of a wire or plastic stylet through the cricothyroid membrane that is then coughed out of the larynx and into the oropharynx by the patient. This may be done in the anesthetized or conscious patient. In the conscious patient, it should be preceded by transtracheal topicalization. In adults, this can be done with a "long-arm CVP" catheter or epidural catheter passed through the accompanying needle. In children, a 20-gauge IV catheter with a .021-inch "J" wire is appropriate. [107] A J-wire technique can also be used in adults. [108] A kit with a J-wire is available that can be used to insert endotracheal tubes as small as 4 mm ID (Fig. 39-28 (Figure Not Available) , Cook Critical Care, Bloomington, Ind). If a nasal tube is desired and the wire or catheter comes out of the mouth, the tip can be secured to a nasally passed catheter and then pulled up and out through the nose. The endotracheal tube is then inserted into the larynx over the wire which is held with mild tension. The tip

Figure 39-28 (Figure Not Available) Retrograde intubation with the Cook Retrograde Intubation Set. (A) After placement of an 18-gauge sheath needle into the larynx, the J end of the wire guide is inserted in a cephalad direction until it exits the mouth or nose. (B) An 11.0 French Teflon catheter is threaded down over the guide wire until it contacts the laryngeal access site. The guide wire is removed from above. (C) After advancing the Teflon catheter 2 to 3 cm, the endotracheal tube is advanced into the trachea while maintaining constant control of the catheter. *(Courtesy of Cook Critical Care, Bloomington, Ind.)*

of the tube may catch on the anterior commissure and therefore not pass. Turning the tube, loosening the wire, or threading the tube onto the wire via the Murphy eye (rather than the bevel tip) may facilitate passage. The use of a catheter rather than a wire as a guide (as in the Cook kit) is very helpful in allowing tube passage. The wire can also be threaded up the suction port of a fiberoptic bronchoscope that serves as a stylet with visual capabilities. [28] Details on retrograde intubation technique can be found in Benumof's monograph on airway management. [109]

Fiberoptic Bronchoscopy

Fiberoptic bronchoscopy is a technique that may be utilized for all of the difficult airway situations previously described in this chapter. In addition, the scope may be used to evaluate possible obstruction of the endotracheal tube, to rule out esophageal intubation, check for endobronchial intubation, and ensure the correct placement of double-lumen endobronchial tubes. Much like that of the traditional laryngoscope, skillful use requires practice in situations that are neither urgent nor extremely difficult. This may initially include practice on a teaching mannequin if possible. Even in experienced hands, successful intubation with the fiberoptic scope usually requires several minutes and therefore another technique should be used if an airway must be established rapidly in the face of severe hypoxia. On the other hand, when use of the bronchoscope is anticipated for the more elective management of a difficult airway, the bronchoscope should be employed first before airway visualization is obscured with blood, secretions, and edema. Pathologic processes such as tumors, infection, and edema that diminish the space between the anterior and posterior pharyngeal wall may make passage of the bronchoscope difficult.

The bronchoscope itself contains thin glass fibers that transmit reflected light along their length. The fiber size (5-25mum diameter) is chosen for flexibility, strength, and light transmission. In addition to the image-transmitting bundle of fibers, there is another light fiber bundle that transmits the light from a powerful source. The instruments also include wire controls for changing angulation of the tip and a port for suction or injection of local anesthetics and oxygen. The bronchoscope is a relatively delicate instrument and must always be handled with care. Because replacement or repairs are very expensive, the scope should be turned only as a unit and not twisted upon its shaft. The monograph by Ovassapian [110] supplies details concerning care and cleaning of the instrument and has many photographs and illustrations of great utility to the bronchoscopist.

If oral intubation is planned, an endoscopic oral airway or bite block is best used to protect the bronchoscope. The oral airway also has the advantage of preventing dorsal displacement of the tongue, keeps the instrument in the midline, and guides the bronchoscope past the epiglottis into the larynx. Such devices include the Patil-Syracuse airway, Williams airway intubator, and the Ovassapian intubating airway. [110] [111] If an anesthetized intubation is planned, a mask with a sealing endoscopy port can be used to maintain anesthesia with spontaneous or controlled ventilation during the bronchoscopy.

Before any fiberoptic procedure, a dose of anticholinergic is strongly recommended to prevent secretions from obscuring the view in the upper airway. The light source should be checked and the bronchoscope prefocused on printed material. The tip of the bronchoscope should be defogged with commercial solution or warm soapy water. The bronchoscope is lightly lubricated along its entire length with a water-soluble agent (K-Y jelly or eye lubricant) to facilitate passage through the endotracheal tube. A patent suction port is important and a syringe of 10 mL of 1 percent lidocaine solution can be attached for further topical spray through the bronchoscope. If oxygen insufflation is desired, an appropriate source adaptable to the bronchoscope port should be available, which is useful in keeping secretions off the tip and diminishing fogging as well as providing a source of 100 percent oxygen. However, it also poses the potential for marked gastric insufflation before the trachea is entered and for barotrauma, after tracheal entry.

The bronchoscopist must decide whether the intubation will be nasal or oral and conscious or anesthetized. Nasal intubation has the advantage that the fiberoptic scope is usually positioned to directly visualize the glottis and is therefore technically easier. During conscious, sedated nasal intubation, there is less interference by the tongue. An intubating airway is not required, but a standard airway may be used to keep the tongue off the posterior pharyngeal wall during anesthetized intubations. Some clinicians use a soft nasal airway that has been split lengthwise to introduce the bronchoscope. The previously discussed contraindications to nasal intubation apply. If there is doubt about the ability to maintain the mask airway, intubation should proceed with conscious sedation only. The patient can be anesthetized for fiberoptic intubation if the mask airway can be maintained but intubation is difficult. Such anesthetized intubations are usually more difficult because of the development of upper airway obstruction.

Sedation and topical anesthesia of the airway have been previously addressed in this chapter. In the conscious, sedated patient, superior laryngeal blocks and translaryngeal anesthesia may be applied. Alternatively, the supraglottic, glottic, and tracheal areas may be topicalized with 1 percent lidocaine sprayed through the injection port.

For conscious, sedated nasal insertion, the patient's nares and nasopharynx must be anesthetized and vasoconstricted as previously described. The endotracheal tube or split nasal airway is inserted into the posterior nasopharynx and the fiberoptic bronchoscope passed through it. In the vast majority of cases, the glottis can then be seen with minimal tip manipulation. Note that the appearance of the glottis is quite different during fiberoptic bronchoscopy than the stretched appearance the laryngoscopist expects during classic rigid laryngoscopy. [110] The endotracheal tube can be inserted into the nose under bronchoscopic guidance if there is concern about a foreign body or if the tube will enter the nares but not pass into the oropharynx. A useful alternative method is to blindly insert the endotracheal tube until breath sounds are heard maximally, as in blind nasotracheal intubation. This usually results in an easily-visualized glottis that is quite close to the bronchoscope tip. On occasion, a deviated septum will cause compression of the endotracheal tube and difficult passage of the bronchoscope.

Oral, sedated fiberoptic intubation is somewhat more difficult than nasal intubation because the epiglottis becomes a greater obstacle and the tube tip is not usually directed towards the glottis. An intubating oral airway, or at least a bite block, is inserted after topicalization of the posterior tongue, soft palate, and lateral oropharyngeal areas. This can be accomplished with 10 percent lidocaine spray, nebulization of 4 percent lidocaine, or gargling with about 30 mL of viscous lidocaine. The endotracheal tube is inserted about 8 to 10 cm into the airway and the bronchoscope passed through the tube. If the posterior pharyngeal wall is encountered (usually a pink blur), the tip of the bronchoscope is turned down to visualize the glottis. Otherwise the posterior tongue, epiglottis, and glottis are visualized in proper sequence. If the epiglottis obstructs vision, the bronchoscope must be manipulated under the epiglottis to see the vocal cords. An Endotrol tube may be helpful in guiding the bronchoscope tip to the position required to visualize the glottis. The view may also be improved by having the patient protrude his tongue or gently pulling the tongue anteriorly with a piece of gauze wrapped around the tongue.

Fiberoptic intubation in the anesthetized patient may be performed with spontaneous or controlled ventilation with a standard or Patil endoscopic mask. Other clinicians use some form of insufflation to provide oxygen without a mask. Spontaneous ventilation has the obvious advantage of avoiding apnea while bronchoscopy takes place. However, a diminished anesthetic level may occur resulting in cough, vomiting, laryngospasm, and bronchospasm. The patient must be ventilated by mask with 100 percent O_2 between intubation attempts. During bronchoscopy, O_2 may be administered through the injection port, but insufflation will require an additional source of oxygen. The endoscope mask has a sealing port that allows for the continuous use of a sealed mask airway during bronchoscopy. If a specialized mask is unavailable, a substitute may be constructed by placing the endotracheal tube cuff into the mask inlet to form a seal and then placing a fiberoptic swivel connector on the endotracheal tube to allow simultaneous bronchoscopy and mask ventilation via the anesthesia circuit. [112] For any fiberoptic anesthetized intubation, an assistant is required to hold the endoscopic mask, maintain the airway, deliver equipment and sometimes help stabilize the endotracheal tube while the bronchoscope is inserted.

If nasal, anesthetized intubation is planned, vasoconstriction of the nares and nasopharynx is again necessary. The actual technique of bronchoscopy is as previously described but may be somewhat more difficult due to soft tissue upper airway obstruction caused by anesthesia and/or paralysis. Pulling the tongue anteriorly as previously described may aid visualization of the glottis. Anesthetized, oral intubation is probably the most difficult of the four possible techniques.

The bronchoscopist may choose to stand at the head or the side of the table. If the patient cannot lie flat, standing at the side is essential, but standing on the side of the bed makes the procedure less awkward. The sitting position may facilitate visualization by gravity drainage of secretions and by pulling the scope tip towards the larynx. Keys to successful intubation include control of secretions, bronchoscopic intervention before extensive bleeding and edema have occurred, adequate topical anesthesia and sedation, proper defogging of the lens, and aligning the scope in the midline. Occasionally the bronchoscope will enter the trachea easily, but the endotracheal tube cannot be advanced over it. This is usually due to the bevel catching on the right arytenoid (oral) or epiglottis (nasal) depending on the approach. [113] This may respond to turning the tube 90 degrees counterclockwise, and then 180 degrees if necessary. Careful laryngeal and neck manipulation may also help. If a small (4-mm) bronchoscope has been used, the substitution of a larger (6-mm) instrument may prove helpful. Alternatively, a smaller endotracheal tube may be necessary. The use of an anode or flexible reinforced tube has been reported to be advantageous. [114] Sometimes, sliding the tube in as the bronchoscope is withdrawn will work. Excessive force should be avoided to minimize laryngeal trauma as well as trauma to the delicate fibers at the tip of the scope.

Bronchoscopy is difficult in the presence of bleeding or airway edema. Severe edema or anatomic airway distortion will occasionally necessitate another approach to airway management if surgery must be performed. The presence of a large epiglottis flopping against the posterior pharyngeal wall can occasionally be an insurmountable problem. [115] If the location of the bronchoscope tip is uncertain, the bronchoscope has usually entered a pyriform fossa that may resemble the glottis in this situation. [116] When direct visualization cannot be accomplished, the room lights can be dimmed and the strong light at the bronchoscope tip observed and manipulated into the midline much like a lightwand stylet. [117]

Finally, removal of the bronchoscope may be difficult. At this time it is essential that the tip manipulation lever is in the unlocked, neutral position. The bronchoscope should not be removed with undue force because the fibers may be damaged, the patient injured, or the endotracheal tube displaced. This is most likely to occur with a poorly lubricated bronchoscope used in a relatively small bore tube. It may also be due to pinching of the tube in a tight nasal passage or an errant tip that has gone out through the Murphy eye. In this situation, bronchoscope and tube may have to be removed as a unit and the procedure begun again.

PEDIATRIC AIRWAY MANAGEMENT

This subject is covered in more detail in textbooks on pediatric anesthesia and is discussed only in general terms here (Ch. 59) .

After about age 8 years, airway differences between adults and children mainly reflect size differences. The newborn has the most dramatically different anatomy from the adult that persists during the first year of life and then slowly evolves to the adult form. Differences include a large head that tends to flex the short neck and obstruct the airway and a disproportionately large tongue that may cause airway obstruction and more difficult laryngoscopy. The larynx is more cephalad in infants because the cricoid cartilage is opposite the fourth cervical vertebra (rather than the sixth in adults). The epiglottis is longer, stiffer and lies more horizontally

than in adults. As noted, the cricoid cartilage is the narrowest point of the airway until about age 8. The shorter trachea also leaves less margin for error in placement of the endotracheal tube. Finally, the angles of the main bronchi take-off points make left-sided endobronchial intubation as likely as right-sided.

The sizes and insertion lengths of uncuffed endotracheal tubes for children are shown in Table 39-5 . Tubes should pass easily and allow for leak at inflation pressures of 15 to 20 cm H_2O. As noted, the use of cuffed tubes for children of all ages has become common practice as has the use of appropriately sized LMAs (see Fig. 39-9) (Figure Not Available) . [53] Awake intubation may be performed in newborns up to about 4 weeks of age. Oxygen, atropine, and topicalization of the tongue with lidocaine jelly on a finger are followed by laryngoscopy with a straight blade and thin-handled laryngoscope. Hyoid pressure with the little finger may aid visualization. Older or more vigorous children will require anesthesia for intubation under most circumstances. Sevoflurane has rapidly become the mask induction agent of choice for most circumstances.

COMPLICATIONS OF SHORT-TERM INTUBATION

Laryngoscopy

When the laryngoscope is used improperly, when laryngoscopy is particularly difficult, or when there is dental/periodontal disease, teeth may be injured. If a tooth is chipped or partially broken, the fragment should be located but cannot be re-affixed to the natural tooth. If an entire tooth is dislodged, the tooth should be carefully handled without touching the root. Dental consultation should be obtained to re-affix the tooth in its socket. If such consultation is not available, the tooth can be placed in saline or milk until dental expertise can be obtained. If fragments or whole teeth cannot be located, chest and abdominal x-rays should be done for localization.

The laryngoscope can also injure the soft tissues, usually the lips or gums, but any area of contact can be injured. These injuries are more likely to occur when intubation is difficult and the finer points of technique are sacrificed to expedite intubation. The details of the injury should be well documented in the anesthetic record and chart and the patient informed of the injury.

When laryngoscopy is performed under inadequate anesthesia, coughing, laryngospasm, bronchospasm, and vomiting (with the possibility of aspiration) may occur. Cough should be especially avoided in the settings of an open-eye injury, increased intracranial pressure, or an intracranial vascular anomaly. Laryngospasm should be treated with oxygen, jaw thrust, and gentle mask pressure but may require muscle relaxants to avoid a period of severe desaturation. If cervical spine disease is present due to traumatic, congenital, inflammatory, or neoplastic disease, the spinal cord can be injured during neck movement. [118] Eye trauma may occur due to accidental injury with an instrument or by the laryngoscopist.

Laryngoscopy and Intubation

Hypoxemia and hypercarbia are potential complications of laryngoscopies and intubations that are not successful in a reasonable amount of time. Careful evaluation of the airway will screen out most patients who cannot be adequately ventilated by mask or intubated. The pulse oximeter is essential for detecting desaturation during this time. If neither mask ventilation nor intubation can be accomplished, the insertion of a supraglottic airway device such as the LMA or Combitube should be performed with TTJV or a surgical airway reserved for when less invasive maneuvers are unsuccessful.

There is an increased risk of aspiration in the patient with a full stomach and a difficult airway, but aspiration can also occur in the properly fasting patient who does not present special difficulties. Rapid sequence induction and conscious intubation have been described as means of protecting the patient from aspiration. Aspiration remains a concern but a much lesser one in the patient with a properly placed, cuffed endotracheal tube.

Cardiovascular responses to laryngoscopy include hypertension, tachycardia, and dysrhythmias. In children, bradycardia may occur, but hypoxemia must always be considered as the primary cause. In healthy patients these responses are generally well tolerated; however, in patients with limited coronary or myocardial reserve, myocardial ischemia or failure may follow. The patient with a vascular lesion at risk such as an intracranial vascular anomaly or trauma of the thoracic aorta may also suffer serious sequelae. The clinician must be careful so as not to overtreat these responses and create more difficulties than the responses themselves. Because the MAC for endotracheal intubation is about 30 percent higher than MAC for surgical incision, a relatively deep level of anesthesia must be established. Because deep anesthesia may not be tolerated by many patients, drugs that tend to block the response to airway instrumentation or antihypertensives may be used. Narcotics are one option as an adjunct. Fentanyl has been best studied and requires doses of at least 3 to 4 mug/kg to be effective. [119] Alfentanil has a more rapid onset of action and is effective for this purpose, and remifentanil is also likely to be similarly effective. [120] In addition to its local anesthetic actions, lidocaine reduces anesthetic requirements by 30 percent with a 1.5 mg/kg IV bolus that is minimally depressive to the cardiovascular system. [121] Intravenous lidocaine may be used to supplement the narcotic effect on hemodynamics. [122] Other studies have called the effectiveness of lidocaine in this setting into doubt. [123] Topical anesthesia with lidocaine has been a less effective method for blunting hemodynamic responses because laryngoscopy precedes intratracheal administration of lidocaine. Transtracheal anesthesia avoids laryngoscopy but is stimulating in its own right. Glossopharyngeal and superior laryngeal nerve blocks may also be effective methods to blunt adverse hemodynamic responses. A variety of antihypertensive agents have also been used to diminish the blood pressure and heart rate responses to intubation. These include beta-adrenergic blockers, phentolamine, nitroprusside, clonidine, captopril, nitroglycerin, and hydralazine, [124] [125] [126] [127] [128] but their relative efficacy is not established. However, one study reported that a 150 mg esmolol bolus was superior to

IV high-dose lidocaine or low-dose fentanyl in preventing the tachycardia associated with intubation. [129] All three treatments provided equivalent blunting of blood pressure increases. In treated (with drugs other than beta blockers) hypertensive adult patients, a single 100-mg intravenous bolus of esmolol given before laryngoscopy appears to control heart rate and blood pressure without excessive hypotension. [130] Dysrhythmias during or immediately following laryngoscopy and intubation generally resolve with adequate ventilation, and establishment of adequate anesthetic depth.

The respiratory response of laryngospasm has been described. In predisposed individuals, laryngoscopy alone may also cause bronchospasm. In healthy volunteers, intubation results in an increase in airway resistance that is greater than the resistance of breathing through the tube held externally. This doubling of the expected resistance even in topically anesthetized airways represents reflex bronchoconstriction to the mechanical irritation of the tube. [131] Bronchospasm may be especially severe in the lightly anesthetized patient with reactive airways. Propofol may be the intravenous induction agent of choice in patients prone to bronchospasm. [132] Clinically, it appears that bronchospasm is blunted by the prior administration of anticholinergics, steroid, inhaled beta $_2$ -agonists, lidocaine (topical, nerve block, intravenous), and narcotics. [133] After intubation, deepening anesthesia with intravenous or inhaled agents and the administration of inhaled or IV beta agonists will help treat the bronchospasm. Muscle relaxants may improve ventilation, and in extreme situations, a small amount of positive end-expiratory pressure may improve oxygenation when it is unsatisfactory on 100 percent oxygen. [134] With the tube *in situ,* it is important to ensure that the audible wheezing is not due to some form of mechanical obstruction of the tube: kinking, clot, mucus, active biting or passive mouth closure, foreign body, cuff-overinflation, bevel against tracheal wall, or endobronchial intubation. Other less likely problems such as tension pneumothorax, a nasogastric tube in the trachea, heart failure, or the negative pressure of a descending ventilator bellows must also be eliminated before definitively treating wheezing as bronchospasm. Visual inspection, passage of a suction catheter (or preferably, a fiberoptic bronchoscope) along with cuff deflation and 90 degree rotation of the tube will rule out several of these possibilities.

The patient with elevated intracranial pressure (ICP) who has minimal reserve in intracranial compliance is actually at risk for brain-stem herniation and sudden death during laryngoscopy and intubation. Instrumentation of the airway may result in a sudden increase in cerebral blood flow due to increases in cerebral metabolic activity and systemic cardiovascular effects. The normal autoregulation mechanism may not be effective because of disease or because its upper pressure limit (normally, mean arterial pressure 150 mm Hg) may be exceeded. Coughing or bucking will decrease venous return from the head and may increase ICP as well. Induction drugs that result in cerebral vasoconstriction are most useful. In practice, this has included thiopental and lidocaine, although etomidate and propofol can also be considered. [135] [136] [137] Narcotics are somewhat useful, although they do not have a great direct effect on central brain function. [138] On the other hand,

ketamine is best avoided. Adjunctive measures may include voluntary and/or mask hyperventilation, mannitol, steroids, and establishment of ICP monitoring before laryngoscopy and intubation. [36]

Intubation

In addition to failed intubation, a most feared complication of intubation is esophageal intubation. [139] Although this occurs most frequently in the setting of inexperience, it can happen to experienced practitioners. Unfortunately, except for direct visualization of the tube passing through the cords, fiberoptic confirmation of placement, and presence and persistence of appropriate levels of end-tidal carbon dioxide levels, the usual clinical means for determining endotracheal placement of the tube may not always be reliable. These include presence of bilateral breath sounds, chest movement, exhaled tidal volumes, tube condensation, epigastric auscultation, reservoir bag filling and compliance, and chest radiography. [140] Routine monitoring of end-tidal CO_2 is helpful in the definitive determination of tube placement when visualization is impossible and fiberoptic equipment is not available. A colorimetric single-use carbon dioxide detector (FEF end-tidal carbon dioxide detector, Fenem, New York, NY) may be employed when capnometry is unavailable. [141] The esophageal detector device (EDD) employs a self-inflating bulb that is connected to the endotracheal tube and can be carried in a mobile airway case when capnography is not available. The principle of use is that the esophagus will collapse when the subatmospheric pressure is applied, and therefore, the bulb should stay collapsed if esophageal intubation has occurred. This is in contrast to the more rigid trachea that allows for free aspiration of gas and reinflation of the bulb. The EDD was initially reported to be quite effective, but subsequent studies have noted problems in the obese and in the parturient. [142] [143] This device may have a place in intubations when capnography is not available but independent confirmation is encouraged. A new device that differentiates tracheal from esophageal intubation by recognition of differences in resonating frequency (sonomatic confirmation of tracheal intubation) appears to be no more effective than the simpler, cheaper, bulb device. [144]

The endotracheal tube (and/or stylet) may also cause mechanical damage to the pharynx, esophagus, larynx, and trachea. This may involve blunt injury, dissection, or perforation. The delicate structures of the larynx (vocal cord, arytenoids) are especially susceptible. Infections and/or barotrauma may follow these types of injuries. Acute injury to the trachea is associated with use of a stiff protruding stylet and previous pathology such as trauma. Gentle, careful manipulation of the airway and proper use of a stylet that is removed after the glottis is entered should help avoid most of these types of injury.

Endobronchial intubation is most common when there is the least distance for the tube tip to be placed properly above the carina yet below the vocal cords as in small children. Guidelines for placement distance have been discussed (see Table 39-5) . In patients older than 1 year of age, right-sided endobronchial intubation will be far more common. Hypoxemia, bronchospasm, atelectasis, and coughing may result. Auscultation and observation of the chest may

suggest the diagnosis, but the tube may have to be pulled back a small distance to finalize it. Fiberoptic bronchoscopy is the optimal diagnostic tool. The clinician must be extremely careful when withdrawing the tube in awkward positions or in the difficult airway. Note also that properly placed tubes may change their position during head movement, abdominal insufflation, or repositioning of the patient. [69] [145] [146] Inadvertent extubation may occur during repositioning and surgical manipulation and may even result from head movement and coughing in small children, such that continued vigilance is essential.

In addition to bronchospasm, the endotracheal tube has several other effects on pulmonary mechanics. [147] The tube acts a fixed resistor that substitutes for the normal upper airway resistance. The cross-sectional area of an 8.0-mm ID tube (50 mm^2) is not remarkably less than the mean cross-sectional area of the glottis (narrowest part of the adult airway) during quiet breathing. Thus, the use of 8.0-mm tubes in men or 7.0-mm tubes in women whose glottic aperture is smaller does not impose an undue increase in resistance. Anatomic dead space is reduced by intubation, however. In adults, functional residual capacity is not altered by the presence of an endotracheal tube. [131]

Several complications are peculiar to nasal intubation. Epistaxis may occur even when vasoconstriction, a lubricated tube, and careful manipulation are employed. The inflated cuff may tamponade the hemorrhage if correctly positioned. Patients with pharmacologic or spontaneous coagulopathies judged to be significant by the clinician should not be intubated nasally. Severe hemorrhage may result requiring simple tamponade with devices that include the balloons of Foley catheters and require expert consultation with otolaryngologists. The stream of blood pouring down the pharynx may also make subsequent oral intubation extremely difficult.

The nasal or nasopharyngeal mucosa may be damaged and false passages created. Tracheal or esophageal trauma can lead to the serious complications or pneumothorax and infection, respectively. [148] [149] Adenoids, polyps, and foreign bodies may be displaced, causing bleeding and even airway obstruction. Nasal instrumentation in these situations should be done under direct vision if possible. The problems of bacteremia and basilar skull fracture have been mentioned previously. In the former, endocarditis prophylaxis is indicated. [66] [67] In the latter, intubation is contraindicated for fear of entering the cranium or introducing CNS infection. Nasal necrosis is more likely a complication of chronic intubation but may occur perioperatively, especially with the use of nasal RAE tubes. [150] Ulceration of the inferior turbinate has also been described. [151] Sinusitis and otitis are two more common sequelae of longer-term nasotracheal intubation. [152] [153]

EXTUBATION

Extubation of the trachea may be performed while the patient is deeply anesthetized or is nearly fully awake. "Deep" or more precisely, anesthetized extubation, is performed after muscle relaxants have been fully reversed and the patient is maintaining an acceptable respiratory rate and depth. A difficult mask airway, difficult intubation, risk of aspiration, or surgery that may produce airway edema or maintenance problems are contraindications to such extubation. Adequate recovery of the ability to maintain and protect the airway must be demonstrated after the use of neuromuscular relaxants. [154] It is important to remember that adequate ventilation through an endotracheal tube does not guarantee the muscle strength to maintain the airway. Sustained tetanus using a nerve stimulator is very painful in the conscious patient, but sustained (5 sec) head lift is an excellent way to assess clinically adequate reversal. If head lift is contraindicated or painful, leg lift or sustained tongue protrusion can be similarly assessed. As the anesthetic level diminishes, the patient is suctioned, and the tube is removed after a positive pressure breath has been given with the anesthesia bag to allow subsequent expulsion or secretions out of the glottis. Advantages include reduced coughing on the endotracheal tube that may lessen laryngotracheal trauma and cause less adverse effects. However, the airway must be scrupulously maintained because obstruction and aspiration remain possibilities. Furthermore, as the patient awakens, laryngospasm and cough may occur anyway. Because there is no way to entirely avoid such coughing after an anesthetic, many authors regard "deep" extubations merely as premature extubations. The perspective appears valid because present anesthetic practice seldom utilizes techniques of truly "deep" anesthesia.

When such extubations in the anesthetized state are contraindicated, awake extubation is essential. The patient is not extubated until judged ready to maintain and protect the airway. The patient who is unresponsive to verbal stimuli, has deviation of the eyes, or is breath-holding is not ready for extubation and is prone to laryngospasm, which is most likely to occur when patients are extubated in between awake and anesthetized states. Coughing and bucking probably indicate the ability to protect the airway, but the timing of awake extubation remains a matter of clinical judgment. Lidocaine (1-1.5mg/kg IV) or a small dose of narcotic may help smooth out awake extubation at the cost of prolonging the process of awakening. After extubation, the patient may be maintained in the supine or lateral position. After anesthetized extubation, oral or nasal airways are usually left in place until the patient can no longer tolerate them. Vigilance should not be relaxed at this time.

Difficult removal is usually the result of leaving the endotracheal tube cuff inflated. If the cuff will not deflate because of obstruction in the tubing, it can be punctured by a needle placed through the cricothyroid membrane after the cuff is raised to this level. More serious and somewhat unusual causes of difficult extubation include fixation of the endotracheal tube or pilot tube by a Kirschner (K) wire used in head and neck surgery or a suture placed from the pulmonary artery through the trachea into the endotracheal tube. A tangled nasogastric tube, swollen or tense vocal cords, or a "barb" accidentally cut on the endotracheal tube can all interfere with extubation. [155] The nature of the surgical procedure must be kept in mind when a tube will not come out after cuff deflation or rupture so as to avoid trauma from vigorous extubation attempts. Direct or fiberoptic examination may be required.

Special care must be taken in a variety of potential high-risk extubations when the ability to immediately reestablish

the airway is questionable. [156] The endotracheal tube may be removed while leaving a device such as a tube changer, nasogastric tube, or bronchoscope within the trachea so that the airway can be immediately reestablished if necessary. [157] A variety of tube changer devices are available and may also be employed with jet ventilation (Cook Airway Exchange Catheter, Cook Critical Care, Bloomington, In; Sheridan TTX tracheal tube exchanger, Sheridan Catheter Corp, Argyle, NY; and Endotracheal ventilation catheter, CardioMed Supplies, Gormley, Ontario, Canada). Note that the presence of such a device does *not* guarantee that the tracheal tube can be replaced. Also note that supraglottic devices such as the LMA may or may not be successful in establishing an airway as the pathology may be at the supraglottic level or below. The presence of an individual who can establish a surgical airway (along with the necessary equipment) may be reasonable in selected instances of anticipated difficult extubation, particularly if there is no leak when the endotracheal tube cuff is let down. [158]

Complications of Extubation

Airway obstruction, laryngospasm, and aspiration are complications that have been previously discussed. Note that after intubations lasting 8 hours or more, airway protection may be impaired for 4 to 8 hours. [159] Sore throat is a complication of anesthesia that may have pharyngeal, laryngeal and/or tracheal sources and may occur in the absence of endotracheal intubation. [160] Factors that may affect the incidence of sore throat include area of cuff-trachea contact (tracheitis), use of lidocaine ointment and size of the endotracheal tube (laryngitis), and the use of succinylcholine (pharyngitis). Cuffs with a longer cuff-trachea interface appear to cause a higher incidence of sore throat. [161] The incidence of sore throat may also be related to intracuff pressures. [162] As previously noted, lidocaine ointment has a questionable effect on the incidence of sore throat. The higher incidence of sore throat in women is probably related to the tube size/laryngeal size relationship. One study demonstrated that tube size is related to the incidence and severity of sore throat in both sexes. [163] This study did not find that the use of succinylcholine was related to sore throat but other workers have reported succinylcholine to be a contributing factor and that nondepolarizing pretreatment reduced the incidence somewhat (from 68 to 45%). [63] The mechanism for succinylcholine-related sore throat is postulated to be myalgias due to fasciculation of peripharyngeal muscles. Sore throat is a minor side effect that should resolve within 72 hours and should not be a factor in determining whether endotracheal intubation is required. It may also occur with the use of an LMA. Hoarseness is another minor side effect correlated with endotracheal tube size and should be investigated if persistent.

Laryngeal edema is most commonly symptomatic in children because their small airway size is more severely reduced by edema; i.e. edema producing only hoarseness in an adult may cause a significant reduction in laryngeal cross-sectional area in a small child. Subglottic edema is particularly more common in children as the nonexpandable cricoid cartilage is the narrowest part of the pediatric airway. Edema may also be uvular, supraglottic, retroarytenoid, or at the level of the vocal cords. The precise diagnosis may be made with fiberoptic laryngoscopy, but this is not usually necessary. Stridor is produced by the extrathoracic obstruction that produces mainly inspiratory wheezing. Diminished stridor may represent total airway obstruction, and movement of air must be repeatedly confirmed. The contributing factors to the production of laryngeal edema are somewhat controversial but include too large a tube, trauma from laryngoscopy and/or intubation, excessive neck manipulation during intubation and surgery, excessive coughing or bucking on the tube, and present or recent upper respiratory infection. The prophylactic use of steroids before extubation to reduce edema is an unproven but frequently utilized treatment if the likelihood of postextubation stridor is suspected. Treatment includes warmed, humidified oxygen, nebulized racemic epinephrine (.25-1mL), and IV dexa-methasone (.5 mg/kg up to 10 mg). If obstruction is severe and persistent, reintubation must be considered.

Vocal cord paralysis may be due to surgical injury of the recurrent laryngeal nerve or from the endotracheal tube cuff. [164] Vocal cord edema occurring in the presence of a paralyzed cord may precipitate complete airway obstruction as can bilateral cord paralysis. It may be prudent to pursue preoperative otolaryngologic evaluation of the hoarse patient for elective surgery so that important pathology is detected and so that subsequent vocal problems are not entirely attributed to the anesthesiologist. The arytenoid cartilage may be dislocated by the laryngoscope blade and result in a weak voice after extubation that may require surgical correction. [165] [166] Other complications include ulcerations or granulomas of the vocal cords that may result in persistent hoarseness. [167] More serious complications resulting in laryngeal or tracheal stenosis are extremely rare sequelae of short-term perioperative intubation. [168]

/das/book/view/29494766/875/459.html

THE ANESTHESIOLOGIST AS AIRWAY MANAGEMENT CONSULTANT

In addition to the usual role in providing airway management during the administration of an anesthetic, the anesthesiologist may be consulted as an expert in airway management in settings outside the operating room. These consultations may involve the provision of an acute airway or the management of problems that have arisen in the patient requiring ongoing endotracheal intubation. Considerations in the acute setting include a variety of clinical situations such as trauma, upper airway obstruction, and medical conditions that must be specifically addressed to provide optimal care. [169] These intubations are particularly high-risk because the patients are often hemodynamically unstable. [170] In the patient requiring long-term endotracheal intubation, the issues of site of intubation, leak-free ventilation, tube changes, laryngeal injury, and tracheostomy (among others) may be encountered. [171] Anesthesiologists may also be directly involved in performing percutaneous dilational tracheostomy or anesthetic/airway support for the procedure in the ICU. [172] Both acute and chromic settings require a solid background in airway management principles as well as the ability to deal with unusual and unpredictable problems in a relatively foreign environment. Two recent reviews address these areas in detail. [173] [174]

General Recommendations

1. Preoxygenate all patients (including children) to whatever extent possible. This provides a buffer to tolerate an inability to ventilate or intubate for several additional minutes.
2. Evaluate every airway carefully from the standpoint of history, physical examination, and other indicated investigations. Keep in mind that several small abnormalities may add up to a difficult airway.
3. Approach every patient with the possibility that mask ventilation and/or endotracheal intubation may not be possible. Have a back-up plan formulated before the problem occurs. A transtracheal jet ventilation system cannot be assembled from scratch when the oxygen saturation is falling. Make sure that whatever might be needed is available.
4. Whenever possible, provide mask ventilation before administering any muscle relaxant, especially nondepolarizers. Unless succinylcholine is contraindicated, consider its use when the airway looks potentially difficult and anesthetized intubation is selected. The short-action (as opposed to any currently available nondepolarizing relaxant) of succinylcholine can be life-saving and brain-saving in the "can't mask/can't intubate" situation. However, the duration of a dose of succinylcholine may be longer than the duration of a brain tissue oxygen level compatible with full recovery. [175]
5. Gain confidence and skill with a variety of approaches to conscious intubation so that it can be applied properly when needed. Don't let less cognizant individuals (surgeons, nurses, etc.) unduly influence your decision to employ conscious intubation. The airway is your responsibility, and you, the patient, and the patients' loved ones suffer the consequences of misjudgments.

References

1. Ferris BG, Mead J, Odie LH: Partitioning of respiratory flow resistance in man. J Appl Physiol 19:653, 1964.

2. Camporesi EM, Mortola JP, SantAmbrogio F, et al: Topical anesthesia of tracheal receptors. J Appl Physiol 47:1123, 1979.

3. Liistro G, Stanescu D, Dooms G, et al: Head position modifies upper airway resistance in men. J Appl Physiol 64:1285, 1988.

4. Lawes EG, Campbell I, Mercer D: Inflation pressure, gastric insufflation and rapid sequence induction. Br J Anaesth 59:315, 1987.

5. Boidin MP: Airway patency in the unconscious patient. Br J Anaesth 57:306, 1985.

6. Macklem PT, Wilson NJ: Measurement of intrabronchial pressure in man. J Appl Physiol 20:653, 1965.

7. Arora NS, Gal TJ: Cough dynamics during progressive expiratory muscle weakness in healthy curarized subjects. J Appl Physiol 51:464, 1981.

8. Gal TJ: Effects of endotracheal intubation on normal cough performance. Anesthesiology 52:324, 1980.

9. Atkins RF: Simple method of tracking patients with difficult or failed intubation. Anesthesiology 83:1373, 1995.

10. Mark L, Schauble J, Gibby G, et al: Effective dissemination of critical airway information: The Medic Alert National Difficult Airway/Intubation. In Benumof JL (ed): Airway Management Principles and Practice. St. Louis, Mosby, 1996, p 931.

11. Steward DJ: Manual of Pediatric Anesthesia, 4th ed. New York, Churchill Livingstone, 1994.

12. Block C, Brechner VL: Unusual problems in airway management II: The influence of the temporomandibular joint, the mandible, and associated structures on endotracheal intubation. Anesth Analg 50:114, 1971.

13. Aiello G, Metcalf I: Anaesthetic implications of temporomandibular joint disease. Can J Anaesth 39:610, 1992.

14. Redick LF: The temporomandibular joint and tracheal intubation. Anesth Analg 66:675, 1987.

15. Kawaguchi M, Sakamoto T, Furuya H, et al: Pseudoankylosis of the mandible after supratentorial craniotomy. Anesth Analg 83:731, 1996.

16. Mallampati SR, Gatt SP, Guigino LD, et al: A clinical sign to predict difficult tracheal intubation: A prospective study. Can Anaesth Soc J 32:429, 1985.

17. Pilkington S, Carli F, Dakin MJ, et al: Increase in Mallampati score during pregnancy. Br J Anaesth 74:638, 1995.

18. Lewis M, Keramati S, Benumof JL, et al: What is the best way to determine oropharyngeal classification and mandibular space length to predict difficult laryngoscopy? Anesthesiology 81:69, 1994.

19. Woods GM: Mandibular tori as a cause of inability to visualize the larynx. Anesth Analg 81:870, 1995.

20. Calder I, Calder J, Crockard HA: Difficult direct laryngoscopy in patients with cervical spine disease. Anaesthesia 50:756, 1995.

21. Nichol HC, Zuck D: Difficult laryngoscopy--The "anterior" larynx and the atlanto-occipital gap. Br J Anaesth 55:141, 1983.

22. Wilson ME, Spiegenhalter D, Robertson JA, et al: Predicting difficult intubation. Br J Anaesth 61:211, 1988.

23. Rocke DA, Murray WB, Rout CC, et al: Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 77:67, 1992.

24. Tse JC, Rimm EB, Hussain A: Predicting difficult endotracheal intubation in surgical patients scheduled for general anesthesia: A prospective blind study. Anesth Analg 81:254, 1995.

25. El-Ganzouri AR, McCarthy RJ, Tuman KJ, et al: Preoperative airway assessment: Predictive value of a multivariate risk index. Anesth Analg 82:1197, 1996.

26. Karkouti K, Rose DK, Ferris LE, et al: Inter-observer reliability of ten tests used for predicting difficult tracheal intubation. Can J Anaesth 43:554, 1996.

27. Rose DK, Cohen MM: The incidence of airway problems depends on the definition used. Can J Anaesth 43:30, 1996.

28. Benumof JL: Management of the difficult adult airway with special emphasis on awake tracheal intubation. Anesthesiology 75:1087, 1991.

29. Yamamoto K, Tsubokawa T, Shibata K, et al: Predicting difficult intubation with indirect laryngoscopy. Anesthesiology 86:316, 1997.

30. Jones DH, Cohle SD: Unanticipated difficult airway secondary to lingual tonsillar hyperplasia. Anesth Analg 77:1285, 1993.

31. Newman GG, Weingarton AE, Abramowitz RM: The anesthetic management of the patient with an anterior mediastinal mass. Anesthesiology 60:144, 1984.

32. Kawana S, Nakabayashi K, Kawashima F, et al: Difficult intubation assisted by three-dimensional computed tomography imaging of the pharynx and larynx. Anesthesiology 83:416, 1995.

33. Hotchkiss RS, Hall JR, Braun IF, et al: An abnormal epiglottis as a cause of difficult intubation--Airway assessment using magnetic resonance imaging. Anesthesiology 68:140, 1988.

34. Dorsch JA, Dorsch SE: Understanding Anesthesia Equipment, 3rd ed. Baltimore, Williams and Wilkins, 1994.

35. Benumof JL: The American Society of Anesthesiologists' management of the difficult airway algorithm and explanation-analysis of the algorithm. In Benumof JL (ed): Airway Management Principles and Practice. St. Louis, Mosby, 1996, p 143.

36. Spiekermann BF, Stone DJ, Bogdonoff DL, et al: Airway management in neuroanesthesia. Can J Anaesth 43:820, 1996.

37. Brain AIJ: The laryngeal mask--A new concept in airway management. Br J Anaesth 55:801, 1983.

38. Benumof JL: Laryngeal mask airway. Indications and contraindications. Anesthesiology 77:843, 1992.

39. Joshi GP, Morrison SG, Okonkwo NA, et al: Continuous hypopharyngeal pH measurements in spontaneously breathing anesthetized outpatients: Laryngeal mask airway versus tracheal intubation. Anesth Analg 82:254, 1996.

40. Smith I, White PF: Use of the laryngeal mask airway as an alternative to a face mask during outpatient arthroscopy. Anesthesiology 77:850, 1992.

41. Fisher JA, Ananthanarayan C, Edelist G: Role of the laryngeal mask in airway management. Can J Anaesth 39:1, 1992.

42. Benumof JL: Use of the laryngeal mask airway to facilitate fiberscope-aided tracheal intubation. Anesth Analg 74:311, 1992.

43. Benumof JL: Laryngeal mask airway and the ASA difficult airway algorithm. Anesthesiology 84:686, 1996.

44. Nanji GM, Maltby JR: Vomiting and aspiration pneumonitis with the laryngeal mask airway. Can J Anaesth 39:69, 1992.

45. Barker P, Langton JA, Murphy PJ, et al: Regurgitation of gastric contents during general anaesthesia using the laryngeal mask airway. Br J Anaesth 69:314, 1992.

46. Frass M, Frenzer R, Rauscha F, et al: Evaluation of esophageal tracheal combitube in cardiopulmonary resuscitation. Crit Care Med 15:609, 1986.

47. Green KS, Berger TH: Proper use of the combitube. Anesthesiology 81:513, 1994.

48. Krafft P, Roggia M, Fridrich P, et al: Bronchoscopy via a redesigned Combitube in the esophageal position. Anesthesiology 86:1041, 1997.

49. Bernhard WN, Cottrell JE, Sivakumaran C, et al: Adjustment of intracuff pressure to prevent aspiration. Anesthesiology 50:363, 1979.

50. Petring OV, Adelhoj B, Jensen BN, et al: Prevention of silent aspiration due to leaks around cuffs of endotracheal tubes. Anesth Analg 65:777, 1986.

51. Stanley TH: Effects of anesthetic gases on endotracheal tube cuff gas volumes. Anesth Analg 53:480, 1974.

52. Finholt DA, Audenaert SM, Stirt JA, et al: Endotracheal tube leak pressure and tracheal lumen size and swine. Anesth Analg 65:667, 1986.

53. Khine HH, Corddry DH, Kettrick RG, et al: Comparison of cuffed and uncuffed endotracheal tubes in young children during general anesthesia. Anesthesiology 86:627, 1997.

54. MacIntosh PR: New laryngoscope. Lancet 1:205, 1943.

55. Miller RA: A new laryngoscope. Anesthesiology 2:317, 1941.

56. Hastings RH, Hon ED, Nghiem C, et al: Force and torque vary between laryngoscopists and laryngoscope blades. Anesth Analg 82:462, 1996.

57. Nolan JP, Wilson ME: Orotracheal intubations in patients with potential cervical spine injuries--An indication for the gum elastic bougie. Anaesthesia 48:630, 1993.

58. Latto IP: Management of difficult intubation. In Latto IP, Vaughn RS (eds): Difficulties in Tracheal Intubation, 2nd ed. London, W.B. Saunders, 1997, p 122.

59. Loeser EA, Kaminsky A, Diaz A, et al: The influence of endotracheal tube cuff design and cuff lubrication on postoperative sore throat. Anesthesiology 58:376, 1983.

60. Patel N, Smith CE, Pinchak AC, et al: Taping methods and tape types for securing oral endotracheal tubes. Can J Anaesth 44:330, 1997.

61. Muzi M, Robinson BJ, Ebert TJ, et al: Induction of anesthesia and tracheal intubation with sevoflurane in adults. Anesthesiology 85:536, 1996.

62. Sellick BA: Cricoid pressure to control regurgitation of stomach contents during induction of anesthesia. Lancet 2:404, 1961.

63. Capan LM, Bruce DL, Patel K, et al: Succinylcholine-induced postoperative sore throat. Anesthesiology 59:202, 1983.

64. Patel N, Kamath N, Smith CE, et al: Intubating conditions and neuromuscular block after divided dose mivacurium or single dose rocuronium. Can J Anaesth 44:49, 1997.

65. Horellou MF, Mathe D, Feiss P: A hazard of naso-tracheal intubation. Anaesthesia 33:73, 1978.

66. Berry FA, Blankenbaker WL, Ball CG: A comparison of bacteremia occurring with nasotracheal and orotracheal intubation. Anesth Analg 52:873, 1973.

67. Dinner M, Tjeaw M, Artusio JF: Bacteremia as a complication of nasotracheal intubation. Anesth Analg 66:460, 1987.

68. Takahata O, Kubota M, Mamiya K, et al: The efficacy of the "BURP" maneuver during a difficult laryngoscopy. Anesth Analg 84:419, 1997.

69. Iwama H, Nakane M, Aoki K, et al: Abdominal insufflation pressure during laparoscopic cholecystectomy shifts the tracheal carina cephalad. Anesthesiology 84:491, 1996.

70. Valentine SJ, Marjot R, Mouk C: Preoxygenation in the elderly: A comparison of the four-maximal-breath and three-minute techniques. Anesth Analg 71:516, 1990.

71. Nones MC, Dewan MD: Preoxygenation for caesarian section: A comparison of two techniques. Anesthesiology 62:827, 1985.

72. Tournadre J-P, Chassard D, Berrada KR, et al: Cricoid cartilage pressure decreases lower esophageal sphincter tone. Anesthesiology 86:7, 1997.

73. Brincombe JR, Berry AM: Cricoid pressure. Can J Anaesth 44:414, 1997.

74. Salem MR, Joseph NJ, Heyman HJ, et al: Cricoid compression is effective in obliterating the esophageal lumen in the presence of a nasogastric tube. Anesthesiology 63:443, 1985.

75. Tran DO: The correct position of the head and neck for rapid sequence induction [letter]. Anesthesiology 67:861, 1987.

76. Salem MR, Heyman HJ, Liuschutz V, et al: Cephalad displacement of the larynx facilitates tracheal intubation. Anesthesiology 67:A453, 1987.

77. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal halothane concentration for endotracheal intubation. Anesthesiology 47:386, 1977.

78. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal enflurane concentration for endotracheal intubation. Anesthesiology 50:59, 1979.

79. Gorback MS: Inflation of the endotracheal tube cuff as an aid to blind nasal endotracheal intubation [letter]. Anesth Analg 66:913, 1987.

80. Berry FA: The use of a stylet in blind nasotracheal intubation. Anesthesiology 61:469, 1984.

81. Nolan JP, Wilson ME: An evaluation of the gum elastic bougie. Anaesthesia 47:878, 1992.

82. Carr R, Reyford H, Belani K, et al: Evaluation of the Augustine guide for difficult tracheal intubation. Can J Anaesth 42:1171, 1995.

83. Cohn AI, Hart RT, McGraw SR, et al: The Bullard laryngoscope for emergency airway management in a morbidly obese parturient. Anesth Analg 81:872, 1995.

84. Benumof JL, Scheller MS: The importance of transtracheal jet ventilation in the management of the difficult airway. Anesthesiology 71:769, 1989.

85. Stone DJ: Transtracheal jet ventilation. Anesthesiology 72:774, 1990.

86. Burkey B, Esclamado R, Morganroth M: The role of cricothyroid-otomy in airway management. Clin Chest Med 12:561, 1991.

87. Caplan RA, Posner KL, Ward RJ, et al: Adverse respiratory events in anesthesia: A closed claims analysis. Anesthesiology 72:828, 1990.

88. Cheney FW, Posner KL, Caplan RA: Adverse respiratory events infrequently leading to malpractice suits. Anesthesiology 75:932, 1991.

89. Scott JC, Ponganis KV, Stanski DR: EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234, 1985.

90. Kallos T, Smith TC: The respiratory effects of Innovar given for premedication. Br J Anaesth 41:303, 1976.

91. Bailey PL, Pace NL, Ashburn MA, et al: Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 73:826, 1990.

92. Hertigon ML, Cleary JL, Gross JB, et al: Is nasal cocaine superior to a lidocaine-phenylephrine mixture for blind nasotracheal intubation? Anesth Analg 63:227, 1984.

93. Bourke DL, Katz J, Tonneson A: Nebulized anesthesia for awake endotracheal intubation. Anesthesiology 63:690, 1985.

94. Cahen CR: An aid in cases of difficult tracheal intubation. Anesthesiology 74:197, 1991.

95. Sitzman BT, Rich GF, Rockwell JJ, et al: Local anesthetic administration for awake direct laryngoscopy. Are glossopharyngeal blocks superior? Anesthesiology 86:34, 1997.

96. Bellhouse CP: An angulated laryngoscope for routine and difficult tracheal intubation. Anesthesiology 69:126, 1988.

97. McIntyre JWR: Laryngoscope design and the difficult adult intubation. Can J Anaesth 36:94, 1989.

98. Thomas DV: Laryngoscopy technique in obese patients. Anesthesiology 66:583, 1987.

99. Sivarajan M, Fink BR: The position and the state of the larynx during general anesthesia and muscle paralysis. Anesthesiology 72:439, 1990.

100. McIntyre JWR: The difficult tracheal intubation. Can J Anaesth 34:204, 1987.

101. Salem MR, Mathrubutham M, Bennett EJ: Difficult intubation. New Engl J Med 295:879, 1976.

102. Ellis DG, Jakymec A, Kaplan RM, et al: Guided orotrachel intubation in the operating room using a lighted stylet: A comparison with direct laryngoscopic technique. Anesthesiology 64:823, 1986.

103. Fox DJ, Castro T, Rostrelli AJ: Comparison of intubation techniques in the awake patient: The flexi-lum surgical light (light wand) versus blind nasal approach. Anesthesiology 66:69, 1987.

104. Stone DJ, Stirt JA, Kaplan MJ, et al: A complication of lightwand-guided nasotracheal intubation. Anesthesiology 61:780, 1984.

105. Hung OR, Pytka S, Morris I, et al: Clinical trial of a new lightwand device (Trachlight) to intubate the trachea. Anesthesiology 83:509, 1995.

106. King HK, Wooten DJ: Blind nasal intubation by monitoring end-tidal carbon dioxide. Anesth Analg 69:412, 1989.

107. Borland LM, Swan DM, Leff S: Difficult pediatric endotracheal intubation: A new approach to the retrograde technique. Anesthesiology 55:577, 1981.

108. King HK, Wang LF, Khan AK, et al: Translaryngeal guided intubation for difficult intubation. Crit Care Med 15:869, 1987.

109. Sanchez A, Pallares V: Retrograde intubation technique. In Benumof JL (ed): Airway Management Principles and Practice. St. Louis, Mosby, 1996, p 320.

110. Ovassapian A: Fiberoptic Endoscopy and the Difficult Airway. Philadelphia, Lippincott-Raven, 1996.

111. Rogers SN, Benumof JL: New and easy techniques for fiberoptic endoscopy-aided tracheal intubation. Anesthesiology 59:569, 1983.

112. Higgins MS, Marco AP: An aid in oral fiberoptic intubation. Anesthesiology 77:1236, 1992.

113. Katsnelson T, Frost EAM, Farcon E, et al: When the endotracheal tube will not pass over the flexible bronchoscope. Anesthesiology 76:151, 1992.

114. Brull SJ, Wiklund R, Ferris C, et al: Facilitation of fiberoptic intubation with a flexible tracheal tube. Anesth Analg 78:746, 1994.

115. Ovassapian A, Yelich SJ, Dykes MHM, et al: Fiberoptic nasotracheal intubation--Incidence and causes of failure. Anesth Analg, 62:692, 1983.

116. Raj PP, Forestner J, Watson TD, et al: Techniques for fiberoptic laryngoscopy in anesthesia. Anesth Analg 53:708, 1974.

117. Stone DJ: Another use for the fiberoptic bronchoscope [letter]. Anesthesiology 67:608, 1987.

118. Muckart DJJ, Bhagwanjee S, van der Merwe R: Spinal cord injury as a result of endotracheal intubation in patients with undiagnosed cervical spine fractures. Anesthesiology 87:418, 1997.

119. Martin DE, Rosenberg H, Aukburg SJ, et al: Low-dose fentanyl blunts circulatory responses to tracheal intubation. Anesth Analg 61:680, 1982.

120. Korpinen R, Saarnivaara L, Siren K, et al: Modification of the haemodynamic responses to induction of anaesthesia and tracheal intubation with alfentanil, esmolol and their combination. Can J Anaesth 42:298, 1995.

121. Hines RS, DiFazio CA, Burney RG: Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. Anesthesiology 47:437, 1977.

122. Tam S, Chung F, Campbell M: Intravenous lidocaine: Optimal time of injection before tracheal intubation. Anesth Analg 66:1036, 1987.

123. Miller CD, Warren SJ: IV lignocaine fails to attenuate the cardiovascular response to laryngoscopy and tracheal intubation. Br J Anaesth 65:216, 1990.

124. Van Aken H, Puchstein C, Hidding J: The prevention of hypertension at intubation. Anaesthesia 37:82, 1982.

125. Gold MI, Brown M, Coverman S, et al: Heart rate and blood pressure effects of esmolol after ketamine induction and intubation. Anesthesiology 64:718, 1986.

126. Stoelting RK: Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg 58:116, 1979.

127. Gallagher JD, Moore RA, Jose AB, et al: Prophylactic nitroglycerin infusions during coronary artery bypass surgery. Anesthesiology 64:785, 1986.

128. Davies MJ, Cronin KD, Cowie RW: The prevention of hypertension at intubation. A controlled study of intravenous hydralazine on patients undergoing intracranial surgery. Anaesthesia 36:147, 1981.

129. Helfman SM, Gold MI, DeLisser EA, et al: Which drug prevents tachycardia and hypertension associated with tracheal intubation: Lidocaine, fentanyl, or esmolol? Anesth Analg 72:482, 1991.

130. Sharma S, Mitra S, Grover VK, et al: Esmolol blunts the haemodynamic responses to tracheal intubation in treated hypertensive patients. Can J Anaesth 43:778, 1996.

131. Gal TJ, Surratt PM: Resistance to breathing in healthy subjects following endotracheal intubation under topical anesthesia. Anesth Analg 59:270, 1980.

132. Eames WO, Rooke GA, Wu RS, et al: Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. Anesthesiology 84:1307, 1996.

133. Groeben H, Schwalen A, Irsfeld S, et al: Intravenous lidocaine and bupivacaine dose-dependently attenuate bronchial hyperreactivity in awake volunteers. Anesthesiology 84:533, 1996.

134. Hess D: The use of PEEP in clinical settings other than acute lung injury. Respiratory Care 33:581, 1988.

135. Bedford RF, Persing JS, Pobereskin L, et al: Lidocaine or thiopental for rapid control of intracranial hypertension. Anesth Analg 58:435, 1980.

136. Bedford RF: Circulatory responses to tracheal intubation. Problems in Anesthesia 2:201, 1988.

137. Stone DJ, Sperry RJ, Johnson JO, et al: The Neuroanesthesia Handbook. Mosby, St. Louis, 1996.

138. Michenfelder JD: Anesthesia and the Brain. New York, Churchill Livingstone, 1988.

139. Utting JE, Gray TC, Shelley FC: Human misadventure in anesthesia. Can Anaesth Soc J 26:472, 1979.

140. Birmingham PK, Cheney FW, Ward RJ: Esophageal intubation: A review of detection techniques. Anesth Analg 65:886, 1986.

141. Goldberg JS, Rawle PR, Zehnder JL, et al: Colorimetric end-tidal carbon dioxide monitoring for tracheal intubation. Anesth Analg 70:191, 1990.

142. Zaleski L, Abello D, Gold MI: The esophageal detector device--Does it work? Anesthesiology 79:244, 1993.

143. Baraka A, Khoury PJ, Siddik SS, et al: Efficacy of the self-inflating bulb in differentiating esophageal from tracheal intubation in the parturient undergoing caesarian section. Anesth Analg 84:533, 1997.

144. Lockey DJ, Woodward W: SCOTI vs. WEE--An assessment of two oesophageal intubation detection devices. Anaesthesia 52:242, 1997.

145. Conrady PA, Goodman LR, Lainge F, et al: Alteration of endotracheal tube position. Crit Care Med 4:8, 1976.

146. Toung TJK, Grayson R, Saklad J, et al: Movement of the distal end of the endotracheal tube during flexion and extension of the neck [letter]. Anesth Analg 64:1029, 1985.

147. Gal TJ: How does tracheal intubation alter respiratory mechanics? Problems in Anesthesia 2:191, 1988.

148. Norman EA, Sosis M: Iatrogenic oesophageal perforation due to tracheal or nasogastric intubation. Can Anaesth Soc J 33:222, 1986.

149. Chortkoff BS, Perlman B, Cohen NH: Delayed pneumothorax following difficult tracheal intubation. Anesthesiology 77:1225, 1992.

150. Zwillich C, Pierson DJ: Nasal necrosis: A complication of nasotracheal intubation. Chest 65:376, 1973.

151. Sherry KM: Ulceration of the inferior turbinate: A complication of prolonged nasotracheal intubation. Anesthesiology 59:148, 1983.

152. Arens JF, Lejeune FE, Webre DR: Maxillary sinusitis: A complication of nasotracheal intubation. Anesthesiology 40:415, 1974.

153. Bach A, Boehrer H, Schmidt H, et al: Nosocomial sinusitis in ventilated patients. Nasotracheal versus orotracheal intubation. Anaesthesia 47:335, 1992.

154. Pavlin EG, Holle RH, Schoene RB: Recovery of airway protection compared with ventilation in humans after paralysis with curare. Anesthesiology 70:381, 1989.

155. Hilley MD, Henderson RB, Gieseck AH: Difficult extubation of the trachea. Anesthesiology 59:149, 1983.

156. Cooper RM: Extubation and changing endotracheal tubes. In Benumof JL (ed): Airway Management Principles and Practice. St. Louis, Mosby, 1996, p 864.

157. Miller KA, Harkin CP, Bailey PL: Postoperative tracheal extubation. Anesth Analg 80:149, 1995.

158. Fisher MMcD, Raper RF: The "cuff-leak" test for extubation. Anaesthesia 47:10, 1992.

159. Burgess GE, Cooper JR, Marono RJ, et al: Laryngeal competence after tracheal extubation. Anesthesiology 51:73, 1979.

160. Loeser EA, Orr DL, Bennett GM, et al: Endotracheal tube cuff design and postoperative sore throat. Anesthesiology 45:684, 1976.

161. Loeser EA, Kaminsky A, Diaz A: The influence of endotracheal tube cuff design and cuff lubrication on postoperative sore throat. Anesthesiology 58:376, 1983.

162. Mandoe H, Nikolajsen L, Lintrup V, et al: Sore throat after endotracheal intubation. Anesth Analg 74:897, 1992.

163. Stout DM, Bishop MJ, Swersteg JF, et al: Correlation of endotracheal tube size with sore throat and hoarseness following general anesthesia. Anesthesiology 67:419, 1987.

164. Cavo JW: True vocal cord paralysis following intubation. Laryngoscope 95:1352, 1985.

165. Prasertwanich Y, Schwartz JJH, Vandam LD: Arytenoid cartilage dislocation following prolonged endotracheal intubation. Anesthesiology 41:516, 1974.

166. Frink EJ, Pattison BD: Posterior arytenoid dislocation following uneventful endotracheal intubation and anesthesia. Anesthesiology 70:358, 1989.

167. Jones MW, Catlings S, Evans E, et al: Hoarseness after tracheal intubation. Anaesthesia 47:213, 1992.

168. Yang KL: Tracheal stenosis after a brief intubation. Anesth Analg 80:625, 1995.

169. Bogdonoff DL, Stone DJ: Emergency management of the airway outside the operating room. Can J Anaesth 39:1069, 1992.

170. Schwartz DE, Matthay MA, Cohen NH: Death and other complications of emergency airway management in critically ill adults. Anesthesiology 82:367, 1995.

171. Stone DJ, Bogdonoff DL: Airway considerations in the management of patients requiring long-term endotracheal intubation. Anesth Analg 74:276, 1992.

172. Schwann NM: Percutaneous dilational tracheostomy: Anesthetic considerations for a growing trend. Anesth Analg 84:907, 1997.

173. Spiekermann BF, Bogdonoff DL, Leisure GS, et al: Nonsurgical airway management: General considerations and specific considerations in patients with coexisting disease. Respiratory Care 40:644, 1995.

174. Leisure GS, Stone DJ, Spiekermann BF, et al: Airway management of the chronically intubated patient. Respiratory Care 40:1279, 1995.

175. Benumof JL, Dagg R, Benumof R: Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. Anesthesiology 87:979, 1997.

Chapter 40 - Monitored Anesthesia Care

Monica M. Sa Rego
Paul F. White

INTRODUCTION

Monitored anesthesia care (MAC) has become increasingly important in the practice of anesthesiology. The primary objective in providing MAC is to ensure patient comfort, safety, and satisfaction during surgery. In most instances, the patient is undergoing a procedure under local anesthesia in the operating room (OR). The technologic advances in fiberoptics and lasers have enabled many diagnostic and therapeutic procedures to be performed by use of minimally invasive ("keyhole") techniques. Many of these procedures are being performed outside the operating suite and in the office-based setting. Because anesthesiologists have the greatest expertise in sedation-analgesia, they are often consulted for sedation and monitoring of these patients.

In this chapter, the objectives and techniques used for providing MAC are discussed, along with guidelines and recommendations for intraoperative monitoring. The relevant pharmacology of the commonly used adjuvant drugs, such as sedative-hypnotics, anxiolytics, and analgesics, are also reviewed. [1]

DEFINITION OF MAC

The American Society of Anesthesiologists (ASA) [2] defines MAC as instances in which an anesthesiologist has been called on to provide specific anesthesia services to a particular patient undergoing a planned procedure, in connection with which a patient receives local anesthesia or, in some cases, no anesthesia at all. In such a case, the anesthesiologist is providing specific services to the patient, is in control of his or her vital signs, and is available to administer anesthetics or provide other medical care as appropriate.

The policy of the ASA states that the same standard of care should be provided by an anesthesia practitioner during MAC as for general or regional anesthesia. [3] The provisions of MAC shall include the following:

1. Performance of a preanesthetic examination and evaluation
2. Prescription of the anesthesia care required
3. Personal participation in, or medical direction of, the entire plan of care
4. Continuous physical presence of the anesthesiologist or, in the case of medical direction, of the resident or nurse anesthetist being medically directed
5. Proximate presence or (in the case of medical direction) availability of the anesthesiologist for diagnosis or treatment of emergencies

In addition, all institutional regulations pertaining to anesthesia services shall be observed, and all the usual services performed by the anesthesiologist shall be furnished, including but not limited to the following:

1. Usual noninvasive cardiocirculatory and respiratory monitoring
2. Oxygen administration, when indicated
3. Intravenous administration of sedatives, tranquilizers, antiemetics, narcotics, other analgesics, beta-adrenergic blockers, vasopressors, bronchodilators, antihypertensives, or other pharmacologic therapy as may be required in the judgment of the anesthesiologist

ROLE OF MAC IN THE PRACTICE OF ANESTHESIA

The incidence of MAC as the anesthetic technique of choice varies among institutions. It has been estimated that 6 to 12 percent of all inpatient procedures and 30 to 60 percent of outpatient procedures are performed under MAC. With the technology of minimal invasive surgery and the development of rapid and short-acting sedative and analgesic drugs, the number and the variety of procedures being performed in the outpatient setting continue to increase, and MAC techniques are likely to become even more widely used in the future. [1]

Procedures performed with the patient under local anesthesia with sedation usually have a shorter recovery time than similar procedures performed with the patient under general or regional anesthesia. [4] A decreased use of drugs and disposable anesthetic supplies has also been reported in women undergoing laparoscopic tubal sterilization with a midazolam-alfentanil MAC technique compared with a propofol-alfentanil-atracurium general anesthetic technique ($21 versus $46). The MAC technique was associated with less time in the OR (30±4 versus 34±1 min), a higher "awakeness" score on the evening of the day of surgery (4.3±1.4 versus 3.6±1.4), as well as decreased postoperative pain (33% versus 80%) and sore throats (3% versus 70%), contributing to a significant reduction in perioperative costs. [5] Peterson et al [6] confirmed these findings and added that the incidence of emesis was also lower after MAC. Finally, Patel et al [7] reported that the use of intravenous sedation resulted in a 6- to 7-minute decrease in the OR exit time over that when general anesthesia was used, contributing to a significant cost saving as a result of enhanced turnover of the cases. This is an important consideration in today's practice environment with the emphasis on "fast-tracking" processes.

A wide variety of procedures can be performed under MAC (Table 40-1) . Local infiltration and peripheral nerve block techniques account for at least 40 to 50 percent of the nongeneral anesthetics administered in the United States. The use of local and regional (peripheral block) anesthetic techniques may avoid the common side effects of general anesthesia, minimize the risk of aspiration pneumonitis, decrease the postanesthesia nursing care, and provide residual analgesia in the early postoperative period. Simple surgical procedures can be performed with local wound infiltration, whereas more extensive operation may be undertaken by use of field blocks and intravenous regional anesthetic techniques (Table 40-2) (Table Not Available) . For upper and lower extremity procedures, peripheral nerve block techniques (e.g., axillary, su-praclavicular, interscalene, and ankle blocks) are also useful. However, many patients are reluctant to undergo local or regional anesthesia without supplemental medication because of the discomfort of the local injection and concerns about incisional pain and awareness during surgery (Chs. 43 and 44) . [4] [8] Anxiety regarding these issues can be eliminated by a careful explanation of the anesthesia treatment plan during the preoperative assessment. The patient should be reassured that needed adjuvant therapy is available to control pain and provide sedation, amnesia, and anxiolysis. [9]

The primary goal of MAC is to provide for patient comfort and safety. This objective can be achieved by careful monitoring of vital signs and by provision of anxiolysis, analgesia,

TABLE 40-1 -- Procedures Performed Under Monitored Anesthesia Care

Head and neck procedures
Third molar extractions
Blepharoplasty
Rhytidoplasty
Ptosis repair
Rhinoplasty
Mohs repair
Endoscopic sinus surgery
Repair of lacerations
Cervical node biopsy
Excision of neck mass
Cataract extraction
Trabeculectomy
Superficial thoracic procedures
Breast mass biopsy
Breast mass excision
Excision of axillary node
Removal of lipoma
Chest tube insertion
Bronchoscopy
Extremity procedures
Carpal tunnel release
Trigger finger release
Tendon repair
Removal of superficial pins/wires/screws
Excision of neuromas
Knee arthroscopy
Closed reduction of fractures
Digital amputations
Gastrointestinal abdominal procedures
Herniorrhaphy
Laparoscopy

Endoscopic retrograde cholangiopancreatography
Gastroscopy
Colonoscopy
Percutaneous ultrasonic lithotripsy
Vascular procedures
Hemodialysis access placement
Hickman catheter placement
Mediport placement
Greenfield filter placement
Pacemaker insertion
Angiography
Cardiac catheterization
Pericardial window
Carotid endarterectomy
Gynecologic/urologic procedures
Dilation and curettage
Laparoscopy
Fulguration of vaginal lesions
Fulguration of anal lesions
Cystoscopy
Incision and drainage of Bartholin cyst
Transvaginal ovum retrieval and other *in vitro* fertilization procedures
Circumcision
Vasectomy and orchiopexy
Extracorporeal shock-wave lithotripsy
Percutaneous ultrasonic lithotripsy

amnesia, and sedation without compromising cardiorespiratory function or delaying recovery. [10]

Drug administration may be preoperative, intraoperative, or postoperative, with anesthetic and analgesic drugs from two or more drug groups often being combined. [11] [12] [13] A wide variety of routes of administration (e.g., oral, nasal, trans-mucosal, parenteral, and rectal) as well as techniques (e.g., intermittent bolus, continuous infusion, and patient-controlled

TABLE 40-2 -- Common Techniques for Administering Local Anesthetics During MAC

(Not Available)

Modified from White [16]

analgesia) have also been used in patients receiving MAC. [14] [15] [16] [17]

There is an ever-present risk of synergistic interactions between sedative and analgesic drugs with respect to respiratory and cardiovascular depression. The respiratory depressant effects can be minimized when sedative drugs are administered by carefully titrated infusions versus large intermittent bolus doses. [11] Unwanted cardiovascular problems (e.g., hypotension, hypertension, drug-induced arrhythmias) can also be prevented by use of careful drug administration techniques. Thus, diligent monitoring is needed in order to assess the efficacy of adjunctive drugs during MAC and to minimize their potentially deleterious side effects.

The single greatest danger associated with MAC is a lack of vigilance because so-called minor surgical procedures are often being performed. Guidelines and recommendations for monitoring sedated patients have been published by the American Society of Anesthesia, the American Academy of Pediatrics, and the American Dental Society of Anesthesiology, as discussed later in the chapter.

USE OF SEDATIVE-ANALGESIC DRUGS DURING MAC

Sedation during local anesthesia is often desirable to diminish anxiety and fear associated with the OR activity and surgical preparation. Studies have shown that patients prefer surgery under local anesthesia with sedation to local anesthesia alone. [18] [19] To help relieve the discomfort associated with the painful injection of the local anesthetic solution, small doses of analgesics (e.g., fentanyl, 25-50 mug/70 kg intravenously [IV] or remifentanil, 12.5-25 mug/70 kg IV) can be administered.

Sedation can be useful for diagnostic tests that require immobilization for a significant period of time or for lengthy examinations in the closed confines of a magnetic resonance imaging (MRI) or computed tomographic scanner (Ch. 66) . This is especially useful both in children (Ch. 59) and in adults with claustrophobia, who have great difficulty cooperating with these procedures.

A wide variety of centrally active drugs are used to provide for sedation, anxiolysis, and analgesia (Table 40-3) . Administration should be individualized to the patient's level of discomfort, as well as to the patient's drug and medical history. Potent, rapid-acting sedative-hypnotics with steep dose-response curves (e.g., midazolam, propofol) should be carefully titrated by use of small bolus doses or a continuous variable-rate infusion. Although intermittent boluses of drugs can result in transient respiratory depression, use of continuous intravenous infusions can minimize cardiorespiratory depression. [20] [21] A stable level of intraoperative sedation can also be achieved by use of a continuous infusion.

The usual end point for titration of sedative-anxiolytic drugs is the patient's verbal acknowledgment of comfort and relaxation, which is usually confirmed by vital signs. The patient should remain cooperative and comfortable with airway reflexes intact. Because the need for sedative and analgesic drugs is highly subjective, patient-controlled sedation and analgesic techniques may offer advantages over physician-controlled drug administration. Studies have shown high patient satisfaction with these techniques. [14] [15] [16] Propofol,

TABLE 40-3 -- Recommended Doses of Commonly Used Sedative and Analgesic Drugs During MAC[a] [b]

DRUG	BOLUS DOSAGE	INFUSION RATE
Sedative-anxiolytics		
Diazepam	5-10 mg	
Midazolam	2.5-7.5 mg (alone)	1-2 mug/kg/min
	1-2 mg (with propofol)	
Propofol	25-100 mg	25-75 mug/kg/min
Thiopental	50-150 mg	
Methohexital	10-20 mg	20-60 mug/kg/min
Sedative-analgesics		
Ketamine	20-40 mg	5-15 mug/kg/min
Analgesics		
Alfentanil	0.25-0.75 mg	0.5-1 mug/kg/min
Fentanyl	25-50 mug	
Nalbuphine	5-15 mg	
Remifentanil	12.5-25 mug	0.025-0.15 mug/kg/min
Ketorolac	15-30 mg	
Benzodiazepine antagonist		
Flumazenil	0.5-1.0 mg	
Opioid antagonists		
Naloxone	0.1-0.4 mg	
Nalmefene	0.1 mg	
Nitrous oxide (inhaled concentration)	30-50%	

From Sa Rego et al [1]

[a] In the elderly population, lower doses of the sedative-analgesic drugs should be administered until their sensitivity has been determined (e.g., midazolam, 0.5-1.0 mg IV).
[b] Chs. 8 - 10

midazolam, and alfentanil have all been successfully administered by use of a patient-controlled device.

The ideal drug for sedation should have a rapid onset of action with a predictable dose-effect relationship with respect to its sedative-hypnotic actions. Excitatory effects should be minimal, as should its respiratory and cardiovascular depressant effects. Anxiolysis and amnesia should be predictable, with rapid recovery following discontinuation of its administration. Parenterally administered drugs are most popular in adults, whereas in children, enteral routes are more readily accepted.

The benzodiazepines remain the most widely used drugs for anxiolysis, amnesia, and sedation. Diazepam produces dose-dependent anxiolysis, sedation, and amnesia (Fig. 40-1) (Figure Not Available) [8] [22] However, large doses of diazepam (0.3 mg/kg IV) impair driving skills for at least 10 hours and may prolong recovery to a greater extent than in patients undergoing general anesthesia, a characteristic that makes it less desirable to outpatients. [23] [24] The original formulation of diazepam (Valium) contains propylene glycol, and its parenteral administration is associated with a higher incidence of pain on injection, as well as venoirritation and

phlebitis. [25] However, the newer lipid-based formulation of diazepam (Dizac) is associated with a lower incidence of venoirritation. [26]

Midazolam is more widely used because it is associated with less pain on injection and venous irritation. [8] Midazolam provides more profound perioperative amnesia, anxiolysis, and sedation than diazepam. [8] [27] [28] Although full recovery from the central nervous system (CNS) effects of midazolam is generally considered to be more rapid than recovery from the effects of diazepam, large doses of midazolam (0.2 mg/kg) can result in prolonged postoperative sedation. [29] Although midazolam provided more effective intraoperative sedation and amnesia than methohexital or propofol, it was associated with a slower recovery of psychomotor function. [4] [30] The time required to achieve a peak CNS effect with midazolam (2-4 minutes) may lead to cumulative effects (oversedation) when repeated bolus doses are administered over a short time interval. When midazolam is administered

Figure 40-1 (Figure Not Available) Dose-response curves for the level of sedation as a function of midazolam or diazepam dose. A score of 2 indicates minimal sedation; a score of 6 equals unconscious (hypnotic) state. Steeper dose-response curve for midazolam is illustrated. *(From White et al [8])*

as an infusion (loading dose of 0.025-0.05 mg/kg followed by a maintenance infusion of 1-2 mug/kg/min), it provides a titratable level of sedation during local anesthesia. [4]

White et al [8] noted a similar spectrum of CNS activity with midazolam (0.05-0.15 mg/kg IV) and diazepam (0.1-0.3 mg/ kg IV). However, the slope of the dose-response curve for sedation was much steeper with midazolam than with diazepam (see Fig. 40-1 (Figure Not Available)), suggesting that midazolam possesses a smaller margin of safety and necessitates more careful titration to achieve the desired clinical end point without untoward side effects. [8] Although clinical recovery characteristics were similar for diazepam and midazolam when they are used as adjuvants to ketamine, the incidence of amnesia and overall patient acceptance was significantly higher with midazolam. [8] Magni et al [31] also found a higher patient preference for midazolam (versus diazepam) during upper gastrointestinal endoscopy.

Midazolam has been administered orally (0.5-0.75 mg/ kg) to children. It produces reliable anxiolysis and sedation before surgery, without prolonging recovery time. [32] [33] In comparative studies, parents of children undergoing bone marrow biopsy procedures preferred midazolam to fentanyl for sedation. [34] Some studies have suggested that the combination of oral midazolam, 0.5 mg/kg, and low concentrations of inhaled nitrous oxide (N_2O) for sedation-analgesia is associated with only mild ventilatory depression in children; however, progression from conscious to deep sedation occurs with N_2O concentrations exceeding 30 percent. [35] In adults, oral temazepam (20-40 mg) is an effective alternative to parenteral benzodiazepines for sedation during endoscopy or oral surgery. [36] [37] Rapid reversal of residual benzodiazepine sedation and amnesia is possible with flumazenil, a specific benzodiazepine antagonist. [38] [39] [40]

Clinical studies involving outpatients undergoing dental surgery, endoscopic procedures, and minor ambulatory surgery have reported that flumazenil facilitates early recovery without producing adverse side effects when given in small incremental doses of 0.2 mg IV. [20] [41] [42] Ghouri et al [43] noted that the administration of flumazenil, 1 mg IV, at the end of surgery decreased the time to ambulation and discharge in patients who received large doses of midazolam (10.9±4.2 mg IV) during local anesthesia. The similar intraoperative conditions and early recovery profiles suggest that the use of a midazolam-flumazenil combination or a propofol infusion is equally acceptable during MAC. [43] Cost-effectiveness analyses would suggest that flumazenil should be used only to treat persistent excessive sedation after the MAC procedure. [44] Although there are only a few reported cases of clinically significant resedation after conscious sedation with midazolam followed by flumazenil, a subsequent increase in the level of sedation after discharge is common. [45]

Propofol has a pharmacodynamic-kinetic profile that is ideally suited to administration by continuous infusion. It has a rapid onset of action, a short duration of effect, and minimal side effects (Ch. 9) . Low-dose propofol infusions (25-75 mug/kg/min) have been used as adjuvants to local infiltration anesthesia in patients undergoing central venous catheter placement, [46] oral surgery, [47] and superficial surgical procedures (e.g., breast biopsy and herniorrhaphy). [4] [48] In comparing propofol and midazolam infusions for sedation during procedures performed with the patient under local

anesthesia, loading doses of 69±23 mg and 4.2±1.4 mg, followed by maintenance infusion rates of 61.7±16.7 mug/kg/ min and 2.0±1.1 mug/kg/min, respectively, were used. [4] Use of propofol was associated with a more rapid recovery of cognitive function and less postoperative sedation, drowsiness, confusion, clumsiness, and amnesia than midazolam (Fig. 40-2) (Figure Not Available) .

Both early and intermediate recovery have been found to be superior after a propofol infusion compared with repeated doses or infusion of midazolam [4] [46] and diazepam, [47] even when the benzodiazepine antagonist flumazenil was administered. [43] Compared to midazolam and methohexital, propofol was associated with the least frequent incidence of awareness during injection of the local anesthetic for retro-bulbar and peribulbar blocks and also resulted in more satisfactory sedation during the remainder of the procedure. [49] Several studies suggest that subhypnotic doses of propofol possess specific antiemetic properties, an important benefit in the outpatient setting. [50] [51] [52] Because subhypnotic doses of propofol are associated with minimal intraoperative amnesia, a small dose of midazolam (2 mg IV) is beneficial in enhancing propofol-induced sedation, amnesia, and anxiolysis without delaying recovery. [13] [53] [54]

In a volunteer study comparing midazolam (0.05 mg/kg) or fentanyl (2.0 mug/kg) to a midazolam-fentanyl combination, the incidence of hypoxemia and apnea was significantly increased when the two drugs were combined. [55] Careful

Figure 40-2 (Figure Not Available) Comparison of preoperative (baseline) and postoperative sedation, anxiety, and digit-symbol substitution test (DSST) scores in patients receiving midazolam (open circles) or propofol (solid circles) during local or regional anesthesia. *(From White and Negus [4])*

titration of these drugs and use of supplemental oxygen (e.g., nasal prongs) can diminish these undesirable respiratory depressant effects. The combination of propofol and alfentanil (50 mL of propofol [10 mg/mL] with 4 mL of alfentanil [0.5 mg/mL] can be administered by continuous infusion at 1-2 mL/kg/h) has been used successfully for sedation and analgesia during MAC. [12]

The objective of the use of opioid and nonopioid analgesics during MAC is to decrease the pain associated with the injection of local anesthetics, as well as the discomfort related to nonincisional factors (e.g., back pain secondary to lying on a hard OR table or pressure and traction on deep tissues that are not rendered insensitive by the local anesthetic solutions). [56] Fentanyl, the most commonly used opioid during MAC, has an onset time of 3 to 5 minutes and a duration of effect of 45 to 60 minutes when administered in doses of 50 to 100 mug IV. However, even small doses of fentanyl (25-50 mug) can cause respiratory depression when combined with large doses of sedative drugs. [57] Fentanyl, 1 mug/kg IV, has been used to sedate children undergoing repair of minor lacerations. [58] [59] Fentanyl is also available in a sucrose base for oral transmucosal administration (Oralet). Although this opioid preparation is readily accepted by children and is effective for procedure-related pain, its use is associated with typical opioid-related side effects, including emesis, pruritus, and respiratory depression. [17] [60]

Alfentanil may be given by intermittent boluses during the injection of local anesthetics or by continuous infusion to provide a stable level of analgesia. [61] White et al [62] reported fewer perioperative side effects when alfentanil was administered as a continuous titrated infusion compared with intermittent bolus injections. An equianalgesic dose of alfentanil is associated with a shorter duration of respiratory depression than fentanyl [62] and similar or shorter recovery times in the outpatient setting. [63] [64] The use of alfentanil and midazolam has been reported to provide highly satisfactory conditions for immersion extracorporeal shock-wave lithotripsy (ESWL). [53] Avramov et al [65] described the combined use of alfentanil (0.3-0.4 mug/kg/min) and propofol (25, 50, or 75 mug/kg/min) infusions for MAC. Concomitant use of propofol significantly reduced the opioid dose requirement (30-50%) and the incidence of postoperative nausea and vomiting (0-17% versus 33%) when compared with alfentanil infusion alone.

Remifentanil (Ch. 10) is unique among the opioid analgesics because of its extremely short context-sensitive half-time (3-5 minutes). [66] [67] [68] An infusion of remifentanil, 0.05 to 0.15 mug/kg/min, can provide adequate sedation and analgesia during minor surgical procedures performed with the patient under local anesthesia in combination with midazolam, 2 to 4 mg. [69] Sa Rego et al [70] compared the use of intermittent remifentanil boluses (25 mug) versus a continuous variable-rate infusion (0.025-0.15 mug/kg/min) when administered to patients undergoing ESWL under a MAC technique involving midazolam (2 mg) and propofol (25-50 mug/kg/min). Patients' comfort was higher during the procedure when remifentanil was administered by a variable-rate infusion. However, these patients also experienced a higher incidence of desaturation (30% versus 0%) compared with those receiving intermittent boluses of remifentanil. In comparison of remifentanil and propofol administered by continuous infusion after premedication with midazolam, there was a decreased

level of sedation and a greater degree of respiratory depression with remifentanil (versus propofol) administration. [71] Therefore, remifentanil infusions must be carefully titrated to avoid excessive respiratory depression. [1] [70] The use of remifentanil in combination with local anesthetics obviates the disadvantages of the minimal residual analgesia when remifentanil is used during painful procedures.

Ketorolac, a potent, parenterally active nonsteroidal anti-inflammatory drug, has been used both as a sole supplement and as an adjunct to propofol sedation during local anesthesia. Use of ketorolac is associated with a lower incidence of pruritus, nausea, and vomiting than fentanyl. [48] [56] [72] However, when used with propofol sedation, ketorolac-treated patients required higher intraoperative doses of propofol and more supplemental opioid analgesia compared with the fentanyl-treated patients. [56] The cost-effectiveness of ketorolac use during MAC techniques needs to be further investigated. [73]

Ketamine (0.25-0.5 mg/kg IV) (Ch. 9) produces sedation and analgesia without respiratory depression in adults. In patients undergoing intercostal nerve block procedures, ketamine produced more optimal clinical conditions and higher patient acceptance than diazepam or a droperidol-fentanyl combination. [74] Low-dose ketamine (0.25-0.75 mg/kg) combined with either diazepam or midazolam has also been administered before injection of local anesthetics in outpatients undergoing cosmetic surgical procedures. [75] Furthermore, the use of a diazepam-ketamine combination was not associated with any more side effects or a greater need for postoperative care than an unpremedicated control group undergoing similar nerve block procedures. [75] Benzodiazepines appear to be the most effective drugs in attenuating the psychomimetic actions of ketamine. However, large doses of benzodiazepines may be required (e.g., midazolam 5-15 mg) and can result in prolonged recovery times after ambulatory procedures. In pediatric patients, Green et al [76] demonstrated acceptable sedation with ketamine doses of 4 mg/kg IM. Ketamine-induced dysphoria was not encountered in these studies.

Methohexital has also been used successfully either by intermittent boluses (10-20 mg) or as a variable-rate infusion (0.1-0.2% solution). [30] [77] Although residual sedation appears to be greater with methohexital than with propofol, one study found no statistical difference in the recovery times when comparing infusions of methohexital (40 mug/kg/min) and propofol (50 mug/kg/min) during a MAC technique. However, there was also a higher incidence of pain on injection in the propofol infusion group. [78] [79] [80] Therefore, methohexital may be a safe and cost-effective alternative to propofol for sedation during MAC.

Subanesthetic concentrations of inhaled anesthetics (N_2O, 30-50% in oxygen or one-third of the minimum alveolar concentration of an inhaled anesthetic) can also be used to supplement regional or local anesthesia. [10] However, caution should be used to avoid excessive sedation or an inadvertent unconscious state.

alpha$_2$ -Agonists reduce central sympathetic outflow and have been shown to produce anxiolysis and sedation. [81] Kumar et al [81] demonstrated that oral clonidine (300 mug) provided effective anxiolysis for elderly patients undergoing ophthalmic surgery under local anesthesia and also decreased the incidence of intraoperative hypertension and tachycardia.

TABLE 40-4 -- Classification of Sedative and Analgesic Drugs Used During MAC (Pediatric Dosages)

DRUG	USUAL PEDIATRIC DOSAGES
Opioid analgesics	
Fentanyl	2-5 mug/kg IV
Morphine sulfate	0.05-0.1 mg/kg IV
Sedative-anxiolytics	
Diazepam	0.05-0.2 mg/kg IV
	0.2-0.5 mg/kg PO
Midazolam	0.035-0.1 mg/kg IV/IM
	0.3-0.7 mg/kg PO
Choral hydrate	25-100 mg/kg PO or PR
Pentobarbital	1-7 mg/kg IV/IM
Sedative-analgesics	
Demerol-phenergan-thorazine	2-1-1 mg/kg IM
Ketamine	4 mg/kg IM
	0.2-1 mg/kg IV

Data from Cook et al [85] and Sa Rego et al [1]

Dexmedetomidine, a more selective and potent alpha$_2$ -agonist, significantly decreased anxiety levels and reduced the requirements for supplemental analgesic medications when given before IV regional anesthesia for hand surgery. [82] When comparing dexmedetomidine with midazolam for sedation, Aho et al [83] described a faster recovery from sedation when dexmedetomidine was followed by reversal with the specific alpha$_2$ -antagonist atipamezole. However, the administration of dexmedetomidine has been associated with bradycardia, which may limit its usefulness during MAC. [82] [84]

For pediatric-aged patients, the dosages of sedative and analgesic drugs are higher on a per kilogram basis (Ch. 59) (Table 40-4) . Although midazolam and propofol have been used to sedate children, three other regimens are commonly used for procedures outside the OR. Chloral hydrate is one of the oldest and safest hypnotic drugs used for sedating children. In a survey conducted by Cook et al, [85] chloral hydrate was found to be the most popular sedative drug for painless diagnostic procedures. Chloral hydrate in doses of 25 to 100 mg/kg (oral and/or rectal administration) was shown to be both safe and effective (Ch. 59) . The second most common pediatric drug regimen is the so-called DPT injection, a combination of parenteral Demerol (meperidine), Phenergan (promethazine), and Thorazine (chlor-promazine) (maximum dose of 2-1-1 mg/kg). Although deaths have been reported following use of DPT, these were in children with congenital heart disease undergoing cardiac catheterization. [85] The third most commonly used sedative drug for pediatric sedation was pentobarbital (5-7 mg/kg).

DEFINING LEVELS OF SEDATION DURING MAC

The American Dental Society of Anesthesiology has defined sedation as follows [86]:

1. Conscious sedation: a minimally depressed level of consciousness that retains the patient's ability to maintain the airway independently and continuously and to respond

appropriately to physical stimulation and verbal command; produced by pharmacologic and nonpharmacologic methods, alone or in combination
2. Deep sedation: a controlled state of depressed consciousness, accompanied by partial loss of protective reflexes, including inability to respond purposefully to verbal command; produced by pharmacologic or nonpharmacologic methods, alone or in combination
3. General anesthesia: a controlled state of unconsciousness accompanied by partial or complete loss of protective reflexes, including inability to maintain an airway independently and to respond purposefully to physical stimulation or verbal command

Conscious sedation lies on a dose-dependent continuum leading from minimal sedation to general anesthesia. Table 40-5 (Table Not Available) illustrates the clinically significant differences between conscious and deep sedation.

The objectives of conscious sedation as outlined by Scamman et al [87] follow:

1. To relieve anxiety and produce amnesia. These goals are accomplished by means of good preoperative communication and instruction, low levels of visual and auditory stimuli in the OR, and maintenance of patient warmth and covering.
2. To provide relief from pain and other noxious stimuli. Opioid analgesics are given in order to supplement local or topical anesthetics and to block pain sensations remote from the operative site.
3. To achieve adequate sedation with minimal risk. Sedative medication should not interfere with the patient's ability to communicate verbally, and the usual monitoring devices and emergency systems must be available.

The marked variation in individual patient responses to a given dose of anesthetic drug has led the ASA to avoid the use of the term "conscious sedation" in their "Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists." [88] The ASA prefers the term "sedation-analgesia" and has recommended that all patients receiving this technique be monitored by a designated individual who is primarily

TABLE 40-5 -- Differences Between Conscious Sedation Versus Deep Sedation Techniques

(Not Available)

Modified from Kalkar and Dunwiddie [161]

responsible for administering sedative and analgesic drugs and monitoring the patient's vital signs.

COMPLICATIONS

Serious complications associated with local sedation techniques for dental surgery were initially reported in a British study. [89] Although the overall mortality rate was only 1 in 152,000, one-third of the deaths occurred in association with local sedation anesthesia. The majority of the sedation deaths occurred at the hands of operator-administered anesthetics (e.g., oral surgeons), and the most common precipitating causes included respiratory obstruction, hypoxia, and cardiovascular collapse secondary to arrhythmias. [90] Muir et al [91] found only minor differences in postoperative morbidity when comparing local and general anesthesia for young outpatients undergoing oral surgery.

A survey by the Federated Ambulatory Surgery Association (FASA) found higher overall complication rates after ambulatory surgery with combined local anesthesia and IV sedation (1:106) compared with general (1:120), regional (1:277), or local anesthesia alone (1:268). [92] The length of the operative procedure was another important determinant of morbidity after ambulatory surgery. For procedures lasting less than 1 hour, the incidence of perioperative complications was 1 in 155, and this ratio increased to 1:35 for procedures lasting longer than 3 hours. In this survey, outpatients with preexisting cardiovascular diseases were also reported to be at increased risk for postoperative complications. However, an epidemiologic study at the Mayo Clinic by Warner et al [93] revealed that the overall risk of major morbidity and mortality for outpatients undergoing ambulatory surgery did not differ from that of a similar age-matched population not undergoing an ambulatory surgical procedure.

The risk of adverse drug reactions increases when combinations of sedative and analgesic drugs are administered during local anesthesia. The potential for compromising the respiratory system results from depression of esophageal and laryngeal reflexes, upper airway obstruction, and depression of central hypercarbic and hypoxic ventilatory responses. [55] [94] [95] [96] Interestingly, when sedative drugs are administered by carefully titrated infusions (versus intermittent bolus doses), the respiratory depressant effects can be minimized. [38] However, with the rapid, short-acting opioid analgesic remifentanil, Sa Rego et al [70] reported that the infusion group received a higher total dose of remifentanil than the bolus group, contributing to greater depression of central ventilatory drive. Mora et al [20] found that five of 10 patients given an average diazepam dose of 0.97±0.34 mg/ min developed depressed hypoxic responsiveness and that only one of the five patients had complete reversal of ventilatory depression after flumazenil (1 mg IV) administration. Bailey et al [55] reported no significant respiratory depressant effect after midazolam administration (0.05 mg/kg IV). However, fentanyl (2 mug/kg IV) produced transient hypoxemia in 50 percent of the subjects and significantly depressed the ventilatory response to carbon dioxide. Furthermore, a combination of the same dosages of midazolam and fentanyl increased the incidence of both hypoxemia (92%) and apnea (50%). [55] In another clinical investigation, the incidence

of hypoxemia with a propofol-fentanyl combination was found to be significantly lower than that with midazolam and alfentanil. [53]

Because more than 40 percent of patients breathing room air during local anesthesia with sedation-analgesia for oral surgery experienced clinically significant oxygen desaturation, supplemental oxygen is always recommended when IV adjuvants are utilized during local anesthesia and can be delivered through a nasal cannula with an end-tidal carbon dioxide port to assess ventilatory rate. [97] However, the risk of hypoventilation (hypercarbia) exists despite the administration of supplemental oxygen. Pierce [98] reported that most anesthesia accidents resulting in severe brain damage (or death) were preventable by proper use of available monitoring techniques. [1]

MONITORING

Concerns regarding the safety of sedation practices were raised by reports of increased mortality and morbidity in dental offices and reports of misadventures during sedation for diagnostic procedures (e.g., gastrointestinal endoscopy) by nonanesthesiologists (Chs. 28 - 37) . In response to these reports, the American Academy of Pediatrics developed guidelines for monitoring and managing pediatric patients during and after sedation. [99] In these guidelines, an emphasis was placed on accident prevention and human factor issues to prevent situations in which no one was specifically assigned to monitor the patient and in which attention was directed more to performing the procedure than to observing patient response to the sedative-analgesic drugs. [100] [101] The American Academy of Pediatrics guidelines for deep sedation require that an additional health care provider who is not assisting in the performance of the procedure be available to administer drugs and monitor the child. Maxwell and Yaster [102] claimed that some practitioners attempt to circumvent this requirement by referring to all sedation techniques as "conscious sedation." In 1996, the ASA published its guidelines for sedation-analgesia by nonanesthesiologists. [88] These guidelines state that the individual administering the sedative-analgesic medications should have previous experience with the drugs they are using and should be familiar with the patient's medical history.

The ASA Standards for Basic Intraoperative Monitoring have been adopted as the national standard (see Appendix I). [3] The ASA has specified that the standards for basic monitoring during MAC by anesthesiologists are the same as those for general anesthesia. These recommendations stress quantitative rather than qualitative measurements. Standard I makes provisions for "qualified anesthesia personnel" to be present in the room. Standard II addresses objective measurements of patient oxygenation, ventilation, circulation, and body temperature. Although monitoring standards and guidelines may help detect human errors or mishaps, there is no substitute for vigilance and meticulous attention to detail. The Joint Commission on Accreditation of Health Care Organizations has insisted that the same standards of care that apply for general and regional anesthesia be provided during sedation techniques in all areas of an institution. [103] Because anesthesiologists have the most expertise in sedation-analgesia techniques, anesthesia departments are increasingly required to approve institutional policies and procedures for sedation-analgesia.

Specific Monitoring Requirements

The choice of monitoring devices, particularly when the emphasis is on patient safety, requires concomitant attention to quality control, safety procedures, risk recognition, decision-making, and other efforts to reduce human error (Chs. 28 , 29 , 33 - 37) . [104] The essential characteristics of monitoring techniques for outpatient MAC are that they not only be effective but also simple to apply, noninvasive, and economical. [105] The pulse oximeter has become an invaluable monitor because it fulfills all of these criteria. The monitoring guidelines of the American Academy of Pediatrics and the ASA regarding the routine use of pulse oximetry to assess oxygenation during sedation are based on studies establishing the superiority of pulse oximetry over visual inspection of mucous membranes and nail beds in detecting oxygen desaturation. [106] The initial opposition to the routine use of these devices outside the OR has disappeared as nonanesthesiologists have become more familiar with their clinical use. However, desaturation following sedation is a late event, and the inadequacy of ventilation should be detected and corrective measures instituted as the oxygen saturation value decreases below 90 percent. Unfortunately, impedance plethysmography may fail to detect airway obstruction, and the measurement of exhaled carbon dioxide can be difficult in nonintubated patients.

A simple, inexpensive, disposable oxygen delivery system involving the use of nasal prongs and an intranasal cannula connected to a capnograph can provide the anesthesiologist with a useful monitor of the expired carbon dioxide concentrations (Fig. 40-3) . [107] [108] [109] [110] Oxygen administration nasal cannulas with a sample port specifically for the carbon dioxide monitor line are commercially available (Salter Labs One-No. 4706F, patent 5,335,656, Salter Labs, Arvin, CA). A stable, discernible capnogram tracing is achievable in most patients having transcannula carbon dioxide sampling (Fig. 40-4) with an acceptable correlation between end-expiratory and arterial carbon dioxide tension readings. [111] [112] Problems with these devices include displacement and false sampling, false alarms (secondary to mouth breathing), and delays in alarm responses. Although useful in assessing respiratory rate (or airway obstruction), the capnographic tracing should not be relied on for accurate measurement of end-tidal carbon dioxide values.

Thus, the vigilance of the observer responsible for monitoring the patient receiving sedation-analgesia remains the best protection against adverse respiratory events. As with other types of anesthesia, the optimal level of patient care during MAC is achieved by meticulous attention to detail. [113]

Many monitoring devices are merely mechanical extensions of these senses and may create a barrier between the patient and the anesthesiologist. Vandam [114] pointed out that monitoring is an extension of the physical examination and that by keeping in close contact with the patient (e.g., feeling the pulse, observing respiration, watching the operative field, and using other senses to detect unusual events), anesthesiologists can improve the quality of monitoring during all types of MAC techniques.

Figure 40-3 Oxygen delivery via nasal prongs during MAC, with sedation produced by a midazolam infusion, 0.05 to 0.1 mg/min intravenously. (A) 14-Gauge intravenous cannula inserted into one of the nasal prongs, or (B) nasal adapter set (Datex Instrumentarium Corp., Helsinki, Finland) can be used for monitoring end-expiratory carbon dioxide.

Monitoring the Level of Sedation

A wide variety of objective clinical scoring systems have been developed to reduce individual observer bias and to provide a more consistent method for monitoring temporal changes in the level of sedation during MAC. [115] The most commonly used methods for assessing the level of sedation include the following:

1. The Ramsay scale, an objective scoring system that was originally used to quantitate the level of drug-induced sedation and to measure patient responsiveness and drowsiness in the intensive care unit. Unfortunately, it is difficult to quantify the degree of agitation and oversedation with this scale. [116]
2. The observer's assessment of alertness/sedation (OAA/S)scale was developed to quantify the CNS effects of benzodiazepines. [117] The OAA/S score is based on assessments in four separate categories: (1) responsiveness, (2) speech, (3) facial expression, and (4) ocular appearance. To correlate a greater degree of sedation with a higher OAA/S score, the original five-point OAA/S scoring system is usually reversed (with a score of 1 corresponding to an awake and alert state and 5 representing profound sedation). The OAA/S scale provides a higher discriminatory power of the different levels of sedation. The scale has also been validated against the digit symbol substitution test, a sensitive measure of cognitive and psychomotor impairment produced by sedative-hypnotic drugs. [118] The major disadvantages of these methods of CNS assessment are that the patients must be stimulated to perform the testing procedure during the operation, the patients' cooperation is required, and they are subject to testing fatigue.
3. The sedation visual analogue scale has also been used to quantify the level of sedation during MAC. [4] [48] [54] A 100-mm visual analogue scale for sedation is anchored at one end by the adjective "awake and alert" and at the opposite end by "asleep." Although this assessment tool also requires that the patients be

stimulated for the testing procedure, it requires minimal patient cooperation. Smith et al [54] demonstrated a good correlation between visual analogue scale sedation scores assessed simultaneously by the patient and by an independent observer during fixed-rate propofol infusions.

4. The most common neurophysiologic techniques for monitoring the depth of sedation involve the use of the electroencephalogram (EEG), a noninvasive, objective and continuous measure of brain function that has been shown to correlate with the depth of sedation. [119] Because sedative and analgesic drugs alter the EEG in a drug-specific fashion, interpretation of EEG changes can be difficult when drug combinations are used. [119] [120] The interpretation of EEG changes has been simplified by use of computerized EEG analysis (e.g., power bands [a, b, d, and q], frequency variables [95% spectral edge frequency and median frequency], and interfrequency phase-coupling numbers [bispectral {BIS} index]). Studies with the EEG-BIS index suggest that the BIS value correlates best with the "depth of sedation." [121] [122] Liu et al [123] [124] demonstrated that the EEG-BIS index correlates with the depth of both midazolam and propofol-induced sedation as validated by use of the OAA/S rating scale (Fig. 40-5) (Figure Not Available) . With an increasing depth of sedation with either midazolam or propofol, there are consistent and predictable decreases in the EEG-BIS index, with recovery following a similar pattern. These preliminary data suggest that anesthesiologists may be able to improve the titration of sedative-hypnotic drugs during MAC by utilizing the EEG-BIS monitor as an adjunct to the clinical assessment of CNS depression.

Figure 40-4 (A) Ohmeda 600 multiple gas monitor capnograph tracing during MAC in a patient receiving midazolam infusion, 0.05 to 0.1 mg/mL intravenously, for sedation during a urologic procedure. (B) After supplementation with an opioid analgesic (fentanyl, 25 mug intravenously), a marked slowing of the respiratory rate and an increase in end-expiratory carbon dioxide concentration were noted.

Figure 40-5 (Figure Not Available) Electroencephalogram (EEG) bispectral index as a function of the level of propofol (A) and midazolam (B) induced sedation during the onset and recovery phases. Observer assessment of alertness/sedation scale (OAA/S) score: 5=awake/alert to 1=deeply sedated. The values are either mean or individual (scatter plot). *(From Liu et al [123] [124])*

Global Patient Monitoring

Monitored anesthesia care provides a unique opportunity for the anesthesiologist and the patient to discuss the effectiveness of the therapeutic modalities being used (e.g., local anesthesia and adjuvant sedative-analgesic therapy) during surgery. To be effective, the anesthesiologist must remain in close verbal and/or tactile contact with the patient, particularly when centrally active drugs that can produce cardiorespiratory depression are being administered. A closed claims analysis of unexpected cardiac arrests during spinal anesthesia identified a lack of verbal responsiveness, resulting from an excessive depth of sedation, as one of the two recurring patterns. [125] The level of sedation was often reported to have produced a comfortable-appearing sleep-like state with no spontaneous verbalization.

It is useful to explain to patients at the time of the preoperative visit that feedback from them will be encouraged during the procedure (e.g., in preparation for the surgical stimulus) because this will be helpful in achieving the desired level of comfort and safety. Development of good rapport with the patient facilitates both the evaluation process and the intraoperative management of the case.

The age and the physical status of the patient are useful guides in evaluating organ system reserves and in determining their sensitivity to the sedative-analgesic drugs commonly used during MAC. [126] Other important issues include (1) past experiences with general, regional, and local anesthesia; (2) preoperative anxiety level; (3) previous problems with local anesthetics and sedative-analgesic medications; and (4) history of postoperative complications (e.g., nausea and vomiting). Apart from the desirable aim of attaining satisfactory patient acceptance, there are practical issues to be considered, such as delayed discharge from ambulatory surgical facilities because of intractable nausea and vomiting (secondary to opioid analgesics) and excessive drowsiness after benzodiazepine-induced sedation.

Monitoring After MAC

One of the principal aims in recovery room monitoring is to assess the residual effects of drugs administered intraoperatively and to determine when the patient is fit for discharge (Ch. 68) . One important difference between the recovery period and the operative phase is that the patient recovering from MAC with local anesthesia may not be experiencing the same degree of pain or discomfort as the patient emerging from general anesthesia, thereby increasing the potential for delayed side effects related to the use of sedative-analgesic drugs (e.g., excessive sedation, airway obstruction, respiratory depression).

The overall rate of recovery room morbidity varies from 18 to 30 percent and includes airway obstruction, hypoventilation, hypotension or hypertension, arrhythmias, in-adequate analgesia, nausea and vomiting, and postanesthetic shivering. [127] [128] [129] Postanesthesia care unit monitoring after MAC is a natural extension of intraoperative monitoring,

with particular emphasis on respiratory adequacy, cardiovascular stability, and return to baseline levels of cerebral functioning. This requires clinical evaluation as well as use of pulse oximetry, blood pressure, and temperature monitoring. An appropriate level of staffing, good patient supervision, and allowance for adequate recovery time are all essential components for providing for a safe recovery after MAC. [130]

The American Academy of Pediatrics guidelines suggest the same degree of monitoring (vital signs, pulse oximetry, heart rate monitoring) be maintained after the procedure as during the procedure (i.e., until the patient is fully alert and/or appropriate discharge criteria are met). [131] Recommended discharge criteria after intravenous sedation-analgesia include the following:

1. Cardiovascular function and airway patency are satisfactory and stable.
2. The patient is easily arousable, and protective reflexes are intact.
3. The patient can talk (if age-appropriate).
4. The patient can sit up unaided (if age-appropriate).
5. For a very young or handicapped child, incapable of the usually expected responses, the presedation level of responsiveness or a level as close as possible to the normal level for that child should be achieved.
6. The state of hydration is adequate.

USE OF MAC OUTSIDE THE OPERATING ROOM

There has been an increase in the number of diagnostic, radiologic, and minor surgical procedures performed outside the traditional OR setting (Ch. 66) . Although many procedures are painless, some necessitate immobility (e.g., MRI and radiation therapy). Therefore, anesthesiologists are often called on to administer intravenous sedationanalgesia outside the OR environment.

Optimal monitoring conditions rarely exist outside the OR; therefore, the anesthesiologist must often provide a mobile anesthesia machine with monitors and the necessary supplies. In these situations, supplemental oxygen and suction should be available. Because these specialized diagnostic units are not normally designed with anesthesia in mind, the addition of anesthesia equipment and personnel can create a crowded work environment. Advance planning and preparation on the part of both the anesthesiologist and the diagnostic specialist involved in the procedure minimize the possibility of serious complications.

Patients with preexisting medical conditions, such as critically ill patients, mentally handicapped patients, uncooperative children, and patients with psychiatric disorders, are more likely to require anesthesia for diagnostic procedures. These complex patients may be at increased risk for developing complications and, coupled with the difficulties in providing anesthesia care under less than ideal conditions, can make providing anesthesia remote from the OR a challenging experience for anesthesiologists.

Over the past 5 years, a multitude of articles have been published regarding guidelines and techniques for monitoring in locations remote from the OR (e.g., radiologic and angiographic units; cardiology, pulmonary, and gastroenterology procedure suites; lithotripsy; and free-standing MRI facilities). A few of the most pertinent issues related to MAC in areas remote from the OR are summarized in the following sections. [131] [132] [133]

Magnetic Resonance Imaging

Magnetic resonance imaging has become an increasingly popular noninvasive radiologic diagnostic procedure because of the high-quality images provided. MRI requires that the patients be confined for 30 to 60 minutes in a magnetic, closed, noisy space. Therefore, some patients, because of age, altered mental state, or pain, cannot cooperate for this length of time and require either general anesthesia or MAC to accomplish a high-quality image. [133] [134] Patient movement during any part of the examination can degrade the quality of the image. Therefore, anesthesiologists are increasingly involved in patient care for MRI and spectroscopy. There are special anesthetic considerations surrounding MRI because of the high magnetic field and the specialized rooms and buildings for housing the MRI scanners. [134] [135] The problems in monitoring patients undergoing MRI include the following:

1. Ferromagnetic equipment must be removed from the magnetic field, including credit cards, key chains, paper clips, pins, and pens, as well as conventional monitoring devices
2. Limited access to the patient and limited view of the patient while in the scanner
3. Malfunction of monitoring equipment, or interference, produced by the changing magnetic field (e.g., syringe infusion pumps)
4. Degradation of image and special quality arising from stray radiofrequency current produced by monitoring equipment and leads

These issues make it difficult to achieve an adequate balance between meeting the ASA standards for monitoring during anesthesia and acquiring a high-quality image. [133] Newer anesthesia machines and nonferrous monitoring equipment are available. Because the older monitors may have to be located far from the patient (e.g., outside the room), the chances of disconnects and kinks in intravenous tubing, anesthesia circuit tubing, monitoring leads, and cables are increased. The ideal situation is to have two anesthesia personnel: one close to the patient and an assistant outside the room with the monitoring equipment. Unfortunately, the costs of this type of care would be higher.

MAC in the Gastroenterology Suite

For many years, endoscopists have utilized conscious sedation techniques for these patients. Sedation not only improves patient comfort during the examination but also improves patient acceptance of follow-up examinations. [136] Specific monitoring guidelines and sedation techniques for assisting the endoscopist are available. [137] [138] [139] However, many situations arise that can benefit from the services of an anesthesiologist, such as endoscopic procedures that are

performed on patients with complex coexisting medical conditions or in situations in which previous attempts at operator-administered sedation were unsuccessful.

An important consideration in the planning of an anesthetic technique is the position of the patient during the examination. Patients undergoing endoscopic procedures are often positioned lateral or prone to facilitate the examination, and these positions may pose difficulty should resuscitative efforts be required. During upper endoscopic procedures or endoscopic retrograde cholangiopancreatography, the endoscope is inserted orally, which necessitates sharing the patient's airway with the endoscopist. Cooperation and a team approach by the endoscopist, the radiology staff, and the anesthesiologist is essential.

Extracorporeal Shock-Wave Lithotripsy

Extracorporeal shock-wave lithotripsy is the treatment of choice for urinary tract calculi. ESWL has also been used in the treatment of biliary calculi. Although these procedures can be performed with the patient under general and regional anesthesia, these techniques are time consuming, and epidural anesthesia is associated with urinary retention and delayed recovery. [140] [141] MAC techniques reduce the anesthesia and recovery times without compromising patient safety and satisfaction. [53] [132] [142] Monk et al [132] compared alfentanil and ketamine infusions in combination with mid-azolam and described both techniques as effective, although patients receiving alfentanil had a better recovery profile and calculi fragmentation. A MAC technique involving midazolam-alfentanil and fentanyl-propofol has also been utilized for ESWL procedures with a high degree of patient satisfaction. [53] Patient-controlled analgesia with alfentanil has also been described for gallstone and urinary tract calculi lithotripsy. [143] [144] A MAC technique involving midazolam (2 mg), propofol infusion (25-50 mug/kg/min), and a continuous infusion of remifentanil (0.025-0.15 mug/kg/min) has been described. [70]

Office-Based Anesthesia

Office-based surgery and anesthesia are not new concepts. At the beginning of this century, as physicians started to specialize in the practice of anesthesia, one of the pioneering American anesthesiologists, Ralph Waters, opened an office-based anesthetic practice (the Downtown Anesthesia Clinic) in Sioux City, Iowa. In response to an occasional call from a dentist for anesthesia, Dr.Waters set up "a modest office with a waiting room and a small operating room with an adjoining room

containing a cot on which a patient could lie down after his anesthetic before going home." [145]

The role that regulations would play in office-based anesthesia perhaps first became evident in 1968, at the Dudley Street facility in Providence, Rhode Island. In a letter entitled "Surgery in an Office Suite" in the Medical Economics magazine, Charles Hill wrote "In Rhode Island, we have come up with what we hope will be the answer: incorporating in a medical office building an operating suite complete with OR facilities and a recovery room." Unfortunately, the facility was financially insolvent because it was not supported by the state's regulatory agencies (which ruled that the suite was no more than a doctor's office) and also lacked support from Blue Cross and third-party carriers. [146] [147]

For many years, relatively simple, minimally invasive surgical procedures have been performed in physicians' offices. Certified registered nurse anesthetists, dental anesthesiologists, and a small number of anesthesiologists have been active in office-based surgery.

Office-based anesthesia is a rapidly growing practice of ambulatory surgery. Anesthesiologists have begun to assume their position in this shift of surgical procedures to the office facility. A survey by the Society for Ambulatory Anesthesia found that 20 percent of anesthesiologists were devoting an increasing portion of their practice to office anesthesia. Office-based anesthesia has grown from 400,000 procedures in 1984 to 1.2 million in 1990. It is estimated that up to 20 percent of all elective surgery will be performed in an office-based setting by the year 2001. [148]

A number of reasons have been identified for the growth of office-based anesthesia. Not surprisingly, health care reform and economics issues are a major driving force in this growth as the potential exists for office-based surgery to further reduce costs by decreasing facility fees and overhead. The availability of anesthesiologists can ensure the delivery of high-quality patient care in a setting where overhead is lower than in a hospital or free-standing surgical center, thereby decreasing the cost of providing surgical services. A cost comparison of laparoscopic inguinal herniorrhaphy performed by Shultz [149] reported that the total cost for this procedure in their hospital was $5,494, compared with $1,533.84 in the surgical office. The hospital fees for a conventionally performed inguinal herniorrhaphy was $2,237, compared with a fee of $894.79 in the office. [149]

Another reason for the growth in office-based surgery relates to improvements in anesthesia techniques and new surgical technologies. Utilizing these advances in surgical and anesthesia care, the "limits" are continually being pushed as practitioners attempt to determine what procedures can be safely performed in office surgery suites. The office is also likely to provide more convenient and comfortable patient care. Although office-based surgery is likely to continue to grow, the success of providing anesthesia in a surgeon's office will increasingly depend on the ability of the surgery/anesthesia team to perform an astute preoperative assessment of outpatients scheduled for surgical procedures in the office setting. The preoperative work-up should be guided by the same clinical acumen and common sense that drives the decision-making process at free-standing surgery centers. The selection criteria of patients are based on ASA physical status (1-2) and age (7-70 years). In addition, patients with potentially difficult airways are not considered good candidates for office-based anesthesia.

The most popular office-based anesthetic technique involves the use of local anesthesia in combination with rapid and short-acting intravenous (propofol) and inhaled (N_2 O, sevoflurane and/or desflurane) anesthetics. For transient intense discomfort, the potent opioid analgesic fentanyl or one of its newer analogues is recommended. Tang et al [150] described the use of a propofol infusion versus a propofol infusion

---

in combination with N_2 O (60-70%) in patients undergoing superficial surgical procedures in an office-based facility. These investigators reported a decrease in the propofol dosage requirement in the group receiving N_2 O without increasing the incidence of postoperative emesis or prolonging the discharge times. [150] Because most office suites do not have stretchers or recovery beds, patients have to be able to get up from the OR table and transfer themselves to a reclining chair or ambulate to an area where they can rest until they are ready to get dressed and go home.

The major issues in the provision of safe anesthetic care in the office setting are the set-up, maintenance of equipment and supplies, and assessment of the quality of the services provided. A few states (e.g., California and Florida) in the United States have started to address the concerns related to the administration of anesthetics for office-based surgery procedures. The clinical practice guidelines should be consistent with the recommendations and standards established by the ASA, the American Association of Nurse Anesthetists, and the Joint Commission on Accreditation of Healthcare Organizations. These groups have recommended the following office-based practice guidelines [151] :

1. Employment of appropriately trained and credentialed anesthesia personnel
2. Availability of properly maintained anesthesia equipment appropriate to the anesthesia care being provided
3. Documentation of the care provided must be as complete as that required at other surgical sites
4. Use of standard monitoring equipment according to the ASA policies and guidelines
5. Provision of a postanesthesia care unit or recovery area that is staffed by appropriately trained nursing personnel. Specific discharge instructions should be provided
6. Availability of emergency equipment (e.g., airway equipment, cardiac resuscitation)
7. Establishment of a written plan for emergency transport of patients to a site that provides more comprehensive care should an untoward event or a complication occur that requires more extensive monitoring or overnight admission of the patient
8. Maintenance and documentation of a quality assurance program
9. Establishment of a continuing education program for physicians and other facility personnel

Beyond their responsibility to provide safe care in the office, the modern day office anesthesiologist has an opportunity to expand his or her role as a perioperative physician. This practice has the potential to heighten public awareness of the vital role of anesthesiologists in the office setting and can enhance the professional image of our specialty. Patients must be confident that the office setting adheres to the same standards of care required in a hospital-based or a free-standing ambulatory surgery facility. Safety standards can- not be jeopardized for patient convenience or cost savings.

SUMMARY

Monitored anesthesia care has become the anesthetic technique of choice for an increasing number of diagnostic and therapeutic procedures because recovery profiles appear to be improved compared with those of general and regional anesthesia. [1] [5] [6] The administration of sedative and analgesic drugs to enhance patient comfort requires careful titration and adequate monitoring to achieve the desired goal without compromising patient safety. The effective use of a MAC technique can provide highly acceptable patient comfort while optimizing intraoperative conditions. The so-called Iowa satisfaction with anesthesia scale was developed to evaluate patient satisfaction with MAC and may prove to be a useful tool for comparing different MAC techniques. [152] Patient cooperation, effective local anesthesia, and gentle surgical technique are all essential elements for the successful application of a MAC technique. Although local anesthetic-based techniques are generally assumed to be safer than general or regional anesthesia, supplementation with potent sedative-hypnotic and analgesic drugs may result in significant depression of central respiratory drive and/or transient upper airway obstruction. Therefore, the decision to use MAC in place of general or regional anesthesia should be made only after careful assessment of both patient and surgeon preferences, as well as any coexisting medical conditions.

The importance of vigilant monitoring, use of supplemental oxygen when IV sedative-analgesic drugs are administered, and availability of resuscitation equipment are all essential elements for the safe practice of MAC, whether it is administered in a hospital-based unit, an ambulatory surgery center, or an office-based facility. The choice of a regimen of sedative/analgesic drugs for use during MAC should be based on the anticipated degree of pain and the sedation requirements for the successful completion of the operation. Pain and anxiety must be treated with appropriate pharmacologic agents, targeting the intervention at the specific problem and titrating all drugs to the desired effect. [153] If the procedure is relatively pain free and anxiolysis is the main consideration, it may be justified to use only a benzodiazepine (e.g., diazepam, midazolam). For diagnostic procedures that are pain free (e.g., radiation therapy), a low-dose propofol infusion should be utilized. If brief periods of pain are anticipated during the procedure, administration of a rapid short-acting analgesic opioid is indicated (e.g., fentanyl, alfentanil, remifentanil). For procedures in which analgesia is provided by a regional anesthetic technique (e.g., peripheral nerve block), a stable level of sedation can be easily achieved by use of a variable-rate infusion of propofol or methohexital. An effective regimen for MAC might include midazolam, 1 to 3 mg IV, followed by propofol, 25 to 100 mug/kg/min or methohexital 20 to 60 mug/kg/min in combination with intermittent boluses of fentanyl (25 mug), sufentanil (5 mug), alfentanil (250 mug), or remifentanil (12.5 mug). [13] [70] Alternatively, in patients premedicated with midazolam, 1 to 5 mg IV, a basal infusion of alfentanil (0.5-1.0 mug/kg/min) or remifentanil (0.025-0.15 mug/kg/min) can be supplemented with small bolus doses of the same analgesic. Careful titration to ensure adequate cardiorespiratory stability by use of variable-rate infusions of sedative and analgesic drugs minimizes the possibility of adverse side effects during MAC. [1] [154]

In conclusion, concerns regarding the effects of the increasing health-care costs on the medical decision process have led to a reexamination of many anesthetic practices. [155] In general, the overall cost of a MAC technique is less than

that of either general or regional anesthesia. [5] [68] [156] In order to realize the savings resulting from decreased discharge time, reduced postoperative pain, and lower incidence of sore throats and emesis with MAC techniques, recovery procedures and discharge criteria will have to allow the direct transfer of all MAC patients from the OR to a phase II recovery area (i.e., fast tracking). [5] [157] [159] With the growing interest in office-based surgery, the use of MAC techniques will continue to increase in popularity. [1]

References

1. Sa Rego MM, Watcha MF, White PF: The changing role of monitored anesthesia care in the ambulatory setting. Anesth Analg 85:1020, 1997.

2. American Society of Anesthesiologists: Position on Monitored Anesthesia Care. Directory of Members. Park Ridge, Illinois, American Society of Anesthesiologists, 1997, p 413.

3. American Society of Anesthesiologists (ASA): Standards for Basic Anesthetic Monitoring. Directory of Members. Park Ridge, Illinois, American Society of Anesthesiologists, 1997, p 394.

4. White PF, Negus JB: Sedative infusions during local and regional anesthesia: A comparison of midazolam and propofol. J Clin Anesth 3:32, 1991.

5. Bordahl PE, Raeder JC, Nordentoft J et al: Laparoscopic sterilization under local or general anesthesia? A randomized study. Obstet Gynecol 81:137, 1993.

6. Peterson HB, Hulka JF, Spielman FJ et al: Local versus general anesthesia for laparoscopic sterilization: A randomized study. Obstet Gynecol 70:903, 1987.

7. Patel N, Smith CE, Pinchak AC et al: Desflurane is not associated with faster operating room exit times in outpatients. J Clin Anesth 8:130, 1996.

8. White PF, Vasconez LO, Mathes SA et al: Comparison of midazolam and diazepam for sedation during plastic surgery. J Plast Reconstr Surg 81:703, 1988.

9. Egbert LD, Battit GE, Turndorf H et al: The value of the preoperative visit by an anesthetist. JAMA 185:553, 1963.

10. Philip BK: Supplemental medication for ambulatory procedures under regional anesthesia. Anesth Analg 64:1117, 1985.

11. White PF: Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology 59:294, 1983.

12. Sherry E: Admixture of propofol and alfentanil: Use for intravenous sedation and analgesia during transvaginal oocyte retrieval. Anaesthesia 47:477, 1992.

13. Taylor E, Ghouri AF, White PF: Midazolam in combination with propofol for sedation during local anesthesia. J Clin Anesth 4:213, 1992.

14. Osborne GA, Rudkin GE, Curtis NJ et al: Intra-operative patientcontrolled sedation: Comparison of patient-controlled propofol with anaesthetist-administered midazolam and fentanyl. Anaesthesia 46:553, 1991.

15. Zelcer J, White PF, Chester S et al: Intraoperative patient-controlled analgesia: An alternative to physician administration during outpatient monitored anesthesia care. Anesth Analg 75:41, 1992.

16. Ghouri AF, Taylor E, White PF: Patient-controlled drug administration during local anesthesia: A comparison of midazolam, propofol, and alfentanil. J Clin Anesth 4:476, 1992.

17. Jenkins P, La S, Noe C et al: Use of transmucosal drug delivery for providing analgesia during procedures performed under local anesthesia [abstract]. Anesth Analg 82:S205, 1996.

18. Lundgren S, Rosenquist JB: Amnesia, pain experience, and patient satisfaction after sedation with intravenous diazepam. J Oral Maxillofac Surg 41:99, 1983.

19. Lundgren S, Rosenquist JB: Comparison of sedation, amnesia, and patient comfort produced by intravenous and rectal diazepam. J Oral Maxillofac Surg 42:646, 1984.

20. Mora CT, Torjman M, White PF: Effects of diazepam and flumazenil on sedation and hypoxic ventilatory response. Anesth Analg 68:473, 1989.

21. Newson C, Joshi GP, Victory R et al: Comparison of propofol administration techniques for sedation during monitored anesthesia care. Anesth Analg 81:486, 1995.

22. Conner JT, Bellville JW, Wender RH et al: Evaluation of intravenous diazepam as a surgical premedicant. Anesth Analg 56:211, 1977.

23. Korttila K, Linnoila M: Recovery and skills related to driving after intravenous sedation: Dose-response relationship with diazepam. Br J Anaesth 47:457, 1975.

24. Gale GD: Recovery from methohexitone, halothane and diazepam. Br J Anaesth 48:691, 1976.

25. Hegarty JE, Dundee JW: Sequelae after the intravenous injection of three benzodiazepines: Diazepam, lorazepam, and flunitrazepam. Br Med J 2:1384, 1977.

26. White PF: Ambulatory anesthesia and surgery: Past, present and future. In White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 3.

27. Dundee JW, Wilson DB: Amnesic action of midazolam. Anaesthesia 35:459, 1980.

28. Philip BK: Hazards of amnesia after midazolam in ambulatory surgical patients. Anesth Analg 66:97, 1987.

29. McClure JH, Brown DT, Wildsmith JA: Comparison of the i.v. administration of midazolam and diazepam as sedation during spinal anaesthesia. Br J Anaesth 55:1089, 1983.

30. Urquhart ML, White PF: Comparison of sedative infusions during regional anesthesia: Methohexital, etomidate, and midazolam. Anesth Analg 68:249, 1989.

31. Magni VC, Frost RA, Leung JW et al: A randomized comparison of midazolam and diazepam for sedation in upper gastrointestinal endoscopy. Br J Anaesth 55:1095, 1983.

32. Feld LH, Negus JB, White PF: Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 73:831, 1990.

33. Weldon BC, Watcha MF, White PF: Oral midazolam in children: Effect of time and adjunctive therapy. Anesth Analg 75:51, 1992.

34. Sandler ES, Weyman C, Conner K et al: Midazolam versus fentanyl as premedication for painful procedures in children with cancer. Pediatrics 89:631, 1992.

35. Litman RS, Berkowitz RJ, Ward DS: Levels of consciousness and ventilatory parameters in young children during sedation with oral mid-azolam and nitrous oxide. Arch Pediatr Adolesc Med 150:671, 1996.

36. Douglas JG, Nimmo WS, Wanlesss R et al: Sedation for upper gastro-intestinal endoscopy: A comparison of oral temazepam and i.v. diazepam. Br J Anaesth 52:811, 1980.

37. O'Boyle CA, Harris D, Barry H: Sedation in outpatient oral surgery: Comparison of temazepam by mouth and diazepam i.v. Br J Anaesth 58:378, 1986.

38. Mora CT, Torjman M, White PF: Sedative and ventilatory effects of midazolam infusion: Effect of flumazenil reversal. Can J Anaesth 42:677, 1995.

39. Torjman M, Mora CT, White PF: Does flumazenil antagonize midazolam-induced depression of ventilatory response to hypoxia? Anesthesiology 80:233, 1994.

40. Pearson RC, McCloy RF, Morris P et al: Midazolam and flumazenil in gastroenterology. Acta Anaesthesiol Scand Suppl 92:21, 1990.

41. White PF, Shafer A, Boyle WA et al: Benzodiazepine antagonism does not provoke a stress response. Anesthesiology 70:636, 1989.

42. McKay AC, McKinney MS, Clarke RS: Effect of flumazenil on mid-azolam-induced amnesia. Br J Anaesth 65:190, 1990.

43. Ghouri AF, Ruiz MA, White PF: Effect of flumazenil on recovery after midazolam and propofol sedation. Anesthesiology 81:333, 1994.

44. Watcha MF: Cost minimization, cost-benefit and cost-utility analyses. In White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 648.

45. McCloy RF: Reversal of conscious sedation by flumazenil: Current status and future prospects. Acta Anaesthesiol Scand Suppl 108:35, 1995.

46. Pratila MG, Fischer ME, Alagesan R et al: Propofol versus midazolam for monitored sedation: A comparison of intraoperative and recovery parameters. J Clin Anesth 5:268, 1993.

47. Valtonen M, Salonen M, Forssell H et al: Propofol infusion for sedation in outpatient oral surgery: A comparison with diazepam. Anaesthesia 44:730, 1989.

48. Ramirez-Ruiz M, Smith I, White PF: Use of analgesics during propofol sedation: A comparison of ketorolac, dezocine, and fentanyl. J Clin Anesth 7:481, 1995.

49. Ferrari LR, Donlon JV: A comparison of propofol, midazolam, and methohexital for sedation during retrobulbar and peribulbar block. J Clin Anesth 4:93, 1992.

50. McCollum JS, Milligan KR, Dundee JW: The antiemetic action of propofol. Anaesthesia 43:239, 1988.

51. Watcha MF, Simeon RM, White PF et al: Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. Anesthesiology 75:204, 1991.

52. Borgeat A, Wilder-Smith OH, Saiah M et al: Subhypnotic doses of propofol possess direct antiemetic properties. Anesth Analg 74:539, 1992.

53. Monk TG, Boure B, White PF et al: Comparison of intravenous sedative-analgesic techniques for outpatient immersion lithotripsy. Anesth Analg 72:616, 1991.

54. Smith I, Monk TG, White PF et al: Propofol infusion during regional anesthesia: Sedative, amnestic, and anxiolytic properties. Anesth Analg 79:313, 1994.

55. Bailey PL, Pace NL, Ashburn MA et al: Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 73:826, 1990.

56. Bosek V, Smith DB, Cox C: Ketorolac or fentanyl to supplement local anesthesia? J Clin Anesth 4:480, 1992.

57. Rigg JR, Goldsmith CH: Recovery of ventilatory response to carbon dioxide after thiopentone, morphine and fentanyl in man. Can Anaesth Soc J 23:370, 1976.

58. Cote CJ: Sedation for the pediatric patient: A review. Pediatr Clin North Am 41:31, 1994.

59. Pohlgeers AP, Friedland LR, Keegan-Jones L: Combination fentanyl and diazepam for pediatric conscious sedation. Acad Emerg Med 2:879, 1995.

60. Ashburn MA, Streisand JB: Oral transmucosal fentanyl: Help or hindrance? Drug Saf 11:295, 1994.

61. Yee JB, Schafer PG, Crandall AS et al: Comparison of methohexital and alfentanil on movement during placement of retrobulbar nerve block [see comments]. Anesth Analg 79:320, 1994.

62. White PF, Coe V, Shafer A et al: Comparison of alfentanil with fentanyl for outpatient anesthesia. Anesthesiology 64:99, 1986.

63. Kay B, Venkataraman P: Recovery after fentanyl and alfentanil in anaesthesia for minor surgery. Br J Anaesth 55:169S, 1983.

64. Cooper GM, O'Connor M, Mark J et al: Effect of alfentanil and fentanyl on recovery from brief anaesthesia. Br J Anaesth 55:179S, 1983.

65. Avramov MN, White PF: Use of alfentanil and propofol for outpatient monitored anesthesia care: Determining the optimal dosing regimen. Anesth Analg 85:566, 1997.

66. Egan TD, Lemmens HJ, Fiset P et al: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 79:881, 1993.

67. Kapila A, Glass PS, Jacobs JR et al: Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology 83:968, 1995.

68. Rosow C: Remifentanil: A unique opioid analgesic. Anesthesiology 79:875, 1993.

69. Avramov MN, Smith I, White PF: Interactions between midazolam and remifentanil during monitored anesthesia care. Anesthesiology 85:1283, 1996.

70. Sa Rego MM, Inagaki Y, White PF: Use of remifentanil during lithotripsy: Intermittent boluses vs continuous infusion [abstract]. Anesth Analg 84:S541, 1997.

71. Smith I, Avramov MN, White PF: A comparison of propofol and remifentanil during monitored anesthesia care. J Clin Anesth 9:148, 1997.

72. Higgins MS, Givogre JL, Marco AP et al: Recovery from outpatient laparoscopic tubal ligation is not improved by preoperative administration of ketorolac or ibuprofen. Anesth Analg 79:274, 1994.

73. Souter AJ, Fredman B, White PF: Controversies in the perioperative use of nonsteroidal antiinflammatory drugs. Anesth Analg 79:1178, 1994.

74. Thompson GE, Moore DC: Ketamine, diazepam, and Innovar: A computerized comparative study. Anesth Analg 50:458, 1971.

75. White PF: Use of ketamine for sedation and analgesia during injection of local anesthetics. Ann Plast Surg 15:53, 1985.

76. Green SM, Nakamura R, Johnson NE: Ketamine sedation for pediatric procedures: Part 1, A prospective series. Ann Emerg Med 19:1024, 1990.

77. Philip BK, Covino BG: Local and regional anesthesia. In Wetchler BV (ed): Anesthesia for Ambulatory Surgery. Philadelphia, JB Lippincott, 1991, p 309.

78. Logan MR, Duggan JE, Levack ID et al: Single-shot i.v. anaesthesia for outpatient dental surgery: Comparison of 2,6 di-isopropyl phenol and methohexitone. Br J Anaesth 59:179, 1987.

79. Meyers CJ, Eisig SB, Kraut RA: Comparison of propofol and methohexital for deep sedation. J Oral Maxillofac Surg 52:448, 1994.

80. Sa Rego MM, Inagaki Y, Diez R-Labajo A et al: Is methohexital a cost-effective alternative to propofol for sedation during local anesthesia [abstract]? Anesth Analg 84:S21, 1997.

81. Kumar A, Bose S, Bhattacharya A et al: Oral clonidine premedication for elderly patients undergoing intraocular surgery. Acta Anaesthesiol Scand 36:159, 1992.

82. Jaakola ML: Dexmedetomidine premedication before intravenous regional anesthesia in minor outpatient hand surgery. J Clin Anesth 6:204, 1994.

83. Aho M, Erkola O, Kallio A et al: Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. J Clin Anesth 5:194, 1993.

84. Aho MS, Erkola OA, Scheinin H et al: Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. Anesth Analg 73:112, 1991.

85. Cook BA, Bass JW, Nomizu S et al: Sedation of children for technical procedures: Current standard of practice. Clin Pediatr (Phila) 31:137, 1992.

86. ADSA: ADSA guidelines for intraoperative monitoring of patients undergoing conscious sedation. ADSA Newsletter 20:2, 1988.

87. Scamman FL, Klein SL, Choi WW: Conscious sedation for procedures under local or topical anesthesia. Ann Otol Rhinol Laryngol 94:21, 1985.

88. Task Force on Sedation and Analgesia by Non-Anesthesiologists: Practice guidelines for sedation and analgesia by non-anesthesiologists: A report by the American Society of Anesthesiologists task force on sedation and analgesia by non-anesthesiologists. Anesthesiology 84:459, 1996.

89. Coplans MP, Curson I: Deaths associated with dentistry. Br Dent J 153:357, 1982.

90. McKay WP, Noble WH: Critical incidents detected by pulse oximetry during anaesthesia. Can J Anaesth 35:265, 1988.

91. Muir VM, Leonard M, Haddaway E: Morbidity following dental extraction: A comparative survey of local analgesia and general anaesthesia. Anaesthesia 31:171, 1976.

92. Federated Ambulatory Anesthesia Association (FASA): Special Study I, Number 520, 1986.

93. Warner MA, Shields SE, Chute CG: Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. JAMA 270:1437, 1993.

94. Nishino T, Takizawa K, Yokokawa N et al: Depression of the swallowing reflex during sedation and/or relative analgesia produced by inhalation of 50% nitrous oxide in oxygen. Anesthesiology 67:995, 1987.

95. Takasaki M: Ventilation and ventilatory response to carbon dioxide during caudal anaesthesia with lidocaine or bupivacaine in sedated children. Acta Anaesthesiol Scand 32:218, 1988.

96. Alexander CM, Gross JB: Sedative doses of midazolam depress hypoxic ventilatory responses in humans. Anesth Analg 67:377, 1988.

97. White CS, Dolwick MF, Gravenstein N et al: Incidence of oxygen desaturation during oral surgery outpatient procedures. J Oral Maxillofac Surg 47:147, 1989.

98. Pierce EC Jr: Does monitoring have an effect on patient safety? Monitoring instruments have significantly reduced anesthetic mishaps. J Clin Monit 4:111, 1988.

99. Committee on Drugs and Section on Anesthesiology: Guidelines for the elective use of conscious sedation, deep sedation, and general anesthesia in pediatric patients. Committee on Drugs. Section on Anesthesiology. Pediatrics 76:317, 1985.

100. Cooper JB, Newbower RS, Long CD et al: Preventable anesthesia mishaps: A study of human factors. Anesthesiology 49:399, 1978.

101. Eichhorn JH, Cooper JB, Cullen DJ et al: Standards for patient monitoring during anesthesia at Harvard Medical School. JAMA 256:1017, 1986.

102. Maxwell LG, Yaster M: The myth of conscious sedation. Arch Pediatr Adolesc Med 150:665, 1996.

103. Joint Commission on Accreditation of Healthcare Organizations: Comprehensive Accreditation Manual for Hospitals. Oakbrook Terrace, Illinois: JCAHO, 1996.

104. Bendixen HH: Foreward: the tasks of the anesthesiologist. In Saidman LJ, Smith NT (eds): Monitoring in Anesthesia. Boston, Butterworth, 1984, p xi.

105. Whitcher C, Ream AK, Parsons D et al: Anesthetic mishaps and the cost of monitoring: A proposed standard for monitoring equipment. J Clin Monit 4:5, 1988.

106. Cote CJ, Rolf N, Liu LM et al: A single-blind study of combined pulse oximetry and capnography in children. Anesthesiology 74:980, 1991.

107. Goldman JM: A simple, easy, and inexpensive method for monitoring ETCO $_2$ through nasal cannulae. Anesthesiology 67:606, 1987.

108. Pressman MA: A simple method of measuring ETCO $_2$ during MAC and major regional anesthesia. Anesth Analg 67:905, 1988.

109. Bowe EA, Boysen PG, Broome JA et al: Accurate determination of end-tidal carbon dioxide during administration of oxygen by nasal cannulae. J Clin Monit 5:105, 1989.

110. Roth JV, Barth LJ, Womack LH et al: Evaluation of two commercially available carbon dioxide sampling nasal cannulae. J Clin Monit 10:237, 1994.

111. Louwsma DL, Silverman DG: Reproducibility of end tidal CO $_2$ by nasal cannula [abstract]. Anesthesiology 69:A268, 1988.

112. Tobias JD, Flanagan JF, Wheeler TJ et al: Noninvasive monitoring of end-tidal CO $_2$ via nasal cannulas in spontaneously breathing children during the perioperative period. Crit Care Med 22:1805, 1994.

113. Moyers J: Does monitoring have an effect on patient safety? Monitoring instruments are no substitute for careful clinical observation. J Clin Monit 4:107, 1988.

114. Vandam LD: The senses as monitors. In Blitt CD (ed): Monitoring in Anesthesia and Critical Care Medicine. New York, Churchill Livingstone, 1985, p 5.

115. Avramov MN, White PF: Methods for monitoring the level of sedation. Crit Care Clin 11:803, 1995.

116. Ramsay MA, Savege TM, Simpson BR et al: Controlled sedation with alphaxalone-alphadolone. Br Med J 2:656, 1974.

117. Chernik DA, Gillings D, Laine H et al: Validity and reliability of the observer's assessment of alertness/sedation scale: Study with intravenous midazolam. J Clin Psychopharmacol 10:244, 1990.

118. Johnson LC, Chernik DA: Sedative-hypnotics and human performance. Psychopharmacology 76:101, 1982.

119. Hung OR, Varvel JR, Shafer SL et al: Thiopental pharmacodynamics. II. Quantitation of clinical and electroencephalographic depth of anesthesia. Anesthesiology 77:237, 1992.

120. Veselis RA, Reinsel R, Sommer S et al: Use of neural network analysis to classify electroencephalographic patterns against depth of midazolam sedation in intensive care unit patients. J Clin Monit 7:259, 1991.

121. Sebel P, Rampil I, Cork R: Bispectral analysis for monitoring anesthesia: A multicenter study [abstract]. Anesthesiology 79:A178, 1993.

122. Kearse LA Jr, Manberg P, Chamoun N et al: Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia.

Anesthesiology 81:1365, 1994.

123. Liu J, Singh H, White PF: Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. Anesthesiology 84:64, 1996.

124. Liu J, Singh H, White PF: Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. Anesth Analg 84:185, 1997.

125. Caplan RA, Ward RJ, Posner K et al: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

126. White PF: Anesthetic techniques for the elderly outpatient. Int Anesthesiol Clin 26:105, 1988.

127. van der Walt JH, Mackay P: Patient safety in the recovery room. Anaesth Intensive Care 16:77, 1988.

128. Zelcer J, Wells DG: Anaesthetic-related recovery room complications. Anaesth Intensive Care 15:168, 1987.

129. Cullen DJ: The recovery room. Semin Anesth 1:333, 1982.

130. Faculty of Anaesthetists, Royal Australasian College of Surgeons: Guidelines for the care of patients recovering from anesthesia. Policy Statement 4, 1983.

131. Anonymous: American Academy of Pediatrics Committee on Drugs: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 89:1110, 1992.

132. Monk TG, Rater JM, White PF: Comparison of alfentanil and ketamine infusions in combination with midazolam for outpatient lithotripsy. Anesthesiology 74:1023, 1991.

133. Jorgensen NH, Messick JM Jr, Gray J et al: ASA Monitoring Standards and Magnetic Resonance Imaging. Anesth Analg 79:1141, 1994.

134. Peden CJ, Menon DK, Hall AS et al: Magnetic resonance for the anaesthetist. Part II: Anaesthesia and monitoring in MR units. Anaesthesia 47:508, 1992.

135. Menon DK, Peden CJ, Hall AS et al: Magnetic resonance for the anaesthetist. Part I: Physical principles, applications, safety aspects. Anaesthesia 47:240, 1992.

136. Cousins MJ: Monitoring: The anaesthetist's view. Scand J Gastroenterol Suppl 179:12, 1990.

137. Anonymous: Sedation and monitoring of patients undergoing gastrointestinal endoscopic procedures. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc 42:626, 1995.

138. Quine MA, Colin-Jones DG: Gastrointestinal endoscopy: To sedate or not to sedate? Endoscopy 28:306, 1996.

139. Rey JF: Sedation for upper gastrointestinal endoscopy: As much as possible, or without? Endoscopy 28:308, 1996.

140. Abbott MA, Samuel JR, Webb DR: Anaesthesia for extracorporeal shock wave lithotripsy. Anaesthesia 40:1065, 1985.

141. Kopacz DJ, Mulroy MF: Chloroprocaine and lidocaine decrease hospital stay and admission rate after outpatient epidural anesthesia. Reg Anesth 15:19, 1990.

142. Knudsen F, Jorgensen S, Bonde J et al: Anesthesia and complications of extracorporeal shock wave lithotripsy of urinary calculi. J Urol 148:1030, 1992.

143. Schelling G, Mendl G, Weber W et al: Patient controlled analgesia for extracorporeal shock wave lithotripsy of gallstones. Pain 48:355, 1992.

144. Kortis HI, Amory DW, Wagner BK et al: Use of patient-controlled analgesia with alfentanil for extracorporeal shock wave lithotripsy. J Clin Anesth 7:205, 1995.

145. Waters RM: The Downtown Anesthesia Clinic. Am J Surg Anesthesia Suppl 71, 1919.

146. Conlay LA: The history of office-based anesthesia. Society for Ambulatory Anesthesia Mid Year Meeting Proceedings 1997: Office-Based Anesthesia 1, 1997.

147. Vandam LD: A History of Ambulatory Anesthesia. Anesth Clin North Am 5:1, 1987.

148. Mingus ML: A Growing Segment of Ambulatory Anesthesia. Ambulatory Anesth 12:5, 1997.

149. Schultz LS: Cost analysis of office surgery clinic with comparison to hospital outpatient facilities for laparoscopic procedures. Int Surg 79:273, 1994.

150. Tang J, Chen L, White PF et al: Use of propofol for office-based anesthesia: Effect of nitrous oxide [abstract]. Anesthesiology 87:A9, 1997.

151. Boysen PG: Ancillary Site and Office Based Anesthetic Care. 48th Annual Refresher Course Lectures and Clinical Update Program--ASA 154-1, 1997.

152. Dexter F, Aker J, Wright WA: Development of a measure of patient satisfaction with monitored anesthesia care. The Iowa Satisfaction with Anesthesia Scale. Anesthesiology 87:865, 1997.

153. Smith I: Monitored anesthesia care: How much sedation, how much analgesia? J Clin Anesth 8:76S, 1996.

154. White PF: Clinical uses of intravenous anesthetic and analgesic infusions. Anesth Analg 68:161, 1989.

155. Watcha MF, White PF: Economics of anesthetic practice. Anesthesiology 86:1170, 1997.

156. Cox G, Didlake R, Powers C et al: Choice of anesthetic technique for needle localized breast biopsy. Am Surg 57:414, 1991.

157. Behnia R, Hashemi F, Stryker SJ et al: A comparison of general versus local anesthesia during inguinal herniorrhaphy. Surg Gynecol Obstet 174:277, 1992.

158. D'Alessio JG, Rosenblum M, Shea KP et al: A retrospective comparison of interscalene block and general anesthesia for ambulatory surgery shoulder arthroscopy. Reg Anesth 20:62, 1995.

159. Patel NJ, Flashburg MH, Paskin S et al: A regional anesthetic technique compared to general anesthesia for outpatient knee arthroscopy. Anesth Analg 65:185, 1986.

160. White PF: What is new in ambulatory anesthesia techniques? Annual Refresher Course Lectures 411.1, 1997.

161. Kallar SK, Dunwiddie WC: Conscious sedation. In Wetchler BV (ed): Problems in Anesthesia. Philadelphia, JB Lippincott, 1988, p 93.

Appendix-Standards for Basic Anesthetic Monitoring

These standards apply to all anesthesia care although, in emergency circumstances, appropriate life support measures take precedence. These standards may be exceeded at any time based on the judgment of the responsible anesthesiologist. They are intended to encourage quality patient care, but observing them cannot guarantee any specific patient outcome. They are subject to revision from time to time, as warranted by the evolution of technology and practice. They apply to all general anesthetics, regional anesthetics and monitored anesthesia care. This set of standards addresses only the issue of basic anesthetic monitoring, which is one component of anesthesia care. In certain rare or unusual circumstances, (1) some of these methods of monitoring may be clinically impractical, and (2) appropriate use of described monitoring methods may fail to detect untoward clinical developments. Brief interruptions of continual [a] monitoring may be unavoidable. Under extenuating circumstances, the responsible anesthesiologist may waive the requirements marked with an asterisk ([*]); it is recommended that when this is done, it should be so stated (including the reasons) in a note in the patient's medical record. These standards are not intended for application to the care of the obstetrical patient in labor or in the conduct of pain management.

STANDARD I

Qualified anesthesia personnel shall be present in the room throughout the conduct of all general anesthetics, regional anesthetics, and monitored anesthesia care.

Objective

Because of the rapid changes in patient status during anesthesia, qualified anesthesia personnel shall be continuously present to monitor the patient and provide anesthesia care. In the event there is a direct known hazard, e.g., radiation, to the anesthesia personnel, which might require intermittent remote observation of the patient, some provision for monitoring the patient must be made. In the event that an emergency requires the temporary absence of the person primarily responsible for the anesthetic, the best judgment of the anesthesiologist will be exercised in comparing the emergency with the anesthetized patient's condition and in the selection of the person left responsible for the anesthetic during the temporary absence.

STANDARD II

During all anesthetics, the patient's oxygenation, ventilation, circulation, and temperature shall be continually evaluated.

Oxygenation

Objective

To ensure adequate oxygen concentration in the inspired gas and the blood during all anesthetics.

Methods

1. Inspired gas: During every administration of general anesthesia using an anesthesia machine, the concentration of oxygen in the patient breathing system shall be measured by an oxygen analyzer with a low oxygen concentration limit alarm in use. [*]
2. Blood oxygenation: During all anesthetics, a quantitative method of assessing oxygenation such as pulse oximetry shall be employed. [*] Adequate illumination and exposure of the patient are necessary to assess color. [*]

Ventilation

Objective

To ensure adequate ventilation of the patient during all anesthetics.

Methods

1. Every patient receiving general anesthesia shall have the adequacy of ventilation continually evaluated. While qualitative clinical signs such as chest excursion, observation of the reservoir breathing bag, and auscultation of breath sounds may be useful, quantitative monitoring of the CO_2 content and/or volume of expired gas is strongly encouraged.
2. When an endotracheal tube or laryngeal mask is inserted, its correct positioning must be verified by clinical assessment and by identification of CO_2 in the expired gas. Continual end-tidal CO_2 analysis, in use from the time of endotracheal tube/laryngeal mask placement, until extubation/removal or initiating transfer to a postoperative care location, shall be performed using a quantitative method such as capnography, capnometry, or mass spectroscopy. [*]
3. When ventilation is controlled by a mechanical ventilator, there shall be in continuous use a device that is capable of detecting disconnection of components of the breathing system. The device must give an audible signal when its alarm threshold is exceeded.
4. During regional anesthesia and monitored anesthesia care, the adequacy of ventilation shall be evaluated, at least, by continual observation of qualitative clinical signs.

Circulation

Objective

To ensure the adequacy of the patient's circulatory function during all anesthetics.

Methods

1. Every patient receiving anesthesia shall have the electrocardiogram continuously displayed from the beginning of anesthesia until preparing to leave the anesthetizing location. [*]
2. Every patient receiving anesthesia shall have arterial blood pressure and heart rate determined and evaluated at least every five minutes. [*]
3. Every patient receiving general anesthesia shall have, in addition to the above, circulatory function continually evaluated by at least one of the following: palpation of a pulse, auscultation of heart sounds, monitoring of a tracing of intra-arterial pressure, ultrasound peripheral pulse monitoring, or pulse

plethysmography or oximetry.

Body Temperature

Objective

To aid in the maintenance of appropriate body temperature during all anesthetics.

Methods

There shall be readily available a means to continuously measure the patient's temperature. When changes in body temperature are intended, anticipated, or suspected, the temperature shall be measured.

---

[a] Note that 'continual' is defined as 'repeated regularly and frequently in steady rapid sucession.'whereas 'continuous' means 'prolonged without any interruption at any time.'

* Approved by ASA House of Delegates on October 21, 1986, and last amended on October 23, 1996. From the American Society of Anesthesiologists, [3] with permission.

Chapter 41 - Deliberate Hypotension

Hugo Van Aken
Edward D. Miller Jr.

INTRODUCTION

The concept of intentionally decreasing arterial blood pressure to hypotensive levels during surgery was first proposed by Cushing [1] in 1917 for intracranial surgery and was introduced into clinical practice by Gardner [2] in 1946. Deliberate hypotension gained popularity in Great Britain after Griffiths and Gillies [3] advocated the "hypotensive spinal technique" in 1948. In 1950 Enderby [4] introduced ganglionic blockade using pentamethonium to decrease arterial blood pressure. Subsequent techniques included decreasing cardiac output with volatile anesthetics such as halothane [5] and administering vasodilators such as sodium nitroprusside; beta-adrenergic receptor blocking drugs, which were initially used with trimethaphan [6] ; or a combination of alpha- and beta-adrenergic receptor blocking drugs. [7] More recently, nitroglycerin, [8] purine derivatives, [9] and isoflurane [10] have also been used.

As early as 1950, Enderby [4] emphasized that bleeding could be controlled not only by decreasing mean arterial blood pressure (MAP) but also by properly positioning the patient (Ch. 52) . Since that time, the decision to induce hypotension has often been controversial, primarily because of an inability to define the lowest safe MAP with confidence. [11] The terms *controlled hypotension, induced hypotension, deliberate hypotension,* and *hypotensive anesthesia* have all been used. This chapter uses *deliberate hypotension.*

Most studies define deliberate hypotension as a reduction in systolic blood pressure to 80 to 90 mm Hg. According to another definition, deliberate hypotension is a decrease in MAP to 50 to 65 mm Hg in normotensive patients.

The main purpose of deliberately inducing hypotension is to decrease blood loss, thereby improving operating conditions or decreasing the need for blood transfusions. Therefore, benefit to the patient should be the single criterion determining the need for deliberate hypotension. The potential for transmitting disease by blood transfusion has made deliberate hypotension an even more important consideration today than ever before (Ch. 46) . The possible benefit to the surgeon of improved visibility of the operative field during delicate procedures (e.g., plastic surgery) is a strong incentive, but it is more difficult to quantitate.

This chapter provides a general overview of deliberate hypotension, leaving the discussion of most specific clinical applications to specialty chapters (e.g., neuroanesthesia in Ch. 52).

THE ABILITY OF DELIBERATE HYPOTENSION TO REDUCE BLOOD LOSS

Enderby's [4] first report demonstrated that of 35 patients, 18 had excellent and 8 had moderate reduction in blood loss during deliberate hypotension, and 9 patients had no reduction. This inconsistency was attributed to differing vascular responsiveness to the hypotensive drugs and, in some cases, inadequate positioning. Enderby emphasized that the absolute MAP may not be as important to bleeding as positioning of the surgical field. He maintained that bleeding at the surgical site would be minimized if the wound were kept uppermost (rather than dependent): arterial vessels would have less pressure, veins would drain more easily, and bleeding at the surgical site would be less.

Deliberate hypotension certainly can decrease blood loss in many surgical procedures. In 1953 Boyan [12] used hexa-methonium (C_6) to lower systolic blood pressure to 65 to 70 mm Hg in 112 patients undergoing radical cancer surgery. Although the impression of the surgical team was that blood

loss was less, no data were provided. Several subsequent reports also claiming a decrease in blood loss noted, however, that some patients continued to bleed during deliberate hypotension and that other patients not undergoing deliberate hypotension had minimal blood loss. Whether these differences can be ascribed to positioning, ventilation, or other factors is unknown.

Assigning importance to the possible influences on blood loss is difficult because few clinicians have actually measured this variable. Also, such studies have had major flaws in experimental design, execution, or data analysis. [13] Usually MAP of 50 to 65 mm Hg is considered a safe range for deliberate hypotension.

Eckenhoff and Rich [14] supplied objective data that deliberate hypotension can indeed decrease blood loss. Blood loss was compared for patients undergoing rhinoplasty, portacaval shunt, or craniotomy for aneurysm or suspected tumor with (*n* = 115) or without (*n* = 116) deliberate hypotension. For each of these procedures, blood loss decreased by 50 percent or more with hypotension. Most of the other studies evaluating different hypotensive agents for a variety of surgical procedures had no control group, and assessment of blood loss was visual. [15] [16] [17] [18]

The best documentation that decreasing arterial blood pressure decreases blood loss applies to patients undergoing major orthopedic procedures. Often blood loss is significant during these procedures, and the effect of deliberate hypotension can be documented more readily. For example, a well-controlled study of 55 patients undergoing total hip arthroplasty found that the 38 patients given pentolinium tartrate, halothane, and *d*-tubocurarine for deliberate hypotension had less blood loss. [19] In another study, 25 patients given sodium nitroprusside to lower arterial blood pressure during total hip arthroplasty had significantly less blood loss than the 25 patients not undergoing deliberate hypotension. [20] Operating room time was also slightly lower for the hypotensive group.

Other studies have also had success reducing blood loss during total hip arthroplasty. Thirty patients undergoing this procedure had MAP reduced to 50 mm Hg by administration of sodium nitroprusside (*n* = 12) or high inspired concentrations of halothane (*n* = 9). [21] Nine control patients were normotensive. Blood loss was 1,200 mL for the normotensive controls but only approximately 400 mL for both hypotensive groups. No complications were seen. Another study had similar results--almost a 50 percent reduction in blood loss--when MAP was decreased to 55 mm Hg by sodium nitroprusside. [22] An interesting aspect of the study was the use of hemodilution to determine whether total blood loss could be reduced by this method. Even with hemodilution, patients given sodium nitroprusside had the lowest blood loss. Table 41-1 shows blood losses for a variety of hypotensive techniques during total hip arthroplasty. [19] [20] [21] [22] [23] [24] Another study on primary total hip arthroplasty (under epidural anesthesia) showed that the degree of hypotension significantly influenced blood loss. [25] Intraoperative blood loss was 179 ± 73 ml when MAP was kept at 50 ± 5 mm Hg and 263 ± 98 mL when MAP was kept at 60 ± 5 mm Hg.

Deliberate hypotension has also been used successfully for a variety of other surgical procedures, including head and neck surgery, [26] procedures on the cranium [18] and middle ear, [17] and radical cancer operations. [27] A retrospective study of 37 patients undergoing radical cystectomy for bladder cancer found that the average blood loss was 50 percent less with deliberate hypotension (versus standard normotensive anesthesia). [28] Elsewhere, the use of sodium nitroprusside-induced hypotension reduced blood loss by 50 percent in patients undergoing lienorenal shunts for portal hypertension. [29] When esmolol was compared with sodium nitroprusside for controlled hypotension during orthognathic surgery, the surgeons generally rated bleeding as mild to moderate and the field as "drier" with esmolol. [26] Furthermore, total measured blood loss with esmolol was 49 percent of that with sodium nitroprusside (436 versus 895 mL, respectively).

Although deliberate hypotension usually decreases surgical blood loss, some exceptions have occurred. For unknown reasons, not all patients respond as predicted. For other patients, the correlation between decrease in arterial blood pressure and blood loss is not linear. [30] Some studies report

TABLE 41-1 -- Reported Blood Losses for Total Hip Arthroplasty

REPORTED INTRAOPERATIVE INVESTIGATORS	HYPOTENSIVE TECHNIQUE	BLOOD PRESSURE (mm Hg)	BLOOD LOSS (mL)
Amaranath et al (1975) [23]	Halothane, N_2O	Normotensive	1,514 ± 273
	Morphine, N_2O, trimethaphan	<30% control	884 ± 89
	Morphine, N_2O, SNP	<30% control	820 ± 96
Thompson et al (1978) [21]	Halothane, N_2O	20% control	1,183
	Halothane, N_2O	50 MAP	407 ± 102
	Halothane, N_2O, SNP	50 MAP	326 ± 42
Eerola et al (1979) [19]	Halothane, N_2O	>80 systolic	2,336 ± 212
	Halothane, N_2O, pentolinium	<80 systolic	730 ± 80
Vazeery and Lunde (1979) [20]	N_2O, fentanyl	94 MAP	1,038 (500-1,750)
	N_2O, fentanyl, SNP	64 MAP	212 (160-350)
Barbier-Bohm et al (1980) [22]	Halothane, N_2O	Normotensive	900 ± 130
	Halothane, N_2O, SNP	55 MAP	320 ± 35
Qvist et al (1982) [24]	N_2O, fentanyl, droperidol	99 MAP	2,093 ± 1,332

	Halothane, N_2 O	73 MAP	718 ± 482
Sharrock et al (1993) [25]	Epidural anesthesia	50 MAP	179 ± 73
	Epidural anesthesia	60 MAP	263 ± 98

Abbreviations: BP, blood pressure; SNP, sodium nitroprusside; MAP, mean arterial blood pressure; N_2 O, nitrous oxide

TABLE 41-2 -- Mean Arterial Blood Pressure Versus Cardiac Output as the Primary Determinant of Blood Loss [a]

(Not Available)

(Adapted from Sivarajan et al [33])

[a] Total blood loss was similar for both trimethaphan (170 ± 102 mL) and SNP (183 ± 92 mL).

that deliberate hypotension did not reduce blood loss significantly and that the incidence of postoperative wound hematoma even increased. [31] It is difficult to evaluate these last two studies because of the scant data presented and the imprecision with which blood losses were measured.

Shortly after the introduction of deliberate hypotension, drug therapy focused on keeping arterial blood pressure at the surgical site at 50 to 65 mm Hg, a level believed to decrease blood loss significantly. Because intraoperative measurement of cardiac output was not done routinely, the specific mechanism by which reduction of arterial blood pressure decreased blood loss could not be defined precisely. Didier et al [32] suggested that depression of cardiac output correlated better with a dry field than did MAP. To determine whether a decrease in arterial blood pressure or cardiac output was the primary cause of decreasing blood loss, Sivarajan et al [33] studied 20 healthy subjects undergoing bilateral sagittal osteotomy of the mandible. Cardiac output decreased 37 percent with trimethaphan but increased 27 percent with sodium nitroprusside. Blood loss was similar for both groups, even though cardiac output was two times greater with sodium nitroprusside (Table 41-2) (Table Not Available) . Sivarajan et al concluded that blood pressure, not cardiac output, determined blood loss.

In summary, most patients will have less blood loss if MAP is decreased to 50 to 65 mm Hg. Patient positioning and attention to ventilation, both of which influence venous return, play important roles in minimizing blood loss. Clinical experience suggests that blood loss can be decreased with less severe degrees of hypotension and that attention to the surgical field may be a better monitor than the absolute value for MAP. Most clinical studies do not support the belief that deliberate hypotension decreases operating room time.

TECHNIQUES TO INDUCE DELIBERATE HYPOTENSION

Physiologic Techniques

Body positioning, the hemodynamic effects of mechanical ventilation, and changes in heart rate and circulatory volume can be used with drugs to lower blood pressure to the desired level. The appropriate use of physiologic maneuvers helps decrease the dose of potentially toxic drugs needed to produce hypotension.

Pharmacologic Techniques

The ideal agent for inducing hypotension would have ease of administration, a predictable and dose-dependent effect, rapid onset and recovery from effects, quick elimination without the production of toxic metabolites, and minimal effects on blood flow to vital organs. In addition, the ideal agent would not increase brain size or affect cerebral autoregulation during neurosurgery. Although such an agent does not yet exist, many anesthetic and vasoactive drugs have been used successfully to produce deliberate hypotension, including (1) spinal and epidural anesthesia, (2) volatile anesthetics (halothane, enflurane, isoflurane, sevoflurane, desflurane), (3) direct-acting vasodilating drugs (sodium nitroprusside, nitroglycerin, hydralazine, purine derivatives), (4) autonomic ganglion-blocking drugs (trimethaphan), (5) alpha-adrenergic receptor blocking drugs (phentolamine, urapidil), (6) beta-adrenergic receptor blocking drugs (propranolol, esmolol), (7) combined alpha- and beta-adrenergic receptor blocking drugs (labetalol), (8) calcium channel entry blocking drugs (nicardipine), and (9) prostaglandin E_1 (PGE_1).

Spinal and Epidural Anesthesia

In 1948 Griffiths and Gillies [3] used subarachnoid block to produce intentional hypotension. In 1952 Greene [34] advocated the use of general anesthesia in which hypotension was induced using a high spinal technique to relieve the distressing symptoms of hypotension. Epidural anesthesia (Ch. 42) was introduced in the early 1950s and is now considered an effective method of inducing hypotension. [35] [36] Pharmacologic sympathectomy with local anesthetics is a very effective way of inducing hypotension. Epidural or spinal anesthesia produces arteriolar and venous dilation and hypotension. These effects are enhanced by a pooling of blood in the venous system that decreases venous return and cardiac output. If the block is extended to the midthoracic region, sympathetic innervation of the heart (T1-T4) is also affected, thereby preventing compensatory tachycardia. [37] The unpredictable degree of hypotension and the necessity for large infusions of fluids are the principal drawbacks of this technique. It was recently demonstrated, however, that if hemodynamic stability is maintained by intravenous infusion of low-dose epinephrine (1-5 mug/min), this technique

can be used safely. [25] [35] An epidural anesthetic technique is most commonly used to minimize blood loss during lower abdominal or pelvic surgery.

Volatile Anesthetic Drugs

Clearly one can decrease MAP by increasing the inspired concentration of inhaled anesthetic (Ch. 5).

Cardiovascular Effects

Hypotension after halothane results primarily from myo-cardial depression that produces a dose-dependent decrease in arterial blood pressure, cardiac output, and stroke volume, plus a dose-dependent increase in right heart filling pressure (Fig. 41-1) (Figure Not Available) . Although halothane also dilates vessels in the skin, brain, and viscera, systemic vascular resistance (SVR) does not decrease significantly because skeletal muscle tone increases; in addition, renal vascular resistance increases. [38]

In studies on patients and animals, isoflurane decreased blood pressure by decreasing SVR, whereas cardiac output was maintained constantly at clinically relevant concentrations of the anesthetic. [10] [39] In another study of 10 patients given isoflurane to reduce MAP to 40 mm Hg, cardiac index showed a small but significant decrease. [40] The two studies on patients [10] [40] may have different results because the latter study used the awake value as control.

The intravascular volume status of the patient before induction of hypotension affects the degree of reduction in cardiac output during isoflurane anesthesia. In healthy young people, 2 to 3 percent isoflurane decreases MAP by decreasing SVR. In older or chronically hypertensive patients, similar concentrations of isoflurane may also decrease cardiac output. For these individuals, combining a moderate concentration of isoflurane with agents that tend to maintain cardiac output would be more appropriate than using high concentrations of isoflurane alone.

Cerebrovascular Effects

Halothane decreases cerebrovascular resistance and increases cerebral blood flow (CBF) in a concentration-related manner, provided autoregulatory limits are not exceeded. As a result, intracranial pressure (ICP) may increase. Cerebral autoregulation is lost when the concentration of halothane increases. [41]

By increasing the normal production of cerebrospinal fluid, enflurane is also capable of increasing ICP. [42] In addition, enflurane has induced seizure activity in some patients, especially during hypocapnia.

The administration of low concentrations of isoflurane (
1 MAC) produces controllable decreases in MAP and a concentration-related depression of cerebral metabolism while preserving the physiologic relationships between flow and pressure, and flow and metabolism. With higher concentrations of isoflurane, the direct vasodilatory effects predominate: CBF increases, and autoregulation is impaired. [39] [43] However, even low concentrations of isoflurane may increase ICP in patients who have reduced intracranial compliance. [44] In the presence of cerebral vasodilation, cerebral edema is more likely to occur if systemic blood

Figure 41-1 (Figure Not Available) Effect of increasing concentrations of halothane anesthesia on mean arterial blood pressure (MAP), stroke volume (SV), and systemic vascular resistance (SVR) during the awake state, spontaneous ventilation (SpV), and controlled ventilation (intermittent positive-pressure ventilation, IPPV). Elevation in right arterial pressure (RAP) is evidence of myocardial depression. *(From Prys-Roberts et al [38])*

pressure is allowed to increase. Therefore, the possibility of secondary neurologic injury exists. A recent study on dogs with cryogenic brain lesions showed that brain edema was greater when hypotension was induced with isoflurane than with labetalol. [45] Adenylate kinase, a marker of brain cell injury, was found in the cerebrospinal fluid of patients undergoing isoflurane-induced hypotension for corrective surgery of dentofacial deformities. [46] However, this study did not include a control group. In a subsequent investigation the same authors found that adenylate kinase occurred also in patients after isoflurane anesthesia under normotensive conditions for orthognathic surgery. [47] In conclusion, adverse effects on the brain were found, using a sensitive biochemical method and a battery of psychometric examinations. Arterial hypotension, however, was not shown to have a direct causal relationship to the adverse effects found.

Volatile anesthetics should not be used as the sole agent to induce hypotension in patients who have intracranial disease because the high concentrations that may be required can worsen brain edema. Such a technique may also increase ICP before opening of the dura and may affect autoregulation. The combination of increased ICP and decreased MAP can reduce cerebral perfusion pressure to less than 40 mm Hg, a circumstance that can produce brain ischemia. Recent studies in animals and patients showed that combining isoflurane with either an alpha-adrenergic receptor blocking drug or a combined alpha- and beta-adrenergic receptor blocking drug attenuated the negative effects of using isoflurane as the sole hypotensive agent. [48] [49] In summary, isoflurane should only be used as an adjuvant drug (and in low concentrations) during induced hypotension. This method has the advantages of decreased cerebral metabolism and preserved pulmonary gas exchange. [50] The profile of hemodynamic changes induced by sevoflurane and desflurane is very similar to that of isoflurane. However, due to the pharmacokinetic properties of these volatile agents, including a low blood/gas solubility, these hemodynamic effects can be better controlled with them as compared with isoflurane. Therefore, sevoflurane and desflurane appear to be superior to isoflurane when used as an agent to facilitate deliberate hypotension. Surprisingly, these drugs have not been investigated yet with respect to their suitability in deliberate hypotension.

Information on the cerebral effects of the newer anesthetic agents is limited. Hypotensive anesthesia with desflurane reduces CBF by 36 percent and reduces $CMRO_2$ by a similar amount, [51] and 4 MAC of sevoflurane has no adverse effects on brain energy metabolism. [52]

Intravenous Drugs

Many intravenous drugs have been used to decrease arterial blood pressure acutely. Certainly, drugs that permit moment-to-moment control of blood pressure are the most popular. Most of these drugs are titrated to obtain the desired surgical field or predetermined MAP, or both. The differences in pharmacologic properties among agents suggest that combinations of these drugs may provide a better pharmacologic profile than could be provided by any agent used alone.

Sodium Nitroprusside

Sodium nitroprusside is a vasodilating drug most commonly used to induce hypotension during surgery. Its onset of action is rapid, of short duration, and readily controllable. Sodium nitroprusside acts primarily on arteriolar tone; only 65 to 70 percent of arterial sodium nitroprusside is recovered in venous plasma. [53]

Studies on the cardiovascular effects of sodium nitroprusside have yielded contradictory results. Some studies report an increase in heart rate and cardiac output with no change in stroke volume. [54] [55] Yet others report either no change in cardiac output [57] [58] [59] or a decrease. [60] [61] However, sodium nitroprusside clearly has no adverse effect on myocardial contractility. [57] [58]

The different results concerning cardiac output and stroke volume probably relate to differences in circulatory volume and cardiac filling pressures before hypotension. Patients with subarachnoid hemorrhage have low circulatory volume, [62] a condition that can decrease preload and cardiac output. [61] Lawson et al [63] found that stroke volume and cardiac output increased during sodium nitroprusside-induced hypotension in deliberately overhydrated patients undergoing orthopedic surgery. The importance of circulatory volume was demonstrated by experiments in dogs in which fluid balance was shown to be an important determinant of the cardiovascular response to sodium nitroprusside. [64] When sodium nitroprusside was given, cardiac output decreased during hypovolemia but not normovolemia.

Because the intact sodium nitroprusside contains five cyanide groups, toxicity is a concern [65] (Fig. 41-2) (Figure Not Available) . The breakdown of sodium nitroprusside in the blood produces free cyanide, the concentration of which depends on the quantity of sodium nitroprusside infused. [66] Cyanide diffuses rapidly into the tissue, where it binds with high affinity to cytochrome oxidase. Such binding causes interference with electron transport and produces tissue hypoxia. Some of the cyanide ions diffuse out of the erythrocytes and are metabolized in the liver and kidney to thiocyanate, which is excreted in the urine. Bisset et al [67] challenged the concept that cyanide is released *in vivo,* arguing that any cyanide found in the blood of patients given sodium nitroprusside is caused by photodegradation of the drug *in vitro,* either before infusion or during assay of the samples. These investigators also stated that "it may well be safe to infuse quantities larger than those currently recommended."

Experiments examining the question of photodegradation concluded that cyanide measured in the blood of patients given sodium nitroprusside did not appear to be an artifact of assay methods. [68] Furthermore, degraded nitroprusside remains biologically active and may be more toxic than intact nitroprusside, as free cyanide is a product of degradation.

Shortly after the widespread use of sodium nitroprusside, reports of toxicity began to appear. [69] [70] In some of the initial reports, large concentrations of sodium nitroprusside had been infused. However, in some individual cases, younger patients appeared to show resistance to the effects of nitroprusside, and the mechanisms were sought. Studies designed to investigate the complex physiologic changes that occur whenever arterial blood pressure is decreased focused, for example, on resetting of baroreflex sensitivity in

---

Figure 41-2 (Figure Not Available) Schematic representation of the breakdown of sodium nitroprusside *in vivo.* The high affinity of cytochrome oxidase for cyanide leads to tissue hypoxia. *(Modified from Tinker and Michenfelder [65])*

control of heart rate. [71] The sympathetic nervous system and the renin-angiotensin system are activated. Also, the release of vasopressin increases. [72] Although these increases in vasopressin were greater than the increases in plasma catecholamines or plasma-renin activity during sodium nitroprusside-induced hypotension, the significance of this result remains speculative and will not be resolved until a specific antagonist of the vascular properties of vasopressin is found.

The question of resistance or tachyphylaxis to sodium nitroprusside is complex, and each of the previous possibilities needs further discussion. In one study, normal patients had significant increases in plasma levels of norepinephrine and epinephrine during sodium nitroprusside-induced hypotension. [73] This response does not occur in patients with subarachnoid hemorrhage, possibly because the adrenergic system is already maximally activated before induction of hypotension. Such activation of the adrenergic system could also contribute to the low circulatory volume found in subarachnoid hemorrhage. [62] Consequently, the hemodynamic effects of sodium nitroprusside in patients with subarachnoid hemorrhage will differ from that in normal subjects because of differences in circulatory volume and activity of the sympathetic nervous system. This increase in the plasma catecholamine level may produce resistance to the effects of sodium nitroprusside.

One study on the effect of pretreatment with propranolol 1 day before cerebral aneurysm surgery found that plasma catecholamine levels were significantly lower during surgery (including the time of deliberate hypotension) with propranolol. [74] Similarly, the intraoperative intravenous administration of incremental doses of propranolol reduced heart rate and the amount of sodium nitroprusside necessary to maintain hypotension. [75]

The renin-angiotensin system is also activated when hypotension is induced with sodium nitroprusside. Infusion of sodium nitroprusside increased plasma-renin activity in rats 4-fold. [76] When the production of angiotensin II was inhibited by saralasin, arterial blood pressure decreased further. Subsequently, Khambatta et al [77] reported a 5-fold increase in plasma renin activity in patients made hypotensive with sodium nitroprusside. Because the renin-angiotensin system plays an important role in tachyphylaxis to sodium nitroprusside-induced hypotension, two approaches use this system to circumvent the problem.

The first approach is based on the fact that the renin response was attenuated (but not abolished) when patients were pretreated with propranolol for 1 day before surgery. [78] Furthermore, the dose of sodium nitroprusside necessary to produce hypotension was reduced, and rebound hypertension did not occur on

discontinuation of the drug. The second approach tries to inhibit the renin-angiotensin system directly by pretreating patients with a single oral dose of captopril, a drug that prevents conversion of angiotensin I to angiotensin II. [79] The dose of sodium nitroprusside needed to produce the same degree of hypotension was one-fifth that needed for untreated patients. In addition, the desired level of hypotension was easier to maintain, and rebound hypertension did not occur on discontinuation of sodium nitroprusside.

Because of the decreased requirement for sodium nitroprusside, pretreatment with captopril resulted in significantly lower plasma levels of cyanide. Converting-enzyme inhibition can also be done by IV administration of enalaprilat (2.5 mg) 60 minutes before hypotension is started. [80]

Investigators have sought other causes of resistance to the effects of sodium nitroprusside. Grayling et al [81] found that free cyanide can cause contraction of an aortic ring after the ring has been contracted by norepinephrine and then relaxed by sodium nitroprusside. If this phenomenon occurs in humans, then as the plasma level of cyanide increases, an increasing dose of sodium nitroprusside would be necessary to produce a comparable degree of relaxation. A potentially lethal cycle could thus begin.

Aging also plays an important role in the response to sodium nitroprusside. Early reports of resistance to sodium nitroprusside involved younger patients. Wood et al [82] studied 16 patients 18 to 76 years of age. The vasodepressor effect of sodium nitroprusside was enhanced in the elderly (Fig. 41-3) (Figure Not Available) . Plasma norepinephrine and epinephrine concentrations were similar for both groups. This increased sensitivity to sodium nitroprusside may be owing in part to resistance of cardiac adrenergic receptors to catecholamine stimulation as a consequence of reduced affinity to beta-adrenergic receptors.

Because the question of resistance to tachyphylaxis to sodium nitroprusside is so complex, guidelines for the administration of this agent should be followed to prevent toxicity. Simply titrating sodium nitroprusside against arterial blood pressure alone cannot be justified. Accurate knowledge of dose, rate of administration, and total dose given is prerequisite to the use of sodium nitroprusside. The recommended maximum dosages of 1.5 mg/kg for acute administration and 0.5 mg/kg/h (8 mug/kg/min) for chronic administration appear to be safe. [83]

Data on the effects of sodium nitroprusside on CBF during controlled hypotension are inconsistent. Some studies reported no change in CBF from baseline. [84] [85] [86] Other studies reported that CBF decreased [87] [88] [89] or, along with ICP, increased (in animals and neurosurgical patients). [90] [91] The reasons for these conflicting results are not easy to determine; differences in species, anesthetic technique, and baseline conditions may play a role. Delayed measurement

Figure 41-3 (Figure Not Available) Plotting the age of 16 patients against change in mean arterial pressure (BP) per mug/kg/min dose of sodium nitroprusside (SNP) shows that the elderly need less SNP than the young to produce the same degree of deliberate hypotension. *(From Wood et al [82])*

of CBF after the start of sodium nitroprusside may be the reason that early changes in flow are not observed.

One study showed the importance of the degree of hypotension induced by sodium nitroprusside on cerebral blood flow. [92] Initially, when sodium nitroprusside was given to decrease MAP moderately, CBF also increased. However, as larger doses of sodium nitroprusside were administered to decrease MAP further, CBF remained near its baseline value until MAP reached 65 mm Hg. When MAP fell below this level, the pressure-flow relationship was linear.

In rats the effects of profound hypotension (MAP of 30 mm Hg for 30 minutes), using trimethaphan or sodium nitroprusside CBF on basal cerebral blood flow was investigated. [93] Hypotension induced with nitroprusside caused a smaller reduction in CBF. EEG activity, which indicates continuing neuronal function, was maintained for longer in the nitroprusside group.

Impairment or loss of autoregulation of CBF is a primary concern when hypotensive agents are used in neurosurgical anesthesia. Clearly, sodium nitroprusside impairs autoregulation in normal animals. [92] Impairment of autoregulation by sodium nitroprusside precludes any modulation of CBF in response to acute alterations in systemic arterial blood pressure. Under these circumstances, the intracranial contents not only are subjected to the specific pharmacologic activity of these drugs but will also closely reflect changes in the systemic circulation.

Nitroglycerin

Nitroglycerin directly dilates venous capacitance vessels. [94] It has a short half-life and no clinically significant toxic metabolites. The effect of nitroglycerin on cardiac output is variable. Although most studies suggest that cardiac output does not change, this result may depend on the volume status of the patient. Although both resistance and capacitance vessels are dilated, nitroglycerin has its major effect on the latter. Because capacitance of the venous circulation increases markedly with nitroglycerin, cardiac output may decrease if preload is compromised. [95] However, the effect of reduced preload would be offset by an increase in nervous sympathetic activity, elicited through baroreceptor activity and resulting in increased heart rate and myocardial contractility. [96] The baroreceptor reflex mechanism would also counteract the decrease in SVR, resulting in a biphasic response (initial arteriolar vasodilation followed by vasoconstriction in the mesenteric, iliac, coronary, and systemic beds). [97]

Because the adrenergic response will be partially blocked by anesthesia, the cardiovascular effects of nitroglycerin will be different in anesthetized subjects. [96] Recent research indicates that cardiac index is lower when MAP is decreased to 40 mm Hg with nitroglycerin rather than sodium nitroprusside. [40] Yaster et al [98] studied 14 patients 9 to 14 years of age. Mean arterial blood pressure was reduced to 55 mm Hg or less by infusion of sodium nitroprusside or nitroglycerin. At infusion rates as high as 40 mug/kg/min, nitroglycerin was not able to produce rapid, predictable, and sustained decreases in arterial blood pressure during general anesthesia. Nitroglycerin did not decrease MAP below 60 mm Hg in six of the eight patients studied.

The decrease in blood pressure with sodium nitroprusside is more rapid. Significant differences also seem to exist on discontinuation of the two drugs. Significant rebound hypertension frequently occurs after acute termination of sodium nitroprusside, [77] whereas acute termination of nitroglycerin has produced a prolonged period of vasodilation in animals. [99] As with sodium nitroprusside, low intracranial compliance contraindicates the use of nitroglycerin prior to opening of the dura mater. [100] Even when the dura has been opened, both nitrates incur some risk of increased cerebral blood volume and significant brain swelling. [101] Differences between sodium nitroprusside and nitroglycerin clearly exist. Although both drugs are able to decrease arterial blood pressure, the effect of sodium nitroprusside is more rapid and consistent.

Hydralazine

Hydralazine, a smooth muscle relaxant, effectively induces hypotension when low concentrations of enflurane are administered. [102] Hydralazine significantly reduces SVR without changing cardiac output, pH, or venous admixture. Rebound hypertension does not occur, and ICP increases significantly. [102]

Purine Derivatives

A natural substance that produces hypotension would be an attractive alternative to the previously discussed drugs. Both adenosine triphosphate (ATP) and adenosine meet these criteria. [103] Adenosine triphosphate rapidly degrades into adenosine and phosphate, adenosine being the component producing vasodilation. Adenosine is metabolized to uric acid; the amount is in dispute. [104] Hypotension occurs rapidly, owing to marked dilation of resistance vessels, the subsequent hyperkinetic circulation, and an increase in cardiac output. Plasma-renin activity and plasma catecholamines do not increase. [105] [106] Similar degrees of hypotension can be achieved as with sodium nitroprusside, but recovery is more rapid, and no rebound hypertension occurs. [8] [104] Unfortunately, ATP and adenosine dilate cerebral vessels, increase CBF, increase ICP when intracranial compliance is low, and impair cerebral autoregulation [104] [107] [108] (Fig. 41-4) (Figure Not Available) .

Adenosine is a potent coronary vasodilator that can produce an unfavorable redistribution of coronary blood flow, leading to ischemia. Some patients with coronary artery disease have shown signs of ischemia during administration of adenosine. [109] Administration through a central venous catheter is advocated to increase

efficacy of the drug. With peripheral administration, partial breakdown of the drug occurs before it can reach the arteriolar vascular smooth muscle. As a result, drug requirements are 40 percent higher. The dose requirement can be reduced by concomitant administration of dipyridamole, which inhibits adenosine uptake, primarily by blocking carrier-mediated diffusion into cells. [105] Another potential disadvantage of adenosine and ATP is their ability to cause heart block. [110]

Figure 41-4 (Figure Not Available) Changes in cerebral blood flow (DeltaCBF) after acute increases in mean arterial pressure (MAP) before, during, and after adenosine triphosphate (ATP)-induced hypotension demonstrate that cerebrovascular reactivity is normal before hypotension but impaired during and after hypotension. Specifically, five anesthetized baboons had acute increases in MAP of approximately 20 mm Hg (by means of intravenous administration of angiotensin II amide) at three times: before ATP-induced hypotension; during infusion of ATP, once MAP had decreased to approximately 40 percent of control; and after infusion of ATP, once CBF had returned to control. Mean values ±SD. * $P < .05$; ** $P < .01$. *(Modified from Van Aken et al [104])*

Trimethaphan

Ganglionic blockade has long been the mainstay of deliberate hypotension. Hypotension results from occupation of the receptor sites and stabilization of the postsynaptic membrane, both of which block neural transmission through the autonomic ganglia. Because autonomic ganglion-blocking drugs such as trimethaphan lack selectivity, both parasympathetic and sympathetic activity are depressed. Parasympathetic depression produces unwanted effects like tachycardia, mydriasis, cycloplegia, reduced gastrointestinal tone and motility, and urinary retention.

Trimethaphan has maintained some popularity because of its short half-life (1-2 minutes), owing to rapid inactivation by plasma cholinesterase with subsequent renal excretion. This characteristic makes it easy to control blood pressure. Potential problems include histamine release (related to the rate of infusion), bronchospasm, tachyphylaxis, and potentiation of succinylcholine-induced myoneural blockade. [111] Trimethaphan seldom increases ICP, as ganglionic blockade generally does not affect the cerebral circulation. However, trimethaphan may increase ICP when rapidly infused during low intracranial compliance (possibly because of histamine release). In addition, cerebral ischemia has occurred in dogs given trimethaphan to induce hypotension to a MAP of 55 mm Hg. [112] These results contrast with the safety of comparable levels of hypotension produced by sodium nitroprusside, nitroglycerin, adenosine, and isoflurane, presumably because these drugs are cerebral vasodilators. It should be noted that dilation of the pupils is a pharmacologic

property of trimethaphan caused by blockade of the ciliary ganglion. This effect might erroneously be attributed to cerebral ischemia by those unfamiliar with the drug.

Combined Therapy (Sodium Nitroprusside and Trimethaphan)

Large doses of sodium nitroprusside can produce cyanide toxicity. Large doses of trimethaphan may result in prolonged hypotension. To avoid these problems, the use of a 10:1 mixture of trimethaphan and sodium nitroprusside has been advocated. This ratio was proposed because of the relative potencies of the two agents. The mixture proved to be an efficient and rapid hypotensive agent with the potential for rapid recovery; also, the total dose of sodium nitroprusside could be reduced substantially. [113]

Miller et al [114] compared sodium nitroprusside with a 10:1 trimethaphan-sodium nitroprusside mixture in 20 patients undergoing neurosurgical procedures. Controlled ventilation kept arterial carbon dioxide partial pressure (Pa_{CO_2}) at 25 to 30 mm Hg. Cardiac output was significantly lower with the mixture than with sodium nitroprusside alone. However, the total dose of sodium nitroprusside needed to produce a similar degree of reduction in blood pressure was five times lower with the mixture. This type of combined therapy might be beneficial for prolonged periods of hypotension.

Phentolamine

Phentolamine decreases MAP by blockade of alpha-adrenergic receptors within 2 minutes of intravenous administration. Blood pressure returns to control values within 15 minutes. Intracranial pressure does not change significantly, but cerebral perfusion pressure is lower for 10 minutes after drug administration. [115]

Urapidil

Urapidil, an antihypertensive drug not available in the United States, has two mechanisms of action: antagonism of peripheral alpha-adrenergic receptors and interaction with 5-hydroxytriptamine$_{1A}$ receptors in the brain. This pharmacologic profile explains the vasodilation and lack of significant sympathetic activation observed during administration of urapidil. [116] Intracranial pressure and compliance have not been affected in animals or patients given urapidil. [117] [118] Cerebral blood flow of baboons did not change when MAP was decreased from 107 ± 13 to 70 ± 13 mm Hg with urapidil. [119] A greater degree of hypotension could not be achieved by increasing the dose. Rebound hypertension did not occur. Urapidil seems to be a suitable agent for the induction of moderate degrees of hypotension (MAP of 70 mm Hg). Administration of urapidil with isoflurane in animals has attenuated the undesirable effects and diminished the required concentration of the volatile anesthetic. [48] This technique is often used in clinical practice in Europe.

Esmolol

Esmolol is a short-acting cardioselective intravenous beta-adrenergic receptor-blocking drug having a very rapid onset of action (Ch. 14). [120] It has been used by itself to decrease blood pressure [26] [121] [122] or in combination with other drugs. [123] In contrast to sodium nitroprusside-induced hypotension, plasma renin activity decreased slightly during esmolol-induced hypotension. This absence of renin release improved the stability of hypotension. [123]

One study on 30 patients undergoing resection of arterio-venous malformations with deliberate hypotension showed the potential of esmolol to produce marked myocardial depression. [122] Patients were randomly assigned to receive isoflurane (
4%), sodium nitroprusside (
8 mug/kg/min), or esmolol (
24 mg/min) for a 20 percent reduction in MAP to 60 to 65 mm Hg. Esmolol was associated with a 39 percent decrease in cardiac output, which, because of a 22 percent increase in SVR, far exceeded the reduction in MAP. The increase in SVR occurred despite a 32 percent decrease in plasma-renin activity. In contrast, with sodium nitroprusside or isoflurane, the decrease in MAP was accompanied by a decrease in SVR of similar magnitude but no change in cardiac output (Fig. 41-5). (Figure Not Available) Plasma-renin activity increased 48 percent with sodium nitroprusside and 126 percent with isoflurane. Heart rate increased 13 percent with sodium nitroprusside, did not change with isoflurane, and decreased 23 percent with esmolol. Because of its potential for marked myocardial depression, it seems prudent to combine esmolol with other drugs or to use it when only modest reductions in blood pressure are required.

Labetalol

Labetalol produces hypotension by blocking both alpha$_1$- and beta$_1$-receptors (Ch. 14). Labetalol also blocks beta$_2$-receptors. As a result of decreases in cardiac output and peripheral vascular resistance, blood pressure decreases promptly after intravenous administration of labetalol. Although the peak effect of intravenous labetalol occurs within 5 minutes, its half-life is relatively long (4 hours) compared with that of sodium nitroprusside or nitroglycerin. [124]

Hypotension induced with labetalol produces only minimal increase in intrapulmonary shunting and no increase in heart rate, whereas both variables increase significantly with sodium nitroprusside. [124] Combining labetalol with inhalation agents such as halothane and isoflurane produces a remarkable hypotensive synergism; labetalol is less potent in this regard when combined with intravenous anesthetics. [125] An important advantage of labetalol is the absence of any increase in ICP, even when intracranial compliance is reduced. [126] Experiments in rats showed that blood flow to vital organs was significantly better when the hypotensive agent was isoflurane combined with labetalol rather than isoflurane alone. [127] A study on patients also confirmed that preservation of renal blood flow was superior with labetalol. [49] The same investigators also showed that hypotension induced by labetalol with isoflurane anesthesia did not cause more impairment of mental functions than normotensive general anesthesia. [128] However, clinicians should be

Figure 41-5 (Figure Not Available) Percentage change from baseline for hemodynamic variables and plasma-renin activity (PRA) during hypotension induced by esmolol, sodium nitroprusside, or high-dose isoflurane in 30 patients undergoing resection of intracranial arteriovenous malformations. For mean arterial blood pressure (MAP) and heart rate (HR), *n* = 10 for esmolol and nitroprusside and *n* = 9 for isoflurane. For cardiac output (CO), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR), *n* = 9 for esmolol and isoflurane and *n* = 7 for nitroprusside. For plasma renin activity, *n* = 8 for all groups. *Significantly (*P* < .05) different from the other two groups. *(From Ornstein et al [122])*

aware that labetalol masks the adrenergic response to acute blood loss. Because of the relatively long half-life of labetalol, this effect lasts through the early postoperative period.

Nicardipine

Nicardipine is a calcium channel blocking drug that dilates peripheral, coronary, and cerebral vessels while maintaining myocardial contractility and cardiac output without tachycardia. [129] Careful titration of nicardipine infusions (10-250 mug/kg/h) is mandatory because nicardipine-induced hypotension resists conventional treatment such as phenylephrine. [130] [131]

Prostaglandin E_1

Prostaglandin E_1 (PGE_1) is another naturally occurring substance that has been evaluated as a possible hypotensive drug. One study of 14 mastectomy patients given PGE_1 reported that all but two had a decrease of approximately 40 mm Hg in arterial blood pressure, which returned to control values on termination of the drug. [132] None of these patients complained of abdominal pain, diarrhea, or other known side effects of prostaglandin infusion after recovery from general anesthesia. Renal blood flow increased, and no arrhythmias were noted. Other studies reported that local CBF and carbon dioxide reactivity were well maintained during PGE_1-induced hypotension for cerebral aneurysm surgery. [133] [134] PGE_1 appears to be a mildly hypotensive agent that may not be able to produce profound hypotension in all patients.

EFFECT OF HYPOTENSION ON ORGAN FUNCTION

Deliberate hypotension decreases arterial blood pressure by decreasing cardiac output or SVR, or both. However, a reduction in cardiac output may not be the most appropriate method because keeping cardiac output stable is crucial for maintaining blood flow to the tissues. Cardiac output should remain sufficiently high not only to provide adequate oxygen and energy substrates but also to remove metabolic waste products before their accumulation causes tissue damage. The final effect of hypotensive anesthesia on cardiac output depends on the balance of its effects on afterload, preload, myocardial contractility, and heart rate. These effects interact with homeostatic mechanisms. Other important factors include the physical state of the patient, the administration of additional drugs, and the pattern of ventilation used intraoperatively. Because deliberate hypotension is clearly designed to decrease arterial blood pressure but still preserve organ blood flow and function, it must be emphasized that decreasing blood pressure by hemorrhage also decreases organ blood flow. The use of deliberate

---

hypotension requires constant assessment of intravascular fluid volume throughout surgery, to ensure optimal organ function.

The effects of hypotension on various organ beds are complex, depending on the drugs used and the magnitude and length of hypotension. Differences in species may also be important when evaluating the many animal studies on organ function during deliberate hypotension.

Central Nervous System

Because ischemia of the brain and myocardium are the principal hazards of deliberate hypotension, the effects of arterial hypotension on the cerebral circulation (Chs. 19 and 52) are particularly important. The adequacy of cerebral perfusion during induced hypotension has been studied using clearance of radioactive xenon, electroencephalographic monitoring, and measurement of jugular venous oxygen content. [135] [136] [137] Although these tools are relatively crude measurements of cerebral function, all have shown that deliberate hypotension does not produce permanent changes in cerebral hemodynamics. Furthermore, the performance of elderly patients on psychologic tests given several days after total hip arthroplasty with deliberate hypotension did not differ from their performance before surgery. [21] The current rationale for setting the "safe" lower limit for MAP at 50 to 55 mm Hg in normothermic patients is based on the belief that this range represents the lowest MAP at which autoregulation of CBF is still in force. [136] Once MAP falls below this limit, CBF decreases in parallel with pressure. For chronically hypertensive patients, the curve for autoregulation (CBF versus MAP) shifts to the right, that is, the lowest blood pressure at which autoregulation of CBF is still in force is higher for these patients than for normotensive patients [138] (Fig. 41-6) . With effective antihypertensive therapy, however, the curve for autoregulation moves back to its normal position. [139] Sharrock et al [35] showed that induced hypotension is a safe technique for patients with medically controlled hypertension.

The factor most important to cerebral autoregulation is cerebral perfusion pressure and not blood pressure as such. Perfusion pressure is the difference between arterial input and venous outflow pressures. Because pressure in the cerebral venous system approximates ICP, cerebral perfusion pressure is usually calculated as MAP - ICP. An important consequence is that patients with increased ICP should never undergo deliberate hypotension before the dura is opened unless measurement of ICP is available before the surgical procedure. According to several investigators, normal cerebral oxygen metabolism can continue with a reduction in CBF to a value as low as 18 mL/100 g/min. A "normal" man has CBF this low when cerebral perfusion pressure decreases to 30 to 40 mm Hg. Children are able to tolerate even lower levels. When the skull is opened, cerebral perfusion pressure corresponds to MAP of approximately 30 to 40 mm Hg, measured at the level of the internal carotid artery. When such extreme hypotension is applied, the use of brain retractors should be avoided, blood oxygenation should be optimal, and the margin for error is zero. In our opinion, this situation creates an unjustifiably high risk for the patient. We believe that deliberate hypotension should not be pushed to this limit. Higher cerebral perfusion pressure is required for patients with chronic hypertension and altered cerebral autoregulation. Autoregulation may be absent in the tissue surrounding brain tumors, [140] in the acute phase of a subarachnoid hemorrhage, [141] and after brain trauma. [142]

Pinaud et al [143] studied the consequences of this very low level of hypotension in nine adults undergoing repair of cerebral aneurysms. MAP was decreased to 40 mm Hg with sodium nitroprusside. Intraoperative CBF and the cerebral metabolic rate for oxygen were measured before, during, and after hypotension. This reduction in MAP seemed to be safe for the area of the brain studied. In poorly perfused regions, however, the occurrence of local brain and cerebrospinal fluid lactic acidosis, especially in the retracted areas, might increase risk at such low pressures. Unfortunately, the study technique did not allow such a determination.

Figure 41-6 The curve for autoregulation of cerebral blood flow (CBF); that is, CBF versus mean arterial blood pressure (MAP) shifts to the right for chronically hypertensive patients. The lowest MAP at which autoregulation of CBF is still in force is higher for these patients than for normotensive patients. "Breakthrough" refers to the upper limit, in normotensive and hypertensive individuals, of autoregulation of CBF beyond which CBF suddenly increases, this upper limit being displaced toward higher pressures in hypertensive patients. [138]

Figure 41-7 (Figure Not Available) The relationship between cerebral blood flow (CBF) and arterial carbon dioxide partial pressure (Pa CO_2) at normal blood pressure and during extreme hypotension (mean arterial blood pressure of 35 mm Hg). The complete relationship between CO_2 and CBF at normotension is sigmoid in shape, but the relationship between CBF and Pa CO_2 values in the range of 20 to 70 mm Hg is virtually linear. *(Modified from Harper et al [144])*

Pa CO_2 is an important consideration during deliberate hypotension. During normotension, CBF changes linearly with Pa CO_2 when Pa CO_2 is 20 to 70 mm Hg. An increase of 1 mm Hg in Pa CO_2 produces a 2.65 percent increase in CBF. However, when a progressive degree of hypotension is induced, this relationship becomes progressively flatter, so that when the MAP falls below 50 mm Hg, CBF no longer responds to changes in Pa CO_2 [144] (Fig. 41-7) (Figure Not Available) . A partial exception may be sodium nitroprusside-induced hypotension: in one study, hypocapnia did not further reduce CBF during trimethaphan hypotension but did so with sodium nitroprusside. [145] It must be emphasized that hypocapnia reduces CBF only at moderate levels of hypotension, and that at very

Figure 41-8 (Figure Not Available) Change in cerebral blood flow (DeltaCBF) in dogs subjected to varying degrees of hypotension induced by trimethaphan or sodium nitroprusside. When cerebral perfusion pressure (CPP, which is systemic arterial blood pressure minus cerebrospinal fluid pressure) was decreased incrementally from 80 to 30 mm Hg, CBF decreased with trimethaphan but not SNP. *(Modified from Stoyka and Schutz [84])*

low blood pressures (deep hypotension) Pa CO_2 no longer influences CBF.

Whether one drug is better than another in preserving CBF is often debated. Stoyka and Schutz [84] examined the effects of sodium nitroprusside and trimethaphan in dogs subjected to a cerebral perfusion pressure of 80 to 30 mm Hg. With trimethaphan, autoregulation was lost below 60 mm Hg and CBF decreased as cerebral

perfusion pressure decreased. However, with sodium nitroprusside, CBF remained at a stable level despite the decrease in cerebral perfusion pressure (Fig. 41-8) (Figure Not Available) . Similarly, another study demonstrated that the normal ionic gradients established across cell membranes were depressed by hypotension, more so with trimethaphan than with nitroprusside. [146] Ishikawa et al [147] used Evans blue dye to examine the blood-brain barrier in dogs. Dysfunction of the blood-brain barrier was more pronounced with sodium nitroprusside than with trimethaphan. Because each of these studies used extreme degrees of hypotension, their results cannot be applied automatically to the usual clinical practice of decreasing MAP to 50 to 65 mm Hg. This level of MAP appears to keep CBF at rates adequate for the needs of the brain. For the moderate degrees of hypotension used routinely, both sodium nitroprusside and trimethaphan are equally effective. At deeper levels of hypotension, sodium nitroprusside may be preferable.

The use of isoflurane alone to induce hypotension has gained popularity. For normocapnic dogs, isoflurane appeared to offer certain advantages over other techniques commonly used to induce hypotension. [148] At low cerebral perfusion pressures (<30 mm Hg), the cerebral metabolic rate for oxygen was better preserved, suggesting cerebral protection. Isoflurane also favorably influenced the global cerebral oxygen supply/demand ratio in humans having a MAP of 50 mm Hg [149] (Fig. 41-9) (Figure Not Available) .

The data of Seyde and Longnecker [150] in rats indicate that isoflurane is not harmful to the central nervous system during hypotension. When MAP was decreased to 40 mm Hg with sodium nitroprusside, adenosine, or deep levels of isoflurane anesthesia and tissue oxygen pressures were measured, the lowest incidence of low values for tissue oxygen

Figure 41-9 (Figure Not Available) The changes in cerebral blood flow and cerebral metabolic rate for oxygen ($CMRO_2$) in 12 patients before, during, and after decrease in mean arterial blood pressure induced by isoflurane. * $P < .25$ compared with prehypotension value. *(From Newman et al [149])*

occurred with deep isoflurane. Again, current data suggest that either isoflurane or sodium nitroprusside is safe to use for deliberate hypotension.

Heart

Clinical and experimental studies demonstrate that cardiac function is better preserved with isoflurane than with equihypotensive doses of halothane or enflurane (Ch. 16) . [10] [38] [151] [152] Investigators believe that isoflurane is the volatile anesthetic most suitable for healthy patients undergoing deliberate hypotension. Experimental data indicate that the cardiovascular effects of the newly developed volatile anesthetics sevoflurane and desflurane are comparable to those of isoflurane. [153] [154] Although the low blood solubility of these drugs would allow even more rapid control of blood pressure, [155] further clinical experience and studies on potential side effects are required.

Recent clinical reports describe the successful use of continuous infusion of propofol to produce deliberate hypotension. [156] The cardiovascular effects of anesthetic doses of propofol are very similar to those of isoflurane: arterial blood pressure decreases primarily because of venodilation and a reduction of SVR. [157] However, using the cardiovascular side effects of anesthetic drugs to produce arterial hypotension may entail excessive doses that increase the risk of cardiac depression [152] [158] [159] and toxic side effects. For this reason, a technique combining anesthetic drugs with specific vasodilating drugs has recently gained popularity.

During deliberate hypotension, maintenance of an oxygen supply sufficient for the metabolic needs of the myo-cardium is of primary importance. The intact coronary circulation undergoes a high degree of pressure-flow autoregulation that is mildly disrupted by volatile anesthetic agents. [160] However, progressive systemic hypotension gradually depletes coronary vasodilatory reserve and diminishes the ability of the heart to cope with stresses that increase myocardial oxygen demand. [161] Arterial hypotension obtained with direct vasodilating drugs such as sodium nitroprusside and with the calcium channel blocker nicardipine frequently incurs reflex tachycardia. [60] [162] In addition to increasing myocardial metabolism, tachycardia shortens diastole and may thus reduce myocardial perfusion. [161]

Many drugs have been used to suppress tachycardia. The cardioselective beta$_1$-receptor antagonist esmolol decreases heart rate but has profound negative inotropic properties. [122] In combination with vasodilating drugs, however, esmolol can be used at lower doses to block reflex tachycardia, thus avoiding excessive cardiac depression. [123] A similar approach using ganglionic blocking drugs to suppress reflex tachycardia induced by nitroprusside has been effective in humans and animals. [114]

Some drugs having a unique pharmacologic profile do not induce reflex tachycardia despite their predominantly vasodilatory action. With labetalol and urapidil, reflex tachycardia in response to alpha$_1$-mediated vasodilation is counterbalanced by the drug's concomitant beta$_1$-antagonistic and central serotoninergic properties, respectively. [116] [124] Adenosine, a powerful vasodilator, directly depresses the sinus node and may also cause less tachycardia. [163]

As a compensatory mechanism to preserve myocardial perfusion at rest, the vasodilatory reserve of patients with coronary artery lesions is diminished even at normal coronary perfusion pressure. Under these circumstances, systemic hypotension will directly decrease myocardial perfusion. [164] Whether myocardial ischemia will develop as a result of hypotension depends on the concomitant changes in myocardial metabolic requirements. [165] Drugs that reduce metabolic requirements (e.g., anesthetic agents and beta$_1$-antagonists) may protect the heart from ischemia. [166] [167] Nitroglycerin can also be advantageous, as it improves perfusion to jeopardized myocardium. [168] In contrast, potent arteriolar coronary vasodilators, such as adenosine and sodium nitroprusside should be avoided unless appropriate monitoring is used because they may redistribute coronary blood flow away from ischemic myocardium, that is, cause coronary steal. [169] [170]

Controversy still exists over the ability of isoflurane, also an arteriolar vasodilator, to cause coronary steal. Clinical and experimental studies indicate that hypotension induced by isoflurane causes more regional myocardial ischemia than

halothane. [171] [172] [173] Other experimental studies, however, provide evidence against this hypothesis. [169] [174] That is, the vasodilating properties of isoflurane are weak and probably offset by the concomitant reduction in metabolic requirements. Isoflurane may even favor collateral myocardial perfusion. [175] [176]

As a general rule, however, patients with known or suspected ischemic heart disease should not undergo deliberate hypotension unless appropriate monitoring is used. For these patients, other techniques that can partially replace the use of systemic hypotension for a given indication (e.g., reduction of blood loss) must be considered.

Finally, considerable interest has developed in the combined use of deliberate hypotension and normovolemic hemodilution to reduce the requirements for perioperative autologous blood transfusion. Preliminary data from animals, however, indicate that hemodilution reduces coronary vasodilatory reserve and the tolerance to myocardial ischemia during hypotension, even in the intact coronary circulation. [177]

Lungs

Eckenhoff et al [178] noted a higher than normal carbon dioxide tension in the blood during hypotension induced with either pentolinium or trimethaphan. Measuring physiologic dead space in 25 patients, they concluded that hypotension combined with increased mean airway pressure, head-up tilt, and surgery may all lead to increased dead space. Khambatta et al [179] measured dead space in patients undergoing hypotensive anesthesia with sodium nitroprusside. They concluded that if cardiac output were maintained by replacement of intravascular fluids during induced hypotension, physiologic dead space would not increase. This conclusion is supported by Suwa et al [180] who earlier demonstrated that a decrease in cardiac output would increase dead space; this result may explain the findings of Eckenhoff et al. [178]

Oxygenation may also change during deliberate hypotension (Ch. 15) . In one study, arterial oxygenation decreased markedly with infusion of sodium nitroprusside. [181] In another study, normal subjects had a similar decrease in oxygenation and an increase in shunt fraction when sodium nitroprusside was infused. [182] For patients with chronic obstructive pulmonary disease whose shunt fractions were already increased, no change in shunt fraction could be demonstrated. The response to

infusion of nitroglycerin in both normal patients and those with chronic obstructive pulmonary disease was similar to the response to sodium nitroprusside. A third study compared hypotension induced with sodium nitroprusside versus isoflurane in 16 patients undergoing total hip arthroplasty. [183] Pulmonary shunt fraction increased with sodium nitroprusside but not isoflurane. Animal data support this clinical observation. [184]

Other effects of hypotensive agents on pulmonary function have been minimal. Trimethaphan caused a slight increase in respiratory rate and a mild degree of alveolar hyperventilation. [185] Lung mechanics did not change. Because of changes in oxygenation and possibly carbon dioxide elimination, controlled ventilation is preferable for patients undergoing deliberate hypotension.

Kidneys

Renal blood flow normally equals 20 to 25 percent of cardiac output (Ch. 18) . The renal circulation is characterized by a well-functioning autoregulatory mechanism. Renal arterioles have low resting vascular tone and therefore limited ability to dilate further in response to hypotensive drugs. The glomerular filtration rate is maintained until MAP falls below 75 mm Hg. [186] At this level, perfusion is still sufficient to meet the metabolic needs of the kidney cells, although oliguria may ensue. Because most clinical studies have demonstrated that normovolemic patients have rapid recovery of urine production on discontinuation of induced hypotension, strict maintenance of urine production during deliberate hypotension is unnecessary. [187] [188] [189]

Thompson et al [21] could find no significant changes in serum creatinine, blood urea nitrogen, or serum or urinary electrolytes for 30 patients having deliberate hypotension. Because renal dysfunction is not a frequent complication of deliberate hypotension, short periods of decreased renal flow are apparently not detrimental.

Recently Toivonen et al [49] demonstrated that kidney function is better preserved during hypotension induced with a combination of labetalol and isoflurane than with deep levels of isoflurane anesthesia alone (Table 41-3) (Table Not Available) .

TABLE 41-3 -- Effect of Induced Hypotension on Kidney Function [a]

(Not Available)

(From Toivonen at al [49])

[a] Mean values (±SEM) for urinary flow rate (UF), creatinine clearance (C_{Creat}), urine osmolality (U_{Osm}), and fractional excretion of sodium (FE_{Na}) for 10 patients in two hypotensive groups. Variables were determined during anesthesia, before the start of hypotension (before); during hypotension (during); and after anesthesia (after).

Splanchnic Circulation

Because pressure-flow autoregulation is limited in the hepatic arterial bed and probably absent in the portal venous circulation, profound changes in liver perfusion may occur during deliberate hypotension. [190] Consequently, preference should be given to drugs that preserve cardiac output during systemic hypotension. Extrinsic control of hepatic blood flow occurs primarily through alpha $_1$ -mediated vasoconstriction. [191] Baroreflex activation, surgical stress, or exogenous vasopressors will therefore decrease hepatic blood flow. [191] Autoregulation in the intestine is less pronounced than in the kidney or brain, and the circulatory control of splanchnic perfusion is poorly understood. Again, increased sympathetic nervous outflow following baroreflex stimulation induces splanchnic vasoconstriction. [192]

Clinical monitoring of the splanchnic circulation is extremely difficult. In addition, only a few animal studies provide data on splanchnic perfusion during systemic hypotension. Chronically instrumented dogs had better preservation of hepatic oxygen supply with isoflurane than with halothane or enflurane. [193] [194] Also, using a combination of intravenous adjuvants with isoflurane to induce hypotension was better at preserving hepatic blood flow than using isoflurane alone. [48] Whether some hypotensive adjuvant drugs offer advantages over others regarding homeostasis of splanchnic circulation is unknown. Finally, the combination of hemodilution and isoflurane-induced hypotension adversely affected hepatic perfusion, oxygenation, and function in acutely instrumented laparotomized pigs. [195]

Eye

Intraocular pressure consists of the combined pressure of blood and aqueous humor within the eye (Ch. 63) . When arterial blood pressure decreases, intraocular pressure also decreases. The eye has two separate systems of blood vessels: the retinal and the uveal. The uveal vessels are peculiar in possessing both precapillary sphincters and, hence, having a steady blood flow. Because the uveal system carries most of the blood supplying the eye, sudden decreases in MAP are transmitted to the eye as decreases in intraocular pressure. [196] The effect of hypotension on blood flow to the eye accounts for some of the complications of deliberate hypotension, including blurring of vision and, on rare occasion, blindness. Therefore, proper positioning with special attention to local pressure on the eyes is extremely important.

Skin and Muscle

Measurement of blood flow to skin and muscle has relied on microsphere studies in animals. As relative blood flow to skin and muscle is small, this method is suspect. Hoffman et al [197] found that blood flow to the skin of rats decreased with sodium nitroprusside, nitroglycerin, and 2 percent enflurane, whereas blood flow to skeletal muscle increased. In another study, 20 patients given sodium nitroprusside or trimethaphan to induce hypotension for middle-ear surgery had no change in lactate, pyruvate, or standard bicarbonate with either drug. [198] Extensive clinical experience with a variety of hypotensive drugs seems to support the claim that deliberate hypotension is not injurious to these tissues, as myoglobinuria, skin necrosis, and muscle weakness do not occur.

However, experimental studies report differences between sodium nitroprusside and nitroglycerin regarding oxygen pressure in muscle. Hauss et al [199] found that the oxygen pressure in canine skeletal muscle decreased markedly with sodium nitroprusside but not nitroglycerin. These investigators suggested that sodium nitroprusside but not nitroglycerin severely impairs autoregulation of the microcirculation. This study used a surface technique and generation of a histogram to assess oxygen pressure in tissue. Some investigators believed this method is too crude and, because of the size of the electrode used, does not give an accurate estimate of tissue oxygenation.

When Endrich et al [200] used more complex methods to compare the effects of sodium nitroprusside versus nitroglycerin on striated hamster muscle, they also found significant differences. Endrich and coworkers not only examined tissue oxygenation but also measured microvascular pressures, vascular diameters and density, and blood cell velocity, in addition to visualizing the microvasculature directly. Although both sodium nitroprusside and nitroglycerin affected resistance vessels similarly, venous capillaries dilated only in response to nitroglycerin. Accordingly, the pressure difference between the arterioles and the venules, which determines capillary perfusion, did not change with nitroglycerin but decreased significantly with sodium nitroprusside (Fig. 41-10) (Figure Not Available) . Furthermore, a significant amount of blood was diverted through arteriovenous shunts during sodium nitroprusside-induced hypotension. This mechanism probably explains why tissue oxygenation decreased with sodium nitroprusside but not with nitroglycerin. Endrich et al [200] concluded that nitroglycerin has a distinct advantage over sodium nitroprusside. Unfortunately, the desired degree of hypotension cannot always be achieved with nitroglycerin.

CLINICAL CONSIDERATIONS

When considering the many facets of deliberate hypotension, the concern of the anesthesiologist should be directed toward not only selection of the most appropriate hypotensive drug but also the type of surgery, length of procedure, need to decrease blood loss, and patient suitability.

Indications and Contraindications

Many circumstances and conditions indicate the possible need for deliberate hypotension: neurosurgery, large orthopedic procedures such as total hip arthroplasty or complicated back surgery, surgery on large tumors, surgery of the head and neck, and a variety of plastic surgical procedures. Deliberate hypotension has also been used when religious beliefs preclude blood transfusion. [201] As mentioned, positioning the patient may be as important in controlling bleeding as decreasing arterial blood pressure. Before beginning a surgical procedure, the logistics of patient positioning should be discussed by the anesthesiologist and surgeon.

Figure 41-10 (Figure Not Available) The pressure in arterioles and collecting venules of hamsters before, during, and after hypotension was induced with either sodium nitroprusside (SNP) or nitroglycerin (NTG). Numbers in parentheses indicate the diameters of the vessels studied. h70 and h40, mean arterial blood pressure of 70 and 40 mm Hg, respectively; 10 ph, 10 minutes after hypotension. *(From Endrich et al [200])*

The contraindications to deliberate hypotension have relaxed over the years. Better drugs and monitoring and more experience with the technique have permitted more patients to benefit from deliberate hypotension during surgery. Even when a clear indication for deliberate hypotension exists, several relative contraindications must be considered. For example, a history of cerebrovascular disease, renal dysfunction, liver dysfunction, or severe peripheral claudication suggests that the patient is less likely to have good organ perfusion during hypotension. Similarly, patients with hypovolemia or severe anemia would not be suitable candidates, as their reserves for adequate organ perfusion are markedly diminished.

The decision to use deliberate hypotension in a patient with long-standing hypertension is more difficult. Strandgaard [202] studied 13 untreated or ineffectively treated hypertensive patients (MAP of 145 mm Hg). Blood pressure was decreased by trimethaphan and head-up tilt. The lower limit of CBF autoregulation was higher for these patients (113 ± 17 mm Hg) than for similarly treated normotensive patients (73 ± 9 mm Hg). The shift in the autoregulatory curve to the right for hypertensive patients puts these patients at higher risk of death and morbidity during deliberate hypotension. Treatment of hypertension returns cerebral autoregulation toward normal. [139] [202] Furthermore, deliberate hypotension seems to be safe for patients with medically controlled hypertension. [35]

The usefulness of deliberate hypotension during clip ligation of cerebral aneurysms is controversial. [203] [204] Because wall stress at any given pressure depends on the thinness of the aneurysm sac, decreasing transmural pressure in the aneurysm during manipulation theoretically decreases the potential for rupture. Therefore, either an increase in MAP or a decrease in ICP prior to opening of the skull will increase transmural pressure (which is equal to MAP - ICP), thereby increasing wall stress and the risk of rupture.

Unfortunately, review of the literature does not produce any firm conclusions regarding the usefulness of deliberate hypotension for preventing rupture of cerebral aneurysms. [203] Furthermore, there is an acceptable alternative that facilitates clipping of a cerebral aneurysm: temporary occlusion of the proximal vessel. [205] In addition, Farrar et al [206] argue that deliberate hypotension increases the incidence of vasospasm, seriously compromises borderline ischemic brain tissue, and impairs cerebral autoregulation. Thus, controlled hypotension may place focal areas and the entire brain at risk of ischemia.

It is also controversial whether patients with myocardial infarction or a history of angina should undergo deliberate hypotension. Our growing knowledge of coronary artery disease and increased ability to monitor these patients more effectively have enabled many more patients with coronary artery disease to undergo induction of deliberate hypotension.

Monitoring During Induced Hypotension

Beat-to-beat measurement of arterial blood pressure is mandatory for patients undergoing clinically significant, deliberate decreases in blood pressure. The usual practice is to insert an arterial catheter for continuous monitoring of

---

blood pressure. The catheter also allows for intermittent sampling of arterial blood for blood gas analysis. The pressure transducer should be referenced to zero and positioned at the level of the head. Electrocardiographic monitoring is essential for detecting the signs of inadequate myocardial perfusion that indicate excessive hypotension--ectopic beats and changes in the ST segment (Chs. 30 - 32) .

The correlation between end-respiratory and Pa CO_2 is unreliable during hypotension. The changes in physiologic dead space, cardiac output, and body metabolism produced by hypotensive anesthesia obscure the interpretation of end-respiratory CO_2 monitoring. Nevertheless, capnography still provides useful information during hypotensive anesthesia. For example, a sudden decrease in end-expiratory P CO_2 may be caused by a sudden decrease in cardiac output (pulmonary embolism) or by disconnection of the breathing system. Capnography may help avoid hyperventilation, which could be harmful, as the decrease in Pa CO_2 would further reduce CBF during moderate hypotension.

Pulse oximetry and temperature monitoring (especially important because body heat is lost more rapidly from dilated skin vessels) should be used routinely. If large blood loss is anticipated, a central venous line should be inserted. For long procedures, measurement of urinary output is also mandatory. Serum electrolytes, blood gases, and hematocrit level should be measured routinely.

Other monitors that could be used include evoked potentials, the EEG, and tissue pH. [207] These need further evaluation before they are used routinely. Because of the potential problems with deliberate hypotension, monitoring should be optimized for the type and length of surgery performed (Chs. 28 and 35) .

/das/book/view/29494766/875/479.html

COMPLICATIONS

The precise incidence of complications with deliberate hypotension is difficult to determine. In response to a questionnaire circulated during the early 1950s by Hampton and Little, [208] 96 deaths were reported for 27,930 responses, for an incidence of 0.34 percent. Of these deaths, 0.24 percent were attributed to anesthesia and hypotension. This initial report almost caused the abolition of deliberate hypotension in the United States. [209] However, in 1961 Enderby [210] reported 9 deaths among 9,107 cases, but only 0.055 percent of the deaths were attributed to anesthesia and hypotension. Table 41-4 summarizes the published mortality rates for various forms of deliberate hypotension. [208] [210] [211] [212] [213] [214] Mortality appears not to differ from that for all anesthetics (0.01 to 0.007%) (Ch. 22) .

Nonfatal complications, which are more common, were described several decades ago. Hampton and Little [208] reported 908 major and minor complications, for an incidence of 3.3 percent. Complications usually related to the nervous system, such as dizziness, prolonged awakening, and cerebral thrombosis. [215] For Prys-Roberts et al [38] there were two cases of cerebral damage among 15 patients. One 27-year-old patient had hemiplegia after surgery, and a 56-year-old patient who failed to regain consciousness was found to have extensive cerebral and cerebellar infarction. Way and Clarke [216] reported 1 death (cerebral artery thrombosis) among 50 patients undergoing deliberate hypotension. For Linacre, [217] no cerebral complications occurred among 1,000 patients. In another series, retinal thrombosis occurred in 3 of 27,930 patients. [218] Comparable series of patients undergoing present-day techniques to induce hypotension have not been reported. Other potential complications include anuria and oliguria. The more recent literature does not contain reports of these complications, with the exception of postoperative bleeding into the operative site. [31]

Current data indicate that hypotension of 50 to 65 mm Hg is safe for young healthy patients. Unfortunately, many of the most appropriate candidates for deliberate hypotension have underlying organ dysfunction that cannot be appreciated easily by routine examination. Certainly these patients are at risk of complications related to hypotension. Thus all candidates for deliberate hypotension should undergo thorough and complete examination before surgery. The decision to use deliberate hypotension should not be made in the operating room without careful consideration of the potential complications.

SUMMARY

Deliberate hypotension is effective in decreasing blood loss and providing better visibility in the surgical field. Many drugs and techniques have been successful in lowering arterial blood pressure. The mechanisms of action of these drugs differ and produce complex changes in reflexes and, subsequently, blood flow to various organs. Because deliberate hypotension is not without risk, the advantages and disadvantages must be considered.

For the healthy young patient, complications are rare. The elderly and those with underlying organ dysfunction are probably at higher risk. Therefore, the anesthesiologist must assess each patient carefully so that the decision to use deliberate hypotension is based on reason. The intelligent use of deliberate hypotension has distinct advantages for certain procedures and may promote surgical success.

TABLE 41-4 -- Mortality in Deliberate Hypotension

INVESTIGATORS	YEARS	DELIBERATE HYPOTENSION (NO. OF PATIENTS)	DEATHS (NO. [%])
Hampton and Little (1953) [208]	1950-1953	27,930	96 (0.34)
Enderby (1961) [210]	1950-1960	9,107	9 (0.10)
Larson (1964) [211]	1958-1964	13,264	113 (0.10)
Enderby (1980) [212]	1960-1976	9,256	2 (0.02)
Pasch and Huk (1986) [213]	1977-1984	1,802	1 (0.06)
Enderby (1985) [214]	1950-1979	20,558	10 (0.04)

References

1. Cushing H: Tumors of the Nervus Acusticus. Philadelphia, WB Saunders, 1917.

2. Gardner JW: The control of bleeding during operation by induced hypotension. JAMA 132:572, 1946.

3. Griffiths HWC, Gillies J: Thoraco-lumbar splanchnicectomy and sympathectomy: Anaesthetic procedure. Anaesthesia 3:134, 1948.

4. Enderby GEH: Controlled circulation with hypotensive drugs and posture to reduce bleeding during surgery. Preliminary results with pentamethonium iodide. Lancet 1:1145, 1950.

5. Enderby GEH: Halothane and hypotension. Anaesthesia 15:25, 1960.

6. Hellewell J, Potts MW: Propranolol during controlled hypotension. Br J Anaesth 38:794, 1966.

7. Scott DB, Buckley FP, Littlewood DG, et al: Circulatory effects of labetalol during halothane anaesthesia. Anaesthesia 33:145, 1978.

8. Fahmy NR: Nitroglycerin as a hypotensive drug during general anesthesia. Anesthesiology 49:17, 1978.

9. Fukunaga AF, Flacke WE, Bloor BC: Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside. Anesth Analg 61:273, 1982.

10. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742, 1983.

11. Leigh JM: The history of controlled hypotension. Br J Anaesth 47:745, 1975.

12. Boyan CP: Hypotensive anesthesia for radical pelvic and abdominal surgery. Arch Surg 67:803, 1953.

13. Donald JR: Induced hypotension and blood loss during surgery. J R Soc Med 75:149, 1982.

14. Eckenhoff JE, Rich JC: Clinical experiences with deliberate hypotension. Anesth Analg 45:21, 1966.

15. Khambatta HJ, Stone JG, Matteo RS, et al: Hypotensive anesthesia for spinal fusion with sodium nitroprusside. Spine 3:171, 1978.

16. Salem MR, Toyama T, Wong AY, et al: Haemodynamic responses to induced arterial hypotension in children. Br J Anaesth 50:489, 1978.

17. Kerr AR: Anaesthesia with profound hypotension for middle ear surgery. Br J Anaesth 49:447, 1977.

18. Diaz JH, Lockhart CH: Hypotensive anaesthesia for craniectomy in infancy. Br J Anaesth 51:233, 1979.

19. Eerola R, Eerola M, Kaukinen L, et al: Controlled hypotension and moderate haemodilution in major hip surgery. Ann Chir Gynaecol 69:109, 1979.

20. Vazeery AK, Lunde O: Controlled hypotension in hip joint surgery. An assessment of surgical haemorrhage during sodium nitroprusside infusion. Acta Orthop Scand 50:433, 1979.

21. Thompson GE, Miller RD, Stevens WC, et al: Hypotensive anesthesia for total hip arthroplasty: A study of blood loss and organ function (brain, heart, liver and kidney). Anesthesiology 48:91, 1978.

22. Barbier-Bohm G, Desmonts JM, Couderc E, et al: Comparative effects of induced hypotension and normovolaemic haemodilution on blood loss in total hip arthroplasty. Br J Anaesth 52:1039, 1980.

23. Amaranath L, Cascorbi HF, Singh-Amaranath AV, et al: Relation of anesthesia to total hip replacement and control of operative blood loss. Anesth Analg 54:641, 1975.

24. Qvist TF, Skovsted P, Sorensen MB: Moderate hypotensive anaesthesia for reduction of blood loss during total hip replacement. Acta Anaesthesiol Scand 26:351, 1982.

25. Sharrock NE, Mineo R, Urquhart B, et al: The effect of two levels of hypotension on intraoperative blood loss during total hip arthroplasty performed under lumbar epidural anesthesia. Anesth Analg 76:580, 1993.

26. Blau WS, Kafer ER, Anderson JA: Esmolol is more effective than sodium nitroprusside in reducing blood loss during orthognathic surgery. Anesth Analg 75:172, 1992.

27. Powell JL, Mogelnicki SR, Franklin EW III, et al: A deliberate hypotensive technique for decreasing blood loss during radical hysterectomy and pelvic lymphadenectomy. Am J Obstet Gynecol 147:196, 1983.

28. Ahlerling TE, Henderson JB, Skinner DG: Controlled hypotensive anesthesia to reduce blood loss in radical cystectomy for bladder cancer. J Urol 129:953, 1983.

29. Sood S, Jayalaxmi TS, Vijayaraghavan S, et al: Use of sodium nitroprusside induced hypotension for reducing blood loss in patients undergoing lienorenal shunts for portal hypertension. Br J Surg 74:1036, 1987.

30. Donald JR: Epidural anaesthesia, induced hypotension and blood loss during surgery. Acta Anaesthesiol Scand 27:91, 1983.

31. Simpson DA, Ireland J: Hypotensive and normotensive anaesthesia in total hip replacement. A comparative study. Br J Clin Pract 37:16, 1983.

32. Didier EP, Clagett OT, Theye RA: Cardiac performance during controlled hypotension. Anesth Analg 44:379, 1965.

33. Sivarajan M, Amory DW, Everett GB, et al: Blood pressure, not cardiac output, determines blood loss during induced hypotension. Anesth Analg 59:203, 1980.

34. Greene NM: Hypotensive spinal anesthesia. Surg Gynecol Obstet 95:331, 1952.

35. Sharrock NE, Mineo R, Urquhart B: Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty. Br J

Anaesth 67:17, 1991.

36. Sharrock NE, Salvati EA: Hypotensive epidural anesthesia for total hip arthroplasty. Acta Orthop Scand 67:91, 1996.

37. Meisner A, Rolf N, Van Aken H: Thoracic epidural anesthesia and the patient with heart disease: Benefits, risks and controversies. Anesth Analg 85:517, 1997.

38. Prys-Roberts C, Lloyd JW, Fisher A, et al: Deliberate profound hypotension induced with halothane: Studies of haemodynamics and pulmonary gas exchange. Br J Anaesth 46:105, 1974.

39. Van Aken H, Fitch W, Graham DI, et al: Cardiovascular and cerebrovascular effects of isoflurane-induced hypotension in the baboon. Anesth Analg 65:565, 1986.

40. Maktabi M, Warner D, Sokoll M, et al: Comparison of nitroprusside, nitroglycerin, and deep isoflurane anesthesia for induced hypotension. Neurosurgery 19:350, 1986.

41. Keaney NP, Pickerodt VWA, McDowall DG, et al: CBF autoregulation, CSF acid-base parameters and deep halothane hypotension [abstract]. Stroke 4:324, 1973.

42. Artru AA, Nugent M, Michenfelder JD: Enflurane causes a prolonged and reversible increase in the rate of CSF production in the dog. Anesthesiology 57:255, 1982.

43. Madsen JB, Cold GE, Hansen ES, et al: Cerebral blood flow and metabolism during isoflurane-induced hypotension in patients subjected to surgery for cerebral aneurysms. Br J Anaesth 59:1204, 1987.

44. Grosslight K, Foster R, Colohan AR, et al: Isoflurane for neuroanesthesia: Risk factors for increases in intracranial pressure. Anesthesiology 63:533, 1985.

45. Bendo AA, Kozlowski PB, Capuano C, et al: Cerebral edema formation in dogs following hypotension induced with isoflurane and labetalol. Acta Anaesthesiol Belg 44:103, 1993.

46. Enlund M, Ahlstedt B, Revenas B, et al: Adverse effects on the brain in connection with isoflurane-induced hypotensive anaesthesia. Acta Anaesthesiol Scand 33:413, 1989.

47. Enlund M, Mentell O, Engstrom C, et al: Occurrence of adenylate kinase in cerebrospinal fluid after isoflurane anesthesia and orthognatic surgery. Upsala J Med Sci 101:97, 1996.

48. Kick O, Van Aken H, Wouters PF, et al: Vital organ blood flow during deliberate hypotension in dogs. Anesth Analg 77:737, 1993.

49. Toivonen J, Virtanen H, Kaukinen S: Labetalol attenuates the negative effects of deliberate hypotension induced by isoflurane. Acta Anaesthesiol Scand 36:84, 1992.

50. Nicholas JF, Lam AM: Isoflurane-induced hypotension does not cause impairment in pulmonary gas exchange. Can Anaesth Soc J 31:352, 1984.

51. Milde LN, Milde JH: The cerebral and systemic hemodynamic and metabolic effects of desflurane-induced hypotension in dogs. Anesthesiology 74:513, 1991.

52. Fujibayashi T, Sugiura Y, Yanagimoto M, et al: Brain energy metabolism and blood flow during sevoflurane and halothane anesthesia: Effects of hypocapnia and blood pressure fluctuations. Acta Anaesthiol Scand 38:413, 1994.

53. Kreye VAW: Sodium nitroprusside. In Scriabine A (ed): Pharmacology of Antihypertensive Drugs. New York, Raven Press, 1980, p 373.

54. Rowe GG, Henderson RH: Systemic and coronary hemodynamic effects of sodium nitroprusside. Am Heart J 87:83, 1974.

55. Wildsmith JAW, Marshall RL, Jenkinson JL, et al: Haemodynamic effects of sodium nitroprusside during nitrous oxide/halothane anaesthesia. Br J Anaesth 45:71, 1973.

56. Styles M, Coleman AJ, Leary WP: Some hemodynamic effects of sodium nitroprusside. Anesthesiology 38:173, 1973.

57. Adams AP, Clarke TNS, Edmonds-Seal J, et al: The effects of sodium nitroprusside on myocardial contractility and haemodynamics. Br J Anaesth 46:807, 1974.

58. Hess W, Tarnow J, Patschke D, et al: Haemodynamik und Sauerstoff-versorgung des Herzens bei kontrollierter Hypotension mit Natriumnitroprussid und Trimetaphan. Anaesthesist 25:27, 1976.

59. Stoelting RK, Viegas O, Campbell RL: Sodium nitroprusside-produced hypotension during anesthesia and operation in the head-up position. Anesth Analg 56:391, 1977.

60. Schlant RC, Tsagaris TS, Robertson RJ Jr: Studies of the acute cardiovascular effects of intravenous sodium nitroprusside. Am J Cardiol 9:51, 1962.

61. Lagerkranser M, Gordon E, Rudehill A: Cardiovascular effects of sodium nitroprusside in cerebral aneurysm surgery. Acta Anaesthesiol Scand 24:426, 1980.

62. Maroon JC, Nelson PB: Hypovolemia in patients with subarachnoid hemorrhage: Therapeutic implications. Neurosurgery 4:223, 1979.

63. Lawson NW, Thompson DS, Nelson CL, et al: Sodium nitroprusside-induced hypotension for supine total hip replacement. Anesth Analg 55:654, 1976.

64. Boon JC, Westbroek DL, Stelter WJ, et al: Sodium nitroprusside-induced hypotension in dogs. Drug sensitivity and resistance experimentally provoked by circulating blood volume alterations. Eur Surg Res 10:382, 1978.

65. Tinker JH, Michenfelder JD: Sodium nitroprusside: Pharmacology, toxicology and therapeutics. Anesthesiology 45:340, 1976.

66. Vesey CJ, Cole PV, Simpson PJ: Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. Br J Anaesth 48:651, 1976.

67. Bisset WIK, Butler AR, Glidewell C, et al: Sodium nitroprusside and cyanide release: Reasons for re-appraisal. Br J Anaesth 53:1015, 1981.

68. Arnold WP, Longnecker DE, Epstein RM: Photodegradation of sodium nitroprusside: Biologic activity and cyanide release. Anesthesiology 61:254, 1984.

69. Aitken D, West D, Smith F, et al: Cyanide toxicity following nitroprusside induced hypotension. Can Anaesth Soc J 24:651, 1977.

70. Davies DW, Kadar D, Steward DJ, et al: A sudden death associated with the use of sodium nitroprusside for induction of hypotension during anaesthesia. Can Anaesth Soc J 22:547, 1975.

71. Chen RYZ, Matteo RS, Fan F-C, et al: Resetting of baroreflex sensitivity after induced hypotension. Anesthesiology 56:29, 1982.

72. Zubrow AB, Daniel SS, Stark RI, et al: Plasma renin, catecholamine and vasopressin during nitroprusside-induced hypotension in ewes. Anesthesiology 58:245, 1983.

73. Rawlinson WAL, Loach AB, Benedict CR: Changes in plasma concentration of adrenaline and noradrenaline in anaesthetized patients during sodium nitroprusside-induced hypotension. Br J Anaesth 50:937, 1978.

74. Khambatta HJ, Stone JG, Matteo RS, et al: Propranolol premedication blunts stress response to nitroprusside hypotension. Anesth Analg 63:125, 1984.

75. Bedford RF, Berry FA Jr, Longnecker DE: Impact of propranolol on hemodynamic response and blood cyanide levels during nitroprusside infusion: A prospective study in anesthetized man. Anesth Analg 58:466, 1979.

76. Miller ED Jr, Ackerly JA, Vaughan ED Jr, et al: The renin-angiotensin system during controlled hypotension with sodium nitroprusside. Anesthesiology 47:257, 1977.

77. Khambatta HJ, Stone JG, Khan E: Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 51:127, 1979.

78. Khambatta HJ, Stone JG, Khan E: Propranolol alters renin release during nitroprusside-induced hypotension and prevents hypertension on discontinuation of nitroprusside. Anesth Analg 60:569, 1981.

79. Woodside J Jr, Garner L, Bedford RF, et al: Captopril reduces the dose requirement for sodium nitroprusside induced hypotension. Anesthesiology 60:413, 1984.

80. Van Aken J, Leusen I, Lacroix E, et al: Influence of converting enzyme inhibition on isoflurane-induced hypotension for cerebral aneurysm surgery. Anaesthesia 47:261, 1992.

81. Grayling GW, Miller ED Jr, Peach MJ: Sodium cyanide antagonism of the vasodilator action of sodium nitroprusside in the isolated rabbit aortic strip. Anesthesiology 49:21, 1978.

82. Wood M, Hyman S, Wood AJJ: A clinical study of sensitivity to sodium nitroprusside during controlled hypotensive anesthesia in young and elderly patients. Anesth Analg 66:132, 1987.

83. Michenfelder JD, Tinker JH: Cyanide toxicity and thiosulfate protection during chronic administration of sodium nitroprusside in the dog: Correlation with a human case. Anesthesiology 47:441, 1977.

84. Stoyka WW, Schutz H: The cerebral response to sodium nitroprusside and trimetaphan controlled hypotension. Can Anaesth Soc J 22:275, 1975.

85. Fitch W, Ferguson GG, Sengupta D, et al: Autoregulation of cerebral blood flow during controlled hypotension in baboons. J Neurol Neurosurg Psychiatry 39:1014, 1976.

86. Larsen R, Teichmann J, Hilfiker O, et al: Nitroprusside-hypotension: Cerebral blood flow and cerebral oxygen consumption in neurosurgical patients. Acta Anaesthesiol Scand 26:327, 1982.

87. Crockard HA, Brown FD, Mullan JF: Effects of trimetaphan and sodium nitroprusside on cerebral blood flow in rhesus monkeys. Acta Neurochir 35:85, 1976.

88. Brown FD, Hanlon K, Crockard HA, et al: Effect of sodium nitroprusside on cerebral blood flow in conscious human beings. Surg Neurol 7:67, 1977.

89. Miletich DJ, Gil KSL, Albrecht RF, et al: Intracerebral blood flow distribution during hypotensive anesthesia in the goat. Anesthesiology 53:210, 1980.

90. Turner JM, Powell D, Gibson RM, et al: Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. Br J Anaesth 49:419, 1977.

91. Cottrell JE, Patel KP, Turndorf H, et al: Intracranial pressure changes induced by sodium nitroprusside in patients with intracranial mass lesions. J Neurosurg 48:329, 1978.

92. Fitch W, Pickard JD, Tamyra A, et al: Effects of hypotension induced with sodium nitroprusside on the cerebral circulation before, and one week after, the subarachnoid injection of blood. J Neurol Neurosurg Psychiatry 120, 1982.

93. Tsutsui T, Maekawa T, Goodchild C et al: Cerebral blood flow distri-bution during induced hypotension with haemorrhage, trimetaphan or nitroprusside in rats. Br J Anaesth 74:686, 1995.

94. Mason DT, Zelis R, Amsterdam EA: Actions of the nitrates on the peripheral circulation and myocardial oxygen consumption: Significance in the relief of angina pectoris. Chest 59:296, 1971.

95. Lagerkranser M: Cardiovascular effects of nitroglycerin as a hypotensive agent in cerebral aneurysm surgery. Acta Anaesthesiol Scand 26:453, 1982.

96. Vatner SF, Higgins CB, Millard RW, et al: Direct and reflex effects of nitroglycerin on coronary and left ventricular dynamics in conscious dogs. J Clin Invest 51:2872, 1972.

97. Vatner SF, Pagani M, Rutherford JD, et al: Effects of nitroglycerin on cardiac function and regional blood flow distribution in conscious dogs. Am J Physiol 234:H244, 1978.

98. Yaster M, Simmons RS, Tolo VT, et al: A comparison of nitroglycerin and nitroprusside for inducing hypotension in children: A double-blind study. Anesthesiology 65:175, 1986.

99. Todd MM, Morris PJ, Moss J, et al: Hemodynamic consequences of abrupt withdrawal of nitroprusside or nitroglycerin following induced hypotension. Anesth Analg 61:261, 1982.

100. Rodgers MC, Hamburger C, Owen K, et al: Intracranial pressure in the cat during nitroglycerine-induced hypotension. Anesthesiology 51:227, 1979.

101. Cottrell JE, Gupta B, Rappaport H, et al: Intracranial pressure during nitroglycerin-induced hypotension. J Neurosurg 53:309, 1980.

102. James DJ, Bedford RF: Hydralazine for controlled hypotension during neurosurgical operations. Anesth Analg 61:1016, 1982.

103. Emmelin N, Feldberg W: Systemic effects of adenosine triphosphate. Br J Pharmacol 3:273, 1948.

104. Van Aken H, Puchstein C, Fitch W, et al: Haemodynamic and cerebral effects of ATP-induced hypotension. Br J Anaesth 56:1409, 1984.

105. Sollevi A, Lagerkranser M, Irestedt L, et al: Controlled hypotension with adenosine in cerebral aneurysm surgery. Anesthesiology 61:400, 1984.

106. Kien ND, White DA, Reitan JA, et al: Cardiovascular function during controlled hypotension induced by adenosine triphosphate or sodium nitroprusside in the anesthetized dog. Anesth Analg 66:103, 1987.

107. Van Aken H, Puchstein C, Anger C, et al: Changes in intracranial pressure and compliance during adenosine triphosphate-induced hypotension in dogs. Anesth Analg 63:381, 1984.

108. Lagerkranser M, Bergstrand G, Gordon E, et al: Cerebral blood flow and metabolism during adenosine-induced hypotension in patients undergoing cerebral aneurysm surgery. Acta Anaesthesiol Scand 33:15, 1989.

109. Owall A, Jarnberg P-O, Brodin L-A, et al: Effects of adenosine-induced hypotension on myocardial hemodynamics and metabolism in

fentanyl anesthetized patients with peripheral vascular disease. Anesthesiology 68:416, 1988.

110. Belardinelli L, Mattos EC, Berne RM: Evidence for adenosine mediation of atrioventricular block in the ischemic canine myocardium. J Clin Invest 68:195, 1981.

111. McCubbin JW, Page IH: Nature of the hypotensive action of a thiophanium derivative (RO 2-222) in dogs. J Pharmacol Exp Ther 105:437, 1952.

112. Michenfelder JD, Theye RA: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimetaphan, halothane, or nitroprusside. Anesthesiology 46:188, 1977.

113. Wildsmith JAW, Sinclair CJ, Thorn J, et al: Haemodynamic effects of induced hypotension with a nitroprusside-trimetaphan mixture. Br J Anaesth 55:381, 1983.

114. Miller R, Toth C, Silva DA, et al: Nitroprusside versus a nitroprusside-trimetaphan mixture: A comparison of dosage requirements and hemodynamic effects during induced hypotension for neurosurgery. Mt Sinai J Med 54:308, 1987.

115. Giffin JP, Thantum E, Shwiry B, et al: Effects of phentolamine on intracranial pressure [abstract]. Anesthesiology 55:A234, 1981.

116. Kolassa N, Beller K-D, Sanders KH: Evidence for the interaction of urapidil with 5-HT 1A receptors in the brain leading to a decrease in blood pressure. Am J Cardiol 63:36c, 1989.

117. Puchstein C, Van Aken H, Anger C, et al: Influence of urapidil on intracranial pressure and intracranial compliance in dogs. Br J Anaesth 55:443, 1983.

118. Anger C, Van Aken H, Feldhaus P, et al: Permeation of the blood-brain barrier by urapidil and its influence on intracranial pressure in man in the presence of compromised intracranial dynamics. J Hypertens 6(suppl 2):S63, 1988.

119. Sicking K, Puchstein C, Van Aken H: Blutdrucksenkung mit Urapidil: Einfluss auf die Hirndurchblutung. Anaesth Intensivmed 27:147, 1986.

120. Turlapaty P, Laddu A, Murthy VS, et al: Esmolol: A titratable short-acting intravenous beta blocker for acute critical care settings. Am Heart J 114:866, 1987.

121. Ornstein E, Matteo RS, Weinstein JA, et al: A controlled trial of esmolol for the induction of deliberate hypotension. J Clin Anesth 1:31, 1988.

122. Ornstein E, Young WL, Ostapkovich N, et al: Deliberate hypotension in patients with intracranial or arteriovenous malformations: Esmolol compared with isoflurane and sodium nitroprusside. Anesth Analg 72:639, 1991.

123. Edmondson R, Del Valle O, Shah N, et al: Esmolol for potentiation of nitroprusside-induced hypotension: Impact on the cardiovascular, adrenergic, and renin-angiotensin systems in man. Anesth Analg 69:202, 1989.

124. Goldberg ME, McNulty SE, Azad SS, et al: A comparison of labetalol and nitroprusside for inducing hypotension during major surgery. Anesth Analg 70:537, 1990.

125. Scott DB, Buckley FP, Drummond GB, et al: Cardiovascular effects of labetalol during halothane anaesthesia. Br J Clin Pharmacol 3(suppl):817, 1976.

126. Van Aken H, Puchstein C, Schweppe M-L, et al: Effect of labetalol on intracranial pressure in dogs with and without intracranial hypertension. Acta Anaesthesiol Scand 26:615, 1982.

127. Speng RJ, Monk CR, Durieux ME, et al: The influence of hemorrhage on organ perfusion during deliberate hypotension in rats. Anesthesiology 77:1171, 1992.

128. Toivonen J, Kuikka P, Kaukinen S: Effects of deliberate hypotension induced by labetalol with isoflurane on neuropsychological function. Acta Anaesthesiol Scand 37:7, 1993.

129. Kaplan JA: The role of nicardipine during anesthesia and surgery. Clin Ther 11:84, 1985.

130. Flamm ES, Adams HP Jr, Beck DW, et al: Dose-escalation study of intravenous nicardipine in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 68:393, 1988.

131. Bernard JM, Passuti N, Pinaud M: Long-term hypotensive technique with nicardipine and nitroprusside during isoflurane anesthesia for spinal surgery. Anesth Analg 75:179, 1992.

132. Goto F, Otani E, Kato S, et al: Prostaglandin E 1 as a hypotensive drug during general anaesthesia. Anaesthesia 37:530, 1982.

133. Abe K, Demizu A, Kamada K, et al: Local cerebral blood flow with prostaglandin E 1 or trimetaphan during cerebral aneurysm clip ligation. Can J Anaesth 38:831, 1991.

134. Abe K, Demizu A, Mima T, et al: Carbon dioxide reactivity during prostaglandin E 1 induced hypotension for cerebral aneurysm surgery. Can J Anaesth 39:253, 1992.

135. Eckenhoff JE, Crompton JR, Larson A, et al: Assessment of the cerebral effects of deliberate hypotension by psychological measurements. Lancet 2:711, 1969.

136. Slack WK, Walther WW: Cerebral circulation studies during hypotensive anaesthesia using radioactive xenon. Lancet 1:1082, 1963.

137. Patel H: Experience with the cerebral function monitor during deliberate hypotension. Br J Anaesth 53:639, 1981.

138. Lassen NA, Christensen MS: Physiology of cerebral blood flow. Br J Anaesth 48:719, 1976.

139. Hoffman WE, Miletich DJ, Albrecht RF: The influence of antihypertensive therapy on cerebral autoregulation in aged hypertensive rats. Stroke 13:701, 1982.

140. Palvolgyi R: Regional cerebral blood flow in patients with intracranial tumors. J Neurosurg 31:149, 1969.

141. Heilbrun MP, Olesen J, Lassen NA: Regional cerebral blood flow studies in subarachnoid hemorrhage. J Neurosurg 37:36, 1972.

142. Cold GE: Cerebral blood flow in acute head injury. Acta Neurochir Suppl (Wien) 49:1, 1990.

143. Pinaud M, Souron R, Lelausque J-N, et al: Cerebral blood flow and cerebral oxygen consumption during nitroprusside-induced hypotension to less than 50 mmHg. Anesthesiology 70:255, 1989.

144. Harper AM, Glass HI: Effects of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures. J Neurol Neurosurg Psychiatry 28:449, 1965.

145. Gregory P, Ishikawa T, McDowall DG: CO_2 responses of the cerebral circulation during drug-induced hypotension in the cat. J Cereb Blood Flow Metab 1:195, 1981.

146. Morris PJ, Heuser D, McDowell DG, et al: Cerebral cortical extracellular fluid H+ and K+ activities during hypotension in cats. Anesthesiology 59:10, 1983.

147. Ishikawa T, Funatsu N, Okamoto K, et al: Blood-brain barrier function following drug-increased hypotension in the dog. Anesthesiology 59:526, 1983.

148. Newberg LA, Milde JH, Michenfelder JD: Systemic and cerebral effects of isoflurane-induced hypotension in dogs. Anesthesiology 60:541, 1984.

149. Newman B, Gelb AW, Lam AM: The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. Anesthesiology 64:307, 1986.

150. Seyde WC, Longnecker DE: Cerebral oxygen tension in rats during deliberate hypotension with sodium nitroprusside, 2-chloroadenosine, or deep isoflurane anesthesia. Anesthesiology 64:480, 1986.

151. Hysing ES, Chelly JE, Doursout M-F, et al: Comparative effects of halothane, enflurane, and isoflurane at equihypotensive doses on cardiac performance and coronary and renal blood flows in chronically instrumented dogs. Anesthesiology 76:979, 1992.

152. Pagel PS, Kampine JP, Schmeling WT, et al: Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. Anesthesiology 74:539, 1991.

153. Bernard J-M, Wouters PF, Doursout M-F, et al: Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology 72:659, 1990.

154. Merin RG, Bernard J-M, Doursout M-F, et al: Comparison of the effects of isoflurane and desflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. Anesthesiology 74:568, 1991.

155. Eger EI II, Johnson BH: Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: A test of the effect of anesthetic concentration and duration in rats. Anesth Analg 66:977, 1987.

156. Valtonen M, Rutilla K, Kanto J, et al: Hypotensive anesthesia for middle ear surgery: A comparison of propofol infusion and isoflurane. Methods Find Exp Clin Pharmacol 5:383, 1992.

157. Sebel PS, Lowdon JD: Propofol: A new intravenous anesthetic. Anesthesiology 71:260, 1989.

158. Van Aken H, Meinshausen E, Prien T, et al: The influence of fentanyl and tracheal intubation on the hemodynamic effects of anesthesia induction with propofol/N_2O in humans. Anesthesiology 68:157, 1988.

159. Mulier JP, Wouters PF, Van Aken H, et al: Cardiodynamic effects of propofol in comparison with thiopental: Assessment with a transesophageal echocardiographic approach. Anesth Analg 72:28, 1991.

160. Hickey RF, Sybert PE, Verrier ED, et al: Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. Anesthesiology 68:21, 1988.

161. Feigl EO: Coronary physiology. Physiol Rev 63:1, 1983.

162. Bernard J-M, Pinaud M, Francois T, et al: Deliberate hypotension with nicardipine or nitroprusside during total hip arthroplasty. Anesth Analg 73:341, 1991.

163. Belardinelli L, Linden J, Berne RM: The cardiac effects of adenosine. Prog Cardiovasc Dis 32:73, 1989.

164. Gould KL, Lipscomb K, Calvert C: Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. Circulation 51:1085, 1975.

165. Braunwald E: Control of myocardial oxygen consumption. Physiologic and clinical considerations. Am J Cardiol 27:416, 1971.

166. Bland JHL, Lowenstein E: Halothane-induced decrease in experimental myocardial ischemia in the non-failing canine heart. Anesthesiology 45:287, 1976.

167. Braunwald E, Muller JE, Kloner RA, et al: Role of beta-adrenergic blockade in the therapy of patients with myocardial infarction. Am J Med 74:113, 1983.

168. Ertl G, Simm F, Wichmann J, et al: The dependence of coronary collateral blood flow on regional vascular resistances. Pharmacological studies with glyceryl trinitrate, adenosine and verapamil. Naunyn-Schmiedebergs Arch Pharmacol 308:265, 1979.

169. Hartman JC, Kampine JP, Schmeling WT, et al: Steal-prone coronary circulation in chronically instrumented dogs: Isoflurane versus adenosine. Anesthesiology 74:744, 1991.

170. Chiarello M, Gold HK, Leinbach RC, et al: Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. Circulation 54:766, 1976.

171. Reiz S, Balfors E, Sorensen MB, et al: Isoflurane--a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 59:91, 1983.

172. Buffington CW, Romson JL, Levine A, et al: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 66:280, 1987.

173. Priebe H-J: Isoflurane causes more severe regional myocardial dysfunction than halothane in dogs with critical coronary artery stenosis. Anesthesiology 69:72, 1988.

174. Cason BA, Verrier ED, London MJ, et al: Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: Their capacity to induce coronary steal. Anesthesiology 67:665, 1987.

175. Hartman JC, Kampine JP, Schmeling WT, et al: Volatile anesthetics and regional myocardial perfusion in chronically instrumented dogs: Halothane versus isoflurane in a single-vessel disease model with enhanced collateral development. J Cardiothorac Anesth 4:558, 1990.

176. Wouters P, Van Aken H, Schreinemakers H, et al: Effects of halothane and isoflurane on coronary collateral circulation in chronically instrumented dogs [abstract]. Anesthesiology 75:A504, 1991.

177. Crystal GJ, Salem MR: Myocardial and systemic hemodynamics during isovolemic hemodilution alone and combined with nitroprusside-induced controlled hypotension. Anesth Analg 72:227, 1991.

178. Eckenhoff JE, Enderby GEH, Larson A, et al: Pulmonary gas exchange during deliberate hypotension. Br J Anaesth 35:750, 1963.

179. Khambatta HJ, Stone JG, Matteo RS: Effect of sodium nitroprusside-induced hypotension on pulmonary deadspace. Br J Anaesth 54:1197, 1982.

180. Suwa K, Hedley-Whyte J, Bendixen HH: Circulation and physiologic dead space changes on controlling the ventilation of dogs. J Appl Physiol 21:1855, 1966.

181. Wildsmith JAW, Drummond GB, MacRae WR: Blood-gas changes during induced hypotension with sodium nitroprusside. Br J Anaesth 47:1205, 1975.

182. Casthely PA, Lear S, Cottrell JE, et al: Intrapulmonary shunting during induced hypotension. Anesth Analg 61:231, 1982.

183. Bernard JM, Pinaud M, Ganansia MF, et al: Systemic haemodynamic and metabolic effects of deliberate hypotension with isoflurane anaesthesia or sodium nitroprusside during total hip arthroplasty. Can J Anaesth 34:135, 1987.

184. Naeije R, Lejeune P, Leeman M, et al: Pulmonary arterial pressure-flow plots in dogs: Effects of isoflurane and nitroprusside. J Appl Physiol 63:969, 1987.

185. Hannhart B, Bertrand D, Peslin R, et al: Effects of induced hypotension on breathing pattern in halothane-anaesthetized man. Eur J Clin Invest 13:379, 1983.

186. Ganong WF: Review of Medical Physiology, 14th ed. E. Norwalk, Appleton & Lange, 1989, p 600.

187. McDougal WS: Renal perfusion/reperfusion injuries. J Urol 140:1325, 1988.

188. Behnia R, Siqueira EB, Brunner EA: Sodium nitroprusside-induced hypotension: Effect on renal function. Anesth Analg 57:521, 1978.

189. Behnia R, Martin A, Koushanpour E, et al: Trimetaphan-induced hypotension: Effect on renal function. Can Anaesth Soc J 29:581, 1978.

190. Torrance HB: The control of the hepatic arterial circulation. J Physiol (Lond) 158:39, 1961.

191. Richardson PDI, Withrington PG: Liver blood flow, I. Intrinsic and nervous control of liver blood flow. Gastroenterology 81:159, 1981.

192. Lundgren O: Physiology of the intestinal circulation. In Marston A, et al (eds): Splanchnic Ischemia and Multiple Organ Failure. St. Louis, CV Mosby, 1989, p 29.

193. Gelman S, Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 61:726, 1984.

194. Bernard J-M, Doursout M-F, Wouters P, et al: Effects of enflurane and isoflurane on hepatic and renal circulations in chronically instrumented dogs. Anesthesiology 74:298, 1991.

195. Noldge GFE, Priebe H-J, Geiger K: Splanchnic hemodynamics and oxygen supply during acute normovolemic hemodilution alone and with isoflurane-induced hypotension in the anesthetized pig. Anesth Analg 75:660, 1992.

196. Dias PLR, Andrew DS, Romanes GJ: Effect on the intraocular pressure of hypotensive anaesthesia with intravenous trimetaphan. Br J Ophthalmol 66:721, 1982.

197. Hoffman WE, Bergman S, Miletich DJ, et al: Regional vascular changes during hypotensive anesthesia. J Cardiovasc Pharmacol 4:310, 1982.

198. Wildsmith JAW, Drummond GB, MacRae WR: Metabolic effects of induced hypotension with trimetaphan and sodium nitroprusside. Br J Anaesth 51:875, 1979.

199. Hauss J, Schonleben K, Spiegel HU, et al: Nitroprusside- and nitroglycerin-induced hypotension: Effects on hemodynamics and on the microcirculation. World J Surg 6:241, 1982.

200. Endrich B, Franke N, Peter K, et al: Induced hypotension: Action of sodium nitroprusside and nitroglycerin on the microcirculation. Anesthesiology 66:605, 1987.

201. Wong KC, Webster LR, Coleman SS, et al: Hemodilution and induced hypotension for insertion of a Harrington rod in a Jehovah's Witness patient. Clin Orthop 152:237, 1980.

202. Strandgaard S: Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. Circulation 53:720, 1976.

203. Lagerkranser M: Controlled hypotension in neurosurgery: Pro. J Neurosurg Anesth 3:150, 1991.

204. Ruta TS, Mutch WAC: Controlled hypotension for cerebral aneurysm surgery: Are the risks worth the benefits? J Neurosurg Anesth 3:153, 1991.

205. McDermott MW, Durity FA, Borozny M, et al: Temporary vessel occlusion and barbiturate protection in cerebral aneurysm surgery. Neurosurgery 25:54, 1989.

206. Farrar JK, Gamache FW Jr, Ferguson GG, et al: Effects of profound hypotension on cerebral blood flow during surgery for intracranial aneurysms. J Neurosurg 55:857, 1981.

207. Grundy BL, Nash CL Jr, Brown RH: Deliberate hypotension for spinal fusion: Prospective randomized study with evoked potential monitoring. Can Anaesth Soc J 29:452, 1982.

208. Hampton LJ, Little DM Jr: Complications associated with the use of "controlled hypotension" in anesthesia. Arch Surg 67:549, 1953.

209. Eckenhoff JE: Deliberate hypotension. Anesthesiology 48:87, 1978.

210. Enderby GEH: A report on mortality and morbidity following 9,107 hypotensive anaesthetics. Br J Anaesth 33:109, 1961.

211. Larson AG: Deliberate hypotension. Anesthesiology 25:682, 1964.

212. Enderby G: Hypotensive anesthesia. In Gray TC, Nunn JF, Utting JE (eds): General Anaesthesia, vol 2, 4th ed. London, Butterworth, 1980, p 1140.

213. Pasch T, Huk W: Cerebral complications following induced hypotension. Eur J Anaesth 3:299, 1986.

214. Enderby G: Safe hypotensive anaesthesia. In Hypotensive Anaesthesia. New York, Churchill Livingstone, 1985, p 262.

215. Lindop MJ: Complications and morbidity of controlled hypotension. Br J Anaesth 47:799, 1975.

216. Way GL, Clarke HL: An anaesthetic technique for prostatectomy. Lancet 2:888, 1959.

217. Linacre JL: Induced hypotension in gynaecological surgery. A review of 1,000 major cases. Br J Anaesth 33:45, 1961.

218. Little DM Jr: Induced hypotension during anesthesia and surgery. Anesthesiology 16:320, 1955.

Chapter 42 - Spinal, Epidural, and Caudal Anesthesia*

David L. Brown

INTRODUCTION

Neuraxial blocks (spinal, epidural, and caudal) result in sympathetic block, sensory analgesia, and motor block (depending on dose, concentration, or volume of local anesthetic) after insertion of a needle in the plane of the centroneuraxis. Despite these similarities, there are significant physiologic and pharmacologic differences. Spinal anesthesia requires a small mass (i.e., volume) of drug, virtually devoid of systemic pharmacologic effect, to produce profound, reproducible sensory analgesia. In contrast, epidural anesthesia necessitates use of a mass (i.e., large volume) of local anesthetic that produces pharmacologically active systemic blood levels, which may be associated with side effects and complications unknown with spinal anesthesia. The introduction of combined spinal and epidural techniques blurs some of these differences but also adds flexibility to clinical care.

The blurring of differences between spinal and epidural anesthesia began early, when Corning reported on spinal anesthesia and local medications of the cord (Ch. 1) [1] . It remains unclear whether his injection of cocaine "between spinous processes" produced spinal or epidural anesthesia. It was clear that Bier understood he was producing spinal anesthesia in 1898, and through self-investigation of spinal anesthesia he had personal knowledge of the symptoms of postdural puncture headache. These early years were principally involved with the advancement of spinal rather than epidural anesthesia for at least three reasons. First, the only practical local anesthetic available until 1904 (when procaine was synthesized) was cocaine, which was more suited to spinal than epidural anesthesia because of systemic side effects at doses required for each. Second, the equipment available for neuraxial blocks favored spinal anesthesia because the end point of cerebrospinal fluid (CSF) return was well defined and did not demand sophisticated glass syringes and needles required for epidural anesthesia. Third, muscle relaxants had not been introduced, and spinal anesthesia produced superb skeletal muscle relaxation facilitating surgical exposure.

These advantages of spinal anesthesia historically created many enthusiastic clinicians. Morton promoted high spinal anesthesia for surgical procedures carried out on the head and neck, whereas Koster used total spinal blockade for thoracic and intracranial procedures. [2] [3] Spinal anesthesia was not limited to surgical conditions but was touted for the treatment of medical conditions (e.g., pulmonary edema) by taking advantage of its venodilatory effect. Still, a number of impediments have prevented more widespread use of spinal and epidural blocks.

Despite the many advantages and safety of spinal anesthesia, Kennedy et al in 1950 described "grave spinal cord paralysis" accompanying the use of spinal anesthesia; this report was followed by one in 1954 detailing the well-publicized Woolley and Roe trial in England. [4] [5] In the latter instance, two patients, Woolley and Roe, had neurologic injury after receiving their spinal anesthetics, which were administered in the same hospital, on the same day, by the same anesthetist in 1947. The exact cause of their neurologic dysfunction remains cloudy: was it contaminated ampules or a toxic substance administered into the subarachnoid space by mistake? [6]

Anesthesiologists continue to face confusion about balancing the risks and benefits of spinal anesthesia, specifically those involving continuous spinal anesthesia or the use of 5 percent lidocaine. The U.S. Food and Drug Administration (FDA) withdrew some spinal catheters in 1992 owing to concerns over a perceived association between the small-bore catheters and development of cauda equina syndrome. [7] This decision appears to have been made with as many political implications as scientific ones. Since that time, attention turned to the question of what are safe variables for the use of intrathecal 5 percent lidocaine. [8] [9]

** See Appendix 1, practice Guidelines for Active Pain Management in the Perioperative Setting, Practice Guidelines for Chronic for Chronic Pain Management, and Practice Guidelines for Obstetrical Anesthesia*

Other impediments to the effective use of neuraxial blocks are the predictable decreases in arterial blood pressure and heart rate through the accompanying sympathectomy with its attendant vasodilation and blockade of cardioaccelerator fibers. Maintaining arterial blood pressure and heart rate at normal values during these blocks often requires administration of vasoactive drugs and intravenous fluids. The extent to which these steps are necessary are discussed later.

Another clinically important impediment to successful use of these blocks is the idea that the "blocks should do it all." It seems unreasonable to expect a single injection of local anesthetic into either the subarachnoid or epidural space to provide ideal conditions for all patients undergoing varied surgical procedures, even in the face of an adequate block. It seems likely that far more spinal and epidural anesthetics have failed due to inadequate intravenous sedation and anxiolysis than due to technically flawed blocks.

Evidence is accumulating that the use of neuraxial blocks, principally continuous epidural techniques to provide postoperative analgesia, may be able to decrease perioperative morbidity (Ch. 69) . These techniques may also decrease length of hospital stay and allow more efficient use of our ever-increasingly stretched health-care monies. [10] [11] [12] To gain maximum benefit and minimize complications from these blocks, attention to technique and anatomy is essential, and of course, the blocks should be utilized when the risk-benefit equation for the block is favorable. [13] [14] [15]

Indications and Contraindications

At the most basic level, neuraxial block is indicated whenever the surgical procedure can be accomplished with a sensory level of anesthesia that does not produce adverse patient outcome. The surgical procedure must include the amount and type of supplemental medications and even capacity for administering "light general anesthesia" to ensure effective sedation and anxiolysis. The level of sensory analgesia required is of prime importance. It is clear that low spinal anesthesia (i.e., a T10 or lower sensory level) carries different physiologic impact than does a block performed to produce high (T5) spinal anesthesia. [16]

There are few strong contraindications to neuraxial block. Some of the most important ones include patient refusal; patient inability to maintain stillness during the needle puncture, thus exposing the neural structures to unacceptable risk of injury; and raised intracranial pressure, which theoretically may predispose to brain stem herniation. Relative contraindications that must be weighed against the potential benefits include coagulopathy, both intrinsic and idiopathic, such as that occurring with administration of coumadin or heparin; skin or soft tissue infection at the proposed site of needle insertion; severe hypovolemia; and lack of anesthesiologist experience. The often cited relative contraindication of preexisting neurologic disease (e.g., lower-extremity peripheral neuropathy) is not usually based on medical criteria but rather on legal considerations.

When deciding between epidural and spinal anesthesia, a number of variables should be considered. Is the procedure (or surgeon's typical time) of predictable length, minimizing the need to consider a continuous catheter technique? Is the surgical procedure so short that waiting for the epidural to take effect makes spinal anesthesia more practical? Is the patient a candidate for prolonged postoperative analgesia, making a continuous epidural or combined spinal-epidural technique preferred? Can the procedure be equally well handled with either spinal or epidural anesthesia, thus allowing consideration of patient variables affecting headache incidence (e.g., age and gender)? Are there concurrent patient diseases, such as hypertrophic cardiomyopathy, that might be of concern with either technique? Will the patient be traveling a significant distance immediately after the procedure, making epidural blood patch therapy for a postdural puncture headache problematic?

These are a sampling of many questions that should be considered when contemplating the risk and benefit of neuraxial blocks.

Anatomy

Once a decision is made to utilize one of these blocks, the key feature of performing the block is combining appropriate technique with a three-dimensional understanding and tactile appreciation of anatomy.

Subarachnoid local anesthetics affect their sensory block at the spinal cord, which is continuously cephalad with the brain stem via the foramen magnum and terminates distally in the conus medullaris. This distal termination, because of differential growth rates between the bony vertebral canal and central nervous system, varies from L3 in the infant to the lower border of L1 in the adult. Most of us develop the impression that the spinal nerve roots are uniform in size and structure, yet Hogan has shown that there is a large interindividual variability of nerve root sizes. [17] These differences may help in explaining the interpatient differences in neuraxial block quality when equivalent techniques are used on seemingly similar patients. Furthermore, CSF volume is variable from patient to patient, in part due to differences in body habitus and weight. [18]

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to the periphery): the pia mater, arachnoid mater, and dura mater (Fig. 42-1 and Plate 6 [see Color Atlas following Chapter 43]). The pia mater is a highly vascular membrane that closely invests the spinal cord (and brain). The arachnoid mater is a delicate nonvascular membrane closely attached to the outermost layer, the dura. Between these two innermost membranes is the space of interest in spinal anesthesia, the subarachnoid space. In this space are the CSF, spinal nerves, a trabecular network between the two membranes, and blood vessels that supply the spinal cord and the lateral extensions of the pia mater and the dentate ligaments, which supply lateral support from the spinal cord to the dura mater (Fig. 42-2 and Plate 6). [19] Although the spinal cord ends at the lower border of L1 in adults, the subarachnoid space continues to S2. The third and outermost membrane in the spinal canal is the longitudinally organized fibroelastic membrane, the dura mater (or theca). This layer is the direct extension of the cranial dura mater and extends as spinal dura mater from the foramen magnum to S2, where the filum terminale (an extension of the pia mater beginning at the conus medullaris) blends with the periostium on the coccyx (see Fig. 42-1 and Plate 9). There is a potential space between the dura mater

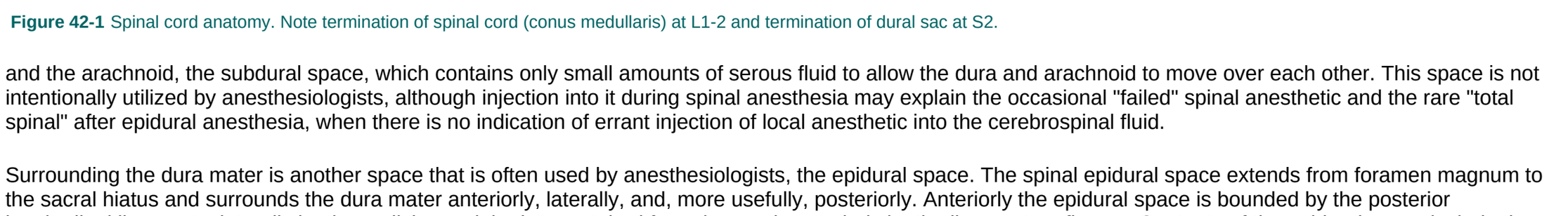

Figure 42-1 Spinal cord anatomy. Note termination of spinal cord (conus medullaris) at L1-2 and termination of dural sac at S2.

and the arachnoid, the subdural space, which contains only small amounts of serous fluid to allow the dura and arachnoid to move over each other. This space is not intentionally utilized by anesthesiologists, although injection into it during spinal anesthesia may explain the occasional "failed" spinal anesthetic and the rare "total spinal" after epidural anesthesia, when there is no indication of errant injection of local anesthetic into the cerebrospinal fluid.

Surrounding the dura mater is another space that is often used by anesthesiologists, the epidural space. The spinal epidural space extends from foramen magnum to the sacral hiatus and surrounds the dura mater anteriorly, laterally, and, more usefully, posteriorly. Anteriorly the epidural space is bounded by the posterior longitudinal ligaments, laterally by the pedicles and the intervertebral foramina, and posteriorly by the ligamentum flavum. Contents of the epidural space include the nerve roots that traverse it from foramina to peripheral locations, as well as fat, areolar tissue, lymphatics, and blood vessels, which include the well-organized Batson venous plexus. Hogan [20] suggests from frozen cryomicrotome cadaver sections that the epidural space is more

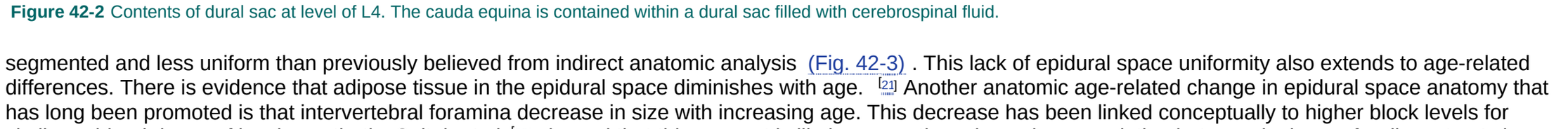

Figure 42-2 Contents of dural sac at level of L4. The cauda equina is contained within a dural sac filled with cerebrospinal fluid.

segmented and less uniform than previously believed from indirect anatomic analysis (Fig. 42-3) . This lack of epidural space uniformity also extends to age-related differences. There is evidence that adipose tissue in the epidural space diminishes with age. [21] Another anatomic age-related change in epidural space anatomy that has long been promoted is that intervertebral foramina decrease in size with increasing age. This decrease has been linked conceptually to higher block levels for similar epidural doses of local anesthetic. Saitoh et al [22] showed that this concept is likely wrong; they showed no correlation between leakage of radiocontrast via intervertebral foramina and age. When Igarashi et al and Saitoh et al data are considered together, it may be that the decrease in epidural space adipose tissue with age may dominate the age-related changes in epidural dose requirements.

Posterior to the epidural space is the ligamentum flavum (the "yellow ligament"), which also extends from the foramen magnum to the sacral hiatus. Although classically portrayed as a single ligament, it is really composed of two ligamenta flava, the right and the left, which join in the middle, forming an acute angle with a ventral opening (Fig. 42-4) and Plate 8). [20] [23] The ligamentum flavum is not uniform from skull to sacrum, nor even within an intervertebral space. The ligament thickness, distance to dura, and skin to dura distance vary with the area of vertebral canal (Table 42-1) . Additionally, the two ligamenta flava are variably joined (fused) in the midline, and this fusion, or lack of fusion of the ligamenta flava, even occurs at different vertebral levels in individual patients. [20] Immediately posterior to the ligamentum flavum are either lamina and spinous processes of vertebral bodies or the interspinous ligaments. Extending from the external occipital protuberance to the coccyx posterior to these structures is the supraspinous ligament, which joins the vertebral spines (see Fig. 42-4).

One anatomic clarification that has been made through epiduroscopy and epidurography confirms prior clinical observations

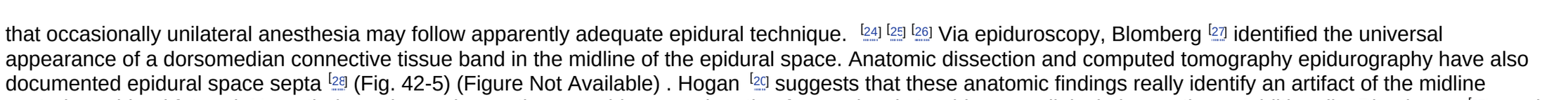

Figure 42-3 (A) Sagittal section of epidural space demonstrates that the contents of the epidural space depend on level of section. (B) Three-dimensional drawing of the epidural space shows the discontinuity of the epidural contents, but this potential space can be dilated by injection of fluid into the epidural space.

that occasionally unilateral anesthesia may follow apparently adequate epidural technique. [24] [25] [26] Via epiduroscopy, Blomberg [27] identified the universal appearance of a dorsomedian connective tissue band in the midline of the epidural space. Anatomic dissection and computed tomography epidurography have also documented epidural space septa [28] (Fig. 42-5) (Figure Not Available) . Hogan [20] suggests that these anatomic findings really identify an artifact of the midline posterior epidural fat pad. Nevertheless, these observations provide an explanation for previously troublesome clinical observations. Additionally, Blomberg [27] used fiberoptic technique to demonstrate that the subdural extra-arachnoid space is easily entered in 66 percent of autopsy attempts in humans. In spite of this being an infrequent clinical problem with epidural anesthesia, it does allow a visual understanding of subdural complications of epidural anesthesia. [29] Blomberg [27] continued his endoscopic approach to understanding neuraxial anatomy with a subarachnoid study. [30] He identified in the autopsy subjects that a distinct posterior midline membranous structure was present in lower thoracic and upper lumbar regions. He also found that fibrous attachments were present between nerve roots and other subarachnoid structures in many subjects. He postulated that these fibrous structures and attachments may help explain some variation in spinal anesthesia.

Figure 42-4 Vertebral anatomy. (A) Sagittal view. (B) Oblique view of lumbar vertebra showing ligamentum flavum thickening in the caudad extent of intervertebral space and in the midline. (C) Oblique view of single lumbar vertebra.

TABLE 42-1 -- Characteristics of Ligamentum Flavum at Different Vertebral Levels

SITE	SKIN TO LIGAMENT (cm)	THICKNESS OF LIGAMENT (mm)
Cervical	--	1.5-3.0
Thoracic	--	3.0-5.0
Lumbar	3.0-8.0 [a]	5.0-6.0 [b]
Caudal	Variable	2.0-6.0

Data from Cousins and Bromage [173] and other sources

[a] Distance is 4 cm for 50 percent of patients and 4 to 6 cm for 80 percent of patients.
[b] Within each interlaminal space the ligamentum flavum varies in thickness from cephalad to caudad: near the rostral lamina 1.3 to 1.6 mm, near the caudad lamina 6.9 to 9.1 mm.

The performance of caudal anesthesia calls for an expanded understanding of epidural anatomy and especially of the frequent variations in sacral anatomy. [31] The sacrum results from the fusion of the five sacral vertebrae. The sacral

Figure 42-5 (Figure Not Available) Anteroposterior view of lumbosacral epidural space after contrast injection. Arrow indicates a median dorsal band in the epidural space. *(From Savolaine and Pandya [26])*

hiatus, which is the failure of the laminae of S5 and usually part of S4 to fuse in the midline, is the detail of interest. This results in a variably shaped and sized inverted V-shaped bony defect, covered by the posterior sacrococcygeal ligament (a functional counterpart to the ligamentum flava). This sacral hiatus may be identified by locating the sacral cornua (the remnants of the S5 articular processes) (Fig. 42-6) . This bony defect allows access to the sacral canal, although needle insertion through this defect may be difficult because of the frequency of anatomic variation. For example, the shape of the space may vary from slit-like to a wide-based, inverted V, and in 1 of 20 patients the bony defect may be absent, precluding the caudal approach (Fig. 42-7) (Figure Not Available) . [32] [33]

The sacral canal contains the terminal portion of the dural sac, which typically ends cephalad to a line joining the posterior superior iliac spines, or S2. Variation is found in this feature as well, with the termination of the dural sac being lower in children, although the ease of palpating the sacral hiatus in children may make pediatric caudal technique easier overall. In addition to the dural sac, the sacral canal also contains a venous plexus, which is part of the valveless internal vertebral venous plexus. It is estimated from magnetic resonance (MR) imaging that in adults the volume of the caudal canal, excluding the foraminae and dural sac, ranges from about 10 mL to 27 mL. Perhaps this wide variability in volume accounts for some the variation in block height with caudal anesthesia. [31]

Once the anatomy pertinent to neuraxial blocks is understood, it is tempting to administer the blocks immediately. Nevertheless, safe conduct of spinal, epidural, and caudal anesthesia requires an appreciation for the physiologic effects of these blocks if they are to be used appropriately.

Figure 42-6 Sacral surface anatomy. An equilateral triangle can be drawn to connect the posterior superior iliac spines and the sacral hiatus. This can be useful in confirming palpation of the sacral hiatus.

Figure 42-7 (Figure Not Available) Anatomic variants of sacrum and sacral hiatus. Sacral hiatus variants. (A) Normal. (B) Longitudinal slit-like hiatus. (C) Second midline hiatus. (D) Transverse hiatus. (E) Large hiatus with absent cornua. (F) Transverse hiatus with absent coccyx and two prominent cornua and two proximal "decoy hiatuses lateral to the cornua." (G-I) Large midline defects contiguous with sacral hiatus. (J-L) Enlarged longitudinal hiatuses, each with an overlying "decoy" hiatus. *(From Willis [186])*

Physiologic Effects

The physiologic effects of neuraxial blocks are often misinterpreted as complications, which are highlighted by observers who list hypotension under complications of the techniques. [34] A clear distinction should be made between physiologic effects of an anesthetic technique and complications that imply some harm to the patient. [35] This distinction is important to determine the risk-benefit equation of the technique in question.

Cardiovascular Effects

The cardiovascular effects of neuraxial blocks are similar in some ways to the combined use of intravenous alpha $_1$ - and beta-adrenergic blockers: heart rate and arterial blood pressure decrease (Ch. 16) . The sympathectomy that accompanies the techniques is dependent upon height of the block, with the sympathectomy typically described as extending for two to six dermatomes above the sensory level with spinal anesthesia and at the same level with epidural anesthesia. [36] This result causes both venous and arterial vasodilation, but because of the large amount of blood in the venous system (approximately 75% of total blood volume), the venodilation effect predominates because of the limited amount of smooth muscle in venules, whereas the vascular smooth muscle on the arterial side of the circulation retains a considerable degree of autonomous tone. After neuraxial block-induced sympathectomy, if normal cardiac output is maintained, total peripheral resistance should decrease only 15 to 18 percent in normovolemic healthy patients, even with near total sympathectomy. In elderly patients with cardiac disease, systemic vascular resistance may decrease almost 25 percent following spinal anesthesia, whereas cardiac output decreases only 10 percent. Heart rate during high neuraxial block typically decreases as a result of blockade of the cardioaccelerator fibers arising from T1 to T4. Additionally, the heart rate may decrease as a result of a fall in right atrial filling, which decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins. [36]

The clinical question of what level of arterial blood pressure decrease after neuraxial block is acceptable remains to be answered. This likely will remain speculative because conducting ethical human investigations designed to define a dose-response curve of decreased arterial blood pressure accompanying neuraxial block will be difficult.

There are some data available to help determine the extent to which arterial blood pressure should be allowed to decrease. Although there are methodologic problems with the study, * Kety et al [37] demonstrated that producing spinal anesthesia to midthoracic levels with procaine, even in patients with essential hypertension, resulted in a decrease in mean arterial pressure of 26 percent (155-115 mm Hg) accompanied by only a 12 percent (52-46 mL/100 g/min) decrease in cerebral blood flow. When the level of spinal anesthesia was purposely increased to produce higher levels of block (T4) in normotensive and hypertensive patients, the mean arterial pressure decreased by 32 percent (93-63 mm Hg) and 50 percent (158-79 mm Hg), respectively. Although cerebral blood flow was unchanged in the normotensive group (45-46 mL/100 g/min), a 19 percent decrease occurred in the apparently untreated hypertensive patients (46.5-37.5 mL/100 g/min). [38] When coronary artery blood flow and myocardial metabolism were determined in humans during spinal anesthesia to T4 in both hypertensive and normotensive patients, decreases in coronary blood flow (153-74 mL/100 g/min) paralleled the decrease in mean arterial blood pressure (119 to 62 mm Hg) and the percentage extraction of myocardial oxygen was unchanged (75-72%). The extraction of oxygen was unchanged because myocardial work, as expressed by myocardial utilization of oxygen, paralleled the decrease in mean arterial pressure and coronary blood flow (16-7.5 mL/100 g/min). [39]

These human studies are limited by cerebral and myocardial blood flow methodologies that were not limiting factors when Sivarajan et al [39A] investigated organ blood flow via microspheres in rhesus monkeys during spinal anesthesia at both T10 and T1 levels. During T10 block there was no significant change in organ blood flow; during the T1 block, with a 22 percent decrease in mean arterial pressure, cerebral and myocardial blood flows were insignificantly altered. Thus, prevention of decreases in mean arterial pressure of more than 30 percent has some basis, but these data were collected in severely hypertensive, presumably untreated patients.

For normotensive and treated hypertensive patients, a wider undocumented margin of safety probably exists.

Once arterial blood pressure decreases to a level for which treatment is believed necessary, ephedrine (a mixed adrenergic agonist) provides more appropriate therapy for the noncardiac circulatory sequelae of neuraxial block than either a pure or pure-adrenergic agonist (Ch. 16) . [40] It has long been taught that the decrease in blood pressure following neuraxial block can be minimized by administration of crystalloids intravenously prior to the block; however this logic may need rethinking. Buggy et al showed that withholding prehydration before spinal anesthesia in elderly patients undergoing elective procedures is not associated with any greater degree of hypotension or need for vasopressor therapy compared with crystalloid or colloid prehydration.

Is there any indication that epidural and spinal anesthesia differ in the effect on arterial blood pressure? A common concept is that the decrease in arterial blood pressure is more gradual and of less magnitude with epidural than spinal anesthesia of comparable levels. In spite of this belief, there is evidence that when tetracaine (10 mg) spinal anesthesia was compared with lidocaine (20-25 mL of 1.5%) epidural anesthesia, there was a larger decrease in arterial blood pressure, approximately 10 percent, with the epidural technique than with the spinal. [41] Furthermore, the proposed advantage of slower onset of epidural blockade is often mitigated by anesthesiologists administering a decreased volume of local anesthetic with the initial epidural therapeutic dose; then, when the block height does not rise as rapidly as desired, additional epidural local anesthetic is administered and a higher block than necessary may result. The extent to which arterial blood pressure decreases with either technique is obviously dependent on multiple factors, including patient age and intravascular volume status.

Respiratory Effects

Alterations in pulmonary variables in healthy patients during neuraxial block are usually of little clinical consequence. Tidal volume remains unchanged during high spinal anesthesia, and vital capacity decreases a small amount from 4.05 to 3.73 L. [42] This decrease in vital capacity is a result of a decrease in expiratory reserve volume related to paralysis of abdominal muscles necessary for forced exhalation, rather than a decrease in phrenic or diaphragmatic function. [16] This minimal impact on pulmonary function also holds for elderly patients undergoing lumbar and thoracic epidural anesthesia. [43] Pulmonary function testing in cesarean section patients undergoing epidural anesthesia shows that using lidocaine provides larger decrements in peak expiratory pressure (abdominal musculature dependent maneuver) than using bupivacaine. [44]

The rare respiratory arrest associated with spinal anesthesia is also unrelated to phrenic or inspiratory dysfunction, but rather, is related to hypoperfusion of the respiratory centers in the brain stem. Supportive evidence for this concept is observed after resuscitation, when apnea almost always disappears as soon as pharmacologic and fluid therapies have restored cardiac output and blood pressure. This would not be the case if phrenic paralysis due to high levels of local anesthetic were the cause of apnea. [16] There is experimental evidence in rabbits that during epidural anesthesia their response to hypoxia results in apnea, which is different than the response without neuraxial anesthesia. [45] This finding may have implications for understanding some episodes of cardiovascular depression during neuraxial blocks in humans, although confirmation is needed. Conversely, in a canine model of hypoxia epidural anesthesia and hypoxic challenge results in the same outcome but with more normal acid-base function, compared to animals receiving general anesthesia alone. [46]

Neuraxial block should be used cautiously in respiratory cripples because of paralysis of respiratory muscles. Except for the severely compromised patient with respiratory failure, inspiratory muscle function during neuraxial blocks

*Cerebral blood flow (CBF) studied with nitrous oxide; only global CBF measured; patients studied were severely hypertensive (i.e., average mean arterial blood pressure was 155 mm Hg).

should be adequate to maintain ventilatory function. The physiologic consideration related to muscle paralysis with neuraxial block should focus on the expiratory muscles in these severely compromised patients because these muscles are important for effective coughing and clearing of intrapulmonary secretions. [36] [42]

Gastrointestinal Function

Another organ system affected during neuraxial block is the gastrointestinal (GI) tract. Nausea and vomiting may be associated with neuraxial block in up to 20 percent of patients and is primarily related to GI hyperperistalsis due to unopposed parasympathetic (vagal) activity. [47] Accordingly, atropine is effective in treating nausea associated with high (T5) subarachnoid anesthesia. [48] [49] This GI hyperperistalsis has the advantage of providing excellent surgical conditions because of a contracted gut. [50] An often cited advantage of regional anesthesia in patients with compromised GI function (e.g., hepatic dysfunction) is that less physiologic impairment is possible as compared with general anesthesia. Nevertheless, it appears that if intra-abdominal surgery is performed, the magnitude of decrease in hepatic blood flow parallels the site of operation, rather than anesthetic technique chosen. Additionally, the decrease in hepatic blood flow during spinal anesthesia parallels the decrease in mean arterial blood pressure. [51] When epidural analgesia is continued into the postoperative period, there may be a protective effect on the gastric mucosa because intramucosal pH is higher during postoperative epidural analgesia than with systemic analgesia. [52]

Renal Function

Renal function has a wide physiologic reserve. Despite predictable decreases in renal blood flow accompanying neuraxial block, the decrease is of little physiologic importance. [53] One aspect of genitourinary function that is of clinical importance is the belief that neuraxial blocks are a frequent cause of urinary retention, which either delays discharge of outpatients or necessitates bladder catheterization in inpatients. It is clear that lower concentrations of local anesthetic are necessary for paralysis of bladder function than for motor nerves to lower extremities. Still, some studies do not support this belief. For example, in orthopedic patients undergoing hip replacement, it was demonstrated that bladder catheterization was no more frequent after neuraxial (spinal or epidural) block than after general anesthesia and narcotic analgesics. [54] Still, it is prudent to avoid administration of excessive volumes of crystalloid solutions intravenously to patients undergoing spinal anesthesia.

Physiologic Effects Specific to Epidural Anesthesia

The physiologic effects of epidural anesthesia are similar to those of spinal anesthesia, with the exception that local anesthetic blood levels reach concentrations sufficient

Figure 42-8 (Figure Not Available) Meperidine requirements during the first and second postoperative days in patients receiving intravenous lidocaine (shaded bars) and in control patients (open bars). Data expressed as mean ± SEM. *, $P < 0.02$; **, $P < 0.01$ compared to control data. *(Modified from Cassuto et al [55])*

enough to produce systemic effects on their own. Even intravenously administered lidocaine (resulting in blood levels similar to those following continuous epidural analgesia) can decrease postoperative narcotic requirements (Fig. 42-8) (Figure Not Available) . [55] When blood levels are excessive, adverse central nervous system and cardiovascular effects occur (Ch. 13) .

SPINAL ANESTHESIA

Technique

To perform spinal anesthesia, pertinent anatomy must be constantly kept in mind as one is inserting the spinal needle. It is often helpful for the technique to be broken down into a series of steps (the four "Ps"): preparation, position, projection, and puncture.

Preparation

Preparation of the equipment and drugs is essential for subarachnoid injection. When choosing a drug for subarachnoid injection the duration of block should be matched not only to the surgical procedure but also to patient variables. It may be more time-efficient to use a hypobaric solution in a patient in the prone-jackknife position, rather than turning the patient after a hyperbaric solution has been allowed time to take effect. Is the patient planning to go home after an outpatient procedure, thus dictating a shorter-acting drug? Will a prolonged period of lower extremity analgesia, such as that obtained from adding an opioid to the spinal drugs, be advantageous to a patient undergoing knee reconstruction and immediate postoperative use of a range-of-motion machine? These are only a few of the many clinical permutations that dictate familiarity with the combinations of drugs available for subarachnoid use.

When choosing equipment for spinal anesthesia, the initial choice involves reusable or disposable equipment. Most

Figure 42-9 Spinal needle assortment, including disposable (A) 25-gauge Whitacre, (B) 24-gauge Sprotte, and (C) 25-gauge Quincke. The first two have conical tips, and the Quincke has a cutting-tip design.

anesthesiologists are forced to accept disposable spinal trays, which may seem limiting. Still, most suppliers are willing to customize trays to meet one's preferences. Despite the emphasis on disposable trays, there is no indication that these trays shift the spinal anesthesia risk-benefit equation in the patient's favor. [56]

Spinal needles fall into two main categories: those that cut the dura and those designed to spread dural fibers. The former include the "traditional" disposable spinal needle, the Quincke-Babcock needle, and the latter contain the Greene, Whitacre, and Sprotte needles (Fig. 42-9) . If a continuous spinal technique is chosen, the use of a Tuohy or other thin-walled needle will facilitate passage of the catheter. The use of small needles reduces the incidence of postdural puncture headache, whereas the use of larger needles improves the tactile "sense" of needle placement. Also, multiple punctures probably increase the incidence of headaches. If use of a smaller needle increases the number of punctures, the difference between small and large needles in producing headaches may be reduced. There is also a decrease in postdural puncture headache incidences when a conical-tipped needle is used, even when needle sizes are comparable. [57] [58] Nevertheless, as facility with spinal anesthesia increases, the use of a smaller, similarly "tipped" needle will decrease headache incidence, if the number of dural punctures does not increase.

Position

Positioning (Ch. 26) is frequently the most poorly managed part of spinal technique for at least two reasons. First, the assistant often does not understand the rationale for positioning a patient, and second, patients are often inadequately or excessively sedated, making cooperation poor. The three primary methods of patient positioning include lateral decubitus, sitting, and prone, each with advantages in specific situations.

The lateral decubitus position is the most commonly used because it allows safe administration of more sedation and is less dependent on a well-trained assistant than with the sitting position. Patients are placed with the back parallel to the edge of the operating table nearest the anesthesiologist, with thighs flexed upon the abdomen, and the neck flexed to allow the forehead to be as close as possible to the knees. The assistant may be invaluable during this positioning, by encouraging and assisting a patient in assuming the ideal lateral decubitus position (Fig. 42-10) . The patient should be positioned so that spread of hypo-, iso-, or hyperbaric solution to the operative site is optimized.

Choose the sitting position when low lumbar and sacral levels of sensory anesthesia are adequate for the surgical procedure, such as perineal and urologic operations, or when obesity or scoliosis makes identification of midline anatomy difficult in the lateral position. When placing patients in this position, a stool can be provided as a footrest, and a pillow is placed in their lap. The assistant then maintains the patient in a vertical plane while flexing the patient's neck and arms over the pillow to open up the lumbar vertebral space (Fig. 42-11) . If the reason for choosing the sitting position is to keep the sensory level low, the patient should be maintained sitting for 5 minutes; if the choice was made because of obesity or scoliosis and a higher sensory level is needed, the patient should be put supine immediately after

Figure 42-10 Lateral decubitus positioning for centroneuraxis block. The assistant can help the patient assume the ideal position of "forehead-to-knees."

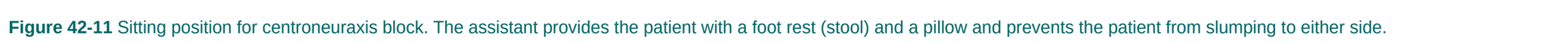

Figure 42-11 Sitting position for centroneuraxis block. The assistant provides the patient with a foot rest (stool) and a pillow and prevents the patient from slumping to either side.

subarachnoid injection, with the table manipulated appropriately. The most common error made in placing patients in this position is allowing the patient to slump, with the advantage of improved midline identification lost.

The prone position should be chosen when the patient is to be maintained in that position (often with jackknife modification) during the surgical procedure. This position is often appropriate for rectal, perineal, or lumbar procedures. An advantage of hypobaric technique is that patients can help in positioning themselves, thus minimizing the opportunity for positioning injuries. Once the patient is in position, lumbar lordosis should be minimized and, most often, the paramedian approach should be used. Also, one may have to aspirate for CSF because CSF pressures are minimized when lumbar needle insertion is carried out in this position.

Projection and Puncture

Once the equipment, local anesthetics and additives, and the patient have been properly prepared, the spinal puncture, either midline or paramedian, can be performed. The midline approach relies on the ability of patients and assistants to minimize lumbar lordosis and allow access to the subarachnoid space between adjacent spinous processes, usually at the L2-L3, L3-L4, or sometimes the L4-L5 spaces. The palpating fingers (usually index and third fingers) should identify the interspinous area by identifying the caudad extent of the more cephalad spine and the midline by rolling the fingers medial to lateral (Fig. 42-12) . A subcutaneous skin wheal is developed overlying this space and the introducer is inserted into the substance of the interspinous ligament. The introducer is grasped with the palpating fingers and steadied, while the other hand is used to hold the spinal needle like a dart, with the fifth finger used as a tripod against the patient's back to prevent patient movement producing unintentional insertion to a level deeper than intended. The needle, with bevel parallel to longitudinal dural fibers, is advanced slowly both to heighten the sense of tissue planes traversed and to prevent skewing of nerve roots until the characteristic change in resistance is noted as the needle passes through ligamentum flavum and dura. The stylet is then removed, and CSF should appear at the needle hub. If it does not, the needle is rotated in 90-degree increments until CSF appears. If CSF does not appear in any quadrant, the needle should be advanced a few millimeters and rechecked in all four quadrants. If CSF still has not appeared, and the needle is at a depth appropriate for the patient, the needle and introducer should be withdrawn and insertion steps repeated, recognizing that the most common reason for lack of CSF return is that the needle is being inserted off the midline. Another common error preventing subarachnoid placement is too large a cephalad angulation on the initial needle insertion.

Once CSF is freely obtained, the dorsum of the anesthesiologist's nondominant hand steadies the spinal needle against the patient's back while the syringe containing the therapeutic dose is attached to the needle. CSF is again freely aspirated into the syringe and the dose injected at a rate of approximately 0.2 mL/s. After completion of the injection, 0.2 mL of CSF is again aspirated into the syringe and reinjected subarachnoid, both to reconfirm location and to clear the needle of the remaining local anesthetic. The patient and operating table should then be placed in the position appropriate for the surgical procedure and drugs chosen.

The midline approach is the technique of first choice because it requires anatomic projection in only two planes (Fig. 42-13) (Figure Not Available) and provides a relatively avascular plane. When difficulties with needle insertion are encountered with the midline approach, one option is to use the paramedian route, which does not require the same level of patient cooperation or reversal of lumbar lordosis for success.

The paramedian approach exploits the larger "subarachnoid target" that exists if a needle is inserted slightly lateral to the midline (see Fig. 42-13) (Figure Not Available) . The most common error made in utilizing the paramedian technique is that the needle entry site is placed too far off the midline, making the vertebral lamina barriers to needle insertion. In the paramedian approach, the palpating fingers again identify the caudad edge of the cephalad spinous process, and a skin wheal is raised 1 cm lateral and 1 cm caudad to this point. A longer needle (e.g., 12-inch) is then used to infiltrate deeper tissues

Figure 42-12 Spinal needle insertion. (A) The palpating fingers are "rolled" in both a side-to-side and cephalad-to-caudad direction to identify interspinous space. (B) During needle insertion, the needle should be stabilized in a tripod fashion while placed in the hand, similar to a dart being thrown.

Figure 42-13 (Figure Not Available) Vertebral anatomy of midline and paramedian approaches to centroneuraxis blocks. The midline approach highlighted in the inset requires anatomic projection in only two planes: sagittal and horizontal. The paramedian approach shown in both the inset and the posterior view requires an additional oblique plane to be considered, although the technique may be easier in patients who are unable to cooperate in minimizing their lumbar lordosis. The paramedian needle insertion is made 1 cm lateral and 1 cm caudad to the caudad edge of the more superior vertebral spinous process. The paramedian needle is inserted approximately 15 degrees off the sagittal plane, as shown in the inset. *(Modified by permission of the Mayo Foundation)*

Figure 42-14 (Figure Not Available) Centroneuraxis anatomy of the Taylor approach to spinal anesthesia. This is really a paramedian approach at the L5-S1 vertebral level. A skin mark is made 1 cm caudad and 1 cm medial to one of the posterior superior iliac spines. Through this skin mark, the needle is inserted cephalad and medial. The needle is walked off the sacrum and into the largest interspinous space, the L5-S1 intervertebral space. The posterior superior iliac spines are located immediately anterior to the often present "skin dimples" found overlying the superior aspect of the sacrum. *(By permission of the Mayo Foundation)*

in a cephalomedial plane. The spinal introducer and needle are then inserted 10 to 15 degrees off the sagittal plane in a cephalomedial plane (see Fig. 42-13 (Figure Not Available)). Similar to the midline approach, the most common error is to angle the needle too far cephalad on initial insertion. Nevertheless, if the needle contacts bone, it is redirected slightly in a cephalad direction. If bone is again contacted, but at a deeper level, the slight cephalad angulation is continued because it is likely that the needle is being "walked up" the lamina. As in the midline approach, the characteristic feel of the ligaments and dura is possible, although needle angulation will require more of the needle to be inserted. Once CSF is obtained, the block is carried out in a manner similar to that described for the midline approach.

Figure 42-15 Continuous spinal needle examples, including disposable (A) 18-gauge Hustead, and (B) 17-gauge Tuohy. Both have distal tips designed to direct the catheters inserted through the needles along the course of the bevel opening; 20-gauge epidural catheters are used with these particular needle sizes.

A variation on the paramedian approach is the lumbosacral approach described by Taylor. [59] This technique is carried out at the L5-S1 interspace, the largest interlaminal interspace of the vertebral column. A 5-inch spinal needle is inserted in a cephalomedial direction through a skin wheal raised 1 cm medial and 1 cm caudad to the lowermost prominence of the posterosuperior iliac spine. If bone is encountered on first needle insertion, the needle is walked off the sacrum into subarachnoid space. Once CSF is obtained, the steps are similar to those previously outlined (Fig. 42-14) (Figure Not Available) .

If a continuous spinal anesthetic is prescribed, a needle with a lateral-faced opening is used to perform the lumbar puncture (Fig. 42-15) . Either a midline or paramedian approach may be used, with some suggesting that use of the paramedian approach facilitates catheter insertion. [60] The catheter should be threaded 2 to 3 cm into the subarachnoid space, and then the needle is withdrawn over the catheter. Care must be taken to ensure that the catheter is not inserted more deeply into the subarachnoid space when the needle is withdrawn over the catheter.

Pharmacology

Useful Drugs

There are three drugs (Ch. 12) commonly used in the United States to produce spinal anesthesia: lidocaine (Xylocaine), tetracaine (Pontocaine), and bupivacaine (Marcaine or Sensorcaine) (Fig. 42-16) . Lidocaine provides a short- to intermediate-acting spinal drug; tetracaine and bupivacaine provide intermediate- to long-duration block (Table 42-2) .

Figure 42-16 Ampules of drugs commonly used in the United States for spinal anesthesia. (A) Lidocaine 5 percent, with glucose 7.5 percent. (B) Bupivacaine 0.75 percent, in glucose 8.25 percent. (C) Tetracaine 1 percent. (D) Tetracaine niphanoid crystals, 20 mg.

TABLE 42-2 -- Drug Selection for Hyperbaric Spinal Anesthesia

LOCAL ANESTHETIC MIXTURE	DOSE (mg)[a]		DURATION (min)	
	TO T10	TO T4	PLAIN	0.2 mg EPINEPHRINE
Lidocaine (5% in 7.5% dextrose)	50-60	75-100	60	75-100
Tetracaine (0.5% in 5% dextrose)	6-8	10-16	70-90	100-150
Bupivacaine (0.75% in 8.5% dextrose)	8-10	12-20	90-110	100-150

[a] Doses are for use in a 70-kg adult male of average height.

Lidocaine is often chosen for procedures, such as inguinal herniorrhaphy, that can be completed in 1 hour or less. It has measurable effect in less than 5 minutes and is most commonly used as the 5 percent solution in 7.5 percent dextrose; however, many are exploring reducing the concentration of the drug during spinal anesthesia. [61] [62] It is not clear that reducing the concentration of lidocaine affects the incidence of what is being termed "transient radicular irritation." [63] It is important to caution against abandoning the use of our most useful short-acting spinal anesthetic drug, lidocaine, until the infrequent back pain associated with lidocaine spinal anesthetics is better defined. At present, my use of lidocaine for spinal anesthesia is directed by the following suggestions: limit dose to 60 to 70 mg; inject the dose at a rate exceeding 0.2 mL/s; keep needle apature directed cephalad; and limit use of the drug for continuous spinal techniques as much as is practical.

Previously, it was thought that epinephrine did not prolong the length of spinal anesthesia with lidocaine because duration was most often defined by two-segment regression in the thoracic dermatomes. In spite of that, the duration of lidocaine spinal anesthesia was found to be prolonged at the operative site by 0.2 mg of epinephrine. [64] Additionally, the use of epinephrine with spinal drugs may do more than simply prolong the duration of the block at the operative site. An improvement in the quality of block probably occurs as well. [65] [66] In dogs, subarachnoid lidocaine (plain) increases spinal cord blood flow (21-35 mL/100 g/min), whereas when epinephrine is added to lidocaine no statistically significant change (30-24 mL/100 g/min) in spinal cord blood flow results. [67] Two-segment regression is a measure of duration of neuraxial blocks. The time from injection of local anesthetic mixture until the maximum level of the spinal or epidural anesthetic (usually thoracic) has decreased by two dermatome levels.

Tetracaine has been used in spinal anesthesia for years and is packaged as both niphanoid crystals (20 mg) and a 1 percent solution (20 mg). This drug has an onset of 5 to 10 minutes and is selected for procedures lasting up to 2 to 3 hours when epinephrine is added, and up to 5 hours for lower extremity procedures when phenylephrine (0.5 mg) is added as the vasoconstrictor. When niphanoid crystals are used, a 1 percent solution is mixed by adding 2 mL of sterile water (without preservatives) to the crystals. Then the appropriate milligram dose of 1 percent solution is mixed in equal volumes of 10 percent dextrose to produce a 0.5 percent tetracaine solution weighted with 5 percent dextrose. Subsequently, the vasoconstrictor may be added. Once again, epinephrine and phenylephrine both prolong spinal anesthesia with tetracaine (Table 42-3) (Table Not Available) . [68] In dogs, subarachnoid tetracaine increases spinal cord blood flow (21-47 mL/100 g/min); addition of epinephrine to tetracaine leaves blood flow unaltered (24-24 mL/100 g/min). [69]

Bupivacaine spinal anesthesia is commonly carried out with 0.75 percent and 0.5 percent solutions in dextrose. Increasingly though, the clinical isobaric forms of the drug, the 0.5 percent and the 0.75 percent plain solutions, are also used. The clinical difference between tetracaine 0.5 percent and bupivacaine 0.75 percent as hyperbaric solutions is minimal. It appears that when "isobaric" 0.5 and 0.75 percent bupivacaine are compared, the mass of drug (mg dose) injected is more important in determining the eventual block height than the volume of isobaric drug administered. [70] [71] Bupivacaine is appropriate for procedures lasting up to 2 to 2.5 hours. [72] Subarachnoid bupivacaine in dogs decreases lumbosacral spinal cord blood flow with (35 to 20 mL/100 g/min) or without (31-22 mL/100 g/min) added epinephrine. [73] In spite of this laboratory finding, the clinical significance seems minimal.

Spinal Anesthetic Additives

Some physicians have been concerned that the use of additives, particularly vasoconstrictors, may be risky. The concept

TABLE 42-3 -- Effect of Adding Epinephrine or Phenylephrine to Tetracaine Spinal Anesthesia

(Not Available)

Modified from Caldwell et al [68]

is that epinephrine and phenylephrine have such potent vasoconstrictive action as to put the blood supply of the spinal cord at risk. There are no human data supporting this theory. Kozody et al [74] have shown that administering subarachnoid epinephrine (0.2 mg) or phenylephrine (5 mg) does not decrease spinal cord blood flow in dogs. These traditional vasoconstrictors are not the only adrenergomimetic agents being studied. Clonidine, an alpha $_2$ -agonist, prolonged motor block associated with tetracaine spinal anesthesia in dogs as much as epinephrine while prolonging sensory blockade for an even longer interval. [75] The mechanism for this prolongation may involve both vasoconstriction and anti-nociception from alpha-stimulation. [76] Another drug being investigated for spinal use as an additive is neostigmine. [77] It may prolong and intensify analgesia through release of nitric oxide in the spinal cord.

The interaction of various vasoconstrictors and local anesthetics is better understood. Traditionally, epinephrine was thought to prolong only tetracaine spinal anesthesia but not bupivacaine or lidocaine spinal anesthesia. [78] This theory was postulated because of differences in vasodilatory actions of the local anesthetic drugs: plain lidocaine and bupivacaine cause vasodilation, whereas plain tetracaine does not. Additionally, the original investigations of spinal anesthetic duration used two-dermatome regression in the thoracic dermatomes to establish duration. [79] [80] [81] Since that time, it has become clearer that two-dermatome regression in the mid- to high-thoracic dermatomes may be misleading when measuring spinal anesthetic duration in the lower thoracic and lumbar dermatomes. There are data that lidocaine spinal anesthesia is prolonged by epinephrine when measured by two-dermatome regression in the lower thoracic dermatomes and by occurrence of pain at the operative site for procedures carried out at the level of lumbosacral dermatomes. [64] [82]

When epinephrine has been compared to phenylephrine as a means of prolonging spinal anesthesia, conflicting information again appears to exist. Concepcion et al [83] compared epinephrine (0.2 and 0.3 mg) and phenylephrine (1 and 2 mg) added to tetracaine and did not find a difference in increased duration with the two vasoconstrictors. Caldwell et al [68] used higher doses of vasoconstrictors, epinephrine at 0.5 mg and phenylephrine at 5 mg, and showed that phenylephrine

prolonged tetracaine spinal anesthesia significantly more than epinephrine (see Table 42-3 (Table Not Available)). Additionally, phenylephrine has been shown to prolong lidocaine spinal anesthesia, but it appears that the length of prolongation is more similar to that produced with epinephrine than significantly longer. [82] [84] Duration of bupivacaine spinal anesthesia does not appear to be prolonged by phenylephrine. [80] [85] Whichever local anesthetic solution and additives are selected for subarachnoid injection, special care should be taken to assure that one knows what substance is being injected and that all procedures have been carried out aseptically.

Hypobaric and Isobaric Spinal Anesthesia

The density of any solution is the weight in grams of 1 mL of the solution at a standard temperature. Specific gravity is the density of a solution compared in a ratio to the density of water. In contrast, baricity is a ratio comparing the density of one solution to another. If the other solution happens to be water, the baricity will be the same as the specific gravity. In order to make a drug hypobaric to CSF, it must be less dense than CSF, having a baricity appreciably less than 1.0000 or a specific gravity appreciably less than 1.0069 (the mean value of CSF specific gravity).

In the United States, the most common method of formulating a hypobaric solution is to mix tetracaine in a 0.1 to 0.33 percent solution with sterile water. This makes the baricity of the solution less than 0.9977 and allows clinically useful anesthesia to be produced. In the prone position for anorectal procedures or in the lateral position for hip repairs, 4 to 6 mg of selected hypobaric dilution is often adequate. There is evidence that rate of injection (0.02 mL/s versus 0.5 mL/s) of hypobaric (0.2 percent) tetracaine influences spread of the drug. [86]

Another method of formulating a hypobaric-like solution is to use warmed 0.5 percent bupivacaine. [87] [88] These data show that 0.5 percent bupivacaine warmed to 37°C, compared with 4°C, demonstrates hypobaric characteristics when the block is administered to sitting patients. Additionally, these investigators suggest that warmed bupivacaine provides more predictable cephalad spread of sensory level, in contrast to a cold or room temperature drug.

Another drug that has been investigated as a "clinically" hypobaric spinal drug is 2 percent lidocaine. Its physiochemical characteristics make it more similar to an isobaric than hypobaric drug; however, some clinicians have found it useful in situations generally reserved for hypobaric techniques. [89]

When isobaric spinal anesthesia is planned, the drugs most often chosen today are 0.5 or 0.75 percent bupivacaine. Another drug that can be used is tetracaine. It is formulated into an isobaric solution by diluting the niphanoid tetracaine crystals (20 mg) with CSF and then injecting the selected mass of drug in an isobaric fashion.

Factors Affecting Block Height

More than 20 factors may alter spinal anesthetic block height (Table 42-4) . [90] Table 42-5 lists the most important documented factors. Age has a statistically significant effect on block height, yet, when examined, the difference in block height using isobaric bupivacaine and comparing the 3rd to 9th decades is small (i.e., T9 for those 20-28 years and T6 for those older than 80 years of age). [91] [92] Unlike epidural dose requirements, weight is not related to block height during spinal anesthesia. Patient height is related, although again the contribution is minor compared to more important factors (Table 42-6) . Similarly, injection rate and barbotage of isobaric and hyperbaric solutions have not been shown to affect block height, although injection rates in these studies have been above 0.1 to 0.2 mL/s. [93] [94] It is becoming clear that the direction of spinal needle lateral-facing openings impact block height levels, even with isobaric spinal solutions. [95] [96] Other maneuvers that do not appear to affect block height are coughing and straining after local anesthetic injection. This is related to the physics of injecting drugs into a closed column of CSF, which instantaneously transmits pressure changes throughout the CSF column, such as those that occur with coughing or straining. [90]

TABLE 42-4 -- Factors Postulated to Be Related to Spinal Anesthetic Block Height

Patient characteristics
Age
Height
Weight
Gender
Intra-abdominal pressure
Anatomic configuration of spinal column
Position
Technique of injection
Site of injection
Direction of injection (needle)
Direction of bevel
Use of barbotage
Rate of injection
Characteristics of spinal fluid
Volume
Pressure (cough/strain/Valsalva)
Density
Characteristics of anesthetic solution
Density
Amount (mass)
Concentration
Temperature
Volume
Vasoconstrictors

When more global factors affecting block quality are examined, at least in some teaching programs, the spinal "failure rate" may be as high as one in six blocks. [97] To understand "failure rate" fully, the definition must be examined. These investigators considered need to supplement the block with any inhaled anesthetic as failure. This is a key point because to provide comprehensive regional anesthesia supplementation of the block must be considered appropriate rather than a de facto failure. [98] These data do emphasize an important contributor to failed blocks, that is, the lack of free flow of CSF after needle placement. There is obviously some level of experience necessary to carry out spinal anesthesia successfully, but even in a teaching program, this should not prohibit the successful use of spinal anesthesia because the failure rate can be as low as 1 percent. [47] [72]

TABLE 42-5 -- Factors Documented to Be Related to the Height of a Spinal Anesthetic Block

	EFFECT	
	MAJOR	*MINOR*
Patient characteristics		
Age		0
Height		0
Anatomic configuration of spinal column		0
Position/baricity	0	
Intra-abdominal pressure		0
Technique of injection		0
Characteristics of spinal fluid		0
Characteristics of anesthetic solution		
Baricity/position	0	
Dosage (mass of drug)	0	
Temperature		0

TABLE 42-6 -- Factors Probably Unrelated to the Height of Spinal Anesthetic Block

Added vasoconstrictor
Coughing/straining/bearing down (labor)
Barbotage
Rate of injection (except hypobaric)
Needle bevel (except Whitacare needle)
Gender
Weight

Complications

Complications include neurologic changes, headache after dural puncture, backache that accompanies 25 percent of procedures performed with spinal anesthesia, and unexpected cardiac arrests. [99]

As outlined earlier, neurologic injury after spinal anesthesia has received considerable media attention through the years, including the Wooley and Roe case in England, the "investigation" published by Kennedy [4] in 1950 in the United States, and the cases of cauda equina syndrome associated with small-bore continuous spinal anesthesia. [100] Overlooked by many is information from Marinacci, [101] whose investigation was performed after Kennedy's publication. Marinacci, a neurologist, evaluated 542 patients who were thought to have neurologic complications related to a previous spinal anesthetic. After neurologic evaluation, in only 4 of the 542 patients was there any indication that the prior spinal anesthetic was the cause of the postoperative neurologic change. It should be emphasized that the total number of patients undergoing spinal anesthesia that resulted in the four cases of neurologic symptoms related to spinal anesthesia is unknown.

There are reports that outline both the numerator and denominator of neurologic change after spinal anesthesia. Vandam and Dripps [102] documented 10,098 patients who underwent spinal anesthesia and reported no severe neurologic sequelae related to spinal anesthesia. Likewise, Moore and Bridenbaugh [57] failed to find a single permanent neuropathy after spinal anesthesia in 11,574 patients undergoing spinal anesthesia. A review of neurologic complications associated with neuraxial blocks, prompted by the chloroprocaine epidural controversy in the early 1980s (Ch. 13) , tabulated [86] 304 patients undergoing spinal anesthesia with only one permanent lesion potentially related to spinal anesthesia (a lumbar plexus injury). [103] Rigler et al reported four patients developing cauda equina syndrome following continuous spinal anesthesia. [100] The pool of patients from which the four patients were drawn is unknown. This research team has continued to highlight perceived difficulties with the use of spinal use of lidocaine (Drasner, unpublished study) and has added significant data to the question. The ultimate decision about using lidocaine for spinal anesthesia still needs consideration of alternatives as well as consideration of the suggestions outlined in the earlier section of this chapter on pharmacology of spinal drugs.

The large series and case reports documenting only rare neurologic lesions after spinal anesthesia should not provide one with a false sense of security. [104] Neurologic changes can occur; the important point is that severe neurologic change

can also occur after general anesthesia. The risk-benefit equation of anesthesia and neurologic injury must include those cases of neurologic injury (e.g., hypoxic central nervous system lesions), that are possible during general anesthesia if a logical and well-informed decision based on neurologic outcome is to be made.

A more common complication of spinal anesthesia is postoperative headache. This postdural puncture headache is not exclusively related to spinal anesthesia but occurs after myelography and diagnostic lumbar puncture as well. Lybecker et al have popularized a postdural puncture headache rating scale that may make comparison between future studies of postoperative headache more meaningful. [105] Factors increasing the incidence of postdural puncture headache or unrelated to its development are listed in Table 42-7 . [106]

Mihic's investigation of bevel "direction" during insertion of a spinal needle clearly demonstrated that splitting, rather than cutting the longitudinally directed dural fibers, resulted in a lower incidence of postdural puncture headache [107] (Fig. 42-17) (Figure Not Available) . Although needle type was unspecified in Mihic's report, it is likely that a Quincke-type needle was used. This clinical observation has been supported by the laboratory investigation by Ready et al showing that simulated dural puncture by cone-shaped spinal needle tips produces a slower transdural loss of fluid than similar puncture with cutting-tipped needles. [58] Perhaps more importantly, meta-analysis has shown that noncutting needle tip designs have a lower frequency of postspinal dural puncture headaches than cutting needle tip designs. [108]

Also to be emphasized is that an arbitrary period of recumbancy after spinal anesthesia has not been found to decrease the incidence of postdural puncture headache, [109] and some data indicate that early ambulation may actually decrease the incidence of postdural puncture headache. [110] [111]

Possibly more important than knowing all the variables resulting in an increased incidence of postdural puncture headache is understanding how and when to carry out the definitive therapy--epidural blood patch--for this complication. The successful use of spinal anesthesia necessitates the early use of epidural blood patching when indicated. This therapy was introduced by Gormley, [112] although its safety and efficacy (more than 90 percent effective in relieving headache per epidural patch) have been well documented. [113] [114] [115]

TABLE 42-7 -- The Relationship Among Variables and Postdural Puncture Headache

Factors *related* to increased incidence of postdural puncture headache	
Age:	Younger more frequent
Gender:	Females > males

Needle size:	Larger > smaller
Needle bevel:	More when dural fibers cut transversely
Pregnancy:	More when pregnant
No. dural punctures:	More with multiple punctures
Factors *not increasing* postdural puncture headache incidence	
Continuous spinals	
Timing of ambulation	

Figure 42-17 (Figure Not Available) Types of needle insertion in Mihic report. In the vertical versus parallel insertion, the bevel of the spinal needle is inserted through the dura mater interna perpendicular to, instead of parallel to, the long axis of the vertebral column. *(Modified from Mihic [107])*

A question that has been debated since its introduction concerns the volume of blood that is most effective in balancing blood patch efficacy and risks. Szeinfeld et al [116] have shown, via radionucleotide-labeled red blood cells injected epidurally, that approximately 15 mL of blood provides efficacy and allows spread over a mean distance of nine spinal segments, thus providing some latitude for blood patch needle placement. They demonstrated that the blood was spread over more segments in the cephalad direction than the caudad direction. As a result, they recommend inserting the blood patch needle in a more cau-dad site if it is impossible to insert the needle at the same level as that of the prior dural puncture. Their data about primarily cephalad spread of an epidural blood patch has been validated by MR imaging of epidural blood patch spread. [117]

Data from Brown and Elman [118] demonstrate that approximately 25 percent of all our surgical patients undergoing anesthesia, regardless of anesthetic technique, experience backache. Thus backache after neuraxial block should not immediately be attributed to "needling" of the back or to use of 5 percent lidocaine.

When properly conducted, spinal anesthesia has proved to be extremely safe. Caplan et al [99] identified 14 cases of sudden cardiac arrest in healthy patients receiving spinal anesthesia. Because these cases seemed to appear suddenly after stable hemodynamic status, they concluded that a poorly understood potential exists for sudden cardiac arrest in healthy patients. It can be debated whether this represented a lack of vigilant monitoring and treatment as opposed to some mysterious physiologic explanation. [119] It is clear that hypoxemia and oversedation are not required for severe bradycardia and asystole to develop during well-conducted spinal anesthesia. [45] [120] Likewise, it is clear that the development of severe bradycardia following spinal anesthesia is not a new phenomenon and has been recognized for many years. [121] [122] In any case, it should be emphasized that cardiovascular changes can occur rather suddenly following spinal anesthesia.

Clinical Pearls

Often the "little things" necessary to carry out effective spinal anesthesia are unstated because they somehow seem less important than the broader issues, such as the incidence of neurologic complications after spinal anesthesia. Nevertheless, the little things often spell the difference between successful use of the technique and failure.

The successful integration of neuraxial blocks into an anesthesia practice requires that anesthesiologists be willing to supplement their blocks with CNS depressants. [98] A concept has developed that a regional anesthetic should need no supplementation and, if it does, it should be considered a failed block. This reasoning needs rethinking. For example, an anesthesiologist would not be expected to pick an arbitrary concentration of isoflurane before a general anesthetic and, on discovering that the concentration needs to be altered during the anesthetic, consider the technique a failure! Likewise, supplementation of a spinal or epidural anesthetic contributes to its comprehensive use and should not be a marker of failed blocks. Once this concept is accepted, neuraxial blocks can be adapted to many more situations, thus allowing an anesthesiologist's experience and confidence with the techniques to grow.

Additionally, to prevent prolongation of a patient's recovery room stay, and thus unnecessarily introduce institutional inefficiency, inpatients should be allowed to leave the recovery room after spinal anesthesia once it can be demonstrated their block is receding appropriately (at least four dermatomes' regression or *a spinal level < T10*), they are hemodynamically stable, and they are comfortable. After spinal anesthesia, outpatients should be able to ambulate without orthostatic changes and void prior to their discharge (Ch. 65) .

Intraoperatively, during high spinal anesthesia, patients occasionally complain excessively about dyspnea. This is not a result of significantly decreased inspiratory capacity but most often seems related to loss of chest-wall sensation. This does not allow patients to experience the reassurance of a deep breath. This impediment to patient acceptance can often be overcome by instructing the patients to raise a hand near the mouth and exhale forcefully. The tactile appreciation of the deep breath seems to provide reassurance.

If a neurologic complication is noted after an operation performed with spinal anesthesia, it is useful to obtain neurologic consultation early, so that ideally an unbiased consultant can examine the patient and determine whether the "new" neurologic finding was preexistent, related to a peripheral neuropathy, or, more rarely, potentially related to the spinal anesthetic. The latency in electromyographic alterations associated with denervation due to neurologic injury takes time to develop in the lower extremities (14-21 days). Therefore, one should obtain electromyography studies early and serially after a potential spinal-related lesion. In this manner it is possible to document whether the lesion was preexisting or give evidence that it is a peripheral rather than central lesion.

Probably more important than any single factor for the success of spinal anesthesia in the day-to-day use of anesthesia is that it must be time-efficient. It cannot add measurably to the surgical day if nurses and surgeons are to be coadvocates of the technique. Thus, one should plan ahead to maximize time efficiency. Often overlooked is that the patient preparation for surgery can begin almost as soon as the block is administered if patient sedation is at an appropriate level.

EPIDURAL AND CAUDAL ANESTHESIA

Epidural Technique

The technique of epidural anesthesia relies on the same four "Ps" as does spinal anesthesia, with minor modifications.

Preparation

In addition to patient preparation, selection of epidural equipment is essential. One must decide on a continuous or single-shot technique. This is the principal determinant of needle selection. If a single-shot epidural technique is chosen, a Crawford needle is appropriate; if a continuous catheter technique is indicated, either a Tuohy or another needle with a lateral facing opening is chosen (Fig. 42-18) . A method of identifying the epidural space also must be chosen, with most using a loss-of-resistance technique. If a loss-of-resistance technique is utilized, an additional decision on type of syringe (glass versus plastic, Luer-lok versus friction hub) is required. The theoretic ideal is the Luer-lok, finely ground glass syringe because it minimizes the chance of misidentification of the epidural space. Once again, most disposable equipment can be customized to an individual's needs if the advantages of reusable equipment are not available.

Position

The patient positions necessary for epidural puncture are the same as those for spinal anesthesia, with the exception of the prone position for the caudal approach. Once again, inadequate positioning of the patient will negate otherwise meticulous technique and should be prevented. Limitation of block spread (height) is not clinically predictable with position alterations during epidural anesthesia because gravity and solution baricity are not intimately related to block spread. In spite of this, Seow et al [122A] have demonstrated slightly faster block onset times in patients' dependent body regions when the lateral decubitus position was utilized for epidural block.

Three positions are available for caudal anesthesia, with the prone position most often chosen in adults, the lateral decubitus position in children, and the knee-chest position infrequently used. The lateral decubitus position is utilized in children because it is easier to maintain a patent airway in this position than in the prone position, and the landmarks are more easily palpable than in adults (Ch. 44) . This consideration is valuable because caudal anesthesia is often combined with general anesthesia in pediatric patients either to decrease the amount of volatile agent intraoperatively

or to provide postoperative analgesia. In contrast, a caudal block is often administered during preoperative sedation in adults and when the prone position is applicable. When placing a patient in the prone position, a pillow should be inserted beneath the iliac crests to rotate the pelvis and make cannulation of the caudal canal easier. An additional help is to spread the lower extremities about 20 degrees with the heels rotated laterally, which minimizes gluteal muscle contraction and eases needle insertion (Fig. 42-19) .

Projection and Puncture

Epidural technique requires placement of the needle tip into the ligamentum flavum for both loss-of-resistance and hanging drop methods. Placing the needle (with stylet) into the ligamentum flavum before attaching the syringe or placing solution into the needle hub allows an improved appreciation of epidural anatomy for the operator. If the needle is merely inserted into the supraspinous ligament and then either loss-of-resistance or hanging drop insertion is begun, an increased chance of false release seems likely.

When a lumbar approach is used, the depth from skin to ligamentum flavum commonly approaches 4 cm, with most (80%) patients between 3.5 and 6 cm. In this region the ligamentum flavum is 5 to 6 mm thick in the midline, thus requiring needle control if unintentional dural puncture is to be prevented. When a thoracic approach is chosen, control is of equal or greater importance because injury to the spinal cord is possible if the needle is advanced too far. Theoretically, the increased angle of needle insertion in the thoracic region may provide an element of safety because the more acute angle necessary to gain epidural cannulation provides some margin of safety (Fig. 42-20) . Clinically, thoracic epidural anesthetics do not appear associated with an increased

Figure 42-18 Epidural needle with catheter assortment. (A) A 19-gauge reusable Crawford epidural needle. (B) A 19-gauge disposable Tuohy needle. (C) Single-end-hole epidural catheter. (D) Closedtip, multiple-side-hole catheter. (E) Spring-wire reinforced polymer-coated epidural catheter.

incidence of neurologic injury because those choosing to use the technique are most often anesthesiologists with considerable experience with lumbar epidural anesthesia. [123] In any event, significant caution about performing thoracic epidural techniques in adult patients receiving general anesthesia is warranted because these patients are unable to provide feedback to the operator about neural stimulation during needle insertion.

Figure 42-19 Prone position for caudal technique. Pillow used under anterior iliac crests to rotate pelvis, legs spread 20 degrees to ease identification of sacral hiatus and heels rotated laterally to relax gluteal musculature.

The preferred method of carrying out the loss-of-resistance technique involves inserting the needle to the ligamentum flavum and then attaching a 3- to 5-mL glass syringe filled with 2 mL saline and a small (0.25-mL) air bubble. The needle is grasped with the nondominant hand

Figure 42-20 (A) Lumbar and thoracic epidural technique. The increased angle of needle insertion during thoracic epidural cannulation may provide a slightly longer distance of "needle travel" prior to entering the subarachnoid space (B), in contrast to lumbar epidural cannulation (C), where the distance traveled is modified by more perpendicular angle of needle insertion.

and pulled toward the epidural space, while the dominant hand (thumb) applies constant steady pressure on the syringe plunger, compressing the air bubble. When the epidural space is entered, the pressure applied to the syringe plunger will allow the solution to flow without resistance into the epidural space (Plate 7A).

An alternative, although with a less precise end point, is the technique of hanging-drop identification of entry into the epidural space. Once the needle is placed into the ligamentum flavum, a drop of solution is placed within the hub of the needle. When the needle is advanced into the epidural space the solution should be "sucked in" (Plate 7B). The theory behind this maneuver has been attributed to a subatmospheric pressure in the epidural space. The subatmospheric pressure has been related to the expansion of the epidural space as the needle pushes the dura away from ligamentum flavum. [124] The negative intrathoracic pressure may influence the pressure in the epidural space in the thoracic region.

Regardless of the method selected for needle insertion, when one chooses to cannulate the epidural space with a catheter success may be increased by advancing the needle 1 to 2 mm once the space is identified. Additionally, the incidence of unintentional intravenous cannulation with an epidural catheter may be lessened by injecting air or solution prior to threading the catheter. [125] [126] Unless radiographic guidance is used for some special reason, epidural catheters should be inserted only 2 to 3 cm into the epidural space for surgical patients or obstetric patients needing rapid onset of analgesia. [127] Threading more catheter may increase the likelihood of catheter malposition. If malposition does occur, data suggest that one of the more common sites of misposition is entry of the catheter into the anterior epidural space. [128] Additionally, in obstetric patients it appears that catheters should be inserted between 4 and 6 cm to optimize efficacy and prevent unintentional movement of the catheters during prolonged labor analgesia. [129] [130] When choosing a catheter either multiport (three lateral ports) or single-end-hole (uniport or distal port) catheters are available. Choice is practically up to individual clinicians, although it has been shown in laboring patients that multiport catheters reduce the incidence of inadequate analgesia compared to uniport catheters. [131]

In spite of an adequately positioned catheter during first use of local anesthetic, each subsequent injection should be preceded by aspiration and an epidural test dose because catheter migration into vessels and subarachnoid or subdural spaces does occur. In the event that the epidural catheter hub becomes disconnected from the epidural catheter, many in the past have considered the catheter unusable. It appears that the catheter can be reused if strict reconnection criteria are followed. [133]

Caudal Technique

Caudal anesthesia requires identification of the sacral hiatus. The sacrococcygeal ligament (an extension of ligamentum flavum) overlying the sacral hiatus lies between the sacral cornu. To facilitate locating the cornu, the posterior superior iliac spines should be located and, by using the line between them as one side of an equilateral triangle, the location of the sacral hiatus approximated (Fig. 42-21) . Once

Figure 42-21 Caudal technique. (A) Palpating fingers locate the sacral cornua by using equilateral triangle (shown in Fig. 42-6). (B) Needle insertion is carried out by insertion and withdrawal in stepwise fashion ("1-2-3-insertion"), until needle can be advanced into the caudal canal and solution can be injected easily (without creation of a subcutaneous "lump" of fluid).

the sacral hiatus is identified, the index and middle finger of the palpating hand are placed on the sacral cornu and the caudal needle is inserted at an angle of approximately 45 degrees to the sacrum. While advancing the needle, a decrease in resistance to needle insertion should be appreciated as the needle enters the caudal canal. The needle is advanced until bone (the dorsal aspect of the ventral plate of the sacrum) is contacted, and then slightly withdrawn, and the needle redirected so that the angle of insertion relative to the skin surface is decreased. In males this angle is almost parallel to the coronal plane; in females a slightly steeper angle (15 degrees) is necessary. During redirection of the needle and once loss of resistance is again encountered, the needle is advanced approximately 1 to 2 cm into the caudal canal. Further advance is not attempted because dural puncture and unintentional intravascular cannulation become more likely. One method of increasing the likelihood of correct caudal needle placement is to inject 5 mL of saline rapidly through the caudal needle while palpating the skin overlying the sacrum. If no midline "bulge" is detected, the needle is probably correctly positioned. In contrast, if a midline bulge is detected during saline injection, the needle is incorrectly positioned.

After ensuring correct needle position and prior to injection of the therapeutic dose of caudal anesthetic, aspiration and a test dose should be administered because as in lumbar epidural anesthesia, a vein or the subarachnoid space can be entered unintentionally.

Pharmacology

Useful Drugs

Successful choice of drug for epidural anesthesia (Ch. 13) requires an understanding of the local anesthetic potency and duration as well as estimation of surgical requirements and duration and postoperative analgesia requirements. As with any regional anesthetic the surgeon, anesthesiologist, procedure, and anesthetic technique must all be included in the drug choice equation.

Drugs available for epidural use can be categorized into short-, intermediate-, and long-acting local anesthetics, and with the addition of epinephrine to these agents surgical anesthesia ranging from 45 to 240 minutes is possible (Table 42-8) . Chloroprocaine, an ester local anesthetic, is a short-acting agent that was associated with neurotoxicity (adhesive arachnoiditis) when unintentionally injected in large volumes subarachnoid prior to a formulation change. [133] [134] Since 1985, reduced bisulfate concentrations have been available; since 1987 bisulfate-free 2-chloroprocaine has been available; and since 1996 preservative-free 2-chloroprocaine has been available. Since these formulation changes there have not been reports of neurotoxicity attributable to 2-chloroprocaine. In the era of ever-increasing numbers of surgical outpatients, combining 2-chloroprocaine and a catheter technique allows an efficient matching of surgical procedure and duration of epidural analgesia and enables patients to spend a minimal recovery time in the facility. It is available in 2 and 3 percent concentrations, with the latter preferable for surgical anesthesia and the former for techniques not requiring muscle relaxation.

There is evidence that back pain developing after larger volumes (>25 mL) of 2-chloroprocaine was related to the EDTA used as a preservative in the chloroprocaine. [135] It remains to be seen whether the preservative-free chloroprocaine will be associated with back pain in larger doses.

Lidocaine is the prototypical amide local anesthetic and is used in 1.5 to 2 percent concentrations epidurally. Mepivacaine is similar to lidocaine in the concentrations necessary for epidural anesthesia and lasts 15 to 30 minutes longer. Epinephrine significantly prolongs the duration of surgical anesthesia, approximately 50 percent, with both lidocaine and mepivacaine. [101] Another additive to these drugs that may influence clinical use is fentanyl in the intermediate-acting amide epidural drug. When fentanyl was added to mepivacaine, it accelerated the onset of analgesia and enhanced the analgesic effect during epidural anesthesia. [136] One technique receiving more attention to minimize length of an epidural motor block once surgery is completed is the use of saline in 15 to 30 mL volumes through the epidural catheter before it is removed. [137]

Bupivacaine is the most widely used long-acting local anesthetic; it is used in 0.5 and 0.75 percent concentrations for surgical anesthesia. Analgesic techniques can be performed with concentrations from 0.125 to 0.25 percent. Its duration of action is less consistently prolonged by addition of epinephrine, although up to 240 minutes of surgical anesthesia can be obtained when epinephrine is added. In 1983, the FDA stated that 0.75 percent bupivacaine was no longer recommended in obstetric anesthesia, as a result of a perception that systemic toxicity with that concentration resulted in more difficult resuscitations than occurred with the lower concentrations. The evidence for this action remains

TABLE 42-8 -- Comparative Onset Times and Analgesic Durations of Local Anesthetics Administered Epidurally in 20- to 30-ml Volumes

DRUG	CONCN.(%)	ONSET (MIN)	DURATION (MIN)	
			PLAIN	1: 200,000 EPINEPHRINE
2-Chloroprocaine	3	10-15	45-60	60-90
Lidocaine	2	15	80-120	120-180
Mepivacaine	2	15	90-140	140-200
Bupivacaine	0.5-0.75	20	165-225	180-240
Etidocaine	1	15	120-200	150-225

Data from Cousins and Bromage [173] and other sources

controversial, although it does appear that bupivacaine and etidocaine are more likely to impair myocardial performance and conduction than other local anesthetics when systemic toxicity occurs. [138] [139]

Etidocaine is an infrequently used epidural anesthetic principally because of the perception, and some data, that motor block is more profound than sensory block with the drug. [140] The reason for this may be that etidocaine is less effective than bupivacaine in producing small fiber blockade. [141]

Another amide, ropivacaine, is likely to become another useful agent for epidural anesthesia. It has an anesthetic effect quite similar to that of bupivacaine, although its central nervous system-cardiovascular toxicity profile may provide an increased safety margin. [142] It appears to produce less motor block and has a slightly shorter duration of action than bupivacaine. [143] Its place in regional anesthesia is believed by many to be best suited to obstetric anesthesia and postoperative infusion techniques.

Additives

As for spinal anesthetic drugs, some advocate combining agents with local anesthetics either to make epidural anesthesia last longer, to improve the quality of blockade, or to accelerate onset of block. Epinephrine will increase the duration of useful anesthesia with all the agents, though the proportional effect is greatest with lidocaine, mepivacaine, and 2-chloroprocaine and shows a lesser effect with bupivacaine and etidocaine (see Table 42-8). Phenylephrine has been used in epidural anesthesia less widely than in spinal anesthesia, perhaps because it does not reduce peak blood levels of local anesthetic as effectively as epinephrine during epidural use. [144]

Carbonation of the local anesthetic solution has been suggested as a means of increasing both speed of onset and quality of block by producing more rapid intraneural diffusion and more rapid penetration of connective tissue surrounding the nerve trunk. [145] [146] There are data suggesting that there are no clinical advantages of the carbonated solutions, [147] and some disadvantages may occur more rapidly because peak blood levels of the drug are higher after carbonation of the local anesthetic and blood pressures decreases (Ch. 13) . [148] [149]

The addition of bicarbonate has also been suggested as a means of increasing the pH of local anesthetic solution, thus increasing the concentration of nonionized free base, which will theoretically increase the rate of diffusion of the drug and speed onset of block. Clinically, the addition of 1 mEq of sodium bicarbonate to each 10 mL of commercially prepared 1.5 percent lidocaine solution produces a significantly faster onset of anesthesia and more rapid spread of sensory block. [150] The clinical applicability of this modification should be considered individually on its merits by each institutions' anesthesia group.

One other alteration of drugs for epidural use involves combining long- and short-acting drugs, theoretically to gain the benefits of each. This practice does not seem necessary or prudent because familiarity with the local anesthetics and additives available allows a spectrum of block lengths to be produced. Further, the purported advantage of faster onset with the combinations of local anesthetics seems clinically inconsequential.

Complications

Intravascular Injection

Epidural anesthesia has the potential to produce local anesthetic systemic toxicity (Ch. 13) , primarily through the unintentional administration of drug into an epidural vein. Considerable research has been undertaken to define the ideal test dose for continuous epidural catheter use. The use of test doses should minimize unintentional intravascular injections, although there are concepts in treating a local anesthetic-induced systemic toxicity reaction that all anesthesiologists should understand.

The toxic effects of local anesthetics primarily affect the central nervous and cardiovascular systems, with the central nervous system (CNS) affected at lower blood levels. For example, four to seven times the dose of local anesthetic necessary to produce convulsions in dogs is required to produce cardiovascular collapse. [151] The CNS stimulation is a result of local anesthetic-induced inhibition of the CNS. The initial excitatory phase of a reaction is due to selective inhibition of inhibitory neurons in the cerebral cortex, thus allowing facilitatory neurons to discharge in an unopposed fashion. [152] Once blood levels increase high enough, both inhibitory and facilitatory pathways are inhibited, leading to CNS depression.

Initially, potential for local anesthetic-induced toxicity, both CNS and cardiovascular, was thought to parallel anesthetic potency. [153] [154] Information suggests that bupivacaine and etidocaine may be proportionally more cardiotoxic than their anesthetic potency predicts. [155] [156] This relative increase in cardiotoxicity appears to result from more potent electrophysiologic effects of the long-acting amides due to their fast-in-slow-out sodium channel blockade. Ropivacaine, another long-acting amide local anesthetic, has a CNS-to-cardiotoxicity ratio intermediate between lidocaine and buipivacaine. [157] The clinical importance of these observations about toxicity must be balanced against clinical studies showing limited cardiovascular depression in patients undergoing bupivacaine-induced seizures during regional anesthetics. [158]

If signs of CNS toxicity or frank convulsions occur, a number of steps must be followed if adverse outcomes are to be prevented (Ch. 13) . Early in local anesthetic-induced seizures hypoxemia, hypercarbia, and acidosis develop rapidly, and symptomatic treatment of the toxicity must involve treatment of these factors. Oxygen should be given by bag and mask, and tracheal intubation is not mandated unless ventilation is ineffective. [159] The next step in therapy remains controversial, with either succinylcholine or anticonvulsant administered. Succinylcholine is often recommended because the local anesthetic-induced seizures are usually short-lived, and the muscle relaxation obtained facilitates ventilation and decreases the magnitude of metabolic acidosis. [159] Nevertheless, it does not decrease cerebral metabolism; thus CNS oxygen requirements remain increased. Others suggest that diazepam is effective in controlling local anesthetic-induced seizures, although 2 to 3 minutes is required to control seizures once administered. [160] [161]

The most effective method of treating toxic reactions is prevention. Administration of excessive doses of local anesthetics should be prevented, and test doses of local anesthetics should be used prior to the injection of therapeutic

doses. If a toxic reaction does occur, it is imperative that oxygen, a method of administering it, succinylcholine, and anticonvulsant drugs are immediately available.

Subarachnoid Injection

The adverse effects of unintentionally administering an epidural dose of local anesthetic into the spinal fluid are highlighted by the neurologic changes that followed subarachnoid injection of 2-chloroprocaine. However, most subarachnoid injections of epidural local anesthetics are less dramatic; rather, the issue is how one should treat the cardiopulmonary effects resulting from such an injection. As in any neuraxial block that reaches high levels, arterial blood pressure and heart rate should be supported. The Trendelenberg position should be instituted to maximize venous return. Intravenous atropine and ephedrine are often effective and will provide the time to administer a more potent catecholamine, if needed. Additionally, ventilation should be supported, and if the entire dose (20-25 mL) of local anesthetic has been administered into the CSF, tracheal intubation and mechanical ventilation are indicated because patients may require approximately 1 to 2 hours to maintain adequate spontaneous ventilation consistently. After a large dose of local anesthetic into the CSF, patients will also develop dilated pupils, which may seem to indicate CNS injury if this phenomenon is not recognized for what it is. The pupils will return to baseline state as the high block recedes. Fortuitously, the necessity for sedation during the period of tracheal intubation and mechanical ventilation is minimal. These patients generally do not recall such events. [162]

When an epidural is performed and the higher-than-expected block develops only after a delay of 15 to 30 minutes, subdural placement of local anesthetic must be considered. Treatment is once again symptomatic; the most difficult aspect is recognizing the possibility of a subdural injection.

Neurologic Injury

With the exception of the publicity surrounding the 2-chloroprocaine-induced adhesive arachnoiditis, epidural anesthesia has not been linked with neurologic injury more frequently than other anesthetics, regional or general. [102] [104] No particular local anesthetic, needle versus catheter technique, addition or omission of epinephrine, or location of epidural puncture seems to be associated with an increased incidence of neurologic injury. In spite of this information, neurologic injury is often feared and epidural anesthesia avoided in patients in whom antiplatelet drugs or other anticoagulants have been used preoperatively. Is this justified? There are no data in patients taking antiplatelet drugs, such as aspirin, that there is an increased incidence of neurologic injury secondary to epidural bleeding (hematoma) when epidural anesthesia is utilized. [163] It is doubtful that a perceived lack of data indicates that the problem has been overlooked, because epidural anesthesia is frequently used in patients undergoing orthopedic procedures, in whom aspirin use is widespread. Nevertheless, there are isolated case reports of neurologic injury after both epidural and spinal anesthesia in patients in whom antiplatelet drugs were used. It may be significant that in these case reports the initial neuraxial technique was abandoned after technical difficulties with needle placement. [164] [165]

The use of epidural anesthesia for patients receiving anticoagulants is less clear-cut because epidural anesthesia is often avoided in these patients. There are data from Odoom and Sih, [167] who used continuous epidural anesthesia in 1,000 vascular operations, in patients receiving preoperative oral anticoagulants without problem. The acceptable magnitude of preoperative anticoagulation and risk-benefit ratio of performing epidural anesthesia must remain undetermined at this time. Once again, despite lacking data, the use of epidural techniques in patients receiving subcutaneous hep-arin therapy is probably acceptable if the block can be performed atraumatically, although the risk-benefit ratio must be determined for each patient. Some speculate that proof of minimal systemic effect from the subcutaneous heparin (normal PTT) is necessary prior to neuraxial block. [167]

There is growing consensus that when low-molecular-weight heparin--enoxaparin (Lovenox)--is used perioperatively, neuraxial block techniques need to be managed differently. It is clear that there is an increased risk of neuraxial bleeding when enoxaparin and neuraxial techniques are combined if the following recommendations are not followed [168] : (1) neuraxial block should be delayed for at least 10 to 12 hours after the last dose of enoxaparin for patients receiving the drug preoperatively; (2) postoperative treatment with enoxaparin should be delayed at least 12 hours after completion of the surgical procedure; and (3) removal of epidural and spinal catheters used for postoperative analgesia should occur 10 to 12 hours after the last dose, with subsequent dosing delayed for at least 2 hours. [169] [170]

It does seem that the issue of intraoperative anticoagulation after epidural catheter insertion is as settled as clinical data allow. There are now approximately 5,000 patients who have undergone epidural anesthesia for vascular surgery, with intraoperative heparinization, without a neurologic injury attributable to epidural bleeding. [166] [171] [172] In spite of minimal problems with epidural anesthesia and neurologic dysfunction related to anticoagulation, if a patient has neurologic symptoms consistent with neuraxial mass after regional block, immediate neurosurgical consultation is indicated because time is of the essence if permanent sequelae are to be prevented. Furthermore, if the patient appears to be at increased risk for neuraxial bleeding and yet the neuraxial technique remains indicated, it may be prudent to use a shorter-acting epidural local anesthetic even if it means reinjecting more frequently so that the block will resolve as rapidly as possible following the surgical procedure.

Clinical Pearls

The adage, "Success covers a multitude of blunders"
is certainly appropriate for use of epidural anesthesia. To be successful one must perform the technique often enough to be technically facile. To increase the use of the technique, a number of practical observations may be helpful.

George Bernard Shaw (1856-1950).

If catheters can be avoided during epidural anesthesia (e.g., by selecting the appropriate local anesthetic), a potential source of difficulties with the technique can be made moot. It is important to allow the block enough "soak time" prior to the surgical procedure; this can be facilitated if the block is carried out in an induction room separate from the operating room. One must recognize that there appears to be a plateau effect in dosing epidural local anesthetics. That is, once some quantity of the local anesthetic has been injected, additional local anesthetic does not significantly increase the block height but rather may make the block more dense (i.e., improve quality). [173] To be successful with the technique, one should be prepared at all times to treat complications associated with epidural anesthesia: airway equipment and drugs, especially oxygen and resuscitation, must be immediately available.

CLINICAL CONTROVERSY AND NEURAXIAL BLOCKS

In spite of the many years neuraxial blocks have been used, there remain a number of controversies about the appropriate use of these blocks. Some continue to suggest that spinal anesthesia is inappropriate for outpatients because of the occurrence of postdural puncture headache, yet there are data that the occasional headache can be successfully treated even in the outpatient [174] and considerable other data supporting the use of the technique in outpatients. [175] Similarly, spinal anesthesia seems well suited to use for cesarean section because of the short interval from injection to surgical anesthesia. Once again, if epidural blood patch therapy is utilized in a timely fashion, the increased incidence of headache in this patient population should not necessarily limit the technique's use for cesarean section. An outgrowth of the management of postdural puncture headache was the development of the "micro" or small-bore spinal catheter. [176] This technique's appropriate place in anesthesia practice has not been established because there must be a point at which the risk-benefit ratio of a decreased incidence of spinal headache versus difficulties in technique with the "micro" catheter becomes unacceptable. These catheters (i.e., 27-gauge or smaller) are not available because the FDA withdrew the 510k approval in 1992 following concerns over possible association with development of cauda equina syndrome. [7]

One reason that epidural anesthesia is not used as widely as may be indicated is that controversies surrounding its use create indecision. One of the most controversial adjuncts to epidural anesthesia has been the use of the epinephrine-containing test dose. [177] The original description used 15 mug of epinephrine in 3 mL of local anesthetic to indicate intravascular placement of an epidural catheter or needle. Most controversy surrounds the use of epinephrine in obstetric patients, in whom uterine blood flow may be decreased by the intravascular injection, thereby putting the fetus at risk. Some experimental data suggest that epinephrine may place the fetus at risk [178] ; nevertheless, no clinical data suggest that any fetus has been harmed by a test-dose use, and many anesthesiologists believe epinephrine-containing epidural test doses are useful in obstetric anesthesia. [179] Patients receiving beta-adrenergic blockers also confound the use of a test dose. In these patients, heart rate may not change after intravascular injection of 15 mug of epinephrine; rather, heart rate may decrease as blood pressure increases. [180] The use of epidural anesthesia during general anesthesia may also confound interpretation of the epinephrine test dose. [181] Because there is no fail-safe method of guaranteeing an extravascular location of an epidural local anesthetic, prevention of systemic toxicity should also involve aspiration of the catheter and incremental dosing of the local anesthetic. It has been shown that onset of block, quality of block, and block height are unaffected by administration of the epidural drug in 5-mL fractions. [182]

Related to systemic toxicity with neuraxial blocks is information about benzodiazepines. In spite of a widely held belief that benzodiazepines should be used with regional anesthesia to minimize systemic toxicity by elevating seizure threshold, available data indicate that this concept requires rethinking. [183] It has been shown that resuscitation may be more difficult after cardiovascular collapse due to bupivacaine when diazepam is used as a premedication. It has also been demonstrated that animals premedicated with benzodiazepines may not evidence seizures prior to cardiovascular collapse. [183] Thus, it may be that the benzodiazepines cover up one of the early signs of systemic toxicity, thus potentially delaying definitive therapy.

The clinical arena has not been immune from controversy about epidural anesthesia. Yeager et al demonstrated a significant decrease in morbidity and mortality in high-risk patients undergoing epidural anesthesia and postoperative analgesia, compared to patients receiving high-dose narcotic anesthesia and parenteral narcotic analgesia. [11] This information provided impetus to many investigators to design studies to answer whether the anesthetic technique, especially postoperative analgesic technique, may be able to modify patient outcome. In the case of Yeager et al, it remains unclear whether their data support the benefits of the epidural techniques or condemn the use of high-dose narcotics and postoperative mechanical ventilation. Tuman et al [12] addressed many of the criticisms directed at Yeager et al's work and documented fewer complications in vascular surgery patients when epidural analgesia was used in an integrated perioperative regimen. Christopherson and Rose et al have begun to link the analgesic regimens with possi-ble mechanisms of improved patient outcomes. They iden-tified that using epidural anesthesia and analgesia into the postoperative period limit the adverse effects of surgery on the fibrinolytic system. [13] Further investigations into the appropriate place of neuraxial blocks in anesthetic practice will have to be as concerned with the issue of cost in relation to outcome as with risk in relation to benefit to the patient.

Another development in neuraxial block technique that demands our attention is the development of effective methods of combining epidural and spinal anesthesia via a single-needle system). [184] [185] [186] [187] These methods use epidural needle placement, followed by insertion of the spinal needle through either a side lumen on the epidural needle, or directly via the epidural needle lumen (Fig. 42-22) (Figure Not Available) . The combined technique allows flexibility in a number of clinical settings; some of the possible combinations and advantages are listed in Table 42-9 .

Figure 42-22 (Figure Not Available) An illustration highlighting the concept used in the Coombs epidural-spinal needle combination, which allows placement of a 20-gauge epidural catheter via a modified Hustead-Tuohy needle, as well as placement of a 27-gauge spinal needle (short-cutting or pencil point [conical] bevel), via an additional lumen. *(With permission of Neurodelivery Technology, Inc., Lebanon, NH)*

TABLE 42-9 -- Possible Clinical Advantages of Using Combined Spinal-Epidural Anesthesia

Initial epidural needle placement allows the spinal needle to be guided near the dura, minimizing the number of times the spinal needle tip impacts bone and potentially becomes dulled.
Lower local anesthetic blood levels are possible when an initial spinal anesthetic is used for operation, and the epidural catheter is used for analgesia.
More rapid onset of spinal block allows the operative procedure to begin earlier, while the epidural catheter allows effective analgesia to be provided.
During labor, an opioid may be injected via a small spinal needle and then epidural analgesia added if needed.
Lower initial mass of drug may be used during spinal anesthesia, thereby minimizing the physiologic perturbations, while the epidural catheter is available to provide a higher level if needed.

References

1. Corning JL: Spinal anesthesia and local medications of the cord. NY Med J 42:483-5, 1885.

2. Morton AW: The subarachnoid injection of cocaine for operations upon the upper part of the body. JAMA 39:1162, 1902.

3. Koster H: Spinal analgesia with special reference to its use in surgery of the head, neck and thorax. Am J Surg 5:554, 1928.

4. Kennedy F, Effron AS, Perry G: The grave spinal cord paralysis caused by spinal anesthesia. Surg Gynecol Obstet 91:385, 1950.

5. Cope RW: The Woolley and Roe case: Woolley and Roe versus the Ministry of Health and others. Anesthesia 9:247, 1954.

6. Hutter CDD: The Woolley and Roe case: A reassessment. Anaesthesia 45:859, 1990.

7. Benson JS: FDA Safety Alert: Cauda equina syndrome associated with the use of small-bore catheters in continuous spinal anesthesia. Food and Drug Administration, Rockville, MD, 1992.

8. Carpenter RL: Hyperbaric lidocaine spinal anesthesia: Do we need an alternative? [editorial]. Anesth Analg 81:1125-1128, 1995.

9. Pollock JE, Neal JM, Stephenson CA et al: Prospective study of the incidence of transient radicular irritation in patients undergoing spinal anesthesia. Anesthesiology 84:1361-1367, 1996.

10. Pflug AE, Murphy TM, Butler SH et al: The effects of postoperative peridural analgesia on pulmonary therapy and pulmonary complications. Anesthesiology 41:8, 1974.

11. Yeager MP, Glass DD, Neff RK et al: Epidural anesthesia and analgesia in high risk surgical patients. Anesthesiology 66:729, 1987.

12. Tuman KJ, McCarthy RJ, March RJ et al: Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 73:696, 1991.

13. Christopherson R, Beattie C, Frank SM et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Anesthesiology 79:422-434, 1993.

14. Mangano DT, Siliciano D, Hollenberg M et al: Postoperative myocardial ischemia: Therapeutic trials using intensive analgesia following surgery. Anesthesiology 76:342-353, 1992.

15. Jellish WS, Thalji Z, Stevenson K et al: A prospective randomized study comparing short- and intermediate-term perioperative outcomes variables after spinal or general anesthesia for lumbar disk and laminectomy surgery. Anesth Analg 83:559-564, 1996.

16. Greene NM: Perspectives in spinal anesthesia. Reg Anesth 7:55, 1982.

17. Hogan Q: Size of human lower thoracic and lumbosacral nerve roots. Anesthesiology 85:37, 1996.

18. Hogan QH, Prost R, Taylor ML et al: Magnetic resonance imaging of cerebrospinal fluid and the influence of body habitus and abdominal pressure. Anesthesiology 84:1341, 1996.

19. Parkinson D: Human spinal arachnoid septa, trabeculae, and "rogue strands." Am J Anat 192:498, 1991.

20. Hogan QH: Lumbar epidural anatomy: A new look by cryomicrotome section. Anesthesiology 75:767, 1991.

21. Igarashi T, Hirabayashi Y, Shimizu R et al: The lumbar extradural structure changes with increasing age. Br J Anaesth 78:149-152, 1997.

---

22. Saitoh K, Hirabayashi Y, Smimizu R et al: Extensive extradural spread in the elderly may not relate to decreased leakage through intervertebral foramina. Br J Anaesth 75:688-691, 1995.

23. Zarzur E: Anatomic studies of the human lumbar ligamentum flavum. Anesth Analg 63:499, 1984.

24. Santos DJ, Bridenbaugh PO, Heins S et al: Unilateral epidural analgesia for labor. Reg Anesth 10:41, 1985.

25. Nunn G, Mackinnon RPG: Two unilateral epidural blocks [letter]. Anesthesia 41:439, 1986.

26. Gallart L, Blanco D, Samso E et al: Clinical and radiologic evidence of the epidural plica mediana dorsalis. Anesth Analg 71:698, 1990.

27. Blomberg R: The dorsomedian connective tissue band in the lumbar epidural space of humans: An anatomic study using epiduroscopy in autopsy cases. Anesth Analg 65:747, 1986.

28. Savolaine ER, Pandya JB, Greenblatt SH et al: Anatomy of the human lumbar epidural space: New insights using CT-epiduroscopy. Anesthesiology 68:217, 1988.

29. Blomberg RG: The lumbar subdural extraarachnoid space of humans: An anatomical study using spinaloscopy in autopsy cases. Anesth Analg 66:177, 1987.

30. Blomberg RG: Fibrous structures in the subarachnoid space: A study with spinaloscopy in autopsy subjects. Anesth Analg 80:875-879, 1995.

31. Crighton IM, Barry BP, Hobbs GJ: A study of the anatomy of the caudal space using magnetic resonance imaging. Br J Anaesth 78:391-395, 1997.

32. Thompson JE: An anatomical and experimental study of sacral anaesthesia. Ann Surg 66:718, 1917.

33. Trotter M: Variations of the sacral canal: Their significance in the administration of caudal anesthesia. Anesth Analg 26:192, 1947.

34. Murphy TM: Spinal, epidural and caudal anesthesia. In Miller RD (ed): Anesthesia, 2nd ed. New York, Churchill Livingstone, 1986, p 1061.

35. Mackey DC: Physiologic effects of regional block. In Brown DL (ed): Regional Anesthesia and Analgesia. Philadelphia, WB Saunders, 1996, pp 397-422.

36. Greene NM: Physiology of Spinal Anesthesia, 3rd ed. Baltimore, Williams & Wilkins, 1981.

37. Kety SS, King BD, Horvath SM et al: The effects of an acute reduction in blood pressure by means of differential spinal sympathetic block on the cerebral circulation of hypertensive patients. J Clin Invest 29:403, 1950.

38. Kleinerman J, Sancetta SM, Hackel DB: Effects of high spinal anesthesia on cerebral circulation and metabolism in man. J Clin Invest 37:285, 1958.

39. Hackel DB, Sancetta S, Kleinerman J: Effect of hypotension due to spinal anesthesia on coronary blood flow and myocardial metabolism in man. Circulation 13:92, 1956.

39A. Sivarajan M, Amory DW, Lindbloom LE et al: Systemic and regional blood-flow changes during spinal anesthesia in the rhesus monkey. Anesthesiology 43:78, 1975.

40. Butterworth JF, Piccione W Jr, Berrizbeitia LD et al: Augmentation of venous return by adrenergic agonists during spinal anesthesia. Anesth Analg 65:612, 1986.

41. Defalque RJ: Compared effects of spinal and extradural anesthesia upon the blood pressure. Anesthesiology 23:627, 1962.

42. Egbert LD, Tamersoy K, Deas TC: Pulmonary function during spinal anesthesia: The mechanism of cough depression. Anesthesiology 22:882, 1961.

43. Sakura S, Saito Y, Kosaka Y: The effects of epidural anesthesia on ventilatory response to hypercapnia and hypoxia in elderly patients. Anesth Analg 82:306, 1996.

44. Yun E, Topulos GP, Body SC et al: Pulmonary function changes during epidural anesthesia for cesarean delivery. Anesth Analg 82:750, 1996.

45. Hogan Q, Amuzu J, Bosnjak ZJ et al: Hypoxia during epidural anesthesia results in apnea in rabbits. Reg Anesth 22:2S, 1997.

46. Shibata K, Taki Y, Futagami A et al: Epidural anesthesia modifies cardiovascular responses to severe hypoxia in dogs. Acta Anaesthesiol Scand 39:748-753, 1995.

47. Carpenter RL, Caplan RA, Brown DL et al: Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology 76:906, 1992.

48. Ward RJ, Kennedy WF, Bonica JJ et al: Experimental evaluation of atropine and vasopressors for the treatment of hypotension of high subarachnoid anesthesia. Anesth Analg 45:621, 1966.

49. Ramaioli F, De Amici D: Central antiemetic effect of atropine: Our personal experience [letter]. Can J Anaesth 43:1079, 1996.

50. Thompson GE: Pharmacology, physiology, and use of spinal and epidural anesthesia. Semin Anesth 2:24, 1983.

51. Greene NM, Bunker JP, Kerr WS et al: Hypotensive spinal anesthesia: Respiratory, metabolic, hepatic, renal and cerebral effects. Ann Surg 140:641, 1954.

52. Sutcliffe NP, Mostafa SM, Gannon J et al: The effect of epidural blockade on gastric intramucosal pH in the peri-operative period. Anaesthesia 51:37, 1996.

53. Suleiman MY, Passannante AN, Onder RL et al: Alteration of renal blood flow during epidural anesthesia in normal subjects. Anesth Analg 84:1076, 1997.

54. Walts LF, Kaufman RD, Moreland JR et al: Total hip arthroplasty: An investigation of factors related to postoperative urinary retention. Clin Orthop 194:280, 1985.

55. Cassuto J, Wallin G, Hogstrom S et al: Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. Anesth Analg 64:971, 1985.

56. McMahon D: Managing regional anesthesia equipment. Probl Anesth 1:592, 1987.

57. Moore DC, Bridenbaugh LD: Spinal (subarachnoid) block: A review of 11,574 cases. JAMA 195:907, 1966.

58. Ready LB, Cuplin S, Haschke RH et al: Spinal needle determinants of rate of transdural fluid leak. Anesth Analg 69:457, 1989.

59. Taylor JA: Lumbosacral subarachnoid tap. J Urol 43:561, 1940.

60. Covino BG, Scott DB: Handbook of Epidural Anesthesia and Analgesia. Orlando, Grune & Stratton, 1985.

61. Douglas MJ: Editorial: Neurotoxicity of lidocaine--does it exist? Can J Anaesth 42:181-185, 1995.

62. Lui S, Pollock JE, Mulroy MF et al: Comparison of 5% with dextrose, 1.5% with dextrose, and 1.5% dextrose-free lidocaine solutions for spinal anesthesia in human volunteers. Anesth Analg 81:697-702, 1995.

63. Hampl KF, Schneider MC, Pargger H, et al: A similar incidence of transient neurologic symptoms after spinal anesthesia with 2% and 5% lidocaine. Anesth Analg 1996; 83:1051.

64. Moore DC, Chadwick HS, Ready LB: Epinephrine prolongs lidocaine spinal: Pain in the operative site the most accurate method of determining local anesthetic duration. Anesthesiology 67:416, 1987.

65. Smith HS, Carpenter RL, Bridenbaugh LD: Failure rate of tetracaine spinal anesthesia with and without epinephrine. Anesthesiology 65:A193, 1986.

66. Abouleish EI: Epinephrine improves the quality of spinal anesthesia of bupivacaine. Anesthesiology 65:A375, 1986.

67. Kozody R, Swartz J, Palahniuk RJ et al: Spinal cord blood flow following subarachnoid lidocaine. Can J Anaesth 32:472, 1985.

68. Caldwell C, Nielsen C, Baltz T et al: Comparison of high-dose epinephrine and phenylephrine in spinal anesthesia with tetracaine. Anesthesiology 62:804, 1985.

69. Kozody R, Palahniuk RJ, Cumming MO: Spinal cord blood flow following subarachnoid tetracaine. Can J Anaesth 32:23, 1985.

70. Logan MR, McClure JH, Wildsmith JAW: Plain bupivacaine: An unpredictable spinal anaesthetic agent. Br J Anaesth 58:292, 1986.

71. Tuominen M: Bupivacaine spinal anaesthesia. Acta Anaesthiol Scand 35:1, 1991.

72. Moore DC: Spinal anesthesia: Bupivacaine compared with tetracaine. Anesth Analg 59:743, 1980.

73. Kozody R, Ong B, Palahniuk RJ et al: Subarachnoid bupivacaine decreases spinal cord blood flow in dogs. Can J Anaesth 32:216, 1985.

74. Kozody R, Palahniuk RJ, Wade JG et al: The effect of subarachnoid epinephrine and phenylephrine on spinal cord blood flow. Can J Anaesth 31:503, 1984.

75. Bedder MD, Kozody R, Palahniuk RJ et al: Clonidine prolongs tetracaine spinal anesthesia. Can J Anaesth 33:591, 1986.

76. Eisenach JC, De Kock M, Klimscha W: Alpha-2-adrenergic agonists for regional anesthesia: A clinical review of clonidine (1984-1995). Anesthesiology 85:655-674, 1996.

77. Xu Z, Tong C, Eisenach JC: Acetylcholine stimulates the release of nitric oxide from rat spinal cord. Anesthesiology 85:107-111, 1996.

78. Greene NM: Uptake and elimination of local anesthetics during spinal anesthesia. Anesth Analg 62:1013, 1983.

79. Chambers WA, Littlewood DG, Logan MR et al: Effect of added epinephrine on spinal anesthesia with lidocaine. Anesth Analg 60:417, 1981.

80. Chambers WA, Littlewood DG, Scott DB: Spinal anesthesia with hyperbaric bupivacaine: Effect of added vasoconstrictors. Anesth Analg 61:49, 1982.

81. Spivey DL: Epinephrine does not prolong lidocaine spinal anesthesia in term parturients. Anesth Analg 64:468, 1985.

82. Leicht CH, Carlson SA: Prolongation of lidocaine spinal anesthesia with epinephrine and phenylephrine. Anesth Analg 65:365, 1986.

83. Concepcion M, Maddi R, Francis D et al: Vasoconstrictors in spinal anesthesia with tetracaine--a comparison of epinephrine and phenylephrine. Anesth Analg 63:134, 1984.

84. Vaida GT, Moss P, Capan LM et al: Prolongation of lidocaine spinal anesthesia with phenylephrine. Anesth Analg 65:781, 1986.

85. Feldman HS, Covino BG: Effect of vasoconstrictor agents on the duration of action of intrathecal tetracaine, bupivacaine and lidocaine in the dog. Reg Anesth 10:133, 1985.

86. Atchison SR, Wedel DJ, Wilson PR et al: Effect of injection rate on level and duration of hypobaric spinal anesthesia. Anesthesiology 67:A255, 1987.

87. Steinstra R, van Poorten JF: The temperature of bupivacaine 0.5% affects the sensory level of spinal anesthesia. Anesth Analg 67:272, 1988.

88. Steinstra R, Gielen M, van Poorten F et al: Spinal anesthesia with plain bupivacaine 0.5%: Regression of sensory and motor blockade with different temperatures of the anesthetic solution. Anesth Analg 69:593, 1989.

89. McKeown DW, Stewart K, Littlewood DG et al: Spinal anesthesia with plain solutions of lidocaine (2%) and bupivacaine (0.5%). Reg Anesth 11:68, 1986.

90. Greene NM: Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 64:715, 1985.

91. Cameron AE, Arnold RW, Ghoris MW et al: Spinal analgesia using bupivacaine 0.5% plain: Variation in the extent of the block with patient age. Anaesthesia 36:318, 1981.

92. Pitkanen M, Haapaniemi L, Tuominen M et al: Influence of age on spinal anesthesia with isobaric 0.5% bupivacaine. Br J Anaesth 56:279, 1984.

93. Neigh JL, Kane PB, Smith TC: Effects of speed and direction of injection on the level and duration of spinal anesthesia. Anesth Analg 49:912, 1970.

94. McClure JH, Brown DT, Wildsmith JAW: Effect of injected volume and speed of injection on the spread of spinal anesthesia with isobaric amethocaine. Br J Anaesth 54:917, 1982.

95. Holman SJ, Robinson RA, Beardsley D et al: Hyperbaric dye solution distribution characteristics after pencil-point needle injection in a spinal cord model. Anesthesiology 86:966-973, 1997.

96. Urmey WF, Stanton J, Bassin P et al: The direction of the Whitacre needle aperture affects the extent and duration of isobaric spinal anesthesia. Anesth Analg 84:337-341, 1997.

97. Levy JH, Islas JA, Ghia JN et al: A retrospective study of the incidence and causes of failed spinal anesthetics in a university hospital. Anesth Analg 64:705, 1985.

98. Curatolo M, Orlando A, Zbinden AM et al: A multifactorial analysis to explain inadequate surgical analgesia after extradural block. Br J Anaesth 75:274-281, 1995.

99. Caplan RA, Ward RJ, Posner K et al: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

100. Rigler M, Drasner K, Krejcie TC et al: Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 72:275, 1991.

101. Marinacci AA: Neurologic aspects of complications of spinal anesthesia. Los Angeles Neurol Soc Bull 25:170, 1960.

102. Vandam LD, Dripps RD: A long-term follow-up of patients who received 10,098 spinal anesthetics. II: Incidence and analyses of minor sensory neurologic defects. Surgery 38:463, 1955.

103. Kane RE: Neurologic deficits following epidural or spinal anesthesia. Anesth Analg 60:150, 1981.

104. Bromage PR: Editorial--Neurologic complications of subarachnoid and epidural anaesthesia. Acta Anaesthesiol Scand 41:439-444, 1997.

105. Lybecker H, Djernes M, Schmidt JF: Postdural puncture headache (PDPH): Onset, duration, severity and associated symptoms. Acta Anaesthesiol Scand 39:605-612, 1995.

106. Denny N, Masters R, Pearson D et al: Postdural puncture headache after continuous spinal anesthesia. Anesth Analg 66:791, 1987.

107. Mihic DN: Postspinal headache and relationship of the needle bevel to longitudinal dural fibers. Reg Anesth 10:76, 1985.

108. Halpern S, Preston R: Postdural puncture headache and spinal needle design. Anesthesiology 81:1376-1383, 1994.

109. Jones RJ: The role of recumbancy in the prevention and treatment of postspinal headache. Anesth Analg 53:788, 1974.

110. Thornberry EA, Thomas TA: Posture and post-spinal headache: A controlled trial in 80 obstetric patients. Br J Anaesth 60:195, 1988.

111. Baumgarten RK: Should caffeine become the firstline treatment for postdural puncture headache? Anesth Analg 66:913, 1987.

112. Gormley JB: Treatment of postspinal headache. Anesthesiology 21:565, 1960.

113. DiGiovanni AJ, Dunbar BS: Epidural injections of autologous blood for post-lumbar puncture headache. Anesth Analg 49:268, 1970.

114. DiGiovanni AJ, Galbert MW, Wahle WM: Epidural injection of autologous blood for post-lumbar puncture headache. II: Additional clinical experiences and laboratory investigation. Anesth Analg 51:226, 1972.

115. Ostheimer GW, Palahniuk RJ, Shnider SM: Epidural blood patch for post-lumbar-puncture headache [letter]. Anesthesiology 41:307, 1974.

116. Szeinfeld M, Ihmeidan IH, Moser MM et al: Epidural blood patch: Evaluation of the volume of spread of blood injected into the epidural space. Anesthesiology 64:820, 1986.

117. Beards SC, Jackson A, Griffiths AG et al: Magnetic resonance imaging of extradural blood patches: Appearance from 30 min to 18 h. Br J Anaesth 71:182-188, 1993.

118. Brown EM, Elman DS: Postoperative backache. Anesth Analg 40:683, 1961.

119. Zornow MH, Scheller MS: Cardiac arrest during spinal anesthesia. II. Anesthesiology 68:970, 1988.

120. Mackey DC, Carpenter RL, Thompson GE et al: Bradycardia and asystole during spinal anesthesia: A report of three cases without morbidity. Anesthesiology 70:866, 1989.

121. Thompson KW: Fatalities from spinal anesthesia. Anesth Analg 13:75-79, 1934.

122. Wetstone DL, Wong KC: Sinus bradycardia and asystole during spinal anesthesia. Anesthesiology 41:87, 1974.

122A. Seow LT, Lips FJ, Cousins MJ: Effect of lateral position on epidural blockade for surgery. Anaesth Intensive Care 11:97,1973.

123. Giebler RM, Scherer RU, Peters J: Incidence of neurologic complications related to thoracic epidural catheterization. Anesthesiology 86:55-63, 1997.

124. Zarzur E: Genesis of "true" negative pressure in the lumbar epidural space: A new hypothesis. Anaesthesia 39:1101, 1984.

125. Philip BK: Effect of epidural air injection on catheter complications: Experience in obstetric patients. Reg Anesth 10:21, 1985.

126. Verniquet AJW: Vessel puncture with epidural catheters. Anaesthesia 35:660, 1980.

127. D'Angelo R, Berkebile BL, Gernacher JC: Prospective examination of epidural catheter insertion. Anesthesiology 84:88, 1996.

128. Asato F, Goto F: Radiographic findings of unilateral epidural block. Anesth Analg 83:519-522, 1996.

129. Hamilton CL, Riley ET, Cohen SE: Changes in the position of epidural catheters associated with patient movement. Anesthesiology 86:778, 1997.

130. Beilin Y, Bernstein HH, Zucker-Pinchoff B: The optimal distance that a multiorifice epidural catheter should be threaded into the epidural space. Anesth Analg 81:301, 1995.

131. D'Angelo R, Foss ML, Livesay CH: A comparison of multiport and uniport epidural catheters in laboring patients. Anesth Analg 84:1276, 1997.

132. Langevin PB, Gravenstein N, Langevin SO et al: Epidural catheter reconnection: Safe and unsafe practice. Anesthesiology 85:883, 1996.

133. Ravindran RS, Bond VK, Tasch MD et al: Prolonged neural blockade following regional anesthesia with 2-chloroprocaine. Anesth Analg 59:447, 1980.

134. Moore DC, Spierdijk J, vanKleef JD et al: Chloroprocaine neurotoxicity: Four additional cases. Anesth Analg 61:155, 1982.

135. Stevens RA, Urmey WF, Urquhart BL et al: Back pain after epidural anesthesia with chloroprocaine. Anesthesiology 78:492-497, 1993.

136. Kasaba T, Yoshikawa G, Seguchi T et al: Epidural fentanyl improves the onset and spread of epidural mepivacaine analgesia. Can J Anaesth 43:1211-1215, 1996.

137. DiFazio CA, Sitzman BT, Playfair PA et al: Reversal of dense lido-caine epidural block with epidural saline washout. Reg Anesth 22:4, 1997.

138. Lynch C: Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine. Anesth Analg 65:551, 1986.

139. Kasten GW: Amide local anesthetic alterations of effective refractory period temporal dispersion: Relationship to ventricular arrhythmias. Anesthesiology 65:61, 1986.

140. Moore DC, Bridenbaugh PO, Bridenbaugh LD et al: A double-blind study of bupivacaine and etidocaine for epidural (peridural) block. Anesth Analg 53:690, 1974.

141. Stanton-Hicks M, Murphy TM, Bonica JJ et al: Effects of extradural block: Comparison of the properties, circulatory effects and pharmacokinetics of etidocaine and bupivacaine. Br J Anaesth 48:575, 1976.

142. Akerman B, Sandberg R, Covino BG: Local anesthetic efficacy of LEA 103: An experimental xylidide agent. Anesthesiology 65:A217, 1986.

143. McClure JH: Ropivacaine. Br J Anaesth 76:300-307, 1996.

144. Stanton-Hicks M, Berges PU, Bonica JJ: Circulatory effects of peridural block. IV: Comparison of the effects of epinephrine and phenylephrine. Anesthesiology 39:308, 1973.

145. Park WY, Hagins FM: Comparison of lidocaine hydrocarbonate with lidocaine hydrochloride for epidural anesthesia. Reg Anesth 11:128, 1986.

146. Bokesch PM, Raymond SA, Strichartz GR: Dependence of lidocaine potency on pH and PCO_2. Anesth Analg 66:9, 1987.

147. Brown DT, Morison DH, Covino BG et al: Comparison of carbonated bupivacaine and bupivacaine hydrochloride for extradural anaesthesia. Br J Anaesth 52:419, 1980.

148. Martin R, Lamarche Y, Tetreault L: Effects of carbon dioxide and epinephrine on serum levels of lidocaine after epidural anaesthesia. Can J Anaesth 28:224, 1981.

149. Parnass SM, Curran MA, Becker GL: Comparison of hypotensive responses of the carbonated and hydrochloride salts of lidocaine in epidural blocks. Anesth Analg 66:S134, 1987.

150. Di Fazio CA, Carron HO, Grosslight KR et al: Comparison of pH adjusted lidocaine solutions for epidural anesthesia. Anesth Analg 65:760, 1986.

151. Liu PL, Feldman HS, Giasi R et al: Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and tetracaine in awake dogs following rapid intravenous administration. Anesth Analg 62:375, 1983.

152. Tanaka K, Yamasaki M: Blocking of cortical inhibitory synapses by intravenous lidocaine. Nature 209:207, 1966.

153. Munson ES, Tucker WK, Ausinsch B et al: Etidocaine, bupivacaine, and lidocaine seizures thresholds in monkeys. Anesthesiology 42:471, 1975.

154. Block A, Covino B: Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth 6:55, 1981.

155. de Jong RH, Ronfeld RA, DeRosa RA: Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 61:3, 1982.

156. Kotelko DM, Shinder SM, Dailey PA et al: Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 60:10, 1984.

157. Moller R, Covino BG: Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiology 72:322-329, 1990.

158. Brown DL, Ransom DM, Hall JA et al: Regional anesthesia and local anesthetic-induced systemic toxicity: Seizure frequency and accompanying cardiovascular changes. Anesth Analg 81:321-328, 1995.

159. Moore DC, Bridenbaugh LD: Oxygen: The antidote for systemic toxic reactions from local anesthetic drugs. JAMA 174:842, 1960.

160. Munson ES, Wagman IH: Diazepam treatment of local anesthetic-induced seizures. Anesthesiology 37:523, 1972.

161. Moore DC, Balfour RI, Fitzgibbons D: Convulsive arterial plasma levels of bupivacaine and the response to diazepam therapy. Anesthesiology 50:454, 1979.

162. Evans TI: Total spinal anesthesia. Anaesth Intensive Care 2:158, 1974.

163. Horlocker TT, Wedel DJ, Schroeder DR et al: Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. Anesth Analg 80:303-309, 1995.

164. Mayumi T, Dohi S: Spinal subarachnoid hematoma after lumbar puncture in a patient receiving antiplatelet therapy. Anesth Analg 62:777, 1983.

165. Greensite FS, Katz J: Spinal subdural hematoma associated with attempted epidural anesthesia and subsequent continuous spinal anesthesia. Anesth Analg 59:72, 1980.

166. Odoom JA, Sih IL: Epidural analgesia and anticoagulant therapy: Experience with one thousand cases of continuous epidurals. Anesthesia 38:254, 1983.

167. Owens EL, Kasten GW, Hessel EA: Spinal subarachnoid hematoma after lumbar puncture and heparinization: A case report, review of the literature, and discussion of anesthetic implications. Anesth Analg 65:1201, 1986.

168. Hynson JM, Katz JA, Bueff HU: Epidural hematoma associated with enoxaparin. Anesth Analg 82:1072-1075, 1996.

169. Vandermeulen EP, Van Aken H, Vermylen J: Anticoagulants and spinal-epidural anesthesia. Anesth Analg 79:1165-1177, 1994.

170. Tryba M: Epidural regional anesthesia and low molecular weight heparin: Pro (German). Anaesth Intensivmed Notfallmed Schmerzther 28:179-181, 1993.

171. Rao TLK, El-Etr AA: Anticoagulation following placement of epidural and subarachnoid catheters: An evaluation of neurologic sequelae. Anesthesiology 55:618, 1981.

172. Baron HC, LaRaja RD, Rossi G et al: Continuous epidural analgesia in the heparinized vascular surgery patient: A retrospective review of 912 patients. J Vasc Surg 6:144, 1987.

173. Cousins MJ, Bromage PR: Epidural neural blockade. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain. Philadelphia, JB Lippincott, 1988, p 255.

174. Ravindran RS: Epidural autologous blood patch on an outpatient basis [letter]. Anesth Analg 63:962, 1984.

175. Lui S, Ware PD, Allen HW et al: Dose-response characteristics of spinal bupivacaine in volunteers: Clinical implications for ambulatory anesthesia. Anesthesiology 85:729-736, 1996.

176. Hurley RJ, Lambert DH: Continuous spinal anesthesia with a microcatheter technique. Reg Anesth 12:53, 1987.

177. Moore DC, Batra MS: The components of an effective test dose prior to epidural block. Anesthesiology 55:693, 1981.

178. Hood DD, Dewan DM, James FM: Maternal and fetal effects of epinephrine in gravid ewes. Anesthesiology 64:610, 1986.

179. Chadwick HS, Benedetti C, Ready LB et al: Epinephrine-containing test doses--don't throw the baby out with the bath water, [letter]. Anesthesiology 66:571, 1987.

180. Hom M, Johnson P, Mulroy M: Blood pressure response to an epinephrine test dose in beta-blocked subjects. Anesthesiology 67:A268, 1987.

181. Lui S, Carpenter RL: Hemodynamic response to intravascular injection of epinephrine-containing epidural test doses in adults during general anesthesia. Anesthesiology 84:81-87, 1996.

182. Batra MS, Bridenbaugh LD, Levy S: Epidural anesthesia for cesarean section: Comparison of bolus and fractionated injection. Reg Anesth 10:32, 1985.

183. Bernards CM, Carpenter RL, Brown DL et al: Effect of midazolam and diazepam premedication on central nervous system and cardiovascular toxicity of bupivacaine in pigs. Anesthesiology 70:318, 1989.

184. Brownridge P: Epidural and subarachnoid analgesia for elective cesarean section [letter]. Anaesthesia 36:70, 1981.

185. Carrie LES: Epidural versus combined spinal epidural block for cesaerean section. Acta Anaesthesiol Scand 32:595, 1988.

186. Dennsion B: Combined subarachnoid and epidural block for cesarean section. Can J Anaesth 34:105, 1987.

187. Rawal N, Schollin J, Wesstrom G: Epidural versus combined spinal epidural block for cesaerean section. Acta Anaesthesiol Scand 32:61, 1988.

188. Willis RJ: Caudal epidural block. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 2nd ed. Philadelphia, JB Lippincott, 1988, p 365.

Chapter 43 - Nerve Blocks *

Denise J. Wedel

INTRODUCTION

The techniques of peripheral neural blockade were developed early in the history of anesthesia (Ch. 1) . The American surgeons Halsted and Hall [1] [2] described the injection of cocaine into peripheral sites, including the ulnar, musculocutaneous, supratrochlear, and infraorbital nerves, for minor surgical procedures in the 1880s. James Leonard Corning [3] recommended the use of an Esmarch bandage in 1885 to arrest local circulation, thus prolonging the cocaine-induced block and decreasing the uptake of that local anesthetic from the tissues. This concept was furthered by Heinrich F. W. Braun, [4] who substituted epinephrine, a "chemical tourniquet," in 1903. Braun [5] also introduced the term "conduction anesthesia" in his 1905 textbook on local anesthesia, which described techniques for every region of the body.

Whereas early discoveries in regional anesthesia involved surgeons and basic scientists, the developing specialty of anesthesiology gradually dominated the use of regional anesthetic techniques. During this period, Sydney Ormond Goldan, credited with publication of the first anesthesia chart, a record designed to record the course of "intraspinal cocainization," [6] and Gaston Labat, the French regional anesthesiologist invited to lecture at the Mayo Clinic by surgeon William Mayo, provided the basis on which regional anesthesia grew.

Peripheral neural blockade is now a well-accepted component of comprehensive anesthetic care. Its role has expanded from the operating suite into the arena of postoperative and chronic pain management (Chs. 69 and 70) . With appropriate selection and sedation, these techniques can be used in all age groups. Skillful application of peripheral neural blockade broadens the anesthesiologist's range of options in providing optimal anesthetic care.

UPPER EXTREMITY BLOCKS

Successful regional anesthesia of the upper extremity requires knowledge of brachial plexus anatomy from its origin as the nerves emerge from the intervertebral foramina to its termination in the peripheral nerves. Detailed anatomic knowledge enables the anesthesiologist to choose the appropriate technique for the intended surgical procedure and to salvage "inadequate" blocks with local anesthetic supplementation. Without mastery of the anatomy, luck rather than skill will be the primary determinant of successful neural blockade. Also important is a knowledge of the side effects and complications of peripheral nerve blocks in the upper extremity as well as the clinical application of available local anesthetics for these blocks. Finally, one must not underestimate the role of appropriate sedation during placement of the block as well as during the surgical procedure. Many a "perfect" regional anesthetic technique has been undone by inadequate management of sedation.

*See Appendix 1, Practice Guidelines for Chronic Pain Management

Figure 43-1 Roots, trunks, divisions, cords, and branches of the brachial plexus.

Anatomy

The brachial plexus is derived from the anterior primary rami of the fifth, sixth, seventh, and eighth cervical nerves and the first thoracic nerve, with variable contributions from the fourth cervical and second thoracic nerves. After leaving their intervertebral foramina, these nerves course anterolaterally and inferiorly to lie between the anterior and middle scalene muscles, which arise from the anterior and posterior tubercles of the cervical vertebra, respectively. The anterior scalene muscle passes caudad and laterally to insert into the scalene tubercle of the first rib; the middle scalene muscle inserts on the first rib posterior to the subclavian artery, which passes between these two scalene muscles along the subclavian groove. The prevertebral fascia invests both the anterior and middle scalene muscles, fusing laterally to enclose the brachial plexus in a fascial sheath.

Between the scalene muscles, these nerve roots unite to form three trunks, which emerge from the interscalene space to lie cephaloposterior to the subclavian artery as it courses along the upper surface of the first rib. Therefore, the "superior" (C5 and C6), "middle" (C7), and "inferior" (C8 and T1) trunks are arranged accordingly and are not in a strict horizontal formation, as often depicted. At the lateral edge of the first rib, each trunk forms anterior and posterior divisions that pass posterior to the midportion of the clavicle to enter the axilla. Within the axilla, these divisions form the lateral, posterior, and medial cords, named for their relationship with the second part of the axillary artery. The superior divisions from the superior and middle trunks form the lateral cord, the inferior divisions from all three trunks form the posterior cord, and the anterior division of the inferior trunk continues as the medial cord.

At the lateral border of the pectoralis minor, the three cords divide into the peripheral nerves of the upper extremity. The lateral cord gives rise to the lateral head of the median nerve and the musculocutaneous nerve; the medial cord gives rise to the medial head of the median nerve, as well as the ulnar, the medial antebrachial, and the medial brachial cutaneous nerves; and the posterior cord divides into the axillary and radial nerves (Fig. 43-1) .

Aside from the branches from the cords that form the peripheral nerves as described, several branches arise from the roots of the brachial plexus providing motor innervation to the rhomboid muscles (C5), the subclavian muscles (C5 and C6), and the serratus anterior muscle (C5, C6, and C7). The suprascapular nerve arises from C5 and C6 and supplies the muscles of the dorsal aspect of the scapula as well as making a significant contribution to the sensory supply of the shoulder joint.

Branches arising from the cervical roots are usually blocked only with the interscalene approach to the brachial plexus. Sensory distributions of the cervical roots and the peripheral nerves are shown in Figure 43-2 .

The brachial plexus shares a close physical relationship with several structures, some serving as important landmarks for the performance of neural blockade. In its course between the anterior and middle scalene muscles, the plexus is superior and posterior to the second and third parts of the subclavian artery. The dome of the pleura lies anteromedial to the inferior trunk.

Interscalene Block

Clinical Applications

The interscalene approach to the brachial plexus is well suited to procedures in which a cervical plexus block is also desired (i.e., shoulder surgery). This technique can be performed with the patient's arm in any position and is technically simple because of easy palpation of necessary landmarks. [7] Although this approach can be used for forearm and hand surgery, blockade of the inferior trunk (C8 through

Figure 43-2 (A) Cutaneous distribution of the cervical roots. (B) Cutaneous distribution of the peripheral nerves.

T1) is often incomplete and requires supplementation at the ulnar nerve for adequate surgical anesthesia in that distribution. [8] The use of a nerve stimulator or elicitation of paresthesias is recommended with this technique in order to place the local anesthetic solution accurately. The risk of pneumothorax is low when the needle is correctly placed at the C5 or C6 level because of the distance from the dome of the pleura.

Side Effects/Complications

Ipsilateral phrenic nerve block resulting in diaphragmatic paresis occurs in 100 percent of patients undergoing interscalene blockade, [9] even with dilute solutions of local anesthetics, and is associated with a 25 percent reduction in pulmonary function. [10] [11] This effect is probably due to anterior spread of the solution over the

anterior scalene muscle and may cause subjective symptoms of dyspnea. Although rare, respiratory compromise can occur in patients with severe respiratory disease. Involvement of the vagus, recurrent laryngeal, and cervical sympathetic nerves is rarely significant, but the patient experiencing symptoms related to these side effects may require reassurance. Nerve damage or neuritis can occur in any peripheral nerve block, but it is uncommon and usually is self-limited. Some surgical approaches to the shoulder are associated with neurologic risk to the brachial plexus, for example, total shoulder replacements. In such cases, interscalene block should be placed postoperatively for pain relief after the surgical service has ascertained and documented that no neurologic damage has occurred. Epidural and intrathecal injections have been reported with this block, a finding emphasizing the importance of inserting the needle in a caudad direction. Several vascular structures are in close proximity to a correctly placed needle. Local anesthetic toxicity as a result of intravascular injection should be guarded against by careful aspiration and incremental injection. Seizure activity secondary to this complication is particularly undesirable following rotator cuff surgery, because the repair can be compromised by the associated muscular activity.

Technique

The patient should be in the supine position with the head turned away from the side to be blocked. The posterior border of the sternocleidomastoid muscle is readily palpated by having the patient briefly lift the head. The interscalene groove may be palpated by rolling the fingers posterolaterally from this border over the belly of the anterior scalene muscle into the groove. A line is extended laterally from the cricoid cartilage to intersect the interscalene groove indicating the level of the transverse process of C6. Although the external jugular vein often overlies this point of intersection, it is not a constant or reliable landmark.

Figure 43-3 Interscalene block. The fingers palpate the interscalene groove, and the needle is inserted with a caudad and slightly posterior angle.

After ordinary sterile precautions and injection of a skin wheal, a 22-gauge, 4-cm short-bevel needle is inserted perpendicular to the skin with a 45-degree caudad and slightly posterior angle (Fig. 43-3) . The needle is then advanced until a paresthesia (usually C5 and C6 dermatomes) is elicited. This will usually occur at a very superficial level. If a blunt needle bevel is used, a "click" may be detected as the needle passes through the prevertebral fascia. If bone is encountered within 2 cm of the skin, it is likely to be a transverse process, and the needle may be "walked" across this structure in order to locate the nerve. The use of a nerve stimulator may be helpful in confirming the correct needle position.

Once a paresthesia is obtained, the needle is stabilized. The use of flexible extension tubing facilitates the maintenance of the needle position while aspiration and injection occur. After negative aspiration, 10 to 40 mL of solution is injected incrementally, depending on the desired extent of blockade. Radiographic studies suggest a volume-to-anesthesia relationship with 40 mL of solution associated with complete cervical and brachial plexus block. [7] Clinical studies, however, indicate variable blockade of the lower trunk (i.e., ulnar nerve) even with large volumes of solution. [8] Digital pressure above the injection site and downward massage along with a 45-degree head-up position may facilitate caudad spread and blockade of the lower trunk.

Supraclavicular Block

Clinical Applications

The supraclavicular approach to the brachial plexus is anesthetically efficient; a small volume of solution can be delivered at a point in which the three trunks are compactly arranged, resulting in rapid onset of reliable blockade of the brachial plexus. The block can also be performed with the patient's arm in any position, to provide excellent anesthesia for elbow, forearm, and hand surgery.

Reliable supraclavicular blockade requires elicitation of a paresthesia. The classic block may be somewhat difficult to describe and to teach. Observation of an experienced anesthesiologist is perhaps the best way to learn the technique. A proposed modification of the technique, the so-called "plumb-bob" approach, may decrease complications and may simplify the concept of this block. [12]

Side Effects/Complications

The prevalence of pneumothorax following supraclavicular block ranges from 0.5 to 6 percent and diminishes with experience. The onset of symptoms is usually delayed and may take up to 24 hours. Routine chest radiography after the block is, therefore, not justified. The supraclavicular approach is best avoided when the patient is uncooperative or cannot tolerate any degree of respiratory compromise because of underlying disease. Other complications include frequent phrenic nerve block (40-60%), Horner syndrome, and neuropathy. The presence of phrenic or cervical sympathetic nerve block usually requires only reassurance. Although nerve damage can occur, it is uncommon and usually is self-limited.

Technique

Several anatomic points are important in the performance of the supraclavicular approach. The three trunks are clustered vertically over the first rib cephaloposterior to the subclavian artery, which can often be palpated in a slender, relaxed patient. The neurovascular bundle lies inferior to the clavicle at about its midpoint. The first rib acts as a medial barrier to the needle's reaching the pleural dome and is short, broad, and flat with an anteroposterior orientation at the site of the plexus.

The patient is placed in a supine position, with the head turned away from the side to be blocked. The arm to be

Figure 43-4 (A) Supraclavicular block. The needle is systematically walked anteriorly and posteriorly along the rib until the plexus is located. (B) The three trunks are compactly arranged at the level of the first rib.

anesthetized should be adducted and the hand should be extended along the side toward the ipsilateral knee as far as possible. In the classic technique, the midpoint of the clavicle should be identified and marked. The posterior border of the sternocleidomastoid can be easily palpated when the patient raises the head slightly. The palpating fingers can then roll over the belly of the anterior scalene muscle into the interscalene groove, where a mark should be made approximately 1.5 to 2.0 cm posterior to the midpoint of the clavicle. Palpation of the subclavian artery at this site confirms the landmark.

After appropriate preparation and injection of a skin wheal, the anesthesiologist stands at the side of the patient facing the patient's head. A 22-gauge, 4-cm short-bevel needle is directed in a caudad, slightly medial and posterior direction until either a paresthesia is elicited or the first rib is encountered. If a syringe is attached, this orientation causes the needle shaft and syringe to lie almost parallel to a line joining the skin entry and the patient's ear. If the first rib is encountered without elicitation of a paresthesia, the needle can be systematically walked anteriorly and posteriorly along the rib until the plexus or the subclavian artery is located (Fig. 43-4 and Plate 3 [color plate Atlas of Regional Anesthesia Procedures follows this chapter]). Location of the artery provides a useful landmark; the needle can be withdrawn and reinserted in a more posterolateral direction that will usually result in a paresthesia. When a paresthesia has been obtained, aspiration for blood should be performed prior to incremental injections of a total volume of 20 to 30 mL of solution. A nerve stimulator can also be used to identify the brachial plexus.

Usually, the rib is contacted at a needle depth of 3 to 4 cm; however, in an obese patient or in the presence of tissue distortion resulting from hematoma or injection of solution, the depth may exceed the needle length. Nonetheless, gentle probing in the anterior and posterior directions should be done at the 2- to 3-cm depth if paresthesias are not obtained before the needle is advanced farther. Multiple injections may improve the quality or may shorten the onset of blockade.

The modified, plumb-bob approach uses similar patient positioning, although the needle entry site is at the point at which the lateral border of the sternocleidomastoid

muscle inserts into the clavicle. After preparation and injection of a skin wheal, a 22-gauge, 4-cm short-bevel needle is inserted while mimicking a plumb bob suspended over the needle entry site. Often, a paresthesia is elicited prior to contacting the first rib or artery. If no paresthesia is elicited, the needle is reinserted while angling the tip of the needle cephalad. If still no paresthesias are obtained, the needle tip is angled caudad in small steps until the first rib is contacted (Fig. 43-5) .

Axillary Block

Clinical Applications

The axillary approach to the brachial plexus is the most popular because of ease of block, reliability of hand and forearm anesthesia, and safety. [13] Furthermore, central neural blockade and pneumothorax are not complications, as in other approaches to the brachial plexus. This block is ideally suited for outpatients and is easily adapted to the pediatric population. [14] [15] Paresthesias are not necessary, although

Figure 43-5 Supraclavicular block. Plumb-bob approach.

multiple injections may shorten the onset and may improve the reliability of blockade.

Axillary block is unsuitable for surgical procedures on the upper arm or shoulder. Anesthesia of the musculocutaneous nerve is not always produced with this approach, but it can be supplemented at the level of the axilla or at the elbow. The patient must be able to abduct the arm to perform the block.

Side Effects/Complications

If large volumes are injected through an "immobile" needle, particularly if a transarterial approach is used, there is an increased risk of intravascular injection resulting in systemic local anesthetic toxicity. The assertion that neuropathies are more common if paresthesias are sought may be valid, but it is not supported by the available data. [16] Hematoma and infection are rare complications.

Technique

Anatomic concepts that should be considered prior to performing an axillary block include the following:

1. The neurovascular bundle is multicompartmental [17] (Fig. 43-6) .
2. The axillary artery is the most important landmark; the nerves maintain a predictable orientation to the artery.
3. The median nerve is found superior to the artery, the ulnar nerve is inferior, and the radial nerve is posterior and somewhat lateral (Fig. 43-7 .and Plate 5)
4. At this level, the musculocutaneous nerve has already left the sheath and lies in the substance of the coracobrachialis muscle.
5. The intercostobrachial nerve, a branch of the T2 intercostal nerve, is usually blocked by the skin wheal overlying the artery; however, adequate anesthesia for the tourniquet can be ensured by extending the wheal 1 to 2 cm caudad and cephalad.

The patient should be in the supine position with the arm to be blocked placed at a right angle to the body, with the elbow flexed to 90 degrees. The dorsum of the hand rests on the bed or pillow; hyperabduction of the arm with placement of the hand beneath the patient's head is not recommended because this position frequently obliterates the pulse.

The axillary artery is palpated, and a line is drawn tracing its course from the lower axilla as far proximally as possible. The artery is then fixed against the patient's humerus by the index and middle fingers of the left hand, and a skin wheal is raised directly over the artery at a point in the axilla approximating the skin crease. Proximal needle placement and maintenance of distal pressure facilitate proximal spread of the solution.

Figure 43-6 Axillary block. Computed tomogram after axillary block with bupivacaine 0.5 percent and iodothalamate. Separate injections of 10-mL solution were made after obtaining median and radial nerve paresthesias and transarterially. Contrast medium appears to remain in three separate compartments.

Figure 43-7 Axillary block. The arm is abducted at right angles to the body. Distal digital pressure is maintained during needle placement and injection of local anesthetic.

At this stage, several methods have been described, with reportedly good results:

1. Paresthesias can be sought with a 25-gauge, 2-cm needle, beginning either deep (radial nerve) or with the nerves supplying the surgical site. Needles longer than 2 cm are rarely needed to reach the neurovascular bundle; smaller needles may be associated with a lower risk of nerve damage. [14] Ten milliliters of local anesthetic is injected at each paresthesia.
2. A nerve stimulator can also be employed with an insulated needle to locate the nerves. This technique obviates the need for paresthesias, and, although unproven, it may lower the risk of nerve damage. [18]
3. A short-bevel needle can be advanced until the "axillary sheath" is entered, as evidenced by a "fascial click," whereupon 40 to 50 mL of solution is injected after negative aspiration. [13] [19]
4. A transarterial technique can be employed, whereby the needle pierces the artery and 40 to 50 mL solution is injected posterior to the artery; or, alternatively, half the solution is injected posterior and half anterior to the artery. Great care must be taken to avoid intravascular injection with this technique, particularly because the pressure of injection within the compartments of the axillary sheath may move anatomic structures in relation to the immobile needle. Some practitioners avoid intentional arterial puncture in the belief that it is unnecessarily traumatic.
5. Field block of the brachial plexus with a fanwise injection of 10 to 15 mL of local anesthetic solution on each side of the artery is a variation of the sheath technique. Paresthesias, although not sought, are often encountered in this technique and provide evidence of correct placement.

The elicitation of paresthesias is controversial because of a reportedly higher risk of nerve damage, although actual data are limited. [16] [20] However, even when intentional paresthesias are not sought, they are often impossible to avoid with any of the proposed techniques. Furthermore, success rates with single-injection techniques can be variable. [21] [22] Thompson and Rorie [17] concluded that the presence of multiple compartments limits diffusion of the solution (i.e., necessary for single-shot technique). More recently, Partridge et al [23] confirmed the presence of these compartments, but these investigators concluded that the "septa" dividing them were incomplete on the basis of injections of methylene blue and latex solutions into cadavers. The controversy surrounding single- versus multiple-injection techniques remains unresolved. Familiarity with a variety of techniques for axillary block of the brachial plexus allows the anesthesiologist maximal flexibility in tailoring the anesthetic approach to the clinical situation.

When the injection is completed, the arm should be adducted and returned to the patient's side. This prevents the humeral head from obstructing proximal flow of the

solution; distal pressure and massage may also help. Vester-Andersen

et al [24] were unable to block the musculocutaneous nerve reliably with volumes up to 80 mL. Thus, if the musculocutaneous nerve is not blocked by the axillary approach, it can be blocked by injection within the body of the coraco-brachialis muscle or at the elbow superficially at the lateral aspect of the antecubital fossa just above the interepicondylar line.

Infraclavicular Block

Clinical Applications

This block offers the theoretic advantages of avoiding pneumothorax while injecting at a level affording block of the musculocutaneous and axillary nerves. No special arm positioning is required. A nerve stimulator is required because there are no palpable vascular landmarks to aid in directing the needle.

Side Effects/Complications

Because of the necessarily blind approach to the plexus, the risk of intravascular injection may be increased. Exaggerated medial needle direction may result in pneumothorax. Other rare complications such as infection and hematoma are theoretically possible.

Technique

The needle is inserted 2 cm below the midpoint of the inferior clavicular border and is advanced laterally, using a nerve stimulator to identify the plexus. [25] Marking a line between the C6 tubercle and the axillary artery with the arm abducted is helpful in visualizing the course of the plexus. An incremental injection of 20 to 30 mL of solution is sufficient once the needle is correctly placed. Modifications of this technique suggesting more lateral insertion sites may result in the absence of blockade of the musculocutaneous nerve, thus removing the major advantage of this approach over the simpler axillary block.

Brachial Plexus Catheters

Methods of providing continuous brachial plexus anesthesia have been described since at least the 1940s, [26] and they frequently offer ingenious solutions for the placement and securing of the needle or catheter. The advantages cited for these techniques are prolongation of surgical anesthesia, decreased risk of toxicity because of lower incremental doses, and postoperative pain relief and sympathectomy.

Risks of infection, difficulty in securing the catheter, and inadequate surgical anesthesia are the major disadvantages. Catheter migration, catheter kinking or coiling, and nerve damage are theoretic complications.

Techniques using both over- and through-needle methods have been described. Longer catheters may be easier to secure and provide superior blockade if the tip lies more proximal in the plexus. [27] Commercial kits offering catheter, needle, and stimulating electrodes are now available.

This technique is especially applicable to patients with upper extremity or digit replantation, total elbow arthroplasty, or reflex sympathetic dystrophies, for which prolonged pain relief and sympathectomy are advantageous.

Peripheral Blocks at the Elbow and Wrist

Clinical Applications

As techniques for brachial plexus blockade have gained popularity, indications for peripheral nerve blockade at the wrist and elbow have diminished. However, these techniques can be useful when limited anesthesia is required, when contraindications to brachial plexus block (e.g., infection, bilateral surgery, coagulation abnormalities, bleeding diasthesis, difficult anatomy) exist, or when brachial plexus blockade is incomplete.

Peripheral nerve blocks do not provide anesthesia for the use of a tourniquet. Most patients tolerate an inflated tourniquet for only a brief period.

A midhumeral approach to the brachial plexus has been described. This novel approach involves blocking each nerve separately in the humeral canal. Blockade of the four major nerves of the upper extremity at the midhumeral level using a peripheral nerve stimulator has been reported to have a higher success rate than traditional (defined as stimulation of two nerves) axillary brachial plexus block. [28] In this study, time to complete the block did not differ between the two techniques; however, onset of complete sensory block was shorter in the axillary approach, whereas the success rate of blockade of all four major nerves was higher in the midhumeral group. This technique may have applications when anatomic difficulties preclude a traditional approach or when the surgical procedure requires a dense block of all four major nerves. The safety and clinical practicality of the midhumeral approach remain to be proven.

Side Effects/Complications

In general, distal peripheral blocks are associated with a lower risk of complications. However, intravascular injection can occur, and the usual precautions of incremental injection after aspiration are recommended. The risk of nerve injury is theorized to be higher when more distal peripheral blocks are performed. This may be due to superficial nerve placement between bony and ligamentous structures, thereby offering ready access to the probing needle point.

Elbow Versus Wrist

The forearm cutaneous nerves arise in the upper arm and are not anesthetized by block of the peripheral nerves at the elbow. Hence, there is no advantage of block of the peripheral nerves of the upper extremity when comparing elbow with wrist techniques; both provide sensory anesthesia of the hand.

Figure 43-8 Anatomic landmarks for median and radial nerve block at the elbow.

Median Nerve

Block of the median nerve provides anesthesia of the palmar aspects of the thumb and index finger, middle finger and radial half of the ring finger, and the nail beds of the same digits. Motor block includes the muscles of the thenar eminence, lumbric muscles of the first and second digits, and, in the case of the block at the elbow, median-innervated wrist flexor muscles of the forearm.

Technique at the Elbow

With the patient's arm placed in the anatomic position (palm up), a line is drawn connecting the medial and lateral epicondyles of the humerus. The major landmark for this technique is the brachial artery, which is found medial to the biceps tendon at the intercondylar line. The median nerve lies medial to the artery (Fig. 43-8) and

can be blocked with 3 to 5 mL of solution after eliciting a paresthesia. If no paresthesia is obtained, the solution can be injected fanwise medial to the palpated artery.

Technique at the Wrist

The median nerve is located between the flexor carpi radialis and palmaris longus tendons and can be blocked at a point 2 to 3 cm proximal to the wrist crease (Fig. 43-9) . (The palmaris longus tendon is congenitally or postsurgically absent from some patients.) A loss of resistance is felt as the

Figure 43-9 Anatomic landmarks for median and ulnar nerve block at the wrist. An alternative method for ulnar nerve block, from the ulnar side of the wrist, is shown.

needle passes through the flexor retinaculum, at which point 2 to 4 mL of solution should be injected. A superficial palmar branch supplying the skin of the thenar eminence can be blocked by injecting 0.5 to 1 mL of solution subcutaneously above the retinaculum. Paresthesias should not be sought because of the confinement of this nerve within the carpal tunnel.

Radial Nerve

Block of the radial nerve provides anesthesia to the lateral aspect of the dorsum of the hand (thumb side) and the proximal portion of the thumb, index, middle, and lateral half of the ring fingers.

Technique at the Elbow

The radial nerve can be blocked at the elbow as it passes over the anterior aspect of the lateral epicondyle. The intercondylar line and lateral edge of the biceps tendon are marked. A 22-gauge, 3- to 4-cm needle is inserted at a point 2 cm lateral to the biceps tendon and is advanced until bone is encountered (see Fig. 43-8) . A fanwise injection is made using 3 to 5 mL of solution.

Technique at the Wrist

The radial nerve block at the wrist is a field block of the multiple peripheral branches descending along the dorsum and radial side of the wrist. The extensor pollicis longus tendon can be identified when the patient extends the thumb. The needle insertion is over this tendon at the base of the first metacarpal; the injection is superficial to the tendon. Two milliliters of local anesthetic is injected proximally along the tendon, and an additional 1 mL is injected as the needle passes at a right angle across the "anatomic snuffbox" (Fig. 43-10) .

Ulnar Nerve

Blockade of the ulnar nerve provides anesthesia of the ulnar side of the hand, the little finger, and the ring finger and all the small muscles of the hand, except those of the thenar eminence and the first and second lumbric muscles.

Technique at the Elbow

Although the ulnar nerve is easily accessible at its subcutaneous position posterior to the medial epicondyle, blockade at this site is associated with a high incidence of neuritis. The nerve is surrounded by fibrous tissue at this point, requiring an intraneural injection for successful blockade. Use of a very fine needle along with a small volume of solution (1 mL) diminishes the risk; however, the nerve can be satisfactorily blocked with 5 to 10 mL of solution at a site 3 to 5 cm proximal to the elbow. The local anesthetic should be injected in a fanwise fashion without elicitation of a paresthesia.

Figure 43-10 Anatomic landmarks and method of needle insertion for radial nerve block at the wrist.

Technique at the Wrist

At the wrist, the ulnar nerve lies beneath the flexor carpi ulnaris tendon between the ulnar artery and the pisiform bone. At this point, it has already given off its palmar cutaneous and dorsal branches. The nerve can be approached by directing the needle medially from the radial side of the tendon or, alternatively, by directing the needle radially from the ulnar side of the tendon (see Fig. 43-9) . After eliciting a paresthesia, 3 to 5 mL of solution is injected or spread in a fanwise fashion.

Musculocutaneous Nerve

The musculocutaneous nerve terminates as the lateral cutaneous nerve of the forearm. This nerve provides sensory innervation to the skin on the radial side of the forearm up to the radiocarpal joint. This block is usually performed to supplement the axillary approach to brachial plexus anesthesia.

Technique at the Elbow

The lateral cutaneous nerve of the forearm can be blocked 1 cm proximal to the intercondylar line immediately lateral to the biceps tendon. Fanwise infiltration of 3 to 5 mL of solution subcutaneously at this site provides excellent anesthesia of this nerve.

Intravenous Regional Blocks

Intravenous regional blocks were first described by a German surgeon, August Bier, in 1908. [29] Early methods involved two tourniquets and the first synthetic local anesthetic, procaine. The technique lost popularity as reliable methods of blocking the brachial plexus evolved.

Clinical Applications

The Bier block has multiple advantages, including ease of administration, rapidity of recovery, rapid onset, muscular relaxation, and controllable extent of anesthesia. It is an excellent technique for short (<90 min) open surgical procedures and for closed reductions of bony fractures.

Side Effects/Complications

Technical problems with this block include tourniquet discomfort, rapidity of recovery leading to postoperative pain, difficulty in providing a bloodless field, and the necessity of exsanguination in the case of a painful injury. Accidental or early deflation of the tourniquet or use of excessive doses of local anesthetics can result in toxic reactions. Injection of the drug as distally as possible at a slow rate has been shown to decrease blood levels and theoretically to increase safety. [30] The use of bupivacaine for intravenous regional anesthesia has been associated with local anesthetic toxicity and death [31] and is not recommended. Cyclic deflation of the tourniquet at 10-second intervals has been shown to increase the time to peak arterial lidocaine levels that may decrease potential toxicity. [32] Other rare

complications associated with this technique include development of compartment syndrome and loss of limb.

Technique

An intravenous cannula is placed in the upper extremity to be blocked as distally as possible (the patient should also have an intravenous cannula in the nonoperative upper extremity for administration of fluids and other drugs). Traditionally, a double tourniquet is placed on the operative side; both cuffs should have secure closures and reliable pressure gauges. After exsanguination of the arm, the proximal cuff is inflated to approximately 150 mm Hg more than the systolic pressure (absence of a radial pulse confirms adequate tourniquet pressure). Total dose of local anesthetic is based on the patient's weight and is injected slowly (4-6 mg/kg of 0.5% prilocaine or lidocaine, without epinephrine). The onset of anesthesia is usually within 5 minutes. When the patient complains of tourniquet pain, the distal tourniquet, which overlies anesthetized skin, is inflated, and the proximal tourniquet is released. There are data suggesting that the use of a single wide cuff allows use of lower inflation pressures during intravenous regional anesthesia. The postulated advantage is that the lower pressures will decrease the incidence of neurologic complications related to high inflation pressures with the narrow double cuffs. [33] The tourniquet may be safely released after 25 minutes, but the patient should be closely observed for local anesthetic toxicity for several minutes after the tourniquet release. Slow injection of local anesthetic solutions at a distal site has been shown to lower the risk of toxicity. [30]

LOWER EXTREMITY BLOCKS

Blocks of the lower extremity are less popular than those routinely employed for surgical procedures of the upper extremity. In part, this is due to the widespread acceptance and safety of spinal and epidural anesthesia. Furthermore, unlike the brachial plexus, the nerves supplying the lower extremity are not anatomically clustered where they can be easily blocked with a relatively superficial injection of local anesthetic. Because of the anatomic considerations, these blocks are technically more difficult and require more training and practice before expertise is acquired. Finally, persistent block of any of the major nerves of the lower extremity leaves the patient unable to ambulate, an unacceptable side effect in the outpatient population. Nonetheless, knowledge of the anatomy of the lumbosacral plexus and peripheral nerves of the lower extremity enables anesthesiologists to provide more comprehensive anesthetic care. These blocks are safe and have certain advantages, such as postoperative pain relief and lack of complete sympathectomy, which make them ideal for selected patients.

Anatomy

The nerve supply to the lower extremity is derived from the lumbar and sacral plexuses. The lumbar plexus is formed by the anterior rami of the first four lumbar nerves, frequently including a branch from T12 and occasionally from L5 (Fig. 43-11 and Plate 11). The plexus lies between the psoas major and quadratus lumborum muscles, in the so-called psoas compartment.

The lower components of the plexus, L2, L3, and L4, primarily innervate the anterior and medial thigh. The anterior divisions of L2, L3, and L4 form the obturator nerve; the posterior divisions of the same components form the femoral nerve; and the lateral femoral cutaneous nerve is formed from posterior divisions of L2 and L3.

The posterior cutaneous nerve of the thigh and the sciatic nerve are derived from the first, second, and third sacral nerves plus branches from the anterior rami of L4 and L5, respectively. These nerves pass together through the pelvis and the greater sciatic foramen and are blocked by the same technique. The sciatic nerve is actually a combination of two major nerve trunks, the tibial (ventral branches of the anterior rami of L4, L5, S1, S2, and S3) and the common peroneal (dorsal branches of the anterior rami of L4, L5, S1, S2, and S3), which form the sciatic nerve. At or above the popliteal fossa they separate, the tibial nerve passing medially and the common peroneal laterally. The cutaneous distributions of the lumbosacral and peripheral nerves are shown in Figure 43-12 .

Psoas Compartment Block

The psoas compartment block utilizes a technique in which a needle is placed into the space between the psoas major and quadratus lumborum muscles. A large volume of injected solution anesthetizes the hip and anterolateral thigh. [34]

Clinical Applications

This technique offers a single injection rather than three separate needle insertions for anesthesia of the lumbar plexus. The technique must be combined with a sciatic block for anesthesia of the entire lower extremity.

Side Effects/Complications

The deep needle placement increases the risk of possible epidural, subarachnoid, or intravascular injection. Peripheral

Figure 43-11 The lumbar plexus lies in the psoas compartment between the psoas major and quadratus lumborum muscles.

nerve damage is also a potential risk with this technique. A side effect of the paravertebral approach to the lumbar plexus is the development of a sympathetic block secondary to extravasation of local anesthetic. This unilateral sympathectomy is usually of little consequence. However, because one of the reasons for choosing a lower extremity block over spinal or epidural blockade is prevention of sympathectomy, the advantage of a psoas compartment block is diminished should this effect occur.

Technique: Posterior Approach

The patient is placed in the lateral position, hips flexed and operative leg uppermost. A line is drawn to connect the iliac crests (intercristal line) identifying the fourth lumbar spine. After skin preparation, a skin wheal is raised 3 cm caudad and 5 cm lateral to the midline on the side to be blocked. A 22-gauge, 15-cm needle is then advanced perpendicular to the skin entry site until it contacts the fifth lumbar transverse process. The needle is redirected cephalad until it slides off the transverse process. At this point, a 20-mL syringe filled with air is attached, and the needle is slowly advanced until a loss of resistance is detected. The depth of the psoas compartment is about 12 cm. When the needle is in place, the compartment can be dilated with 20 mL of air prior to injecting 30 mL of solution. A nerve stimulator can be useful for locating and verifying correct needle position.

Technique: Perivascular Approach ("3-in-1 Block")

The perivascular approach to the psoas compartment is based on the premise that injection of a large volume of local anesthetic within the femoral canal while maintaining distal pressure will result in proximal spread of the solution into the psoas compartment and consequent lumbar plexus block. [35] The key anatomic assumption is that the fascial sheath surrounding the lumbar roots extends into the femoral canal and acts as an enclosed conduit for the spread of local anesthetic solutions. The patient lies in the supine position. The inguinal ligament is marked as a line connecting the pubic tubercle and the anterior superior iliac spine. The femoral artery is marked. A short-beveled 22-gauge, 5- cm needle is advanced lateral to the artery in a cephalad direction until a paresthesia is obtained. The needle is held immobile while distal pressure is applied digitally to the femoral sheath. A total of 20 to 40 mL of solution is injected incrementally after negative aspiration. Reliable anesthesia of the femoral and lateral femoral cutaneous nerves can be predicted with 20 mL; however, obturator nerve block may require volumes greater than 30 mL.

Femoral Nerve Block

The femoral nerve is formed within the psoas major muscle by posterior divisions of the second, third, and fourth

Figure 43-12 (A) Cutaneous distribution of the lumbosacral nerves. (B) Cutaneous distribution of the peripheral nerves of the lower extremity.

lumbar nerves. It emerges from the lateral border of the psoas muscle to descend in the groove between the psoas and iliacus muscles and enters the thigh by passing beneath the inguinal ligament lateral to the femoral artery. At this point, the nerve divides into multiple terminal branches, which have been classified as anterior and posterior. The anterior branches are primarily cutaneous, the deep branches chiefly motor.

The femoral nerve supplies the anterior compartment muscles of the thigh (quadriceps, sartorius) and the skin of the anterior thigh from the inguinal ligament to the knee. Its terminal branch is the saphenous nerve, which supplies an area of skin along the medial side of the leg from the knee to the big toe.

Clinical Applications

The femoral block is primarily used in concert with other peripheral blocks. However, it can be used alone for muscle biopsies of the quadriceps muscle or other surgical procedures limited to the anterior thigh, and it has been reported effective for anesthetic management of knee arthroscopy and surgical repair of midfemoral shaft fractures. [36] [37]

Side Effects/Complications

Intravascular injection and hematoma are possible because of the close proximity of the femoral artery. However, anatomically, the nerve and artery are located in separate sheaths approximately 1 cm apart. In most patients with normal anatomy, the femoral artery can be easily palpated, allowing correct, safe needle positioning lateral to the pulsation. The presence of femoral vascular grafts is a relative contraindication to this block. Nerve damage is rare with this technique.

Technique

The patient is placed in the supine position. A line is drawn between the anterior superior iliac spine and the pubic tubercle, identifying the inguinal ligament. The femoral artery is marked. A 22-gauge, 4-cm short-bevel needle is advanced lateral to this line (Fig. 43-13A and Plate 13A). When the needle reaches the depth of the artery, a pulsation of the hub is visible. Elicitation of a paresthesia or use of a nerve stimulator is also helpful in verifying correct needle position. Local anesthetic, 20 mL, is injected fanwise lateral to the artery. If a paresthesia is obtained, 7 to 10 mL of solution should be injected at that site.

Figure 43-13 (A) Anatomic landmarks for lateral femoral cutaneous, femoral, and obturator nerve blocks. (B) Obturator nerve block. The needle is walked off the inferior pubic ramus in a medial and cephalad direction until it passes into the obturator canal.

Lateral Femoral Cutaneous Nerve Block

The lateral femoral cutaneous nerve (L2 and L3) emerges at the lateral border of the psoas muscle immediately caudad to the ilioinguinal nerve. It descends under the iliac fascia to enter the thigh deep to the inguinal ligament 1 to 2 cm medial to the anterior superior iliac spine. The nerve emerges from the fascia lata 7 to 10 cm below the spine and divides into anterior and posterior branches. The skin of the lateral portion of the thigh from the hip to midthigh is supplied by the posterior branch; the anterior branch supplies the anterolateral thigh to the knee.

Clinical Applications

This block is useful for skin graft harvesting and can be used in concert with other peripheral nerve blocks for complete anesthesia of the lower extremity.

Side Effects/Complications

The extent of anesthesia is quite limited with this block, but there is a low risk of associated complications. Neuritis of this nerve secondary to needle trauma or drug toxicity is a potential but unlikely complication. There are no large blood vessels in the vicinity of this nerve; therefore, the likelihood of rapid uptake or intravascular injection is very small.

Technique

A point is marked 2 cm medial and 2 cm caudad to the anterior superior iliac spine. A short-bevel 22-gauge, 4-cm needle is advanced perpendicular to the skin entry site until a sudden release indicates passage through the fascia lata. As the needle is moved fanwise laterally and medially, 10 to 15 mL of solution is injected, depositing local anesthetic above and below the fascia (see Fig. 43-13 .A and Plate 13A)

The nerve can also be blocked just medial and posterior to the anterior superior iliac crest with 10 mL of solution. Combining the two techniques (belt-and-suspenders method) increases the success rate, but the total volume of solution used may be limiting. Because this is a pure sensory nerve, a nerve stimulator is not helpful in performing this block.

Obturator Nerve Block

The obturator nerve is derived primarily from the third and fourth lumbar nerves with an occasional minor contribution from L2. The nerve lies deep in the obturator canal, having descended from the medial border of the psoas muscle. As the nerve leaves the obturator canal, it divides into anterior and posterior branches. The anterior branch supplies an articular branch to the hip and the anterior adductor muscles and a variable cutaneous branch to the lower medial thigh. The posterior branch innervates the deep adductor muscles and may send an articular branch to the knee.

Clinical Applications

Usually, the obturator nerve is blocked as part of regional anesthesia for knee surgery. Because it is primarily a motor nerve, it is rarely blocked on its own; however, obturator nerve block can be useful in treating or diagnosing the extent of adductor spasm in patients with cerebral palsy and other muscle or neurologic diseases affecting the lower extremities prior to surgical intervention (adductor tenotomy).

Side Effects/Complications

Complications are rare; however, this block is technically more difficult than other lower extremity blocks. The obturator canal contains vascular and neural structures; thus, there is a theoretic risk of intravascular injection, hematoma, and nerve damage. Absence of anesthesia in the obturator nerve distribution can render an otherwise perfect lower extremity block inadequate for surgical procedures on the knee.

Technique

The patient is placed in the supine position, and a mark is made 1 to 2 cm lateral and 1 to 2 cm caudad to the pubic tubercle. A skin wheal is raised, and a short-bevel 22-gauge, 8- to 10-cm needle is advanced perpendicular to the skin entry site with a slight medial direction. The inferior pubic ramus is encountered at a depth of 2 to 4 cm, and the needle is walked in a lateral and caudad direction, until it passes into the obturator canal. The obturator nerve is located 2 to 3 cm past the initial point of contact with the pubic ramus (see Fig. 43-13 and Plate 13B). After negative aspiration, 10 to 15 mL of local anesthetic is injected. A nerve stimulator is helpful in locating the obturator nerve; correct needle position is evidenced by contraction of the adductor muscles of the medial thigh.

The classic approach to obturator nerve block involves painful periosteal contact and multiple needle redirectioning. An alternate interadductor approach was described by Wasseff. [38] In this technique, the needle is inserted behind the adductor tendon, near its pubic insertion, and is directed laterally toward a mark on the skin 1 to 2 cm medial to the femoral artery and immediately below the inguinal ligament representing the obturator canal. The nerve is identified by a motor response to peripheral nerve stimulation in the adductor muscle.

Sciatic Nerve Block

The sciatic nerve (L4 and L5, S1 through S3) is the largest of the four peripheral nerves of the lower extremity, with a width of 2 cm as it leaves the pelvis with the posterior cutaneous nerve of the thigh. After passing through the sacrosciatic foramen beneath the piriformis muscle, it lies between the greater trochanter of the femur and the ischial tuberosity. The nerve becomes superficial at the lower border of the gluteus maximus muscle, where it begins its descent down the posterior aspect of the thigh to the popliteal fossa. It supplies cutaneous innervation to the posterior thigh and all of the leg and foot below the knee, except a thin medial strip supplied by the saphenous nerve.

Clinical Applications

Because of its wide sensory distribution, the sciatic nerve block can be used, together with a saphenous or femoral nerve block, for any surgical procedure below the knee that does not require a thigh tourniquet. It can also be combined with other peripheral nerve blocks to provide anesthesia for surgical procedures involving the thigh and knee. This form of anesthesia avoids the sympathectomy associated with centroneuraxis blocks, and therefore, its use may be advantageous when any shift in hemodynamics could be deleterious, such as in patients with significant aortic stenosis.

Side Effects/Complications

The block is technically difficult to perform and can be quite painful. Hematoma formation is possible; the risk of nerve damage is also reported, although persistent paresthesias are usually self-limited. A minimal degree of vasodilation may occur with sciatic nerve block.

Technique: Classic Approach of Labat (Posterior)

The patient is positioned laterally, with the leg to be blocked rolled forward onto the flexed knee as the heel rests on the knee of the dependent (nonoperative) leg [39] (Fig. 43-14 and Plate 12A). A line is drawn to connect the posterior superior iliac spine to the greater trochanter of the femur. A perpendicular line is drawn bisecting this line and extending 5 cm caudad. A second line is drawn from the greater trochanter to the sacral hiatus. The intersection of

Figure 43-14 Posterior approach to the sciatic nerve: patient positioning.

Figure 43-15 Anatomic landmarks for the posterior approach to sciatic nerve block.

this line with the perpendicular line indicates the point of needle entry and falls 3 to 5 cm along the line. A 22-gauge, 10- to 12-cm needle is advanced until a paresthesia is elicited or bone is contacted (Fig. 43-15 and Plate 12B). If bone is encountered, the needle is redirected systematically in a lateral or medial direction. A nerve stimulator can be useful in locating the nerve. Once the needle is properly placed, a total of 20 to 30 mL of solution should be injected.

Technique: Anterior Approach

This technique is useful when the patient cannot be positioned for the classic posterior approach because of pain or lack of cooperation. [40] Initial blockade of the femoral nerve decreases the pain associated with this approach.

With the patient in the supine position, a line drawn along the inguinal ligament from the anterior superior iliac crest to the pubic tubercle is trisected. A second line parallel to the inguinal ligament is drawn, beginning at the tuberosity of the greater trochanter. A 22-gauge, 10.5- to 12-cm needle is inserted perpendicularly with a slightly lateral angulation at the point where the line representing the juncture of the middle and medial thirds crosses the second line. This needle is advanced until it contacts bone, the lesser trochanter of the femur (Fig. 43-16) . The needle is redirected medially past the femur, and a paresthesia is sought at a depth of about 5 cm past bone. A total of 20 to 25 mL of solution is injected incrementally after careful aspiration.

Technique: Other Approaches

The sciatic nerve can also be blocked with the patient in the lateral [41] and lithotomy positions, [42] although these are rarely employed clinically.

Nerve Blocks at the Ankle

Four of the five individual nerves that can be blocked at the ankle to provide anesthesia of the foot are terminal branches of the sciatic nerve: the posterior tibial, sural, superficial peroneal, and deep peroneal branches. The sciatic nerve divides at or above the apex of the popliteal fossa to form the common peroneal and tibial nerves. The common

Figure 43-16 Anatomic landmarks for the anterior to sciatic nerve block.

peroneal nerve descends laterally around the head of the fibula, where it divides into the superficial and deep peroneal nerves.

The tibial nerve divides into the posterior tibial and sural nerves in the lower leg. The posterior tibial nerve becomes superficial at the medial border of the Achilles tendon near the artery of the same name, and the sural nerve emerges lateral to the Achilles tendon.

Clinical Applications

Ankle blocks are simple to perform and offer adequate anesthesia for surgical procedures of the foot not requiring a tourniquet above the ankle.

Side Effects/Complications

Multiple needlesticks are required for some techniques, resulting in discomfort for the patient. Persisting paresthesias may occur, but they are self-limited. The presence of edema or induration in the area of the ankle block can make palpation of landmarks difficult. Intravascular injection is possible but unlikely if aspiration for blood is negative. The volume of local anesthetic used is small, thereby decreasing the risk of local anesthetic toxicity.

Technique: Posterior Tibial Nerve

The posterior tibial nerve can be blocked with the patient in either the prone or the supine position. The posterior tibial artery is palpated, and a 22-gauge, 3-cm needle is inserted posterolateral to the artery at the level of the medial malleolus (Fig. 43-17A and B and Plate 15A and B). A paresthesia is often elicited; however, it is not necessary for a successful block. If a paresthesia is obtained, 3 to 5 mL of local anesthetic should be injected. Otherwise, 7 to 10 mL of solution should be injected as the needle is slowly withdrawn back from the posterior aspect of the tibia. Blockade of the posterior tibial nerve provides anesthesia of the heel, plantar portion of the toes, and the sole of the foot as well as some motor branches in the same area.

Technique: Sural Nerve

The sural nerve is located superficially between the lateral malleolus and the Achilles tendon. A 25-gauge, 3-cm needle is inserted lateral to the tendon and is directed toward the malleolus as 5 to 10 mL of solution is injected subcutaneously (see Fig. 43-17A and C and Plate 15A and C). This block provides anesthesia of the lateral foot and the lateral aspects of the proximal sole of the foot.

Figure 43-17 (A) Anatomic landmarks for block of the posterior tibial and sural nerves at the ankle. (B) Posterior tibial nerve. Method of needle placement for block at the ankle. (C) Sural nerve. Method of needle placement for block at the ankle.

Technique: Deep Peroneal, Superficial Peroneal, and Saphenous Nerves

The deep peroneal, superficial peroneal, and saphenous nerves can be blocked through a single needle entry site (Fig. 43-18 and Plate 14). A line is drawn across the dorsum of the foot connecting the malleoli. The extensor hallucis longus tendon is identified by having the patient dorsiflex the big toe. The anterior tibial artery lies between this structure and the tendon of the extensor digitorum longus muscle and is palpable at this level. A skin wheal is raised just lateral to the pulsation between the two tendons on the intermalleolar line. A 25-gauge, 3-cm needle is advanced perpendicular to skin entry site, and 3 to 5 mL of local anesthetic injected deep to the extensor retinaculum to block the deep peroneal nerve. This technique anesthetizes the skin between the first and second toes and the short extensors of the toes.

The needle can now be directed laterally through the same skin wheal while injecting 3 to 5 mL of solution subcutaneously, thus blocking the superficial peroneal nerve and resulting in anesthesia of the dorsum of the foot, excluding the first interdigital cleft. The same maneuver can now be performed in the medial direction, thereby anesthetizing the saphenous nerve, a terminal branch of the femoral nerve that supplies a strip along the medial aspect of the foot.

Figure 43-18 (A) Anatomic landmarks for block of the deep peroneal, superficial peroneal, and saphenous nerves at the ankle. (B) Method of needle placement for block of the deep peroneal, superficial peroneal, and saphenous nerves through a single needle entry site.

Figure 43-19 (A-D) Anatomic landmarks and method of needle placement for maxillary and mandibular nerve blocks.

BLOCKS OF THE HEAD AND NECK

Regional anesthesia of the head and neck has become less popular as safer methods of general anesthesia have developed. However, applications for these techniques still exist, especially in the postoperative and chronic pain settings. Furthermore, airway anesthesia is often needed to facilitate endotracheal intubation.

The cutaneous innervation of the head and neck is provided by sensory fibers from the trigeminal nerve and the cervical plexus. Innervation of the airway comes from the vagus and glossopharyngeal nerves. Sympathetic blockade of the face and upper extremity is achieved by anesthetizing the stellate ganglion.

Trigeminal Nerve Blocks

The trigeminal nerve divides into three main branches in the middle cranial fossa. These divisions, the ophthalmic, maxillary, and mandibular nerves, provide sensation to the eye and forehead, midface and upper jaw, and lower jaw, respectively (Fig. 43-19 A). With the exception of the motor fibers to the muscles of mastication, carried by the mandibular nerve, these nerves are wholly sensory.

The gasserian ganglion block, approached classically through the foramen ovale, is infrequently used for producing surgical anesthesia. In the past, it was primarily applied to the diagnosis and treatment of trigeminal neuralgia; however, the increasing popularity and safety of thermocoagulation

---

for ablation of the ganglion have rendered neurolytic blocks obsolete.

Clinical Applications

Blockade of the second and third divisions of the trigeminal nerve, as well as blockade of the peripheral branches, is still occasionally useful in the diagnosis and management of pain syndromes and for discrete surgical procedures in selected patients (Fig. 43-19 B).

Side Effects/Complications

The block of the maxillary nerve can be associated with hematoma formation, as well as with the spread of the local anesthetic solution to the optic nerve, causing temporary blindness. Mandibular nerve block is not associated with major complications. If the needle is advanced past the pterygoid plate more than the recommended 0.5 cm, the pharynx may be entered, thus increasing the theoretic risk of contaminating the infratemporal fossa. Rarely, subarachnoid spread of local anesthetic, resulting in brain-stem anesthesia, may occur. [43]

Technique: Mandibular and Maxillary Nerves

The mandibular and maxillary nerves, two divisions of the trigeminal nerve, can be blocked through the same needle entry site (see Fig. 43-19 B). The maxillary nerve (second division) is blocked as it exits the skull via the foramen rotundum and crosses the pterygopalatine or infratemporal fossa between the skull and the upper jaw. The nerve terminates as the infraorbital nerve as it exits via the infraorbital foramen, where it can also be anesthetized.

The coronoid notch of the mandible is located, and with the patient's mouth closed, a 22-gauge, 8-cm needle is inserted at the inferior edge of the coronoid notch perpendicular to the skin entry site. The needle contacts the lateral pterygoid plate at a depth of about 5 cm. It is then withdrawn and redirected anteriorly and superiorly to "walk off" the plate and is advanced approximately 0.5 cm into the pterygopalatine fossa (Fig. 43-19 C). From 3 to 5 mL of local anesthetic solution will produce anesthesia to the upper jaw and skin of the lower eyelid, cheek, and upper lip.

The mandibular nerve (third division) leaves the cranium via the foramen ovale and innervates the skin of the lower jaw and the skin anterior and superior to the ear via its posterior division. Peripheral sensory branches of V3 include the buccal, auriculotemporal, lingual, and inferior alveolar (terminating in the mental nerve) nerves. The anterior division supplies motor innervation to the muscles of mastication.

The mandibular nerve is blocked via the same entry site as the maxillary nerve. The needle is again advanced along the inferior margin of the coronoid notch until the bone of the lateral pterygoid plate is contacted (
5 cm). The needle is withdrawn and is redirected to walk off the posterior border of the pterygoid plate, and it is advanced in an attempt to elicit a paresthesia. The needle should not be inserted farther than 0.5 cm past the plate (Fig. 43-19 D). Injection of 3 to 5 mL of solution at this site is adequate.

Terminal Sensory Branches of the Trigeminal Nerve

Clinical Applications

Blockade of the terminal branches of the three divisions of the trigeminal nerve is primarily used for diagnosis of trigeminal neuralgia. Individual nerve blocks can also be used for minor surgical procedures.

Side Effects/Complication

Direct injection of the peripheral nerves within the bony foramina may result in nerve damage.

Technique: Supraorbital and Supratrochlear Nerves

The supraorbital and supratrochlear nerves, branches of the ophthalmic nerve (V1), are derived from the frontal nerve, which supplies the skin of the medial upper eyelid and forehead. The supraorbital notch can be easily palpated. This landmark lies on a vertical line with the pupil (when the eye is looking directly forward), the infraorbital foramen, and the mental foramen (Fig. 43-20 . and Plates 1 and 2)

Figure 43-20 Blockade of the terminal sensory branches of the trigeminal nerve. A vertical line connects the supraorbital notch, infraorbital foramen, and mental foramen.

A 25-gauge, 2-cm needle is inserted immediately superior to the supraorbital notch, and 2 to 4 mL of local anesthetic solution is injected. A paresthesia is sometimes elicited, but it is not essential. The supratrochlear nerve can be blocked by extending the supraorbital injection site medially with an additional 2 to 4 mL of solution.

Technique: Infraorbital Nerve

This nerve can be blocked to provide anesthesia of the upper lip and skin of the cheek. The infraorbital notch lies on the line connecting the supraorbital and mental foramina and the pupil of the eye. The nerve can be blocked by advancing a 25-gauge, 3-cm needle laterally and cephalad toward the foramen from a point 1 cm inferior to it. A paresthesia is frequently elicited. When the needle tip is in the region of the foramen, 3 to 4 mL of solution is injected. It is not essential that the needle enter the foramen (see Fig. 43-20) .

Technique: Mental Nerve

Blockade of the mental nerve as it exits the mental foramen provides anesthesia of the lower lip and chin. The mental foramen lies on the vertical line connecting the pupil of the eye with the foramina of the peripheral nerves of V1, V2, and V3. The foramen is palpated in the mandible, and a 25-gauge, 3-cm needle is inserted inferomedially. Infiltration of 2 to 4 mL of solution, either after elicitation of a paresthesia or in the region of the foramen, results in anesthesia of the mental nerve (see Fig. 43-20) .

Cervical Plexus Blockade

The cervical plexus is derived from the C1, C2, C3, and C4 spinal nerves and supplies branches to the prevertebral muscles, strap muscles of the neck, and phrenic nerve. The

Figure 43-21 Anatomic landmarks and method of needle placement for superficial cervical plexus block.

deep cervical plexus supplies the musculature of the neck segmentally, as well as the cutaneous sensation of the skin between the trigeminally innervated face and the T2 dermatome of the trunk. Blockade of the superficial cervical plexus results in anesthesia of only the cutaneous nerves.

Clinical Applications

Blocks of the cervical plexus are easy to perform and provide anesthesia for surgical procedures in the distribution of C2 to C4, including lymph node dissections, plastic repairs, and carotid endarterectomy. The ability to monitor the awake patient's neurologic status continuously is an advantage of this anesthetic technique for the latter procedure and has resulted in an upsurge in the popularity of this technique. [44] [45] Bilateral blocks can be used for tracheostomy and thyroidectomy.

Side Effects/Complications

Although these blocks are technically straightforward, needle placement for the deep cervical block allows local anesthetic injection in close proximity to a variety of neural and vascular structures. Reported complications and side effects include intravascular injection, blockade of the phrenic and superior laryngeal nerve, and spread of local anesthetic solution into the epidural and subarachnoid spaces.

Technique: Superficial Cervical Plexus

The superficial cervical plexus is blocked at the midpoint of the posterior border of the sternocleidomastoid muscle. A skin wheal is made at this point, and a 22-gauge, 4-cm needle is advanced, injecting 5 mL of solution along the posterior border and medial surface of the sternocleidomastoid muscle (Fig. 43-21) . It is possible to block the accessory nerve with this injection, resulting in temporary ipsilateral trapezius muscle paralysis.

Technique: Deep Cervical Plexus

The deep cervical plexus block is a paravertebral block of the C2 to C4 spinal nerves as they emerge from their foramina in the cervical vertebrae (Fig. 43-22 and Plate 4). The traditional approach utilizes three separate injections at C2, C3, and C4. The patient lies supine with the neck slightly extended and the head turned away from the side to be blocked. A line is drawn connecting the tip of the mastoid process and the Chassaignac tubercle (transverse process of C6); a second line is drawn 1 cm posterior to this first line. The C2 transverse process lies 1 to 2 cm caudad to the mastoid process, where it can usually be palpated. The C3 and C4 transverse processes lie at 1.5-cm intervals along the second line. After skin wheals are raised over the transverse processes of C2, C3, and C4, three 22-gauge, 5-cm needles are advanced perpendicular to the skin entry site with a slight caudad angulation. The transverse process is contacted at a depth of 1.5 to 3 cm. If a paresthesia is obtained,

Figure 43-22 Anatomic landmarks and method of needle placement for deep cervical plexus blocks at C2, C3, and C4.

3 to 4 mL of solution is injected after careful aspiration for blood and cerebrospinal fluid. If no paresthesia is elicited initially, the needle is walked along the transverse process in the anteroposterior plane until a paresthesia is obtained.

This block can also be performed with a single injection of 10 to 12 mL at the C4 transverse process. [46] Cephalad spread of the local anesthetic usually anesthetizes the C2 and C3 nerves. Cervical plexus anesthesia can also be observed after injection at the interscalene level for brachial plexus blockade. Maintenance of distal pressure and a horizontal or slightly head-down position may facilitate the onset of cervical plexus blockade using the interscalene technique.

Accessory Nerve Block

The accessory (11th cranial) nerve is occasionally blocked to supplement the interscalene brachial plexus approach for shoulder procedures. Blockade of the accessory nerve results in motor paralysis of the trapezius muscle, ensuring lack of patient movement during the surgical procedure. The nerve traverses the posterior triangle of the neck (bordered by the posterior border of the sternocleidomastoid muscle, middle third of the clavicle, and anterior border of the trapezius muscle) in a very superficial position, after emerging from the substance of the sternocleidomastoid muscle at the junction of the superior and middle thirds of that muscle's posterior border. It can easily be blocked at that site by an injection of 6 to 10 mL of local anesthetic. This nerve is often unintentionally anesthetized when a superficial cervical plexus block is performed.

Local Anesthesia of the Airway

Clinical Applications

Anesthesia of the airway can be used to facilitate diagnostic laryngoscopy and bronchoscopy, as well as to allow the comfortable placement of a tracheal tube in those patients whose anatomy dictates an awake endotracheal intubation. Blocks of the superior laryngeal nerves bilaterally, along with translaryngeal injection of local anesthetic, provide anesthesia of the airway from the infraglottic area to the epiglottis. Additional topical application of local anesthetic to the oral and nasal mucosa, along with appropriate sedation, provides satisfactory analgesia for endoscopic procedures.

Side Effects/Complications

The mucosa of the upper airway is well perfused, resulting in rapid uptake of local anesthetics injected or topically applied in this area. Careful attention to total drug dosages, close observation of the patient, and compulsive aspiration prior to injection diminish the risk of local anesthetic toxicity. Other problems and complications are rare; however,

Figure 43-23 (A) Anatomic landmarks and method of needle placement for superior laryngeal nerve block. (B) The needle is walked off the greater cornu of the hyoid bone inferiorly.

caution should be employed in the patient with a full stomach, because these blocks abolish the airway reflexes.

Technique: Superior Laryngeal Nerve

The patient is placed supine with the neck extended. The hyoid bone is displaced laterally toward the side to be blocked, and a 25-gauge, 2.5-cm needle is walked off the greater cornu of the hyoid bone inferiorly and is advanced 2 to 3 mm (Fig. 43-23) . As the needle passes through the thyrohyoid membrane, a slight loss of resistance is felt, and 3 mL of local anesthetic solution is injected superficial and deep to this structure. The block is then repeated on the opposite side. This technique produces anesthesia from the inferior aspect of the epiglottis to the vocal cords.

Technique: Translaryngeal Block

The translaryngeal block is simple to perform and results in anesthesia of the trachea below the vocal cords. However, the injection of local anesthetic usually stimulates the cough reflex, and this block should be avoided in patients in whom coughing is undesirable.

With the patient in the supine position, the cricothyroid membrane is located, and a 20-gauge or smaller 3- to 5-cm plastic catheter over a needle is introduced in the midline (Fig. 43-24) . The inner steel cannula is withdrawn with the plastic catheter held firmly in place; aspiration of air confirms correct catheter placement. From 3 to 5 mL of 4 percent lidocaine solution is injected rapidly, usually resulting in a vigorous cough, which aids in the spread of the solution within the trachea.

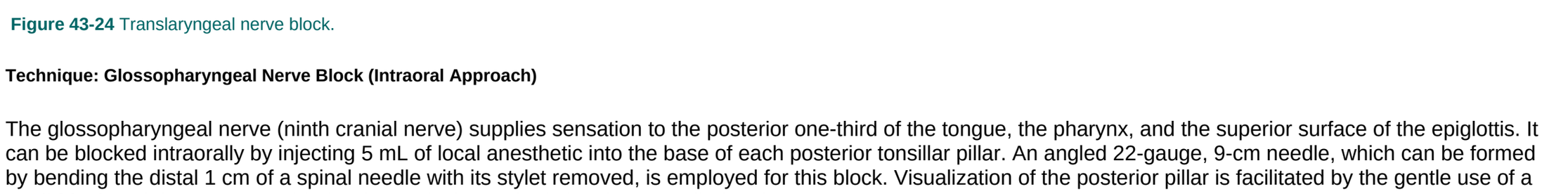

Figure 43-24 Translaryngeal nerve block.

Technique: Glossopharyngeal Nerve Block (Intraoral Approach)

The glossopharyngeal nerve (ninth cranial nerve) supplies sensation to the posterior one-third of the tongue, the pharynx, and the superior surface of the epiglottis. It can be blocked intraorally by injecting 5 mL of local anesthetic into the base of each posterior tonsillar pillar. An angled 22-gauge, 9-cm needle, which can be formed by bending the distal 1 cm of a spinal needle with its stylet removed, is employed for this block. Visualization of the posterior pillar is facilitated by the gentle use of a no. 3 MacIntosh laryngoscope blade after topical anesthetic has been applied to the

tongue. Careful aspiration prior to injection is mandatory because of the close proximity of the carotid artery.

Miscellaneous Head and Neck Blocks

Retrobulbar Block

Clinical Applications

The retrobulbar block (Ch. 63) provides anesthesia for corneal, anterior chamber, and lens procedures when combined with a block of the orbicularis oculi muscle. These blocks are often performed by the surgeon rather than the anesthesiologist, and they have gained increasing popularity for cataract surgery in the elderly outpatient population. The safety of this regional anesthetic technique was documented by Backer and coworkers, [47] who demonstrated a zero incidence of reinfarction or death in 288 patients with a history of myocardial infarction undergoing local anesthesia and/or retrobulbar block for ophthalmologic procedures.

Side Effects/Complications

Retrobulbar blocks are associated with several possible complications, including hematoma formation, local anesthetic toxicity, development of the oculocardiac reflex, and possible spinal anesthesia via the optic nerve sheath. [48] Retrobulbar block is uncomfortable for the patient. A small dose of a short-acting sedative, such as propofol, just prior to the injection prevents pain and patient movement.

Technique

The retrobulbar block is performed with the patient supine and looking straight ahead. A 23-gauge, 3-cm blunted needle is inserted at the inferolateral border of the bony orbit and is directed toward the apex of the orbit. A pop is often felt as the needle tip enters the orbital muscle cone, and 2 to 4 mL of solution is injected. Blockade of the facial nerve fibers that innervate the orbicularis oculi muscle is also performed to complete the anesthesia.

Stellate Ganglion Block

Clinical Applications

Blockade of the stellate ganglion is used primarily in the treatment of upper extremity sympathetic dystrophy and for increase of blood flow to this area (Ch. 70) .

Side Effects/Complications

Because of the close proximity of several major neural and vascular structures to the site of needle insertion, side effects and complications can occur. These include block of the brachial plexus and recurrent laryngeal nerves, hematoma formation, intravascular injection resulting in convulsions, and epidural and subarachnoid injections. [49]

Technique

The patient lies supine with the neck slightly extended. The most prominent cervical transverse process--the Chassaignac tubercle, C6--is palpated between the sternocleidomastoid muscle and the trachea. The anesthesiologist then palpates the C6 tubercle between the index and middle fingers, pushing the carotid artery laterally. A skin wheal is raised between the fingers, over the tubercle, and a 22-gauge, 4-cm short-bevel needle with a 12-mL syringe attached is inserted in a perpendicular direction until the tip contacts the C6 transverse process (Fig. 43-25) . The needle is then withdrawn 3 mm and is fixed. After careful aspiration, 8 to 12 mL of local anesthetic solution is injected. Signs of a successful stellate ganglion block include Horner syndrome, anhidrosis, injection of the conjunctiva, nasal stuffiness, vasodilation, and increased skin temperature.

BLOCKS OF THE THORAX AND ABDOMEN

Intercostal Nerve Block/Interpleural Catheter

Clinical Applications

Few surgical procedures can be performed with intercostal block alone, and the application of these blocks in

Figure 43-25 (A) Anatomic landmarks and method of needle placement for stellate ganglion block. (B) Stellate ganglion block: cross-sectional view.

Figure 43-26 (A) Intercostal nerve block: patient positioning. (B) The index finger displaces the skin up over the rib. The needle is inserted at the tip of the finger and rests on the rib. The needle is walked off the lower rib edge and inserted 3 to 5 mm. (C) An intercostal nerve and its branches.

combination with other techniques has largely been supplanted by epidural blockade. However, there are still special instances, for example, in the presence of anticoagulation or other contraindications to central neuraxial blockade, when these techniques can be used alone or combined with celiac plexus blocks and light general anesthesia to provide excellent surgical conditions for intra-abdominal procedures. In a similar fashion, intrathoracic surgery can be accomplished using intercostal and stellate ganglion blocks with endotracheal sedation.

Interpleural catheter placement for management of postoperative pain was first described by Reiestad and Stromskag in 1986. [50] Enthusiasm for this technique has waxed and waned. The mechanism of action is poorly understood, and reports of efficacy vary. Overall, the results with cholecystectomy have been most favorable. [51] [52] The advantages of interpleural analgesia are more difficult to prove in patients undergoing thoracotomy, perhaps because of technical problems relating to blood in the pleural space, chest tube drainage, and pleural disease. [53] [54] [55]

Side Effects/Complications

The major complication feared with intercostal blockade is pneumothorax. The actual incidence, however, was as low as 0.07 percent in a large series performed by anesthesiologists at all levels of training. Routine postoperative chest radiographs showed an incidence of nonsymptomatic pneumothorax of 0.42 percent. [56] Should this unusual complication occur, treatment is usually limited to observation, administration of oxygen, or needle aspiration. Rarely, chest tube drainage is required when these treatments are unsuccessful.

The risk of systemic local anesthetic toxicity is present with multiple intercostal blocks because of the large volumes and rapid absorption of the solutions. Use of epinephrine has been shown to decrease blood levels. Patients should be monitored and observed carefully during the block and for at least 20 to 30 minutes afterward. Interpleural block should not be performed in patients with pleural fibrosis or inflammation, pleural effusion, lung parenchymal disease associated with pleural disease, or bleeding diathesis. Pleural disease can result in poor spread of local anesthetic solutions or rapid uptake in the case of inflammation. Patients with severe pulmonary disease who rely on their intercostal muscles may evidence respiratory decompensation after bilateral intercostal blockade. [57]

Anatomy and Technique

The intercostal nerves are the primary rami of T1 through T11. T12 is technically a subcostal nerve and supplies branches to the ilioinguinal and iliohypogastric nerves. Fibers from T1 contribute to the brachial plexus; T2 and T3 provide a few fibers to the formation of the intercostobrachial nerve, which supplies the skin to the medial aspect of the upper arm. Each intercostal nerve has four branches: the gray ramus communicans, which passes anteriorly to the sympathetic ganglion; the posterior cutaneous branch, supplying skin and muscle in the paravertebral area; the lateral cutaneous branch, arising just anterior to the midaxillary line and sending subcutaneous branches both anteriorly and posteriorly; and the anterior cutaneous branch, which is the termination of the nerve (Fig. 43-26 C).

Medial to the posterior angles of the ribs, the intercostal nerves lie between the pleura and the internal intercostal

fascia. At the posterior angle of the rib, the nerve lies in the costal groove accompanied by the intercostal vein and artery.

The intercostal nerve can be readily blocked at the angle of the rib just lateral to the sacrospinalis muscle group. The patient is placed in the prone position with a pillow placed under the abdomen to reduce the lumbar curve (Fig. 43-26 A). A line is drawn along the posterior vertebral spines. Nearly parallel lines are drawn along the posterior angles of the rib, which can be palpated 6 to 8 cm from the midline. These lines angle medially at the upper levels in order to prevent overlying of the scapula. The inferior edge of each rib is palpated and is marked on the line intersecting the posterior angle of the rib. After appropriate skin preparation, skin wheals are injected at each of these points. A 22-gauge, short-bevel 4-cm needle is attached to a 10-mL syringe. Beginning at the lowest rib, the index finger of the left hand displaces the skin up over the patient's rib. The needle is inserted at the tip of the finger until it rests on the rib. The fingers of the left hand are shifted to grasp the needle hub firmly. The left hand then walks the needle 3 to 5 mm off the lower rib edge, where 3 to 5 mL of local anesthetic is injected (Fig. 43-26 B). This process is repeated at each rib. Appropriate intravenous sedation providing analgesia and some degree of amnesia is desirable for patient comfort.

Alternatively, intercostal block can be performed in the supine patient at the midaxillary line. Although, theoretically, the lateral cutaneous branch of the nerve can be missed, in reality, computed tomography studies show that injected solutions spread several centimeters along the costal groove. [58] Further injection of 1 to 2 mL of solution as the needle is withdrawn blocks the subcutaneous branches.

The technique for interpleural catheter placement is quite simple and can be performed with the patient in a lateral (and slightly oblique) or sitting position. The sixth or seventh intercostal space is identified. Needle insertion is performed about 10 cm lateral from the posterior midline, and an epidural needle tip is advanced until it

rests on the cephalad edge of the rib below the intercostal space to be entered. A glass syringe filled with saline or air is then attached to the needle, and the unit is advanced slowly over the superior edge of the rib. When the tip of the needle enters the parietal pleura, the solution in the syringe is drawn into the chest cavity because of the negative intrathoracic pressure. This effect can be observed in both mechanically and spontaneously ventilating patients, but it is accentuated in the latter group.

The catheter is then inserted approximately 5 to 8 cm into the interpleural space and is secured on the chest wall. During needle positioning and catheter placement, care must be taken to minimize entrainment of air through the needle. Lung parenchymal damage can occur with loss of resistance techniques or insertion of excessive lengths of catheter.

Celiac Plexus Block

Clinical Applications

The celiac plexus block can be combined with intercostal block to provide anesthesia for intra-abdominal surgery (Ch. 70) . Because it results in blockade of the autonomic nervous system, this block may help to reduce stress and endocrine responses to surgery.

Side Effects/Complications

Side effects associated with celiac plexus block include the following: hypotension; spinal, epidural, or intravascular injection; pneumothorax; puncture of viscera (kidney, ureter, gut); and retroperitoneal hematoma.

Anatomy and Technique

The celiac plexus contains visceral afferent and efferent fibers derived from T5 to T12 via the greater, lesser, and least splanchnic nerves. The plexus has no somatic fibers and is composed of a number of ganglia and nerve fibers. It innervates most of the abdominal viscera. A knowledge of the surrounding structures is important for correct needle placement. The plexus lies in close relation to the L1 vertebrae. The vena cava lies anteriorly to the right, and on the left anteriorly is the aorta. The kidneys lie laterally, with the pancreas anterior. The number of ganglia varies from one to five, and the size is 0.5 to 4.5 cm in diameter. Left-sided ganglia are usually lower than those on the right.

Bony surface landmarks can be reliably utilized for needle placement. With the patient in the prone position with a pillow beneath the abdomen, lines are drawn connecting the spine of T12 with points 7 to 8 cm lateral at the lower edges of the 12th ribs. These lines form a flattened isosceles triangle, the equal sides of which serve as directional guides for the needles (Fig. 43-27 B). A 20-gauge, 10- to 15-cm needle is inserted on the left side through a skin wheal at a 45-degree angle toward the body of T12 or L1. Bony contact should be made at an average depth of 7 to 9 cm. The needle is then withdrawn and is reinserted to allow the tip to slide off the vertebral body anterolaterally. The needle is advanced 1.5 to 2 cm past this point; aortic pulsations can be felt as they are transmitted along the needle when it is correctly placed (see Fig. 43-27). Once this depth is ascertained, the right-sided needle is inserted in a similar fashion to a depth of 1.0 to 1.5 cm farther (Fig. 43-27 A)

When the needles are in position, observation for leakage of blood, urine, or cerebrospinal fluid is made prior to careful aspiration. A 3- to 5-mL test dose of local anesthetic is given prior to injection of 20 to 25 mL of solution through each needle.

Paravertebral Block

Clinical Applications

This block can be added to multiple intercostal and/or bilateral celiac plexus blocks to provide anesthesia for abdominal, pelvic, and upper leg surgery. Application for paravertebral block alone is limited, although it is useful in the diagnosis and treatment of certain pain disorders.

Figure 43-27 (A) Celiac plexus block: the needle is inserted at a 45-degree angle toward the body of L1. The tip slides off the vertebral body anterolaterally and is advanced 1.5 to 2 cm. A, aorta; IVC, inferior vena cava. (B) Celiac plexus block: patient position and surface landmarks.

Side Effects/Complications

Because of the close proximity of the centroneuraxis, epidural or subarachnoid injection of local anesthetic is a risk. Intravascular injection via the lumbar vessels, vena cava, or aorta is possible.

Technique

Lumbar nerves exit the vertebral foramina inferior to the caudad edge of the transverse process. Each nerve divides into anterior and posterior branches; the anterior branches of L1 through L4 (with a contribution from T12) form the lumbar plexus.

The patient is placed in the prone position as described for intercostal blockade. Lines are drawn across the cephalad edges of the lumbar vertebral spinous processes. These lines lie opposite the caudad edges of the homologous transverse processes (Fig. 43-28 A). A skin wheal is raised 3 cm lateral to the midline, and a 20-gauge, 8-cm needle is advanced perpendicularly until it contacts the transverse process at a depth of 3 to 5 cm. The needle is then redirected to walk off the caudad edge of the transverse process. At 1 to 2 cm (the thickness of the transverse process) beyond this point, 6 to 10 mL of local anesthetic is injected (Fig. 43-28 B and Plate 10A and B). Elicitation of a paresthesia or use of a nerve stimulator is helpful in confirming correct needle placement.

CHOICE OF LOCAL ANESTHETIC

The choice of local anesthetic for a peripheral nerve block obviously depends to some degree on the duration of the surgical procedure; however, other factors are also important (Ch. 13) . Prolonged blockade for up to 24 hours is often seen with the long-acting agents such as bupivacaine. Although this feature results in superb postoperative pain relief for the inpatient, it may be undesirable for the ambulatory patient because of the possible risk of nerve or tissue injury in a partially blocked limb. A short- or medium-acting agent may be more appropriate in the outpatient setting. Whatever drug is chosen, the total dosage should be calculated for each patient and should be kept within acceptable safe limits (Table 43-1) (Ch. 13) .

The highest concentrations of local anesthetic drugs are not appropriate for peripheral neural blockade. Therefore, 0.75 percent bupivacaine, 2 percent lidocaine, 2 percent mepivacaine, and 3 percent 2-chloroprocaine are not recommended.

TABLE 43-1 -- Local Anesthetics for Peripheral Nerve Block[a]

DRUG	MAXIMUM DOSE (MG) (WITH EPINEPHRINE)	CONCENTRATION (%)	DURATION (H)
2-Chloroprocaine	1,000	1-2	0.5-1
Lidocaine	500	0.5-1.5	1-3
Mepivacaine	500	0.5-1.5	2-3
Bupivacaine	250	0.25-0.5	4-24
Etidocaine	400	0.5-0.75	3-12

[a] See Ch. 13 for more details.

Figure 43-28 (A) Paravertebral nerve block: patient position and surface landmarks. (B) Paravertebral nerve block: the needle is advanced perpendicularly until it contacts the transverse process. It is redirected to walk off the caudad edge of the transverse process and advanced 1 to 2 cm.

The lowest concentrations of the same agents (e.g., 0.25 percent bupivacaine and 0.5 percent mepivacaine or lidocaine) may not provide complete motor blockade.

Vasoconstrictors, usually epinephrine, can be added to the chosen local anesthetic to improve onset of action, to decrease drug uptake, and to prolong action. A concentration of 1:200,000 epinephrine is usually recommended. Ideally, the epinephrine should be added to the local anesthetic at the time the block is to be performed. Commercially prepared solutions with epinephrine have a lower pH than those in which it is freshly added, resulting in a higher percentage of ionized drug molecules. These ionized molecules do not readily cross the neural membrane, thus delaying the onset of drug action after injection. Epinephrine should not be added to the local anesthetic for blocks of the digits or penis because tissue ischemia may result. Various other additives including clonidine, opioids, and ketamine have been reported to enhance or to prolong local anesthetic peripheral nerve blockade.

SUMMARY

It is possible to perform all surgical procedures while the patient is under general anesthesia; however, the addition of peripheral nerve block techniques to the anesthesiologist's armamentarium adds flexibility and skills that benefit the patient intraoperatively as well as postoperatively. Successfully mastering these techniques and applying them to the appropriate clinical situations add valuable options to the anesthetic care. Finally, for the anesthesiologist, knowledge of regional anesthesia is essential for the diagnosis and treatment of acute and chronic pain syndromes (Chs. 69 and 70) .

References

1. Hall RJ: Hydrochlorate of cocaine. N Y Med J 40:643, 1884.

2. Halsted WS: Practical comments on the use and abuse of cocaine: Suggested by its invariably successful employment in more than a thousand minor surgical operations. N Y Med J 42:294, 1885.

3. Corning JL: On the prolongation of the anaesthetic effect of the hydrochlorate of cocaine, when subcutaneously injected: An experimental study. N Y Med J 42:317, 1885.

4. Braun H: Ueber den Einfluss der Vitalitat der Gewebe auf die ortlichen und allgemeinen Giftwirkungen local anasthesirender Mittel und uber die Bedeutung des Adrenalins fur die local anasthesie. Arch Klin Chir 69:541, 1903.

5. Braun H: Local Anesthesia: Its Scientific Basis and Practical Use, 3rd ed. Philadelphia, Lea & Febiger, 1914.

6. Goldan SO: Intraspinal cocainization for surgical anesthesia. Phila Med J 6:850, 1900.

7. Winnie AP: Interscalene brachial plexus block. Anesth Analg 49:455, 1970.

8. Lanz E, Theiss D, Jankovic D: The extent of blockade following various techniques of brachial plexus block. Anesth Analg 62:55, 1983.

9. Urmey WF, Talts KH, Sharrock NE: One hundred percent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg 72:498, 1991.

10. Urmey WF, McDonald M: Hemidiaphragmatic paresis during interscalene brachial plexus block: Effects on pulmonary function and chest wall mechanics. Anesth Analg 74:352, 1992.

11. Fujimura N, Namba H, Tsunoda K et al: Effect of hemidiaphragmatic paresis caused by interscalene brachial plexus block on breathing pattern,

chest wall mechanics and arterial blood gases. Anesth Analg 81:962, 1995.

12. Brown DL, Cahill DR, Bridenbaugh LD: Supraclavicular nerve block: Anatomic analysis of a method to prevent pneumothorax. Anesth Analg 76:530, 1993.

13. deJong RH: Axillary block of the brachial plexus. Anesthesiology 22:215, 1961.

14. Serlo W, Haapanemi L: Regional anaesthesia in paediatric surgery. Acta Anaesthesiol Scand 29:283, 1985.

15. Eriksson E: Axillary brachial plexus anaesthesia in children with Citanest. Acta Anaesthesiol Scand Suppl 16:291, 1965.

16. Selander D, Edshage S, Wolff T: Paresthesia or no paresthesia. Acta Anaesthesiol Scand 23:27, 1979.

17. Thompson GE, Rorie DK: Functional anatomy of the brachial plexus sheaths. Anesthesiology 59:117, 1983.

18. Montgomery SJ, Raj PP, Nettles D et al: The use of the nerve stimulator with standard unsheathed needles in nerve blockade. Anesth Analg 52:827, 1973.

19. Winnie AP, Collins VJ: The subclavian perivascular technique to brachial plexus anesthesia. Anesthesiology 25:353, 1964.

20. Selander D, Dhuner KG, Lundborg G: Peripheral nerve injury due to injection needles used for regional anesthesia. Acta Anaesthesiol Scand 21:182, 1977.

21. Vester-Andersen T, Christiansen C, Sorensen M et al: Perivascular axillary block. I. Blockade following 40 mL 1% mepivacaine with adrenaline. Acta Anaesthesiol Scand 26:519, 1982.

22. Baranowski AP, Pither CE: A comparison of three methods of axillary brachial plexus anaesthesia. Anaesthesia 45:362, 1990.

23. Partridge BL, Katz J, Benirschke K: Functional anatomy of the brachial plexus sheath: Implications for anesthesia. Anesthesiology 66:743, 1987.

24. Vester-Andersen T, Husum B, Lindburg T et al: Perivascular block. IV. Blockade following 40, 50, or 60 mL of mepivacaine 1% with adrenaline. Acta Anaesthesiol Scand 28:99, 1984.

25. Raj PP, Montgomery SJ, Nettles D, Jenkins MT: Infraclavicular brachial plexus block: A new approach. Anesth Analg 52:897, 1973.

26. Ansbro PF: A method of continuous brachial plexus block. Am J Surg 71:716, 1946.

27. Gaumann DM, Lennon RL, Wedel DJ: Continuous axillary block for postoperative pain management. Reg Anesth 13:77, 1988.

28. Bouaziz H, Narchi P, Mercier FJ et al: Comparison between conventional axillary block and a new approach at the midhumeral level. Anesth Analg 84:1058, 1997.

29. Bier A: Ueber einen neuen Weg Lokalanasthesie an den gliedmassen zu Erzcugen. Verh Dtsch Ges Chir 27:204, 1908.

30. Duggan J, McKeown DW, Scott DB: Venous pressures in intravenous regional anesthesia. Reg Anesth 9:70, 1984.

31. Davies JAH, Wilkey AD, Hall ID: Bupivacaine leak past inflated tourniquets during intravenous regional analgesia. Anaesthesia 39:996, 1984.

32. Sukhani R, Garcia CJ, Munhall RJ et al: Lidocaine disposition following intravenous regional anesthesia with different tourniquet deflation techniques. Anesth Analg 68:633, 1989.

33. Moore MA, Garfin SR, Hargens AR: Wide tourniquets eliminate blood flow at low inflation pressures. J Hand Surg 12A:1006, 1987.

34. Chayden D, Nathan H, Chayden M: The psoas compartment block. Anesthesiology 45:95, 1976.

35. Winnie AP, Ramamurthy S, Durrani Z: The inguinal paravascular technique of lumbar plexus anesthesia: The "3-in-1 block." Anesth Analg 52:989, 1973.

36. Berry FR: Analgesia in patients with fractured shaft of femur. Anaesthesia 32:576, 1977.

37. Patel NJ, Flashburg MH, Paskin S et al: A regional anesthetic technique compared to general anesthesia for outpatient knee arthroscopy. Anesth Analg 65:185, 1986.

38. Wasseff MR: Interadductor approach to obturator nerve blockade for spastic conditions of adductor thigh muscles. Reg Anesth 18:13, 1997.

39. Labat G: Regional Anesthesia: Its Technique and Clinical Application. Philadelphia, WB Saunders, 1924.

40. Beck GP: Anterior approach to sciatic nerve. Anesthesiology 24:222, 1963.

41. Ichiyanagi K: Sciatic nerve block: Lateral approach with the patient supine. Anesthesiology 20:601, 1959.

42. Raj PP, Parks RI, Watson TD et al: New single position supine approach to sciatic-femoral nerve block. Anesth Analg 54:489, 1975.

43. Nique TA, Bennett CR: Inadvertent brainstem anesthesia following extraoral trigeminal V 2-V 3 blocks. Oral Surg 51:468, 1981.

44. Tissot S, Frering B, Gagnieu MC et al: Plasma concentrations of lidocaine and bupivacaine after cervical plexus block for carotid surgery. Anesth Analg 84:1377, 1997.

45. Peitzman AB, Webster WM, Loubeau JM et al: Carotid endarterectomy under regional (conductive) anesthesia. Ann Surg 196:59, 1982.

46. Winnie AP, Ramamurthy S, Durrani Z et al: Interscalene cervical plexus block: A single injection technic. Anesth Analg 54:370, 1975.

47. Backer CL, Tinker JH, Robertson DM et al: Myocardial reinfarction following local anesthesia for ophthalmic surgery. Anesth Analg 59:257, 1980.

48. Nicoll JMV, Acharya PA, Ahlen K et al: Central nervous system complications after 6000 retrobulbar blocks. Anesth Analg 66:1298, 1987.

49. Scott DL, Ghia JN, Teeple E: Aphasia and hemiparesis following stellate ganglion block. Anesth Analg 62:1038, 1983.

50. Reiestad F, Stromskag KE: Interpleural catheter in the management of postoperative pain. Reg Anesth 11:89, 1986.

51. Murphy DF: Continuous intercostal nerve blockade for pain relief following cholecystectomy. Br J Anaesth 55:521, 1983.

52. Frank ED, McKay W, Rocco A et al: Interpleural bupivacaine for postoperative analgesia following cholecystectomy: A randomized prospective study. Reg Anesth 15:26, 1990.

53. Rosenberg PH, Scheinin BM, Lepantalo MJ et al: Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 67:811, 1987.

54. Ferrante FM, Chan VWS, Arthur GR et al: Interpleural analgesia after thoracotomy. Anesth Analg 72:105, 1991.

55. Francois T, Blanloeil Y, Pillet F et al: Effect of interpleural administration of bupivacaine or lidocaine on pain and morphine requirement after esophagectomy and thoracotomy: A randomized, double-blind and controlled study. Anesth Analg 80:718, 1995.

56. Moore DC, Bridenbaugh LD: Pneumothorax: Its incidence following intercostal nerve block. JAMA 174:842, 1960.

57. Cory PC, Mulroy MF: Postoperative respiratory failure following intercostal block. Anesthesiology 54:418, 1981.

58. Moore DC: Intercostal nerve block: Spread of India ink injected into the subcostal groove. Br J Anaesth 53:325, 1981.

Atlas of Regional Anesthesia Procedures

Figure 43-1 Plate 1. Blockade of the terminal sensory branches of the trigeminal nerve. A vertical line connects the supraorbital notch, infraorbital foramen, and mental foramen.

Figure 43-2 Plate 2. Dermatomes of the head, neck, and face.

Figure 43-3 Plate 3. Supraclavicular block. The three trunks are compactly arranged at the level of the first rib. The needle is systematically walked anteriorly and posteriorly along the rib until the plexus is located.

Figure 43-4 Plate 4. Anatomic landmarks and method of needle placement for deep cervical plexus blocks at C2, C3, and C4.

Figure 43-5 Plate 5. Axillary block. The arm is abducted 90 degrees. Distal digital pressure is maintained during needle placement and injection of local anesthetic.

Figure 43-6 Plate 6. Cross-sectional lumbar vertebral centroneuraxis anatomy at the L3-L4 level.

Figure 43-7 Plate 7. Techniques of epidural needle insertion most often used in locating the epidural space. (A) In the loss-of-resistance technique, the needle is inserted into the ligamentum flavum, and then a syringe containing an air bubble is attached to the hub. After compression of the air bubble is obtained by applying pressure to the syringe plunger, the needle is carefully advanced until its entry into the epidural space is noted by the characteristic loss-of-resistance to syringe plunger pressure, and the fluid enters the space easily. (B) In the hanging-drop technique, the needle is inserted into the ligamentum flavum, and then a drop of saline (or local anesthetic) is placed in the hub. The needle is then carefully advanced until its entry into the epidural space is noted by the drop of solution being "sucked" into the epidural space.

Figure 43-8 Plate 8. Posterior lumbar vertebral centroneuraxis anatomy.

Figure 43-9 Plate 9. Lateral lumbar vertebral centroneuraxis anatomy, from L1 through the coccyx.

Figure 43-10 Plate 10. Paravertebral nerve block. (A) Patient position and surface landmarks. (B) The needle is advanced perpendicularly until it contacts the transverse process. It is redirected to walk off the caudad edge of the transverse process and advanced 1 to 2 cm.

Figure 43-11 Plate 11. The lumbar plexus lies in the psoas compartment between the psoas major and quadratus lumborum muscles.

Figure 43-12 Plate 12. A and B. Anatomic landmarks for the posterior approach to sciatic nerve block.

Figure 43-13 Plate 13. Anatomic landmarks for lateral femoral cutaneous, femoral, and obturator nerve blocks. Obturator nerve block. The needle is walked off the inferior pubic ramus in a medial and cephalad direction until it passes into the obturator canal.

Figure 43-14 Plate 14. Anatomic landmarks for block of the deep peroneal, superficial peroneal, and saphenous nerves at the ankle.

Figure 43-15 Plate 15. (A) Anatomic landmarks for block of the posterior tibial and sural nerves at the ankle. (B) Posterior tibial nerve. Method of needle placement for block at the ankle. (C) Sural nerve. Method of needle placement for block at the ankle.

Figure 43-16 Plate 16. Intervertebral epidural anesthesia. (A) Recommended position of the patient. (B) Influence of spinous processes on needle orientation. (C) Anatomy of the epidural space.

Figure 43-17 Plate 17. Caudal anesthesia. (A) Anatomic landmarks. (B) Position of the patient and surface landmarks. (C) Puncture technique: (1) skin penetration (60- to 90-degree angle to the skin); (2) redirection of the needle; (3) slight penetration (1-2 mm) within the spinal canal.

Figure 43-18 Plate 18. Supraclavicular brachial plexus block. (A) Relationship of the brachial plexus trunks to the clavicle and lower insertions of the anterior and middle scalene muscles. (B) Insertion routes of the most common supraclavicular approaches to the brachial plexus.

Figure 43-19 Plate 19. Proximal lower extremity blocks. (A) Fascia iliaca compartment block. (B) Classical femoral nerve block. (C) Relationship of the femoral nerve in the groin. (D) Insertion routes of the most common proximal blocks of the lower extremity (cross-section of the thigh).

Figure 43-20 Plate 20. Iliohypogastric and ilioinguinal nerve blocks. (A) Relationship of the ilioinguinal and iliohypogastric nerves. (B) Puncture technique (two sites of injection).

Figure 43-21 Plate 21. Intercostal nerve blocks. (A) Recommended position of the patient. (B) Intercostal space and puncture technique: (1) insertion of the needle until it contacts the lower border of the upper rib; (2) caudad redirection of the needle so as to pass immediately below the rib while continuous pressure is exerted on the barrel of the syringe. (C) Intercostal nerves and branches.

Figure 43-22 Plate 22. Penile block. (A) Relationship of dorsal nerves and orientation of the needle (sagittal section at the level of the pubic symphysis). (B) Position of the patient and needle orientation (almost perpendicular to the skin, with slight slope both medially and caudally).

Chapter 44 - Regional Anesthesia in Children *

Bernard J. Dalens

INTRODUCTION

Regional anesthetic techniques have regained an established place in pediatric anesthesia, and their field of application is rapidly expanding. The pharmacologic properties of available local anesthetics are fully evaluated, even in neonates, and the fear of nerve lesions and neurologic sequelae has proved unfounded as confirmed by a recent prospective study involving 24,409 children given a regional block. [1] Most of the technical difficulties have been overcome with the general use of physical means of nerve/space location independent of the (young) patient's cooperation such as loss-of-resistance techniques or use of nerve stimulators aimed at eliciting muscle twitches in relevant muscles. Devices specifically designed for use in pediatric patients are now commonly available, and safer approaches have been extensively studied. Most outpatient surgery can be managed successfully with regional anesthetic techniques, either as the sole anesthetic or, as usual in pediatric practice (in approximately 90% of cases), in combination with light general anesthesia. [1] Central blocks are partic-ularly well tolerated by infants and young children, which make them mandatory in many operations of the lower limbs and infraumbilical part of the abdomen. Additionally, the use of regional anesthesia reduces the cost of patient care.

SPECIFICITY OF THE PEDIATRIC PERIOD

Embryologic Development of the Vertebral Column and Spinal Cord

Many organs and their functions are not fully developed at birth. During the embryonic period, the spinal cord occupies the entire spinal canal, but from the fetal period onward, the growth of the spinal canal exceeds that of neural structures. Thus the termination of the spinal cord and that of the dural sac project at progressively higher levels, L4 and S3/S4 respectively, up to the end of the 1st year of life. During the 2nd year, it approaches adult levels (i.e., L1 and S2, respectively). As a consequence, lumbar epidural approach above L4 should be avoided in infants as the spinal cord can be directly damaged by the needle.

Myelinization begins during the fetal period in cervical neuromeres and extends progressively but is not fully completed until the end of the 12th year of life. [2] [3] This lack of myelin in young patients favors the penetration of local anesthetics within the nerve fibers, which are thinner, with reduced distance between successive nodes of Ranvier. Thus, diluted local anesthetics can produce consistent nerve blockade. Ossification of the vertebral column is not

** See Appendix 1, Practice Guidelines for Chronic Pain Management*

achieved at birth. The vertebral arches fuse posteriorly during the 1st year of life, and their junction with the vertebral body becomes ossified from the 3rd to the 6th year. [4] The sacrum is made up of distinct vertebral pieces, the fusion and ossification of which are not fully achieved before the 25th year of life. Posterior approach to the epidural space is possible, at sacral levels in the same way as at lumbar levels. On the other hand, because the sacrum is cartilaginous, it can be traversed easily by sharp needles.

At birth, the spine has a single regular flexure. Whatever the intervertebral space, any epidural needle is inserted with the same orientation. With the development of the cervical flexure (head sustained) and then the lumbar lordosis (sitting position), the orientation of the epidural needle has to be modified accordingly. Another important feature is the loose attachment of fasciae and sheaths to nerve trunks in young patients, allowing extended spread of local anesthetics, thus resulting in high-quality nerve blockade whatever the technique, but also, occasionally, in unwanted or undesirable distant nerve blocks.

Perception of Pain

Somatic pain is a subjective sensory experience resulting from the intermixing of three main components: [5] [6] (1) motivational-directive, conveyed by unmyelinated C fibers ("slow" pain or "true" pain), which leads to protective reflexes such as autonomic reactions, muscle contraction, and rigidity; (2) sensory-discriminatory, propagated by myelinated A delta fibers (fast pain), which allows accurate identification and location of the nociceptive stimuli and elicits withdrawal reactions; and (3) cognitive-evaluative, a multifactorial but typically cerebral process not involving any peripheral receptors. C fibers are functional from early fetal life onward; thus, the motivational-directive component ("true" pain) is perceived by the neonate and the fetus. As A delta fibers are thinly myelinated, the velocity of nerve impulses depends on the progression of myelinization. The main difference in pain perception between children and adults is related to the cognitive-evaluative component that develops throughout childhood and adolescence. This is influenced by environmental, educational, social, cultural, and individual factors, including previous experiences of pain. A major difficulty is the assessment, and at times even the identification, of pain in children, especially in infants. The younger the patient, the greater the difficulty to communicate because the ability to express distress and discomfort is limited. During the last decade, pediatric pain has received considerable attention, and reliable age-related pain scales have been developed to evaluate both the severity of pain and the efficacy of its treatment.

Pharmacology of Local Anesthetics, Narcotics, and Other Additives

Local Anesthetics

The pharmacology of local anesthetics in children is similar to that in adults (Chs. 13 and 59) . However, certain differences have to be taken into account before a regional block is performed, especially in neonates and infants. The effects of local anesthetics depend on (1) their spread from the site of injection, which is often considerable in infants, both in the epidural space and along the nerve sheaths; (2) their fixation at the local binding sites such as surface proteins and lipids, especially myelin [3] [7] and (3) the permeability of nerve fibers. In young patients, the endoneurium is loose and easily traversed in both directions. As the child grows up, the endoneurium becomes enriched in connective fibers and is less permeable. Both the latency and the duration of nerve blockade increase with age.

In their nonionized form, local anesthetics can cross almost freely the endothelium of the capillaries surrounding the site of injection. As the cardiac output and the local blood flow of infants are two to three times greater than in adults, the systemic absorption of local anesthetics is increased accordingly, and vasoactive agents such as epinephrine are effective in slowing down this systemic uptake. Within the blood stream, the local anesthetic binds to (1) albumin (and can compete with molecules previously bound to albumin, including bilirubin and various drugs), and (2) alpha $_1$ -acid glycoprotein (or orosomucoid), the plasma concentration of which is low in infants less than 9 months old. Because of this low concentration of plasma proteins, there is a significant increase in the unbound free form of all aminoamides with subsequent danger of systemic toxicity. [8] [9] [10]

Toxic levels of local anesthetics are not clearly established. The administration of common doses of local anesthetics (i.e., 6-8 mg/kg of lidocaine or mepivacaine and 1.5-2 mg/kg of bupivacaine) leads to peak plasma concentration ranging from 3 to 5 mug/mL for lidocaine or mepivacaine, and 0.5 to 1 mug/kg for bupivacaine. [9] Clinical signs of toxicity have been reported with plasma concentration ranging from 7 to 10 mug/mL for lidocaine or mepivacaine and from 1.5 to 2 mug/mL (intraoperatively) to 2 to 2.5 mug/mL (postoperatively) with bupivacaine. However, plasma concentrations of bupivacaine exceeding 4 mug/mL have been commonly detected without any clinical sign of toxicity. The toxic form of all local anesthetics is the free unbound form, which is difficult to measure and correlates poorly with measured concentrations. For bupivacaine, the toxic level of the free unbound form is believed to be around 0.2 mug/mL. [11] Thus, agents with a high protein affinity such as bupivacaine must be used cautiously in the very young, and etidocaine should be avoided in children less than 1 year old, even though there is an increase in the plasma concentration of alpha$_1$ -acid glycoprotein postoperatively. [12] [13] [14] [15] Greater attention will probably be paid, in the very near future, to enantiomers, especially for bupivacaine and mepivacaine, as considerable differences exist in their plasma-protein binding properties, cardiac toxicity, half-life, and pharmacodynamic effects. [16]

In the blood stream, the local anesthetic is also distributed in the red blood cells. In neonates, as erythrocytes are greater in number (polycythemia) and larger in size (macrocythemia), the amount of drug entrapped in red blood cells is relatively higher, and this significantly contributes to the neonatal increase in their half-life.

After systemic absorption and protein binding, the local anesthetic is redistributed to different body fluid compartments and tissues. The degree of tissue hydration

decreases with age. Water accounts for 80 percent of body weight in premature, 75 percent in full-term neonates, 65 percent in

Figure 44-1 Changes in body fluid compartments according to patient's age.

infants, and 60 percent in older children and adults (Fig. 44-1) At the same time, the relative importance of body fluid compartments changes considerably. Intracellular fluids increase from 20 percent of body weight in premature infants to 30 percent in adolescents, whereas extracellular fluids are reduced by 50 percent from birth to adulthood (see Fig. 44-1) The pharmacokinetics of local anesthetics is considerably affected by these major changes (Table 44-1) . The distribution volume of all agents is markedly increased in the very young. Therefore, the peak plasma concentration following injection of a single given dose is less in infants than in adults, thus reducing toxicity, and counteracts the increased systemic absorption due to greater local blood flow. At the same time, during the first 2 years of life, the clearance of all aminoamides is low, [9] [13] and their half-life is considerably increased. This can result in drug accumulation in case of repeated injections. [17] [18] [19] By the 2nd year of life, clearance of these agents increases progressively, becoming higher than that in adults. For this reason young children tolerate doses of local anesthetics that would be toxic in adults (however, this peculiarity should not encourage the administration of excessive doses of local anesthetics).

After systemic distribution, the local anesthetic is progressively eliminated by plasma or hepatic metabolism, and a small amount is excreted in the unchanged form in the urine and in gastric secretions, especially in neonates. Aminoesters are mainly hydrolyzed by plasma cholinesterases, the activity of which gradually increases throughout the first year of life. [20] Aminoamides are principally metabolized in the liver by microsomal enzymes (P_{450} cytochrome), the activity of which is reduced during the first months after birth, [21] but does not really impede the metabolism of clinically used local anesthetics after the first 2 or 3 weeks of life. The danger of systemic toxicity cannot be correlated to the patient's age. However, the rate of hydroxylation of lidocaine and moreover that of mepivacaine is significantly lowered in infants (see Table 44-1) in pathologic circumstances (respiratory distress, cardiac failure). Prilocaine must be avoided in infants as its biotransformation yields 6-hydroxytoluidine, which can cause severe methemoglobinemia following administration of even subtherapeutic doses. Repeated injections of high concentrations of local anesthetics may also result in local myotoxicity. [22]

Narcotics

The pharmacology of narcotics (Chs. 10 and 59) has no special features in infants and children and has been recently reviewed. [23] [24] After intrathecal administration, morphine reaches high concentration levels in the cerebrospinal fluid (CSF), whereas the plasma concentration remains very

TABLE 44-1 -- Influence of Age on Pharmacokinetic Parameters of Aminoamides

AGENTS	V_{DSS} (L/kg)	PROTEIN BINDING (%)	CLEARANCE L/kg/(h)	ELIMINATION HALF-LIFE (h)	ELIMINATION IN UNCHANGED FORM (%)
Lidocaine					
Neonate	1.4-4.9	25	0.30-1.14	2.9-3.3	0.16
Adult	0.2-1.0	55-65	0.30-1.09	1.0-2.2	0.-0.2
Mepivacaine					
Neonate	1.2-2.8	36	0.10-0.18	5.3-11.3	0.36
Adult	0.6-1.5	75-80	0.17-1.10	1.7-6.9	0.04
Bupivacaine					
Neonate	--	50-70	--	6.0-22.0	--
Adult	0.8-1.6	85-95	0.30-0.50	1.2-2.9	0.03
Etidocaine					
Neonate	--	--	--	6.0-22.0	--
Adult	1.5-1.8	90-95	0.75-1.15	2.0-5.6	0.03

low, making it difficult to estimate the half-life. After lumbar epidural injection, systemic uptake of morphine is comparable to that after intramuscular injection. [25] [26] Peak plasma concentration is reached within 10 minutes but does not account for the pharmacodynamic effects, which depend on the drug crossing the dura mater. From the 15th to 20th hour after epidural injection, the CSF concentration of morphine is 50 to 250 times higher than that of plasma. The elimination half-life from CSF is similar to that from plasma, following the same monoexponential elimination curve, but as original concentrations are very high, it takes 12 to 24 hours before the spinal concentration falls below the minimal effective concentration of approximately 10 ng/mL. As morphine is hydrosoluble, its distribution volume, when administered epidurally, equals that of the CSF volume. Addition of epinephrine to the narcotic solution decreases systemic uptake and increases CSF concentration of morphine, [27] which results in a slight but significant increase in duration of pharmacodynamic effects.

Morphine injection along the neuraxis is indicated for long-lasting pain relief. It improves the outcome of many major operations on both healthy and high-risk pediatric patients. [28] However, adverse effects occur in about 50 percent of patients. These include pruritus, nausea, vomiting, urinary retention, and respiratory depression, [29] which can be delayed several hours after the injection, thus making postoperative monitoring of respiratory parameters mandatory for the first 24 hours. The use of apnea monitors and/or pulse oximeters can be helpful but can never replace hourly clinical evaluation. Respiratory depression is almost always preceded by generalized pruritus and sedation, which must be carefully identified, before the respiratory rate progressively decreases over a period of 2 to 3 hours (a sudden apneic spell does not occur with either epidural or intrathecal administration of morphine). Thus, the practitioner has several hours to cure the problem before it becomes dangerous. Currently recommended doses via the lumbar route are 30 mug/kg for epidural morphine and only 10 mug/kg for intrathecal morphine. Higher dosages were commonly administered formerly with a concomitant increase in the adverse effects that could be prevented, without restoring pain, by the administration postoperatively of a continuous intravenous infusion of small doses (2 mug/kg/h) of naloxone. [30] [31] [32] The administration of nalbuphine instead of naloxone has been recommended to counteract adverse effects of epidural morphine. [33] Patients given epidural morphine are not eligible for day surgery. [34] [35]

Short-acting narcotics such as fentanyl (1 to 2 mug/kg) and sufentanil (0.5 mug/kg) can be administered epidurally instead of morphine. They improve intraoperative analgesia, especially when diluted solutions of local anesthetics are used, but have little effect on the prolongation of postoperative pain relief unless a continuous infusion or reinjections are made. Part of their action is due to systemic effects following vascular absorption, which can result in early respiratory depression (but delayed respiratory depression is unlikely). Owing to contradictory clinical effects and debatable pharmacologic basis, their administration for peripheral nerve blocks is not recommended in children. Buprenorphine has been used as an additive to local anesthetics, even in children [36] and can provide long-lasting postoperative analgesia (up to 24 hours). However, as buprenorphine adheres strongly to mu receptors, making reversal with naloxone inconstant and leading to the possibility of respiratory depression on the ward, its use as an adjuvant to centrally administered local anesthetics should be restricted to patients managed in intensive care units.

Other Additives

Epinephrine is the most commonly added alpha-agonist to a local anesthetic. Using solutions with epinephrine (1:200,000, or 1:400,000 before 1 year of age) has several advantages, as it reduces the vascular absorption of the local anesthetics, thus increasing their safety margin. Addition of epinephrine prolongs the duration of effects of short-acting agents (especially lidocaine and mepivacaine) and allows detection of an inadvertent intravascular injection by producing early (within 20 seconds) ST-segment elevation, T-wave change, [37] and hypertension [38] [39] provided the injected dose of epinephrine is at least 0.5 mug/kg. [40]

Clonidine, an $alpha_2$ -adrenergic agonist that can be safely administered along the neuraxis, [41] is being used increasingly as an adjuvant to local anesthetics

administered either centrally [42] [43] [44] [45] [46] or peripherally. [47] [48] At a dose of 1 to 3 mug/kg, clonidine significantly increases (by a factor of 2 approximately) the effects of the local anesthetic with no hemodynamic effects and decreases the peak plasma concentration of the local anesthetic (at least lidocaine). [49] Light to moderate sedation is commonly observed postoperatively for 1 to 3 hours, but it is more beneficial than detrimental, especially in the very young; and, unless the highest doses (i.e.,
2 mug/kg) are given, this sedation does not preclude discharge in cases planned for day surgery. Adding clonidine to the solution makes the insertion of a reinjection catheter unnecessary in many cases (thus reducing the overall morbidity of the procedure, the time required to perform the block, and the overall cost of the procedure). No respiratory depression has been reported, and its occurrence is very unlikely as suggested by adult studies. [50]

Ketamine is currently undergoing a renewed interest as an additive to local anesthetics because of its effects on *N*-methyl- D-aspartate receptors. The administration of a local solution containing 0.5 to 1 mg/kg provides a long-lasting analgesic effect. [51] [52] Behavioral side effects may be observed following the higher dosage but are virtually absent with the low dosage (i.e., 0.5 mg/kg). [53]

In two studies evaluating injectable biodegradable bupivacaine/polyester microspheres, [54] [55] dexamethasone has proved effective in prolonging sciatic nerve blocks in rats, up to 5.5 days after the injection; other data show that methylprednisolone shortens the effects of bupivacaine on C fibers (not A fibers) in rats. [56] The mechanism underlying dexamethasone-prolonged block effect is not understood; a recent study suggested this action could be mediated by suppression of ectopic neural discharges from injured nerve fibers. [57] Although corticosteroids are commonly injected along the neuraxis or spinal roots in rheumatologic diseases, corticosteroids should not be used as additives to local anesthetics for analgesic purpose in children, as severe complications may result from such injections. [58]

Neostigmine also seems to have analgesic properties when administered along the neuraxis, with a protective

effect against hypotension during spinal anesthesia. [59] However, these experimental data have not been established in humans, and the safety of spinal administration of neostigmine is not established.

Warning.

Most of these additives (with the exception of epinephrine, morphine, and, recently in the United States, clonidine) have no legal approval for use as adjuvants of local anesthetics. This does not necessarily mean that their use is forbidden, [60] but precautions should be taken and, in case of a medicolegal claim, the anesthesiologist will have the burden of proving that adding any particular additive was a sound decision. Any other additive (deliberately not mentioned in this chapter) would probably be considered irrelevant or even detrimental according to the current state of the art, particularly so as the stability of mixtures of local anesthetics with additives has not been properly evaluated, with little data being available. [61]

Physiologic and Psychologic Considerations

Surgery generates a neuroendocrine stress response in neonates, infants and children [62] [63] resulting in undesirable alterations of the metabolic state and immune function. [64] Epidural anesthesia diminishes or even suppresses this stress response [65] [66] and is well tolerated in children. Central blocks do not affect left ventricular function [67] and are virtually free of measurable hemodynamic effects, at least up to the age of 8 years. In older patients, the sympathetic block results in a slight but constant decrease in blood pressure, rarely exceeding 20 to 25 percent of systolic preinduction values. [68] [69] [70] [71] Preloading with saline is not recommended in children and, even in adolescents, fluids or vasoactive agents are rarely required to treat the hemodynamic effects of central blocks.

Children are frightened by new environmental conditions in the operating room, and most of them cannot cope with their anxiety (Ch. 59) . They feel abandoned by their parents and threatened by the strangers who intend to use needles, which they fear. Furthermore, even if they wanted to cooperate, they do not have their complete body image until the age of 10 years, which does not let them clearly distinguish between adjacent parts of their body such as forearm and arm. Additionally, they usually cannot understand the concept of paresthesia and that of differential block ("touch" is not "pain"). Thus, localization of nerve trunks and anatomic spaces has to be achieved by physical means such as electric stimulation or loss-of-resistance techniques that do not depend on the patient's cooperation; and sedation or, preferably, light general anesthesia before any block is desirable, as most of these patients are healthy and express the desire to be unconscious during the surgery.

Regional anesthesia has important psychologic effects on the patient, parents, and medical team. A pain-free postoperative course improves the morale of the patient, parents, and nurses. Also, the surgeon is happy to examine a calm, alert, and manageable patient in the postoperative period. Occasionally, regional anesthesia can result in negative psychologic effects. Persistence of motor (and even sensory) block during the postoperative course may be frightening to some children, especially those from 3 to 5 years of age, and sometimes to their parents. This anxiety can be reduced by friendly environmental conditions and precise preoperative explanations as to the expected course of events during the postoperative period. In any case, a motor block must be avoided when not absolutely required for surgery.

SAFETY CONDITIONS FOR PERFORMING REGIONAL BLOCKS IN CHILDREN

Indications and Contraindications

Indications [5] [6] [72] [73]

Regional anesthesia, especially peripheral nerve blocks, are indicated in patients with a full stomach and who require emergency surgery or pain relief. Pain-free clinical and radiologic examinations, wound dressings, and reduction of limb fractures can be safely achieved without compromising vital functions or affecting the evaluation of the status of the central nervous system. In elective surgery, regional techniques are recommended for intraoperative and postoperative pain relief for a number of procedures on the abdomen, pelvis, and extremities, and are applicable even to preterm neonates [74] provided adequate postoperative management is guaranteed. They are particularly suitable for outpatient surgery [75] either as the sole anesthetic or combined with light general anesthesia, which allows rapid and complete awakening at the end of surgery (Table 44-2) . Also, in some clinical conditions such as diabetes mellitus, cardiac failure, and respiratory abnormalities, general anesthesia is better avoided, and regional techniques may be the only alternative allowing a safe and efficient management of the patient. Other indications include relief of nonsurgical pain, physiotherapy of tallipus equinus deformity in children recovering from severe brain damage, and some nonanalgesic applications such as vasodilation in ischemic disorders or maintenance of motor block throughout the recovery period in patients with an unstable fracture, nerve, or tendon repair. The concept of preemptive analgesia, although controversial, [76] has brought new insights on the indications of all antinociceptive treatments, including regional block procedures. Performing a block before rather than at the end of the surgery seems to provide better and more long-lasting postoperative analgesia.

Contraindications

Absolute contraindications to regional anesthesia are similar to those in adults. These include [34] (1) infection at the puncture site, septicemia, and meningitis; (2) bleeding disorders or a patient on anticoagulant therapy; (3) true allergy to local anesthetics, which is rare even with aminoesters; [77] and (4) uncorrected hypovolemia (central blocks). Major vertebral anomalies are contraindications to central block procedures, at least at the level of the anomalies. Minor to moderate lumbosacral spinal anomalies, including tethered cord syndrome for some authors, a functioning ventriculoperitoneal shunt, or patients with mild seizure disorders are not contraindications per se for performing a central

TABLE 44-2 -- Recommended Indications of Regional Techniques for Outpatient Surgery

TYPE OF SURGERY	REGIONAL ANESTHESIA RECOMMENDED	REGIONAL ANESTHESIA NOT RECOMMENDED
Orthopedics	Usual fractures of the limbs, change of plaster, removal of wires and most implants, joint testing/mobilization, arthroscopy, arthrography, tenotomy, aponeurotomy, distal surgery (fingers, toes)	Other procedures
Plastic surgery	Correction of prominent ears, removal of superficial lesions and sutures, revision of scars, dressing changes, ingrowing toe nails	Cleft palate surgery, endonasal surgery
Odontology and stomatology [a]	Dental: conservation, extraction, orthodontics, drainage of sinuses	Multiple extractions, surgery of the mandible or maxilla
General surgery	Inguinal and crural hernia repairs, anal dilation, rectoscopy, epigastric or umbilical hernia repair [b]	Gastric or colonic fiberoscopies
Urology	Excision of hydrocele, cystoscopy, orchidopexy, circumcision, change of urethral catheter, urethral dilatation, submucosal teflon injection, glans plasty, meatotomy	Surgery of the kidney and upper urinary tract, hypospadias repair.
ENT	Myringotomy/grommets, nasal/aural foreign body removal, short-lasting endoscopic examination, antral lavage, nasal cautery	Adenoidectomy, tonsillectomy [c] , antrotomy, surgery of deep structures.
Ophthalmology	Simple skin lesions of eyelids, probing of tear ducts	Strabismus surgery, intraocular surgery, measurement of intraocular pressure.
Miscellaneous	Bone marrow sampling, skin/node biopsy, lumbar puncture, intrathecal injection, radiotherapy, venesection, arteriovenous fistula, blood tests, metabolic/endocrine tests	Computed tomography, magnetic resonance imaging, radiotherapy, interventional cardiology, electromyograms

[a] Regional techniques for odontology and stomatology are usually not performed by anesthesiologists.
[b] Epigastric and umbilical hernia repair is best managed as outpatient surgery with rectus sheath block (not caudal or lumbar epidural anesthesia).
[c] These procedures are not carried out as outpatient surgery in some countries.

block. [78] Degenerative axonal diseases have long been considered as contraindications, but no data support the hypothesis that regional anesthesia could worsen their course (equally, no data support the hypothesis that regional anesthesia could not worsen their course). Regional techniques must be avoided when there is a danger of compressive disorders in closed fascial compartments. In the presence of a plaster cast, the hemodynamic condition of the limb must be closely monitored. If local conditions do not permit reliable monitoring by trained nurses, regional anesthesia must not be provided. Parental refusal and severe psychoneurotic disorders should be considered as contraindications. Specific contraindications are mentioned with the description of the relevant technique.

Selection of Materials, Techniques, and Agents

General Considerations

Usual indications for regional anesthesia in children are pain relief and patient comfort. Therefore, regional techniques should be considered as methods of analgesia and not anesthesia. Their advantages and disadvantages must be compared with other techniques of analgesia (e.g., intraoperative and postoperative parenteral narcotics). Also, in chil-dren, general anesthesia and regional anesthesia are usually complementary. In selecting a regional technique, the anesthesiologist must carefully check the potential complications of this technique and restrict the choice to a technique virtually free of complications, even if less effective, and the

reliability and safety of which have been evaluated in a large series of pediatric patients.

Selection of a Suitable Block Procedure

Selecting the most appropriate technique is a matter of experience and common sense. Several factors must be considered: (1) the ability of the technique to abolish pain not only in the operative field, but also in all the areas involved in the surgery (e.g., site of tourniquet placement, sites where skin or bone grafts are to be taken); (2) the adequacy of the duration of the sensory block with the expected duration of postoperative pain; (3) the physical condition of the patient; (4) the local conditions at the site of puncture; (5) the suitability of the position required for performing the block according to the lesions and/or the physical condition of the child; (6) the similar importance of anesthetic and surgical techniques--under normal conditions, central blocks should be avoided for minor surgery; and (7) the experience of the anesthesiologist. The possibility that technical difficulties may be encountered in attempting to locate a nerve trunk or a spinal space must be envisaged preoperatively with the patient's family, and alternate procedures that would be used in such an event should be clearly detailed.

TABLE 44-3 -- Pediatric Doses and Clinical Characteristics of Usual Local Anesthetics

LOCAL ANESTHETIC	USUAL CONCENTRATION (%)	USUAL DOSES (mg/kg)	MAXIMUM[a] DOSE (PLAIN) (mg/kg)	MAXIMUM[a] DOSE WITH EPINEPHRINE (mg/kg)	LATENCY (min)	DURATION OF EFFECTS (h)
AMINOESTERS						
Procaine	1-2	7	10	10	10-15	0.3-1
Chloroprocaine	2-3	7	10	10	7-15	0.5-1
AMINOAMIDE[b]						
Lidocaine	0.5-2	5	7.5	10	5-15	0.75-2
Prilocaine [c]	0.5-1.5	5	7	10	15-25	0.75-2
Mepivacaine	0.5-1.5	5-7	8	10	5-15	1-1.25
Bupivacaine	0.25-0.5	2	2.5	3	15-30	2.5-6
Etidocaine [d]	1	3-5	5	7	5-10	2-5

These data are not applicable to spinal anesthesia, intravenous regional anesthesia or local anesthesia. Ropivacaine has no legal approval for use in children younger than age 12 years.

[a] Maximum doses are controversial and, in fact, irrelevant because toxicity is due to the free unbound form and neither to the total dose given nor the plasma peak concentration. The doses mentioned above are safe when given as single injections, but they may or may not be safe following multiple previous injections (or continuous infusion), especially during the postoperative course. This holds particularly true for long-lasting local anesthetics (bupivacaine and etidocaine, and, probably ropivacaine).
[b] Ropivacaine has not been included because of lack of information and approval for use in children younger than 12 years old.
[c] Danger of severe methemoglobinemia in infants (even with low therapeutic doses).
[d] Etidocaine should not be administered alone because sensory blockade can be insufficient.

Also, when confronted with a technical failure, the anesthesiologist should not make a second attempt without verifying both the position of the patient and the landmarks used. In any case, it is unreasonable to attempt to perform the same procedure more than three times in the same patient.

Selection of the Anesthetic Solution

Sound selection of local anesthetics [79] depends on the planned surgery, the expected duration of postoperative pain, and the pharmacologic characteristics of the drugs. The most suitable local anesthetics and their recommended doses are detailed in Table 44-3 . As previously mentioned, prilocaine should not be used in infants, and mepivacaine should be avoided during the first 2 or 3 weeks of life. Ropivacaine [80] has recently become available and will probably play a consistent role in pediatric regional anesthesia; but, currently, little information is available in children, and there is no approval for use in patients younger than 12 years old. The use of mixtures of local anesthetics has gained acceptance in recent years but remains controversial. [81] Expected advantages of such combinations include compensation against relative limitations of each agent (especially in regard to latency until completion of sensory block) and reduction of the hazards of systemic toxicity by producing low and separated peak blood concentrations of each agent. It should be kept in mind, however, that the toxicity of mixtures of local anesthetics is additive. [82] I regularly use mixtures of lidocaine with bupivacaine or, rarely, bupivacaine with etidocaine. Warming the anesthetic solution before injection reduces pain on infiltration. [83]

With regard to adjuvants, the addition of epinephrine is mandatory for the reasons mentioned (reduction of vascular uptake, increased duration of effects, early detection of an intravascular injection). However, epinephrine can produce ischemic disorders and gangrene when injected in areas supplied by terminal arteries; therefore, it is contraindicated for penile, peribulbar, pudendal, and digital nerve blocks. Narcotics, and especially morphine, have many indications when given epidurally or, although not accepted by some authors, [24] intrathecally, provided appropriate monitoring of respiratory parameters can be ensured for the first 24 postoperative hours.

Selection of Material

The (sterile) material necessary for performing a regional block is rather simple: a (nonreusable) block needle, a syringe, a local anesthetic, skin preparation solutions, and drapes. Different types of needles are available, and the anesthesiologist has to make a selection so that any regional block can be performed safely and sufficient experience gained with all the selected needles, especially with regard to the sensation felt during insertion.

Local infiltrations and field blocks can be performed with a single standard needle, (e.g., a 21- to 23-gauge and 30-50 mm long). Intradermal wheals are made with a short (no more than 30 mm long) and thin (25- to 27-gauge) needle. Compartment blocks (e.g., fascia iliaca compartment block, penile block via the subpubic space, rectus sheath block, peribulbar anesthesia) depend on the precise localization of a fascial plane. When the relevant fascia is unique and does not cover any vital structure, a large number of needles can be safely used; in any other case, especially when there are several successive fascial planes, the use of a short beveled needle (or a pinpoint needle) of adequate length is required. [84] [85]

Plexus and mixed nerve blocks should not be performed by seeking paresthesias with standard intramuscular needles because of a danger of direct nerve damage [86] [87] ; unsheathed short-beveled needles connected to a nerve stimulator proved to be suitable, [88] but the safest way to proceed is by using an insulated and short-beveled needle. Needles 35 mm long are appropriate for more than 80 percent of all peripheral blocks. Sciatic nerve blocks require longer needles,

especially when the lateral or the anterior route is selected and depending on patient size, 50-, 100-, 150-, and, occasionally, 180-mm needles should be available. Caudal blocks have been performed using virtually any type of needle available. This is no longer acceptable, and only a suitable needle must be used (i.e., 25-30 mm long, short-beveled, and using an obturator needle to avoid tissue coring [89]). Needles suitable for lumbar taps in the neonate are suitable for caudal blocks.

Tuohy needles are best suited for intervertebral epidural blocks (sacral, lumbar, and thoracic). At least two sizes of needles must be available: 20 gauge and 50 mm long for children younger than 8 years old and 18 to 19 gauge and 90 to 100 mm long for older patients. In infants, especially during the 1st year of life, a shorter needle is desirable (30 mm long and 22-21 gauge). Crawford needles can be safely used. Appropriately sized catheters should be available for each of these epidural

needles. Spinal blocks can be performed using lumbar tap (22 gauge) needles (especially in premature or ex-premature infants who are not to be given general anesthesia) or a standard spinal needle (24 or 25 gauge). Thinner spinal needles and Whitacre spinal needles are suitable, but they are not as advantageous in children as they are in adults [90] because children are less prone than adults to develop postspinal puncture headache. Furthermore, CSF reflux is delayed owing to the small size of the lumen, and the overall failure rate is significantly increased (10% with 29-gauge needles versus 0% with 25-gauge needles in the study by Kokki and Hendolin [91]). Of course, all spinal needles must be styletted, [89] but even with such needles, tissue coring can occur, [92] thus potentially leading to epidermoid tumors that become symptomatic 10 or 15 years later.

Techniques of Location of Nerves and Anatomic Spaces

Location of nerve trunks and anatomic spaces must be ascertained by physical means, as most children cannot reliably cooperate or are under general anesthesia. Plexus and mixed nerves are best localized by using electric stimulation to elicit muscle twitches. This requires a nerve stimulator delivering squared electric impulses lasting 50 to 100 musec at the rate of 1 to 5 impulses per second. The anode is connected to a skin electrode preferably fixed distal to the site of puncture, and the cathode to the block needle. [93] [94] To avoid traumatic nerve lesions, depolarization of motor fibers must occur before the needle contacts the nerve trunk and, at the same time, when it is close enough to it to allow a successful block. Thus, the key factor is intensity of the stimulus, which should range from 0.5 to 1.5 mA. With such intensities, motor fibers are depolarized, and muscle twitches are elicited, when the tip of the needle is approximately 1 mm away. At this distance, the injection site is within the perineural fascial sheath and the bevel far enough away to avoid damaging the nerve fibers.

The epidural space can occasionally be located by the hanging-drop method or the MacIntosh balloon technique, especially at thoracic levels. When the tip of the block needle enters the epidural space, the negative pressure thus created aspirates the hanging drop or deflates the balloon. However, the most common technique of identification is by seeking a loss of resistance while exerting a continuous (with fluid) or intermittent (with gas) pressure on the plunger of an airtight (glass or, preferably, plastic) syringe that offers no resistance to movement while the needle is advanced, until a sudden loss of resistance is felt as the ligamentum flavum is pierced. The medium used to fill in the syringe has generated much controversy. Air has been used for decades because of its availability, simplicity of use, and suitability for precisely identifying the ligamentum flavum. [95] [96] [97] For approximately 10 years, several complications have been reported, some minor such as transient headache [98] or patchy anesthesia due to air bubbles, [99] but others extremely severe such as spinal cord compression, [100] [101] multiradicular syndrome, [102] subcutaneous cervical emphysema, [103] or air embolism [104] [105] [106] [107] even following the hanging drop technique. [108] These complications led some authors to recommend abandoning this technique and use saline instead of air. [109] [110] In a well-conducted study using transesophageal echocardiography, Jaffe et al [111] detected a few air microbubbles in the blood stream (easily cleared by the pulmonary circulation in the absence of intracardiac shunt) but established that no significant air embolism occurred after quick injection of 5 mL of air into the epidural space. They also established that intravascular penetration constantly occurred, within 15 seconds, of consistent amounts of any solution (saline as well as local anesthetics) introduced into the epidural space, so that greater attention should be paid to the speed (and pressure) of injection and the injected volume [111] [112] rather than to the medium used. On the other hand, whereas the loss-of-resistance technique (LORT) using saline seems to be as suitable in grown-up children as in adults, this is not true in infants and young children whose ligaments are less densely packed and thus less easily detectable. Reports of adverse effects following fluid-LORT are still scarce. [113] The morbidity of this technique, however, is probably not negligible, as it implies several changes of syringes; results in diluting the local anesthetic (up to one fourth the volume administered to an infant), which could lead to insufficient blockade; increases the final volume given (with hazards of respiratory depression due to an excessive upper limit of anesthesia); and generates new problems in case of reflux of clear liquid on disconnection of the syringe (inadvertent dural tap or reflux of saline?). Because of the limitations of this technique in the very young, some authors developed LORT combining air and saline [114] [115] [116] [117] [118] or even more complicated techniques. All these techniques are more time-consuming and require several [106] changes of syringes (which implies hazards of syringe mismatches and bacterial contamination), and their safety and suitability in large series of patients are not established. In conclusion, air-LORT should be avoided in grown-up children where the saline-LORT is as reliable as in adults. Conversely, in younger patients, saline-LORT is not as dependable as air-LORT, and its use will probably introduce new dangers that could not compare favorably with air-LORT. [119] [120] Furthermore, using CO_2 , instead of air, as reported several years ago and still in general use in our department, without a single adverse effect, [29] would probably represent the best and safest compromise whatever the age and size of the patient.

The subarachnoid space is located by seeking CSF reflux. The diameter of the lumen of the needle and the position of the patient during the approach (which affects the hydrostatic pressure of the CSF) must be considered. It is recommended to approach the subarachnoid space while a negative pressure

is continuously exerted on the plunger of a syringe connected to the spinal needle (preferably with an extension line in between to ensure free movements of the needle).

Technique of Injection

The technique of injection is an essential factor of safety. Whatever the block procedure, five basic safety rules must be systematically followed: (1) aspiration test before any injection; in case of unexpected reflux of biologic fluid, especially blood, the procedure must be stopped and the needle withdrawn; (2) cardiac monitoring after the injection of a test dose (0.5 to 1 mL) containing 0.5 to 1 mug/kg of epinephrine (when not contraindicated) for 30 to 60 seconds; inadvertent intravascular injection is suspected in case of early (within 15 seconds) elevation of ST segment and T-wave amplitude changes, [121] [122] [123] then constantly followed by an increase in blood pressure [123] [124] [125] [126] and only occasionally by tachycardia that is often preceded by bradycardia; any of these symptoms require immediate cessation of the technique; in patients not eligible for administration of epinephrine (and this will probably be the case in the future with the use of ropivacaine) isoproterenol (0.1 mug/kg) has been used successfully as an alternative for the test dose [127] ; (3) injection at a slow rate (no more than 10 mL/min) (i.e., from 60 to 120 seconds depending on the volume [128]); (4) immediate cessation of injection if any unusual resistance is felt (to avoid potential danger of intraneural injection); (5) repeated aspiration tests during injection (every 5 mL) and before reinjection through a catheter (to verify that the tip of needle or catheter has not moved and pierced a vessel).

Environmental Conditions for Safe Regional Procedures

Monitoring Procedures

Regional anesthesia is not without consequences. Therefore, it must be performed by anesthesiologists in the operating room with the same monitoring equipment as used for general anesthesia. An intravenous line must be established before any injection of local anesthetic. As stated by Eyres, [79] "it may be deemed negligent not to have access to a reliable open vein during administration of significant doses of local anaesthetics." Placement of a precordial stethoscope and monitoring of electrocardiographic tracings, blood pressure, temperature, and respiratory rate are the minimal monitoring necessary. Evaluation of tidal volume, end-tidal CO_2 and peripheral oxygen saturation by pulse oximetry is desirable, especially in infants. All the data should be noted on a complete anesthesia chart.

Sedation of the Patient

Regional blocks can be performed on cooperative and unpremedicated patients. During emergency procedures, especially in the presence of a full stomach, general anesthetics and sedatives should be avoided. It is surprising how well children accept these techniques when they are in pain. During elective surgery, many children fear needles, and general anesthesia is usually requested by the patient. If not contraindicated for medical reasons, light general anesthesia can be safely used and is widely accepted in pediatrics. [109] [129] [130] In the prospective study undertaken by ADARPEF involving 24,409 regional procedures, almost 90 percent of all the blocks were performed under general anesthesia, with only 5 percent without any sedation. [1] New halogenated agents have been little evaluated in association with regional anesthetic techniques but, based on experimental data, sevoflurane seems to be able to attenuate the cardiac and neurologic toxicity of bupivacaine, in the same way as isoflurane. [131] However, they are not able to prevent adverse effects in case of inadvertent intravascular injection or overdose of local anesthetics. [132] Potentially dangerous procedures such as interscalene blocks or thoracic epidurals must not be attempted on unanesthetized patients, even if they are apparently cooperative, as it cannot be guaranteed that the patient will not panic during the procedure; but injection of muscle relaxants must be delayed until the block procedure is fully achieved. [133] Occasionally, general anesthesia can be detrimental to the patient as symptoms of complications can be unrecognized.

Assessment of the Block

The efficacy and extent of any block have to be evaluated systematically whatever the patient's age. This evaluation is not easy in children, even when conscious, in the absence of a motor block. It cannot be achieved properly in alert patients unless the anesthesiologist (1) has gained the confidence of the child, (2) disguises what is being done (especially handling of needles), and (3) makes comparative tests in nonblocked areas. Gentle skin pinching is the most dependable technique of

sensory testing, especially in lightly anesthetized patients, whereas answers by very anxious alert patients can be misleading. Eliciting muscle twitches and using concentrated local anesthetics aimed at providing a motor block can be helpful in reassuring awake patients. Additionally, when the patient is awake, it is important that the anesthesiologist provides psychologic support during the first minutes following skin incision to avoid panic until the patient is convinced of the success of the block procedure.

Medicolegal Implication

In pediatric practice, the patient and parents must be convinced that no malpractice has occurred. Therefore, the recommendations appearing in Table 44-4 should be followed whenever possible so as to avoid irrelevant medicolegal problems.

Complications: Early Diagnosis and Management

Regional anesthetic procedures can infrequently lead to local, regional, or general complications, some of which can be lethal. From 1985 to 1992, the Committee on Professional Liability of the American Society of Anesthesiologists

TABLE 44-4 -- Basic Safety Rules for Any Type of Regional or Local Anesthesia

1. Select the least hazardous technique for a given block.

* * *

2. Even in emergency situations, provide full details concerning the scheduled anesthetic management, including beneficial and potentially detrimental effects.

* * *

3. Envisage the possibility of a block failure and explain what replacement procedure(s) will then be used.

* * *

4. Obtain written consent for anesthesia care.

* * *

5. Evaluate carefully the physical status of the patient and ask for complementary laboratory, radiographic, or any other examinations when useful.

* * *

6. Manage the patient in the same way and with the same monitoring procedures as for general anesthesia; a full anesthesia chart must be completed.

* * *

7. Treat all complications (if any).

* * *

8. Complete a postanesthetic chart to evaluate precise recovery of the block and to avoid irrelevant claims.

* * *

9. Hospitalize all patients given epidural or intrathecal morphine in postanesthetic care units where respiratory parameters will be recorded hourly for the first 24 hours postoperatively.

collected 238 pediatric closed malpractice claims, which included only seven records of children who had received a regional anesthesia. [134] This very low morbidity rate is more apparent than real because the overall proportion of children given conduction anesthesia in the United States was extremely low during the evaluation period. With the increasing use of regional anesthetic techniques, an increasing number of complications is to be expected; however, as established by the ADARPEF's prospective study, the overall morbidity rate in a large number of patients (24,409) is still low. [1] Similarly, the number of regional anesthesia-related maternal deaths have decreased considerably throughout the United States since 1984 (at the same time, the number of regional anesthesias have dramatically increased), whereas the number of deaths involving general anesthesia has remained stable. [135]

Complications can be assessed in four groups: (1) complications resulting from the block procedure itself (i.e., true complications); (2) complications resulting from poor selection of patients, inappropriate environmental conditions, and inadequate safety precautions--these complications are entirely avoidable; (3) effects that were not anticipated because of a lack of knowledge of all the consequences of the technique used (these are not complications but malpractice); and (4) complications, usually resulting in severe damage to the patient, attributed to a concomitant regional block procedure but with no established, sometimes even improbable, causal link with the regional technique. [136] [137] Only the first group ("true complications") are considered here.

Local adverse effects usually result from nerve damage due to incorrect needle placement [86] [87] [138] [139] rather than from toxicity of the injected solution. However, inappropriate formulations (hypotonic solutions, antioxidants, preservatives, wrong solutions) and, especially, the use of epinephrine in areas supplied by terminal arteries may result in tissue ischemia and gangrene. Some local complications such as needle trauma or intraneural injection can potentially be undetected, and thus worsened, by simultaneous general anesthesia. The importance of using appropriate devices, especially short-beveled needles, which are less traumatic, and of locating the position of the needle tip by physical means cannot be overemphasized.

Placement of catheters for reinjection is also a potential source of complications. Leakage around the puncture point occurs in approximately 10 percent of cases, [140] and inadvertent removal is not infrequent. [141] The danger of bacterial contamination is difficult to evaluate. It seems rather low in some studies [142] [143] and unexpectedly high in others [144] ; several pediatric cases have been reported. [15] Even though the luminal content of the epidural catheter can remain sterile for 8 hours if the fluid in the catheter remains static, [145] after accidental disconnection, the epidural catheter should be removed, especially in infants.

Several complications become apparent on removal of the catheter such as cutting and knotting. These complications are often directly related to the length of catheter introduced into the epidural space, which should usually not exceed 2 to 4 cm. [146] The overall number of catheter-related complications has been measured as high as 19 percent in a series of 1,014 continuous epidurals in adults [142] and 11 percent in a pediatric series. [140] Malfunctioning of infusion pumps is not unusual. [1] [140] All these complications must be identified as early as possible so as to avoid any delay in abandoning the technique.

Regional complications are usually due to the interruption of nerve conduction. They occur mainly during epidural and spinal blocks, including (1) hypoventilation secondary to respiratory muscle paralysis (spread of the local anesthetic to cervical spinal segments), [147] (2) urinary retention following caudal epidurals, and (3) complications, such as Horner syndrome, hypoglycemia, hypotension (in patients older than 8 years old), and other hemodynamic abnormalities due to paralysis of sympathetic nerve fibers. Undiagnosed conditions and tumor compression can suddenly be worsened by the block technique, which can possibly lead to intracranial hypertension, paraplegia, or activation of latent viral diseases. Inadvertent dural penetration with subsequent subarachnoid injection of an epidural dose of local anesthetic results in total spinal anesthesia, which requires respiratory assistance with tracheal intubation until complete spontaneous breathing is restored, and, occasionally, hemodynamic support. The potential morbidity of this complication could be reduced by aspirating CSF, as a significant amount of local anesthetic can thus be removed. [148]

Systemic toxicity results from inadvertent intravascular injection of local anesthetics, which is often due to neglect of basic safety rules, such as the use of an aspiration test, evaluation of a test dose, and slow speed of injection. In awake patients, the first symptoms are neurologic, with complaints of drowsiness, tinnitus, visual disturbances, dysarthria, and muscular twitches, followed by convulsions, coma, respiratory and circulatory depression. [149] Seizures must be treated immediately with inhaled oxygen; and, if they persist, intravenous injection of an anticonvulsant such as diazepam (0.1 mg/kg), midazolam (0.05 mg/kg), or thiopental (4 mg/kg) (thiopental is preferable as it is faster

acting) is required. Persistent convulsions require succinylcholine injection (1.5-2 mg/kg), intubation, and assisted ventilation to prevent acidosis (Table 44-5) .

Even though local anesthetics are antiarrhythmic agents, they slow down intraventricular conduction and can produce ventricular arrhythmias and fibrillation. The most cardiotoxic agents are bupivacaine and etidocaine. The cardiotoxicity of bupivacaine is mainly due to its blocking effect on sodium channels, but also on calcium and, even more, potassium channels. [150] [151] [152] Stimulation of the parasympathetic nervous system (due to nerve toxicity) and hypothermia can aggravate this toxicity. Cardiotoxicity is minimized by prevention of hypoxia and acidosis. Cardiac arrest is managed by external cardiac massage, assisted ventilation with oxygen, IV sodium bicarbonate and inotropic support (Table 44-6) . Ventricular tachycardia or fibrillation requires electric defibrillation (3-6 J/kg); bretylium tosilate (5 mg/kg) may also be used. Immediate single injection of clonidine (10 mug/kg) followed by continuous infusion of dobutamine (5 mug/kg/min) can suppress intraventricular conduction disorders and restore normal cardiac output within 2 minutes in experiments on dogs, [153] but no confirmation of this efficacy has been demonstrated in humans, and especially in children. Atropine may be helpful, as it decreases the refractory period of the auriculoventricular node [154] and, in patients experiencing toxic reactions during continuous epidurals, phenytoin infusions (5 mg/kg over 10 minutes), [155] but efficacy of either or both treatments has not been proven. Also, based on experimental data, [156] amrinone might be helpful, but its efficacy in clinical situations in humans has to be established. Systemic toxicity (both neurologic and cardiac) is increased in patients with right-left cardiac shunts.

Toxicity can also result from interactions with drugs or biologic products (e.g., bilirubin in the neonate) by competition at plasma protein binding sites. Other mechanisms may also be involved. Cimetidine and propanolol reduce hepatic blood flow, thus increasing the toxicity of agents (lidocaine), the metabolism of which depends on blood extraction by the liver. Agents such as verapamil potentiate cardiac toxicity by their action on myocardial fibers. Benzodiazepines have complex interactions. Whereas diazepam results in increasing plasma concentration of bupivacaine after caudal injection (probably due to their action on hepatic blood flow and liver metabolism), midazolam decreases both plasma peak and plateau concentrations of the same agent given by the same route. Therefore, premedication with midazolam appears to be advantageous.

TABLE 44-5 -- Emergency Treatment of Seizures During a Regional Block Procedure

1. Treat immediately with oxygenation (sufficient in most cases)
2. If convulsions persist:
a. IV thiopental 4 mg/kg
b. short-acting muscle relaxant: either
-succinylcholine (1.5-2 mg/kg)
-atracurium (0.5 mg/kg)
-(mivacurium 0.2-0.3 mg/kg) [a]
c. tracheal intubation and mechanical ventilation
d. IV diazepam (0.1 mg/kg) or IV midazolam (0.05 mg/kg)

[a] Mivacurium has not yet been evaluated in this situation.

TABLE 44-6 -- Emergency Treatment of Cardiac Complications During a Regional Block Procedure

COMMON TREATMENT FOR ALL CARDIAC COMPLICATIONS
1. Face mask oxygenation followed by tracheal intubation and assisted ventilation with oxygen
2. Restore hemodynamics (external cardiac massage if required)
3. Prevention of metabolic acidosis with sodium bicarbonate
-semimolar (4.2%) into a central vein: 2 mg/kg/10 min
-isotonic (1.4%) into a peripheral vein: 6 mg/kg/min
IF HEMODYNAMICS NOT RESTORED: INOTROPIC SUPPORT
1. IV atropine: 0.02 mg/kg (not exceeding 0.6 mg)
2. IV vasoactive agents: either
-epinephrine: 0.1 mL/kg of a 1/10,000 solution
-dopamine or dobutamine: 2 to 10 mug/kg/min
-occasionally: isoprenaline 0.1 mug/kg
3. Calcium chloride: 10 to 30 mg/kg
ADDITIONAL TREATMENT IN CASE OF VENTRICULAR TACHYCARDIA OR FIBRILLATION
1. Defibrillation: 3 J/kg (up to a maximum of 6 J/kg)
2. Antiarrhythmic agents:
-IV bretylium tosilate (5 mg/kg) (injection can be repeated up to a maximum dose of 30 mg/kg)
-clonidine [a] : 0.01 mg/kg (should not be repeated), then IV dobutamine: 5 mug/kg/min
3. Anticonvulsants [b] : either
-IV diazepam (0.1 to 0.2 mg/kg)
-IV midazolam (0.05 to 0.1 mg/kg)
-or IV phenytoin (5 mg/kg over a period of 10 minutes)
4. Inotropic support [a] : either or both
-IV atropine: 0.02 mg/kg (not exceeding 0.6 mg)
-IV dobutamine: 5 mug/kg/min (immediately after clonidine injection)
5. Amrinone [a] ?

[a] Indication based on experimental data only.
[b] Thiopental should preferably not be administered in this situation.

Allergic reactions to local anesthetics are extremely unusual. They may occur more frequently with aminoesters than with aminoamides or when adjuvants have been added to the commercial solution (such as metabisufite in solutions containing epinephrine or methylparaben). In fact, investigations with prick and intracutaneous

tests in a patient with a history of an event after application of local anesthetics show that true allergic reactions are extremely rare. [77]

BLOCKS ALONG THE NEURAXIS

Caudal Anesthesia

Anatomic Considerations

The two halves of the vertebral arches of the fifth and usually the fourth sacral vertebrae are not fused posteriorly, thus creating the sacral hiatus. This V-shaped orifice located just above the sacrococcygeal joint is limited by two easily palpable bony crests, the sacral cornua, and is covered by the sacrococcygeal membrane, which is the sacral continuation of the ligamentum flavum. The sacral hiatus allows access to the sacral epidural space below the termination of the dural sac, at a level where most roots of the cauda equina are no longer inside the sacral canal. In infants, the sacral canal is filled with fluid fat and loose areolar connective tissue, which allows easy spread of anesthetic solutions. In children older than 6 or 7 years, the epidural fat becomes more densely packed, thus reducing this spread. The epidural fat is traversed by many veins that are valveless; thus, any injection in such veins will result in immediate systemic distribution with possible toxic effects. The sacral epidural space communicates freely with the perineural space surrounding the sacral and the lumbar roots (especially the lumbar-sacral trunk). Because of considerable leakage, a large volume of local anesthetic is necessary to achieve an appropriate upper limit of sensory block.

Indications and Contraindications

Most surgical procedures of the lower part of the body (mainly below the umbilicus) can be performed under caudal anesthesia. The most common indications include herniorrhaphies; operations on the urinary tract, anus, and rectum; and orthopedic procedures on the pelvic girdle and lower extremities. [71] [72] [76] Specific contraindications include major malformations of the sacrum, myelomeningocele, and meningitis.

Block Procedure

The patient is placed in the lateral position with the side to be operated lying lowermost, but also can be placed in the prone position with a pillow slipped under the pelvis. The landmarks are the two sacral cornua, located by palpation at the caudal extremity of the vertebral spinous process line. These delineate a triangular zone at the center of which the block needle is inserted. Several insertion routes have been reported, but the most reliable is to insert the needle at right angles to the skin until it pierces the sacrococcygeal membrane (Fig. 44-2) . The needle is then redirected rostrally, at a 20- to 30-degree angle to the skin and advanced for 2 to 3 mm into the sacral canal. The distance from skin to the sacral epidural space is hardly influenced by the age and weight of the patient (Fig. 44-3) ; in virtually all cases, it is less than 20 mm from the skin.

With appropriately sized needles, it is extremely easy to insert a catheter within the sacral canal. This procedure can occasionally be used for providing high epidural block [157] [158] [159] (i.e., at lumbar or even thoracic levels) when a direct posterior approach appears too hazardous. Before the catheter is introduced within the epidural space, the distance from the sacral hiatus to the desired vertebral level is measured, and the final position of the catheter tip must be verified radiologically before any injection, as erratic placement is common. [159] [160] There are several drawbacks to this technique. In addition to exposure of the patient to x-rays and, often, iodine contrast material, it may be impossible to withdraw the catheter. Because of the proximity of the anus, there is a danger of bacterial contamination, especially in children who have not acquired sphincter control, if a catheter is kept in place postoperatively. Despite several publications suggesting that inserting a caudal catheter could be safe, caudal anesthesia is basically a single shot procedure, and if a catheter has been inserted for (rare) intraoperative purposes, it must be withdrawn at the end of the operation.

The upper limit of sensory block does not depend on the speed of injection [161] but on the total volume injected into the epidural space according to patient's age and weight. The optimal volume of local anesthetic to be administered is controversial, and several mathematical models and equations have been presented, the most dependable of which is that of Busoni and Andreucetti. [162] From a practical point of view, the prescription scheme of Armitage is valuable and easy to use. [163] Injecting 0.5, 1.0, or 1.25 mL/kg of a local anesthetic results in a high sacral, high lumbar, or a midthoracic upper limit of the sensory block, respectively. Occasionally, the larger volume (1.25 mL/kg) can lead to excessive rostral spread (above T4). [29] [71] Thus, if more than 1 mL/kg (to a maximum of 20 mL) of local anesthetic needs to be administered, it is preferable to avoid the caudal route and use a higher epidural approach.

Complications

Complications are unusual, about 1 per 1,000 procedures, [1] and usually minor. They result from misplacement of the needle into superficial soft tissues resulting in failure of the block, intravascular or intraosseous injections leading to systemic toxicity, and intrathecal penetrations with subsequent spinal anesthesia. [164] Penetration into pelvic viscera and vessels have been reported. These complications are easily avoided by using appropriate devices with a proper technique and following the basic safety rules of injection. Hypotension may occur in patients older than 8 years. [70] Postoperative voiding can be somewhat delayed, but true urinary retention is rare. Vomiting has been reported in up to 30 percent of patients, but is usually much less. Bacterial contamination of the epidural space has been reported only when an epidural catheter had been inserted caudally. In

Figure 44-2 Caudal block. (A) Insertion of the needle at right angles to the skin: (1) Right sacral cornua, (2) Sacrococcygeal membrane. (B) Cephalad redirection of the needle after piercing the sacrococcygeal membrane.

Figure 44-3 Distance from skin to epidural/subarachnoid space at different intervertebral levels.

fact, the most common adverse effect is the development of an inappropriate level of sensory block, either excessive, lateralized, or too low. Complete failure of the block is not unusual (3-5%). They occur mainly in children older than 7 years of age, but even in younger patients the failure rate can be rather high. [124]

Intervertebral Epidural Anesthesia

Anatomic Considerations of the Epidural Space

The epidural space surrounds the spinal cord and the meninges. It extends from the foramen magnum to the sacral hiatus. It is limited posteriorly by the vertebral laminae and the ligamentum flavum, and communicates with both the paravertebral spaces and the perineural space surrounding the spinal nerves. In the "dural cuff" region, near the spinal ganglia, it has intimate relations with the subarachnoid space due to the protrusion of arachnoid granulations, which are easily traversed by local anesthetics. It contains blood vessels and lymphatics and is filled with fat in infants and more densely packed and less permeable to local anesthetics in children older than 7 to 8 years of age. The epidural veins are numerous and plexiform. They are connected with both the azygous system and the inferior vena cava. They have no valves; thus, an inadvertent intravascular injection results in immediate systemic distribution. In the cadaver, the epidural space is shown to be triangular in shape in transverse sections, with its widest part lying poste-riorly in the median sagittal plane. Thus, midline approaches are usually considered safer than paramedian approaches.

Figure 44-4 Epidural blocks. (1) Thoracic approach (paramedian route). (2) Thoracic approach (midline route). (3) Lumbar approach (paramedian route). (4) Lumbar approach (midline route). (5) Sacral intervertebral approach.

Classically, the dorsal part of the epidural space is considered to have no restrictions, but several investigations [165] [166] [167] have shown that it is frequently divided in the midline by a median epidural band, the plica mediana dorsalis, which is areolar and easily traversed by epidural solutions but can occasionally account for unilateral blockade or difficulty in the insertion of an epidural catheter. Hogan [168] did not observe such a median band in his study very close to physiologic conditions, but he found that the epidural space was not as homogeneous and continuous as commonly believed. In fact, the epidural space consists of a succession of small pyramidal spaces (near the ligamentum flavum) separated by strictures at the level of the laminae. This segmentation of the posterior compartment is incomplete during early childhood. [169] By the age of 10 years, the adult pattern is evident, with posterior compartments separated from dural contact with the bony lamina.

Under physiologic conditions, the epidural space has probably only a potential volume. [168] Epidural anesthesia cannot be considered as a passive filling of a rather large and rigid tubing but as a dynamic process because any epidural injection produces changes in pressure and a variation in the normal anatomy. The compliance of the epidural space was found to be equal to 0.39 ± 0.13 mL/mm Hg and correlated with patient's age. [170] The subatmospheric pressure used for detecting epidural penetration is, in fact, due to the displacement of the dura mater by the block needle. As subcutaneous tissues and vertebral ligaments are less densely packed in infants and young children, the loss of resistance felt as the needle penetrates the ligamentum flavum is less significant than in adults and influences the choice of the LORT technique to be used. Also, previous extradural anesthesia may result in proliferation of connective tissue, adhesions between the dura mater and the ligamentum flavum, and granulation and changes in the ligamentum flavum due to inflammation, which may reduce the spread of local anesthetics during further epidural anesthesia. [171]

Indications and Contraindications

Epidural anesthesia can be used for operations of the lower extremities and almost any part of the trunk, including the chest. [163] [172] [173] [174] [175] However, its main indications are the same as those of caudal anesthesia (i.e., low abdominal and retroperitoneal surgery). The selection between either the caudal, sacral intervertebral, or lumbar routes may be difficult. Most operations on the pelvis and lower limbs in infants and young children are performed under caudal anesthesia, provided that a single shot technique is adequate. In patients older than 6 years of age or when a reinjection catheter is mandatory, intervertebral epidural approaches are preferred. Specific contraindications include severe malformations of the vertebral column and the spinal cord such as complete spina bifida or meningocele. Also, patients with a history of hydrocephalus or severe convulsive disorders, and those with vertebral implants, reduced intracranial compliance, or elevated intracranial pressure should preferably not be given epidural anesthesia (however, these are not absolute contraindications). [78]

Block Procedures

Lumbar Epidural Anesthesia

The midline lumbar intervertebral approach is the most common technique of epidural block in children. Although the patient can be in the sitting position if awake, or, rarely, in the prone position, the most usual position is the lateral position with the side to be operated lying lowermost and the hips and knees flexed by 90 degrees (Fig. 44-4) . The spine is bent so as to open the interspinous spaces and enlarge the interlaminar space. As the spinal cord ends at a lower level in children, it is safer to select the L4-L5 or the L5-S1 interspace ("Taylor" approach). [174] The line joining

the two iliac crests passes over the skin projection of the fifth lumbar vertebral body, and the relevant spinous process is located by palpation. The site of puncture is in the midline at an equal distance from the spinous processes of the two vertebrae limiting the selected interspace.

The epidural needle is inserted at right angles to the skin until it contacts the interspinous ligament. The introducer needle is then removed, and the syringe used for detecting the epidural space is connected. The epidural needle is then slowly advanced toward the laminae while constant pressure (with fluid), or intermittent pressure (with gas) is exerted on the barrel of the syringe. An increased resistance is detected when the needle touches the ligamentum flavum, followed by a sudden loss of resistance as the tip of the needle enters the epidural space. The epidural space is detected at a distance from the skin depending on both the age and weight of the patient (see Fig. 44-3) ; 1 mm/kg of body weight can be taken as a useful guideline for children between 6 months and 10 years of age as recently confirmed. [88] Once the needle is in the epidural space, the syringe is disconnected and the absence of any blood or CSF reflux is verified. Aspiration tests are made before insertion of an epidural catheter. A test dose of the local anesthetic with epinephrine is administered before every injection.

Difficulties may be encountered during the procedure due to an inappropriate insertion route, insufficient flexion of the spine, or deformities of the vertebral column. In these cases, the oblique paramedian route can be attempted; the technique is basically the same as in adults and does not require more experience to perform it successfully in children. [29] A lumbar plexus block (see later) following the Chayen technique [176] can occasionally be used as an alternative procedure to a failed or impossible lumbar epidural approach, as the anesthetic solution can spread medially along the lumbosacral trunk and reach the epidural space in about 80 percent of patients. The recommended volume of anesthetic solution depends on the upper level of analgesia necessary for completion of the surgery. In children older than 10 years of age, this volume is best evaluated by the formula reported by Schulte-Steinberg: [177]

V (in mL) = 1/10 × (age in years)

where V is the volume necessary to block one spinal segment. In younger children, it is preferable to take into account the weight of the patient. With the administration of 1 mL/kg (up to a maximum of 20 mL), the final height of sensory block ranges from T9 to T6 in more than 80 percent of cases.

A single shot epidural anesthesia is appropriate for many pediatric cases, especially when adjuvants such as clonidine (1-2 mug/kg) and, in appropriate indications only, morphine (30 mug/kg) are added to the local anesthetic. In other cases, placement of an epidural catheter will permit (intraoperative) reinjections (same volume but half the initial concentration of bupivacaine), then continuous infusion of plain bupivacaine (0.3 to 0.5 mg/kg/h of a 1.25% or 1.0% solution). Infants less than 12 months old are more prone to accumulation with prolonged continuous infusions. [14] [17] It is mandatory to avoid administering doses exceeding 0.375 mg/kg/h for the first 24 hours and then to decrease the infusion rate (if still necessary) to half this dose for up to 5 or 6 days (assays of plasma concentration of bupivacaine are recommended every other day).

Occasionally, as for caudals, a catheter can be introduced at low lumbar interspaces and inserted over a long distance with the aim of reaching high thoracic neuromeres; however, this procedure is unreliable and in almost 80 percent of cases the tip of the catheter is in the wrong place. [178] Combined spinal and epidural anesthesia, which is now commonly practiced in obstetrics, is not frequently used in children, although there are no theoretical contraindications to using this

technique, especially as children tolerate extended sympathetic blockade very well.

Sacral Epidural Anesthesia

Because of incomplete ossification of the sacrum, there are true posterior sacral interspaces suitable for epidural approach at virtually any sacral level. The easiest approach is via the S2-S3 interspace with the patient in the lateral position [179] (see Fig. 44-4) . This interspace is located by palpation 0.5 to 1 cm below the line joining the two posterosuperior iliac spines. The puncture site is at a midpoint between the second and third sacral spinous processes. The Tuohy needle is usually inserted at right angles to the skin but, as the sacral spinous processes are atrophic, the orientation of the needle can vary considerably. It is advisable to direct the needle at an angle of 45 degrees or more, with the bevel facing the coccyx so as to decrease the hazards of damaging the dural sac, which ends approximately at this level. The distance from skin to epidural space is significantly less than at lumbar levels (i.e., two interspaces above) due to the absence of lordosis (see Fig. 44-3) Intervertebral sacral epidurals are alternative procedures to both caudal anesthesia and lumbar epidurals when inapplicable or failed, especially for surgical procedures on the pelvic girdle and lower extremities.

Thoracic Epidural Anesthesia

Thoracic epidurals are rarely performed in pediatric patients. They accounted for 6 percent of all epidurals in the ADARPEF's prospective study, which included 15,013 central blocks. [1] The main indications are for operations on the chest and the upper part of the abdomen. The techniques are similar to those used in adults. For the midline approach, the needle is inserted at the midpoint between adjacent spinous processes and, due to their steep angulation, at a 45- to 60-degree angle to the skin, pointing rostrally, but in a strict median plane (see Fig. 44-4) . Alternatively, the paramedian route can be used. [6] [29] Whatever the route used, thoracic approaches to the epidural space are more hazardous than lumbar approaches, as there is a danger of direct needle trauma to the spinal cord. Thus, they should be performed only by experienced pediatric anesthesiologists on anesthetized children. A reinjection catheter can be safely maintained in place for postoperative pain relief. [175]

Cervical Epidural Anesthesia

Cervical epidural anesthesia has no place in pediatric anesthesia.

Adverse Effects and Complications

Basically, complications of epidural anesthesia in children are the same as in adults. Inadvertent vascular injection can result in ischemic disorders and systemic toxicity. Direct trauma of the spinal cord can occur during thoracic and upper lumbar approaches and may result in the same neurologic sequelae as reported in adults. Fortunately, they are extremely unusual in children. In the ADARPEF's prospective study, [1] no complication was reported following thoracic epidurals (nor was a complication observed after spinal anesthesia), whereas the overall morbidity rate was 0.37 percent and 0.68 percent for lumbar and sacral epidurals respectively. The morbidity rate was probably so low in these two high-risk groups because only experienced anesthesiologists performed such blocks with maximum precautions. By implication this suggests that complications could be virtually avoided if all the safety precautions are taken. Interestingly, a recent paper evaluated the morbidity of thoracic epidurals with catheter placement in 4,185 patients (including 2,059 cases evaluated prospectively) and also found a low morbidity rate in adults (0.7%). [180]

Epidural catheters may be inappropriately placed or ruptured. [181] [182] Complete failure of the block usually results from misplacement of the needle (or catheter). It is not unusual to observe an inadequate upper limit of block, either too low, excessive, unilateral or with persistence of unblocked segments. Unilateral blockade in patients having an epidural catheter is often due to migration of the catheter into the anterior epidural space. [183] Secondary displacement of the catheter, especially inward migration, can be reduced by using a subcutaneous tunnel. [184] The administration of epidural narcotics may lead to several complications, especially delayed respiratory depression. [185] [186] [187] [188] Therefore, children given epidural or intrathecal morphine must be monitored carefully during the first 24 hours postoperatively.

Spinal Anesthesia

Anatomic Considerations

The subarachnoid space is incompletely divided by the denticulate ligament laterally, and the subarachnoid septum medially. The main difference related to patient's age is due to the volume of CSF, which is doubled in infants (4 mL/kg) as compared with adults (2 mL/kg). Additionally, half the total volume of CSF is located within the spinal subarachnoid space in infants, whereas in adults this volume accounts for only 25 percent. These differences considerably influence the pharmacokinetics of intrathecally administered local anesthetics. The spinal fluid hydrostatic pressure ranges from 30 to 40 mm H_2O in the horizontal position, which is significantly less than in adults. This pressure is further decreased in patients under general anesthesia and when the patient is placed in the Trendelenburg position. It must also be remembered that, as in adults, the vascularization of the lumbar part of the spinal cord often depends on one small artery (Adamkiewicz artery) entering the spinal canal between T8 and L3. Any lesion of this artery can result in spinal ischemia leading to paraplegia.

Indications and Contraindications

Spinal anesthesia is used mainly for surgery of the lower part of the body, especially irreducible inguinal hernia repair, [189] but also for operations on the lower limbs and spine. [190] It is of major interest in premature infants whose conceptional age is less than 60 weeks, [191] especially those who experienced neonatal respiratory distress syndromes or presenting with anemia (hematocrit level below 30%). [192] [193] [194] [195] However, only 15 percent of such patients were operated on under spinal anesthesia according to the Hernia Survey of the Section on Surgery of the American Academy of Pediatrics. [196] These patients are at risk of postoperative apnea if they are operated on under general anesthesia, whereas this complication is virtually (but not always [197]) unknown following spinal anesthesia without any concomitant sedation. [198] [199] [200] In older children, despite occasional papers recommending its use for minor procedures due to its efficacy and apparent simplicity, [201] spinal anesthesia has to be restricted to conditions in which general anesthesia is contraindicated such as a congenital muscle disease. [202] In some developing countries, the technique is commonly used because it is the only available and safe technique of anesthesia. Children undergoing major operations (open heart surgery, spinal fusions) may benefit from the administration of intrathecal narcotics [37] [203] [204] for postoperative pain relief. However, this is a serious decision that requires careful postoperative monitoring due to risks of delayed respiratory depression (see epidural morphine). Spinal blocks have the same contraindications and complications as epidural blocks. Additionally, the limitations of the technique in regard to the extension and duration of the block can be regarded as contraindications. The younger the patient, the shorter the duration of the blocks. In premature infants, spinal anesthesia does not last longer than 45 minutes with lidocaine and 60 to 75 minutes with bupivacaine.

Block Procedure

Basically, the technique is a lumbar puncture that can be performed in the same positions as for lumbar epidural approaches. It is easier when the infant is in the sitting position, but it is safer, especially in high-risk infants, when performed in the lateral decubitus position. In any case, considerable attention must be paid to the position of the head, which must be maintained extended throughout the duration of the procedure. [205] [206] In experimental models, the distribution of local anesthetics within the subarachnoid space depends on the orientation angle of the flow on injection (at high injection rates). [207] This has been found to be clinically relevant with the use of Whitacre needles (in adults), the directional flow of which exerts a major influence on sensory level, as well as the duration of isobaric lidocaine spinal anesthesia. [208] Several local anesthetics are suitable in children, including 0.5 percent dibucaine, 5 percent lidocaine, 1 percent tetracaine, 0.75 percent, and 0.5 percent bupivacaine, either in hyperbaric solutions or in standard solutions. Use of a bupivacaine solution with epinephrine does not have any pharmacologic advantage. [209] The safety of hyperbaric lidocaine has recently been questioned in adults, [210] [211] [212] and the U.S. Food and Drug Administration (FDA) now recommends that

---

TABLE 44-7 -- Usual Doses of Hyperbaric Local Anesthetics for Spinal Anesthesia in Infants and Children

LOCAL ANESTHETIC[a]	0 - 5 kg	5 - 15 kg	> 15 kg
0.5% hyperbaric bupivacaine	0.5 mg/kg (0.1 mL/kg)	0.4 mg/kg (0.08 mL/kg)	0.3 mg/kg (0.06 mL/kg)
1% hyperbaric tetracaine	0.5 mg/kg (0.05 mL/kg)	0.4 mg/kg (0.04 mL/kg)	0.3 mg/kg (0.03 mL/kg)
5% hyperbaric lidocaine [b]	2.5 mg/kg (0.05 mL/kg)	2 mg/kg (0.04 mL/kg)	1.5 mg/kg (0.03 mL/kg)

[a] Hyperbaric solutions have legal approval for intrathecal injection. Nonhyperbaric and conservative-free solutions are being used increasingly but have no legal approval (which does not necessarily preclude their use). [60]

[b] The FDA recommends diluting 5% lidocaine with an equal volume of cerebrospinal fluid before injecting the total dose.

5 percent hyperbaric lidocaine should be diluted with CSF (1:1) before subarachnoid injection. To reach an upper limit of block between T10 and T7, the recommended doses of hyperbaric bupivacaine are 0.5 mg/kg in infants weighing less than 5 kg (Table 44-7) . In larger patients, 5 to 15 kg, the dose has to be reduced to 0.4 mg/kg, and in patients weighing more than 15 kg to 0.03 mg/kg. The same doses are recommended for tetracaine. For 5 percent hyperbaric lidocaine similar heights of block are obtained with doses ranging from 1.5 to 2.5 mg/kg.

EXTREMITY CONDUCTION NERVE BLOCKS

Block of Nerves Supplying the Upper Extremity

Anatomic Considerations of the Brachial Plexus and its Sheaths

The brachial plexus supplies sensory and motor innervation to the upper extremity. It is formed by the union of the ventral rami of the fifth cervical to the first thoracic spinal nerves. It is located in the interscalene space, being enveloped by a continuous sheath derived from the deep cervical fascia. Thus, a single injection within this envelope produces complete plexus block. The interscalene space does not communicate with the axillary region due to the presence of a transverse barrier at the level of the coracoid process of the scapula. [213] Supraclavicular and axillary blocks are not equiv-alent, and the nerves leaving the brachial plexus above this limit (suprascapular, axillary, and, in half the patients, musculocutaneous nerve) are not anesthetized by axillary blocks. In addition, both the interscalene and the axillary spaces are longitudinally subdivided, at least partially, with a fascial compartment for each nerve, [214] [215] which can occasionally limit the circumferential spread of injected local anesthetics.

Indications and Contraindications [5] [6]

Brachial plexus blocks are recommended for emergency surgery on the upper extremities. [216] [217] [218] [219] [220] In elective surgery, they have many indications as they provide adequate intra- and postoperative analgesia for many operations [221] [222] depending on the local anesthetic used. Use of mepivacaine seems to improve significantly the success rate and quality of blockade. [223] They are of particular interest in outpatient surgery, with high degree of patient satisfaction, [218] [224] whether they are used as the sole anesthetic technique or in combination with light general anesthesia. [220] Axillary blocks are considered first, especially when the lesions involve the forearm and the hand, as they are virtually free of complications. Supraclavicular blocks are recommended when the lesion (or a tourniquet) is located on the proximal part of the arm. They are often preferred in boisterous children, especially in case of an unstable fracture or a weak tendon or nerve repair. Specific contraindications of axillary blocks include axillary lymph adenopathies (infection, malignancies), unstable fractures, or lesions in which the movement of the upper extremity is prohibited, and proximal lesions or placement of a tourniquet. Contraindications to supraclavicular blocks depend on the insertion route (see later). Basically, they must be avoided in case of respiratory insufficiency or when a bilateral block is necessary. The parascalene approach is virtually free of complications.

Supraclavicular Blocks of the Brachial Plexus

Interscalene Approach[225]

The technique aims at entering the interscalene space at its upper end, near the transverse process of C6. The patient is placed in the supine position with the head turned opposite to the side to be blocked. The landmarks are (1) the interscalene groove between the anterior and middle scalene muscles, and (2) the anterior ramus of the transverse process of the sixth cervical vertebra (the Chassaignac tubercle), which projects at the intersection of the interscalene groove, with the circular line passing over the cricoid cartilage. This intersection corresponds to the site of puncture. The block needle is inserted medially at an 80-degree angle (not perpendicularly) to the skin, (i.e., slightly dorsal and caudad until muscle twitches (or paresthesias) are elicited in the upper limb (Fig. 44-5 A). The local anesthetic is then injected following the basic safety rules. The interscalene block provides a very effective block of the lower

Figure 44-5 Supraclavicular brachial plexus blocks. (A) Interscalene (1) and perisubclavian (2) artery approaches. (B) Parascalene approach. (1) Skin projection of Chassaignac tubercle. (2) Midpoint of the clavicle.

branches of the cervical plexus and upper branches of the brachial plexus, whereas the caudal branches of the brachial plexus may be poorly anesthetized. [226] [227] In pediatric anesthesia, its indications must be evaluated carefully, as it can lead to severe adverse effects: vascular lesions (especially vertebral artery injury), undesirable nerve blocks (phrenic nerve, recurrent laryngeal nerve, stellate ganglion), and accidental epidural or intrathecal penetration (especially when the needle is inserted at a 90- instead of an 80-degree angle to the skin). Still more worrying is the extremely high frequency of diaphragmatic paresis produced by the block procedure, [228] which precludes its use in patients with respiratory impairment (including healthy young infants) and for bilateral procedures, as this paresis results in significant Pa O_2 decrease even in healthy adult volunteers. [229]

Perisubclavian Artery Approaches

The brachial plexus trunks gather at the lower part of the interscalene space where they surround the subclavian artery. They can be approached by several insertion routes derived from the original technique by Kulenkampff and Persky, [230] which basically consists of penetrating the interscalene space slightly above the first rib (see Fig. 44-5 A). All these techniques are very effective on virtually all branches of the brachial plexus, but they require considerable experience on the part of the anesthesiologist, particularly when performing these blocks in young children, as they can result in severe complications, especially pneumothorax, undesirable nerve blocks, and subclavian vessel puncture. They cannot be considered safe techniques and, thus, have no place in routine pediatric practice.

The Parascalene Approach[231]

This technique aims at penetrating the interscalene space at a distance from the apical pleura [232] and avoids damaging the great vessels, the vagus and phrenic nerves, the stellate ganglion, and the spinal canal. The patient is placed supine with the arm extended along the chest wall and the head turned to the contralateral side. A pillow is slipped under the shoulders to extend the neck, thereby stretching and bringing the components of the brachial plexus more superficial. The landmarks are the clavicle, the posterior edge of the sternocleidomastoid muscle, and the Chassaignac tubercle. The site of puncture is at the junction of the upper two thirds, with the lower third of the line joining the Chassaignac tubercle and the midpoint of the clavicle (Fig. 44-5 B). The needle is inserted posteriorly at right angles to the skin until twitches are elicited in the upper limb. The depth at which the plexus is found is correlated with the patient's age and weight. It ranges from 7 mm (±3 mm) in

TABLE 44-8 -- Recommended Volumes of Local Anesthetic Solution for Most Conduction Nerve Blocks

BLOCK	2 - 10 kg	15 kg	20 kg	25 kg	30 kg	40 kg	50 kg	60 kg	> 70 kg
Supraclavicular	1	12.5	15	17.5	20	22.5	25	27.5	30
Axillary	0.5	7.5	10	10	12.5	15	17.5	20	25
Lumbar plexus (Winnie)	1	15	17.5	20	22.5	25	27.5	30	32-35
Lumbar plexus (Chayen)	1	15	20	20	20	20	20	20	20
Femoral	0.7	8	12	15	15	17.5	20	22.5	25
Fascia iliaca	1	12.5	15	17.5	20	22.5	25	27.5	30
Sciatic	1	15	17.5	20	22.5	25	27.5	30	32-35

Figure 44-6 Distance from skin to plexus/nerve following the most commonly used techniques of peripheral nerve blocks.

neonates to 25 mm (±6 mm) in adolescents weighing more than 80 kg (Fig. 44-6) . Volumes of anesthetic solution usually administered are shown in Table 44-8 . The success rate of this block is high. [231] [233] The anesthetized area is that supplied by the brachial plexus and, in more than 50 percent of cases, that supplied by the lower branches of the cervical plexus. Proximal branches of the brachial plexus (i.e., those supplying the shoulder and the arm) are blocked earlier and sometimes more profoundly than the distal branches. Complications, including Horner syndrome, are unlikely with this procedure and only a very faulty technique ("... as suggested by the marked resistance to injection, by the agonizing pain experienced by the patient .... ") can result in adverse effects. [234]

Axillary Blocks of the Brachial Plexus

Axillary blocks are performed with the patient placed in the supine position. The relevant arm is both supinated and abducted to a 90-degree angle to the body. The landmarks are the pectoralis major muscle, the coracobrachialis muscle, and the axillary/brachial arteries. Several sites of puncture have been described due to loose attachment of fasciae; they do not influence the distribution of anesthesia in children, even in regard to the musculocutaneous nerve, the block of which depends on the site of emergence from the perineural space and not on the site or the technique of puncture (see previously). The most usual puncture site is at the upper border of the axillary artery, "as high as possible" in the axilla. The needle is inserted at a 45-degree angle to the skin, pointing toward the midpoint of the clavicle, until it crosses the perineurovascular sheath with a characteristic "click." At this stage, muscle twitches (or paresthesias) are elicited.

Several technical variants have been recommended occasionally, but they are of little interest, and are probably detrimental, in children. The use of a tourniquet does not allow upward spread of the local anesthetic toward the interscalene space and may lead to vascular and nerve compression. Also, exerting a digital pressure on the axillary sheath does not change either the proximal flow of the local anesthetic or the distribution of anesthesia. [235] Transaxillary artery approaches should not be used in children, as they can result in compressive hematomas. Two-injection techniques (i.e., with one injection at the upper edge and the other at the lower edge of the axillary artery) are not usual in children and may result in overdose of local anesthetics. I regularly use a more distal site of puncture, lying at the crossing of the coracobrachialis muscle with the lower edge of the pectoralis major muscle (Fig. 44-7) . The needle is introduced perpendicularly to the skin and advanced in the direction of the humerus, just above the axillary artery, which is firmly held by finger compression, until a "click" is perceived and twitches are elicited. Recommended volumes of anesthetic solution are shown in Table 44-8 . Irrespective of the technique used, axillary blocks are virtually free of complications. Accidental arterial puncture is the most undesirable occurrence, which may occasionally result in transient vascular insufficiency or a compressive hematoma. [236] Pneumothorax has been observed after the use of inappropriate insertion routes, but is unusual.

Distal Conduction Blocks

Distal conduction blocks at the shoulder, elbow, or wrist are only complementary blocks in pediatrics; and their indications result from the failure of a proximal brachial plexus block procedure (especially via the axillary route). These blocks are not usual in children and require fairly extensive experience. [5] [6]

Block of the Nerves Supplying the Lower Extremity

Anatomic Considerations of the Lumbar and Sacral Plexus

Nerve supply of the lower extremity is more complex than that of the upper limb, as it depends on two plexus, the lumbar (L1 to L4 spinal nerves) and the sacral (L5 to S4). The lumbar plexus supplies the anterior aspect of the limb and lies within the substance of the psoas muscle, in a fascial plane termed the *psoas compartment,* [237] where it can be approached percutaneously posteriorly through the quadratus lumborum muscle. The sacral plexus supplies the posterior

Figure 44-7 Axillary blocks. (1) Standard approach, (2) The author's technique.

aspect of the limb; it lies on the anterior aspect of the piriformis muscle, behind the posterior wall of the pelvic cavity, and cannot be directly approached by a block needle. Considerable attention must be paid to the fascial compartments of the thigh and the gluteal area, as injected solution cannot traverse fasciae but instead spread along their surface and then reach distant areas, which may be either favorable or detrimental. Schematically, the thigh is enclosed in a cylindrical envelope formed by the fascia lata and divided by two medial septa extending laterally and medially from this fascia to the posterior border of the femur. The posterior compartment is further divided by a reinforcement of the posterior fascia of the adductor magnus into a posterolateral compartment where the femoral vessels and saphenous nerve run, and a posteromedial compartment where the sciatic nerve runs. Injection of sufficient amounts of a local anesthetic in a compartment would ensure its diffusion to all the nerves traversing this compartment, whereas its penetration into adjacent compartments is prevented by the aponeurotic limits.

Indications and Contraindications

Lumbar Plexus Nerve Blocks

Femoral nerve blocks are the lower limb blocks most often used in pediatrics. Multieffective techniques are especially recommended in children with a fractured shaft of the femur and should be performed as early as possible after the accident to improve the conditions during transport, the ease of physical and radiologic examinations, wound dressings, and orthopedic procedures. These blocks are also suitable for providing intra- and postoperative pain relief during and after elective surgery of the soft tissues of the thigh (especially outpatient surgery) and operations on the femur. They are particularly useful in the latter case when epidural anesthesia is contraindicated. Conscious and slightly sedated pediatric patients tolerate quite well the performance of a muscle biopsy under femoral and lateral cutaneous nerve block. [238] Placement of a reinjection catheter allows long-lasting pain relief following femoral fractures. [239] [240] These block procedures have no specific contraindications.

Sacral Plexus Nerve Blocks

Sciatic nerve blocks are recommended for operations on the foot and leg (a femoral nerve block or a local infiltration is often necessary in the latter case). They have no specific contraindications. Damage to the sciatic nerve has been reported following intragluteal injections, [241] [242] [243] especially in infants, but both experimental

data and clinical experience with the use of local anesthetics have confirmed the safety of the procedure. [244] [245]

Lumbar Plexus and Lumbar Plexus Nerve Blocks

Direct Lumbar Plexus Block (Psoas Compartment Block)

The psoas compartment [237] enclosing the lumbar plexus can be approached percutaneously with the patient in the semiprone position, the side to be blocked lying uppermost. The landmarks are the ipsilateral posterior superior iliac spine, the line joining both iliac crests, and the spinous process of L5. Two puncture sites are suitable: (1) the midpoint between the posterior iliac spine and the spinous process of L5 [246] and (2) the line joining the iliac crests with a perpendicular line passing over the posterior iliac spine [247] (Fig. 44-8) . Whatever the puncture site, the needle is inserted perpendicularly to the skin until twitches are elicited,

Figure 44-8 Direct lumbar plexus block: (1) Winnie technique, (2) Chayen technique (slightly modified).

Figure 44-9 Lumbar plexus nerve blocks: (1) Fascia iliaca compartment block, (2) Femoral nerve block.

in the foot with the first puncture site or in the thigh with the latter puncture site. The distribution of anesthesia depends on the insertion route. When injected via the more medial puncture site, the anesthetic solution frequently reaches the epidural space in infants and young children, thus providing anesthesia to both sides of the lower part of the body, whereas the other technique results in an unilateral block of areas supplied by ipsilateral lumbar and, in about 75 percent of patients, sacral plexus nerves. [246]

Femoral Nerve Block

Femoral nerve blocks [247] [248] [249] [250] are performed with the patient in the supine position. Preferably, the ipsilateral limb should be slightly abducted, but any position is suitable. The landmarks are the inguinal ligament and the femoral artery. The needle is inserted perpendicularly to the skin 0.5 to 1 cm below the inguinal ligament and lateral to the femoral artery (Fig. 44-9) . It is moved dorsally until twitches are elicited in the quadriceps muscle. Alternately, a successful block can be obtained by injecting the local anesthetic blindly in a fan-like manner without attempting to elicit twitches. Both techniques anesthetize the upper aspect of the thigh, the medial aspect of the leg, and the periosteum of the femur.

Multieffective Blocks

"3-in-1" Block [251]

The technique consists of injecting an anesthetic solution within the femoral nerve sheath and forcing it cephalad with the aim of reaching the lumbar plexus within its psoas compartment. The technique is basically the same as that of the classic femoral nerve block, but, instead of being inserted vertically, the needle is advanced rostrally at a 30-degree (or less) angle to the skin until paresthesias or muscle twitches are elicited in the thigh. Firm finger pressure is then applied distally to the site of injection on the femoral artery before injecting the local anesthetic. This compression is maintained for several minutes while the swollen area is massaged to favor upward diffusion of the local anesthetic. Although constant femoral nerve block is obtained, the lateral cutaneous nerve and furthermore the obturator are

unblocked in many patients. This failure rate is consistent with the results of a recent anatomic study showing no femoral nerve sheath capable of conveying local anesthetic to the lumbar plexus and the obturator nerve. [252]

Fascia Iliaca Compartment Block [253] [254] [255]

The technique aims at injecting local anesthetics just below the fascia iliaca under which run all the nerves emerging from the lumbar plexus. The patient is placed in the supine position as for classic femoral nerve block. The line joining the pubic spine to the anterior superior iliac spine (skin projection of the inguinal ligament) is divided in three equal parts. The site of puncture lies 0.5 to 1 cm below the union of the lateral one third with the medial two thirds, (i.e., at least 2-3 cm lateral to the femoral artery) (see Fig. 44-9) . The (noninsulated) needle is connected via an extension line to the syringe filled with the anesthetic solution. It is then inserted at right angles to the skin while gentle pressure is exerted on the barrel. Two resistances followed by a loss of resistance are sought. The first one occurs as the tip of the needle crosses the fascia lata, and the second one occurs as the fascia iliaca is pierced. The injection is made at this level. Injecting a sufficient volume and massaging the swollen area favor spread of the solution to the inner surface of the fascia iliaca, thus improving the chances to block distant lumbar plexus nerves such as the obturator nerve. With this technique, the femoral and lateral cutaneous nerves are almost always blocked, whereas the obturator nerve is reached in more than 75 percent of patients. The anesthetized area also includes areas supplied by upper branches of the lumbar plexus in more than 70 percent of procedures, such as the genitofemoral nerve. Doyle et al [256] measured plasma bupivacaine levels after injection of 2 mg/kg of bupivacaine with or without epinephrine and found that plasma concentrations were acceptable with both solutions even though higher concentrations were observed after injection of plain bupivacaine (mean values: 1.1 versus 0.35 mug/mL); conversely, the median time to C_{max} was shorter with plain bupivacaine (20 versus 45 minutes in patients given bupivacaine with epinephrine).

Saphenous Nerve Block

The block of the saphenous nerve is a complementary block; its main indication is for extending the anesthetized area provided by a sciatic nerve block. The classic approach is performed at knee level, with the patient placed in either the semiprone or supine position with the knees flexed by 90 degrees. The landmarks are the anterior edge of the medial head of the gastrocnemius muscle and the tibial tuberosity. A line is drawn at a 45-degree angle with the intercondylar line, from the tibial tuberosity to the anterior edge of the gastrocnemius muscle. The technique consists of subcutaneously injecting a ring of local anesthetic along this line. This very simple technique is virtually free of complications, but its failure rate is rather high. Two alternate techniques, the transsartorial and the vastus medialis nerve approach, are promising because of their high success rate and low morbidity.

Transsartorial Approach [257]

The patient is placed supine with the leg extended. The landmarks are the patella and the sartorius muscle, on the medial aspect of the thigh. The puncture site lies 1 to 2 cm above the transverse plane tangential to the upper border of the patella, right on the body of the sartorius muscle. A 22-gauge (or 20-gauge) Tuohy needle, first blunt, then connected to a syringe filled with medium (local anesthetic) after the skin had been pierced, is introduced slightly posteriorly and caudad through the substance of the muscle until a loss of resistance is felt as the needle enters the fat pad beneath the sartorius muscle where the saphenous nerve runs. The injection of 15 mL was originally claimed to provide complete blockade of the saphenous nerve in virtually all patients [257] [258] then the success rate was reported to be close to 75 percent by the same team. [259] In children, the injection of 0.2 mL/kg (up to 10 mL) of local anesthetic results in consistent blockade of the saphenous in up to 90 percent of patients (personal data).

Saphenous/Vastus Medialis Nerve Block [260]

Whereas the saphenous nerve is a purely sensory nerve, the division branch of the femoral nerve supplying the vastus medialis that runs just medial to the saphenous nerve can be located easily by nerve stimulation. With the patient in the supine position, the landmarks are the femoral artery and the inguinal ligament

(see Fig. 44-9) . The insulated needle is inserted at right angles to the skin 0.5 cm lateral to the femoral artery and 3 to 6 cm (depending on patient's age and size) below the inguinal ligament until twitches are elicited in the vastus medialis, which occurs rather superficially (from less than 1 cm to no more than 3 cm from the skin). Then 0.1 to 0.2 mL of local anesthetic is injected and a saphenous nerve block is obtained in virtually 100 percent of cases.

Even though these two techniques have not been extensively evaluated, they appear promising and are particularly interesting in that they provide effective saphenous nerve block without requiring the high doses necessary to perform a complete femoral nerve block. Thus they are safe and (in regard to local anesthetic toxicity) suitable to complement a sciatic nerve block and provide complete anesthesia of the leg, ankle, and foot.

Other Lumbar Plexus Nerve Blocks

Obturator nerve block has virtually no indications in children for anesthetic purposes. The block of the lateral cutaneous nerve is usually performed for extending the area anesthetized by a femoral nerve block for performing a muscle biopsy. With the patient lying supine, the needle is inserted perpendicularly to the skin 1 cm below the union of the lateral one fourth with the medial three fourths of the inguinal ligament. [261] As the needle penetrates the fascia lata with a characteristic give, two thirds of the local anesthetic is injected in a fan-shaped manner almost parallel to the skin. The needle is then withdrawn, and the remaining solution is injected superficial to the fascia lata. Brown and Dickens [262]

Figure 44-10 Proximal sciatic nerve block: posterior approach: (1) Greater trochanter of the femur, (2) Coccyx.

recommended inserting the needle above the inguinal ligament at a point immediately medial to the anterosuperior iliac spine until a loss of resistance is felt as the needle enters the canal through which the nerve passes.

Sacral Plexus and Sacral Plexus Nerve Blocks

Proximal Sciatic Nerve Blocks[263]

Three proximal approaches to the sciatic nerve are suitable. The most classic is via the posterior route with the child in the lateral position, the side to be blocked lying uppermost. The landmarks are the greater trochanter of the femur and the end of the coccyx (Fig. 44-10) . The site of puncture lies at the midpoint of these landmarks, and the needle is inserted at right angles to the skin (i.e., both medially and ventrally), toward the ischial tuberosity until twitches are elicited in the foot. An anterior approach has been described for use in patients who should remain in the dorsal position. [264] [265] The landmarks are the inguinal ligament and the greater trochanter of the femur. The site of puncture lies at the crossing of (1) a line parallel to the inguinal ligament passing over the greater trochanter with (2) the parallel to the major axis of the body passing over the union of the medial one third with the lateral two thirds of the inguinal ligament (Fig. 44-11) . The needle is inserted almost perpendicularly to the skin toward the medial edge of the femur until twitches are elicited in the foot (a loss-of-resistance technique can also be used). This technique is more difficult than the posterior approach and can result in inadvertent puncture of the femoral vessel. A lateral approach has been described for use in patients lying supine, [266] [267] with the leg slightly rotated medially. The main landmark is the greater trochanter. The needle is inserted horizontally 1 to 3 cm below its lateral skin projection, until it contacts the lower edge of the femur (see Fig. 44-11) . Then, it is withdrawn and reinserted slightly more posteriorly until twitches are elicited in the foot (a loss-of-resistance technique can also be used). The depth at which the sciatic nerve is found depends on the insertion route

Figure 44-11 Proximal sciatic nerve block: anterior and lateral approaches: (1) anterior approach, (2) lateral approach.

(see Fig. 44-7) . Recommended volumes of anesthetic solution are shown in Table 44-8 The anesthetized area is that supplied by the sciatic nerve and, in virtually all patients, that supplied by the posterior femoral nerve block (i.e., the dorsal part of the thigh).

Sacral Nerve Blocks in the Popliteal Fossa[5] [6] [268]

The sciatic nerve and its two main branches can be approached in the popliteal fossa using virtually the same procedure. Two positions are suitable: (1) semiprone with the limb to be blocked lying uppermost and, preferably, (2) prone with the legs flexed 30 degrees from the table to make the limits of the popliteal fossa more apparent. The bisecting line of the upper angle of the popliteal fossa is marked down to its crossing with the skin crease behind the knee joint. The puncture site for each of the three nerve blocks lies on this line: (1) at the union of the upper two thirds with the lower one third, for the sciatic nerve; (2) slightly more

Figure 44-12 Intercostal nerve block: (1) Insertion of the needle at an 80-degree angle to the skin, (2) Caudal and dorsal redirection of the needle.

lateral, closer to the lateral border of the popliteal artery, for the tibial nerve; and (3) still more medial, close to the medial border of the tendon of the biceps femoris muscle, for the common peroneal nerve. The needle is inserted at a 45- to 60-degree angle with the skin, pointing to the thigh (sciatic nerve) or perpendicularly to the posterior aspect of the popliteal fossa (tibial and common peroneal nerves) until twitches are elicited in supplied areas. The last two nerves lie 2 to 5 mm below the popliteal membrane, which is easily identified by the characteristic "crack" felt as it is pierced by the block needle. This technique is safe and reliable. [269] A lateral approach [270] [271] with the patient in the supine position has been described in adults, but no data are available in children. A new approach to the tibial and peroneal nerve block has been described in adults [272] ; however, in my experience, its application to pediatric patients was not as easy or reliable as reported.

OTHER REGIONAL AND LOCAL PROCEDURES

Block of Nerves Supplying the Trunk

Intercostal Nerve Blocks

The thorax is supplied by the two main division branches of the spinal nerves, dorsal and ventral, which maintain a metameric disposition of sensory supply. The intercostal nerves are the continuation of the ventral branches. They run within the intercostal spaces along the lower border of the rib, accompanied by an intercostal vein (draining to the azygous venous system) and an intercostal artery. The intercostal space is triangular in section with (1) a medial border formed by the posterior intercostal muscle, and the innermost intercostal muscle, and (2) a lateral border formed by the external intercostal muscles. Intercostal nerve block is obtained by injecting a local anesthetic within the intercostal space; and, provided several adjacent intercostal spaces are infiltrated, adequate intra- and postoperative pain relief is obtained for thoracotomy, liver transplantation, pleural drainage, and management of rib fractures. This block must be avoided in the presence of impaired blood/gas exchange, and all patients must be kept under intensive medical observation because of the danger of clinically delayed pneumothorax; it is thus being contraindicated for outpatient surgery.

The safest approach to the intercostal space is in the midaxillary line with the child lying semiprone, using a short (30 mm or less), short-beveled, and not too thin (24-gauge or more) needle. Intradermal needles (25-gauge) are not appropriate, whereas 20-gauge or, preferably, 22-gauge Tuohy needles are almost ideal. The needle, connected to a syringe with interposition of an extension line, is inserted just below the lower border of the upper rib at an 80-degree angle to the chest, pointing cephalad, until it contacts the rib (Fig. 44-12) . It is then slightly withdrawn and, while continuous pressure is exerted on the barrel of the syringe, redirected both more caudad (so as to pass immediately below the rib) and dorsally (to avoid pleural damage). [273] A loss of resistance is felt at entry into the intercostal space where 1 mL of 0.125 to 0.25 percent bupivacaine with 1:400,000 epinephrine is injected. This provides 8 to 18 hours of analgesia (0.25-1% of either lidocaine or mepivacaine is also suitable, but pain relief lasts no longer than 3-4 hours).

Several adjacent intercostal spaces have to be blocked to produce adequate sensory block (thus multiplying the dangers of complications). As systemic uptake is considerable, almost equivalent to intravenous injection, [274] [275] only diluted solutions are suitable and the overall dose of bupivacaine should not exceed 2 mg/kg. Great attention must also be paid to the total dose of epinephrine, which must not exceed 4 mug/kg. A catheter can be introduced in the intercostal space located at the center of the area to be anesthetized to allow reinjections. Spread of large volume anesthetic solution can reach distant intercostal spaces (even contralateral ones), thus providing in a number of patients adequate prolongation of pain relief with a single injection. Spread to adjacent paravertebral spaces and to the epidural space can also occur. Thus, the patient should be admitted to the intensive care unit for careful monitoring of respiratory function and for delayed pneumothorax.

Iliohypogastric and Ilioinguinal Nerve Blocks [276] [277]

The iliohypogastric and ilioinguinal nerves are branches of the lumbar plexus, both originating from the first lumbar spinal nerve. The iliohypogastric nerve emerges from the lateral border of the psoas, perforates the transversus abdominis muscle, and runs obliquely, adjacent to the posterior aspect of the internal oblique muscle. Near the iliac crest, the nerve divides into two terminal cutaneous branches, lateral supplying the buttock, and medial supplying the abdominal wall, above the pubis. The ilioinguinal nerve has a similar course, below the iliohypogastric nerve. It crosses the quadratus lumborum and the iliacus muscle obliquely, pierces the transversus abdominis (at the level of the iliac crest) and the oblique muscles, then reaches the lower border of either the spermatic cord (in the male) or the round ligament of the uterus (in the female), within the inguinal canal. It provides sensory innervation to the upper medial part of the thigh and either the upper part of the scrotum and penis (male) or the labium major and the mons pubis (female).

Iliohypogastric and ilioinguinal nerve blocks usually provide adequate pain relief for operations on the inguinal region (herniorrhaphy, orchidopexy, hydrocele), including emergency procedures (strangulated hernia with intestinal obstruction). The patient is placed in the dorsal recumbent position and, according to the classic technique, two sites of puncture are identified--one at the union of the lateral one fourth, with the medial three fourths of the line joining the anterior superior iliac spine to the umbilicus, the other immediately lateral to the pubic tubercle (Fig. 44-13) . At both puncture sites, the needle is inserted subcutaneously and one fourth (one per site) of the total dose is injected in a fan-shaped manner. It then is inserted under the aponeurosis of the external oblique muscle (i.e., within the substance of the muscle) where a second quarter (one per site) is similarly injected. Any anesthetic agent can be used, but long-acting local anesthetics are usually preferred, especially 0.5 percent prilocaine or 0.25 to 0.5 percent bupivacaine, both with 1/200,000 epinephrine. The recommended total volume of injection ranges from 0.5 to 1 mL per year of age. Intraoperative infiltration of the hernia sac (which, in fact, is the same technique) effectively relieves postoperative pain [278] [279] but does not protect against intraoperative pain.

Ilioinguinal and iliohypogastric nerve blocks are easy to perform and virtually free of "true" complications, but their failure rate (>10%) is not negligible with the classic technique. Undesired nerve blocks (especially femoral nerve blocks) are occasionally observed [280] [281] [282] [283] because of the spread of the local anesthetic caudad to the inguinal ligament. The only problem with this undesired effect is that it can delay the discharge of the patient by a few hours. More worrying is a recent study on a small pediatric series (30 patients divided in two groups) showing unexpectedly high plasma bupivacaine concentrations (without clinical symptoms) in patients weighing 10 to 15 kg, thus inciting the authors to recommend injecting not more than 1.25 mg/kg when performing this block in infants. [284] These goals can be easily achieved by simplifying the technique. [285] With the patient in the same dorsal recumbent position, only the puncture site close to the anterosuperior iliac spine is used. Instead of being introduced perpendicularly to the skin at this point, the short-beveled needle is inserted at a 45- to 60-degree angle, pointing to the midpoint of the inguinal ligament, until the superficial layer of the external oblique muscle is pierced with a clearly identifiable "crack" (the piercing is sometimes rather difficult). Then a single injection of 0.3 to 0.4 mL/kg of 0.25 percent bupivacaine is made in a fan-shaped manner. With this insertion route, the tip of the needle pierces the fascia at a level where both the ilioinguinal and iliohypogastric nerves have crossed the fascia covering the internal oblique muscle. Additionally, because of the spread of the local anesthetic at the inner surface of the fascia of the external oblique muscle, which contributes to the constitution of the inguinal ring, the genital branch of the genitofemoral nerve, which enters the inguinal ring at close proximity, will usually be reached and anesthetized, thus making unnecessary any injection at the level of the pubic tubercle.

Figure 44-13 Iliohypogastric and ilioinguinal nerve blocks: (1) Umbilicus, (2) Anterior iliac crest, (3) Pubic spine.

Penile Blocks [286]

Except for its proximal part, which receives sensory fibers from the ilioinguinal and genitofemoral nerves, the penis is supplied by the two dorsal nerves of the penis, which are terminal branches of the pudendal nerves (sacral plexus nerves). Each dorsal nerve passes under the pubic bone, runs within the subpubic space and then through the substance of the suspensory ligament, accompanies the dorsal artery of the penis at the inner aspect of the Buck fascia close to the corpora cavernosa, and ends in the glans penis. During its course, the dorsal nerve gives off numerous branches to the corpora cavernosa, the skin of the penis, the glans, and the frenulum. The only safe approach to the dorsal nerves of the penis is within the subpubic space, a pyram- idal space limited by the perineal membrane and symphysis pubis (above), the pelvic part of the corpora cavernosa (laterally and below), the suspensory ligament, and the superficial fascia of the abdomen. At this level, the fascia superficialis divides into two layers. The superficial layer is

Figure 44-14 Penile block via the subpubic space: landmarks.

loose, fatty, and areolar in texture. The deep layer is membranous, thin but resistant, and aponeurotic in structure. It is also termed the *Scarpa fascia* and is continuous with the fascia penis (the Buck fascia).

Penile blocks are recommended for surface operations on the penis (i.e., foreskin [circumcision] and glans). They are suitable for providing long-lasting pain relief when performed at the end of surgery for hypospadias repair but are not usually sufficient for the surgery itself, which is best completed under caudal anesthesia. As the penis is supplied by terminal arteries, *epinephrine must not be added to the anesthetic solution.* With the patient in the supine position and the penis pulled down, either by manual traction or by taping, two sites of punctures are marked 0.5 to 1 cm both below the symphysis pubis and lateral to the midline (Fig. 44-14) . A 30-mm long needle, the bevel of which is not too short as Scarpa's fascia is not easily traversed due to its elasticity (a caudal or a neonatal lumbar tap needle is ideal), is inserted almost perpendicularly to the skin (see Fig. 44-14) , with a slight slope medially and caudally until it pierces the Scarpa fascia with a characteristic "give," at a distance ranging from 10 to 25 mm irrespective of the age and weight of the patient. As the subpubic space is frequently divided into two separate compartments by a medial division, a twoinjection technique is preferable. The volume of 0.5 percent bupivacaine *without epinephrine* to be injected is 0.1 mL/kg per side up to a maximum of 5 mL per side.

Several other techniques of penile blocks have been reported. Most of them aim at approaching the dorsal nerves at the proximal part of the penis where they run between the Buck fascia and the outer surface of the corpora cavernosa. These techniques are dangerous and should not be used in children. A safer alternative [287] [288] consists of performing a subcutaneous ring of local anesthetic at the base of the penis; however, this technique requires relatively large amounts of local anesthetic (2 mg/kg bupivacaine) and fails to provide adequate analgesia in less than 20 percent of patients. Topical anesthesia can occasionally be used as an alternative to penile blocks for urethral meatotomy [289] or even neonatal circumcision. [290] [291]

Other Techniques

Paravertebral Blocks

Spinal nerves can be directly blocked at their emergence from the spinal canal when they run in the paravertebral space. At thoracic levels, paravertebral blocks can be an alternative to intercostal nerve blocks. [292] At lumbar levels, they can be helpful for postoperative pain relief after surgery on the kidney. The technique for approaching the thoracic paravertebral space has recently been reevaluated in children. [293] [294] [295] The paravertebral space is poorly described in textbooks of anatomy. In the transverse plane, [296] the paravertebral space is limited medially by the vertebral bodies and intervertebral discs; posteriorly by the transverse processes, the ribs, and costotransverse ligaments; anterolaterally by the parietal pleura. Caudally, this space is closed by the psoas muscle at the level of T12, whereas its cranial extremity is not well defined but might communicate with the fascial planes of the neck. It is crossed by the intercostal pedicles, azygos and hemiazygos veins, the sympathetic chains and lymphatic ducts. The anesthetized patient is placed in the lateral decubitus position with the side to be blocked uppermost. The landmarks are the spinous and transverse processes of T7 to T9 (in case of thoracotomy, the block will be performed at T4-T6 levels), and the puncture site is marked 1 to 2 cm lateral to the spinous process (Fig. 44-15) . The same Tuohy needle that would be used for performing an epidural on the patient is inserted at right angles to the skin, while continuous pressure is exerted on the barrel of a loss-of-resistance syringe connected to the block

Figure 44-15 Paravertebral space block.

needle and filled with saline, until it contacts the transverse process. The needle is then "walked" along the surface of the process so as to pass over its cranial border and enter the paravertebral space after piercing the costotransverse ligament with a clearly identifiable loss of resistance. An epidural catheter is then inserted for 2 to 3 cm and, after a negative aspiration test and test dose, is securely taped on the skin, as for a continuous epidural. A starting dose of 0.5 mL/kg of 0.25 percent bupivacaine is then injected followed either by reinjection or continuous infusion of the same local anesthetic (0.25 mL/kg/h). The distance (mm) from skin to paravertebral space can be calculated by the following equation: [297]

Distance (mm) = 21.2 + [0.53 × (weight in kg)]

The injected local anesthetic can spread longitudinally (lateral to the spine, from T12 to T6 or above), or in a cloud-like, ill-defined manner (at least five dermatomes are blocked, even in this latter case). Continuous infusion provides better quality postoperative pain relief than intermittent bolus, and plasma concentrations remain rather low, both for lidocaine [298] and bupivacaine, at least in adults. [299] The technique compares favorably with continuous interpleural anesthesia [292] ; its failure rate is low and complications are rare. [300]

Interpleural (or Intrapleural) Block[301] [302] [303]

The pleura is formed by two sheets, the visceral pleura, which is in contact with the lungs, and the parietal pleura which is tightly adherent to the thoracic wall. These sheets enclose a potential space, the pleural cavity (one per lung), with a subatmospheric pressure. Intrapleural blocks (also termed *interpleural blocks*) consist of injecting a local anesthetic within this cavity without creating a pneumothorax. Indications for the technique are not well established in children, and, contradictory results concerning spread of analgesia have been reported. Biliary duct surgery and parietal pain due to thoracotomy are the most commonly accepted indications. The technique requires using a block needle, preferably a Tuohy needle (20 or 22 gauge, depending on patient's size), a syringe similar to that used for identifying the epidural space, and an appropriately sized "epidural" catheter. The best anesthetic solution is 0.5 percent bupivacaine with 1/200,000 epinephrine and recommended volumes to be injected range from 0.2 to 0.4 mL/kg up to a maximum of 20 mL.

With the patient in the semiprone (or ventral) position, usually at the end of the surgery, the eighth intercostal space is identified. The needle is connected to the syringe filled with 1 to 3 mL of either gas (preferably medical CO_2) or fluid (preferably local anesthetics). It is then introduced perpendicularly to the skin, in the midaxillary line (but any other point is suitable) immediately below the eighth rib with the bevel turned cephalad. A first loss of resistance is felt as the needle pierces the intercostal membrane, followed by a second one when the parietal pleura is traversed (with a characteristic "click"). The solution is then injected at this time while paying considerable attention to avoiding air penetration if the syringe has to be disconnected. Although the technique is not free of complications, [304] it has proved suitable for providing post-thoracotomy pain relief with continuous infusion of local anesthetics through the catheter that had been maintained in place. Several regimens have been evaluated, without or with a starting dose (0.625 mg/kg of 0.25% bupivacaine), followed by a continuous infusion of either 1.25 mg/kg/h, then 0.75 ± 0.32 mg/kg/h, [305] or 0.5 to 1 mL/kg/h of 0.1 percent bupiv-acaine. [306] However, at least one case of central nervous system toxicity has been reported (in an adult) with this technique. [307]

Pudendal/Perineal Nerve Block

Because of its better benefit/risk ratio, ilioinguinal/iliohypogastric nerve block is being increasingly used instead of caudal anesthesia for minor perineal surgery. Thus, the pudendal/perineal nerve block, which was ruled out from use in obstetrics by the emergence of the epidural era, is regaining interest, mainly in the male when a scrotal incision is necessary. The pudendal nerve is a terminal branch of the sacral plexus that runs along the lateral wall of the ischiorectal fossa within a sheath derived from the obturator fascia (Alcock canal). It gives off the inferior hemorrhoidal nerve, the perineal nerve, and the dorsal nerve of the penis (or clitoris). It can be easily blocked at the level of the ischial tuberosity. The patient is placed in the supine position, with the knee flexed and the plantar aspects of the feet conjoined (as for female bladder catheterization). The landmark is the skin projection of the ipsilateral ischial tuberosity in the frontal plane. A short and short-beveled needle is inserted in the same frontal plane in the direction of the ischial tuberosity, aiming at passing just medially to it until a give is felt as the obturator fascia is pierced. Then 0.1 mL/kg up to 5 mL of plain solution of local anesthetic is injected (the pudendal artery, which is close to the nerve is a terminal artery; therefore, epinephrine must be avoided). If no give is felt before contacting the medial aspect of the ischial tuberosity, the needle is removed a little, and local anesthetics are injected. An excellent block will be obtained in virtually all patients (unpublished data). An alternative to this technique consists of infiltrating the incisional line directly on the scrotum, [308] but the reliability of the technique is not as good as that of the pudendal/perineal nerve block and requires several changes in needle orientation, which could threaten the scrotal content.

Rectus Sheath Block/Paraumbilical Block

The rectus sheath block [309] also know as paraumbilical block [310] has gained renewed interest in pediatric anesthesia for providing both intra- and postoperative analgesia in patients undergoing umbilical and paraumbilical hernia repairs. The periumbilical area receives its sensory supply from the tenth right and left intercostal nerves after they have pierced and penetrated the rectus sheath (fascia covering the rectus abdominis muscle). The block procedure consists of introducing a rather short-beveled needle through the rectus sheath, on either side of the abdomen, at the crossing of the outer border of the muscle with the line

drawn downward from the umbilicus at a 45-degree angle to the horizontal line. The block needle is inserted obliquely toward the umbilicus at a 60-degree angle to the skin until it pierces the rectus sheath (with a characteristic "pop"). The local anesthetic (0.2 mL/kg of 0.5% bupivacaine with or without epinephrine) is then injected in a fan-shaped manner and excellent analgesia of the ipsilateral periumbilical region is provided almost instantly. This block is virtually free of complications provided a sharp needle is not used with the wrong insertion route (i.e., perpendicularly to the skin and through the parietal peritoneum). The technique is quite simple and the success rate extremely high. When it is used the surgeons may complain of some degree of "edema" at the site of incision, which they consider advantageous later on as dissection of fascial planes is then made easier.

Other Blocks of Nerves of the Trunk

Other blocks of nerves of the trunk, including paravertebral ganglion, genitofemoral, paracervical (uterosacral), and transsacral nerve blocks are not used in pediatric patients.

Block of Nerves Supplying the Head and Neck

Cervical Plexus Blocks

The cervical plexus is formed by the union of the ventral rami of the first four cervical spinal nerves. It lies just lateral to the relevant vertebrae and provides sensory supply to the shoulders, neck, and posterior aspect of the head. Specific cervical plexus blocks are unusual in children because "high" supraclavicular brachial plexus blocks (interscalene and parascalene blocks) provide adequate analgesia for most of the operations performed on the neck. The cutaneous branches can be anesthetized by a series of subcutaneous injections along the posterior border of the sternocleidomastoid muscle from C2 to C5. The various (and unusual) techniques for blocking this plexus are fully detailed elsewhere. [5] [6]

Laryngeal Nerve Block

The laryngeal nerve is a branch of the vagus nerve supplying the pharynx and larynx. The block of the laryngeal nerve allows laryngeal endoscopic examinations lasting no more than 30 minutes in an awake patient. It can be particularly helpful when tracheal intubation is difficult, as it allows awake intubation (or an attempt at intubation). A variant of the lateral approach is especially easy and safe in children. It consists of a subcutaneous injection of local anesthetics just lateral to the extremity of the hyoid horn. [311] The intradermal needle is inserted perpendicularly to the skin until it contacts the cartilage (Fig. 44-16) . After a negative aspiration test, 0.1 to 0.2 mL/kg (i.e., rather large volumes in this narrow area) up to a maximum of 8 mL of 1 percent lidocaine is injected subcutaneously.

Cervicothoracic (Stellate) Ganglion Block

The cervicothoracic (or stellate) ganglion belongs to the (ortho)sympathetic system. It extends from the transverse process of C7 to the neck of the first rib, between the longus colli muscle posteriorly, and the carotid and vertebral arteries anteriorly. It is in close contact with the subclavian artery, the recurrent laryngeal nerve, the inferior thyroid artery, and the cupola of the lung (right side mainly). Therefore, blocking the cervicothoracic ganglion is hazardous. The technique has two main pediatric indications: [312] (1) severe circulatory disturbances of one of the upper limbs (as it produces considerable vasodilation) and (2) severe ventricular tachyarrhythmias due to familial syndromes with prolonged QT interval on electrocardiographic tracings. [313] [314] [315] [316]

The patient is placed in the dorsal recumbent position, the hands extended along the chest. A pillow is slipped under the neck to extend the esophagus, and the head is strictly maintained in a median plane. The puncture site corresponds to the skin projection of the transverse process of C6, at the crossing of the circular line passing over the cricoid cartilage with the medial border of the sternocleidomastoid muscle. With his or her fingers, the anesthesiologist moves the carotid artery and trachea laterally before inserting the needle vertically until it contacts the transverse process. The needle is then slightly withdrawn (1 to 2 mm) before 0.3 mL/kg (up to a maximum of 15 mL) of lidocaine or bupivacaine is injected. The solution can spread a considerable distance along the sympathetic chain. [317] The sympathetic block produced covers the thorax, the axillary region, and the upper limb. It constantly results in Horner syndrome.

Figure 44-16 Laryngeal nerve block.

Blocks of Nerves Supplying Facial Sensory Innervation

Sensory Innervation of the Face

The face is supplied by the voluminous sensory branch of the fifth cranial or trigeminal nerve, which expands to form the trigeminal ganglion from which arise three divisions:

1. The ophthalmic nerve (V1), which supplies sensory innervation to the orbit and the upper third of the face (including the scalp) via its three division branches: the nasociliary, frontal, and lacrimal nerves.
2. The maxillary nerve (V2), which crosses the pterygopalatine fossa, reaches the infraorbital groove and canal in the orbital floor and then becomes the infraorbital nerve. Via its division branches, the meningeal nerve, a ganglionic branch to the sphenopalatine ganglion, and the anterior superior alveolar nerve, it

supplies sensory innervation to the dura mater, the maxillary bone, the nose, and the skin of the middle third of the face, including the upper lip.

3. The mandibular nerve (V3), which is the largest division of the trigeminal nerve, divides into (1) a small anterior trunk that gives off the (sensory) buccal nerve, and the (motor) masseteric, deep temporal, and lateral pterygoid nerves; and (2) a large posterior trunk, mainly sensory, which divides into the auriculotemporal, lingual, and inferior alveolar (dental) nerves. The inferior alveolar nerve reaches the mental foramen, becoming the mental nerve, which supplies sensory innervation to the soft tissues of the chin, lower lip, and its underlying mucosa and gingiva.

Most of these nerves are purely sensory nerves (precluding the use of a nerve stimulator), and although they are commonly blocked in adults, there are few indications for block in children, particularly in infants. However, three infiltration techniques as described later are easy to perform, safe, reliable, and recommended for analgesia for surgery involving facial skin, either in emergency (skin lacerations) or for superficial elective procedures.

Block of the Supraorbital and Supratrochlear Nerves

The supraorbital and the supratrochlear nerves are the two terminal branches of the frontal nerve that supply sensory innervation to the forehead and scalp. These two nerves can be easily blocked by a single injection technique (on each side). The landmark is the supraorbital foramen, easily palpable at the junction of the lateral two thirds and the medial one third of the superior orbital rim, in line with the centered pupils and both the infraorbital and mental foramina (Fig. 44-17) . An intradermal needle (25-gauge and 25 mm long) is inserted 0.5 to 1.5 cm below the foramen, on the vertical line uniting the three foramina. As the tip of the needle reaches the lower border of the foramen, 0.1 mL/kg (up to 3 mL) of local anesthetic (plain 1% lidocaine or mepivacaine, or 0 .25% bupivacaine) is slowly injected to block the supraorbital nerve. The needle is then withdrawn a little and redirected medially toward the angle formed by the union of the orbital rim with the nasal bone, and the same

Figure 44-17 Block of nerves supplying the face (supraorbital, infraorbital, and mental nerve blocks). (A) Supraorbital foramen. (B) Infraorbital foramen. (C) Mental foramen: (1) Block of the supratrochlear nerve, (2) Block of the mental nerve, (3) Block of the supraorbital nerve, (4) Block of the infraorbital nerve.

volume of local anesthetic is then injected while slowly withdrawing the needle (infiltration along the medial upper border of the orbit). If necessary, the same procedure is repeated on the other side to obtain complete anesthesia of the upper eyelids, forehead, and scalp.

Block of the Infraorbital Nerve

The landmark is the infraorbital foramen, easily palpable on the line joining the centered pupil and both the supraorbital and mental foramina, below the junction of the medial and the middle thirds of the lower border of the orbit. The puncture site lies on this line, at the crossing of the perpendicular line passing just below the nostrils (see Fig. 44-17) . The intradermal needle is directed cephalad toward the lower border of the infraorbital foramen (that must not be entered) and 0.1 mL/kg (up to 3 mL) of local anesthetic is injected. Alternatively, the block can be performed using an endobuccal route. The needle is inserted just above the upper canine tooth, then directed upward and laterally in the direction of the infraorbital foramen while palpating the canal orifice to avoid needle penetration into the foramen.

Block of the Mental Nerve

The landmark is the mental foramen, in line with the centered pupil and both the supraorbital and infraorbital foramina, at the level of the second premolars (adolescent) or the second deciduous molar teeth in a younger child. The mental foramen is directed backwards and upwards. The puncture

site lies 0.5 cm above the mental foramen (see Fig. 44-17) . The simplest procedure consists of inserting the needle pointing caudally, in the direction of the mental foramen and injecting 0.1 mL/kg (up to 3 mL) of local anesthetic. The endobuccal route is more reliable. The needle is inserted at first perpendicularly to the mucosa and then redirected at a 45-degree angle in the direction of the mental foramen until bony contact (or paresthesia) is felt. The local anesthetic is then injected slowly. The main indication of mental nerve block is surgery involving lower incisor and canine teeth. Bilateral blocks allow procedures on the lower lip.

Blocks of the Scalp

The scalp is supplied by branches of the trigeminal nerve (ventral portion) and the cervical plexus, both of which can be blocked by a subcutaneous injection of local anesthetics. Scalp blocks are performed using short 25-gauge intradermal needles. After cleaning the scalp with a bactericidal solution, a circular line is drawn from the glabella to the occiput and divided into four parts at the intersections of the sagittal and frontal planes. A ring of anesthesia is provided along the selected quarter depending on the site of the lesions by injecting a solution of 0.5 to 1 percent lidocaine with 1/200,000 epinephrine, subcutaneously and intraperiosteally (and intramuscularly in the temporal fossa). Great attention must be paid to the total dose given, which must not exceed 10 mg/kg of lidocaine. These blocks are not very common in pediatrics, and they are usually restricted to surgical repair of large wounds of the scalp in adolescents with a full stomach. (In most patients, local anesthesia by infiltrating the edges of the wound is preferable.)

Other Blocks

Several other conduction blocks of nerves supplying the head are commonly used in adults but only occasionally in children for ophthalmic surgery, operations involving the facial bones, or dental procedures. These blocks are not performed by anesthesiologists, and most of them require considerable expertise. Dental blocks especially may lead to severe complications, some of them being lethal. In dentistry, articaine is commonly used and appears to be both effective and safe. [318] A complete description of these techniques can be found elsewhere. [6]

Intravenous Regional Anesthesia

Intravenous regional anesthesia, also termed *Bier block,* has been used in children for upper limb operations distal to an inflated tourniquet. [319] [320] Occasionally, some authors still recommend its application in pediatric patients. [321] [322] Bupivacaine must not be used, whatever the concentration; chloroprocaine (thrombophlebitis), procaine (methemoglobinemia), and mepivacaine (acidosis and hyperkalemia) should also be avoided. Lidocaine (0.25-0.5%) without epinephrine is the safest agent and is administered on the basis of 1 mL/kg up to a maximum volume of 40 mL and a maximum dose of 3 mg/kg. The technique is the same as for adults. After placement of an intravenous plastic cannula, as close as possible to the site of surgery, the limb is exsanguinated, preferably by compression with an Esmarch bandage. A tourniquet is placed proximally and inflated (two to three times the systolic pressure) before the Esmarch bandage is removed and the anesthetic solution injected. Ten minutes later a second tourniquet is placed immediately below the first one (i.e., in an anesthetized area) and inflated to the same pressure values. The upper tourniquet is then removed and the surgeon can proceed. In no case should the tourniquet be deflated before the 20th or later than the 90th minute.

The tourniquets are not well tolerated by children, and the technique has many contraindications such as extensive wounds, ischemic disorders, unstable fractures, convulsive disorders, septicemia, cardiac dysrhythmias, hypovolemia, and sickle cell disease. Furthermore, Bier blocks cannot be considered safe procedures, as they depend on the inflation of a tourniquet. There is danger of systemic toxicity, and fatalities have been reported in children. [323] In children, the technique should not be used routinely for upper limb operations, and it is definitely contraindicated for lower limb procedures.

Local Infiltrations and Topical Anesthesia

Surface Anesthesia

Surface anesthesia of the larynx by local anesthetic sprays is commonly used in adults before tracheal intubation. This method of anesthesia has long been contraindicated in children, but the efficacy and safety of its use have been established [324] provided low doses of 5 percent lidocaine are administered (i.e., 8 mg in infants weighing less than 10 kg, and 16 mg in infants weighing more than 10 kg). Topical anesthesia, by spraying lidocaine on operative wounds such as the tonsillar

bed after tonsillectomy, or by applying anesthetic ointments on the incision site before or after circumcision, [290] [291] can provide adequate postoperative pain relief. The interest in topical anesthesia has been renewed in pediatrics by the availability of several new ointments containing a mixture of local anesthetics such as Emla cream, TAC cream, lidocaine-adrenaline-tetracaine gel, or Bupiv-anor. [325] [326] [327] [328] When Emla is applied on the skin and maintained in place with a sterile dressing for at least 1 hour, shorter periods with other formulations, complete analgesia of the skin and subcutaneous structures is provided. Thus venous cannulation and most techniques requiring needle puncture such as lumbar taps and repair of oral or scalp lacerations can now be made without pain, [325] [327] [328] which makes this technique highly recommendable.

Intradermal Wheals

Intradermal wheals are performed routinely to anesthetize the skin covering deeper structures. The technique consists of inserting a 25-gauge short needle almost tangentially to the skin, with the bevel facing downwards, without penetrating the subcutaneous layers. A small amount (less

than 0.5 mL) of local anesthetic (0.5-1% lidocaine or prilocaine, with or without epinephrine) is then injected. The skin covering the wheal looks like an orange peel, and almost immediate anesthesia of the relevant area is obtained.

Local Infiltrations and Field Blocks

Infiltration of local anesthetics (lidocaine or prilocaine, with or without epinephrine) in a fan-shaped manner in subcutaneous tissues and muscles surrounding the operative site (or the edges of a wound) provide adequate analgesia for soft tissue operations and wound repair. Great attention must be paid to avoid bacterial contamination and overdosage, especially in case of extensive wounds or reinjections, as serum concentration of lidocaine after subcutaneous administration is related linearly to the dose per kilogram of body weight. [329]

Intracapsular Injections

Intra-articular injection of local anesthetics provides consistent analgesia of joint capsules. The technique can be used for diagnostic or therapeutic procedures (injection of painful joints), but it is not widely used, as its efficacy is variable.

Transtracheal Injections

Instillation of local anesthetics into the trachea by cricothyroid membrane puncture is commonly used in adults for awake intubation and prevention of laryngospasm. This procedure is not usual in children because of dangers of systemic toxicity and producing lesions of both the cricoid cartilage and vocal cords.

Intraperitoneal Injections

The increasing use of laparoscopic surgery in children has generated new types of abdominal pain. Injections of rather large amounts of bupivacaine have occasionally been made at the end of the operation, but this procedure has not been evaluated in children, both with regard to efficacy and safety. According to data available from adult series, therefore, this type of intraperitoneal injections should be avoided. [330]

CONCLUSION

Regional block procedures have gained an established place in pediatric anesthesia, especially for outpatient surgery and postoperative pain relief. This increasing interest results from technical improvements, including the use of nerve stimulators for precise location of nerve trunks and the availability of equipment designed specifically for children. This greater acceptance and use of regional procedures in pediatrics are also a consequence of better understanding of the basic anatomic, physiologic, and pharmacologically relevant differences between children and adults, as well as a broader definition of anesthesia in which general and regional procedures are considered complementary to one another rather than being exclusive. The selection of an anesthetic procedure, either general, regional, or a combination of both, is made on a case-by-case evaluation of what is best for a given patient and reflects the ability of the anesthesiologist to make sound judgments about the technique that will provide the greatest comfort and safety to the patient.

References

1. Giaufre E, Dalens B, Gombert A: Epidemiology and morbidity of regional anesthesia in children: A one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists (ADARPEF). Anesth Analg 83:904, 1996.

2. Carpenter MB: Development and histogenesis of the nervous system. In Carpenter MB (ed): Human Neuroanatomy. 7th ed. Baltimore, Williams & Wilkins, 1976, p 49.

3. Benzon HT, Strichartz GR, Gisen AJ et al: Developmental neurophysiology of mammalian peripheral nerves and age-related differential sensitivity to local anaesthetics. Br J Anaesth 61:754, 1988.

4. Verbout AJ: The development of the vertebral column. Adv Anat Embryol Cell Biol 90:1, 1985.

5. Dalens BJ (ed): Pediatric Regional Anesthesia. Boca Raton, CRC Press, 1990.

6. Dalens BJ (ed): Regional Anesthesia in Infants, Children and Adolescents. London, Williams & Wilkins, 1995.

7. Rosenberg PH, Kytta J, Alila A: Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into N-heptane, rat sciatic nerve, and human extradural subcutaneous fat. Br J Anaesth 58:310, 1986.

8. Morselli PL, Franco-Morselli R, Bossi L: Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokinet 5:485, 1980.

9. Mazoit JX, Denson DD, Samii K: Pharmacokinetics of bupivacaine following caudal anesthesia in infants. Anesthesiology 68:387, 1988.

10. Lerman J, Strong A, LeDez KM et al: Effects of age on the serum concentration of alpha 1-acid glycoprotein and the binding of lidocaine in pediatric patients. Clin Pharmacol Ther 46:219, 1989.

11. Tucker GT, Mather LE: Properties, absorption, and disposition of local anesthetic agents. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockades in Clinical Anesthesia and Management of Pain. 2nd ed. Philadelphia, JB Lippincott, 1988; pp 47-110.

12. Booker PD, Taylor C, Saba G: Perioperative changes in alpha1-acid glycoprotein concentrations in infants undergoing major surgery. Br J Anaesth 76:365, 1996.

13. Luz G, Innerhofer P, Bachmann B et al: Bupivacaine plasma concentrations during continuous epidural anesthesia in infants and children. Anesth Analg 82:231, 1996.

14. Peutrell JM, Holder K, Gregory M: Plasma bupivacaine concentrations associated with continuous extradural infusions in babies. Br J Anaesth 78:160, 1997.

15. Larsson BA, Lonnqvist PA, Olsson GL: Plasma concentrations of bupivacaine in neonates after continuous epidural infusion. Anesth Analg 84:501, 1997.

16. Burm AG, Cohen IM, van Kleef JW et al: Pharmacokinetics of the enantiomers of mepivacaine after intravenous administration of the racemate in volunteers. Anesth Analg 84:85, 1997.

17. Agarwal R, Gutlove DP, Lockhart CH: Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine. Anesth Analg 75:284, 1992.

18. Berde CB: Convulsions associated with pediatric regional anesthesia. Anesth Analg 75:164, 1992.

19. McCloskey JJ, Haun SE, Deshpande JK: Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. Anesth Analg 75:287, 1992.

20. Zsigmond EK, Downs JR: Plasma cholinesterase activity in newborns and infants. Can Anaesth Soc J 18:278, 1971.

21. DiFazio CA: Metabolism of local anaesthetics in the fetus, newborn and adult. Br J Anaesth 51:29S, 1979.

22. Hogan Q, Dotson R, Erickson S et al: Local anesthetic myotoxicity: A case and review. Anesthesiology 80:942, 1994.

23.

Kart T, Christrup LL, Rasmussen M: Recommended use of morphine in neonates, infants and children based on a literature review. Part 1: Pharmacokinetics. Paediatr Anaesth 7:5, 1997.

24. Kart T, Christrup LL, Rasmussen M: Recommended use of morphine in neonates, infants and children based on a literature review. Part 2: Clinical use. Paediatr Anaesth 7:93, 1997.

25. Attia J, Ecoffey C, Sandouk P et al: Epidural morphine in children: Pharmacokinetics and CO_2 sensitivity. Anesthesiology 65:590, 1986.

26. Wolf AR, Hughes D, Hobbs AJ et al: Combined morphinebupivacaine caudals for reconstructive penile surgery in children: Systemic absorption of morphine and postoperative analgesia. Anaesth Intensive Care 19:17, 1991.

27. Nordberg G, Mellstrand T, Borg L et al: Extradural morphine: Influence of adrenaline admixture. Br J Anaesth 58:598, 1986.

28. McNeely JK, Farber NE, Rusy LM et al: Epidural analgesia improves outcome following pediatric fundoplication. Reg Anesth 22:16, 1997.

29. Dalens B, Chrysostome Y: Intervertebral epidural anaesthesia in paediatric surgery: Success rate and adverse effects in 650 consecutive procedures. Paediatric Anaesth 1:107, 1991.

30. Thind GS, Wells JCD, Wilkes RG: The effects of continuous intravenous naloxone on epidural morphine analgesia. Anaesthesia 41:582, 1986.

31. Rawal N, Schott U, Dahlstrom B et al: Influence of naloxone infusion on analgesia and respiratory depression following epidural morphine. Anesthesiology 64:194, 1986.

32. Dalens B, Tanguy A: Intrathecal morphine for spinal fusion in children. Spine 13:494, 1988.

33. Cohen SE, Ratner EF, Kreitzman TR et al: Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. Anesth Analg 75:747, 1992.

34. Dalens B, Mansoor O: Safe selection and performance of regional anaesthetic techniques in children. Curr Opin Anaesthesiol 7:257, 1994.

35. Mulroy MF: Monitoring opioids. Reg Anesth 21 (suppl):89, 1996.

36. Kamal RS, Khan FA: Caudal analgesia with buprenorphine for postoperative pain relief in children. Paediatr Anaesth 5:101, 1995.

37. Freid EB, Bailey AG, Valley RD: Electrocardiographic and hemodynamic changes associated with unintentional intravascular injection of bupivacaine with epinephrine in infants. Anesthesiology 79:394, 1993.

38. Liu SS, Carpenter RL: Hemodynamic responses to intravascular injection of epineprine-containing epidural test-doses in adults during general anesthesia. Anesthesiology 84:81, 1996.

39. Sethna NF, Sullivan LJ, McGowan F et al: Hemodynamic responses to intravascular injection of epinephrine-containing epidural test-dose in children anesthetized with isoflurane. Anesthesiology 85A:1086, 1996.

40. Felberg MA, Berkowitz RA, Chowdhury P et al: Variable epinephrine concentrations in local anesthetic test doses for caudal anesthesia in pediatric patients. Anesthesiology 85A:1073, 1996.

41. Eisenach JC, De Kock M, Klimscha W: Alpha 2 adrenergic agonists for regional anesthesia. Anesthesiology 85:655, 1996.

42. Lee JJ, Rubin AP: Comparison of a bupivacaine-clonidine mixture with plain bupivacaine for caudal analgesia in children. Br J Anaesth 72:258, 1994.

43. Jamali S, Monin S, Begon C et al: Clonidine in pediatric caudal anesthesia. Anesth Analg 78:663, 1994.

44. Cook B, Grubb DJ, Aldridge LA et al: Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. Br J Anaesth 75:698, 1995.

45. Cook B, Doyle E: The use of additives to local anaesthetic solutions for caudal epidural blockade. Paediatr Anaesth 6:353, 1996.

46. Ivani G, Mattioli G, Rega M et al: Clonidine-mepivacaine mixture vs plain mepivacaine in paediatric surgery. Paediatr Anaesth 6:111, 1996.

47. Singelyn FJ, Dangoisse M, Bartholomee S et al: Adding clonidine to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Reg Anesth 17:69, 1992.

48. Singelyn FJ, Gouverneur JM, Robert A: A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Anesth Analg 83:1046, 1996.

49. Mazoit JX, Benhamou D, Veillette Y et al: Clonidine and or adrenaline decrease lignocaine plasma peak concentration after epidural injection. Br J Clin Pharmacol 42:242, 1996.

50. Penon C, Ecoffey C, Cohen SE: Ventilatory response to carbon dioxide after epidural clonidine injection. Anesth Analg 72:761, 1991.

51. Naguib M, Sharif AMY, Seraj M et al: Ketamine for caudal analgesia in children: Comparison with caudal bupivacaine. Br J Anaesth 67:559, 1991.

52. Tverskoy M, Oren M, Vaskovich M et al: Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: A study in postoperative patients. Neurosci Lett 215:5, 1996.

53. Semple D, Findlow D, Aldridge LM et al: The optimal dose of ketamine for caudal epidural blockade in children. Anaesthesia 51:1170, 1996.

54. Curley J, Castillo J, Hotz J et al: Prolonged regional nerve blockade. Injectable biodegradable bupivacaine/polyester microspheres. Anesthesiology 84:1401, 1996.

55. Castillo J, Curley J, Hotz J et al: Glucocorticoids prolong rat sciatic nerve blockade in vivo from bupivacaine microspheres. Anesthesiology 85:1157, 1996.

56. Johansson A: Methylprednisolone shortens the effects of bupivacaine on sensory nerve fibers in vivo. Acta Anaesthesiol Scand 40:595, 1996.

57. Johansson A, Bennett GJ: Effect of local methylprednisolone on pain in a nerve injury model. A pilot study. Reg Anesth 22:59, 1997.

58. Cooper AB, Sharpe MD: Bacterial meningitis and cauda equina syndrome after epidural steroid injections. Can J Anaesth 43:471, 1996.

59. Rose G, Xu Z, Tong C et al: Spinal neostigmine diminishes, but does not abolish, hypotension from spinal bupivacaine in sheep. Anesth Analg 83:1041, 1996.

60. Cote CJ: Unapproved uses of approved drugs (Editorial). Paediatr Anaesth 7:91, 1997.

61. Kreeger L, Cowin P, Noble-Gresty J et al: Epidural diamorphine and bupivacaine stability study. Palliat Med 9:315, 1995.

62. Anand KJS, Ward-Platt MP: Neonatal and pediatric stress response to anesthesia and operation. Int Anesthesiol Clin 26:218, 1988.

63. Deshpande S, Ward-Platt MP, Aynsley-Green A: Patterns of the metabolic and endocrine response to surgery and medical illness in infancy and childhood. Crit Care Med 21:S359, 1993.

64. Anand KJS: Relationship between stress response and clinical outcome in newborns. Crit Care Med 21:S358, 1993.

65. Nakamura T, Takasaki M: Metabolic and endocrine responses to surgery during caudal analgesia in children. Can J Anaesth 38:969, 1991.

66. Wolf AR, Eyres RL, Laussen PC et al: Effect of extradural analgesia on stress response to abdominal surgery in infants. Br J Anaesth 70:654, 1993.

67. Tsuji MH, Horigome H, Yamashita M: Left ventricular functions are not impaired after lumbar epidural anesthesia in young children. Paediatr Anaesth 6:405, 1996.

68. McGown RG: Caudal analgesia in children: Five hundred cases for procedures below the diaphragm. Anaesthesia 37:806, 1982.

69. Arthur DS, McNicol LR: Local anaesthetic techniques in paediatric surgery. Br J Anaesth 58:760, 1986.

70. Murat I, Delleur MM, Esteve C et al: Continuous extradural anaesthesia in children. Clinical and haemodynamic implications. Br J Anaesth 69:1441, 1987.

71. Dalens B, Hasnaoui A: Caudal anesthesia in pediatric surgery: Success rate and adverse effects in 750 consecutive patients. Anesth Analg 68:83, 1989.

72. Desparmets JF: Central blocks in children and adolescents. In Schechter N, Berde CHB, Yaster M (eds): Pain in Infants, Children, and Adolescents. Baltimore, Williams & Wilkins, 1993, p 245.

73. Dalens BJ: Peripheral nerve blockade in the management of postoperative pain in children. In Schechter N, Berde CHB, Yaster M (eds): Pain in Infants, Children, and Adolescents. Baltimore, Williams & Wilkins, 1993, p 261.

74. Tobias JD, Flannagan J: Regional anesthesia in the preterm neonate. Clin Pediatr (Phila) 31:668, 1992.

75. Morton NS: Modern paediatric day case anaesthesia: A review. Paediatr Anaesth 2:235, 1992.

76. Goodarzi M: The effect of perioperative and postoperative caudal block on pain control in children. Paediatr Anaesth 6:475, 1996.

77. Gall H, Kaufmann R, Kalveran CM: Adverse reactions to local anesthetics: Analysis of 197 cases. J Allergy Clin Immunol 97:933, 1996.

78. Cooper MG, Sethna NF: Epidural analgesia in patients with congenital lumbosacral spinal abnormalities. Anesthesiology 75:370, 1991.

79. Eyres RL: Local anaesthetic agents in infancy. Paediatr Anaesth 5:213, 1995.

80. Halldin MM, Bredberg E, Angelin B et al: Metabolism and excretion of ropivacaine in humans. Drug Metab Dispos 24:962, 1996.

81. Ribotsky BM, Berkowitz KD, Montague JR: Local anesthetics. Is there an advantage to mixing solutions? J Am Podiatr Med Assoc 86:487, 1996.

82. Mets B, Janicki PK, James MF et al: Lidocaine and bupivacaine cardiorespiratory toxicity is additive: A study in rats. Anesth Analg 75:611, 1992.

83. Fialkov JA, McDougall EP: Warmed local anesthetic reduces pain of infiltration. Ann Plast Surg 36:11, 1996.

84. Sparks CJ, Rudkin GE, Agiomea K et al: Inguinal field block for adult inguinal hernia repair using a short-bevel needle. Description and clinical experience in Solomon Islands and an Australian teaching hospital. Anaesth Intensive Care 23:143, 1995.

85. Scott RA, Jakeman CM, Perry SR et al: Peribulbar anaesthesia and needle length. J R Soc Med 88:594P, 1995.

86. Selander D, Edshage S, Wolff T: Paraesthesia or no paraesthesia. Acta Anaesthesiol Scand 23:27, 1979.

87. Chambers WA: Peripheral nerve damage and regional anesthesia. Br J Anaesth 69:429, 1992.

88. Bosenberg AT, Gouws E: Skin-epidural distance in children. Anaesthesia 50:895, 1995.

89. Broadman L: Where should advocacy for pediatric patients end and concerns for patient safety begin (Editorial). Reg Anesth 22:205, 1997.

90. Lambert DH, Hurley RJ, Hertwig L et al: Role of needle gauge and tip configuration in the production of lumbar puncture headache. Reg Anesth 22:66, 1997.

91. Kokki H, Hendolin H: Comparison of 25G and 29G Quincke spinal needles in paediatric day case surgery. A prospective randomized study of the puncture characteristics, success rate and postoperative complaints. Paediatr Anaesth 6:115, 1996.

92. Campbell DC, Douglas MJ, Taylor G: Incidence of tissue coring with the 25-gauge Quincke and Whitacre spinal needles. Reg Anesth 21:582, 1996.

93. Pither CE, Raj PP, Ford DJ: The use of peripheral nerve stimulators for regional anesthesia. A review of experimental characteristics, technique and clinical applications. Reg Anesth 10:49, 1985.

94. Tulchinsky A, Weller RS, Rosenblum M et al: Nerve stimulator polarity and brachial plexus block. Anesth Analg 77:100, 1993.

95. Leiman BC, Warters RD, Katz J et al: Minimizing friction in glass syringes for locating the epidural space. Anesth Analg 66:S103, 1987.

96. Wait CM: Identification of the epidural space. Anaesthesia 42:1231, 1987.

97. Ananthanarayan C, Fisher JA: Comment on syringe medium. Reg Anesth 20:463, 1995.

98. Ash KM, Cannon JE, Biehl DR: Pneumocephalus following attempted epidural anaesthesia. Can J Anaesth 38:772, 1991.

99. Dalens B, Bazin JE, Haberer JP: Epidural bubbles as a cause of incomplete analgesia during epidural anesthesia. Anesth Analg 66:679, 1987.

100. Kennedy TM, Ullman DA, Harte FA et al: Lumbar root compression secondary to epidural air. Anesth Analg 67:1184, 1988.

101. Nay PG, Milaszkiewicz R, Jothilingam S: Extradural air as a cause of paraplegia following lumbar analgesia. Anaesthesia 48:402, 1993.

102. Miguel R, Morse S, Murtagh R: Epidural air associated with multiradicular syndrome. Anesth Analg 73:92, 1991.

103. Laman EN, McLeskey CH: Supraclavicular subcutaneous emphysema following lumbar epidural anesthesia. Anesthesiology 48:219, 1978.

104. Naulty JS, Ostheimer GW, Datta S et al: Incidence of venous air embolism during epidural catheter insertion. Anesthesiology 57:410, 1982.

105. Schwartz N, Eisenkraft JB: Probable venous air embolism during epidural placement in an infant. Anesth Analg 76:1136, 1993.

106. Sethna NF, Berde CB: Venous air embolism during identification of the epidural space. Anesth Analg 76:925, 1993.

107. Guinard JP, Borboen M: Probable venous air embolism during caudal anesthesia in a child. Anesth Analg 76:1134, 1993.

108. Jackson KE, Rauck RL: Suspected venous air embolism during epidural anesthesia. Anesthesiology 74:190, 1991.

109. Goldman LJ: Complications in regional anaesthesia (Editorial). Paediatr Anaesth 5:3, 1995.

110. Saberski LR, Kondamuri S, Osinubi Pinnock CA et al: Identification of the epidural space: Is loss of resistance to air a safe technique? A review of the complications related to the use of air. Reg Anesth 22:3, 1997.

111. Jaffe RA, Siegel LC, Schnittger I et al: Epidural air injection assessed by transesophageal echocardiography. Reg Anesth 20:152, 1995.

112. Petty R, Stevens R, Erickson S et al: Inhalation of nitrous oxide expands epidural air bubbles. Reg Anesth 21:144, 1996.

113. Iwama H: Injection volume of saline with loss of resistance method may affect the spread of epidural anesthesia. Anesthesiology 86:507, 1997.

114. Candido KD, Winnie AP: A dual-chambered syringe that allows identification of the epidural space using the loss-of-resistance technique with air and with saline. Reg Anesth 17:163, 1992.

115. Glantz L, Gozal Y, Gertel M: A loss-of-resistance technique using both air and saline. Reg Anesth 19:294, 1994.

116. Barros S: Loss-of-resistance technique using both air and saline. Reg Anesth 20:462, 1995.

117. Kumagai M, Yamashita M: Sacral intervertebral approach for epidural anaesthesia in infants and children: Application of "drip and tube" method. Anaesth Intensive Care 23:469, 1995.

118. Jacob S, Tierney E: A dual technique for identification of the epidural space. Anaesthesia 52:141, 1997.

119. Busoni P, Messeri A: Loss-of-resistance technique to air for identifying the epidural space in infants and children. Use an appropriate technique ! Paediatr Anaesth 5:396, 1995.

120. Scott B: Identification of the epidural space: Loss of resistance to air or saline? (Editorial). Reg Anesth 22:1, 1997.

121. Freid EB, Bailey AG, Valley RD: Electrocardiographic and hemodynamic changes associated with unintentional intravascular injection of bupivacaine with epinephrine in infants. Anesthesiology 79:394, 1993.

122. Darrow EJ, Badgwell JM, Heavner JE et al: Bupivacaine and epinephrine act synergistically to produce ventricular arrhythmias in young pigs. Anesthesiology 81A:1357, 1994.

123. Fisher QA, Shaffner DH, Yaster M: Detection of intravascular injection of regional anaesthetics in children. Can J Anaesth 44:592, 1997.

124. Veyckemans F, Van Obbergh LJ, Gouverneur JM: Lessons from 1100 pediatric caudal blocks in a teaching hospital. Reg Anesth 17:119, 1992.

125. Mulroy MF: Epidural test doses. Anesth Clin North Am 10:45, 1992.

126. Felberg MA, Berkowitz RA, Chowdhury P et al: Variable epinephrine concentrations in local anesthetic test doses for caudal anesthesia in pediatric patients. Anesthesiology 85A:1073, 1996.

127. Kozek-Langenecker S, Chiari A, Semsroth M: Simulation of an epidural test dose with intravenous isoproterenol in awake and in halothane-anesthetized children. Anesthesiology 85:277, 1996.

128. Jiang X, Wen X, Gao B, et al: The plasma concentrations of lidocaine after slow versus rapid administration of an initial dose of epidural anesthesia. Anesth Analg 84:570, 1997.

129. Olsson GL: Complications of paediatric anaesthesia. Curr Opin Anaesthesiol 3:385, 1990.

130. Bosenberg AT: Recent developments in paediatric regional anaesthesia. Curr Opin Anesthesiol 9:233, 1996.

131. Fukuda H, Hirabayashi Y, Shimizu R et al: Sevoflurane is equivalent to isoflurane for attenuating bupivacaine-induced arrhythmias and seizures in rats. Anesth Analg 83:570, 1996.

132. Saitoh K, Tsukamoto N, Mitsuhata H et al: Convulsions associated with epidural analgesia during sevoflurane anaesthesia. Paediatr Anaesth 6:495, 1996.

133. Bromage PR: Neurological complications of subarachnoid and epidural anaesthesia. Acta Anaesthesiol Scand 41:439, 1997.

134. Morray JP, Geiduschek JM, Caplan RA et al: A comparison of pediatric and adult anesthesia closed malpractice claims. Anesthesiology 78:461, 1993.

135. Hawkins JL, Koonin LM, Palmer SK et al: Anesthesia-related deaths during obstetric delivery in the United States, 1979-1990. Anesthesiology 86:277, 1997.

136. Marinacci AA, Courville CB: Electromyogram in evaluation of neurological complications of spinal anesthesia. JAMA 168:1337, 1991.

137. Dahlgren N, Tornebrandt K: Neurological complications after anaesthesia. A follow-up of 18,000 spinal and epidural anaesthetics performed over three years. Acta Anaesthesiol Scand 39:872, 1995.

138. Selander D, Dhuner KG, Lundborg G: Peripheral nerve injury due to injection needles used for regional anesthesia. Acta Anaesthesiol Scand 21:182, 1977.

139. Stanley D, Conolly WB: Iatrogenic injection injuries of the hand and upper limb. J Hand Surg [Br] 17:442, 1992.

140. Wood CE, Goresky GV, Klassen KA et al: Complications of continuous epidural infusions for postoperative analgesia in children. Can J Anaesth 41:613, 1994.

141. Henneberg SW, Hole P, Madsen de Haas I et al: Epidural morphine for postoperative pain relief in children. Acta Anaesthesiol Scand 37:664, 1993.

142. Scott DA, Beilby DS, McClymont C: Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1014 patients. Anesthesiology 83:727, 1995.

143. Strafford MA, Wilder RT, Berde CB: The risk of infection from epidural analgesia in children: A review of 1620 cases. Anesth Analg 80:234, 1995.

144. Holt HM, Andersen SS, Andersen O et al: Infections following epidural catheterization. J Hosp Infect 30:253, 1995.

145. Langevin PB, Gravenstein N, Langevin SO et al: Epidural catheter reconnection. Safe and unsafe practice. Anesthesiology 85:883, 1996.

146. Gozal D, Gozal Y, Beilin B: Removal of knotted epidural catheters. Reg Anesth 21:71, 1996.

147. Lumb AB, Carli F: Respiratory arrest after a caudal injection of bupivacaine. Anaesthesia 44:324, 1989.

148. Southorn P, Vasdev GM, Chantigian RC et al: Reducing the potential morbidity of an unintentional spinal anaesthetic by aspirating cerebrospinal fluid. Br J Anaesth 76:467, 1996.

149. Brown DL, Ransom DM, Hall JA et al: Regional anesthesia and local anesthetic-induced systemic toxicity: Seizure frequency and accompanying cardiovascular changes. Anesth Analg 81:321, 1995.

150. De La Coussaye JE, Brugada J, Allessie MA: Electrophysiologic and arrhythmogenic effects of bupivacaine. A study with high-resolution ventricular epicardial mapping in rabbit hearts. Anesthesiology 77:132, 1992.

151. Coyle DE, Speralakis N: Bupivacaine and lidocaine blockade of calcium-mediated slow action potentials in guinea-pig ventricular muscle. J Exp Pharmacol Ther 242:1001, 1987.

152. Valenzuella C, Delpon E, Tamkun MM et al: Stereoselective block of a human cardiac potassium channel (Kv1.5) by bupivacaine enantiomers. Biophys J 69:418, 1995.

153. De La Coussaye JE, Bassoul B, Brugada J et al: Reversal of electrophysiologic and hemodynamic effects induced by high dose of bupivacaine by the combination of clonidine and dobutamine in anesthetized dogs. Anesth Analg 74:703, 1992.

154. De La Coussaye JE, Eledjam JJ, Bruelle P et al: Mechanisms of the putative cardioprotective effect of hexamethonium in anesthetized dogs given a large dose of bupivacaine. Anesthesiology 80:595, 1994.

155. Maxwell LG, Martin LD, Yaster M: Bupivacaine-induced cardiac toxicity in neonates: Successful treatment with intravenous phenytoin. Anesthesiology 80:682, 1994.

156. Fujita Y: Amrinone reverses bupivacaine-induced regional myocardial dysfunction. Acta Anaesthesiol Scand 40:47, 1996.

157. Bosenberg AT, Bland BAR, Schulte-Steinberg O et al: Thoracic epi-dural anesthesia via caudal route in infants. Anesthesiology 69:265, 1988.

158. Rasch DK, Webster DE, Pollard TG et al: Lumbar and thoracic epidural analgesia via caudal approach for postoperative pain relief in infants and children. Can J Anaesth 37:359, 1990.

159. Gunter JB, Eng C: Thoracic epidural anesthesia via the caudal approach in children. Anesthesiology 76:935, 1992.

160. Van Niekerk J, Bax Vermieire BM, Geurts JW et al: Epidurography in premature infants. Anesthesiology 76:935, 1990.

161. Blanco D, Mazo V, Ortiz M et al: Spread of local anesthetic into the epidural caudal space for two rates of injection in children. Reg Anesth 21:442, 1996.

162. Busoni P, Andreucetti T: The spread of caudal analgesia in children: A mathematical model. Anaesth Intensive Care 14:140, 1986.

163. Armitage EN: Regional anaesthesia in paediatrics. Clin Anesthesiol 3:553, 1985.

164. Afshan G, Khan FA: Total spinal anaesthesia following caudal block with bupivacaine and buprenorphine. Paediatr Anaesth 6:239, 1996.

165. Blomberg R: The dorsomedian connective tissue band in the lumbar epidural space of humans: An anatomical study using epiduroscopy in autopsy cases. Anesth Analg 65:747, 1986.

166. Savolaine ER, Pandya JB, Greenblatt SH et al: Anatomy of the human lumbar epidural space: New insights using CT-epidurography. Anesthesiology 68:217, 1988.

167. Blomberg RG, Olsson S: The lumbar epidural space in patients examined with epiduroscopy. Anesth Analg 68:157, 1989.

168. Hogan QH: Lumbar epidural anatomy. A new look by cryomicrotome section. Anesthesiology 75:767, 1991.

169. Hogan QH: Epidural anatomy examined by cryomicrotome section. Reg Anesth 21:395, 1996.

170. Hirabayashi Y, Shimizu R, Matsuda I et al: Effect of extradural compliance and resistance on spread of extradural analgesia. Br J Anaesth 65:508, 1990.

171. Igarashi T, Hirabayashi Y, Shimizu R et al: Inflammatory changes after extradural anaesthesia may affect the spread of local anaesthetic within the extradural space. Br J Anaesth 77:347, 1996.

172. Dalens B, Tanguy A, Haberer JP: Lumbar epidural anesthesia for operative and postoperative pain relief in infants and young children. Anesth Analg 65:1069, 1986.

173. Ecoffey C, Dubousset AM, Samii K: Lumbar and thoracic epidural anesthesia for urologic and upper abdominal surgery in infants and children. Anesthesiology 65:87, 1986.

174. Busoni P, Messeri A, Sarti A: The lumbosacral epidural block: A modified Taylor approach for abdominal urologic surgery in children. Anaesth Intensive Care 19:325, 1991.

175. McBride WJ, Dicker R, Abajian JC et al: Continuous thoracic epidural infusions for postoperative analgesia after pectus deformity repair. J Pediatr Surg 105:107, 1996.

176. Dalens B, Tanguy A, Vanneuville G: Lumbar plexus block in children. A comparison of two procedures in 50 patients. Anesth Analg 67:750, 1988.

177. Schulte-Steinberg O: Regional anaesthesia for children. Ann Chir Gynaecol 73:158, 1984.

178. Blanco D, Llamazares J, Rincon R et al: Thoracic epidural anesthesia via the lumbar approach in infants and children. Anesthesiology 84:1312, 1996.

179. Busoni P, Sarti A: Sacral intervertebral epidural block. Anesthesiology 67:993, 1987.

180. Giebler RM, Scherer RU, Peters J: Incidence of neurological complications related to thoracic epidural catheterization. Anesthesiology 86:55, 1997.

181. Scott DB, Wilson J: Insertion of epidural catheters. Anaesthesia 38:1108, 1983.

182. Koch J, Nielsen JU: Rare misplacements of epidural catheters. Anesthesiology 65:556, 1986.

183. Asato F, Goto F: Radiographic findings of unilateral epidural block. Anesth Analg 83:519, 1996.

184. Bougher RJ, Corbett AR, Ramage DT: The effect of tunnelling on epidural catheter migration. Anaesthesia 51:191, 1996.

185. Knill RL, Clement JL, Thompson WR: Epidural morphine causes delayed and prolonged ventilatory depression. Can Anaesth Soc J 28:537, 1981.

186. Rawal N, Watwill M: Respiratory depression after epidural morphine: An experimental and clinical study. Anesth Analg 63:8, 1984.

187. Attia J, Ecoffey C, Sandouk P et al: Epidural morphine in children: Pharmacokinetics and CO_2 sensitivity. Anesthesiology 65:590, 1986.

188. Thompson PI, Joel SP, John L et al: Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. Br J Clin Pharmacol 40:145, 1995.

189. Webster AC, McKishnie JD, Kenyon CF et al: Spinal anaesthesia for inguinal hernia repair in high-risk neonates. Can J Anaesth 38:281, 1991.

190. Aronsson DD, Gemery JM, Abajian JC: Spinal anesthesia for spine and lower extremity surgery in infants. J Pediatr Orthop 16:259, 1996.

191. Cote CJ, Zalavsky A, Downes JJ: Postoperative apnea in former preterm infants after inguinal herniorrhaphy: A Combined analysis. Anesthesiology 82:809, 1995.

192. Steward DJ: Preterm infants are more prone to complications following minor surgery than are term infants. Anesthesiology 56:304, 1982.

193. Liu LMP, Cote CJ, Goudsouzian NG et al: Life-threatening apnea in infants recovering from anesthesia. Anesthesiology 59:506, 1983.

194. Wellborn LG: Post-operative apnoea in the former preterm infant: A review. Paediatr Anaesth 2:37, 1992.

195. Abajian JC, Mellish RWP, Browne AF, et al: Spinal anesthesia for surgery in the high risk infant. Anesth Analg 63:359, 1984.

196. Wiener ES, Touloukian RJ, Rodgers BM et al: Hernia survey of the Section on Surgery of the American Academy of Pediatrics. J Pediatr Surg 31:1166, 1996.

197. Cox RG, Goresky GV: Life-threatening apnea following spinal anesthesia in former preterm infants. Anesthesiology 73:345, 1990.

198. Blaise GA, Roy WL: Spinal anaesthesia for minor paediatric surgery. Can Anaesth Soc J 33:227, 1984.

199. Harnik EV, Hoy GR, Potolicchio S et al: Spinal anesthesia in premature infants recovering from respiratory distress syndrome. Anesthesiology 64:95, 1986.

200. Gallacher TM, Crean PM: Spinal anaesthesia for infants born prematurely. Anaesthesia 44:434, 1989.

201. Kokki H, Hendolin H: Comparison of spinal anaesthesia with epidural anaesthesia in paediatric surgery. Acta Anaesthesiol Scand 39:896, 1995.

202. Dalens BJ, Khandwala RS, Tanguy A: Staged segmental scoliosis surgery during regional anesthesia in high risk patients: Report of six cases. Anesth Analg 76:434, 1993.

203. Jones SEF, Beasley JM, Macfarlane DWR et al: Intrathecal morphine for postoperative pain relief in children. Br J Anaesth 56:137, 1984.

204. Krechel SW, Eggers GW Jr, Helikson MA: Intrathecal morphine for postoperative analgesia in an infant with bronchopulmonary dysplasia following upper abdominal surgery. Paediatr Anaesth 6:423, 1996.

205. Gleason CA, Martin RJ, Anderson JV et al: Optimal position for a spinal tap in preterm infants. Pediatrics 71:31, 1983.

206. Weisman LE, Merenstein GB, Steenbarger JR: The effect of lumbar puncture position in sick neonates. Am J Dis Child 137:107, 1983.

207. Myers MR: A numerical investigation into factors affecting anesthetic distribution during spinal anesthesia. J Biomech 29:139, 1996.

208. Urmey WF, Stanton J, Bassin P et al: The direction of the Whitacre needle aperture affects the extent and duration of isobaric spinal anesthesia. Anesth Analg 84:337, 1997.

209. Beauvoir C, Rochette A, Desch G et al: Spinal anaesthesia in newborns: Total and free bupivacaine plasma concentration. Paediatr Anaesth 6:195, 1996.

210. Lambert DH, Hurley RJ: Cauda equina syndrome and continuous spinal anesthesia. Anesth Analg 72:817, 1991.

211. Rigler ML, Drasner K, Krejcie TC et al: Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 72:275, 1991.

212. Schneider M, Ettlin T, Kaufmann M et al: Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. Anesth Analg 76:1154, 1993.

213. Vester-Andersen T, Broby-Johansen U, Bro-Rasmussen F: Perivascular axillary block VI: The distribution of gelatin solution injected into the axillary neurovascular sheath of cadavers. Acta Anaesthesiol Scand 30:18, 1986.

214. Thompson GE, Rorie DK: Functional anatomy of the brachial plexus sheaths. Anesthesiology 59:117, 1983.

215. Partridge BL, Katz J, Benirschke K: Functional anatomy of the brachial plexus sheath: Implications for anesthesia. Anesthesiology 66:743, 1987.

216. Rouholamin E, Harris D: Axillary block anaesthesia in acute and elective hand surgery: A report on 300 procedures. Ann R Coll Surg Engl 72:90, 1990.

217. Wedel DJ, Krohn JS, Hall JA: Brachial plexus anesthesia in pediatric patients. Mayo Clin Proc 66:583, 1991.

218. Waters JH, Leivers D, Maher D et al: Patient and surgeon satisfaction with extremity blockade for surgery in remote locations. Anesth Analg 84:773, 1997.

219. Cramer KE, Glasson S, Mencio G et al: Reduction of forearm fractures in children using axillary block anesthesia. J Orthop Trauma 9:407, 1995.

220. Davis WJ, Lennon RL, Wedel DJ: Brachial plexus anesthesia for outpatient surgical procedures on an upper extremity. Mayo Clin Proc 66:470, 1991.

221. Urban M, Urquhart B: Evaluation of brachial plexus anesthesia for upper extremity surgery. Reg Anesth 19:175, 1994.

222. Inberg P, Kassila M, Vilkki S et al: Anaesthesia for microvascular surgery in children. A combination of general anaesthesia and axillary plexus block. Acta Anaesthesiol Scand 39:518, 1995.

223. Schroeder LE, Horlocker TT, Schroeder DR: The efficacy of axillary block for surgical procedures about the elbow. Anesth Analg 83:747, 1996.

224. Cooper K, Kelley H, Carrithers J: Perceptions of side effects following axillary block used for outpatient surgery. Reg Anesth 20:212, 1995.

225. Winnie AP: Interscalene brachial plexus block. Anesth Analg 49:455, 1970.

226. Vester-Andersen T, Christiansen C, Hansen A et al: Interscalene brachial plexus block: Area of analgesia, complications and blood concentrations of local anaesthetics. Acta Anaesthesiol Scand 25:81, 1981.

227. Lanz E, Theiss D, Jankovic D: The extent of blockade following various techniques of brachial plexus block. Anesth Analg 62:55, 1983.

228. Urmey WF, Talts KH, Sharrock NE: One hundred per cent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg 72:498, 1991.

229. Fujimura N, Namba H, Tsunoda K, et al: Effect of hemidiaphragmatic paresis caused by interscalene brachial plexus block on breathing pattern, chest wall mechanics, and arterial blood gases. Anesth Analg 81:962, 1995.

230. Kulenkampff D, Persky MA: Brachial plexus anesthesia: Its indications, technic and dangers. Ann Surg 87:883, 1928.

231. Dalens B, Vanneuville G, Tanguy A: A new parascalene approach to the brachial plexus in children: Comparison with the supraclavicular approach. Anesth Analg 66:1264, 1987.

232. Vongvises P, Beokhaimook N: Computed tomographic study of parascalene block. Anesth Analg 84:379, 1997.

233. McNeely JK, Hoffman GM, Eckert JE: Postoperative pain relief in children from the parascalene injection technique. Reg Anesth 16:20, 1991.

234. Baraka A, Hanna M, Hammoud R: Unconsciousness and apnea complicating parascalene brachial plexus block: Possible subarachnoid block. Anesthesiology 77:1046, 1992.

235. Koschielniak-Nielsen ZJ, Christensen LQ, Pedersen HL et al: Effect of digital pressure on the neurovascular sheath during perivascular axillary block. Br J Anaesth 75:702, 1995.

236. Merril DG, Brodsky JB, Hentz RV: Vascular insufficiency following axillary block of the brachial plexus. Anesth Analg 60:162, 1981.

237. Chayen D, Nathan H, Chayen M: The psoas compartment block. Anesthesiology 45:95, 1976.

238. Maccani RM, Wedel DJ, Melton A et al: Femoral and lateral cutaneous nerve block for muscle biopsy in children. Paediatr Anaesth 5:223, 1995.

239. Johnson CM: Continuous femoral nerve blockade for analgesia in children with femoral fractures. Anaesth Intensive Care 22:281, 1994.

240. Tobias JD: Continuous femoral nerve block to provide analgesia following femur fracture in a paediatric ICU population. Anaesth Intensive Care 22:616, 1994.

241. Combes MA, Clark WK, Gregory CF et al: Sciatic nerve injury in infants: Recognition and prevention of impairment resulting from intragluteal injections. JAMA 173:1336, 1960.

242. Gilles FH, French JH: Postinjection sciatic nerve palsies in infants and children. J Pediatr 58:195, 1961.

243. Johnson EW, Raptou AD: A study of intragluteal injection. Arch Phys Med 46:167, 1965.

244. Kytta J, Heinonen E, Rosenberg PH et al: Effects of repeated bupivacaine administration on sciatic nerve and surrounding muscle tissue in rats. Acta Anaesthesiol Scand 30:625, 1986.

245. Myers RR, Kalichman MW, Reisner LS et al: Neurotoxicity of local anesthetics: Altered perineural permeability, edema, and nerve fiber injury. Anesthesiology 64:29, 1986.

246. Dalens B, Tanguy A, Vanneuville G: Lumbar plexus block in children: Comparison of two procedures in 50 patients. Anesth Analg 67:750, 1988.

247. Winnie AP: Regional anesthesia. Surg Clin North Am 55:861, 1975.

248. Khoo ST, Brown TCK: Femoral nerve block: The anatomical basis for a single injection technique. Anaesth Intensive Care 11:40, 1983.

249. Ronchi L, Rosenbaum D, Athouel A et al: Femoral nerve blockade in children using bupivacaine. Anesthesiology 70:622, 1989.

250. Bosenberg AT: Lower limb nerve blocks in children using unsheathed needles and a nerve stimulator. Anaesthesia 50:206, 1995.

251. Winnie AP, Ramamurthy S, Durrani Z: The inguinal paravascular technic of lumbar plexus anesthesia: The "3-in-1" block. Anesth Analg 52:989, 1973.

252. Ritter JW: Femoral nerve "sheath" for inguinal paravascular lumbar plexus block is not found in human cadavers. J Clin Anesth 7:470, 1995.

253. Dalens B, Vanneuville G, Tanguy A: Comparison of the fascia iliaca compartment block with the 3-in-1 block in children. Anesth Analg 69:705, 1989.

254. Dalens B, Tanguy A, Vanneuville G: Lumbar plexus blocks and lumbar plexus nerve blocks. Anesth Analg 69:852, 1989.

255. Dalens B: Anatomic consideration of the fascia iliaca compartment block: In response. Anesth Analg 71:211, 1990.

256. Doyle E, Morton NS, McNicol LR: Plasma bupivacaine levels after fascia iliaca compartment block with and without adrenaline. Paediatr Anaesth 7:121, 1997.

257. Van der Wal M, Lang S, Yip RW: Transsartorial approach for saphenous nerve block. Can J Anaesth 40:542, 1993.

258. Morris GF, Lang SA, Dust WN et al: The parasacral sciatic nerve block. Reg Anesth 22:223, 1997.

259. Comfort VK, Lang SA, Yip RW: Saphenous nerve anaesthesia: A nerve stimulator technique. Can J Anaesth 43:852, 1996.

260. Bouaziz H, Benhamou D, Narchi P: A new approach for saphenous nerve block. Reg Anesth 21:490, 1996.

261. McNicol LR: Lower limb blocks for children: Lateral cutaneous and femoral nerve blocks for postoperative pain relief in paediatric practice. Anaesthesia 41:27, 1986.

262. Brown TCK, Dickens DRV: A new approach to lateral cutaneous nerve of thigh block. Anaesth Intensive Care 14:126, 1986.

263. Dalens B, Tanguy A, Vanneuville G: Sciatic nerve block in children: Comparison of the posterior, anterior and lateral approaches in 180 pediatric patients. Anesth Analg 70:131, 1990.

264. Beck GP: Anterior approach to sciatic nerve block. Anesthesiology 24:222, 1963.

265. McNicol LR: Sciatic nerve block for children: Sciatic nerve block by the anterior approach for postoperative pain relief. Anaesthesia 40:410, 1985.

266. Ichiyanagi K: Sciatic nerve block: Lateral approach with the patient supine. Anesthesiology 20:601, 1959.

267. Guardini R, Waldron BA, Wallace WA: Sciatic nerve block: A new lateral approach. Acta Anaesthesiol Scand 29:515, 1985.

268. Kempthorne PM, Brown TCK: Nerve blocks around the knee in children. Anaesth Intensive Care 12:14, 1984.

269. Rongstad K, Mann RA, Prieskorn D et al: Popliteal sciatic nerve block for postoperative analgesia. Foot Ankle Int 17:378, 1996.

270. McLeod DH, Wong DH, Claridge RJ, Merrick PM: Lateral popliteal sciatic nerve block compared with subcutaneous infiltration for analgesia following foot surgery. Can J Anaesth 41:673, 1994.

271. Vloka JD, Hadzic A, Kitain E et al: Anatomic considerations for sciatic nerve block in the popliteal fossa through the lateral approach. Reg Anesth 21:414, 1996.

272. Mansour NY: Compartment block for foot surgery. A new approach to tibial nerve and common peroneal nerve block. Reg Anesth 20:95, 1995.

273. Shelly MP, Park GR: Intercostal nerve blockade for children. Anaesthesia 42:541, 1987.

274. Moore DC, Mather LE, Bridenbaugh PO et al: Arterial and venous plasma levels of bupivacaine following epidural and bilateral intercostal nerve blocks. Anesthesiology 45:39, 1976.

275. Rothstein P, Arthur GR, Feldman HS et al: Bupivacaine for intercostal nerve blocks in children: Blood concentrations and pharmacokinetics. Anesth Analg 65:625, 1986.

276. Markham SJ, Tomlinson J, Hain WR: Ilioinguinal nerve block in children: A comparison with caudal block for intra and postoperative analgesia. Anaesthesia 41:1098, 1986.

277. Hannallah RS, Broadman LM, Belman AB et al: Comparison of caudal and ilioinguinal/iliohypogastric nerve block for control of postorchiopexy pain in pediatric ambulatory surgery. Anesthesiology 66:832, 1987.

278. Casey WF, Rice LJ, Hannallah RS et al: A comparison between bupivacaine instillation versus ilioinguinal/iliohypogastric nerve block for postoperative analgesia following inguinal herniorrhaphy in children. Anesthesiology 72:637, 1990.

279. Trotter C, Martin P, Youngson G et al: A comparison between ilioinguinal-iliohypogastric nerve block performed by anaesthetist or surgeon for postoperative analgesia following groin surgery in children. Paediatr Anaesth 5:363, 1995.

280. Greig JD, McArdle CS: Transient femoral nerve palsy complicating preoperative ilioinguinal nerve blockade for inguinal herniorrhaphy. Br J Surg 81:1829, 1994.

281. Rosario DJ, Skinner PP, Raftery AT: Transient femoral nerve palsy complicating preoperative ilioinguinal nerve blockade for inguinal herniorrhaphy. Br J Surg 81:897, 1994.

282. Lehmann JM, Beckermann S: Transient femoral nerve palsy complicating preoperative ilioinguinal nerve blockade for inguinal herniorrhaphy. Br J Surg 82:853, 1995.

283. Derrick JL, Aun CS: Transient femoral nerve palsy after ilioinguinal block. Anaesth Intensive Care 24:115, 1996.

284. Smith T, Moratin P, Wulf H: Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block. Br J Anaesth 76:452, 1996.

285. Dalens B: Bloc ilioinguinal et iliohypogastrique chez l'enfant. In Dartayet B (ed): Paris, MAPAR. 1997, p 235.

286. Dalens B, Vanneuville G, Dechelotte P: Penile block via the subpubic space in 100 children. Anesth Analg 69:41, 1989.

287. Broadman LM, Hannallah RS, Belman AB et al: Post-circumcision analgesia: A prospective evaluation of subcutaneous ring of the penis. Anesthesiology 67:399, 1987.

288. Irwin MG, Cheng W: Comparison of subcutaneous ring block of the penis with caudal epidural block for post-circumcision analgesia in children. Anaesth Intensive Care 24:365, 1996.

289. Cartwright PC, Snow BW, McNees DC: Urethral meatotomy in the office using topical EMLA cream for anaesthesia. J Urol 156:857, 1996.

290. Taddio A, Stevens B, Craig K et al: Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. N Engl J Med 336:1197, 1997.

291. Taddio A, Katz J, Ilersich AL et al: Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet 349:599, 1997.

292. Richardson J, Sabanathan S, Mearns AJ et al: A prospective, randomized comparison of interpleural and paravertebral analgesia in thoracic surgery. Br J Anaesth 75:405, 1995.

293. Lonnqvist PA: Continuous paravertebral block in children. Initial experience. Anaesthesia 47:607, 1992.

294. Lonnqvist PA, Hesser U: Radiological and clinical distribution of thoracic paravertebral blockade in infants and children. Paediatr Anaesth 3:83, 1993.

295. Karmakar MK, Booker PD, Franks R et al: Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants. Br J Anaesth 76:811, 1996.

296. Eason MJ, Wyatt R: Paravertebral thoracic block: A reappraisal. Anaesthesia 34:638, 1979.

297. Lonnqvist PA, Hesser U: Depth from skin to the thoracic paravertebral space in infants and children. Paediatr Anaesth 4:99, 1994.

298. Lonnqvist PA: Plasma concentrations of lignocaine after thoracic paravertebral blockade in infants and children. Anaesthesia 48:958, 1993.

299. Catala E, Casas JI, Unzueta MC et al: Continuous infusion is superior to bolus doses with thoracic paravertebral blocks after thoracotomies. J Cardiothorac Vasc Anesth 10:586, 1996.

300. Lonnqvist PA, MacKenzie J, Soni AK et al: Paravertebral blockade: Failure rate and complications. Anaesthesia 50:813, 1995.

301. Reiestad F, Stromskag KE: Interpleural catheter in the management of postoperative pain. A preliminary report. Reg Anesth 11:89, 1986.

302. Rocco A, Reiestad F, Gudman J et al: Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures. Preliminary report. Reg Anesth 12:10, 1987.

303. Rosenberg P, Scheinin B, Lepantalo M et al: Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 67:811, 1987.

304. Stromskag KE, Minor B, Steen PA: Side effects and complications related to interpleural analgesia: An update. Acta Anaesthesiol Scand 35:473, 1990.

305. Semsroth M, Plattner O, Horcher E: Effective pain relief with continuous intrapleural bupivacaine after thoracotomy in infants and children. Paediatr Anaesth 6:303, 1996.

306. Giaufre E, Bruguerolle B, Rastello C et al: New regimen for interpleural block in children. Paediatr Anaesth 5:125, 1995.

307. Kreitzer JM, Reuben SS: Central nervous system toxicity in a patient receiving continuous intrapleural bupivacaine. J Clin Anesth 8:666, 1996.

308. Pinnock CA, Fischer HBJ, Jones RP: Scrotal infiltration. In Pinnock CA, Fischer HBJ, Jones RP (eds): Peripheral Nerve Blockade. London, Churchill Livingstone, 1996, p 95.

309. Ferguson S, Thomas V, Lewis I: The rectus sheath block in paediatric anaesthesia: New indications for an old technique? Paediatr Anaesth 6:463, 1996.

310. Courreges P, Poddevin F, Lecoutre D: Para-umbilical block: A new concept for regional anaesthesia in children. Paediatr Anaesth 7:211, 1997.

311. Vannier JL, Vilette M, Bouazaz H et al: Le bloc du nerf larynge superieur pour les endoscopies ORL. Description d'une technique simplifiee. Ann Fr Anesth Reanim 8:379, 1988.

312. Parris WCV, Reddy BC, White HW et al: Stellate ganglion blocks in pediatric patients. Anesth Analg 72:552, 1991.

313. Moss AJ, McDonald J: Unilateral cervico-thoracic sympathetic ganglionectomy for the treatment of long Q-T interval syndrome. N Engl J Med 285:903, 1971.

314. Rogers MC, Abildskov JA, Preston JB: Cardiac effects of stimulation and block of stellate ganglion. Anesthesiology 39:525, 1973.

315. Yanagida H, Kemi C, Suwa K: The effects of stellate ganglion block on idiopathic prolongation of the Q-T interval with cardiac arrhythmia (the Romano-Ward syndrome). Anesth Analg 55:782, 1976.

316. Milne JR, Ward DE, Spurrell AJ et al: The long Q-T syndrome: Effects of drugs and left stellate ganglion block. Am Heart J 104:194, 1982.

317. Hogan QH, Erickson SJ, Haddox JD et al: The spread of solutions during stellate ganglion block. Reg Anesth 17:78, 1992.

318. Jakobs W, Ladwig B, Cichon P et al: Serum levels of articaine 2% and 4% in children. Anesth Prog 42:113, 1995.

319. Fitzgerald B: Intravenous regional anaesthesia in children. Br J Anaesth 48:485, 1976.

320. Rudzinski JP: Pediatric application of intravenous regional anesthesia. Reg Anesth 8:69, 1983.

321. Bratt HD, Eyres RL, Cole WG: Randomized double-blind trial of low and moderate-dose lidocaine regional anesthesia for forearm fractures in childhood. J Pediatr Orthop 16:660, 1996.

322. Blasier RD, White R: Intravenous regional anesthesia for management of children's extremity fractures in the emergency department. Pediatr Emerg Care 12:404, 1996.

323. Heath M: Deaths after intravenous regional anaesthesias. Br J Anaesth 285:913, 1982.

324. Sitbon P, Laffon M, Lesage V et al: Lidocaine plasma concentrations in pediatric patients after providing airway topical anesthesia from a calibrated device. Anesth Analg 85:1003, 1996.

325. Ernst AA, Marvez E, Nick TG et al: Lidocaine adrenaline tetracaine gel versus tetracaine adrenaline cocaine gel for topical anesthesia in linear scalp and facial laceration in children aged 5 to 17 years. Pediatrics 95:255, 1995.

326. Bonadio WA: Safe and effective method for application of tetracaine, adrenaline, and cocaine to oral lacerations. Ann Emerg Med 28:396, 1996.

327. Vinci RJ, Fish SS: Efficacy of topical anesthesia in children. Arch Pediatr Adolesc Med 150:466, 1996.

328. Smith GA, Strausbaugh SD, Harbeck-Weber C, et al: Comparison of topical anesthetics without cocaine to tetracaine-adrenaline-cocaine and lidocaine infiltration during repair of lacerations: Bupivacaine-norepinephrine is an effective new topical anesthetic agent. Pediatrics 97:301, 1996.

329. Cassidy SC, Jones PR, Cox S et al: Serum lidocaine concentrations after subcutaneous administration in patients undergoing cardiac catheterization in a pediatric institution. J Pediatr 129:464, 1996.

330. Raetzell M, Maier C, Schroder D et al: Intraperitoneal application of bupivacaine during laparoscopic cholecystectomy: Risk or benefit? Anesth Analg 81:967, 1995.

Chapter 45 - Fluid and Electrolyte Physiology

Alan D. Kaye
Alan W. Grogono

Routine Intraoperative Administration
Compensatory Intravascular Volume Expansion

DEFICITS
Maintenance Fluid

LOSSES
Redistribution
The Pediatric Patient
The Postoperative Patient With Bowel Obstruction
The Patient With Liver Failure
The Patient With Heart Failure
The Patient With Cerebral Edema
The Patient With Anuric Renal Failure Undergoing Nontransplant Surgery
The Patient With Adult Respiratory Distress Syndrome
The Acutely Burned Patient
The Pregnant Patient With Preeclampsia

INTRODUCTION

Water is the major component of all fluid compartments within the body. Total body water represents approximately 60 percent of total body weight in an average adult. In a 70 kg man, total body water is about 600 mL/kg or 40 L. The relative percentage of water varies significantly with age, gender, and adiposity. For example, muscle contains 75 percent water, whereas adipose tissue contains only 10 percent water. Water content of the fetus is high initially but decreases progressively during late gestation and the first 3 to 5 years of life.

The intracellular and extracellular compartments are separated by water-permeable cell membranes. The intracellular fluid volume averages 400 to 450 mL/kg (e.g., about 30 L), which includes 2 L of red blood cells. The extracellular

TABLE 45-1 -- Electrolyte Composition in Body Fluids

(Not Available)

Modified from Rhoades RA, Tanner GA: Medical Physiology. Little, Brown & Co., Boston, 1995.

TABLE 45-2 -- Daily Loss of Water (mL)

(Not Available)

From Rhoades RA, Tanner GA: Medical Physiology. Little, Brown & Co., Boston, 1995.

fluid volume averages 150 to 200 mL/kg, (e.g., about 14 L), which includes the plasma volume 30 to 35 mL/kg, interstitial fluid volume 120 to 165 mL/kg, and transcellular fluids including pleural, peritoneal, aqueous humor, sweat, urine, lymph, and cerebrospinal fluid. Extracellular fluid volume is greater in the young and in the male than in the elderly or the female (Table 45-1) (Table Not Available) . The blood volume is 60 to 65 mL/kg and is distributed 15 percent in the arterial and 85 percent in the venous system. The main metabolic reactions of the blood occur inside the red blood cells and thus within the intracellular fluid compartment.

The extracellular fluid compartment contains high concentrations of sodium, chloride, and bicarbonate. Plasma and interstitial fluid are rich in proteins, which determine plasma colloid osmotic pressure. Permeability to ions and proteins varies in each organ, with the brain having the least and the liver the most permeability.

Control of body water and its composition is multifactorial and involves (1) atrial natriuretic peptide, (2) vasopressin, (3) aldosterone (renin, angiotensin), (4) parathyroid hormone, (5) calcitonin, (6) prostaglandins, (7) dopaminergic receptors, (8) alpha-adrenergic receptors, (9) the thirst mechanism, and (10) intrinsic renal properties.

Water balance represents the difference between water intake and water loss. The kidneys are the major regulators of water output. Approximately 60 percent of the daily water loss is excreted in the urine. At high ambient temperatures or with significant exercise, the amount of water lost by sweating increases and may reflect the majority of total daily loss of water.

Heavy exercise can increase the loss of water via sweating up to 50 times the normal rate. In addition the increase in the ventilation increases the insensible loss of water through the respiratory tract (Table 45-2) (Table Not Available) . Under these conditions, renal water loss decreases to compensate for the increased sweating and insensible water losses. [1]

SODIUM PHYSIOLOGY

Sodium is the most abundant positive ion of the extracellular fluid compartment and is critical in determining the extracellular and intracellular osmolality. The distribution of sodium between plasma and interstitial fluid is roughly 5 or 6 to 1 at equilibrium, with the distribution equilibrium time being 15 to 20 minutes. Extracellular sodium balance is determined by sodium intake relative to sodium excretion. Most humans consume far more salt than they need. In certain states such as Addison disease, there is an inadequate aldosterone secretion resulting in a salt-craving behavior.

Sodium requirements vary with age. For infants born before 32 weeks' gestation, requirements are 3 mEq/kg/d; and at full term, 2 to 3 mEq/kg/d. [2] Neonatal stool losses are about 1 mEq/kg/d, and the growth process utilizes 0.5 mEq/kg/d. Adult requirements decrease to about 1.5 mEq/kg/d. Urinary sodium excretion represents the majority of sodium loss and approximately equals the daily intake of sodium. Under certain conditions, however, extrarenal sodium loss via profuse sweating, burns, severe vomiting, or diarrhea can be significant.

Normally, as much as 10 mL of urine can be formed for each milliosmole of solute excreted by the kidney. Normal kidneys respond to a volume challenge with diuresis and to a sodium load with natriuresis; if there is a decreased sodium intake or volume depletion, the kidney responds with antinatriuresis and antidiuresis (e.g., a patient undergoing surgery may excrete only 1.2 to 1.6 mOsm/mL of solute [3]). Under various pathophysiologic processes, abnormally high

---

TABLE 45-3 -- Major Causes of Natriuresis and Antinatriuresis

	NATRIURESIS
Volume-expanded states	High sodium intake; inappropriate antidiuretic hormone secretion
Volume-depleted states	Addison disease; renal salt wasting; Diuretic abuse
	ANTINATRIURESIS
Edematous states	Heart failure; chronic liver disease; nephrotic syndrome; acute glomerulonephritis; idiopathic edema
Nonedematous states	Hemorrhage; low sodium intake; diuretic withdrawal; acute mineralocorticoid administration; nonrenal sodium loss by sweating and/or vomiting

or low urinary sodium excretion can occur and are outlined below.

Many of the factors that control tubular sodium reabsorption are affected during the perioperative period including hemodynamic and physical factors, hormonal factors, and renal sympathetic nerve activity. The balance of Starling forces is responsible for sodium and water transport across peritubular capillary walls. The net pressure in the peritubular capillaries is about 10 mm Hg in favor of uptake of reabsorbed fluid. Volume expansion with isotonic saline decreases plasma protein concentration and, therefore, lowers colloid osmotic pressure in peritubular capillaries.

The renin-angiotensin system (RAS) is involved in control of blood pressure and blood volume along with the sympathetic nervous system, the kinin-kallikrein system, and arginine-vasopressin. The RAS plays a role in sodium homeo-stasis and renal function, particularly under stress conditions. The RAS may be initiated by decreases in blood pressure in the renal artery, by decreases in sodium delivery to the macula densa, or by sympathetic nervous system activation. In response, renin is synthesized from its precursor prorenin and secreted by the juxtaglomerular cells of the kidney. Renin, an aspartyl-protease (similar to pepsin and cathepsin), cleaves its substrate, angiotensinogen, an alpha$_2$-globulin, to generate the decapeptide angiotensin I. Although renin is mostly produced by the kidney, renin isoenzymes have been found in many tissues including brain, adrenal gland, vascular beds, uterus, and placenta. [4] [5] [6] [7] The gene for human renin has recently been cloned. Angiotensinogen levels are increased after nephrectomy, by estrogens, thyroid hormones, glucocorticoids, and during angiotensin I-converting enzyme inhibition. [8] [9] [10] [11]

Angiotensin I is rapidly converted to the octapeptide angiotensin II by angiotensin I-converting enzyme or by an endopeptidase. The pulmonary circulation appears to be the major site of angiotensin-converting enzyme activity, although angiotensin converting enzyme is also found in the vascular endothelium of the heart, kidney, adrenal cortex, testes, and brain, in addition to the lung. [12]

Angiotensin II is a potent vasopressor that stimulates aldosterone secretion via the adrenal cortex. Angiotensin II has a vagal inhibitory effect and causes ganglionic stimulation. [13] [14] [15] Angiotensin II partially suppresses renin secretion by a direct effect on the juxtaglomerular cells. [16] [17] Studies suggest that angiotensin II may stimulate a local increase of adenosine, a known inhibitor of renin release, and could therefore participate in a negative feedback loop whereby angiotensin II could limit its own biosynthesis. [18] Angiotensin II is degraded in the plasma to the carboxyterminal heptapeptide angiotensin III or the amino-terminal heptapeptide angiotensin (1-7), both of which appear to be biologically active. [19] [20] Thus, a fall in blood pressure, a decrease in sodium delivery to the macula densa, or sympathetic stimulation, may activate the RAS, generating angiotensin II. This results in an increase in blood pressure as well as sodium retention caused by enhanced aldosterone secretion. The renin-angiotensin system does not have an active role in maintaining blood pressure in the normal, sodium-replete, intact individual. In short, hydrostatic forces act to maintain a stable glomerular filling pressure. This, in turn, affects venous return, cardiac output, and blood pressure. Superimposed on this mechanism, under stress conditions, are a variety of neurohumoral control systems that include the sympathetic nervous system, antidiuretic hormone, atrial natriuretic hormone, and prostaglandins (Table 45-3) .

The anesthesiologist should understand that nitroprusside-induced hypotension is associated with increases in renin activity and marked elevations in the plasma concentrations of antidiuretic hormone, which are not seen with trimethaphan-induced blood pressure reductions. [21] [22] Propranolol administration during nitroprusside-induced hypotension prevents rises in plasma renin activity. [23]

Hyponatremia

Hyponatremia, typically defined as a plasma sodium less than 135 mEq/L, can result from excessive loss of sodium from excessive sweating, vomiting, diarrhea, burns, and the administration of diuretics. The most common cause of hyponatremia, however, is not a deficiency of total body sodium, but an excess of total body water.

Factitious hyponatremia can be seen in hyperlipidemia (chylomicronemia) or hyperproteinemia. Hyperosmolality resulting from nonsodium molecules (hyperglycemia,

mannitol overdose) draws water from the intracellular space to dilute the extracellular sodium concentration. Significant decreases in total body sodium most commonly occur from diuretic administration.

Transurethral prostate (TURP) syndrome is a recognized cause of hyponatremia and caused by intravascular absorption of irrigation solution, which typically contains glycine [24] ; hyponatremia, hyperglycemia, and hyperammonemia can result.

TABLE 45-4 -- Major Causes of Hyponatremia

(Not Available)

Modified from Oh M, Carrol H: Disorders of sodium metabolism: Hypernatremia and hyponatremia. Crit Care Med 20:94, 1992; Andreoli TE: Disorders of fluid volume, electrolyte, and acid-base balance. In Wyngaarden JB, Smith LH Jr (eds): Cecil Textbook of Medicine. 17th ed. Philadelphia, WB Saunders Co, 1985, p 525.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is seen in association with a number of processes including pulmonary and cranial disorders and in a number of neoplasms, particularly bronchogenic carcinoma. High levels of vasopressin are secreted intermittently at an abnormally low threshold or continuously despite low osmolality. The presence of hyponatremia plus a urine osmolality higher than maximal dilution confirms the diagnosis. Diagnosis of SIADH rather than SIADH due to extrarenal causes is made when the urinary sodium concentration is less than 10 to 15 mEq/L and the fractional excretion of sodium is below 1 percent. In patients with SIADH, the urinary sodium concentration usually exceeds 30 mEq/L, the fractional excretion of sodium is greater than 1 percent, and the serum uric acid is reduced. Patients with SIADH exhibit a characteristic response to water restriction; a 2- to 3-kg weight loss is accompanied by correction of hyponatremia and cessation of salt wasting over 2 to 3 days. [25]

Hyponatremia also occurs in mixed disorders, in which nonosmotic antidiuretic hormone release and reductions in the rate of urinary sodium excretion blunt urinary diluting capacity. This can occur in advanced volume contraction, in intractable heart failure, and in advanced hepatic cirrhosis with ascites.

The signs and symptoms associated with hyponatremia are critical for the anesthesiologist particularly during TURP managed with regional anesthesia. Nausea, vomiting, visual disturbances, depressed level of consciousness, agitation, confusion, coma, seizures, muscle cramps, weakness, or myoclonus can be seen depending on the level of hyponatremia. Cerebral edema occurs at or below a serum level of 123 mEq/L, and cardiac symptoms occur at 100 mEq/L. Hyponatremia in association with increased intravascular volume can result in pulmonary edema, hypertension, and heart failure. [26]

The dose of sodium required to correct a deficit may be calculated using the following formula:

The optimal rate of correction appears to be 0.6 to 1 mmol/L/h until the sodium concentration is 125 mEq/L, then at a slower rate. Half the deficit can be administered over the first 8 hours and the next half over 1 to 3 days if symptoms remit. Sodium concentration should be monitored every 1 to 2 hours during rapid correction. When slow correction of hyponatremia in a volume-expanded patient is indicated, water restriction is preferred. If this is unsuccessful, diuresis with a loop diuretic such as furosemide is indicated. A number of different agents that interfere with urine concentration at the collecting duct have been used to manage chronic hyponatremia including lithium and demeclocycline. Antidiuretic hormone antagonists and the administration of urea as an osmotic diuretic are currently under investigation, although further studies are needed.

It is important to remember that rapid treatment of hyponatremia can lead to central pontine myelinolysis. Management of hyponatremia involves elimination of the underlying condition when possible (e.g., stop the TURP as soon as possible). The use of normal saline (308 mOsm/L) alone may make the hyponatremia worse depending on the patient's serum and urine osmolality. [27] Severe coma or seizures can be managed with a combination of hypertonic saline 3 percent (513 mEq/L), fluid restriction, and/or furosemide. [28] The most likely cause of postoperative hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (Table 45-4) (Table Not Available) .

Hypernatremia

Hypernatremia is defined as an increase in extracellular sodium concentration and may be accompanied by the presence of low, normal, or high total body sodium content. The major causes of hypernatremia are excessive loss of water, inadequate intake of water, a lack of antidiuretic hormone (vasopressin), or excessive intake of sodium (e.g., with solutions containing a high sodium concentration such as sodium bicarbonate). Diabetes insipidus may result from deficiency of vasopressin or inability of the kidney to produce a hypertonic medullary interstitium. Vasopressin deficiency is seen following pituitary surgery, basal skull fracture, and severe head injury. Nephrogenic causes include any systemic or kidney disease that impairs tubular function.

In the presence of an intact thirst mechanism, a slight increase in serum sodium concentration (e.g., 3 to 4 mmol/L) above baseline values elicits intense thirst. The lack of thirst in the presence of hypernatremia in a mentally alert patient indicates a defect either in the osmoreceptor or in the cortical thirst center. The most common objective sign of hypernatremia is lethargy or mental status changes, which can proceed to coma and convulsions. Additional signs and symptoms of hypernatremia include thirst, shock, peripheral edema, myoclonus, ascites, muscular tremor, muscular rigidity, hyperactive reflexes, pleural effusion, and expanded intravascular fluid volume. With acute and severe hypernatremia, the osmotic shift of water from the cells can lead to shrinkage of the brain with tearing of the meningeal vessels and intracranial hemorrhage. Slowly developing hypernatremia is usually well tolerated because of the brain's ability to regulate its volume. Treatment involves restoring normal osmolality and volume and includes removal of excess sodium through the administration of diuretics, hypotonic crystalloid solutions, and/or identification and removal of solutes. The speed of correction depends on the rate of development of hypernatremia and associated symptoms. Because chronic hypernatremia is well tolerated, rapid correction offers no advantage and may be extremely harmful or lethal because it may result in brain edema. [29] [30] Typically, a maximum of 10 percent of the serum sodium concentration or about 0.7 mmol/L/h should be the goal rate of correction. Hypernatremia increases the minimum alveolar concentration of inhalational anesthetic agents possibly because of enhanced sodium conductance during depolarization of excitatory membranes. [31] (Table 45-5) (Table Not Available) .

POTASSIUM PHYSIOLOGY

Potassium is the most abundant positive ion in the intracellular fluid. In the short term (minutes), potassium balance is influenced by insulin, pH, beta-adrenergic agonists, and bicarbonate concentration. Long-term regulation of potassium excretion and balance primarily involves the kidney and aldosterone. Several factors cause potassium concentration to average 0.4 to 0.5 mEq/L lower when measured on heparinized arterial samples, as compared with clotted venous samples.

Elevations in potassium intake increase renal excretion of potassium via a variety of cellular mechanisms. In response to increases in extracellular potassium levels, aldosterone is secreted from the zona glomerulosa of the adrenal gland

TABLE 45-5 -- Major Causes of Hypernatremia

(Not Available)

Modified from Andreoli TE: Disorders of fluid volume, electrolyte, and acid-base balance. In Wyngaarden JB, Smith LH Jr (eds): Cecil Textbook of Medicine. 17th ed. Philadelphia. WB Saunders CO, 1985, p 528.

and acts on cortical collecting ducts to increase potassium secretion into the tubular fluid and therefore increase potassium excretion.

Potassium requirements vary with age and growth. The typical full-term baby requires 2 to 3 mEq/kg/d, [32] whereas the adult uses 1.0 to 1.5 mEq/kg/d. Potassium demands are related to metabolic rate (2.0 mEq/100 kcal). In this regard, requirement increases dramatically during cell growth following establishment of nutrition in previously starved individuals. Extremely high or low levels of potassium can be life threatening.

Hypokalemia

Hypokalemia (<3.5 mEq/L) may occur owing to an absolute deficiency or redistribution into the intracellular space. A reduction in serum potassium of 1 mEq/L indicates a net loss of 100 to 200 mEq of potassium in a normal adult. Hypokalemia in the range of 2 to 2.5 mEq/L is likely to cause muscular weakness, arryhythmias, and electrocardiographic abnormalities including sagging of the ST segment, depression of the T wave, and U-wave elevation. These morphologic changes do not correlate with the severity of potassium depletion. However, cardiac dysrhythmias are more predictable and most frequently involve atrial fibrillation and premature ventricular systoles.

The four most common causes of hypokalemia include reduced intake, gastrointestinal losses, excessive renal losses of potassium (e.g., with excess of mineralocorticoids or diuretics), and potassium shifts from the extracellular to the intracellular fluid. These shifts can occur with acute alkalosis, insulin therapy, stress-related catecholamine activity, and hypokalemic periodic paralysis. Surgical stress may reduce the serum potassium concentration by 0.5 mEq/L and the administration of exogenous catecholamines such as isoproterenol, terbutaline, epinephrine, and ritodrine also decreases potassium levels. [33] [34] [35] [36] Clinically, this includes pregnant patients on tocolytic therapy or respiratory treatment with beta $_2$ -agonists and critically ill patients requiring pharmacologic cardiovascular support.

No studies demonstrate an increased morbidity or mortality for patients undergoing an anesthetic with a potassium level of at least 2.6 mEq/L. Even though administration of supplemental potassium chloride is a common practice for the anesthesiologist, studies demonstrate that in many instances therapy is ineffective, with most of the supplemental potassium being excreted in the urine despite continued hypokalemia. [37] [38] If therapy is indicated, the anesthesiologist uses intravenous potassium chloride. Because the rate of administration of potassium must be adjusted for the rate of distribution through the extracellular space before entry into the intracellular space, the rate of potassium administration is limited to 0.5 to 1.0 mEq/kg/h, with a typical replacement rate of 10 to 20 mEq/h for a normal adult with constant monitoring of the electrocardiogram [39] [40] (Table 45-6) (Table Not Available) .

Hyperkalemia

Hyperkalemia (>5.5 mEq/L) may occur in various disease states, in response to drugs that diminish renal potassium

TABLE 45-6 -- Major Causes of Hypokalemia

(Not Available)

Modified from Andreoli TE: Disorders of fluid volume, electrolyte, and acid-base balance. In Wyngaarden JB, Smith LH Jr (eds): Cecil Textbook of Medicine. 17th ed. Philadelphia, WB Saunders Co, 1985, p 532.

TABLE 45-7 -- Major Causes of Hyperkalemia

(Not Available)

Modified from Solomon RJ, Katz JD: Disorders of potassium homeostasis. In Stoelting RK (ed): Advances in Anesthesia, Chicago, Year Book Medical Publishers, 1986

excretion, or after sudden transcellular shifts of potassium from the intracellular to the extracellular fluid. Any condition or drug resulting in adrenal inhibition or decreasing aldosterone levels can cause potassium retention. Factitious hyperkalemia should also be considered in the differential diagnosis and occurs in response to lysis of the cellular components of blood.

Clinically, hyperkalemia can cause muscle weakness and even paralysis. Alterations in initiation and conduction of cardiac conduction increase automaticity and enhance repolarization. Mild elevations in potassium levels (6-7 mEq/L) may present with peaked T waves and can progress to a prolonged P-R interval, widening of the QRS complex, ventricular fibrillation, or even asystole as levels approach 10 to 12 mEq/L. [41]

Clinical treatment of hyperkalemia is determined by the setting and presence of electrocardiographic changes; it involves stabilization of the heart from effects of the potassium with intravenous calcium and redistribution of potassium from the plasma into cells. Intravenous glucose, insulin, bicarbonate, and hyperventilation are the major therapies used in the operating room setting. However, resin exchange, dialysis, diuretics, aldosterone agonists, and beta-adrenergic agonists are

well-established additional therapies (Table 45-7) (Table Not Available) .

/das/book/view/29494766/875/511.html

CALCIUM PHYSIOLOGY

Calcium is the key component that mediates muscle contraction, exocrine, endocrine and neurocrine secretion, cell growth, and the transport and secretion of fluids and electrolytes. There are approximately 1,300 g of calcium in a 70 kg adult, 99 percent of which is in the bones and teeth. The kidneys are the major organ responsible for regulating calcium between 4.5 and 5 mEq/L. Calcium is abundant in milk and milk products, is poorly absorbed by the intestine, and is excreted primarily in the feces and urine. Circulating calcium exists in three forms: (1) bound to plasma proteins

(primarily albumin) and not filtered by glomerular capillaries (40%); (2) ionized, physiologically active, filtered at the glomerular membrane, and maintained at a concentration of 2.0 to 2.5 mEq/L (50%); and (3) nonionized and chelated with phosphate, sulfate, and citrate (10%). Changes in pH alter the fraction of calcium that is bound to albumin, so the level of ionized calcium can change without alteration of total calcium. The majority of filtered calcium is reabsorbed in the proximal tubule, the thick ascending limb of the loop of Henle, and the distal tubule.

The concentration of serum proteins is an important determinant of calcium ion concentration. Ionized calcium can be measured directly with the use of calcium-specific electrodes. When ionized calcium cannot be measured, the approximate amount of calcium bound to protein is:

Plasma calcium levels must also be evaluated with careful consideration of plasma albumin concentration. To estimate ionized calcium in patients with subnormal serum proteins, a correction of 1 mg/dL is added to the serum calcium for every g/dL that serum albumin is below 4.0 g/dL. [42] For example, if the serum calcium is 7.8 mg/dL (a subnormal value) and the serum albumin is only 3.0 mg/dL; the stated serum calcium is then corrected by adding 1 mg/dL; the corrected value of 8.8 mg/dL is within the normal range.

Within minutes of a slight decrease in extracellular calcium concentration, the parathyroid glands release parathyroid hormone, which increases calcium reabsorption in the thick ascending limb and distal tubule, thus decreasing calcium excretion. Excision of the parathyroid glands eliminates parathyroid hormone secretion, which can significantly disrupt calcium homeostasis.

Calcitonin, produced in the thyroid gland, decreases renal reabsorption of calcium acutely but has little effect on chronic calcium homeostasis. Surgical removal of the thyroid gland eliminates calcitonin without changing extracellular calcium ion concentration.

Hypercalcemia

Hypercalcemia is associated with many disease processes and has many signs and symptoms. Hypercalcemia produces changes primarily in the central nervous system (mental status changes), the gastrointestinal tract (vomiting), the kidneys (polyuria, renal calculi, oliguric renal failure), and the heart (cardiac conduction disturbances). Today, hypercalcemia is most commonly diagnosed in asymptomatic patients, whereas, previously, clinical features were the earliest manifestation. Treatment essentially involves diuresis and administration of normal saline to dilute plasma calcium. These primary treatments are also useful because sodium inhibits the renal reabsorption of calcium. Additional therapies include bisphosphonates, calcitonin, ambulation, and treatment of the underlying condition. Certain conditions, including numerous cancer-related hypercalcemias, can be treated with calcium-lowering agents such as mithramycin and glucocorticoids. Thus, the anesthetic management of a patient with hypercalcemia should involve maintenance of hydration and urine output with sodium-containing fluids. Monitoring of the electrocardiogram is useful to detect cardiac conduction defects with prolonged P-R or Q-T intervals and/or widening of the QRS complex. Patients who have muscle weakness should receive decreased doses of nondepolarizing muscle relaxants (Table 45-8) (Table Not Available) .

Hypocalcemia

In the operating room, hypocalcemia is most commonly caused by acute hyperventilation or the infusion of citrated blood in excess of 1.5 mL/kg/min. The most common cause of hypocalcemia (plasma concentration less than 4.5 mEq/L) is a low albumin (e.g., in critically ill patients with severe sepsis, burns, acute renal failure, and extensive transfusions). Many critically ill patients will have low plasma albumin and low plasma calcium with normal ionized calcium levels. [43] The major signs and symptoms of hypocalcemia include mental status changes, tetany, Chvostek and Trousseau signs, laryngospasm, hypotension, and dysrhythmias.

TABLE 45-8 -- Major Causes of Hypercalcemia

(Not Available)

Modified from Potts JT: Diseases of the parathyroid gland and other hyper-and hypocalcemic disorders. In Isselbacher KJ. Braunwald E. Wilson JD et al: Harrison's Principles of Internal Medicine. 13th ed. New York, MeGraw-Hill, Inc., 1995, p 2151.

TABLE 45-9 -- Major Causes of Hypocalcemia (Excluding Neonatal Conditions)

(Not Available)

Modified from Poitts JT: Diseases of the parathyroid gland and other hyper- and hypoclcemic disorders. In Isselbacher KJ, Braunwald E, Wilson JD et al: Harrison's Principles of Internal Medicine. 13th ed. New York, McGraw-Hill, Inc., 1995, p 2165.

Treatment involves intravenous infusion of 10 percent calcium chloride (1.36 mEq/mL) or calcium gluconate (0.45 mEq/mL). When equivalent calcium doses are administered, both preparations are equally efficacious in restoring the calcium level to normal (Table 45-9) (Table Not Available) .

/das/book/view/29494766/875/512.html

MAGNESIUM PHYSIOLOGY

Magnesium sulfate has been used for many years on an empirical basis to control convulsions in patients with preeclamptic toxemia. Magnesium ions are essential for many biochemical reactions, and a deficiency may produce clinically important consequences. Many of the pharmacologic properties have only recently been appreciated. Magnesium is excreted via the gastrointestinal tract and kidneys.

Total body magnesium is approximately 2,000 mEq. Magnesium is the fourth most important cation in the body and the second most important intracellular cation. Magnesium activates approximately 300 enzyme systems, including many involved in energy metabolism. It is essential for the production and functioning of adenosine triphosphate, which is fully functional only when chelated to magnesium. Other processes dependent on magnesium include the production of DNA, RNA, and protein synthesis. Magnesium is an essential regulator of calcium access into the cell and of the actions of calcium within the cell. Magnesium plays an essential role in the regulation of most cellular functions and may be regarded as a natural physiologic calcium antagonist.

Hypomagnesemia

With an absence of magnesium in the diet, the kidneys are able to significantly decrease excretion; however, hypomagnesemia is common in hospitalized patients, especially those in critical care areas, and presents with findings similar to hypocalcemia. Slight hypomagnesemia occurs in athletes, in hypermetabolic states such as pregnancy, and cold acclimatization. Magnesium deficiency alone and/or in combination with diuretic-induced hypokalemia and digitalisinduced arrhythmia can respond to magnesium therapy. [44] Furthermore, it is likely that anesthetizing patients with magnesium deficiency increases the risk of perioperative arrhythmias. Respiratory muscle power is impaired by hypomagnesemia, which may have important clinical consequences for anesthesia and critical care. Additional manifestations include central nervous system irritability with seizures and hyperreflexia, and skeletal muscle spasm (i.e., positive Trousseau and Chvostek signs). Treatment includes magnesium sulfate (1 g IV) with careful measurement and assessment of electrolyte levels. For acute arrhythmias, magnesium can be administrated in a dose of 8 to 12 mmol/L (200-300 mg) intravenously over 1 to 5 minutes with close monitoring of blood pressure and heart rate. Arterial pressure, deep tendon reflexes, and magnesium concentration should be monitored during either asymptomatic or life-threatening replacement. Beyond the theoretical risks of magnesium deficiency and neuromuscular blockade, the critical clinical importance of hypomagnesemia relates to the associated conditions and pathophysiologic processes associated with management of these conditions (Table 45-10) (Table Not Available) .

Hypermagnesemia

Hypermagnesemia (>2.5 mEq/L) occurs most commonly from iatrogenic causes and excessive use of antacids or laxatives. It is rare in clinical medicine, as magnesium is relatively

TABLE 45-10 -- Major Causes of Hypomagnesemia

(Not Available)

Modified from Potts JT: Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. In Isselbacher KJ. Braunwald E, Wilson JD et al: Harrison's Principles of Internal Medicine. 13th ed. New York. McGraw-Hill, Inc., 1995, p 2188.

poorly absorbed from the gastrointestinal tract, and renal elimination of excess magnesium is extremely rapid (within 4-8 hours of a magnesium load). Because elimination is directly related to glomerular filtration rate, patients with kidney failure are at increased risk of developing hypermagnesemia. Signs and symptoms are directly related to the blood level and include alterations in the nervous, cardiovascular, respiratory, and genitourinary systems.

Magnesium depresses the central nervous system and, in the early 1900s, was used effectively as a general anesthetic. Magnesium penetrates the blood-brain barrier poorly, however, and its level in the cerebrospinal fluid is well controlled by an active transport mechanism. Thus, magnesium probably does not have major anticonvulsant properties unless the convulsions result from magnesium deficiency. It is believed that the anticonvulsant activity of magnesium is related to its powerful cerebral vasodilator action, which reverses cerebral vasospasm, thought to be an important cause of convulsions. [45]

In the peripheral nervous system, magnesium interferes with the release of neurotransmitter substances at all synaptic junctions and potentiates the action of local anesthetics. At the neuromuscular junction, magnesium concentrations of 5 mmol/L cause significant presynaptic neuromuscular blockade and enhance the action of the nondepolarizing muscle relaxants. It may precipitate severe muscle weakness in patients with Eaton-Lambert syndrome or myasthenia gravis. Magnesium prolongs the action of depolarizing relaxants (succhinycholine); administration before the use of succinylcholine prevents the release of potassium provoked by the relaxant.

In the cardiovascular system, magnesium produces vasodilation by direct action on blood vessels and by interfering with a wide range of vasoconstrictor substances. It also reduces peripheral vascular tone by sympathetic blockade and inhibition of catecholamine release. In the isolated heart, increased concentrations of extracellular magnesium ion markedly depress contractile force. Decreased myocardial performance has been demonstrated after a bolus of 2.5 g of magnesium sulfate. Reports have been published of severe myocardial depression with combinations of magnesium and diltiazem. Also in the isolated heart, magnesium produces bradycardia. However, in the intact subject, the inhibition of vagal acetylcholine release produced by magnesium overrides the intrinsic slowing, and a mild tachycardia occurs. Magnesium is effective in treating a variety of arrhythmias, including ventricular arrhythmias, arrhythmias associated with epinephrine administration, and digitalis-associated arrhythmias. It is also efficacious in certain arrhythmias induced by hypokalemia, alcoholism, and myocardial infarction and may protect against bupivacaine-induced arrhythmias.

In the respiratory system, magnesium has no effect on central respiratory drive, and its only respiratory depressant effect is due to the neuromuscular block that it produces. It is an effective bronchodilator and has been successfully used in severe asthma. As magnesium inhibits catecholamineinduced arrhythmias, the possibility that magnesium may increase the effectiveness of beta-agonists in the management of asthma is currently being evaluated in clinical trials.

In the genitourinary system, magnesium is a powerful tocolytic and has been used for many years in the management of premature labor. In the kidney, magnesium is a renal vasodilator and a diuretic.

Symptoms and electrocardiographic changes of hypermagnesemia correspond to serum levels; depressed cardiac conduction, widened QRS complexes, prolonged P-Q intervals, and nausea appear between 5 and 10 mg/dL. Sedation, hypoventilation, decreased deep tendon reflexes, and muscle weakness appear at levels between 20 and 34 mg/dL, with hypotension, bradycardia, and diffuse vasodilation occurring at levels of 24 to 48 mg/dL. Areflexia, coma, and respiratory paralysis

occur at 48 to 72 mg/dL. For these reasons, all patients being treated with magnesium therapy are clinically observed for magnesium intoxication.

Elimination of magnesium involves fluid loading followed by or with concomitant diuresis. Definitive therapy involves dialysis. Temporary reversal of the effects of magnesium can be managed with calcium therapy. Because hypermagnesemia potentiates the effects of depolarizing and nondepolarizing muscle relaxants, these agents must be carefully titrated in conjunction with appropriate assessment of neuromuscular blockade. [46]

The deleterious effects of magnesium deficiency are now well recognized, and most critical care units now monitor magnesium levels. In coronary care units, several studies have shown that the infusion of magnesium sulfate can reduce the incidence and severity of cardiac arrhythmias associated with myocardial infarction. Numerous reports in the literature describe the bronchodilator effect of magnesium and of its successful use in the management of asthma. Magnesium may decrease the incidence of adrenergically mediated arrythmias without interfering with the bronchodilating action of beta-stimulants and contribute to smooth muscle relaxation of bronchioles.

In summary, magnesium has several important pharmacologic actions. Its only major toxic effect is neuromuscular paralysis. Its route of elimination is renal. Magnesium should be regarded as a cardiovascular drug, first and foremost, with calcium antagonistic and antiadrenergic properties, that may be accompanied by minimal myocardial depression.

PHOSPHATE PHYSIOLOGY

About 1 g of phosphorus is ingested daily. Approximately 70 percent (700 mg) is absorbed primarily from the small intestine, with the rest (300 mg) eliminated in the feces. The gut secretes phosphate into the lumen and then reabsorbs it, unless it is bound there by calcium or antacids or it is lost by diarrhea or drainage via ostomies or fistulas. The kidneys normally excrete 700 mg/d by filtering 6 g and reabsorbing 5.3 g. Thus, urine phosphate elimination approximately equals intestinal absorption.

Phosphate functions to store and release energy via high energy phosphates and is integral to the structure of proteins, lipids, and bone. Factors favoring cellular uptake include glucose, fructose, alkalosis, insulin, beta-adrenergic stimulation, and anabolism. Phosphate occurs in either organic or inorganic forms. Most of the intracellular phosphate is organic. Plasma contains lipid phosphates, organic ester phosphates, and inorganic phosphates, including divalent (HPO_4^{2-}) and monovalent ($H_2PO_4^-$) phosphate. At physiologic pH, 80 percent of the inorganic phosphate is divalent.

TABLE 45-11 -- Major Causes of Hyperphosphatemia

(Not Available)

Modified from Potts JT: Diseases of the parathyroid gland and other hyper- and hkypocalcemic disorders. In Isselbacher KJ, Braunwald E, Wilson JD et al: Harrison's Principles of Internal Medicine. 13th ed. New York, McGraw-Hill, Inc., 1995, p 2186.

Normally, plasma inorganic phosphate is maintained between 3.0 and 4.5 mg/100 mL in adults and 4.0 to 5.0 mg/100 mL in children. Parathyroid hormone inhibits proximal tubular inorganic phosphate reabsorption and increases inorganic phosphate excretion. In animals that are thyroparathyroidectomized, parathyroid hormone is absent, and reabsorption of inorganic phosphate increases significantly and ultimately increases plasma inorganic phosphate levels. In patients with primary hyperparathyroidism, parathyroid hormone secretion is elevated and plasma levels of inorganic phosphate are low; however, steady-state urinary inorganic phosphate excretion is not markedly increased, because it depends largely on intestinal inorganic phosphate absorption. Dietary restriction of inorganic phosphate leads to almost 100 percent reabsorption of filtered inorganic phosphate and to reduction of urinary phosphate to zero. [47]

Hyperphosphatemia

Severe hyperphosphatemia occurs following tissue damage or cell death. A moderate to severe hyperphosphatemia may be caused by an impaired ability to excrete phosphorus secondary to renal failure. Other causes include iatrogenic, hypothermia, massive liver failure, and certain hematologic malignancies associated with high cell turnover. The increased cell turnover can be part of the malignancy or may be because of cell destruction when chemotherapy is instituted. Treatment involves administration of phosphate-binding antacids such as aluminum antacids and sucralfate, calcium citrate, calcium carbonate, and/or dialysis, especially in association with renal failure. [48] (Table 45-11) (Table Not Available) .

Hypophosphatemia

Hypophosphatemia has many causes and is severe when serum phosphorous levels fall below 1.0 mg/dL. Conditions causing such low phosphate levels include prolonged respiratory alkalosis or rapid cellular uptake. Severe hypophosphatemia with total-body deficiency usually reflects poor dietary intake and/or consumption of phosphate-binding antacids.

Hypophosphatemia occurs in alcoholism (50% of hospitalized alcoholics), ketoacidosis, osmotic diuresis, acidosis, and catabolic states. Depressed intake or absorption and increased urinary losses are common causes. In chronic alcoholics, reduction of the phosphorus content of skeletal muscle occurs as a result of renal phosphate loss. The hypophosphatemic syndrome includes phosphate trapping, rhabdomyolysis, cardiomyopathy, respiratory insufficiency secondary to profound muscle weakness, erythrocyte and leukocyte dysfunction, skeletal demineralization, metabolic acidosis, and nervous system dysfunction (Table 45-12) (Table Not Available) .

Before initiating treatment, the cause should be clearly identified with measurement of arterial blood gases, ionized calcium, magnesium, potassium, and serum and urinary phosphorus. Phosphate salts such as sodium or potassium phosphate are available enterally or intravenously. Multiplying the volume of distribution (400 mL/kg) by the desired change in inorganic phosphate provides the total amount to be administered. The rate of administration should not exceed 0.25 mmol/kg IV over 4 to 6 hours to avoid hypocalcemia and tissue damage. Oral supplementation is often limited to 30 mmol/d (1 g/d) due to induction of diarrhea. Hyperphosphatemia should be avoided because it can cause hypocalcemia and crystal deposition in the eyes, heart, lung, blood vessels, and kidneys. Most hypophosphatemic patients, for example with diabetic ketoacidosis or recovering

TABLE 45-12 -- Major Causes of Hypophosphatemia

(Not Available)

Modified from Poots JT: Diseases of the parathyroid gland and other hyper-and hypocalcemic disorders. In Isselbacher KJ, Braunwald E, Wilson JD et al: Harrison's Principles of Internal Medicine. 13th ed. New York, McGraw-Hill, Inc.1995, p 2185.

from exercise, are not severely phosphorus depleted unless they have been sick for an extended time. They may typically be treated with a glass of milk (100 mg/dL or 33 mmol/L of phosphorus). After achieving normal serum phosphate levels, serum inorganic phosphate, ionized calcium, and a 24-hour urine sample should be followed to ensure that balance has been achieved.

/das/book/view/29494766/875/514.html

CHLORIDE PHYSIOLOGY

Chloride is the predominant anion in the extracellular fluid volume. Hyperchloremic, metabolic acidosis results from excess intake, and/or inadequate excretion due to renal dysfunction. When administering infusions to such patients, bicarbonate, acetate, citrate, or phosphate salts should be substituted for chloride salts.

Excess loss of chloride in gastric secretions or urine causes hypochloremic alkalosis. Chloride depletion tends to limit bicarbonate excretion, and this may be due to reduced delivery of chloride to the collecting tubules where chloride is needed for bicarbonate secretion via bicarbonate-chloride exchange. Additionally, sodium reabsorption is enhanced in chloride-depleted states, as it is generally associated with extracellular fluid volume depletion. When less chloride is available for reabsorption, a greater fraction of the sodium must be reabsorbed with bicarbonate via increased proton secretion. [49] Sodium or potassium chloride should be administered if intravascular volume depletion or hypokalemia is present. If these are not a problem, 0.1 N HCl should be administered via a central catheter. The dose of chloride is

GLUCOSE PHYSIOLOGY

Glucose is a crucial fuel source, and insulin facilitates glucose movement into cells in a process that also requires potassium and phosphate. Red blood cells, healing wounds, the brain, and the adrenal medulla require glucose for fuel, totaling approximately 2 mg/kg/min. When controlling blood glucose, close monitoring is crucial. Reagent strips containing glucose oxidase, used in conjunction with glucometers, provide rapid and reliable results. It is imperative to know the insulin regimen or oral hypoglycemic agent of each patient and then measure the blood glucose preoperatively, intraoperatively, and postoperatively. In addition the degree of end-organ damage, coronary artery disease, and autonomic neuropathy can contribute to the risk of aspiration, myocardial infarction, and peripheral neuropathy.

Hyperglycemia

Hyperglycemia (>180 to 200 mg/dL) is most often due to insulin deficiency, insulin receptor resistance, or glucose overadministration. Hyperglycemia produces osmotic diuresis, exacerbation of brain, spinal cord, [50] and renal damage by ischemia, [51] delayed gastric emptying, [52] hypophosphatemia, [52] delayed wound healing, [52] [53] and impaired white blood cell function. [53] [54] Maternal hyperglycemia increases

TABLE 45-13 -- Classification of Diabetes

(Not Available)

Modified from Foster DW: Diabetes mellitus. In Isselbacher KJ, Braunwald E, Wilson JD et al: Harrison's Principles of Internal Medicine. 13th ed. New York, McGraw-Hill, Inc., 1995, p 1980.

the risk of neonatal jaundice, the risk of neonatal brain damage, and fetal acidosis if the fetus becomes hypoxic.

Even with supramaximal levels of insulin, adults can only use glucose at a rate of 3 to 5 mg/kg/min at rest (approximately 240 mL/h of 5 percent solutions). The maximal rate of metabolism is less in stress states and more with increased metabolic rates. In general the rate of administration should be limited to 2 to 3 mg/kg/min (120 to 180 mg/kg/h), that is, 100 g/h for a 70 kg person (200 mL of a 5 percent dextrose solution/h). Healthy infants and children become hyperglycemic if 5 percent dextrose is included in maintenance fluids. [55] The maximal rate of glucose disposition in young children is 4 to 8 mg/kg/min, and the optimal rate is less than 5 mg/kg/min. [56] It is not clear that glucose administration is necessary for intraoperative management of most patients. [57]

DIABETES MELLITUS

Diabetes mellitus (Ch. 25) is the most common endocrine disease and is characterized by long-term complications involving the eyes, kidneys, nerves, and blood vessels. Diabetes is a major risk factor for heart disease, stroke, kidney disease, blindness, and nontraumatic amputations. The cause of diabetic complications is multifactorial including glycosylation of proteins and glucose reduction to sorbital, which functions as a tissue toxin. This pathophysiologic process is associated with a decrease in myoinositol content and metabolism, and with a decrease in sodium-potassium-adenosine triphosphatase activity. Hyperglycemia has been recognized as a major factor in the development of complications associated with diabetes. The patient population is not homogeneous, and several diabetic syndromes have been delineated. There are nearly 8 million diagnosed diabetics in the United States and another 8 million who are unaware of their diabetes. These numbers approach 10 percent of the overall population in this country. [58] (Table 45-13) (Table Not Available)

Management and Evaluation of Diabetes Mellitus

Treatment and evaluation of diabetes (Ch. 25) includes diet, oral hypoglycemic drugs, exercise, exogenous insulin,

TABLE 45-14 -- Classification of Insulin Preparations

(Not Available)

Modified from Stoelting RK, Dierdorf SF: Endocrine disease. In Anesthesia and Co-Existing Disease: 3rd ed. New York, Churchill Livingstone, 1993, p 340.

and weight reduction if warranted. There are a number of different insulin preparations including pork, beef, and human or recombinant. Most diabetics are prescribed a combination of a rapid-acting and intermediate-acting insulin before breakfast and before bedtime. Rebound hyperglycemia may follow a hypoglycemic reaction (the Somogyi effect). In the last decade, new therapies for new-onset insulin-dependent diabetes mellitus (IDDM) have been introduced including transplantation of pancreatic tissue as well as immunosuppression. It is important to realize that 15 percent of patients with IDDM have other autoimmune processes and that the IDDM probably is secondary to destruction of pancreatic beta cells in these instances (Table 45-14) (Table Not Available) .

Insulin therapy can result in anaphylactic and anaphylactoid reactions, especially in protamine-containing insulin preparations. Protamine-derived insulin is made from fish sperm and can cause immunologic sensitization when protamine reversal is administered after cardiopulmonary bypass or heparin reversal. [59] This protamine reaction can be devastating and includes profound hypotension, pulmonary vasoconstriction, and noncardiogenic pulmonary edema.

Successful perioperative glucose management depends on careful monitoring. Perioperative management of blood glucose during a brief surgical procedure in the diet-controlled diabetic will generally involve only monitoring of blood glucose immediately perioperatively and every 3 hours until oral intake is resumed. [60] [61] The preoperative physical examination and history may reveal extensive diabetic neuropathy, which may be seen as orthostatic hypotension, syncopal episodes, mono- or polyneuropathies, erectile or bladder dysfunction, and an electrocardiogram showing a loss of R to R variability. Patients may present with a number of additional findings including nonfamilial short stature, cerebrovascular disease, renal dysfunction, microalbuminemia, and tight waxy skin. In an estimated 30 to 40 percent of diabetic patients, glycosylation of the atlantooccipital joint may limit joint mobility and cause difficulty with airway management ("stiff-neck syndrome"). [62] [63] Laboratory evaluation of glycosylated hemoglobin (HbA_{1c}) is an accurate measure of the severity of hyperglycemia and has been shown to correlate directly with increasing rates of complications. Conversely, lower HbA_{1c} values are associated with decreased risk and can be considered a measure of the quality of the diabetic care. HbA_{1c} provides the best evidence of overall blood glucose control over the last 1 to 2 months and should replace the oral glucose tolerance test as the "gold standard" for diagnosing diabetes. [64] Basic electrolyte and renal function tests should be evaluated, especially if the patient has frequent urinary tract infections or renal impairment. [65]

The regimen selected to manage diabetics undergoing surgery depends on the severity of the diabetes and the magnitude of the surgery. Frequent glucose monitoring and preparation for insulin administration are essential for the diabetic patient requiring less than 50 units of insulin per day or oral hypoglycemic agents for control, and who requires brief surgery; and the diet-controlled diabetic having major surgery. Recommendations include discontinuation of long-acting insulin or oral hypoglycemic agents 1 to 2 days preoperatively, six evenly spaced meals per day, and short-acting insulin every 4 to 6 hours subcutaneously, with the dose adjusted according to glucose levels just before administration. Urine glucose and ketone bodies should be measured periodically.

The typical "sliding scale" is destined to fail because it involves the administration of a fixed dose after documentation of hyperglycemia. A small modification improves control. The selected dose should be administered every 4 to 6 hours, based on response. If the glucose is below 60 mg/dL, the dose should be held for at least an hour, and 50 percent dextrose IV, 0.01 to 0.02 ml/kg/min administered, with blood glucose monitored hourly. When the blood glucose is above 125 mg/dL without supplemental dextrose infusion, the next insulin dose should be 20 to 40 percent lower. If the glucose is less than 100 or is less than 125 mg/dL and falling, the scheduled dose should be maintained until the hourly measured glucose is above 125, followed by resumption with a 10 to 20 percent lower dose. If the glucose level is 100 to 200 mg/dL and stable, the current dose and interval are continued. If the glucose level is 200 to 350 mg/dL, the scheduled dose is increased by 10 to 20 percent. If the glucose level is over 350 mg/dL, the dose is increased by 20 to 40 percent.

On the day of surgery, a dextrose infusion (2 mg/kg/min) is started at the time a meal would have been ingested and glucose measured preoperatively. For patients currently receiving insulin, an insulin infusion (0.25 units/mL) is started at a rate of 0.5 to 1.25 units/h, depending on the amount of insulin normally administered and the current glucose level. Blood glucose is monitored hourly and the infusion rate adjusted to maintain glucose 100 to 200 mg/dL. After the blood glucose is stable, urine glucose and ketone bodies are checked to ensure that glycosuria due to a low threshold will not confuse interpretation of urine output.

A more intense monitoring and treatment regimen is recommended for (1) patients requiring more than 50 units/d for control, (2) diabetics in poor control, or (3) the insulin-treated

diabetic undergoing major surgery. Long- and intermediate-acting insulin is discontinued, and the patient is managed with an intravenous insulin infusion or scheduled subcutaneous insulin perioperatively. Oral intake must be stopped 12 hours before anesthesia because some element of gastroparesis will exist in these patients. Typically, patients are administered a histamine $_2$ -blocker along with a gastric-emptying drug such as metoclopramide the night before and the morning of surgery.

The gastrointestinal tract is a prime target for autonomic neuropathy, and there may be esophageal dysfunction with difficulty swallowing, constipation, or diarrhea. When oral intake stops, maintenance fluids containing dextrose at 2 mg/kg/min are started and should be continued throughout the procedure. Glucose is measured before induction and hourly until stable postoperatively. Urinary ketones are measured every 6 hours. An insulin infusion is started with an initial rate of 1 to 2 units/h, or to match the amount administered hourly the previous day if good control was achieved. Patients with obesity, liver disease, steroid therapy, or severe infection require higher doses. Glucose levels should be maintained at 100 to 200 mg/dL and urinary ketones negative. Extremely high rates (up to 80 units/h) may be required during stressful procedures (e.g., cardiopulmonary bypass). [66] When the glucose level has remained stable and within the desired range for 3 hours, the frequency of glucose measurement can be decreased.

Provided a patient has reasonable glucose control (<250 mg/dL), an alternative to an infusion would be to hold all short-acting insulin and give half the intermediate or long-acting insulin the morning of the surgery. It is imperative to provide close preoperative, intraoperative, and postoperative glucose and electrolyte monitoring. Additionally, careful titration of a D_5W drip with an initial intravenous rate of 75 mL/h will prevent hypoglycemia or hyperglycemia. Diabetic ketoacidosis, dehydration, impaired wound healing, and electrolyte imbalance are minimized with the proper use of exogenous insulin. There is no clear consensus either to the method of insulin therapy or the exact range of blood glucose that will affect morbidity or mortality. [67] If a general anesthetic is used, clinical consideration would include a rapid-sequence induction owing to the high rate of gastroparesis. Cerebrovascular accidents, peripheral vascular disease, and cardiovascular infarction are 2- to 10-fold more common in diabetics. Strategies designed to reduce the risk of labile blood pressures and myocardial ischemia related to autonomic or vascular disease might include beta-blockade to blunt the stress of induction, a narcotic based anesthetic to minimize cardiopulmonary depression, and prophylactic nitroglycerin in these patients with their significant risk of coronary artery disease. Commonly associated conditions include obesity and stiff cervical joints, which may make airway management challenging. Associated cardiovascular conditions often result in the need for additional invasive monitoring.

Diabetic Ketoacidosis

Diabetic ketoacidosis is an emergent condition that often presents in the diabetic patient with leukocytosis and an acute surgical abdominal emergency and/or with nausea, vomiting, lethargy and signs of hypovolemia. The priorities are to restore intravascular volume (usually 1 L of saline IV rapidly), administer regular insulin (0.2 units/kg) followed by an infusion at a rate of 0.1 units/kg/h, eliminate the ketonemia, control blood glucose, and correct the underlying problem (e.g., antibiotics for urosepsis or pneumonia). Patients with ketoacidosis are dehydrated as a result of glucosuria; because the dehydration is due to water and electrolyte loss, colloids are not indicated. If the patient's osmolality is elevated, 0.45 percent sodium chloride can be administered, and the volume administered should be guided by the hemodynamic response and urinary output. When the blood glucose falls below 300 mg/dL, dextrose should be added to the fluids. Urine ketones are monitored every 2 hours after the blood glucose is within 100 to 200 mg/dL. If ketones are still present, the rate of glucose and insulin infusions should both be increased. The osmotic diuresis promotes loss of sodium, potassium, magnesium, and phosphate. Despite total body deficiencies, however, their concentrations may be elevated at the time of presentation owing to severe water loss. Alternatively, severe hyperglycemia may extract water from the intracellular space and may dilute the electrolyte concentrations. If the initial potassium is elevated or the patient is anuric, potassium should not be administered. As hydration improves and urinary output increases, potassium, magnesium, and phosphorous should be administered and monitored frequently. In general, the acidosis per se should not be treated with buffers. The ketoacidosis will correct as insulin and glucose levels improve, and the lactic acidosis resulting from poor perfusion will respond to intravascular fluid replacement. If the pH approaches 7.15, the bicarbonate ion concentration is less than 10 mEq/L and hypotension fails to respond to intravascular fluid administration, sodium bicarbonate therapy may be required.

Hypoglycemia

Hypoglycemia (<50 mg/dL) is dangerous, as glucose is the sole fuel source for much of the brain. Threshold levels depend on age range. Signs of hypoglycemia include irritability, seizures, bradycardia, hypotension, and respiratory failure. Symptoms commonly occur in adults at blood glucose concentrations below 57 mg/dL or 30 to 50 mg/dL in infants. Symptoms are seen at higher levels in diabetics than in nondiabetics and are obscured by general anesthesia. A biochemical stress response occurs at about 70 mg/dL, including sympathetic nervous system stimulation and elevated growth hormone and/or cortisol levels. Neurologic and electroencephalographic depression appears at 50 to 55 mg/dL in nondiabetics and 70 to 85 mg/dL in diabetics. [68] Selective neuronal necrosis, not infarction, occurs in the caudate, putamen, and cortex. There is a compensatory increase in cerebral blood flow. During labor, maternal starvationinduced ketosis has adverse fetal effects, including fetal ketonemia, hypoxia, and fetal lactic acidosis. [69] Neonates are at an increased risk for hypoglycemia because of limited glycogen stores and from large amounts of fetal insulin production in response to gestational hyperglycemic states. Adults are also at risk of hypoglycemia from either inadequate gluconeogenesis coupled with inadequate nutritional intake, or from excess insulin (e.g., due to an insulinoma, pancreatic islet cell adenoma or carcinoma, or iatrogenic overadministration).

Hypoglycemia can also follow too abrupt cessation of dextrose infusion during total parenteral nutrition (reactive hyperinsulinemic states). Inadequate gluconeogenesis occurs in liver failure, cortisol deficiency (primary or secondary), inadequate glucagon response, growth hormone deficiency, and during beta-adrenergic blockade. Fasting in women is likely to produce hypoglycemia in 24 hours, whereas men tolerate about 72 hours of fasting. [52] The incidence of hypoglycemia in healthy infants and children is low (2 of 446) with 4 to 8 hours of fasting. [56] Fetal hypoglycemia occurs if maternal glucose is greater than 150 mg/dL, because glucose crosses the placenta, inducing fetal insulin secretion. Treatment consists of an intravenous bolus of 5 g of dextrose followed by increasing the rate of dextrose infusion by 1 to 2 mg/kg/min.

ACID-BASE FACTORS

The necessity for treating a metabolic acidosis is judged largely on clinical grounds, with the metabolic acid level base excess (BE) used to determine the correct dose of bicarbonate (Ch. 38) . This prediction is based on the size of the treatable space and the magnitude of the problem:

The dose calculated will be sufficient to return the metabolic disturbance to about zero. However, bicarbonate therapy is reserved for emergencies and situations in which indications for therapy are compelling. It is usual to give a reduced dose, about half, because:

1. The bicarbonate is injected initially into the plasma volume, about 3 L, instead of into the calculated treatable space, 21 L.
2. When bicarbonate is added to acid it "fizzes." Fortunately, this does not occur literally in the blood. Nevertheless, the majority of the bicarbonate is converted to carbon dioxide and has to be eliminated. For each 100 mEq that is converted, about 2.24 L of carbon dioxide has to be exhaled, equivalent to 10 minutes of normal production.
3. The carbon dioxide that is produced enters the cells freely, unlike the bicarbonate ions that have been administered. Therefore, the inside of the cell might initially become even more acid. However, direct studies with nuclear magnetic resonance have not confirmed this (Severinghaus, personal communication 1986).
4. The bicarbonate is accompanied by sodium ions that will be responsible for a residual increase in the osmolality of the extracellular fluid. In combination with other therapy, such as intravenous glucose, the hyperosmolality may be critical and cause coma. In neonates, rapid infusion of bicarbonate may cause intracranial hemorrhage.
5. If the body deals with its metabolic acidosis there is a residual metabolic alkalosis.

Anion Gap

Some causes of metabolic acidosis release anions into the extracellular fluid that are not normally measured. When this occurs, there is an unexpected discrepancy between the sums of the principal cations and anions. The usual sum is the following:

When there are any additional, unmeasured anions, they become part of the "gap," which is then correspondingly larger. A gap greater than 30 suggests that there is an increase in the concentration of the unmeasured anions. Unfortunately, this method relies on the accuracy of the other measurements. Small errors in these large numbers cause a proportionately greater error in the result. If information is required about these anions, it is more appropriate to measure their concentration. In practice it suffices to analyze lactate in tissue hypoxia, 3-hydroxybutyrate in diabetic ketosis, and phosphate or sulfate in renal failure.

The common causes of perioperative metabolic alkalosis include antacid therapy, incidental administration of citrate with blood products, $NaHCO_3$ administration, gastric drainage, or renal bicarbonate retention owing to diuresis, or in compensation for respiratory acidosis. NaCl or KCl can be administered orally or via a peripheral intravenous catheter, or 0.1 normal HCl may be administered slowly through a central venous catheter. The required dose is calculated as follows:

CLINICAL ACID-BASE BALANCE DISTURBANCES

This section provides practical clinical cases and examples which can be reviewed to assist in understanding acid-base balance.

Metabolic Acidosis Resulting From Low Cardiac Output

A patient with coronary artery disease and an ejection fraction of 15 percent suffers myocardial perforation while undergoing balloon angioplasty in the cardiac catheterization laboratory. After resuscitation, intubation, insertion of an arterial line, and initiation of dopamine by infusion, the patient is transferred to the operating room for emergency thoracotomy. Blood pressure is 80/50 mm Hg, and the heart rate is 120 beats/min. During preparation for central venous cannulation, the blood pressure falls, followed by cardiac arrest. The patient undergoes immediate thoracotomy; blood gases obtained at the time reveal: pHa = 7.15, Pa $_{CO_2}$ = 35 mm Hg, BE = -15 mEq/L, bic = 12, Pa $_{O_2}$ = 90 mm Hg--a severe metabolic acidosis with mild respiratory alkalosis. After the administration of four units of packed red cells and the administration of 88 mEq of sodium bicarbonate, repeat blood gases reveal: pHa = 7.14, Pa $_{CO_2}$ = 39 mm Hg, BE = -14 mEq/L, bic = 13, Pa $_{O_2}$ = 95 mm Hg--still a severe metabolic acidosis but now with no respiratory alkalosis.

Clinical Pearl.

The first blood gas reveals a metabolic acidosis attributable to the low cardiac output with tissue ischemia, with slight hyperventilation. The second blood gas shows almost no benefit from the bicarbonate probably due to the continuing low cardiac output. Bicarbonate is converted to CO_2, which could explain the slightly higher Pa $_{CO_2}$.

Metabolic Acidosis During Anhepatic Phase

A patient with end-stage liver disease secondary to viral hepatitis is undergoing orthotopic liver transplantation. Blood gas analysis performed late in the anhepatic phase (Ch. 55) , after earlier administration of bicarbonate, reveals: pHa = 7.10, Pa $_{CO_2}$ = 28 mm Hg, BE = -18 mEq/L, bic = 8.6, Pa $_{O_2}$ = 260 mm Hg, Na^+ = 153 mEq/L--a severe metabolic acidosis with a moderate respiratory alkalosis. The patient is treated with 500 mL (150 mEq, 18 g) of 0.3 molar solution of tris(hydroxymethyl)-aminomethane (THAM) by infusion over 20 minutes. Repeat blood gas analysis shows: pHa = 7.09, Pa $_{CO_2}$ = 30 mm Hg, BE = -18 mEq/L, bic = 9.0, Pa $_{O_2}$ = 251 mm Hg, Na^+ = 154 mEq/L. A second dose of THAM is administered by infusion. After the transplantation is completed, blood gas analysis shows: pHa = 7.30, Pa $_{CO_2}$ = 33 mm Hg, BE = -9 mEq/L, bic = 16, Pa $_{O_2}$ = 283 mm Hg, Na^+ = 149 mEq/L--a marked metabolic acidosis with a mild respiratory alkalosis typical of a partially compensated metabolic disturbance.

Clinical Pearl.

The metabolic acidosis during the anhepatic phase demonstrates the importance of the liver in metabolizing lactate to bicarbonate. The high sodium mitigated against repeat administration of sodium bicarbonate. In this case, THAM was used to minimize sodium administration while controlling the metabolic acidosis. On reperfusion (phase 3), the new liver started to function, and there was improvement in the metabolic acidosis.

Metabolic Alkalosis Following Diuretics

A 4-kg male infant aged 3 months presents for repair of an atrioventricular canal (Ch. 50) . The patient's congenital heart failure has been controlled with digitalis and furosemide. Before induction of anesthesia, the blood gases were: Pa $_{O_2}$ = 110 mm Hg, pHa = 7.53, Pa $_{CO_2}$ = 44 mm Hg, bic = 35.9, BE = 14 mEq/L--a severe metabolic alkalosis with a minimal respiratory acidosis typical of a partially compensated metabolic disturbance. Following induction of anesthesia, blood gas analysis showed: pHa = 7.61, Pa $_{CO_2}$ = 35 mm Hg, BE = 14Eq/L, bic = 34, Pa $_{O_2}$ = 60 mm Hg. Following completion of the procedure and cessation of cardiopulmonary bypass, the blood gases showed: pHa = 7.40, Pa $_{CO_2}$ = 33 mm Hg, BE = -4 mEq/L, bic = 20.

Clinical Pearl.

The hypochloremic alkalosis that accompanies prolonged administration of furosemide explains the first set of results. After induction the hyperventilation decreased the Pa $_{CO_2}$ but had no effect on the base excess. Two major factors explain the change during the procedure: (1) hemodilution tends to return the pHa toward neutral (6.8 at body temperature) and (2) low perfusion during bypass frequently produces a metabolic acidosis which, in this case, also helped to overcome the initial metabolic alkalosis.

Chronic Respiratory Failure in a Neonate

A 3.5 kg male infant aged 2½ months with bronchopulmonary dysplasia is intubated and receiving oxygen (F $_{IO_2}$ = 0.3). He presents for cryoablation for proliferative retinopathy (Chs. 58 and 59). After the patient was transported to the operating room, blood gas analysis showed: pHa = 7.27, Pa $_{CO_2}$ = 65 mm Hg, BE = 3 mEq/L, bic = 29, Pa $_{O_2}$ = 35 mm Hg. Anesthesia is induced, and ventilation is controlled with a V_T of 60 mL, peak inspiratory pressure = 25 cm H_2O, positive end-expiratory pressure = 4 cm H_2O, respiratory rate = 40 breaths/min, no inspiratory pause, F $_{IO_2}$ = 0.3. Repeat blood gases show: pHa = 7.36, Pa $_{CO_2}$ = 50 mm Hg, BE = 3 mEq/L, bic = 28, Pa $_{O_2}$ = 48 mEq/L.

Clinical Pearl.

The mild metabolic alkalosis of the first analysis is compatible with compensation for chronic respiratory failure. The high Pa $_{CO_2}$ represented hypoventilation during transport. Appropriate selection of the ventilator settings returned the Pa $_{CO_2}$ to a value more typical for a neonate with bronchopulmonary dysplasia with a pHa about half way between no compensation and complete compensation.

Preparation for Chronic Hyperventilation

The author (AK) was a member of a team providing plastic surgery at high altitude. For two days preceding the trip, he was advised to take a carbonic anhydrase

inhibitor, acetazolamide, which would effectively slow the normal reversible reaction between carbonic acid and its dissociation products, carbonic acid and water. The effect of this drug is to alkalinize the urine and produce a moderate metabolic acidosis, the typical response to hypoxic hyperventilation at altitude. A typical blood gas after acclimatization to altitude might be: pHa = 7.42, Pa CO_2 = 31 mm Hg, BE = 4 mEq/L, bic = 19, Pa O_2 = 80 mm Hg.

Clinical Pearl.

The benefit of taking acetazolamide is debated by climbers, and the drug is not without side effects. During the initial experience of taking acetazolamide at sea level, a striking, if minor, side effect is the metallic taste associated with drinking any carbonated beverage, presumably attributable to the inability to convert the high CO_2 content in the beverages to carbonic acid.

Acute Hyperventilation and Hypotension

An elderly female, height 5 ft, weight 48 kg, blood pressure 115/75 mm Hg, heart rate 70 bpm, receiving no medications and in otherwise normal health, was scheduled for laparotomy and hysterectomy. After induction and orotracheal intubation, controlled ventilation was initiated with a tidal volume of 900 mL and a respiratory rate of 12 breaths/min. Shortly before incision, arterial blood pressure was 58/35 mm Hg and the end-tidal P CO_2 was 22 mm Hg. (Blood gases were not drawn, but typical values for a patient experiencing such acute hyperventilation would be: pHa = 7.53, Pa CO_2 = 26 mm Hg, bic = 21 mg/L, BE = 0 mg/L). The ventilator was immediately reset to provide 4 breaths per minute at a tidal volume of 500 mL. Arterial blood pressure about 2 minutes later was 85/55 mm Hg, and the next reading about 2 minutes later still was 95/65 mm Hg. The patient's end-tidal P CO_2 increased more slowly, and after about 8 minutes had returned to 36 mm Hg when the ventilatory rate was increased to 8 breaths/min. (Typically her blood gases would now be near normal, e.g., pHa = 7.44, Pa CO_2 = 38 mm Hg, bic = 23.3 mEq/L, BE = 0 mg/L).

Clinical Pearl.

Hyperventilation following induction is common and frequently contributes to hypotension by various methods including raised intrathoracic pressure, diminished venous return, and depressed cardiac output.

Acute Hypoventilation

An obese middle-aged female was undergoing laparoscopic cholecystectomy. After a routine induction and orotracheal intubation, low flow anesthesia was initiated and the ventilator was set to provide a tidal volume of 700 mL at a rate of 10 breaths/min (measured exhaled tidal volume was 560 mL). Ten minutes after induction of anesthesia, the P CO_2 was 35 mm Hg, the peak airway pressure was 28 mm Hg. Arterial blood gases drawn then showed: pHa = 7.43, Pa CO_2 = 35 mm Hg, bic = 22.4, BE = -1 mEq/L. Thirty minutes into the procedure, the peak airway pressure was 48 mm Hg, the end-expired P CO_2 was 49 mm Hg, and the measured exhaled tidal volume was 380 mL. Repeat blood gases showed: pHa = 7.27, Pa CO_2 = 55 mm Hg, bic = 24.9, BE = -1 mEq/L. The principal abnormality is a marked respiratory acidosis with no metabolic acidosis. It is characteristic of an acute respiratory disturbance.

Clinical Pearl.

The rise in Pa CO_2 can be attributed to two factors: (1) uptake of the inflating gas, CO_2, in the abdomen and (2) reduction of effective ventilation due to raised airway pressure required to overcome abdominal distention. The discrepancy between end-tidal P CO_2 and arterial blood gas Pa CO_2 is typical and results from the patient's temperature being slightly less than that of the analyzer, lack of time between breaths to reach true end-tidal equilibration, normal pulmonary maldistribution, and the slight loss occurring on the length of the tubing.

FLUID BALANCE AND FLUID REPLACEMENT SOLUTIONS

More than 22 million blood components are transfused each year in the United States, [70] many to surgical and obstetric patients. The transfusions of red blood cells, platelets, fresh frozen plasma, and cryoprecipitate have the potential for improving clinical outcomes in perioperative and peripartum settings. Benefits include improved tissue oxygenation and decreased bleeding; however, transfusions are not without risks or costs. Transmission of infectious diseases (e.g., hepatitis, human immunodeficiency virus infection), hemolytic and nonhemolytic transfusion reactions, immunosuppression, alloimmunization, and other complications are potential sequelae of blood component therapy. Although red blood cells and coagulation products have excellent volume-expanding capacity, they are not considered in this chapter (Ch. 46) .

In 1994, the American Society of Anesthesiologists convened the Task Force on Blood Component Therapy to develop evidence-based guidelines on the proper indications for perioperative and peripartum administration of red blood cells (RBCs), platelets, fresh frozen plasma, and cryoprecipitate. This section details only basic crystalloid, colloid, and hypertonic solution recommendations applicable to typical surgical and obstetric patients. Infants, children, and special clinical settings are found elsewhere in this book (Ch. 59) (Table 45-15) .

SURGICAL FLUID BALANCE

Physiologic changes during surgery and anesthesia lead to shifts in fluid balance. For example, epidural, spinal, or caudal anesthesia may all cause variable amounts of sympathetic blockade. Although younger and healthier patients may tolerate sympathectomy, patients who are severely dehydrated, or on antihypertensive drugs or diuretics, may not be able to respond to the effects of sympathectomy. It is common to administer up to 1 L of fluid before placement of a spinal or to concurrently administer fluid when epidural anesthesia is being induced. Vasopressors, typically ephedrine or phenylephrine, are needed to overcome the hemodynamic effects of sympathetic block.

Although inhaled anesthetics do not directly alter fluid losses, all anesthetics may blunt the normal physiologic responses to hypovolemia and the stress response. The stress response to surgery involves an increase in antidiuretic hormone production, which can be blocked with anesthetics. Superimposed are the variable effects of intravenous and inhalational agents on the myocardium, venous return, blood pressure, and the vasculature. Mechanical ventilation can decrease the release of atrial natriuretic hormone and increase the release of antidiuretic hormone resulting in retention of sodium and fluids.

In addition to blood loss, significant third space loss may occur, which essentially involves fluid that is still in the body but not contributing to intravascular volume, oxygen delivery, or waste removal; this is difficult to measure. Simple restoration of blood volume can be inadequate to ensure survival. [71] Patients undergoing major surgical procedures

TABLE 45-15 -- Composition of Replacement Fluids

	NA mEq/L	K mEq/L	DEXTROSE g/L	Osm	pH	OTHER
Whole blood in CPD [a]	168-156	3.9-21.0			7.20-6.84	Hct = 35-40
PRBC, AS-1	117	?-49	552		6.6	Hct = 59
PRBC, CPD		?-95			6.6	Hct = 77
PRBC, CPDA-1	169-111	5.1-78.5			7.55-6.71	Hct = 65-80
FFP	15.4					
5% albumin	145 ± 15	<2.5	0	330	7.4	COP = 32-35 mm Hg
2.5% albumin	145 ± 15	<2.0	0	330		
Plasmanate	145 ± 15	<2.0			7.4	COP = 20 mm Hg
10% Dextran 40	0	0	50	255	4.0	
Hetastarch	154	0	0	310	5.9	
0.9% NaCl	154	0	0	308	6.0	
Ringer lactate	130	4.0	0	273	6.5	Lactate = 28
5% Dextrose	0	0	50	252	4.5	
D_5 LR	130	4.0	50	525	5.0	
D_5 0.45%	77	0	50	406	4.0	
Normosol	140	5.0	100	555	7.4	Mg = 3, acetate = 27 gluconate = 23
Normosol M	40	13	50	363	5.0	Mg = 3, acetate = 16
Normosol R	140	5.0	0	294	6.6	Mg = 3, acetate = 27 gluconate = 23
D_5 Normosol R	140	5.0	0	547	5.2	Mg = 3, acetate = 27 gluconate = 23
Normosol R pH 7.4	140	5.0	0	295	7.4	Mg = 3, acetate = 27 gluconate = 23

[b] Fructose substituted for dextrose

Hct, hematocrit; PRBC, packed red blood cells; D_5 LR, 5% dextrose in Ringer lactate; FFP, fresh frozen plasma; D_5 0.45% NaCl, 5% dextrose in 0.45% NaCl

[a] The range of values refers to concentrations on day 1 and day 21 (CPD), 35 (CPDA-1), or 42 (AS-1) of storage.

require fluid replacement beyond simple blood loss, and the anesthesiologist plays a vital role in assessing and ultimately administering appropriate fluid therapy in intraoperative and postoperative clinical settings.

Crystalloids

Crystalloids are fluids that contain water and electrolytes. They are grouped as balanced, hypertonic, and hypotonic salt solutions. Crystalloid solutions are used to both provide maintenance water and electrolytes and expand intravascular fluid. The replacement requirement is 3- or 4-fold the volume of blood lost because administered crystalloid is distributed in a ratio 1:4 like extracellular fluid, which is composed of about 3 L intravascularly (plasma) and about 12 L extravascularly (i.e., about 20% should remain in the intravascular space).

Balanced Salt Solutions

Balanced salt solutions have an electrolyte composition similar to extracellular fluid (ECF), (e.g., lactated Ringer solution, Plasma-Lyte, and Normosol). With respect to sodium, they are hypotonic. A buffer is included in place of bicarbonate, which hydrates to carbonic acid, with production of carbon dioxide, which diffuses from the solution. Compared with 0.9 percent NaCl, these solutions provide small quantities of other electrolytes, which are inadequate to meet daily maintenance requirements.

Normal Saline

Normal saline, 0.9 percent NaCl, is isotonic and isoosmotic but contains more chloride than ECF. When used in large volumes, mild hyperchloremia (non-anion gap metabolic acidosis) results. It contains no buffer or other electrolytes. It is preferred to lactated Ringer solution (which contains a hypotonic concentration of sodium) when brain injury, hypochloremic metabolic alkalosis, or hyponatremia is present. Many patients with hyperkalemia, including patients with renal failure who are frequently in the operating room for vascular access bypass procedures, routinely receive normal saline, as it contains no potassium.

Hypertonic Salt Solutions

These solutions are less commonly used, and their sodium concentrations range from 250 to 1,200 mEq/L. The greater the sodium concentration, the less the total volume required for satisfactory resuscitation. This difference reflects the movement due to osmotic forces of water from the intracellular space into the extracellular space. In addition the reduced volume of water injected may reduce edema formation. This could be crucial in patients predisposed to tissue edema (e.g., prolonged bowel surgery, burns, brain injuries). Clinical studies have confirmed that a moderately hypertonic solution (Na = 250 mEq/L) can be associated with lower muscle interstitial pressure than lactated Ringer solution. Additionally, bowel function returned earlier, although pulmonary shunt fraction was no different. [72] Experimental

studies have demonstrated lower intracranial pressures in animals receiving hypertonic solutions. However, the intravascular half-life of hypertonic solutions is no longer than isotonic solutions of an equivalent sodium load. In most studies, sustained plasma volume expansion was achieved only when colloid was present in the resuscitation solution. Moreover, the osmolality of these solutions can cause hemolysis at the point of injection. [73] Hypertonic solutions have not gained widespread acceptance as resuscitation or intraoperative maintenance solutions, and these solutions are used primarily in the correction of hyponatremia.

Five Percent Dextrose

Five percent dextrose functions as free water, because the dextrose is metabolized. It is iso-osmotic and thus does not cause the hemolysis that would occur if pure water were injected intravenously. It may be used to correct hypernatremia, but is most often used in the prevention of hypoglycemia in diabetic patients who have had insulin administered.

Crystalloids Versus Colloids

Much controversy exists about the role of crystalloids and colloids (Ch. 45) in fluid therapy. Proponents of colloid fluid point out that resuscitation with crystalloid solution dilutes the plasma proteins, with a subsequent reduction of plasma oncotic pressure resulting in fluid filtration from the intravascular to the interstitial compartment and the development of interstitial pulmonary edema. Proponents of crystalloid solutions have argued that albumin molecules normally enter the pulmonary interstitial compartment freely and then are cleared via the lymphatic system returning to the systemic circulation. Thus, additional albumin should merely increase the albumin pool cleared by the lymphatics. A review of the literature by Moss and Gould [74] confirmed that all unflawed clinical and experimental studies showed that isotonic solutions are effective plasma volume expanders for resuscitation without the addition of a variety of colloid fluids. The additional cost and potential risks of colloids compared with crystalloids is another argument against colloid administration.

Colloids used in the United States include albumin, hydroxyethyl starch (hetastarch), and dextran. Because the molecules are large, colloids usually do not cross capillary membranes and remain intravascular. Distribution of fluid throughout the body is represented by the Starling-Landis equation:

where J_v represents the net volume of fluid moving across the capillary wall per unit of time (cubic microns per minute); K_h is the hydraulic conductivity for water, which is the fluid permeability of the capillary wall, expressed as cubic microns per minute per square micron of capillary surface area per mm Hg pressure difference. The value of K_h increases up to 4-fold from the arterial to the venous end of a typical capillary. P_{MV} is the capillary hydrostatic pressure; P_T is the tissue hydrostatic pressure; A is the capillary surface area; delta is the reflection coefficient for plasma proteins. This coefficient is necessary because the plasma proteins are slightly permeable to the microvascular wall, preventing full expression of the two colloid osmotic pressures. When delta is 0, molecules freely cross the membrane; when delta is 1, molecules cannot cross the membrane. Typical delta values for plasma proteins in the microvasculature exceed 0.9 in most organs, and these values remain constant but can be decreased significantly by pathophysiologic processes including hypoxia, inflammatory processes, and tissue injury. COP_{MV} is the colloid oncotic pressure; and COP_T is the colloid oncotic pressure in the tissue.

The hydrostatic and colloid pressure differences across capillary walls (Starling forces) cause movement of water and dissolved solutes into the interstitial spaces. These movements play a minor role with regard to tissue nutrition relative to simple diffusion. The reflection coefficient that expresses the ability of the semipermeable membrane to prevent movement of a solute varies greatly among tissues. The lungs are moderately permeable relative to other organs and during pathophysiologic processes such as surgical trauma, the reflection coefficient may further change to alter capillary permeability, resulting in increased capillary permeability or leak. In this setting, colloids move more easily into the interstitium and increase interstitial edema.

With leakage of colloid molecules into the interstitial space, further swelling of tissues occurs due to the unfavorable oncotic pressure gradient, and these molecules are removed by the lymphatic system. Removal of colloids requires longer periods than for crystalloids and is a significant problem in burn and major surgical patients. A well-known meta-analysis is by Velanovich [74A] of mortality from eight studies concluded that trauma patients should be resuscitated with crystalloid solutions, whereas colloids were more effective in nonseptic, nontraumatic elective surgical patients.

COLLOID SOLUTIONS AND BLOOD SUBSTITUTES

Colloid solutions are generally administered in a volume equivalent to the volume of blood lost (Ch. 46) . The initial volume of distribution is equivalent to the plasma volume. The half-life in circulation of albumin is normally 16 hours, but it can be as short as 2 to 3 hours in pathophysiologic conditions. [75] The synthetic colloids, processed albumin, and protein fractions have minimal if any risk of infection. Blood substitutes are useful to restore intravascular fluid volume temporarily until definitive treatment can be established. They are inexpensive, have a long storage life, and lack the risk of transmitting viral diseases.

Five Percent Albumin

Five percent albumin or plasma protein fractions (e.g., Plasmanate) have a colloid osmotic pressure of about 20 mm Hg (i.e., near-normal colloid osmotic pressure). Preparation methods eliminate infectious agents. These solutions are chosen when crystalloids fail to sustain plasma volume for

more than a few minutes owing to low colloid osmotic pressure. These solutions are most appropriate when there is an abnormal loss of protein from the vascular space, for example, in peritonitis or in extensive burns.

Twenty-Five Percent Albumin

A colloid solution of 25 percent, or "salt-poor," albumin contains purified albumin at five times the normal concentration. When administered, it has the potential to expand the plasma volume by up to five times the volume provided. It is selected when the current plasma volume is diminished, but blood pressure is acceptable, and the total extracellular fluid volume is expanded.

Six Percent Dextran 70

Dextran is available as either dextran 40 or dextran 70. The numbers 40 and 70 refer to the average molecular weight of the molecules in the solution. The mean molecular weight of dextran 40 is about 40,000, and the mean molecular weight of dextran 70 is about 70,000. The dextran solutions are water-soluble glucose polymers synthesized by certain bacteria from sucrose. Both dextran solutions are ultimately degraded enzymatically to glucose. A colloid solution of 6 percent Dextran 70 is administered for the same indications as 5 percent albumin. Dextran 40 is used in vascular surgery to prevent thrombosis and is rarely used as a volume expander.

Side effects include anaphylactic or anaphylactoid reactions in about 1 in every 3,300 administrations, increased bleeding time caused by decreased platelet adhesiveness (at doses of 20 mL/kg/24 h), rouleaux formation (interfering with cross-matching of blood), and rare cases of noncardiogenic pulmonary edema thought to be a direct toxic effect on pulmonary capillaries following intravascular absorption. [76] [77]

Hydroxyethyl Starch

Hydroxyethyl starch (hetastarch) is a synthetic colloid solution in which the molecular weight of at least 80 percent of the polymers ranges from 10,000 to 2,000,000. It is available in the United States as a 6 percent solution in 0.9 percent sodium chloride (Hespan). The pH of hetastarch is about 5.5 and the osmolarity is near 310 mOsm/L. The larger molecules are degraded enzymatically by amylase. It is stored in the reticuloendothelial system for several hours and is believed to be ultimately renally excreted. It produces dilutional effects similar to other volume expanders and also reduces factor VIII:C levels by 50 percent in a dose of 1 L with prolongation of the partial thromboplastin time. [78] Hetastarch can also interfere with clot formation by direct movement into the fibrin clot by the hetastarch molecules. In clinically recommended volumes, (i.e., 20 mL/kg), there is minimal interference with subsequent crossmatching. Repeated doses can result in accumulation and side effects, which include allergic reactions and bleeding as described with higher doses (20 to 25 mL/kg.)

Pentastarch

Pentastarch is a lower molecular weight hetastarch with less hydroxyethyl groups per molecule. It is currently undergoing clinical trials in the United States and has similar anticoagulant effects as hetastarch.

Perfluorochemical Emulsions and Stroma-Free Hemoglobin

Perfluorochemical emulsions have linear oxygen-carrying capacity but are insufficient to sustain human cellular function and therefore are not clinically useful at this time. [79] Stroma-free hemoglobin solutions are produced by processing human or animal red blood cells. Initial studies of stroma-free hemoglobin have shown potential harm in renal function and are not approved for clinical use, although these compounds have similar oxygen-carrying capacity as normal hemoglobin.

FLUID MANAGEMENT OF SPECIFIC CLINICAL CONDITIONS

The following guidelines are intended to facilitate initiating therapy, but the choice of fluid and rate of administration must be adjusted to achieve physiologic goals (i.e., the guidelines below are *a* starting point (not *the* starting point) for patients without other major comorbidity of vital organs. Careful observation of the patient's response forms the basis for ongoing modification in a continuous feedback loop.

Routine Maintenance Fluids

Routine maintenance fluids for a 70-kg postoperative patient include the following. The patient requires 110 mL H_2O and 110 kcal/h, or 2,640 mL and 2,640 kcal/d. This example is based on the 4-2-1 rule (Table 45-16) , which provides a close approximation of water requirements. The sodium requirement (1.5 mEq/kg/d) is dissolved in the daily fluid requirement of 2.64 L; 100 mEq/kg/d requirement for potassium is placed in the 2.64 L/d water requirement: 100 mEq K/2.64 L = 42 mEq/L. However, the potassium concentration needs to be limited if the fluid is to be infused into a peripheral vein because of the chemical irritation induced

TABLE 45-16 -- Example of Calculations of Fluid Requirements by the 4-2-1 Rule [a]

BODY WT (kg)	FLUID RATE (mL/kg)	WEIGHT CATEGORY (kg)	FLUID (mL/h)
0-10	4	10	40
11-20	2	10	20
21+	1	5	5
Total	--	25	65

[a] Assumes a patient weighing 25 kg, resulting in an estimated fluid requirement of 65 mL/h

TABLE 45-17 -- Volume and Composition of Gastrointestinal Fluids

	24-HR VOLUME mL	NA^+ mEq/L	K^+ mEq/L	CL^- mEq/L	HCO_3^- mEq/L
Saliva	500-2,000	2-10	20-30	8-18	30
Stomach	1,000-2,000	60-100	10-20	100-130	0
Pancreas	300-800	135-145	5-10	70-90	95-120
Bile	300-600	135-145	5-10	90-130	30-40
Jejunum	2,000-4,000	120-140	5-10	90-140	30-40
Ileum	1,000-2,000	80-150	2-8	45-140	30
Colon	--	60	30	40	--

by high concentrations of potassium. The obligatory glucose needs of the brain and RBCs consume roughly 2 mg/kg/min glucose. Dextrose contains 3.41 kcal/g instead of 4 kcal/g of glucose, so about 17 percent more dextrose than glucose is required. If carbohydrate is not provided, glycogenolysis and gluconeogenesis from amino acid pools will provide the necessary glucose, but will accelerate protein catabolism.

Thus, carbohydrate is said to prevent catabolism (i.e., protein sparing); however, the benefit of this dose of dextrose is not clear. Total starvation may be preferable because insulin concentrations decrease to very low levels, facilitating lipolysis as a caloric source. The osmolarity of 7.5 percent dextrose is 417 mOsm/L, to which one adds 156 mOsm/kg H_2O, resulting in a highly hyperosmolar solution. A compromise between the need for glucose and hyperosmolality has been 5 percent dextrose.

If there are other losses (e.g., gastric drainage), additional sodium and water are required. Gastric drainage of 0.5 L/d will lose 30 to 50 mEq of sodium and 50 to 65 mEq of chloride (Table 45-17) . When these are added to the maintenance fluid, the concentration approximates 0.45 percent NaCl. This solution is commonly used as a maintenance intravenous fluid postoperatively in patients with nasogastric drainage.

Routine Intraoperative Administration

The goals of intraoperative fluid administration are to maintain adequate oxygen delivery, normal electrolyte concentrations, and normoglycemia. The total fluid requirement is composed of compensatory intravascular volume expansion (CVE), deficit replacement, maintenance fluids, restoration of losses and substitution for fluid redistribution (third space fluids):

Rate = CVE + deficit + maintenance + loss + third space

Compensatory Intravascular Volume Expansion

Intravascular volume must generally be supplemented to compensate for the venodilation and cardiac depression caused by anesthesia. Sustaining adequate oxygen delivery in relation to oxygen consumption is an important goal of fluid therapy. Tissue oxygen delivery depends on hemoglobin concentration, oxygen tension, organ perfusion pressures, and organ vascular resistance. Organ perfusion pressures depend on systemic arterial pressure and the higher of organ venous pressure or tissue pressure. Arterial pressure depends on cardiac output and systemic vascular resistance. Cardiac output (CO) is related to stroke volume and heart rate; and stroke volume is dependent on preload, contractility, and afterload. Most general and regional anesthetics cause arteriolar and venous dilation, expanding the vascular capacity. The latter reduces peripheral venous pressure and, therefore, venous return and CO. Therefore, fluid must be administered to expand the blood volume to compensate for venodilation. Additionally, general anesthestics produce myocardial depression (Ch. 5) . Increasing cardiac preload, by infusing fluid intravascularly to take advantage of the Starling mechanism, often returns stroke volume to an acceptable range. Postoperatively, venodilation and myocardial

depression rapidly subside when administration of the anesthetic is stopped. Patients with impaired cardiac or renal responses may then become acutely hypervolemic. CVE with 5 to 7 mL/kg of balanced salt solution must occur before, or simultaneous with, the onset of anesthesia.

DEFICITS

The fluid deficit equals the maintenance fluid requirement multiplied by the hours since last intake plus unreplaced preoperative external and third space losses. When hypovolemia is present, sufficient fluid should be infused to restore mean arterial pressure, heart rate, and filling pressures to near normal values before induction. If sufficient time is available, restoration of normal urine flow rate is also desirable. If clinical signs of hypovolemia are present (neck vein distention, elevated central venous pressure (CVP) or pulmonary artery occlusion pressure, hemodynamics should be closely monitored without infusing a bolus of fluid intravascularly. The fluid infusion rate for normal patients should then be set to deliver three to four times the maintenance rate until the calculated deficit has been corrected.

Electrolyte abnormalities are common among hospitalized patients. Surgical urgency often forces us to evaluate and correct preexisting abnormalities that may be directly related to the surgical problem, or to comorbid diseases or their therapy. The principles of management of these are outlined in other sections of this chapter. The induction of anesthesia and the onset of mechanical ventilation, fluid

---

shifts, and stress responses induced by surgical trauma all lead to redistribution of water, protein, and electrolytes. The common and most studied of these are abnormalities of potassium, calcium, and magnesium.

Maintenance Fluid

The maintenance fluid meets ongoing basal needs for water and electrolytes as described earlier. The onset of surgical stimulation and to a smaller extent onset of anesthesia elicits changes in catecholamines, cortisol, and growth hormone. These tend to reduce insulin secretion or impede its glucose-lowering effect, leading to hyperglycemia. If dextrose-containing solutions are infused at the usual 5 percent concentration at the rates often required during surgery, severe hyperglycemia will result. Thus, the fluid used for volume maintenance should not contain dextrose.

LOSSES

External losses (e.g., blood, ascites) should be replaced to maintain normal blood volume and normal composition of the ECF volume. Blood loss is replaced initially with either 3 mL of balanced salt solution or 0.9 percent NaCl for each milliliter of blood loss. For each milliliter of blood lost, 1 mL of colloid solution should be administered to provide improvement of filling pressures, arterial blood pressure and heart rate. Packed RBC infusions are used at roughly 1 mL for each 2 mL of blood lost plus either crystalloid or colloid as described. Although the effect on volume is 1:1, the hematocrit of packed RBCs (PRBC) (60-70%) is about twice the necessary hematocrit of the patient. In patients with reasonable cardiac reserve and without compromised regional circulations (e.g., coronary, cerebral, renal, intestinal), hemoglobin levels of 7.5 g/dL and above are usually well tolerated. [80] If blood volume is normal and cardiac failure is not a problem, then signs of sympathetic activation, mixed venous oxygen desaturation, or electrocardiogram signs of myocardial ischemia suggest the need for RBC administration. The following equation is used to calculate the necessary volume of RBCs to be infused. Because packed RBCs have a hematocrit of 60 percent, the volume to be infused is found by dividing the volume of RBCs desired by the hematocrit of the unit of PRBCs.

Ascites and pleural effusions drained during surgery reform at extremely variable rates. The electrolyte composition is the same as that at the ECF volume, but it also contains protein at concentrations 30 to 100 percent of the plasma value. Balanced salt solutions are most appropriate for replacement, but colloid should be added when dilution of the patient's colloidal osmotic pressure (COP) becomes severe (<15-17 mm Hg) and the apparent volume of redistribution of crystalloid begins to increase.

The electrolyte composition of gastrointestinal tract losses is site dependent (see Table 45-17) . Most gastrointestinal losses removed at the time of surgery entered the bowel lumen preoperatively and should be considered to be part of the deficit. Evaporation from exposed viscera is entirely water, but the electrolyte is left behind, leading to a need for free water. The amount evaporated is directly proportional to temperature and exposed surface area and inversely proportional to relative humidity. Excess urine due to diuretics, glycosuria, or diabetes insipidus should be replaced with a solution based on urinary electrolyte measurements. In general, sodium concentration ranges between 50 and 100 mEq/L; potassium concentration ranges between 20 and 60 mEq/L.

Redistribution

Redistribution, or so-called third-space losses, are due primarily to tissue edema and transcellular fluid displacement. Functionally, this fluid is not available to the vascular space. [81] [82] The volume of edema formed is governed by the principles discussed earlier. Colloid enters the injured tissue at a more rapid rate than normal, but at a slower rate than electrolyte. For example, bowel wall edema is lessened by utilizing colloid containing fluids compared with crystalloid. [83] The composition of third-space losses is equivalent to the ECF volume electrolyte concentration plus a smaller amount of protein. Therefore, balanced salt solution is the most appropriate replacement fluid. The volume redistributed correlates roughly with the degree of tissue manipulation. Intra-abdominal procedures with small incisions (e.g., hysterectomy) may require an additional 2 mL/kg/h, whereas a major bowel resection requires an additional 4 to 6 mL/kg/h.

Table 45-18 describes the fluid management for a 70-kg patient undergoing gastrectomy, starting with a hemoglobin of 15 g/dL, who has been fasting for 10 hours. The maintenance rate is 110 mL/h, producing a deficit of 1,100 mL.

During the first and second hours of intra-abdominal activity, 100 mL of blood was lost and replaced at 3:1 with a balanced salt solution. By the fourth hour, the deficit had been replaced, and because the abdomen was being closed during part of that hour, the third-space (redistribution) losses estimate was likewise reduced and no further blood loss was noted. The assumption is made that urine flow was 50 to 80 mL/h and that heart rate and arterial blood pressure were in an acceptable range and the CVP remained 6 to 9 mm Hg. Had the CVP or urine output begun to increase, the rate of fluid administration would have been slowed. If oliguria and tachycardia had occurred, a fluid bolus would have been administered.

The Pediatric Patient

There are few special considerations relevant to pediatric fluid management in addition to those for the adult (Ch. 59) . The neonate has limited ability to dilute or concentrate urine and has a high fluid requirement. Thus, neonates should not be without fluid for more than 3 to 4 hours; otherwise, significant dehydration may result. Food should be offered until 6 to 8 hours before induction, and glucose-containing clear liquids should be given about 4 hours before induction. Clear liquids are defined as transparent liquids

TABLE 45-18 -- Example of Fluid Calculations [a]

TIME	COMPENSATORY	DEFICIT	MAINTENANCE	BLOOD LOSS [b] (mL) [e]	THIRD SPACE (mL)	THIS HOUR [c] (mL)	CUMULATIVE [d]
P-I [e]	350	220	110	0	0	680	680
I-S [f]	--	220	110	0	0	330	1,010
1st hour [g]		220	110	300	350	980	1,990
2nd hour [g]		220	110	300	350	980	2,970
3rd hour [g]		220	110	150	350	830	3,800
4th hour [g]		0	110	0	200	330	4,130

[a] Simulated case. See text for details.
[b] This column reflects fluid replacement for blood loss.
[e] Preinduction phase, lasting 15 to 20 minutes
[c] Total fluid administered during the hour
[d] Grand total since beginning the case
[f] Induction until intra-abdominal surgical entry (assumed to be 1 hour)
[g] Operative time

and do not contain particulate material or protein, which coagulate in the acid medium of the stomach. Using the same principles as outlined for adults, the neonate requires maintenance fluids of 0.3 percent NaCl with potassium. Dextrose administration should not exceed 5 mg/kg/min. This can generally be met by using 2.5 percent dextrose-containing fluids. During extensive prolonged procedures, blood glucose should be monitored and the rate of dextrose administration modified accordingly. Otherwise, the choice and volumes of fluid are as described for an adult.

The Postoperative Patient With Bowel Obstruction

Patients with bowel obstruction are often older, with limited reserves in several organ systems. Estimating the degree of loss of fluids is difficult because fluid is retained in the bowel lumen where it cannot be measured. The slowly developing volume depletion allows time for full expression of compensatory mechanisms that mask the degree of the deficit. Patients have often ingested no fluids for many hours before entering the hospital and are often vomiting. The patient may have ischemic bowel injury with severe bowel wall edema and continued sequestration of luminal fluid and formation of ascites. Perioperative fluid intake will be much greater than measured output, leading consultants to suggest diuresis for *fluid overload.* Nutrition is impaired preoperatively and protein losses into the bowel are increased, leading to hypoalbuminemia and exacerbating the loss of fluid from the vascular space. The clinical picture is one of ongoing fluid requirement in the absence of external fluid loss, commonly referred to as *third spacing.*

The goals of fluid management in this group are similar to those of other patients and include restoration of the vascular volume and interstitial volume, correction of electrolyte depletion, correction of acidosis, reduction of systemic vascular resistance into the normal range, and optimization of oxygen delivery and utilization. Initial fluid infusion can restore intravascular volume sufficiently for blood pressure and heart rate to improve. Yet intravascular volume may still be depleted with a low cardiac output and severe arterial and venous vasoconstriction. The ECF volume (except for the bowel) remains dehydrated and will continue to accept fluids from the vascular space. The vasoconstricted patient will fail to perfuse all tissue, limiting the rate at which the ECF volume can be replenished. If fluids are infused more rapidly than the rate at which they can enter the ECF volume, increased filling pressures may result in pulmonary edema. It is crucial to estimate filling pressures, cardiac, output and systemic vascular resistance, while aggressive intravascular fluid with balanced salt solution and colloid is pursued. It may be necessary to administer arterial vasodilators such as nitroprusside to facilitate correction.

Management of a typical patient includes frequent monitoring of arterial blood pressure, heart rate, CVP, pulse pressure and respiratory variation, urine output, and electrolytes. If these are stable, hemoglobin and COP should be monitored every 2 to 4 hours until stable. A rising hemoglobin level indicates ongoing loss of plasma water, with or without protein loss. An increasing COP indicates continued loss of plasma water in excess of protein loss. Because maintenance fluid requirements persist, dextrose 5 percent is infused in 0.45 percent NaCl with 20 to 40 mEq of KCl/L at maintenance rate.

The fluid lost to the bowel and ECF volume is similar to plasma water in electrolyte composition, so a balanced salt solution is a reasonable first choice for the fluid boluses required to sustain plasma volume. The fluid lost will also contain protein, so either albumin or colloid osmotic pressure should be monitored and colloid infused. If a low COP (<15-18 mm Hg) coexists with hemodynamic instability, replacement should be started at 3 mL/kg/h if the CVP (and PAOP if pulmonary artery catheter has been placed) is within the patient's usual range. If it is high, replacement should start at 1 to 2 mL/kg/h. If the urine output rises above 1.5 mL/kg/h, one should check for glucos-uria. If glucosuria is absent, the fluid infusion rate is reduced by 0.5 mL/kg/h. If the CVP or pulmonary artery occlusion pressure (PAOP) rises above the patient's usual values and urine output is 0.5 to 1.5 mL/kg/h, the fluid infusion rate is reduced by 0.5 mL/kg/h. If the CVP (and/or PAOP) decreases below the patient's baseline and urine flow rate is low, balanced salt or colloid solution is administered rapidly (0.5 to 2 mL/kg/min) with close monitoring of filling pressures.

The Patient With Liver Failure

Fluid management of the patient with liver failure (Chs. 54 and 55) is complicated by several interacting problems. These patients appear to be simultaneously hyper- and hypovolemic. Most infused fluid is retained, yet renal function deteriorates, with avid sodium retention and arterial underfilling. Neither explains all the clinical findings or leads to consistently successful therapy.

According to the arterial underfilling (primary vasodilation) [84] hypothesis, some factor produced by, or not catabolized by, the failing liver causes inappropriate arterial dilation. The relative hypotension leads to activation of the systematic nervous system, the RAS, and vasopressin release. These lead to subsequent sodium and water retention, resulting in ascites and tissue edema.

In fact, cirrhotic patients have a low systemic vascular resistance, high cardiac output, and relative hypotension. Persistent endotoxemia (shunting via portosystemic anastomoses and enhanced endotoxin absorption from the intestine due to bile salt deficiency) may contribute to the vasodilation via activation of a cascade of secondary mediators beginning with tumor necrosis factor and interleukins. In addition, other vasodilator neurotransmitters may be produced or may not be cleared by the damaged liver.

The primary sodium retention hypothesis explains the avid sodium retention on the basis of hormonal (aldosterone) hyperactivity due to failure of the liver to metabolize aldosterone. Given the ECF volume expansion, the distribution into ascites and tissue edema is explained by the abnormally high portal venous pressures and hypoalbuminemia. More recently, abnormalities of atrial natriuretic peptide (ANP) have been investigated. ANP levels are normal or low in cirrhotic patients; this contrasts with the increase usually found in volume expanded patients. [85] ANP increased with water immersion or fluid administration, but natriuresis was not closely correlated with ANP levels. (Water immersion of the lower body compresses the venous capacitance system, resulting in centralization of blood volume. This simulates a volume infusion without adding any sodium or water to the body and should cause ANP release.) Water immersion did not increase ANP levels in patients with ascites who, therefore, apparently have blunted responses. Thus, impaired ANP release failed to explain sodium retention. [85] Patients with tense ascites had increased ANP, renin, and aldosterone concentrations. After paracentesis, ANP increased, but renin and aldosterone decreased. [86] The reasons for these findings were not clarified, but a reduction in intra-abdominal pressure would have decreased inferior caval pressure, facilitated venous return, and increased ANP levels. Decreased intra-abdominal pressures would also improve renal perfusion pressure, causing a reduction in renin release and subsequent aldosterone generation.

The role of increased intra-abdominal pressure may be important in sustaining sodium retention after ascites develops. Increased intra-abdominal pressure raises caval pressure. This decreases renal blood flow and glomerular filtration rate (GFR) because the renal perfusion pressure gradient (MAP minus renal venous pressure) is decreased both by systemic hypotension and increased caval pressure. The hypotension and reduction in renal blood flow can lead to renin activation, with aldosterone production. Hypotension, increased aldosterone, and decrease in GFR lead to enhanced sodium reabsorption, and low fractional excretion of sodium.

Hypoalbuminemia results from impaired synthesis by the liver, transudation into ascitic fluid due to portral hypertension, and malnutrition. Low COP favors loss of fluid from the vascular space into the interstitial space, producing intravascular hypovolemia. Ascites results from high portal venous pressure and hypoalbuminemia, markedly increasing the volume of transcellular fluid, which is functionally excluded from rapid exchange in the ECF volume.

Splanchnic blood pooling resulting from increased portal venous resistance plus lower body pooling resulting from elevated caval pressures from ascites tend to decrease net systemic venous return. Patients are thus functionally hypovolemic despite normal or elevated total blood volume. Heart failure owing to alcoholic cardiomyopathy may further complicate the clinical picture.

The goals in these patients are to avoid increasing interstitial fluid overload, maintain normal potassium concentration, and maintain intravascular volume. If cardiac failure is present, treatment must include administration of inotropic drugs and diuretics when filling pressures are increased. Restore intravascular COP by infusion of 25 percent albumin when possible. If the patient is acutely hypovolemic, 5 percent albumin solutions should be preferred to crystalloid, which will tend to further expand the already overexpanded ECF volume (i.e., produce more edema and ascites). In addition, intra-abdominal pressure should be estimated from urinary bladder pressure and paracentesis performed whenever it increases above 20 to 25 mm Hg. Finally, trials of dopamine, norepinephrine, phenylephrine, or vasopressin may be performed in hypotensive patients with low vascular resistance and hypotension in attempts to increase renal perfusion pressure and renal blood flow.

The Patient With Heart Failure

Fluid management of heart failure is directed to optimize cardiac preload, avoid overadministration of sodium, diminish edema, and correct common electrolyte abnormalities. Maintaining ideal cardiac preload during rapid fluid shifts that occur perioperatively is facilitated with direct or indirect measures of both preload and cardiac contractile function. Measures of preload include CVP, thermodilution cardiac output, end-diastolic volume, echocardiography, pulmonary artery occlusion pressure, and left atrial pressure. Measures of cardiac contractile function include stroke volume, ejection fraction, and stroke work. Patients with a history of cardiac failure scheduled for major or prolonged surgery should have monitoring instituted preoperatively and an intravascular fluid challenge (i.e., 500-1,000 mL/70 kg of crystalloid) performed to identify the optimal preload. Tissue edema is avoided by frequent monitoring of preload and arterial blood pressure coupled with support of contractility and control of vascular resistance. These patients have impaired ability to excrete fluids during the fluid mobilization, which occurs postoperatively. Because the ECF volume

is usually already expanded in these patients, the initial rates of fluid infusion intraoperatively should be at the lower ranges of estimates. Similarly, maintainance of intravascular volume without expansion of the interstitial space favors the use of colloid during the immediate perioperative period. Postoperatively, hemodynamic monitoring is continued until fluid mobilization is complete. The goal postoperatively is to give as little crystalloid as required to maintain adequate overall cardiovascular performance. Perioperative patients commonly receive more than 200 mEq of sodium per day including maintenance fluids, saline used to measure cardiac output, sodium from antibiotics administration, and sodium infused with vasoactive medications and inotropic agents. Thus, fluid should be maintained at a low maintenance, and flush fluids and sodium dosage should be measured. As soon as either urine output begins to increase or filling pressures or diastolic volume begin to rise, maintenance fluids should be stopped completely. If preload becomes excessive, diuretics should be administered.

Patients with heart failure have primary electrolyte problems owing to compensatory physiologic mechanisms activated by the impaired cardiac performance. These are then complicated by therapy with diuretics, digitalis, vasodilators, and angiotensin-converting enzyme inhibitors. Hyponatremia is common because of excess activation of the vasopressin system despite sodium retention. Treatment is directed at excreting the excess water load with diuretics, which should increase free water excretion more than sodium excretion. Sodium administration is not indicated unless volume depletion is documented. Aldosterone activation and diuretics lead to loss of potassium and magnesium. These ions are crucial for maintaining the stability of cardiac electrophysiology, as well as the effectiveness of digitalis and catecholamine. Ionized calcium is crucial for cardiac contractility, and hypocalcemia is extremely common during the perioperative period. Ionized calcium must be measured and corrected routinely. Severe hypophosphatemia often coexists with abnormalities of calcium, potassium, and magnesium and leads to depressed contractility.

The Patient With Cerebral Edema

Fluid management of patients with cerebral edema (Ch. 52) is directed at maintaining cerebral perfusion pressure, avoiding elevations of cerebral venous pressure and hypertension, preventing large changes in plasma osmolality (particularly depression of plasma osmolality), and avoiding hyperglycemia. Cerebral perfusion pressure (CPP) should be maintained in the normal range, 80 to 90 mm Hg, because autoregulation is impaired in the damaged brain, with a baseline increase in cerebrovascular resistance. Avoidance of intracranial hypertension, the other determinant of CPP, is crucial to preserve blood flow to compromised but viable brain. Cerebral edema formation is related to capillary pressure, COP, and permeability. The capillary pressure is between the arterial and venous pressures. Thus, systemic arterial or venous hypertension needs to be prevented. The normal brain capillary bed is essentially impermeable to sodium, mannitol, and protein, although water crosses freely. The damaged capillary bed becomes excessively permeable, with conductivity being greatest for the smallest molecules, but less for colloids. A degree of water dehydration without hypovolemia is desired to maintain the plasma sodium between 142 and 148 mEq/L. Thus, it is common to provide 75 to 90 percent of maintenance fluids with 0.9 percent NaCl or lactated Ringer solution and to minimize water volume required for other medications. Isotonic crystalloids or colloids do not cause edema in normal brain and can be used to sustain intravascular volume. [87] In fact, hyponatremia is often due to hypovolemia with inappropriate sodium loss [88] and subsequent water retention. This should be treated with intravascular volume expansion with isotonic or hypertonic sodium chloride. Parenteral nutrition can be prepared with 15 percent amino acid solutions, 20 percent lipid, and 70 percent dextrose to give full protein and caloric support in a minimal volume. Similarly, tube feeding formulations with 2 cal/mL should be prescribed. Hypovolemia must be carefully avoided. Colloid infusion to sustain intravascular volume, guided by hemodynamic monitoring, tends to provide better long-term control of the intravascular volume than crystalloid. If diuretics or diabetes insipidus cause loss of more than 2 mL/kg/h for more than 2 to 4 hours, a pulmonary artery catheter may be indicated for closer monitoring. Blood glucose should be maintained at 80 to 175 mg/dL by close monitoring, initially hourly, with decreasing frequency as stability is demonstrated. During acute resuscitation, dextrose administration is limited to no more than 2 mg/kg/min. Fortunately, indications for steroid use have become fewer in recent years, lessening the problems of hyperglycemia.

The Patient With Anuric Renal Failure Undergoing Nontransplant Surgery

Fluid management of the patient with anuric renal failure for nontransplant surgery (Ch. 53) should avoid excessive intravascular fluid administration and ECF volume expansion and maintain, or correct, electrolyte and acid-base status. The clinical anesthesiologist should also attempt to prevent precipitating conditions that would require dialysis during the immediate postoperative period (hyperkalemia, pulmonary edema, metabolic acidosis). Dialysis is difficult or impossible in the hemodynamically unstable patient and anticoagulation may be strongly contraindicated for several hours postoperatively. Patients with chronic renal failure often present with hypertension, diabetes, and vascular disease. Thus, avoidance of hypotension may be indicated to maintain coronary or cerebral perfusion pressure. In patients with acute renal failure, hypotension may worsen ischemic renal injury. This contrasts with the lack of concern for an adverse effect on renal function in the patient with chronic renal failure. Furthermore, recent dialysis often induces acute electrolyte shifts and hypovolemia and acidosis. The best compromise appears to be dialysis 12 to 24 hours preoperatively. If dialysis is performed close to the time of surgery, volume removal should be minimal. Patients with renal failure are often malnourished, have hypoproteinemia, are anemic, and have poor glucose tolerance. Hemodynamics should be closely monitored. If hypovolemia develops, colloid should be used early, but one should avoid producing vascular overexpansion. Likewise,

one must avoid interstitial fluid overload, which would require acute postoperative dialysis. Crystalloid replacement of third-space losses should be limited to 1 to 2 mL/kg/h, whereas blood loss should be replaced with colloid or RBCs. Correction of sodium, potassium, and acidosis can be achieved by the use of isotonic fluid without potassium, with reduced amounts of chloride, and increased amount of buffer. Initially, an infusion of 30 percent of calculated maintenance fluid rate is important because approximately 70 percent of normal fluid requirements are used in excreting solute via the kidney, a route no longer available. Na^{+}, K^{+}, pH, HCO_3^{-}, and glucose should be monitored at regular intervals.

The Patient With Adult Respiratory Distress Syndrome

Fluid management of the patient with adult respiratory distress syndrome (ARDS) (Ch. 72) involves maintaining colloid osmotic pressure and requires a CVP and PAOP as low as possible consistent with good ventricular function. Oxygen delivery should be sustained, ideally above 600 mL/min/m^2, by increasing cardiac index and hemoglobin concentration. Compensation for hemodynamic effects of increased airway pressure is achieved by maintaining adequate right and left ventricular filling volumes. When airway pressure increases, the lung expands in proportion to its compliance. The intrapleural pressure increases in direct proportion to lung expansion, and inversely with chestdiaphragm compliance. The increased intrapleural pressure increases CVP, which reduces the gradient between the periphery and the CVP. This reduces venous return unless peripheral venous tone increases or fluids are administered. The increased venous pressure increases fluid filtration out of the capillary bed, tending to produce hypovolemia. The increased pleural pressure is transmitted via the pericardium to reduce the filling pressure gradient for all cardiac chambers. The consequent reduction in end-diastolic volume diminishes preload to all chambers. The elevation of intrapulmonary pressure increases pulmonary artery pressure, which leads to augmented right ventricular afterload. The reduced venous return, decreased right ventricular preload, and increased afterload may severely compromise right ventricular stroke volume, cause stiffening of the interventricular septum and reduce preload for the left ventricle.

All these consequences can be improved by intravascular volume expansion, except for the increased afterload on the right ventricle. Thus, CVP and right ventricular enddiastolic volume are monitored to aid in the decision to institute inotropic therapy. An increase in CVP also compromises lymphatic return from the lung and periphery. Additionally, sepsis, the most common coexisting condition with ARDS, causes increased vascular capacity and vasodilation, decreases COP, and results

in tissue edema. The net clinical outcome of these factors is that fluid intake usually exceeds output until the ARDS (and sepsis) begins to subside. Additionally, studies comparing crystalloid and colloid management over the entire time course of ARDS are currently being evaluated. However, after 48 hours, pulmonary function may be somewhat better in patients managed with colloid, in part, than with crystalloids alone.

The Acutely Burned Patient

Fluid management of the acutely burned patient focuses on restoration of plasma volume and a shift of the ECF volume into the burned but viable tissue, accompanied by increased losses caused by loss of the normal barrier function of the skin. The tissue injury produced by the burn leads to an abrupt disruption of the capillary bed, manifested by local vasodilation, increased permeability, and, presumably, decreased reflection coefficient to proteins. Vasodilation increases the surface area for filtration and tends to increase capillary pressure. The lowered reflection coefficient diminishes the ability of colloids to retain fluid in the capillaries. Thus, water, electrolytes, and protein enter the burned tissue at the expense of the intravascular volume. Fluid is mobilized from uninjured tissues by a variety of processes, with a net result of transfer of fluid from normal tissue into the injured tissue and intravascular hypovolemia. Capillary permeability was formerly thought to increase in all tissues after a serious burn injury, but this is not the currently held view. [89] In addition to the tissue edema, there is a marked increase in loss of water by evaporation from the wound surface, and the metabolic rate increases dramatically, leading to proportionate increases in fluid requirements. Several formulas have been developed to aid in writing the initial fluid prescription. The key to success is close hemodynamic monitoring with titration of therapy to the individual patient's physiology. For example, if urine output increases progressively, or if filling pressures increase, fluid administration must be decreased. The Parkland formula [90] prescribes fluids based on the percentage of the body surface area (BSA) burned (percent BSA-burned): 2 mL/kg/percent BSA-burned during the first 8 hours and 2 mL/kg/percent BSA-burned during the next 16 hours.

The formula prescribes ([0.25 mL/kg]/[percent BSA-burned])/h for 8 hours, then ([0.125 mL/kg]/[percent BSA-burned])/h for 16 hours, then 5 percent dextrose in water, ([0.8 mL/kg]/[percent BSA-burned])/h, plus 5 percent albumin, ([0.015 mL/kg]/[percent BSA-burned])/h for 24 hours. For example, a 50-kg person with 50 percent BSA burn should receive (50 kg) × (0.25 mL/kg) × (50 percent BSA-burned), which equals 625 mL/h for 8 hours, followed by (50 kg) × (0.125 mL/kg) × (50 percent BSA-burned), which equals 310 mL/h for 16 hours. During the second 24 hours, one should administer (50 kg) × (0.08 mL/kg) × (50 percent BSA-burned), which equals 200 mL/h of 5 percent dextrose in water, plus (50 kg) × (0.015 mL/kg) × (50 percent BSA-burned), which equals 37.5 mL/h of 5 percent albumin. Colloids are not contraindicated, even during the acute phase of fluid resuscitation. Although they will pass into the injured tissue at an accelerated rate, they have a more sustained effect on plasma volume than does crystalloid alone.

The Pregnant Patient With Preeclampsia

Goals of fluid management of the pregnant patient with preeclampsia (Ch. 57) are to (1) restore the contracted intravascular volume, [91] (2) avoid excessive intravascular fluid administration because of normal postpartum fluid mobilization,

(3) replace increased sensible (sweat) and insensible (respiratory) losses due to labor, (4) be prepared to replace rapid blood loss, (5) avoid hypotension due to anesthetic induced vasodilation to preserve uteroplacental flow, (6) maintain normoglycemia, (7) avoid decreasing the COP further, and (8) prevent pulmonary and cerebral edema.

Restoration of depleted plasma volume to normal is crucial for control of hypertension and for administration of anesthesia. Plasma volume is decreased in preeclamptic patients secondary to elevated lower body venous pressure due to uterine compression, pressure-induced natriuresis as seen in hypertension, severe vasoconstriction, and hypoproteinemia secondary to proteinuria. After parturition, fluid retained during pregnancy is usually quickly mobilized and excreted. The preeclamptic patient, however, may have compromised hepatic, renal, or cardiac function, impeding the timely excretion of this fluid. These patients are at risk of pulmonary edema due to cardiac failure secondary to severe hypertension and lowered COP. Cardiac filling pressures should be monitored and a PAOP of less than 12 to 15 mm Hg maintained. Plasma tonicity must be maintained by administration of isotonic fluid because these patients are at risk of developing cerebral edema.

References

1. Rhoades RA, Tanner GA: Medical Physiology, 1st ed. Boston, Little, Brown & Co., 1995, pp 448-449.

2. Coran AG: Perioperative care of the pediatric patient. Surg Ann 23(Pt 1):31, 1991.

3. Haynes MA, Goldenberg IS: Renal effects of anesthesia and operation mediated by endocrines. Anesthesiology 24:487, 1963.

4. Imai Y, Abe K, Seino M: Attenuation of pressor responses to norepinephrine and pitressin and potentiation of pressor response to angiotensin II by captopril in human subjects. Hypertension 4:444, 1982.

5. Peach M: Renin-angiotensin system: Biochemistry and mechanisms of action. Physiol Rev 57:313, 1977.

6. Millar J, Leckie B, Semple P: Different responses of active and inactive plasma renin to various stimuli. Clin Sci Mol Med 55:155s, 1978.

7. Barajas L, Powers K: The structure of the juxtaglomerular apparatus (JGA) and the control of renin secretion. An update. J Hypertens 2:3, 1984.

8. Oelkers W, Blumel A, Schoneshofer M: Effects of ethinyl estradiol on the renin-angiotensin system and on plasma transcortin in women and men. J Clin Endocrinol Metab 43:1036, 1976.

9. Herrmann H, Dzau V: The feedback regulation of angiotensiogen production by components of the renin-angiotensin. Circ Res 52:328, 1983.

10. Clauser E, Bouhnik J, Coezzy E et al: Synthesis and release of immunoreactive angiotensinogen by rat liver slices. Endocrinology 112:1188, 1983.

11. Bouhnik J, Galen F, Clauser E et al: The renin-angiotensin system in thyroidectomized rats. Endocrinology 108:647, 1981.

12. Campbell D: The site of angiotensin production. J Hypertens 3:199, 1985.

13. Ganong W: The brain renin-angiotensin system. Annu Rev Physiol 46:17, 1984.

14. Reid I: The renin-angiotensin system and body function. Arch Intern Med 145:1475, 1985.

15. Reid I: Actions of angiotensin II on the brain: Mechanisms and physiologic role. Am J Physiol 246:F533, 1984.

16. Re R, Novelline R, Escourrou M et al: Inhibition of angiotensin-converting enzyme for diagnosis of renal artery stenosis. N Engl J Med 298:582, 1978.

17. Haber E: The role of renin in normal and pathological cardiovascular hemostasis. Circulation 54:849, 1976.

18. Kost C: Effect of angiotensin II on plasma adenosine concentrations in the rat. J Cardiovasc Pharmacol 17:838, 1991.

19. Ferrario C, Santos R, Brosnihan K et al: A hypothesis regarding the function of angiotensin peptides. Clin Exp Hypertens 10A:107, 1988.

20. Goodfriend T, Peach M: Angiotensin III (DES-aspartic acid-1)-angiotensin II: Evidence and speculation for its role as an important agonist in the renin-angiotensin system. Circ Res 36:38, 1975.

21. Knight PR, Lane GA, Hensinger RN et al: Catecholamine and renin-angiotensin response during hypotensive anesthesia induced by sodium nitroprusside or trimethaphan camsylate. Anesthesiology 55:277, 1981.

22. Zubrow AB, Daniel SS, Stark RI et al: Plasma renin, catecholamine, and vasopressin during nitroprusside-induced hypotension in ewes. Anesthesiology 58:245, 1983.

23. Marshal WK, Bedford RF, Arnold WP et al: Effects of propranolol on the cardiovascular and renin-angiotensin systems during hypotension produced by sodium nitroprusside in humans. Anesthesiology 55:277, 1981.

24. Jensen V: The TURP syndrome. Can J Anaesth 38:90, 1991.

25. Andreoli TE, Carpenter CC, Plum F et al (eds): Cecil Essentials of Medicine. Philadelphia, WB Saunders, 1986, pp 195-196.

26. Zaloga GP, Prough DS: Fluids and electrolytes. In Barash PG, Cullen BF, Stoelting RK (eds): Clinical Anesthesia, 2nd ed. Philadelphia, JB Lippincott, 1992, pp 214-236.

27. Black RM: Disorders of serum sodium and serum potassium. In Rippe JM, Irwin RS, Alpert JS et al (eds): Intensive Care Medicine, Boston, Little, Brown, 1985.

28. Sarnaik AP, Meert K, Hackbarth R et al: Management of hyponatremic seizures in children with hypertonic saline. A safe and effective strategy. Crit Care Med 19:758, 1991.

29. Oh M, Carrol H: Disorders of sodium metabolism: Hypernatremia and hyponatremia. Crit Care Med 20:94, 1992.

30. Perez GO, Oster JR, Robertson GL: Severe hypernatremia with impaired thirst. Am J Nephrol 9:421, 1989.

31. Tanifuji Y, Eger EI: Brain sodium, potassium and osmolarity: Effects on anesthetic requirement. Anesth Analg 57:404, 1978.

32. Coran AG: Perioperative care of the pediatric patient. Surg Ann 23(Pt 1):31, 1991.

33. Rosa RM, Silva P, Young JB et al: Adrenergic modulation of extrarenal potassium disposal. N Engl J Med 302:431, 1980.

34. Brown MJ, Brown DL, Murphy MB: Hypokalemia from beta2 receptor stimulation by circulating epinephrine. N Engl J Med 309:1414, 1983.

35. Hurlbert BJ, Edelman JD, David K: Serum potassium levels during and after terbutaline, Anesth Analg 60:723, 1981.

36. Vincent HH, Boomsma F, Man in't Veld AJ et al: Effects of selective and nonselective beta agonists on plasma potassium and norepinephrine. J Cardovasc Pharmacol 6:107, 1984.

37. Papademetrious V, Fletcher R, Khatri IM et al: Diuretic-induced hypokalemia in uncomplicated systemic hypertension: Effect of plasma potassium correction on cardiac arrhythmias. Am J Cardiol 52:1017, 1983.

38. Papademetrious V, Burris J, Kukish SIM et al: Effectiveness of potassium chloride or triamterene in thiazide hypokalemia. Arch Intern Med 145:1986, 1985.

39. DeFronzo RA: Intravenous potassium chloride therapy. JAMA 245:2446, 1981.

40. Solomon RJ, Katz JD: Disturbances of potassium homeostasis. In Stoelting RK (ed): Advances in Anesthesia, vol 3. Chicago, Year Book Medical Publishers, 1986.

41. Surawicz B: Relationship between electrocardiogram and electrolytes. Am Heart J 73:814, 1967.

42. Holick MF, Krane SM, Potts JT: Calcium, phosphorus, and bone metabolism: Calcium-regulating hormones. In Isselbacher KJ, Braunwald E, Wilson JD et al (eds): Harrison's Principles of Internal Medicine. 13th ed. Boston, McGraw-Hill, 1994, p 2139.

43. Zaloga GP, Chernow B: Hypocalcemia in critical illness. JAMA 256, 1924, 1986.

44. Harris MNE, Crowther A, Jupp RA et al: Magnesium and coronary revascularization. Br J Anesth 60:779, 1988.

45. James MFM: Clinical use of magnesium infusions in anesthesia. Anesth Analg 74:129, 1992.

46. Ghoneim MM, Long JP: The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 32:23, 1970.

47. Rhoades RA, Tanner GA: Medical Physiology, 1st ed. pp 458-459.

48. Potts JT: Diseases of the parathyroid gland and other hyper- and hypocalcemic disorders. In Isselbacher KJ, Braunwald E, Wilson JD et al (eds): Harrison's Principles of Internal Medicine, 13th ed. Boston, McGraw-Hill, Inc., 1995, p 2170.

49. Levinsky NG: Acidosis and alkalosis. In Isselbacher KJ, Braunwald E, Wilson JD et al (eds): Harrison's Principles of Internal Medicine, 13th ed. McGraw-Hill, Inc., 1995, p 255.

50. Drummond JC, Moore SS: The influence of dextrose administration on neurologic outcome after temporary spinal cord ischemia in the rabbit. Anesthesiology 70:64, 1989.

51. Sieber FE, Traystman RJ: Special issues: Glucose and the brain. Crit Care Med 20:104, 1992.

52. Stagnaro-Green A: Perioperative glucose control: Does it really matter? Mt Sinai J Med 58:299, 1991.

53. McMurry JF Jr: Wound healing with diabetes mellitus. Better glucose control for better wound healing in diabetes. Surg Clin North Am 64:769, 1984.

54. Bagdale JD, Nielson KL, Bulger JF: Reversible abnormalities in phagocytic function in poorly controlled diabetic patients. Am J Med Sci 263:451, 1972.

55. Welborn LG, McGill WA, Hannallah RS et al: Perioperative blood glucose concentrations in pediatric outpatients. Anesthesiology 65:543, 1986.

56. Welborn LG, McGill WA, Hannallah RS et al: Glucose concentrations for routine intravenous infusion in pediatric outpatient surgery. Anesthesiology 67:427, 1987.

57. Degoute CS, Ray MJ, Manchon M et al: Intraoperative glucose infusion and blood lactate:Endocrine and metabolic relationships during abdominal aortic surgery. Anesthesiology 71:355, 1989.

58. The Carter Center of Emory University: Closing the gap: The problem of diabetes mellitus in the United States. Diabetes Care 8:391, 1985.

59. Stewart WJ, McSweeney SM, Kellet MA et al: Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. Circulation 70:788, 1984.

60. Schaade DS: Surgery and diabetes. Med Clin North Am 72:1531, 1988.

61. Gavin LA: Management of diabetes mellitus during surgery. West J Med 151:525, 1989.

62. Reissel E, Orko R, Maunuksela E et al: Predictability of difficult laryngoscopy in patients with long-term diabetes mellitus. Anaesthesia 43:1024, 1990.

63. Hogan K, Rusty D, Springman SR: Difficult laryngoscopy and diabetes mellitus. Anesth Analg 67:1162, 1988.

64. Davidson MB, Schriger DC, Peters AL et al: A clinical approach for the diagnosis of diabetes mellitus: An analysis using glycosylated hemoglobin levels. JAMA 276:1246, 1996.

65. Nathan DM: Hemoglobin A_{1c} : Infatuation or the real thing? N Engl J Med 323:1062, 1990.

66. Watson BG, Pay DA, Williamson M et al: Practical closed-loop insulin infusion. Life Support Syst 3(suppl 1):519, 1985.

67. Hirsch IB, Magill JB, Cryer PE et al: Perioperative management of surgical patients with diabetes mellitus. Anesthesiology 74:346, 1991.

68. Boyle PJ, Schwartz NS, Shah SD et al: Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 318:11487, 1988.

69. Wasserstrum N: Issues in fluid management during labor: General considerations. Clin Obstet Gynecol 35:505, 1992.

70. Wallace EL, Surgenor DM, Hao HS et al: Collection and Transfusion 33:139, 1993.

71. Shires T, Cohn D, Carrico J et al: Fluid therapy in hemorrhagic shock. Arch Surg 88:688, 1964.

72. Schakford SR, Fortlage DA, Peters RM et al: Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients undergoing aortic reconstruction. Surg Gynecol Obstet 164:127, 1987.

73. Rocha e Silva M, Velasco IT, Portirio MMF: Hypertonic saline resuscitation: Saturated salt-dextran solutions are equally effective, but induce hemolysis in dogs. Crit Care Med 18:203, 1990.

74. Moss GS, Gould SA: Plasma expanders: An update. Am J Surg 155:425, 1988.

74A. Velanovich V: Crystalloid versus colloid fluid resuscitation: A meta-analysis of mortality. Surgery 105:65-71, 1989.

75. Tuullis JL: Albumin. Background and uses. JAMA 237:355, 1977.

76. Ibister JP, Fisher MM: Adverse effects of plasma volume expanders. Anaesth Intensive Care 8:145, 1980.

77. Mangar D, Gerson JI, Constantine RM et al: Pulmonary edema and coagulopathy due to hyskon (32% dextran-70) administration. Anesth Analg 68:686, 1989.

78. Straus RG: Volume replacement and coagulation: A comparative review. J Cardiothorac Vasc Anesth 2(Suppl 1):24, 1988.

79. Spence RK, McCoy S, Costablie J et al: Fluosol DA-20 in the treatment of severe anemia: Randomized, controlled study of 46 patients. Crit Care Med 18:1227, 1990.

80. Leone BJ, Spahn DR: Anemia, hemodilution, and oxygen delivery. Anesth Analg 75:651, 1992.

81. Shires T, Williams J, Brown F: Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 154:803, 1961.

82. Roth E, Lax L, Maloney J: Ringer's lactate solution and extracellular fluid volume in the surgical patient: A critical analysis. Ann Surg 169:149, 1969.

83. Prien T, Backhaaus N, Pelster F et al: Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. J Clin Anesth 2:317, 1990.

84. Schrieer RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis and pregnancy. N Engl J Med 319:1065, 1127, 1988.

85. Epstein M: Atrial natriuretic factor in patients with liver disease. Am J Nephrol 9:89, 1989.

86. Salerno F, Badalamenti S, Moser P et al: Atrial natriuretic factor in cirrhotic patients with tense ascites. Effect of large-volume paracentesis. Gastroenterology 98:1063, 1990.

87. Wisner D, Busche F, Sturm J et al: Traumatic shock and head injury: Effects of fluid resuscitation on the brain. J Surg Res 46:49, 1989.

88. Jackowski A: Disordered sodium and water in neurosurgery. Br J Neurosurg 6:173, 1992.

89. Dietsch EA: The management of burns. N Engl J Med 323:1249, 1990.

90. Dietsch EA: Burn management. In Ripe JM, Irwin RS, Alpert JS et al (eds): Intensive Care Medicine. 2nd ed. Boston, Little, Brown, 1991, p 1507.

91. Waserstrum N: Issues in fluid management during labor: Maternal plasma volume status and volume loading. Clin Obstet Gynecol 35:514, 1992.

Chapter 46 - Transfusion Therapy *

Ronald D. Miller

BLOOD THERAPY

According to a survey conducted by the Committee on Blood and Blood Products of the American Society of Anesthesiologists, [1] anesthesiologists administer more than half of all blood given to patients. Obviously, the anesthesiologist should be an expert on the implications and the complications associated with blood transfusions.

Indications for Transfusion

Allogeneic (Homologous) Blood

Blood transfusions are given to increase oxygen-carrying capacity and intravascular volume. Theoretically, increasing vascular volume is not an indication for blood transfusions, because volume can be augmented with administration of fluids that do not transmit infections (e.g., crystalloids or some colloids). On the practical side, when a patient is hemorrhaging, blood is given to increase both oxygen-carrying capacity and intravascular volume. However, increasing oxygen-carrying capacity is the only real indication for blood transfusions.

The critical question is "What is/are the specific indications for blood transfusions?" With a specific indication (i.e., increase oxygen-carrying capacity), this question should be easy to answer. Unfortunately, there is little or no way, except in severe life-and-death situations, to determine whether oxygen-carrying capacity is inadequate. The controversy revolves around how much emphasis should be placed on hemoglobin or hematocrit values. The limitation of such values is based on a potential extreme variability from one patient to another regarding their need for increased oxygen-carrying capacity. For example, young healthy patients with normal cardiorespiratory function may easily compensate for anemia (either chronic or acutely induced by hemorrhage), whereas at an identical hematocrit value, elderly patients with cardiac disease may have serious problems with surgery and anesthesia. This concern has led many medical organizations to place emphasis on overall medical judgment rather than a specific laboratory value, [2] [3] with some debate. [4] Conversely, other organizations have chosen to make far more complex directions, such as those in Table 46-1 from the American College of Surgeons. Despite the intellectual appeal of the latter approach, most of the American College of Surgeons' criteria cannot distinguish inadequate intravascular volume from diminished oxygen-carrying capacity. *Therefore, in this author' s opinion, the hemoglobin concentration should be the basis around which clinical judgment revolves in order to define transfusion requirements for an individual patient.*

The foundation for using the hemoglobin or hematocrit value as the initial consideration for defining transfusion requirements follows. A National Institutes of Health Consensus Conference [5] concluded that otherwise healthy patients with a hematocrit value greater than 30 percent rarely require perioperative blood transfusions, whereas patients with acute anemia (as in intraoperative blood loss) of less

*See Practice Guidelines for Blood Component Therapy

TABLE 46-1 -- American College of Surgeons Classes of Acute Hemorrhage

FACTORS	I	II	III	IV
Blood loss, *mL*	750	750-1,500	1,500-2,000	2,000 or more
Blood loss, % BV	15	15-30	30-40	40 or more
Pulse, *bpm*	>100	>100	>120	140 or higher
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal/increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respirations *per minute*	14-20	20-30	30-40	>35
Urine output, *mL/h*	30	20-30	5-10	Negligible
CNS (mental status)	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3:1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

BV, blood volume; bpm, beats per minute; CNS, central nervous system

than 21 percent frequently require blood transfusions. They also recognized that patients with chronic anemia (as in renal failure) may tolerate a hemoglobin concentration of less than 7 g/dL. The ultimate determination of that hematocrit or hemoglobin value at which blood should be given will have to be a clinical judgment based on many factors, such as cardiovascular status, age, anticipated additional blood loss, arterial oxygenation, mixed venous oxygen tension, cardiac output, and blood volume. To further complicate this issue, indications for blood transfusions also probably depend on the source of the blood. For example, indications for autologous blood may be more liberal because it is unlikely to transmit diseases (e.g., hepatitis and acquired immunodeficiency syndrome [AIDS]) than is allogeneic blood. However, autologous blood should not be viewed as completely safe because of the possibility of laboratory error or a hemolytic transfusion reaction.

More recently, usually in intensive care patients, several groups have attempted to define the point at which blood transfusions should be given by measures of tissue oxygenation and hemodynamics (e.g., increase in oxygen consumption in response to added oxygen content). [6] [7] [8] [9] [10] [11] [12] [13] [14] No specific measure could consistently predict when a patient would benefit from a blood transfusion. Yet, there is suggestive evidence that the quality (e.g., age) of the blood and its increased oxygen capacity (e.g., hemoglobin value >10 g/dL) may benefit very sick patients. In fact, one study found that when blood stored for more than 15 days was given, evidence of splanchnic ischemia occurred. [9] More recently, this concept was confirmed by Purdy et al, [15] who found that patients who received 17-day-old blood (range, 5-35 days) versus 25-day-old blood (range, 9-36 days) had a higher survival rate. The influence of the age of blood infused is discussed later in this chapter. Perhaps the development of more sensitive indicators of tissue oxygenation (e.g., intramucosal pH) will provide indicators for transfusion. [9] [15] By use of outcome data in an orthopedic surgery population, variations in hemoglobin levels were unrelated to duration of hospitalization, [16] yet trained athletes and postoperative cardiac patients showed improved physical capabilities when hemoglobin levels were increased. [17] Conversely, Weiskopf et al [18] found that in healthy patients, decreases in hemoglobin concentration to 5.0 g/dL did not produce any evidence of inadequate oxygenation. However, these patients were not subjected to the stresses of

recovery from surgery and anesthesia. However, Weiskopf et al [19] found that these patients compensated for their low hemoglobin levels by increasing heart rate and stroke volume. One might then argue that patients who have a higher than expected heart rate or who cannot increase their cardiac output should receive a transfusion to a higher hemoglobin level than 10 g/dL. Unfortunately, precise conclusions cannot be derived from these helpful and suggestive data.

In the absence of physiologic indicators, arbitrary guidelines are recommended. In fact, in the July 1989 Food and Drug Administration (FDA) Drug Bulletin, even more stringent guidelines were proposed for red blood cell (RBC) administration. That bulletin states, "adequate oxygencarrying capacity can be met by a hemoglobin of 7 g/dL or even less when the intravascular volume is adequate for perfusion." There are medical conditions (e.g., coronary artery disease) that justify giving blood to achieve a higher hemoglobin level. Nevertheless, the general concern of many individuals in regulatory positions that blood is often given inappropriately will inevitably lead to more scrutinizing of our transfusion practice. For example, many hospital transfusion committees are conducting audits in which patients who have postoperative hematocrit values higher than a certain percentage (e.g., 33-36%) [19] and who have received blood will have the original indications for blood transfusion reevaluated to determine whether blood was given inappropriately. This increased scrutiny dictates that anesthesiologists clearly state in the hospital record the reasons for giving blood transfusions. [3]

To arrive at some conclusions in the presence of incomplete data, two complementary recommendations are given. First, the recommendations of the American Society of Anesthesiologists Practice Guidelines: [2]

1. Transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.
2. The determination of whether intermediate hemoglobin concentrations (6 to 10 g/dL) justify or require red blood cell (RBC) transfusion should be based on the patient's risk for complications of inadequate oxygenation.
3. The use of a single hemoglobin "trigger" for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation are not recommended.
4. When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery,

acute normovolemic hemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacologic agents) may be beneficial.
5. The indications for transfusion of autologous RBCs may be more liberal than those for allogeneic RBCs because of lower (but still significant) risks associated with the former.

With the help of Habibi et al, [20] the following guidelines are recommended with the rule of thumb that administration of one unit of packed RBCs will increase hematocrit value by 3 to 5 percent. Indications are

1. Blood loss >20 percent of blood volume when more than 100 mL
2. Hemoglobin <8 g/dL
3. Hemoglobin <10 g/dL with major disease (e.g., emphysema, ischemic heart disease)
4. Hemoglobin 10 g/dL with autologous blood
5. Hemoglobin <12 g/dL and ventilator dependent

Although the recommendations of Habibi et al [20] are current, the elusive "transfusion trigger" remains in a prominent part of the debates in not only anesthesia specifically, but in medicine in general. In 1999, Herbert et al [20A] found that in critically ill patients, a restrictive transfusion strategy (hemoglobin <10 gm/dL) was as effective as a more liberal transfusion (hemoglobin 10-12 gm/dL) except in patients with acute myocardial infarction and unstable angina. Despite the problem with identifying a specific transfusion trigger, Ely and Bernard [20B] have generally confirmed the conclusions of Habibi et al. As concluded by Weiskopf [20C] , "we merely await advances in technology that will enable us to measure directly the value of concern and thereby free us from arguments over which surrogate (e.g., hemoglobin) to measure and what value indicates the need for augmented oxygen delivery."

Autologous Blood

Autologous blood is assumed to be (and probably is) much safer than allogeneic blood, mainly because of the decreased risk of infection. Because of a marked decrease in infectivity from allogeneic blood (see Infectivity of Blood), the difference in safety compared with autologous blood is much less. [21] [22] For example, Kanter et al [23] found that 25 of 140 patients undergoing hysterectomy who donated blood received blood transfusions, whereas 1 of 123 patients who did not donate autologous blood was transfused. Therefore, they concluded that elimination of preoperative autologous blood donation does not increase the risk of allogeneic blood transfusion. They further argued that autologous blood does have risks. One of every 16,000 autologous blood donations results in a reaction severe enough to require hospitalization. [24] Complications associated with autologous blood transfusions include the following:

1. Anemia
2. Preoperative myocardial ischemia from anemia
3. Administration of the wrong unit (1:100,000)
4. Need for more frequent blood transfusions

However, the relative value of autologous blood is based on the assumption that the risks of allogeneic blood have been properly assessed. The advocates for the elimination of autologous blood transfusion have not included immunosuppression or outbreaks of other infections in allogeneic blood. For example, from 1986 to 1991, 182 transfusionassociated fatalities were reported to the FDA, 29 (16%) of which were caused by bacterial contamination. [25] Since then, 10 cases of *Yersinia enterocolitica* have been reported. These cases all involved allogeneic blood, although two patients also received autologous blood. Furthermore, autologous blood can affect the immune system (see Transfusion-Induced Immunodepression). In addition, the testing and screening of blood donors is by no means perfect. [26] Ask yourself the question: If given a choice, would you want your own blood or allogeneic blood?

Nevertheless, the conclusion still is that autologous blood is preferred over allogeneic (homologous) blood with a more generous hemoglobin level (<10 g/dL) than that at which autologous blood can be given. [2] [27]

Compatibility Testing

The ABO-Rh type, crossmatch, and antibody screen are frequently referred to as *compatibility tests.* These tests were designed to demonstrate harmful antigen-antibody interactions *in vitro* so that harmful *in vivo* antigen-antibody interactions could be prevented. Donor blood used for emergency transfusion of group-specific blood must be screened for hemolytic anti-A and/or anti-B antibodies. Also, all donor blood must be tested for the correct ABO and Rh type and screened for unexpected antibodies. Similarly, recipient blood must also undergo ABO-Rh typing, as well as testing for unexpected antibodies. Once this has been completed, proper selection of donor blood requires a test for compatibility between recipient blood and donor blood; this test is known as a crossmatch (Fig. 46-1) .

ABO-Rh Typing

Determination of the patient's correct blood type is exceedingly important because the most serious and tragic reactions are usually caused by accidental transfusion of ABO-incompatible blood. These reactions are due to naturally occurring antibodies (anti-A and anti-B), which activate, complement, and lead to rapid intravenous hemolysis. Anti-A and/or anti-B antibodies are formed whenever the individual lacks either or both of the A and B antigens. In essence, antibodies are directed against those antigens that are lacking in the individual's own cells. ABO typing is performed by testing RBCs for the A and B antigens and the serum for the A and B antibodies before transfusion (Table 46-2) .

The only additional required testing is that for the Rh(D) antigen. Antigen D is a very common one and, except for the A and B antigens, the one most likely to produce immunization. Approximately 60 to 70 percent of Rh(D)-negative recipients are immunized (produce anti-D) if they are given blood transfusions with Rh(D)-positive blood. About 85 percent of individuals possess the D antigen and are termed Rh(D)-positive; the remaining 15 percent, who lack the D antigen, are termed

Rh(D)-negative. Because anesthesiologists and surgeons often have difficulty understanding the

Figure 46-1 Outline of the tests used for a crossmatch. The X over the word *crossmatch* means that the crossmatch is not included in the type and screen.

blood grouping system, Table 46-3 is included to facilitate identification of donor blood groups whose blood patients can receive.

Crossmatching

A crossmatch is essentially a trial transfusion within a test tube in which donor RBCs are mixed with recipient serum to detect a potential for serious transfusion reaction. The crossmatch can be completed in approximately 45 to 60 minutes and is carried out in three phrases: an immediate phase, an incubation phase, and an antiglobulin phase.

The first phase is conducted at room temperature and is a check against errors in ABO typing. It detects ABO incompatibilities and those caused by naturally occurring antibodies in the MN, P, and Lewis systems. This takes approximately 1 to 5 minutes to complete.

The second phase involves incubation of the first-phase reactions at 37°C in albumin or low-ionic strength salt solution. The addition of albumin and low-ionic-strength salt solution aids in the detection of incomplete antibodies or those antibodies that are able to attach to a specific antigen (sensitization) but are unable to cause agglutination in a saline suspension of RBCs. This phase primarily detects antibodies in the Rh system. The incubation of 30 to 45 minutes in albumin and of 10 to 20 minutes in lowionic-strength salt solution in this phase is of sufficient duration to allow antibody uptake sensitization by cells so that incomplete

TABLE 46-2 -- ABO Compatibility Testing

BLOOD GROUP	RED CELLS TESTED WITH		SERUM TESTED WITH	
	ANTI-A	***ANTI-B***	***A CELLS***	***B CELLS***
A	+	-	-	+
B	-	+	+	-
AB	+	+	-	-
O	-	-	+	+

TABLE 46-3 -- Donor Blood Groups That Patients Can Receive

DONOR	RECIPIENT
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

antibodies missed in this phase can be detected in the subsequent antiglobulin phase.

The last, and third, phase of the crossmatch, the indirect antiglobulin test, involves the addition of antiglobulin sera to the incubated test tubes. With this addition, antihuman antibodies present in the sera become attached to the antibody globulin on the RBCs, thus causing agglutination. This antiglobulin phase detects most incomplete antibodies in the blood group systems, including the Rh, Kell, Kidd, and Duffy blood group systems.

Although all three phases of the crossmatch are important, the first two stages are of prime importance in preventing serious hemolytic transfusion reactions (see Type and Screen). The incubation and antiglobulin phases are especially important because the antibodies appearing in these phases are capable of causing serious hemolytic reactions. Except for hemolytic reactions involving anti-A and anti-B, reactions caused by antibodies appearing in the immediate phase (RT) are frequently less severe. This is because many of the antibodies appearing in this phase are naturally occurring antibodies present in a low titer and are not reactive at physiologic temperatures.

Antibody Screening

The antibody screen is also carried out in three phases and is similar in length to the crossmatch. The screen, however, is a trial transfusion between the recipient serum and commercially supplied RBCs that are specifically selected to contain optimal numbers of RBC antigens, or those antigens that will react with antibodies that are commonly implicated in hemolytic transfusion reactions.

The screen for unexpected antibodies is also used on donor serum and is performed shortly after withdrawal of blood from the donor. It is necessary to screen donor serum for unexpected antibodies in order to prevent their introduction into the recipient serum. This screen is performed primarily to prevent reactions between transfused donor units.

Approaches Requiring Less Than a Complete Crossmatch

Type and Screen

The term *type and screen* refers to elimination of the crossmatch in which blood is set aside with only the ABO-Rh type having been determined and antibody screening having been performed. The type and screen without crossmatch determines both the ABO-Rh of the patient and the presence of the most commonly found unexpected antibodies. Specifically, the patient's serum is screened for the presence of unexpected antibiotics by incubating it with selected reagent RBCs (screen cells). [28] These cells contain all antigens capable of inducing clinically significant RBC antibody reactions.

Complete transfusion testing for compatibility between donor and recipient blood ensures optimal safety and therapeutic effect of transfused blood. In some cases, however, the crossmatch is eliminated, and blood can be set aside in which only the ABO-Rh type and antibody screen are performed (type and screen). For those few patients in whom the antibody screen reveals the presence of unexpected antibody, the antibody is subsequently identified in the blood bank, and units of blood lacking the corresponding antigen are set aside for surgery. If an emergency transfusion is required after type and screen alone, an immediate-phase crossmatch is performed before transfusion to eliminate reactions that may result from human errors in ABO-Rh typing. Blood given in this manner is more than 99 percent effective in preventing incompatible transfusion reactions due to unexpected antibodies. [29] The type and screen without the complete crossmatch does not protect against reactions due to antibodies reactive against lower-incidence antigens, those not represented on the screening cells but present on the donor RBCs. Generally, antibodies that are not detected in the type and screen are weakly reactive antibodies that do not result in serious hemolytic transfusion reactions. In a study of 13,950 patients, Oberman et al [30] discovered only 8 "clinically significant" antibodies after complete crossmatch that were not detected during the antibody screening.

The antibodies were all in lower titer and were believed by Oberman and coworkers to be unlikely to cause serious hemolytic reactions.

The type and screen should not be confused with the term *type and hold.* The latter term refers to a sample of blood from a potential blood recipient received by the blood bank in which the blood type but no crossmatch has been ordered. This term is misleading because it does not denote how long the blood should be held, nor does it indicate that an antibody screen has been performed on the sample. However, in most cases in which a type and hold has been ordered, an antibody screen is performed on that sample. Because of the confusion that has arisen with type and screen, the type and hold terminology and method of ordering blood have been abandoned by most blood banks.

Maximal Surgical Blood Order Schedule

Routine preoperative crossmatching of blood for surgical cases means that crossmatched blood is unavailable for others for 24 to 48 hours. During this time, 1 to 2 days is lost, and the chance for outdating increases. A second aspect relates to the growing realization that, for certain elective surgical procedures, the number of crossmatched units that are ordered frequently far exceeds the number actually transfused. To quantify this problem better, the crossmatch-to-transfusion (C/T) ratio has been used. If the C/T ratio is high, the blood bank is burdened with keeping a large blood inventory, using excessive personnel time, and having a high incidence of outdated units. Sarma [31] recommended that for surgical procedures in which the average number of units transfused per case is less than 0.5, determination of the ABO-Rh type and a screen of the patient serum for unexpected antibodies (type and screen) should be used. This would be in lieu of a complete type and crossmatch for patients with negative antibody screens. For those with a positive antibody screen, the blood bank must provide compatible units that lack the corresponding antigen. Blood banks attempt to maintain C/T ratios of 2.1 to 2.7. [31] To increase utilization rate and lower the C/T ratio, blood banks attempt to decrease the emphasis on crossmatching of blood through such means as the type and screen and such programs as the maximal surgical blood order schedule. [32] This schedule consists of a list of surgical procedures and the maximum number of units of blood that the blood bank will crossmatch for each procedure. This schedule is based on the blood transfusion experience for surgical cases in hospitals in which the schedule is employed. Each hospital's maximal surgical blood order schedule is developed by both the suppliers and the users of blood in that hospital, such as blood bankers, anesthesiologists, and surgeons.

Is the Crossmatch Really Needed?

In previously transfused or pregnant patients, only about 1 patient in 100 may have an irregular antibody other than the anti-A and/or anti-B antibodies. However, some of these irregular antibodies are reactive only at temperatures below 30°C and therefore are insignificant in most transfusions. Others that are reactive at about 30°C can produce serious reactions if the transfused cells contain appropriate antigen. In order of probable significance, anti-Rh(D), Kell, C, E, and Kidd are the most common of clinically significant antibodies. After anti-A and anti-B, anti-Rh(D) is the most common significant antibody. If the correct ABO and Rh blood type is given, the possibility of transfusing incompatible blood is less than 1 chance in 1,000. Put in other terms, ABO-Rh typing alone results in a 99.8 percent chance of a compatible transfusion, the addition of an antibody screen increases the safety to 99.94 percent, and a crossmatch increases this to 99.95 percent. [33]

The blood bank can reduce the chance of incompatibility by performing an antibody screen. The chances of this screening test's missing an antibody that is potentially dangerous has been estimated to be no more than 1 in 10,000.

Emergency Transfusion

In many situations, there is urgent need for blood before completion of compatibility testing (ABO-Rh, antibody

screen, and crossmatch) (Ch. 62) . For those situations that do not allow time for complete testing, an abbreviated format for testing can be used. The preferred order for the selection of partially crossmatched blood is as follows.

Type-Specific Partially Crossmatched Blood

When using uncrossmatched blood, it is best to obtain at least an ABO-Rh typing and an immediate-phase crossmatch. This incomplete crossmatch is accomplished by adding the patient's serum to donor RBCs at room temperature, centrifuging it, and then reading it for macroscopic agglutination. This takes 1 to 5 minutes and eliminates serious hemolytic reactions resulting from errors that may occur in ABO typing. Only a few unexpected antibodies outside the ABO systems are detected, such as those directed against antigens in the MN, P, and Lewis systems, most of which are not clinically significant.

Type-Specific, Uncrossmatched Blood

For proper use of type-specific blood, the ABO-Rh type must be determined during the patient's hospitalization. Blood types from historical records, relatives, ambulance drivers, and other hospitals are frequently inaccurate. For those who have never been exposed to foreign RBCs, most ABO type-specific transfusions are successful. Caution should be used for those patients who have previously received transfusions or have had pregnancies. In the author's experience in the military, type-specific uncrossmatched blood was frequently used in emergencies with no serious consequence. In the civilian setting, using 1 year's experience with 56 patients, uncrossmatched, type-specific blood for emergency transfusion produced no adverse effects, even though complete serologic testing had not been performed. [34] These authors concluded that although the use of uncrossmatched blood is usually safe, the potential for serious reaction still exists, and they thus cautioned against its indiscriminate use. Specifically, about 1 in 1,000 patients has an unexpected antibody detected in crossmatch. For those who have previously been exposed to RBC antigens, transfusion of the ABO-Rh type-specific uncrossmatched blood may be more hazardous. For every 100 of these individuals, one has an antibody detected in the crossmatch.

Type O Rh-Negative (Universal Donor), Uncrossmatched Blood

Type O blood lacks both the A and B antigens and consequently cannot be hemolyzed by anti-A or anti-B antibodies in the recipient's blood (see Tables 46-2 and 46-3) . Because of this, type O blood has been termed the *universal donor* and can be used in emergency transfusion when typing or crossmatching is not available. However, some type O donors produce high titers of hemolytic IgG, IgM, anti-A, and anti-B antibodies. High titers of these hemolysins in donor units are capable of causing destruction of A or B red blood cells of a non-type O recipient. Thus, type O Rhnegative uncrossmatched packed RBCs should be used in preference to type O Rh-negative whole blood because packed erythrocytes have smaller volumes of plasma and are almost free of hemolytic anti-A and anti-B antibodies. If type O Rh-negative whole blood is to be used, the blood bank must supply type O blood that is free of hemolytic anti-A and anti-B antibodies.

During emergency transfusion of more than two units of type O Rh-negative uncrossmatched whole blood, the patient probably cannot be switched to his or her blood type (A, B, or AB) once the blood bank determines the correct blood type. Switching could cause major intravascular hemolysis of donor RBCs by increasing titers of transfused anti-A and anti-B. Continued use of O Rh-negative whole blood results only in minor hemolysis of recipient RBCs, with hyperbilirubinemia as the only complication. The patient must not be transfused with his or her correct blood type until the blood bank determines that the transfused anti-A and anti-B has fallen to levels that permit safe transfusion of type-specific blood.

Specific Recommended Protocol

In view of the aforementioned considerations, the following steps are recommended in patients who are hypovolemic and require blood transfusion:

1. Infuse crystalloids or colloids
2. Draw a blood sample for typing and cross-matching
3. If crossmatched blood is not ready to give: typespecific or type O Rh-negative cells, or type O Rh-positive cells for males or postmenopausal females without a history of transfusions; type-specific, partially crossmatched blood; type-specific, crossmatched blood

Storage of Blood

Citrate phosphate dextrose adenine (CPDA-1) is an anticoagulant preservative in which blood is stored at 1 to 6°C. Citrate is an anticoagulant, phosphate serves as a buffer, and dextrose is a red cell energy source. The addition of adenine to CPD solution allows RBCs to resynthesize adenosine triphosphate (ATP), which extends the storage time from 21 to 35 days. As a result, RBCs or whole blood can be stored for 35 days when stored in CPDA-1. [35] The shelf life can be extended to 42 days when AS-1 (Adsol) or AS-3 (Nutricel) is used. [36] [37] Adsol contains adenine, glucose, mannitol, and sodium chloride; Nutricel contains glucose, adenine, citrate, phosphate, and sodium chloride. This duration of storage has been set by U.S. federal regulation and is determined by the requirement that at least 70 percent of the transfused RBCs remain in circulation for 24 hours after infusion. RBCs that survive 24 hours after transfusion disappear from the circulation at a normal rate. Those that do not survive are subsequently removed from the circulation by the blood recipient.

The citrate ion prevents clotting by binding calcium; dextrose allows the RBCs to continue glycolysis and thus maintain sufficient concentrations of high-energy nucleotides (ATP) to ensure continued RBC metabolism and subsequent viability during storage. The storage at 1 to 6°C assists

TABLE 46-4 -- Properties of Whole Blood and Packed Red Cell Concentrates Stored in CPDA-1

PARAMETER	DAYS OF STORAGE		
	0	***35 (WHOLE BLOOD)***	***35 (PACKED CELLS)***
pH	7.55	6.73	6.71
Plasma hemoglobin (mg/dL)	0.5	46	246.0
Plasma potassium (mEq/L)	4.2	17.2	76.0
Plasma sodium (mEq/L)	169	153	122
Blood dextrose (mg/dL)	440	282	84
2,3-Diphosphoglycerate (muM/mL)	13.2	<1	<1
Percent survival [a]	--	79	71

CPDA-1, citrate phosphate dextrose adenine-1

[a] Percent recovery of O_R -tagged red blood cells at 24 hours

preservation by slowing the rate of glycolysis approximately 40 times the rate at body temperature. The addition of adenine prolongs storage time by increasing RBC survival by allowing RBCs to resynthesize the ATP needed to fuel metabolic reactions. Without adenine, RBCs gradually lose their ATP and their ability to survive after transfusion.

During storage of whole blood and packed RBCs, a series of biochemical reactions occur that alter the biochemical makeup of blood and account for some of the complications that are discussed later. During storage, RBCs metabolize glucose to lactate, hydrogen ions accumulate, and plasma pH decreases. The storage temperatures of 1 to 6°C stimulate the sodium-potassium pump, and RBCs lose potassium and gain sodium. The osmotic fragility of RBCs increases during storage, and some cells undergo lysis, resulting in elevated plasma hemoglobin levels. Also, storage is associated with progressive decreases in RBC concentrations of ATP and 2,3-diphosphoglycerate (2,3-DPG).

Interestingly packed RBCs have a slightly lower survival than whole blood (Table 46-4) , although values for hemoglobin and potassium concentrations may appear somewhat high in 35-day stored RBC concentrates. However, it should be remembered that the total plasma volume in the concentrates is only 70 mL.

Frozen Storage

Satisfactory storage of RBCs in the frozen state became possible when these cells, mixed with glycerol, could be frozen and thawed without damage. RBCs previously frozen to 79°C in glycerol survive well in humans. RBCs must be free from glycerol before being transfused; unfortunately, a simple and inexpensive method of removing the glycerol has been difficult to develop. Valeri [38] studied the efficacy of using frozen RBCs and has attempted to simplify the method of freezing and thawing RBCs to make it a more viable process. The advantages of frozen and thawed RBCs are the following: (1) blood of rare types can be stored for long periods, increasing viability and eliminating outdating; (2) frozen, reconstituted blood is believed to be safer in patients who are especially susceptible to allergic reactions, because the freezing and washing process reduces sites with histocompatible antigens; (3) frozen washed blood may reduce risk of transfusion hepatitis; (4) frozen blood, low in fibrin and leukocytic aggregates, would be safer in patients requiring massive blood transfusion; and (5) frozen RBCs may be desirable in clinical conditions requiring prompt tissue oxygenation because normal levels of 2,3-DPG are retained in frozen erythrocytes. The efficacy of using frozen, thawed RBCs on a large-scale basis was proved possible at Cook County Hospital in Chicago, during a 28-month period. [39] In my opinion, there can be no doubt that blood can be stored for years, and this certainly would help alleviate the problem of having uncommon blood types not readily available. The incidence of transfusion reactions can clearly be reduced. Furthermore, the use of frozen RBCs can minimize alloimmunization to human leukocyte antigen and to membrane-specific antigens present on transfused white blood cells. However, these advantages can be more readily achieved by use of currently available washing devices. However, the original claim that the use of frozen RBCs would decrease the incidence of hepatitis seems to be unfounded. [40] As a result, frozen storage will continue to be used only on a limited basis.

Heparin

Whole blood stored in heparin is used in some situations for priming the pump during cardiopulmonary bypass. Heparinized whole blood is used by some clinicians in open-heart surgery to prevent cardiac abnormalities that might result from depression of ionized calcium levels by the citrate in other storage solutions. Furthermore, factor VIII complex is more stable than when other storage solutions are used for storage. Heparin anticoagulant is not a RBC preservative because it lacks glucose. Its anticoagulant effect is also neutralized during storage by the thromboplastic substances liberated by the cellular elements of blood during storage. Consequently, blood stored in heparin must be used within 24 to 48 hours of collection.

Complications

Changes in Oxygen Transport

RBCs are transfused primarily to increase transport of oxygen to tissues. An increase in the circulating red cell mass produces an increase in oxygen uptake in the lungs and a corresponding probable increase in oxygen delivery to tissues. The respiratory function of red cells may be impaired during preservation, making it difficult for them to release oxygen to the tissues immediately after transfusion.

In 1954, Valtis and Kennedy [41] first described a leftward shift of the oxygen dissociation curve *in vitro,* the magnitude of which was directly related to the length of time the acid citrate dextrose (ACD) blood had been stored. After transfusion of 7-day or older ACD blood, the oxygen dissociation curves of all patients also shifted to the left. The magnitude of the left shift was related to the volume and storage time of the infused ACD blood. In some cases, the curve remained shifted to the left for as long as 24 hours after transfusion.

Figure 46-2 Factors that shift the oxygen dissociation curve. *(From Miller [176])*

Review of the Oxygen Dissociation Curve

The oxygen dissociation curve is determined by plotting the partial pressure of oxygen (P_{O_2}) in blood against the percentage of hemoglobin saturated with oxygen (Fig. 46-2) . As hemoglobin becomes more saturated, the affinity of hemoglobin for oxygen also increases. This is reflected in the sigmoid shape of the curve, which indicates that a decrease in Pa_{O_2} makes considerably more oxygen available to the tissues. Thus, the sigmoid shape of the curve implies greater efficiency of blood transportation of oxygen from the lungs to tissues.

Shifts in the oxygen dissociation curve are quantitated by the P_{50}, which, by convention, is the partial pressure of oxygen at which hemoglobin is half saturated with oxy-gen at 37°C and pH 7.4. A low P_{50} indicates a left shift in the oxygen-dissociation curve and an increased affinity of hemoglobin for oxygen; in other words, the left shift of the curve indicates that a lower-than-normal oxygen ten-sion saturates hemoglobin in the lung and the subsequent release of oxygen to the tissues occurs at a lower than normal capillary oxygen tension. An increased affinity may be enough to ensure that oxygen is released to the tissues unless the tissue P_{O_2} is in the hypoxic range. The theoretical and clinical evidence supporting the accuracy of this hypothesis during infusion is discussed in the following sections.

Theoretical Evidence

A close relationship between the oxygen affinity of stored blood and intraerythrocytic 2,3-DPG has been established. [42] The intraerythrocytic 2,3-DPG levels decrease stored bank blood. Alkalosis and hypothermia shift the curve to the left even more (Fig. 46-2) . Support for the importance of these shifts in the curve base can be derived from studies that manipulate the Fick equation, that is, that cardiac output (CO) equals oxygen consumption (O_2) divided by the arteriovenous oxygen difference (Ca_{O_2} - Cv_{O_2}, or $C(a\text{-}v)O_2$). Rearranged, the equation reads

$$Cv_{O_2} = Ca_{O_2} - VO_2/CO$$

Therefore, mixed venous oxygen content or tension reflects the relationship between oxygen consumption and cardiac output. A low mixed-venous oxygen tension suggests that cardiac output cannot meet the tissue oxygen demands.

Clinical Evidence

The clinical evidence is not consistent, reflecting the difficulty of conducting a systematic study of seriously ill patients in varied clinical settings. Kopriva et al [43] found that 2,3-DPG levels decreased in 31 seriously injured battle

casualties, each of whom received 12 or more units of ACD-stored blood. Furthermore, transfusion of fresh or stored blood did not influence the 2,3-DPG levels. The more common finding is that the P_{50} and 2,3-DPG levels do decrease after infusion of stored blood. [44] Although Sheldon [45] did find low P_{50} and 2,3-DPG values after infusion of CPD-stored blood (at 90% of the blood volume), no correlation between these values and cardiac index was found. On a theoretical basis, however, the left shift in the oxygen dissociation curve and the increased affinity for oxygen may increase cardiac output and work of the heart. [44] If a patient has marginal cardiac reserve and cannot increase cardiac output, tissue hypoxia may occur.

Although this evidence is suggestive, specific organ hypoxia has not been shown to result from infusion of blood with a low P_{50} or from increased affinity for oxygen. Valeri and Collins [46] performed a study in a group of patients who especially depended on adequate levels of 2,3-DPG for oxygen transport. Patients who had anemic hypoxia were transfused with three to five units of washed, liquid-stored RBCs that were depleted of 2,3-DPG and experienced an increased affinity for oxygen. No change in cardiac index or oxygen consumption resulted. Therefore, even in patients in whom 2,3-DPG is especially important for oxygen transport, no changes occurred. In fact, Bowen and Fleming [47] showed that although oxyhemoglobin affinity increases after transfusion of stored blood, arteriovenous oxygen extraction by organs or tissue may not be altered by changes in oxyhemoglobin affinity, particularly if a compensatory flow mechanism takes place at the capillary level. Such mechanisms may open capillaries, permitting increased blood flow to tissue, thereby increasing cardiac output and reducing the capillary tissue oxygen gradient to maintain the rate of tissue oxygen extraction. Because of the low P_{50} and the increased oxyhemoglobin affinity of stored blood, assessment of specific organ function is necessary to substantiate the possible injurious effect of stored blood. Marik and Sibbard [9] found that the administration of blood that had been stored for more than 15 days actually decreased intramucosal pH, suggesting that splanchnic ischemia had occurred. Was this effect due to low 2,3-DPG levels in the stored blood and to an increased affinity of hemoglobin for oxygen? Despite these data, the evidence that possible changes in oxygen affinity from blood transfusions are important is not available. Therefore, it is difficult to come to definitive conclusions.

Coagulation

A bleeding tendency is often present in massively transfused patients. This coagulopathy is caused by a combination of factors of which the most important are the volume of blood given and the duration of hypotension or hypoperfusion. [48] Patients who are well perfused and are not hypotensive for a long period of time (e.g., 1 hour) can tolerate multiple units of blood without developing a coagulopathy. Clearly, the patient who is hypotensive and has received many units of blood probably has a coagulopathy from both disseminated intravascular coagulation (DIC) and dilution of coagulation factors from stored bank blood. When such bleeding occurs, the differential diagnosis for a patient who did not have a pretransfusion coagulopathy (e.g., hemophilia) is dilutional thrombocytopenia, low factors V and VIII, DIC, or hemolytic transfusion reaction. Clinical manifestations include oozing into the surgical field, hematuria, gingival bleeding, petechial bleeding from venipuncture sites, and ecchymoses.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia is a cause of a hemorrhagic diathesis in a patient who has received multiple units of bank blood. At a storage temperature of 4°C, platelets in stored blood are damaged sufficiently to be readily trapped and absorbed by the reticuloendothelial system soon after infusion. Even those platelets that are not immediately stored have a reduced survival time. Considering survival time and viability, total platelet activity is only 50 to 70 percent of the original *in vivo* activity after 6 hours of storage in bank blood at 4°C. After 24 or 48 hours of storage, platelet activity is only about 10 or 5 percent of normal, respectively. Thus, infusion of bank blood stored for longer than 24 hours dilutes the available platelet pool. In one study during the Vietnam conflict, platelet counts were found to decrease to below 100,000/mm^3 when 10 to 15 units of blood had been given to acutely wounded, previously healthy soldiers. [49] Obviously, the platelet count in smaller, older patients may decrease to 100,000/mm^3 after fewer units of blood because these patients have a smaller blood volume and possibly a lower preoperative platelet count than soldiers. I strongly emphasize the importance of the platelet count because when it is approximately 75,000/mm^3 or lower, a hemorrhagic diathesis is likely to occur (Table 46-5) .

Although major emphasis had been placed on monitoring the platelet count, several authors [48] [50] [51] have questioned the role of dilutional thrombocytopenia in the coagulopathy of massively transfused patients. They correctly point out that the platelet count rarely decreases as low as what would be predicted from dilution alone (Fig. 46-3) (Figure Not Available) . This is probably because platelets are released into the circulation from the spleen and bone marrow and because of the presence of nonfunctional platelets. Furthermore, Reed et al [51] found no benefit to prophylactic platelet administration during massive transfusion. Platelets should not be given to treat laboratory evidence of thrombocytopenia unless clinical coagulopathy is also present. Treating laboratory numbers without correlation with the clinical status is fundamentally contrary to good medical practice; transfusion medicine is no exception. Clearly, when the platelet count is below 50,000 to

TABLE 46-5 -- Correlation Between Platelet Count and Incidence of Bleeding

PLATELET COUNT (cells/mm^3)	TOTAL NO. OF PATIENTS	NO. OF PATIENTS WITH BLEEDING

>100,000	21	0
75,000-100,000	14	3
50,000-75,000	11	7
<50,000	5	5

Data from MIller et al [49]

Figure 46-3 (Figure Not Available) Mean platelet counts after massive transfusions in relation to number of units of blood transfused. Observed versus predicted values calculated on the basis of blood exchange model. *(From Myllyla* [179] *)*

75,000/mm^3 , a bleeding problem is likely and is probably a combination of dilutional thrombocytopenia and DIC. Platelet therapy would be appropriate in this situation (see Platelet Concentrates).

To place such emphasis on the platelet count as a guide is appropriate, as defended previously, with some exceptions. For example, patients with chronic thrombocytopenia or leukemia are commonly known to survive and not have a hemorrhagic diathesis with a platelet count lower than 15,000 cells/mm ^{3} . However, this does not negate the general guideline that patients with a platelet count of less than 75,000 cells/mm ^{3} are likely to bleed. For unexplained reasons, patients with an acutely induced thrombocytopenia (e.g., from blood transfusions) develop a hemorrhagic diathesis at a much higher platelet count than do patients with a chronically induced thrombocytopenia (e.g., idiopathic thrombocytopenia purpura). Furthermore, a higher platelet count is required to maintain adequate hemostasis with a surgical incision or trauma, because damaged capillaries require platelets to plug the holes. Thus, the platelet count is a reasonably accurate guide as to when patients will develop a bleeding problem from dilutional thrombocytopenia (see Table 46-5) .

Low Factors V and VIII

Most of the factors are stable in stored blood, with two exceptions: factors V and VIII. [52] These factors gradually decrease to 15 and 50 percent of normal, respectively, after 21 days of storage. Furthermore, packed RBCs even have fewer coagulation factors. Consequently, administration of fresh frozen plasma (FFP), which contains all the factors except platelets, has been recommended on either a therapeutic or a prophylactic basis. However, this practice is of questionable benefit because only 5 to 20 percent of factor V and 30 percent of factor VIII are needed for adequate hemostasis during surgery. In other words, in spite of a patient's receiving massive blood transfusion, factors V and VIII rarely decrease below those levels required for hemostasis. Miller et al [49] examined this problem by giving 500 to 1,000 mL of FFP to five patients who had received more than 15 units of bank blood and who had a clinically significant hemorrhagic diathesis. Despite the partial thromboplastin times (which measure all factors except VII and XIII) and platelets' having returned to normal, bleeding persisted in every patient. Only when platelets in the form of fresh blood were administered did bleeding cease. [49] Thus, although low factors V and VIII appear to be an unlikely primary cause of bleeding during massive blood transfusion, such deficiencies may intensify bleeding from other causes, usually dilutional thrombocytopenia in the case of blood transfusion.

Despite evidence to the contrary, FFP continues to be commonly given for treatment of transfusion-induced coagulopathies. The overall increased use of FFP in the 1970s led the National Institutes of Health to conduct a consensus conference on this issue in 1985. [53] The conference concluded that there was little or no scientific evidence for the administration of FFP as part of the therapy for coagulopathy induced by multiple blood transfusion. Despite the National Institutes of Health statement, component blood therapy, especially FFP, continues to be given. [54] If the clinician insists on seriously considering giving FFP, the following criteria should be established:

1. Generalized bleeding that cannot be controlled with surgical sutures or cautery
2. Partial thromboplastin time at least 1.5 times normal
3. Platelet count greater than 70,000/mm^3 (to ensure that thrombocytopenia is not the cause of bleeding)

Disseminated Intravascular Coagulation

The coagulation system consists of clotting and fibrinolytic mechanisms. The function of the former is to prevent excessive blood loss, and that of the latter is to ensure circulation within the vasculature. With DIC, the clotting system is deranged, and this leads to disseminated fibrin deposition, which renders the fluid blood unclottable. The deposited fibrin may severely alter the microcirculation and lead to ischemic necrosis in various organs, particularly the kidney. The unclottable blood or circulating serum may induce a severe hemorrhagic diathesis.

The specific reasons for the development of DIC are usually not apparent. However, hypoxic acidotic tissues with stagnant blood flow probably release tissue thromboplastin either directly or through liberation of some toxin. In sepsis and eventual organ failure, the pathogenesis of DIC is more apparent. Apparently the extrinsic route of coagulation is activated by tumor necrosis factor and endotoxins. Presumably, tumor necrosis factor induces tissue factor expression on the surface of activated monocytes and possibly by exposure to subendothelially localized tissue factor in blood. [55] Although the intrinsic system does not induce DIC, it may contribute to hypotension. This triggers the coagulation

Figure 46-4 (Figure Not Available) Schematic representation of primary fibrinolysis and fibrinol-ysis secondary to disseminated intravascular coagulation (DIC). Although epsilon-aminocaproic acid (EACA) inhibits primary fibrinolysis, it also inhibits secondary fibrinolysis, one of the main defenses against DIC. *(From Miller* [52] *)*

process (Fig. 46-4) (Figure Not Available) , resulting in consumption of factors I, II, V, and VIII and platelets. Supposedly, thrombi and fibrin are deposited in the microcirculation of vital organs, interrupting their blood flow.

In an attempt to counteract the hypercoagulable state, the fibrinolytic system is activated to lyse the excessive fibrin almost simultaneously; this is termed *secondary fibrinolysis.* Primary fibrinolysis is very rare and refers to activation of the fibrinolytic system without concomitant DIC (Fig. 46-4) (Figure Not Available) . With secondary fibrinolysis, activation of plasminogen to plasmin (fibrinolysis; see Fig. 46-4) is a protective mechanism that tends to prevent further DIC. With fulminate DIC and subsequent rapid depletion of coagulation factors, plasmin is formed from plasminogen at a rapid rate. The resultant fibrinolysis caused by plasmin creates a paradoxical state. Fibrinolysis does protect against further DIC but may also contribute to the severity of the bleeding diathesis. Plasmin digests fibrinogen, further reducing the fibrinogen level. The digestion of fibrinogen results in the formation of fibrin-split products in the serum; the presence of these products indicates fibrinolysis. While the fibrinolytic system is actively trying to counteract DIC in early stages, plasminogen activator activity and plasmin generation rapidly decline, leaving DIC to progress unopposed. [55] It is at this stage that severe morbidity and eventually mortality are likely to occur.

Disseminated intravascular coagulation should not be considered a distinct disease entity but rather a sign of another disease. Accordingly, DIC has been associated with nearly all life-threatening diseases. Any condition in which tissue damage is sufficient to release tissue products or toxins into the circulation can be associated with DIC. Should enough thromboplastin lodge in the circulating blood, the result is massive focal necrosis or more generalized activation of the coagulation system.

That DIC is a primary cause of organ failure, as suggested earlier, is an attractive hypothesis but has been challenged. Attar et al [56] observed probable DIC in 294 patients with shock but found no fibrin deposits in 52 of them examined at autopsy. Furthermore, survival rates of patients who have DIC associated with hypovolemia or septic shock are not increased by the administration of heparin. [57] [58] Mant and King [59] provided an excellent evaluation of 47 patients with severe acute DIC mostly resulting from shock, infections, trauma, hepatic disease, and malignancy. Routine treatment included aggressive therapy of the underlying diseases and administration of blood products and vitamin K when indicated. Of the 47 patients, 12 were treated with heparin; bleeding worsened in seven (58%) and DIC diminished in five (42%). A total of 35 patients did not receive heparin; the DIC diminished in 13 (37%), but overall, 30 patients (86%) died. The investigators felt death could not have been prevented by heparin therapy. Also, microvascular thrombi were not found in 25 patients examined at autopsy. On the basis of these

findings, Mant and King [59] provided the following conclusions, which we feel accurately summarize the current knowledge of DIC:

1. DIC is a relatively uncommon entity.
2. Accompanying microvascular thrombosis is uncommon.
3. DIC rarely causes significant organ damage and infarction.
4. Accompanying large vessel thrombosis is relatively common but is probably not primarily caused by DIC.
5. Although bleeding is common, severe bleeding usually originates from sites of local disorder (e.g., lacerated liver).
6. Heparin is seldom useful and often causes hemorrhage.
7. DIC is associated with high mortality primarily because of the severity of the patient's underlying disorder.
8. DIC is perhaps best regarded as an incidental preterminal event in most patients.

More recently, Fourrier et al [60] confirmed the aforementioned statements and concluded that DIC is a strong predictor of death. These investigators found that measurements of antithrombin III, protein C, and protein S levels were consistent with sustained DIC and inhibition of fibrinolysis. In fact, they stated that initial antithrombin III levels were the best predictor of death in septic patients.

Hemolytic Transfusion Reaction

The appearance of a hemorrhagic diathesis after blood transfusion should signal the possibility of a hemolytic transfusion; this entity is discussed later in this chapter.

Figure 46-5 (Figure Not Available) Correlation between units of blood administered and percent of patients who had a hemorrhagic diathesis. The numbers in parentheses represent the number of patients at each data point. *(From Miller [180])*

Diagnosis and Treatment of a Hemorrhagic Diathesis After Whole Blood Transfusions

Although treatment is more likely to be successful when the cause of the bleeding problem has been identified, precise diagnosis is often difficult. The more common, readily available laboratory tests seldom yield information precise enough to establish an accurate diagnosis. [52] For example, thrombocytopenia is most likely on a dilutional basis but could be secondary to DIC alone or DIC associated with a hemolytic transfusion reaction. Laboratory tests offering more precise information, such as euglobulin lysis time, often are not readily available or take too long to perform to be practical in an emergency situation.

When the problem of a clinical hemorrhagic diathesis associated with blood transfusions occurs, one approach is to obtain a blood specimen on which the following tests can be performed: platelet count, partial thromboplastin time, plasma fibrinogen level, and observation of a clot for size, stability, and lysis and of the plasma for evidence of hemolysis. For many years, thromboelastography and assessment of the viscoelastic properties of plasma (Sonoclot) [61] have occasionally been recommended for monitoring the influence of blood loss and transfusions on coagulation. However, these techniques have not been widely accepted.

Although many other diagnostic approaches probably are equally valid, the preceding approach works well for me. Provided that the partial thromboplastin time is 1.5 times normal or more increased and other tests are normal, the bleeding is probably a result of very low levels of factors V and VIII. This can be treated with FFP, which contains all the coagulation factors except platelets. Although the preceding situation is a nice textbook description, I have never observed clinical situation involving blood transfusions in which the partial thromboplastin time was increased without the presence of thrombocytopenia.

As indicated, dilutional thrombocytopenia in association with DIC is the most likely cause of bleeding from blood transfusion. [49] [52] When the platelet count is less than 100,000/mm^3 , a bleeding problem is likely to develop (see Table 46-4) ; therefore, platelets are ordered. Unfortunately, the common delay between ordering and receiving the platelets dictates that they be ordered before the appearance of a hemorrhagic diathesis. Our rule of thumb is based on the fact that a bleeding diathesis probably will develop after infusion of 20 units of stored blood in healthy patients and after lesser amounts in debilitated or small patients (Fig. 46-5) (Figure Not Available) . Therefore, platelets should be ordered after infusion of 9 or 10 units of blood when several more will probably be required. Ideally, the platelets are available when 20 to 25 units of blood has been administered. The timing of ordering platelets in relation to when they will actually be required depends on the capabilities and the limitations of the local blood bank, which differ widely throughout the United States. Thus, the anesthesiologist and the surgeon must consult the blood bank before the need for platelets or any other blood component emerges.

Whether platelets are administered in the form of fresh blood, platelet-rich plasma, or platelet concentrates depends on volume replacement requirements, personal preference, and availability of laboratory personnel. Fresh blood (<6 hours old) supplies the greatest number of platelets per donation. More than 80 percent of the platelets can be given by platelet-rich plasma, which has half the volume of a unit of blood. However, because most blood banks advocate giving patients only those components that are necessary, platelet concentrates are frequently recommended. The remainder of the unit of blood, such as RBCs, plasma, and albumin, can be saved for other patients. Platelet concentrates are contained in a 50-mL unit and provide about 70 percent of the platelets in a unit of blood. In a 70-kg person, about 10 units of platelet concentrates is required to increase the platelet count by 100,000/mm ^{3} Although platelet concentrates are usually recommended, when a hypovolemic patient also needs replacement of RBCs, albumin, and other plasma coagulation factors, the infusion of fresh whole blood, if available, may be more practical than trying to infuse each of the components individually.

Although logistically difficult to obtain, fresh blood has been found to be extremely effective in treating transfusion-induced coagulopathies. My personal and subjective observations in Vietnam indicated that fresh blood (i.e., 6 hours or less and unrefrigerated blood) had a dramatic effect in patients with extensive hemorrhage. [49] About 20 years later, Lavee et al [62] found that 1 unit of fresh whole blood was as effective as, if not superior to, 8 to 10 platelet units. In 1996, Erber et al, [63] used fresh unrefrigerated whole blood in surgical patients with ongoing extensive bleeding despite adequate component replacement therapy and adequate surgical hemostasis. An accompanying editorial expressed caution and described the unfortunate problems with conducting a larger trial with fresh blood. [64] I believe that fresh blood also contains unidentified factors that make it far more effective than blood components.

Determining the plasma fibrinogen level is useful because this coagulation factor does not decrease in bank blood. Therefore, if the *in vivo* plasma fibrinogen level is low (<150 mg/100 mL), this is not a result of a dilutional coagulopathy and strongly suggests DIC. DIC is likely with thrombocytopenia, hypofibrinogenemia, and lysis of a clot within 2 hours. [52] Unfortunately, fibrinogen levels in packed

---

RBCs decrease with increasing storage time. As a result, hy-pofibrinogenemia occurs on a dilutional basis when multiple units of packed RBCs are given. [65] Thus, the separation of thrombocytopenia on a dilutional basis versus DIC cannot be accomplished by the use of fibrinogen level when packed RBCs have been given. Perhaps more specific readily available tests will be available in the future, [60] which will be especially important with potential therapies that are currently unavailable (e.g., monoclonal antibodies, anti-tumor necrosis factor antibodies, recombinant interleukin/receptor antagonists). [55] As indicated previously, the most effective treatment of DIC is removal or treatment of the basic disease process causing the DIC; these diseases usually cause DIC by release of damaged tissue products into the circulation. For example, the DIC associated with abruptio placentae usually ceases after emptying of the uterus and restoration of blood volume.

epsilon-Aminocaproic acid (EACA) inhibits the formation of plasmin and attenuates fibrinolysis (see Fig. 46-4) (Figure Not Available) . Obviously, EACA should not be used in the treatment of DIC. Blocking the fibrinolytic system and having the coagulation system activated have resulted in disseminated thrombosis. Because primary fibrinolysis is extremely rare other than in prostatectomy and liver transplantation [66] (Ch. 55) , EACA probably should not be given unless the preceding diagnosis is clearly established after expert consultation. As indicated, administration of EACA (for what was thought to be primary fibrinolysis but was really fibrinolysis secondary to DIC) can result in severe thrombotic episodes. Because the tests to distinguish primary from secondary fibrinolysis are not usually available, the risks of thrombotic episodes from EACA can be minimized by concomitant administration of heparin. Obviously, this becomes a complicated coagulation problem that exceeds the expertise of most surgeons and anesthesiologists.

Drugs Used to Improve Hemostasis

In addition to EACA, three other drugs have been recommended for perioperative coagulation problems. Two of those drugs have received special attention. The first is desmopressin (DDAVP), which is a synthetic analogue of the antidiuretic hormone vasopressin. It increases factor VIII and von Willebrand factor. It is, therefore, wellestablished therapy for hemophilia and von Willebrand disease. It has also been shown to reduce blood loss and transfusion requirement in patients with normal preoperative coagulation status who are undergoing spinal or cardiac surgery. However, the ultimate role of DDAVP remains to be determined. [66] [67] [68] DDAVP can cause hypotension, hyponatremia, and increased platelet adhesion.

Another drug is aprotinin, a serine protease inhibitor that inhibits fibrinolysis and improves platelet function. [69] It has been used to decrease blood loss in multiple surgical procedures, including cardiopulmonary bypass. However, its ultimate place in the treatment of coagulopathies has not been established.

The third drug is tranexamic acid, which is also an antifibrinolytic drug. Two studies found a decreased blood loss from total knee arthroplasty. [70] [71] Presumably, release of the pneumatic tourniquet releases fibrinolytic material, which is inhibited by tranexamic acid.

A large meta-analysis using perioperative blood transfusion as the outcome in cardiac surgery concluded that aprotinin and tranexamic acid, but not DDAVP, decreased the exposure of patients to allogeneic blood transfusion perioperatively. [72]

Clearly, the ultimate use of these drugs is evolving.

Diagnosis and Treatment of Hemorrhagic Diathesis After Packed RBC Transfusions

Most studies have examined the influence of massive transfusion of whole blood on coagulation because many trauma centers use whole blood. However, packed RBCs (see Packed Red Blood Cells) are often given because whole blood may not be available. With much less plasma, dilution of certain coagulation values may be more profound with the use of packed RBCs rather than whole blood.

Murray et al [65] specifically examined the question of using packed RBCs for major blood loss. In general, the direction of coagulation changes was similar to that seen with whole blood, with one major exception. With use of packed RBCs, fibrinogen levels decreased significantly in contrast to use of whole blood, in which fibrinogen levels remained unchanged unless DIC was present (Fig. 46-6) (Figure Not Available) . Although all the coagulation factors decreased, the decrease was less than expected from dilution. The researchers felt that factors such as VIII are probably stored in endothelial cells and released from the endothelium during surgical stress. When packed RBCs are used to replace major blood loss, the cli-nician may be tempted to give FFP prophylactically. However, Murray et al [65] specifically recommended not following the policy; they stated that FFP was needed only when prothrombin time and partial thromboplastin time were at least 1.5 times normal and fibrinogen levels were less than 75 mg/dL. These recommendations are similar to those stated in the section Fresh Frozen Plasma. More recently, Leslie and Toy [73] provided more specific guidelines when packed red cells are used for massive transfusions. They believed that when 12 or more units of packed red cells or cell-saver blood had been given, coagulation factors (i.e., FFP) were

Figure 46-6 (Figure Not Available) Decreases in fibrinogen level as blood volume is replaced with Adsol-packed red blood cells and crystalloid solutions. Each patient is represented by a solid line. *(From Murray et al [65])*

Figure 46-7 (Figure Not Available) Algorithm of the evaluation and initial therapy of the patient with suspected perioperative coagulopathy. Evaluation is based on the clinical scenario and is readily affected by type and location of injury, the amount of fluid administered, and the age and body temperature of the patient. DDAVP, trademark for preparation of desmopressin acetate; PT, prothrombin time; PTT, partial thromboplastin time. *(From Habibi et al [20])*

necessary. Those patients who received 20 or more units often required platelet therapy, a finding identical to that of patients given whole blood.

An algorithm for the evaluation and initial therapy of a patient with a suspected coagulopathy is given in Figure 46-7 (Figure Not Available) .

Citrate Intoxication and Hyperkalemia

Citrate intoxication is not caused by the citrate ion per se, but because citrate binds calcium. Thus, the signs of citrate intoxication are those of hypocalcemia, that is, hypotension, narrow pulse pressure, and elevated intraventricular enddiastolic pressure and central venous pressure. However, if circulatory volume is reasonably well maintained, these cardiovascular changes do not occur unless ACD blood is given at a rate greater than 150 mL/70 kg/min, or about 1 unit of blood per 5 minutes in an average-sized adult. With newer preservatives with less citrate, intoxication is even less likely.

Decreased levels of serum ionized calcium do occur in low flow states, especially in out-of-hospital cardiac arrests. [74] These decreases have no predictable relationship to total plasma concentration. A possible conclusion is that if blood is given to such a critically ill patient, the serum ionized calcium levels may decrease even more. However, Drop and Laver [75] found that these abnormally low concentrations of ionized calcium were not readily corrected by intravenous administration of calcium salts in doses generally recommended (i.e., 1.0 g of calcium chloride). However, ionized calcium levels returned toward normal when hemodynamic status was improved by increasing the isoproterenol infusion rate. The beneficial effect of isoproterenol probably indicates that mobilization ionized calcium from body stores may be inadequate because of abnormal distribution of blood flow. Thus, improvement of a patient's circulatory status (blood transfusion) may ultimately increase ionized calcium levels without calcium administration. If calcium is given to patients with low-output states, calcium chloride may have to be administered at rates as high as 1.5 mg/kg/min. Drop and Laver [75] recommended that this amount of calcium chloride not be given without close monitoring of serum ionized calcium levels, because a constant relationship with total serum calcium level is not established.

With the absence of ionized calcium electrodes, the well-known inotropic stimulation may lead the clinician to administer calcium any time evidence of inadequate cardiac output is present, especially when multiple blood transfusions have been given.

Thus, even in patients with low-output states, I believe that emphasis should be placed on correcting the underlying disorder (i.e., hypovolemia) and that calcium administration is rarely necessary. [76] The reason that serum ionized calcium levels rapidly return to normal immediately after cessation of the blood transfusion (Fig. 46-8) (Figure Not Available) probably is rapid citrate metabolism by the liver and rapid calcium mobilization from available endogenous stores. Hypothermia, liver disease, liver transplantation, and hyperventilation increase the possibility of citrate intoxication. In fact, the appearance of severe hypocalcemia during liver transplantation is well documented (Ch. 55) . Obviously, the combination of infusion of large amounts of citrate (i.e., via blood transfusions) and of reduced metabolism from absent or reduced liver blood flow (i.e., in the anhepatic phases of liver transplantation) leads to citrate intoxication. As a result, calcium infusions are common during liver transplantation (Kelley S, personal communication, 1999). The rate of citrate metabolism is decreased by 50 percent when body temperature is decreased from 37° to 31°C. Excluding these conditions, infusion of more than 1 unit of blood every 10 minutes is necessary for ionized calcium levels to begin to decrease. Even at these rates of infusion, ionized calcium levels do not decrease enough to cause bleeding. As indicated previously, if a hemorrhagic diathesis starts after administration of blood, low calcium levels are not part of the differential diagnosis.

As evidenced from the preceding discussion, citrate intoxication is obviously rare. Serum potassium levels may be as high as 19 to 30 mEq/L in blood stored for 21 days. Although hyperkalemia is occasionally reported, [77] large amounts of blood must be given. For significant hyperkalemia to occur clinically, bank blood must be given at a rate of 120 mL/min or more. The fact that such rapid infusion rates of blood are required for the production of hyperkalemia suggests that the potassium ion must leave the intravascular spaces by diffusion into extravascular spaces, by reuptake into red cells, or via the kidneys. As with citrate intoxication, hyperkalemia is rare, and this again rules against the routine administration of calcium. In fact, calcium may cause cardiac arrhythmias, particularly in patients anesthetized with

halothane. Calcium administration should be based on diagnostic signs of hyperkalemia (peak T wave).

Even though it is reported to be irritating to veins, 10 percent calcium chloride provides three times more calcium than an equal volume of 10 percent calcium gluconate because chloride has a molecular weight of 147 and gluconate a molecular weight of 448.

Temperature

Administration of unwarmed blood that has been stored at 4°C can decrease the recipient's temperature. If the temperature decreases to less than 30°C, ventricular irritability and even cardiac arrest may occur. This can be prevented by warming the blood to body temperature before transfusion. I believe that there are more subtle reasons for warming all

Figure 46-8 (Figure Not Available) Correlation between the time during and after citrated whole blood infusion and serum-ionized calcium (mM/L.). *(From Denlinger et al [181])*

blood, even in patients receiving only 1 to 2 units intraoperatively. Because of the cool temperature of the operating room, body temperature often decreases, particularly in patients undergoing extensive abdominal surgery [79] (Ch. 37) ; administration of cold blood further decreases temperature. A decrease in body temperature as small as 0.5 to 1.0°C may induce shivering postoperatively; this in turn may increase oxygen consumption by as much as 400 percent. To meet the demands of elevated oxygen consumption, cardiac output must be increased. Is this too much stress for the patient with marginal cardiac reserve? More studies are required to confirm this fear.

Perhaps the safest and most common method of warming blood is to pass it through plastic coils immersed in warm water (37° to 38°C) bath. With increased use of packed RBCs (e.g., in contrast to whole blood), other methods of warming blood have been suggested. For example, Zorko and Polsky [79] added normal saline warmed to 45°C to packed RBCs. Clearly, maximal flow rates are achieved with diluted cells not passed through a warmer, but delivery temperature is higher when passed through a warmer (Table 46-6) (Table Not Available) . Despite the aforementioned well-documented information, five cases of overheated hemolyzed blood have been reported to the FDA during the past 10 years. [80] A variety of warming techniques have been reviewed by Iserson and Heustis. [81]

TABLE 46-6 -- Four Methods of Warming Packed Red Blood Cells

(Not Available)

From Zorko and Polsky [79]

Acid-Base Abnormalities

The pH of most storage media is very acidotic (CPD, 5.5). When this solution is added to a unit of freshly drawn blood, the pH of the blood immediately decreases to approximately 7.0 to 7.1. As a result of accumulation of lactic and pyruvic acids by RBC metabolism and glycolysis, the pH of bank blood continues to decrease to about 6.9 after 21 days of storage. A large portion of the acidosis can be accounted for by the P_{CO_2} of 150 to 220 mm Hg. The P_{CO_2} is high mainly because the plastic container of blood does not provide an escape mechanism for carbon dioxide. With adequate ventilation in the recipient, the high P_{CO_2} should be of little consequence. Even when the P_{CO_2} is returned to 40 mm Hg, metabolic acidosis is still present in blood (see Table 46-4) , and some clinicians empirically recommend giving alkalizing agents. Also, other reasonably well-controlled clinical studies have indicated that not only is empirical administration of sodium bicarbonate not indicated but it may also actually be unwise without concomitant analysis of arterial blood for P_{CO_2} and pH. [82] Miller et al [83] found that the metabolic acid-base response to blood transfusion was variable (Fig. 46-9) (Figure Not Available) . Actually, blood transfusions provide a substrate, namely citrate, in large quantities for the endogenous generation of bicarbonate, and this accounts for the significant incidence of metabolic alkalosis after blood transfusions. [82] Therefore, there is little logic in the empirical administration of bicarbonate for prophylactic treatment of an unpredictable acid-base abnormality. Bicarbonate therapy should be initiated when metabolic acidosis is diagnosed. This can be accomplished by analysis of arterial blood for P_{CO_2} and pH. When a suitable artery cannot be palpated because an

Figure 46-9 (Figure Not Available) Correlation between the amount of blood administered (mL) and corrected base excess intraoperatively. *(From Miller et al [83])*

extremity is inaccessible during a particular operative procedure, peripheral venous blood can be used for P_{CO_2} and pH determinations. During anesthesia, peripheral venous blood usually has a P_{O_2} of more than 60 mm Hg. Therefore, because this blood is arterialized, P_{CO_2} and pH can be determined, and the amount of bicarbonate required can be calculated. [84]

Although treatment of metabolic acidosis with bicarbonate has been viewed as being important, can any harm result from excessive bicarbonate administration or from metabolic alkalosis (Chs. 38 and 75) ? Actually, large doses of bicarbo-nate (e.g., 1-10 mEq/kg) can interfere with coagulation, as evidenced by prolonged prothrombin and thrombin clotting times. [85] Also, alkalosis augments a left shift of the oxygen dissociation curve. Because of citrate metabolism, exogenous bicarbonate, and administration of lactated Ringer solution, metabolic alkalosis commonly occurs after infusion of several units of blood. Thus, bicarbonate administration should be reserved for patients in whom severe metabolic acidosis (base excess >7 mEq/L) has been diagnosed.

Infusion of Microaggregates

In 1970, Moseley and Doty [86] demonstrated that amounts of clot and debris in bank blood increased with duration of storage. Some of this particulate matter is not filtered by the standard 170-m filter during routine transfusion and enters the recipient's blood stream. [86] These authors suggest, therefore, that respiratory insufficiency in patients with severe trauma and hemorrhage (so-called shock lung) or adult respiratory distress syndrome may be a result of the accumulation of this particulate material in the lungs, resulting in vascular obstruction. Several filters with pore sizes less than 40 m (micropore filters) are now available to remove microaggregates from bank blood. When massive transfusions of stored blood are involved, the use of micropore filters, in theory, should eliminate this important contributor to the development of adult respiratory distress syndrome. However, the evidence supporting the preceding concept and the need for micropore filters during massive transfusions of stored blood is unproved.

More recent information suggests that the thrombocytopenia associated with transfusions can be attenuated by the use of micropore filters. [87] [88] Also, the removal of white blood cells may reduce the infectivity of blood. [89] In fact, it is likely that prefiltered blood designed to remove most of the white blood cells will be routinely provided by blood banks in the future. Lastly, newer preservative solutions will probably eliminate microaggregates. Clearly, the use of micropore filters is evolving and is not resolved. [90]

Transfusion Reactions

Hemolytic Transfusion Reaction

Since 1975, the FDA has required that all fatal reactions occurring in blood recipients or donors be reported within 24 hours by telephone, or within 7 days in writing, by all FDA-registered transfusion services. In the 10-year period from 1976 to 1985, 328 deaths have been reported and ana-lyzed. [91]

Of these deaths, 159 were acute from hemolytic reactions and 23 from delayed reactions. Of the 159 deaths due to acute hemolytic reaction, 137 were caused by errors involving ABO incompatibility. More than half of these mistakes occurred after the blood had been issued by the blood bank and were committed by nurses and physicians in the operating room, emergency room, or ward. The incidence of hemolytic transfusion reaction is in the range of 1/300,000 to 1/700,000 RBC transfusions. [92] [92] However, when delayed hemolytic reactions (discussed in a later section) are included, the incidence of ABO-incompatible RBC transfusion is much more frequent. [94] Even though the incidence is low, the anesthesiologist must know the principles of recognizing and treating hemolytic transfusion reactions

because of the high morbidity and mortality rate. One of the most catastrophic transfusion reactions is that arising from intravascular hemolysis. Intravascular hemolysis occurs when there is a direct attack on transfused donor cells by recipient antibody and complement. Such a reaction can occur from infusion of as little as 10 mL of blood. [95] Mortality may occur in 20 to 60 percent of those patients with severe symptomatic hemolytic reactions, and these deaths usually result from ABO blood group incompatibility between the donor and the patient. Hemolytic transfusion reactions involving extravascular RBC destruction are generally less serious than those of the intravascular variety. In these cases, recipient antibody coats but does not immediately hemolyze the transfused RBCs. Destruction occurs primarily in the reticuloendothelial system.

Signs and Symptoms

The clinical consequences of incompatible blood transfusions are very serious and yet quite variable. Factors include volume of transfused blood, number of antigenic sites on the red cell membrane, and activity of the reticuloendothelial system. The properties of the antibody, including concentration and ability to activate complement, are also important.

The classic signs and symptoms (Table 46-7) of a hemolytic transfusion reaction--chills, fever, chest and flank pain, and nausea--are masked by anesthesia. Under general anesthesia, the only signs may be hemoglobinuria, bleeding diathesis, or hypotension. In my and Huh and Lichtiger's experience [96] with six and four hemolytic transfusion reactions, respectively, the presenting sign was hemoglobinuria in nine

TABLE 46-7 -- Frequency and Signs and Symptoms From Hemolytic Transfusion Reactions in 40 Patients

SIGN OR SYMPTOM	NO. OF PATIENTS
Fever	19
Fever and chills	16
Chest pain	6
Hypotension	6
Nausea	2
Flushing	2
Dyspnea	2
Hemoglobinuria	1

Figure 46-10 Schematic representation of what happens to hemolyzed erythrocytes as a result of the administration of incompatible blood.

of the ten cases. As little as 50 mL of incompatible blood may exceed the binding capacity of haptoglobin, which is a protein that can bind about 100 mg of hemoglobin per 100 mL of plasma. When hemoglobin not exceeding this amount is injected or liberated into the blood stream, the hemoglobin circulates as a complex with haptoglobin, which is cleared by the reticuloendothelial system (Fig. 46-10) . A sample of plasma that contains 2 mg/dL of hemoglobin is faintly pink or light brown. When the level of hemoglobin reaches 100 mg/dL, then the plasma is red. When the level of plasma hemoglobin reaches 150 mg/dL, hemoglobinuria occurs. In general, the quantity of the free hemoglobin in the plasma is correlated with the volume of incompatible blood transfused. Thus, the symptomatology can be so alarming that cessation of blood is indicated, even if hemoglobin is not seen in plasma. Laboratory tests that should be performed if hemolytic transfusion reaction is suspected include serum haptoglobin, plasma and urine hemoglobin, bilirubin, and direct antiglobulin determinations. The direct antiglobulin test can confirm the presence of hemolytic transfusion reaction because it shows that there is antibody attached to transfused donor red blood cells. [97]

Treatment

If a hemolytic reaction is suspected, blood and urine samples should be sent to the laboratory for examination. The blood bank should check all paperwork to ensure that the correct blood component was transfused to the patient. Laboratory tests should be performed to determine the presence of hemoglobinemia: a direct antiglobulin test, repeat compatibility testing, repeat other serologic tests (i.e., ABO and Rh) and analysis of urine for hemoglobinuria.

Although there are several consequences of intravascular hemolysis, mainly the renal and coagulation systems are affected. The exact cause of acute renal failure from intravascular hemolysis is controversial, but the most common hypothesis is that hemoglobin in the form of acid hematin precipitates in the distal tubule and causes mechanical tubular blockage. The magnitude of the precipitation probably is inversely related to the volume of urine flow and its pH. The primary emphasis of therapy should be directed toward maintaining urinary output in excess of 75 mL/h by generous administration of intravenous fluids and diuretics. My

approach is summarized in Table 46-8 and includes the administration of lactated Ringer solution to maintain the central venous pressure between 10 and 15 cm H_2O while initially administering 12.5 to 50 g of mannitol. If ineffective, then the dose of mannitol may be increased and/or the use of more potent diuretics, such as furosemide, which increases blood flow to the renal cortex, may be required to maintain adequate urinary output. Alkalinization of the urine to prevent precipitation of acid hematin in the distal tubules is of questionable value but is easy and therefore recommended. DIC commonly occurs with hemolytic transfusion reactions, probably because RBC stroma is severed, releasing erythrocytin, which activates the intrinsic system of coagulation. This activated coagulation leads to fibrin formation. Subsequently, platelets and factors I, II, V, and VII are consumed. As soon as a hemolytic transfusion reaction is recognized, platelet count, prothrombin time, and partial thromboplastin time should be determined to provide baseline values with which subsequent laboratory values can be compared. Hypotension during a hemolytic transfusion reaction may be due to activation of the kallikrein system. [98] After a series of reactions, plasma kininogen is converted to bradykinin, a potent vasodilator that can cause hypotension.

Another approach to treatment of a severe hemolytic transfusion reaction has been proposed by Seager et al, [99] who postulated that the kidneys might be spared from exposure to massive amounts of hemolyzed red cells by removing all blood from a patient and replacing it with compatible blood. This was accomplished in a patient who had received 3,000 mL of incompatible blood by hemodilution by use of an extracorporeal circuit. Because the patient had rapid recovery of urinary function, this method shows much promise.

In summary, hemoglobinuria or hemolysis should be assumed to be a hemolytic transfusion reaction until proved otherwise. The steps outlined in Table 46-8 should be taken when the diagnosis is suspected or confirmed.

Delayed Hemolytic Transfusion Reaction (Immune Extravascular Reaction)

As described earlier, an immediate hemolytic transfusion reaction often is a dramatic event because the concentration of the antibody is high enough to cause immediate and appreciable RBC destruction. However, in many cases of hemolytic transfusion reaction, the transfused donor cells may survive well initially but after a variable delay (2-21 days) is hemolyzed. [100] [101] This type of reaction occurs mainly in recipients sensitized to RBC antigens by previous blood transfusions or pregnancy. As a result, this type of delayed reaction is more common in females who have a known disposition of alloimmunization. These reactions are delayed hemolytic transfusion reactions and are those in which the level of antibody at the time of transfusion is too low to be detected or too low to cause RBC destruction. RBC destruction occurs only when the level of antibody is increased after a secondary stimulus (anamnestic response). These delayed reactions are often manifested only by a decrease in the posttransfusion hematocrit value. However, jaundice and/or hemoglobinuria can occur in these patients and can

TABLE 46-8 -- Steps for the Treatment of a Hemolytic Transfusion Reaction

1. STOP THE TRANSFUSION.

2. Maintain the urine output at a minimum of 75 to 100 mL/h by the following methods:

a. Generously administer fluids intravenously and possibly mannitol, 12.5 to 50 g, given over a 5- to 15-minute period.

b. If intravenously administered fluids and mannitol are ineffective, then administer furosemide, 20 to 40 mg, IV.

3. Alkalinize the urine; because bicarbonate is preferentially excreted in the urine, only 40-70 mEq/70 kg of sodium bicarbonate is usually required to raise the urine pH to 8, whereupon repeat urine pH determinations indicate the need for additional bicarbonate.

4 Assay urine and plasma hemoglobin concentrations.

5. Determine platelet count, partial thromboplastin time, and serum fibrinogen level.

6. Return unused blood to blood bank for re-crossmatch.

7. Send patient blood and urine sample to blood bank for examination (see text for details).

8. Prevent hypotension to ensure adequate renal blood flow.

---

also cause some impairment in renal function, but only rarely do they lead to death. Unlike immediate reactions, antibodies most commonly involved in delayed hemolytic reactions are those in the Rh and Kidd systems rather than the ABO system. Although improved blood banking procedures have decreased the incidence of immediate hemolytic transfusion reactions, the delayed hemolytic reaction may not be preventable, because pretransfusion testing is unable to detect very low levels of antibody present in potential blood recipients.

Although impairment of renal function is uncommon, the surgical team should include in their differential diagnosis a delayed hemolytic transfusion reaction in any patient who has an unexplained decrease in hematocrit 2 to 21 days after a transfusion, even without obvious manifestation of hemolysis. This is especially important in a postoperative patient when the decrease in hematocrit value is thought to be from blood loss and may be an important criterion as to whether additional surgery is necessary.

Nonhemolytic Transfusion Reactions

These reactions to blood transfusions usually are not serious and are either febrile or allergic in nature. On occasion, fever could be the first sign of a hemolytic reaction or of bac-terial contamination. If the temperature increase is more than 1°C, a hemolytic reaction should be considered. [93] Bacterial contamination usually occurs with transfusion of platelets.

For less serious febrile reactions, the most common adverse reactions to blood transfusions are the febrile reactions. The symptoms consist of chills, fever, headache, myalgia, nausea, and nonproductive cough occurring shortly after blood transfusion. Less frequently, the patient may have hypotension, chest pain, vomiting, and dyspnea. Even pulmonary infiltrations with x-ray evidence of prehilar nodule formation and lower lung infiltrates along with overt pulmonary edema have been reported. [102] Because febrile reactions obviously involve fever, they can be easily confused with a hemolytic transfusion reaction. A direct antiglobulin

---

test readily differentiates a hemolytic reaction from a febrile reaction because this test rules out the attachment of an RBC antibody to transfused donor RBCs.

There is no clear consensus on whether the transfusion should be terminated when a febrile reaction occurs. [93] [103] [104]

Most allergic transfusion reactions are mild and are considered to be caused by the presence of foreign protein in the transfused blood. The most common symptom is urticaria associated with itching. Occasionally, the patient has facial swelling. Allergic reactions occur in about 3 percent of all transfusions. When these reactions are accompanied by fever or any other symptoms suggestive of a serious hemolytic reaction, it is not necessary to discontinue the transfusion. Antihistamines are used to relieve the symptoms of the allergic reaction. Infrequently, a more severe form of allergic reaction involving anaphylaxis occurs in which the patient has dyspnea, hypotension, laryngeal edema, chest pain, and shock. These are anaphylactic reactions caused by the transfusion of IgA to patients who are IgA deficient and have formed anti-IgA. This type of reaction does not involve red cell destruction and occurs very rapidly, usually after the transfusion of only a few milliliters of blood or plasma. The patients who experience these anaphylactic reactions must be given transfusions with washed red blood cells from which all traces of donor IgA have been removed, or with blood lacking the IgA protein. [105]

There are many other rare transfusions reactions, which have been reviewed by several authors. [91] [95] [96]

Infectivity of Blood

With the introduction of transfusion-induced AIDS, the infectivity by homologous blood transfusion has received renewed attention. In fact, for many years, blood banks use one or two tests (i.e., syphilis and hepatitis B surface antigen) to screen blood. In recent years, many more tests have been added (Table 46-9) (Table Not Available) . Overall, blood is probably safer than it has been for years.

Hepatitis

When blood transfusions became a reality in the 1940s, viral hepatitis was recognized as a major complication. Now, in the past 10 years, the incidence of viral hepatitis has dramatically

TABLE 46-9 -- Infectious Disease Testing for Blood Transfusions

(Not Available)

From JAMA 1995:274:1374

decreased. Nevertheless, when it occurs, it is very serious. Classically, icteric hepatitis develops 50 to 180 days after a blood transfusion and has a variable clinical course, ranging from asymptomatic to fatal. However, two to five anicteric cases occur for every case of overt icteric hep-atitis. Generally, the diagnosis of acute anicteric posttransfusion hepatitis is made with the observation, between 14 and 180 days after transfusion, of two consecutive elevations (at least 14 days apart) of the recipient's alanine aminotransferase level. Other possible causative factors, such as congestive heart failure, alcohol, and certain drugs that can mimic or simulate viral hepatitis, obviously must be considered. Both transaminase elevations must be at least 2 standard deviations above the geometric mean value for healthy persons.

Serologic requirements for the diagnosis of hepatitis B include the *de novo* appearance of hepatitis B surface antigen or hepatitis B surface or core antibody. Hepatitis A antibody seroconversion is considered evidence for hepatitis A infection. However, 90 percent of posttransfusion hepatitis is caused by the hepatitis C virus. Less than one-third of these patients develop jaundice. [106] To determine their ultimate fate, Tong et al [106] monitored 131 patients with chronic posttransfusion hepatitis C for several years and found the following incidence of signs, symptoms, and conditions:

1. Fatigue (67%)
2. Hepatomegaly (67%)
3. Chronic hepatitis (23%)
4. Chronic active hepatitis (51%)
5. Hepatocellular carcinoma (11%)

On follow-up, it was found that 20 patients had died, from

1. Complications of cirrhosis (eight patients)

2. Hepatocellular carcinoma (11 patients)
3. Chronic active hepatitis-pneumonia (one patient)

Before 1983 to 1985, the overall incidence of posttransfusion hepatitis ranged from a low of 3 percent to a high of 19 percent, depending on the institution and the location (e.g., donors from large cities have a higher incidence of the hepatitis virus). In most areas, the incidence of hepatitis has ranged from 3 to 10 percent. Since 1985, the incidence of posttransfusion hepatitis has decreased, probably for three reasons. First is improved donor screening. In 1984, donors who were in a high-risk category for AIDS were requested not to donate blood on a volunteer basis. Second, in 1985 all donor blood was tested for antibodies to the AIDS virus (see Acquired Immunodeficiency Syndrome). Third, a specific test for hepatitis C was developed. Specifically, molecular techniques were used to derive clones from the genome of hepatitis C. The derived proteins from these clones were used to develop an enzyme-linked immunosorbent assay to detect antibodies to hepatitis C. As a result, the incidence of posttransfusion hepatitis is lower by far than it has been for more than 20 years (Table 46-10) . [107] Despite the effectiveness of this test, donor infectivity is important as a screening device. Demographics of infectivity among donors is variable and is especially frequent in intravenous drug users. [108] Finally, it should be remembered that many blood components, such as packed red cells, FFP, and platelet concentrates, also transmit hepatitis at an incidence equal to that of whole blood.

There has been a concern about the relationship between transfusions and hepatitis delta virus. This virus is a defective RNA virus that cannot survive on its own and requires the helper function of a DNA virus, hepatitis B, to support its replication and expression. Therefore, the hepatitis delta virus can infect only persons with hepatitis B, either one in whom infections occur simultaneously or one who is a hepatitis B carrier. [109] This is a very virulent form of hepatitis, which can transform a mild chronic hepatitis B infection to severe progressive chronic active hepatitis and cirrhosis. Delta hepatitis can be prevented by vaccinating susceptible or high-risk individuals, such as anesthesiologists (Ch. 84) , with hepatitis B vaccine. However, the delta virus can be transmitted by blood transfusions. Rosina et al [110] concluded that screening donors for hepatitis B provides a high degree of safety in preventing infection with hepatitis delta virus but that the risk is greater in patients who are already carriers of hepatitis B. They concluded that hepatitis B carriers should be given only blood derivatives from a single donor or minipool donors.

Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome is characterized by severe depression of cellular immunity. Clinically, opportunistic infections and/or Kaposi sarcoma appears, progressing to debility and death. Pattern of transmission is similar to that of hepatitis B. Although AIDS is most frequently transmitted by intimate homosexual contact and intravenous drug abuse, nevertheless, whole blood, plasma, blood cellular products, or clotting factors can transmit AIDS. [111] Several measures have been recommended to decrease the chances that donor blood will be infected with AIDS. Blood banks have instituted procedures to discourage members of high-risk groups from donating blood. Designated donors and surrogate testing have been recommended. [112] [113] Despite these measures, there were hundreds of cases of transfusion-transmitted AIDS. In March 1985, all donor blood was tested for the presence of antibodies to the AIDS virus (human immunodeficiency virus type 1 [HIV-1]). This testing has dramatically reduced the incidence of transfusion-transmitted AIDS (Table 46-10) . [107]

TABLE 46-10 -- Percentage Risk of Transfusion-Transmitted Infection With a Unit of Screened Blood in the United States

	RISK	WINDOW PERIOD (DAYS)
HIV	1/493,000	22
HTLV	1/641,000	51
Cytomegalovirus	<1.0%	rapidly
HCV	1/103,000	82
HBV	1/63,000	59
Aggregate infection risk	1/34,000	--

[a] 88% of which is HBV and HCV

HIV, human immunodeficiency virus type 1; HTLV, human T-cell lymphotropic virus; HCV, hepatitis C virus; HBV, hepatitis B virus

Human T-Cell Lymphotropic Virus Type I

Human T-cell lymphotropic virus type I (HTLV-I) can be transmitted by blood transfusions and has been causally associated with adult T-cell leukemia and progressive myelopathy. Cohen et al [114] found that there is a very small risk of HTLV-I infection from transfused blood and blood products that have been screened for antibodies to HIV, but that risk is nearly 10-fold higher than risk of HIV infections. Specifically, they found the risk to be 0.003 percent/U for HIV infection and 0.024 percent/U for HTLV-I infection. Even though there is no firm association between transfusion and leukemia or myelopathy, the decision was made to test all donor blood for antibodies to the HTLV-I virus.

Cytomegalovirus

Asymptomatic chronic infection with cytomegalovirus (CMV) is so common in healthy adults that this agent can almost be viewed as normal flora. CMV survives best within cells and is thought to exist in latent form in the leukocytes of many people with antibodies indicative of earlier infection. CMV causes a heterophil antibody-negative response that closely resembles infectious mononucleosis in many respects. An infectious mononucleosis-like syndrome that can occur 1 to 2 months after open heart surgery is known as the postperfusion syndrome or posttransfusion mononucleosis. The evidence for transmission of CMV is most convincing when the recipient changes from a seronegative state before transfusion to a seropositive state accompanied by the mononucleosis-like illness several weeks after transfusion.

Transfusion-transmitted CMV can cause significant clinical problems in certain patient populations, such as premature neonates, allograph recipients, and patients who have had their spleens removed. [115] To prevent infection in high-risk populations, use of leukocyte-depleted blood, use of frozen deglycerolized RBCs, and screening of donors for the absence of antibody to CMV have been sometimes recommended. The risk of seroconversion is about 0.14 percent overall or 0.38 percent per unit of seropositive donor blood. [116] Wilhelm et al [117] concluded that it is not necessary to provide blood products from CMV-seronegative donors for most patients who receive blood transfusions. They con-tinue to use CMV-seronegative blood to prevent CMV infection in preterm and newborn babies. Whether CMVneg-ative blood should be used for other immunocompromised patients and pregnant women has not yet been resolved.

Other Transfusion-Associated Infectious Diseases

Although many other infectious diseases can theoretically be transmitted by blood transfusion, only a few are of real concern. They include *Y. enterocolitica* infection, syphilis, and malaria.

During the late 1980s, Tripple et al [118] described seven cases of fatal transfusion-associated *Yersinia enterocolitica* sepsis. These investigators also reviewed the literature and

found 26 cases of gram-negative bacterial sepsis with whole blood or packed RBCs. *Y. enterocolitica* is a bacterium that can cause mostly mild gastrointestinal problems. However, in severe cases, sepsis and death can occur. Unfortunately, storage of blood at 4°C in phosphate buffer enhances its growth. Aber [119] suggested that the donor screening process include assessment as to whether gastrointestinal problems occurred within 4 weeks of donation and that the storage time be minimized. More specific recommendations were not provided, although some were suggested by Grossman et al. [120]

Posttransfusion syphilis is unlikely because the infective agent cannot survive during storage at 1° to 6°C. The only blood products that have the potential to transmit syphilis are those stored at room temperature. Platelet concentrates are the blood component most likely to be implicated because they commonly are stored at room temperature.

Posttransfusion malaria has never been a significant cause of blood recipient morbidity. Nevertheless, malaria can occur, especially if blood donors at risk of harboring parasites are not excluded. Consequently, blood banks thoroughly question donors for history of travel or migration from areas where malaria is endemic.

Several other diseases have also been reported to be transmitted by blood transfusion, including herpes virus infections, infectious mononucleosis (Epstein-Barr virus), toxoplasmosis, trypanosomiasis, leishmaniasis, brucellosis, typhus, filariasis, measles, salmonellosis, and Colorado tick fever.

The Future of the Infectivity and Testing of Blood

Although the data in Table 46-10 are correct as of 1999, they will change fairly soon. With new tests that identify the nucleic acid of the virus, the "window period" will be reduced to as short as 1 day. This could decrease the incidence of HIV and hepatitis C to 1:1,000,000, making allogeneic blood incredibly safe from an infectivity point of view.

Other Adverse Effects of Blood Transfusion

Transfusion-Associated Graft-Versus-Host Disease

This disease occurs when donor lymphocytes from transfused blood products engraft in the recipient, initiating an immune reaction against host tissue. A generalized rash, leukopenia, and thrombocytopenia occur. Sepsis and death usually result. Irradiation of blood can prevent transfusion-associated graft-versus-host disease from occurring, although there is a report of one case occurring despite leukocyte filtering. [121]

Transfusion-Related Acute Lung Injury

This injury manifests as noncardiogenic pulmonary edema resulting from immune reactivity of certain leukocyte antibodies a few hours after transfusion. Specifically, it involves an antigen-antibody mechanism involving human leukocyte antigen and granulocyte antigens. Transfusionrelated acute lung injury is associated with a mortality rate (<10%) much lower than that from the adult respiratory distress syndrome.

Adverse Ocular Reaction

In 1997, 112 cases of bilateral conjunctival erythema were reported to have occurred within 24 hours of transfusion. The Centers for Disease Control and Prevention studied 49 other cases in 1997 and 1998 and concluded that they were toxic reactions to a chemical or material used in the blood collection filtration system, most likely a leukocyte-reducing filter system. [123]

Transfusion-Induced Immunodepression

Homologous (allogeneic) blood transfusion exerts a nonspecific immunosuppressive action on the recipient. This effect is therapeutic for kidney transplant recipients. However, many authors have presented data to indicate that blood transfusions increase susceptibility to infection and enhance progression of malignant tumors. Although many factors may be involved with seriously ill patients (e.g., patients who receive blood transfusions probably have more extensive and invasive disease), convincing evidence indicates that there is a relationship between perioperative transfusion and tumor recurrence or survival in patients with many types of cancer.

The mechanism of this effect on cancer is unknown but has been related to increased synthesis of prostaglandin E, decreased interleukin 2 generation, and fibrinogen degradation products in FFP. [124] This later finding has led to some concern about giving FFP to immunodepressed patients. Blumberg [125A] found that patients transfused with packed RBCs had a better survival rate than those patients receiving whole blood. As a result, it has been recommended that packed RBCs be given instead of whole blood when transfusions are indicated in patients with cancer. If this observation can be applied to the broad practice of transfusion medicine, the fewer problems with packed RBCs may be related to the presence of fewer white blood cells. This and other problems stimulated the Blood Products Advisory Committee of the FDA to recommend universal leukocyte reduction of cellular blood components. [125B] As with all aspects of transfusion medicine, careful evaluation of the indications for blood transfusions and emphasis on autologous blood transfusions (Ch. 47) are especially helpful in these patients.

Although much emphasis has been placed on the importance of transfusion-induced immunodepression, more recent evidence suggests the contrary, at least as far as cancer is concerned. For example, Younes et al [125] examined 116 patients who underwent resection of colorectal liver metastasis and concluded that number of hypotensive episodes, site of primary tumor, number of metastases, and preoperative carcinoembryonic antigen levels (and not blood transfusions) were the primary factors that could predict freedom

---

from disease 1 to 2 years postoperatively. One might conclude that autologous blood may be better than allogeneic blood because of the former's lack of effect on the immune system. As a result, allogeneic blood depresses cytokine production because of immunodepression. Anders et al [126] found that administration of autologous blood increases cytokine production. Cytokines play a central role in hemolytic reactions, and anaphylatoxins (C3a, C4a, and C5a) can cause release of vasoactive amines, smooth muscle contraction, increased vascular permeability, and release of lysosomal enzymes. Could it be that autologous blood actually has a disadvantage when compared to allogeneic blood (Ch. 47) ? Busch et al [127] compared the use of autologous versus allogeneic (i.e., homologous) blood with regard to prognosis. They concluded that regardless of the type of transfusion, transfusions are associated with a poor prognosis, probably because of the reasons that necessitated the use of blood. These observations emphasize the problems with attempting to assess the impact of one factor (i.e., transfusions) in complicated seriously ill patients. Because immunologic effects and "reactivation" of latent viral activity (e.g., HIV) are likely to be influenced by white blood cells, it is likely that increasing amounts of blood released for clinical use by the blood bank will be prefiltered to remove most of the white blood cells before transfusion.

Immunodepression is a complicated and controversial topic that ultimately could be very important. The mechanisms (Table 46-11) (Table Not Available) and downregulated immune functions (Table 46-12) (Table Not Available) have been reviewed by Landers et al. [128] Be-cause

TABLE 46-11 -- Mechanisms of Transfusion-Induced Immunomodulation

(Not Available)

From Landers et al [128]

TABLE 46-12 -- Downregulated Immune Functions Following Allogeneic Blood Transfusions

(Not Available)

From Landers et al [128]

hundreds of studies have been published, review articles in various anesthesia journals may be the best source of overall information. [128] [129] [130]

Overall Safety of Blood

This chapter is directed toward blood transfusion therapy as it relates to the practice of anesthesia. Reviews by authorities regarding the overall safety of blood

transfusion provide helpful information regarding the practice of medicine in general. [130] [131]

/das/book/view/29494766/875/528.html

BLOOD COMPONENT THERAPY

A major advance in the field of blood banking has been the development of blood component therapy. It is beyond the scope of this chapter to describe the various separation steps in detail, but a superficial outline of the scheme by which various blood components are derived is shown later in Figure 46-11 . The basic philosophy is based on the concept that patients are best treated by administration of the specific fraction of blood that they lack. This concept has presented problems to the surgical team, who often desire whole blood.

Packed Red Blood Cells

In essence, packed RBCs contain the same amount of hemoglobin as whole blood, but much of the plasma has been removed. Thus, the hematocrit value is 40 percent in whole blood and 70 percent in packed erythrocytes (Table 46-13) . The position of the American Association of Blood Banks has been that transfusion of whole blood is required primarily for blood loss acute enough to cause hypovolemic shock. More specifically, they state that the primary indication for whole blood is for patients who are actively bleeding and have sustained a loss of greater than 25 percent of their total blood volume. In other words, whole blood provides both oxygen-carrying capacity and blood volume expansion. Less severe degrees of hemorrhage may be effectively treated with packed RBCs, thus retaining the plasma and the components

TABLE 46-13 -- Comparison of Whole Blood and Packed Red Blood Cells

VALUE	WHOLE BLOOD	PACKED RED BLOOD CELLS
Volume (mL)	517	300
Erythrocyte mass (mL)	200	200
Hematocrit (%)	40	70
Albumin (g)	12.5	4
Globulin (g)	6.25	2
Total protein (g)	48.8	36
Plasma sodium (mEq)	45	15
Plasma potassium (mEq)	15	4
Plasma acid (citric-lactic) (mEq)	80	25
Donor/recipient ratio	1 unit per patient	1 unit every 4-6 patients

Figure 46-11 Diagrammatic scheme of separation of whole blood for component therapy.

thereof for other patients (see Fig. 46-11) . Many blood banks have religiously followed this principle, so that whole blood cannot be obtained in the operating rooms except by special request. In essence, blood bankers are saying that except for a rare situation (i.e., hypovolemic shock), whole blood is not necessary.

For the patient who has lost blood and needs both erythrocytes and intravascular volume, what advantage is there in receiving packed erythrocytes instead of whole blood? There are no prospective data that document reduced risk of posttransfusion hepatitis. Furthermore, the incidence of transfusion reactions is not reduced unless "buffy-poor" or previously washed cells are used. It is doubtful whether small plasma and white blood antigenic load are of any benefit. For those patients in whom anaphylactic reactions to IgA develop, the erythrocytes must be completely free of plasma. Finally, the use of packed RBCs does not reduce potassium load unless the erythrocytes are packed immediately before infusion. If the RBCs are packed when the blood is freshly drawn, as is the usual case, the amount of potassium removed is minimal.

Despite all the preceding evidence to the contrary, I believe packed RBCs should still be used instead of whole blood, except in cases of severe hemorrhage. My rule is to use packed RBCs for losses of blood of less than 1,500 to 2,500 mL/70 kg. With greater losses, whole blood probably should be used. The concept that whole blood should be used for losses of blood greater than 2,500 mL/70 kg is now widely accepted, even in blood banking circles. In our hospital, patients undergoing operative procedures known to require more than 3 to 4 units of blood (e.g., aortoiliac reconstruction) are automatically crossmatched for whole blood instead of packed RBCs. The greater use of packed RBCs will allow blood banks to use the plasma to make other components of blood readily available. Depending on the type of surgery, anywhere from 50 to 80 percent of the RBCs given should be in the form of packed RBCs.

Because of this trend, some hospitals do not have whole blood readily available. This may force the surgical team to use packed RBCs for losses of blood greater than 1,000 to 1,500 mL/70 kg. One fear has been that if large volumes of packed RBCs reconstituted with a crystalloid are given, serum albumin deficiencies may result. On the basis of limited clinical data, Howland et al [132] proposed that infusion of saline-reconstituted RBCs would lead to low serum levels of fibrinogen and albumin, which could be an etiologic factor in postoperative pulmonary edema. This fear has not been substantiated. Despite this controversy, administration of saline-reconstituted RBCs for losses of blood less than 2,500 mL/70 kg usually does not induce low serum levels of albumin, although fibrinogen concentration can be decreased in the recipient. [133]

The administration of packed RBCs is facilitated by reconstituting them with a crystalloid or colloid; however, not all crystalloids are suitable. If the solution contains calcium, clotting occurs. Therefore, lactated Ringer solution is usually not recommended for use as a diluent for packed RBCs (Table 46-14) . Conversely, using flow rates and clot formation, Cull et al [134] found both lactated Ringer's solution and normal saline to be equally acceptable. A more important

TABLE 46-14 -- Compatibility of Blood With Intravenous Solutions

BLOOD TO INTRAVENOUS SOLUTION: 1 : 1 RATIO	HEMOLYSIS AT 30 MIN	
	ROOM TEMPERATURE	37 ° C
5% dextrose in water	1+	4+

Plasmanate [a]	1+	3+
5% dextrose in 0.2% saline	0	3+
5% dextrose in 0.4% saline	0	0
5% dextrose in 0.9% saline	0	0
0.9% saline	0	0
Normosol-R, pH.4 [b]	0	0
Lactated Ringer solution	0 (clotted)	0 (clotted)

[a] Cutter Laboratories, Berkeley, California
[b] Abbott Laboratories, Chicago, Illinois

factor may be whether the diluent is hypotonic with respect to plasma. If so, then the RBCs will swell and eventually lyse. Those solutions that cause hemolysis are listed in Table 46-14 . Clinicians who fear that the crystalloid-reconstituted RBCs may cause low serum concentrations may be tempted to use a plasma derivative, such as Plasmanate. [135] However, these solutions can cause hemolysis also. In the case of Plasmanate, its osmolality is only 180 mOsm/kg. Thus, those solutions recommended for reconstituted packed erythrocytes are 5 percent dextrose in 0.4 percent saline, 5 percent dextrose in 0.9 percent saline, 0.9 percent saline, and Normosol-R with a pH of 7.4.

Blood banks have made available packed RBCs that have been diluted with the addition of 100 mL of an adenine-saline-dextrose solution (Adsol) as described earlier. This addition allows the blood to flow readily without the addition of saline. If improved flow is desired, however, the clinician should not use 5 percent dextrose in water or lactated Ringer solution. [136] Also some centers have used modified whole blood (i.e., the platelets are removed but much more plasma remains than that with packed RBCs) in which the flow characteristics are similar to those of whole blood. [137]

Leukocyte-Reduced Blood

The number of leukocytes in packed RBCs can be markedly reduced by three approaches. First, one can use an in-line filter that is integral to the collection system used to obtain blood from donors. Second, after collection, blood can be filtered through a filter attached to the collection bag. Third, the blood can be filtered immediately before or at transfusion.

Usually, leukocyte-reduced blood is used to minimize the likelihood of febrile, nonhemolytic transfusion reactions. However, it can be used to reduce alloimmunization and transfusion-transmitted infection. Leukocyte-reduced blood will probably be used more frequently in the future. As indicated earlier, the Blood Products Advisory Committee of the FDA has recently recommended universal leukocyte reduction of cellular blood components. [125A] This approach showed reduced infectivity, transfusion reactions, and immunosuppression.

Platelet Concentrates

Platelet concentrates are prepared by differential centrifugation, either from freshly drawn units of blood or from donors who specifically donate large amounts of platelets by recently developed plateletpheresis techniques. If platelets are stored at room temperature, they are satisfactory to use 5 days after collection with constant and gentle agitation. However, in the report of 10 septic platelet transfusions between 1982 and 1985, half were platelets stored for 5 days or more. A prospective analysis from 1987 to 1990 resulted in seven cases of sepsis in patients receiving platelets for thrombocytopenia secondary to bone marrow failure. [138] Because use of multidonor platelet products stored for 5 days results in an incidence of sepsis five times higher than use of those stored for 4 days, shorter storage times are being emphasized. In fact, platelet-related sepsis is about 1/12,000. [125A] The increased risk of bacterial overgrowth is related to the storage temperature of 20 to 24°C. Because there is no test to identify bacterially contaminated blood products, any patient who develops a fever within 6 hours after receiving platelets, sepsis from platelets should be considered. If blood products are stored at 4°C, then they should not be used longer than 24 or possibly 48 hours after collection. The allowable storage time is based on *in vivo* survival. The longer allowable storage time at room temperature adds flexibility to the blood bank.

Indications for the use of platelets are somewhat difficult to define. The July 1989 FDA Drug Bulletin stated that platelets should not be given (1) to patients with immune thrombocytopenia purpura (unless there is life-threatening bleeding), (2) prophylactically with massive blood transfusion, (3) prophylactically after cardiopulmonary bypass. However, the use of fresh blood rather than platelet concentrates as a source of platelets is still emphasized by some cardiac groups [139] and is advocated by some for treatment of hemorrhage in general. [70] [71] More recently, the ASA Task Force 2 recommended that

1. Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction (e.g., idiopathic thrombocytic purpura).
2. Prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia due to decreased platelet production when the platelet count is greater than 100×10^9 /L and is usually indicated when the platelet count is below 50×10^9 /L. The determination of whether patients with intermediate platelet counts ($50\text{-}100 \times 10^{1C}$ /L) require therapy should be based on the patient's risk of bleeding.
3. Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50×10^9 /L and rarely require therapy if it is greater than 100×10^9 /L. With intermediate platelet counts ($50\text{-}100 \times 10^9$ /L), the determination should be based on the patient's risk for more significant bleeding.
4. Vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50×10^9 /L.
5. Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

Patients with severe thrombocytopenia (<20,000 cells/ m^3) and clinical signs of bleeding usually require platelet transfusion. However, patients may have very low platelet counts (much less than 20,000 cells/m^3) and not have any clinical bleeding. Patients such as these probably do not need platelet transfusion. Individuals who have undergone trauma or require surgery need higher platelet counts. As indicated previously, these patients probably need a platelet count of 100,000 cells/m^3 to maintain adequate hemostasis (see Table 46-5) . Thus, both laboratory determinations and clinical evaluations must be taken into account before a decision to transfuse platelets is made.

Whenever possible, ABO-compatible platelets should be used. The need to use them, however, is not well documented. Specific testing is difficult. Aggregation, the end point of RBC crossmatch, cannot be used because platelets cause clumping. The platelet membrane has immunoglobu-lins. Any additional deposit of recipient antibodies is diffi-cult

to detect. Despite the fact that platelets can be destroyed by antibodies directed against class I human leukocyte antigen proteins on their membranes and to a lesser extent by antibodies against ABO, platelets chosen for transfusion will continue to usually be chosen without regard to antigen systems. [140] ABO-incompatible platelets clearly produce very adequate hemostasis.

Platelets may be pooled into a single transfer bag or a syringe for administration or they may be administered as individual units. Several platelet administration sets are available for use. These all have filters with a pore size of about 170 m. Filters with smaller pore size (microaggregate filters) should not be used, because they tend to remove a significant number of platelets. Conversely, small filters are increasingly being used to hopefully decrease infectivity. Standard blood administration sets with 170-m filters are also acceptable. To decrease the loss of platelets, a 19-gauge needle, or greater, should be used. In order to ensure complete delivery of

all the platelets available, the containers should be rinsed with saline.

The effectiveness of platelet transfusions is difficult to monitor. Under ideal circumstances, one platelet concentrate usually produces an increase of about 7,000 to 10,000 platelets/m^3 1 hour after transfusion to the 70-kg adult. Thus, 10 units of platelet concentrates is required to increase the platelet count by 100,000 cells/m^3. However, many factors, including splenomegaly, previous sensitization, fever, sepsis, and active bleeding, may lead to decreased survivals and decreased recovery of transfused platelets.

In recent years, various different types of platelet concentrates have been proposed, including apheresis (i.e., collecting more platelets from one donor to avoid pooling of platelets from multiple donors), leukocyte-depleted platelets, and ultraviolet B-irradiated platelets. Whether these products will ultimately be used commonly is reviewed by Kruskall. [140]

Fresh Frozen Plasma

FFP is prepared at the time that blood is obtained from a donor. It contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. The use of FFP carries with it certain inherent risks that are observed with the use of essentially any blood product. The major risk is transmission of infectious diseases, such as hepatitis B, C, and AIDS. Other risks include sensitization to foreign proteins.

Despite all the problems associated with FFP, its use has increased tenfold during 1974 to 1984 and had reached almost 2 million units annually. This alarming increase caused the National Institutes of Health to conduct a Consensus Development Conference on Fresh Frozen Plasma in September 1984, of which I was a member. [53] More recently, the American Society of Anesthesiologists Task Force 2 recommended the administration of FFP with the following guidelines:

1. For urgent reversal of warfarin therapy.
2. For correction of known coagulation factor deficiencies for which specific correlates are unavailable.
3. For correction of microvascular bleeding in the presence of increased (>1.5 times normal) prothrombin time or partial thromboplastin time.
4. For correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when prothrombin time and partial thromboplastin time cannot be obtained in a timely fashion.
5. FFP should be given in doses calculated to achieve a minimum of 30 percent of plasma factor concentration (usually achieved with administration of 10-15 mL/kg of FFP), except for urgent reversal of warfarin anticoagulation, for which 5 to 8 mL/kg of FFP usually suffice. Four to five platelet concentrates, one unit of single donor apheresis platelets, or one unit of whole blood provides a quantity of coagulation factors similar to that contained on one unit of FFP (except for decreased, but still hemostatic, concentrations of factors V and VIII in whole blood).
6. FFP is contraindicated for augmentation of plasma volume or albumin concentration.

> As indicated in the section on coagulation problems with massive transfusions, they concluded that there is little scientific evidence to support the increasing use of FFP in clinical medicine. While FFP is a reliable solution for intravascular volume replacement in acute blood loss, alternative therapies are equally satisfactory and considerably safer. There is no documentation that FFP has a beneficial effect when used as part of transfusion management of patients with massive hemorrhage.
>
> A further comment: The practice of administering both packed red cells and FFP to the same patient should be discouraged, as this adds to the cost and doubles the infection exposure. When conditions are appropriate, whole blood should be given.

The only indications for FFP administration they agreed on were the following:

1. Replacement of isolated factor deficiencies (as documented by laboratory evidence)
2. Reversal of warfarin effect
3. In antithrombin III deficiency
4. Treatment of immunodeficiencies
5. Treatment of thrombotic thrombocytopenia purpura
6. Massive blood transfusion (rarely, and only when factors V and VIII are <25% of normal)
7. Requirements for indications 1 and 6 would be a prothrombin and partial thromboplastin time at least 1.5 times longer than normal.

Cryoprecipitate

Cryoprecipitate is prepared in such a way that it contains significant levels of factor VIII and fibrinogen. It also contains von Willebrand factor and fibronectin. All other plasma proteins are present in only trace amounts in cryoprecipitate. The use of cryoprecipitate in the treatment of factor VIII deficiency or hemophilia A has been outlined by Brown et al. [141] Cryoprecipitate contains factor VIII:C (the procoagulant activity), factor VIII:vWF (von Willebrand factor), fibrinogen, factor XIII, and fibronectin, which is a glycoprotein that may play a role in reticuloendothelial clearance of

foreign particles and bacteria from the blood. Cryoprecipitate can also be used in the treatment of fibrinogen deficiencies and is preferable to commercially prepared fibrinogen preparations. This is because commercially prepared fibrinogen preparations have a very high incidence of hepatitis, whereas the risk of hepatitis in cryoprecipitate is no greater than that from a single unit of blood.

Cryoprecipitate is frequently administered as ABO compatible; however, this probably is not very important, because the concentration of antibodies in cryoprecipitate is extremely low. Cryoprecipitate may contain red cell fragments, and thus cryoprecipitate prepared from Rh-positive individuals can possibly sensitize Rh-negative individuals to the Rh 0 antigen.

"Paradoxical bleeding" has been described during infusion of cryoprecipitate. [142] This means that bleeding persists during infusion of cryoprecipitate despite factor VIII levels of 30 to 50 percent of normal, which should be adequate for hemostasis. Cryoprecipitate has a large amount of fibrinogen, so that if the hemophiliac is transfused with enough cryoprecipitate, serum fibrinogen levels may also rise, increasing the risk of bleeding, even in the presence of normal amounts of factor VIII. Conversely, hyperfibrinogenemia is not observed when commercial factor concentrates are used.

Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/h, and infusion should be completed within 6 hours of thawing.

Commercial concentrates of factor VIII have been the standard therapy for hemophilia. Although heat inactivation of factor VIII concentrate reduces infectivity, such a risk is still present. Recombinant DNA techniques have been used to develop factor VIII, which is free of disease transmission. [143] Mild cases of hemophilia may be treated without blood products by administration of DDAVP. Appropriate therapy is difficult to ascertain for patients who have inhibitors (alloantibodies) to factor VIII.

Fibrin glue is used occasionally by surgeons to create local hemostatis. It is prepared in a manner similar to that of cryoprecipitate. When FFP is thawed, the precipitate contains large amounts of fibrinogen. When centrifuged, about 4 mL of concentrated precipitate results. With added thrombin, it is applied locally, the efficacy of which is difficult to determine.

Prothrombin Complex

Factor IX can be recovered from plasma or plasma fractions by absorption with ion exchanges or inorganic chemicals. These products are all complexes of factors II, VII, IX, and X. Two commercial preparations available are Konyne (Cutter Laboratories, Berkeley, Calif) and Proplex (Hyland Division of Travenol Laboratories, Costa Mesa, Calif).

The main indication for this product is treatment of factor IX deficiency, or hemophilia B (Christmas disease). This is a hemorrhagic disorder that is distinguishable from hemophilia A only by laboratory tests. Factor IX or prothrombin complex has also been used for the treatment of acquired hypoprothrombinemic bleeding disorders, principally sodium warfarin overdose; however, its use is limited because of the risk of hepatitis.

Single-Donor Plasma

Single-donor plasma is plasma that has been removed from stored blood without any effort being made to preserve coagulation factors. Single-donor plasma is very effective as a volume expander. All the precautions outlined for the administration of FFP should be followed when single-donor plasma is administered. It obviously cannot be used to correct deficiencies in coagulation factors.

Other Options to Reduce Infectivity of FFP [143A]

Solvent-Detergent

Plasma from multiple donors is pooled and subjected to a lipid-destroying mixture of a solvent (tri- *n*-butyl phosphate) and a detergent (Triton X-100) to inactivate lipid-enveloped infectious agents, including HIV, HTLV, hepatitis C virus, and hepatitis B virus. It has several disadvantages, including the risk of contamination of nonenveloped agents. Recalls can occur after any fraction of a lot has been released. It could be much more expensive.

Single-Donor Plasma, Donor Retested

A donation is made, and FFP is prepared. The unit (the first donation) is kept if all history and infectious diseases markers are negative. That unit is not released for use until the same donor donates a second unit at least 3 months after the first donation and again passes all donor intake and serologic testing. At that time, the first unit is released. The second unit is not released until the donor returns more than 3 months later for a third donation and again passes all the testing. At that time, the second unit can be released for use. This approach has obvious advantages but would be administratively complex.

Frequent-Donor Plasma

An inverse relationship exists between the number of donations a person has given and the chance that he or she will become seropositive. The relationship is independent of the time over which the donations were given. One appears to reach a maximum reduction of the incidence of seropositivity at four or more donations. Predictions are that reduction in seropositivity (and therefore transmission) to one-third to one-half the current figures is possible.

These options were presented at the University of California, San Francisco, Transfusion Committee meeting, and indicate that clinicians will have many ways of ensuring safer plasma for patients.

Summary

With the new tests of infectivity, the above FFP approaches may not be necessary.

Albumin and Plasma Protein Preparations

Several commercial products containing albumin are available for use as clinical volume expanders. Albumin is available as either a 5 or a 25 percent solution in isotonic saline. Furthermore, plasma protein fractions containing albumin and alpha- and beta-globulins are available. These solutions are prepared commercially from albumin fractions from large pools of plasma reconstituted in isotonic electrolyte solutions. Such solutions can be given without regard to ABO blood type and without crossmatch and should be used primarily as volume expanders. They are very expensive and in short supply. In fact, bacterial sepsis has been associated with albumin administration. [144] For much of 1997, there was a shortage of 5 percent albumin because of the concern about contamination with Creutzfeldt-Jakob disease, or "mad-cow disease." If available, albumin should be administered within 4 hours of initiation of the infusion because of potential contamination after entering the bottle.

Administration of plasma protein fraction solutions can result in hypotension, primarily as a result of a decrease in systemic vascular resistance [145] probably caused by the generation of bradykinin in recipients. [146] This type of prekallikrein activator activity rarely occurs with albumin. That administration of 5 percent albumin solution does not cause hypotension suggests that one of the globulin fractions in the plasma protein fraction is the cause.

We believe that administration of plasma protein fraction of 5 percent serum albumin solutions should be restricted for the treatment of documented hypoproteinemia or those conditions, such as burns and peritonitis, in which hypoproteinemia is likely. These solutions expand the vascular space for a longer period of time than balanced electrolyte solutions. [147] However, albumin's osmotic ability draws fluid into the vascular space from other extracellular fluid compartments. In most states of hypovolemia and dehydration, the entire extracellular fluid space already is depleted. Fluids such as 0.9 percent saline or lactated Ringer solution, which expand the entire extracellular fluid space, should be given.

The crystalloid versus colloid conflict has been debated for many years. The University Hospital Consortium developed guidelines for the use of albumin, nonprotein colloid, and colloid solutions. [148] Unfortunately, no anesthesiologists were represented in the Consensus Exercise. Their conclusions were not different from those described earlier.

Granulocyte Concentrates

Granulocyte concentrates have been obtained either by continuous-flow or intermittent-flow leukopheresis or by filtration leukopheresis. Such concentrates are difficult to obtain, require great time commitment on the part of the donor, survive for only short periods of time in the recipient, and have yet to be definitely proved efficacious in the treatment of recipients. In spite of these cautions, granulocyte transfusions are frequently used in larger centers for the treatment of severely leukopenic (a leukocyte count of 500/mm^3) patients with evidence of septicemia and fever.

Granulocytes should be ABO- and Rh-compatible. Furthermore, many centers also check the recipient's serum for the presence of antibodies reacting against the donor white blood cells. Granulocytes should be administered through a filter and should be administered slowly over 2 to 4 hours because more rapid infusion may cause severe pulmonary reactions. Fever and chills are common after administration of granulocytes. Granulocyte concentrates should be administered daily for at least 4 to 5 days or until a satisfactory clinical response is observed.

/das/book/view/29494766/875/529.html

ARTIFICIAL COLLOID SOLUTION THERAPY

The most commonly used artificial colloids are the dextrans, which are polysaccharides built up from glucose molecules. Dextran 70, with a molecular weight of about 70,000 (Macrodex), is an effective volume expander. [149] However, after infusion of more than 20 mL/kg/24 h, dextran 70 may interfere with normal blood clotting, causing a deficiency with crossmatching procedures and possibly causing bleeding diathesis. These clotting defects are due to reduced platelet adhesiveness secondary to an antithrombin effect. Of prime importance is a significant incidence of severe anaphylactoid or anaphylactic reactions. [150] [151] These reactions are mediated by dextran-reactive antibodies that are IgG immunoglobulins. Dextran-reactive antibodies are formed in response to dextran polysaccharides. This process can be prevented if the potentially reactive sites on the dextranreactive antibody are blocked before the antibody is given. By prior administration of a hapten, a substance capable of combining with immunoglobulins but not producing a reaction, the reactive sites are occupied and unable to react to the antigen. Prior administration of dextran I (Promit, mo-lecular weight 1,000) has proved effective as a hapten, and decreases, but does not eliminate, the incidence of severe reactions. [152] [153] In addition, dextran 70 exerts a higher colloid osmotic pressure than blood. Thus, both dextran 70 and albumin may deplete the extracellular fluid space of water as does albumin. [154]

Dextran 40, molecular weight of 40,000 (Rheomacrodex), has been used primarily to reduce blood viscosity and cellular aggregation and to improve microcirculation during low-flow states. It is often given prophylactically to decrease the incidence of postoperative thromboembolism. Blood viscosity may be increased by trauma, blood loss, burns, and endotoxin shock. Although viscosity can be decreased by dextran 40, the presumed improvement in flow through the microcirculation has not been well documented.

Expansion of the intravascular space by dextran 40 is of less duration and consistency than that observed with dextran 70. Carey et al [147] suggested that the addition of dextran 40 to crystalloid solutions with blood is beneficial for treatment of hypovolemia. Renal failure has been reported in several patients after administration of dextran 40 in an amount greater than 20 mL/kg. Obviously, with loss of blood greater than 20 percent of the blood volume, therapy with dextran 40 must be augmented with balanced electrolyte solution and blood.

Gelatin and starch preparations also have been produced to be used as intravascular volume expanders. [154] Although gelatin is the least effective, all of these synthetic products are as effective in expanding the intravascular volume as 5

percent albumin. However, they all can produce anaphylactoid reactions. [154]

In addition to the dextrans, hydroxyethyl starch (Hespan) is frequently used in the United States. It is a synthetic starch molecule that resembles glycogen and is given as a 6 percent solution. Several studies have substantiated that Hespan is as effective as albumin as an intravascular volume expander. [155] [156] [157] The elimination of Hespan has not been completely resolved, although it is stored in the reticuloendothelial system of the liver for hours. Apart from its dilutional effect, it does decrease factor VIII when more than 1,000 mL/70 kg is given. [158] Although the precise dose required to cause a coagulopathy is not clear, a general recommendation is that no more than 20 mL/kg/day of 6 percent hetastarch be given. [159] Also, urinary specific gravity can be elevated when Hespan is given to patients with acute oliguric renal failure. [160] This emphasizes using urinary osmolality rather than specific gravity when Hespan is used. Finally, an additional problem was difficulty in interpretation of typing and antibody screening in samples that contained more than 30 percent of the hydroxyethyl starch solution. [161]

Hypertonic Saline Possibly With Dextran

The sodium concentration of hypertonic saline solutions is 250 to 1,200 mEq/L. The theoretical advantage is that the greater the sodium concentration, the less total volume required for adequate resuscitation. The lower infusion volume is probably related to osmotically related movement of intracellular water into the extracellular space. Other mechanisms include a direct inotropic effect on the myocardium and a direct peripheral vasodilator effect. The main problem is severe hypernatremia, which can cause brain dehydration and can be fatal. The reader is referred to an excellent review by Moss and Gould [162] for further information.

Various hyperosmotic-hyperoncotic solutions have been used for resuscitation in hypovolemic patients. The most common combination is with hypertonic saline and 6 percent dextran 70. In animals, these fluids restore gut and kidney microcirculation more effectively than does normal saline. [163] [164] [165] Clinical practice will be required to ascertain the ultimate role, if any, of these fluids.

Synthetic Oxygen-Carrying Substances

Various substances that carry or facilitate the transport of oxygen have been made. The most notable is the perfluorochemical emulsion called Fluosol-DA. However, it will probably have little use because it carries oxygen (i.e., a small amount) only when the Pa O_2 is greater than 300 mm Hg. [165] Fluosol-DA was given to patients who had extensive surgical blood loss but who refused blood transfusions on religious grounds. In essence, administration of Fluosol-DA was of no benefit even in severe anemia. [166] Furthermore, there are many adverse effects. [167] [168] A newer perfluoro compound, perfluorocytylbromide, has been developed that carries three to four times more oxygen and has a longer half-life and presumably fewer problems than are associated with Fluosol-DA. Clinical trials will be required to determine its ultimate usefulness.

Hemoglobin can now be prepared from outdated human blood by a crystallization procedure and then dissolved in an isotonic medium. This solution can then be used as an intravascular volume expander. Animal studies indicate that this lysophilized crystalline solution is very effective. [169] However, these solutions are not without complications, [170] the most concerning of which are kidney toxicity and an increase in affinity for oxygen (i.e., left shift in the oxygen dissociation curve). A variety of approaches are being used, including crosslinking, pyridoxylation and polymerization, and conjugation and encapsulation, to decrease oxygen affinity, to decrease deposition in the reticuloendothelial system, and to increase half-life. Genetic engineering has provided hope for blood products. Initially, recombinant erythropoietin was developed for treatment of anemias and facilitation of autologous blood donation (Ch. 47) . In 1992, a human recombinant hemoglobin was designed as a blood substitute. [171] By use of genetic engineering, it was made from *Es-cherichia coli.* It functions just like normal hemoglobin in terms of oxygen-carrying capacity, but it does not require crossmatching nor does it transmit disease or become rapidly outdated. How much recombinant material can be tolerated by humans remains to be determined.

As of 1998, several synthetic blood products are under investigation:

1. Stroma-free hemoglobin solutions containing some modifications of the hemoglobin molecule
2. Genetically engineered hemoglobin (e.g., having *E. coli* produce human red cells)
3. Liposome-encapsulated hemoglobin solutions containing hemoglobin with a synthetic membrane

4. Perfluorocarbons, organic solutions with high oxygen solubility

To prevent many of the complications seen with the use of synthetic blood products (e.g., renal damage, endotoxin release), various approaches have been used, such as cross-linking, polymerization, and conjugators with chemical or genetic engineering, as summarized earlier. With stroma-free hemoglobin, outdated human cells strip the oxygencar-rying substance out of the cell coating and then chemically modify it by one or more of the aforementioned approaches. By removing the cell lining, allergic reactions are prevented.

Originally, these products were viewed as blood substitutes. However, comparing safety is easy, but efficacy compared with that of bank blood is difficult to determine. FDA criteria of efficacy are difficult to establish. [172] Now, more emphasis is on their ability to transport oxygen. [173]

Dietz has provided an excellent review of this entire topic. [174] Goodnough et al [143A] have updated their status.

INFORMED CONSENT

Before any transfusion is given, an informed consent should be obtained (Ch. 85) . What constitutes such a consent varies across the United States and is under constant change. If a patient is damaged by a transfusion adminis-tered without a valid consent, damages may be recovered

even though the defendant did everything properly. [174] During the past decade, the public has demanded to know more about transfusions. A dramatic example was the passage of the Paul Gann Blood Safety Act in California. This law mandates that patients be informed of the risks of blood transfusions and of any alternatives (Ch. 47) . This law has appar-ently already had a restrictive impact on transfusion practice in California. [175] Clearly, the rapid changes in transfusion medicine probably dictate an intense ongoing educational process for those clinicians who administer blood products to patients. [176] [177]

References

1. Stehling LC, Ellison N, Faust RJ et al: A survey of transfusion practices among anesthesiologists. Vox Sang 52:60, 1987.

2. ASA Task Force: Practice guidelines for blood component therapy. Anesthesiology 84:32, 1996.

3. Royal College of Physicians of Edinburgh: Consensus statement on red cell transfusion. Br J Anaesth 73:857, 1994.

4. Miller RD, Stehling L: What is the transfusion trigger? What is the message? Anesthesiology 86:750, 1997.

5. National Institutes of Health Consensus Development Conference Statement: Perioperative red cell transfusion. vol 7, no. 4, June 27-29, 1988.

6. Dietrick KA, Conrad SA, Hebert CA et al: Cardiovascular and metabolic response to red blood cell transfusion in critically ill volumeresuscitated nonsurgical patients. Crit Care Med 18:940, 1990.

7. Steffes CP, Bender JS, Levison MA: Blood transfusion and oxygen consumption in surgical sepsis. Crit Care Med 19:512, 1991.

8. Mink RB, Pollack MM: Effect of blood transfusion on oxygen consumption in pediatric septic shock. Crit Care Med 18:1087, 1990.

9. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 269:3024, 1993.

10. Corwin HL, Parsonnet KC, Gettinger A: RBC transfusion in the ICU: Is there a reason? Chest 108:767, 1995.

11. Hebert PC, Wells G, Marshall J et al: for the Canadian Critical Care Trials Group: Transfusion requirements in critical care--A pilot study. JAMA 273:1439, 1995.

12. Bishop MH, Shoemaker WC, Appel PL et al: Relationship between supranormal circulatory values, time delays and outcome in severely traumatized patients. Crit Care Med 21:56, 1993.

13. Bishop MH, Shoemaker WC, Appel PL et al: Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma Injury Infect Crit Care 38:780, 1995.

14. Boyd O, Grounds RM, Bennett DE: A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 270:2699, 1993.

15. Purdy RF, Tweeddale MG, Merrick PM: Association of mortality with age of blood transfused in septic ICU patients. Can J Anaesth 44:1256, 1997.

16. Kim DM, Brecher ME, Estes TJ et al: Relationship of hemoglobin level and duration of hospitalization after total hip arthroplasty: Implications for the transfusion target. Mayo Clin Proc 68:37, 1993.

17. Thurer RL: Evaluating transfusion triggers. JAMA 279:238, 1998.

18. Weiskopf RB, Viele MK, Feiner et al: Human cardiovascular and metabolic responses to acute, severe isovolemic anemia. JAMA 279:217, 1998.

19. McSwiney MM, O'Farrell D, Joshi GP et al: Blood transfusion in total hip arthroplasty: Guidelines to eliminate overtransfusion. Can J Anaesth 40:222, 1993.

20. Habibi S, Corrsin DB, McDermott JC et al: Trauma and massive hemorrhage. In Muravchick S, Miller RD (eds): Atlas of Anesthesia: Subspecialty Care. New York, Churchill-Livingstone, 1998, pp 6.2-6.17.

20A. Hebert PC, Wells G, Blajchman MA et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. New Engl J Med 340:409, 1999.

20B. Ely EW, Bernard GR: Transfusions in critically ill patients. New Engl J Med 340:467, 1999.

20C. Weiskopf RB: Do we know when to transfuse red cells to treat acute anemia? Transfusion 38:517, 1998.

21. Renner SW, Howanitz PJ, Bachner P: Preoperative autologous blood donation in 612 hospitals: A College of American Pathologists' Q-probes study of quality issues in transfusion practice. Arch Pathol Lab Med 116:613-619, 1992.

22. Etchason J, Petz L, Keeler E et al: The cost effectiveness of preoperative autologous blood donations. N Engl J Med 332:719, 1995.

23. Kanter MH, Van Maanen D, Anders KH et al: Preoperative autologous blood donations before elective hysterectomy. JAMA 276:798, 1996.

24. Popovsky MA, Whitaker B, Arnold NL: Severe outcomes of allogeneic and autologous blood donations: Frequency and characterization. Transfusion 35:734-737, 1995.

25. Centers for Disease Control and Prevention (CDC): Red blood cell transfusions contaminated with *Yersinia enterocolitica.* JAMA 278:553, 1997.

26. Williams AE, Thompson RA, Schreiber GB et al: Estimates of infectious disease risk factors in US blood donors. JAMA 277:967, 1997.

27. Miller RD, Von Ehrenberg W: Should the same indication be used for both autologous and homologous transfusions? Transfusion 35:703, 1995.

28. American Society of Anesthesiologists: Transfusion Practices: Questions and Answers. 3rd ed. Chicago, American Society of Anesthesiologists, 1998, pp 8-9.

29. Boyd PR, Sheedy KC, Henry JB: Type and screen: Use and effectiveness in elective surgery. Am J Clin Pathol 74:694, 1980.

30. Oberman AJ, Barnes BA, Friedman BA: The risk of abbreviating the major crossmatch in urgent or massive transfusion. Transfusion 18:137, 1978.

31. Sarma DP: Use of blood in elective surgery. JAMA 243:1536, 1980.

32. Friedman BA: An analysis of surgical blood use in United States hospitals with application to the maximum surgical blood order schedule. Transfusion 19:268, 1979.

33. Walker RH: What is a clinically significant antibody? In Polesky HF, Walker RH (eds): Safety and Transfusion Practices. Skokie, Illinois, College of American Pathologists, 1982, p 79.

34. Gervin AS, Fischer RP: Resuscitation of trauma patients with type-specific uncrossmatched blood. J Trauma 24:327, 1984.

35. Moore GL, Peck CC, Sohmer PR et al: Some properties of blood stored in CPDA-1 solution. Transfusion 21:135, 1981.

36. Valeri CR: Measurement of viable ADSOL-preserved human red cells. N Engl J Med 312:377, 1985.

37. Vovric VA, Archer GT, Wisdom L et al: Thirty-five-day modified red cells and 7-day stored platelet concentrates from triple bags of identical PVC formation. Vox Sang 49:181, 1985.

38. Valeri CR: Simplification of the methods for adding and removing glycerol during freeze-preservation of human red blood cells with high or low glycerol methods: Biochemical modification prior to freezing. Transfusion 15:195, 1975.

39. Telischi M, Hoiberg R, Rao KPP et al: The use of frozen, thawed erythrocytes in blood banking. Am J Clin Pathol 68:250, 1977.

40. Haugen RK: Hepatitis after the transfusion of frozen red cells and washed red cells. N Engl J Med 301:393, 1979.

41. Valtis DJ, Kennedy AC: Defective gas-transport function of stored red blood cells. Lancet 1:119, 1954.

42. Bunn HF, May MH, Kocholaty WF et al: Hemoglobin function in stored blood. J Clin Invest 48:311, 1969.

43. Kopriva CJ, Ratliff JL, Fletcher JR et al: Biochemical and hematological changes associated with massive transfusion of ACD-stored blood in severely injured combat casualties. Ann Surg 176:585, 1972.

44. McConn R, Derrick JB: The respiratory function of blood: Transfusion and blood storage. Anesthesiology 36:119, 1972.

45. Sheldon GF: Diphosphoglycerate in massive transfusion and erythrophoresis. Crit Care Med 7:407, 1979.

46. Valeri CR, Collins FB: Physiologic effects of 2,3-DPG-depleted red cells with high affinity for oxygen. J Appl Physiol 31:823, 1971.

47. Bowen JC, Fleming WH: Increased oxyhemoglobin affinity alters transfusion of stored blood: Evidence for circulatory compensation. Ann Surg 180:760, 1974.

48. Collins JA: Recent developments in the area of massive transfusion. World J Surg 11:75, 1987.

49. Miller RD, Robbins TO, Tong MJ et al: Coagulation defects associated with massive blood transfusions. Ann Surg 174:794, 1971.

50. Counts RB, Haisch C, Simon TL et al: Hemostasis in massively transfused trauma patients. Ann Surg 190:91, 1979.

51. Reed RL, Heimback DM, Counts RB et al: Prophylactic platelet administration during massive transfusion. Ann Surg 203:40, 1986.

52. Miller RD: Complications of massive blood transfusions. Anesthesiology 39:82, 1973.

53. NIH Consensus Conference: Fresh frozen plasma: Indications and risks. JAMA 253:551, 1985.

54. Phillips TF, Soulier BA, Wilson RF: Outcome of massive transfusion exceeding two blood volumes in trauma and emergency surgery. J Trauma 27:903, 1987.

55. Levi M, ten Cate H, van der Poll T, van Deventer JH: Pathogenesis of disseminated intravascular coagulation. JAMA 270:975, 1993.

56. Attar S, Hanashiro P, Mansberger A: Intravascular coagulation: Reality or myth. Surgery 68:27, 1970.

57. Corrigan JJ, Jordan CM: Heparin therapy in septicemia with disseminated intravascular coagulation. N Engl J Med 283:778, 1970.

58. Priano LL, Wilson RD, Traber DL: Lack of significant protection afforded by heparin during endotoxic shock. Am J Physiol 220:901, 1971.

59. Mant MJ, King EG: Severe, acute disseminated intravascular coagulation. Am J Med 67:557, 1979.

60. Fourrier F, Chopin C, Goudemand J et al: Septic shock, multiple organ failure, and disseminated intravascular coagulation. Chest 101:816, 1992.

61. Saleem A, Blifeld C, Saleh SA et al: Viscoelastic measurement of clot formation: A new test of platelet function. Ann Clin Lab Sci 13:115, 1983.

62. Lavee J, Martinowitz U, Mohr R et al: The effect of transfusion of fresh whole blood versus platelet concentrates after cardiac operations. J Thorac Cardiovasc Surg 97:204, 1989.

63. Erber WN, Tan J, Grey D et al: Use of unrefrigerated fresh whole blood in massive transfusion. Med J Aust 165:11, 1996.

64. Harvey MP, Dwyer P, Dean MG: Fighting a rearguard action in the massively transfused patient. Med J Anest 165:9, 1996.

65. Murray DJ, Olson J, Strauss R, Tinker JH: Coagulation changes during packed red cell replacement of major blood loss. Anesthesiology 69:839, 1988.

66. Kang Y, Lewis JH, Navalgung A et al: Epsilon-aminocaproic acid for treatment of fibrinolysis during liver transplantation. Anesthesiology 66:766, 1987.

67. Mannucci PM: Desmopressin: A nontransfusional form of treatment for congenital and acquired bleeding disorders. Blood 72:1449, 1988.

68. Morgan PD, Hosking MP: The role of desmopressin acetate in patients undergoing coronary artery bypass surgery. Anesthesiology 77:38, 1992.

69. Feeley TW, Rinsky LA: Use of aprotinin to reduce intraoperative bleeding. West J Med 159:189, 1993.

70. Huppala S, Strid L, Wennerstrand M et al: Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth 74:534, 1995.

71. Huppala ST, Strid LJ, Wennerstrand MI, et al: Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg 84:839, 1997.

72. Laupacis A, Fergusson D, The International Study of Perioperative Transfusion Investigators: Drugs to minimize perioperative blood loss in cardiac surgery: Meta-analyses using perioperative blood transfusion as the outcome. Anesth Analg 85:1258, 1997.

73. Leslie SD, Toy PTCY: Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. Am J Clin Pathol 96:770, 1991.

74. Urban P, Scheidegger D, Buchmann B et al: Cardiac arrest and blood ionized calcium levels. Ann Intern Med 109:110, 1988.

75. Drop LJ, Laver MB: Low plasma ionized calcium and response to calcium therapy in critically ill man. Anesthesiology 43:300, 1975.

76. Bashour TT, Ryan C, Kabbani SS et al: Hypocalcemic acute myocardial failure secondary to rapid transfusion of citrated blood. Am Heart J 108:1040, 1984.

77. Linko K, Tigerstedt I: Hyperpotassemia during massive blood transfusions. Acta Anaesthesiol Scand 28:220, 1984.

78. Morris RH: Influence of ambient temperature on patient temperature during intra-abdominal surgery. Ann Surg 173:230, 1971.

79. Zorko MF, Polsky SS: Rapid warming and infusion of packed red blood cells. Ann Emerg Med 15:907, 1986.

80. Sazama K: Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion 30:583, 1990.

81. Iserson KV, Huestis DW: Blood warming: Current application and techniques. Transfusion 31:558, 1991.

82. Collins JA, Simmons RL, James PM et al: The acid-base status of seriously wounded combat casualties. I: Resuscitation with stored blood. Ann Surg 173:6, 1971.

83. Miller RD, Tong MJ, Robbins TO: Effects of massive transfusion of blood on acid-base balance. JAMA 216:1762, 1971.

84. France CJ, Eger EI II, Bendixen HH: The use of peripheral venous blood for pH and carbon dioxide tension determinations during general anesthesia. Anesthesiology 40:311, 1974.

85. Wong DW, Mishkin FS, Tanaka TT: The effects of bicarbonate on blood coagulation. JAMA 244:61, 1980.

86. Moseley RV, Doty DB: Changes in the filtration characteristics of stored blood. Ann Surg 171:329, 1970.

87. Bradford D, Chandler ST, Hawker RJ et al: Splenic plateletsequestration following routine blood transfusion is reduced by filtered/washed blood products. Br J Haematol 67:177, 1987.

88. Lim S, Boughton BJ, Bareford D: Thrombocytopenia following routine blood transfusion: Micro-aggregate blood filters prevent worsening thrombocytopenia in patients with low platelet counts. Vox Surg 56:40, 1989.

89. Gilbert GL: Prevention of transfusion-acquired cytomegalovirus infection in infants by blood filtration to remove leukocytes. Lancet 1:1228, 1989.

90. Hassig A, Collins JA, Hogman C et al: When is microfiltration of whole blood and red cell concentrates essential? When is it superfluous? Vox Surg 50:54, 1986.

91. Capon SM, Sacher RA: Hemolytic transfusion reactions: A review of mechanisms, sequelae, and management. J Intensive Care Med 4:100, 1989.

92. Linden JV, Kaplan HS: Transfusion errors: Cause and effects. Trans Med Rev 8:169, 1994.

93. American Society of Anesthesiologists: Questions & Answers about transfusion practices. 1997.

94. Linden JV, Tourault MA, Schribner CL: Decrease in frequency of transfusion fatalities. Transfusion 37:243, 1997.

95. Seyfried H, Walewska I: Immune hemolytic transfusion reactions. World J Surg 11:25, 1987.

96. Huh YO, Lichtiger B: Transfusion reactions in patients with cancer. J Clin Pathol 87:253, 1987.

97. Pineda AA, Brzica SM, Jr, Taswell HF: Hemolytic transfusion reaction. Mayo Clin Proc 53:378, 1978.

98. Lopas H: Immune hemolytic transfusion reactions in monkeys: Activation of the kallikrein system. Am J Physiol 225:372, 1973.

99. Seager OA, Nesmith MA, Begelman KA et al: Massive acute hemodilution for incompatible blood reaction. JAMA 229:788, 1974.

100. Solanki D, McCurdy PR: Delayed hemolytic transfusion reactions: An often-missed entity. JAMA 239:729, 1978.

101. Hewitt PE, Macintyre EA, Devenish A et al: A prospective study of the incidence of delayed haemolytic transfusion reactions following perioperative blood transfusion. Br J Haemat 69:541, 1988.

102. Poipvsky MS, Abel MD, Moore SB: Transfusion-related acute lung injury associated with passive transfer of anti-leukocyte antibodies. Am Rev Respir Dis 128:185, 1983.

103. Oberman HA: Should a febrile transfusion response occasion the return of the blood component to the blood bank? CON Transfusion 34:353, 1994.

104. Widman FK: Should a febrile transfusion response occasion the return of the blood component to the blood bank? PRO Transfusion 34:356, 1994.

105. Pineda AA, Taswell HS: Transfusion reactions associated with anti-IgA antibodies: Report of 4 cases and review of the literature. Transfusion 15:10, 1975.

106. Tong MJ, El-Farra NS, Reikes AR et al: Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 332:1463, 1995.

107. Schreiber GB, Busch MP, Kleinman SH et al: The risk of transfusion-transmitted viral infections. N Engl J Med 334:1685, 1996.

108. Murphy EL, Bryzman S, Williams AE et al: Demographic determinants of hepatitis C virus seroprevalence among blood donors. JAMA 275:995, 1996.

109. Nishioka NS, Dienstag JL: Delta hepatitis. N Engl J Med 312:1515, 1989.

110. Rosina F, Saracco G, Rizzetto M: Risk of post-transfusion infection with the hepatitis delta virus. N Engl J Med 312:1488, 1985.

111. Curran JW, Lawrence DN, Jaffe H et al: Acquired immunodeficiency

syndrome (AIDS) associated with transfusions. N Engl J Med 310:69, 1984.

112. Simon TL, Bankhurst AD: A study of surrogate tests to prevent transmission of acquired immunodeficiency syndrome. Blood 62 (suppl 1):238a, 1984.

113. Ballas SK, Draper EK, Harris M et al: Designated blood donations. N Engl J Med 310:124, 1984.

114. Cohen ND, Munoz A, Reitz BA et al: Transmission of retroviruses by transfusion of screened blood in patients undergoing cardiac surgery. N Engl J Med 320:1173, 1989.

115. Preiksaitis VK, Grumet FC, Smith WK et al: Transfusion-acquired cytomegalovirus infection in cardiac surgery patients. J Med Virol 15:283, 1985.

116. Preiksaitis JK, Brown L, McKenzie M: The risk of cytomegalovirus infection in seronegative transfusion recipients not receiving exogenous immunodepression. J Infect Dis 157:523, 1988.

117. Wilhelm JA, Matter L, Schopfer K: The risk of transmitting cytomegalovirus to patients receiving blood transfusions. J Infect Dis 154:169, 1986.

118. Tripple MA, Bland JJ, Murphy MJ et al: Sepsis associated with transfusion of red cells contaminated with *Yersinia enterocolitica.* Transfusion 30:207, 1990.

119. Aber RC: Transfusion-associated *Yersinia enterocolitica.* Transfusion 30:193, 1990.

120. Grossman BJ, Kollins PM, Lau JL et al: Screening blood donors for gastrointestinal illness: a strategy to eliminate carriers of *Yersinia enterocolitica.* Transfusion 31:500, 1991.

121. Hayashi H, Nishiuchi T, Tamura H et al: Transfusion-associated graft-versus-host disease caused by leukocyte-filtered stored blood. Anesthesiology 79:1419, 1992.

122. Florell SR, Velasco SE, Fine PG: Perioperative recognition, management, and pathologic diagnosis of transfusion-related acute lung injury. Anesthesiology 81:508, 1994.

123. MMWR: adverse ocular reactions following transfusion--United States 1997-1998. JAMA 279:49, 1998.

124. Donnell CA, Daniel SJ, Ferrara JJ: Fibrinogen degradation products in fresh frozen plasma. Am Surgeon 55:505, 1989.

125. Younes RN, Rogato A, Brennan MF: The influence of intraoperative hypotension and perioperative blood transfusion on disease-free survival in patients with complete resection of colorectal liver metastases. Ann Surg 214:107, 1991.

125A. Blumberg N, Neal JM, Murphy P et al: Association between transfusion of whole blood and recurrence of cancer. Br Med J 293:503, 1986.

125B. Goodnough LT, Brecher ME, Kanter MH et al: Transfusion medicine I: Blood transfusion. N Engl J Med 340:438, 1999.

126. Anders A, Hyllner M, Bengston JP et al: Postoperative inflammatory response after autologous and allogeneic blood transfusion. Anesthesiology 87:511, 1997.

127. Busch ORC, Hop WCJ, van Papendrecht MAWH et al: Blood transfusions and prognosis in colorectal cancer. N Engl J Med 328:1372, 1993.

128. Landers DF, Hill GE, Wong KC et al: Blood transfusion-induced immunomodulation. Anesth Analg 82:187, 1996.

129. Wheatley T, Veitch PS: Effect of blood transfusion on postoperative immunocompetence. Br J Anaesth 78:489, 1997.

130. Sloand EM, Pitt E, Klein HG: Safety of the blood supply. JAMA 274:1368, 1995.

131. Au Buchon JP, Birkmeyer JD, Busch MP: Safety of the blood supply in the United States: Opportunities and controversies. Ann Intern Med 127:904, 1997.

132. Howland WS, Schweizer O, Fleisher M et al: Fibrinogen and albumin deficiencies associated with packed red blood cell transfusion. Anesth Analg 54:89, 1975.

133. Roberson HD, Polk HC: Blood transfusions in elective operations: Comparison of whole blood versus packed red cells. Ann Surg 181:778, 1975.

134. Cull DL, Lally KP, Murphy KD: Compatibility of packed erythrocytes and Ringer's lactate solution. Surg Gynecol Obstet 173:12, 1991.

135. Brown WJ, Kim BS, Weeks DB et al: Physiologic saline solution, Normosol R pH 7.4, and Plasmanate as reconstituents of packed human erythrocytes. Anesthesiology 49:99, 1978.

136. Strautz RL, Nelson JM, Meyer EA, Shulman IA: Compatibility of ADSOL-stored red cells with intravenous solutions. Am J Emerg Med 7:162, 1989.

137. Lovric VA, Schuller M, Rose G et al: Flow properties of modified packed red cells. Anaesth Intensive Care 15:407, 1987.

138. Morrow JF, Braine HG, Kickler TS et al: Septic reactions to platelet transfusions. JAMA 266:255, 1991.

139. Mohr R, Goor DA, Yellin A et al: Fresh blood units contain large potent platelets that improve hemostasis after open heart operations. Ann Thorac Surg 53:650, 1992.

140. Kruskall MS: The perils of platelet transfusions. N Engl J Med 337:1914, 1997.

141. Brown B, Steed DL, Webster MW et al: General surgery in adult hemophiliacs. Surgery 99:154, 1986.

142. Hathaway WE, Mahasondana C, Clarke S et al: Paradoxical bleeding in intensively transfused hemophiliacs. Transfusion 13:6, 1973.

143. White GC, McMillan CW, Kindon HS et al: Use of recombinate antihemophiliac factor in the treatment of two patients with classic hemophilia. N Engl J Med 320:164, 1989.

143A. Goodnough LT, Brecher ME, Kanter MH: Transfusion medicine II: Blood conservation. N Engl J Med 340:525, 1999.

144. MMWR: Bacterial sepsis associated with the receipt of albumin. JAMA 276:1373, 1996.

145. Bland JHL, Laver MB, Lowenstein E: Vasodilator effect of commercial 5% plasma protein fraction solutions. JAMA 224:1721, 1973.

146. Alving BM, Huima Y, Pisano JJ et al: Hypotension associated with prekallikrein activator (Hageman-factor fragments) in plasma protein fraction. N Engl J Med 299:66, 1978.

147. Carey JS, Woodward NW, Tao Y et al: Comparison of hemodynamic responses to whole blood and plasma expanders in clinical traumatic shock. Surg Gynecol Obstet 121:1059, 1965.

148. Vermeulen LC, Ratko TA, Erstad BL et al: The university hospital consortium guidelines for the use of albumin, nonprotein colloid and crystalloid solutions. Arch Intern Med 155:373, 1995.

149. Kayser L, Reiger A: Changes in blood volume and plasma proteins on administration of different substitutes after operations in man. Acta Clin Scand 134:15, 1968.

150. Alexander B: Recent studies on plasma colloid substitutes: Their effects on coagulation and hemostasis. In Fox CL, Jr, Nahas GG (eds): Body Fluid Replacement in the Surgical Patient. Orlando, Grune & Stratton, 1970, p 157.

151. Hedin H, Richter W, Messmer K et al: Incidence, pathomechanism and prevention of dextran-induced anaphylactoid/anaphylactic reactions in man. Biol Stand 48:179, 1980.

152. Bernstein RL, Rosenberg AD, Pada EY et al: A severe reaction to dextran despite hapten inhibition. Anesthesiology 67:567, 1987.

153. Ljungstrom KG, Renck H, Hedin H et al: Hapten inhibition and dextran anaphylaxis. Anaesthesia 43:729, 1988.

154. Doenicke A, Grote B, Lorenz W: Blood and blood substitutes. Br J Anaesth 49:681, 1977.

155. Lazrove S, Waxman K, Shippy C et al: Hemodynamic, blood volume, and oxygen transport responses to albumin and hydroxyethyl starch infusions in critically ill postoperative patients. Crit Care Med 8:302, 1980.

156. Shatney CH, Krishnapradad D, Militello PR et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. Arch Surg 118:804, 1983.

157. Puri V, Paidipty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. Crit Care Med 9:833, 1981.

158. Stump DC, Strauss RG, Henriksen RA et al: Effect of hydroxyethyl starch on blood coagulation, particularly factor VIII. Transfusion 25:349, 1985.

159. Gold MS, Russo J, Tissot M et al: Comparison of Hetastarch to albumin for perioperative bleeding in patients undergoing abdominal aortic aneurysm surgery. Ann Surg 211:482, 1990.

160. Haskell LP, Tannenberg AM: Elevated urinary specific gravity in acute oliguric renal failure due to hetastarch administration. NY State J Med 68:387, 1988.

161. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and crossmatching. Transfusion 22:226, 1981.

162. Moss GS, Gould SA: Plasma expanders. Am J Surg 155:425, 1988.

163. Kreimeier V, Bruckner UB, Niemczyk S et al: Hyperosmotic saline dextran for resuscitation from traumatic-hemorrhage hypotension. Circ Shock 32:83, 1990.

164. Behrman SW, Fabian TC, Kudsk KA et al: Microcirculatory flow changes after initial resuscitation of hemorrhagic shock with 7.5% hypertonic saline/6% dextran 70. J Trauma 31:589, 1990.

165. Tremper KK, Friedman AE, Levine EM et al: The preoperative treatment of severely anemic patients with perfluorochemical oxygen transport fluid, Fluosol-DA. N Engl J Med 307:277, 1982.

166. Gould SA, Rosen AL, Sehgal LR et al: Fluosol-DA as red cell substitute in acute anemia. N Engl J Med 314:1653, 1986.

167. Police AM, Waxman K, Tominage G: Pulmonary complications after fluosol administration to patients with life-threatening blood loss. Crit Care Med 13:96, 1985.

168. Waxman K, Tremper KK, Cullen BF et al: Perfluorocarbon infusion of bleeding patients refusing blood transfusions. Arch Surg 119:721, 1984.

169. DeVenuto F, Zegna AI, Busse KR: Lyophilization of crystalline hemoglobin solution and exchange transfusions with lyophilized, reconstituted hemoglobin. Surg Gynecol Obstet 148:69, 1979.

170. Vogel WM, Dennis RC, Cassidy G et al: Coronary constrictor effect of stroma-free hemoglobin solutions. Am J Physiol 251:H420, 1986.

171. Looker D, Abbott-Brown D, Cozart P: A human recombinant haemoglobin designed for use as a blood substitute. Nature 356:258, 1992.

172. Centers for Biologics Evaluation and Research: Points to consider in the safety evaluation of hemoglobin-based oxygen carriers. Transfusion 31:369, 1991.

173. Hughes GS, Yancey EL, Albrecht R et al: Hemoglobin-based oxygen carriers preserves submaximal exercise capacity in humans. Clin Pharmacol Ther 58:434, 1995.

174. Dietz NM, Joyner MJ, Warner MA: Blood substitutes: fluids, drugs, or miracle solutions? Anesth Analg 82:390, 1996.

175. Engel HL: Medicolegal considerations in blood transfusion. In Petz LD, Swisher SN (eds): Clinical Practice of Blood Transfusion. 2nd ed. New York, Churchill Livingstone, 1989, p 355.

176. Carey JS, Cukingnan RA, Carson E: Transfusion therapy in cardiac surgery: Impact of the Paul Gann Blood Safety Act in California. Am Surg 12:830, 1991.

177. Soumerai SB, Salem-Schatz S, Avorn J et al: A controlled trial of educational outreach to improve blood transfusion practice. JAMA 270:961, 1993.

178. Miller RD: The oxygen dissociation curve and multiple transfusions of ACD blood. In Howland WS, Schweizer O (eds): Management of Patients for Radical Cancer Surgery. Clinical Anesthesia Series, vol 9. Philadelphia, FA Davis, 1972, p 43.

179. Myllyla G: New transfusion practice and haemostasis. Acta Anaesthesiol Scand Suppl 89:76, 1988.

180. Miller RD: Transfusion therapy and associated problems. Reg Refresher Courses Anesthesiol 1:101, 1973.

181. Denlinger JK, Narhwold ML, Gibbs PS et al: Hypocalcemia during rapid blood transfusion in anaesthetized man. Br J Anaesth 48:995, 1976.

Chapter 47 - Autologous Transfusion *

Linda Stehling

INTRODUCTION

Autologous transfusion is not a new concept. Reinfusion of shed blood was employed as early as 1818, [1] and preoperative donation of autologous blood was advocated in the 1930s, when the first blood banks were established. [2] Several factors are responsible for the current popularity of autologous transfusion. The introduction of complex operative procedures, such as cardiac surgery and organ transplantation, stimulated the search for alternatives to allogeneic (homologous) transfusion. Technologic advances made possible the development of safe, easy-to-use devices for recovery and reinfusion of shed blood, and fear of transfusion-transmitted disease stimulated growth of autologous programs.

There are three types of autologous transfusion: preoperative blood donation, acute normovolemic hemodilution (ANH), and intraoperative and postoperative blood recovery (blood salvage). The advantages and disadvantages, applications, and complications vary with the techniques being used. It is often appropriate to employ more than one technique for patients undergoing surgical procedures associated with significant blood loss.

ADVANTAGES OF AUTOLOGOUS TRANSFUSION

The two primary reasons for employing autologous transfusion are (1) avoidance of complications associated with allogeneic transfusion and (2) conservation of blood resources. The altruistic public has thus far donated sufficient blood to meet the needs of virtually all patients, but blood shortages do occur. Patients with rare blood phenotypes can benefit from autologous transfusion because compatible allogeneic blood may not always be available. Potential complications of allogeneic transfusion that can be eliminated or minimized when autologous blood is administered include acute and delayed hemolytic reactions, alloimmunization, allergic and febrile reactions, transfusion-transmitted infectious diseases, and immunosuppression. Intraoperative blood recovery may be the only option for providing a sufficient volume of compatible blood when severe, rapid blood loss occurs. ANH provides the only practical source of fresh whole blood.

HISTORY OF AUTOLOGOUS TRANSFUSION

The early history of autologous transfusion is confined to descriptions of recovery and reinfusion of blood shed by surgical and obstetric patients. Blood salvage was first reported in the American literature in 1917. [3] By 1936, 277 cases had been reported. [4] [5] [6] [7] Sporadic reports of use of the technique in patients with hemothorax appeared in the surgical literature from 1931 [8] through the early 1970s. However, the technique was used only as a life-saving measure, and little was known about the quality of the product reinfused. In 1966, Symbas [9] undertook a series of laboratory and clinical studies leading

* *See Practice Guidelines for Blood Component Therapy*

Figure 47-1 Bentley autotransfusion system.

to adoption of an autotransfusion protocol for managing patients with acute traumatic hemothorax that was employed in more than 400 patients between 1966 and 1978.

Reports of instrumentation developed specifically for intraoperative blood recovery and autologous transfusion began to appear in 1966. [10] In 1969, investigators reported on the use of a continuous-flow centrifuge bowl that was capable of separating and concentrating erythrocytes in the irrigating fluid returned during transurethral resection of the prostate. [11]

The first commercially available apparatus for intraoperative blood recovery and reinfusion was marketed by Bentley Laboratories. It employed a disposable cardiotomy reservoir and a DeBakey-type roller pump (Fig. 47-1) . Initial clinical trials were performed in Vietnam and reported in 1970. [12] The first article in the anesthesia literature appeared in 1975 and detailed experience with the device in 71 patients who received a mean volume of 4,000 mL of reinfused blood. [13] Systemic anticoagulation was not employed, but the reservoir was primed with crystalloid containing 3 units of heparin per mL of priming fluid. The unit was demonstrated to be safe and effective in patients sustaining blunt and penetrating trauma to the chest and abdomen and ruptured ectopic pregnancies, as well as in patients undergoing a variety of elective and emergency intra-abdominal operations. Although the apparatus was equipped with a device for detecting air and a safety alarm, air embolism did occur as a result of operator error, and the Bentley device was withdrawn from the market.

In 1974, the Haemonetics Corporation introduced the Cell Saver, a system that washes and concentrates recovered red blood cells (RBC) before reinfusion (Fig. 47-2) (Figure Not Available) . Two years later, experience with an inexpensive canister collection system was reported. [14] A variety of disposable blood collection and reinfusion devices for intraoperative and postoperative blood collection have been introduced since that time. Apheresis technology has also been adapted for the collection of platelet-rich plasma (PRP) in the operating room.

Figure 47-2 (Figure Not Available) Haemonetics Cell Saver 5. *(Courtesy of Haemonetics Corporation, Braintree, Mass.)*

The role of the anesthesiologist in autologous transfusion is still evolving. An anesthesiologist may be responsible for the perioperative autologous transfusion program. At a few institutions, members of the anesthesia care team monitor high-risk patients during predonation. The one technique that is the purview of the anesthesiologist--ANH--has received the least attention. A few papers appeared in the literature during the early 1970s, but it was several years before the technique became known to many anesthesiologists.

PREOPERATIVE BLOOD DONATION

Preoperative autologous blood donation (PABD) should be considered before elective surgical procedures during which significant blood loss may occur and for which blood would ordinarily be crossmatched. The technique is both underutilized [15] and overutilized. [16] Some patients who should donate do not; others are donating without indication. Although it has been suggested that the transfusion requirements of 50 percent of patients having elective surgical procedures could be met by predonation, [17] 10 percent is a more reasonable estimate. [18] In 1992, approximately 8 percent of whole blood collections in the United States were autologous. [19]

Patient Selection

The criteria for autologous donors are not as stringent as those for allogeneic donors. The Standards of the American Association of Blood Banks require that the donor-patient's hemoglobin (Hb) be no less than 11 g/dL or the hematocrit (HCT) 33 percent before each donation. [20] There are no age or weight limits. Patients weighing 50 kg or more may donate 450±50 mL, in addition to testing samples, whereas those weighing less than 50 kg can donate proportionately smaller volumes. Donations may be scheduled more than once a week, but the last should occur no less than 72 hours before surgery to allow time for restoration of intravascular volume and for transport and testing of the donated blood. Donation is contraindicated when the patient has, or is being treated for, bacteremia or has a significant bacterial infection that can be associated with bacteremia. [20]

Blood center and transfusion service policies differ regarding collection and use of autologous blood with positive viral markers. It is common practice to preclude use of blood reactive for hepatitis B surface antigen and the human immunodeficiency virus because of concerns for the safety of both patients and personnel. Some hospitals accept and transfuse autologous blood with any positive viral markers, and denying patients infected with human immunodeficiency virus the opportunity to receive their own blood could be a violation of the Americans with Disabilities Act. [21]

Adolescents requiring corrective surgery for scoliosis are often ideal candidates for PABD. [22] [23] Experience is limited in very young children, but blood has been donated at the time of cardiac catheterization by children younger than 1 year who have weighed as little as 5 kg and were scheduled to undergo cardiac surgery. [24] Avoidance of allogeneic transfusion was reported in over 90 percent of children as young as 3 years who donated an average of three times before cardiac surgery. [25] Predonation of approximately 20 mL/kg has also been reported in children scheduled for general surgical procedures who ranged in age from 9 months to 10 years and weighed as little as 7.3 kg. [26] Factors limiting PABD by pediatric patients are commitment of parents, surgeons, and blood center personnel; patient cooperation; and vascular access.

There is extensive experience with PABD by older patients, especially those undergoing total joint arthroplasty [27] [28] [29] [30] and cardiac surgery. [31] [32] [33] [34] [35] [36] [37] Patients with unstable angina, left anterior descending coronary artery disease, congestive heart failure, or myocardial infarction within the previous 3 months are usually excluded. Critical aortic stenosis may be a contraindication, but one publication supports the safety of donation before aortic valve surgery. [38]

Predonation by obstetric patients does not adversely affect the mother or the baby. [39] [40] [41] [42] [43] However, PABD can be justified only in patients with placenta previa. The need for peripartum transfusion cannot be predicted with sufficient accuracy to justify donation by other obstetric patients.

Patients scheduled for procedures during which transfusion is rarely necessary should be discouraged from donating. Approximately 50 percent of predonated units are not transfused to the donor-patient and are destroyed. [19] A survey of 600 hospitals in which 40 percent of predonated units were not transfused found that almost 25 percent were collected for procedures in which transfusion was only a remote possibility, and 40 percent of the patient-donors required no transfusions in the perioperative period. [16] Inappropriate donation by gynecologic surgery patients is especially common and can lead to inappropriate transfusion. A retrospective review of 263 patients having elective abdominal or vaginal hysterectomy demonstrated that PABD was the major risk factor for transfusion, independent of all other considered variables, including admission Hb level and estimated RBC loss. Twenty-five of 140 patients who predonated were transfused, whereas only one of 123 who did not was transfused. [44] It was concluded that the increased transfusion rate was most likely the result of iatrogenic anemia resulting from blood donation and a more liberal threshold for transfusing autologous blood.

Establishing a schedule of optimal preoperative collection of autologous blood, which is similar to a schedule for allogeneic maximum surgical blood ordering, can lead to more appropriate autologous blood collections. [45] The likelihood of a surgical patient requiring RBC transfusion can be predicted more accurately if, in addition to the type of surgical procedure, the patient's preoperative Hb value and weight are considered. [46] One group who calculated the predicted and tolerated blood loss for each surgical patient in order to determine the best transfusion strategy decreased wastage of autologous blood to less than 15 percent. [47]

Erythropoietic Response to Donation

RBC production in autologous donors is dependent on adequate iron stores and is influenced by the number of units donated and the frequency of donation. Ferrous sulfate is usually prescribed in order to prevent anemia, allowing some patients to donate up to six units if donation is begun early. Twice-weekly phlebotomy is associated with

greater erythropoiesis than is weekly donation. [37] Administration of recombinant human erythropoietin stimulates erythropoiesis and allows donation of more units. [48] [49] [50] [51] Patients with Hb levels of less than 13.5 g/dL appear to benefit most from administration of recombinant human erythropoietin. [51] Various dosage regimens have been reported, with the drug being administered subcutaneously or intravenously a few days to 3 weeks before surgery. The optimal dosage regimen for recombinant human erythropoietin has not been determined.

Processing of Autologous Units

If CPDA-1 preservative is employed and blood is stored as liquid whole blood, the shelf life is 35 days. Separation into plasma and RBCs allows addition of a preservative solution (e.g., Adsol, Nutricel) to the RBCs, thereby extending the shelf life to 42 days. The plasma can be frozen or retained in the liquid state, but it is often discarded. Although RBCs can be frozen, the procedure is time consuming, expensive, and usually unnecessary. If surgery is delayed, liquid preserved RBCs can be frozen any time before 42 days.

Predonated units are conspicuously labeled as autologous, and the patient-donor's name and identifying number are written on the attached tag. Blood intended for autologous transfusion is tested for ABO type and Rh as a confirmation of patient identification. At this time, testing for infectious disease is not mandatory if blood is drawn and transfused at the same facility. However, most donations occur at blood centers, and the units are tested in the same manner as allogeneic blood. Testing

of all units maximizes safety by allowing units with positive test results to be identified and tagged with biohazard labels or destroyed.

The issue of "crossover" of unused autologous units for allogeneic use is controversial. Although proponents argue that the blood supply could be increased, opponents point out that only about 30 percent of autologous units would be suitable for transfusion to other patients. [52] Units may be unsuitable on the basis of the donor's medical or risk behavior history and/or reactive test results. Blood centers may omit questions regarding risk behavior when obtaining autologous donor histories, precluding crossover of those units even if all test results are negative. When the questions are asked, there is a possibility that donors will not disclose disqualifying information because they assume the blood is only for their use. Thus, crossover of autologous units might result in transfusion of blood that is less safe than that from volunteer donors. Because many units are donated several days to weeks in advance of surgery and are reserved for the patient for a period of time after surgery, the potential shelf life for allogeneic use is short.

Complications of Donation and Transfusion

Autologous donors may sustain complications in association with the donation process or when the blood is transfused. Reaction rates among autologous donors of 1.5 to 5.5 percent [17] [53] [54] are similar to those in allogeneic donors. Most are transient vasovagal reactions requiring no treatment. As with allogeneic donors, younger donors experience more reactions than older donors. The reaction rate is highest among first-time donors and is greater in women than in men. In one series of approximately 187,000 allogeneic and 8,900 autologous donations, the reaction rate was 2.4 percent for allogeneic and 2.5 percent for autologous donors, whereas it was 13 percent in first-time donors. [55] AuBuchon and Popovsky [56] compared donors who did not meet allogeneic donor criteria (usually on the basis of cardiovascular disease) with those who met the criteria and found reaction rates of 4.3 percent and 2.7 percent, respectively. They were unable to identify any distinguishing features that were predictive of reactions. A review of approximately 4 million donor records found the prevalence of very severe outcomes (defined as events requiring hospitalization) to be 1 in 16,783 autologous donations and 1 in 198,119 allogeneic donations. [57]

Three groups have reported experience with cardiovascular monitoring of autologous donors. Eighty-six percent of patients scheduled for coronary artery bypass grafting (CABG) evaluated with continuous electrocardiographic monitoring for 24 hours before and 24 hours after donation demonstrated at least one episode of ST-segment depression, but the incidence was not greater after donation. [58] In a similar study, 37 percent of patients had ischemic episodes during or after donation, and all indices of ischemia were more common on the day following donation. [59] A significant percentage of high-risk patients monitored during 224 donations exhibited hypotension, arrhythmias, ST-T wave changes, syncope, and tachycardia. [60] Five were treated with ephedrine and/or atropine, but it is unknown whether any morbidity would have occurred in the absence of treatment.

Although controversy regarding the advisability of PABD by patients scheduled for cardiac surgery continues, [61] [62] [63] several investigators have demonstrated its safety. [31] [32] [33] [34] [35] [36] [37] [38] [57] [58] [59] Donation of up to eight units by patients awaiting heart and lung transplantation has also been reported. [64] [65] Although PABD was without apparent adverse effects, even in patients receiving small doses of vasopressors, the authors [64] [65] caution that such donations are best performed in a hospital-based donor facility where full medical support is readily available.

The greatest potential hazard associated with transfusion of predonated blood is administration of an autologous unit to an unintended recipient. In an editorial, Linden and Kruskall [66] reviewed results of two surveys related to autologous transfusion. A 1992 American College of Pathologists survey found that autologous blood had been issued to the wrong patient on at least one occasion in the previous year by 0.9 percent of facilities and that almost half of those facilities reported that autologous units had been transfused to the wrong patient on one or more occasions. In a 1994 American Association of Blood Banks survey, 1.2 percent of respondents indicated errors involving transfusion of autologous blood to other patients during the previous year. Half of the errors occurred in institutions that permitted transfusion of units with positive viral markers.

A study of autologous donation error rates in Canada indicated that errors were associated with one of 149 autologous units. [67] About half of the errors involved late receipt of units or delivery of blood to the wrong hospital, but no data were presented to indicate whether the errors resulted in allogeneic transfusions. One unit of autologous fresh frozen

plasma was transfused to the wrong patient. Errors were most frequent when components were produced and when shipment between hospitals or blood centers was involved.

An analysis of autologous donations by 175 pediatric orthopedic patients revealed 13 errors. [68] Three patients received allogeneic blood when autologous units were available. Several units expired, and some had to be destroyed because of difficulties related to storage, necessitating allogeneic transfusion. One patient received the wrong type of allogeneic blood. A prospective study by the Belgian SANGUIS group found that three of 55 patients with autologous blood available received allogeneic blood instead. [66]

The clinician's index of suspicion for a transfusion reaction may be low when the patient is receiving blood thought to be his or her own, reducing the probability of early diagnosis and intervention and increasing the likelihood of serious consequences. In addition to hemolytic reactions due to inadvertent administration of the wrong unit of blood, there is potential for administration of contaminated blood. Two of 10 cases of sepsis due to transfusion of blood contaminated with *Yersinia enterocolitica* reported in the United States between 1991 and 1996 were associated with administration of autologous RBCs. [69] Additional reported complications are acute intravascular hemolysis resulting from transfusion of inadequately deglycerolized previously frozen RBCs [70] and hypotension, possibly resulting from hypersensitivity to stabilizers or sterilizing agents used in plastic blood bags. [71]

Transfusion of Predonated Blood

The mere availability of autologous blood should not be an indication for transfusion. There is controversy regarding whether the indications for autologous and allogeneic transfusion should be the same. [72] [73] The "Practice Guidelines for Blood Component Therapy" of the American Society of Anesthesiologists [74] state that the indications for transfusion of autologous RBCs may be more liberal because of the lower (but still significant) risks associated with autologous blood. The "Guidelines for Red Blood Cell and Plasma Transfusion for Adults and Children" published by the Canadian Medical Association [75] state that the indications for transfusion of autologous and allogeneic blood should be the same.

Cost-Effectiveness of Predonation

The conventional measure of efficacy of PABD is the extent to which patients avoid allogeneic transfusion. Numerous studies have demonstrated attainment of that goal in about 70 percent of patients. [76] If avoidance of allogeneic transfusion is the only factor considered, PABD is efficacious. But is it cost-effective?

Charges for autologous units are usually more than those for allogeneic blood. The surcharge imposed by collecting facilities is based on personnel time required for scheduling and processing autologous donors and the complex logistics of handling and transporting the blood. One center estimated the direct costs of collecting, testing, and processing autologous and allogeneic blood to be $198.04 and $149.80, respectively. [77] Most units are drawn at blood centers and are subsequently shipped to, and purchased by, hospitals. Wastage rates of approximately 50 percent account for much of the expense of autologous blood because hospitals incur nonreimbursable costs for nontransfused units.

Decision analysis techniques have been applied to determinations of the cost-effectiveness of PABD. With this methodology, cost-effectiveness is expressed in dollars per quality-adjusted year of life saved (QALY). Most accepted medical and surgical interventions cost less than $50,000 per QALY, a benchmark commonly applied as a threshold of cost-effectiveness. [78] Predonation for CABG costs $508,000 to $909,000 per QALY. [79] Estimates for primary unilateral hip replacement and unilateral knee replacement are $373,000 to $740,000 and $1,147,000 to $1,467,000, respectively. [80] For abdominal hysterectomy and transurethral resection of the prostate, the costs per QALY are $1,358,000 and $23,643,000, respectively. [77] Critics of QALY analysis point out that it includes only known, quantifiable risks and costs and uses death and dollars as the primary end points. [81] The peace of mind provided by PABD and additional potential benefits from avoiding risks of allogeneic transfusion other than currently identified infectious diseases cannot be measured.

Predonation practices must periodically be reviewed in light of changing surgical techniques and transfusion practices. For example, PABD has become standard practice for radical retropubic prostatectomy in some institutions, but some reports document decreasing transfusion requirements and question the need for

predonation. [82] [83] [84] Not only was the recommendation for PABD eliminated at one institution, crossmatching was also discontinued and only a type-and-screen was routinely ordered. [83] After reviewing the records of 200 consecutive patients and the charges associated with PABD, another group concluded that PABD should be an option, but not a routine practice. [82]

ACUTE NORMOVOLEMIC HEMODILUTION

The term *acute normovolemic hemodilution* refers to the removal of blood from the surgical patient immediately before or just after induction of anesthesia, replacement with asanguinous fluid, and later reinfusion of the withdrawn blood. [85] [86] *Acute limited* or *moderate normovolemic hemodilution* is the term applied when the HCT is reduced to approximately 28 percent. [65] *Acute extreme normovolemic hemodilution* designates a reduction of the HCT to levels below 20 percent. [66] *Augmented acute normovolemic hemodilution* is the term coined by the author to refer to administration of an oxygen-carrying RBC substitute in addition to other asanguinous fluid.

Advantages

As with other autologous transfusion techniques, ANH is employed to reduce the need for allogeneic RBCs and to avoid the potential complications of transfusion. There are additional benefits of ANH that are not common to other autologous transfusion modalities. When the blood is kept in

---

the same operating room with the patient, the chances of clerical error are eliminated. Unlike stored predonated autologous units, blood withdrawn during ANH does not undergo biochemical alterations associated with the "storage lesion." Levels of 2,3-diphosphoglycerate are maintained, and there is no influence on the oxygen-Hb dissociation curve. [87] If the units are maintained at room temperature, platelet function is preserved, and hypothermia associated with transfusion of refrigerated blood is avoided. An additional potential advantage of ANH is improvement in tissue perfusion as a result of decreased viscosity.

There are also logistic advantages. [87] Scheduling difficulties may preclude the use of intraoperative blood recovery in urgent or emergent circumstances. The presence of malignancy or wound infection may contraindicate intraoperative blood recovery, but not ANH. It is simpler and less expensive to obtain autologous blood by ANH than by PABD. [88] [89] Patients with cardiovascular or neurologic disease may not be appropriate candidates for PABD but may safely undergo ANH while being intensively monitored in the operating room. When potential bacteremia (e.g., the presence of an indwelling urinary catheter or chronic osteomyelitis) precludes predonation, ANH may be the ideal solution. Because all of the blood is ordinarily reinfused in the operating room or shortly thereafter, the iatrogenic anemia and blood wastage often associated with PABD do not occur.

Efficacy

A decrease in allogeneic transfusion requirements of 20 to 90 percent has been reported for a wide variety of surgical procedures. [87] [90] [91] [92] [93] [94] However, early studies were flawed by the use of historic controls and did not consider the influence of increasing surgical experience or changing transfusion practices. Multiple blood conservation strategies were often employed, making the contribution of ANH difficult to evaluate. Transfusion criteria usually were not specified. The first prospective controlled study comparing ANH and PABD involved 50 patients undergoing radical retropubic prostatectomy performed by the same surgeon. The anesthetic technique was also standardized. The two autologous transfusion techniques were equally effective in decreasing the need for allogeneic transfusion. [95] In a larger nonrandomized study of 250 patients having radical retropubic prostatectomy, Monk et al [89] found the two techniques comparable in decreasing allogeneic transfusion and also demonstrated that ANH was more cost-effective than PABD.

Three small studies in which patients undergoing total hip or knee arthroplasty were randomized to a hemodilution or control group have been published. [96] [97] [98] Each study included only 30 to 40 patients, and the average volume of blood removed was about 1 L. One group reported that transfusion requirements were the same in both groups, [96] whereas a second group reported a decrease in the total number of allogeneic units transfused in the ANH patients. [98] The third group of investigators, who also utilized PABD and intraoperative blood recovery, considered the technique successful because fewer patients in the ANH group required transfusion of their predonated units. [97]

When employed during cardiac surgery, ANH is also referred to as *blood pooling*[99] or *intraoperative autologous donation.*[100] Most reported studies are retrospective. Schonberger et al [101] studied 100 patients undergoing CABG, 50 of whom had approximately 800 mL heparinized blood removed before cardiopulmonary bypass (CPB). They found that the net blood loss, amount of reinfused shed blood, and postoperative blood requirements were less in the ANH group. Sixty-five percent of ANH patients did not receive allogeneic blood, compared with 10 percent of control patients. Petry et al [99] retrospectively studied 90 patients having CABG, half of whom had heparinized blood (500-1000 mL) removed before CPB. Although 16 percent of control patients received no allogeneic blood, 44 percent of ANH patients did not require allogeneic transfusion. Canver et al [102] compared 140 patients who had a mean of 1,430 mL heparinized blood removed before CPB with 64 control patients in whom ANH was not performed. Although RBC transfusion requirements were no different, fewer units of platelets and fresh frozen plasma were administered to patients in whom ANH was performed.

In the first of two prospective studies, Helm et al [100] randomized 90 patients undergoing CABG or valvular operations to have ANH performed or to serve as controls. An average of 1,540±302 mL was removed before anticoagulation in the treatment group. Uniform transfusion criteria were applied. The investigators found a significant decrease in both the percentage of patients who received allogeneic RBCs (17 versus 52%) and the number of RBC units transfused per patient (0.28±0.66 versus 1.14±1.19 units) in the ANH group. There was no difference in chest tube output, incidence of excessive postoperative bleeding, or coagulation factor transfusion requirements. In a second prospective study, 100 patients undergoing CABG were randomized to have 10 mL/kg heparinized blood withdrawn before CPB or to serve as controls. [103] Transfusion indications were standardized. Patients in the ANH group had a 28 percent reduction in chest tube drainage at 8 hours and a 45 percent reduction in total allogeneic units transfused. Fifty-two percent of ANH patients received no transfusion, whereas 31 percent of control patients were not transfused.

Mathematic and computer modeling have been used to assess the efficacy of ANH. [104] [105] [106] Results are somewhat conflicting, but several of the conclusions are reasonable. First, the RBC "savings" depends on the patient's initial HCT value, the volume of blood removed, and the blood loss. [105] Second, the amount of RBCs saved is overestimated by the simple formula conventionally utilized for ANH. [104] Most importantly, efficacy is greatest when substantial hemodilution is followed by significant blood loss. For example, a savings of four units of allogeneic transfusion can be realized when a patient with an estimated blood volume of 5 L and HCT of 45 percent is hemodiluted to a HCT of 15 percent. If only two units are removed, resulting in a HCT of approximately 37 percent, only about 100 mL is saved. [106]

Hemodilution is efficacious in reducing RBC transfusion requirements in patients undergoing cardiac surgery, but the potential advantage of fresh whole autologous blood in decreasing postoperative bleeding remains to be proved. There are limited data from controlled studies to document the efficacy of ANH in other surgical populations.

Physiologic Effects

The withdrawal of blood and its replacement with acellular fluid are accompanied by a decrease in arterial oxygen content, but oxygen delivery is usually unaffected. A number of mechanisms are invoked as physiologic compensation for the acute reduction in Hb. The most important is an increase in cardiac output. The primary factor responsible for the increased cardiac output seen with ANH is decreased viscosity. The decrease in viscosity is most pronounced between HCT values of 45 and 30 percent, and the effect is progressively less significant when the HCT is below 25 percent. [107] Decreased viscosity results in increased venous return, decreased peripheral resistance, and reduced afterload. The reduced peripheral resistance may also be due to reflex vasodilation or local regulatory factors, such as endogenous release of nitric oxide. [108] In the canine model, there is evidence of increased myocardial contractility, in addition to decreased afterload, as a contributing factor to the increased cardiac output. [109] Increased sympathetic stimulation of the heart may also contribute. [107]

The relative importance of an increase in heart rate or stroke volume to the increased cardiac output depends on the species studied, the subject's state of awareness (i.e., awake versus anesthetized), and the type of anesthesia administered. In the anesthetized adult, an increase in stroke volume is most important; heart rate does not ordinarily increase in the absence of hypovolemia. Anesthetized children tend to respond with tachycardia, as do awake dogs. An increase in heart rate occurs in awake baboons, whereas stroke volume increases during ANH in anesthetized baboons. [107]

Although increases in total and local blood flow are sufficient to maintain oxygenation in resting normovolemic, moderately hemodiluted subjects, other mechanisms are involved with more extreme degrees of ANH. These include redistribution of blood flow to the heart and brain and increased tissue oxygen extraction. A significant increase in coronary and myocardial blood flow occurs with ANH in subjects with normal coronary circulation. Coronary vasodilation and decreased viscous resistance are responsible for the increased coronary blood flow. Myocardial blood flow and arterial oxygen delivery are maintained at HCT values as low as 12 percent in dogs and 9 percent in pigs. The myocardial oxygen extraction ratio remains unchanged in baboons and pigs hemodiluted to HCT values of 4 percent and 9 percent, respectively. Redistribution of myocardial blood flow away from the subendocardium is observed at HCT levels of approximately 9 percent, signifying exhaustion of the subendocardial vasodilator capacity and thus the limit of tolerance to hemodilution. [107] The limits of ANH have been studied in a canine model of coronary artery disease. [110] The median lowest Hb level tolerated without contractile dysfunction in animals with surgically induced stenosis of the left anterior descending coronary artery was 7.5 g/dL. Marked contractile dysfunction was seen at a mean Hb level of 6.0 ± 0.4 g/dL. Increasing the Hb level by approximately 2 g/dL restored contractile function. The cardiovascular compensatory mechanisms remained intact for at least 4 hours. [111]

Patient Selection

Hemodilution should be considered for any patient with an adequate Hb who is expected to lose more than 25 percent of estimated blood volume. Because the Hb decreases approximately 1 g/dL for each unit of blood removed and because ANH is not efficacious if only a small volume of blood is withdrawn, it usually is inappropriate to employ the technique when the Hb is less than 11 g/dL, particularly if limited ANH is to be performed.

Although some anesthesiologists limit use of the technique to healthy adults, ANH has been employed in small children [112] [113] [114] [115] [116] [117] [118] [119] and the elderly. [120] [121] [122] [123] Two groups of investigators have studied the tolerance of patients with known coronary artery disease to acute limited hemodilution. Catoire et al [122] employed transesophageal echocardiography in patients undergoing abdominal aortic surgery who were hemodiluted to a target HCT of 30 percent and a comparable group who were not hemodiluted. Hemodynamic changes associated with aortic clamping were less marked in the ANH group. The authors concluded that ANH did not worsen myocardial ischemia and may actually improve hemodynamic tolerance to aortic clamping. Herregods et al [124] studied patients with left main coronary artery stenosis undergoing semiurgent CABG who were hemodiluted to HCT levels of 34 percent and patients with similar lesions in whom ANH was not performed. They found no increase in frequency, degree, or duration of ST-segment changes in the ANH group. Allogeneic transfusion requirements were decreased by ANH: 64 percent of treated patients did not require allogeneic blood, compared with 38 percent of control patients.

The patient's overall health status, rather than chronologic age should be considered. In a group of patients aged 66 to 88 years (mean, 76±2 years), Spahn et al [123] demonstrated that ANH to a mean Hb of 8.8±0.3 g/dL was well tolerated. In a separate study, the investigators hemodiluted patients receiving chronic beta-adrenergic blocker therapy to Hb levels of 9.9±0.2 g/dL before CABG was performed. The patients tolerated ANH well, and it was concluded that compensatory mechanisms during ANH are largely independent of age and left ventricular ejection fraction. [125]

Experience with extreme ANH in children and adolescents has been reported by several groups. Fontana et al [118] demonstrated that global oxygen consumption was maintained in healthy children hemodiluted to a mean Hb level of 3.0±0.8 g/dL. The oxygen extraction ratio increased from 17 to 44 percent, and mixed venous oxygen saturation decreased from 90.8±5.4 to 72.3±7.8 percent. In children of the Jehovah's Witness faith in whom the HCT was reduced to 16 percent, the oxygen extraction ratio increased from 22 to 33 percent, and mixed venous oxygen saturation declined from 80 to 70 percent. [115] Aly Hassan et al [117] also demonstrated that global tissue oxygenation was preserved at HCT levels of approximately 17 percent. The safety of extreme ANH to HCT values of 12 to 14 percent in combination with mild hypothermia and controlled hypotension to mean arterial pressures of 40 to 50 mm Hg has been shown in patients undergoing spinal fusions. [116]

Patients of the Jehovah's Witness usually agree to ANH if the blood is maintained in a closed-circuit continuous-flow

---

system. [112] Combining ANH with intraoperative blood recovery is also an option for such patients. [115]

Contraindications

Patients with decreased renal function are not suitable candidates for ANH because excretion of diluent fluids may be impaired. Significant restrictive or obstructive pulmonary disease is a contraindication because decreased arterial oxygen content is inherent with ANH and tissue oxygenation may be inadequate. Preexisting coagulopathy precludes the use of the technique. Caution is required in patients with hepatic disease or other disorders associated with a reduction in coagulation factors, thrombocytopenia, or impaired platelet function.

Technique

The amount of blood to be withdrawn depends on the patient's estimated blood volume (EBV), preoperative HCT, and the lowest HCT desired. [126] The volume (V) to be removed equals the EBV multiplied by the patient's initial HCT (H_o) minus the minimum allowable HCT (H_f), divided by the average HCT (H_{av}):

$$V = EBV \times [(H_o) - (H_f)]/H_{av}$$

For a patient with an EBV of 5 L, an HCT of 45 percent, and a desired lower HCT of 30 percent, the approximate amount of blood to withdraw is calculated as

$$V = 5\ L \times [45 - 30]/37.5 = 2{,}000\ mL$$

Serial HCT determinations should be performed during blood removal and at intervals throughout the surgical procedure.

Hemodilution is usually performed in the operating room following induction of anesthesia. If an induction room or holding area is adequately equipped with monitoring equipment, it may be advantageous in terms of efficiency of operating room utilization to perform ANH in such an area. The procedure can also be initiated before induction of anesthesia. Atallah et al [127] compared the stress response to ANH performed before and after induction. On the basis of hemodynamic, hematologic, biochemical, and hormonal indexes, the investigators concluded that ANH is not a stress-producing technique and can be performed in awake or anesthetized patients.

Crystalloid and/or colloid are infused as blood is withdrawn. When crystalloid is used, the amount must be approximately three times the volume of blood removed because much of the crystalloid moves out of the intravascular compartment. Colloids have the primary advantage of intravascular retention. Therefore, the amount infused can be approximately equal to the amount of blood removed. Some evidence suggests that when albumin is used as a diluent, the volume may need to be greater than the volume of blood removed to ensure normovolemia. [128] Hemodynamic studies comparing dextran, albumin, and hydroxyethyl starch have demonstrated no significant differences among diluents. [129] The advantage of crystalloid, in addition to cost, is that ex-cess fluid can easily be excreted if a diuretic such as furosemide is administered before reinfusion of the blood.

Blood is withdrawn from a central or large peripheral vein or radial artery. Use of veins distal to the antecubital area is not recommended, because poor blood flow often results in clotting. When an artery is used, blood pressure can be transduced intermittently by incorporation of a stopcock in the system. Blood is collected in standard blood bags containing anticoagulant, usually citrate-phosphate-dextrose. Hemodilution kits containing bags with an anticoagulant, a Y-type connection set with Luer-Lok adapter, and a blood recipient identification band are available (Autologous Blood Collection Kit 4R5012, Fenwal Division, Baxter Healthcare, Deerfield, Ill.). In cardiac surgery, heparinized blood can be collected from the venous line into transfer bags, or an autologous kit can be used (Autologous Blood Collection Kit 4R5010, Fenwal Division, Baxter Healthcare, Deerfield, Ill.). A scale should be used to weigh the bags to ensure that they contain the appropriate amount of blood relative to anticoagulant. Ideally, an automated blood collection and mixing device or blood "shaker" is used to monitor collection volumes and prevent clotting (Blood Shaker/Flow and Weight Monitor Model 1040, Sebra, Tucson, Ariz.).

Monitoring requirements depend on the patient's physical status, the operative procedure and anticipated blood loss, and the degree of hemodilution. Use of a pulmonary artery catheter during extreme ANH is advisable to permit determination of mixed venous oxygen saturation as a measure of global oxygenation. Preliminary data utilizing a synthetic perfluorochemical temporary oxygen carrier during ANH indicate that it increases mixed venous oxygen tension. [130] It may be possible to increase the number of units withdrawn by using a temporary oxygen carrier to provide an additional margin of safety.

Each unit is labeled with the patient's name, hospital number, and time of blood withdrawal and is numbered sequentially. The blood is kept in the same operating room as the patient and is maintained at room temperature to preserve platelet function. If it is anticipated that more than 8 hours will elapse before reinfusion, refrigeration of the blood is required. Refrigerated units must be reinfused within 24 hours or be discarded. [20] Blood is reinfused after major blood loss has ceased, or sooner if indicated. The units are reinfused in the reverse order of collection so that the first unit, which has the highest HCT and the most clotting factors, is administered last. Estimation of blood loss and serial HCT determinations are used to guide transfusion therapy.

Complications

The minimal safe HCT depends on the patient's ability to compensate for the decreased arterial oxygen content. Myocardial ischemia and cerebral hypoxia are the major potential complications. The augmented cardiac output increases myocardial oxygen consumption while the oxygen content of blood supplying the myocardium is reduced. Tachycardia and decreased cardiac output resulting from hypovolemia can further impair myocardial oxygen supply-demand relationships. In the adult, tachycardia should be

considered an indication of hypovolemia and should be corrected immediately.

Laboratory studies of the effects of extreme ANH on the intestine indicate that jejunal mucosal oxygen supply is well maintained at HCT values of 10 percent. [131] In the canine model, myocardium compromised by coronary stenosis is more sensitive to hemodilution-induced ischemia than is normally perfused gut mucosa. [132] These findings limit the potential usefulness of gastric tonometry as a guide to tolerable levels of hemodilution.

Animal studies indicate that cerebral function may not be affected until the HCT is less than 5 to 10 percent. [133] [134] In the canine model, hemodilution to a HCT of 19 percent impairs hypocapnia-induced vasoconstriction in the brain and spinal cord. [135] A potential clinical implication is that induced hypocapnia might be a less effective maneuver to reduce increased intracranial pressure during ANH. Conversely, the blunted vascular response to hypocapnia may confer brain protection by maintaining cerebral blood flow in the presence of decreased oxygen-carrying capacity. Experience with children hemodiluted to Hb levels of approximately 3 g/dL demonstrates the safety of extreme ANH in young patients without cerebrovascular disease. [118] Hemodilution to Hb levels of 7 to 9 g/dL in elderly patients, some of whom would be expected to have cerebrovascular disease, has not been reported to result in neurologic dysfunction. [122] [123] However, no studies have specifically addressed the issue, and caution is advised in patients with carotid or vertebral artery disease.

Coagulopathy related to dilution of clotting factors and increased bleeding resulting from enhanced capillary blood flow are potential complications. However, pediatric patients subjected to a 75 percent volume exchange during ANH still had a mean platelet count of 158±26 × 10^9 /L, which is ordinarily adequate for hemostasis. [119] Monitoring coagulation parameters is advisable with extreme ANH but is not required during moderate ANH.

Peripheral edema is common in hemodiluted patients, especially when crystalloid is administered as the sole diluent. However, pulmonary edema should not occur if ANH is properly performed.

INTRAOPERATIVE BLOOD RECOVERY

There are several techniques for recovery or salvage of shed blood. The most complex systems employ semicontinuous flow centrifugation to process the recovered blood. Blood collected in rigid canisters with sterile disposable liners can be washed before reinfusion or administered without processing. Shed blood can also be collected and filtered in sterile disposable single-use reservoirs for immediate reinfusion. The newest additions to the market are similar in concept to conventional cell processing devices but employ different technology for blood separation.

Semicontinuous Flow Centrifugation Devices

Several devices are available. The degree of automation, size, cost, and clinical applications vary. The disposable equipment consists of an anticoagulation and aspiration assembly, a reservoir with filter, a centrifuge bowl, a waste bag, and tubing (Fig. 47-3) (Figure Not Available) . The double-lumen aspiration set incorporates an anticoagulant line through which either a heparin or a citrate solution is administered at a controlled rate. Recovered blood, mixed with anticoagulant, is collected in the disposable reservoir containing a filter. The filtered blood is then pumped into a wash bowl with a centrifugation speed of approximately 5,000 repetitions per minute. Once the bowl is filled, the contents are washed with saline. The RBCs suspended in saline are pumped into a reinfusion bag. Most of the white blood cells, platelets, activated clotting factors, plasma Hb, cell fragments, and other debris are eliminated into the waste bag along with excess saline wash solution. The washing and concentrating process requires 3 to 10 minutes, depending on the device.

Characteristics of Processed Blood

The HCT of processed blood is 50 to 60 percent and can be varied by altering the processing parameters. The oxygen transport properties and survival of recovered RBCs are equal or superior to those of stored allogeneic RBCs. The 2,3-diphosphoglycerate content of recovered blood has been measured as a marker of RBC function. Processed blood consistently has higher 2,3-diphosphoglycerate levels than allogeneic blood. [136] [137] [138] The survival of RBCs has been studied by use of ^{51}Cr-tagged cells recovered during spine, [139] aortic, [137] [140] [141] and cardiac [142] surgery. The life span is comparable to that of transfused allogeneic RBCs. The pH of processed blood is alkaline, and potassium and sodium levels are normal. [138]

Plasma Hb levels may exceed 400 mg/dL in blood recovered during cardiac surgery and may be several times higher in orthopedic surgery. Adequate washing removes over 90 percent of the free Hb. [143] Residual leukocytes and platelets are present in washed blood, but their function and significance are uncertain. [144] Tumor necrosis factor-alpha, a cytokine produced by stimulated monocytes that has immunomodulatory activity, has been detected in unwashed, recovered blood. [145] Plasma elastase, an enzyme implicated in the pathogenesis of respiratory distress syndrome, has also been demonstrated in unprocessed blood. Washing removes these substances, thereby reducing the potential deleterious effects associated with reinfusion of unprocessed blood. [146]

When citrate is used as an anticoagulant, it is metabolized by the liver. Processed RBCs do not contain a clinically significant amount of residual heparin. [143] [147] [148] Instruments conventionally employed in cardiac surgery for determining activated clotting time and heparin assays (e.g., Hepcon, Medtronic Blood Management, Parker, Col.) cannot be used to measure residual heparin because coagulation proteins and antithrombin III, which are required for the test, are removed during the wash cycle. [143] [149]

Catecholamines are not removed during processing, and significant hypertension has been reported when blood recovered during surgery for pheochromocytoma was reinfused. [150] Washing does remove tissue factor in blood contaminated with amniotic fluid. [151] D-dimer levels have been measured in recovered blood as an indication of activation of the coagulation and fibrinolytic systems and the presence

Figure 47-3 (Figure Not Available) Diagram representing the recovery of blood from the surgical field, the processing cycle, and the return of washed red blood cells to the patient. *(Courtesy of COBE Cardiovascular Inc., Arvada, Col.)*

of fibrin degradation products. Although D-dimer levels may be increased 85 times in unwashed blood, normal levels are found in processed blood. [152]

Reports describing the quality of blood processed with newer devices employing technology different from semicontinuous flow centrifugation are beginning to appear. [153] [154] [155] [156] Unacceptable residual heparin levels were demonstrated with one ultrafiltration device. [153] Initial reports indicate that the continuous autologous transfusion system (CATS, Fresenius AG, Bad Homburg, Germany) produces a product with a mean HCT of 62 percent, greater than 99 percent heparin elimination, and removal of most plasma proteins. [154] An *in vitro* study using soya oil, which has a fatty acid composition similar to that of fat found in bone marrow, indicated complete removal of fat particles. [155]

Complications

Potential complications associated with use of cell processing devices include air and fat embolism, pulmonary dysfunction secondary to infusion of debris in recovered blood, coagulopathy, renal dysfunction, sepsis, and dissemination of malignant cells. The most serious complication--air embolism--is rare if the devices are used in accordance with the manufacturer's instructions. However, one report cited an incidence of fatal air embolism of 1:30,000 to 1:38,000 in approximately 127,000 blood recovery procedures. [157] All cases involved infusion of recovered blood under pressure. Contributing causes were deviations from accepted practice, lack of operator vigilance, and insufficient knowledge of the procedure. Suggested measures to prevent air embolism include transferring the blood to a reinfusion bag before transfusion (i.e., not reinfusing directly from the recovery container) and avoiding reinfusion under pressure.

Although processed blood, particularly that collected during orthopedic procedures, contains visible fat particles, there is no documented instance of fat embolism associated with the technique. There are also concerns about transfusing blood containing leukocytes, platelets, and other cellular debris that can lodge in the lungs, potentially causing pulmonary dysfunction. Despite reinfusion of shed blood in thousands of patients, no adverse effects on pulmonary function have been documented.

Lysis of RBCs can occur as a result of high vacuum suction levels or aspiration techniques that cause turbulence during blood collection. Two cases of renal dysfunction requiring dialysis have been reported. [158] In both cases, excessive vacuum levels and insufficient washing of recovered blood were implicated. Most operator's manuals recommend a maximum vacuum level of 100 to 150 mm Hg. A laboratory study demonstrated the absence of excessive hemolysis when levels of up to 300 mm Hg were employed, but the author stressed that the lowest level of vacuum compatible with a clear surgical field should be used. [159] Use of a suction regulator with a factory-set maximum vacuum level is recommended, and the accuracy of the suction regulator should periodically be verified. [158] Suctioning small amounts of blood mixed with air (skimming) may induce greater degrees of hemolysis than high suction vacuum levels. [159] This is most likely to occur during

orthopedic surgery. Greater wash volumes are usually recommended during orthopedic surgery. In any case, the blood should be washed until the effluent is clear.

Processed blood is depleted of coagulation proteins and functional platelets. It is not surprising that coagulopathy

has been reported in patients receiving more than 15 units of processed blood. [160] The same guidelines for platelet and fresh frozen plasma administration apply when shed blood and allogeneic RBCs are infused. [74] There is a report of two cases of disseminated intravascular coagulation in patients undergoing spine surgery during which recovered blood was reinfused. [161] By the authors' own admission, vacuum levels of 300 mm Hg were used throughout the procedure. Coagulopathy may have been the fault of the procedure, but it is more likely that a faulty procedure caused the coagulopathy.

As a general principle, blood contaminated with intestinal contents should not be reinfused. However, there are reports of intraoperative blood recovery and reinfusion in patients with blunt and penetrating abdominal injuries associated with disruption of bowel integrity. [162] [163] One report evaluated trauma patients who received potentially culturepositive blood. [164] Wound infection rates were identical to those in patients with similar injuries who were not autotransfused. *In vitro* studies demonstrate that cell washing reduces the bacterial count but does not remove all bacteria. [165] The risk-benefit ratio of employing the technique when the wound is contaminated (or potentially contaminated) with intestinal contents should be carefully evaluated.

Bacteriologic and endotoxin analysis of blood recovered during cardiac surgery has shown a significant incidence of bacterial contamination with gram-positive commensals of the skin, as well as low concentrations of endotoxin. No adverse clinical outcomes were noted. [166] [167] Similar results have been found with blood recovery during liver transplantation. [168] It is speculated that the sources of contamination are the skin and room air and that the quantity of bacteria is too small to be of clinical significance in patients receiving prophylactic antibiotics. This hypothesis is supported by a study in which blood recovered during hip arthroplasty in patients receiving antibiotic prophylaxis with cefuroxime was compared with blood from patients not receiving antibiotics. [169]

The presence of tumor cells in the operative field has traditionally been considered a relative contraindication to intraoperative blood recovery. Although experience with the technique in patients with genitourinary tumors undergoing radical cystectomy, nephrectomy, prostatectomy, and radical hysterectomy indicates that it may be acceptable, [170] [171] [172] laboratory studies using human tumor cell lines have demonstrated that tumor cells remain in the washed RBC suspension. [173] [174] Filtration of the RBC concentrate with a third-generation leukocyte-reduction filter removes the tumor cells. [175] [176] [177] [178]

An additional safety issue when blood is recovered during urologic procedures is contamination of the surgical field with urine. Biochemical analysis of concentrated RBCs mixed with an equal volume of urine has demonstrated complete removal of urine constituents. [176] Concentrated RBCs inoculated with bacteria demonstrated bacterial growth, indicating that bacteria were not removed by the washing process. The investigators suggested preoperative elimination of bacterial urinary tract infection when blood recovery is planned in patients undergoing urologic surgery. [176]

Blood should not be aspirated during application of topical hemostatic agents, such as thrombin and microfibrillar collagen hemostat (Avitene). *In vitro* studies indicate that it can pass through the filtering system and become lodged in tissues. [179] Laboratory investigations have demonstrated that either a leukocyte-reduction filter or a 20-mum microaggregate filter can remove approximately 97 percent of potentially thrombogenic particles of Avitene. [180] Blood also should not be aspirated when the wound is irrigated with antibiotics that are not licensed for parenteral use or during the application of methylmethacrylate. The wound should be copiously irrigated following use of these substances before blood recovery is resumed.

Clinical Applications

Intraoperative blood recovery should be considered when it is anticipated that blood will be shed into a clean wound from which it can be aspirated without undue hemolysis. Limiting use of the procedure to situations in which the following criteria are met can serve as a guideline: blood would normally be crossmatched, the anticipated blood loss is at least 20 percent of the patient's estimated blood volume, 10 percent or more of patients undergoing the procedure require transfusion, the mean transfusion for the procedure is more than one unit. The major applications are cardiac, [181] [182] [183] [184] vascular, [137] [140] [185] [186] orthopedic, [187] [188] [189] [190] [191] and trauma surgery [162] [163] [164] [165] [192] [193] and liver transplantation. [194] [195]

Utilization appears to be increasing in neurosurgery. Following the tradition of Harvey Cushing, [5] the Mayo Clinic group reported experience with blood recovery during resection of intracranial arteriovenous malformations. [196] More recently, Cataldi et al [197] infused recovered blood in patients undergoing intracranial surgery, and Jimenez and Barone [198] demonstrated a 46 percent decrease in allogeneic transfusion requirements with intraoperative blood recovery in children undergoing surgery for craniosynostosis.

Preliminary clinical data indicate that the technique can safely be utilized during cesarean delivery if a separate suction apparatus is used for removing the amniotic fluid. [199] Laboratory studies confirming removal of tissue factor in aspirated blood that contains amniotic fluid also suggest that the technique can be utilized after delivery of the baby when unexpected hemorrhage occurs. [151]

Cost-Effectiveness

The expenses associated with cell processing units include not only the apparatus and the software but also the time of a dedicated, trained operator. The institution's experience with allogeneic transfusion for comparable procedures should be periodically reviewed when the procedures for which the technique will be used are determined.

Three groups of investigators studied patients undergoing primary total hip replacements and concluded that intraoperative blood recovery was not cost-effective and was unnecessary in patients who donated two or three units before surgery. [189] [190] [200] Siller et al [201] compared the efficacy and the cost of PABD and intraoperative blood recovery in adolescents undergoing posterior spinal instrumentation and fusion. The cost of intraoperative blood recovery was approximately $240, and patients were billed approximately $640. The addition of intraoperative blood recovery had no

effect on blood exposure, and the investigators do not recommend it if sufficient predonated blood is available.

After reviewing their experience with blood recovery during emergency spine surgery, Cavallieri et al [192] suggested that cost-effectiveness could be improved if use of the technique was restricted to patients with thoracolumbar spine injury with preoperative HCT values of less than 35 percent and Injury Severity Scores of greater than 20. Smith et al [193] calculated the total cost of intraoperative blood recovery for patients sustaining abdominal trauma to be $63,252, whereas the cost of bank blood would have been $114,523. Use of the technique was considered cost-effective in 75 percent of the cases.

Two groups evaluated cost-effectiveness of intraoperative autologous transfusion during abdominal aortic surgery. Using $50,000/QALY as a threshold, Huber et al [185] concluded it was not cost-effective. The cost was $263.75 per case, or $120,794/QALY. They recommended the technique be restricted to select cases in which large volumes of blood loss are anticipated. Goodnough et al [186] calculated that the RBC volume recovered represented the equivalent of 1.6 allogeneic RBC units. The mean blood bank cost saved by use of the device was $248, or 79 percent of the $315 spent on use of the technique. There was no decrease in the percentage of patients transfused unless recovered volumes infused exceeded 750 mL.

Although intraoperative blood recovery is not cost-effective for most patients undergoing primary total joint replacements, it may be for those having hip arthroplasty revisions. For intra-abdominal aortic surgery, spine, and abdominal trauma procedures, it is often reasonable to use an anticoagulant-suction apparatus and blood collection reservoir but not to open a centrifuge bowl unless sufficient blood is collected to make processing worthwhile.

Unprocessed Blood

The primary stimulus for developing devices that do not require processing of recovered blood was the desire to eliminate the need for expensive equipment that required the constant attention of dedicated operators. Intraoperative use is usually restricted to vascular surgery. The devices are more commonly used in the postoperative period.

POSTOPERATIVE BLOOD RECOVERY

Cardiac surgeons have long advocated recovery and reinfusion of mediastinal drainage following cardiac surgery. Collection and reinfusion of blood shed following orthopedic surgery was introduced later.

Cardiac Surgery

Blood within the mediastinum undergoes coagulation and subsequent fibrinolysis. It contains virtually no fibrinogen, and no anticoagulation is required before reinfusion. The HCT value usually ranges from 20 to 25 percent, and free Hb levels are 300 to 400 mg/dL. [143] [202] [203] [204] [205] The transfused RBCs have normal survival [206] and oxygen delivery capacity. [207]

Fibrin degradation products are detected in most patients when unwashed shed mediastinal blood is reinfused. [208] [209] [210] The presence of fibrin degradation products should not be interpreted as indicative of disseminated intravascular coagulation in the absence of clinical bleeding. The greatest danger posed by the fibrin degradation products is misinterpretation of laboratory tests for disseminated intravascular coagulation and unnecessary blood component administration. [208] Serum creatine kinase, serum glutamic-oxaloacetic transaminase (SGOT), and lactate dehydrogenase levels are also elevated after reinfusion of unwashed mediastinal blood. [211] [212] [213] [214] [215] Conflicting results have been reported regarding elevation of the MB band of creatine kinase. Caution must be exercised when cardiac enzyme levels in patients who receive shed mediastinal blood are interpreted. The enzyme elevations caused by reinfused blood can mimic a myocardial infarction. Alternatively, falsely attributing enzyme abnormalities to the shed blood may result in a myocardial infarction going undiagnosed.

The cost-effectiveness of reinfusing shed mediastinal blood has been questioned by several investigators. [209] [216] [217] The volume of blood collected is often small and the amount reinfused insufficient to decrease allogeneic RBC transfusion requirements. Potential complications resulting from transfusion of the blood include difficulties in diagnosing perioperative myocardial infarction, activation of the fibrinolytic and kallikrein-kinin system, enhanced reperfusion injury related to administration of activated platelets, and infection from contaminated blood. [217] Proponents of routine collection and reinfusion of shed blood cite studies demonstrating decreased allogeneic transfusion requirements [218] [219] [220] and emphasize that it is impossible to know in advance who will bleed excessively (and benefit from the technique) and who will not. [221] Processing of recovered blood obviates most of the problems potentially associated with reinfusion, but it is expensive, and the volume is often insufficient to make it worthwhile.

Orthopedic Surgery

Postoperative blood recovery is employed most often for total hip and knee arthroplasties. [222] [223] [224] [225] [226] Experience with the technique following spine surgery is limited. [227] [228] [229] Two questions arise: (1) is it effective and (2) is it safe?

The volume of wound drainage recovered in most series is 400 to 500 mL, but unilateral and bilateral hip and knee procedures are often reported together, making evaluation of the data difficult. The HCT of the reinfused blood is variable, depending on the procedure and the collection period. Most investigators do not provide these data. One group measured the volume and the HCT of recovered blood and found the mean postoperative RBC loss following total hip and knee replacement to be 55±29 mL and 121±50 mL, respectively. [230] The 6-hour wound drainage represented 8.7 and 16.8 percent of overall RBC loss during hospitalization for hip and knee replacements, respectively. Only three of 51 patients lost the equivalent of one or more RBC units in recovered drainage. The volume of RBCs recovered after surgery bore no relationship to total perioperative RBC loss.

Although several groups have demonstrated decreased allogeneic transfusion requirements, [224] [225] [226] others have concluded

---

that routine postoperative blood recovery is not justified, particularly in patients who participate in PABD programs. [230] [231] [232] [233] Selective use of postoperative blood recovery in patients undergoing bilateral total knee replacements or hip revision surgery or those in whom other forms of autologous transfusion are not employed may be costeffective.

There is considerable controversy regarding the necessity for processing the blood before reinfusion. Complement activation has been demonstrated in recovered blood, but not in the recipients of amounts up to 15 percent of estimated blood volume. [234] Recovered blood has elevated levels of cytokines (tumor necrosis factor-alpha, interleukin-1alpha, interleukin-6, interleukin-8) [235] [236] [237] and fibrin degradation products. [238] [239] Bone fragments, fat, and other debris are often visible, and fat particles too small to be removed by microaggregate filters have been demonstrated. [240] Levels of methylmethacrylate monomer in shed blood peak within minutes of drain insertion following total joint arthroplasty but are not detectable after the blood remains at room temperature for 6 hours--the maximum recommended collection period before reinfusion. [240]

Despite the potential complications of reinfusing blood recovered after total joint arthroplasty, there are few reported complications. Faris et al [241] found a 22 percent incidence of febrile reactions associated with reinfusion of blood collected for 6 to 12 hours after operation, compared with a 2 percent incidence when the period of collection was 6 hours or less. Hypotension [242] and upper airway edema [243] have been reported with transfusion of unwashed blood. Despite laboratory evidence of activation of the coagulation and fibrinolytic systems, coagulation studies in recipients are no different than those in patients who receive liquid-preserved RBCs. [225] Reinfused RBCs have a normal life span. [244] [245] [246]

COLLECTION OF PLATELET-RICH PLASMA

Cardiopulmonary bypass is associated with hemostatic abnormalities, the most significant being impaired platelet function. In an attempt to decrease postoperative bleeding and allogeneic transfusion requirements, autologous PRP may be collected before CPB and then reinfused following bypass. Conventional apheresis apparatus can be employed, but plasma collection kits designed specifically for intraoperative use with cell processing devices are preferable.

Conflicting results have been reported regarding the efficacy of PRP in reducing allogeneic transfusion requirements. Some differences can be attributed to study design, volume of collected platelets, time of collection (before or after heparinization), types of surgical procedures included, and absence of defined transfusion criteria. Two blinded, randomized studies did not demonstrate a decrease in transfusion requirements. Ereth et al [247] collected 600 to 700 mL of PRP in patients undergoing repeat valvular surgery and performed a sham procedure in control patients. Tobe et al [248] collected 8 to 10 mL/kg of PRP and reinfused it immediately in control patients and after heparin reversal in treated patients undergoing primary CABG. Shore-Lesserson et al [249] included patients undergoing repeat CABG and/or valve replacement in a prospective randomized controlled study in which treated patients had 1,000 mL of PRP (mean platelet count, 1.2×10^{11}/L) removed. In addition to no effect on bleeding or transfusion requirements, there was a 60 percent incidence of hypotension requiring treatment when the PRP was reinfused. When the effect of fresh whole blood (mean volume 924±130 mL) obtained by intraoperative hemodilution was compared with that of PRP (mean volume, 650±124 mL; mean platelet count, $1.42\pm0.74\times10^{11}$/L), a comparable hemostatic effect that manifested as reduced postoperative bleeding was demonstrated, but neither technique influenced allogeneic transfusion requirements. [250] No differences in coagulation tests, platelet counts, chest tube drainage, or allogeneic transfusion requirements were demonstrated between control patients undergoing elective primary cardiac surgery and those who had PRP (mean volume, 892±150 mL; mean platelet count, 1.4×10^{11}/L) removed and reinfused. [251]

In contrast to the foregoing, two other studies have demonstrated decreased blood loss and transfusion requirements. Christenson et al [252] studied a small group of patients undergoing repeat CABG in whom approximately 20 percent of circulating platelets were harvested. Blood loss and transfusion requirements were significantly decreased in treated patients. In addition, postoperative ventilation time and intensive care unit stay were shorter, and postextubation gas exchange was better. In a larger study, Armellin et al [253] evaluated 293 consecutive patients undergoing cardiac surgery, 147 of whom had PRP (10 mL/kg) removed before heparinization. Mediastinal drainage was less in treated patients during the first 12 postoperative hours, but no difference in total postoperative blood loss was noted. The volume of RBCs and fresh frozen plasma administered was less in treated patients than in control subjects. Transfusion criteria were defined in both of these studies.

What can be concluded from the aforementioned studies? As pointed out by Boldt [254] in his review, collection of PRP is time consuming, requires additional staff, and adds to the cost of surgery. However, collection and reinfusion of PRP are less expensive than transfusion of an equal amount of allogeneic fresh frozen plasma and platelets. Routine use of the technique in cardiac surgery does not appear warranted, but selective use may be beneficial. For example, patients undergoing complicated procedures who are expected to have prolonged CPB and significant blood loss may benefit.

An aliquot of the PRP can also be used for preparation of fibrin sealant or glue. [255] The PRP (or autologous cryoprecipitate prepared from predonated whole blood) is applied to bleeding tissues simultaneously with bovine thrombin and calcium. Numerous reports have documented improved hemostasis with application of fibrin sealant. [256] It is anticipated that a product prepared from solvent-detergent inactivated plasma recently licensed in the United States will reduce the collection of autologous blood for this purpose.

SUMMARY

Autologous transfusion can significantly decrease allogeneic transfusion requirements in surgical patients, and it is often appropriate to employ several blood conservation

techniques. However, the time has come to refine the indications for, and the limitations of, each technique. Destroying approximately 50 percent of predonated autologous units is not acceptable. Patients who can reasonably be expected to profit from predonation should do so, but predonation should be discouraged when it is inappropriate. ANH can be beneficial when large volumes of blood are removed and significant blood loss occurs. Additional controlled studies are needed to define the role of this technique. Intraoperative and postoperative blood recovery should be utilized in cases in which adequate data substantiate efficacy. Routine use is not justified. Newer processing devices requiring less operator intervention may improve cost-effectiveness. The role of PRP in cardiac surgery (and some noncardiac procedures) has not been defined.

References

1. Blundell J: Some account of a case of obstinate vomiting in which an attempt was made to prolong life by the injection of blood into the veins. Med Chir Trans 10:296, 1819.

2. Fantus B: The therapy of the Cook County Hospital. JAMA 109:128, 1937.

3. Lockwood CD: Surgical treatment of Banti's disease. Surg Gynecol Obstet 25:188, 1917.

4. Watson CM, Watson JR: Autotransfusion: Review of the literature with report of two additional cases. Am J Surg 33:232, 1936.

5. Davis LE, Cushing H: Experiences with blood replacement during or after major intracranial operations. Surg Gynecol Obstet 40:310, 1925.

6. Farrar LK: Autotransfusion-blood transfusion in gynecology. Surg Gynecol Obstet 36:454, 1923.

7. Griswold RA, Ortner AB: The use of autotransfusion in surgery of the serous cavities. Surg Gynecol Obstet 77:167, 1943.

8. Brown AAL, Debenham MW: Autotransfusion use of blood from hemothorax. JAMA 96:1223, 1931.

9. Symbas PN: Extraoperative autotransfusion from hemothorax. Surgery 84:722, 1978.

10. Dyer RH: Intra-operative autotransfusion, a preliminary report and a new method. Am J Surg 112:874, 1966.

11. Wilson JD, Utz DC, Taswell HF: Autotransfusion during transurethral resection of the prostate: Technique and preliminary clinical evaluation. Mayo Clin Proc 44:374, 1969.

12. Klebanoff G: Early experience with a disposable unit for intra-operative salvage and reinfusion of blood loss (intraoperative autotransfusion). Am J Surg 120:351, 1970.

13. Stehling LC, Zauder HL, Rogers W: Intraoperative autotransfusion. Anesthesiology 43:337, 1975.

14. Noon GP, Solis RT, Natelson EA: A simple method of intraoperative autotransfusion. Surg Gynecol Obstet 143:65, 1976.

15. Toy PCTY, Strauss RG, Stehling LC et al: Predeposited autologous blood for elective surgery: A national multicenter study. N Engl J Med 316:517, 1987.

16. Renner SW, Howanitz PJ, Bachner P: Preoperative autologous blood donation in 612 hospitals: A College of American Pathologists' Q-probes study of quality issues in transfusion medicine. Arch Pathol Lab Med 116:613, 1992.

17. Nicholls MD, Janu MR, Davies VJ et al: Autologous blood transfusion for elective surgery. Med J Aust 144:396, 1986.

18. Vamvakas EC, Moore BS: Total potential frequency of autologous blood transfusion in Olmsted Country, Minnesota. Mayo Clin Proc 70:37, 1995.

19. Wallace EL, Churchill WH, Surgenor DM et al: Collection and transfusion of blood and blood components in the United States, 1992. Transfusion 35:802, 1995.

20. American Association of Blood Banks: Standards for Blood Banks and Transfusion Services. 18th ed. Bethesda, Maryland, American Association of Blood Banks, 1997.

21. Mintz PD: Participation of HIV-infected patients in autologous blood programs. JAMA 269:2892, 1993.

22. Bailey TE, Mahoney OE: The use of banked autologous blood in patients undergoing surgery for spinal deformity. J Bone Joint Surg Am 69:329, 1987.

23. Silvergleid AJ: Safety and effectiveness of predeposit autologous transfusion in preteen and adolescent children. JAMA 257:3403, 1987.

24. Fukahara K, Murakami A, Ueda T et al: Scheduled autologous blood donation at the time of cardiac catheterization in infants and children. J Thorac Cardiovasc Surg 114:504, 1997.

25. Masuda M, Kawachi Y, Inaba S et al: Preoperative autologous blood donations in pediatric cardiac surgery. Ann Thorac Surg 60:1994, 1995.

26. Kemmotsu H, Joe K, Nakamura H et al: Predeposited autologous blood transfusion for surgery in infants and children. J Pediatr Surg 30:659, 1994.

27. Haugen RK, Hill GE: A large-scale autologous blood program in a community hospital. JAMA 257:1211, 1987.

28. Woolson ST, Marsh JS, Tanner JB: Transfusion of previously deposited autologous blood for patients undergoing hip replacement surgery. J Bone Joint Surg Am 69:325, 1987.

29. Goodnough LT, Shatron D, Marcus RE: The impact of preoperative autologous blood donation on orthopedic surgical practice. Vox Sang 59:65, 1990.

30. Biesma DH, Marx JJM, Van De Wiel A: Collection of autologous blood before elective hip replacement. J Bone Joint Surg Am 76:1471, 1994.

31. Love TR, Hendren WG, O'Keefe DO et al: Transfusion of predonated autologous blood in elective cardiac surgery. Ann Thorac Surg 43:508, 1987.

32. Britton LW, Eastlund DT, Dziuban SW et al: Predonated autologous blood use in elective cardiac surgery. Ann Thorac Surg 47:529, 1989.

33. Owings DV, Kruskall MS, Thurer RL et al: Autologous blood donations prior to elective cardiac surgery: Safety and effect on subsequent blood use. JAMA 262:1963, 1989.

34. Pinkerton PH: Autologous blood donation in support of cardiac surgery: A preliminary report on a hospital-based autologous donor programme. Can J Anaesth 41:1036, 1994.

35. Zussa C, Polesel E, Salvador L et al: Efficacy and safety of predeposit blood autodonation in 500 cases of myocardial revascularization. Scand J Thorac Cardiovasc Surg 24:171, 1990.

36. Sandrelli L, Pardini A, Lorusso R et al: Impact of autologous blood predonation on a comprehensive blood conservation program. Ann Thorac Surg 59:730, 1995.

37. Kasper SM, Gerlich W, Buzello W: Preoperative red cell production in patients undergoing weekly autologous blood donation. Transfusion 37:1058, 1997.

38. Dzik WH, Fleisher AG, Ciavarella D et al: Safety and efficacy of autologous blood donation before elective aortic valve operation. Ann Thorac Surg 54:1177, 1992.

39. Droste S, Sorensen T, Price T et al: Maternal and fetal hemodynamic effects of autologous blood donation during pregnancy. Am J Obstet Gynecol 167:89, 1992.

40. Combs CA, Murphy EL, Laros RK: Cost-benefit analysis of autologous blood donation in obstetrics. Obstet Gynecol 80:621, 1992.

41. Herbert WNP, Owen HG, Collins ML: Autologous blood storage in obstetrics. Obstet Gynecol 72:166, 1988.

42. Kruskall MS, Leonard S, Klapholz H: Autologous blood donation during pregnancy: Analysis of safety and blood use. Obstet Gynecol 70:938, 1987.

43. McVay PA, Hoag RW, Hoag MS et al: Safety and use of autologous blood donation during the third trimester of pregnancy. Am J Obstet Gynecol 160:1479, 1989.

44. Kanter MH, van Maanen D, Anders KH et al: Preoperative autologous blood donations before elective hysterectomy. JAMA 276:798, 1996.

45. Axelrod FB, Pepkowitz SH, Goldfinger D: Establishment of a schedule of optimal preoperative collection of autologous blood. Transfusion 29:677, 1989.

46. Larocque BJ, Gilbert K, Brien WF: A point score system for predicting the likelihood of blood transfusion after hip or knee arthroplasty. Transfusion 37:463, 1997.

47. Mercuriali F, Inghilleri G: Proposal of an algorithm to help the choice of the best transfusion strategy. Curr Med Res Opin 13:465, 1996.

48. Milbrink J, Birgegard G, Danersund A et al: Preoperative autologous donation of 6 units of blood during rh-EPO treatment. Can J Anaesth 44:1315, 1997.

49. Faris PM, Ritter MA, Abels RI: The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. J Bone Joint Surg Am 78:62, 1996.

50. Price TH, Goodnough LT, Vogler WR et al: The effect of recombinant human erythropoietin on the efficacy of autologous blood donation in patients with low hematocrits: A multicenter, randomized, double-blind, controlled trial. Transfusion 36:29, 1996.

51. Canadian Orthopedic Perioperative Erythropoietin Study Group: Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. Lancet 341:1227, 1993.

52. Kruskall MS, Yomtovian R, Dzik WH et al: On improving the costeffectiveness of autologous blood transfusion practices. Transfusion 34:259, 1994.

53. McVay PA, Andrews A, Kaplan EB et al: Donation reactions among autologous donors. Transfusion 30:249, 1990.

54. Hillyer CD, Hart KK, Lackey DA et al: Comparable safety of blood collection in "high-risk" autologous donors versus non-high-risk autologous and directed donors in a hospital setting. Am J Clin Pathol 102:275, 1994.

55. Stehling LC: Predeposited autologous blood donation. Acta Anaesthiol Scand Suppl 89:58, 1988.

56. AuBuchon JP, Popovsky MA: The safety of preoperative autologous blood donation in the non-hospital setting. Transfusion 31:513, 1991.

57. Popovsky MA, Whitaker B, Arnold NL: Severe outcomes of allogeneic and autologous blood donation: Frequency and characterization. Transfusion 35:734, 1995.

58. Kasper SM, Baumann M, Radbruch L et al: A pilot study of continuous ambulatory electrocardiography in patients donating blood for autologous use in elective coronary artery bypass grafting. Transfusion 37:829, 1997.

59. Van Dyck MJ, Baele PL, Leciercq P et al: Autologous blood donation before myocardial revascularization: A Holter-electrocardiographic analysis. J Cardiothorac Vasc Anesth 8:162, 1994.

60. Spiess BD, Sassetti R, McCarthy RJ et al: Autologous blood donation: Hemodynamics in a high-risk population. Transfusion 32:17, 1992.

61. Gravlee GP: Con: Autologous blood collection is not useful for elective coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 8:238, 1994.

62. Spiess BD: Pro: Autologous blood should be available for elective cardiac surgery. J Cardiothorac Vasc Anesth 8:231, 1994.

63. Hardy JF, Belisle S, Decary F: Cardiac surgical patients must not be denied the benefits of autologous blood predonation. Can J Anaesth 41:1021, 1994.

64. Goldfinger D, Capon S, Czer L et al: Safety and efficacy of preoperative donation of blood for autologous use by patients with end-stage heart or lung disease who are awaiting organ transplantation. Transfusion 33:336, 1993.

65. Klapper E, Pepkowitz SH, Czer L et al: Confirmation of the safety of autologous blood donation by patients awaiting heart or lung transplantation: A controlled study using hemodynamic monitoring. J Thorac Cardiovasc Surg 110:1594, 1995.

66. Linden JV, Kruskall MS: Autologous blood: Always safer? Transfusion 37:455, 1997.

67. Goldman M, Remy-Prince S, Trepanier A et al: Autologous donation error rates in Canada. Transfusion 37:523, 1997.

68. Simpson MB, Georgopoulos G, Orsini E et al: Autologous transfusions for orthopaedic procedures at a children's hospital. J Bone Joint Surg Am 74:652, 1992.

69. CDC: Red blood cell transfusions contaminated with *Yersinia enterocolitica*--United States, 1991-1996, and initiation of a national study to detect bacteria-associated transfusion reactions. MMWR Morb Mortal Wkly Rep 46:553, 1997.

70. Cregan P, Donegan E, Gotelli G: Hemolytic transfusion reaction following transfusion of frozen and washed autologous red cells. Transfusion 31:172, 1991.

71. Miller AC, Scherba-Krugliak L, Toy PT et al: Hypotension during transfusion of autologous blood. Anesthesiology 74:624, 1991.

72. Gould SA, Forbes JM: Indications for autologous and allogeneic transfusion should be the same: Pro. Transfusion 35:446, 1995.

73. Miller RD, von Ehrenburg W: Indications for autologous and allogeneic transfusion should be the same: Con. Transfusion 35:450, 1995.

74. American Society of Anesthesiologists Task Force on Blood Component Therapy: Practice guidelines for blood component therapy. Anesthesiology 84:7323, 1996.

75. Expert Working Group: Guidelines for red blood cell and plasma transfusion for adults and children. Can Med Assoc J 156(suppl 11):S1, 1997.

76. Thomas MJG, Gillon J, Desmond MJ: Preoperative autologous donation. Transfusion 36:633, 1996.

77. Etchason J, Petz L, Keeler E et al: The cost effectiveness of preoperative autologous donation. N Engl J Med 332:719, 1995.

78. AuBuchon JP: Cost-effectiveness of preoperative autologous blood donation for orthopedic and cardiac surgeries. Am J Med 101 (suppl 2A):38S, 1996.

79. Birkmeyer JD, AuBuchon JP, Littenberg B et al: Cost-effectiveness of preoperative autologous donation in coronary artery bypass grafting. Ann Thorac Surg 57:161, 1994.

80. Birkmeyer JD, Goodnough LT, AuBuchon JP et al: The cost-effectiveness of preoperative autologous blood donation for total hip and knee replacement. Transfusion 33:544, 1996.

81. Rutherford CJ, Kaplan HS: Autologous blood donation: Can we bank on it? N Engl J Med 332:740, 1995.

82. Goh M, Kleer C, Kielczwski P et al: Autologous blood donation prior to anatomical radical retropubic prostatectomy: Is it necessary? Urology 49:569, 1997.

83. Koch MO, Smith JA: Blood loss during radical retropubic prostatectomy: Is preoperative autologous blood donation indicated? J Urol 156:1077, 1996.

84. Goad JR, Eastham JA, Fitzgerald KB et al: Radical retropubic prostatectomy: Limited benefit of autologous blood donation. J Urol 154:2103, 1995.

85. Stehling L, Zauder HL: Acute normovolemic hemodilution. Transfusion 31:857, 1991.

86. Kreimeier U, Messmer K: Hemodilution in clinical surgery: State of the art 1996. World J Surg 20:1208, 1996.

87. Stehling L, Zauder HL: Perioperative hemodilution: Pro. Transfusion 34:265, 1994.

88. Monk TG, Goodnough LT, Birkmeyer JD et al: Acute normovolemic hemodilution is a cost-effective alternative to preoperative autologous blood donation by patients undergoing radical retropublic prostatectomy. Transfusion 35:559, 1995.

89. Monk TG, Goodnough LT, Brecher ME et al: Acute normovolemic hemodilution can replace preoperative autologous blood donation as a standard of care for autologous blood procurement in radical prostatectomy. Anesth Analg 85:953, 1997.

90. Martin E, Ott E: Extreme hemodilution in the Harrington procedure. Bibl Haematol 47:322, 1981.

91. Scott WJ, Rode R, Castlemain B et al: Efficacy, complications, and cost of a comprehensive blood conservation program for cardiac operations. J Thorac Cardiovasc Surg 103:1001, 1992.

92. Lisander B, Jonsson R, Nordwall A: Combination of blood-saving methods decreases homologous blood requirements in scoliosis surgery. Anaesth Intensive Care 24:555, 1996.

93. Olsfanger D, Jedeikin R, Metser U et al: Acute normovolaemic haemodilution and idiopathic scoliosis surgery: Effects on homologous blood requirements. Anaesth Intensive Care 21:429, 1993.

94. Sejourne P, Poirier A, Meakins JL et al: Effect of hemodilution on transfusion requirements in liver resection. Lancet 2:11380, 1989.

95. Ness PM, Bourke DL, Walsh PC: A randomized trial of perioperative hemodilution versus transfusion of preoperatively deposited autologous blood in elective surgery. Transfusion 32:226, 1992.

96. Bennett SR: Perioperative autologous blood transfusion in elective total hip prosthesis operations. Ann R Coll Surg Engl 76:95, 1994.

97. Oishi CS, D'Lima DD, Morris BA et al: Hemodilution with other blood reinfusion techniques in total hip arthroplasty. Clin Orthop 339:132, 1997.

98. Olsfanger D, Fredman B, Goldstein B et al: Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement. Br J Anaesth 79:317, 1997.

99. Petry AF, Jost T, Sievers H: Reduction of homologous blood requirements by blood-pooling at the onset of cardiopulmonary bypass. J Thorac Cardiovasc Surg 107:1210, 1994.

100. Helm RE, Klempereer JD, Rosengart TK et al: Intraoperative autologous blood donation preserves red cell mass but does not decrease postoperative bleeding. Ann Thorac Surg 1996;62:1431, 1996.

101. Schonberger JPAM, Bredee JJ, Tjian D et al: Intraoperative predonation contributes to blood saving. Ann Thorac Surg 56:893, 1993.

102. Canver CC, Kroncke GM, Nichols RD et al: The effects of intraoperative autologous whole blood sequestration on the need for transfusion

of allogeneic blood and blood products in coronary bypass operations. J Cardiovasc Surg 36:423, 1995.

103. Kochamba GS, Pfeffer TA, Sintek CF et al: Intraoperative autotransfusion reduces blood loss after cardiopulmonary bypass. Ann Thorac Surg 61:900, 1996.

104. Brecher ME, Rosenfeld M: Mathematical and computer modeling of acute normovolemic hemodilution. Transfusion 34:176, 1994.

105. Feldman JM, Roth JV, Bjoraker DG: Maximum blood savings by acute normovolemic hemodilution. Anesth Analg 80:108, 1995.

106. Weiskopf RB: Mathematical analysis of isovolemic hemodilution indicates that it can decrease the need for allogeneic blood transfusion. Transfusion 35:37, 1995.

107. Spahn DR, Leone BJ, Reves JG et al: Cardiovascular and coronary physiology of acute isovolemic hemodilution: A review of nonoxygen-carrying and oxygen-carrying solutions. Anesth Analg 78:1000, 1994.

108. Doss DN, Estafanous FG, Ferrario CM et al: Mechanism of systemic vasodilation during normovolemic hemodilution. Anesth Analg 81:30, 1995.

109. Habler OP, Kleen MS, Podtschaske AH et al: The effect of acute normovolemic hemodilution (ANH) on myocardial contractility in anesthetized dogs. Anesth Analg 83:451, 1996.

110. Spahn DR, Smith LR, Veronee CD et al: Acute isovolemic hemodilution and blood transfusion: Effects on regional function and metabolism in myocardium with compromised coronary blood flow. J Thorac Cardiovasc Surg 105:694, 1993.

111. Bowens C, Spahn DR, Frasco PE et al: Hemodilution induces stable changes in global cardiovascular and regional myocardial function. Anesth Analg 76:1027, 1993.

112. Schaller RJ, Schaller J, Morgan A et al: Hemodilution anesthesia: A valuable aid to major cancer surgery in children. Am J Surg 1146:79, 1983.

113. Schaller RJ, Schaller J, Furman EF: The advantages of hemodilution anesthesia for major liver resection in children. J Pediatr Surg 19:705, 1984.

114. Kraft M, Dedrick D, Goudsouzian N: Hemodilution in an eight-month-old infant. Anaesthesia 36:402, 1981.

115. van Iterson M, van der Waart FJM, Erdmann W et al: Systemic haemodynamics and oxygenation during haemodilution in children. Lancet 346:1127, 1995.

116. Haberkern M, Dangel P: Normovolaemic haemodilution and intraoperative autotransfusion in children: Experience with 30 cases of spinal fusion. Eur J Pediatr Surg 1:30, 1992.

117. Aly Hassan A, Lochbuehler H, Frey L et al: Global tissue oxygenation during normovolaemic haemodilution in young children. Paediatr Anaesth 7:197, 1997.

118. Fontana JL, Welborn L, Mongan PD et al: Oxygen consumption and cardiovascular function in children during profound intraoperative normovolemic hemodilution. Anesth Analg 80:219, 1995.

119. McLoughlin TM, Fontana JL, Alving B et al: Profound normovolemic hemodilution: Hemostatic effects in patients and in a porcine model. Anesth Analg 83:459, 1996.

120. Rose D, Coutosftides T: Intraoperative normovolemic hemodilution. J Surg Res 31:375, 1981.

121. Vara-Thorbeck R, Guerrero-Fernandez Marcote JA: Hemodynamic response of elderly patients undergoing major surgery under moderate normovolemic hemodilution. Eur J Surg Res 17:372, 1985.

122. Catoire P, Saada M, Liu N et al: Effect of preoperative normovolemic hemodilution on left ventricular segmental wall motion during abdominal aortic surgery. Anesth Analg 75:654, 1992.

123. Spahn DR, Zollinger A, Schlumpf RB et al: Hemodilution tolerance in elderly patients without known cardiac disease. Anesth Analg 82:681, 1996.

124. Herregods L, Moerman A, Foubert L et al: Limited intentional normovolemic hemodilution: ST-segment changes and use of homologous blood products in patients with left main coronary artery stenosis. J Cardiothorac Vasc Anesth 11:18, 1997.

125. Spahn DR, Schmid ER, Seifert B et al: Hemodilution tolerance in patients with coronary artery disease who are receiving chronic beta-adrenergic blocker therapy. Anesth Analg 82:687, 1996.

126. Gross JB: Estimating allowable blood loss: Correction for dilution. Anesthesiology 58:277, 1983.

127. Atallah MA, Abdelbaky SM, Saied MMA: Does timing of hemodilution influence the stress response and overall outcome? Anesth Analg 76:113, 1993.

128. Payen J-F, Vuillez J-P, Geoffray B et al: Effects of preoperative intentional hemodilution on the extravasation rate of albumin and fluid. Crit Care Med 25:243, 1997.

129. Martin E, Hansen E, Peter K: Acute limited normovolemic hemodilution: A method for avoiding transfusion. World J Surg 11:52, 1987.

130. Wahr JA, Trouwborst A, Spence RK et al: A pilot study of the effects of a perflubron emulsion, AF 0104, on mixed venous oxygen tension in anesthetized surgical patients. Anesth Analg 82:103, 1996.

131. Haisjackl M, Luz G, Sparr H et al: The effects of progressive anemia on jejunal mucosal and serosal tissue oxygenation in pigs. Anesth Analg 84:538, 1997.

132. Layland M, Mythern MG, Wang K-Y et al: Measurement of gastrointestinal intramucosal pH is a poor guide to tolerable levels of anemia during isovolemic hemodilution in a canine model of coronary stenosis. Arch Surg 132:547, 1997.

133. Maruyama M, Shinoji K, Ichikawa T et al: The effect of extreme hemodilution on the autoregulation and cerebral metabolic rate of oxygen in the dog. Stroke 4:675, 1985.

134. Nago S, Roccaforte P, Moody RA: The effects of isovolemic hemodilution and reinfusion of packed erythrocytes on somatosensory and visual evoked potentials. J Surg Res 25:530, 1978.

135. Czinn EA, Ramez Salem M, Crystal GJ: Hemodilution impairs hypocapnia-induced vasoconstrictor responses in the brain and spinal cord in dogs. Anesth Analg 80:492, 1995.

136. Baele PL: Intraoperative red cell retrieval in a multiple theatre programme. Transfus Sci 15:455, 1994.

137. O'Hara PJ, Hertzer NR, Santilli PH et al: Intraoperative autotransfusion during abdominal aortic reconstruction. Am J Surg 145:215, 1983.

138. McShane AJ, Power C, Jackson JF et al: Autotransfusion: Quality of blood prepared with a red cell processing device. Br J Anaesth 59:1035, 1987.

139. Ray JM, Flynn JC, Bierman AH: Erythrocyte survival following intraoperative autotransfusion in spinal surgery: An in vivo comparative study and 5-year update. Spine 11:879, 1986.

140. Ansell J, Parrilla N, King M et al: Survival of autotransfused red blood cells recovered from the surgical field during cardiovascular operations. J Thorac Cardiovasc Surg 84:387, 1982.

141. Kent P, Ashley S, Thorley PJ et al: 24-Hour survival of autotransfused red cells in elective aortic surgery: A comparison of two intraoperative autotransfusion systems. Br J Surg 78:1472, 1991.

142. Cordell AR, Lavender SU: An appraisal of blood salvage techniques in vascular and cardiac operations. Ann Thorac Surg 31:421, 1981.

143. Yawn DH: Ensuring quality during intraoperative blood salvage. Lab Med 25:626, 1994.

144. Perttila J, Leino L, Poyhonen M et al: Leukocyte content in blood processed by autotransfusion devices during open-heart surgery. Acta Anaesthesiol Scand 39:445, 1995.

145. Sieunarine K, Lawrence-Brown MMD, House AK et al: Plasma tumour necrosis factor alpha levels in intraoperative salvaged blood. Med Sci Res 19:85, 1991.

146. Sieunarine K, Langton S, Lawrence-Brown MMD et al: Elastase levels in salvaged blood and the effects of cell washing. Aust NZ J Surg 60:613, 1990.

147. Gravlee GP, Hopkins MB, Yetter CR et al: Heparin content of washed red blood cells from the cardiopulmonary bypass circuit. J Cardiothorac Vasc Anesth 6:140, 1992.

148. Rouge P, Fourquet D, Depoix-Joseph JP et al: Heparin removal in three intraoperative blood savers in cardiac surgery. Appl Cardiopulm Pathophysiol 5:5, 1993.

149. Loubser PG: Detection of heparin in salvaged blood. Anesthesiology 87:719, 1997.

150. Rice MJ, Violante EV, Kreul JF: The effect of autotransfusion on catecholamine levels during pheochromocytoma. Anesthesiology 67:1017, 1987.

151. Bernstein HH, Rosenblatt MA, Gettes M et al: The ability of the Haemonetics 4 Cell Saver System to remove tissue factor from blood contaminated with amniotic fluid. Anesth Analg 85:831, 1997.

152. Lawrence-Brown MMD, Couch C, Holliday M et al: D-dimer levels in blood salvaged for autotransfusion. Aust NZ J Surg 59:67, 1989.

153. Varga ZA, Thompson JF, Locke-Edmunds JC et al: Clinical and experimental studies of intraoperative autotransfusion using a new filtration device. Br J Surg 82:765, 1995.

154. Walpoth BH, Eggensperger N, Walpoth-Aslan BN et al: Qualitative assessment of blood washing with the continuous autologous transfusion system (CATS). Int J Artif Organs 20:234, 1997.

155. Booke M, Fobker M, Fingerhut D et al: Fat elimination during intraoperative autotransfusion: An in vitro investigation. Anesth Analg 85:959, 1997.

156. Duffy CM, Manninen PH, Chung F et al: Assessment of a new ultrafiltration blood processing system. Can J Anaesth 44:1204, 1997.

157. Linden JV, Kaplan HS, Murphy MT: Fatal air embolism due to perioperative blood recovery. Anesth Analg 84:422, 1997.

158. ECRI: Hemolysis and renal dysfunction associated with autotransfusion. Health Devices 19:25, 1990.

159. Gregoretti S: Suction-induced hemolysis at various vacuum pressures: Implications for intraoperative blood salvage. Transfusion 36:57, 1996.

160. Horst HM, Dlugos S, Farth JJ: Coagulopathy and intraoperative blood salvage (IBS). J Trauma 32:646, 1992.

161. Murray DJ, Gress K, Weinstein SH: Coagulopathy after reinfusion of autologous scavenged red blood cells. Anesth Analg 75:125, 1992.

162. Timberlake GA, McSwain NE: Autotransfusion of blood contaminated by enteric contents: A potentially life-saving measure in the massively hemorrhaging trauma patient? J Trauma 28:855, 1988.

163. Glover JL, Broadie TZ: Intraoperative autotransfusion. World J Surg 11:60, 1987.

164. Ozmen V, McSwain NE, Nichols RE et al: Autotransfusion of potentially culture-positive blood (CPB) in abdominal trauma: Preliminary data from a prospective study. J Trauma 32:36, 1992.

165. Bordreaux P, Bornside GH, Cohn I: Emergency autotransfusion: Partial cleansing of bacteria-laden blood by cell washing. J Trauma 23:31, 1983.

166. Schwieger IM, Gallagher CJ, Finlayson DC et al: Incidence of cell-saver contamination during cardiopulmonary bypass. Ann Thorac Surg 48:51, 1989.

167. Bland LA, Villarino ME, Ardvino MJ et al: Bacteriologic and endotoxin analysis of salvaged blood used in autologous transfusions during cardiac surgery. J Thorac Cardiovasc Surg 103:582, 1992.

168. Kang Y, Aggarwal S, Pasculle AW et al: Bacteriologic study of autotransfusion during liver transplantation. Transplant Proc 21:3538, 1989.

169. Wollinsky KH, Oethinger M, Buchele M et al: Autotransfusion-- bacterial contamination during hip arthroplasty and efficacy of cefuroxime prophylaxis: A randomized controlled study of 40 patients. Acta Orthop Scand 68:225, 1997.

170. Klimberg I, Sirois R, Wajsman Z et al: Intraoperative autotransfusion in urologic oncology. Arch Surg 121:1326, 1986.

171. Hart OJ, Klimberg JQ, Wajsman Z et al: Intraoperative autotransfusion in radical cystectomy for carcinoma of the bladder. Surg Gynecol Obstet 168:302, 1989.

172. Connor JP, Morris PC, Alagoz T et al: Intraoperative autologous blood collection and autotransfusion in the surgical management of early cancers of the uterine cervix. Obstet Gynecol 86:373, 1995.

173. Dale RF, Kipling RM, Smith MF et al: Separation of malignant cells during autotransfusion. Br J Surg 75:581, 1988.

174. Hansen E, Wolff N, Knuechel R et al: Tumor cells in blood shed from the surgical field. Arch Surg 130:387, 1995.

175. Edelman MJ, Potter P, Mahaffey KG et al: The potential for reintroduction of tumor cells during intraoperative blood salvage: Reduction of risk with use of the RC-400 leukocyte depletion filter. Urology 47:179, 1996.

176. Park KI, Kojima O, Tomoyoshi T: Assessment of the availability of intraoperative autotransfusion in urological operations. J Urol 157:1777, 1997.

177. Miller GV, Ramsden CW, Primrose JN: Autologous transfusion: An alternative to transfusion with banked blood during surgery for cancer. Br J Surg 78:713, 1991.

178. Kongsgaard UE, Wang MY, Kvalheim G: Leucocyte depletion filter removes cancer cells in human blood. Acta Anaesthesiol Scand 40:118, 1996.

179. Robicsek F, Duncan GD, Born GVR et al: Inherent dangers of simultaneous application of microfibrillar collagen hemostat and bloodsaving devices. J Thorac Cardiovasc Surg 92:766, 1986.

180. Orr MD, Ferdman AG, Maresh G: Removal of Avitene microfibrillar collagen hemostat by use of suitable transfusion filters. Ann Thorac Surg 57:1007, 1994.

181. Giordano GF, Giordano DM, Wallace BA et al: An analysis of 9,918 consecutive perioperative autotransfusions. Surg Gynecol Obstet 176:103, 1993.

182. Laub GW, Dharan M, Riebman JB et al: The impact of intraoperative autotransfusion on cardiac surgery: A prospective randomized double-blind study. Chest 104:686, 1993.

183. McCarthy PM, Popovsky MA, Schaff HV et al: Effect of blood conservation efforts in cardiac operations at the Mayo Clinic. Mayo Clin Proc 63:225, 1988.

184. Jones JW, Rawitcher RE, McLean TR et al: Benefit from combining blood conservation measures in cardiac operations. Ann Thorac Surg 51:541, 1991.

185. Huber TS, McGorray SP, Carlton LC et al: Intraoperative autologous transfusion during elective infrarenal aortic reconstruction: A decision analysis model. J Vasc Surg 25:984, 1997.

186. Goodnough LT, Monk TG, Sicard G et al: Intraoperative salvage in patients undergoing elective abdominal aortic aneurysm repair: An analysis of cost and benefit. J Vasc Surg 24:213, 1996.

187. Goulet JA, Bray TJ, Timmerman LA et al: Intraoperative autologous transfusion in orthopaedic patients. J Bone Joint Surg Am 71:3, 1989.

188. Wilson WW: Intraoperative autologous transfusion in revision total hip arthroplasty. J Bone Joint Surg Am 71:8, 1989.

189. Rollo VJ, Hozack WJ, Rothman RH et al: Prospective randomized evaluation of blood salvage techniques for primary total hip arthroplasty. J Arthroplasty 10:532, 1995.

190. Mah ET, Davis R, Seshadri P et al: The role of autologous blood transfusion in joint replacement surgery. Anaesth Intensive Care 23:472, 1995.

191. Behrman MJ, Keim HA: Perioperative red blood cell salvage in spine surgery: A prospective analysis. Clin Orthop 278:51, 1992.

192. Cavallieri S, Riou B, Roche S et al: Intraoperative autologous transfusion in emergency surgery for spine trauma. J Trauma 36:639, 1994.

193. Smith LA, Barker DE, Burns RP: Autotransfusion utilization in abdominal trauma. Am Surg 63:47, 1997.

194. Dzik WH, Jenkins R: Use of intraoperative blood salvage during orthotopic liver transplantation. Arch Surg 120:1946, 1985.

195. Williamson KR, Taswell HF, Rettle SR et al: Intraoperative autologous transfusion: Its role in orthotopic liver transplantation. Mayo Clin Proc 64:340, 1989.

196. Williamson KR, Taswell HF: Intraoperative blood salvage: A review. Transfusion 31:622, 1991.

197. Cataldi S, Bruder N, Dufor H et al: Intraoperative autologous blood transfusion in intracranial surgery. Neurosurgery 40:765, 1997.

198. Jimenez DF, Barone CM: Intraoperative autologous blood transfusion in the surgical correction of craniosynostosis. Neurosurgery 37:1075, 1995.

199. Jackson SH, Lanser RE: Safety and effectiveness of intracesarean blood salvage. Transfusion 33:181, 1993.

200. Guerra JJ, Cuckler JM: Cost effectiveness of intraoperative autotransfusion in total hip arthroplasty surgery. Clin Orthop 315:212, 1995.

201. Siller TA, Dickson JH, Erwin WD: Efficacy and cost considerations of intraoperative autologous transfusion in spinal fusion for idiopathic scoliosis with predeposited blood. Spine 21:848, 1996.

202. Bouboulis N, Kardara M, Kesteven PJ et al: Autotransfusion after coronary artery bypass surgery: Is there any benefit? J Card Surg 9:314, 1994.

203. Kongsgaard UE, Tollosrud S, Brosstad F et al: Autotransfusion after open heart surgery: Characteristics of shed mediastinal blood and its influence on the plasma proteases in circulating blood. Acta Anaesthiol Scand 35:71, 1991.

204. Hartz RS, Smith JA, Green D: Autotransfusion after cardiac operation. J Thorac Cardiovasc Surg 96:178, 1988.

205. Solem J, Steen S, Tengborn L et al: Mediastinal drainage blood: Potentialities for autotransfusion after cardiac surgery. Scand J Thorac Cardiovasc Surg 21:149, 1987.

206. Schmidt H, Lund JO, Nielsen SL: Autotransfused shed mediastinal blood has normal erythrocyte survival. Ann Thorac Surg 62:105, 1996.

207. Schmidt H, Kongsgaard U, Kofstad J et al: Autotransfusion after open heart surgery: The oxygen delivery capacity of shed mediastinal blood is maintained. Acta Anaesthesiol Scand 39:754, 1995.

208. Griffith LD, Billman GF, Daily PO et al: Apparent coagulopathy caused by infusion of shed mediastinal blood and its prevention by washing of the infusate. Ann Thorac Surg 47:400, 1989.

209. Vertress RA, Conti VR, Lick SD et al: Adverse effects of postoperative infusion of shed mediastinal blood. Ann Thorac Surg 62:717, 1996.

210. Schonberger JPAM, van Oeveren W, Bredee JJ et al: Systemic blood activation during and after autotransfusion. Ann Thorac Surg 57: 1256, 1994.

211. Wahl GW, Feins RH, Alfieres G et al: Reinfusion of shed blood after coronary operation causes elevation of cardiac enzyme levels. Ann Thorac Surg 53:625, 1992.

212. Nguyen DM, Gilfix BM, Dennis F et al: Impact of transfusion of mediastinal shed blood on serum levels of cardiac enzymes. Ann Thorac Surg 62:109, 1996.

213. Schmidt H, Mortensen PE, Folsgaard SL et al: Cardiac enzymes and autotransfusion of shed mediastinal blood after myocardial revascularization. Ann Thorac Surg 63:1288, 1997.

214. Adoumie R, Lockanathan R, Yen A et al: Character of shed blood in cardiac and thoracic surgery patients: Implications for reinfusion. Can J Surg 37:203, 1994.

215. Hannes W, Keilich M, Koster W et al: Shed blood autotransfusion influences ischemia-sensitive laboratory parameters after coronary operations. Ann Thorac Surg 57:1289, 1994.

216. Schirmer U, Hemmer W, Lindner KH et al: Shed mediastinal blood in 500 elective cardiac surgery patients: Is there enough for retransfusion routinely? J Cardiovasc Surg 38:45, 1997.

217. Mazer CD: Con: Shed mediastinal blood should not be reinfused after cardiac surgery. J Cardiothorac Vasc Anesth 9:100, 1995.

218. de Varennes B, Nguyen D, Denis F et al: Reinfusion of mediastinal blood in CABG patients: Impact on homologous transfusions and rate of re-exploration. J Cardiac Surg 11:387, 1996.

219. Schmidt H, Mortensen PE, Folsgaard SL et al: Autotransfusion after coronary bypass grafting halves the number of patients needing blood transfusion. Ann Thorac Surg 61:1177, 1996.

220. Morris JJ, Tan YS: Autotransfusion: Is there a benefit in a current practice of blood conservation? Ann Thorac Surg 58:502, 1994.

221. Dietrich W: Pro: Shed mediastinal blood retransfusion should be used routinely in cardiac surgery. J Cardiothorac Vasc Anesth 9:95, 1995.

222. Slagis SSV, Benjamin JB, Volz RG et al: Postoperative blood salvage in total hip and knee arthroplasty: A randomized controlled trial. J Bone Joint Surg Br 73:591, 1991.

223. Heddle NM, Brox WT, Klama LN et al: A randomized trial on the efficacy of an autologous blood drainage and transfusion device in patients undergoing elective knee arthroplasty. Transfusion 32:742, 1992.

224. Newman JH, Bowers M, Murphy J: The clinical advantages of autologous transfusion: A randomized, controlled study after knee replacement. J Bone Joint Surg Br 79:630, 1997.

225. Healy WL, Pfeiffer BA, Kurtz SR et al: Evaluation of autologous shed blood for autotransfusion after orthopaedic surgery. Clin Orthop 299:53, 1994.

226. Han C-D, Shin D-E: Postoperative blood salvage and reinfusion after total joint arthroplasty. J Arthroplasty 12:511, 1997.

227. Flynn JC, Price CT, Zink WP: The third step of total autologous blood transfusion in scoliosis surgery: Harvesting blood from the postoperative wound. Spine 16:S328, 1991.

228. Blevins YF, Shaw B, Valeri RC: Reinfusion of shed blood after orthopaedic procedures in children and adolescents. J Bone Joint Surg Am 75:363, 1993.

229. Riou B, Arock M, Guerrero M et al: Haematological effects of postoperative autotransfusion in spinal surgery. Acta Anaesthesiol Scand 38:336, 1994.

230. Umlas J, Foster RR, Dalal SA et al: Red cell loss following orthopedic surgery: The case against postoperative blood salvage. Transfusion 34:402, 1994.

231. Ayers DC, Murray DG, Duerr DM: Blood salvage after total hip arthroplasty. J Bone Joint Surg Am 77:1347, 1995.

232. Huo MH, Paly WL, Keggi KJ: Effect of preoperative autologous blood donation and intraoperative and postoperative blood recovery on homologous blood transfusion requirement in cementless total hip replacement operation. J Am Coll Surg 180:561, 1995.

233. Pike J, Hollingsworth R: Audit of post-operative auto-transfusion of shed blood in hip arthroplasty. J R Soc Med 88:522P, 1995.

234. Bengtson J-P, Backman L, Stenqvist O: Complement activation and reinfusion of wound drainage blood. Anesthesiology 73:376, 1990.

235. Southern EP, Huo MH, Mehta JR et al: Unwashed wound drainage: What are we giving our patients? Clin Orthop 320:235, 1995.

236. Arnestad JP, Bengtsson A, Bengtson JP et al: Formation of cytokines by retransfusion of shed whole blood. Br J Anaesth 72:422, 1994.

237. Arnold JP, Haeger M, Bengtson JP et al: Release of inflammatory mediators in association with collection of wound drainage blood during orthopaedic surgery. Anaesth Intensive Care 23:683, 1995.

238. Kristiansson M, Soop A, Keisu K et al: Local wound and systemic coagulation/fibrinolysis responses in hip arthroplasty. Acta Orthop Scand 68:221, 1997.

239. Blaylock RC, Carlson KS, Morgan JM et al: In vitro analysis of shed blood from patients undergoing total knee replacement surgery. J Clin Pathol 101:365, 1994.

240. Healy WL, Wasilewski SA, Pfeiffer BA et al: Methylmethacrylate monomer and fat content in shed blood after total joint arthroplasty. Clin Orthop 286:15, 1993.

241. Faris PM, Ritter MA, Keating EM et al: Unwashed filtered shed blood collected after knee and hip arthroplasties. J Bone Joint Surg Am 73:1169, 1991.

242. Clements DH, Sculco TP, Burke SW et al: Salvage and reinfusion of postoperative sanguineous wound drainage: A preliminary report. J Bone Joint Surg Am 74:646, 1992.

243. Woda R, Telzlaff JE: Upper airway oedema following autologous blood transfusion from a wound drainage system. Can J Anaesth 39:290, 1992.

244. Gronborg H, Otte KS, Jensen TT et al: Survival of autotransfused red cells. ^{51} Cr studies in 10 knee arthroplasty patients. Acta Orthop Scand 67:439, 1996.

245. Umlas J, Jacobson MS, Kevy SV: Survival and half-life of red cells salvaged after hip and knee replacement surgery. Transfusion 33:591, 1993.

246. Wixon RL, Kwaan HC, Spies SM et al: Reinfusion of postoperative wound drainage in total joint arthroplasty: Red blood cell survival and coagulopathy risk. J Arthroplasty 9:351, 1994.

247. Ereth MH, Oliver WC, Beynen FM et al: Autologous platelet-rich plasma does not reduce transfusion of homologous blood products in patients undergoing repeat valvular surgery. Anesthesiology 79:547, 1993.

248. Tobe CE, Vocelka C, Sepulvada R et al: Infusion of autologous platelet rich plasma does not reduce blood loss and product use after coronary artery bypass: A prospective, randomized, blinded study. Cardiovasc Surg 105:1007, 1993.

249. Shore-Lesserson L, Reich DL, DePerio M et al: Autologous platelet-rich plasmapheresis: Risk versus benefit in repeat cardiac operations. Anesth Analg 81:229, 1995.

250. Triuzli DJ, Gilmor GD, Ness PM et al: Efficacy of autologous fresh whole blood or platelet-rich plasma in adult cardiac surgery. Transfusion 35:627, 1995.

251. Wong CA, Franklin ML, Wade LD: Coagulation tests, blood loss, and transfusion requirements in platelet-rich plasmapheresed versus nonpheresed cardiac surgery patients. Anesth Analg 78:29, 1994.

252. Christenson JT, Reuse J, Badel P et al: Plateletpheresis before redo CABG diminishes excessive blood transfusion. Ann Thorac Surg 62:1373, 1996.

253. Armellin G, Sorbara C, Bonato R et al: Intraoperative plasmapheresis in cardiac surgery. J Cardiothorac Vasc Anesth 11:13, 1997.

254. Boldt J: Acute platelet-rich plasmapheresis for cardiac surgery. J Cardiothorac Vasc Anesth 9:79, 1995.

255. Oz MC, Jeevanandam V, Smith CR et al: Autologous fibrin glue from intraoperatively collected platelet-rich plasma. Ann Thorac Surg 53:530, 1992.

256. Reiss RF, Oz MC: Autologous fibrin glue: Production and clinical use. Transfus Med Rev 10:85, 1996.

Section 4 - Subspecialty Management

Chapter 48 - Anesthesia for Thoracic Surgery *

Jonathan L. Benumof
David D. Alfery

INTRODUCTION

The techniques for administering anesthesia for thoracic surgery have undergone a dramatic, progressively refined, and scientifically based evolution. Initially, the general problem of gas exchange with an open thorax was defined and its physiology understood; the problem was solved with the use of controlled positive-pressure ventilation. The introduction of clinically useful muscle relaxants facilitated the use of controlled ventilation. The need for isolating one lung from another became apparent during surgery for lung abscess, bronchopleural fistula, and hemoptysis; a plethora of methods for providing separation of the lungs was developed. Considerable clinical experience subsequently defined and refined the indications and techniques for one-lung anesthesia. Concomitantly, the changes in the distribution of blood flow and ventilation, in the awake state and in the anesthetized and mechanically ventilated state in both the supine and the lateral decubitus positions, became understood. Methods have been developed to manage one-lung ventilation so that arterial oxygenation levels are close to those achieved during two-lung ventilation. The postoperative period can now be almost pain-free and without great risk with the use of epidural narcotics, patient-controlled analgesia, and/or cryoanalgesia (Ch. 69) .

This chapter is divided into two sections. The first part moves temporally through the perioperative period and provides the essentials for the management of a patient under-going thoracic surgery. Preoperative considerations include pulmonary evaluation and optimal pulmonary preparation. Intraoperative period considerations are monitoring requirements, choice of anesthesia, respiratory physiology of the lateral decubitus position and one-lung ventilation/anesthesia, and most importantly, the indications and techniques for providing one-lung ventilation/anesthesia. Finally, the postoperative problems of immediate lifethreatening complications, management of mechanical ventilation, therapeutic respiratory care maneuvers, and control of pain are discussed. The second part of this chapter deals with specific anesthetic techniques and problems encountered in a variety of special diagnostic, elective, and emergency thoracic procedures.

THE PREOPERATIVE PERIOD

Preoperative Evaluation

The vast majority of noncardiac, noncardiopulmonary bypass thoracic surgery procedures consist of resectional or repair procedures for cancer and other masses of the lung and bronchi. Consequently, this section emphasizes these lesions and gives special attention to the respiratory and cardiovascular systems. [1] [2] [3] [4] [5] Also see Chapter 23 .

Respiratory System

History

The history (Chs. 23 and 25) often raises suspicion of the diagnosis of lung cancer. The average patient with cancer of

* *See Appendix 1, Practice Guidelines for Management of the Difficult Airway*

the lung (carcinoma constitutes approximately 90 percent, adenomas 8 to 10 percent, and benign masses 1 percent of lung tumors) is in the sixth or seventh decade of life, has a history of heavy cigarette smoking and recent weight loss, and resides in an urban area. However, a small percentage of lung carcinomas occur in nonsmokers (<10%) (many of these can be traced to a history of passive or involuntary smoking), [6] [7] [8] and lung carcinoma has a higher incidence of occurrence in workers in some chemical industries (such as asbestos, arsenic, chromates, and nickel) than in the general population. Uranium miners have a greatly increased risk for the development of lung carcinoma, especially if they smoke. All age groups are affected, but the disease is rare in persons less than 30 years of age. Five percent of patients are asymptomatic, and in this group the tumor is discovered only by routine roentgenographic examination of the chest. The vast majority of patients, however, have one or more symptoms related to the presence of the tumor. The symptoms may be designated as bronchopulmonary, extrapulmonary intrathoracic, extrathoracic metastatic, extrathoracic nonmetastatic, and nonspecific. On the average, symptoms have been present for 6 to 7 months before the time the patient seeks medical advice; because the first chest roentgenographic findings frequently antedate the first symptoms by several months, lung carcinoma will be at least 1 year old (and perhaps 2-5 years old) by the time of clinical presentation.

Bronchopulmonary Symptoms.

Bronchopulmonary symptoms arising from involvement of the lung (cough, sputum, chest pain, dyspnea, wheeze) are due to bronchial irritation, ulceration, obstruction, infection distal to the obstruction, or a combination of these processes. In a large series of patients with carcinoma of the lung, 75 percent had cough as one of the major symptoms, and this symptom was severe in 40 percent of patients. However, cough is possibly the most common manifestation of respiratory disease in general. It is so common among cigarette smokers that many of them regard a morning cough as "normal." The most common stimulus to cough is the formation of sputum in the respiratory tract (see below), and the cough process is an essential element in keeping the tract clear.

The normal adult produces about 100 mL of mucus from the respiratory tract in a day. When excess mucus is formed, it may accumulate, stimulate the mucous membrane, and be coughed up as sputum. Sputum in patients with bronchogenic carcinoma may be formed in response to physical, chemical, or infective insult to the mucous membrane of the airways. Mucoid sputum is clear or white. Black sputum is due to the detritus of cigarette or atmospheric smoke. Purulent sputum can vary from small streaks to gross hemoptysis (see later) and always warrants investigation for carcinoma. Hemoptysis generally manifests itself as episodic blood streaking of the trophils. Failure to clear a recent change in the quality and quantity of sputum within a few days of initiating antibiotic therapy should raise suspicion of a neoplasm. Blood-stained sputum can vary from small streaks to gross hemoptysis (see below) and always warrants investigation for carcinoma. Hemoptysis, generally manifest as episodic blood streaking of the sputum, is present in 57 percent of patients with bronchogenic carcinoma and is the first symptom in many.

Chest pain is present in 40 percent of patients presenting with a new carcinoma. It is usually a mild, constant, dull ache on the side with the tumor. Another important form of chest pain with lung carcinoma is pleuritic pain. It is due to direct tumor extension to the pleura, is characteristically worse on breathing and coughing, and can usually be accurately localized by the patient. Mediastinal tumors can cause pain that is usually aching and retrosternal but poorly localized.

Dyspnea is a common complaint in patients with both chronic lung disease and lung carcinoma (30%). In chronic diseases, it is common to find that the patient begins to complain of dyspnea only after the respiratory reserve is quite severely impaired, whereas in patients with lung carcinoma dyspnea occurs more abruptly and with less objective functional impairment.

Wheezing is described by 10 percent of patients and is frequently localized to one side. It is due to airway obstruction, and, if the obstruction is located in the trachea, severe dyspnea and stridor may develop.

Extrapulmonary Intrathoracic Symptoms.

Other symptoms of chest disease occur as a result of growth of the tumor beyond the confines of the lung. These symptoms are due to involvement of the pleura (effusion), chest wall (pain), esophagus (dysphasia), superior vena cava (superior vena cava syndrome), pericardium (pericarditis), brachial plexus (arm pain, Horner syndrome), and right or left recurrent laryngeal nerve (hoarseness). Approximately 15 percent of patients with carcinoma of the lung have these kinds of extrapulmonary intrathoracic symptoms.

Extrathoracic Metastatic Symptoms.

Symptoms resulting from metastatic spread of the tumor outside the thorax account for a small percentage of the presenting or major complaints of patients with carcinoma of the lung. These extrathoracic metastatic symptoms can be referable, in order of general decreasing frequency, to brain, skeleton, liver, adrenals, gastrointestinal tract, kidneys, and pancreas. The history with regard to these other organs is extremely important because any positive history referable to these organs requires specific organ workup for metastatic disease (for staging, see the section *Pulmonary Function Testing*), and the finding of such metastases precludes surgery.

Extrathoracic Nonmetastatic Symptoms.

Extrathoracic nonmetastatic symptoms are usually due to a paraneoplastic syndrome caused by secretion of endocrine or endocrine-like substances by the tumor. The endocrine-like manifestations include Cushing syndrome, excessive antidiuretic hormone secretion, carcinoid syndrome, hypercalcemia, ectopic gonadotropin secretion, and hypoglycemia. The neuromuscular manifestations consist of carcinomatous myopathies (Eaton-Lambert Syndrome) and various myopathies related to brain dysfunction. Other manifestations can be skeletal (clubbing, pulmonary hypertrophic osteoarthropathy), dermatologic (scleroderma, acanthosis nigricans), vascular (thrombophlebitis), and hematologic.

Nonspecific Symptoms.

Weight loss, anemia, weakness, anorexia, lethargy, and malaise occur in a large number of patients. Vague febrile respiratory (cold-like) syndromes

Figure 48-1 (Figure Not Available) In patients with lung carcinoma the chest radiograph findings result from the presence of the tumor within the lung (parenchymal mass), changes in the pulmonary parenchyma distal to a bronchus obstructed by the tumor (atelectasis and infection), and spread of the tumor to extrapulmonary intrathoracic sites (hilar and mediastinal masses and other direct extension pathology). *(From Benumof [604])*

may be present in 22 percent of these patients. In 10 to 15 percent of patients, these symptoms are responsible for the initial visit to the physician.

Physical Examination

The basic tools of inspection, palpation, auscultation, and percussion should allow the physician to assess, in a gross way, the overall severity of chronic lung disease, regardless of whether major consolidation, atelectasis, or pleural effusion is present and whether there is any obvious extrathoracic complication of thoracic carcinoma. Because it is mandatory subsequently to use much more sensitive radiologic means of determining resectability, further discussion of physical examination methods for making these determinations is not included here. The detection of bronchospasm, however, is particularly important in that it requires further documentation, is usually reversible with treatment, and has important anesthetic management implications, which are discussed in the section *Preoperative Preparation.*

Common Laboratory Tests

Some of the routine laboratory tests (Ch. 23) that are performed on all patients are especially relevant to the preoperative evaluation of the patient with a lung or bronchial mass. The complete blood count may indicate polycythemia, which may reflect decreased arterial hemoglobin saturation; leukocytosis may be indicative of active pulmonary infection. Gram stain of the sputum provides a qualitative index of infection; cultures and sensitivity studies direct specific antibiotic therapy. Sputum cytology is useful in diagnosing neoplasms. Liver and bone enzymes, blood urea nitrogen and creatinine, and urinalysis can help establish the diagnosis of metastatic lung cancer. However, the chest roentgenogram is, by far, the most useful common laboratory test.

The Chest Radiograph

It has been estimated that when a tumor of the lung is first detected on a chest radiograph, it has completed three fourths of its natural history, [9] and this first radiographic abnormality frequently antedates the first symptoms or signs of the disease by 7 or more months. [10] By the time bronchial carcinoma becomes symptomatic, the chest radiograph is abnormal in 98 percent of all patients, and the abnormality is most suggestive of tumor in over four fifths of these.

The radiographic findings due to carcinoma of the lung (Fig. 48-1) (Figure Not Available) may be the result of the presence of the tumor within the lung [11] (Table 48-1) (Table Not Available) (70% are centrally located), of changes in the pulmonary parenchyma distal to a bronchus obstructed by the tumor (atelectasis, infection, and cavitation), and of spread of the tumor to extrapulmonary intrathoracic sites (hilar and mediastinal lymph nodes, pleura, chest wall, and diaphragm).

The usual radiographic manifestations of lung carcinoma frequently include the hilar and extrapulmonary intrathoracic manifestations in addition to the pulmonary parenchymal manifestations. In a review of the radiographs of the chest of 600 patients with carcinoma of the lung, [12] the average lung cancer mass at radiologic presentation was 3 to 4 cm in diameter. A large parenchymal mass was present in 22 percent of patients and a smaller mass in 20 percent; multiple masses were present in only 1 percent. Obstructive pneumonitis, collapse, or consolidation was present in 41 percent. A hilar abnormality, either alone or associated with other abnormalities, was present in 41 percent of the patients.

TABLE 48-1 -- Radiologic Criteria for Differentiating Malignant From Benign Pulmonary Opacities

(Not Available)

From Batra et al [11]

The various extrapulmonary intrathoracic manifestations, of which mediastinal widening, pleural effusion, and raised hemidiaphragm were the more common, were present in 11 percent.

Several radiographic findings can have specific anesthetic implications. These lesions consist of tracheal deviation or obstruction (difficulty with intubation or ventilation); mediastinal mass (difficulty with ventilation, superior vena cava syndrome, compression of pulmonary artery); pleural effusions (decreased vital capacity and functional residual capacity [FRC]); cardiac enlargement (susceptibility to anesthetic agents that depress the heart); bullous cyst (hazard of rupture, compression of adjacent lung); air-fluid levels (abscess with hazard of spread of infection); and parenchymal reticulation, consolidation, atelectasis, or edema (increased ventilation/perfusion [V/Q] inequality and transpulmonary shunt). It is important to note that as many as 10 percent of patients with chronic diffuse infiltrative lung disease may have normal chest radiographs. [13]

Pulmonary Function Testing

Preoperative pulmonary evaluation (Ch. 24) of patients with cancer of the lung should resolve questions concerning both resectability and operability. The question of resectability requires local tumor, regional node, and distant metastasis (T, N, and M, respectively) staging of the disease and is based on clinical examination, radiographic (including computed tomographic [CT]) studies (T staging), bronchoscopic and mediastinoscopic examination (N staging), and individual organ evaluation and scanning (M staging). Operability addresses the question of how much pulmonary tissue can be safely removed without rendering the patient a pulmonary cripple (the remaining lung may be diseased by a long history of smoking), and this question is best answered by pulmonary function tests. When making an evaluation of operability, the physician must remember that untreated carcinoma of the lung is associated with a mean survival of less than 1 year and that the only currently effective method for curing carcinoma of the lung is surgical excision.

There is a general consensus that in the performance of a pneumonectomy, pulmonary function testing should proceed in three phases [14] [15] (Table 48-2) . The first phase evaluates total lung function and consists of analysis of room air arterial blood gases as well as simple spirometry and determination of lung volumes. More recent reports indicate carbon monoxide diffusing capacity and exercise testing may be indicated as well (Table 48-3) . Increased risk is present when hypercapnia ($Pa_{CO_2} > 45$ mm Hg) is present on a room air blood gas sample, the forced expired volume in 1 second (FEV_1), and/or the maximum breathing capacity is less than 50 percent of predicted, and/or the residual volume is greater than 50 percent of total lung capacity. If any of these whole-lung pulmonary function values is worse than the stated limits, testing should proceed to the second phase, which evaluates the function of each lung separately; this phase consists of measurement of the ventilation [16] [17] [18] and, more recently, the perfusion [19] [20] of each individual lung (as a fraction of the total) by radioisotopic (^{133}Xe and ^{99}Tc) scanning. Combining right-left fractional lung function tests with conventional spirometry should yield a predicted postoperative FEV_1 greater than 0.85 L. [16] [17] [18] For example, if the

perfusion of the lung to be removed is 40 percent of the total perfusion and the preoperative FEV_1 is 1.4 L, the predicted postoperative FEV_1 is 0.84 L. That is, predicted postoperative FEV_1 equals preoperative FEV_1 multiplied by contralateral perfusion (expressed as a percentage).

If the second-level criterion of acceptable predicted postoperative FEV_1 cannot be met and surgery is still contemplated or desired, the postoperative condition of the patient can be simulated (the third phase of testing) by functionally resecting the vascular bed of the lung to be taken out by temporary balloon occlusion of the major pulmonary artery on that side, with and without exercise. [19] [21] [22] [23] [24] Under these conditions, the distensibility (compliance) of the remaining pulmonary vascular bed is tested, and an increase in mean pulmonary artery pressure to greater than 40 mm Hg, and/or an increase in Pa CO_2 above 60 mm Hg, and/or a decrease in Pa O_2 less than 45 mm Hg indicates an inability to tolerate the removal of this amount of lung.

Ventilatory function postpneumonectomy (or after any resection) can also be simulated preoperatively by passing, with the aid of a fiberoptic bronchoscope, a balloon occlusion catheter, which can occlude either lung (or any lobe), and then measuring spirometry of the remaining lung tissue (after careful withdrawal of the bronchoscope). Supplemental

TABLE 48-2 -- Preoperative Pulmonary Function Tests (PFTs) and Operative Risk of Pneumonectomy

TESTING PHASE	PFT*	INCREASED OPERATIVE RISK RESULT
1. Whole-lung tests	Arterial blood gases	Hypercapnia on room air
	Spirometry	FEV_1 < 50% of FVC
		FEV_1 < 2 L
		MBC < 50% predicted
	Lung volume	RV/TLC > 50%
2. Single-lung tests	Right-left (individual-lung) split-function tests	Predicted postoperative FEV_1 < 0.85 L or > 70% blood flow to diseased lung
3. Mimic postoperative condition	Temporary unilateral balloon occlusion of right or left main stem bronchus or right or left pulmonary artery (must provide supple- mental O_2)	Mean pulmonary artery pressure > 40 mm Hg, severe breathlessness, Pa CO_2 > 60 mm Hg, or Pa O_2 < 45 mm Hg

Abbreviations: RV, residual volume; TLC, total lung capacity; MBC, maximum breathing capacity; FEV_1, forced expired volume in first second; FVC, forced vital capacity.

*The testing phases and PFT are listed in order of proper temporal performance and increasing invasiveness. (Also see Chs. 24 and 25 for more details.)

TABLE 48-3 -- Minimal Pulmonary Function Test Criteria for Variously Sized Pulmonary Resections

TEST	UNIT	NORMAL	PNEUMONECTOMY	LOBECTOMY	SEGMENTECTOMY
MBC	L/min	>100	>70	40-70	40
	% predicted	100	>55	>40	>35
	L	>5.0	>2.1		
	Predicted postoperative, L		>1.3		
FVC	% predicted	100	>51-64	--	--
	Predicted postoperative % predicted		>41		
	L	>2	>1.7-2.1	>1-1.2	>0.6-0.9
	Predicted postoperative, L		>0.8-0.9	>1.0	
FEV_1	% predicted	100	>55-65	40-50	>40
	Predicted postoperative % predicted		>30-40		
FEV_{25-75}	L	2	>1.6	>0.6-1.6	>0.6
	% predicted	100	>60		
DL	Predicted postoperative % predicted		>40	--	--
	VO_2 max	2.8 L/min			
			>1.0 L/min		

	VO_2 max	40 mL/kg	
			>10-15 mL/kg
Exercise testing	DeltaSa O_2	No change	
			2%
	Stair climbing	5 flights	3 flights

Abbreviations: MBC, maximum breathing capacity; FVC, forced vital capacity; FEV_1 , forced expiratory volume in 1 second; FEV_{25-75} , forced expiratory volume between 25 and 75% of FVC; DL
, carbon dioxide diffusing capacity; VO_2 max, maximum C_2 consumption; SaO_2 , arterial O_2 saturation.

Data from refs. [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37]

oxygen must be administered during bronchial blockade because the blocked segment would still be perfused, and all this perfusion would be right-to-left shunt flow, which would create a risk of hypoxemia.

This pulmonary function testing cascade is logical because it starts out with simple, relatively inexpensive, noninvasive tests and only increases the degree of difficulty, expense, and invasiveness as indicated.

Although less restrictive pulmonary function test criteria for operability for pulmonary resections less radical than pneumonectomy have been published [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] (see Table 48-3) , there are several reasons why, at least in some patients, it may be prudent to think of a lobectomy (and lesser procedures) as a functional pneumonectomy. [38] First, during the immediate postoperative period, the function of the lung tissue remaining on the operative side may be significantly impaired by atelectasis and perhaps infection; consequently, these patients may experience significant transient postoperative functional impairment. [39] Patients who are most likely to have a stormy postoperative course with minor resections are those who have had intraoperative exposure problems that required severe and prolonged lung manipulation. Intraoperative exposure problems are most likely to occur when the lung being operated on is large and moving (large tidal volume with positive-pressure ventilation). Second, at the time of thoracotomy more accurate staging of the disease is possible, and it may become apparent that it is necessary to perform a pneumonectomy. [15] Third, the function of the lung on the nonoperated side may be impaired preoperatively [39] and may acutely deteriorate intraoperatively as a result of spillage of blood and/or pus from the operated to nonoperated lung or by inability of the nonoperated lung to tolerate a prolonged period of dependency and compression in the lateral decubitus position. Finally, postlobectomy function studies have shown that although the ventilation and perfusion of the lung remaining on the operated side become significantly greater during the long-term interval (3-51 months), the volume of the remaining lung gradually increases and becomes significantly greater than the increase in either ventilation or perfusion to this lung. [40] The compensatory hyperinflation represents dilation of the preexisting respiratory units without disruption or fragmentation of the elastic tissue as seen in pathologic emphysema; however, the pulmonary hyperinflation decreases the compliance and therefore the ventilation per unit volume of the ipsilateral remaining pulmonary tissue. In addition, the hyperinflated lung stretches and thins out the capillaries in the alveolar walls, decreasing the perfusion per unit volume of the ipsilateral remaining pulmonary tissue.

Cardiovascular System

Pulmonary Vascular and Right Ventricular Function Testing

The vast majority of patients with pulmonary tumors have had a long history of smoking; consequently, they have varying degrees of chronic obstructive pulmonary disease (COPD). The cardiovascular response to the pathologic alveolar and airway changes in COPD consists of the development of pulmonary hypertension and increased pulmonary vascular resistance (PVR), followed by right ventricular (RV) hypertrophy and dilation.

Increased PVR has important implications for patients undergoing pulmonary resection. Whereas a normal pulmonary vasculature is distensible and capable of accommodating large increases in pulmonary blood flow (to approximately 2 to 2.5 times normal, as would occur through the remaining lung after a pneumonectomy) with only minor increases in pulmonary artery pressure (Fig. 48-2) (Figure Not Available) , the relatively

Figure 48-2 (Figure Not Available) Mean pulmonary artery pressure (y axis) does not increase until cardiac output (x axis) has been increased 2- to 2.5-fold when the pulmonary vascular bed is normal, whereas mean pulmonary artery pressure increases linearly with increasing cardiac output is increased when the pulmonary vascular bed is restricted. *(From Robin and Gaudio [41])*

rigid and restricted pulmonary vascular bed of chronic lung disease patients cannot accommodate even small increases in pulmonary blood flow without concomitant increases in pulmonary vascular pressure. [41] The inability to tolerate increases in blood flow occurs over the entire range of physiologic cardiac output and may be an important contributing factor to the development of postpneumonectomy pulmonary edema when it occurs. [42]

The preoperative pulmonary function testing cascade as outlined in pulmonary function testing phases 1 and 2 in Table 48-2 (which, in reality, is the extent to which the great majority of patients are studied preoperatively) does not allow diagnosis of increased PVR and RV disease. Increased PVR may be noninvasively suspected preoperatively by the presence of the auscultatory and radiographic signs of pulmonary hypertension and by electrocardiographic (ECG) evidence of right atrial and ventricular hypertrophy (Table 48-4) . The development of a positive hepatojugular reflex, ascites, and peripheral edema indicates the onset of cor pulmonale. In COPD patients without waking hypoxemia, cor pulmonale can be detected twice as sensitively and frequently by echocardiography (definition criteria are pulmonary hypertension and RV enlargement and/or hypertrophy) as by the preceding clinical methods. [43]

Measurements of PVR have been made directly by determining mean pulmonary artery and pulmonary artery wedge pressures at various levels of cardiac output produced by varying treadmill exercises. Thus, using the patient's own cardiac output, pulmonary vascular compliance can be determined. PVR measurements made in this way have been good indicators of risk for pneumonectomy. [44] [45] Operative risk was considered to be increased if PVR was greater than 190 dyne/s/cm. [5] However, if the risk, expense, and time to pass a pulmonary artery catheter have been accepted, it is logical to take one further step and measure pulmonary vascular pressures during temporary unilateral pulmonary artery balloon occlusion in states of rest and exercise (see pulmonary function testing, phase 3). This maneuver specifically tests the compliance of just the pulmonary vascular bed that will remain after pneumonectomy. Performing this procedure during exercise is the most realistic preoperative approximation of pulmonary vascular and right ventricular

TABLE 48-4 -- Noninvasive Diagnosis of Pulmonary Hypertension, Increased Pulmonary Vascular Resistance, Right Atrial and Ventricular Hypertrophy, and Cor Pulmonale

AUSCULTATORY SIGNS OF PAP AND PVR	RADIOGRAPHIC SIGNS OF PAP AND PVR	ELECTROCARDIOGRAPHIC SIGNS OF RA AND RV	ADDITIONAL SIGNS OF CP
		RV	
Pulmonary component of second heart sound	Dilation of main pulmonary artery	Clockwise vector rotation	All those of PAP, PVR, RA, RV
Loss of normally present split in second heart sound	Fullness of apical pulmonary vessels	Right axis deviation	Pulmonary diastolic murmur
Presence of fourth heart sound	Counterclockwise cardiac rotation: globular shape on P-A film (RV comprises left and right heart border, aortic knob)	R and ing S wave V_2 -V_6	Third heart sound
Appearance of high-pitched early systolic ejection click	Lateral film showing encroachment of retrosternal air space (RV dilation)	Inverted T wave V_1 -V_6	Prominent right sternal border pulsation plus retration over left chest rocking motion synchronous with heartbeat
		RA	
		ST segment V_2 -V_6	
		P wave II and III: diphasic P wave V_1	Chronic dependent edema, large tender liver, ascites, distension neck veins (large A waves)

Abbreviations and symbols:
PAP, pulmonary hypertension;
PVR, increased pulmonary vascular resistance;
RA, right atrial hypertrophy;
RV, right ventricular hypertrophy; CP, cor pulmonale.

function to be expected in the ambulatory postpneumonectomy patient. [14] [21] [22] [23] [24] Also, echocardiography is increasingly being used to estimate right ventricular alterations and pulmonary hypertension [43] (see earlier).

In addition to the preoperative condition of the pulmonary vasculature, the intraoperative anesthetic and surgical experience can introduce numerous other causes for further acute increases in PVR, including episodes of hypoxia, [46] [47] acidosis, [48] increased airway resistance during spontaneous exhalation [49] (which causes air trapping, increased alveolar pressure, and compression of the small intra-alveolar vessels), positive end-expiratory pressure (PEEP), [50] [51] and sepsis. [52] In addition, resection of a significant amount of the pulmonary vascular bed further increases PVR, especially if the remaining pulmonary vascular bed is diseased to begin with and the cardiac output is increased. [41] [53] [54] Finally, the remaining (nonresected) lung may become further diseased either intraoperatively (surgically traumatized) or postoperatively. [38] [39] Thus, PVR in patients undergoing thoracic surgery may be additively and sequentially increased preoperatively, intraoperatively, and postoperatively.

Left Ventricular Function Testing

The possible independent causes that may contribute to left ventricular (LV) dysfunction in patients with lung disease consist of coronary artery or valvular disease, [55]

[56] systemic hypertension, [55] [56] presence of carboxyhemoglobin, [57] systemic hypoxemia and acidosis, [58] marked alterations in intrathoracic pressure, [59] [60] and RV dysfunction. [55] [61] [62] [63] [64] Considering the usual age, the long and heavy smoking history, and the frequently sedentary life-style of patients undergoing thoracic surgery, it is not surprising that coronary artery disease is by far the most likely independent cause of LV dysfunction. Myocardial ischemia leading to infarction may occur throughout the perioperative period, although peaks of incidence occur during operation and on the third day after operation. The first peak is caused by intraoperative changes in hemodynamics and the second peak is caused by episodes of hypoxia, uneven administration of pain medication, and withdrawal or alteration of drug therapy. [65]

There are only two proven preoperative clinical predictors of perioperative cardiac morbidity (defined as occurrence of myocardial infarction, unstable angina, congestive heart failure, serious dysrhythmia, or cardiac death during the intraoperative or in-hospital postoperative periods); these predictors are recent (<6 months) myocardial infarction and current congestive heart failure. [66] The classic historical intraoperative predictors of morbidity--emergency surgery, prolonged (>3 hours) operations, and thoracic or upper abdominal surgery--also appear to be independent predictors of perioperative morbidity, whereas choice of anesthetic is not. The dynamic intraoperative predictors of perioperative cardiac morbidity are intraoperative hypotension and tachycardia. Hypertension remains a controversial predictor.

If a history of angina or the ECG is suggestive, then further preoperative evaluation of coronary artery function is necessary (suggestive evidence includes Q waves [previous infarction], left bundle branch block, ST segment elevation [transmural ischemia], ST segment depression [subendocardial ischemia], T-wave inversions, and positive U-wave [left main coronary artery disease]). The first step should be noninvasive exercise testing. ECG and thallium scans (in that order) appear to be the best such exercise tests at this time. An exercise study provides information about the functional level of the patient. Unfortunately, the degree of exercise stress may be limited by low ventilatory reserve as well as by low cardiac reserve. If the exercise ECG is normal, surgery should proceed; if the exercise ECG indicates ischemia, a thallium exercise test is indicated. [67] If the thallium exercise test is negative, the planned pulmonary resection should proceed; if the thallium exercise scan is positive for ischemia, coronary angiography should be performed. [68] However, if for any reason there is a strong suspicion that the patient is indeed having significant angina, even though exercise testing is negative or equivocal, coronary angiography is indicated. Consideration should always be given to coronary angiography in the patient with proven previous myocardial infarction, especially if the patient currently has angina. Echocardiography is increasingly being used to estimate LV function.

If significant coronary artery disease is present, the patient needs coronary artery bypass grafting before or at the time of pulmonary resection. For lesser degrees of coronary artery disease, pulmonary resection for carcinoma of the lung should be performed after appropriate medical therapy for coronary insufficiency has been initiated. If the patient needs coronary artery bypass grafting and a limited resection can encompass the cancer, both procedures can be performed under the same anesthetic, but the coronary artery bypass grafting should be done before pulmonary resection. [69] [70] After bypass, if the patient is stable, has good myocardial function, and is not bleeding, a pulmonary wedge resection can be done. For patients who require coronary artery bypass grafting and have pulmonary lesions that require segmentectomy, lobectomy, or pneumonectomy, there is a good possibility that the prolonged nature of the pulmonary procedures will increase the operative mortality (and therefore should not be done), although a small number of successful combined procedures have been reported. [70] [71] In one series of 21 patients, the pulmonary mass was discovered on the preoperative chest x-ray film (for cardiac surgery) and therefore before the occurrence of any symptoms and by definition constituted a fortuitously early diagnosis. Not surprisingly, resection at the time of cardiac surgery (17 wedge resections, 4 lobectomies) resulted in a 95 percent 5-year survival. [72]

In cases that require large resections in compromised patients, coronary artery bypass grafting should be done first, and pulmonary resection should be delayed until the patient has gained weight and muscle mass (usually 4-6 weeks). The risk of general anesthesia for a noncardiac operation in the patient with previous coronary artery bypass grafting is similar to that in patients without proven coronary artery disease. [73] [74] Although it is not possible to estimate the true effects of delay in pulmonary resection in terms of tumor spread in a possibly immunocompromised patient (especially after general anesthesia), [75] it seems reasonable that in the latter group (those requiring bypass grafting and major pulmonary resection), the operative risk of combined procedures probably exceeds the risk of tumor spread.

Figure 48-3 (Figure Not Available) There are preoperative, intraoperative, and postoperative reasons why thoracic surgery impairs postoperative lung function (see text for details). *(From Benumof [604])*

Preoperative Preparation

Thoracic surgical patients are at high risk for the development of postoperative pulmonary complications. In most of the medical literature, "postoperative complications" refers to the development of atelectasis and/or pneumonia. [76] The incidence of pneumonia usually parallels that of atelectasis, and the onset of pneumonia lags behind the onset of atelectasis because atelectasis provides the ventilatory and mucociliary stasis conditions necessary for the development and growth of the organisms that cause pneumonia. [77] [78]

There are three major reasons why thoracic surgery promotes postoperative pulmonary complications; these reasons originate in the preoperative, intraoperative, and postoperative periods (Fig. 48-3) (Figure Not Available) . First, the incidence of postoperative respiratory complications after any surgery is positively correlated with the degree of preoperative respiratory dysfunction, and most thoracic surgical patients come to surgery with some degree of preoperative lung dysfunction. Compared with nonsmokers, smokers have a sixfold increase in the incidence of pulmonary complications after major operative procedures. [79] [80] In patients with chronic lung disease as compared with normal healthy patients, there is a 20-fold increase in the incidence of postoperative pulmonary complications. [81] Preoperative pulmonary function testing will identify the patients at high risk because of poor preoperative lung function. The impact of this first factor (presence of preoperative respiratory dysfunction) can be significantly reduced by preoperative prophylactic respiratory preparation measures (see later). [82] [83] [84] [85] [86]

The second reason thoracic surgery promotes postoperative pulmonary complications is that the performance of surgery can impair lung function in any patient. During actual surgery, nondependent lung function may be impaired by resection of functional lung and/or by trauma to the remaining nondependent lung (due to various nondependent lung manipulations), and dependent lung function may be impaired as a result of the development of atelectasis and edema formation. This second factor can be minimized by appropriate intraoperative management (such as one-lung ventilation, PEEP, or continuous positive airway pressure [CPAP]--see later).

The third cause of increased pulmonary complications in these patients is that thoracotomy and upper abdominal incisions are most painful and cause patients to resist deep breathing and coughing in the postoperative period, leading to retained secretions, atelectasis, and pneumonia. [82] [87] [88] [89] [90] [91] [92] [93] [94] It is painful for these patients to deep breathe and to stretch either the chest or the abdominal wall (i.e., the incision); consequently, they fail to cough (which requires a deep breath), and they retain secretions (promoting the development of atelectasis and infection). The third factor can be minimized by appropriate postoperative pain management (e.g., epidural narcotics) (Ch. 69) .

Preoperative Respiratory Preparation Maneuvers

The preceding data indicate that patients undergoing thoracic surgery are particularly susceptible to postoperative respiratory complications [79] [80] [81] [82] [83] [87] [88] [89] [90] [91] [92] [93] [94] and that prophylactic measures do decrease such complications. [82] [83] [84] [85] [86] [93] [94] Consequently, preoperative evaluation should be followed by preoperative preparation efforts (Ch. 23) directed toward optimally managing any preexisting pulmonary disease. [95] In general, a full preoperative respiratory preparation regimen involves a five-pronged attack on airway disease. The five elements of the preoperative regimen are stopping smoking, dilating airways, loosening and removing secretions, and taking measures to increase motivation and education and to facilitate postoperative care (Table 48-5 and Fig. 48-4) (Figure Not Available) .

TABLE 48-5 -- Preoperative Respiratory Care Regimen

1. Stop smoking
2. Dilate airways

a. beta$_2$ -Agonists

b. Theophylline

c. Steroids

d. Cromolyn sodium

3. Loosen secretions

a. Airway hydration (humidifier/nebulizer)

b. Systemic hydration

c. Mucolytic and expectorant drugs

d. Antibiotics

4. Remove secretions

a. Postural drainage

b. Coughing

c. Chest physiotherapy (percussion and vibration)

5. Increased education, motivation, and facilitation of postoperative care

a. Psychologic preparation

b. Incentive spirometry

c. Exposure to secretion removal maneuvers

d. Exercise

e. Weight loss/gain

f. Stabilize other medical problems

The five treatment modalities are instituted and proceed in parallel fashion. Before discussing each element separately, it is important to point out that the desirable results of these maneuvers should be, for the purpose of understanding their interaction, achieved in a sequential manner (see Fig. 48-4) (Figure Not Available) . The logic behind this concept is as follows. First, stopping smoking eliminates the stimulus for the production of airway secretions and bronchoconstriction. Next, the airways should be dilated to facilitate secretion removal. Similarly, thick, tenacious, and adherent secretions must be loosened in order to be removed. Once the airways are dilated and the secretions loosened, then it makes sense to use physical maneuvers to remove the secretions. Finally, patients should assist, as much as possible, in their preoperative preparation and postoperative respiratory care. The studies cited below indicate that using the maneuvers in this sequence (dilating the airways, loosening the secretions, removing the secretions) allows the maneuvers to complement one another in improving mucociliary transport function. Of course, it is recognized that patients who do not have bronchospasm will not benefit from bronchodilator treatment, and patients who do not have secretions will not benefit from measures to enhance secretion removal. [96]

Discontinuing Smoking

An improvement in mucociliary transport and small airway function and a decrease in airway secretions and reactivity occur over several weeks after cessation of smoking. [97] [98] Consequently, preoperative cessation of smoking for more than 4 to 8 weeks is associated with a decrease in the incidence of postoperative respiratory complications. [97] [98] Although stopping smoking for only 24 hours will do nothing to decrease the amount of secretions (at least 1-2 weeks is required), [96] [99] airway irritability, and incidence of postoperative respiratory complications, a number of important benefits accrue in the first 1 to 2 days of abstinence. [97] [98] [95] Cessation of smoking for as short a time as 12 to 48 hours has been shown to decrease carboxyhemoglobin levels significantly (increasing hemoglobin available for oxygen transport), to shift the oxyhemoglobin dissociation curve to the right (increasing the availability of oxygen to the tissues), [100] and to reduce nicotine-induced tachycardia [98] [99] in addition, cessation of smoking for a few days may greatly improve ciliary beating. [98] [99] All these acute effects may confer a critical benefit to the marginal patient. [84]

For a few select patients, the risks of stopping smoking for 1 or 2 days may outweigh the benefits. These risks include excessive anxiety, [101] causation of a hypersecretory and bronchospastic state, [100] and increased incidence of deep vein thrombosis [98] [99] nevertheless, a good argument can be made that these potential benefits of continuing smoking during the 1 or 2 days before surgery can just as easily be accomplished with anxiolytics, bronchodilators, and anticoagulants.

Dilating the Airways

The next preparatory step should be to dilate the airways (Ch. 14) . beta$_2$ -Sympathomimetic drugs, such as albuterol, terbutaline, and metaproterenol, are administered to patients

Figure 48-4 (Figure Not Available) A full, aggressive, preoperative respiratory preparation regimen consists of a five-pronged attack: *(1)* require the patient to stop smoking, *(2)* dilate the airways, *(3)* loosen secretions, *(4)* remove secretions, and *(5)* increase patient participation. Using these five maneuvers in the numbered sequence allows them to complement one another in improving secretion removal. *(From Benumof [604])*

TABLE 48-6 -- Two Basic Different Approaches to the Use of Bronchodilators in Asthma and COPD

STEP	APPROACH TO BRONCHODILATION IN ASTHMA AND COPD			
	BONE[120]		*LAM AND NEWHOUSE*[121] *AND NEWHOUSE*[122]	
	ASTHMA	*COPD*	*ASTHMA*	*COPD*
1	Inhaled beta$_2$ agonists	Inhaled anticholinergics	Inhaled steroids	Inhaled steroids/? inhaled cromolyn
2	Inhaled anticholinergics	Inhaled beta$_2$ -agonists	Inhaled beta$_2$ agonists	Inhaled beta$_2$ agonists (rarely anticholinergics)
3	Inhaled steroids + cromolyn	Theophylline and steroids	Inhaled anticholinergics	Oral or intravenous steroids and theophylline
4	Theophylline	Theophylline and steroids	Theophylline	Oral or intravenous steroids and theophylline
5	Oral or intravenous steroids	Theophylline and steroids	Oral or intravenous steroids	Oral or intravenous steroids and theophylline

Abbreviation: COPD, chronic obstructive pulmonary disease.

who have a demonstrable reversible bronchospastic airway component to their respiratory disease. Patients who have increased airway responsiveness and therefore are candidates for preoperative bronchodilation are smokers, [102] atopic individuals, [102] patients with airway symptoms of allergies, [102] patients with COPD, [103] [104] [105] [106] [107] [108] and asthmatics. [109] [110] The sympathomimetics (so-called first messengers) are believed to act on their target cells in the lungs by increasing the activity of adenyl cyclase, an enzyme in the cell membrane, which catalyzes the formation of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP functions as a "second messenger" in the cell, where it acts on smooth muscle to decrease tension and motility. In addition, adrenergic compounds (epinephrine, ephedrine, isoproterenol) can also increase ciliary activity; this may help in removing secretions. [111] [112]

cAMP is broken down by a cytoplasmic enzyme, phosphodiesterase, whose activity can be inhibited by methylxanthines such as theophylline and aminophylline.

Thus, the methylxanthines also increase cAMP but by a mechanism different from that of beta$_2$ -adrenergic receptor agonists. Because the methylxanthines and beta$_2$ -agonists act by different mechanisms, theophylline is often given to patients with bronchospasm already receiving beta-adrenergics, and thus they work in synergy to increase intracellular concentrations of cAMP [113] [114] (Table 48-6) . In addition, aminophylline improves the contractility of the diaphragm and renders it less susceptible to fatigue. [115] Recently, however, there has been considerable concern about the short-term toxicity of inhaled beta-adrenergic agents when used in the presence of methylxanthines; specifically, myocardial ischemia might occur as a result of the drugs' combined effect on the heart, with resultant (and possibly fatal) ventricular arrhythmias. [116] [117] Therefore, appropriate caution should be exercised when combining inhaled beta $_2$ -agonists with methylxanthines. [118]
Adrenocorticosteroids may also be given, by either oral, parenteral, or aerosol routes, to the subgroup of patients with COPD who have especially reactive airways. [119] Steroids are not considered to be bronchodilators but probably act by decreasing mucosal edema and preventing the release of bronchoconstricting substances.

At present there are two basic different approaches (plans) to the use of bronchodilators in asthma and COPD patients; the essential difference between the two approaches is whether the inhaled beta$_2$ -agonists and/or anticholinergics are considered the front-line drugs with inhaled steroids considered the second-line drugs or vice versa (i.e., inflammation is considered most important [120] [121] [122]) (see Table 48-6) . Although the patient's subjective feeling of relief is an important end point, the effect of bronchodilator drug treatment should be quantified by pulmonary function tests.

Loosening the Secretions

The next step in preparing patients for thoracic surgery should be to thin and loosen thick adherent secretions. The most important method of thinning and loosening secretions is by hydration. When tracheal mucus transport velocity is quantitatively measured by radioactive tracer methods, it can clearly be shown that dehydration decreases and rehydration increases velocity. [123] The most common method of hydrating secretions is by use of a jet humidifier or ultrasonic nebulizer to produce a heated, sterile water aerosol that is delivered by a close-fitting mask for 20 minutes to a patient breathing spontaneously with large tidal volumes. Concurrently, continuous systemic hydration must be ensured by adequate oral intake or intravenously.

Pulmonary infection, if present, is treated according to the results of culture and sensitivity tests; broad-spectrum antibiotics such as ampicillin or a cephalosporin frequently have the required specificity and potency. If the antibiotic treatment clears the infection to any extent, it may also decrease the tenacity, viscosity, and volume of secretions.

Removing the Secretions

The next preoperative respiratory preparation step is the actual removal of secretions, and this is accomplished by a combination of postural drainage (several different positions may be required), coughing, and chest percussion and vibration (common methods include tapping with cupped hands and use of electric vibrators) for 15 to 20 minutes several times a day. [101] [124] [125]

When removal of tracheobronchial secretions is quantitatively measured with radioactive tracer methods in patients with COPD, chest physiotherapy (chest percussion and vibration along with postural drainage) with cough is effective in increasing both central and peripheral airway clearance and sputum yield, whereas cough alone is effective in increasing

only central airway clearance and sputum yield. [126] Thus, chest physiotherapy moves peripheral bronchial secretions to more central airways for expectoration by coughing. The reason cough alone cannot clear peripheral airways is that an effective cough must attain a high enough airflow rate so as to shear secretions away from the airway wall. In patients with chronic lung disease, flow rates are low (especially peripherally), and the shearing of secretions by cough may well be limited to the trachea and perhaps just the first two airway generations. [127] Obviously, with either chest physiotherapy or cough it will be much easier to expel the secretions if the airways have already been dilated and the secretions loosened.

Chest physical therapy is relatively contraindicated in patients with lung abscesses, metastases to the ribs, a history of significant hemoptysis, and inability to tolerate the postural drainage positions. It is generally agreed that intermittent positive-pressure breathing regimens do not have sufficient efficacy to warrant the excessive cost of routine use. [128] [129] [130] [131]

The forced expiration technique (FET) is increasingly being regarded as more effective in removing secretions than a cough. [132] The FET comprises a forced expiration starting from midlung volume (50% of inspiratory reserve lung volume) to a low lung volume, usually the RV, followed by a period of relaxation and diaphragmatic breathing. This forceful expiration maneuver differs from a cough because it is performed without closure of the glottis and without the accompanying compressive phase that characterizes cough. The transpulmonary pressure is less during the FET than during cough, resulting in less airway compression and permitting improved proximal and distal clearance of bronchial secretions as compared with a conventional cough (documented by radioaerosol techniques). [132] The FET is now being increasingly used as an alternative to cough during chest physiotherapy. [132]

Measures to Increase Motivation and Postoperative Care

The last step of preoperative preparation consists of general measures designed to increase motivation and education and to facilitate postoperative respiratory care. These measures include stabilization of all other medical conditions, psychologic preparation, improvement of nutrition, exercise, weight loss in the obese, use of oxygen (where appropriate), antibiotics, instruction about realistic expectations of postoperative pain, and education in postoperative respiratory care procedures (including incentive spirometry, chest physiotherapy, postural drainage, and ambulation and exercise programs).

Preoperative Use of Digitalis

The preoperative use of digitalis in the thoracic surgical patient deserves special comment. Resection of pulmonary tissue reduces the available pulmonary vascular bed for perfusion and can cause postoperative RV and right atrial enlargement. Thus, it is not surprising that the incidence of postoperative arrhythmias (due to atrial stretching) increases progressively with age and amount of lung resected. In addition, there is a higher incidence of atrial arrhythmias after left than after right pneumonectomy because a greater degree of manipulation of the atrium occurs during the former operation. Although the postoperative incidence of arrhythmias has provided the basis for the prophylactic use of digitalis in thoracic surgical patients without evidence of congestive heart failure, this practice is still controversial. [133] [134] [135] [136] Widely accepted indications for preoperative digitalization in patients without cor pulmonale undergoing thoracic surgery include congestive (left-sided) heart failure and supraventricular arrhythmias with a rapid ventricular response. [137]

The indications for preoperative digitalization are more straightforward in patients with cor pulmonale. However, it is important to note that these patients have a propensity to develop hypoxemia, hypercarbia, and acidosis, and they are therefore at an increased risk of developing digitalis toxicity; thus the drug should be used with caution. [138] [139] If these patients do receive digitalis preoperatively, it is important to normalize the serum potassium in order to decrease the risk of arrhythmias. Digitalis should probably be withheld on the day of surgery to help prevent confusion with digitalis intoxication if arrhythmias occur postoperatively. [140]

THE INTRAOPERATIVE PERIOD

Monitoring Requirements

Monitoring requirements (Chs. 30 - 33) differ among individual patients for two reasons. First, patients undergoing thoracic operations have varying degrees of preexisting cardiorespiratory disease. Second, the very nature of thoracic procedures (e.g., one-lung ventilation) causes further derangements in respiratory and cardiovascular function in the perioperative period. On the basis of these two considerations and their interactions, individual patients can and should be categorized into a progressively sophisticated and complex tier system with regard to what monitoring is necessary to make possible accurate and rapid diagnosis and therapy during anesthesia. It should be apparent from this monitoring approach that an individual with severe pulmonary disease who is to undergo a minor surgical procedure may well require as extensive a monitoring system as a patient with normal lungs who is to have extensive thoracic surgery.

Table 48-7 presents three major categories for patients undergoing thoracic surgery and recommends the monitoring required for each category. The first category (tier I) includes healthy patients without special intraoperative conditions, such as a young patient undergoing pleurodesis. This tier contains the minimal, yet essential, monitoring required for any patient undergoing a thoracic procedure.

Because failure to check equipment properly before the induction of anesthesia is responsible for 22 percent of critical incidents that occur during anesthesia, [141] the function of the anesthesia machine and ventilator must be assessed preoperatively in an orderly and complete fashion. [142] * Failure of the oxygen delivery system to the patient must be signaled

* FDA Checkout Recommendations.

TABLE 48-7 -- Tiered Monitoring System Based on Amount of Pre-existing Lung Disease and Presence of Special Intraoperative Conditions

TIERED MONITORING SYSTEM	REQUIRED MONITORING RELATED TO RESPIRATORY FUNCTION								
	A ANESTHESIA MACHINE	B OXYGEN DELIVERY	C APNEA	D MINUTE VENTILATION	E GAS EXCHANGE	F AIRWAY MECHANICS	G CARDIOVASCULAR FUNCTIONS	H MUSCLE RELAXATION	I TEMP
Tier I [a] Essential (used in all patients)	Complete check plus ventilator	Inspired O_2 monitor; pulse oximetry	Stethoscope, alarm system, observa-tion, $ETCO_2$	Respiratory rate, bag and chest movements; $ETCO_2$	Color of shed blood, cya-nosis, capillary and venous blood gas ten-sions, pulse oximetry, $ETCO_2$	Stethoscope, feel of breathing bag $ETCO_2$, PIP	Heart rate, blood pressure, ECG, $ETCO_2$	Simple motor tests, blockade monitor	Probe
Tier II [b] Special intermittent and/or continuous monitoring	As above	As above	As above plus D, E, G, F	As above plus respirometer, spirometer	As above plus arterial blood gas tensions	Whole-lung and individual compliance, vital capacity, peak inspiratory force (postoperative)	As above plus accurate input vs. output, and frequent automated central venous and arterial pressures	As above	As above
Tier III [c] Advanced monitoring	As above	As above	As above	As above	As above plus Q_S/Q_T, [d] V_D/V_T, [d] Q_T, VO_2 , mass spectrometry	As above plus airway resistance [d]	As above plus pulmonary vascular pressures, mixed venous oxygen saturation, cardiac out-put, lung water measurements [d]	As above	As above

Abbreviations:$ETCO_2$, end-tidal CO_2 ; ECG, electrocardiogram; Q_S/Q_T, transpulmonary shunt; Q_T, cardiac output; VO_2 , oxygen consumption; V_D/V_T, dead space; PIP, peak inspiratory pressure.

[a] Tier I: Routine healthy patients without special intraoperative conditions.
[b] Tier II: Routine healthy patients with special intraoperative conditions and/or patients with moderate preexisting lung disease without special intraoperative conditions.
[c] Tier III: Patients with severe preexisting respiratory disease with special intraoperative conditions.
[d] Mainly confined to research.

by audiovisual alarms from an inspired oxygen monitor. Pulse oximetry will also serve as a relatively late indicator of inappropriately decreased inspired oxygen fraction (F_{IO_2}) to the patient. Observation of the respiratory rate and movements of the rebreathing bag, ventilator bellows, and chest wall permits rough estimation of minute ventilation and, along with constant use of a stethoscope to hear breath sounds, provides for rapid diagnosis of a breathing circuit disconnect or apnea. However end-tidal carbon dioxide ($E_{T\ CO_2}$) monitoring allows precise breath-by-breath analysis and diagnosis of all of these respiratory functions (apnea, minute ventilation, gas exchange) and is therefore now an essential monitor. In addition, because the slope of the alveolar plateau correlates positively with airway resistance, $E_{T\ CO_2}$ can function as a rough continuous monitor of airway mechanics. The stethoscope is also used to assess airway mechanics (detection of bronchospasm), along with an "educated" hand on the rebreathing bag (manual detection of total lung compliance and resistance). Adequacy of gas exchange is further assessed by observing the color of shed blood, looking for cyanosis (nailbeds, lips, mucous membranes, skin), and listening to the character of the breath sounds. More importantly, pulse oximetry allows precise, on-line, beat-by-beat, continuous monitoring of arterial oxygenation and is therefore now an essential

monitor. Pulse oximetry also indicates desaturation when blood pressure or blood flow is very low and is therefore an on-line monitor of severe changes in cardiovascular function. Because pulse oximetry is a crude monitor in this regard, cardiovascular function must be monitored by frequent use of the blood pressure cuff or, increasingly commonly, an automated oscillometric blood pressure monitor and by continuous ECG. With constant minute ventilation, acute changes in $E_T CO_2$ are proportional to acute changes in cardiac output (i.e., pulmonary blood flow). Muscle relaxation is assessed by simple observation for motor activity and by a peripheral nerve stimulator. Body temperature is continuously measured by a probe. These recommendations for monitoring are routine for anesthesia for nearly all kinds of surgery.

It should be emphasized that if a serious question arises about the adequacy of arterial oxygenation and/or minute ventilation while the pulse oximeter and $E_T CO_2$ monitor, respectively, are being used, arterial blood gases should be drawn (see tier II); thus, pulse oximetry and $E_T CO_2$ monitoring should not be regarded as a total substitute for arterial blood gases. However, venous blood from the back of a warmed hand or large neck vein obtained with no tourniquet or a short-time low-pressure tourniquet has a P_{CO_2} near enough to that of arterial blood (usually 4-8 mm Hg) to be useful for most clinical purposes. [143] [144] In addition, under these sampling conditions a sufficiently high oxygen tension and saturation of venous blood (>40 mm Hg and 75%, respectively) provides a good indication that arterial hypoxemia is most probably absent. As an alternative sampling site, capillary earlobe blood (obtained by needle prick or cut) is usually acceptable for clinical management, because this blood has a Pa_{CO_2} ± 2.0 percent of simultaneous arterial samples. [145]

The second tier in Table 48-7 represents an increase in risk, caused by either special unfavorable intraoperative conditions for relatively healthy patients or significant preexisting cardiopulmonary disease in patients who will not experience special intraoperative conditions. An example of the former circumstance is a patient with mild lung disease having a lobectomy. An example of the latter circumstance is a patient with moderate to severe interstitial lung disease who requires an open lung biopsy. Anyone with some lung disease undergoing one-lung ventilation for a major thoracic procedure must be considered to be in a tier II category. For this second monitoring level, in addition to the preceding essential system (tier I), the following monitoring modalities are required: a respirometer to permit accurate measurement of tidal volume and minute ventilation (the ventilator bellows can be very inaccurate); arterial blood gas analysis to ensure adequate ventilation and oxygenation; an inspiratory pressure gauge to calculate and to follow changes in whole-lung and individual-lung dynamic and static compliance; accurate measurements of intake (intravenous fluids) and output (blood loss, urine output, irrigation fluids, estimation of third space loss); central venous pressure measurement to assess intravascular volume status (depending on expected fluid shifts, condition of the patient's heart); and an automated oscillotonometric blood pressure device or directly transduced arterial pressure for more continuous and accurate systemic blood pressure measurements.

Finally, a third tier of monitoring requirements is constructed for patients with significant preexisting cardiopulmonary disease who will experience further compromising intraoperative conditions. An example of such a patient is one with cor pulmonale undergoing lobectomy or pneumonectomy. For this high-risk group of patients, the anesthesiologist should consider the following additional monitoring: the adequacy of tissue oxygenation continuously assessed by in-line arterial or mixed venous P_{O_2} and P_{CO_2}; measurement of mixed venous oxygen saturation (Sv_{O_2}), which is especially helpful as an index of global well-being in that a major decrease is probably never a good event (Sv_{O_2} is decreased by either a decrease in cardiac output, an increase in oxygen consumption, or a decrease in arterial oxygen content [Ca_{O_2}]); an esophageal ECG obtained by modifying an esophageal stethoscope and used to differentiate atrial arrhythmias [146]; a V_5 ECG lead to detect myocardial ischemia by analysis of the ST segment of the ECG, which is especially important in patients with coronary artery disease; and a pulmonary artery catheter with a thermistor to permit continuous measurement of intravascular filling pressures and rapid determination of cardiac output (and therefore myocardial work indices and assessment of myocardial contractility). Advanced monitoring mainly confined to research at this time includes measurement of right-to-left transpulmonary shunt, ventilation dead space, airway resistance, and aortic pulse pressure contour for beat-to-beat estimation of cardiac output and myocardial contractility.

Two of the preceding monitoring recommendations deserve special discussion and emphasis: arterial cannulation and pulmonary artery catheterization. Direct arterial cannulation (usually of the radial artery) permits frequent arterial blood gas analysis (and perhaps continuous in-line measurement of arterial P_{O_2} and P_{CO_2}); this alone is sufficient justification for arterial line placement for patients with double-lumen endotracheal tubes and/or serious respiratory disease. In addition, an arterial line permits continuous measurement of systemic blood pressure; similarly, this alone is frequently sufficient justification for arterial line

placement in patients with serious cardiovascular compromise. When it is used with a paper readout, the "trend" in arterial pressure is demonstrated. An electrical mean pressure can be calculated, allowing a more precise measurement of perfusion pressure. Finally, an increase in positive-pressure-induced variation in systolic blood pressure may be an early indicator of hypovolemia. [147]

Normally, the central venous pressure is an adequate index of intravascular volume status. With progressive pulmonary disease and/or LV dysfunction, however, the left- and right-sided cardiac circulations must be assessed separately, because the central venous pressure may no longer reflect left-sided filling pressure (pulmonary artery wedge pressure [Ppaw]). In addition, with significant pulmonary disease and/or tachycardia, the pulmonary artery diastolic pressure will be elevated above the pulmonary artery wedge pressure, and a significant pulmonary artery diastolic-to-wedge pressure gradient will be present. In this situation only the wedge pressure can be used to reflect left-sided cardiac volume/ compliance status. Finally, cardiac output is easily determined by using pulmonary artery catheter thermodilution techniques. For these reasons, the use of a pulmonary artery rather than a central venous catheter should be considered if pulmonary hypertension and/or cor pulmonale and coronary artery disease are present, especially if extensive perioperative fluid shifts or blood loss is anticipated.

Special Pulmonary Vascular Monitoring Considerations Related to Thoracotomy in the Lateral Decubitus Position

Pulmonary artery catheters usually (in >90% of cases) float to and locate in the right lung. [148] Consequently, during a right thoracotomy (left lateral decubitus position), the pulmonary artery catheter will be in the nondependent lung and therefore either in a collapsed lung if one-lung ventilation is used or possibly in a zone 1 or 2 region of the lung if large tidal volume two-lung ventilation is used. Conversely, when a left thoracotomy is performed (patient in the right lateral decubitus position), the pulmonary artery catheter will be in the dependent lung and will probably be in a zone 3 region. Thus, it is theoretically possible that the pulmonary artery catheter might function differently or yield different pulmonary vascular pressure and cardiac output data during right versus left thoracotomies and during two-lung versus one-lung ventilation.

Indeed, with the pulmonary artery catheter tip located in the right lung, the cardiac output is lower during right thoracotomy with one-lung ventilation (right lung collapsed) than during left thoracotomy with one-lung ventilation (left lung collapsed) in patients who were otherwise similar [149] (Fig. 48-5 (Figure Not Available) A). Consequently, it is possible that when the pulmonary artery catheter is located in the collapsed lung, where blood flow patterns may be distorted or the function of the thermistor interfered with (so that it is not free in the lumen of the vessel), the measured output is indeed lower. This hypothesis is supported by the concurrent finding that continuously measured Sv_{O_2} is also decreased during right thoracotomies as compared with left thoracotomies when the pulmonary artery catheter is located in the collapsed nondependent lung. The decrease in Sv_{O_2} may have been caused by stagnant blood flow and therefore not truly representative of whole-patient Sv_{O_2}. [149] When the nondependent lung is ventilated with varying levels of PEEP (in contrast to nondependent lung collapse), there is no difference in the cardiac output measured simultaneously from thermistors located in the nondependent and dependent lungs. [150] This finding implies that when the pulmonary artery catheter tip is in the nondependent lung and the nondependent lung is ventilated, blood flow to the nondependent lung is undistorted and/or there is no interference with the function of the thermistor.

When the pulmonary artery catheter is in the nondependent lung and the nondependent lung is ventilated with large tidal volume, PEEP, or CPAP, the wedge pressure may not reflect left atrial pressure (Pla) [151] (Fig. 48-5 (Figure Not Available) B). When the pulmonary artery catheter is in the dependent lung and presumably in the zone 3 region, wedge pressure should accurately reflect Pla, even when PEEP is applied to the dependent lung. [151]

In summary, the lateral decubitus position is important with regard to pulmonary artery catheter monitoring in three situations. First, when the nondependent lung is collapsed and the catheter is in the nondependent lung, the measured cardiac output and mixed venous blood P_{O_2} (Pv_{O_2}) may be decreased compared with more normal conditions or the "real" value. Second, when the nondependent lung is ventilated with PEEP and the catheter is in the nondependent lung, Ppaw may not equal Pla. Third, when the catheter is in the dependent lung, Ppaw will be a faithful index of Pla, even if PEEP is used.

Finally, after pneumonectomy, inflation of the balloon of the pulmonary artery catheter to obtain Ppaw can result in considerable occlusion of the remaining cross-sectional area of the pulmonary circulation. This occlusion acutely decreases the preload on the left ventricle and increases the right ventricular afterload, resulting in reduced cardiac output and reduced Pla. Although the Ppaw under these circumstances still accurately reflects the Pla, both these values have been

artificially lowered by the blocked pulmonary circulation; hence, they result in a falsely low Ppaw reading. [152] This falsely low value for the left ventricular filling pressure is misleading and may result in fluid management that contributes to the development of pulmonary edema and to the excessively high mortality reported in postpneumonectomy patients. Advancing the catheter carefully without inflating the balloon and wedging it into a smaller peripheral vessel can minimize the reduction in the cross-sectional area of the pulmonary vasculature. Thus, a more accurate value for Ppaw, reflecting the true Pla, can be obtained.

Choice of Anesthesia and Arterial Oxygenation During One-Lung Ventilation

Effect of Anesthetics on Hypoxic Pulmonary Vasoconstriction

Thoracic surgery may be greatly facilitated by causing selective atelectasis of the lung being operated on (one-lung

Figure 48-5 (Figure Not Available) Conditions during thoracotomy in the lateral decubitus position when pulmonary artery catheter data may be inaccurate. (A) During right thoracotomy with a pulmonary artery (PA) catheter located in the collapsed right lung (one-lung ventilation [1 LV]), the cardiac output (CO) may be lower than when the right lung is ventilated. The thermistor in the collapsed lung may be exposed to abnormal flow patterns or vascular wall interference. (B) When the PA catheter is in the nondependent lung and the nondependent lung is exposed to CPAP or PEEP, the pulmonary artery wedge pressure (P_{paw}) may be inaccurate. Nondependent lung CPAP or PEEP may cause zone 1 conditions in the nondependent lung. The P_{paw} is probably always reasonably accurate when the PA catheter is in the dependent lung, even if the dependent lung is exposed to PEEP. *(From Benumof [604])*

ventilation/anesthesia conditions). The normal response of the pulmonary vasculature to atelectasis is an increase in PVR (in just the atelectatic lung). The mechanism of the increase in PVR is thought to be due almost entirely to hypoxic pulmonary vasoconstriction (HPV). [153] [154] [155] The selective increase in atelectatic lung PVR diverts blood flow from the atelectatic lung toward the remaining normoxic or hyperoxic ventilated lung. Figure 48-6 shows the theoretically expected effect of HPV on Pa_{O_2} as the amount of lung that is made hypoxic increases. When the percentage of lung that is hypoxic is between 30 and 70 percent, which encompasses the one-lung ventilation/anesthesia condition, there is a large difference between the Pa_{O_2} expected with a normal amount of HPV and that when there is no HPV. In fact, in this range of hypoxic lung, HPV increases the Pa_{O_2} from levels that might cause arrhythmias to much higher and safer values. Thus, HPV is an autoregulatory mechanism that protects the Pa_{O_2} by decreasing the amount of shunt flow that can occur through hypoxic lung.

General anesthesia with controlled ventilation is the safest method of anesthetizing patients for the vast majority of elective thoracic procedures. Inhibition of HPV in the

Figure 48-6 Effect of hypoxic pulmonary vesoconstriction (HPV) on PaO_2. As the amount of lung that is made hypoxic is increased (x axis), the arterial oxygen tension (Pa_{O_2}) decreases (y axis). In the range of 30 to 70 percent of hypoxic lung, the normal expected amount of HPV increases Pa_{O_2} from arrhythmogenic levels to much higher and safer levels. Normal cardiac output, hemoglobin concentration, and mixed venous oxygen tension (PvO_2) are assumed. *(Data from Marshall and Marshall [205])*

TABLE 48-8 -- Effect of Halothane on Hypoxic Pulmonary Vasoconstriction in Various Experimental Preparations

	EXPERIMENTAL PREPARATION	SPECIES	REGIONAL (R) VS. WHOLE (W) LUNG HYPOXIA	DOSE (CONVERTED TO MAC)	EFFECT ONHPV/MAGNITUDE OF CHANGE*	REFERENCE
In vitro:	Vessel strips	Rabbit	W	1.2-2.4	/DR-to ?	[156]
	Heart-lung	Rat	W	1.3-2.1	/D-to 100%	[157]
	Heart-lung	Rat	W	1-3	/DR-to 100%	[158]
	Heart-lung	Rat	W	2	100%	[159]
	Heart-lung	Rat	W	0-2	/DR-to 90%	[160]
	Heart-lung	Rat	W	2-4	/DR-to 90%	[155]
	Lung	Cat	W	0.5-2.5	/DR-to 95%	[161]
	Lung	Rat	W	0.5	150%	[162]
In vivo:	Not intact, pump perfused	Cat	W	0.5	/50%	[163]
		Cat	W	1-3	/DR-to 60%	[164]
		Dog	R	0.5	/100%	[165]
		Dog	R	2.0	/100%	[166]
		Dog	W	1.5	/Moderate	[167]
		Dog	W	0.5-1	Slight HPV/slight	[168]
		Dog	R	to 1.7	Slight	[169]
In vivo:	Intact, perfused normally	Dog	R	1	Slight	[170]
		Dog	R	0.5-1.5	0	[171]
		Dog	R	1-3	Slight or 0	[172]
		Dog	R	0-2	Slight	[173]
		Goat	W	1	/90%	[174]

Human	Human	R	0.5-2.0	/20-30% ?	[175]
	Human	R	1.0	0	[176]
	Human	R	1.0	0	[177]

Abbreviations and symbols: HPV, hypoxic pulmonary vasoconstriction; MAC, minimum alveolar concentration;
, decrease;
, increase;
/DR-to %, HPV was progressively decreased to the maximum shown in column 5 over the concentration range shown in column 4.

nonventilated nondependent lung by the anesthetic should be prevented. All the inhaled and many of the injectable anesthetics have been studied with regard to their effect on HPV; halothane has been studied most extensively (Table 48-8) . [156] [157] [158] [159] [160] [161] [162] [163] [164] [165] [166] [167] [168] [169] [170] [171] [172] [173] [174] [175] [176] [177] The experimental preparations may be divided into four basic categories: (1) *in vitro;* (2) *in vivo*-not intact (pumped perfused lungs, no systemic circulation or neural function); (3) *in vivo*-intact (normally perfused lungs, normal systemic circulation); and (4) humans (volunteers or patients). It appears from this breakdown of experimental preparations that inhibition of HPV by halothane is a universal finding in the *in vitro* and *in vivo*-not intact preparations. However, in the more normal or physiologic *in vivo*-intact and human studies, halothane has caused no or only a very slight decrease in HPV response. Thus, it appears that a fundamental property of halothane is its inhibition of HPV in experimental preparations that can be controlled for other physiologic influences (e.g., pulmonary vascular pressure, cardiac output, mixed venous oxygen tension, carbon dioxide level, temperature) that can have an effect on the HPV response. In the more biologically complex *in vivo*-intact models, other factors that greatly diminish the inhibitory effect of halothane on HPV seem to be involved. Important methodologic differences between the *in vitro* and *in vivo*-not intact preparations and the *in vivo*-intact and human models that could account for the observed differences in halothane effect on HPV are the presence (or absence) of perfusion pulsations; perfusion fluid composition; size of perfusion circuit [171] ; baroreceptor influences, absence of bronchial blood flow (which abolishes all central and autonomic nervous activity in the lung) [178] ; chemical influences (e.g., pH, P_{O_2}); humoral influences (e.g., histamine and prostaglandin release from body tissues); lymph flow influences; and, very importantly, unaccounted for or uncontrolled changes in physiologic variables (e.g., cardiac output, Pv_{O_2} , and pulmonary vascular pressures) that might have directionally opposite effects on HPV, and use of different species. [179] [180] [181]

Ether has been the next most studied drug, and it appears that the quantitative effect of ether on HPV is also dependent on the type of experimental preparation used. Thus, the *in vitro* and *in vivc*-not intact models show much more inhibition of HPV by ether than the *in vivo*-intact and human models [155] [157] [158] [161] [164] [182] [183] (Table 48-9) . Although the number of studies involving halogenated drugs other than halothane, namely isoflurane, [160] [172] [173] [177] [184] [185] [186] [187] [188] [189] [190] [191] enflurane, [155] [160] [192] [193] [194] methoxyflurane, [156] [157] [158] [195] [196] fluroxene, [172] [173] and trichloroethylene [161] has been too small to permit recognition of an experimental preparation result pattern, most of these anesthetics have demonstrated inhibition of HPV (at least in the *in vitro* models) (see Table 48-9) . Nitrous oxide seems to cause a small, somewhat consistent inhibition of HPV [158] [168] [172] [173] [197] [198] [199] (see Table 48-9) . None of the injectable anesthetics studied to date have an effect on HPV [157] [158] [169] [172] [194] [200] [201] [202] [203] [204] [205] (see Table 48-9) .

To summarize previous animal studies, it appears that a fundamental property of inhaled anesthetics is to decrease HPV. However, in intact animal preparations some biologic or physiologic property seems to remove or greatly lessen the inhibitory effect of anesthetic drugs on HPV. It may be

TABLE 48-9 -- Effect of Ether, Isoflurane, Enflurane, Methoxyflurane, Fluroxene, Trichloroethylene, Nitrous Oxide, and Injectable Anesthetics on Hypoxic Pulmonary Vasoconstriction

ANESTHETIC DRUG	EXPERIMENTAL PREPARATION		SPECIES	REGIONAL (R) VS.WHOLE (W) LUNG HYPOXIA	DOSE (CONVERTED TO MAC)	EFFECT ON HPV/MAGNITUDE OF CHANGE	REFERENCE
Ether	*In vitro:*	Heart-lung	Rat	W	0.5-1.0	/DR-to 100%	[157]
		Heart-lung	Rat	W	1-2	/DR-to 100%	[158]
		Heart-lung	Rat	W	4-6	60 + 70%	[155]
		Lung	Cat	W	0.5-5.0	90 - 95%	[161]
		Lung	Cat	W	1	85%	[182]
	In vivo:	Not intact, pump perfused	Cat	W	2.5-5.0	/DR-to 95%	[164]
	In vivo:	Intact, normally perfused	Dog	R	1.5-3.0	/55%	[183]
		Human	Human	R	1-2	/33%	[174]
Isoflurane	*In vitro:*	Not intact, pump perfused	Rat	W	0.2	/DR-to 90%	[160]
	In vivo:	Not intact, pump perfused	Dog	R	0-2	0	[185]
	In vivo:	Intact, normally perfused	Dog	R	1-3	/DR-to 60%	[172]
			Dog	R	1-2	/DR-to 50%	[173]
			Dog	R	1-2	0	[184]
			Dog	R	0-2.4	/DR-to 50%	[186]
			Dog	R	1.3	0	[187]
			Dog	W	1.0	0	[188]
			Rabbit	R	1.2	0	[189]
		Human	Human	R	1.0-1.5	0	[190]
			Human	R	1.0	0	[177]
			Human	R	1.0	0	[191]
Enflurane	*In vitro:*	Heart-lung	Rat	W	0-2	/DR-to 90%	[160]
		Heart-Lung	Rat	W	1-3	/60%	[155]

		Heart-lung	Rat		W	1-3	/DR-to 100%	[192]
		Human	Human		R	1.2	0	[193]
Methoxyflurane	*In vitro:*	Vessel strips	Rabbit	W		1-5	Variable	[156]
		Heart-lung	Rat		W	0.3-0.5	/DR-to 100%	[157]
		Heart-lung	Rat		W	0.3-1.3	/DR-to 50%	[158]
		Lung	Cat		W	1-10	/DR-to 100%	[195]
	In vivo:	Intact, normally perfused	Dog		R	3	0	[196]
Fluroxene	*In vivo:*	Intact, normally perfused	Dog		R	1-3	/DR-to 80%	[172]
			Dog		R	1-2	/DR-to 55%	[173]
Trichloroethylene	*In vitro:*	Lung	Cat		W	0.5-2.5	/DR-to 90%	[161]
N_2O	*In vitro:*	Heart-lung	Rat		W	1.4	0	[158]
	In vivo:	Not intact, pump perfused	Cat		W	0.1-0.3	/DR-to 50%	[197]
	In vivo:	Intact, normally perfused	Dog		W	0.3	/Moderate	[168]
			Dog		R	0.6	/30%	[172]
			Dog	R		0.3	/10%	[173]
			Dog		R	0.5	/40%	[198]
			Dog		W	0.6	/Slight (10%)	[199]
Injectable anesthetics	*In vitro:*	Heart-lung	Rat		W	*	0	[157]
		Heart-lung	Rat		W	*	0	[158]
		Heart-lung	Rat		W	*	0	[200]
		Lung	Rabbit		W	*	0	[201]
	In vivo:	Not intact, pump perfused	Cat		W	*	0	[202]
			Dog		R	*	0	[202]
	In vivo:	Intact, normally perfused	Dog		R	*	0	[169]
			Dog		R	*	0	[172]
			Dog		W	*	0	[203]
	Human		Human		R	*	0	[204]
			Human		R	*	0	[205]

Abbreviations and symbols: HPV, hypoxic pulmonary vasoconstriction; MAC, minimum alveolar concentration;
, decrease;
, increase;
/DR-to %, HPV progressively decreased to the maximum shown in column 6 over the concentration range shown in column 5.

* Drugs used in these experiments were fentanyl, propofol, meperidine, morphine, thiopental, pentobarbital, hexobarbital, droperidol, diazepam, chlorpromazine, ketamine, pentazocine, lidocaine, buprenorphine. For doses and blood levels see references.

that the cause(s) of the difference in effect of anesthetic drugs on regional HPV from preparation to preparation, anesthetic to anesthetic, and species to species (see later) are closely related to the fundamental mechanism of HPV, which is still unknown.

Effect of Anesthetics on Arterial Oxygenation During One-Lung Ventilation

An often-made extrapolation of the much more numerous *in vitro* and *in vivo*-not intact HPV studies is that anesthetic drugs might impair arterial oxygenation during one-lung anesthesia by inhibiting HPV in the nonventilated lung. One of the previously cited studies on the effect of isoflurane on regional canine HPV was especially well controlled and showed that when all nonanesthetic drug variables that might change regional HPV are kept constant, isoflurane inhibits single-lung HPV in a dose-dependent manner. [186] Additionally, the study is valuable because the authors offer the reader an easily comprehensible quantitative summary of the relationship between dose of isoflurane administered and degree of inhibition of the single-lung canine HPV response. If the summary can be extrapolated or applied to the clinical one-lung ventilation situation (at least as an approximation), insights can be gained into what might be expected with regard to arterial oxygenation when such patients are anesthetized with isoflurane. To put this insight into clinical focus, it is necessary first to understand what should happen to blood flow, shunt flow, and arterial oxygenation as a function of a normal amount of HPV when two-lung ventilation is changed to one-lung ventilation in the lateral decubitus position (LDP). Once the stable one-lung ventilation condition has been described, it is possible, by using the data from the previously mentioned study, to see how isoflurane administration would affect the one-lung ventilation blood flow distribution, shunt flow, and arterial oxygen tension (Pa_{O_2}).

Two-Lung Ventilation: Blood Flow Distribution

Gravity causes a vertical gradient in the distribution of pulmonary blood flow in the LDP for the same reason that it does in the upright position. Consequently, blood flow to the dependent lung is significantly greater than blood flow tothe nondependent lung. When the right lung is nondependent, it should receive approximately 45 percent of total blood flow as opposed to the 55 percent that it received in the upright and supine positions. When the left lung is nondependent, it should receive approximately 35 percent of total blood flow as opposed to the 45 percent that it receivedin the upright and supine positions (closed-chest data with normal pulmonary

artery pressure). [206] [207] [208] If these blood flow distributions are combined (both the right and left lungs being nondependent an equal number of times), average two-lung ventilation blood flow distribution in the lateral decubitus position would consist of 40 percent of total blood flow perfusing the nondependent lung and 60 percent of total blood flow perfusing the dependent lung (Fig. 48-7 (Figure Not Available) , left-hand panel).

One-Lung Ventilation: Blood Flow Distribution, Shunt Flow, and Arterial Oxygen Tension

When the nondependent lung is nonventilated (made at-electatic), HPV in this lung will increase its PVR and de-crease its blood flow. In the absence of any confounding or inhibiting factors to the HPV response, a single-lung HPV response should decrease the blood flow to that lung by 50 percent. [209] Consequently, the nondependent lung should be able to reduce its blood flow from 40 to 20 percent of total blood flow, and the nondependent/dependent lung blood flow ratio during one-lung ventilation should be 20:80 (see Fig. 48-7 (Figure Not Available) , middle panel).

Figure 48-7 (Figure Not Available) Effect of 1 MAC isoflurane anesthesia on shunt during one-lung ventilation (1LV) of normal lungs. This diagram shows that for two-lung ventilation the ratio of the percentages of blood flow to the nondependent and dependent lungs is 40:60 (left-hand side). When two-lung ventilation is converted to one-lung ventilation (as indicated by atelectasis of the nondependent lung), the HPV response decreases the blood flow to the nondependent lung by 50 percent, so that the nondependent/dependent lung blood flow ratio is now 20:80 (middle). According to the data of Domino et al [186] administration of 1 MAC isoflurane anesthesia should cause a 21 percent decrease in the HPV response, which would decrease the blood flow reduction from 50 to 40 percent. Consequently, the nondependent/dependent lung blood flow ratio would now become 24:76, representing a 4 percent increase in the total shunt across the lungs (right-hand side). *(From Benumof [603])*

All the blood flow to the nonventilated nondependent lung is shunt flow, and therefore one-lung ventilation creates an obligatory right-to-left transpulmonary shunt flow that was not present during two-lung ventilation. If no shunt existed during two-lung ventilation (ignoring the normal 1-3% shunt flow due to the bronchial, pleural, and thebesian circulations), we would expect the ideal total shunt flow during one-lung ventilation (i.e., with intact HPV) to be 20 percent of total blood flow. With a normal hemodynamic and metabolic state, the Pa O_2 should be approximately 280 mm Hg. [210] Other much more complicated models have been constructed to describe what to expect in terms of shunt during one-lung ventilation when varying degrees of shunt exist during two-lung ventilation. [211]

Effect of Isoflurane on One-Lung Ventilation Blood Flow Distribution, Shunt Flow, and Arterial Oxygen Tension

Domino et al [186] found the percentage inhibition of regional HPV response to equal 22.8 (percentage alveolar isoflurane) minus 5.3 (see Fig. 48-7 (Figure Not Available) , top equation). [186] The top equation and right-hand panel of Fig. 52-7 (Figure Not Available) show that isoflurane anesthesia at one minimum alveolar concentration unit (1 MAC) would inhibit the nondependent lung HPV response by approximately 21 percent, which would decrease this response from a 50 to 40 percent blood flow reduction in this lung; this in turn would increase nondependent lung blood flow from 20 to 24 percent of total blood flow, causing shunt to increase by 4 percent of the cardiac output and Pa O_2 to decrease a moderate amount to 205 mm Hg (F_{IO_2} = 1.0). A decrease in Pa O_2 and an increase in shunt of this magnitude are small and may not be detectable given the usual accuracy of clinical methodology. In fact, in clinical one-lung ventilation studies involving intravenously anesthetized patients with this level of shunting, administration of 1 MAC isoflurane (and halothane) anesthesia during stable one-lung ventilation conditions causes no detectable decrease in Pa O_2 . [177] [212] In one of these clinical studies, [212] stable one-lung ventilation conditions in the lateral decubitus position were established in patients who were anesthetized with only intravenous drugs. While stable one-lung ventilation was maintained, inhaled anesthetics were administered (halothane and isoflurane end-tidal concentrations were greater than 1 MAC for at least 15 minutes) and then discontinued (halothane and isoflurane end-tidal concentrations decreased to near zero). In the other study, [177] steady-state one-lung ventilation conditions in the LDP were established in patients who were anesthetized with only inhaled drugs (halothane and isoflurane end-tidal concentrations were greater than 1 MAC for more than 40 minutes). While one-lung ventilation was continued, inhaled anesthesia was then discontinued and intravenous anesthesia administered (halothane and isoflurane end-tidal concentrations decreased to near 0). There was no significant difference in Pa O_2 during inhaled anesthesia with either halothane or isoflurane as compared with intravenous anesthesia during one-lung ventilation in either of the two experimental sequences. In addition, there were no significant changes in physiologic variables, such as cardiac output, PVR, and Pv O_2 , that might secondarily alter nondependent lung HPV. Thus, irrespective of whether inhaled anesthesia is administered before or after intravenous anesthesia during one-lung ventilation, inhaled anesthesia does not further impair arterial oxygenation. These findings are consistent with the interpretation that 1 MAC halothane or isoflurane in patients with a moderate level of shunting does not inhibit HPV enough to cause a significant decrease in Pa O_2 during one-lung ventilation in the LDP. Almost identical results have been obtained during one-lung ventilation with nitrogen (while the other lung was ventilated with 100 percent oxygen) of volunteers who were alternately anesthetized with isoflurane and intravenous drugs [191] and enflurane and intravenous drugs. [193]

Recommended Anesthesia Induction and Maintenance Drugs and Techniques

Summary of Advantages of Anesthetic Drugs

Inhaled Anesthetics.

General anesthesia with controlled ventilation (Chs. 3 - 7) is the safest method of anesthetizing patients for the vast majority of elective thoracic procedures. Although a variety of general anesthesia techniques can be used, the volatile halogenated anesthetic drugs are good choices for several reasons. First, the halogenated drugs have a salutary effect on airway irritability. The mechanism of this action is controversial, but as previously discussed, there is evidence that these drugs can block specific forms of bronchoconstriction, [213] [214] as well as having a nonspecific bronchodilating effect related to the depth of anesthesia. [215] Obtundation of airway reflexes in patients who have reactive airways (i.e., smokers) and who may have their airways directly manipulated by the surgeon is a highly desirable property of the general anesthesia produced by these drugs. Second, the use of volatile halogenated drugs allows delivery of a high inspired oxygen concentration without loss of anesthesia. Although a nitrous oxide-oxygen-narcotic-relaxant anesthesia technique can be used, nitrous oxide necessitates a significant decrease in F_{IO_2} and increases the chance of developing hypoxemia (especially if one-lung ventilation is used). [216] Unless very high doses of narcotics are used, airway reflexes and reactivity may remain at a high level. Third, because the volatile halogenated drugs can be rapidly eliminated, concern about postoperative hypoventilation in extubated patients may be diminished. Relatively high doses of intravenous anesthetics, such as narcotics, ketamine, and barbiturates, may cause the patient to require a period of postoperative ventilation. Fourth, in the usual clinical doses (near 1 MAC), the halogenated anesthetic drugs provide a reasonable degree of cardiovascular stability. This may be of particular importance in patients who have a history of smoking and therefore a high incidence of coronary artery disease and systemic hypertension. [217] [218] Fifth, the halogenated drugs do not appear to decrease Pa O_2 any more than intravenous anesthetics during one-lung ventilation (see the following section). [177] [212]

Intravenous Anesthetics.

The narcotics, especially fentanyl, have a number of desirable properties (Chs. 8 - 11) that could be used to advantage for patients undergoing thoracic surgery. First, fentanyl has no significant adverse hemodynamic

effects and therefore is a useful drug in patients who have coronary artery disease. Second, if significant blood levels exist at the end of surgery, the narcotics can allow an intubated patient to have a smooth transition from surgery into the postoperative period. Third, the narcotics, if used in moderate dosage, diminish the amount of volatile halogenated drug anesthesia required to achieve surgical levels of anesthesia. Fourth, high doses of narcotics or moderate doses in conjunction with halogenated drugs allow the use of a high F_{IO_2} without loss of anesthesia. Fifth, the narcotics are thought not to diminish regional HPV and, therefore, should permit optimal oxygenation during one-lung ventilation.

Ketamine, in combination with nitrous oxide and a muscle relaxant, has also been used for anesthesia for thoracic surgery. [219] Although we do not ordinarily use ketamine for elective thoracic procedures, the drug is useful for induction of general anesthesia in critically ill patients undergoing emergency thoracic surgery for several reasons. First, ketamine has sympathomimetic properties [220] that are highly desirable because many emergency thoracic procedures are associated with hypovolemia (gunshot and stab wounds of the chest, blunt trauma, and massive hemoptysis). However, it should be remembered that ketamine depresses cardiovascular function (systemic blood pressure, cardiac contractility) if the degree of hypovolemia is severe and the patient is sympathetically exhausted. Second, ketamine has a rapid onset of action and can be used safely, along with cricoid pressure, to induce anesthesia in patients with full stomachs. Third, ketamine may

reduce bronchospasm in asthmatic patients [221] ; the clinical extrapolation of this effect to thoracic surgical patients is uncertain but seemingly reasonable at this time. Fourth, ketamine does not impair arterial oxygenation during one-lung ventilation (perhaps because of its lack of effect on HPV). [204]

Recommended Anesthetic Drugs and Techniques

It should be obvious from the foregoing discussions that there are advantages and disadvantages to both inhaled and intravenous anesthetic drugs. One recent study made this point very well by examining the respiratory and cardiac differences between various anesthetic regimens (intravenous-based, inhalation-based, epidural-based) before and during one-lung ventilation. [222] The 36 patients were randomly allocated to one of the following groups: A--propofol 10 mg/kg/h, fentanyl; B--1 MAC enflurane, fentanyl; C--thoracic epidural anesthesia, 0.4 percent enflurane. Before induction of anesthesia significant differences were not found. During two-lung ventilation cardiac index was significantly decreased in the B in comparison with the C group (*P*
.01). During one-lung ventilation significant differences were not found except for an increased shunt fraction (Q_S/Q_T) in group B (A versus B, *P*
.05; B versus C, *P*
.05; A versus C, not significant). Since Q_S/Q_T was significantly increased and hypoxemia occurred with regimen B, regimen A or C might be preferred in patients at high risk for hypoxia or in situations where the application of CPAP to the nondependent lung is not possible. Cardiac index was best maintained in group C. Regimen C might be of value in patients at high risk for poor perfusion, taking into account both the possible complications of the epidural block and the reduced need for postoperative analgesic agents.

The following recommended anesthetic technique takes advantage of the desirable properties and minimizes the undesirable properties of these drugs. Thus, the halogenated drugs are used for their effect on bronchomotor tone, to allow administration of 100 percent oxygen, and to allow early extubation without decreasing hemodynamic function and arterial oxygenation; fentanyl is used to ensure hemodynamic stability without jeopardizing early extubation if desired. If it is thought that the patient will not be extubated early or if greater hemodynamic stability is desired, anesthesia consisting of more fentanyl and less halogenated drug can be used.

Induction of Anesthesia.

The patient is preoxygenated by spontaneously breathing 100 percent oxygen through an anesthesia mask that is connected to an anesthesia circle system. Fentanyl is administered intravenously until the respiratory rate is approximately 8 to 10 breaths/min. This usually corresponds to a dose of 3 to 6 mug/kg and is generally administered over several minutes. When the respiratory rate is relatively slow and deep and response to commands is becoming sluggish, a small dose of sodium thiopental (2-3 mg/kg) or ketamine (1.0-2.0 mg/kg) (if the patient is thought to have an especially reactive airway or to be minimally to moderately hypovolemic) is administered to render the patient unconscious and usually apneic. Control of the airway is then established and ventilation is begun with intermittent positive-pressure oxygen via the mask. While the patient is being ventilated with positive pressure, a concentration of 0.5 to 2.5 percent isoflurane is administered. The higher isoflurane concentration is used initially for a short period of time (overpressure, 1-2 minutes); as the patient demonstrates signs of deepening anesthesia, the inspired isoflurane concentration is decreased. In view of the fact that general anesthetics significantly decrease the ventilatory response to carbon dioxide (to a much greater degree in patients with mechanical ventilatory impairment than in normal patients), patients are not allowed to breathe spontaneously until the end of the procedure; alarming degrees of hypercapnia have been observed in similar circumstances when spontaneous ventilation was allowed. [223]

Early during the period of positive-pressure ventilation with isoflurane, paralysis is induced with a nondepolarizing muscle relaxant. The development of full paralysis is noted with a neuromuscular blockade monitor. During the period of deepening isoflurane anesthesia and paralysis, blood pressure is supported with an infusion of approximately 10 mL/kg crystalloid followed by small doses of vasopressors if needed. When the patient has been judged to have been adequately (surgical stage) anesthetized (as ascertained by changes in blood pressure, heart rate, and eye signs [the eyes should be central, conjugate, fixed, staring, without tears, and with nondilated pupils]) and paralyzed in this manner, 1 mg/kg lidocaine is administered intravenously, laryngoscopy is performed, the tracheobronchial tree is sprayed with a laryngotracheobronchial topical anesthesia spray system, and the trachea is intubated with a doublelumen

tube. The intravenous and intratracheal lidocaine should diminish both airway and cardiovascular response to endotracheal intubation. [224] The patient is then ventilated with maintenance doses of isoflurane and given maintenance doses of narcotics and relaxants. Use of maintenance paralysis decreases isoflurane requirements, possibly allowing for a more rapid emergence from anesthesia.

Maintenance of Anesthesia.

Anesthesia is maintained with both isoflurane (concentration approximately 0.5-1.0 MAC) and narcotics. Isoflurane is used primarily if the patient is thought to have a reasonable chance of being extubated within the first couple of hours postoperatively. Narcotics (fentanyl) are primarily used if the patient is thought not to have a reasonable chance of being extubated in the immediate postoperative period and to require a significant period of postoperative ventilation. Relaxants are administered in small doses to keep the level of neuromuscular blockade, as judged by a neuromuscular blockade monitor, near the 90 percent paralysis level. If there is a reasonable chance of extubating the trachea in the first postoperative hour, the patient is turned supine, the double-lumen tube changed to a single-lumen tube, paralysis reversed, and spontaneous ventilation allowed to recur. Fentanyl is administered in extremely small increments (0.3 mug/kg) while the patient is breathing spontaneously. The goal of the fentanyl administration is to have the patient breathing relatively slowly (approximately 10 to 12 breaths/min) and deeply when surgery is completed. The presence of a moderate narcotic base allows the patient to be returned to the recovery room for a short period of mechanical ventilatory support (if needed) and weaned and extubated in a relatively smooth manner.

THE INTRAOPERATIVE PERIOD - continued

Physiology of Spontaneous Ventilation with an Open Chest

Mediastinal Shift

An examination of the physiology of the open chest during spontaneous ventilation reveals why controlled positive-pressure ventilation is the only practical way to provide adequate gas exchange during thoracotomy. In the spontaneously breathing closed-chest patient in the LDP, gravity causes the pleural pressure in the dependent hemithorax to be less negative than in the nondependent hemithorax, but there is still negative pressure in each hemithorax on each side of the mediastinum. In addition, the weight of the mediastinum causes some compression of the lower lung, contributing to the pleural pressure gradient. With the nondependent hemithorax open, atmospheric pressure in that cavity exceeds the negative pleural pressure in the dependent hemithorax; this imbalance of pressure on the two sides of the mediastinum causes a further downward displacement of the mediastinum into the dependent thorax. During inspiration the caudad movement of the dependent-lung diaphragm increases the negative pressure in the dependent lung and causes a still further displacement of the mediastinum into the dependent hemithorax. During expiration, as the dependent-lung diaphragm moves cephalad, the pressure in the dependent hemithorax becomes relatively positive, and the mediastinum is pushed upward out of the dependent hemithorax (Fig. 48-8) (Figure Not Available) . Thus, the tidal volume in the dependent lung is decreased by an amount equal to the inspiratory displacement caused by mediastinal movement. This phenomenon is called *mediastinal shift* and is one mechanism that results in impaired ventilation in the open-chested,

Figure 48-8 (Figure Not Available) Schematic representation of mediastinal shift and paradoxical respiration in the spontaneously ventilating patient with an open chest who is placed in the lateral decubitus position. The open chest is always exposed to atmospheric pressure (+). During inspiration, negative pressure (-) in the intact hemithorax causes the mediastinum to move downward (mediastinal shift). In addition, during inspiration, movement of gas from the nondependent lung in the open hemithorax into the dependent lung in the closed hemithorax and movement of air from the environment into the open hemithorax causes the lung in the open hemithorax to collapse (paradoxic respiration). During expiration, relative positive (+) in the closed hemithorax causes the mediastinum to move upward (mediastinal shift). In addition, during expiration, the gas moves from the dependent lung to the nondependent lung and from the open hemithorax to the environment; consequently, the nondependent lung expands during expiration (paradoxic respiration). *(From Benumof [604])*

spontaneously breathing patient in the LDP. The mediastinal shift can also cause circulatory changes (decreased venous return) and reflexes (sympathetic activation) that result in a clinical picture similar to shock: the patient is hypotensive, pale, and cold, with dilated pupils. Local anesthetic infiltration of the pulmonary plexus at the hilum and the vagus nerve can diminish these reflexes. More practically, controlled positive-pressure ventilation abolishes these ventilatory and circulatory changes associated with mediastinal shift.

Paradoxic Respiration

When a pleural cavity is exposed to atmospheric pressure, the lung is no longer held open by negative intrapleural pressure, and it tends to collapse because of unopposed elastic recoil. [225] Thus, the lung in an open chest is at least partially collapsed. It has long been observed during spontaneous ventilation with an open hemithorax that lung collapse is accentuated during inspiration, and, conversely, the lung expands during expiration. This reversal of lung movement during respiration with an open chest has been termed *paradoxic respiration.* The mechanism of paradoxic respiration is similar to that of mediastinal shift. During inspiration, the descent of the diaphragm on the side of the open hemithorax causes air from the environment to enter the pleural cavity on that side through the thoracotomy opening and to fill the space around the exposed lung. The descent of the hemidiaphragm on the closed-chest side causes gas to enter the closed-chest lung in the normal manner. However, gas also enters the closed-chest lung (which has a relatively negative pressure) from the open-chest lung (which remains at atmospheric pressure); this results in further reduction in the size of the open-chest lung during inspiration. During expiration the reverse occurs, with the collapsed, open-chest lung filling from the intact lung and air moving back out of the exposed hemithorax through the thoracotomy incision. The phenomenon of paradoxic respiration is illustrated in Figure 48-8 (Figure Not Available) . Paradoxic breathing is increased by a large thoracotomy and by increased airway resistance in the intact lung. Paradoxic respiration may be prevented either by manual collapse of the open-chest lung or, more commonly, by controlled positive-pressure ventilation.

Physiology of the Lateral Decubitus Position and the Open Chest During Controlled Two-Lung Ventilation: Distribution of Perfusion and Ventilation

Awake, Closed-Chest, Lateral Decubitus Position

Gravity causes a vertical gradient in the distribution of pulmonary blood flow in the LDP for the same reason that it does in the upright position (Ch. 15) . Because the vertical hydrostatic gradient is less in the LDP than in the upright position, there is ordinarily less zone 1 blood flow (in the nondependent lung) in the former than in the latter position. Nevertheless, blood flow to the dependent lung is still significantly greater than that to the nondependent lung (Fig. 48-9) (Figure Not Available) . Thus, when the right lung is nondependent, it should receive approximately 45 percent of total blood flow as opposed to the 55 percent that it receives in the upright and supine positions. When the left lung is nondependent, it should receive approximately 35 percent of total blood flow, as opposed to the 45 percent that it receives in the upright and supine positions. [206] [207]

Because gravity also causes a vertical gradient in pleural pressure (Ppl) in the LDP, ventilation is relatively increased in the dependent as compared with the nondependent lung (Fig. 48-10) (Figure Not Available) . In addition, in the LDP the dome of the lower diaphragm is pushed higher into the chest than the dome of the upper diaphragm; therefore, the lower diaphragm is more sharply curved than the upper diaphragm. As a result, the lower diaphragm is able to contract more efficiently during spontaneous respiration. Thus, in the awake patient in

Figure 48-9 (Figure Not Available) Schematic representation of the effects of gravity on the distribution of pulmonary blood flow in the lateral decubitus position. The vertical gradient in the lateral decubitus position is less than in the upright position. Consequently, there is less zone 1 and more zone 2 and 3 blood flow in the lateral decubitus position than in the upright position. Nevertheless, pulmonary blood flow increases with lung dependency and is greater in the dependent lung than in the nondependent lung. $P_{A,}$ alveolar pressure; P_{pa} , pulmonary artery pressure; P_{pv} , pulmonary venous pressure. *(From Benumof [604])*

Figure 48-10 (Figure Not Available) Awake, closed chest distribution of ventilation. (A) Pleural pressure (Ppl) in the awake upright patient is most positive in the dependent portion of the lung, and alveoli in this region are therefore most compressed and have the least volume. Pleural pressure is least positive (most negative) at the apex of the lung, and alveoli in this region are therefore least compressed and have the largest volume. When these regional differences in alveolar volume are translated over to a regional transpulmonary pressure-alveolar volume curve, the small dependent alveoli are on a steep (large-slope) portion of the curve, and the large nondependent alveoli are on a flat (small-slope) portion of the curve. In this diagram regional slope equals regional compliance. Thus, for a given and equal change in transpulmonary pressure, the dependent part of the lung receives a much larger share of the tidal volume than the nondependent part of the lung. (B) In the

lateral decubitus position gravity also causes pleural pressure gradients and therefore similarly affects the distribution of ventilation. The dependent lung lies on a relatively steep portion and the nondependent lung lies on a relatively flat portion of the pressure-volume curve. Thus, in the lateral decubitus position the dependent lung receives the majority of the tidal ventilation. V, alveolar volume; P, transpulmonary pressure. *(From Benumof [604])*

the LDP, the lower lung is normally better ventilated than the upper lung, regardless of the side on which the patient is lying, although there remains a tendency toward greater ventilation of the larger right lung. [226] Because there is greater perfusion to the lower lung, the preferential ventilation to the lower lung is matched by its increased perfusion, so that the distribution of the V/Q ratios of the two lungs is not greatly altered when the awake subject assumes the LDP. Because perfusion increases to a greater extent than ventilation with lung dependency, the V/Q ratio decreases from the nondependent to the dependent lung (just as it does in upright and supine lungs).

Anesthetized, Closed-Chest, Lateral Decubitus Position

Comparison of the awake with the anesthetized patient in the LDP (Ch. 26) reveals no difference in the distribution of pulmonary blood flow between the dependent and nondependent lungs. Thus, in the anesthetized patient, the dependent lung continues to receive relatively more perfusion than the nondependent lung. The induction of general anesthesia, however, does cause significant changes in the distribution of ventilation between the two lungs.

In the LDP, more ventilation is switched from the dependent lung in the awake subject to the nondependent lung in the anesthetized patient [227] [228] (Fig. 48-11) (Figure Not Available) . There are several interrelated reasons for this change in the relative distribution of ventilation between the nondependent and dependent lungs. First, the induction of general anesthesia usually causes a decrease in FRC, and both lungs share in the loss of lung volume. Because each lung occupies a different initial position on the pulmonary pressure-volume curve while the subject is awake, a general anesthesia-induced reduction in the FRC of each lung causes each lung to move to a lower, but still different, portion of the pressure-volume curve (see Fig. 48-11) (Figure Not Available) . The dependent lung moves from an initially steep part of the curve (with the subject awake) to a lower and flatter part of the curve (after anesthesia is induced), while the nondependent lung moves from an initially flat portion of the pressure-volume curve

Figure 48-11 (Figure Not Available) The distribution of ventilation in the patient in the lateral decubitus position when awake (A) and when anesthetized (B). The induction of anesthesia has caused a loss of lung volume in both lungs, with the nondependent lung moving from a flat, noncompliant portion to a steep, compliant portion of the pressure-volume curve and the dependent lung moving from a steep, compliant part to a flat, noncompliant part of the pressure-volume curve. Thus, the anesthetized patient in a lateral decubitus position has more of the tidal ventilation in the nondependent lung (where there is the least perfusion) and less of the tidal ventilation in the dependent lung (where there is the most perfusion). V, alveolar volume; P, transpulmonary pressure. *(From Benumof [604])*

Figure 48-12 (Figure Not Available) Schematic depiction of a patient in the lateral decubitus position, comparing the closed-chested anesthetized condition with the open-chested anesthetized and paralyzed condition. Opening the chest increases nondependent lung compliance and reinforces or maintains the larger part of the tidal ventilation going to the nondependent lung. Paralysis also reinforces or maintains the larger part of tidal ventilation going to the nondependent lung because the pressure of the abdominal contents (P_{AB}) pressing against the upper diaphragm is minimal (smaller arrow), and it is therefore easier for positive-pressure ventilation to displace this lesser resisting dome of the diaphragm. V, alveolar volume; P, transpulmonary pressure. *(From Benumof [604])*

(with the subject awake) to a lower and steeper part of the curve (after anesthesia is induced). In fact, in the LDP the ratio of nondependent to dependent lung FRC is approximately 1.5 (average values are 1,400 and 900 mL, respectively) in the adult patient. [229] [230] [231] [232] Similar findings may be expected in children. [230] Furthermore, in the LDP the compliances of the nondependent and dependent lung are 30 and 23 cm H_2O, respectively. [229] Thus, with the induction of general anesthesia, the lower lung moves to a less favorable (flat, noncompliant) portion and the upper lung to a more favorable (steep, compliant) portion of the pressure-volume curve. Second, if the anesthetized patient in the LDP is also paralyzed and mechanically ventilated, the high, curved diaphragm of the lower lung no longer confers any advantage in ventilation (as it does in the awake state), as it is no longer actively contracting. [231] [232] Third, the mediastinum rests on the lower lung and physically impedes lower lung expansion, as well as selectively decreasing lower lung FRC. Fourth, the weight of the abdominal contents pushing cephalad against the diaphragm is greatest in the dependent lung, which physically impedes lower lung expansion the most and disproportionately decreases lower lung FRC. Finally, suboptimal positioning, which fails to provide room for lower lung expansion, may considerably compress the dependent lung. Opening the nondependent hemithorax further disproportionately increases ventilation to the nondependent lung (see below).

In summary, the anesthetized patient, with or without paralysis, in the LDP and with a closed chest has a nondependent lung that is well ventilated but poorly perfused and a dependent lung that is well perfused but poorly ventilated, which results in an increased degree of V/Q mismatching. The application of PEEP to both lungs restores more of the ventilation to the lower lung. [207] Presumably, the lower lung returns to a steeper, more favorable part of the pressure-volume curve, and the upper lung resumes its original position on a flat, unfavorable portion of the curve.

Anesthetized, Open-Chest, Lateral Decubitus Position

As compared with the condition of the anesthetized, closed-chested patient in the LDP, opening the chest wall and pleural space alone does not ordinarily cause any significant alteration in the partitioning of pulmonary blood flow between the dependent and nondependent lungs; thus, the dependent lung continues to receive relatively more perfusion than the nondependent lung. Opening the chest wall and pleural space, however, does have a significant impact on the distribution of ventilation (which must now be delivered by positive pressure). The change in the distribution of ventilation may result in further V/Q mismatching [233] (Fig. 48-12) (Figure Not Available) .

If the upper lung is no longer restricted by a chest wall and the total effective compliance of that lung is equal to that of the lung parenchyma alone, it will be relatively free to expand and will consequently be overventilated (and remain underperfused). Conversely, the dependent lung may continue to be relatively noncompliant and poorly ventilated and overperfused. [206] Surgical retraction and compression of the exposed upper lung can provide a partial, although nonphysiologic, solution to this problem in that if expansion of the exposed lung is mechanically or externally restricted ventilation will be diverted to the dependent, better-perfused lung. [208]

Anesthetized, Open-Chest, Paralyzed Lateral Decubitus Position

In the open-chested anesthetized patient in the LDP, induction of paralysis alone does not cause any significant alteration in the partitioning of pulmonary blood flow between the dependent and nondependent lungs. Thus, the dependent lung continues to receive relatively more perfusion than the nondependent lung. There are, however, strong theoretical and experimental considerations indicating that paralysis might cause significant changes in the distribution of ventilation between the two lungs under these conditions.

In the supine position and the LDP, the weight of the abdominal contents pressing against the diaphragm is greatest on the dependent part of the diaphragm (posterior lung and lower lung, respectively) and least on the nondependent part of the diaphragm (anterior lung and upper lung, respectively) (see Fig. 48-12) (Figure Not Available) . In the awake, spontaneously

breathing patient, the normally present active tension in the diaphragm overcomes the weight of the abdominal contents, and the diaphragm moves the most (largest excursion) in the dependent portion and least in the nondependent portion. This is a healthy circumstance because this is another factor that maintains the greatest amount of ventilation where there is the most perfusion (dependent lung) and the least amount of ventilation where there is the least perfusion (nondependent lung). During paralysis and positive-pressure breathing, the passive and flaccid diaphragm is displaced preferentially in the nondependent area, where the resistance to passive diaphragmatic movement by the abdominal contents is least; conversely, the diaphragm is displaced minimally in the dependent portion where the resistance to passive diaphragmatic movement by the abdominal contents is greatest. [234] This is an unhealthy circumstance because the greatest amount of ventilation may occur where there is the least perfusion (nondependent lung), and the least amount of ventilation may occur where there is the most perfusion (dependent lung). [234]

Summary of Physiology of the Lateral Decubitus Position and the Open Chest

In summary (Fig. 48-13) (Figure Not Available) , the preceding section has developed the concept that the anesthetized, paralyzed patient in the LDP with an open chest may have a considerable V/Q mismatch, consisting of greater ventilation but less perfusion to the nondependent lung and less ventilation but more perfusion to the dependent lung. The blood flow distribution is mainly and simply determined by gravitational effects. The relatively good ventilation of the upper lung is caused in part by the open-chest and paralyzed conditions. The relatively poor ventilation of the dependent lung is caused in part by the loss of dependent lung volume with general anesthesia and by compression of the dependent lung by the mediastinum, abdominal contents, and suboptimal positioning effects. In addition, poor mucociliary clearance and absorption atelectasis with an increased F_{IO_2} may cause further dependent-lung volume loss. Indeed, on rare occasion the dependent lung may be massively atelectatic and edematous. [235] Consequently, two-lung ventilation under these circumstances may result in an increased alveolar-arterial oxygen tension difference [$P(A\text{-}a)_{O_2}$] and less than optimal oxygenation.

A physiologic solution to the adverse effects of anesthesia and surgery in the LDP on the distribution of ventilation and perfusion during two-lung ventilation would be selective application of PEEP to the dependent lung (via a double-lumen endotracheal tube). [236] Selective PEEP to the lower lung should increase the ventilation to this lung by moving it up to a steeper, more favorable portion of the lung pressure-volume curve. Indeed, this has been done with reasonably good success. [236] [237] A series of 22 mechanically ventilated patients (both lungs) undergoing thoracotomy in the LDP was divided into two groups. [237] Group I patients had 10 cm H_2O of PEEP applied to the dependent

Figure 48-13 (Figure Not Available) Schematic summary of ventilation-perfusion relationships in the anesthetized patient in the lateral decubitus position who has an open chest and is paralyzed and suboptimally positioned. The nondependent lung is well ventilated (as indicated by the large dashed lines) but poorly perfused (small perfusion vessel); the dependent lung is poorly ventilated (small dashed lines) but well perfused (large perfusion vessel). In addition, the dependent lung may also develop an atelectatic shunt compartment (indicated on the left side of the lower lung) because of the circumferential compression of this lung. (See text for detailed explanation.) P_{AB} , pressure of the abdominal contents. *(Modified from Benumof [604])*

lung while zero end-expiratory pressure (ZEEP) was applied to the nondependent lung. Group II (control) patients were intubated with a standard endotracheal tube, and both lungs were ventilated with ZEEP. Selective PEEP to the dependent lung in group I patients resulted in an adequate Pa_{O_2} with a lower F_{IO_2} during surgery and a smaller $P(A\text{-}a)_{O_2}$ at the end of surgery than when both lungs were ventilated with ZEEP. Thus, even if the selec-tive PEEP to the dependent lung increased dependent lung PVR and diverted some blood flow to the nondependent lung, the diverted blood flow could still participate in gas exchange with the ZEEP-ventilated nondependent lung. [238] However, it should be noted that this technique requires that the nondependent (and operative) lung be ventilated, and this may impede the performance of surgery. The physiology of one-lung ventilation and distribution of perfusion is discussed in the chapter on respiratory physiology.

One-Lung Anesthesia/Ventilation

Indications for Separation of the Two Lungs

There are several absolute and relative indications for separation of the two lungs during thoracic operations or procedures (Table 48-10) .

TABLE 48-10 -- Indications for Separation of the Two Lungs (Double-Lumen Tube Intubation) and/or One-Lung Ventilation

ABSOLUTE

1. Isolation of one lung from the other to avoid spillage or contamination
   - A. Infection
   - B. Massive hemorrhage
2. Control of the distribution of ventilation
   - A. Bronchopleural fistula
   - B. Bronchopleural cutaneous fistula
   - C. Surgical opening of a major conducting airway
   - D. Giant unilateral lung cyst or bulla
   - E. Tracheobronchial tree disruption
   - F. Life-threatening hypoxemia due to unilateral lung disease
3. Unilateral bronchopulmonary lavage
   - A. Pulmonary alveolar proteinosis

RELATIVE

1. Surgical exposure--high priority
   - A. Thoracic aortic aneurysm
   - B. Pneumonectomy
   - C. Upper lobectomy
   - D. Mediastinal exposure
   - E. Thoracoscopy
2. Surgical exposure--medium (lower) priority
   - A. Middle and lower lobectomies and subsegmental resections
   - B. Esophageal resection
   - C. Procedures on the thoracic spine
3. Postcardiopulmonary bypass status after removal of totally occluding chronic unilateral pulmonary emboli
4. Severe hypoxemia due to unilateral lung disease

Absolute Indications

Separation of the two lungs for any of the absolute indications discussed here should be considered a lifesaving maneuver because failure to separate the lungs under any of these conditions could result in a life-threatening complication or situation. There are three general absolute indications for separating the lungs (see Table 48-10) . First, separation of one lung from the other is absolutely necessary to prevent spillage of pus or blood from an infected (abscessed) lung or bleeding lung, respectively, to a noninvolved lung. Acute contamination of a lung with either blood or pus from the other lung usually results in severe massive (bilateral) atelectasis, pneumonia, and sepsis. Second, there are a number of unilateral lung problems that can prevent adequate ventilation of the noninvolved side. A large bronchopleural or bronchopleural-cutaneous fistula or a surgically opened conducting airway has such a low resistance to gas flow that a tidal inspiration delivered by positive pressure will exit via the low-resistance pathway, and it may become impossible to ventilate the other, more normal, lung adequately. A giant unilateral bulla or cyst may rupture if exposed to positive-pressure ventilation and result in a tension pneumothorax or pneumomediastinum. Very severe or life-threatening hypoxemia due to unilateral lung disease may require differential lung ventilation and PEEP. [239] Finally, positive-pressure ventilation of a lung with a tracheobronchial tree disruption can result in dissection of gas into the pulmonary interstitial space or mediastinum, causing a tension pneumomediastinum. Third, separation of the

lungs is absolutely necessary to perform unilateral bronchopulmonary lavage in patients with pulmonary alveolar proteinosis (and rarely, asthma or cystic fibrosis).

Relative Indications

There are a large number of relative indications for separation of the lungs, and they are all for the purpose of facilitating surgical exposure by collapsing the lung in the operative hemithorax. These relative indications can be divided into high-priority and low-priority categories (see Table 48-10) . Of the relative indications, repair of a thoracic aortic aneurysm usually has the highest priority because it may require exposure of the thoracic aorta as it runs the entire length of the left hemithorax. A pneumonectomy, especially if performed through a median sternotomy, [240] is greatly aided by the wide exposure of the lung hilum that is afforded by collapse of the operative lung. Similarly, an upper lobectomy, which is technically the most difficult lobectomy, and many mediastinal exposures may be made much easier by eliminating ventilation to the lung on the side of the procedure. Examination of the pleural space (thoracoscopy) and pulmonary resections through a thoracoscope are considerably aided by collapse of the ipsilateral lung. The surgical items in the medium-priority category do not routinely require collapse of the lung on the operative side but still significantly aid surgical exposure and eliminate the need for the surgeon to handle (retract, compress, pack away) the operative lung. Severe intraoperative retraction of the lung on the operated side can traumatize the operative lung and impair gas exchange both intraoperatively [241] [242] and postoperatively. [243] [244] The lower-priority items consist of middle and lower lobectomies, less extensive pulmonary resections, thoracic spinal procedures that are approached anteriorly through the chest, and esophageal surgery. However, even relatively small operations such as wedge and segmental resections benefit by double-lumen tube insertion because of the ability to alternate easily and quickly between lung collapse and inflation, which is sometimes required to better visualize lung morphology and facilitate identification and separation of planes and fissures. Additionally, the separation of the lungs after removal of totally occluding and predominantly unilateral chronic pulmonary emboli (postcardiopulmonary bypass) can be very helpful because of the possibility of massive transudation of hemorrhagic fluid across the alveolar capillary membrane in the region of the lung supplied by the previously occluded vessel (reperfusion of a previously and chronically nonperfused vascular bed). Should significant and predominantly unilateral pulmonary edema occur following thromboembolectomy with cardiopulmonary bypass, the patient should be returned to cardiopulmonary bypass and a double-lumen endotracheal tube should be inserted so that differential lung ventilation may be used. Finally, significant hypoxemia due to unilateral lung disease may be more easily treated by differential lung ventilation and PEEP. [239]

Techniques of Lung Separation

In general, three types of devices are available for providing one-lung ventilation during anesthesia: double-lumen

endotracheal tubes (DLT), bronchial blockers, and endobronchial tubes. DLTs have come to be considered the lung separation technique of choice for the majority of thoracic surgery cases and are discussed later in detail. Bronchial blockade with the Univent tube and with independently passed bronchial blockers (Fogarty embolectomy catheter) in adults is greatly increasing in use and is also described at length below. Endobronchial tubes are not often used today and are only briefly described at the end of the chapter. The primary reason that DLTs are favored over bronchial blockers or endobronchial tubes for lung separation is that they are more versatile than the other two devices. The most important DLT function not available with a bronchial blocker is independent bilateral suctioning. In addition, it is easier to apply CPAP to the nonventilated operative lung with a DLT than with a bronchial blocker, and it is also easier to rapidly convert from two-lung to one-lung ventilation and vice versa with a DLT than with a bronchial blocker. Endobronchial tubes are very limited in function and only allow one-lung ventilation.

There are two firm disadvantages (contraindications) to the use of a DLT as compared with a bronchial blocker. First, very distorted tracheobronchial tree anatomy, including exophytic and stenotic lesions, as well as tortuosity, may preclude successful correct placement or positioning of a DLT. Second, changing from a DLT to a single-lumen tube during or at the end of an operation can be expected to be a difficult and/or risky procedure on occasion. Such a situation might occur in a patient with a relatively difficult airway before operation who undergoes a long operation requiring considerable intravenous fluids; one would expect the airway to be edematous and thus a postoperative tube change more hazardous in that setting.

There are two relatively minor disadvantages to DLTs, both related to the fact that the lumina of a DLT may be narrow. First, suctioning may be more difficult down a narrow lumen, but this is usually not a problem with the new disposable Robertshaw type of DLTs which have nonadhering suction catheters that slide easily down the lumina. Second, although airway resistance may be increased with a narrow lumen, the increased resistance can be easily overcome by positive-pressure ventilation. [245]

Double-Lumen Endotracheal Tubes

Commonly Used Double-Lumen Endotracheal Tubes

A DLT is essentially two catheters bonded together side by side, with each lumen intended to ventilate one of the two lungs. DLTs are made as left- and right-sided tubes. With a left-sided tube, the left lung catheter is placed into the left mainstem bronchus, whereas the right lung catheter ends in the trachea; therefore, for a left-sided tube, the left lung catheter is longer than the right lung catheter (Fig. 48-14) (Figure Not Available) . With a right-sided tube the right lung catheter is placed into the right mainstem bronchus, whereas the left lung catheter ends in the trachea; therefore, for a right-sided tube, the right lung catheter is longer than the left lung catheter (see Fig. 48-14) (Figure Not Available) . All DLTs have a proximal cuff for the trachea and a distal cuff for a mainstem bronchus; the endobronchial cuff causes separation and sealing off of the lungs from each other, and the tracheal cuff causes separation and sealing off of the lungs from the environment. The part of the right lung catheter of the right-sided DLT that is in the right mainstem bronchus must be slotted to allow ventilation of the right upper lobe (see Fig. 48-14) (Figure Not Available) because the right mainstem bronchus is too short to accommodate both the right lumen tip and the right endobronchial cuff. All double-lumen endotracheal tubes have two curves that lie in planes approximately 90 degrees apart from one another. The distal curve is designed to facilitate placement of the distal catheter tip into the appropriate mainstem bronchus, and the proximal curve is designed to approximate the oropharyngolaryngeal curve.

The DLTs that are now used for lung separation and one-lung ventilation are the Carlens and the Robertshaw. The Robertshaw type of tube is by far the more commonly used, and the disposable polyvinylchloride (PVC) Robertshaw tube has significantly replaced the red rubber Robertshaw tube (the former is easier to pass, is positioned more quickly, and causes less mucosal damage). [246] Consequently, the modern PVC tube will be described in great detail.

The left-sided Carlens tube (Fig. 48-15) (Figure Not Available) was the first DLT used for one-lung ventilation. [247] The tube has a carinal

Figure 48-14 (Figure Not Available) Schematic diagram depicting the essential features and parts of left-sided and right-sided double-lumen endotracheal tubes. RUL, right upper lobe; LUL, left upper lobe. *(From Benumof [604])*

Figure 48-15 (Figure Not Available) (A) Sketch of the red rubber (nondisposable) Carlens double-lumen endotracheal tube. (B) Close-up of the placement of the red rubber Carlens double-lumen endotracheal tube at the carina. Note that the left endobronchial lumen and carinal hook straddle the carina. *(From Benumof [604])*

hook to aid in its proper placement and minimize tube movement after placement. Potential problems with carinal hooks include increased difficulty (more rotations) and laryngeal trauma during intubation, amputation of the hook during or after passage, malpositioning of the tube caused by the hook, and physical interference during pneumonectomy. [248] Therefore, some anesthesiologists prefer to use the tube with the hook removed. The tube is available in four sizes: 41, 39, 37, and 35 French (which correspond to an internal diameter of each lumen of approximately 6.5, 6.0, 5.5, and 5.0 mm, respectively). The cross-sectional shape of each lumen is oval, and this accounts for the occasional difficulty in passing a suction catheter down the lumen.

The original Robertshaw DLT, introduced in 1962, was made as a reusable red rubber tube (Fig. 48-16) (Figure Not Available) . [249] This tube was designed to provide the largest possible lumen to decrease airway resistance and facilitate removal of secretions. The lumina are D-shaped and lie side by side, like those of the Carlens tube, but are larger in size. As with the other DLTs, it has two curves (in planes approximately 90 degrees apart), which facilitate intubation and proper endobronchial placement. Both a right- and a left-sided tube are available, and the absence of a carinal hook allows for easier tracheal intubation and perhaps correct positioning. The right-sided tube has a slotted endobronchial cuff to effect ventilation of the right upper lobe. The right upper lobe ventilation slot is relatively long, which facilitates ventilation of this lobe. However, the endobronchial cuff has an additional area of inflation on the nonslotted side above the slot to effect a more reliable seal (see Fig.

48-16 (Figure Not Available) A). On the slotted side, inflation of the endobronchial cuff is restricted. However, the right endobronchial cuff design forces the right upper lobe slot to lie flat against the right upper lobe orifice, and if this slot is not perfectly aligned with the right upper lobe orifice, the ventilation slot will be blocked (obstructed) by the right mainstem bronchial wall (and vice versa). Nevertheless, because of its many good features, the original Robertshaw DLT rapidly gained wide popularity. [250]

The Robertshaw type of tube is now made of a clear nontoxic tissue-implantable plastic (denoted by the marking Z-79) and is disposable (see Fig. 48-14) (Figure Not Available) . The tubes are made in sizes 41, 39, 37, 35, 28, and 26 French (internal diameter

Figure 48-16 (Figure Not Available) (A) Sketch of the left-sided red rubber Robertshaw double-lumen endotracheal tube. (B) Close-up of the placement of the left-sided Robertshaw double-lumen endotracheal tube at the carina. (C) Sketch of the right-sided Robertshaw double-lumen endotracheal tube. (D) Close-up of the placement of the right-sided Robertshaw double-lumen endotracheal tube at the carina. *(From Benumof [604])*

Figure 48-17 (Figure Not Available) Use of left-sided and right-sided double-lumen endotracheal tubes for left and right lung surgery (as indicated by the clamp). (A) When surgery is performed on the right lung, a left-sided double-lumen endotracheal tube should be used. (B) When surgery is performed on the left lung, a right-sided double-lumen endotracheal tube can be used. However, because of uncertainty about the alignment of the right upper lobe ventilation slot with the right upper lobe orifice, a left-sided double-lumen endotracheal tube can also be used for left lung surgery. (C) If the left lung surgery requires a clamp to be placed high on the left main stem bronchus, the left endobronchial cuff should be deflated, the left-sided double-lumen endotracheal tube pulled back into the trachea, and the right lung ventilated through both the lumina (use the double-lumen endotracheal tube as a singlelumen tube). *(From Benumof [604])*

of each lumen is approximately 6.5, 6.0, 5.5, 5.0, 4.5, or 4.0 mm, respectively). The 26 and 28 French tubes are available only as left-sided models. These tubes are relatively easy to insert and have appropriate end-of-lumen and cuff arrangements that minimize lobar obstruction. The endobronchial cuff is colored brilliant blue, which is an important recognition feature when using a fiberoptic bronchoscope. The ends of both lumina have a black radiopaque line, which is an essential recognition marker when viewing a chest radiograph. The tubes have high-volume, low-pressure tracheal and endobronchial cuffs. The slanted doughnut-shaped endobronchial cuff on the Bronchocath model right-sided DLT allows the right upper lobe ventilation slot to ride off (away from) the right upper lobe orifice, which minimizes the chance of right upper lobe obstruction by the tube. The clear tubing is helpful because it permits continuous observation of the tidal movement of respiratory moisture as well as observation of secretions from each lung. The tubes are packaged with malleable stylets and are relatively easy to insert and position. These tubes have large internal to external diameter ratios and therefore are relatively easy to suction through, and they are packaged with their own nonadhering suction catheters. The large internal to external diameter ratio also provides a relatively low resistance to ventilation. For all these reasons, these disposable tubes are now considered the DLTs of choice by most anesthesiologists. Several companies are currently manufacturing them. Reviews of other DLTs are available. [251]

A left-sided DLT should be used for right thoracotomies requiring collapse of the right lung and ventilation of the left lung (Fig. 48-17) (Figure Not Available) . A left- or right-sided tube may be used for left thoracotomies requiring collapse of the left lung and ventilation of the right lung (see Fig. 48-17) (Figure Not Available) . However, because the right upper lobe ventilation slot of a right-sided tube has to be closely apposed to the right upper lobe orifice to allow unobstructed right upper lobe ventilation and since there is considerable anatomic variation in the exact position of the right upper lobe orifice and therefore in the length of the right mainstem bronchus (in fact, it is well known that an anomalous right upper lobe can take off from the trachea), use of a right-sided tube for left lung collapse introduces the risk of inadequate right upper lobe ventilation. For this reason, a left-sided tube is preferable for most cases requiring one-lung ventilation. If clamping of the left mainstem bronchus is necessary, the tube can be withdrawn at that time into the trachea and then used in the same manner as a single-lumen endotracheal tube (ventilation of the right lung with both lumina) (see Fig. 48-17) (Figure Not Available) . Contraindications to use of a left-sided DLT are carinal and proximal left mainstem bronchial lesions that could be traumatized by the passage of a left-sided tube. These lesions include strictures, endoluminal tumors, tracheobronchial disruptions, compression of the airway by an external mass, and tenting of the left mainstem bronchus so that the angle of the take-off from the trachea is approximately 90 degrees. The largest size of tube that can comfortably pass the glottis should be used, as a relatively small DLT may require excessive cuff volume for endobronchial cuff seal and may cause difficulty with suctioning secretions or ventilating the patient. In general, as height and weight increase, the appropriate DLT size (as defined above) increases, although height is much more important than weight. [252]

In summary, the plastic disposable Robertshaw-type tubes are by far the most commonly used DLTs. Because a right-sided tube incurs the risk of inadequate right upper lobe ventilation, left-sided tubes are used far more often. Consequently, the rest of this chapter emphasizes the insertion and precise positioning of the left-sided Robertshaw-type DLT.

Conventional Double-Lumen Tube Intubation Procedure

Before intubation with a double-lumen endotracheal tube, both cuffs and the lumen connections are checked. A 3-mL syringe with stopcock should be placed on the end of the bronchial cuff pilot tube, because proper bronchial cuff inflation rarely requires more than 1 to 2 mL of air; a 5- or 10-mL syringe with stopcock should also be placed on the

Figure 48-18 (Figure Not Available) Schematic diagram depicting the passage of the left-sided double-lumen endotracheal tube in a supine patient. (A) The tube is held with the distal curvature concave anteriorly and the proximal curve concave to the right and in a plane parallel to the floor. The tube is then inserted through the vocal cords until the bronchial cuff passes the vocal cords. The stylet is then removed. (B) The tube is rotated 90 degrees counterclockwise so that the distal curvature is concave anteriorly and the proximal curvature is concave to the left and in a plane parallel to the floor. (C) The tube is inserted until either a mild resistance to further passage is encountered or the end of the common molding of the two lumina is at the teeth. Both cuffs are then inflated, and both lungs are ventilated. Finally, one side is clamped while the other side is ventilated and vice versa. (See text for further explanation.) *(From Benumof [604])*

tracheal cuff pilot tube. Because the high-volume, low-pressure cuffs can be easily torn by teeth, the distal tube is coated with a lubricating ointment (preferably containing a local anesthetic) to minimize this possibility. If a less than optimal view of the larynx is anticipated, the stylet that is packaged with the tube is lubricated, inserted into the left lumen, and appropriately curved. The patient is then anesthetized and paralyzed as described previously. A curved open-phalanged blade (MacIntosh) is usually preferred for laryngoscopy, because it approximates the curvature of the tube and therefore provides the largest possible area through which to pass the tube. However, a straight (Miller) blade may be a better choice in patients with overriding upper teeth or an excessively anterior larynx.

Double-lumen endotracheal tubes with carinal hooks are first inserted through the vocal cords with the hook facing posteriorly. When the tip of the tube has passed the vocal cords, the tube is rotated 180 degrees so that the hook passes anteriorly through the glottis. If this maneuver is not done, then one can damage the vocal apparatus by dislocating an arytenoid cartilage should the hook snare or hang up on the arytenoid cartilage. After the tube tip and hook pass the larynx, the tube is rotated 90 degrees so that the tube tip enters the appropriate bronchus.

The Robertshaw-type DLT is passed with the distal curvature initially concave anteriorly (Fig. 48-18 (Figure Not Available) A). After the tube tip passes the larynx and while anterior force on the laryngoscope is continued, the stylet (if used) is removed, and the tube is carefully rotated 90 degrees (so that the distal curve is now concave toward the appropriate side and the proximal curve is concave anteriorly) to allow endobronchial intubation on the appropriate side (Fig. 48-18 (Figure Not Available) B). Continued anterior force by the laryngoscope during tube rotation prevents hypopharyngeal structures from falling in around the tube and interfering with a free 90-degree distal tube tip rotation. Failure to obtain a near 90-degree rotation of the distal tube tip while the proximal end rotates 90 degrees will cause either a kink or a twist in the shaft of the tube and/or prevent the distal end of the lumen from lying free in the mainstem bronchus (i.e., not up against the bronchial wall). After rotation, the tube is advanced until most of it is inserted [252] (Fig. 48-18 (Figure Not Available) C). When the proper depth of insertion has been achieved (defined as when the cephalad surface of the bronchial cuff is immediately below the carinal bifurcation), the average depth of insertion for both male and female patients 170 cm tall is 29 cm, and for each 10-cm increase or decrease in height, average placement depth is increased or decreased by 1 cm. [252] The correlation between depth of insertion and height is highly significant ($P < .0001$) for both male and female patients. Nevertheless, it should be understood that the depth of DLT insertion at any given height is still normally distributed, and correct DLT position should always be confirmed fiberoptically after initial placement. DLTs may also be passed successfully via tracheostomy, although it should be remembered that the tracheal cuff may be at the tracheal stoma or lie partly outside

the trachea in this situation. [253] [254] Because of this, one may prefer to use a specially manufactured (i.e., short) nondisposable double-lumen endotracheal tube for these particular patients. [255]

Once the tube tip is thought to be in an endobronchial position, the following checklist is used to ensure proper functioning of the tube. Inflate the tracheal and endobronchial cuffs until moderate tension is palpated in the external pilot balloons (the endobronchial cuff should not require more than 1-2 mL of air); deliver several positive-pressure ventilations, auscultate, and observe the chest bilaterally to determine that the trachea rather than the esophagus has been intubated and that both lungs are being ventilated (see Fig. 48-18 (Figure Not Available) C). In addition to seeing the tube go through the vocal cords, check correct intubation position by feeling and observing the anesthesia reservoir bag to make sure it has the appropriate compliance and movement while maintaining normal pulse oximetry and E_T CO_2 values, and perhaps palpating the tracheal cuff in the neck. If only unilateral breath sounds or chest movement is present, it is likely that both lumina of the tube have entered a mainstem bronchus (if both lumina enter the left main stem bronchus, the findings may mimic an esophageal intubation, and vice versa). In this situation, quickly deflate the cuffs, withdraw the tube 1 to 2 cm at a time, inflate the cuffs, and reassess ventilation until bilateral breath sounds are heard. If bilateral breath sounds are not heard and the tube has been withdrawn a significant amount, the entire procedure must be repeated, beginning with establishing the airway and oxygen ventilation via mask, laryngoscopy, and reinsertion of the DLT through the vocal cords. If bilateral breath sounds are present, then one side is clamped and breath sounds and chest movement should disappear on the ipsilateral side and remain on the contralateral side. Breath sounds should be at least as audible anteriorly, at the apex of the lung, as they are along the lateral chest. If they are not heard clearly at the lung apex, it is likely that the tube has been advanced too far distally and that the upper lobe on that side is not being ventilated adequately. In that case the tube must be pulled back 1 cm at a time until apical breath sounds are clearly heard. In addition, when the lumen cap is opened proximal to the clamp, there should be no leakage of air out of that lumen, indicating that the bronchial cuff has effected a proper seal. Next, the clamped side should be unclamped and the lumen cap replaced, and the breath sounds and chest movement should reappear on that side. During unilateral clamping, the breath sounds on the ventilated side should be compared with and calibrated against unilateral chest wall movements and the inspiratory disappearance and expiratory appearance of respiratory gas moisture in the clear tubing of the ventilated side. In addition, the compliance of the lung should be gauged by using hand ventilation. The unilateral clamping and unclamping and removal of the lumen cap proximal to the clamp should then be repeated on the opposite side to ensure adequate lung separation and cuff seal.

In summary, when DLT position is correct, the breath sounds are normal and follow the expected unilateral pattern with unilateral clamping, the chest rises and falls in accordance with the breath sounds, the ventilated lung feels reasonably compliant, no leaks are present, and respiratory gas moisture appears and disappears with each tidal ventilation. Conversely, when the DLT is malpositioned, any or all of the following may occur: the breath sounds may be poor and correlate poorly with unilateral clamping, the chest movements may not follow the expected pattern, the ventilated lung may feel noncompliant, leaks may be present, or the respiratory gas moisture in the clear tubing may be relatively stationary. It is very important to realize, however, that even if the DLT is thought to be properly positioned by clinical signs, subsequent fiberoptic bronchoscopy may reveal an incidence of malpositioning that ranges from 38 to 78 percent. [256] [257]

When it is believed, on the basis of clinical signs, that the DLT is malpositioned, it is theoretically possible to diagnose the malposition of the tube more precisely by a combination of several unilateral clamping, chest auscultation, and left endobronchial cuff inflation-deflation maneuvers (Fig. 48-19) (Figure Not Available) . With reference to a left-sided DLT, there are three possible gross malpositions: in too far on the left (both lumina in left mainstem bronchus), out too far (both lumina in the trachea), and in or down the right mainstem bronchus (at least the left lumen in the right mainstem bronchus). When the right (tracheal) side is clamped and the tube is in too far on the left side, breath sounds are heard only on the left side. When the tube is out too far and the right side is clamped, breath sounds are heard bilaterally. When the tube is in or down the right side and the right side is clamped, breath sounds are heard only on the right side. When the left side is clamped and the left endobronchial cuff is inflated, the right lumen is blocked by the left cuff in all three malpositions. Consequently, with the left side clamped and the left cuff inflated, no or very diminished breath sounds are heard bilaterally in all three of the malpositions. When the left side is clamped and the left cuff is deflated, so that the right lumen is no longer blocked by the left cuff, breath sounds are heard only on the left side when the tube is in too far on the left, bilaterally when the tube is out too far, and only on the right side when the tube is in the right side. The left cuff inflation and deflation findings provide the key diagnostic data because they essentially define the position of the right tracheal lumen by blocking and unblocking it with the left cuff.

There are, however, several situations in which these unilateral clamping, auscultation, and cuff inflation and deflation maneuvers for determining the integrity of lung separation are either unreliable or impossible. First, and most importantly, when the patient is in the LDP, has had a skin preparation, and is draped, access to the chest wall is impossible, and the anesthesiologist cannot listen to the chest. Second, the presence of unilateral or bilateral lung disease, either preexisting before anesthesia and surgery or anesthesia-induced, may markedly obscure the crispness of the chest auscultation end points. Third, the diagnosis of exactly where the DLT is located may be confused when the tube is just slightly malpositioned. Fourth, the tube may have moved as a result of some event, such as coughing, head flexion or extension while turning into the LDP, or tracheal manipulation and hilar retraction by the surgeon. Finally, some combination of these factors may culminate in uncertainty about where the DLT has located. The solution to any uncertainty about the exact position of the DLT is to determine the position by fiberoptic bronchoscopy.

Figure 48-19 (Figure Not Available) There are three major malpositions (involving a whole lung) of a left-sided double-lumen endotracheal tube. The tube can be in too far on the left (both lumina are in the left main stem bronchus), out too far (both lumina are in the trachea), or down the right main stem bronchus (at least the left lumen is in the right main stem bronchus). In each of these three malpositions the left cuff, when fully inflated, can completely block the right lumen. Inflation and deflation of the left cuff while the left lumen is clamped create a breath sound differential diagnosis of tube malposition. (See text for full explanation.) L, left; R, right;
, decreased. *(From Benumof [604])*

Use of Fiberoptic Bronchoscope to Determine Precise Double-Lumen Tube Position

As noted, even when a DLT is thought to be in proper position on the basis of clinical signs, subsequent fiberoptic bronchoscopy will reveal an incidence of malpositioning as high as 78 percent. [256] Indeed, when the position of the DLT is checked only by clinical signs, in up to 25 percent of cases there may be intraoperative problems with either deflating the nondependent lung, ventilating the dependent lung, or completely separating the two lungs. [256] [258] Given the high incidence of malpositioned DLTs when DLT position is determined by only auscultation (i.e., "blindly") and the potentially serious consequences associated with a malpositioned DLT, it is only a matter of simple common sense to routinely use a fiberoptic bronchoscope to easily, quickly, and precisely determine the position of the DLT.

The exact position of a left-sided DLT can be ascertained at any time, in less than a minute, by simply passing a pediatric-size fiberoptic bronchoscope through the tracheal lumen of the DLT. It is rarely necessary also to have to pass the fiberoptic bronchoscope down the left endobronchial lumen. With reference to a left-sided DLT, looking down the right (tracheal) lumen the endoscopist should have a clear straight-ahead view of the tracheal carina, the left lumen going off to the left, and the upper surface of the blue left endobronchial balloon just below the tracheal carina (Fig. 48-20) (Figure Not Available) . Because the distance between the right and left lumen tips for the clear plastic tube (69 mm) is longer than the length of the left mainstem bronchus (average 50 mm) in a typical patient and if the blue upper surface of the endobronchial balloon is not visible, it is possible for the right lumen to be above the tracheal carina while the left lumen tip obstructs the left upper lobe. [259] However, no matter which manufactured tube or size of tube is used and no matter how long or short the left mainstem bronchus is (within the range of extremes observed in extensive studies), [259] when the upper surface of the left endobronchial balloon is just below the tracheal carina, it is not possible for the left lumen tip to obstruct the left upper lobe or for the right (tracheal) lumen to be near a mainstem bronchus. It is important that the volume of air used to fill the left endobronchial cuff not cause the endobronchial cuff to herniate over the tracheal carina or cause the tracheal carina to deviate to the right (see Fig. 48-20) (Figure Not Available) ; both cuff herniation and carinal deviation can be readily appreciated by looking down the tracheal lumen. Looking down the left lumen (as is sometimes done when inserting a left-sided DLT with a fiberoptic bronchoscope [see the section immediately below] and in all cases of bronchopulmonary lavage where perfect tube position and tight cuff seal are extremely critical), the endoscopist should see a very slight narrowing of the left lumen (due to endobronchial cuff pressure) as well as the bronchial carina distal to the end of the tube (see Fig. 48-20) (Figure Not Available) . The endoscopist should not see excessive left luminal narrowing (due to excessive left cuff pressure) (see Fig. 48-20) (Figure Not Available) Thus, aside from gross malposition, important undesirable findings on endoscopy are related to excessive left cuff inflation and pressure and consist of cuff herniation over the tracheal carina, carinal deviation to the right (both of which may block the right mainstem bronchial orifice and impair right lung ventilation), and excessive left lumen constriction (invagination), which may impair left lung ventilation [260] (see Fig. 48-20) (Figure Not Available) . In addition, when an inappropriately undersized tube is used, the large endobronchial cuff volume required for endobronchial cuff seal tends to force the entire DLT cephalad, making a functional bronchial seal more difficult. [261]

With reference to a right-sided DLT, looking down the left (tracheal) lumen, the endoscopist should see a clear straight-ahead view of the tracheal carina and the right lumen going off to the right (Fig. 48-21 (Figure Not Available) A). The upper surface

Figure 48-20 (Figure Not Available) This schematic diagram depicts the complete fiberoptic bronchoscopy picture of left-sided double-lumen endotracheal tubes (both the desired view and the view to be avoided from both of the lumina). (A) When the bronchoscope is passed down the left lumen of the left-sided tube, the endoscopist should see a very slight left luminal narrowing and a clear straight-ahead view of the bronchial carina off in the distance. Excessive left luminal narrowing should be avoided. (B) When the bronchoscope is passed down the right lumen of the left-sided tube, the endoscopist should see a clear straight-ahead view of the tracheal carina and the upper surface of the blue left endobronchial cuff just below the tracheal carina. Excessive pressure in the endobronchial cuff, as manifested by tracheal carinal deviation to the right and herniation of the endobronchial cuff over the carina, should be avoided. *(From Benumof [604])*

of the right endobronchial balloon may not be visible below the tracheal carina. Looking down the right lumen, the endoscopist should see a very slight narrowing of the right lumen as well as the right middle-lower lobe bronchial carina distal to the end of the tube. Most importantly, the endoscopist should locate the right upper lobe ventilation slot and be able to look directly into the right upper lobe orifice through the right upper lobe ventilation slot by simply flexing the tip of the fiberoptic bronchoscope superiorly and laterally (Fig. 48-21 (Figure Not Available) B). There should be no overriding of the right upper lobe ventilation slot on the bronchial mucosa, and the bronchial mucosa should not be covering any of the right upper lobe ventilation slot.

In our experience, in 8 to 9 out of 10 cases, the clinical signs (breath sounds, chest movements, compliance of the lung[s], movement of respiratory gas moisture) indicate that the lungs are apparently clearly and without doubt completely separated when the DLT is first inserted with the patient in the supine position. However, in view of the finding that up to 78 percent of DLTs are malpositioned to some extent in the supine position, even though clinical signs indicate no problem, [256] it is strongly advisable to check the position of the tube with a fiberoptic bronchoscope in the supine position (especially in view of the fact that the procedure takes less than 1 minute). Even if no problem is identified, the procedure still allows the endoscopist to become familiar with the patient's anatomy and facilitates the more important endoscopy after turning the patient into the LDP. In approximately 1 to 2 out of 10 cases, there is a definite doubt about tube location in the supine position, and in these patients

Figure 48-21 (Figure Not Available) This schematic diagram portrays use of a fiberoptic bronchoscope to determine precise right-sided double-lumen tube position. (A) When the fiberoptic bronchoscope is passed down the left (tracheal) lumen, the endoscopist should see a clear straight-ahead view of the tracheal carina and the right lumen going off into the right main stem bronchus. (B) When the fiberoptic bronchoscope is passed down the right (bronchial) lumen, the endoscopist should see the bronchial carina off in the distance; when the fiberoptic bronchoscope is flexed cephalad and passed through the right upper lobe ventilation slot, the right upper lobe bronchial orifice should be visualized. *(From Benumof [604])*

the fiberoptic bronchoscope is always used to correct the DLT malposition. The fiberoptic bronchoscope is again used to confirm DLT position after the patient has been turned into the LDP. Of course, a determined effort is made to prevent dislodgement of the tube during turning by holding on to the tube at the level of the incisors and by keeping the head absolutely immobile in a neutral or slightly flexed position. Head extension can cause movement of the tube in a cephalad direction, which may result in bronchial decannulation; head flexion can cause movement of the tube in a caudad direction, which may result in an upper lobe obstruction or in both luminas being in a mainstem bronchus (see next section). [262] [263] Finally, the fiberoptic bronchoscope is used whenever during the case there is a question about DLT position. This is not an infrequent occurrence and is usually caused by surgical manipulation and traction on the hilum, carina, or trachea.

Use of Fiberoptic Bronchoscope to Insert the Double-Lumen Tube

The insertion of the bronchial lumen of a DLT into the appropriate mainstem bronchus may be aided by the use of a fiberoptic bronchoscope. This may be especially helpful if anatomic variation or a pathologic condition has caused carinal distortion. The DLT is first placed in the trachea in a conventional manner (laryngoscopy, manual tube insertion) until the tracheal cuff just passes the vocal cords, the tracheal cuff is inflated, and both lungs are ventilated through both lumina (the DLT should be used as if it were a single-lumen tube). A pediatric-sized fiberoptic bronchoscope can then be inserted into the bronchial lumen through a self-sealing diaphragm in the elbow connector to the bronchial lumen (which permits continued positive-pressure ventilation through that lumen around the fiberoptic bronchoscope) and passed into the appropriate mainstem bronchus. The tracheal cuff is then deflated and the bronchial lumen is passed over the fiberoptic bronchoscope stylet into the appropriate mainstem bronchus. The fiberoptic bronchoscope is then withdrawn from the bronchial lumen and passed down the tracheal lumen to determine the precise DLT position (see the preceding section).

Alternatively, once the DLT is in the trachea, the fiberoptic bronchoscope can be inserted into the tracheal lumen and passed just proximal to the tracheal carina. While the carina and the two mainstem bronchial orifices are in view, the DLT can be advanced and the degree of lateral rotation adjusted so that the appropriate lumen enters the appropriate mainstem bronchus. Final precise positioning (see the preceding section) can be done with the fiberoptic bronchoscope remaining in the tracheal lumen if a left-sided tube is used. If a right-sided tube is used, precise positioning must be confirmed with the bronchoscope passed through the bronchial lumen.

Relationship of Fiberoptic Bronchoscope Size to Double-Lumen Tube Size

The clear plastic disposable right and left double-lumen endotracheal tubes are manufactured in four sizes: 35, 37, 39, and 41 French. In addition, 26 and 28 French-sized tubes are available only as left-sided models. A 5.6-mm outside diameter diagnostic fiberoptic bronchoscope will not pass down the lumina of any size DLT. A 4.9-mm outside diameter fiberoptic bronchoscope passes easily through the lumina of the 41 French tube and moderately easily with lubrication through the 39 French tube; it causes a tight fit that needs a liberal amount of lubrication and a strong pushing force to pass through the lumen of the 37 French tube and does not pass through the lumen of the 35 French tube. A silicon-based fluid (such as that made by the American Cystoscope Co.) is the best lubricant for a fiberoptic bronchoscope because it does not dry out or crust and does not interfere with the view even if it coats the tip of the bronchoscope. Fortunately, from the point of view of using a 4.9-mm outside diameter fiberoptic bronchoscope, a 37 French tube or larger can be used in almost all adult females and 39 French tube or larger in almost all adult males. A 3.6- to 4.2-mm outside diameter (pediatric-sized) fiberoptic bronchoscope passes easily through the lumina of all adult-sized DLTs and because the bronchoscope has an increased amount of space, the maneuverability of the tip of the bronchoscope is greatly increased. Therefore, the 3.6- to 4.2-mm outside diameter bronchoscope is obviously the bronchoscope of choice for DLTs. Table 48-11 summarizes these fiberoptic bronchoscope-DLT relationships. Several companies (Olympus, Machida, Pentax) presently manufacture 4.9- and 3.6- to 4.2-mm outside diameter fiberoptic bronchoscopes that are of adequate length and have a suction channel.

Use of Chest Radiograph to Determine Double-Lumen Tube Position

The chest radiograph can be used to determine DLT position. The chest radiograph may be more useful than conventional unilateral auscultation and clamping in some patients, but it is always less precise than fiberoptic bronchoscopy. To use the chest radiograph, the DLT must have radiopaque markers at the end of the right and left lumina. The key to discerning DLT position on the chest radiograph

TABLE 48-11 -- Relationship of Fiberoptic Bronchoscope Size to Adult Double-Lumen Endotracheal Tube Size

FIBEROPTIC BRONCHOSCOPE SIZE (OUTSIDE DIAMETER) (mm)	ADULT DLT SIZE (FRENCH)	FIT OF FIBEROPTIC BRONCHOSCOPE INSIDE DLT
5.6	All sizes	Does not fit
	41	Easy passage
	39	Moderately easy passage
4.9	37	Tight fit, need lubricant,* hard push
	35	Does not fit
3.6-4.2	All sizes	Easy passage

Abbreviation: DLT, double-lumen tube.

*Lubricant recommended is a silicon-based fluid similar to that made by the American Cystoscope Co.

Figure 48-22 (Figure Not Available) Schematic diagram showing the air bubble detection method for checking adequacy of the seal of the left endobronchial cuff of a left-sided double-lumen tube. (A) When the left lung is selectively ventilated or exposed to any desired distending pressure and the left cuff is adequately sealed, no air will escape around the left cuff and out the open right suction port, and thus no bubbles will be observed passing through the beaker of water. (B) When the left lung is ventilated or exposed to any desired distending pressure and the left endobronchial cuff is not adequately sealed, air will escape around the left cuff and out the open right suction port, and thus air bubbles will be observed passing through the beaker of water. *(From Benumof [604])*

is seeing where the marker at the end of the tracheal lumen is in relation to the tracheal carina and whether the endobronchial lumen is located in the correct main stem bronchus. The end of the tracheal lumen marker must be above the tracheal carina; however, this does not guarantee correct position because this technique may not reveal a subtle obstruction of an upper lobe. If the tracheal carina cannot be seen (as sometimes happens with portable anteroposterior film), the chest radiograph method of determining DLT position is not usable. Furthermore, the chest radiograph method is time-consuming (for film transport and film development), costly, and awkward to perform and may dislodge the tube (the cassettes are often difficult to place under the operating room table and require moving the patient).

Other Methods to Determine Double-Lumen Tube Position

Three other methods may help to determine the position of a DLT. First, comparison of capnography (waveform and end-tidal CO_2 pressure [PET CO_2] value) from each lumen may reveal a marked discrepancy. For example, with all other conditions equal, one lung may be very poorly ventilated in relation to the other lung (high PET CO_2), indicating obstruction to that lung; one lung may be very overventilated in relation to the other lung (low PET CO_2), perhaps indicating ventilation of just a lobe of that lung; or the capnogram from one lung may have a much steeper slope to the alveolar plateau, indicating expiratory obstruction. [264] [265] Second, continuous spirometric data (Datex Capnomac Ultima) from both lungs and from each lung separately, such as pressure-volume or flow-volume loops, may be displayed and compared with a control loop that is stored in memory. [266] Third, the surgeon may be able to palpate the position of the DLT from within the chest and may be able to redirect or assist in changing its position (by deflecting the DLT away from the wrong lung, etc.). [267]

Quantitative Determination of Cuff Seal Pressure Hold

The use of fiberoptic bronchoscopy to determine DLT position does not provide evidence or a guarantee that the lungs are functionally separated (i.e., against a fluid and/or air pressure gradient). There are times, such as during the performance of unilateral pulmonary lavage, when the anesthesiologist must be absolutely certain that functional separation has been achieved. Complete separation of the lungs by the left endobronchial cuff can be demonstrated in a left-sided tube by clamping the connecting tube to the right lung proximal to the right suction port and attaching a small tube (i.e., intravenous extension tubing) to the open right suction port (by appropriate adaptors) (Fig. 48-22) (Figure Not Available) . The free end of this tube is submerged in a beaker of water. When the left lung is statically inflated to any pressure considered necessary and the left endobronchial cuff is not sealed, air will enter the left lung and will also escape from around the unsealed left cuff, move up the right lumen to the small connecting tube, and bubble through the beaker of water (Fig. 48-22 (Figure Not Available) B). If the left endobronchial cuff is sealed, no bubbles should be observed passing through the beaker of water (Fig. 48-22 (Figure Not Available) A). After demonstration of functional lung separation, the right connecting tube is unclamped, the right suction port closed, and ventilation to both lungs resumed. To test for lung separation with the pressure gradient across the endobronchial balloon reversed, the left airway connecting tube is clamped proximal to the left suction port, the left suction port opened to the beaker of water via the small tube, the right lung statically inflated to any desired pressure, and the absence or presence of air bubbles in the beaker of water noted. It should be remembered that even though the left endobronchial cuff may be adequately sealed, it is possible that during these maneuvers, compression of the nonventilated lung by the ventilated lung may initially cause some small amount of bubbling in the beaker, which will cease with repetitive inflation of the ventilated lung (no bubbles should be seen after several inflations). [251] [260]

TABLE 48-12 -- Endobronchial Cuff Considerations to Minimize Tracheobronchial Wall Damage (Disruption)

1. Be particularly cautious in patients with bronchial wall abnormalities.
2. Pick an appropriately sized tube.
3. Be certain tube is not malpositioned. * Use fiberoptic bronchoscopy to confirm the position of the double-lumen tube (especially if N_2O is introduced into the inspired gases).
4. Avoid overinflation of endobronchial cuff. *
5. Deflate endobronchial cuff during turning.
6. Inflate endobronchial cuff slowly.
7. Inflate endobronchial cuff with inspired gases.
8. Do not allow tube to move during turning. *

*Most important considerations.

The absence of airflow from the nonventilated lung suction port is a very simple but sensitive indicator of functional separation of the two lungs.

Complications of Double-Lumen Endotracheal Tubes

In addition to the impediment to arterial oxygenation that is inherent in the use of DLTs for one-lung anesthesia, the tubes themselves occasionally cause other serious complications. These complications include tracheobronchial tree disruption (with the Carlens tube, [268] the red rubber Robertshaw tube, [269] the red rubber White tube, [270] and the disposable low-pressure cuff plastic tubes [271] [272] , traumatic laryngitis, [248] and suturing of a pulmonary vessel to the DLT. [273] With regard to tracheobronchial tree disruptions, a common thought in the reports cited is that excessive air volume and pressure in the bronchial balloon may be major factors in the genesis of these tears after DLT insertion. Recommendations to minimize tracheobronchial wall damage due to the cuffs include being particularly cautious in the use of DLTs in patients with bronchial wall abnormalities, choosing an appropriately sized clear plastic tube, [246] being certain the tube is not malpositioned, preventing overinflation of the endobronchial cuff, deflating the endobronchial cuff during turning, inflating the endobronchial cuff slowly, inflating the endobronchial cuff with inspired gases if nitrous oxide is used, and preventing the tube from moving during turning (Table 48-12) .

Relative Contraindications to Use of Double-Lumen Endotracheal Tubes

Lung separation by a DLT may be relatively contraindicated in several situations because insertion of the tube is either difficult or dangerous. These situations involve patients who have a full stomach (risk of aspiration); patients who have a lesion (airway stricture, [274] endoluminal tumor) that is present somewhere along the pathway of the DLT and thus could be traumatized; small patients for whom a 35 French tube is too large to fit comfortably through the larynx and for whom a 28 French tube is considered too small; patients whose upper airway anatomy precludes safe insertion of the tube (recessed jaw, prominent teeth, bull neck, anterior larynx); extremely critically ill patients who have a single-lumen tube already in place and who will not tolerate being taken off mechanical ventilation and PEEP even for a short time; and patients having some combination of these problems. Under these circumstances, it is still possible to separate the lungs safely and adequately by using a single-lumen tube and fiberoptic bronchoscopic placement of a bronchial blocker or by fiberoptic bronchoscopic placement of a single-lumen tube in a main stem bronchus.

Bronchial Blockers (With Single-Lumen Endotracheal Tubes)

Lung separation can be effectively achieved with the use of a single-lumen endotracheal tube and a fiberoptically placed bronchial blocker. This is often necessary in children because DLTs are too large to be used in them. The smallest DLT available is a left-sided 26 French tube, which may be used in patients 8 to 12 years old and weighing 25 to 35 kg. Bronchial blockers that are balloon-tipped luminal catheters have the advantage of allowing suctioning and injection of oxygen down the central lumen. The bronchial blocker most widely used for adults is the movable bronchial blocker that is contained in and is an integral part of the Univent single-lumen tube system (made by Fuji Systems Corp., Tokyo) [275] [276] [277] [278] [279] [280] [281] (Fig. 48-23) . The physiology of one-lung ventilation produced by bronchial blockade is identical to that produced by clamping one lumen of a DLT.

Figure 48-23 Single-lumen tube of Univent bronchial blocker system.

Figure 48-24 The sequential steps of the fiberoptic-aided method of inserting and positioning the Univent bronchial blocker (BB) in the left mainstem bronchus are illustrated. One- or two-lung ventilation is achieved by simply inflating or deflating, respectively, the bronchial blocker balloon.

Insertion of the Univent Tube and Positioning of the Bronchial Blocker

The tube is inserted in the following manner. First, the single-lumen tube along with the bronchial blocker (in the fully retracted position) is inserted as a unit into the trachea (Fig. 48-24 A). The cuff on the main endotracheal tube lumen is inflated, and the patient is ventilated and oxygenated (see Fig. 48-24 A). A fiberoptic bronchoscope is inserted through a self-sealing diaphragm in the elbow connector to a single-lumen tube while ventilation is maintained around the bronchoscope (but within the single-lumen tube) (Fig. 48-24 C). The right and left mainstem bronchi are identified (by noting the relationship of the main stem bronchi to the posterior membrane and the anterior cartilaginous rings [Fig. 48-24 B.]), and the tube of the bronchial blocker is located (by moving the bronchial blocker in and out just beyond the end of its own lumen and the main lumina of the Univent tube [Fig. 48-24 .]). The bronchial blocker cuff is colored blue and is easy to see. It will be seen that the bronchial blocker will usually (almost always) enter the right mainstem bronchus if it is simply pushed in (and the main single-lumen tube is not turned). If the left mainstem bronchus is to be blocked, the main single-lumen tube is turned 90 degrees to the left (counterclockwise) so that the concavity of the tube is facing toward the left side (Fig. 48-24 C). (and vice versa for the right side, if necessary). The bronchial blocker can also be rotated a slight amount at its distal end (obtain 1-3 mm of laterality) by twirling the proximal end in the fingers. The bronchial blocker is then advanced into the mainstem bronchus under direct vision (Fig. 48-24 D).. Attempting to advance the bronchial blocker blindly into the appropriate mainstem bronchus (particularly the left) will be unsuccessful 87 percent of the time, and repeated attempts may cause excoriation of the tracheal mucosa. [227] In fact, blindly pushing the somewhat stiff bronchial blocker may result in perforation of the tracheobronchial tree and consequent tension pneumothorax. [278]

TABLE 48-13 -- Advantage/Noteworthy Positive Attributes of the Univent Bronchial Blocker Tube (Relative to a Double-Lumen Tube and Other Bronchial Blockers)

1. Easier to insert and properly position
2. Can be properly positioned during continuous ventilation and in the lateral decubitus position
3. No need to change the tube for postoperative mechanical ventilation
4. No need to change the tube intraoperatively when turning from the supine to the prone position
5. Selective blockade of some lobes of each lung
6. Possible to apply nonventilated operative lung CPAP

Abbreviation: CPAP, continuous positive airway pressure.

The balloon is inflated until the cephalad surface of the balloon is just below the tracheal carina (Fig. 48-24 E). (so that the upper lobe of the blocked lung may also distend if CPAP is applied to the blocked lung [see below], and the fiberoptic bronchoscope is then withdrawn (Fig. 48-24 F).

Advantages and Noteworthy Positive Attributes of the Univent Bronchial Blocker Tube System

The Univent bronchial blocker tube has six important attributes that require special mention (Table 48-13) . First and foremost, the degree of difficulty in inserting the Univent tube is equivalent to a standard single-lumen tube and therefore in many instances will be an easier and quicker way to separate the lungs to obtain simple one-lung ventilation (as compared with a DLT). [91] [93] Thus and as an example, the Univent tube may be preferable when difficult intubation is anticipated and when the patient has been treated with anticoagulants. Second, the patient can be continuously ventilated while the bronchial blocker is being placed into a mainstem bronchus, and the bronchial blocker can be placed into a mainstem bronchus just as easily in the LDP as in the supine position. Third, and provided that the postanesthesia care unit and intensive care unit personnel are instructed in the design and function of the Univent tube (particularly the ventilatory consequence of inflating the bronchial blocker cuff just distal to the main lumen [i.e., the main lumen will be obstructed]), the Univent tube may be left *in situ* for postoperative mechanical ventilation and the risk of a potentially difficult tube change (e.g., from a DLT to a single-lumen tube) thereby avoided. Fourth and similarly, the Univent tube may be left *in situ* if a patient is turned from the supine to the prone position midway through a surgical procedure (a common occurrence with surgery on the thoracic spine). Fifth, the unique characteristic of a movable endobronchial blocker permits the Univent endotracheal tube to create selective partial collapse (e.g., of a lobe) or total collapse of the targeted lung. [282] The capability of selectively blocking lung segments is extremely important in cases of isolated pulmonary hemorrhage. Partial versus total one-lung ventilation may allow for an improvement in Pa O_2 in cases of intraoperative hypoxemia during thoracic operations. Finally, although this is not a distinct advantage over a DLT, it should be noted that it is possible to apply CPAP to the nonventilated operative lung through the lumen of the bronchial blocker, [283] and therefore the Univent tube provides the same best solution to hypoxemia during one-lung ventilation as does a DLT. In fact, except for independent unilateral intermittent positive-pressure ventilation and suctioning, all selective differential lung functions possible with a DLT are possible with a Univent bronchial blocker tube.

Potential Limitations of the Univent Bronchial Blocker Tube System and Solutions to the Limitations

There are several distinct limitations to the Univent bronchial blocker tube system, but fortunately all have a relatively simple remedy (Table 48-14) . First, the small lumen of the bronchial blocker results in slow inflation of the lung if gases are just insufflated (e.g., at a flow rate of 10 L/min, a lung will require at least 20 seconds to reach total lung capacity) or pushed in by conventional positive pressure. The operative lung may be made to expand rapidly if the bronchial blocker cuff is deflated

(the operative lung will expand with one positive-pressure breath from the main single lumen) or if one very short (e.g., <0.5-sec) burst of wall oxygen-powered 20- to 30-psi jet ventilation (reduced from 50 psi) is administered. However, connection of the bronchial blocker lumen to a jet ventilator is potentially dangerous (i.e., it can cause barotrauma) because the lung can expand extremely rapidly, and it is of paramount importance that the anesthesiologist directly observe the lung and that the ventilation be very short or the pressure limited to 20 to 30 psi by an additional in-line regulator. Second, and also because the bronchial blocker lumen is small, the lung will deflate very slowly when blocked. This is easily remedied by deflating the bronchial blocker cuff (which reestablishes continuity between the operative lung and the main single lumen), disconnecting the patient from the ventilator, and

TABLE 48-14 -- Limitations to the Use of the Univent Bronchial Blocker Tube and Solutions to the Limitations

LIMITATION	SOLUTION
1. Slow inflation time	1. (a) Deflate bronchial blocker cuff and administer a positive pressure breath through the main single lumen; (b) carefully administer one short high pressure (20-30 psi) jet ventilation.
2. Slow deflation time	2. (a) Deflate bronchial blocker cuff and compress and evacu-ate the lung through the main single lumen; (b) apply suction to bronchial blocker lumen.
3. Blockage of bronchial blocker lumen by blood, pus	3. Suction, stylet, and then suction.
4. High-pressure cuff	4. Use just-seal volume of air.
5. Intraoperative leak in bronchial blocker cuff	5. Make sure bronchial blocker cuff is subcarinal, increase inflation volume, rearrange surgical field.

leaving the endotracheal tube open to air while the surgeon gently compresses the lung to evacuate air from the operative lung through the main single lumen. After the lung is thus fully collapsed, the blocker balloon is inflated and ventilation resumed. [91] [92] Alternatively, the lumen of the bronchial blocker may be connected to the suction apparatus while the cuff is inflated; a normal amount of wall suction greatly facilitates lung collapse. Third, and also because the bronchial blocker lumen is small, the lumen is relatively easily blocked by blood and/or pus. High suction will occasionally clear the lumen of these materials and total blockage by inspissated secretions can be broken up by a wire stylet. Fourth, the Univent bronchial blocker behaves as a high-pressure cuff when intracuff volume is greater than 2 mL (the resting volume of the cuff) and may be expected to have an intracuff pressure between 150 and 250 mm Hg and a transmural pressure (intracuff pressure within the airway minus intracuff pressure outside the airway [free in the room]) between 50 and 60 mm Hg when intracuff volumes of 4 to 6 mL are used to seal 12- to 18-mm airways against the usual proximal airway pressure. [284] [285] Thus, the order of usual bronchial cuff pressures is left-sided PVC DLT < right-sided polyvinylchloride DLT < Univent Bronchial Blocker cuff < red rubber double-lumen tube. [286] These findings underscore the need to inflate the bronchial blocker cuff with a just-seal volume of air. Fifth, the Univent bronchial blocker has on occasion been reported to have a minor leak during surgery (25% in one series), [277] but this is not understandable in view of experiments showing that the Univent bronchial blocker cuff seals within normal-sized mainstem bronchi against proximal airway pressures as great as 100 cm H_2 O with inflation volumes that are within the manufacturer's recommendation. [285] Consequently, if an intraoperative leak occurs when less than a 6- to 7-mL intracuff volume has been used and the bronchial blocker cuff is completely subcarinal (as determined by fiberoptic bronchoscopy) and intact, the intracuff volume should be increased. If an intraoperative leak develops even though an adequate cuff inflation volume has been used (the bronchial blocker can be seen [fiberoptically] to fill the mainstem bronchus in question) and the bronchial blocker cuff is completely subcarinal (as determined fiberoptically) and intact, the relationship between the mainstem bronchus and the bronchial blocker cuff may no longer be a simple matter of a sphere or ellipsoid being inflated within a cylinder. Under these circumstances the surgeon may need to rearrange the surgical field so that the mainstem bronchus and bronchial blocker cuff are less distorted. Finally, the addition of the lumen for the bronchial blocker results in an endotracheal tube that has a large outside anteroposterior diameter relative to its inside diameter.

Methods to Obtain a Just-Seal Volume in the Bronchial Blocker Cuff

There are two methods to obtain a just-seal volume of air in the bronchial blocker cuff. The first method is the same as that already described for obtaining a just-seal volume of air in the endobronchial cuff of a DLT. It consists of pressurizing the main single lumen until air ceases to escape from the bronchial blocker lumen (detected by connecting the

Figure 48-25 (Figure Not Available) Capnogram tracing showing normal respiratory waveform changing to a straight line as bronchial seal occurs. *(From Essig K and Freeman JA [605])*

bronchial blocker lumen to a catheter that is submerged beneath the surface of a beaker of water; when air bubbles cease to come out, the bronchial blocker cuff has sealed) (see Fig. 48-22) (Figure Not Available) .

The second method appears promising and uses capnography. End-tidal CO_2 analyzers draw gas samples from the anesthesia breathing circuit via tubing that terminates, at the patient end of the tubing, in a standard Luer lock male connector that inserts into a female port in the breathing circuit. The male connector also inserts into/attaches to the female port at the proximal end of the Univent's bronchial blocker. The tracing from a gas analyzer, connected to the blocker with its cuff deflated, shows a typical respiratory waveform. As the cuff of the bronchial blocker is steadily inflated, a point is reached at which the respiratory waveform abruptly ceases, and a straight line is seen, indicating that lung isolation has occurred (Fig. 48-25) (Figure Not Available) . The CO_2 concentration remains near its end-tidal value until the blocked lung has collapsed and then rapidly decreases. The strengths of this method include simplicity, repeatability, and ability to ventilate the unblocked lung continuously throughout the procedure.

Clinical Indications for Use of the Univent Bronchial Blocker System

There are several clinical situations in which use of the Univent bronchial blocker tube is relatively indicated. First, whenever it is anticipated that postoperative ventilation will be necessary (e.g., poor pulmonary function preoperatively, anticipated lung damage or massive fluid and/or blood infusion intraoperatively, anticipated very long case), use of the Univent bronchial blocker tube for lung separation may avoid a risky postoperative DLT to single-lumen tube change. Second and similarly, use of the Univent bronchial blocker tube will avoid a potentially dangerous DLT to single-lumen tube change in cases of surgery on the thoracic spine in which a thoracotomy in the supine or lateral decubitus position is followed by surgery in the prone position. Third, a very severely distorted airway may prevent successful placement of a DLT, whereas such distortion may have much less of an effect on the proper placement of the Univent tube. Finally, but least predictable or compelling, are situations in which both lungs may need to be blocked (e.g., bilateral operations, indecisive surgeons).

Figure 48-26 (Figure Not Available) Lung separation with a single-lumen tube, fiberoptic bronchoscope, and right lung bronchial blocker. The sequence of events is as follows: (A) A single-lumen tube is inserted and the patient is ventilated. (B) A bronchial blocker is passed alongside the indwelling endotracheal tube. (C) A fiberoptic bronchoscope is passed through a self-sealing diaphragm in the elbow connecter to the endotracheal tube and is used to place the bronchial blocker into the right mainstem bronchus under direct vision. (D) The balloon on the bronchial blocker is also inflated under direct vision and is positioned just below the tracheal carina. (E) The fiberoptic bronchoscope is then removed (right lower diagram). During the lower panel sequence (insertion and use of fiberoptic bronchoscope, Figs. C to E) the self-sealing diaphragm allows the patient to continue to be ventilated with positive-pressure ventilation (around the fiberoptic bronchoscope, but within the lumina of the endotracheal tube). LL, left lung; RL, right lung. *(From Benumof [604])*

Bronchial Blockers That Are Independent of a Single-Lumen Tube

The bronchial blocker that is independent of the single-lumen tube most often used for adults is a Fogarty occlusion (embolectomy) catheter with a 3-mL balloon. [287] The Fogarty catheter includes a stylet so that it is possible to place a curvature at the distal tip to facilitate entry into the larynx and either mainstem bronchus (by twirling the proximal end). If no endotracheal tube is in place, the operator exposes the larynx and places a single-lumen tube with a high-volume cuff in the trachea. The Fogarty catheter is then placed either inside [288] [289] or alongside the single-lumen tube (Fig. 48-26) (Figure Not Available) . In either case (bronchial blocker inside or outside the single-lumen tube), a fiberoptic bronchoscope is passed down to the end of the single-lumen tube through a self-sealing diaphragm in the elbow connector (which permits continued positive-pressure ventilation around the fiberoptic bronchoscope), and the Fogarty catheter is visualized below the tip of the

single-lumen tube. The proximal end of the bronchial blocker is then twirled in the fingertips and advanced until the distal tip locates in the desired mainstem bronchus. The catheter balloon is then inflated under direct visualization and the fiberoptic bronchoscope withdrawn through the self-sealing diaphragm.

Finally, other balloon-tipped luminal catheters (such as the Magill or Foley type) may be used as bronchial blockers.

For bronchial blockage in very small children (10 kg or less) a Fogarty embolectomy catheter with a balloon capacity of 0.5 mL or a Swan-Ganz catheter (1-mL balloon) should be used. [29C] Of course, these catheters have to be positioned under direct vision; a fiberoptic bronchoscope method, as depicted in Figure 48-26 (Figure Not Available) , is perfectly acceptable, except the fiberoptic bronchoscope outside diameter must be approximately 2 mm to fit inside the endotracheal tube (3-mm internal diameter or greater). Otherwise, the bronchial blocker must be situated with a rigid bronchoscope. Pediatric patients of intermediate size require intermediate size occlusion catheters and judgment on the mode of placement (i.e., via rigid versus fiberoptic bronchoscope).

Disadvantages of bronchial blockage with a blocker that is independent of the single-lumen tube as compared with DLT lung separation include inability to suction and/or to ventilate the lung distal to the blocker, increased placement time, and the definite need for a fiberoptic or rigid bronchoscope. In addition, if a mainstem bronchial blocker backs out into the trachea, the seal between the two lungs will be lost, and two catastrophic complications may occur. First, if the bronchial blocker was being used to seal off fluid (blood or pus) in one lung, then both lungs may

become contaminated with the fluid. Second, the trachea will be at least partially obstructed by the blocker, and ventilation will be greatly impaired. Therefore, bronchial blockage requires that the anesthetist continuously and intensively monitor the compliance and breath sounds of the ventilated lung.

Endobronchial Intubation With Single-Lumen Tubes

In adults presenting with hemoptysis, endobronchial intubation with a single-lumen tube is often the easiest, quickest way of effectively separating the two lungs, especially if the left lung is bleeding, in which case one can simply take an uncut single-lumen endotracheal tube and advance it inward until moderate resistance is felt. In the vast majority of patients, the single-lumen tube will locate in the right mainstem bronchus, thereby blocking off the bleeding left lung and allowing selective ventilation of only the right lung. Under these circumstances it is highly possible that the right upper lobe bronchus will be blocked off as well, resulting in ventilation of only the right middle and lower lobes. Ventilation of only a soiled right lung or ventilation of only the right middle and lower lobes (even if they are unsoiled) incurs the risk of serious hypoxemia due to the very large transpulmonary shunt that is necessarily created by single-lung endobronchial intubation.

If the right lung is bleeding, there are two ways of selectively intubating the left mainstem bronchus. First, this may be done blindly with approximately a 92 percent success rate by turning the patient's head to the right and passing the single-lumen tube with the concavity of the tube facing posterior (rotated 180 degrees from its normal position and relationship to the trachea). [291] The single-lumen tube enters the right or left mainstem bronchus when the concavity of the tube faces anteriorly or posteriorly, respectively, because the bevel is left- or right-facing, respectively (i.e., a left-facing bevel enters the right mainstem bronchus and a right-facing bevel enters the left mainstem bronchus). [292] Second, a fiberoptic bronchoscope can be passed through a self-sealing diaphragm in the single-lumen tube elbow connector and directed into the left mainstem bronchus. Persistent large, soft catheter suctioning of the carinal area through the single-lumen tube before use of the fiberoptic bronchoscope and suctioning through the fiberoptic bronchoscope (through the single-lumen tube) may be required to visualize the tracheal carina. The single-lumen tube can then be passed over the fiberoptic bronchoscope into the left mainstem bronchus, thereby isolating the bleeding right lung and allowing selective ventilation of the left lung. Passing the fiberoptic bronchoscope through a self-sealing diaphragm allows the continuance of positive-pressure ventilation and PEEP around the bronchoscope. However, it should be realized that visualization of the carina may not be possible when the bleeding is copious and that the only hope for the patient may lie in rapid thoracotomy and control of bleeding from within the chest. In addition, under these adverse conditions, conventional passage of a DLT tube may more rapidly and effectively separate the two lungs than visualization of the anatomy with a fiberoptic bronchoscope.

In summary, use of DLTs is the method of choice for separating the lungs in most adult patients. If there is any question, the precise location of a DLT can be determined by fiberoptic bronchoscopy at any time. There are a number of situations in which insertion of a DLT may be difficult and/or dangerous, and under these circumstances consideration should be given to separating the lungs with a single-lumen tube alone or in combination with a bronchial blocker (e.g., the Univent tube). However, when using a single-lumen tube in a mainstem bronchus or when using a bronchial blocker, ability to suction the operative site and control oxygen uptake (the blocked lung cannot be ventilated with oxygen at any time) is limited. In addition, placement of the single-lumen tube into one or the other mainstem bronchus and proper placement of a bronchial blocker usually require fiberoptic bronchoscopy. Therefore, no matter what method of separating the lungs is chosen, there is a real need for the immediate availability of a small-diameter fiberoptic bronchoscope (for checking the position of the DLT, placing a single-lumen tube in the left mainstem bronchus, and placing a bronchial blocker) that has a suction port to clear secretions and blood from the airway.

Physiology of One-Lung Ventilation

Comparison of Arterial Oxygenation and Carbon Dioxide Elimination During Two-Lung Versus One-Lung Ventilation

As discussed previously, the matching of ventilation and perfusion is impaired during two-lung ventilation in an anesthetized, paralyzed, open-chested patient in the LDP. The reason for the mismatching is relatively good ventilation but poor perfusion of the nondependent lung and poor ventilation and good perfusion of the dependent lung (see Figs. 48-13 (Figure Not Available) and 48-26 (Figure Not Available) A). The blood flow distribution has been seen to be mainly and simply determined by gravitational effects. The relatively good ventilation of the nondependent lung has been seen to be caused, in part, by the open chest and paralysis. The relatively poor ventilation of the dependent lung has been seen to be caused, in part, by the loss of dependent lung volume with general anesthesia and by circumferential compression of the dependent lung by the mediastinum, abdominal contents, and suboptimal positioning effect. The compression of the dependent lung may cause the development of a shunt compartment in this lung (see Fig. 48-13 (Figure Not Available) ; Fig. 48-27 (Figure Not Available) A). Consequently, two-lung ventilation under these circumstances may result in an increased $P(A\text{-}a)_{O_2}$ and impaired oxygenation.

If the nondependent lung is nonventilated, as during one-lung ventilation, then any blood flow to the nonventilated lung becomes shunt flow, in addition to whatever shunt flow might exist in the dependent lung (Fig. 48-27 (Figure Not Available) B). Thus, one-lung ventilation creates an obligatory right-to-left transpulmonary shunt through the nonventilated nondependent lung, which is not present during two-lung ventilation. Consequently, it is not surprising to find that, given the same inspired oxygen concentration (F_{IO_2}) and hemodynamic and metabolic status, one-lung ventilation results in a much larger $P(A\text{-}a)_{O_2}$ and lower Pa_{O_2} than two-lung ventilation. This contention is best supported by one study that compared

Figure 48-27 (Figure Not Available) Schematic representation of two-lung ventilation versus one-lung ventilation. Typical values for fractional blood flow to the nondependent and dependent lungs as well as arterial oxygen tension (Pa_{O_2}) and shunt (Q_S/Q_T) for the two conditions are shown. The Q_S/Q_T during two-lung ventilation is assumed to be distributed equally between the two lungs (5 percent to each lung). The essential difference between two-lung and one-lung ventilation is that during one-lung ventilation the nonventilated lung has some blood flow and therefore has an obligatory shunt, which is not present during two-lung ventilation. The 35 percent of total flow perfusing the nondependent lung, which was not shunt flow, was assumed to be able to reduce its blood flow by 50 percent by hypoxic pulmonary vasoconstriction. The increase in Q_S/Q_T from two-lung to one-lung ventilation is assumed to be solely due to the increase in shunt through the nonventilated, nondependent lung during one-lung ventilation. *(From Benumof [604])*

arterial oxygenation during two-lung and one-lung ventilation, wherein each patient served as his or her own control. [293]

One-lung ventilation has much less of a steady-state effect on Pa_{CO_2} than on Pa_{O_2}. Blood passing through underventilated alveoli retains more than a normal amount of carbon dioxide and does not take up a normal amount of oxygen; blood traversing overventilated alveoli gives off more than a normal amount of carbon dioxide but cannot take up a proportionately increased amount of oxygen because of the flatness of the top end of the oxyhemoglobin dissociation curve. Thus, during one-lung ventilation (the one-lung minute ventilation equals the two-lung minute ventilation) the ventilated lung can eliminate enough carbon dioxide to compensate for the nonventilated lung, and P_{ACO_2} to Pa_{CO_2} gradients are small; however, the ventilated lung cannot take up enough oxygen to compensate for the nonventilated lung, and P_{AO_2} to Pa_{O_2} gradients are usually large. With a constant minute ventilation (two-lung ventilation as compared with one-lung ventilation), the retention of carbon dioxide by blood traversing the nonventilated lung usually slightly exceeds the increased elimination of carbon dioxide from blood traversing the ventilated

lung, and the Pa CO_2 will usually slowly increase (along with the $E_T CO_2$).

The initiation of one-lung ventilation has much more of an acute effect (first 5 minutes) on PET CO_2 . When one-lung ventilation is begun (keeping total tidal volume and respiratory rate constant), the ventilated lung is immediately hyperventilated in relation to its perfusion (i.e., has an increased V/Q ratio) and PET CO_2 from this lung decreases in the first minute (e.g., by 5 mm Hg). [294]

Over the next 5 minutes, HPV in the nonventilated lung shifts blood flow over to the ventilated lung, increases ventilated lung perfusion, decreases ventilated lung V/Q ratio and increases the PET CO_2 back to the baseline two-lung ventilation value. [294] Thereafter, and as discussed previously, PET CO_2 will slowly increase (along with Pa CO_2) because the same total minute ventilation to one lung is not as effective as when it is delivered to both lungs (i.e., there is an increased alveolar dead space within the one ventilated lung). [294]

Blood Flow Distribution During One-Lung Ventilation

Blood Flow to the Nondependent, Nonventilated Lung

Fortunately, both passive mechanical and active vasoconstrictor mechanisms are usually operant during one-lung ventilation that minimize the blood flow to the nondependent, nonventilated lung and thereby prevent Pa O_2 from decreasing as much as might be expected on the basis of the distribution of blood flow during two-lung ventilation. The passive mechanical mechanisms that decrease blood flow to the nondependent lung are gravity, surgical interference with blood flow, and perhaps the extent of preexisting disease in the nondependent lung (Fig. 48-28) (Figure Not Available) . Gravity causes a vertical gradient in the distribution of pulmonary blood flow in the LDP for the same reason that it does in the upright position (see Fig. 48-9) (Figure Not Available) . Consequently, blood flow to the nondependent lung is less than that to the dependent lung. The gravity component of blood flow reduction to the nondependent lung should be constant with respect to both time and magnitude.

Surgical compression (directly compressing lung vessels) and retraction (causing kinking and tortuosity of lung vessels) of the nondependent lung may further passively reduce nondependent lung blood flow. In addition, ligation of pulmonary vessels during pulmonary resection greatly decreases nondependent lung blood flow. The surgical interference component of blood flow reduction to the nondependent lung should be variable with respect to both time and magnitude.

The amount of disease in the nondependent lung is also a significant determinant of the amount of blood flow to the nondependent lung. If the nondependent lung is severely diseased, there may be a fixed reduction in blood flow to this lung preoperatively and collapse of such a diseased lung may not cause much of an increase in shunt. The notion that a diseased pulmonary vasculature might be incapable of HPV is supported by the observations that administration of

Figure 48-28 (Figure Not Available) Schematic diagram of the determinants of blood flow distribution during one-lung ventilation. The major determinants of blood flow to the nondependent lung are gravity, surgical interference with blood flow, amount of nondependent lung disease, and magnitude of nondependent lung hypoxic pulmonary vasoconstriction. The determinants of dependent lung blood flow are gravity, amount of dependent lung disease, and dependent lung hypoxic pulmonary vasoconstriction. *(From Benumof [604])*

sodium nitroprusside and nitroglycerin (which should abolish any preexisting HPV) to COPD patients (who have a fixed reduction in the cross-sectional area of their pulmonary vascular bed) does not cause an increase in shunt, [295] whereas these drugs do increase shunt in patients with acute regional lung disease who have an otherwise normal pulmonary vascular bed. [296] If the nondependent lung is normal and has a normal amount of blood flow preoperatively, collapse of such a normal lung may be associated with a higher nonventilated nondependent lung blood flow and shunt. A higher one-lung ventilation shunt through the nondependent lung may be more likely to occur in patients who require thoracotomy for nonpulmonary disease. [297] Two studies have systematically validated the inverse correlation between the amounts of nondependent lung disease and shunt during one-lung ventilation. [298] [299]

The most significant reduction in blood flow to the nondependent lung is caused by an active vasoconstrictor mechanism. The normal response of the pulmonary vasculature to atelectasis is an increase in PVR (in just the atelectatic lung); this increase, thought to be due almost entirely to HPV, [153] [154] [155] diverts blood flow from the atelectatic lung toward the remaining normoxic or hyperoxic ventilated lung. The diversion of blood flow minimizes the amount of shunt flow that occurs through the hypoxic lung. Figure 48-6 shows the theoretically expected effect of HPV on arterial oxygen tension (Pa O_2) as the amount of lung that is made hypoxic increases. [209] When very little of the lung is hypoxic (near 0%) it does not matter, in terms of Pa O_2 , whether the small amount of lung has HPV operating or not because in either case the shunt will be small. When most of the lung is hypoxic (near 100%) there is no significant normoxic region to which the hypoxic region can divert flow, and again it does not matter, in terms of Pa O_2 , whether or not the hypoxic region has HPV operating. When the percentage of lung that is hypoxic is intermediate (between 30 and 70%), which is the amount of lung that is typically hypoxic during the one-lung ventilation-anesthesia condition, there is a large difference between the Pa O_2 expected with a normal amount of HPV (which is a 50% blood flow reduction for a single lung) [209] as compared with no HPV. In fact, in this range of hypoxic lung, HPV can increase Pa O_2 from hypoxemic levels to much higher and safer values. It is not surprising, then, that numerous clinical studies on one-lung ventilation have found that the shunt through the nonventilated lung is usually 20 to 30 percent of the cardiac output, as opposed to the 40 to 50 percent shunt that might be expected if there were no HPV operating in the nonventilated lung. [297] [300] [301] [302] [303] [304] [305] Thus, HPV is an autoregulatory mechanism that protects the Pa O_2 by decreasing the amount of shunt flow that can occur through hypoxic lung.

Figure 48-29 (Figure Not Available) . outlines the major determinants of the amount of atelectatic lung HPV that might occur during anesthesia. In the following discussion, the HPV issues or considerations are numbered as they are in Figure 48-29 (Figure Not Available) .

1. The distribution of the alveolar hypoxia is probably not a determinant of the amount of HPV; all regions of the lung (either the basilar or dependent parts of the lungs [supine or upright] or discrete anatomic units such as a lobe

   or single lung) respond to alveolar hypoxia with vasoconstriction. [306] However, recent evidence suggests that on a sublobar level, collateral ventilation may be the first line and HPV the second line of defense against the development of arterial hypoxemia. [307]
2. As with low V/Q ratios and nitrogen-ventilated lungs, it appears that the preponderance of blood flow reduction in acutely atelectatic lung is due to HPV and none of it to passive mechanical factors (such as vessel tortuosity). [153] [154] [155] This conclusion is based on the observation that reexpansion and ventilation of a collapsed lung with nitrogen (removing any mechanical factor) do not increase the blood flow to the lung, whereas ventilation with oxygen restores all the blood flow to precollapse values. This conclusion applies whether ventilation is spontaneous or due to positive pressure and whether the chest is open or closed. [154] In canines, a slight amount of further subacute (>30 min) decrease in blood flow to atelectatic lung may have been due to some mechanical effect of the atelectasis on lung blood vessels. [308] However, in humans a prolonged unilateral hypoxic challenge during anesthesia results in an immediate vasoconstrictor response with no further potentiation or diminution of the HPV response. [309]
3. Most systemic vasodilator drugs either inhibit regional HPV directly or have an effect in a clinical situation that is consistent with inhibition of regional HPV (i.e., decreasing Pa O_2 and increasing shunt in patients with acute respiratory disease). The vasodilator drugs that have been shown to inhibit HPV or to have a clinical effect con-sistent with inhibition of HPV are nitroglycerin, [296] [310] [311] [312] [313] [314] [315] [316] nitroprusside, [296] [317] [318] [319] [320] [321] [322] [323] dobutamine, [324] [325] several calcium antagonists, [326] [327] [328] [329] [330] [331] and many beta$_2$ -agonists (isoproterenol,ritodrine, orciprenaline, salbutamol, ATP, and glucagon). [325] [332] [333] [334] [335] [336] [337] [338] Nitric oxide, a potent inhaled pulmonaryvasodilator, has been studied extensively and is considered to inhibit HPV. [339] [340] [341] [342] [343] [344] Aminophylline and hydralazine may not decrease HPV. [345]
4. The effect of anesthetic drugs on regional HPV was previously discussed in the section *Effect of Anesthetics on Hypoxic Pulmonary Vasoconstriction.*
5. The HPV response is maximal at normal and decreased at either high or low pulmonary vascular pressure. The mechanism for high pulmonary vascular pressure inhibition of HPV (whether the cardiac output is high or low [346] [347] is simple; the pulmonary circulation is poorly endowed with smooth muscle and cannot constrict against an increased vascular pressure. Furthermore, in the one-lung ventilation situation in the LDP, it is obvious, with all other factors remaining constant, that the fraction of the cardiac output perfusing the collapsed nondependent lung will increase with increasing pulmonary arterial pressure (i.e., the effect of gravity will be overcome). [348] The mechanism for low pulmonary vascular pressure inhibition of HPV is more complex. For this to occur, the hypoxic compartment must be atelectatic. Under these circumstances, when pulmonary vascular pressure decreases, it is possible for part of the ventilated lung (but not the atelectatic lung) to be in a zone 1 condition (alveolar pressure increases in relation to pulmonary artery pressure) and to experience a

disproportionate increase in PVR, which would divert blood flow back over to the atelectatic lung, thereby inhibiting atelectatic lung HPV. [349]

6. The HPV response also is maximal when Pv O_2 is normal and is decreased by either high or low Pv O_2 . The mechanism for high PvO_2 inhibition of HPV is presumably due to reverse diffusion of oxygen, causing the oxygen tension of either the vessels, the interstitial or alveolar spaces, or all of these to be increased above the HPV threshold. [350] That is, if enough oxygen can reach some receptor in the small arteriole-capillary-alveolar area, then the vessels will not vasoconstrict. The mechanism for low Pv O_2 inhibition of HPV is a result of the low Pv O_2 decreasing alveolar oxygen tension in the normoxic compartment down to a level sufficient to induce HPV in the supposedly normoxic lung. [351] The HPV in the presumably normoxic lung competes against and offsets the HPV in the originally hypoxic lung and results in no blood flow diversion from the more obviously hypoxic lung.
7. Selectively decreasing the F IO_2 in the normoxic compartment (from 1.0 to 0.5 to 0.3) causes an increase in normoxic lung vascular tone, thereby decreasing blood flow diversion from hypoxic to normoxic lung. [351] Indeed, with unilateral lung injury, ventilation of both lungs with a hypoxic gas mixture (F IO_2 of 0.12) induces much more vasoconstriction in the normal, previously nonconstricted lung than in the injured and already hypoxically constricted lung, which redirects blood flow to, increases the shunt through, and increases edema in the injured lung. [352] In addition, the development of systemic hypoxemia, either when bilateral hypoxic ventilation is used or when there is a very largehypoxic compartment and a small normoxic compartment, may indirectly inhibit regional HPV by stimulation of arterial chemoreceptors. [353] At the other extreme, prolonged exposure to hyperoxia (F IO_2 of 1.0) for 68 hours blunts a subsequent whole-lung HPV response. [354]
8. Older studies have suggested that the vasoconstrictor drugs (dopamine, epinephrine, phenylephrine) constrict normoxic lung vessels preferentially, thereby disproportionately increasing normoxic lung [325] [329] [335] PVR. The increase in normoxic lung PVR would be expected to decrease normoxic lung blood flow and increase atelectatic lung blood flow. The HPV-inhibiting effect of vasoconstrictor drugs is similar to that of decreasing normoxic lung F IO_2 (see item 7). In recent years, dopamine has been extensively studied. Although one reasonably straightforward study [355] agrees well with previous studies, [325] [329] [335] [347] most recent studies [356] [357] [358] have shown no significant effect of dopamine on HPV and/or arterial oxygenation. On the basis of these latter more recent studies, dopamine appears to be a reasonable cardiovascular stimulant to use in patients with lung disease provided that arterial oxygenation is monitored.
9. Hypocapnia has been thought to directly inhibit and hypercapnia to directly enhance regional HPV. [346] [359] In addition, during one-lung ventilation conditions, hypocapnia can be produced only by hyperventilation of the one lung. The hyperventilation requires an increased ventilated lung airway pressure, which may cause increased ventilated lung PVR, which in turn may divert blood flow back into thehypoxic lung. Hypercapnia during one-lung ventilation seems to act as a vasoconstrictor by selectively increasing ventilated lung PVR (which would divert blood flow back to the nonventilated lung). In addition, hypercapnia is ordinarily caused by hypoventilation of the ventilated lung, which greatly increases the risk of developing low V/Q and atelectatic regions in the dependent lung. However, it should

be noted as a theoretical possibility that if hypoventilation of the dependent lung is associated with decreased ventilated lung airway pressure, ventilated lung pulmonary vascular resistance may be decreased, thus in turn promoting or enhancing HPV in the nonventilated lung.

10. The effects of changes in airway pressure due to PEEP and tidal volume changes are discussed in detail in the sections *Dependent Lung PEEP* and *Selective Dependent Lung PEEP.* In brief, selective application of PEEP to only normoxic ventilated lung will selectively increase PVR in the ventilated lung and shunt blood flow back into thehypoxic nonventilated lung (i.e., decrease nonventilated lung HPV). [360] [361] On the other hand, high-frequency ventilation of the gas-exchanging lung is associated with low airway pressure and enhancement of HPV in the collapsed lung. [362]

Figure 48-29 (Figure Not Available) Listing of many of the components of the anesthetic experience that might determine the amount of regional hypoxic pulmonary vasoconstriction (HPV). The clockwise numbering of considerations corresponds to the order in which these considerations are discussed in the text. V/Q, ventilation/perfusion ratio; PVP, pulmonary vascular pressure; Pv O_2 , mixed venous oxygen tension; F IO_2 , inspired oxygen fraction; P $AC O_2$, alveolar carbon dioxide tension; PEEP, positive end-expiratory pressure. *(From Benumof [604])*

Finally, there is some evidence that certain types of infections (which may cause atelectasis), particularly granulomatous and pneumococcal infections, may inhibit HPV. [363] [364]

Blood Flow to the Dependent Ventilated Lung

The dependent lung usually has an increased amount of blood flow due to both passive gravitational effects and active nondependent lung vasoconstrictor effects. However, the dependent lung may also have a hypoxic compartment (area of low V/Q ratio and atelectasis) that was present preoperatively or that developed intraoperatively. This hypoxic compartment may develop intraoperatively for several reasons. First, in the LDP the ventilated dependent lung usually has a reduced lung volume resulting from the combined factors of induction of general anesthesia and circumferential (and perhaps severe) compression by the mediastinum from above, by the abdominal contents pressing against the diaphragm from the caudad side, and by suboptimal positioning effects (rolls, packs, chest supports) pushing in from the dependent side and axilla [207] [231] [334] [365] (see Fig. 48-13) (Figure Not Available) . Second, absorption atelectasis can also occur in regions of the dependent lung that have low V/Q ratios when they are exposed to high inspired oxygen concentration. [366] [367] Third, difficulty in secretion removal may cause the development of poorly ventilated and atelectatic areas in the dependent lung. Finally, maintaining the LDP for prolonged periods may cause fluid to transude into the dependent lung (which may be vertically below the left atrium) and cause further decrease in lung volume and increase in airway closure in the dependent lung. [368]

The development of low V/Q ratio and/or atelectatic areas in the dependent lung increases vascular resistance in the dependent lung [365] [369] (because of dependent lung HPV), [306] thereby decreasing dependent lung blood flow and increasing nondependent lung blood flow. [370] Stated differently, the PVR in the ventilated compartment of the lung determines the ability of the ventilated, and supposedly normoxic, lung to accept redistributed blood flow from the hypoxic lung. Clinical conditions that are independent of specific dependent lung disease but that may still increase dependent lung vascular resistance in a dose-dependent manner are a decreasing inspired oxygen tension in the dependent lung (from 1.0 to 0.5 to 0.3) [351] [370] and decreasing temperature (from 40 to 30°C). [371]

Miscellaneous Causes of Hypoxemia During One-Lung Ventilation

Still other factors may contribute to hypoxemia during one-lung ventilation. Hypoxemia due to mechanical failure of the oxygen supply system or the anesthesia machine is a recognized hazard of any kind of anesthesia. Gross hypoventilation of the dependent lung can be a major cause of hypoxemia. Malfunction of the dependent lung airway lumen (blockage by secretions) and malposition of the DLT are, in our experience, frequent causes of increased P(A-a) O_2 and hypoxemia. Resorption of residual oxygen from the nonventilated lung is time-dependent and accounts for a gradual increase in shunt and decrease in Pa O_2 after one-lung ventilation is initiated. [369] With all other anesthetic and surgical factors constant, anything that decreases the Pv O_2 (decreased cardiac output, increased oxygen consumption [excessive sympathetic nervous system stimulation, hyperthermia, shivering]) causes increased P(A-a) O_2 . [372] [373] Finally, transfusion of blood may cause pulmonary dysfunction, and the dysfunction has been attributed to the action of isoantibodies against leukocytes, which causes cellular aggregation, microvascular occlusion, and capillary leakage. Indeed, such a reaction has been described during prolonged one-lung ventilation. [374] Interestingly, the noncollapsed lung was preferentially injured, and the collapsed lung showed only minimal radiologic signs of edema after reexpansion. [374]

Conventional Management of One-Lung Ventilation

The proper initial conventional management of one-lung ventilation is logically based on the preceding determinants of blood flow distribution during one-lung ventilation. In view of the fact that one-lung ventilation incurs a definite risk of causing systemic hypoxemia, it is extremely important that dependent lung ventilation, as it affects these determinants, be optimally managed. This section considers the usual management of one-lung ventilation in terms of the most appropriate F IO_2 , tidal volume, and respiratory rate (Table 48-15) .

Inspired Oxygen Concentration

Although the theoretical possibilities of absorption atelectasis and oxygen toxicity exist, the benefits of ventilating the

TABLE 48-15 -- Initial Conventional Ventilatory Management of One-Lung Anesthesia

1. Maintain two-lung ventilation as long as possible.
2. Use F IO_2 = 1.0.
3. Begin one-lung ventilation with tidal volume of 10 mL/kg.

4. Adjust respiratory rate so that Pa CO_2 = 40 mm Hg.

5. Use continuous monitoring of oxygenation and ventilation.

dependent lung with 100 percent oxygen far exceed the risks. A high F IO_2 in the single ventilated lung may critically increase Pa O_2 from arrhythmogenic and life-threatening levels to safer levels.

In addition, a high F IO_2 in the dependent lung causes vasodilation, thereby increasing the dependent lung capability of accepting blood flow redistribution due to nondependent lung HPV. Direct chemical 100 percent oxygen toxicity does not occur during the operative period, [375] and absorption atelectasis in the dependent lung [375] is unlikely to occur in view of the remaining one-lung ventilation management characteristics (moderately large tidal volumes with intermittent positive-pressure, low-level PEEP). If the anesthesiologist is concerned about and wishes to limit the F IO_2 in patients treated with either bleomycin or mitomycin, it is possible to carefully increase or decrease F IO_2 to both lungs independently in an attempt to have the lowest F IO_2 to both lungs (even when CPAP is administered to the nonventilated lung). [376]

Tidal Volume

The dependent lung should be ventilated with a tidal volume of approximately 10 mL/kg. A much smaller tidal volume might promote dependent-lung atelectasis; a much greater tidal volume might excessively increase dependent lung airway pressure and vascular resistance [369] and thereby increase nondependent lung blood flow (decrease nondependent lung HPV). [360] [377] [378] If a tidal volume of 10 mL/kg causes excessive airway pressure, it should be lowered (after mechanical causes [i.e., tube malfunction] have been ruled out) and the respiratory rate increased (see later).

A dependent-lung tidal volume of 10 mL/kg is in the middle of a range of tidal volumes (8-15 mL/kg) that have been found in one study not to affect arterial oxygenation greatly during one-lung ventilation. [302] In that study, changes in Pa O_2 with alterations in tidal volume (during stable one-lung ventilation conditions) in individual patients were variable and unpredictable in both degree and direction (although the mean value for the group did not change). Thus, it appears that changing the tidal volume from 15 to 8 mL/kg during one-lung ventilation has an unpredictable but usually not great impact on arterial oxygenation. [302]

Dependent Lung PEEP

No, or just a very low level of, dependent lung PEEP (<5 cm H_2O) should be used initially because of concern of unnecessarily increasing dependent lung PVR. Although this is unlikely to occur when dependent lung PEEP is less than 5 cm H_2O, [379] the presence of intrinsic PEEP during one-lung ventilation may make the total PEEP excessive [380] (see the section, *Selective Dependent-Lung PEEP*).

Respiratory Rate

The respiratory rate should be set so that the Pa CO_2 remains at 40 mm Hg. Because a dependent lung tidal volume of 10 mL/kg represents a 20 percent decrease from the usual two-lung tidal volume of 12 mL/kg, the respiratory rate usually has to be increased by 20 to 30 percent to maintain carbon dioxide hemostasis. The trade-off between decreased tidal volume and increased respiratory rate usually results in a constant minute ventilation; although ventilation and perfusion are considerably mismatched during one-lung ventilation, an unchanged minute ventilation during one-lung ventilation (as compared with two-lung ventilation) can continue to eliminate a normal amount of carbon dioxide because of the high diffusibility of carbon dioxide. [369] [381] [382] [383] Hypocapnia should be prevented because use of the airway pressure in the dependent lung necessary to produce systemic hypocapnia may excessively increase dependent lung vascular resistance. Furthermore, hypocapnia may directly inhibit HPV in the nondependent lung. [346] [359]

In summary, at the commencement of one-lung ventilation, 100 percent oxygen, a tidal volume of 10 mL/kg, and a 20 percent increase in respiratory rate are used as initial ventilation settings (see Table 48-15) . Ventilation and arte-rial oxygenation are monitored by use of arterial blood gases, end-tidal carbon dioxide concentration, and pulse oximetry. If there is a problem with either ventilation or arterial oxygenation, one or more of the differential lung management techniques described next are used.

Differential Lung Management of One-Lung Ventilation

Intermittent Inflation of the Nondependent Operative Lung

Intermittent inflation with oxygen of the collapsed lung during one-lung ventilation may be expected to increase Pa O_2 for a variable period of time. In a group of thoracic surgery patients undergoing one-lung ventilation with an inspired nitrous oxide fraction (F IN_2O) of 0.5 and an F IO_2 of 0.5, the collapsed lung was manually inflated with a breath every 5 minutes with 2 L of oxygen and the lung was then allowed to collapse again; Pa O_2 increased by more than 28 mm Hg following each inflation. [384] The beneficial effect of each inflation persisted to a large extent to the next breath even if at a gradually decreasing level. Although Pa O_2 decreased between inflations, it never reached the level observed in controls (no lung inflation) during 19 minutes of one-lung ventilation.

Selective Dependent Lung PEEP

Because the ventilated dependent lung often has decreased lung volume during one-lung ventilation (see Figs. 48-13 (Figure Not Available) , 48-28 (Figure Not Available) , and 48-30) , it is not surprising that several attempts have been made to improve oxygenation by selectively treating the ventilated lung with PEEP. [207] [237] [304] [360] [377] [378] An accepted risk of selective dependent lung PEEP is that the PEEP-induced increase in lung volume can cause compression of the small dependent lung intra-alveolar vessels and increase dependent lung PVR; this diverts blood flow from the ventilated lung to the nonventilated lung (see Fig. 48-30 , upper right panel), increasing the shunt and decreasing the Pa O_2 . That increases

Figure 48-30 Four-part schematic diagram showing the effects of various differential lung management approaches. (A) The one-lung ventilation situation. The DOWN (dependent) lung is ventilated (VENT) but is compressed by the weight of the mediastinum (M) from above, the pressure of the abdominal contents against the diaphragm (D), and by positioning effects of rolls, packs, and shoulder supports (P). The UP (nondependent) lung is nonventilated (NONVENT), and blood flow through this lung is shunt flow. (B) The dependent lung has been selectively treated with PEEP, which improves V/Q relationships in the dependent lung but also increases dependent lung vascular resistance; this diverts blood to, and thereby increases shunt flow through, the nonventilated lung. (C) Selective application of CPAP to the nondependent lung permits oxygen uptake from this lung; even if the CPAP causes an increase in vascular resistance and diverts blood flow to the dependent lung, the diverted blood flow can still participate in gas exchange in the ventilated dependent lung. Consequently, selective nondependent lung CPAP can greatly increase Pa O_2 . (D) With differential lung CPAP (nondependent lung)/PEEP (dependent lung), it does not matter where the blood flow goes, since both lungs can participate in O_2 uptake. With this latter one-lung ventilation pattern, Pa O_2 can be restored to levels near those achieved by two-lung ventilation.

in both PEEP and tidal volume in the dependent ventilated lung have an additive effect in decreasing Pa O_2 during one-lung ventilation greatly supports the one-ventilated lung volume versus vascular resistance hypothesis. [377] Therefore, the effect of dependent lung PEEP on arterial oxygenation is a trade-off between the

positive effect of increasing dependent lung FRC and V/Q ratio and the negative effect of increasing dependent lung PVR and shunting blood flow to the nonventilated lung. Not surprisingly, then, the various one-lung ventilation-PEEP studies have had patients who have had an increase, [304] [377] [385] no change, [377] [385] [386] [387] or a decrease [304] [377] [385] [388] [389] [390] in oxygenation. It may be expected that in patients with a very diseased dependent lung (low lung volume and low V/Q ratio), the positive effects of selective dependent lung PEEP (increased lung volume and increased V/Q ratio) might outweigh the negative effects (shunting of blood flow to the nonventilated, nondependent lung), whereas in patients with a normal dependent lung, the negative effects would outweigh the benefits. Indeed, in one study in which 10 cm H_2O PEEP was selectively applied to the dependent lung, Pa O_2 increased in those patients with an initial Pa O_2 of less than 80 mm Hg (F_{IO_2} of 0.5), whereas Pa O_2 decreased or remained constant in patients with an initial Pa O_2 higher than 80 mm Hg (F_{IO_2} of 0.5). [385] [390] Presumably, in the patients with Pa O_2 lower than 80 mm Hg, the dependent lung had a low FRC (low V/Q ratio and atelectatic regions); therefore, the positive effect of increased dependent lung volume predominated over the negative effect of shunting blood flow to the nonventilated lung. Conversely, the patients with the higher Pa O_2 presumably had a dependent lung with an adequate FRC and V/Q ratio, and the negative effect of shunting blood flow to the nonventilated lung predominated over the positive effect of increased dependent lung volume. Although a dose (ventilated lung PEEP) versus response (Pa O_2, Q_S/Q_T value) relationship has been poorly described, it seems reasonable to postulate on the basis of these results [304] [377] [385] [386] [387] [388] [389] [390] that the therapeutic margin of using PEEP to increase Pa O_2 during one-lung ventilation is quite narrow. PEEP only to the dependent ventilated lung may be delivered by the same anesthesia apparatus that is ordinarily used to deliver PEEP to the whole lung. Other studies have shown that high tidal volumes, [301] variations in the inspiratory/expiratory ratio, [386] and intermittent manual hyperventilation of the lower lung are not beneficial in increasing Pa O_2 during one-lung ventilation. [386]

Low levels of positive pressure can be selectively and statically applied to only the nonventilated, nondependent lung. Because under these conditions the nonventilated lung is only slightly but constantly distended by oxygen, an appropriate term for this ventilatory arrangement is *nonventilated lung CPAP.* The application of CPAP (without tidal ventilation) to only the nonventilated lung significantly increases oxygenation. [388] [391] Also, the institution of 10 cm H_2O nondependent lung CPAP in patients has no significant hemodynamic effect. [385] [389] Low levels of CPAP simply maintain the patency of nondependent lung airways, allowing some oxygen distention of the gas exchanging alveolar space in the nondependent lung (Fig. 48-30 C) without significantly affecting the pulmonary vasculature. In all clinical studies, [385] [388] [389] [392] the application of 5 to 10 cm H_2O CPAP has not interfered with the performance of surgery and may, in fact, facilitate intralobar dissection. This is not surprising in view of the fact that the initial compliance of a collapsed lung is only 10 mL/cm H_2O, and 5 to 10 cm H_2O CPAP should create only a slightly distended lung that occupies a volume of 50 to 100 mL, which is hardly or not at all noticed by the surgeon.

On the other hand, in a canine study, [391] 15 cm H_2O of nondependent lung CPAP caused changes in Pa O_2 and shunt similar to those of 5 to 10 cm H_2O of nondependent lung CPAP, whereas blood flow to the nonventilated nondependent lung decreased significantly. Therefore, high levels of nonventilated lung CPAP act by permitting oxygen uptake in the nonventilated lung as well as by causing blood flow diversion to the ventilated lung, where both oxygen and carbon dioxide exchange can take place (see Fig. 48-30 C). Because low levels of nonventilated lung CPAP are as efficacious as high levels and have less surgical interference and hemodynamic implications, it is logical to use low levels of nonventilated CPAP first.

In all patients in all clinical studies to date, 5 to 10 cm H_2O of nondependent lung CPAP has significantly increased Pa O_2 during one-lung ventilation. [385] [388] [389] [392] [393] [394] [395] It should be concluded that the single most efficacious maneuver to increase Pa O_2 during one-lung ventilation is to apply 5 to 10 cm H_2O of CPAP to the nondependent lung. In our experience, low levels of nonventilated lung CPAP have corrected severe hypoxemia (Pa O_2 <50 mm Hg) more than 95 percent of the time, provided that the DLT was correctly positioned. However, the nondependent lung CPAP must be applied during the deflation phase of a large tidal volume so that the deflating lung can lock into a CPAP level with uniform expansion and obviate the need to overcome critical opening pressures of airways and alveoli.

In both the human [388] and canine [391] studies, oxygen insufflation at zero airway pressure did not significantly improve Pa O_2 and shunt, and this result was probably due to the inability of zero transbronchial airway pressure to maintain airway patency and overcome critical alveolar opening pressures. Although one study in patients has concluded that insufflation of O_2 at zero airway pressure does increase Pa O_2, the study is difficult to interpret, because the patients did not serve as their own controls. [396]

Several selective nondependent lung CPAP systems that are easy to assemble have been described. [389] [393] [394] [395] All these nondependent lung CPAP systems have three features in common (Fig. 48-31) (Figure Not Available) . First, there must be a source of oxygen to flow into the nonventilated lung. Second, there must be some sort of restrictive mechanism (hand-screw valve, pop-off valve, weight-loaded valve) to retard the egress of oxygen from the nonventilated lung so that the nonventilated lung may become distended. Thus, oxygen from a free-flowing pressurized source flows into a lung, but the escape of the oxygen is restricted; the unrestricted flow in and the restricted flow out create a constant distending pressure. Third, the distending pressure must be measured by a manometer. In practice, it is often simplest to keep the restrictive mechanism constant and adjust the distending pressure with a relatively fine sensitivity by changing the oxygen flow rate. If the nondependent lung CPAP system includes a reservoir bag (which is highly desirable),

Figure 48-31 (Figure Not Available) The three essential components of a nondependent lung CPAP system consist of (1) an oxygen source, (2) a pressure relief valve, and (3) a pressure manometer to measure the CPAP. The CPAP is created by the free flow of oxygen into the lung versus the restricted outflow of oxygen from the lung by the pressure relief valve. ZEEP, zero end-expiratory pressure. *(From Benumof [604])*

Figure 48-32 The Mallinckrodt Broncho-Cath CPAP System. (A) Photograph of entire CPAP system connected to a double-lumen tube. (B) Schematic of the entire CPAP system. (C) Close-up of the CPAP-generating restrictive mechanism. *(Photography courtesy of Mallinckrodt Medical, Inc., St. Louis, MO.)*

the reservoir bag will reflect the amount of CPAP (by distention), and the nondependent lung may also be ventilated with intermittent positive pressure whenever desired.

The availability of a commercial nondependent nonventilated lung CPAP device (Mallinckrodt Medical, Inc.) replaces the need for all homemade devices. The Broncho-Cath CPAP System (Fig. 48-32) is similar in concept to the

system shown in Figure 48-31 (Figure Not Available) except that the restrictive mechanism is a continuously vented slot (opening); the larger the vent slot, the lower the CPAP level delivered, and the smaller the vent slot, the higher the CPAP level. The level of CPAP is selected by simply turning an outer calibrated cylinder (calibrated for an oxygen flow rate of 5 L/min), which progressively uncovers the inner (pop-off) slot. Because the dial is calibrated and marked with the CPAP level selected, a pressure manometer is unnecessary. The rest of the CPAP system consists of the other components shown in Figure 48-31 (Figure Not Available) . (oxygen tubing, reservoir bag). A unique feature of the Broncho-Cath CPAP System is the fact that the valve is continuously vented. Because the vent slot cannot be totally occluded, the danger of overpressurization of the nondependent lung is minimized. In addition, the CPAP system is calibrated from 1 to 10 cm H_2O pressure, which permits accurate delivery of very low levels of CPAP. This may be desirable with extremely compliant lungs or where maximum surgical exposure is required. This small, lightweight CPAP device can be included within the DLT package (the DLT is available with or without the CPAP device), is extremely easy to use, and is preassembled, cost-effective, sterile, reliable, and disposable. Perhaps its most important attribute is that a preassembled device is obviously more readily available than devices that require a search for spare parts, and the commercial product has built-in quality assurance that cannot be duplicated by individual remedies.

Differential Lung PEEP/CPAP

In theory and from the preceding considerations, it appears that the ideal way to improve oxygenation during one-lung ventilation is the application of differential lung PEEP/CPAP (see Fig. 48-30 D) (see the following section for the step-by-step approach). In this situation, the ventilated (dependent) lung is given PEEP in the usual conventional manner in an effort to improve ventilated lung volume and V/Q relationships. Simultaneously, the nonventilated (nondependent) lung receives CPAP in an attempt to improve oxygenation of the blood perfusing this lung. Therefore, with differential lung PEEP/CPAP, it does not matter where the blood flow goes nearly as much as during simple one-lung ventilation, because wherever it goes (to either ventilated or nonventilated lung), it has at least some chance to participate in gas exchange with alveoli that are expanded with oxygen. In indirect support of this contention, arterial oxygenation has been increased significantly in patients during thoracotomy in the LDP (using two-lung ventilation) when PEEP has been added to the ventilated dependent lung, while the nondependent lung was also able to participate in gas exchange by virtue of being ventilated at zero end-expiratory pressure (ZEEP). [237] In direct support of this contention, in patients undergoing thoracotomy and one-lung ventilation, arterial oxygenation was unchanged by the application of 10 cm H_2O dependent lung PEEP alone (consistent with an equal positive/negative effect trade-off), was significantly improved by 10 cm H_2O nondependent lung CPAP alone, and was further and even more significantly increased by use of 10 cm H_2O nondependent lung CPAP and 10 cm H_2O dependent lung PEEP together (differential lung PEEP/CPAP ventilation). [385] [389] The use of 10 cm H_2O nondependent lung CPAP together with 10 cm H_2O dependent lung PEEP in patients caused only small, clinically insignificant hemodynamic effects. [385] [389]

There are multiple reports of significant increases in oxygenation obtained with the application of differential lung ventilation and PEEP (either PEEP/PEEP, PEEP/CPAP, or CPAP/CPAP) through DLTs to intensive care unit patients with acute respiratory failure due to predominantly unilateral lung disease. [397] In all cases conventional two-lung therapy (mechanical ventilation, PEEP, CPAP) had been administered via a standard single-lumen tube and either failed to improve or actually decreased oxygenation. In these patients the single-lumen tube was replaced with a DLT. In most cases the amount of PEEP initially administered to each lung was inversely proportional to the compliance of each lung; ideally, this PEEP arrangement should result in equal FRC in each lung. In some cases, the amount of PEEP that each lung received was later adjusted and titrated in an effort to find a differential lung PEEP combination that resulted in the lowest right-to-left transpulmonary shunt. This treatment modality for severe unilateral lung disease is discussed more fully in Chapter 72 .

Recommended Combined Conventional and Differential Lung Management of One-Lung Ventilation

Figure 48-33 summarizes the recommended plan for obtaining satisfactory arterial oxygenation during one-lung anesthesia. Two-lung ventilation is maintained for as long as possible (usually until the pleura is opened). When one-lung ventilation is commenced, a tidal volume of 10 mL/kg is used, and the respiratory rate is adjusted so that Pa_{CO_2} equals 40 mm Hg. A high inspired oxygen concentration (F_{IO_2} of 0.8-1.0) should be used, and Sa_{O_2} should be monitored continuously.

Figure 48-33 An overall one-lung ventilation plan. F_{IO_2}, inspired oxygen concentration; TV, tidal volume; RR, respiratory rate; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure; ASAP, as soon as possible.

TABLE 48-16 -- Characteristics of the Three Types of High-Frequency Ventilation

TYPE OF HFV	RATE/MIN	TYPE OF VENTILATOR	GAS ENTRAINMENT	PROCESS	
				INSPIRATION	EXHALATION
HFPPV	60-100	Volume	No	Active [a]	Passive [a]
HFJV	100-400	Jet pulsation	Yes	Active	Passive
HFOV	400-2,400	Piston pump	Yes	Active	Active

Abbreviations: HFPPV, High-frequency positive pressure ventilation; HFJV, high-frequency jet ventilation; HFOV, high-frequency oscillatory ventilation.

[a] Active, caused by the ventilator. Passive, caused by elastic recoil of lung.

If hypoxemia is present after this initial conventional approach, two major causes of hypoxemia, namely malposition of the DLT and poor hemodynamic status, must be ruled out. Proper tube position should be confirmed via fiberoptic bronchoscopy. If the DLT is correctly positioned and the hemodynamic status is satisfactory, simple tidal volume and respiratory rate adjustments should be made. [302] For example, if the tidal ventilation is thought to be too high, it should be decreased, and if the tidal ventilation is thought to be too low, it should be increased. If these simple maneuvers do not quickly resolve the problem, the studies of selective nondependent lung CPAP [385] [388] [389] [390] [391] [392] [393] [394] [395] and differential lung PEEP [397] dictate that the next treatment should be to apply 5 to 10 cm H_2O of CPAP to the nondependent lung. Nondependent lung CPAP should be applied during the deflation phase of a large tidal volume breath to overcome critical opening pressures in the atelectatic lung. If oxygenation does not improve with nondependent lung CPAP (as it does in the large majority of cases), 5 to 10 cm H_2O of PEEP should then be applied to the ventilated dependent lung. If dependent lung PEEP does not improve oxygenation, nondependent lung CPAP should be increased to 10 to 15 cm H_2O while the dependent lung is maintained at 5 to 10 cm H_2O of PEEP. If arterial oxygenation is still not satisfactory, the nondependent lung CPAP level should be matched with an equal amount of dependent lung PEEP. In this way, a differential lung PEEP/CPAP search for the maximum compliance and a minimum right-to-left transpulmonary shunt are made in an attempt to find the optimal end-expiratory pressure for each lung and the patient as a whole.

If severe hypoxemia persists after the application of differential lung PEEP/CPAP (which would be extremely rare), it should be remembered that the nondependent lung may be intermittently ventilated with positive pressure with oxygen (see Fig. 48-33) . Finally, most of the V/Q imbalance is eliminated during a pneumonectomy by tightening a ligature around the nonventilated lung pulmonary artery as early as possible, thus directly eliminating all shunt flow through the nonventilated lung (see Fig. 48-33) . Indeed, clamping the pulmonary artery to a collapsed lung functionally resects the entire lung, and the Pa_{O_2} is restored to a level not significantly different from a two-lung ventilation or postpneumonectomy one-lung ventilation value.

Because nondependent lung CPAP has been shown to relieve hypoxemia consistently and reliably during one-lung ventilation, [388] [389] its routine use to prevent hypoxemia during thoracic surgery using DLTs should be considered. Low levels of CPAP used in this manner have not compromised surgical conditions and have occasionally improved surgical exposure by facilitating the identification of intralobar planes. [385] [388] [389] [395]

High-Frequency Ventilation Management of Thoracic Surgery

Conventional intermittent positive-pressure ventilation delivers relatively large tidal volumes (10-15 mL/kg) at respiratory rates usually less than 30 breaths/min. In contrast, high-frequency ventilation (HFV) delivers very small tidal volumes (<2 mL/kg) at rates between 60 and 2,400 breaths/min. Because HFV uses much smaller tidal volumes (and much lower peak inspiratory airway pressures), which can be delivered through very small airway catheters, it may be uniquely useful in facilitating the performance of thoracic surgery in the following three ways.

High-frequency ventilation is an umbrella term encompassing different delivery systems and respiratory rate ranges. Current methods used to provide HFV are quite diverse, but by using the criteria of ventilation rate and type of gas delivery mechanism, it is possible to separate HFV into three general categories (Table 48-16) . With regard to oxygenation, all forms of HFV should be regarded as a method of achieving PEEP (or above ambient airway pressure) and thereby minimizing shunt without the necessity of imposing a large volume (and pressure) excursion on top of this to eliminate carbon dioxide. It is conceptually similar to the approach of holding the lung slightly to moderately distended with an increased mean airway pressure and thereby minimizing shunt while removing carbon dioxide by an extracorporeal membrane. [398] [399]

Use in Major Conducting Airway Surgery

The most important advantage of HFV in thoracic surgery is that the small rapid tidal volumes may be delivered through small airway tubes; thus, if a major conducting airway (trachea, carinal area, main stem bronchus) has to be divided, the transit of a small airway tube through the surgical field causes much less interference with surgery than the passage of a large standard or double-lumen endotracheal tube. The small airway catheters present the surgeon with a relatively unobstructed, accessible circumference of trachea

and bronchus, so that the ends of a divided airway can be properly aligned for the construction of an unstressed and airtight anastomosis. Both high-frequency positive pressure ventilation (HFPPV) and high-frequency jet ventilation (HFJV) have been used successfully with small airway catheters for several different types of airway surgery. [400] In contradistinction to these findings with HFPPV, high-frequency oscillatory ventilation delivered through a standard single-lumen tube has been found to cause changes in the diameter of large airways and to produce a large "mediastinal bounce" with each oscillation, which "made surgery on the major airways and around the hilum and mediastinal structures almost impossible." [401] With all types of HFV for airway surgery, the logistics of small catheter placement and securement are formidable, and suctioning the airway and distal lung may be problematic.

Use in Bronchopleural Fistula

The second proposed advantage of HFV for thoracic surgery is that the lower inspiratory pressures and tidal volumes may result in a smaller gas leak through pathologic low-resistance pathways such as bronchopleural fistulas and tracheobronchial disruptions. Consequently, air leaks (loss of tidal volume) and mediastinal and interstitial emphysema may be minimized with this form of ventilatory treatment, and HFV has been successfully used in the treatment of major bronchopleural fistulas and tracheobronchial disruptions. [400] In most of the bronchopleural fistula cases, Pa CO_2 was unacceptably high despite a high minute ventilation on volume-controlled intermittent positive-pressure ventilation, whereas HFJV restored normocarbia. However, it appears that the reduction in air leak flow through the fistula is directly related to reduced airway pressure with HFV as compared with conventional mechanical ventilation; when peak and mean tracheal pressures are decreased by HFV, fistula leak is decreased, and when peak and mean tracheal pressures are increased by HFV, fistula flow increases. Thus, in a report by Albelda et al [402] of seven consecutive patients with an average bronchopleural fistula leak greater than 5 L/min, HFJV (125-150/min) caused only two patients to have clinically important decreases in airway pressure and air leak fistula flow, and none had significant improvement in gas exchange. The authors recommend measurement of tracheal pressures to predict what is happening to air leak fistula flow. [402] Thus, it is likely that investigations in the use of HFV to treat patients with pathologic low-resistance airway pathways will continue.

Use in Minimizing Movement of the Operative Field

The third proposed advantage of HFV for thoracic surgery is to minimize the tidal movement of the operative field; theoretically, the lower peak inspiratory pressures and tidal volumes of HFV should result in much smaller inflation and deflation movements of the lung. Therefore, HFV of the nondependent lung might provide a relatively "quiet" operative lung field, and HFV of the dependent lung could contribute to the quiet lung field by providing a minimally moving mediastinum. [400] Unfortunately, in no report was the use of HFV compared with conventional one-lung ventilation, with or without nondependent lung CPAP, in terms of operating conditions and efficiency of gas exchange.

The studies of selective nondependent lung CPAP indicate that delivery of any amount of oxygen to the nondependent lung alveolar space will cause some oxygen uptake from the nondependent lung and decrease the right-to-left shunt in this lung. Consequently, it is not surprising that selective HFV of the nondependent lung, while the dependent lung is ventilated with conventional intermittent positive-pressure breathing, increases Pa O_2 compared with simple collapse of the nondependent lung and conventional mechanical ventilation of the dependent lung. [403] However, because the same increase in arterial oxygenation and operative conditions may be obtained by selective nondependent lung CPAP with much simpler equipment than HFV apparatus, it is more logical to use selective nondependent lung CPAP than HFV to improve arterial oxygenation and operative conditions during one-lung ventilation.

In one report the dependent lung was selectively ventilated with HFV while the operated lung was completely collapsed. [404] As compared with selective dependent lung intermittent positive-pressure ventilation, selective dependent lung HFV significantly improved arterial oxygenation, presumably because of lower dependent lung PVR (due to either lower dependent lung airway pressures [405] or release of dependent lung vasodilator prostaglandins [406]) and enhanced operating conditions (because of minimal mediastinal movements). However, the use of dependent lung HFV to minimize mediastinal and hilar movements must remain controversial in view of a 1986 report describing a mediastinal bounce with each oscillation, which made surgery around these structures nearly impossible. [401]

In summary, in view of the limitations of HFV, its use as a routine procedure for all three possible thoracic surgery situations (airway surgery, bronchopleural fistulas, minimizing operative field movement) cannot be recommended.

Low-Flow Apneic Ventilation (Apneic Insufflation)

The need for an absolutely quiet surgical field for short periods often arises during a thoracotomy in which a standard endotracheal tube and two-lung ventilation are used. This can be accomplished relatively safely by using the principle of apneic mass-movement oxygenation. Indeed, this method gained considerable popularity around the time DLTs were being introduced into clinical practice. If ventilation is stopped during the administration of 100 percent oxygen and the airway is left connected to a fresh gas supply, oxygen will be drawn into the lung by mass movement to replace the oxygen that crossed the alveolocapillary membrane. There is usually no difficulty in maintaining an adequate Pa O_2 (especially if 5-10 cm H_2O of CPAP is used) during at least 20 minutes of apneic mass-movement oxygenation.

If the flow of oxygen into the lungs is relatively low (<0.1 L/kg/min) almost all the carbon dioxide produced is retained, and the arterial carbon dioxide tension (Pa CO_2) rises approximately 6 mm Hg in the first minute because of the

washin of venous blood into the arterial compartment (venous blood has a carbon dioxide tension 6 mm Hg higher than that of arterial blood) and then 3 to 4 mm Hg each minute thereafter because of normal carbon dioxide production. [407] [408] On the basis of these considerations, if a patient had normal carbon dioxide production, was hyperventilated to a Pa CO_2 of 30 mm Hg, and was then made apneic and had oxygen insufflated into the lungs with a low flow, the Pa CO_2 after 10 minutes of apnea would be 63 to 72 mm Hg. Indeed, one report describes a series of eight patients in whom apneic mass-movement oxygenation was used for 18 to 55 minutes after normal ventilation. [407] Although the lowest arterial saturation that resulted was 98 percent, the Pa CO_2 in the five patients in whom it was measured ranged from 103 to 250 mm Hg, and the pH ranged from 6.72 to 6.97. Although severe degrees of hypercapnia and respiratory acidosis may be well tolerated in some healthy patients, it would appear that the safe period of low-flow apneic oxygenation during thoracotomy would be well below 10 minutes. Although it has not been studied, low-flow apneic oxygenation should theoretically be able to be used when a DLT is used. In all cases in which this technique is used, arterial oxygen saturation monitoring via pulse oximetry is mandatory.

THE POSTOPERATIVE PERIOD

Early Serious Complications Specifically Related to Thoracic Surgery

Herniation of the Heart

An intrapericardial approach may be used for radical pneumonectomy to facilitate access to major vessels and allow a wider hilar dissection. This technique may result in a large pericardial defect that the surgeon is not able to close after the pneumonectomy is completed. There have been several reports of herniation of the heart [409] through the pericardial opening into the empty hemithorax. The herniation can be into either the right or left hemithorax, and herniation into either side can cause profound cardiac functional impairment; the mortality rate is 50 percent.

With herniation, the heart protrudes through the defect into one of the hemithoraces, potentially causing twisting of the superior vena cava (superior vena cava syndrome), inferior vena cava (cardiovascular collapse), distal trachea (wheezing), pulmonary veins (pulmonary edema), and pericardial constriction of the heart (myocardial ischemia and ventricular arrhythmia). These symptoms may occur individually or in various combinations.

In most reports herniation of the heart has occurred either immediately after the patient is turned from the LDP to the supine position (75%) or during the first few hours of postoperative mechanical ventilation. However, this complication can also occur as late as several days after surgery. Events that increase intrapleural pressure in the nonsurgical (ventilated) hemithorax or that decrease intrapleural pressure in the surgical (empty) hemithorax may predispose the patient to cardiac herniation. Placing the patient with the empty hemithorax in a dependent position allows the heart to be pulled by gravity into the empty hemithorax. Use of high levels of pressure and volume during mechanical ventilation of the remaining lung can push the heart into the empty hemithorax. Similarly, coughing can increase pleural pressure in the remaining lung and thereby promote displacement of the heart into the empty hemithorax. Conversely, inadvertently applying suction to a chest drain in the empty hemithorax can pull the heart through a pericardial defect (tension vacuthorax).

The diagnosis of cardiac herniation is made by the sudden appearance of catastrophic symptoms in a patient who had a radical pneumonectomy, the presence of a predisposing condition (see earlier), and a chest radiograph that shows the apex of the heart to be pointing to a lateral chest wall at a right angle. [410] A diagnosis of cardiac herniation almost always necessitates immediate reexploration.

Five conservative measures may improve cardiopulmonary function before and during transfer to the operating room (they are the reverse of the causes of herniation of the heart discussed previously), and they should be instituted as soon as the diagnosis is entertained. First, the patient should be positioned so that the ventilated nonsurgical side is in a dependent position and the empty surgical side is in a nondependent position. Gravity may return the heart and mediastinum to their normal anatomic positions. Even if the heart does not reenter the pericardium, the repositioning may decrease atriocaval kinking and increase cardiac output. Second, avoidance of high levels of pressure and volume in the ventilated lung may allow the return of the heart to the pericardium. Consequently, the tidal volume should be reduced, PEEP should be removed, and the respiratory rate should be increased slightly. Third, suction to the empty hemithorax should be discontinued. Fourth, pharmacologic support of the circulation should be provided as needed. Fifth, injecting 1 to 2 L of air into the surgical hemithorax may push the heart and mediastinum back to a normal anatomic position and perhaps the heart back into the pericardium. Success with this latter technique has been variable. [409]

Pulmonary Torsion

Pulmonary torsion refers to rotation of the parenchyma on its bronchovascular pedicle and is thought to be due to increased mobility of a lobe (as may occur to the remaining lobes in one hemithorax after a lobectomy). Any patient with atelectasis or an expanding intrathoracic mass and perhaps with severe chest pain following thoracotomy should have lung torsion included in the differential diagnosis, which also includes intrathoracic bleeding and progressive atelectasis. Because torsion compromises the pulmonary vasculature (both arteries and veins) as well as the bronchi, prompt recognition and surgical intervention are required to avoid the attendant morbidity and mortality (i.e., infarction and gangrene). [410]

A double-lumen endotracheal tube should be inserted before surgery if pulmonary torsion is suspected because during surgical correction of this condition (either completion pneumonectomy or untwisting and stabilization of the lobe to another lobe or chest wall), massive hemorrhage into

the airways may occur owing to release of entrapped blood and continuing bleeding from necrotic lung tissue (i.e., vessels and airways), drowning the dependent lung and producing severe hypoxia or death. Other intraoperative therapeutic modalities that the anesthesiologist should consider include use of intravenous steroids to decrease any reactive pulmonary inflammation, use of PEEP to reexpand atelectatic lung tissue, and saline lavage for the removal of any excess blood that might form clots in the normal airways and thereby obstruct healthy lung parenchyma.

Major Hemorrhage

Postoperative bleeding that necessitates emergency thoracotomy [409] may occur in as many as 3 percent of all thoracot-omy patients. [411] The mortality of major postoperative bleeding is approximately 23 percent. [411] The potential sources of major postoperative hemorrhage are bleeding from divided pulmonary arteries and veins due to slippage of surgical ligatures, diffuse bleeding from raw surfaces, and systemic arte-rial bleeding (bronchial and intercostal arteries).

The drainage from a patent chest tube is an excellent monitor of the amount of intrathoracic bleeding. In addition, the hematocrit of the usual fluid in the chest drainage is always less than 20 percent, and intrathoracic bleeding increases the hematocrit to some higher value. Significant hemorrhage, of course, is accompanied by the hemodynamic signs of hypovolemia. Significant hemorrhage cannot always be ruled out by the absence of chest tube drainage, because the chest tube may be blocked by clotted blood or otherwise obstructed. Nevertheless, the patient will still show signs and symptoms of hypovolemia and a shift in the mediastinum to the opposite side.

Bronchial Disruption

Development of a bronchopleural fistula is a serious complication of pulmonary resection and as recently as 1978 carried a mortality of 23 percent. [412] The symptoms and signs are variable and depend on the size of the communication, the presence or absence of a chest drain, and the presence of fluid of any sort within the pleural space.

Gross disruption of a bronchial stump is usually signaled by massive bubbling of gas through the chest tube drainage system, if present, tension pneumothorax if the

chest tube is not present, hypoxemia, and hypercapnia. Prompt resuscitation is essential and may need to include mechanical and differential or one-lung ventilation with a DLT and support of the circulation. A functioning chest tube, if not present, must be inserted immediately to evacuate the air (to prevent a tension pneumothorax) and fluid (to prevent further contamination of the opposite lung) from the pneumonectomy cavity; a needle can decompress the hemithorax while a chest tube is being inserted. The patient should be recumbent, with the normal side in a nondependent position. The stump must be closed surgically as soon as possible. [412]

It should be remembered that a tension pneumothorax may occur in the contralateral side if very high inflation pressures are used to expand a previously collapsed lung (as commonly occurs for one-lung ventilation); the tension pneumothorax may become apparent only after closure of the chest. Other causes of acute postoperative contralateral pneumothorax relevant to thoracic surgery include damage to the contralateral pleura during surgery, puncture of the pleura during insertion of a central venous cannula or thoracic epidural needle, or damage to the bronchus by use of an endobronchial catheter.

Development of a chronic bronchopleural fistula may be expected to occur in 1 to 3 percent of pulmonary resection patients. [412] A chronic bronchopleural fistula most frequently becomes evident within the first 2 weeks after operation and may run a fulminating course characterized by sepsis, empyema, purulent sputum, and respiratory insufficiency. Factors that predispose to the formation of a chronic bronchopleural fistula after pulmonary resection are preoperative irradiation, infection, residual neoplasm at the site of the closure, and the presence of a long or avascular stump.

Respiratory Insufficiency

Acute respiratory insufficiency (within 30 days of resection) is probably the most common serious complication after pulmonary resection. Recent data from a large thoracic surgery service indicate an incidence of 4.4 percent after bronchial carcinoma resections, and in this study, the patients who developed acute respiratory failure had a mortality rate of 50 percent. [413] Mortality from respiratory failure after right-sided pneumonectomy is greater than after pneumonectomy on the left side because the remaining functioning lung is smaller. [413] In addition to the usual mechanism of respiratory failure (Ch. 72) , pulmonary resection per se involves additional new mechanisms of hypoxemia and hypercarbia.

First, the remaining lung in either hemithorax may be edematous and/or soiled with blood. The lung that was dependent during surgery may be edematous and/or may have aspirated blood (if a DLT was not used) as a result of gravitational effects (in zones 3 and 4). The lung that was nondependent during surgery may be edematous and hemorrhagic because of surgical compression and trauma. Second, the size of the remaining pulmonary vascular bed is decreased; this decrease can lead to pulmonary edema. The treatment of respiratory insufficiency is discussed in detail in Chapter 72 .

Unilateral Reexpansion (Intraoperative) Pulmonary Edema

Sudden evacuation of a chronic or subacute pneumothorax or pulmonary effusion may cause edema of the ipsilateral lung (reexpansion pulmonary edema). [414] [415] Still other reports describe an even more acute form of reexpansion pulmonary edema associated with lung reexpansion after only several hours of atelectasis, [416] [417] including reexpansion of the nondependent lung after one-lung ventilation to facilitate thoracic surgery [418] [419] [420] [421] and following correction of an inadvertent main stem bronchial intubation. [416] [422]

Most clinical and experimental observations support increased pulmonary vascular permeability as a major factor in the development of reexpansion pulmonary edema. [423] [424] [425]

All the above clinical literature indicates that the rate of reexpansion may be more important than the duration of collapse in the development of reexpansion pulmonary edema. [414] [420] Thus, other mechanisms of reexpansion pulmonary edema include generation of markedly negative intrathoracic pressure during reexpansion and increased pulmonary capillary pressure and flow on lung reexpansion. Therefore, the most important factor in preventing reexpansion pulmonary edema is to reexpand the lung slowly and in a gradual fashion. The treatment of established reexpansion pulmonary edema is mechanical ventilation, PEEP, restriction of fluids, and diuretics.

Right Heart Failure

Major pulmonary resection results in a decrease in the cross-sectional area of the pulmonary vasculature and an increase in right ventricular afterload, which in some patients can result in acute right heart failure. Although patients at risk for developing right heart failure after pulmonary resection can usually be identified preoperatively, right heart failure may also occur if additional stresses, such as infection and increased pulmonary blood flow and new active pulmonary vasoconstriction (such as that caused by hypoxia, acidosis, vasoactive amines and peptides), are placed on the right side of the heart.

The diagnosis of selective right heart failure is established when the right atrial pressure exceeds the left atrial pressure (i.e., the pulmonary artery wedge pressure) in the presence of an abnormally low cardiac output. In addition, pulmonary hypertension with a pulmonary artery diastolic-wedge pressure gradient will usually be present, along with the systemic signs of left heart failure (oliguria, decreased mentation, peripheral edema). The treatment of acute right heart failure follows the same principles used to treat left-sided failure: control heart rate, optimize preload and the inotropic state of the right ventricle, and reduce PVR (Chs. 49 and 51) .

Right-to-Left Shunting Across a Patent Foramen Ovale

Many adults have a patent foramen ovale [409] ; at autopsy, the incidence of a probe-patent foramen ovale is highest at 34 percent during the first 3 decades of life and decreases to 20 percent by the 9th and 10th decades. There is normally no right-to-left shunting across the foramen ovale because left atrial pressure exceeds right atrial pressure; this pressure gradient keeps the one-way flap valve of the foramen ovale pressed against the opening, resulting in a functionally competent seal. If right atrial pressure exceeds left atrial pressure (as may be the result of any factor that increases PVR and right ventricular pressure), the one-way flap valve can open, and right-to-left shunting can occur through the newly opened foramen ovale. [409] Thus, new onset right-to-left shunting across a patent foramen ovale or atrial septal defect after pneumonectomy and lobectomy, as a cause of otherwise unexplained postoperative dyspnea and systemic oxygen desaturation, has occurred. [409] Use of contrast two-dimensional echocardiography combined with a saline bubble injection study is an excellent method of diagnosing this process, if suspected. Contrast angiography and dye dilution curve analysis are other available diagnostic methods. Nonsurgical treatment consists of decreasing right atrial preload and afterload; this procedure permits functional closure of the foramen ovale in the majority of patients.

Neural Injuries

During radical hilar dissection or excision of mediastinal tumors, phrenic, vagus, and recurrent laryngeal nerves may be injured accidentally or may be sacrificed deliberately. [409] Phrenic nerve injury causes respiratory embarrassment by a flail chest effect and also causes elevation of the ipsilateral hemidiaphragm. The diagnosis should be suspected in patients who have relatively clear chest radiographs, have adequate gas exchange, and cannot be weaned from the ventilator. The diagnosis can be confirmed by paradoxic movements of the diaphragm on fluoroscopy. Injury to the vagus nerve causes gastric and intestinal atony, which usually is not problematic in the first few postoperative days. Bilateral partial injury of the recurrent laryngeal nerve causes adductor spasm of the vocal cords, which, after extubation, may result in upper airway obstruction. This must be diagnosed promptly and treated with immediate reintubation and possible tracheotomy until the dysfunction is resolved.

Aside from clamping of the thoracic aorta with resultant ischemia to the spinal cord, there are two other causes of paraplegia after thoracotomy. First, damage to the spinal branches of intercostal arteries by dissection or diathermy at the posterior end of a rib may cause spinal cord ischemia. [427] This is most likely to occur with damage to the intercostal arteries of the left lower lobe. [428] Second, surgical dissection may create a communication between the epidural space and the pleural cavity. Clotted blood, or blood that can later clot, can then enter the epidural space and cause postoperative spinal cord compression and ischemia. [429] Similarly, expansion of hemostatic material (such as Surgisil) may result in cord injury.

Management of Postoperative Mechanical Ventilation

Most relatively healthy patients who have not had extensive thoracic operations may have their tracheas safely extubated in the operating room or shortly after arrival in the recovery room (Chs. 68 , 71 , and 72) . However, patients with severe chronic pulmonary disease who undergo extensive thoracic operations require a period of postoperative mechanical respiratory support. Careful clinical assessment and judgment are necessary for postoperative tracheal extubation of patients who are intermediate in terms of their respiratory health and the extent of their thoracic procedures. Precise criteria for continued intubation and mechanical ventilatory support are presented in Chapters 39 , 68 , and 72 . Whenever doubt exists, we urge caution in removing mechanical ventilatory support too rapidly from these patients; it is safest to support patients until clinical and laboratory data clearly indicate that extubation is safe. The following briefly describes our current practice of mechanical ventilation, weaning, and extubation.

TABLE 48-17 -- Mechanical Ventilation and Weaning Plan

GOAL NO. (TEMPORAL SEQUENCE TO BE FOLLOWED)	GOAL		ACHIEVED PRIMARILY BY
1. F_{IO_2}	$F_{IO_2} < 0.5$	$PaO_2 > 60$ mm Hg	PEEP titration
2. PEEP	$F_{IO_2} < 0.5$ PEEP < 10 cm H_2O	$PaO_2 > 60$ mm Hg	Respiratory care regimen
3. IMV rate	$F_{IO_2} < 0.5$, PEEP < 10 cm H_2O IMV < 1 breath/min	$PaO_2 > 60$ mm Hg	Patient with adequate breathing power

Abbreviations: F_{IO_2} , inspired oxygen concentration; PEEP, positive end-expiratory pressure; IMV, intermittent mandatory ventilation; Pa_{O_2} , arterial oxygen tension.

For most postoperative thoracotomy patients who require respiratory support, controlled mechanical ventilation is initiated after reintubation with a single-lumen tube, with a tidal volume equal to 12 mL/kg, an intermittent mandatory ventilation (IMV) rate so that the Pa_{CO_2} is 40 mm Hg (which usually requires an initial rate of 8 to 12 breaths/min), and with an inspired oxygen concentration of 60 to 100 percent. IMV used in this way is a full-support ventilation modality. The patients may breathe spontaneously, but at this initial ventilator stage, the spontaneous ventilation is not regarded as significantly contributing to the minute ventilation. The spontaneous ventilation with IMV may increase cardiac output and thereby decrease intravenous fluid requirements as well as eliminate the need for paralysis and heavy sedation. IMV may also facilitate the transition to weaning. Arterial blood gas values and chest radiographs are obtained shortly after the institution of mechanical ventilation in the recovery room.

An F_{IO_2} greater than 0.5 is toxic to the lungs, [430] and the first and compelling goal is to reduce the F_{IO_2} to less than 0.5 while maintaining an acceptable Pa_{O_2} (Table 48-17) . The decrease in F_{IO_2} below 50 percent is achieved by performing a dose (PEEP)-response (Pa_{O_2}) titration. PEEP is progressively added (range 0 to 20 mm Hg) until the Pa_{O_2} is relatively normal for that patient (or at least >60 mm Hg) with an F_{IO_2} less than 0.5. PEEP should be raised in increments of 2.5 to 5.0 cm H_2O. The patient should be allowed to stabilize with regard to respiratory mechanics (peak inspiratory pressure and compliance), hemodynamics (pulse rate and rhythm, systemic and central filling pressures, and cardiac and urine output), and gas exchange (arterial blood gases). Usually each PEEP increment requires 0.5 to 1 hour to complete. Consequently, the performance of a PEEP-F_{IO_2}/Pa_{O_2} titration may take several hours. Of course, as the PEEP titration is being performed, other respiratory care modalities (see below), such as suctioning, turning, and administration of antibiotics, are instituted. The advent of fiberoptic bronchoscopy has eliminated the need for use of "super-PEEP" (PEEP >20 to 25 cm H_2O) because regions of collapsed lung that are resistant to opening by PEEP are usually obvious on chest radiograph and can be suctioned and lavaged open under direct vision via a bronchoscope.

If a patient requires more than 10 cm H_2O of PEEP to have a Pa_{O_2} greater than 60 mm Hg with an F_{IO_2} of less than 0.5, the V/Q mismatch is so great that it is illogical to make the patient spontaneously ventilate to any significant degree. In other words, lungs that have a PEEP requirement greater than 10 cm H_2O are inefficient to the point that the work of breathing is likely to be excessive, and the patient will fatigue and fail.

Thus, the second goal is to reduce the PEEP to less than 10 cm H_2O; of course, it is assumed that what was achieved before (F_{IO_2} <0.5, acceptable Pa_{O_2}) is retained. This second goal is achieved primarily by instituting an intensive and aggressive respiratory care regimen. Such a regimen has four components (Table 48-18) , and all four proceed in parallel. Although there are no hard data to prove that any one of these respiratory care treatments is beneficial when used alone, there is a widespread consensus that when used together and in the context of the other care necessary in the postoperative management of respiratory failure, they produce a clearing of atelectasis, eradication of infection, and a decrease in the PEEP requirements. [431] [432]

Use of the respiratory care regimen outlined above usually allows the physician, within a few days, to decrease PEEP to less than 10 cm H_2O with continued maintenance of an adequate Pa_{O_2} along with a low F_{IO_2} . Once the PEEP requirement is less than 10 cm H_2O, no special attempt is made to reduce it further. Maintenance of some PEEP is desirable in terms of maintaining normal FRC and lung compliance and providing a subjective sensation of good

TABLE 48-18 -- Aggressive and Intensive Respiratory Care Regimen

I. Removing secretions
  1. Coughing routines
  2. Tracheal suctioning
  3. Fiberoptic bronchoscopy
  4. Chest percussion and vibration
  5. All of the above aided by posture
  6. Turning frequently

II. Diagnosing and treating infections
  1. Protected brush specimen Accurate culture and sensitivity
  2. Bronchoalveolar lavage
  3. Antibiotics according to culture and sensitivity

III. Dilating the airways
  1. Bronchodilators ($beta_2$ agonists, anticholinergics, aminophylline)
  2. Steroids

IV. Other general/systemic maneuvers
  1. Humidification
  2. Incentive spirometry
  3. Diuretics and fluid restrictions
  4. Inotropics

5. Aminophylline to increase diaphragmatic contractility
6. Inhalation of 60% helium

TABLE 48-19 -- Bedside Physiologic Parameters Conventionally and Commonly Used to Predict Success in Weaning From Ventilatory Support and Weakness of Each Test

TEST	PROBLEM WITH TEST
1. Tidal volume > 5 mL/kg	1. Ignores determining inspiratory reserve
2. Vital capacity > 10-15 mL/kg	2. Requires cooperation
3. Respiratory rate < 25-35 breaths/min	3. Multifactorial
4. Minute ventilation > 10 L/min	4. Multifactorial
5. Maximum voluntary ventilation > 2 × minute ventilation	5. Requires cooperation
6. Maximum inspiratory pressure more negative than 20-25 cm H_2O	6. Ignores respiratory mechanics
7. Respiratory rate/tidal volume ratio	7. Combination of above, but the ratio defines rapid shallow breathing

lung expansion. The achievement of an F_{IO_2} less than 0.5 and a PEEP level less than 10 cm H_2O with an acceptable Pa_{O_2} means that the blood and gas within the lungs are matched well enough that the lungs perform their basic gas exchange function in a reasonably efficient manner. It now makes sense to have the patient do some of the work of breathing on his own, and the patient is now a candidate for weaning from mechanical ventilation.

The third goal is to retain what was achieved before (F_{IO_2} less than 0.5, PEEP less than 10 cm H_2O, and acceptable Pa_{O_2}) and to reduce the IMV rate to less than 1 breath/min. This weaning process is accomplished by a progressive decrease in the IMV rate, allowing a gradual transition rate from 100 to 0 percent ventilator dependence. The rapidity by which the IMV rate can be reduced is dictated by and directly proportional to the vital capacity and peak inspiratory force. Other simple indices of readiness for decreasing the IMV rate are shown in Table 48-19 . When the decrease in IMV rate is begun, the head of the bed should be elevated as much as possible to reduce the pressure of the abdominal contents on the diaphragm and also to allow the patient to reestablish contact with the environment. During the transition, IMV provides a progressively decreasing amount of partial ventilatory support. [433]

As the IMV rate is decreased, the patient is monitored by the spontaneous respiratory rate, vital capacity, peak inspiratory force, and Pa_{CO_2} . In addition, the patient should be asked to indicate whether a sensation of dyspnea is perceived. When the rate of IMV withdrawal is appropriate and is being tolerated, the patient's spontaneous respiratory rate remains constant or only slightly increases, the vital capacity and peak inspiratory force remain constant or improve, the arterial blood gas concentrations do not deteriorate, and the patient remains reasonably comfortable. Conversely, when the IMV withdrawal rate is too rapid and is not being tolerated, the spontaneous respiratory rate increases greatly (which is usually the first indication of tolerance), the vital capacity and peak inspiratory force decrease, and the arterial blood gas values deteriorate; the patient becomes hypertensive and tachycardiac, may have arrhythmias, and communicates a sensation of air hunger.

The patient is ready for extubation when Pa_{O_2} is adequate, with the F_{IO_2} less than 0.5 (goal 1), the PEEP level less than 10 cm H_2O (goal 2), VC greater than 15 mL/kg, peak inspiratory force (PIF) greater than -25 cm H_2O, IMV less than or equal to 1 breath/min, spontaneous respiratory rate less than 20 to 30/min, and Pa_{O_2} approximately 40 mm Hg (goal 3), when no other major organ systems are in acute major failure or are unstable, and when the chest roentgenogram findings are reasonably equivalent to the premorbid findings or are rapidly improving and no new changes have appeared (such as infiltrates or pneumothorax). It should be emphasized that throughout this entire mechanical ventilation and weaning process analgesics and sedatives must be administered and titrated so that the patient is comfortable, is not bucking on the endotracheal tube, and is without active expiratory efforts.

The logic of the preceding approach is that the patient's lungs are first required to have the ventilation and perfusion well enough matched, as indicated by an adequate or reasonable Pa_{O_2} with an F_{IO_2} less than 0.5 and a PEEP level less than 10 cm H_2O, that the lungs function as an efficient gas exchange organ. Next, the patient's lungs are required to sustain this efficient gas exchange without respirator aid as indicated by an adequate or reasonable vital capacity, PIF, spontaneous respiratory rate, respiratory rate to tidal volume ratio of less than 105 breaths/min/L (which defines absence of rapid shallow breathing, [434] and Pa_{CO_2} on a low IMV rate. Finally, the process requires that no new complicating factor has occurred as indicated by lack of new chest radiographic findings, resolution of previous pathologic chest radiographic findings, and the absence of any significant disorder or complication in any of the other major organ systems.

During postextubation, the ideal respiratory care maneuver, a high alveolar inflating pressure is sustained for a relatively long time, and this can be achieved only with a large inhaled volume. Such deep breathing exercises with emphasis on achieving a sustained inspiration to total lung capacity can be accomplished by using the incentive spirometer.

In addition, a variety of other techniques can help to minimize postoperative pulmonary complications. Both upright position in bed and early ambulation increase FRC and help restore a favorable FRC-closing volume relationship. Percussion and postural drainage aid in the mobilization of secretions in patients with chronic bronchitis. Continuing the administration of bronchodilating drugs or steroids that were given preoperatively is important in continuing to keep reactive airways quiescent.

Management of Postoperative Pain

The treatment of pain after thoracotomy (Ch. 69) is important not only to ensure patient comfort, but also to minimize pulmonary complications by enabling patients to breathe normally (without active exhalation and/or splinting) and deeply (so that they can cough) and to ambulate. Normal and deep breathing requires stretching of the skin incision, which is painful. Postoperative patients normally try to prevent stretching of the skin incision by contracting their expiratory muscles (splinting), thus limiting the stretch on the incision during inspiration, and by actively exhaling, thus rapidly diminishing whatever stretch was caused by inspiration. Failure to inspire deeply before a forceful exhalation results in an ineffective cough. Splinting, active exhalation, and failure to cough promote retention of secretions, airway closure, and atelectasis.

Two very efficacious methods of post-thoracotomy pain treatment have become widely used and are considered by many to be the methods of choice. They are cryoanalgesia and administration of epidural narcotics. In addition, interpleural regional analgesia has recently been introduced as an alternative method for treating pain after thoracotomy. This section discusses only these three methods.

Cryoanalgesia

Extremely long-lasting intercostal nerve block may be obtained by intercostal nerve freezing (cryoanalgesia). [435] [436] [437] [438] [439] [440] [441] [442] [443] [444] [445] Direct application of an ice ball to the nerve causes degeneration of nerve axons without damage to the support structure of the nerve (the neurolemma), thereby reversibly disrupting nerve activity. Thus, intraneural and perineural connective tissue are preserved, providing a scaffolding for regenerating capillaries, axons, and Schwann cells. [442] The area of anesthesia is along the dermatomes treated. During the 2 to 3 weeks after nerve freezing, nerve structure and function begin to recover in parallel, and by 1 to 3 months after freezing, they usually are fully restored, without untoward sequelae (neuritis or neuroma formation). The numbness that persists during this period is not especially bothersome. Young women, however, have admitted to some distress during the period of axonal regeneration due to loss of sensation in the nipple

area if the fifth and higher intercostal nerves have been frozen. [441]

Currently used cryoprobes are about the size of a pen; the core of the instrument has an exit port that permits rapid expansion of a gas (usually nitrous oxide). The rapid expansion of gas cools a surrounding metal sheath. Because the metal sheath is in contact with a fluid, an ice ball (temperature -60°C) forms at the tip of the cryoprobe. The intercostal nerves are approached from within the chest, because the probe has to pierce the parietal pleura to reach the intercostal nerves in the subcostal groove. This is easily accomplished by the surgeon's lifting the nerve out of the groove with a small nerve hook. The cryoprobe is applied directly to the nerves as far posteriorly as possible from within the chest at the level of the incision plus two or three interspaces above and below this level, just before closure of the thoracotomy wound. The cryoprobe is activated so that the center of the resultant ice ball encapsulates the nerve. During the freeze, nerve tissue temperature is approximately -20°C. [441] If 2 to 3 mm of tissue remains between the tip of the cryoprobe and the nerve to be blocked, the nerve will not become adequately frozen, and nerve function might not be totally eliminated. If the pleura is thickened, local peeling of the pleura is advisable. [441] Usually two 30-second freeze cycles, which are separated by a 5-second thaw period, are applied to each of the nerves selected. However, recent experience with one 30-second freeze exposure has resulted in no loss of postoperative pain control with a significant reduction in the period of numbness (from 3.0 to 1.2 months). [441]

The use of cryoanalgesia in this way has effectively reduced postoperative narcotic requirements and improved pulmonary function. [434] [437] [438] [439] Cryoanalgesia patients have had moderate pain at the end of the first postoperative day and only slight pain after that (as compared with patients receiving intravenous narcotics, who experience moderate to severe pain at 24 hours). Most of the pain experienced by the cryoanalgesia patients has not been incisional discomfort, but rather shoulder or arm pain secondary to chest tube irritation of the pleura. Further advantage of the cryoanalgesic method can be gained if the chest tubes can be placed within an intercostal space whose nerves have been subjected to cryoanalgesia. [441] Once the chest tubes are removed, usually on the second or third postoperative day, pain in the cryoanalgesia patients has become barely noticeable. Consequently, these patients are more able to cooperate with the postoperative pulmonary physiotherapy maneuvers described in Chapter 72 . Return of sensation occurs in most patients by the thirtieth postoperative day. Long-term follow-up for 6 months has shown that the procedure is associated with a certain worrisome incidence of dysesthesias and intercostal muscle paralysis, [443] but it is impossible to distinguish between injury to the nerves and muscle during surgery (which does occur [e.g., 44% of patients in one long-term follow-up study had persistent post-thoracotomy pain [444]]) and injury due to the cryoprobe [445] as the cause of these problems.

Because cryoanalgesia has been shown to reliably and effectively relieve pain and to allow significant improvements in postoperative pulmonary function, it has become an important addition to the modalities used in the treatment of post-thoracotomy pain. Cryoanalgesia may be a treatment of choice in thoracic pain situations that are expected to last a long time (e.g., pain from chest trauma) and to limit respiratory function significantly.

Epidural Narcotic Administration

Treatment of pain after thoracic surgery with epidural narcotics (Ch. 69) has several important advantages. First, there is no sympathetic blockade and neither motor nor sensory loss; second, success in relieving pain is usually predictable; and third, the duration of pain relief is generally much longer and the quality of pain relief better than those that result from using parenteral narcotics. [446] [447] [448] [449] [450] [451] [452]

Epidural opioids have had a moderately extensive trial in relief of post-thoracotomy pain. The epidural catheter should be placed before the induction of general anesthesia and checked for correct position by using a small dose of local

anesthetic. Alternatively, but less preferably, it may be placed in the lumbar region postoperatively before emergence from anesthesia, while the patient is still in the LDP. The initial injection can be made in the operating room (most usual), recovery room, or intensive care unit. Several important clinical points have emerged from the post-thoracotomy epidural opioid analgesia experience.

First, although the thoracic epidural route has been used, the procedure has risks (primarily dural puncture and spinal cord damage), and the lumbar area for catheter insertion has been found to be equally satisfactory for pain relief if a slightly higher dose of morphine and adequate diluent volumes are used. [448] [451] [452] [453] [454] [455] [456] [457] Morphine can be used with a lumbar epidural injection for the relief of thoracic pain because it is lipophobic and will therefore remain in, and have time to spread throughout, the epidural and cerebrospinal fluid (CSF) spaces. For relief of thoracic pain, instillation of 6 mg of morphine in 10 to 15 mL of diluent (preservative-free normal saline) in the lumbar epidural region has been used successfully. [451] [455] Although studied to a much smaller degree, fentanyl, [458] [459] methadone, [460] hydromorphone, [461] and nalbuphine [462] may also be used by either the thoracic or the lumbar epidural route. Not surprisingly, the lumbar route requires a greater diluent volume to push the narcotic into a wider distribution mechanically, because these lipophilic narcotics bind too quickly to the spinal cord at, and a few dermatomes above and below, the segmental level of introduction. Because the lumbar route is safer than the thoracic route and because fentanyl has not been associated with respiratory depression, use of the lumbar epidural route with fentanyl is considered by many to be the post-thoracotomy pain management technique of choice. It should be noted that low-volume thoracic instillation of fentanyl may be safer than large-volume lumbar morphine and is therefore also a widely used technique. However, there remains a wide selection of drugs (and dosages) for use by the lumbar and thoracic epidural routes (Table 48-20) .

Second, epidural morphine [456] and fentanyl [453] have been reported to be effective after thoracic trauma. In patients with multiple fractured ribs, epidural morphine resulted in well over 6 hours of analgesia with each dose. Alternatively, continuous epidural infusion of fentanyl (1-2 mug/kg/h after a 1- to 2-mug/kg bolus) is a good choice in the thoracic trauma situation (as well as for post-thoracotomy pain) because it has a decreased likelihood of causing respiratory depression. Because there is no sympathetic blockade with epidural opioids, there is no need for the patient to lie supine for top-up doses, and patients with some degree of hypovolemia may be managed more safely than with epidural local anesthetic administration.

Third, in the post-thoracotomy pain relief experience (summarized in Table 48-20) , there have been relatively few significant side effects. Urinary retention is generally not a problem because most patients have a bladder catheter in place.

Fourth, catheters have been left *in situ* and used for as long as 5 days without development of tolerance. [463]

Fifth, pain relief failures have usually been due to improper catheter localization because no pain relief could be demonstrated after injection of local anesthetics. [463]

Sixth, the expected increase in the mean post-thoracotomy expiration flow rate, forced vital capacity, FRC, and ability to tolerate respiratory care maneuvers after epidural pain relief have been demonstrated. [463] Even larger increases in ventilatory capacity have been demonstrated in the much larger experience with epidural pain relief after upper abdominal surgery. [464] These increases are generally greater than or equal to those obtained by parenteral narcotic or epidural local anesthetic administration.

Finally, epidural narcotics have been used to treat intractable pain due to thoracic tumors. [465] Lower dosage is required, and longer duration of analgesia with each intermittent dose is obtained for intractable cancer pain as compared with acute postoperative pain. [465] However, although results have been satisfactory after the first few series of injections for intractable pain, tolerance has developed, and dosages have had to be increased because of continuous bathing of the spinal cord with a CSF concentration

TABLE 48-20 -- Epidural Narcotics That Have Been Used for Postoperative Thoracic Surgery Pain Management: Routes, Dosages, and Pharmacodynamics

SITE OF INCISION	EPIDURAL ROUTE	DRUG	LIPID[a] SOLUBILITY	EPIDURAL DOSE (DILUENT SALINE): CONTINUOUS INFUSION	ONSET (min)	DURATION (h)
Thoracotomy	Thoracic	Morphine	1.4	2-4 mg (8 mL):0.1 mg/h	40-60	12-24
		Meperidine	39	30-75 mg (10 mL)	10	4-8
		Methadone	116	5 mg (10 mL)	15	8-10
		Alfentanil	126	200 mug (10 mL)	10	2
		Fentanyl	813	50-100 mug (10 mL):0.5-1.5 mug/kg/h	10	2-3
		Sufentanil	1778	20-40 mug (10 mL):5 mug/h	5	1-5

	Lumbar	Morphine	1.4	6-8 mg (10-15 mL)	40-60	12-24
		Hydromorphine	8	1-2 mg (10-15 mL)	20	8-12
		Meperidine	39	1 mg/kg (10-15 mL)	10	4-8
		Methadone	116	5-10 mg (10-15 mL)	15	8-10
		Fentanyl	813	1-2 mug/kg (18 mL):1-2 mug/kg/h	10	2-3
		Sufentanil	1778	30-50 mug (20 mL)	5	1-5
Abdominal	Lumbar	Morphine	1.4	6-8 mg (10 mL)	40-60	12-24
		Methadone	116	5-10 mg (10-15 mL)	15	8-10
		Fentanyl	813	1-2 mug/kg (10 mL)/1-2 mug/kg/h	10	2-3

[a] Octanol/water partition coefficient.

of opioid. [453] For treatment of chronic pain, permanent catheters have been implanted in the subarachnoid and epidural space and connected to reservoirs or perfusion pumps. [453] These systems have been found to be effective, but again tachyphylaxis has been observed. [453]

Interpleural Regional Analgesia

Interpleural regional analgesia has recently been introduced for the treatment of pain due to a number of conditions, including rib fractures, [466] pancreatitis, [467] and postoperative pain from mastectomy, cholecystectomy, and renal operations. [468] [469] [470] In addition, this technique has been evaluated in patients who have undergone thoracic procedures. [471] [472] [473] [474]

Interpleural regional analgesia is the percutaneous introduction of a catheter (usually an epidural catheter) into the thoracic cage between the parietal and visceral pleura. Because the catheter tip is located, and a local anesthetic is deposited, between the two layers of the pleura, this technique is better termed *interpleural* rather than intrapleural regional analgesia. [475]

Bupivacaine, in concentrations ranging from 0.25 to 0.5 percent, usually containing epinephrine, is the local anesthetic that has been studied most often. Analgesia is thought to occur as a result of (1) diffusion of local anesthetic through the parietal pleura and the innermost intercostal muscles to reach the intercostal nerves where blockage occurs, (2) blockage of the intrathoracic sympathetic chain, and (3) direct action of local anesthetic on nerve endings within the pleura. A more detailed discussion of this technique can be found in Chapters 43 and 69 .

For thoracic surgery patients, the catheter is usually placed intraoperatively by the surgeon at an interspace just below the level of the incision. [471] [472] [473] Alternatively, and less commonly, a chest tube can be used for the instillation of local anesthetic. [474] The chest tube should be clamped for 5 to 15 minutes after each administration of bupivacaine. If the chest tube is not clamped, approximately 30 to 40 percent of any administered dose of local anesthetic will be lost via the thoracostomy tube. [476] The patient should be kept in a supine position during the injection and for the next 10 to 15 minutes.

Most of the many studies have had good results with interpleural analgesia [466] [467] [468] [469] [470] [471] [472] [473] [474] [475] (good pain relief and/or increased pulmonary function and/or decreased narcotic requirements). However, several reports have been only mildly positive [476] or frankly negative. [472] [477] [478] [479] The most important reason for failure to achieve adequate analgesia after interpleural administration of local anesthetics has been failure to clamp the chest tube before administration causing the local anesthetic to be suctioned out of the pleural space into the chest tube. Indeed, when one group [472] changed technique to include clamping of the chest tube, [480] negative results were converted to positive results. Other reasons for failure of the technique are posterior placement of local anesthetic, preventing adequate analgesia for anterior thoracotomy, dilution of local anesthetic by pleural effusion, blood, and/or infected fluid; loculation of local anesthetic by adhesions, fibrosis, and/or infection; and loss of local anesthetic through a bronchopleural fistula.

A recent review covering a total of 703 cases has detailed the complications of interpleural analgesics. [481] Pneumothorax was the most frequently registered complication (2.0%), followed by signs of systemic toxicity (1.2% [in one patient seizures were thought to be due to rapid uptake because of the presence of a highly inflamed pleura [482]]) and pleural effusion (0.42%). Horner syndrome, pleural infections, and catheter rupture have also been reported. [481]

Because the initial results of treating pain due to thoracotomy with interpleural regional analgesia have been mixed at best, the routine use of this technique cannot be recommended at this time. Its ultimate role in the treatment of post-thoracotomy pain will be determined by the results of further studies.

ANESTHESIA FOR SPECIAL THORACIC SURGERY PROCEDURES

Special Diagnostic Procedures

Mediastinoscopy

Indications

Mediastinoscopy is commonly performed before thoracotomy to establish a diagnosis and/or to determine the resectability of a lung carcinoma. After a suprasternal notch incision, a tunnel is created (through the pretracheal fascia) by blunt dissection along the anterior and lateral walls of the trachea into the mediastinum, behind (posterior to) the aortic arch down to the subcarinal area (Fig. 48-34) . This procedure allows for direct inspection and biopsy of the superior mediastinal lymph nodes, which lie posterior to the aortic arch (the anterior and lateral para-mainstem bronchial, anterior subcarinal, anterior, and lateral paratracheal lymph nodes) (see Fig. 48-34) . Tumors of the thymus and anterior mediastinum are not examined by the usual diagnostic mediastinoscopic approach because they are anterior to the great vessels; thus, an anterior mediastinotomy is required to examine this area (this procedure uses a parasternal second innerspace incision and is a less complicated procedure than mediastinoscopy). Previous mediastinoscopy is a near absolute contraindication to a repeat procedure because scarring eliminates the plane of dissection. Relative contraindications to mediastinoscopy include superior vena cava syndrome, severe tracheal deviation, cerebrovascular disease, and thoracic aortic aneurysm. [483] With the advent of CT and magnetic resonance imaging, the role of mediastinoscopy may diminish considerably in the future because negative scans may obviate the need for invasive staging.

Anesthetic Technique

In addition to the usual preanesthetic evaluation of patients, one should specifically look for the signs and symptoms of the relative contraindications to mediastinoscopy, such as obstruction or distortion of the upper airway and superior vena caval obstruction, signs and symptoms of impaired cerebral circulation (which may be compounded during

Figure 48-34 Schematic diagram showing placement of a mediastinoscope into the superior mediastinum. The mediastinoscope passes anterior to the trachea but behind the thoracic aorta. This location allows for sampling of anterior and lateral para-mainstem bronchial lymph nodes, anterior subcarinal lymph nodes, and anterior and lateral paratracheal lymph nodes. Anatomic structures that can be compressed by the mediastinoscope (see areas marked by *) and that can cause major complications are the thoracic aorta (rupture, reflex bradycardia), innominate artery (decreased right carotid blood flow can cause cerebrovascular symptoms, and decreased right subclavian flow can cause loss of right radial pulse), trachea (inability to ventilate, stimulus to cough), and vena cava (risk of hemorrhage with superior vena cava syndrome).

mediastinoscopy by compression of the innominate artery), and evidence of the myasthenic syndrome caused by lung carcinoma. Because there is the potential risk of hemorrhage, a large-bore intravenous catheter should be inserted, and blood should be immediately available during the procedure. If the superior vena cava is obstructed, a lower extremity intravenous catheter is mandatory.

Although mediastinoscopy can be performed under local anesthesia, [484] [485] general anesthesia with controlled positive-pressure ventilation is preferred because it allows the surgeon more flexibility in the dissection, minimizes the potential for air embolus (see later), and facilitates management of major complications such as massive hemorrhage. [486] However, local anesthesia may be considered for patients with active cerebrovascular disease to continuously monitor cerebral function in the awake state.

After the intravenous induction of general anesthesia and paralysis with either succinylcholine, atracurium, or vecuronium, lidocaine is sprayed directly on the trachea and given intravenously to minimize coughing during orotracheal intubation and the procedure itself. A nonkinking tube should be considered in cases in which tracheomalacia is a possibility. Neuromuscular blockade is also used during the procedure to prevent coughing, venous engorgement from straining, and movement during the procedure. The head-up position minimizes venous engorgement but maximizes the potential for venous air embolism. During mediastinoscopy the anesthesiologist's attention is primarily focused on detecting the occurrence of the complications of the procedure. This is performed by monitoring the right upper extremity blood pressure (vessels most commonly compressed are the innominate and the right subclavian and carotid arteries) and by observing for reflex bradycardia (compression of the aorta), arrhythmias (mechanical stimulation of the aorta), hypovolemia, tension pneumothorax, and compression of trachea (see later). Blood pressure and oxygen saturation should be measured in the left arm; if an arterial line is placed, the right wrist may be preferable because it can immediately signal when compression of the innominate artery has occurred. Alternatively, a pulse oximeter probe placed on a finger of the right hand can be monitored by quantitative changes in signal strength, indicating a diminution of blood flow caused by the mediastinoscope. Immediately after the procedure patients can usually be extubated. Postoperatively patients should be nursed in a head-up position to minimize venous engorgement.

The anesthetic considerations for anterior mediastinotomy are similar to those for mediastinoscopy except that the incision is larger, the incidence of complications is lower because structures can be visualized and controlled more readily, the position of the head is unimportant, and the blood pressure can be measured in either arm because there is little chance of compression of the innominate artery.

Complications

Although overall mortality from this procedure is low (0.1%), [487] and one institution has even undertaken to perform ambulatory (outpatient) mediastinoscopies in a hospital-based surgical suite, [488] serious complications can occur and the anesthesiologist must be prepared to diagnose and

to treat them. In a series of 6,490 patients undergoing mediastinoscopy, the major complications reported (numbers of patients in parentheses) consisted of hemorrhage (48), pneumothorax (43), recurrent laryngeal nerve injury (22), infection (22), tumor implantation in the wound (8), phrenic nerve injury (3), esophageal injury (1), chylothorax (1), air embolism (1), and transient hemiparesis (1). [487] The overall complication rate in various studies has been 1.5 to 3.0 percent. [487] [488] [489] [490] [491] [492] [493] [494] At the time of occurrence, most of the complications listed required a specific anesthetic management response.

Significant (occasionally massive) hemorrhage has been the most frequent major problem encountered during mediastinoscopy. If it occurs, thoracotomy must be performed immediately. While preparations for median sternotomy are in progress, the surgeon should attempt to control hemorrhage by compressing the bleeding site with a sponge forceps or a small pack, although the relative inaccessibility of the operative field may make this maneuver difficult or ineffective. The anesthesiologist should (1) rapidly begin volume replacement thorough one (or more) large-bore intravenous cannulae that have been placed before the induction of anesthesia, (2) send for blood that was reserved for the patient preoperatively, (3) support the circulation pharmacologically until volume replacement is achieved, (4) ensure adequate oxygenation and ventilation, (5) administer atropine for reflex bradycardia from aortic compression (if it occurs), and (6) discontinue or reduce the dose of all anesthetic drugs until normovolemia is reestablished. Rarely, it may be necessary to induce deliberate hypotension to control bleeding in this setting. [490] If hemorrhage originates from a superior vena cava tear, volume replacement and drug treatment may be lost into the surgical field unless they are administered via a peripheral intravenous line placed rapidly in the lower extremity. [490]

Pneumothorax is another relatively frequently encountered complication of mediastinoscopy. It is usually not apparent until the postoperative period, and the majority of patients do not require chest tube decompression. All patients should be monitored for signs of pneumothorax in the postoperative period and a chest radiograph obtained when doubt exists. Pneumothorax that occurs intraoperatively, as evidenced by increased peak inspiratory pressure, tracheal shift, distant breath sounds, hypotension, and cyanosis, requires immediate treatment by chest tube decompression. [495]

When mediastinoscopy causes a recurrent laryngeal nerve injury (see Fig. 48-34) , it is permanent in approximately 50 percent of patients. [487] If injury to the recurrent laryngeal nerve is suspected, the vocal cords should be visualized while the patient is spontaneously breathing (usually at the time of extubation). If the vocal cords are nonmoving and/or are in midline position, consideration has to be given to the problem of postoperative laryngeal obstruction.

During mediastinoscopy, the mediastinoscope tip is located intrathoracically and therefore directly exposed to pleural pressure. Venous air embolism (when venous bleeding is present) can occur much more easily if patients are breathing spontaneously because of the development of negative intrathoracic pressure during inspiration; therefore, controlled positive-pressure ventilation during this procedure minimizes the risk of air embolism.

As noted, the mediastinoscope can exert pressure against the innominate artery and cause diminished blood flow to the right carotid and right subclavian arteries (see Fig. 48-34) . This phenomenon may be of special significance in patients with preexisting compromised cerebral circulation. Compression of the right carotid artery has been proposed as the cause of a left hemiparesis that occurred in one patient and subsequently cleared 48 hours after the procedure. [487] In another patient compression of the right subclavian artery caused the loss of the pulse and blood pressure in the right arm and was misdiagnosed as an intraoperative cardiac arrest. [496] In another study, blood pressure in the right arm was significantly decreased from 15 to 360 seconds in four of seven patients who underwent mediastinoscopy. [497] This last report, therefore, recommended that blood pressure be measured in the left arm and the right radial artery be continuously monitored by palpation or finger plethysmography during mediastinoscopy. A right radial arterial line, of course, would very sensitively and continuously monitor the occurrence of innominate or right subclavian artery compression. An oxygen saturation monitor would do this task less sensitively. Any decrease in the right radial artery pressure requires repositioning of the mediastinoscope, especially in patients with cerebral vascular insufficiency. Preventing excessive extension of the neck, which might contribute to pinching of neck vessels, is also important in this group of patients.

Autonomic reflexes may result from compression or stretching of the trachea, vagus nerve, or great vessels. Sudden changes in pulse and/or blood pressure during mediastinoscopy may initially be empirically treated by repositioning the mediastinoscope. Atropine is given for persistent bradycardia.

Thoracoscopy

Indications

Diagnostic thoracoscopy (pleuroscopy) permits an examination of the intrathoracic cavity and is most commonly performed to aid in the diagnosis of pleural and parenchymal disease, to help establish the staging of suspected neoplasms, and to determine the etiology of recurrent pleural effusions. [498] [499] [500] [501] [502] It is most often performed after thoracocentesis or closed-chest pleural or lung biopsy has been performed and a diagnosis has still not been established.

The development of endoscopic video systems and instrumentation (stapling devices, dissectors, coagulators, autotyping sutures and the neodymium:yttrium-aluminum-garnet [Nd:YAG] laser has permitted therapeutic thoracoscopy for a wide variety of major thoracic procedures. These procedures include biopsy of many intrathoracic structures, peripheral wedge and sublobar resections, lobectomy, removal of mediastinal cysts, closure of persistent/or recurrent pneumothoraces and leaking blebs, pleurodesis, dorsal thoracic sympathectomy, drainage of spinal abscesses, resection of posterior mediastinal neurogenic tumor, retrieval of intrathoracic (pleural) foreign bodies, definitive treatment of a

postpneumonectomy chylothorax, and facilitation of pericardectomy. [503] [504] [505] [506] [507] [508] Thoracoscopy is done by making a small incision in the lateral thoracic wall (usually at the level of the sixth intercostal space) and then introducing a thorascope, laparoscope, or mediastinoscope into the pleural cavity. The procedure allows for complete inspection of the pleural space of a hemithorax. Fluid and biopsy specimens can usually be obtained easily through the incision, although many surgeons prefer to use a separate incision for additional instruments such as biopsy forceps.

Anesthetic Technique

Thoracoscopy can be done with either local, regional, or general anesthesia with one-lung ventilation. Local anesthetic infiltration of the lateral thoracic wall and parietal pleura is the simplest way to provide anesthesia, [509] although some patients may experience considerable discomfort when this method is used. Partial collapse of the lung on the operated side occurs when air enters the pleural cavity. This allows for good visualization of the pleural space by the surgeon. It is both hazardous and unnecessary to insufflate gases under pressure into the hemithorax under examination to increase visualization of the pleural space. Surprisingly, even though many of these patients suffer from advanced pulmonary disease, changes in Pa_{O_2} , Pa_{CO_2} , and cardiac rhythm are usually minimal during the procedure when it is performed under local anesthesia and the patient is breathing spontaneously. [510] [511] However, it is prudent to use a high F_{IO_2} to overcome the loss in lung volume due to the unavoidable pneumothorax.

Intercostal nerve blocks performed at the level of the incision and for two interspaces above and below may provide more complete analgesia for thoracoscopy, especially if they are placed far enough posteriorly to anesthetize the parietal pleura. The addition of an ipsilateral stellate ganglion block helps to prevent the cough reflex that is sometimes elicited during visualization and manipulation of the hilum.

When thoracoscopy is performed under general anesthesia, a DLT should be used. Positive-pressure ventilation seriously interferes with visualization of thoracic contents, and thoracoscopy is therefore a relatively strong indication for one-lung ventilation. If the procedure is short and the ipsilateral lung needs to be deflated for only a brief period, blood gases are not routinely monitored during the procedure. However, for patients with marginal pulmonary status in whom the period of one-lung ventilation lasts for more than a few minutes, the usual monitoring precautions should be taken.

Complications

Complications are rare during this simple procedure, although it is possible that any structure that the surgeon has to manipulate may be damaged. A few critically ill spontaneously breathing patients may experience impaired gas exchange during the procedure. Some air may transiently remain in the pleural space after the procedure, and this situation may require chest tube insertion.

Special Elective Procedures

Tracheal Resection

General Considerations

Tracheal resection is indicated, if technically feasible, in patients who have tracheal obstruction due to a primary tracheal tumor (the majority are carcinomas), prior tracheal trauma (e.g., stenosis due to prolonged intubation), congenital anomalies, and vascular lesions. For patients who have operable tumors, approximately 80 percent have a segmental resection (may include carina or larynx) with primary anastomosis, 10 percent have segmental resection with prosthetic reconstruction, and 10 percent have insertion of a T-tube stent. Adjuncts to surgical extirpation include preoperative and postoperative external radiation, internal radioactive seed radiation (transferred by endobronchial catheter or directly placed by thoracotomy), and preoperative laser debulking therapy.

Many previous technical limitations to the performance of tracheal surgery can now be overcome by careful preoperative delineation of the site and degree of obstruction, close intraoperative communication between the surgeon and anesthesiologist, improved anesthetic management techniques, and meticulous postoperative care. All these components contribute to the ability to provide adequate ventilation throughout the perioperative period. Although the results of this very complicated surgery on primary tracheal tumors depend on tumor cell type, location, and method of resection, it is generally accepted that in the few institutions that have a reasonable degree of surgical experience, a worthwhile survival rate can be achieved in most patients. This section discusses the care of patients undergoing tracheal resection and describes several different methods of airway management [512] [513] [514] [515] [516] [517] [518] [519] [520] [521] [522] [523] [524] [525] [526] [527] [528] [529] [530] [531] [532] [533] [534] [535] [536] (Chs. 39 and 63) .

Anesthetic Considerations

Unless airway obstruction is imminent, pulmonary function should be routinely studied preoperatively. The presence of preoperative lung disease that is severe enough to indicate a need for postoperative ventilatory support is a relative contraindication to tracheal resection, because the trauma of positive airway pressure and an endotracheal tube cuff at the tracheal suture line may cause wound dehiscence. [515] Obtaining a history of position-dependent airway obstruction is important because the induction of anesthesia should be accomplished with those patients in a position that does not cause airway obstruction. Preoperative evaluation should also include tracheal tomograms, CT (to define the exact position of the lesion), bronchoscopy (usually deferred until the time of operation in order not to precipitate airway obstruction due to edema or hemorrhage), flow-volume loops (upper airway obstructions have characteristic shapes to the loop--extrathoracic obstructions cause an inspiratory limb plateau, and intrathoracic obstructions cause an expiratory limb plateau), and arterial blood gas determinations.

During surgery, all patients should have an arterial catheter placed to facilitate analysis of arterial blood gases. It should be placed in the left radial artery because the innominate artery (which supplies the right radial artery) crosses the trachea and may be compressed during surgery. A variety of methods for providing adequate oxygenation and carbon dioxide elimination have been used during tracheal resection and are described in Table 48-21 . These can be divided into five approaches: (1) standard orotracheal intubation, (2) insertion of a tube into the opened trachea distal to the area of resection, (3) HFJV through the stenotic area, (4) HFPPV, and (5) cardiopulmonary bypass.

The first technique uses a standard but uncut long orotracheal tube, which is placed above the tracheal lesion after the induction of general anesthesia and is merely manipulated by the surgeon past (distal to) the area of stenosis or mass. [516] [518] Although this method is relatively easy to use, a large tube may traumatize the lesion and cause bleeding or dislodgement of tissue, resulting in further airway obstruction. Furthermore, the technique is limited to patients with relatively mild stenosis, and the presence of an endotracheal tube in the surgical field makes completing the tracheal anastomosis more difficult.

To overcome these problems, endotracheal or endobronchial tubes have been inserted into the opened trachea distal to the site of resection (second approach). [515] [519] [520] [521] [522] [523] [524] [525] With this second approach, initially either a small endotracheal tube is passed distal to the obstruction or a standard endotracheal tube is placed proximal to it (see Figs. 48-35 (Figure Not Available) A. and 48-36 (Figure Not Available) A.; Fig. 48-37 (Figure Not Available) A). All further tracheal and endobronchial intubations are performed with armored tubes passed into the airway, which is surgically opened distal to the lesion. The surgeon must have a complete set of sizes of endotracheal tubes to choose from because either mainstem bronchus or any lobar bronchus may need to be intubated.

With a high tracheal lesion, a cervical incision, possibly combined with a median sternotomy, provides adequate surgical exposure. An opening is made in the trachea distal to the area to be resected, and a sterile endotracheal tube is inserted by the surgeon into the distal trachea. [515] [519] [520] (see Fig. 48-35 (Figure Not Available) B). This second endotracheal tube is connected to a Y-piece and a second set of anesthetic hoses and handed off to the anesthesiologist in order to continue ventilation. After excision of the tracheal lesion and placement of the posterior tracheal sutures, the second (distal) endotracheal tube is removed from the trachea, the original (first) endotracheal tube is advanced past the anastomosis line and reconnected to the anesthetic circuit, and the anastomosis is completed Figs. 48-35 (Figure Not Available) A. (see Fig. 48-35 (Figure Not Available) C and D).

With a low tracheal lesion, a right thoracotomy provides the necessary surgical exposure. If there is sufficient trachea distal to the area of resection, a Foley catheter with the tip cut off just distal to the balloon may be used as a single-lumen endotracheal tube. It is inserted by the surgeon and secured just above the carina, avoiding endobronchial intubation and the need for one-lung anesthesia. [521] Otherwise, if there is not enough distance between the tracheal lesion and carina to provide placement of even this homemade endotracheal tube, endobronchial intubation and one-lung ventilation are necessary [522] [523] [524] (see Fig. 48-36 (Figure Not Available) B). If oxygenation or ventilation is inadequate, it may be possible to decrease blood flow to the atelectatic lung by tightening reversible snares around the pulmonary artery of the nonventilated lung [515] [516] however, this maneuver may be technically difficult. An alternative technique is to pass a second endobronchial tube into the other bronchus to provide ventilation to both lungs [524] (see later). As with the high tracheal lesion, after the posterior anastomosis is completed, the endobronchial tube(s) is removed and the original endotracheal tube pushed past the site of resection; in this situation, however, it is likely that an endobronchial intubation may again be required to complete the anastomosis (see Fig. 48-36 (Figure Not Available) C and D).

Several methods have been described for managing the airway during carinal resection. [515] [516] [534] While the affected segment is being resected, left lung ventilation may be carried out via an endobronchial intubation of the left mainstem bronchus below this lesion [515] (see Fig. 48-37 (Figure Not Available) B). After the right mainstem bronchus and trachea have been reattached,

Figure 48-35 (Figure Not Available) Airway management and surgical procedure for resection of a high tracheal lesion. (A) Initial intubation above the lesion. (B) Second endotracheal intubation distal to the lesion after the trachea has been opened. (C) Placement of sutures for the posterior anastomosis. (D) The second endotracheal tube has been removed, and the original endotracheal tube has been advanced distal to the anterior anastomosis. *(Modified from Geffin et al [515])*

TABLE 48-21 -- Approaches to Airway Management During Tracheal Resection

GENERAL APPROACH	YEAR	SURGICAL APPROACH	TECHNIQUE	REMARKS
OROTRACHEAL INTUBATION				
Belsey [517]	1950	Right thoracotomy	Orotracheal tube	First description of this type of management--tube advanced distally as resection carried out
Kemvyssi-Dea et al [518]	1975	Right thoracotomy	Orotracheal tube	Tube advanced distally as resection carried out
Beyer and Wilson [532]	1988	Various combinations of right thoracotomy, cervical incision, and median sternotomy	Orotracheal tube	Summarizes the literature (particularly recent) using this approach

INSERTION OF TUBE INTO OPENED TRACHEA DISTAL TO AREA OF RESECTION				
Geffin et al [515]	1969	Cervical incision for high lesion; right thoracotomy for low lesion	Endotracheal tube Endobronchial tube	Excellent review article described experience with 31 patients; stressed avoiding tracheostomy and cardiopulmonary bypass for this procedure
Debrand et al [519]	1979	Cervical incision	4-mm endotracheal tube into distal trachea	Patient 4 months old
Boyan and Privitera [520]	1976	Median sternotomy	Cuffed endotracheal tube into distal tracheal stump	Stressed preoperative forced vital capacity loop of airflow versus volume to confirm diagnosis of airway obstruction
Abou-Madi et al [521]	1979	Median sternotomy	28 Foley catheter into distal tracheal stump	End cut off just distal to balloon allowed bilateral lung ventilation through short tracheal stump
Lippman and Mok [522]	1977	Right thoracotomy	Left endobronchial tube	Tube quickly inserted following intra operative tracheal resection
Akdikmen and Landmesser [523]	1965	Right thoracotomy	Right endobronchial tube	Patient died postoperatively; authors suggested use of cardiopulmonary bypass for this procedure
Dodge et al [524]	1977	Right thoracotomy.	Right and left endobronchial tubes	Two anesthesia circuits used
Theman et al [516]	1976	Right thoracotomy	Right and left endobronchial tubes	Two ventilation systems used; selective occlusion of contralateral pulmonary artery during one-lung ventilation
Beyer and Wilson [532]	1988	Various combinations of right thoracotomy, cervical incision, and median sternotomy	Right and left endobronchial	Summarizes the literature (particularly tubes recent) using this approach
Neville et al [534]	1990	Various combinations of right thoracotomy, cervical incision, and medial sternotomy	Right and left endobronchial tubes	Surgery involved tracheal reconstruction tubes with a tracheal prothesis
HIGH-FREQUENCY JET VENTILATION				
Lee and English [525]	1974	Median sternotomy	8 French suction catheter passed through stenotic area; bronchoscope injector	Patient 8 years old
McNaughton [526]	1975	Not stated	No. 12 catheter; jet ventilation	No significant effects on the circulation tion noted
Baraka [527]	1977	Right thoracotomy	5-mm cuffed endotracheal tube; jet ventilation	Tube pushed (from above) past lesion during anastomoses
Ellis et al [528]	1976	Not stated	1.52-mm diameter manometer line; bronchoscope injector	Patient 13 years old
Darteville et al [533]	1988	Ipsilateral thoracotomy	Small tube	Surgeries were sleeve pneumonectomies
Baraka et al [536]	1986	Right thoracotomy	6.0-mm ID cuffed tube	Technique includes F_{IO_2} = 1.0 (no air entrainment), summarizes recent literature
HIGH-FREQUENCY POSITIVE PRESSURE VENTILATION (HFPPV)				
Eriksson et al [514]	1975	Cervical incision	No. 14 catheter; rate 60/min	First report of HFPPV for tracheal resection
El-Baz et al [513]	1982	Cervical incision	2-mm catheter; rate 150/min	Used with uncuffed tracheal T-tube stent
El-Baz et al [512]	1982	Right thoracotomy	2-mm catheter; rate 150/min	Two patients for carinal resection and one for tracheal resection; only left lung ventilated
CARDIOPULMONARY BYPASS				
Woods et al [530]	1961	Right thoracotomy	Cardiopulmonary bypass	First reported case; instituted after chest was open
Coles et al [531]	1976	Right thoracotomy	Cardiopulmonary bypass	Bypass instituted under local anesthesia before operation
Benca et al [535]	1988	Median sternotomy	Cardiopulmonary bypass	Summarizes the airway management approaches used for tracheal reconstruction in neonates (especially cardiopulmonary bypass)

Figure 48-36 (Figure Not Available) Airway management and surgical procedure for resection of a low tracheal lesion. (A) Initial intubation above the lesion. (B) Left endobronchial intubation distal to the lesion after the trachea has been opened. (C) Placement of sutures for the posterior anastomosis. (D) The endobronchial tube has been removed, and the original endotracheal tube has been advanced distal to the anterior anastomosis into an endobronchial position. *(Modified from Geffin et al [515])*

the left endobronchial tube is removed, and the original endotracheal tube is advanced distal to the suture line. The right lung is then ventilated via this tube, while the left main bronchus is reanastomosed to the trachea at a different point of origin (see Fig. 48-37 (Figure Not Available) C and D). Again, blood flow to the nonventilated lung can be reduced by tightening ties placed around the appropriate pulmonary artery. An alternate method of ventilation during carinal resection is to perform endobronchial intubation of both severed bronchi, a technique that allows two-lung ventilation for a much longer period during the procedure. [516] This latter technique requires the use of two ventilating systems. As the posterior anastomosis is being made, ventilation is achieved through both the distal mainstem bronchi. During repair of the anterior wall, ventilation is performed via the original endotracheal tube (above the anastomosis site). The air leak that initially occurs through the anastomosis site diminishes progressively as the anterior sutures are placed. If the anastomosis site leak is excessive, the endotracheal tube can be pushed into an endobronchial position until the placement of additional sutures reduces the leak.

It is apparent that the conventional techniques of airway management for tracheal resection are fraught with hazard. During operation a slight head-down tilt helps to minimize aspiration of blood and secretions. Intermittent sighs help prevent bronchiolar obstruction and atelectasis. A high F_{IO_2} is used, as an oxygen-filled FRC permits a few extra minutes to correct relatively common episodes of airway obstruction and/or tube displacement. Ventilation is continuously monitored by pulse oximetry, capnography, auscultation and observation of the chest, measurement of compliance (peak inspiratory pressure), and arterial blood gas determinations.

Figure 48-37 (Figure Not Available) Airway management and surgical procedure for resection of a carinal lesion. (A) Initial intubation above the lesion. (B) Left endobronchial intubation distal to the lesion after the left mainstem bronchus has been severed. (C) The trachea is anastomosed to the right mainstem bronchus. (D) The left endobronchial tube has been removed to allow for anastomosis between the trachea and left mainstem bronchus. Ventilation is accomplished via the original endotracheal tube. *(Modified from Geffin et al [515])*

Several different sizes of armored endotracheal tubes must be available for use throughout the procedure. Finally, close communication must exist between the surgery and anesthesia teams. Disadvantages of these complex airway techniques include soiling of the lung with blood and debris, the presence of tubes in the surgical field, and the occasional necessity for using one-lung (or less) ventilation.

In an effort to overcome these problems, a third approach to airway management during tracheal resection was developed, which consists of HFJV through small-bore endotracheal tubes or catheters. [525] [526] [527] [528] [529] [533] With this technique a small-bore uncuffed catheter is placed through the stenotic area, and ventilation is accomplished by exposing the lung to rapid intermittent, high-flow, fresh gas through the catheter. Oxygen jets entrain ambient air, which in turn provides the volume necessary for adequate ventilation. With this technique, acceptable blood gases have been maintained, and there have been no deleterious effects on the circulation. With only a small catheter in the field, the surgeon can more easily perform the tracheal resection and anastomosis. The disadvantages of this technique, however, include possible inadequate escape of air around the jet catheter during exhalation when the catheter is passed through a tight stenotic area, plugging of the catheter with blood, displacement of the catheter, aspiration of blood, and technical difficulties with high-pressure injectors.

The fourth approach to airway management during tracheal resection uses HFPPV. [514] This technique uses small tidal volumes (50-250 mL) delivered via a small catheter at relatively rapid rates (50-150/min). Advantages of using HFPPV for tracheal resection include a relatively unobstructed surgical field, no interruption of ventilation during operation, minimized contamination of the lungs from blood and debris by a continuous outflow of gas, and minimized lung and mediastinal movement. In addition, production of CPAP lessens the risk of alveolar collapse. This technique has been used successfully by others for both tracheal [512] [513] and carinal resections. [512] During carinal operations HFPPV to the left lung alone generally provides adequate oxygenation and ventilation, although a system of two catheters and bilateral HFPPV could be used if necessary. [514]

The fifth approach to airway management during tracheal resection, especially in cases of carinal resection, has been the institution of cardiopulmonary bypass either at the time of resection [530] or before the start of surgery. [531] After resection, anesthesia can be continued by conventional techniques using a standard endotracheal tube. Although many surgical teams perform difficult tracheal resections with the cardiopulmonary bypass team standing by, the risk of intrapulmonary hemorrhage due to heparinization precludes its use in most cases. [515]

Helium-oxygen breathing mixtures can significantly decrease the resistance to gas flow through stenotic areas and may be considered preoperatively for some of these patients. [531] However, the use of helium-oxygen mixtures prevents the use of a high F_{IO_2} during anesthesia, and it is therefore not often recommended. [515]

Postoperatively, most patients are kept in a position of head flexion to reduce tension on the suture line. If ventilatory support is necessary postoperatively, the endotracheal tube must be positioned so that the cuff does not rest on any suture line. Early extubation is highly desirable to minimize the compromise of blood flow to the trachea, which might be caused by an inflated tracheal cuff. Chest physiotherapy to remove secretions should not be too vigorous and may need augmentation by fiberoptic bronchoscopy. Systemic antibiotics or steroids are not routinely given unless infection or excessive edema, respectively, is strongly anticipated. If massive bleeding into the airway or chest occurs postoperatively, it is likely due to erosion into the pulmonary artery or aorta (high incidence after insertion of a tracheal prosthesis) and is usually fatal.

Giant Bullous Emphysema and Air Cysts

General Considerations

A *bulla* is defined as an air-filled, thin-walled space within the lung that results from the destruction of alveolar tissue. The walls of bullae are formed by connective tissue septa, compressed lung parenchyma, or pleura. A bulla usually represents a local end-stage area of emphysematous destruction. As separate but related entities, air cysts in the lung have their own epithelial margins, and they may also be associated with COPD [537] or found in the absence of other pulmonary pathology. [538]

Bullectomy is the surgical resection of one or more bullae and is performed only in selected patients. The most important physiologic effect of the bullae is to compress the surrounding lung, and the release of lung compression following bullectomy is considered to be the most important factor in symptom relief (rather than eliminating dead space ventilation). Indications for bullectomy in COPD patients include intolerable breathlessness even after full medical therapy, rapidly enlarging bullae, and repeated occurrence of pneumothorax. [539] Patients with otherwise healthy lungs may undergo removal of a giant air cyst or bulla if it compresses a large area of normal lung and causes functional impairment. The compression of a large area of lung can be visualized on the chest roentgenogram (as well as on an angiogram) as the crowding together of pulmonary vessels. A strong case for functional impairment can be made if radioisotope studies show that the compressed area has good perfusion and some, but reduced, ventilation. [540] [541]

The goal of surgery is to remove the bullae while preserving as much functioning lung as possible. Therefore lobectomy is not only undesirable but often unnecessary. Patients who are considered too compromised to tolerate an open approach may tolerate a closed thoracoscopic approach; the reason thoracoscopic carbon dioxide laser ablation of bullae has been so successful is that it maximizes preservation of normal lung better than any open thoracotomy approach. It is likely that this approach to bullectomy will be used with increasing frequency in the next few years. [542]

Anesthetic Considerations

Anesthesia for the removal of bullae involves several specific ventilation hazards. First, most of these patients have severe generalized chronic lung disease with little or no

ventilatory reserve. Thus, ventilation (which must be controlled once the chest is opened) of one severely diseased lung (the one without the giant bullae) may be hazardous and entails the risks of hypoxemia, hypercarbia, and pneumothorax on the ventilated side. If the ventilated lung also contains bullae, the risks are obviously even greater. In addition, because general anesthesia is necessary for the procedure, most patients with severe lung disease will be committed to at least a short period of postoperative mechanical ventilatory support. Second, when a bulla or air cyst is in communication with a bronchus, positive-pressure ventilation may cause it to increase in size. [543] If a significant portion of the tidal volume enters the bullous cavity, alveolar dead space ventilation will be greatly increased, and unless there is an equivalent increase in minute ventilation, the rest of the lung may be inadequately ventilated. This complication is most likely to occur when the chest is opened, because the chest wall no longer limits the expansion of the bulla. Third, because of the rapidity with which closed air spaces take up nitrous oxide and expand in size, [544] this agent is best avoided (especially in patients whose bullae are thought to have poor communication with the bronchial system). [545] Fourth, if a check valve is present in the airway that communicates with the cavity, overinflation and air trapping may occur within the cavity. Fifth, positive pressure within a bulla might cause it to rupture, creating a pneumothorax, which would likely be under tension if the chest were closed (especially in patients whose bullae are thought to have good communication with the bronchial system). [543] Tension pneumothorax in these patients is usually a catastrophic event because of the impairment of venous return and cardiac output as well as further compromise of ventilation. Insertion of a chest tube at this point would create, in effect, a large bronchopleural cutaneous fistula that could divert much of the ventilation out through the chest tube. HFV with low tidal volumes and airway pressure has been used successfully to prevent positive-pressure rupture of a bulla according to a 1985 report. [546] Sixth, after bullectomy the remaining lung may be so overexpanded (as a result of residual bullae and/or bronchospasm) that considerable force is required to "stuff" the lung back into the hemithorax. The resultant obstruction of venous return and physical encroachment on the heart may require the use of inotropes to maintain adequate hemodynamics. Seventh, it is common for multiple small air leaks to be present after bullectomy. Collectively, these leaks cause considerable loss of delivered tidal ventilation through a chest tube. Effective ventilation and oxygenation are accomplished by trial and error using a variety of tidal volumes, airway pressures, inspiratory/ expiratory ratios, flow rates, and ventilation rates or, alternatively, HFV.

The cornerstone of the anesthetic management of patients with giant bullae or cysts is the insertion of a DLT to allow differential treatment of the two lungs. Thus, in patients with unilateral disease, the DLT can allow adequate ventilation of the nondiseased side while preventing rupture of the diseased side. In patients with bilateral disease the DLT still allows differential lung treatment to maximize gas exchange as well as providing an increased capability to deal with the complications of a ruptured bulla. For example, a DLT allows all possible permutations of HFV, CPAP, PEEP, and ZEEP to the two lungs, depending on the pathology in each lung. In addition, as each bulla is resected, the DLT allows ventilation to the operated lung to be reestablished for short periods, enabling the surgeon to identify and suture any air leaks that may be present. The versatility of the DLT is particularly important in thoracoscopic procedures, which may average 3 hours in duration. [542]

A DLT can be inserted with the patient either awake with the airway topically anesthetized (for those with histories of repeated pneumothorax and/or severe bilateral bullae) or under general anesthesia (for the majority of patients) to isolate the affected lung and provide positive-pressure ventilation to the contralateral lung. [547] [548] While the depth of general anesthesia is being increased, spontaneous ventilation may be maintained (primarily indicated in patients with a history of repeated pneumothorax or bilateral bullae), but it should be realized that spontaneously breathing patients with significant pulmonary disease under general anesthesia may

not be able to ventilate themselves adequately. Alternatively, and preferably in the majority of patients, the patient can be anesthetized and both lungs ventilated by using a limited amount of positive airway pressure; gentle ventilation by hand is the best way to ensure low airway pressures. If a major air leak develops intraoperatively while positive pressure ventilation is being used with a volume cycled ventilator, inadequate ventilation may occur (the machine delivers the preset volume but it does not go into the lungs). Under these circumstances a pressure cycled high inspiratory flow ventilator must be used (e.g., Siemens Servo 900C, Solna, Sweden). [542]

If limited positive-pressure ventilation is chosen, it is important that the anesthesiologist be able to diagnose and treat a pneumothorax rapidly. External stethoscopes should be attached over each hemithorax at the points where breath sounds are maximal to monitor for pneumothorax on each side. [549] However, advanced bullous disease may completely prevent breath sounds from being heard externally at all. In addition to a decrease in breath sounds, a pneumothorax or check-valve mechanism in a cyst may be signaled by an increase in airway pressure, tracheal shift to the opposite side, or hypotension disproportionate to the depth of anesthesia. Thus, equipment for chest tube placement must be immediately available for these patients.

Theoretically, after bullectomy the patient's pulmonary status should be improved since the "healthy" lung tissue that was previously compressed by the bullae should now be able to expand. However, in our experience and that of others, [542] the weaning and extubation process often takes up to several days in those patients with advanced disease. When mechanical ventilation is required postoperatively, positive airway pressure should again be minimized to decrease the possibility of producing a pneumothorax from rupture of suture lines and/or residual bullae [550] and to minimize air leaks from remaining lung tissue.

When bilateral bullectomy is performed because of extensive disease in both lungs, a sternal splitting incision with the patient supine is usually made. [551] However, sequential posterolateral thoracotomies may be planned if it is desired to see how the patient responds to the first bullectomy. With bilateral bullectomy, the same anesthetic principles apply as with unilateral bullectomy.

Lung Volume Reduction Surgery

General and Surgical Considerations

Advanced emphysema is a debilitating lung disease that afflicts 2 million people in the United States. [552] In emphysema, the lungs are hyperinflated with poor elastic recoil, the airways are dynamically compressed, the flattened diaphragms contract poorly, and cardiac filling may be impaired. These pathophysiologic changes result in hypoxemia, hypercapnia, an increased work of breathing, and a debilitating shortness of breath. The goal of lung volume reduction surgery is to partially reverse these pathophysiologic mechanisms. [553]

Current approaches to bilateral lung volume reduction surgery include median sternotomy and thoracoscopy, using either a linear cutting stapler or laser ablation, and reinforcement of incised lung parenchyma with exogenous buttressing materials (such as bovine pericardial strips). [553] The lung tissue to be resected is determined by visual assessment of the most diseased lung (which remains inflated during contralateral one-lung ventilation); it most often consists of multiple small regions, is nonanatomic, and usually composes 20 to 30 percent of that lung. [553] In some patients, however, only a few large blebs or bullae are resected. In either case, the most abnormally appearing tissue is resected to allow expansion of the more normal remaining lung tissue. The majority of patients who have undergone this operation have experienced improvement in lung function and quality of life. The two principal causes of morbidity and mortality in patients undergoing this procedure are respiratory impairment due to the induction of general anesthesia and the trauma of the operative incision in these already critically ill patients, and the complications arising from the resection of emphysematous lung tissue, most notably persistent air leaks.

Anesthetic Management

The overriding goal of anesthetic management is to have the patient adequately and quietly breathing spontaneously as soon as possible at the end of surgery to minimize positive pressure-induced lung air leaks. The main components of the anesthetic management that allow achievement of this goal are to use general anesthesia supplemented with thoracic epidural anesthesia intraoperatively and continued after surgery to provide postoperative analgesia, minimal to no intravenous narcotics, fluid restriction, and often a prolonged emergence and recovery (can be a few hours) with mask ventilation assistance is required in the operating room.

Essential invasive monitoring consists of arterial and central venous catheters. The usual indications for a pulmonary artery catheter remain. A thoracic epidural catheter is placed before induction of general anesthesia and the position of the catheter pharmacologically and/or fluoroscopically determined. Optimally the catheter tip is at an upper thoracic (T3-T5) level, being located in the mid-dermatome area of the incision. These very respiratorily debilitated patients are either unpremedicated or receive only small doses of midazolam, if they are anxious. Anesthesia is induced intravenously (without narcotics), the patient paralyzed, a left-sided double-lumen tube passed, and the position confirmed with fiberoptic bronchoscopy. Anesthesia is maintained via the thoracic epidural catheter and a propofol infusion, with or without an added low-dose of volatile anesthetic. During one-lung ventilation, the tidal volume should be adjusted to achieve a peak inspiratory pressure of approx-imately 25 cm H_2O and long expiratory times utilized. With these ventilator settings, hypercapnia is often unavoidable and entirely permissible as long as patients are normo-xemic. [554] After periods of one-lung ventilation, the previously atelectatic lung should be very slowly and gently reexpanded. Hypotension is treated with vasopressors and fluid infusion is restricted to less than 1,000 mL (blood loss is usually minimal). The patients are usually tracheally extubated in a surgical plane of anesthesia and adequate gas exchange maintained via assisted mask ventilation until adequate spontaneous ventilation returns. During the prolonged assisted emergence, intensive respiratory care, consisting of bronchodilators and chest physical therapy, may be required/desired. Postoperatively pain control is achieved by infusion of a dilute local anesthetic solution (e.g., 0.125 percent bupivacaine) in an effort to block afferent pain signals with minimal effect on motor function (Ch. 69) . If required, a very low dose of narcotic can be added to the infusion for a synergistic analgesic effect.

Unilateral Bronchopulmonary Lavage

General Considerations

Unilateral bronchopulmonary lavage, or massive irrigation of the tracheobronchial tree of one lung, has been used with good success in patients with pulmonary alveolar proteinosis as a means of removing the enormous accumulations of alveolar lipoproteinaceous material characteristically present in these patients. [555] [556] [557] [558] [559] The lipoproteinaceous material is thought to be surfactant, [560] and the abnormal accumulation is due to failure of clearance mechanisms rather than to enhanced formation. [561] The abnormal accumulation of alveolar lipoproteinaceous material is bilateral and symmetric and causes the classic chest radiographic picture of air space consolidation with patchy, poorly defined shadows throughout the lung. [562] The radiographic picture reflects the course of the disease. The air space consolidation causes progressive hypoxemia and shortness of breath (first on exertion and then at rest), [562] [563] and the lungs have a low compliance. The diagnosis of alveolar proteinosis is made by correlating the clinical, radiologic, and laboratory data with the results of a lung biopsy. The indication for lung lavage is Pa o_2 less than 60 mm Hg at rest or hypoxemic limitation of normal activity. [564] [565] Infrequently, lung lavage may be performed in patients with asthma, cystic fibrosis, and radioactive dust inhalation. [552] [557] [565] [566] [567]

Unilateral lung lavage is performed under general anesthesia with a double-lumen endotracheal tube, allowing lavage of one lung while the other lung is ventilated (Fig. 48-38) (Figure Not Available) . In patients with alveolar proteinosis, lavage is performed on one lung and then, after a few days' rest, on the

Figure 48-38 (Figure Not Available) Technique for providing unilateral bronchopulmonary lavage. A left clear plastic double-lumen endotracheal tube allows ventilation to the left lung during lavage of the right lung (and vice versa). Normal saline is infused and drained by gravity; clamps on the connection tubes determine direction of fluid flow. (See text for details.) *(From Benumof [604])*

other lung. After lung lavage these patients usually have marked subjective improvement, which correlates with increases in Pa o_2 during rest and exercise, increased vital capacity and diffusion capacity, and clearing of the chest radiograph. [568] [569] Some patients require lavage every few months, whereas others remain in remission for several years, and the disease may even eventually completely remit. [568] [569]

Anesthetic Considerations

This section discusses the technique for anesthetic management of bronchopulmonary lavage in patients with pulmonary alveolar proteinosis. [260] When the patient is admitted to the hospital, V/Q scans of the lung are obtained. Ventilation can be maximized during lung lavage by performing the first lavage on the most severely affected lung, allowing the "better" lung to provide gas exchange. If the scan indicates relatively equal involvement (as is usually the case), the left lung is lavaged first, leaving the larger right lung to support gas exchange.

After several minutes of preoxygenation (see below), general anesthesia is induced with thiopental in divided doses and inhalation of either isoflurane or halothane in 100 percent oxygen. Isoflurane is relatively indicated in patients in whom therapeutic levels of theophylline (and the risk of arrhythmias) are present. Neuromuscular blockade is induced with a nondepolarizing muscle relaxant. When a suitable level of anesthesia has been reached, the trachea is intubated with the largest left-sided DLT that can be passed atraumatically through the glottis. A clear plastic disposable left-sided DLT is used because of the ease and certainty with which it is correctly positioned, the reliable left cuff seal obtained (the right endobronchial cuff is small and inflates asymmetrically), and the ability to continuously observe the tidal movements of respiratory gas moisture (ventilated lung) and the lavage drainage fluid for leaking air bubbles (lavaged lung). The largest tube is used because the left endobronchial cuff will make contact over a greater bronchial mucosal area with less air in the left cuff (as compared with a small DLT). In addition, a large tube facilitates suctioning, which is an important consideration at the end of the case when the lungs must be made as clear as possible. Precise placement of the tube and detection of leaks are essential because of the serious hazard of spillage during the lavage procedure. The position of the DLT must be confirmed with a fiberoptic bronchoscope, and left cuff seal must be demonstrated to hold against 50 cm H_2O left lung air pressure by a right lumen to catheter-under-water technique (see the section *Quantitative Determination of Cuff Seal Pressure Hold*).

The question of patient position during unilateral lung lavage is important, for there are major advantages and disadvantages related to each position (Table 48-22) . The LDP with the lavaged lung dependent minimizes the possibility of accidental spillage of lavage fluid from the dependent lavaged lung to the nondependent ventilated lung. However, during periods of lavage fluid drainage, pulmonary blood flow, which is gravity-dependent, would preferentially perfuse the nonventilated dependent lung, and the right-to-left transpulmonary shunt would be maximal. The LDP with the lavaged lung nondependent minimizes blood flow to the nonventilated lung, but, on the other hand, increases the possibility of accidental spillage of lavage fluid from the lavaged lung to the dependent ventilated lung. As a compromise, the supine position is used to balance the risk of aspiration with the risk of hypoxemia.

After insertion and checking of the DLT and positioning of the patient, baseline total and individual lung compliances are measured. Airway pressure can be electronically transduced and continuously recorded on a paper write-out, and a Wright spirometer should be placed in the expiratory

TABLE 48-22 -- Unilateral Lung Lavage: Position of Lavaged Lung

Lateral decubitus with lavaged lung nondependent
Advantage: Minimizes blood flow to nonventilated lung
Disadvantage: Maximizes possibility of spillage
Lateral decubitus with lavaged lung dependent
Advantage: Minimizes possibility of spillage
Disadvantage: Maximizes blood flow to nonventilated lung
Supine position
Balances spillage and blood flow distribution problems

limb of the anesthesia circle system to measure tidal volume accurately. A volume ventilator that can deliver relatively high inflation pressures is required, because these patients have diseased and noncompliant lungs. Prelavage total dynamic compliance (chest wall and lung) of both lungs together (using 15 mL/kg tidal volume) and then of each lung separately (using 10 mL/kg tidal volume) is measured. After measurement of total and individual lung compliance and with the patient breathing 100 percent oxygen, baseline arterial blood gases are measured.

The patients are completely preoxygenated before induction of anesthesia and lavage for two reasons. First, as with the induction of general anesthesia in any patient, an oxygen-filled FRC greatly minimizes the risk of hypoxemia during the apneic period required for laryngoscopy and endotracheal intubation. This consideration has added importance for patients with alveolar proteinosis because they are already severely hypoxemic. Second, preoxygenation eliminates nitrogen from the lung that is to be lavaged. Alveolar gas is then composed only of oxygen and carbon dioxide. During fluid filling, these gases will be absorbed, allowing the lavage fluid maximal access to the alveolar space. Failure to remove nitrogen from the lung before filling the lavage fluid may leave peripheral nitrogen bubbles in the alveoli and thus limit the effectiveness of the lavage.

Warmed isotonic saline is used as the lavage fluid and is infused by gravity from a height of 30 cm above the midaxillary line. After the lavage fluid ceases to flow (i.e., lung filling is complete), drainage is accomplished by clamping the inflow line and unclamping the drainage line, which runs to a collection bottle placed 20 cm below the midaxillary line (see Fig. 48-38) (Figure Not Available) . The inflow and outflow fluid lines are connected to the appropriate endotracheal tube lumen by a Y-adapter. Each tidal lavage filling is accompanied by mechanical chest percussion and vibration to the lavaged hemithorax before drainage. The lavage fluid that is drained is typically light brown, and the sediment layers out at the bottom of the collection bottle after a short time. Filling and drainage of approximately 500- to 1,000-mL aliquots are repeated until the lavage effluent clears (see Fig. 48-38) (Figure Not Available) . Volumes delivered to and recovered from each tidal lavage are recorded. Total lavage fluid volumes of 10 to 20 L are usually used.

Most patients studied have been hemodynamically stable throughout the entire lavage procedure. In particular, lavage itself has caused no significant changes in systemic and transmural pulmonary artery pressures and cardiac output. [570] In these patients, the arterial saturation, as measured by pulse oximetry, has increased and decreased, with each lung filling and drainage, respectively. [570] In addition, cardiac output has decreased and increased with each lung filling and drainage, respectively. Arterial saturation increases during lung filling because blood flow to the nonventilated lung is decreased by the lavage fluid infusion pressure. [571] The opposite set of events (increased nonventilated lung blood flow, decreased arterial oxygen saturation) occurs during lung drainage. [571] Not surprisingly, the cardiac output decreases with each lavage fluid instillation because of the increase in PVR. [570] The opposite set of events (increased nonventilated lung blood flow, decreased arterial oxygen saturation) occurs during drainage. [571] In addition, with drainage of the lavage fluid, PVR decreases and cardiac output increases. [570] An adequate degree of neuromuscular blockade must be maintained because unexpected vigorous coughing during the procedure could alter DLT position and allow spillage of fluid from the lavaged lung to the ventilated lung.

If a small leak should occur during lavage, the following may be observed sequentially: (1) the appearance of bubbles in the lavage fluid draining from the lavaged lung, (2) rales and rhonchi in the ventilated lung, (3) a difference between lavage volumes administered and those drained from the lavaged lung (the former exceeds the latter), and (4) a fall in arterial oxygen saturation. If a small leak is suspected or detected by any of these signs and the lavaged lung has been only minimally treated, the lavaged lung should be drained of all fluid, and the position of the DLT, the adequacy of cuff seal, and separation of the lungs should be rechecked with a fiberoptic bronchoscope. Before beginning the lavage procedure again and no matter what the DLT malposition was, the functional separation of the two lungs and adequacy of cuff seal should be tested and found adequate by using the previously described air bubble leak detection method.

Massive spillage of fluid from the lavaged lung to the ventilated lung is not a subtle event and results in a dramatic decrease in ventilated lung compliance and a rapid and profound decrease in arterial oxygen saturation. Under these circumstances, the lavage procedure must be terminated no matter how much treatment has been accomplished. The patient should be moved quickly to the LDP with the lavaged side dependent, and the operating room table should be placed in a head-down position to facilitate removal of lavage fluid. Vigorous suctioning and inflation of both lungs should be carried out. The DLT should be changed to a standard single-lumen tube, and the patient should additionally receive a period of mechanical ventilatory support with PEEP. Timing of further unilateral lung lavage attempts will be dictated by the patient's subsequent clinical course and gas exchange status.

After the effluent lavage fluid becomes clear, the procedure is terminated. The lavaged lung is thoroughly suctioned, and ventilation to that lung is resumed. Because the compliance of the lavaged side will be much less than that of the ventilated side at this time, large tidal ventilations (sighs) (15-20 mL/kg) to that side alone (with the nonlavaged side temporarily nonventilated) are necessary to reexpand alveoli. Arterial blood oxygenation may decrease precipitously during this time, but this can be minimized by clamping the nonlavaged side after a large inspiration of 100 percent oxygen.

After lavage, the recovery procedure consists of repetitive periods of large tidal ventilations, suctioning and chest wall percussion to the previously lavaged side, conventional two-lung ventilation with PEEP, and bilateral suctioning and postural drainage while intermittently measuring combined (total) and individual lung dynamic compliance. As the compliance of the lavaged lung returns to prelavage values, ventilation with an air-oxygen mixture may help lavaged lung alveoli with low V/Q ratios to remain open. When the compliance of the hemothorax of the lavaged side returns to its prelavage value, the neuromuscular blockade is reversed. Mechanical ventilation and extubation guidelines are the same as for any patient with pulmonary disease; most patients are able to be extubated while still in the operating room.

In the immediate postlavage period, deep breathing (incentive spirometry), coughing exercises, chest percussion, and postural drainage are used to remove remaining fluid and secretions and to reexpand the lavaged lung further. After 3 to 5 days of recovery, the patient is returned to the operating room to have the opposite side lavaged. The anesthetic considerations for the second lavage are the same as for the first lavage, although oxygenation is usually not nearly as severe a problem as during the first lavage because the treated and now near normal lung will be used to support gas exchange.

Special problems associated with pulmonary lavage that may be encountered are that a few very critically ill patients may be unable to tolerate the conventional procedure, and unilateral lavage through a DLT is not easily done in children. Alternative (and more complicated) ways of accomplishing lung lavage in these patients include use of extracorporeal membrane oxygenation and lobar lavage via a fiberoptic bronchoscope inserted under topical anesthesia. [260]

Tumors at the Confluence of the Superior, Anterior, and Middle Mediastinum

General Considerations

At the confluence of the superior, anterior, and middle mediastinum are the middle portion of the superior vena cava, the tracheal bifurcation, the main pulmonary artery, the aortic arch, and parts of the cephalad surface of the heart. [260] In adults, the majority of tumors in this region originate from involvement of the hilar lymph nodes with bronchial carcinoma or lymphoma, whereas in babies the masses are most often benign bronchial cysts, esophageal duplication, or teratoma. Tumors of this region can cause compression and obstruction of three of the vital mediastinal structures: the tracheobronchial tree in the region of the tracheal carina, the main pulmonary artery and atria, and the superior vena cava. A CT scan of the chest is probably the single most important diagnostic procedure because it defines the size and degree of compression of these vital structures. The most common complication that occurs during anesthesia for masses involving these three vital mediastinal structures is airway obstruction; this was a feature in 20 of 22 patients recently reviewed (1969-1983) and succinctly summarized. [572] Although airway obstruction has been predominant in terms of symptomatology, it is not uncommon for compression of two or three of the major organs to be present in varying degrees and to cause complications in the same patient. [572] Each of these complications is life-threatening and can cause acute deterioration and death during anesthesia if not handled with the most extreme caution and expertise. Each major complication and anesthetic management problem is discussed separately below, and Figure 48-39 (Figure Not Available) shows the overall strategy for managing these three problems.

Figure 48-39 (Figure Not Available) Flow diagram showing the essential management strategies for the three major anesthetic problems that mediastinal masses may cause. TBT, tracheobronchial tree; SVC, superior vena cava; PA, pulmonary artery; FOB, fiberoptic bronchoscopy; ETT, endotracheal tube; CPB, cardiopulmonary bypass. *(From Benumof [604].)*

Compression of the Tracheobronchial Tree

Most anterior mediastinal masses that cause airway obstruction [260] are lymphomatous in origin. However, a number of benign conditions such as cystic hygroma, teratoma, thymoma, and thyroid tumors can occur in a similar fashion. A tissue diagnosis, therefore, should be made before radiation or chemotherapy can be undertaken. Thus, most patients with a mediastinal mass causing airway obstruction will first require anesthesia for a diagnostic procedure (e.g., cervical or scalene node biopsy, staging laparotomy for Hodgkin's disease). Importantly, not all patients who have developed severe intraoperative respiratory problems have respiratory symptoms and signs preoperatively.

The anesthetic management of these patients is based on two overriding considerations. First, the obstruction of major airways by a tumor is usually life-threatening because the obstruction usually occurs around the bifurcation of the tracheobronchial tree and is therefore distal to the endotracheal tube. The loss of spontaneous ventilation seems to precipitate the airway obstruction. It may be that loss of chest wall tone and the distending forces of active inspiration after administration of muscle relaxants release extrinsic support of a critically narrowed airway. Alternatively, intubation in the presence of distortion or compression of the trachea may cause complete obstruction if the orifice of the tube impinges on the tracheal wall or if the lumen of the tube is occluded where it passes a narrowed section or turns a sharp angle. In view of the potential for fatal airway obstruction during general anesthesia, all possible attempts to perform the procedure under local anesthesia should be undertaken.

Second, the response of lymphomatous tumors to radiation or chemotherapy is normally dramatic. Chest radiographs reveal a marked decrease in tumor size, and the symptoms are usually improved. Consequently, it behooves the treating physicians to use radiotherapy or chemotherapy if at all possible (sometimes the cell type can be known with a reasonable degree of certainty without a biopsy) before general anesthesia is used. [573] [574] It should be noted that during radiation, a small window can be created to spare some tissue for adequate histologic diagnosis. [575] [576]

The following management plan is based on the principles outlined [560] [572] [573] [574] [575] [576] (Table 48-23 and see Fig. 48-39) (Figure Not Available) . If a patient with a mediastinal mass near the confluence of the superior, anterior, and middle mediastinum exhibits dyspnea and/or intolerance of the supine position and is scheduled for biopsy, it should be performed under local anesthesia if at all possible. If the cell type is thought to be radiosensitive or chemosensitive, appropriate types of therapy should be undertaken before any further surgery is performed. After these types of therapy, the radiologic appearance of the tumor must be reviewed along with a dynamic evaluation of pulmonary function (see later).

If the patient does not have dyspnea or intolerance of the supine position (i.e., is asymptomatic), a CT scan, flow-volume loop, and echocardiogram should be obtained to evaluate the anatomic and functional position of the tumor. If any of these three tests has positive results, local anesthesia should be used for biopsy even if the patient is asymptomatic.

TABLE 48-23 -- Important Management Principles for Tumors at the Confluence of the Superior, Anterior, and Middle Mediastinum

1.	Perform all procedures under local anesthesia if possible.
2.	Use radiation and/or chemotherapy if possible before general anesthesia.
3.	If general anesthesia is required, consider inspection of tracheobronchial tree with fiberoptic bronchoscope and intubate awake.
4.	If general anesthesia is required, maintain spontaneous ventilation.

If general anesthesia is to be used, the airway should be evaluated by fiberoptic bronchoscopy with topical anesthe-sia before induction of general anesthesia. [576] The fiberoptic bronchoscope should be jacketed with an armored endotracheal tube, and after the fiberoptic bronchoscopy examination has been completed, the patient is intubated. General anesthesia should be induced with the patient in the semi-Fowler position. The patient should be allowed to breathe spontaneously

throughout the procedure; muscle relaxants should be avoided. Large changes in intrathoracic pressure, which may promote collapse of a weakened tracheobronchial tree, must be prevented. The operating room team should retain the capability of changing the patient's position rapidly to the lateral or prone position. A rigid ventilating bronchoscope should be on hand to bypass distal tracheal and carinal obstructions, and the appropriate personnel and equipment for cardiopulmonary bypass also should be available.

These patients must be watched extremely closely in the first few postoperative hours. Airway obstruction requiring reintubation and mechanical ventilation has occurred, possibly secondary to an increase in tumor size due to tumor edema after instrumentation.

Compression of the Pulmonary Artery and Heart

Compression of the pulmonary artery and heart is very rare, because the pulmonary trunk is more or less protected by the aortic arch and tracheobronchial tree; there are only a few case reports of this problem in the literature. [260]

Principles similar to those for compression of the tracheobronchial tree apply to compression of the pulmonary artery. Most patients have their first anesthetic experience because they require a diagnostic procedure (e.g., a biopsy). These patients should be evaluated preoperatively in a manner similar to that used for patients with compression of the tracheobronchial tree. If the cell type is known or is highly suspected, preoperative irradiation should be seriously considered. All diagnostic procedures should be performed under local anesthesia if at all possible. If general anesthesia is required and if the symptoms worsen in the supine position, the sitting, leaning forward, or even face-down position is advised, and spontaneous ventilation should be maintained throughout the procedure. Measures to maintain venous return, pulmonary artery pressure, and cardiac output, such as volume loading and use of ketamine, should be considered. Arrangements for extracorporeal oxygenation should be completed preoperatively.

Superior Vena Cava Syndrome

The superior vena cava syndrome is caused by mechanical obstruction of the superior vena cava. The causes of superior vena caval obstruction, in order of decreasing incidence, are bronchial carcinoma (87%), malignant lymphoma (10%), and benign causes (3%), such as central venous hyperalimentation and pacemaker catheter-induced thrombosis of the superior vena cava, idiopathic mediastinal fibrosis, mediastinal granuloma, and multinodular goiter. [260] The classic features of the superior vena cava syndrome include dilated distended veins in the upper half of the body due to increased peripheral venous pressure (which can be as high as 40 mm Hg); edema of the head, neck, and upper extremities; dilated venous collateral channels in the chest wall; and cyanosis. Venous distention is most prominent in the recumbent position, but in most instances the veins do not collapse in the normal manner with the patient upright. Edema can be so great as to cause swelling of periorbital fissures, preventing patients from opening their eyes. Such advanced cases of edema usually obscure the dilated veins as well. The majority of patients have respiratory symptoms (shortness of breath, cough, orthopnea), which are due to obstruction of the airways by engorged veins and mucosal edema, and these are ominous signs. Similarly, a change in mentation, due to cerebral venous hypertension and edema, is a sign of particularly significant obstruction. In some cases the superior vena cava becomes occluded quite slowly, and the signs and symptoms may be insidious in onset. When the occlusion occurs relatively rapidly, all clinical manifestations are more prominent. The most common radiologic sign is widening of the superior mediastinum. Venography confirms the diagnosis (but not the cause). Determination of etiology may require thoracotomy, sternotomy, bronchoscopy, lymph node biopsy, etc.

Most patients with superior vena cava syndrome due to a malignant process are treated with irradiation and chemotherapy (for patients with incomplete obstruction). [577] However, in patients with near complete to complete obstruction (who usually have signs of cerebral venous hypertension and/or airway obstruction) or in whom irradiation or chemotherapy proves ineffective, surgical bypass or resection of the lesion via median sternotomy is indicated. [577] These operations are usually technically quite difficult because tissue planes are poorly delineated, anatomy is grossly distorted, central venous pressures are abnormally high, and varying degrees of fibrosis are present.

The preoperative anesthetic evaluation of a patient for superior vena caval decompression should include careful assessment of the airway. The same degree of edema that is present externally in the face and neck can be expected to be present in the mouth, oropharynx, and hypopharynx. In addition, the airway may be compromised by external compression, fibrosis limiting normal movement, or recurrent laryngeal nerve involvement. If tracheal compression is suspected, it should be evaluated by CT.

The patient is transported to the operating room in the head-up position to minimize airway edema. A radial artery catheter is inserted in all patients and depending on the medical condition of the patient, a central venous or pulmonary artery catheter is inserted via the femoral vein before induction of anesthesia. At least one large-bore intravenous cannula should be inserted into the leg or femoral vein before operating. Premedication is best limited to an antisialagogue to reduce airway secretions. The method chosen for induction of anesthesia and intubation depends on the preoperative airway evaluation. If it is necessary for the patient to maintain the sitting position to achieve adequate ventilation before induction, intubation with the patient awake may be facilitated by using a fiberoptic laryngoscope or bronchoscope.

The most significant intraoperative problem encountered is bleeding. Substantial venous blood loss results from the abnormally high central venous pressure. Further, unexpected arterial bleeding may occur because of the difficulty of dissecting in a distorted surgical field. Crossmatched blood should therefore be available in the operating room at the time of sternotomy.

Postoperatively, especially after diagnostic procedures such as mediastinoscopy and bronchoscopy wherein the superior vena caval obstruction has not been relieved, acute severe respiratory failure requiring intubation and mechanical ventilation may occur. [260] The mechanisms of the acute respiratory failure are obscure, but the most likely ones that are unique to the superior vena cava syndrome are acute laryngospasm and/or acute bronchospasm (both due to continued and perhaps increased obstruction of the superior vena cava), impaired respiratory muscle function (patients with malignant disease may have an abnormal response to muscle relaxants), and increased airway obstruction by the tumor (due to tumor swelling). Consequently, these patients must be closely monitored in the first few postoperative hours.

Emergency Thoracic Procedures

Massive Hemoptysis

General Considerations

Massive hemoptysis [578] is uncommon, occurring in less than 0.5 percent of patients admitted to a large pulmonary medicine service. It has been arbitrarily defined, on the basis of the amount of daily volume of blood expectorated, as 200 to 600 mL in 24 to 48 hours, or from the standpoint of causing acute airway obstruction or major hypotension. [578]

More than 90 percent of reported cases of massive hemoptysis have a chronic infectious cause [579] because chronic inflammation leads to profuse vascularization of the high-pressure bronchial artery system. Subsequently, any erosion or rupture of enlarged bronchial arteries will result in massive hemoptysis. Active tuberculosis is the most common and bronchiectasis the second most common infection causing massive hemoptysis. [580] The majority of the remaining causes of hemoptysis are due to bleeding neoplasms.

Surgical Considerations

In a series of 55 pulmonary resections performed for massive hemoptysis (600 mL in 16 hours), a mortality rate of 18 percent was reported [581] ; this was markedly better than with conservative treatment, which resulted in a mortality rate of

Figure 48-40 (Figure Not Available) Treatment algorithm for massive hemoptysis. The most important function of emergency bronchoscopy is to establish or to diagnose the cause and site of bleeding. In addition, the amount and spread of bleeding can be controlled during emergency bronchoscopy (see items listed in the algorithm under "Diagnosis of Cause"). *(Modified from Benumof [604])*

75 percent in patients who bled 600 mL or more in 16 hours and 54 percent in those who bled 600 mL or more in 48 hours. [582] [583] However, routine use of surgery has been debated, as other authors have found that somewhat lesser degrees of hemoptysis may be successfully managed conservatively regardless of the amount of bleeding in the first 24 hours. [578] Nevertheless, surgery (resection) is probably indicated in patients who require multiple transfusions, in those in whom bleeding results in progressive impairment of pulmonary function (aspiration should be evaluated by serial chest radiographs and arterial blood gases), and in those in whom hemoptysis persists for several days despite optimum medical treatment. Contraindications to surgery include inoperable carcinoma of the lung, inability to localize the bleeding site, and the presence of severe bilateral pulmonary disease and systemic disease (debilitation). These patients are candidates for bronchial artery embolization (Fig. 48-40) (Figure Not Available) (see later).

Bronchoscopy during active bleeding is the single most important technique for determining the cause and location of bleeding and should be performed in all patients; the procedure should be done in the operating room so that immediate resection can be performed [583] (see Fig. 48-40) (Figure Not Available) . Most surgeons use a rigid bronchoscope because of the much greater suctioning and ventilating capability. However, the flexible fiberoptic bronchoscope may be used if there is no active bleeding and/or the site of bleeding is thought to be in the upper lobes.

The surgeon may be able to control bleeding and the spread of bleeding during bronchoscopy (see Fig. 48-40) (Figure Not Available) . Topical iced saline and vasoconstrictors can be administered through the bronchoscope to control bleeding, provided the bleeding is not so massive as to preclude visualization of its origin. [584] Control of spread of blood from one lung to the other can be achieved by use of a bronchial blocker (e.g., balloon-tipped Fogarty catheter) in the main bronchus of the bleeding side or by use of a gauze packing of the bleeding segment or side. [578] The Nd:YAG laser has proved efficacious in the treatment of hemoptysis in patients with lung cancer. [585] [586] In a very exciting new development in pulmonary medicine, two recent reports describe complete cessation of bleeding in almost all patients by selective intrabronchial spraying of fibrin precursors through a catheter in the suction port of a fiberoptic bronchoscope without any adverse effect. [587] [588] During bronchoscopy, the surgeon should frequently restore adequate oxygenation and ventilation by intubating the uninvolved main stem bronchus. If the patient can withstand surgery and has an identified operable lesion, surgery should be performed. If the patient cannot withstand surgery and/or has an inoperable lesion,

bronchial embolization should be attempted (see Fig. 48-40) (Figure Not Available) .

Anesthetic Considerations

There are several important preoperative priorities. For patients with massive hemoptysis, asphyxiation must be prevented by administering 100 percent oxygen; placing the bleeding lung in a dependent position; separating the lungs with a DLT, endobronchial single-lumen tube, or bronchial blocker; and using intermittent positive-pressure ventilation and vigorous suction. After the airway is secured and the bleeding lung isolated, the patient is placed so that the bleeding lung is in a nondependent position.

Coughing may increase bleeding. The advisability of using sedatives and cough suppressants is time-dependent. In the unintubated patient, the ability to cough may be lifesaving, and suppressants should be avoided. In the intubated patient, suctioning can replace the cough mechanism, and suppression of cough may decrease bleeding. A coagulation profile should be drawn early; if any abnormalities are noted, they should be corrected. During and after bronchoscopy, the surgeon and pulmonologist can control bleeding by iced saline lavage, placement of topical vasoconstrictors, placement of a bronchial blocker or gauze packing, laser coagulation, fibrin seal, and use of bronchial artery embolization (see earlier).

As soon as possible, several large-bore intravenous cannulae are inserted. The patient's blood is typed and cross-matched for adequate amounts of blood products (whole blood, packed red blood cells, platelets, fresh frozen plasma). Transfusion should begin if appropriate. Antibiotics are administered preoperatively, and antituberculous drugs are started in patients with tuberculosis. Finally, the appropriate monitoring (e.g., arterial line, central venous line) is instituted. Many of these procedures should be undertaken simultaneously.

If the patient with massive hemoptysis is without an indwelling endotracheal tube, preoxygenation should be instituted immediately. Adequate suctioning must be available. It may be necessary for the patient to be awake for intubation during massive, active, spontaneous bleeding to prevent the hazard of trying to visualize a blood-obscured airway in a paralyzed patient. Intubation performed in the semiupright position may minimize coughing that results in the presence of blood in the upper airway and thereby may provide a clearer field of vision.

If the patient without an indwelling endotracheal tube is to be anesthetized, aspiration precautions (e.g., cricoid pressure) should be used, because many patients have swallowed expectorated blood. Because these patients are likely to be hypovolemic, the induction of anesthesia should be accomplished with a small dose of short-acting barbiturate or ketamine or with narcotics followed in rapid sequence by relaxation. If the larynx can be visualized, insertion of a DLT is preferable to insertion of a single-lumen tube. It should be remembered that if the patient is not actively bleeding but has a blood-filled cavity (i.e., a hemorrhagic lobe), this cavity will likely empty its contents into the dependent unsoiled lung when the patient is turned to the LDP; therefore, this situation is a strong indication for placement of a DLT. If a single-lumen tube is inserted, it might as well be the Univent bronchial blocker tube, which additionally allows lung separation.

If a single-lumen tube is already in place, consideration should be given to conversion to a DLT, addition of a bronchial blocker, and/or achieving an endobronchial position of the existing tube. Once the airway has been secured, the patient must be placed in the LDP with the bleeding lung in the nondependent position. Use of this position, of course, emphasizes the importance of separating the lungs. In all situations if active tuberculosis is present or suspected, contamination precautions should be taken.

At the end of surgery, the endotracheal tube should be left in place and the patient should be ventilated mechanically. Most of these patients will have impaired gas exchange postoperatively as a result of preexisting lung disease, the probability that the nonbleeding lung has been soiled by the recent hemoptysis from the diseased lung, and the physiologic consequence of having just undergone a major anesthetic and surgical experience.

Bronchopleural Fistula

General Considerations

A bronchopleural fistula may be caused by the rupture of a lung abscess, bronchus, bulla, cyst, or parenchymal tissue (as in the case of high levels of PEEP during mechanical ventilation) into the pleural space; by erosion of a bronchus by a carcinoma or chronic inflammatory disease; and by breakdown of a bronchial suture line after pulmonary resection.

Surgical Considerations

The diagnosis of bronchopleural fistula is usually made clinically. In early postpneumonectomy patients, the diagnosis is based on sudden dyspnea, subcutaneous emphysema, contralateral deviation of the trachea, and disappearance of the fluid level on radiographs of the chest. In patients after lobectomy, persistent air leak, purulent drainage, and expectoration of purulent material are usually diagnostic. When the fistula appears after removal of the chest tube, the diagnosis of a bronchopleural fistula is made on the basis of fever, purulent sputum, and a new air fluid level in the pleural cavity on the chest radiograph. The diagnosis is confirmed by bronchoscopic examination in most, bronchography in a few, and sinograms (of the fistula) in occasional patients. [589] Other methods consist of injection of an indicator such as methylene blue into the pleural space and its recovery from the sputum, accumulation of radionuclide in the pleural space after inhalation of

xenon, or a bronchogram showing spillage of contrast into the vacant hemithorax.

In postpneumonectomy patients, if the disruption occurs early, it is possible to resuture the stump. Late postpneumonectomy bronchial disruption associated with empyema has been managed by conservative drainage, but definitive operative closure is now considered the treatment of choice.

In non-postpneumonectomy cases, if the lung expands to fill the thoracic cavity, the leak can usually be controlled with chest tube drainage alone. However, if the fistula is

large and a significant leak through a large persistent pleural space occurs, it is unlikely that the fistula will close, and surgical resection is usually necessary. [589] An empyema complicating a bronchopleural fistula should, if possible, be drained before surgery (see next section).

Finally, a spontaneous pneumothorax (no prior lung resection involved) is pathophysiologically similar to a bronchopleural fistula. There are three situations in which definitive surgical treatment is indicated in management of spontaneous pneumothorax. First, surgery is required when conventional tube drainage and suction have been unsuccessful in clearing the pleural space and when, in effect, a bronchopleural fistula has formed. Second, surgical intervention is usually indicated when a second ipsilateral or first contralateral spontaneous pneumothorax occurs. Third, considering that a spontaneous pneumothorax has a recurrence rate of 10 to 25 percent, if after the initial event the patient's life-style is such that a recurrence might be life-threatening or highly inconvenient, definitive treatment is indicated. Surgical procedure options are pleurectomy and chemical pleurodesis. [590]

Anesthetic Considerations

Preoperatively, it is useful to estimate the loss of tidal volume through the bronchopleural fistula. This may be done in two ways. First, one should determine whether air bubbles intermittently or continuously through the chest tube. If air bubbles intermittently, it means the fistula is small. In contrast, when a patient has a large, low-resistance bronchopleural fistula or bronchial rupture, air may bubble continuously through the water seal chamber of the chest tube drainage system. Second, the size of the bronchopleural fistula may be quantitated by the difference between inhaled and exhaled tidal volumes. In the nonintubated patient, this may be determined with a tight-fitting mask and a fast-responding spirometer; in the intubated patient it is determined by direct attachment of the spirometer to the endotracheal tube. The larger the leak, the greater need to isolate the bronchopleural fistula (DLT, bronchial blocker).

There have been several nonsurgical approaches (use of various mechanical ventilation-chest tube drainage systems) to the treatment of patients with bronchopleural fistula. These approaches consist of one-lung ventilation and differential lung ventilation, including HFV, PEEP to the pleural cavity equal to the intrathoracic PEEP, and unidirectional chest tube valves.

For patients undergoing operative repair, the ability to deliver intraoperative positive-pressure ventilation adequately must be carefully considered preoperatively. If a fistula is obviously small, chronic, and uninfected, a standard endotracheal tube can likely be used safely. When in doubt, positive-pressure ventilation can be tested, and if it is found inadequate, the standard endotracheal tube can be replaced with a DLT. During the induction of anesthesia, suction on the chest tube should be discontinued to decrease the loss of tidal volume with the initiation of positive-pressure ventilation. If, after the chest is opened, an excessive leak is encountered when using a standard endotracheal tube, ventilation can be improved by lung packing and manual control of the air leak. [591]

For large fistulas or fistulas of unknown size and for those in which an associated abscess or empyema is known or suspected to be present, intraoperative use of a DLT has the dual benefits of permitting positive-pressure ventilation of the normal lung without loss of the minute ventilation through the fistula and preventing the hazard of contamination of the uninfected lung with infected material when the patient is turned to the LDP. [592] [593] [594] Indeed, in one series of 22 patients undergoing operations for bronchopleural fistula after pulmonary resection for tuberculosis or tuberculous empyema, management with a single-lumen endotracheal tube, despite intubation in the head-up position and frequent suctioning, resulted in extensive contamination of normal lung in two patients. [595] In one patient the operation had to be terminated, and in the other emergency bronchoscopy had to be performed. The use of a DLT effectively isolates the leaking and perhaps infected lung cavity from the normal lung. For patients who cannot have a DLT (e.g., very small children, patients with inability to tolerate being taken off the ventilator, those with anatomic difficulties), bronchial blockade and endobronchial intubation are less satisfactory alternatives.

Lung Abscesses and Empyema

General Considerations

Pulmonary aspiration secondary to alcoholic stupor has classically been reported as the most common factor that precipitates lung abscess. Other historical factors that predispose patients to lung abscess formation consist of abuse of other drugs, prior pneumonia, lung carcinoma, immunosuppression with steroid drugs, diabetes mellitus, the presence of a distant septic focus (hematogenous spread), and COPD. [596]

Empyema is the accumulation of pus in the pleural cavity. All the causes of a lung abscess described above may produce empyema. Empyema may also be caused by infection of residual clotted blood after a hemothorax (which was treated by chest tube placement) and after diagnostic thoracentesis, especially if there is a concurrent intra-abdominal injury or infection. [597] Both a lung abscess and an empyema may erode a bronchus and cause a bronchopleural fistula (see earlier).

Surgical Considerations

Simple empyemas (without abscess) may be treated by repeat thoracentesis, tube thoracostomy, thoracoscopy, or open drainage with rib resection. [598] In any patient who does not improve with any of these therapies, an open drainage procedure followed by either lobectomy or segmentectomy is required. [599] [600]

Anesthetic Considerations

If a surgical procedure is to be performed with the patient under general anesthesia in a patient with either a lung abscess or an empyema, DLT intubation is absolutely indicated

to prevent contamination of the uninfected lung by the infected lung. In addition, if an empyema is to be treated with thoracoscopy, collapse of the diseased lung greatly aids access to the empyema. [601] [602] The seal of the endobronchial cuff should be tight and can be quantitated by a bubble-underwater technique. The position of the tube should be determined by fiberoptic bronchoscopy. Both these maneuvers should be done before the patient is turned to the LDP.

During the surgical procedure, the diseased side should be suctioned frequently (fiberoptically if necessary). Whenever possible, but particularly at the end of the procedure, the diseased lung should be fully expanded manually. When the lung has been fully expanded, the surgeon should check carefully for the presence of a bronchopleural fistula. The pleural cavity may be irrigated with antibiotics at the end of the procedure, and one must be mindful of the neuromuscular blockade effects of antibiotics.

/das/book/view/29494766/875/550.html

References

1. Anderson WG: Respiratory aspects of the preoperative examination. Br J Anaesth 46:549, 1974.

2. Shields TW: Carcinoma of the lung. p. 729. In Shields TW (ed): General Thoracic Surgery. Lea & Febiger, Philadelphia, 1983.

3. Spiro SG: The diagnosis and staging of lung cancer. p. 36. In Smyth JF (ed): The Management of Lung Cancer. Edward Arnold, 1984.

4. Le Roux BT: Bronchial Carcinoma. E. & S. Livingstone, London, 1968.

5. Jones DP: Symposium on noncardiac thoracic surgery: diagnostic work-up of chest disease. Surg Clin North Am 60:743, 1980.

6. Fielding JE, Phenow KJ: Health effects of involuntary smoking. N Engl J Med 319:1450, 1988.

7. Capewell S, Sankaran R, Lamb D et al: Lung cancer in lifelong nonsmokers. Thorax 46:565, 1991.

8. Janerich DT, Thompson WD, Varela LR et al: Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 323:632, 1990.

9. Garland LH: The rate of growth and natural duration of primary bronchial cancer. AJR 96:604, 1966.

10. Rigler LG: The earliest roentgenographic signs of carcinoma of the lung. JAMA 195:655, 1966.

11. Batra P, Brown K, Aberle DR et al: Imaging techniques in the evaluation of pulmonary neoplasms. Chest 101:239, 1992.

12. Byrd RB, Carr DT, Miller WE et al: Radiographic abnormalities in carcinoma of the lung as related to histological cell type. Thorax 24:573, 1969.

13. Epler GR, McLoud TC, Gaensler EA et al: Normal chest roentgenograms in chronic diffuse infiltrative lung disease. N Engl J Med 298:934, 1978.

14. Tisi GM: Preoperative evaluation of pulmonary function. Am Rev Respir Dis 119:293, 1979.

15. Brindley GV Jr, Walsh RE, Schnarr WT et al: Pulmonary resection in patients with impaired pulmonary function. Surg Clin North Am 62:199, 1982.

16. Kristersson S, Lindell SE, Svanberg L: Prediction of pulmonary function loss due to pneumonectomy using Xe ^{133} -radiospirometry. Chest 62:694, 1972.

17. DeMeester TR, Van Heertum RL, Karas JR et al: Preoperative evaluation with differential pulmonary function. Ann Thorac Surg 18:61, 1974.

18. Olsen GN, Block AJ, Tobias JA: Prediction of postpneumonectomy function using quantitative macroaggregate lung scanning. Chest 66:13, 1974.

19. Boysen PG, Block AJ, Olsen GN, et al: Prospective evaluation for pneumonectomy using the ^{99} technetium quantitative perfusion lung scan. Chest 72:422, 1977.

20. Boysen PG, Harris JO, Block AJ et al: Prospective evaluation for pneumonectomy using perfusion scanning. Chest 80:163, 1981.

21. Uggla LG: Indications for and results of thoracic surgery with regard to respiratory and circulatory function tests. Acta Chir Scand 111:197, 1956.

22. Laros CD, Swierengo J: Temporary unilateral pulmonary artery occlusion in the preoperative evaluation of patients with bronchial carcinoma. Med Thorac 24:269, 1967.

23. Sloan H, Morris JD, Figley M, Lee R: Temporary unilateral occlusion of the pulmonary artery in the preoperative evaluation of thoracic patients. J Thorac Surg 30:591, 1955.

24. Soderholm B: The hemodynamics of the lesser circulation in pulmonary tuberculosis. Effect of exercise, temporary unilateral pulmonary artery occlusion and operation. Scand J Clin Lab Invest (suppl.) 26:1957.

25. Miller JI, Grossman GD, Hatcher CR: Pulmonary function test criteria for operability and pulmonary resection. Surg Gynecol Obstet 153:893, 1981.

26. Miller JI: Thoracic surgery. p. 9. In Kaplan J (ed): Thoracic Anesthesia. Churchill Livingstone, New York, 1983.

27. Gass GD, Olsen GN: Clinical significance of pulmonary function tests. Preoperative pulmonary function testing to predict postoperative morbidity and mortality. Chest 89:127, 1986.

28. Bechard D, Wetstein L: Assessment of exercise oxygen consumption as preoperative criterion for lung resection. Ann Thorac Surg 44:344, 1987.

29. Wahi R, McMurtrey MJ, DeCaro LF et al: Determinants of perioperative morbidity and mortality after pneumonectomy. Ann Thorac Surg 48:33, 1989.

30. Putnam JB, Lammermeier DE, Colon R et al: Predicted pulmonary function and survival after pneumonectomy for primary lung carcinoma. Ann Thorac Surg 49:909, 1990.

31. Markos J, Mullan BP, Hillman DR et al: Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis 139:902, 1989.

32. Nakahara K, Ohno K, Hashimoto J et al: Prediction of postoperative respiratory failure in patients undergoing lung resection for lung cancer. Ann Thorac Surg 46:549, 1988.

33. Miller JI, Hatcher CR Jr: Limited resection of bronchogenic carcinoma in the patients with marked impairment of pulmonary function. Ann Thorac Surg 44:340, 1987.

34. Ferguson MK, Little L, Rizzo L et al: Diffusion capacity predicts morbidity and mortality after pulmonary resection. J Thorac Cardiovasc Surg 96:894, 1988.

35. Eugene J, Brown SE, Light RW et al: Maximum oxygen consumption: a physiologic guide to pulmonary resection. Surg Forum 33:260, 1982.

36. Smith TP, Kinawsewitz GT, Tucker WY et al: Exercise capacity as a predictor of post-thoracotomy morbidity. Am Rev Respir Dis 129:730, 1984.

37. Botton JWR, Weiman DS, Haynes JL et al: Stair climbing as an indicator of pulmonary function. Chest 92:783, 1987.

38. Boysen PG: Pulmonary resection and postoperative pulmonary function. Chest 77:718, 1980.

39. Boysen PG, Block AG, Moulder PV: Relationship between preoperative pulmonary function tests and complications after thoracotomy. Surg Gynecol Obstet 152:813, 1981.

40. Ali MK, Mountain CF, Ewer MS et al: Predicting loss of pulmonary function after pulmonary resection for bronchogenic carcinoma. Chest 77:337, 1980.

41. Robin ED, Gaudio R: Cor pulmonale. Dis Mon (May):138, 1970.

42. Zeldin RA, Normandin D, Landtwing D et al: Postpneumonectomy pulmonary edema. J Thorac Cardiovasc Surg 87:359, 1984.

43. Himelman RB, Struve SN, Brown JK et al: Improved recognition of cor pulmonale in patients with severe chronic obstructive pulmonary disease. Am J Med 84:891, 1988.

44. Fee HJ, Holmes EC, Gewirltz HS et al: Role of pulmonary vascular resistance measurements in preoperative evaluation of candidates for pulmonary resection. J Thorac Cardiovasc Surg 75:519, 1978.

45. Pecora DV, Hohenberger M: Effects of postpneumonectomy distension on pulmonary compliance and vascular resistance. Am Surg 45:797, 1979.

46. Bishop JM: Cardiovascular complications of chronic bronchitis and emphysema. Med Clin North Am 57:711, 1973.

47. Abraham AS, Cole RB, Green ID et al: Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure: Studies by serial observations during recovery. Circ Res 24:51, 1969.

48. Enson Y, Guintini C, Lewis ML et al: The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest 43:1146, 1964.

49. Harris P, Segal N, Green I et al: The influence of the airway's resistance and alveolar pressure on the pulmonary vascular resistance in chronic bronchitis. Cardiovasc Res 2:84, 1968.

50. Hobelmann CF Jr, Smith DE, Virgilio RW et al: Hemodynamic alterations with positive end-expiratory pressure: the contribution of the pulmonary vasculature. J Trauma 15:951, 1975.

51. Canada E, Benumof JL: Pulmonary vascular resistance correlates in intact normal and abnormal lungs. Crit Care Med 10:719, 1982.

52. Kinchi A, Ellrodt GA, Berman DS et al: Right ventricular performance in septic shock: radionuclide and hemodynamic observations. Crit Care Med 11:229, 1983.

53. Zapol WM, Snider MT: Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476, 1977.

54. Matthay RA, Berger HJ: Cardiovascular performance in chronic obstructive pulmonary diseases. Med Clin North Am 65:489, 1981.

55. Zimmerman GA, Morris AH, Cegiz M: Cardiovascular alterations in the adult respiratory distress syndrome. Am J Med 73:25, 1982.

56. Kassis E: Systemic hypertension, left ventricular hypertrophy and myocardial infarction in patients with chronic obstructive lung disease. Scand J Respir Dis 58:324, 1977.

57. Aronow WS: Aggravation of angina pectoris by 2% carboxyhemoglobin. Am Heart J 101:154, 1981.

58. Downing SE, Talner NS, Gardner TH: Influences of hypoxemia and acidemia on left ventricular function. Am J Physiol 210:1327, 1966.

59. Buda AJ, Pinsky MR, Ingels NB Jr et al: Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 301:453, 1979.

60. Robothan JL: Cardiovascular disturbances in chronic respiratory insufficiency. Am J Cardiol 47:941, 1981.

61. Laver MB, Strauss HW, Pohost GM: Right and left ventricular geometry: adjustments during acute respiratory failure. Crit Care Med 7:509, 1979.

62. Baum GI, Schwartz A, Llamas R et al: Left ventricular function in chronic obstructive lung disease. N Engl J Med 285:361, 1971.

63. Krayenbuehl HT, Turina J, Hess O: Left ventricular function and chronic pulmonary hypertension. Am J Cardiol 41:1150, 1978.

64. Kachel RG: Left ventricular function in chronic obstructive pulmonary disease. Chest 74:286, 1978.

65. Pateman JA, Hanning CD: Postoperative myocardial infarction and episodic hypoxaemia. Br J Anaesth 63:648, 1989.

66. Mangano DT: Perioperative cardiac morbidity. Anesthesiology 72:153, 1990.

67. Peters RM, Swain JA: Management of the patient with emphysema, coronary artery disease and lung cancer. Am J Surg 143:701, 1982.

68. Chaitman BR, Bourassa MG, Davis K et al: Angiographic prevalence of high risk coronary artery disease in patient subsets (CASS). Circulation 64:360, 1981.

69. Peters RM: The role of limited resection in carcinoma of the lung. Am J Surg 143:706, 1982.

70. Piehler JM, Trastek VF, Pairolero PC et al: Concomitant cardiac and pulmonary operations. J Thorac Cardiovasc Surg 90:662, 1985.

71. Dalton ML Jr, Parker TM, Mistrot J et al: Concomitant coronary artery bypass and major noncardiac surgery. J Thorac Cardiovasc Surg 85:621, 1978.

72. Canver CC, Bhayana JN, Lajos TZ et al: Pulmonary resection combined with cardiac operations. Ann Thorac Surg 50:796, 1990.

73. Crawford ES, Morris GC Jr, Howell JF et al: Operative risk in patients with previous coronary artery bypass. Ann Thorac Surg 26:215, 1978.

74. McCollum CJ, Garcia-Rinaldi R, Graham JM et al: Myocardial revascularization prior to subsequent major surgery in patients with coronary artery disease. Surgery 81:302, 1977.

75. Shapiro J, Jersky J, Katzav S et al: Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors. J Clin Invest 68:678, 1981.

76. Ford GT, Guenta CA: Toward prevention of postoperative pulmonary complications. Am Rev Respir Dis 130:4, 1984.

77. Lansing AM, Jamilson MG: Mechanisms of fever in atelectasis. Arch Surg 87:168, 1963.

78. Harris JD, Johanson WG Jr, Pierce AK: Bacterial lung clearance in hypoxic mice. Am Rev Respir Dis 111:910, 1975.

79. Latimer G, Dickman M, Clinton DW et al: Ventilatory patterns and pulmonary complications after upper abdominal surgery determined by preoperative and postoperative computerized spirometry and blood gas analysis. Am J Surg 122:622, 1971.

80. Morton HJV, Camb DA: Tobacco smoking and pulmonary complications after operation. Lancet 1:368, 1944.

81. Stein M, Koota GM, Simon M et al: Pulmonary evaluation of surgical patients. JAMA 181:765, 1962.

82. Gracey DR, Divertie MB, Didier EP: Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease. Chest 76:123, 1979.

83. Palmer KN, Sellick BA: The prevention of postoperative pulmonary atelectasis. Lancet 1:164, 1953.

84. Veith FJ, Rocco AG: Evaluation of respiratory function in surgical patients: importance of preoperative preparation and in the prediction of pulmonary complications. Surgery 45:905, 1959.

85. Stein M, Cassara EL: Preoperative pulmonary evaluation and therapy for surgical patients. JAMA 211:787, 1970.

86. Swenson EW, Stallberg-Stenhagen S, Beck M: Arterial oxygen, carbon dioxide, and pH levels in patients undergoing pulmonary resection. J Thorac Cardiovasc Surg 42:179, 1961.

87. Tisi GM: Preoperative evaluation of pulmonary function. Am Rev Respir Dis 119:293, 1979.

88. Van De Water JM: Preoperative and postoperative techniques in the prevention of pulmonary complications. Surg Clin North Am 60:1339, 1980.

89. Johnson WC: Postoperative ventilatory performance. Dependence upon surgical incision. Am J Surg 41:615, 1967.

90. Ali J, Weisel RD, Layng AB et al: Consequences of postoperative alterations and respiratory mechanics. Am J Surg 128:376, 1974.

91. Anderson WH, Dosett BE Jr, Hamilton GE: Prevention of postoperative pulmonary complications. JAMA 186:763, 1963.

92. Tarhan S, Moffitt EA, Sessler AD et al: Risk of anesthesia and surgery in patients with chronic bronchitis and chronic obstructive pulmonary disease. Surgery 74:720, 1973.

93. Harmon E, Lillington G: Pulmonary risk factors in surgery. Med Clin North Am 63:1289, 1979.

94. Thoren L: Postoperative pulmonary complications: observations on their prevention by means of physiotherapy. Acta Chir Scand 107:193, 1954.

95. Gaensler EA, Weisel RD: The risks of abdominal and thoracic surgery in COPD. Postgrad Med 54:183, 1973.

96. Kirilloff LH, Owens GR, Rogers RM et al: Does chest physical therapy work? Chest 88:436, 1985.

97. Warner MA, Tinker JH, Divertie MB: Preoperative cessation of smoking and pulmonary complications in pulmonary dysfunction. Anesthesiology 59:A60, 1983.

98. Pearce AC, Jones RM: Smoking and anesthesia: preoperative abstinence and perioperative morbidity. Anesthesiology 61:576, 1984.

99. Jones RM: Smoking before surgery: the case for stopping smoking. Br Med J 290:1763, 1985.

100. Davies JM, Latto IP, Jones JG et al: Effects of stopping smoking for 48 hours on oxygen availability from the blood: a study on pregnant women. Br Med J 2:355, 1979.

101. Haas A, Peneda H, Haas F, Axen K: Therapeutic modalities. In Haas A (ed): Pulmonary Therapy and Rehabilitation: Principles and Practice. Williams & Wilkins, Baltimore, 1979, p 110.

102. O'Connor G, Sparrow D, Segal MR, Weiss ST: Smoking, atopy, and methacholine airway responsiveness among middle-aged and elderly men: the normative aging study. Am Rev Respir Dis 140:1520, 1989.

103. Lertzman MM, Cherniack RM: Rehabilitation of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 114:1145, 1976.

104. Snider GL: Control of bronchospasm in patients with chronic obstructive disease. Chest 73 (suppl):927, 1978.

105. Berger R, Smith D: Acute post bronchodilator changes in pulmonary function parameters in patients with chronic airways obstruction. Chest 93:541, 1988.

106. Nisar M, Walshaw M, Earis JE et al: Assessment of reversibility of airway obstruction in patients with chronic obstructive airways disease. Thorax 47:446, 1992.

107. Easton PA, Jadue C, Dhingra S, Anthonisen NR: A comparison of the bronchodilating effects of a beta-2 adrenergic agent (albuterol) and an anticholinergic agent (ipratropium bromide) given by aerosol or in sequence. N Engl J Med 315:735, 1986.

108. LeDoux EJ, Morris JF, Temple WP, Duncan C: Standard and double dose ipratropium bromide and combined ipratropium bromide and inhaled metaproterenol in COPD. Chest 95:1013, 1989.

109. Burrows B, Martinez FD: Bronchial responsiveness, atopy, smoking, and chronic obstructive pulmonary disease. Am Rev Respir Dis 140:1515, 1989.

110. Hopp RJ, Townley RG, Biven RE et al: The presence of airway reactivity before the development of asthma. Am Rev Respir Dis 141:2, 1990.

111. Melville GN, Horstmann G, Irvani J: Adrenergic compounds and the respiratory tract. A physiological and electronic microscopal study. Respiration 33:261, 1976.

112. Foster WM, Bergofsky EH, Bohning DE et al: Effect of adrenergic agents and their modes of action of mucociliary clearance in man. J Appl Physiol 41:146, 1976.

113. Webb-Johnson DC, Chir B, Andrews JL: Bronchodilator therapy. N Engl J Med 297:476, 1977.

114. Isles AF, Newth CJL: Combined beta agonists and methylxanthines in asthma. N Engl J Med 309:432, 1983.

115. Aubier M, De Troyer A, Sampson M et al: Aminophylline improves diaphragmatic contractility. N Engl J Med 305:249, 1981.

116. Jackson RT, Beaglehold R, Rea HH et al: Mortality from asthma: a new epidemic in New Zealand. Br Med J 285:771, 1982.

117. Wilson JD, Sutherland DC: Combined beta agonists and methylxanthines in asthma. N Engl J Med 307:1707, 1982.

118. Lehr D, Guideri G: More on combined beta agonists and methylxanthines in asthma. N Engl J Med 309:1581, 1983.

119. Petty TL, Brink GA, Miller MW et al: Objective functional improvement in chronic airway obstruction. Chest 57:216, 1970.

120. Bone RC: Step care for asthma. JAMA 260:543, 1988.

121. Lam A, Newhouse MT: Management of acute asthma and chronic airflow limitation: are methylxanthines obsolete? Chest 98:44, 1990.

122. Newhouse MT: Is theophylline obsolete? Chest 98:1, 1990.

123. Chopra SK, Taplin GV, Simmons DH et al: Effects of hydration and physical therapy on tracheal transport velocity. Am Rev Respir Dis 115:1009, 1977.

124. May DB, Munt PW: Physiologic effects of chest percussion and postural drainage in patients with stable chronic bronchitis. Chest 75:29, 1979.

125. Oldenburg FA Jr, Dolovich MB, Montgomery JM et al: Effects of postural drainage, exercise, and cough on mucus clearance in chronic bronchitis. Am Rev Respir Dis 120:739, 1979.

126. Bateman JRM, Newman ST, Daunt KM et al: Is cough as effective as chest physiotherapy in the removal of excessive tracheobronchial secretions? Thorax 36:683, 1981.

127. Harris RS, Lawson TV: The relative mechanical effectiveness and efficiency of successive voluntary coughs in healthy young adults. Clin Sci 34:569, 1968.

128. Cherniack RM, Sanvhill E: Long-term use of intermittent positive-pressure breathing (IPPB) in chronic obstructive pulmonary disease. Am Rev Respir Dis 113:721, 1976.

129. Gold MI: The present status of IPPB therapy. Chest 67:469, 1975.

130. Loren M, Chai H, Miklich D et al: Comparison between simple nebulization and intermittent positive-pressure in asthmatic children with severe bronchospasm. Chest 72:145, 1977.

131. Gold MI: Is intermittent positive-pressure breathing therapy (IPPB Rx) necessary in the surgical patient? Ann Surg 184:122, 1976.

132. Pavin D, Agnew JE, Clarke SW: Cough and mucociliary clearance. Bull Eur Physiopathol Respir 23 (suppl. 10):41S, 1987.

133. Shields TW, Ujiki GT: Digitalization for prevention of arrhythmias following pulmonary surgery. Surg Gynecol Obstet 126:743, 1968.

134. Juler GL, Stemmer EA, Connolly JE: Complications of prophylactic digitalization in thoracic surgical patients. J Thorac Cardiovasc Surg 58:352, 1969.

135. Burman SO: The prophylactic use of digitalis before thoracotomy. Ann Thorac Surg 14:359, 1972.

136. Wheat MW, Burford TH: Digitalis in surgery: extension of classical indications. J Thorac Cardiovasc Surg 41:162, 1961.

137. Deutsch S, Dalen JE: Indications for prophylactic digitalization. Anesthesiology 30:648, 1969.

138. Green LH, Smith TW: The use of digitalis in patients with pulmonary disease. Ann Intern Med 87:459, 1977.

139. Mason DT, Zelis R, Lee G et al: Current concepts and treatments of digitalis toxicity. Am J Cardiol 27:546, 1971.

140. Dreifus LS, Rabbino MD, Watanabe Y et al: Arrhythmias in the postoperative period. Am J Cardiol 12:431, 1963.

141. Cooper JB, Newbower RS, Kitz RJ: An analysis of major errors. Anesthesiology 60:34, 1984.

142. Paulus DA, Basta JW, Klie H, Radson EA: Preanesthetic checklist. Anesth Analg 64:264, 1985.

143. France CJ, Eger EI, Bendixen HH: The use of peripheral venous blood for pH and carbon dioxide tension determinations during general anesthesia. Anesthesiology 40:311, 1974.

144. Harrison EM, Galloon S: Venous blood as an alternative to arterial blood for the measurement of carbon dioxide tensions. Br J Anaesth 37:13, 1965.

145. Kassim D, Kenny S: The accuracy of capillary sampling for acid base estimations. Br J Anaesth 37:840, 1965.

146. Kates RA, Zaidan JR, Kaplan JA: Esophageal lead for intraoperative electrocardiographic monitoring. Anesth Analg 61:781, 1982.

147. Perel A, Pizov R, Cotey S: Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesia 67:498, 1987.

148. Benumof JL: Where do pulmonary artery catheters go: intrathoracic distribution. Anesthesiology 46:336, 1977.

149. Cohen E: Hemodynamics and oxygenation during one-lung anesthesia: right vs. left. Anesthesiology 63:A566, 1985.

150. Hasan FM, Malanga A, Corrao WM, Braman FS: Effect of catheter position on thermodilution cardiac output during continuous positive-pressure ventilation. Crit Care Med 12:387, 1984.

151. Berryhill RE, Benumof JL: PEEP-induced discrepancy between pulmonary arterial wedge pressure and left atrial pressure: the influence of controlled vs. spontaneous ventilation and compliant vs. noncompliant lungs. Anesthesiology 46:383, 1979.

152. Wittnich C, Trudel J, Zidulka A, Chiu RCJ: Misleading "pulmonary wedge pressure" after pneumonectomy: its importance in postoperative fluid therapy. Ann Thorac Surg 42:192, 1986.

153. Benumof JL: Mechanism of decreased blood flow to atelectatic lung. J Appl Physiol 46:1047, 1978.

154. Pirlo AF, Benumof JL, Trousdale FR: Atelectatic lung lobe blood flow: open vs. closed chest, positive pressure vs. spontaneous ventilation. J Appl Physiol 50:1022, 1981.

155. Bjertnaes LJ, Mundal R, Hauge A, Nicolaysen A: Vascular resistance in atelectatic lungs: effect of inhalation anesthetics. Acta Anaesthesiol Scand 24:109, 1980.

156. Gorsky B, Schneider AJL: Interaction of anesthetics and hypoxia on pulmonary vessels, Abstract. In Abstracts of Scientific Papers, 1972. American Society of Anesthesiology Annual Meeting, 1972, p 179.

157. Bredesen J, Bjertnaes L, Hauge A: Effects of anesthetics on the pulmonary vasoconstrictor response to acute alveolar hypoxia. Microvasc Res 10:236, 1975.

158. Bjertnaes LJ: Hypoxia-induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalation anesthetics. Acta Anaesthesiol Scand 21:133, 1977.

159. Bjertnaes LJ, Hauge A, Torgrinsen T: The pulmonary vasoconstrictor response to hypoxia. The hypoxia-sensitive site studied with a volatile inhibitor. Acta Physiol Scand 109:447, 1980.

160. Marshall C, Lindgren L, Marshall BE: The effect of inhalation anesthetics on HPV. Anesthesiology 59:A527, 1983.

161. Sykes MK, Davies DM, Chakrabarti MK, Loh L: The effects of halothane, trichloroethylene and ether on the hypoxic pressor response and pulmonary vascular resistance in the isolated, perfused lung. Br J Anaesth 45:655, 1973.

162. Marshall C, Kim SD, Marshall BE: The actions of halothane, ibuprofen, and BW 755C on hypoxic pulmonary vasoconstriction. Anesthesiology 66:537, 1987.

163. Gibbs JM, Sykes MK, Tait AR: Effects of halothane and hydrogen ion concentration on the alteration of pulmonary vascular resistance induced by graded alveolar hypoxia in the isolated perfused cat lung. Anaesth Intensive Care 2:231, 1974.

164. Loh L, Sykes MK, Chakrabarti MK: The effects of halothane and ether on the pulmonary circulation in the isolated perfused cat lung. Br J Anaesth 49:309, 1977.

165. Johnson D, Mayers I: The effects of halothane in hypoxic pulmonary vasoconstriction. Anesthesiology 72:125, 1990.

166. Johnson DH, Hurst TS, Mayers I: Effects of halothane on hypoxic pulmonary vasoconstriction in canine atelectasis. Anesth Analg 72:440, 1991.

167. Babjak AF, Forrest JB: Effects of halothane on the pulmonary vascular response to hypoxia in dogs. Can J Anaesth 26:6, 1979.

168. Buckley MJ, McLaughlen JS, Fort L III et al: Effects of anesthetic agents on pulmonary vascular resistance during hypoxia. Surg Forum 15:183, 1964.

169. Lumb TD, Silvay G, Weinreich AI, Shiang W: A comparison of the effects of continuous ketamine infusion and halothane on oxygen-ation during one lung anesthesia in dogs. Can J Anaesth 26:394, 1979.

170. Hall SM, Chapleau M, Cairo J, Levitzky MG: The effect of high frequency ventilation on halothane ablation of hypoxic pulmonary vasoconstriction. FASEB J 42:595, 1983.

171. Sykes MK, Gibbs JM, Loh L et al: Preservation of the pulmonary vasoconstrictor response to alveolar hypoxia during the administration of halothane to dogs. Br J Anaesth 50:1185, 1978.

172. Benumof JL, Wahrenbrock EA: Local effects of anesthetics on regional hypoxic pulmonary vasoconstriction. Anesthesiology 43:525, 1975.

173. Mathers J, Benumof JL, Wahrenbrock EA: General anesthetics and regional hypoxic pulmonary vasoconstriction. Anesthesiology 46:111, 1977.

174. Pavlin EG, Reed RL, Winn RK: Pulmonary vascular pressure-flow curves in intact goats demonstrate hypoxic pulmonary vasoconstriction is abolished by halothane. Anesthesiology 63:A532, 1985.

175. Bjertnaes LJ: Hypoxia-induced pulmonary vasoconstriction in man: inhibition due to diethyl ether and halothane anesthesia. Acta Anaesthesiol Scand 22:570, 1978.

176. Rogers SN, Benumof JL: Halothane and isoflurane do not decrease PaO_2 during one-lung ventilation in intravenously anesthetized patients. Anesth Analg 64:946, 1985.

177. Benumof JL, Augustine SD, Gibbons JA: Halothane and isoflurane only slightly impair arterial oxygenation during one lung ventilation in patients undergoing thoracotomy. Anesthesiology 67:910, 1987.

178. Allison PR, Daly ID, Waaler BA: Bronchial circulation and pulmonary vasomotor nerve responses in isolated perfused lungs. J Physiol 157:462, 1961.

179. Grover RF, Vogel JHK, Averill KH, Blount SG: Pulmonary hypertension. Individual and species variability relative to vascular reactivity. Am Heart J 66:1, 1963.

180. Tucker A, McMurtry IF, Alexander AF et al: Lung mast cell density and distribution in chronically hypoxic animals. J Appl Physiol 42:174, 1977.

181. Tucker A, McMurtry IF, Reeves JT et al: Lung vascular smooth muscle as a determinant of pulmonary hypertension at high altitude. Am J Physiol 228:762, 1975.

182. Hurtig JB, Tait AR, Sykes ML: Reduction of hypoxic pulmonary vasoconstriction by diethyl ether in the isolated perfused cat lung: the effect of acidosis and alkalosis. Can J Anaesth 24:433, 1977.

183. Sykes MK, Hurtig JB, Tait AR, Chakrabarti MK: Reduction of hypoxic pulmonary vasoconstriction during diethyl ether anesthesia in the dog. Br J Anaesth 49:293, 1977.

184. Saidman LJ, Trousdale FR: Isoflurane does not inhibit hypoxic pulmonary vasoconstriction. Anesthesiology 57:A472, 1982.

185. Gardaz JP, Morel PH, Py P, Gemperle M: Isoflurane and regional pulmonary vascular resistance during lobar ventilation hypoxia and collapse in dogs. Anesthesiology 63:A531, 1985.

186. Domino KB, Borowee L, Alexander CM et al: Influence of isoflurane on hypoxic pulmonary vasoconstriction in dogs. Anesthesiology 64:423, 1986.

187. Chuda RM, Yao FS, Harvey RC: Cardiopulmonary function during one-lung anesthesia with alfentanil or isoflurane in the dog. Anesthesiology 63:A562, 1985.

188. Naeije R, Lejeune P, Leeman M et al: Pulmonary arterial pressure-flow plots in dogs: effects of isoflurane and nitroprusside. J Appl Physiol 63:969, 1987.

189. Groh J, Kuhnle G, Kubler W et al: Direct measurement of the effects of isoflurane anesthesia on hypoxic pulmonary vaconstriction (HPV) during one-lung ventilation. Anesthesiology 75:A341, 1991.

190. Jolin-Carlsson A, Bindslev L, Hedenstierna G: Hypoxia-induced pulmonary vasoconstriction in the human lung. The effect of isoflurane anesthesia. Anesthesiology 66:312, 1987.

191. Carlsson AJ, Bindslev L, Hedenstierna G: Hypoxia-induced pulmonary vasoconstriction in the human lung. The effect of isoflurane anesthesia. Anesthesiology 66:312, 1987.

192. Bjertnaes LJ, Mundal R: The pulmonary vasoconstrictor response to hypoxia during enflurane anesthesia. Acta Anaesthesiol Scand 24:252, 1980.

193. Carlsson AJ, Hedenstierna G, Bindslev L: Hypoxia-induced vasoconstriction in human lung exposed to enflurane anaesthesia. Acta Anesthesiol Scand 31:57, 1987.

194. Rees DI, Gaines GY: One-lung anesthesia--a comparison of pulmonary gas exchange during anesthesia with ketamine or enflurane. Anesth Analg 63:521, 1984.

195. Sykes MK, Davies DM, Loh L et al: The effect of methoxyflurane on pulmonary vascular resistance and hypoxic pulmonary vasoconstriction in the isolated perfused cat lung. Br J Anaesth 48:191, 1976.

196. Marin JLB, Carruthers B, Chakrabarti MK, Sykes MK: Preservation of the hypoxic pulmonary vasoconstrictor mechanism during methoxyflurane anesthesia in the dog. Br J Anaesth 51:99, 1979.

197. Hurtig JB, Tait AR, Loh L, Sykes MK: Reduction of hypoxic pulmonary vasoconstriction by nitrous oxide administration in the isolated perfused cat lung. Can J Anaesth 24:540, 1977.

198. Sykes MK, Hurtig JB, Tait AR, Chakrabarti MK: Reduction of hypoxic pulmonary constriction in the dog during administration of nitrous oxide. Br J Anaesth 49:301, 1977.

199. Lejeune P, Deloof T, Leeman M et al: Multipoint pulmonary vascular pressure/flow relationships in hypoxic and in normoxic dogs: effects of nitrous oxide with and without cyclooxygenase inhibition. Anesthesiology 68:92, 1988.

200. Bjertnaes L, Hauge A, Kritz M: Hypoxia induced pulmonary vasoconstriction: effects of fentanyl following different routes of administration. Acta Anaesthesiol Scand 24:53, 1980.

201. Marshall C, Ishibe Y, Marshall BE: Pentobarbital and the hypoxic pulmonary vasoconstriction response. Anesth Analg 68:S184, 1989.

202. Gibbs JM, Johnson H: Lack of effect of morphine and buprenorphine on hypoxic pulmonary vasoconstriction in the isolated perfused cat lung and the perfused lobe of the dog lung. Br J Anaesth 50:1197, 1978.

203. Naeije R, Lejeune P, Leeman M et al: Effects of propofol on pulmonary and systemic arterial pressure-flow relationships in hyperoxic and hypoxic dogs. Br J Anaesth 62:532, 1989.

204. Weinreich AI, Silvay G, Lumb PD: Continuous ketamine infusion for one-lung anesthesia. Can J Anaesth 27:485, 1980.

205. Van Keer L, Van Aken H, Vandermeersch E: Propofol does not inhibit hypoxic pulmonary vasoconstriction in humans. J Clin Anesth 1:284, 1989.

206. Wulff KE, Aulin I: The regional lung function in the lateral decubitus position during anesthesia and operation. Acta Anaesthesiol Scand 16:195, 1972.

207. Rehder K, Wenthe FM, Sessler AD: Function of each lung during mechanical ventilation with ZEEP and with PEEP in man anesthetized with thiopental-meperidine. Anesthesiology 39:597, 1973.

208. Werner O, Malmkvist G, Beckman A et al: Gas exchange and haemodynamics during thoracotomy. Br J Anaesth 56:1343, 1984.

209. Marshall BE, Marshall C: Continuity of response to hypoxic pulmonary vasoconstriction. J Appl Physiol 59:189, 1980.

210. Lawler PGP, Nunn JF: A reassessment of the validity of the iso-shunt graph. Br J Anaesth 56:1325, 1984.

211. Benumof JL: Special physiology of the lateral decubitus position, the open chest, and one-lung ventilation. In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, p 113.

212. Rogers SN, Benumof JL: Halothane and isoflurane do not decrease PaO_2 during one-lung ventilation in intravenously anesthetized patients. Anesth Analg 64:946, 1985.

213. Hirshman CA, Edelstein G, Peetz S et al: Mechanism of action of inhalational anesthesia on airways. Anesthesiology 56:107, 1982.

214. Coon RL, Kampine JP: Hypocapnic bronchoconstriction and inhalation anesthetics. Anesthesiology 43:635, 1975.

215. Patterson RW, Sullivan SF, Malm JR et al: The effects of halothane on human airway mechanics. Anesthesiology 29:900, 1986.

216. Boutrous AR, Weisel MR: Arterial blood oxygenation during thoracotomy using 70 percent nitrous oxide in oxygen. Anesthesiology 28:705, 1968.

217. Department of Health and Human Services: The Health Consequences of Smoking: Cardiovascular Disease: A Report of the Surgeon General. Rockville, MD, 1983.

218. The Pooling Project Research Group: Relationship of blood pressure, serum cholesterol, smoking habit, relative weight, and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J Chronic Dis 31:201, 1978.

219. Vaughan RW, Stephen CR: Abdominal and thoracic surgery in adults with ketamine, nitrous oxide, and d-tubocurarine. Anesth Analg 53:271, 1974.

220. Tweed WA, Minuck M, Mywin D: Circulation responses to ketamine anesthesia. Anesthesiology 77:613, 1972.

221. Corssen G, Gutierrez J, Reeves JG et al: Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 51:588, 1972.

222. Spies C, Zaune U, Boeden G, Martin E: Different anesthetic regimens in pulmonary surgery. Anesth Analg 72:S270, 1991.

223. Pietak S, Weenig CS, Hickey RF et al: Anesthetic effects on ventilation in patients with chronic obstructive pulmonary disease. Anesthesiology 72:160, 1975.

224. Denlinger JK, Ellison N, Ominsky AJ: Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. Anesthesiology 41:409, 1974.

225. Tarhan S, Moffitt EA: Principles of thoracic anesthesia. Surg Clin North Am 53:813, 1973.

226. Svanberg L: Influence of posture on lung volumes, ventilation and circulation in normals. Scand J Clin Lab Invest (suppl. 25)9:1, 1957.

227. Rehder K, Sessler AD: Function of each lung in spontaneously breathing man anesthetized with thiopental-meperidine. Anesthesiology 38:320, 1973.

228. Potgieter SV: Atelectasis: its evolution during upper urinary tract surgery. Br J Anaesth 31:472, 1959.

229. Larsson A, Malmkvist G, Werner O: Variations in lung volume and compliance during pulmonary surgery. Br J Anaesth 59:585, 1987.

230. Larsson A, Jonmarker C, Jogi P, Werner O: Ventilatory consequences of the lateral position and thoracotomy in children. Can J Anaesth 34:141, 1987.

231. Rehder K, Hatch DJ, Sessler AD, Fowler WS: The function of each lung of anesthetized and paralyzed man during mechanical ventilation. Anesthesiology 37:16, 1972.

232. Larsson A, Jonmarker C, Lindahl SGE, Werner O: Lung function in the supine and lateral decubitus positions in anesthetized infants and children. Br J Anaesth 62:378, 1989.

233. Nunn JF: The distribution of inspired gas during thoracic surgery. Ann R Coll Surg Engl 28:223, 1961.

234. Froese AB, Bryan CA: Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242, 1974.

235. Baraka A, Moghrabi R, Yazigi A: Unilateral pulmonary oedema/atelectasis in the lateral decubitus position. Anaesthesia 42:171, 1987.

236. Klingstedt C, Hedenstierna G, Baehrendtz S et al: Ventilation-perfusion relationships and atelectasis formation in the supine and lateral positions during conventional mechanical and differential ventilation. Acta Anaesthesiol Scand 34:421, 1990.

237. Brown DR, Kafer ER, Roberson VO et al: Improved oxygenation during thoracotomy with selective PEEP to the dependent lung. Anesth Analg 56:26, 1977.

238. Benumof JL, Rogers SN, Moyce PR et al: Hypoxic pulmonary vasoconstriction and regional and whole-lung PEEP in the dog. Anesthesiology 51:503, 1979.

239. Kvetan V, Carlon GC, Howland WS: Acute pulmonary failure in asymmetric lung disease: approach to management. Crit Care Med 10:114, 1982.

240. Urschel HC Jr, Razzuk MA: Median sternotomy as a standard approach for pulmonary resection. Ann Thorac Surg 41:130, 1986.

241. Anderson HW, Benumof JL: Intrapulmonary shunting during one-lung ventilation and surgical manipulation. Anesthesiology 55:A377, 1981.

242. Thomson DF, Campbell D: Changes in arterial oxygen tension during one-lung anesthesia. Br J Anaesth 45:611, 1973.

243. Boysen PG: Pulmonary resection and postoperative pulmonary function. Chest 77:718, 1980.

244. Boysen PG, Block AG, Moulder PV: Relationship between preoperative pulmonary function tests and complications after thoracotomy. Surg Gynecol Obstet 152:813, 1981.

245. Lack JA: Endobronchial tube resistances. Br J Anaesth 46:461, 1974.

246. Clapham MCC, Vaughan RS: Bronchial intubation. A comparison between polyvinyl chloride and red rubber double lumen tubes. Anaesthesia 40:1111, 1985.

247. Bjork VO, Carlens E: The prevention of spread during pulmonary resection by the use of a double-lumen catheter. J Thorac Surg 20:151, 1950.

248. Newman RW, Finer GE, Downs JE: Routine use of the Carlens double-lumen endobronchial catheter: an experimental and clinical study. J Thorac Cardiovasc Surg 42:327, 1961.

249. Robertshaw FL: Low resistance double-lumen endotracheal tubes. Br J Anaesth 34:576, 1962.

250. Pappin JC: The current practice of endobronchial intubation. Anaesthesia 34:57, 1979.

251. Benumof JL: Separation of the two lungs (double-lumen tube intubation). In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1988, p 223.

252. Brodsky JB, Benumof JL, Ehrenwerth J, Ozaki GT: Depth of placement of left double-lumen endobronchial tubes. Anesth Analg 73:570, 1991.

253. Simpson PM: Tracheal intubation with a Robertshaw tube via a tracheostomy. Br J Anaesth 48:373, 1976.

254. Seed RF, Wedley JR: Tracheal intubation with a Robertshaw tube via a tracheostomy, letter. Br J Anaesth 49:639, 1977.

255. Brodsky JB, Tobler HG, Mark JBD: A double-lumen endobronchial tube for tracheostomies. Anesthesiology 74:387, 1991.

256. Benumof JL: Double-lumen tube position should be routinely determined by fiberoptic bronchoscopy. J Cardiothoracvasc Anesth 7:513, 1993.

257. Smith G, Hirsch N, Ehrenwerth J: Sight and sound: can double-lumen endotracheal tubes be placed accurately without fiberoptic bronchoscopy? Anesth Analg 65:S1, 1986.

258. Read RC, Friday CD, Eason CN: Prospective study of the Robertshaw endobronchial catheter in thoracic surgery. Ann Thorac Surg 24:156, 1977.

259. Benumof JL, Partridge B, Salvatierra C, Gibbins J: Margin of safety in positioning modern double-lumen tubes. Anesthesiology 67:729, 1987.

260. Benumof JL: Anesthesia for special elective therapeutic procedures. In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, p 343.

261. Spragg RG, Benumof JL, Alfery DD: New methods for performance of unilateral lung lavage. Anesthesiology 57:535, 1982.

262. Conrady PA, Goodman LR, Cainge R et al: Alteration of endotracheal tube position: flexion and extension of the neck. Crit Care Med 4:8, 1976.

263. Saito S, Dohi S, Naito H: Alteration of double-lumen endobronchial tube position by flexion and extension of the neck. Anesthesiology 52:696, 1985.

264. Shankar KB, Mosley HSL, Kumar AY: Dual end-tidal CO_2 monitoring and double-lumen tubes. Can J Anaesth 39:100, 1991.

265. Shafieha MJ, Sit J, Kartha R et al: End-tidal CO_2 analyzers in proper positioning of the double-lumen tubes. Anesthesiology 64:844, 1986.

266. Simon BA, Hurford WE, Alfille PH et al: An aid in the diagnosis of malpositioned double-lumen tubes. Anesthesiology 76:862, 1992.

267. Cohen E, Kirschner PA, Goldofsky S: Intraoperative manipulation for positioning of double-lumen tubes. Anesthesiology 68:170, 1988.

268. Guernelli N, Bragaglia RB, Briccoli A et al: Tracheobronchial ruptures due to cuffed Carlens tubes. Ann Thorac Surg 28:66, 1979.

269. Heiser M, Steinberg JJ, MacVaugh H et al: Bronchial rupture, a complication of use of the Robertshaw double-lumen tube. Anesthesiology 51:88, 1979.

270. Foster JNG, Lau OJ, Alimo EB: Ruptured bronchus following endobronchial intubation. Br J Anaesth 55:687, 1983.

271. Wagner DL, Gammage GW, Wong ML: Tracheal rupture following the insertion of a disposable double-lumen endotracheal tube. Anesthesiology 63:698, 1985.

272. Burton NA, Fall SM, Lyons T, Graeber GM: Rupture of the left main-stem bronchus with a polyvinylchloride double-lumen tube. Chest 83:928, 1983.

273. Dryden GE: Circulatory collapse after pneumonectomy (an unusual complication from the use of a Carlens catheter): case report. Anesth Analg 56:451, 1977.

274. Cohen JA, Denisco RA, Richards TS et al: Hazardous placement of a Robertshaw-type endobronchial tube. Anesth Analg 65:100, 1986.

275. Inoue H, Shohtsu A, Ogawa J et al: New device for one lung anesthesia: endotracheal tube with moveable blocker. J Thorac Cardiovasc Surg 83:940, 1982.

276. Kamaya H, Krishna PR: New endotracheal tube (Univent tube) for selective blockade of one lung. Anesthesiology 63:342, 1985.

277. MacGillivray RG: Evaluation of a new tracheal tube with a movable bronchus blocker. Anaesthesia 43:687, 1988.

278. Schwartz DE, Yost CS, Larson MD: Pneumothorax complicating the use of a Univent ® endotracheal tube. Anesth Analg 76:443, 1993.

279. Hultgren BL, Krishna PR, Kamava H: A new tube for one lung ventilation: experience with Univent tube, abstracted. Anesthesiology 65:A481, 1986.

280. Karwande SV: A new tube for single lung ventilation. Chest 92:761, 1987.

281. Herenstein R, Russo JR, Moonka N, Capan L: Management of one-lung anesthesia in an anticoagulated patient. Anesth Analg 67:1120, 1988.

282. Gayes JM: The Univent tube is the best technique for providing one-lung ventilation. Pro: one-lung ventilation is best accomplished with the Univent endotracheal tube. J Cardiothorac Vasc Anesth 7:103, 1993.

283. Benumof JL, Gaughan S, Ozaki GT: Operative lung constant positive airway pressure with the Univent bronchial blocker tube. Anesth Analg 74:406, 1992.

284. Kelley JG, Gaba DM, Brodsky JB: Bronchial cuff pressures of two tubes used in thoracic surgery. J Cardiothorac Vasc Anesth 6:190, 1992.

285. Benumof JL, Gaughan SD, Ozaki GT: The relationship among bronchial blocker cuff inflation volume, proximal airway pressure, and seal of the bronchial blocker cuff. J Cardiothorac Vasc Anesth 6:404, 1992.

286. Slinger P: The Univent® tube is the best technique for providing one-lung ventilation. Con: The Univent ® tube is not the best method of providing one-lung ventilation. J Cardiothorac Vasc Anesth 7:108, 1993.

287. Ginsberg RJ: New technique for one lung anesthesia using an endobronchial blocker. J Thorac Cardiovasc Surg 82:542, 1981.

288. Larson CE, Gaisor TA: A device for endobronchial blocker placement during one-lung anaesthesia. Anesth Analg 71:311, 1990.

289. Zilberstein M, Katz RI, Levy A et al: An improved method for introducing an endobronchial blocker. J Cardiothorac Vasc Anesth 4:481, 1990.

290. Veil R: Selective bronchial blocking in a small child. Br J Anaesth 41:453, 1969.

291. Kubota H, Kubota Y, Toyoda Y et al: Selective blind endobronchial intubation in children and adults. Anesthesiology 67:587, 1987.

292. Baraka A, Akel S, Muallem M et al: Bronchial intubation in children: does the tube bevel determine the side of intubation? Anesthesiology 67:869, 1987.

293. Tarhan S, Lundborg RO: Carlens endobronchial catheter versus regular endotracheal tube during thoracic surgery: a comparison of blood gas tensions and pulmonary shunting. Can J Anaesth 18:594, 1971.

294. Johnson D, Chang P, Hurst T et al: Changes in $P_{ET}CO_2$ and pulmonary blood flow after bronchial occlusion in dogs. Can J Anaesth 39:184, 1992.

295. Casthely PA, Lear F, Cottrell JE, Lear E: Intrapulmonary shunting during induced hypotension. Anesth Analg 61:231, 1982.

296. Benumof JL: Hypoxic pulmonary vasoconstriction and sodium nitroprusside infusion. Anesthesiology 50:481, 1979.

297. Kerr JH, Smith AC, Prys-Roberts C et al: Observations during endobronchial anesthesia. H: Oxygenation. Br J Anaesth 46:84, 1974.

298. Hurford WE, Kolker AC, Strauss HW: The use of ventilation/perfusion lung scans to predict oxygenation during one-lung anesthesia. Anesthesiology 67:841, 1987.

299. Nomoto Y: Preoperative pulmonary blood flow and one-lung anesthesia. Can J Anaesth 34:447, 1987.

300. Torda TA, McCulloch CH, O'Brien HD et al: Pulmonary venous admixture during one-lung anesthesia. The effect of inhaled oxygen tension and respiration rate. Anaesthesia 29:272, 1974.

301. Khanom T, Branthwaite MA: Arterial oxygenation during one-lung anesthesia. A study in man. Anaesthesia 28:132, 1973.

302. Flacke JW, Thompson DS, Read RC: Influence of tidal volume and pulmonary artery occlusion on arterial oxygenation during endobronchial anesthesia. South Med J 69:619, 1976.

303. Tarhan S, Lundborg RO: Blood gas and pH studies during use of Carlens catheter. Can J Anaesth 15:458, 1968.

304. Tarhan S, Lundborg RO: Effects of increased expiratory pressure on blood gas tensions and pulmonary shunting during thoracotomy with use of the Carlens catheter. Can J Anaesth 17:4, 1970.

305. Fiser WP, Friday CD, Read RC: Changes in arterial oxygenation and pulmonary shunt during thoracotomy with endobronchial anesthesia. J Thorac Cardiovasc Surg 83:523, 1982.

306. Prefau CH, Engel LA: Vertical distribution of perfusion and inspired gas in supine man. Respir Physiol 43:209, 1981.

307. Kuriyama T, Wagner WW Jr: Collateral ventilation may protect against high-altitude pulmonary hypertension. J Appl Physiol 51:1251, 1981.

308. Glasser SA, Domino KB, Lindgren L et al: Pulmonary pressure and flow during atelectasis. Anesthesiology 57:A504, 1982.

309. Carlsson AJ, Bindslev L, Santesson J et al: Hypoxic pulmonary vasoconstriction in the human lung: the effect of prolonged unilateral hypoxic challenge during anesthesia. Acta Anaesthesiol Scand 29:346, 1985.

310. Hill NS, Antman EM, Green LH, Alpert JS: Intravenous nitroglycerin. A review of pharmacology, indications, therapeutic effects and indications. Chest 79:69, 1981.

311. Colley PS, Cheney FW, Hlastala MP: Pulmonary gas exchange effects of nitroglycerin in canine endematous lungs. Anesthesiology 55:114, 1981.

312. Chick TW, Kochukoshy KN, Matsumoto S, Leach JK: The effect of nitroglycerin on gas exchange, hemodynamics and oxygen transport in patients with chronic obstructive pulmonary disease. Am J Med Sci 276:105, 1978.

313. Kadowitz PJ, Nandiwada P, Grueter CA et al: Pulmonary vasodilator responses to nitroprusside and nitroglycerin in the dog. J Clin Invest 67:893, 1981.

314. Anjou-Lindskog E, Broman L, Holmgren A: Effects of nitroglycerin on central hemodynamics and V_a/Q distribution early after coronary bypass surgery. Acta Anaesthesiol Scand 26:489, 1982.

315. Kochukoshy KN, Chick TW, Jenne JW: The effect of nitroglycerin in gas exchange on chronic obstructive pulmonary disease. Am Rev Respir Dis 111:177, 1975.

316. Holmgren A, Anjou E, Broman L, Lundberg S: Influence of nitroglycerin on central hemodynamics and V_a/Q_c of the lungs in the postoperative period after coronary bypass surgery. Acta Med Scand S562:135, 1982.

317. Parsons GH, Leventhal JP, Hansen MM, Goldstein JD: Effect of sodium nitroprusside on hypoxic pulmonary vasoconstriction in the dog. J Appl Physiol 51:288, 1981.

318. Sivak ED, Gray BA, McCurdy TH, Phillips AK: Pulmonary vascular response to nitroprusside in dogs. Circ Res 45:360, 1979.

319. Hill AB, Sykes MK, Reyes A: Hypoxic pulmonary vasoconstrictor response in dogs during and after sodium nitroprusside infusion. Anesthesiology 50:484, 1979.

320. Colley PS, Cheney FW, Hlastala MP: Ventilation-perfusion and gas exchange effects of nitroprusside in dogs with normal and edematous lungs. Anesthesiology 50:489, 1979.

321. Colley PS, Cheney FW: Sodium nitroprusside increases Q_s/Q_T in dogs with regional atelectasis. Anesthesiology 47:338, 1977.

322. Wildsmith JAW, Drummond GB, Macrae WR: Blood gas changes during induced hypotension with sodium nitroprusside. Br J Anaesth 47:1205, 1975.

323. Veltzer JL, Doto JO, Jacoby J: Depressed arterial oxygenation during sodium nitroprusside administration for intraoperative hypertension. Anesth Analg 55:880, 1976.

324. McFarlane PA, Mortimer AJ, Ryder WA et al: Effects of dopamine and dobutamine on the distribution of pulmonary blood flow during lobar ventilation hypoxia and lobar collapse in dogs. Eur J Clin Invest 15:53, 1985.

325. Furman WR, Summer WR, Kennedy PP, Silvester JT: Comparison of the effects of dobutamine, dopamine and isoproterenol on hypoxic pulmonary vasoconstriction in the pig. Crit Care Med 10:371, 1982.

326. Bishop MJ, Cheney FW: Minoxidil and nifedipine inhibit hypoxic pulmonary vasoconstriction. J Cardiovasc Pharmacol 5:184, 1983.

327. Tucker A, McMurtry IF, Grover RF et al: Attenuation of hypoxic pulmonary vasoconstriction by verapamil in intact dogs. Proc Soc Exp Biol Med 151:611, 1976.

328. Simounneau J, Escourrou P, Duroux P, Lockhart A: Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. N Engl J Med 304:1582, 1981.

329. Redding GJ, Tuck R, Escourrou P: Nifedipine attenuates hypoxic pulmonary vasoconstriction in awake piglets. Am Rev Respir Dis 129:785, 1984.

330. McMurtry IF, Davidson AB, Reeves TJ, Grover RF: Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. Circ Res 38:99, 1976.

331. Brown SE, Linden GS, King RR et al: Effect of verapamil on pulmonary haemodynamics during hypoxaemia at rest, and during exercise in patients with chronic obstructive pulmonary disease. Thorax 38:840, 1983.

332. Ward CF, Benumof JL, Wahrenbrock EA: Inhibition of hypoxic pulmonary vasoconstriction by vasoactive drugs. In Abstracts of Scientific Papers, abstracted. American Society of Anesthesiology Annual Meeting, 1976, p 333.

333. Johansen I, Benumof JL: Reduction of hypoxia-induced pulmonary artery hypertension by vasodilator drugs. Am Rev Respir Dis 199:375, 1979.

334. Conover WB, Benumof JL, Key TC: Ritodrine inhibition of hypoxic pulmonary vasoconstriction. Am J Obstet Gynecol 146:652, 1983.

335. Marin JLB, Orchard C, Chakrabarti MK, Sykes MK: Depression of hypoxic pulmonary vasoconstriction in the dog by dopamine and isoprenaline. Br J Anaesth 51:303, 1979.

336. Reyes A, Sykes MK, Chakrabarti MK et al: Effect of orciprenaline on hypoxic pulmonary vasoconstriction in dogs. Respiration 38:185, 1979.

337. Reyes A, Sykes MK, Chakrabarti MK et al: The effect of salbutamol on hypoxic pulmonary vasoconstriction in dogs. Bull Eur Physiopathol Respir 14:741, 1978.

338. Rubin LJ, Lazar JD: Nonadrenergic effects of isoproterenol in dogs with hypoxic pulmonary vasoconstriction: possible role of prostaglandins. J Clin Invest 71:1366, 1983.

339. Frostell C, Blomqvist H, Lundberg J et al: Inhaled nitric oxide dilates human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. Anesthesiology 75:A989, 1991.

340. Girard C, Lehot JJ, Clerc J et al: Inhaled nitric oxide (NO) in pulmonary hypertension following mitral valve replacement. Anesthesiology 75:A984, 1991.

341. Pepeke-Zaba J, Higenbottam TW, Dinh-Xuan AT et al: Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet 338:1173, 1991.

342. Bone RC: A new therapy for the adult respiratory distress syndrome. N Engl J Med 328:431, 1993.

343. Roissant R, Falke KJ, Lopez F et al: Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 328:399, 1993.

344. Martling CR: Effects of nitroglycerin on pulmonary functions. Acta Anaesthesiol Scand 97(Suppl):26, 1992.

345. Bishop MJ, Kennard S, Artman LD, Cheney FW: Hydralazine does not inhibit canine hypoxic pulmonary vasoconstriction. Am Rev Respir Dis 128:998, 1983.

346. Benumof JL, Wahrenbrock EA: Blunted hypoxic pulmonary vasoconstriction by increased lung vascular pressures. J Appl Physiol 38:846, 1975.

347. Marshall C, Kim SD, Marshall BE: The influence of vascular pressure on hypoxic pulmonary vasoconstriction. Anesthesiology 73:A1139, 1990.

348. Malmkvist G, Fletcher R, Nordstrom L, Werner O: Effect of pulmonary arterial pressure on venous admixture during thoracotomy and one-lung ventilation. J Cardiothorac Vasc Anesth Suppl 3:36, 1989.

349. Colley PS, Cheney FW, Butler J: Mechanism of change in pulmonary shunt flow with hemorrhage. J Appl Physiol 42:196, 1977.

350. Domino KB, Glasser SA, Wetstein L et al: Influence of $P_v O_2$ on blood flow to atelectatic lung. Anesthesiology 57:A471, 1982.

351. Pease RD, Benumof JL: $P_A O_2$ and $P_v O_2$ interaction on hypoxic pulmonary vasoconstriction. J Appl Physiol 53:134, 1982.

352. Takeda K, Knapp MJ, Wolfe W, Grapo JD: Hypoxia enhances unilateral lung injury by increasing blood flow to the injured lung. J Appl Physiol 63:2516, 1987.

353. Wilson LB, Levitsky MG: Chemoreflex blunting of hypoxic pulmonary vasoconstriction is vagally mediated. J Appl Physiol 66:782, 1989.

354. Truog WE, Redding GJ, Standaert TA: Effects of hyperoxia on vasoconstriction and V_A/Q matching in the neonatal lung. J Appl Physiol 63:2536, 1987.

355. Loick HM, Traber LD, Tokyay R, Traber DL: The dose dependent effect of dopamine on hypoxic pulmonary vasoconstriction in anesthetized sheep. Anesthesiology 73:A606, 1990.

356. Nomoto Y, Kawamura M: Pulmonary gas exchange effects by nitroglycerin, dopamine and dobutamine during one-lung ventilation in man. Can J Anaesth 36:273, 1989.

357. Light RB, Ali J, Breen P, Wood LDH: The pulmonary vascular effects of dopamine, dobutamine and isoproterenol in unilobar pulmonary edema in dogs. J Surg Res 44:26, 1988.

358. Lejeune P, Naeije R, Leeman M et al: Effects of dopamine and dobutamine on hyperoxic and hypoxic pulmonary vascular tone in dogs. Am Rev Respir Dis 136:29, 1987.

359. Benumof JL, Mathers JM, Wahrenbrock EA: Cyclic hypoxic pulmonary vasoconstriction induced by concomitant carbon dioxide changes. J Appl Physiol 41:466, 1976.

360. Benumof JL, Rogers SN, Moyce PR et al: Hypoxic pulmonary vasoconstriction and regional and whole-lung PEEP in the dog. Anesthesiology 51:503, 1979.

361. Benumof JL: One-lung ventilation and hypoxic pulmonary vasoconstriction: implications for anesthetic management. Anesth Analg 64:821, 1985.

362. Hall SM, Chapleau M, Cairo J et al: Effect of high-frequency positive-pressure ventilation on halothane ablation of hypoxic pulmonary vasoconstriction. Crit Care Med 13:641, 1985.

363. Irwin RS, Martinez-Gonzalez-Rio H, Thomas HM III, Fritts HW Jr: The effect of granulomatous pulmonary disease in dogs on the response of the pulmonary circulation to hypoxia. J Clin Invest 60:1258, 1977.

364. Light RB, Mink SN, Wood LDH: Pathophysiology of gas exchange and pulmonary perfusion in pneumococcal lobar pneumonia in dogs. J Appl Physiol 50:524, 1981.

365. Craig JOC, Bromley LL, Williams R: Thoracotomy and contralateral lung. A study of the changes occurring in the dependent and contralateral lung during and after thoracotomy in the lateral decubitus position. Thorax 17:9, 1962.

366. Benumof JL: General respiratory physiology and respiratory function during anesthesia. In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, p 39.

367. Dantzker DR, Wagner PD, West JB: Instability of lung units with low V/Q ratios during O_2 breathing. J Appl Physiol 38:886, 1975.

368. Ray JF III, Yost L, Moallem S et al: Immobility, hypoxemia and pulmonary arteriovenous shunting. Arch Surg 109:537, 1974.

369. Kerr JH: Physiological aspects of one lung (endobronchial) anesthesia. Int Anesthesiol Clin 10:61, 1972.

370. Johansen I, Benumof JL: Flow distribution in abnormal lung as a function of $F_l O_2$, abstracted. Anesthesiology 51:369, 1979.

371. Benumof JL, Wahrenbrock EA: Dependency of hypoxic pulmonary vasoconstriction on temperature. J Appl Physiol 72:56, 1977.

372. Kelman GF, Nunn JF, Prys-Roberts C et al: The influence of the cardiac output on arterial oxygenation: a theoretical study. Br J Anaesth 39:450, 1967.

373. Prys-Roberts C: The metabolic regulation of circulatory transport. In Scurr C, Feldman S (eds): Scientific Foundations of Anesthesia. Yearbook Medical Publishers, Chicago, 1982.

374. DeWolf AM, Van Den Berg BW, Hoffman HJ, Zundert AA: Pulmonary dysfunction during one-lung ventilation caused by HLA-specific antibodies against leukocytes. Anesth Analg 66:463, 1987.

375. Winter PM, Smith G: The toxicity of oxygen. Anesthesiology 37:210, 1972.

376. Hughes S, Benumof JL: Use of operative lung CPAP to decrease $F_l O_2$ during one-lung ventilation in a bleomycin treated patient. Anesth Analg 71:92, 1990.

377. Katz JA, Laverne RG, Fairley HB, Thomas AN: Pulmonary oxygen exchange during endobronchial anesthesia: effects of tidal volume and PEEP. Anesthesiology 56:164, 1982.

378. Finley TN, Hill TR, Bonica JJ: Effect of intrapleural pressure on pulmonary shunt to atelectatic dog lung. Am J Physiol 205:1187, 1963.

379. Cannon D, Kalso EJ, Sykes MK: Effects of the pattern of ventilation and of an increase in cardiac output on the distribution of blood flow to a hypoxic lung. Br J Anaesth 60:81, 1988.

380. Slinger PD, Hickey DR, Lenis SG, Gottfried SB: Intrinsic PEEP during one-lung ventilation. Anesth Analg 68:S269, 1989.

381. Bachand RR, Audet J, Meloche R et al: Physiological changes associated with unilateral pulmonary ventilation during operations on one lung. Can J Anaesth 22:659, 1975.

382. Kerr J, Smith AC, Prys-Roberts C et al: Observations during endobronchial anaesthesia. I. Ventilation and carbon dioxide clearance. Br J Anaesth 45:159, 1973.

383. Hatch D: Ventilation and arterial oxygenation during thoracic surgery. Thorax 21:310, 1966.

384. Malmkvist G: Maintenance of oxygenation during one-lung ventilation: effect of intermittent reinflation of the collapsed lung with oxygen. Anesth Analg 68:763, 1989.

385. Cohen E, Eisenkraft JB, Thys DM et al: Oxygenation and hemodynamic changes during one-lung ventilation: effects of $CPAP_{10}$, $PEEP_{10}$, and $CPAP_{10}$/$PEEP_{10}$. J Cardiothorac Vasc Anesth 2:34, 1988.

386. Khanam T, Branthwaite MA: Arterial oxygenation during one-lung anesthesia (2). Anaesthesia 23:280, 1973.

387. Aalto-Setala M, Heinonen J, Salorinne Y: Cardiorespiratory function during thoracic anesthesia: comparison of two-lung ventilation and one-lung ventilation with and without PEEP. Acta Anaesthesiol Scand 19:287, 1975.

388. Capan LM, Turndorf H, Chandrakant P et al: Optimization of arte-rial oxygenation during one-lung anesthesia. Anesth Analg 59:847, 1980.

389. Eisenkraft JB, Thys DM, Cohen E, Kaplan JA: Hemodynamic effects of CPAP and PEEP during one-lung anesthesia with isoflurane. Anesthesiology 61:A520, 1984.

390. Cohen E, Thys DM, Eisenkraft JB, Kaplan JA: PEEP during one-lung anesthesia improves oxygenation in patients with low arterial $P_a O_2$. Anesth Analg 64:201, 1985.

391. Alfrey DD, Benumof JL, Trousdale FR: Improving oxygenation during one-lung ventilation: the effects of PEEP and blood flow restriction to the nonventilated lung. Anesthesiology 55:381, 1981.

392. Merridew CG, Jones RDM: Nondependent lung CPAP (5 cm $H_2 O$) with oxygen during ketamine, halothane or isoflurane anesthesia and one-lung ventilation. Anesthesiology 63:A567, 1985.

393. Thiagarajah S, Job C, Rao A: A device for applying CPAP to the nonventilated upper lung during one lung ventilation. I. Anesthesiology 60:253, 1984.

394. Hannenberg AA, Satwicz PR, Pienes RS Jr, O'Brien JC: A device for applying CPAP to the nonventilated upper lung during one lung ventilation. II. Anesthesiology 60:254, 1984.

395. Brown DL, Davis RS: A simple device for oxygen insufflation with continuous positive airway pressure during one-lung ventilation. Anesthesiology 61:481, 1984.

396. Rees DI, Wansbrough SR: One-lung anesthesia: percent shunt and arterial oxygen tension during continuous insufflation of oxygen to the nonventilated lung. Anesth Analg 61:507, 1982.

397. Benumof JL: Conventional and differential lung management of one-lung ventilation. In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, p 282.

398. Frose AB, Bryan AC: High frequency ventilation. Am Rev Respir Dis 135:1363, 1987.

399. Pesenti A, Kolobow T, Buckhold DK et al: Prevention of hyaline membrane disease in premature lambs by apneic oxygenation and extracorporeal carbon dioxide removal. Intensive Care Med 8:11, 1982.

400. Benumof JL: High-frequency and high-flow apneic ventilation during thoracic surgery. In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, p 288.

401. Glenski JA, Crawford M, Rehder K: High-frequency, small-volume ventilation during thoracic surgery. Anesthesiology 64:211, 1986.

402. Albelda SM, Hanson-Flaschen JH, Taylor E et al: Evaluation of high-frequency jet ventilation in patients with bronchopleural fistulas by quantitation of the airleak. Anesthesiology 63:551, 1985.

403. Sjostrand UH, Wattwil LM, Borg UR et al: Volume-controlled HFPPV as a useful mode of ventilation during open-chest surgery--a report on three cases. Respir Care 27:1380, 1982.

404. El-Baz N, Kittle CF, Faber LP et al: High-frequency ventilation with an uncuffed endobronchial tube. J Thorac Cardiovasc Surg 84:823, 1982.

405. Hall SM, Strawn WB, Levitsky MG: Effect of high-frequency oscillation on blood flow to an atelectatic lung in closed-chested dogs. Crit Care Med 12:447, 1984.

406. Wetzel RC, Gordon JB, Gregory TJ et al: High-frequency ventilation attenuation of hypoxic pulmonary vasoconstriction. Am Rev Respir Dis 132:99, 1985.

407. Frumin MJ, Epstein RM, Cohen G: Apneic oxygenation in man. Anesthesiology 20:789, 1959.

408. Eger EI, Severinghaus JW: The rate of rise of $PaCO_2$ in the apneic anesthetized patient. Anesthesiology 22:419, 1961.

409. Benumof JL: Early serious complications specifically related to thoracic surgery. In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, p 434.

410. Kirsch MM, Rotman H, Behrendt DM et al: Complications of pulmonary resection. Ann Thorac Surg 20:215, 1975.

411. Peterffy A, Henze A: Hemorrhagic complications during pulmonary resections: a retrospective review of 1428 resections with 113 hemorrhagic episodes. Scand J Thorac Cardiovasc Surg 17:283, 1983.

412. Hankins JR, Miller JE, Attar S et al: Bronchopleural fistula: thirteen-year experience with 77 cases. J Thorac Cardiovasc Surg 76:755, 1978.

413. Hirschler-Schulte CJW, Hylkema BS, Meyer RW: Mechanical ventilation for acute postoperative respiratory failure after surgery for bronchial carcinoma. Thorax 40:387, 1985.

414. Makood S, Hix WR, Aaron BL et al: Reexpansion pulmonary edema. Ann Thorac Surg 45:340, 1988.

415. Desideris DP, Meister M, Bedford RF: Intraoperative re-expansion pulmonary edema. Anesthesiology 67:821, 1987.

416. Ravin CE, Dahmash NS: Re-expansion pulmonary edema. Chest 77:709, 1980.

417. Sherman S, Ravikrishnan KP: Unilateral pulmonary edema following reexpansion of pneumothorax of brief duration. Chest 77:714, 1980.

418. Matsumiya N, Dohi S, Kimura T, Naits H: Re-expansion pulmonary edema after mediastinal tumor removal. Anesth Analg 73:646, 1991.

419. Khoo ST, Chen FG: Acute localized pulmonary edema: re-expansion pulmonary edema following surgical repair of a ruptured hemidiaphragm. Anaesthesia 43:486, 1988.

420. Waller DA, Turner N: Re-expansion pulmonary oedema. Anaesthesia 44:446, 1989.

421. Shanahan MX, Monk I, Richards HJ: Unilateral pulmonary oedema following re-expansion of pneumothorax. Anaesthesia Intensive Care 3:19, 1975.

422. Kramer MR, Metzer E, Sprung CL: Unilateral pulmonary edema after intubation of the right mainstem bronchus. Crit Care Med 17:472, 1989.

423. Sprung CL, Loewenherz JW, Baier H, Hauser MJ: Evidence for increased permeability in reexpansion pulmonary edema. Am J Med 71:497, 1981.

424. Marland AM, Glauser FL: Hemodynamic and pulmonary edema protein measurements in a case of reexpansion pulmonary edema. Chest 81:250, 1982.

425. Pavlin DJ, Nessly ML, Cheney FW: Increased pulmonary vascular permeability as a cause of re-expansion edema in rabbits. Am Rev Respir Dis 124:422, 1981.

426. Timby J, Reed C, Zeilander S, Glauser FL: "Mechanical" causes of pulmonary edema. Chest 94:973, 1990.

427. Henson RA, Parsons M: Ischemic lesions of the spinal cord: an illustrated review. Q J Med 142:205, 1967.

428. Mathew NT, John S: Iatrogenic ischemic paraplegia. Med J Aust 2:29, 1970.

429. Perez-Guerra F, Holland JM: Epidural hematoma as a cause of post-pneumonectomy paraplegia. Ann Thorac Surg 39:282, 1985.

430. Lambertsen CJ: Effects of oxygen at high partial pressure. In Fenn WO, Rahn H (eds): Handbook of Physiology. Vol. 2. Williams & Wilkins, Baltimore, 1965, p 1027.

431. Petty TL: Critical care for chronic air-flow limitation: emphysema, chronic bronchitis, and cystic fibrosis. Semin Respir Med 3:263, 1982.

432. O'Donohue WJ: National survey of the usage of lung expansion modalities for the prevention and treatment of postoperative atelectasis following abdominal and thoracic surgery. Chest 87:76, 1985.

433. Cane RD, Shapiro B: Mechanical ventilatory support. JAMA 254:87, 1985.

434. Yang KL, Tobin MJ: A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med 324:1445, 1991.

435. Katz J: The management of pain. In Benumof JL (ed): Clinical Frontiers in Anesthesiology. Grune & Stratton, Orlando, 1983.

436. Rooney S, Jain S, McCormack P et al: A comparison of pulmonary function tests for postthoracotomy pain using cryoanalgesia and transcutaneous nerve stimulation. Ann Thorac Surg 41:204, 1986.

437. Glynn CJ, Lloyd JW, Barnard JDW: Cryoanalgesia in the management of pain after thoracotomy. Thorax 34:325, 1980.

438. Maiwand O, Makey AR: Cryoanalgesia for relief of pain after thoracotomy. Br Med J 282:1749, 1981.

439. Nelson KM, Vincent RG, Bourke RS et al: Intraoperative intercostal nerve freezing to prevent post-thoracotomy pain. Ann Thorac Surg 18:280, 1974.

440. Orr IA, Keenan DJM, Dundee JW: Improved pain relief after thoracotomy: use of cryoprobe and morphine infusion. Br Med J 283:945, 1981.

441. Maiwand MO, Makey AR, Rees A: Cryoanalgesia after thoracotomy. Improvement of technique and review of 600 cases. J Thorac Cardiovasc Surg 92:291, 1986.

442. Myers RR, Powell HC, Heckman HM et al: Biophysical and pathological effects of cryogenic nerve lesion. Ann Neurol 10:478, 1981.

443. Muller LC, Salzer GM, Ransmayr G, Neiss A: Intraoperative cryoanalgesia for postthoracotomy pain relief. Ann Thorac Surg 48:15, 1989.

444. Kalso E, Perttunen K, Kassinen S: Pain after thoracic surgery. Acta Anaesthesiol Scand 36:96, 1992.

445. Katz J: Cryoanalgesia for post-thoracotomy pain. Ann Thorac Surg 48:5, 1989.

446. Behar M, Olshwang D, Magora F et al: Epidural morphine in the treatment of pain. Lancet 1:527, 1979.

447. Torda TA, Pybus DA: Comparison of four narcotic analgesics for extradural analgesia. Br J Anaesth 54:291, 1982.

448. Nordberg G, Hedner T, Mellstrand T et al: Pharmacokinetic aspect of epidural morphine analgesia. Anesthesiology 58:545, 1983.

449. Pybus DA, Torda TA: Dose-effect relationships of extradural morphine. Br J Anaesth 54:1259, 1982.

450. Magora F, Olshwang D, Eimerl D et al: Observations on extradural morphine analgesia in various pain conditions. Br J Anaesth 52:247, 1980.

451. Shulman MS, Brebner J, Sandler A: The effect of epidural morphine on post-operative pain relief and pulmonary function in thoracotomy patients. Anesthesiology 59:A192, 1983.

452. Rawal N, Sjostrand U, Dahlstrom B: Postoperative pain relief by epidural morphine. Anesth Analg 60:726, 1981.

453. Coombs DW, Saunders RL, Gaylor M et al: Epidural narcotic infusion: implantation technique and efficacy. Anesthesiology 55:469, 1981.

454. Welch DB, Hrynaszkiewicz AT: Postoperative analgesia using epidural methadone: administration by the lumbar route for thoracic pain relief. Anaesthesia 36:1051, 1981.

455. Steidl LJ, Fromme GA, Danielson DR: Lumbar versus thoracic epidural morphine for post-thoracotomy pain. Anesth Analg 63:277, 1984.

456. Johnston JR, McCaughey W: Epidural morphine: a method of management of multiple fractured ribs. Anaesthesia 35:155, 1980.

457. Fromme GA, Steidl LJ, Danielson DR: Comparison of lumbar and thoracic epidural morphine for relief of postthoracotomy pain. Anesth Analg 64:454, 1985.

458. Lomessy A, Magnin C, Viale J et al: Clinical advantages of fentanyl given epidurally for postoperative analgesia. Anesthesiology 61:466, 1984.

459. Wolf MJ, Davies GK: Analgesic action of extradural fentanyl. Br J Anaesth 52:357, 1980.

460. Welch DB, Hrynaszkiewicz A: Postoperative analgesia using epidural methadone: Administration by the lumbar route for thoracic pain relief. Anaesthesia 36:1051, 1981.

461. Wakerlin G, Shulman MS, Yamaguchi LY et al: Experience with lumbar epidural hydromorphone for pain relief after thoracotomy. Anesth Analg 65:S163, 1986.

462. Mok MS, Louie BW, Hwong BF et al: Epidural nalbuphine for the relief of pain after thoracic surgery. Anesth Analg 64:S258, 1985.

463. Torda TA, Tybus DA: Clinical experience with epidural morphine. Anaesth Intensive Care 9:129, 1981.

464. Bromage PR, Camporesi E, Chestnut D: Epidural narcotics for postoperative analgesia. Anesth Analg 59:473, 1980.

465. Glynn CJ, Mather LE, Cousins MJ et al: Peridural meperidine in humans: analgetic response, pharmacokinetics and transmission into CSF. Anesthesiology 55:520, 1981.

466. Rocco A, Reiestad F, Gudman J, McKacy W: Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures. Preliminary report. Reg Anaesth 12:10, 1987.

467. Durrani Z, Winnie AP, Ikuta P: Interpleural catheter analgesia for pancreatic pain. Anesth Analg 67:479, 1988.

468. Reiestad F, Stromskag KE: Interpleural catheter in the management of postoperative pain. A preliminary report. Reg Anaesth 11:89, 1986.

469. Reiestad F, Stromskag KE, Holmqvist E: Intrapleural administration of bupivacaine in postoperative management of pain. Anesthesiology 65:A204, 1986.

470. Seltzer JL, Larijani GE, Goldberg ME, Marr AT: Intrapleural bupivacaine--a kinetic and dynamic evaluation. Anesthesiology 67:798, 1987.

471. Kambam JR, Handte RE, Flanagan J et al: Intrapleural anesthesia for post-thoracotomy pain relief. Anesth Analg 66:S90, 1987.

472. Rosenberg PH, Scheinin BM, Lepantalo MJA, Lindfors O: Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 67:811, 1987.

473. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M: Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 69:261, 1988.

474. Lee VC, Abram SE: Intrapleural administration of bupivacaine for post-thoracotomy analgesia. Anesthesiology 66:586, 1987.

475. Ferrante FM, Chan VWS, Arthur GR, Rocco AG: Intrapleural analgesia after thoracotomy. Anesth Analg 72:105, 1991.

476. Covino BG: Interpleural regional analgesia. Anesth Analg 67:427, 1988.

477. Elman A, Debaene B, Orbent E et al: Intrapleural analgesia with bupivacaine following thoracotomy is inefficient: results of a controlled study and pharmacokinetics. Anesthesiology 78:A767, 1990.

478. McEllistrom RF, Hurley J, O'Toole DP et al: Intrapleural bupivacaine versus saline placebo after thoracotomy. Anesthesiology 73:A759, 1990.

479. El-Boz N, Faber LP, Ivankovitch AD: Intrapleural infusion of local anesthetic: a word of caution. Anesthesiology 68:809, 1988.

480. Scheinin B, Lindgren L, Rosenberg PH: Treatment of post-thoracotomy pain with intermittent instillations of intrapleural bupivacaine. Acta Anaesthesiol Scand 33:156, 1988.

481. Stromskag KE, Minor B, Stein PA: Side effects and complications related to intrapleural analgesia: an update. Acta Anaesthesiol Scand 34:473, 1990.

482. Seltzer JL, Lariyani GE, Goldberg ME, Marr AT: Intrapleural bupivacaine--a kinetic and dynamic evaluation. Anesthesiology 67:798, 1987.

483. Preciano MC, Duvall AJ, Koop SH: Mediastinoscopy. A review of 450 cases. Laryngoscope 83:1300, 1973.

484. Ward PH, Stephenson SE Jr, Harris PF: Mediastinoscopy: a valuable diagnostic procedure for the evaluation of lesions of the mediastinum. South Med J 60:51, 1967.

485. Morton JR, Guinn GA: Mediastinoscopy using local anesthesia. Am J Surg 122:696, 1971.

486. Fassoulaki A: Anesthesia for mediastinoscopy. Anaesthesia 34:75, 1978.

487. Ashbaugh DG: Mediastinoscopy. Arch Surg 100:568, 1970.

488. Valheis E, Page A, Verdant A: Ambulatory mediastinoscopy and anterior mediastinostomy. Ann Thorac Surg 52:1122, 1991.

489. Weissberg D, Herczed E: Perforation of thoracic aortic aneurysm--a complication of mediastinoscopy. Chest 78:119, 1980.

490. Roberts JT, Gissen AJ: Management of complications encountered during anesthesia for mediastinoscopy. Anesthesiol Rev 6:31, 1979.

491. Lee CM, Grossman LB: Laceration of the left pulmonary artery during mediastinoscopy. Anesth Analg 56:226, 1977.

492. Foster ED, Munro DD, Dobell ARC: Mediastinoscopy. Ann Thorac Surg 13:273, 1972.

493. Trinkle JK, Bryant LR, Hiller AJ: Mediastinoscopy--experience with 300 consecutive cases. J Thorac Cardiovasc Surg 60:297, 1970.

494. Barash PG, Tsai B, Kitahata IM: Acute tracheal collapse following mediastinoscopy. Anesthesiology 44:67, 1976.

495. Furgang FA, Saidman LJ: Bilateral tension pneumothorax associated with mediastinoscopy. J Thorac Cardiovasc Surg 63:329, 1972.

496. Lee J, Salvatore A: Innominate artery compression simulating cardiac arrest during mediastinoscopy: a case report. Anesth Analg 55:748, 1976.

497. Petty C: Right radial artery pressure during mediastinoscopy. Anesth Analg 58:428, 1979.

498. Rodgers BM, Ryckman FC, Moazam F et al: Thoracoscopy for intrathoracic tumors. Ann Thorac Surg 31:414, 1981.

499. Canto A, Blasco E, Casillas M et al: Thoracoscopy in the diagnosis of pleural effusion. Thorax 32:550, 1977.

500. Bloomberg AE: Thoracoscopy in perspective. Surg Gynecol Obstet 147:433, 1978.

501. Lewis RJ, Kunderman PJ, Sisler GE et al: Direct diagnostic thoracoscopy. Ann Thorac Surg 21:536, 1976.

502. Miller JI, Hatcher CR: Thoracoscopy: a useful tool in the diagnosis of thoracic disease. Ann Thorac Surg 26:68, 1978.

503. Lewis RJ, Caccavale RJ, Sisler GE, Mackenzie JW: One hundred consecutive patients undergoing video-assisted thoracic operations. Ann Thorac Surg 54:421, 1992.

504. Miller DL, Allen MS, Trastek VF et al: Videothoracoscopic wedge excision of the lung. Ann Thorac Surg 54:410, 1992.

505. Landreneau RJ, Hazelrigg SR, Ferson PF et al: Thoracoscopic resection of 85 pulmonary lesions. Ann Thorac Surg 54:415, 1992.

506. Mack MJ, Aronoff RJ, Acuff TE et al: Present role of thoracoscopy in the diagnosis and treatment of diseases of the chest. Ann Thorac Surg 54:403, 1992.

507. Brodsky JB: Thoracoscopy for retrieval of intrathoracic foreign bodies. Anesthesiology 54:91, 1981.

508. Shirai T, Amano J, Takabe K: Thoracoscopic diagnosis and treatment of chylothorax after pneumonectomy. Ann Thorac Surg 52:306, 1991.

509. Morton JR, Guinn GA: Thoracoscopy using local anesthesia. Am J Surg 122:696, 1971.

510. Faurschou P, Madsen F, Viskum K: Thoracoscopy: influence of the procedure on some respiratory and cardiac values. Thorax 38:341, 1983.

511. Oldenburg FA, Newhouse MT: Thoracoscopy. Chest 75:45, 1979.

512. El-Baz N, Jensik R, Faber P et al: One-lung high frequency ventilation for tracheoplasty and bronchoplasty: a new technique. Ann Thorac Surg 34:564, 1982.

513. El-Baz N, Holinger L, El-Ganzouri A et al: High-frequency positive-pressure ventilation for tracheal reconstruction by tracheal T-tube. Anesth Analg 61:796, 1982.

514. Eriksson I, Nilsson LG, Nordstrom S et al: High-frequency positive-pressure ventilation (HFPPV) during transthoracic resection of tracheal stenosis and during perioperative bronchoscopic

515. Geffin B, Bland J, Grillo HC: Anesthetic management of tracheal resection and reconstruction. Anesth Analg 48:884, 1969.

516. Theman TE, Kerr JH, Nelems JM et al: Carinal resection. A report of two cases and a description of the anesthetic technique. J Thorac Cardiovasc Surg 71:314, 1976.

517. Belsey R: Resection and reconstruction of the intrathoracic trachea. Br J Surg 38:200, 1950.

518. Kemvyssi-Dea S, Kritikon P, Exarhos N et al: Anaesthetic management of reconstruction of the lower part of the trachea. Br J Anaesth 47:82, 1975.

519. Debrand M, Tseuda K, Browning SK et al: Anesthesia for extensive repair of congenital trachea stenosis in an infant. Anesth Analg 58:431, 1979.

520. Boyan PC, Privitera PA: Resection of stenotic trachea: a case presentation. Anesth Analg 55:191, 1976.

521. Abou-Madi MN, Caudrado L, Domb B et al: Anaesthesia of tracheal resection: a new way to manage the airway. Can J Anaesth 26:26, 1979.

522. Lippman M, Mok MS: Tracheal cylindroma: anaesthetic management. Br J Anaesth 49:383, 1977.

523. Akdikmen S, Landmesser CM: Anesthesia for surgery of the intrathoracic portion of the trachea. Anesthesiology 26:117, 1965.

524. Dodge TL, Mahaffey JE, Thomas JD: The anesthetic management of a patient with an obstructing intratracheal mass: a case report. Anesth Analg 56:295, 1977.

525. Lee P, English ICW: Management of anesthesia during tracheal resection. Anaesthesia 29:305, 1974.

526. McNaughton FI: Catheter inflation ventilation in tracheal stenosis. Br J Anaesth 47:1225, 1975.

527. Baraka A: Oxygen-jet ventilation during tracheal reconstruction in patients with tracheal stenosis. Anesth Analg 56:429, 1977.

528. Ellis RH, Hinds CJ, Gadd LT: Management of anaesthesia during tracheal resection. Anaesthesia 31:1076, 1976.

529. Baraka A, Mansour R, Jaoude CA et al: Entrainment of oxygen and halothane during jet ventilation in patients undergoing excision of tracheal and bronchial tumors. Anesth Analg 65:191, 1986.

530. Woods F, Neptune W, Palatchi A: Resection of the carina and main-stem bronchi with extracorporeal circulation. N Engl J Med 264:492, 1961.

531. Coles JC, Doctor A, Lefcoe M et al: A method of anesthesia for imminent tracheal obstruction. Surgery 80:379, 1976.

532. Beyer PY, Wilson RS: Anesthetic management of tracheal resection and reconstruction. J Cardiol Anesth 2:821, 1988.

533. Darteville PG, Khalife J, Chapelin A et al: Tracheal sleeve pneumotherapy for bronchogenic carcinoma: report of 55 cases. Ann Thorac Surg 46:68, 1988.

534. Neville WE, Blanowski PJP, Kotis GG: Clinical experience with the silicone trachea prosthesis. J Thorac Cardiovasc Surg 99:604, 1990.

535. Benca JF, Hickey PR, Dornbusch JN et al: Ventilatory management assisted by cardiopulmonary bypass for distal tracheal reconstruction in a neonate. Anesthesiology 68:270, 1988.

536. Baraka A, Mansour R, Jaoude CA et al: Entrainment of oxygen and halothane during jet ventilation in patients undergoing excision of tracheal and bronchial tumors. Anesth Analg 65:191, 1986.

537. Laurenzi G, Turino G, Fishman A: Bullous disease of the lung. Am J Med 32:361, 1962.

538. Baldwin EP, Harden KA, Greene DG et al: Pulmonary air cysts of bullae. Medicine (Baltimore) 29:169, 1950.

539. Foreman S, Weill H, Duke R et al: Bullous disease of the lung: physiologic improvement after surgery. Ann Intern Med 69:757, 1968.

540. Peters RM: Indications for operative treatment of bullous emphysema. Ann Thorac Surg 35:479, 1983.

541. Nakahara K, Nakaoka K, Ohno K et al: Functional indications for bullectomy of giant bulla. Ann Thorac Surg 35:480, 1983.

542. Barker SJ, Clarke C, Trivedi N et al: Anesthesia for thoracoscopic laser ablation of bullous emphysema. Anesthesiology 78:44, 1993.

543. Ting EY, Klopstock R, Lyons HA: Mechanical properties of pulmonary cysts and bullae. Am Rev Respir Dis 87:538, 1963.

544. Eger EI II, Saidman LJ: Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. Anesthesiology 26:61, 1965.

545. Gold MI, Joseph SI: Bilateral tension pneumothorax following induction of anesthesia in two patients with chronic obstructive airway disease. Anesthesiology 38:93, 1973.

546. Normandale JP, Feneck RO: Bullous cystic lung disease. Anaesthesia 40:1182, 1985.

547. Isenhower N, Cucchiara RF: Anesthesia for vanishing lung syndrome: report of a case. Anesth Analg 55:750, 1976.

548. Mudge BJ, Kilaru P, Pandit U et al: Anesthetic management for resection of a giant emphysematous bulla in a patient with bilateral bullous disease. Anesthesiol Rev 9:34, 1982.

549. Caseby NG: Anaesthesia for the patient with a coincidental giant lung bulla: a case report. Can J Anaesth 28:272, 1981.

550. Tinker J, Vandam L, Cohn LH: Tension lung cyst as a complication of postoperative positive-pressure ventilation therapy. Chest 64:518, 1973.

551. Iwa T, Watanabe Y, Fukatani G: Simultaneous bilateral operations for bullous emphysema by median sternotomy. J Thorac Cardiovasc Surg 82:732, 1981.

552. American Lung Association: Facts about Emphysema. American Lung Association, New York, 1990.

553. Cooper JD, Patterson GA: Lung volume reduction surgery for severe emphysema. Semin Thorac Cardiovasc Surg 8:52, 1996.

554. Triantafillou AN: Anesthetic management for bilateral lung volume reduction surgery. Semin Thorac Cardiovasc Surg 8:94, 1996.

555. Blenkarn GD, Lanning CF, Kylstra JA: Anaesthetic management of volume controlled unilateral lung lavage. Can J Anaesth 22:154, 1975.

556. Busque L: Pulmonary lavage in the treatment of alveolar proteinosis. Can J Anaesth 24:380, 1977.

557. Rogers RM, Tantam KR: Bronchopulmonary lavage: a "new" approach to old problems. Med Clin North Am 54:755, 1970.

558. Rogers RM, Szidon JP, Shelburne J et al: Hemodynamic response of the circulation to bronchopulmonary lavage in man. N Engl J Med 296:1230, 1972.

559. Smith JD, Miller JE, Safer P et al: Intrathoracic pressure, pulmonary vascular pressures and gas exchange during pulmonary lavage. Anesthesiology 33:401, 1970.

560. McClenahan JB, Mussenden R: Pulmonary alveolar proteinosis. Arch Intern Med 133:284, 1974.

561. Ramirez J, Harlan WJ Jr: Pulmonary alveolar proteinosis. Nature and origin of alveolar lipid. Am J Med 45:502, 1968.

562. Ramirez J: Pulmonary alveolar proteinosis. A roentgenologic analysis. AJR 92:571, 1964.

563. Martin RJ, Rogers RM, Myers NM: Pulmonary alveolar proteinosis: shunt fraction and lactic acid dehydrogenase concentration as aids to diagnosis. Am Rev Respir Dis 117:1059, 1978.

564. Rogers RM, Levin DC, Gray BA et al: Physiological effects of bronchopulmonary lavage in alveolar proteinosis. Am Rev Respir Dis 118:255, 1978.

565. Smith LJ, Ankin MG, Katzenstein A et al: Management of pulmonary alveolar proteinosis. Chest 78:765, 1980.

566. Rausch DC, Spock A, Kylstra JA: Lung lavage in cystic fibrosis. Am Rev Respir Dis 101:1006, 1970.

567. McClellan RO, Boyd HA, Benjamin RG et al: Recovery of ^{239}Pu following bronchopulmonary lavage and DTPA treatment after an accidental inhalation exposure case. Health Phys 31:315, 1976.

568. Selecky PA, Wasserman K, Benfield JR et al: The clinical and physiological effect of whole lung lavage in pulmonary alveolar proteinosis: a ten-year experience. Ann Thorac Surg 24:451, 1977.

569. Kariman K, Kylstra JA, Spock A: Pulmonary alveolar proteinosis: prospective clinical experience in 23 patients for 15 years. Lung 162:223, 1984.

570. Cohen E, Eisenkraft JB: Bronchopulmonary lavage: effects on oxygenation and hemodynamics. J Cardiothorac Vasc Anesth 4:609, 1990.

571. Alfery DD, Zamost BG, Benumof JL: Unilateral lung lavage: blood flow manipulation by ipsilateral pulmonary artery balloon inflation. Anesthesiology 55:376, 1981.

572. Mackie AM, Watson CB: Anaesthesia and mediastinal masses. A case report and review of the literature. Anaesthesia 39:899, 1984.

573. Ferrari LR, Bedford RF: General anesthesia prior to treatment of anterior mediastinal masses in pediatric cancer patients. Anesthesiology 72:991, 1990.

574. Zormous MH, Benumof JL: Safety of anesthesia for patients with anterior mediastinal masses: II. Anesthesiology 73:1061, 1990.

575. Pullerits J, Holzman R: Anaesthesia for patients with mediastinal masses. Can J Anaesth 36:681, 1989.

576. Neuman GG, Weingarten AE, Abramowitz RM et al: The anesthetic management of the patient with an anterior mediastinal mass. Anesthesiology 60:144, 1984.

577. Stanford W, Doty DB: The role of venography and surgery in the management of patients with superior vena cava obstruction. Ann Thorac Surg 41:158, 1986.

578. Benumof JL: Anesthesia for emergency thoracic surgery. In Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987, p 375.

579. Wedel M: Massive hemoptysis. p. 194. In Moser KM, Spragg RG (eds): Respiratory Emergencies. 2nd Ed. CV Mosby, St. Louis, 1982.

580. Bone RC: Massive hemoptysis. p. 255. In Sahn SA (ed): Pulmonary Emergencies. Churchill Livingstone, New York, 1982.

581. Crocco JA, Rooney JJ, Frankushen DS et al: Massive hemoptysis. Arch Intern Med 121:495, 1968.

582. Gourin A, Garzon AA: Operative treatment of massive hemoptysis. Ann Thorac Surg 18:52, 1974.

583. Simmons DH, Wolfe JD: Hemoptysis. Diagnosis and management. West J Med 127:383, 1977.

584. Conlan AA, Hurwitz SS: Management of massive haemoptysis with the rigid bronchoscope and cold saline lavage. Thorax 35:901, 1980.

585. Arabian A, Spagnolo S: Laser therapy in patients with primary lung cancer. Chest 86:519, 1984.

586. Gelb AF, Epstein JD: Laser in treatment of lung cancer. Chest 86:662, 1984.

587. Bense L: Intrabronchial selective coagulation treatment of hemoptysis: report of three cases. Chest 97:990, 1990.

588. Tsukamoto T, Sasaki H, Nakamura H: Treatment of hemoptysis patients by thrombin and fibrinogen-thrombin infusion therapy using a fiberoptic bronchoscope. Chest 96:473, 1989.

589. Steiger Z, Wilson RF: Management of bronchopleural fistulas. Surg Gynecol Obstet 158:267, 1984.

590. Riordan JF: Management of spontaneous pneumothorax. Br Med J 189:71, 1984.

591. Baker WL, Faber LP, Osteermiller WE et al: Management of bronchopleural fistulas. J Thorac Cardiovasc Surg 62:393, 1971.

592. Dennison PH, Lester ER: An anaesthetic technique for the repair of bronchopleural fistula. Br J Anaesth 33:655, 1961.

593. Francis JG, Smith KG: An anaesthetic technique for the repair of bronchopleural fistula. Br J Anaesth 33:655, 1961.

594. Parkhouse J: Anaesthetic aspects of bronchial fistula. Br J Anaesth 29:217, 1957.

595. Khurana JS, Sharma VN: Bronchopleural fistula management during general anaesthesia. Br J Anaesth 36:302, 1964.

596. Pohlson EC, McNamara JJ, Char C et al: Lung abscess: a changing pattern of disease. Am J Surg 150:97, 1985.

597. Coselli JS, Mattox KL, Beall AC Jr: Reevaluation of early evacuation of clotted blood hemothorax. Am J Surg 148:786, 1984.

598. Lemmer JH, Botham MJ, Orringer MB: Modern management of adult thoracic empyema. J Thorac Cardiovasc Surg 90:849, 1985.

599. Blades BB, Higgins GA Jr: Pulmonary suppurations: empyema, bronchiectasis, and lung abscess. In Effler DB (ed): Blade's Surgical Diseases of the Chest. 4th ed. CV Mosby, St. Louis, 1978, p 69.

600. Mitchell RS: Lung abscess. In Baum GL (ed): Textbook of Pulmonary Diseases. 2nd ed. Little, Brown, Boston, 1974, p 388.

601. Hutter JA, Harari D, Braimbridge MV: The management of empyema thoracis by thoracoscopy and irrigation. Ann Thorac Surg 39:517, 1985.

602. Oakes DD, Sherck JP, Brodsky JB, Mark BD: Therapeutic thoracoscopy. J Thorac Cardiovasc Surg 87:269, 1984.

603. Benumof JL: Isoflurane anesthesia and arterial oxygenation during one-lung ventilation. Anesthesiology 64:419, 1986.

604. Benumof JL: Anesthesia for Thoracic Surgery. WB Saunders, Philadelphia, 1987.

605. Essig K, Freeman JA: Alternative bronchial cuff inflation technique for the Univent tube. Anesthesiology 76:478, 1992.

Chapter 49 - Anesthesia for Adult Cardiac Surgery *

Jack S. Shanewise
Carl C. Hug Jr.

INTRODUCTION

There have been and continue to be major changes in anesthesia care of cardiac surgical patients. Life expectancy of the general population continues to increase, and the proportion of the population that is elderly and retired is growing. Technologic developments have extended the limits of diagnostic and therapeutic capabilities and created the possibility of rescuing almost all patients from the ravages of cardiovascular disease. At the same time, the costs of medical care have been increasing at a prodigious rate and have approached or exceeded the limits of what individuals, employees, and governments are willing and able to pay. There has been an increasing emphasis on relating cost to outcome. With more than 37 percent of medical care expenditures occurring in the last 6 months of life, serious consideration is being given to developing criteria of patient eligibility for expensive procedures and to establishing medical practice guidelines that will limit the application of diagnostic techniques and therapeutic measures beyond those required for relief of pain and suffering of the terminally ill and those incapable of a meaningful life (e.g., those with senile dementia).

A number of factors specifically affect the care of patients with cardiovascular disease, particularly coronary artery disease (CAD). The outcome studies of the late 1970s and early 1980s by the U.S. Veterans Administration and the Collaborative Study in Coronary Artery Surgery (CASS group) questioned the value of coronary artery bypass grafting (CABG) operations in prolonging life in most groups of CAD patients. [1] [2] New drugs (e.g., calcium channel blockers, angiotensin-converting enzyme inhibitors) are available to control the symptoms of angina pectoris and congestive heart failure. Percutaneous transluminal coronary angioplasty (PTCA) has become the first line of intervention for obstructive lesions in coronary arteries for many patients, and the insertion of stents has increased the success rate and possibly the time until another intervention is required. Percutaneous coronary artery arthrectomy is now being used to reduce obstructive lesions not amenable to PTCA. The consequences of these changes are that greater proportions of cardiac surgical patients are older, are sicker in general, and have more advanced cardiovascular disease. Hence, there is a conflict between the demand for expensive, sophisticated procedural interventions and the costs of such care with the prospect of only modest extension of longevity.

The issues of costs versus outcome are focusing on individual institutions as they compete for managed care contracts and on individual physicians. Even the popular press is publishing mortality data for individual cardiac surgeons in certain metropolitan areas, and medical journal articles are presenting data on the contributions of individual anesthesiologists to morbidity and mortality. [3] [4] [5] Within institutions, quality improvement programs are presenting data comparing the impact of individual practitioners on productivity and utilization of resources (e.g., economic credentialing) and on the incidence of morbidity and mortality. On top of all of this, there is a progressive reduction of physician compensation by government programs, insurance carriers, and managed care plans. In the short term, there is little doubt that cardiothoracic anesthesiologists and surgeons will be working harder for less remuneration.

Successful management of anesthesia and life support for patients undergoing cardiac surgery requires the same knowledge and skill as any other type of surgery plus a detailed understanding of cardiac disease, the current functional status of the patient's cardiovascular system, and the special requirements of the intended surgery. To provide satisfactory anesthetic conditions for both patient and surgeon and to maintain optimal cardiovascular function, all details of the anesthetic plan must be carefully considered. Communication with the cardiologist and the cardiac surgeon is essential. They should both be made aware of the circumstances that the anesthesiologist faces in meeting the objectives cited, the role that the anesthesiologist is prepared to play in seeing the patient successfully through the perioperative period, and the advances that have been made in the anesthesia, monitoring, and life support of patients undergoing cardiac surgery. Incidentally, the principles underlying the management of patients with cardiac disease are the same for cardiac and noncardiac surgery. The last point is particularly important in light of the prevalence of cardiac diseases in the general population. [6]

The incidence of death attributable to cardiovascular disease is summarized in Table 49-1 . The most prevalent form of cardiovascular disease is CAD, and coronary artery surgery represents approximately 80 percent of the total adult cardiac operations in most medical centers in the United States. Given the prevalence of heart disease, especially that involving the coronary arteries, the anesthesiologist can expect to spend a great deal of time and effort caring for patients with these problems. [7]

This chapter considers anesthesia for cardiac surgery from three points of view--the patient, the surgery, and the anesthetic plan--focusing on adult patients. The chapter provides an overview; the details can be found in the many textbooks on this subject that have been published since the early 1980s.

** See Appendix 1, Practice Guidelines for Pulmonary Artery Catheterization and Practice Guidelines for Perioperative Transesophageal Echocardiography*

TABLE 49-1 -- Causes of Death in the United States, 1990

CAUSES OF DEATH	NUMBER OF DEATHS (× 1,000)		
	ALL AGES	45- 74 YEARS	> 75 YEARS
Total number: all causes	2,148	849	1,065
All cardiovascular diseases	916	327	567
Diseases of the heart	720	269	433
Ischemic	489	185	296
Hypertensive	21.1	9.0	11.3
Rheumatic	6.0	2.9	2.8
All others	201	71	122
Cerebrovascular disease	144	41	99

Congenital heart disease, less than 1 year of age: 2.6

Total deaths all causes, less than 1 year of age: 38.3

From National Center for Health Statistics [6]

/das/book/view/29494766/875/553.html

THE PATIENT

Anxiety

Although anxiety is common to all patients facing surgery, those with cardiac disease often have a higher than usual level of apprehension because of awareness of the life-threatening risks and adverse consequences and the symbolic significance of the heart in many aspects of life. Unfortunately, the patient's condition may limit the use of certain drugs to suppress anxiety. The physicians and nurses caring for the patient can reduce apprehension by discussing the usual circumstances of the perioperative period; by assuring the patient that all needs, especially pain relief, will be attended to promptly by experienced personnel; by explaining the procedures that will be followed; and by answering questions. Minimizing anxiety is important not only for patient comfort, but also for reduction of stress reactions (e.g., sympathetic activation) that may adversely affect cardiovascular function. The use of premedicant drugs is discussed later as part of the anesthetic plan.

Hemodynamic Status

In most cases, the specific nature of the cardiac disease and required surgery is defined preoperatively by laboratory examinations (Table 49-2) . These tests can provide information about the functional status of the heart. Still, the functional status of the patient should be estimated by a critical historical interview and a selective physical examination. These are especially important when the laboratory examinations are remote in time and the patient's condition may have changed, when the data from the examinations are incomplete, and when other factors that have not been evaluated in the laboratory (e.g., arrhythmias, labile hypertension) may be present. The major items of interest are listed in Tables 49-3 and 49-4 . Textbooks of medicine should be consulted for methods of discovering and estimating the severity of these problems.

Of prime importance is the presence of cardiac failure, either compensated or not, because it is the major factor affecting the outcome of the surgery as well as the choice of hemodynamic monitoring techniques and anesthetic drugs. Because the degree of failure may be minimal at rest, cardiac reserve should be estimated through questioning about exertional tolerance. Patients in acute distress at rest (i.e., those short of breath, orthopneic, or showing evidence of increased sympathetic nervous system tone) should be approached with extreme caution. The stresses imposed by operative conditions can be as demanding on cardiac function as physical exertion (e.g., hypertensive responses, changes in circulating blood volume, alterations of oxygen demand). Indications of limited cardiac reserve--poor ventricular function--are summarized in Table 49-5 .

Noncardiac Diseases

Those noncardiac diseases that have a significant impact on cardiovascular function need to be evaluated and appropriately treated (Table 49-6 ; Ch. 27) . Clinical scoring systems in part based on the presence of noncardiac medical conditions have been devised that estimate the risk of morbidity and mortality from cardiac surgery. [8] When the surgery is elective, such noncardiac diseases should be treated preoperatively so that the patient is in the best possible condition to withstand the stresses of the perioperative

TABLE 49-2 -- Laboratory Tests of Cardiac Function That Provide Information of Value to the Anesthesiologist

TEST	INFORMATION ABOUT CARDIAC FUNCTION
	Coronary artery disease and ventricular function
Exercise electrocardiography	1. Heart rate and systolic blood pressure at which ischemia was evident; a lower heart rate and perhaps a lower blood pressure should be maintained in the perioperative period
	2. ECG leads showing ischemic changes; suggestive of the most useful leads to monitor during anesthesia
	3. Evidence of ventricular dysfunction (e.g., premature ventricular contractions, hypotension, rales); indicates potential problems, which determine monitoring, anesthetic, and therapeutic plans
Echocardiography	1. Condition of aorta and main coronary arteries (dissection, obstruction, plaque)
	2. Global ventricular function ± stress (dobutamine challenge): ejection fraction
	3. Regional wall motion abnormalities
	4. Mitral valvular regurgitation (due to left ventricular dilation or due to papillary muscle dysfunction or rupture)
Coronary angiography and left ventriculography	1. Location of lesions indicative of most useful ECG leads to monitor and of potential complications (e.g.,arrhythmias, ventricular dysfunction)
	2. Condition of IMA and SVGs from previous CABG operations; presence of stents and complications of PTCA
	3. Diffuseness of obstructive disease and condition of distal portions of coronary arteries; incomplete revascularization increases risk of complications after cardiopulmonary bypass
	4. Adequacy of previous angioplasty procedures
	5. Observation of coronary artery spasm (see discussion of Prinzmetal angina in text)
	6. Evidence of ventricular dysfunction; areas of hypokinesis, akinesis, dyskinesia, aneurysm; left ventricular enddiastolic pressures >15 mm Hg or increasing by >5 mm Hg after contrast injection; ejection fraction <0.5
Radionuclide angiocardiography	1. Myocardial perfusion (thallium uptake) ± stress (exercise, dobutamine)
	2. Infarction detection (technetium uptake)
	3. Ventricular function (equilibrium-gated blood pool imaging); estimation of ejection fraction
	4. Evidence of inducible myocardial ischemia (stress thallium scanning shows reperfusion to ischemic areas)
	Valvular disease and ventricular function
Echocardiography	1. Specific valvular abnormalities and dysfunction

	2. Cardiac chamber enlargement and hypertrophy
	3. Ventricular dysfunction (e.g., regional wall motion abnormalities, low ejection fraction)
	4. Presence of intracardiac masses (e.g., tumor or thrombus)
Radionuclide angiocardiography	1. Pulmonary vascular abnormalities (e.g., emboli)
	2. Valvular dysfunction, shunts (first-pass imaging)
	3. Cardiac chamber enlargement and hypertrophy
	4. Ventricular dysfunction, ischemia, infarction
Cardiac catheterization	1. Pulmonary vascular pressures and resistances
	2. Diagnosis of shunts and quantitation of shunt flow
	3. Pressure gradients across valves and shunts; degree of regurgitation
	4. Estimates of valvular luminal area
	5. Determination of cardiac output and vascular resistance
	6. Estimates of ventricular pressures, volumes, and ejection fraction

ECG, electrocardiograph; IMA, internal mammary artery; SVGs, saphenous vein grafts; PTCA, percutaneous transluminal coronary angioplasty

period. Eradication of systemic or localized infection, control of hypertension and diabetes mellitus, correction of coagulopathy and anemia, pulmonary therapy to achieve maximal function, treatment of primary renal insufficiency or dialysis, and reduction of excessive obesity are helpful in the successful completion of cardiac surgery with the minimum possible morbidity, mortality, and expense. Obviously the burden of managing most of those conditions will fall primarily on the internist. However, the anesthesiologist may need to offer encouragement and enlightenment about the benefits to be derived by careful and thorough preparation of the patient for anesthesia and surgery. Such preparation probably minimizes the risks of complications and facilitates postoperative care, in which the internist will also participate.

The cardiac surgeon and anesthesiologist are especially challenged by the patient with two or more cardiovascular problems amenable only to surgery. For example, patients present regularly with evidence of both CAD and an abdominal aortic aneurysm. Questions arise as to which lesion should be repaired first or whether both should be repaired at the same time. It is our experience that the patient's condition is more carefully monitored and more precisely controlled during anesthesia than at any other time in the perioperative period. For these reasons, we have found the combined carotid and coronary artery operative procedures to be appropriate for some patients. [9] [10] In most cases, separate operations are planned in the sequence that is judged to present the least risk to the patient. One analysis suggests that proceeding directly to infrainguinal vascular surgery would result in a better outcome than routinely performing coronary arteriography and the indicated coronary revascularization. [11] Unrelenting angina with impending myocardial infarction or cardiogenic shock gives priority to coronary revascularization. In any event, the anesthesiologist has to consider all cardiovascular problems in developing the anesthetic plan. Certainly the anesthesiologist is the key person in maintaining adequate perfusion to all body organs while one or the other lesion is being repaired.

TABLE 49-3 -- Assessment of Cardiac Performance by History and Symptoms

Coronary artery disease
Chest pain and discomfort with characteristics of angina pectoris; factors precipitating and relieving angina; stable versus unstable angina
Previous myocardial infarction and its complications
Prior coronary angioplasty or aortocoronary bypass grafting
Heart failure
Dyspnea, cyanosis, edema, nocturia, fatigue
History of infarction, rheumatic fever, congenital heart disease, cardiovascular complications of pregnancy
History of recurrent bronchitis, pulmonary infection
Arrhythmias
Syncope, dizziness, palpitations
Hypertension and vascular disease
History and symptoms of stroke, claudication, renal disease, diabetes mellitus
Phlebitis, pulmonary embolus
Drugs or therapy for any of the above
Responses to therapy
History of symptoms of diseases affecting cardiovascular function (see Table 49-6)

TABLE 49-4 -- Assessment of Cardiovascular Function by Physical Examination in Preparation for Anesthesia and Cardiac Surgery

Blood pressure (BP): measurement in both arms, range of BP through the day (from data on chart)
Heart rate (HR) and rhythm
Responses to exercise, if appropriate: HR, BP, angina, dyspnea
Arterial pulse quality at different locations, suitable cannulation sites with evidence of collateral flow (Allen test) [a]
Capillary filling, cyanosis
Peripheral edema, hepatomegaly
Venous filling, distention, pulsation; suitable cannulation sites, anatomy of neck at sites of internal and external jugular venous cannulation
Precordial pulsations, cardiac borders
Auscultation of heart and lungs
Ventilatory rate and pattern
Evidence of peripheral vascular disease (temperature of hands and feet, aneurysm, bruits, retinal changes)
Body temperature
Body weight, height, surface area

[a] One group of investigators concluded that an abnormal Allen test result was not a predictor of complications from short-term cannulation of radial artery. [29] Until this conclusion is supported by data from other institutions and obtained under other conditions, it is prudent to continue to evaluate collateral flow.

Chronic Drug Therapy

Certain drugs given in the perioperative period have potential benefits and risks for any patient undergoing anesthesia for any type of surgery. However, drug therapy for a patient with heart disease, particularly for one facing cardiac surgery, should be scrutinized in the special light of the disease and the surgical conditions anticipated. Drugs commonly encountered in patients with heart disease are listed in Table 49-7 , along with the potential benefits and risks of continuing or discontinuing their use before surgery. The following details are of special importance in the management of patients undergoing cardiac surgery.

TABLE 49-5 -- Indications of Poor Ventricular Function

Dyspnea
At rest, with exertion, nocturnal, with angina, orthopnea
Edema
Peripheral swelling, recurrent bronchitis or pneumonia, rales, hepatomegaly
Veins
Distention and engorgement, hepatojugular reflux
Hypoperfusion
Confusion (CNS), oliguria and increased serum creatinine and blood urea nitrogen (kidney), fatigue (muscle), angina (heart), anorexia (gut, CNS), cyanosis and poor capillary refilling (skin, mucous membranes)
Hypotension
Especially with exertion (indicates ischemic dysfunction)
With signs of sympathetic autonomic activity (tachycardia, diaphoresis)
Enlarged heart
Gallop rhythm
S_3 indicates cardiac decompensation
Electrocardiogram
Evidence of ischemia or infarction
Hemodynamics during dysrhythmia(s)
Data from laboratory examination of cardiac function
Areas of hypokinesis, akinesis, dyskinesia, aneurysm of the ventricle
Left ventricular end-diastolic pressures >15 mm Hg
Ejection fraction <0.5
Cardiac index <2.5 L/min/m^2

TABLE 49-6 -- Noncardiac Diseases Affecting Cardiac Function

Congenital anomalies
Nutritional deficiencies, obesity
Endocrine
Diabetes mellitus, hypothyroidism and hyperthyroidism, pheochromocytoma, aldosteronism, adrenocortical insufficiency
Hematologic
Anemia, coagulopathy, sickle cell disease and other hemoglobinopathies
Pulmonary
Asthma, chronic bronchitis, emphysema, pneumonia, tuberculosis, alveolar disease, pulmonary embolism, phlebitis
Renal failure, hypertension
Cirrhosis, portal hypertension, ascites
Psychiatric
Drug abuse and dependence, alcoholism, tobacco smoking
Connective tissue diseases

Discontinuation of beta-adrenergic receptor-blocking therapy before anesthesia and surgery is dangerous because of the high incidence of rebound exacerbation of angina pectoris (including infarction) and hypertension. [12] Moreover, discontinuation of such therapy is unnecessary in terms of its potential interactions with anesthetic drugs; and in fact, its continuation may be beneficial in limiting the intraoperative occurrence of tachycardia, dysrhythmias, hypertension, and myocardial ischemia. [13] [14] Some internists may elect to taper large doses if the patient remains at rest and does not experience angina while awaiting surgery. The following details are of special importance in the management of patients undergoing cardiac surgery. Except for long-acting

TABLE 49-7 -- Chronic Drug Therapy in Cardiac Disease: Advantages and Disadvantages of Continuing Therapy up to Time of Surgery [a]

DRUG CATEGORY	PERIOPERATIVE POTENTIAL	
	ADVANTAGES	DISADVANTAGES
Calcium channel blockers	Control dysrhythmias Prevent coronary artery spasm Reduce hypertension	Reduced responses to inotropes and vasopressors; atrioventricular conduction block Peripheral vasodilation after CPB
beta-Adrenergic receptor blocking drugs	Less tachycardia, dysrhythmias, and hypertension	Bronchospasm; less inotropic response to beta-stimulants; greater vasoconstriction to sympathomimetics (nonselective $beta_1$ -and $beta_2$ -blocking drugs)
Antihypertensive drugs	Less hypertension	Drug interactions Peripheral vasodilation after CPB
Diuretics	Probably none	Hypokalemia, hypovolemia
Digitalis glycosides	Inotropic effect Control of ventricular response to rapid atrial rates	Arrhythmias, conduction abnormalities, other toxicity Exacerbation of hypokalemia risks

Antiarrhythmic drugs	Suppression of dysrhythmias	Enhanced toxicity with changes in pH and electrolytes
Insulin	Less hyperglycemia and ketoacidosis	Hypoglycemia (easily treated)
Aspirin	Reduced risk of thrombosis	Increased risk of excessive bleeding
Antidepressants	None	Drug interactions, especially with sympathomimetic drugs, arrhythmias

CPB, cardiopulmonary bypass

[a] Also see Chapter 14 .

drugs (e.g., nadolol), the patient's usual morning dose is often given orally along with other preanesthetic medications on the morning of surgery, and intravenous doses may be given in the operating room as needed to control heart rate and angina.

The calcium entry blocking drugs are being prescribed widely for patients with cardiovascular disease, including angina pectoris, dysrhythmias, and hypertension. [15] Although their role in preventing intraoperative ischemia has been questioned [13] [16] and data on their interactions with anesthetic drugs are limited, the generally accepted practice is to continue their chronic administration up to the morning of surgery. [13] [17]

Antihypertensive medications should also be continued through the night before or the morning of surgery because they contribute to less perioperative hemodynamic stress and their interactions with anesthetic and cardiovascular drugs are manageable. [18] [19] Episodes of rebound hypertension occur when antihypertensive therapy is abruptly discontinued; this is especially so in the case of clonidine (Catapres). [18] [20] Of course, potassium deficiency should be corrected before elective surgery in patients taking diuretic-type antihypertensive drugs. Evidence of digitalis toxicity in a patient scheduled for elective surgery is a substantial reason to consider postponing the surgery. [21]

Angiotensin-converting enzyme inhibitor (ACEI) drugs are frequently prescribed to patients with cardiovascular diseases. [22] They are not only effective antihypertensive agents, but have been shown to decrease the incidence of congestive heart failure (CHF) and mortality when given chronically to patients with impaired ventricular function following myocardial infarction (MI). [23] [24] The concern of possible severe, intractable hypotension during cardiac surgery in patients taking ACEI drugs was originally raised in case reports. [25] A large, prospective series did find that ACEI therapy increased the chance that multiple pressor infusions would be used after cardiopulmonary bypass (CPB), but this effect was not present postoperatively in the intensive care unit (ICU). [26] Patients on ACEI therapy do have a blunted blood pressure response to catecholamine infusions [27] and may require higher doses than usual, but these effects are easily managed when recognized, and our practice is to continue ACEI therapy until surgery and reinstitute it as soon as possible postoperatively.

Most other drugs administered on a chronic basis may be continued up to the day before surgery, and the anesthesiologist should be prepared to deal with their potential toxicities, including their interactions with drugs used in anesthesia. [19] [28]

Previous Surgical and Diagnostic Procedures

In addition to the usual preoperative evaluation for any type of anesthesia and surgical operation, the cardiac anesthesiologist should pay particular attention to the following considerations.

Use of the brachial artery for cardiac catheterization or its involvement in trauma or surgery may have produced changes in vascular resistance at that point, so that arterial blood pressures measured at more distal sites may not accurately reflect central aortic pressures. A normal rate of refilling of the palmar arterial arch should occur when either the radial or ulnar artery occlusion is released (a modified Allen test). However, Slogoff et al [29] have suggested that the Allen test is not necessary before cannulation of the radial (or ulnar) artery.

Previous surgery in the neck (e.g., carotid endarterectomy, thyroidectomy) may complicate cannulation of the internal jugular vein. The landmarks for localizing the vein may be distorted, the anatomic course of the vein and carotid artery may be abnormal, the "feel" of the probing needle is altered, there is increased resistance to insertion of the blunt dilator and cannula, and any accidental holes in the carotid artery or jugular vein may not be sealed off readily. Ultrasonographic localization of the vein may facilitate this process. [30]

Vein stripping procedures in the legs may necessitate the use of one or both arms to obtain suitable vein grafts for aortocoronary bypass surgery. Under such conditions, alternate sites for venous and arterial cannulation may have to be used.

Prior surgery on the mediastinum and heart increases the surgical difficulty and risks associated with opening the sternum and exposing the heart. A longer time before CPB will ensue unless femoral artery-femoral vein bypass is used. There is risk of sudden blood loss from tearing of the heart or vessels during sternotomy and greater hemorrhage from large areas of scarred surfaces in the operative site. Intravenous access should be available through the right arm or neck because injury to the innominate vein during opening of the chest will cause fluids infused into the left arm or neck to extravasate into the surgical field. Dysrhythmias from dissection of the pericardium and manipulation of the heart are common, and loss of atrial augmentation of ventricular filling (e.g., atrial fibrillation) and ventricular tachycardia or fibrillation are best treated by electric cardioversiondefibrillation. The application of low-impedance conductive gel defibrillation electrodes to the patient's posterior and lateral chest wall before induction of anesthesia allows synchronous cardioversion or defibrillation to be done rapidly without disrupting the surgical field in patients with scarring that prevents insertion of internal defibrillator paddles on the heart. These electrodes may also be used for transthoracic cardiac pacing if necessary.

Laboratory Data

Information obtained from reviewing the chart and interviewing and examining the patient may indicate the need for one or more special laboratory investigations. Of particular interest to the anesthesiologist are those findings related to disease states and therapeutic measures that affect cardiovascular function and the conduct of anesthesia and surgery. In the absence of abnormal findings in the historical or physical examinations, certain laboratory examinations are performed routinely and thought to be worthwhile for the patient scheduled for cardiac surgery (Table 49-8) . However, efforts to reduce costs are causing many practitioners to rethink the need for some of these tests.

Reasons to Postpone Surgery

Depending on the urgency of the planned surgery (Table 49-9) , the requirements listed in Table 49-10 should be met

TABLE 49-8 -- Laboratory Examination of the Cardiac Surgical Patient

TYPE OF TEST	INDICATION
Hematocrit/hemoglobin	Oxygen supply to myocardium (and other tissues)
	Primary determinant of blood viscosity (important element of total peripheral resistance)
	Reduced markedly by CPB hemodilution
	If elevated, pre-CPB removal of blood for autologous transfusion after CPB should be considered
White blood cell differential count [a]	Indications of infection, immune reactivity

Electrolytes: K^+	Affects cardiac irritability
	May be low with diuretic or antihypertensive therapy
	Altered by CPB and potassium cardioplegia, ventilation, etc.
Arterial blood-gas analysis [b]	Assessment of ventilatory function, acid-base balance
SMA-12 screening	LDH, SGOT, CPK enzyme elevations may indicate myocardial damage; further studies are indicated to determine if enzyme elevation is due to myocardial specific isoenzyme (CPK, MB, LDH 1 and 2)
	Total protein and albumin may be low and will be reduced further by CPB; replacement may be indicated
	Elevated BUN or serum creatinine suggests impaired renal function, which is at risk during and after surgery
	Blood glucose (fasting) elevation may indicate diabetes mellitus, which is exacerbated by surgical stress and which complicates management of fluid, potassium, and acid-base balance
Coagulation survey [a]	Clotting abnormalities require diagnosis and possibly correction before elective surgery
Prothrombin time	Coagulopathy increases perioperative hemorrhage and requires specific therapy
Partial thromboplastin time	
Platelet count and morphology	
Bleeding time	
Urinalysis [a]	Abnormal renal function; diabetes mellitus or insipidus
	Urinary tract infection

CPB, cardiopulmonary bypass; LDH, lactic dehydrogenase; SGOT, serum glutamine-oxaloacetic transaminase, also known as aspartate aminotransferase (AST); CPK, creatine phosphokinase, BUN, blood urea nitrogen

[a] Not recommended or required by all practitioners
[b] May be obtained in the operating room after arterial cannulation and before anesthetic induction for the patient without pulmonary disease; should be obtained 1 or more days before surgery for the patient with signs and symptoms of clinically significant lung disease

TABLE 49-9 -- Indications for Emergency Cardiac Surgery

TYPE OF SURGERY	INDICATIONS
Aortocoronary artery bypass grafting	Unremitting angina in patient with isolated obstruction(s) of coronary blood flow to a large mass of normal ventricular muscle
	Acute occlusion or dissection of coronary artery as a complication of coronary angiography or angioplasty
Valvular replacement	Acute, rapidly developing cardiac failure in patient with sudden malfunction of a valve or valvular prosthesis
Pericardiotomy	Acute cardiac tamponade with hypotension; may be ameliorated temporarily by pericardiocentesis
Pacemaker implantation	Persistent or recurring bradycardia associated with syncopal episodes, cardiac failure, and inability to establish or maintain endocardial pacing with a temporary transvenous pacemaker
Pulmonary embolectomy	Demonstration of large (surgically accessible) embolic obstruction of a pulmonary artery by pulmonary angiography, lung scan, or echocardiography
Thoracic aortic aneurysmal repair	Acute dissection of the thoracic aorta with risk of impairment of heart, brain, spinal cord, kidney, or splanchnic organ function

before transferring the patient to the operating room. When they are not met, the decision to proceed or to delay may be difficult. Obviously, the best chances for making a correct decision exist when knowledgeable, reasonable, and cooperative anesthesiologists, surgeons, and cardiologists discuss the circumstances together. The anesthesiologist should foster and, if necessary, demand the discussion before accepting responsibility for the patient. Where disagreements exist, they should be documented in the chart along with the contingency plans for the patient in question.

THE SURGERY

In this section, the major features of certain types of cardiac disease and surgery that may affect the management of anesthesia and vital functions by the anesthesiologist in the preoperative, intraoperative, and postoperative periods are stressed. The reader is referred to specialized textbooks for more detailed discussions of disease states and surgical procedures. The section is divided into the more common types of surgical procedures that are performed.

Surgery for CAD

CAD may be defined as obstruction in the coronary arterial blood flow to the myocardium and is almost always caused by the process of atheromatous arteriosclerosis. It is the most common cause of death in the United States, accounting for approximately 500,000 deaths per year. [6] [7] The primary pathophysiologic effect of CAD is disruption of the

TABLE 49-10 -- Checklist of Requirements for Cardiac Surgery That Should Be Met Before the Patient is Transferred to the Care of the Anesthesiologist in the Operating Room

Chart contains documentation of diagnosis and detailed information about cardiac performance as determined by specialized tests (e.g., echocardiography, cardiac catheterization, angiography)
History and physical examination completed and recorded
Laboratory data
Hemogram
Electrolytes
SMA-12 screening [a]
Coagulation survey [a]
Electrocardiogram
Chest roentgenograph
Consultation and other data concerning noncardiac diseases affecting the outcome of anesthesia and cardiac surgery (e.g., carotid bruit, coagulopathy, pulmonary disease, renal dysfunction)
Patient (or guardian) is informed and has given written consent to the operation and all related procedures, including anesthesia
Medications received in hospital and chronic drug therapy before hospitalization are recorded
Prophylactic antibiotics are administered or available for administration on arrival in operating room
Skin shaving and preparation are completed (controversial: practice varies)
Blood products are available for transfusion
Time of last intake of food or drink is recorded; if recent, does the urgency of the surgery justify the risks of aspiration and airway protection procedures?

[a] Not recommended or required by all practitioners

normal balance of myocardial oxygen supply and demand due to narrowing or obstruction by atheroma and thrombus in one or more branches of the coronary arterial tree.

The clinical manifestations of CAD fall into four categories:

1. Angina pectoris (literally, "chest pain"). Several types of angina are recognized.
2. Stable angina: Chest pain predictably occurring with an increase in myocardial oxygen demand (exertion, anxiety) that is not met with an adequate increase in supply, resulting in ischemia. Relieved promptly by rest or medication.
   a. Unstable angina: Chest pain induced by progressively decreasing exertion or occurring at rest, without evidence of infarction. Patients with unstable angina are at high risk of myocardial infarction and should be evaluated for urgent revascularization. Also called crescendo angina or preinfarction angina.
   b. Angina equivalent: Occasionally myocardial ischemia manifests with symptoms other than chest pain, such as dyspnea and easy fatigability. This may be secondary to transient left ventricular (LV) dysfunction due to ischemia.
   c. Prinzmetal or variant angina: Chest pain associated with ST changes on the electrocardiogram (ECG) due to coronary artery spasm. It responds well to vasodilator therapy, but it is important to note that 50 percent of these patients have significant atheromatous coronary lesions.
   d. Silent ischemia: Many episodes of myocardialischemia in CAD patients are asymptomatic. [31]

   They may be detected by ECG, thallium scanning, or echocardiography. This carries the same prognostic implication as symptomatic ischemia and is more common in patients with diabetes mellitus.
3. Myocardial infarction: Sudden, complete obstruction (usually by thrombus formation) of a coronary artery resulting in necrosis of a portion of myocardium. Death from MI may be due to (1) dysrhythmia (ventricular tachycardia [VT] or ventricular fibrillation [VF]); (2) ventricular dysfunction; or (3) ventricular rupture.
4. Sudden death: VT or VF not associated with premonitory symptoms and not due to infarction. Usually initiated by myocardial ischemia.
5. Ischemic cardiomyopathy: The syndrome of CHF and cardiac dilation due to impaired ventricular function as a consequence of one or more MIs.

The severity of CAD is determined by the location and degree of narrowing caused by the obstructing atheromas and is assessed by coronary arteriography. A lesion causing a 75 percent or greater reduction in the cross-sectional area of the vessel is significant. This is equivalent to a 50 percent decrease in the vessel diameter in a two-dimensional view of the arteriogram. Proximal, discrete obstructions are more amenable to revascularization than diffuse lesions involving more distal branches of the coronary arterial tree. Obstruction of the left main coronary artery or of its two primary branches, the left anterior descending and circumflex arteries ("left main equivalent") (Fig. 49-1) (Figure Not Available) places a majority of the left ventricle (LV) muscle in jeopardy. Most patients presenting for CABG surgery have significant obstruction of all the major branches of both the right and left coronary arteries (triple- or multiple-vessel disease) and may have most or all of their

myocardium at risk for ischemia.

It is important to evaluate LV function in any patient with CAD. MI impairs the cardiac pumping action by causing loss of function of the involved myofibrils. The function of those in the central area of necrosis is lost permanently owing to cell death; the function of those in the surrounding ischemic area may recover if the ischemia is reversed ("hibernating myocardium"). Perhaps less obvious is the fact that contractile function is impaired by myocardial ischemia even in the absence of infarction and necrosis. [32] Indeed, loss of contractile function occurs almost immediately with ischemia and may persist for prolonged periods in otherwise viable myocardium after the resolution of ischemia ("stunned" myocardium). [33] Viable myocardium that is noncontractile due to chronic ischemia is said to be "hibernating" and an important but often difficult aspect of evaluation of ventricular function in CAD is to distinguish irreversibly damaged scar from potentially recoverable, hibernating myocardium. Dobutamine stress echocardiography and positron emission tomography scan are two imaging techniques that have been applied to this problem.

Chronic cardiac failure that may result from infarction is characterized by easy fatigability, dyspnea on exertion, orthopnea, peripheral edema, and generalized impairment of function in many organs. The pathogenesis, therapeutic management, and functional characteristics of patients with chronic heart failure with variable degrees of compensation are well described in most textbooks of medicine. [34] Briefly, noninfarcted portions of the left ventricle may hypertrophy in compensation for the nonfunctioning myocardium. [35] Chronic hypertrophy eventually leads to systolic and diastolic dysfunction of noninfarcted muscle, which lowers cardiac reserve and raises diastolic filling pressures, leading to sympathetic and neuroendocrine responses that produce the syndrome of CHF.

Acute, transient episodes of cardiac failure associated with ischemia may be subtle in their presentation. They may be evident as shortness of breath during or after an episode of angina. Acute failure may be precipitated by the recumbent position (angina decubitus, nocturnal angina), which increases the return of venous blood to the heart and increases LV end-diastolic volume (LVEDV), thereby increasing oxygen demand. There may be a sudden, large increase in LV end-diastolic pressure (LVEDP) (a more than 5 mm Hg increase) during ventriculography when injection of contrast material (with a low oxygen content) displaces blood from the coronary circulation. Such information may provide at least a crude estimate of the risk of similar episodes of altered cardiac pumping during anesthesia and surgery. Most important, such episodes indicate the need for precise hemodynamic monitoring to detect and treat the LV failure precipitated by ischemia, which may not otherwise be evident in the anesthetized patient.

In terms of developing an anesthetic plan, it is useful to summarize cardiac pumping function as good or poor (Table 49-11) . Most patients presenting for elective CABG surgery will have some objective measurement of LV function (e.g., ventriculogram, echocardiogram, radionuclide angiogram) available to the anesthesiologist. When such evidence is not available (e.g., emergency surgery), a suspicion of impaired ventricular pumping is an indication for advanced monitoring techniques, including the use of a pulmonary artery catheter (PAC) or transesophageal echocardiography (TEE) to obtain the missing information and to be prepared to detect and promptly treat myocardial ischemia and its consequences.

The primary goals of surgery (and indeed, of medical treatment) for CAD are (1) to relieve anginal symptoms and thereby improve the quality of life and (2) to prevent MI, preserve ventricular function, and improve long-term survival. Outcome studies have demonstrated CABG surgery's effectiveness in relieving anginal symptoms. Improved survival after CABG has been shown for patients with significant

TABLE 49-11 -- Classification of Left Ventricular Function

GOOD FUNCTION	POOR FUNCTION
No history, symptoms, signs of congestive heart failure	Congestive heart failure
Hypertension	Recent or multiple infarctions
Normal cardiac index (>2.5 L/min/m^2)	Cardiac index <2 L/min/m^2
Normal LVEDP (<12 mm Hg)	LVEDP > 15 mm Hg
Normal ventriculogram	Ventricular dysrhythmias
Normal wall motion and thickening (echocardiogram)	Areas of hypokinesis, akinesis, dyskinesia, or aneurysm in ventriculogram or echocardiogram

LVEDP, left ventricular end-diastolic pressure

Figure 49-1 (Figure Not Available) Anatomy of the *(A)* left and *(B)* right coronary arteries showing the nomenclature recommended by the American Heart Association. LAD, left anterior descending; SA, sinoatrial; RCA, right coronary artery; AV, atrioventricular; LV, left ventricular. *(From King SB III, Douglas JS: Coronary arteriography and left ventriculography. In Hurst JW (ed): The Heart. 4th ed. New York, McGraw-Hill, 1978.)*

left main coronary artery obstruction and those with involvement of three or more coronary arteries. [36]

CABG surgery involves the anastomosis of blood-bearing conduits to the involved coronary arteries distal to the obstructing atheromas. Conduits are usually autologous saphenous veins or internal mammary arteries; the latter have better long-term patency than vein grafts when placed to the left anterior descending coronary artery. [37] The gastroepiploic and inferior epigastric arteries may be used as conduits and theoretically have the same advantages as internal mammary grafts, but this remains to be documented with long-term patency studies. On rare occasions, autologous arm veins, prosthetic material, or animal-derived conduits have been used, but these have proved to be less satisfactory. More recent developments in surgery for CAD includes minimally invasive direct coronary artery bypass surgery through a limited thoracotomy without using cardiopulmonary bypass. Challenges to the anesthesiologist include providing a slowly beating quiet heart to assist the surgeon in performing the coronary anastomosis while maintaining adequate overall hemodynamics. In our experience, unless unexpected problems develop, almost all of these patients can be extubated in the operating room at the end of the case.

The primary goal of the anesthetic management of a patient for CABG surgery (or any patient with CAD) is the

avoidance of myocardial ischemia and MI. This is accomplished (1) by preventing ischemia through measures that improve the myocardial oxygen supply-demand balance, primarily by controlling the patient's hemodynamics, and (2) by detecting and treating myocardial ischemia when it does occur.

Myocardial Oxygen Supply-Demand Balance

Even in the normal individual at rest, the myocardium extracts most of the oxygen from the blood flowing through the coronary arteries. Increased cardiac work for any reason (e.g., physical exertion, emotional stress, hypertension) increases myocardial oxygen demand, which is met in the healthy person by the increased coronary blood flow. [38] [39] With CAD the arteries are narrowed and the maximal rate of coronary blood flow is reduced. When oxygen demand by the myocardium exceeds its oxygen supply, myocardial ischemia develops and may be manifest in one or more ways. Prevention and treatment of myocardial ischemia are based on improving oxygen supply and reducing oxygen demand. Conditions detrimental to myocardial oxygen balance (Table 49-12) are important to know because they are encountered frequently in the perioperative period, and most factors contributing to an imbalance can be manipulated to some degree by the anesthesiologist.

The following are important points:

1. Tachycardia is especially detrimental to myocardial oxygen supply-demand balance, increasing demand while decreasing supply. Heart rate is a major determinant of myocardial oxygen consumption, and tachycardia increases oxygen demand. On the other side of the supply-demand balance, tachycardia decreases coronary blood flow. About 80 percent of coronary artery blood flow occurs during diastole [40] ; by decreasing the duration of diastole more than that of systole, tachycardia results in less time for coronary artery flow during the cardiac cycle. [41]
2. Increases in LV preload (LVEDV and LVEDP) also increase oxygen demand while diminishing supply. Elevation in preload raises LV wall tension, which

increases oxygen consumption. Higher preload diminishes coronary flow by decreasing the coronary artery perfusion pressure (diastolic arterial pressure minus LVEDP).

3. With fixed coronary artery obstruction, increasing arterial pressure above normal produces minimal increase in coronary flow because the perfusion pressure would have to be increased drastically to overcome the reduction in lumen size of the artery (blood flow perfusion pressure/resistance; resistance varies inversely with the fourth power of the radius). However, elevated arterial pressure significantly increases oxygen demand by raising LV wall tension and therefore has a net detrimental effect on oxygen supply-demand balance.
4. Hypotension simultaneously lowers oxygen supply and demand but clearly has a net detrimental effect and is more likely than hypertension to cause ischemia.

TABLE 49-12 -- Conditions Detrimental to Myocardial Oxygen Balance

DECREASED OXYGEN SUPPLY	INCREASED OXYGEN DEMAND
Decreased coronary blood flow	Tachycardia
Tachycardia (↓ diastolic perfusion time)	Increased wall tension
Hypotension (especially diastolic)	↑ Increased preload ↑ Increased afterload (hypertension)
Increased preload (↓ perfusion pressure)	Increased myocardial contractility
Hypocapnia (coronary vaso-constriction)	
Coronary artery spasm	
Decreased oxygen content and availability	
Anemia	
Hypoxemia	
Reduced oxygen release from hemoglobin (e.g., ↓ pH, ↑ 2,3-DPG, ↑ temperature)	
2,3-DPG, 2,3-diphosphoglycerate	

The ideal hemodynamic state for the patient with CAD is a low heart rate, low filling pressures, normal (or usual for the particular patient) arterial blood pressure, and normal to low inotropic state.

Prevention of Ischemia

Prevention of perioperative ischemia begins with the continuation of the patient's chronic antianginal therapy into the immediate preoperative period. Abrupt discontinuation of beta-adrenergic receptor blocker therapy may precipitate ischemia or infarction. Oral nitrates, beta-blocking agents, and calcium channel entry blocking medication may be given the morning of the surgery with a sip of water. Topical nitrates should be left on the patient in the immediate preoperative period, at least until intravenous nitroglycerin (NTG) is available. Patients with unstable angina controlled with infusions of NTG and/or heparin should have these medications continued until arriving in the operating room. Although there may be concern about the risk of inserting vascular cannulas into an anticoagulated patient, the risk of myocardial ischemia due to discontinuation of a heparin infusion is more important. [42]

The anxiety that may be caused by the prospect of major surgery, as well as the pain and discomfort caused by the insertion of vascular cannulas, may precipitate angina in the unpremedicated patient. We prefer to see our CABG patients calm, even somnolent, in the preoperative period and prescribe sedatives and narcotic analgesics accordingly. Care should be taken to minimize any discomfort caused by insertion of invasive monitoring devices, and consideration should be given to placing some or all of them after the induction of anesthesia, especially if the patient is experiencing myocardial ischemia. Oxygen saturation should be monitored by pulse oximetry and supplemental oxygen provided while the patient is prepared for surgery. Unstable patients with ongoing ischemia should be lifted from the stretcher to the operating table rather than being asked to move themselves in order to minimize exertion and myocardial oxygen demand.

Maintenance of stable hemodynamics is an important factor in prevention of myocardial ischemia. Induction of anesthesia should be cautious to avoid hypotension, but an adequate depth of anesthesia must be achieved before tracheal intubation. Endogenous catecholamines released in response to noxious stimulation produce many undesired effects, namely tachycardia, hypertension, and increased myocardial contractility, all of which increase oxygen demand. Adequate anesthesia will diminish the sympathetic response to noxious stimulation (i.e., laryngoscopy and surgery). Beta blockers can be used to inhibit tachycardia, and NTG can be infused to reduce both arterial vasoconstriction (hypertension) and venoconstriction (increased preload) induced by sympathetic and endocrine responses to noxious stimulation. Slower heart rates, lower filling pressures, and normal systemic blood pressures are desirable. Finally, the oxygen-carrying capacity of the blood (adequate hemoglobin and oxygen saturation) needs to be maintained at adequate levels to prevent myocardial ischemia.

Detection of Ischemia

Chest pain in the awake patient, especially if similar to previous anginal pain, indicates the presence of myocardial ischemia. This may occasionally be confused with biliary spasm caused by an opioid medication given in the preoperative period. Biliary pain will be relieved with naloxone and angina will not. A small dose of naloxone will competitively and transiently antagonize the opioid effects, both biliary spasm and analgesia. NTG can be used to relieve true angina, and if necessary, a larger dose of opioid can be given as needed to treat anginal pain once the differential diagnosis is made.

ECG-ST analysis is the most common method to monitor for myocardial ischemia. Continuous ECG monitoring of CAD patients undergoing surgery showed that lead V_6 detected 82 percent of episodes documented by 12-lead recordings, V_5 72 percent, V_4 54 percent, and lead II 33 percent. [43] [44] Lead II is useful for diagnosis of atrial dysrhythmias. Ischemia is manifest usually as ST depression but can cause ST elevation, which is not entirely specific but highly suggestive of ischemia in a patient with known CAD. Some monitors continuously measure ST segment depression or elevation in several leads and can be configured to give an alarm when significant changes occur. [45] ST trend analysis cannot be done in patients with left bundle branch block or ventricular pacing.

Hemodynamic changes that indicate myocardial ischemia producing impaired global LV function include elevated pulmonary artery occlusion pressure (PAOP), the appearance of large V waves in the PAOP tracing (which may be due to altered LV compliance and papillary muscle dysfunction manifest as mitral valvular regurgitation), and a fall in cardiac output. The last is probably the least sensitive way to monitor for ischemia. [46]

TEE can be used to detect ischemia. The appearance of a new ventricular regional wall motion abnormality (RWMA) in a patient with known CAD is highly suggestive of myocardial ischemia. [47] TEE is more sensitive than ECG in that it will detect more episodes than ECG, but the two methods may be complementary in that some episodes not detected by one may be apparent with the other. TEE monitoring equipment is expensive and cannot be automated as yet. In addition, proper use of TEE requires significant training and skill, and it is not suitable for continuous monitoring throughout the perioperative period.

Use of these more sensitive techniques to detect ischemia in CABG patients has shown that most episodes are not associated with acute hemodynamic perturbations. [48] Pre-CPB ischemia is less common than post-bypass episodes, and different authors disagree as to whether they are associated with adverse outcomes. [49] [50] Ischemic episodes in the post-bypass period are more common and are clearly related to adverse clinical outcomes (perioperative MI, malignant ventricular

dysrhythmias, and death). [49]

Treatment of Ischemia

Although it seems intuitively obvious, it has not been conclusively demonstrated that the detection and successful treatment of perioperative ischemic events improve outcome in CABG patients. [7] Nonetheless, we feel that the prompt recognition and treatment of this condition is an important aspect of the anesthetic management of patients with CAD. Following are several methods to treat myocardial ischemia; most often several will be instituted simultaneously.

Correction of hemodynamic abnormalities: This first step includes decreasing tachycardia and increasing arterial blood pressure if low or decreasing it if high.

Intravenous NTG: This is the mainstay of medical treatment for myocardial ischemia. NTG is especially helpful when the arterial pressure and filling pressures are high. However, it may cause hypotension and reflex tachycardia. Part of its benefit may be due to inhibition of platelet function. [51]

beta-Adrenergic receptor blockers: These drugs diminish myocardial oxygen demand by decreasing heart rate and contractility. They have been shown to reduce recurrent ischemia and MI in patients with unstable angina. They should be used with caution in patients with impaired LV function or bronchospastic pulmonary disease.

Heparin: Pathologic thrombosis plays a prominent role in myocardial ischemia, and heparin has been shown to be effective in reversing ischemia and preventing infarction. Patients must be heparinized before CPB anyway, and prompt anticoagulation should be accomplished if there is ischemia in the pre-bypass period.

Calcium channel blockers: These drugs may provide effective treatment for myocardial ischemia, especially if due to coronary artery spasm or associated with hypertension. However, they have been shown to be effective only if combined with other forms of therapy, such as anticoagulation or beta-blockade. [15]

Cardiopulmonary bypass: Patients for CABG surgery with myocardial ischemia who are hemodynamically unstable should be supported with CPB as soon as possible. Those with ischemia refractory to the usual treatments should be placed on CPB also. While on CPB, the heart is emptied of blood and allowed to "rest," which greatly diminishes myocardial oxygen demand while coronary perfusion pressure is maintained by CPB. Once CPB is instituted, betablocking

---

drugs may be given without fear of causing hemodynamic instability.

Intra-aortic balloon pump (IABP): This device has been shown to be effective therapy for ischemia refractory to medical management. [52] It improves myocardial oxygen supply-demand balance by decreasing impedance to LV ejection, thereby decreasing myocardial work, and by raising diastolic arterial pressure, which increases coronary blood flow. An IABP may be inserted preoperatively in patients with persistent symptoms. However, the insertion of an IABP should not cause a delay in placing an unstable patient on CPB. Insertion of an IABP should be considered for patients with evidence of refractory ischemia after CPB, especially if the hemodynamics are marginal or inadequate.

After CPB, the adequacy of revascularization should be evaluated if there is evidence of myocardial ischemia. A new RWMA seen with TEE may help direct attention to a problem graft. Grafts should be inspected for kinks and other technical problems. Spasm of an internal mammary artery graft may respond to vasodilator and/or calcium channel blocker therapy. Occasionally, return to CPB and placement of additional bypass grafts may be of benefit. Air embolization is another possible cause of ischemia after CPB, especially in the distribution of the right coronary artery, and the resulting right ventricular failure is best managed by returning to CPB and resting the heart while maintaining a relatively high coronary perfusion pressure and giving a coronary dilator such as NTG.

Choice of Anesthetic Technique

Does the choice of anesthetic affect the incidence of perioperative myocardial ischemia or infarction? To date, there is no substantial evidence that it does. [53] [54] [55] [56] [57] However, this answer has to be qualified by the following considerations:

1. Few real outcome studies have been made. Measurement of the presence or absence of intraoperative hemodynamic changes in relation to a particular anesthetic technique does not allow prediction of outcome (e.g., perioperative MI). [58] Also, it is not possible to separate the effects of anesthesia from those of the surgical operation. [59]
2. Few patients are anesthetized with a single anesthetic drug. Preanesthetic and intraoperative medications, including central nervous system (CNS) and cardiovascular drugs, modify the patient's response to the primary anesthetic in ways that are still largely unknown or at least not accurately determined in a controlled manner. [13] [53]
3. Monitoring and treatment of potentially adverse hemodynamic changes might improve outcome, and it is clear that no anesthetic technique does away with the need for such monitoring and therapy. It is important to note that most perioperative MIs related to noncardiac surgery occur in the postoperative rather than the intraoperative period. [60]
4. Theoretical concerns related to a specific anesthetic (e.g., coronary steal produced by isoflurane) have not been found to be detrimental in clinical practice. [57] [61] [62] [63] [64] [65] [66] Perhaps this is because of offsetting pharmacologic effects of the anesthetic (e.g., isoflurane raises the threshold heart rate to pacing-induced ischemia), use of supplemental drugs that reduce the dose of the anesthetic required, careful monitoring, and prevention or treatment of even moderate hemodynamic changes.
5. Finally, it is important to remember a basic principle of scientific scrutiny: Coincidence of events in time is not proof of a cause-and-effect relationship. [58] [59]

Valvular Surgery

Determinants of Cardiac Output

Blood pressure is the product of cardiac output (Ch. 16) and total peripheral resistance (BP = CO × TPR). Blood pressure alone is not a reliable indicator of cardiac performance, because blood pressure can be maintained by increased peripheral vascular resistance even with a marked reduction of cardiac output. Cardiac output is an indicator of overall cardiac performance because it represents the volume of blood available for perfusion of body tissues, which is the purpose of cardiac function.

Table 49-13 lists factors affecting cardiac output, which is the product of stroke volume and heart rate (CO = SV × HR). Decreases in stroke volume can be compensated by increasing heart rate until the tachycardia encroaches on the minimum diastolic time required for adequate ventricular filling and perfusion of the subendocardium. Dysrhythmias usually decrease cardiac output and make the work of the heart less efficient. Coordinated activity of ventricular myofibrils is essential for development of maximum pressure

TABLE 49-13 -- Factors Affecting Cardiac Output[a]

Rate
Proportional increase in cardiac output unless shortening of diastolic time reduces ventricular preload or impairs contractility as a result of reduced coronary perfusion
Cardiac output is rate-dependent with fixed stroke volume (ventricular and valvular dysfunction)
Rhythm
Coordinated ventricular contraction essential (impaired by conduction abnormalities and ventricular pacing)
Properly timed atrial contraction augments ventricular preload, especially important with impaired diastolic ventricular function (compliance) (lost with atrial fibrillation, first-degree heart block, ventricular pacing)

Preload
Increased ventricular filling stretches myofibrils and increases contractility (Frank-Starling principle)
Overdistention of ventricle increases oxygen demand and impairs contractility
Afterload
Determined in part by vascular resistance and indicative of the pressure work the ventricle must do to overcome the impedance to ejection
Reduction of afterload increases cardiac output unless hypotension reduces coronary perfusion and impairs contractility
Reduced by increased ventricular wall thickness--compensatory hypertrophy
Ventricular contractility (inotropic state)
Intrinsic state of cardiac muscle that can be described by cardiac performance curves
Affected by myocardial metabolism, oxygen supply, ionized calcium concentration, drugs, hypertrophy, and myocardiopathies

[a] Also see Chapters 16 and 30 .

Figure 49-2 Frank-Starling principle: measures of left ventricular performance (vertical axis) increase up to a maximal level as ventricular preload (horizontal axis) is increased. Low-perfusion states exist when cardiac output is insufficient to meet the oxygen demand of all body tissues. Pulmonary and venous congestion results when capillary hydrostatic pressure increases and produces a net transfer of water and electrolytes out of capillary blood into the interstitial spaces of the lung. Measures of ventricular performance are LVSWI, left ventricular stroke work index; SV, stroke volume; CO, cardiac output; CI, cardiac index; and in some cases blood pressure, BP. Measures of ventricular preload are LVEDV, left ventricular end-diastolic volume; LVEDP, left ventricular end-diastolic pressure; LAP, left atrial pressure; PCWP, pulmonary capillary wedge pressure; or PAOP, pulmonary artery occlusion pressure; and in some cases central venous pressure, CVP, especially with right ventricular (RV) dysfunction.

by the ventricle. An effective atrial contraction properly timed with ventricular diastole is usually essential for optimal loading of the ventricle just before the onset of systole.

Stroke volume depends on the interaction of three factors:

1. Preload determines the degree of stretch of ventricular fibers and thereby determines the amount of work that can be done by the ventricle at any particular level of contractility.
2. Contractility is an intrinsic property of cardiac myofibrils and represents the amount of work they can produce at any end-diastolic fiber length (preload). The relationship between preload and contractility is best illustrated by cardiac performance curves based on the Frank-Starling principle (Fig. 49-2) .
3. Afterload represents the tension developed in the ventricular well and determines the relationship between pressure and volume work during ventricular systole. Afterload is determined in part by vascular resistance in the absence of aortic or pulmonic valvular stenosis. High levels of vascular resistance mean that proportionately greater amounts of ventricular work will be expended for pressure development (to overcome resistance); correspondingly, lesser proportions of ventricular work will go toward the actual ejection of blood (stroke volume). Increase in ventricular diameter will also increase wall tension and afterload.

Appropriate management of hemodynamic problems depends on the anesthesiologist's understanding the role of each of the factors and of the interactions among them in health and disease. All anesthetic drugs affect one or more of the individual factors and in some cases alter their interrelationships. Furthermore, with modern drugs and advanced monitoring techniques, it is possible to choose therapeutic measures directed somewhat selectively at one or more of these determinants of cardiac output. These determinants also operate in compensatory mechanisms for acute and chronic cardiovascular disease.

Compensatory Changes in Disease

Acute hemodynamic alterations elicit reflex changes directed toward maintenance of cardiac performance. Chronic problems may elicit reflex activity and also lead to long-lasting or permanent alterations in organ structure and function. Reflex changes tend to be more readily measured, more susceptible to therapeutic intervention, and more rapidly reversible with correction of the basic problem than those involving structural alterations.

All types of valvular heart disease reduce the effective (forward) stroke volume. A number of compensatory mechanisms may be called into play (Table 49-14) ; the most important for each type of valvular heart disease are discussed below. Several points should be emphasized in relation to these compensatory mechanisms.

Each mechanism produces symptoms and signs, the intensities of which are not necessarily correlated with the severity of valvular disease or the functional status of cardiac muscle. These symptoms depend on both the severity of the mechanical overload and the degree of impairment of contractility secondary to the valvular disease or due to coexisting myocardial disease (e.g., coronary atherosclerosis, cardiomyopathy). It is necessary to evaluate both valvular

TABLE 49-14 -- Mechanisms of Compensation for Reduced Left Ventricular Stroke Work and Ejection Volume [a]

Increased sympathetic nervous system activity
Results from hypotension leading to decreased arterial baroreceptor inhibition of autonomic centers in the brain stem
Increases heart rate and contractility (depending on the functional status of ventricular myofibrils)
Produces arterial vasoconstriction and increases systemic and pulmonary vascular resistances
Stimulates release of renin, which increases vascular resistance and promotes salt and water retention through release of aldosterone
Frank-Starling mechanisms of increased left ventricular diastolic volume (preload)
Results from reduced stroke volume and accumulation of venous return
Increases stroke volume (depending on functional status of ventricular myofibrils)
Provides geometric mechanical advantage; the same stroke volume can be ejected with less circumferential shortening of myofibrils (but may reduce right ventricular volume and function)
Is supplemented by the retention of salt and water by the kidney
Ventricular hypertrophy
Results from increased intramyocardial tension caused by increased pressure or volume overloading of the ventricle
Ventricular thickness increases and compliance decreases
Increased number of sarcomeres tends to increase stroke work and to maintain stroke volume
Increased wall thickness decreases systolic wall tension and thereby reduces afterload (tension = pressure × radius/ wall thickness)

[a] Also see Chapter 16 .

disease and ventricular contractility objectively, usually by cardiac catheterization.

Certain compensatory processes (e.g., ventricular hypertrophy, increased pulmonary vascular resistance [PVR]) alter the relationships between blood pressure and blood volume or flow. Pressure values outside the range of normal are commonly seen in patients with cardiac disease. It is important to recognize that the abnormal values are part of the compensatory processes and that it may be necessary to maintain them at the abnormal but usual level for that particular patient both before and after surgery. Under such circumstances the anesthesiologist should be guided more by trends of change than by absolute values--hence the importance of continuous, precise monitoring techniques.

On the other hand, the sudden replacement of a diseased valve with a more normally functioning valvular prosthesis may acutely alter the impact of compensating mechanisms on cardiovascular (and other organ) functions and indicate therapy aimed at neutralizing those mechanisms that have suddenly become detrimental to cardiovascular function.

Finally, the stress imposed by anesthesia and surgery may exceed the upper limits of cardiovascular reserve even after the primary problem has been corrected. The anesthesiologist should be prepared to initiate the appropriate therapy intraoperatively. This responsibility obviously requires a thorough understanding of the drugs and devices (e.g., pacemakers, IABPs) that may be needed.

Valvular Versus Contractile Functions

Valvular diseases interfere mechanically with cardiac function and ultimately lead to abnormalities of ventricular contractility. As indicated previously, the evaluation of contractility may be complicated by the valvular malfunction and by the chronic compensatory changes that result. The indexes of good and poor ventricular function stated here for patients with CAD may not apply to those with valvular disease. For example, ventricular end-diastolic pressure is not a good index of ventricular function in the presence of aortic or mitral regurgitation because LVEDP and LVEDV are determined by both the contractile state of the heart and the severity of regurgitation. LVEDP is also a function of ventricular compliance. In the presence of aortic stenosis with ventricular hypertrophy and stiffness, LVEDP may increase out of proportion to LVEDV and with only minor reductions in contractility. Potentially elevated LVEDP may be reduced to normal levels by a reduction of the circulating blood volume.

Preoperatively, the ejection fraction is probably the best index of contractility that is usually available, although it too has limitations. [67]

As the ejection fraction falls progressively below 0.5, it is indicative of progressively more severe impairment of ventricular function, especially if the systemic vascular resistance is normal or low at the time of measurement. In the presence of mitral valvular insufficiency, the ejection fraction is not a reliable indicator of LV reserve because much of the ejected volume is regurgitant flow against low resistance.

Intraoperatively, the determination of ventricular function relationships (see Fig. 49-2) is probably the most efficient means of defining optimal or maximal cardiac performance. The change in cardiac output in response to different degrees of ventricular loading, as indicated by the LVEDV or LVEDP, left atrial pressure (LAP), PAOP, or in the case of the right ventricle, central venous pressure, defines the ventricular status and indicates the need for specific therapeutic measures.

Specific Valvular Diseases

Under each of the following headings, only the pathophysiologic features of immediate importance to the anesthetic management of patients with valvular heart disease

are summarized. More detailed and comprehensive treatises are available.

Mitral Stenosis

Mitral stenosis is almost always rheumatic in origin and usually follows a prolonged course of development. Symptoms appear early but usually progress slowly until there is a suddenly increased demand for cardiac output (e.g., because of pregnancy or infection) or until atrial fibrillation supervenes. Atrial contraction contributes up to 40 percent of LV filling in the presence of mitral stenosis as compared with 15 percent in the normal heart. Estimation of the severity of the stenosis in terms of the end-diastolic pressure gradient between the left atrium and ventricle is not reliable because the gradient is dependent on heart rate, blood flow, and other variables. Estimates of mitral valve area provide a somewhat more reliable indication of the severity of the disease. [68] The area of the normal adult mitral valve ranges from 4 to 6 cm^2 , and stenosis is graded as mild (1.5-2.5 cm^2), moderate (1.1-1.5 cm^2), or severe (1 cm^2). The pathophysiologic progression is summarized in Figure 49-3 (Figure Not Available) .

Several features of the disease are especially important in terms of maintaining cardiac output:

1. Heart rate is the primary consideration. It should be maintained in a normal range. Bradycardia markedly reduces cardiac output because the stroke volume is limited by the stenotic valve and by the relatively small size of the left ventricle. Tachycardia can be even more detrimental because it severely reduces LV preload (decreased diastolic filling rate due to the stenotic valve) and cardiac output. Pulmonary edema can develop suddenly if atrial fibrillation occurs with a rapid ventricular response; the latter must be treated aggressively (i.e., cardioversion, diltiazem, or beta blocker). Continuation of maintenance therapy with a cardiac glycoside through the time of surgery is indicated to control the ventricular rate in the presence of atrial arrhythmias.
2. Near maximally tolerated LAP should be maintained, yet pulmonary edema should be prevented. Precise monitoring of LAP or PAOP is obviously desirable. However, increased PVR and pulmonary hypertension entail the following effects: (1) the risk of pulmonary artery (PA) rupture by inflation of the balloon on a PAC is probably increased; (2) it may not be possible to obtain a PAOP tracing; (3) the PA diastolic pressure is not an accurate estimate of either LAP or LVEDP (although the pressures may show similar trends of change); and (4) it is sometimes difficult to float the catheter tip into the PA. For these reasons, in certain patients it may be advisable to ask the surgeon to insert a left atrial catheter for LAP monitoring, especially before attempting to discontinue extracorporeal circulation. An LAP to LVEDP mean gradient of 4 to 7 mm Hg is to be expected across most prosthetic mitral valves. [69] [70]
3. Progression of the disease to include PA hypertension has two other consequences. Increased PVR may limit left atrial and LV filling, and the right ventricle (RV) may fail as it works to overcome impedance to its ejection of blood. It is advisable to monitor pulmonary artery pressure and to eliminate factors that increase it (e.g., hypercarbia, hypoxia, and nitrous oxide). It is also important to monitor right atrial or central venous pressure (CVP) to detect signs of RV failure.

Incidentally, contractility of the chronically underloaded, usually small LV is seldom a problem in otherwise uncomplicated mitral valvular surgery for "pure" mitral stenosis. However, LV output may be inadequate in the presence of RV failure because of (1) inadequate LV filling due to low pulmonary blood flow and (2) RV dilation with bulging of the interventricular septum into the LV cavity, thereby reducing LVEDV and impairing LV ejection. [71] [72]

4. Pulmonary hypertension, RV failure, and tricuspid regurgitation usually improve in the days and weeks following correction of mitral stenosis. However, structural changes due to long-standing disease limit the extent of improvement. [73]

Figure 49-3 (Figure Not Available) Pathophysiology of mitral stenosis. *(Modified from Thomas SJ, Lowenstein E: Anesthetic management of the patient with valvular heart disease. Int Anesthesiol Clin*

17:67, 1979.)

In summary, the important cardiovascular management goals for mitral stenosis are (1) to prevent tachycardia and maintain a sinus rhythm; (2) to maintain LV preload and stroke volume while preventing pulmonary edema; and (3) to prevent further increases in PVR and treat RV failure if it occurs.

Mitral Regurgitation

Mitral regurgitation has numerous causes and may occur suddenly (e.g., because of papillary muscle rupture) or develop gradually and progressively (e.g., in association with mitral stenosis of rheumatic origin). Mitral regurgitation produces volume overloading of the left ventricle.

In the acute case, sudden and dramatic hemodynamic changes may result from the increased LAP and the reduction of cardiac output. Elevated LAP is transmitted to the pulmonary circulation and can cause pulmonary congestion, pulmonary hypertension, and right heart failure. Compensating increases in sympathetic nervous system activity lead to tachycardia and increased systemic vascular resistance, which exacerbates the regurgitant flow. The outcome of surgery is guarded relative to the severity and suddenness of hemodynamic stress, especially when there is an associated impairment of LV function (e.g., infarction, endocarditis, or cardiomyopathy).

Chronic mitral regurgitation is compensated by the more gradual processes of LV hypertrophy and dilation (increased compliance) and left atrial dilation. Generally, there is minimal involvement of the pulmonary vasculature and RV until late in the progress of the disease, when severe CHF may develop and a rapid downhill course ensues. The contrasts between acute and chronic mitral regurgitation are illustrated in Figure 49-4 (Figure Not Available) .

The severity of mitral valvular incompetence is estimated in terms of the regurgitant fraction, which expresses the regurgitant volume as a fraction of the total stroke volume; a regurgitant fraction greater than 0.6 is associated with CHF. Although these volumes can be estimated by either indicator dye dilution or ventriculography, it is usually adequate and more convenient to grade the amount of contrast material entering the left atrium during ventricular systole as part of ventriculography. A grading scale analogous to that used for aortic regurgitation (see later) can be applied. Semiquantitative assessment of the severity of mitral valvular regurgitation is possible with echocardiography, which may also identify the etiology of the regurgitation. Estimates of ventricular ejection fraction may be misleading because blood is leaving the ventricle by two routes. The incompetent mitral valve provides a low-pressure, low-resistance route, and the regurgitant volume can be greater than the blood volume entering the aorta. If only the aortic route were available, the degree of ventricular emptying would be less. [74]

The functional features of mitral regurgitation of most importance to the anesthesiologist are the following:

1. Heart rate should be maintained at normal or elevated levels to maintain cardiac output. Bradycardia is associated with increased LV volume, increased regurgitant fraction, and reduced systemic cardiac output. Many patients with chronic mitral regurgitation are in atrial fibrillation.
2. Increases in systemic vascular resistance should be prevented because they increase regurgitant flow. The use of arterial vasodilators to reduce systemic vascular resistance and increase "forward" cardiac output while decreasing regurgitant flow through the mitral valve may be beneficial, provided that excessive hypotension is avoided. [75]
3. Myocardial contractility is impaired in both acute and chronic mitral regurgitation and sensitive to cardiac depressant drugs. Increasing ventricular preload in an attempt to maintain or increase stroke volume has the disadvantages of dilating the compliant LV and increasing the regurgitant flow.
4. After mitral valvular replacement, there is a risk toLV integrity, especially in elderly patients. [76] Transverse rupture of the LV has occurred on resumption of ventricular pumping soon after valvular replacement and is thought to result from loss of ventricular support by the mitral valve apparatus. Many surgeons now preserve the posterior leaflet and attached chorda tendinea during initial valve replacement to help avoid this complication. (The apex of the heart is supported by attachment to the annulus by the papillary muscles, chordae tendinae, and valve leaflets.) The possibility of rupture is also increased by the loss of ventricular tone due to the residual effects of the cardioplegia solution administered for myocardial preservation during surgery. Measures to reduce the risk of ventricular disruption include operating on the beating heart unloaded by CPB but avoiding the use of cardioplegia, prolongingthe period of rest on CPB after valvular placement to allow recovery of ventricular tone, and using vasodilators to limit ventricular pressure and distention during diastole. [76] Vasodilators may also be needed to facilitate LV ejection after mitral valvular replacement, which eliminates restricted ventricular filling in the case of stenosis and stops the low-resistance regurgitant flow in the case of regurgitation. Insertion of an IABP may serve a similar purpose in this situation.

The goals of cardiovascular management of the patient with mitral regurgitation are (1) maintenance of a normal to slightly elevated heart rate, (2) reduction of systemic vascular resistance to the degree that it will promote systemic flow and reduce regurgitation without compromising cerebral and coronary perfusion, and (3) preservation of ventricular contractility while not increasing preload excessively.

Figure 49-4 (Figure Not Available) The syndrome of mitral regurgitation. (A) Acutely developing mitral regurgitation into small left atrium produces high pressures and changes in the left atrium (LA), pulmonary vein (PV), pulmonary artery (PA), right ventricle (RV), and right atrium (RA). (B) Chronic, slowly progressive mitral regurgitation produces dilation of the left atrium, so that pressures remain low and there is little change in the pulmonary vessels or right side of the heart. *(Modified from Roberts WC, Perloff JK: Mitral valvular disease. Ann Intern Med 77:939, 1972.)*

Aortic Insufficiency

Aortic insufficiency develops acutely from bacterial endocarditis, aortic aneurysmal dissection, connective tissue disease, and trauma. Chronic aortic regurgitation results from rheumatic disease, hypertension, syphilis, and other causes. The pathophysiology is outlined in Figure 49-5 (Figure Not Available) .

Acute aortic insufficiency places a sudden volume overload on the LV and raises both LVEDP and PAOP (unless there is premature closure of the mitral valve when LVEDP is greater than LAP). Tachycardia and peripheral vasoconstriction result from sympathetic stimulation and produce a further decrease in forward cardiac output. Acute LV failure can develop and progress rapidly.

Chronic aortic insufficiency results in ventricular hypertrophy and dilation (increased compliance). A competent mitral valve protects the pulmonary circulation until late in the disease process, when contractility becomes impaired, forward cardiac output falls, and peripheral vascular resistance increases. The progress of the disease is gradual, often without the development of symptoms for 10 to 20 years, but there is rapid deterioration once LV failure occurs. [77] [78] Surgery is usually recommended as soon as there is evidence that the ventricle is enlarging.

Figure 49-5 (Figure Not Available) Pathophysiology of aortic insufficiency. *(Modified from Thomas SJ, Lowenstein E: Anesthetic management of the patient with valvular heart disease. Int Anesthesiol Clin 17:67, 1979.)*

The severity of aortic valvular regurgitation is graded angiographically after contrast injection in the aortic root as follows:

1+: Small amount of contrast material enters LV during diastole, but LV is cleared with systole.

2+: LV is faintly opacified during diastole and not cleared with systole.

3+: LV is progressively opacified.

4+: LV is completely opacified during the first diastole and remains so for several beats.

In terms of regurgitant volume, 1 to 3 L/min is mild, 3 to 5 L/min is moderate, and more than 6 L/min is considered to be severe; regurgitant volumes up to 25 L/min have been reported. Other indicators of severe chronic aortic insufficiency are a sudden increase in ventricular size and the onset of CHF, often with the development

of secondary mitral insufficiency. [79]

Salient features of aortic insufficiency include the following:

1. A slightly higher than normal heart rate is often beneficial because it reduces ventricular distention (reduced time for diastolic regurgitation) and oxygen consumption (effect of smaller LVEDV outweighs that of increased heart rate) while improving subendocardial blood flow (higher diastolic blood pressure with lower LVEDP). Bradycardia should be prevented.
2. Arterial blood pressure often is labile and very responsive to vasoactive drugs. Nevertheless, with careful monitoring of blood pressure and left ventricular filling pressures (i.e., PAOP), vasodilators can be used to advantage to increase forward cardiac output and to decrease LV distention, secondary mitral regurgitation, and pulmonary venous pressure. [80] [81] Diastolic hypotension with the lowering of coronary perfusion should be prevented. After aortic valvular replacement, vasodilators may be needed to control hypertension.
3. Ventricular contractility is usually impaired in patients undergoing valve replacement for either acute or chronic aortic regurgitation. [82] Myocardial oxygen demand is increased only moderately by aortic insufficiency, because volume work increases oxygen use by only 5 to 10 percent and LV wall tension increases only slightly until the late stages of the disease (see Fig. 49-5) (Figure Not Available) .

In summary, the cardiovascular management goals are to maintain a higher than normal heart rate (80-100 beats/min), reduce afterload appropriately, and avoid myocardial depressants.

The presence of aortic regurgitation has significant implications during cardiopulmonary bypass. Once the heart ceases to eject blood (as with ventricular fibrillation), the left ventricle will quickly distend as the pressure between the aorta and LV equalize through the incompetent aortic valve. Administration of a beta blocker (e.g., 50-100 mg esmolol, 5-10 mg metoprolol, 2-5 mg propranolol) IV 3 to 5 minutes before initiating CPB can significantly delay the onset of ventricular fibrillation during cooling of the heart on CPB. The surgeons may decompress the LV with a vent, but this may result in a low arterial pressure if the aortic regurgitation is severe and result in a significant portion of the pump flow passing from the aorta through the LV and back to the bypass machine through the vent, not perfusing the patient. Application of the aortic cross-clamp may be the only way to remedy this situation. Significant aortic regurgitation will also make the delivery of cardioplegia in the antegrade mode difficult or ineffective.

Aortic Stenosis

Aortic stenosis (Fig. 49-6) (Figure Not Available) usually occurs as a result of thickening or degeneration and calcification of a congenitally abnormal valve. It can also be of rheumatic origin, usually in association with mitral valvular disease. Stenosis of the aortic valve places a pressure overload on the LV, which hypertrophies but does not dilate; that is, there is low ventricular compliance. [83] Major consequences of decreased ventricular compliance include the following:

Figure 49-6 (Figure Not Available) Pathophysiology of aortic stenosis. *(Modified from Thomas SJ, Lowenstein E: Anesthetic management of the patient with valvular heart disease. Int Anesthesiol Clin 17:67, 1979.)*

1. Higher filling pressures are needed for optimal cardiac performance, and these are reflected into the pulmonary circulation and can result in pulmonary congestion if they become too high. Precise monitoring of PAOP and cardiac output is important. In the noncompliant ventricle, the mean PAOP underestimates the LVEDP, which is more closely approximated by the a-wave on the PAOP tracing. [84]
2. A normal sinus rhythm is very beneficial because the atrial "kick" may account for up to 40 percent of ventricular filling. Cardioversion should be done promptly for an acute onset of atrial fibrillation. It should be noted that cardiopulmonary resuscitation is extremely difficult in the patient with aortic stenosis and ventricular hypertrophy. Dysrhythmias should be prevented and treated promptly. A moderate

heart rate (70-90 beats/min) is probably best to maintain cardiac output and to prevent myocardial ischemia.
3. Pressure overloading of the LV and the resulting hypertrophy lead to major alterations of myocardial oxygen demand and supply. Demand is increased by the increased mass of the ventricle and increased ventricular pressure work. Supply is reduced by decreased diastolic perfusion time (longer systole for ejection of stroke volume through the stenotic valve), increased LVEDP (impaired subendocardial perfusion), and decreased systemic blood pressure (lower coronary perfusion pressure). In addition, the density of capillaries may be decreased in the hypertrophied ventricular muscle, and CAD frequently coexists with aortic stenosis. [85] [86] Patients with aortic stenosis experience angina even without CAD and have little or no coronary flow reserve. They are especially at risk from peripheral vasodilation, which can produce sudden and profound hypotension that can impair both cerebral and coronary perfusion.

The severity of aortic stenosis is most accurately stated in terms of the estimated valve area, which normally is 2.5 to 3.5 cm^2. Areas less than 1 cm^2 indicate surgical correction; angina and syncope due to arrhythmias or to an inability to meet a sudden demand (e.g., exertion) for an increased cardiac output are common with areas less than 0.7 cm^2 and pose a risk of sudden death. [84] Other signs of severe disease are systemic arterial pulse pressure less than 30 mm Hg and CHF. A low aortic valvular pressure gradient may indicate LV failure; high systolic blood pressure suggests less severe disease. A low LV ejection fraction may be misleading, because a strong ventricle may be pumping against a very high impedance to ejection.

The cardiovascular management goals for patients with aortic stenosis are (1) to maintain a sinus rhythm at a normal rate, (2) to maintain systemic diastolic blood pressure and coronary perfusion, and (3) to maintain cardiac output by appropriately high preload and by avoidance of myocardial depressants. The potential benefit of attempting to reduce myocardial work and oxygen demand by depressant anesthetics is offset by the risk of lowering diastolic and coronary perfusion pressures; the overall benefit-risk relationship is unknown.

Diseases Resembling Aortic Stenosis

Several disease processes resemble aortic stenosis in their hemodynamic effects.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a genetically transmitted disease that results in increase in ventricular mass, which may result in obstruction of the LV outflow tract in some patients. [87] Hypertrophic obstructive cardiomyopathy is often referred to as idiopathic hypertrophic subaortic stenosis (IHSS), an asymmetric hypertrophy of the interventricular septum. The obstruction to ventricular ejection is due to abnormal anterior movement of the mitral valve leaflet across the left ventricular outflow tract to contact the septum during systole. This produces a highly variable and dynamic amount of functional aortic stenosis as well as mitral regurgitation. Factors that increase the degree of obstruction and the pressure gradient between the LV and aorta include lower arterial pressure, lower LV volume, and increased ejection velocity. As a result of the obstruction, myocardial oxygen consumption increases, the LV hypertrophies and becomes less compliant, and the higher filling pressures are reflected to the atrium, which is often dilated and hypertrophied. The obstruction is usually progressive, and eventually LV failure occurs. [87] There is a high incidence of conduction abnormalities associated with the disease and also occurring after surgery (ventriculomyotomy and myomectomy) that involves dissection of the hypertrophied septum near the atrioventricular conduction system. With improved medical therapy, including beta-adrenergic receptor and calcium channel blocking drugs, and the effectiveness of atrioventricular sequential pacing, indications for surgical correction have been present less frequently. [88] [89]

Should surgery be indicated, hemodynamic management is directed toward minimizing the systolic pressure gradient between the LV and the aorta. Hence, arterial blood pressure and ventricular volume should be maintained or increased and ejection velocity should be reduced. [90] [91] Vasoconstrictors (e.g., phenylephrine), beta-adrenergic receptor blockers (e.g., propranolol), and myocardial depressant anesthetics (e.g., halothane [92]) have proven to be useful. Reductions in venous return (e.g., by high airway pressure) and dysrhythmias are poorly tolerated. Mitral regurgitation may occur with IHSS as a result of the abnormality of the anterior mitral leaflet and the high ventricular pressures. It must be remembered that pharmacologic interventions affect mitral regurgitation occurring with IHSS in a manner opposite to their effects in other forms of mitral regurgitation (i.e., inotropes and vasodilators worsen and vasoconstrictors improve ventricular ejection).

Other Diseases

Other diseases that lead to pressure overloading of the LV and the resultant hypertrophic and compliance changes include chronic systemic arterial hypertension and

coarctation of the aorta. Management of patients with these diseases is discussed in Chapters 16 , 50 , and 51 . Control of the acute LV pressure overloading resulting from clamping the aorta (e.g., during aortic surgery) is also important (Ch. 50) .

Tricuspid Regurgitation

Tricuspid regurgitation as an isolated cardiac abnormality is rare, although its incidence is rising as a complication of endocarditis from intravenous drug abuse. It imposes volume overload on the RV, which is tolerated well unless it is combined with a pressure overload such as that caused by high PVR or LV failure. [93] Purely functional tricuspid regurgitation can occur in the late stages of aortic and mitral valvular diseases and usually is markedly reduced or eliminated by correction of the primary disease. It is sometimes necessary to examine the tricuspid valve at the time of surgery to determine whether it should be repaired or replaced, because accurate preoperative evaluation of its function

is difficult with the relatively low pressure gradients existing across the valve. TEE can be used intraoperatively to assess tricuspid valvular regurgitation.

Hemodynamic considerations should be directed toward maintaining moderately high CVP and preventing increases in PVR. Anything that reduces forward RV output reduces LV filling and output. [71] [72]

Other Types of Cardiac Disease and Surgery

Cardiomyopathy and Transplantation

By strict definition, the term *cardiomyopathy* includes any and all structural and functional abnormalities of the ventricular myocardium. In common parlance, the term is more often focused on advanced cardiac disease not amenable to medical or surgical treatment. There are multiple etiologies (e.g., familial, infectious, ischemic, alcoholic, pregnancy-related) and several subtypes (i.e., dilated, hypertrophic, restrictive, and obliterative). Dilated cardiomyopathy is the most common form and is the most common indication for cardiac transplantation.

Issues of recipient and donor selection, organization and coordination of transplantation teams (which include anesthesiologists), perioperative evaluation, anesthetic management and life support of the recipient and donor, and immunosuppressive and antibiotic therapy are beyond the scope of this chapter. However, with the progressively increasing frequency of heart transplantation, all anesthesiologists are likely to encounter donors and recipients in their practice. Hence, they should have ready access to a current text or other reference that details the anesthetic and life support objectives and guidelines for care of these patients. [94] In the case of the donor (brain dead), the focus is on maintaining ventilation, circulation, body temperature, and acid-base and electrolyte balance until organs can be harvested. For the heart transplant recipient, the challenge is to maintain cardiac and other vital functions at the best possible level until CPB is established. After the transplanted heart is in place, weaning from CPB follows the same principles as for any other cardiac surgical patient with emphasis on two particular aspects of the transplanted heart: (1) the heart must be denervated and (2) its RV frequently has to pump against an elevated PVR that has developed in response to long-term progressive worsening of LV function in the recipient's diseased heart.

Congenital Heart Disease

Congenital heart disease (Ch. 50) includes a large number of defects, some of which involve complicated anatomic and functional abnormalities that are beyond the scope of the usual practices of anesthesia and surgery outside of a highly specialized medical center. The particular functional and anatomic features influence the choice of anesthetic drugs and techniques. Moreover, there are very specialized conditions and requirements related to the pediatric patient and especially to the newborn infant (e.g., physician-child-parent relationships, monitoring techniques appropriate for the small body size, and criteria for blood replacement). Only conditions encountered in the adult population are described here.

Atrial Septal Defects

Atrial septal defects in the absence of any other anomalies usually have few hemodynamic consequences, and their signs are often discovered incidentally during a physical examination. Such a defect has three potentially detrimental consequences: (1) embolic material (e.g., air and bacteria) ordinarily filtered by the lung may enter the systemic circulation through the defect; (2) the defect may offer a site for lodgement and growth of microorganisms; and (3) a left-to-right shunt will develop progressively because differences in pulmonary and systemic vascular resistances lead to differences in ventricular diastolic pressures, which are reflected into the atria. When there is significant left-to-right blood flow, there is an increase in PVR, the development of RV hypertrophy follows, and CHF can occur.

The anesthesiologist has two goals in managing a patient with an atrial septal defect: to prevent the intravenous introduction of air or contaminated substances and to prevent any increase in and perhaps to reduce systemic vascular resistance.

Ventricular Septal Defects

Ventricular septal defects are encountered in infants as a congenital defect and in adults as the consequence of rupture of the septum after infarction. In both instances, the large systolic pressure gradient between the ventricles leads to a left-to-right shunt, which overloads the pulmonary circulation and reduces systemic vascular perfusion.

In the adult with MI, the situation develops acutely and usually is accompanied by cardiogenic shock. Under such conditions, the surgical mortality rate exceeds 50 percent. Better results have been reported in patients who could be maintained for a period of days or weeks by medical management aimed at reducing left-to-right shunt and increasing systemic perfusion (e.g., inotropic and vasodilator drugs and IABP). Under conditions of left-to-right shunting, cardiac output determinations made with a thermodilution PAC are misleading; they do not represent LV output to the systemic circulation.

Anesthetic management of such patients is really an extension of their intensive care and involves extensive monitoring, continuation of measures for hemodynamic support, and use of anesthetic drugs that do not impair ventricular contractility or increase cardiac work.

Cardiac Tamponade and Chronic Constrictive Pericarditis

Cardiac tamponade and chronic constrictive pericarditis produce similar hemodynamic alterations at different rates. Cardiac tamponade involves accumulation of fluid or blood in the closed pericardial space, and the urgency of the condition is determined by the rate and degree of accumulation.

Chronic constrictive pericarditis results in a gradual obliteration of the pericardial space. In either case, diastolic filling of both ventricles is restricted so that stroke volume and cardiac output are reduced. [95] Myocardial function may be further depressed by inadequate oxygen delivery as a result of systemic hypotension, elevated ventricular diastolic pressure, compression of epicardial vessels, and tachycardia. [96] Tachycardia and arterial and venous vasoconstriction occur as a result of reflex sympathetic activation. When the compensatory tachycardia is unable to maintain cardiac output in the face of declining stroke volume, cardiogenic shock results. In some cases of acute tamponade, cardiovascular collapse may occur within minutes, and death can be prevented only by immediately relieving the intrapericardial pressure by subxiphoid insertion of a needle or a subxiphoid pericardial incision under local anesthesia.

Consideration of the preceding hemodynamic alterations is essential to the development of an appropriate anesthetic plan. This plan should include monitoring of the important hemodynamic variables, and it should omit drugs and minimize manipulations that decrease venous return, reduce heart rate, produce hypotension, result in hypoxemia, or impair ventricular contractility. [97] Particular attention should be paid to the mode of ventilation; positive pressure ventilation further embarrasses

venous return and cardiac output. Spontaneous ventilation should be maintained until the tamponade is relieved. [98] [99] Positive measures such as expansion of the circulating blood volume, infusion of an inotrope, and maintenance of a high oxygen content of arterial blood are often beneficial. [100] Antidysrhythmic drugs and extracorporeal circulation may be needed during pericardiectomy when surgical manipulation of the heart leads to dysrhythmias and impairs cardiac output.

Pacemaker Implantation

Pacemaker implantation may be temporary or permanent. [101] Temporary pacemaker leads are introduced through a central venous cannula inserted percutaneously under local anesthesia, with the pulse generator remaining outside the body. Permanent pacemaker leads may be inserted transvenously after surgically exposing a vein or may be placed on the epicardial surface through a subxiphoid or lateral thoracotomy incision; the pulse generator is implanted subcutaneously over the upper anterior thorax or lower abdomen. Permanent pacemaker insertion may be performed under local or general anesthesia.

The indications for a permanent pacemaker are complete heart block, which may be congenital, acquired by disease or by an ablation procedure for treatment of supraventricular tachycardia; sick sinus syndrome; and bradycardia with symptoms. Most often, patients with continuous or frequently recurring slow ventricular rates enter the operating room with a temporary pacemaker in place. Under such circumstances, the choice of anesthetic technique can be made primarily with regard to other cardiac and noncardiac diseases that the patient may have. With a slow ventricular rate and no pacemaker in place, anesthetic techniques that maintain or even increase the rate of cardiac depolarization and conduction should be used. Depression of the sympathetic nervous system can be prevented and activity of the vagal nerves can be blocked by atropine. In all cases, a temporary pacemaker should be immediately available for insertion, and if possible, a central vein should be cannulated in advance to facilitate rapid insertion of the temporary pacing leads if they are needed. The anesthesiologist should be familiar with the operation of temporary and permanent pacemakers that may be used. Continuous ECG monitoring is essential not only to detect bradycardia, but also to recognize the dysrhythmias that frequently occur on placement of the leads. Because many of the patients in need of pacemakers have other systemic diseases, their anesthetic management should be planned accordingly.

Dysrhythmia Surgery

The development of sophisticated techniques for electrophysiologic study of the heart makes it possible to identify abnormal conduction pathways responsible for dysrhythmias involving an impulse reentry mechanism. [102] [103] Such pathways may represent a congenital abnormality (e.g., Wolff-Parkinson-White syndrome) or may be the consequence of myocardial ischemia and infarction (e.g., recurrent ventricular tachycardia). When pharmacologic therapy is unsuccessful in suppressing the dysrhythmias, the patient may be a candidate for surgical or electric ablation of an accessory pathway or an abnormally conducting area of the ventricle or for implantation of an automatic implantable cardioverter-defibrillator (AICD). [104] [105] [106]

The development of steerable catheters that can be inserted percutaneously under local anesthesia and directed into cardiac chambers to identify and then electrically ablate accessory pathways has virtually eliminated the surgical treatment of preexcitation dysrhythmias. [107] Occasionally the anesthesiologist is requested to administer sedation for patient comfort and cooperation or to provide brief general anesthesia on an urgent basis in the electrophysiology laboratory for external cardioversion of atrial tachycardia or fibrillation during the ablation procedure done by the cardiologist.

AICD systems (transvenous endocardial leads, epicardial or subcutaneous patches, abdominal subcutaneous implanted generator) may be inserted in an operating room or electrophysiology laboratory by a surgeon or a cardiologist. General anesthesia is required for the insertion (multiple skin incisions and subcutaneous tunneling or thoracotomy) and for functional testing of the leads and generator, a process that involves multiple episodes of inducing ventricular tachycardia/fibrillation and electrical defibrillation. Patients whose dysrhythmias result from ischemia or infarction often undergo CABG and ventricular aneurysmectomy along with the antidysrhythmic procedure through a median sternotomy.

The anesthesiologist's challenges in anesthesia and life support are (1) to avoid precipitation of the dysrhythmias before the electrophysiologic study; (2) to avoid drugs that might interfere with the electrophysiologic study; and (3) to deal with the adverse hemodynamic consequences of the dysrhythmia, chronic antidysrhythmic therapy (e.g., amiodarone [108] [109]), and the operation. The principles underlying anesthesia and life support for patients undergoing these operations are based on common sense, a few laboratory experiments,

and case reports; definitive clinical investigations are lacking because of the obvious difficulties in controlling all the variables affecting the diagnosis and therapy of dysrhythmias. The details of current practices in the limited number of major cardiac surgical centers at which these operations are performed have not been published. A variety of anesthetic drugs have been used without evidence that any one technique is to be preferred. [105]

A few practical points arising from our practices at Emory University Hospital are the following:

1. The preoperative preparation of the patient scheduled for AICD implantation is carried out as for any other patient with the following points in mind. The decision to continue or discontinue chronic antidysrhythmic therapy is left to the cardiologist, who has to balance the risk of spontaneous onset of a dysrhythmia preoperatively against the need to induce the dysrhythmia intraoperatively while testing the AICD system and against the need to program the AICD according to the defibrillation threshold that will exist under the postoperative drug regimen. It is prudent for the anesthesiologist to avoid heavy preoperative sedation that may lead to hypoxemia and hypercarbia, which may precipitate a dysrhythmia.
2. Monitoring of the patient for AICD insertion includes ECG leads best suited to evaluate cardiac rhythm and ischemia, an intra-arterial catheter for systemic blood pressure monitoring on a beat-to-beat basis, and a central venous cannula for rapid injection of drugs into the central circulation. The decision to use a PAC balances its disadvantages against its advantages. A PAC may induce dysrhythmias, may complicate fluoroscopic localization of the transvenous leads, and when it is removed may become entangled and dislodge the leads. Most patients tolerate repeated brief episodes of ventricular fibrillation and defibrillation without substantial deterioration in cardiac function. If the latter should occur, a PAC can be inserted at that time. A PAC is seldom of immediate benefit when resuscitating a patient from ventricular fibrillation or asystole; rather, its value is in adjusting hemodynamic therapy after successful resuscitation. We have found TEE to be a useful monitor during AICD implantation, allowing direct, real-time assessment of cardiac function throughout the procedure.
3. Provisions for postoperative analgesia as well as intraoperative reduction of anesthetic dose requirements may include the preoperative insertion of a thoracic epidural catheter.
4. A choice of general anesthetic technique has not been demonstrated to be critical in the intraoperative testing of the AICD system, although full anesthetic doses of the potent volatile agents have modified fibrillation thresholds and suppressed ventricular tachycardia in animal models. Whether or not low concentrations of the potent volatile anesthetics modify AICD testing significantly remains to be demonstrated. If nitrous oxide is to be used, the risk of pneumothorax has to be recognized when the insertion procedure will not involve a thoracotomy. Also, it is advisable to administer 100 percent oxygen during the induction of ventricular fibrillation in order to maximize the oxygen availability to tissues. In choosing anesthetic drugs, we plan for the recovery of spontaneous ventilation and extubation of the trachea at the end of the operation.
5. Low-impedance conductive gel defibrillation electrodes are routinely applied to the patient's chest and back before the induction of anesthesia to allow synchronous cardioversion or defibrillation to be performed conveniently and quickly during any phase of general anesthesia and the operation. An external cardioverter defibrillator should be immediately available at all times perioperatively, even af-ter completion of the insertion of the AICD system, which is turned off for several days postoperatively to avoidits inappropriate triggering by supraventricular tachycardias common in the immediate postoperative period. The AICD battery has a limited amount of energy (300 shocks), which should not be wasted. The cardiologist should activate and program the AICD device several days postoperatively.
6. The AICD module should be deactivated during periods of electrocauterization, which will trigger it.
7. The avoidance of antidysrhythmic drugs does not preclude the judicious use of a local anesthetic (e.g., 1% procaine or 0.5% lidocaine) to infiltrate the skin before vascular cannulation.
8. Although definitive data to support the practice are lacking, we avoid drugs with anticholinergic (e.g., atropine, pancuronium) or sympathomimetic (e.g., ketamine) properties.
9. Finally, although every effort is made to comply with the guidelines noted, the patient's overall welfare remains the first priority. Fortunately, the anesthesiologist has multiple options in providing comfort for procedures done with local anesthesia or general anesthesia, maintaining vital functions, and limiting the extremes of hemodynamic compromise imposed by the operation.

Thoracic Aortic Aneurysms

The management of patients undergoing surgical repair of certain types of thoracic aortic aneurysms has many similarities to the management of those undergoing cardiac operations. [110] [111] [112] Hypothermic CPB is used, aortic valvular insufficiency may be present, CAD is prevalent, and cardiac function is at risk from the surgical procedure imposed on preexisting disease.

Four major types of problems involving the thoracic aorta are of concern to the anesthesiologist: dissection, aneurysm, traumatic rupture, and coarctation. There are several classification schemes for aortic dissections and aneurysms, but from the point of view of surgical correction there are three major types: (1) ascending aorta with or without aortic valvular involvement (Debakey type II, Stanford type A); (2) ascending aorta and aortic arch (Debakey type I, Stanford type A); (3) descending aorta (i.e., distal to the left subclavian artery; Debakey type III, Stanford type B). The last is discussed in Chapters 48 and 51 .

Monitoring considerations for patients undergoing repair of the ascending aorta with or without aortic valve replacement include placement of the arterial cannula for systemic blood pressure monitoring in the left upper extremity or a lower extremity because of the potential need to cross-clamp the innominate artery. A thermodilution PAC is indicated because of the high risk of impaired ventricular function (LV wall stress, ischemia, aortic insufficiency)

---

and the need to guide blood volume replacement and the use of vasodilators to decrease afterload, limit aortic dissection, reduce tension on aortic suture lines, and reduce bleeding. TEE is useful in identifying the site of intimal tear and the extent of dissection, and in assessing cardiac function. [113] [114] In operations to repair the aortic arch, deep hypothermia (15-18°C) and circulatory arrest are used. The electroencephalogram (EEG) is useful to verify complete suppression of cerebral cortical electrical activity by hypothermia with or without the use of thiopental.

Vascular cannulation for CPB usually involves cannulation of the femoral artery and occasionally the femoral vein before sternotomy, after which more complete venous return can be achieved by cannulation through the right atrium. When aortic valvular insufficiency is present, an LV vent is used.

A number of specific issues require the attention of the anesthesiologist caring for patients undergoing deep hypothermia and circulatory arrest for operations on the aortic arch. [111] In addition to thiopental to produce and maintain EEG burst suppression during cooling and rewarming, it is common practice to administer methylprednisolone, mannitol, and furosemide to limit cerebral edema and to promote diuresis. The use of phenytoin or nimodipine for cerebral protection continues to be investigated. Before reestablishing circulation, the patient should be placed in the deep Trendelenburg position to minimize the risks of cerebral embolization of air and debris. Nitrous oxide is to be avoided because of its expansion of air emboli, which are certain to be present in the arterial circulation. Complete muscular paralysis is used to limit oxygen utilization and to minimize the risk of the gasping response to deep hypothermia. Severe degrees of hyperglycemia should be avoided by omission of dextrose-containing intravenous fluids, intermittent measurement of blood glucose concentrations, and administration of insulin as necessary to maintain serum glucose in the 100 to 250 mg/dL range.

Because of the long periods of time required for rewarming during CPB with heparinization, the loss of blood is very large, and the need for transfusion of red blood cells and coagulation factors is great. In anticipation of the need to replace large volumes of blood rapidly after the completion of CPB, when hemorrhage usually persists for a considerable time, it is wise to insert two large-bore venous cannulas before commencement of the surgical operation. Renal function is at risk for obvious reasons during this type of operation, and renal blood flow should be sustained by adequate volume replacement and the use of mannitol; furosemide and a dopamine infusion may be required to maintain adequate urine flow.

Incidentally, aortic dissection is a relatively rare complication of aortic cannulation for any type of operation involving CPB. [112] It is now common practice to reduce the risk of this complication by deliberately lowering systolic and mean arterial blood pressures with a central intravenous bolus dose of nitroprusside or NTG at the time of aortic cannulation as well as at the time of removal of the aortic cannula. In addition, the surgeon should ask the perfusionist to reduce the arterial inflow from the CPB circuit at times when the aortic cross-clamp is applied and removed.

THE ANESTHETIC PLAN

The anesthesiologist's responsibility to the patient begins with the preoperative visit and extends through the time required for complete recovery from the effects of anesthetic drugs and procedures, including any complications that may be related to anesthesia, monitoring, and intraoperative life-supporting therapy. To prepare for effective and safe management of the patient through the perioperative period, an anesthetic plan should be developed based on a good understanding of the patient and the disease, the operation and surgeon, the anesthetic drugs and procedures, and the personnel and facilities available before, during, and after surgery. What follows is a discussion of the more important aspects of the anesthetic plan.

With the focus on reducing costs by shortening the length of stay in the ICU, the anesthesiologist is encouraged to design an anesthetic plan that not only fulfills the requirements of general anesthesia (i.e., unconsciousness, autonomic, and somatic reflex suppression) during intense noxious stimulation intraoperatively but also allows an appropriately rapid recovery of consciousness and spontaneous ventilation postoperatively. In the uncomplicated case, the goal is to allow tracheal extubation very soon after the patient's condition is stabilized in the ICU, usually within 2 to 4 hours postoperatively. Hence, there is continuing effort to develop rapid-onset, short-acting anesthetics, opioids, hypnotics, and muscle relaxants that allow efficient titration of dose (infusion rate) according to the individual patient's needs both intra- and postoperatively.

Monitoring

Many of the hemodynamic monitoring techniques used by the current well-trained anesthesiologist are invasive and expensive. Their use should be justified by a reasonable cost-benefit analysis that includes the risks of not using them and the costs of using the alternatives. It is wise to indicate in the preoperative note a summary of the anesthetic plan, including monitoring techniques to be used, and to justify the need for any unusual monitors. Such documentation helps the anesthesiologist to focus critically on the patient's problems and presents justification for the risks and expense incurred by the patient.

Essential Monitoring

Essential monitoring for any patient undergoing cardiac surgery includes the procedures discussed below.

Arterial Blood Pressure

Arterial blood pressure (Ch. 30) is monitored continuously and directly by way of an arterial cannula. Sudden changes in blood pressure are encountered routinely during cardiac surgery as a consequence of hemodynamic instability related to the patient's disease, surgical manipulation of the heart and great vessels, marked changes in circulating

blood volume, and frequent use of potent drugs that affect the cardiovascular system. Such monitoring is essential for mean blood pressure measurement while blood flow is nonpulsatile during CPB. The intra-arterial cannula facilitates convenient blood sampling for the laboratory determinations discussed below. A continuous oscillographic display or recording of the arterial pressure waveform provides valuable clues about cardiac contractility, cardiac output, and systemic vascular resistance and gives instantaneous indications of the hemodynamic consequences of dysrhythmias, electrical pacing, artificial ventilation, surgical manipulations, and other interventions.

Electrocardiogram

The ECG (Ch. 32) is monitored continuously, preferably with a properly standardized recorder to capture selected events for precise analysis (e.g., P-R interval, dysrhythmias, ST-T segment changes) and for comparison with earlier and later findings. Changes in rhythm occur at least transiently in every cardiac operation as a result of surgical manipulation and electrolyte, metabolic, and temperature alterations. Moreover, cardiac disease often predisposes the heart to abnormalities of rate and rhythm and to ischemia. Modern monitors can automatically measure and trend ST segment changes in multiple leads and may be configured to alarm if significant ischemic changes are detected. [115] [116] With CAD, two ECG leads usually are observed simultaneously (e.g., V_5 for anterolateral and II or aVf for inferior ischemia). Valvular surgery carries the risk of at least temporary impairment of the cardiac conduction system; diagnosis of conduction problems and monitoring of the effectiveness of pacemaker devices or other therapy require continuous ECG monitoring.

Ventricular Preload

Preload (Ch. 30) , an important determinant of cardiac function, changes dramatically throughout cardiac surgery. Fundamentally, preload is defined as the degree of stretch placed on the myofibrils at end-diastole. Intraoperative assessment of preload may be by direct visual inspection of the heart, filling pressure measurements, and TEE.

The heart is visible throughout most of a cardiac surgical procedure, and a gross estimation of the preload can be made based on its appearance (empty, full, or overdistended). This requires some experience and usually provides information primarily about the preload of the RV, as most of the LV is not visible through a median sternotomy incision.

Ventricular filling pressures are the most common means of assessing preload during cardiac surgery. The CVP directly reflects RV filling and function and is a reasonable, indirect measurement of LV preload in the absence of pulmonary vascular disease and LV dysfunction. The CVP is also useful in the early detection of superior vena cava obstruction by the vena cava cannula draining blood into the CPB reservoir. When there are discrepancies in the functional status of the right and left ventricles (e.g., poor LV function [see Table 49-11]) , it is important to determine the PAOP or the LAP to adjust the LV preload to an optimal level and to detect elevated pressures before they lead to pulmonary edema. A left atrial catheter (inserted by the surgeon) may be used cautiously (avoidance of systemic air emboli) to monitor LAP and to infuse drugs for their systemic effects while minimizing their actions on the pulmonary circulation.

Images of the ventricular chambers obtained by TEE allow measurement of end-diastolic volume, a more direct reflection of preload than end-diastolic pressure. Significant abnormalities and acute changes in ventricular compliance (change in volume as a function of change in pressure) during surgery may cause the filling pressures to be elevated despite inadequate preload. We have found this to be particularly true in cases with concentric hypertrophy of the LV, such as occurs with aortic stenosis. TEE allows this situation to be detected and provides a more accurate assessment of the hemodynamic status than pressure measurements alone.

Cardiac Output

Determinations of cardiac output (Ch. 30) are helpful in the management of patients with impaired ventricular function. Because blood pressure reflects the product of cardiac output and peripheral vascular resistance, cardiac output determinations are the only reliable means of rapidly assessing overall cardiac performance. This is usually done by the thermodilution technique with a PAC containing a thermistor, but it may also be accomplished by a PAC with continuous RV cardiac output measurement capability, and in a qualitative manner with TEE. Normal or elevated blood pressure may be found in the presence of inadequate cardiac output and compensating vasoconstriction. The inadequacy of tissue perfusion will eventually appear as failure of organ function, which is the cause of long-term morbidity and mortality. With estimates of cardiac output and peripheral vascular resistance, drug therapy can be directed effectively and safely to improve cardiac output and tissue perfusion.

Urine Output

Measurements of urine output (Ch. 34) are helpful in adjusting fluid balance. The volume and quality of urine (e.g., specific gravity) are good indicators of the adequacy of renal function. Renal function is closely linked to renal perfusion, which may be altered during cardiac operations by extracorporeal circulation, variations in cardiac output, cardiovascular drug therapy, and many other factors. Radiocontrast media used in preoperative radiographic studies and hemolysis during CPB pose direct threats to renal integrity. Preservation of renal function is essential for long-term survival. Furosemide and dopamine (low-dose rate) may be needed to improve renal blood flow, sustain diuresis, and promote the excretion of excess potassium and edema fluid.

Body Temperature

Body temperature (Ch. 37) should be monitored for any patient undergoing general anesthesia and surgery in which

the risks of hypothermia and malignant hyperthermia are substantial. A special indication exists when extracorporeal circulation is used with or without deliberate hypothermia. The temperature of the central circulation is commonly monitored with a nasopharyngeal or esophageal probe or by using the thermistor in the PAC. Either the rectal or urinary bladder temperature should be monitored, and finger or toe temperature should be estimated by palpation or actual measurement to determine the temperature gradients that exist between the body's central core and peripheral tissues; such gradients should be estimated to evaluate the completeness of rewarming during CPB after hypothermia. A large gradient indicates the likelihood of recooling after discontinuation of CPB as heat moves down its gradient from central to more peripheral tissues. It is important to avoid hyperthermia, which increases the risk of ischemia due to increased metabolic rate, especially in the CNS and heart. Limiting the temperature of blood entering the aorta to 38°C and monitoring nasopharyngeal temperature, which should remain below 38°C, is essential to reduce the incidence of CNS injury. [117]

Esophageal Stethoscope

An esophageal stethoscope can be inserted to evaluate heart and breath sounds (i.e., to detect bronchospasm, pulmonary edema, etc.). Modifications of the esophageal stethoscope include the incorporation of a thermistor to measure core temperature, two electrical leads to facilitate the recording of the ECG, and possibly two electrodes to enable transesophageal cardiac pacing. An esophageal stethoscope provides valuable information, especially if the electronic monitoring device fails during transfer of the patient from the operating room to the ICU (i.e., breath sounds, heart rate, rhythm, contractility). The anesthesiologist must remember to remove it once the ICU monitoring protocol is established.

It is our practice to insert an oro- or nasogastric tube after tracheal intubation and before placement of an esophageal stethoscope to remove any gastric air and fluid that may accumulate during surgery. A nasogastric tube is better tolerated than an oral tube, but the nasal approach is avoided in patients with abnormal coagulation preoperatively and abandoned if nasal obstruction is encountered. With normal coagulation, any bleeding produced by insertion of a nasogastric tube usually has time to stop before administration of heparin before CPB. Removal of gastric air and fluid improves TEE images, reduces the risk of tracheal aspiration, removes gastric distention as a potential cause of decreased pulmonary compliance, and seems to reduce patient discomfort (e.g., gastric distention, hiccupping, nausea, abdominal cramping) in the postoperative period.

Blood Gas Analysis

Blood gas (Ch. 38) and serum potassium analyses are essential for precise adjustments of artificial ventilation and gas flows in the CPB circuit oxygenator. Devices are available that can continuously monitor on a real time basis blood gas tensions, oxygen saturation of hemoglobin, and hematocrit in the blood passing through the bypass circuit. Determinations of mixed venous oxygen tension (or hemoglobin oxygen saturation) and acid-base balance are helpful in evaluating the adequacy of peripheral perfusion and detecting excessive oxygen consumption (e.g., by skeletal muscle shivering during hypothermia).

Coagulation Analysis

Measurement of anticoagulant activity is essential in the management of CPB to verify the adequacy of heparinization and to minimize the risks of thrombosis, embolism, and the one absolutely fatal complication of CPB, namely, clotting of the extracorporeal and intravascular blood volume. Such measurements are also needed to verify the adequacy of heparin antagonism by protamine to minimize postoperative hemorrhage. Tests of coagulability are important, because patients vary considerably in their response to the initial dose of heparin as well as in their rate of elimination of heparin under hypothermic and normothermic conditions. The activated clotting time (ACT) [118] and a heparin assay (Hepcon) [119] are usually used intraoperatively. Rapid access to laboratory analysis of coagulation should be available for the diagnosis and management of post-bypass coagulopathy. Thromboelastography has been used to assess coagulation during cardiac surgery, [120] but its exact role and usefulness remain to be defined. [121] [122] It should be remembered that aprotinin can prolong the ACT when done with celite-containing tubes; the use of kaolin-containing tubes for ACT determinations minimizes the problem, but some recommend the administration of additional heparin doses every 2 hours in patients receiving aprotinin.

Specialized Monitoring

Specialized monitoring is indicated under certain circumstances in some patients undergoing cardiac surgery.

Echocardiography

Echocardiography (Ch. 31) , [123] [124] [125] especially two-dimensional, can provide direct images of the anatomy and function of the heart and its surrounding structures, including the aorta and pericardium. Anatomic and pathologic landmarks are relatively easy to recognize when displayed on a video screen in real time or on a videotape recording. The addition of contrast (microbubbles of air) or use of Doppler techniques (especially color mapping) facilitates recognition of the direction and velocity of blood flow within the cardiovascular system. In the operating room, the anesthesiologist is able to use TEE for continuous monitoring of cardiac function and diagnosis of abnormalities. With views of all four cardiac chambers, the ascending aorta, aortic arch, and descending thoracic aorta, and the pericardium, it is relatively easy to obtain qualitative and semiquantitative information about chamber filling and contractility, intracardiac shunting, valvular function, air emboli, aortic dissection, and blood flow velocity. Such information can be useful in detecting myocardial ischemia as segmental wall motion and

wall thickening abnormalities or as papillary muscle dysfunction, indicating the need for further surgical revascularization, assessing valvular repair or replacement, and guiding medical therapy (e.g., balancing inotropic and vasodilator therapy with intravascular volume replacement). Because ventricular compliance and contractility may change frequently and dramatically in the perioperative period, it is not surprising that marked changes in ventricular filling and contraction may be

seen without proportionally dramatic changes in blood pressures (systemic arterial blood pressure, PAOP, CVP). On-line evaluation of valvular function, intracardiac shunts, coronary perfusion, pericardial constriction, and aortic dissection allows the surgeon to judge the adequacy of the operation (e.g., valvuloplasty) or to identify the need for modification of the surgical plan (e.g., valve replacement) immediately after CPB, with obvious benefits to the patient and savings in time and costs. In some cases, two-dimensional TEE with color Doppler has aided in the intraoperative recognition of a previously undiagnosed problem and allowed definitive correction along with the planned operation. The device is expensive, but its judicious use should create sufficient savings in hospital costs to justify its purchase for a busy cardiac surgical program. A committee made up of representatives of the Society of Cardiovascular Anesthesiologists and the American Society of Anesthesiologists has published guidelines for training and experience of those using TEE for diagnosis in addition to monitoring.

Serum Electrolyte and Glucose Determinations

Serum electrolyte and glucose determinations are indicated in patients with diabetes mellitus and those suspected of hypokalemia (e.g., preoperative use of diuretics). They are also essential for the safe intraoperative use of digitalis glycosides and glucose-insulin-potassium infusions. [126] Hyperkalemia occurs as a result of hyperkalemic cardioplegia and excessively rapid repletion of potassium; hypokalemia may exist preoperatively and is exacerbated by diuresis during CPB. Measurement of serum magnesium is not routine in the operating room, but recognition of hypomagnesemia as a factor contributing to dysrhythmias, especially in patients treated with digitalis, has led to the administration of intravenous doses (2-4 g, 4-8 mEq) to patients with problematic dysrhythmias in the operating room and ICU. Magnesium administration immediately after CPB has been shown to decrease ventricular dysrhythmias and to increase cardiac index. [127] It seems reasonable to expect such therapy to be guided by knowledge of serum magnesium concentrations. [128] [129] Occasionally low ionized calcium concentration may contribute to poor ventricular contractility and coagulopathy. [130]

The body's stress responses to surgery and CPB are usually manifest by increasing blood glucose concentrations after CPB. Catecholamine infusions also produce insulin resistance and hyperglycemia. In diabetic patients and in patients managed with normothermic CPB and cardioplegia, serum glucose may exceed 300 mg/dL and metabolic acidosis and hypokalemia may develop. In insulin-dependent diabetics, perhaps all diabetics, it is prudent to infuse regular insulin at 2 to 5 U/h from the very beginning of the operation and to add intravenous bolus doses as needed to control hyperglycemia and to maintain normal acid-base and electrolyte balance. Hypoglycemia rarely occurs; if it does, it is easily corrected by administration of glucose, 10 to 20 g IV, while continuing the insulin infusion at a lower rate. Measurements of serum glucose on an hourly basis are usually sufficient to monitor this therapy.

Cerebral Monitoring

EEG monitoring (Ch. 35) has been used during cardiac surgery since its early years, primarily in an attempt to detect and modify events leading to postoperative neurologic injury. Modern devices are available that process the raw EEG signal into an easily interpretable, graphic display, making the technology generally accessible. However, significant controversy remains about the practical benefits of monitoring the EEG during heart surgery, [131] [132] except to ensure electric silence of the brain during deep hypothermia with total circulatory arrest and during the use of cerebral protective doses of barbiturates. [133] [134]

New forms of neurologic monitoring such as transcranial Doppler [135] and transcranial oximetry [136] require further evaluation before their roles in cardiac surgery can be defined.

Controversial Topics

Controversy exists in relation to two aspects of hemodynamic monitoring: costs versus benefits and establishment of invasive monitoring before or after induction of anesthesia.

A cost-benefit analysis is difficult to obtain and so must be decided individually. The benefits of monitoring are cited above, and the potential complications are summarized in Chapters 28 to 38 . Economic costs are substantial and have to be included in the overall evaluation of each device and procedure. It is also necessary to estimate the costs of not using a particular technique or device. Not only do "cheaper" alternatives have some intrinsic costs, but they may be less useful in some situations, often those occurring suddenly and unexpectedly. It does not require many improperly diagnosed and treated conditions that extend the duration of intensive care or cost patient lives to wipe out the savings of not using a monitoring technique that could have warned of the adverse trend and allowed prevention of the complication, or at least facilitated the correct diagnosis and choice of therapy.

Although many centers advocate routine placement of PACs in most cardiac surgical patients, studies have failed to demonstrate consistent benefits in their routine use over central venous catheters and some have suggested that PACs per se are associated with increased morbidity, unnecessary therapy, and mortality. [137] PACs allow the measurement of left-sided cardiac filling pressures, mixed venous oxygen saturation, and thermodilution cardiac output, which taken together, provide a more complete evaluation of a patient's hemodynamic status and may lead to modification of therapy in about half the patients in an ICU setting. [138] The American Society of Anesthesiologists has published guidelines

regarding the use of PACs and recommends considering (1) the health status of the patient, (2) the type of surgical procedure, and (3) the characteristics of the practice setting in deciding whether to use a PAC. [139] Clearly, further controlled studies evaluating outcomes are needed to shed light on this complex topic. Our current approach in many patients is to insert an introducer sheath with a single lumen catheter into a central vein, allowing continuous infusion of fluids while monitoring CVP. If unexpected problems develop during the case, the single lumen catheter may be easily exchanged for a PAC.

Whether invasive monitoring should be established before or after the induction of anesthesia has been debated with respect to insertion of central venous and PA catheters and perhaps cannulation of peripheral arteries. These procedures are considered to be a source of stress and risk because of pain, uncomfortable positioning, and distraction of anesthesia personnel from monitoring ventilation and other vital signs while inserting the cannulas. [140] Conversely, induction of anesthesia is a period of instability in multiple organ systems and is frequently associated with stressful conditions. An untoward event is more readily detected and properly treated if data from the monitoring devices are immediately available. [137] [141] Stress from anxiety and discomfort can be reduced or eliminated by careful patient instruction preoperatively, judicious use of sedative and analgesic drugs before the patient enters the operating room, and supplementation as needed after an intravenous fluid infusion is established. [142]

In a life-threatening emergency situation in which survival of the patient's heart and nervous system is dependent on establishing extracorporeal circulation as rapidly as possible, there is no doubt that only basic monitoring of blood pressure, ECG, and ventilation (oximetry and exhaled carbon dioxide) are necessary to begin anesthesia and surgery. Sophisticated monitoring and vascular cannulation can be accomplished after CPB is established. If necessary, the surgeons can insert intravenous and arterial cannulas (e.g., in femoral vessels) with sterile tubing passed off the sterile field to the anesthesiologist. Left and right atrial cannulas can be inserted by the surgeon to measure filling pressures, and a TEE probe can be inserted by the anesthesiologist to evaluate cardiac contractility and filling. Once the patient is stabilized after CPB or after the operation, a PAC can be inserted via a jugular or subclavian vein. Hence, multiple options are available to meet monitoring needs, which should not delay the measures essential to the patient's survival in the best possible condition.

Premedication

The cardiac anesthesiologist uses drugs acting on the CNS to allay anxiety, produce amnesia, and minimize pain associated with vascular cannulation in the preanesthetic period without producing dangerous degrees of ventilatory or cardiac depression. These objectives are no different from those for any type of patient or surgery, but the choice of drugs and especially the doses prescribed are affected by the nature of the cardiac disease, the coexistence of lung and other diseases, chronic drug therapy, and the type of anesthesia planned for cardiac surgery.

Patients with CAD, adequate LV function at rest, and no pulmonary insufficiency are generally premedicated heavily with an opioid and any one of many sedative-hypnotic-tranquilizer-type drugs. A typical inexpensive prescription might read as follows:

Diazepam, 0.1 to 0.2 mg/kg, orally with a sip of water 1 to 2 hours before transfer to the operating room

Morphine, 0.1 mg/kg, intramuscularly ½ hour before transfer.

Another approach involves lorazepam 25 to 50 mug/kg PO 1 to 2 hours before transfer to the OR and intravenous doses of fentanyl 0.5 to 1 mug/kg administered by the anesthetist according to the patient's needs after the first IV cannula is inserted.

This premedication also provides amnesia (diazepam), which may be desirable intraoperatively when light levels of anesthesia can be associated with awareness. [143] [144] [145] [146] [147] The use of relatively larger doses of long-acting drugs is indicated by anticipation of a long duration of operation. Even if tracheal extubation soon after surgery is planned, the continuing effects of these premedicant drugs are beneficial. The cardiac depressant effects of this prescription are minimal or nil. Respiratory depression is generally within acceptable limits, but close observation of the patient and occasional encouragement to take a deep breath may help counteract the development of atelectasis and hypercarbia. It may be beneficial for the patient to breathe oxygen-enriched air (by nasal prongs or face mask) during preparation for anesthesia and surgery.

For patients with valvular heart disease and especially those with impaired ventricular function at rest and minimal cardiac reserve, lesser amounts of preanesthetic medication are usually sufficient, and heavy premedication may be dangerous. Some patients with limited cardiac output may be more susceptible to depressant drugs and at greater risk when even mild ventilatory depression is superimposed on their compromised cardiopulmonary function. A typical prescription might include only intramuscular morphine (0.05-0.08 mg/kg) with or without scopolamine (0.002- 0.003 mg/kg) 1 hour or less before surgery. Although scopolamine has sedative, amnesic, and antiemetic actions (especially advantageous in combination with an opioid) some clinicians prefer to avoid scopolamine because of its intense antisialagogue action, which makes some patients very uncomfortable, and because of its potential to cause prolonged postoperative confusion, especially in the elderly. If the degree of sedation proves inadequate, supplemental drugs can be administered intravenously while the patient is under constant observation by the anesthesiologist.

In addition to drugs acting on the CNS, the anesthesiologist should consider the benefits (and risks) to the patient of including in the premedication scheme drugs affecting other organ systems. Patients with CAD, especially those with unstable angina and good ventricular function, may have less risk of myocardial ischemia if a dose of a beta-adrenergic receptor blocker is administered orally 1 to 2 hours before surgery. It tends to suppress tachycardia, hypertension, and dysrhythmias before CPB. Moderate doses of propranolol administered up to that time do not complicate the discontinuation of extracorporeal circulation. [14] Therapeutic and prophylactic NTG should be continued until and perhaps beyond the induction of anesthesia, and supplemental

doses (e.g., sublingual or intravenous) should be at hand to treat symptoms and signs of ischemia.

Continuation of therapy with calcium channel blocking drugs up to the time of surgery is controversial. Controlled clinical investigations of this issue are still incomplete, and one study has demonstrated no benefit of either nifedipine or diltiazem in the prevention of perioperative ischemia. [13] [147] However, intravenous infusion of nifedipine decreased the incidence of ischemia and myocardial infarction in patients undergoing CABG operations. [148] We believe that it is preferable to continue such therapy up to the time of surgery, including an oral dose on the morning of the cardiac or noncardiac operation, for the following reasons:

1. If the calcium channel blocking therapy has been successful in controlling angina pectoris, hypertension, or dysrhythmias, these benefits should be continued into the operative period when the patient is exposed to stresses that can be expected to provoke myocardial ischemia, hypertension, and dysrhythmias.
2. Knowledge of the principal side effects of the calcium channel blockers (e.g., reduced systemic vascular resistance, atrioventricular conduction block) and their interactions with anesthetic and cardiovascular drugs allows the anesthesiologist to treat untoward effects should they occur. [16] [149] [150]
3. In the management of patients for emergency aortocoronary surgery who have just received unusually large doses of nifedipine in an attempt to dilate coronary arteries after an angioplasty complication, we have noted the need for larger than usual doses of vasopressors but no qualitative difference in responses to such therapy. [151]

It may be beneficial to order the first daily dose of other drugs taken routinely by the patient. This is especially true when the surgery is scheduled for late morning or afternoon. Such medications may include adrenergic receptor and calcium channel blockers, as well as long-acting nitrates, certain antihypertensive drugs, and possibly antidysrhythmic agents, including digoxin in the patient with a normal or elevated heart rate who is at risk from a rapid ventricular response to atrial dysrhythmias (see Table 49-7) . This practice must be individualized, with a complete understanding of the patient's cardiovascular status and knowledge of drug toxicity and interactions, and it should be accompanied by precise communications between the anesthesiologist and other persons caring for the patient.

Clonidine, an alpha$_2$ -adrenergic agonist, is an antihypertensive medication that has received a great deal of attention for its ability to improve hemodynamics and decrease anesthetic requirements in a number of clinical settings. [152] Premedication of CABG patients with clonidine has been suggested by Flacke et al [153] as a means of reducing opioid dosage and shortening the period of postoperative mechanical ventilation. Other authors have not seen the same benefits and have noted problems with low systemic vascular resistance, requiring vasopressor support postoperatively in patients premedicated with clonidine. [154] Further study of this issue is warranted.

The ACEIs are thought to be responsible, at least in part, for the low blood pressure and its refractoriness to vasopressors during CPB. Because the ACEIs are long lasting, omitting them on the day of surgery is appropriate, but the patient may still require large doses of phenylephrine (0.5-1 mg) or norepinephrine to treat hypotension intraoperatively.

Other common problems that can benefit from appropriate preanesthetic medication are peptic ulcer and esophageal reflux. The combined administration of oral antacids and antisecretory drugs (e.g., cimetidine and glycopyrrolate) can prevent symptoms and minimize mucosal damage in the perioperative period. Patients with narrow-angle glaucoma should instill pilocarpine or their usual eye drops the morning of surgery, and additional doses should be administered according to the usual schedule throughout the perioperative period. The use of systemic anticholinergic drugs is not contraindicated in glaucoma if topical miotic therapy is continued.

The management of insulin-dependent diabetes mellitus is controversial in practice but obviously essential for the patient. [155] This is a particularly important and sometimes challenging task in the overall management of the patient undergoing hypothermic CPB. The most important aspect of any routine is the monitoring of serum glucose throughout the perioperative period to maintain serum concentrations between 100 and 250 mg/dL. [156] The sympathetic-endocrine stress responses to CPB and the administration of sympathomimetic inotropes produce resistance to insulin and can lead to marked hyperglycemia, especially if intravenous fluids contain glucose. High intravenous bolus doses and infusion rates of insulin may be required to lower serum glucose concentrations to acceptable levels and prevent the consequences of severe hyperglycemia (e.g., excessive diuresis, hyperosmolar coma, exacerbation of ischemic insult to the CNS). As a matter of routine, we infuse regular insulin 2 to 5 U/h in diabetic patients (insulin-dependent or not) from the beginning of the operation, monitor serum glucose hourly, administer 10 to 20 g glucose if the serum level falls below 100 mg/dL (a very rare occurrence), and adjust the insulin infusion rate upward with the addition of intravenous bolus doses of 10 to 20 units of regular insulin as necessary after CPB so as to maintain serum glucose in the range of 100 to 200 mg/dL.

Anesthesia Induction and Maintenance

For convenience, the usual preparations for management of a patient undergoing cardiac surgery are summarized in Table 49-15 . Only certain aspects of the preparations are discussed here; more comprehensive treatises should be consulted for details.

Good Versus Poor Cardiac Performance

Patients can be divided into two groups based on their cardiac performance at rest without acute therapeutic support. Those with an ejection fraction greater than 0.5, a normal cardiac index (2.5 L/min/m^2), a normal stroke volume index (40-60 mL/beats/m^2), and no preoperative evidence of abnormal ventricular function can be considered to have good cardiac performance. Those with an ejection fraction less

TABLE 49-15 -- Checklist of Special Preparations by Anesthesiologist for Managing Patients Scheduled for Cardiac Surgery

CATEGORY	SPECIAL CONSIDERATIONS
Airway management	Soft cuffed endotracheal tube for potentially prolonged intubation
Monitors	Arterial cannula for pulse pressure tracing and blood sampling
	Central venous cannula for pressure measurement and drug administration
	Pulmonary artery (Swan-Ganz) catheter for pressure measurements (PAP, PAOP), cardiac output determinations by thermodilution, and sampling of mixed venous blood; special catheters for specific indications (e.g., cardiac pacing, diagnosis of atrial and ventricular dysrhythmias, continuous oximetry, right ventricular ejection fraction)
	Electrocardiogram with multiple lead selection (i.e., to facilitate diagnosis of arrhythmias and ischemia)
	Transesophageal echocardiogram (if indicated)
Anesthetic drugs	Ready availability of drugs to supplement or to substitute for primary anesthetic choice
Cardiovascular drugs	Ready availability of drugs to treat
	Rate and rhythm disturbances
	Hypo- and hypertensive episodes
	Cardiac failure and metabolic acidosis
	Myocardial ischemia, decreased ventricular compliance
	Pulmonary hypertension
	Oliguria
	Hypo- and hyperkalemia
Other drugs	Heparin and protamine, epsilon-aminocaproic acid (Amicar), desmopressin (DDAVP), antibiotics, steroids
Blood products	Cell saver available to process shed blood
	Packed red blood cells
	5% albumin or hetastarch
	Coagulation factors (platelets, fresh frozen plasma, cryoprecipitate)

PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure

than 0.3 or a low cardiac index (<2.0 L/min/m^2 with normal or elevated ventricular preload) because of either abnormal ventricular contractility or mechanical abnormalities (e.g., valvular heart disease) are characterized as having poor cardiac performance. In addition to ejection fraction and cardiac index, it is important to consider the type of cardiac disease, their response to stress, and the presence of other disease processes (such as hypertension) affecting cardiac function. It may be helpful to determine cardiac index, stroke index, and other hemodynamic variables in the operating room before inducing anesthesia to devise the anesthetic plan most appropriate for that particular patient. This determination is especially needed when evaluation of the cardiovascular status is incomplete, uncertain, or remote in time.

Regional wall motion abnormalities (e.g., hypokinesis) may not be evident in such global measures as ejection fraction, cardiac output, and stroke volume; yet they may be clinically important and become manifest when additional work is demanded of the heart. Regional dysfunction may be detected by transthoracic (before anesthesia) or transesophageal (after induction of anesthesia) two-dimensional echocardiography. [123] [124] [157] [158]

An important principle to remember is that the hemodynamic responses to most anesthetic drugs are dose-related. Hence a drug that may be unsatisfactory when used as the primary anesthetic may nevertheless serve a useful role as a supplemental drug. For example, a full anesthetic dose of isoflurane (1-3 volume %) may be unacceptable because of its depression of cardiac performance, but supplemental concentrations (0.25-0.5 volume %) may be useful in limiting responses to noxious stimulation (e.g., tracheal intubation and skin incision). In any case, it behooves the anesthesiologist to remain flexible and to be prepared to change the anesthetic drugs should the responses to the initial selections prove unsatisfactory.

If the characteristics of the specific disease are known and the hemodynamic status of the particular patient has been determined, any one of a combination of anesthetic drugs can be selected on the basis of both their anesthetic properties and their hemodynamic effects. Summaries of the hemodynamic actions of anesthetic drugs are found in Chapters 6 and 8 to 10 . A somewhat simplified approach to the choice of anesthetic drugs is to consider the use of a potent inhaled anesthetic (e.g., isoflurane) versus an opioid (e.g., fentanyl). It is most often true in clinical practice that a combination of inhaled and intravenous drugs is used (see later). It also is a common but often unnecessary (and sometimes unwise [143] [144] [145]) practice to use fully paralyzing doses of muscle relaxants throughout the operation regardless of the choice of primary anesthetic.

Potent Inhaled Anesthetics

Potent inhaled anesthetics (Chs. 4 and 5) such as halothane or isoflurane may be used as primary anesthetics in patients with good cardiac performance. Desflurane and sevoflurane, new potent inhaled anesthetics with very rapid onset and rapid recovery, have been used for cardiac surgery and appear to have hemodynamic effects similar to those of isoflurane. [159] The volatile anesthetics are especially useful in patients with CAD and normal ventricular function. Their advantages include the ability to fulfill all the objectives of anesthesia: unconsciousness and muscular relaxation, rapid recovery of ventilatory function so that tracheal extubation can be accomplished early in the postoperative period, and

dose-related decreases in ventricular work and oxygen consumption. [160] Their principal disadvantages are their limited ability to provide suppression of reflex responses (e.g., sympathetic, airway) to noxious stimulation (but this is easily managed by their supplementation with moderate doses of an opioid), excessive cardiovascular depression under some conditions, lack of analgesia in subanesthetic concentrations during the recovery phase, and postoperative shivering and increased oxygen demand due to heat loss exaggerated by peripheral vasodilation in the exposed patient. [161]

Isoflurane has come under scrutiny because of the demonstration of its association with coronary artery steal under certain conditions. [61] [62] [63] [64] [65] [66] In the presence of a critical coronary artery stenosis, isoflurane dilates normal coronary arterioles and lowers overall coronary perfusion pressure with the consequences that flow through normal arteries increases and flow through stenotic arteries and their distal arterioles is reduced (steal phenomenon). Becker [162] has concluded that isoflurane should be avoided in patients with coronary artery stenosis as well as in any patient at risk for CAD (virtually everyone over 50 years of age in industrialized societies). This recommendation is extreme and unreasonable for several reasons. [63] First, the phenomenon of coronary steal has not been demonstrated under typical clinical conditions, and isoflurane has even been shown to protect against ischemia induced by electrical pacing in patients with coronary stenosis. [163] Second, isoflurane is seldom used alone at high concentrations for general anesthesia in patients with cardiovascular disease. Third, isoflurane can be used to advantage as a supplement to other anesthetic agents (e.g., nitrous oxide, opioids) to suppress undesirable sympathetic and hemodynamic responses to noxious stimuli and to compensate for the deficiencies of the other anesthetics. [64] Fourth, there is no evidence of different outcomes for coronary revascularization operations in patients anesthetized primarily with isoflurane, enflurane, halothane, or sufentanil. [54] Finally, isoflurane has certain unique pharmacologic properties that may be beneficial to

some patients. At the moment, the judicious approach is not to abandon the use of isoflurane but to take advantage of its benefits and limit the dosage.

It is a common practice to administer an opioid or other drug, either as part of preanesthetic medication or intraoperatively, to reduce the concentration of an inhaled anesthetic that is required to produce a satisfactory depth of anesthesia and thereby to minimize the incidence and intensity of side effects from the inhaled anesthetic. In turn, the potent inhaled anesthetics are useful as supplemental agents to provide unconsciousness in the patient receiving primarily opioids for anesthesia, to increase anesthetic depth temporarily in anticipation of strong noxious stimulation, and to control hypertension and tachycardia.

Our experience suggests that most cardiac patients tolerate potent inhalation anesthesia well, even those with moderate impairment of ventricular function. By placing a vaporizer in the gas circuit of the CPB machine, these drugs may also be used to maintain anesthesia during bypass.

Opioids

Opioids (Ch. 10) have become the anesthetic mainstay for patients with impaired cardiac performance. Their characteristics

TABLE 49-16 -- Opioid Anesthesia for Cardiac Surgery[a]

Advantages
Absence of direct effects on heart; no change in
Contractility
Automaticity (but vagal activity)
Conduction
Sensitivity to catecholamines
No interference with autonomic or cardiovascular drug actions
Preservation of blood flow autoregulation in CNS, heart, kidneys
Few moment-to-moment adjustments required
Easily supplemented with intravenous hypnotic and inhaled anesthetics
Increased patient tolerance of endotracheal tube and airway manipulation (e.g., suctioning, nasogastric tube)
Postoperative analgesia
No organ toxicity
Disadvantages
Bradycardia and hypotension during induction, especially when combined with any hypnotic
Muscular rigidity during induction and sometimes during emergence
Awareness may go unrecognized if patient is totally paralyzed; recall of intraoperative events may occur without concurrent administration of an amnesic drug
Prolonged recovery time, especially for spontaneous ventilation (can be minimized by careful titration of dosage of opioid and other CNS depressants to the needs of the individual patient)

[a] Also see Chapter 10 .

are summarized in Table 49-16 . With the exception of meperidine (and possibly its congeners, anileridine and alphaprodine), the opioids are noted for their lack of direct cardiac depressant effects. They have actions that indirectly influence cardiac performance: bradycardia mediated by the vagus nerves; arterial and venous dilation as a result of selective suppression of sympathetic reflexes (e.g., orthostatic hypotension); and in the case of morphine, meperidine, and some of their congeners, histamine release. These indirect actions can be prevented or treated readily and do not contraindicate the use of large doses of opioids for anesthetic purposes. The indirect effects can be prevented or treated: anticholinergic drugs (e.g., atropine, glycopyrrolate) can prevent or antagonize bradycardia; only minor hypotension is seen in a normovolemic patient maintained in the supine position and given an opioid intravenously at a slow rate (e.g., morphine at 5 mg/min in the adult); and the hemodynamic consequences of histamine release can be prevented by pretreatment with a combination of histamine $_1$ and histamine$_2$ receptor blocking drugs. [164] Furthermore, hypotension responds to a legs-up position, intravenous infusion of fluids, and if necessary, a vasoconstrictor such as phenyl-ephrine; ephedrine is indicated for hypotension related to vasodilation and bradycardia.

Currently, fentanyl is the most commonly used opioid; used alone in very large doses (20-50 mug/kg to start plus 2-3 mug/min), it can produce profound analgesia, sleep, and usually unconsciousness (see later). Equivalently large doses of morphine, meperidine, and most other currently available opioids are usually avoided because of their side effects in such large doses. However, moderate doses of morphine (0.5-3 mg/kg) and its congeners are useful for anesthetic purposes in chronically ill patients [165] or when combined with a hypnotic or volatile anesthetic. Among the major disadvantages of the opioids are the following:

1. With the exception of remifentanil, [166] a new and very short-acting fentanyl derivative hydrolyzed by tissue esterases, the elimination of opioids from the body is relatively slow, and consequently, the times for recovery of consciousness and spontaneous ventilation can be prolonged after large doses. [167] Prolonged recovery is not a problem and may even be an advantage when mechanical support of ventilation is to be continued into the postoperative period for several hours or overnight. The use of opioid antagonists can be hazardous, especially in patients with cardiovascular disease. [168] [169]
2. Opioids can induce both apnea and skeletal muscular rigidity that impedes positive-pressure ventilation. If the patient has been breathing pure oxygen before and during the induction of anesthesia, there is no need to panic if rigidity prevents positive-pressure ventilation. First of all, when the lungs are filled with oxygen, apneic oxygenation is effective in preventing desaturation of oxyhemoglobin for a much longer time than will be required to relieve the rigidity. Also, the rise in carbon dioxide tension will be moderate over a few minutes' time and is tolerated without incident by most patients. Of course, it is prudent to correct the hypercarbia and the associated hemodynamic changes (systemic hypotension and elevated PA pressure) promptly upon relieving the rigidity. Second, attempts to force positive-pressure ventilation of the patient with markedly decreased thoracic compliance will further embarrass cardiovascular function by increasing intrathoracic pressure, which impedes the venous return of blood and creates a tamponade-like condition for the heart. Rigidity can be relieved within 1 to 2 minutes by a fully paralyzing dose of a muscle relaxant administered intravenously.

Rigidity can occur during the induction of anesthesia and also during emergence. [170] [171] In our opinion, the rigidity represents a phenomenon of disinhibition occurring at the threshold for unconsciousness. The intensity of rigidity is probably reduced by treatment with a small dose of a muscle relaxant and can be relieved by a paralyzing dose of muscle relaxant (or by naloxone, which is inappropriate in most cases). The manifestations of rigidity are varied and in some instances may be thought to represent seizures. There are substantial data to speak against the production of seizures even by the highest doses of fentanyl used for anesthetic purposes in humans. [172] (It is true that seizures are produced by extremely high doses of opioids in rodents.)

TABLE 49-17 -- Signs of Inadequate Anesthesia

Somatic (obscured by relaxants)
Movement, especially in association with noxious stimulation [a]
Coughing, bucking on endotracheal tube
Increased electromyographic activity

Hemodynamic (obscured by cardiovascular disease and drug therapy)	
Increase in blood pressure, especially a sudden increase in association with noxious stimulation	
Increase in heart rate (less common than increase in blood pressure)	
Other sympathetic signs	
Sweating	
Tearing	
Mydriasis (requires careful observation and interpretation in presence of drugs affecting autonomic nervous system)	
Endocrine (not measurable on-line)	
Increased release of stress-related hormones	
Electrical activity of CNS	
Arousal patterns in electroencephalogram	
Recovery of evoked potentials (e.g., auditory)	

[a] Very intense noxious stimuli include tracheal intubation and subsequent manipulation of the endotracheal tube, skin incision, sternotomy, electrocauterization of skin and especially periosteum, and movement of the patient (e.g., transfer from operating table to bed).

1. Awakening of the patient, especially in response to intense noxious stimulation, can occur during the operation, despite administration of the usual dose at the induction of anesthesia. [144] [145] [146] In most cases, the recovery of consciousness can be related to the decline of drug concentration to less than that required to maintain unconsciousness in the particular patient under the particular conditions or intensity of stimulation. [173] The possibility of awakening is of great concern because (1) the paralyzed patient cannot exhibit somatic signs of inadequate anesthesia [144] and (2) autonomic and hemodynamic responses are not reliable indicators of the patient's awakening. [144] [145] [174] [175] A reliable guide to anesthetic depth in the paralyzed patient is needed; special processing of the EEG is being investigated as a possibility (Ch. 29) , but as yet, its reliability remains to be demonstrated. [176] The anesthesiologist can minimize the possibility of awareness by (1) administering sufficient preanesthetic medication [146] or intraoperative anesthetic supplement (e.g., benzodiazepine), (2) titrating the induction dose to effect and then maintaining the drug concentrations by infusion or less efficiently by intermittent injections, [173] [177] [178] (3) using muscle relaxants only when necessary and then only in the minimum required doses, and (4) remaining acutely aware of all signs of inadequate anesthesia (Table 49-17) .

Is the administration of an amnesic drug (e.g., benzodiazepine, scopolamine) to induce lack of recall of intraoperative events a satisfactory solution to the problem of intraoperative awareness? In our view, it is not for several reasons. First of all, if the patient and the anesthesiologist agree on general anesthesia, then the anesthesiologist is obligated by the verbal contract with the patient to produce and to maintain unconsciousness for the duration of the operation. Second, even though the patient experiences no pain because of the analgesic efficacy of the opioid, awakening in a paralyzed state during the operation is a frightful experience because the patient cannot communicate anxiety or escape from the situation. Whether or not the awakening is recalled later, the patient experiences the anxiety and fright at the time of awakening. Finally, there are indications that intraoperative awakening can lead to sleep disturbances, anxiety attacks, and other undesirable consequences in the postoperative period even when the patient does not recall the episode. [143] [145]

Hypnotics and Tranquilizers

Because of the inability of opioids to produce unconsciousness reliably in all patients, a large number of drugs have been used in combination with them (Ch. 9) . Because of minimal effects on the cardiovascular system, midazolam has emerged as a popular drug with which to supplement opioids in anesthesia. Its depressant effect on myocardial

contractility is mild and probably not dose-dependent. [179] Etomidate maintains sympathetic nervous tone and reflex responsiveness, but its use has been limited by concerns about its inhibition of steroid synthesis. [180] Propofol produces vasodilation and mild negative inotropy but has the advantages of rapid control of responses to noxious stimulation and a short recovery time. [181] Thiopental resembles propofol but has a longer recovery time.

There are several important features of the interactions of hypnotics (including barbiturates, benzodiazepines, etomidate, propofol, and probably all other intravenously administered sleep-inducing drugs) and opioids:

1. Although the hypnotics may reduce the dosage requirements of an opioid, the length of the recovery time may not be shortened. And if the doses of both the hypnotic and the opioid are not reduced by careful titration to effect, the recovery time can be longer than that attributable to either drug alone.
2. There is a synergistic interaction between opioids and sleep (natural or drug-induced) in regard to ventilatory depression. This is most dangerously manifest in the postoperative period after the intensity of noxious stimulation is reduced and the patient is less carefully monitored for signs of ventilatory depression. [182]
3. When opioids in anesthetic doses are combined with any one of the hypnotics during the induction of anesthesia, a reduction of systemic blood pressure is frequently observed. [183] Conversely, a very small dose of an opioid (e.g., 75 mug of fentanyl or 20 mug of sufentanil) injected after unconsciousness is produced by a hypnotic usually results in a decline of systemic blood pressure, sometimes to a dangerously low level. Clinically significant hypotension usually responds to a sympathomimetic vasopressor.
4. Because it is easy to recognize and treat hypotension, we usually combine a hypnotic and an opioid to ensure unconsciousness during periods of total paralysis when it is not possible to have somatic signs of arousal. If a patient is so critically ill that mild to moderate decreases in blood pressure are potentially dangerous, it is prudent to avoid the opioid-hypnotic effects on hemodynamics. [144]
5. Sudden unexpected arousal of the central somatic and sympathetic nervous systems can occur, especially with intense noxious stimulation (see Table 49-17) . The most effective and immediate treatment of arousal is accomplished with a drug having a very short latency to the peak CNS effect of an intravenous bolus dose (e.g., thiopental 50-150 mg, propofol 25-75 mg, alfentanil 15-50 mug/kg, remifentanil 0.5-2 mug/kg). CNS drugs are to be preferred to sympatholytics and vasodilators because of the possibility of awareness (with or without pain) associated with the somatic and/or sympathetic manifestations.

Nitrous Oxide

Nitrous oxide (Chs. 4 and 5) can be used to supplement both potent inhaled anesthetics and intravenous anesthetics. It is often the primary anesthetic used in conjunction with muscle relaxants. Its effects on the cardiovascular system are mild but can be detrimental, especially in patients with poor cardiac performance. Nitrous oxide tends to decrease cardiac output and increase systemic vascular resistance when given alone or in combination with an opioid. In some patients, the degree of hypotension and myocardial depression may be sufficient to require that nitrous oxide be discontinued; recovery of cardiac function is usually evident within a few minutes, during which time most of the nitrous oxide is exhaled. The rapid onset and recovery allow the patient's tolerance of its effects to be tested safely; if the responses are undesirable, they are rapidly reversed by discontinuing nitrous oxide. A recent finding relevant to the care of patients with CAD is the potential for nitrous oxide to induce ischemia in an area supplied by a critically stenotic coronary artery and thereby induce regional myocardial dysfunction. [184] Clinical studies, however, have not found nitrous oxide to cause ischemia when used to supplement fentanyl anesthesia in CABG patients with either good or poor ventricular function. [185] [186]

Besides its direct cardiac depressant effects, nitrous oxide has other actions that may be detrimental to the patient undergoing cardiac surgery. It expands air-filled spaces, including air emboli, which may occur in the arterial circulation as a result of failure to eliminate air trapped in cardiac chambers or in saphenous vein grafts during surgery. Some advise the complete avoidance of nitrous oxide in cardiac operations involving extracorporeal circulation because of the ever-present risk of air emboli; microemboli of air are always present during CPB with hypothermia. Certainly, if arterial air embolization is suspected, nitrous oxide administration should be discontinued and avoided for the remainder of the anesthetic. [187] Also, nitrous oxide should not be used in the presence of a pneumothorax unless a functioning thoracotomy tube is in place. Nitrous oxide may potentiate truncal rigidity induced by small to moderate doses of opioids. Nitrous oxide limits the inspired oxygen

concentration in relation to its own concentration in the inspired gas mixture and does not allow for apneic oxygenation.

The advantages of nitrous oxide as a rapid onset/offset inhaled anesthetic are now shared with desflurane and sevoflurane, which do not have the problematic side effects related to nitrous oxide expansion of air-filled spaces.

Muscle Relaxants

Muscle relaxants (Ch. 12) are almost always used as a part of an anesthetic plan for cardiac surgery. The usual indications for their use are to facilitate endotracheal intubation, to counteract rigidity induced by opioids, to suppress body movement in response to electrical defibrillation or cardioversion, to limit oxygen consumption, to prevent shivering associated with hypothermia, and to facilitate the surgeon's work and prevent sudden, unexpected movement during delicate and critical portions of the operation. Their customary use to maintain paralysis throughout the intraoperative period is predicated on the avoidance of sudden body or diaphragmatic movements under light levels of general anesthesia. Even if prolonged paralysis occurs, these patients routinely receive mechanical ventilatory support for at least a short time in the postoperative period. The drawback of continuous muscular paralysis is its interference with somatic signs of light anesthesia. [144] [145]

The choice of a particular neuromuscular junction-blocking drug is usually based on its autonomic and hemodynamic side effects. For example, pancuronium-induced tachycardia may be useful in the patient with excessive bradycardia due to the vagotonic effects of an opioid superimposed on the residual effects of a beta-adrenergic receptor-blocking drug. Tachycardia is an undesirable side effect of sympathomimetic inotropes and is enhanced by pancuronium, which may make it a poor choice near the end of CPB and afterward. The generally benign effects of vecuronium, pipecuronium, and doxacurium make them agents of choice for the hemodynamically unstable patient with limited cardiovascular reserve. [188] [189] Proper dosing of the long-acting relaxants is necessary to avoid prolonged recovery and delayed tracheal extubation. Concerns about drug costs enter into the choice of relaxants; proper comparisons of costs need to take into account the total dose requirements and indirect costs of their administration (e.g., infusion devices) during operations typically lasting more than 3 hours.

Local and Regional Anesthesia

Local and regional anesthetics (Chs. 42 - 44) have limited roles in cardiac surgery, although they may be the anesthetics of choice for various types of noncardiac surgery in patients with heart disease. The risks of patient anxiety and discomfort (e.g., due to positioning and surgical manipulation) leading to sympathetic responses and hemodynamic instability under regional anesthesia must be weighed against the potential benefits of avoiding the systemic effects of general anesthetic drugs. Also, the supplementation of local or regional anesthesia with systemic hypnotics and analgesics can be risky because ventilation, protective airway reflexes, and other functions may be depressed as they would be by general anesthesia; but there is a false sense of security associated with the concept that the patient is "only undergoing local anesthesia and sedation." Often there is a fine line between "conscious sedation" and general anesthesia (unconsciousness), and the anesthesiologist must be prepared to intervene and establish the conditions of monitoring and life support that would be indicated for general anesthesia in the particular patient. Local anesthesia is useful for the prevention of pain associated with vascular cannulation (e.g., cutaneous puncture or surgical cut-down for venous and arterial cannulation, transvenous pacemaker implantation and pacemaker battery replacement procedures, and femoral vessel cannulation for CPB or insertion of an IABP). Topical anesthesia of the pharynx and trachea is useful in reducing the sympathetic responses to endotracheal intubation and airway manipulation in the lightly anesthetized patient. Local anesthetic infiltration of the stellate ganglion has been suggested as a means of preventing and controlling postoperative hypertension, which is common after cardiac surgery and especially common after CABG. [190] Epidural analgesia has been used during cardiac surgery to decrease systemic anesthetic requirements and for postoperative analgesia. [191] However, the risk of hemorrhagic complications associated with systemic heparinization and post-bypass coagulopathy, and the lack of clearly documented clinically significant benefit hindered the widespread adoption of this technique. [192] Similarly, although intrathecal opioids have been used in cardiac surgery patients, [193] [194] evidence of a benefit justifying the extra effort and risk is lacking.

The Cardiovascular System During Cardiac Surgery

The anesthesiologist assumes primary responsibility for intraoperative management of the cardiovascular system. This responsibility is entirely appropriate because the surgeon's attention should be focused primarily on the surgical operation, and the anesthesiologist is in the best position to monitor and respond to hemodynamic alterations whatever their cause. Of prime importance is coordination of the entire surgical team, which requires active communication, mutual respect, and cooperation. Effective interactions are facilitated by a common understanding of each other's objectives, procedures, knowledge, and skills. The anesthesiologist should be well informed about the patient's disease status, the surgeon's operative plans, and the specific aspects of cardiac surgery discussed later.

Intravascular Volume

Intravascular volume is a key factor in determining the hemodynamic responses not only to anesthetic drugs but also to surgical manipulations, such as cannulation of the venae cavae. Patients coming to cardiac surgery often have a surprisingly low circulating blood volume, reflecting limited intake of fluids and foods in the days preceding surgery. This limited intake may result from anxiety and physical inactivity or from a requirement to abstain from food and drink before anesthesia. Patients are usually ordered to abstain after midnight, but many hospitalized patients ingest little or nothing after their early evening meal, and some may not have surgery until the next afternoon. Vigorous diuretic therapy to eliminate CHF before surgery produces reductions in circulating blood volume. Hypovolemia can be detected before and during induction of anesthesia by monitoring hemodynamic variables and their responses to positional changes, positive-pressure ventilation, and anesthetic drugs. Small volume and high specific gravity of urine obtained during catheterization of the bladder provide additional clues to the presence of hypovolemia. It may be necessary to treat hypotension by a legs-up position and vasopressors until hypovolemia can be corrected by infusion of fluids.

During CPB, diuresis usually is induced by several factors: inclusion of mannitol (an osmotic diuretic) in the CPB reservoir prime solution; hypothermia, which interferes with renal tubular reabsorption mechanisms; and good perfusion of renal glomeruli with blood low in protein as a result of hemodilution by the CPB prime solution. A minimally acceptable urine flow is 1 mL/kg/h to ensure that adequate renal perfusion has occurred and to minimize any renal insult from hemoglobinuria caused by hemolysis during CPB.

At the conclusion of CPB with hypothermia, peripheral vasoconstriction commonly occurs as a result of persistent peripheral hypothermia. Consequently, the vascular capacity is below normal until rewarming of the entire body is completed. Venodilators (e.g., NTG) may be infused and the

Figure 49-7 (Figure Not Available) Cardiopulmonary bypass from the vena cava (1) to the ascending aorta (2a) or, alternatively, to the femoral artery (2b). Blood is also carried to the reservoir from the left ventricular vent cannula (3) and from suckers (4) used to clear the operative site. *(Modified from Nose Y: Manual on Artificial Organs. Vol. 3. The Oxygenator. St Louis, CV Mosby, 1973.)*

patient placed in the reverse Trendelenburg position to increase venous capacitance, thereby facilitating the return of most or all of the blood in the CPB reservoir to the patient. Not only does this conserve the patient's own red blood cells, but it ensures continuing diuresis and minimizes the discrepancy between vascular capacity and circulating blood volume as rewarming occurs.

Cardiopulmonary Bypass

CPB (also termed extracorporeal circulation) is a complex subject, a complete discussion of which is beyond the scope of this text. Several comprehensive reviews of the topic are available. [195] [196] The following is a brief summary, with an emphasis on issues of importance to the anesthesiologist.

Extracorporeal Systems

Extracorporeal perfusion systems consist of the basic components shown in Figure 49-7 (Figure Not Available) , in an arrangement similar to that illustrated. Several varieties of each component are available commercially, the most important differences being those between the two basic types of oxygenators in common use today, namely bubble and membrane oxygenators. Bubble oxygenators have advantages over the membrane type in terms of simplicity, lower cost, lower priming

volume, ease of CPB circuit assembly, and greater oxygenation efficiency. However, the turbulence and foaming created by gas bubbling in blood promote disruption of blood cells, which occurs progressively during CPB. When prolonged CPB (90 to 120 minutes) is anticipated, a membrane-type oxygenator is preferable. [197] [198] Newer types of membrane oxygenators are cost-effective and convenient to use.

Because of the disruption of blood cells during CPB and the risks of infusing debris and air bubbles into the circulatory system of the patient, the use of filters on both the venous return tubing and the arterial inflow tubing is essential. A 27-mm pore filter in the arterial tubing is recommended because it removes most of the debris without marked impedance to the flow of blood. [199] [200] Filters cause a loss of platelets. [201]

A nonocclusive roller pump developed by DeBakey is the type most commonly used, but other types continue to be developed in attempts to reduce blood cell trauma and provide pulsatile flow. [202] [203] The costs and complexity have not been shown to be justified by the limited benefits of pulsatile flow.

The most common routine for establishing extracorporeal circulation for cardiac operations is to drain venous blood from the venae cavae and to pump arterialized blood into the ascending aorta (see Fig. 49-7) (Figure Not Available) . Other arrangements (Table 49-18) are indicated for special circumstances; for example, femoral artery and vein cannulation (with a long

TABLE 49-18 -- Arrangements of Cardiopulmonary Bypass Circuits

Venous return
Superior and inferior venae cavae
Femoral vein (requires long cannula to reach right atrial level or subsequent atrial cannulation to obtain more complete venous return to cardiopulmonary bypass circuit)
Left atrium (left ventricular-aortal bypass; uses patient's lungs for oxygenation of blood)
Arterial infusion
Ascending aorta
Femoral artery--descending aorta
Pulmonary artery (right heart bypass; patient's lungs oxygenate blood)
Types of cardiopulmonary bypass
Partial (venous blood can flow past cannula into right heart)
Total (all systemic venous blood flows into venous cannulas because venae cavae are occluded around cannulas; coronary sinus and bronchial artery flows continue to drain into pulmonary circulation; see Fig. 49-7) (Figure Not Available)

venous cannula inserted to the level of the right atrium to drain the superior vena cava) may be used in the hemodynamically unstable patient in whom rapid access to the great vessels is not possible because of scarring from a previous mediastinal operation.

CPB is considered to be total if tapes are drawn snugly around both the superior and inferior venae cavae to prevent any flow of systemic venous blood around the cannulas into the right atrium (see Table 49-18) . Total CPB is used when the cardiac chambers are to be opened or when the systemic venous blood return to the heart proves troublesome. Partial CPB is satisfactory for most aortocoronary bypass grafting operations or other procedures in which the heart is not opened. Partial CPB allows blood to enter the heart and this can be used to advantage for the following purposes: (1) to check the CPB system before establishing total CPB (if a problem exists, the patient's spontaneous circulation can be immediately restored); (2) to fill the heart to its usual size and facilitate more precise estimation of coronary graft length; (3) near the end of CPB to allow some pulsatile flow (provided by the patient's heart) to improve tissue perfusion, facilitate rewarming of peripheral tissues, and for washout of cardioplegia components from the heart; (4) to assess the heart's function at the end of CPB by increasing its filling and work gradually to prevent excessive ventricular distention and failure; and (5) to allow coronary sinus blood to drain into the venae cavae and reduce flow into the pulmonary vasculature and left heart.

LV venting (see Fig. 49-7 (Figure Not Available) , site 3) through a catheter (usually inserted by way of a pulmonary vein and left atrium) may be necessary to prevent harmful ventricular distention due to (1) an incompetent aortic valve (also prevented by cross-clamping the ascending aorta), (2) large blood flow from the coronary sinus and bronchial circulation into the pulmonary veins, and (3) surgical positioning of the heart to cause displacement of blood into it or to prevent its backward flow into the venae cavae. Venting of either the ventricle or PA also reduces the risks associated with elevated pulmonary capillary pressures. Monitoring PA pressures during CPB facilitates early detection of elevated pressures.

Signs of potential complications of CPB are listed in Table 49-19 . The anesthesiologist, surgeon, and perfusionist must work closely together to detect real or potential problems as early as possible and to correct them promptly and safely. A checklist (e.g., Table 49-20) may be useful in the prevention and early detection of problems. Three of the most serious complications that indicate immediate cessation of CPB and reestablishment of the patient's own cardiac output are aortic dissection, [204] superfusion of a carotid artery, and air in the aortic inflow tubing. [205] [206] The extracorporeal system is usually primed with a heparinized and buffered physiologic salt solution to which may be added (1) an osmotically active substance (e.g., albumin, hetastarch) to normalize colloid osmotic pressure, (2) an osmotic diuretic (e.g., mannitol), (3) an antibiotic, and (4) aminocaproic acid (Amicar) or aprotonin if indicated. If the patient's hematocrit level is unusually low, it may be appropriate to add packed red blood cells to the priming fluid in anticipation of hemodilution. It is usually desirable to maintain a hematocrit level in the range of 20 to 25 percent during hypothermic CPB. [207] [208] [209] [210]

Heparin Anticoagulation

Heparin anticoagulation of the patient's blood is the single most important preparative step for CPB; failure to establish heparin anticoagulation means death to the patient on initiation of CPB. The usual initial dose of heparin is 300 to 400 U/kg (equivalent to 3-4 mg/kg) administered into a central venous catheter (after verifying its intravascular position by blood withdrawal) by the anesthesiologist or into the aorta by the surgeon several minutes before insertion of any CPB cannula. Because of variability among patients in their response to heparin, it is customary to use an *in vitro* test of coagulation (e.g., ACT). The ACT should remain above 400 seconds for the duration of CPB cannulation and should return to the preheparin baseline level (usually 90-120 seconds) after administration of protamine following decannulation. [211] [212] The ACT is markedly prolonged during hypothermia and celite-based ACT determinations are prolonged by aprotinin. Such prolongations may give a false impression of adequate heparin concentrations. Under such circumstances, it is advisable to administer supplemental heparin doses at regular intervals (e.g., 100 U/kg every 90 minutes). The elimination of heparin is slowed by hypothermia but rapidly recovers to a normal rate with rewarming. [213] Therefore, it is important to verify the adequacy of heparin anticoagulation frequently (every half hour) during normothermic CPB. Important signs of inadequate anticoagulation are accumulation of fi-brin on the walls of the CPB reservoir and thickening of blood in the pericardium. Obviously, the presence of any blood clot during CPB indicates the need for immediate administration of additional heparin. The one uniformly lethal and irreversible complication of CPB is clotting of blood in the patient and the CPB circuit. The other consequence of inadequate heparinization during CPB is the clinically inapparent activation of coagulation with consumption of the clotting factors, leading to subsequent coagulopathic bleeding. Aprotinin inhibits inflammatory responses to CPB and surgery that are responsible for platelet activation and consumption during CPB. Preservation of functional platelets improves blood coagulation after CPB.

TABLE 49-19 -- Signs of Potential Complications of Cardiopulmonary Bypass (CPB)

High aortic tubing pressure

- Aortic tubing occlusion by kinking, clamp
- Improperly positioned aortic cannula (e.g., aortic dissection, cannula tip inserted into branch of aorta)
- Aortic cannula too small for required CPB flow

Low venous return

- Aortic dissection
- Bleeding from an open blood vessel
- Pooling of blood in dependent portions of body
- Anaphylactic or anaphylactoid reaction
- Obstruction of vena caval cannula (malposition)
- Insufficient difference in height of vena cava versus CPB reservoir for gravity drainage
- Obstruction of venous tubing (e.g., kinking, air lock, clamp)
- Leak in venous return tubing, connectors, CPB reservoir

Hypotension

- Anything limiting CPB pump flow (e.g., low venous return)
- Aortic dissection
- Low peripheral resistance (e.g., anaphylactic or anaphylac-toid reaction, hematocrit <18-20%, drug [anesthetic, va-sodilator] effect)

Abnormal blood gases

- Oxygenator failure (Pa_{O_2} , Pa_{CO_2})
- Inadequate perfusion (pH, base deficit, Pv_{O_2} < 40 mm Hg,venous hemoglobin saturation <50%)
- Increased oxygen demand (e.g., due to shivering, inadequate skeletal muscle relaxation)

Suffusion, plethora, cyanosis or edema of head, face, eyelids, and conjunctiva

- If unilateral, aortic cannula flow into carotid artery
- Obstruction of superior vena caval cannula
- Obstruction of jugular venous drainage by caval cannula, head position, neck compression

Isoelectric encephalogram

- Inadequate cerebral perfusion (e.g., due to carotid artery occlusion, hypotension, hypoxemia)
- High anesthetic concentration (thiopental used for cerebral protection [134])
- Extreme hypothermia

Oliguria or anuria

- Aortic dissection

Fibrin deposition or clot in CPB reservoirs or in operative field

- Inadequate heparin concentration (e.g., dose too low, rapid elimination at normothermia)
- Insufficient heparin cofactor (antithrombin III)

Abdominal distention

- Obstruction of inferior vena caval cannula
- Intra-abdominal hemorrhage, ascites
- Gastrointestinal distention by gas, fluid

Elevated central venous pressure

- Obstruction of vena caval cannula

Elevated pulmonary artery pressure, distention of heart

- Obstruction of vena caval cannula (on partial CPB)
- Incompetent aortic valve (before aortic cross-clamping)
- Excessive coronary sinus and bronchial artery flow
- Malposition of heart

Diaphragmatic movement

- Hypercarbia
- Inadequate muscular relaxation or inadequate anesthesia

Hypertension

- Excessive CPB flow
- Inadequate anesthesia
- Drug-induced

Hemodynamic Changes

Hemodynamic changes become evident with the initiation of hypothermic CPB. Initially, peripheral resistance falls as the cold CPB priming fluid, which has low viscosity, low oxygen content, and no hormonal vasoconstrictors, enters the vascular system. Hypotension may not become evident until LV ejection stops. As the pump-priming fluid mixes with the patient's blood and vascular tone recovers, the mean perfusion pressure begins to rise, in some cases to above 110 mm Hg, which indicates arterial vasoconstriction and impaired perfusion of some tissues. Hypertension carries the risk of intracerebral hemorrhage. The range of acceptable perfusion pressures and flows during CPB is controversial, [214] [215] [216] concern having been registered about the adequacy of cerebral and coronary perfusion if mean arterial pressures are not maintained in the usual range for the patient at rest. Some have suggested the routine use of vasopressors as necessary to maintain a mean arterial blood pressure 70 mm Hg or greater in all adult patients during CPB. Yet, practitioners who routinely accept low perfusion pressures report no increased incidence of complications from CPB. Until this debate is settled, the following guidelines represent a middle-of-the-road approach to the problem.

1. The first objective is to maintain tissue perfusion. Thus, the pump flow should be set at the calculated normal resting cardiac output for that patient. Mean blood pressure can then be adjusted into a range of 50 to 100 mm Hg by the use of vasopressors (e.g., phenylephrine, norepinephrine) and vasodilators (e.g., isoflurane, NTG, nitroprusside). Flow can be reduced in relation to the degree of hypothermia and slowing of metabolism. [216]
2. Vasopressors are not without complications. They can reduce renal perfusion, produce spasm of peripheral arteries, and lead to metabolic acidosis due to

underperfusion of peripheral tissues. Therefore, it may be better to forego the administration of large doses of vasopressors and accept a lower blood pressure as long as tissue perfusion appears to be adequate.

3. Signs of inadequate tissue perfusion include oliguria, progressive metabolic acidosis, venous oxygen tension less than 40 mm Hg, venous hemoglobin saturation less than 60 percent, and wide discrepancies between temperatures measured in the nasopharynx or esophagus and those measured in the urinary bladder, rectum, skeletal muscle, or skin. Careful monitoring of the pupils and EEG may reveal subtle changes indicative of inadequate cerebral perfusion, but the significance of such changes has to be related to all the other factors that may cause them.
4. Factors affecting total peripheral resistance should be monitored. Low hematocrit level and consequent low viscosity of blood can result in hypotension; at moderate hypothermia (26-30°C), the hematocrit level can remain between 20 and 25 percent during CPB. Hypercarbia

produces vasodilation, as does an anaphylactoid response (e.g., to blood products, dextran, or antibiotics). Insufficient anesthesia can result in increased sympathetic activity and vasoconstriction in response to noxious stimulation and hypothermia.

5. Discrepancies between radial artery and central aortic blood pressures, especially systolic pressures, have been noted at the end of CPB. [217] The favored explanation is marked vasodilation in the extremity analogous to the situation existing distal to an arteriovenous shunt. One way to determine the degree of discrepancy is to compare the pulse pressure tracings from the radial arterial catheter with those obtained through a needle inserted into the ascending aorta by the surgeon, who passes sterile extension tubing to the anesthetist for attachment by a stopcock to the same arterial pressure transducer. If there is a substantial difference in the systolic pressures, the surgeon can insert a femoral arterial catheter and connect it to the extension tubing for continuous monitoring thereafter or until the peripheral vasculature recovers its normal tone. Another means of verifying the accuracy of radial artery pressures is to determine the upper arm cuff pressure at which Korotkoff sounds or arterial pulse waves return (the so-called return-to-flow pressure).

TABLE 49-20 -- Checklist of Preparations for Initiating Cardiopulmonary Bypass (CPB)

I. Before aortic and vena caval cannulation
  A. Heparin dose
    Activated clotting time (ACT) >300 s (Hemochron)
  B. Hemodynamics
    Systemic blood pressure appropriate for aortic cannulation (systolic <100 mm Hg)
    ECG recorded before and after sternum spread open (especially V_5 lead)
    Central venous pressure adequate to sustain preload during vena caval cannulation
  C. Ventilation
    Compliance evaluated (for post-CPB comparison)
    Lung inflation appropriate (for surgical access to internal mammary arteries and venae cavae)
    Arterial blood gases and acid-base balance satisfactory (for current status and for comparison during and after CPB)
II. Before turning on CPB pump
  A. Anesthetic depth and CNS status
    Adequacy judged by presence or absence of responses to sternotomy
    Muscular paralysis to limit shivering (O_2 demand) and dangerous movement
    Examination of face (color), eyes (pupils), and EEG recording (if used)
  B. Aortic cannula and tubing
    No evidence of air
    Correct orientation of cannula in aorta
    Clamps off aortic and venous CPB tubing
    Normal aortic tubing pressure with infusion of 100-200 mL pump prime (checked by perfusionist)
  C. Fluid balance
    Intravenous fluid administration stopped and pre-CPB fluid administration recorded
    Pre-CPB urine output recorded
III. First few minutes of CPB
  A. CPB function (before beginning hypothermia)
    Aortic tubing pressure normal
    Systemic blood pressure as expected
    Venous return satisfactory
    Bright red color of blood in aortic cannula
  B. Ventilation of lungs
    Discontinued when ventricular ejection stops
    O_2 flow continued and lung inflation appropriate (i.e., avoid obstruction of surgical field by distended lungs)
  C. Arterial blood analysis
    Gases, pH, and acid-base balance
    ACT
IV. Monitoring during CPB
  A. Heparin
    ACT (>400 s)
    Inspection of CPB reservoir, pericardial fluid (evidence of fibrin)
  B. Blood gases, pH, acid-base balance
    Arterial
    Venous (Pv_{O_2} > 40 mm Hg; Sv_{O_2} > 60%)
    Hematocrit (18-22%)
  C. Blood pressures
    Systemic arterial (40-90 mm Hg)
    Pulmonary arterial (<15 mm Hg [usually close to or below zero])
    Central venous (normally below zero)

D. Temperatures

Pharyngeal, esophageal

Peripheral (skin, toe, muscle)

Rectal, urinary bladder

Myocardial (if probe used)

Pericardial iced superfusion fluid running (if used)

E. ECG

Quiescent (i.e., isoelectric, absence of fibrillation)

F. CNS status

Color of face, edema formation?

Pupil size, conjunctival swelling

EEG activity appropriate for CPB conditions (hypothermia, anesthesia)

Muscle paralysis adequate (normal Pv o_2 and Hb saturation)

G. Urine output

Volume (>1 mL/kg/h)

Color (evidence of hemolysis?)

H. CPB conditions

Aortic tubing pressure (appropriate for flow and aortic cannula size)

Pump flow (1.5-2.5 L/min/m^2)

Venous return satisfactory

Fluid balance appropriate

ECG, electrocardiogram; CNS, central nervous system; EEG, electroencephalogram; Pv o_2 , mixed venous O_2 pressure; Sv o_2 , mixed venous O_2 saturation

THE ANESTHETIC PLAN - continued

The Cardiovascular System During Cardiac Surgery

Cardiopulmonary Bypass

Myocardial Preservation

Myocardial preservation [218] [219] includes (1) myocardial cooling by hypothermic CPB, by epicardial surface cooling with ice and pericardial irrigation with iced fluid, and by intracoronary infusion of cold cardioplegia solution or continuous direct hypothermic coronary perfusion by the CBP pump; (2) myocardial arrest by hyperkalemic cardioplegia solution; and (3) prevention of ventricular distention and edema by venting of the left ventricle and inclusion of mannitol in the cardioplegia solution. Improvement in myocardial preservation since the early 1970s has been evident in the markedly better cardiac contractility at the termination of CPB and in the reduced need for inotropic drugs. [218] [219] Recent advances in cardioplegia techniques include insertion of a special cannula into the coronary sinus for retrograde perfusion of the coronary vasculature with cardioplegia solution, [220] and the use of normothermic, blood-containing cardioplegia solutions. [221]

The role of cardioplegia solutions in myocardial preservation has been discussed by Buckberg. [222] These solutions have some manageable side effects. There is an increased incidence of atrioventricular conduction block due to intramyocardial hyperkalemia, which usually resolves within the first hour after CPB and can be treated temporarily by atrioventricular sequential pacing. The rate of recovery can be speeded by administration of calcium and of insulin with or without glucose as needed. The ventricular flaccidity due to hyperkalemia may be responsible for transverse LV rupture in elderly patients undergoing mitral valve replacement (see previously). Resting of the ventricle on CPB for a time sufficient to allow recovery of membrane function, electrolyte gradients, myocardial metabolism, ventricular tone, administration of calcium and other inotropes, and control of LVEDV with vasodilators facilitates the recovery of ventricular pumping function.

Discontinuation of Cardiopulmonary Bypass

Discontinuing CPB requires preparations by the anesthesiologist. A checklist of the essential steps is shown in Table 49-21 . Several points deserve emphasis.

During the rewarming phase the anesthesiologist may easily overlook the paralyzed patient's return to consciousness and the need to administer additional anesthetic drugs that do not have cardiac depressant effects (e.g., an opioid or benzodiazepine). The recovery of metabolic functions speeds the elimination of heparin, and the adequacy of anticoagulation should be verified more frequently (every half hour) at normothermia.

In discontinuing CPB, the perfusionist gradually allows the heart to fill and pump blood by progressively occluding the venous return cannula while decreasing the pump arterial inflow as the patient's heart ejects more and more blood. This process may be done rather quickly when there is good heart function, but with poor cardiac performance, sufficient time should be taken in discontinuing CPB to allow recovery of cardiac electrolyte and metabolic balance, to evaluate cardiovascular function, and to establish the appropriate therapeutic regimen. It is not enough that blood pressure be within the normal range--overall cardiac performance should be assessed by measuring cardiac output and calculating stroke volume in relationship to preload (see Fig. 49-2) ; optimal conditions, including heart rate and rhythm (Table 49-22) , preload, and vascular resistance, should be established; and if necessary, drug therapy should be begun before extracorporeal circulatory assistance is discontinued. It is extremely important to avoid injury to the ventricles by overdistention. Reasonably satisfactory and stable hemodynamic conditions should be maintained for a time after discontinuing CPB and before removing the vena caval and aortic cannulas. The ability to reestablish CPB rapidly should be preserved (i.e., the CPB circuit maintained and cannulation devices available and ready to use). An algorithm that may aid the anesthesiologist and surgeon in their analysis and management of low cardiac output is shown in Figure 49-8 . Inotropic, vasopressor, and vasodilator drugs that may be useful are listed in Tables 49-23 through 49-27 . [223]

After CPB has been terminated, a number of potential problems may occur, two of which, air embolism and complications of heparin neutralization, deserve special mention.

Sudden embolization of air lodged in one of the left chambers of the heart or in the aorta can occur when the orientation of the heart and great vessels is altered by manipulation of the heart, closure of the sternum, or movement of the patient (e.g., transfer from the operating table to the ICU bed). Embolization to the brain or heart can lead to obvious undesired consequences. Temporary CNS functional deficits resembling a cerebrovascular accident may result; they usually resolve several days after surgery as the air is resorbed provided that irreversible ischemic damage has not occurred. Air embolism into the coronary arteries, most frequently the right coronary artery, may be manifested by ST-T segment elevation, bradycardia, conduction abnormalities, dysrhythmias, ventricular fibrillation, and impaired contractility. Treatment of air embolism involves resuscitative measures as indicated, maintenance of a high perfusion

TABLE 49-21 -- Checklist of Preparations for Discontinuing Cardiopulmonary Bypass (CPB)

I. Rewarming
- A. Responsiveness of patient
- B. Adequacy of heparin anticoagulation
- C. Oxygenation and CO_2 elimination
- D. Metabolic acid-base balance
- E. Vasodilation to facilitate warming of peripheral tissues (e.g., toe temperature)
- F. Defibrillation (spontaneous, lidocaine, electric)
- G. Recalibration of monitoring devices

II. Just before discontinuing CPB
- A. Arterial pH, P_{CO_2} , P_{O_2}
- B. Hematocrit level
  1. O_2 delivery

2. Viscosity (peripheral resistance)

C. Serum potassium

1. Urine flow
2. Insulin ± glucose (to decrease K^+ > 6 mEq/L)
3. Calcium (to antagonize K^+ > 6 mEq/L)
4. Furosemide (to decrease K^+ > 6 mEq/L)

D. Body temperatures

1. Core versus peripheral tissues

E. Heart rate and cardiac rhythm (see Table 49-22)

1. Cardiovascular/defibrillation
2. Pacemaker (atrial, ventricular, atrioventricular sequential)
3. Antidysrhythmic drugs

F. Mean systemic arterial pressure

1. Vasodilator/vasopressor

G. Venous and pulmonary artery pressures

1. Vasodilators
2. Blood volume in CPB reservoir

H. Ventilation of lungs

1. Air flow (wheezing, air trapping)
2. Compliance (pulmonary edema, gastric distention, tense diaphragm)
3. Elimination of atelectasis
4. Pneumothorax, hydrothorax (irrigation fluid)

I. Venting of arterial air

1. Cardiac chambers (verification by TEE if used for other purposes)
2. Aorta
3. Saphenous vein grafts
4. Head-down position, carotid artery compression with ventricular ejection

III. Gradual discontinuation of CPB (see Fig. 49-8)

A. Preload

1. PAOP or LAP
2. CVP

B. Ventricular ejection

1. dP/dt on arterial pressure tracing
2. Cardiac output
3. TEE imaging
4. Inotropic drugs

Catecholamine injection/infusion

5. Vasodilators

C. Return of CPB reservoir blood to patient

1. Venodilator and head-up position

IV. After discontinuation of CPB, surgical control of major bleeding, and decannulation of venae cavae and aorta

A. Protamine antagonism of heparin

B. Maintenance of circulating blood volume and coagulation

1. Transfusion of packed red blood cells
2. Fresh frozen plasma
3. Platelets
4. epsilon-Aminocaproic acid, desmopressin (?)
5. Cryoprecipitate

C. Hemodynamic adjustments

D. Anesthesia

E. Preparations for transfer of patient from operating room to intensive care unit

1. Monitoring
2. Ventilation
3. Hemodynamic therapy
4. Anesthesia-analgesia

TEE, transesophageal echocardiography; PAOP, pulmonary artery occlusion pressure; LAP, left atrial pressure; CVP, central venous pressure

TABLE 49-22 -- Therapy of Abnormal Heart Rate and Rhythm at End of Cardiopulmonary Bypass

DIAGNOSIS	THERAPEUTIC STEPS

Asystole or heart block due to potassium cardioplegia, surgery (trauma to nodal and conducting tissues), or preoperative pathophysiology	Pacemaker: atrial, ventricular, atrioventricular sequential Calcium chloride, 1-2 g Sodium bicarbonate, 50 mEq Insulin, 10 units, regular, ±glucose, 10 g Furosemide, start with 3 mg and increase doses logarithmically (10, 30, 100) every 15 min up to 100 mg as needed to establish diuresis Temporary epicardial pacing wires for postoperative use Atropine, incremental doses up to total of 2-2.5 mg/70 kg over 5-10 minutes Isoproterenol, 0.5-10 mug/min
Supraventricular tachyarrhythmia	Increase core temperature to 37°C Correct electrolyte abnormalities (K^+, Mg^{2+}) Correct arterial pH, P_{CO_2}, and hematocrit level Check position of CVP or other monitoring catheters Overdrive atrial pacing Synchronous cardioversion (internal paddles, 5-10 watt-seconds) Adenosine initial 6 mg rapidly IV, then 12 mg if needed to diagnose dysrhythmia Ouabain, 0.1-0.2 mg, or digoxin, 0.25-1 mg Propranolol, 0.5-3 mg; esmolol 25-75 mg bolus plus 5-200 mug/kg/min infusion Diltiazem 5-25 mg IV over 1-3 min plus infusion Procainamide 100 mg IV every 5 min to effect (5-15 mg/kg total), then 1-4 mg/min infusion
Recurrent ventricular tachycardia or fibrillation	Increase core temperature to 37°C Correct electrolyte abnormalities (K^+, Mg^{2+}) Correct arterial pH, P_{CO_2}, P_{O_2}, and hematocrit level Check position of pulmonary artery catheter Maintain satisfactory BP, PAOP, CO Lidocaine 1-2 mg/kg bolus plus 2-4 mg/min infusion Defibrillation (internal paddles, 10-60 watt-seconds) Procainamide (see above) Bretylium 5-10 mg/kg IV over 10 min plus 1-2 mg/min infusion

CVP, central venous pressure; BP, blood pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output.

Figure 49-8 Algorithm for therapy of low cardiac output. PAOP is an indirect measure of LVEDP; PAOP greater than 15 mm Hg may be necessary in patients with a pressure gradient across the mitral valve and in those with elevated PAOP before surgery as a result of low ventricular compliance. BP, blood pressure; CVP, central venous pressure; PAOP, pulmonary capillary wedge pressure; CO, cardiac output; TPR, total peripheral resistance; WNL, within normal limits;
, increase. Measurement units are mm Hg for pressure, dynes/cm^5 /s for resistance, and L/min for CO.

TABLE 49-23 -- Vasopressors[a]

DRUG	INITIAL[b] DOSE	ADRENERGIC RECEPTOR STIMULATION		
		VASCULAR		
		alpha	beta $_2$	HEART, beta $_1$
Methoxamine (Vasoxyl)[c]	2-100 mg	+++	0	0
Phenylephrine (Neo-Synephrine)	50-100 mug	++	0	±
Metaraminol (Aramine)	100 mug	++	±	+
Ephedrine[d]	5-25 mg	+	±	+
Norepinephrine (Levophed)	1-4 mug	+++	0	+++

0, no effect; ±, may or may not have an effect; +, weakest effect; ++, moderate effect; +++, strongest effect

[a] Also see Chapter 14 .
[b] Geometric (1,2,4,8 x) or logarithmic (1,3,10,30 x) increases in dose may be required to achieve desired degree of response. An infusion may be required to sustain the effect.
[c] Methoxamine is rarely used because of its long duration of action.
[d] Ephedrine doses above 50 mg are seldom used because of its limited efficacy; infusions are not used.

TABLE 49-24 -- Inotropic Therapy

DRUG	INTRAVENOUS BOLUS	INFUSION	LIMITATIONS
Amrinone (Inocor)	1.5-3 mg/kg[a]	5-10 mug/kg/min	Hypotension (TPR)
Milrinone (Primacor)	50-75 mug/kg	0.4-0.8 mug/kg/min	Hypotension (TPR)
Dobutamine (Dobutrex)	--	2-20 mug/kg/min	Tachycardia Dysrhythmias
Dopamine (Intropin)	--	2-15 mug/kg/min	Tachycardia Dysrhythmias Vasoconstriction
Epinephrine (Adrenalin)	2-50 mug[b]	2-60 mug/min	Tachycardia Vasoconstriction
Norepinephrine (Levophed)	1-10 mug[b]	1-60 mug/min	Vasoconstriction Tachycardia
Isoproterenol (Isuprel)	1-5 mug[b]	0.5-5 mug/min	Hypotension Tachycardia Dysrhythmias

TPR, total peripheral resistance

[a] Higher dose than recommended in package insert is necessary to achieve effective drug concentrations. [223]
[b] Per 70-kg individual

TABLE 49-25 -- Other Inotropic Drugs

DRUG	DOSE[a]	LIMITATIONS
Calcium chloride [b]	0.25-1 g	Dysrhythmias, AV block
Digoxin		
Initial	1-1.5 mg	Dysrhythmias
Maintenance (daily)	0.125-0.5 mg	Bradycardia
Ouabain	0.3-0.5 mg	AV block
Glucagon	3-10 mg	Tachycardia
		AV block (ventricular rate)
		Hyperglycemia

, increase;
, decrease; AV, atrioventricular

[a] Per 70-kg individual
[b] Inotropic effect is weak and superseded by vasoconstriction, which is a more prominent effect. Intravenous bolus dose is useful to increase systemic blood pressure transiently without increasing heart rate.

TABLE 49-26 -- Relative Efficacy of Intravenous Vasodilators on Hemodynamic Variables

VASODILATOR	DILATION			
	VENOUS	PULMONARY ARTERIAL	SYSTEMIC ARTERIAL	CARDIAC OUTPUT
Nitric oxide	0	+++	0	±
Nitroglycerin IV (Tridil)	+++	+	+	[a]
Nitroprusside (Nipride)	+++	+++	+++	[a]
Phentolamine (Regitine)	+	+	+++	
Hydralazine (Apresoline)	0	?	+++	
Nicardipine (Cardene)	0	?	+++	
Amrinone [b] (Inocor)	+	+	+	
Milrinone [b] (Primacor)	+	+	+	
Prostaglandin E_1 [c]	+	+++	+++	[a]

0, none; ± small, variable; + mild; +++ strongest effect of that particular drug.

[a] Effect on cardiac output depends on net balance of effects on preload, afterload, and myocardial oxygenation.
[b] Inodilators have inotropic plus vasodilating effects; see Table 49-24 .
[c] Almost always requires left atrial infusion of norepinephrine to sustain adequate systemic blood pressure.

TABLE 49-27 -- Dosage of Vasodilators

DRUG	DOSING REGIMEN[a]	
	INITIAL	MAXIMUM
Administered as infusion:		
Nitroglycerin (Tridil) [b]	50 mug/min	500 mug/min [c]
Nitroprusside (Nipride) [d]	10-25 mug/min	8 mug/kg/min
Nicardipine	100-300 mug	3-5 mg/h
Trimethaphan (Arfonad)	0.3 mg/min	6 mg/min
Phentolamine	10-100 mug/min	7 mug/kg/min
Prostaglandin E_1	0.05 mug/kg/min	0.5 mug/kg/min
Administered as intravenous bolus:		
Chlorpromazine (Thorazine)	1 mg	5-25 mg/24 h [e]
Droperidol (Inapsine)	2.5 mg	10-20 mg/24 h [e]
Hydralazine (Apresoline)	5 mg	40 mg over 1 h [f]

Phentolamine (Regitine)	1 mg	0.5 mg/min [g]

[a] Per 70-kg individual
[b] IV bolus doses of 25-100 mug may be useful to produce transient effect rapidly.
[c] Highest dose rate reported; no maximum yet defined in terms of toxicity or efficacy.
[d] IV bolus doses of 20-200 mug (geometric or logarithmic progression) are useful for rapid reduction of systemic blood pressure lasting 2-3 minutes, with more or less complete recovery depending on degree of reduced venous return.
[e] Limits are suggested because higher doses are probably no more effective in controlling hypertension and may lead to marked and prolonged CNS effects.
[f] Peak effects may not occur until 30 to 60 minutes after injection; seldom will more than 40 mg be needed to produce effects lasting several hours. Temporarily withdrawn from market by manufacturer, who is trying to develop a more economical formulation.
[g] Intravenous bolus doses of 5 to 10 mg may be used, depending on the situation; a maximum infusion rate has not been defined in terms of efficacy or toxicity but rarely is more than 0.5 mg/min.

pressure in the hope of flushing the emboli out of the arterial circulation, and perhaps administration of corticosteroids.

To prevent arterial air embolism, the following have been suggested for CABG surgery: fine-gauge needle puncture at the highest level of each saphenous vein graft and massage of the graft to express air before allowing aortocoronary blood flow; large-bore needle puncture at the highest level of the aorta, with the patient's head at a slightly lower level than the ascending aorta; and positive-pressure ventilation before, with passive Valsalva maneuver maintained during, removal of the LV vent cannula. To prevent air entry into the heart, some surgeons omit the LV vent cannula provided that ventricular distention and elevated pulmonary vascular pressures do not occur during CPB. For open-heart surgery, additional measures include massage of the left atrium and ventricle by the surgeon, lateral rotation of the patient (operating table) back and forth along the long axis of the body, and omission of nitrous oxide administration after CPB. In cases of left atrial enlargement--especially with chronic atrial fibrillation, LV aneurysms, and aortic valvular vegetation or calcification--embolization of air, clot, and other debris

can occur. [224] [225] [226] TEE is being used to assess the presence of potential emboli in the heart and aorta.

Protamine administration after removal of the aortic and vena caval cannulas should be done carefully and slowly (infusion or small intermittent doses) because of the risk of hypotension due to myocardial depression, histamine release, systemic vasodilation, pulmonary vasoconstriction, and anaphylactic or anaphylactoid reactions. [227] [228] The last two categories can also be associated with bronchospasm and pulmonary edema. An anaphylactic reaction with severe hemodynamic consequences requires immediate administration of heparin and reestablishment of CPB. It appears that intra-aortic or left atrial administration of protamine reduces (but does not eliminate) its hemodynamic and pulmonary side effects. [228] [229] The hemodynamic effects may be due to the protamine-heparin complex rather than to protamine per se. [230]

The adequacy of heparin neutralization can be verified by *in vitro* testing of the coagulability of the patient's blood (e.g., ACT). There is the possibility of recurrent heparin anticoagulation from the breakdown of heparin-protamine complexes by sulfatases and from late reperfusion of vascular beds containing heparinized blood. [119] [231] Platelet function and, less commonly, clotting factors may be deficient after CPB, and these possibilities should be considered in the differential diagnosis of excessive bleeding in the post-CPB period. [119] Thromboelastography is being used for rapid assessment of coagulation deficiencies. [119] [120]

Other Systems During and After Cardiac Surgery

The same concerns about preservation of organ function are required for cardiac as for any other type of surgery. However, a few topics are of particular importance in relation to the patient with cardiac disease and to the conditions associated with cardiac surgery. These are briefly summarized here.

Ventilation and the Lung

Complete oxygen saturation of hemoglobin is essential to providing the maximum supply of oxygen to the myocardium. Normocarbia is preferable to either hypercarbia (sympathetic stimulation, systemic vasodilation, pulmonary vasoconstriction) or hypocarbia (cerebral and coronary vasoconstriction). It is essential to achieve these ventilatory goals (Chs. 15 and 33) even if there are a number of obstacles. Tidal volume may need to be reduced at certain points in the procedure to prevent interference with the surgery. Moreover, a number of problems with pulmonary function can arise as a result of the use of vasoactive drugs (alterations of ventilation-perfusion relationships), accumulation of cellular and other debris in the pulmonary capillaries, interstitial and frank pulmonary edema, pneumothorax, atelectasis, and improper operation or function of the CPB pump oxygenator. Arterial blood gases (ABG) should be analyzed as often as necessary to allow optimal settings of the ventilator before and after CPB and optimal adjustment of gas and blood flow conditions during CPB. At a minimum, it is advisable to obtain ABG analyses after tracheal intubation, soon after initiation of CPB, during rewarming, just before discontinuing CPB, and after CPB. If the patient's condition is unstable, more frequent ABG analysis may be indicated to guide life-support therapy. Devices are continuing to be developed to allow continuous monitoring of arterial and mixed venous pH and gas tensions.

Continuous monitoring by mixed venous (PA) oximetry is potentially useful for judging the overall adequacy of ventilation and circulation and also for providing an early warning of adverse changes (e.g., degree and rapidity of hemoglobin desaturation during pulmonary suctioning via the endotracheal tube). [232] A careful and complete differential diagnosis may be required to correct every factor that may impair optimal ventilation and adequate oxygenation of tissues.

The controversy about the appropriateness of temperature correction of ABG values for the hypothermic state remains unsettled. [216] [233] [234] [235] The data available for cardiac surgical patients suggest that there are relatively minor hemodynamic consequences of omitting versus adding carbon dioxide to the CPB reservoirs in an attempt to maintain the hypothermic pH at 7.4 and the temperature-corrected Pa CO_2 close to 40 mm Hg. However, the majority opinion has swayed to the viewpoint of Rahn, [233] that ABG results (measured at 37°C) should not be corrected for the body temperature of the hypothermic patient. The latter option can be implemented by simply telling the blood gas laboratory technician that the patient's temperature is 37°C, regardless of what the patient's actual temperature is; this is known as the Alpha-Stat management of carbon dioxide during CPB.

Postoperatively, endotracheal intubation and mechanical ventilatory assistance should be maintained (usually intermittent mandatory ventilation) until the following are accomplished: the patient is transferred to the intensive care setting, reasonable hemodynamic stability is evident, postsurgical bleeding is at an acceptable (low) rate, body rewarming is complete, the patient is conscious and able to respond to commands (e.g., to cough), and there is evidence (e.g., normal muscle strength, acceptable ventilatory mechanics) that the patient can maintain satisfactory spontaneous ventilation and protect the airway. Antagonists to arouse the patient (e.g., physostigmine) and to restore neuromuscular function (e.g., neostigmine with atropine) can be used with cautious regard for their potentially adverse consequences. However, we believe that the use of naloxone or any other opioid antagonist to restore ventilatory function is to be discouraged in the immediate postoperative period for several reasons: the opioid antagonist unmasks pain and causes discomfort; it results in sympathetic stimulation with potentially adverse hemodynamic consequences; it increases the incidence of nausea, retching, and vomiting, all of which contribute to ventilatory and circulatory instability; and it makes restoring analgesia and calm difficult until the antagonist is eliminated from the body. [168]

Urine Output and the Kidney

During hypothermic CPB, renal tubular function is depressed, [236] and a large volume of dilute urine (Chs. 18 and 34) is usually produced as a result of hemodilution, mannitol

(in CPB priming solution), and maintenance of renal glomerular perfusion and filtration. If urine volume is less than 1 mL/kg/h during CPB, mechanical obstruction to urine flow through the bladder catheter drainage system should be excluded before undertaking steps to increase renal perfusion and to promote urine output, which is essential for the excretion of potassium administered as a component of the cardioplegic solution. If hemolysis is occurring, it is especially important to maintain a high-volume urine flow to prevent the accumulation of hemoglobin and its metabolites in the renal tubules. Usually, renal tubular function is restored rapidly after CPB

provided that good renal perfusion is maintained (i.e., adequate cardiac output, minimal renal vasoconstriction). As always, renal failure is an ominous and life-threatening complication. [237]

Body weight gain due to accumulation of fluid is typical of patients after cardiac surgery. Usually patients experience a spontaneous diuresis during the second or third postoperative day, which continues until body fluids are brought into balance by the resumption of normal homeostatic mechanisms. [238] [239] Anticipation of the spontaneous diuresis is thought by some to indicate curtailment of the administration of potent diuretics such as furosemide unless there is another indication (e.g., pulmonary edema, CHF). Unnecessary use of diuretics leads to a variety of problems with fluid and electrolyte balance, creates hemodynamic instability, and interferes with the return of normal renal function. Excessive diuresis contracts circulating blood volume and entails the risk of reduced renal perfusion. Infusion of dopamine at a low dose rate may be useful to maintain renal perfusion and to promote diuresis. [240] [241]

Body Temperature and Metabolism

Hypothermia affects all cellular functions (Ch. 37) . These changes are reversible when normal body temperature is restored. Of special concern during the rewarming phase are the recovery of consciousness and the requirement of additional anesthetic drugs (potent inhaled anesthetics may be tolerated only in low concentrations because of their myocardial depressant properties and nitrous oxide should be avoided because of the risk of expansion of air emboli); an increased rate of biotransformation of heparin and increased coagulability of blood; and the uptake of potassium by cells, leading to hypokalemia. [242] With regard to potassium uptake, use of 500 to 1,000 mL of cardioplegic solution (approximately 25 mEq K^+/L) provides 12.5 to 25 mEq, some of which enters the circulation when coronary perfusion resumes. However, this amount of potassium may not equal that lost in urine during CPB. [242]

Two other important considerations are the possible difficulty in defibrillating the heart and maintaining a regular cardiac rhythm until the body core temperature exceeds 34°C, and the danger of body recooling unless the CPB rewarming time is sufficient to bring most of the body mass to a normal temperature. Persistence of temperature gradients (e.g., nasopharyngeal versus skin) is an indication of the inadequacy of rewarming and of the risk of recooling after CPB is discontinued. Surface rewarming by a heating blanket is inefficient and cannot be relied on to maintain body temperature, let alone to correct heat deficits in the adult patient. Pulsatile perfusion improves rewarming and can be accomplished by allowing the patient's heart to eject before discontinuing CPB. [243] Peripheral tissue perfusion and rewarming can be facilitated by use of a vasodilator. [244]

Persistent hypothermia contributes to postoperative problems, including coagulopathy, hypertension, and tachycardia, reflecting increased sympathetic activity, and shivering, which increases oxygen demand. [245] Muscle relaxants may be necessary to counteract the detrimental effects of shivering and excessive oxygen utilization in the critically ill patient.

Hypothermia, stress reactions, and administration of sympathomimetic inotropes decrease the response to insulin and may result in hyperglycemia, which can be exacerbated by the intravenous infusion of fluids containing dextrose. [246] [247] These conditions are exacerbated in the diabetic patient. Hyperglycemia contributes to diuresis and, if severe, can produce coma. Also, hyperglycemia may be detrimental to CNS and cardiac recovery in the event of a global or a focal ischemic insult. [248] [249] A satisfactory range of serum glucose is 100 to 250 mg/dL. Certainly, serum glucose should be determined regularly during the operative and postoperative periods in any diabetic patient, in any patient given insulin (with or without glucose) in the treatment of hyperkalemia or poor cardiac performance, and in persistently comatose patients.

Hyperthermia due to rapid or excessive rewarming on discontinuing CPB is dangerous because it increases metabolism and risks the development of ischemia in all tissues and organs, especially the CNS and heart. The temperature of arterial inflow during CPB should not exceed 38°C.

Protection of the Central Nervous System

The CNS (Chs. 19 and 35) , being very vulnerable to hypoxemia and hypoperfusion, is at risk from hemodynamic instability during cardiac surgery. In elderly patients, especially those with atherosclerosis, the cerebral circulation may be tenuous under normal conditions. Perfusion may be compromised by changes in arterial blood pressure and flow (e.g., changes produced by hypothermic CPB, [216] hypocarbia, vertebral or carotid artery occlusion by certain positions of the neck), by increases in venous blood pressure (such as superior vena caval obstruction by the CPB cannula), and by embolization of air, thrombus, and debris from the operative site.

At present, the EEG is the only practical means of monitoring the integrity of the CNS in the cardiac surgical patient. Whether the EEG should be monitored routinely is debatable. Some have suggested that if cerebral perfusion is satisfactory, overall perfusion of the body is probably also satisfactory. However, the issue remains controversial because (1) the full 21-lead EEG used by the neurologist for diagnosis is impractical as a monitoring device and anything less leaves open the possibility of missing regional CNS ischemia; and (2) processing of the EEG to produce easily recognizable patterns of abnormality makes EEG monitoring more useful to the anesthesiologist, but the devices are expensive and usually suitable for monitoring only two pairs of leads. Bilateral placement of these leads allows comparison of a similar point in both cerebral hemispheres, which

may be sufficient to detect global reductions in cerebral perfusion. [249] One clear indication for global EEG monitoring is to guide the use of thiopental for CNS protection against incomplete ischemia. Such protection requires thiopental doses sufficient to produce EEG burst suppression and the corresponding reduction in cerebral metabolic rate. Patients vary considerably in their thiopental requirements, and it is advisable to use the lowest necessary dose to minimize the side effects of thiopental on the cardiovascular system. [134] [250]

Hypothermia during CPB has a protective effect on the CNS as well as on other body organs. However, the risks to CNS integrity noted previously are present both before and after the period of hypothermia, and some surgeons see benefits in maintaining near-normal body temperatures for cardiac operations, although most now allow the body temperature to "drift" to 33° to 34°C, which reduces CNS metabolism and provides a measure of CNS protection. Other measures to prevent or minimize the consequences of CNS insult may be needed. The use of thiopental to protect against CNS ischemia has been noted. [250] [251]

Other preventive measures may include diagnostic evaluation of symptomatic carotid bruits and possible endarterectomy before heart surgery [10] ; maintenance of usual or slightly higher than usual mean arterial pressure during surgery and CPB, especially in patients with known cerebrovascular disease [252] ; scrupulous prevention of air embolization and avoidance of nitrous oxide after hypothermic CPB, which always produces micro air emboli; and possibly the unproven use of prophylactic corticosteroids in patients at particular risk (e.g., cerebrovascular disease, valvular surgery). The tradition of manually compressing the common carotid arteries during the first minute of resumed LV ejection, when embolization is most likely to occur, may be helpful; but it carries the risk of reducing cerebral blood flow and of dislodging carotid arterial atherosclerotic plaque. It is best to prevent hyperglycemia, which can exacerbate a global (and perhaps even a focal) ischemic insult to the CNS. [247] [248] Incidentally, a recent cerebrovascular accident is believed by some to be an absolute contraindication to the use of anticoagulants and therefore to cardiac surgery involving CPB. Treatment of potential catastrophic events is outlined in Chapter 56 .

Coagulation System

Management of blood coagulation (Ch. 46) during and after cardiac surgery is of critical importance from several standpoints. The coagulation cascade must be inactivated with heparin before initiating CPB and the heparin neutralized by protamine after CPB to prevent uncontrolled bleeding. CPB itself has several deleterious effects on the coagulation system that can contribute to post-bypass hemorrhage, thereby increasing blood product administration (with the attendant risks of transfusion reaction and transmission of infectious disease) and occasionally necessitating return to the operating room for reexploration.

Several measures may be taken to minimize bleeding and transfusion requirements after cardiac surgery. Preoperative donation of autologous blood has safely and effectively been used to decrease homologous blood transfusion. [253] Withdrawal of 1 to 2 units of the patient's blood via a central venous cannula before CPB should be considered for large patients with a normal hematocrit level and stable hemodynamics. The blood is collected in citrate phosphate dextrose (CPD) containing bags, periodically mixed by rotation, and reinfused after CPB. The intraoperative collection of shed blood for separation, washing, and readministration to the patient is routinely used in many cardiac centers [254] and can significantly reduce the use of bank blood. [255] The pre-bypass withdrawal of autologous platelet-rich plasma by pheresis for reinfusion after bypass [256] and hemoconcentration by ultrafiltration during CPB [257] are other bloodconserving techniques used during heart surgery.

Several drugs have been used in attempts to decrease bleeding after cardiac surgery. Desmopressin, a synthetic analogue of vasopressin, which stimulates the release of von Willebrand factor from vascular endothelial cells, does not appear to diminish bleeding when used on a routine basis [258] but may be effective in certain subgroups of patients, such as those taking aspirin [259] or with evidence of preexisting platelet dysfunction. [260] Two synthetic drugs that inhibit fibrinolysis, epsilon-aminocaproic acid (EACA) [261] and tranexamic acid, [258] have been shown to decrease postoperative blood loss when given during and after CPB, but questions remain regarding the ability of these drugs to lessen the amount of banked blood ultimately transfused to a patient. We give EACA to patients expected to have long and potentially complicated operations such as repeat surgery, multiple valve replacement, or combined valve-CABG surgery. Aprotinin, a naturally occurring polypeptide, which inhibits the inflammatory response and activation of several proteolytic enzymes, has been shown to decrease both bleeding and transfusion requirements when given to cardiac surgical patients. [262] Aprotinin's primary beneficial effect is believed to be preservation of platelet function during CPB, but it also inhibits fibrinolysis by blocking the action of plasmin. [263] Aprotinin is expensive, can confuse interpretation of the ACT, and has been associated with severe anaphylactic reactions. Hence, it is recommended that a test dose be given to all patients and that aprotinin not be used in first-time, uncomplicated heart operations in order to avoid sensitizing the patient who may later benefit from its use during a reoperation.

The diagnosis and treatment of coagulopathy associated with cardiac surgery are ideally guided by objective laboratory data that provide a rational basis for intervention. [119] [264] The routine prophylactic administration of coagulation factors is to be discouraged but appears to be a common practice. [265] As a practical matter, however, situations arise in the operating room in which bleeding is clearly due to coagulopathy, and treatment is needed before a complete laboratory analysis of the problem is available. Knowledge of the common coagulation defects after CPB is useful in deciding about empiric therapy.

The severity of coagulopathy caused by CPB is related to CPB duration; CPB lasting longer than 2 hours should alert one to the possibility of bleeding problems. Suturing sites of surgical bleeding and complete antagonism of heparin are the first and second steps in treating post-bypass bleeding. Inadequate platelet function is the most common cause of abnormal coagulation after CPB once heparin anticoagulation has been reversed. [266] Bypass causes both a decrease in

the number of circulating platelets and function of those platelets remaining may be impaired by CPB and by drugs (e.g., aspirin) taken preoperatively by the patient. Therefore, platelet transfusion should be the next therapeutic intervention if coagulopathic bleeding is present. Less commonly, CPB causes clinically significant depletion of the coagulation proteins, especially factors V and VIII, for which fresh frozen plasma is the treatment of choice. Fibrinogen levels below 100 mg/dL should be treated with cryoprecipitate. Administration of desmopressin and antifibrinolytic drugs such as EACA should be considered if bleeding persists and is severe. Severe coagulopathy after CPB, especially after very prolonged bypass, is usually multifactorial and often seems to improve only with the rapid, almost simultaneous administration of all of the above.

Postoperative Considerations

The anesthesiologist's responsibility to the patient does not end until there is complete recovery from anesthetic effects and complications (Chs. 68 and 69) . Nursing and other personnel in the ICU and wards can be helpful in discharging this responsibility. [267] Their cooperation should be elicited by the anesthesiologist through a recognition of their professional standing, maintenance of a respectful attitude, acknowledgment and appreciation of their services to the patients, and support of their professional needs (e.g., timely responses to inquiries about the patient, participation in their in-service training programs).

Transfer of the Patient

Transferring the patient from the operating room to the ICU involves a continuation of the monitoring and life-support procedures established during anesthesia and surgery. In all cases it is desirable to make the following provisions for the transfer: (1) portable oxygen and the means of delivering positive-pressure ventilation; (2) continuous monitoring of arterial blood pressure and the ECG, using a stethoscope (preferably esophageal) as a backup means of assessing ventilation and heart rate, rhythm, and contractility; (3) maintenance of constant intravenous infusion of drugs needed for support of the circulation; (4) ready accessibility of the pacemaker controls (if one is in place) and of resuscitative drugs and devices, including a defibrillator; (5) another physician or assistant experienced in the resuscitation and care of cardiac surgical patients; (6) analgesic and sedative drugs; (7) direct route for the transfer, free of any delays (i.e., an elevator waiting for the patient, not vice versa); and (8) advance notification of ICU personnel of imminent transfer of the patient from the operating room.

On arrival in the ICU, the monitoring and life-support procedures should be continued by the anesthesiologist until the orderly transfer of these functions to the nurse and the intensive care specialist physician is completed. The specialist and nurse should be informed of any unusual events or complications that occurred before and during surgery and any problems that are anticipated in the postoperative period. They should be given a summation of the patient's vital signs, optimal hemodynamic variables, ventilatory status, fluid and electrolyte balance, adequacy of blood replacement and coagulability, and anesthetic and drug therapy. All orders should be written clearly and reviewed by the nurse to detect any ambiguities before the anesthesiologist leaves the patient. Furthermore, the nurse should be informed of the means of contacting the anesthesiologist if any questions or problems arise.

Anticipation of Problems Early in the Postoperative Period

From observations in the operating room, the anesthesiologist probably knows more than anyone else about the patient's condition in the early postoperative period. Valuable insight can be provided to the physicians and others caring for the patient in the intensive care setting.

Pain Management

Detailed discussions of postoperative acute and chronic pain therapy [268] and specifically of pain management after thoracotomy are found in Chapters 69 and 70 . Most cardiac surgical operations today are performed through a median sternotomy. In general, midline surgical incisions are less painful, and there is a widely held clinical impression that the intensity of pain following a median sternotomy is considerably less than that experienced after thoracotomy. In fact, most patients undergoing CABG surgery complain more about the discomfort in their legs from which saphenous vein grafts have been harvested. In addition to the localized discomfort of a median sternotomy, there are sometimes painful complications of spreading the sternotomy, which results in fractured and dislocated ribs, intercostal nerve trauma, and myofascial pain involving the costochondral junctions, rib-vertebral joints, shoulder girdle, and anterior chest muscles. In addition, visceral-type pain can arise from persistent angina pectoris, pericarditis, pleuritic chest pain aggravated by the presence of chest tubes, and pain from other mediastinal and thoracic structures such as the esophagus, lungs, and aorta. The latter sources need to be kept in mind in terms of differential diagnosis.

Given the dispersed sources of discomfort to the cardiac surgical patient in the early postoperative period, from discomfort due to the endotracheal tube and shoulder pain to leg incisional pain, there are a limited number of options for pain management. [268] The use of spinal-epidural anesthesia-analgesia intraoperatively and postoperatively is contraindicated by the use of fully anticoagulating doses of heparin and the risk of persistent coagulopathy postoperatively and by marked changes in circulating blood volume, body temperature, and other variables that affect or are dependent on sympathetic nervous system activity. Therefore, systemic administration of opioids is by far the most frequently used analgesic therapy. In the immediate postoperative period, the residual effects of opioids administered intraoperatively as part of the anesthetic are supplemented by intermittent intravenous injections as needed or by a low-dose continuous infusion until the patient's vital functions are stabilized and the weaning of mechanical ventilation is anticipated. Thereafter, patient-controlled analgesia may be useful as the

patient regains consciousness and is able to operate the control device. At that point, the continuous epidural analgesia can be considered but seldom is used in practice. Rather, oral analgesics, including the nonsteroidal anti-inflammatory drugs, are administered as the indications for intravenous opioids diminish.

Learning About Anesthetic Complications

Even though the patient usually remains in the hospital for several days after cardiac surgery, it is difficult for the busy anesthesiologist to follow the patient carefully enough to become aware of complications that may be related to intraoperative events. Again, cooperation and communication with those caring for the patient on a

daily basis are helpful; thus the anesthesiologist should ask about problems and complaints that have been encountered postoperatively. The surgeon and cardiologist can provide the necessary feedback of information, especially that discovered during a follow-up visit after the patient's discharge from the hospital. Usually they will be eager to communicate and share the problems once they are aware of the anesthesiologist's interest and concern. This concern, in and of itself, often fosters a mutual feeling of respect.

All the preceding communications do not preclude the necessity of a personal visit to the patient by the anesthesiologist in the postoperative period. Such a visit should ideally include a survey of the patient's chart, a discussion with the responsible nurse, and an interview with the patient. After some general questions, the anesthesiologist may find it useful to ask the patient about specific items related to the following: recall of surgical events (many patients relate dreams and ICU experiences to the intraoperative period) [269] ; problems with vision (prolonged effects of drugs on the pupils and accommodation may contribute to visual difficulties); pharyngeal discomfort and complications related to airway management (these are no different than for other types of surgery); discomfort related to positioning of the body and extremities during surgery (this may lead to greater awareness of the problems and improvement in positioning techniques); and complaints related to needle puncture sites, phlebitis, arterial cannulation and its complications, skin burns and irritation, etc. These should be fully discussed with the patient and noted on the chart. Obviously, any indicated therapy should be provided. Even though such procedures may be time-consuming, they reward the anesthesiologist and patient by better rapport between physicians and patients, an improved image of the anesthesiologist by the public, and a reduced incidence of malpractice suits.

References

1. Murphy ML, Hultgren HN, Detre K et al: Veterans Administration Cooperative Study. Treatment of chronic stable angina: A preliminary report of survival data. N Engl J Med 297:621, 1977.

2. Kennedy JW, Kaiser GC, Fisher LD et al: Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery. J Thorac Cardiovasc Surg 80:876, 1980.

3. O'Connor GT, Plume SK, Olmstead EM et al: A regional prospective study on in-hospital mortality associated with coronary bypass grafting. JAMA 266:803, 1991.

4. Williams SV, Nash DB, Goldfarb N: Differences in mortality from coronary artery bypass graft surgery at five teaching hospitals. JAMA 266:810, 1991.

5. Merry AF, Ramage MC, Whitlock RML et al: First-time coronary artery bypass grafting: The anaesthetist as a risk factor. Br J Anaesth 68:6, 1992.

6. National Center for Health Statistics, Centers for Disease Control and Prevention, Monthly Vital Statistics Report 41(7):suppl., Jan. 7, 1993.

7. Mangano DT: Perioperative cardiac morbidity. Anesthesiology 72:153, 1990.

8. Higgins TL, Estafanous FG, Loop FD et al: Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. JAMA 267:2344, 1992.

9. Reed GL III, Singer DE, Picard EH et al: Stroke following coronary artery bypass surgery: A case-control estimate of the risk from carotid bruits. N Engl J Med 319:1246, 1988.

10. Jones EL, Craver JM, Michalik RA et al: Combined carotid and coronary operations: When are they necessary? J Thorac Cardiovasc Surg 87:7, 1984.

11. Mason JJ, Douglas DK, Harris RA et al: The role of coronary angiography and coronary revascularization before noncardiac vascular surgery. JAMA 273:1919, 1995.

12. Nattel S, Rangno RE, Van Loon G: Mechanism of propranolol withdrawal phenomenon. Circulation 59:1158, 1979.

13. Slogoff S, Keats AS: Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 68:676, 1988.

14. Slogoff S, Keats AS, Ott E: Preoperative propranolol therapy and aortocoronary bypass operations. JAMA 240:1487, 1978.

15. Beller GA: Calcium antagonists in the treatment of Prinzmetal's angina and unstable angina pectoris. Circulation 80(suppl. IV):78, 1989.

16. Chung F, Houston PL, Cheng DCH et al: Calcium channel blockage does not offer adequate protection from perioperative myocardial ischemia. Anesthesiology 69:343, 1988.

17. Reves JG, Kissin I, Lell WA et al: Calcium entry blockers: Uses and implications for anesthesiologists. Anesthesiology 57:504, 1982.

18. Prys-Roberts C: Hypertension and anesthesia--50 years on. Anesthesiology 50:281, 1979.

19. Smith NT, Corbascio AN (eds): Drug Interactions in Anesthesia, 2nd ed. Philadelphia, Lea & Febiger, 1986.

20. O'Connor DE: Accelerated acute clonidine withdrawal syndrome during coronary artery bypass surgery. Br J Anaesth 53:431, 1981.

21. Lown B, Black H, Moore FD: Digitalis, electrolytes, and the surgical patient. Am J Cardiol 6:309, 1960.

22. Colson P: Angiotensin-converting enzyme inhibitors in cardiovascular anesthesia. J Cardiothorac Vasc Anesth 7:734, 1993.

23. Pfeffer MA, Braunwald E, Moye LA et al: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. N Engl J Med 327:669, 1994.

24. SOLVD Investigators: Effects of enalapril on mortality and development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 327:685, 1992.

25. Thaker U, Geary V, Chalmers P et al: Low systemic vascular resistance during cardiac surgery: Case Reports, brief review, and management with angiotensin II. J Cardiothorac Vasc Anesth 4:360, 1990.

26. Tuman KJ, McCarthy RJ, O'Connor CJ et al: Angiotensin-converting enzyme inhibitors increase vasoconstrictor requirements after cardiopulmonary bypass. Anesth Analg 80:473, 1995.

27. Licker M, Neidhart P, Lustenberger et al: Long-term angiotensin-converting enzyme inhibitor treatment attenuates adrenergic responsiveness without altering hemodynamic control in patients undergoing cardiac surgery. Anesthesiology 84:789, 1996.

28. Stoelting RK: Pharmacology and Physiology in Anesthetic Practice, 2nd ed. Philadelphia, Lippincott-Raven, 1991.

29. Slogoff S, Keats AS, Arlund C: On the safety of radial artery cannulation. Anesthesiology 59:42, 1983.

30. Troianos CA, Kuwik RJ, Pasqual JR et al: Internal jugular vein and carotid artery anatomic relation as determined by ultrasonography. Anesthesiology 85:43, 1996.

31. Epstein SE, Quyyumi AA, Bonow RO: Myocardial ischemia--silent or symptomatic. N Engl J Med 318:1038, 1988.

32. Carroll JD, Hesso M, Hirzel HO et al: Dynamics of left ventricular filling at rest and during exercise. Circulation 68:59, 1983.

33. Braunwold E, Kloner RA: The stunned myocardium: Prolonged, post ischemic ventricular dysfunction. Circulation 66:1146, 1982.

34. Schlant RC, Sonnenblick EH: Pathophysiology of heart failure. In Hurst JW (ed): The Heart, Arteries and Veins, 7th ed. New York, McGraw-Hill, 1990.

35. McKary RG, Pfeffer MA, Pasternak RC et al: Left ventricular remodeling after myocardial infarction: A corollary to infarct expansion. Circulation 74:693, 1986.

36. Kirklin JW, Akins CW, Blackstone EH et al: ACC/AHA Task Force report: Guidelines and indications for coronary bypass graft surgery. J Am Coll Cardiol 17:543, 1991.

37. Loop FD, Lytle BW, Cosgrove DM et al: Influence of the internal mammary-artery graft on 10 year survival and other cardiac events. N Engl J Med 314:1, 1986.

38. Weber KT, Janicki JS: The metabolic demand and oxygen supply of the heart: Physiologic and clinical consideration. Am J Cardiol 44:722, 1979.

39. Braunwald E: Control of myocardial oxygen consumption: Physiologic and clinical considerations. Am J Cardiol 37:416, 1971.

40. Berne RM, Levy MN: Cardiovascular Physiology, 5th ed. St. Louis, CV Mosby, 1986.

41. Boudoulas H, Rittger SE, Lewis RP: Changes in diastolic time with various pharmacologic agents: Implications of myocardial perfusion. Circulation 60:165, 1979.

42. Theroux P, Waters D, Lam J et al: Reactivation of unstable angina after the discontinuation of heparin. N Engl J Med 327:141, 1992.

43. London MS, Hollenberg M, Wong MG et al: Intraoperative myocardial ischemia: Localization by continuous 12-lead electrocardiography. Anesthesiology 69:232, 1988.

44. Mason RE, Likar I, Biern RO et al: Multiple-lead exercise electrocardiography: Experience in 107 normal subjects and 67 patients with angina pectoris, and comparison with coronary cinearteriography in 84 patients. Circulation 36:517, 1967.

45. Slogoff S, Keats AS, David Y et al: Incidence of perioperative myocardial ischemia detected by different electrocardiographic systems. Anesthesiology 73:1074, 1990.

46. Lieberman RW, Orkin FK, Jobes DR et al: Hemodynamic predictors of myocardial ischemia during halothane anesthesia for coronary artery revascularization. Anesthesiology 59:36, 1983.

47. Clements FM, de Bruijn NP: Review article: Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. Anesth Analg 66:248, 1987.

48. Leung JM, O'Kelly BF, Mangano DT: Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand in patients undergoing CABG surgery. Anesthesiology 73:802, 1990.

49. Leung JM, O'Kelly BF, Browner WS et al: Prognostic importance of postbypass regional wall-motion abnormalities in patients undergoing coronary artery bypass graft surgery. Anesthesiology 71:16, 1989.

50. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107, 1985.

51. Diodati J, Theroux P, Latour JG et al: Effects of nitroglycerin at therapeutic doses on platelet aggregation in unstable angina pectoris and acute myocardial infarction. Am J Cardiol 66:683, 1990.

52. Flaherty JT: Unstable angina. Rational approach to management. Am J Med 76:52, 1984.

53. Hug CC Jr: New perspectives on anesthetic agents. Am J Surg 156:406, 1988.

54. Slogoff S, Keats AS: Randomized trial of primary anesthetic agents on outcome of coronary bypass operations. Anesthesiology 70:79, 1989.

55. Tuman KJ, McCarthy RJ, Spiess BD et al: Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? Anesthesiology 70:189, 1989.

56. Mangano DT: Anesthetics, coronary artery disease, and outcome: Unresolved controversies. Anesthesiology 70:175, 1989.

57. Leung JM, Goehner P, O'Kelly BF et al: Isoflurane anesthesia and myocardial ischemia: Comparative risk versus sufentanil anesthesia in patients undergoing coronary artery bypass graft surgery. Anesthesiology 74:838, 1991.

58. Keats AS: The Rovenstine Lecture 1983: Cardiovascular anesthesia: Perceptions and perspectives. Anesthesiology 60:467, 1984.

59. Keats AS: What do we know about anesthetic mortality? Anesthesiology 50:387, 1979.

60. Steen PA, Tinker JH, Tarahan S: Myocardial infarction after anesthesia and surgery. JAMA 239:2566, 1978.

61. Reiz S, Balfors E, Sorensen MB et al: Isoflurane: A powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 59:91, 1983.

62. Buffington CW, Romson JL, Levine A et al: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 66:280, 1987.

63. Merin RG, Hamilton WK, Abramowitz J: Is isoflurane dangerous for the patient with coronary artery disease? Another view. I-III. Anesthesiology 53:439, 1980; 55:341, 1981; 64:137, 1986.

64. Merin RG: Is anesthesia beneficial for the ischemic heart? I-III. Anesthesiology 53:439, 1980; 55:341, 1981; 64:137, 1986.

65. Pulley DD, Kirvassilis GV, Kelermenos N et al: Regional and global myocardial circulatory and metabolic effects of isoflurane and halothane in patients with steal-prone coronary anatomy. Anesthesiology 75:756, 1991.

66. Priebe HJ: Isoflurane and coronary hemodynamics. Anesthesiology 71:960, 1989.

67. Robotham JL, Takata M, Berman M et al: Ejection fraction revisited. Anesthesiology 74:172, 1991.

68. Gorlin R, Gorlin SG: Hydraulic formula for calculation of the stenotic mitral valve, other cardiac valves, and central circulating shunts. Am Heart J 41:1, 1951.

69. Reisner SA, Meltzer RS: Normal values of prosthetic valve Doppler echocardiographic parameters: A review. J Am Soc Echocardiogr 1:201, 1988.

70. Zabalogoitia M: Echocardiographic assessment of prosthetic heart valves. Curr Probl Cardiol 17:269, 1992.

71. Hurford WE, Zapol WM: The right ventricle and critical illness: A review of anatomy, physiology, and clinical evaluation of its function. Intensive Care Med 14:448, 1988.

72. Calvin JE: Acute right heart failure: Pathophysiology, recognition, and pharmacological management. J Cardiothorac Vasc Anesth 5:507, 1991.

73. McIlduff JB, Daggett WM, Buckley MJ et al: Systemic and pulmonary hemodynamic changes immediately following mitral valve replacement in man. J Cardiovasc Surg 21:261, 1980.

74. Eckberg DL, Gault JH, Bouchard RL et al: Mechanics of left ventricular contraction in chronic severe mitral regurgitation. Circulation 47:1252, 1973.

75. Harshaw CW, Grossman W, Munro AB et al: Reduced systemic vascular resistance as therapy for severe mitral regurgitation of valvular origin. Ann Intern Med 83:312, 1975.

76. Cobbs BW Jr, Hatcher CR, Craver JM et al: Transverse mid-ventricular disruption after mitral valve replacement. Am Heart J 99:33, 1980.

77. Bonow RO, Rosing DR, McIntosh CL et al: The natural history of asymptomatic patients with aortic regurgitation and a normal left ventricular function. Circulation 68:509, 1983.

78. Hammermeister KE, Sethe GK, Henderson WG et al: A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. Veterans Affairs Cooperative Study on Valvular Heart Disease. N Engl J Med 328:1289, 1993.

79. Dodge HT, Kennedy JW, Peterson JL: Quantitative angiocardiographic methods in evaluation of valvular heart disease. Prog Cardiovasc Dis 16:1, 1973.

80. Bolen JL, Alderman EL: Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. Circulation 53:879, 1976.

81. Greenberg BH, DeMots H, Murphy E et al: Mechanism for improved cardiac performance with arteriolar dilators in aortic insufficiency. Circulation 63:263, 1981.

82. Gault JH, Covell JW, Braunwald E et al: Left ventricular performance following correction of free aortic regurgitation. Circulation 42:773, 1970.

83. Simon H, Krayenbuehl HP, Rutishauser W et al: The contractile state of the left ventricular myocardium in aortic stenosis. Am Heart J 79:587, 1970.

84. Lee SK, Jonsson B, Bevegard S et al: Hemodynamic changes at rest and during exercise in patients with aortic stenosis of varying severity. Am Heart J 79:318, 1970.

85. Hancock EW: Aortic stenosis, angina pectoris, and coronary artery disease. Am Heart J 93:382, 1977.

86. Vekshtein VI, Alexander RW, Yeung AC et al: Coronary atherosclerosis is associated with left ventricular dysfunction and dilatation in aortic stenosis. Circulation 82:2068, 1990.

87. Maron BJ, Bonow RO, Cannon RO et al: Hypertrophic cardiomyopathy: Interrelations of clinical manifestations, pathophysiology, and therapy. N Engl J Med 316:780, 844, 1987.

88. Jeanrenaud X, Goy JJ, Kappenberger L: Effects of dual-chamber pacing in hypertrophic obstructive cardiomyopathy. Lancet 339:1318, 1992.

89. McIntosh CL, Maron BJ: Current operative treatment of obstructive hypertrophic cardiomyopathy. Circulation 78:487, 1988.

90. Epstein SE, Henry WL, Clark CE et al: NIH conferences: Asymmetric septal hypertrophy. Ann Intern Med 81:650, 1974.

91. Thompson RC, Liberthson RR, Lowenstein E: Perioperative anesthetic risk of noncardiac surgery in hypertrophic obstructive cardiomyopathy. JAMA 254:2419, 1985.

92. Reitan JA, Wright RG: The use of halothane in a patient with asymmetrical septal hypertrophy: A case report. Can J Anaesth 29:154, 1982.

93. Ahn AJ, Segal BL: Isolated tricuspid insufficiency: Clinical features, diagnosis, and management. Prog Cardiovasc Dis 9:166, 1966.

94. Gelman S (ed): Anesthesia and Organ Transplantation. Philadelphia, WB Saunders Co., 1987.

95. Grose R, Greenberg M, Steingard R et al: Left ventricular volume and function during relief of cardiac tamponade in man. Circulation 66:149, 1982.

96. Wechsler AS, Auerbach BJ, Graham TC et al: Distribution of intramyocardial blood flow during pericardial tamponade. J Thorac Cardiovasc Surg 68:847, 1974.

97. Miller JI, Mansour KA, Hatcher CR: Pericardiectomy: Current indications, concepts, and results in a university center. Ann Thorac Surg 34:40, 1982.

98. Koller ME, Smith RB, Sjostrand U et al: Effects of hypo-, normo-, and hypercardia in dogs with acute cardiac tamponade. Anesth Analg 62:181, 1983.

99. Mattila I, Takkunen O, Mattila P et al: Cardiac tamponade and different modes of artificial ventilation. Acta Anaesthesiol Scand 23:236, 1984.

100. Martins JB, Manual WJ, Marcus ML et al: Comparative effects of catecholamines in cardiac tamponade: Experimental and clinical studies. Am J Cardiol 46:59, 1980.

101. Zaidan JR: Pacemakers. Anesthesiology 60:319, 1984.

102. Scherlag BJ, Lou SH, Helfant RA et al: Catheter technique for recording His-bundle activity in man. Circulation 39:13, 1969.

103. Jackman WM, Friday KJ, Fitzgerald DM et al: Use of intracardiac recordings to determine the site of drug action in paroxysmal supraventricular tachycardia. Am J Cardiol 62:8L, 1988.

104. Platia EV, Griffith LS, Watkins L et al: Treatment of malignant ventricular arrhythmias with endocardial resection and implantation of the automatic cardioverter-defibrillator. N Engl J Med 314:213, 1986.

105. Deutsch N, Hantler CB, Morady F et al: Perioperative management of the patient undergoing automatic internal cardioverter-defibrillator implantation. J Cardiothorac Anesth 4:236, 1990.

106. Kutalek SP, Dreifus LS: Implantable cardioverter-defibrillators. Adv Intern Med 38:421, 1993.

107. Avitall B, Kahn M, Krum D et al: Physics and engineering of transcatheter cardiac tissue ablation. J Am Coll Cardiol 22:921, 1993.

108. Gallagher JD, Liebermann RW, Meranze J et al: Amiodarone-induced complications during coronary artery surgery. Anesthesiology 55:186, 1981.

109. Feinberg BI, LaMantia KR, Levy WJ: Amiodarone and general anesthesia. A retrospective analysis. Anesth Analg 65:549, 1986.

110. Cabrol C, Pavie A, Mesnildrey P et al: Long-term results with total replacement of the ascending aorta and reimplantation of the coronary arteries. J Thorac Cardiovasc Surg 91:17, 1986.

111. Crawford ES, Snyder DM: Treatment of aneurysms of the aortic arch. J Thorac Cardiovasc Surg 85:237, 1983.

112. Murphy DA, Craver JM, Jones EL et al: Recognition and management of ascending aortic dissection complicating cardiac surgical operations. J Thorac Cardiovasc Surg 134:706, 1982.

113. Troianos CA, Savino JS, Weiss RL: Transesophageal echocardiographic diagnosis of aortic dissection during cardiac surgery. Anesthesiology 75:149, 1991.

114. Louri JK, Appelbe A, Martin RP: Detection of complex intimal flaps in aortic dissection by transesophageal echocardiography. Am J Cardiol 69:1361, 1992.

115. Kotter GS, Kotrly KJ, Kalbfleisch JH et al: Myocardial ischemia during cardiovascular surgery as detected by an ST segment trend monitoring system. J Cardiothorac Vasc Anesth 1:190, 1987.

116. Gottlieb SO: Perioperative myocardial ischemia and infarction. Detection of myocardial ischemia using continuous electrocardiography. Int Anesthesiol Clin 30:19, 1991.

117. Mora CT, Henson MB, Weintraub WS et al: The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. J Thorac Cardiovasc Surg 112:514, 1996.

118. Bull BS, Korpman RA, Huse WM et al: Heparin therapy during extracorporeal circulation. I: Problems inherent in existing heparin protocols. J Thorac Cardiovasc Surg 69:674, 1975.

119. Elison N, Jobes DR (eds): Effective Hemostasis in Cardiac Surgery. Philadelphia, WB Saunders Co., 1988.

120. Mallett SV, Cox JA: Thromboelastography. Br J Anaesth 69:307, 1992.

121. Dorman BH, Spinale FG, Bailey MK et al: Identification of patients at risk for excessive blood loss during coronary artery bypass surgery: Thromboelastography versus coagulation screen. Anesth

Analg 76:694, 1993.

122. Wang JS, Lin CY, Hung WT et al: Thromboelastogram fails to predict postoperative hemorrhage in cardiac patients. Ann Thorac Surg 53:435, 1992.

123. Cahalan MK, Litt L, Botvinik EH et al: Advances in noninvasive cardiovascular imaging: Implications for the anesthesiologist. Anesthesiology 66:356, 1987.

124. DeBruijn NP, Clements FM: Transesophageal Echocardiography. Boston, Martinus Nijhoff, 1987.

125. De Bruijn NP, Clements FM: Intraoperative Use of Echocardiography: A Society of Cardiovascular Anesthesiology Monograph. Lippincott-Raven, Philadelphia, 1991.

126. Mantle JA, Rogers WJ, Smith LR et al: Clinical effects of glucose-insulin-potassium on left ventricular function and acute myocardial infarction: Results from a randomized clinical trial. Am Heart J 102:313, 1981.

127. England MR, Gordon G, Salem M et al: Magnesium administration and dysrhythmias after cardiac surgery: A placebo-controlled, double-blind, randomized trial. JAMA 268:2395, 1992.

128. Zwerling HK: Does exogenous magnesium suppress myocardial irritability and tachyarrhythmias in the nondigitalized patient? Am Heart J 113:1046, 1987.

129. Gambling DR, Birmingham GL, Jenkins LC: Magnesium and the anesthetist. Can J Anaesth 35:644, 1988.

130. Robertson WG: Measurement of ionized calcium in body fluids--review. Ann Clin Biochem 13:540, 1976.

131. Levy WJ: Monitoring of the electroencephalogram during cardiopulmonary bypass. Anesthesiology 76:876, 1992.

132. Bashein G, Nessly ML, Bledsoe SW et al: Electroencephalography during surgery with cardiopulmonary bypass and hypothermia. Anesthesiology 76:878, 1992.

133. Mizrahi EM, Patel VM, Crawford ES et al: Hypothermic-induced electrocerebral silence, prolonged circulatory arrest, and cerebral protection during cardiovascular surgery. Electroencephalogr Clin Neurophysiol 72:81, 1989.

134. Zaidan JR, Klochany A, Martin WM et al: Effect of thiopental on neurologic outcome following coronary artery bypass grafting. Anesthesiology 74:406, 1991.

135. Van der Linden J, Casimir Ahn H: When do cerebral emboli appear during open heart operations? A transcranial Doppler study. Ann Thorac Surg 52:583, 1991.

136. Smith DS, Levy W, Maris M et al: Reperfusion hyperoxia in brain after circulatory arrest in humans. Anesthesiology 73:12, 1990.

137. Tuman KJ, McCarthy RJ, Spiess BD et al: Effect of pulmonary artery catheterization on outcome in patients undergoing coronary artery surgery. Anesthesiology 70:199, 1989.

138. Stengrub JS, Celoria G, Vickers-Lahi M et al: Therapeutic impact of pulmonary artery catheterization in a medical/surgical ICU. Chest 99:1451, 1991.

139. Practice Guidelines for Pulmonary Artery Catheterization. Anesthesiology 78:380, 1993.

140. Lunn JK, Stanley TH, Webster LR et al: Arterial blood-pressure and pulse-rate responses to pulmonary and radial arterial catheterization prior to cardiac and major vascular operations. Anesthesiology 51:265, 1979.

141. Waller JL, Johnson SP, Kaplan JA: Usefulness of pulmonary artery catheters during aortocoronary bypass surgery. Anesth Analg 61:221, 1982.

142. Waller JL, Zaidan JR, Kaplan JA et al: Hemodynamic responses to

preoperative vascular cannulation in patients with coronary artery disease. Anesthesiology 56:219, 1982.

143. Rosen J, Lunn LN (eds): Consciousness, Awareness, and Pain in General Anesthesia. London, Butterworth, 1987.

144. Hug CC: Does opioid "anesthesia" exist? Anesthesiology 73:1, 1990.

145. Hug CC Jr: Awareness during cardiac surgery. In Sevel PS, Bonke B, Winograd E (eds): Memory and Awareness in Anesthesia. Englewood Cliffs, NJ, Prentice-Hall, 1993, p 400.

146. Hug CC Jr, Hall RI, Angert KC et al: Alfentanil plasma concentration versus effect relationships in cardiac surgical patients. Br J Anaesth 61:435, 1988.

147. Lowenstein E, McPeek B: Capitalizing on research findings that appear to conflict. Anesthesiology 68:668, 1988.

148. Seitelberger R, Zwolfer W, Huber S et al: Nifedipine reduces the incidence of myocardial infarction and transient ischemia in patients undergoing coronary bypass grafting. Circulation 83:460, 1991.

149. Reves JG: The relative hemodynamic effects of Ca^{++} entry blockers. Anesthesiology 61:3, 1984.

150. Roach GW, Moldenhauer CC, Hug CC Jr et al: Hemodynamic responses to fentanyl or diazepam-fentanyl anesthesia in patients on chronic nifedipine therapy. Anesthesiology 61:A374, 1984.

151. Massagee JT, McIntyre RW, Kates RA et al: Effects of preoperative calcium entry blocker therapy on alpha-adrenergic responsiveness in patients undergoing coronary revascularization. Anesthesiology 67:485, 1987.

152. Maze M, Tranquill W: Alpha-2 adrenoceptor agonists: Defining the role in clinical anesthesia. Anesthesiology 74:581, 1991.

153. Flacke JW, Bloor BC, Flacke WE et al: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 67:11, 1987.

154. Abi-Jaoude F, Brusset A, Ceddaha A et al: Clonidine premedication for coronary artery bypass grafting under high-dose alfentanil anesthesia: Intraoperative and postoperative hemodynamic study. J Cardiothorac Vasc Anesth 7:35, 1993.

155. Hirsch IB, McGill JB, Cryer PE et al: Perioperative management of surgical patients with diabetes mellitus. Anesthesiology 74:346, 1991.

156. Elliott MJ, Gill GV, Home PM et al: A comparison of two regimens for the management of diabetes during open heart surgery. Anesthesiology 60:364, 1984.

157. Clements FM, de Bruijn NP: Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. Anesth Analg 66:249, 1987.

158. London MJ, Tubau JF, Wong MG et al: The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. Anesthesiology 73:644, 1990.

159. Thomson IR, Bowering JB, Hudson RJ et al: A comparison of desflurane and isoflurane in patients undergoing cardiac artery surgery. Anesthesiology 75:776, 1991.

160. Merin RG: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? Anesthesiology 55:398, 1981.

161. Marshall BE, Longnecker DE: General anesthetics. In Gilman AG, Goodman LS, Rall TW et al (eds): The Pharmacologic Basis of Therapeutics, 8th ed. New York, Macmillan, 1990, p 285.

162. Becker LC: Is isoflurane dangerous for the patient with coronary artery disease? Anesthesiology 66:259, 1987.

163. Tarnow J, Markschies-Hornung S, Schulte-Sasse U: Isoflurane improves the tolerance to pacing induced myocardial ischemia. Anesthesiology 64:147, 1986.

164. Philbin DM, Moss J, Akins CW et al: The use of H_1 and H_2 histamine antagonists with morphine anesthesia: A double-blind study. Anesthesiology 55:292, 1981.

165. Lowenstein E, Hallowell P, Levine FH et al: Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 281:1389, 1969.

166. Michelsen LG, Beique FA, Hoke JF et al: Pharmacokinetics of remifentanil in cardiac surgical patients. Abstracts, 16th Annual Meeting, Society of Cardiovascular Anesthesiologists, Montreal, Quebec, April 23-27, 1994.

167. Hug CC Jr: Pharmacokinetics and dynamics of narcotic analgesics. In Prys-Roberts C, Hug CC Jr (eds): Pharmacokinetics of Anaesthesia. London, Blackwell Scientific Publications, 1984, p 187.

168. Moldenhauer CC, Hug CC Jr: Use of narcotic analgesics as anesthetics. Clin Anesthesiol 2:107, 1984.

169. Prough DS, Roy R, Bumgarner J et al: Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. Anesthesiology 60:485, 1984.

170. Waller JL, Hug CC Jr, Nagle DM et al: Hemodynamic changes during fentanyl-oxygen anesthesia for aortocoronary bypass operation. Anesthesiology 55:212, 1981.

171. Christian CM II, Waller JL, Moldenhauer CC: Postoperative rigidity following fentanyl anesthesia. Anesthesiology 58:275, 1983.

172. Murkin JM, Moldenhauer CC, Hug CC Jr et al: Absence of seizures during induction of anesthesia with high-dose fentanyl. Anesth Analg 63:489, 1984.

173. Hall RI, Moldenhauer CC, Hug CC Jr: Fentanyl plasma concentrations maintained by a simple infusion scheme in patients undergoing cardiac surgery. Anesth Analg 76:957, 1993.

174. Ausems ME, Hug CC Jr, de Lange S: Variable rate of infusion of alfentanil as a supplement to nitrous oxide anesthesia for general surgery. Anesth Analg 62:982, 1983.

175. Philbin DM, Rosow CE, Schneider RC et al: Fentanyl and sufentanil anesthesia revisited: How much is enough? Anesthesiology 73:5, 1990.

176. Hug CC Jr: Lipid solubility, pharmacokinetics, and the EEG: Are you better off today than you were four years ago? Anesthesiology 62:221, 1985.

177. Alvis JM, Reves JG, Govier AV et al: Computer-assisted continuous infusions of fentanyl during cardiac anesthesia: Comparison with a manual method. Anesthesiology 61:41, 1985.

178. Ausems ME, Vuyk J, Hug CC Jr et al: Comparison of a computer-assisted infusion versus bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 68:851, 1988.

179. Reves JG, Fragen RJ, Vinik HR: Midazolam: Pharmacology and uses. Anesthesiology 62:310, 1985.

180. Ebert TJ, Muzi M, Berens R et al: Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology 76:725, 1992.

181. Hug CC Jr, McLeskey CH, Nahrwold ML et al: Hemodynamic effects of propofol: Data from 25,000 patients. Anesth Analg 77(suppl. 4):S21, 1993.

182. McClain DM, Hug CC Jr: Pharmacodynamics and dynamics of opiates. Int Anesthesiol Clin 22:75, 1984.

183. Newsom LR, Moldenhauer CC, Hug CC Jr et al: Hemodynamic interactions of moderate doses of fentanyl with etomidate and ketamine. Anesth Analg 64:260, 1985.

184. Philbin DM, Foex P, Drummond G et al: Postsystolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. Anesthesiology 62:166, 1985.

185. Cahalan MK, Prakash O, Rulf NR et al: Addition of nitrous oxide to fentanyl anesthesia does not induce myocardial ischemia in patients with ischemic heart disease. Anesthesiology 67:925, 1987.

186. Mitchell MM, Prakash O, Rulf ENR et al: Nitrous oxide does not induce myocardial ischemia in patients with ischemic heart disease and poor ventricular function. Anesthesiology 71:526, 1989.

187. Tuman KJ, McCarthy RJ, Spiess BD et al: Effects of nitrous oxide on coronary perfusion after coronary air embolism. Anesthesiology 67:952, 1987.

188. Tassonyi E, Neidhart P, Pittet JF et al: Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 69:793, 1988.

189. Stoops CM, Curtis CA, Kovach DA et al: Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentanil anesthesia for coronary artery bypass grafting or valve replacement. Anesthesiology 69:365, 1988.

190. Bidwai AV, Rogers CR, Pearce M et al: Preoperative stellate-ganglion blockade to prevent hypertension following coronary artery operations. Anesthesiology 51:345, 1979.

191. Liem TH, Booji LHDJ, Hasenbos MAWM et al: Coronary artery bypass grafting using two different anesthetic techniques: Part I: Hemodynamic results. J Cardiothorac Vasc Anesth 6:148, 1992.

192. Stenseth R, Berg EM, Bjella L et al: Effects of thoracic epidural analgesia on coronary hemodynamics and myocardial metabolism in coronary artery bypass surgery. J Cardiothorac Vasc Anesth 9:503, 1995.

193. Chaney MA, Smith KR, Barclay JC et al: Large-dose intrathecal morphine for coronary artery bypass grafting. Anesth Analg 83:215, 1996.

194. Swenson JD, Hullander RM, Wingler K et al: Early extubation after

cardiac surgery using combined intrathecal sufentanil and morphine. J Cardiothorac Vasc Anesth 8:509, 1994.

195. Galletti PM, Brecher GA: Heart-Lung Bypass: Principles and Techniques of Extracorporeal Circulation. Orlando, Florida, Grune & Stratton, 1962.

196. Gravelee GP, David RF, Utley JR (eds): Cardiopulmonary Bypass Principles and Practice. Baltimore, Williams & Wilkins, 1993.

197. Van Oeveren W, Kazatchkin MD, Descamps-Latscha B et al: Deleterious effects of cardiopulmonary bypass: A prospective study of bubble versus membrane oxygenation. J Thorac Cardiovasc Surg 89:888, 1985.

198. Masters RG: Pro: The superiority of the membrane oxygenator. J Cardiothorac Anesth 3:235, 1989.

199. Loop FD, Szabo J, Rowlinson RD et al: Events related to microembolism during extracorporeal perfusion in man: Effectiveness of in-line filtration recorded by ultrasound. Ann Thorac Surg 21:412, 1976.

200. Guidoin R, Laperche Y, Martin L et al: Disposable filters for microaggregate removal from extracorporeal circulation. J Thorac Cardiovasc Surg 71:502, 1976.

201. Dunbar RW, Price KA, Cannarella CF: Microaggregate blood filters: Effect on filtration time, plasma hemoglobin, and fresh blood platelet counts. Anesth Analg 53:577, 1974.

202. Edmunds LH: Pulseless cardiopulmonary bypass. J Thorac Cardiovasc Surg 84:805, 1982.

203. Philbin DM, Hickey PR, Buckley MS: Should we pulse? J Thorac Cardiovasc Surg 84:805, 1982.

204. Benedict JS, Buhl TL, Henney RP: Acute aortic dissection during cardiopulmonary bypass. Arch Surg 108:810, 1974.

205. Mils NL, Ochsner JL: Massive air embolism during cardiopulmonary bypass--causes, prevention and management. J Thorac Cardiovasc Surg 80:708, 1980.

206. Spampinato N, Stassano P, Gagliardi C et al: Massive air embolism during cardiopulmonary bypass: Successful treatment with immediate hypothermia and circulatory support. Ann Thorac Surg 32:602, 1981.

207. Verska JJ, Ludington LG, Brewer LA: A comparative study of cardiopulmonary bypass with non-blood and blood prime. Ann Thorac Surg 18:72, 1974.

208. Gordon RJ, Ravin M, Raiwitscher RE et al: Changes in arterial pressure, viscosity, and resistance during cardiopulmonary bypass. J Thorac Cardiovasc Surg 69:552, 1975.

209. Yeh T Jr, Shelton L, Yeh TJ: Blood loss and bank blood requirement in coronary bypass surgery. Ann Thorac Surg 26:11, 1978.

210. Nadjaabadi MH, Rastan H, Saide MT et al: Haemodynamic effects of acute intra-operative haemodilution in open heart surgery. Anaesthesia 27:364, 1978.

211. Bull BS, Korpman RA, Huse M et al: Heparin therapy during extracorporeal circulation II: The use of a dose response curve to individualize heparin and protamine dosage. J Thorac Cardiovasc Surg 69:685, 1975.

212. Kaul TK, Crow MJ, Somasundram MR et al: Heparin administration during extracorporeal circulation. J Thorac Cardiovasc Surg 78:95, 1979.

213. Cohen JA, Frederickson EL, Kaplan JA: Plasma heparin activity and antagonism during cardiopulmonary bypass with hypothermia. Anesth Analg 56:564, 1977.

214. Hecker BR, Knopes KD. Con: Pressure is more important than flow. J Cardiothorac Vasc Anesth 5:402, 1991.

215. Garman JK: Optimal pressures and flows during cardiopulmonary bypass. Pro: A low-flow, low-pressure technique is acceptable. J Cardiothorac Vasc Anesth 5:399, 1991.

216. Murkin JM, Farrar JK, Tweed WA et al: Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: The influence of Pa CO_2 . Anesth Analg 66:825, 1987.

217. Rich GF, Lubanski RE, McLoughlin TM: Differences between aortic and radial artery pressure associated with cardiopulmonary bypass. Anesthesiology 77:63, 1992.

218. Gay WA Jr, Ebert PA: Functional, metabolic and morphological effects of potassium-induced cardioplegia. Surgery 74:284, 1973.

219. Kirklin JW, Conti VR, Blackstone EH: Prevention of myocardial damage during cardiac operations. N Engl J Med 301:135, 1979.

220. Menache P, Piwnica A: Cardioplegia by way of the coronary sinus for valvular and coronary surgery. J Am Coll Cardiol 18:628, 1991.

221. Yau TM, Weisel RD, Mickel DA et al: Alternative techniques for cardioplegia. Circulation 86:377, 1992.

222. Buckberg GD: A proposed "solution" to the cardioplegia controversy. J Thorac Cardiovasc Surg 77:803, 1979.

223. Bailey JM, Levy JH, Rogers HG et al: Pharmacokinetics of amrinone during cardiac surgery. Anesthesiology 75:961, 1991.

224. Peirce EC: Specific therapy for arterial air embolism and other accidents using pump oxygenators. Ann Thorac Surg 29:300, 1980.

225. Stoney WS, Alford WC, Burrus GR et al: Air embolism and other accidents using pump oxygenators. Ann Thorac Surg 29:336, 1980.

226. McKibbin DW, Buckley BH, Green WR et al: Fatal cerebral atheromatous embolization after cardiopulmonary bypass. J Thorac Cardiovasc Surg 71:741, 1976.

227. Horrow JC: Protamine: A review of its toxicity. Anesth Analg 64:348, 1985.

228. Lowenstein E, Johnston WE, Lappas DG et al: Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Anesthesiology 59:470, 1983.

229. Pauca AL, Graham JE, Hudspeth AS: Hemodynamic effects of intraaortic administration of protamine. Ann Thorac Surg 35:637, 1983.

230. Rogers K, Milne B, Salerno TA: The hemodynamic effects of intra-aortic versus intravenous administration of protamine for reversal of heparin in pigs. J Thorac Cardiovasc Surg 85:851, 1983.

231. Pifarre R, Babka R, Sullivan HJ et al: Management of postoperative heparin rebound following cardiopulmonary bypass. J Thorac Cardiovasc Surg 85:174, 1983.

232. Nelson LD: Application of venous saturation monitoring. In Civetta JM, Taylor RW, Kirby RR (eds): Critical Care. Philadelphia, Lippincott-Raven, 1988, p 32.

233. Rahn H: Body temperature and acid-base regulation. Pneumonologie (Stuttg) 151:87, 1974.

234. Bashein G, Townes BD, Nessly ML et al: A randomized study of carbon dioxide management during hypothermic cardiopulmonary bypass. Anesthesiology 72:7, 1990.

235. Prough DS, Stump DA, Troost BT: Pa CO_2 management during cardiopulmonary bypass: Intriguing physiologic rationale, convincing clinical data, evolving hypothesis? Anesthesiology 72:3, 1990.

236. Hilberman M, Myers BD, Carrie BJ et al: Acute renal failure following cardiac surgery. J Thorac Cardiovasc Surg 77:880, 1979.

237. Abel RM, Buckley MJ, Austen WG et al: Etiology, incidence and prognosis of renal failure following cardiac operations. J Thorac Cardiovasc Surg 71:332, 1976.

238. Beattie HW, Evans G, Garnett ES et al: Sustained hypovolemia and extracellular fluid expansion following cardiopulmonary bypass. Surgery 71:891, 1972.

239. Yashar JJ, Hallman GL, Leachman RD et al: Cardiac output and blood volume changes after open-heart surgery. J Thorac Cardiovasc Surg 61:724, 1971.

240. Davis RF, Lappas DG, Kirklin JK et al: Acute oliguria after cardiopulmonary bypass: Renal function improvement with low-dose dopamine. Crit Care Med 10:852, 1982.

241. Schaer GL, Fink MP, Parrillo JE: Norepinephrine alone versus norepinephrine plus low-dose dopamine: Enhanced renal blood flow with combination pressor therapy. Crit Care Med 13:492, 1985.

242. Dieter RA, Neville WE, Pifarre R: Hypokalemia following hemodilution cardiopulmonary bypass. Ann Surg 171:17, 1970.

243. Williams GD, Seifen AB, Lawson NW et al: Pulsatile perfusion versus conventional high-flow nonpulsatile perfusion for rapid core cooling and rewarming of infants for circulatory arrest in cardiac operation. J Thorac Cardiovasc Surg 78:667, 1979.

244. Noback CR, Tinker JH: Hypothermia after cardiopulmonary bypass in man: Amelioration by nitroprusside-induced vasodilation during rewarming. Anesthesiology 53:277, 1980.

245. Bay J, Nunn JF, Prys-Roberts C: Factors influencing arterial P $_{C_2}$ during recovery from anesthesia. Br J Anaesth 40:398, 1968.

246. Hewitt RL, Wood RD, Ryan JR et al: Plasma insulin and glucose relationships during CPB. Surgery 71:905, 1972.

247. Lanier WL, Stangland KJ, Scheithauer BW et al: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. Anesthesiology 66:39, 1987.

248. Zasslow MA, Pearl RG, Shuer LM et al: Hyperglycemia increases acute neuronal ischemia changes after middle cerebral artery occlusion in cats. Stroke 20:519, 1989.

249. Levy WJ: Intraoperative EEG patterns: Implications for EEG monitoring. Anesthesiology 60:430, 1984.

250. Nussmeier NA, Arlund C, Slogoff S: Neurophysiologic complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. Anesthesiology 64:165, 1986.

251. Michenfelder JD: A valid demonstration of barbiturate-induced brain protection in man--at last. Anesthesiology 64:140, 1986.

252. Fitch W: Anesthesia for carotid artery surgery. Br J Anaesth 48:791, 1976.

253. Owings DV, Kruskall MS, Thurer RL et al: Autologous blood donations prior to elective cardiac surgery. Safety and effect on subsequent blood use. JAMA 262:1963, 1989.

254. Ikead S, Johnston MF, Yagi K et al: Interoperative autologous blood salvage with cardiac surgery: An analysis of five years experience in more than 3,000 patients. J Clin Anesth 4:359, 1992.

255. Hall RI, Schwieger IM, Finlayson DC: The benefit of the Hemonetics cell saver apparatus during cardiac surgery. Can J Anaesth 37:618, 1990.

256. Delrossi AJ, Cernaianu AC, Vertrees RA et al: Platelet rich plasma reduces postoperative blood loss after cardiopulmonary bypass. J Thorac Cardiovasc Surg 100:281, 1990.

257. Boldt J, Kling D, von Bormann B et al: Blood conservation in cardiac operations. Cell separation versus hemofiltration. J Thorac Cardiovasc Surg 97:832, 1989.

258. Horrow JC, Van Riper DF, Strong MD et al: Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. Circulation 84:2063, 1991.

259. Gratz I, Koehler J, Olsen D et al: The effect of desmopressin acetate on postoperative hemorrhage in patients receiving aspirin therapy before coronary bypass operations. J Thorac Cardiovasc Surg 104:1417, 1992.

260. Mongan PD, Hosking MP: The role of desmopressin acetate in patients undergoing coronary artery bypass surgery: A controlled clinical trial with thromboelastographic risk stratification. Anesthesiology 77:38, 1992.

261. Delrossi AJ, Cernaianu AC, Botros S et al: Prophylactic treatment of postperfusion bleeding using EACA. Chest 96:27, 1989.

262. Dietrich W, Barankay A, Hahnel C, Richter JA: High-dose aprotinin in cardiac surgery: Three years experience in 1,784 patients. J Cardiothorac Vasc Anesth 6:324, 1992.

263. Hardy JF, Desroches J: Natural and synthetic antifibrinolytics in cardiac surgery. Can J Anaesth 39:353, 1992.

264. Harker L: Bleeding after cardiopulmonary bypass. N Engl J Med 314:1446, 1986.

265. Goodnough LT, Johnston MF, Toy PT: The variability of transfusion practice in coronary artery bypass surgery. JAMA 265:97, 1991.

266. Woodman RC, Harker LA: Bleeding complications associated with cardiopulmonary bypass. Blood 76:1690, 1990.

267. McCauley KM, Brest AN, McGoon DC: McGoon's Cardiac Surgery: An Interprofessional Approach to Patient Care. Philadelphia, FA Davis, 1985.

268. Gravelee GP, Rauch RL (eds): Pain Management in Cardiothoracic Surgery. Philadelphia, Lippincott-Raven, 1993.

269. Becker R, Katz J, Polonius MJ et al (eds): Psychopathological and Neurological Dysfunctions Following Open-Heart Surgery. Berlin, Springer-Verlag, 1982.

270. King SB III, Douglas JS: Coronary arteriography and left ventriculography. In Hurst JW (ed): The Heart, 4th ed. New York, McGraw-Hill, 1978.

271. Thomas SJ, Lowenstein E: Anesthetic management of the patient with valvular heart disease. Int Anesthesiol Clin 17:67, 1979.

272. Roberts WC, Perloff JK: Mitral valvular disease. Ann Intern Med 77:939, 1972.

273. Nose Y: Manual on Artificial Organs, vol. 2. The Oxygenator. St. Louis, CV Mosby, 1973.

Chapter 50 - Anesthesia for Pediatric Cardiac Surgery

William J. Greeley
James M. Steven
Susan C. Nicolson
Frank H. Kern

INTRODUCTION

Cardiac surgery is an established and effective treatment for children with congenital heart defects. Early successes in surgical treatment have led to a new therapeutic era in the management of congenital heart disease and have fostered the development of the subspecialties pediatric cardiology and cardiac surgery and their collaboration. Through this cooperative effort, tremendous progress in medical diagnosis and surgical treatment has been achieved. In turn, these accomplishments gave rise to the development of pediatric cardiac anesthesiologists, individuals who understand the pathophysiology of congenital heart malformations, the diagnostic and surgical procedures used to treat heart disease, and the principles of pediatric and cardiac anesthesia as well as intensive care medicine. Pediatric cardiac anesthesia continues to evolve as an exciting and technically demanding subspecialty in which anesthetic management is based on physiologic principles.

Congenital cardiovascular surgery and anesthesia are often performed under unusual physiologic conditions. Rarely in clinical medicine are patients exposed to such biologic extremes as during congenital heart surgery. Commonly, patients are cooled to 15 to 18°C, acutely hemodiluted by more than 50 percent of their extracellular fluid volume, and undergo periods of total circulatory arrest lasting up to 1 hour. The ability to manage patients under these physiologic extremes is a vital function of the pediatric cardiovascular anesthesiologist. As with other areas of medicine, the application and management of technology preceded a comprehensive understanding of its physiologic effects. Relevant clinical information, primarily generated from investigations in pediatric intensive care units (ICUs) as well as in operating rooms, has been especially valuable in contributing to the understanding of anesthetic management for children undergoing cardiac surgery.

Clearly, the perioperative management of these complex cases requires a group of physicians (surgeon, anesthesiologist, cardiologist, critical care specialist) and nurses to work as a team. This team orientation is essential to the achievement of an optimal outcome. Although the quality of the surgical repair, the effects of cardiopulmonary bypass, and postoperative care are the major determinants of outcome, meticulous anesthetic management is also imperative. Ideally,

despite the complexity of the cases and the marked physiologic changes attributed to cardiopulmonary bypass (CPB) and the surgical procedures, anesthetic care should never contribute substantially to morbidity or mortality. [1] The challenge is to understand the principles underlying the management of patients with congenital heart disease and to apply them to clinical anesthesia. Assuming the reader already understands the fundamentals of adult cardiac and general pediatric anesthesia, detailed in Chapters 49 and 59 , respectively, the first section of this chapter provides an overview of some of the unique features of the pediatric patient, congenital heart disease, and the surgical procedures, which are essential to understanding the anesthetic management of children undergoing cardiac surgery. The second section addresses the perioperative anesthetic management for procedures requiring CPB. The last section discusses closed-heart procedures and anesthesia for interventional catheterization.

UNIQUE FEATURES OF PEDIATRIC CARDIAC ANESTHESIA

Although many of the principles governing modern pediatric cardiovascular anesthesia are similar to those that guide anesthetic management of the adult cardiac patient, several important differences do exist. It is essential to consider the differences that make pediatric cardiovascular management unique (Table 50-1) . Broadly, certain characteristics of the patient, congenital heart disease, and surgery account for these unique features, and are reviewed below. These differences are attributable to normal organ system maturation in the neonate and young infant, differing pathophysiologic

TABLE 50-1 -- Unique Characteristics of Pediatric Cardiac Anesthesia

Patient
Normal organ system development and maturational changes of infancy
Cardiovascular: blood flow patterns of circulation at birth, myocardial compliance, systemic and pulmonary vasculature, and beta-adrenergic receptors
Pulmonary: respiratory quotient, closing capacity, chest compliance
Central nervous system: brain growth, cerebral blood flow, autonomic regulation
Renal: glomerular filtration rate, creatinine clearance
Hepatic: liver blood flow, microsomal enzyme activity
Disease-growth interrelationship
Effects of systemic disease alter somatic and organ growth
Compensatory ability of developing organs to recover from injury
Immunologic immaturity of the infant
Obligatory miniaturization (i.e., small patient size and body surface area)
Congenital heart disease
Diverse anatomic defects and physiologic changes
Altered ventricular remodeling owing to myocardial hypertrophy and ischemia
Chronic sequelae of congenital cardiac disease
Surgical procedures
Diversity of operations
Frequent intracardiac and right ventricular procedures
Use of deep hypothermia and circulatory arrest during repair
Trend toward repair in early infancy
Evolution of surgical techniques to avoid residua and sequelae
Trend toward wider application of certain operations

conditions in congenital heart disease, the diversity of surgical repairs, and the use of specialized cardiopulmonary bypass techniques such as deep hypothermia and total circulatory arrest.

Physiologic Considerations and Maturational Features of the Pediatric Patient

Recognition of the changes associated with growth and development is fundamental to understanding the pediatric patient. All the major organ systems of the neonate and young infant undergo maturational changes that involve a dynamic change in physiologic function. Only those changes associated with the cardiovascular system are presented (for a more detailed discussion of the maturation of other organ systems, see Chapter 59 on general pediatric anesthesia).

The cardiovascular system changes markedly at birth because of a dramatic alteration in blood flow patterns (Fig. 50-1) . [2] During fetal life, blood flow returning to the right atrium bypasses the unventilated fluid-filled lungs. Blood is then preferentially shunted across the patent foramen ovale into the left atrium or passes from the right ventricle (RV) across the patent ductus arteriosus (PDA) to the systemic circulation. At birth, physiologic closure of the PDA and of the foramen ovale brings about the normal adult circulatory pattern. The presence of certain congenital heart defects or pulmonary disease can disrupt this normal adaptive process, creating a transitional circulation, in which right-to-left shunting persists across the foramen ovale or the PDA. Under such circumstances, the continued presence of a transitional circulation can lead to severe hypoxemia, acidosis, and hemodynamic instability, which are poorly tolerated in the neonate. By contrast, when initially treating some forms of congenital heart disease, the prolongation of this transitional circulation is actually beneficial, promoting systemic or pulmonary blood flow and postnatal viability. An example of the latter is pulmonary atresia, in which pulmonary blood flow is supplied via the PDA. In the absence of collateral vessels, closure of the PDA eliminates the principal source of pulmonary blood flow, resulting in hypoxemia and death. Ductal patency can be maintained with the administration of prostaglandin E_1 . Importantly, the transitional circulation can be manipulated by pharmacologic ventilatory strategies, thereby promoting hemodynamic stability in the young patient.

Another unique feature of the normal neonatal and infant cardiovascular system is the reduced myocardial reserve, as compared with that in the healthy adult. The newborn left ventricular function is restricted by a reduced number of beta-receptors, high resting levels of circulating catecholamines, limited recruitable stroke work, an immature calcium transport system, and decreased ventricular compliance. [3] This limits contractile reserve and results in a left ventricle with a high level of resting tone. [4] Although the resting performance of the neonatal myocardium may be greater than in adults and older children, there is a greater sensitivity to beta-blockade and only modest increases in cardiac performance to the beta-agonist drugs dobutamine and isoproterenol. [5]

On the ultrastructural level, a variety of cellular synthetic functions are occurring in immature myofibrils, which dominate

Figure 50-1 Course of the fetal circulation in late gestation. Note the selective blood flow patterns across the foramen ovale and the ductus arteriosus.

the newborn heart. [4] Large nuclei, mitochondria, and surface membranes predominate within the myofibrils. In neonates, there is a 50 percent reduction in the number of myofibrils, and myofibrils are arranged in a nonlinear, disordered array. As a direct result, the contractile mass of the heart is effectively reduced, resulting in a ventricle with low compliance. [6] Preload augmentation is effective at low filling pressures (1-7 mm Hg). However, when left-sided filling pressures exceed 7 to 10 mm Hg, further increases in left ventricular stroke volume are minimal. [3] As a consequence, neonates are more dependent on heart rate and, to a lesser extent, on preload, to maintain cardiac output at filling pressures of 7 to 10 mm Hg or greater. [7] [8]

In addition to a reduced contractile mass, the calcium transport system in the neonatal myocardium is underdeveloped. The transverse tubular system is absent, and the sarcoplasmic reticulum, which has to store and release calcium, is small and inefficient. the neonatal heart is therefore more dependent on extracellular calcium levels than the adult myocardium. [9] [10] [11] [12] Because intracellular calcium concentrations play a central role in myocardial contractility, normal or even elevated plasma levels of ionized calcium may be necessary to augment or maintain an effective stroke volume. [13] This is in contrast to adult cardiac patients in whom calcium use during cardiac surgery has fallen in to some disfavor owing to direct concerns over myocardial ischemia and reperfusion injury.

Another unique feature relates to the pulmonary circulation. The pulmonary circulation undergoes significant change during the first months of life. These changes are largely characterized by regression of the hypertrophied medial smooth muscular layer in the pulmonary arteries

that exists in utero, resulting in a concomitant drop in pulmonary vascular resistance (PVR). [14] In the immediate newborn period, the large decrease in PVR is due to lung expansion and the vasodilatory effects of a higher Pa O_2 than existed in utero. Further decline in PVR throughout the next 2 months of life is attributable to regression of the smooth muscle layer in the pulmonary arterioles. A corresponding fall in pulmonary artery pressure occurs as PVR declines. Acute physiologic stress in the newborn period, such as hypoxemia or acidosis, can increase pulmonary artery pressure and thus PVR. If the resulting RV hypertension causes reduced RV compliance, right-to-left shunting can occur at the foramen ovale. Once PVR exceeds systemic vascular resistance (SVR), right-to-left shunting develops at the PDA. Either phenomenon will worsen the hypoxemia and eventually limit tissue oxygen delivery to the point of lactic acidosis. By contrast, left-to-right shunts, such as with a ventricular septal defect (VSD), produce intimal changes in the pulmonary vasculature and delay regression of medial muscle hypertrophy. [14] This results in persistent elevation of PVR.

Size differences between adult and pediatric cardiac patients require miniaturization. Anatomically, pediatric patients have small upper and lower airways, small veins and arteries, and a decreased body surface area, as compared with adult patients. There are several anesthetic implications related to patient size. Some centers believe that the placement of arterial catheters by cutdown in neonates and infants represents the most expedient approach, particularly when optimal sites are limited. Pulmonary artery catheters are used infrequently, both because of the technical difficulties in positioning the tip in the pulmonary artery and because of the fundamental fact that pulmonary flow bears no obligatory relationship to systemic output in children with either intra- or extracardiac communications. Transthoracic catheters for pressure monitoring and delivery of vasoactive substances are commonly placed from the surgical field. Adequacy of the repair and function can be assessed by transesophageal or epicardial echocardiography with Doppler color flow imaging. [15] [16] Cardiopulmonary bypass serves as another example of the influence of patient size on management. The ratio of pump priming volume to patient blood volume is considerably higher in small children than in adults, resulting in a greater degree of hemodilution. Several studies have demonstrated a heightened inflammatory response to CPB in children when compared with adults. [17] [18] This effect is related to the disproportionate exposure to the nonendothelialized surfaces of the pump circuit per body surface area. Greater damage to the formed blood elements and plasma proteins is incurred, resulting in activation of the mediators of inflammation.

Finally, in pediatric patients with congenital heart disease, the cardiovascular system often represents the sole cause of the medical problem. This is in contrast to the multiplicity of diagnoses and organ system involvement frequently found in adults with acquired cardiovascular disease. Moreover, there is a special disease-growth interrelationship unique to growing infants and children that does not exist in adults. This special interrelationship permits developing organs to compensate for and modify existing disease processes. Reparative and recuperative processes in children are greater as a result of this compensatory ability of developing organ systems. Adult cardiac patients unfortunately do not exhibit the same recuperative ability. And although children adapt well to cardiovascular pathology, there are some negative aspects to longstanding heart disease. Congenital heart disease has detrimental effects on somatic growth as well as on the growth and development of the brain, myocardium, and lung.

Congenital Heart Disease

The marked array of anatomic and physiologic conditions seen with congenital heart disease distinguish these processes from acquired adult cardiac disease. The spectrum of intracardiac shunts, valve pathology (stenoses, regurgitation, or atresia), disrupted great artery connections, and the absence of one or more chambers of the heart preclude a uniform anesthetic approach to patients with congenital heart disease. Moreover, there are myocardial changes resulting from the hemodynamic impact and increased cardiac work incurred by these defects. Functionally, these myocardial changes place the ventricles at great risk for the development of intraoperative ischemia and failure. Therefore, an understanding of the isolated defect, associated myocardial changes, and hemodynamic consequences is fundamental to planning an appropriate anesthetic. [6] Too often, because of the complexity and diversity of the defects, the anesthesiologist, cardiologist, and surgeon are focused on the specific anatomic considerations and the physiologic implications are overlooked. Distilling congenital heart disease into a finite number of physiologic categories enables the anesthesiologist to construct a strategy that employs the qualitatively predictable impact of pharmacologic agents, ventilatory management, and fluid administration to optimize cardiovascular performance. Although an isolated heart malformation may be identified, the entire cardiopulmonary system is usually affected.

Physiologic Approach to Congenital Heart Disease

Although the structural variations seen in congenital heart disease constitute an encyclopedic list of malformations, anesthetic management is more logically designed to achieve physiologic goals. A general physiologic classification is listed in Table 50-2 . Fortunately, although structurally complex, these defects can be understood in a more limited physiologic spectrum. Identification and classification on the basis of physiology provide an organized framework for the intraoperative anesthetic management and postoperative care of children with complex congenital cardiac defects. In general, congenital heart lesions fit into one of four categories: shunts, mixing lesions, flow obstruction, and regurgitant valves (see Table 50-2) . Each category imposes at least one of three pathophysiologic states: ventricular volume overload, ventricular pressure overload, or hypoxemia. Ultimately, these pathophysiologic conditions can result in myocardial failure or pulmonary vascular disease. Medical and surgical perioperative management strategies should be focused on minimizing the pathophysiologic consequences of these lesions.

TABLE 50-2 -- Classification of Congenital Heart Defects

PHYSIOLOGIC CLASSIFICATION	PULMONARY BLOOD FLOW	COMMENTS
Shunts		
Left-to-right		
VSD		Volume-overload ventricle
ASD		Develop CHF
PDA		
AV canal		
Right-to-left		

Tetralogy of Fallot		Pressure-overloaded ventricle
Pulmonary atresia/VSD		Cyanotic
Eisenmenger complex		Hypoxemia
Mixing lesions		
Transposition/VSD	Generally	Variable pressure versus volume loaded
Tricuspid atresia		Usually cyanotic
Anomalous venous return	but variable Qp/Qs	
Univentricular heart		
Obstructive lesions		
Interrupted aortic arch		Ventricular dysfunction
Critical aortic stenosis		Pressure-overloaded ventricle
Critical pulmonic stenosis		Ductal dependence
Hypoplastic left heart syndrome		
Coarctation of the aorta		
Mitral stenosis		
Regurgitant lesions		
Ebstein's anomaly		Volume overloaded
Other secondary causes		Develop CHF

Abbreviations: ASD--atrial septal defect; AV canal--atrioventricular canal; CHF--congestive heart failure; PDA--patent ductus arteriosus; Qp--pulmonary blood flow; Qs--systemic blood flow; VSD--ventricular septal defect

Shunt Lesions

Shunts are intracardiac connections between chambers or extracardiac connections between a systemic and pulmonary artery; examples are an atrial septal defect (ASD), a VSD, and a PDA. The direction of blood flow through the shunt is dependent on the relative resistances on either side of the shunt and on the size of the shunt orifice. [19] With a nonrestrictive VSD or PDA that does not impede blood flowing freely in each direction, the main determinant of blood flow is the resistance of the pulmonary and systemic vascular beds. The direction and magnitude of shunt at the atrial level are governed by the relative differences in ventricular compliance and respective atrioventricular (AV) valve function. The effect a shunt lesion has on the cardiovascular system depends on its size and direction, either right-to-left or left-to-right. Left-to-right shunts occur when the pulmonary vascular resistance is lower than the systemic vascular resistance and blood flow is preferentially directed toward the lungs, resulting in increased pulmonary blood flow. In patients with large left-to-right shunts and low pulmonary vascular resistance, a substantial increase in pulmonary blood flow can occur. This results in three pathophysiologic problems: (1) congestion of the pulmonary circulation; (2) volume overload with resulting increased cardiac work for the left ventricle, which is required to increase stroke volume and heart rate to ensure adequate systemic perfusion; and (3) excessive pulmonary blood flow, resulting in progressive elevation in PVR. Volume overload causes ventricular dilation that places the heart at a mechanical and physiologic disadvantage, resulting in reduced diastolic compliance. [20] These diastolic changes lead to engorgement of the respective venous beds, which produces the signs and symptoms of clinical congestive heart failure early in the natural history of volume-overload condition. The demand for increased cardiac output placed on the left ventricle (LV) is limited in the infant by virtue of its immature structure, so that large left-to-right shunts may outstrip the capacity of the left heart to maintain adequate systemic perfusion, and congestive heart failure will result. Surgical closure of a hemodynamically significant VSD usually provides immediate benefit by dramatically lowering LV volume output demands. Occasionally, the sudden increase in wall stress imposed on a dilated ventricle that must now pump solely against systemic vascular resistance can produce worsening ventricular failure during the early postoperative period after eliminating the low resistance "popoff" into the pulmonary circulation. If the left-to-right shunt is not repaired, prolonged exposure to increased pulmonary blood flow results in progressive elevations in PVR. Fixed changes in pulmonary arterioles may occur, leading to pulmonary vascular obstructive disease. Table 50-2 lists the common left-to-right shunt lesions.

Right-to-left shunts occur when pulmonary vascular or right ventricular outflow tract resistance exceeds systemic vascular resistance, thereby reducing pulmonary blood flow. The systemic circulation receives an admixture of deoxygenated blood via the shunt and manifests clinically as cyanosis and hypoxemia. Pure right-to-left shunting due to raised PVR is seen in the Eisenmenger complex and in persistent pulmonary hypertension of the newborn with atrial and ductal level shunting. More commonly, PVR is low, and a more complex lesion with obstruction to pulmonary outflow, proximal to the pulmonary vasculature, produces right-to-left shunting. Defects such as tetralogy of Fallot represent classic right-to-left shunts. The shunting occurs

through the VSD because of pulmonary outflow obstruction. Systemic perfusion is generally normal with right-to-left shunting lesions unless hypoxemia becomes severe enough to impair oxygen delivery to tissue. Thus, there are two pathophysiologic problems: (1) reduced pulmonary blood flow resulting in systemic hypoxemia and cyanosis, and (2) an increased impedance to RV ejection resulting in pressure overload, which may ultimately lead to ventricular dysfunction and failure of the RV. However, the physiologic mechanisms designed to compensate for pressure overload rarely create abnormalities in systolic or diastolic function early in the natural history of the disease process. In contradistinction to lesions that produce ventricular volume overload, ventricular dysfunction and failure typically take years to develop in the context of isolated pressure overload.

Mixing Lesions

Mixing lesions constitute the largest group of cyanotic congenital heart defects (see Table 50-2) . In these defects, the mixing between the pulmonary and the systemic circulation are so large that they essentially act as a common chamber. The pulmonary-to-systemic flow ratio (Qp/Qs) is independent of shunt size and totally dependent on vascular resistance or outflow obstruction. The pulmonary and systemic circulations tend to be in parallel with one another rather than in series (see Table 50-2) . In patients with no outflow obstruction, flow to the systemic or pulmonary circulation is dependent on the relative vascular resistances of both circuits, such as with univentricular hearts or double-outlet RV. If SVR exceeds PVR, as in the typical circumstance, the tendency is toward excessive pulmonary blood flow, and the predominant pathophysiologic process is left-to-right shunting. These patients have increased pulmonary blood flow, ventricular volume overload, and a gradual elevation of PVR over time. If PVR exceeds SVR, as may occur episodically in ductal-dependent lesions such as hypoplastic left heart syndrome, systemic blood flow predominates and pulmonary blood flow dramatically decreases, causing progressive hypoxemia (Table 50-3) . In patients with a mixing lesion and LV outflow obstruction, pulmonary blood flow may be sufficiently excessive to impair systemic perfusion. In patients with mixing lesions and an RV outflow obstruction such as a single ventricle with subpulmonic stenosis, systemic-to-pulmonary flow can vary from balanced flow to significantly decreased pulmonary blood flow in which the severity of hypoxemia depends on the degree of obstruction. Typical mixing lesions include truncus arteriosus, univentricular

TABLE 50-3 -- Ductal-Dependent Lesions

PDA PROVIDES SYSTEMIC FLOW	PDA PROVIDES PULMONARY FLOW
Coarctation of the aorta	Pulmonary atresia
Interrupted aortic arch	Critical pulmonary stenosis
Hypoplastic left heart syndrome	Severe subpulmonic stenosis with VSD
Critical aortic stenosis	Tricuspid atresia with pulmonic stenosis

Abbreviations: PDA--patent ductus arteriosus; VSD--ventricular septal defect

heart, total anomalous pulmonary venous return, pulmonary atresia with large VSD, and single atrium.

Obstructive Lesions

Obstructive lesions range from mild to severe. Severe lesions present in the newborn period with a pressureoverloaded, diminutive, or profoundly dysfunctional ventricle proximal to the obstruction. These lesions include critical aortic stenosis, critical pulmonic stenosis, coarctation of the aorta, or interrupted aortic arch. Although aortic and pulmonary atresia represent the most extreme variants of outflow tract obstruction, they are associated with such extreme hypoplasia of the ventricle (hypoplastic left heart syndrome and certain pulmonary atresia with intact ventricular septum, respectively) that the ventricle's function does not contribute to the circulatory physiology. As with other critical obstructive lesions, these extreme variants have ductal-dependent circulations, but beyond that similarity, they are perhaps better understood as univentricular hearts for which the management characteristics of a mixing lesion dominate in importance. In critical neonatal left-sided obstructive defects, systemic perfusion is dependent on blood flow (desaturated) from the RV via the PDA, and coronary perfusion is supplied by retrograde flow from the descending aorta (see Table 50-3) . In right-sided lesions, pulmonary blood flow is supplied from the aorta via the PDA, and RV function is impaired. Pathophysiologic problems in critical neonatal left heart obstructive lesions include (1) profound LV failure, (2) impaired coronary perfusion with an increased incidence of ventricular ectopy, (3) systemic hypotension, (4) PDAdependent systemic circulation, and (5) systemic hypoxemia. The pathophysiologic problems of critical neonatal right heart obstructive lesions include (1) RV dysfunction, (2) decreased pulmonary blood flow, (3) systemic hypoxemia, and (4) PDA-dependent pulmonary blood flow. Apart from the most extreme variants that become evident in the neonatal period, infants and children with outflow obstruction (e.g., mild to moderate aortic or pulmonary stenosis, coarctation of the aorta) manifest the effective compensatory mechanisms for pressure overload, often remaining clinically asymptomatic for many years.

Regurgitant Valves

Regurgitant valves are uncommon as primary congenital defects. Ebstein's malformation of the tricuspid valve is the only pure regurgitant defect presenting in the newborn period. However, regurgitant lesions are frequently associated with an abnormality of valve structure, such as incomplete or partial atrioventricular canal defect, truncus arteriosus, or tetralogy of Fallot with an absent pulmonary valve. The pathophysiology of regurgitant lesions includes (1) volume-overloaded circulation and therefore (2) progression toward ventricular dilation and failure.

Summary

When considering the incidence of all the congenital heart defects, three uncomplicated left-to-right shunts

(VSD, ASD, PDA) and two obstructive lesions (pulmonic stenosis, coarctation) constitute 60 percent of all congenital cardiac defects. Mixing lesions, complicated obstructive defects, and right-to-left shunting lesions account for the vast majority of the remaining 40 percent. The latter group of defects, which are more difficult to manage, are more labor intensive and have a significantly higher morbidity and mortality rate. This observation is directly attributed to the complexity of the cardiovascular abnormalities seen in this 40 percent group, in which there is an absence of a chamber or a major ventricular-arterial connection.

Chronic Consequences of Congenital Heart Disease

The chronic effects of congenital heart disease are a consequence of the imposed hemodynamic stress of the defect or the residua and sequelae after cardiac surgery. These effects continue to alter normal growth and development of the cardiovascular system as well as other organ systems throughout life. [21] Complete surgical cures are rarely achieved, and some repairs are palliative rather than corrective; therefore, abnormalities before and after repair produce long-term effects in patients with congenital heart disease. [22] Although the overall outlook for these patients is good in most instances, every defect has associated myocardial changes, and every repair leaves certain obligatory abnormalities. Many of the abnormalities are trivial and have no major import. Others affect major organ system processes, such as ventricular function, central nervous system growth, the conduction system of the heart, or pulmonary blood flow. Under these circumstances, the long-term quality of life is affected. Whether anesthetizing these patients for their primary or subsequent cardiac repair or for noncardiac surgery, these chronic changes should be ascertained and reflected in the anesthetic plan.

The myocardium is continually remodeled by specific hemodynamic stresses in utero and throughout life. Right ventricular growth and development are influenced by the low-resistance afterload of the pulmonary circulation. The LV is coupled to the high-resistance systemic circulation, which accelerates its rate of growth and development. This situation gives rise to the adult condition in which LV dominance of myocardial muscle mass occurs. This entire developmental process is referred to as dynamic ventricular modeling. [6] Abnormal hemodynamic loading conditions associated with congenital heart disease interrupt the normal ventricular modeling process (Fig. 50-2) . [23] Abnormal ventricular remodeling typically begins in utero and stimulates an increase in ventricular mass. Increased ventricular mass is due to both hyperplasia and hypertrophy of myocytes in response to altered wall stress on the developing ventricle. The resultant biomechanical deformation of the ventricle alters its geometry, affecting normal systolic and diastolic function.

Abnormalities of ventricular performance at rest and with exercise can be detected in patients with chronic hemodynamic overload and complex cyanotic lesions. These abnormalities in ventricular function are the consequences of chronic ventricular overload, repeated episodes of myocardial ischemia and residua or sequelae of surgical treatment

Figure 50-2 Comparison of ventricular hypertrophy patterns demonstrating altered ventricular remodeling in two different congenital heart defects. *(A)* Note the right ventricular hypertrophy and the diminutive left ventricle (LV) in tetralogy of Fallot. *(B)* Note the severe left ventricular hypertrophy and septal bulging into the right ventricle (RV) in aortic stenosis.

(ventriculotomy, altered coronary artery supply, inadequate myocardial protection). [21] The physiologic adaptive responses to chronic hypoxemia and ventricular pressure or volume overload are the primary stimuli producing the long-term ventricular dysfunction. Although chronic volume overload of the LV as seen with left-to-right shunts or a chronic pressure-loaded LV due to left-sided obstructive lesions result in congestive heart failure, the compensatory mechanisms for pressure overload create less physiologic disturbance, particularly in diastolic function. Consequently, congestive heart failure occurs later in the natural history of isolated obstructive lesions that do not require treatment in the neonatal period. Similarly, chronic RV volume overload as seen in pulmonic insufficiency after tetralogy of Fallot repair is more likely to be associated with chronic ventricular dysfunction and failure than a pressure-loaded RV manifests with residual pulmonic stenosis. [24] In fact, the most potent combination for inducing ventricular dysfunction and failure occurs when a pressure overload is superimposed on a dilated, volume-overloaded ventricle (e.g., postoperative tetralogy of Fallot with pulmonary insufficiency and branch pulmonary artery stenosis). The mechanism for the dysfunction and failure is multifactorial. Initial manifestations of congestive heart failure reflect alterations in ventricular compliance that result from a variety of biophysical responses to abnormal loading conditions. The ventricular dilation and compensatory hypertrophy that accompany volume overload provide effective compensation to preserve

Figure 50-3 (Figure Not Available) Changes in ventricular physiology that accompany abnormal pressure and volume loading in human adolescents and adults. Schematic represents the changes in cross-sectional ventricular geometry that accompany abnormal pressure and volume loads. Data are measured and derived from catheterization and echocardiography of 30 adolescent and adult human subjects. Pressure overload triggers significant increases in wall thickness and wall thickness:radius ratio (h/r), but these compensatory mechanisms preserve sigma within normal limits. Whereas volume overload causes dilation and enough hypertrophy to preserve normal sigma $_S$, diastolic function deteriorates significantly. LVp--left ventricular pressure; h--LV posterior myocardial wall thickness; r--radius of the LV chamber; sigma$_S$ --peak systolic wall stress; sigma$_D$ --end-diastolic wall stress; * *P* <.01. *(From Grossman et al [20])*

normal systolic wall stress, but alterations in diastolic wall stress become evident (Fig. 50-3) (Figure Not Available) . [20] Ultimately, chronic or severe pressure loads

manifest similar changes as the resultant myocardial hypertrophy outgrows vascular supply and results in ischemia and fibroblast proliferation. Permanent changes in myocardial structure and function are the end result.

In patients with cyanotic conditions, the long-term compensation for chronic hypoxemia shows a major redistribution of organ perfusion with selected blood flow to the heart, brain, and kidney, and decreased flow to the splanchnic circulation, skin, muscle, and bone. Chronic hypoxemia is associated with increased work of breathing in an attempt to increase oxygen uptake and delivery. The most dramatic complications are the decreased rate of somatic growth, increased metabolic rate, and an increase in hemoglobin concentration seen in children with palliated or unrepaired defects.

Surgical Procedures and Special Techniques

The ultimate objectives for congenital heart surgery are (1) the physiologic separation of the circulation, (2) relief of outflow obstruction, (3) the preservation or restoration of ventricular mass and function, and (4) normalization of life expectancy and maintenance of quality of life. The available surgical procedures to accomplish these objectives are diverse and complex (Table 50-4) . Compared with cardiac operations in adult patients, congenital heart repairs involve more intracardiac surgery with a greater preponderance performed via the right atrium and right ventricle. In general, operations performed for congenital heart defects can be divided into palliative and corrective procedures. [25] The type and timing of repair depend on the age of the patient, the specific anatomic defect, and the experience of the surgeon and the team (see Table 50-4) . Palliation in infancy is usually performed when there are missing anatomic parts, as in pulmonary atresia (absent RV and pulmonary artery), tricuspid atresia (absent RV and tricuspid valve), hypoplastic left heart syndrome (aortic atresia and hypoplastic LV), univentricular heart (absent RV or LV), or mitral atresia (absent LV). These palliative procedures can be further subdivided into those that will increase pulmonary blood flow (PBF), those that decrease PBF, and those that increase mixing (see Table 50-4) . Palliative procedures that increase PBF include shunts (Blalock-Taussig, central, or Glenn), outflow patch, and enlargement of the VSD. Those that decrease PBF include pulmonary artery banding or ligation of a PDA. Those that improve intracardiac mixing include atrial septostomy (balloon, blade, or Blalock-Hanlon).

The improvements in surgical technique, coupled with advancements in anesthetic and technologic support, make repair in early infancy not only feasible but in many cases preferable. [26] Currently, repair in infancy can be offered for a number of congenital heart defects, as shown in Table 50-4 . The timing of surgical intervention reflects medical necessity, physiologic and technical feasibility, and optimal outcome. Cardiac defects that require a PDA to sustain sufficient systemic or pulmonary blood flow (e.g., pulmonary atresia, hypoplastic left heart syndrome, interrupted aortic arch, critical aortic stenosis, and critical pulmonic stenosis) require an intervention in the neonatal period. A variety of defects are optimally repaired in early infancy. Lesions like transposition of the great arteries may exhibit better LV function if the arterial switch operation is performed in the first few weeks of life when the PVR has recently been high

TABLE 50-4 -- Congenital Cardiac Defects and Their Repair

ANATOMIC DEFECTS	PALLIATION	COMPLETE REPAIR
Tetralogy of Fallot		VSD closure and RVOT patch
With PA atresia	Shunt	
With anomalous right coronary	Rastelli	
HLHS	Norwood I/transplant	
Transposition of the great arteries		Arterial switch
Unfavorable coronary anatomy	Atrial switch (Senning)	
Tricuspid atresia	Shunt followed by Fontan	
Pulmonary atresia with VSD	Shunt followed by Fontan	
With intact septum	Shunt followed by Fontan	
Critical aortic stenosis		Aortic valvotomy
Interrupted aortic arch		End-end anastomosis/reverse subclavian flap/tube graft
Total anomalous pulmonary venous return		Anastomosis of pulmonary veins to left atrium and ASD closure
Single ventricle/normal PAs	Band followed by Fontan	
With small PAs	Shunt followed by Fontan	
Truncus arteriosus		RV-PA conduit and VSD closure
Atrioventricular canal		Repair valve clefts/patch closure of ASD/attach valves to patch

Abbreviations: ASD--atrial septal defect; HLHS--hypoplastic left heart syndrome; PA--pulmonary artery; RV--right ventricle; RVOT--right ventricle outflow tract; VSD--ventricular septal defect

enough to increase LV systolic pressure, whereas other repairs may manifest less volatile postoperative physiology if deferred a few weeks or months until PVR has consistently fallen (e.g., tetralogy of Fallot, AV canal defect). Each defect may have mitigating factors for which deferred definitive repair will enable optimal surgical result (e.g., tetralogy of Fallot with aberrant coronary branching pattern or multiple VSDs; transposition of the great arteries with VSD and severe LV outflow tract obstruction). Although some lesions merit repair whenever they are diagnosed (e.g., total anomalous pulmonary venous return, coarctation of the aorta), others exhibit such a wide spectrum of physiologic disturbance that the timing of an intervention must be made individually (e.g., VSD, aortic stenosis, pulmonic stenosis). A few cardiac malformations produce pathophysiologic changes that are sufficiently mild that repair is typically deferred to later infancy or childhood (e.g., isolated ASD). Palliative surgery is entertained when a physiologic derangement requires intervention, but circumstances preclude definitive repair.

In general, the recent trend in pediatric cardiovascular surgery has been to repair defects in infancy rather than palliate. [26] This trend reflects improved technical capabilities coupled with a desire to limit the morbidity and mortality associated with long-term medical management and the sequelae of multiple palliative operations. Early corrective surgery is expected to decrease the incidence of the chronic complications of congenital heart disease, such as the problems associated with ventricular overload, cyanosis, and pulmonary vascular obstructive disease. [27] Early infant repair may also have the selective advantage of enhancing organ system protection during repair because of poorly understood factors promoting resistance to injury and enhanced recovery potential (i.e., enhanced plasticity). With the continued improvement in surgical techniques and the early treatment of congenital heart disease, specific organ systems such as the brain, heart, and lungs will be spared the detrimental effects of chronic derangements of hemodynamics and oxygen delivery.

Procedures for the treatment of congenital heart disease continue to evolve to decrease long-term morbidity and enhance survival. For example, the long-term problems with RV dysfunction and failure associated with the Mustard procedure for repair of transposition of the great arteries encouraged many surgical groups to develop the neonatal arterial switch operation. [28] Early indications suggest that the latter procedure provides an anatomic correction with better long-term results. A second example of the continuing evolution of technique is surgery for tetralogy of Fallot. Longstanding pulmonary insufficiency after RV outflow repair for tetralogy of Fallot is associated with RV dysfunction and failure. Preservation of the pulmonary valve at initial repair using a combined transatrial and transpulmonary approach during correction or the early insertion of a pulmonary homograft in the setting of pulmonary insufficiency are techniques being used in an attempt to avoid the long-term problems of RV dysfunction and failure. [29] Surgery for hypoplastic left heart syndrome, once considered a fatal disease, has achieved significant long-term survival in a growing number of institutions after a series of staged reconstructive procedures. [30] [31]

Surgical management has evolved in a broader application of certain surgical procedures initially designed for a specific defect. For example, modifications of the Fontan operation, which was originally devised for patients with tricuspid atresia, are now being used to repair a variety of univentricular hearts, including hypoplastic left heart syndrome. [32] [33] Initially, the wider application of the Fontan operation to include complex defects once considered inoperable was associated with a rise in morbidity and mortality. However, this trend has been reversed in recent years by several groups who have demonstrated improved outcome with the creation of a fenestration between the right and left atrium at the time of the Fontan operation. [34] The communication allows for right-to-left shunting, thereby preserving cardiac

output at lower systemic venous pressure in the early postoperative period. When necessary, once the patient has convalesced from the acute postoperative changes, the fenestration can be closed at the bedside with a snare placed at the time of the operation or in the catheterization

laboratory with a clamshell device. In a substantial proportion of cases, these fenestrations close spontaneously without further intervention.

Ingenuity and innovation such as that demonstrated with the difficult Fontan patient has permitted continued improvements in survival for all patients with congenital heart disease. As incisions in the myocardium become smaller and sutures more precisely placed, and improvements in surgical techniques continue to evolve, the complications of ventricular dysfunction, arrhythmias, and residual obstruction should decline, contributing to improved patient quality of life.

One final difference unique to congenital heart surgery that has a major impact on anesthetic management relates to the type of cardiopulmonary support. Because of the complexity of repair in small patients, surgery often requires significant alterations in the bypass techniques, such as the use of deep hypothermic CPB at temperatures between 15 and 18°C and total circulatory arrest. [35] [36] Many operations are undertaken in this setting of extreme biologic conditions of temperature and perfusion. Current methods of CPB management in neonates, infants, and children involve extensive alterations in temperature, hemodilution, systemic perfusion pressure, and flow. Despite widespread use of these techniques during bypass, their physiologic effects on major organ system function are just beginning to be understood. These effects are discussed in subsequent sections.

In summary, there are unique features that need to be considered when caring for children with congenital heart disease who are undergoing pediatric cardiac surgery. These features include the patient's growth and development, unique features of the developing cardiovascular system of the young, the pathophysiology of congenital heart disease, the surgical procedures, and the CPB techniques. A basic understanding of these differences coupled with the fundamental knowledge of adult and pediatric cardiac anesthesia principles underlie the approach to the perioperative management of these patients.

PREOPERATIVE MANAGEMENT

Preoperative Evaluation

Caring for children with congenital heart disease presents the anesthesiologist with a wide spectrum of anatomic and physiologic abnormalities. Patients range from young, healthy, asymptomatic children who are having a small ASD closed to the newborn infant with hypoplastic left heart syndrome requiring aggressive perioperative hemodynamic and ventilatory support. Intertwined with the medical diversity of these patients are the psychologic factors affecting both the patient and the parents. Preparation of the patient and the family is time consuming, but omitting or compromising this aspect of patient care is a major deterrent to a successful outcome and patient/parental satisfaction. This approach mandates that cardiac surgeons, cardiologists, anesthesiologists, intensivists, and nurses work as a team in preparing the patient and the family for surgery and postoperative recovery. This team-oriented approach also serves as a safeguard to prevent errors and omissions in the exacting perioperative care necessitated by the complexity of cardiac surgery for congenital heart disease. The preoperative visit offers the family the opportunity to meet the surgeon and anesthesiologist.

The preoperative evaluation should always start with a careful history and physical examination. The history should concentrate on the cardiopulmonary system. Parents should be questioned about the general health and activity of their child. Fundamentally, a child's general health and activity will reflect cardiorespiratory reserve. Deficiencies may point toward cardiovascular or other systems that may influence anesthetic or surgical risk. It is important to determine whether the child has normal or impaired exercise tolerance. Is he or she gaining weight appropriately or exhibiting signs of failure to thrive on the basis of cardiac cachexia? Does the child exhibit signs of congestive heart failure (diaphoresis, tachypnea, poor feeding, recurrent respiratory infections)? Is there progressive cyanosis or new onset of cyanotic spells? Any intercurrent illness such as a recent upper respiratory tract infection or pneumonia must be ascertained. Lower respiratory tract infections may require a delay in proposed surgery, based on the negative impact that airway reactivity and elevations in PVR may have on surgical outcome. Recurrent pneumonia is frequently associated with pulmonary overcirculation altered lung compliance in patients with increased pulmonary blood flow.

A good history must delineate previous surgical and cardiologic interventions. These may have an impact on both surgical and anesthetic plans for the current procedure. Patients who have had their subclavian artery sacrificed for a subclavian flap angioplasty to correct coarctation or a Blalock-Taussig shunt will not accurately display systemic arterial pressure or perhaps even pulse oximetry when the monitoring is applied to the left arm. Likewise, children who have femoral venous occlusion following catheterization are not optimal candidates for femoral venous access, particularly for femoral CPB should sternotomy prove impossible. It is equally important to ascertain current medications, previous anesthetic problems, or family history of anesthetic difficulties.

In the modern era of echocardiography and cardiac catheterization, physical examination rarely contributes additional anatomic information about the underlying cardiac lesion. However, it is extremely useful in assessing the overall clinical condition of the child. For example, an illappearing, cachectic child in respiratory distress has limited cardiorespiratory reserve, and the use of excessive premedication or a prolonged inhalational induction could result in significant hemodynamic instability.

Laboratory evaluation should include analysis of hemoglobin, hematocrit, pulse oximetry, and, in selected patients (e.g., those on diuretics or with renal impairment), serum electrolytes. An elevated hematocrit in a normovolemic child gives an indication of the magnitude and chronicity of their hypoxemia. Levels above 60 percent may predispose to capillary sludging and secondary end organ damage, including stroke. [37] Despite these risks, liberalized nothing-by-mouth guidelines that permit children to consume clear liquids up to 2 hours before anesthetic induction have virtually eliminated the need to admit these patients for preoperative intravenous hydration. [38] [39]

Echocardiography with Doppler color flow imaging is an invaluable tool that provides a noninvasive means of assessing

intracardiac anatomy, blood flow patterns, and estimates of physiologic data. [40] For many cardiac defects, more invasive studies are generally not required if a good echocardiographic assessment is made. Echo-Doppler is especially helpful for defining intracardiac abnormalities. Extracardiac abnormalities, such as pulmonary artery or vein stenosis, are more difficult to define by echo-Doppler and often require cardiac catheterization. The ability to interpret anatomy and physiology accurately requires a skilled echocardiographer, reaffirming the need for a well-integrated interactive team. Although the complexities posed by extreme anatom-ic variation and changing loading conditions render intraoperative echo-Doppler challenging even for experienced echocardiographers, the pediatric cardiac anesthesiologist should develop some familiarity with its capabilities and limitations to participate in critical intraoperative management decisions.

Cardiac catheterization remains the gold standard for assessing anatomy and physiologic function in congenital heart disease. Although many anatomic questions can now be reliably answered noninvasively, cases that present complex anatomic questions or those for which physiologic data are required, catheterization remains a vital tool. Important catheterization data for the anesthesiologist include the following:

1. Child's response to sedative medications.
2. Pressure and oxygen saturation in all chambers and great vessels.
3. Location and magnitude of intra- and extracardiac shunt (Qp:Qs)
4. Pulmonary vascular resistance, systemic vascular resistance.
5. Chamber size and function.
6. Valvular anatomy and function.
7. Distortion of systemic or pulmonary arteries related to prior surgery.
8. Coronary artery anatomy.
9. Anatomy, location, and function of previously created shunts.
10. Acquired or congenital anatomic variants that might have an impact on planned vascular access or surgery.

Careful review of the cardiac catheterization data and an understanding of its pontenital impact on the operative and anesthetic plan are essential. Not all the medical problems can be evaluated and corrected preoperatively; the surgeon, cardiologist, and anesthesiologist must discuss the potential management problems and any need for further evaluation or intervention before arrival in the operating room. Appropriate communication and cooperation between the two physicians will optimize patient care and facilitate perioperative clinical management. Typically, institutions have a regularly scheduled combined cardiology/cardiac surgery meeting to discuss candidates for surgery during which all of the essential information is displayed and discussed. Such a meeting provides an invaluable opportunity for learning about specific patients proposed for surgery as well as a continuing educational forum that promotes an interdisciplinary exchange directed at contemporary concepts in congenital heart disease and its treatment, both medical and surgical.

Premedication

By 6 months of age, pentobarbital (2-4 mg/kg) can be administered orally. A calm, cooperative, sedated child is the usual result. Alternatively, children over 9 months of age may receive a benzodiazepine as an oral premedication. The authors' current preference is midazolam 0.3 to 0.7 mg/kg by mouth 10 to 20 minutes before induction. The higher dose is used in the smallest patients.

INTRAOPERATIVE MANAGEMENT

Operating Room Preparation

Advanced, careful preparation of the operating room is essential. The anesthesia machine must have the capacity to provide air as well as oxygen and nitrous oxide to help balance pulmonary and systemic blood flow. Intravenous tubing must be free from air bubbles to prevent paradoxical air embolism. Resuscitative drugs, labeled and ready for administration, should include calcium gluconate or calcium chloride, sodium bicarbonate, atropine, phenylephrine, lidocaine, and epinephrine. An inotropic infusion, usually dopamine, should be premixed and ready for administration in high-risk cases, but additional infusions are prepared if their need is strongly suspected. For all pediatric cases, certain anesthetic drugs are made available for use on an emergency basis (thiopental, propofol, ketamine, succinylcholine, and atropine). These drugs are selected because of the potential for airway reactivity, hypotension, and bradycardia during anesthetic induction. In pediatric cardiac anesthesia, many patients have limited reserve as well as high endogenous catecholamine levels released in an adaptive response to their underlying cardiac disease. The resuscitative drugs should therefore be prepared and immediately available prior to anesthetic induction.

For congenital heart surgery, the ability to alter body temperature rapidly for cooling and rewarming is essential. During deep hypothermic CPB, patients are cooled to 15 to 18°C. Surface cooling with a heating/cooling water mattress and an efficient room ambient temperature control system are important in the operative management of these patients.

Physiologic Monitoring

The monitoring used for any specific patient should depend on the child's condition and the magnitude of the planned surgical procedure. The perioperative monitoring techniques available are listed in Table 50-5 . Noninvasive monitoring is placed prior to induction of anesthesia. In the crying pediatric patient, the anesthesiologist may elect to defer application of monitoring devices until immediately after the induction of anesthesia. Standard monitoring includes an electrocardiographic system, pulse oximetry, capnography, precordial stethoscope, and an appropriate-sized blood pressure cuff (either oscillometric or Doppler). Additional monitoring includes an indwelling arterial catheter, temperature probes, and an esophageal stethoscope. Foley catheters are generally employed when surgical

TABLE 50-5 -- Monitoring of Organ Systems

Cardiopulmonary system	
Esophageal stethoscope	
Electrocardiogram	
Standard seven-lead system, ST-T wave analysis, esophageal electro- cardiographic lead	
Pulse oximetry	
Automated oscillatory blood pressure	
Capnograph	
Ventilator parameters	
Indwelling arterial catheter	
Central venous pressure catheter	
Pulmonary artery catheter	
Transthoracic pressure catheter	
Left or right atrium, pulmonary artery	
Echocardiography with Doppler color flow imaging	
Epicardial or transesophageal	
Central nervous system	
Peripheral nerve stimulator	
Processed electroencephalography	
Specialized	
Cerebral blood flow--xenon clearance methodology	
Cerebral metabolism--near-infrared spectroscopy, oxygen consump-tion measurements	
Transcranial Doppler	
Jugular venous bulb saturations	
Temperature	
Nasopharyngeal, rectal, esophageal, tympanic	
Renal function	
Foley catheter	

intervention entails cardiopulmonary bypass or might produce renal ischemia, or when the anesthetic management includes a regional technique associated with urinary retention. Some centers routinely employ central venous pressure monitoring for major cardiovascular surgery. Alternatively, the authors typically use directly placed transthoracic atrial lines to obtain that information for separation from cardiopulmonary bypass and the postoperative period. In that setting, the benefits of the information or access provided by percutaneous central venous pressure catheters in the pre-bypass period must be weighed against the risks they pose.

Continuous monitoring of arterial pressure is only possible through an indwelling intra-arterial catheter. In young children cannulation of the radial artery with a 22-gauge catheter is preferred. In older children and adolescents, a 20-gauge catheter may be substituted. Careful inspection, palpation, and four-extremity noninvasive blood pressure determinations help ensure that previous or currently planned operative procedures, such as a previous radial artery cutdown, subclavian flap for coarctation repair, or a Blalock-Taussig shunt, do not interfere with the selected site of arterial pressure monitoring. Other sites available for cannulation include the ulnar, femoral, axillary, or umbilical (in neonates) arteries. Cannulation of the posterior tibial or dorsalis pedis arteries is not usually sufficient for complex operative procedures. Peripheral arterial catheters, principally of the distal lower extremities, function poorly after CPB and do not reflect central aortic pressure when distal extremity temperature remains low. [41]

Myocardial and cerebral preservation is principally maintained through hypothermia; therefore, the accurate and continuous monitoring of body temperature is crucial. Rectal and nasopharyngeal temperatures are monitored, as they reflect core and brain temperature, respectively. Monitoring of esophageal temperature is a good reflection of cardiac and thoracic temperature. Tympanic probes, although a useful reflection of cerebral temperature, can cause tympanic membrane rupture.

Pulse oximetry and capnography provide instantaneous feedback concerning adequacy of ventilation and oxygenation. They are useful guides in ventilatory and hemodynamic adjustments to optimize Qp:Qs before and after surgically created shunts and pulmonary artery bands. Peripheral vasoconstriction in patients undergoing deep hypothermia and circulatory arrest renders digital oxygen saturation probes less reliable. The use of a tongue sensor has been advocated in the newborn to provide a more central measure of oxygen saturation, with less temperature-related variability. [42]

The use of transthoracic (in the right or left atrium, pulmonary artery) or transvenous pulmonary artery catheters is determined on an individual basis based on the disease process, physiologic state, and surgical intervention. For example, in children undergoing a Fontan procedure for tricuspid atresia or univentricular heart, these measurements are especially useful. Following a Fontan operation, pulmonary blood flow must occur without benefit of a ventricular pumping chamber. Subtle changes in preload, PVR, and pulmonary venous pressure will influence pulmonary blood flow and thus systemic cardiac output. Data derived from systemic venous and left atrial pressure (LAP) help distinguish the relative importance of intravascular volume (central venous pressure [CVP]), PVR (CVP-LAP gradient), or ventricular compliance (LAP), each of which requires a different therapeutic approach.

As a general guideline, a transvenous pulmonary artery catheter (PAC) may be placed using the internal jugular approach in children weighing more than 7 kg. A 5.0 Fr PAC is used between body weights of 7 and 25 kg; a 7.0 French PAC for children weighing greater than 25 kg. For infants weighing less than 7.0 kg, percutaneous placement of a PAC can be performed from the femoral vein. Occasionally the latter technique will require fluoroscopy. The use of intraoperative transthoracic monitoring lines and echo-Doppler limit the need for transvenous pulmonary artery catheters in most cases.

Special Monitoring

Intraoperative Echocardiography

In recent years, newer techniques for monitoring patients during pediatric cardiovascular surgery have been introduced. The most promising of these techniques is echocardiography with Doppler color flow imaging. Several re- ports have described the usefulness of intraoperative echo-Doppler during congenital heart surgery. [43] [44] [45] Twodimensional echocardiography combined with pulsed-wave Doppler ultrasonography and color flow mapping is able to provide detailed morphologic as well as physiologic information in the majority of operative cases. Using echo-Doppler in the operating room, anatomic and physiologic data can be obtained prior to CPB, thus refining the operative plans.

Pre-bypass echo-Doppler precisely defines anesthetic and surgical management. [16] [44] Because of the unrestricted epicardial and transesophageal echocardiography (TEE) approaches in anesthetized patients, new findings are frequently discovered and management plans changed accordingly (Fig. 50-4) . Post-bypass echo-Doppler evaluation is able to immediately assess the quality of the surgical repair as well as assess cardiac function by examining ventricular wall motion and systolic thickening. [16] [44] This technique can show residual structural defects after bypass, which can be immediately repaired in the same operative setting and prevents leaving the operating room with significant residual structural defects that will require reoperation at a later time (Fig. 50-5) . By identifying patients with new RV and LV contraction abnormalities after bypass, as determined by a change in wall motion or systolic thickening, echo-Doppler provides guidance for immediate pharmacologic interventions. Importantly, post-bypass ventricular dysfunction and residual structural defects identified by echo-Doppler are associated with an increased incidence of reoperation and higher morbidity and mortality rate. [46] Thus this monitoring tool is helpful in assessing surgical outcome and identifying operative risk factors. Whether early identification of these abnormalities, which directs appropriate medical and surgical interventions, will improve outcome remains to be determined.

Two techniques for intraoperative echo-Doppler have been described: TEE and epicardial. Using TEE, the probe is placed after induction of anesthesia and intubation and is then available for monitoring of the patient. The advantage of this technique is its utility as a continuous monitor of cardiac structure and function, without interrupting surgery. [16] [47] Because of its ideal imaging location, TEE has been especially helpful in evaluating pulmonary venous return and the integrity of the left AV valve following mitral valvuloplasty, complete AV valve repair, and correction of complex congenital heart disease. Early limitation in views

Figure 50-4 Intraoperative pre-cardiopulmonary bypass epicardial echocardiogram in the long-axis view. Note the insertion of the papillary muscle of the tricuspid valve on the interventricular septum. Based on this view, the surgeon decided that ventricular septal defect (VSD) closure was possible in a child thought preoperative to be only a candidate for palliation. RV, right ventricle; LV, left ventricle; LA, left atrium.

Figure 50-5 *(A)* Echocardiogram with a Doppler flow map in the long-axis view illustrating a residual ventricular septal defect (VSD) resulting from patch dehiscence after initial repair. Turbulent flow through the VSD appears as a mosaic of white particles (arrow). This finding necessitated immediate reinstitution of cardiopulmonary bypass and re-repair. *(B)* Repeat Doppler flow map in the long-axis view illustrates patch closure (arrow) of the VSD after re-repair. Note the absence of turbulent flow with the loss of the mosaic of white, RV, right ventricle; LV, left ventricle; LA, left atrium; Ao, aorta.

have been virtually eliminated with clinical experience and improved biplane images. Pediatric biplane TEE probes have extended the patient size limits to neonates between 2.5 and 3 kg. [48] Potential hazards of TEE that merit particular vigilance include descending aorta and airway compression due to probe size or during probe flexion.

The second technique for intraoperative echocardiographic analysis in children is the epicardial approach. [17] [44] [48] This approach requires that a clean, shortfocused 5.0- or 7.0-MHz transducer be passed over the anesthesia screen into a sterile sheath, where it then can be placed on the epicardial surface of the heart. This technique best facilitates the probe manipulations necessary for thorough interrogation of the major structures and dynamic function of the heart. The advantage of this approach is that all views can be obtained in any size patient. Among the disadvantages are the need for sufficient operator skill and experience for manipulations, [46] the need to interrupt surgery to manipulate the probe, and any deleterious impact of direct myocardial mechanical manipulation. With the current TEE capabilities, epicardial imaging is rarely employed.

Specialized Central Nervous System Monitoring

The primary goal of brain monitoring is to improve our understanding of cerebral function and dysfunction during cardiac surgery so that effective brain protection

strategies can be developed. Because many of the determinants of normal brain perfusion become externally controlled by the cardiac team during CPB, such as flow rate (cardiac output), perfusion pressure, temperature, hematocrit, and Pa CO_2 , a knowledge of the effect of these factors on the brain in neonates, infants, and children is essential. Furthermore, the examination of the brain under unusual biologic circumstances, such as after deep hypothermic circulatory arrest (DHCA) or during continuous-flow CPB at deep hypothermia (15 to 18°C), permits a unique opportunity to describe cerebrovascular physiology and pathophysiology. Processed electroencephalography, transcranial Doppler (TCD), cerebral blood flow, and metabolism measurements have provided important information during pediatric cardiovascular surgery.

Electroencephalography is helpful in monitoring physiologic function of the central nervous system during deep hypothermic bypass and total circulatory arrest. For example, during deep hypothermia and before total circulatory arrest, the processed electroencephalogram can identify residual cerebral electrical activity. [49] Isoelectric silence can then be induced by further cooling, and any further brain activity detected by electroencephalography. Since this residual electrical activity during arrest is associated with ongoing cerebral metabolism, an isoelectric state may prevent ischemic injury to the brain during circulatory arrest. The electroencephalogram may also be useful in detecting the level and depth of anesthesia. Postoperative electroencephalographic analysis has demonstrated subclinical seizure activity in a number of high-risk patients, potentially linking these abnormalities with poorer neuropsychologic outcome. The value of intraoperative electroencephalographic monitoring after CPB and the significance of the findings remain to be determined.

TCD is one of a number of methods currently being used to monitor cerebral blood flow (CBF) during pediatric cardiac surgery. [50] [51] TCD technology uses the Doppler principle to detect shifts in the frequency of reflected signals from blood in the middle cerebral artery to calculate blood flow velocity. [52] Since the diameter of this large cerebral artery is relatively constant, flow velocity should approximate CBF. There are several advantages of TCD: (1) it is noninvasive, (2) it does not require radiation exposure, and (3) it is a continuous monitor. An additional advantage of this technique is the capability of assessing rapid alterations in blood flow velocity due to temperature or perfusion changes, as commonly occur during cardiac surgery. The limitations of transcranial Doppler monitoring include (1) reproducibility, especially at low flows, where minute movement of the patient's head can dramatically alter signal intensity and alter baseline measurements, and (2) the lack of validating studies of TCD during hypothermic CPB, when temperature, reduced flow rates, and the laminar flow characteristics of nonpulsatile perfusion may limit the accuracy of CBF velocity measurements. Although CBF velocity measurements by TCD have reasonable correlation with more standard meas-ures of CBF during normothermia, there have been some studies examining its validity during hypothermic CPB. [53]

TCD has been used to investigate the effect of CPB and deep hypothermic circulatory arrest on cerebral hemodynamics in children as well as to assess the incidence of cerebral emboli. Recent studies examining the brain using TCD have enabled several investigative groups to provide important information regarding questions of normal and abnormal brain perfusion during cardiac surgery in children. Questions regarding cerebral perfusion pressure, autoregulation, effect of Pa CO_2 , and temperature have been addressed using TCD in children and are discussed subsequently. [50] [51] [53] TCD has also provided qualitative information regarding the presence of gaseous emboli in the middle cerebral artery during cardiac surgery. [54] [55] Quantification of this important mechanism of cerebral injury during cardiac surgery would be instructive. Future investigations using TCD should address this mechanism of injury as well.

CBF studies using xenon clearance technology have improved the understanding of cerebrovascular dynamics in young children during CPB and especially during deep hypothermia and after periods of circulatory arrest. [56] [57] [58] [59] [60] In general, this investigational tool has described the effects of CPB, temperature, and various perfusion techniques on CBF and, indirectly, on brain metabolism (Fig. 50-6) (Figure Not Available) . Studies using this methodology have shown that some of the mechanisms of cerebral blood flow autoregulation, such as pressure-flow regulation, are lost with deep hypothermia and that cerebral reperfusion is impaired after a period of total circulatory arrest.

There now exists the capability of measuring cerebral metabolic activity during cardiac surgery. Methods for monitoring cerebral metabolic activity include determining the cerebral metabolic rate for oxygen (CMR O_2), jugular venous bulb saturation, and the use of near-infrared spectroscopy (NIRS). Using CMR O_2 as a metabolic index, the effects of temperature and DHCA on brain metabolism have been described. [58] The primary effect of cooling during cardiac surgery is to reduce energy metabolism so that low-flow states and DHCA can be used. Monitoring the efficacy of brain cooling can be performed by measuring the venous oxygen saturation of the brain. The higher the saturation level during cooling, the greater the oxygen metabolic suppression and the protective cooling effects. This catheter is easily placed in the right internal jugular vein and threaded retrograde to the venous bulb, positioned to assess the cerebral venous effluent. [60] Using this technique, potential mechanisms for brain injury have been identified and effective protection strategies developed. NIRS has the capability of measuring regional brain tissue oxyhemoglobin and cytochrome a,a_3 , the terminal mitochondrial enzyme in the respiratory chain. Using NIRS intracellular brain tissue, oxygen delivery and utilization during CPB have been preliminarily observed. [62] These growing improvements in our knowledge of the effects of CPB on the brain are of great importance, since the last major area of morbidity associated with cardiac surgery is neurologic in origin.

Induction and Maintenance of Anesthesia

The principles of intraoperative management of cardiothoracic surgical procedures are based on an understanding of the pathophysiology of each disease process and a working

Figure 50-6 (Figure Not Available) Bar chart of the changes in cerebral blood flow (CBF) before, during, and after CPB in 67 infants and children (mean ± SD). Group A underwent repair with moderate hypothermic bypass (MoCPB) at 28 to 32°C; group B, with deep hypothermic bypass (DHCPB) at 18 to 22°C; group C, with total circulatory arrest at 18°C. Stage I, pre-bypass; stages II and III, during hypothermic bypass; stage IV, rewarmed on bypass; stage V, after bypass. Note the impaired cerebral reperfusion after TCA (group C). *(From Greeley et al [61])*

knowledge of the effects of the various anesthetic and other pharmacologic interventions on a particular patient's condition. Selecting an induction technique is dependent on the degree of cardiac dysfunction, the cardiac defect, and the degree of sedation provided by the premedication. In children with good cardiac reserve, induction techniques can be quite varied as long as induction is careful and well monitored. The titration of induction agents is more important than the specific anesthetic technique in patients with reasonable cardiac reserve. A wide spectrum of anesthetic induction techniques with a variety of agents has been used safely and successfully, such as sevoflurane, halothane, and nitrous oxide; intravenous or intramuscular ketamine; or intravenous propofol, fentanyl, midazolam, or thiopental. [63] For neonates undergoing open heart surgery, opioidrelaxant inductions are most prevalent, whereas older children with sufficient cardiac reserve typically receive inhalation inductions with either halothane or sevoflurane. The application of Emla cream (emulsion of lidocaine 2.5 percent and prilocaine 2.5 percent) at the site of intravenous cannula insertion facilitates cannulation and minimizes patient pain and stress. Ketamine has been the most popular agent for anesthetic induction in patients with cyanotic conditions because it increases systemic vascular resistance and cardiac output, thereby diminishing the magnitude of right-to-left shunting. Administration of ketamine can be intravenous or intramuscular. An intramuscular injection may result in pain, agitation, and subsequent arterial desaturation.

Inhalation inductions are generally well received and tolerated by most children. An inhalation induction with halothane or sevoflurane can easily and safely be performed even in cyanotic patients such as those with tetralogy of Fallot (Fig. 50-7) (Figure Not Available) . In these patients, who are at risk of right-to-left shunting and systemic desaturation, oxygenation is well maintained with a good airway and ventilation, despite halothane-induced reduction in systemic arterial pressure. [64] Skilled airway management and efficiency of ventilation are an equally essential component of anesthetic induction. Although it is essential to understand the complexities of shunts and vascular resistance changes, airway and ventilation effects on the cardiovascular system are of primary importance during the induction of anesthesia.

After anesthetic induction, intravenous access is established or augmented as appropriate. A nondepolarizing muscle relaxant is usually administered and an intravenous opioid and/or inhalation agent chosen for maintenance anesthesia. The child is preoxygenated with 100 percent Fi O_2 and a lubricated nasal endotracheal tube is carefully positioned. A nasal tube is usually selected because most patients require a period of postoperative mechanical ventilation and the nasal route provides greater stability and patient comfort compared with the oral route. Some degree of alveolar preoxygenation is recommended, even in the infant whose systemic perfusion might be jeopardized by lowering PVR with resulting increase in pulmonary blood flow. This maneuver delays desaturation during intubation. If the

Figure 50-7 (Figure Not Available) Comparative changes in arterial oxygen saturation (Sa O_2) and mean blood pressure (MAP) during mask halothane N_2O (*n* = 7) and intramuscular ketamine (*n* = 7) inductions in children with tetralogy of Fallot at risk of right-to-left shunting. Note the maintenance of Sa O_2 in the halothane group despite the significant drop in MAP. *(From Greeley et al [64])*

child arrives in the operating room with an endotracheal tube in place, it is our practice to change it. Inspissated secretions in a tube with a small internal diameter can cause significant obstruction to gas flow. During periods of bypass when humidified ventilation is discontinued, significant endotracheal tube obstruction can occur. This can be minimized by placing a new endotracheal tube at the beginning of the procedure.

Because of the diverse array of congenital heart defects and surgical procedures, an individualized anesthetic management plan is essential. The maintenance of anesthesia in these patients depends on the age and condition of the patient, the nature of the surgical procedure, the duration of cardiopulmonary bypass, and the need for postoperative ventilation. An assessment of the hemodynamic objectives designed to lessen the pathophysiologic loading conditions should be developed for each patient, taking advantage of the known qualitative effects of specific anesthetic agents and ventilatory strategies. These individualized plans must also integrate with the overall perioperative goals to configure the optimal anesthetic. In patients with complex defects requiring preoperative inotropic and mechanical ventilatory support, a carefully controlled hemodynamic induction and maintenance anesthetic with a potent opioid is generally chosen. In patients with a simple ASD or VSD, a potent inhalation agent is preferred as the principal anesthetic agent. This allows for early postoperative extubation and a less prolonged period of intensive care monitoring. More important than the specific anesthetic techniques and drugs is the skilled execution of the anesthetic plan, taking into account patient response to drugs, the changes associated with surgical manipulation, and early recognition of intraoperative complications.

The reported changes in blood pressure and heart rate for the inhalation agents in normal children are observed in pediatric cardiac surgical patients as well. Although both halothane and isoflurane decrease blood pressure in neonates, infants, and children, the vasodilatory properties of isoflurane may improve overall myocardial contractility, compared with the effects of halothane. [65] Despite improved cardiac reserve with isoflurane, the incidence of laryngospasm, coughing, and desaturation during induction of anesthesia limits its use as an induction agent in children with congenital heart defects. [66] The use of potent inhalation agents as primary anesthetics should be reserved for the child with adequate cardiovascular reserve who is a candidate for early postoperative extubation. In these patients, the myocardial depression and hypotension associated with the use of inhalation agents is well tolerated. Examples include closure of an ASD or VSD, excision of a discrete subaortic membrane, pulmonic or aortic stenosis, ligation of a PDA, and repair of coarctation of the aorta.

Desflurane has cardiorespiratory properties similar to those of isoflurane. [67] Its main advantage is a low blood and tissue solubility. This allows for rapid equilibration between the inspired and alveolar concentrations and rapid decrease of alveolar concentrations during elimination. [68] This provides greater precision in drug dosing during the operative period and may make desflurane a more titratable adjunctive drug for pediatric cardiac anesthesia. The three main disadvantages of desflurane are potency, pungency, and negative inotropic effect. [69] [70] Studies in normal infants and children suggest that 1 minimum alveolar concentration of desflurane requires concentrations of 8 to 10 percent. [71] [72] Desflurane is also quite pungent and, although its uptake is rapid, early experience with this drug for inhalation induction in children has reported a fairly high incidence of airway reactivity and laryngospasm. [71] [73] [74] Although its negative inotropic effect is significantly less potent than that of halothane, desflurane should not be used as the sole anesthetic in patients with significant cardiac dysfunction. [74]

Sevoflurane offers a more tolerable aroma without the magnitude of myocardial depression that accompanies halothane. [75] In addition, its blood gas solubility is nearly as low as desflurane. Hemodynamically, sevoflurane tends to produce some tachycardia, particularly in older children, and preserve systemic arterial pressure. [76] Reductions in heart rate and systemic arterial pressure are more modest in infants anesthetized with sevoflurane than in control subjects anesthetized with halothane, and the former exhibit echocardiographic evidence of normal contractility and cardiac index. [77] [78] Controversies continue to surround the potential toxic byproducts of sevoflurane anesthesia, related both to patient metabolism and to the production of Compound A in the anesthesia breathing circuit. Although the importance of Compound A in adult practice remains uncertain, evidence suggests that production of this toxin is significantly diminished in children. [79]

Children with complex congenital heart disease and limited cardiac reserve demand an anesthetic technique that provides hemodynamic stability. Inhalation agents are less well tolerated as a primary anesthetic in patients who have limited cardiac reserve, especially after cardiopulmonary bypass. Fentanyl and sufentanil are excellent induction and maintenance anesthetics for this group of patients. Low to moderate doses of these opioids can be supplemented with inhalation anesthetics. Adding low concentrations of inhalation agents to smaller doses of opioids shortens or eliminates the need for postoperative mechanical ventilation while maintaining the advantage of intraoperative hemodynamic stability. Postoperative mechanical ventilation will be required when a high-dose opioid technique is used. The hemodynamic effects of fentanyl at a dose of 25 mug/kg with pancuronium given to infants in the postoperative period after operative repair of a congenital heart defect include no change in left atrial pressure, pulmonary artery pressure, pulmonary vascular resistance, and cardiac index and a small decrease in systemic vascular resistance and mean arterial pressure. [80] Higher doses of fentanyl at 50 to 75 mug/kg with pancuronium result in a slightly greater fall in arterial pressure and heart rate in infants undergoing repair for complex congenital heart defects. [81] Despite the wide safety margin exhibited by these opioids, a selected population of infants and children with marginally compensated hemodynamic function sustained by endogenous catecholamines may manifest more extreme cardiovascular changes with these doses. Fentanyl has also been shown to block stimulusinduced pulmonary vasoconstriction and contributes to the stability of the pulmonary circulation in neonates after congenital diaphragmatic hernia repair. [82] Thus, the use of fentanyl may be extrapolated to the operating room where stabilizing pulmonary vascular responsiveness in newborns and young infants with reactive pulmonary vascular beds is crucial to weaning from cardiopulmonary bypass and stabilizing shunt flow.

Sufentanil and pancuronium provide the same cardiovascular stability as fentanyl and pancuronium in pediatric cardiovascular patients. Children receiving a sufentanil induction as a single dose of 5 to 20 mug/kg have a stable preintubation period. [83] [84] Intubation and other stimuli such as sternotomy do not produce clinically significant alterations in hemodynamics, although changes are greater than with equipotent doses of fentanyl. The use of fentanyl as an infusion (.1 mug/kg/min) produces fewer alterations in heart rate and blood pressure. This is particularly important in infants in whom significant hemodynamic changes are poorly tolerated. For neonates with critical congenital heart disease, sufentanil anesthetic and postoperative infusion have been shown to reduce morbidity after cardiac surgery when compared with a halothane anesthetic and routine morphine postoperatively. [85] The blunting of the stress response observed in this study probably accounted for the differences in morbidity; there was no comparison group representing a more typical dose of a phenylpiperidine opioid (e.g., fentanyl 50-75 mug/kg) to permit conclusions as to whether such large opioid doses are optimal.

Alfentanil is a short-acting potent opioid that has also been used for cardiac surgery in children; it shows some promise in selected pediatric anesthesia cases because of its short elimination half-life and hemodynamic stability. As a primary anesthetic in children undergoing cardiopulmonary bypass, however, it must be continuously infused because of its short half-life. Also, when alfentanil infusion is discontinued, the release of stress hormones may increase at a more rapid rate compared with longer-acting opioids such as fentanyl. The use of alfentanil in congenital cardiac patients may therefore be limited to simple repairs such as an ASD, in which the bypass time is short and temperature extremes are less severe, and prompt tracheal extubation is a goal.

Compared with other agents in its class, remifentanil, a new ultrashort-acting opioid, offers the unique advantage of metabolism via nonspecific and tissue esterases thereby limiting the potential for accumulation related to protracted elimination. [86] Remifentanil may provide the advantages of alfentanil in the selected group for whom the blunting of endogenous responses is desirable intraoperatively, but potentially deleterious at the end of the procedure. A randomized controlled trial comparing equipotent doses of alfentanil and remifentanil for outpatient pediatric surgery revealed delayed emergence, requiring naloxone only in the alfentanil group. [87] In both adults and children, remifentanil is associated with qualitative hemodynamic changes similar to other opioids, a variable tendency to bradycardia as well as a small reduction in systolic blood pressure. [87] [88] [89]

Because of the widespread use of the opioids for pediatric cardiac surgery and the availability of invasive monitoring, the pharmacokinetics and pharmacodynamics of these drugs have been well studied. [84] [90] In general, the clinical pharmacology of fentanyl and sufentanil share the same age-related pharmacokinetic and pharmacodynamic features. For example, sufentanil has increased clearance in patients aged 1 month to 12 years, achieved comparable adult clearance in adolescents (12-16 years of age), and decreased clearance during the neonatal period (newborn to 1 month) (Table 50-6) . [73] [78] Furthermore, sequential sufentanil anesthetics in neonates with congenital heart disease show marked increases in clearance and elimination between the 1st week and the 3rd or 4th week of life [75] (Fig. 50-8) . The latter observation is most likely attributable to maturational changes in hepatic microsomal activity and improved hepatic blood flow from closure of the ductus venosus. The variability in clearance and elimination, coupled with limited cardiovascular reserve in the neonate during the first month of life, makes opioid dosing difficult in this age group. Careful titration of 5 to 10 mug/kg of fentanyl or 1 to 2 mug/kg of sufentanil or a continuous infusion technique provides the most reliable method of achieving hemodynamic stability and an accurate dose response. Cardiopulmonary bypass, different institutional anesthetic practices, and individual patient differences all influence pharmacokinetic and pharmacodynamic disposition of the opioids in ways that are not predictable. Even certain disease

states such as tetralogy of Fallot [80] or pathophysiologic conditions such as increased intraabdominal pressure [81] alter pharmacokinetic processes.

CARDIOPULMONARY BYPASS

Differences Between Adult and Pediatric CPB

The physiologic effects of CPB on neonates, infants, and children are significantly different than the effects on adults (Table 50-7) . During CPB, pediatric patients are exposed to biologic extremes not seen in adults, including deep hypothermia (15-20°C), hemodilution (3- to 15-fold greater dilution of circulating blood volume), low perfusion pressures (20-30 mm Hg), wide variation in pump flow rates (ranging from highs of 200 mL/kg/min to total circulatory arrest), and differing blood pH management techniques (alpha-stat or pH-stat, or both sequentially). These parameters significantly differ from normal physiology and affect preservation of normal organ function during and after

TABLE 50-6 -- Sufentanil Pharmacokinetics in Pediatric Cardiovascular Patients [a]

AGE GROUP	t½ a (min)	t½ b (min)	CLEARANCE (mL/kg/min)	Vd_{as} (L/kg)
1-30 d	23 ± 17	737 ± 346	6.7 ± 6.1	4.2 ± 1.0
1-24 mon	16 ± 5	214 ± 41	18.1 ± 2.7	3.1 ± 1.0
2-12 y	20 ± 6	140 ± 30	16.9 ± 2.2	2.7 ± 0.5
12-18 y	20 ± 6	209 ± 23	13.1 ± 0.4	2.7 ± 0.5

Abbreviations: t½ a--slow distribution half-life; t½b--elimination half-life; Vd_{as} --volume of distribution at steady state

Also see Chs. 10 and 59 for comparative numbers and thoughts.

[a] All values are mean ± standard deviations; see reference [51] .

Figure 50-8 Sequential sufentanil clearance during the 1st month of life in three neonates with congenital heart disease. Clearance of sufentanil increases above adult rates within the neonatal period. (Values from Greeley and de Bruijn)

CPB. In addition to these prominent changes, subtle variations in glucose supplementation, cannula placement, presence of aortopulmonary collaterals, and patient age may also be important factors affecting organ function during cardiopulmonary bypass. Adult patients are infrequently exposed to these biologic extremes. In adult cardiac patients, temperature is rarely lowered below 25°C, hemodilution is more moderate, perfusion pressure is generally maintained at 50 to 80 mm Hg, flow rates are maintained at 50 to 65 mL/kg/min, and pH management strategy is less influential because of moderate hypothermic temperatures and rare use of circulatory arrest. Variables such as glucose supplementation rarely pose a problem in adult patients owing to large hepatic glycogen stores. Venous and arterial cannulas are larger and less deforming of the atria and aorta, and their placement is more predictable. Although superficially similar, the conduct of CPB in children is considerably different from that in adults. One would therefore expect marked physiologic differences in the response to CPB in the child.

Prime Volume

The priming solutions used in pediatric CPB take on great importance because of the disproportionately large prime volume/blood volume ratio in children. In adults, the priming volume is equivalent to 25 to 33 percent of the patient's blood volume, whereas in neonates and infants, the priming volume may exceed the patient's blood volume by 200 percent. Even contemporary low-volume bypass circuits rarely reduce this figure much below 150 percent in the smallest neonates. Care must be taken, therefore, to achieve a physiologically balanced prime and limit the volume as much as possible. Most pediatric priming solutions, however, have quite variable levels of electrolytes, calcium, glucose, and lactate. Electrolytes, glucose, and lactate levels may be quite high if the prime includes large amounts of banked blood, or quite low if a minimal amount of banked blood is added. Calcium levels are generally very low in pediatric prime solutions; this may contribute to the rapid

TABLE 50-7 -- Differences Between Adult and Pediatric Cardiopulmonary Bypass

PARAMETER	ADULT	PEDIATRIC
Hypothermic temperature	Rarely below 25-32°C	Commonly 15-20°C
Use of total circulatory arrest	Rare	Common
Pump prime		
Dilution effects on blood volume: addi-tional additives in pediatric primes	25-33%	150-300% Blood, albumin
Perfusion pressures	50-80 mm Hg	20-50 mm Hg
Influence of alpha- vs. pH-stat management strategy	Minimal at moderate hypothermia	Marked at deep hypothermia
Measured Pa CO_2 differences	30-45 mm Hg	20-80 mm Hg
Glucose regulation		
Hypoglycemia	Rare--requires significant hepatic injury	Common--reduced hepatic glycogen stores
Hyperglycemia	Frequent--generally easily controlled with insulin	Less common--rebound hypoglycemia may occur

slowing of the heart with the initiation of bypass. The main constituents of the priming solution include crystalloid, banked blood (to maintain a temperature-appropriate hematocrit), and colloid. Other supplements that may be added to the prime are mannitol, a buffer (sodium bicarbonate or tris [hydroxymethyl] aminomethane), and steroids. Many institutions add colloid or fresh frozen plasma to the pump prime in neonates and small infants or use whole blood in the priming solution. Low concentrations of plasma proteins have been shown experimentally to impair lymphatic flow and alter pulmonary function by increasing capillary leak. [94] [95] Although adding albumin to pump prime has not been shown to alter outcome in adults during CPB, one study suggested that maintaining normal colloid osmotic pressure may improve survival in infants undergoing CPB. [96] [97] The addition of fresh frozen plasma or whole blood is an attempt to restore the level of procoagulants, which are severely diluted with CPB in infants. For neonates and infants, blood must be added to the priming solution. Most institutions use packed red blood cells in their prime solution, but some use whole blood. The use of whole blood supplements both red blood cells and the coagulation factors with a single donor exposure. In fact, lowvolume bypass circuits may enable perfusionists and anesthesiologists to share a single unit of whole blood, thereby limiting the donor exposure to one throughout the entire perioperative course. The addition of any blood products will cause a much higher glucose load in the prime. Hyperglycemia may increase the risk of neurologic injury if brain ischemia occurs. Mannitol is added to promote an osmotic diuresis and to scavenge oxygen free radicals from the circulation. Steroids are added to stabilize membranes to produce the theoretical advantage of reducing ion shifts during periods of ischemia. Steroids, however, may raise glucose levels and this may be detrimental if there is a period of cerebral ischemia. Steroids remain one of the more controversial additives in priming solutions.

Temperature

Hypothermic CPB is used to preserve organ function during cardiac surgery. Three distinct methods of CPB are used: moderate hypothermia (25-32°C), deep hypothermia (15-20°C), and DHCA. The choice of method of bypass is based on the required surgical conditions, patient size, the type of operation, and the potential physiologic impact on the patient.

Moderate hypothermic CPB is the principal method of bypass employed for older children and adolescents. In these patients, venous cannulae are less obtrusive, and the heart can easily accommodate superior and inferior vena cava cannulation. Bicaval cannulation reduces right atrial blood return and improves the surgeon's ability to visualize intracardiac anatomy. Moderate hypothermia may also be chosen for less demanding cardiac repairs in infants, such as an ASD or an uncomplicated VSD. Most surgeons are willing to cannulate the inferior and superior venae cavae in neonates and infants. In these patients, however, this approach is technically more difficult and likely to induce brief periods of hemodynamic instability. Additionally, the pliability of the cava and the rigidity of the cannulas may result in caval obstruction, impaired venous drainage, and elevated venous pressure in the mesenteric and cerebral circulation.

Deep hypothermic CPB is generally reserved for neonates and infants requiring complex cardiac repair. However, certain older children with complex cardiac disease or severe aortic arch disease benefit from deep hypothermic temperatures. For the most part, deep hypothermia is selected to allow the surgeon to operate under conditions of low-flow CPB or total circulatory arrest. Low pump flows (50 mL/kg/min) improve the operating conditions for the surgeon by providing a near bloodless field. DHCA allows the surgeon to remove the atrial or aortic cannula. Utilizing this technique, surgical repair is more precise because of the bloodless and cannula-free operative field. Arresting the circulation, even at deep hypothermic temperatures, introduces the concern of how well deep hypothermia preserves organ function, with the brain being at greatest risk. [98]

Hemodilution

Although hemoconcentrated blood has an improved oxygen-carrying capacity, its viscosity reduces efficient flow through the microcirculation. With hypothermic temperatures, blood viscosity increases significantly and flow decreases. Hypothermia, coupled with the nonpulsatile flow of CPB, impairs blood flow through the microcirculation. Blood sludging, small vessel occlusion, and multiple areas of tissue hypoperfusion may result. Therefore, hemodilution is an important consideration during hypothermic CPB. The appropriate level of hemodilution for a given hypothermic temperature, however, is not well defined. Experimental evidence suggests that reducing hematocrit levels to as low as 15 percent provides a sufficient quantity of oxygen delivery to the myocardium at normothermia, provided intravascular volume, colloid osmotic pressure, and normotension are maintained. [99] At hypothermic temperatures, hematocrit levels reduced to as low as 10 percent provide adequate oxygen delivery during CPB, as long as flow rates and perfusion pressure are maintained. [100] [101] Because red blood cells serve as the major reservoir of oxygen during circulatory arrest, hematocrit values closer to 20% are generally preferred for deep hypothermia when this technique is contemplated. Most centers maintain hematocrit levels at 20±2 percent during deep hypothermia (15-20°C) and will allow the hematocrit level to drift as low as 18 percent before transfusing additional red blood cells. Although this is an arbitrary limit, lower hematocrit values have not been systematically evaluated to ensure adequate oxygen delivery to tissue. Cerebral oxygen delivery is an especially important consideration, since cerebral autoregulation is impaired at deep hypothermic temperatures and after DHCA.

To achieve a hematocrit level of 20 to 25 percent in neonates and infants, banked blood should be added to the priming solution. A calculation of the mixed hematocrit level on CPB (the hematocrit level of the total priming volume plus the patient's blood volume) can be calculated by the following formula:

where Hct_{CPB} is mixed Hct (TPV + BV $_{pt}$), BV_{pt} is patient's blood volume (weight in kg × estimated blood volume in mL/kg), TPV is total priming volume, and Hct_{pt} is starting hematocrit level of the patient. This calculation allows an estimate of the hematocrit level of the patient using an asanguineous prime and is therefore useful for older children and adolescents. In neonates and infants, the perfusionist must add blood to the pump prime to achieve a desired hematocrit level during hypothermic CPB. The following formula estimates the amount of red blood cells that must be added to achieve this hematocrit level:

where *added RBCs* represents milliliters of packed red blood cells added to the prime volume, BV_{pt} is patient's blood volume, TPV is total priming volume, *Hct desired* is the desired hematocrit level on CPB, and Hct_{pt} is the starting hematocrit level of the patient.

Currently, no evidence exists for defining the optimal hematocrit level after weaning from CPB. Decisions concerning post-CPB hematocrit levels are made based on the patient's post-repair function and anatomy. Patients with residual hypoxemia or those with moderate to severe myocardial dysfunction benefit from the improved oxygencarrying capacity of hematocrit levels of 40 percent or higher. Patients with a physiologic correction and excellent myocardial function may tolerate hematocrit levels of 20 to 25 percent. [99] In children with mild to moderate myocardial dysfunction, accepting hematocrit levels between these extremes seems prudent. Therefore, in patients with physiologic correction, moderately good ventricular function, and hemodynamic stability, the risks associated with blood and blood product transfusion should be strongly considered during the immediate post-bypass period.

Initiation of CPB

Arterial and venous cannulation of the heart prior to initiating CPB may result in significant problems in the peribypass period. A malpositioned venous cannula has the potential for vena caval obstruction. The problems of venous obstruction are magnified during CPB in the neonate because arterial pressures are normally low (20-40 mm Hg), and large, relatively stiff cannulas easily distort these very pliable venous vessels. [94] [95] [96] A cannula in the inferior vena cava may obstruct venous return from the splanchnic bed, resulting in ascites from increased hydrostatic pressure or directly reduced perfusion pressure across the mesenteric, renal, and hepatic vascular beds. Significant renal, hepatic, and gastrointestinal dysfunction may ensue and should be anticipated in the young infant with unexplained ascites. Similar cannulation problems may result in superior vena cava obstruction. This condition may be more ominous during bypass. Under these circumstances, three problems may ensue: (1) cerebral edema, (2) a reduction in regional or global cerebral blood flow, and (3) reduced proportion of pump flow reaching the cerebral circulation, causing inefficient brain cooling. In the operating room, it is advisable to monitor superior vena cava pressures via an internal jugular catheter or by looking at the patient's head for signs of puffiness or venous distention after initiating bypass. Discussions with the perfusionist regarding adequacy of venous return and large cooling gradients between the upper and lower body should alert the anesthesiologist and the surgeon to potential venous cannula problems. Patients with

anomalies of the large systemic veins (persistent left superior vena cava or azygous continuation of an interrupted inferior vena cava) are at particular risk for problems with venous cannulation and drainage.

Problems with aortic cannula placement also occur. The aortic cannula may slip beyond the takeoff of the innominate artery and therefore selectively flow to the right side of the cerebral circulation. Also, the position of the tip of the cannula may promote preferential flow down the aorta or induce a Venturi effect to steal flow from the cerebral circulation. This problem has been confirmed during cerebral blood flow monitoring by the appearance of large discrepancies in flow between the right and left hemisphere after initiating CPB. Other clues to cannula misplacement include better cooling in the lower body than the upper body. The presence of large aortic to pulmonary collaterals, such as a large PDA, may also divert blood to the pulmonary circulation from the systemic circulation thereby reducing CBF and the efficiency of brain cooling during CPB. [102] The surgeon should gain control of the ductus either prior to or immediately after instituting CPB to eliminate this problem and, if possible, large aortopulmonary collaterals should be embolized in the cardiac catheterization laboratory prior to the operative procedure. Neonates with significant aortic arch abnormalities (e.g., aortic atresia, interrupted aortic arch) may require radical modifications of cannulation techniques, such as placing the arterial cannula in the main pulmonary artery and temporarily occluding the branch pulmonary arteries to perfuse the body via the PDA, or even dual arterial cannulation of both the ascending aorta and main pulmonary artery. Such adaptations require careful vigilance to ensure effective, thorough cooling of vital organs.

Once the aortic and venous cannulae are positioned and connected to the arterial and venous limb of the extracorporeal circuit, bypass is initiated. The arterial pump is slowly started, and, once forward flow is ensured, venous blood is drained into the oxygenator. Pump flow rate is gradually increased until full circulatory support is achieved. If venous return is diminished, arterial line pressure high, or mean arterial pressure excessive, pump flow rates must be reduced. High line pressure and inadequate venous return are usually caused by malposition or kinking of the arterial and venous cannulas, respectively. The rate at which venous blood is drained from the patient is determined by the height difference between the patient and the oxygenator inlet and the diameter of the venous cannula and line tubing. Venous drainage can be enhanced by increasing the height difference between the oxygenator and the patient or by using a larger venous cannula. Venous drainage can be reduced by either decreasing the height difference between the oxygenator and the patient or by partially clamping the venous line.

In neonates and infants, deep hypothermia is commonly used. For this reason, the pump prime is kept cold (18-22°C). When the cold perfusate contacts the myocardium

during the institution of CPB, heart rate slows immediately and contraction is impaired. The contribution of total blood flow pumped by the infant's heart rapidly diminishes. Therefore, to sustain adequate systemic perfusion at or near normothermic temperatures, the arterial pump must reach full flows quickly. CPB is initiated in neonates and infants by beginning the arterial pump flow first. Once aortic flow is ensured, the venous line is unclamped and blood is siphoned out of the right atrium into the inlet of the oxygenator. Flowing before unclamping the venous line prevents the potential problem of exsanguination if aortic dissection, or misplacement of the aortic cannula occurs. Neonates and infants have a low blood volume/prime volume ratio, and intravascular volume falls precipitously if the venous drainage precedes aortic inflow. Once aortic cannula position is verified, pump flow rates are rapidly increased to maintain effective systemic perfusion. As coronary artery disease is rarely a consideration, the myocardium should cool evenly unless distortion caused by the cannulas compromises the coronary arteries. When a cold prime is used, caution must be exercised in using the pump to infuse volume prior to initiating CPB. Infusion of cold perfusate may result in bradycardia and impaired cardiac contractility before the surgeon is prepared to initiate CPB.

Once CPB begins, careful observation should be focused to ensure appropriate circuit connections, myocardial perfusion, and optimal cardiac decompression. Ineffective venous drainage can rapidly result in ventricular distention. This is especially true in infants and neonates, in whom ventricular compliance is low and the heart is relatively intolerant of excessive preload augmentation. If ventricular distention occurs, pump flow must be reduced and the venous cannula repositioned. Alternatively, the heart may be decompressed by placing a cardiotomy suction or small vent in the appropriate chamber.

Pump Flow Rates

Recommendations for optimal pump flow rates for children have historically been based both on the patients' body mass and on evidence of efficient organ perfusion as determined by arterial blood gases, acid-base balance, and whole body oxygen consumption during cardiopulmonary bypass. [49] [103] At hypothermic temperatures, metabolism is reduced. Pump flow rates can therefore be reduced and still meet or exceed the tissue's metabolic needs (see the discussion of low-flow CPB in the following section.

Special Techniques

Deep Hypothermic Circulatory Arrest

Neonates and small infants weighing less than 8 to 10 kg who require extensive repair of complex congenital heart defects may have their repair using DHCA. This technique facilitates precise surgical repair under optimal conditions, free of blood or cannulas in the operative field, providing maximal organ protection, and often resulting in shortened total CPB time. The scientific rationale for the use of deep hypothermic temperatures rests primarily on a temperature-mediated reduction of metabolism. Whole body and cerebral oxygen consumption during induced hypothermia decreases the metabolic rate for oxygen by a factor of 2 to 2.5 for every 10°C reduction in temperature. [104] These results are consistent with in vitro models, which relate temperature reduction to a decrease in the rate constant of chemical reactions, as originally described by Arrhenius using the equation $k = Ae^{-RT}$. The reduction in oxygen supply during deep hypothermic low-flow CPB is associated with preferential increases in vital organ perfusion (e.g., to the brain) and increased extraction of oxygen. [105] Therefore, to some extent, deep hypothermic low-flow CPB exerts a protective effect by reducing the metabolic rate for oxygen, promoting preferential organ perfusion, and increasing tissue oxygen extraction.

Extensive clinical experience using DHCA has shown that the safe circulatory arrest period may last 35 to 40 minutes. [98] Beyond this duration, the incidence of permanent and transient neurologic sequelae may increase. Both the duration of the arrest period and variations in perfusion technique during cooling and rewarming influence the development of these problems. The effect of deep hypothermia on tissue metabolism and oxygen consumption and extraction clearly does not explain the entire protective effect of "safe" DHCA, however. Cortical P_{O_2} and P_{CO_2} levels indicate basal cerebral metabolic activity during DHCA (i.e., anaerobic metabolism). During brain ischemia, excitatory amino acids such as glutamate and aspartate are released and are putative mediators of ischemic damage. [49] [100] [101] [103] [106] [107] Hypothermia has been shown to significantly decrease the release of excitatory amino acids, suggesting another mechanism besides metabolism reduction for its protective effect. [108] In addition, membrane changes that transform a normal semiliquid to a semisolid form during hypothermia may act to prevent calcium influx during reperfusion and thereby account for additional protection noted in some experimental models. [109]

Although all organ systems are at risk for the development of ischemic and reperfusion injury, as manifested by lactate and pyruvate production during DHCA, the brain appears to be the most sensitive and the least tolerant of these effects. Brain stem and cortical evoked potentials as well as processed electroencephalogram are altered after DHCA. [110] [111] [112] The abnormalities in the evoked potentials appear to be related to the duration of DHCA and are attributed to altered metabolism. During reperfusion after the arrest period, CBF and metabolism remain depressed in neonates and small infants (Fig. 50-9 and see Fig. 50-6) (Figure Not Available) . [56] Importantly, during the use of these extremes of temperature, it appears that autoregulation is lost and cerebral perfusion becomes highly dependent on the conduct of extracorporeal perfusion and presumably post-bypass hemodynamic performance.

Current controversy exists regarding the immediate-term and long-term neuropsychologic effects of DHCA. Early reports regarding the long-term consequences of DHCA on brain development and intelligence were conflicting. [113] Transient neurologic dysfunction and other reversible cerebral injuries have been reported. These transient, subtle neuropsychologic disturbances have led investigators to examine more systematically the long-term outcome after DHCA.

Figure 50-9 Bar graph of variations in cytochrome oxidase (cyt a,a_3) NIR signals and cerebral metabolic rate for oxygen ($CMRO_2$) in hypothermic bypass with total circulatory arrest subjects (DHCA). Each point of cyt a,a_3 represents mean ± SE in six subjects; $CMRO_2$ values are mean ± SD. Negative values in cyt a,a_3 represent relative decreases in quantity of oxidized enzyme. *$CMRO_2$

and cyt a,a_3 are significantly different from control, P <.05. Measurement points are identical to those in Figure 54-6.

More recently, a number of more sophisticated studies examining the outcome after DHCA have been performed. In a recent randomized clinical trial comparing the incidence of brain injury following DHCA or low-flow CPB, DHCA was demonstrated to have longer electroencephalographic recovery times and a higher incidence of clinical seizures in the early postoperative period. [114] Patients in the DHCA group also had a higher incidence of neurologic abnormalities and poor motor function at 1 year of age and poor expressive language and motor development at 2½ years, particularly those who exhibited early postoperative seizures. [115] Recent reports from the same clinical trial show that patients in the DHCA cohort continued to have worse motor coordination and planning and speech abnormalities at 4 years of age. [116] [117] [118] Of interest, both the DHCA and the low-flow CPB groups have lower cognitive and motor performance compared to a general population. This latter finding suggests that factors outside DHCA and low-flow bypass, but within the perioperative period, are associated with poor neuropsychologic development.

A recent clinical study has suggested that a pH-stat blood gas management strategy during CPB is associated with an improved neuropsychologic outcome in children. [117] This study was a retrospective developmental study with a core of patients who have undergone surgery for transposition of the great arteries. The authors found a strong positive correlation between arterial P CO_2 during cooling before circulatory arrest and developmental score. This suggested that children undergoing alpha-stat blood gas management strategy had a worse developmental outcome than those in whom a pH-stat strategy was employed. In a recent randomized clinical trial of neonates undergoing cardiac surgery using deep hypothermic circulatory arrest, pH-stat management was noted to have faster electroencephalographic recovery times and fewer postoperative seizures compared with an alpha-stat bypass group. [119] [120] The beneficial effect of pH-stat management clinically remains preliminary.

Certain experimental studies have also suggested the superiority of pH-stat strategy (Fig. 50-10) (Figure Not Available) . In one recent study, pH-stat animals had greater cerebral blood flow during cooling and better recovery of cerebral adenosine triphosphate (ATP) and intracellular pH after arrest and reperfusion. [122] Brain water content was also less in the pH-stat group. These studies suggested that pH-stat CPB may have protective mechanisms due to an increased rate of brain cooling. In more recent experimental studies comparing pH-stat and alpha-stat cardiopulmonary bypass on cerebral oxygenation, the cerebral protective effect of pH-stat management was demonstrated and indicated that the kinetics of cerebral deoxygenation might contribute to the mechanism of protection (Fig. 50-11) (Figure Not Available) . [123] [124] [125] Clearly more work needs to be done in this area before pH-stat is definitively recommended. [126] However, preliminary experimental and clinical studies suggest a superiority of this technique in certain patient groups, especially those with aortopulmonary collateral circulation.

Because of the potential for neurologic dysfunction after DHCA, some institutions use low-flow deep hypothermic CPB as an alternative technique. [26] Since low-flow bypass can produce ischemia if flow is too low and because it lengthens the CPB time, as compared with DHCA, serious concerns over this technique have also arisen. [127] [128] A recent experimental study demonstrated worse brain injury with low-flow bypass than with DHCA. [129]

Other factors such as surface cooling, anesthetic agents, and cerebral protective agents may influence and modify the effects of deep hypothermic low-flow CPB and DHCA. The potential use of certain pharmacologic agents such as anesthetic drugs, barbiturates, lidocaine, and calcium channel blockers is unknown. There are no clinical studies in children systematically examining the influence of these pharmacologic agents on cerebrovascular physiology or neurologic outcome. Therefore, the use of these agents remains entirely speculative and unfounded. Clearly, further study of the long-term effects of DHCA on neuropsychologic outcome in children is necessary. Fundamental questions regarding DHCPB with low-flow versus DHCA also need to be addressed further. Equally important, the manner in which the patient is cooled and rewarmed may affect outcome [58] [59] and merits further investigation, even before the testing of pharmacologic therapies.

Figure 50-10 (Figure Not Available) Cortical and basilar brain temperature at the end of circulatory arrest (90 minutes) in animals with systemic-pulmonary shunts. Note the significantly lower brain temperatures in the pH-stat animals. *(From Kirshbom et al [121])*

Effects of CPB

Glucose Regulation

In recent years, a substantial amount of clinical and experimental data have shown conclusive evidence of the detrimental effects of hyperglycemia during complete, incomplete, and focal cerebral ischemia. [130] [131] [132] The role of glucose in potentiating cerebral injury appears to rest on two factors: ATP utilization and lactic acidosis. [133] [134] The anaerobic metabolism of glucose requires phosphorylation and the expenditure of two molecules of ATP before ATP production can occur. This initial ATP expenditure may result in a rapid depletion of ATP and may explain why hyperglycemia worsens neurologic injury. Lactic acidosis is also important in glucose-augmented cerebral injury. An important role, however, may be as a glycolytic enzyme inhibitor. Lactate slows anaerobic ATP production by inhibiting glycolysis

Figure 50-11 (Figure Not Available) Cortical oxygen saturation (ScO_2) during deep hyothermic circulatory arrest in the pH-stat and the alpha-stat groups. The ScO_2 half-life during arrest was significantly greater in the pH-stat than in the alpha-stat group. *(From Kurth et al [125])*

immediately after ATP is consumed in the phosphorylation of glucose. [135]

Hyperglycemia

Although a strong scientific argument can be made for the detrimental effects of hyperglycemia during ischemia, there is very little evidence supporting worsening neurologic outcome in hyperglycemia during CPB or DHCA in children. A retrospective review of 34 children undergoing DHCA suggested a worse neurologic outcome in the hyperglycemic children; however, the results were reported as a nonsignificant statistical trend. [136] A pathologic review of acquired neurologic lesions in patients undergoing the Norwood Stage I procedure for hypoplastic left heart syndrome suggested hyperglycemia as a significant associated finding in patients with extensive cerebral necrosis or intraventricular hemorrhage. Although associated, a host of other potentially damaging factors (e.g., periods of hypoxia, low diastolic and systolic pressure, and thrombocytopenia) were statistically associated with the observed neuropathology. [137] Since hyperglycemia accompanies a generalized stress response, this literature has failed to distinguish whether glucose directly contributes to neurologic injury or merely serves as a marker for a high-risk population who ultimately suffer neurologic insult as a result of other factors.

Hypoglycemia

Hypoglycemia is a frequent concern in neonates during the perioperative period. Reduced hepatic gluconeogenesis coupled with decreased glycogen stores place the newborn at increased risk of hypoglycemic events. In newborns with congenital heart disease, reduced systemic perfusion (e.g., critical coarctation, hypoplastic left heart syndrome, critical aortic stenosis) may result in worsening hepatic biosynthesis, further impairing glucose production. These patients may be fully dependent on exogenous glucose; therefore, it is not uncommon for them to require 20 to 30 percent dextrose infusions to maintain euglycemia in the pre-bypass period. Older children are not immune to hypoglycemic events and are therefore susceptible to hypoglycemia-induced neurologic injury. Patients with low cardiac output states (cardiomyopathies, pretransplant patients, critically ill postoperative patients) requiring reoperation and on substantial inotropic support are at risk of reduced glycogen stores and intraoperative hypoglycemia. [138]

The impact of hypoglycemia during bypass is further complicated by the consequences of hypothermia, CO_2 management, and other factors that may modify normal cerebrovascular responses during bypass. In a dog model, insulin-induced hypoglycemia to 30 mg/dL does not alter the electroencephalographic findings. However, after 10 minutes of hypocapnic hypoglycemia, the electroencephalogram becomes flat. [115] When regional blood flow was examined in these animals, cortical and hippocampal blood flow remained normal, whereas other regions of the brain had reduced flow. The loss of electroencephalographic activity from hypoglycemia alone does not normally occur above glucose levels of 8 mg/dL. [139]

During deep hypothermic CPB and DHCA, CBF and metabolism are altered. The additive effect of hypoglycemia, even if mild, may cause alterations in cerebral

autoregulation and culminate in increased cortical injury. [137] [140] The common practice of using hyperventilation to reduce pulmonary vascular resistance in neonates and infants during weaning from CPB and in the early post-bypass period could further exacerbate hypoglycemic injury. Glucose monitoring and rigid maintenance of euglycemia are an important part of CPB management in the congenital heart patient.

Renal Effects

After CPB, the combined effects of hypothermia, nonpulsatile perfusion, and reduced mean arterial pressure cause release of angiotensin, renin, catecholamines, and antidiuretic hormone. [141] [142] [143] These circulating hormones promote renal vasoconstriction and reduce renal blood flow. Yet despite the negative impact of CPB on renal function, studies have been unable to link low-flow, low-pressure, nonpulsatile perfusion with postoperative renal dysfunction (Table 50-8) . [141] [144] The factors that best correlate with postoperative renal dysfunction are preoperative renal dysfunction and profound reductions in post-CPB cardiac output. Preoperative factors include primary renal disease, low cardiac output, and dye-related renal injury after cardiac catheterization. [143]

The incidence of acute renal insufficiency after pediatric cardiac surgery is approximately 8 percent. Multiple causative factors are involved, the final common pathway of which is oliguria and an elevated serum creatinine. Diuretics have been the mainstay of promoting urine flow after pediatric cardiopulmonary bypass. Furosemide in a dose of 1

TABLE 50-8 -- Sequelae of Pediatric Cardiopulmonary Bypass

END-ORGAN INJURY	ETIOLOGY/SIGNS
Renal injury	Organ immaturity, pre-existing renal disease
	Post-cardiopulmonary bypass low CO, use of DHCA
	Renal dysfunction: characterized by reduced GFR and ATN
Pulmonary injury	Endothelial injury, increased capillary leak, complement activation, and leukocyte degranulation
	Pulmonary dysfunction: characterized by reduced compliance, reduced FRC, and increased A-a gradient
Cerebral injury after DHCA	Loss of autoregulation, suppressed metabolism and cerebral blood flow, cellular acidosis, and cerebral vasoparesis
	CNS dysfunction: characterized by seizures, reduced developmental quotients, choreoathetosis, learning disabilities, behavioral abnormalities

Abbreviations: ATN--acute tubular necrosis; CNS--central nervous system; CO--cardiac output; DHCA--deep hypothermic circulatory arrest; GFR--glomerular filtration rate

to 2 mg/kg or ethacrynic acid 1 mg/kg every 4 to 6 hours, or both, induces a diuresis and may reverse renal cortical ischemia associated with CPB. After DHCA, it is not unusual to observe a 24-hour period of oliguria or anuria that resolves over the next 12- to 24-hour period. The use of diuretics is effective only after spontaneous urine output has been initiated in these patients.

Glomerular filtration rate, creatinine clearance, and medullary concentrating ability are substantially reduced in neonates and young infants. Therefore, the use of CPB in these patients is associated with greater fluid retention than is typically seen in older children and adult patients. The net result may be increased total body water, increased organ weight (e.g., lungs, heart), and greater difficulty with postoperative weaning from ventilatory support. The use of ultrafiltration during rewarming or after CPB is effective in reducing total body water, limiting the damaging effects of CPB, and decreasing the postoperative ventilation period. [145] [146]

Pulmonary Effects

While cardioplegia protects the heart, there is no parallel protection afforded the lung during bypass. Pulmonary dysfunction is common after cardiopulmonary bypass and its pathogenesis is poorly understood (see Table 50-8) . In broadest terms, lung injury is mediated in one of two ways: first, an inflammatory response due to leukocyte and complement activation, and second, a mechanical effect culminating in surfactant loss, atelectasis with resultant ventilation/perfusion mismatch, loss of lung volumes, and altered mechanics of breathing.

Pulmonary function after cardiopulmonary bypass is characterized by reduced static and dynamic compliance, reduced functional residual capacity, surfactant deficiency, and an increased A-a gradient. [147] [148] Atelectasis and increased capillary leak due to hemodilution, and hypothermic CPB are the most likely etiologies. Hemodilution reduces circulating plasma proteins, reducing intravascular oncotic pressure, and favors water extravasation into the extravascular space. Hypothermic CPB causes complement activation and leukocyte degranulation. [149] Leukocytes and complement are important in causing capillary-alveolar membrane injury and microvascular dysfunction through platelet plugging and release of mediators, which increase pulmonary vascular resistance. The technique of modified ultrafiltration is highly effective in reducing lung water and pulmonary morbidity during the postoperative period.

Stress Response and CPB

The release of a large number of metabolic and hormonal substances, including catecholamines, cortisol, growth hormone, prostaglandins, complement, glucose, insulin, endorphins, and other substances, characterizes the stress response during hypothermic CPB. [18] [150] [151] The likely causes for the elaboration of these substances include contact of blood with the nonendothelialized surface of the pump tubing and oxygenator, nonpulsatile flow, low perfusion pressure, hemodilution, hypothermia, and light anesthesia depth. Other factors that may contribute to elevations of stress hormones include delayed renal and hepatic clearance during hypothermic CPB, myocardial injury, and exclusion of the pulmonary circulation from bypass. The lung is responsible for metabolizing and clearing many of these stress hormones. The stress response generally peaks during rewarming from cardiopulmonary bypass. There is strong evidence that the stress response can be blunted by increasing the depth of anesthesia. [18] [150] [151]

It is unclear at what level elevated circulating stress hormones, a normal neonatal adaptive response, become detrimental. There is little question that these substances could mediate undesirable effects such as myocardial damage (catecholamines), systemic and pulmonary hypertension (catecholamines, prostaglandins), pulmonary endothelial damage (complement, prostaglandins), and pulmonary vascular reactivity (thromboxane). The benefits of controlling the stress response with fentanyl in premature infants undergoing PDA ligation and with sufentanil in neonates with complex congenital heart disease have been demonstrated. [85] [152] Although blunting the stress response seems warranted, there is additional evidence suggesting that the newborn stress response, especially the endogenous release of catecholamines, may be an adaptive metabolic response necessary for survival at birth. [153] Thus the complete elimination of an adaptive stress response may not be desirable. To what extent acutely ill neonates with congenital heart disease are dependent on their stress response for maintaining hemodynamic stability is currently unknown.

It is, therefore, prudent to maintain a depth of anesthesia adequate to attenuate the stress response, but to attempt to block the response altogether may not be necessary. Acceptable anesthesia during CPB may be best accomplished by either the continuous administration of an inhalation anesthetic via a vaporizer connected to the pump oxygenator, careful titration of incremental doses of opioids, or the precise administration of an opioid or opioid and benzodiazepine by a continuous infusion technique. Primary opioid anesthetic techniques result in reduced stress hormone release and decreased postoperative metabolic acidosis and lactate production when compared with primary halothane anesthesia and may therefore be a preferred technique in complex congenital heart disease. [85] If depth of anesthesia is accomplished by the administration of excessively large doses of opioids (e.g., fentanyl or sufentanil), postoperative mechanical ventilation will be necessary. By contrast, residual levels of inhalation anesthetic drugs (e.g., halothane or isoflurane) can produce transient myocardial depression at the termination of CPB, complicating separation from CPB.

Discontinuation of CPB

When weaning from CPB, blood volume is assessed by direct visualization of the heart and monitoring right atrial or left atrial filling pressures. When filling pressures

are adequate, the patient fully warmed, acid-base status normalized, heart rate adequate, and sinus rhythm achieved, the venous drainage is stopped and the patient can be weaned from bypass. The arterial cannula is left in place so that a slow infusion of residual pump blood can be used to optimize filling pressures. Myocardial function is assessed by direct

cardiac visualization and either a transthoracic left or right atrial catheter, by a percutaneous internal jugular catheter, or by the use of intraoperative echocardiography. Pulse oximetry can also be used to assess the adequacy of cardiac output. [154] Low systemic arterial saturation or the inability of the oximeter probe to register a pulse may be a sign of very low output and high systemic resistance. [155]

After the repair of complex congenital heart defects, the anesthesiologist and surgeon may have difficulty separating patients from cardiopulmonary bypass. Under these circumstances, a diagnosis must be made and includes (1) an inadequate surgical result with a residual defect requiring repair, (2) pulmonary artery hypertension, and (3) right or left ventricular dysfunction. Two general approaches are customarily used, either independently or in conjunction with one another. An intraoperative "cardiac catheterization" can be performed to assess isolated pressure measurements from the various great vessels and chambers of the heart (i.e., catheter pullback measurements or direct needle puncture to evaluate residual pressure gradients across repaired valves, sites of stenosis and conduits, and oxygen saturation data to examine for residual shunts). [156] Alternatively, echo-Doppler may be used to provide an intraoperative image of structural or functional abnormalities to assist in the evaluation of the postoperative cardiac repair. [16] [157] If structural abnormalities are found, the patient can be placed back on CPB, and residual defects can be repaired before the patient leaves the operating room. Leaving the operating room with a significant residual structural defect adversely affects survival and increases patient morbidity (see Fig. 50-5) . [16] [157] For the anesthesiologist, echo-Doppler can rapidly identify right and left ventricular dysfunction and suggest the presence of pulmonary artery hypertension. In addition, echo-Doppler can identify regional wall motion abnormalities due to ischemia or intramyocardial air that will direct specific pharmacologic therapy and provide a means of assessing the results of these interventions (Fig. 50-12) . [158]

Modified Ultrafiltration

One important factor affecting morbidity and mortality after cardiac surgery in children is the effect of CPB. During the initiation of CPB, considerable hemodilution occurs. This hemodilution is the result of the priming volume required for the CPB circuit. Under many circumstances this hemodilutional effect is intentional, decreasing blood viscosity and thereby preventing sludging when the patient is cooled to temperatures below 20°C. After CPB, hemodilution is associated with tissue edema and organ dysfunction. Because blood elements are exposed to the nonendothelialized circuitry of CPB, there is also a significant inflammatory response as a result of CPB. Both these effects of hemodilution and inflammation are exaggerated in neonates, infants, and young children because of their disproportionate exposure to the circuit relative to their body size. This inflammatory response leads to an increase in capillary permeability, leading to an overall increase in total body edema postoperatively.

Efforts to reduce the hemodilution and inflammatory effects of CPB have included reducing priming volume, perioperative anti-inflammatory and diuretic therapies, and the use of postoperative peritoneal dialysis. The technique of modified ultrafiltration (MUF) was first used clinically as an alternative method to reduce the adverse effects of CPB in children. [159]

The technique of MUF is performed after CPB is complete and allows filtration of both the patient and remaining contents of the CPB circuit, including the venous reservoir. [160] [161] [162] Using the MUF technique, an ultrafilter is interposed in the CPB circuit between the aortic arterial line and the venous canula, which is located in the right atrium. After weaning from CPB, the blood is removed from the patient via the aortic canula and fed through the ultrafilter along with blood from the venous reservoir and oxygen. The outlet of the ultrafilter is fed to the right atrium of the patient. Blood flow through the ultrafilter approximates 200 mL per

Figure 50-12 *(A)* Two-dimensional echocardiogram in the short-axis view across the ventricles demonstrating the presence of intramyocardial air (arrow) in the ventricular septum and right ventricular (RV) wall. The intramyocardial air appears as a dense, "snowy" echogenic area. Note the associated wall motion abnormality appearing as flattening of the ventricular septum. *(B)* The patient was treated with phenylephrine, increasing systemic and coronary perfusion pressure, resulting in clearance of the air and the echogenic density and restoration of normal left ventricular (LV) wall motion and configuration.

minute, which is maintained by a roller pump. Suction is applied to the filter port of the ultrafilter, resulting in an ultrafiltration rate of 100 to 150 mL per minute. A constant left atrial or right atrial pressure is maintained, achieving continued hemodynamic stability in the patient. Ultrafiltration is carried out with the end point being either time (15-20 minutes) or the achievement of a hematocrit value of approximately 40. [161]

Ultrafiltration appears to offer two major advantages. First, total body water is reduced as a direct result of removing the ultrafiltrate. [159] This effect counteracts the hemodilution effects associated with the institution of CPB. In addition, the hematocrit is raised after cardiopulmonary bypass, enhancing oxygen delivery to the tissues. Secondly, MUF has been shown to remove some of the deleterious vasoactive substances associated with inflammatory response to CPB. [163] [164] This effect is mediated by reducing circulating cytokines, which are associated with capillary leak syndrome. Examination of the ultrafiltrate shows that it contains low-molecular-weight inflammatory mediators, including C3a, C5a, interleukin-6alpha, interleukin-8alpha, tumor necrosis factor, myocardial depressant factor, and various other cytokines. Several studies have shown that, compared with control patients, patients who undergo MUF after CPB have substantially less increase in total body water, demonstrate less complement and interleukin release, require fewer blood transfusions, and show a faster recovery of systolic blood pressure (Fig. 50-13) (Figure Not Available) . [159] [161] [165]

In a clinical study examining the effect of MUF on left ventricular systolic function in children, MUF was associated with an increase in intrinsic left ventricular systolic function and a decrease in end-diastolic pressure, thereby improving left ventricular compliance. [166] In an experimental study, MUF has also been demonstrated to improve CBF, cerebral metabolic activity, and cerebral oxygen delivery after DHCA (Fig. 50-14) (Figure Not Available) . [167] This last effect acutely improves cerebral metabolism after DHCA and may reduce and reverse the known deleterious effects of DHCA on brain function after CPB. In another clinical study MUF was demonstrated to reduce postoperative blood use, chest

Figure 50-13 (Figure Not Available) Systolic blood pressure (BP) after separating from cardiopulmonary bypass and 15 minutes after separating with and without modified ultrafiltration (MUF). Note the significant improvement in systolic BP with the use of MUF. *(From Ungerleider, [161] reprinted with permission from the Society of Thoracic Surgeons)*

Figure 50-14 (Figure Not Available) Cerebral metabolic rate for oxygen measurements ($CMRO_2$) before and after deep hypothermic circulatory arrest. Note the significant increase in $CMRO_2$ in the MUF animals compared with the control and transfusion groups at stage 3. CTL, control; MUF, modified ultrafiltration; tx, tranfusion. *(From Skaryak et al [167])*

tube drainage, plural effusions, and hospital stay in patients after cavopulmonary operations. [168]

An alternative to MUF is conventional filtration during the rewarming period of CPB. In an experimental model examining MUF versus conventional ultrafiltration, only MUF was effective in reducing weight gain and myocardial edema, and was associated with improving left ventricular function. [169] Possible complications of MUF include air embolus, patient cooling during ultrafiltration, and bleeding. [161] These theoretical and technical potential complications appear not to be of substantial concern. It is the view of most groups that the benefits of MUF far exceed the risk. [162]

In summary, MUF is a safe adjunct, reversing the deleterious effects of hemodilution and the inflammatory response associated with CPB in children. Perioperative blood loss and blood use is significantly reduced when MUF is used. MUF also improves left ventricular function and systolic blood pressure and increases oxygen delivery. Pulmonary compliance and brain function after CPB are also improved. Therefore, the use of MUF is becoming more routine in pediatric patients after CPB.

Specific Problems Encountered in Discontinuing CPB

Left Ventricular Dysfunction

The contractile state of the LV may be reduced after pediatric cardiac surgery. This is due to surgically induced ischemia during the repair, the preoperative condition of the myocardium, the effects of deep hypothermia and circulatory arrest on myocardial compliance, and new altered loading conditions on the LV caused by the repair. [170] [171] [172] LV dysfunction can be treated by optimizing preload, increasing heart rate, increasing coronary perfusion pressure, correcting ionized calcium levels, and adding inotropic support. The neonate's heart rate-dependent cardiac output, reduced

myocardial compliance, and diminished response to calcium and catecholamines are factors influencing the need for inotropic support. Inotropic support is usually begun with dopamine (3-10 mug/kg/min). Several studies suggest that the effect of dopamine in children is age-dependent. In young children after cardiac surgery, dopamine increases cardiac output, which correlates more with elevations in heart rate than augmentation of stroke volume, [173] whereas in young adults, dopamine clearly increases stroke volume. [13] Nonetheless, infants and neonates respond favorably to dopamine infusions with increased systemic blood pressure and cardiac output and improved systemic perfusion.

Calcium supplementation is also important in augmenting cardiac contractility. Although calcium has fallen into some disfavor because of concerns over reperfusion injury, calcium supplementation remains an important therapy after pediatric cardiac surgery. Fluctuations in ionized calcium levels occur commonly in the immediate post-CPB period in children. This is most often due to the relatively large transfusions of citrate and albumin-rich blood products such as whole blood, fresh frozen plasma, platelets, and cryoprecipitate necessary for hemostasis, all of which bind calcium. [174] Routine calcium supplementation during the early post-CPB period is especially helpful in patients with diminished LV function. In patients with a slow sinus or junctional rate, calcium must be administered cautiously, as marked slowing of AV conduction may occur.

Epinephrine (0.02-0.2 mug/kg/min) is useful in patients with significant LV dysfunction who remain hypotensive with high left atrial filling pressures or echo-Doppler evidence of reduced contractility or regional ischemia. [175]

Amrinone is a nonglycoside, noncatecholamine inotropic drug whose mechanism of action is through the inhibition of phosphodiesterase, which prevents the breakdown of cyclic adenosine monophosphate and results in increased calcium transport. Amrinone causes an increase in myocardial contractility and systemic and pulmonary artery vasodilation. [176] [177] Neonates and infants show considerable benefit from the phosphodiesterase inhibitors, especially those whose myocardium is afterload sensitive, such as postoperative arterial switch patients. [177] Pharmacokinetic studies suggest that loading dosages for children are twice the recommended adult dose (i.e., 2-4.5 mg/kg). [178] In the authors' experience, amrinone in loading doses of 2 to 3 mg/kg and infusion rates of 5-15 mug/kg/min are very useful in the management of low cardiac output states in neonates, infants, and children. Higher loading doses (3-4 mg/kg) have been associated with a profound systemic vasodilation in the pediatric cardiac patient. Because the onset of peripheral vasodilation precedes the increase in inotropy during the loading phase, significant hypotension may occur if amrinone is loaded too rapidly. It may therefore be prudent to load slowly or while the patient is on CPB. In so doing, however, upward adjustment in the loading dose becomes necessary to compensate for the substantially larger circulating volume and the fact that 20 percent of the dose is bound to the CPB circuit. [179]

Milrinone, a more potent phosphodiesterase-3 inhibitor, is also an effective inotrope-vasodilator in infants and children. Studies in neonates after open heart surgery reveal significant reductions in SVR and PVR and increases in cardiac index, primarily due to larger stroke volume. [180] Infants and children demonstrate a larger volume of distribution and clearance of milrinone compared to adults; thus, the loading dose necessary to achieve therapeutic levels may be as high as 100 mug/kg. [181] When loading occurs on CPB, appropriate adjustment should be made (~.3 mg/L priming volume), but unlike amrinone, milrinone does not appear to bind the bypass circuit.

Dobutamine is an effective, albeit weaker, inotropic agent in children. Although it is reported to have fewer chronotropic effects than dopamine, in neonates, significant tachy-arhythmias may occur. This may relate to structural similarities between dobutamine and isoproterenol. [175] In children after cardiac surgery, dobutamine increases cardiac output primarily through increased heart rate. The efficacy of dobutamine seems to be reduced in immature animals. [182] This is consistent with reduction in beta-receptors and a higher level of circulating catecholamines in newborns.

Right Ventricular Dysfunction

Primary RV dysfunction is a common finding after CPB in neonates, infants, and children. For example, after repair of tetralogy of Fallot, pre-existing RV hypertrophy, a right ventriculotomy, and the placement of a transannular patch across the RV outflow tract, resulting in acute pulmonary regurgitation and RV volume overload, are common causes of postoperative RV dysfunction. [23] The treatment of RV dysfunction consists of measures directed at lowering PVR and preserving coronary perfusion without distending the RV. Metabolic acidosis should be addressed and inotropic agents selected for their vasodilating properties (e.g., dopamine, amrinone, or milrinone). In cases of extreme ventricular dysfunction, low-dose epinephrine (0.01-0.03 mug/kg/min) may provide inotropy without vasoconstriction. [171] [183] [184] Mechanical ventilation should be adjusted to assist RV function and minimize PVR.

In contrast to the LV, the low intracavitary pressure of the normal RV receives two-thirds of its coronary filling during ventricular systole. [185] In patients with RV dysfunction, maintaining a normal or slightly elevated systolic arterial pressure maximizes coronary perfusion to the RV and augments contractility. If the need for inotropic support persists after the early post-CPB period, a critical evaluation for other structural and functional abnormalities should be aggressively pursued. Preload should be maintained at a normal to slightly elevated level. Since RV contractility is reduced, it is important to maximize preload to the highest portion of the Starling curve. [183] Overdistention of the RV, however, is not well tolerated owing to diminished ventricular compliance and diastolic dysfunction. Excessive volume loading may result in significant diastolic dysfunction, tricuspid regurgitation, and worsening forward flow. Generally, CVPs much above 12 to 14 mm Hg are poorly tolerated in neonates and infants with RV dysfunction. [186] If RV dysfunction is severe, the sternum should be left open. [187] This eliminates the impedance imposed by the chest wall and mechanical ventilation, allowing the RV to maximize its end-diastolic volume. An additional strategy in neonates, infants, and children with significant post-CPB RV dysfunction is to allow right-to-left shunting at the atrial level. Typical patients who would benefit from this strategy include neonates

undergoing repairs for tetralogy of Fallot and truncus arteriosus. Allowing an atrial communication to remain open, with blood shunting in a right-to-left direction, preserves cardiac output and oxygen delivery to the systemic circulation. Although these patients have somewhat diminished systemic oxygen saturation, as their effective cardiac output and tissue oxygen delivery are enhanced, systemic perfusion pressure improves and coronary perfusion of the RV is maintained. As RV function improves, right atrial pressure falls, right-to-left shunting decreases, and systemic arterial saturation rises.

If RV dysfunction persists to the extent that systemic cardiac output is compromised, consideration should be given to extracorporeal life support (ECMO). When ECMO is used for circulatory support, venoarterial cannulation is chosen. Venous and arterial access may be achieved through a large central artery and vein, usually the carotid artery and internal jugular vein, or by direct chest cannulation. Recovery from severe ventricular dysfunction is predicated on the concept that the myocardium has sustained a transient injury (i.e., "stunned myocardium") and is capable of recovery with time. [188] [189] ECMO is used to decrease ventricular wall tension, increase coronary perfusion pressure, and maintain systemic perfusion with oxygenated blood. ECMO may also be used for LV failure, although success with this condition is less common than that seen with RV dysfunction or pulmonary artery hypertension. Patients placed on ECMO because they fail to separate from CPB demonstrate significantly higher mortality than those for whom ECMO was instituted later in the postoperative course. [190] The children who consistently suffer the lowest survival are those who require ECMO after a Fontan operation. [191] The role of ECMO in patients with myocardial injury or pulmonary hypertension is to provide adequate systemic oxygen transport and systemic perfusion while allowing the ventricles to rest and recover. ECMO may even provide an effective means of resuscitation for postoperative cardiac patients, particularly if instituted promptly. [192] In larger infants and children with predominantly RV dysfunction and satisfactory pulmonary function, a selective RV assist device may be preferable to ECMO. [193]

Pulmonary Artery Hypertension

Therapy for elevated pulmonary artery pressures is directed at lowering PVR and unloading the RV. Reduction of PVR is accomplished by altering ventilation pattern, inspired oxygen concentration, and blood pH. Specifically, manipulating the pulmonary vascular bed in newborns and infants is a matter of regulating Pa $_{CO_2}$, pH, Pa $_{O_2}$, P $_{AO_2}$, and ventilatory mechanics. [194] [195] Pa $_{CO_2}$ is a potent mediator of PVR, especially in the newborn and young infant. Reducing Pa $_{CO_2}$ to 20 mm Hg and increasing pH to 7.6 produces a consistent and reproducible reduction in PVR in infants with pulmonary artery hypertension. [194] Manipulating serum bicarbonate levels to achieve a pH of 7.5 to 7.6 while maintaining a Pa $_{CO_2}$ of 40 mm Hg has equal salutary effects on PVR. [196] Both the Pa $_{O_2}$ and the P $_{AO_2}$ decrease PVR as well. [197] In the circumstance of intracardiac shunts, changes in Fi $_{O_2}$ have little effect on Pa $_{O_2}$. Thus, by inference, a reduction in PVR induced by increasing the inspired oxygen concentration is probably a direct pulmonary vasodilatory effect of P $_{AO_2}$ rather than Pa $_{O_2}$.

Ventilatory mechanics also play a major role in reducing PVR. [198] [199] Newborns and infants have a closing volume above functional residual capacity. Thus, at the end of a normal breath, some airway closure occurs. [200] This process results in areas of lung that are perfused and yet underventilated. As these lung segments become increasingly hypoxemic, secondary hypoxic vasoconstriction occurs. The net effect is an increase in PVR. Therefore, careful inflation of the lungs to maintain functional residual capacity will selectively reduce PVR. In practice, this is accomplished with relatively large tidal volumes and low respiratory rates, which produce an exaggerated chest excursion. Generally, tidal volumes of 15 to 25 mL/kg are required. Respiratory rates of 15 to 25 breaths per minute are used for newborns and infants. A reduced ventilatory rate with large tidal volumes reduces mean airway pressure and provides a longer expiratory phase of ventilation. Since pulmonary blood flow occurs predominantly during the expiratory phase of the respiratory cycle, the ventilatory pattern should be adjusted to allow an adequate distribution of gas throughout the lung during inspiration and a more prolonged expiratory phase to promote blood flow through the lungs. End-expiratory pressure must be applied cautiously during the post-CPB period. Low positive end-expiratory pressure (3-5 mm Hg) prevents narrowing of the capillary and precapillary blood vessels, thereby reducing PVR. [201] Higher positive endexpiratory pressure or excessive mean airway pressure results in alveolar overdistention and compression of the capillary network in the alveolar wall and interstitium. This condition elevates PVR and reduces pulmonary blood flow. [147]

The final and perhaps the least well-recognized use of the mechanical ventilator is to assist in unloading the RV. During inspiration, intrathoracic pressure increases and creates an increased pressure gradient from the lung to the left atrium, promoting cardiac output. This ventilatory assist is commonly seen in patients with pulmonary artery hypertension or RV dysfunction. An augmentation of the arterial pressure trace during inspiration is seen. The use of the ventilator to augment systemic blood flow is very similar to the thoracic pump concept used to explain blood flow during CPR. [202] The inspiratory assist must be balanced by the potential negative effects of increased mean airway pressure on PVR and RV afterload. To maximize these cardiopulmonary interactions, high tidal volume with low respiratory rates should be employed.

Attempts to manipulate PVR through pharmacologic interventions have been generally unsatisfactory. Drugs that have shown the greatest promise in decreasing PVR both clinically and experimentally have been the phosphodiesterase inhibitors. Amrinone and milrinone are the only drugs of this class currently available in the United States. Both reduce PVR and systemic vascular resistance and increase RV contractility. [177] [178] Isoproterenol has mild pulmonary artery vasodilating properties in the normal pulmonary circulation. [203] Isoproterenol reduces PVR in adults after cardiac transplantation, but there are very few data to support PVR reduction in infants and young children after cardiac surgery. In immature animals, the myocardium is less responsive to isoproterenol and causes tachycardia and

increased myocardial oxygen consumption. [204] [205] These latter effects may reduce coronary perfusion and result in relative myocardial ischemia. Both prostaglandin E_1 and prostacyclin have a pulmonary vasodilating effect [206] [207] however, both drugs produce systemic hypotension, which severely limits their use.

Because of the lack of specificity of vasodilator drugs on the pulmonary bed, newer pharmacologic methods of controlling pulmonary artery hypertension and elevated PVR are being sought. Two new concepts include ultra-shortacting intravenous vasodilators and inhaled vasodilating agents such as nitric oxide. Ultra-short-acting intravenous vasodilators are nonspecific potent vasodilators, with a half-life measured in seconds. Infusion of these drugs into the right side of the circulation produces a potent short-lived relaxation of the pulmonary artery smooth muscle. Once the drug reaches the systemic circulation, it is no longer functional. Adenosine and ATP-like compounds have these properties and may have clinical applicability in pulmonary artery hypertension in the future. [208]

Nitric oxide, an endothelium-derived vasodilator that is administered as an inhaled gas, represents the most promising development in the therapy of elevated PVR in patients with congenital heart disease. Although nonselective, it is rapidly inactivated by hemoglobin and, when inhaled, produces no systemic vasodilation. [209] Nitric oxide reduces pulmonary artery pressure in adult patients with mitral valve stenosis and in selected pediatric cardiac patients with pulmonary artery hypertension. [210] [211] [212] The congenital cardiac patient population in whom nitric oxide appears to be effective are those patients with acute PVR elevations following open heart surgery, as well as preoperative pulmonary hypertension accompanying specific anatomic conditions (e.g., total anomalous pulmonary venous return, congenital mitral stenosis). [211] [212] Because it acts directly on vascular smooth muscle, nitric oxide remains effective despite the post-CPB endothelial injury frequently encountered in children. [213] Some centers routinely employ nitric oxide in low dose (1-5 ppm) following Fontan operation when the CVP-left artrial pressure gradient exceeds 10 mm Hg. [214] Finally, nitric oxide can provide diagnostic information that helps distinguish reactive pulmonary vasoconstriction from fixed anatomic obstructive disease either in the postoperative surgical patient or in the patient undergoing pretransplant evaluation. [215] [216] In the latter, the distinction between pulmonary vasoconstriction and advanced pulmonary vascular occlusive disease will influence the prediction as to whether a child with pulmonary hypertension in association with either congenital heart disease or cardiomyopathy will survive a heart transplant or requires replacement of both heart and lungs.

ANTICOAGULATION, HEMOSTASIS, AND BLOOD CONSERVATION

Modern pediatric cardiac anesthesia must include the principles and practice of effective anticoagulation, hemostasis, and blood conservation. Bleeding after cardiopulmonary bypass remains a significant problem in pediatric cardiac surgery. [217] Continuing blood loss post-CPB requiring blood component replacement is associated with hemodynamic compromise as well as morbidity from multiple donor exposures. In pediatric patients, restoration of hemostasis has proved difficult; diagnosis of the problem and treatment are marginally effective.

Neonates, infants, and children undergoing cardiac surgery with CPB have a higher rate of postoperative bleeding than that seen in older patients. [217] This is due to several factors. First, there is disproportionate exposure to the nonendothelialized extracorporeal circuit, which produces an inflammatory-like response. [17] This inflammatory response to cardiopulmonary bypass is inversely related to patient age; the younger the patient, the more pronounced the response. [17] [18] As complement and platelet activation are linked to the activation of other protein systems in the blood (i.e., fibrinolytic), it is probable that this hemostatic activation, which results in impaired hemostasis and increased bleeding tendency, plays a major role during pediatric cardiac surgery. Second, the type of operations performed in neonates and infants usually involves more extensive reconstruction and suture lines, creating more opportunities for surgical bleeding than in adult cardiac patients. Operations are also frequently performed using deep hypothermia or circulatory arrest, which may further impair hemostasis. [218] Third, the immature coagulation system in neonates may also contribute to impaired hemostasis. [219] While procoagulant and factor levels may be reduced in young patients with congenital heart disease due to immature or impaired hepatosynthesis, [220] functional bleeding tendencies are usually not present before surgery. Finally, patients with cyanotic heart disease demonstrate an increased bleeding tendency before and after CPB. [221]

Cardiopulmonary bypass is a significant thrombogenic stimulus requiring anticoagulation with heparin prior to its initiation. Heparin is usually administered empirically based on patient weight, and its effect is followed by activated clotting time monitoring. Because heparin effect is primarily due to coupling with antithrombin III and because there are age-related differences in quantitative differences in procoagulants and inhibitors, variability of heparin dosing and its effect have been a concern. High heparin sensitivity is observed in the 1st week of life and then decreases progressively until about 3 years of age, when values approach those observed in adults. [222] These findings are consistent with evidence in infants of variable quantities of both procoagulants and inhibitors, especially prothrombin and antithrombin III. [223] Heparin administration to the patient must also include a consideration of the quantity and composition of the priming volume for CPB, especially if fresh frozen plasma is added. The authors recommend a heparin dose of 200 U/kg plus an additional dose of 1 to 3 U/mL of prime and maintaining the activated clothing time above 400 seconds.

Heparin is neutralized with protamine dosed according to the quantity of heparin administered or based on body weight. Protamine excess may actually contribute to postoperative bleeding. [224] It appears that the protamine dose requirement is high for neonates and decreases with age. The relatively increased protamine requirement for young as compared with older children and adults is indicative of higher circulating heparin levels after CPB. [225] Delayed hepatic clearance of heparin due to organ immaturity and the predominant use of hypothermic circulatory arrest in the young will decrease metabolism and excretion of heparin.

We typically administer 4 mg/kg protamine in neonates, whereas 2 mg/kg usually restores the activated clotting time to baseline values in adolescents and adults. Interpatient variability mandates some form of individual assessment to guide drug dose, to prevent excess protamine. [224]

Neonates and young infants with congenital heart disease will have low circulating levels of procoagulants and inhibitors. The thrombogenic and dilutional effects of CPB further contribute to hemostatic abnormalities after CPB. Formed blood elements such as leukocytes and platelets may be activated and procoagulants diluted by CPB. Furthermore, deep hypothermic circulatory arrest causes increased clotting and fibrinolytic activity. The lower the temperature, the higher the degree of hemostatic activation. Therefore, the causes of bleeding post-CPB are many. Injudicious use of blood products to correct individual coagulation abnormalities separately can further exacerbate dilution of existing procoagulants as well as carry the risks of multiple donor exposure. Because the transfusion of blood products is associated with numerous complications, transfusion is to be assiduously avoided, unless specifically indicated by an impairment in tissue oxygenation or documented coagulopathies with clinically significant bleeding. All efforts at blood conservation during cardiac surgery should be routinely employed by all members of the operative team, intraoperatively as well as postoperatively.

Bleeding after CPB is not an unusual occurrence. The surgeon should first attempt to identify any obvious source of surgical bleeding at the sites of repair. Next, adequate protamine reversal of heparin is assessed by measuring an activated clotting time. In general, standard coagulation tests show a prolongation of the partial thromboplastin time, prothrombin time, hypofibrinogenemia, and dilution of other procoagulants as well as a prolonged bleeding time in many pediatric patients, with and without bleeding (Fig. 50-15) . The most common reason for persistent bleeding is platelet dysfunction. [226] [227] Under such circumstances, administration of platelets is warranted in the presence of bleeding. Routine administration of blood products to correct laboratory coagulation abnormalities in the absence of bleeding is never clinically indicated. After platelets have been given and if bleeding is still present, reassessment and repeat platelet infusion or the administration of cryoprecipitate or fresh frozen plasma may be beneficial. Under most circumstances, meticulous surgical technique, appropriate administration of protamine, adequate patient temperature, and platelet infusion will correct excessive bleeding. In neonates, excessive bleeding as well as the escalating dilutional effects of selective component therapy on the remaining procoagulants in small patients make the treatment of bleeding difficult. The use of fresh whole blood may be warranted under these circumstances. The administration of fresh whole blood (less than 48 hours old) after CPB can meet all the hematologic requirements with minimum donor exposure. The efficacy of whole blood in restoring hemostasis and reducing blood loss after CPB has been demonstrated in patients younger than 2 years of age undergoing complex surgical repairs. [217]

Many attempts have been made to reduce bleeding after CPB by pharmacologic interventions. Desmopressin acetate [228] [229] and the antifibrinolytics aminocaproic acid and tranexamic acid [230] have been tried with variable success in significantly reducing postoperative blood loss after cardiac surgery. However, the most impressive results have been demonstrated with the use of aprotinin. [231] A proteinase inhibitor, aprotinin has antifibrinolytic properties in low concentrations and acts as kallikrein inhibitor at higher levels. CPB causes increased kallikrein by contact activation, promoting thrombus and fibrin generation, which promotes fibrinolysis. The inhibition of kallikrein results in an inhibition of the contact phase of coagulation, and the inhibition of fibrinolysis reduces bleeding. Reduced thrombin generation leads to a diminished platelet stimulation. Better preserved platelet function has been described for patients with aprotinin. [231]

Figure 50-15 Plot of blood coagulation profile changes before, during, and after cardiopulmonary bypass (CPB) in 25 children. Clotting times and coagulant factors are shown as percent change from control. Stage I, baseline, before CPB; stage II, post-CPB, before protamine reversal of heparin; stage III, after protamine; stage IV, just prior to leaving the operating room; stage V, after 3 hours in the intensive care unit (ICU). PTT, partial thromboplastin time; PT, prothrombin time.

Not surprisingly, then, aprotinin significantly reduces the intraoperative and postoperative blood loss in cardiac surgery. [232] [233] [234] [235] Aprotinin use during pediatric cardiac surgery attenuates fibrinolytic activation in a dosedependent fashion, reducing the formation of fibrinsplit products. [218] [236] Higher doses of aprotinin reduce thrombin/antithrombin III complex and F1/F2 fibrin fragments, supporting the hypothesis of suppression of clotting activation with higher aprotinin doses and plasma concentrations. Although several studies have demonstrated efficacy in reducing hemorrhage and donor exposures after congenital heart surgery, this benefit may not be evident with simple primary cardiac repairs (e.g., VSD, ASD, tetralogy of Fallot). [237] [238] To date, the use of aprotinin for congenital heart surgery has been generally confined to certain patients requiring re-operation, such as Ross procedure, and in cardiac/lung transplantation procedures.

The techniques of blood conservation must be continued during the postoperative period. Isolated coagulation abnormalities are often present in the uncomplicated postoperative cardiac patient (see Fig. 50-15) . Usually these coagulation abnormalities self-correct during the first postoperative day and are not associated with excessive bleeding. Therefore, routine correction of these abnormalities with infusion of blood products is not warranted. Administration of blood products should not occur in the absence of clinical evidence of bleeding and the identification of a specific defect requiring targeted component therapy. Routine use of blood products for volume replacement is also to be avoided; lactated Ringer's or saline solution can be satisfactorily administered at a reduced cost without the hazards associated with transfusion.

POSTOPERATIVE MANAGEMENT

Immediate postoperative care of the pediatric patient who has undergone cardiothoracic surgery is an important period in the overall sequence of anesthetic and surgical management. Although the primary influence on outcome is determined by the conduct of the operation, postoperative care is an important factor. As a member of the operative team, it is necessary that the anesthesiologist understand and become involved during the immediate postoperative period. Detailed principles of postoperative management of the pediatric cardiac surgical patients are beyond the scope of this chapter. However, a few general guiding principles and approach are given to provide some fundamental knowledge for the anesthesiologist.

The postoperative period can be characterized by a series of physiologic and pharmacologic changes as the body convalesces from the abnormal biologic conditions of CPB and cardiac surgery. [239] During this period, the effects of the cardiac operation, the patient's underlying diseases, the effects of hypothermic CPB, and special techniques such as DHCA may create special problems. In the immediate postoperative setting, abnormal convalescence and specialized problems must be recognized and managed appropriately. Fortunately, most patients are able to balance the cost imposed by the physiologic trespass created by the surgical repair and the effects of CPB against the benefit of reduced pathophysiologic loading conditions, resulting in low morbidity and mortality. Therefore, the guiding principle in the management of the postoperative patient is an understanding of both normal and abnormal convalescence after anesthesia and cardiac surgery. The immediate postoperative period, even that of normal convalescence, is one of continuous physiologic change because of the pharmacologic effects of residual anesthetic agents and the ongoing physiologic changes secondary to abrupt alteration in hemodynamic loading conditions, surgical trauma, and extracorporeal circulation. Anesthesia and surgery affect not only the patient's conscious state but also cardiovascular, respiratory, renal, and hepatic function; fluid and electrolyte balance; and immunologic defense mechanisms. In spite of all these changes, postoperative care should be predictable and standardized for most patients undergoing cardiac procedures.

In general, there are four temporal phases of postoperative management in the cardiac patient: (1) transport to the ICU, (2) stabilization in the ICU, (3) weaning from inotropic and ventilatory support, and (4) mobilization of fluids. Patients proceed through these phases at variable rates based on such factors as underlying disease process, preoperative medical condition, sequelae of the surgical procedure, duration of CPB, and presence or absence of intraoperative complications. One of the most important functions of the ICU team is to identify postoperative complications in the patient who convalesces abnormally and to provide interventional therapy. Because physiologic change after cardiac surgery is dramatic but self-limiting during normal convalescence, recognition of abnormal processes can be difficult. Under such circumstances a uniform, multidisciplinary approach with experienced clinicians and nurses facilitates the identification of any abnormalities in convalescence. These abnormalities often are indications for closer observation, more invasive monitoring, pharmacologic intervention, and increased cardiopulmonary technical support. Complications include hypovolemia, residual structural heart defect, right and left ventricular failure, hyperdynamic circulation, pulmonary artery hypertension, cardiac tamponade, arrhythmias, cardiac arrest, pulmonary insufficiency, oliguria, seizures, and brain dysfunction. It is critical to detect these departures from the normal convalescent course and to treat them aggressively.

One important area in which the anesthesiologist can aid the recovery of the cardiac patient is pain control. Pain and sedation are among the most common problems requiring ICU intervention. Many factors influence the onset, incidence, and severity of postoperative pain. The attenuation of the stress response in the immediate postoperative period using infusions of potent opioids in the critically ill infant reduces morbidity. [85] Attenuation of postoperative pain can be attempted with a preoperative medication and an intraoperative anesthetic management technique that includes the use of potent opioids. Patients who receive no opioid preoperatively or during the operative procedure will require analgesics in the immediate postoperative period once the inhalation anesthetic is eliminated. Most cases of postoperative pain can be managed by the administration of small intravenous doses of opioids, usually morphine. This is important in a patient being weaned from the ventilator during the early postoperative period. Patients who are intubated and ventilated overnight should receive adequate sedation and pain control until ventilatory weaning is begun. This is

---

usually accomplished by a continuous infusion of a benzodiazepine and an opioid. Continuous infusion of sedatives and analgesics results in a more consistent and reliable control of postoperative pain. When separated from mechanical ventilation, the patient is concurrently weaned from the sedatives and analgesics. Under these circumstances, careful titration of opioids often results in prompt pain relief. In patients with reactive pulmonary artery hypertension, opioids have been shown to prevent hypertensive crisis. [82]

Regional anesthesia may be used for postoperative pain control in infants and children after thoracotomies, sternotomies, and simple procedures requiring CPB. This method avoids opioid-induced respiratory depression from intravenous doses of these drugs. The administration of opioids in the epidural space is a very effective approach to pain management. This technique is used in children for postoperative pain control when given in the epidural space via the caudal route as a "single shot" or via a small caudal catheter. Morphine or Dilaudid provides effective analgesia with a duration of 6 to 12 hours, with no significant respiratory depression. Caudal morphine diluted in 0.05 to 0.075 mg/kg delivered in a total volume of 1.25 mL/kg of sterile saline has been used with good success in our practice. The use of regional anesthesia for postoperative pain appears to be best suited for the child extubated in the early postoperative period. Relative contraindications of this technique include hemodynamic instability and patients with abnormal clotting profiles with continued active bleeding. Using this regional technique, better arterial oxygenation, a more rapid ventilator wean, and decreased postoperative respiratory complications may be expected. However, urinary retention occurs frequently in patients without a bladder catheter. Generally, no treatment is required. Children requiring large thoracotomies of a bilateral thoracosternotomy incision (i.e., "clamshell") merit consideration for thoracic epidural analgesia. This technique significantly reduces the respiratory depression and pulmonary mechanics abnormalities that accompany the quantity of systemic opioids that would be necessary to provide adequate analgesia for these excruciatingly painful incisions. If the procedure requires systemic heparinization, we will typically defer placement of these catheters until the heparin effect is neutralized. For patients undergoing heart/lung transplantation, a thoracic epidural can be placed early in the postoperative period (8-16 hours after surgery) to facilitate early extubation and excellent pain control.

ANESTHESIA FOR HEART AND LUNG TRANSPLANTATION

Although perioperative management for thoracic organ transplantation is considered elsewhere in this text, the application of these procedures to children requires some specific modification. Differences include the characteristics of the candidates, preparation of these children, anesthetic management, surgical considerations, post-bypass management, and outcome.

Even though some of the earliest heart transplants were performed for congenital heart malformations, this indication became rare by the early 1980s. In 1984, over 60% of the few pediatric heart transplants were performed in patients with cardiomyopathy, usually adolescents. In the next decade, a dramatic rise in the number of infants and young children with congenital heart malformations treated with heart transplantation resulted in a marked shift in the demographics (Fig. 50-16) .[240] By 1995, over 70% of the children receiving heart transplants were under 5 years of age, half of those under age 1. The overwhelming majority of these infants undergo transplant for congenital heart malformations for which reconstructive options either have failed or are not believed to exist (Fig. 50-17) .[240] The implications of this shift reach into every element of perioperative management.

Children considered for heart transplantation are more likely to have pulmonary hypertension than adults. Most adult transplant programs will not offer heart transplant therapy to patients with PVR over 6 Wood units/m^2 .[241] The exclusion threshold in infants and children remains controversial. Some programs accept patients with PVR as high as 12 Wood units/m^2 , particularly if the pulmonary vasculature responds to vasodilators such as oxygen, NO, calcium channel blockers, or prostacycline.[242] Neonates are generally assumed to have elevated PVR, but outcome data from some programs suggest that the importance of this factor on postoperative outcome is substantially less in the first year of life, perhaps because the infant donor hearts, having recently undergone transitional circulation, are better prepared to cope with the right ventricular pressure load that elevated PVR imposes.[243]

The anesthetic plan for pediatric heart transplantation must accommodate a wide spectrum of pathophysiologies. Recipients with congenital heart malformations benefit from the same analysis of loading conditions and optimizing hemodynamics discussed previously. Although a few of these patients undergo heart transplant because the natural history of reconstructive heart surgery poses greater risk despite reasonable ventricular function, most candidates exhibit some manifestations of impaired ventricular performance. As such, they require careful titration of anesthetic agents with minimal myocardial depressant characteristics to avoid cardiovascular collapse. In this fragile population, even modest doses of opioids can be associated with marked deterioration in systemic hemodynamics, presumably by reducing endogenous catecholamine release. As with most congenital heart patients, skilled management of the airway and ventilation represent crucial elements in a satisfactory induction, particularly in the face of elevated PVR. No matter how elegant the anesthetic plan in conception and implementation, a certain proportion of these children will decompensate upon induction, necessitating resuscitative therapy.

Although orthotopic heart transplantation poses some technical challenges in neonates and young infants, the replacement of an anatomically normal heart is less complex than several reconstructive heart procedures commonly performed in patients at this age. However, the need to adapt this procedure to incorporate repair of major concurrent cardiovascular malformations requires the consummate skill and creativity that remain the province of the few exemplary congenital heart surgeons.[244] [245] Having withstood extended ischemic periods, heart grafts are extraordinarily intolerant of superimposed residual hemodynamic loads that might accompany imperfect vascular reconstruction.

Figure 50-16 Demographic data for pediatric heart transplantation by age. Stacked bar graph illustrates the total number and age distribution for heart transplantation in patients less than 16 years of age. Note the rapid rise in transplants performed during the late 1980s, with particular growth in the population of children aged 5 years and under. Having peaked in the mid 1990s, the total number of transplants (both adult and pediatric) has declined slightly, but the relative age proportions within the pediatric population remain relatively constant. *(Data from the Registry of the International Society for Heart and Lung Transplantation [246])*

The extensive vascular repair and, particularly in older children with long-standing hypoxemia, the propensity to coagulopathy together elevate hemorrhage to a major cause of morbidity and even mortality in pediatric heart transplantation. Nevertheless, once successfully implanted, these grafts will respond to physiologic factors that stimulate growth and adaptation in the developing infant and child.[246]

Management considerations during separation from CPB and the early postoperative period are primarily focused on three pathophysiologic conditions; myocardial preservation,

Figure 50-17 Indication for heart transplantation in children. Over the past 14 years, the major indications for pediatric heart transplantation are nearly equally divided between congenital malformation and cardiomyopathy. In recent years, pediatric recipients with congenital malformations assumed a slight plurality due to shifting age demographics. As illustrated, younger children are more likely to undergo heart transplant because of congenital malformation. *(Data from the Registry of the International Society for Heart and Lung Transplantation [240])*

denervation, and PVR. Even expeditious transplants usually force the heart to endure ischemic periods that exceed those encountered for reconstructive surgery. Although some centers believe the infant heart is more tolerant of extended ischemia,[243] these hearts will demonstrate a period of reperfusion injury and virtually all require pharmacologic, and in some cases mechanical, support. In addition, endogenous adaptive responses and exogenous pharmacologic agents that act via myocardial sympathetic activation are ineffective in the denervated graft. Since the majority of children presenting for heart transplantation exhibit some element of elevated PVR, even with isolated end-stage cardiomyopathy, the RV of a newly implanted heart is particularly vulnerable to failure.

As such, ventilatory and pharmacologic interventions are usually configured to exert a favorable impact on PVR and provide inotropic and chronotropic support. Once the lungs are fully expanded, we ventilate to Pa CO_2 values in the low 30s using an Fi O_2 of 1. Virtually all recipients receive low-dose dopamine (3-5 mug/kg/min) and isoproterenol (0.02-0.05 mug/kg/min) to promote inotropy, chronotropy, and lower PVR. In the event that these do not provide sufficient inotropy in the face of more significant postischemic dysfunction, additional agents are added (e.g., milrinone, epinephrine). Most transplant centers have a specific regimen for immunosuppression to be initiated in the perioperative period. As with adults, pediatric transplant programs typically employ triple drug immunosuppression with a calcineurin inhibitor (e.g., cyclosporine, tacrolimus), antimetabolite (e.g., azathioprine), and steroid. Following an interval without rejection, some pediatric programs will taper and discontinue one or even two of these agents, particularly

in neonates in whom they believe some element of tolerance develops. [247] [248]

National statistics indicate that the outcome from pediatric heart transplant is slightly less favorable than comparable adult results. [240] The principal risk factors are age under 1 year and congenital heart defects. Since these factors are highly related (i.e., the vast majority of infants under 1 undergo transplantation for congenital heart defect), it is difficult to determine the independent effect of age. Concurrent repair of structural cardiovascular anomalies substantially increases perioperative risk of hemorrhage, residual hemodynamic loading conditions, and right heart failure from elevated PVR. Taken together, infants under 1 year of age have an operative mortality rate (at <30 days) of 24%, more than twice that of older children. [240] Beyond the early postoperative period, mortality rates are quite comparable for all age groups. Nevertheless, the sequelae of rejection and the consequences of the requisite immunosuppression result in significant ongoing morbidity and mortality. Since even the best transplant recipients have only achieved a 28% 14-year survival rate, these procedures must be considered palliative for children. [240]

Lung and heart-lung transplantation have achieved respectable operative survival rates in children. [249] [250] They remain the only viable surgical therapy for infants and children with severe pulmonary vascular disease and selected progressive pulmonary diseases. These remain uncommon procedures in pediatrics. Lung transplantation carries the additional morbidity of obliterative bronchiolitis, a debilitating small airway disease that results in gradual deterioration in flow-related pulmonary functions over time. Despite an operative mortality rate that is currently less than 20%, the 3-year survival rate is only 50% to 60%. [240] [250]

ANESTHESIA FOR CLOSED HEART OPERATIONS

Early corrective repair in infancy has significantly reduced the number of noncorrective, palliative closed heart operations. Corrective closed heart procedures include PDA ligation and repair of coarctation of the aorta. Noncorrective closed heart operations include pulmonary artery banding and extracardiac shunts such as the Blalock-Taussig shunt. These procedures are performed without cardiopulmonary bypass. Therefore, venous access and intra-arterial monitoring are important in evaluating and supporting these patients. A pulse oximeter remains an invaluable monitor during intraoperative management.

Ligation of PDA is typically performed through a left thoracotomy, although video-assisted thoracoscopic techniques are increasingly common. [251] [252] Physiologic management is that of a left-to-right shunt producing volume overload. Patients with a large PDA and low PVR generally present with excessive pulmonary blood flow and congestive heart failure. Neonates and premature infants also run the risk of having substantial diastolic runoff to the pulmonary artery, potentially impairing coronary perfusion. Thus patients range from an asymptomatic healthy young child to the sick ventilator-dependent premature infant on inotropic support. The former patient allows for a wide variety of anesthetic techniques culminating in extubation in the operating room. The latter patient requires a carefully controlled anesthetic and fluid management plan. Generally a trial of medical management with indomethacin and fluid restriction is attempted in the premature infant prior to surgical correction. In the premature infant, transport to the operating room can be especially difficult and potentially hazardous, requiring great vigilance to avoid extubation, excessive patient cooling, or venous access disruption. For these reasons, many centers are now performing ligation in the neonatal ICU. Intraoperatively, retractors may interfere with cardiac filling and ventilatory management so that hypotension, hypoxemia, and hypercarbia occur. Complications include inadvertent ligation of the left pulmonary artery or descending aorta, recurrent laryngeal nerve damage, and excessive bleeding due to inadvertent PDA disruption. After ductal ligation in premature infants, worsening pulmonary compliance can precipitate a need for increased ventilatory support, and manifestations of an acute increase in LV afterload should be anticipated, especially if LV dysfunction has developed preoperatively. More recently, PDA ligation has been performed in infants and children using thoracoscopic surgical techniques. This approach has the advantage of limited incisions at thoracoscopic sites, promoting less postoperative pain and discharge from the hospital the same day of surgery.

Coarctation of the aorta is a narrowing of the descending aorta near the insertion of the ductus arteriosus. Obstruction to aortic flow is the result and this may range from severe obstruction with compromised distal systemic perfusion to mild upper extremity hypertension as the only manifestation. Associated anomalies of both the mitral and aortic valves can occur. In the neonate with severe coarctation, systemic perfusion is dependent on right-to-left shunting across the PDA. In these circumstances, LV dysfunction is very common and prostaglandin E_1 is necessary to preserve sufficient systemic perfusion. Generally, a peripheral intravenous line and an indwelling arterial catheter, preferably in the right arm, are recommended for intraoperative and postoperative management. In patients with LV dysfunction, a central venous catheter may be desirable for pressure monitoring and inotropic support. The surgical approach is through a left thoracotomy, whereby the aorta is cross-clamped and the coarctation repaired with an onlay prosthetic patch, a subclavian artery flap, or resection of the coarctation with an end-to-end anastomosis. During cross-clamp, we usually allow significant proximal hypertension (20-25% increase over baseline), based on evidence that vasodilator therapy may jeopardize distal perfusion and promote spinal cord ischemia. [253] Intravascular volume loading with 10 to 20 mL/kg of crystalloid is given just before removal of the clamp. The anesthetic concentration is decreased, and additional blood volume support is given until the blood pressure rises. Post-repair rebound hypertension due to heightened baroreceptor reactivity is common and often requires medical therapy. After cross-clamp, aortic wall stress due to systemic hypertension is most effectively lowered by institution of beta blockade with esmolol or alpha/beta-blockade with labetalol. [254] Propranolol is useful in older patients but can cause severe bradycardia in infants and young children. Although it actually increases calculated aortic wall stress in the absence of beta blockade by accelerating dP/dT, the addition of sodium nitroprusside

---

may become necessary to control refractory hypertension. Captopril or an alternative antihypertensive regimen is begun in the convalescent stage of recovery in those patients with persistent hypertension.

The management of infants undergoing placement of extracardiac shunts without cardiopulmonary bypass centers around goals similar to those of other shunt lesions: balancing pulmonary and systemic blood flow by altering Pa $_{CO_2}$, Pa $_{O_2}$, and ventilatory dynamics. Central shunts are usually performed through a median sternotomy, while Blalock-Taussig shunts may be performed through a thoracotomy or sternotomy. In patients in whom pulmonary blood flow is critically low, partial cross-clamping of the pulmonary artery required for the distal anastomosis causes further reduction of pulmonary blood flow and desaturation, necessitating meticulous monitoring of pulse oximetry. Careful application of the cross-clamp to avoid pulmonary artery distortion will help maintain pulmonary blood flow. Under circumstances in which severe desaturation and bradycardia occur with cross-clamping, CPB will be required for the procedure. Intraoperative complications include bleeding and severe systemic oxygen desaturation during chest closure, usually indicating a change in the relationship of the intrathoracic contents that results in distortion of the pulmonary arteries or kink in the shunt. Pulmonary edema may develop in the early postoperative period in response to the acute volume overload that accompanies the creation of a large surgical shunt. Measures directed at increasing PVR, such as lowering inspired O_2 to room air, allowing the Pa $_{CO_2}$ to rise, and adding positive end-expiratory pressure are helpful maneuvers to decrease pulmonary blood flow until the pulmonary circulation can adjust. Decongestive therapy such as diuretics and digoxin may alleviate the manifestations of congestive heart failure. Under such circumstances, early extubation is inadvisable.

Pulmonary artery banding is used to restrict pulmonary blood flow in infants whose defects are deemed uncorrectable for either anatomic or physiologic reasons. These patients are generally in congestive heart failure with reduced systemic perfusion and excessive pulmonary blood flow. The surgeon places a restrictive band around the main pulmonary artery to reduce pulmonary blood flow. Band placement is very imprecise and requires careful assistance from the anesthesia team to accomplish successfully. Many approaches have been suggested. We place the patient on 21 percent inspired oxygen concentration and maintain the Pa $_{CO_2}$ at 40 mm Hg, to simulate the postoperative state. Depending on the malformation, a pulmonary artery band is tightened to achieve hemodynamic (e.g., distal pulmonary artery pressure 50-25% systemic pressure) or physiologic (e.g., Qp:Qs approaching 1) goals. Should the attainment of these objectives produce unacceptable hypoxemia, the band is loosened.

Blalock-Hanlon atrial septectomy is now an uncommon procedure for enlarging an intra-atrial connection. This procedure is done by occluding caval flow and creating an intra-atrial communication through the atrial septum. In patients with hypoplastic left heart syndrome with an intact atrial septum, this procedure is life-saving and must be performed within hours of birth. Balloon atrial septostomies (Rashkind procedure) and blade septectomies performed in the cardiac catheterization laboratory have replaced surgical intervention, except when left atrial size is very small or the atrial septum is thickened. Improved safety of CPB has led to the virtual elimination of such intracardiac procedures using inflow occlusion. Surgical septectomies, because they are currently confined to the most difficult subset, are rarely performed without benefit of CPB.

/das/book/view/29494766/875/568.html

ANESTHESIA FOR INTERVENTIONAL OR DIAGNOSTIC CARDIAC PROCEDURES

Advances in interventional and diagnostic cardiac catheterization techniques are significantly changing the operative and nonoperative approach to the patient with a congenital heart defect. Nonoperative interventional tech- niques are being used instead of procedures requiring surgery and CPB for safe closure of secundum ASDs, VSDs, and PDAs. Stenotic aortic and pulmonic valves, recurrent aortic coarctations, and branch pulmonary artery stenoses can be dilated in the catheterization lab, avoiding surgical intervention as well. [255] [256] [257] [258] These techniques shorten hospital stay and are particularly beneficial to patients with recurrent coarctation and muscular or apical VSDs, who are at a higher risk of operative intervention. Many patients with complex cardiac defects are poor operative risks. Innovative interventional procedures improve vascular anatomy, reduce pressure loads on ventricles, and decrease the operative risk for these patients. For example, in tetralogy of Fallot with hypoplastic pulmonary arteries, balloon angioplasty and vascular stenting procedures create favorable pulmonary artery anatomy and reduce pulmonary artery pressure and right ventricular end-diastolic pressure. High-risk patients undergoing diagnostic evaluation of pulmonary artery hypertension in anticipation of heart-lung transplantation also require anesthetic management. Despite the attendant high risks of the procedure in these patients with suprasystemic RV pressure, these patients are best managed with general anesthesia and controlled ventilation.

Anesthetic management of interventional or diagnostic procedures in the catheterization laboratory must include the same level of preparation that would apply in caring for these patients in the operating room. The patients have the same complex cardiac physiology and, in some cases, greater physiologic complexity and less cardiovascular reserve because they are deemed high operative risks. Interventional catheterization procedures can impose acute pressure load on the heart during balloon inflation. Large catheters placed across mitral or tricuspid valves create acute valvular regurgitation or, in the case of a small valve orifice, transient valvular stenosis. When catheters are placed across shunts, severe reductions in pulmonary blood flow and marked hypoxemia may occur. [258] [259] The anesthetic plan must consider the specific cardiology objectives of the procedure and the impact of anesthetic management in facilitating or hindering the interventional procedure. In general, there are three distinct periods involved in an interventional catheterization: the data acquisition period, the interventional period, and the post-procedural evaluation period.

During the data acquisition period, the cardiologist performs a hemodynamic catheterization to evaluate the need

for and extent of the planned intervention. Catheterization data are obtained under normal physiologic conditions; that is, room air, physiologic Pa CO_2 , and spontaneous ventilation are preferred. Increased Fi O_2 or changes in Pa CO_2 may obscure physiologic data. During the procedural period, the patient is usually intubated and mechanically ventilated. A secured airway allows the anesthesiologist to concentrate on hemodynamic issues. Positive-pressure ventilation also reduces the risk of air embolism. During spontaneous ventilation, a large reduction in intrathoracic pressure can entrain air into vascular sheaths and result in moderate to large pulmonary or systemic air emboli. Precise device placement is also facilitated with muscle relaxants that eliminate patient movements and controlled ventilation, thereby reducing the respiratory shifting of cardiac structures. Substantial blood loss and changes in ventricular function occur commonly during the intervention. Blood volume replacement and inotropic support may be necessary during or immediately after the interventional procedure. In the postprocedural period, the success and the physiologic impact of the intervention are evaluated. Blood pressure, mixed venous oxygen saturation, ventricular end-diastolic pressure, and cardiac output, when available, are used to assess the impact of the intervention. Persistent severe hemodynamic derangement indicates the need for ICU monitoring and respiratory or cardiovascular support. Because of the hemodynamic variability of many of these patients, as well as changing anesthetic requirements, continuous intravenous infusion with ketamine/midazolam or, more recently, propofol, is appropriate. Potent inhaled anesthetics are generally not used as the primary anesthetic and are reserved for adjunctive anesthesia.

A brief description of some of the interventional procedures and the associated anesthetic implications follows. The success of these interventions will undoubtedly result in widespread availability and use over the next few years.

Transcatheter Technique for ASD Closures

A collapsed double-umbrella clamshell device is loaded into a large introducer sheath placed through the femoral vein, advanced to the right atrium, and placed across the atrial septal defect into the left atrial chamber. Each side of the device consists of a Dacron mesh patch suspended in six spring-loaded arms that open like an automatic umbrella. Using biplane fluoroscopy and TEE, the catheter is positioned in the left atrium away from the mitral valve. [257] The sheath is pulled back to open the six distal arms and its Dacron mesh cover into the left atrium. The sheath and device are then pulled back so the distal arms contact the left atrial septum. Fluoroscopy and TEE are used to confirm that the arms are on the left atrial side and do not interfere with mitral valve motion. Once adequately seated, the sheath is pulled further back to expose the proximal side of the device and the proximal arms, which spring open to engage the right side of the atrial septum. When proper positioning is certain, the device is released. [257] In a recent report of 122 children undergoing transcatheter ASD closures, there was a 9 percent incidence of procedural complications, resulting in hemodynamic complications requiring treatment. [258] Despite nearly a decade of experience, these devices remain under investigational protocol and are therefore available only at a limited number of study centers.

Transcatheter VSD Closure

Most VSDs that are electively closed in the catheterization laboratory are mid-muscular or apical VSDs that are either difficult to close in the operating room or would require a left ventriculotomy. Left ventriculotomies are associated with a high incidence of LV dysfunction and have been relegated to a position as the least desirable surgical option. The transcatheter approach requires a blade atrial septostomy and a retrograde catheter placed through the femoral artery and advanced to the left atrium. This catheter is pulled across the atrial septum into the right atrium and is used to guide a superior vena cava catheter (placed through the internal jugular vein) across the atrial septal defect into the left atrium, across the mitral valve, and into the left ventricle. The ventricular septal defect is approached from the LV side. The large sheath containing the double-umbrella clam-shell device prevents closure of the mitral valve, resulting in acute mitral regurgitation or, in cases in which the VSD is large or the mitral annulus small, acute severe mitral stenosis. In this latter case, systemic output is decreased and a period of severe hypotension is unavoidable. Judicious use of vasoconstrictors to maintain coronary perfusion may be required during the catheter placement, followed by volume and inotropic resuscitation after the VSD device is deployed. This highly specialized application of the clamshell device is confined to very few pediatric centers in the United States.

Angioplasty of Branch Pulmonary Artery Stenosis

One of the most important areas of interventional catheterization has been the dilation and stenting of hypoplastic or stenotic branch pulmonary arteries. In patients with tetralogy of Fallot with hypoplastic pulmonary arteries, pulmonary atresia, or single ventricle with surgically induced peripheral stenoses, the use of balloon angioplasty and stenting procedures creates favorable pulmonary artery anatomy and reduces the risk of subsequent surgical repairs (Fig. 50-18) . Balloon angioplasty is accomplished by tearing the vascular intima and media, allowing the vessel to remodel and heal with a larger diameter. The balloon is placed across

the stenotic lesion so the middle of the balloon is at the stenosis. The balloon is inflated until the waist of the balloon is eliminated. Ideally, the most stenotic lesions are dilated first to minimize the impact on pulmonary blood flow and cardiac output. When the balloon is inflated, pulmonary blood flow is reduced, RV afterload is increased, and cardiac output falls. In patients with an associated VSD or ASD, right-to-left shunting and desaturation occur with balloon inflation. Occasionally, balloon catheters must be placed across aortopulmonary shunts, significantly reducing pulmonary blood flow. The procedure is successful in approximately 60percent of patients. In an early series, complications

Figure 50-18 *(A)* Severe bilateral branch pulmonary artery stenoses at the distal end of a conduit in a patient with pulmonary trunk atresia and ventricular septal defect. Stents were placed in right and left pulmonary arteries. *(B)* Follow-up angiogram in the same projection and magnification showed marked improvement of both right and left stenoses.

include hypotension (40 percent), pulmonary artery rupture (3 percent), unilateral reperfusion pulmonary edema (4 percent), aneurysmal dilation of the dilated pulmonary vessel (8 percent), death (1.5 percent), and transient post-procedural RV dysfunction. [260] Improved techniques and patient selection have favorably influenced the results with superior balloon catheters and stents, while significantly reducing serious complications. Anesthetic sup- port minimizes hemodynamic compromise by anticipating changes in blood flow patterns, treating transient hypotension, and providing airway support to minimize the risks associated with pulmonary artery disruption and acute unilateral pulmonary edema. [260]

Balloon Valvulotomies

Balloon valvulotomies conducted in well-compensated infants and children can often be accomplished without anesthetic support. Exceptions include neonates with critical aortic or pulmonary stenosis and patients with significant ventricular dysfunction who exhibit unstable hemodynamics.

Coil Embolization

Transcatheter methods can also be adapted to occlude undesired vascular structures. Intravascular coils have been used to close PDAs, aortopulmonary collaterals, and some arteriovenous malformations. In selected instances, to minimize the risk that coils escape to threaten vital organ perfusion, cardiologists may request general anesthesia with a muscle relaxant.

Radiofrequency Ablation of Accessory Pathways

Radiofrequency ablation is a nonsurgical approach designed to eliminate atrial or ventricular re-entrant tachyarrhythmias. The technique requires pathway mapping and precision ablation of the aberrant pathway using a radiofrequency ablation catheter. During the ablation, unexpected patient movement may result in catheter dislodgment and damage to normal conducting tissue, so general anesthesia is usually required in younger children. Anesthetic agents and techniques should be chosen to maintain circulating catecholamines and avoid suppression of arrhythmogenesis, for identification of the aberrant pathway. Our current preference is a propofol continuous intravenous anesthetic, although low-dose volatile anesthetics are equally satisfactory. Rapid atrial pacing and, occasionally, an isoproterenol infusion are required during the mapping procedure. Severe post-procedural cardiomyopathy has been described but is very unusual. An underlying cardiomyopathy from frequent episodes of supraventricular tachycardia and myocardial oxygen imbalance caused by prolonged periods of rapid atrial pacing and isoproterenol infusions are the presumed causative factors. An arterial line is helpful during these lengthy procedures for continuous monitoring of blood pressure and blood gases.

References

1. Hickey PR, Hansen DD, Norwood WI: Anesthetic complications in surgery for congenital heart disease. Anesth Analg 63:657, 1984.

2. Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book, 1974.

3. Teital DF, Sidi D, Chin T et al: Developmental changes in myocardial contractile reserve in the lamb. Pediatr Res 19:948, 1985.

4. Legato MJ: Ultrastructural changes during normal growth in the dog and rat ventricular myofiber. In Lieberman M, Sano T (eds): Developmental and Physiological Correlates of Cardiac Muscle. New York, Raven Press, 1975, [p 249].

5. Teitel DF, Klautz R, Steendijk P et al: The end-systolic pressurevolume relationship in the newborn lamb: Effects of loading and inotropic interventions. Pediatr Res 29:473, 1991.

6. Becker AE, Caruso G: Congenital heart disease--a morpholo- gist's view on myocardial dysfunction. In Becker AE, Losekoot G, Marcelletti C, Anderson RH (eds): Paediatric Cardiology. Edinburgh, Churchill Livingstone, 1981, [p 307].

7. Thornburg KL, Morton MJ: Filling and arterial pressure as determinants of RV stroke volume in the sheep fetus. Am J Physiol 244:H656, 1983.

8.

Downing SE, Talner NS, Gardner TH: Ventricular function in the newborn lamb. Am J Physiol 208:931, 1965.

9. Jarmakani JM, Nakanishi T, George BL, Bers D: Effect of extracellular calcium on myocardial mechanical function in nenonatal rabbit. Dev Pharmacol Ther 5:1, 1982.

10. Humpherys JE, Cummings P: Atrial and ventricular tropomysin and troponin-I in the developing bovine and human heart. J Mol Cell Cardiol 16:643, 1984.

11. Nasser R, Reedy MC, Anderson PAW: Developmental changes in the ultrastructure and sarcomer shortening of the isolated rabbit myocardium. Circ Res 61:465, 1987.

12. Vetter R, Will H, Kuttner I et al: Developmental changes of Ca $^{++}$ transport systems in chick heart. Biomed Biochem Acta 45:219, 1986.

13. Nakanishi T, Seguchi M, Takao A: Intracellualr calcium concentrations in the newborn myocardium. Circulation 76 (suppl IV):455-IV, 1987.

14. Haworth SG: Normal pulmonary vascular development and its disturbance in congenital heart disease. In Godman MJ (ed): Paediatric Cardiology, vol 4. Edinburgh, Churchill Livingstone, 1981, [p 46].

15. Ungerleider RM, Greeley WJ, Kisslo J: Intraoperative echocardiography in congenital heart disease surgery: Preliminary report on a current study. Am J Cardiol 63:3F, 1989.

16. Muhiudeen IA, Roberson DA, Silverman NH et al: Intraoperative echocardiography for evaluation of congenital heart defects in infants and children. Anesthesiology 76:165, 1992.

17. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW: Complement and the damaging effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 86:845, 1983.

18. Greeley WJ, Bushman GA, Kong DL et al: Effects of cardiopulmonary bypass on eicosanoid metabolism during pediatric cardiovascular surgery. J Thorac Cardiovasc Surg 95:842, 1988.

19. Berman W Jr: The hemodynamics of shunts in congenital heart disease. In Johansen KM, Burggren WW (eds): Cardiovascular Shunts: Phylogenetic, Ontogenetic, and Clinical Aspects. New York, Raven Press, 1985, [p 399].

20. Grossman W, Jones D, McLaurin LP: Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 56(1):56, 1975.

21. Graham T: Ventricular performance in adults after operation for congenital heart disease. Am J Cardiol 50:612, 1982.

22. Stark J: Do we really correct congenital heart defects? J Thorac Cardiovasc Surg 97:1, 1989.

23. Perloff J: Development and regression of increased ventricular mass. Am J Cardiol 50:605, 1982.

24. Engle MA, Perloff JK: Congenital Heart Disease After Surgery: Benefits, Residua, and Sequelae. New York, Yorke, 1983.

25. Arciniegas E: Pediatric Cardiac Surgery. Chicago, Year Book, 1985.

26. Castaneda AR, Mayer JEJ, Jonas RA et al: The neonate with critical congenital heart disease: Repair--a surgical challenge. J Thorac Cardiovasc Surg 98:869, 1989.

27. Turley K, Tucker WY, Ebert PA: The changing role of palliative procedures in the treatment of congenital heart disease. J Thorac Cardiovasc Surg 79:194, 1980.

28. Castaneda AR, Trusler GA, Paul MA et al: The early results of treatment of simple transposition in the current era. J Thorac Cardiovasc Surg 95:14, 1988.

29. Pacifico AD, Sand ME, Bargeron LM, Colvin EC: Transatrial-transpulmonary repair of tetralogy of Fallot. J Thorac Cardiovasc Surg 93:919, 1987.

30. Norwood WI Jr: Hypoplastic left heart syndrome. Ann Thorac Surg 52:688, 1991.

31. Norwood WIJ, Jacobs ML, Murphy JD: Fontan procedure for hypoplastic left heart syndrome. Ann Thorac Surg 54:1025, 1992.

32. Gildein HP, Ahmadi A, Fontan F, Mocellin R: Special problems in Fontan-type operations for complex cardiac lesions. Int J Cardiol 29:21, 1990.

33. Kopf GS, Kleinman CS, Hijazi ZM et al: Fenestrated Fontan operation with delayed transcatheter closure of atrial septal defect: Improved results in high-risk patients. J Thorac Cardiovasc Surg

103:1039, 1992.

34. Mayer JEJ, Bridges ND, Lock JE et al: Factors associated with marked reduction in mortality for Fontan operations in patients with single ventricle. J Thorac Cardiovasc Surg 103:444, 1992.

35. Barratt-Boyes B, Simpson M, Neutze J: Intracardiac surgery in neonates and infants using deep hypothermia with surface cooling and limited cardiopulmonary bypass. Circulation 53:25, 1971.

36. Barratt-Boyes BG, Simpson MM, Neutze JM: Intracardiac surgery in neonates and infants using deep hypothermia. Circulation 62:73, 1980.

37. Richardson JP, Clark CP: Tetralogy of Fallot. Risk factors associated with complete repair. Br Heart J 38:926, 1976.

38. Schreiner MS, Triebwasser A, Keon TP: Ingestion of liquids compared with preoperative fasting in pediatric outpatients. Anesthesiology 72(4):593, 1990.

39. Nicolson SC, Dorsey AT, Schreiner MS: Shortened preanesthetic fasting interval in pediatric cardiac surgical patients. Anesth Analg 74(5):694, 1992.

40. Sahn DJ: Real-time two-dimensional Doppler echocardiographic flow mapping. Circulation 71:849, 1985.

41. Stern DH, Gerson J, Allen FB et al: Can we trust the direct radial artery pressure immediately following cardiopulmonary bypass? Anesthesiology 62:557, 1985.

42. Reynolds LM, Nicolson SC, Steven JM et al: Influence of sensor site location on pulse oximetry kinetics in children. Anesth Analg 76(4):751, 1993.

43. Hagler DJ, Tajik AJ, Seward JB et al: Intraoperative two-dimensional Doppler echocardiography. A preliminary study for congenital heart disease. J Thorac Cardiovasc Surg 95:516, 1988.

44. Ungerleider RM, Kisslo JA, Greeley WJ et al: Intraoperative prebypass and postbypass epicardial color flow imaging in the repair of atrioventricular septal defects. J Thorac Cardiovasc Surg 98:90, 1989.

45. Muhiudeen IA, Roberson DA, Silverman NH et al: Intraoperative echocardiography in infants and children with congenital cardiac shunt lesions: Transesophageal versus epicardial echocardiography. J Am Coll Cardiol 16:1687, 1990.

46. Ungerleider RM, Greeley WJ, Kanter RJ, Kisslo JA: The learning curve for intraoperative echocardiography during congenital heart surgery. Ann Thorac Surg 54:691, 1992.

47. Cyran SE, Myers JL, Gleason MM et al: Application of intraoperative transesophageal echocardiography in infants and small children. J Cardiovasc Surg (Torino) 32:318, 1991.

48. Shah PM, Stewart DA, Calalang CC, Alexson C: Transesophageal echocardiography and the intraoperative management of pediatric congenital heart disease: Initial experience with a pediatric esophageal 2D color flow echocardiographic probe. J Cardiothorac Vasc Anesth 6:8, 1992.

49. Hickey PR, Wessel DL: Anesthesia for treatment of congenital heart disease. In Kaplan JA (ed): Cardiac Anesthesia, 2nd Ed. Orlando, Florida, Grune & Stratton, 1987, [p 635].

50. Lundar T, Lindberg H, Lindegaard KF et al: Cerebral perfusion during major cardiac surgery in children. Pediatr Cardiol 8:161, 1987.

51. Hillier SC, Burrows FA, Bissonnette B, Taylor RH: Cerebral hemodynamics in neonates and infants undergoing cardiopulmonary bypass and profound hypothermic circulatory arrest: Assessment by transcranial Doppler sonography. Anesth Analg 72:723, 1991.

52. Bishop CCR, Powell S, Rutt D, Browse NL: Transcranial Doppler measurement of middle cerebral artery blood flow velocity: A validation study. Stroke 17:913, 1986.

53. Zimmerman AA, Burrows FA, Jonas RA, Hickey PR: The limits of detectable cerebral perfusion by transcranial Doppler sonography in neonates undergoing deep hypothermic low-flow cardiopulmonary bypass. J Thorac Cardiovasc Surg 114(4):594, 1997.

54. Padayachee TS, Parsons S, Theobold R et al: The detection of microemboli in the middle cerebral artery during cardiopulmonary bypass: A transcranial Doppler ultrasound investigation using membrane and bubble oxygenators. Ann Thorac Surg 44:298, 1987.

55. Van der Linden J, Casimir AH: When do cerebral emboli appear during open heart operations? A transcranial Doppler study. Ann Thorac Surg 51:237, 1991.

56. Greeley WJ, Ungerleider RM, Smith LR, Reves JG: The effects of deep hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral blood flow in infants and children. J Thorac Cardiovasc Surg 97:737, 1989.

57. Greeley W, Ungerleider R, Smith LR, Reves J: Cardiopulmonary bypass alters cerebral blood flow in infants and children during and after cardiovascular surgery. Circulation 78II:356, 1988.

58. Greeley WJ, Kern FH, Ungerleider RM et al: The effect of hypothermic cardiopulmonary bypass and total circulatory arrest on cerebral metabolism in neonates, infants, and children. J Thorac Cardiovasc Surg 101:783, 1991.

59. Kern FH, Ungerleider RM, Quill TJ et al: Cerebral blood flow response to changes in arterial carbon dioxide tension during hypothermic

cardiopulmonary bypass in children. J Thorac Cardiovasc Surg 101:618, 1991.

60. Kern FH, Jonas RA, Mayer JE et al: Temperature monitoring during infant CPB: Does it predict efficient brain cooling? Ann Thorac Surg 54:749, 1992.

61. Greeley WJ, Brusino FG, Ungerleider RM et al: The effects of cardiopulmonary bypass on cerebral blood flow in neonates, infants and children. Circulation 80:I209, 1989.

62. Greeley WJ, Bracey VA, Ungerleider RM et al: Recovery of cerebral metabolism and mitochondrial oxidation state is delayed after hypothermic circulatory arrest. Circulation, 84 (suppl III):III--400, 1991.

63. Laishley RS, Burrows FA, Lerman J et al: Effects of anesthetic induction on oxygen saturation in cyanotic congenital heart disease. Anesthesiology 65:673, 1986.

64. Greeley WJ, Bushman GA, Davis DP, Reves JG: Comparative effects of halothane and ketamine on systemic arterial oxgyen saturation in children with cyanotic heart disease. Anesthesiology 65:666, 1986.

65. Murray D, Vandewalker G, Matherne P, Mahoney LT: Pulsed Doppler and two dimensional echocardiography: Comparison of halothane and isoflurane on cardiac function in infants and small children. Anesthesiology 67:211, 1987.

66. Friesen RH, Lichtor JL: Cardiovascular effects of inhalational induction with isoflurane in infants. Anesth Analg 62:411, 1983.

67. Eger EI II: Desflurane animal and human pharmacology: Aspects of kinetics, safety, and MAC. Anesth Analg 75:53, 1992.

68. Davis PJ, Cohen IT, McGowan FX Jr, Latta K: Recovery characteristics of desflurane versus halothane for maintenance of anesthesia in pediatric ambulatory patients. Anesthesiology. 80(2):298, 1994.

69. Warltier DC, Pagel PS: Cardiovascular and respiratory actions of desflurane: Is desflurane different from isoflurane? Anesth Analg 75:517, 1992.

70. Taylor RH, Lerman J: Induction, maintenance and recovery characteristics of desflurane in infants and children. Can J Anaesth 39(1):6, 1992.

71. Smiley RM: An overview of induction and emergence characteristics of desflurane in pediatric, adult, and geriatric patients. Anesth Analg 75:538, 1992.

72. Taylor RH, Lerman J: Minimum alveolar concentration of desflurane and hemodynamic responses in neonates, infants, and children. Anesthesiology 75(6):975, 1991.

73. White PF: Studies of desflurane in outpatient anesthesia. Anesth Analg 75:547, 1992.

74. Zwass MS, Fisher DM, Welborn LG, et al: Induction and maintenance characteristics of anesthesia with desflurance and nitrous oxide in infants and children. Anesthesiology 76(3):373, 1992.

75. Sarner JB, Levine M, Davis PJ et al: Clinical characteristics of sevoflurane in children: A comparison with halothane. Anesthesiology 82(1):38, 1995.

76. Kern C, Erb T, Frei FJ: Haemodynamic responses to sevoflurane compared with halothane during inhalational induction in children. Paediatr Anaesth 7(6):439, 1997.

77. Woodey E, Pladys P, Copin C et al: Comparative hemodynamic depression of sevoflurane versus halothane in infants: An echocardiographic study. Anesthesiology 87(4):795, 1997.

78. Holzman RS, van der Velde ME, Kaus SJ, et al: Sevoflurane depresses myocardial contractility less than halothane during induction of anesthesia in children. Anesthesiology 85:1260, 1996.

79. Frink EJ Jr, Green WB Jr, Brown EA et al: Compound A concentrations during sevoflurane anesthesia in children. Anesthesiology 85(3):684, 1996.

80. Hickey PR, Hansen DD, Wessel DL et al: Pulmonary and systemic hemodynamic responses to fentanyl in infants. Anesth Analg 64:483, 1985.

81. Hickey PR, Hansen DD: Fentanyl- and sufentanil-oxygenpancuronium anesthesia for cardiac surgery in infants. Anesth Analg 63:117, 1984.

82. Hickey PR, Hansen DD, Wessel DL et al: Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Anesth Analg 64:1137, 1985.

83. Moore RA, Yang SS, McNicholas KW et al: Hemodynamic and anesthetic effects of sufentanyl as the sole anesthetic for pediatric cardiovascular surgery. Anesthesiology 63:725, 1985.

84. Greeley WJ, deBruijn NP, Davis DP: Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesth Analg 66:1067, 1987.

85. Anand KJS, Hickey PR: Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 326:1, 1992.

86. Guy J, Hindman BJ, Baker KZ, et al: Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions. Anesthesiology 86(3):514, 1997.

87. Davis PJ, Lerman J, Suresh S, et al: A randomized multicenter study of remifentanil compared with alfentanil, isoflurane, or propofol in anesthetized pediatric patients undergoing elective strabismus surgery. Anesthes Analg 84(5):982, 1997.

88. Thompson JR, Hall AP, Russell J, Cagney B, Rowbotham DJ: Effect of remifentanil on the haemodynamic response to orotracheal intubation. Br J Anaesth 80(4):467, 1998.

89. Sebel PS, Hoke JF, Westmoreland C, et al: Histamine concentrations and hemodynamic responses after remifentanil. Anesth Analg 80(5): 990, 1995.

90. Davis, PJ, Cook DR, Stiller RL, Davin-Robinson KA: Pharmacodynamics and pharmacokinetics of high-dose sufentanil in infants and children undergoing cardiac surgery. Anesth Analg 66:203, 1987.

91. Greeley WJ, deBruijn NP: Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg 67:86, 1988.

92. Koren G, Goresky G, Crean P: Pediatric fentanyl dosing based on pharmacokinetics during cardiac surgery. Anesth Analg 63:577, 1984.

93. Gauntlett MG, Fisher DM, Hertzka RE: Pharmacokinetics of fentanyl in neonatal humans and lambs: Effects of age. Anesthesiology 69:683, 1988.

94. Byrick RJ, Kay JC, Noble WH: Extravascular lung water accumulation in patients following coronary artery surgery. Can J Anaesth 24:332, 1977.

95. Schupbach P, Pappova E, Schilt W et al: Perfusate oncotic pressure during cardiopulmonary bypass: optimum level as determined by metabolic acidosis, tissue edema, and renal function. Vox Sang 35:332, 1978.

96. Haneda K, Thomas R, Breazeale DG, Dillard DH: The significance of colloid osmotic pressure during induced hypothermia. J Cardiovasc Surg (Torino) 28:614, 1987.

97. Marelli D, Paul A, Samson CP et al: Does the addition of albumin to the prime solution in cardiopulmonary bypass affect clinical outcome? J Thorac Cardiovasc Surg 98:751, 1989.

98. Kirklin JW, Barratt-Boyes BG (eds): Cardiac Surgery, 2nd ed. New York, Churchill Livingstone, 1993.

99. Leone BJ, Spahn DR, Smith LR et al: Acute isovolemic hemodilution and blood transfusion: Effects on regional function and metabolism in myocardium with compromised coronary blood flow. J Thorac Cardiovasc Surg 105(4):694, 1993.

100. Kawashima Y, Yamamoto Z, Manabe H: Safe limits of hemodilution in cardiopulmonary bypass. Surgery 76:391, 1974.

101. Henling CE, Carmichael MJ, Keats AS, Cooley DA: Cardiac operation for congenital heart disease in children of Jehovah's Witnesses. J Thorac Cardiovasc Surg 89:914, 1985.

102. Spach MS, Serwer GA, Anderson PAW et al: Pulsatile aortopulmonary pressure-flow dynamics of patent ductus arteriosus in patients with various hemodynamic states. Circulation 61:110, 1980.

103. Fox LS, Blackstone EH, Kirklin JW et al: Relationship of whole body oxygen consumption to perfusion flow rate during hypothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 83:239, 1982.

104. Michenfelder JD, Theye RA: Hypothermia: Effect of canine brain and whole-body metabolism. Anesthesiology 29:1107, 1968.

105. Fox L, Blackstone E, Kirklin J et al: Relationship of brain blood flow and oxygen consumption to perfusion flow rate during profoundly hypothermic cardiopulmonary bypass. J Thorac Cardiovasc Surg 87:658, 1984.

106. Benveniste H, Drejer J, Schousboe A, Diemer NH: Elevations of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem 43:1369, 1984.

107. Pulsinelli WA, Levy DE, Sigsbee B et al: Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 74:540, 1983.

108. Busto R, Mordecai Y-T, Dietrich D et al: Effects of mild hypothermia on brain ischemia. Stroke 20:904, 1989.

109. Sutton LN, Clark BJ, Norwood CR et al: Global cerebral ischemia in piglets under conditions of mild and deep hypothermia. Stroke 22:1567, 1991.

110. Rebeyka IM, Coles JG, Wilson GJ et al: The effect of low-flow cardiopulmonary

bypass on cerebral function: An experimental and clinical study. Ann Thorac Surg 43:391, 1987.

111. Henriksen L: Cerebral blood flow during early cardiopulmonary bypass in man. Effect of procaine in cardioplegic solutions. Thorac Cardiovasc Surg 34:116, 1986.

112. Burrows FA, Hillier SC, McLeod ME et al: Anterior fontanel pressure and visual evoked potentials in neonates and infants undergoing profound hypothermic circulatory arrest. Anesthesiology 73:632, 1990.

113. Greeley WJ, Ungerleider RM: Assessing the effect of cardiopulmonary bypass on the brain [editorial; comment]. Ann Thorac Surg 52:417, 1991.

114. Newburger JW, Jonas RA, Wernovsky G et al: A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart

surgery. N Engl J Med 329:1057, 1993.

115. Rappaport LA, Wypij D, Bellinger DC et al: Relation of seizures after cardiac surgery in early infancy to neurodevelopmental outcome. Boston Circulatory Arrest Study Group. Circulation 97(8):773, 1998.

116. Bellinger DC, Jonas RA, Rappaport LA et al: Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med 332:549, 1995.

117. Bellinger DC, Rappaport LA, Wypij D et al: Patterns of developmental dysfunction after surgery in infancy to correct transposition of the great arteries. J Dev Behav Ped 18:75, 1997.

118. Wernovsky G, Wypij D, Jonas RA et al: Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants: A comparison of low-flow cardiopulmonary bypass versus circulatory arrest. Circulation 92:222, 1995.

119. du Plessis AJ: Neurologic complications of cardiac disease in the newborn. Clin Perinatol 24(4):807, 1997.

120. Jonas RA, Bellinger DC, Rappaport LA et al: Relation of pH strategy and developmental outcome after hypothermic circulatory arrest. J Thorac Cardiovasc Surg 106:362, 1993.

121. Kirshbom RM, Skaryak LA, DiBernardo LR et al: Effect of aortopulmonary collaterals on cerebral cooling and metabolic recovery during cardiopulmonary bypass and circulatory arrest. Circulation II92(9): 490, 1995.

122. Kawata H, Flackler JK, Aoki M et al: Recovery of cerebral blood flow and energy state after hypothermic circulatory arrest versus low flow bypass in piglets. J Thorac Cardiovasc Surg 102:671, 1993.

123. Kurth CD, O'Rourke MM, O'Hara IB, Uher B: Brain cooling efficiency with pH-stat and alpha-stat cardiopulmonary bypass in newborn pigs. Circulation 96(9 Suppl):II-358, 1997.

124. O'Rourke MM, Nork KM, Kurth CD: Altered brain oxygen extraction with hypoxia and hypotension following deep hypothermic circulatory arrest. Acta Neurochirurg 70:78, 1997.

125. Kurth CD, O'Rourke MM, O'Hara IB: Comparison of pH-stat and alpha-stat cardiopulmonary bypass on cerebral oxygenation and blood flow in relation to hypothermic circulatory arrest in piglets. Anesthesiology 89(1):110, 1998.

126. Greeley WJ, Ungerleider RM: Assessing the effect of cardiopulmonary bypass on the brain. Ann Thorac Surg 52:417, 1991.

127. Rossi R, van der Linden J, Ekroth R et al: No flow or low flow? A study of the ischemic marker creatine kinase BB after deep hypothermic procedures. J Thorac Cardiovasc Surg 98:193, 1989.

128. Swain JA, McDonald TJ, Griffith PK et al: Low flow hypothermic cardiopulmonary bypass protects the brain. J Thorac Cardiovasc Surg 102:76, 1991.

129. Scheller MS, Branson PJ, Cornacchia LG, Alksne JF: A comparison of the effects on neuronal Golgi morphology, assessed with electron microscopy, of cardiopulmonary bypass, low-flow bypass, and circulatory arrest during profound hypothermia. J Thorac Cardiovasc Surg 104:1396, 1992.

130. Pulsinelli WA, Waldman S, Rawlinson D, Plum F: Moderate hyperglycemia augments ischemic brain damage: A neuropathologic study in the rat. Neurology 32:1239, 1982.

131. Lanier WL, Stangland KJ, Scheithauer BW et al: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. Anesthesiology 66:39, 1987.

132. Nakakimura K, Fleischer JE, Drummond JC: Glucose administration before cardiac arrest worsens neurologic outcome in cats. Anesthesiology 72:1005, 1990.

133. Plum F: What causes infarction in ischemic brain? Neurology 33:222, 1983.

134. Farias LA, Willis BS, Gregory GA: Effects of fructose-1,6-diphosphate, glucose, and saline on cardiac resuscitation. Anesthesiology 65:595, 1986.

135. Kubler W, Katz AM: Mechanism of early "pump" failure of the is-chemic heart: Possible role of adenosine triphosphate depletion and inorganic phosphate accumulation (editorial). Am J Cardiol 40:467, 1977.

136. Steward DJ, Da Silva CA, Flegel T: Elevated glucose levels may increase the danger of neurologic deficit following profound hypothermic cardiac arrest. Anesthesiology 68:653, 1988.

137. Glauser TA, Rorke LB, Weinberg PM, Clancy RR: Acquired neuropathologic lesions associated with the hypoplastic left heart syndrome. Pediatrics 85:991, 1990.

138. Auer RN: Progress review: Hypoglycemic brain damage. Stroke 17:699, 1986.

139. Sieber FE, Derrer SA, Saudek CD, Traystman RJ: Effect of hypoglycemia on cerebral metabolism and carbon dioxide responsivity. Am J Physiol 256:H697, 1989.

140. Siesjo BK, Ingvar M, Pelligrino D: Regional differences in vascular autoregulation in the rat brain in severe insulin-induced hypoglycemia. J Cereb Blood Flow Metab 3:478, 1983.

141. Hilberman M, Myers BD, Carrie G et al: Acute renal failure following cardiac surgery. J Thorac Cardiovasc Surg 77:880, 1979.

142. Kron IL, Joob AW, Van Meter C: Acute renal failure in the cardiovascular surgical patient. Ann Thorac Surg 39:590, 1985.

143. Gomez-Campdera FJ, Maroto-Alvaro E, Galinanes M et al: Acute renal failure associated with cardiac surgery. Child Nephrol Urol 9:138, 1988.

144. Goodman TA, Gerard DF, Bernstein EF, Dilley RB: The effects of pulseless perfusion on the distribution of renal cortical blood flow and renin. Surgery 80:31, 1976.

145. Nakik SK, Knight A, Elliott MA: A successful modification of ultrafiltration for cardiopulmonary bypass in children. Perfusion 6:41, 1991.

146. Nakik SK, Knight A, Elliott MA: A prospective randomized study of a modified technique of ultrafiltration during pediatric open heart surgery. Circulation 84(suppl III):422, 1992.

147. Jenkins J, Lynn A, Edmonds J, Barker GA: Effects of mechanical ventilation on cardiopulmonary function in children after open-heart surgery. Crit Care Med 13:77, 1985.

148. McGowan FX, Ikegami M, DelNido PJ et al: Cardiopulmonary bypass signficantly reduces surfactant activity in children. J Thorac Cardiovasc Surg 106(6):968, 1993.

149. Howard RJ, Crain C, Franzini DA et al: Effects of cardiopulmonary bypass on pulmonary leukostasis and complement activation. Arch Surg 123:1496, 1988.

150. Hindmarsh KW, Sankaran K, Watson VG: Plasma beta-endorphin concentrations in neonates associated with acute stress. Dev Pharmacol Ther 7:198, 1984.

151. Anand KJS, Hansen DD, Hickey PR: Hormonal-metabolic stress response in neonates undergoing cardiac surgery. Anesthesiology 73:661, 1990.

152. Anand KJS, Sippell WG, Aynsley-Green A: Randomized trial of fentanyl anesthesia in preterm neonates undergoing surgery: Effects on the stress response. Lancet 1:243, 1987.

153. Langercrantz H, Slotkin TA: The "stress" of being born. Sci Am 1:100, 1986.

154. Oshita S, Uchimoto R, Oka H et al: Correlation between arterial blood pressure and oxygenation in tetralogy of Fallot. J Cardiovasc Anesth 3:597, 1989.

155. Severinghaus JW, Spellman BA: Pulse oximeter failure thresholds in hypotension and vasoconstriction. Anesthesiology 73:532, 1990.

156. Gold JP, Jonas RA, Lang P, Castaneda A: Transthoracic intracardiac monitoring lines in pediatric surgical patients: a ten year experience. Ann Thorac Surg 42:185, 1986.

157. Ungerleider R: Decision making in pediatric cardiac surgery using intraoperative echo. Int J Cardiol Imaging 4:33, 1989.

158. Greeley WJ, Kern FH, Ungerleider RM, Kisslo JA: Intramyocardial air causes right ventricular dysfunction after repair of a congenital heart defect. Anesthesiology 73:1042, 1990.

159. Naik SK, Knight A, Elliott MJ: A prospective randomized study of a modified technique of ultrafiltration during pediatric open-heart surgery. Circulation 84(suppl III):422, 1991.

160. Elliott JJ: Ultrafiltration and modified ultrafiltration in pediatric open-heart operations. Ann Thorac Surg 56(6):1518, 1993.

161. Ungerleider RM: Effects of cardiopulmonary bypass and use of modified ultrafiltration. Ann Thorac Surg 65:S35, 1998.

162. Darling E, Nanry K, Shearer I et al: Techniques of paediatric modified ultrafiltration: 1996 survey results. Perfusion 13(2):93, 1998.

163. Journois D, Pouard P, Greeley WJ et al: Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery. Anesthesiology 81:1181, 1994.

164. Wang MJ, Chiu IS, Hsu CM et al: Efficacy of ultrafiltration in removing inflammatory mediators during pediatric cardiac operations. Ann Thorac Surg 61(2):651, 1996.

165. Friesen RH, Campbell DN, Clarke DR, Tornabene MA: Modified ultrafiltration attenuates dilutional coagulopathy in pediatric open-heart operation. Ann Thorac Surg 65(6):1787, 1997.

166. Davies MJ, Nguyen K, Gaynor JW, Elliott MJ: Modified ultrafiltration improves left ventricular systolic function in infants after cardiopulmonary bypass [discussion, 369]. J Thorac Cardiovasc Surg 115(2): 361, 1998.

167. Skaryak LA, Kirshbom PM, DiBernardo LR et al: Modified ultrafiltration improves cerebral metabolic recovery after circulatory arrest. J Thorac Cardiovasc Surg 109(4):744, 1995.

168. Koutlas TC, Gaynor JW, Nicolson SC et al: Modified ultrafiltration reduces postoperative morbidity after cavopulmonary connection. Ann Thorac Surg 64(1):37, 1997.

169. Daggett CW, Lodge AJ, Scarborough JE, Chai PJ, Jaggers J, Ungerleider RM: Modified ultrafiltration versus conventional ultrafiltration: A randomized prospective study in neonatal piglets. J Thorac Cardiovasc Surg 115(2):336, 1998.

170. Borow KM, Green LH, Castaneda AR, Keane JF: Left ventricular function after repair of tetralogy of Fallot and its relationship to age at surgery. Circulation 61:1150, 1980.

171. Berner M, Oberhansli I, Rouge JC, Jaccard C: Chronotropic and inotropic supports are both required to increase cardiac output early after corrective operations for tetralogy of Fallot. J Thorac Cardiovasc Surg 97:297, 1989.

172. Graham TP, Franklin RCG, Wyse RKH et al: Left ventricular wall stress and contractile function in childhood: Normal values and comparison of Fontan repair versus palliation only in patients with tricuspid atresia. Circulation 74:61, 1986.

173. Lang P, Williams RG, Norwood WI: The hemodynamic effects of dopamine in infants after corrective cardiac surgery. J Pediatr 96:630, 1980.

174. Rebeyka IM, Hanan SA, Borges MR et al: Rapid cooling contracture of the myocardium: The adverse effect of prearrest cardiac hypothermia. J Thorac Cardiovasc Surg 100:240, 1990.

175. Bohn DJ, Poirer CS, Edmonds JF: Efficacy of dopamine, dobutamine, and epinephrine during emergence from cardiopulmonary bypass in children. Crit Care Med 8:367, 1980.

176. Konstam MA, Cohen SR, Salem DN: Effect of amrinone on right ventricular function: predominance of afterload reduction. Circulation 74:359. 1986.

177. Wessel DL, Triedman JK, Wernovsky G: Pulmonary and systemic hemodynamics of amrinone in neonates following cardiopulmonary bypass. Circulation 80(suppl II):488, 1989.

178. Lawless S, Burckart G, Diven W: Amrinone pharmacokinetics in neonates and infants. J Clin Pharmacol 28:283, 1988.

179. Williams GD, Sorensen GK, Oakes R et al: Amrinone loading during cardiopulmonary bypass in neonates, infants, and children. J Cardiothorac Vasc Anesth 9(3):278, 1995.

180. Chang AC, Atz AM, Wernovsky G et al: Milrinone: Systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. Crit Care Med 23(11):1907, 1995.

181. Ramamoorthy C, Anderson GD, Williams GD, Lynn AM: Pharmacokinetics and side effects of milrinone in infants and children after open-heart surgery. Anesth Analg 86(2):283, 1998.

182. Driscoll DJ, Gillette PC, Fukushige J et al: Comparison of the cardiovascular action of isoproterenol, dopamine and dobutamine in the neonatal and mature dog. Pediatr Cardiol 1:307, 1980.

183. Friedman WF: The intrinsic properties of the developing heart. Prog Cardiovasc Dis 15:87, 1972.

184. Hines R, Barash PG: Right ventricular failure. In Kaplan JA (ed): Cardiac Anesthesia, vol 2. Orlando, Florida, Grune & Stratton, 1987, [p 995].

185. Berne RM, Levy MN: Coronary circulation and cardiac metabolism. In Berne RM, Levy MN (eds): Cardiovascular Physiology. St. Louis, CV Mosby, 1981, [p 211].

186. Rudolph AM: Distribution and regulation of blood flow in the fetal and newborn lamb. Circ Res 57:811, 1985.

187. Pearl JM, Laks H, Drinkwater DC et al: Repair of truncus arteriosus in infancy. Ann Thorac Surg 52:780, 1991.

188. Klein MD, Shaheen KW, Whittlesey GC et al: Extracorporeal membrane oxygenation for the circulatory support of children after repair of congenital heart disease. J Thorac Cardiovasc Surg 100:498, 1990.

189. Golding LAR: Postcardiotomy mechanical support. Semin Thorac Cardiovasc Surg 3:29, 1991.

190. Walters HL 3rd, Hakimi M, Rice MD et al: Pediatric cardiac surgical ECMO: Multivariate analysis of risk factors for hospital death (discussion, 336). Ann Thorac Surg 60(2):329, 1995.

191. Meliones JN, Custer JR, Snedecor S et al: Extracorporeal life support for cardiac assist in pediatric patients. Review of ELSO Registry data. Circulation 84(5 Suppl):III-168, 1991.

192. Duncan BW, Ibrahim AE, Hraska V et al: Use of rapid-deployment extracorporeal membrane oxygenation for the resuscitation of pediatric patients with heart disease after cardiac arrest. J Thorac Cardiovasc Surg 116(2):305, 1998.

193. Karl TR: Extracorporeal circulatory support in infants and children. Semin Thorac Cardiovasc Surg 6(3):154, 1994.

194. Drummond WH, Gregory GA, Heymann MA, Phibbs RA: The independent effects of hyperventilation, tolazoline and dopamine on infants with persistant pulmonary hypertension. J Pediatr 98:603, 1981.

195. Custer JR, Hales CA: Influence of alveolar oxygen on pulmonary vasoconstriction in newborn lambs vs sheep. Am Rev Respir Dis 132:326, 1985.

196. Lyrene RK, Welch KA, Godoy G, Philips JB: Alkalosis attenuates hypoxic pulmonary vasoconstriction in neonatal lambs. Pediatr Res 19:1268, 1985.

197. Rudolph AM, Yuan S: Response of the pulmonary vasculature to hypoxia and H ion concentration changes. J Clin Invest 45:399, 1966.

198. Zapletal A, Paul T, Samenek M: Pulmonary elasticity in children and adolescents. J Appl Physiol 40:953, 1976.

199. Fagan DG: Shape changes in V-P loops for children's lungs related to growth. Thorax 32:198, 1977.

200. Mansell A, Bryan C, Levinson H: Airway closure in children. J Appl Physiol 33:711, 1972.

201. Hammond JW, Wolfe WG, Moran JF et al: The effect of positive end expiratory pressure on regional ventilation and perfusion in the normal and injured primate lung. J Thorac Cardiovasc Surg 72:680, 1976.

202. Weisfeldt ML, Halperin HR: Cardiopulmonary resuscitation: beyond cardiac massage. Circulation 74:443, 1986.

203. Molloy DW: Effects of noradrenaline and isoproterenol on cardiopulmonary function in a canine model of acute pulmonary hypertension. Chest 88:432, 1985.

204. Schwartz DA, Grove FL, Horowitz LD: Effect of isoproterenol on regional myocardial perfusion and tissue oxygenation in acute myocardial infarction. Am Heart J 97:339, 1979.

205. Park IS, Michael LH, Driscoll DJ: Comparative responses of the developing canine myocardium to inotropic agents. Am J Physiol 242:H13, 1982.

206. Heymann MA, Hoffman JIE: Persistent pulmonary hypertension syndromes in the newborn. In Weir EK, Reeves JT (eds): Pulmonary Hypertension. Mt. Kisko, New York, Futura, 1984, [p 45].

207. Bush A, Busset C, Knight WB et al: Modification of pulmonary hypertension secondary to congenital heart disease. Am Rev Respir Dis 136:767, 1987.

208. Zall S, Milocco I, Rickstein S-E: Effects of adenosine on myocardial blood flow and metabolism after coronary artery bypass surgery. Anesth Analg 73:689, 1991.

209. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT et al: Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet 338(8776):1173, 1991.

210. Girard C, Lehot JJ, Clerc J, French P: Inhaled nitric oxide (NO) in pulmonary hypertension following mitral valve replacement. Anesthesiology 75:A984, 1991.

211. Russell IA, Zwass MS, Fineman JR et al: The effects of inhaled nitric oxide on postoperative pulmonary hypertension in infants and children undergoing surgical repair of congenital heart disease. Anesthes Analg 87(1):46, 1998.

212. Curran RD, Mavroudis C, Backer CL et al: Inhaled nitric oxide for children with congenital heart disease and pulmonary hypertension. Ann Thorac Surg 60(6):1765, 1995.

213. Wessel DL, Adatia I, Giglia TM et al: Use of inhaled nitric oxide and

acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. Circulation 88(5 Pt 1):2128, 1993.

214. Zobel G, Gamillscheg A, Schwinger W, et al: Inhaled nitric oxide in infants and children after open-heart surgery. J Cardiovasc Surg 39)1):79, 1998.

215. Adatia I, Perry S, Landzberg M, et al: Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation. J Am Coll Cardiol 25(7):1656, 1995.

216. Adatia I, Atz AM, Jonas RA, Wessel DL: Diagnostic use of inhaled nitric oxide after neonatal cardiac operations. J Thorac Cardiovasc Surg 112(5):1403, 1996.

217. Manno CS, Hedberg KW, Kim HC et al: Comparison of the hemostat-ic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. Blood 77:930, 1991.

218. Dietrich W, Mossinger H, Spannagl M et al: Hemostatic activation during cardiopulmonary bypass with different aprotinin dosages in pediatric patients having cardiac operations. J Thorac Cardiovasc Surg 105:712, 1993.

219. Andrew M, Paes B, Milner R et al: Development of the human coagulation system in the full-term infant. Blood 70:165, 1987.

220. Colon-Otero G, Gilchrist GS, Holcomb GR et al: Preoperative evaluation of hemostasis in patients with heart disease. Mayo Clin Proc 62:379, 1987.

221. Henriksson P, Varendh G, Lundstrom NR: Haemostatic defects in cyanotic congenital heart disease. Br Heart J 41:23, 1979.

222. Vieira A, Berry L, Ofoso F, Andrew M: Heparin sensitivty and resistance in the neonate: An explanation. Thromb Res 63:85, 1991.

223. Kern FH, Morana NJ, Sears J, Hickey PR: Coagulation defects in neonates during CPB. Ann Thorac Surg 54:541, 1992.

224. Horkay F, Martin P, Rajah SM, Walker DR: Response to heparinization in adults and children undergoing cardiac operations. Ann Thorac Surg 53:822, 1992.

225. Jobes DR, Shaffer GW, Aitken GL: Increased accuracy and precision of heparin and protamine dosing reduces blood loss and transfusion in patients undergoing primary cardiac operations. J Thorac Cardiovasc Surg 110(1):36, 1995.

226. Harker LA: Bleeding after cardiopulmonary bypass. N Engl J Med 314:446, 1986.

227. Woodman RC, Harker LA: Bleeding complications associated with cardiopulmonary bypass. Blood 76:1680, 1990.

228. Salzman EW, Weinstein MJ, Weintraub RM et al: Treatment with desmopressin acetate to reduce blood loss after cardiac susrgery . N Engl J Med 314:1402, 1986.

229. Reynolds LM, Nicolson SC, Jobes DR, et al: Desmopressin does not decrease bleeding after cardiac operation in young children. J Thorac Cardiovasc Surg 106(6):954, 1993.

230. Horrow JC, Hlavacek J, Strong MD et al: Prophylactic tranexamic acid decreases bleeding after cardiac operations. J Thorac Cardiovasc Surg 99:70, 1990.

231. Royston D, Taylor KM, Bidstrup BP, Sapsford RN: Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet 2:1289, 1987.

232. Dietrich W, Henze R, Barankay A et al: High-dose aprotinin application reduces homologous blood requirement in cardiac surgery. J Cardiothorac Anesth 3:79, 1989.

233. Dietrich W, Spannagl M, Jochum M et al: Influence of high-dose aprotinin treatment on blood loss and coagulation patterns in patients undergoing myocardial revascularization. Anesthesiology 73:1119, 1990.

234. Dietrich W, Spannagl M, Schramm W et al: The influence of preoperative anticoagulation on heparin response during cardiopulmonary bypass. J Thorac Cardiovasc Surg 102:505, 1991.

235. Dietrich W, Barankay A, Hahnel C, Richter JA: High-dose aprotinin in cardiac surgery: Three years' experience in 1,784 patients. J Cardiothorac Vasc Anesth 6:324, 1992.

236. Davies MJ, Allen A, Kort H, et al: Prospective, randomized, double-blind study of high-dose aprotinin in pediatric cardiac operations. Ann Thorac Surg 63(2):497, 1997.

237. Penkoske PA, Entwistle LM, Marchak BE et al: Aprotinin in children undergoing repair of congenital heart defects. Ann Thorac Surg 60(6 Suppl):S529, 1995.

238. Carrel TP, Schwanda M, Bogt Pr, Turina MI: Aprotinin in pediatric cardiac operations: A benefit in complex malformations and with high-dose regimen only. Ann Thorac Surg 66(1):153, 1998.

239. Kirklin JW, Archie JP Jr: The cardiovascular subsystem in surgical patients. Surg Gynecol Obstet 139:17, 1974.

240. Hosenpud JD, Bennett LE, Berkeley M et al: The registry of the international society for heart and lung transplantation: Fifteenth official report 1998. J Heart Lung Transplant 17:656, 1998.

241. Kirklin JK, Naftel DC, McGiffin DC, et al: Analysis of morbid events and risk factors for death after cardiac transplantation. J Am Coll Cardiol 11(5):917, 1998.

242. Gajarski RJ, Towbin JA, Bricker JT, et al: Intermediate follow-up of pediatric heart transplant recipients with elevated pulmonary vascular resistance index. J Am Coll Cardiol 23:1682, 1994.

243. Fukushima N, Gundry Sr, Razzouk AJ, Bailey LL: Risk factors for graft failure associated with pulmonary hypertension after pediatric heart transplantation. J Thorac Cardiovaasc Surg 107(4):985, 1994.

244. Bailey LL: Heart transplantation techniques in complex congenital heart disease. J Heart Lung Transplant 12(6 Pt 2):S168, 1993.

245. Chartrand C, Guerin R, Kangah M, Stanley P: Pediatric heart transplantation: Surgical considerations for congenital heart diseases (discussion, 616). J Heart Transplant 9(6):608, 1990.

246. Zales VR, Wright KL, Pahl E, et al: Normal left ventricular muscle mass and mass/volume ratio after pediatric cardiac transplantation. Circulation 90(5 Pt 2):II61, 1994.

247. Canter CE, Moorhead S, Saffitz JE et al: Steroid withdrawal in the pediatric heart transplant recipient initially treated with triple immunosuppression (discussion, 79). J Heart Lung Transplant 12(1 Pt 1):74, 1994.

248. Boucek MM, Kanakriyeh MS, Mathis CM, et al: Cardiac transplantation in infancy: Donors and recipents. Loma Linda University Pediatric Heart Transplant Group. J Pediatr 116(2):171, 1990.

249. Bridges ND, Malory GB Jr, Huddleston CB, et al: Lung transplantation in children and young adults with cardiovascular disease (discussion, 820). Ann Thorac Surg 59(4):813, 1995.

250. Conte JV, Robbins RC, Reichenspurner H, et al: Pediatric heart-lung transplantation: intermediate-term results. J Heart Lung Transplant 15(7):692, 1996.

251. Burke RP, Wernovsky G, van der Velde M, et al: Video-assisted thoracoscopic surgery for congenital heart disease (discussion 508). J Thorac Cardiovasc Surg 109(3):499, 1995.

252. Laborde F, Folliguet T, Batisse A, et al: Video-assisted thoracoscopic surgical interruption: The technique of choice for patent ductus arteriosus. Routine experience in 230 pediatric cases (discussion 1684). J Thorac Cardiovasc Surg 110(6):1681, 1995.

253. Gelman S, Reves JG, Fowler K, et al: Regional blood flow during cross-clamping of the thoracic aorta and infusion of sodium nitroprusside. J Thorac Cardiovasc Surg 85(2):287, 1983.

254. DeSanctis RW, Doroghazi RM, Austen WG, Buckley JJ: Aortic dissection. N Engl J Med 317(17):1060, 1987.

255. Mullins CE: Pediatric and congenital therapeutic cardiac catheterization. Circulation 79:1153, 1989.

256. Hellenbrand WE, Fahey JT, McGowan FX et al: Transesophageal echocardiographic guidance for transcatheter closure of atrial septal defects. Am J Cardiol 66:207, 1990.

257. Lock JE, Rome JJ, Davis R et al: Transatrial closure of atrial septal defects: Experimental studies. Circulation 79:1091, 1989.

258. Hickey PR, Wessel DL, Streitz SL et al: Transcatheter closure of atrial septal defects: Hemodynamic complications and anesthetic management. Anesth Analg 74:44, 1992.

259. Malviya S, Burrows FA, Johnston AE, Benson LN: Anaesthetic experience with paediatric interventional cardiology. Can J Anaesth 36:320, 1989.

260. Rothman A, Perry SB, Keane JF, Lock JE: Early results and follow-up of balloon angioplasty for branch pulmonary artery stenoses. J Am Coll Cardiol 15:1109, 1990.

Chapter 51 - Anesthesia for Vascular Surgery

Edward J. Norris
Steven M. Frank

INTRODUCTION

The perioperative management of patients undergoing vascular surgery is one of the most challenging and controversial areas in the field of anesthesiology. Given the high incidence of coexisting disease, the hemodynamic and metabolic stress associated with cross-clamping and unclamping, and the ischemic insults to the brain, heart, kidneys, and spinal cord, it is not surprising that perioperative morbidity is exceedingly high relative to that of other surgical procedures. The controversy associated with routine preoperative screening for coronary artery disease (CAD) has been fueled by issues related to cost containment and managed care. Ongoing controversy continues over anesthetic technique and outcome because vascular procedures often lend themselves to local, regional, general, or combined regional/general anesthetics.

Much progress has been made in the management of vascular patients in the past 3 decades. In the 1970s, it was recognized that vascular surgery, relative to other surgeries, was a risk factor for perioperative cardiac morbidity. In the 1980s, the focus shifted to risk stratification in an effort to identify patients who were at greatest risk for morbid outcomes. In the 1990s, there have been numerous clinical trials studying anesthetic technique, sympatholytic drugs, hemodynamic control, and analgesic regimens that provide insight into the prevention, treatment, and mechanisms of cardiac and other morbidity. The goal of this chapter is to review issues related to the perioperative care of the vascular surgery patient and to address the underlying controversies. For simplicity, each of four major categories of vascular procedures is discussed separately: (1) abdominal aortic surgery, (2) thoracoabdominal aortic surgery, (3) lowerextremity vascular surgery, and (4) carotid surgery. Additional sections on preoperative and postoperative issues specific to each category of surgical procedure are included.

ATHEROGENESIS

Atherosclerosis is a disease process that compromises the arterial blood supply to any or all of the vital organs or the extremities. Risk factors include hypercholesterolemia, diabetes, hypertension, male sex, cigarette smoking, and family history. Because atherosclerosis is usually without early warning signs, prevention and/or risk modification is difficult until the patient has progressed to an advanced stage of disease. The progression of atherosclerosis occurs in three stages. [1] As early as the 2nd decade of life, fatty streaks begin to occur beneath the normal endothelium. These consist of lipid-laden macrophages (foam cells), smooth muscle cells, and elastic and collagen fibers. The fatty streak progresses to a fibrous plaque consisting of degenerated foam cells covered by a layer of proliferated smooth muscle cells. Unlike

the fatty streak, these lesions may compromise blood flow through a vascular bed and cause ischemia or thrombosis to the vital organs or extremities. The complex lesion of atherosclerosis represents a progression of the fibrous plaque with an expanded lipid-rich core, accumulation of calcium, disruption of endothelial integrity, and platelet thrombus and hemorrhage into the lesion.

The exact mechanism of atherogenesis and the explanation for the anatomic distribution of lesions are unknown. One theory is the "response to injury hypothesis," which was proposed by Virchow [2] 150 years ago and has come back into favor. [3] [4] The hypothesis is that endothelial injury is caused by a variety of chemical and physical factors, leading to desquamation and exposure of the subendothelium. Platelet adherence and degranulation stimulate arterial smooth muscle migration from the media into the intima, a phenomenon that promotes intimal smooth muscle proliferation. Other theories include the monoclonal hypothesis of atherogenesis proposed by Benditt and Benditt [5] in 1973, which suggests that each lesion is derived from a single smooth muscle cell that proliferates around a focus. This hypothesis draws an analogy to malignancy whereby a cell proliferates uncontrollably in response to a mutagen or, possibly, a virus to produce a lesion. The clonal senescence hypothesis proposed by Martin and Sprague [6] also focuses on smooth muscle cell proliferation that is controlled by local feedback from inhibitory hormones. In aging vessels, a decrease in inhibitory feedback stimulates growth of these cells and formation of the lesion.

The anatomic distribution of atherosclerotic lesions is shown in Figure 51-1 (Figure Not Available) . The most common sites are the coronary arteries, the carotid bifurcation, the abdominal aorta, and the iliac and femoral arteries. [1] It is known that atherosclerotic lesions tend to develop near arterial branch points and along the outer surfaces of arterial curves. Their development may be related to increased shear stress and injury to the endothelial surface. [7] Estrogens protect against atherosclerosis in part by increasing high-density lipoproteins and decreasing low-density lipoproteins. [8] Some evidence supports the role of antioxidants in preventing atherosclerotic lesions. Vitamins C and E, carotenoids, and folic acid may be beneficial in this regard. [9] Aspirin, by means of its anti-inflammatory and antiplatelet effects, is effective in preventing stroke and myocardial infarction (MI). When cholesterol level is lowered to less than 150 mg/dL, lipids are mobilized from atherosclerotic lesions, and regression gradually occurs. [10] A review of risk and prevention of arterial aging has been published [9] and is also available on the Internet. [11]

PREOPERATIVE EVALUATION

Coexisting Disease

Patients having peripheral vascular surgery are a select group of patients with a high incidence of coexisting disease (Ch. 25) associated with advanced age, cigarette smoking, diabetes mellitus, and hypertension, all of which should be assessed and optimized before surgery (Ch. 23) . It is also well recognized that CAD is the leading cause of perioperative mortality at the time of peripheral vascular surgery and

Figure 51-1 (Figure Not Available) Distribution of atherosclerotic lesions. Plaques occur at the origins of large vessels and at bifurcations. Distribution and relative severity differ based on risk factors. *(From Zwolak and Cronenwett [1])*

that long-term survival after vascular procedures is significantly limited by a high incidence of morbid cardiac events. [12] Given the systemic nature of atherosclerotic disease, less than 10 percent of patients who present for vascular surgery have normal coronary arteries, and more than 50 percent of patients have advanced or severe CAD. [13] The preoperative period thus presents an opportunity to perform diagnostic and therapeutic interventions that may affect not only perioperative survival but also long-term morbidity from cardiac events.

Perioperative and Long-Term Morbidity

To appreciate the importance of preoperative evaluation, one must consider the incidence of MI and death in patients

TABLE 51-1 -- Rates of Myocardial Infarction and Death for Patients Undergoing Vascular Surgery

AUTHOR (REFERENCE)	MI (%)	DEATH (%)	COMMENTS
SHORT-TERM FOLLOW-UP (IN HOSPITAL)			
Ouyang et al [59]	8	0	Small study
Raby et al [437]	2.3	0.06	Aortic, lower extremity, carotid
Mangano et al [62]	4.1	2.3	Vascular patients only reported
Bode et al [304]	4.5	3.1	All lower extremity vascular
Christopherson et al [54]	4.0	2.0	All lower extremity vascular
Mangano et al [51]	5.0	0	Vascular patients only reported
Fleisher et al [94]	6.0	3.0	Vascular patients only reported
Hertzer [438]	8.8		Older study (1982)
Pasternack et al [61]	4.5	1.0	Aortic, lower extremity, carotid
Krupski et al [28]	2.1	2.9	Aortic, lower extremity
Average	5.0	1.6	
LONG-TERM FOLLOW-UP (IN HOSPITAL + AFTER DISCHARGE)			
Raby et al [437]	7.4	5.1	20-month follow-up
Mangano et al [62]	4.7	3.5	15-month follow-up
Mangano et al [439]	19.4	13.5	24-month follow-up
Hertzer et al [77]		12	5-year follow-up
Krupski et al [29]	3.9	11.2	24-month follow-up
Average	8.9	9.1	3-4 year average follow-up

For short-term follow-up, outcomes are reported for the duration of the hospital stay, and death from MI was classified as both "MI" and "Death." For long-term follow-up, "MI" was not included as a subset of "Death," because often the cause of death was unknown. Thus, the incidence of MI is underestimated in the long-term table.

undergoing peripheral vascular surgery (Table 51-1) (Ch. 22) . When multiple studies are pooled, the overall prevalence of perioperative MI and death is 5.0 percent and 1.6 percent, respectively. When outcomes are assessed over the long-term postoperative period (3-4 years), the prevalence of MI and death is 8.9 percent and 9.1 percent, respectively.

The challenge for clinicians is to accurately assess risk for cardiac morbidity while maintaining a cost-effective strategy. After risk assessment, there is the additional challenge of modifying perioperative management to reduce risk by (1) adjusting cardiac medication, (2) direct coronary intervention with percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), or (3) modifying perioperative management. Coordination is essential between surgeons, anesthesiologists, and cardiologists, each of whom may have different criteria for risk modification. Although some investigations have enthusiastically promoted the use of preoperative testing, cardiologists, surgeons, and anesthesiologists do not agree on which patients should be tested and how. The cost of these tests is a limiting feature; Mangano [12] estimated that annual health care costs would rise by $100 million if preoperative dipyridamole thallium imaging (DTI) were used for only half of all vascular surgery patients. Even when selective criteria are used to determine which vascular patients need preoperative testing, one estimate is that $2,936 per patient would be the average cost of testing, with subsequent coronary intervention by PTCA or CABG for patients with correctable CAD. [14]

Because both PTCA and CABG have inherent risks, additional controversies arise. Also, because it is ethically difficult or impossible to study these preoperative interventions in a randomized clinical trial, no such trials have been performed. In interpreting the few published outcome studies, one must recognize that overall mortality must include both the mortality related to the coronary intervention and the mortality related to the vascular surgery procedure itself, and that improved

survival following vascular surgery after PTCA or CABG may merely represent the elimination of patients who are less likely to survive surgery. [13]

An excellent review of the literature and recommendations for preoperative evaluation were published by the American College of Cardiology and the American Heart Association (ACC/AHA). [15] This document was produced by a task force that included cardiologists, internists, anesthesiologists, and surgeons. Preoperative testing is discussed, preoperative risk variables are identified, and anesthetic care and hemodynamic monitoring are reviewed. An explicit algorithm for preoperative testing is outlined in these guidelines.

Risk Assessment and Optimization

Risk Indices

Assessing cardiac risk in patients before vascular surgery is a controversial and difficult task (Ch. 22) . In the mid 1970s, Goldman and colleagues [16] pioneered the concept of a risk index to account for the multifactorial nature of contributors to risk for cardiac morbidity. In this landmark study, 1,000 patients scheduled for major surgical procedures were prospectively enrolled, and a multivariate model was used to determine the independent risk contribution of each of several clinical variables. Independent predictors of morbidity were identified as (1) age >70 years; (2) MI in the previous 6 months; (3) an S_3 gallop or jugular venous dis- tention; (4) any preoperative cardiac rhythm other than sinus; (5) aortic stenosis; (6) general medical problems (abnormal arterial blood gases, electrolytes, creatinine); and (7) emergency, intrathoracic, or intra-abdominal surgery. Limitations of Goldman et al's [16] study include a relatively low-risk population (only 8% were vascular surgery patients), which limits the application of the risk index for this group of patients.

Since the publication of Goldman et al's [16] paper, several other investigators have published risk indices in an attempt to increase the sensitivity and specificity for predicting perioperative morbidity. [17] [18] [19] [20] [21] The patients in these series were also relatively low risk because only a small percentage underwent vascular surgery. Although risk indices are a cost-effective screening method for determining which patients require further cardiac evaluation, the high pretest probability of CAD in vascular surgery patients makes the risk index less useful. For this reason, the remainder of this section focuses on risk assessment specifically for vascular surgery patients.

The history and physical examination are not very reliable for detecting CAD in the general population. In patients with peripheral vascular disease whose exercise tolerance is limited by claudication, the history and physical are even less reliable. In addition, the symptoms of ischemic heart disease are often not manifested in diabetic patients, and silent myocardial ischemia goes unrecognized. [22] Nonetheless, several risk indicators can be obtained from the history and physical examination. History of a previous MI or congestive heart failure has been shown in multiple studies to predict risk for perioperative cardiac morbidity. [16] [23] [24] [25] Exercise tolerance is valuable information that may eliminate the need for further testing. [26] Patients with adequate lower-extremity blood flow (e.g., patients with isolated carotid disease) may have exercise tolerance that indicates good left ventricular function and low likelihood of significant CAD.

It is not clear whether any specific category of vascular disease is associated with a greater likelihood of coexisting CAD. Some investigators have shown a similar incidence and severity of CAD in patients with aortic, lower-extremity, and carotid disease. [27] Others have shown that patients with lower-extremity vascular disease are more likely to have significant CAD and to experience perioperative morbidity. [28] [29] [30] In the ACC/AHA guidelines, aortic and lowerextremity procedures are considered high risk and carotid procedures intermediate risk for perioperative cardiac morbidity. The difference in these subgroups of vascular patients is related not to the incidence or the severity of coexisting disease but rather to the invasiveness of the surgery.

Hypertension

Although hypertension is well recognized as a risk factor for atherosclerotic disease, multiple studies have shown that moderate hypertension is not an independent risk factor for perioperative cardiac morbidity. [18] [31] [32] Hypertensive patients may be more hemodynamically labile intraoperatively and postoperatively. [33] In addition, because of anxiety, patients often have acutely elevated blood pressures on admission to the hospital, especially the morning of surgery, and this should be taken into account before patients are diagnosed with or treated for hypertension. [34] Patients should be maintained with their usual antihypertensive medications throughout the perioperative period, with an oral dose given the morning of surgery and parenteral doses given thereafter in patients unable to take oral medications. Care should be taken to prevent withdrawal from beta-adrenergic blockers and clonidine to avoid a rebound increase in heart rate and blood pressure. The perioperative use of beta blockers and the control of heart rate have been shown to reduce the incidence of perioperative myocardial ischemia and subsequent cardiac morbidity. [12] [35] [36] [37] [38] [39] Clonidine decreases anesthetic requirements, catecholamine levels, and blood pressure lability. [40] [41] The effect of calcium channel blockers on perioperative cardiac morbidity has not been studied in a randomized fashion, but there is evidence that the incidence of myocardial ischemia is unaffected. [35] Because angiotensin-converting enzyme inhibitors may lead to intraoperative hypotension, it has been recommended that these drugs be avoided in the immediate preoperative period. [42] If necessary, blood pressure can be controlled with shorter-acting acute therapy during the intraoperative and postoperative periods.

Previous Myocardial Infarction

Patients who have had prior MI are at greater risk for reinfarction in the perioperative period than others (Table 51-2) . Studies from the 1970s reported prevalence of perioperative MI of about 30 percent, 15 percent, and 5 percent in patients who had a prior MI less than 3 months, 3 to 6 months, and more than 6 months before the procedure, respectively. [16] [23] [24] [25] In the 1980s, Rao et al [43] demonstrated that risk for perioperative reinfarction could be reduced with careful intraoperative and postoperative care that included invasive hemodynamic monitoring with arterial and pulmonary artery catheters, control of hemodynamic parameters, and intensive care following surgery. With this "extra care," the risk of reinfarction was reduced to 6 percent, 2.5 percent, and 1.5 percent in patients who had had a prior MI less than 3 months, 3 to 6 months, and more than 6 months before the procedure, respectively. [43] Nevertheless, this study had significant limitations, including the retrospective design, the lack of careful outcome surveillance, and the unidentified changes in practice over time that may have influenced outcome given the historical control group.

TABLE 51-2 -- Reinfarction Rates in Patients With Previous Myocardial Infarction

TIME ELAPSED BETWEEN PRIOR MYOCARDIAL INFARCTION AND OPERATION (MONTHS)	TARHAN ET AL[25]	RAO ET AL[43]		SHAH ET AL[44a]
	1972	*BEFORE 1977*	*1977 AND AFTER*	*1990*
0-3	37	36	5.8	4.3
4-6	16	26	2.3	0
>6	5.6	5	1.5	5.7
Time unknown	--	--	--	3.3

Despite these limitations, the study by Rao et al is often cited as justification for invasive monitoring and intensive care in patients with significant cardiac risk. Table 51-2 shows the significant decrease in reinfarction rates over the past 2 decades, indicating an overall improvement in our ability to care for these high-risk patients.

Given the increased risk for morbidity in patients with recent MI, traditional anesthetic practice dictates that elective surgery be postponed until a 6-month interval has passed. Vascular surgery, however, is often not elective. Urgent surgery is often necessary for patients experiencing transient ischemic attacks from carotid stenosis or limb-threatening ischemia from iliac or femoral disease. For this reason, each patient with recent MI must be assessed from the riskbenefit standpoint.

Assessment of Cardiovascular Risk

Electrocardiogram

A preoperative electrocardiogram (ECG) should be obtained for all patients undergoing vascular surgery. This ECG is necessary for comparison if myocardial ischemia or infarction is suspected postoperatively. If Q waves or other evidence of prior MI is present, then previous records should be reviewed to determine the timing of the infarct for the purposes of risk stratification. Dysrhythmias should be evaluated preoperatively to optimize risk, for example, rate control for patients in atrial fibrillation. The presence of a cardiac rhythm other than sinus indicates risk for perioperative cardiac morbidity, [16] [20] although it is unclear whether treatment of dysrhythmias reduces risk. Approximately 50 percent of patients with CAD have a normal resting ECG, and therefore the ECG lacks sensitivity for predicting cardiac morbidity. [44]

Exercise ECG

Exercise stress testing is a widely available and costeffective method of screening for CAD in the general population. A substantial proportion of vascular surgery patients (30-70%), however, cannot attain target heart rates that allow detection of ischemia. [45] In addition, many elderly patients are limited by knee and hip disorders or previous stroke that limit their exercise capacity. One alternative is arm exercise, [46] but fatigue often precedes the increase in heart rate, and there has been little enthusiasm for this technique. If vascular surgery patients are able to exercise and are able to achieve 85 percent of their maximal heart rate, they are at substantially lower risk for perioperative morbidity. [47] One small study demonstrated a 5-fold increase in risk for patients who were able to attain the target heart rate with significant ST changes, but other, larger, studies do not support these findings, showing poor predictive values for exercise stress testing. [48] [49]

Dipyridamole Thallium Imaging

Dipyridamole thallium imaging is the most commonly used noninvasive test to screen vascular surgery patients for CAD and risk for perioperative cardiac morbidity. Thallium 201, a radioactive potassium analogue, is distributed into perfused areas of myocardium after intravenous injection. Areas of myocardium that are hypoperfused show up on scintigraphic scanning as a relative "cold spot." Dipyridamole vasodilates normal coronary arteries by blocking reuptake of adenosine, but stenotic vessels have a fixed diameter and cannot dilate. This creates a "steal phenomenon," whereby blood flow is redirected away from diseased coronary vascular beds. Thallium imaging is usually performed to detect hypoperfused areas of myocardium soon after the dipyridamole is given. A second image is obtained 3 to 6 hours later after the vasodilator effect has dissipated (redistribution phase). There are three general outcome results from this test. The first is a normal test result with complete perfusion on the first and second images. The second is one that shows myocardium at risk ("redistribution"), with the first image showing a hypoperfusion defect and the second image showing normal perfusion. This indicates coronary narrowing and ischemia that is induced by the vasodilator. The anatomic location of the area at risk can usually be assessed on the images. The third is a fixed perfusion defect indicating an old infarction that has scarred the myocardium to such a degree that blood flow is absent.

There is ongoing controversy over the value of DTI for risk stratification in patients scheduled for vascular surgery. Two large studies in vascular surgery patients showed low sensitivity for DTI's predicting cardiac morbidity. [50] [51] This may be related to the fact that the population in these large studies had a lower risk than that of populations in other studies, in which selected patients were enrolled who had clinical risk factors (a higher pretest probability of morbidity). Table 51-3 illustrates the predictive value for DTI in vascular surgery patients.

The most rational use of DTI was proposed by Eagle et al [52] in 1989. In this study, vascular surgery patients were stratified by clinical variables and then studied with DTI (Fig. 51-2). (Figure Not Available) The clinical variables were (1) Q waves on ECG, (2) history of ventricular ectopic activity, (3) diabetes, (4) advanced age (>70 years), and (5) angina. In patients with one or two of these variables, a positive DTI result was associated with a tenfold greater incidence of cardiac morbidity. The authors recommended proceeding to coronary angiography in these patients. Patients with three or more clinical risk variables had such a high risk for morbidity that the authors recommended not using DTI but instead proceeding directly to cardiac catheterization. Patients with no clinical variables had such a low risk for morbidity that DTI did not add significantly to risk assessment, and it was stated that DTI is unnecessary. Despite ongoing debate, DTI remains the most widely used test for risk stratification in patients scheduled for vascular surgery.

Ambulatory Electrocardiographic Monitoring

Ambulatory electrocardiographic (AECG) monitoring has been used for many years to detect dysrhythmias, but only recently has ambulatory monitoring for myocardial ischemia been used to predict risk for perioperative cardiac morbidity. As with DTI, the sensitivity of AECG monitoring is

TABLE 51-3 -- Preoperative Testing for Assessment of Cardiac Risk: Dipyridamole Thallium, Dobutamine Stress Echocardiography, and Ambulatory Electrocardiography

AUTHOR	n[a]	EVENTS (MI or DEATH), *No. (%)*	PERIOPERATIVE EVENTS,[b] *No. (%)*		COMMENTS
DIPYRIDAMOLE THALLIUM			***+ PRED. VALUE (POSITIVE TEST)***	***- PRED. VALUE (NEGATIVE TEST)***	
Boucher et al [441]	48	3(6)	3/16(19)	32/32(100)	First to define risk using DTI
Leppo et al [442]	89	15(16)	14/42(33)	46/47(98)	
Eagle et al [52]	200	15(8)	13/82(16)	61/62(98)	Combined clinical variables with DTI
Mangano et al [51]	60	3(5)	1/22(5)	19/20(95)	Managing physicians blinded to DTI results
Baron et al [50]	457	22(5)	7/160(4)	195/203(96)	Did not analyze for cardiac death (nonfatal MI only)
Bry et al [14]	237	17(7)	12/110(11)	97/97(100)	Cost-effectiveness data included
DOBUTAMINE STRESS ECHOCARDIOGRAPHY			***+ PRED. VALUE (POSITIVE TEST)***	***- PRED. VALUE (NEGATIVE TEST)***	
Lalka et al [66]	60	9(15)	7/30(23)	28/30(93)	Aortic surgery (multivariate analysis)
Langan et al [67]	74	3(4)	3/18(17)	56/56(100)	Aortic surgery
Eichelberger et al [70]	75	2(3)	2/27(7)	48/48(100)	Managing physicians blinded to DSE results
Poldermans et al [68]	131	5(4)	5/35(14)	96/96(100)	Managing physicians blinded to DSE results (multivariate analysis)
Davila et al [69]	88	2(2)	2/20(10)	68/68(100)	Included long-term follow-up
AMBULATORY ECG			***+ PRED. VALUE (POSITIVE TEST)***	***- PRED. VALUE (NEGATIVE TEST)***	
Raby et al [55]	176	4(2)	3/32(10)	143/144(99)	24-48 h during ambulation
Pasternack et al [61]	200	9(5)	7/78(9)	120/122(98)	Multivariate analysis
Mangano et al [62]	474	6(4)	1/26(4)	113/118(96)	AECG immediately before surgery
Fleisher et al [94]	67	4(6)	2/16(13)	49/51(96)	AECG immediately before surgery

Fleisher et al [53]	86	4(5)	2/20(10)	64/66(97)	Quantitative monitoring not predictive

MI, myocardial infarction

Adapted from Eagle et al [15]

[a] *n* indicates the number of patients that underwent surgery.
[b] Patients with fixed DTI perfusion defects were omitted from calculations of positive and negative predictive value.

greatest in patients with high pretest probability. Preoperative ST segment changes consistent with myocardial ischemia occur in 20 to 40 percent of vascular surgery patients, and 80 to 90 percent of these ischemic episodes are silent. [53] [54] [55] The advantage of AECG monitoring over DTI is that AECG is approximately one-third the cost of DTI. [55] Disadvantages include the inability to test patients with significant ECG abnormalities that preclude ECG monitoring for ischemia (left bundle branch blocks, pacemaker dependency, and left ventricular hypertrophy with significant strain or digitalis effect). [56] Silent myocardial ischemia is known to predict adverse outcomes not only as a preoperative

Figure 51-2 (Figure Not Available) Algorithm for combining clinical variables and dipyridamole-thallium results to stratify cardiac risk in vascular surgery patients. Cardiac events include unstable angina, myocardial infarction, ischemic pulmonary edema, or cardiac death. Clinical variables are Q wave on electrocardiogram, age >70 years, history of angina, ventricular ectopic activity requiring treatment, and diabetes mellitus requiring treatment. *(From Eagle et al [52])*

test but also in other clinical settings. Silent ischemia predicts morbidity after MI [57] and in unstable angina. [58] Postoperative silent ischemia is also predictive of cardiac morbidity [59] and mortality [60] after peripheral vascular surgery.

Studies by Pasternack et al [61] and Raby et al [55] that included only vascular surgery patients found AECG to be highly sensitive (0.80-0.90) and specific (0.70-0.90). Other studies, including the largest series (474 patients) by Mangano et al, [62] included general surgery patients, as well with a resulting lower sensitivity (0.30-0.50) and a similar specificity (0.70-0.80). Fleisher et al [53] found that preoperative AECG monitoring had predictive value similar to that of DTI, although the two tests together provided more predictive ability than either test alone. Two disadvantages of AECG testing follow: (1) the highest-risk patients could not be monitored, because of baseline ECG abnormalities, and (2) the risk was not quantifiable by the severity of ischemia on AECG but was quantifiable by DTI. Table 51-3 compares the results of several studies on AECG monitoring for risk stratification before vascular surgery.

Echocardiography

Two-dimensional echocardiography is a noninvasive, relatively inexpensive technique that provides measurements of left ventricular function, ejection fraction, regional wall motion, and valvular function. Although the left ventricular function measured by echocardiography is a more qualitative measure than a quantitative one, this method is generally less expensive than radionuclide ventriculography, which is more quantitative. [63] Echocardiography has limited ability to measure ejection fraction. These measurements are dependent on loading conditions (both preload and afterload). [64] In addition, measurements of ventricular function are often made in the acute post-MI setting, resulting in patients' being labeled with a poor ejection fraction long after the myocardium has recovered from the ischemic insult. Although studies have correlated left ventricular function with outcome in patients with acute MI, [65] the value of echocardiographic assessment as a predictor of perioperative cardiac morbidity is unknown.

Pharmacologic Stress Echocardiography

Echocardiography can be used with pharmacologic stress testing to provoke myocardial ischemia, as detected by new or worsening wall motion abnormalities. For the preoperative assessment of patients for vascular surgery, dobutamine stress echocardiography (DSE) has a sensitivity of 80 to 90 percent and a specificity of 80 to 90 percent for predicting perioperative cardiac morbidity. [66] [67] [68] [69] [70] DSE does not add risk discrimination for patients with no clinical markers according to the criteria of Eagle et al, [52] because morbid events are rare in this subgroup. [71] DSE does stratify patients with one or two clinical markers, and perioperative cardiac events are unlikely to occur in patients with a negative result on stress echocardiogram in this subgroup. [71] A meta-analysis found DSE to be the best predictor of cardiac morbidity (relative risk [rr] =6.2), followed by DTI (rr=4.6), radionuclide ventriculography (rr =3.7), and AECG (rr =2.7). [72] Table 51-3 compares the results for several studies on DSE for risk stratification before vascular surgery.

Radionuclide Ventriculography

Radionuclide ventriculography provides an accurate assessment of left ventricular function during rest or with exercise. The test is performed by quantitative analysis of sequential count densities of gated blood-pool images. In patients undergoing lower-extremity arterial bypass or abdominal aortic resection, radionuclide ventriculography has been shown to be an independent predictor of perioperative cardiac morbidity. Pasternack et al [73] [74] found that an ejection fraction of less than 35 percent was associated with a 75 to 85 percent rate of perioperative MI, and an ejection fraction of greater than 35 percent was associated with a 19 to 20 percent rate. Other investigators, however, have not been able to reproduce these results by use of radionuclide ventriculography either at rest or with exercise. [75] [76]

In summary, all three of the most commonly used preoperative tests (DTI, AECG, and DSE) have relatively high negative predictive values. Thus, if a patient tests negative on these screening tests, it is unlikely that a morbid cardiac event will occur. None of the tests, however, has high positive predictive value, indicating that many patients with positive test results will not have a morbid event. Because the primary reason for testing before surgery is for screening purposes, these tests serve their purpose. Further risk assessment requires cardiac catheterization.

Cardiac Catheterization

The largest series on outcome in vascular surgery patients is that of Hertzer and colleagues [27] from the Cleveland Clinic. These investigators performed cardiac catheterization in 1,000 consecutive patients presenting for peripheral vascular surgery (aortic, carotid, or lower-extremity revascularization). The incidence and severity of CAD was assessed according to the following classification: (1) normal coronary arteries; (2) mild-to-moderate CAD with no lesion exceeding 70 percent stenosis; (3) advanced, compensated CAD with one or more lesions exceeding 70 percent stenosis but with adequate collateral circulation; (4) severe, correctable CAD with greater than 70 percent stenosis in one or more coronary arteries; and (5) severe inoperable CAD with greater than 70 percent stenosis in one or more coronary arteries with severe distal disease or poor ventricular function. The most remarkable findings were that only 8.5 percent of patients had normal coronary arteries and that 60 percent of patients had advanced or severe coronary lesions (>70% stenosis). [27] Even when CAD was not suspected by clinical history, more than one-third of patients had advanced or severe coronary lesions. The results are shown in Table 51-4 .

In Hertzer et al's series, the patients with severe correctable CAD were offered coronary bypass surgery, and if they consented, this surgery was performed before their peripheral vascular procedure. Patients who had normal or mild-to-moderate CAD went on to undergo vascular surgery, and those with severe inoperable disease were treated on an individual basis. Combined mortality rates

TABLE 51-4 -- Results of Coronary Angiography in 1,000 Patients With Peripheral Vascular Disease

ANGIOGRAPHIC CLASSIFICATION	CLINICAL CAD					
	NONE		*SUSPECTED*		*TOTAL*	
	NO.	%	*NO.*	%	*NO.*	%

Normal coronary arteries	64	14	21	4	85	8.5
Mild-to-moderate CAD	218	49	99	18	317	32
Advanced compensated CAD	97	22	192	34	289	29
Severe, correctable CAD	63	14	188	34	251	25
Severe, inoperable CAD	4	1	54	10	58	5.8

CAD, coronary artery disease

Data from Hertzer et al [27]

over the immediate and long-term (4.6-year follow-up) postoperative periods are shown in Table 51-5 (Table Not Available) . [77] Of the 216 patients who underwent coronary revascularization (CABG), 12 (5.5%) died after this surgery. This mortality rate is greater than the mortality rate reported for patients undergoing CABG surgery without peripheral vascular disease (1-2%), which suggests that the risks of CABG should be seriously considered as part of the preoperative evaluation of these patients. When overall early and late mortality (>5 years) are considered in Hertzer et al's series, death occurred in 12 percent, versus 26 percent of patients who underwent CABG or did not undergo CABG, respectively. [77] Although these data appear to support the beneficial effect of CABG on outcome, the mortality from CABG itself (5.5%) reduces its apparent benefits. It is important to recognize that no large-scale randomized trial has been performed to determine the impact of routine coronary angiography (with subsequent PTCA or CABG) before vascular surgery.

Prior Coronary Artery Bypass

Patients who have undergone prior coronary artery bypass who are without current symptoms of angina or heart failure appear to have a relatively low incidence of perioperative cardiac morbidity. When 12 studies were pooled to include more than 2,000 patients, the prevalence of postoperative MI was 0 to 1.2 percent versus 1.1 to 6 percent, and the mortality rate was 0.5 to 0.9 percent versus 1 to 2.4 percent in patients with and without prior bypass surgery, respectively. [12] From the registry of the Coronary Artery Surgery Study, perioperative mortality from noncardiac surgery was 0.9 percent and 2.4 percent in patients with and without previous bypass surgery, respectively. [78] Evidence suggests that survivors of successful CABG surgery have mortality rates similar to those of patients without coronary disease when undergoing noncardiac surgery (0.9 versus 0.5%, respectively). [12]

Prior Percutaneous Transluminal Coronary Angioplasty

An even more difficult question is the role of interventional cardiology in the preoperative management of the vascular surgery patient. Patients with peripheral vascular disease are often not ideal candidates for PTCA, because this procedure requires a large-diameter introducer sheath in the femoral artery, which predisposes to pseudoaneurysms

TABLE 51-5 -- Perioperative and Late Cardiac Deaths After Peripheral Vascular Reconstruction Among 846 Patients Followed Up Over 5 Years

(Not Available)

From Hertzer et al [77]

and compromised blood flow to the lower extremities. It is technically difficult to perform PTCA through the brachial artery. No randomized trials have been performed to determine the effects of PTCA on subsequent risk for cardiac morbidity in patients undergoing noncardiac surgery. In the past 3 to 5 years, atherectomy and intracoronary stents have improved both short-term and long-term results. There is evidence from published series of high-risk patients who were treated with PTCA that risk of perioperative morbidity is relatively low. In a retrospective review of 148 patients undergoing noncardiac surgery an average of 90 days after PTCA, only one patient had an MI. [79] In another series with 50 patients whose surgery was performed an average of 9 days after PTCA, there were three MIs and one death. These patients had class 3 and 4 angina before their PTCA. [80] Because many of these patients did not have peripheral vascular disease, PTCA may have been technically easier to perform than in vascular patients.

Assessment of Pulmonary Function and Risk

Respiratory complications are potentially serious in patients undergoing vascular procedures. Given the prevalence of cigarette smoking in this population, chronic obstructive pulmonary disease and chronic bronchitis are common. When clinical assessment suggests severe pulmonary compromise, pulmonary function tests are useful in evaluating and optimizing respiratory function (Ch. 24) . Preoperative blood gas determination can be used to establish a baseline for postoperative comparison. Baseline hypercapnia (partial pressure of arterial carbon dioxide >45 mm Hg) indicates a higher risk for postoperative morbidity. [81] Given proper pulmonary care, even patients with severe pulmonary insufficiency, however, may undergo surgery with acceptable morbidity and mortality. Preoperative treatment with a short course of glucocorticoids (prednisone, 40 mg/day for 2 days) is helpful for patients with significant chronic obstructive pulmonary disease or asthma. [82] Although there is limited evidence for improved pulmonary outcome with regional anesthesia, [83] patients with sig- nificant pulmonary disease may benefit from epidural anesthesia/analgesia that is maintained into the postoperative period because this technique avoids respiratory depression from systemic opiates.

Assessment of Renal Function

Underlying renal disease is common in vascular surgery patients. Hypertension itself may cause renal insufficiency or failure. Atherosclerotic disease in the abdominal aorta or renal arteries may compromise renal blood flow and renal function. Conversely, renal artery stenosis causes hypertension through renin-induced and angiotensin-induced vasoconstriction. Diabetic nephropathy is also common. Superimposed on baseline abnormalities in renal function are the angiographic dye load, which is directly nephrotoxic, [84] and the interruption in renal blood flow from aortic crossclamping. Even with infrarenal aortic cross-clamps, there can be a significant reduction in renal blood flow despite a normal systemic arterial blood pressure and cardiac output. [85] Embolic plaque can be showered into the renal arteries, especially when suprarenal aortic cross-clamps are applied and released. [86] Fluctuations in intravascular volume and cardiac output can compromise renal perfusion during the intraoperative and postoperative periods. In one series of more than 500 patients, the prevalence of acute renal failure was 7 percent after abdominal aortic reconstruction. [87]

PERIOPERATIVE MYOCARDIAL ISCHEMIA

Etiology and Prevention

Ischemic cardiac morbidity is the most common cause of perioperative (and nonperioperative) death in the United States. [12] Myocardial ischemia results from an imbalance between myocardial oxygen supply and demand, for which there are many causes during the perioperative period. [88] The determinants of supply and demand are shown in Figure 51-3 (Figure Not Available) The most detrimental changes (tachycardia, hypervolemia, and anemia) are those that simultaneously decrease oxygen supply and increase oxygen demand.

Figure 51-3 (Figure Not Available) Determinants of myocardial oxygen supply and demand that lead to myocardial ischemia. During the perioperative period, virtually every determinant is altered by factors such as fluid shifts, blood loss, pain, catecholamines, altered coagulability, and ventilatory insufficiency. *(Adapted from Beattie and Fleisher [86])*

Tachycardia increases myocardial oxygen demand by increasing myocardial work, while at the same time myocardial oxygen supply is decreased because diastole is shortened and most coronary blood flow occurs during diastole. Intravascular volume is equally important. Hypervolemia increases ventricular wall tension and thus myocardial oxygen demand. At the same time, coronary perfusion (oxygen supply) is reduced in the distended ventricle because the increased left ventricular end-diastolic pressure limits coronary flow. Anemia can also upset both sides of the supply/demand equation. [89] Decreased oxygen content decreases supply, whereas increased heart rate and cardiac output from anemia increase demand. The prevention and treatment of perioperative myocardial ischemia require careful control of these and other determinants of myocardial oxygen supply and demand as well as other perioperative physiologic changes that can precipitate ischemia.

When the entire perioperative period is considered, myocardial ischemia occurs most commonly postoperatively, and less commonly preoperatively and intraoperatively. [90] [91] The incidence of intraoperative ischemia is relatively low because anesthesia suppresses adrenergic tone, [92] and there is minute-to-minute control of the hemodynamic and other determinants of myocardial oxygen supply and demand. In the postoperative period, the patient is transferred from the operating room to the postanesthetic care unit or intensive care unit, where the ratio of physicians or nurses to patients is reduced and control of these variables is less complete. The early postoperative period is associated with pain, tachycardia, hypertension, third spacing, intravascular volume changes, and hypercoagulability. Most postoperative myocardial ischemia is silent (asymptomatic) as a result of masking by surgical pain or by opioid analgesia. [59] [93] [94] [95] The peak incidence of ischemia probably occurs on postoperative day 3, [90] which may correlate with the release of patients to the surgical wards, where they receive less attention from the medical staff. Table 51-6 summarizes five studies showing the relative incidence of preoperative, intraoperative, and postoperative myocardial ischemia.

Several clinical studies have increased our understanding of the clinical variables that precipitate myocardial ischemia. There has been a long-standing debate over whether the rate pressure product (heart rate × mean arterial blood pressure) [96] [97] or the pressure/rate quotient (mean arterial blood pressure divided by heart rate) [98] [99] is most correlated with ischemic episodes. Work by Buffington [100] supports the pressure/rate quotient, showing in a canine model that a quotient of less than 1.0 was associated with ischemia. In simpler terms, hypotension and tachycardia are a dangerous combination. In patients undergoing CABG surgery, the pressure/rate quotient was not predictive of ischemia in two different studies. [101] [102] Nonetheless, the importance of heart rate is well recognized as a determinant of myocardial ischemia in the vascular surgery patient. After vascular surgery, unlike CABG, patients leave the operating room with the same coronary disease they came in with, only to experience the stress of the postoperative period. Some vascular patients exhibit heart rate-related myocardial ischemia at "subtachycardic" heart rates. [6C] In certain high-risk patients, heart rates of
85 beats per minute consistently trigger ischemic ST segment changes (Fig. 51-4) (Figure Not Available) The primary role of the anesthesiologist is not merely to control heart rate but also to diagnose and treat the underlying cause of heart rate changes.

The optimal hematocrit value for vascular surgery patients is unknown. In the mid 1980s, the tendency was to withhold transfusion to avoid the risk of human immunodeficiency virus and hepatitis infection. In 1988, the National Institutes of Health indicated that no "threshold" hemoglobin concentration could be defined for routine transfusion. [103] The American College of Physicians then stated that hemoglobin concentrations of greater than 7.0 g/dL are well tolerated in patients without cardiovascular disease. [104] These guidelines, however, did not include recommendations for patients with CAD or risk factors for CAD. Although there are no controlled trials, there appears to be an increased incidence of myocardial ischemia and cardiac morbidity in vascular surgery patients if hemoglobin concentrations are less than 9.0 g/dL in the early postoperative period. [105] [106] This evidence, along with our understanding of the effects of anemia on myocardial oxygen supply and demand, [89] supports the practice of maintaining hemoglobin concentrations above 9.0 g/dL in the vascular patient, especially patients at significant risk for ischemic cardiac morbidity.

Monitoring for Myocardial Ischemia

There are three methods used to detect myocardial ischemia during the perioperative period: (1) surface ECG, (2) transesophageal echocardiography (TEE), and (3) pulmonary artery catheterization (Chs. 30 - 32). The sensitivity and specificity for ischemia detection, the level of training required, and the cost of these methods differ and are important

TABLE 51-6 -- Incidence of Myocardial Ischemia[a] During the Preoperative, Intraoperative, and Postoperative Periods in Vascular Surgery Patients

AUTHORS	PREOPERATIVE	INTRAOPERATIVE	POSTOPERATIVE
Pasternack et al [61]			
Aortic/lower extremity	40	38	48
Carotid	38	41	54
Ouyang et al [59]	12	21	63
McCann and Clements [443]	14	--	--
Christopherson et al [54]	20	10	40
Mangano et al [62]	20	25	41
Average	24	27	49

[a] Percent of patients with myocardial ischemia as detected by continuous Holter monitor and ST segment analysis

Figure 51-4 (Figure Not Available) Heart rate and ST segment trends the evening prior to surgery from an ambulatory ECG monitor on a patient scheduled for femoropopliteal bypass. Note the "mirror image" heart rate-related ST segment depression occurring at subtachycardic heart rates (
85 beats/ minute). *(From Frank et al, [60] with permission from Elsevier Science)*

considerations. Evidence suggests that ischemia monitoring is important during and after vascular surgery. Ischemia may lead to infarction, [33] especially when the ischemia is sustained over time (>2 hours). [107] Although no controlled clinical trials have demonstrated a reduction in perioperative morbidity with ischemia monitoring and treatment, the anesthesiologist should optimize the clinical determinants of myocardial oxygen supply and demand in an attempt to resolve the ischemic condition.

Electrocardiographic monitoring for ischemia is the least expensive method and requires the least training. Subendocardial ischemia is the most common type of ischemia in the perioperative setting and is manifested by ST segment depression on the ECG. [108] Transmural ischemia is less common and is usually accompanied by ST segment elevation in the leads facing the injury, with reciprocal ST segment depression in one or more of the other 12 leads. A variety of independent measures of ischemia, including abnormalities of myocardial perfusion, [109] regional left ventricular dysfunction, [110] and pulmonary and left ventricular pressure changes, [111] have been correlated with ST segment changes that meet the following criteria (1×1×1 rule): [112] (1) horizontal or downward sloping ST segment depression, 60 to 80 milliseconds after the J point of at least 1 mm from the isoelectric baseline, (2) duration of at least 1 minute, and (3) separation from other discrete episodes by at least 1 minute of normal baseline.

Electrocardiographic monitoring should be performed in the diagnostic mode (0.05-Hz low-frequency cutoff) rather than the monitoring mode (0.5-Hz cutoff). [112] The increased filtering in the monitoring mode can create artifactual ischemic changes as a tradeoff for decreased baseline wandering. ECG morphology should always be assessed from a printed hard copy because monitors do not accurately show ECG morphology. [113] ECG changes consistent with ischemia are difficult to detect in patients with right bundle branch blocks, left ventricular hypertrophy with a strain pattern, or atrial fibrillation. [112] Ischemia monitoring by ECG is not possible in patients with left bundle branch block or pacemaker dependency. [112] In one large study, [55] 15 percent of vascular surgery patients had ECG abnormalities that precluded ischemia monitoring. During the intraoperative period, London and colleagues [114] studied noncardiac surgery patients and concluded that although V5 was the single most sensitive lead for detecting intraoperative ischemic changes (75% of episodes were evident in this lead), the sensitivity was increased to only 80% by monitoring leads II and V5 together. With a three-lead system (leads II, V4, and V5) 96 percent of ischemic changes were detected.

Over the past decade, computerized ST segment analysis has become one of the most valuable tools for ischemia monitoring. There is, however, no computerized system that is reliable enough to use without the interpretation of a trained clinician who can differentiate true ischemic changes from artifact. Computers are often fooled by baseline ST segment depression from abnormalities such as left ventricular hypertrophy and strain patterns. In addition, these systems are not sophisticated enough to analyze morphology (slope of the ST segment), and they rely primarily on the degree of change from an isoelectric baseline. Nonetheless, the most reliable way to monitor for ischemia is to follow the trend for ST segment elevation or depression over time by use of a computer algorithm. Computerized ST segment analysis, when used properly, is one of the most significant advances in perioperative monitoring.

Two-dimensional TEE has emerged over the past decade to become one of the most sensitive monitors of cardiac function. Evidence suggests that segmental wall motion abnormalities occur earlier than ECG changes at the onset of ischemia. [115] The echocardiographic changes during

ischemia are characterized by decreased ventricular wall thickening during systole, but the clinician needs to be relatively well trained to recognize such changes. Another drawback is the significant cost of the echocardiographic equipment. Although it is possible to perform TEE in awake or sedated patients, the procedure is often not well tolerated, making this technique less desirable during regional anesthesia or during the postoperative period.

Detection of ischemia is possible by use of a pulmonary artery catheter, but this technique is a distant third choice when compared with other methods (TEE or ECG). Episodes of ischemia are manifested as an abnormal pulmonary capillary wedge pressure waveform or an absolute increase in mean pulmonary capillary wedge pressure of 10 mm Hg or greater. [116] This technique has low feasibility because ideally the balloon-tipped catheter needs to be constantly or frequently inflated to detect such changes.

HEMODYNAMIC MONITORING

The appropriate level of invasive hemodynamic monitoring (Ch. 30) for the patient undergoing vascular surgery is a controversial issue. Multiple considerations determine the need for monitoring, and it is difficult to generalize for all vascular patients. Given the frequency of coexisting disease, the potential for fluid shifts and blood loss, and the physiologic changes associated with cross-clamping and unclamping, virtually all patients undergoing major vascular surgery should be monitored with an intra-arterial catheter. This allows not only beat-to-beat blood pressure monitoring but also arterial blood sampling for diagnostic purposes. The radial artery is most commonly selected for cannulation because of its superficial location and the presence of collateral circulation. The need to verify collateral blood flow is questionable. The Allen test [117] can be used to assess collateral flow in the palmar arch, but there is evidence that ischemic injury can occur in patients with a normal Allen test result [118] and that no injury occurs in patients with an abnormal Allen test result when the radial artery is cannulated. [119] When the radial artery is difficult to cannulate, the ulnar or axillary arteries are alternative sites. The axillary artery can be cannulated by use of the Seldinger technique, but care should be taken to avoid air injection when flushing an axillary catheter because the tip may lie close to or inside the aortic arch, allowing air to enter the cerebral circulation. Whenever possible, the femoral arteries should be avoided in patients with peripheral vascular disease.

Vascular surgery patients often have a large discrepancy in arterial blood pressure between the right and left arms as a result of atherosclerotic lesions in the subclavian or axillary arteries, resulting in a falsely low pressure in the ipsilateral arm. [120] We have seen patients with systolic differences as great as 100 mm Hg between arms, and 20 to 40 mm Hg differences are common. Patients scheduled for carotid surgery have the greatest incidence of right/left arm blood pressure differences. To avoid "pseudohypotension," the blood pressure should be verified in both arms, and the arm with the higher pressure should be monitored during surgery. It is possible that both arms would have falsely low blood pressures as a result of bilateral disease. In this case, the femoral artery may be the best option for monitoring.

There is significant controversy over the utility of central venous and pulmonary artery catheters for monitoring patients during vascular surgery. The surgical procedure determines the degree of fluid shifting and blood loss and thus the usefulness of these monitors. The patient's underlying cardiac condition also needs to be considered. The indications for central venous pressure and pulmonary artery catheter monitoring are discussed in further detail in the subsequent sections.

ABDOMINAL AORTIC RECONSTRUCTION

Anesthesia for abdominal aortic reconstruction requires an understanding of the pathophysiology, an extensive knowledge of the surgical procedure, an ability to interpret sophisticated hemodynamic data, and a skillful pharmacologic control and manipulation of hemodynamics. Preoperative and intraoperative communication with the surgical team is essential. All operative procedures on the abdominal aorta and its major branches require large incisions and extensive dissection, clamping and unclamping of the aorta and/or its major branches, varying duration of organ ischemia, significant fluid shifts and temperature fluctuations, and activation of the neuroendocrine stress response. The major objectives of surgical treatment are to relieve symptoms, reduce the frequency of associated complications, and, in the case of aortic aneurysm, prevent rupture.

Natural History and Surgical Mortality

Abdominal Aortic Aneurysm

Abdominal aortic aneurysm is a multifactorial disease associated with aortic aging and atherosclerosis. [121] Although no unified concept of pathogenesis exists, there are genetic, biochemical, metabolic, mechanical, and hemodynamic factors that may contribute to the development of abdominal aortic aneurysmal disease. [122] [123] Adventitial elastin degradation (elastolysis), a hallmark of abdominal aortic aneurysm formation, may be the primary event. [124] The incidence of abdominal aortic aneurysms appears to be rising. [125] Concomitant aortoiliac occlusive disease is present in approximately 20 to 25 percent of patients with abdominal aortic aneurysms. [126] Approximately 5 percent of patients undergoing abdominal aortic resection have inflammatory aneurysms. [126] Rare causes of abdominal aortic aneurysm disease include trauma, mycotic infection, syphilis, and Marfan syndrome.

The natural history of abdominal aortic aneurysmal disease is one of progressive enlargement and ultimate rupture and death. In 1950, Estes [127] published a classic study of the natural history of abdominal aortic aneurysms in 102 patients. Only 19 percent of these patients survived 5 years, and rupture was the cause of death in 63 percent. The first successful abdominal aortic aneurysm resection and graft replacement (homograft implantation) was accomplished by Dubost and colleagues [128] in 1951. In 1966, Szilagyi et al [129] confirmed the principle of elective graft replacement to prevent

the eventual rupture of abdominal aortic aneurysm and to prolong life. Perioperative mortality from elective infrarenal aortic aneurysm resection has progressively declined from 18 to 20 percent during the 1950s, to 6 to 8 percent in the mid-1960s, to 5 to 6 percent in the early 1970s, to 2 to 4 percent in the 1980s, when it plateaued. [130] A publication of 1,000 consecutive elective infrarenal aneurysms over a 15-year period reported a perioperative mortality rate of 2.4 percent. [131] For ruptured abdominal aortic aneurysms, perioperative mortality has not changed significantly and remains nearly 50 percent [132] [133] [134] with few exceptions. [135] If one takes into consideration patients with rupture who die before reaching a hospital, the overall mortality rate after rupture may very well exceed 90 percent. [134]

The diameter and rate of expansion of abdominal aortic aneurysms are currently the best predictors of the risk of rupture. [136] [137] There is near-uniform agreement that elective repair should be undertaken in all abdominal aortic aneurysms with a diameter of 6 cm or greater. [129] Although some controversy exists regarding elective abdominal aortic aneurysm repair when diameter is in the 5.0- to 5.9-cm range, [138] most agree that the risk of rupture for a 5-cm aneurysm (per year) is equal to or greater than perioperative mortality, and thus surgical repair is indicated. The natural history of abdominal aortic aneurysms 4 to 5 cm in diameter is not well defined, and significant controversy exists regarding surgical repair. [139] [140] [141] However, surgical repair is recommended if such aneurysms become symptomatic or expand more than 0.5 cm in a 6-month period. Aneurysms less than 4 cm in diameter are felt to be relatively benign in terms of rupture and expansion. [142] Late survival after repair of nonruptured abdominal aortic aneurysms is 92 percent at 1 year and 67 percent at 5 years. [134]

Aortoiliac Occlusive Disease

As noted earlier, the infrarenal aorta and the iliac arteries are two of the most common sites of chronic atherosclerosis. [143] Because of the diffuse and progressive nature of aortoiliac atherosclerosis, plaque enlargement may reduce blood flow to the lower extremities below a critical level, resulting in symptoms of ischemia. Unlike patients with aortic aneurysmal disease, patients undergo surgery for aortoiliac occlusive disease only if they are symptomatic. Surgical intervention is indicated for disabling intermittent claudication and limb-threatening ischemia. Intervention is directed toward restoring peripheral pulsatile circulation to relieve claudication and toward preventing amputation. Patients with localized aortoiliac occlusive disease typically present with claudication because collateral circulation adequate to prevent critical lower-extremity ischemia usually exists. [144] Most patients undergoing aortoiliac reconstruction for limb-threatening ischemia have multilevel occlusive disease with infrainguinal involvement, [145] and the indication for surgery is more often limb salvage rather than relief of claudication. [144] [146] Perioperative mortality is lower for patients undergoing aortoiliac reconstruction than for those undergoing abdominal aortic surgery. [146] [147]

Therapeutic options for managing aortoiliac occlusive disease include anatomic or direct reconstruction (aortobifemoral bypass), extra-anatomic or indirect bypass grafts (axillofemoral bypass), and catheter-based endoluminal techniques (percutaneous transluminal angioplasty with or without stent insertion). Aortobifemoral bypass is viewed as the gold standard in treating aortoiliac occlusive disease. [147] Extra-anatomic bypass grafts are usually reserved for specific indications, usually involving infection, failure of previous reconstruction, or prohibitive risk patients. Reduced long-term patency and inferior functional results are frequently the tradeoff for lower perioperative morbidity and mortality. [148] [149] Catheter-based endoluminal techniques, such as percutaneous transluminal angioplasty, are used for relatively localized disease and may be reasonable alternatives to aortobifemoral bypass in 10 to 15 percent of patients with aortoiliac occlusive disease. [147]

Renal and Visceral Arterial Insufficiency

Atherosclerosis is the most common cause of renal artery stenosis. Occlusive lesions are located almost exclusively in the proximal segment and orifice of the renal artery and are usually an extension of aortic atherosclerosis. Fibromuscular dysplasia involving the renal arteries occurs primarily in the distal two-thirds. Hemodynamically significant renal artery stenosis may cause hypertension via activation of the renin-angiotension system, and bilateral involvement may result in renal failure. Indications for intervention include control of hypertension and salvage of renal function. Operative interventions include aortorenal bypass, extra-anatomic bypass (hepatorenal or splenorenal bypass), or transaortic endarterectomy. Percutaneous transluminal angioplasty of the renal artery is used as the first-line treatment in selected patients. Suprarenal or supraceliac aortic cross-clamping is frequently required for operative interventions. Patients with renovascular hypertension frequently have poorly controlled hypertension despite maximal medical therapy.

Stenosis at the origin of the celiac and mesenteric arteries occurs from extension of aortic atherosclerosis. The inferior mesenteric artery is by far the most commonly involved, followed by the superior mesenteric artery and the celiac artery. Occlusion of a single vessel rarely causes ischemic symptoms because of the extensive nature of visceral collateralization. However, occlusion or significant stenosis of any two vessels may sufficiently compromise collateral flow and give rise to chronic visceral ischemia. Operative repair of visceral artery stenosis is reserved for symptomatic patients. Operative interventions include transaortic endarterectomy and/or

bypass grafts, which frequently require supraceliac aortic cross-clamping. For reasons that are unclear, this condition affects women about four times as often as men. [133] Mortality rates for such procedures range from 7 to 18 percent. Acute mesenteric artery occlusion can be caused by embolus or, less commonly, thrombosis. To avoid the extremely high mortality associated with this condition, diagnosis and surgical intervention must occur before gangrene of the bowel develops.

Aortic Cross-Clamping

The pathophysiology of aortic cross-clamping and unclamping is complex and depends on many factors, including

the level of cross-clamp, the extent of CAD and myocardial function, the degree of periaortic collateralization, the blood volume and distribution, the activation of the sympathetic nervous system, and the anesthetic agents and techniques. Most abdominal aortic reconstructions require clamping at the infrarenal level. However, clamping at the suprarenal and supraceliac levels is required for suprarenal aneurysms and renal/visceral reconstructions and is frequently necessary for juxtarenal and inflammatory aneur-ysms and aortoiliac occlusive disease with proximal extension. These higher levels of aortic occlusion have a significant impact on the cardiovascular system as well as on other vital organs rendered ischemic or hypoperfused. Ischemic complications may result in renal failure, hepatic ischemia and coagulopathy, bowel infarction, and paraplegia.

Hemodynamic and Metabolic Changes

The hemodynamic changes associated with aortic cross-clamping and unclamping are summarized in Tables 51-7 and 51-8 . The systemic cardiovascular consequences of aortic cross-clamping can be dramatic, depending primarily on the level at which the cross-clamp is applied. Arterial hypertension

TABLE 51-7 -- Physiologic Changes and Therapeutic Interventions With Aortic Cross-Clamping [a]

HEMODYNAMIC CHANGES
Arterial blood pressure
Segmental wall motion abnormalities
Left ventricular wall tension
Cardiac output
Renal blood flow
Ejection fraction
Pulmonary artery occlusion pressure
Central venous pressure
Coronary blood flow
METABOLIC CHANGES
Total body oxygen consumption
Total body carbon dioxide production
Mixed venous oxygen saturation
Total body oxygen extraction
Epinephrine and norepinephrine
Respiratory alkalosis [b]
Metabolic acidosis
THERAPEUTIC INTERVENTIONS
Afterload reduction
Sodium nitroprusside
Inhalational anesthetics
Amrinone
Preload reduction
Nitroglycerine
Shunts and left heart bypass
Renal protection
Mannitol
Low-dose dopamine
Fluid administration
Other
Minute ventilation
Sodium bicarbonate

[a] These changes are of greater significance with more proximal cross-clamping.
[b] When ventilatory settings are unchanged from preclamp values

TABLE 51-8 -- Physiologic Changes and Therapeutic Interventions With Aortic Unclamping [a]

HEMODYNAMIC CHANGES
Myocardial contractility
Arterial blood pressure
Central venous pressure
Venous return
Cardiac output
METABOLIC CHANGES
Total body oxygen consumption
Lactate
Mixed venous oxygen saturation
Prostaglandins
Activated complement
Myocardial-depressant factor(s)
Metabolic acidosis
THERAPEUTIC INTERVENTIONS
Inhalational anesthetics
Vasodilators
Fluid administration
Vasoconstrictor drugs
Reapply cross-clamp for severe hypotension

[a] These changes are of greater significance with longer duration of cross-clamp and with more proximal cross-clamping.

is the most consistent component of the hemodynamic response to aortic cross-clamping at any level. Cross-clamping of the aorta at or above the diaphragm can result in profound increases in arterial blood pressure [150] [151] unless diverting circulatory support and/or intravenous vasodilators are used. [150] [152] This increase in arterial blood pressure is most likely due to the sudden increase in impedance to aortic blood flow and the resultant increase in systolic ventricular wall tension or afterload. However, factors such as myocardial contractility, preload, blood volume, and sympathetic nervous system activation may also be important. Changes in cardiac output and filling pressures with aortic cross-clamping are not consistent and require an integrated approach in an attempt to understand the direction and magnitude of such changes (Fig. 51-5) (Figure Not Available) .

Cross-clamping of the proximal descending thoracic aorta increases mean arterial, central venous, mean pulmonary arterial, and pulmonary capillary wedge pressures by 35 percent, 56 percent, 43 percent, and 90 percent, respectively, and decreases cardiac index by 29 percent. [150] Heart rate and left ventricular stroke work are not significantly changed. Supraceliac aortic cross-clamping increases mean arterial pressure by 54 percent and pulmonary capillary wedge pressure by 38 percent. [151] Ejection fraction, as determined by two-dimensional echocardiography, decreases by 38 percent. Despite normalization of systemic and pulmonary capillary wedge pressures, supraceliac aortic cross-clamping causes significant increases in left ventricular end-systolic and end-diastolic areas (69% and 28%, respectively), as well as wall motion abnormalities indicative of ischemia in 11 of 12 patients (Table 51-9) (Table Not Available) . Aortic cross-clamping at the suprarenal level causes similar but smaller cardiovascular changes, and clamping at the infrarenal level is associated with only minimal changes and no wall motion abnormalities.

The marked increases in pulmonary capillary wedge pressure with high aortic cross-clamping have been attributed to

Figure 51-5 (Figure Not Available) Systemic hemodynamic response to aortic cross-clamping. *Preload does not necessarily increase with infrarenal clamping. Depending on splanchnic vascular tone, blood volume can be shifted into the splanchnic circulation and preload will not increase. AoX, aortic cross-clamping; Ao, aortic; R art, arterial resistance. *(From Gelman [176])*

blood volume redistribution and increased afterload. A substantial body of evidence supports the hypothesis of blood volume redistribution during thoracic aortic cross-clamping. The splanchnic circulation, an important source of functional blood volume reserve, is central to this hypothesis. Primarily because of a lower splanchnic venous capacitance, blood volume is redistributed from vascular beds distal to the clamp to the vascular beds proximal to the clamp (see Fig. 51-5 (Figure Not Available)). Cross-clamping the aorta above the splanchnic system results in passive recoil of the venous circulation distal to the clamp. Thoracic aortic cross-clamping results in significant increases in plasma epinephrine and norepinephrine, [153] [154] which may enhance venomotor tone both above and below the clamp. Several animal studies that support the blood redistribution hypothesis merit mention. Cross-clamping the thoracic aorta in dogs resulted in marked increases in mean arterial and end-diastolic left ventricular pressures (84% and 188%, respectively) and no significant change in stroke volume. [155]

In this same experimental model, simultaneous cross-clamping of the thoracic aorta and the inferior vena cava resulted in no significant change in preload or mean arterial pressure (Fig. 51-6) (Figure Not Available) . Stroke volume was reduced by 74 percent. By transfusing blood during this period of simultaneous clamping, the authors reproduced the hemodynamic effect of thoracic aortic cross-clamping alone. This study also demonstrated that thoracic aortic cross-clamping is associated with a significant and dramatic increase (155%) in blood flow above the level of the clamp, whereas no change occurred with simultaneous aortic and inferior vena cava clamping. In another animal model, the proximal aortic hypertension and increased central venous pressure occurring after thoracic aortic cross-clamping were reversed by phlebotomy. [156] Lastly, aortic cross-clamping at the thoracic and suprarenal levels both resulted in proximal aortic hypertension, but only occlusion at the thoracic level increased central venous pressure. [157] In addition, thoracic aortic occlusion increased blood volume in organs and tissues proximal to the clamp, whereas no such increase occurred with suprarenal aortic cross-clamping. These experimental data strongly support the hypothesis of blood volume redistribution during aortic cross-clamping and help to explain the marked differences in hemodynamic responses observed after aortic cross-clamping at different levels. [151]

Afterload-dependent increases in preload also occur with aortic cross-clamping, usually in the setting of impaired myocardial contractility and reduced coronary

reserve. The impaired left ventricle may respond to increased afterload with an increase in end-systolic volume and a concomitant reduction in stroke volume (afterload mismatch). The reduction in stroke volume may be due to limited preload reserve, myocardial ischemia, and/or inability of the heart to generate a pressure-induced increase in contractility (the Anrep effect). If right ventricular function remains normal, the preclamp right ventricular stroke volume is added to the elevated left ventricular end-systolic volume, resulting in left ventricular dilation and elevated end-diastolic volume. If corrective measures are not undertaken, overt left ventricular overload may result, with severe peripheral organ dysfunction and pulmonary edema.

Most clinical studies indicate that cardiac output decreases with thoracic aortic cross-clamping, whereas most animal studies show no significant change. The normal heart can withstand large increases in afterload without significant ventricular distention or dysfunction. Although impaired myocardial contractility and reduced coronary reserve are rare in animal experiments, such disorders are frequent in the elderly population undergoing aortic reconstruction. As

TABLE 51-9 -- Percent Change in Cardiovascular Variables on Initiation of Aortic Occlusion

(Not Available)

From Roizen et al [151]

Figure 51-6 (Figure Not Available) Schematic drawing of the circulation. Stippled lines--compliant regions of upper and lower part of the body and end-diastolic volumes of the left ventricle in control state, before occlusion of aorta alone (middle panel), and combined occlusion of aorta and IVC (right panel). IVC, inferior vena cava; SVC, superior vena cava; LV, left ventricle; Pvs and Pvi, pressure in compliant regions of the upper and lower body respectively; shunt, physiologic shunt. *(From Stokland et al* [155] *)*

discussed earlier, the increase in proximal aortic pressure seen with thoracic and supraceliac cross-clamping [150] [151] may increase left ventricular wall stress (afterload), with resultant acute deterioration in left ventricular function and/or myocardial ischemia. Impaired subendocardial perfusion caused by high intramyocardial pressure may be the cause of wall motion abnormalities and changes in ejection fraction. Reflex mechanisms causing immediate feedback inhibition may also explain the reduction in cardiac output with aortic cross-clamping. For example, baroreceptor activation resulting from increased aortic pressure should depress heart rate, contractility, and vascular tone.

The metabolic effects of cross-clamping and unclamping are summarized in Tables 51-7 and 51-8 . Cross-clamping of the thoracic aorta decreases total body oxygen consumption by approximately 50 percent. [158] [159] For reasons that are unclear, oxygen consumption decreases in the tissues above the clamp. [158] In clinical studies, increased mixed venous oxygen saturation occurs with aortic cross-clamping above the celiac axis. [160] [161] This increase in mixed venous oxygen saturation may be explained by a reduction in oxygen consumption that exceeds the reduction in cardiac output, thus decreasing total body oxygen extraction. [161] Central hypervolemia [155] and/or increased arteriovenous shunting [162] in the tissues proximal to the aortic clamp may play a role in reducing total body oxygen extraction.

Arterial blood pressure, blood flow, and oxygen consumption distal to a thoracic aortic cross-clamp decrease by 78 to 88 percent, [154] [163] [164] 79 to 88 percent, [155] [158] and 62 percent, [158] respectively, from baseline values before clamping. Blood flow through tissues and organs below the level of aortic occlusion is dependent on the perfusion pressure and is independent of cardiac output. [163] Administration of sodium nitroprusside in order to maintain proximal aortic pressure above the cross-clamp at preclamp levels has been shown to further reduce arterial pressure distal to the clamp by 53 percent. [163] As is discussed later in the chapter, these data may have significant implications regarding vital organ protection during aortic cross-clamping.

The cardiovascular response to infrarenal aortic cross-clamping is less significant than with high aortic cross-clamping (see Table 51-9 (Table Not Available)). Although several clinical reports have noted no significant hemodynamic response to infrarenal cross-clamping, [165] [166] the hemodynamic response generally consists of increases in arterial pressure (7-10%) and systemic vascular resistance (20-32%) with no significant change in heart rate. [167] [168] [169] Cardiac output is most consistently decreased by 9 to 33 percent. [166] [167] [169] [170] Reported changes in ventricular filling pressures have been inconsistent. [151] [165] [166] [167] [168] [169] [170] [171] Blood volume redistribution may affect preload with infrarenal aortic cross-clamping (see Fig. 51-5 (Figure Not Available)). In this situation, blood volume below the clamp shifts to the compliant venous segments of the splanchnic circulation above the clamp, dampening the expected increase in preload. Preload changes with infrarenal aortic crossclamping may also be dependent on the status of the coronary circulation. [167] [171] An early report found that patients with severe ischemic heart disease responded to infrarenal aortic cross-clamping with significantly increased central venous (35%) and pulmonary capillary (50%) pressures, whereas patients without CAD had decreased filling pressures. [167] Echocardiographically detected segmental wall

motion abnormalities occur in up to 30 percent of patients during infrarenal aortic reconstruction, [172] with 66 percent occurring at the time of aortic cross-clamping. [172] [173] Clinical studies imply that patients with aortoiliac occlusive disease have less hemodynamic response to infrarenal aortic cross-clamping than patients with abdominal aortic aneurysmal disease, [169] [174] perhaps as a result of more extensive periaortic collateral vascularization. [175]

Renal Function and Protection

Acute renal failure occurs in approximately 3 percent of patients undergoing elective infrarenal aortic reconstruction, and mortality resulting from postoperative acute renal failure is greater than 40 percent. [176] Thus, preservation of renal function is of significant importance during aortic reconstructive surgery. Adequacy of renal perfusion cannot be assumed by urine output, because intraoperative urine output does not predict postoperative renal function. [177] Procedures requiring aortic cross-clamping above the renal arteries dramatically reduce renal blood flow. Experimental studies report an 83 to 90 percent reduction in renal blood flow during thoracic aortic cross-clamping. [163] [178] Infrarenal aortic cross-clamping in humans is associated with a 75 percent increase in renal vascular resistance, a 38 percent decrease in renal blood flow, and a redistribution of intrarenal blood flow toward the renal cortex. [166] These rather profound alterations in renal hemodynamics occurred despite no significant change in systemic hemodynamics, and they persisted after unclamping. The sustained deterioration in renal perfusion and function during and after infrarenal aortic cross-clamping has been attributed to renal vasoconstriction, but the pathophysiology remains unknown. [85] [166] Renal sympathetic blockade with epidural anesthesia to a T6 level does not prevent or modify the severe impairment of renal perfusion and function that occurs during and after infrarenal aortic cross-clamping. [85] Although plasma renin activity is increased during aortic cross-clamping, [179] pretreatment with converting enzyme inhibitors before infrarenal aortic cross-clamping does not attenuate the decreased renal blood flow and glomerular filtration rate. Other mediators, such as plasma endothelin, myoglobin, and prostaglandins, may contribute to the decreased renal perfusion and function after aortic cross-clamping.

Acute tubular necrosis accounts for nearly all renal dysfunction and failure after aortic reconstruction. Intravascular volume depletion, embolization of atherosclerotic debris to the kidneys, and surgical trauma to the renal arteries all contribute to renal dysfunction. Mannitol, loop diuretics, and dopamine are used clinically in an attempt to preserve renal function during aortic surgery. Significant controversy exists regarding the use of these agents as well as the mechanisms by which they may offer a protective effect. Despite studies demonstrating little or no benefit, [180] [181] [182] many clinicians administer these drugs. The use of mannitol (12.5 g/70 kg) to induce an osmotic diuresis before aortic crossclamping is ubiquitous in clinical practice. Mannitol improves renal cortical blood flow during infrarenal aortic cross-clamping. [183] In addition, mannitol can reduce ischemia-induced renal vascular endothelial cell edema and vascular congestion. [184] Other mechanisms by which mannitol may be beneficial include acting as a scavenger of free radicals, decreasing renin secretion, and increasing renal prostaglandin synthesis. [185] Loop diuretics and low-dose dopamine (1-3 mug/kg/min) have been advocated to protect the kidneys from aortic cross-clamp-induced injury by increasing renal blood flow and urine output intraoperatively. Some clinicians advocate the routine use of these agents for patients with preoperative renal insufficiency and for procedures requiring suprarenal aortic cross-clamping. Intraoperative use of these agents requires increased surveillance of intravascular volume and electrolytes during the postoperative period. Therapy with these agents could actually be harmful because of hypovolemia and resultant renal hypoperfusion. In addition, dopamine's positive inotropic and chronotropic activity may cause tachycardia and may increase myocardial oxygen consumption in patients with limited coronary reserve.

Most clinical studies suggest that optimization of systemic hemodynamics, including maintenance of intravascular volume, is the most effective means of renal protection during and after aortic cross-clamping. [186] [187] [188] [189] In providing such therapy, it is equally important to avoid overhydration, which may lead to inappropriate increases in preload and/or pulmonary edema in patients with decreased myocardial reserve. The degree of preoperative renal insufficiency, the extent of aortic reconstruction, the duration of cross-clamping, and the severity of juxtarenal atherosclerosis are important factors that may contribute to the development of renal failure.

Therapeutic Strategies

Patients with preexisting impaired ventricular function and reduced coronary reserve are most vulnerable to the stresses imposed on the cardiovascular system by aortic cross-clamping. Rational therapeutic strategies to prevent the deleterious effect of aortic cross-clamping primarily include measures to reduce afterload and normalize preload. Coronary vasodilators, positive and negative inotropes, and controlled volume depletion (phlebotomy) may be utilized selectively.

Patients with impaired ventricular function requiring supraceliac aortic cross-clamping are the most challenging. Myocardial ischemia, reflecting an unfavorable balance between myocardial oxygen supply and demand, may result from the hemodynamic consequences of aortic crossclamping. Controlled supraceliac aortic cross-clamping is important to avoid abrupt and extreme stresses on the heart. Afterload reduction, most commonly accomplished by use of sodium nitroprusside (predominantly an arteriolar dilator), is necessary to "unload" the heart and reduce ventricular wall tension. In a large series of patients requiring cross-clamping of the descending thoracic aorta, stable left ventricular function was maintained during cross-clamping with sodium nitroprusside. [152] The authors also concluded that sodium nitroprusside allowed adequate volume loading before unclamping, which resulted in stable unclamping hemodynamics. Normalization of preload involves careful fluid titration and/or vasodilator administration. Infusion of nitroglycerin during abdominal aortic surgery has been shown to maintain ventricular function during the cross-clamp period. [190]

During thoracic aortic cross-clamping, isoflurane can provide hemodynamics comparable to those provided by sodium nitroprusside. [159] Amrinone provides hemodynamic control equivalent to that of sodium nitroprusside during abdominal aortic surgery. [191] Blood flow below the clamp, which is pressure dependent, [163] decreases during therapy with vasodilators. [158] [163] Vital organs and tissues distal to the clamp are thus exposed to reduced perfusion pressure and blood flow. In patients without evidence of left ventricular decompensation or myocardial ischemia during supraceliac aortic cross-clamping, a proximal aortic mean arterial pressure of up to 120 mm Hg is acceptable. Although infrequent, maintenance of adequate cardiac output may require active intervention with inotropic agents. In general, anesthetic agents that depress myocardial function are avoided during aortic procedures.

Aortic Unclamping

The hemodynamic and metabolic effects of unclamping are listed in Table 51-8 . The hemodynamic response to unclamping depends on the level of aortic occlusion, the total occlusion time, the use of diverting support, and the intravascular volume. Hypotension, the most consistent hemodynamic response to aortic unclamping, can be profound after removal of a supraceliac cross-clamp (Fig. 51-7) (Figure Not Available) . Reactive hyperemia distal to the clamp and the resultant relative central hypovolemia are the dominant mechanisms of the hypotension. Washout of vasoactive and cardiodepressant mediators from ischemic tissues, as well as humoral factors, may also contribute to the hemodynamic responses after unclamping the aorta. These humoral factors and mediators, which may also play a role in organ dysfunction after aortic occlusion, include lactic acid, renin-angiotensin, oxygen free-radicals, prostaglandins, neutrophils, activated complement, cytokines, and myocardial-depressant factors. [176]

The avoidance of significant hypotension with unclamping requires communication with the surgical team, awareness of the technical aspect of the surgical procedure, and appropriate administration of fluids and vasoactive agents. It is essential that preoperative fluid deficits, intraoperative maintenance requirements, and replacement of blood loss be accomplished before unclamping. Vasodilators, if utilized, should be gradually reduced and/or discontinued before unclamping. Potent inhalational agents should be decreased. Moderate intravascular volume loading (approximately 500 mL) during the immediate prerelease period is indicated for infrarenal unclamping. [165] [192] More aggressive volume loading is required in the period immediately preceding supraceliac unclamping. Volume loading in an attempt to maintain an elevated central venous or pulmonary capillary wedge pressure during the cross-clamp period is not indicated and may result in significant overtransfusion of fluids and blood products. Gradual release of the aortic clamp and reapplication or digital compression if significant hypotension results are important measures in maintaining hemodynamic stability during unclamping. Although vasopressors are rarely required after release of the infrarenal clamp, they are frequently required after removal of

Figure 51-7 (Figure Not Available) Systemic hemodynamic response to aortic unclamping. AoX, aortic cross-clamping; Cven, venous capacitance; R art, arterial resistance; Rpv, pulmonary vascular resistance. *(From Gelman [176])*

supraceliac clamps. Caution must be observed when vasopressor support is utilized because profound proximal hypertension may occur if reapplication of the cross-clamp is required above the celiac axis. In addition, hypertension should be avoided to prevent damage to, or bleeding from, the vascular anastomoses.

Anesthetic Management

Intraoperative Monitoring

The potential for significant and rapid blood loss cannot be underestimated. We most commonly utilize one 8.5 French internal jugular catheter and one or two large-bore peripheral catheters. A hemostatic valve with a side port is placed on the 8.5 French catheter to accept either a central venous or a pulmonary artery catheter. Placement of arterial catheters should be routine for all patients undergoing abdominal aortic reconstruction. As with other vascular procedures, the radial artery is most commonly selected for cannulation because of its superficial location, easy accessibility, and low complication rate. A noninvasive blood pressure cuff should be placed on the arm contralateral to the arterial catheter in the event of catheter malfunction.

Placement of central venous catheters is routine for all aortic procedures. Such catheters allow central venous pressure monitoring and administration of drugs into the central circulation. The routine, nonselective use of pulmonary artery catheter monitoring is not recommended for all patients undergoing infrarenal abdominal aortic reconstruction. For these procedures, pulmonary artery catheters should be considered for patients with significant left ventricular dysfunction (ejection fraction <30 percent), history of congestive heart failure, significant renal impairment (preoperative creatinine >2.0 mg/dL), or cor pulmonale. In patients with good left ventricular and pulmonary function, central venous pressure correlates well with left ventricular filling pressures. [193] A pulmonary artery catheter should be inserted for all patients requiring suprarenal aortic cross-clamping. The invasive monitoring catheters can be placed before or after the induction of anesthesia. The advantage of preinduction catheter placement is assessment of the awake ("baseline") cardiovascular status, which allows correction of severe abnormalities in cardiac filling and function before induction.

Two-dimensional TEE has been used intraoperatively to assess global ventricular function, guide fluid therapy, and monitor for myocardial ischemia. Continuous monitoring of ventricular function is commonly obtained from a single short-axis view at the level of the midpapillary muscle. Using this same view, visualization of the left ventricle at enddiastole allows rapid assessment of ventricular filling (preload). Ejection fraction area can be calculated by use of left ventricular end-diastolic and end-systolic areas. In patients undergoing abdominal aortic reconstruction, echocardiographic short-axis left ventricular end-diastolic area, end-systolic area, and ejection fraction area correlate closely with changes in corresponding left ventricular volumes and ejection fraction obtained by radionuclide angiography. [194] [195] Patients requiring supraceliac aortic cross-clamping have significant increases in end-diastolic area and significant decreases in ejection fraction by echocardiography that are not completely normalized with vasodilators and frequently are not detected by pulmonary artery catheter monitoring. [151]

Transesophageal echocardiography can also reveal abnormalities of left ventricular wall motion and wall thickening. The relationship between these abnormalities and coronary perfusion has been established experimentally [196] [197] and clinically, [198] [199] and such abnormalities may precede ECG evidence of ischemia. [115] The short-axis view at the level of the midpapillary muscles allows assessment of all three major coronary distributions. TEE-detected segmental wall motion abnormalities may occur in up to 37 percent of patients during infrarenal aortic reconstruction [200] and in more than 90 percent of patients requiring supraceliac aortic cross-clamping. [151] [172] The natural history of echocardiographic segmental wall motion abnormalities was studied in 156 patients at risk for cardiac morbidity undergoing noncardiac surgery. [200] The 24 patients undergoing aortic surgery had the highest incidence of new segmental wall motion abnormalities (38%). Surprisingly, the incidence of new segmental wall motion abnormalities did not differ for patients with known CAD and those with cardiac risks factors only. Ischemic episodes detected by TEE correlated poorly with postoperative cardiac complications. The authors also reported a discordant relation between new segmental wall

motion abnormalities and ECG ischemic changes. In a subsequent report, a subset of 285 patients who were at high risk for cardiac complications and were undergoing noncardiac surgery were studied with continuous intraoperative use of two-lead ECG, 12-lead ECG, and TEE for the detection of ischemia. [201] A lack of concordance was found between the three different ischemia monitors. When compared with preoperative clinical data and intraoperative monitoring in which two-lead ECG was used, routine monitoring for myocardial ischemia with TEE or 12-lead ECG during noncardiac surgery had little incremental clinical value in identifying patients at high risk for perioperative ischemic outcomes. Thus, available data are insufficient to define the sensitivity and specificity of segmental wall motion abnormalities as a marker for myocardial ischemia or as a predictor of perioperative ischemic outcomes.

The optimal intraoperative monitoring techniques for patients undergoing abdominal aortic reconstruction have not been established. Existing clinical studies offer insufficient data to conclusively answer the question of whether pulmonary artery catheter or TEE monitoring improves outcome. The clinical usefulness of any monitoring technique ultimately depends on patient selection, accurate interpretation of data, and appropriate therapeutic intervention.

Autotransfusion during aortic surgery reduces exposure to allogeneic blood products and the associated risks of transfusion-related complications (Chs. 46 and 47). However, the equipment is expensive and requires significant training and expertise. Although there are no randomized prospective trials, one study showed a 25 to 57 percent reduction in the number of allogeneic blood products given. [202] The routine use of autotransfusion (Cell Saver, Haemonetics, Braintree, MA), however, may not be costeffective ($250-$350 per case), and thus it should be reserved for a select group of patients with high expected blood loss. [203]

Anesthetic Drugs and Techniques

A variety of anesthetic techniques and drugs, including general anesthesia, regional (epidural) anesthesia, and combined techniques, have been used successfully for abdominal aortic reconstruction. Combined techniques most commonly employ a lumbar or low thoracic epidural catheter in addition to a "light" general anesthetic. Local anesthetics, opioids, or more commonly, a combination of the two, may be administered by bolus or by continuous epidural infusion. Some evidence suggests that maintenance of vital organ perfusion and function by the provision of stable perioperative hemodynamics is more important to overall outcome than the choice of anesthetic agent or technique. Therefore, the specific anesthetic technique for patients undergoing abdominal aortic reconstruction is important insofar as it allows rapid and precise control of hemodynamic parameters. Given the high incidence of cardiac morbidity and mortality in patients undergoing aortic reconstruction, special emphasis must be placed on factors that influence ventricular work and myocardial perfusion. In general, a balanced anesthetic using relatively short-acting agents maximizes management flexibility, which is most desirable in this patient population.

Induction of general anesthesia should proceed in a controlled fashion such that stable hemodynamics are maintained during loss of consciousness, laryngoscopy and intubation, and the immediate postinduction period. A variety of intravenous hypnotic agents (thiopental, etomidate, propofol) are suitable. The addition of a short-acting, potent opioid, such as fentanyl (3 to 8 mug/kg) usually provides stable hemodynamics during and after induction. Halogenated agents may be administered in low concentration before intubation during assisted ventilation as an adjunct to blunt the hyperdynamic response to laryngoscopy and intubation. Esmolol (10-25 mg), sodium nitroprusside (5-25 mug), nitroglycerin (50-100 mug), and phenylephrine (50-100 mug) should be available for bolus administration during induction if needed to maintain appropriate hemodynamics.

Anesthetic maintenance may be accomplished with a combination of a potent opioid (fentanyl or sufentanil) and an inhaled anesthetic (sevoflurane, desflurane, or isoflurane). Patients with severe left ventricular dysfunction may benefit from a pure opioid technique, but a balanced anesthetic technique allows the clinician to take advantage of the most desirable characteristics of potent opioids and inhalational agents while minimizing their undesirable side effects. We typically use low-dose isoflurane in 50 percent nitrous oxide and 20 to 25 mug/kg of fentanyl. Approximately 50 percent of the opioid dose is administered during induction and before skin incision. When epidural local anesthetics are used, we employ the same balanced technique and reduce the fentanyl dose to 8 to 10 mug/kg.

Nitrous oxide can be used to supplement either an opioid or an inhalational-based anesthetic. In general, nitrous oxide has a tendency to decrease cardiac output and arterial pressure while increasing systemic vascular resistance. One report indicated that in patients undergoing abdominal aortic surgery, nitrous oxide increased the need for vasodilator therapy to treat increases in pulmonary capillary wedge pressure and myocardial ischemia. [204] We typically use 50 percent nitrous oxide as part of a balanced anesthetic technique, particularly when extubation is planned at the termination of the procedure.

Various regional anesthetic and analgesic techniques have been used effectively during and after aortic reconstruction. An overview of the advantages and limitations of regional techniques for vascular surgery is included in the discussion of lower-extremity vascular surgery, and the discussion here is limited to the clinical issues specific to abdominal aortic reconstruction. Over the past decade considerable interest has been focused on the use of regional anesthetic and analgesic techniques to reduce the incidence of perioperative morbidity in patients undergoing aortic reconstruction. The benefits of combined general-epidural anesthesia intraoperatively, with or without epidural analgesia continued into the postoperative period, remain controversial, and conflicting results have been reported. [205] [206] [207] [208] Moreover, studies that have reported improved outcome do not determine whether the benefit results from the intraoperative anesthetic technique or from the postoperative pain regimen (or from a combination of the two). In a randomized trial using epidural morphine in patients undergoing aortic surgery, Breslow et al [209] found an attenuation of the adrenergic response and a lower incidence of hypertension in the postoperative period. The effects of anesthetic/analgesic techniques on the incidence of perioperative myocardial ischemia have also received considerable attention. Three publications, with nearly 200 combined patients undergoing aortic reconstruction, failed to demonstrate a reduction in the incidence of perioperative, [210] intraoperative, [173] or postoperative [208] myocardial ischemia when epidural techniques were employed.

Clinical studies have identified several disadvantages in the use of epidural local anesthetics in combination with general anesthesia during aortic reconstruction, including significant hypotension at the time of aortic unclamping [165] and increased fluid [211] and vasopressor [207] requirements. Supraceliac aortic cross-clamping may significantly exaggerate these disadvantages, and as a result, some clinicians avoid epidural local anesthetics for such procedures. We frequently use epidural opioids without local anesthetics for procedures requiring supraceliac aortic cross-clamping. Epidural local anesthetic can be given later, after reperfusion, when hemodynamics and intravascular volume have stabilized. For low thoracic or high lumbar epidural catheters, we limit the initial bolus to 6 to 8 mL of local anesthetic. Additional local anesthetic is administered via continuous infusion at 4 to 6 mL/h with adjustments based on hemodynamics and inhalational anesthetic requirements during surgery. Although elective aortic reconstruction via the retroperitoneal approach using straight epidural anesthesia (no general anesthetic) has been reported, [212] [213] this technique is not recommended for routine use.

We begin preparation for emergence from anesthesia after restoration of circulation and establishment of adequate organ perfusion. Hemodynamic, metabolic, and temperature homeostasis must be achieved before skin closure; otherwise, patients are transported to the intensive care unit intubated, with their ventilation controlled. Extubation of the trachea is generally not attempted in patients with supraceliac aortic cross-clamp times greater than 30 minutes, patients with poor baseline pulmonary function, or patients

requiring large volumes of blood or crystalloid during surgery. At the start of skin closure, inhaled anesthetics are discontinued, nitrous oxide is increased to 70 percent, and residual neuromuscular blockade is reversed. We routinely place a large nasal airway after induction but before systemic heparinization in all patients for whom extubation is planned in the operating room. Hypertension and tachycardia are aggressively controlled during emergence by use of short-acting agents, such as esmolol, nitroglycerin, and sodium nitroprusside. Patients are placed in a recumbent, head-up position, and nitrous oxide is discontinued. If spontaneous ventilation is adequate, the trachea is extubated. Some centers advocate extubation of all patients in the intensive care unit after a period of stability has been established. In these cases, mild sedation with a benzodiazepine such as midazolam is appropriate.

Temperature Control

Postoperative hypothermia is associated with many undesirable physiologic effects [214] [215] [216] [217] and may contribute to adverse outcome (Ch. 37) . [218] [219] [220] [221] We maintain normothermia before skin incision by increasing ambient temperature in the operating room, applying warm cotton blankets, and warming the intravenous fluids. If significant hypothermia occurs early in the procedure, normothermia is extremely difficult to achieve, and emergence and extubation may be delayed. During surgery, all fluids and blood products should be warmed before administration. We routinely apply a forced-air warming blanket over the upper body. The lower body

should not be warmed, because doing so can increase injury to ischemic tissue distal to the cross-clamp by increasing metabolic demands.

THORACOABDOMINAL ANEURYSM SURGERY

Thoracic aortic surgery and thoracoabdominal aneurysm (TAA) repair are perhaps the most challenging surgical cases in terms of overall anesthetic and perioperative management. To successfully care for these patients, the anesthesiologist must be knowledgeable in the areas of one-lung ventilation; extracorporeal circulatory support, including circulatory arrest; renal and spinal cord protection; induced hypothermia; TEE; massive transfusion; and management of coagulopathy. Intraoperative management requires a team effort with intimate cooperation between surgeons, anesthesiologists, perfusionists, nurses, and electrophysiologic monitoring staff. Even in centers where numerous procedures are performed, morbidity and mortality are high, especially in patients with dissecting or ruptured aneurysms.

Etiology and Classification

A true aortic aneurysm is a dilation of the entire aorta, as measured across from one endothelial wall to the other. A false aneurysm is one with a normal internal diameter with the bulk of the aneurysm originating from a dissected channel. Although atherosclerosis accounts for 95 percent of abdominal aortic aneurysms, only one-half of thoracic and thoracoabdominal aortic aneurysms are atherosclerotic in origin. [222] The remainder are caused either by trauma or by connective tissue diseases involving the aortic wall from conditions such as Marfan syndrome, cystic medial degeneration, Takayasu arteritis, or syphilitic aortitis. [223] Patients with aneurysmal disease have a poor prognosis without surgery. Nutritional blood flow to the aorta is compromised, and the increasing diameter is associated with increased wall tension, even when arterial pressure is constant (law of LaPlace).

The most popular classification schemes are those of Crawford [224] and DeBakey. [225] The Crawford classification defines aneurysms as types I, II, III, and IV according to their anatomic location (Fig. 51-8) (Figure Not Available) . Type I includes aneurysms involving most of the descending thoracic and the upper abdominal aorta. Type II includes aneurysms involving most of the descending thoracic and most of the abdominal aorta. Type III involves the lower portion of the thoracic aorta and most of the abdominal aorta, and type IV includes most or all of the abdominal aorta. Types II and III are most difficult to repair because they involve both the thoracic and the abdominal segments of the aorta. Patients with Crawford type II aneurysms are at greatest risk for paraplegia and renal failure from ischemia to the spinal cord and kidneys during cross-clamp. Even with extracorporeal circulatory support, there is an obligatory period of time when blood flow to these organs is interrupted because the origin of the blood flow is between the cross-clamps. For this reason, protective measures to prevent ischemic injury are important in reducing morbidity.

The DeBakey classification defines dissecting aneurysms as types I, II, and III (Fig. 51-9) (Figure Not Available) . [225] Type I aneurysms begin in the ascending aorta and extend throughout the entire aorta. These lesions are usually repaired by use of a two-stage approach, with the first procedure on the ascending aorta and arch and the second procedure on the descending portion. Type II aneurysms are confined to the ascending aorta. Both types I and II often involve the aortic valve, causing aortic regurgitation, and sometimes involve the ostia of the coronary arteries. Type III aneurysms begin just distal to the left subclavian artery and extend either to the diaphragm or to the aortoiliac bifurcation. DeBakey type III B is a subclass that indicates dissection of the aneurysm wall involving both the thoracic and the abdominal aorta. Type III B has the greatest risk of spinal cord and renal injury with surgical repair.

Morbidity and Mortality

The incidence of paraplegia in patients undergoing surgical repair of TAA is reported to be from 5 to 40 percent, depending on the anatomic location, the duration of cross-clamp, the use of protective measures, the degree of dissection, and whether the aneurysm has ruptured. [226] [227] [228] Renal failure is reported to occur in 3 to 30 percent of patients, depending on similar factors. [224] [229] [230] Overall, approximately 6 percent of patients need postoperative dialysis after TAA repair, which is associated with high mortality (30-60%). [230] Advances in surgical practice and in anesthetic

---

Figure 51-8 (Figure Not Available) The Crawford classification of thoracoabdominal aortic aneurysms is defined by anatomic location and the extent of involvement. *(From Crawford [224])*

management have reduced overall mortality from TAA repair to approximately 5 to 15 percent. [231]

Preoperative Preparation and Monitoring

Surgical TAA repair requires extensive preoperative planning. The evaluation and management of coexisting cardiac and pulmonary disease are previously discussed in this chapter. Before the day of surgery, the anesthesiologist and the vascular surgeon should discuss the following issues: extent of the aneurysm and technique of surgical repair, plans for extracorporeal support (if any), spinal cord ischemia monitoring, renal and spinal cord protection, hemodynamic monitoring, and ventilation strategy.

At least 15 units of packed red blood cells and 15 units of thawed fresh frozen plasma should be immediately available, and additional units should be obtainable. We use a large cooler to store blood products on ice in the operating room so that they can be returned to the blood bank if they are not used. Platelets should be available. A dedicated critical care technician is helpful in assisting with laboratory testing and retrieving products from the blood bank.

Large-bore intravenous access is obviously important, especially if partial bypass (in contrast to full bypass) is planned, because it is difficult or impossible for the perfusionist to administer fluid or blood products into the closed circuit. We usually insert three 8.5 French catheters into either the internal jugular or the antecubital veins. One of these accepts the pulmonary artery catheter, and the other two are connected to the rapid infuser system (RIS, Haemonetics, Braintree, MA). This system allows the delivery of up to 1,500 mL/min of blood products at a temperature of 37 to 38°C. A right radial arterial catheter is used for aneurysms of the descending thoracic aorta because occasionally the cross-clamp is placed proximal to the left subclavian artery, thus occluding flow to the left upper extremity. When left atrial-to-femoral artery (LA-FA) bypass is planned, a right femoral artery catheter is placed to monitor arterial blood

Figure 51-9 (Figure Not Available) The DeBakey classification of dissecting aneurysms of the aorta. Type I has an intimal tear in the ascending aorta with dissection extending down the entire aorta. Type II has an intimal tear in the ascending aorta with dissection limited to the ascending aorta. Type III has an intimal tear in the proximal descending thoracic aorta with dissection either limited to the thoracic aorta, or extending distally to the abdominal aorta or bifurcation (Type IIIB). *(From DeBakey et al [225])*

---

pressure distal to the cross-clamps. This catheter monitors perfusion pressure to the kidneys, spinal cord, and mesenteric circulation during the time when the

cross-clamps are high on the descending aorta and the lower body is perfused by the bypass circuit. The radial and femoral arterial pressures should be simultaneously displayed on the anesthesiologist's monitor, which should be visible to the surgeons and the perfusionists. TEE is often helpful during TAA repair. When used by a properly trained individual, the assessment of left ventricular end-diastolic volume, myocardial ischemia, and valvular function is possible. It is also possible to determine the size and the extent of the aneurysm.

A double-lumen endobronchial tube should be inserted for the purposes of one-lung ventilation because surgical exposure is optimal when the left lung is deflated. A left-sided endobronchial tube is ideal because there is risk of occluding the right upper lobe bronchus with a right-sided tube. Occasionally, when the left mainstem bronchus is compressed by a large aneurysm, [232] the lumen does not accommodate an endobronchial tube. In this situation, a right-sided endobronchial tube might be necessary. Rarely, the right mainstem bronchus may be compressed by a large aneurysm. [233] The double-lumen tube is usually changed to a single-lumen tube by use of a tube-changing catheter at the completion of surgery. This facilitates intensive care unit management of pulmonary hygiene and reduces the resistance to breathing during weaning in the postoperative period. The airway is often edematous after surgery, and it may be difficult or impossible to change the tube without a tube-changing catheter.

Many centers use electrophysiologic monitoring with somatosensory evoked potentials (SSEP) and motor evoked potentials to monitor for spinal cord ischemia (Ch. 35) . These monitoring techniques may be helpful in identifying the important intercostal arteries that perfuse the spinal cord so they can be implanted into the graft. If ischemia is identified, cross-clamps can often be moved, upper or lower body blood pressure can be increased to provide perfusion through collaterals, or other measures may be taken to protect the cord (cerebrospinal fluid [CSF] drainage, induced hypothermia, or intrathecal papaverine). These techniques are discussed later. There are three general problems with SSEP monitoring. First, sensory monitoring is more likely to detect posterior column ischemia and is a poor monitor for the anterior columns. As a result, paraplegia can occur in spite of normal SSEP signals. [234] Second, inhaled anesthetics [235] and hypothermia [236] can interfere with SSEP signals. Third, ischemia affects peripheral nerves, and ischemia to the lower extremities delays conduction from the usual stimulation sites (posterior tibial nerve). [237] To eliminate the peripheral nerves as a confounding factor, we use spinal stimulation via a lumbar epidural electrode, which is more specific for ischemic injury than is peripheral monitoring. [237] Motor evoked potentials have been used successfully to monitor the anterior columns of the spinal cord. [238] [239] Stimulation over the motor cortex or the cervical spine with sensing over the popliteal nerve is the most commonly used technique. Although this technique appears to be useful in monitoring for ischemia, it is somewhat technically demanding. Also, hypothermia and inhaled anesthetics interfere with the signals.

Body temperature should be monitored at two sites (core and peripheral) to assess cooling and warming on bypass. There is an important difference, however, between full and partial bypass with regard to temperature monitoring. [240] With full bypass, perfusion is usually into the ascending aorta, and typically the upper body core temperature (nasopharynx or esophagus) cools and warms fastest, whereas the lower body temperature changes more slowly. With partial bypass, the opposite is true. The blood from bypass is returned into the femoral artery, and the lower body (rectum or bladder) changes before the upper body changes. This difference is important to recognize in order to achieve complete cooling and warming because the lagging temperature should be the end point for cooling and warming.

Intraoperative Management

Extracorporeal Support

Thoracic and thoracoabdominal aortic surgery can be performed without extracorporeal support. Large series of the "clamp and run" technique have been published with relatively favorable outcomes, but these cases are from institutions with the greatest clinical experience and the shortest cross-clamp times. [226] [228] Other than the location and the extent of the aneurysm, the duration of cross-clamp on the aorta is the single most important determinant of paraplegia and renal failure when bypass is not employed. Clamp times of less than 20 to 30 minutes are associated with almost no paraplegia. [228] [241] When clamp times are between 30 and 60 minutes (the vulnerable interval), the incidence of paraplegia increases from
10 percent to
90 percent as time progresses. [242] [243] Because clamp times are typically in this range or longer, efforts are usually made to perfuse the distal aorta to protect the viscera, kidneys, and spinal cord from ischemic injury.

The simplest method of providing distal perfusion is a passive conduit or shunt. The heparin-bonded Gott shunt [244] was developed to avoid the need for systemic heparinization and is used to divert flow passively from the left ventricle or the ascending aorta to the distal aorta. Partial bypass (left heart bypass) is more commonly used; this technique allows the adjustment of blood flow (Fig. 51-10). This method, which is sometimes referred to as LA-FA bypass, usually draws blood from the left atrium and returns blood into the left femoral artery. For Crawford type I aneurysms, there should be little or no ischemia for the gut, spinal cord, or kidneys because blood flows retrograde up the aorta. A centrifugal pump is used (Biomedicus, Eden Prarie, MN), and there is no need for full-dose heparin because the circuit is heparin-coated. The typical heparin dose for LA-FA bypass is 100 units/kg. An oxygenator is unnecessary because only the left side of the heart is bypassed. Insertion of a heat exchanger into the circuit allows for cooling and warming, which is beneficial but not essential. [245] Variations of left heart bypass include cannulating the aortic arch instead of the left atrium. With this circuit, the left ventricle is relieved of the increased afterload during aortic cross-clamp. With left atrial cannulation, the ventricle is relieved of preload. Either way, the work of the ventricle is decreased during cross-clamp, and perfusion is provided to the distal aorta. We have had even greater success with cannulation of a pulmonary vein instead of the left atrium; this method accomplishes

Figure 51-10 Diagram of left heart (LA-FA) bypass. The left atrium and the left femoral artery are cannulated, and a centrifugal pump is used with heparin-coated tubing. A heat exchanger may be added into the circuit for cooling and rewarming.

the same effect as atrial cannulation but is associated with less atrial irritability. When hypothermia is combined with atrial cannulation, approximately 15 percent of patients experience new atrial fibrillation that usually reverts to sinus rhythm on rewarming but sometimes requires direct cardioversion. [240]

During left heart bypass, it is helpful to monitor arterial blood pressure above and below the aortic cross-clamps. We simultaneously display the radial and femoral artery pressures and aim for a mean arterial pressure of 70 to 80 mm Hg for both. [240] Careful control of intravascular volume, pump flow, and vasoactive drugs is required to achieve the target blood pressures. This requires communication and cooperation between the anesthesiologist and the perfusionist because, unlike during full cardiopulmonary bypass, both individuals manage the hemodynamics together during LA-FA bypass.

Aneurysms involving the aortic arch often require deep hypothermic circulatory arrest (DHCA) because cerebral blood flow is transiently interrupted during surgery. This can be accomplished by cannulation of the femoral artery and the femoral vein (fem-fem bypass). Some centers also use anterograde (innominate artery) or retrograde (internal jugular vein) selective cerebral perfusion with cold oxygenated blood to extend the safe maximum duration of DHCA. [246] Without this technique, 45 to 60 minutes is thought to be the safe limit of DHCA, but 90 minutes has been reported with selective cerebral perfusion. [247] DHCA may be necessary for patients with previous aortic arch repairs that are scheduled for a descending aortic repair because adhesions and scarring make application of the proximal aortic cross-clamp difficult or impossible. In this situation, DHCA allows a bloodless field for the proximal aortic anastomosis. After the anastomosis is finished under DHCA, full cardiopulmonary bypass can be instituted to complete the thoracic and/or the abdominal aortic anastomoses because it is difficult to complete an entire TAA repair during the safe period of DHCA.

Anesthetic Technique

There is no single best anesthetic technique for TAA repair. Usually, a balanced anesthetic is given with a combination of an opioid, a low-dose potent inhalation agent, a benzodiazepine, and a long-acting muscle relaxant. The induction should be slow and controlled without hypotension or hypertension because stress on the aneurysm can cause rupture. Heart rate should be maintained near baseline because myocardial ischemia is often heart rate related. As discussed in the section on abdominal aortic surgery, postoperative analgesia may be accomplished by use of an epidural catheter. Caution is necessary when the epidural is placed because surgery should be canceled and rescheduled in the event of a bloody tap because of the risks of spinal/epidural hematoma.

Spinal Cord Ischemia and Paraplegia

Paraplegia is a devastating complication of aortic surgery. The incidence of paraplegia is reported to be 0.5 to 1.5 percent for coarctation repair, zero to 10 percent for

thoracic aneurysm repair, 10 to 20 percent for thoracoabdominal repair, and as high as 40 percent for extensive dissecting TAA repair. [225] [248] [249] [250] [251] [252]

The spinal cord receives its blood supply from two posterior arteries and one anterior spinal artery (Fig. 51-11) (Figure Not Available) . The anterior spinal artery, which supplies the motor tracts in the spinal cord, is formed by two branches of the intracranial portion of the vertebral arteries. [253] The upper cervical segment of the spinal cord receives most of its blood flow from the vertebrals. [254] [255] The thoracic portion of the anterior spinal artery is supplied by the radicular arteries (one or two cervical, two or three thoracic, and one or two lumbar). [256] The largest of the radicular arteries is called the arteria radicularis magna or the artery of Adamkiewicz. The origin of this artery is variable but is located between T9 and T12 in 75 percent of cases. [257] [258] The variation in origin of the arteria radicularis magna explains why even with infrarenal aortic aneurysm repair, a 0.25 percent incidence of paraplegia has been reported. [243] The posterior spinal arteries, which supply the sensory tracts in the spinal cord, receive flow from the posterior and inferior cerebellar arteries, the vertebral arteries, and the radicular arteries. [255] [259]

Various methods have been used to prevent ischemic injury to the spinal cord. Distal perfusion with extracorporeal support has been shown to reduce the incidence of paraplegia. [260] [261] [262] Some form of bypass is likely to be beneficial when the anticipated cross-clamp time is greater than 30 minutes but is probably not beneficial when cross-clamp time is less than 20 to 30 minutes. CSF drainage is frequently used to improve spinal cord perfusion during TAA

Figure 51-11 (Figure Not Available) Diagram of the blood supply to the spinal cord showing the anterior and posterior radiculomedullary branches seen in a lateral view. The primary blood supply to the thoracolumbar portion of the spinal cord is derived from the artery of Adamkiewicz, which is variable in its origin, but usually branches off the aorta in the T-9 to T-12 region. *(From Djindjian [259])*

repair. Spinal cord perfusion pressure is defined as distal mean aortic pressure minus CSF pressure (or central venous pressure), whichever is greatest. Autoregulation of spinal cord blood flow is similar to cerebral autoregulation, and blood flow is relatively constant over the range of 50 to 125 mm Hg. [263] During hypoxia or hypercarbia, autoregulation is lost, and flow becomes linearly related to perfusion pressure. Thus, significant flow may remain, even at very low perfusion pressures. Drainage of CSF is thought to be important because CSF pressure often increases (by 10-15 mm Hg) with application of thoracic aortic cross-clamps, which increases the likelihood of ischemic spinal cord injury. [264]

Despite evidence from animal studies that CSF drainage protects the spinal cord, [265] the clinical use of this technique is controversial. Some studies have shown a reduced incidence of paraplegia, [266] but others have not. [267] [268] The most encouraging evidence in support of CSF drainage is from studies in which this technique is used in combination with other adjuncts, such as intrathecal papaverine [269] and hypothermia and partial bypass. [229] [237] [240] [270]

Hypothermia is probably the most reliable method of neuroprotection from ischemic injury. By reducing oxygen requirements by
5 percent for each degree centigrade, [217] a twofold prolongation of tolerated cross-clamp time is achieved by cooling even to mild hypothermia (34°C). [271] Because the reduction in metabolic rate is linearly related to temperature, moderate or profound hypothermia provides even greater protection. Both systemic and local spinal cord cooling have been shown to be beneficial. Systemic hypothermia can been achieved with either full cardiopulmonary bypass (with or without DHCA) [272] or partial bypass. [240] [270] Cooling to 30 to 32°C with LA-FA bypass in combination with CSF drainage was associated with no permanent neurologic sequelae in our series of 20 patients, despite a relatively long average cross-clamp time (
70 minutes). [240] We have since used this technique in more than 50 patients cooled to 32°C, with a 5 percent incidence of paraplegia. Although some risk is incurred when a beating heart is subjected to moderate hypothermia, the benefits appear to outweigh the risks. Both supraventricular and ventricular dysrhythmias respond well to cardioversion and/or mild warming to
33 to 34°C. Localized cooling of the spinal cord by cold perfusion of the artery of Adamkiewicz with blood [273] or crystalloid [274] provides significant protection during spinal ischemia in animal models. Local cooling has been shown to be beneficial in humans who received epidural infusions of 4°C saline. [275] Even if active cooling is not used, it is advantageous to allow patients to passively cool to 33 to 34°C during TAA repair. With passive cooling, the challenge is rewarming after the surgical repair. This is most easily accomplished by use of a forced-air blanket over the upper body. The lower body should not be actively warmed, because warming ischemic tissue increases metabolic requirements, acidosis, and ischemic injury.

A variety of drugs have been the focus of laboratory and clinical investigation in an attempt to reduce the incidence of ischemic spinal cord injury. Barbiturates have been shown to provide significant protection. [276] [277] Corticosteroids have been shown to provide protection in dogs [278] but were beneficial in humans only when they were combined with CSF drainage. [279] Calcium channel blockers were protective against spinal cord ischemia in some studies [280] [281] but not in others. [282] [283] *N*-methyl- D-aspartame receptor antagonists have been investigated because ischemic injury appears to be related to increased levels of excitatory amino acids (particularly glutamate), which allow increased permeability to calcium ions and high intracellular calcium concentrations. Dextrorphan (a noncompetitive *N*-methyl- D-aspartame antagonist) shows promise during spinal cord ischemia. [284] Magnesium, another *N*-methyl- DV-aspartame receptor blocker, improves recovery from spinal cord ischemia in rat and dog models when administered intrathecally. [285] [286] Naloxone appears to be protective in patients with traumatic spinal cord injuries [287] and in a rabbit model of spinal ischemia. [288] [289] Naloxone also shows promise when combined with CSF drainage in patients undergoing TAA

repair. [290] Intrathecal papaverine appears to be protective [269] especially when combined with CSF drainage. [291]

Renal and Mesenteric Ischemia and Protection

Renal failure following TAA repair results from preexisting renal dysfunction, ischemia during cross-clamp, thrombotic or embolic interruption in renal blood flow, and hypovolemia and hypotension. Approximately 6 percent of patients require postoperative dialysis, even in centers with the most clinical experience. [230] The primary predictor of postoperative renal failure is preoperative renal dysfunction. The duration of the cross-clamp time is also very important. Hypothermia, by reducing oxygen requirements, protects the kidneys during ischemia. The role of pharmacologic protection is somewhat controversial. Mannitol (12.5-25.0 g/70 kg) is often given before cross-clamp. Mannitol improves renal cortical blood flow and glomerular filtration rate in animal models of ischemia. [292] Endothelial cell swelling is decreased, and an osmotic diuresis occurs. [184] There is evidence of free radical scavenging with mannitol and subsequent protection from ischemia in animals. [185] Loop diuretics are sometimes given, but these drugs have been less effective than mannitol in experimental models. [293] In clinical studies, the prophylactic use of loop diuretics has not been shown to improve outcome or to reduce the need for dialysis for patients with acute renal failure. [294] [295] Dopamine given in low doses (3 mug/kg/min) dilates renal blood vessels and increases renal blood flow and urine output. Despite these beneficial effects, these is no clear evidence from clinical trials that dopamine provides renal protection during ischemia. Optimal patient care for renal protection during TAA surgery should rely on mild hypothermia, mannitol, and selective use of low-dose dopamine in patients at risk for renal failure. Intravascular volume must also be maintained to prevent hypotension and hypoperfusion of the kidneys.

Coagulation and Metabolic Management

Coagulopathy is a frequent complication during TAA repair. A dilutional coagulopathy develops during massive transfusion in which platelets become deficient after 1 blood volume of replacement. At somewhere between one and two blood volumes of replacement, coagulation factors are diluted to levels low enough to increase bleeding. Other contributing factors are residual heparin, ischemia to the liver where most coagulations factors are produced, and hypothermia that persists after weaning from bypass. By using a one-to-one ratio of packed red blood cells to fresh frozen plasma throughout the surgical procedure, coagulation factors are usually maintained. The prothrombin time, partial thromboplastin time, fibrinogen, and platelet counts should be measured frequently. Cryoprecipitate may be necessary to correct coagulopathy, especially when the prothrombin time and partial thromboplastin time are prolonged and hypervolemia prevents the administration of significant volumes of fresh frozen plasma. When coagulopathy persists despite these efforts, epsilon-aminocaproic acid is beneficial as antifibrinolytic therapy, and desmopressin can be given in order to increase circulating levels of von Willebrand factor and factor VIII. Normothermia should be achieved by complete rewarming before separation from bypass, increasing the ambient temperature after separation from bypass, and by forced air warming over the upper body skin surface. Arterial blood gases and electrolyte levels should be measured frequently. Sodium bicarbonate should be given to treat the metabolic acidosis that occurs during and after crossclamping. Hyperkalemia should be aggressively treated, especially in oliguric or anuric patients. Calcium chloride and sodium bicarbonate are the primary acute treatments for hyperkalemia.

Endovascular Stents

A development in the field of invasive radiology is the use of the endovascular stent to treat thoracic aortic aneurysms. [296] [297] These stents, which are individually constructed, expandable, Dacron-covered stainless steel tubes, are introduced through the femoral artery by use of a 26 French outer-diameter introducer catheter. The stents are placed in the operating room with the patient under general anesthesia. After anatomic positioning is confirmed with fluoroscopy and TEE, the stent is released into place. The stent supports the wall of the aneurysm and prevents rupture. The anesthesiologist should be prepared with large-bore intravenous access for the possibility of aneurysm rupture or open surgical repair. For thoracoabdominal aortic aneurysms, the thoracic segment may be stented and the abdominal segment surgically repaired as a combined procedure.

LOWER-EXTREMITY REVASCULARIZATION

Indications and Surgical Approach

Arterial insufficiency in the lower extremities can present with either acute or chronic limb ischemia. Acute ischemia is often due to embolism, thrombus, or pseudoaneurysm following invasive procedures in which the femoral artery is cannulated. Patients with acute ischemia need to be rapidly evaluated because irreversible tissue injury occurs within 4 to 6 hours. [298] Chronic ischemia is most often secondary to atherosclerotic plaque and presents with claudication. The ankle/arm index is a simple, noninvasive method of evaluating the severity of arterial insufficiency and is defined as the ankle systolic blood pressure divided by the brachial systolic blood pressure. Normally, the ankle/arm index is greater than 1.0. In patients with claudication, the ankle/arm index is often less than 0.6, and in patients with rest pain, the ankle/arm index is often less than 0.25. [299] Arteriography is used to determine the severity and the anatomic location of arterial occlusion. Angioplasty and/or thrombolytic therapy is occasionally performed in conjunction with arteriography. Patients are then often given thrombolytic drugs and/or heparin overnight and are scheduled for lower-extremity bypass surgery the following day, pending evaluation of

lower-extremity blood flow. This practice has significant implications for the anesthesiologist because regional anesthesia is associated with significant risk of spinal/epidural hematoma and is not an option in the anticoagulated patient.

There are several surgical approaches to patients with lower-extremity arterial insufficiency. For occlusion distal to the inguinal ligament, the femoral popliteal bypass with reverse saphenous vein graft is most often the procedure of choice. Graft patency with this approach is reported to be 59 percent at 5 years and 38 percent at 10 years. [300] The saphenous vein may be used *in situ* (not reversed), but this technique requires excision of the valves to allow adequate flow. Human umbilical vein and polytetrafluoroethylene (Gore-Tex) can be used when saphenous vein is unavailable, which is often the case when patients have had previous coronary artery bypass or lower-extremity bypass. In patients with aortoiliac disease who are not candidates for aortobifemoral bypass because of coexisting medical diseases, an extra-anatomic procedure (axillofemoral or femorofemoral bypass) is an alternative approach that is thought to be a less stressful procedure. [301]

Significant complications from femoral arteriography occur in 1.7 percent of patients, with death occurring in 0.03 percent. Puncture site hematoma, thrombosis or dissection of the vessel wall, hemorrhage, and pseudoaneurysm are the most common surgically correctable complications. A pseudoaneurysm is an area of chronic hemorrhage that has developed an organized thrombotic wall. Pseudoaneurysms communicate with the vessel lumen but are not surrounded by any vessel layers. Although surgical repair of these angiographic complications is considered to be relatively noninvasive, these patients are high-risk surgical candidates because they often have severe coronary disease that brought them to angiography originally, as well as other coexisting diseases.

Preoperative Preparation and Monitoring

Preoperative assessment and optimization of cardiac risk have been previously discussed in this chapter. It is extremely important that long-term cardiac and respiratory medications be given the morning of surgery. beta-Adrenergic blockers are most important because they have been shown to reduce the incidence of perioperative myocardial ischemia and subsequent cardiac morbidity. [36] [37] [38] [39] Monitoring for lower-extremity arterial revascularization should include an intra-arterial catheter that permits (1) continuous blood pressure monitoring to optimize coronary artery perfusion, (2) continuous blood pressure monitoring to optimize lower-extremity graft perfusion, and (3) blood sampling for diagnostic laboratory testing. A urinary bladder catheter is usually adequate for assessing intravascular volume and cardiac output, and central venous catheters are not necessarily helpful in routine cases. They should, however, be considered for patients with significant renal dysfunction in whom intravascular volume should be carefully monitored, and for patients with significantly impaired ventricular dysfunction or CAD. In these patients, a pulmonary artery catheter may be helpful, but given the relatively low potential for blood loss and third-space fluid losses with lower-extremity vascular procedures, the pulmonary artery catheter is usually reserved for patients with active congestive heart failure or unstable angina. Our criteria for using invasive hemodynamic monitoring have been previously described. [54] As discussed earlier in this chapter, computerized ST segment monitoring is helpful in monitoring for myocardial ischemia.

Anesthetic Management

Regional Versus General Anesthesia

The question of whether regional or general anesthesia is preferable for vascular surgery has been debated for years, but only in the past decade have well-designed prospective randomized trials been completed. Earlier nonrandomized trials were prone to bias because many clinicians had the unfounded belief that regional anesthesia was safer for patients with advanced cardiac or pulmonary disease. Even the prospective studies must be cautiously interpreted. It should be recognized that most clinical trials have optimized the delivery and management of the anesthetic techniques, which may mask the true risks of the anesthetic. An example of this is the strict hemodynamic control, transfusion thresholds, and postoperative analgesia regimens that have been used in clinical trials. It is often best to choose the anesthetic technique that is most familiar to a particular institution because, for example, unfamiliarity and mismanagement of epidural catheters can cause serious complications.

Occasionally, surgical procedures, such as embolectomy and femoral pseudoaneurysm repair, can be completed with the patient under local anesthesia with intravenous sedation. Because these procedures often progress to more invasive arterial reconstruction, a regional or general anesthetic initiated before the procedure begins avoids an unplanned conversion to general anesthesia.

In some conditions, one anesthetic technique (regional or general) is preferable to the other. Patients who undergo anticoagulation with heparin, warfarin (Coumadin), or thrombolytic drugs before surgery should not be given regional anesthesia, because spinal/epidural hematoma is a devastating complication that can lead to permanent neurologic injury. Regional anesthesia may be used in patients who are given anticoagulants during the surgical procedure, but it has been recommended that surgery be canceled when blood is obtained through the needle on placement of the regional block. [302] It has also been recommended that epidural catheters not be removed until anticoagulants have been discontinued in the postoperative period. [302] The use of low-molecular-weight heparins has increased, and there is evidence to suggest a significant risk of spinal/epidural hematoma when regional anesthesia is used in conjunction with these drugs. [303] Long-term use of aspirin is a controversial topic, and regional anesthesia should be chosen only when the advantages outweigh the risks. Some centers routinely check a bleeding time in patients who have taken aspirin in the 7 days before a planned regional anesthetic. When possible, spinal anesthesia is preferable to epidural anesthesia for patients with any question of a coagulation abnormality, and the smallest-diameter needle should be used. [303]

TABLE 51-10 -- Cardiac and Vascular Outcomes in Studies of Regional Versus General Anesthesia in Vascular Surgery Patients

AUTHOR	*n*	CONGESTIVE HEART FAILURE		MYOCARDIAL INFARCTION		DEATH		VASCULAR GRAFT OCCLUSION	
		RA	*GA*	*RA*	*GA*	*RA*	*GA*	*RA*	*GA*
Tuman et al [305]	80	5%	10%	0%	8%	0%	0%	3%	20%
Baron et al [206]	173	6%	8%	6%	6%	3%	5%		
Christopherson et al [54]	100	--	--	4%	4%	2%	2%	4%	20%
Bode et al [304]	423	8%	6%	6%	3%	3%	2%	6%	4%
Bois et al [208]	124	5%	0%	4%	8%	0%	0%	--	--

GA, general anesthesia; RA, regional anesthesia

There has traditionally been a prevailing belief that regional anesthesia is preferable in patients with significant pulmonary disease. It is true that instrumentation of the airway may precipitate bronchospasm or may increase the risk of nosocomial infection; however, there is little evidence from well-designed clinical studies to demonstrate improved pulmonary outcome with regional anesthesia.

Cardiac morbidity is the most common cause of death in patients undergoing surgery, and the incidence of perioperative cardiac morbidity is 10 times greater in vascular surgery patients than in nonvascular surgery patients. [12] Five prospective randomized trials have examined the effects of regional versus general anesthesia on cardiac outcomes in vascular surgery patients. Two studies (Christopherson et al [54] and Bode et al [304]) compared pure regional versus general anesthetic techniques in lower-extremity vascular patients. Three others (Tuman et al, [305] Baron et al, [206] and Bois et al [208]) compared combined regional/general versus general anesthetics in aortic and/or lower-extremity surgical patients. The results of these studies are shown in Table 51-10 . In summary, only Tuman et al's study revealed a difference in cardiac outcome. Even in Tuman et al's series, outcome was significantly improved by regional anesthesia only when more subtle outcomes, such as congestive failure and dysrhythmias, were included. Christopherson and colleagues [54] (the PIRAT Study) found no difference in cardiac events or myocardial ischemia as detected by continuous Holter monitor over a 3-day postoperative period. In this study, strict intraoperative and postoperative protocols were used to manage hemodynamics and postoperative analgesia. Bode and colleagues [304] reported on the largest randomized trial, which included a spinal anesthesia group in addition to general and epidural groups. Again, there were no differences in cardiac events in any of the three groups. The studies by Bois et al [208] and Baron et al [206] also showed no differences in cardiac morbidity with regional anesthesia/analgesia.

Perhaps the most interesting and clinically significant finding in these randomized trials is the beneficial effect of regional anesthesia on lower-extremity graft patency in the postoperative period. Two of the studies (Tuman et al [305] and Christopherson et al [54]) reported a fivefold greater incidence of graft occlusion following general (relative to regional) anesthesia. Most graft occlusions occurred in the first 1 to 3 days following surgery, after which the established difference in the incidence of graft occlusion between anesthetic techniques was maintained over time (6 weeks and beyond) (Fig. 51-12) (Figure Not Available) . This time course suggests that anesthetic technique played a role in graft occlusion. Bode et al [306] reported an overall very low incidence of graft occlusion, but differences in hemodynamic management, surgical technique, and the patient population may explain these findings. For example, intraoperative intravascular angioscopy was used to inspect the grafts to confirm patency before completion of surgery, and all patients were cared for in an intensive care setting for 48 hours after surgery.

The proposed mechanism for the benefits of regional anesthesia are the effects of anesthetic technique on coagulation. General anesthesia is associated with a hypercoagulable state in the early postoperative period, whereas regional anesthesia attenuates this effect. [307] Tuman et al [305] demonstrated this nicely by thromboelastography, and Rosenfeld et al, [307] by increased plasminogen activator inhibitor and fi-brinogen levels following general anesthesia. Thus, it appears that fibrinolysis is decreased after general anesthesia and is normal after regional anesthesia. These findings are probably related to attenuation of the stress response with regional anesthesia because there appears to be a link between stress, catecholamines, and acute phase reactants, such as plasminogen activator inhibitor and fibrinogen. [308] [309]

Figure 51-12 (Figure Not Available) Cumulative probability of reoperation for regrafting, thrombectomy, or amputation over a 6-week follow-up period. Reoperation was significantly more frequent after general than after epidural anesthesia. *(From Christopherson et al [54])*

Platelet reactivity is also enhanced in the presence of a stress response. [309] Another important mechanism for increased lower-extremity graft patency with regional anesthesia may be the increased lower-extremity blood flow associated with sympathectomy. [310]

In the postoperative period, Breslow et al [92] demonstrated differences in the adrenergic response with general compared with regional anesthesia (Fig. 51-13) (Figure Not Available) . Both epinephrine and norepinephrine are increased after general anesthesia relative to regional anesthesia. The cortisol response following general anesthesia is also greater than that following regional anesthesia. [92] This "stress response" is associated with increased blood pressure and hemodynamic lability during the intraoperative and early postoperative periods following general anesthesia compared with regional anesthesia. [54] [311] When the hemodynamic parameters are controlled pharmacologically, however, there is no difference

Figure 51-13 (Figure Not Available) Plasma norepinephrine and epinephrine concentrations before induction of anesthesia (P), at skin closure (C), and at 1, 6, 12, and 18 hours after lower extremity revascularization. GA, general anesthesia with postoperative parenteral morphine by patient controlled analgesia (PCA); RA, regional (epidural) anesthesia with postoperative epidural analgesia by PCA. *(From Breslow et al [92])*

related to anesthetic technique in myocardial ischemia or cardiac morbidity. [54] [304]

Anesthetic Technique

General anesthesia for lower-extremity vascular surgery is usually delivered by use of a balanced technique with opioids, potent inhalation anesthetics, nitrous oxide, and neuromuscular blockade. Virtually all patients are extubated in the operating room, so high doses of opioid are generally avoided. The goal is to avoid hemodynamic extremes in order to prevent myocardial ischemia during the intraoperative and postoperative periods. Judicious use of beta-adrenergic blockers and vasoactive drugs is often necessary.

Regional anesthesia can be accomplished with either spinal or epidural techniques. Disadvantages of spinal anesthesia include the limited duration of action because the surgical procedures are somewhat unpredictable in length and complexity. Also, the level of sympathetic block is somewhat less controllable than that of the epidural block, and hypotension can occur. An additional advantage of an epidural technique is the ability to continue drug delivery into the postoperative period for analgesia and attenuation of the stress response. A lumbar epidural catheter is ideal for lower-extremity vascular procedures. The dermatomes that need to be anesthetized are innervated at the same level where the catheter is inserted because the incision is usually in the L1 to L4 region. Small volumes of local anesthetic are required because a T10 block is usually sufficient. Usually, 10 to 12 mL (including the test dose) is sufficient for the initial dose, and more drug is given as needed. Because vascular surgery patients are generally advanced in age and because elderly patients are prone to higher block levels, larger doses may result in high blocks with total sympathectomy and severe hypotension. A high sympathetic block is problematic because of decreased coronary perfusion and excessive fluid and vasopressor requirements. Congestive heart failure may result in the postoperative period when the sympathectomy resolves and the intravascular space contracts. When the test dose is given, careful attention should be directed at both the heart rate and the blood pressure because many vascular surgery patients take beta-adrenergic blockers and little or no heart rate change is noticed when epinephrine is given through an intravascular catheter. When hypotension results from sympathectomy, a low-dose phenylephrine infusion is helpful in reducing intravenous fluid requirements. This approach is also more physiologic than administration of large fluid volumes.

Postoperative Management

Pain and anxiety should be carefully controlled in the postoperative period because the stress response and myocardial ischemia are of greatest concern at this time. Intravascular volume should be optimized, anemia avoided (hemoglobin <9.0 g/dL), and heart rate and blood pressure should be carefully controlled. Computerized ST segment analysis is helpful in identifying ischemic changes. Peripheral pulses should be checked frequently to verify lowerextremity graft patency. Blood pressure manipulation and/or

---

anticoagulants may be necessary when peripheral perfusion is limited. Urgent surgery may be required to reopen clotted or stenotic grafts.

Postoperative analgesia can be provided by intravenous or epidural opioids delivered by patient-controlled analgesia or epidural opioids with local anesthetics delivered by continuous infusion or patient-controlled analgesia. For epidural patient-controlled analgesia, a dilute concentration of local anesthetic should be utilized to allow neurologic evaluation of the lower extremities to rule out spinal/epidural hematoma. Bupivacaine (0.0625%) is ideal in this regard. Fentanyl (5 mug/mL) can be added and the solution infused at 2 mL/h, with an on-demand (patient-controlled analgesia) bolus of 2 to 4 mL and a lockout interval of 10 minutes.

CAROTID ENDARTERECTOMY

Indications

Stroke is the third leading cause of mortality in the United States. [312] Annually, there are more than 500,000 hospitalizations and 150,000 deaths due to stroke. [313] The aggregate lifetime cost associated with an estimated nearly 400,000 first strokes in 1990 was $40.6 billion. [314] Despite a welldocumented decline in stroke mortality, the annual incidence rate of stroke may be increasing. [315]

The strong association between stroke and carotid artery occlusive disease is well known. The principal cause of occlusive disease is atherosclerosis, which most commonly involves the bifurcation of the common carotid artery, with frequent extension into both the internal and the external carotid arteries. [316] Cerebrovascular sequelae of carotid atherosclerosis may result from either embolization of thrombus and/or atheromatous debris or reduction in flow (hypoperfusion) secondary to stenosis. The latter probably accounts for less than 10 percent of the cerebrovascular sequelae of carotid atherosclerosis. [317] Although much is known about the genesis and evolution of atherosclerosis, significantly less is known about the circumstances that lead to plaque instability and rupture. Regardless of the mechanism, the degree of cerebral injury depends on such factors as plaque morphology, characteristics of the embolus, duration of hypoperfusion, cerebrovascular vasoreactivity, integrity of the circle of Willis, and cerebral collateral circulation. Clinical manifestations of carotid disease represent a spectrum of conditions, with fatal or debilitating stroke secondary to cerebral infarction at one end of the spectrum, ranging successively through nondebilitating stroke, reversible ischemic neurologic deficit, transient ischemic attack, and amaurosis fugax (transient attack of monocular blindness), to an asymptomatic bruit.

Endarterectomy of the carotid bifurcation has been used to reduce symptoms and prevent stroke for nearly 40 years. Carotid endarterectomy is the most common major vascular surgical procedure performed in the United States. More than 90,000 carotid endarterectomies are performed annually, [318] and this number is increasing. The rate and number of carotid endarterectomies have fluctuated significantly since the early 1970s. With marked growth in the specialty of vascular surgery and an expanding list of surgical indications, the number of carotid endarterectomies performed in nonfederal hospitals increased from 15,000 in 1971 to 107,000 in 1985, [319] then declined over the next 5 to 6 years. [320]

In 1992, a marked increase in the number of carotid endarterectomies occurred after the results of two large-scale, prospective, randomized trials were published. [320] The North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial both reported definitive results for symptomatic patients with high-grade carotid stenosis (70-99%). [321] [322] In the North American Symptomatic Carotid Endarterectomy Trial, the long-term stroke rate for surgical patients was 9 percent, compared with 26 percent for medical patients. [322] In the European Carotid Surgery Trial, the long-term stroke rate was 2.8 percent for surgical patients, excluding a perioperative stroke and death rate of 7.5 percent, and 16.8 percent for medically managed patients. [321]

The efficacy of carotid endarterectomy in asymptomatic patients with carotid stenosis has been evaluated in four randomized trials. [323] [324] [325] [326] A fifth, the European Asymptomatic Carotid Surgery Trial, is ongoing. [327] The Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin trial, the first to publish its results, concluded that carotid endarterectomy was not indicated for asymptomatic patients with 50 to 90 percent carotid stenosis. [323] Unfortunately, this study was seriously flawed and the results questioned. The Mayo Asymptomatic Carotid Endarterectomy trial was terminated early because of a significantly increased number of MIs and transient cerebral ischemic events in the surgical group. [324] Most of these events were not related to surgery itself but rather to the absence of aspirin in the surgical group. The Department of Veterans Affairs trial was designed to compare the effects of carotid endarterectomy plus aspirin with medical treatment (aspirin) in asymptomatic male patients with 50 percent or greater carotid stenosis. [326] This trial demonstrated a significant reduction in ipsilateral neurologic events in the surgical group (8%) compared with the medical group (20.6%). However, the combined incidence of stroke and death was not different between study groups. The Asymptomatic Carotid Atherosclerosis Study, the largest of the five trials, demonstrated that patients with asymptomatic carotid stenosis (
60%) who were treated with carotid endarterectomy and aspirin have a reduced 5-year risk of ipsilateral stroke compared with patients treated with aspirin alone (5.1% versus 11.0%). [325] These results reflect only a 5.9 percent absolute risk reduction in 5 years, which is just above 1 percent per year.

Perioperative Morbidity

For carotid endarterectomy, most centers report a perioperative stroke rate of between 3 percent and 5 percent. [328] [329] [330] [331] [332] [333] The incidence of perioperative stroke is highest for patients diagnosed with stroke, lower for patients with transient ischemic attack, and lowest in asymptomatic patients. [334] [335] [336] Neurologic deficits occur most commonly in patients with poorly controlled preoperative hypertension or in those with hypertension or hypotension postoperatively. [337] [338] More than half of these deficits occur more than 4 hours postoperatively. [337] The incidence of perioperative

MI in patients undergoing carotid endarterectomy ranges from zero to 4 percent. [328] [329] [331] [332] [333] [337] [339] MI is the leading cause of both perioperative and late mortality following carotid endarterectomy.

Preoperative Evaluation

As discussed previously, the successful evaluation of patients with arterial occlusive disease must address the systemic and progressive nature of atherosclerosis. CAD is common in patients presenting for carotid endarterectomy and is the leading cause of both early and late mortality. Despite the known high incidence of CAD in patients presenting for carotid endarterectomy, we rarely request preoperative studies (DTI or DSE) aimed at the evaluation of myocardial function or ischemic potential. Exceptions to this practice are patients with unstable angina, recent MI with evidence of ongoing ischemia, decompensated congestive heart failure, and significant valvular disease. It is our contention that unless the surgical plan can be altered, the perioperative management improved, or the mortality reduced, specialized studies are not appropriate in most patients presenting for carotid endarterectomy. Our approach is based on the following rationale. First, randomized trials have definitively established that carotid endarterectomy can prevent stroke in appropriately selected patients. Second, an alternative, or less stressful, procedure is not an option at the present time. Percutaneous transluminal angioplasty of the carotid artery may evolve into an appropriate alternative for high-risk patients, but at present, it is still experimental. [340] Third, based on the previous two reasons, it would be unlikely that the results of specialized testing would result in the procedure's being canceled. Fourth, because careful intraoperative and postoperative monitoring and medical management is standard for all patients undergoing carotid endarterectomy, specialized testing has little potential to alter perioperative management. Last, we do not believe that preoperative strategies leading to coronary angiography and ultimately coronary revascularization are appropriate in patients undergoing carotid endarterectomy, given the rates of perioperative cardiac morbidity and mortality. Reduction in short-term mortality has not been shown with prophylactic coronary revascularization before noncardiac surgery. Thus, in patients with asymptomatic or stable CAD, we believe that the best strategy is to proceed with carotid endarterectomy without additional studies. This approach does not take into consideration the potential long-term benefits from aggressive preoperative cardiac assessment and ultimate coronary revascularization. However, there is no convincing evidence that such benefit exists.

Patients with both unstable CAD and severe carotid artery occlusive disease represent somewhat of a management dilemma [341] because it is often unclear which disease should be treated first. The severity of cerebrovascular and coronary disease must be evaluated in terms of clinical symptoms and anatomic lesions, and a decision must be made for either a combined or a staged procedure. A staged approach with carotid endarterectomy as the first procedure may result in significant mortality from cardiac causes. [330] Conversely, coronary revascularization first may result in a high incidence of fatal stroke. [342] For patients with both unstable CAD and symptomatic carotid artery disease, a combined procedure has been advocated. [343] Unfortunately, no randomized trials have been performed to assess the benefit of combined verses staged procedures.

Anesthetic Management

Anesthetic management goals for carotid endarterectomy include protection of the heart and brain from ischemic injury, control of heart rate and blood pressure, and ablation of the surgical pain and stress responses. These goals must be achieved with another goal in mind--to have an awake patient at the end of surgery for the purposes of neurologic examination. The preoperative visit is particularly important in patients undergoing carotid surgery. During this visit, a series of blood pressure and heart rate measurements is obtained from which acceptable ranges for perioperative management can be determined. Patients are instructed to continue all long-term cardiac medications up to and including the morning of surgery. Unless contraindications exist, aspirin therapy should be continued throughout the perioperative period. As noted earlier, discontinuation of aspirin therapy may be related to an increased rate of MI and transient ischemic events in patients undergoing carotid endarterectomy. [324] When patients arrive at the hospital on the day of surgery, they are queried regarding any new cardiovascular or cerebrovascular symptoms. Any long-term cardiovascular medications not taken at home are administered in our preoperative holding area whenever possible. Patient reassurance is particularly important at this time because anxiety is associated with increases in heart rate, systemic vascular resistance, and myocardial oxygen consumption, which in this patient population could precipitate significant cardiac morbidity. [96] [344]

We routinely monitor leads II and V5 for detection of rhythm disturbances and ST segment changes. On-line ST segment analysis is particularly helpful and is used routinely. Placement of an intra-arterial catheter for beat-to-beat blood pressure monitoring is utilized in all patients. Central venous and pulmonary artery catheters are usually unnecessary for carotid surgery. If such monitors are used, the subclavian or femoral insertion sites are most practical because inadvertent carotid puncture could compromise blood flow as a result of hematoma. In our experience, the most common reason for central access is difficult or inadequate peripheral access. Intravenous access for fluid and drug administration can be accomplished with a single, secure, medium-bore (16-gauge) catheter. Given that both arms will be tucked to the patient's side, the intravenous catheter must run well after patient positioning.

General Anesthesia

Any of the commonly used induction agents, maintenance anesthetics, and short- to intermediate-acting nondepolarizing muscle relaxants can be safely used during carotid endarterectomy, given that stable hemodynamics are maintained and the patient is awake at the end of the procedure. Our induction technique using sufentanil is as follows. After placement of routine monitors and oxygen by face mask, a

---

sufentanil infusion (0.5-1.0 mug/kg) is initiated. If the patient becomes at all sedated during the planned 10- to 15-minute infusion period, as evidenced by slowed speech or delayed response to questioning, the infusion is discontinued. No additional opioids are administered intraoperatively. Induction of anesthesia is accomplished with incremental doses of thiopental (
8 mg/kg) followed by succinylcholine, unless contraindications exist. Etomidate or propofol may also be used. Esmolol is particularly effective in blunting the increases in heart rate and blood pressure during laryngoscopy and intubation and is used liberally during the induction period. [345] Blood pressure responses during and after endotracheal intubation are unpredictable in this patient population, and the clinician must be prepared for immediate treatment of extremes in blood pressure. Our preference is to use short-acting drugs, such as phenylephrine (50-100 mug) for hypotension and sodium nitroprusside (5-25 mug) for hypertension. Patients with poorly controlled hypertension (diastolic blood pressure >100 mm Hg) require special care. These patient are often intravascularly volume depleted and may have significant hypotension with induction. Administration of fluids intravenously (5 mL/kg), careful titration of anesthetics, and immediate treatment of hypotension are especially important.

Anesthesia is maintained with 50 percent nitrous oxide in oxygen and low-dose (less than one-half MAC) potent inhaled anesthetics. Isoflurane may be preferred because fewer ischemic electroencephalographic (EEG) changes occur during carotid occlusion when compared with halothane [346] [347] or enflurane. [346] [347] [348] In addition, studies utilizing EEG and regional cerebral blood flow measurements suggest that the critical cerebral blood flow (the threshold below which cerebral ischemia develops) is lower for isoflurane than for halothane or enflurane. [346] [347] Although the newer low-solubility agents (sevoflurane and desflurane) may facilitate a more rapid emergence, their use has not been reported for patients undergoing carotid endarterectomy. We typically use vecuronium for muscle relaxation because the procedure rarely lasts longer than 90 minutes. We do not utilize cervical plexus block or request local anesthetic infiltration for skin incision because the surgical stimulation is minimal and is frequently necessary to support blood pressure.

Despite only modest surgical stimulation, hemodynamic fluctuations are common during carotid endarterectomy. Blood pressure and heart rate are controlled within predetermined and individualized ranges during the surgical procedure with short-acting agents whenever possible (esmolol, phenylephrine, nitroglycerin, and sodium nitroprusside). It is generally accepted that blood pressure should be maintained in the high-normal range throughout the procedure and particularly during the period of carotid clamping in an attempt to increase collateral flow and to prevent cerebral ischemia. In patients with contralateral internal carotid artery or severe stenosis, induced hypertension to approximately 10 to 20 percent above baseline is advocated during the period of carotid clamping when neurophysiologic monitoring is not utilized. Blood pressure preservation and/or augmentation can be accomplished by maintaining light levels of general anesthesia or by administering sympathomimetic drugs, such as phenylephrine and ephedrine. Caution must be exercised when utilizing vasopressors to augment blood pressure during carotid endarterectomy because the increases in blood pressure and heart rate may increase myocardial oxygen requirements and increase the risk of myocardial ischemia [349] or infarction. [350] The restrictive use of vasopressors for specific instances of cerebral ischemia has been advocated. [351] In one report, induced hypertension during the period of carotid occlusion was not associated with myocardial ischemia. [352]

Surgical manipulation of the carotid sinus with activation of baroreceptor reflexes can cause abrupt bradycardia and hypotension. Cessation of surgical manipulation promptly restores hemodynamics, and infiltration of the carotid bifurcation with 1 percent lidocaine usually prevents further episodes. [353] Infiltration may increase the incidence of postoperative hypertension. [354]

With closure of the deep fascial layers in the neck, isoflurane is discontinued, nitrous oxide is increased to 70 percent, and ventilation is controlled manually. On application of the surgical dressings, neuromuscular reversal agents are administered, and oxygen is increased to 100 percent. At this time, we decrease external stimuli to the patient by quieting the room, turning off overhead surgical lights, and placing the patient in a head-up recumbent position. Ventilation is gently assisted until the patient spontaneously opens his or her eyes or moves. With rare exceptions, all patients are extubated after neurologic integrity is established. Neurologic deficits on emergence require immediate discussion with the surgeon as to the need for angiography and/or reoperation. The period of emergence and extubation may be associated with marked hypertension and tachycardia, which may require aggressive pharmacologic intervention. Tight hemodynamic control during this period is likely to be more demanding than during induction. [352] Greater hemodynamic stability and decreased pharmacologic intervention during emergence have been reported in patients undergoing carotid endarterectomy with propofol as compared with isoflurane. [352] In addition, a significantly lower incidence of myocardial ischemia on emergence was found in the propofol group compared with the isoflurane group (one of 14 versus six of 13). Of particular note, all patients with myocardial ischemia on emergence had systolic blood pressures greater than 200 mm Hg.

Regional and Local Anesthesia

Regional and local anesthetic techniques for carotid endarterectomy have been in use for more than 35 years, [355] and many centers consider these to be the techniques of choice. [356] [357] Regional anesthesia is accomplished by blocking the C2 to C4 dermatomes by use of a superficial and deep cervical plexus block (Ch. 43) . Subcutaneous infiltration of the surgical field can also provide the necessary sensory blockade. Regional anesthesia allows continuous neurologic assessment of the awake patient, which is believed to be the most sensitive method for detecting inadequate cerebral perfusion and function. Other advantages that have been reported include avoidance of expensive cerebral monitoring, reduced need for shunting, [337] [358] [359] greater stability of blood pressure and decreased vasopressor requirements, [339] [359] and reduced hospital costs. [333] [358] [360]

Local or regional anesthesia requires significant patient cooperation throughout the procedure and is best maintained with constant communication and gentle handling of

tissues. Supplemental infiltration of local anesthetic by the surgeon, especially at the lower border and ramus of the mandible, is frequently helpful. Sedation, if used at all, must be kept to a minimum to allow continuous neurologic assessment. Levels of consciousness, speech, and contralateral hand grip are assessed throughout the procedure. We control blood pressure at or near preoperative levels by use of the same agents used for patients receiving general anesthesia. Blood pressure augmentation with phenylephrine is employed when patients have neurologic changes during carotid artery test clamping or after shunt placement. A 2- to 3-minute test clamp in the awake patient allows prompt identification of patients who would benefit from shunt placement. [361] Patient acceptance of regional anesthesia is high, as evidenced by a 92 percent preference for repeat cervical plexus block for future carotid endarterectomy. [362] The surgical drapes are "tented" over the head and face areas to minimize claustrophobic anxiety. It has been suggested that no absolute contradiction to regional anesthesia for carotid endarterectomy exists. [356] In our practice, we avoid regional anesthesia under the following circumstances: a strong preference for general anesthesia is expressed by the patient (i.e., claustrophobia), language barriers that make communication difficult, and difficult vascular anatomy. Difficult anatomy is usually manifested by a patient with a short neck and a high (more cephalad) bifurcation and may require vigorous submandibular retraction.

Regional Versus General Anesthesia

Most reports comparing local or regional anesthesia with general anesthesia indicate no differences in perioperative stroke or death rate on the basis of anesthetic tech-nique. [333] [356] [357] [358] [360] [363] [364] [365] Three reports have found an increased incidence of perioperative stroke in patients under general anesthesia. [339] [366] [367] An increased incidence of cardiopulmonary complications in patients under general anesthesia has been reported in three studies. [358] [363] [366] Potential disadvantages of local or regional anesthesia include (1) inability to use pharmacologic cerebral protection with anesthetics, (2) patient panic and/or loss of cooperation, (3) seizure or loss of consciousness with carotid clamping, and (4) inadequate access to the airway should conversion to general anesthesia be necessary. Although the incidence of serious complications from cervical plexus block is low, near-toxic levels of local anesthetic have been reported in nearly half of patients after superficial and deep cervical plexus block. [369] Although no major complications related to local anesthetic toxicity were reported, some caution should be used when requesting that a surgeon supplement with additional local anesthetic. Phrenic nerve paresis is common after cervical plexus block [370] and is of little clinical consequence except in patients with severe chronic obstructive pulmonary disease or contralateral diaphragmatic dysfunction. Rates of conversion from regional anesthesia to general anesthesia of approximately 2 to 3 percent have been reported. [356] [371] In patients undergoing carotid endarterectomy under cervical plexus block, ST segment depression occurring during clamping or shortly after declamping was highly predictive of adverse cardiac complications. [372]

Intraoperative neurologic changes during carotid endarterectomy under local or regional anesthesia occur in 2.4 to 24 percent of patients. [371] [373] [374] Patients undergoing carotid endarterectomy under cervical plexus block who experience intraoperative neurologic changes are six times more likely (6.6% versus 1.1%) to have a postoperative stroke. [371] Compared with general anesthesia, regional anesthesia for carotid endarterectomy may be associated with increased levels of blood catecholamines. [375] A high incidence of tachycardia has been reported in patients undergoing regional anesthesia for carotid endarterectomy. [362] To date, no large-scale, prospective, randomized trials have evaluated whether neurologic or cardiac outcomes differ with regional versus general anesthesia. The ultimate decision to use one technique over the other must be based on the surgeon's and the anesthesiologist's experience and the patient's preference.

Carbon Dioxide and Glucose Management

Control of ventilation and carbon dioxide is a matter of some controversy. Hypocapnia is associated with cerebral vasoconstriction, whereas hypercapnia may cause a "steal" phenomenon. It is common practice, therefore, to maintain normocapnia during carotid endarterectomy. There is evidence of increased ischemic injury to neural tissue when ischemia occurs in the presence of hyperglycemia. Although there are no good outcome studies in humans, it is appropriate to maintain a blood glucose level below 250 mg/dL in patients undergoing carotid endarterectomy. [376] Glucose level should be carefully monitored, especially during general anesthesia, to avoid the dangers of hypoglycemia.

Neurologic Monitoring and Cerebral Perfusion

Intraoperative monitoring for cerebral ischemia and/or hypoperfusion, and more recently cerebral emboli, during carotid endarterectomy is controversial (Chs. 19 and 35). Monitoring techniques includes internal carotid artery stump pressure determinations, regional cerebral blood flow measurements, EEC, SSEP measurements, and transcranial Doppler (TCD) imaging. The rationale for the use of such monitoring is based on the need to prevent intraoperative strokes. The primary clinical utility of cerebral monitoring is to identify patients in need of carotid artery shunting; secondarily, the method is used to identify patients who may benefit from blood pressure augmentation.

The internal carotid artery stump pressure represents the back pressure resulting from collateral flow through the circle of Willis via the contralateral carotid artery and the vertebrobasilar system. The advantages of carotid stump pressure monitoring are that it is inexpensive, is relatively easy to obtain, and is continuously available during carotid clamping (dynamic stump pressure). Few centers employ stump pressure monitoring because the accuracy in determining adequacy of collateral flow and the need for selective shunting have been questioned. [374] [377] [378] [379] [380] Although the critical stump pressure is unknown, pressures below 50 mm Hg are thought to be associated with hypoperfusion. [381]

Regional cerebral blood flow measurements during carotid endarterectomy are obtained by intravenous or ipsilateral

carotid artery injection of radioactive xenon and analysis of decay curves obtained from detectors placed over the area of the ipsilateral cortex supplied by the middle cerebral artery. Measurements are typically obtained before, during, and immediately after carotid clamping. This technology, combined with EEG monitoring, has provided important insight into the relationship between regional cerebral blood flow and EEG evidence of cerebral ischemia and the critical regional cerebral blood flow associated with various anesthetics. [347] [348] The expense and the expertise required to make and interpret these blood flow measurements have limited the use of this technology to only a few centers.

Many centers advocate the intraoperative use of EEG monitoring for the detection of cerebral ischemia and subsequent selective shunting. The full 16-channel strip-chart EEG and the processed (compressed spectral array) EEG monitor are utilized for this purpose. Although the processed EEG is more easily interpreted, it is less sensitive than the raw EEG. Significant ischemic EEG changes occur in 10 to 20 percent of monitored patients during carotid clamping under general anesthesia. [351] [382] [383] [384] [385] [386] The presence of a contralateral carotid occlusion may increase the rate of significant ischemic EEG changes to nearly 50 percent during carotid clamping. [385] Ischemic EEG changes may be seen with shunt malfunction, hypotension, or cerebral emboli.

The clinical usefulness of intraoperative EEG as an ischemia monitor during carotid endarterectomy is limited by several factors. [384] First, the EEG may not detect subcortical or small cortical infarcts. Second, false-negative results (neurologic deficit with no ischemic EEG changes intraoperatively) are not uncommon. Patients with preexisting stroke or reversible neurologic deficits may have a particularly high incidence of such results. Third, the EEG is not ischemia specific and may be affected by changes in temperature, blood pressure, and anesthetic depth. Fourth, false-positive results (no perioperative neurologic deficit with significant ischemic EEG changes intraoperatively) occur because not all cerebral ischemia uniformly proceeds to infarction. Last, intraoperative EEG monitoring is inherently limited because most intraoperative strokes are felt to be thromboembolic and most perioperative strokes occur postoperatively. At present, no consistent data demonstrate that EEG is clearly superior to other methods of intraoperative cerebral monitoring or that the use of EEG monitoring improves outcome.

Somatosensory evoked potential monitoring is based on the response of the sensory cortex to electrical impulses from peripheral sensory nerve stimulation. The sensory cortex, being primarily supplied by the middle cerebral artery, is at risk during carotid artery clamping. SSEP monitoring, unlike EEG, is able to detect subcortical sensory pathway ischemia. Characteristic SSEP tracings (decrease in amplitude and/or increase in latency) occur with decreased regional cerebral blood flow and are abolished in primates when flow decreases to less than 12 mL/100 g of brain tissue per minute. [387] No specific amplitude reduction or increase in latency

has been established as a physiologic marker of impaired regional cerebral blood flow under operative conditions in humans. Anesthetics, hypothermia, and blood pressure may affect SSEP significantly, and false-negative results have been reported. [388] The validity of SSEP as an intraoperative monitor of cerebral ischemia during carotid endarterectomy has not been definitively established.

Transcranial Doppler ultrasonography allows continuous measurement of mean blood flow velocity and detection of embolic events in the middle cerebral artery. These param-eters have important clinical implications because most perioperative neurologic deficits are felt to be thromboembolic in origin. [389] With TCD, intraoperative embolization has been detected in more than 90 percent of patients undergoing carotid endarterectomy. [390] [391] Most intraoperative emboli are characteristic of air and are not associated with adverse neurologic outcome. TCD may provide useful information regarding shunt function, malfunction, and incidence of emboli during shunt insertion. Embolization during carotid artery dissection may indicate plaque instability and the need for early carotid artery clamping. [391] One center has reported that combined TCD monitoring and completion angiography resulted in a reduction in intraoperative stroke rate from 4 percent to 0 percent. [392] Early postoperative embolization has been detected in more than 70 percent of patients after carotid endarterectomy [391] and is exclusively particulate in nature. [393] Most TCD-detected emboli occur in the first 2 to 3 hours after surgery. [394] Persistent particulate embolization in the early postoperative period has been shown to predict thrombosis and development of major neurologic deficit. [390] Frequent early postoperative TCD embolic signals have been shown to be highly predictive of early postoperative ipsilateral focal cerebral ischemia. [391] Intervention with dextran has been shown to reduce and ultimately stop sustained embolization after carotid endarterectomy. [394] TCD monitoring has also been reported to detect early asymptomatic carotid artery occlusion and hyperperfusion syndrome after carotid endarterectomy. [395] Although TCD monitoring holds much promise, conclusive evidence demonstrating improved outcome has not been reported.

Postoperative Considerations

Most neurologic complications (transient and permanent) after carotid endarterectomy are explained by intraoperative embolization, hypoperfusion during carotid clamping, and embolization or thrombosis from the endarterectomy site. Other important, but less common, factors include intracerebral hemorrhage and hyperperfusion. Thromboembolic rather than hemodynamic factors appear to be the major mechanism of perioperative neurologic complications, [337] [389] [396] and most perioperative neurologic deficits occur in the postoperative period. [337] [396] [397] [398] [399] It is generally accepted that most neurologic complications are related to surgical technique. Hemodynamic factors may account for up to 21 percent of perioperative strokes. [389] Neurologic complications due to carotid artery thrombosis may occur with an incidence as high as 3.3 percent and are associated with a high rate of major stroke or death, despite immediate operative intervention. [371] [390] [400] [401] [402] The reported incidence of intracerebral hemorrhage after carotid endarterectomy ranges from 0.4 to 2.0 percent. [399] Most intracerebral hemorrhages occur 1 to 5 days after the operation and are associated with significant morbidity and mortality. [403] [404]

Hypertension is common in the postoperative period after carotid endarterectomy. [330] [405] [406] Not surprisingly, patients with poorly controlled preoperative hypertension often have severe hypertension postoperatively. The causes are not well understood, but surgical denervation of the carotid sinus baroreceptors is contributory. [407] [408] Regional anesthesia is associated with less hypertension. [409] Other causes of postoperative hypertension, such as hypoxemia, hypercarbia, bladder distention, and pain, should be excluded and/or treated. Because neurologic and cardiac complications may be associated with postoperative hypertension, [330] [405] [410] [411] [412] [413] blood pressure should be aggressively controlled near preoperative values after surgery. Shortacting drugs are safest and most effective. Patients with persistent hypertension are ultimately converted to longeracting intravenous or oral agents before discharge from the intensive care unit.

Postoperative hyperperfusion syndrome is an abrupt increase in blood flow with loss of autoregulation in the surgically reperfused brain manifesting as headache, seizure, focal neurologic signs, brain edema, and possibly intracerebral hemorrhage. [411] Typically, this syndrome does not occur until several days after carotid endarterectomy. Patients with severe postoperative hypertension and severe preoperative internal carotid artery stenosis are at increased risk for developing this syndrome. [411] [412] [414]

Postoperative hypotension occurs almost as frequently as hypertension after carotid endarterectomy. [415] [416] Carotid sinus baroreceptor hypersensitivity or reactivation likely plays an important role. Postoperative hypotension may be more common after regional anesthesia. [372] [410] [415] [416] [417] To avoid cerebral and myocardial ischemia, hypotension should be corrected promptly. Cardiac output is frequently normal or elevated and systemic vascular resistance reduced in hypotensive patients after carotid endarterectomy. [415] Intensive surveillance for evidence of myocardial and cerebral ischemia and judicious use of fluids and vasopressors are recommended for postoperative hypotension. In most cases, hypotension resolves over a period of 12 to 24 hours.

Cranial and cervical nerve dysfunction after carotid endarterectomy is well documented in the literature. [418] [419] [420] [421] [422] [423] [424] Although most injuries are transient, permanent injuries can lead to significant disability. [418] Patients should be examined for injury to the recurrent laryngeal, superior laryngeal, hypoglossal, and marginal mandibular nerves shortly after extubation. Unilateral recurrent laryngeal nerve injury may result in ipsilateral true vocal cord paralysis in the paramedian position. Although most patients have hoarseness and an impaired cough mechanism, the injury is usually well tolerated. However, bilateral recurrent laryngeal nerve injury and resultant bilateral vocal cord paralysis can result in life-threatening upper airway obstruction. This situation must be anticipated in patients who have undergone previous contralateral carotid endarterectomy or neck surgery.

Carotid body denervation may occur after carotid endarterectomy as a result of surgical manipulation. Although rarely of clinical significance, unilateral loss of carotid body function may result in impaired ventilatory response to mild hypoxema. [425] Bilateral carotid endarterectomy is associated with loss of normal ventilatory and arterial pressure responses to acute hypoxia and increased resting partial pressure of arterial carbon dioxide. [426] In this situation, the central chemoreceptors are the primary sensors to maintain ventilation, and serious respiratory depression may result from opioid administration. [427] Fortunately, most patients require little more than acetaminophen or ketorolac for postoperative pain.

Wound hematoma probably occurs more frequently than is reported in the literature. Most cases are the result of venous oozing and require little more than external compression for 5 to 10 minutes. Expanding hematomas require prompt evaluation at the bedside and immediate evacuation if airway compromise is evident. Aggressive postoperative blood pressure control may help to reduce the incidence of hematoma.

We believe that all patients should be monitored in an intensive care setting for 16 to 24 hours after carotid endarterectomy because most events requiring intervention occur within this time frame. [428] [429] [430] Although some clinicians believe that intensive care monitoring is not routinely required, a significant number of patients do require such monitoring and intervention. [428] [431]

POSTOPERATIVE MANAGEMENT OF VASCULAR PATIENTS

Vascular surgery patients require special attention during the postoperative period because most cardiac complications occur postoperatively, and other problems may arise that require immediate attention. Conventional practice is to monitor all vascular surgery patients in an intensive care unit setting after surgery. Some centers have set up specialized vascular stepdown units, where lower-risk patients can be evaluated frequently by trained nursing staff. There are, however, no clinical trials to support this practice, and most centers admit all vascular surgery patients to the intensive care unit postoperatively.

Myocardial ischemia and cardiac morbidity occur most frequently in the postoperative period. Patients should be carefully monitored for signs and symptoms of ischemia, but up to 90 percent of these episodes are asymp-tomatic. [59] [90] [93] [95] [432] [433] The determinants of myocardial oxygen supply and demand should be optimized for all patients (see Fig. 51-3 (Figure Not Available)) to prevent ischemia before it develops. Dysrhythmias may be secondary to ischemia or to sympathectomy associated with regional anesthesia.

Besides myocardial ischemia and cardiac morbidity, other problems include coagulopathy, either from residual heparin or dilutional coagulopathy after massive transfusion. Even in the absence of coagulopathy, bleeding through fresh vascular anastomoses may occur when significant postoperative hypertension is untreated. Hypovolemia occurs following aortic surgery as a result of significant third-space fluid losses and bleeding. Hypovolemia may lead to hypotension and hypoperfusion of the coronary arteries and/or lower-extremity vascular grafts. Graft occlusion in the lower extremities occurs in 3 to 10 percent of patients [54] [304] [305] after lower-extremity or aortic surgery and should be recognized immediately and surgically corrected. Lowerextremity pulses should be checked at hourly intervals. Some patients require administration of heparin or dextran to prevent thrombosis when the surgical repair is questionable or when patients have diffuse atherosclerotic disease.

Residual hypothermia in the early postoperative period is associated with an increased incidence of myocardial ischemia and cardiac morbidity; therefore, body temperature should be carefully monitored and controlled in all vascular surgery patients. In a prospective randomized trial, the relative risk of early postoperative cardiac morbidity was reduced by 55 percent when normothermia was maintained by use of a forced-air warming system (Fig. 51-14) (Figure Not Available) . [219] In the early postoperative period, vascular surgery patients have a twofold to threefold greater incidence of myocardial ischemia when core temperature is less than 35°C. [220] Even mild hypothermia of
35°C is associated with a 200 to 700 percent increase in norepinephrine levels, [216] [434] generalized vasoconstriction, [435] and increased blood pressure in postoperative patients. [216] Shivering occurs, which increases total body oxygen consumption, but only by about 40 percent in the typical elderly vascular patient. [215]

It is important to control the stress response in the postoperative period. This includes preventing the potential triggers for myocardial ischemia (pain, anemia, hypothermia, hemodynamic extremes, and ventilatory insufficiency). In mechanically ventilated patients, the weaning period is especially stressful, and myocardial ischemia occurs frequently during this time. [436] Careful sedation and expeditious weaning are desirable. When possible, extubation in the operating room is less stressful and is preferable for carotid and lower-extremity vascular surgery patients. For more invasive surgical procedures (TAA and abdominal aortic aneurysm), postoperative mechanical ventilation is usually necessary.

Figure 51-14 (Figure Not Available) (A) Incidence of postoperative cardiac morbidity in patients who were actively warmed with a forced-air system (normothermic) and those who received no warming (hypothermic). Morbid cardiac events (unstable angina, myocardial infarction, or cardiac arrest) occurred more frequently in the hypothermic patients ($P = .03$). Ventricular tachycardia and combined electrocardiographic or morbid events also occurred more frequently in the hypothermic patients ($P = .04$ and $P = .001$, respectively). *(Adapted from Frank et al [219])* (B) Incidence of myocardial ischemia following lower extremity vascular surgery by core temperature on admission to the intensive care unit, anesthetic technique, and age. Patients below 35°C had a two- to threefold greater incidence of ischemia. Patients older than 65 years of age had a twofold greater incidence of ischemia. *(Adapted from Frank et al [220])*

Vascular surgery continues to challenge the anesthesiologist, given the significant physiologic stress superimposed on a relatively elderly patient population with a high incidence of coexisting disease. Clinical studies provide insight into the preoperative assessment and optimization of cardiac risk, the implications of anesthetic technique, and the diagnosis, prevention, and treatment of myocardial ischemia in vascular surgery patients. These studies have improved our ability to care for the vascular surgery patient with reduced morbidity and better overall outcome.

References

1. Zwolak RM, Cronenwett JL: Pathophysiology of vascular disease. In Yeager MP, Glass DD (eds): Anesthesiology and Vascular Surgery. East Norwalk, CT, Appleton & Lange, 1990, p 3.

2. Virchow R: Phlogose und Thrombose im Gefassystem. In Gesammelte Abhandlungen zur Wissenschaftlichen Medicin. Frankfurt-am-Main, Meidinger Sohn & Company, 1856, p 458.

3. Ross R, Glomset JA: The pathogenesis of atherosclerosis (first of two parts). N Engl J Med 295:369, 1976.

4. Ross R, Glomset JA: The pathogenesis of atherosclerosis (second of two parts). N Engl J Med 295:420, 1976.

5. Benditt EP, Benditt JM: Evidence for a monoclonal origin of human atherosclerotic plaques. Proc Natl Acad Sci U S A 70:1753, 1973.

6. Martin GM, Sprague CA: Symposium on in vitro studies related to atherogenesis: Life histories of hyperplastoid cell lines from aorta and skin. Exp Mol Pathol 18:125, 1973.

7. Fry DL: Acute vascular endothelial changes associated with increased blood velocity gradients. Circ Res 22:165, 1968.

8. Burkman RT: Lipid and lipoprotein changes in relation to oral contraception and hormonal replacement therapy. Fertil Steril 49:39S, 1988.

9. Roizen MF: Arterial aging: Keeping the roadways clear. In Real Age: Are You as Young as You Can Be? New York, Harper Collins, February 1999.

10. Small DM: George Lyman Duff Memorial Lecture. Progression and regression of atherosclerotic lesions: Insights from lipid physical biochemistry. Arteriosclerosis 8:103, 1988.

11. Roizen MF: http://www.realage.com/.

12. Mangano DT: Perioperative cardiac morbidity. Anesthesiology 72:153, 1990.

13. Hertzer NR: Cardiac risk factors in peripheral vascular surgery. In Estafanous FG (ed): Anesthesia and the Heart Patient. Ohio, Butterworths, 1989, p 173.

14. Bry JD, Belkin M, O'Donnell TF et al: An assessment of the positive predictive value and cost-effectiveness of dipyridamole myocardial scintigraphy in patients undergoing vascular surgery. J Vasc Surg 19:112, 1994.

15. Eagle KA, Brundage BH, Chaitman BR et al: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 27:910, 1996.

16. Goldman L, Caldera DL, Nussbaum SR et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 297:845, 1977.

17. Lette J, Waters D, Lassonde J et al: Multivariate clinical models and quantitative dipyridamole-thallium imaging to predict cardiac morbidity and death after vascular reconstruction. J Vasc Surg 14:1991.

18. Lette J, Waters D, Bernier H et al: Preoperative and long-term cardiac risk assessment: Predictive value of 23 clinical descriptors, 7 multivariate scoring systems, and quantitative dipyridamole imaging in 360 patients. Ann Surg 216:192, 1992.

---

19. Detsky AS, Abrams HB, Forbath N et al: Cardiac assessment for patients undergoing noncardiac surgery. Arch Intern Med 146:2131, 1986.

20. Detsky AS, Abrams HB, McLaughlin JR et al: Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1:211, 1986.

21. Zeldin RA: Assessing cardiac risk in patients who undergo noncardiac surgical procedures. Can J Surg 27:402, 1984.

22. Chiariello M, Indolfi C: Silent myocardial ischemia in patients with diabetes mellitus. Circulation 93:2089, 1996.

23. Goldman L, Caldera DL, Southwick FS et al: Cardiac risk factors and complications in non-cardiac surgery. Medicine 57:357, 1978.

24. Steen PA, Tinker JH, Tarhan S: Myocardial reinfarction after anesthesia and surgery. JAMA 239:2566, 1978.

25. Tarhan S, Moffitt EA, Taylor WF et al: Myocardial infarction after general anesthesia. JAMA 220:1451, 1972.

26. Fleisher LA, Barash PG: Preoperative cardiac evaluation for noncardiac surgery: A functional approach. Anesth Analg 74:586, 1992.

27. Hertzer NR, Beven EG, Young JR et al: Coronary artery disease in peripheral vascular patients: A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 199:223, 1984.

28. Krupski WC, Layug EL, Reilly LM et al: Comparison of cardiac morbidity between aortic and infrainguinal operations: Study of Perioperative Ischemia (SPI) Research Group. J Vasc Surg 15:354, 1992.

29. Krupski WC, Layug EL, Reilly LM et al: Comparison of cardiac morbidity rates between aortic and infrainguinal operations: Two-year follow-up. Study of Perioperative Ischemia Research Group. J Vasc Surg 18:609, 1993.

30. Fleisher LA, Nelson AH, Rosenbaum SH: Failure of negative dipyridamole thallium scans to predict perioperative myocardial ischaemia and infarction. Can J Anaesth 39:179, 1992.

31. Ashton CM, Petersen NJ, Wray NP et al: The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 118:504, 1993.

32. Raby KE, Barry J, Creager MA et al: Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. JAMA 268:222, 1992.

33. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107, 1985.

34. The fifth report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 153:154, 1993.

35. Slogoff S, Keats AS: Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 68:676, 1988.

36. Stone JG, Foex P, Sear JW et al: Myocardial ischemia in untreated hypertensive patients: Effect of a single small oral dose of a betaadrenergic blocking agent. Anesthesiology 68:495, 1988.

37. Pasternack PF, Grossi EA, Baumann FG et al: Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. Am J Surg 158:113, 1989.

38. Mangano DT, Layug EL, Wallace A et al: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery: Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 335:1713, 1996.

39. Wallace A, Layug B, Tateo I et al: Prophylactic atenolol reduces postoperative myocardial ischemia. Anesthesiology 88:7, 1998.

40. Flacke JW, Bloor BC, Flacke WE et al: Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 67:11, 1987.

41. Ghignone M, Calvillo, Quintin KL: The effect of clonidine on perioperative hemodynamics and isoflurane requirements. Anesthesiology 67:3, 1987.

42. Coriat P, Richer C, Douraki T et al: Influence of chronic angiotensin-converting enzyme inhibition on anesthetic induction. Anesthesiology 81:299, 1994.

43. Rao TL, Jacobs KH, El-Etr AA: Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 59:499, 1983.

44. Fisch C: Evolution of the clinical electrocardiogram. J Am Coll Cardiol 14:1127, 1989.

45. Palda VA, Detsky AS: Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. Ann Intern Med 127:309, 1997.

46. Cutler BS, Wheeler HB, Paraskos JA et al: Applicability and interpretation of electrocardiographic stress testing in patients with peripheral vascular disease. Am J Surg 141:501, 1981.

47. McPhail N, Calvin JE, Shariatmadar A et al: The use of preoperative exercise testing to predict cardiac complications after arterial reconstruction. J Vasc Surg 7:60, 1988.

48. Takase B, Younis LT, Byers SL et al: Comparative prognostic value of clinical risk indexes, resting two-dimensional echocardiography, and dipyridamole stress thallium-201 myocardial imaging for perioperative cardiac events in major nonvascular surgery patients. Am Heart J 126:1099, 1993.

49. Kaaja R, Sell H, Erkola O et al: Predictive value of manual ECGmonitored exercise test before abdominal aortic or peripheral vascular surgery. Angiology 44:11, 1993.

50. Baron JF, Mundler O, Bertrand M et al: Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. N Engl J Med 330:663, 1994.

51. Mangano DT, London MJ, Tubau JF et al: Dipyridamole thallium-201 scintigraphy as a preoperative screening test: A reexamination of its predictive potential. Study of Perioperative Ischemia Research Group. Circulation 84:493, 1991.

52. Eagle KA, Coley CM, Newell JB et al: Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 110:859, 1989.

53. Fleisher LA, Rosenbaum SH, Nelson AH et al: Preoperative dipyridamole thallium imaging and ambulatory electrocardiographic monitoring as a predictor of perioperative cardiac events and long-term outcome [see comments]. Anesthesiology 83:906, 1995.

54. Christopherson R, Beattie C, Frank SM et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery: Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 79:422, 1993.

55. Raby KE, Goldman L, Creager MA et al: Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. N Engl J Med 321:1296, 1989.

56. Gottlieb SO: Perioperative myocardial ischemia and infarction: Detection of myocardial ischemia using continuous electrocardiography. Int Anesthesiol Clin 30:19, 1992.

57. Gottlieb SO, Gottlieb SH, Achuff SC et al: Silent ischemia on Holter monitoring predicts mortality in high risk postinfarction patients. JAMA 259:1030, 1988.

58. Gottlieb SO, Weisfeldt ML, Ouyang P et al: Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med 314:1214, 1986.

59. Ouyang P, Gerstenblith G, Furman WR et al: Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. Am J Cardiol 64:1113, 1989.

60. Frank SM, Beattie C, Christopherson R et al: Perioperative raterelated silent myocardial ischemia and postoperative death. J Clin Anesth 2:326, 1990.

61. Pasternack PF, Grossi EA, Baumann FG et al: The value of silent myocardial ischemia monitoring in the prediction of perioperative myocardial infarction in patients undergoing peripheral vascular surgery. J Vasc Surg 10:617, 1989.

62. Mangano DT, Browner WS, Hollenberg M et al: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery: The Study of Perioperative Ischemia Research Group. N Engl J Med 323:1781, 1990.

63. Goldman L: Cardiac risk assessment in patients with arteriosclerotic vascular disease. In Kaplan JA (ed): Vascular Anesthesia. New York, Churchill Livingstone, 1991, p 1.

64. Robotham JL, Takata M, Berman M et al: Ejection fraction revisited. Anesthesiology 74:172, 1991.

65. Nishimura RA, Reeder GS, Miller FAJ et al: Prognostic value of predischarge 2-dimensional echocardiogram after acute myocardial infarction. Am J Cardiol 53:429, 1984.

66. Lalka SG, Sawada SG, Dalsing MC et al: Dobutamine stress echocardiography as a predictor of cardiac events associated with aortic surgery. J Vasc Surg 15:831, 1992.

67. Langan EM, Youkey JR, Franklin DP et al: Dobutamine stress echocardiography for cardiac risk assessment before aortic surgery. J Vasc Surg 18:905, 1993.

68. Poldermans D, Fioretti PM, Forster T et al: Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular surgery. Circulation 87:1506, 1993.

69. Davila RV, Waggoner AD, Sicard GA et al: Dobutamine stress echocardiography predicts surgical outcome in patients with an aortic aneurysm and peripheral vascular disease. J Am Coll Cardiol 21:957, 1993.

70. Eichelberger JP, Schwarz KQ, Black ER et al: Predictive value of dobutamine echocardiography just before noncardiac vascular surgery. Am J Cardiol 72:602, 1993.

71. Poldermans D, Arnese M, Fioretti P et al: Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. J Am Coll Cardiol 26:648, 1995.

72. Mantha S, Roizen MF, Barnard J et al: Relative effectiveness of four preoperative tests for predicting adverse cardiac outcomes after vascular surgery: A meta-analysis. Anesth Analg 79:22, 1994.

73. Pasternack PF, Imparato AM, Bear G et al: The value of radionuclide angiography as a predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysm resection. J Vasc Surg 1:320, 1984.

74. Pasternack PF, Imparato AM, Riles TS et al: The value of the radionuclide angiogram in the prediction of perioperative myocardial infarction in patients undergoing lower extremity revascularization procedures. Circulation 72(suppl II):13, 1985.

75. Franco CD, Goldsmith J, Veith FJ et al: Resting gated pool ejection fraction: A poor predictor of perioperative myocardial infarction in patients undergoing vascular surgery for infrainguinal bypass grafting. J Vasc Surg 10:656, 1989.

76. McCann RL, Wolfe WG: Resection of abdominal aortic aneurysm in patients with low ejection fractions. J Vasc Surg 10:240, 1989.

77. Hertzer NR, Young JR, Beven EG et al: Late results of coronary bypass in patients with peripheral vascular disease. II. Five-year survival according to sex, hypertension, and diabetes. Cleve Clin J Med 54:15, 1987.

78. Foster ED, Davis KB, Carpenter JA et al: Risk of noncardiac operation in patients with defined coronary disease: The coronary artery surgery study (CASS) registry experience. Ann Thorac Surg 41:42, 1986.

79. Allen JR, Helling TS, Hartzler GO: Operative procedures not involving the heart after percutaneous transluminal coronary angioplasty. Surg Gynecol Obstet 173:285, 1991.

80. Huber KC, Evans MA, Bresnahan JF et al: Outcome of noncardiac operations in patients with severe coronary artery disease successfully treated preoperatively with coronary angioplasty. Mayo Clin Proc 67:15, 1992.

81. Tisi GM: Preoperative evaluation of pulmonary function: Validity, indications, and benefits. Am Rev Respir Dis 119:293, 1979.

82. Hirshman CA: Perioperative management of the asthmatic patient. Can J Anaesth 38:R26, 1991.

83. Yeager MP, Glass DD, Neff RK et al: Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 66:729, 1987.

84. Byrd L, Sherman RL: Radiocontrast-induced acute renal failure: A clinical and pathophysiologic review. Medicine 58:270, 1979.

85. Gamulin Z, Forster A, Simonet F et al: Effects of renal sympathetic blockade on renal hemodynamics in patients undergoing major aortic abdominal surgery. Anesthesiology 65:688, 1986.

86. Cronewett JL, Lindenauer SM: Distribution of intrarenal blood flow following aortic clamping and declamping. J Surg Res 22:469, 1977.

87. Diehl JT, Cali RF, Hertzer NR et al: Complications of abdominal aortic reconstruction: An analysis of perioperative risk factors in 557 patients. Ann Surg 197:49, 1983.

88. Beattie C, Fleisher LA: Perioperative myocardial ischemia and infarction. In Beattie C, Fleisher LA (eds): International Anesthesiology Clinics. Boston, Little, Brown, 1992, p 12.

89. Nyhan D, Schultheis L: The role of oxygen-carrying capacity in myocardial ischemia. In Beattie C, Fleisher LA (eds): Perioperative Myocardial Ischemia and Infarction. Boston, Little, Brown, 1992, p 101.

90. Mangano DT, Wong MG, London MJ et al: Perioperative myocardial ischemia in patients undergoing noncardiac surgery: II. Incidence and severity during the 1st week after surgery. J Am Coll Cardiol 17:851, 1991.

91. Mangano DT, Wong MG, London MJ et al: Perioperative myocardial ischemia in patients undergoing noncardiac surgery: I. Incidence and severity during the 4 day perioperative period. J Am Coll Cardiol 17:843, 1991.

92. Breslow MJ, Parker SD, Frank SM et al: Determinants of catecholamine and cortisol responses to lower extremity revascularization: The PIRAT Study Group. Anesthesiology 79:1202, 1993.

93. Mangano DT: Characteristics of electrocardiographic ischemia in high-risk patients undergoing surgery. J Electrocardiol 23(suppl): 20-27, 1990.

94. Fleisher LA, Rosenbaum SH, Nelson AH et al: The predictive value of preoperative silent ischemia for postoperative ischemic cardiac events in vascular and nonvascular surgery patients. Am Heart J 122(4 Pt 1):980-986, 1991.

95. Knight AA, Hollenberg M, London MJ et al: Perioperative myocardial ischemia: Importance of the preoperative ischemic pattern. Anesthesiology 68:681, 1988.

96. Roy WL, Edelist G, Gilbert B: Myocardial ischemia during noncardiac surgical procedures in patients with coronary-artery disease. Anesthesiology 51:393, 1979.

97. Robinson BF: Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. Circulation 35:1073, 1967.

98. Moffitt EA, Sethna DH, Gray RJ et al: Rate-pressure product correlates poorly with myocardial oxygen consumption during anaesthesia in coronary patients. Can Anaesth Soc J 31:5, 1984.

99. Lieberman RW, Orkin FK, Jobes DR et al: Hemodynamic predictors of myocardial ischemia during halothane anesthesia for coronary-artery revascularization. Anesthesiology 59:36, 1983.

100. Buffington CW: Hemodynamic determinants of ischemic myocardial dysfunction in the presence of coronary stenosis in dogs. Anesthesiology 63:651, 1985.

101. Gordon MA, Urban MK, O'Connor T et al: Is the pressure rate quotient a predictor or indicator of myocardial ischemia as measured by ST-segment changes in patients undergoing coronary artery bypass surgery? Anesthesiology 74:848, 1991.

102. Leung JM, O'Kelly BF, Mangano DT: Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand in patients undergoing CABG surgery. Anesthesiology 73:802, 1990.

103. Consensus Conference: Perioperative red blood cell transfusion. JAMA 260:2700, 1988.

104. American College of Physicians: Practice strategies for elective red blood cell transfusion. Ann Intern Med 116:403, 1992.

105. Christopherson R, Frank SM, Norris EJ et al: Low postoperative hematocrit is associated with cardiac ischemia in high risk patients [Abstract]. Anesthesiology 75:A99, 1991.

106. Nelson AH, Fleisher LA, Rosenbaum SH: Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. Crit Care Med 21:860, 1993.

107. Landesberg G, Luria MH, Cotev S et al: Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 341:715, 1993.

108. London MJ: Monitoring for myocardial ischemia. In Kaplan JA (ed): Vascular Anesthesia. New York, Churchill Livingston, 1991, p 249.

109. Deanfield JE, Shea M, Ribiero P et al: Transient ST-segment depression as a marker of myocardial ischemia during daily life. Am J Cardiol 54:1195, 1984.

110. Cohn PF, Brown EJ, Wynne J et al: Global and regional left ventricular ejection fraction abnormalities during exercise in patients with silent myocardial ischemia. J Am Coll Cardiol 1:931, 1983.

111. Levy RD, Shapiro LM, Wright C et al: The haemodynamic significance of asymptomatic ST segment depression assessed by ambulatory pulmonary artery pressure monitoring. Br Heart J 56:526, 1986.

112. Gottlieb SO: Detection of myocardial ischemia using continuous electrocardiography. In Beattie C, Fleisher LA (eds): Perioperative Myocardial Ischemia and Infarction. Boston, Little, Brown, 1992,

p 19.

113. Arbeit SR, Rubin IL, Gross H: Dangers in interpreting the electrocardiogram from the oscilloscope monitor. JAMA 211:453, 1970.

114. London MJ, Hollenberg M, Wong MG et al: Intraoperative myocardial ischemia: Localization by continuous 12-lead electrocardiography. Anesthesiology 69:232, 1988.

115. Battler A, Froelicher VF, Gallagher KP et al: Dissociation between regional myocardial dysfunction and ECG changes during ischemia in the conscious dog. Circulation 62:735, 1980.

116. Kaplan JA, Wells PH: Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 60:789, 1981.

117. Allen EV: Thromboangiitis obliterans: Methods of diagnosis of chronic occlusive arterial lesions distal to the wrist with illustrative cases. Am J Med Sci 178:237, 1929.

118. Mangano DT, Hickey RF: Ischemic injury following uncomplicated radial artery catheterization. Anesth Analg 58:55, 1979.

119. Slogoff S, Keats AS, Arlund C: On the safety of radial artery cannulation. Anesthesiology 59:42, 1983.

120. Frank SM, Norris EJ, Christopherson R et al: Right- and left-arm blood pressure discrepancies in vascular surgery patients. Anesthesiology 75:457, 1991.

121. Anidjar S, Kieffer E: Pathogenesis of acquired aneurysms of the abdominal aorta. Ann Vasc Surg 6:298, 1992.

122. He CM, Roach MR: The composition and mechanical properties of abdominal aortic aneurysms. J Vasc Surg 20:6, 1994.

123. Sonesson B, Hansen F, Lanne T: Abdominal aortic aneurysm: A general defect in the vasculature with focal manifestations in the abdominal aorta? J Vasc Surg 26:247, 1997.

124. White JV, Haas K, Phillips S et al: Adventitial elastolysis is a primary event in aneurysm formation. J Vasc Surg 17:371, 1993.

125. Melton LJI, Bickerstaff LK, Hollier LH et al: Changing incidence of abdominal aortic aneurysms: A population-based study. Am J Epidemiol 120:379, 1984.

126. Johnston KW, Scobie TK: Multicenter prospective study of nonruptured abdominal aortic aneurysms. I. Population and operative management. J Vasc Surg 7:69, 1988.

127. Estes JEJ: Abdominal aortic aneurysm: A study of one hundred and two cases. Circulation 2:258, 1950.

128. Dubost C, Allary M, Oeconomos N: Resection of an aneurysm of the abdominal aorta: Re-establishment of the continuity by a preserved arterial graft, with result after five months. Arch Surg 64:405, 1952.

129. Szilagyi DE, Smith RF, DeRusso FJ et al: Contribution of abdominal aortic aneurysmectomy to prolongation of life. Ann Surg 164:678, 1966.

130. Crawford ES, Saleh SA, Bobby JW et al: Infrarenal abdominal aortic aneurysms: Factors influencing survival after operation performed over a 25-year period. Ann Surg 193:699, 1981.

131. Lloyd WE, Paty PSK, Darling RC III et al: Results of 1000 consecutive elective abdominal aortic aneurysm repairs. Cardiovasc Surg 4:724, 1996.

132. Chen JC, Hildebrand HD, Salvain AJ et al: Progress in abdominal aortic aneurysm surgery: Four decades of experience at a teaching center. Cardiovasc Surg 5:150, 1997.

133. Katz DJ, Stanley JC, Zelenock GB: Gender differences in abdominal aortic aneurysm prevalence, treatment, and outcome. J Vasc Surg 25:561, 1997.

134. Ernst CB: Current concepts: Abdominal aortic aneurysm. N Engl J Med 328:1167, 1993.

135. Darling RCI, Kubaska S, Shah DM et al: Bilateral carotid endarterectomy during the same hospital admission. Cardiovasc Surg 4:759, 1996.

136. Nevitt MP, Ballard DJ, Hallett JW: Prognosis of abdominal aortic aneurysm: A population based study. N Engl J Med 321:1009, 1989.

137. Limet R, Sakalikassan N, Adelin A: Determination of the expansion rate and incidence of rupture of abdominal aortic aneurysms. J Vasc Surg 14:541, 1991.

138. Scott RA, Wilson NM, Kay DN: Is surgery necessary for abdominal aortic aneurysm less than 6 cm in diameter? Lancet 342:1395, 1993.

139. Hollier LH, Taylor LM, Ochsner J: Recommended indications for operative treatment of abdominal aortic aneurysms: Report of a subcommittee of the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. J Vasc Surg 15:1046, 1992.

140. Brown PM, Pattenden R, Vernooy C et al: Selective management of abdominal aortic aneurysms in a prospective measurement program. J Vasc Surg 23:213, 1996.

141. Katz DA, Littenberg B, Cronenwett JL: Management of small abdominal aortic aneurysms: Early surgery vs watchful waiting. JAMA 268:2678, 1992.

142. Watson CJ, Walton J, Shaw E et al: What is the long-term outcome for patients with very small abdominal aortic aneurysms. Eur J Vasc Endovasc Surg 14:299, 1997.

143. Gordon T, Kannel WB: Predisposition to atherosclerosis in the head, heart, and legs: The Framingham study. JAMA 221:661, 1972.

144. Brewster DC, Perler BA, Robison JG et al: Aortofemoral graft for multilevel occlusive disease: Predictors of success and need for distal bypass operations. Arch Surg 117:1593, 1982.

145. Brewster DC, Veith FJ: Combined aortoiliac and femoropopliteal occlusive disease. In Veith FJ, Hobson RW, Williams RA et al (eds): Vascular Surgery: Principles and Practice. 2nd ed. New York, McGraw-Hill, 1994, p 459.

146. Szilagyi DE, Elliott JP Jr, Smith RF et al: A thirty-year survey of the reconstructive surgical treatment of aorto-iliac occlusive disease. J Vasc Surg 3:421, 1986.

147. Brewster DC: Current controversies in the management of aortoiliac occlusive disease. J Vasc Surg 25:365, 1997.

148. Harrington ME, Harrington EB, Haimov M et al: Axillofemoral bypass: Compromised bypass for compromised patients. J Vasc Surg 20:195, 1994.

149. Schneider JR, McDaniel MD, Walsh DB et al: Axillofemoral bypass: Outcome and hemodynamic results in high-risk patients. J Vasc Surg 15:952, 1992.

150. Kouchoukos NT, Lell WA, Karp RB et al: Hemodynamic effects of aortic clamping and decompression with a temporary shunt for resection of the descending thoracic aorta. Surgery 85:25, 1979.

151. Roizen MF, Beaupre PN, Alpert RA et al: Monitoring with twodimensional transesophageal echocardiography. J Vasc Surg 1:300, 1984.

152. Shenaq SA, Chelly JE, Karlberg H et al: Use of nitroprusside during surgery for thoracoabdominal aortic aneurysm. Circulation 70(suppl I):7, 1984.

153. Norman NA, Taylor AA, Crawford S et al: Catecholamine release during and after cross-clamping of the descending thoracic aorta. J Surg Res 34:97, 1983.

154. Symbas PN, Pfaender LM, Drucker MH et al: Cross-clamping of the descending aorta. J Thorac Cardiovasc Surg 85:300, 1983.

155. Stokland O, Miller MM, Ilebekk A et al: Mechanisms of hemodynamic responses to occlusion of the descending thoracic aorta. Am J Physiol 238:H423, 1980.

156. Mutch WAC, Thomson IR, Teskey JM et al: Phlebotomy reverses the hemodynamic consequences of thoracic aortic cross-clamping: Relationships between central venous pressure and cerebrospinal fluid pressure. Anesthesiology 74:320, 1991.

157. Gelman S, Khazaeli MB, Orr R et al: Blood volume redistribution during cross-clamping of the descending aorta. Anesth Analg 78:219, 1994.

158. Gregoretti S, Gelman S, Henderson T et al: Hemodynamics and oxygen uptake below and above aortic occlusion during cross-clamping of the thoracic aorta and sodium nitroprusside infusion. J Thorac Cardiovasc Surg 100:830, 1990.

159. Godet G, Bertrand M, Coriat P et al: Comparison of isoflurane with sodium nitroprusside for controlling hypertension during thoracic aortic cross-clamping. J Cardiothorac Anesth 4:177, 1990.

160. Shenaq SA, Casar G, Chelly JE et al: Continuous monitoring of mixed saturation during aortic surgery. Chest 92:796, 1987.

161. Viale JP, Annat GJ, Ravat FM et al: Oxygen uptake and mixed venous oxygen saturation during aortic surgery and the first three postoperative hours. Anesth Analg 73:530, 1991.

162. Gelman S, Patel K, Bishop SP et al: Renal and splanchnic circulation during infrarenal aortic cross-clamping. Arch Surg 119:1394, 1984.

163. Gelman S, Reves JG, Fowler K et al: Regional blood flow during cross-clamping of the thoracic aorta and infusion of sodium nitroprusside. J Thorac Cardiovasc Surg 85:287, 1983.

164. Marini CP, Grubbs PE, Toporoff B et al: Effect of sodium nitroprusside on spinal cord perfusion and paraplegia during aortic cross-clamping. Ann Thorac Surg 47:379, 1989.

165. Lunn JK, Dannemiller FJ, Stanley TH: Cardiovascular responses to clamping of the aorta during epidural and general anesthesia. Anesth Analg 58:372, 1979.

166. Gamulin Z, Forster A, Morel D et al: Effects of infrarenal aortic cross-clamping on renal hemodynamics in humans. Anesthesiology 61:394, 1984.

167. Attia RR, Murphy JD, Snider M et al: Myocardial ischemia due to infrarenal aortic cross-clamping during aortic surgery in patients with severe coronary disease. Circulation 53:961, 1976.

168. Carroll RM, Laravuso RB, Schauble JF: Left ventricular function during aortic surgery. Arch Surg 111:740, 1976.

169. Meloche R, Pottecher T, Audet J et al: Haemodynamic changes due to clamping of the abdominal aorta. Can Anaesth Soc J 24:20, 1977.

170. Colson P, Ribstein J, Seguin JR et al: Mechanisms of renal hemodynamic impairment during infrarenal aortic cross-clamping. Anesth Analg 75:18, 1992.

171. Gooding JM, Archie JP Jr, McDowell H: Hemodynamic response to infrarenal aortic cross-clamping in patients with and without coronary artery disease. Crit Care Med 7:382, 1980.

172. Gewertz BL, Kremser PC, Zarins CK et al: Transesophageal echocardiographic

monitoring of myocardial ischemia during vascular surgery. J Vasc Surg 5:607, 1987.

173. Dodds TM, Burns AK, DeRoo DB et al: Effects of anesthetic technique on myocardial wall motion abnormalities during abdominal aortic surgery. J Cardiothorac Vasc Anesth 11:129, 1997.

174. Damask MC, Weissman C, Rodriguez J et al: Abdominal aortic cross clamping: Metabolic and hemodynamic consequences. Arch Surg 119:1332, 1984.

175. Johnston WE, Balestrieri FJ, Plonk G et al: The influence of periaortic collateral vessels on the intraoperative hemodynamic effects of acute aortic occlusion in patients with aorto-occlusive disease or abdominal aortic aneurysm. Anesthesiology 66:386, 1987.

176. Gelman S: The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 82:1026, 1995.

177. Alpert RA, Roizen MF, Hamilton WK et al: Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. Surgery 95:707, 1984.

178. Roberts AJ, Nora JD, Hughes WA et al: Cardiac and renal responses to cross-clamping of the descending thoracic aorta. J Thorac Cardiovasc Surg 86:732, 1983.

179. Kataja JHK, Kaukinen S, Viinamaki OVK et al: Hemodynamic and hormonal changes in patients pretreated with captopril for surgery of abdominal aorta. J Cardiovasc Anesth 3:425, 1989.

180. Paul MD, Mazer CD, Byrick RJ et al: Influence of mannitol and dopamine on renal function during elective infrarenal aortic clamping in man. Am J Nephrol 6:427, 1986.

181. Pass LJ, Eberhart RC, Brown JC et al: The effect of mannitol and dopamine on the renal response to thoracic aortic cross-clamping. J Thorac Cardiovasc Surg 95:608, 1988.

182. Baldwin L, Henderson A, Hickman P: Effect of postoperative low dose dopamine on renal function after elective major vascular surgery. Ann Intern Med 120:744, 1994.

183. Abbott WM, Austen WG: The reversal of renal cortical ischemia during aortic occlusion by mannitol. J Surg Res 16:482, 1974.

184. Flores J, DiBona DR, Beck CH et al: The role of cell swelling in ischemic renal damage and the protective effect of hypertonic solute. J Clin Invest 51:118, 1972.

185. Stewart JR, Blackwell WH, Crute SL et al: Inhibition of surgically induced ischemia/reperfusion injury by oxygen free radicals. J Thorac Cardiovasc Surg 86:262, 1983.

186. Thompson JE, Vollman RW, Austin DJ et al: Prevention of hypotension and renal complications of aortic surgery using balanced salt solution: Thirteen year experience with 670 cases. Ann Surg 167:767, 1968.

187. Bush HL, Huse JB, Johnson WC et al: Prevention of renal insufficiency after abdominal aortic aneurysm resection by optimal volume loading. Arch Surg 116:1517, 1981.

188. Whittemore AD, Clowes AW, Hechtman HB et al: Aortic aneurysm repair: Reduced operative mortality associated with maintenance of optimal cardiac performance. Ann Surg 192:414, 1980.

189. Hesdorffer CS, Milne JF, Meyers AM et al: The value of Swan-Ganz catheterization and volume loading in preventing renal failure in patients undergoing abdominal aneurysmectomy. Clin Nephrol 28:272, 1987.

190. Zaidan JR, Guffin AV, Perdue G et al: Hemodynamics of intravenous nitroglycerin during aortic clamping. Arch Surg 117:1285, 1982.

191. Dentz ME, Lubarsky DA, Smith LR et al: A comparison of amrinone with sodium nitroprusside for control of hemodynamics during infrarenal abdominal aortic surgery. J Cardiothorac Vasc Anesth 9:486, 1995.

192. Reiz S, Peter T, Rais O: Hemodynamic and cardiometabolic effects of infrarenal aortic and common iliac artery declamping in man: An approach to optimal volume loading. Acta Anaesth Scand 23:579, 1979.

193. Mangano DT: Monitoring pulmonary arterial pressure in coronary-artery disease. Anesthesiology 53:364, 1980.

194. Harpole DH, Clements FM, Quill T et al: Right and left ventricular performance during and after abdominal aortic aneurysm repair. Ann Surg 209:356, 1989.

195. Clements FM, Harpole DH, Quill T et al: Estimation of left ventricular volume and ejection fraction by two-dimensional transesophageal echocardiography: Comparison of short axis imaging and simultaneous radionuclide angiography. Br J Anaesth 64:331, 1990.

196. Gallagher K, Kumada T, Koziol J et al: Significance of regional wall thickening abnormalities relative to transmural myocardial perfusion in anesthetized dogs. Circulation 62:1266, 1980.

197. Kerber R, Marcus M, Ehrhardt J et al: Correlation between echocardiographically demonstrated segmental dyskinesis and regional myocardial perfusion. Circulation 52:1097, 1975.

198. Massie BM, Botvinick EH, Brundage BH et al: Relationship of regional myocardial perfusion to segmental wall motion: A physiological basis for understanding the presence of reversibility of asynergy. Circulation 58:1154, 1978.

199. Hauser AM, Gangadharan V, Ramos R et al: Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: Echocardiographic observations during coronary angioplasty. J Am Coll Cardiol 5:193, 1985.

200. London MJ, Tubau JF, Wong MG et al: The "natural history" of segmental wall motion abnormalities in patients undergoing noncardiac surgery. Anesthesiology 73:644, 1990.

201. Eisenberg MJ, London MJ, Leung JM et al: Monitoring for myocardial ischemia during noncardiac surgery. A technology assessment of transesophageal echocardiography and 12-lead electrocardiography. JAMA 268:210, 1992.

202. Hallett JW Jr, Popovsky M, Ilstrup D: Minimizing blood transfusions during abdominal aortic surgery: Recent advances in rapid autotransfusion. J Vasc Surg 5:601, 1987.

203. Huber TS, McGorray SP, Carlton LC et al: Intraoperative autologous transfusion during elective infrarenal aortic reconstruction: A decision analysis model. J Vasc Surg 25:984, 1997.

204. Hohner P, Backman C, Diamond G et al: Anaesthesia for abdominal aortic surgery in patients with coronary artery disease, Part II: Effects of nitrous oxide on systemic and coronary haemodynamics, regional ventricular function and incidence of myocardial ischemia. Acta Anaesthesiol Scand 38:793, 1994.

205. Her C, Kizelshteyn G, Walker V et al: Combined epidural and general anesthesia for abdominal aortic surgery. J Cardiothorac Anesth 4:552, 1990.

206. Baron JF, Bertrand M, Barre E et al: Combined epidural and general anesthesia versus general anesthesia for abdominal aortic surgery. Anesthesiology 75:611, 1991.

207. Davies MJ, Silbert BS, Mooney PJ et al: Combined epidural and general anaesthesia versus general anaesthesia for abdominal aortic surgery: A prospective randomized trial. Anaesth Intensive Care 21:790, 1993.

208. Bois S, Couture P, Boudreault D et al: Epidural analgesia and intravenous patient-controlled analgesia result in similar rates of postoperative myocardial ischemia after aortic surgery. Anesth Analg 85:1233, 1997.

209. Breslow MJ, Jordan DA, Christopherson R et al: Epidural morphine decreases postoperative hypertension by attenuating sympathetic nervous system hyperactivity. JAMA 261:3577, 1989.

210. Garnett RL, MacIntyre A, Lindsay P et al: Perioperative ischemia in aortic surgery: Combined epidural/general anesthesia and epidural analgesia vs general anesthesia and I.V. analgesia. Can J Anaesth 43:769, 1996.

211. Blunt TJ, Manzuk M, Varley K: Continuous epidural anesthesia for aortic surgery: Thoughts on peer review and safety. Surgery 101:706, 1987.

212. Pecoraro JP, Dardik H, Mauro A et al: Epidural anesthesia as an adjunct to retroperitoneal aortic surgery. Am J Surg 160:187, 1990.

213. Rosenbaum GJ, Arroyo PJ, Sivina M: Retroperitoneal approach used exclusively with epidural anesthesia for infrarenal aortic disease. Am J Surg 168:136, 1994.

214. Frank SM, Raja SN, Fleisher LA et al: Cardiovascular and adrenergic manifestations of cold stress. In Zeisberger E, Schonbaum D, Lomax P (eds): Thermal Balance in Health and Disease: Advances in Pharmacological Sciences. Basel, Birkhauser Verlag, 1994, p 325.

215. Frank SM, Fleisher LA, Olson KF et al: Multivariate determinants of early postoperative oxygen consumption in elderly patients: Effects of shivering, body temperature, and gender. Anesthesiology 83:241, 1995.

216. Frank SM, Higgins MS, Breslow MJ et al: The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia: A randomized clinical trial. Anesthesiology 82:83, 1995.

217. Frank SM: Thermoregulation. In Hemmings HC Jr, Hopkins PM (eds): Fundamental Anesthesia: Integrated Basic and Clinical Sciences. London, Mosby-Wolfe (In press).

218. Bush HLJ, Hydo LJ, Fischer E et al: Hypothermia during elective abdominal aortic aneurysm repair: The high price of avoidable morbidity. J Vasc Surg 21:392, 1995.

219. Frank SM, Fleisher LA, Breslow MJ et al: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. JAMA 277:1127, 1997.

220. Frank SM, Beattie C, Christopherson R et al: Unintentional hypothermia is associated with postoperative myocardial ischemia. Anesthesiology 78:468, 1993.

221. Cheney FW: Should normothermia be maintained during major surgery? JAMA 277:1165, 1997.

222. Culliford AT, Ayvaliotis B, Schemin R et al: Aneurysms of the descending aorta. J Thorac Cardiovasc Surg 85:98, 1983.

223. Williams GM: Thoracoabdominal aneurysm. In Cameron JL (ed): Current Surgical Therapy--3. Toronto, BC Decker, 1989, pp 364-373.

224. Crawford ES: Thoracoabdominal and supra-renal abdominal aortic aneurysm. In Ernst CB, Stanley JC (eds): Current Therapy in Vascular Surgery. Philadelphia, Decker, 1987, p 96.

225. DeBakey ME, Beall AJ, Cooley DA et al: Dissecting aneurysms of the aorta. Surg Clin North Am 46:1045, 1966.

226. Livesay JJ, Cooley DA, Ventemiglia RA et al: Surgical experience in descending thoracic aneurysmectomy with and without adjuncts to avoid ischemia. Ann Thorac Surg 39:37, 1985.

227. Hollier LH, Money SR, Naslund TC et al: Risk of spinal cord dysfunction patients undergoing thoracoabdominal aortic replacement. Am J Surg 164:210, 1992.

228. Crawford SE, Crawford JL, Safi HJ et al: Thoracoabdominal aortic aneurysms: Preoperative and intraoperative factors determining immediate and long term results of operations in 605 patients. J Vasc Surg 3:389, 1986.

229. Hollier LH, Money SR, Naslund TC et al: Thoracoabdominal aortic aneurysm repair: Analysis of postoperative morbidity. Arch Surg 123:871, 1988.

230. Svensson LG, Coselli JC, Safi HJ et al: Appraisal of adjuncts to prevent acute renal failure after surgery on the thoracic or thoracoabdominal aorta replacement. J Vasc Surg 10:230, 1989.

231. Banoub M, Kagan-Koepke TD, Shenaq S: Anesthesia for thoracic aortic surgery. In Estafanous FG, Barash PG, Reves JG (eds): Cardiac Anesthesia: Principles and Clinical Practice. Philadelphia, JB Lippincott, 1994, p 545.

232. Mori M, Chuma R, Kiichi Y et al: The anesthetic management of a patient with a thoracic aneurysm that caused compression of the left mainstem bronchus and the right pulmonary artery. J Cardiothorac Vasc Anesth 7:579, 1993.

233. Gorman RB, Merritt WT, Greenspun H et al: Aneurysmal compression of the trachea and right mainstem bronchus complicating thoracoabdominal aneurysm repair. Anesthesiology 79:1424, 1993.

234. Coles JG, Wilson GJ, Sima AF: Intraoperative detection of spinal cord ischemia using somatosensory evoked potentials during thoracic occlusion. Ann Thorac Surg 34:299, 1980.

235. McPherson RW, Mahla M, Johnson R, Traystman RJ: Effects of enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials during fentanyl anesthesia. Anesthesiology 62:626,

1985.

236. Markland ON, Warren CH, Moorthy SS: Monitoring of multimodality evoked potentials during open heart surgery under hypothermia. Electroencephalogr Clin Neurophysiol 59:432, 1984.

237. Drenger B, Parker SD, McPherson RW et al: Spinal cord stimulation evoked potentials during thoracoabdominal aortic aneurysm surgery. Anesthesiology 76:689, 1992.

238. Svensson LG, Patel V, Robinson MF: Influence of preservation or perfusion of intraoperatively identified spinal cord blood supply on spinal motor evoked potentials and paraplegia after aortic surgery. J Vasc Surg 13:355, 1991.

239. Laschinger JC, Owen J, Rosenbloom N: Direct non-invasive monitoring of spinal function during thoracic aortic occlusion: Use of motor evoked potentials. J Vasc Surg 7:161, 1988.

240. Frank SM, Parker SD, Rock P et al: Moderate hypothermia, with partial bypass and segmental sequential repair for thoracoabdominal aortic. J Vasc Surg 19:687, 1994.

241. Katz NM, Blackstone EH, Kirklin JW et al: Incremental risk factors for spinal cord injury following operations for acutely traumatic aortic transection. J Thorac Cardiovasc Surg 81:669, 1981.

242. Gloviczki P, Bower TC: Visceral and spinal cord protection during thoracoabdominal aortic reconstructions. Semin Vasc Surg 5:163, 1992.

243. Shenaq SA, Svensson LG: Paraplegia following aortic surgery. J Cardiothorac Vasc Anesth 7:81, 1993.

244. Gott VL: Heparinized shunts for thoracic vascular operations. Ann Thorac Surg 14:219, 1972.

245. Clark AM, Frank SM, Williams GM et al: Descending aortic aneurysm repair utilizing moderate hypothermia (30°C) in conjunction with left heart bypass. J Extracorpor Tech 26:172, 1994.

246. Ueda Y, Miki S, Kusuhara K et al: Surgical treatment of aneurysm or dissection involving the ascending aorta and aortic arch, utilizing circulatory arrest and retrograde cerebral perfusion. Cardiovasc Surg 31:553, 1990.

247. Takamoto S, Matsuda T, Harada M et al: Simple hypothermic retrograde cerebral perfusion during aortic arch replacement. J Thorac Cardiovasc Surg 104:1106, 1992.

248. Najafi H, Javid H, Hunter J et al: Descending aortic aneurysmectomy without adjuncts to avoid ischemia. Ann Thorac Surg 30:326, 1980.

249. Cox GS, O'Hara PJ, Hertzer NR et al: Thoracoabdominal aneurysm repair: A representative experience. J Vasc Surg 15:780, 1992.

250. Svensson LG, Crawford ES, Hess KR: Dissection of the aorta and dissecting aortic aneurysms. Circulation 82(suppl 4):24, 1990.

251. Crawford ES, Rubio PA: Reappraisal of adjuncts to avoid ischemia in the treatment of aneurysms of the descending thoracic aorta. J Thorac Cardiovasc Surg 66:693, 1973.

252. Mauney MC, Blackbourne LH, Langenburg SE et al: Prevention of spinal cord injury after repair of the thoracic or thoracoabdominal aorta. Ann Thorac Surg 59:245, 1995.

253. Costello TG, Fisher A: Neurological complications following aortic surgery. Anaesthesia 38:230, 1983.

254. Svensson LG, Klepp P, Hinder RA et al: Spinal cord anatomy of the baboon: Comparison with man and implications on spinal cord blood flow during thoracic aortic cross-clamping. S Afr J Surg 24:32, 1986.

255. Svensson LG, Rickards E, Coull A et al: Relationship of spinal cord blood flow to vascular anatomy during thoracic aortic cross-clamping and shunting. J Thorac Cardiovasc Surg 91:71, 1986.

256. Urban M: Spinal cord ischemia: Recognition and prevention. In Blanck TJJ (ed): Neuroprotection. Baltimore, Williams & Wilkins, 1997, p 135.

257. Doppman JL, Di CG, Morton DL: Arteriographic identification of spinal cord blood supply prior to aortic surgery. JAMA 204:174, 1968.

258. Wadouh F, Lindemann E, Arndt CF et al: The arterial radicularis magna anterior as a decisive factor influencing spinal cord and damage during aortic occlusion. J Thorac Cardiovasc Surg 88:1, 1984.

259. Djindjian R: Arteriography of the spinal cord. Am J Roentgenol 107:461, 1969.

260. Verdant A, Page A, Cossette R et al: Surgery of the descending thoracic aorta: Spinal cord protection with the Gott shunt. Ann Thorac Surg 46:147, 1988.

261. Duhaylongsod FG, Glower DD, Wolfe WG: Acute traumatic aortic aneurysm: The Duke experience from 1970 to 1990. J Vasc Surg 15:331, 1992.

262. Hilgenberg AD, Logan DL, Akins CW et al: Blunt injuries of the thoracic aorta. Ann Thorac Surg 53:233, 1992.

263. Hickey R, Sloan TB, Rogers JN: Functional organization and physiology of the spinal cord. In Porters SS (ed): Anesthesia for Surgery of the Spine. New York, McGraw-Hill, 1995, pp 124-132.

264. Piano G, Gewertz BL: Mechanism of increased cerebrospinal fluid pressure with thoracic aortic occlusion. J Vasc Surg 11:695, 1990.

265. Miyamoto K, Veno A, Wada T et al: A new and simple method of preventing spinal cord damage following temporary occlusion of the thoracic aorta by draining the cerebrospinal fluid. J Cardiovasc Surg 16:188, 1960.

266. Oka Y, Miyamoto T: Prevention of spinal cord injury after cross-clamping of the thoracic aorta. Jpn J Surg 14:159, 1984.

267. Woloszyn T, Corrado P, Marini P et al: Cerbrospinal fluid drainage does not counteract the negative effect of sodium nitroprusside on spinal cord perfusion pressure during aortic cross-clamping. Curr Surg 489:1989.

268. Crawford ES, Svensson LG, Hess KR et al: A prospective randomized study of cerebrospinal fluid drainage to prevent paraplegia after high-risk surgery on the thoracoabdominal aorta. J Vasc Surg 13:36, 1990.

269. Svensson LG, Grum DF, Bernarski M et al: Intrathecal papaverine for the prevention of paraplegia after operation of the thoracic or thoracoabdominal aorta. J Thorac Cardiovasc Surg 96:823, 1988.

270. Drenger B, Parker SD, Frank SM et al: Changes in cerebrospinal fluid pressure and lactate concentrations during thoracoabdominal aortic aneurysm surgery. Anesthesiology 86:41, 1997.

271. Vacanti FX, Ames AI: Mild hypothermia and Mg^{++} protect against irreversible damage during CNS ischemia. Stroke 15:695, 1984.

272. Kouchouskas NT, Wareing TH, Izumoto H et al: Elective hypothermic

cardiopulmonary bypass and circulatory arrest for spinal cord protection during operations on the thoracoabdominal aorta. J Thorac Cardiovasc Surg 99:659, 1990.

273. Colon R, Fraizer OH, Cooley DA et al: Hypothermic regional perfusion for protection of the spinal cord during periods of ischemia. Ann Thorac Surg 43:639, 1987.

274. Coles JG, Wilson GJ, Sima AF et al: Intraoperative management of thoracic aortic aneurysm. J Thorac Cardiovasc Surg 85:292, 1983.

275. Cambria RP, Davidson JK, Zannetti S et al: Clinical experience with epidural cooling for spinal cord protection during thoracic and thoracoabdominal aneurysm repair. J Vasc Surg 25:234, 1995.

276. Nylander WA, Plunkett RJ, Hammon JW et al: Thiopental modification of ischemic spinal cord injury in the dog. Ann Thorac Surg 33:64, 1982.

277. Robertson CS, Foltz R, Grossman RG et al: Protection against experimental ischemic spinal cord injury. J Neurosurg 64:633, 1986.

278. Laschinger JC, Cunningham JN, Cooper MM et al: Prevention of ischemic spinal cord injury following aortic cross-clamping: Use of corticosteroids. Ann Thorac Surg 38:500, 1984.

279. Woloszyn TT, Marini CP, Coons MS et al: Cerebrospinal fluid drainage and steroids provide better spinal cord protection during aortic cross-clamping than does either treatment alone. Ann Thorac Surg 49:79, 1990.

280. Johnson SH, Kraimer JM, Graeber GM: Effects of flunarizine on neurological recovery and spinal cord blood flow in experimental spinal cord ischemia in rabbits. Stroke 24:1547, 1993.

281. Pointillart V, Gense D, Gross C et al: Effects of nimodipine on posttraumatic spinal cord ischemia in baboons. J Neurotrauma 10:201, 1993.

282. Shi RY, Lucas JH, Wolf A et al: Calcium antagonists fail to protect mammalian spinal neurons after physical injury. J Neurotrauma 6:261, 1989.

283. Lyden PD, Zivin JA, Kochhar A et al: Effects of calcium channel blockers on neurologic outcome after focal ischemia in rabbits. Stroke 19:1020, 1988.

284. Rokkas CK, Helfrich LJ, Lobner DC et al: Dextrorphan inhibits the release of excitatory amino acids during spinal cord ischemia. Ann Thorac Surg 58:312, 1994.

285. Simpson JI, Eide TR, Schiff GA et al: Intrathecal magnesium sulfate protects the spinal cord from ischemic injury during thoracic aortic cross-clamping. Anesthesiology 81:1493, 1994.

286. Folis R, Miller K, Scremin OU et al: NMDA receptor blockade and spinal cord ischemia due to aortic cross-clamping in the rat model. Can J Neurol Sci 21:227, 1994.

287. Baskin DS, Hosobuchi Y: Naloxone reversal of ischemic neurological deficits in man. Lancet 2:272, 1981.

288. Faden AI, Jacobs TP, Holaday JW: Comparison of early and late naloxone treatment in experimental spinal cord injury. Neurology 32:677, 1982.

289. Faden AI, Jacobs TP, Smith MT et al: Naloxone in experimental spinal cord ischemia: Dose-response studies. Eur J Pharmacol 103:115, 1984.

290. Acher CW, Wynn MM, Archibald J: Naloxone and spinal fluid drainage as adjuncts in the surgical treatment of thoracoabdominal and thoracic aneurysms. Surgery 108:755, 1990.

291. Svensson LG, Grum DF, Bernarski et al: Appraisal of cerebrospinal fluid alterations during aortic surgery with intrathecal papaverine administration and cerebrospinal fluid drainage. J Vasc Surg 11:243, 1990.

292. Blantz RC: Effect of mannitol on glomerular ultrafiltration in the hydropenic rat. J Clin Invest 54:1135, 1974.

293. Hanley MJ, Davidson K: Prior mannitol and furosemide infusion in a model of ischemic acute renal failure. Am J Physiol 241:F556, 1981.

294. Brown CB, Ogg CS, Cameron JS: High-dose furosemide in acute renal failure: A controlled trial. Clin Nephrol 15:90, 1981.

295. Kleinknecht D, Ganeval D, Gonzales-Duque LA et al: Furosemide in acute oliguric renal failure: A controlled trial. Nephron 17:51, 1976.

296. Dake MD, Miller DC, Semba CP et al: Transluminal placement of endovascular stent-grafts for the treatment of descending thoracic aortic aneurysms. N Engl J Med 331:1729, 1994.

297. Mitchell RS, Dake MD, Sembra CP et al: Endovascular stent-graft repair of thoracic aortic aneurysms. J Thorac Cardiovasc Surg 111:1054, 1996.

298. Stewart MT: Assessment of peripheral vascular disease. In Hurst JW, Schlant RC, Rackley CE et al (eds): The Heart. New York, McGraw-Hill, 1990, p 368.

299. Yao ST: Haemodynamic studies in peripheral arterial disease. Br J Surg 57:761, 1970.

300. Smith RB, Fulenwider JT: Reversed autogenous vein graft for lower extremity occlusive disease. In Ernst CB, Stanley JC (eds): Current Therapy in Vascular Surgery. Toronto, BC Decker, 1987, p 206.

301. Bunt TJ: Aortic reconstruction vs extra-anatomic bypass and angioplasty: Thoughts on evolving a protocol for selection. Arch Surg 121:1166, 1986.

302. Rao TL, El-Etr AA: Anticoagulation following placement of epidural and subarachnoid catheters: An evaluation of neurologic sequelae. Anesthesiology 55:618, 1981.

303. Horlocker TT, Heit JA: Low molecular weight heparin: Biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. Anesth Analg 85:874, 1997.

304. Bode RJ, Lewis KP, Zarich SW et al: Cardiac outcome after peripheral vascular surgery: Comparison of general and regional anesthesia. Anesthesiology 84:3, 1996.

305. Tuman KJ, McCarthy RJ, March RJ et al: Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. Anesth Analg 73:696, 1991.

306. Pierce ET, Pomposelli FB Jr, Stanley GD et al: Anesthesia type does not influence early graft patency or limb salvage rates of lower extremity arterial bypass. J Vasc Surg 25:226, 1997.

307. Rosenfeld BA, Beattie C, Christopherson R et al: The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Anesthesiology 79:435, 1993.

308. Rosenfeld BA: Perioperative hemostatic changes and coronary ischemic syndromes. In Beattie C, Fleisher LA (eds): Perioperative Myocardial Ischemia and Infarction. Boston, Little, Brown, 1992, p 131.

309. Rosenfeld BA, Faraday N, Campbell D et al: Hemostatic effects of stress hormone infusion. Anesthesiology 81:1116, 1994.

310. Haljamae H, Frid I, Holm J et al: Epidural vs. general anesthesia and leg blood flow in patients with occlusive atherosclerotic disease. Eur J Vasc Surg 2:395, 1988.

311. Christopherson R, Glavan NJ, Norris EJ et al: Control of blood pressure and heart rate in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. J Clin Anesth 8:578, 1996.

312. American Heart Association. 1999 Heart and Stroke Statistical Update. Dallas, American Heart Association, 1998, p 13.

313. Matchar DB, Duncan PW: Cost of stroke. Stroke Clin Updates 5:9, 1994.

314. Taylor TN, Davis PH, Torner JC et al: Lifetime cost of stroke in the United States. Stroke 27:1459, 1996.

315. Brown RD, Whisnant JP, Sicks JD et al: Stroke incidence, prevalence, and survival: Secular trends in Rochester, Minnesota, through 1989.Stroke 27:373, 1996.

316. Imparato AM, Riles TS, Gorstein F: The carotid bifurcation plaque: Pathologic findings associated with cerebral ischemia. Stroke 10:238, 1979.

317. Bladin CF, Chambers BR: Frequency and pathogenesis of hemodynamic stroke. Stroke 25:2179, 1994.

318. Stanley JC, Barnes RW, Ernst CB et al: Vascular surgery in the United States: Workforce issues. Report of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery, North American Chapter, Committee on Workforce Issues. J Vasc Surg 23:172, 1996.

319. Pokras R, Dyken ML: Dramatic changes in the performance of endarterectomy for diseases of the extracranial arteries of the head. Stroke 19:1289, 1988.

320. Gillum RF: Epidemiology of carotid endarterectomy and cerebral arteriography in the United States. Stroke 26:1724, 1995.

321. European Carotid Surgery Trialists Collaborative Group: MRC European carotid surgery trial: Interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 337:1235, 1991.

322. North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 325:445, 1991.

323. CASANOVA Study Group: Carotid surgery versus medical therapy in asymptomatic carotid stenosis. Stroke 22:1229, 1991.

324. Mayo Asymptomatic Carotid Endarterectomy Study Group: Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. Mayo Clin Proc 67:513, 1992.

325. Executive Committee for the Asymptomatic Carotid Atherosclerosis

Study: Endarterectomy for asymptomatic carotid artery stenosis. JAMA 273:1421, 1995.

326. Hobson RWI, Weiss DG, Fields WS et al: Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 328:221, 1993.

327. Halliday AW, Thomas D, Mansfield A: The Asymptomatic Carotid Surgery Trial (ACST): Rationale and design. Eur J Vasc Surg 8:703, 1994.

328. Prough DS, Scuderi PE, Stuklen E et al: Myocardial infarction following regional anesthesia for carotid endarterectomy. Can Anaesth Soc J 31:192, 1984.

329. Asiddao CB, Donegan JH, Whitesell RC et al: Factors associated with perioperative complications during carotid endarterectomy. Anesth Analg 61:631, 1982.

330. Ennix CL Jr, Lawrie GM, Morris GC Jr et al: Improved results of carotid endarterectomy in patients with symptomatic coronary disease: An analysis of 1,546 consecutive carotid operations. Stroke 10:122, 1979.

331. Palmer MA: Comparison of regional and general anesthesia for carotid endarterectomy. Am J Surg 157:329, 1989.

332. Zuccarello M, Yeh H, Tew JM: Morbidity and mortality of carotid endarterectomy under local anesthesia: A retrospective study. Neurosurgery 23:445, 1988.

333. Gabelman C, Gann DS, Ashworth CJ et al: One hundred consecutive carotid reconstructions: Local versus regional anesthesia. Am J Surg 145:477, 1983.

334. Thompson JE, Patman RD, Talkington CM: Asymptomatic carotid bruit: Long-term outcome of patients having endarterectomy compared with unoperated controls. Ann Surg 188:308, 1978.

335. Takolander RJ, Bergentz SE, Ericsson BF: Carotid artery surgery in patients with minor stroke. Br J Surg 70:13, 1983.

336. Moore DJ, Modi JR, Finch WT, Sumner DS: Influence of contralateral carotid artery on neurologic complications following carotid endarterectomy. J Vasc Surg 1:409, 1984.

337. Steed DL, Peitzman AB, Grundy BL, Webster MW: Causes of stroke in carotid endarterectomy. Surgery 92:634, 1982.

338. Slavish LG, Nicholas GG, Gee W: Review of a community hospital experience with carotid endarterectomy. Stroke 15:956, 1984.

339. Corson JD, Chang BB, Shah DM et al: The influence of anesthetic choice on carotid endarterectomy outcome. Arch Surg 122:807, 1987.

340. Gil-Peralta A, Mayol A, Gonzalez Marcos JR et al: Percutaneous transluminal angioplasty of the symptomatic atherosclerotic carotid arteries: Results, complications, and follow-up. Stroke 27:2271, 1996.

341. Hertzer NR, Loop FD, Beven EG et al: Surgical staging for simultaneous coronary and carotid disease: A study including prospective randomization. J Vasc Surg 9:455, 1989.

342. Mehigan JT, Buch WS, Pipkin RD et al: A planned approach to coexistent cerebrovascular disease in coronary artery bypass candidates. Arch Surg 112:1403, 1977.

343. Rizzo RJ, Whittemore AD, Couper GS et al: Combined carotid and coronary revascularization: The preferred approach to the severe vasculopath. Ann Thorac Surg 54:1099, 1992.

344. Freeman LJ, Nixon PGF, Sallabank P et al: Psychological stress and silent myocardial ischemia. Am Heart J 114:477, 1987.

345. Cucchiara RF, Benefiel DJ, Matteo RS et al: Evaluation of esmolol in controlling increases in heart rate and blood pressure during endotracheal intubation in patients undergoing carotid endarterectomy. Anesthesiology 65:528, 1986.

346. Blume WT, Ferguson GG, McNeill DK: Significance of EEG changes at carotid endarterectomy. Stroke 17:891, 1986.

347. Michenfelder JD, Sundt TM, Fode N et al: Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischemia during carotid endarterectomy. Anesthesiology 67:336, 1987.

348. Messick JMJ, Casement B, Sharbrough FW et al: Correlation of regional cerebral blood flow (rCBF) with EEG changes during isoflurane anesthesia for carotid endarterectomy: Critical rCBF. Anesthesiology 66:344, 1987.

349. Smith JS, Roizen MF, Cahalan MK et al: Does anesthetic technique make a difference? Augmentation of systolic blood pressure during carotid endarterectomy: Effects of phenylephrine versus light anesthesia and of isoflurane versus halothane on the incidence of myocardial ischemia. Anesthesiology 69:846, 1988.

350. Riles TS, Kopelman I, Imparato AM: Mycardial infarction following carotid endarterectomy: A review of 686 operations. Surgery 85:249, 1979.

351. Modica PA, Tempelhoff R, Rich KM et al: Computerized electroencephalographic monitoring and selective shunting: Influence on intraoperative administration of phenylephrine and myocardial infarction after general anesthesia for carotid endarterectomy. Neurosurgery 30:842, 1992.

352. Mutch WAC, White IWC, Donen N et al: Haemodynamic instability and myocardial ischaemia during carotid endarterectomy: A comparison of propofol and isoflurane. Can J Anaesth 42:60, 1995.

353. Elliott B, Collins G, Youkey J et al: Intraoperative local anesthetic injection of the carotid sinus nerve. Am J Surg 152:695, 1986.

354. Gottlieb A, Satariano-Hayden P, Schoenwald P et al: The effects of carotid sinus nerve blockade on hemodynamic stability after carotid endarterectomy. J Cardiothorac Vasc Anesth 11:67, 1997.

355. Spencer FC, Elsemann B: Technique of carotid endarterectomy. Surg Gynecol Obstet 115:115, 1962.

356. Rockman CB, Riles TS, Gold M et al: A comparison of regional and general anesthesia in patients undergoing carotid endarterectomy. J Vasc Surg 24:946, 1996.

357. Shah DM, Darling RCI, Chang BB et al: Carotid endarterectomy in awake patients: Its safety, acceptability and outcome. J Vasc Surg 19:1015, 1994.

358. Allen BT, Anderson CB, Rubin BG et al: The influence of anesthetic technique on perioperative complications after carotid endarterectomy. J Vasc Surg 19:834, 1994.

359. Forssell C, Takolander R, Bergquist D et al: Local versus general anesthesia in carotid surgery: A prospective randomized study. Eur J Vasc Surg 3:503, 1989.

360. Muskett A, McGreevy J, Miller M: Detailed comparison of regional and general anesthesia for carotid endarterectomy. Am J Surg 152:691, 1986.

361. Benjamin ME, Silva MB Jr, Watt C et al: Awake patient monitoring to determine the need for shunting during carotid endarterectomy. Surgery 114:673, 1993.

362. Davies MJ, Murrell GC, Cronin KD et al: Carotid endarterectomy under cervical plexus block: A prospective clinical audit. Anaesth Intensive Care 18:219, 1990.

363. Ombrellaro MP, Freeman MB, Stevens SL et al: Effect of anesthetic technique on cardiac morbidity following carotid artery surgery. Am J Surg 171:387, 1996.

364. Andersen CA, Rich NM, Collins GJ et al: Carotid endarterectomy: Regional versus general anesthesia. Am Surg 46:323, 1980.

365. Becquemin JP, Paris E, Valverde A et al: Carotid surgery: Is regional anesthesia always appropriate? J Cardiovasc Surg (Torino) 32:592, 1991.

366. Bergeron P, Benichou H, Rudondy P et al: Stroke prevention during carotid surgery in high risk patients (value of transcranial Doppler and local anesthesia). J Cardiovasc Surg (Torino) 32:713, 1991.

367. Fiorani P, Sbarigia E, Speziale F et al: General anesthesia versus cervical block and perioperative complications in carotid artery surgery. Eur J Vasc Endovasc Surg 13:37, 1997.

368. Peitzman AB, Webster MW, Loubeau JM: Carotid endarterectomy under regional (conductive) anesthesia. Ann Surg 196:59, 1982.

369. Tissot S, Frering B, Gagnieu M et al: Plasma concentrations of lidocaine and bupivacaine after cervical plexus block for carotid surgery. Anesth Analg 84:1377, 1997.

370. Castrensana MR, Masters RD, Castrensana EJ et al: Incidence and clinical significance of hemidiaphragmatic paresis in patients undergoing carotid endarterectomy during cervical plexus block anesthesia. J Neurol Anesth 6:21, 1994.

371. Davies MJ, Mooney PH, Scott DA et al: Neurologic changes during carotid endarterectomy under cervical block predict a high risk of postoperative stroke. Anesthesiology 78:829, 1993.

372. Landesberg G, Erel J, Anner H et al: Perioperative myocardial ischemia in carotid endarterectomy under cervical plexus block and prophylactic nitroglycerin infusion. J Cardiothorac Vasc Anesth 7:259, 1993.

373. Slutzki S, Behar M, Negri M et al: Carotid endarterectomy under local anesthesia supplemented with neuroleptic analgesia. Surg Gynecol Obstet 170:141, 1990.

374. Evans WE, Hayes JP, Waltke EA et al: Optimal cerebral monitoring during carotid endarterectomy: Neurological response under local anesthesia. J Vasc Surg 2:775, 1985.

375. Takolander R, Bergquist D, Hulthen UL et al: Carotid artery surgery: Local versus general anaesthesia as related to sympathetic activity and cardiovascular effects. Eur J Vasc Surg 4:265, 1990.

376. Hirsch IB, McGill JB, Cryer PE et al: Perioperative management of surgical patients with diabetes mellitus. Anesthesiology 74:346, 1991.

377. McKay R, Sundt T, Michenfelder J et al: Internal carotid artery stump pressure and cerebral blood flow during carotid endarterectomy. Anesthesiology 45:390, 1976.

378. Whitley D, Cherry KJ: Predictive value of carotid artery stump pressures during carotid endarterectomy. Neurosurg Clin North Am 7:723, 1996.

379. Harada RN, Comerota AJ, Good GM et al: Stump pressure, electroencephalographic changes, and the contralateral carotid artery: Another look at selective shunting. Am J Surg 170:148, 1995.

380. Rosenthal D, Stanton PE, Lamis PA: Carotid endarterectomy: The unreliability of intraoperative monitoring in patients having had stroke or reversible ischemic neurologic deficit. Arch Surg 116:1569, 1981.

381. Youngberg JA, Gold MD: Carotid artery surgery: Perioperative anesthetic considerations. In Kaplan JA (ed): Vascular Anesthesia. New York, Churchill Livingstone, 1991, p 349.

382. Plestis KA, Kantis G, Haygood K et al: Carotid endarterectomy with homologous vein patch angioplasty: A review of 1006 cases. J Vasc Surg 24:109, 1996.

383. Plestis KA, Loubser P, Mizrahi EM et al: Continuous electroencephalographic monitoring and selective shunting reduces neurologic morbidity rates in carotid endarterectomy. J Vasc Surg 25:620, 1997.

384. Kresowik TF, Worsey JJ, Khoury MJ et al: Limitations of electroencephalographic monitoring in the detection of cerebral ischemia accompanying carotid endarterectomy. J Vasc Surg 13:439, 1991.

385. Mackey WC, O'Donnell TF, Callow AD: Carotid endarterectomy contralateral to an occluded carotid artery: Perioperative risk and late results. J Vasc Surg 11:778, 1990.

386. Lam AM, Manninen PH, Ferguson GG et al: Monitoring electrophysiologic function during carotid endarterectomy: A comparison of somatosensory evoked potentials and conventional electroencephalogram. Anesthesiology 75:15, 1991.

387. Branston NM, Symon L, Crockard HA et al: Relationship between the cortical evoked potential and local cortical blood flow following acute middle cerebral artery occlusion in the baboon. Exp Neurol 45:195, 1974.

388. De Vleeschauwer P, Horsch S, Matamoros R: Monitoring of somatosensory evoked potentials in carotid surgery: Results, usefulness and limitations of the method. Ann Vasc Surg 2:63, 1988.

389. Krul JMJ, Van Gijn J, Ackerstaff RGA et al: Site and pathogenesis of infarcts associated with carotid endarterectomy. Stroke 20:324, 1989.

390. Gaunt ME, Martin PJ, Smith JL et al: Clinical relevance of intraoperative embolization detected by transcranial Doppler ultrasonography during carotid endarterectomy: A prospective study. Br J Surg 81:1435, 1994.

391. Levi CR, Roberts AK, Fell G et al: Transcranial Doppler microembolus detection in the identification of patients at high risk of perioperative stroke. Eur J Vasc Endovasc Surg 14:170, 1997.

392. Gaunt ME, Smith JL, Martin PJ et al: A comparison of quality control methods applied to carotid endarterectomy. Eur J Vasc Endovasc Surg 11:4, 1996.

393. Smith JL, Evans DH, Fan L et al: Interpretation of embolic phenomena during carotid endarterectomy. Stroke 26:2281, 1995.

394. Lennard N, Smith J, Dumville J et al: Prevention of postoperative thrombotic stroke after carotid endarterectomy: The role of transcranial Doppler ultrasound. J Vasc Surg 26:579, 1997.

395. Gossett B, Martinelli O, Guerricchio R et al: Transcranial Doppler in 178 patients before, during, and after carotid endarterectomy. J Neuroimaging 7:213, 1997.

396. Sundt TMJ, Sharbrough FW, Piepgras DG et al: With results of surgery and hemodynamics of cerebral ischemia. Mayo Clin Proc 56:533, 1981.

397. Brott T, Thalinger K: The practice of carotid endarterectomy in a large metropolitan area. Stroke 15:950, 1984.

398. Toronto Cerebrovascular Study Group: Risk of carotid endarterectomy. Stroke 17:848, 1986.

399. Pedrini L, Paragona O, Pisano E et al: Morbidity and mortality following carotid surgery. J Cardiovasc Surg 32:720, 1991.

400. Sieber FE, Toung TJ, Diringer MN et al: Preoperative risks predict neurological outcome of carotid endarterectomy related stroke. Neurosurgery 30:847, 1992.

401. Riles TS, Imparato AM, Jacobowitz GR et al: The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 19:206, 1994.

402. Painter TA, Hertzer NR, O'Hara PJ et al: Symptomatic internal carotid thrombosis after carotid endarterectomy. J Vasc Surg 5:445, 1987.

403. Piepgras DG, Morgan MK, Sundt TM et al: Intracerebral hemorrhage after carotid endarterectomy. J Neurosurg 68:532, 1988.

404. Solomon RA, Loftus CM, Quest DO et al: Incidence and etiology of intracerebral hemorrhage following carotid endarterectomy. J Neurosurg 64:29, 1986.

405. Lehv MS, Salzman EW, Silen W: Hypertension complicating carotid endarterectomy. Stroke 1:307, 1970.

406. Sabawala PB, Strong MJ, Keats AS: Surgery of the aorta and its branches. Anesthesiology 33:229, 1970.

407. Englund R, Dean RH: Blood pressure aberrations associated with carotid endarterectomy. Ann Vasc Surg 1:304, 1986.

408. Bove E, Fry W, Gross W et al: Hypotension and hypertension as consequences of baroreceptor dysfunction following carotid endarterectomy. Surgery 85:633, 1979.

409. Corson JD, Chang BB, Leopold PW et al: Perioperative hypertension in patients undergoing carotid endarterectomy: Shorter duration under regional block anesthesia. Circulation 74:I, 1986.

410. Skydell SL, Machleder HI, Baker JD et al: Incidence and mechanism of post-carotid endarterectomy hypertension. Arch Surgery 122:1153, 1987.

411. Breen JC, Caplan LR, DeWitt LD et al: Brain edema after carotid surgery. Neurology 46:175, 1996.

412. Caplan LR, Skillman J, Ojemann R et al: Intracerebral hemorrhage following carotid endarterectomy: A hypertensive complication? Stroke 9:457, 1978.

413. Towne JB, Bernhard VM: The relationship of postoperative hypertension to complications following carotid endarterectomy. Surgery 88:575, 1980.

414. Reigel MM, Hollier LH, Sundt TMJ et al: Cerebral hyperperfusion syndrome: A cause of neurological dysfunction after carotid endarterectomy. J Vasc Surg 5:628, 1987.

415. Prough DS, Scuderi PE, McWhorter JM et al: Hemodynamic status following regional and general anesthesia for carotid endarterectomy. J Neurosurg Anesth 1:35, 1989.

416. Scuderi PE, Prough DS, Davis CH et al: The effect of regional and general anesthesia on blood pressure control after carotid endarterectomy. J Neurosurg Anesth 1:41, 1989.

417. Brown OW, Brown M: Control of hypertension following carotid endarterectomy. Am Surg 52:581, 1986.

418. Schauber MD, Fontenelle LJ, Solomon JW et al: Cranial/cervical nerve dysfunction after carotid endarterectomy. J Vasc Surg 25:481, 1997.

419. Weiss K, Kramar R, Firt P: Cranial and cervical nerve injuries: Local complications of carotid artery surgery. J Cardiovasc Surg 28:171, 1987.

420. Maniglia AJ, Han AP: Cranial nerve injuries following carotid endarterectomy: An analysis of 336 procedures. Head Neck 13:121, 1991.

421. Hertzer NR, Feldman BJ, Beven EG et al: A prospective study of the incidence of injury to the cranial nerves during carotid endarterectomy. Surg Gynecol Obstet 151:781, 1980.

422. Knight FW, Yeager RM, Morris DM: Cranial nerve injuries during carotid endarterectomy. Am J Surg 154:529, 1987.

423. Verta MJJ, Applebaum EL, McClusky DA et al: Cranial nerve injury during carotid endarterectomy. Ann Surg 185:192, 1977.

424. Massey EW, Heyman A, Utely C et al: Cranial nerve paralysis following carotid endarterectomy. Stroke 15:157, 1984.

425. Roeggla G, Roeggla M, Laggner AN: Poor ventilation response to mild hypoxia may inhibit acclimatization at moderate altitude in elderly patients after carotid surgery. Br J Sports Med 29:110, 1995.

426. Wade JG, Larson P, Hickey RF et al: Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. N Engl J Med 282:823, 1970.

427. Lee JK, Hanowell S, Kim YD et al: Morphine-induced respiratory depression following bilateral carotid endarterectomy. Anesth Analg 60:64, 1981.

428. Lipsett PA, Tierney S, Gordon TA et al: Carotid endarterectomy: Is intensive care unit care necessary? J Vasc Surg 20:403, 1994.

429. Rosenthal D, Zeichner WD, Lamis PA et al: Neurologic deficit after carotid endarterectomy: Pathogenesis and management. Surgery 94:776, 1983.

430. Geary KJ, Ouriel K, Geary JE et al: Neurologic events following carotid endarterectomy: Prediction of outcome. Ann Vasc Surg 7:76, 1993.

431. Kaufman JL, Frank D, Rhee SW et al: Feasibility and safety of 1-day postoperative hospitalization for carotid endarterectomy. Arch Surg 131:751, 1996.

432. Fleisher LA: Perioperative myocardial ischemia and infarction. Int Anesthesiol Clin 30:1, 1992.

433. Fleisher LA, Nelson AH, Rosenbaum SH: Postoperative myocardial ischemia: Etiology of cardiac morbidity or manifestation of underlying disease? J Clin Anesth 7:97, 1995.

434. Frank SM, Higgins MS, Fleisher LA et al: Adrenergic, respiratory, and cardiovascular effects of core cooling in humans. Am J Physiol 272:R557, 1997.

435. Frank SM, Raja SN, Wu PK et al: Alpha-adrenergic mechanisms of thermoregulation in humans. Ann NY Acad Sci 813:101, 1997.

436. Abalos A, Leibowitz AB, Distefano D et al: Myocardial ischemia during the weaning period. Am J Crit Care 1:32, 1992.

437. Raby KE, Goldman L, Cook EF et al: Long-term prognosis of myocardial ischemia detected by Holter monitoring in peripheral vascular disease. Am J Cardiol 66:1309, 1990.

438. Hertzer NR: Fatal myocardial infarction following peripheral vascular operations: A study of 951 patients followed 6 to 11 years postoperatively. Cleve Clin Q 49:1, 1982.

439. Mangano DT, Browner WS, Hollenberg M et al: Long-term cardiac prognosis following noncardiac surgery. JAMA 268:233, 1992.

440. Shah KB, Kleinman BS, Sami H et al: Reevaluation of perioperative myocardial infarction in patients with prior myocardial infarction undergoing noncardiac operations. Anesth Analg 71:231, 1990.

441. Boucher CA, Brewster DC, Darling RC et al: Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. N Engl J Med 312:389, 1985.

442. Leppo J, Plaja J, Gionet M: Noninvasive evaluation of cardiac risk before elective vascular surgery. J Am Coll Cardiol 9:269, 1987.

443. McCann RL, Clements FM: Silent myocardial ischemia in patients undergoing peripheral vascular surgery: Incidence and association with perioperative cardiac morbidity and mortality. J Vasc Surg 9:583, 1989.

/das/book/view/29494766/875/582.html

Chapter 52 - Neurosurgical Anesthesia

John C. Drummond
Piyush M. Patel

INTRODUCTION

This chapter provides management guidelines for common situations in neurosurgical anesthesia (Table 52-1) . It begins with a review of issues that arise in connection with many procedures. Procedure-specific discussions follow. This chapter assumes familiarity with the cerebral physiology and effects of anesthetics as described in Chapter 19 . Neurologic monitoring is described in Chapter 35 . Carotid endarterectomy is discussed in Chapter 51 .

RECURRENT ISSUES IN NEUROANESTHESIA

There are several basic elements of neurosurgical/neuroanesthetic management that are recurrent and that should be discussed and agreed on with the surgical team at the outset of every neurosurgical procedure. The list varies with the procedure and may include the following: the intended surgical position and requisite positioning aids; the intentions with respect to the use of steroids, diuretics, anticonvulsants, and antibiotics; the surgeon's perception of the "tightness" of the intracranial space and of the remaining intracranial compliance reserve; the appropriate objectives for management of blood pressure, CO_2 tension, and body temperature; the anticipated blood loss; the intended use of neurophysiologic monitoring (which may impose constraints on the use of anesthetic agents and/or on the use of muscle relaxants), and, occasionally, the perceived risk of air embolization. The considerations driving the decisions made about these issues are presented in the following subsections. One additional recurrent issue, brain protection, is discussed briefly in the second part of this chapter and in detail in Chapter 19 .

Intracranial Pressure Control/Brain Relaxation

The necessity to prevent increases in intracranial pressure (ICP) or to reduce an ICP that is already elevated is recurrent in neuroanesthesia. When the cranium is closed, the objective is to maintain an adequate cerebral perfusion pressure (CPP) (CPP = mean arterial pressure [MAP] - ICP) and/or to prevent herniation of brain tissue between intracranial compartments or through the foramen magnum (Fig. 52-1) (Figure Not Available) . When the cranium is open, the issue may be one of providing relaxation of the intracranial contents to facilitate surgical access or, in extreme circumstances, to reverse the process of brain herniation through a craniotomy (see Fig. 52-1) (Figure Not Available) . The principles that apply are similar whether the cranium is open or closed.

The various clinical indicators of increased ICP include headache (particularly a postural headache that awakens the patient at night), nausea and vomiting, blurred vision, somnolence, and papilledema. Suggestive findings on a computed tomography (CT) scan include midline shift, obliteration of the basal cisterns, loss of sulci, ventricular effacement (or enlarged ventricles in the event of hydrocephalus), and edema. Edema appears on a CT scan as a region of hypodensity. The basal cisterns appear as a black (fluid) halo around the upper end of the brain stem. They include the interpeduncular cistern, which lies between the

TABLE 52-1 -- Abbreviations

AVM	Arteriovenous malformation
BBB	Blood-brain barrier
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CBV	Cerebral blood volume
CMR	Cerebral metabolic rate
CMRg	Cerebral metabolic rate for glucose
CMR_{O_2}	Cerebral metabolic rate for oxygen
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CSFP	Cerebrospinal fluid pressure
CVR	Cerebral vascular resistance
EEG	Electroencephalogram
GCS	Glasgow coma scale
ICP	Intracranial pressure
l-CBF	Local cerebral blood flow
l-CMR	Local cerebral metabolic rate
LLA	Lower limit of autoregulation
MAP	Mean arterial pressure
NO	Nitric oxide
N_2O	Nitrous oxide
PET	Positron emission tomography
r-CBF	Regional cerebral blood flow
Sjv_{O_2}	Jugular venous oxygen saturation
TCD	Transcranial Doppler
TEE	Transesophageal echocardiography
VAE	Venous air embolism

Figure 52-1 (Figure Not Available) Schematic representation of various herniation pathways: (1) subfalcine, (2) uncal (transtentorial), (3) cerebellar, and (4) transcalvarial. *(From Fishman [243])*

two cerebral peduncles, the quadrigeminal cistern, which overlies the four colliculi, and the ambient cisterns, which lie lateral to the cerebral peduncles.

Figure 52-2 presents the pressure-volume relationship of the intracranial space. The plateau phase occurring at low volumes reveals that the intracranial space is not completely closed, and there is some compensatory latitude. Compensation is accomplished principally by the translocation of

Figure 52-2 The intracranial pressure-volume relationship. The horizontal portion of the curve indicates that there is initially some latitude for compensation in the face of an expanding intracranial lesion. That compensation is accomplished largely by displacement of cerebrospinal fluid (CSF) and venous blood from intracranial to extracranial spaces. Once the compensatory latitudes are exhausted, small volume increments result in large increases in intracranial pressure, with the associated hazards of either herniation or decreased cerebral perfusion pressure (CPP) resulting in ischemia.

cerebrospinal fluid (CSF) and venous blood to the spinal CSF space and to extracranial veins, respectively. Ultimately, when the compensatory potential is exhausted, even tiny increments in the volume of the intracranial contents can result in substantial ICP increases. These increases have the potential to result in either herniation of brain tissue from one compartment to another (or into the surgical field) (see Fig. 52-1) (Figure Not Available) , with resultant mechanical injury to brain tissue, or reduction in perfusion pressure with a concomitant ischemic injury.

There are several potential variables that can interact to cause or aggravate intracranial hypertension (Fig. 52-3) . For the clinician faced with the problem of managing increased ICP, the objective is, in general, to reduce the volume of the intracranial contents. For mnemonic purposes, in developing a clinical approach, the clinician can divide the intracranial space into four subcompartments: cells (including neurons, glia, tumors, and extravasated collections of blood), fluid (intracellular and extracellular), CSF, and blood. Again for mnemonic purposes, the blood compartment can be subdivided into venous and arterial components. It is this last compartment, the blood compartment, that is most amenable to rapid manipulation by the clinician, and accordingly, it is the compartment to which the greatest level of attention is directed.

1. The cellular compartment. This is largely the province of the surgeon. However, it may be the anesthesiologist's responsibility to pose a well-placed diagnostic question. When the brain is bulging into the surgical field at the conclusion of the evacuation of an extradural hematoma, the clinician should ask whether there is a subdural or extradural hematoma on the contralateral side that warrants either immediate bur holes or immediate postprocedure radiologic evaluation.
2. The CSF compartment. There is no pharmacologic manipulation of the size of the CSF space whose time

course and magnitude are relevant to the neurosurgical setting. The only relevant means for manipulating the size of this compartment is by drainage (Table 52-2) . A tight surgical field can sometimes be improved by the passage of a brain needle, by the surgeon, into a lateral ventricle to drain CSF. This maneuver may be relevant in both supratentorial procedures and in infratentorial operations when poor conditions in the posterior fossa are thought to be the result of downward pressure by the contents of the supratentorial space. Lumbar CSF drainage can be used to improve surgical exposure when there is no substantial hazard of uncal or trans-foramen magnum herniation.

3. The fluid compartment. This compartment can be addressed with steroids and diuretics. The use of these drugs is discussed in later sections.
4. The blood compartment. This is the compartment that receives the anesthesiologist's greatest attention because it is the most amenable to rapid alteration. The blood compartment should be considered as two separate components: venous and arterial.

Figure 52-3 The pathophysiology of intracranial hypertension. Those elements that are potentially under the control of the anesthesiologist are indicated by asterisks (*). BP, blood pressure.

TABLE 52-2 -- Intracranial Compartments and Techniques for Manipulation of Their Volume

COMPARTMENT	VOLUME CONTROL METHODS
Cells (including neurons, glia, tumors, and extravasated blood)	Surgical removal
Fluid (intracellular and extracellular)	Diuretics
	Steroids (principally tumors)
Cerebrospinal fluid	Drainage
Blood	
Arterial Side	Decrease cerebral blood flow
Venous side	Improve cerebral venous drainage

We suggest giving first consideration to the venous side of the circulation. It is largely a passive compartment that is frequently overlooked. Passive though it is, engorgement of this compartment is a common cause of increased ICP or poor conditions in the surgical field (Fig. 52-4) . A head-up posture, to ensure good venous drainage, is routine in neurosurgical

Figure 52-4 The effect of cerebral venous outflow obstruction on intracranial pressure in a patient with an intracerebral hematoma. Bilateral jugular compression was applied briefly to verify the function of a newly placed ventriculostomy. The intracranial pressure response illustrates the importance of maintaining free cerebral venous drainage.

anesthesia and critical care. Obstruction of cerebral venous drainage by extremes of head position or circumferential pressure (Philadelphia collars, endotracheal tube ties) should be avoided. Phenomena occurring downstream from the venous structures of the neck may also be relevant. Anything that causes increased intrathoracic pressure can result in obstruction of cerebral venous drainage. This possibility includes a variety of commonplace events such as kinked or partially obstructed endotracheal tubes, tension pneumothorax, coughing/straining against the endotracheal tube, or gas trapping from bronchospasm. These, too, should be sought and remedied. Most practitioners carefully maintain the patient's paralysis during a craniotomy procedure unless there is a contraindication because a sudden cough can result in dramatic herniation of cerebral structures through a craniotomy.

Thereafter, the anesthesiologist should address the arterial side of the circulation. Attention to the effect of anesthetic agents and techniques on cerebral blood flow (CBF) is an established part of neuroanesthesia (Ch. 19) . This attention is relevant because, in general, increases in CBF are associated with increases in cerebral blood volume (CBV). [1] [2] [3] The notable exception to this rule occurs in the context of cerebral ischemia caused by hypotension or vessel occlusion, when CBV may increase as the cerebral vasculature dilates in response to a sudden reduction in CBF. However, the relationship generally applies, and attention to the control of CBF is relevant when volume compensation mechanisms are exhausted or ICP is already increased. The general approach is to select anesthetic agents and to control physiologic parameters in a manner that avoids unnecessary increases in CBF. The parameters that influence CBF are listed in Table 52-3 and are discussed in Chapter 19 .

Anesthetic Selection

The question of which anesthetic agents are appropriate, especially in the context of unstable ICP, arises often. Chapter 19 provides relevant information in detail, and only broad generalizations are made here.

In general, intravenous anesthetic, analgesic, and sedative agents are associated with parallel reductions in CBF and

TABLE 52-3 -- Factors That Influence Cerebral Blood Flow[a]

Arterial oxygen tension
Arterial carbon dioxide tension
Cerebral metabolic rate
Arousal/pain
Seizures
Temperature
Anesthetics
Blood pressure/status of autoregulation
Vasoactive agents
Anesthetics
Pressors
Inotropes
Vasodilators
Blood viscosity
Neurogenic pathways (intra-axial and extra-axial)

[a] Discussed in detail in Chapter 19

cerebral metabolic rate (CMR) and have no adverse effects on intracranial compliance. Ketamine, given in large doses to patients with a generally normal level of consciousness before anesthesia, may be the exception. It appears that, in general, autoregulation and CO_2 responsiveness are preserved during administration of intravenous agents (Ch. 19) .

All the volatile agents cause dose-dependent cerebral vasodilation. The order of vasodilating potency is approximately halothane >> enflurane > isoflurane
sevoflurane
desflurane. The net CBF effect of introducing a volatile agent depends on the interaction of several factors: the concentration; the extent of prior CMR depression; simultaneous blood pressure changes acting in conjunction with prior or anesthetic-induced autoregulation abnormalities; and simultaneous changes in the arterial CO_2 tension (Pa_{CO_2}) acting in conjunction with any disease-related impairment of CO_2 responsiveness. Nitrous oxide (N_2O) is also a cerebral vasodilator, the CBF effect of which is greatest when it is administered as a sole agent, least when it administered against a background of narcotics, propofol, or benzodiazepines, and intermediate when administered in conjunction with volatile agents (Ch. 19) . Nonetheless, experience dictates that both N_2O and volatile agents, the latter usually in sub-MAC concentrations, administered as components of a balanced anesthetic technique in combination with narcotics, can be used in most elective and many emergency neurosurgical procedures. Exceptions are rare. When they occur (the somnolent, vomiting patient with pap-illedema, a large mass, and compressed basal cisterns; the head-injury victim with an expanding mass lesion or obliterated cisterns and sulci on CT scan), the clinician may be well advised to use a predominantly intravenous technique until such time as the cranium and dura are open and the effect of the anesthetic technique can be directly assessed. Inhaled agents are entirely acceptable components of most anesthetic regimens for neurosurgery. However, when ICP is persistently elevated (in a closed cranium procedure) or the surgical field is persistently "tight," N_2O and volatile agents should be viewed as potential contributing factors and should be eliminated from the anesthetic regimen in favor of intravenous agents.

Muscle relaxants (Chs. 12 and 19) that have the potential to release histamine (curare, metocurine, mivacurium, atracurium) should be given in small, divided doses. Although succinylcholine has been associated with ICP increases, those increases are small and transient. Moreover, these increases can be blocked by a preceding dose of metocurine, 0.03 mg/kg, [4] and, in at least some instances, they do not even occur in patients with common emergency neurosurgical conditions such as head injury or subarachnoid hemorrhage (SAH). [5] Accordingly, in a clinical situation that calls for rapid relaxation for the purposes of controlling or protecting an airway, succinylcholine, in conjunction with proper management of the airway and MAP, is reasonable.

From the foregoing material and the discussion of cerebral physiology in Chapter 19 , a systematic clinical approach should follow readily. A schema for approaching the problem of acute elevation of ICP or of an acute deterioration in conditions in the surgical field is presented in Table 52-4 . If, after following the approach in Table 52-4 , the problem has not resolved satisfactorily, what then? Table 52-5 presents the options.

TABLE 52-4 -- High Intracranial Pressure/"Tight Brain" Checklist

1. Are the relevant pressures controlled?
Jugular venous pressure
Extreme head rotation or neck flexion?
Direct jugular compression?
Airway pressure
Airway obstruction?
Bronchospasm?
Straining, coughing, adequately relaxed?
Pneumothorax?
Partial pressure of CO_2 and O_2 (Pa_{CO_2}, Pa_{O_2})
Arterial pressure
2. Is metabolic rate controlled?
Pain/arousal?
Seizures?
3. Are any potential vasodilators in use? (nitrous oxide, volatile agents, nitroprusside, calcium channel blockers)
4. Are there any unrecognized mass lesions? (blood, air ± nitrous oxide)

TABLE 52-5 -- Methods for Rapid Reduction of Intracranial Pressure/Brain Volume

Cerebrospinal fluid drainage (ventriculostomy, brain needle)

Diuresis (usually mannitol)
Cerebral metabolic rate suppression (usually barbiturates)
Mean arterial pressure reduction (if dysautoregulation) (Lobectomy)

CSF drainage is discussed earlier. The use of an additional osmotic diuretic is theoretically limited by an upper acceptable osmolarity limit of 320 mOsm/L. However, in extreme circumstances, the use is frequently empirical, and repeated doses, such as 12.5 g, are administered until a clinical response is no longer observed. Barbiturates, sometimes supplemented by lidocaine, have been used most frequently to induce CMR reduction, with the objective of causing a coupled reduction in CBF and CBV. Propofol is gaining popularity for this application. Note, however, that whereas the use of barbiturates is supported by an intensive care unit (ICU) experience demonstrating efficacy in ICP control [6] (if not outcome), no such experience has been accumulated for propofol. MAP reduction occasionally reduces vascular engorgement and thereby reduces total brain bulk. This effect is most likely to be relevant in the event of dysautoregulation occurring in the context of resection of arteriovenous malformations (AVM) (see later).

Partial Pressure of Carbon Dioxide Management

At the outset, the anesthesiologist and the surgeon should agree on the objectives with respect to Pa $_{CO_2}$. The induction of hypocapnia is a time-honored part of the management of intracranial neurosurgical procedures. The rationale is principally that the concomitant reduction in CBF (see Fig. 19-4) and CBV will result in a reduction of ICP or "brain relaxation." The rationale is valid. However, there are two considerations that should influence the clinician's use of hyperventilation. First, the vasoconstrictive effect of hypercapnia has the potential to cause ischemia in certain situations. Second, the CBF-lowering effect is not sustained.

Hypocapnia-Induced Cerebral Ischemia

There was at first skepticism that hyperventilation could actually result in ischemia, and it does, in fact, appear that normal brain is unlikely to be damaged by typical clinical use of hyperventilation. However, that may not be the case in certain pathologic conditions.

Normal Brain.

The data [7] [8] [9] [10] [11] [12] [13] [14] indicate that, in healthy subjects, ischemia does not occur at a Pa $_{CO_2}$ greater than 20 mm Hg. This generalization appears also to apply during induced hypotension. [15] [16] [17] However, physiologic alterations, as evidenced by both metabolic and electroencephalographic (EEG) abnormalities, have been observed in human volunteers [10] [12] [18] and in healthy animals [7] [11] [14] at extreme hypocapnia (Pa $_{CO_2}$ < 15 mm Hg), as well as in dogs submitted to the combination of severe hypocapnia (Pa $_{CO_2}$, 10 mm Hg) and severe anemia (hemoglobin, 5 g/dL). [9] In one of these studies, [12] EEG abnormalities and paresthesias occurred in volunteers hyperventilating to Pa $_{CO_2}$ values less than 20 mm Hg, and these effects were reversed by hyperbaric oxygenation, a finding suggesting that these effects may truly have been caused by ischemia. In two separate investigations in cats at Pa $_{CO_2}$ levels of 10 to 12 mm Hg, [7] [14] modest reductions in brain phosphocreatine levels with increased brain lactate but normal levels of adenosine triphosphate (ATP) were observed. It has been suggested [14] that the observed changes may, in part, reflect pH-related alterations in enzyme function (specifically, an increase in the activity of phosphofructokinase causing increased lactate formation), [18] rather than ischemia. Accordingly, given that a Pa $_{CO_2}$ of less than 20 to 25 mm Hg offers very little additional benefit in terms of improvement of intracranial compliance, it seems prudent to limit acute Pa $_{CO_2}$ reduction to 25 mm Hg in previously normocarbic individuals. Normal brain is not injured by this degree of hypocapnia.

Injured Brain.

Although preventing herniation, maintaining ICP at less than 20 mm Hg, minimizing retractor pressure, and facilitating surgical access remain priorities that may justify hypocapnia, there is also accumulating evidence that hyperventilation is potentially deleterious, [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] and it should not be overused. In the setting of head injury, there is evidence that hyperventilation can result in ischemia, [21] [34] especially when baseline CBF is low, [34] as is commonly the case in the first 24 hours after injury. [24] [35] [36] [37] An increased frequency of brain regions with very low CBF in head-injured patients who were acutely hyperventilated has been demonstrated. [21] In addition, from centers that monitor jugular venous oxygen saturation (Sjv $_{O_2}$), there have been numerous observations that a low Sjv $_{O_2}$ can be increased and lactate levels in the jugular venous effluent can be decreased by reducing the degree of hyperventilation. [24] [34] [38] [39] However, at present there is little information to confirm a deleterious effect of hyperventilation. The closest thing to "proof" resides in a study by Muizelaar et al. [23] These authors studied patients with moderate head injuries.

They divided the patients into a near-normocapnic group in whom Pa $_{CO_2}$ was maintained at approximately 35 mm Hg, a hypocapnic group in whom Pa $_{CO_2}$ was maintained in the vicinity of 25 mm Hg, and a third group in whom the Pa $_{CO_2}$ was maintained at 25 mm Hg and the buffer tromethamine (Tham) was administered. Tromethamine is a buffer that can cross the blood-brain barrier (BBB), and it has been theorized that this buffer can attenuate the adverse effect of the reduction of bicarbonate levels in CSF and brain extracellular fluid that occurs with chronic hyperventilation. These investigators examined outcome at 3 and 6 months following injury and observed a poorer status in a post hoc subpopulation of the hyperventilation group. That subpopulation included those patients with the best initial motor scores, that is, a subgroup in whom the severity of injury was such that these patients merited intubation by conventional criteria, but whose clinical condition may have been such that hyperventilation was not necessarily required for ICP control and who therefore had little to gain from hyperventilation.

Accordingly, hyperventilation should not be an automatic component of every "neuroanesthetic" regimen. It should be treated like any other therapeutic intervention. There should be an indication for instituting it, usually elevated or uncertain ICP and/or the need to improve conditions in the surgical field. It should be used with the knowledge that there is the potential for an adverse effect, and, as is the case with any other therapeutic intervention, it should be withdrawn as the indication for it subsides. The concern regarding the hazards of hypocapnia, which evolved in the context of head injury, has influenced all of neurosurgery. In particular, hyperventilation is now widely avoided in the management of SAH because of the postictal low CBF state that is known to occur. [40] In addition, brain beneath retractors can have a similarly reduced CBF. [28]

Duration of Hypocapnia-Induced Cerebral Blood Flow Reduction

The effect of hypocapnia on CBF is not sustained. Figure 52-5 is a nonquantitative representation of changes in CBF and CSF pH occurring in association with a sustained period of hyperventilation. With the onset of hyperventilation, the pH of both CSF and the brain's extracellular fluid space increases, and CBF decreases abruptly. However, the cerebral alkalosis is not sustained. By alterations in the function of the carbonic anhydrase enzyme, the concentration of bicarbonate in the CSF and the brain's extracellular fluid space is reduced, and, with a time course of 6 to 18 hours, the pH of those compartments returns to normal. [41] At an equal pace, CBF returns toward normal levels. [41] [42] The implications are 2-fold. First, the clinician should ideally hyperventilate patients for only as long as brain volume reduction is required. Prolonged but unnecessary hyperventilation may lead to a circumstance wherein subsequent clinical events call for additional maneuvers to reduce the volume of the intracranial contents. However, if Pa $_{CO_2}$ is already in the range of 23 to 25 mm Hg, it would be difficult to impose sufficient additional hyperventilation once again to accomplish the original reduction of CBF without the hazard of pulmonary barotrauma. Second, in the patient who has been hyperventilated

Figure 52-5 Arterial CO_2 tension (Pa $_{CO_2}$), cerebral blood flow (CBF), and cerebrospinal fluid (CSF) pH changes with prolonged hyperventilation. Whereas the decreased arterial Pa $_{CO_2}$ and the systemic alkalosis persist for the duration of the period of hyperventilation, the pH of the brain and CBF return toward normal over 8 to 12 hours.

for a sustained period of time (e.g., 2 days in an ICU setting), rapid restoration of Pa $_{CO_2}$ from values in the vicinity of 25 mm Hg to typical normal values, such as 40 mm Hg, should ideally be accomplished slowly. A sudden increase in Pa $_{CO_2}$ from 25 to 40 mm Hg in an individual who has been hyperventilated on a long-term basis will have the same physiologic effect that a rapid change from 40 to 55 mm Hg would have in a previously normocapnic subject. If hypocapnia has been required as

an adjunct to brain relaxation during craniotomy, CO_2 levels should also be allowed to rise once retractors are removed (if dural closure requirements permit) in order to minimize the residual intracranial pneumatocele (see the later discussion of pneumocephalus).

Blood Pressure Management

Acceptable blood pressure limits should similarly be agreed on at the beginning of a neurosurgical procedure. One of the prominent themes of contemporary neurosurgery is that CPP should be maintained at normal or even high normal levels following acute insults to the central nervous system (CNS) and during most intracranial neurosurgical procedures. This concept evolves from the growing appreciation that CBF is frequently perilously low in some brain regions following acute neurologic insults, in particular, head injury (see the additional discussion later) and SAH. [24] [35] [40] There are two additional factors. The first is that the autoregulatory response to decreasing blood pressure may not be intact throughout the brain. Figure 52-6 depicts the ischemic hazard that attends the circumstance of a low resting CBF and absent autoregulation even at blood pressures considered safe when autoregulation is intact. In addition, there is the appreciation that maintenance of arterial pressure is also relevant to brain compressed under retractors, [28] because the effective perfusion pressures there are lowered by increased local tissue pressure. Although

Figure 52-6 Normal and absent autoregulation curves. The "absent" curve indicates a pressure-passive condition in which cerebral blood flow (CBF) varies in proportion to cerebral perfusion pressure (CPP). This curve is drawn to indicate subnormal CBF values during normotension, as have been shown to occur immediately after both head injury [24] and subarachnoid hemorrhage. [40] The potential for modest hypotension to cause ischemia is apparent. MAP, mean arterial pressure.

there are few data to support the notion, it seems reasonable that this attitude regarding blood pressure should be extrapolated to patients who have sustained a recent spinal-cord injury, patients whose spinal cord is under compression because of a disease process (most commonly cervical spinal stenosis), or patients undergoing surgery involving retraction of the spinal cord.

Steroids

The administration of steroids for the purpose of reducing or limiting the formation of edema is another time-honored practice in neurosurgery. The efficacy of steroids in reducing the edema associated with tumors is well confirmed. [43] [44] [45] The time course of this effect is relatively rapid, although not so rapid as to be relevant to the management of intraoperative events. However, administration of steroids beginning 48 hours prior to an elective surgical procedure has the potential to reduce edema formation and to improve clinical condition by the time of the craniotomy. [43] [44] [46] It has been noted that whereas clinical improvement, that is, a decreased frequency of ICP plateau waves and an improvement in the pressure-volume response (the ICP increment in response to a standardized intracranial volume challenge), occurs within 24 hours, [43] a reduction of ICP may not occur for 48 to 72 hours after initiation of therapy. [43] This finding has been interpreted to indicate that steroids in some way improve the "viscoelastic properties" of the intracranial space before edema reduction occurs, although the mechanism is undefined. [46] Steroids are usually given intraoperatively and postoperatively to maintain the effects achieved with preoperative treatment.

The practice of administering steroids to the adult patient with head injury has largely been abandoned as the result of controlled trials that demonstrated either no benefit or a deleterious effect in patients who received steroids. [47] [48] [49] No such studies have been performed in the pediatric trauma victim, and practices vary among pediatric neurosurgeons with respect to the administration of steroids following head injury in this population. One European trial reported a benefit in adult victims of head injury of the administration of large doses of triamcinolone. [50] The potent fluorinated steroids had not been studied previously in this population. It is possible that there will be reconsideration of the use of steroids in adult victims of head injury.

Diuretics

Diuretics are used widely in neurosurgery to reduce the volume of the brain's intracellular and extracellular fluid compartments. It is probably largely the extracellular compartment that is influenced because neurons and glia have quick and efficient cell volume-regulation mechanisms. Both osmotic and loop diuretics have been employed. Although there are data to suggest that loop diuretics can be effective, [51] osmotic diuretics, principally mannitol, are preferred clinically because of their speed and efficacy. The only osmotic diuretic available on most formularies is mannitol, although urea once had its proponents. However, urea is a smaller molecule that clearly has greater potential to enter brain parenchyma. That is not to say that mannitol does not enter brain parenchyma. There are data to indicate that it enters brain and, over a reasonably short time course, appears in the CSF space. [52] The possibility that the mannitol that gains access to the parenchyma aggravates swelling has resulted in varying degrees of reluctance among clinicians to administer this drug. [53] Most clinicians, nonetheless, find mannitol a mainstay of ICP management. There is the concern that it will be effective only when some degree of BBB integrity is preserved in a significant portion of the brain. Most clinicians respond to this concern by making empirical use of this agent, that is, if it is effective in reducing ICP or improving conditions in the surgical field, repeated doses can be administered or will be administered. If it is ineffective (or if serum osmolarity reaches the traditional limit of 320 mOsm/L), its administration is withheld.

The dosages of mannitol employed vary from 0.25 g/kg to 100 g "for all comers." One gram per kilogram appears to be the most common dose. However, a systematic study in

head-injured patients demonstrated that an equivalent initial ICP-reducing effect can be achieved with 0.25 g/kg, although that effect may not be as sustained as with larger doses. [54]

Some clinicians advocate the combined administration of a loop diuretic (usually furosemide) and an osmotic diuretic. The superficial rationale is that mannitol establishes an osmotic gradient that draws fluid out of brain parenchyma, and furosemide, by hastening excretion of water from the intravascular space, facilitates the maintenance of that gradient. A second mechanism may add additional justification for the practice of combining the two agents. Neurons and glia, as mentioned earlier, appear to have powerful homeostatic mechanisms to ensure regulation of cell volume. Neurons and glia that shrink in response to an increased osmolarity in the external environment recover their volume rapidly as a consequence of the accumulation of so-called "idiogenic" osmoles that serve to minimize the gradient between the internal and external environment. One of those idiogenic osmoles is chloride. It has been demonstrated in the laboratory that the loop diuretics inhibit the chloride channel through which this ion must pass and thereby retard the normal volume-restoring mechanism. [55]

The normal volume-regulatory mechanisms of neurons and glia may also be relevant to the phenomenon of rebound swelling. Rebound is commonly attributed to the prior use of mannitol and is assumed to be a function of the accumulation of mannitol in cerebral tissue. Although this may be part of the story, the rebound may, in fact, be "hypertonic rebound," rather than "mannitol rebound." It seems reasonable to be concerned that, after a sustained period of hyperosmolarity of any cause, rebound swelling of neurons and glia may occur in the event that systemic osmolarity decreases rapidly toward normal levels. It is certainly well known that rebound cerebral swelling can occur after an episode of extreme blood glucose elevation. Accordingly, it should not be assumed that the use of, for instance, hypertonic saline rather than mannitol will obviate this phenomenon.

Anticonvulsants

The general principle is that any acute irritation of the cortical surface has the potential to result in seizures. This includes acute neurologic events such as head injury and SAH. Cortical incisions and brain surface irritation by retractors may similarly be potential foci. Given the relatively benign nature of phenytoin, provided it is given judiciously (i.e., at rates of
50 mg/min), routine administration in patients undergoing most supratentorial craniotomies as well as in patients who have sustained a significant head injury or SAH seems appropriate in the absence of a contraindication.

Positioning

The intended surgical position and the necessary position aids should be agreed on at the outset (Ch. 26) . The commonly used positions and positioning aids/supports are

TABLE 52-6 -- Common Neurosurgical Positions and Positioning Aids

Positions
Supine
Lateral (park bench)
Semilateral (Jannetta)
Prone
Sitting
Positioning aids/supports
Pin head holder
Radiolucent pin head holder
Horseshoe headrest
Foam "block" head support
Vacuum mattress ("bean bag")
Wilson-type frame
Andrews ("hinder binder")-type frame
Relton-Hall (four-poster) frame

listed in Table 52-6 and are described in the following sections.

General Considerations

The prolonged duration of many neurosurgical procedures should be taken into account in all positions. Pressure points should be identified and padded carefully. Pressure and traction on nerves must be avoided. Thromboembolic precautions including support hose and sequential pneumatic compression devices are often appropriate. Almost invariably, some component of head-up posturing, such as 15 to 20 degrees, is appropriate to ensure optimal venous drainage. The conspicuous exception occurs with evacuation of a chronic subdural hemorrhage, after which patients are usually nursed flat, to discourage reaccumulation. Patients are often also maintained flat after CSF shunting to avoid overly rapid collapse of the ventricles.

Supine Position

The supine position is used with the patient's head neutral or rotated for frontal, temporal, or parietal access. Extremes of head rotation can obstruct the jugular venous drainage, and a shoulder roll can combat this problem. The head is usually in a neutral position for bifrontal craniotomies and for transphenoidal approaches to the pituitary. The head-up posture is best accomplished by adjusting the operating table to a chaise lounge (lawn chair) position (flexion, pillows under the knees, slight reverse Trendelenburg position). This orientation, in addition to promoting cerebral venous drainage, decreases the patient's back strain.

Semilateral Position

The semilateral position, also known as the Jannetta position after the neurosurgeon who popularized its use for microvascular decompression of the fifth cranial nerve, is used for retromastoid access. It is achieved by lateral tilting of the table 10 to 20 degrees, combined with a generous shoulder

roll. Again, extreme head rotation causing compression of the contralateral jugular vein by the chin should be avoided.

Lateral Position

The lateral position can be used for access to the posterior parietal and occipital lobes and the lateral posterior fossa including tumors at the cerebellopontine angle and aneurysms of the basilar artery and vertebrobasilar junction. A vacuum mattress that can be molded to the patient's anatomic features greatly facilitates maintenance of a stable lateral position. An axillary roll is important for preventing brachial plexus injury.

Prone Position

The prone position is used for spinal cord, occipital lobe, craniosynostosis, and posterior fossa procedures. The prone position has also been referred to, aptly, as the Concorde position because, for cervical spine and posterior fossa procedures, the final position usually entails neck flexion, reverse Trendelenburg positioning, and elevation of the legs, usually with pillows. This orientation serves to bring the surgical field to a horizontal position.

Before turning the patient to the prone position, the anesthesiologist should ensure that the intravenous catheter and endotracheal tube are secure and that appropriate personnel are available to prevent injury during the turn. The anesthesiologist should have a plan for detaching and reattaching monitors in an orderly manner to prevent an excessive monitoring "window." Awake tracheal intubation and prone positioning can be employed in patients with an unstable cervical spine in whom an unchanged neurologic status should be confirmed before induction of anesthesia in the final surgical position. It is also occasionally performed in very obese patients.

The head can be positioned in a pin head holder (applied before the turn), a horseshoe headrest, or a disposable foam headrest. Complications of the prone position to which there must be constant attention are retinal ischemia and blindness from orbital compression. This problem may be compounded by low arterial pressure, low hematocrit level, and poor cerebral venous drainage. [56] It must be intermittently ascertained, such as every 15 minutes and after any surgery-related head/neck movement, that pressure has not come to bear on the eye. Various degrees of pressure necrosis of the forehead and maxillae can also occur, especially during prolonged spinal procedures. Other pressure points to be checked include the axillae, breasts, iliac crests, femoral canals, genitalia, knees, and heels. An antisialogogue, such as glycopyrrolate, may help to reduce loosening of tape used to secure the endotracheal tube.

An objective during prone positioning, especially for lumbar spine surgery, is the avoidance of inferior vena caval compression. Impairment of vena caval return diverts blood to the epidural plexus and increases the potential for bleeding during laminectomy. This avoidance is an objective of all the spinal surgery frames and is accomplished very effectively by both the Relton-Hall and the Andrews variants. This does, however, introduce a risk of air embolism, [57] although clinical occurrences have been very infrequent.

There should be attention to preventing injury to the patient's tongue in the prone position. With both cervical and posterior fossa procedures, it is frequently necessary to flex the patient's neck substantially to facilitate surgical access. This reduces the anteroposterior dimension of the hypopharynx, and compression ischemia of the base of the tongue (as well as the soft palate and posterior wall of the pharynx) can occur in the presence of foreign bodies (endotracheal tube, esophageal stethoscope, oral airway). The consequence is "macroglossia" and unexpected postextubation airway obstruction. Accordingly, unnecessary

paraphernalia in the pharynx should be avoided. Omitting the oral airway entirely is unwise because the tongue may then protrude between and be trapped by the teeth as progressive swelling of facial structures occurs during a prolonged procedure with the patient in the prone position. A bite block akin to those used with laryngeal masks prevents this problem without adding bulk to the hypopharynx.

Sitting Position

There have been three reviews of large experiences with procedures performed with patients in the sitting position. [58] [59] [60] All concluded that the sitting position can be employed with acceptable rates of morbidity and mortality. However, these reports were prepared by groups performing 50 to 100 or more of these procedures per year, and the hazards of the sitting position may be greater for teams who have less frequent occasion to use it. With increasing frequency, the sitting position is being avoided through the use of one of its alternatives (prone, semilateral, lateral positions). However, we are likely to continue encountering it because even surgeons who are inclined to use alternative positions may opt for the sitting position when access to midline structures (the floor of the fourth ventricle, the pontomedullary junction, and the vermis) is required. Nonetheless, alternative positions for posterior fossa surgery exist and should be considered when a patient has contraindications to the sitting position.

Achieving the Sitting Position.

The properly positioned patient is more commonly in a modified recumbent position, as shown in Figure 52-7 (Figure Not Available) , rather than truly sitting. The patient's legs should be kept as high as possible (usually with pillows under the knees) to promote venous return, thereby enhancing circulatory stability. Ideally, the head holder should be attached to the back portion of the table (see Fig. 52-7 (Figure Not Available) A) rather than to the portions under the patient's thighs or legs (see Fig. 52-7 (Figure Not Available) B). This technique permits lowering of the head, and closed chest massage if necessary, without the necessity to take the patient out of the head holder.

When procedures are performed with the patient in the sitting position, the clinician should think in terms of measuring and maintaining perfusion pressure at the level of the surgical field. This is best accomplished by referencing transducers to the interaural plane or at the level of the cervical spine in the event of cervical laminectomy. If a manual

---

Figure 52-7 (Figure Not Available) The sitting position. The patient is typically semirecumbent rather than sitting. (A) The head holder support is correctly positioned such that the patient's head can be lowered without the necessity to first detach the head holder. (B) This configuration, with the support attached to the thigh portion of the table, should be avoided. *(From Martin [244])*

blood pressure cuff on the patient's arm is employed, a correction to allow for the hydrostatic difference between the arm and the operative field should be applied.

Hazards are associated with the sitting position. Circulatory instability, macroglossia, and quadriplegia are discussed in this section. Venous air embolism, paradoxic air embolism, and pneumocephalus are discussed later in this chapter. Several of these hazards are also relevant when cervical spine and posterior fossa procedures are performed with patients in nonsitting positions, but they occur with greater frequency in the sitting position.

Cardiovascular Effects.

Placing the anesthetized patient in the sitting position conveys some risk of impaired cardiovascular function, in particular hypotension (Ch. 26) . Pressor administration is required in some patients. Measures to avoid hypotension include prepositioning hydration, wrapping of the patient's legs with elastic bandages to counteract gravitational shifts of blood and slow, incremental adjustment of table position. Both aggressive volume loading and the G suit (also known as pneumatic antishock trousers or MAST suit) have been shown to attenuate the effects of assuming the sitting position. [61] [62] [63] [64] However, neither of these measures has been widely applied. In the majority of healthy persons, the hemodynamic changes are of a nonthreatening magnitude. In a study of healthy (American Society of Anesthesiologists [ASA] I and II) anesthetized adult subjects, ages 22 to 64 years, Marshall et al [65] observed relatively modest changes. MAP was relatively unaffected, whereas wedge pressure, stroke volume and cardiac index decreased, the latter by approximately 15 percent, although there was some variation with the anesthetic agents employed. The combination of an unchanged MAP (which in general requires the use of a "light" anesthetic with high sympathetic tone) and a reduced cardiac index implies that systematic vascular resistance (SVR) rose. These calculations and the observations of other investigators, [66] in fact, reveal significant elevation of SVR. Accordingly, for patients in whom an abrupt increase in SVR may be poorly tolerated, the sitting position may represent a physiologic threat, and alternative positions should be considered. A pulmonary artery catheter may be warranted when there is clinical or historical evidence of antecedent coronary artery or valvular heart disease, and it may be used arbitrarily in patients older than 60 to 65 years of age.

During procedures performed with the patient in the sitting position, MAP should be transduced at or corrected to head level in order to obtain a meaningful index of CPP. Specifically, CPP (MAP minus estimated ICP) should be maintained at a minimum value of 60 mm Hg in healthy patients in whom it is reasonable to assume a normal cerebral vasculature. The safe lower limit should be raised for elderly

---

patients, for those with hypertension and/or known cerebral vascular disease, for those with degenerative disease of the cervical spine or cervical spinal stenosis who may be at risk for decreased spinal-cord perfusion, and in the event that substantial or sustained retractor pressure must be applied to brain or spinal-cord tissue.

Macroglossia.

There have been sporadic reports of upper airway obstruction following posterior fossa procedures in which swelling of pharyngeal structures including soft palate, posterior wall, pharynx, and base of tongue have been observed. [67] These episodes have been attributed to trauma/ischemia occurring as the result of foreign bodies (usually oral airways) causing pressure on these structures in the circumstances of lengthy procedures with sustained neck flexion (which is usually required to improve access to posterior structures). It is ideal to maintain at least a fingerbreadth's distance between the chin and the sternum to prevent excessive reduction of the anteroposterior diameter of the oropharynx. In addition, it is our practice to position patients with the oral airway in place and then, once the final head position is achieved, to withdraw the airway until its tip functions as a bite block between the teeth. Consideration of the macroglossia phenomenon may also be relevant as clinicians contemplate moving their transesophageal echocardiogram (TEE) from the cardiology department and using them in the neurosurgery suite. The centers that routinely employ the TEE in neurosurgery, for the most part, use either pediatric or custom-made small-diameter probes to avoid trauma to pharyngeal and perilaryngeal structures.

Quadriplegia.

The sitting position per se has been implicated as a cause of rare instances of unexplained postoperative paraplegia. It has been hypothesized [68] that neck flexion, which is a common concomitant of the seated position, may result in stretching or compression of the cervical spinal cord. This possibility may represent a relative contraindication to the use of this position in patients with significant degenerative disease of the cervical spine, especially when there is evidence of associated cerebral vascular disease. The blood pressure management implications are mentioned in the preceding paragraph. It may also represent a justification for somatosensory evoked response monitoring during the positioning phase of a sitting procedure for patients perceived to be at high risk.

Pneumocephalus

The issue of pneumocephalus arises most often in connection with posterior fossa craniotomies performed with the patient in a head-up posture because these operations entail the probability that air will be retained within the cranium. [69] During the procedure, the intracranial air is almost invariably in free communication with the atmosphere. However, on other occasions, it is suspected that air may enter the supratentorial space, much as air enters an inverted pop bottle. Depending on the relationship of the brain stem and temporal lobes to the incisura, the pressure in the air collection may or may not be able to equilibrate with atmospheric pressures consistently. This phenomenon has relevance to the use of N_2O because any N_2O that enters a trapped gas space augments the volume of that space. In those

(probably uncommon) intraoperative circumstances in which there is, in fact, a completely closed intracranial gas space, the use of N_2O may result in an effect comparable to that of an expanding mass lesion. We do not view N_2O as absolutely contraindicated because, prior to dural closure, intracranial gas is probably only rarely trapped. Nonetheless, attention to this possibility is important when one is presented with the problem of an increasingly "tight" brain during a posterior fossa craniotomy. [70] [71]

When surgical closure has reached a stage such that the intracranial space has been completely sealed from the atmosphere, it is probably appropriate to omit N_2O when performing posterior fossa procedures with the patient in a head-up posture because of the possibility of contributing to a tension pneumocephalus. Note that the use of N_2O up to the point of dural closure may actually represent a clinical advantage, [72] in that the gas pocket can be expected to shrink more rapidly because of the presence of N_2O (because N_2O diffuses out much more quickly than nitrogen).

Tension pneumocephalus can occur as a complication of intracranial neurosurgery unrelated to the use of N_2O. It is one cause of delayed awakening or nonawakening following both posterior fossa [73] and supratentorial procedures (Fig. 52-8) . It occurs because air enters the cranium when the patient is in a head-up position at a time when the volume of the intracranial contents are at an absolute optimum because of some combination of hypocapnia, good venous drainage, osmotic diuresis, and CSF loss via the operative field. When the cranium is closed and the patient is returned to the near-supine position, CSF, venous blood volume, and extracellular fluid return or reaccumulate, and the

Figure 52-8 Postoperative computed tomography scan demonstrating a large pneumocephalus after a subfrontal approach to a suprasellar glioma. Immediately postoperatively, the patient was confused and agitated and complained of severe headache.

air pocket becomes an unyielding mass lesion (because of the very slow diffusion of nitrogen). It may cause delayed recovery of consciousness or severe headache. Among supratentorial craniotomies, the largest residual air spaces occur after frontal skull base procedures in which energetic brain relaxation measures are used to facilitate subfrontal access (see Fig. 52-8) . Once again, we doubt that the possible occurrence of this phenomenon represents a contraindication to N_2O. However, withdrawal of N_2O may be appropriate at the time of cranial closure. The diagnosis of pneumocephalus is confirmed by a brow-up lateral x-ray film or CT scan. The treatment is a twist-drill hole, followed by needle puncture of the dura. Residual intracranial air should be considered at the time of repeat anesthesia, neurosurgical or nonneurosurgical. Air frequently remains evident on CT scan for more than 7 days after a craniotomy. [74]

Venous Air Embolism

The rate of occurrence of venous air embolism (VAE) varies according to the procedure, the position, and the detection method used. During posterior fossa procedures done with the patient in the sitting position, VAE is detectable by precordial Doppler in approximately 40 percent of patients and in 76 percent using TEE. [75] [76] [77] The incidence of VAE during posterior fossa procedures performed with the patient in other positions is much less (12% using precordial Doppler in the report of Black et al [60]), and it is probable, but unproven, that the average volume of air entrained per event is smaller with the nonsitting positions. The rate of VAE is apparently lower with cervical laminectomy (25% using TEE in the sitting position versus 76% for posterior fossa procedures [77]). Although VAE is principally a hazard of posterior fossa and upper cervical spine procedures, especially when they are performed with the patient in the sitting position, it can occur with supratentorial procedures. The most common situations involve tumors, most often parasagittal or falcine meningiomas, which encroach on the posterior half of the sagittal sinus. Pin sites and trapped gas under pressure can also lead to VAE just as with posterior fossa procedures, although clinically relevant events have been very rare.

The common sources of major VAE are the major cerebral venous sinuses, in particular the transverse, the sigmoid, and the posterior half of the sagittal sinuses, all of which may be noncollapsible because of their dural attachments. Air entry may also occur via emissary veins, particularly to suboccipital musculature, the diploic space of the skull (which can be violated by both the craniotomy and pin fixation), and the cervical epidural veins. It is the authors' belief (not confirmed by systematic study) that VAE risk associated with cervical laminectomy is greatest when the exposure requires dissection of suboccipital muscle with the potential to open emissary veins to the atmosphere at their point of entry into occipital bone. There is also anecdotal evidence [78] that air under pressure in the ventricles or subdural space can occasionally enter the venous system, perhaps following the CSF's normal egress route.

Detection

The monitors employed for the detection of VAE should provide (1) a high level of sensitivity, (2) specificity, (3) a rapid response, (4) a quantitative measure of the VAE event, and (5) an indication of the course of recovery from the VAE event. The combination of precordial Doppler and expired CO_2 monitoring meet these criteria and are the current standard of care. Doppler placement in a left or right parasternal location in the second to fourth intercostal spaces has a very high detection rate for gas embolization, [79] and when good heart tones are obtained, maneuvers to confirm adequate placement appear unnecessary. TEE is slightly more sensitive than the precordial Doppler (Fig. 52-9) (Figure Not Available) to VAE, [80] and TEE offers the advantage of identifying right-to-left shunting of air. [80] [81] [82] However, its safety during prolonged use, especially in patients with pronounced neck flexion, is not well established. Expired nitrogen analysis is theoretically attractive. However, the expired nitrogen concentrations

Figure 52-9 (Figure Not Available) The relative sensitivity of various monitoring techniques to the occurrence of venous air embolism (VAE). BP, blood pressure; CO, cardiac output; CVP, central venous pressure; ECG, electrocardiogram; $E_T CO_2$, end-tidal CO_2 ; PAP, pulmonary artery pressure; T-ECHO, transesophageal echocardiography.

Figure 52-10 (Figure Not Available) The responses of the electrocardiogram, arterial pressure, pulmonary artery pressure (PAP), pan-tidal CO_2 concentration, a precordial Doppler, and central venous pressure (CVP) to the intravenous administration of 10 mL of air over 30 seconds to an 11-kg dog. BP, blood pressure.

involved in anything less than catastrophic VAE are very small and push the available instrumentation to the limits of its sensitivity. [83] Furthermore, effective application requires absolute freedom from air contamination of the ventilator and anesthetic circuit. Figure 52-10 (Figure Not Available) presents the physiologic and monitor response to an air embolic event. Table 52-7 offers an appropriate management response to such an event.

Which Patients Should Have a Right Heart Catheter?

Essentially all patients who undergo posterior fossa procedures in the sitting position should have one. Although catastrophic, life-threatening VAE is relatively uncommon, a catheter that permits immediate evacuation of an air-filled heart occasionally is essential for resuscitation. The latitudes

TABLE 52-7 -- Management of an Acute Air Embolic Event

Prevent further air entry
Notify surgeon (flood or pack field)
Apply jugular compression
Lower the patient's head
Treat the intravascular air
Aspirate right heart catheter
Discontinue nitrous oxide

Inspired oxygen fraction: 1.0
(Administer pressors/inotropes)
(Apply chest compression)

are much wider with the nonsitting positions, and it is frequently appropriate, after a documented discussion with the surgeon, to omit the right heart catheter. The perceived risks of VAE associated with the intended procedure and the patient's physiologic reserve are the variables that contribute to the decision. Microvascular decompression maneuvers of the fifth and seventh cranial nerves for tic douloureux and hemifacial spasm, respectively, are examples of procedures for which the right heart catheter is usually omitted. The essentially horizontal semilateral position and the very limited retromastoid craniectomy have resulted (at our institution) in a very low incidence of Doppler-detectable VAE. However, one should come to know the local surgical practices, particularly with respect to the degree of head-up posture, before becoming casual about right atrial catheterization. For instance, with regard to the Jannetta procedure, recall that the necessary retromastoid craniectomy is performed in the angle between the transverse and sigmoid sinuses, and that venous sinusoids and emissary veins in the suboccipital bone are common. If this procedure is performed with the patient in any degree of head-up posturing, the risk of VAE may still be substantial.

Which Vein Should Be Used for Right Heart Access?

Although some surgeons may ask that neck veins not be used, a skillfully placed jugular catheter is often acceptable. In a very limited number of patients, high ICP may make the head-down posture undesirable. In others, unfavorable anatomy with an increased likelihood of a difficult cannulation

and hematoma formation may also encourage the use of alternate access sites. Access to the brachial veins has been greatly facilitated by the commercial availability of multiorificed catheters that utilize a Seldinger cannulation technique and a lengthy J-tipped guide wire to negotiate the axilla or deltopectoral groove.

Positioning the Right Heart Catheter

The investigation of Bunegin et al [84] suggests that a multiorificed catheter should be located with the tip 2 cm *below* the junction of the superior vena cava and the atrium and a single orificed catheter with the tip 3 cm *above* this junction. Although these small distinctions in location may be relevant for optimal recovery of small volumes of air when cardiac output is well maintained, for the recovery of massive volumes of air in the face of cardiovascular collapse, anywhere in the right atrium should suffice. Confirmation of right heart placement can be accomplished by (1) radiography, (2) pull back from the right ventricle while monitoring intravascular pressure, or (3) intravascular electrocardiography (ECG). [85] While there is no literature to support the practice, with catheter access via the right internal jugular vein, a measured placement to the level of the second right intercostal space should suffice when the catheter passes readily. The intravascular ECG technique makes use of the fact that an ECG "electrode" placed in the middle of the right atrium initially "sees" an increasing positivity as the developing P-wave vector approaches it (Fig. 52-11) and then an increasing negativity as the wave of atrial depolarization passes and moves away from it. The resultant biphasic P wave is characteristic of a midatrial "electrode" position. The technique requires that the CVP catheter become an exploring ECG electrode. This is accomplished by filling the catheter with an electrolyte solution (bicarbonate is best) and attaching an ECG lead (the leg lead if lead II is selected) to the hub of the central venous pressure (CVP) catheter. Commercial CVP kits with an ECG adapter are available. The ECG configurations that are observed at various intravascular locations are shown in Figure 52-11 . To minimize the microshock hazard, a battery-operated ECG unit should be employed, and unnecessary electrical apparatus should be detached from the patient during catheter placement.

Paradoxic Air Embolism

There has been much concern expressed about the possibility of the passage of air across the interatrial septum via a patent foramen ovale (PFO), which is known to be present in approximately 25 percent of adults. [86] The concern is that this phenomenon carries the risk of major cerebral and/or coronary morbidity, although there has been no precise definition of the morbidity that can realistically be attributed to paradoxic air embolism (PAE). Although the precise pressure required to open a probe PFO is not known with certainty, it is thought that the necessary gradient may be as much as 5 mm Hg. It has reasonably been assumed that the risk of the occurrence of PAE is greatest at times when right atrial pressure exceeds left atrial pressure. Clinical investigations

Figure 52-11 Electrocardiographic (ECG) configurations observed at various locations when a central venous catheter is used as an intravascular ECG electrode. The configurations in the figure are observed when lead II is monitored and the positive electrode (the leg electrode) is connected to the catheter. P indicates the sinoatrial node. The heavy black arrow indicates the P-wave vector. Note the equi-biphasic P wave when the catheter tip is in the middle right atrial position. [85]

revealed that the use of positive end-expiratory pressure (PEEP) increased the incidence of a positive right atrial pressure-pulmonary capillary wedge pressure gradient [87] and that generous fluid administration (e.g., 2,800 mL/patient versus 1,220 mL/control patient [88]) reduced it. As a result, the use of PEEP, which had previously been advocated as a means of preventing air entrainment, diminished, and the practice of more generous fluid administration for patients undergoing posterior fossa procedures evolved. However, subsequent data indicated that even when *mean* left atrial pressure exceeds mean right atrial pressure, PAE can still occur because transient reversal of the interatrial pressure gradient can occur during each cardiac cycle. [89] Some centers have explored the possibility of using preoperative precordial echocardiographic examination to identify patients with a PFO with a view to using alternatives to the sitting position in this subpopulation. [82] [90] [91] The practice has not become widespread. Initially, the number of patients identified was sufficiently far less than the incidence of PFO at autopsy or using TEE that widespread enthusiasm for preoperative screening did not evolve. However, more recently, Schwarz et al [92] reported

a precordial method that resulted in a 25 percent preoperative identification rate. A second group reported a similarly high yield using transcranial Doppler (TCD) of the middle cerebral artery to detect galactose microbubbles after peripheral injection. [93] Accordingly, consideration of preoperative screening of candidates for the sitting position may be renewed.

It is substantially easier to identify a PFO using the TEE (with agitated saline as the contrast medium) than it is with the precordial technique. [94] [95] Selecting the surgical position to be used on the basis of TEE performed after induction seems feasible. However, this approach has not been employed on a widespread basis. The expense of the necessary equipment is inevitably part of the reason. However, it also seems likely that, because the morbid events attributable to PAE have been quite infrequent, surgeons who are convinced that the sitting position is the optimal for a given procedure are loathe to be dissuaded from using it on the basis of what may seem like the very remote possibility of an injury to the patient occurring by this mechanism. At this juncture, maneuvers to identify a PFO prior to the use of the sitting position are decidedly not a community-wide standard of care.

Transpulmonary Passage of Air

It appears likely that air can occasionally traverse the pulmonary vascular bed to reach the systemic circulation. [96] [97] Transpulmonary passage is more likely to occur when large volumes of air are presented to the pulmonary vascular "filter." [98] There is also evidence suggesting that pulmonary vasodilators, [98] including volatile anesthetic agents, may lower the threshold for transpulmonary passage. [99] The magnitude of differences among anesthetics does not appear to mandate any related "tailoring" of anesthetic techniques. However, it does reinforce the notion that even apparently minor VAE should be treated with respect and should prompt discontinuation of N_2O.

Techniques for Reducing the Incidence of Venous Air Embolism

As noted earlier, PEEP was advocated in the past as a means both of reducing the incidence of VAE and of responding to an acute VAE event to prevent further air entry. However, a study by Perkins and Bedford [87] presented data that suggest that PEEP increases the risk of PAE and that accordingly argues against the use of PEEP in patients in the sitting position during neurosurgical procedures. Furthermore, as the authors point out, even 10 cm of PEEP would be unlikely to result in positive venous pressures in cerebral venous structures that may be as much as 25 cm above the heart. The inefficacy of PEEP [100] and the relative superiority of

jugular venous compression [101] [102] in raising cerebral venous pressures have been confirmed by other investigations. An inflatable neck tourniquet available for rapid inflation in the event of VAE has been studied in animals and used in humans by Pfitzner and McLean. [103] The G suit has also been shown to be more effective in producing increases in right atrial pressure than 10 cm of PEEP and can do so without increasing the right atrial-wedge pressure gradient. [104] This latter report is available only in a non-peer-reviewed (abstract) form. There are additional arguments against the short-term use of PEEP in the event of VAE. The various investigations of the identification of PFO have confirmed the efficacy of a Valsalva maneuver, in particular its release, as a means of *promoting* paradoxic embolism. [90] [105] In addition, the impairment of systemic venous return caused by the sudden application of substantial PEEP may be undesirable in the face of the cardiovascular dysfunction already caused by the VAE event.

It has been recommended that the patient who has sustained a hemodynamically significant VAE be placed in a lateral position with the right side upward. The rationale is that air will remain in the right atrium, where it will not contribute to an air lock in the right ventricle and where it will remain amenable to recovery via a right atrial catheter. The first difficulty is that this repositioning is all but impossible with a patient in a pin head holder. In addition, the only systematic attempt to examine the efficacy of this maneuver, albeit performed in dogs, failed to identify any hemodynamic benefit. [106]

Nitrous Oxide

N_2O diffuses into air bubbles trapped in the vascular tree, and accordingly N_2O should be eliminated after a clinical VAE event to avoid aggravating the cardiovascular impact. Note that the PAE phenomenon adds an additional reason for eliminating N_2O *after* the occurrence of VAE. When major VAE occurs, no matter how the right atrial pressure-left atrial pressure gradient was manipulated before the event, right atrial pressure rises abruptly with respect to left atrial pressure, [107] and major VAE always results in an acutely increased risk of PAE in those patients with a PFO. Should N_2O be used at all in patients at risk for VAE? Some clinicians decide that it is easier simply to avoid it and thereby to avoid having to worry about the considerations it creates. However, N_2O can be used with the knowledge that it neither increases the incidence of VAE [108] nor aggravates the hemodynamic response to VAE, provided it is eliminated when VAE occurs. [109]

Monitoring

Neurologic monitoring techniques are discussed in Chapter 35 . Invasive monitoring is frequently appropriate in neurosurgery. Some of the numerous indications for an arterial catheter are listed in Table 52-8 . Patients with increased ICP may be intolerant of the vascular engorgement associated with sudden hypertension occurring as a consequence of light anesthesia. Surgical relief of increased ICP may be associated with sudden hypotension as brain-stem compression is relieved. Beat-by-beat arterial pressure monitoring also serves as an important monitor of the depth of anesthesia and as a neurologic injury early-warning system. Much of the brain is insensate. As a consequence, the intracranial portion of many neurosurgical procedures is not very stimulating, and, to achieve circulatory stability, relatively light anesthesia is often necessary. There should be constant attention

TABLE 52-8 -- Relative Indications for Intra-Arterial Pressure Monitoring

Elevated intracranial pressure
Ischemia or incipient ischemia of neurologic tissue
Recent subarachnoid hemorrhage
Recent head injury
Recent spinal-cord injury
Intended or potential temporary vessel occlusion
Circulatory instability
Trauma
Spinal-cord injury (spinal shock)
Sitting position
Possible barbiturate coma
Possibility of induced hypotension
Possibility of induced hypertension
Anticipated/potential major blood loss
Aneurysm clipping
Arteriovenous malformations
Vascular tumors
Tumors involving major venous sinuses
Craniofacial reconstruction
Extensive craniosynostosis procedures
Anticipated light anesthesia without paralysis
Brain-stem manipulation/compression/dissection
Anticipated cranial nerve manipulation (especially CN V)
Advantageous for postoperative intensive care
Hypervolemic therapy
Head injury
Diabetes insipidus
Incidental cardiac disease

to the possibility of sudden arousal, most often associated with cranial nerve traction or irritation. This is especially important when paralysis is precluded by the use of electromyographic (EMG) recording from facial muscles to monitor cranial nerve integrity. Blood pressure responses may reveal imminent arousal. These responses may also serve to warn a surgeon of excessive or unrecognized irritation, traction, or compression of neurologic tissue. These responses occur most often with posterior fossa procedures involving brain stem or cranial nerves, and abrupt changes should be reported to the surgeon immediately.

The use of right heart catheters for air retrieval is discussed earlier. Thereafter, anticipated blood loss and fluid flux (including aggressive mannitol use) and an evaluation of the patient's physiologic reserve should determine the necessity for CVP or pulmonary artery catheters. Doppler use is also described earlier.

Fluid Management

The general principles of fluid management for neurosurgical anesthesia are (1) to maintain normovolemia and (2) to avoid reduction of serum osmolarity. The first principle is a derivative of the concept presented earlier that it is in general ideal to maintain a normal MAP in patients undergoing most neurosurgical procedures. Maintaining normovolemia is simply one element of maintaining a normal MAP. The second principle is a derivative of the common observation that lowering serum osmolarity results in edema of both normal and abnormal brain. Administering fluids that provide free water (i.e., fluids that do not have sufficient nonglucose solutes

to render them iso-osmolar with respect to blood) will lower serum osmolarity if the amount of free water administered is in excess of that required to maintain ongoing free water loss. A fluid such as half-normal saline is probably reasonable for the traditional maintenance fluid allowance. However, fluids administered to replace blood and third-space loss (i.e., iso-osmolar losses) should be ideally essentially iso-osmolar. Normal saline (which is, in fact, very slightly hyperosmolar, 308 mOsm/L) seems an ideal fluid. In practice, many clinicians use lactated Ringer solution (272 mOsm/L), and although this solution is, in theory, not ideal for either maintenance fluids or replacement of losses, it serves as an entirely reasonable compromise and is very suitable in most instances. However, in a normal experimental animal, it is possible to reduce serum osmolarity and to produce cerebral edema with a large volume of lactated Ringer solution. [110] Therefore, in the setting of massive fluid administration, such as multiple trauma, granted that there is very little advantage to lactated Ringer solution over normal saline, it seems reasonable to use normal saline.

The crystalloid versus colloid discussion is a recurrent one. It usually arises in the context of the head-injured victim of multiple trauma. Although there are numerous fervent beliefs regarding this issue, there has, in fact, been only a single demonstration that the reduction of colloid oncotic pressure in the absence of a change of osmolarity can actually contribute to an augmentation of cerebral edema in the setting of head injury. [111] The transcapillary membrane pressure gradients that can be produced by reduction of colloid oncotic pressure are, in fact, very small by comparison with those created by changes in serum osmolarity. Nonetheless, it appears that those small gradients do, probably in the setting of a BBB injury of intermediate severity, have the potential to augment edema. It seems reasonable then to select a fluid administration pattern that, in addition to maintaining normal serum osmolarity, prevents substantial reductions in colloid oncotic pressure. For most elective craniotomies, this will not require the administration of colloid solutions. However, in those situations requiring substantial volume administration (multiple trauma, aneurysm rupture, cerebral venous sinus laceration, fluid administration to support filling pressure during barbiturate coma), a combination of isotonic crystalloid and colloid may be appropriate.

What colloidal solutions should be used? Albumin and plasma protein fraction are both reasonable choices. The dextran-containing solutions are generally avoided because of their effects on platelet function. The various starch-containing solutions have generated some controversy. [112] [113] It appears certain that the starches have a specific inhibitory effect on factor VIII, [112] in addition to a dilutional reduction of coagulation factors. There have been several reported instances of bleeding in neurosurgical patients that has been attributed to hetastarch administration. However, all those episodes involved circumstances in which the manufacturer's recommended limit of 20 mL/kg/d was exceeded. The decision to use or not use these products is frequently a local one. If they are used, the manufacturer's recommended limit (20 mL/kg/24 h) should be observed.

There is substantial current interest in the use of hypertonic fluids, in particular in the circumstance of resuscitation

---

of the multiple trauma victim. [114] It appears unlikely that the effect of these fluids on the brain is substantially different from that of an equi-osmolar exposure to mannitol. [115] Accordingly, when decisions about the appropriateness and relevance of these fluids in the resuscitation process are eventually made, it seems unlikely that those decisions are made on the basis of specific cerebral effects. It seems more likely that the final judgment regarding this class of fluids is made on their effects on the systemic circulation. [116] In general, an intervention that has the advantage of more effectively restoring systemic hemodynamics is likely to be advantageous to the brain. That assertion is made with the provision that sustained hyperosmolarity, such as that greater than 320 mOsm/L, caused by any fluid has the potential to result in rebound swelling of the brain.

Hypothermia

The effects of hypothermia on cerebral physiology and its potential cerebral protective mechanisms are presented in Chapter 19 (Table 19-8; Ch. 37) . There have been numerous laboratory demonstrations of the efficacy of mild hypothermia (32-34°C) in reducing the neurologic injury occurring after standardized cerebral and spinal cord ischemic insults. This has resulted, in spite of the absence of any demonstration of efficacy in humans, in the relatively widespread use of induced hypothermia in the management of cerebral vascular procedures, in particular aneurysms [117] [118] and occasionally AVM. Although mild hypothermia is perceived to convey certain hazards, including coagulation dysfunction and an increased postoperative wound infection rate, neither of these problems has been evident in the context of aneurysm surgery, although once again there has not been systematic study. Anecdotally, hypertension on emergence from anesthesia has been noted to occur in patients who are not adequately rewarmed, and a modest overshoot in temperature has been observed to occur among patients who were cooled intraoperatively. [119] The issue of where body temperature should be recorded in order to reflect brain temperature best during craniotomy has been addressed. [120] It appears that esophageal, tympanic membrane, pulmonary artery, and jugular bulb temperatures are all very similar and provide a reasonable reflection of deep brain temperature, whereas bladder temperature does not. Superficial layers of cortex may be substantially cooler than deep brain and central temperatures.

Because ischemia is recognized to make a postinsult contribution to neuronal injury after head injury, [24] [121] hypothermia was also studied in the laboratory in the context of traumatic brain injury. [122] It was effective, and this resulted in at least four single institution trials of 24 to 48 hours of mild hypothermia after head injury. These trials demonstrated either significant improvement in outcome or favorable trends. [123] [124] [125] [126] A multicenter, prospective trial of hypothermia after head injury is ongoing. A report is anticipated early in 2000. Those investigations have revealed some physiologic dysfunction associated with more prolonged mild hypothermia, all of which has been reversible with restoration of normal temperature. This included decreased creatinine clearance, elevation of pancreatic enzymes, and a suggestion of an increased infection rate. A decreased incidence of seizures was an apparent adjunctive benefit in one study.

On the basis of a lack of demonstrated efficacy in humans, routine use of hypothermia cannot be advocated in a standard text. The decision to employ it, usually in the context of aneurysm surgery, is local. If employed, hypothermia should be used with attention to the possibility of cardiac dysrhythmias and coagulation dysfunction if temperatures become too low and with attention to the necessity to rewarm the patient adequately prior to emergence to avoid shivering and hypertension.

Emergence From Anesthesia

Most practitioners of neuroanesthesia believe that there is a premium on a "smooth" emergence, that is, one free of coughing/straining and arterial hypertension. The avoidance of arterial hypertension is seen as desirable because of the belief that arterial hypertension can contribute to intracranial bleeding and increased edema formation. [127] [128] [129] [130] In the face of a poorly autoregulating cerebral vasculature, hypertension also has the potential, through vascular engorgement, to contribute to elevation of ICP. Much of the concern with coughing/straining has a similar basis. The sudden increases in intrathoracic pressure are transmitted to both arteries and veins, thus producing transient increases in both cerebral arterial and venous pressure with the same potential consequences: edema formation, bleeding, and elevation of ICP. Coughing is a specific concern with certain individual procedures. In transsphenoidal pituitary surgery in which a surgeon has opened, and subsequently taken pains to close, the arachnoid membrane to prevent CSF leakage, there is the belief that coughing has the potential to disrupt this closure because of the sudden and substantial increases in CSF pressure. Opening a pathway from the intracranial space to the nasal cavity conveys a substantial risk of postoperative meningitis. In other procedures, notably those that have violated the floor of the anterior fossa, there is also the potential for air to be driven into the cranium and, in the event of a flap-valve mechanism, to cause a tension pneumocephalus. This latter event can only occur when coughing occurs after the endotracheal tube has been removed.

It should be acknowledged that there is a paucity of systematically obtained clinical data to give perspective to the actual magnitude of the risks associated with emergences from anesthesia that are not "smooth." One clinical investigation confirmed the association of increased CBF velocity in association with hypertension during emergence. [131] A second retrospective study revealed that elevated postoperative blood pressure was a correlate of intracerebral bleeding following craniotomy. [132] However, there is not, in fact, any proof to show that it is specifically hypertension occurring during emergence that is correlated with postoperative intracerebral bleeding. The same acknowledgment must be made with the matter of edema formation. It has been demonstrated in animals that sudden substantial increases in arterial pressure in anesthetized animals can result in a breech of the BBB with extravasation of tracers such as Evans blue. However, there are no data to confirm that the

---

pressure transients associated with the typical coughing episode or typical emergence hypertensive transient are, in fact, associated with increased edema formation. Nonetheless, it seems reasonable to take measures, to the extent that these measures do not themselves add potential patient morbidity, to prevent these occurrences.

A common method for the management of systemic hypertension during the last stages of a craniotomy is the expectant and/or reactive administration of vasoactive agents, most commonly labetalol and esmolol. Several other drugs are acceptable. There are also many approaches to the prevention of coughing and straining. We have several biases and encourage trainees to include in their anesthetic technique as much narcotic as is consistent with spontaneous ventilation at the conclusion of the procedure. That practice is based on the same physiologic effect that justifies the administration of codeine and related compounds as antitussive medication, that is, the depression of airway reflexes by narcotics. We also have the bias that patients emerge more rapidly and smoothly when the last inhalation agent to be withdrawn is N_2O and that clinicians should seek to avoid the "neither here nor there" phase of anesthesia that occurs in patients who are stimulated in the face of residual exhaled concentrations of volatile agent on the order of 0.2 to 0.3 minimum alveolar concentration (MAC). A common practice among neuroanesthetists near the conclusion of a craniotomy is the relatively early discontinuation of the volatile agent with supplementation of residual N_2O with propofol by either bolus increments or infusion at rates in the range of 25 to 100 mug/kg/min.

An additional principle relevant to the emergence from neurosurgical procedures that practitioners will learn either from a book or from experience is that emergence should be timed to coincide not with the final suture (as may be appropriate for a cholecystectomy), but rather with the conclusion of the application of the head dressing. Many a good anesthetic regimen for neurosurgery has been spoiled by severe coughing and straining that occurs in association with endotracheal tube motion during the application of the head dressing. Another nuance of our practice has been to withhold administration of neuromuscular antagonists as long as possible as a hedge against misjudgment while lightening anesthesia in a patient in the later stages of the procedure. An additional popular and apparently effective technique for reducing airway responsiveness and the likelihood of coughing/straining while reducing the depth of anesthesia is the administration of lidocaine. Bolus doses on the order of 1.5 mg/kg are appropriate for this purpose.

The premium placed on minimizing coughing/straining and hypertension usually causes patients to be very expediently extubated once extubation is appropriate. There may, in some instances, be a temptation to extubate patients prior to complete recovery of consciousness. This method may be acceptable in some circumstances. However, it should be undertaken with caution when the circumstances of the surgical procedure make it possible that neurologic events have occurred that will delay recovery of consciousness or when there may be lower cranial nerve dysfunction. In these circumstances, it is generally best to wait until the likelihood of the patient's recovery of consciousness is confirmed and/or until patient cooperation and airway reflexes are likely to have recovered.

SPECIFIC PROCEDURES

Many of the considerations relevant to individual neurosurgical procedures are generic and are presented earlier in this chapter. The descriptions that follow highlight only procedure-specific issues.

Supratentorial Tumors

Craniotomies for excision and/or biopsy of supratentorial tumors are among the most common neurosurgical procedures performed. Gliomas and meningiomas are among the most frequent tumors. The relevant preoperative considerations include the patient's ICP status and the location and size of the tumor. Location and size give the anesthesiologist an indication of the surgical position and the potential for blood loss, and occasionally they reveal a risk of air embolism. The VAE risk is quite low for the majority of other supratentorial tumors. However, lesions (usually convexity meningiomas) that encroach on the sagittal sinus may convey a substantial risk of VAE. Accordingly, full VAE precautions, including an atrially placed CVP catheter, are usually reserved only for supratentorial tumors that lie near the posterior half of the sagittal sinus.

Patients with craniopharyngiomas and pituitary tumors with suprasellar extension may undergo procedures that involve dissection in and around the hypothalamus. Irritation of the hypothalamus can elicit sympathetic responses including hypertension. Damage to the hypothalamus can result in a spectrum of disturbances in consciousness varying from lethargy to obtundation. Disturbances of water balance may also occur. Diabetes insipidus is the most likely disorder, although the cerebral salt-wasting syndrome can potentially occur. The latter has been very infrequent. The various disturbances of water balance typically have a delayed onset, beginning 12 to 24 hours postoperatively, rather than in the operating room. Postoperative temperature homeostasis may also be disturbed.

Patients who undergo a craniotomy involving a subfrontal approach may, on occasion, manifest a disturbance of consciousness in the immediate postoperative period. Retraction/irritation of the inferior surfaces of the frontal lobes can result in a patient who is lethargic and does not awaken "cleanly." Patients exhibiting this phenomenon are sometimes referred to "frontal lobe-y." The phenomenon is more likely to be evident when there has been bilateral subfrontal retraction than when it occurs only unilaterally. The anesthetic implication is that the clinician should be more inclined to confirm the patient's return of consciousness before extubating the patient than to extubate while awaiting the patient's return to consciousness. A further implication taken by these authors (although not confirmed by any systematic study) is that a less liberal use of fixed agents (narcotics, benzodiazepines) may be appropriate. This is based on the rationale that low residual concentrations of these agents that would be compatible with reasonable recovery of consciousness in the majority of patients may be less well tolerated in this population. Subfrontal approaches are most commonly employed in patients with olfactory groove meningiomas and in patients with suprasellar tumors (craniopharyngiomas and pituitary tumors with suprasellar extension).

Preoperative Preparation

Patients with a significant tumor-related mass effect, especially if there is tumor-related edema, should receive preoperative steroids. If the patient is not receiving a steroid, it is the anesthesiologist's responsibility to ask why. A 48-hour course is ideal (see the discussion of steroids earlier), although 24 hours is sufficient for a clinical effect to be evident. Dexamethasone is the most commonly used agent. Regimens such as 10 mg intravenously or orally followed by 10 mg every 6 hours are typical. Because of the concern about producing CO_2 retention in a patient whose intracranial compliance is already abnormal, patients with any substantial mass effect are usually not premedicated with anything beyond full-dose reassurance.

Monitoring

Frequently, the nature of the procedure does not require anything more than routine monitoring. However, some situations do argue for invasive monitors (see earlier). Preinduction placement of an arterial line may be appropriate in patients with severe mass effect and little residual compensatory latitude. It is the period of induction during which hypertension with its attendant risks in a patient with impaired compliance and autoregulation is most likely to occur. Procedures with a substantial perceived blood loss potential (tumors encroaching on the sagittal sinus, large vascular tumors) may also justify arterial and/or CVP catheters. Is ICP monitoring ever warranted for intraoperative management? In our opinion, no. Clinicians have a sufficient understanding of the potential impact of anesthetic agents and techniques that they should be able to manage induction of anesthesia. Then, once the cranium is open, observation of conditions in the surgical field provides equivalent information.

Management of Anesthesia

The principles governing the choice of anesthetic agents are presented in the earlier section on anesthetic selection in the discussion of ICP control.

Aneurysms and Arteriovenous Malformations

Contemporary management of intracranial aneurysms calls for early surgical intervention following SAH. The definition of "early" varies up to and including the first 72 hours after bleeding. [133] This approach is usually applied only in patients in the better neurologic grades: grades I to III and perhaps IV of the World Federation of Neurosurgeons classification (Table 52-9) or grades I to III of the Hunt-Hess classification (Table 52-10) . If early intervention is not feasible, then surgery is usually delayed for at least 2 weeks in order to be safely beyond the period of maximal vasospasm risk, that is, days 4 to 12 after SAH.

TABLE 52-9 -- World Federation of Neurosurgeons Subarachnoid Hemorrhage Scale

WORLD FEDERATION OF NEUROSURGEONS GRADE	GLASGOW COMA SCALE SCORE	MOTOR DEFICIT
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

From Drake et al [235]

TABLE 52-10 -- Hunt-Hess Classification of Neurologic Status After Subarachnoid Hemorrhage

CATEGORY	CRITERIA[a]
Grade I	Asymptomatic or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, no deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion, or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances
Grade V	Deep coma, decerebrate rigidity, moribund appearance

From Hunt and Hess [24]

[a] Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and severe vasospasm seen on arteriography result in placement of the patient in the next less favorable category.

The rationale for early clipping of the aneurysm is several-fold. The sooner the aneurysm is clipped, the less is the likelihood of rebleeding, and rebleeding is the principal cause of death for patients hospitalized after SAH [134] . The management of the ischemia caused by vasospasm involves volume loading and induced hypertension. Early clipping of the aneurysm eliminates the risk of rebleeding associated with this therapy. Vasospasm appears to be related to the presence of blood in the basal cisterns in the vicinity of the circle of Willis. Some of this blood can be removed at the time of the aneurysm clipping, and, accordingly, early clipping not only makes the therapy of vasospasm safer, but also it may reduce the incidence and severity of the problem. Early access to the circle of Willis also allows direct instillation of tissue plasminogen activator into the basal cisterns to aid further in the clearing of clot from the circle of Willis. [135] [136] The results of the initial evaluations of tissue plasminogen activator therapy are suggestive of a substantial benefit, although this therapy remains experimental. Prior surgical practices entailed maintaining the patient at bed rest until approximately day 14, when the period of spasm risk had passed. Early aneurysm clipping reduces the period of hospitalization and reduces the incidence of the medical complications (deep venous thrombosis, atelectasis, pneumonia) associated with a lengthy period of enforced bed rest.

Early intervention can make the intraoperative course more difficult. The brain in the early post-SAH period is likely to be more edematous than following a 2-week delay. A mild degree of hydrocephalus is common after blood contaminates the subarachnoid space. [137] In fact, up to 10 percent of victims of SAH may actually require CSF shunting at some point in their course. [138] Early intervention may also somewhat enhance the risk of intraoperative aneurysmal rupture because of the lesser period of time for clot to organize over the site of the initial bleeding. All this places a substantial premium on techniques designed to reduce the volume of the intracranial contents (see earlier) in order to facilitate exposure and to minimize retraction pressures.

Preoperative Evaluation.

Many patients scheduled for intracranial aneurysm clipping come directly from the ICU, and elements of their management there may influence their immediate preoperative status.

Fluid Management.

Some patients develop syndrome of inappropriate antidiuretic hormone (SIADH) after SAH and are appropriately managed with fluid restriction. However, hyponatremia after SAH is more likely to be the result of the cerebral salt-wasting syndrome, [139] [140] [141] [142] [143] which probably occurs as a result of the release of a natriuretic peptide (which is similar to but may not be the same as that occurring in the heart [144] [145]). The syndrome is characterized by the triad of hyponatremia, volume contraction, and high urine sodium concentrations (>50 mmol/L). The distinction between this syndrome and SIADH is important. SIADH, which is characterized by normovolemia or mild hypervolemia, is treated by volume restriction. Cerebral salt wasting is associated with *contracted* intravascular volume. [143] Fluid restriction and further volume contraction may be especially deleterious in the patient who has had an SAH, [140] and these measures should be avoided.

Vasospasm.

When neurologic deterioration occurs subsequent to the patient's initial period of stabilization, vasospasm is frequently the cause. Drowsiness is a common initial clinical sign. In patients in whom there is a clinical suspicion or an angiographic demonstration of vasospasm, surgery is commonly deferred. If it is to proceed, CPP should be maintained intraoperatively in a high-normal range. This is contrary to the time-honored patterns of intraoperative management that have characteristically emphasized *hypo*tension. However, neurosurgeons are becoming increasingly concerned about the potential for induced hypotension to cause or to aggravate cerebral ischemia in the patient with vasospasm. This concern extends to the World Federation of Neurosurgeons grade I patient who may have regions of cerebral ischemia [40] that are subclinical when the patient is normotensive.

Vasospasm is thought to be caused by the breakdown products of oxyhemoglobin in the blood that has accumulated around the vessels at the base of the brain. Whereas current suspicion is focused on the binding of nitric oxide by exposed heme groups, the specific mechanism/mediator has not been identified.

In the ICU, the regimens employed to treat vasospasm usually involve some combination of hypervolemia, hemodilution, and hypertension. The science behind hypervolemic-hypertensive therapy is "soft." It is not clear whether the rheologic or the pressure effects are the more important, although there is evidence of the relevance of blood pressure elevation in isolation. [146] Empirically, it appears to work. The favored pressor is dopamine. The end point for dopamine administration varies. It may be an increase in MAP of
20 to 30 mm Hg higher than "baseline" systolic pressure. Other surgeons are content to achieve merely a substantial increase in cardiac output, although the available data argue that blood pressure is the important determinant of CBF. [147] Some clinicians believe that the hematocrit should be reduced to the low 30s. Commonly, hematocrit reduction occurs secondarily as a result of attempts to produce hypervolemia (usually with colloid solutions), as part of the effort to raise blood pressure.

Calcium Channel Blockers.

Calcium channel blockers are an established part of the management of SAH. Administration of nimodipine has been shown to decrease the incidence of morbidity from cerebral ischemia after SAH. [148] [149] [150] However, these studies have failed to demonstrate any reduction in the incidence of vasospasm as detected by angiography. [149] This finding suggests that the beneficial effect of these agents may be the result of effects on neurons rather than on vascular smooth muscle. Patients can be expected to come to the operating room after having received nimodipine. The available information suggests that the use of nimodipine causes very little hemodynamic disturbance. [151] Nimodipine must be administered orally, and nicardipine has been evaluated as an intravenous alternative. A multicenter nicardipine trial [152] [153] revealed a reduced incidence of symptomatic vasospasm, but it showed no improvement in outcome. As a consequence, nimodipine is more commonly employed.

Tirilazad.

In a multicenter trial conducted in Europe, Australia, and New Zealand, a better neurologic outcome

and a reduced incidence of the need for hypervolemic-hemodilutional-hypertensive therapy were observed in men who received tirilazad, a free radical scavenger. [154]

The absence of a benefit in women has been attributed to a more rapid rate of metabolism associated with the presence of estrogens. The North American limb of that trial revealed no benefit in either sex. [155] It has been speculated that the absence of a protective effect in North America was the result of a greater frequency of use of anticonvulsants, with the attendant possibility of an increased rate of metabolism of tirilazad in both male and female patients. A follow-up trial using 10 to 15 mg/kg/d is under way.

Antifibrinolytics.

Antifibrinolytics were employed in the past in an attempt to reduce the incidence of rebleeding. Although they accomplish the latter, the overall morbidity is nonetheless worse as a result of an increase in the incidence of ischemic symptoms [156] and hydrocephalus.

ECG Abnormalities.

ECG abnormalities can occur in patients who have sustained an SAH. In addition to the classic "canyon T waves" (Fig. 52-12) , nonspecific T-wave changes, QT prolongation, ST-segment depression, and U waves have been described. [157] The significance of these changes has been debated. It seems likely that the episode of extreme hypertension and autonomic discharge that occurs in association with the initial SAH event does, in fact, result in focal, probably subendocardial, myocardial injury, presumably because of the extreme myocardial wall tension that occurs. [158] Evidence of focal myocardial injury has been found in some, [159] but not all, [157] investigations. The relationship between the ECG changes and myocardial dysfunction is not clear. Davies et al [160] compared the 12-lead ECG and the 2-dimensional precordial echocardiogram in 41 patients with sustained SAH. These authors concluded that myocardial dysfunction was more likely to occur with increasing severity of neurologic condition and that the ECG itself was not an accurate predictor of myocardial dysfunction. Szabo et al [161] observed thallium scan abnormalities in one-third of patients after SAH. However, there was no identifiable relationship between the scan abnormalities and the ECG changes. By contrast to the preceding two studies, Mayer et al [162] did identify an association between impaired left ventricular function and ECG abnormalities including T-wave inversion and QTc prolongation. In either case, it appears that, when ECG patterns other than those that are typical of myocardial ischemia are observed, no specific interventions or modifications of patient management approach are warranted. Brouwers et al [163] followed the clinical course of 61 patients who had at least one abnormal ECG following

Figure 52-12 Electrocardiographic abnormalities associated with subarachnoid hemorrhage. This tracing demonstrates the "canyon" T waves that may be seen after subarachnoid hemorrhage.

SAH. Cardiac dysfunction did not appear to contribute to morbidity or mortality in any of these patients, and these workers concluded that "in patients with aneurysmal SAH, ECG abnormalities do not herald impending cardiac disease." Although the nonspecific ECG changes do not appear to have important implications with respect to myocardial function, they may indicate a risk of dysrhythmias. In particular, an increased Q-T interval (>550 ms) has been associated with an increased incidence of malignant ventricular rhythms including torsades de pointes. [164]

Anesthetic Technique.

The important considerations include the following:

1. The absolute avoidance of acute hypertension with its attendant risk of recurrent rupture.
2. The provision of intraoperative brain relaxation to facilitate surgical access to the aneurysm.
3. The maintenance of a high-normal MAP in order to prevent critical reduction of CBF in recently insulted and now marginally perfused areas of brain.
4. The preparedness to perform precise manipulations of MAP as the surgeon attempts to clip the aneurysm and/or control bleeding from a ruptured aneurysm.

Monitoring.

An arterial line is invariably appropriate. A CVP may be relevant if the institutional practices involve large doses of mannitol to promote brain relaxation, and it may be chosen in older patients to guide volume replacement in the event of bleeding.

Agent Selection.

Any technique that permits proper control of MAP is acceptable. However, in the face of an increased ICP or a tight surgical field, an inhaled agent technique may be less suitable. The prevention of paroxysmal hypertension is the only absolute requirement in patients undergoing aneurysm clipping. Rebleeding kills, [134] and the poorly organized clot over the aneurysms of patients undergoing early post-SAH clipping makes them particularly prone to rebleeding. Rebleeding at induction is an almost invariably fatal event. The escaping arterial blood is more likely to penetrate brain substance because it cannot dissect through the CSF space (filled with clot), and the ICP increase is extreme because of the poor compliance of the intracranial space (swollen brain, hydrocephalus).

Induced Hypotension.

The routine use of induced hypotension is diminishing (see earlier). Nonetheless, the anesthesiologist should be prepared to lower the patient's blood pressure immediately and precisely if called on to do so. Preparation must occur before the episode of bleeding. We prepare a sodium nitroprusside infusion prior to induction. It is placed in line at a Y-injection port at the hub of the CVP or intravenous catheter. A carrier drip flows steadily such that any change in nitroprusside infusion rate is reflected as rapidly as possible in the central compartment. There are theoretical pros and cons for the use of various hypotensive agents. The data indicate that regimens that entail the use of an agent that is also a cerebral vasodilator (isoflurane, nitroprusside) are preferable in terms of brain oxygen delivery to approaches that do not involve cerebral vasodilation (trimethaphan, controlled hypovolemia). [165] Deep isoflurane and nitroprusside are the most commonly used regimens, although other agents may be suitable. The choice should ultimately be made on the basis of which regimen, in the hands of the individual practitioner, results in the most precise control of MAP. There are occasions when the anesthesiologist is asked to control MAP in the range of 30 to 50 mm Hg, in the face of active arterial bleeding. This can be extremely difficult in a patient who is hypovolemic at the beginning of the bleeding episode. Accordingly, it is our practice to maintain normovolemia.

Induced Hypertension.

Hypertension may be requested during periods of temporary arterial occlusion (see the discussion of trapping later) to augment collateral CBF. [117] In addition, following clipping of the aneurysm, some surgeons puncture the dome of the aneurysm to confirm adequate clip placement and may request transient elevation of the systolic pressure to 150 mm Hg. Phenylephrine is suitable in either instance.

Hypocapnia.

Hypocapnia has traditionally been employed as an adjunct to brain relaxation. This, too, has been questioned on the basis of the concern that it will aggravate ischemia (see earlier). The ICP/brain relaxation circumstances should probably dictate its use or avoidance.

Lumbar CSF Drainage.

Some surgeons employ elective drainage to facilitate exposure of the operative site. It is extremely effective, effective to the point that the energetic application of other brain-volume-reducing techniques is almost unnecessary. It is appropriate, when placing a lumbar CSF drain, to avoid excessive loss of CSF. Sudden reduction of the transmural pressure gradient across the dome of the aneurysm (by sudden reduction of ICP consequent on substantial CSF drainage) should be avoided lest this decompression encourage rebleeding. [166] The common practice is, having verified the patency of the lumbar drainage system, to leave it closed until such time

as the surgeon is completing the dural opening. The drain may then be opened and allowed to drain freely with the bag at floor level. Drainage should be discontinued promptly after final withdrawal of the retractors in order to allow CSF to reaccumulate and thereby to reduce the size of the potential pneumocephalus. The drain is usually removed immediately postoperatively.

Mannitol.

Some surgeons make relatively aggressive use of mannitol (e.g., 2 g/kg). In part, it is used to shrink the brain and thereby to facilitate exposure and to reduce retractor pressures. There is evidence that it may have additional benefits. Specifically, there are data derived in both animals and humans that indicate that mannitol may have a CBF-enhancing effect in regions of moderate CBF reduction. [167] [168] [169] The mechanism is not defined. However, reduction of interstitial tissue pressure around capillaries and/or an alteration of blood rheology have been proposed to contribute to this effect.

Trapping.

It is occasionally necessary for the surgeon to "trap" the aneurysm (i.e., to occlude the vessel temporarily on either side of the aneurysm) in order to complete dissection of the neck and to apply the clip. This is more common with larger aneurysms. With giant aneurysms in the vicinity

of the carotid siphon, the inferior occlusion may be performed at the level of the internal carotid artery via a separate incision in the neck. A clinical survey by Samson et al [170] of the results of temporary occlusion in normothermic adults revealed that occlusions of less than 14 minutes were invariably tolerated. The likelihood of an ischemic injury increased with longer occlusion times to 100 percent at more than 31 minutes. [170] In another institution, the threshold for ischemic injury was 20 minutes. [117] Typically, it is appropriate to support MAP at high-normal levels during periods of occlusion to facilitate collateral CBF.

Brain Protection.

Maintenance of MAP to ensure collateral flow and perfusion under retractors, efficient brain relaxation to facilitate surgical access and to reduce retractor pressures, limiting the duration of episodes of temporary occlusion, and perhaps mild hypothermia (see earlier) are the important brain-protection techniques. Specific anesthetic agents have also been used to protect the brain (Ch. 19) . Etomidate and propofol are used currently. However, there have been no convincing laboratory demonstrations that either drug provides any greater tolerance to a standardized ischemic insult than does anesthesia with a volatile agent. With respect to the volatile agents, attempts in the laboratory to confirm the once suspected protective efficacy of isoflurane have demonstrated that there are no differences among the various volatile agents in terms of their influence on outcome after focal or global ischemia in the laboratory. [171] [172] Nor has there been any demonstration of greater protective efficacy with concentrations of volatile agents sufficient to cause EEG suppression as opposed to more modest, levels, such as 1.0 MAC. It may evolve from ongoing investigative work that there is an advantage to a volatile agent technique over a narcotic-based technique, [173] but that issue remains to be defined. Among anesthetic agents, it is only the barbiturates for which additional protective efficacy has been demonstrated convincingly (Ch. 19) . Because of their potentially adverse effects on hemodynamics and arousal, these drugs are not ideal for routine administration. They should probably be reserved for situations in which a prolonged vessel occlusion is unavoidable, and in that circumstance, it would be ideal that the ischemic hazard be first confirmed by observation of the EEG response to a temporary occlusion.

Hypothermia.

As noted earlier, there has been no con-firmation in humans of the efficacy of mild hypothermia. Nonetheless, neurosurgical teams in many institutions are lowering body temperature to the range of 32 to 34°C for procedures in which vessel occlusion may occur. The institutions using the lower temperatures are those in which the team is willing to accept a delay in emergence from anesthesia as a result of the need to maintain anesthesia long enough to achieve rewarming in order to avoid the extreme hypertension that can occur when a patient is awakened at low body temperatures. It has been confirmed by Crowder et al [120] that the systemic temperature reduction does result in a concomitant decrease in brain temperature. In that investigation, during moderate hypothermia with the dura open, cortex temperature was approximately 0.5°C less than tympanic membrane temperature and about 1°C lower than esophageal, pulmonary artery, or jugular bulb temperature. [120]

Neurophysiologic Monitoring.

Both evoked responses and EEG have been employed, [174] [175] although neither is used widely. EEG monitoring can be used as a guide to management during the period of flow interruption and/or to guide the administration of CMR-reducing anesthetic agents given prior to occlusion. [175] At some institutions, the surgeon places an electrode strip over the region of cortex at risk during the intended occlusion. However, the more commonly used skin-surface frontal-mastoid derivation is probably sufficient to reveal a major ischemic event. The EEG can be either the conventional "raw" polygraph or a processed derivative. In most circumstances, if occlusion is deemed necessary, a temporary occlusion is performed, and the EEG is observed. If the EEG shows significant slowing, the usual practice is to reposition the clip and/or elevate MAP by some combination of phenylephrine and lightening of anesthesia in order to find a way of temporary clipping without a major EEG disturbance. If this cannot be accomplished, and if a sustained period of occlusion seems likely, then it may be appropriate to administer barbiturates (see earlier) to produce burst suppression.

Intraoperative Angiography.

Intraoperative angiography is an increasingly common component of the management of intracranial aneurysms. It does not have substantial implications for the anesthesiologist. However, apparatus around the patient's head must be organized so as to allow C-arm access without snagging of airway and monitoring equipment. In addition, the radiologist must have access to the patient's groin vessels. The vascular access sheath, for a patient who will ultimately be in the lateral position, is easiest to use when the nondependent femoral artery is chosen. The rate of administration of heparin "flush" via the vascular access sheath should be monitored.

Special Considerations for Specific Aneurysms.

The most common procedures are performed for aneurysms arising in or close to the circle of Willis. The vessel of origin may be the middle cerebral artery, the anterior communicating artery, the anterior cerebral arteries, the ophthalmic artery, the tip of the basilar artery, the posterior communicating artery, or, less frequently, the posterior cerebral artery. These procedures are all relatively similar for the anesthesiologist.

Ophthalmic Artery Aneurysms.

These aneurysms frequently require temporary vascular occlusion. Access to the origin of the ophthalmic artery is made difficult by the anterior clinoid process and the optic nerve. Surgeons commonly first expose the carotid artery in the patient's neck. When they reach the stage of seeking definitive access to the neck of the aneurysm, they occlude first the carotid artery in the neck and then the intracranial portion of the carotid artery immediately proximal to the origin of the posterior communicating artery. Surgeons may also place the isolated segment to suction, which entails a modest ongoing blood loss as a consequence of retrograde flow from meningeal and hypophyseal vessels.

Vertebrobasilar Aneurysms.

These procedures are typically performed with the patient in the lateral position. The exposure may involve a combined middle and posterior

fossa approach, with some attendant, although minor, risk of VAE. Cortical or skin-surface EEG monitoring is of less relevance with vertebrobasilar aneurysms.

Auditory and/or somatosensory evoked responses have been employed [176] (Ch. 35) . As in any other procedure involving the potential for mechanical or vascular injury to the brain stem, cardiovascular responses should be monitored, and sudden changes in response to surgical manipulation should prompt immediate notification of the surgeon. Spontaneous ventilation has also been shown to play an important role during surgical manipulation of the vertebral arteries, the vertebrobasilar junction, and the middle portion of the basilar artery. Apnea, gasping, and other sudden changes in ventilatory pattern during manipulation of the vasculature provide important, although somewhat nonspecific, warnings of compromise of the vascular supply of the brain stem. [177] [178]

Vein of Galen Aneurysms.

These "aneurysms" are more appropriately managed according to considerations relevant to AVM. These considerations include anticipation of the possibility of the cerebral dysautoregulation phenomenon and are considered later.

Arteriovenous Malformations

For the majority of intracranial AVMs, the general considerations are similar to those appropriate to aneurysm surgery: avoidance of acute hypertension and the capability to manipulate blood pressure accurately in the event of bleeding. A problem that is specific to AVM is the phenomenon known as perfusion pressure breakthrough or cerebral dysautoregulation. [179] It is characterized by an often sudden engorgement and swelling of the brain, sometimes with a relentless cauliflower-like protrusion from the cranium. It tends to occur in the advanced stages of lengthy procedures on large AVMs. The phenomenon is not entirely understood. However, it has been attributed to the acute obliteration of the high-volume, low-resistance pathway (the AVM) that, for many years, has been stealing blood from the surrounding tissue. The result is the abrupt diversion of the AVM's flow to the vasculature in adjacent and previously marginally perfused brain. It is presumed that these tissues have long been maximally vasodilated without the need ever to vasoconstrict and that they are incapable of doing so (although not all the available information is consistent with this premise [180] [181] . Accordingly, the phenomenon is also referred to as "autoregulation breakthrough" or dysautoregulation.

Anesthetic Technique.

The management constraints are essentially the same as those relevant to aneurysm surgery. Institutional practices vary. We do not employ induced hypotension unless required to by the patient's bleeding. The surgeon reasons that the effects on the surrounding brain of devascularizing the AVM will be best appreciated if the devascularization occurs at normal pressures. If refractory brain swelling occurs, we may also lower pressure as part of our attempts to control the swelling, reasoning that blood flow through the involved area is pressure passive and will decrease as MAP declines. With severe episodes of swelling, we have employed (in addition to hypotension, which we use cautiously because of the associated ischemia risk) hypocapnia, hypothermia, and barbiturates. The last three techniques probably serve to reduce the bulk of only normal brain tissue, with hypocapnia acting via a direct effect on CBF, and barbiturates and hypothermia via the coupled effects of reduction of CMR on CBF. Induced hypothermia is also an adjunct to minimizing the barbiturate doses.

Head Injury

Intubating the Trachea of a Head-Injured Patient

The anesthesiologist's first "interface" with the head-injured patient may come as a result of a request for assistance with airway management. It has been determined empirically that patients with Glasgow Coma Scale scores of 7 to 8 (Table 52-11) or less eventually require intubation and controlled ventilation for ICP and/or airway control. Accordingly, these patients are almost invariably intubated promptly. Patients with less severe head injuries may also require intubation because of trauma-related cardiopulmonary dysfunction or, when uncooperative, to facilitate diagnostic procedures. The anesthesiologist, in choosing the intubation technique, may encounter a number of conflicting constraints. These include (1) elevated ICP, (2) a full stomach, (3) an uncertain cervical spine, (4) an uncertain airway (presence of blood, possible laryngeal-tracheal injury, possible skull base fracture), (5) an uncertain volume status, (6) an uncooperative/combative patient, and (7) hypoxemia. There is no "correct" way, and the "best" approach is determined by the relative weight of these various factors, along with the degree of urgency. However, the anesthesiologist must not become distracted by an excessive initial emphasis on ICP and must keep sight of the ABCs of resuscitation: securing the airway, guaranteeing gas exchange, and stabilizing the circulation are higher initial priorities than ICP. One must not risk losing the airway or causing severe hypotension for the sake of preventing coughing while the patient is intubated or brief hypertension with intubation.

TABLE 52-11 -- Glasgow Coma Scale

Eyes open	Never	1
	To pain	2
	To speech	3
	Spontaneously	4
Best verbal responses	None	1
	Garbled/incomprehensible sounds	2
	Inappropriate words	3
	Confused but converses	4
	Oriented	5
Best motor responses	None	1
	Extension (decerebrate rigidity)	2
	Abnormal flexion (decorticate rigidity)	3
	Withdrawal	4
	Localizes pain	5
	Obeys commands	6
Total		3-15

Cervical Spine

The possibility of causing or aggravating an injury to the cervical spine is a relevant concern. Approximately 2 percent of patients with a closed head injury who survive to reach a hospital have a fracture of the cervical spine. [182] Somewhat surprisingly, the incidence of cervical spine injury is similar (1.8-6.0%) for all blunt trauma victims with or without an associated head injury [182] [183] [184] [185]). This incidence suggests that a thiopental-succinylcholine-direct laryngoscopy-endotracheal intubation approach for all patients with a closed head injury may convey a measurable risk of injuring the cervical spinal cord. Nonetheless, although the literature contains contradictions, several published series have concluded that such an approach does not convey significant risk of neurologic injury. [185] [186] [187] [188] [189] However, it is possible that the incidence of intubation-related neurologic injury is underreported. An informal survey reported by Criswell et al [185] indicated that there have been more such events than one can infer from the published literature. [190] Nonetheless, the literature argues that clinicians manage to succeed most of the time, and there are certainly units in which the majority of patients requiring airway control are intubated using a hypnotic-relaxant-direct laryngoscopy sequence. However, it is the (probably minority) opinion of these authors that the possibility of devastating spinal cord injury exists, probably mostly with injuries in the atlantooccipital (A-O) region, which are also difficult to identify radiologically, [191] and that the anesthesiologist should seek to identify circumstances in which time latitudes allow more detailed examination or radiologic evaluation. When there is any uncertainty regarding the airway or the cervical spine, direct laryngoscopy (with vigorous A-O extension) should probably be avoided unless the exigencies of airway control demand it. The bias of the authors of this chapter is in favor, when feasible, of intubation techniques that allow the preservation of muscle tone, that maintain access to the patient's subjective and objective responses to airway maneuvers, and that make use of in-line stabilization or minimize A-O extension. The nasal route can be used in spite of concerns about entering the cranial vault via

a skull base fracture. However, one must use discretion (e.g., in the presence of an obvious facial crush injury it should be avoided) and be sensitive to unusual resistance in passing the endotracheal tube.

When a hypnotic-relaxant sequence is used, the standard approach includes the use of cricoid pressure and in-line axial stabilization. In-line traction was once favored, but it has been supplanted by stabilization because of the perceived risk of overdistraction and spinal-cord injury in the event of gross instability. * The largest of the clinical series that concluded that oral intubation with anesthesia and relaxation is reasonable [186] used in-line stabilization with the patient's occiput held firmly on the backboard, thus limiting the amount of "sniff" that was feasible (Fig. 52-13) (Figure Not Available) . There is no question that in-line stabilization, properly performed, makes laryngoscopy

Figure 52-13 (Figure Not Available) Intubating the patient who has undergone acute trauma and whose cervical spinal status is uncertain. A hypnotic and a relaxant have been administered. One assistant maintains in-line axial stabilization with the occiput held firmly to the backboard; a second assistant applies cricoid pressure. The posterior portion of the cervical collar remains in place. *(From Stene [186])*

somewhat more difficult. However, it serves to decrease the amount of A-O extension necessary to achieve visualization of the glottis. [192] This is probably because performing the laryngoscopy against the assistant's counterpressure results in greater compression of the soft tissue structures of the tongue and floor of mouth. Some clinicians recommend leaving the back half of the Philadelphia collar in place during laryngoscopy (see Fig. 52-13) (Figure Not Available) because it functions as a "strut" between the shoulder and the occiput that serves to limit A-O extension further.

In the resuscitation situation, before initiating a hypnotic-relaxant sequence, the anesthesiologist should confirm the availability both of cricothyrotomy equipment and of someone to make immediate, skilled use of it if necessary. The recently injured brain is very intolerant of hypoxia and hypotension. [193]

As noted in Chapter 19 , whereas succinylcholine can cause ICP increases, these increments are small and may not, in fact, occur at all in patients with serious cerebral injuries. [5] Accordingly, succinylcholine should not be viewed as contraindicated in the victim of head injury. If and when there is an urgent need to secure the airway (in order to control P CO_2 and guarantee oxygenation), and if succinylcholine is in other respects the appropriate drug to achieve that end, it should be used.

In two clinical surveys, alert, nonintoxicated patients with a cervical spine fracture invariably had pain, tenderness, or neurologic signs. [183] [194] Accordingly, in spite of the frequency with which clinicians meet patients still wearing their Philadelphia collars because their neck has not yet been "cleared," no special precautions appear warranted in the asymptomatic, alert patient. Note also that, if the clinical situation or examination suggests a cervical spine injury, a normal lateral x-ray film (the anteroposterior and through-the-mouth odontoid views are frequently not taken during initial evaluation) cannot provide complete reassurance. The lateral radiograph has been reported not to show between 15 percent [195] and 26 percent [183] of fractures.

*Is it not remarkable that in-line traction is considered ill-advised because of the possibility of instability but relaxation and direct laryngoscopy are viewed as begin?

Anesthetic Technique

Choice of Anesthetic Agents.

Craniotomies most commonly are performed for the evacuation of subdural, epidural, or intracerebral hematomas. The anesthetic approach is similar for all three procedures. The guiding principles are discussed earlier. In general, agents that are known to be cerebral vasoconstrictors are preferable to those that have the potential to dilate the cerebral circulation. All the intravenous anesthetic agents except perhaps ketamine cause some cerebral vasoconstriction and are reasonable choices, provided they are consistent with hemodynamic stability. All the inhaled agents (N_2O and all the vapors) have some cerebral vasodilatory effect. Although their administration is frequently consistent with acceptable ICP levels and/or appropriate conditions in the surgical field, when the ICP is out of control (or unknown) or when the surgical field is "tight," eliminating the inhaled agents in favor of fixed agents is appropriate. For patients who are likely to remain intubated postoperatively, an anesthetic regimen based primarily on a narcotic, such as fentanyl, and a muscle relaxant usually serves well. Any muscle relaxant is acceptable, with the provision that drugs that can release histamine should be titrated in careful increments. When immediate extubation is a possibility, such as the patient with an acute epidural hematoma who had a lucid interval before witnessed deterioration, the technique should be modified after opening of the cranium. Introduction of inhaled agents and/or the use of shorter-acting intravenous agents can be undertaken as guided by observation of the surgical field. If N_2O is contemplated at any time, one should remember the possibility, in the setting of missile injury or compound skull fracture, of intracranial air.

Monitoring.

The anesthesiologist should appreciate that the priority is to open the cranium as rapidly as possible. Once intravenous access is achieved, the craniotomy should never be delayed significantly by line placement. An arterial line is appropriate for essentially all craniotomies in patients who have undergone acute trauma. The decision to achieve central venous access can be made on the basis of the patient's hemodynamic status. Infrequently, management of a depressed skull fracture over the sagittal sinus justifies a precordial Doppler image and, subject to the surgeon's opinion of VAE risk, a right heart catheter.

Blood Pressure Management.

The concept that the injured brain is extremely vulnerable to what would otherwise be a minor insult, such as modest hypotension or moderate hypoxia, has been well confirmed in the laboratory. [196] [197] Although there are as yet no completely conclusive data derived in humans, several clinical surveys are strongly supportive of the adverse effect of minor degrees of hypotension in the period after head injury. [193] [198] [199] [200] The explanation for this vulnerability to hypotension probably resides, in part, in the observation that some patients in the postinjury period have regions of brain with precariously low CBF, [24] [35] in which autoregulation may also be defective. [201] In addition, there is ample evidence that the low postinsult CBF values correlate with a poor eventual outcome, [24] [202] [203] and a large percentage of patients who die after head injury have pathologic changes consistent with ischemia. [121] These observations have resulted in a much greater emphasis by many, although not all, neurosurgeons on aggressive support of blood pressure in the head-injured patient.

What constitutes appropriate blood pressure? Systematic studies, in particular those conducted at the University of Edinburgh, have revealed evidence that indexes of the adequacy of cerebral perfusion derived from Sjv O_2 and TCD data begin to deteriorate below mean CPP of 70 mm Hg [199] [204] [205] (recall that CPP = MAP - ICP). Some neurosurgeons have therefore adopted 70 mm Hg as the target CPP. However, an expert panel convened to generate recommendations for the treatment of head injury [206] found the data insufficient to justify establishing 70 mm Hg as the "standard" CPP target, but instead identified it as a reasonable management "option."

Added to this discussion are two alternative opinions regarding blood pressure management (Fig. 52-14) . The first, promoted by the neurosurgery group at the University of Alabama, Birmingham, is that induced hypertension can be employed as an adjunct to ICP control. [24] [207] [208] This idea is based on the beliefs that autoregulation is at least partially preserved after head injury, and an increased CPP results in autoregulation-mediated vasoconstriction with a concomitant reduction in CBV and therefore ICP. These physicians make aggressive use of volume expansion and vasopressors (phenylephrine, dopamine) to maintain a high CPP. They report a very satisfactory local experience with this approach, [208] but it has not been applied widely. The second alternative is the so-called "Lund concept," which is based on the premise that hyperemia commonly makes a substantial contribution to the increased ICP associated with head injury. [209] [210] Patients are managed by relative dehydration, by relative hyperosmolarity, and with a CPP target of 50 to 55 mm Hg using metoprolol, clonidine, and dihydroergotamine to lower blood pressure.

Figure 52-14 The relation of cerebral blood flow (CBF) to blood pressure after head injury. There are three cerebral perfusion pressure (CPP) management strategies (see text), driven by differing beliefs about common pathophysiologic derangements. The most commonly held, "Edinburgh," emphasizes low postinjury CBF, impaired autoregulation, and the necessity to support CPP (mean arterial pressure [MAP] - intracranial pressure [ICP]) to 70 mm Hg. The "Lund concept" emphasizes the contribution of hyperemia to the occurrence of elevated ICP and uses antihypertensive agents to achieve a CPP of 50 to 55 mm Hg. The "Birmingham" approach, which entails pharmacologically induced hypertension, is based on the belief that autoregulation is largely intact and that hypertension will result in cerebral vasoconstriction with concomitantly reduced cerebral blood volume (CBV) and ICP.

Which approach is correct? In particular, can the seemingly opposite objectives of the Edinburgh and Lund approaches be reconciled? In fact, it is possible that they both may be applicable in different patients or perhaps at different times in a given patient's course. Although an initially low postinjury CBF is probably the most common clinical occurrence, hyperemia does occur. [211] [212] [213] It tends to occur in patients with mass lesions rather than contusions, although even those patients have an immediate postinjury period of low CBF, with delayed hyperemia peaking at 24 hours or later. [36] [37] [202] [212] [213] Hyperemia may also be common in children. [214] A triphasic CBF pattern has been noted in some adult patients, in particular those with subarachnoid blood. That pattern is characterized by a period of initially low CBF (day 0), followed by a hyperemic phase (days 1 to 3), followed, in turn, by a period of reduced flow apparently occurring as a result of vasospasm (days 4 to 10). [37] [211] [215]

What is the clinician to do? It has been suggested that management targeted to the pathophysiologic features that prevail in the individual patient is the ideal. [216] However, the ability to discriminate the various flow states (CBF measurement, TCD, Sjv O_2) is not universally available or applied (or yet proven to lead to improvement in outcome). Clearly, convictions vary, and anesthesiologists should come to an understanding with local trauma specialists and neurosurgeons about blood pressure targets. It is likely that the majority of North American practitioners will encounter (and should place) a greater emphasis on the rigid maintenance of normotension in order to maintain a generous CPP, such as 70 mm Hg, in recently head-injured patients. [204] [205] [207] [217] The common view probably is that MAPs that are perfectly acceptable for elective noncranial surgery in young adults, such as 60 mm Hg, are likely to be deleterious in a recent head-injury victim. If the ICP is 20 mm Hg in a head-injured patient (and it may be much higher), an MAP of 60 mm Hg will yield a CPP of 40 mm Hg, which most centers view as much too low immediately after head injury.

Hyperventilation.

The use of hypocapnia is reviewed in detail earlier in this chapter. Hyperventilation has long been a standard component of the management of the head-injured patient who is perceived to be at risk of increased ICP. However, there is an increasing perception that hyperventilation is potentially deleterious, [22] [23] [24] [26] [28] [33] and it should not be overused. The evidence is that hyperventilation and the concomitant vasoconstriction can result in ischemia, [21] [34] especially when baseline CBF is low, [34] as is likely to be the case in the first 24 hours after head injury. [24] [35] We believe that the evolving information argues that hyperventilation should be used selectively, rather than routinely, in the management of head-injured patients. Maintaining ICP at less than 20 mm Hg, preventing or reversing herniation, minimizing retractor pressure, and facilitating surgical access are still important objectives in the management of the head-injured patient, and to the extent that hyperventilation contributes to these objectives, it is still appropriate. Once again the anesthesiologist should agree on management parameters with the surgical team at the outset of a procedure.

Fluid Management.

Fluid management of the head-injured patient is addressed earlier. The important principles are that fluids should be chosen invariably to prevent reduction of serum osmolarity and should probably be chosen to prevent profound reduction of colloid oncotic pressure; that is, in the circumstances of a large volume resuscitation (arbitrarily, greater than half a circulating volume), a mixture of colloids and crystalloids is probably appropriate. The severely injured brain can liberate sufficient thromboplastin into the circulation to result in consumptive coagulopathy. Appropriate laboratory tests and replacement should be performed. [218] The clinician may also find a serum osmolarity determination early in the course of anesthetic management useful in appreciating the cumulative effects of prior mannitol administration. The use of hypertonic solutions and the relevant attributes of colloid solutions are also discussed earlier.

Jugular Venous Oxygen Saturation

Several centers have evaluated the use of Sjv O_2 monitoring as a guide to the clinical management of head-injured patients. [27] [34] [38] [39] [205] [219] The underlying concept is that a marginal or inadequate CBF results in an increasing oxygen extraction, a widening arteriovenous content difference, and a falling jugular venous Pv O_2 or Sjv O_2. There have been numerous reports of improvements in Sjv O_2 as a consequence of reducing hyperventilation, increasing MAP, or inducing hypervolemia. [220] The availability of intravascular catheters that permit the continuous monitoring of Sjv O_2 has made the technique more practical. [221] Even though a method that makes an assessment of *global* oxygen extraction has only limited sensitivity to highly *focal* events, the early experience appears to justify further evaluation.

There are some limitations with the technique. Catheter placement must be very precise to avoid contamination by noncerebral venous blood or attenuation of light return (with optical catheters) because of vessel wall abutment. Even in experienced hands, there can be a significant false-positive rate. [34] An additional limitation inherent to the unilateral placement of the catheter is the observations by Stocchetti et al [222] that there was an average side-to-side difference between simultaneous jugular bulb saturations of 5.3 ± 5 percent, and that side-to-side differences in hemoglobin saturation of up to 15 percent were common. These and other authors have questioned the reliability of data obtained from a unilateral Sjv O_2 catheter. [222] [223] The next clinical problem is the matter of what constitutes an abnormal value. Normal subjects at rest may have Sjv O_2 values between 50 and 75 percent. A currently employed definition of abnormal is less than 50 percent for 5 minutes. [224] However, there has been limited opportunity to correlate Sjv O_2 threshold values with outcome.

In spite of the reported successes with Sjv O_2 monitoring, [39] [220] [225] we do not believe that the method is sufficiently well defined to justify advocating widespread intraoperative application. Further experience and clinical investigation are required to define the correct role and mode of application of Sjv O_2 monitoring. At present, it appears potentially useful as a trend monitor that may serve to identify the level of CPP below which cerebral perfusion *begins* to be compromised. However, the Sjv O_2 level at which that compromise is critical has not been identified. The

technique also has a potential use beyond identifying patients with low Sjv O_2 and inadequate CBF. High Sjv O_2 values may serve to identify the patient with elevated ICP in whom hyperemia is an important contributing factor and in whom aggressive attempts to decrease CBF, such as via hyperventilation and barbiturates, may be beneficial.

Hypothermia

Mild induced hypothermia has already crept into the management of neurosurgical procedures in which there is a perceived risk of ischemic injury. To date, this has encompassed principally aneurysm surgery. However, the efficacy of this technique in reducing damage when induced after experimental head injury has also been demonstrated, [122] and its relevance to the management of the head-injured patient has been the subject of small, prospective controlled trials in at least four centers. [123] [124] [125] [126] These single center trials appear to indicate good patient tolerance of sustained mild hypothermia (32-34°C) as well as improvement in ICP, cerebral oxygen supply/demand, and outcome. A multicenter trial sponsored by the National Institutes of Health is under way. The results of that trial, due late in 1999, will determine the role of hypothermia.

Intracranial Pressure Monitoring for Nonneurologic Surgery in the Head-Injured Patient

In the ideal, neurosurgical consultation will be readily available and, appropriately, the anesthesiologist will rarely have to make this decision. It may, however, be necessary for the anesthesiologist to participate in this decision. The relevant variables include the following:

1. Level of consciousness. If there has been a loss of consciousness at any time or if the GCS score is less than 15, a CT scan should be obtained. If the CT scan reveals compressed basal cisterns (indicative of an exhaustion of supratentorial compensatory latitudes), midline shift, or effaced ventricles and probably any intracranial lesion (contusion, small subdural), an ICP monitor should be placed. Excessive comfort should not be taken from a good GCS score. Patients with a good GCS score can "talk and deteriorate" or "talk and die" following a head injury associated with loss of consciousness. Delayed deterioration has been observed up to as much as 48 hours after the initial injury (average, 17 h). [226] Patients with lesions, usually contusions, in the frontotemporal region and especially those with medial temporal lesions are most at risk for this phenomenon. Modest expansion of lesions in this location (i.e., close to the uncus and the incisura, where herniation occurs) can result in herniation even at relatively low ICP (e.g.,

20 mm Hg). At our institution, neurosurgeons recommend avoiding anesthesia in these patients and certainly advise ICP monitoring when general anesthesia is unavoidable.

2. Time since injury. The longer the patient has had to declare a clinical course, the less pressing is the need for ICP monitoring. However, delayed deterioration, as noted earlier, has been observed for up to 48 hours, and a patient with a demonstrable CT lesion is a candidate for a monitor for at least this period of time.
3. Intended aortic occlusion, that is, repair of a ruptured aorta. Dramatic increases in ICP have been associated with aortic occlusion. This may, in large part, be the result of the abrupt increase in blood pressure and/or the agents used to control it. In addition, the increased airway and venous pressures associated with the lateral position and one-lung ventilation plus occasional difficulties in maintaining hypocapnia during one-lung ventilation should result in a low threshold for ICP monitoring in this situation. Note, however, that the intent to heparinize systemically essentially precludes the placement of a monitor.
4. Nature and duration of the intended procedure. The risks of an untoward ICP event are inevitably greater in a 6-hour Edward instrumentation in the prone position than for a 20-minute debridement and suturing of an arm laceration.

TABLE 52-12 -- Considerations Relevant to Posterior Fossa Procedures

Hemodynamic effects of the sitting position
Venous air embolism
Paradoxic air embolism
Hemodynamic effects of brain-stem or cranial nerve manipulation
Quadriplegia
Macroglossia
Pneumocephalus

Posterior Fossa Procedures

Most of the topics relevant to posterior fossa procedures (Table 52-12) are discussed in preceding sections. These include the sitting position and its cardiovascular effects and complications (quadriplegia, macroglossia), pneumocephalus. Those sections should be read in conjunction with this segment. The use of the sitting position to facilitate surgery in the posterior fossa increases the likelihood of all of these phenomena, although they are relevant to nonsitting positions as well. This section reviews the cardiovascular events associated with direct stimulation of the brain stem and their possible implications for postoperative management.

Brain-Stem Stimulation

Irritation of the lower portion of the pons and of the upper medulla and of the extra-axial portion of the fifth cranial nerve can result in a number of cardiovascular perturbations. The former two areas are most often stimulated during procedures on the floor of the fourth ventricle and the last during surgery at or near the cerebellopontine angle, such as for acoustic neuromas and microvascular decompression of the fifth (tic douloureux), seventh (hemifacial spasm), or ninth (glossopharyngeal neuralgia) nerves. The cardiovascular responses may include bradycardia and hypotension, tachycardia and hypertension, bradycardia and hypertension, and ventricular dysrhythmias. [227] Meticulous attention to the ECG and a directly transduced arterial pressure during manipulation in this region is necessary in order

to provide the surgeon with immediate warning of the risk of damage to the adjacent cranial nerve nuclei and respiratory centers. Pharmacologic treatment of the dysrhythmias that occur may serve to attenuate the very warning signs that should be sought.

Balloon compression of the trigeminal ganglion is another situation in which a dysrhythmia may occur. The procedure attempts to produce a neuropraxia of the fifth cranial nerve by the rapid inflation of a Fogarty-type balloon within the Meckel cave. [228] The balloon is introduced percutaneously through the cheek and beneath the maxilla. A relatively profound, albeit transient, bradycardia occurs and is, in fact, sought as confirmation of adequate compression. External pacemaker pads have been advocated, but they are, in our experience, unnecessary.

Irritation and injury of posterior fossa structures that may have occurred during surgery should be taken into account in planning extubation and postoperative care. In particular, procedures involving dissection on the floor of the fourth ventricle entail the possibility of injury to cranial nerve nuclei and/or postoperative swelling in that region. There should be attention to the fact that cranial nerve dysfunction, particularly of 9, 10, and 12, can result in loss of control/patency of the upper airway and that swelling of the brain stem can result in impairment of both cranial nerve function and respiratory drive. The posterior fossa is a relatively small space, and its compensatory latitudes are even more limited than those of the supratentorial space. Relatively little swelling can result in disorders of consciousness, respiratory drive, and cardiomotor function. There should be an interaction between the anesthesiologist and the surgeon to make decisions about whether extubation is appropriate and where postoperative observation should occur, that is, ICU or non-ICU.

Spontaneous ventilation was once advocated for procedures that entailed a risk of damage to the respiratory centers. Spontaneous ventilation is now rarely used because the proximity of the cardiomotor areas to the respiratory centers should permit cardiovascular signs to serve as an indicator of impending injury to the latter. It is our opinion that respiratory pattern is more likely to be a relevant monitor when the "threat" to the brain stem is the result of vessel occlusion (as may occur with accidental interruption of perforating vessels during vertebrobasilar aneurysm surgery [177]) than when it is because of direct mechanical damage caused by retraction of or dissection in the brain stem.

Various electrophysiologic monitoring techniques may be used during posterior fossa surgery. These include somatosensory evoked responses, brain-stem auditory evoked responses, and EMG monitoring of the facial nerve. The last technique requires that the patient not be paralyzed or have a constant state of incomplete paralysis. Somatosensory evoked response monitoring imposes some constraints with respect to the selection of anesthetic agents. These are discussed in Chapter 35 .

Transsphenoidal Hypophysectomy

The transsphenoidal approach to the pituitary is used for the excision of tumors that lie within the sella or that have extension to the immediate suprasellar area. The most common lesions are prolactin-secreting microadenomas (Table 52-13) . These patients are usually women who present with secondary amenorrhea. There are three other less common pituitary tumors: growth hormone-secreting lesions result in acromegaly; adrenocorticotropic hormone (ACTH)-secreting tumors cause Cushing disease; and a very rare thyroid-stimulating hormone (TSH)-secreting lesion that results in hyperthyroidism.

Preoperative Evaluation

The important preoperative considerations relate to the patient's endocrine status. In general, as a pituitary lesion expands and compresses the pituitary tissue, the sequence in which hormonal function is lost is as follows: (1) gonadotropins; (2) growth hormone; (3) ACTH; and (4) TSH. The precise definition of the adrenal status of these patients is often not important because, in general, they all receive adrenal hormone supplementation at least temporarily. However, profound hypocortisolism, with associated hyponatremia, should be corrected preoperatively. It is, in fact, uncommon for thyroid deficiency to occur. However, hypothyroidism should be sought and corrected preoperatively because hypothyroid patients have a diminished tolerance for the cardiovascular-depressant effects of anesthetic agents. Patients with advanced acromegaly can develop an enlarged tongue, and the airway should be evaluated.

TABLE 52-13 -- Tumors of the Pituitary Region

LOCATION	HORMONE SECRETED	CLINICAL PRESENTATION	COMMENT

Anterior pituitary	Prolactin	Galactorrhea, amenorrhea hypogonadism, infertility	Bromocriptine sensitivity
	Adrenocorticotropin	Cushing disease (hypercortisolism)	Basophilic adenoma
	Growth hormone	Acromegaly/gigantism, glucose intolerance	Eosinophilic adenoma, difficult airway
	Nonsecretory	Mass effect, panhypopituitarism	Chromophobe adenoma, preoperative hormones?
Suprasellar	Nonsecretory	Panhypopituitarism, syndrome of inappropriate antidiuretic hormone, visual (optic chiasm) symptoms	Craniopharyngioma or suprasellar extension of pituitary lesion

Monitoring

Many practitioners place an arterial catheter, but it is not absolutely necessary. Blood sampling access is a valuable adjunct to postoperative care if diabetes insipidus develops. Blood loss is usually modest. However, the cavernous sinus is an immediate lateral relation of the pituitary and may be entered during the resection of large tumors. In addition, in some patients, there is a venous sinusoid that lies in front of the pituitary gland and connects the two cavernous sinuses. This can be the origin of substantial blood loss. It has, on occasion, actually precluded this approach to the pituitary gland.

Anesthetic Technique

The latitudes are broad with respect to choice of agent, although tumors with suprasellar extension can cause hydrocephalus and thereby can add increased ICP constraints to the anesthetic technique. The procedure is performed with the patient in a supine position, usually with some degree of head-up posture to avoid venous engorgement. A pharyngeal pack prevents an accumulation of blood in the stomach (which causes vomiting) or in the glottis (which contributes to coughing at extubation). An RAE-type tube secured to the lower jaw at the corner of the mouth opposite the surgeon's dominant hand, such as the left corner of the mouth for a right-handed surgeon, is suitable. A small esophageal stethoscope and a temperature probe can lie with the endotracheal tube. Covering the entire bundle with a towel drape (a plastic sheet with an adhesive edge) placed just below the patient's lower lip so that it hangs from the lower jaw like a veil protects it from the preparation solutions.

The procedure requires a C-arm image intensifier (lateral views), and the patient's head and arms are relatively inaccessible once the patient is draped. It is appropriate to establish the nerve stimulator at a lower extremity site. The surgical approach is via the nasal cavity through an incision made under the upper lip. During the approach, the mucosal surfaces within the nose are infiltrated with a local anesthetic and epinephrine solution, and the patient should be observed for the occurrence of dysrhythmias.

Surgical preferences for CO_2 management vary. In some instances, hypocapnia is requested to reduce brain volume and thereby to minimize the degree to which the arachnoid bulges into the sella. One of the important surgical considerations is the avoidance, when possible, of opening the arachnoid. Postoperative CSF leaks can be persistent and are associated with a considerable risk of meningitis. By contrast, when there is suprasellar extension of a tumor, a normal or increased CO_2 helps to deliver the lesion into the sella for excision. As an alternative way to accomplish this, some surgeons have resorted to pumping of saline or air into the lumbar CSF space. [229] [230]

Diabetes insipidus is a potential complication of this procedure. The antidiuretic hormone (ADH) is synthesized in the supraoptic nuclei of the hypothalamus and is transported down the supraoptic-hypophyseal tract to the posterior lobe of the pituitary. This portion of the pituitary gland is frequently spared. Even when it is excised, water homeostasis commonly normalizes, presumably because the ADH is released from the cut end of the tract. However, even when the posterior lobe of the pituitary is left intact, transient diabetes insipidus may occur. This disorder usually occurs 4 to 12 hours postoperatively and very rarely arises intraoperatively. The clinical picture is one of polyuria in association with a rising serum osmolality. The diagnosis is made by comparison of the osmolalities of urine and serum. Hypo-osmolar urine in the face of an elevated and rising serum osmolality strongly supports the diagnosis. Urine specific gravity is a useful bedside test. In the presence of bona fide diabetes insipidus, specific gravity is low, that is, less than or equal to 1.002.

When the diagnosis of diabetes insipidus is established, an appropriate fluid management regimen is hourly maintenance fluids plus two-thirds of the previous hour's urine output. (An acceptable alternative is the previous hour's urine output minus 50 mL plus maintenance.) The choice of fluid is dictated by the patient's electrolyte picture. In general, the patient is losing fluid that is hypo-osmolar and relatively low in sodium. Half-normal saline and 5 percent dextrose in water (D_5W) are commonly used as replacement fluids. Beware of hyperglycemia when large volumes of D_5W are employed. An *un*acceptable fluid regimen that has been employed calls for maintenance fluids plus the previous hour's urine output. This regimen has the potential to create a vicious circle. Should the patient become iatrogenically fluid overloaded, this regimen precludes a return to isovolemia, and, in fact, when the maintenance fluid allowance is generous, it guarantees that the patient will become increasingly hypervolemic. If the hourly requirement exceeds 350 to 400 mL, ADH is usually administered.

A smooth emergence from anesthesia (see earlier) is desirable especially if the CSF space has been opened (and resealed with fibrin glue or by packing the sphenoid sinus with fat or muscle). Repeated, intense Valsalva maneuvers, such as with coughing or vomiting, may contribute to the reopening of a CSF leak and may worsen the risk of subsequent meningitis. The airway should be cleared of debris including formed clot. Some clinicians routinely inspect the pharynx using a laryngoscope. This also permits one to assess whether or not there is still active bleeding. This allows one more confidently to extubate the patient promptly at the first signs of reactivity to the endotracheal tube. In situations in which there is concern that a persistent CSF leak may occur, some surgeons place a lumbar CSF drain to maintain CSF decompression in the early postoperative period.

Seizure Surgery/Awake Craniotomy

Awake craniotomies are performed when tumors or epileptic foci lie close to cortical areas required for either speech or motor function or to mesial temporal structures critical to short-term memory. The majority of patients will have so-called temporal lobe epilepsy. There is commonly a structural lesion visible on magnetic resonance imaging (MRI). Sometimes there is a history of trauma. More commonly, the cause is presumed to be an asphyxial birth injury.

Presurgical Evaluation

Prior to the resection, most patients have undergone either or both a Wada test and videotelemetry. The Wada test

involves selectively anesthetizing the cerebral hemispheres by injection of sodium amytal into the carotid artery to localize the hemisphere that controls speech and/or to confirm that there is bilateral representation for short-term memory. Speech is an issue when the lateral portions of the temporal lobe are involved, and memory is the concern when the involvement is medial.

Anesthesia for EEG Electrode Placement

Videotelemetry is performed to permit localization of the seizure focus that is responsible for the clinically problematic events. This usually requires prior placement of either subdural strip electrodes (via bur holes) or a subdural electrode grid (requiring a craniotomy). Occasionally, electrodes are placed deep into parenchyma, usually within the temporal lobe (placed stereotaxically via bur holes), or they are positioned so as to "look at" the inferior surfaces of the temporal lobe. The latter is commonly accomplished with so-called foramen ovale electrodes. These are placed using a needle similar to an epidural needle. The point of entry is about 2 cm lateral to the angle of the mouth. The needle is passed through soft tissue, under the temporal process of the zygomatic bone and medial to the ramus of the

mandible, up to the base of the skull in the vicinity of the foramen ovale. Typically, this procedure is performed as a "MAC," although doses of methohexital or propofol are usually required at the time of stimulation by the needle of the periosteum at the base of the skull. After placement of the relevant electrodes, the patient's seizure medication is discontinued, and the patient remains in an observation unit with EEG and behavior recorded continuously. In this manner, the EEG events associated with the clinically significant seizure events and their anatomic origin can be identified.

Preanesthetic Evaluation/Preparation

At the preoperative interview, the patient should be educated about the nature and duration of the procedure and the limitations on patient movement. The clinician should obtain a description of both the aura and the seizures to facilitate recognition of them. One should ascertain whether the patient is subject to grand mal convulsions. If intraoperative electrocorticography to identify seizure foci is intended, it is common to discontinue or to reduce by half the anticonvulsants according to the perceived risk of uncontrolled seizures. Premedicants with an anticonvulsant effect, such as benzodiazepines, should not be used because they may interfere with intraoperative EEG localization.

Anesthetic Technique

The objectives of the anesthetic technique are as follows:

1. To minimize patient discomfort associated with the potentially painful portions of the procedure and with the prolonged restriction of movement.
2. To ensure patient responsiveness and compliance during the phases of the procedure that require assessment of either speech or motor/sensory responses to cortical stimulation.
3. To select anesthetic techniques that produce minimal inhibition of spontaneous seizure activity.

There are probably many ways of providing sedation that are consistent with these objectives. Several active centers use a droperidol/synthetic narcotic combination [231] (e.g., droperidol, 2.5-7.5 mg; alfentanil, 5-10 mug/kg load, 0.25-0.5 mug/kg/min infusion; fentanyl, 0.7 mug/kg load, 0.7 mug/kg/h infusion). [232] Others use principally propofol by either physician-controlled or patient-controlled infusion. [232] Care should be taken in administering additional sedative agents, especially narcotics, whose respiratory-depressant effects may be synergistic with propofol. This is especially relevant when pin fixation is employed. Pin fixation severely restricts the anesthesiologist's capacity to intervene quickly in the event of excessive respiratory depression or loss of patency of the airway. Propofol, if used, should be discontinued at least 15 minutes before EEG recording. In spite of prompt awakening, propofol leaves a residual EEG "footprint" characterized by high-frequency, high-amplitude beta activity that can obscure the abnormal activity that is being sought in the cortical surface EEG. [233]

Routine, noninvasive monitors are almost always sufficient. Reliable capnography, to provide breath-by-breath confirmation of airway patency and respiratory drive, is an essential component of the technique if deep sedation is intended for any portion of the procedure. These procedures are often lengthy, and attention to the details of patient comfort (warming blankets, a sheepskin, room temperature) improve patient tolerance.

The uncomfortable phases of the procedure are pin head holder placement (Not all groups use a pin head holder) and the craniotomy. Many patients also find manipulation of the dura, in particular traction, painful. The actual manipulation of supratentorial brain parenchyma is painless. These procedures cannot be accomplished without thorough local anesthetic technique. Note that in some institutions, awake craniotomies are performed as straight local procedures without sedation. The anesthesiologist must not think that it is his or her responsibility to provide a general anesthetic-equivalent in a spontaneously breathing patient with an unprotected and all but inaccessible airway. The volume of local anesthetic used to infiltrate pin sites and to perform the field block of the scalp can be substantial. It is appropriate for the anesthesiologist, in particular the anesthesiologist working with surgical trainees, to keep track of the doses of local anesthetic agents used.

The anesthesiologist should participate actively at the time of head positioning. The more "sniff" that can be achieved before the final lock-down of the head holder, the wider the latitudes will be for sedating the patient while maintaining spontaneous ventilation and a patent airway. During positioning of the patient, there should also be attention to the need to maintain visual access to the face. A clear line of sight to the face is necessary both to present the patient with images to name as part of speech testing and to identify the occurrence of facial motor responses during mapping of the motor strip.

In general, after the dural opening is complete, cortical surface EEG recording is performed to locate the seizure

focus. If no seizure activity is observed, provocative maneuvers may be requested. Methohexital, in a dose of approximately 0.3 mg/kg, is in general safe and effective. Etomidate, approximately 0.05 to 0.1 mg/kg, has also been used. Seizure focus localization can also be accomplished during light general anesthesia, such as, N_2 O/fentanyl/low-dose isoflurane. During general anesthesia, alfentanil, in a bolus dose of 50 mug/kg, [234] and etomidate, in doses of 0.2 to 0.3 mg/kg, [235] [236] have been reported effective in activating seizure foci.

After localization by EEG, functional testing may be performed by stimulating the cortical surface electrically and observing for motor, sensory, or speech interruption effects. During stimulation, the anesthesiologist should be prepared to treat grand mal convulsions that are not self-limited. Thiopental in 1 mg/kg increments is appropriate. However, thiopental should be withheld until it is clear that the seizure is not going to terminate spontaneously because this drug may interfere with subsequent EEG localization of the seizure focus for some time. A comprehensive review of the anesthetic implications of epilepsy, status epilepticus, and epilepsy surgery has appeared. [237]

Neuroradiologic Procedures

Magnetic Resonance Imaging

The major constraints for this procedure are created by the powerful magnetic field employed. This procedure creates three conditions that have an impact on anesthetic technique. The first is that any ferromagnetic object that approaches the magnet has the potential to become a dangerous projectile. The second is that a wide variety of electronic instruments will not function properly in the vicinity of the magnet. These instruments include most notably those that contain oscilloscopes, solenoids (e.g., some noninvasive blood pressure devices), or galvanometer-type gauges. The third is that when moderately large metal objects, even nonferromagnetic objects, are brought into the vicinity of the magnet, they may degrade the image. The equipment limitations have largely been circumvented. At present, MRI-compatible oximeters, capnographs, noninvasive blood pressure monitors, and gas machines are available.

It is most frequently children, claustrophobic adults, and patients with painful conditions who require anesthesia. Sedation with propofol and an unprotected airway and general anesthesia with either a laryngeal mask airway or an endotracheal tube have all been employed successfully.

Interventional Neuroradiology

Many different procedures are performed for the evaluation and treatment of intracranial and extracranial disease. These include principally attempts to obliterate aneurysms or to devascularize tumors and AVMs using balloons, coils, or glue. Stenting of extracranial carotid disease is occasionally performed. Vasospasm can be treated by selective intra-arterial instillation of papaverine or more commonly by balloon dilation. The majority of these procedures can be accomplished without the involvement of an anesthesiologist. The duration of a procedure, individual patient factors, and, occasionally, the necessity for precise physiologic control may result in requests for monitored anesthesia care or general anesthesia. In addition, anesthesiologists may become involved during the resuscitation stage in the event of vascular rupture or of the migration of an intravascular device to an incorrect location. When detachable devices are misplaced and ischemia ensues, fluid loading and pressor administration may be requested to improve collateral CBF while the device is retrieved.

Hyperventilation may be appropriate in an attempt to divert flow away from normal brain and toward a lesion that is intended to receive the occlusive device or material. Occasionally, the anesthesiologist is asked to lower systemic blood pressure and, it is hoped, cardiac output, to facilitate the initial trapping of glue or coils within a vascular lesion by briefly reducing the flow through it. Adenosine has proven effective for this purpose. [238]

The anesthesiologist may also be asked to participate in test occlusions of various cerebral vessels that are candidates for sacrifice at a subsequent procedure. In these circumstances, it is on occasion necessary to manage a patient who is restless, confused, or abruptly unconscious.

Procedures that are likely to entail requests for blood pressure manipulation are best done with an arterial catheter in place. The radiologist's arterial line cannot be dedicated to blood pressure monitoring, and accordingly, an independent arterial catheter should be placed.

Cerebrospinal Fluid Shunting Procedures

CSF shunts are inserted for the relief of a variety of hydrocephalic states and pseudotumor cerebri. Hydrocephalus can be communicating or noncommunicating. In noncommunicating hydrocephalus, CSF egress from the ventricular system is obstructed. This can occur as a result of blood or infection in the ventricular system or tumors in or adjacent to the ventricular system. In communicating hydrocephalus, the CSF escapes from the ventricular system but is not absorbed by the arachnoid villi. This occurs most commonly secondary to infection or blood in the CSF space. Some degree of communicating hydrocephalus is particularly common after SAH.

The ventriculoperitoneal shunt is the most commonly employed device. Usually, a catheter is inserted via a bur hole into the frontal horn of the lateral ventricle on the nondominant (usually the right) side. A reservoir is placed subcutaneously adjacent to the bur hole, and the drainage limb passes via a subcutaneous tunnel to a point near the epigastrium, where it is inserted into the peritoneal space via a very small laparotomy. A moderate degree of muscle relaxation may be helpful. A distended stomach can result in an inadvertent "gastrostomy." Occasionally, most commonly in pediatric patients, there may be an obstruction at more than one level in the ventricular system, and a so-called "double-barreled" shunt becomes appropriate. In this instance, there are two proximal ends, usually one in the lateral ventricle and one in the fourth ventricle. This latter procedure is usually performed with the patient in the prone position,

whereas most ventriculoperitoneal shunts are done with the patient supine.

Occasionally, when there is a communicating hydrocephalus, a lumboperitoneal shunt is inserted. The patient is placed in a lateral position, and a catheter is put in the lumbar CSF space via a Tuohy-type needle. The catheter is then tunneled subcutaneously around to the anterior abdominal wall and is inserted into the peritoneal space via a small laparotomy. In the past, ventriculoatrial shunts were employed, though they have largely been abandoned because of the occurrence of pulmonary embolus. For these shunts, the noncerebral end is inserted into the venous system via the jugular vein. The atrial location of the noncerebral end is confirmed using the same ECG technique that is employed to place VAE recovery catheters (see earlier).

Anesthetic Management

Invasive monitoring is generally not required. The anesthetic technique should be chosen to avoid further increases in ICP. Moderate hyperventilation (Pa CO_2 , 25-30 mm Hg) is customary. However, aggressive ICP reduction measures are not warranted because collapsing the ventricles may render them more difficult to "hit" with the ventricular catheter. Ventriculoperitoneal shunting is usu-ally performed with the patient supine, with the table turned 90 degrees and the patient's head turned toward the anesthesiologist. Blood pressure may drop abruptly (as brain-stem pressure is relieved) when the ventricle is first cannulated. Infrequently, brief pressor support is required. Burrowing the subcutaneous tunnel can produce a sudden painful stimulus. There is only minor postoperative discomfort.

Unlike the majority of neurosurgical patients, patients with shunts are often nursed flat following their procedures in an attempt to prevent an excessively rapid collapse of the ventricular system. Empirically, there is a small incidence of subdural hematoma following shunting, and the tearing of bridging veins at the time of rapid brain shrinkage is a suspected cause.

TABLE 52-14 -- Common Pediatric Neurosurgical Problems and Their Anesthetic Considerations

AGE GROUP	LESION	PATHOGENESIS	ANESTHETIC CONSIDERATIONS
Neonates	Intraventricular hemorrhage	Subependymal vascular rupture	Associated problems of prematurity
	Depressed skull fracture	Forceps injury	Associated cerebral edema
Infants	Hydrocephalus	Varied	Increased ICP, especially dangerous in shunt-dependent revisions
	Meningocele	Outpocketing of meninges through skull defect	Large size creating airway management problems Prone-lateral position Substantial blood loss Repair may increase ICP
	Encephalocele	Outpocketing of meninges through skull defect with brain tissue enclosed	
	Myelomeningocele	Projection of spinal meninges and roots through spina bifida	Prone or lateral Substantial blood loss Respiratory restriction after covering large defects
	Arnold-Chiari malformation	Impaction of posterior fossa contents into foramen magnum	Brain-stem compression with head flexion
		±Hydrocephalus	Increased ICP; latex allergy
		±Myelomeningocele	Postoperative respiratory depression
	Craniosynostosis	Premature cranial suture fusion	Substantial blood loss Air embolism Supine or prone
	Craniofacial dysostosis	Developmental abnormality	Lengthy procedures Substantial blood loss Brain retraction Air embolism Endotracheal tube damage
	Vascular malformations	Varied	Congestive heart failure Large blood loss Elective hypotension
	Subdural hematoma/effusion	Trauma	Associated injuries
Older pediatrics	Posterior fossa tumors	Ependymoma	Malnutrition-dehydration

		Astrocytoma	Hydrocephalus Increased ICP Prone or sitting position Air embolism Brain-stem compression Postoperative cranial nerve dysfunction or brain-stem swelling or compression

ICP, intracranial pressure

Pediatric Ventriculoperitoneal Shunts

Shunts are probably more commonly performed in children than adults. Common indications are hydrocephalus occurring in association with meningomyelocele, neonatal intraventricular hemorrhage, and posterior fossa tumors. Although one can never be casual about the management of these patients, open fontanelles seem to provide some margin for error in younger patients, and, in addition, palpation of the fontanelles provides on-line trend monitoring of "ICP." In spite of the theoretical considerations, inhalation inductions using volatile agents are empirically well tolerated even in children with closed fontanelles. However, we avoid that induction technique in a child who is already stuporous. When an intravenous line is available, we usually employ a thiopental-relaxant induction sequence. For children in whom cannulation of a peripheral vein cannot be accomplished readily, an inhalation induction with halothane or sevoflurane is the common approach.

If, in the absence of sevoflurane, halothane were employed for induction, immediately following loss of consciousness, we would generally change to isoflurane and control ventilation manually using the bag and mask. If an assistant is available, an ideal course at this point is to establish an intravenous line and to administer a muscle relaxant (with or without atropine according to personal bias) and perhaps thiopental and to intubate the patient in these optimal circumstances. Anesthesia is most commonly maintained thereafter with 60 to 70 percent N_2O, mechanical hyperventilation, and isoflurane or sevoflurane, as required. For children older than 6 months of age who are not stuporous at the outset, we commonly administer 2 to 3 mug/kg of fentanyl in the belief that this procedure is not entirely pain-free postoperatively and, in addition, that a smoother emergence from anesthesia can be accomplished with a narcotic background.

Pediatric Neurosurgery

Table 52-14 identifies common pediatric procedures and their anesthetic considerations. The most frequent procedures

TABLE 52-15 -- Anesthetic Considerations and Position Requirements Associated With Various Spinal Surgical Procedures

SPINAL REGION OR SURGICAL CONDITION	PROBLEMS/CONSIDERATIONS	POSITIONS USED AND COMMENTS
Lumbar region: degenerative disease, spinal stenosis, trauma	Major position change	Prone, lateral, or knee-chest
	Awake intubation and position	If unstable after trauma and major position change required
	Blood loss	Especially with repeat procedures, instrumentations and spinal stenosis; risk of occult aortoiliac or major venous tear
	Air embolism	Infrequent; perhaps with knee-chest and Relton-Hall frames
	Anaphylaxis with chymopapain chemonucleolysis	Infrequently done because of anaphylaxis and neurologic injury if intrathecal injection
Cervical region: degenerative disk disease, stenosis, trauma	Maintenance of neutral neck position to avoid cord compression	Supine/anterior approach for most diskectomies; posterior approach (prone or sitting) for laminectomy and occasional diskectomy
	Maintenance of perfusion pressure	If existing cord compression, recent cord injury, or if cord retraction required
	Hypotension (spinal shock)	Occurs with complete cervical cord injury
	Postoperative respiratory insufficiency	Occurs with cervical cord injury
	Methylprednisolone [241] [242]	30 mg/kg over 1 hr, then 5.4 mg/kg/h for 23 h
	Air embolism	With sitting laminectomies
Anterior cervical diskectomy	Traction required for anterior graft insertion? Retractor compression of airway Postoperative swelling/airway compression Postoperative cranial nerve dysfunction	
Cervical instability	Awake intubation Awake positioning	Prone or supine
	Axial stabilization for intubation	(If awake intubation not feasible)
Vertebral metastasis	Large blood loss	Prone or anterolateral/retroperitoneal Double-lumen tube for lesions above L1
Spinal cord tumors	Maintain perfusion pressure during retraction Methylprednisolone	Prone
Procedures with major neurologic risk	Wake-up test	Prone; rehearse with patient
	Somatosensory evoked responses	Anesthetic agent restrictions
	Motor evoked responses	Anesthetic/relaxant restrictions

are probably the placement and revision of CSF shunts. These are discussed earlier. Most pediatric tumors occur in the posterior fossa. Most are near the midline, and many are associated with hydrocephalus. For pediatric posterior fossa procedures, VAE risk, monitoring, and treatment are similar for adults and children, as discussed earlier. A Doppler study is invariably indicated, and right heart catheters are generally placed when procedures are done with the patient in the sitting position. Craniosynostosis procedures have the potential for a substantial blood loss that is roughly proportional to the number of sutures involved. There is a small risk of VAE that justifies the use of a precordial Doppler.

Spinal Surgery

Table 52-15 surveys the many issues that may arise in the context of spinal-cord and column procedures undertaken by neurosurgeons. The spinal cord has been described as a microcosm of the brain because its physiology is, in general, similar to that of the brain: CO_2 responsiveness, blood-"brain" barrier, autoregulation,

high metabolic rate and blood flow (although somewhat less than the brain), and substantial ischemic vulnerability of gray matter. Measures to reduce spinal cord swelling, analogous to ICP reduction maneuvers are, however, rarely used.

ACKNOWLEDGMENT

The authors gratefully acknowledge the contribution of Harvey M. Shapiro to the development of this chapter.

References

1. Grubb RL, Raichle ME, Eichling JO et al: The effects of changes in Pa CO_2 on cerebral blood volume, blood flow, and vascular mean transit time. Stroke 5:630, 1974.

2. Archer DP, Labreque P, Tyler JL et al: Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. Anesthesiology 67:642, 1987.

3. Greenberg JH, Alavi A, Reivich M et al: Local cerebral blood volume response to carbon dioxide in man. Circ Res 43:324, 1978.

4. Stirt JA, Grosslight KR, Bedford RF et al: "Defasciculation" with metocurine prevents succinylcholine-induced increases in intracranial pressure. Anesthesiology 67:50, 1987.

5. Kovarik DW, Mayberg TS, Lam AM et al: Succinylcholine does not change intracranial pressure, cerebral blood flow velocity, or the electroencephalogram in patients with neurologic injury. Anesth Analg 78:469, 1994.

6. Eisenberg HA, Frankowski RF, Constant CJ et al: High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 69:15, 1988.

7. Grote J, Zimmer K, Schubert R: Effects of severe arterial hypocapnia on regional blood flow regulation, tissue P O_2 and metabolism in the brain cortex of cats. Pflugers Arch 391:195, 1981.

8. Stoyka WW, Schutz H: Cerebral response to hypocapnia in normal and brain-injured dogs. Can J Anaesth 21:205, 1974.

9. Michenfelder JD, Theye RA: The effects of profound hypocapnia and dilutional anemia on canine cerebral metabolism and blood flow. Anesthesiology 31:449, 1969.

10. Alexander SC, Smith TC, Stroebel G et al: Cerebral carbohydrate metabolism of man during respiratory and metabolic alkalosis. J Appl Physiol 24:66, 1968.

11. Hansen NB, Nowicki PT, Miller RR et al: Alterations in cerebral blood flow and oxygen consumption during prolonged hypocarbia. Pediatr Res 20:147, 1986.

12. Reivich M, Cohen PJ, Greenbaum L: Alterations in the electroencephalogram of awake man produced by hyperventilation: Effects of 100% oxygen at 3 atmospheres (absolute) pressure. Neurology 16:304, 1966.

13. Hagerdal M, Harp JR, Siesjo BK: Influence of changes in arterial P CO_2 on cerebral blood flow and cerebral energy state during hypothermia in the rat. Acta Anaesthesiol Scand 57:25, 1975.

14. Bruce DA: Effects of hyperventilation on cerebral blood flow and metabolism. Clin Perinatol 11:673, 1984.

15. Artru AA: Cerebral vascular responses to hypocapnia during nitroglycerin-induced hypotension. Neurosurgery 16:468, 1985.

16. Artru AA, Katz RA, Colley PS: Autoregulation of cerebral blood flow during normocapnia and hypocapnia in dogs. Anesthesiology 70:288, 1989.

17. Boarini DJ, Kassell NF, Sprowll JA et al: Cerebrovascular effects of hypocapnia during adenosine-induced arterial hypotension. J Neurosurg 63:937, 1985.

18. VanderWorp HB, Kraaier V, Wieneke GH et al: Quantitative EEG during progressive hypocarbia and hypoxia: Hyperventilation-induced EEG changes reconsidered. Electroencephalogr Clin Neurophysiol 79:335, 1991.

19. Obrist WD, Langfitt TW, Jaggi JL et al: Cerebral blood flow and metabolism in comatose patients with acute head injury. J Neurosurg 61:241, 1984.

20. Darby JM, Yonas H, Marion DW et al: Local "inverse steal" induced by hyperventilation in head injury. Neurosurgery 23:84, 1988.

21. Cold GE: Does acute hyperventilation provoke cerebral oligaemia in comatose patients after acute head injury? Acta Neurochir 96:100, 1989.

22. Sutton LN, McLaughlin AC, Dante S et al: Cerebral venous oxygen content as a measure of brain energy metabolism with increased intracranial pressure and hyperventilation. J Neurosurg 73:927, 1990.

23. Muizelaar JP, Marmarou A, Ward JD et al: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. J Neurosurg 75:731, 1991.

24. Bouma GJ, Muizelaar JP, Choi SC et al: Cerebral circulation and metabolism after severe traumatic brain injury: The elusive role of ischemia. J Neurosurg 75:685, 1991.

25. Cruz J, Miner ME, Allen SJ et al: Continuous monitoring of cerebral oxygenation in acute brain injury: Assessment of cerebral hemodynamic reserve. Neurosurgery 29:743, 1991.

26. Yoshida K, Marmarou A: Effects of tromethamine and hyperventilation on brain injury in the cat. J Neurosurg 74:87, 1991.

27. Sheinberg M, Kanter MJ, Robertson CS et al: Continuous monitoring of jugular venous oxygen saturation in head-injured patients. J Neurosurg 76:212, 1992.

28. Andrews RJ, Muto RP: Retraction brain ischaemia: Cerebral blood flow, evoked potentials, hypotension and hyperventilation in a new animal model. Neurol Res 14:19, 1992.

29. Ruta TS, Drummond JC, Cole DJ: The effect of acute hypocapnia on local cerebral blood flow during middle cerebral artery occlusion in isoflurane anesthetized rats. Anesthesiology 78:134, 1993.

30. Yamaguchi T, Regli F, Waltz AG: Effect of Pa CO_2 on hyperemia and ischemia in experimental cerebral infarction. Stroke 2:139, 1971.

31. Michenfelder JD, Sundt TM: The effect of Pa CO_2 on the metabolism of ischemic brain in squirrel monkeys. Anesthesiology 38:445, 1973.

32. Michenfelder JD, Milde JH: Failure of prolonged hypocapnia, hypothermia, or hypertension to favorably alter acute stroke in primates. Stroke 8:87, 1977.

33. McLaughlin MR, Marion DW: Cerebral blood flow and vasoresponsivity within and around cerebral contusions. J Neurosurg 85:871, 1996.

34. Gopinath SP, Robertson CS, Contant CF et al: Jugular venous desaturation and outcome after head injury. J Neurol Neurosurg Psychiatry 57:717, 1994.

35. Bouma GJ, Muizelaar JP, Stringer WA et al: Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg

77:360, 1992.

36. Kelly DF, Martin NA, Kordestani R et al: Cerebral blood flow as a predictor of outcome following traumatic brain injury. J Neurosurg 86:633, 1997.

37. Martin NA, Patwardhan RV, Alexander MJ et al: Characterization of

cerebral hemodynamic phases following severe head trauma: Hypoperfusion, hyperemia, and vasospasm. J Neurosurg 87:9, 1997.

38. Miller JD, Dearden NM, Piper IR et al: Control of intracranial pressure in patients with severe head injury. J Neurotrauma 9:S317, 1992.

39. Matta BF, Lam AM, Mayberg TS et al: A critique of the intraoperative use of jugular venous bulb catheters during neurosurgical procedures. Anesth Analg 79:745, 1994.

40. Ishii R: Regional cerebral blood flow in patients with ruptured intracranial aneurysms. J Neurosurg 50:587, 1979.

41. Raichle ME, Posner JB, Plum F: Cerebral blood flow during and after hyperventilation. Arch Neurol 23:394, 1970.

42. Muizelaar JP, Poel HG, Li ZC et al: Pial arteriolar vessel diameter and CO_2 reactivity during prolonged hyperventilation in the rabbit. J Neurosurg 69:923, 1988.

43. Miller JD, Leech P: Effects of mannitol and steroid therapy on intracranial volume-pressure relationships in patients. J Neurosurg 42:274, 1975.

44. Miller JD, Sakalas R, Ward JD et al: Methylprednisolone treatment in patients with brain tumors. Neurosurgery 1:114, 1977.

45. Yeung WTI, Lee T-Y, Maestro RFD et al: Effect of steroids on iopamidol blood-brain transfer constant and plasma volume in brain tumors measured with x-ray computed tomography. J Neurooncol 18:53, 1994.

46. Bell BA, Kean KM, Macdonald HL et al: Brain water measured by magnetic resonance imaging: Correlation with direct estimation and changes after mannitol and dexamethasone. Lancet 1:66, 1987.

47. Braakman R, Schouten HJ, Dishoeck MB et al: Megadose steroids in severe head injury. J Neurosurg 58:326, 1983.

48. Dearden NM, Gibson JS, McDowall DG et al: Effect of high-dose dexamethasone on outcome from severe head injury. J Neurosurg 64:81, 1986.

49. Gudeman SK, Miller JD, Becker DP: Failure of high-dose steroid therapy to influence intracranial pressure in patients with severe head injury. J Neurosurg 51:301, 1979.

50. Grumme T, Baethmann A, Kolodziejczyk D et al: Treatment of patients with severe head injury by triamcinolone: A prospective, controlled multicenter clinical trial of 396 cases. Res Exp Med 195:217, 1995.

51. Cottrell JE, Robustelli A, Post K et al: Furosemide- and mannitol-induced changes in intracranial pressure and serum osmolality and electrolytes. Anesthesiology 47:28, 1977.

52. Rudehill A, Gordon E, Ohman G et al: Pharmacokinetics and effects of mannitol on hemodynamics, blood and cerebrospinal fluid electrolytes, and osmolality during intracranial surgery. J Neurosurg Anesthesiol 5:4, 1993.

53. Kaufmann AM, Cardoso ER: Aggravation of vasogenic cerebral edema by multiple-dose mannitol. J Neurosurg 77:584, 1992.

54. Marshall LF, Smith RW, Rauscher LA et al: Mannitol dose requirements in brain-injured patients. J Neurosurg 48:169, 1978.

55. Staub F, Stoffel M, Berger S et al: Treatment of vasogenic brain edema with the novel chloride ion transport inhibitor torasemide. J Neurotrauma 11:679, 1994.

56. Williams EL, Hart WM, Tempelhoff R: Postoperative ischemic optic neuropathy. Anesth Analg 80:1018, 1995.

57. Albin MS, Ritter RR, Pruett CE et al: Venous air embolism during lumbar laminectomy in the prone position: Report of three cases. Anesth Analg 73:346, 1991.

58. Standefer M, Bay JW, Trusso R: The sitting position in neurosurgery: A retrospective analysis of 488 cases. Neurosurg 14:649, 1984.

59. Matjasko J, Petrozza P, Cohen M et al: Anesthesia and surgery in the seated position: Analysis of 554 cases. Neurosurgery 17:695, 1985.

60. Black S, Ockert DB, Oliver WC et al: Outcome following posterior fossa craniectomy in patients in the sitting or horizontal positions. Anesthesiology 69:49, 1988.

61. Murr R, Biller H, Enzenbach R: Influence of volume loading on the cardiovascular pattern in the sitting position. Br J Anaesth 56:1305P, 1984.

62. Martin JT: Neuroanesthetic adjuncts for surgery in the sitting position: The antigravity suit. Anesth Analg 49:588, 1970.

63. Brodrick PM, Ingram GS: The antigravity suit in neurosurgery. Anaesthesia 43:762, 1988.

64. Meyer PG, Cuttaree H, Charron B et al: Prevention of venous air embolism in paediatric neurosurgical procedures performed in the sitting position by combined use of MAST suit and PEEP. Br J Anaesth 73:795, 1994.

65. Marshall WK, Bedford RF, Miller ED: Cardiovascular responses in the seated position: Impact of four anesthetic techniques. Anesth Analg 62:648, 1983.

66. Dalrymple DG, MacGowan SW, MacLeod GF: Cardiorespiratory effects of the sitting position in neurosurgery. Br J Anaesth 51:1079, 1979.

67. Pivalizza EG, Katz J, Singh S et al: Massive macroglossia after posterior fossa surgery in the prone position. J Neurosurg Anesthesiol 10:34, 1998.

68. Wilder BL: Hypothesis: The etiology of midcervical quadriplegia after operation with the patient in the sitting position. Neurosurgery 11:530, 1982.

69. Toung TJK, McPherson RW, Ahn H et al: Pneumocephalus: Effects of patient position on the incidence and location of aerocele after posterior fossa and upper cervical cord surgery. Anesth Analg 65:65, 1986.

70. Drummond JC: Tension pneumocephalus and intermittent drainage of ventricular CSF (letter). Anesthesiology 60:609, 1984.

71. Goodie D, Traill R: Intraoperative subdural tension pneumocephalus arising after opening of the dura. Anesthesiology 74:193, 1991.

72. Skahen S, Shapiro HM, Drummond JC et al: Nitrous oxide withdrawal reduces intracranial pressure in the presence of pneumocephalus. Anesthesiology 65:192, 1986.

73. Toung TT, Donham RT, Lehner A et al: Tension pneumocephalus after posterior fossa craniotomy: Report of four additional cases and review of postoperative pneumocephalus. Neurosurgery 12:164, 1983.

74. Reasoner DK, Todd MM, Scamman FL et al: The incidence of pneumocephalus after supratentorial craniotomy. Anesthesiology 80:1008, 1994.

75. Michenfelder JD, Miller RH, Gronert GA: Evaluation of an ultrasonic device (Doppler) for the diagnosis of venous air embolism. Anesthesiology 36:164, 1972.

76. Marshall WK, Bedford RF: Use of a pulmonary-artery catheter for detection and treatment of venous air embolism. Anesthesiology 52:131, 1980.

77. Papadopoulos G, Kuhly P, Brock M et al: Venous and paradoxical air embolism in the sitting position: A prospective study with transesophageal echocardiography. Acta Neurochir 126:140, 1994.

78. Matjasko J: Lessons learned (editorial). J Neurosurg Anesthesiol 8:1, 1996.

79. Schubert A, Drummond JC, Peterson DO et al: A comparison of CO_2 and bolus saline injection as tests of adequate doppler placement in neurosurgery. Anesth Analg 65:S135, 1986.

80. Cucchiara RF, Nugent M, Seward JB et al: Air embolism in upright neurosurgical patients: Detection and localization by two-dimensional transesophageal echocardiography. Anesthesiology 60:353, 1984.

81. Cucchiara RF, Seward JB, Nishimura RA et al: Identification of patent foramen ovale during sitting position craniotomy by transesophageal echocardiography with positive airway pressure. Anesthesiology 63:107, 1985.

82. Black S, Muzzi DA, Nishimura RA et al: Preoperative and intraoperative echocardiography to detect right-to-left shunt in patients undergoing neurosurgical procedures in the sitting position. Anesthesiology 72:436, 1990.

83. Drummond JC, Prutow RJ, Scheller MS: A comparison of the sensitivity of pulmonary artery pressure, end-tidal carbon dioxide, and end-tidal nitrogen in the detection of venous air embolism in the dog. Anesth Analg 64:688, 1985.

84. Bunegin L, Albin MS, Helsel PE et al: Positioning the right atrial catheter: A model for reappraisal. Anesthesiology 55:343, 1981.

85. Martin JT: Anesthetic adjuncts to patients in the sitting position. III. Intravascular electrocardiography. Anesth Analg 49:793, 1970.

86. Hagen PT, Scholz DG, Edwards WD: Incidence and size of patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. Mayo Clin Proc 59:17, 1984.

87. Perkins NAK, Bedford RF: Hemodynamic consequences of PEEP in seated neurological patients: Implications for paradoxical air embolism. Anesth Analg 63:429, 1984.

88. Colohan ART, Perkins AK, Bedford RF et al: Intravenous fluid loading as prophylaxis for paradoxical air embolism. J Neurosurg 62:839, 1985.

89. Black S, Cucchiara RF, Nishimura RA et al: Parameters affecting occurrence of paradoxical air embolism. Anesthesiology 71:235, 1989.

90. Guggiari M, Lechat P, Garen-Colonne C et al: Early detection of patent foramen ovale by two-dimensional contrast echocardiography

for prevention of paradoxical air embolism during sitting position. Anesth Analg 67:192, 1988.

91. Cucchiara RF, Nishimura RA, Black S: Failure of preoperative echo testing to prevent paradoxical air embolism: Report of two cases. Anesthesiology 71:604, 1989.

92. Schwarz G, Fuchs G, Weihs W et al: Sitting position for neurosurgery: Experience with preoperative contrast echocardiography in 301 patients. J Neurosurg Anesthesiol 6:83, 1994.

93. Jauss M, Kaps M, Keberle M et al: A comparison of transesophageal echocardiography and transcranial Doppler sonography with contrast medium for detection of patent foramen ovale. Stroke 25:1265, 1994.

94. Konstadt SN, Louie EK, Black S et al: Intraoperative detection of patent foramen ovale by transesophageal echocardiography. Anesthesiology 74:212, 1991.

95. Losasso TJ, Muzzi DA, Weglinski MR: The risk of paradoxical air embolism (PAE) in sitting neurosurgical patients with and without a demonstrable right-to-left (R-L) shunt (abstract). J Neurosurg Anesthesiol 4:298, 1992.

96. Bedell EA, Berge KH, Losasso TJ: Paradoxic air embolism during venous air embolism: Transesophageal echocardiographic evidence of transpulmonary air passage. Anesthesiology 80:947, 1994.

97. Tommasino C, Rizzardi R, Beretta L et al: Cerebral ischemia after venous air embolism in the absence of intracardiac defects. J Neurosurg Anesthesiol 8:30, 1996.

98. Butler BD, Hills BA: The lung as a filter for microbubbles. J Appl Physiol 47:537, 1979.

99. Yahagi N, Furuya H, Sai Y et al: Effect of halothane, fentanyl, and ketamine on the threshold for transpulmonary passage of venous air emboli in dogs. Anesth Analg 75:720, 1992.

100. Zentner J, Albrecht T, Hassler W: Prevention of an air embolism by moderate hypoventilation during surgery in the sitting position. Neurosurgery 28:705, 1991.

101. Grady MS, Bedford RF, Park TS: Changes in superior sagittal sinus pressure in children with head elevation, jugular venous compression and PEEP. J Neurosurg 65:199, 1986.

102. Toung TJK, Miyabe M, McShane AJ et al: Effect of PEEP and jugular venous compression on canine cerebral blood flow and oxygen consumption in the head elevated position. Anesthesiology 68:53, 1988.

103. Pfitzner J, McLean AG: Controlled neck compression in neurosurgery. Anaesthesia 40:624, 1985.

104. Tassani P, Eberl-Lehmann P, Enzenbach R: Interatrial pressure difference during inflation of pneumatic antishock garments and positive end-expiratory pressure ventilation. J Neurosurg Anesthesiol 4:160, 1992.

105. Jaffe RA, Pinto FJ, Schnittger I et al: Aspects of mechanical ventilation affecting interatrial shunt flow during general anesthesia. Anesth Analg 75:484, 1992.

106. Geissler HJ, Allen SJ, Mehlhorn U et al: Effect of body repositioning after venous air embolism. Anesthesiology 86:710, 1997.

107. Sokoll MM, Gergis SD: Effects of venous air embolism on the cardiovascular system and acid base balance in the presence and absence of nitrous oxide. Acta Anaesthesiol Scand 28:226, 1984.

108. Losasso TJ, Muzzi DA, Dietz NM et al: Fifty percent nitrous oxide does not increase the risk of venous air embolism in neurosurgical patients operated upon in the sitting position. Anesthesiology 77:21, 1992.

109. Losasso TJ, Black S, Muzzi DA et al: Detection and hemodynamic consequences of venous air embolism. Does nitrous oxide make a difference? Anesthesiology 77:148, 1992.

110. Tommasino C, Moore S, Todd MM: Cerebral effects of isovolemic hemodilution with crystalloid or colloid solutions. Crit Care Med 16:862, 1988.

111. Drummond JC, Patel PM, Cole DJ et al: The effect of reduction of colloid oncotic pressure, with and without reduction of osmolality, on post traumatic cerebral edema. Anesthesiology 88:993, 1998.

112. Claes Y, VanHemelrijck J, Gerven MV et al: Influence of hydroxyethyl starch on coagulation in patients during the perioperative period. Anesth Analg 75:24, 1992.

113. Prough DS, Kramer G: Medium starch, please (editorial). Anesth Analg 79:1034, 1994.

114. Smerling A: Hypertonic saline in head trauma: A new recipe for drying and salting. J Neurosurg Anesthesiol 4:1, 1992.

115. Zornow MH, Oh YS, Scheller MS: A comparison of the cerebral and haemodynamic effects of mannitol and hypertonic saline in an animal model of brain injury. Acta Neurochir Suppl 51:324, 1990.

116. Huang PP, Stucky FS, Dimick AR et al: Hypertonic sodium resuscitation is associated with renal failure and death. Ann Surg 221:543, 1995.

117. Ogilvy CS, Carter BS, Kaplan S et al: Temporary vessel occlusion for aneurysm surgery: Risk factors for stroke in patients protected by induced hypothermia and hypertension and intravenous mannitol administration. J Neurosurg 84:785, 1996.

118. Todd MM, Carras D, Hindman B et al: A pilot trial of hypothermia during aneurysm surgery (abstract). J Neurosurg Anesthesiol 8:323, 1996.

119. Baker KZ, Young WL, Stone JG et al: Deliberate mild intraoperative hypothermia for craniotomy. Anesthesiology 81:361, 1994.

120. Crowder CM, Tempelhoff R, Theard A et al: Jugular bulb temperature: Comparison with brain surface and core temperatures in neurosurgical patients during mild hypothermia. J Neurosurg 85:98, 1996.

121. Graham DI, Ford I, Adams JH et al: Ischaemic brain damage is still common in fatal nonmissile head injury. J Neurol Neurosurg Psychiatry 52:346, 1989.

122. Clifton GL, Jiang JY, Lyeth BG et al: Marked protection by moderate hypothermia after experimental traumatic brain injury. J Cereb Blood Flow Metab 11:114, 1991.

123. Marion DW, Obrist WD, Carlier PM et al: The use of moderate therapeutic hypothermia for patients with severe head injuries: A preliminary report. J Neurosurg 79:354, 1993.

124. Shiozaki T, Sugimoto H, Taneda M et al: Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 79:363, 1993.

125. Clifton GL, Allen S, Barrodale P et al: A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 10:263, 1993.

126. Metz C, Holzschuh M, Bein T et al: Moderate hypothermia in patients with severe head injury: Cerebral and extracerebral effects. J Neurosurg 85:533, 1996.

127. Johansson B, Li C-L, Olsson Y et al: The effect of acute arterial hypertension on the blood-brain barrier to protein tracers. Acta Neuropathol (Berl) 16:117, 1970.

128. Forster A, Horn KV, Marshall LF et al: Anesthetic effects on blood-brain barrier function during acute arterial hypertension. Anesthesiology 49:26, 1978.

129. Hatashita S, Hoff JT, Ishii S: Focal brain edema associated with acute arterial hypertension. J Neurosurg 64:643, 1986.

130. Mayhan WG: Disruption of blood-brain barrier during acute hypertension in adult and aged rats. Am J Physiol 258:H1735, 1990.

131. Lewelt W, Hummel R, Littlewood K et al: Recovery from anesthesia and cerebral blood flow velocity (abstract). Anesth Analg 74:S186, 1992.

132. Kalfas IH, Little JR: Postoperative hemorrhage: A survey of 4992 intracranial procedures. Neurosurgery 23:343, 1988.

133. Haley ECJ, Kassell NF, Torner JC: The international cooperative study on the timing of aneurysm surgery: The North American experience. Stroke 23:205, 1992.

134. Broderick JP, Brott TG, Duldner JE et al: Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke 25:1342, 1994.

135. Findlay JM, Kassell NF, Weir BK et al: A randomized trial of intraoperative, intracisternal tissue plasminogen activator for the prevention of vasospasm. Neurosurgery 37:168, 1995.

136. Sasaki T, Ohta T, Kikuchi H et al: A phase II clinical trial of recombinant human tissue-type plasminogen activator against cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurgery 35:597, 1994.

137. Heros RC: Acute hydrocephalus after subarachnoid hemorrhage. Stroke 20:715, 1989.

138. Tapaninaho A, Hernesniemi J, Vapalahti M: Shunt-dependent hydrocephalus after subarachnoid haemorrhage and aneurysm surgery: Timing of surgery is not a risk factor. Acta Neurochir 123:118, 1993.

139. Nelson PB, Seif S, Gutal J et al: Hyponatremia and natriuresis following subarachnoid hemorrhage in a monkey model. J Neurosurg 60:233, 1984.

140. Wijdicks EFM, Vermeulen M, tenHaaf JA et al: Volume depletion and natriuresis in patients with a ruptured intracranial aneurysm. Ann Neurol 18:211, 1985.

141. Wijdicks EFM, Ropper AH, Hunnicut EJ et al: Atrial natriuretic factor and salt wasting after aneurysmal subarachnoid hemorrhage. Stroke 22:1519, 1991.

142. Sivakumar V, Rajshekhar V, Chandy MJ: Management of neurosurgical

patients with hyponatremia and natriuresis. Neurosurgery 34:269, 1994.

143. Damaraju SC, Rajshekhar V, Chandy MJ: Validation study of a central venous pressure-based protocol for the management of neurosurgical patients with hyponatremia and natriuresis. Neurosurgery 40:312, 1997.

144. Okuchi K, Fujioka M, Fujiikawa A et al: Rapid natriuresis and preventive hypervolaemia for symptomatic vasospasm after subarachnoid haemorrhage. Acta Neurochir 138:951, 1996.

145. Wijdicks EFM, Schievink WI, Burnett JC: Natriuretic peptide system and endothelin in aneurysmal subarachnoid hemorrhage. J Neurosurg 87:275, 1997.

146. Muizelaar JP, Becker DP: Induced hypertension for the treatment of cerebral ischemia after subarachnoid hemorrhage. Surg Neurol 25:317, 1986.

147. Bouma GJ, Muizelaar JP: Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation. J Neurosurg 73:368, 1990.

148. Pickard JD, Murray GD, Illingworth R et al: Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 298:636, 1989.

149. Petruk KC, West M, Mohr G et al: Nimodipine treatment in poor-grade aneurysm patients. J Neurosurg 68:505, 1988.

150. Barker FG, Ogilivy CS: Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: A metaanalysis. J Neurosurg 84:405, 1996.

151. Stullken EH, Balestrieri FJ, Prough DS et al: The hemodynamic effects of nimodipine in patients anesthetized for cerebral aneurysm clipping. Anesthesiology 62:346, 1985.

152. Haley EC, Kassell NF, Torner JC et al: A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage: A report of the Cooperative Aneurysm Study. J Neurosurg 78:537, 1993.

153. Haley EC, Kassell NF, Torner JC et al: A randomized trial of nicardipine in subarachnoid hemorrhage: Angiographic and transcranial Doppler ultrasound results. A report of the Cooperative Aneurysm Study. J Neurosurg 78:548, 1993.

154. Kassell NF, Haley EC, Apperson-Hansen C et al: Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: A cooperative study in Europe, Australia, and New Zealand. J Neurosurg 84:221, 1996.

155. Haley EC, Kassell NF, Apperson-Hansen C et al: A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: A cooperative study in North America. J Neurosurg 86:467, 1997.

156. Adams HP, Kassell NF, Torner JC et al: Predicting cerebral ischemia after aneurysmal subarachnoid hemorrhage: Influences of clinical conditions, CT results, and antifibrinolytic therapy. Neurology 37:1586, 1987.

157. Rudehill A, Gordon E, Sundkvist K et al: A study of ECG abnormalities and myocardial specific enzymes in patients with subarachnoid haemorrhage. Acta Anaesthesiol Scand 26:344, 1982.

158. Shivalkar B, Loon JV, Wieland W et al: Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. Circulation 87:230, 1993.

159. Kolin A, Norris JW: Myocardial damage from acute cerebral lesions. Stroke 15:990, 1984.

160. Davies KR, Gelb AW, Manninen PH et al: Cardiac function in aneurysmal subarachnoid haemorrhage: A study of electrocardiographic and echocardiographic abnormalities. Br J Anaesth 67:58, 1991.

161. Szabo MD, Crosby G, Hurford WE et al: Myocardial perfusion following acute subarachnoid hemorrhage in patients with an abnormal electrocardiogram. Anesth Analg 76:253, 1993.

162. Mayer SA, LiMandri G, Sherman D et al: Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg 83:889, 1995.

163. Brouwers PJAM, Wijdicks EFM, Hasan D et al: Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage. Stroke 20:1162, 1989.

164. Lanzino G, Kongable GL, Kassell NF: Electrocardiographic abnormalities after nontraumatic subarachnoid hemorrhage. J Neurosurg Anesth 6:156, 1994.

165. Maekawa T, McDowall DG, Okuda Y: Brain-surface oxygen tension and cerebral cortical blood flow during hemorrhagic and drug-induced hypotension in the cat. Anesthesiology 51:313, 1979.

166. Pare L, Delfino R, LeBlanc R: The relationship of ventricular drainage to aneurysmal rebleeding. J Neurosurg 76:422, 1992.

167. Meyer FB, Anderson RE, Sundt TM et al: Treatment of experimental focal cerebral ischemia with mannitol. J Neurosurg 66:109, 1987.

168. Jafar JJ, Johns LM, Mullan SF: The effect of mannitol on cerebral blood flow. J Neurosurg 64:754, 1986.

169. Ogilvy CS, Chu D, Kaplan S: Mild hypothermia, hypertension, and mannitol are protective against infarction during experimental intracranial temporary vessel occlusion. Neurosurgery 38:1202, 1996.

170. Samson D, Batjer HH, Bowman G et al: A clinical study of the parameters and effects of temporary arterial occlusion in the management of intracranial aneurysms. Neurosurgery 34:22, 1994.

171. Ridenour TR, Warner DS, Todd MM et al: Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. Anesthesiology 76:807, 1992.

172. Drummond JC, Cole DJ, Patel PM et al: Focal cerebral ischemia during anesthesia with etomidate, isoflurane or thiopental: A comparison of the extent of cerebral injury. Neurosurgery 37:742, 1995.

173. Soonthon V, Patel P, Drummond J et al: Effect of fentanyl on cerebral injury after focal ischemia in rats (abstract). Anesth Analg 86:S357, 1998.

174. Symon L, Wang AD, Silva IEC et al: Perioperative use of somatosensory evoked responses in aneurysm surgery. J Neurosurg 60:269, 1984.

175. Young WL, Solomon RA, Pedley TA et al: Direct cortical EEG monitoring during temporary vascular occlusion for cerebral aneurysm surgery. Anesthesiology 71:794, 1989.

176. Little JR, Lesser RP, Luders H: Electrophysiological monitoring during basilar aneurysm operation. Neurosurgery 20:421, 1987.

177. Manninen PH, Cuillerier DJ, Nantau WE et al: Monitoring of brainstem function during vertebral basilar aneurysm surgery: The use of spontaneous ventilation. Anesthesiology 77:681, 1992.

178. Manninen PH: Spontaneous ventilation is a useful monitor of brain stem function during posterior fossa surgery. J Neurosurg Anesthesiol 7:63, 1995.

179. Batjer HH, Devous MD, Meyer YJ et al: Cerebrovascular hemodynamics in arteriovenous malformation complicated by normal perfusion pressure breakthrough. Neurosurgery 22:503, 1988.

180. Young WL, Prohovnik I, Ornstein E et al: Pressure autoregulation is intact after arteriovenous malformation resection. Neurosurgery 32:491, 1993.

181. Young WL, Kader A, Ornstein E et al: Cerebral hyperemia after arteriovenous malformation resection is related to "breakthrough" complications but not to feeding artery pressure. Neurosurgery 38:1085, 1996.

182. O'Malley KF, Ross SE: The incidence of injury to the cervical spine in patients with craniocerebral injury. J Trauma 28:1476, 1988.

183. Bachulis BL, Long WB, Hynes GD et al: Clinical indications for cervical spine radiographs in the traumatized patient. Am J Surg 153:473, 1987.

184. Sinclair D, Schwartz M, Gruss J et al: A retrospective review of the relationship between facial fractures, head injuries and cervical spine injuries. J Emerg Med 6:109, 1988.

185. Criswell JC, Parr MJ, Nolan JP: Emergency airway management in patients with cervical spine injuries. Anaesthesia 49:900, 1994.

186. Stene JD: Anesthesia for the critically ill trauma patient. In Siegel JH (ed): Trauma: Emergency Surgery and Critical Care. New York, Churchill Livingstone, 1987.

187. Talucci RC, Shaikh KA, Schwab CW: Rapid sequence induction with oral endotracheal intubation in the multiply injured patient. Am Surg 54:185, 1988.

188. Suderman VS, Crosby ET, Lui A: Elective oral tracheal intubation in cervical spine-injured adults. Can J Anaesth 38:785, 1991.

189. Shatney CH, Brunner RD, Nguyen TQ: The safety of orotracheal intubation in patients with unstable cervical spine fracture or high spinal cord injury. Am J Surg 170:676, 1995.

190. Hastings RH, Kelley SD: Neurologic deterioration associated with airway management in a cervical spine-injured patient. Anesthesiology 78:580, 1993.

191. Kirschenbaum KJ, Nadimpalli SR, Fantus R et al: Unsuspected upper cervical spine fractures associated with significant head trauma: Role of CT. J Emerg Med 8:183, 1990.

192. Hastings RH, Wood PR: Head extension and laryngeal view during laryngoscopy with cervical spine stabilization maneuvers. Anesthesiology 80:825, 1994.

193. Chesnut RM, Marshall LF, Klauber MR et al: The role of secondary

brain injury in determining outcome from severe head injury. J Trauma 34:216, 1993.

194. Fischer RP: Cervical radiographic evaluation of alert patients following blunt trauma. Ann Emerg Med 13:905, 1984.

195. Ross SE, Schwab CW, David ET et al: Clearing the cervical spine: Initial radiologic evaluation. J Trauma 27:1055, 1987.

196. DeWitt DS, Prough DS, Taylor CL et al: Reduced cerebral blood flow, oxygen delivery, and electroencephalographic activity after traumatic brain injury and mild hemorrhage in cats. J Neurosurg 76:812, 1992.

197. Marmarou A, Anderson RL, Ward JD et al: Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 75:S59, 1991.

198. Pietropaoli JA, Rogers FB, Shackford SR et al: The deleterious effects of intraoperative hypotension an outcome in patients with severe head injuries. J Trauma 33:403, 1992.

199. Jones PA, Andrews PJ, Midgley S et al: Measuring the burden of secondary insults in head-injured patients during intensive care. J Neurosurg Anesthesiol 6:4, 1994.

200. Stocchetti N, Furlan A, Volta F: Hypoxemia and arterial hypotension at the accident scene in head injury. J Trauma 40:764, 1996.

201. DeWitt DS, Prough DS, Taylor CL et al: Regional cerebrovascular responses to progressive hypotension after traumatic brain injury in cats. Am J Physiol 163:H1276, 1992.

202. Marion DW, Darby J, Yonas H: Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg 74:407, 1991.

203. Schroder ML, Muizelaar JP, Kuta AJ et al: Thresholds for cerebral ischemia after severe head injury: Relationship with late CT findings and outcome. J Neurotrauma 13:17, 1996.

204. Chan K-H, Miller JD, Dearden NM et al: The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury. J Neurosurg 77:55, 1992.

205. Chan KH, Dearden NM, Miller JD et al: Multimodality monitoring as a guide to treatment of intracranial hypertension after severe brain injury. Neurosurgery 32:547, 1993.

206. Guidelines for the Management of Severe Head Injury. Park Ridge, Ill, Brain Trauma Foundation and the American Association of Neurological Surgeons, 1995.

207. Rosner MJ, Daughton S: Cerebral perfusion pressure management in head injury. J Trauma 30:933, 1990.

208. Rosner MJ, Rosner SD, Johnson AH: Cerebral perfusion pressure: Management protocol and clinical results. J Neurosurg 83:949, 1995.

209. Asgeirsson B, Grande PO, Nordstrom CH: A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. Intensive Care Med 20:260, 1994.

210. Asgeirsson B, Grande PO, Nordstrom CH: The Lund concept of post-traumatic brain oedema therapy. Acta Anaesthesiol Scand 39:103, 1995.

211. Romner B, Bellner J, Kongstad P et al: Elevated transcranial Doppler flow velocities after severe head injury: Cerebral vasospasm or hyperemia? J Neurosurg 85:90, 1996.

212. Steiger HJ, Ciessinna E, Seiler RW: Identification of posttraumatic ischemia and hyperfusion by determination of effect of induced arterial hypertension on carbon dioxide reactivity. Stroke 27:2048, 1996.

213. Kelly DF, Kordestani RK, Martin NA et al: Hyperemia following traumatic brain injury: Relationship to intracranial hypertension and outcome. J Neurosurg 85:762, 1996.

214. Muizelaar JP, Marmarou A, DeSalles AAF et al: Cerebral blood flow and metabolism in severely head-injured children. I. Relationship with GCS score, outcome, ICP, and PVI. J Neurosurg 71:63, 1989.

215. Martin NA, Doberstein C, Zane C et al: Posttraumatic cerebral arterial spasm: Transcranial Doppler ultrasound, cerebral blood flow, and angiographic findings. J Neurosurg 77:575, 1992.

216. Miller JD, Piper IR, Dearden NM: Management of intracranial hypertension in head injury: Matching treatment with cause. Acta Neurochir 57:152, 1993.

217. Bouma GJ, Muizelaar JP, Bandoh K et al: Blood pressure and intracranial pressure-volume dynamics in severe head injury: Relationship with cerebral blood flow. J Neurosurg 77:15, 1992.

218. Hulka F, Mullins RJ, Frank EH: Blunt brain injury activates the coagulation process. Arch Surg 131:923, 1996.

219. Robertson CS, Gopinath SP, Goodman JC et al: Sjv O_2 monitoring in head-injured patients. J Neurotrauma 12:891, 1995.

220. Schneider GH, Helden AV, Lanksch WR et al: Continuous monitoring of jugular bulb oxygen saturation in comatose patients: Therapeutic implications. Acta Neurochir 134:71, 1995.

221. Gunn HC, Matta BF, Lam AM et al: Accuracy of continuous jugular bulb venous oximetry during intracranial surgery. J Neurosurg Anesthesiol 7:174, 1995.

222. Stocchetti N, Paparella A, Bridelli F et al: Cerebral venous oxygen saturation studied with bilateral samples in the internal jugular veins. Neurosurgery 34:38, 1994.

223. Metz C, Holzschuh M, Bein T et al: Monitoring of cerebral oxygen metabolism in the jugular bulb: Reliability of unilateral measurements in severe head injury. J Cereb Blood Flow Metab 18:332, 1998.

224. Muizelaar JP, Schroder ML: Overview of monitoring of cerebral blood flow and metabolism after severe head injury. Can J Neurol Sci 21:S6, 1994.

225. Gopinath SP, Cormio M, Ziegler J et al: Intraoperative jugular desaturation during surgery for traumatic intracranial hematomas. Anesth Analg 83:1014, 1996.

226. Marshall LF, Toole BM, Bowers SA: The National Traumatic Coma Data Bank. II. Patients who talk and deteriorate: Implications for treatment. J Neurosurg 59:285, 1983.

227. Drummond JC, Todd MM: Acute sinus arrhythmia during surgery in the fourth ventricle: An indicator of brain-stem irritation. Anesthesiology 60:232, 1984.

228. Lobato RD, Rivas JJ, Sarabia R et al: Percutaneous microcompression of the gasserian ganglion for trigeminal neuralgia. J Neurosurg 72:546, 1990.

229. Nath G, Korula G, Chandy MJ: Effect of intrathecal saline injection and Valsalva maneuver on cerebral perfusion pressure during transsphenoidal surgery for pituitary macroadenoma. J Neurosurg Anesthesiol 7:1, 1995.

230. Spaziante R, DeDivitiis E: Forced subarachnoid air in transsphenoidal excision of pituitary tumors (pumping technique). J Neurosurg 71:864, 1989.

231. Archer DP, McKenna JMA, Morin L et al: Conscious-sedation analgesia during craniotomy for intractable epilepsy: A review of 354 consecutive cases. Can J Anaesth 35:338, 1988.

232. Herrick IA, Craen RA, Gelb AW et al: Propofol sedation during awake craniotomy for seizures: Patient-controlled administration versus neurolept analgesia. Anesth Analg 84:1280, 1997.

233. Drummond JC, Iragui-Madoz VJ, Alksne JF et al: Masking of epileptiform activity by propofol during seizure surgery. Anesthesiology 76:652, 1992.

234. Cascino GD, So EL, Sharbrough FW et al: Alfentanil-induced epileptiform activity in patients with partial epilepsy. J Clin Neurophysiol 10:520, 1993.

235. Ebrahim ZY, DeBoer GE, Luders H et al: Effect of etomidate on the electroencephalogram of patients with epilepsy. Anesth Analg 65:1004, 1986.

236. Gancher S, Laxer KD, Krieger W: Activation of epileptogenic activity by etomidate. Anesthesiology 61:616, 1984.

237. Kofke WA, Tempelhoff R, Dasheiff RM: Anesthetic implications of epilepsy, status epilepticus, and epilepsy surgery. J Neurosurg Anesthesiol 9:349, 1997.

238. Pile-Spellman J, Young WL, Joshi S et al: Adenosine-induced cardiac pause for endovascular embolization of cerebral arteriovenous malformations: Case report. Neurosurgery (in press), April, 1999.

239. Drake CG, Hunt WE, Sano K et al: Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. J Neurosurg 68:985, 1988.

240. Hunt WE, Hess RM: Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 28:14, 1968.

241. Bracken MB, Shepard MJ, Collins WF: A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury: Results of the second National Acute Spinal Cord Injury Study. N Engl J Med 322:1405, 1990.

242. Bracken MB, Shepard MJ, Holford TR et al: Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. JAMA 277:1597, 1997.

243. Fishman RA: Brain edema. N Engl J Med 293:706, 1975.

244. Martin JT: Positioning in Anesthesia and Surgery. Philadelphia, WB Saunders, 1988.

Chapter 53 - Anesthesia and the Renal and Genitourinary Systems

Vinod Malhotra
Sudhir Diwan

INTRODUCTION

Patients requiring anesthesia for renal and genitourinary surgery belong frequently to the extremes of age. Concomitant cardiovascular and respiratory disease is common in the elderly in addition to the physiologic changes of aging. Medical history, physical examination, and appropriate laboratory tests are necessary to evaluate concomitant disease. In the pediatric urologic patient, upper respiratory infections are not uncommon. Careful history should be obtained to exclude other congenital lesions if the urologic procedure is planned for congenital urologic anomalies such as exstrophy of the bladder or Wilms tumor. [1]

Urologic procedures are mostly performed on the kidneys, adrenals, ureters, urinary bladder, prostate, urethra, penis, scrotum, testis, and spermatic cord. Because their sensory nerve supply is primarily thoracolumbar and sacral outflow (Table 53-1) , these structures are well adapted for regional anesthesia.

INNERVATION OF THE GENITOURINARY SYSTEM

The parts of the genitourinary system that are in the abdomen receive their nerve supply from the autonomic nervous system via both sympathetic and parasympathetic pathways. The pelvic urinary organs and the genitalia are supplied by the somatic in addition to the autonomic nerves. Table 53-1 summarizes the pain conduction pathways and spinal levels of the genitourinary system.

Kidney and Abdominal Ureter

Sympathetic nerves to the kidney originate as preganglionic fibers from the eighth through the first lumbar segments and converge to the celiac plexus and the aorticorenal ganglia (Fig. 53-1) (Figure Not Available) . Postganglionic fibers to the kidney arise mainly from the celiac and aorticorenal ganglia. Some sympathetic fibers may reach the kidney via the splanchnic nerves. Parasympathetic input is from the vagus nerve. [2] Sympathetic fibers to the ureter originate from the tenth thoracic through the second lumbar segments and synapse with postganglionic fibers in the aorticorenal and superior

TABLE 53-1 -- Pain Conduction Pathways and Spinal Segment Projection of Pain of the Genitourinary System

ORGAN	SYMPATHETICS, SPINAL SEGMENTS	PARASYMPATHETICS	SPINAL LEVELS OF PAIN CONDUCTION
Kidney	T8-L1	X (vagus)	T10-L1
Ureter	T10-L2	S2-S4	T10-L2
Bladder	T11-L2	S2-S4	T11-L2 (dome)
			S2-S4 (neck)
Prostate	T11-L2	S2-S4	T11 to L2, S2-S4
Penis	L1 & L2	S2-S4	S2-S4
Scrotum	NS	NS	S2-S4
Testes	T10-L2	NS	T10-L1

NS, not significant for nociceptive function

and inferior hypogastric plexus. Parasympathetic input is from second through fourth sacral spinal segments. [2] Nociceptive fibers travel along the sympathetics to the same spinal segments. Pain from the kidney and ureter, therefore, is referred mainly to the somatic distribution of the tenth thoracic through the second lumbar segments, namely, the lower back, flank, ilioinguinal region, and scrotum or labia. Effective neural block of these segments is necessary to provide adequate analgesia or anesthesia.

Figure 53-1 (Figure Not Available) Autonomic and sensory innervation of the kidney and ureters. Solid line = preganglionic fibers; dashed line = postganglionic fibers; dotted line = sensory fibers. *(From Gee WF, Ansell JF: Pelvic and perineal pain of urologic origin. In Bonica JJ [ed]: The Management of Pain. 2d ed. Philadelphia, Lea & Febiger, 1990: 1368-1378.)*

Bladder and Urethra

Sympathetic nerves to these organs originate from the eleventh thoracic to the second lumbar segments, travel through the superior hypogastric plexus, and supply the bladder via the right and the left hypogastric nerves. [3] Parasympathetic nerves arise from the second through the fourth sacral segments and form the pelvic parasympathetic plexus, which is joined by the hypogastric plexus. Vesical branches then proceed toward the bladder base, where they provide the nerve supply to the bladder and the proximal urethra (Fig. 53-2) (Figure Not Available) . Parasympathetic fibers are the main motor supply to the bladder (with the exception of the trigone) and hence far outnumber the sympathetic fibers in the bladder. [3]

The afferents carrying sensations of stretch and fullness of bladder are parasympathetic, whereas pain, touch, and temperature sensations are carried by the sympathetic nerves. Sympathetic fibers are predominantly alpha-adrenergic in the bladder base and the urethra and beta-adrenergic in the bladder dome and lateral wall. Knowledge of these aspects of neuroanatomy is important to appreciate the pharmacologic effects on the urologic system of neural ablation or regional block and of drugs with adrenergic or cholinergic effects. [3]

Prostate and Prostatic Urethra

The prostate and prostatic urethra receive both sympathetic and parasympathetic supply from the prostatic plexus arising from the pelvic parasympathetic plexus, which is joined by the hypogastric plexus. The spinal origin of the nerve supply is primarily lumbosacral (see Fig. 53-2) (Figure Not Available) . [3]

Penis and Scrotum

The autonomic supply to the penile urethra and the cavernous tissue comes from the prostatic plexus. Somatic fibers from the pudendal nerve (S2-S4) supply the external sphincter. The dorsal nerve of the penis, the first branch of the pudendal nerve, is its main sensory supply. The scrotum is innervated anteriorly by the iliolingual and genitofemoral nerves (L1 and L2) and posteriorly by the perineal branches of the pudendal nerve (S2 and S4). [3]

Figure 53-2 (Figure Not Available) *A.* Nerve supply of the urinary bladder and prostate showing the relationship of the various nerve structures to the large intestine and their distribution in the bladder and prostate. *B.* Schematic illustration showing the segmental nerve supply to the bladder, penis, and scrotum. Solid lines = preganglionic fibers; dashed lines = postganglionic fibers; dotted lines = sensory fibers. *(From Gee WF, Ansell JS: Pelvic and perineal pain of urologic origin. In Bonica JJ [ed]: The Management of Pain. 2d ed. Philadelphia, Lea & Febiger, 1990: 1368-1378.)*

Testes

The testes descend from their intra-abdominal location to the scrotum during fetal development. Because they share their embryologic origin with the kidney, their nerve supply is similar to that of the kidney and upper ureter and extends up to the T10 spinal segment. [3]

Although knowledge of the neuroanatomy is essential to provide adequate anesthesia, a thorough understanding of renal physiology and pharmacology is equally important. Frequently the genitourinary surgical patient has mechanical or functional renal disease. Anesthetics and surgery will significantly alter renal function. Conversely, renal dysfunction will significantly affect the pharmacokinetics and pharmacodynamics of anesthetics and adjuvant drugs. The evaluation of a patient with renal disease is discussed later.

Renal Blood Flow

Kidneys receive approximately 15 to 25 percent of total cardiac output or 1.0 to 1.25 L blood/min via renal arteries depending on the state of body. Most of the blood is received by renal cortex, and only 5 percent of cardiac output flows through renal medulla, which makes renal papillae vulnerable to ischemic insults. Renal blood flow is regulated by a variety of mechanisms that control activity of vascular smooth muscles and thereby alter vascular resistance. The sympathetic tone of renal vessels increases during exercise to shunt renal blood flow to exercising skeletal muscle, similarly renal blood vessels relax during the resting condition of the body. Sympathetic stimulation due to surgery can increase the vascular resistance to reduce the renal blood flow, whereas anesthetic may reduce the renal blood flow by decreasing cardiac output. Glomerular capillaries separate afferent arterioles from efferent arterioles. The glomerular capillaries are high pressure systems, whereas peritubular capillaries are low pressure systems. So the glomerular capillaries are a fluid-filtering system, whereas peritubular capillaries are a fluid-absorbing system. Vasa recta are a specialized portion of peritubular capillaries that are formed from efferent arterioles and are important in the formation of concentrated urine by countercurrent mechanism. An intrinsic mechanism that causes vasodilation and vasoconstriction of renal afferent arterioles regulates the autoregulation of renal blood flow. A fall in mean arterial pressure will also decrease renal blood flow and eventually affect glomerular filtration rate (GFR) when the pressure decreases below 60 mm Hg. The persistent low mean arterial pressure above 60 mm Hg affects renal blood flow but does not affect the GFR due to the intrinsic mechanism of autoregulation (Fig. 53-3) (Figure Not Available) . This autoregulation is maintained between 60 and

---

Figure 53-3 (Figure Not Available) Autoregulation of renal blood flow (RBF) and glomerular filtration rate (GFR). The relationships between RBF, GFR, and urine flow rate (UFR) and mean renal arterial pressure in dogs are shown as renal arterial pressure is varied from 20 to 280 mm Hg. Autoregulation of RBF and GFR is observed between about 80 and 180 mm Hg. *(From Hemmings HC: Anesthetics, Adjuvants and Drugs and the Kidney. In Malhotra V [ed]: Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, p 18.)*

160 mm Hg mean arterial pressure (MAP) in intact as well as denervated kidneys. [4]

Although knowledge of the neuroanatomy and renal blood flow is essential to provide adequate anesthesia, a thorough understanding of renal physiology and pharmacology is equally important. Frequently the genitourinary surgical patient has mechanical or functional renal disease. Anesthetics and surgery will significantly alter renal function. Conversely, renal dysfunction will significantly affect the pharmacokinetics and pharmacodynamics of anesthetics and adjuvant drugs. The evaluation of a patient with renal disease is discussed later.

ANESTHESIA FOR THE PATIENT WITH RENAL DISEASE

Evaluation of Renal Function

The best indication that a patient has renal disease is usually obtained from the medical history (Ch. 34) . Physical findings often are minimal until renal disease is far advanced unless hypertension is present. Urinalysis is sufficient laboratory screening for identification of kidney disease if the patient does not have a history of genitourinary abnormalities. If renal disease is thought to be present, more precise methods of assessing renal function are necessary. Laboratory tests useful in evaluating renal function are described next (Table 53-2) (Table Not Available) .

Urinalysis

Gross and microscopic observation of the urine and its sediment, with determination of urinary pH, specific gravity,

TABLE 53-2 -- Commonly Ordered Renal Function Tests

(Not Available)

From Miller ED Jr: Understanding renal function and its preoperative evaluation. In Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, p 9.

protein content, and sugar content, is one of the most readily available, inexpensive, and informative laboratory tests.

Appearance

The gross appearance of the urine may indicate the presence of bleeding or infection in the genitourinary tract. Microscopic examination of urinary sediment may reveal the presence of casts, bacteria, and various cell forms, supplying diagnostic information in patients with renal disease.

pH Value

Urinary pH is a measure of the ability of the kidneys to acidify urine. The kidneys share regulation of acid-base balance with the lungs and provide the sole pathway of excretion for the 60 mEq of hydrogen ion (nonvolatile acid) produced each day by normal metabolism. [5] The three renal mechanisms that prevent the development of acidemia are the reabsorption of filtered bicarbonate, the acidification of buffers in the tubular urine (i.e., the excretion of titratable acid) and the production of ammonia in tubular cells and its excretion as ammonium ion. The inability to excrete an acid urine in the presence of systemic acidosis is indicative of renal insufficiency.

Concentration

Urinary specific gravity is an index of concentrating ability, specifically, renal tubular function. Determination of urinary

osmolality, that is, measurement of the number of moles of solute (osmoles) per kilogram of solvent, is a similar, more specific test. Excretion of concentrated urine (specific gravity 1.030, 1050 mOsm/kg) is indicative of excellent tubular function, whereas urinary osmolality fixed at that of plasma (specific gravity 1.010, 290 mOsm/kg) is indicative of renal disease. The urinary dilution mechanism persists after concentrating defects are present, so that a urinary osmolality of 50 to 100 mOsm/kg may still be consistent with advanced renal disease.

Protein

Patients without renal disease may excrete up to 150 mg of protein per day; greater amounts may be present after strenuous exercise or after standing for several hours. Massive proteinuria (i.e., >750 mg/d) is always abnormal and is usually indicative of severe glomerular damage. However, proteinuria also may be due to (1) failure of tubular reabsorption of the small amount of protein that is normally filtered, (2) abnormally increased concentrations of normal plasma proteins, or (3) the presence of abnormal plasma proteins, which are then excreted in the urine.

Sugar

Glucose is freely filtered at the glomerulus and subsequently is reabsorbed in the proximal tubule. Glycosuria signifies that the ability of the renal tubules to reabsorb glucose has been exceeded by an abnormally heavy glucose load and is usually indicative of diabetes mellitus. However, glycosuria also may be present in hospitalized patients without diabetes who are receiving intravenous glucose infusions.

Complete Blood Count

Anemia may be present in patients with renal disease because of abnormalities in production of erythropoietin (erythropoiesis-stimulating factor [ESF].) The exact mechanism of ESF formation is unknown. [6] [7] [8] One view is that in response to hypoxia, the kidney elaborates a precursor of ESF, which combines with a plasma protein to form active ESF. [7] Another theory is that the kidney produces an enzyme, renal erythropoietic factor, which converts a precursor in plasma to ESF. [7] In advanced renal disease there appears to be decreased ESF activity and hence anemia. [8] The absence of ESF, as may occur in the anephric patient, results in hemoglobin levels of 6 to 8 g/100 mL. Recently available commercial preparation of erythropoietin has been effective in alleviating the chronic anemia associated with end-stage renal disease. Hemoglobin concentrations of 10 g/100 mL or greater are not uncommon in patients with end-stage renal disease treated with recombinant erythropoietin. White blood cell and platelet counts are of particular importance in patients who have a transplanted kidney, as immunosuppressive therapy may cause bone marrow suppression.

Creatinine and Urea Concentrations and Clearances

Measurements of creatinine and urea concentrations and clearances provide valuable information regarding general kidney function. Creatinine in the serum results

from the turnover of muscle tissue and is dependent on daily dietary intake of protein; normal values are in the range of 0.5 to 1.5 mg/100 mL, with values of 0.5 to 1.0 mg/100 mL present during pregnancy. Creatinine is freely filtered at the glomerulus and apart from an almost negligible increase in content due to secretion in the distal nephron; it is neither reabsorbed nor secreted. Therefore, serum creatinine measurements reflect glomerular function [9] (Fig. 53-4) (Figure Not Available) , and creatinine clearance is a specific measurement of GFR. Because there is such a wide range in normal values, a 50 percent increase in serum creatinine concentration, indicative of a 50 percent reduction in GFR, may go undetected unless baseline values are known. It also should be apparent that the excretion of drugs dependent on glomerular filtration may be significantly decreased despite what might seem to be only slightly elevated serum creatinine values (1.5-2.5 mg/100 mL). Serum creatinine concentration and clearance are better indicators of general kidney function and GFR than similar measurements of urea nitrogen. Urea nitrogen concentration and clearance are subject to wide intraindividual variations secondary to changes in hydration, rate of urine flow, and dietary protein intake.

Creatinine clearance measurement is made over a 24-hour period and calculated as follows:

A 24-hour clearance is more accurate than a 2-hour creatinine clearance test, which is frequently used because it is more convenient. Normal values are 85 to 125 mL/min in women and 95 to 140 mL/min in men. Creatinine clearance decreases with age and the value approaches 70 at age 70.

Serum Electrolytes

Sodium, potassium, chloride, and bicarbonate concentrations should be determined if impairment of renal function is suspected. However, these tests usually remain normal until frank renal failure is present, and hyperkalemia does not occur until patients are uremic. [10]

pH and Blood Gases

If significant renal disease is present, patients consuming a diet high in animal protein may have metabolic acidosis

---

Figure 53-4 (Figure Not Available) Theoretical relationship between blood urea nitrogen (BUN) and creatinine versus glomer-ular filtration rate (GFR). *(From Kassirer JP: Clinical evaluation of kidney function--glomerular function. N Engl J Med 285:385, 1971. Copyright 1971, Massachusetts Medical Society. All rights reserved.)*

due to the inability to excrete nonvolatile acid metabolites. Arterial blood pH, bicarbonate, and P_{CO_2} should be determined to measure the extent of acid-base imbalance (Ch. 38) .

Chest Radiograph

Standard posteroanterior and lateral radiographic exposures (Ch. 23) of the chest may be of value in determining the presence and extent of hypertensive cardiovascular disease, pericardial effusion, and uremic pneumonitis.

Electrocardiogram

The electrocardiogram (ECG) (Ch. 32) reflects the toxic effects of potassium excess more closely than does determination of serum potassium concentration. As hyperkalemia progresses, tall peaked T waves, depression of the ST segment, and widening of the QRS complex are seen. When potassium values increase above 8.0 mEq/L, ventricular standstill and bizarre arrhythmias may occur. Digitalis toxicity is a real danger in patients with advanced renal disease, particularly if electrolyte imbalance is present; it is best detected with the ECG. Digitalis will shorten the Q-T interval, depress the ST segment, and cause ventricular premature contractions that may be coupled or tripled, producing bigeminal or trigeminal rhythms. Hypocalcemia is associated with prolongation of the Q-T interval on the ECG. Hypocalcemia, hyperkalemia, and digitalis excess are the most likely causes of arrhythmias during anesthesia in uremic patients. Finally, the ECG may be of value in diagnosing hypertensive and ischemic heart disease.

These laboratory tests will define the degree of acute or chronic renal impairment that is present. Until approximately 50 percent of renal function is lost, the usual biochemical indices of renal function, except for creatinine clearance, are within normal limits; other signs and symptoms of renal impairment are absent. Patients with this degree of impairment are said to have decreased renal reserve [10] ; their anesthetic management is no different from that of patients with normal renal function.

Renal insufficiency is said to be present when patients have mild azotemia, nocturia, decreased maximum urinary concentrating ability, and slight anemia. Patients in this category require special attention, as further small decrements in renal function could lead to significant deterioration of their condition. Drugs excreted primarily by the kidney may have a clinically discernible, prolonged duration of action.

Renal failure is characterized by progressive anemia, hypocalcemia, hyperphosphatemia, and loss of urinary concentrating and diluting ability. Polyuria, hyponatremia, and hyperchloremia may be present, but hyperkalemia is rare. Creatinine levels in the range of 3.5 to 4.0 mg/100 mL are common, as are creatinine clearance values of 15 to 20 mL/min. The clinical condition of these patients is precarious, and management must be directed at avoiding further loss of renal function. They are unable to adapt to rapid and significant changes in fluid balance, and they run the risk of becoming acutely hypovolemic or fluid overloaded. Further deterioration in renal function will cause them to become grossly uremic and to require hemodialysis to control the signs and symptoms of renal failure. Drugs excreted primarily by the kidney should be avoided, or if they must be given, they should be administered in decreased dosage and/or at prolonged intervals.

Effects of Drugs in Patients With Reduced Renal Function

Most drugs are weak electrolytes and lipid-soluble in the un-ionized state; thus, they are extensively reabsorbed by renal tubular cells (Chs. 18 and 34) . Termination of their action is not dependent on renal excretion; redistribution and metabolism produce this effect. After biotransformation, these drugs are excreted in the urine as water-soluble, polar forms of the parent compound. They are usually pharmacologically inactive, and their retention is not harmful. [11] The majority of drugs with prominent central and peripheral nervous system activity fall into this category, including most narcotics, barbiturates, phenothiazines, butyrophenone derivatives, benzodiazepines, ketamine, and local anesthetics. [11] [12] [13] However, several drugs are relatively lipid-insoluble or are highly ionized in the physiologic pH range and are eliminated unchanged in the urine. Their duration of action may be extended in patients with impaired renal function. Drugs in this category include muscle relaxants, cholinesterase inhibitors, thiazide diuretics, digoxin, and many antibiotics [12] (Table 53-3) (Table Not Available) .

Because patients with severe renal disease often are debilitated, caution should be exercised when administering any therapeutic agent; dosage reductions of 25 to 50 percent are appropriate in most cases. At times, it may not be possible to avoid the administration of certain nonanesthetic drugs, such as digitalis or aminoglycoside antibiotics, excreted primarily or solely by the kidney. Blood concentration determinations of many of these agents are regularly performed in many hospitals. When levels cannot be determined, formulas have been derived for calculation of dosage, based on serum creatinine concentration or creatinine clearance, so that nontoxic therapeutic levels may be maintained. [13] Drugs frequently used by anesthesiologists are considered next.

Drugs Used for Premedication

Barbiturates

Except for phenobarbital, which is still used for premedication for epileptic adults and children, barbiturates are rarely used today (Ch. 8) . Approximately 24 percent of

phenobarbital is excreted in the urine in unchanged form. [14] Little problem is encountered when it is used in this circumstance.

Belladonna Alkaloids (and Their Substitutes)

Approximately 20 to 50 percent of a dose of atropine is recovered unchanged in the urine or in the form of active metabolites. [15] [16] The same is true for quaternary ammonium atropine-like compounds such as glycopyrrolate. [13] Thus, there is a potential for accumulation of these drugs in patients with renal failure, but a single dose will not cause clinical difficulties. Only one-tenth as much scopolamine is recovered from urine as atropine [16] ; however, because of its

TABLE 53-3 -- Drugs Used or Encountered in Anesthesia Practice for Which Renal Excretion Is a Significant Elimination Pathway

(Not Available)

Modified from Prescot LF: Mechanisms of renal excretion of drugs (with special reference to drugs used by anaesthetists). Br J Anaesth 44:246, 1972.

untoward central nervous system (CNS) effects, scopolamine should not be substituted for atropine or glycopyrrolate when large or repeated doses of an antimuscarinic agent are required. As a premedicant, scopolamine is satisfactory for patients with renal failure.

Phenothiazine and Benzodiazepine Compounds

Both phenothiazine and benzodiazepine derivates (Ch. 9) are extensively metabolized in the liver before excretion. [17] [18] Thus, any apparent increased duration or intensity of action associated with their administration is probably related to the general systemic effects of renal failure rather than to specific drug actions. A possible disadvantage of the phenothiazine derivatives is that they produce alpha-adrenergic blockade; this could accentuate cardiovascular instability in recently dialyzed patients who may be hypovolemic.

Opioids

Protein binding of morphine decreases by approximately 10 percent in chronic renal failure (Ch. 10) . [19] This does not result in a significant alteration in the free-fraction of morphine, as it usually is protein-bound to only a small extent (23-42%), and it has a large volume of distribution. [20] Morphine is almost completely metabolized in the liver mostly to the inactive glucuronide, which is then excreted in the urine. [21] [22] Thus, its administration to patients with renal failure, particularly in analgesic doses, should not cause prolonged depression. Nevertheless, a report of severe respiratory and cardiovascular depression in a patient with renal failure was attributed to administration of a single 8-mg dose of morphine. [23] This can be attributed to the accumulation of morphine-6-glucuronide, which possesses opioid activity and is excreted by the kidney. The distribution, protein binding, and excretion of meperidine are similar to those of morphine. [24] [25] Accumulation of its metabolite normeperidine can produce excitatory central nervous system (CNS) effects including convulsions in extreme cases. Fentanyl also is metabolized in the liver, with only 7 percent excreted unchanged

in the urine. [26] [27] It is moderately bound to plasma protein (free fraction, 19 percent), and its volume of distribution is large. [26] [27] Thus, fentanyl should be suitable for premedication of patients with renal failure. The pharmacokinetics and pharmacodynamics of sufentanil and alfentanil are not significantly different in patients with reduced renal function as compared with normal individuals. [28] [29] An ester linkage in remifentanil renders it susceptible to rapid metabolism by blood and tissue esterases. Therefore, the pharmacokinetics and pharmacodynamics of remifentanil are unaltered in patients with renal disease. Although the renal elimination of its principal metabolite is reduced, it is of no clinical significance. [30]

Anesthetic Agents and Adjuvant Drugs

Inhaled Anesthetics

All inhaled anesthetics (Chs. 4 and 6) are biotransformed to some extent, with the nonvolatile products of metabolism eliminated almost entirely by the kidney. [31] However, reversal of the CNS effects of inhaled anesthetics is dependent on pulmonary excretion, so that impaired kidney function will not alter the response to these agents. From the viewpoint of selecting an anesthetic agent that will not be harmful for patients with mild or moderate impairment of renal function, all the modern potent agents are suitable. Methoxyflurane, an inhaled anesthetic of the 1960s and 1970s, was contraindicated in patients with renal disease because of its extensive biotransformation to nephrotoxic inorganic fluoride and oxalic acid. [32] [33] Enflurane is also biotransformed to inorganic fluoride, but levels after 2 to 4 hours of anesthesia average only 19 muM in patients with mild to moderate kidney disease, [34] significantly lower than the nephrotoxic threshold of 50 muM. [33] This level of fluoride should not cause further renal impairment. Fluoride levels after isoflurane increase by only 3 to 5 muM [35] and by only 1 to 2 muM [32] [33] after halothane, so these agents have no nephrotoxic potential.

Desflurane and sevoflurane, the two new inhaled anesthetics, are remarkably different in their molecular stability and biotransformation. Desflurane is highly stable and resists degradation by soda lime [36] and the liver. Even in enzyme-induced animals, the excretion of organic or inorganic fluoride has been shown to be minimal. [37] [38] Mean inorganic fluoride concentration after 1.0 MAC (minimum alveolar concentration)-hour exposure to desflurane was less than 1 mumol/L. [39] In addition, recently developed, more sensitive indices of renal function, namely urine retinol-binding protein and beta-N-acetylglucosaminidase, showed no evidence of renal damage. Prolonged exposure to desflurane (7.0 MAC-hours) has been associated with normal renal function. [40]

Sevoflurane, on the other hand, is not very stable. Soda lime causes its decomposition, [41] and it is biotransformed by the liver to an extent similar to enflurane. There have been reports of plasma inorganic fluoride concentrations approaching nephrotoxic levels (50 mumol/L) [42] [43] after prolonged inhalation of sevoflurane. However, there is no evidence of gross changes in renal function in humans. [44]

Inhaled anesthetics cause a transient reversible depression of renal function. GFR, renal blood flow, urine output, and urinary excretion of sodium are decreased (Table 53-4) (Table Not Available) . Likely mechanisms include reduced renal blood flow, loss of renal autoregulation, neurohumoral factors (e.g., antidiuretic hormone, vasopressin, renin), or neuroendocrine responses. Although most inhalation anesthetics have been shown to reduce GFR and urinary excretion of sodium, their

TABLE 53-4 -- Effects of Various Anesthetics on Renal Function

(Not Available)

From Hemmings HC Jr: Anesthetics, adjuvant drugs and the kidney. In Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996 p 20.

effects on renal blood flow have yielded conflicting results. This can be explained by differences in experimental methodology. Data suggest that renal blood flow is maintained with halothane, isoflurane, and desflurane [45] [46] [47] but decreased with enflurane and sevoflurane. [48] [49]

Patients with severe renal disease frequently have hemoglobin levels of 6 to 8 g/100 mL. Although oxygen-carrying capacity may be adequate in the unanesthetized state, intrapulmonary shunting and reduced cardiac output may occur during general anesthesia. Therefore, to avoid intraanesthetic hypoxemia, it is advisable not to administer high concentrations of nitrous oxide, as might be necessary with balanced anesthetic techniques, unless arterial oxygen saturation can be continuously monitored.

Intravenous Anesthetics

Reversal of CNS effects after administration of ultrashort-acting barbiturates, such as thiopental and methohexital, occurs as a result of redistribution (Chs. 8 to 10) ; hepatic metabolism is the sole route of elimination of these drugs. Thiopental is 75 to 85 percent bound to albumin, [50] the concentration of which may be markedly reduced in uremia. Because it is a highly bound drug, reduced binding permits a greater proportion of an administered dose of thiopental to reach receptor sites. In addition, thiopental is a weak acid, with its pKa in the physiologic range; acidosis will result in more un-ionized, nonbound, active thiopental. In combination, these changes produce an increase in the free fraction of thiopental from 15 percent in normal patients to 28 percent in patients with chronic renal failure. [51] Because the metabolism of thiopental is essentially unchanged in renal disease, the amount of thiopental necessary to produce and maintain anesthesia is reduced. [51] [52] The same considerations are true for methohexital, [53] although metabolism plays a slightly greater part in termination of its therapeutic effect. [54]

There are no reports of the disposition of narcotics and tranquilizers when used in high dosage for anesthesia in uremic patients. These agents are extensively metabolized before excretion so that, in combination with 30 to 50 percent nitrous oxide, they should not have a particularly prolonged effect. Of course, the benzodiazepines, especially diazepam, [18] have a long half-life so they will tend to accumulate in any case. Because uremic patients are anemic and may require high inspired oxygen concentrations and because of the greater ease of reversibility of the potent inhaled anesthetics as compared with the intravenous drugs, inhaled anesthetics may be preferable for the production of general anesthesia.

Muscle Relaxants and Their Antagonists

Succinylcholine has been used without difficulty in patients with decreased or absent renal function (Ch. 12) . Its metabolism is catalyzed by pseudocholinesterase, yielding the nontoxic end products succinic acid and choline. The metabolic precursor of these two compounds, succinylmonocholine, is excreted by the kidney. Thus, large doses of succinylcholine, which might result from prolonged administration of an infusion, should be avoided in patients with renal failure. It has been reported that pseudocholinesterase levels are reduced in uremia. [55] [56] However, values are rarely so low as to cause prolonged block. Hemodialysis has been reported to have no effect on cholinesterase levels. [57] [58]

Succinylcholine administration causes a rapid, transient rise in serum potassium concentration of 0.5 mEq/L. In traumatized, burned, or neurologically injured patients, the increase may be as great as 5 to 7 mEq/L, probably as a consequence of denervation supersensitivity of the muscle membrane to succinylcholine and to acetylcholine. [59] [60] In some instances, cardiovascular collapse has occurred. [59] An exaggerated rise in serum potassium could be particularly dangerous in uremic patients with elevated potassium levels, so that the use of succinylcholine is inadvisable unless the patient has undergone dialysis within 24 hours before operation. If the patient has recently undergone dialysis, the use of succinylcholine is reported to be safe. [61] [62]

The disposition of the nondepolarizing muscle relaxants has been well studied in recent years. In patients with normal renal function, the largest excreted fraction of a dose of *d*-tubocurarine (dTc) is found in the urine (i.e., 45 percent is recovered in 24 hours, with an additional 12 percent recovered in bile. [63] As can be appreciated from examination of the pharmacokinetic data in Table 53-3 (Table Not Available) , excretion of dTc is delayed in patients with renal failure. [64] Clearance is reduced and volume of distribution is unchanged--hence the increased terminal elimination half-life. Because protein binding [65] and sensitivity of the neuromuscular junction to dTc [66] are unchanged in patients with renal failure, the consequence of delayed excretion would be prolonged duration of action. However, this would not be apparent after administration of a single small dose, as redistribution rather than excretion is responsible for termination of action. [67] On the contrary, recovery after a single large dose or several small doses of dTc is directly related to the terminal elimination half-life. Thus, maintenance doses for patients with decreased renal function should be smaller than for patients with normal renal function, the interval between doses should be increased, [20] and administration should be monitored with a nerve stimulator.

Pharmacokinetic data for metocurine [68] and gallamine [69] (Table 53-5) indicate that these agents differ quantitatively rather than qualitatively from dTc. More than 90 percent of an injected dose of gallamine is eliminated unchanged in the urine within 24 hours, whereas only 43 percent of a dose of metocurine is excreted unchanged in that time. Recovery from a small dose of gallamine occurs by redistribution, so theoretically it could be used in patients with reduced renal function. However, prolonged paralysis requiring hemodialysis for reversal has been reported after gallamine administration to a patient with renal failure. [70] The availability of other more suitable muscle relaxants (see later) argues against its use.

Approximately 40 to 50 percent of pancuronium is excreted in the urine. A portion of this occurs after biotransformation to the less active metabolite 3-hydroxypancuronium. [20] [71] [72] Pancuronium has a prolonged terminal elimination half-life in patients with reduced renal function (Table 53-5) , [73] [74] so it should be administered cautiously, particularly when several doses are required.

TABLE 53-5 -- Pharmacokinetic Data for Nondepolarizing Muscle Relaxants in Normal and Anephric Patients

DRUG	PATIENTS STUDIED	ELIMINATION HALF-LIFE (h) (t½ s)	CLEARANCE (L/kg/min)	VOLUME OF DISTRIBUTION (L/kg)	REFERENCE
Vecuronium	Normal	0.9	5.3	0.20	[80]
	Anephric	1.4	3.1	0.24	
Atracurium	Normal	0.3	6.1	0.18	[76]
	Anephric	0.4	6.7	0.22	
d-Tubocurarine (dTc)	Normal	1.4	2.4	0.25	[64]
	Anephric	2.2	1.5	0.25	
Pancuronium	Normal	2.2	1.8	0.26	[73]
	Anephric	4.3	0.9	0.30	
Pancuronium	Normal	1.7	1.0	0.14	[74]
	Anephric	8.2	0.3	0.14	
Metocurine	Normal	6.0	1.2	0.57	[68]
	Anephric	11.4	0.4	0.48	
Gallamine	Normal	2.2	1.2	0.24	[69]
	Anephric	12.5	0.2	0.28	

Two nondepolarizing muscle relaxants, atracurium and vecuronium, were introduced into clinical practice during the early 1980s. After initial reports that the action of neither drug was prolonged in patients with decreased renal function, [75] [76] [77] [78] [79] it now appears that this is only true for atracurium. [80] [81] Atracurium and cisatracurium are broken down by enzymatic ester hydrolysis and by nonenzymatic alkaline degradation (Hofmann elimination) to inactive products and are not dependent on renal excretion for termination of action. [75] Predictably, their terminal elimination half-life (Table 53-5) and indices of neuromuscular block (onset, duration, and recovery) are the same in patients with normal and with absent renal function. [76] [77] Although atracurium may cause histamine release in patients undergoing renal transplantation, this usually does not result in clinical signs or symptoms with doses less than 0.4 mg/kg. [78]

The pharmacokinetics and pharmacodynamics of vecuronium in patients with normal renal function and with renal failure have recently undergone reexamination. [80] [81] There now appears to be general agreement that about 30 percent of a dose of vecuronium is eliminated by the kidneys. Thus, it is not surprising that Lynam et al [80] found that the duration of neuromuscular blockade after administration of vecuronium was longer in patients with renal failure than in those with normal renal function (99 versus 54 minutes), secondary to longer elimination half-life (83 versus 52 minutes) and lower plasma clearance (3.1 versus 5.3 mL/kg/min). In a related area, an interaction between the solvent of cyclosporin, cremophor, and both atracurium and vecuronium, which potentiates the action of these muscle relaxants in

cats, has been reported [82] ; it is not known if this also occurs in human renal transplant recipients.

Of the newer relaxants, doxacurium is a long-acting muscle relaxant, whose duration of action is further prolonged in patients with renal failure. [83] [84] The duration of action of another long-acting muscle relaxant, pipecuronium, shows a large variability in patients with renal failure. [85] The new short-acting drug mivacurium is metabolized by plasma pseudocholinesterase. Its effect has been shown to be lengthened by 10 to 15 minutes in patients with end-stage renal disease; this is most likely due to a decrease in plasma cholinesterase activity in these patients associated with uremia or after hemodialysis. [86] [87] [88] Phillips and Hunter [87] demonstrated a decrease in mivacurium requirement by infusion in the anephric patient.

The elimination half-life of rocuronium is increased in renal failure due to an increase in volume of distribution with no change in clearance. This may explain a somewhat longer duration of action in anephric patients, although its clinical significance is uncertain. [89]

In summary, the pharmacokinetic data in Table 53-3 (Table Not Available) indicate that for agents excreted by the kidney (i.e., all drugs except cisatracurium and atracurium) lower doses and a longer dosing interval are appropriate for maintenance of neuromuscular blockade in patients with abnormal renal function. Additionally, a clinical monitor of neuromuscular function, such as a train-of-four nerve stimulator, is useful in most cases.

Pharmacokinetic data for the cholinesterase inhibitors neostigmine, pyridostigmine, and edrophonium for normal, anephric, and renal transplant recipients are presented in Table 53-6 ; there are no major differences among the three drugs. [90] [91] [92] Renal excretion is of major importance for the elimination of all three agents, with approximately 50 percent of neostigmine and 70 percent of pyridostigmine and edrophonium excreted in the urine. The excretion of all the cholinesterase inhibitors is delayed in patients with impaired renal function to the same or perhaps to a slightly greater extent than is the elimination of the muscle relaxants. Thus, "recurarization" after reversal of neuromuscular block in a patient with renal failure in most cases is due to some other cause, such as an interaction of the residual muscle relaxant with an antibiotic or a diuretic. Of interest in Table 53-4 (Table Not Available) are the data that indicate that the pharmacokinetics of all the cholinesterase inhibitors are similar in normal patients and in those with well-functioning newly transplanted kidneys. Similar findings have been reported for dTc pharmacokinetics, [66] and they probably also hold for pancuronium disposition. Thus, as a category, transplant recipients with well-functioning kidneys can be considered normal in the way they eliminate renally excreted drugs. However, there is sufficient interindividual variability in

TABLE 53-6 -- Pharmacokinetic Data for Cholinesterase Inhibitors in Normal, Anephric, and Renal Transplant Patients

DRUG	PATIENTS STUDIED	ELIMINATION HALF-LIFE (h) ($t_{½}$ s)	CLEARANCE (mL/kg/min)	VOLUME OF DISTRIBUTION (L/kg)	REFERENCE
Neostigmine	Normal	1.3	8.4	0.7	[90]
	Anephric	3.0 [a]	3.9 [a]	0.8	
	Renal transplant	1.7	9.4	1.1	
Pyridostigmine	Normal	1.9	8.6	1.1	[91]
	Anephric	6.3 [a]	2.1 [a]	1.0	
	Renal transplant	1.4	10.8	1.0	
Edrophonium	Normal	1.9	8.2	0.9	[92]
	Anephric	3.6 [a]	2.7 [a]	0.7	
	Renal transplant	1.4	9.9	0.9	

[a] $P < .05$ versus normal.

these data to indicate that treatment with muscle relaxants and their antagonists should be individualized, as indicated by clinical signs and by the results of tests with a nerve stimulator.

Digitalis

Digoxin is the most frequently used digitalis glycoside in both uremic and nonuremic patients. Approximately 72 percent of a parenteral dose is excreted unchanged in the urine. [93] Thus, its administration to patients with reduced renal function is potentially dangerous, and maintenance doses must be reduced in proportion to the reduction in renal function. Ultimately, blood digoxin levels are the most reliable guide to therapy (therapeutic level, >0.8 ng/mL; toxic level, >1.8 ng/mL). [94] Whenever possible, initial digitalization or changes in digitalis dosage should be avoided immediately before surgery.

Vasopressors and Antihypertensive Agents

Patients with severe renal disease frequently are given antihypertensive and other cardiovascular medications (Ch. 14) . More than 90 percent of the thiazides [14] [95] and 70 percent of furosemide [91] are excreted by the kidney and have prolonged durations of action in patients with abnormal or absent renal function. Propranolol is almost completely metabolized in the liver, and esmolol is biodegraded by the esterases in the cytosol of red blood cells, so their effects are not prolonged in patients with abnormal or absent renal function. [97] The calcium channel blocking agents nifedipine, verapamil, and diltiazem are extensively metabolized in the liver to pharmacologically inert products; they may be administered in usual doses to patients with renal insufficiency. [98] Among the older agents, methyldopa may have a prolonged duration of action because it is excreted unchanged in the urine. [99] Methyldopa acts by reducing both central and peripheral norepinephrine levels; it interacts with anesthetic agents to cause a reduction in MAC. [100] Guanethidine is excreted almost completely by the kidney, much of it in active form. [101] Guanethidine administration results in a reduction of peripheral, but not central, norepinephrine stores; it does not alter MAC.

During anesthesia, if arterial blood pressure reduction is necessary, several drugs may be used safely. Trimethaphan (Arfonad), a ganglionic blocking agent, is suitable because its action is terminated enzymatically rather than by renal excretion. Nitroglycerin is useful as it is rapidly metabolized, with less than 1 percent excreted unchanged in the urine. [102] Sodium nitroprusside has had a resurgence in use because its initial introduction as a hypotensive agent in the 1920s. Cyanide is an intermediate in the metabolism of sodium nitroprusside, with thiocyanate the final metabolic product. Whereas cyanide toxicity as a complication of sodium nitroprusside therapy is well described, [103] it is less well appreciated that thiocyanate is also potentially toxic. The half-life of thiocyanate is normally more than 4 days, and it is prolonged in patients with renal failure. [103] Hypoxia, nausea, tinnitus, muscle spasm, disorientation, and psychosis have been reported when thiocyanate levels exceed 10 mg/100 mL. Thus, sodium nitroprusside is less desirable for prolonged administration than either trimethaphan or nitroglycerin. Hydralazine is slower acting than the other three agents discussed previously, but it is often used for postoperative blood pressure control. Its action is terminated by hydroxylation and subsequent glucuronidation in the liver, with approximately 15 percent excreted unchanged in the urine. [104] The elimination half-life of hydralazine is prolonged in uremic patients, so caution is required when it is administered. [105] Following a single intravenous dose of 0.5 mg/kg of labetolol, the volume of distribution, clearance, and the elimination half-life were similar in patients with end-stage renal disease and normal volunteers. [106] Esmolol is independent of renal function as it is metabolized by red blood cell cytosol esterases. [107]

If administration of a vasopressor is necessary, a direct alpha-adrenergic-stimulating drug, such as phenylephrine, will be effective. Unfortunately, this type of vasopressor causes the greatest interference with renal circulation. Although beta-adrenergic-stimulating drugs, such as isoproterenol, maintain heart and brain perfusion without renal vasoconstriction, they also increase myocardial irritability. Therefore, when possible it is best to substitute simple measures

such as blood volume expansion for drug therapy. If these measures are inadequate, alpha-adrenergic-stimulating drugs or dopamine should be used.

Psychotropic Drugs

Monoamine oxidase inhibitors occasionally are used by patients with renal disease to counteract mental depression. Cardiovascular instability may occur in anesthetized patients treated with these drugs. [108] Their effect in uremic anesthetized patients is unknown.

Acute Renal Failure and Hemodialysis

Acute Renal Failure

The following material is provided as background information for consideration of the anephric patient and the patient undergoing renal transplantation.

Acute renal failure is defined as the sudden inability of the kidneys to vary urine volume and content appropriately in response to homeostatic needs. Synonymous terms are acute tubular necrosis and lower nephron nephrosis. The three major types of acute renal failure when classified according to their predominant etiologic antecedents are prerenal (i.e., owing to acute circulatory problems that impair renal perfusion); renal, (i.e., owing to primary or secondary renal disease, toxins, and pigments); and postrenal (i.e., owing to obstruction of the urinary tract.) [109] Common prerenal, renal, and postrenal causes of perioperative oliguria are listed in Table 53-7 (Table Not Available) . Prerenal failure is usually reversible if the circulatory status is promptly improved; postrenal failure is reversible when the obstruction is removed. Acute renal failure due to primary renal disease is the most serious of the three types and most often requires hemodialysis. [110]

Renal failure also is classified according to urine flow rates, so the terms *oliguric, nonoliguric,* and *polyuric renal failure* often are encountered. The diagnosis of acute oliguric renal failure is made when creatinine and blood urea nitrogen concentrations progressively increase while urine flow remains below 20 mL/h in an adequately hydrated patient who has a stable blood pressure and a patent urinary outflow tract. Urine and blood chemistry values are as indicated in Table 53-8 . In some cases, patients with acute renal failure may have normal or high (>2.5 L/d) urine flow rates, but they have biochemical abnormalities that are similar to

TABLE 53-7 -- Perioperative Causes of Oliguria

(Not Available)

those occurring in patients with low urine output. [111] Their management is less complex than that of oliguric patients because adequate drug therapy and proper nutrition are easier to maintain owing to the less stringent limitations on daily fluid intake.

The major problem arising from acute renal failure is the inability to maintain the dynamic balance between dietary intake of essential substances and production of waste products. This results in (1) a progressive rise in serum urea, creatinine, uric acid, magnesium, sulfate, phosphate, some amino and organic acids, and polypeptides; (2) a daily rise in serum potassium of 0.3 to 3 mEq/L except when there is concomitant potassium loss from diarrhea or vomiting (greater increases may occur in traumatized or postsurgical patients); (3) a decrease in serum sodium and calcium; (4) a decrease in serum proteins, particularly albumin; (5) a consistent increase in total reducing substance in the serum, frequently occurring with true hyperglycemia, which may be either sensitive or resistant to insulin; (6) elevation of total

TABLE 53-8 -- Urinary Composition in Oliguria

	PHYSIOLOGIC OLIGURIA	PRERENAL FAILURE	ACUTE TUBULAR NECROSIS
Urinary sodium	<10 mEq/L	<25 mEq/L	>35 mEq/L
Urinary specific gravity	>1.024	>1.015	1.010-1.015
Urinary osmolality	>700 mOsm/kg	>500 mOsm/kg	<350 mOsm/kg
Urinary/plasma osmolality	>2.5:1	>1.8:1	1.1:1
Urinary/plasma urea	>100:1	>20:1	3:1, rarely >10:1
Urinary/plasma creatinine	>60:1	>30:1, rarely <10:1	<10:1
Fractional sodium excretion	>0.5	<1	>1

lipids, cholesterol, phosphorus, and neutral fats; and (7) metabolic acidosis. The kidney functions both as an endocrine and as an excretory organ. Thus, disorders of renin-angiotensin and aldosterone secretion occur, contributing to the hypertension that develops in patients with severe renal disease. Reduced erythropoietin production leads to anemia. Heart failure and abnormalities in liver function and blood coagulation also may occur in patients with renal shutdown. Infection is common and difficult to treat because the altered excretion of antibiotics leads to rapid development of toxic levels of these drugs.

Once established, oliguria is usually present for 10 to 18 days but may persist for as long as 30 to 45 days. During this period, hemodialysis is required every 2 to 4 days. When diuresis occurs, the beginning of the recovery phase is signaled. During the diuretic phase, urine volume gradually increases until as much as 5 to 6 L of urine is produced daily. Management of the patient is directed at maintaining fluid and electrolyte balance in the face of these large losses. Finally, concentrating ability gradually returns toward normal. There is a complete return of all measurable parameters of renal function in approximately two-thirds of patients who survive. However, 50 to 60 percent of patients with acute renal failure do not survive long enough to recover or to develop chronic renal failure. [112] Arrhythmias, bleeding, and infection are the most frequent causes of death. Analyses of outcome indicate that the overall mortality rate from acute renal failure has not been significantly reduced in recent years despite earlier and more frequent dialysis. In fact, it is likely that there has been an increase in the survival rate of some categories of patients with the absence of a change in the overall rate due to an increase in the proportion of seriously ill patients who are now treated in dialysis units. This conclusion is suggested by the steady improvement in mortality data of obstetric patients with renal failure. The low (15%) mortality rate for this group emphasizes that the most significant feature determining survival is the physical status of the patient before the onset of renal failure.

As noted earlier, many patients with acute renal failure [111] have normal or high urinary flow rates. In these patients, the antecedent cause of renal failure may be the same as in patients with classic oliguric renal failure, but an oliguric or anuric phase is not identifiable. Patients are unable to alter urinary volume and content appropriately, with average daily output often in excess of 2.5 L/d. The higher incidence of nonoliguric and polyuric renal failure in recent years as compared with the 1940s and 1950s is thought to be due, in part, to more vigorous early treatment of patients with incipient oliguric renal failure. The majority of patients who suffered renal dysfunction following methoxyflurane anesthesia had normal or high urinary output. [33] [113]

Hemodialysis

The steady improvement in hemodialysis techniques (Ch. 55) from the first artificial kidney developed in 1944 by Kolf and Berk [114] to the current practice of home dialysis has resulted in additional years of productive life for patients with chronic renal failure. That, coupled with the 1976 federal legislation that extended Medicare coverage to renal failure patients, has resulted in a large increase in the number of hemodialysis patients in recent years. Many of these patients ultimately require anesthesia not only for renal transplantation but for surgical procedures unrelated to their renal disease. Dialysis improves most of the signs and symptoms of uremia (e.g., volume overload, acid-base and electrolyte imbalance, abnormal mental function, peripheral neuropathy, muscle weakness, and defective coagulation). Hypertension is improved except in those patients with high renin levels. Some patients have been hemodialyzed for more than 10 years. The 3-year survival rate for

U.S. patients aged 20 to 25 years treated by hemodialysis is 85 percent; for those aged 60 to 65 it is 60 percent.

Presently, two basic dialysis techniques are used: peritoneal dialysis, either chronic intermittent or continuous ambulatory, both performed at home; and chronic intermittent hemodialysis, performed at home or at a dialysis center. In most circumstances, hemodialysis is used, and it is generally the method of choice. However, peritoneal dialysis is preferred for patients who have had (1) recent cerebral surgery or a cerebral vascular accident or trauma, as the risk of fluid shifts or bleeding following heparinization is greater with hemodialysis; (2) recent cardiac surgery or a myocardial infarction, as the risk of hypotension and arrhythmias is greater with hemodialysis; (3) a recent acute hemorrhage; or (4) a severe coagulopathy. It also is frequently used in children.

The dialysis principle involves equilibration of waste products in the patient's blood across a semipermeable membrane to the dialysis bath. Peritoneal dialysis relies on the patient's peritoneum as the exchange membrane, avoiding the need for vascular cannulae and expensive equipment. Exchange volumes during peritoneal dialysis are 1 to 3 L/h. Clearance of small molecules is less than with hemodialysis (e.g., urea, 25 mL/min versus 150 mL/min), but clearance of large molecules is greater. The ionic content of the dialysate may be altered to suit the patient's needs, and the fluid may be hypertonic or hypotonic to plasma to remove or add fluid to the patient's extracellular fluid volume, respectively. Peritoneal dialysis is less efficient than hemodialysis, so dialysis times are longer. Also, peritonitis is a danger, and pain during dialysis may be severe. Future refinements may make this a more acceptable form of chronic dialysis.

Hemodialysis is by far the most common dialysis technique used today. Originally, Teflon shunts were inserted between the radial artery and a forearm vein with a connector between them, allowing access to the circulation. Today, vascular access is usually obtained by creation of an end-to-side arteriovenous fistula in the forearm or by insertion of a prosthetic arteriovenous (AV) graft when the vessels are inadequate. During hemodialysis, which is performed two or three times weekly, both the patient and the external circuit are heparinized to prevent clotting. Flow rates are usually 500 mL/min, so the patient's blood is exposed to 120 L of fluid during a standard 4-hour dialysis. Variation of the ionic content and osmolarity of the dialysate permit correction of abnormalities in fluid and electrolyte balance. However, if fluid and electrolyte shifts are too rapid, dialysis disequilibrium may occur. This syndrome is characterized by weakness, nausea, vomiting, and occasionally, convulsions and coma. In the interval between treatments, clotting does not occur because the shunted circuit is short and blood flow is rapid (150-300 mL/min).

Local infiltration, axillary block, and general anesthesia have been successfully used for creation of AV fistulas (Chs. 42 and 43) . Several anesthetic precautions are appropriate. Uremic patients may be debilitated, in which case smaller doses of all drugs, including local anesthetics, should be administered. Hyperkalemia, acidosis, and overhydration can combine to cause myocardial irritability; therefore, local anesthetic solutions that contain epinephrine should be used with caution. If epinephrine is used, concentrations greater than 1,200,000 are not necessary and solutions as dilute as 1,400,000 are probably adequate. Brachial plexus block may greatly facilitate introduction of cannulae by producing analgesia combined with peripheral vasodilation. Of interest, Bromage and Gertel [115] reported that brachial plexus block had a 38 percent shorter duration in renal failure patients than in those with normal renal function. However, this finding could not be confirmed in a recent study of renal failure patients. [116]

RENAL AND GENITOURINARY PROCEDURES

Transurethral Resection of the Prostate

Transurethral resection of the prostate (TURP) is one of the most commonly performed surgical procedures in men older than 60 years of age. The operation is performed through a modified cystoscope and consists of excising the hypertrophied lateral and median lobes of the prostate gland with an electrically energized wire loop; bleeding is controlled with a coagulating current. Continuous irrigation is used to distend the bladder and to wash away blood and dissected prostatic tissue.

Absorption of Irrigating Solution

Because the prostate gland contains large venous sinuses, it is inevitable that irrigating solution will be absorbed. Simple principles govern the amount of absorption: (1) the height of the container of irrigating solution above the surgical table determines the hydrostatic pressure driving fluid into prostatic veins and sinuses, and (2) the time of resection is proportional to the quantity of fluid that is absorbed. On average, 10 to 30 mL of fluid is absorbed per minute of resection time, with as much as 6 to 8 L absorbed in some cases lasting up to 2 hours. [117] [118] Whether patients suffer complications as a consequence of absorption of irrigating fluid depends on the amount and type of fluid absorbed. [119]

For many years distilled water was used for bladder irrigation during TURP, as it interfered least with visibility. However, absorption of large quantities of water led to dilutional hyponatremia, which resulted in hemolysis of red blood cells and CNS symptoms, ranging from confusion to convulsions and coma. Because of this, distilled water was abandoned in favor of isosmotic or near isosmotic solutions for TURP. Solutions such as normal saline and Ringer lactate would be well tolerated when absorbed intravascularly, but these electrolyte solutions are highly ionized and facilitate dispersion of high-frequency current from the resectoscope. Thus, solutions of nonelectrolytes, such as glucose, urea, glycine, mannitol, sorbitol, or Cytal (a combination of mannitol and sorbitol), have replaced distilled water. Today, glycine and Cytal are the two most commonly used irrigating solutions for TURP. [120] [121]

Replacement of distilled water with near isosmotic solutions has eliminated hemolysis and its sequelae as a complication of TURP. Also, the incidence of severe CNS problems, such as convulsions and coma, associated with extreme hyponatremia has been reduced. However, the other major problem associated with absorption of large volumes of irrigating solution, overhydration, still remains. Under usual conditions, only 20 to 30 percent of a load of crystalloid solution remains in the intravascular space; the remainder enters the interstitial space. When intravascular pressure is increased, movement of fluid into the interstitial space and development of pulmonary edema are favored. Whether a given patient will develop symptoms of circulatory overload depends on his or her cardiovascular status, the amount and rapidity of absorption of irrigating fluid, and the extent of surgical blood loss. It is obvious that the situation is dynamic and that patients must be monitored carefully. In this regard, spinal or epidural anesthesia, supplemented with only light intravenous sedation, has the advantage of allowing the patient's subjective judgment to contribute to the assessment of his or her condition during operation. In addition, cardiovascular depression associated with administration of the potent inhaled anesthetics is avoided. Another advantage of regional anesthesia is that the sympathetic block it produces increases venous capacitance and tends to mitigate intraoperative fluid overload. A note of caution: when the block dissipates, venous capacity acutely decreases and circulatory overload can occur.

Yet another advantage of regional anesthesia for TURP is that it allows early recognition of bladder perforation, which occurs in less than 1 percent of cases. If bladder perforation occurs, patients complain of back pain, abdominal pain, or shoulder pain, depending on the site of perforation and the resultant collection of fluid intra- or retroperitoneally. It is of utmost importance to the spinal block level to T10 or below or else this very advantage is lost because the patients would no longer sense the abdominal or back discomfort. The use of nonelectrolyte isosmotic irrigating solutions has reduced the incidence of severe CNS complications because extreme extracellular fluid hypoosmolality does not occur and the subsequent development of cerebral edema is avoided. That CNS symptoms occur at all is probably because the incidence and extent of hyponatremia are unchanged. It is now proposed that the TURP syndrome occurs if hyponatremia is accompanied by hypoosmolality and that CNS signs and symptoms usually do not manifest themselves if the osmolality remains normal. Glycine, urea, mannitol, and sucrose found in irrigating solutions tend to retain near normal osmolality. [122] The concentration of extracellular sodium must be in the physiologic range for depolarization of excitable cells and for production of the action potential. When extracellular sodium levels fall below 100 mEq/L, consciousness is lost and convulsions may ensue. [123] Signs and symptoms of cardiovascular dysfunction secondary to hyponatremia also may occur, such as arrhythmias, hypotension, and pulmonary edema. [124] However, it is often impossible to separate the latter events from those due to fluid overload.

Since the early 1980s, attention has turned to the absorption of glycine (HO_2-CCH_2-NH_2), a nonessential amino acid, as a possible cause of some of CNS symptoms associated with TURP. For example, in one publication, five cases of transient blindness were attributed to glycine toxicity. [125] Glycine has a distribution similar to that of gamma-aminobutyric acid, the latter an inhibitory transmitter in the brain; it has been suggested that glycine also is a major inhibitory transmitter acting in the spinal cord, brain stem, and retina. Glycine induced blindness is usually partially accompanied by widely dilated pupils, absent light and accommodation reflexes but preserved blink reflex. In contrast, cortical blindness is total with loss of blink reflex but preservation of light and accommodation reflexes. [126] Normal plasma glycine levels are 13 to 17 mg/L, whereas levels as high as 1,029 mg/L were measured during one episode of blindness. [125] Twelve hours later, the glycine level in this case had fallen to 143 mg/L, by which time vision had returned. However, an overall correlation between plasma glycine levels and CNS toxicity has not been established, so the relationship, although interesting, must still be considered speculative.

Absorption of glycine may result in CNS toxicity as a result of its oxidative biotransformation to ammonia. [127] [128] In a report of delayed awakening after TURP in three patients, [127] an association with elevated blood ammonia concentrations was noted. Blood ammonia levels as high as 500 muM were noted in this and in another case report. [128] Deterioration of CNS function is said to occur when ammonia levels exceed 150 M. In a prospective study examining glycine metabolism, blood ammonia levels were increased postoperatively in 12 of 26 patients in whom 1.5 percent glycine was used as the irrigating solution for TURP. [127] Blood glycine levels also were measured. Interestingly, glycine and ammonia levels did not correlate; in fact, the opposite relationship was prevalent. Furthermore, high ammonia levels were not necessarily associated with CNS symptoms of toxicity. Although the investigators postulated that delayed awakening and other CNS symptoms were due to ammonia toxicity, it is not at all clear that this is correct.

Perforation

Another relatively common complication of TURP is perforation of the bladder. [129] Perforations usually occur during difficult resections and are most often made by the cutting loop or knife electrode. Some, however, are made by the tip of the resectoscope, whereas others may result from overdistention of the bladder with irrigation fluid. Most perforations are extraperitoneal, and in the conscious patient they result in pain in the periumbilical, inguinal, or suprapubic regions; additionally, the urologist may note the irregular return of irrigating fluid. Less often, the perforation is through the wall of the bladder and is intraperitoneal, or a large extraperitoneal perforation may extend into the peritoneum. In such cases, pain may be generalized, in the upper abdomen, or referred from the diaphragm to the precordial region or the shoulder. Other signs and symptoms such as pallor, sweating, abdominal rigidity, nausea, vomiting, and hypotension have been reported;

their number and severity depend on the location and size of the perforation and the type of irrigating fluid. In an early series of 2,015 cases that examined the incidence of complications of TURP, perforation occurred in 25 patients (1.1 percent). [130] A multicenter study conducted 25 years later confirms this. Four deaths and five additional major complications occurred in the 12 patients in whom suprapubic cystostomy was delayed more than 2 hours after perforation. Distilled water was the bladder irrigant in most of these cases, so it is not clear whether these morbidity and mortality data still are relevant. The subject of complications associated with transurethral surgery was reviewed by Marx and Orkin [117] in 1962; their discussion of the topic is still valid today. [131]

Transient Bacteremia and Septicemia

The prostate harbors many bacteria, which can be a source of intraoperative and postoperative bacteremia via the prostatic venous sinuses. This risk is further increased by the presence of an indwelling urinary catheter. Bacteremia is usually asymptomatic and easily treated with commonly used antibiotic combinations that are effective against gram-positive and gram-negative bacteria. In 6 to 7 percent of patients, however, septicemia may occur. [132] Common manifestations include chills, fever, and tachycardia. In severe cases, bradycardia, hypotension and cardiovascular collapse may occur, with mortality rates between 25 and 75 percent.

Irrigating fluids stored at room temperature are frequently used during TURP. Heat loss due to irrigation and significant absorption of this fluid may result in a decrease in the patient's body temperature and cause shivering (Ch. 37) . [133] Use of warmed irrigating solutions has been shown to be efficacious in reducing this heat loss and the resultant shivering. [134] Although one may believe that warming of fluids might cause increased bleeding due to vasodilation, such is not the case, as shown by the study of Heathcote and Dyer. [135]

Bleeding and Coagulopathy

Hypertrophied prostate is highly vascular, and operative bleeding is usually significant (Ch. 46) . The blood is washed into the draining bucket and mixed with ample quantities of irrigant fluid. Hence, estimation of blood loss is quite inaccurate and extremely difficult. Efforts have been made to quantify blood loss based on resection time (2-5 mL/min of resection time) and size of the prostate in grams (20-50 mL/g). However, these guidelines are rough estimates at best, and the patient's vital signs and serial hematocrit levels should be followed to better assess the blood loss and the need for transfusion. Because alpha-adrenergic receptors are abundant in the prostate tissue, the use of alpha-adrenergic agonists would cause vasoconstriction of prostatic blood vessels and a decrease in blood loss. In a 1993 study, the blood loss during TURP was reduced by 50 percent with preoperative use of methoxamine. [136]

Abnormal bleeding after TURP occurs in less than 1 percent of cases. It is believed by some to be due to systemic fibrinolysis caused by plasmin. The prostate releases plasminogen activator, which converts plasminogen into plasmin. Others believe that the fibrinolysis is secondary to disseminated

intravascular coagulation triggered by the systemic absorption of resected prostate tissue, which is thromboplastin-rich. [131] If primary fibrinolysis is suspected, aminocaproic acid may be effective when given intravenously in a dose of 4 to 5 g in the first hour followed by 1 g/h. [131]

TURP Syndrome

TURP syndrome is a term applied to a constellation of symptoms and signs caused primarily by excessive absorption of the irrigating fluid. Neurologic manifestations such as restlessness, agitation, confusion, altered sensorium, seizure, and coma result from water intoxication and dilutional hyponatremia, which collectively produce cerebral edema. Neurotoxic effects of glycine and ammonia may further compound the clinical situation. The cardiovascular effects reflect volume overload and hyponatremia. Hypertension and bradycardia are frequently seen because of acute hypervolemia. If serum sodium levels rapidly decrease to less than 120 mEq/L, negative inotropic effects are manifest as hypotension and ECG changes of widened QRS complexes and ventricular ectopy. [131] [137] Pulmonary edema, congestive heart failure, and cardiorespiratory arrest have been reported in these patients.

The treatment of TURP syndrome consists of fluid restriction and a loop diuretic such as furosemide. Hypertonic saline (3 percent sodium chloride) is rarely if ever necessary and should be considered only in cases of severe hyponatremia. CNS complications of hypertonic saline include cerebral edema and pontine myelinolysis. [131] [137] [138]

Anesthetic Technique

Spinal anesthesia is the most frequently used anesthetic for TURP in the United States [138] and is believed to be the technique of choice by many. Anesthetic level to T10 is required. A spinal anesthetic provides adequate anesthesia for the patient and good relaxation of the pelvic floor and the perineum for the surgeon. The signs and symptoms of water intoxication and fluid overload can be recognized early because the patient is awake. Accidental bladder perforation also is recognized easily if the spinal level is limited to T10 because the patient would experience abdominal or shoulder pain.

General anesthesia may be necessary in patients who require ventilatory or hemodynamic support. In a 1990 study, [139] blood loss was less with spinal than with general anesthesia. However, short-term morbidity and mortality and long-term outcome for TURP are similar for both regional and general anesthesia. [140] [141]

Anesthetic considerations for TURP should include positioning. TURP is usually performed in the lithotomy position with a slight Trendelenburg tilt. This would result in changes in pulmonary blood volume, a decrease in pulmonary compliance, a cephalad shift of the diaphragm, and a decrease in lung volume parameters such as residual volume, functional residual volume, tidal volume, and vital capacity. Cardiac preload may increase. Nerve injuries to the common peroneal, sciatic, and femoral nerves are likely (Ch. 26) .

Laser Surgery

Lasers (Ch. 64) have recently been introduced into urologic surgery and are being used increasingly. Anesthetic considerations for laser surgery are considered elsewhere; specific concerns pertaining to urologic surgery are discussed here.

Laser Lithotripsy

Laser lithotripsy is used for ureteral stones that are low in the ureter and not amenable to extracorporeal shock wave lithotripsy. Pulsed dye laser is generated with a laser beam of 504 nm wavelength passing through an organic green dye. [142] This laser beam is easily absorbed by the stones, releasing pulsatile energy that causes their disintegration. The beam is carried over a bare wire passed through a rigid ureteroscope, which is longer and more pointed than a cystoscope, so that the risk of ureteral perforation exists. General anesthesia should be maintained to avoid patient movement. For regional anesthesia, a spinal level of T8 to T10 is required. The bare laser wire is sharp and can cause mucosal injury to the ureter. However, these lasers are not well absorbed by the red blood cells or other tissues, which provides safety against tissue coagulation or thermal injury. Because the laser beam is reflective, the user, the other personnel, and the patient should wear protective eyeglasses. Some hematuria always occurs; hence, good intravenous hydration is recommended. [143]

Laser Prostatectomy

Recently approved by the Food and Drug Administration for clinical use, laser prostatectomy is being conducted in several centers in clinical trials. Based on initial experience, it promises to replace conventional TURP in many cases in the near future. The neodymium: yttrium-aluminum-garnet (Nd:YAG) laser is used, which produces coagulation and vaporization of prostate tissue. The main advantages over conventional TURP include minimal blood loss (as little as 50-70 mL) and minimal fluid absorption, which should nearly eliminate these two major complications of TURP. For these reasons, laser prostatectomy is frequently conducted in patients otherwise considered too ill to undergo TURP. In critically ill patients, caudal anesthesia has been successfully used for laser prostatectomy because the use of continuous irrigation combined with minimal bleeding obviates copious irrigation and minimizes bladder distention. [144] However, other potential complications are introduced, including coagulation through the prostatic fossa and sloughing of prostatic debris in the postoperative period, with urinary obstruction and urinary retention. Once again, protective eyewear should be used, and a means to evacuate the smoke plume should be used.

Pelvic lymph node dissection is the most commonly performed laparoscopic urologic procedure in adults. Other

urologic procedures for which laparoscopy has been used include variocelectomy, hernia repair, adrenalectomy, percutaneous stone retrieval from the renal pelvis or ureter, and nephrectomy. Although all the conventional complications and concerns of laparoscopy are applicable to the urologic procedures (Ch. 56) , two unique problems are also identified. First, because the urogenital system is mainly retroperitoneal, the large retroperitoneal space and its communications with thorax and the subcutaneous tissue are exposed to the insufflated carbon dioxide. Subcutaneous emphysema in these patients is frequent and may extend all the way up to the head and neck. The upper airway is at risk of compromise in the most severe cases because of pharyngeal swelling due to submucous carbon dioxide. This should be kept in mind before extubation of these patients. Second, the procedures tend to be lengthy, thus allowing for sufficient absorption of carbon dioxide to result in acidemia and marked acidosis. [145] Because of significant increases in intra-abdominal and intrathoracic pressures due to insufflated carbon dioxide, a steep Trendelenburg position, and lengthy procedures, general anesthesia with controlled ventilation is the method of choice. Despite adequate hydration, intraoperative oliguria may occur followed by diuresis in the immediate postoperative period. While the exact mechanism for this is unclear, it is believed to be due to an increased perirenal pressure exerted by the insufflated gas in the retroperitoneal space.

Extracorporeal Shock Wave Lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) was first conducted in Munich, Germany in 1980, and in 1984 the lithotripter was introduced into the United States. Since then, ESWL has become the treatment of choice for disintegration of urinary stones in the kidney and upper ureter. The first clinical model of the lithotripter introduced into common practice (Dornier HM-3) uses a water bath in a steel tub and a metal gantry chair to support the patient suspended in a sitting position. This, the first-generation lithotripter, is still commonly used and presents complex challenges of immersion physiology and monitoring difficulties. Second- and third-generation lithotripters (Siemens, Lithostar, Wolf Piezolith, Dornier HM-4, MFL 5000, etc.) have since been developed and introduced into clinical practice. They have evolved mainly in the direction of eliminating the water bath and producing a pain-free lithotripter. However, all lithotripters share similar technologic principles in having three main components: (1) an energy source, most commonly a spark plug (alternatively an electromagnetic membrane or piezoelectric elements may be used in some machines); (2) a system to focus the shock wave, such as an ellipsoid or reflecting mirrors; and (3) a system to visualize and localize the stone in focus, namely fluoroscopy or ultrasound. [146]

Technical Aspects

The Dornier HM-3 lithotripter, the gold standard, uses a water bath for treatment and x-ray equipment to localize the stone. These are contained in the all too familiar steel tub. The patient is strapped in a gantry chain in a semisitting position, with support under the shoulders and hips and with the flank exposed. The chair is hoisted to the ceiling, travels on ceiling rails, and is then slowly lowered into the tub. The patient is immersed in the water up to the clavicles. An electrode (or spark plug) is placed in the water at the base of the tub in an ellipse and is connected to a generator that supplies 16 to 24 kV of electricity. The electrical energy creates a spark across the gap in the electrode with generation of a loud noise, intense heat, and explosive vaporization of water. The sudden expansion of air bubbles thus created sets up a pressure wave (shock wave) with distinct mechanical and acoustic properties. The shock wave is focused by the ellipse to a focal point called the Fz focus (the tip of electrode is the first focus). The shock wave travels through water and body tissues without significant localized dissipation of energy because the acoustic impedance of the two media is similar. However, when the shock wave arrives at the entry surface of the stone, it encounters a sudden change in impedance, causing it to release compressive energy of the magnitude of several atmospheres. Similarly, when the wave exits on the opposite surface of the stone, an interface is again encountered, and shock wave energy is released in a blast. Repeat applications cause the stone to disintegrate. Shock wave energy is most concentrated in the Fz focal zone and rapidly decreases beyond it. [147] [148] [149] These physical properties of the shock wave must be understood to prevent injury to tissue or to any prostheses and to ensure that the shock wave passes unimpeded to its focal point for most effective lithotripsy results. The following discussion elucidates this further.

Biomechanical Effects of Shock Wave

For shock waves to be most effective, the stone should remain in the Fz focus during treatment. [149] Pressure energy measurements show an exponential decrease beyond this small focal zone. The kidneys and hence the kidney stone follow the up-and-down movements of the diaphragm during respiration. It is likely, therefore, that the stone will move in and out of focus during respiration. This issue has been studied, and innovative ventilatory techniques have been tried to minimize stone movement during ventilation. [150] [151] [152] [153] [154] [155] High-frequency jet ventilation has been shown to decrease stone movement and has been claimed to increase the efficacy of the treatment. [151] High-frequency conventional ventilation using fast respiratory rates and small tidal volumes has also been effective in decreasing stone excursions during respiration. [155] However, other data [156] and wide clinical experience with success rates of lithotripsy do not support or justify the routine use of these techniques, which add their own complexity and complications to the procedure. [153] Furthermore, regional anesthesia and analgesia-sedation are frequently used for lithotripsy, in which case spontaneous ventilation is the only option. Studies in sedated patients with intercostal block and local infiltration anesthesia have documented that the stone movement with spontaneous respiration is mainly restricted to the Fz focal zone during ESWL. [157] Therefore, conventional ventilation during general anesthesia or spontaneous respiration during

regional anesthesia is acceptable for lithotripsy. Occasionally in an awake patient, one may have to carefully titrate sedation or, if the patient is under general anesthesia, may need to manipulate respiratory parameters to decrease abnormally large stone movement.

For effective stone disintegration, shock waves should reach the stone with very little loss of energy. Therefore, the flank area should be kept free of any medium that would provide an interface for dissipation of shock wave energy. For example, nephrostomy dressings should be removed and the nephrostomy catheter should be taped clear of the blast path. If epidural anesthesia is used, great care should be taken that the catheter and the gauze are taped well clear of the blast path in the flank on the side being treated. Pandit et al [158] [159] noticed an unusually high rate of failure of lithotripsy in their patients receiving epidural fentanyl analgesia. They discovered that the foam tape placed to secure the epidural catheter was frequently in the blast path of the shock waves and could absorb up to 80 percent of the shock wave energy.

Except when piezoelectric lithotripters or lithotripters with very low shock-wave energy are used, the procedure is painful and requires some form of anesthesia. Shock waves produce sharp stinging pain at the entry site in the flank combined with a sensation of deep visceral pressure discomfort.

Although shock waves pass through most tissues relatively unimpeded, they do cause tissue injury, the extent of which depends on the tissue exposed and the shock wave energy at the tissue level. For example, skin bruising and flank ecchymoses are not uncommon at the entry site. Painful hematoma in the flank muscles may occur. Hematuria is almost always present at the end of the procedure and results from shock wave-induced endothelial injury to the kidney and ureter. [147] [148] Adequate hydration is necessary to prevent clot retention. A decrease in postoperative hematocrit should arouse suspicion of a large perinephric hematoma. Punctate hemorrhages have been observed in the stomach and bowel; and this injury might be responsible for abdominal distention, nausea, and vomiting in some patients.

Lung tissue is especially susceptible to injury by shock waves. Air trapped in alveoli presents the classic water (tissue)-air interface to the shock wave, causing dissipation of energy with alveolar rupture and hemoptysis. Massive hemoptysis and death from pulmonary damage have been reported in laboratory animals after a single exposure of the thorax to shock wave. [160] Shock wave-induced hemoptysis in a child and a pulmonary contusion with life-threatening hypoxemia in an adult have been reported. [161] [162] Children are more likely to suffer pulmonary damage from shock waves because of the shorter distance of the lung bases from kidneys as compared with adults. It is recommended that a Styrofoam sheet or Styrofoam board be placed under the back in children to shield the lung bases from shock waves during ESWL. [163]

Shock wave-induced cardiac arrhythmias occur in 10 to 14 percent of patients undergoing lithotripsy despite the fact that shock waves are synchronized with the patient's ECG and are delivered in the refractory period of the cardiac cycle. [164] These arrhythmias are believed to be due to mechanical stresses on the conduction

system exerted by the shock waves. Even though the shock waves are produced

TABLE 53-9 -- Changes on Immersion During Lithotripsy

Cardiovascular	Increased	Central blood volume
		Central venous pressure
		Pulmonary artery pressure
Respiratory	Increased	Pulmonary blood flow
	Decreased	Vital capacity
	Decreased	Functional residual capacity
	Decreased	Tidal volume
	Increased	Respiratory rate

by electrical energy, the intricate grounding system of the lithotripter is such that the current density reaching the myocardium is minuscule compared with other sources (e.g., cardiac pacemakers). Hence, current-induced arrhythmias are unlikely. As mentioned previously, arrhythmias do occur frequently and are due to mechanical effects of shock waves. Atrial and ventricular premature complexes, atrial fibrillation, and supraventricular and ventricular tachycardia have been reported. [164] [165] [166] ECG artifacts are also common. Artifacts and arrhythmias usually disappear once the lithotripsy is stopped. Occasionally, however, arrhythmias may persist, requiring treatment.

Physiologic Changes During Immersion Lithotripsy

Water immersion with the Dornier HM-3 lithotripter produces significant changes in the cardiovascular and respiratory systems (Table 53-9) . Cardiovascular changes include an increase in central blood volume, with an increase in central venous and pulmonary artery pressures. [167] [168] [169] [170] [171] [172] Weber et al [167] observed that increases in central venous pressure and pulmonary artery pressure were directly correlated with the depth of immersion. On the other hand, the sitting position, together with general or epidural anesthesia, would tend to cause peripheral pooling and decreased venous return. A 1987 study noted a decrease in cardiac output and an increase in systemic vascular resistance during ESWL under general anesthesia. [172] Respiratory changes with immersion up to the clavicles are significant: functional residual capacity and vital capacity are reduced by 20 to 30 percent; pulmonary blood flow has been shown to increase [170] [171] [172] [173] [174] ; and tight abdominal straps and the hydrostatic pressure of water on the thorax impart a characteristic of shallow, rapid breathing pattern. [174] Ventilation/perfusion mismatch and hypoxemia are thus more likely. The renal effects of immersion include diuresis, natriuresis, and kaliuresis. A decrease in antidiuretic hormone and renal prostaglandins occurs. The temperature of the bath water can cause profound changes in the patient's temperature. This heat transfer is further augmented by vasodilation produced by general or epidural anesthesia. Both hypothermia and hyperthermia have been reported. [175] [176]

Anesthetic Choices for Lithotripsy

Anesthetic regimens successfully used for lithotripsy include general anesthesia, epidural anesthesia, spinal anesthesia,

flank infiltration with or without intercostal blocks, and analgesia-sedation. [177] [178] [179] [180] [181] [182] [183] [184] General anesthesia offers the advantages of rapid onset and control of patient movement. Ventilatory parameters can be controlled to decrease stone movement with respiration. Extra-long circuit tubing and monitoring cables are required. Disadvantages include a likelihood of positional injury and the possible need to transport an anesthetized patient to other locations if adjunctive procedures become necessary.

Epidural anesthesia offers the advantage that the patient is awake and can help with transfer in and out of the gantry chair, thus reducing the likelihood of injury. With epidural anesthesia and use of loss of resistance to air for identifying the epidural space, only the smallest amount of air necessary should be injected. Air in the epidural space will provide an interface and cause dissipation of shock wave energy resulting in local tissue injury. Korbon et al [185] found a decrease in epidural compliance and pain on injection in repeat epidurals for subsequent lithotripsies in their patients. In animal experiments, they were able to show epidural tissue damage following injection of air and exposure to shock waves. [186] It is reassuring, however, that in the vast number of lithotripsies performed under epidural anesthesia worldwide, neurologic injury has not been a problem.

The main disadvantage of epidural anesthesia is its slow onset. Spinal anesthesia offers a reasonable alternative with its rapid onset. However, the incidence of hypotension (the patient is in sitting position for treatment) is higher. In one series, the incidence of hypotension with general, epidural, and spinal anesthesia was 13, 18, and 27 percent, respectively. [187] Local anesthetic infiltration of the flank with or without intercostal blocks provides adequate anesthesia when combined with intravenous sedation and avoids hypotension. [178] Intravenous analgesia-sedation in various combinations has been successfully used by many anesthetists. [180] [181] [182]

Newer Lithotripters

The second- and third-generation lithotripters offer many advantages. First, there is no water bath; hence all the problems of immersion are avoided. Second, they tend to use multifunctional tables allowing other procedures such as cystoscopy and stent placement to be accomplished without moving the patient off the table. Third, the shock waves are focused, so that they cause less pain at the entry site. With the exception of the piezoelectric lithotripters (Wolf, EDAP, Diasonic) and the use of lowest energy levels with the other lithotripters, ESWL is not pain-free and intravenous analgesia-sedation is the mainstay of anesthesia with these newer lithotripters. Other incidental interventions such as cystoscopy, stone manipulation, or stent placement will alter anesthetic requirements. Many of these newer lithotripters have a much smaller focal zone for the shock waves. Hence, it is even more imperative with these to provide adequate analgesia and sedation so that the stone excursions with respirations are limited to the focal zone. Most analgesiasedation combinations are adequate. Even patientcontrolled analgesia with alfentanil has been used. [188] [189]

Contraindications

Pregnancy and untreated bleeding disorders and abdominally placed pacemakers are the only absolute contraindications to lithotripsy. Women of childbearing age must have a pregnancy test that is documented negative before lithotripsy. Standard tests of coagulation such as platelet count, prothrombin time, and partial thromboplastin time should be obtained. Other conditions that were labeled previously as absolute contraindications are no longer believed to be so provided that appropriate precautions are taken. These conditions include pacemakers, automatic implanted cardioverter defibrillators (AICD) abdominal aortic aneurysm, orthopedic prostheses, and obesity.

Patients with pacemakers can be treated safely if the pacemaker is pectorally placed and the following precautions are observed. [190] [191] [192] Pacemaker programmability should be established prior to the treatment, and a programmer should be available to switch the pacemaker to a nondemand mode should the shock waves interfere with pacemaker function. Alternating means of pacing should be available. Although most pacemakers located pectorally are at a safe distance from the blast path, some may be damaged. Weber et al [190] examined 43 different pacemakers and found that 3 were affected. Dual-chamber pacemakers tend to be more sensitive to interference. Treatment must be started at the lowest energy level and gradually increased while observing pacemaker function.

Manufacturers of AICDs and lithotripters generally consider an AICD a contraindication for lithotripsy. Patients with AICDs have been treated successfully with lithotripsy, however. [193] Transvenous AICDs are less of a concern than the older abdominally implanted defibrillators. AICD devices should be shut off immediately before lithotripsy and then reactivated immediately after the treatment.

Patients with small aortic aneurysms have been treated safely provided that the stone is not close to the aneurysm. Orthopedic prostheses such as hip prostheses and even Harrington rods are not a problem if they are not in the blast path, which is usually the case. Positioning of these patients may sometimes be problematic.

Not only do extremely obese patients present with anesthetic challenges related to obesity, but focusing of the stone may be extremely difficult in the very obese, and it is not uncommon for the procedure to be abandoned in these patients because of inability to bring the kidney stone in the Fz focal zone. It is prudent, therefore, that focusing of the stone be attempted before administering any anesthetic in this high-risk population. With the newer lithotripters, some of these patients may have to be placed prone, a position that they may not be able to tolerate safely.

Renal Tumors

Procedures associated with recent changes in anesthetic management include operations for renal cell carcinoma. [194] Of those patients with tumors of the vena cava, some may have tumors that extend above the insertion of the hepatic vein and into the right atrium. Several problems can occur in these patients, ranging from circulatory failure due to

complete occlusion of the vena cava by tumor to acute pulmonary embolization of tumor fragments during operation. To operate safely on these patients, the extent of the lesion must be defined preoperatively. Approximately 10 to 15 percent of lesions extend into the atrium. [194] Cardiopulmonary bypass is required in these cases to prevent tumor embolization; it may also be necessary in some cases with extension into the upper portion of the hepatic vena cava or when venous return is significantly compromised. Right-heart catheterization is potentially hazardous, because there is a danger that a part of the tumor may be dislodged and embolize. Some use a central venous pressure (CVP) catheter inserted via left internal jugular or external jugular vein so as not to place it beyond the superior vena cava. CVP in such case may not reflect intravascular volume accurately because the venous return via the inferior vena cava is impaired by the thrombus. This decrease in venous return also predisposes the patient to hypotension during induction of anesthesia. Furthermore, the venous obstruction leads to dilation of epidural veins and development of abdominal wall and retroperitoneal collaterals. Again, the emphasis is on appropriate preoperative preparation, which is possible only when the full extent of the lesion has been defined. [195]

Radical Surgery in Urology

Radical surgery is becoming commonplace in the urologic suite with the introduction of radical nephrectomy, radical cystectomy, and radical retropubic prostatectomy. Common features are that the procedures tend to be lengthy, may be associated with sudden and significant blood loss, and require special attention to preservation of renal function. With radical nephrectomy, significant cardiorespiratory changes attendant to the flank position are a concern. Respiratory changes include decreases in thoracic compliance, tidal volume, vital capacity, and functional residual capacity. Dependent atelectasis is common and may lead to hypoxemia. Pneumothorax may occur and can have significant respiratory and hemodynamic consequences intraoperatively. It is not uncommon to see a decrease in blood pressure when the kidney rest is raised. This is usually due to inferior vena cava compression. In addition, hepatic encroachment on the vena cava and mediastinal shift may further reduce venous return and stroke volume. Cervical plexus, brachial plexus, and common peroneal neuropathies may occur due to stretch or compression of the nerves in the lateral position.

Radical Prostatectomy

Localized prostate cancer is treated with either radiation therapy or radical prostatectomy. Radical prostatectomy is now more commonly used because the popularization of the nerve-sparing surgery that reduces the risk of impotence. The most common intraoperative problem is hemorrhage and massive blood loss. Most patients require blood transfusion. Autologous predonation and isovolemic hemodilution are commonly practiced to reduce the patient exposure to allogenic blood. Early postoperative complications include deep venous thrombosis, pulmonary embolism, and wound infection and occur in 0.5 to 2 percent of cases. [196] Death within 30 days has been reported by several centers to be approximately 0.2 percent. [197] Late complications include incontinence, impotence, and bladder neck contracture.

Patients undergoing radical prostatectomy are placed supine in the Trendelenburg position with the back extended, which places the pubis above the head. Air embolism from the prostatic fossa due to a gravitational gradient between the prostatic veins and the heart has been reported. [198]

Epidural anesthesia, spinal anesthesia, general anesthesia, and combined epidural and general anesthesia has been used for this surgery. A decrease in intraoperative blood loss, operative time, and thromboembolic complications with epidural anesthesia has been reported. [199] Others have reported no difference in postoperative morbidity comparing epidural anesthesia and general anesthesia for this procedure. [200] There is no reported benefit of combining the two techniques over either technique used alone. Postoperative pain is well controlled with patient controlled analgesia, epidural analgesia, or a combination of ketorolac and rescue opiates.

UROGENITAL PAIN SYNDROMES

The pain syndromes of the urogenital system result from inflammatory disease, anatomic anomalies, obstructive uropathies, and malignancies. The visceral type of renal pain is frequently caused by pyelonephritis or ischemic events due to an embolus or a thrombus. Hematuria in sickle cell disease or trait is typically painless. The site of pain, characteristics of referred pain, and the quality of pain help the clinician to identify the source of pain.

Benign Renal Neoplasms

Flank pain is a common symptom in adults with angiomyolipoma (more common in women than men), and in children with mesoblastic nephroma and Wilms tumor or nephroblastoma. Nephroblastomas may be combined with several congenital malformations such as sporadic anidria (lack of sweating), microcephaly, mental retardation, and spina bifida. Treatment consists of surgical resection of the tumor supplemented by chemotherapy and adequate pain management. Opiates are the mainstay of pain management.

Renal Cell Carcinoma

Renal cell carcinoma, also known as hypernephroma, presents with the classic triad of hematuria, flank pain, and a renal mass. The development of pain may be a warning sign for metastatic disease. Pain control becomes an important issue in the metastatic disease. Intrathecal implantable pump or a permanent epidural catheter placement for continuous delivery of pain medications may be indicated. Fewer than 5 percent of tumors of the renal origin are sarcomas.

The majority of them are leiomyosarcomas. The peak age is the fourth and fifth decade of life. Flank pain is usually the presenting symptom. Pain is mainly due to stretching of the Gerota fascia and/or compression and invasion of intercostal nerves.

Inflammatory Renal Diseases

Inflammatory renal diseases commonly producing flank pain include acute pyelonephritis, pyelitis, renal carbuncle, and perinephritic abscess. Spiking fever is an important associated finding to suggest presence of infection. The most prominent sign is the tenderness in the flank. As kidneys are retroperitoneal organs, peritoneal signs develop very late. Differential diagnosis must include pneumonitis, pancreatitis, appendicitis, and cholecystitis. Oral or parenteral narcotics are very effective for pain control. Systemic antibiotics and fluid resuscitation are important for management of renal infections.

Perinephritic fasciitis is an inflammation of renal capsule and fascia of Gerota and it may follow perinephritic abscess. Depression of the immune system (due to human immu-nodeficiency virus infection, chemotherapy, radiotherapy) and sickle cell disease are the major risk factors. Peri-nephritic abscess needs to be drained. Nonsteroidal antiinflammatory drugs (NSAIDs) are effective in treating associated reflex skeletal muscle spasm.

Idiopathic nephralgia is a rare condition that mimics renal pain and other urologic symptoms. The pain is thought to originate from incoordinated hyperactivity and spasms of calyces and renal pelvis. A comprehensive psychologic evaluation may be required to eliminate psychologic factors as a source of pain. Diagnostic and therapeutic paravertebral blocks may help diagnose and treat this disabling pain condition.

Pseudorenal pain syndromes are caused by genital nerve entrapment and ilioinguinal neuropathy following inguinal surgery and may mimic renal pain. The referred pain in the dermatomal distribution is very characteristic of these conditions. Diagnostic and therapeutic ilioinguinal or genitofemoral nerve blocks help establish the diagnosis and treat this pain. In congenital polycystic kidney disease, renal pain is caused by distention of the cysts and stretching of the Gerota fascia. Hemorrhage in the cysts, rupture of the cysts, or infection produce exacerbation of pain. Surgical intervention including percutaneous drainage of solitary renal cyst may relieve symptoms. Renal vein thrombosis and renal infarctions cause acute or acute-on-chronic pain syndromes. Along with treatment of shock and embolectomy, narcotics are used to control pain.

Obstructive Uropathy

Obstruction of the urinary tract causes severe pain in the flank. Chronic conditions cause constant dull ache as compared with spasmodic episodic pain in acute obstruction. Surgery may be indicated. As a general rule, pain from the upper one-third of the ureter is referred to the loin, from the middle one-third to the iliac fossa, and from the lower one-third to the suprapubic and groin area. The pain due to ureteric calculi is often felt in the upper and inner thigh and ipsilateral testicle in males and labia majora in females. NSAIDs are helpful in relieving pain. This is believed to be due to the antiprostaglandin effect of NSAIDs. Calcium channel blockers (verapamil, diltiazem, and nifedipine) have been effective in treating ureteric colic. Although there are some controversies that morphine and meperidine may have a spasmogenic effect on the ureter, opiates remain the mainstay of treatment of ureteric colic.

Bladder Pain

Bladder pain is mostly dull ache and usually localized to the suprapubic region. Most common causes of pain are bladder distention by obstruction and cystitis. Bladder distention accompanied with acute or chronic inflammation presents with severe suprapubic spasmodic pain, urinary frequency, and dysuria. The treatment of the cause of inflammation (e.g., obstruction, stone, enlarged prostate, vesicoureteral reflux) is the treatment of choice for pain. Untreated cystitis may result in upper urinary tract infection. Pregnancy, diabetes mellitus, and immune deficiency are additional risk factors.

Interstitial cystitis is a condition with unknown etiology that frequently poses a challenge to the physicians. The pathologic features of interstitial cystitis are nonspecific chronic inflammatory infiltrate, edema, and vasodilation. Suprapubic pain is due to bladder spasm or incoordinated detrusor muscle contraction. Suprapubic pain and frequency of micturition may become so incapacitating that a cystectomy may be required in extreme cases. Options of pain control include bladder denervation (rhizotomy), transurethral electrocautery, cystolysis, presacral nerve blocks, and neurolytic blocks. Medical management includes antihistamine, corticosteroids, anticholinergics, and calcium channel blockers. [201] [202]

Urothelial Tumors

The most common urothelial tumor is the transitional cell carcinoma of the urinary bladder. Painless hematuria is the most common presentation. Thirty percent of patients may present with bladder irritability, which is thought to be due to muscular involvement. Surgical treatment includes fulguration, transurethral resection, or

more extensive radical cystectomy with urinary diversion. Pain control is an integral part of treatment in the metastatic disease of the bladder.

Testicular Pain

Most common testicular congenital anomaly producing pain is cryptoorchidism. Pain in an undescended testis without trauma usually indicates infection or torsion. Emergency surgical exploration is the treatment of choice. The incidence of malignancy is 20 times higher in an undescended testis as compared with a descended testis. The bacterial or viral orchitis or epididymoorchitis is a painful condition that needs urgent attention.

Tumors of the testis are generally malignant; however, extratesticular tumors within the scrotum are usually benign. The earliest sign of the tumor is a painless, testicular mass. Pain is a late sign, usually described as dull ache, testicular heaviness, or dragging. The treatment of testicular tumor depends on the cell type and disease stage. Seminoma is generally radiosensitive.

Prostatic Pain

Acute or chronic prostatitis is very painful. Acute prostatitis is usually due to a bacterial infection and responds to antibiotic therapy. Chronic prostatitis is due to inadequate treatment of acute infection, recurrent infection, or prostatic uroliths. Treatment includes prostatic massage, NSAIDs, antibiotics, and surgical drainage.

Adenocarcinoma of the prostate is the most common male cancer and usually painless. Rectal or sacral pain with prostatic cancer may be a sign of metastatic disease. Patients with sacral or pelvic pain should be investigated for bone metastasis. Oral or parenteral high-dose opiates are the mainstay of treatment initially. Permanent epidural catheter or intrathecal implantable pump for continuous delivery of medications and radiation therapy should be considered for metastatic disease.

Priapism

Priapism is a prolonged pathologic and painful erection caused by engorgement and thrombosis of pelvic veins. It is seen in patients with metastatic malignant diseases like pancreatic cancer and leukemia, pelvic trauma, sickle cell disease, or spinal trauma. Pathology of corpora and local neurovascular abnormality can also cause priapism. Prompt therapy should be instituted to control pain and to prevent subsequent impotence from fibrosis of the corpora cavernosa. Cause of priapism may be important in defining the treatment. Sickle cell priapism is treated with hydration, alkalinization, and blood transfusion to increase hemoglobin to greater than 10 mg/dL. Priapism due to leukemia responds to radiation. Intracorporeal injection of phenylephrine is recommended for selected cases of priapism. Stepwise institution of pain medications from NSAIDs to opiates is recommended. Severe pain will warrant parenteral administration of morphine or hydromorphone.

Peyronie's disease is a sexually crippling condition that causes severe penile pain during sexual intercourse due to curvature. The treatment of choice is surgery and NSAIDS for pain.

Female Genital Pain

Vulvodynia is a chronic pain condition with unknown etiology associated with sexual inactivity or dysfunction, depression, anxiety, and obsessive behavior.

Vestibulitis is characterized by painful penetration during coitus. It is more common in Caucasian females and resistant to most of the medical treatment. Some success with tricyclic antidepressants and antihistamines has been reported. Heat treatment (sitz bath) is also helpful.

Chronic dysmenorrhea is a severe pain-producing condition caused by hypercontractility of uterine muscles during menstruation. Ovulation suppression and the use of NSAIDs are effective due to its antiprostaglandin effect. A 1987 study by Helms [203] found that acupuncture is effective in resistant cases. Presacral neurectomy can be considered as a last resort after other options have been tried and failed.

Incoordinated contraction of the muscles of the pelvic floor (levator ani, pubococcygeus, and deep transverse perineal) causes vaginismus. It produces extreme spasms and painful sexual dysfunction. Psychologic factors such as rigid sexual upbringing and traumatic sexual experience inadvertently reinforce the vaginal spasm. Treatment involves correction of any physical condition and then behavior modification that includes desensitization techniques.

Dyspareunia is defined as recurrent and persistent genital pain before or after intercourse that may be due to infection, trauma, or lack of lubrication. Treatment includes psychotherapy and systemic desensitization.

Chronic pelvic pain is also known as pelvic congestion, pelvic fibrosis, pelvic neurodynia, and pelvic sympathetic syndrome. Pain is often multifactorial and requires multidisciplinary pain management, which involves psychotherapy, medications, and trigger point injections. In selected cases, nerve root blocks and neuraxial opioid therapy are promising. Metastatic disease of the cervix and uterus can cause severe vulvovaginal pain syndrome and requires aggressive opioids and adjuvant pain treatment. [201]

General Considerations

General considerations for genitourinary pain management follow the same principles of pain management elsewhere. For nonmalignant acute pain, medical management is the first choice. Narcotics and nonnarcotic medications such as acetaminophen, aspirin and NSAIDs are indicated for the control of acute pain. When oral administration is not feasible, parenteral administration of narcotics should be used. Patient controlled epidural analgesia or continuous epidural infusion produces segmental dose-related analgesia and prevents atelectasis. Use of lipophilic versus hydrophilic narcotics depends on the segmental level of epidural catheter placement. Intravenous patient-controlled analgesia should be the next option. Meperidine should be avoided in the patients with compromised renal functions because the half-life of normeperidine (metabolite of meperidine, which lowers the seizure threshold and induces CNS excitability) is significantly prolonged. Hydromorphone, a semisynthetic opioid, is recommended for patients with renal failure because of lack of identifiable metabolites. Antiprostaglandin effect of NSAIDs affects the regulation of renal blood flow in susceptible patients. Therefore, patients requiring long-term NSAIDs should be appropriately monitored for renal function.

Interventional techniques are an integral part of pain control in chronic nonmalignant and malignant pain syndromes. Continuous epidural infusion of opioids causes minimum fluctuations of the drug level in the cerebrospinal fluid. Before consideration of a tunneled epidural catheter, pain should be treated aggressively with sustained release morphine preparations, methadone, and fentanyl transdermal

patches to optimize the medication requirement. If intractable pain persists despite aggressive systemic opioids and adjuvant drug therapy, treatment with an implantable drug delivery system should be considered. Because of the safety, efficacy, and relative ease of intraspinal administration of opioids for the control of intractable pain resulting from metastatic disease, implantable intrathecal and epidural drug administration systems are being used increasingly.

/das/book/view/29494766/875/594.html

References

1. Lanzkowsy P: Manual of Pediatric Hematology and Oncology, 2nd ed. New York, Churchill Livingstone, 1995.

2. Kabalin JN: Anatomy of the retroperitoneum and the kidney. In Walsh PC, Retik AB, Staurey TA, Vaughan ED (eds): Campbell's Urology, 7th ed. Philadelphia, WB Saunders, 1998.

3. Taragho EA: Anatomy of the lower urinary tract. In Walsh PC, Retik AB, Staurey TA, Vaughan ED (eds): Campbell's Urology, 7th ed. Philadelphia, WB Saunders, 1998.

4. Hemmings HC Jr: Anesthesia, adjuvant drugs and the kidney. In Malhotra V: Anesthesia for Renal and Genito-urologic Surgery. New York, McGraw-Hill, 1996, p. 18.

5. Elkington JR, Huth EJ, Webster GD Jr et al: The renal excretion of hydrogen ion in renal tubular acidosis. I. Quantitative assessment of the response to ammonium chloride as an acid load. Am J Med 29:554, 1960.

6. Erslev AJ, Shapiro SS: Hematologic aspects of renal failure. In Strauss MB, Welt LG (eds): Diseases of the Kidney. Boston, Little, Brown, 1988, p 273.

7. Fisher JW: Introduction to a conference on erythropoietin. Ann N Y Acad Sci 149:9, 1968.

8. Adamson JW, Eschbach J, Finch CA: The kidney and erythropoiesis. Am J Med 44:725, 1978.

9. Kassirer JP: Clinical evaluation of kidney function--glomerular function. N Engl J Med 285:385, 1971.

10. May RC, Mitch WE: The pathophysiology of uremia. In Brenner BM, Rector FC Jr (eds): The Kidney, 5th ed. Philadelphia, WB Saunders, 1996, p 2148.

11. Anderson RJ, Gambertoglio JG, Schier RW: Clinical Use of Drugs in Renal Failure. Springfield, Illinois, Charles C Thomas, 1976.

12. Prescot LF: Mechanisms of renal excretion of drugs (with special reference to drugs used by anaesthetists). Br J Anaesth 44:246, 1972.

13. Reidenberg MM: Effects of renal insufficiency on the action of specific drugs. In Reidenberg MM (ed): Renal Function and Drug Action. Philadelphia, WB Saunders, 1971, p 39.

14. Benet LZ, Svein O, Schwartz JB: Appendix II. Design and optimization of dosage regimens; pharmacokinetic data. In Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York, Macmillan, 1996, p 1707.

15. Gosselin RE, Gabourel JD, Willis JH: The fate of atropine in man. Clin Pharmacol Ther 1:597, 1960.

16. Tonnesen M: The excretion of atropine and allied alkaloids in urine. Pharmacol Toxicol 6:147, 1950.

17. Hollister LE: Clinical Pharmacology of Psychotherapeutic Agents, 3rd ed. New York, Churchill Livingstone, 1990.

18. Kaplan SA, Jack ML, Alexander K et al: Pharmacokinetic profile of diazepam in man following single intravenous and oral and chronic oral administrations. J Pharmacol Sci 62:1739, 1973.

19. Olsen GD, Bennett WM, Porter GA: Morphine and phenytoin binding to plasma proteins in renal and hepatic failure. Clin Pharmacol Ther 17:677, 1975.

20. Stanski DR, Watkins WD: Drugs Disposition in Anesthesia. Orlando, Florida, Grune & Stratton, 1982.

21. Yeh SY: Urinary excretion of morphine and its metabolites in morphine dependent subjects. J Pharmacol Exp Ther 192:201, 1975.

22. Spector S, Vessel ES: Disposition of morphine in man. Science 74:421, 1972.

23. Don HF, Dieppa RA, Taylor P: Narcotic analgesics in anuric patients. Anesthesiology 42:745, 1975.

24. Mather LE, Meffin PJ: Clinical pharmacokinetics of pethidine. Clin Pharmacokinet 3:352, 1978.

25. Verbeeck RK, Branch RA, Wilkinson GR: Meperidine disposition in man: Influence of urinary pH and route of administration. Clin Pharmacol Ther 30:619, 1981.

26. McClain DA, Hug CC: Intravenous fentanyl kinetics. Clin Pharmacol Ther 28:106, 1980.

27. Hug CC, Murphy MR: Tissue redistribution of fentanyl and its termination of effects in rats. Anesthesiology 55:369, 1981.

28. Davis PJ, Stiller RL, Cook DR: Pharmacokinetics of sufentanil in adolescent patents with chronic renal failure. Anesth Analg 67:268, 1988.

29. Davis PJ, Stiller RL, Cook DR: Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. Anesth Analg 68:579, 1989.

30. Hoke JF, Schlugman D, Dershwitz M et al: Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers. Anesthesiology 87(3):533, 1997.

31. Mazze RI: Metabolism of the inhaled anaesthetics: Implications of enzyme induction. Br J Anaesth 56:275, 1985.

32. Mazze RI, Trudell JR, Cousins MJ: Methoxyflurane metabolism and renal dysfunction: Clinical correlation in man. Anesthesiology 35:247, 1971.

33. Cousins M, Mazze RI: Methoxyflurane nephrotoxicity: A study of dose response in man. JAMA 255:1611, 1973.

34. Mazze RI, Sievenpiper TS, Stevenson J: Renal effects of enflurane and halothane in patients with abnormal renal function. Anesthesiology 60:161, 1984.

35. Mazze RI, Cousins MJ, Barr GA: Renal effects and metabolism of isoflurane in man. Anesthesiology 40:536, 1974.

36. Eger EI II: Stability of I-653 in soda-lime. Anesth Analg 66:983, 1987.

37. Koblin DD, Eger EI II, Johnson BH et al: I--653 resists degradation in rats. Anesth Analg 67:534, 1988.

38. Koblin DD, Wesikopf RB, Holmes MA et al: Metabolism of I-653 and isoflurane in swine. Anesth Analg 68:147, 1989.

39. Jones RM, Koblin DD, Cashman JN et al: Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653). Br J Anaesth 64:482, 1990.

40. Weiskopf RB, Eger EI II, Ionescu P et al: Desflurane does not produce hepatic or renal injury in human volunteers. Anesth Analg 74:570, 1992.

41. Hanaki C, Fujii K, Mono M, Tashima T: Decomposition of sevoflurane by soda-lime. Hiroshima J Med Sci 36:61, 1987.

42. Kobayashe Y, Ochiai R, Takeda J et al: Serum and urinary inorganic fluoride levels after prolonged inhalation of sevoflurane in man. Anesthesiology 75:A348, 1991.

43. Jones RM: Clinical comparison of inhalation anesthetic agents. Br J Anaesth 56:57S, 1984.

44. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 54:100, 1981.

45. Priano LL: Effect of halothane on renal hemodynamics during normovolemia and hemorrhagic hypovolemia. Anesthesiology 63:357, 1985.

46. Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 63:557, 1984.

47. Merin RG, Bernard JM, Doursout MR: Comparison of the effects of isoflurane and desflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. Anesthesiology 74:568, 1991.

48. Cousin MJ, Greenstein LR, Hitt BA, Mazze RI: Metabolism and renal effects of enflurane in man. Anesthesiology 44:44, 1976.

49. Cook TL, Beppu WJ, Hitt BA et al: Renal effects and metabolism of sevoflurane in Fischer 344 rats. Anesthesiology 43:70, 1975.

50. Ghoneim MM, Pandya HB, Kelley SE et al: Binding of thiopental to plasma proteins: Effects on distribution in the brain and heart. Anesthesiology 45:635, 1976.

51. Burch PG, Stanski DR: Decreased protein binding and thiopental kinetics. Clin Pharmacol Ther 32:212, 1982.

52. Dundee JW, Richards RK: Effect of azotemia upon the action of intravenous barbiturate anesthesia. Anesthesiology 15:333, 1954.

53. Breimer DD: Pharmacokinetics of methohexitone following intravenous infusion in humans. Br J Anaesth 48:643, 1976.

54. Hudson RJ, Stanski DR, Burch PG: Pharmacokinetics of methohexital and thiopental in surgical patients. Anesthesiology 59:215, 1983.

55. Thomas JL, Holmes JH: Effect of hemodialysis on plasma cholinesterase. Anesth Analg 49:323, 1970.

56. Wyant GM: The anesthetist looks at tissue transplantation: Three years' experience with kidney transplants. Can J Anaesth 14:255, 1967.

57. Ryan DW: Preoperative serum cholinesterase concentration in chronic renal failure. Br J Anaesth 49:945, 1977.

58. Desmond JW, Gordon RA: The effect of haemodialysis on blood volume and plasma cholinesterase levels. Can J Anaesth 16:292, 1969.

59. Mazze RI, Escue HM, Houston JB: Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. Anesthesiology 31:540, 1969.

60. Gronert GA, Theye RA: Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 43:89, 1975.

61. Miller RD, Way WL, Hamilton WK et al: Succinylcholine induced hyperkalemia in patients with renal failure? Anesthesiology 36:138, 1972.

62. Koide M, Waud BE: Serum potassium concentrations after succinylcholine in patients with renal failure. Anesthesiology 36:142, 1972.

63. Matteo RS, Nishitateno K, Pau EK et al: Pharmacokinetics of d-tubocurarine in man: Effect of an osmotic diuretic on urinary excretion. Anesthesiology 52:335, 1980.

64. Sheiner LB, Stanski DR, Vozek S et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. Clin Pharmacol Ther 25:358, 1979.

65. Ghoneim MM, Kramer E, Bannow R et al: Binding of tubocurarine to plasma proteins in normal man and in patients with hepatic or renal failure. Anesthesiology 39:410, 1979.

66. Miller RD, Matteo RS, Benet LZ et al: The pharmacokinetics of d-tubocurarine in man with or without renal failure. J Pharmacol Exp Ther 202:1, 1977.

67. Gibaldi M, Levy G, Hayton WL: Tubocurarine and renal failure. Br J Anaesth 44:163, 1972.

68. Brotherton WP, Matteo RS: Pharmacokinetics and pharmacodynamics of metocurarine in humans with and without renal failure. Anesthesiology 55:273, 1981.

69. Ramzan MI, Shanks CA, Triggs EJ: Gallamine disposition in surgical patients with chronic renal failure. Br J Clin Pharmacol 12:141, 1981.

70. Feldman SA, Levi JA: Prolonged paresis following gallamine: A case report. Br J Anaesth 35:804, 1963.

71. Agoston S, Vermeer GA, Kersten UW et al: The fate of pancuronium and its metabolites in anesthetized man. J Pharmacol Exp Ther 207:539, 1978.

72. Miller RD, Agoston S, Booij LHDJ et al: The comparative potency and pharmacodynamics of pancuronium and its metabolites in anesthetized man. J Pharmacol Exp Ther 207:539, 1978.

73. Somogyi AA, Shanks CA, Triggs EJ: The effect of renal failure on the disposition and neuromuscular blocking action of pancuronium bromide. Eur J Clin Pharmacol 12:23, 1977.

74. McLeod K, Watson MJ, Rawlins MD: Pharmacokinetics of pancuronium in patients with normal and impaired renal function. Br J Anaesth 48:341, 1976.

75. Hughes R, Chapple DJ: The pharmacology of atracurium: A new competitive neuromuscular blocking agent. Br J Anaesth 53:31, 1981.

76. Fahey MR, Rupp SM, Fisher DM et al: The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 61:699, 1984.

77. Kisor DF, Schmith VD, Wargin WA et al: Importance of the organindependent elimination of cisatracurium. Anesth Analg 83(5):901, 1996.

78. Orko R, Heino A, Bjorksten F et al: Comparison of atracurium and vecuronium in anaesthesia for renal transplantation. Acta Anaesthesiol Scand 31:450, 1987.

79. Fahey MR, Morris RB, Miller RD: Pharmacokinetics of ORG NC45 (Norcuron) in patients with and without renal failure. Br J Anaesth 53:1049, 1981.

80. Lynam DP, Cronnelly R, Castagnoli KP et al: The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. Anesthesiology 69:227, 1988.

81. Bencini AF, Scaf AHJ, Sohn YJ et al: Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. Anesth Analg 65:245, 1986.

82. Gramstad L, Gjerlow JA, Hysing ES, Rugstad HE: Interaction of cyclosporin and its solvent, cremophor, with atracurium and vecuronium: Studies in the cat. Br J Anaesth 58:1149, 1986.

83. Cashman JN, Luke JJ, Jones RM: Neuromuscular block with doxacurium (BW A938 U) in patients with normal or absent renal function. Br J Anaesth 64:186, 1990.

84. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics and pharmacodynamics of doxacurium in normal patients and in those with liver or renal failure. Anesth Analg 72:145, 1991.

85. Caldwell JE, Canfell PC, Castagnoli KP et al: The influence of renal failure on the pharmacokinetics and duration of action of pipecuronium bromide in patients anesthetized with halothane and nitrous oxide. Anesthesiology 70:7, 1989.

86. Cook DR, Freeman JA, Lai AA et al: Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 69:580, 1992.

87. Phillips BJ, Hunter JM: Use of mivacurium chloride by constant infusion in the anephric patient. Br J Anaesth 69:492, 1992.

88. Mangar D, Kirchoff GT, Rose PL, Castellano FC: Prolonged neuromuscular block after mivacurium in a patient with end stage renal disease. Anesth Analg 76:866, 1993.

89. Szenohradsky J, Fisher DM, Segredo V et al: Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. Anesthesiology 77:899, 1992.

90. Cronnelly R, Stanski DR, Miller RD et al: Renal function and the pharmacokinetics of neostigmine in anesthetized man. Anesthesiology 51:222, 1979.

91. Cronnelly R, Stanski DR, Miller RD et al: Pyridostigmine kinetics with and without renal function. Clin Pharmacol Ther 28:78, 1980.

92. Morris RB, Cronnelly R, Miller RD et al: Pharmacokinetics of edrophonium in anephric and renal transplant patients. Br J Anaesth 53:1311, 1981.

93. Koup JR, Greenblatt DJ, Jusko WJ et al: Pharmacokinetics of digoxin in normal subjects after intravenous bolus and infusion doses. J Pharmacokinet Biopharm 3:181, 1975.

94. Iisalo E, Dahl M, Sundquist H: Serum digoxin in adults and children. Int J Clin Pharmacol 7:219, 1973.

95. Beermann B, Groschinsky-Grind M, Rosen A: Absorption, metabolism and excretion of hydrochlorothiazide. Clin Pharmacol Ther 19:531, 1976.

96. Smith DE, Brater DC, Lin ET et al: Attenuation of furosemide diuretic effect by indomethacin: Pharmacokinetics evaluation. J Pharmacokinet Biopharm 7:265, 1979.

97. Kornhauser DM, Wood AJJ, Vesta RE et al: Biological determinants of propranolol disposition in man. Clin Pharmacol Ther 23:165, 1978.

98. Henry PD: Comparative pharmacology of calcium antagonists: Nifedipine, verapamil and diltiazem. Am J Cardiol 46:1047, 1980.

99. Kwan KC, Foltz EL, Breault GO et al: Pharmacokinetics of methyldopa in man. J Pharmacol Exp Ther 198:264, 1976.

100. Miller RD, Way WL, Eger EI II: The effects of alpha-methyldopa, reserpine, guanethidine and iproniazid on minimum alveolar anesthetic requirement (MAC). Anesthesiology 29:1153, 1968.

101. McMartin C, Simpson P: The absorption and metabolism of guanethidine in hypertensive patients requiring different doses of the drug. Clin Pharmacol Ther 12:73, 1971.

102. Neurath GB, Dunger M: Blood levels of the metabolites of glyceryl trinitrate and pentaerythritol tetranitrate after administration of a two-step preparation. Arzneimittelforschung 27:416, 1977.

103. Smith RP: Cyanate and thiocyanate: Acute toxicity. Proc Soc Exp Biol Med 142:1041, 1973.

104. Talseth T: Studies on hydralazine. III. Bioavailability of hydralazine in man. Eur J Clin Pharmacol 10:395, 1976.

105. Talseth T: Studies on hydralazine. II. Elimination rate and steady state concentration in patients with impaired renal function. Eur J Clin Pharmacol 10:311, 1976.

106. Luke DR, Awni WM, Halstenson CE et al: Bioavailability of labetolol in patients with end-stage renal disease. Ther Drug Monit 14(3):203, 1992.

107. Wiest D: Esmolol: A review of its therapeutic efficacy and pharmacokinetic characteristics. Clin Pharmacokinet 28(3):190, 1995.

108. Schmidt KF, Roth RH: Interaction of psychotropic drugs with agents employed in clinical anaesthesia. Clin Anaesth 3:60, 1967.

109. Levinsky NG, Alexander EA: Acute renal failure. In Brenner BM, Rector FC Jr (eds): The Kidney, 5th ed. Philadelphia, WB Saunders, 1996.

110. Mazze RI: Critical care of the patient with acute renal failure. Anesthesiology 47:138, 1977.

111. Vertel RM, Knochel JP: Nonoliguric acute renal failure. JAMA 200:118, 1967.

112. Brown CB, Cameron JS, Ogg CS et al: Established acute renal failure following surgical operations. In Friedman EA, Eliahue HE (eds):

Proceedings of the Conference on Acute Renal Failure, DHEW Publication No. (NIH) 74-608. Washington, DC, U.S. Government Printing Office, 1973, p 187.

113. Churchill D, Knaack J, Chirito E et al: Persisting renal insufficiency after methoxyflurane anesthesia. Am J Med 56:575, 1974.

114. Kolf WJ, Berk HTJ: Artificial kidney dialyzer with great area. Acta Med Scand 117:121, 1944.

115. Bromage PR, Gertel M: Brachial plexus anesthesia in chronic renal failure. Anesthesiology 36:488, 1972.

116. Martin R, Beauregard MD, Tetrault MD: Brachial plexus blockade and chronic renal failure. Anesthesiology 69:405, 1988.

117. Marx GF, Orkin LR: Complications associated with transurethral surgery. Anesthesiology 23:802, 1962.

118. Hagstrom RS, Dennise SA, Rowland HS et al: Studies on fluid absorption during transurethral prostatic resection. J Urol 73:852, 1955.

119. Emmet J, Gilbough JH, McLean P: Fluid absorption during transurethral resection: Comparison of mortality and morbidity after irrigation with water and non-hemolytic solutions. J Urol 101:884, 1969.

120. Desmond J: Serum osmolality and plasma electrolytes in patients who develop dilutional hyponatremia during transurethral resection. Can J Surg 13:116, 1970.

121. Nesbit TE: The use of glycine in transurethral prostatic surgery. J Urol 59:1212, 1948.

122. Gravenstein D: Transurethral resection of prostate (TURP) syndrome: A review of pathophysiology and management. Anesth Analg 84:438, 1997.

123. Henderson DJ, Middleton RG: Coma from hyponatremia following transurethral resection of prostate. Urology 15:267, 1980.

124. Aasheim GM: Hyponatremia during transurethral surgery. Can J Anaesth 20:274, 1973.

125. Ovassapian A, Joshi CW, Brunner EA: Visual disturbance: An unusual symptom of transurethral prostatic resection reaction. Anesthesiology 57:332, 1982.

126. Azar I: Transurethral resection of prostate. In Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, pp 93-109.

127. Hockstra PT, Kahnoski R, McCamish MA et al: Transurethral prostatic resection syndrome--a new perspective: Encephalopathy with associated hyperammonemia. J Urol 130:704, 1983.

128. Roesch RP, Stoelting RK, Lingeman JE et al: Ammonia toxicity resulting from glycine absorption during a transurethral resection of the prostate. Anesthesiology 58:577, 1983.

129. Kenyon HR: Perforation in transurethral operations; technic for immediate diagnosis and management of extravasations. JAMA 142:798, 1950.

130. Holtgrewe HL, Valk WL: Factors influencing the mortality and morbidity of transurethral prostatectomy: A study of 2015 cases. J Urol 87:450, 1962.

131. Hatch PD: Surgical and anaesthetic considerations in transurethral resection of the prostate. Anaesth Intensive Care 15:203, 1987.

132. Mebust WK, Valk WL: Transurethral prostatectomy. In Hinman F Jr (ed): Benign Prostatic Hypertrophy. New York, Springer-Verlag, 1983, p 829.

133. Allen TD: Body temperature changes during prostatic resection as related to the temperature of the irrigating solution. J Urol 110:433, 1973.

134. Harioka T, Marakawa M, Noda J, Mori K: Effect of continuously warmed irrigating fluids during transurethral resection. Anaesth Intensive Care 16:324, 1988.

135. Heathcote PS, Dyer PM: The effect of warm irrigation on blood loss during transurethral prostatectomy under spinal anesthesia. Br J Urol 58:669, 1986.

136. Chambers FA, Corcoran M, O'Toole DP, Keane PW: The effects of pre-operative methoxamine on blood loss and hemodynamics during transurethral prostatic resection under spinal anesthesia. Anesthesiology 79(3A):A161, 1993.

137. Jensen V: The TURP syndrome. Can J Anaesth 38:90, 1991.

138. Mebust WK, Holtgreive HL, Cockett ATK et al: Transurethral prostatectomy--immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. J Urol 141:243, 1989.

139. MacKenzie AR: Influence of anaesthesia on blood loss in transurethral prostatectomy. Scott Med J 35:14, 1990.

140. Chung FF, Chung A, Meier RH et al: Comparison of perioperative mental function after general anesthesia and spinal anaesthesia with intravenous sedation. Can J Anaesth 36:382, 1989.

141. Hosking MP, Lobdell CM, Warner MA et al: Anesthesia for patients over 90 years of age. Outcomes after regional and general anesthetic techniques for two common procedures. Anaesthesia 44:142, 1989.

142. Rampil IJ: Anesthetic considerations for laser surgery. Anesth Analg 74:424, 1992.

143. Beck EM, Vaughan ED Jr, Sosa RE: The pulsed dye laser in the treatment of ureteral calculi. Semin Urol 7:25, 1989.

144. Malhotra V, Perlmutter A: Caudal anesthesia provides effective anesthesia for laser prostatectomy. Reg Anesth 22(2S):93, 1997.

145. Weingram J, Sosa RE, Stein B, Poppas D: Subcutaneous emphysema (SCE) during laparoscopic pelvic lymph node dissection (LPLND). Anesth Analg S460, 1993.

146. Rassweiler J, Henkel TO, Kohrmann KU et al: Lithotripter technology: Present and future. J Endourol 6:1, 1992.

147. Chaussy CG, Fuchs GJ: World experience with extracorporeal shock wave lithotripsy for the removal of urinary stones: An assessment of its role after 5 years of clinical use. J Endourol 1:7, 1986.

148. Drach DW, Dretler S, Fair W et al: Report of the United States cooperative study of extracorporeal shock wave lithotripsy. J Urol 135:1127, 1986.

149. Gravenstein JS, Peter K (eds): Extracorporeal Shock Wave Lithotripsy for Renal Stone Disease. Technical and Clinical Aspects. Boston, Butterworth, 1986, p. 9.

150. Carlson CA, Boysen PG, Banner MJ et al: Conventional vs high frequency jet ventilation for extracorporeal shock wave lithotripsy. Anesthesiology 63 (3A):A177, 1985.

151. Esch JS, Kochs E, Meyer WH: Improved efficiency of extracorporeal shock wave lithotripsy during high frequency jet ventilation. Anesthesiology 63 (3A):A177, 1985.

152. Carlson CA, Gravenstein JS, Banner MJ et al: Monitoring techniques during anesthesia and high frequency jet ventilation for extracorporeal shock wave lithotripsy. Anesthesiology 63 (3A):A178, 1985.

153. Berger JJ, Boysen PG, Gravenstein J et al: Failure of high frequency jet ventilation to ventilate patients adequately during extracorporeal shock wave lithotripsy. Anesth Analg 66:262, 1987.

154. Berger JJ, Boysen PG, Gravenstein JS et al: Optimal settings for tidal volume with high frequency ventilation for extracorporeal shock wave lithotripsy. Anesthesiology 65 (3A):A485, 1986.

155. Perel A, Hoffman B, Podeh D et al: High frequency conventional ventilation also minimizes respiratory-related movement of kidney stone during extracorporeal shock wave lithotripsy; is it, however, indicated? Anesthesiology 65 (3A):A160, 1986.

156. Zeitlin GL, Roth RA: Effect of three anesthetic techniques on the success of extracorporeal shock wave lithotripsy in nephrolithiasis. Anesthesiology 68:272, 1988.

157. Malhotra V, Benetos F: Kidney stone movement with spontaneous respiration during extracorporeal shock wave lithotripsy with intercostal blocks and local infiltration anesthesia. Reg Anaesth 14:25:39, 1989.

158. Pandit SK, Powell RB, Crider B et al: Epidural fentanyl: A simple and novel approach to anesthetic management for extracorporeal shock wave lithotripsy, abstracted. Anesthesiology 67 (3A):A225, 1987.

159. Pandit SK, Powell RB, Crider B et al: Epidural fentanyl is not effective for analgesia for extracorporeal shock wave lithotripsy. Anesthesiology 68:176, 1988.

160. Chaussy CG: Extracorporeal Shock Wave Lithotripsy: New Aspects in the Treatment of Kidney Stone Disease. Munich, Karger, 1986, p. 24.

161. Malhotra V, Gomillion MC, Artusio JF Jr: Hemoptysis in a child during extracorporeal shock wave lithotripsy. Anesth Analg 69:526, 1989.

162. Malhotra V, Rosen RJ, Slepian RL: Life-threatening hypoxemia in an adult due to shock wave induced pulmonary contusion. Anesthesiology 75:529, 1991.

163. Tredrea CR, Pathak D, From RP et al: Lung protection in children during extracorporeal shock wave lithotripsy. Anesth Analg 66:S178, 1987.

164. Carlson CA, Gravenstein JS, Gravenstein N: Ventricular tachycardia during extracorporeal shock wave lithotripsy for renal stone disease. In Gravenstein JS, Peter K (eds): Renal Stone Disease: Technical and Clinical Aspects. Boston, Butterworth, 1986, p 119.

165. Simon CA, LeHenzey NY, Baras E et al: Cardiac arrhythmias during extracorporeal shock wave lithotripsy under general anesthesia. Anesthesiology 65 (3A):A147, 1986.

166. Walts LF, Atlee JL: Supraventricular tachycardia associated with extracorporeal shock wave lithotripsy. Anesthesiology 65:521, 1986.

167. Weber W, Chaussy C, Madler C et al: Cardiocirculatory changes during anesthesia for extracorporeal shock wave lithotripsy. J Urol 4:246A, 1984.

168. Arborelius M Jr, Balldin UI, Lilja B et al: Hemodynamic changes in man during immersion with head above water. Aviat Space Environ Med 43:592, 1972.

169. Farhi LE, Linnarsson D: Cardiopulmonary readjustments during graded immersion in water at 35°C. Respir Physiol 30:35, 1977.

170. Loellgen H, Von Neiding G, Howes R: Respiratory and hemodynamic adjustment during head out of water immersion. Int J Sports Med 1:25, 1980.

171. Risch WD, Koubenec HJ, Beckmann U et al: The effect of graded immersion on heart volume, central venous pressure, pulmonary blood distribution heart rate in man. Pflugers Arch 374:115, 1978.

172. Behnia R, Shanks CA, Ovassapian A et al: Hemodynamic responses associated with lithotripsy. Anesth Analg 66:354, 1987.

173. Begin R, Epstein M, Sackner MA et al: Effects of water immersion to the neck on pulmonary circulation and tissue volume in man. J Appl Physiol 40:293, 1976.

174. Bromage PR, Bonsu AK, El-Fagih SR, Husain I: Influence of Dornier HM3 system on respiration during ESWL. Anesth Analg 68:363, 1989.

175. Higgins TL, Miller EV, Roberts J: Accidental hyperthermia as a complication of extracorporeal shock wave lithotripsy under general anesthesia. Anesth Analg 66:389, 1987.

176. Malhotra V: Hyperthermia and hypothermia as complications of extracorporeal shock wave lithotripsy. Anesthesiology 67:448, 1987.

177. Duvall JO, Griffith DP: Epidural anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 64:544, 1985.

178. Malhotra V, Long CW, Meister MJ: Intercostal blocks with local infiltration anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 66:85, 1987.

179. Abbott MA, Samuel JR, Webb DR et al: Anaesthesia for extracorporeal shock wave lithotripsy. Anaesthesia 40:1065, 1985.

180. Monk TG, Rater JM, White PF: Comparison of alfentanil and ketamine infusions in combination with midazolam for outpatient lithotripsy. Anesthesiology 74:1023, 1991.

181. Monk TG, Boure B, White PF et al: Comparison of intravenous sedative-analgesic techniques for outpatient immersion lithotripsy. Anesth Analg 72:626, 1991.

182. Freilich JD, Brull SJ, Schiff S et al: Anesthesia for lithotripsy: Efficacy of monitored anesthesia care with alfentanil. Anesth Analg 70:S115, 1990.

183. Bromage PR, Al-Faqih S, Kadiwal GH et al: Evaluation of bupivacaine and fentanyl analgesia for extracorporeal shock wave lithotripsy, (abstracted). Anesthesiology 57 (3A):1987.

184. Gissen D, Naroll M, Katz RL: Epidural fentanyl for extracorporeal shock wave lithotripsy. Reg Anaesth 3:40, 1988.

185. Korbon GA, Lunch C, Arnold WP et al: Repeated epidural anesthesia for extracorporeal shock wave lithotripsy unreliable. Anesth Analg 66:669, 1987.

186. Lander CJ, Korbon GA, Monk CR et al: Epidural anesthesia and extracorporeal shock wave lithotripsy: Pathologic effects on the epidural space. Anesthesiology 67 (3A):A227, 1987.

187. London RA, Kudlak T, Riehle RA: Immersion anesthesia for extracorporeal shock wave lithotripsy: Review of two hundred-twenty treatments. Urology 86, 1986.

188. Schelling G, Mendl G, Weber W, Joacham D: Patient controlled analgesia for shock wave lithotripsy of renal stones. Anesthesiology 72:A803, 1990.

189. Coleman SA, Davies JB: Alfentanil for extracorporeal shock wave lithotripsy. Pain 52:372, 1993.

190. Weber W, Back P, Wildgans H et al: Anesthetic considerations in patients with cardiac pacemakers undergoing extracorporeal shock wave lithotripsy. Anesth Analg 67:S251, 1988.

191. Landberg J, Abber J, Thuroff JW et al: The effects of extracorporeal shock wave lithotripsy on pacemaker function Pacing Clin Electrophysiol 10:1142, 1987.

192. Cooper D, Wilkoff B, Masterson M et al: Effects of extracorporeal shock wave lithotripsy on cardiac pacemakers and its safety in patients with implanted cardiac pacemakers. Pacing Clin Electrophysiol 11:1607, 1988.

193. Vassolas G, Roth RA, Venditti FJ Jr: Effects of extracorporeal shock wave lithotripsy on implantable cardioverter defibrillators. Pacing Clin Electrophysiol 16:1245, 1993.

194. Lieskovsky G, Pritchett R, Skinner DG: Surgical management of renal cell carcinoma. Monogr Urol 5:98, 1984.

195. Shah N: Radical cystectomy, radical nephrectomy and retroperitoneal lymph node dissection. In Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, pp 197-226.

196. Monk TG: Cancer of the prostate and radical prostatectomy. In Malhotra V (ed): Anesthesia for Renal and Genitourinary Surgery. New York, McGraw-Hill, 1996, pp 177-195.

197. Catalona WJ: Surgical management of prostate cancer. Contemporary results with anatomic surgical prostatectomy. Cancer 75:1903, 1995.

198. Albin MS, Ritter RR, Reinhart R et al: Venous air embolism during radical retropubic prostatectomy. Anesth Analg 74:151, 1992.

199. Malhotra V, Girardi S: A comparison of epidural, general and combined epidural: General anesthesia for radical prostatectomy. Anesthesiology 81(3A):973, 1994.

200. Shir Y, Frank SM, Brendler CB, Raja SN: Postoperative morbidity is similar in patients anesthetized with epidural and general anesthesia for radical prostatectomy. Urology 44:232, 1994.

201. Patt RB, Plancarte RS: Pelvic pain. In Raj PP (ed): Pain Medicine. St Louis, Mosby, 1996, p 440.

202. Patt RB, Plancarte RS: Superior hypogastric plexus block. In Waldman SD, Winnie AP (eds): Interventional Pain Management. Philadelphia, WB Saunders, 1996, p 384.

203. Helms, JM. Acupuncture for the management of primary dysmenorrhoea. Obstet Gynecol 69(1):51, 1987.

Chapter 54 - Anesthesia and the Hepatobiliary System

Mervyn Maze
Nathan M. Bass

INTRODUCTION

Mortality from liver disease has almost doubled in the last three decades in the United States and is increasing at an even faster rate in Canada, where it is now the fifth major cause of death for men in the productive ages from 25 to 64 years. [1] The most likely reason for this increase is the increasing consumption of alcohol, which has been found to parallel the rate of liver disease, especially cirrhosis, in all countries where statistics are kept. [2] Regardless of cause, more patients with liver disease are presenting for anesthesia and surgery than ever before and, with the advent of liver transplantation in many centers, an even greater number may be expected in the future.

Anesthesia and surgery may exacerbate liver dysfunction in patients with preexisting liver disease and in some cases may precipitate life-threatening hepatic failure. [3] [4] The degree to which this occurs depends more on the type and extent of the functional liver impairment than on its precise etiology. Accordingly, the preanesthetic work-up of patients with liver disease should focus on the pattern of liver injury and the severity of the functional abnormality present. In this chapter, the patterns of liver disease have been divided into parenchymal (acute and chronic) and cholestatic liver disease.

ACUTE PARENCHYMAL LIVER DISEASE

Hepatocellular damage is caused by a variety of drugs, toxins, and viruses. Viral or drug-induced hepatitis is commonly encountered in patients presenting for surgery. The cause of hepatitis is often difficult to ascertain from the clinical picture alone. Careful history, including specific questions about drug use, a sexual history, and an understanding of serologic markers are essential in differentiation of the various types of hepatitis.

Acute Viral Hepatitis

Acute viral hepatitis of any type has a broad clinical spectrum. Patients may be completely asymptomatic or critically ill. Many patients experience a nonspecific illness characterized by nausea, vomiting, anorexia, and malaise. Vague abdominal discomfort is more common than localized right upper quadrant pain; low-grade fever is common. Overt jaundice occurs in about half the patients with acute viral hepatitis. Extrahepatic manifestations such as arthralgias and myalgias may be present.

Hepatitis A is an enterovirus spread by the fecal-oral route. The virus is endemic throughout the world. In industrial nations, food-borne common-source outbreaks are an important source of virus. Viral outbreaks are also common in institutions and daycare centers. Hepatitis A is not usually a nosocomial problem because patients generally present themselves after the period of viral shedding, but hospital outbreaks have been reported. [5] Viral shedding in feces occurs as early as 9 days after exposure and decreases after the onset of jaundice; therefore, patients are highly infectious for several weeks.

Acute hepatitis A is diagnosed serologically by elevated titers of immunoglobulin M antihepatitis A virus (IgM anti-HAV). This marker peaks within a month of clinical illness then disappears by 3 to 6 months. IgG antibody develops several months after infection and persists indefinitely.

Most patients with acute hepatitis A recover within weeks, and no chronic carrier state has been reported. A rare cholestatic variant may cause persistent jaundice, [6] but these patients are not infectious. Acute fulminant hepatic failure from hepatitis A is an unusual presentation. Transfusion-acquired hepatitis A is an extremely rare disease. [7]

Hepatitis B is transmitted percutaneously via infected serum or blood or by sexual contact. Serologic diagnosis of acute hepatitis B is confirmed by the presence of hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core antigen (IgM anti-HBc). Hepatitis e antigen follows

TABLE 54-1 -- Serologic Status at Different Stages of HBV Infection

	ACUTE INFECTION		POSTINFECTION		PERSISTENT INFECTION	
	EARLY	LATE	EARLY	LATE	NONREPLICATIVE	REPLICATIVE
HBsAg	++	±	-	-	+	++
Anti-HBc	-	-	+	-	++	++
Anti-HBc IgM	-	+	-	-	-	-
Anti-HBs	-	±	+	+	-	-
HBV-DNA	+	-	-	-	-	+
HBeAg	+	-	-	-	-	+
HBcAg (liver)	+	-	-	-	-	-

the pattern of HBsAG, so that patients who recover normally should clear HBeAg by 6 months. [8] Antibody to the surface antigen (anti-HBs) is not present during the acute illness, developing instead about 6 months after exposure in patients who recover from the disease. This antibody is protective against future infection. Recovered patients also develop antibody to the E antigen (Table 54-1) .

Delta hepatitis or hepatitis D may complicate the course of patients with hepatitis B. The delta virus is an RNA strand that requires hepatitis B for replication. Hepatitis B and D may be acquired together, or delta hepatitis may be a superinfection in patients who are carriers of hepatitis B virus. The combination of hepatitis B and hepatitis D infection is a more severe illness than isolated type-B hepatitis. [9] IgM anti-HDV is present in patients with both acute and chronic delta infections, and high titers in chronic carriers may indicate a poor prognosis. [10] Chronically infected patients develop an IgG antibody. [11] Molecular hybridization assays may be the best way to monitor the hepatitis D viral RNA associated with viral replication. Alternatively, the hepatitis D antigen can be detected by immunoblotting. [12] Hepatitis D is largely confined to intravenous drug abusers and commonly leads to chronic liver disease.

Hepatitis C (formerly, non-A, non-B) virus infection occurs in 2 to 4 percent of patients receiving a transfusion with blood or blood products. The incubation period following transfusion can be from 1 to 4 months; an enteric form of hepatitis C viral infection is responsible for up to 40 percent of cases in which there is no association with transfusion of any kind. [13] Recently, the viral genome for hepatitis C virus has been cloned. This has resulted in the development of very sensitive and specific serologic tests that can diagnose more than 90 percent of the chronic and more than 60 percent of the acute cases. Since the development of the sensitive serologic tests for hepatitis, the incidence of posttransfusion hepatitis from any cause has dropped 10-fold to 6 percent. More recently, hepatitis C RNA by polymerase chain reaction (HCV RNA by PCR) has become available and is indicative of acute or chronic infection with hepatitis C.

Acute Drug-Induced Hepatitis

Drugs, including alcohol, are common causes of acute hepatic parenchymal injury. Toxins in the workplace, such as carbon tetrachloride and vinyl chloride, may also cause hepatocellular damage. Unfortunately, drinking histories are notoriously unreliable, so the diagnosis of alcoholic hepatitis often rests on a high index of suspicion and diagnostic laboratory tests. Similarly, a history of drug abuse may be difficult to elicit. Therapeutic drugs most frequently implicated in acute hepatitis include acetaminophen, isoniazid, methyldopa, rifampicin, acetylsalicylic acid, and other nonsteroidal anti-inflammatory drugs (NSAIDs). [14] The most common reaction leading to liver cell necrosis is the formation of covalent bonds between a reactive metabolite of the parent compound and the cell proteins or DNA.

If drug-induced hepatitis is suspected, it may be possible to assay for a particular drug in the plasma or urine. For example, because alcoholic hepatitis usually follows a period of particularly heavy drinking, alcohol may still be detected in the plasma. Serum salicylate concentrations above 250 ng/mL are associated with

abnormalities in liver function. [15] Acetaminophen levels above 4 to 5 ng/mL 24 hours after ingestion are associated with acute hepatitis. [16] Acute acetaminophen is particularly important to identify, because a specific antidote, N-acetylcysteine, may be life-saving therapy by restoring the available glutathione stores. [17] Acetaminophen hepatotoxicity is potentiated by alcohol. [18] Acute drug-induced injury to the liver is often mediated by cytochrome P-450, which is capable of transforming drugs into reactive electrophilic compounds or oxygen intermediates (such as the superoxide anion or free radicals and metabolites such as electrophiles or free radicals). These metabolites then induce a series of toxic reactions. [19]

Most drugs only rarely produce toxic reactions and may be related to enzyme polymorphism in which a genetic variant of P-450 contributes either to a lack of metabolism of the parent compound or excess formation of the toxic metabolite.

Acute Toxin-Induced Hepatitis

This is most commonly seen after exposure to toxins such as *Amanita phalloides*, a mushroom particularly prevalent in northern California in the winter and early spring. Patients suffering from acute liver cell failure may need urgent liver transplantation, and may also need intracranial pressure monitoring and hence care by an anesthesiologist. *Amanita* and other acute liver toxins can essentially ablate hepatic function a while, but the liver will eventually regenerate. Hence there has been successful use of auxiliary liver transplantation

in some patients. A left lateral segment of the left hepatic lobe is transplanted into the recipient after removal of the recipient's own left lobe. The recipient's own necrosed right lobe eventually regenerates and the transplanted left segment is allowed to reject and is then removed some days to weeks later. This procedure is referred to as a partial liver graft.

Assessment of Liver Function

Liver function (Ch. 25) tests in patients with acute parenchymal disease may reflect hepatocellular injury and abnormalities in hepatic synthetic function. Within the liver cells, the aminotransferases convert amino acids into their corresponding alpha ketoacids for further metabolism. Significant elevations of serum glutamic oxaloacetic transaminase (SGOT or aspartate aminotransferase [AST]) and serum glutamic pyruvic transaminase (SGPT or alanine aminotransferase [ALT]) are characteristic of hepatocellular damage. In most patients the AST/ALT ratio is 1:1. However, when the AST level is more than twice that of the ALT a diagnosis of alcoholic hepatitis is likely. [20] Although the extent to which the serum transaminase levels rise may reflect acuity and extent of injury, these levels do not correlate well with prognosis. SGPT is found predominantly but not exclusively in the liver, whereas SGOT is found in a variety of tissues, especially muscle. Lactate dehydrogenase (LDH) is abundant in the liver and is released into the blood during hepatocellular injury but may rise from many sources including red blood cells (RBC). Acute ischemic injury to the liver may also result in a picture similar to an acute viral or toxic hepatitis.

Prothrombin time is a useful test of liver cell function, as it reflects the impaired ability of the acutely damaged liver to synthesize clotting factors. Although synthesis of other products from the liver such as albumin may also be affected, albumin has a longer plasma half-life than the clotting factors; albumin levels may remain within normal limits for days even if hepatic production ceases entirely. The prothrombin time measures the rate of conversion of prothrombin to thrombin in the presence of thromboplastin, calcium ions, and several activated factors. A prothrombin time more than 4 seconds above control is distinctly abnormal (to standardize the prothrombin time, values are now expressed as an international normalized ratio [actual/control ratio]). In acute parenchymal injury, the prothrombin time reflects the severity of liver dysfunction and has definite prognostic significance. [21] [22]

In addition to elevated transaminases and abnormal prothrombin time, mild elevation of bilirubin and alkaline phosphatase are the rule. Hypoglycemia is also seen occasionally, especially if hepatic injury is severe.

Liver biopsy may be useful in establishing the qualitative pattern of injury, even in the case of acute drug-induced hepatitis. [19] In addition, in patients with fulminant hepatic failure, a quantitative estimate of hepatocyte damage can be made by examining a biopsy specimen; in the severest cases no hepatocytes are seen. In cases of acute alcoholic hepatitis, Mallory hyaline bodies may be present. [23] Viral inclusion bodies seen on pathologic examination of a biopsy specimen may point to a diagnosis.

Preoperative Considerations

The diagnosis of viral hepatitis is established by measuring viral proteins (antigens) in the blood and identifying characteristic immunologic responses (antibodies) during and after acute infection. Because of the risk to operating room personnel (Ch. 84) , the diagnosis of infectious hepatitis should be actively pursued in any patient with liver disease of unknown cause. If hepatitis B is suspected, serologic studies of the carrier may help determine the infectious risk to hospital personnel. [24] All patients with acute hepatitis B should be considered infectious.

Hepatitis B is an occupational risk for anesthesiologists. One multicenter study demonstrated a 12.7 percent rate of seropositivity in anesthesia residents and a 23.3 percent seropositivity in anesthesia faculty. [25] Hepatitis B vaccination is protective in the vast majority of health-care workers, [26] and vaccine responders are also protected against delta infection. The yeast-recombinant hepatitis B vaccine theoretically carries no risk of infection for vaccinated persons. [27] Vaccination for anesthesiologists is strongly recommended by the Centers for Disease Control and Prevention, [28] especially in light of a retrospective study suggesting that gloves are not sufficient protection for this disease. [29]

If a health-care worker is exposed to a needle stick, both the health-care worker and the source (contact) should be tested for HCV antibody and HBV serologic markers (surface antigen, surface antibody, core antibody, and E antigen). If the patient has markers for HBV infection (surface antigenemia), the health-care worker should receive a dose of HB immune globulin [30] , and a course of HBV vaccination should be commenced within 7 days. If the health-care worker is immune to HBV (surface antibody positive), no treatment is needed. With exposure by needle stick to HCV, the current recommendation is to monitor the health-care worker for seroconversion to HCV antibody positive status at 3 and 6 months. If seroconversion occurs, interferon at conventional dosage (3 million units three times a week) should be commenced. A more aggressive approach is to detect infection by performing HCV RNA by PCR at 3 and 6 months in addition to HCV antibody. If conversion occurs, interferon, 5 to 10 million units daily, has been recommended for a minimum of 6 months.

If possible, elective surgery should be postponed in patients with acute hepatocellular injury because of increased risk of morbidity and mortality. In particular, surgery carried out in the presence of acute viral hepatitis is associated with a higher than normal incidence of major complications. In one study, 9.5 percent of patients with acute viral hepatitis undergoing laparotomy died, and a further 12 percent developed significant morbidity. The unusual patient with a cholestatic pattern of injury associated with hepatitis probably should also not undergo elective surgery and anesthesia.

The preoperative management of a patient with acute parenchymal liver disease will depend on the severity of liver dysfunction. The clinical picture may be so mild that no treatment is required, or so severe that acute liver failure occurs and aggressive intervention is required. In patients with acute encephalopathy, sedative drugs for premedication may dramatically exacerbate encephalopathy and, therefore, should be avoided. Frequent blood glucose monitoring is important in preoperative management, as these

patients may rapidly develop hypoglycemia and secondary neurologic damage. Acid-base disturbances, particularly respiratory alkalosis, may be profound. Electrolyte disturbances may contribute to encephalopathy, and appropriate therapy should be initiated before the surgical procedure. Hypoxemia is a frequent finding [31] despite hyperventilation. Many patients with acute hepatocellular injury also develop renal insufficiency. [32] Damage to kidneys may be caused by the same toxin affecting the liver or, more commonly, is secondary to hepatic damage.

If coagulopathy is present, surgical bleeding may be severe. Correction of clotting factor deficits with vitamin K and fresh frozen plasma may be indicated. Similarly,

appropriately timed platelet transfusions may aid the surgeon. Patients with liver disease are also more susceptible to bacterial infection.

In the preoperative management of a patient with an isolated abnormality of liver function tests (Fig. 54-1) , one should never assume that the abnormality is definitely due to alcohol (e.g., an elevated alkaline phosphatase cannot be explained on the basis of alcohol). An isolated elevation of gamma-glutamyl transpeptidase is typical of most drinkers and does not imply liver disease. The degree to which the transaminase levels are elevated dictates further management; if less than twice normal values are observed, it is important to try to elicit whether there has been recent exposure to potentially

Figure 54-1 Algorithm for work-up of unexpected abnormality in transaminase levels.

hepatotoxic medications or toxins (especially alcohol), and what the risk factors are for the acquisition of infectious liver disease (viral hepatitis) in the individual patient. If the patient has a twice normal increase in aminotransferases and/or gamma-glutamyltransferase, complete abstinence should be advised and the tests should be repeated after a week. If the tests are still abnormal, a full work-up, including complete blood count (CBC) and platelets, viral serologies, autoantibodies, ceruloplasmin, and iron studies are indicated. A right upper quadrant ultrasound is also indicated in the work-up of a persistent abnormality. Tests that are abnormal only in the setting of drinking suggest that more alcohol ingestion is occurring than is admitted, and attempts to get the patient to stop drinking should be initiated. Caring for the problem drinker in the perioperative period is a challenging task. If alcohol abuse is suspected, a careful preoperative evaluation of alcohol-dependent patients should include a CBC, blood urea nitrogen, serum electrolyte levels, creatinine and glucose levels, liver function tests, coagulation studies, an electrocardiogram, and a chest radiograph. Smoking cessation and aggressive postoperative respiratory care are especially important for alcoholic patients who have chronic obstructive pulmonary disease. Elective surgery should not be considered in patients with acute hepatitis or cirrhosis, because the operative mortality rate is quite high in these patients. In the event that the liver function tests are markedly elevated (>3 times normal), elective cases that require general or regional anesthesia should be delayed until further work-up is completed, as each of these forms of anesthesia reduced hepatic blood flow by 30 to 50 percent, which may set the stage for rapid deterioration in liver function. [4] Patients undergoing exploratory laparotomy with unsuspected parenchymal liver disease have a 31 percent mortality rate. [33]

Intraoperative Considerations

The reason for the poor prognosis in patients undergoing surgery in the presence of acute viral hepatitis may be related to decreased total hepatic blood flow that accompanies all forms of anesthesia. Additionally, total hepatic necrosis may be precipitated by relative hypoperfusion in an already diseased liver. Thus, if the diagnosis is uncertain or emergency surgery is necessary in patients with acute parenchymal disease, attempts to maintain hepatic blood flow at near normal levels should be the goal of intraoperative therapy. Although the relationship between anesthetic-induced changes in liver blood flow and liver function is not clear, it seems reasonable to maintain liver blood flow as close to normal as possible. Isoflurane, in animal models, has no major deleterious effect on hepatic circulation. [34] Mechanical ventilation with positive pressure is theoretically more deleterious to liver blood flow than spontaneous ventilation. On the other hand, hypercarbia initiates sympathetic stimulation of the splanchnic vasculature, resulting in decreased portal blood flow. Because the nature and anatomic location of the surgery, anesthetic drugs, and techniques may all modify liver blood flow, CO_2 probably should be maintained in the range of 35 to 40 mm Hg.

Drug disposition in the presence of acute parenchymal disease may be difficult to predict because of the marked differences in liver response to high and low extraction ratio drugs. [35] For example, the half-life of meperidine is considerably prolonged in patients with parenchymal liver disease. [36] Furthermore, certain intravenous drugs such as chlorpromazine, which act on the central nervous system (CNS) have a more pronounced depressant effect in patients with hepatic impairment. [37] In addition, the liver synthesizes hydrolytic enzymes that catalyze the intravascular inactivation of certain local anesthetic esters and other drugs such as succinylcholine. Because pseudocholinesterase is relatively stable, prolonged apnea from pseudocholinesterase deficiency after succinylcholine administration is rare, even in patients with fulminant hepatic failure (Ch. 12) .

CHRONIC PARENCHYMAL LIVER DISEASE

This pattern of liver disease may produce little alteration in standard liver tests and may be clinically and biochemically undetectable. Hepatic reserve, however, may be limited and decompensation may occur when an additional insult, often iatrogenic, is introduced. Chronic parenchymal disease can be subdivided into two major categories: chronic hepatitis (precirrhotic) and cirrhosis.

Chronic hepatitis is an hepatic inflammatory process that has persisted for at least 24 weeks and has resulted in abnormalities in hepatic function. [38] Patients have been classified as having chronic persistent or chronic active hepatitis based on liver biopsy, but the distinction is often difficult to make. Chronic persistent hepatitis is the milder hepatic lesion, characterized by inflammation in the portal tracts with minimal cell necrosis and no disruption of the normal architecture. [39] Abnormalities in liver function are trivial, with modest elevations of transaminase being the only notable feature.

Liver biopsies of patients with chronic active hepatitis reveal scar tissue and inflammatory cells, which disrupt normal hepatic structure. Not surprisingly, patients with chronic active hepatitis have higher rates of morbidity and mortality than those with chronic persistent hepatitis. The estimated 5-year survival rate is 97 percent for patients with chronic persistent hepatitis, 86 percent for chronic active hepatitis, and 55 percent for chronic active hepatitis. [40] Despite these percentages, the natural history of chronic active hepatitis in an individual patient is extremely variable. Patients with chronic active hepatitis in remission may be totally asymptomatic, but most complain of fatigue and malaise. Stigmata of chronic liver disease should be sought on clinical examination. In symptomatic cases, liver function tests are usually markedly abnormal, with evidence of hepatocellular injury (high transaminases) and diminished synthetic function (low albumin, prolonged prothrombin time).

Patients with persistence of HBsAg 6 months after exposure are considered chronic carriers of hepatitis B (Table 54-2) . A chronic state develops in 5 to 10 percent of acutely infected patients. These patients do not develop the protective anti-HBs. Chronic carriers of virus have low, fluctuating, or absent titers of IgM anti-HBc. [41] Persistent high titers of IgG anti-HBc may indicate increased infectivity. The presence of hepatitis B DNA polymerase is considered a marker

TABLE 54-2 -- Serologic Markers of Hepatitis B Viral Infection

MARKER	DEFINITION	SIGNIFICANCE
HBsAg	HBV surface antigen	Acute or chronic infection
Anti-HBs	Antibody to HBV surface antigen	Past infection resolved, immune
Anti-HBc	Antibody to HBV core antigen	Acute, chronic, or past infection (not protective)
HBeAg	HBV e antigen	High state of viral replication (= host very infectious) - acute or chronic infection
Anti-HBe	Antibody to e antigen	Low state of viral replication
HBV-DNA	HBV genomic DNA	Same as HbeAg

of active viral replication and infectivity and may be assayed in the absence of conventional hepatitis B markers. [42] A chronic carrier state follows infection with hepatitis C virus in 40 percent of cases. These patients may be infectious for prolonged periods. [43]

Until recently, therapeutic options for these patients with chronic viral disease were extremely limited. Corticosteroid therapy alone is not useful in patients with chronic hepatitis B. [44] Interferon therapy showed some promise when used alone, [45] [46] but a regimen of prednisone withdrawal followed by interferon shows particular promise. [47] Recent studies suggest that recombinant human alpha-interferon can improve the biochemical abnormalities associated with hepatitis C virus. [48] Furthermore, a combination of ribavirin together with alpha-2B interferon appears to be especially efficacious. [49]

Several drugs are known to cause chronic liver disease that is pathologically identical to virally induced forms of hepatitis. [19] These drugs include methyldopa [50] and isoniazid. [51] In most cases, drug-induced hepatitis resolves after drug ingestion ceases.

Autoimmune hepatitis is characterized by the presence of humoral and cellular markers of immunologic disease. Patients may have smooth muscle antibody or antinuclear antibody in their serum. Selected patients may benefit from treatment with steroids or immunosuppressants, drugs that must be considered in the anesthetic plan.

Diagnosis of metabolic causes of chronic hepatocellular disease requires specific laboratory studies. For example, serum alpha-1 antitrypsin [52] may be assayed and phenotyped by isoelectric focusing of serum proteins, whereas the genotype can be established by PCR. Diagnosis may be confirmed by the demonstration of characteristic periodic acid-Schiff- positive diastase-resistant globules adjacent to liver portal tracts. Adult patients with this disorder often have emphysema. [53]

Wilson disease is an inherited disorder characterized by copper accumulation, especially in the liver, kidneys, central nervous system, and eyes. [54] Copper deposits in the eyes seen under slit-lamp, Kayser-Fleischer rings, are pathognomonic for Wilson disease. Most patients with this disease have low serum ceruloplasmin levels and increased urinary copper levels. [55] The chelating agent, penicillamine, is first-line therapy. [56]

Cirrhosis is a syndrome characterized by severe hepatic fibrosis and nodular regeneration. Worldwide, 50 percent of cirrhosis is linked to alcohol abuse, but in some countries the rate is as high as 90 percent. All types of alcoholic beverages cause liver disease, and their tendency to do so depends only on alcohol content. Regular daily consumption in excess of 80 g of alcohol for more than 9 years is more dangerous than intermittent sprees. [57] Women are more susceptible to liver damage from alcohol than are men. Chronic active hepatitis of any cause may progress to cirrhosis.

In addition to the types of hepatitis discussed previously, other rare causes of liver disease with a propensity to progress to cirrhosis include hemochromatosis and primary biliary cirrhosis. In patients with hemochromatosis, iron accumulates in hepatic parenchymal cells. [58] Patients with cirrhosis resulting from hemochromatosis have a high rate of liver cancer. [59] Characteristically, patients with hemochromatosis have elevated serum ferritin levels and an increase in transferrin saturation, but the diagnosis is often best made by liver biopsy. [60]

Primary biliary cirrhosis, which predominantly affects women, is characterized by cholestasis progressing to hepatic fibrosis. Women with this disorder frequently have malabsorption, osteoporosis, and autoimmune diseases. [61] Serum cholesterol levels are very high, and serum is usually positive for antimitochondrial antibodies.

Cryptogenic cirrhosis (no cause found) is another rare diagnosis.

The clinical presentation of cirrhosis ranges from the asymptomatic patient with normal or nearly normal liver function to the severely decompensated patient with deep jaundice and ascites. Patients with compensated cirrhosis may be completely asymptomatic or have nonspecific symptoms such as malaise, weight loss, loss of libido, and menstrual disturbances. Physical signs, if any, may include such changes as white skin spots, paper-money skin, palmar erythema, and white nails. Clubbing and cyanosis are occasionally seen.

A high-output circulatory state is a frequent feature of advanced cirrhosis, [62] associated with arteriovenous shunting, especially in the lungs. Hepatosplenomegaly may be present. Occasionally, the left lobe of the liver is prominent (particularly in alcoholics), resulting in an easily palpable and diagnostically confusing epigastric mass. Regardless of the cause, the complications of cirrhosis are similar and protean.

Preoperative Considerations

Various complications associated with cirrhosis may require intervention before a patient undergoes anesthesia and surgery. Portal hypertension is associated with complications often refractory to medical therapy including ascites, varices, and hepatorenal syndrome. Normally, pressure in the portal vein ranges between 5 and 10 mm Hg but rises when progressive disruption of the hepatic architecture distorts the normal channels for portal blood flow. When the portal pressure exceeds 10 mm Hg, a collateral circulation develops between the high pressure portal system and neighboring low pressure splenic veins, and hence portal blood is diverted to the systemic circulation. The most clinically important portal system shunts are in the gastric and esophageal veins. These varices may rupture, resulting in gastrointestinal tract (GI) hemorrhage.

Initial management of patients with GI hemorrhage involves intravenous fluid resuscitation to correct hypovolemic

shock; however, overvigorous fluid resuscitation can cause variceal rebleeding. Simultaneously, the specific source of bleeding is sought. Although varices are common in patients with alcoholic cirrhosis, they are not the only source of bleeding, [63] and endoscopy is necessary to establish the source of hemorrhage. Thereafter, a combination of mechanical and pharmacologic interventions is used to limit the bleeding.

Vasopressin lowers portal venous pressure principally by constricting the splanchnic arteriolar bed and increasing resistance to inflow of blood to the gut. Because the drug effect is not confined to the gut vasculature, serious hemodynamic consequences, including a decrease in cardiac output and vasoconstriction of the coronary arteries, may occur. Octreotide is as effective as vasopressin at decreasing variceal bleeding, but appears to have considerably fewer adverse effects on the cardiovascular system. [64]

Balloon tamponade with a Sengstaken-Blakemore tube (SBT) has been a valuable primary therapy for controlling active variceal hemorrhage, allowing resuscitation and transport of a patient to a main center for definitive therapy. Complications that may follow balloon tamponade include airway obstruction from dislocation of the tube and pulmonary aspiration of saliva. As a result, endotracheal intubation is performed in many institutions before passage of the SBT. Fewer than half the patients who have balloon tamponade as part of therapy have their bleeding controlled in a long-term fashion. Injection of sclerosing solutions via the esophagoscope directly into varices is now the treatment of choice in the definitive management of bleeding esophageal varices and can control bleeding in up to 90 percent of cases; however, this strategy is less effective if rebleeding occurs. [65] Transjugular intrahepatic portosystemic shunt is a relatively new advance in the management of variceal hemorrhage that involves anesthesiologists perioperatively. [66] In this interventional radiologic procedure, a communication is created between the hepatic and portal veins through the hepatic parenchyma with an expandable metallic stent, and it has proved to be an attractive alternative to the more invasive portacaval shunt surgery. [67] However, even though the procedure is less demanding for the patient, the anesthesiologist must be just as vigilant because the patient is likely to be a Pugh-Child B or C with a high propensity for severe morbidity.

Ascites and generalized fluid retention are due to portal hypertension and sodium retention that occurs with cirrhosis. Ascitic fluid is in dynamic equilibrium with plasma. If massive abdominal paracentesis is performed, a marked reduction in plasma volume occurs, resulting in hypotension and oliguria unless intravenous crystalloid and colloid solutions are given simultaneously. Ascites is usually treated by sodium and water restriction and administration of diuretics. More recently therapeutic paracentesis has been used successfully. The goal of therapy for ascites is loss of no more than 0.5 kg of body weight per day because a brisker diuresis may precipitate the hepatorenal syndrome. [68] Spontaneous bacterial infection of ascitic fluid resulting in peritonitis occurs in up to 10 percent of cirrhotic patients with ascites. Hyponatremia is a common complication after treatment with proximally acting diuretics and hyperkalemia after distally acting diuretics. Thus, serum electrolytes should be checked frequently, especially in the initial stages of treatment, and any disturbances should be corrected promptly.

The onset of progressive renal failure (hepatorenal failure) is a common preterminal complication in patients with end-stage liver disease. This is the result of a severe intrarenal vasoconstriction, which is precipitated by a neurohumoral response to a sensed intravascular volume depletion (from peripheral vasodilation) and possibly to the existence of portal hypertension. If a cirrhotic patient with ascites does become intravascularly volume depleted, the hepatorenal syndrome may be precipitated; also vigorous use of very potent diuretics (e.g. Zaroxolyn) can contribute to the onset of the hepatorenal syndrome, especially in patients who have ascites that has become relatively refractory to diuretics. More diuretics in this setting induce a prerenal state. More powerful diuretics (e.g., Zaroxolyn) are even more hazardous. After the hepatorenal syndrome has been established, the kidneys are extremely sensitive to various insults including volume depletion and nephrotoxic drugs (e.g., aminoglycoside antibiotics, which are absolutely contraindicated; NSAIDs; and renal contrast). The recommended therapy is with dopamine infusions. The average duration of life after the onset of azotemia is less than 6 weeks, but death is usually attributable to a major complication of the liver disease rather than to renal decompensation. Treatable causes of renal failure, especially dehydration, should always be sought. Paracentesis of tense ascites may occasionally improve renal function in this setting.

Hepatic encephalopathy is a reversible neuropsychiatric syndrome seen in association with severe acute or chronic liver disease. Clinical features may be subtle at first, including changes in personality and dulling of the intellect. Later, progressive neurologic disturbances including incoordination, dysarthria, a flapping tremor, and increased tone with hyperreflexia may supervene. The development of hepatic encephalopathy may merely reflect a gradual worsening of the liver disease with worsening of portal systemic shunting. On the other hand, encephalopathy is often precipitated by infection, GI hemorrhage, hypokalemia, alkalosis, azotemia and constipation, or dietary excess of protein. Iatrogenic factors precipitating encephalopathy include injudicious use of sedatives (especially long-acting benzodiazepines), opiates, and diuretics. Treatment for encephalopathy focuses on reversal of precipitating factors. Lactulose and neomycin are often used to limit bacterial production of toxins that cannot be cleared by the dysfunctional liver. Flumazenil, the benzodiazepine receptor antagonist, has been shown to reverse the coma in selected patients over a prolonged period. [69]

The electroencephalography in hepatic encephalopathy typically shows bilateral slow waves that are synchronous and symmetric (delta wave activity) and are superimposed on the normal alpha rhythm. The pattern is also seen in several other metabolic encephalopathies but is not pathognomonic. Blood ammonia concentration is generally higher on average in patients with hepatic encephalopathy than in patients with chronic liver disease without encephalopathy, but this test is not specific or diagnostic.

The Child-Turcotte laboratory and clinical criteria are good predictors of operative survival [70] (Table 54-3) . These predictions were based on a surgical cohort of patients undergoing portosystemic shunts. However, these guidelines have been adopted for all types of surgical procedures in patients

TABLE 54-3 -- Laboratory and Clinical Criteria for Estimating Hepatic Reserve (Child-Turcotte Classification)

CRITERIA	CLASS A	CLASS B	CLASS C
Serum bilirubin mg/100 mL	<2.0	2.0-3.0	>3.0
Serum albumin g/100 mL	>3.5	3.0-3.5	<3.0

Ascites	None	Easily controlled	Not easily controlled
Encephalopathy	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor
Prothrombin time [a] (sec > control)	1-4	4-6	>6
Surgical risk mortality rate	5%	10%	50%

[a] Pugh modification.

with cirrhosis. Subsequently Pugh et al [71] provided a predictive scoring system using the same laboratory and clinical criteria adding evaluation of the prothrombin time.

Intraoperative Considerations

Complicated alterations in drug pharmacokinetics occur in patients with chronic liver disease, making it difficult to predict, except in very general terms, the appropriate drug therapy for a particular patient. [35] Parenchymal liver disease most predictably alters metabolism of drugs with high extraction ratios (e.g., lidocaine, meperidine, and morphine) due to their exquisite sensitivity to altered hepatic blood flow. If possible, drugs that are excreted via the liver probably should be avoided or given in small doses. Most of the commonly used intravenous drugs for induction of anesthesia are metabolized by the liver, but recovery from their effects depends on redistribution rather than metabolism. This has recently been confirmed for propofol in well-compensated cirrhotic patients. [72] Also, there appears to be considerable extrahepatic metabolism of propofol, which can be appreciated during the anhepatic phase of orthotopic liver transplantation. [73] Although the plasma protein binding of thiopental is decreased in patients with cirrhosis, this effect is compensated for by a decreased capacity for thiopental metabolism by the diseased liver [74] ; therefore the total body clearance of thiopental is unaltered in cirrhosis. [74] Additionally, higher doses are needed for patients with alcoholic liver disease in whom cross-tolerance between alcohol and barbiturates may be present. [75] In adults with uncomplicated alcoholic cirrhosis, the elimination half-life after a single bolus dose of either fentanyl [76] or sufentanil [77] is unaltered. Given the fact that remifentanil is metabolized by nonspecific blood and tissue esterases, it too would appear to be a safe alternative for patients with liver disease. Large doses of nondepolarizing muscle relaxants may have prolonged duration of action in patients with cirrhosis. [78] [79] However, if the dose of vecuronium and atracurium are kept below 0.15 and 0.6 mg/kg, respectively, the kinetics and duration of action will not be altered in patients with hepatic cirrhosis. [80] [81] In theory, atracurium should offer an advantage because its metabolism is apparently independent of the liver. It is metabolized by Hoffman elimination, a nonenzymatic degradation that proceeds rapidly in serum by a pseudocholinesterase-independent ester hydrolysis (Ch. 12) . In contrast, termination of the action of succinylcholine is dependent on pseudocholinesterase, which is synthesized in the liver. Although pseudocholinesterase levels often decline in liver disease, levels are seldom low enough to significantly prolong succinylcholine-induced apnea. There is sufficient pseudocholinesterase in 1 unit of fresh frozen plasma to hydrolyze the residual succinylcholine in the plasma. The amide class of local anesthetics may also pose a problem for patients with severe liver disease; not only will its hepatic metabolism be impaired, but the associated reduction in plasma proteins (especially alpha $_1$ -glycoprotein and albumin) will expose the patient to increased total and free plasma local anesthetic concentrations.

When choosing the appropriate agent for maintenance of anesthesia, the anesthetist should consider not only the metabolism of that agent by the liver and its hepatotoxicity, but also its effect on liver blood flow. Although volatile anesthetics may be associated with hepatic dysfunction, they are not contraindicated in patients with chronic liver disease and may even be preferable in many circumstances. In one study, cirrhotic rats exposed to 1.8 percent halothane in oxygen for 3 hours showed no further deterioration of liver function. [82] Regardless of the technique chosen, higher than usual concentrations of oxygen should be used because of the likelihood of intrapulmonary shunting. In patients with hepatic encephalopathy, factors that cause further deterioration such as electrolyte disturbances, long-acting CNS depressants, and opiates should be avoided, [83] especially for short surgical procedures.

Intravascular fluid balance may be particularly difficult to manage intraoperatively, especially in patients with ascites who are subjected to laparotomy. Ascitic fluid is in dynamic equilibrium with plasma so that abdominal paracentesis will result in intravascular volume depletion. Thus, rapid rehydration with a sodium-free colloid solution should be initiated as soon as ascitic fluid is lost. Exclusive use of saline-containing crystalloid solutions tends to cause rapid reaccumulation of ascites. Each liter of ascitic fluid lost should be replaced with at least 50 mL of 25 percent albumin because 1 L of ascites contains about 10 g of protein.

In patients with GI hemorrhage, aggressive blood replacement, preferably with whole fresh blood, in which the

coagulation factors have been preserved, is the goal. In theory, citrate from blood preservatives (e.g., citrate-phosphate-dextrose solution) may not be metabolized, resulting in hypocalcemia (Ch. 46) . This probably means that ionized calcium levels should be monitored, especially during liver transplantation. If the ionized calcium levels become low, calcium chloride should be given. The bleeding diathesis of liver cell failure should be treated with fresh frozen plasma because this product contains all the procoagulants and inhibitors that are absent. The goal of therapy is to correct the protime to within 3 seconds of normal by transfusing 12 to 20 mL/kg of fresh frozen plasma. If the patient cannot tolerate excessive fluid volume, the fresh frozen plasma can be substituted with the use of prothrombin complex. Total body stores of vitamin K become depleted in malnourished states within 10 days; therefore, it is always worthwhile to administer vitamin K to patients with a bleeding diathesis from liver disease. If the platelet count falls below a threshold of 100,000/muL, enough units (10,000/muL) need to be transfused to restore the platelet count to this threshold. Abnormal bleeding time in the presence of liver disease can also be treated with diamino-8- D-arginine vasopressin. [84]

In alcoholic patients, secondary effects of alcohol on organs other than the liver must be considered in the anesthetic plan. Normal acid clearance of the esophagus in supine patients is impaired after alcohol ingestion. [85] These patients, then, deserve special attention to acid-aspiration prophylaxis. Osteoporosis is a frequent finding in alcoholics [86] [87] thus, special attention should be devoted to position and padding of exposed bony prominences. Acute alcohol ingestion has a myocardial depressant effect. [88] Chronic cardiomyopathy due to alcoholism is often accompanied by ventricular arrhythmias. Alcohol also caused impaired host immune defenses. [89] Postoperative monitoring should focus on the potential for delirium tremens, which is characterized by sympathetic hyperstimulation. [90]

CHOLESTATIC LIVER DISEASE

Cholestasis literally means "standstill of bile." The term "intrahepatic cholestasis" is used when obstruction to bile flow occurs at the level of the hepatocyte or the biliary canalicular membrane, whereas obstructive jaundice is used when impediment to bile flow is in the extrahepatic biliary tree. The histologic appearance and functional effects of cholestasis, however, are similar whatever the cause.

Extrahepatic biliary obstruction is more commonly associated with progressive severe jaundice, dark urine, and pale stools than is intrahepatic cholestasis. Pruritus is normally present. High fever and chills often herald coexisting cholangitis. Pathologic entities causing obstruction include calculus, stricture, and cancer. Weight loss suggests a neoplastic lesion, and central abdominal or back pain together with a recent onset of diabetes makes a diagnosis of pancreatic cancer very likely. Abdominal pain may be misleading; some patients with common bile duct calculi have painless jaundice, whereas some patients with hepatitis have distressing pain in the right upper quadrant.

Intrahepatic cholestasis has a number of causes. Viral hepatitis uncommonly leads to severe and prolonged jaundice with bilirubin concentrations greater than 15 mg/100

TABLE 54-4 -- Drugs Associated With Cholestasis

Pure cholestasis
7-Alpha-alkyl-substituted testosterones
Methyl testosterone
Nortestosterones (e.g., norethandrolone)
Synthetic estrogens
Ethinyl estradiol
Contraceptive pill
Mestranol
Cholestatic hepatitis
Phenothiazines
Chlorpromazine
Promazine
Trifluoperazine
Others (rarely)
Carbamazepine
Erythromycin estolate
Griseofulvin
Phenytoin
Chlorothiazide
Nitrofurantoin
Azathioprine
4
, 4-Diaminodiphenylmethane (causes Epping jaundice)
Chlorpropamide
Valium
Imipramine
Iprindole
Phenindione

mL. Pruritus is a prominent symptom. Because it may be difficult to differentiate this condition from obstructive jaundice, the investigation of all patients with cholestasis should include serologic assays for acute viral hepatitis.

A variety of drugs may also cause cholestasis (Table 54-4) . Typically, the jaundice appears early with associated pruritus but little alteration in the patient's well-being, and the cholestasis resolves after discontinuing drug use (e.g., synthetic estrogens). [91] Some drugs produce cholestasis as part of a hepatitis-like lesion due to hypersensitivity. Thus a "mixed" lesion is observed with both cholestasis and liver cell necrosis accompanied by raised levels of serum transaminase. The prognosis is usually good, although rarely patients will die from acute liver cell failure or develop secondary biliary cirrhosis.

The complications of cholestasis are proportional to the intensity and duration of the jaundice. In patients with biliary obstruction, ascending infection of the biliary tree or septic cholangitis may be life-threatening. Biliary obstruction eventually destroys liver cells and causes the irreversible structural changes of secondary biliary cirrhosis. Fibrous tissue spreads from the portal tracts and eventually true cirrhosis with nodular regeneration develops. The end results are liver cell failure and portal hypertension. Failure of bile salts to reach the intestine results in fat malabsorption and steatorrhea. In addition, the fat-soluble vitamins A, D, E, and K are not absorbed, resulting in multiple vitamin deficiencies. Disordered hemostasis with an abnormally prolonged prothrombin time may further complicate the course of these patients. Cholestyramine, used to treat pruritus, binds to bile salts and exacerbates the vitamin deficiencies. Persistent cholestasis from any cause may be associated with deposits of cholesterol in the skin (cutaneous xanthomatosis) and occasionally in bones and peripheral nerves. Patients with biliary obstruction who undergo biliary

tract surgery may develop postoperative acute oliguric renal failure. The complication may be due to nephrotoxic bile salts and pigments, endotoxin, or inflammatory mediators. [92]

The cause of cholestasis is investigated with a variety of imaging techniques including noninvasive procedures such as ultrasonic scanning and computed tomography and magnetic resonance imaging. [93] Endoscopic retrograde cholangiopancreatography has the advantage of direct visualization of pancreatic and bile ducts and duodenal loop, but the biliary tree proximal to the obstruction is not visualized. Dye may be introduced percutaneously into the intrahepatic biliary tree with a Chiba needle. Complications of this technique include biliary peritonitis, sepsis, and hemorrhage. [94] Serologic markers of viral infection may point to the cause of cholestasis; a positive antimitochondrial antibody is indicative of primary biliary cirrhosis. Primary sclerosing cholangitis is usually found in association with inflammatory bowel disease. [95]

Regardless of the cause of cholestasis, serum bilirubin levels (especially conjugated) are usually high. Alkaline phosphatase, a membrane-bound enzyme localized to the bile canalicular pole of hepatocytes is also markedly elevated, but high levels of the enzyme are not specific to cholestasis. The bone isoenzyme is important in bone turnover, and up to three times the normal adult value may be seen in adolescents during a normal growth spurt. To determine whether the enzyme is likely to be of hepatic origin, measurement of the 5
-nucleotidase is undertaken, as this tends to parallel the alkaline phosphatase levels in liver disease. The concentrations of serum transaminases are usually only moderately elevated in cholestasis but may occasionally be markedly increased, especially if there is cholangitis. The prothrombin time may be prolonged because of malabsorption of vitamin K. Correction of the prothrombin time by parenteral administration of vitamin K may help to distinguish hepatocellular failure from cholestasis.

Preoperative Considerations

Twenty-five percent of jaundiced patients who are suspected on clinical grounds of having biliary obstruction eventually are diagnosed as having hepatocellular disease. [96] These patients should not be subjected to surgery and anesthesia until the diagnosis is clear. Thus, every effort should be made to visualize the biliary tree in jaundiced patients by appropriate use of noninvasive and invasive techniques as described previously.

Intraoperative Considerations

Parenteral vitamin K should be given up to the time of surgery as vitamin K-sensitive coagulation factors (II, VII, IX, and X) are dependent for their activity on a post-translational modification consisting of gamma-glutamyl carboxylation by a vitamin K-dependent enzyme. Although the package insert recommends that Vitamin K be given subcutaneously, it has been administered in a dose of 3 to 5 mg intravenously over 20 to 30 minutes because cardiovascular collapse can occur with more rapid administration. [97] However, vitamin K is insufficient therapy in the presence of coexisting parenchymal disease. Fresh frozen plasma should be administered to those patients in whom vitamin K alone has not restored the prothrombin time to normal, with attention to serum sodium levels and intravascular volume status.

Volatile anesthetics are probably the drugs of choice because they require neither hepatic biotransformation nor elimination via the biliary system. Although isoflurane is associated with less decrease in hepatic blood flow, [34] halothane has also been used with no adverse liver consequences in a pediatric population of patients with chronic cholestasis. [98] Drugs excreted by the biliary system have a prolonged elimination half-life in patients with cholestasis. [99] Specifically, in patients with extrahepatic cholestasis and normal glomerular filtration pancuronium elimination, half-life of pancuronium is prolonged 1.6-fold. [100] Cholestatic patients have both decreased plasma clearance and increased volume of distribution for pancuronium. Therefore, this neuromuscular blocker may produce unsatisfactory relaxation after a single administration yet have a prolonged duration of action. Narcotics may induce spasm of the sphincter of Oddi, producing biliary colic in patients with cholelithiasis and difficulty with interpretation of intraoperative cholangiograms. Glucagon can be used to relieve nonmechanical spasm of the sphincter of Oddi.

Elderly, deeply jaundiced patients are more likely to develop postoperative oliguric renal failure than patients of the same age without jaundice. [101] Maintenance of a perioperative diuresis has also been stressed as an important prophylactic measure.

POSTOPERATIVE LIVER DYSFUNCTION

Reversible minor changes in liver function are common in the period immediately after operation, but the relative contributions of anesthesia and surgery cannot easily be quantitated. [102] The reduction of hepatic blood flow by both regional and general anesthesia together with the general stresses (including tissue damage and caloric deprivation) produce a mild impairment of liver function. [103] If sensitive indicators of liver function are used, abnormalities can be detected postoperatively in up to 50 percent of patients. These transient abnormalities are not associated with morphologic changes in the liver and are usually clinically insignificant. However, if jaundice becomes apparent, the serum bilirubin usually exceeds 4 mg % and a more serious derangement of liver function may be assumed. Postoperative jaundice is present in up to 20 percent of patients undergoing major surgery, and the cause should be sought. Most cases are never diagnosed because there are few pathognomonic features, and liver function often normalizes quickly without specific treatment. A pathophysiologic classification of the causes of postoperative jaundice has been devised by LaMont and Isselbacher [104] (Table 54-5) .

A common cause of postoperative jaundice is relative overproduction of bilirubin. Approximately 10 percent of aged and damaged erythrocytes in stored blood will break down within 24 hours of transfusion, releasing hemoglobin which is converted to bilirubin. Thus, for 500 mL of transfused blood, 7.5 g of hemoglobin, which is equivalent to 250 mg of bilirubin, will be released. In most circumstances, this

TABLE 54-5 -- Classification of Postoperative Jaundice [104]

1. Overproduction of bilirubin
Hemolytic anemia
Hemolysis of transfused blood
Resorption of hematomas
2. Hepatocellular damage
Postoperative intrahepatic cholestasis
Circulatory failure
Halothane and methoxyflurane
Drug-induced jaundice
Preexisting liver disease
3. Extrahepatic obstruction
Common duct stone
Bile duct injury
Postoperative pancreatitis
4. Miscellaneous
Postoperative cholecystitis
Gilbert syndrome

small increase in bilirubin is easily handled by the liver, but if larger amounts of blood are transfused in the face of mild liver impairment due to anesthesia, unconjugated and conjugated hyperbilirubinemia may result. Through a similar mechanism, resorption of extravasated blood may also contribute to postoperative jaundice in patients with severe crush injuries or in patients having extensive surgical dissection. Gilbert syndrome is present in 7 to 10 percent of otherwise normal persons. Because of reduction in hepatic uridine diphosphate glucuronyl transferase, these patients are unable to handle increases in unconjugated bilirubin such as that caused by preoperative fasting. The resulting unconjugated hyperbilirubinemia, however, quickly remits as oral feedings are resumed.

Hepatocellular damage may be drug-induced and may be produced by a variety of drugs used preoperatively. The diagnosis of drug-induced disorders of the liver is often tentative and requires careful exclusion of other causes of liver disease. The spectrum of hepatic reactions is broad, ranging from cholestasis with such drugs as phenothiazines, to hepatitis, which rarely may be seen with certain halogenated anesthetic agents. [105] Concurrent clinical and hematologic manifestations of hypersensitivity such as fever, skin rash, and eosinophilia can be useful pointers to the drug-induced liver dysfunction; but some drug reactions are indistinguishable from either extrahepatic biliary obstruction or acute viral hep-atitis. Identifying the drug responsible for liver dysfunction in a patient receiving a multitude of drugs can be difficult. Diagnostic challenge to the suspected drug is dangerous because even a small subtherapeutic dose may lead to fatal he-patic necrosis in a susceptible individual. Liver biopsy is of limited usefulness in drug-induced postoperative jaundice because the histologic findings are seldom specific.

Severe postoperative jaundice most frequently follows a prolonged and complicated operation and stormy postoperative course in which hypotension and hypoxemia have occurred, multiple blood transfusions have been given, and sepsis is present. Jaundice is usually first noted on the first or second postoperative day but may be delayed up to the tenth postoperative day. Liver function tests are characterized by high levels of conjugated bilirubin and alkaline phosphatase with near normal levels of transaminases (unless anoxic damage has occurred). It is critical that the correct diagnosis be made and, in particular, extrahepatic biliary obstruction be ruled out so that a risky and unnecessary laparotomy can be avoided. A "shock liver" syndrome can occur in patients in whom marked hypotension has persisted for some hours. A coagulopathy is generally the first indication of liver dysfunction and must be distinguished from disseminated intravascular coagulopathy in these sick patients. Laboratory studies show severe hepatocellular necrosis with peak serum transaminase levels 10-fold or more above normal. Acute liver cell failure may complicate this condition.

A milder form of this shock liver syndrome is seen in cardiac patients following procedures involving cardiopulmonary bypass. [106] The onset of jaundice is on the second or third postoperative day, and there is seldom evidence of hepatocellular necrosis. This condition is usually self-limiting and is similar in course and prognosis to benign postoperative cholestasis.

Persistent jaundice following biliary tract surgery is usually due to retained common bile duct stones and demands delineation of the biliary anatomy via endoscopic retrograde cholangiography. Iatrogenic trauma to the bile duct during surgical exploration may result in stenosis, biliary fistula, or bile peritonitis. Again, prompt

surgical repair is advocated to prevent permanent damage to the liver.

Acute postoperative cholecystitis and pancreatitis are a serious but fortunately rare cause of postoperative liver dysfunction. A mortality rate as high as 25 percent has been reported in patients with postoperative cholecystitis. [107] Acalculous cholecystitis is a serious condition that may further complicate the course of a seriously ill patient and probably results from gallbladder ischemia. High fever and right upper quadrant tenderness should make one suspect the condition. Urgent surgical removal of the gangrenous gallbladder is mandatory.

In addition to intraoperative causes of postoperative liver dysfunction, some patients may have preexisting liver disease that becomes manifest only after surgery. They may be unaware of their malady because of the lack of clinical and even laboratory manifestations. Furthermore, patients may be in a latent phase of an illness (e.g., the incubation phase of viral hepatitis) or in remission. Overt disease may be precipitated by the detrimental effects of hypotension on liver function or may occur because of the natural progression of the preexisting liver disease.

Anesthetic Considerations

Isoflurane, the least metabolized anesthetic, has not yet been associated with serious postoperative liver dysfunction, although, like sevoflurane, it does result in minor elevations in bilirubin and transaminases. [108] However, the consequence of a second hypersensitivity reaction may be so catastrophic that it is probably prudent to avoid all inhalation agents.

References

1. Schmidt W: The epidemiology of cirrhosis of the liver. In Fisher MM, Rankin JG (eds): Alcohol and the Liver. New York, Plenum Press, 1976, p 1.

---

2. Lebach WK: Cirrhosis in the alcoholic and its relation to the volume of alcohol abuse. Ann NY Acad Sci 252:85, 1975.

3. French AB, Barss TP, Fairlie CA et al: Metabolic effects of anesthesia in man. V. A comparison of the effects of ether and cyclopropane anesthesia on the abnormal liver. Ann Surg 135:145, 1952.

4. Harville DD, Dummerskill WHJ: Surgery in acute hepatitis: Causes and effects. JAMA 184:257, 1963.

5. Goodman RA: Nosocomial hepatitis A. Ann Intern Med 103:145, 1985.

6. Gordon SC, Reddy KR, Schiff L et al: Prolonged intrahepatic cholestasis secondary to acute hepatitis A. Ann Intern Med 101:635, 1984.

7. Hollinger FB, Khan NC, Oefinger PE et al: Post transfusion hepatitis type A. JAMA 250:2313, 1983.

8. Hollinger FB: Serologic evaluation of viral hepatitis. Hosp Pract Feb 15, 22:101, 1987.

9. Rosina F, Saracco G, Rizzetto M: Risk of post transfusion infection with the hepatitis delta virus. A multicenter study. N Engl J Med 312:1488, 1985.

10. Farci P, Gerin JL, Aragona M et al: Diagnostic and prognostic significance of the IgM antibody to the hepatitis delta virus. JAMA 255:1443, 1986.

11. Rizzetto M, Gocke DJ, Verme G et al: Incidence and significance of antibodies to delta antigen in hepatitis B virus infection. Lancet 2:986, 1979.

12. Rizzetto M, Hoyer B, Canese MG et al: Delta agent: Association of the delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees. Proc Natl Acad Sci U S A 77:6124, 1981.

13. Dienstag JL, Alaama A, Mosley JW et al: Etiology of sporadic hepatitis B surface antigen-negative hepatitis. Ann Intern Med 87:1, 1977.

14. Tucker RA: Drugs and liver disease: A tabular compilation of drugs and the histopathological changes that can occur in the liver. Drug Intell Clin Pharmacol 16:569, 1982.

15. Miller JJ, Weissman DB: Correlations between transaminase concentrations and serum salicylate concentration in juvenile rheumatoid arthritis. Arthritis Rheum 10:15, 1976.

16. Gazzard BG, Widdop B, Davis M et al: Early prediction of the outcome of a paracetamol overdose based on an analysis of 163 patients. Postgrad Med J 53:243, 1977.

17. Acetylcysteine for acetaminophen overdose. Med Lett 21:98, 1979.

18. Licht H, Seeff LB, Zimmerman HJ: Apparent potentiation of acetaminophen hepatotoxicity by alcohol. Ann Intern Med 92:511, 1980.

19. Kaplowitz N, Aw TY, Simon FR et al: Drug-induced hepatotoxicity. Ann Intern Med 104:826, 1986.

20. Gitnick G: Assessment of liver function. Surg Clin North Am 61:197, 1981.

21. O'Grady JG, Alexander GJM, Cousins K et al: Early prognostic indicators in acute liver failure and application to selection for orthotopic liver transplantation (abstract). Gastroenterology 94:A578, 1988.

22. Caravati CM, Hooker TH: Acute massive hepatic necrosis with fatal liver failure. Am J Dig Dis 16:803, 1971.

23. Rubin E, Lieber CS: Relation of alcoholic liver injury to cirrhosis. Clin Invest Gastroenterol 4:247, 1975.

24. Tedder RS: Hepatitis B in hospitals. Brit J Hosp Med 23:266, 1980.

25. Berry AJ, Isaacson IJ, Kane MA et al: A multicenter study of epidemiology of hepatitis B in anesthesia residents. Anesth Analg 64:672, 1985.

26. Dienstag JL, Werner BG, Polk BF et al: Hepatitis B vaccine in health care personnel: Safety, immunogenicity, and indicators of efficacy. Ann Intern Med 101:34, 1984.

27. McAleer WJ, Buynak EB, Maigetter RA et al: Hepatitis B vaccine from recombinant yeast. Nature 307:178, 1984.

28. Centers for Disease Control: Update on hepatitis B prevention: Recommendations of the immunization practices advisory committee. Ann Intern Med 107:353, 1987.

29. Reingold AL, Kane MA, Hightower AW: Failure of gloves and other protective devices to prevent transmission of hepatitis B virus to oral surgeons. JAMA 259:2558, 1988.

30. Centers for Disease Control: Immune globulins for protection against viral hepatitis. Ann Intern Med 96:193, 1982.

31. Ward ME, Trewby PN, Williams R et al: Acute liver failure. Anesthesia 32:228, 1977.

32. Wilkinson SP, Arroyo VA, Moodie H et al: Abnormalities of sodium excretion and other disorders of renal function in fulminant hepatic failure. Gut 17:501, 1976.

33. Powell-Jackson P, Greenway B, Williams R: Adverse effects of laparotomy in patients with unsuspected liver disease. Br J Surg 69:449, 1982.

34. Gelman S, Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 61:726, 1984.

35. Williams RL: Drug administration in hepatic disease. N Engl J Med 309:1616, 1983.

36. McHorse TS, Wilkinson GR, Johnson RF et al: Effect of acute viral hepatitis in man on the disposition and elimination of meperidine. Gastroenterology 68:775, 1975.

37. Read AE, Laidlaw J, McCarthy CF: Effects of chlorpromazine in patients with hepatic disease. Br Med J 3:497, 1969.

38. Sherlock S: Chronic hepatitis. Postgrad Med 65:81, 1979.

39. Boyer JL: Chronic hepatitis: A perspective on classification and determinants of prognosis. Gastroenterology 70:1161, 1976.

40. Weissberg JI, Andres LL, Smith CI et al: Survival in chronic hepatitis B. Ann Intern Med 101:613, 1984.

41. Sjogren M, Hoofnagle JH: Immunoglobin M antibody to hepatitis B core antigen in patients with chronic type B hepatitis. Gastroenterology 89:252, 1985.

42. Brechot C, Degos F, Lugassy C et al: Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B surface antigen. N Engl J Med 312:270, 1985.

43. Tabor E, Seeff LB, Gerefy RJ: Chronic non-A non-B hepatitis carrier state: Transmissible agent documented in one patient over a six-year period. N Engl J Med 303:140, 1980.

44. Hoofnagle JH, Davis GL, Pappas SC et al: A short course of prednisone in chronic type B hepatitis. Ann Intern Med 104:12, 1986.

45. Alexander GJM, Brahm J, Faga EA et al: Loss of HBsAg with interferon therapy in chronic hepatitis B virus infection. Lancet 2:66, 1987.

46. Hoofnagle JH, Peters M, Mullen KD et al: Randomized controlled trial of recombinant human alpha-interferon in patients with chronic hepatitis B. Gastroenterology 95:1318, 1988.

47. Perrillo RP, Regenstein FG, Peters MG et al: Prednisone withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis. Ann Intern Med 109:95, 1988.

48. Hoofnagle JH, Mullen KD, Jones DB et al: Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon. A preliminary report. N Engl J Med 315:1575, 1986.

49. Reichard O, Norkrans G, Fryden A et al: Randomised, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C: The Swedish Study Group. Lancet 351:83, 1998.

50. Rodman JS, Deutsch DJ, Gutman SI: Methyldopa hepatitis: A report of six cases and review of the literature. Am J Med 60:941, 1976.

51. Mitchell JR, Zimmerman HJ, Ishak KG et al: Isoniazid liver injury: Clinical spectrum, pathology, and probable pathogenesis. Ann Intern Med 84:181, 1976.

52. Alagille D: alpha-1-Antitrypsin deficiency. Hepatology 4:115, 1984.

53. Palmer PE, Wolfe HJ, Gherardi HJ: Hepatic changes in adult alpha-1- antitrypsin deficiency. Gastroenterology 65:284, 1973.

54. Sternlieb I: Wilson's disease--Indications for liver transplants. Hepatology 4:155, 1981.

55. Strickland GT, Leu M: Wilson's disease: Clinical and laboratory manifestations in 40 patients. Medicine 54:113, 1975.

56. Deiss A, Lynch RE, Lee GR et al: Long-term therapy of Wilson's disease. Ann Intern Med 99:314, 1983.

57. Morgan MY, Sherlock S: Sex-related differences among 100 with alcoholic disease. Br Med J 1:939, 1977.

58. Kent G, Popper H: Liver biopsy in diagnosis of hemochromatosis. Am J Med 44:837, 1968.

59. Niederau C, Fischer R, Sonnenberg A et al: Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 313:1256, 1985.

60. Bacon BR: Diagnosis and management of hemochromatosis. Gastroenterology 113:995, 1997.

61. Kaplan MM: Primary biliary cirrhosis. N Engl J Med 316:512, 1987.

62. Murray JF, Dawson AM, Sherlock S: Circulatory changes in chronic liver disease. Am J Med 24:358, 1958.

63. Novis BH, Duys P, Barbezat GO et al: Fibre-optic endoscopy and the use of the Sengstaken tube in acute gastrointestinal hemorrhage in patients with portal hypertension and varices. Gut 17:258, 1976.

64. Law AW, Gales MA: Octreotide or vasopressin for bleeding esophageal varices. Ann Pharmacother 31:237, 1997.

65. Cello JP: Endoscopic management of esophageal variceal hemorrhage:

Injection, banding, glue, octreotide, or a combination. Semin Gastrointest Dis 8:179, 1997.

66. Kam PCA, Tay TM: The role of the anaesthetist during the transjugular intrahepatic porto-systemic stent shunt procedure (TIPPS). Anaesth Intensive Care 25:385, 1997.

67. Jalan R, Redhead DN, Hayes PC: Transjugular intrahepatic portosystemic stent shunt in the treatment of variceal hemorrhage. Br J Surg 82:1158, 1995.

68. Gabuzada GJ: Cirrhosis, ascites and edema. Gastroenterology 58:546, 1970.

69. Ferenci P, Grimm G, Meryn S et al: Successful long-term therapy of portal systemic encephalopathy by the benzodiazepine antagonist flumazenil. Gastroenterology 96:243, 1989.

70. Child CG, Turcotte JG: Surgery and portal hypertension. In Child CG (ed): The Liver and Portal Hypertension. Philadelphia, WB Saunders, 1964, p 50.

71. Pugh RNH, Murray-Lyon IM, Dawson JL et al: Transection of the oesophagus for bleeding varices. Br J Surg 60:646, 1973.

72. Servin F, Desmonts JM, Haberer JT et al: Pharmacokinetics and protein binding of propofol in patients with cirrhosis. Anesthesiology 69:887, 1988.

73. Veroli P, O'Kelley B, Bertrand F et al: Extrahepatic metabolism of propofol in man during the anhepatic phase of orthotopic liver transplantation. Br J Anaesth 68:183, 1992.

74. Pandele G, Chaux F, Salvadori C, Duvaldestin P: Thiopental pharmacokinetics in patients with cirrhosis. Anesthesiology 59:123, 1983.

75. Loft S, Jensen V, Resaard S, Dyrberg V: Influence of moderate alcohol intake on thiopental anesthesia. Acta Anaesth Scand 26:22, 1982.

76. Haberer JP, Schoeffler P, Couderc E, Duvaldestin P: Fentanyl pharmacokinetics in patients with cirrhosis. Br J Anaesth 54:1267, 1982.

77. Chauvin M, Ferrier C, Haberer JP et al: Sufentanil pharmacokinetics in patients with cirrhosis. Anesth Analg 68:1, 1989.

78. Duvaldestin P, Agoston S, Hanzel K et al: Pancuronium pharmacokinetics in patients with liver cirrhosis. Br J Anaesth 50:1131, 1978.

79. Lebrault C, Berger JL, D'Hollander AA et al: Pharmacokinetics and pharmacodynamics of vecuronium (ORG NC45) in patients with cirrhosis. Anesthesiology 62:601, 1985.

80. Bell CF, Hunter JM, Jones RS et al: Use of atracurium and vecuronium in patients with oesophageal varices. Br J Anaesth 57:160, 1985.

81. Arden JR, Lynman DP, Castagnoli KP et al: Vecuronium in alcoholic liver disease: A pharmacokinetic and pharmacodynamic analysis. Anesthesiology 68:771, 1988.

82. Maze M, Smith CM, Baden JM et al: Hepatic function in cirrhotic rats following halothane anesthesia. Anesth Analg 63:248, 1984.

83. Branch RA, Morgan MH, James J et al: Intravenous administration of diazepam in patients with chronic liver disease. Gut 17:975, 1976.

84. Burroughs AK, Matthews K, Quadiri M et al: Desmopressin and bleeding time in patients with cirrhosis. Br Med J 291:1377, 1985.

85. Vitale GC, Cheadle WG, Patel B et al: The effect of alcohol on nocturnal gastroesophageal reflux. JAMA 258:2077, 1987.

86. Bikle DD, Genant HK, Cann C et al: Bone disease in alcohol abuse. Ann Intern Med 103:42, 1985.

87. Spencer H, Rubio N, Rubio E et al: Chronic alcoholism. Frequently overlooked cause of osteoporosis in men. Am J Med 80:393, 1986.

88. Lang RM, Borow KM, Neumann A et al: Adverse cardiac effects of acute alcohol ingestion in young adults. Ann Intern Med 102:742, 1985.

89. O'Connor PG, Schottenfeld RS: Patients with alcohol problems. N Engl J Med 338:592, 1998.

90. Turner RC, Lichstein PR, Peden JG Jr et al: Alcohol withdrawal syndromes: A review of the pathophysiology, clinical presentation, and treatment. J Gen Intern Med 4:432, 1989.

91. Lee WM: Drug-induced hepatotoxicity. N Engl J Med 33:1118, 1995.

92. Kramer HJ: Impaired renal function in obstructive jaundice: Roles of thromboxane and endothelin systems. Nephron 77:1, 1997.

93. Saini S: Imaging of the hepatobiliary tract. N Engl J Med 336:1889, 1997.

94. Zilly W, Liehr H, Hummer N: Chiba-needle percutaneous cholangiography--A method without risk to the patient? Endoscopy 12:12, 1980.

95. Fausa O, Schrumpf E, Elgjo K: Relationship of inflammatory bowel disease and primary sclerosing cholangitis. Semin Liver Dis 11:31, 1991.

96. O'Connor KW, Snodgrass PJ, Swonder JE et al: A blinded prospective study comparing four current noninvasive approaches in the differential diagnosis of medical versus surgical jaundice. Gastroenterology 84:1498, 1983.

97. Songy KA Jr, Layon AJ: Vitamin K-induced cardiovascular collapse. J Clin Anesth 9:514, 1997.

98. Wark H, Earl J, Cooper M, Overton J: Halothane in children with chronic liver disease. Anaesth Intensive Care 19:9, 1991.

99. Somogyi A, Rolan P: Drug disposition and dosing in hepatic disease. Med J Aust 145:284, 1986.

100. Somogyi AA, Shanks CA, Triggs EJ: Disposition kinetics of pancuronium bromide in patients with total biliary obstruction. Br J Anaesth 49:403, 1977.

101. Wait RB, Kahng KU: Renal failure complicating obstructive jaundice. Am J Surg 157:256, 1989.

102. Hayes PC, Bouchier IA: Postoperative jaundice. Ballieres Clin Gastroenterol 3:485, 1989.

103. Becker SD, Lamont JT: Postoperative jaundice. Semin Liver Dis 8:183, 1988.

104. LaMont JT, Isselbacher KJ: Postoperative jaundice. In Wright R, Alberti KGMM, Karran S et al (eds): Liver and Biliary Disease. London, WB Saunders, 1979, p 1087.

105. Plummer JL, Cousins MJ, Hall PM: Volatile anesthetic metabolism and acute toxicity. Q Rev Drug Metab Drug Interact 4:49, 1982.

106. Schmid M, Hefti ML, Gattiker R et al: Benign postoperative intrahepatic cholestasis. N Engl J Med 272:545, 1965.

107. Howard RJ, Delaney JP: Postoperative cholecystitis. Am J Dig Dis 17:213, 1972.

108. Bito H, Ikeda K: Renal and hepatic function in surgical patients after low-flow sevoflurane or isoflurane anesthesia. Anesth Analg 82:173, 1996.

Chapter 55 - Organ Transplantation

Leonard Firestone
Susan Firestone
John R. Feiner
Ronald D. Miller

Multivisceral Transplantation

/das/book/view/29494766/875/603.html

INTRODUCTION

Transplantation of tissue is gaining an increasing role in modern therapeutics. Cornea, heart valves, and blood vessels are relatively immunologically inert and can therefore be transplanted with great success. Similarly, cartilage, tendon, and fascia can be used as a framework for cells of healthy native tissue. Bone marrow replacement has become routine treatment for a growing list of both soft tissue and organ malignancies. Of particular interest to anesthesiologists, transplantation of vital organs with distinct blood supplies, such as the kidneys, liver, heart, and lungs, has now evolved into the preferred therapeutic option for selected patients. Furthermore, survival of both recipients and allografts is excellent, making transplantation of many major organs a very successful therapeutic option (Table 55-1) (Table Not Available) . As a consequence, anesthesia services are needed for both organ

TABLE 55-1 -- Survival of Recipients and Allografts Following Organ Transplantation

(Not Available)

From Firestone and Firestone [271]

donors and recipients. Optimal care requires an understanding of the many recent advances in immunobiology, molecular and clinical pharmacology, organ preservation, and biomedical ethics that together have made organ transplantation feasible in our society.

TRANSPLANTATION IMMUNOLOGY

Organs for transplantation derived from nontwin donors of the same species are termed *allografts.* The immunologic identity of allografts is established by glycoproteins on the cells' surface, termed the major histocompatibility complex (MHC) antigens. Class I MHC antigens (subtypes A, B, and C), also called human leukocyte antigens (HLA), are located on the surface membranes of all nucleated cells. Class II MHC antigens (subtypes DR, DQ, and DP), found on activated macrophages and on T and B cells, are the primary targets for helper T cells. [1] The great diversity of alleles at the chromosomal loci encoding for these antigens accounts for the varying degrees of HLA matching observed. The major blood group antigens (ABO) are the other cell-surface markers important to clinical transplantation. If preformed isohemagglutinins against the organ donor's blood type are present, allografts derived from that donor are likely to provoke fulminant rejection.

Cellular Biology of Tissue Rejection

After transplantation of an allograft, if otherwise untreated, an immunocompetent recipient will mount an immune response to the foreign surface antigens. This response comprises proliferation of both cellular elements (T lymphocytes, macrophages, and other leukocytes) and humoral factors (immunoglobulins elaborated by B lymphocytes and complement). T lymphocytes are central to the immune response to transplanted tissue because they initiate antigen recognition and ultimately mediate allograft destruction (Fig. 55-1) (Figure Not Available) . They may be further subdivided into four categories, based on their specific cell-surface antigens, all of which participate in the response to allograft tissue: helper T cells, cytotoxic T cells, suppressor T cells, and delayed hypersensitivity T cells. [2] The steps involved in T-cell activation are partially elucidated (Fig. 55-2) ; their clinical importance stems from the potential for pharmacologic control of the immune response. In a process termed corecognition, T cells are able to recognize antigens and MHC gene products, but only in conjunction with an activated macrophage of self-type. T-cell activation, in turn, involves binding of the antigen, presented by activated macrophages, to the T-cell receptor. T-cell activation is promoted by macrophage elaboration of the cytokine, interleukin-1 (IL-1), and leads to the secretion of IL-2 by helper (CD4-surface antigen-positive) T cells. IL-2 acts as a mitogen for activated T cells that express the IL-2 receptor, including the cytotoxic ($CD8^+$) subtype, leading to a cycle of local cellular proliferation. Once the supply of antigen is exhausted, the number of cell surface IL-2 receptors decreases and proliferation ceases by negative feedback.

The humoral component of the immune response is also essential to the process of allograft rejection (Fig. 55-3) and vulnerable to suppression by drugs. In general, B lymphocytes are activated by antigens presented by macrophages. After the antigen-MHC complex binds to the receptors of T-helper cells, cytokines are produced, particularly macrophage-elaborated IL-1 and T-cell-derived IL-4. B-cell activation is followed by expression of surface receptors (IL-2, -4, -5 receptors) that promote cell division. Many cycles of cell division ensue; in the human body, the presence of IL-6 and interferon-gamma (IFN-gamma) stimulates B cells to differentiate into antibody-forming cells.

Figure 55-1 (Figure Not Available) Structure of the human T-cell receptor and its subunits. All T lymphocytes express the T-cell receptor complex (called CD3 or T3), to which foreign antigens bind to initiate the immune response. The Tialpha- and Tibeta-subunits are integral membrane proteins, joined by a disulfide bridge. They are noncovalently associated with the 25-kd gamma chain of the T3 molecule, as well as two 20-kd subunits, delta and epsilon. S--S, disulfide bridge. *(Redrawn from Firestone and Firestone [271])*

Pharmacologic Modulation of the Immune Response

Immunosuppressant drugs have been developed to control the immune response and avoid allograft rejection. Although essential drugs, serious side effects and toxicities accompany their use; thus immunosuppression is reserved only for grafts essential to life. For example, immunosuppression for most endocrine transplantation (e.g., thyroid) would be inappropriate, because substitution by medication

Figure 55-2 T-lymphocyte activation. See text for details.

Figure 55-3 B-lymphocyte activation and development. See text for details.

Figure 55-4 Chemical structures of the immunosuppressants.

is far safer. Immunosuppressants in current use are relatively nonspecific, in the sense that they inhibit lymphocyte subsets other than those directed against donor-specific alloantigens.

To minimize side effects, almost all antirejection regimens combine relatively lower doses of several of the following agents: cyclosporine, azathioprine, prednisone, FK-506 or rapamycin, and antibodies (ALG and OKT3).

Cyclosporine

Cyclosporine is a cyclic peptide molecule (Fig. 55-4) derived from a soil fungus, consisting of 11 relatively lipophilic amino acids. It became the linchpin of immunosuppression after recognition that its use promoted transplant survival rates among unrelated subjects comparable with those achieved between identical

twins. Together with azathioprine and prednisone, cyclosporine forms the ubiquitous "triple-therapy" immunosuppression regimen. Its major actions are thought to be inhibition of activated macrophages from producing IL-1, inhibition of T lymphocytes from secreting the key lymphokine IL-2, and blocking activation of helper ($CD4^+$) T cells. [3]

Cyclosporine is a potent nephrotoxin, producing interstitial renal fibrosis with tubular atrophy (Table 55-2) . Blood urea nitrogen (BUN) and creatinine levels rise as a consequence of both acute and chronic use, and most patients maintained on this agent develop systemic hypertension [4] that responds to conventional antihypertensive medications. Cyclosporine can also produce hepatocellular injury, hyperuricemia, gingival hypertrophy, hirsutism, and, at high serum levels, tremors or seizures.

Azathioprine

Azathioprine is an imidazole congener of the purine, 6-mercaptopurine (see Fig. 55-4) . Its metabolite, thioinosinic acid, competes with inosinic acid for conversion to xanthylic acid, which is essential to *de novo* purine synthesis. As a result, the production of both DNA and RNA is affected, inhibiting both T- and B-cell proliferation. [5] Production of

TABLE 55-2 -- Immunosuppressant Side Effects and Toxicities

AGENT	SIDE EFFECTS
Cyclosporine	Hypertension
	BUN, creatinine elevations (secondary to glomerulosclerosis)
	Enhanced renal sensitivity to insults
	Hepatocellular damage (transaminase elevation)
	Tremors, seizures (high doses)
Azathioprine	Profound leukopenia
	Anemia
	Thrombocytopenia
	Hepatocellular and pancreatic damage
	Diminished nondepolarizing relaxant requirement
Prednisone	Abnormal stress responses (adrenal suppression)
	Glucose intolerance
	Aseptic osteonecrosis
	Peptic ulceration
	Integumental fragility
Antilymphocyte globulin	Leukopenia
	Thrombocytopenia
	Serum sickness-like symptoms
OKT3	Serum sickness-like symptoms
	Vulnerability to cytomegalovirus sepsis

other formed elements in the bone marrow is suppressed as well, possibly leading to anemia, thrombocytopenia, and occasionally, marrow aplasia. Azathioprine has also been associated with hepatocellular and pancreatic damage, as well as alopecia and gastrointestinal (GI) upset. It has been shown to increase nondepolarizing relaxant requirements modestly by presynaptic inhibition of the motor nerve terminal. [6]

Prednisone

Prednisone is a 17-hydroxyglucocorticoid (see Fig. 55-4) with potent anti-inflammatory activity. It suppresses helper T-cell proliferation by decreasing macrophage production of IL-1. [7] Glucocorticoids also diminish IL-2 production by T cells, thus blocking clonal expansion of both helper and cytotoxic T cells. [8] In clinical practice, glucocorticoids are a vital component of both maintenance and rejection-rescue immunosuppression regimens, despite association with adrenal suppression, glucose intolerance, peptic ulceration, aseptic osteonecrosis, and integument fragility. It has not been possible to eliminate prednisone from the regimens, [9] although alternate-day administration seems sufficient. Whether it is necessary to administer "stress doses" of glucocorticoids to patients with chronic adrenal suppression is controversial. [10]

FK-506 (Tacrolimus) and Rapamycin

Tacrolimus (FK-506) (see Fig. 55-4) and rapamycin are macrolide antibiotics whose immunosuppressant properties are under investigation. Tacrolimus blocks IL production and T-cell proliferation. Like cyclosporine, these agents block lymphokine (IL) production, as well as activation and proliferation of T lymphocytes. [11] Interest in these agents derives from their relative immunospecificity and potential to be used alone, without other toxic immunosuppressants. [12] Like cyclosporine, FK-506 is nephrotoxic.

Antibodies: Antilymphocyte Globulin and OKT3

Antilymphocyte globulin (ALG) is a polyclonal IgG antibody harvested from animals immunized with human lymphoid cells. It rapidly reduces circulating T lymphocytes and seems to have sustained effects on T-cell populations by promoting formation of suppressor T cells. [13] ALG may cross-react with antigens other than those on T lymphocytes, producing marked leukopenia and thrombocytopenia. Systemic symptoms such as fever and pruritus can also result, as can frank serum sickness.

OKT is a series of murine monoclonal antibodies directed against the T3 (now called CD3) surface antigen on mature T lymphocytes. CD3 is part of the T-cell receptor macromolecular complex involved in T-cell activation following antigen recognition. OKT3 specifically binds to CD3, blocking recognition of MHC antigens on foreign cells and the subsequent immune response. [14] OKT3-bound T cells are then removed from circulation and destroyed by the reticuloendothelial system. [14] The initial dose of OKT3 is usually accompanied by mild systemic symptoms, and only rarely by pulmonary edema or aseptic meningitis. Chronic use has been associated with an unusually high incidence of cytomegalovirus (CMV) susceptibility.

Clinical Immunology of Organ Matching

In the presence of major ABO incompatibilities, renal allografts may undergo a "hyperacute" rejection marked by microvascular thrombosis and fulminant graft necrosis. [15] Kidneys from type O donors may still be transplanted into otherwise compatible nonidentical (e.g., A, B, AB) recipients, although some centers only do so when a living-related donor is available and special immunosuppression protocols are employed (including splenectomy and plasmapheresis). Hyperacute rejection is also likely if preformed cytotoxic antibodies to the donor's T cells ("antilymphocyte antibodies") are present, usually precluding transplantation. [16] Given that renal allografts can survive for days *ex vivo,* HLA matching is feasible, but its specific value is not entirely clear. For example, HLA-incompatible living-related donor transplants yield excellent results, although HLA-matched cadaver allograft survival is superior. Finally, outcome may also be reflected by the panel-reactive antibody (PRA), which cross matches recipient's sera and donor cells to detect preformed antibodies. In one study, [17] the presence of reaction against more than 50 percent of

the random test panel was associated with a greater rejection rate.

Cardiac allografts are also vulnerable to hyperacute rejection on the basis of donor-specific ABO isoagglutinins. [18] Thus ABO matching is essential before transplantation. However, the practical limit of a 4- to 6-hour tolerable donor-heart ischemic time severely restricts prospective matching according to histocompatibility antigens and PRA screens. Moreover, while there are indications that HLA mismatching may promote rejection, [19] other studies fail to correlate mismatching with rejection or survival. [20]

Hyperacute rejection has not been reported during liver transplantation despite major ABO incompatibility, [21] suggesting that the liver is not susceptible to this particular form of antibody-mediated injury. [22] Nonetheless, under these circumstances, the likelihood of rejection is elevated in both the short and long term. [15] [23] [24] By contrast, T-cell crossmatch [25] and HLA histocompatibility [26] are not highly correlated with liver allograft survival.

In summary, renal allograft distribution depends primarily on immunologic factors such as ABO and HLA histocompatibility, as well as T-cell and PRA crossmatching. Distribution of cardiac and hepatic allografts will depend less on immunologic criteria, other than ABO histocompatibility, than on size compatibility with potential recipients and overall medical urgency.

PRINCIPLES OF ORGAN PRESERVATION

Donor organs are temporarily separated from blood supply and must therefore be protected from ischemia. The biologically tolerable limit of survival *ex vivo* has been extended

by combining hypothermia (decreasing metabolism) with the use of preservative solutions (to maintain cellular integrity). These solutions contain electrolytes of specific composition, as well as chemical additives that provide ready sources of energy, are cryoprotective, or prevent vasospasm, cellular swelling, and build-up of toxic metabolites. For example, free-radical scavengers (e.g., mannitol) are added to prevent oxygen-derived free radicals from damaging key intracellular constituents after reperfusion.

Kidney Preservation

The first flushing solutions for renal preservation were isotonic, with a composition resembling intracellular fluid (e.g., potassium 115 mEq/L, sodium 10 mEq/L, chloride 15 mEq/L, bicarbonate 10 mEq/L, dihydrogen phosphate 15 mEq/L, and monohydrogen phosphate 85 mEq/L, pH 7.25). [27] This composition diminished renal cortical respiration, but other additives, including procaine, heparin, and phenoxybenzamine, were used in an attempt to prevent agonal thrombosis and/or vasospasm in cadaver kidneys. An additive-free version of Collins solution, termed modified Euro-Collins, is widely used for kidney flushing and can support kidney viability *ex vivo* for more than 48 hours. [28] Besides the electrolytes already specified, it contains magnesium sulfate 1 g/L and 5 mL/L of 50 percent glucose, resulting in a measured osmolality of 375. Hypertonic intracellular solutions have also been tried (e.g., Sacks, with >400 mOsm), [29] but without any greater success.

Liver Preservation

The liver is relatively vulnerable to ischemia, due to an intrinsically high metabolic rate and large bulk that prevent rapid uniform cooling. As a consequence, until recently, postoperative graft dysfunction due to ischemia was not uncommon. University of Wisconsin (UW), or Belzer, solution was later shown to succeed in markedly diminishing primary graft dysfunction, as well as in prolonging hypothermic liver preservation for at least 24 hours *ex vivo*, [30] [31] greatly facilitating distant procurement. Impermeants, such as lactobionate (100 mM) and raffinose (30 mM), suppress hypothermia-induced cell swelling and are believed to be the key additives. The remainder of the composition is potassium phosphate 25 mM, adenosine 5 mM, magnesium sulfate 5 mM, glutathione 3 mM, and allopurinol 1 mM, as well as insulin 100 units/L, penicillin 40 units/L, dexamethasone 8 mg/L, and hydroxyethyl starch 50 g/L. At 4°C, the pH is 7.4, and the osmolality is 320 to 330 mOsm. [30]

Heart Preservation

Cellular metabolic arrest and cooling are the bases of myocardial protection [32] ; thus techniques of cardioplegia developed shortly before the organ transplantation era facilitated distant procurement of donor hearts. Although numerous preservation regimens have been tried, conventional cardioplegia solutions have had the greatest success as reflected by lack of need for inotropic support following implantation. [33] A typical crystalloid cardioplegia solution is composed of potassium 30 mEq/L, sodium 25 mEq/L, chloride 30 mEq/L, and bicarbonate 25 mEq/L, as well as dextrose 50 g/L and mannitol 12.5 g/L, at a pH of 8.1 to 8.4. [33] The heart is relatively sensitive to ischemia, and despite some promising laboratory reports, [34] the practical ischemic limit in humans remains 4 to 6 hours. [33] [35] [36]

Lung Preservation

The lung is unique among transplanted organs because it remains exposed to the external (nonsterile) environment. Donor lungs may also be jeopardized by aspiration, contusion, massive fluid resuscitation of the donor, and exposure to nonphysiologic oxygen tensions. Ideally, the donor's history should indicate early endotracheal intubation, and absence of chest tubes, pleural disease, and tracheostomy at any time. Suitable donors should have a minimal alveolar- arterial oxygen gradient (i.e., Pa $_{O_2}$ of >400 mm Hg while breathing 100 percent O_2 , or 100 mm Hg on 40 percent O_2 /5 cm H_2 O positive end-expiratory pressure [PEEP]), as well as a clear chest radiograph and sputum examination within 2 hours of harvesting. [37] Because both heart and lungs may be harvested from the same donor, a method has been developed for cardiectomy without jeopardizing the use of the lungs. [38] At some centers, before removal, the donor is treated with a pulmonary vasodilator (e.g., prostaglandin E_1 [PGE_1]) to improve distribution of a large volume of an intracellular-type cold-crystalloid preservative solution, [39] [40] infused through the pulmonary artery. Finally, the lungs may be inflated before immersion in preservation solution and stored for transportation. With such techniques, a maximum ischemic time of 6 to 8 hours has been reported. [40]

CARE OF ORGAN DONORS

Brain-dead organ donors (Ch. 76) are the source of most viscera for transplantation in the United States. Voluntary donor programs have been established by state and federal law, supplemented in some jurisdictions by legislation requiring health-care providers to request permission for donation from a brain-dead donor's family. Organs are distributed through a nationwide organ procurement and transplantation network established under federal contract, the United Network for Organ Sharing (UNOS). UNOS also collects and reports survival statistics and has a role in public education about transplantation. [41] The overall procurement process has recently been described. [41A]

Common causes of brain death include blunt and penetrating head trauma and intracranial hemorrhage. Despite such injuries, suitable organ donors must not have suffered circulatory compromise nor septicemia during subsequent hospitalization. Other infectious processes precluding organ donation include hepatitis B, herpesvirus, tuberculosis, active toxoplasmosis, and acquired immune deficiency syndrome (AIDS). By contrast, serologic evidence of CMV infection does not preclude donation to seropositive recipients. Autoimmune disease is not usually a contraindication to donation, despite a report of idiopathic thrombocytopenia purpura transmission by liver transplantation. [42] Liver function

tests are important when screening suspected alcohol or drug abusers, and BUN and creatinine levels, as well as urinalyses, are obtained from all potential kidney donors. Heart donors are typically younger than 50 years of age, with cardiac function demonstrably normal by echocardiography. The history must also be free of angina and recent need for intracardiac injections. Cardiac arrest, mild cardiac trauma, transient hypoxemia, or the use of high doses of inotropes need not mandate exclusion, provided both echocardiographic and gross examinations indicate reasonable contractility. [43]

Living donors are the other source of organs, primarily kidneys, for transplantation. Living donors must be closely related to recipients, because only high degrees of HLA matching are associated with greater allograft survival. [44] Partial liver [45] [46] and lung [47] resections from living (parental) donors have been performed to provide reduced-size allografts for children. Size considerations place additional constraints on the organ matching process in pediatric recipients, which exacerbates shortages, yet the morbidity and mortality inherent in those donor operations have sparked considerable controversy.

Brain Death Criteria

Before the advent of heart transplantation, harvesting of kidneys could be performed following cessation of the donor's heartbeat (Ch. 76) . However, unlike kidneys, the heart is intolerant of even short intervals of warm ischemia, generating the need for a uniform definition of brain death. In 1981, a special President's Commission [48] published that definition as "irreversible cessation of all function of the entire brain, including the cortex and brain stem, determined in accordance with accepted medical standards." Although those standards continue to evolve, [49] the concept of brain death is now widely accepted by society.

Cerebral cortical infarction is indicated by the absence of consciousness as well as motor activity, either spontaneous or in response to noxious stimuli administered by an experienced neurologist (Table 55-3) . Similarly, brain-stem function

TABLE 55-3 -- Brain Death Criteria[a]

Cerebrocortical function
Unconscious
Loss of spontaneous movement
Unresponsive to external (noxious) stimuli
Brain-stem function
Cranial nerve reflexes absent
Corneal reflex
Pupillary light reflex
Oculocephalic reflex
Oculovestibular reflex
Atropine resistance
Respiratory reflex absent
Supporting clinical studies
Cerebral blood flow
Cerebral angiography
Transcranial Doppler
Xenon-enhanced computed tomography scan
Electroencephalography

[a] Also see Ch. 76 .

is deemed absent when there is a loss of reflexes mediated by both bulbar respiratory and cranial nerve nuclei. The former is assessed by the apnea test, [50] whereby respiratory efforts are judged by serial Pa CO_2 determinations after suspending mechanical ventilation under normoxic, hemodynamically stable conditions. [51] Examples of reflexes mediated by cranial nerve nuclei include: the corneal reflex (blink normally elicited by light touch); the direct pupillary light reflex (bright light normally eliciting homolateral meiosis); the oculocephalic reflex (ocular position normally not fixed [like "doll's eyes"] upon head rotation); and the oculovestibular reflex (nystagmus accompanying ice water irrigation ["cold caloric test"] of the auditory canal). Resistance to atropine's chronotropic effects on the heart is also characteristic of brain-stem infarction. [52]

Clinical studies supporting these physical findings in accordance with current medical standards include both cerebral blood flow studies and electroencephalography (EEG). Four-vessel cerebral angiography, [53] xenon-enhanced computed tomography (CT), [54] and transcranial Doppler [55] have all been used to bolster the diagnosis of brain death. Electrical silence on the EEG is not an absolute indication of brain death, because residual activity has been observed even after cessation of cerebral blood flow, [56] and reversible drug overdose and hypothermia can both produce "flat" EEGs.

Irreversibility is fundamental to the diagnosis of brain death and is established by a lack of improvement in the physical examination or clinical studies for 12 to 24 hours. Potentially reversible factors that must be ruled out include central drug effects, postictal states, cardiovascular or metabolic instability, or hypothermia, thus emphasizing the need to understand the cause of brain death. Age can also confound this diagnosis, because the potential for infants and children to recover from neurologic insults seems less predictable than in adults. [57] Thus, only appropriately experienced pediatricians should undertake brain-death evaluation in these younger age groups. [57] [58]

Clinical Management Following Brain Death

Physiologic instability often accompanies brain death but must be controlled to maintain the viability of donor organs. Hypoxemia, hypotension, cardiac arrhythmias, and hypothermia may be either a cause or an effect of brain-stem infarction. Hypoxemia can be a consequence of excessive fluid resuscitation, gastric aspiration, pulmonary contusion, atelectasis, or pneumothorax. Treatment typically involves adjustment of the F_{IO_2}, minute ventilation, and PEEP to maintain an Sa_{O_2} of greater than 95 percent. Hypotension follows from loss of central vasomotor centers, exacerbated by diuresis from radiographic dyes or diabetes insipidus, or by hemorrhage. Judicious restoration of intravascular volume with colloid and crystalloid solutions, or infusion of vasopressin (Pitressin 0.5-15 U/h) or pressors, may be necessary. Dopamine (2-5 mug/kg/min) is preferred to phenylephrine, which diminishes splanchnic perfusion, thus jeopardizing abdominal donor organs. Hypothermia may result from hypothalamic infarction or exposure and is treated in the conventional manner. Brain death can also be accom-panied by both atrial and ventricular arrhythmias, particularly

bradyarrhythmias, as well as varying degrees of heart block. [59] These conditions are usually attributable to either myocardial contusion or ischemia, electrolyte or acid-base disturbances, hypoxia, intracranial hypertension, or vagal nucleus infarction. Bradycardia is unresponsive to atropine [52] but can be treated with infusion of a direct-acting chronotropic agent (e.g., isoproterenol).

There is no typical endocrine response to brain death. Rarely, catecholamine and cortisol levels may be markedly elevated, and insulin or thyroid hormone (T_3) levels diminished. Replacement therapy under such circumstances may be warranted. Polyuria suggests onset of diabetes insipidus; the diagnosis is confirmed by the presence of relative urine hypo-osmolarity (>300 mOsm/L) despite serum hyperosmolarity (>310 mOsm/L) and hypernatremia (>150 mEq/L). This is treated by replacement of free water losses, normalization of serum osmolarity and electrolyte values, and vasopressin infusion.

Donor Operation

In the operating room, anesthesiologists continue to implement therapies begun in the intensive care unit (ICU) to promote donor organ perfusion and oxygenation. In addition, although cortical and brain-stem function are absent, somatic and visceral reflexes may trigger deleterious physiologic responses [60] that require control. For example, reflex hypertension often accompanies surgery and must be treated to avoid damaging renal microvessels. Vasodilator infusions are adequate in this setting, in which general anesthetics are clearly unnecessary. Motor activity mediated by spinal somatic reflexes is suppressed with relaxants.

The goal of the donor procedure is to minimize warm ischemia time and surgical trauma to the harvested viscera. This is currently accomplished by regional cooling and preservation of organs *in situ,* then removal en bloc [61] (Fig. 55-5) (Figure Not Available) . Specifically, after surgical preparation of the entire anterior chest and abdomen with the patient in the supine position, both sternotomy and full-length midline abdominal incisions are performed. The liver is exposed and freed from its ligamentous attachments to the diaphragm. The abdominal aorta above the celiac artery is encircled with a ligature, while the inferior mesenteric vein is cannulated for drainage; the liver is then flushed with cold preservation solution. The donor then is heparinized systemically, followed by abdominal aortic cannulation, cross-clamping, and perfusion with cold preservative. The donor's kidneys are thus flushed of blood and cooled; once the ureters are dissected and divided, the aorta and vena cava on either side of the renal pedicles are transected, followed by en bloc nephrectomy. The common bile duct and hepatic artery are divided next, freeing the liver for removal.

At the same time that *in situ* preservation of abdominal viscera begins, a second team starts the donor cardiectomy. This approach avoids inadvertent cardiac arrest before cardiectomy, which would damage the donor organs. After pericardiotomy, the epicardial coronary arteries are grossly palpated for atherosclerotic plaques. The ascending aorta is dissected, the superior vena cava (SVC) is ligated, and the inferior vena cava (IVC) and pulmonary veins are then transected to exsanguinate the heart. Finally, cold cardioplegia is administered via the aortic root; after cardiac arrest, the aorta is cross-clamped, the great arteries divided, and the heart rinsed and examined for valvular lesions or a patent foramen ovale. It is then placed in a sterile plastic bag containing iced saline, within an insulated cooler suitable for transport. [62]

The donor operation concludes with the anesthesiologist discontinuing ventilatory and circulatory support. Although death is always certified before this procedure (and not in the operating room), it is important that donors still be treated throughout with the same respect afforded to all other patients.

PREANESTHETIC EVALUATION FOR TRANSPLANTATION: GENERAL PRINCIPLES

Organ transplantation is indicated for patients with end-stage visceral disease when medical or surgical management has failed to improve the quality of life or enhance the chances for long-term survival. General contraindications to organ transplantation (Table 55-4) include factors that rapidly lead to recurrent life-threatening illness or impede recovery. Currently, such factors include incurable malignancy, old (physiologic) age, concurrent poorly controlled systemic illness, active systemic or incurable infection, obesity with physiologic impairment, ongoing substance abuse, evidence of emotional instability, or lack of a strongly supportive social milieu. However, such criteria are undergoing continuous evolution in the light of new information. For example, diabetes mellitus was considered a contraindication to major organ transplantation, until renal allograft survival was shown to be comparable with that found in the absence of this disease. Similarly, survival of the elderly after heart transplantation is comparable with that of younger patients.

Although candidates for organ transplantation frequently are found to have abnormal physical or laboratory findings, these usually indicate secondary organ involvement (e.g., azotemia resulting from left ventricular failure). Such findings must be distinguished from concurrent primary organ failure or a systemic disease that could disqualify candidacy. Occult infection (e.g., tuberculosis) must be ruled out by skin tests and serologies; otherwise postoperative immunosuppression could lead to overwhelming septic complications. Technical factors should also be considered, particularly in patients with atypical vascular anatomy or body

TABLE 55-4 -- General Contraindications to Organ Transplantation

1. Incurable malignancy
2. Old age
3. Active systemic or incurable infection
4. Other major systemic disease
5. Morbid obesity
6. Current alcohol, drug, or tobacco abuse
7. Emotional instability
8. Unsupportive social milieu

Figure 55-5 (Figure Not Available) *In situ* perfusion technique for preservation of the donor heart and abdominal organs. Appropriate preservative solutions are infused by gravity into the ascending aorta, both the portal and systemic circulations, and the aortic root. Drainage occurs via caval transections (not shown) both above and below the diaphragm to prevent venous congestion. *(From Starzl et al [267])*

habitus or in those who have undergone multiple previous surgery. Some transfusion practices are specific to transplantation as well; for example, CMV-seronegative blood products must be available for seronegative patients if CMV sepsis is to be avoided. Likewise, leukocyte-poor blood is mandatory for transplant candidates who must be transfused prior to their transplant procedure, if HLA alloimmunization is to be avoided.

Transplantation procedures are usually performed as emergencies because of the relatively short safe ischemic times for most organs (see the earlier section on principles of organ preservation). Thus, patients will have rarely fasted for an appropriate interval and may not have received the benefits of sedating premedication prior to arrival in the operating room. Finally, the shortage of donor organs may have resulted in "wait-listing" for many months, during which interval change in the patient's medical condition is common.

KIDNEY TRANSPLANTATION

Kidneys are the most common major organ transplanted, accounting for some 9,000 to 10,000 procedures each year in the United States. Roughly 10 percent of patients otherwise dependent on dialysis receive transplants each year; the only factor limiting further growth is the supply of available donor organs. [63] This is because transplantation has now gained acceptance as the preferred option for patients with end-stage renal disease, owing to lower overall morbidity and mortality than dialysis [64] and higher survival (see Table 55-1) (Table Not Available) . [65] For example, data from UNOS demonstrate a 91 percent 1-year allograft survival rate (for living-related donor organs). [66] Longer-term survival statistics, [67] as well as those for cadaveric organs, [66] are not far behind. Other measures of outcome also support the success of kidney transplantation in adults: quality of life is clearly improved [68] while remaining cost-effective. [69] Moreover, in children, kidney

transplantation has a clear advantage in providing superior growth and development. [70] [71]

Pathophysiology of End-Stage Renal Disease and Dialysis

In adults, end-stage renal disease may be a consequence of diabetic glomerulopathy (the diagnosis in 44% of transplant recipients in one large study [72]), other glomerulonephritides (23%), polycystic kidney disease (6%), chronic pyelonephritis (5%), obstructive uropathy, Alport syndrome, or lupus nephritis. Whatever the cause, patients manifest the uremic syndrome, with inability to regulate the volume and composition of their body fluids. Untreated, this results in excessive intravascular volume, acidemia, and imbalance of key electrolytes such as potassium, phosphorus, magnesium, and calcium, leading to secondary dysfunction in other organ systems. For example, the cardiovascular complications associated with uremia may include congestive heart failure (CHF), pericarditis, hypertension, arrhythmias, and capillary fragility; pulmonary edema or pleural effusions may affect the lungs; musculoskeletal manifestations include renal osteodystrophy, generalized muscle weakness, and metastatic calcifications; nervous system involvement may encompass peripheral neuropathy and a spectrum of mental status changes ranging from lethargy to coma. Hematologic effects of uremia include anemia, platelet dysfunction, and a shifted oxyhemoglobin dissociation curve; nausea, vomiting, intestinal ileus, and GI ulceration are also found, as are certain immunologic responses (impaired cellular immunity) and effects on the integument (pruritus) (Table 55-5) (Table Not Available) . Dialysis diminishes many, but not all, of these manifestations.

Indications and Contraindications

Provided there are no general contraindications (see Table 55-4) , most patients receiving dialysis are candidates for kidney transplantation. Contraindications specific to renal transplantation include processes that are highly likely to recur in the allograft (e.g., membranoproliferative glomerulonephritis and hemolytic uremic syndrome). Diabetic nephropathy and metabolic derangements (e.g., gout, cystinosis, and oxalosis) were once included in this category, but studies have shown that such patients can derive years of benefit from renal transplantation.

Preanesthetic Considerations

Living-related kidney transplantation is an elective procedure, whereas cadaver allografts are transplanted semielectively within the kidney's tolerable ischemic interval (24-72 h). [73] In both cases, there is sufficient time for ABO and lymphocyte crossmatching and HLA tissue typing.

Dialysis often precedes transplantation to correct volume or electrolyte derangements. After dialysis, the net volume status of patients must be ascertained, as should the final hematocrit, potassium and calcium levels, and presence of any residual heparin effect. Supplementation of calcium to

TABLE 55-5 -- Pathophysiology of End-Stage Renal Disease

(Not Available)

From Firestone and Firestone [271]

more than 7 mg/dL may be needed to prevent tetanus. Uremic patients are also usually profoundly anemic, but compensatory changes promoting tissue oxygen unloading may influence the decision to transfuse. Despite impending transplantation, it is still important to protect existing vascular and other routes for dialysis. Kidney allografts, particularly those derived from cadavers, may not be functional immediately.

Most adult kidney recipients have diabetes, so the possibility of coexistent ischemic heart disease is evaluated by exercise stress testing and, if indicated, coronary angiography. [74] In this setting, diffuse coronary artery disease has not been considered a contraindication to renal transplantation, provided ventricular function is not seriously compromised and the patient is willing to assume the added risk. In such cases, appropriate invasive monitoring is warranted (e.g., systemic and pulmonary artery [PA] catheters); in all others, a central venous pressure (CVP) catheter is considered sufficient to optimize intravascular volumes and renal perfusion. Finally, functionally significant pleural or pericardial effusion may require treatment, and "stress doses" of glucocorticoids should be considered for patients with adrenal suppression from long-term steroid use.

Living donors account for 20 percent of renal allografts in the United States and 60 percent in Europe. Most donors are healthy adults, as any significant systemic disease increases the risk of general anesthesia and surgery, giving rise to ethical barriers. Living-related kidney donation has gained widespread acceptance, because the overall incidence of serious perioperative morbidity in this population is lower than 2 percent, mortality is extremely rare, [75] [76] and there is no added risk of developing renal failure or hypertension over the long term. [77] Preoperatively, donors undergo

renal arteriography and intravenous pyelography (IVP) and are screened for ABO compatibility and CMV titer. Autologous blood is also donated 2 to 4 weeks prior to the donor procedure. If older than age 45 to 50 years, donors also undergo noninvasive studies to detect occult coronary ischemia. Intravenous crystalloid infusions sometimes are initiated the night before surgery, to promote active diuresis, and shortly before nephrectomy, mannitol and furosemide are administered to achieve a minimum urine output of 1 mL/min. Heparin is administered systemically immediately prior to kidney removal, and the organ is flushed free of blood with cold preservative solution and transplanted immediately. The timing of donor and recipient procedures is coordinated so that the kidney's ischemic interval is minimized.

Induction and Maintenance of Anesthesia

General anesthesia is most commonly employed for renal transplantation, [78] [79] although the use of regional techniques has also been undertaken. [80] [81] The duration of renal transplant surgery at most centers may make regional procedures impractical. In addition, general anesthesia provides superior control of ventilation, particularly when the site of delicate surgical maneuvers is close to the diaphragm. Rapid induction of general anesthesia may be warranted in patients with diabetes with delayed gastric emptying. [82] Succinylcholine may be used for this purpose, provided the serum potassium level is normal following recent dialysis. Drugs that are highly protein bound (e.g., thiopental) should be administered in reduced dosage to patients with end-stage renal disease; further discussion of the pharmacokinetics and dynamics of drugs with concurrent renal disease is found in Chapters 8 to 13 and 53 .

Nitrous oxide is often omitted to avoid distention of the bowel, particularly in small children. Thus, opioids and benzodiazepines, along with a potent inhaled anesthetic, are usually used in combination. Muscle relaxants not primarily dependent on the kidney for elimination should be used, such as vecuronium, atracurium, cisatracurium, mivacurium, and rocuronium (Ch. 12) . Neuromuscular monitoring is still considered essential, because the response to vecuronium with end-stage renal disease can be quite variable, [83] and it is seldom clear when renal function will be restored following transplantation.

In adults, renal allografts are usually implanted retroperitoneally in the upper pelvis, through a paramedian lower abdominal incision. Revascularization occurs by anastomosis of the renal pedicle to the iliac vessels, after temporarily clamping the common iliac veins. This results in some period (usually <60 min) of lower extremity ischemia, and as a consequence, when the vascular clamps are released, both renal preservative solution and venous drainage from the legs are released into the circulation. Both are rich in potassium and acidic metabolites, and pronounced hemodynamic instability may ensue in small children. To promote renal perfusion, the arterial blood pressure is increased by bolus administration of crystalloid, reducing the depth of anesthesia, and infusion of dopamine 2 to 5 mug/kg/min. However, more recently, a prospective controlled trial failed to detect any improved kidney function or survival by a dopamine infusion. [84] Increasing attention is being given to evaluating renal blood flow intraoperatively by methods such as contrast ultrasonography with sonicated albumin microspheres. [85] Such evaluations will facilitate more objective pharmacologic interventions. Finally, ureteral implantation is performed for urinary drainage.

Postoperative Management and Complications

Emergence from anesthesia may be accompanied by pain and hypertension, which is particularly hazardous for those with diabetes and ischemic heart disease. Such deleterious responses can be blunted with antihypertensives or epidural analgesics, or both. Occasionally, atelectasis, bleeding and thrombosis of vascular anastomoses, or oliguria may also be encountered. One-third of cadaveric renal transplants show varying periods of oliguria or anuria due to acute tubular necrosis [86] ; maintenance fluids must therefore be adjusted accordingly. By contrast, immediate urine flow from living-related allografts is typical. A less common cause of anuria is hyperacute rejection, because both ABO matching and crossmatching of recipient's serum to donor lymphocytes are performed routinely.

Special Considerations in Children

Pathologic processes leading to renal transplantation in children differ from those in adults (Ch. 59) . Typically, developmental anomalies and genetic defects, both anatomic and functional (i.e., inborn errors of metabolism), lead to end-stage renal disease in children. [87] Congenital anomalies may be confined to a single organ system (e.g., reflux nephropathy) or be part of a constellation of abnormalities (e.g., Alagille syndrome, characterized by congenital heart disease, renal dysfunction, and end-stage liver disease). Living-related renal transplantation is most often performed in children; the advantages include improved short-term and long-term mortality and allograft survival. [88] [89] However, because perioperative mortality and renal rejection are more frequent in infants, [90] transplantation is avoided until early childhood. In children, medical management of end-stage renal disease has an overall high morbidity and adversely affects growth and development. [91] [92] On dialysis, eventual height and weight are diminished, [93] as is cognitive development, [94] whereas transplantation appears to prevent these complications. [95] [96] This has been used to justify the recommendation to perform renal transplantation "expectantly" in children with progressive renal insufficiency, sometimes before dialysis is absolutely required. [88]

In contrast to adults, renal allografts are usually placed intra-abdominally in pediatric patients. This allows adult-size kidneys to be used in even small children, effectively increasing the donor pool. However, relatively large allografts can sequester a large proportion of a child's blood volume and may also acutely produce hypothermia. Hypotension is avoided by rapid intravenous administration of crystalloid or colloid 250 to 500 mL/70 kg and inotropic infusions to maintain systemic blood pressure in the high-normal range.

Adult kidneys initially produce adult-size volumes of urine, so intravenous maintenance fluids must be adjusted accordingly.

Anesthesia After Kidney Transplantation

General preanesthetic considerations for all patients who have previously received a transplant include the potential for infectious and malignant complications, interactions between immunosuppressants and drugs typically used during the perioperative period (including anesthetics), and special aspects of transfusion in this population. The toxicity of immunosuppressants is another feature common to anesthesia care of post-transplant patients, already considered earlier in this chapter.

Early after transplantation, bacterial infections related to wound infection, urinary catheters, and pneumonia are most common (e.g., with *Staphylococcus aureus, Escherichia coli,* and *Streptococcus pneumoniae,* respectively). Because of the particular susceptibility to pneumonia, early extubation of the trachea following general anesthesia is highly recommended. After the first few months of immunosuppression, vulnerability to opportunistic infection increases (*Pneumocystis carinii* pneumonia, herpes zoster infection, CMV enteritis, or sepsis). If diagnosis is rapid and treatment decisive, survival of such episodes is the rule. [97] CMV is the most frequent viral pathogen, resulting from either primary infection after contaminated allograft implantation or blood transfusion in seronegative recipients or secondary to reactivated infection in a seropositive patient (Ch. 46) . Prophylactic antibiotic regimens are already available for some of these pathogens (e.g., trimethoprim-sulfamethoxazole for *Pneumocystis*[98]); others are under development.

Lymphoproliferative malignancy is more likely to develop in immunosuppressed patients than in a matched population. For example, B-cell lymphoma has a 350-fold increase in incidence after renal transplantation. Such malignancies are clinically aggressive [99] and associated with relatively high mortalities (37% over 5 years in one study [100]). Epstein-Barr virus (EBV) has been implicated in the pathogenesis, and there is evidence that immunosuppressants reduce the cytotoxicity of suppressor T cells toward autologous B cells infected with EBV. With respect to relevant post-transplant drug interactions, both cyclosporine and prednisone are metabolized by the cytochrome P-450 system in hepatocytes. Therefore, drugs that inhibit those enzymes (e.g., calcium channel blockers) may increase their serum concentrations and promote toxic side effects. [101] Other drugs (e.g., barbiturates and phenytoin) may induce the P-450 enzymes and decrease cyclosporine levels below the therapeutic range. [102] In animals, cyclosporine increases the hypnotic duration of pentobarbital, [103] but such effects are probably not pharmacodynamic in nature because inhaled anesthetic potencies are not altered. [104]

Post-transplant patients are particularly susceptible to CMV sepsis, which may arise from transfusion of seropositive cellular blood products (Ch. 46) . Thus, it is mandatory to use only CMV-negative blood in seronegative patients, although use of seropositive products rendered "safe" by depletion of leukocytes with high-efficiency filters has been supported by data. [104] Following transplantation and immunosuppression, concern regarding alloimmunization by blood transfusion is limited, making leukocyte depletion or irradiation unnecessary.

After kidney transplantation, provided the allograft is functioning sufficiently well to maintain normal BUN and creatinine values, renal excretion of drugs is comparable with that produced via normal kidneys. However, some recipients may have mild renal impairment from recurrence of diabetic or other nephropathy, or even a residual dialysis requirement. In patients with diabetes, perioperative glucose control is often complicated by the steroid component of immunosuppression regimens and/or infection, yet perioperative loss of renal allografts is unusual.

Although the principles are the same no matter which surgical procedure is performed, clinical experience in specific clinical settings, such as trauma [105] and coronary artery bypass surgery, [106] is being described. Numerous reviews of anesthetic experience and pharmacology are available for more specific details. [107] [108]

[109] [110]

/das/book/view/29494766/875/609.html

LIVER TRANSPLANTATION

Although generally supportive, medical treatment for chronic end-stage liver disease does little to prolong life or improve its quality. This is especially true after serious complications, such as coma, GI bleeding, or uremia, develop. Salvage after acute hepatic failure through medical treatment is equally discouraging, with rates ranging from 5 to 20 percent. [111] By contrast, in the cyclosporine era, the overall 1-year survival for orthotopic liver recipients is greater than 75 percent (see Table 55-1) (Table Not Available) . [66] Longer-term survival is also relatively high, [112] and the quality of life is considered markedly improved for a high proportion of transplant survivors. [112] [113] As a consequence, some 2,500 liver transplants are performed in the United States annually, representing perhaps one-half the number needed. [112] Almost all these procedures are orthotopic, in which the allograft is implanted in anatomic position following native hepatectomy. Rarely, heterotopic (sometimes called auxiliary) transplantation, in which the native liver is left in place, has been used to treat reversible hepatic failure in patients too unstable for the orthotopic operation. [114]

Pathophysiology and Management of End-Stage Liver Disease

Considering the numerous synthetic and metabolic functions of the liver (Ch. 17) , the manifestations of end-stage liver disease extend to virtually every other organ system. The central nervous system may be affected by encephalopathy ranging from mild confusion to deep coma. This may be exacerbated by electrolyte abnormalities, such as hyponatremia, and worsened by GI bleeding. In fulminant hepatic failure, encephalopathy must be distinguished from cerebral edema, which may require CT scanning. Circulation is usually hyperdynamic with reduced systemic vascular resistance and increased cardiac output, and low-normal blood pressure, despite reduced plasma volume.

Pulmonary gas exchange may be adversely affected by atelectasis from abdominal distention and pleural effusion. The hepatopulmonary syndrome is characterized by intrapulmonary shunting from arteriovenous communications, which is a generalized feature of chronic liver failure. Hypoxemia may be significant, although routine causes of gas-exchange problems are more common.

Renal dysfunction is common and results from diuretic use, intravascular volume depletion, and the hepatorenal syndrome. Azotemia from the hepatorenal syndrome, which is reversible with transplantation, must be distinguished from renal dysfunction resulting from profound hypovolemia, common with aggressive diuretic use and hemorrhage.

Endocrine manifestations include glucose intolerance, although hepatic glycogen depletion may lead to chronic hypoglycemia; coagulopathy, resulting from diminished clotting factor production (particularly I [fibrinogen], II [prothrombin], V, VII, IX, and X); thrombocytopenia from hypersplenism and from low production owing to a lack of thrombopoietin; and reduced hepatic clearance of fibrinolysins and tissue plasminogen activators.

When end-stage liver disease destroys the normal hepatic architecture, portal hypertension follows, and engorged venous collateral vessels develop in the abdominal and GI tract walls, mesentery, and retroperitoneum. Hemorrhage is common from esophageal varices, and arteriovenous communications contribute to the pathologically decreased systemic vascular resistance and intrapulmonary shunting. [115] The latter leads to intractable hypoxemia, exacerbated by pleural effusions and atelectasis. Ascites develops as a result of chronic venous hypertension, diminished albumin synthesis, and sodium and water retention from unmetabolized aldosterone and antidiuretic hormone. Treatment usually consists of diuretics, which may exacerbate electrolyte and acid-base derangements and intravascular volume depletion.

PA hypotension occurs in about 2 percent of patients who present for liver transplantation. [116] Moreover, the hepatopulmonary syndrome, consisting of hypoxemia, pulmonary vasodilation, and hepatic dysfunction, occurs in approximately 30 percent of potential transplant recipients. [116] Currently, outcome studies are being conducted to better define outcome (survival) and costs of performing liver transplantation in patients with these syndromes. [116]

Indications and Contraindications

The timing of liver transplantation is seldom based solely on objective liver function tests, because these values may not reflect disease severity and vary considerably according to the specific pathologic process. Instead, both medical and social factors are balanced against the ongoing mortality associated with nonsurgical management. [112] Ideally, the procedure takes place before the onset of frank liver failure jeopardizes recovery. Diagnoses in adult liver transplant recipients are listed in Table 55-6 (Table Not Available) .

Currently, orthotopic liver transplantation is indicated for nonmalignant end-stage liver disease that will not recur in the allograft, including chronic parenchymal processes (e.g., postnecrotic cirrhosis, Budd-Chiari syndrome, congenital hepatic or cystic fibrosis); acute liver failure (from viral or

TABLE 55-6 -- End-Stage Renal Disease in Adult Renal Transplant Recipients

(Not Available)

From Firestone and Firestone [271]

toxin-induced hepatitis, or Wilson disease); cholestatic processes (biliary atresia or cirrhosis, sclerosing cholangitis, or familial cholestasis); and certain inborn errors of metabolism (e.g., primary hyperoxaluria type 1 or familial hypercholesterolemia). [112] The transplantation option is more controversial when recurrence of disease in the allograft is a possibility, in view of the limited donor supply. For example, primary liver and bile duct cancers, as well as hepatic metastases from GI and endocrine tumors, have been treated with liver transplantation with varying durations of remission. [117] But eventual recurrence is the rule, so the procedure is now reserved for those rare cases with highly circumscribed tumors and rapidly deteriorating liver function. Otherwise, if liver function is maintained, hepatic lobectomy is the preferred approach.

By contrast, patients with cirrhosis resulting from hepatitis B virus infection, once thought to be an absolute contraindication, have had successful long-term outcomes after liver transplantation [112] despite inability to prevent infection in the allograft. Similarly, results obtained in carefully selected patients with alcoholic liver disease are comparable with those obtained in groups with other liver diseases. [118]

Other possible contraindications relate to technical aspects, for example, thrombosis of major abdominal veins, prior portosystemic shunts, or scarring from multiple prior abdominal operations. Moderately advanced age is no longer considered a contraindication, because studies have shown that 5-year survival in recipients older

than 50 years of age is similar to that of younger adults. [119]

Preanesthetic Considerations

Many derangements associated with end-stage liver disease are not correctable until after transplantation. Thus, the major emphasis should be to identify the physiologic systems most seriously compromised and to treat only those that threaten the safe induction of anesthesia. For example, defects in coagulation are usually not corrected at this point, unless there is active hemorrhage or evidence of severe coagulopathy (e.g., prothrombin time [PT] >20 s). Conversely, correction of the coagulopathy may be considered for placement of invasive lines after induction of anesthesia. However, pleural effusions that lead to hypoxemia may on rare occasions necessitate thoracentesis.

The timing of transplantation may be critical to outcome in patients with fulminant hepatic failure. Provided patients

have not become deeply comatose, salvage rates can approach 75 percent, [120] which is usually better than that achieved by medical therapy alone. Certain uncommon diseases treated by liver transplantation have additional implications for anesthesiologists. For example, in children with Crigler-Najjar syndrome (bilirubin UDP-glucuronyl transferase deficiency), drugs that interfere with bilirubin- albumin interactions (e.g., barbiturates) should be avoided. Patients with Budd-Chiari syndrome, characterized by extensive hepatic venous thrombosis, may require perioperative anticoagulation. [121]

In fulminant hepatic failure, the possibility of cerebral edema in a comatose patient needs to be considered, compared with coma from encephalopathy. Brain injury during transplantation is a real possibility in this situation, and monitoring intracranial pressure perioperatively ought to be considered (Ch. 52) .

The potential for active bleeding needs to be considered, as well as appropriate analysis of coagulation and availability of blood products. In addition to standard diagnostic measures, the thromboclastograph has been frequently touted as extremely valuable for liver transplantation. [122] Hett et al [123] have provided an excellent review of this topic. Electrolyte abnormalities, including hyperkalemia and hyponatremia from renal disease or diuretic use, are common, including degrees that would lead to cancellation of almost any other case.

Pulmonary hypertension is associated with cirrhosis in a higher incidence than found in the general population. The increased risk of surgery in the presence of pulmonary hypertension depends on the degree of abnormality, but significantly increased morbidity and mortality are likely, as indicated previously. [116] Severe pulmonary hypertension may be a contraindication to transplantation. Screening for pulmonary hypertension is difficult. Symptoms are frequently delayed until the advanced stages of the disease. Echocardiography is the preliminary study of choice, with right-heart catheterization reserved for questionable cases.

Because the level of physiologic stress of liver transplantation is extremely high, concomitant coronary artery disease needs to be ruled out (Ch. 25) . Hemochromatosis is a common cause of cirrhosis but may be missed because of secondary reasons for cirrhosis, such as hepatitis C virus infection. Because of frequent GI bleeding and transfusion, standard hematologic test results for hemochromatosis may be inconclusive. Iron overload of the myocardium can lead to significant cardiac dysfunction and can potentially increase the morbidity of liver transplantation.

Finally, either as a result of the primary disease process, or of multiple subsequent transfusions, recipients may be seropositive for one or more hepatitis viruses. The anesthesiologist must be aware of the potential for infectious contamination and take appropriate precautions on behalf of the health-care team (Ch. 84) .

Induction and Maintenance of Anesthesia

The ability to transfuse rapidly is vital to successful outcome in liver transplantation, which involves transection and reanastomosis of several major venous structures (e.g., portal vein and IVC). Typically, at least two large-bore peripheral venous cannulas are inserted prior to induction, one of which is 7.0 Fr to facilitate connection to a rapid transfusion system (see later discussion). Invasive monitoring with systemic and PA catheters is standard in most centers, because major shifts in intravascular volume are the rule, and reperfusion of the allograft can be associated with profound hypotension. [124] Both radial and femoral artery catheters are placed, in that distal arterial flow may be compromised transiently by abdominal aortic clamps during hepatic artery anastomosis. The remainder of the monitoring array is analogous to that used for any critically ill patient undergoing a major surgical procedure. Nevertheless, as sicker patients undergo liver transplantation, more sophisticated monitoring is being used by some centers to detect inadequate O_2 delivery to organs such as the brain (i.e., transcranial Doppler to determine middle cerebral artery blood flow velocity), [125] heart (i.e., continuous determination of cardiac output), [126] and gastrointestinal tract (i.e., mucosal pH). [127] In addition, transesophageal echocardiography (TEE) is increasingly used (Ch. 31) .

Ascites, active GI bleeding, or hepatic encephalopathy may result in delayed gastric emptying. Therefore, aspiration precautions are recommended, and general anesthesia should proceed by either rapid-sequence induction or, in patients with hemodynamic instability, awake endotracheal intubation. Thiopental, etomidate, propofol, and ketamine, supplemented with succinylcholine, have all been used successfully for induction of anesthesia. Plasma pseudocholinesterase levels are typically low in this patient population, but prolongation of the relaxant effect of suc cinylcholine is not of clinical significance.

Drugs that do not compromise splanchnic blood flow (e.g., opioids, isoflurane, [128] desflurane, [129] and probably others) are typically used to maintain anesthesia, except in cases of fulminant hepatic failure in which the possibility of intracranial hypertension may contraindicate use of potent inhaled anesthetics. Nitrous oxide is usually avoided due to its potential for bowel distention and increased size of venous air emboli. Liver disease profoundly affects pharmacokinetics, as a result of alterations in hepatic extraction and metabolism, extracellular fluid volumes, levels of serum albumin and alpha $_1$ -acid glycoprotein, and accumulation of bilirubin and other metabolites that displace drugs from protein-binding sites. In general, the net effect of these factors for charged nondepolarizing muscle relaxants is to increase the initial dose requirements and to prolong the duration of action. [130] [131] Newer muscle relaxants, such as cisatracurium [132] and rocuronium, [133] are little affected by liver transplantation (Ch. 12) . Any residual effect is rapidly removed by the newly transplanted liver. [133] In fact, the rate of recovery from vecuronium [134] or rocuronium [135] has been used as a predictor of hepatic allograft function. However, fentanyl and sufentanil kinetics are largely unchanged. [136] [137] Liver allografts rapidly begin to metabolize drugs, [138] but other pharmacokinetic changes (e.g., enlarged volumes of distribution) persist well into the postoperative period. The orthotopic procedure involves total replacement of the diseased native liver with a preserved cadaveric organ, in the most anatomic position possible. Surgery proceeds in three stages: the preanhepatic, anhepatic, and neohepatic (summarized in Table 55-7) .

TABLE 55-7 -- Summary of Orthotopic Liver Transplantation

STAGE	SURGICAL MANEUVERS	PHYSIOLOGIC ALTERATIONS
Preanhepatic	Dissect porta hepatis	Acute decompression of ascites
	Mobilize liver	Hemorrhage (venous collaterals)
Anhepatic	Portal venous clamp	Obstruction of venous return
	Inferior vena cava, hepatic arterial clamp	Oliguria (venous congestion)
	Venovenous bypass (adults)	Atelectasis, decreased compliance
	Retraction on diaphragm	Citrate intoxication
Neohepatic	Inferior vena cava anastomosis	Hemorrhage, coagulopathy
	Flush allograft	Hyperkalemia
	Portal venous, hepatic arterial anastomoses	Hypothermia

Biliary drainage	Metabolic acidosis

During the *preanhepatic* stage, the structures of the porta hepatis are dissected and the native liver is mobilized for removal. Hemodynamic instability is common, due to numerous factors, including acute decompression of ascites, exacerbation of chronic hypovolemia from third-space losses, hemorrhage from venous collaterals in the body wall and mesentery, citrate-induced hypocalcemia, [139] hyperkalemia from rapid transfusion and hemolysis, pericardial effusions rendered significant by hypovolemia, and diminished venous return from abdominal retraction. Hemorrhage may be exacerbated by hemodilution, fibrinolysis, [140] or clotting factor deficiency; differential diagnosis is pursued by means of conventional studies (e.g., PT, partial thromboplastin time [PTT], bleeding time, platelet count, and fibrinogen and fibrin split product levels) and/or thromboelastography. In addition, endogenous heparin-like substances can impair coagulation. [141] Moreover, reperfusion in particular involves release of plasminogen activators that can occur at all stages of liver transplantation, but especially during reperfusion. Drugs such as transexamic acid, aprotinin, and conjugated estrogen have been recommended. [142] epsilon-Aminocaproic acid (Amicar), administered by infusion started prior to incision, may help control hemorrhage secondary to fibrinolysis. At the University of Pittsburgh, a rapid infusion system designed to deliver prewarmed fluids or blood products at a rate of up to 1.5 L/min is employed routinely (Fig. 55-6) (Figure Not Available) . The device consists of reservoirs, heat exchanger, fluid-level sensors, air detectors, line pressure monitors, and filters integrated

Figure 55-6 (Figure Not Available) Schematic of the rapid infusion system developed at the University of Pittsburgh for use during liver transplantation. See text for details. *(Courtesy of John Sassano, MD, Pittsburgh, PA.)*

to minimize trauma to the formed elements of blood and prevent transfusion of air. Autotransfusion systems that salvage extravasated blood are also used, provided there is no infection or malignancy. [143]

Oliguria is common in the preanhepatic phase, and once prerenal causes are eliminated, treatment with potent loop or osmotic diuretics, as well as "renal-dose" dopamine (2 to 5 mug/kg/min) is begun. Metabolic acidosis often accompanies hemodynamic instability, particularly with absent hepatic metabolic function. If severe, an infusion of tromethamine [tris(hydroxymethyl)aminomethane] (THAM) or dichloroacetate will avoid the hyperosmolar hypernatremia associated with repeated boluses of sodium bicarbonate. The aggressiveness with which metabolic acidosis should be treated has been controversial in the literature. [144] When the native liver's blood supply (hepatic artery and portal vein) is transected, and the suprahepatic and infrahepatic IVC is occluded, the *anhepatic* stage begins. A Sengstaken-Blakemore tube may be placed temporarily if large esophageal varices are jeopardized by IVC occlusion. Venovenous bypass is often used to avoid precipitous decline in venous return and cardiac output, as well as venous engorgement in the lower body, bowel, and kidneys. [145] The venovenous circuit reroutes both portal and systemic (femoral) venous blood, extracorporeally, to the axillary vein (then SVC) at 20 to 50 percent normal systemic flow rates. Heparin-bonded tubing obviates the need for systemic anticoagulation. Although venous bypass clearly helps preserve renal function, it has been associated with air and thromboembolism, [146] can prolong the procedure and contribute to heat loss, [147] and does not clearly improve overall morbidity and mortality. [148]

Native hepatectomy and allograft implantation require vigorous retraction near the right hemidiaphragm, resulting in atelectasis, hypoventilation, and diminished respiratory compliance. PEEP and augmentation of inspiratory pressure may compensate to some extent. In patients with pulmonary hypertension, sudden cardiovascular depression is more likely. Gillis et al [149] even used manual compression of the abdominal aorta to increase arterial pressure and coronary perfusion in this situation. Citrate intoxication from rapid transfusion is common during this stage, owing to the absence of the liver's metabolic functions. Rapid transfusion of blood products, especially fresh frozen plasma, which contains the largest amount of citrate, may overwhelm the metabolic activity of the diseased liver. During the anhepatic stage, the complete absence of any metabolism of citrate necessitates the administration of calcium to prevent profound hypocalcemia. Hypotension, which is common during liver transplantation, may be significantly exacerbated by hypocalcemia. Thus, calcium must be supplemented to maintain the ionized level at more than 1.0 mM. Both calcium chloride and gluconate will suffice, even in the absence of the liver. Hyperkalemia, from rapid transfusion, can still be treated in the conventional manner, with glucose and insulin infusion, but metabolic acids, notably lactate, remain uncleared during the anhepatic stage. Even clonidine administration has been recommended to improve fluid requirements and hemodynamic variables. [150]

The *neohepatic,* or postreperfusion, stage begins with reanastomoses of the hepatic major vessels. Prior to unclamping, the allograft is flushed of preservative solution, air, and debris, using portal venous blood. Nonetheless, final removal of the vascular clamps can still be associated with release of a large load of potassium and metabolic acids into the circulation. Hypotension, arrhythmias, and cardiac arrest may follow; inotropic support may be needed to treat myocardial depression from putative cardioactive mediators [151] or venous air embolism. [152] Perhaps the excessive use of antifibrinolytic drugs could contribute to the occurrence of thromboembolism. [153] "Reperfusion syndrome" may cause significant hypotension. The incidence may be 30 to 50 percent. Hypotension occurs within minutes after unclamping the portal vein. Hemodynamically, it is characterized by systemic vascular resistance. Right heart dysfunction has also been described during initial reperfusion. Suggested mediators of reperfusion syndrome include kallikrein-bradykinin syndrome, endotoxin, nitric acid, and prostaglandins. Various predictive approaches (e.g., hemodynamic response to clamping of the IVC, [154] drugs to accelerate graft recovery [155] and avoidance or cardiovascular depressant anesthetics [156] have been recommended with varying degrees of success. Increases in end-tidal nitrogen are useful to distinguish the latter mechanism. Cardiovascular collapse may also be due to pulmonary thromboembolism during reperfusion. [157] [158] [159] With return of allograft function, both metabolic and hemodynamic stability are gradually restored. Urine output typically improves, even in patients with prior hepatorenal syndrome, [150] and inotrope requirements diminish. Clotting variables gradually return to normal, by a combination of specific replacement therapy and production by the allograft. The procedure is completed by biliary reconstruction, either by direct bile "duct-to-duct" anastomosis or by a Roux-en-Y choledochojejunostomy.

Postoperative Management and Complications

Primary nonfunction of liver allografts is rare since the introduction of the UW solution for preservation. [160] Recovery from primary nonfunction has been reported, but more typically, retransplantation is necessary. [161] Provided allograft function is sustained, metabolic acids including lactate continue to be metabolized and systemic alkalosis may result. Postoperative respiratory complications are common, due to nosocomial pneumonia, diaphragmatic injury, adult respiratory distress syndrome (ARDS) from massive transfusion, and nutritional deficiencies. Thus, pulmonary toilet regimens are of paramount importance. Triple immunosuppression (i.e., cyclosporine, azathioprine, prednisone) is begun immediately in the ICU, yet early rejection episodes are common. Rescue with extra steroid boluses or antibodies (ALG or OKT3) is almost always effective. Other perioperative complications include vascular or biliary leaks, hepatic artery or portal vein thrombosis (particularly in small children), or abdominal abscesses. Longer-term complications include recurrence of hepatitis B or neoplasms, [162] opportunistic infection, and the development of a lymphoproliferative malignancy.

Most patients remain intubated and mechanically ventilated in the ICU. Recently, interest in "fast tracking" liver transplant patients has increased efforts at early tracheal intubation. Provided patients are hemodynamically stable, pulmonary gas exchange and mechanics are good, bleeding

and coagulopathy are controlled, and the graft appears to be functioning well, possibly 20 percent of patients may be tracheally extubated immediately at the end of surgery. At two major institutions, major reductions in cost without change in outcome were a result of "fast track" approaches to early tracheal extubation. [163]

Special Considerations in Children

One-fifth of all liver transplants are performed in children, mostly younger than 5 years of age (Ch. 59) . [164] Overall 1-year survival for the orthotopic procedure in children is comparable to that in adults (i.e., 70-75%), but results are not nearly as good in younger (<3-year-old) and smaller (<12-kg) patients (45-50% 1-year survival). [164] [165] Biliary atresia accounts for a high proportion of preoperative diagnoses, followed by inborn errors of metabolism (alpha $_1$ - anti-trypsin deficiency, glycogen storage disease, Wilson disease, tyrosinemia), and syndromes characterized in part by biliary obstruction (e.g., Alagille and Byler syndromes). Children with biliary atresia have usually undergone a prior decompression procedure (e.g., Kasai choledochojejunostomy), which may complicate both transplant surgery and subsequent biliary reconstruction. Venovenous bypass is limited to patients weighing more than 20 kg, so that oliguria and intestinal complications from lower-body venous engorgement are more common in small children. As with kidney transplantation, oversized liver allografts may lead to blood volume sequestration, profound

hyperkalemia after reperfusion, and hypothermia. Peritoneal lavage with warm saline will effectively prevent the last complication.

The limited supply of suitably sized donor organs has led to the development of techniques to transplant part of a liver. Reduced-size ("split") liver allografts enable one donor liver to be used for multiple patients. The method carries with it a significantly higher complication rate, including hemorrhage, [166] organ necrosis, and diminished recipient survival, [165] so it is usually reserved for the desperately ill. In a variation on this theme, living-related (partial) liver donation has been advocated in view of the nearly 50 percent mortality of children waiting for a donor liver. However, there is significant potential for donor morbidity, and considering the relatively reduced survival noted for reduced-size liver recipients, few centers offer this option. Poorer survival among younger and smaller children probably relates to the use of these reduced-sized allografts and to a far greater incidence of hepatic artery thrombosis. [167]

Anesthesia After Liver Transplantation

The potential for infectious and malignant complications in the post-transplant setting, interactions between immunosuppressants and drugs typically used in the perioperative period, toxicity of immunosuppressants, and special aspects of transfusion in organ transplant recipients have already been considered in detail earlier in this chapter.

Liver disease affects pharmacokinetics, and despite a well-functioning allograft, some changes (e.g., enlarged volume of distribution) persist well into the postoperative period whereas others (e.g., hepatic metabolism) return to normal. [168] Early in the postoperative period, the most common reasons liver recipients return to the operating room include exploratory laparotomy for biliary leak or abscess drainage, or open liver biopsy. Ileus or abdominal distention would mandate rapid sequence induction for general anesthesia. Coagulation studies have usually normalized, so regional anesthesia is also a reasonable option. Later, biliary reconstruction procedures are most common.

Conclusion

Liver transplantation is now a major therapeutic approach to patients with liver disease. As our success and skills increase, sicker patients with more severe liver disease are qualifying as recipients, further challenging our perioperative anesthetic skills. [169]

HEART TRANSPLANTATION

After exponential growth in the mid-1980s, the annual number of heart transplants worldwide has leveled out at 3,000 cases (Ch. 49) . The limited supply of donor organs prevents further growth, although it has been estimated that each year in the United States alone, some 15,000 additional patients with end-stage heart disease could benefit from transplantation. [170] The orthotopic procedure accounts for most transplant cases; heterotopic transplants comprise a small minority. [171] The addition of cyclosporine to immunosuppression regimens after heart transplantation dramatically improved overall survival worldwide from 40 percent [172] to 80 percent at 1 year and almost 70 percent at 5 years. [171] Individual experienced transplant centers have reported survivals as high as 90 percent at 4 years (see Table 55-1) (Table Not Available) . [172] Importantly, quality of life is also enhanced after heart transplantation. [173]

Pathophysiology and Management of End-Stage Heart Disease

There are both acquired and congenital causes of end-stage heart disease. In the former category, ischemic and valvular heart disease, and primary (viral or idiopathic) cardiomyopathy are the leading causes. Whatever the cause, a varying period of physiologic compensation is inevitably followed by CHF. The onset of this symptom is ominous and is associated with a less than 50 percent 5-year survival. [174]

The initial compensation for left ventricular failure is an increase in left ventricular end-diastolic volume, [175] which restores stroke volume but increases left atrial pressure, thus leading to pulmonary venous congestion. Later compensations include elevated catecholamine [176] and renin production, resulting in salt and water retention. With progression of disease, ejection fraction falls, and CHF becomes refractory to drug therapy. Most patients are minimally ambulatory at this point and may require inotropic, vasodilator, or mechanical (e.g., intra-aortic balloon or ventricular assist device) circulatory support. Low cardiac output may secondarily compromise function in other organs

---

(e.g., prerenal azotemia), until the coronary bed itself is inadequately perfused, leading to cardiogenic shock and fatal cardiac arrest. Patients may be evaluated for heart transplantation at any of these stages, even when morbidly ill. Yet overall survival remains high, even in those who require mechanical circulatory support as a bridge to transplantation. [177] [178]

Indications and Contraindications

Heart transplantation is indicated when New York Heart Association class IV (NYHA IV) status ("severely compromised") and prognosis ("guarded despite therapy") persist despite maximal medical therapy. Candidates are typically middle-aged men with left ventricular ejection fractions of less than 20 percent because of ischemic cardiomyopathy. Patients with idiopathic and viral cardiomyopathy comprise the next biggest group, and the remainder have systemic diseases (e.g., amyloidosis) or congenital intracardiac defects. In the latter, either long-standing cyanosis or myocardial hypertrophy leads to end-stage heart disease. [179]

Aside from the general contraindications applicable to any major organ transplant (see Table 55-4) , there are few specific to the orthotopic heart procedure. For example, advanced age is no longer considered a major barrier, because many older patients have now undergone heart transplantation without disproportionate morbidity. The same is true for patients with diabetes, particularly since the demonstration that even insulin-dependent patients can be immunosuppressed successfully without the aid of steroids. [180] Even cancer is no longer absolute grounds for exclusion, as long-term cures for certain malignancies (e.g., Hodgkin lymphoma) become routine. In contrast, irreversible pulmonary hypertension remains an absolute contraindication to orthotopic heart transplantation, because the right ventricle of a normal donor heart will rapidly decompensate in the face of high, fixed pulmonary vascular resistance (PVR). [181] The maximum level of pulmonary hypertension deemed acceptable is 6 to 8 Wood units (480-640 dyn/s/cm ^{5}), or a transpulmonary gradient (mean pulmonary artery [PA] pressure minus mean pulmonary capillary wedge pressure) of 10 to 15 mm Hg. Beyond such levels, heterotopic heart transplantation alone or in a combined heart-lung procedure is the remaining option.

Preanesthetic Considerations

End-stage heart disease with low cardiac output may lead to secondary dysfunction in other organ systems. For example, the lungs may be affected by pulmonary venous congestion, interstitial edema, pleural effusions, and atelectasis; there may be prerenal azotemia and oliguria; the liver may be enlarged from chronic passive congestion and the abdomen distended from ascites; and the sensorium clouded from inadequate perfusion and hypoxemia. Preoperative evaluation of acceptable candidates must lead to the conclusion that all such effects will be reversible when cardiac output is restored.

Heart transplant candidates are usually maintained on a multidrug regimen of oral or intravenous inotropes (e.g., digoxin, dobutamine), vasodilators (e.g., captopril, amrinone), diuretics, and antiarrhythmics. Because patients with dilated cardiomyopathy are apt to form intracardiac thrombi, they may be given an anticoagulant (e.g., warfarin) as well. Bacterial pneumonia is common early after heart transplantation, [182] so administration of appropriate broad-spectrum prophylactic antibiotics, as well as use of bacterial filters on breathing circuits, seems reasonable. However, it has not been found necessary to sterilize tracheal intubation equipment.

Induction and Maintenance of Anesthesia

Patients with ischemic or congenital cardiomyopathy may have undergone previous cardiac surgery and are likely to require additional time for invasive monitoring placement and surgical preparation for cardiopulmonary bypass. Such factors must be taken into account by both the surgical and anesthesia teams, if unnecessary prolongation of donor organ ischemia time is to be avoided.

Despite considerable apprehension built up over many months or longer, patients frequently arrive in the operating room without the benefit of sedating premedication. However, because residual cardiac performance critically depends on elevated endogenous catecholamines, only modest doses of conventional sedatives or analgesics are appropriate. At the University of Pittsburgh, the essential hemodynamic monitoring regimen consists of femoral or radial, and PA catheters, as well as TEE. PA catheters are inserted via the right internal jugular vein, which does little to jeopardize access for future endomyocardial biopsies. Positioning such catheters in this setting can be complicated by cardiac dilation (promoting intraventricular coiling), tricuspid regurgitation, atrial fibrillation, severe orthopnea (necessitating a semisitting position), and congenital vascular anomaly. Once positioned, a long sterile sheath is used because the catheter is pulled back to "CVP position" prior to bicaval cannulation.

Considering the short notice for these procedures, most patients may have recently eaten and thus require rapid induction. Various techniques have been described, [183] [184] [185] [186] [187] [188] [189] all compatible with the pathophysiology of end-stage heart disease. For example, a combination of etomidate 0.3 mg/kg with fentanyl 10 mug/kg and succinylcholine 1.5 mg/kg IV will rapidly produce acceptable intubating conditions without cardiovascular depression. [189] Anesthesia can then be

maintained with supplemental fentanyl (35-75 mug/kg total) with scopolamine (0.3 mg), or with a benzodiazepine as tolerated. Following intubation, azathioprine infusion is begun, and the cardiac chambers examined by TEE for the presence of thrombus (Ch. 31) . TEE is also particularly useful for visualizing intracavitary volumes, because the ventricles may be extremely noncompliant in end-stage heart disease, and filling pressures seldom accurately reflect volumes. At this juncture, hypotension may stem from even small changes in preload or afterload but will almost always respond to appropriate adjustments.

After bicaval and aortic cannulation, cardiopulmonary bypass is initiated. Patients with markedly expanded blood volumes benefit from hemoconcentration on bypass, and mannitol or furosemide may be necessary to maintain urine flow.

Cardiac manipulation is kept to a minimum if thrombus was demonstrated by TEE. As the donor organ arrives, the aorta is cross-clamped and the native heart excised, leaving an atrial cuff containing the caval and pulmonary venous orifices and long remnants of the aorta and PA. The back wall of the allograft is trimmed to facilitate anastomosis with the recipient's atrial remnant. The anterior wall of the allograft is most vulnerable to warming, particularly during posterior anastomoses, which may contribute to right ventricular failure later. As the aorta and PA are resewn, the heart is filled with cold saline to displace the air, and after mechanical deairing maneuvers, cross-clamp removal marks the end of the ischemic interval. Immediately prior to release of the aortic cross-clamp, to modulate the possibility of "hyperacute" immune response, methylprednisolone (500 mg IV) is administered.

After cross-clamp release, slow junctional rhythms or AV nodal dysfunction is relatively common. An infusion of either isoproterenol or another catecholamine with positive chronotropic effects is begun to support heart rate. Most of these arrhythmias spontaneously resolve, but some persist postoperatively, even in the absence of rejection. Ultimately, 5 percent of recipients require implantation of a permanent pacemaker. Immediately prior to weaning from cardiopulmonary bypass, the posterior anastomosis is rechecked because leaks in this area are difficult to repair without extracorporeal support. After final deairing, the SVC cannula is removed, the PA catheter is advanced, and the serum ionized calcium restored to normal. If heart rate persists at less than 70 beats/min, epicardial electrodes are placed and pacing begun.

Many transplant centers routinely use inotropic infusions to wean from cardiopulmonary bypass, because cardiac performance is often mildly compromised immediately following heart transplantation. Despite early reports of exaggerated effects, [190] responses to catecholamines are qualitatively similar to those in other cardiac surgical patients. Transient pulmonary vasospasm can occur during weaning, even in patients with previously normal PA pressures, producing life-threatening right heart failure. PGE_1 at infusion rates of 0.025 to 0.2 mug/kg/min can effectively unload the right heart, [191] although simultaneous norepinephrine or phenylephrine infusion may be necessary to support the systemic circulation. Pulmonary vasospasm usually resolves within the first few hours postoperatively, [192] [193] although rarely, mechanical right ventricular assist has been required for varying periods. [194]

Postoperative Management and Complications

In the ICU, short-term management goals include cardiovascular support, as well as rapid and accurate diagnosis of infection and rejection. [182] Excessive mediastinal bleeding and coagulopathy are often seen in patients who have previously undergone a cardiac surgical procedure and are treated in a conventional manner. At most transplant centers, heart recipients are treated with triple immunosuppression [171] and possibly, OKT3. Fever and pulmonary infiltrates are frequently encountered and their sources aggressively sought. Bacterial pneumonias with typical nosocomial organisms are common; opportunistic infection with CMV, *Pneumocystis,* or *Legionella* may occur somewhat later. [195] Bradyarrhythmias and/or atrioventricular (AV) block can appear in the early postoperative course, requiring temporary pacing. Persistently low cardiac output may result from rejection or from reperfusion injury; endomyocardial biopsy will definitively distinguish between these possibilities. If hemodynamic stability is maintained, evidence of mild kidney or liver compromise present prior to transplantation will gradually disappear. If, however, the allograft functions poorly, organs with preoperative impairment may rapidly decompensate.

Heterotopic Heart Transplantation

Heterotopic heart transplantation, reserved for patients with pulmonary hypertension who are ineligible for orthotopic heart transplantation, is becoming increasing rare in an era of mechanical circulatory support. The procedure begins with median sternotomy, followed by the creation of a right pleuropericardial flap. After cannulation and initiation of cardiopulmonary bypass, the native myocardium is protected with cardioplegic arrest, and the allograft is placed in the right hemithorax anterior to the lung. The donor and recipient (SVC) Fig. 55-7) (Figure Not Available) and right atria (RA) are incised and sutured together, and the donor's aorta is sutured end-to-side to the recipient's ascending aorta. The donor and recipient PA are then connected by means of a Dacron graft. After cross-clamp release, weaning from cardiopulmonary bypass proceeds in a reasonably conventional manner. Short-term postoperative management and complications are similar to those discussed for orthotopic transplant recipients.

Special Considerations in Children

Congenital heart disease recently overtook dilated cardiomyopathy as the major indication for heart transplantation

Figure 55-7 (Figure Not Available) Anatomy of heterotopic heart transplantation. See text for abbreviations. *(From Cooper and Lanza [268])*

in children; thus, most recipients are younger than 5 years of age (Ch. 50) . [196] In contrast to older children and adults, overall mortality for young children is higher (76 versus 81% 1-year survival, respectively). [196] In children, cardiac-related deaths are more common, owing to complex vascular anatomy, previous cardiac surgery, and elevated PVR. In infants, it is often difficult to accurately quantify the fixed component of PVR, thus perioperative acute right heart failure is more common than in adults.

In newborns, heart transplantation is indicated for hypoplastic left heart syndrome and aortic atresia. If reconstruction of the aortic arch is required, profound hypothermia and circulatory arrest are usually necessary. Positional or size discrepancies of the great vessels are further sources of complications in this population, suggesting why overall 1-year survival after heart transplantation for neonates is only 66 percent. Rejection contributes relatively little to this figure, because the neonatal immune system seems relatively tolerant of foreign antigens. [197] [198]

Anesthesia Following Heart Transplantation

Cardiac allograft recipients return to the operating room months and even years following transplantation. [199] [200] [201] [202] [203] [204] [205] [206] Overall, one-fourth or more of these patients require general surgical consultation within 2 years of transplantation. [207] [208] [209] [210] Immunocompromise may account for the need for procedures such as incision and drainage of an abscess or laparotomy for diverticulitis; steroid dependence could explain the occurrence of perforated viscus; but a relatively high incidence of cholecystectomy is unexplained. [207] Orthopedic procedures are also common, secondary to the joint complications of long-term steroid use. [211]

This is a physiologically unique population, because the cardiac allograft is denervated following transection of the cardiac plexus located on the surface of the aorta and main PA. In contrast to canine hearts that readily reinnervate after transplantation, [212] human myocardial specimens obtained up to 12 years following transplantation fail to reveal evidence of abundant reinnervation. [213] [214] Most studies of transplanted heart rate responses to exercise and respiratory stimuli in humans also support that autonomic efferent denervation is permanent. [214] [215] [216] [217] However, one report that patients with allograft coronary atherosclerosis may perceive angina pectoris [218] demonstrates that afferent reinnervation may occur in a small minority of patients. Other studies suggest the possibility of some return of efferent function as well. [219] [220]

Despite denervation, in the absence of rejection, resting stroke volume and contractility of cardiac allografts are either normal [221] or only subtly reduced. [222] However, with demands for increased cardiac output (e.g., during exercise), the denervated allograft's performance is demonstrably different (Fig. 55-8) (Figure Not Available) . In contrast to the normal heart, in which rapid increases in cardiac output are mediated by elevation in heart rate, the denervated heart can respond only by increasing stroke volume, not heart rate. Recipients are thus "preload dependent" and must have adequate central volume to meet the demands of stress and of anesthetic

techniques that redistribute vascular volume to the periphery.

Eventually, the denervated heart can increase its rate. However, the maximum achievable pulse rate develops more slowly than in controls, and the return to baseline is slower as well. [223] The period of delay in increases in heart rate corresponds to the time required for secretion and circulation of adrenal catecholamines, whereas the delay in return to baseline is probably related to the absence of vagal input.

With the midatrial orthotopic surgical technique, transplant recipients retain remnants of the native atria, and their electrocardiograms (ECG) may contain both donor and native P waves. Because the sinus node is normally under the continual influence of autonomic (vagal) nerves, [224] the rate of the transplanted atria general exceeds that of the native atria. [225] With parasympathetic activation (e.g., accompanying laryngoscopy or drug effects), the native atrial rate may decrease but the donor atrial rate remains unchanged, because vagal input to the allograft is lacking. In contrast, sympathetic stimulation (from hypoxemia, pain) can still increase the donor heart's sinus rate (via circulating catecholamines). In contrast to effects at the sinoatrial (SA) node, denervation generally has little effect on AV conduction time [225] [226] or ventricular conduction. Another key physiologic finding in denervated patients is an accelerated form of atherosclerosis, such that by the third postoperative year, there is a 30 percent incidence of multivessel coronary disease [227] (Fig. 55-9) (Figure Not Available) . This is characterized by focal concentric narrowings of epicardial coronary lumina [228] that may arise from areas of immune-mediated endothelial damage. Such lesions are often amenable to angioplasty or surgical bypass, and prophylactic drug therapy may even have a role in prevention. [229] Nonetheless, at present, coronary disease

Figure 55-8 (Figure Not Available) Schematic of the physiologic responses to exercise before (left) and after (right) cardiac denervation. *(From Kent and Cooper, [265] copyright 1974 Massachusetts Medical Society. All rights reserved.)*

Figure 55-9 (Figure Not Available) Cumulative incidence of occlusive coronary artery disease in cardiac allograft recipients. A population of 427 adult recipients was evaluated by angiogram over 7 years. *(Adapted from Uretsky et al [270])*

still limits the useful life of most allografts. Despite a report documenting the ability to perceive angina pectoris in a small group of these patients, [218] afferent innervation seems to be lacking in most, rendering episodes of myocardial ischemia silent. Thus, diagnostic ECG monitoring is essential throughout the perioperative period, and paroxysmal dyspnea may be the only indication of ischemia. The effects of cardioactive drugs may also be altered by denervation. Clearly, drugs that usually act indirectly, via autonomic fibers, will fail to produce their classic effects after heart transplantation. For example, atropine and pancuronium will not increase heart rate. By contrast, drugs that act directly on myocardium or cardiac conduction tissue will manifest their usual effects; for example, isoproterenol will increase both contractility and heart rate, whereas propranolol will have the opposite effects. However, neostigmine, once thought to act only indirectly, has been shown to have direct postsynaptic effects producing bradycardia. [230] Similarly, digoxin, which has mixed direct-indirect actions, [231] can act only directly after transplantation. In such circumstances, an intravenous bolus of digoxin will fail to alter either the functional or effective refractory periods of the AV node, [232] instead of significantly increasing the refractory period. Thus, the acute chronotropic effects of digoxin are vagotonic and depend on intact autonomic innervation. Norepinephrine's effects are also altered by denervation; infusions at conventional doses are accompanied by more pronounced chronotropic effects than usual. This is probably because the direct-adrenergic receptor-mediated effects on the sinus node are no longer masked by vagal reflexes. The effects of alpha $_1$ -adrenergic agonists are also persistently blunted [233] in this population, most likely because of peripheral desensitization to the effects of chronically elevated catecholamine levels.

LUNG TRANSPLANTATION

End-stage pulmonary disease resulting from destruction of the pulmonary parenchyma or vasculature is a leading cause of mortality and morbidity among adults. Several transplantation operations have been devised to treat end-stage pulmonary disease, each with particular conceptual or practical advantages. These include the heart-lung, en bloc double lung, single lung, and bilateral sequential lung procedures. Outcome data have shown that when cardiac performance is preserved, isolated lung transplantation is reasonably safe and can benefit carefully selected subgroups (see Table 55-1) (Table Not Available) . [234] [235] For example, at one specialized center, actuarial survival was 90 percent at 1 year after single lung transplantation [234] and 82 percent after the bilateral sequential operation. Exercise tolerance, gas exchange, and PA pressures have all been noted to improve significantly following lung transplant surgery. [234] [236]

Pathophysiology of End-Stage Pulmonary Disease

End-stage parenchymal lung diseases are either obstructive, restrictive, or infectious in nature (Chs. 48 and 72) . Briefly, *obstructive diseases* are characterized by elevated airway resistance, diminished expiratory flow rates, severe ventilation-perfusion mismatching, and pronounced air trapping. The most common cause is smoking-induced emphysema, but others include asthma and several comparatively rare congenital disorders. Among these, alpha $_1$ - antitrypsin deficiency is associated with severe bullous emphysema in the fourth or fifth decade of life. With *restrictive diseases,* interstitial fibrosis results in a loss of lung elasticity and compliance. Most fibrotic diseases are idiopathic in nature but may also be caused by an immune process or inhalation injury. Interstitial lung pathology may affect pulmonary blood vessels as well, so pulmonary hypertension is a frequent concomitant finding. Functionally, diseases in this category are associated with diminished lung volumes and diffusion capacity, but with preserved airflow rates. Respiratory muscle strength is usually excellent, because the work of breathing is chronically increased. Cystic fibrosis (CF) and bronchiectasis are the common *infectious* causes. CF occurs in 0.2 percent of live births in the United States and produces mucous plugging of peripheral airways, pneumonia, chronic bronchitis, and bronchiectasis. Smoking and environmental exposures may also lead to bronchiectasis. End-stage *pulmonary vascular diseases* may arise from diffuse arteriovenous malformations, congenital heart disease with Eisenmenger syndrome, or, primary pulmonary hypertension (PPH). PPH is a relatively rare disease of unknown origin, characterized by a marked increase in PVR from hyperplasia of the muscular PA and fibrosis of small arterioles.

Indications and Contraindications

With all end-stage pulmonary diseases, the general indications for transplantation are progressive exercise intolerance, increasing oxygen requirements and carbon dioxide retention, or right heart failure. Recurrent need for phlebotomy and increasing physical and social debilitation are other factors favoring transplantation. The rate of functional deterioration and ability of the right ventricle to tolerate progression of pulmonary hypertension will determine the timing of surgery. Specific contraindications to isolated lung transplantation relate to processes that would impede recovery, including neuromuscular disease or long-standing ventilator

dependence, severe chest deformity or pleural disease (complicating the surgical procedure), advanced right ventricular failure, or glucocorticoid dependence (complicating the healing of airway anastomoses).

The choice of lung transplant procedure is based on the consequences of leaving the native lung *in situ.* For example, if infection or severe bullous emphysema is present in the contralateral lung, single lung transplantation is not an option. Infection would inevitably cross contaminate a healthy allograft, and bullous disease could lead to gross ventilation-perfusion mismatching and compression of the allograft. Instead, double lung transplantation is chosen for such cases. Similarly, double lung transplantation may also lead to better functional outcomes in the treatment of end-stage pulmonary hypertension. [234] [236] The relative rate of perioperative complications is the other major factor influencing the choice of procedure. For example, single lung transplantation is feasible without cardiopulmonary bypass and seldom complicated by coagulopathy. In contrast, en bloc double lung transplantation mandates extracorporeal circulation with extensive mediastinal dissection and full systemic heparinization--both risk factors for developing a postoperative bleeding diathesis. Single lung transplantation has the added advantage of using bronchial anastomoses, which heal with fewer complications than do the tracheal suture lines inherent in the en bloc double lung procedure. Bilateral sequential lung transplantation, a recently introduced alternative, combines advantages by employing bibronchial anastomoses while (usually) avoiding cardiopulmonary bypass.

Preanesthetic Considerations

Preanesthetic considerations for single and double lung transplantation have been reviewed. [237] [238] [239] [240] Briefly, size matching is facilitated by comparing the vertical and transverse radiologic chest dimensions of donor and recipient. Organs are also matched on the basis of ABO compatibility; because the value of histocompatibility is still unknown and the tolerable ischemic time for the lungs is relatively short (6-8 h), HLA matching is only done retrospectively. Monitoring both systemic and PA pressure is clearly vital during lung transplant procedures, although dyspnea and pulmonary hypertension may complicate PA catheter insertion prior to induction. Pulmonary catheters should be inserted through a long sterile sleeve to facilitate withdrawal during PA anastomoses and subsequent repositioning.

Induction and Maintenance of Anesthesia

Preoperative pulmonary function and right heart catheterization studies, ventilation-perfusion scans, and arterial blood gas values are useful to predict difficulties likely to be encountered during and after induction. For example, elevated PA pressures may indicate a likelihood that cardiopulmonary bypass will be necessary, because right ventricular failure can suddenly result when either one lung ventilation or pulmonary artery ligation is begun. Air trapping and diminished expiratory flow rates may exacerbate hypercapnia and lead to hemodynamic instability during mask ventilation and after tracheal intubation. With borderline arterial blood gas values, "pump standby" is prudent even when single lung transplantation is contemplated. [241]

Single lung transplantation involves pneumonectomy and implantation of a new lung. If the native lungs are equally impaired and pleural scarring is absent, the left lung is chosen for relative technical simplicity: the native right pulmonary veins are less accessible than those on the left; the left hemithorax can more easily accommodate a somewhat oversized donor lung; the recipient's left bronchus is also longer. Most surgeons prefer that the dissected lung be collapsed; both double lumen endobronchial tubes and bronchial blockers have been used for this purpose. Advantages of endobronchial tubes include: easier switching of the ventilated lung, ability to suction the nonventilated lung, ability to apply continuous positive airway pressure (CPAP) to the nonventilated lung, and an option for postoperative independent lung ventilation. Left-sided endobronchial tubes are recommended for both right and left single lung transplants, as well as for the bilateral sequential operation, as the right upper lobe bronchial orifice is relatively close to the origin of the mainstem bronchus and is easily occluded.

Drugs that do not release histamine or depress the myocardium (e.g., etomidate, vecuronium) are preferred for induction of anesthesia by rapid sequence technique (Chs. 9 , 10 , and 12) . Nitrous oxide is avoided in patients with elevated PVR, when 100 percent O_2 is required to maintain acceptable arterial saturation, or with

bullous disease. Both high-dose opioids and potent inhaled anesthetics, supplemented by long-acting relaxants, have been used successfully to maintain anesthesia. After lateral thoracotomy positioning, with the onset of one lung ventilation, acute deterioration in gas exchange and/or hemodynamics is the rule. Strategies for improving oxygenation under these circumstances include: use of PEEP in the dependent lung (provided bullous disease or emphysema is absent), CPAP or high-frequency ventilation in the nondependent lung, or ligation of the (nondependent) PA. If PA pressures provoke right heart failure, vasodilators and/or inotropes may improve hemodynamics, but gas exchange can worsen. If so, one lung ventilation should be abandoned. Similarly, if hemodynamics or systemic arterial saturations deteriorate with PA clamping, cardiopulmonary bypass may be necessary.

Immediately prior to implantation, the donor hilar structures are trimmed to match the size of the recipient bronchus, branch PA, and atrial cuff containing the pulmonary venous orifices. While the allograft is kept scrupulously cold, the atrial, PA, and bronchial anastomoses are completed in sequence. The ischemic interval ends with the removal of vascular clamps but, until ventilation is restored, systemic arterial saturation remains depressed. The allograft is then reinflated, sometimes with the aid of a flexible bronchoscope, and a pedicle of vascularized omentum may be used to wrap the anastomosis to promote healing. [242] [243] Alternatively, a "telescoping" bronchial anastomosis may be used. After restoration of the supine position, the endobronchial tube is either exchanged for a standard endotracheal type, or, with emphysema, retained for independent lung ventilation postoperatively.

In patients with CF or PPH, double lung transplantation is the rule. An en bloc operation is performed with the patient

Figure 55-10 Patient positioning for "clamshell" incision (bilateral anterior thoracotomies with transverse sternotomy) used during bilateral sequential lung transplantation. The patient's arms are padded and suspended from an ether screen.

supine, and either median sternotomy or the "clamshell" incision (Fig. 55-10) may be employed. Cardiopulmonary bypass is mandatory, because both lungs are replaced at once, and cardioplegic arrest is used to accomplish anastomosis of the left atrial cuff containing all four pulmonary venous orifices. The airway is transected at the level of the trachea, so a standard endotracheal tube is appropriate. The extensive retrocardiac dissection often leads to cardiac denervation [244] and postoperative bleeding is difficult to control. Bilateral sequential lung transplantation is used to treat the same spectrum of patients as the en bloc procedure, but it obviates the need for cardiopulmonary bypass, mediastinal dissection, and tracheal anastomosis. Its major disadvantage is that serial implantation prolongs the ischemic time for the second allograft. Access to the hilar structures also requires the "clamshell" transverse sternotomy.

Postoperative Management and Complications

Aside from acute, intensive respiratory support, the great challenge of postoperative management is differentiating between lung infection and rejection, usually by means of transbronchial biopsy obtained by flexible bronchoscopy [245] or occasionally, by open lung biopsy. Early respiratory insufficiency is usually due to reperfusion injury, characterized by large alveolar-arterial O_2 gradients, poor pulmonary compliance, and parenchymal infiltrates despite low cardiac filling pressures. Mechanical ventilation with PEEP is essential, but inflation pressures are kept to a minimum in consideration of the new airway anastomoses. Similarly, F_{IO_2} is maintained at the lowest levels compatible with acceptable systemic oxygen saturations. After single lung transplantation for emphysema, the endobronchial tube is kept in place to facilitate independent ("split") lung ventilation. This technique can be used to avoid overinflation of the native lung, shifting of the mediastinum, and gross ventilation-perfusion mismatching. [246]

Along with their exposure to the external environment, other factors increasing the susceptibility of transplanted lungs to infection include lymphatic disruption, poor mucociliary function, and the presence of suture lines across the airway. In the first postoperative month, nosocomial gram-negative bacteria are the most frequent causes of pneumonia. [247] Thereafter, CMV pneumonitis becomes more common, particularly if organs from a CMV-seropositive donor are used in a CMV-seronegative recipient.

Hemorrhage most frequently occurs after en bloc double lung transplantation, particularly in patients with pleural disease or Eisenmenger syndrome. The vagus, phrenic, and recurrent laryngeal nerves are jeopardized during lung transplantation, and injury will complicate the process of weaning from mechanical ventilation. Tracheal anastomotic leaks often lead to fatal mediastinitis. By contrast, bronchial fistulas lead to strictures that are treated by silicone stents and repeated dilation. Long-term complications include bronchiolitis obliterans, a pathologic condition characterized by luminal destruction of small respiratory bronchioles, [248] and opportunistic lung infections with organisms such as *Candida albicans* and *P. carinii.*

Special Considerations in Children

In children with severe developmental anomalies of the lung (including congenital diaphragmatic hernia with pulmonary hypoplasia) and with cystadenomatous malformations, isolated lung transplantation may offer the only chance for survival (Chs. 50 and 59) . The scarcity of suitable donor organs has led to instances of living-related lung donation, but the success of this approach is not yet fully evaluated. Rarely, heart-lung transplantation may be indicated during childhood for PPH, CF, or Eisenmenger syndrome. [249] [250]

Heart-Lung Transplantation

Heart-lung transplantation is indicated for patients with end-stage lung disease complicated by irreversible right heart failure (cor pulmonale) or end-stage congenital heart disease with secondary pulmonary vascular destruction (Eisenmenger syndrome). Specific pathologic diagnoses in recipients have included PPH, emphysema, multiple pulmonary emboli, CF, and fibrotic and granulomatous diseases of the lung. The donor blocs consist of the entire heart and lungs, including a tracheal segment long enough to facilitate anastomosis. Distal procurement is made possible by flushing the harvested bloc with modified Euro-Collins or UW solution, to which PGE_1 or other pulmonary vasodilators may be added. Because both the heart and lungs must meet the criteria for acceptability, suitable donor blocs are in extremely short supply. Monitoring and induction strategies are similar to those for heart transplantation, but pulmonary hypertension and air trapping are additional factors that may lead to hemodynamic instability. Difficulty when securing the airway during induction can exacerbate hypercarbia or hypoxia and elevate PVR. Under such circumstances, bidirectional

intracardiac shunts may become predominantly right to left and lead to profound hypoxemia. Such shunts may also lead to paradoxic air emboli, so that bubbles in intravenous tubing must be scrupulously avoided. Chronically cyanotic patients are also frequently severely polycythemic (hematocrit >60%) and may manifest clotting derangements and focal central nervous system deficits. Under these circumstances, phlebotomy and hemodilution are beneficial. Large endotracheal tubes are preferred in all recipients to facilitate therapeutic bronchoscopies both intraoperatively and postoperatively.

Prior to cardiopulmonary bypass, surgical dissections may be complicated by extensive pleural adhesions or prior cardiac or thoracic surgery. After the patient receives extracorporeal support, en bloc implantation is readily accomplished by sequential tracheal, right atrial, and aortic anastomoses provided the donor organs are a reasonable size match. Tracheal anastomosis generally involves some technique to prevent dehiscence, for example, wrapping the suture line with vascularized omentum. During this phase of the procedure, the phrenic, vagus, and recurrent laryngeal nerves are particularly vulnerable to injury during both dissection and topical cooling. Reexpansion of the donor lungs may require bronchoscopy to relieve mechanical obstruction by secretions, and occasionally, bronchodilators will be useful to treat bronchospasm. [251] Owing to the extensive mediastinal and/or pleural dissection, and the presence of elaborate vascular collaterals, the early post-bypass period is often complicated by hemorrhage leading to coagulopathy. Pulmonary compliance and gas exchange may deteriorate during this period, owing to intraparenchymal hemorrhage or inadequate preservation, and the use of PEEP and diuretics is often required.

Postoperatively, rejection episodes (characterized by infiltrates, fever, and deteriorating gas exchange), are relatively common. Pulmonary allografts may suffer rejection without significant abnormalities in endomyocardial specimens, [252] so low cardiac output is not necessarily a symptom of rejection. Bacterial pneumonia, which is very common during this phase, may present with the same clinical picture as rejection. Thus bronchoalveolar lavage, or transbronchial biopsy, may be

necessary for definitive diagnosis. The most dreaded complication of heart-lung transplantation is tracheal dehiscence, which can lead to fatal mediastinitis. Nutritional support, prophylactic antibiotics, and careful endotracheal cuff positioning may help prevent this complication. Eventually, most survivors develop bronchiolitis obliterans, as in other lung transplant populations (see previous discussion).

Indications for heart-lung transplantation are diminishing as experience with isolated lung transplantation accumulates. The latter operation will suffice in most cases, when performed *before* right ventricular failure becomes irreversible, or in concert with intracardiac repair of simple congenital defects.

Nonpulmonary Surgery in Lung Transplant and Heart-Lung Transplant Patients

Transplanted lungs can be infected or in the process of being rejected. Clearly, evaluation of this problem is essential. In addition, these patients lack a cough reflex below the tracheal anastomosis, which places prime importance on protecting the airway. Otherwise common anesthetic principles for managing a very sick patient should prevail. Several groups have reviewed their experience and the literature in this area. [253] [254] [255] [256]

OTHER ORGAN TRANSPLANTATION PROCEDURES

In view of the considerable patient populations who stand to benefit, there is considerable interest in transplantation of the pancreas and small intestine. However, these are extremely fragile viscera, and optimal preservation regimens and implantation procedures are currently being defined.

Pancreatic Transplantation

In the United States each year, there are as many as 20,000 new cases of type I (insulin-dependent, juvenile onset) diabetes mellitus. The disease arises from an inflammatory process that destroys pancreatic beta cells. The resulting microangiopathy is among the leading causes of renal failure and blindness. Pancreatic transplantation has been viewed as a potential cure since the 1960s, and by 1989, the annual rate of such procedures reported to an international registry was 554. [257] The reported operative mortality is low (<1%), 1-year survival high (>90%), and insulin independence achieved in 50 to 70 percent of cases at 1 year. [258] In many of the cases described, patients received pancreas allografts at kidney transplantation, to prevent recurrence of diabetic nephropathy, [259] as well as some of the other microvascular complications.

Considering the side effects of immunosuppression, pancreas transplantation is currently reserved for only the patients with the most brittle forms of diabetes who have rapidly progressive complications. Whole organ transplantation is accomplished using the "bladder drainage" technique, [260] involving extraperitoneal placement and exocrine drainage via duodenocystostomy. This technique allows allograft exocrine function to be closely monitored (via urine pH and amylase), which in turn deteriorates during episodes of rejection. Postoperatively, assiduous control of serum glucose by insulin infusion is recommended, which then becomes superfluous with commencement of oral feeding.

Pancreatic islet transplantation, in which only the required cell type is introduced, has recently undergone clinical trials. [261] In this procedure, which does not require surgical intervention, the islets are isolated by cell-separation techniques and then infused into the portal vein. In some cases, islet cells have become fully functional over several weeks and restored insulin independence [261] ; in others, insulin requirement has been diminished but not eliminated.

Multivisceral Transplantation

Replacement of multiple digestive organs simultaneously, termed "cluster operation," was introduced to treat two diseases: locally confined GI tumors and short-gut syndrome. [262]

With short-gut syndrome from any cause, parenteral feeding may lead to liver failure and subsequent need for en bloc replacement of the liver, pancreas, stomach, duodenum, and jejunum. In children, multivisceral transplantation has been performed, with some success, for short-gut syndrome resulting from necrotizing enterocolitis or midgut volvulus. [263]

In adults, hepatomas and cholangiocarcinomas, as well as proximal GI or pancreatic carcinomas, have been treated by cluster operation after upper abdominal exenteration. Although experience is still limited, 1-year survivals have been on the order of 70 percent (with sarcomas or GI-derived endocrine tumors) or 44 percent (primary liver cancer). [264] By contrast, without surgery, the prognoses for patients with these cancers is considerably worse, and even partial resections combined with chemotherapy or radiation offer little improvement in overall survival. Anesthetic management of cluster surgery has been reviewed. [265] Briefly, the types and doses of previous chemotherapy should be ascertained, because some agents may have long-lasting toxic effects on the heart or kidneys. Hormone-secreting tumors producing "carcinoid crises" can be suppressed with ketanserin, a serotonin antagonist; octreotide acetate, a somatostatin analogue; or by arterial embolization. The management issues during surgery resemble those for liver transplantation alone, namely, massive transfusion, coagulopathy, hypothermia, and electrolyte or acid-base abnormalities. Postoperative complications include a high incidence of rejection, particularly of the small bowel, sepsis from loss of the intestinal barrier, and graft-versus-host disease (GVHD). The likelihood of GVHD is roughly proportional to the length of intestine transplanted, probably reflecting the quantity of lymphoid tissue contained in the wall of this organ. [266]

References

1. Bach FH, Sach DH: Current concepts: Transplantation immunology. N Engl J Med 317:489, 1987.

2. Reinherz EL, Sclossman SF: The differentiation and function of human T-lymphocytes. Cell 19:821, 1980.

3. Kahane BD: Cyclosporine. N Engl J Med 321:1725, 1989.

4. Hunt SA, Gamberg P, Stinson EB et al: The Stanford experience: Survival and renal function in the pre-Sandimmune era compared to the Sandimmune era. Transplant Proc 22(suppl 1):1, 1990.

5. Keown PA, Stiller CR: Kidney transplantation. Surg Clin North Am 66:517, 1986.

6. Dretchen KL, Morgenroth VH, Standaert FG et al: Azathioprine: Effects on neuromuscular transmission. Anesthesiology 45:604, 1986.

7. Snyder DS, Unanue ER: Corticosteroids inhibit immune macrophage's Ia expression and interleukin-1 production. J Immunol 129:1803, 1982.

8. Dupont E, Wybran J, Toussant C: Glucocorticosteroids and organ transplantation. Transplantation 37:331, 1984.

9. Stratta RJ, Armbrust MJ, Oh CS et al: Withdrawal of steroid immunosuppression in renal transplant recipients. Transplantation 45:323, 1988.

10. Leapman SB, Vidne BA, Butt KM et al: Elective and emergency surgery in renal transplant patients. Ann Surg 183:262, 1976.

11. Liu J: FK506 and cyclosporine: Molecular probes for studying intracellular signal transduction. Trends Pharmacol Sci 14:182, 1993.

12. Todo S, Fung JJ, Starzl TE et al: Liver, kidney, and thoracic organ transplantation under FK506. Ann Surg 212:295, 1990.

13. Maki T, Simpson M, Monaco MP: Development of suppressor T cells by antilymphocyte serum treatment in mice. Transplantation 34:376, 1982.

14. Acuto O, Reinherz EL: The human T cell receptor: structure and function. N Engl J Med 312:1100, 1985.

15. Iwaki Y, Ashizaga T, Cook D et al: ABO matching in liver transplantation. Transplant Proc 20(suppl 1):564, 1988.

16. Patel R, Terasaki PI: Significance of the positive cross-match test in kidney transplantation. N Engl J Med 14:735, 1969.

17. Opelz G: Effect of HLA matching, blood transfusions, and presensitization in cyclosporine-treated kidney transplant recipients. Transplant Proc 17:2179, 1985.

18. Weil R, Clarke DR, Iwaki Y et al: Hyperacute rejection of a transplanted human heart. Transplantation 32:71, 1981.

19. Zerbe T, Arena V, Kormos R et al: Role of major histocompatibility complex (HLA) matching in cardiac allograft rejection. Transplant Proc 20(suppl 1):74, 1988.

20. Stinson EB, Payne R, Griepp RB et al: Correlation of histocompatibility matching with graft rejection and survival after cardiac transplantation in man. Lancet 2:459, 1971.

21. Starzl TE, Tzakis A, Makowka L et al: The definition of ABO factors in transplantation: Relation to other humoral antibody states. Transplant Proc 19:4492, 1987.

22. Gordon RD, Iwatsuki S, Esquivel CO et al: Liver transplantation across ABO blood groups. Surgery 100:342, 1986.

23. Demetris AJ, Jaffe R, Tzakis A et al: Antibody-mediated rejection of human orthotopic liver allografts: A study of liver transplantation across ABO blood group barriers. Am J Pathol 132:489, 1988.

24. Gordon RD, Fung JJ, Markus B et al: The antibody crossmatch in liver transplantation. Surgery 100:705, 1986.

25. Iwatsuki S, Rabin BS, Shaw BW Jr et al: Liver transplantation against T cell-positive warm crossmatches. Transplant Proc 16:1427, 1984.

26. Markus BH, Duquesnoy RJ, Gordon RD et al: Association of HLA compatibility and decreased liver transplant survival. Transplant Proc 20(suppl 1):43, 1988.

27. Collins GM, Bravo-Shuarman M, Terasaki PI: Kidney preservation for transplantation: Initial perfusion and 30 hours ice storage. Lancet 2:1219, 1969.

28. Baron P, Heil J, Condie R et al: 96-Hour renal preservation with silica gel precipitated plasma cold storage versus pulsatile perfusion. Transplant Proc 22:464, 1990.

29. Sacks SA, Petritsch PH, Kaufman JJ: Canine kidney preservation using a new perfusate. Lancet 1:1024, 1973.

30. Belzer FQ, Southard JH: Principles of solid organ preservation by cold storage. Transplantation 45:673, 1988.

31. Todo S, Nery J, Yanaga K et al: Extended preservation of human liver grafts with UW solution. JAMA 261:711, 1989.

32. Downey JM: Free radicals and their involvement during long-term myocardial ischemia and reperfusion. Annu Rev Physiol 52:487, 1990.

33. Hardesty RL, Griffith BP, Deep GM et al: Improved cardiac function using cardioplegia during procurement and transplantation. Transplant Proc 15:1253, 1983.

34. Guerraty A, Alivizatos P, Warner M et al: Successful orthotopic canine heart transplantation after 24 hours in vitro preservation. J Thorac Cardiovasc Surg 82:531, 1981.

35. Watson DC, Reitz BA, Baumgartner WA et al: Distant heart procurement for transplantation. Surgery 86:56, 1979.

36. Mendez-Picon GJ, Goldman MW, Wolfgang TC et al: Long-distance procurement and transportation of human hearts for transplantation. Heart Transplant 1:63, 1981.

37. Griffith BP, Zenati M: The pulmonary donor. Clin Chest Med 11:217, 1990.

38. Todd TR, Goldberg M, Koshal A et al: Separate extraction of cardiac and pulmonary grafts from a single organ donor. Ann Thorac Surg 46:356, 1988.

39. Jamieson SW, Stinson EB, Oyer PE et al: Operative technique for heart-lung transplantation. J Thorac Cardiovasc Surg 87:930, 1984.

40. Hardesty RL, Aeba R, Armitage JM et al: A clinical trial of University of Wisconsin solution for pulmonary preservation. J Thorac Cardiovasc Surg 105:660, 1993.

41. UNOS receives federal contract to develop OPTN. United Network for Organ Sharing Update 2:1, 1986.

41A. First MR: Cadaveric organ procurement--an overview of two aspects: Donor and hospital networks, and minority donation. Transplant Proc 29:70-72, 1997.

42. Friend PJ, McCarthy LJ, Filo RS et al: Transmission of idiopathic (autoimmune) thrombocytopenic purpura by liver transplantation. Ann Thorac Surg 41:520, 1986.

---

43. Gilbert EM, Krueger SK, Murray JL et al: Echocardiographic evaluation of potential cardiac transplant donors. J Thorac Cardiovasc Surg 95:1003, 1988.

44. Simmons RL, Canafax DM, Fryd DS et al: New immunosuppressive drug combinations for mismatched and cadaveric renal transplantation. Transplant Proc 18(suppl 1):76, 1986.

45. Broelsch CE, Emond JC, Thistlethwaite JR et al: Liver transplantation, including the concept of reduced-size liver transplants in children. Ann Surg 208:410, 1988.

46. Busuttil RW: Living-related liver donation. Transplant Proc 22:1489, 1990.

47. Starnes V, Oyer PE, Bernstein D et al: Heart, heart-lung, and lung transplantation in the first year of life. Ann Thorac Surg 53:306, 1992.

48. Guidelines for the determination of death: Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA 246:2184, 1981.

49. Black PM: Brain death. N Engl J Med 299:338, 1978.

50. Earnest MP, Beresford HR, McIntyre HB: Testing for apnea in suspected brain death: Methods used by 129 clinicians. Neurology 36:542, 1986.

51. Belsh JM, Blatt R, Schiffman PL: Apnea testing in brain death. Arch Intern Med 146:2385, 1986.

52. Vaghadia H: Atropine resistance in brain dead organ donors. Anesthesiology 65:711, 1986.

53. Lynn J: Diagnosis of brain death. JAMA 250:612, 1983.

54. Ashwal S, Schneider S, Thompson J: Xenon computed tomography measuring cerebral blood flow in the determination of brain death in children. Ann Neurol 25:539, 1989.

55. Ropper AH, Kehne SM, Wechsler L: Transcranial Doppler in brain death. Neurology 37:1733, 1987.

56. Grigg MM, Kelly MA, Celesia GG et al: Electroencephalographic activity after brain death. Arch Neurol 44:948, 1987.

57. Report of special task force. Guidelines for determination of brain death in children. Pediatrics 80:298, 1988.

58. Freeman JM, Ferry PC: New brain death guidelines in children--further confusion (editorial). Pediatrics 80:301, 1988.

59. Logigian EL, Ropper AH: Terminal electrocardiographic changes in brain-dead patients. Neurology 35:915, 1985.

60. Conci F, Procaccio F, Arosio M et al: Viscero-somatic and viscerovisceral reflexes in brain death. J Neurol Neurosurg Psychiatry 9:695, 1986.

61. Starzl TE, Miller C, Broznick B et al: An improved technique for multiple organ harvesting. Surg Gynecol Obstet 165:343, 1987.

62. Copeland JG: Heart transplantation. Mod Tech Surg Cardiothorac Surg 66:1, 1984.

63. Elick BA, Sutherland DER, Gillingham K et al: Use of distant relatives and living unrelated donors: A strategy to increase the application of kidney transplantation to treat chronic renal failure. Transplant Proc 22:343, 1990.

64. Hull AR, Parker TF: Proceedings from the Morbidity, Mortality and Prescription of Dialysis Symposium, Dallas, TX, Sept 15-17, 1989. Am J Kidney Dis 15:375, 1990.

65. Hellerstedt WL, Johnson WJ, Axher NL et al: Survival rates of 2728 patients with end-stage renal disease. Mayo Clin Proc 59:776, 1984.

66. United Network for Organ Sharing Newsletter, Richmond, VA, January 21, 1991.

67. Cecka JM, Terasaki PI: The UNOS scientific renal transplant registry. In Terasaki PI, Cecka JM (eds): Clinical Transplants 1992. Los Angeles, UCLA Tissue Typing Laboratory, 1993, p 1.

68. Evans RW, Manninen DL, Garrison LP et al: The quality of life of patients with end-stage renal disease. N Engl J Med 312:553, 1985.

69. Eggers PW: Effect of transplantation on the Medicare end-stage renal disease program. N Engl J Med 318:223, 1988.

70. Inglefinger J, Grupe W, Harmon W et al: Growth acceleration following renal transplantation in children less than 7 years of age. Pediatrics 68:255, 1981.

71. Miller LC, Bock GH, Lum CT et al: Transplantation of the adult kidney into the very small child: Long-term outcome. J Pediatr 100:675, 1982.

72. Belani KG, Palahniuk RJ: Kidney transplantation. In Firestone LL (ed): Anesthesia and Organ Transplantation. Boston, Little, Brown, 1991, p 17.

73. Baron P, Heil J, Condie R et al: 96-Hour renal preservation with silica gel precipitated plasma cold storage versus pulsatile perfusion. Transplant Proc 22:464, 1990.

74. Velez RL, Vergne-Marini P: Pretransplantation evaluation. In Toledo-Pereyra LH (ed): Kidney Transplantation. Philadelphia, FA Davis, 1988, p 50.

75. Najarian JS, Weiland D, Chavers B et al: Studies on living related kidney donors at a single institution. Proc Eur Dial Transplant Assoc Eur Renal Assoc 21:911, 1985.

76. Bay WH, Herbert LA: The living donor in kidney transplantation. Ann Intern Med 106:719, 1987.

77. Spital A, Spital M, Spital R: The living kidney donor: Alive and well. Arch Intern Med 146:1993, 1986.

78. Heino A, Orko R, Rosenberg PH: Anaesthesiological complications in renal transplantation: A retrospective study of 500 transplantations. Acta Anaesthesiol Scand 30:574, 1986.

79. Graybar GB: Choice of anesthesia. In Graybar GB, Bready LL (eds): Anesthesia for Renal Transplantation. Boston, Martinus Nijhoff, 1987, p 139.

80. Vandam LD, Harison JH, Murray JE et al: Anesthetic aspects for renal transplantation in man. Anesthesiology 23:783, 1962.

81. Lincke CL, Merin RG: A regional anesthetic approach for renal transplantation. Anesth Analg 55:69, 1976.

82. Minami H, McCallum RW: The physiology and pathophysiology of gastric emptying in humans. Gastroenterology 86:15592, 1984.

83. Fahey MR, Morris RB, Miller RD et al: Pharmacokinetics of ORG NC45 (Norcuron) in patients with and without renal failure. Br J Anaesth 53:1049, 1981.

84. Kadieva VS, Friedman L, Margolis LP et al: The effect of dopamine on graft function in patients undergoing renal transplantation. Anesth Analg 76:362-365, 1993.

85. Aronson S, Thistlethwaite RJ, Walker BS et al: Safety and feasibility of renal blood flow determination during kidney transplant surgery with perfusion ultrasonography. Anesth Analg 80:353-359, 1995.

86. Chapman JR, Allen RD: Dialysis and transplantation. In Morris PJ (ed): Kidney Transplantation: Principles and Practice. Philadelphia, WB Saunders, 1988, p 37.

87. Turcotte JG, Campbell DA, Dafoe DC et al: Pediatric renal transplantation. In Cerilli GJ (ed): Organ Transplantation and Replacement. Philadelphia, JB Lippincott, 1988, p 349.

88. Chavers BM, Matas AJ, Nevins TE et al: Results of pediatric kidney transplantation at the University of Minnesota. In Terasaki P (ed): Clinical Transplants. Los Angeles, UCLA Tissue Typing Laboratory, 1989, p 253.

89. Van Meurs IP, Terasaki PI, Cecka JM et al: A report from the UNOS scientific renal transplant registry. Transplant Proc 23:53, 1991.

90. Najarian J, So SK, Simmons RL et al: The outcome of 304 primary renal transplants in children (1968-1985). Ann Surg 204:246, 1986.

91. Turcotte JG, Campbell DA, Dafoe DC et al: Pediatric renal transplantation. In Cerelli GJ (ed): Organ Transplantation and Replacement. Philadelphia, JB Lippincott, 1988, p 349.

92. Fine RN, Ettenger RB: Renal transplantation in children. In Morris PJ (ed): Kidney Transplantation: Principles and Practice. Philadelphia, WB Saunders, 1988, p 635.

93. Warady B, Kriley M, Farrell S et al: Growth and development of infants with end-stage renal disease receiving long-term peritoneal dialysis. J Pediatr 112:714, 1988.

94. McGraw ME, Haka-Ikse K: Neurologic developmental sequelae of chronic renal failure in infancy. J Pediatr 106:579, 1985.

95. Ingelfinger J, Grupe W, Harmon W et al: Growth acceleration following renal transplantation in children less than 7 years of age. Pediatrics 68:255, 1981.

96. Fennell K, Rasbury W, Fennell E et al: Effects of kidney transplantation on cognitive performance in a pediatric population. Pediatrics 74:273, 1984.

97. Erice A, Jordin MC, Chace BA: Gancyclovir treatment of cytomegalovirus disease in transplant recipients and other immunocompromised hosts. JAMA 257:3082, 1987.

98. Gryzan S, Paradis IL, Zeevi A et al: Unexpectedly high incidence of *Pneumocystis carinii* infection after lung-heart transplantation: Implications for lung defense and allograft survival. Am Rev Respir Dis 137:1268, 1988.

99. Penn I: The changing pattern of posttransplant malignancies. Transplant Proc 23:1101, 1991.

100. Nalesnik MA, Locker J, Jaffe R et al: Clonal characteristics of posttransplant lymphoproliferative disorders. Transplant Proc 20:280, 1988.

101. Venkataramanan R, Habucky K, Burckart GJ et al: Clinical pharmacokinetics in organ transplantation. Clin Pharmacokinet 16:134, 1989.

102. Cirella VN, Pantuck CB, Lee YJ et al: Effects of cyclosporine on anesthetic action. Anesth Analg 66:703, 1987.

103. Firestone LL, Martin T, Liu P et al: The effect of cyclosporine on the potencies of general anesthetics. Anesth Analg 70:S105, 1990.

104. Bowden RA, Slichter SJ, Sayers MH et al: Use of leukocyte-depleted platelets and cytomegalovirus-seronegative red blood cells for prevention of primary cytomegalovirus infection after marrow transplant. Blood 78:246, 1991.

105. Barone GW, Sailors DM, Hudec WA et al: Trauma management in solid organ transplant recipients. J Emerg Med 15:169, 1997.

106. Donmez A, Kayhan Z, Pirat A et al: Anesthetic management of coronary artery bypass operation in renal transplantation recipients. Transplant Proc 30:790, 1998.

107. Sharpe MD, Gelb AW: Anaesthetic considerations for the previously transplanted patient. Anesth Clin North Am 12:827, 1994.

108. Gelb AW, Sharpe MD: Organ transplantation. Anesthetic considerations for the previously transplanted patient. Anesth Clin North Am 827, 1994.

109. Goldberg L. Taube D: Adult renal transplantation. In Hakin NS (ed): Introduction to Organ Transplantation. London, Imperial College Press, 1997, pp 73-92.

110. Pertek JP, Chaoui K, Junke E et al: Effects of propofol on blood concentration of cyclosporine. Ann Fr Anesth Reanim 15:589, 1996.

111. Bernuau J, Rueff B, Benhamou JP: Fulminant and subfulminant liver failure: Definition and causes. Semin Liver Dis 6:97, 1986.

112. Starzl TE, Demetris AJ, van Thiel DH: Liver transplantation. N Engl J Med 321:1014, 1092, 1989.

113. Tarter RE, Erb S, Biller PA et al: The quality of life after liver transplantation: A preliminary report. Gastroenterol Clin North Am 17:207, 1988.

114. Terpstra OT, Schalm SW, Weimar W et al: Auxiliary partial liver transplantation for end-stage chronic disease. N Engl J Med 319:1507, 1988.

115. Krowka MJ, Cortese DA: Pulmonary aspects of chronic liver disease and liver transplantation. Mayo Clin Proc 60:407, 1985.

116. Starzl TE, Todo S, Tzakis A et al: Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 210:374, 1989.

117. Mandall SM, Krowka MJ: Formation of a national database on pulmonary hypertension and hepatopulmonary syndrome in chronic liver disease. Anesthesiology 87:450, 1997.

118. Starzl TE, van Thiel DH, Tzakis AG et al: Orthotopic liver transplantation for alcoholic cirrhosis. JAMA 260:2542, 1988.

119. Starzl TE, Todo S, Gordon R et al: Liver transplantation in older patients. N Engl J Med 316:484, 1987.

120. Bismuth H, Samuel D, Gugenheim J et al: Emergency liver transplantation for fulminant hepatitis. Ann Intern Med 107:337, 1987.

121. Campbell DA, Rolles K, Jamieson N et al: Hepatic transplantation and long-term anticoagulation as treatment for Budd-Chiari syndrome. Surg Gynecol Obstet 166:511, 1988.

122. Harding SA, Mallet SV, Peachey TD et al: Use of heparinase modified thromboclastography in liver transplantation. Br J Anaesth 78:175, 1997.

123. Hett DA, Walker D, Pilkington SN et al: Sonoclot analysis. Br J Anaesth 75:771, 1995.

124. Aggarwal S, Kang Y, Freeman JA et al: Postreperfusion syndrome: cardiovascular collapse following hepatic reperfusion during liver transplantation. Transplant Proc 19(suppl 3):54, 1987.

125. Skak C, Rasmussen A, Kirkegaard P et al: Cerebral oxygen saturation and blood flow during liver transplantation. Anesth Analg 84:730, 1997.

126. Greim CA, Roewer N, Thiel H et al: Continuous cardiac output monitoring during adult liver transplant: Thermal filament technique versus bolus thermodilation. Anesth Analg 85:483, 1997.

127. Welte M, Pichler B, Groh J et al: Fulminant and late onset hepatic failure. Br J Anaesth 76:90, 1996.

128. Gelman S, Fowler KC, Smith LR: Liver circulation and function during isoflurane and halothane anesthesia. Anesthesiology 61:726, 1984.

129. O'Beirne HA, Young Y, Thornton J et al: Desflurane vs. isoflurane in liver transplantation: a comparison of outcomes. Br J Anaesth 790:132, 1997.

130. Duvaldstin P, Agoston S, Henzel D et al: Pancuronium pharmacokinetics in patients with liver cirrhosis. Br J Anaesth 50:1131, 1978.

131. Arden JR, Lynam DP, Castagnoli KP et al: Vecuronium in alcoholic liver disease: A pharmacokinetic and pharmacodynamic analysis. Anesthesiology 68:771, 1988.

132. De Wolf AM, Freeman JA, Scott VL, et al: Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth 76:624, 1996.

133. Fisher DM, Ramsey MAE, Hein T et al: Pharmacokinetics of rocuronium during three stages of liver transplantation. Anesthesiology 86:1306, 1997.

134. Pittet JF, Denis M, Mentha G et al: Vecuronium neuromuscular blockade reflects liver function during hepatic autotransplantation. Anesthesiology 81:168, 1994.

135. Marcel RJ, Ramsey MAE, Hein HA et al: Duration of rocuroniuminduced neuromuscular blockade during liver transplantation: A predictor of primary allograft function. Anesth Analg 84:870, 1997.

136. Haberer JP, Schoeffler P, Coudere E et al: Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. Br J Anaesth 54:1267, 1982.

137. Chauvin M, Ferrier C, Haberer JP et al: Sufentanil pharmacokinetics in patients with cirrhosis. Anesth Analg 68:1, 1989.

138. Rosenberg PH, Oikkonen MP, Orko RH et al: A transplanted liver rapidly begins to metabolize enflurane in humans. Anesth Analg 63:1131, 1984.

139. Marquez J, Martin D, Virji MA et al: Cardiovascular depression secondary to citrate intoxication during hepatic transplantation in man. Anesthesiology 65:457, 1986.

140. Lewis JH, Bontempo FA, Awad SA et al: Liver transplantation: Intraoperative changes in coagulation factors in 100 first transplants. Hepatology 9:710, 1989.

141. Kettner SC, Gonano C, Seebach F et al: Endogenous heparin-like substances significantly impair coagulation in patients undergoing orthotopic liver transplantation. Anesth Analg 86:691, 1998.

142. Frenette L, Cox J, McArdle P et al: Conjugated estrogen reduces transfusion and coagulation requirements in orthotopic liver transplantation. Anesth Analg 86:1183, 1998.

143. Kang Y, Aggarwal S, Pasculle R et al: Clinical evaluation of autotransfusion during liver transplantation. Anesth Analg 72:94, 1991.

144. Bogdonoff DL, Spiekerman BF, Shangraw RE: Should acidosis during liver transplantation be treated? (letter to the editor). Anesthesiology 82:1540, 1995.

145. Griffith BP, Shaw BW, Hardesty RL et al: Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. Surg Gynecol Obstet 160:270, 1985.

146. Khoury GF, Mann ME, Porot MJ et al: Air embolism associated with veno-venous bypass during orthotopic liver transplantation. Anesthesiology 67:848, 1987.

147. Paulsen AW, Whitten CW, Ramsay MAE et al: Considerations for anesthetic management during veno-venous bypass in adult hepatic transplantation. Anesth Analg 68:489, 1989.

148. Wall WJ, Grant DR, Duff JH et al: Blood transfusion requirement and renal function in patients undergoing liver transplantation without venous bypass. Transplant Proc 19(suppl 3):17, 1987.

149. Gillis BS, Perkins JD, Cheney FW: Abdominal aortic compression to treat circulatory collapse caused by severe pulmonary hypertension during liver transplantation. Anesthesiology 85:420, 1996.

150. De Kock M, Laterre PF, Van Obbergh L: The effects of intraoperative intravenous clonidine on fluid requirements, hemodynamic variables and support during liver transplantation. Anesth Analg 86:468, 1998.

151. Bellamy MC, Salley HF, Webster NR: Changes in inflammatory mediators during orthotopic liver transplantation. Br J Anaesth 79:338, 1997.

152. Prager MC, Gregory GA, Ascher NL et al: Massive venous air embolism during orthotopic liver transplantation. Anesthesiology 72:198, 1990.

153. Sopher M, Braunfeld M, Shackleton C et al: Fatal pulmonary embolism during liver transplantation. Anesthesiology 87:429, 1997.

154. Martinez IG, Olmedilla L, Perez-Pena JM et al: Response to clamping of the inferior vena cava as a factor for predicting postreperfusion syndrome during liver transplantation. Anesth Analg 84:254, 1997.

155. Shangraw RE, Robinson ST: Oxygen metabolism during liver transplantation: The effect of dichloroacetate. Anesth Analg 85:746, 1997.

156. Webster NR, Bellamy MC, Lodge JPA et al: Haemodynamics of liver reperfusion: Comparison of two anaesthetic techniques. Br J Anaesth 72:418, 1994.

157. Ellis JE, Lichtor JL, Feinstein SB et al: Right heart dysfunction, pulmonary embolism and paradoxical embolization during liver transplantation. Anesth Analg 68:777, 1989.

158. Navalgund AA, Kang Y, Sarner JB et al: Massive pulmonary thromboembolism during liver transplantation. Anesth Analg 67:400, 1988.

159. Lustik SJ, Eichelberger JP, Chhibber A et al: Torsade de pointes during orthotopic liver transplantation. Anesth Analg 87:300, 1998.

160. Ontell SJ, Makowka L, Ove P et al: Improved hepatic function in the 24-hour preserved rat liver with UW-lactobionate solution and SRI 63-441. Gastroenterology 95:1617, 1988.

161. Shaw BW, Gordon RD, Iwatsuki S et al: Retransplantation of the liver. Semin Liver Dis 5:394, 1985.

162. Starzl TE, Demetris AJ: Candidacy, original disease and outcome. In Starzl TE, Demetris AJ (eds): Liver Transplantation. Chicago, Year Book Medical Publishers, 1990, p 119.

163. Mandell SM, Lockrem J, Kelly S: Immediate tracheal extubation after liver transplantation. Anesth Analg 84:249, 1997.

164. Gordon RD, Bismuth H: Liver transplant registry report. Transplant Proc 23:58, 1991.

165. Salt A, Barnes ND, Mowat AP et al: Five years experience of liver transplantation in children. Transplant Proc 22:1514, 1990.

166. Lichtor JL, Emond J, Chung MR et al: Pediatric orthotopic liver transplantation: Multifactorial predictions of blood loss. Anesthesiology 68:607, 1988.

167. Bismuth H, Houssin D: Reduced-size orthotopic liver graft in hepatic transplantation in children. Surgery 95:367, 1984.

168. Mehta MU, Venkataramanan R, Burckart GJ et al: Antipyrine kinetics in liver disease and liver transplantation. Clin Pharmacol Ther 39:372, 1986.

169. Carton EG, Plevak DJ, Krammer PW et al: Perioperative care of the liver transplant patient. Anesth Analg 78:382, 1994.

170. Evans RW, Manninen DL, Overcast TD et al: The National Heart Transplantation Study: Final Report. Seattle, Battelle Human Affairs Research Centers, Health Care Financing Administration, 1984.

171. Kriett JM, Kaye MP: The registry of the International Society for Heart Transplantation: Tenth official report--1993. J Heart Lung Transplant 12:541, 1993.

172. Hunt SA, Gamberg P, Stinson EB et al: The Stanford experience: Survival and renal function in the pre-Sandimmune era compared to the Sandimmune era. Transplant Proc 22(suppl 1):1, 1990.

173. Caine N, O'Brien V: Quality of life and psychological aspects of heart transplantation. In Wallwork J (ed): Heart and Heart-Lung Transplantation. Philadelphia, WB Saunders, 1989, p 389.

174. Massie BM, Conway M: Survival of patients with congestive heart failure: Past, present, future prospects. Circulation 75(suppl 4):11, 1987.

175. Braunwald E: Heart failure: Pathophysiology and treatment. Am Heart J 3:486, 1981.

176. Cohn JN, Levine TB, Oliveri MT et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 311:819, 1984.

177. Hardesty RL, Griffith BP, Trento A et al: Mortally ill patients and excellent survival following cardiac transplantation. Ann Thorac Surg 41:126, 1986.

178. Griffith BP, Hardesty RL, Kormos RL et al: Temporary use of the Jarvik-7 total artificial heart before transplantation. N Engl J Med 316:130, 1987.

179. Menkis AH, McKenzie FN, Novick RJ et al: Special considerations for heart transplantation in congenital heart disease. J Heart Transplant 9:602, 1990.

180. Badellino M, Nairns B, Fucci P et al: Influence of diabetes mellitus on the course of cardiac transplantation. J Am Coll Cardiol 11:103A, 1988.

181. Addonizio LJ, Gersony WM, Robbins RC et al: Elevated pulmonary vascular resistance and cardiac transplantation. Circulation 76(suppl 5):52, 1987.

182. Stein KL, Darby JM, Grenvik A: Intensive care of the cardiac transplant recipient. J Cardiothorac Anesth 2:543, 1988.

183. Ozinsky J: Cardiac transplantation. S Afr Med J 41:1268, 1967.

184. Keats AS, Strong JM, Girigis KZ et al: Observations during anesthesia for cardiac homotransplantation in ten patients. Anesthesiology 30:192, 1969.

185. Harrison GA, Bailey RJ, Thomson PG: A heart transplantation. Med J Aust 1:670, 1969.

186. Fernando NA, Keenan RL, Boyan CP: Anesthetic experience with cardiac transplantation. J Thorac Cardiovasc Surg 75:531, 1978.

187. Grebenik CR, Robinson PN: Anaesthesia for surgery in a patient with a transplanted heart. Br J Anaesth 58:1199, 1986.

188. Demas K, Myner J, Mihm FG et al: Anaesthesia for heart transplantation. Br J Anaesth 58:1357, 1986.

189. Waterman PM, Bjerke R: Rapid-sequence induction technique in patients with severe ventricular dysfunction. J Cardiothorac Anesth 2:602, 1988.

190. Borow KM, Neumann A, Arensman FW et al: Cardiac and peripheral vascular responses to adrenoceptor stimulation and blockade after cardiac transplantation. J Am Coll Cardiol 14:1229, 1989.

191. Armitage JM, Hardesty RL, Griffith BP: Prostaglandin E_1 : An effective treatment of right heart failure after orthotopic heart transplantation. J Heart Transplant 6:348, 1987.

192. Bethune DW, Hardy I, Kneeshaw J et al: Anaesthesia and cardiopulmonary bypass for cardiac transplantation. In Wallwork J (ed): Heart and Heart-Lung Transplantation. Philadelphia, WB Saunders, 1989, p 145.

193. Bhatia SJS, Kirshenbaum M, Shemin RJ et al: Time course of resolution of pulmonary hypertension and right ventricular remodeling after orthotopic cardiac transplantation. Circulation 76:819, 1987.

194. Fonger JD, Borkon AM, Baumgartner WA et al: Acute right ventricular failure following heart transplantation: Improvement with PGE_1 and right ventricular assist. J Heart Transplant 5:317, 1986.

195. Renlund DG, Bristow MR, Lee HR et al: Medical aspects of cardiac transplantation. J Cardiothorac Anesth 2:500, 1988.

196. Kriett JM, Kaye MP: The registry of the International Society for Heart and Lung Transplantation: Ninth official report--1992. J Heart Transplant 11:599, 1992.

197. Starnes V, Oyer P, Bernstein D et al: Heart and heart-lung transplantation in the first year of life. J Heart Lung Transplant 10:162, 1991.

198. Bailey L, Kahan B, Nehlsen-Cannarella S: The neonatal immune system: Window of opportunity? J Heart Lung Transplant 10:828, 1991.

199. Camann WR, Goldman GA, Johnson MD et al: Cesarean delivery in a patient with a transplanted heart. Anesthesiology 71:618, 1989.

200. Kanter SF, Samuels SI: Anesthesia for major operations on patients who have transplanted hearts. A review of 29 cases. Anesthesiology 46:65, 1977.

201. Cheng DC, Ong DD: Anaesthesia for non-cardiac surgery in heart-transplanted patients. Can J Anaesth 40:981, 1993.

202. Bricker SRW, Sugden JC: Anaesthesia for surgery in a patient with a transplanted heart. Br J Anaesth 57:634, 1985.

203. Lyons JB, Chambers FA, MacSullivan R et al: Anaesthesia for non-cardiac surgery in post-cardiac transplant patient. Ir J Med Sci 164:132, 1995.

204. Shaw IH, Kirk AJB, Conacher ID: Anaesthesia for patients with transplanted hearts and lungs undergoing non-cardiac surgery. Br J Anaesth 67:772, 1991.

205. Steib A, Freys G, Otteni JC: Anesthesia for non-specific surgery in a post-transplantation patient. Ann Fr Anesth Reanim 12:27, 1993.

206. Camann WR, Goldman GA, Johnson MD et al: Cesarean delivery in a patient with a transplanted heart. Anesthesiology 71:618, 1989.

207. Steed DL, Brown B, Reilly JJ et al: General surgical complications in heart and heart-lung transplantation. Surgery 98:739, 1985.

208. Colon R, Frazier OH, Kahan BD et al: Complications in cardiac transplant patients requiring general surgery. Surgery 103:32, 1988.

209. DiSesa VJ, Kirkman RL, Tilney NL et al: Management of general surgical complications following cardiac transplantation. Arch Surg 124:539, 1989.

210. Jones MT, Menkis AH, Kostuk WJ et al: Management of general surgical problems after cardiac transplantation. Can J Surg 31:259, 1988.

211. Isono SS, Woolson ST, Schurman DJ: Total joint arthroplasty for steroid-induced osteonecrosis in cardiac transplant patients. Clin Orthop 217:201, 1987.

212. Dong E, Hurley EJ, Lower RR et al: Performance of the heart two years after autotransplantation. Surgery 56:270, 1964.

213. Rowan RA, Billingham ME: Myocardial innervation in long-term heart transplant survivors: A quantitative ultrastructural survey. J Heart Transplant 7:448, 1988.

214. Kaye MP: Denervation and reinnervation of the heart. In Randall WC (ed): Nervous Control of Cardiovascular Function. New York, Oxford University Press, 1984, p 278.

215. Pope SE, Stinson EB, Daughters GT et al: Exercise response of the denervated heart in long-term cardiac transplant recipients. Am J Cardiol 46:213, 1980.

216. Kavanagh T, Yacoub MH, Mertens DJ et al: Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. Circulation 77:162, 1988.

217. Mason JW, Harrison DC: Electrophysiology and electropharmacology of the transplanted human heart. In Narula OS (ed): Cardiac Arrhythmias: Electrophysiology, Diagnosis and Management. Baltimore, Williams & Wilkins, 1979, p 66.

218. Stark RP, McGinn AL, Wilson RF: Chest pain in cardiac-transplant recipients. N Engl J Med 324:1791, 1991.

219. Johnson TH, Kubo SH, McGinn AL et al: Physiologic importance of sympathetic reinnervation after cardiac transplantation, abstracted. J Heart Transplant 10:178, 1991.

220. Wilson RF, Christensen BV, Olivari MT et al: Evidence for structural sympathetic reinnervation after orthotopic cardiac transplantation in humans. Circulation 83:1210, 1991.

221. Stinson EB, Griepp RB, Clark DA et al: Cardiac transplantation in man. VIII. Survival and function. J Thorac Cardiovasc Surg 60:303, 1970.

222. Verani MS, George SE, Leon CA et al: Systolic and diastolic ventricular performance at rest and during exercise in heart transplant recipients. J Heart Transplant 7:145, 1988.

223. Stinson EB, Griepp RB, Schroeder JS et al: Hemodynamic observations one and two years after cardiac transplantation in man. Circulation 45:1183, 1972.

224. Higgins CB, Vatner SF, Braunwald E: Parasympathetic control of the heart. Pharmacol Rev 25:119, 1973.

225. Cannom DS, Graham AF, Harrison DC: Electrophysiologic studies in the denervated transplanted human heart: Response to atrial pacing and atropine. Circ Res 32:268, 1973.

226. Firestone LL: Autonomic influence on cardiac performance: Lessons from the transplanted (denervated) heart. Int Anesthesiol Clin 27:283, 1988.

227. Uretsky BF: Physiology of the transplanted heart. In Thompson ME (ed): Cardiac Transplantation. Philadelphia, FA Davis, 1990, p 21.

228. Hunt SA, Stinson EB: Accelerated atherosclerosis in the cardiac allograft. In Wallwork J (ed): Heart and Heart-Lung Transplantation. Philadelphia, WB Saunders, 1989, p 359.

229. Schroeder JS, Gao S-Z, Alderman EL et al: A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. N Engl J Med 328:164, 1993.

230. Backman SB, Ralley FE, Fox GS: Neostigmine produces bradycardia in a heart transplant patient. Anesthesiology 78:777, 1993.

231. Goodman DJ, Rossen RM, Cannom DS et al: Effect of digoxin on A-V conduction: Studies in patients with and without autonomic innervation. Circulation 51:251, 1975.

232. Ricci DR, Orlick AE, Reitz BA et al: Depressant effect of digoxin on atrioventricular conduction in man. Circulation 57:898, 1978.

233. Borow KM, Neumann A, Arensman FW et al: Cardiac and peripheral vascular responses to adrenoceptor stimulation and blockade after cardiac transplantation. J Am Coll Cardiol 14:1229, 1989.

234. Trulock EP, Cooper JD, Kaiser LR et al: The Washington University-Barnes Hospital experience with lung transplantation. JAMA 266:1943, 1991.

235. Lung transplantation: Report of the ATS workshop on lung transplantation. Am Rev Respir Dis 147:772, 1993.

236. Miyoshi S, Trulock EP, Schaefers HJ et al: Cardiopulmonary exercise testing after single and double lung transplantation. Chest 97:1130, 1990.

237. Conacher ID: Isolated lung transplantation: A review of problems and guide to anaesthesia. Br J Anaesth 61:468, 1988.

238. Conacher ID, McNally B, Choudhry AK et al: Anaesthesia for isolated lung transplantation. Br J Anaesth 60:588, 1988.

239. Gayes JM, Giron L, Nissen MD et al: Anesthetic considerations for patients undergoing double-lung transplantation. J Cardiothorac Anesth 4:486, 1990.

240. Thomas BJ, Siegel LC: Anesthetic and postoperative management of single-lung transplantation. J Cardiothorac Vasc Anesth 5:266, 1991.

241. Firestone L, Carrera J, Firestone S et al: Single lung transplants: Who needs bypass? Anesthesiology 79:A46, 1993.

242. Morgan E, Lima O, Goldberg M et al: Improved bronchial healing in canine left lung reimplantation using omental pedicle wrap. J Thorac Cardiovasc Surg 85:134, 1983.

243. Dubois P, Choiniere L, Cooper JD: Bronchial omentopexy in canine lung allotransplantation. Ann Thorac Surg 38:211, 1984.

244. Schaefers H-J, Waxman MB, Patterson GA et al: Cardiac innervation after double lung transplantation. J Thorac Cardiovasc Surg 99:22, 1990.

245. Bierman MI, Stein KL, Stuart RS et al: Critical care management of lung transplant recipients. J Intensive Care Med 6:135, 1991.

246. Smiley RM, Navedo AT, Kirby T et al: Postoperative independent lung ventilation in a single-lung transplant recipient. Anesthesiology 74:1144, 1991.

247. Dauber JH, Paradis IL, Dummer JS: Infectious complications in pulmonary allograft recipients. Clin Chest Med 11:291, 1990.

248. Burke CM, Theodore J, Dawkins KD et al: Post-transplant obliterative bronchiolitis and other late lung sequelae in human heart-lung transplantation. Chest 86:824, 1984.

249. Kaye MP: Intrathoracic transplantation. Transplant Proc 23:51, 1991.

250. Smyth RL, Scott JP, Whiteheat G et al: Heart-lung transplantation in children. Transplant Proc 22:1470, 1990.

251. Cassella ES, Humphrey LS: Bronchospasm after cardiopulmonary bypass in a heart-lung transplant recipient. Anesthesiology 69:135, 1988.

252. Griffith BP, Hardesty RL, Trento A et al: Asynchronous rejection of heart and lungs following cardiopulmonary transplantation. Ann Surg 40:488, 1985.

253. Wekerle T, Klepetko W, Wisser W et al: Incidence and outcome of major non-pulmonary surgical procedures in lung recipients. Eur J Cardiothorac Surg 12:718, 1997.

254. Haddow GR: Anaesthesia for patients after lung transplantation. Can J Anaesth 44:182, 1997.

255. Boscoe M: Anesthesia for patients with transplanted lungs and heart and lungs. Int Anesthesiol Clin 33:21, 1995.

256. Kostopanagiotou G, Smymiotis V, Arkadopoulos N et al: Anesthetic and perioperative management of transplant recipients in nontransplant surgery: Part 2. Anesth Analg 1999, in press.

257. Sutherland DER, Gillingham K, Moudry-Munns KC: Registry report on clinical pancreas transplantation. Transplant Proc 23:55, 1991.

258. Sutherland DER, Dunn DL, Goetz FC et al: A 10-year experience with 290 pancreas transplants at a single institution. Ann Surg 210:274, 1989.

259. Bilous RW, Mauer SM, Sutherland DER et al: The effects of pancreas transplantation on the glomerular structure of renal allografts in patients with insulin-dependent diabetes. N Engl J Med 321:80, 1989.

260. Sollinger HW, Cook K, Kamps D et al: Clinical and experimental experience with pancreaticocystostomy for exocrine pancreatic drainage in pancreas transplantation. Transplant Proc 16:749, 1984.

261. Tzakis AG, Ricordi C, Alejandro R et al: Pancreatic islet transplantation after upper abdominal exenteration and liver replacement. Lancet 336:402, 1990.

262. Starzl TE, Rowe MI, Todo S et al: Transplantation of multiple abdominal viscera. JAMA 261:1449, 1989.

263. Grant D: Intestinal transplantation: Current status. Transplant Proc 21:2869, 1989.

264. Tzakis AG, Todo S, Madariaga J et al: Upper abdominal exenteration in transplantation for extensive malignancies of the upper abdomen: An update. Transplantation 51:727, 1991.

265. DeWolf A: Multiviscera and pancreas transplantation. In Firestone LL (ed): Anesthesia and Organ Transplantation. Boston, Little, Brown, 1991, p 111.

266. Deltz E, Muller-Hermelink HK, Ulrichs K et al: Development of graft-versus-host reaction in various target organs after small intestine transplantation. Transplant Proc 13:1215, 1981.

267. Starzl TE, Shapiro R, Simmons RL (eds): Atlas of Organ Transplantation. New York, Gower, 1992.

268. Cooper DKC, Lanza LP: Heart Transplantation: The Present Status of Orthotopic and Heterotopic Heart Transplantation. Lancaster, UK, MTP Press, 1984.

269. Kent KM, Cooper T: The denervated heart: A model for studying autonomic control of the heart. N Engl J Med 291:1017, 1974.

270. Uretsky BF, Kormos RL, Zerbe TR et al: Cardiac events after heart transplantation: Incidence and predictive value of coronary arteriography. J Heart Lung Transplant 11:S45, 1992.

271. Firestone L, Firestone S: Organ transplantation. In Miller RD, Muravchick S (eds): Subspecialty Care, vol 5 in Miller RD (series editor): Atlas of Anesthesia. Philadelphia, Current Medicine, 1998.

Chapter 56 - Anesthesia for Laparoscopic Surgery

Jean L. Joris

INTRODUCTION

Surgical procedures have been improved to reduce trauma to the patient, morbidity, mortality, and hospital stay, with consequent reductions in health-care costs. The development of better equipment and facilities, along with increased knowledge and understanding of anatomy and pathology, have allowed the development of endoscopy for diagnostic and operative procedures. Starting in the early 1970s, various pathologic gynecologic conditions have been diagnosed and treated using laparoscopy. This endoscopic approach was extended to cholecystectomy in the late 1980s. Since the introduction of the first laparoscopic cholecystectomy procedures, laparoscopy has expanded impressively both in scope and volume. It quickly became apparent that laparoscopy results in multiple benefits compared with open procedures, [1] [2] [3] and is characterized by better maintenance of homeostasis. Overenthusiasm ensued, which explains the effort to use the laparoscopic approach for other surgical procedures, not only in gastrointestinal (colonic, gastric, splenic, hepatic surgery) but also in gynecologic (hysterectomy) and urologic (nephrectomy) surgery.

The pneumoperitoneum and the patient positions required for laparoscopy induce pathophysiologic changes that complicate anesthetic management. The duration of some operative laparoscopies, the risk of unsuspected visceral injury, and the difficulty in evaluating the amount of blood loss are other factors that make anesthesia for laparoscopy a potentially high-risk procedure.

Although laparoscopy was introduced early in the 20th century [4] and developed in the 1970s for gynecologic procedures, the recent extension of laparoscopy to gastrointestinal surgery has created new interest and considerations for the anesthetic management of patients having laparoscopy. Several elements explain this growing interest. Young, healthy women are the largest group of patients undergoing gynecologic laparoscopy, during which minor or modest cardiorespiratory changes are of little concern. For instance, before the systematic use of capnometry, unsuspected hypercapnia frequently developed but was well tolerated by most of these young patients. With the development of laparoscopy for gastrointestinal surgery, we now must care for older patients who are more likely to have known or undiagnosed diseases. Furthermore, because of the multiple benefits reported after laparoscopy, the laparoscopic approach tends to be readily proposed for ill patients.

An understanding of the pathophysiologic consequences of increased intra-abdominal pressure is important for the anesthesiologist who must ideally prevent or, when prevention is not possible, adequately respond to these changes, but also evaluate and prepare the patient preoperatively in light of these disturbances. Therefore, the pathophysiologic changes and the complications of laparoscopy are first reviewed. Then the postoperative period is considered, with examination of the benefits of laparoscopy, as well as certain specific postoperative problems (pain, nausea). Finally, practical consequences for the anesthetic management of laparoscopy are presented. Many animal and human studies of the consequences of lap-aroscopy have been published since the early 1970s. Since much higher intra-abdominal pressures (>20 mm Hg) were previously used, and because of potential species differences, we have focused this review, when possible, on recent human literature (after 1990) using low intra-abdominal pressure (<15 mm Hg) and modern anesthesia techniques.

VENTILATORY AND RESPIRATORY CHANGES DURING LAPAROSCOPY

Intraperitoneal insufflation of CO_2, the current routine technique to create pneumoperitoneum for laparoscopy, results in ventilatory and respiratory changes and can cause four principal respiratory complications: CO_2-subcutaneous emphysema, pneumothorax, endobronchial intubation, and gas embolism.

Ventilatory Changes

Pneumoperitoneum decreases thoracopulmonary compliance. Compliance was reduced by 30 to 50 percent in healthy, [5] [6] [7] [8] [9] [10] [11] obese, [12] and American Society of Anesthesiologists (ASA) III-IV patients [13]; but the shape of the pressure-volume loop does not change (Fig. 56-1). Once the pneumoperitoneum is created and kept constant, compliance is affected neither by subsequent patient tilting, [14] [15] nor by increasing the minute ventilation required to avoid intraoperative hypercapnia. Therefore, on-line compliance and pressure-volume loop monitoring are helpful in diagnosing complications resulting in increased inspiratory airway pressure, such as bronchospasm, changes in muscle relaxation, endobronchial intubation, and pneumothorax. [16] Reduction in functional residual capacity due to elevation of the diaphragm [17] and changes in the distribution of pulmonary ventilation and perfusion secondary to increased airway pressure can be expected. However, increasing intraabdominal pressure to 14 mm Hg with the patient in a 10- to 20-degree head-up or head-down position does not signi-ficantly modify either physiologic dead space or shunt in patients without cardiovascular problems. [18] [19] [20] [21]

Increase in $Paco_2$

During uneventful CO_2-pneumoperitoneum, Pa_{CO_2} progressively increases to reach a plateau 15 to 30 minutes after the beginning of CO_2 insufflation in patients under controlled mechanical ventilation during gynecologic laparoscopy

Figure 56-1 Change in total respiratory compliance during pneumoperitoneum for laparoscopic cholecystectomy. The intra-abdominal pressure was 14 mm Hg, and the head-up tilt 10 degrees. Illustration of the airway pressure (Paw) versus volume (V) curves and data were obtained from the screen of a Datex Ultima. A, before insufflation; B, 30 min after insufflation; TV (mL), tidal volume; Ppeak (cm H_2O), peak airway pressure; Pplat (cm H_2O), plateau airway pressure; C (mL/cm H_2O), total respiratory compliance; $P_{ET}CO_2$ (mm Hg), end-tidal P_{CO_2}.

in the Trendelenburg position, [22] [23] or laparoscopic cholecystectomy in head-up position (Fig. 56-2). [24] [25] Therefore, any significant increase in Pa_{CO_2} after this period requires a search for a cause either independent of or related to CO_2 insufflation, such as CO_2-subcutaneous emphysema (see later). The increase in Pa_{CO_2} depends on the intra-abdominal pressure. [26] [27] During laparoscopy with local anesthesia, Pa_{CO_2} remains unchanged but minute ventilation significantly increases. Hyperventilation is achieved by increasing respiratory rate rather than tidal volume. [28] [29] However, during general anesthesia with spontaneous breathing, the compensatory hyperventilation is insufficient to avoid hypercapnia because of anesthetic-induced ventilatory depression and increased work of breathing secondary to the decreased thoracopulmonary compliance. [30] [31] Because it takes 15 to 30 minutes for Pa_{CO_2} to plateau, anesthetic techniques using spontaneous breathing should be limited to short procedures at low intra-abdominal pressures. [32] [33]

Capnography and pulse oximetry provide reliable monitoring of Pa_{CO_2} and arterial oxygen saturation in healthy patients and in the absence of acute intraoperative disturbances (see Fig. 56-2). [20] [24] [25] [34] Although mean Pa_{CO_2} - $P_{ET}CO_2$ (Deltaa-$_{ET}CO_2$) gradients do not change significantly during peritoneal insufflation of CO_2, individual patient data regularly show an increase of this difference during pneumoperitoneum. However, two other reports recommend that "end-tidal P_{CO_2} ($P_{ET}CO_2$) monitoring should be used as an estimate of Pa_{CO_2} with caution." [35] [36] Wahba and Mamazza found negative Deltaa-$_{ET}CO_2$ in 5 of 28 patients. [36] Pa_{CO_2} and Deltaa-$_{ET}CO_2$ increase more in ASA II-III patients than ASA I patients (Fig. 56-3). [37] Preoperative pulmonary function tests (demonstrating forced expiratory volumes less than 70 percent of predicted values and diffusion defects), but neither age nor duration of surgery, are identified as risk factors for developing intraoperative hypercapnia and acidosis. [38]

Figure 56-2 Ventilatory changes (pH, Pa_{CO_2}, $P_{ET}CO_2$) during CO_2 pneumoperitoneum for laparoscopic cholecystectomy (13 ASA I and II patients). Minute ventilation was kept constant at 100 $mL/kg^{-1}/min^{-1}$ with a respiratory rate of 12 per minute during the study. Intra-abdominal pressure was 14 mm Hg. Data are mean ± SEM.* $P < .05$ as compared with time 0.

Figure 56-3 Ventilatory changes as a function of patient physical status. Pa_{CO_2} and $P_{ET}CO_2$ were measured before and during CO_2 insufflation. Patients were grouped according to ASA classification: group 1 (-
-), ASA I (n = 20); group 2 (-
-), ASA II-III (n = 10). *(Data from Wittgen et al [37])*

These results were confirmed in a canine model of chronic obstructive pulmonary disease (COPD). [39] These data, therefore, highlight the lack of correlation between Pa_{CO_2} and $P_{ET}CO_2$ in sick patients, particularly those with impaired CO_2 excretion capacity, and in otherwise healthy patients with acute cardiopulmonary disturbances. Consequently, arterial blood sampling is recommended when hypercapnia is clinically suspected, even in the absence of abnormal $P_{ET}CO_2$. Postoperative intra-abdominal CO_2 retention results in increased respiratory rate and $P_{ET}CO_2$ of patients breathing spontaneously after laparoscopic cholecystectomy as compared with open cholecystectomy. [40]

During CO_2 pneumoperitoneum, the increase of Pa_{CO_2} may be multifactorial: absorption of CO_2 from the peritoneal cavity, impairment of pulmonary ventilation and perfusion by mechanical factors such as abdominal distention, patient position, and volume-controlled mechanical ventilation, as well as depression of ventilation by premedicant and anesthetic agents in the case of spontaneous breathing (Table 56-1). The observation of an increase in Pa_{CO_2}, when CO_2, but not nitrous oxide (N_2O) or helium, was used as the insufflating gas, suggests that the main mechanism of the increased Pa_{CO_2} during CO_2-pneumoperitoneum is absorption of CO_2 rather than the mechanical ventilatory repercussions of increased intra-abdominal pressure. [41] [42] [43] [44] [45] Accordingly, direct measurement of CO_2 elimination (V_{CO_2}) using a metabolic monitor, combined with investigation of gas exchange showed a 20 to 30 percent increase of V_{CO_2} without significant changes in physiologic dead space in healthy patients undergoing pelvic laparoscopy (intraabdominal pressure: 12-14 mm Hg) in head-down position, [18] [23] [46] or laparoscopic cholecystectomy in head-up position. [23] [47] [48] [49] [50] Furthermore, the time courses of the increase in V_{CO_2} and Pa_{CO_2} are superposable. The absorption of a gas from the peritoneal

cavity depends on its diffusibility, the absorption area, and the perfusion of the walls of that cavity. Because CO_2 diffusibility is high, absorption of large quantities of CO_2 into the blood, and consequently marked increases in Pa CO_2, would be expected to occur. The limited rise of Pa CO_2 actually observed can be explained by the capacity of the body to store CO_2, [51] and by impaired local perfusion due to increased intra-abdominal pressure. [27] [31] Accordingly, during desufflation, CO_2 accumulated in collapsed

TABLE 56-1 -- Causes of Increased Pa CO_2 During Laparoscopy

1. Absorption of CO_2 from the peritoneal cavity
2. V A/Q mismatch: increased physiologic dead space
   - Abdominal distention
   - Position of the patient (steep tilt)
   - Controlled mechanical ventilation
   - Reduced cardiac output

   These mechanisms are accentuated in sick patients (obese, ASA II-III, ...)
3. Increased metabolism (insufficient plane of anesthesia)
4. Depression of ventilation by anesthetics (spontaneous breathing)
5. Accidental events:
   - CO_2 emphysema (subcutaneous or body cavities)
   - Capnothorax
   - CO_2 embolism
   - (Selective bronchial intubation)

peritoneal capillary vessels reaches the systemic circulation, leading to a transient increase in V CO_2. [47] [48]

Respiratory changes during the laparoscopic procedure might also contribute to increasing CO_2 tension. Mismatching of ventilation and pulmonary perfusion can result from the position of the patient, [22] [29] [52] and the increased airway pressures associated with abdominal distention. [29] [31] [53] Lister et al [27] investigated the relationship between V CO_2 and intraperitoneal CO_2 insufflation pressure in pigs. They observed that for intra-abdominal pressure (IAP) up to 10 mm Hg, increased V CO_2 accounts for the increased Pa CO_2. At higher IAP, the continued rise of Pa CO_2 without a corresponding increase in V CO_2 results from an enlargement of respiratory dead space, as reflected by a widening of the Deltaa- $ET CO_2$ gradient. [27] Therefore, if controlled ventilation is not adjusted in response to the increased dead space, alveolar ventilation will decrease and Pa CO_2 will rise. Whereas in healthy patients, absorption of CO_2 from the abdominal cavity represents the main (or the only) mechanism responsible for increased Pa CO_2, in patients with cardiorespiratory problems ventilatory changes also contribute significantly to increasing Pa CO_2. [13] [37] As far as Pa O_2 and intrapulmonary shunt are concerned, they do not change significantly during laparoscopy. [19] [22] [25] [26] [37] [41]

Increases in Pa CO_2 and the ensuing arterial and tissue acidosis may cause dysfunction in several organs. However, current trends are more permissive with regard to hypercapnia than 20 years ago. In the treatment of certain situations, such as acute respiratory distress syndrome (ARDS) and status asthmaticus, marked hypercapnia is even accepted. [54] Although increased Pa CO_2 may be well tolerated by young, otherwise healthy patients, the extent to which hypercapnia is acceptable has not been determined and probably varies according to the patient's physical status. Therefore, it is wise to maintain Pa CO_2 within physiologic ranges by adjusting controlled mechanical ventilation. Except in special circumstances, such as CO_2 -subcutaneous emphysema, correction of increased Pa CO_2 can be easily achieved by a 10 to 25 percent increase in alveolar ventilation.

Respiratory Complications

CO_2 -Subcutaneous Emphysema

CO_2 -subcutaneous emphysema can develop as a complication of accidental extraperitoneal insufflation, [55] but can also be considered as an unavoidable side effect of certain laparoscopic surgical procedures that require intentional extraperitoneal insufflation, such as inguinal hernia repair and pelvic lymphadenectomy (Fig. 56-4). Finally, during laparoscopic fundoplication for hiatal hernia repair, the opening of the peritoneum overlying the diaphragmatic hiatus allows passage of CO_2 under pressure through the mediastinum to the cervicocephalic region. In these three circumstances, V CO_2 and consequently Pa CO_2 and P $ET CO_2$ increase. [22] [48] [49] Therefore, any increase in P $ET CO_2$ occurring after P $ET CO_2$ has plateaued should suggest this complication. The increase in V CO_2 may be such that prevention of hypercapnia by adjustment of ventilation becomes almost impossible. In this case, laparoscopy must be temporarily interrupted to allow CO_2 elimination and can be resumed after correction of hypercapnia using a lower insufflation pressure. Indeed, CO_2 pressure determines the extent of the emphysema and the magnitude of CO_2 absorption. Accordingly, when the preperitoneal space is dissected for inguinal hernia repair by insufflation of a subcutaneous balloon and maintained using low CO_2 pressures (10 mm Hg), the increase in P $ET CO_2$ is

Figure 56-4 Diagnosis of respiratory complications during laparoscopy. *(Data from Wahba et al [16])*

similar to that observed during CO_2 -pneumoperitoneum. [56] CO_2 -subcutaneous emphysema will readily resolve once insufflation has ceased. Therefore, CO_2 -subcutaneous emphysema, even cervical, does not counterindicate tracheal extubation at the end of surgery. [57] We recommend keeping the patient under controlled mechanical ventilation until hypercapnia is corrected, particularly in COPD patients, to avoid excessive increases in work of breathing.

Pneumothorax, Pneumomediastinum, Pneumopericardium

Movement of gas during the creation of a pneumoperitoneum can produce pneumomediastinum, [58] unilateral and bilateral pneumothorax, [59] [60] [61] and pneumopericardium. [62] [63] Embryonic remnants constitute potential channels of communication between the peritoneal cavity and the pleural and pericardial sacs, which can open when intraperitoneal pressure increases. [60] Defects in the diaphragm or weak points in the aortic and esophageal hiatus may allow gas passage into the thorax. Pneumothorax may also develop secondary to pleural tears during laparoscopic surgical procedures at the level of the gastroesophageal junction (fundoplication for hiatal hernia). Whereas opening of peritoneopleural ducts results mainly in right-sided pneumothorax (in the same way that ascites or peritoneal dialysis may be associated with right-sided pleural effusions [64]) pneumothorax during fundoplication is more frequently located on the left. Finally, because of the increased alveolar inflation secondary to increased minute ventilation during pneumoperitoneum, preexisting pulmonary bullae can rupture leading to pneumothorax.

These complications are potentially serious and may lead to respiratory and hemodynamic disturbances. Capnothorax (CO_2 -pneumothorax) reduces thoracopulmonary compliance and consequently airway pressures increase. V CO_2, Pa CO_2, and subsequently P $ET CO_2$ also increase. [65] In effect, not only is the absorption surface of CO_2 increased, but the absorption from the pleural cavity is greater than from the peritoneal cavity. [31] In case of pneumothorax secondary to

alveolar rupture, $P_{ET}CO_2$ does not increase, but instead decreases due to decreased cardiac output. Hemodynamic changes and capillary oxygen desaturation are not constant, but tension pneumothorax with cardiorespiratory compromise can occur. The observation by the laparoscopist of abnormal motion of one hemidiaphragm is also helpful for the diagnosis. Diagnosis must be confirmed by auscultation of the chest and roentgenography. It should be noted that cervical and upper thoracic subcutaneous emphysema can develop without pneumothorax.

When pneumothorax is caused by highly diffusible gas such as N_2O or CO_2 without associated pulmonary trauma, spontaneous resolution of the pneumothorax occurs within 30 to 60 minutes after exsufflation. [60] Therefore, when capnothorax develops during laparoscopy, we provide the following guidelines [65] :

1. Stop N_2O administration.
2. Adjust ventilator settings to correct hypoxemia.
3. Apply positive end-expiratory pressure (PEEP).
4. Reduce IAP as much as possible.
5. Maintain close communication with the surgeon.
6. Avoid thoracocentesis unless necessary, as pneumothorax will spontaneously resolve after exsufflation.

In case of pneumothorax secondary to rupture of preexisting bullae, PEEP must not be applied and thoracocentesis is mandatory.

Endobronchial Intubation

The cephalad displacement of the diaphragm during pneumoperitoneum also results in cephalad movement of the carina, potentially leading to endobronchial intubation (Ch. 39). [66] Cases of endobronchial intubation associated with laparoscopy are now reported during gynecologic laparoscopy in the head-down position, [67] as well as during laparoscopic cholecystectomy, despite the head-up position. [68] [69] [70] This complication results in a decrease in Sp_{O_2} associated with an increase in plateau airway pressure.

Gas Embolism

Although rare, gas embolism (Ch. 52) is the most feared and dangerous complication of laparoscopy [71] and may occur more frequently when laparoscopy is associated with hysteroscopy. [72] [73] Intravascular injection of gas may follow direct needle or trocar placement into a vessel, or it may occur as a consequence of gas insufflation into an abdominal organ. This complication develops principally during the induction of pneumoperitoneum, [74] [75] [76] [77] particularly in patients with previous abdominal surgery. [78] Therefore, peritoneal insufflation with CO_2 must be started slowly (i.e., at a rate not greater than 1 L/min). Indeed, early recognition and treatment of gas embolism reduce the size of the embolism and thus the severity of its effects and sequelae. [79] Gas embolism may also occur later during surgery. [72] [73] [80] [81] [82] CO_2 is used most frequently for laparoscopy because it is more soluble in blood than either air, oxygen, or even N_2O. The capacity for CO_2 carriage of the blood is high due to bicarbonate buffering and combination with hemoglobin and plasma proteins. [51] Rapid elimination also increases the margin of safety in case of intravenous injection of CO_2 . All these characteristics explain the rapid reversal of the clinical signs of CO_2 embolism with treatment. Consequently, the lethal dose of embolized CO_2 is approximately five times greater than that of air. [79]

The pathophysiology of gas embolism is also determined by the size of the bubbles and the rate of intravenous entry of the gas. [83] [84] During neurosurgery, the slow entrainment of small bubbles of air is more likely to result in air entrapment in the pulmonary vessels, whereas during laparoscopy, the rapid insufflation of gas under high pressure probably causes a "gas lock" in the vena cava and right atrium [75] ; obstruction to venous return with a fall in cardiac output or even circulatory collapse will result. Acute right ventricular hypertension may open the foramen ovale, which is patent in 20 to 30 percent of the population, [85] allowing paradoxic gas embolization of the cerebral and coronary beds. [72] [86] Paradoxic embolism, however, may occur without patent

foramen ovale. [87] [88] V_A/Q mismatching develops with increases in physiologic dead space and hypoxemia. CO_2 embolism does not produce bronchoconstriction or the changes in pulmonary compliance that accompany air embolism. [89] Increased airway pressure, however, has been reported during CO_2 embolism. [72]

The diagnosis of gas embolism depends on the detection of gas emboli in the right side of the heart or on recognition of the physiologic changes secondary to embolization. Early events, occurring with 0.5 mL/kg of air or less, include changes in Doppler sounds and increased mean pulmonary artery pressure when these monitors are used. When the size of the embolus increases (2 mL/kg of air), tachycardia, cardiac arrhythmias, hypotension, increased central venous pressure, alteration in heart tones (millwheel murmur), cyanosis, and electrocardiographic changes of right heart strain can develop; all these changes are rarely consistently positive. [90] Pulmonary edema can also be an early sign of gas embolism. [86] [91] Although transesophageal echocardiography, [83] esophageal [92] or precordial Doppler probes, [93] or pulmonary artery catheters [94] are the most sensitive means of detecting small quantities of gas before physiologic changes, the low incidence of gas embolism during laparoscopy precludes the routine use of such invasive or expensive monitors. [95] [96] Whereas pulse oximetry is helpful in recognizing hypoxemia, capnometry and capnography are more valuable in providing early diagnosis of gas embolism and determining the extent of the embolism. $P_{ET}CO_2$ decreases in the case of embolism due to the fall in cardiac output and the enlargement of the physiologic dead space. Consequently, Deltaa-$_{ET}CO_2$ will increase. Interestingly, CO_2 embolization may cause a biphasic change in $P_{ET}CO_2$. The decrease in $P_{ET}CO_2$ is preceded by an initial increase secondary to pulmonary excretion of the CO_2 , which has been absorbed into the blood. [72] [75] [84] Aspiration of gas or foamy blood from a central venous line will definitively establish the diagnosis. Routine preoperative insertion of a central venous line, however, does not appear justified for these procedures. [75]

Treatment of CO_2 embolism consists of immediate cessation of insufflation and release of pneumoperitoneum. The patient is placed in steep head-down and left lateral decubitus (Durant) position. The amount of gas that will advance through the right heart to the pulmonary circulation is less if the patient is in this position, as the buoyant foam will be displaced laterally and caudally away from the right ventricular outflow tract. [75] Discontinuing N_2O will allow ventilation with 100 percent O_2 to correct hypoxemia, and reduce the size of the gas embolus and its consequences. [84] Hyperventilation increases CO_2 excretion and is made necessary by the enlargement of the physiologic dead space. If these simple measures are not effective, a central venous or pulmonary artery catheter may be introduced for aspiration of the gas. Cardiopulmonary resuscitation must be initiated if necessary. External cardiac massage may be helpful in fragmenting CO_2 emboli into small bubbles. The high solubility of CO_2 in blood, resulting in rapid absorption from the blood stream, accounts for the rapid reversal of the clinical signs of CO_2 embolism with treatment. [75] [77] [95] CO_2 embolism, however, may be fatal. [71] [73] Cardiopulmonary bypass has been used successfully to treat massive CO_2 embolism. [72] Hyperbaric oxygen treatment should be strongly considered if cerebral gas embolism is suspected. [86]

Finally, air emboli have been reported during operative endoscopy using the Nd:YAG laser. [81] [97] [98] [99] The Nd:YAG laser is used with an artificial sapphire scalpel, which is protected from laser-induced thermal damage by cooling with a continuous flow of air, CO_2 , or N_2 . Inadvertent penetration of the sapphire tip into an abdominal viscus can result in air embolism. The anesthesiologist, therefore, should be aware of this possibility.

Risk of Aspiration

Patients undergoing laparoscopy might be considered to be at risk of developing the acid aspiration syndrome. [100] [101] However, the increased intra-abdominal pressure results in changes of the lower esophageal sphincter, which allow maintenance of the pressure gradient across the gastro-esophageal junction, and which might therefore reduce the risk of regurgitation. [102] [103] Furthermore, the head-down position should help to prevent any regurgitated fluid from entering the airway.

/das/book/view/29494766/875/617.html

HEMODYNAMIC PROBLEMS DURING LAPAROSCOPY

Hemodynamic changes observed during laparoscopy result from the combined effects of pneumoperitoneum, patient position, anesthesia, and hypercapnia secondary to the absorbed CO_2 . In addition to these pathophysiologic changes, reflex increases of vagal tone and arrhythmias can also develop.

Hemodynamic Repercussions of Pneumoperitoneum in Healthy Patients

Peritoneal insufflation to IAPs higher than 10 mm Hg induces significant alterations of hemodynamics. [104] [105] [106] These disturbances are characterized by decreases of cardiac output, elevations of arterial pressure, and increases of systemic and pulmonary vascular resistances. Heart rate either remains unchanged or increases only slightly. The decrease in cardiac output is proportional to the increase in IAP. [26] [107] Cardiac output has also been reported to be increased [30] [108] or unchanged during pneumoperitoneum. [109] [110] [111] These discrepancies might be due to differences in rates of CO_2 insufflation, IAP, steepness of patient tilt, time intervals between insufflation and collection of data, and techniques used to assess hemodynamics. However, recent studies have shown a fall of cardiac output (10 to 30 percent) during peritoneal insufflation whether the patient was placed in the head-down, [112] [113] [114] or head-up position. [114] [115] [116] These adverse hemodynamic effects of pneumoperitoneum have been confirmed by studies using pulmonary artery catheterization, [114] [115] thoracic electrical bioimpedance, [113] [116] esophageal echo-Doppler, [117] and transesophageal echocardiography. [118] [119] Normal intraoperative values of $Sv^{-}{}_{O_2}$ and lactate concentrations suggest that changes in cardiac output occurring

Figure 56-5 Schematic representation of the different mechanisms leading to decreased cardiac output during pneumoperitoneum for laparoscopy.

during pneumoperitoneum are well tolerated by healthy patients. [19] Cardiac output, which decreases shortly after the beginning of peritoneal insufflation, subsequently increases, probably as a result of surgical stress. Therefore, hemodynamic degradation occurs mainly at the beginning of peritoneal insufflation.

The mechanism of the decrease of cardiac output is probably multifactorial (Fig. 56-5) . A decrease in venous return is observed after a transient increase in venous return seen at low IAPs (<10 mm Hg). [26] [107] [120] [121] Indeed, increased IAP results in caval compression, [122] pooling of blood in the legs, [123] and an increase in venous resistance. [121] The decline in venous return, which parallels the decrease in cardiac output, [26] [107] is confirmed by a reduction in left ventricular end-diastolic volume measured using transesophageal echocardiography. [119] Cardiac filling pressures, however, rise during peritoneal insufflation. [22] [26] [114] [115] The paradoxic increase of these pressures can be explained by the increased intrathoracic pressure associated with pneumoperitoneum. [26] [124] [125] Therefore, right atrial pressure and pulmonary artery occlusion pressure can no longer be considered to be reliable indices of cardiac filling pressures during pneumoperitoneum. The fact that atrial natriuretic peptide concentrations remain low despite increased pulmonary capillary occlusion pressure during pneumoperitoneum further suggests that abdominal insufflation interferes with venous return. [114] The reduction in venous return and cardiac output can be attenuated by increasing circulating volume before the pneumoperitoneum (Fig. 56-6) . [121] [126] Increased filling pressures can be achieved by fluid loading and/or tilting the patient to a slight head-down position before peritoneal insufflation.

Although inotropism is difficult to assess, [118] the ejection fraction of the left ventricle assessed by echocardiography does not appear to decrease significantly when IAP increases to 15 mm Hg. [119] [127] On the other hand, all studies reported to date describe an increase in systemic vascular resistance during pneumoperitoneum. This increase in afterload cannot be considered simply to be a reflex sympathetic response to decreased cardiac output. [115] Indeed, systemic vascular resistance also increased in studies in which no decrease in cardiac output was reported. [110] [127] Whereas the normal heart tolerates increases in afterload under physiologic conditions, the changes in afterload produced by pneumoperitoneum can result in deleterious effects in patients with cardiac diseases and may lead to further decreases in cardiac output. [128] The increase in systemic vascular resistance is affected by patient position. Whereas the Trendelenburg position attenuates this increase, the head-up position aggravates it. [110] [111] [114] [129] Therefore, the patient's circulating volume affects not only changes in venous return, but also changes in afterload. The increase in systemic vascular resistance can be corrected by administra-tion of vasodilating anesthetic agents (isoflurane) [115] or direct vasodilating drugs, such as nitroglycerin [130] or nicardipine. [131]

The increase in systemic vascular resistance is considered to be mediated by mechanical as well as neurohumoral factors. [104] [113] [115] Indeed, the return of hemodynamic variables to baseline is gradual and takes several minutes, suggesting the involvement of neurohumoral factor(s). [22] [104] [113] [128] Catecholamines, the renin-angiotensin system, and especially vasopressin are all released during pneumoperitoneum and may contribute to increasing afterload. [114] [116] [125] [132] [133] [134] [135]

Figure 56-6 Changes in cardiac index and systemic vascular resistance during laparoscopy in two groups of patients. Group 1 (control; filled bar): pneumoperitoneum was induced with patients in 10-degree head-up position. Group 2 (volume loaded; empty bar): patients received 500 mL lactated Ringer's solution before anesthesia induction and were insufflated in the supine position. N = 10 in each group, data are mean ± SEM.

However, only the time course of vasopressin release parallels that of systemic vascular resistance. [116] [134] Increases in plasma vasopressin concentrations have been correlated with changes in intrathoracic pressure and transmural right atrial pressure. [125] Mechanical stimulation of peritoneal receptors also results in increased vasopressin release, [136] systemic vascular resistance, and arterial pressure. [137] However, whether increasing IAP to 14 mm Hg is sufficient to stimulate these receptors is unknown. The increase in systemic vascular resistance also explains why the arterial pressure increases, whereas the cardiac output falls. [104] [105] Use of $alpha_2$ -adrenergic agonists such as clonidine or dexmedetomidine significantly reduces both hemodynamic changes and anesthetic requirements. [134] [138] [139] [140]

Effect of Pneumoperitoneum on Regional Hemodynamics

Increased IAP and the head-up position result in lower limb venous stasis. [123] [141] [142] Femoral vein blood flow decreases progressively with increasing IAP and no adaptation to the reduced femoral venous outflow occurs, even during prolonged procedures. [142] These changes may predispose to the development of thromboembolic complications. Although cases of thromboembolism have been reported in the literature, their actual incidence does not seem to be increased by

laparoscopy. [143] [144]

The effect of CO_2 -pneumoperitoneum on renal function has also been investigated. [145] [146] [147] [148] Urine output, renal plasma flow, and glomerular filtration rate decrease to less than 50 percent of baseline values during laparoscopic cholecystectomy and are significantly lower than those during open cholecystectomy. [145] Urine output significantly increases after desufflation.

Controversy persists with regard to the effect of CO_2 -pneumoperitoneum on splanchnic blood flow. A significant reduction was reported in both animals [146] [149] [150] and humans. [151] However, others have not noted any significant changes. [152] [153] [154] [155] Blobner et al, [153] comparing CO_2 - and air-pneumoperitoneum in pigs, observed a reduction in splanchnic blood flow during air-, but not CO_2 -pneumoperitoneum. They suggest that the direct splanchnic vasodilating effect of CO_2 may counteract the mechanical effect of increased IAP. The rarity of reports of mesenteric ischemia following laparoscopy [156] [157] suggests that the effects of pneumoperitoneum on the splanchnic circulation are not clinically significant.

Cerebral blood flow velocity increases during CO_2 -pneumoperitoneum in response to the increased Pa_{CO_2} . [158] When normocarbia is maintained, pneumoperitoneum combined with the head-down position does not induce harmful changes in intracranial dynamics. [159] Intracranial pres- sure nevertheless rises during CO_2 -pneumoperitoneum, independently of changes in Pa_{CO_2} , in pigs with either preoperative induced intracranial hypertension or normal intracranial pressure, [160] [161] as well as in children with ventriculoperitoneal shunts. [162] Intraocular pressure is not affected by pneumoperitoneum in women with no preexisting eye disease. [163] In an animal model of glaucoma, pneumoperitoneum only slightly increases intraocular pressure. [164]

Hemodynamic Repercussions of Pneumoperitoneum in High-Risk Cardiac Patients

The demonstration of significant hemodynamic changes during pneumoperitoneum raises the question of tolerance of these changes by cardiac patients (Chs. 22 and 25) . In patients with mild to severe cardiac disease, the pattern of change in mean arterial pressure, cardiac output, and systemic vascular resistance is qualitatively similar to that in healthy patients. [128] [130] [165] [166] [167] [168] Quantitatively, these changes appear to be more marked. In a initial study including ASA III-IV patients, $Sv^{-}{}_{O_2}$ decreased in 50 percent of patients despite preoperative hemodynamic optimization using a pulmonary artery catheter. [165] Patients who experienced the most severe hemodynamic changes with inadequate O_2 delivery were patients with low preoperative cardiac output and central venous pressure, and high mean arterial pressure

and systemic vascular resistance (i.e., a profile suggesting depleted intravascular volume). The authors suggest preoperative preload augmentation to offset the hemodynamic effect of pneumoperitoneum. Intravenous nitroglycerin, nicardipine, or dobutamine has been used to manage the hemodynamic changes induced by increased IAP in selected patients with heart disease. [130] [131] [167] Nitroglycerin was chosen to correct the reduction in cardiac output associated with increased pulmonary capillary occlusion pressures and systemic vascular resistance. The administration of nicardipine may be more appropriate than that of nitroglycerin. As mentioned previously, right atrial and pulmonary capillary occlusion pressures are not reliable indices of cardiac filling pressure during pneumoperitoneum. Increased afterload is a major contributor to the altered hemodynamics seen during pneumoperitoneum in cardiac patients. Nicardipine acts selectively on arterial resistance vessels and does not compromise venous return. [169] Finally, this drug is beneficial in case of congestive heart failure. [170] [171] Because normalization of hemodynamic variables does not occur for at least 1 hour postoperatively in certain patients, [56] [128] [168] congestive heart failure can develop in the early postoperative period. Dhoste et al [172] did not observe impaired hemodynamics in elderly ASA III patients, but used low intraperitoneal pressure (10 mm Hg) and slow insufflation rates (1 L/min). Interestingly, the hemodynamic consequences of pneumoperitoneum are minor in heart transplant recipients with good ventricular function. [173] [174] Finally, we have successfully managed laparoscopic adrenalectomy in eight patients with pheochromocytoma using a continuous infusion of nicardipine. [175]

Cardiac Arrhythmias During Laparoscopy

Arrhythmias during laparoscopy may have several causes (Ch. 32).

Attention has been focused on hypercapnia developing during peritoneal insufflation of CO_2 in patients under anesthesia with spontaneous breathing. [176] [177] However, the responsibility of the raised Pa_{CO_2} for the arrhythmias occurring during laparoscopy was questioned. [31] Indeed, arrhythmias are not correlated with Pa_{CO_2} and may develop early during insufflation, when high Pa_{CO_2} is unlikely. [31]

Reflex increases of vagal tone may result from sudden stretching of the peritoneum. Bradycardia, cardiac arrhythmias, and even asystole can develop. Vagal stimulation will be accentuated if the level of anesthesia is too superficial or if the patient is taking beta-blocking drugs. Electrocoagulation of the fallopian tubes can stimulate a vagal reaction. [80] These events are easily and quickly reversible. Treatment consists of interruption of insufflation, atropine administration, and deepening of anesthesia after recovery of heart rate.

Cardiac irregularities most often occur early during insufflation, when pathophysiologic hemodynamic changes are the most intense. [31] [115] For this reason, arrhythmias may also reflect intolerance of these hemodynamic disturbances in patients with known or latent cardiac disease.

Finally, gas embolism can also result in cardiac arrhythmias.

PROBLEMS RELATED TO PATIENT POSITION

Patient positioning (Ch. 26) depends on the site of surgery; whereas head-down tilt is used for pelvic and inframesocolic surgery, the head-up position is preferred for supramesocolic surgery. In addition, the patient is often placed in the lithotomy position. These positions may be responsible for, or contribute to, the development of pathophysiologic changes or injury during laparoscopy. The steepness of the tilt requested directly affects the magnitude of these changes.

Cardiovascular Effects

In normotensive subjects, the head-down position results in an increase in central venous pressure and cardiac output. In fact, the baroreceptor reflex response to increased hydrostatic pressure consists of systemic vasodilation and bradycardia, which stabilizes the cardiovascular status. [178] Although these different reflexes may be impaired during general anesthesia, the hemodynamic changes induced by this position during laparoscopy remain insignificant. [110] [113] [114] [129] However, central blood volume and pressure changes are greater in patients with coronary artery disease, particularly with poor ventricular function, leading to potentially deleterious increased myocardial oxygen demand. [52] The Trendelenburg position may also affect the cerebral circulation, particularly in case of low intracranial compliance, [161] and result in elevation of the intraocular venous pressure (which can worsen acute glaucoma). [164] Although the intravascular pressure increases in the upper torso, the head-down position decreases transmural pressures in the pelvic viscera, reducing blood loss, but increasing the risk of gas embolism. [52]

As concerns the head-up position, a decrease in cardiac output and mean arterial pressure is observed secondary to the reduction in venous return. [110] [114] [115] [129] This decrease in cardiac output compounds the hemodynamic changes induced by pneumoperitoneum. The steeper the tilt, the greater the fall in cardiac output.

Venous stasis in the legs occurs during the head-up position and may be aggravated by the lithotomy position with knees flexed. [52] Because pneumoperitoneum further increases blood pooling in the legs, [123] [141] [142] any additional factor contributing to circulatory dysfunction should be avoided. The legs must be freely supported and not tightly strapped, and pressure on the popliteal space must be prevented.

Respiratory Changes

The head-down position facilitates the development of atelectasis. Steep head-down tilt results in decreased functional residual capacity, total lung volume, and pulmonary compliance. It should be noted that these changes are more marked in obese, elderly, or debilitated patients. In healthy patients no major changes are seen. [52] The head-up position is usually considered to be more favorable to respiration. [52] [179] Changes in patient position during laparoscopy

induce only minimal alterations in gas exchange [22] [25] [25] [28] [29] and thoracopulmonary compliance. [14] [15]

Nerve Injury

Nerve compression is a potential complication during the head-down position. Overextension of the arm must be avoided. Shoulder braces should be used with great caution and must not impinge on the brachial plexus. Lower extremity neuropathies (peroneal neuropathy, meralgia paresthetica, femoral neuropathy) have been reported after laparoscopy. [180] [181] The common peroneal nerve is particularly vulnerable and must be protected when the patient is placed in the lithotomy position. Prolonged lithotomy position, such as required for some operative laparoscopies, can result in lower extremity compartment syndrome. [182] [183]

POSTOPERATIVE BENEFITS AND CONSEQUENCES OF LAPAROSCOPY

Implicit in the decision to use the laparoscopic approach is the assumption that the intraoperative consequences of pneumoperitoneum described in the previous sections are counterbalanced by multiple postoperative benefits. In contrast to laparotomy, improved and more rapid recovery, reduced postoperative fatigue, [184] [185] and a heightened feeling of well-being are commonly reported and reflect better maintenance of homeostasis. [3] [185]

Stress Response

In patients undergoing cholecystectomy, the laparoscopic approach allows for a reduction of the acute phase reaction seen after open cholecystectomy. Plasma concentrations of C-reactive protein and interleukin-6, which reflect the extent of tissue damage, are significantly lower after laparoscopy as compared with laparotomy. [3] [185] [186] [187] [188] The metabolic response (hyperglycemia, leucocytosis) is also reduced after laparoscopy. As a consequence, nitrogen balance and immune function might be better preserved. [189] [190] [191] [192] Laparoscopy avoids prolonged exposure and manipulation of the intestines and decreases the need for peritoneal incision and trauma. Consequently, postoperative ileus and fasting, duration of intravenous infusion, and hospital stay are significantly reduced after laparos-copy. [186] [192] [193] [194] [2] [3] The economic implications of these factors are self-evident and beneficial. [195] [196] [197]

Surprisingly, whereas laparoscopy allows for a reduction of surgical trauma, the endocrine response to laparoscopic and open cholecystectomy does not differ significantly; plasma concentrations of cortisol and catecholamines, [3] [185] [198] [199] urinary concentrations of cortisol and catecholamine metabolites, [186] and anesthetic requirements [3] are similar after both procedures. Combined general and epidural anesthesia for laparoscopic cholecystectomy does not result in a decreased stress response compared with general anesthesia alone. [198] Several hypotheses might be invoked to explain these observations. Pain and discomfort secondary to peritoneal stretching, hemodynamic disturbances, and ventilatory changes induced by pneumoperitoneum might contribute to the stress response of laparoscopy. Whereas parietal afference, which is markedly reduced by laparoscopy, appears to be an important stimulus for postoperative hyperglycemia, visceral nociception, less affected by laparoscopy, might contribute more to the adrenocortical stimulation. [185] The intraoperative stress response, however, can be reduced by preoperative administration of alpha$_2$ -agonists. [134] [138] [139] [140]

Postoperative Pain

Surgical trauma contributes to pain and pulmonary dysfunction. Laparoscopy allows a significant reduction in postoperative pain and analgesic consumption (Ch. 69) . [3] [186] [198] [200] [201] [202] [203] [204] [205] [206] Nevertheless, pain intensity may be significant. [207] [208] The nature of pain varies depending on the surgical technique; after laparotomy, patients complain more of parietal pain (abdominal wall), whereas after laparoscopic cholecystectomy, patients report visceral pain (biliary colic [cholecystectomy], pelvic spasm [tubal ligation]), and shoulder-tip pain resulting from diaphragmatic irritation). [3] [208] Neck and shoulder pain is reported by 80 percent of patients at 24 hours, and by as many as 50 percent at 48 hours. [209] CO_2 insufflation induces more discomfort than use of N_2O as insufflating gas. [210] Different treatments have been proposed to provide pain relief. Topical anesthesia [211] [212] or infiltration of the fallopian tubes decreases postoperative pain and analgesic consumption after laparoscopic sterilization. [213] Intraperitoneal administration of local anesthetic (80 mL of 0.5% lidocaine or 0.125% bupivacaine with epinephrine) in the right subdiaphragmatic area reduces shoulder pain and analgesic requirements after minor gynecologic laparoscopy, [214] [215] but not after laparoscopic cholecystectomy. [208] [216] [217] [218] Residual CO_2 -pneumoperitoneum contributes to postoperative pain. Careful evacuation of residual CO_2 after desufflation was also shown to be effective. [219] [220] [221] Thoracic epidural analgesia significantly decreases postoperative pain, but only during the first 24 hours. [198] The performance of bilateral rectus sheath block for diagnostic laparoscopy leads to the same benefits. [222] Preoperative administration of nonsteroidal anti-inflammatory drugs (NSAID) decreases pain and opiate consumption after gynecologic laparoscopy [223] [224] [225] [226] and laparoscopic cholecystectomy. [227] [228] However, others have failed to demonstrate any significant effect of preoperative NSAID on pain after laparoscopic sterilization more severe than after diagnostic gynecologic laparoscopy. [229] [230] [231] [232] Preoperative multimodal analgesia is also effective in reducing postoperative pain. [233] [234]

Pulmonary Dysfunction

Upper abdominal surgery results in postoperative changes in pulmonary function. Respiratory dysfunction is less severe and recovery is quicker after laparos-copy. [3] [104] [198] [200] [201] [235] [236] [237] [238] Diaphragmatic function remains, nevertheless, significantly impaired after laparoscopy. [239] [240] [241] [242] Thoracic epidural analgesia does not improve lung function after laparoscopic cholecystectomy. [198]

Greater reductions in expiratory volumes and slower recovery of pulmonary function after laparoscopy are reported in older, [243] obese, [204] [244] smokers, and patients with COPD [244] than in healthy patients. Postoperative pulmonary function of these patients, however, is improved after laparoscopy as compared with laparotomy. [204] [244] Post-operative pulmonary function is less impaired after gynecologic laparoscopy than after upper abdominal laparoscopic surgery. [245]

Postoperative Nausea and Vomiting

Laparoscopy also carries a high incidence of minor postoperative sequelae (Ch. 65) , which can persist more than 48 hours, and which can significantly delay discharge of outpatients. [209] In addition to postoperative pain of various types, the most frequent complaints are headache, sore throat (in case of endotracheal intubation), and, more particularly, nausea and vomiting. Postoperative nausea and vomiting is one of the main complaints after laparoscopy (in 40 to 75% of patients), [209] [246] [247] [248] [249] [250] and the most important factor determining the length of stay after ambulatory anesthesia. [251] Whereas intraoperative opioids increase the incidence of nausea and vomiting, [252] [253] propofol anesthesia can markedly reduce the high incidence of these side effects. [247] [251] The effect of N_2O on the incidence of nausea is still controversial. [254] [255] [256] [257] [258] [259] Drainage of gastric contents also reduces nausea and vomiting. [260] Intraoperative administration of droperidol and more recently the use of ondansetron appear to be helpful in the prevention and treatment of these side effects. [261] [262] [263] [264] [265] Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. [248] Finally, analgesic techniques that allow reductions of opioid consumption can contribute to decreasing these symptoms. [212] [266]

/das/book/view/29494766/875/620.html

ALTERNATIVES TO CO_2 -PNEUMOPERITONEUM

New approaches are currently under investigation to reduce pathophysiologic consequences of CO_2 -pneumoperitoneum.

Inert Gases

Insufflation of inert gas (helium, argon) instead of CO_2 avoids the increase in Pa_{CO_2} secondary to absorption. Consequently, hyperventilation is not required. [42] [43] [44] [45] [267] On the other hand, the ventilatory consequences of the increased IAP persist. The hemodynamic changes produced by pneumoperitoneum using inert gas are similar to those observed with CO_2 . However, the use of these gases accentuates the decrease in cardiac output, whereas the increase in arterial pressure is attenuated. [44] [45] [268] Therefore, peritoneal insufflation of CO_2 , even in the absence of hypercapnia, apparently stimulates the cardiovascular system and subsequently partially corrects the hemodynamic repercussions due to increased IAP. [104] Unfortunately, the low blood solubility of the inert gases raises the issue of safety in the event of gas embolism. [269] [270]

Gasless Laparoscopy

Another alternative is gasless laparoscopy. The peritoneal cavity is expanded using abdominal wall lift obtained with a fan retractor. This technique avoids the hemodynamic and respiratory repercussions of increased IAP as well as the consequences of the use of CO_2 . [271] [272] [273] [274] [275] Renal and splanchnic perfusion is not altered. [148] [151] [276] Postoperative pain, nausea, and vomiting are reduced after cholecystectomy, [271] but not after gynecologic laparoscopy. [277] [278] Port-site metastases following laparoscopic surgery for cancer are also reduced after gasless laparoscopy. [279] [280] This technique, therefore, is appealing for patients with severe cardiac or pulmonary disease. However, gasless laparoscopy compromises surgical exposure and increases technical difficulty. [273] [277] [278] Combining abdominal wall lifting with low pressure CO_2 -pneumoperitoneum (5 mm Hg) might improve surgical conditions.

LAPAROSCOPY DURING PREGNANCY AND IN CHILDREN

The most common nonobstetric surgical procedures during pregnancy are appendectomy and cholecystectomy, both amenable to laparoscopic surgery (Chs. 57 and 59) . Laparoscopy during pregnancy raises several concerns. Abdominal surgery increases the risk of miscarriage or premature labor. However, all the reports in the literature of laparoscopy carried out between 4 and 32 weeks of estimated gestational age have resulted in uncomplicated pregnancies. [281] Another concern is the risk of damaging the gravid uterus. This can be avoided by alternative entry sites for the Verres needle and trocars. The effects of increased IAP and hypercarbia on the human fetus were also investigated. CO_2 -pneumoperitoneum induced significant fetal acidosis. Fetal heart rate and arterial pressure increased, but these changes were minimal. [282] All these alterations resulted from hypercarbia, and not from increased IAP, as N_2O-pneumoperitoneum did not affect blood-gas values, heart rate, or blood pressure. After desufflation, all variables quickly returned to normal. [282] Provided maternal Pa CO_2 is maintained at normal levels, fetal placental perfusion pressure and blood flow, pH, and blood gas tensions were unaffected by insufflation or desufflation. [283] Recommendations for safe laparoscopy in pregnant patients are the following [281] :

1. Operation should occur during the second trimester, ideally before the 23rd week of pregnancy, to minimize the risk of preterm labor and to maintain adequate intra-abdominal working room.
2. Tocolytics are beneficial to arrest preterm labor, but their prophylactic use is debatable.
3. Open laparoscopy should be used for abdominal access to avoid damaging the uterus.
4. Fetal monitoring may be performed using transvaginal ultrasonography.
5. Mechanical ventilation must be adjusted to maintain a physiologic maternal alkalosis.

Gasless laparoscopy is an alternative to avoid the potential side effects of CO_2 -pneumoperitoneum, and can sometimes be managed using epidural anesthesia. [284] [285]

2014

Laparoscopy is now frequently performed in infants and children. However, only few data concerning the hemodynamic and ventilatory tolerance of pneumoperitoneum by children are available. The hemodynamic changes observed in piglets are similar to those reported in adults. [286] [287] [288] In this animal model, Pa CO_2 increases and plateaus within 15 minutes as a result of CO_2 absorption from the peritoneal cavity. This absorption may be more intense and faster in infants than in adults because the peritoneal surface area referred to body weight is greater in infants. [287] [289] Accordingly, in young swine, intraperitoneal CO_2 insufflation produces marked acidemia, hypercapnia, and decreased oxygenation. [286] However, during brief laparoscopy (less than 15 minutes), peak airway pressure and $P_{ET}CO_2$ rise only slightly; no increase in ventilation is required. [290] Good cardiorespiratory tolerance of laparoscopic fundoplication has been reported in children, provided that hypovolemia is prevented. [291] Controversy concerning the use of laparoscopy for appendectomy, the most frequent indication for laparoscopy in children, persists. In a recent randomized study, laparoscopy did not improve analgesia or postoperative recovery after appendectomy. [292]

COMPLICATIONS OF LAPAROSCOPY

With the development of more sophisticated endoscopic operations, it is important to consider the risks and benefits of laparoscopy. Whereas the benefits of the laparoscopic approach are well documented, knowledge of the incidence of complications is more imprecise and is frequently based on retrospective studies.

The experience of gynecologic laparoscopists extends over a relatively long time and, as a result, large surveys are available. [293] [294] [295] [296] Mortality rates have varied from 1 per 10,000 to 1 per 100,000 cases. The number of serious complications requiring laparotomy was 2 to 10 per 1,000 cases. Intestinal injuries accounted for 30 to 50 percent of these, and remained undiagnosed during laparoscopy in half of the cases. Vascular complications also accounted for 30 to 50 percent. Burns were responsible for 15 to 20 percent of the reported complications. Whereas the death rate decreased, the complication rate was noted to be slightly higher in the most recent surveys, probably because of the increased complexity of the laparoscopies performed over the last few years.

Although the introduction of laparoscopic cholecystectomy is relatively recent (1989), large surveys are already available. [196] [297] [298] [299] [300] The overall mortality rate is approximately 0.1 to 1 per 1,000 cases. Conversion to laparotomy was necessary in approximately 1 percent of patients. Bowel perforation occurred in about 2 per 1,000 cases, common bile duct injury in 2 to 6 per 1,000 cases, and significant hemorrhage in 2 to 9 per 1,000 cases. Laparoscopic cholecystectomy was accompanied by a greater frequency of minor operative complications, whereas open cholecystectomy had a higher rate of minor general complications. A learning curve was demonstrated for laparoscopic cholecystectomy; experience was associated with decreased operative times and rates of minor or moderate complications. Some of these complications might be prevented by open laparoscopy. [301]

Whereas large vessel injury (aorta, inferior vena cava, iliac vessels) obviously caused emergency situations, retroperitoneal hematoma can develop insidiously and result in significant blood loss without major intraperitoneal effusion, leading to delayed diagnosis. During gynecologic laparoscopy, complications occur more frequently during the creation of pneumoperitoneum and the introduction of trocars, whereas during gastrointestinal surgery they are more closely related to the surgical procedure itself. [196] [302] [303] Injuries provoked by the Verres needle are usually less severe than those by trocars and may even remain undiagnosed. Unrecognized gastrointestinal tract injury and subhepatic abscess formation can lead to potentially lethal septic complications. [304] Although all these events are surgery related, the anesthesiologist must be aware of both the complications and timing of their occurrence. He or she must be ready to respond promptly and adequately to these mishaps and to help the surgeon diagnose a complication.

ANESTHESIA FOR LAPAROSCOPY

Preoperative Evaluation of the Patient and Premedication

Without regard to surgical contraindications, absolute contraindications to laparoscopy and pneumoperitoneum are rare, and certain still require characterization (Ch. 23) . Pneumoperitoneum is undesirable in patients with increased intracranial pressure (tumor, hydrocephalus, head trauma), hypovolemia, ventricular peritoneal shunt, [162] and peritoneojugular shunt. Pneumoperitoneum, however, can be performed safely in patients with these shunts, provided the shunt has been clamped before peritoneal insufflation. [305] In case of glaucoma, the effects on intraocular pressure do not seem to be clinically significant, but deserve further confirmation. Gasless laparoscopy may be a safe alternative to laparoscopy with pneumoperitoneum for all these cases.

In patients with heart disease, cardiac function should be evaluated in light of the hemodynamic changes induced by pneumoperitoneum and patient position, particularly in case of compromised ventricular function (Table 56-2) . Over the last 4 years, patients with progressively more severe cardiac disease have safely undergone laparoscopy because of the improved knowledge of the cardiovascular repercussions of laparoscopy. Patients with severe congestive heart failure and terminal valvular insufficiency are certainly more prone to develop cardiac complications than patients with ischemic cardiac disease during laparoscopy. Whether laparoscopy is more dangerous than laparotomy in these patients has not yet been explored directly, but deserves careful consideration. For these patients, the postoperative benefits of laparoscopy must be balanced against the intraoperative risks when the choice of laparoscopy versus laparotomy is discussed (Table 56-3) . Gasless laparoscopy may represent an alternative for these patients.

Because of the side effects of increased IAP on renal function, patients with renal failure deserve special care to optimize hemodynamics during pneumoperitoneum, and the concomitant use of nephrotoxic drugs should be avoided.

TABLE 56-2 -- Management of Patients With Cardiac Disease for Laparoscopy

Preoperative evaluation: echocardiography
If left ventricular ejection fraction <30%
Intraoperative monitoring
Intra-arterial line
Pulmonary artery catheter
Transesophageal echocardiography?
Continuous ST segment analysis?
Gasless laparoscopy?
Laparotomy?
Intraoperative management
Slow insufflation
Low intra-abdominal pressure
Hemodynamic optimization before pneumoperitoneum (preload augmentation)
Patient tilt after insufflation
Anesthesia: isoflurane vasodilating drugs (nicardipine, nitroglycerin) cardiotonic agents
Experienced surgeon
Postoperative care
Slow recovery from anesthesia (benefit of clonidine)

In patients with respiratory disease, laparoscopy appears preferable to laparotomy because of reduced postoperative respiratory dysfunction. This positive effect counterbalances the risk of pneumothorax during pneumoperitoneum and the risk of inadequate gas exchange secondary to V_A/Q mismatching.

Because of venous stasis in the legs during laparoscopy, prophylaxis of deep vein thrombosis should be initiated before surgery, as for laparotomy.

Premedication should be adapted to the duration of the laparoscopy and to the necessity for quick recovery in the outpatient setting. Preoperative administration of NSAIDs may be helpful in reducing postoperative pain and opiate requirements. Finally, preoperative clonidine and dexmedetomidine decrease the intraoperative stress response and improve hemodynamic stability. [134] [138] [139] [140]

Patient Positioning and Monitoring for Laparoscopy

Patients must be positioned (Ch. 26) with great care to prevent nerve injuries; padding should protect from nerve compression, and shoulder braces, if needed, should be placed overlying the coracoid process. Patient tilt should be reduced as much as possible and should not exceed 15 to 20 degrees. Tilting must be slow and progressive to avoid sudden hemodynamic and respiratory changes. The position of the endotracheal tube must be checked after any change in patient position. Induction and release of the pneumoperitoneum must be smooth and progressive. Mask ventilation before intubation can inflate the stomach with gas, which must be aspirated before trocar placement to avoid gastric perforation, particularly for supramesocolic laparoscopy. The bladder should be emptied before pelvic laparoscopy or prolonged procedures.

During laparoscopy, arterial blood pressure, heart rate, electrocardiogram, capnometry, and pulse oximetry must be continuously monitored. Although this level of

monitoring is valuable for detection of cardiac arrhythmias, gas embolism, CO_2-subcutaneous emphysema, and pneumothorax, it provides only indirect evidence of the hemodynamic changes induced by the pneumoperitoneum. Although more invasive

TABLE 56-3 -- Comparison of Laparotomy and Laparoscopy

	LAPAROTOMY	LAPAROSCOPY
		INTRAOPERATIVELY
Hemodynamic	Stimulation by surgical stress	Depression secondary to pneumoperitoneum > stimulation by surgery
Ventilatory changes	+	++
Elevation of diaphragm	+	++
Increased intrathoracic pressure	0	++
Absorption of CO_2	0	++
Controlled mechanical ventilation (min ventilation)	+	++
Patient position	+	++
Anesthetic requirement	=	=
Endocrine response	++	++
Surgical trauma	++	+
		POSTOPERATIVELY
Pain (analgesic requirement)	++	+
Pulmonary dysfunction	++	+
Metabolic response and acute phase reaction	++	+
Postoperative fatigue	++	+
Recovery	++	+
Fasting	++	+
Nausea, vomiting	+	++
Hospital stay	++	+
Mortality	+	(+)
Morbidity	+	(+)

Symbols: 0, not a factor; =, no difference; +, minimal to moderate problem; ++, major problem

hemodynamic monitoring may be necessary in patients with cardiac diseases, increased intrathoracic pressure complicates the interpretation of measured central venous and pulmonary artery pressures. Transesophageal echocardiography might be more helpful in patients with severe cardiac disease (see Table 56-2) . $P_{ET}CO_2$ and Sp_{O_2} reliably reflect Pa_{CO_2} and Sa_{O_2} . However, we must keep in mind that the Deltaa-$_{ET}CO_2$ may vary from patient to patient, and during the course of laparoscopy in the same patient. $P_{ET}CO_2$ must be monitored carefully to avoid hypercapnia and to detect gas embolism. Because Deltaa-$_{ET}CO_2$ may increase more in patients with cardiac and pulmonary diseases, cannulation of a radial artery is helpful to allow direct measurement of Pa_{CO_2} from an arterial blood sample.

Anesthetic Techniques

General, local, and regional anesthesia have been used successfully and safely for laparoscopy.

General Anesthesia

General anesthesia with endotracheal intubation and controlled ventilation is certainly the safest technique and, therefore, is recommended for inpatients and for long laparoscopic procedures. During pneumoperitoneum, controlled ventilation must be adjusted to maintain $P_{ET}CO_2$ at approximately 35 mm Hg. In our experience, this requires no more than a 15 to 25 percent increase of minute ventilation, except when CO_2-subcutaneous emphysema develops. Increase of respiratory rate rather than of tidal volume might be preferable in patients with COPD, and in patients with a history of spontaneous pneumothorax or bullous emphysema to avoid increased alveolar inflation and reduce the risk of pneumothorax. Anesthetic agents that directly depress the heart should be avoided in patients with compromised cardiac function in favor of anesthetics with vasodilating properties such as isoflurane (see Table 56-2) . [115] Infusion of vasodilating agents, such as nicardipine, reduces the hemodynamic repercussions of pneumoperitoneum and might facilitate management of cardiac patients. [131] Nitrous oxide has been suspected to affect oocyte function. The success rate of *in vitro* fertilization, however, is not decreased by use of N_2O. [306] The contribution of N_2O to nausea and vomiting is still controversial. [254] [257] [258] There is apparently no clinical advantage to omitting nitrous oxide. [307] Whereas N_2O does not seem to be contraindicated for laparoscopic cholecystectomy, [259] omission of N_2O improves surgical conditions for intestinal and colonic surgery. The choice of anesthetic technique does not seem to play a major role in patient outcome. [307] [308] [309] Propofol, nevertheless, results in fewer postoperative side effects. [247] [310] [311] [312] Propofol anesthesia for laparoscopic pronuclear stage transfer, however, is associated with lower clinical and ongoing pregnancy rates compared with isoflurane. [313] IAP should be monitored, kept as low as possible to reduce hemodynamic and respiratory changes, and not allowed to exceed 20 mm Hg. Increases in IAP can be avoided by ensuring a deep plane of anesthesia. Whether profound muscle relaxation is necessary for lap-aroscopy is not clear. [314] [315] Because of the potential for reflex increases of vagal tone during laparoscopy, atropine should be administered before the induction of anesthesia, or should be available for injection if necessary.

The laryngeal mask airway results in less sore throat and might be proposed as an alternative to endotracheal intubation, [316] [317] [318] [319] [320] even if this device does not protect the airway from aspiration of gastric contents. [318] [321] Indeed, it allows controlled ventilation and accurate monitoring of $P_{ET}CO_2$. However, decreased thoracopulmonary compliance during pneumoperitoneum frequently results in airway pressures exceeding 20 cm H_2O. Because the laryngeal mask airway cannot guarantee an airway seal above this pressure, its use for controlled ventilation should be limited to healthy, thin patients.

General anesthesia in patients breathing spontaneously without intubation can be performed safely and avoids tracheal irritation as well as administration of muscle relaxant. [320] [322] However, a report from the Centers for Disease Control revealed that almost one third of deaths associated with laparoscopic procedures were related to anesthetic complications during general anesthesia without intuba-tion. [323] This anesthetic technique should thus be restricted to short procedures performed using low IAP and small degrees of tilt. [33] In these cases, the laryngeal mask airway might improve the safety of anesthesia for laparoscopy in patients breathing spontaneously [316] [320] [324] and is therefore recommended.

Local and Regional Anesthesia

Local anesthesia offers several advantages: quicker recovery, decreased postoperative nausea and vomiting, early diagnosis of complications, and fewer hemodynamic changes. [325] [326] [327] Sequelae of general anesthesia such as sore throat, muscle pain, and airway trauma can be avoided. However, this anesthetic approach requires precise and gentle surgical technique, and may result in increased patient anxiety, pain, and discomfort during the manipulation of pelvic and abdominal organs. For these reasons, local anesthesia is routinely supplemented with intravenous sedation. The combined effect of pneumoperitoneum and sedation can lead to hypoventilation and arterial oxygen desaturation. [328] Success with local anesthesia requires a relaxed and cooperative patient, a supportive operating room staff, and a skilled surgeon. IAP should be as low as possible to reduce pain and ventilatory disturbances. Although laparoscopic tubal ligation might be a good

indication for local anesthesia, multiple constraints explain the lack of enthusiasm of gynecologic laparoscopists for this anesthetic technique. [58] Any other laparoscopic procedure that requires multiple puncture sites, considerable organ manipulation, steep tilt, and voluminous pneumoperitoneum makes spontaneous breathing difficult for the patient, results in discomfort, and must not be managed with local anesthesia. [58]

Regional anesthesia, including epidural and spinal techniques, combined with the head-down position, can be used for gynecologic laparoscopy without major impairment of ventilation. [29] [329] The metabolic response is reduced by regional anesthesia. [330] Globally, epidural and local anesthesia share the same benefits and disadvantages. [56] [329] [331] Regional anesthesia has the advantages of reducing the need

---

for sedatives and narcotics, produces better muscle relaxation and can be proposed for laparoscopic procedures other than sterilization. Shoulder-tip pain secondary to diaphragmatic irritation and discomfort secondary to abdominal distention are incompletely alleviated using epidural anesthesia alone. [331] [332] Extensive sensory block (T4-L5) is necessary for surgical laparoscopy and may also lead to discomfort. The epidural administration of opiates and/or clonidine might help to provide adequate analgesia. [331] The hemodynamic effects of pneumoperitoneum under epidural anesthesia have not been studied. Although sympathetic block might facilitate the development of vagal reflexes, vasodilation and the avoidance of positive pressure ventilation might reduce the cardiovascular changes described during pneumoperitoneum. Once again, patient cooperation, an experienced and skilled laparoscopist, reduced IAP, and tilt are necessary to guarantee the success of epidural anesthesia, which should be avoided for long procedures. Regional anesthesia can provide adequate relief of pain and discomfort in case of gasless laparoscopy, thus avoiding most of the side effects of CO_2 -pneumoperitoneum. [285] [333] [334] Also see chapters 42 and 43 .

Recovery and Postoperative Monitoring

Hemodynamic monitoring should be continued in the postanesthesia care unit (Ch. 68) . Indeed, hemodynamic changes induced by the pneumoperitoneum, and more particularly the increased systemic vascular resistance, outlast the release of the pneumoperitoneum. The hyperdynamic state developing after laparoscopy could conceivably lead to a precarious hemodynamic situation in patients with cardiac disease. [128] [168]

Despite the reduction in postoperative pulmonary dysfunction, Pa_{O_2} still decreases after laparoscopic cholecystectomy. [3] [200] [237] Furthermore, increased O_2 demand is observed after laparoscopy. [19] Although laparoscopy tends to be considered a minor surgical procedure, O_2 should be administered postoperatively, even to healthy patients. [335] During the early postoperative period, respiratory rate and $P_{ET}CO_2$ of patients breathing spontaneously are higher after lap-aroscopy as compared with open surgery. [40]

Finally, prevention and treatment of nausea, vomiting, and pain are important, particularly after outpatient laparoscopic procedures. This issue has been addressed previously.

SUMMARY

Laparoscopy results in multiple postoperative benefits including less trauma, less pain, less pulmonary dysfunction, quicker recovery, and shorter hospital stay. These advantages are regularly emphasized and explain the increasing success of laparoscopy, which is now proposed for many surgical procedures. Intraoperative cardiorespiratory changes occur during pneumoperitoneum. Pa co_2 increases due to CO_2 absorption from the peritoneal cavity. In compromised patients, cardiorespiratory disturbances aggravate this increase in Pa co_2 . Hemodynamic changes are accentuated in high-risk cardiac patients. Improved knowledge of the pathophysiologic hemodynamic changes in healthy patients allows for successful anesthetic management of cardiac patients, by optimizing preload before pneumoperitoneum and through judicious use of vasodilating agents. Alternative insufflating gases (He, Ar, N_2O) do not seem to reduce the hemodynamic changes. Gasless laparoscopy may be more helpful, but unfortunately increases technical difficulty. The incidence of complications has now been reported in several large surveys and compares favorably to that of open surgery. The death rate during operative laparoscopy is approximately 0.1 to 1 per 1,000 cases; the incidence of both hemorrhagic complications and visceral injury is 2 to 5 per 1,000 cases. Whereas no anesthetic technique has proved to be clinically superior to any other, general anesthesia with controlled ventilation seems to be the safest technique for operative laparoscopy. Improved knowledge of the intraoperative repercussions of laparoscopy permits safe management of patients with more and more severe cardiorespiratory disease, who may subsequently benefit from the multiple postoperative advantages offered by this approach.

References

1. Dubois F, Icard P, Berthelot G, Levard H: Coelioscopic cholecystectomy. Ann Surg 211:60, 1990.

2. Grace PA, Quereshi A, Colenian J et al: Reduced postoperative hospitalization after laparoscopic cholecystectomy. Br J Surg 78:160, 1991.

3. Joris J, Cigarini I, Legrand M et al: Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. Br J Anaesth 69:341, 1992.

4. Bernheim BM: Organoscopy: Cystoscopy of the abdominal cavity. Arch Surg 53:764, 1911.

5. Bardoczky GI, Engelman E, Levarlet M et al: Ventilatory effects of pneumoperitoneum monitored with continuous spirometry. Anaesthesia 48:309, 1993.

6. Hirvonen EA, Nuutinen LS, Kauko M: Ventilatory effects, blood gas changes, and oxygen consumption during laparoscopic hysterectomy. Anesth Analg 80:961, 1995.

7. Kendall AP, Bhatt S, Oh TE: Pulmonary consequences of carbon dioxide insufflation for laparoscopic cholecystectomies. Anaesthesia 50:286, 1995.

8. Obeid F, Saba A, Fath J et al: Increases in intra-abdominal pressure affect pulmonary compliance. Arch Surg 130:544, 1995.

9. Oikkonen M, Tallgren M: Changes in respiratory compliance at laparoscopy: Measurements using side stream spirometry. Can J Anaesth 42:495, 1995.

10. Fahy BG, Barnas GM, Flowers JL et al: The effects of increased abdominal pressure on lung and chest wall mechanics during laparoscopic surgery. Anesth Analg 81:744, 1995.

11. Fahy BG, Barnas GM, Nagle SE et al: Changes in lung and chest wall properties with abdominal insufflation of carbon dioxide are immediately reversible. Anesth Analg 82:501, 1996.

12. Yasinski P, Joris J, Desaive C et al: Respiratory changes during CO_2 -pneumoperitoneum in morbidly obese patients. Acta Anaesthesiol Belg 46:P189, 1995.

13. Fox LG, Hein HAT, Gawey BJ et al: Physiologic alterations during laparoscopic cholecystectomy in ASA III-IV patients. Anesthesiology 79 (suppl 3A):A55, 1993.

14. Feinstein R, Ghouri A: Changes in pulmonary mechanics during laparoscopic cholecystectomy. Anesth Analg 76 (suppl 2S):S102, 1993.

15. Grissom TE, Gootos PJ, Brown TER: Pulmonary compliance is not affected by changes in position during laparoscopic surgery. Anesthesiology 79 (suppl 3A):A491, 1993.

16. Wahba RW, Tessler MJ, Kleiman SJ: Acute ventilatory complications during laparoscopic upper abdominal surgery. Can J Anaesth 43:77, 1996.

17. Mutoh T, Lamm WJE, Embree LJ et al: Volume infusion produces abdominal distension, lung compression, and chest wall stiffening in pigs. J Appl Physiol 72:575, 1992.

---

18. Tan PL, Lee TL, Tweed WA: Carbon dioxide absorption and gas exchange during pelvic laparoscopy. Can J Anaesth 39:677, 1992.

19. Joris J, Honore P, Lamy M: Changes in oxygen transport and ventilation during laparoscopic cholecystectomy. Anesthesiology 77 (suppl 3A):A149, 1992.

20. Bures E, Fusciardi J, Lanquetot H et al: Ventilatory effects of laparoscopic cholecystectomy. Acta Anaesthesiol Scand 40:566, 1996.

21. Odeberg-Wernerman S, Sollevi A: Cardiopulmonary aspects of laparoscopic surgery. Curr Opin Anaesthesiol 9:529, 1996.

22. Schoeffler P, Haberer JP, Manhes H et al: Repercussions circulatoires et ventilatoires de la coelioscopie chez l'obese. Ann Fr Anesth Reanim 3:10, 1984.

23. Mullet CE, Viale JP, Sagnard PE et al: Pulmonary CO_2 elimination during surgical procedures using intra- or extraperitoneal CO_2 insufflation. Anesth Analg 76:622, 1993.

24. Baraka A, Jabbour S, Hammoud R et al: End-tidal carbon dioxide tension during laparoscopic cholecystectomy. Anaesthesia 49:304, 1994.

25. Nyarwaya JB, Mazoit JX, Samii K: Are pulse oximetry and end-tidal carbon dioxide tension monitoring reliable during laparoscopic surgery? Anaesthesia 49:775, 1994.

26. Ivankovich AD, Miletich DJ, Albrecht RF et al: Cardiovascular effects of intraperitoneal insufflation with carbon dioxide and nitrous oxide in the dog. Anesthesiology 42:281, 1975.

27. Lister DR, Rudston-Brown B, Warriner CB et al: Carbon dioxide absorption is not linearly related to intraperitoneal carbon dioxide insufflation pressure in pigs. Anesthesiology 80:129, 1994.

28. Brown DR, Fishburne JI, Roberson VO et al: Ventilatory and blood gas changes during laparoscopy with local anesthesia. Am J Obstet Gynecol 124:741, 1976.

29. Ciofolo MJ, Clergue F, Seebacher J et al: Ventilatory effects of laparoscopy under epidural anesthesia. Anesth Analg 70:357, 1990.

30. Hodgson C, McClelland RMA, Newton JR: Some effects of the peritoneal insufflation of carbon dioxide at laparoscopy. Anaesthesia 25:382, 1970.

31. Lewis DG, Ryder W, Burn N et al: Laparoscopy--an investigation during spontaneous ventilation with halothane. Br J Anaesth 44:685, 1972.

32. Kenefick JP, Leader A, Maltby JR et al: Laparoscopy: Blood-gas values and minor sequelae associated with three techniques based on isoflurane. Br J Anaesth 59:189, 1987.

33. Vegfors M, Engborg L, Gupta A, Lennmarken C: Changes in end-tidal carbon dioxide during gynecologic laparoscopy: Spontaneous versus controlled ventilation. J Clin Anesth 6:199, 1994.

34. Brampton WJ, Watson RJ: Arterial to end-tidal carbon dioxide tension difference during laparoscopy. Magnitude and effect of anaesthetic technique. Anaesthesia 45:210, 1990.

35. McMahon AJ, Baxter JN, Kenny G et al: Ventilatory and blood gas changes during laparoscopic and open cholecystectomy. Br J Surg 80:1252, 1993.

36. Wahba RMW, Mamazza J: Ventilatory requirements during laparoscopic cholecystectomy. Can J Anaesth 40:206, 1993.

37. Wittgen CM, Andrus CH, Fitzgerald SD et al: Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. Arch Surg 126:997, 1991.

38. Wittgen CM, Naunheim KS, Andrus CH et al: Preoperative pulmonary function evaluation for laparoscopic cholecystectomy. Arch Surg 128:880, 1993.

39. Fitzgerald SD, Andrus CH, Baudendistel LJ et al: Hypercarbia during carbon dioxide pneumoperitoneum. Am J Surg 163:186, 1992.

40. Tolksdorf W, Strang CM, Schippers E et al: Die Auswirkungen des Kohlendioxid-pneumoperitoneums zur laparoskopischen Cholezystektomie auf die postoperative Spontanatmung. Anaesthetist 41:199, 1992.

41. Magno R, Medegard A, Bengtsson R et al: Acid-base balance during laparoscopy. Acta Obstet Gynecol Scand 58:81, 1979.

42. Bongard FS, Pianim NA, Leighton TA et al: Helium insufflation for laparoscopic operation. Surg Gynecol Obstet 177:140, 1993.

43. McMahon AJ, Baxter JN, Murray W et al: Helium pneumoperitoneum for laparoscopic cholecystectomy: Ventilatory and blood gas changes. Br J Surg 81:1033, 1994.

44. Rademaker BMP, Odoom JA, de Wit LT et al: Haemodynamic effects of pneumoperitoneum for laparoscopic surgery: A comparison of CO_2 with N_2O insufflation. Eur J Anaesthesiol 11:301, 1994.

45. Rademaker BM, Bannenberg JJ, Kalkman CJ et al: Effects of pneumoperitoneum with helium on hemodynamics and oxygen transport: A comparison with carbon dioxide. J Laparoendosc Surg 5:15, 1995.

46. Puri GD, Singh H: Ventilatory effects of laparoscopy under general anaesthesia. Br J Anaesth 68:211, 1992.

47. Blobner M, Felber A, Gogler S et al: Zur Resorption von CO_2 aus dem Pneumoperitoneum bei laparoskopischen Cholezystektomien. Anaesthetist 42:288, 1993.

48. Wurst H, Schulte-Steinberg H, Finsterer U: Pulmonale CO_2 -Elimination bei laparoskopischer Cholezystektomie. Anaesthetist 42:427, 1993.

49. Chiche JD, Joris J, Lamy M: Clonidine decreases VCO_2 during laparoscopic fundoplication. Anesthesiology 81 (suppl 3A):A105, 1994.

50. Kazama T, Ikeda K, Kato T, Kikura M: Carbon dioxide output in laparoscopic cholecystectomy. Br J Anaesth 76:530, 1996.

51. Nunn JF: Applied respiratory physiology, 4th ed. London, Butterworths Heinemann, 1993.

52. Wilcox S, Vandam LD: Alas, poor Trendelenburg and his position. Anesth Analg 67:574, 1988.

53. Alexander GD, Noe FE, Brown EM: Anesthesia for pelvic laparoscopy. Anesth Analg 48:14, 1969.

54. Hickling KG, Henderson SJ, Jackson R: Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372, 1990.

55. Hall D, Goldstein A, Tynan E et al: Profound hypercarbia late in the course of laparoscopic cholecystectomy: Detection by continuous capnometry. Anesthesiology 79:173, 1993.

56. Wright DM, Serpell MG, Baxter JN et al: Effect of extraperitoneal carbon dioxide insufflation on intraoperative blood gas and hemodynamic changes. Surg Endosc 9:1169, 1995.

57. Chien GL, Soifer BE: Pharyngeal emphysema with airway obstruction as a consequence of laparoscopic inguinal herniorrhaphy. Anesth Analg 80:201, 1995.

58. Spielman FJ: Laparoscopic surgery. In Kirby DD, Hood RR, Brown DL (eds): Problems in Anesthesia: Anesthesia in Obstetrics and Gynecology. Philadelphia, JB Lippincott, 1989, p 151.

59. Doctor NH, Hussain Z: Bilateral pneumothorax associated with laparoscopy: A case report of a rare hazard and review of literature. Anaesthesia 28:75, 1973.

60. Batra MS, Driscoll JJ, Coburn WA, Marks WM: Evanescent nitrous oxide pneumothorax after laparoscopy. Anesth Analg 62:1121, 1983.

61. Whiston RJ, Eggers KA, Morris RW, Stamatakis JD: Tension pneumothorax during laparoscopic cholecystectomy. Br J Surg 78:1325, 1991.

62. Nicholson RD, Berman ND: Pneumopericardium following laparoscopy. Chest 76:605, 1979.

63. Knos GB, Sung YF, Toledo A: Pneumopericardium associated with laparoscopy. J Clin Anesth 3:56, 1991.

64. McConnell MS, Finn JC, Feeley TW: Tension hydrothorax during laparoscopy in a patient with ascites. Anesthesiology 80:1390, 1994.

65. Joris J, Chiche JD, Lamy M: Pneumothorax during laparoscopic fundoplication: Diagnosis and treatment with positive end-expiratory pressure. Anesth Analg 81:993, 1995.

66. Inada T, Uesugi F, Kawachi S, Takubo K: Changes in tracheal tube position during laparoscopic cholecystectomy. Anaesthesia 51:823, 1996.

67. Burton A, Steinbrook R: Precipitous decrease in oxygen saturation during laparoscopic surgery. Anesth Analg 76:1177, 1993.

68. Chen P, Chiu P: Endobronchial intubation during laparoscopic cholecystectomy. Anaesth Intensive Care 20:537, 1992.

69. Brimacombe O, Orland H, Graham D: Endobronchial intubation during upper abdominal laparoscopic surgery in the reverse Trendelenburg position. Anesth Analg 78:607, 1997.

70. Morimura N, Inoue K, Miwa T: Chest roentgenogram demonstrates cephalad movement of the carina during laparoscopic cholecystectomy. Anesthesiology 81:1301, 1994.

71. Philips J, Keith D, Hulka J et al: Gynecologic laparoscopy in 1975. J Reprod Med 16:105, 1976.

72. Diakun TA: Carbon dioxide embolism: Successful resuscitation with cardiopulmonary bypass. Anesthesiology 74:1151, 1991.

73. Gomar C, Fernandez C, Villalonga A et al: Carbon dioxide embolism during laparoscopy and hysteroscopy. Ann Fr Anesth Reanim 4:380, 1985.

74. Morison SL, Riggs JRA: Cardiovascular collapse in laparoscopy. Can Med Assoc J 111:433, 1974.

75. Shulman D, Aronson HB: Capnography in the early diagnosis of carbon dioxide embolism during laparoscopy. Can Anaesth Soc J 31:455, 1984.

76. De Plater RMH, Jones ISC: Non-fatal carbon dioxide embolism during laparoscopy. Anaesth Intensive Care 17:359, 1989.

77. Ostman PL, Pantle-Fisher FH, Faure EA et al: Circulatory collapse during laparoscopy. J Clin Anesth 2:129, 1990.

78. Cottin V, Delafosse B, Viale JP: Gas embolism during laparoscopy: A report of seven cases in patients with previous abdominal surgical history. Surg Endosc 10:166, 1996.

79. Graff TD, Arbegast NR, Phillips OC et al: Gas embolism, a comparative study of air and carbon dioxide as embolic agents in the systemic venous system. Am J Obstet Gynecol 78:259, 1959.

80. Brantley JC, Riley PM: Cardiovascular collapse during laparoscopy: A report of two cases. Am J Obstet Gynecol 159:735, 1988.

81. Greville AC, Clements AF, Erwin DC et al: Pulmonary air embolism during laparoscopic laser cholecystectomy. Anaesthesia 46:113, 1991.

82. Root B, Levy MN, Pollack S et al: Gas embolism death after laparoscopy delayed by trapping in the portal circulation. Anesth Analg 57:232, 1978.

83. Couture P, Boudreault D, Derouin M et al: Venous carbon dioxide embolism in pigs: An evaluation of end-tidal carbon dioxide, transesophageal echocardiography, pulmonary artery pressure, and precordial auscultation as monitoring modalities. Anesth Analg 79:867, 1994.

84. Nyarwaya JB, Pierre S, Mazoit JX et al: Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets. Br J Anaesth 76:428, 1996.

85. Hagen PT, Scholz FDG, Edwards WD: Incidence and size of patent foramen ovale during the first 10 decades of life: An autopsy study of 965 normal hearts. Mayo Clin Proc 59:17, 1984.

86. McGrath BJ, Zimmerman JE, Williams JF et al: Carbon dioxide embolism treated with hyperbaric oxygen. Can J Anaesth 36:586, 1989.

87. Butler BD, Hills BA: Transpulmonary passage of venous air emboli. J Appl Physiol 59:543, 1985.

88. Albin MS, Ritter RR, Pruett CE, Kalff K: Venous air embolism during lumbar laminectomy in the prone position: Report of three cases. Anesth Analg 7:346, 1991.

89. Khan MA, Alkalay I, Suetsugu S et al: Acute changes in lung mechanisms following pulmonary emboli of various gases in dogs. J Appl Physiol 33:774, 1972.

90. English JB, Westenskow D, Hodges MR et al: Comparison of venous air embolism monitoring methods in supine dog. J Appl Physiol 48:425, 1978.

91. Desai S, Roaf E, Liu P: Acute pulmonary edema during laparoscopy. Anesth Analg 61:699, 1982.

92. Michenfelder JD, Miller RH, Gronert GA: Evaluation of an ultrasonic device (Doppler) for the diagnosis of venous air embolism. Anesthesiology 36:164, 1972.

93. Martin RW, Colley PS: Evaluation of transesophageal Doppler detection of air embolism in dogs. Anesthesiology 58:117, 1983.

94. Marshall WK, Bedford RF: Use of a pulmonary-artery catheter for detection and treatment of venous air embolism: A prospective study in man. Anesthesiology 52:131, 1980.

95. Yacoub OF, Cadona I, Coveler LA et al: Carbon dioxide embolism during laparoscopy. Anesthesiology 57:533, 1982.

96. Wadhwa RK, McKenzie R, Wadhwa SR et al: Gas embolism during laparoscopy. Anesthesiology 48:74, 1989.

97. Perry PM, Baughman VL: A complication of hysteroscopy: Air embolism. Anesthesiology 73:546, 1990.

98. Schroder TM, Puolakkainen PA, Hahl H et al: Fatal air embolism as a complication of laser-induced hyperthermia. Lasers Surg Med 9:183, 1989.

99. Baggish MS, Daniell JF: Catastrophic injury secondary to the use of coaxial gas-cooled fibers and artificial sapphire tips for intrauterine surgery: A report of five cases. Lasers Surg Med 9:581, 1989.

100. Tay HS, Chiu HH: Acid aspiration during laparoscopy. Anaesth Intensive Care 6:134, 1978.

101. Duffy BL: Regurgitation during pelvic laparoscopy. Br J Anaesth 51:1089, 1979.

102. Jones MJ, Mitchell RW, Hindocha N: Effect of increased intra-abdominal pressure during laparoscopy on the lower esophageal sphincter. Anesth Analg 68:63, 1989.

103. Halevy A, Kais H, Efrati Y et al: Continuous esophageal pH monitoring during laparoscopic cholecystectomy. Surg Endosc 8:1294, 1994.

104. Wahba RWM, Beique F, Kleiman SJ: Cardiopulmonary function and laparoscopic cholecystectomy. Can J Anaesth 42:51, 1995.

105. Sharma KC, Brandstetter RD, Brensilver JM et al: Cardiopulmonary physiology and pathophysiology as a consequence of laparoscopic surgery. Chest 110:810, 1996.

106. Safran DB, Orlando R: Physiologic effects of pneumoperitoneum. Am J Surg 167:281, 1994.

107. Richardson JD, Trinkle JK: Hemodynamic and respiratory alterations with increased intraabdominal pressure. J Surg Res 20:401, 1976.

108. Kelman GR, Swapp GH, Smith I et al: Cardiac output and arterial blood gas tension during laparoscopy. Br J Anaesth 44:1155, 1972.

109. Versichelen L, Serreyn R, Rolly G et al: Physiopathologic changes during anesthesia administration for gynecologic laparoscopy. J Reprod Med 29:697, 1984.

110. Odeberg S, Ljungqvist O, Svenberg T et al: Haemodynamic effects of pneumoperitoneum and the influence of posture during anaesthesia for laparoscopic surgery. Acta Anaesthesiol Scand 38:276, 1994.

111. Gannedahl P, Odeberg S, Brodin L-A et al: Effects of posture and pneumoperitoneum during anaesthesia on the indices of left ventricular filling. Acta Anaesthesiol Scand 40:160, 1996.

112. Johannsen G, Andersen M, Juhl B: The effect of general anaesthesia on the haemodynamic events during laparoscopy with CO_2 insufflation. Acta Anaesthesiol Scand 33:132, 1989.

113. Torrielli R, Cesarini M, Winnock S et al: Modifications hemodynamiques durant la coelioscopie: Etude menee par bioimpedance electrique thoracique. Can J Anaesth 37:46, 1990.

114. Hirvonen EA, Nuutinen LS, Vuolteenaho O: Hormonal responses and cardiac filling pressures in head-up or head-down position and pneumoperitoneum in patients undergoing operative laparoscopy. Br J Anaesth 78:128, 1997.

115. Joris JL, Noirot DP, Legrand MJ et al: Hemodynamic changes during laparoscopic cholecystectomy. Anesth Analg 76:1067, 1993.

116. Walder AD, Aitkenhead AR: Role of vasopressin in the haemodynamic response to laparoscopic cholecystectomy. Br J Anaesth 78:264, 1997.

117. Muchada R, Lavandier B, Cathignol D et al: Surveillance hemodynamique non-invasive dans la coelioscopie gynecologique. Ann Fr Anesth Reanim 5:14, 1986.

118. McLaughlin JG, Scheeres DE, Dean RJ et al: The adverse hemodynamic effects of laparoscopic cholecystectomy. Surg Endosc 9:121, 1995.

119. Dorsay DA, Greene FL, Baysinger CL: Hemodynamic changes during laparoscopic cholecystectomy monitored with transesophageal echocardiography. Surg Endosc 9:128, 1995.

120. Rubinson RM, Vasko JS, Doppman JL et al: Inferior vena canal obstruction from increased intra-abdominal pressure. Arch Surg 94:766, 1967.

121. Kashtan J, Green JF, Parsons EQ et al: Hemodynamic effects of increased abdominal pressure. J Surg Res 30:249, 1981.

122. Takata M, Wise RA, Robotham JL: Effects of abdominal pressure on venous return: Abdominal vascular zone conditions. J Appl Physiol 69:1961, 1990.

123. Goodale RL, Beebe DS, McNevin MP et al: Hemodynamic, respiratory, and metabolic effects of laparoscopic cholecystectomy. Am J Surg 166:533, 1993.

124. Diamant M, Benumof JL, Saidman LJ: Hemodynamics of increased intra-abdominal pressure: Interaction with hypovolemia and halothane anesthesia. Anesthesiology 48:23, 1978.

125. Solis-Herruzo JA, Moreno D, Gonzalez A et al: Effect of intrathoracic pressure on plasma arginine vasopressin levels. Gastroenterology 101:607, 1991.

126. Ho HS, Saunders CJ, Corso FA et al: The effects of CO_2 pneumoperitoneum on hemodynamics in hemorrhaged animals. Surgery 114:381, 1993.

127. Cunningham AJ, Turner J, Rosenbaum S et al: Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy. Br J Anaesth 70:621, 1993.

128. Harris SN, Ballantyne GH, Luther MA et al: Alterations of cardiovascular performance during laparoscopic colectomy: A combined hemodynamic and echocardiographic analysis. Anesth Analg 83:482, 1996.

129. Hirvonen EA, Nuutinen LS, Kauko M: Hemodynamic changes due to Trendelenburg positioning and pneumoperitoneum during laparoscopic hysterectomy. Acta Anaesthesiol Scand 39:949, 1995.

130. Feig BW, Berger DH, Dougherty TB et al: Pharmacologic intervention can reestablish baseline hemodynamic parameters during laparoscopy. Surgery 116:733, 1994.

131. Duale C, Bazin JE, Ferrier C et al: Hemodynamic effects of laparoscopic

cholecystectomy in patients with coronary disease. Br J Anaesth 72 (suppl S1):A31, 1994.

132. Le Roith D, Barn H, Nyska M et al: The effect of abdominal pressure on plasma antidiuretic hormone levels in the dog. J Surg Res 32:65, 1982.

133. Punnonen R, Viinamaki O: Vasopressin release during laparoscopy: Role of increased intra-abdominal pressure. Lancet 1:175, 1982.

134. Joris JL, Chiche JD, Canivet JL et al: Hemodynamic changes induced by laparoscopy and their endocrine correlates: Effects of clonidine. J Am Coll Cardiol 32:1389, 1998.

135. O'Leary E, Hubbard K, Tormey W, Cunningham AJ: Laparoscopic cholecystectomy: Haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. Br J Anaesth 76:640, 1996.

136. Melville RL, Forsling ML, Frizis HI et al: Stimulus for vasopressin release during elective intra-abdominal operations. Br J Surg 72:979, 1985.

137. Longhurst JC, Spilker HL, Ordway GA: Cardiovascular reflexes elicited by passive gastric distension in anesthetized cats. Am J Physiol 240:H539, 1981.

138. Aho M, Lehtinen AM, Laatikainen T et al: Effects of intramuscular clonidine on hemodynamic and plasma beta-endorphin responses to gynecologic laparoscopy. Anesthesiology 72:797, 1990.

139. Aho M, Scheinin M, Lehtinen AM et al: Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. Anesth Analg 75:932, 1992.

140. Joris J, Chiche JD, Lamy M: Clonidine reduces the hemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. Br J Anaesth 74 (suppl S1):A124, 1995.

141. Jorgensen JO, Lalak NJ, North L et al: Venous stasis during laparoscopic cholecystectomy. Surg Laparosc Endosc 2:128, 1994.

142. Jorgensen JO, Gillies RB, Lalak NJ et al: Lower limb venous hemodynamics during laparoscopy: An animal study. Surg Laparosc Endosc 4:32, 1994.

143. Caprini JA, Arcelus JI: Prevention of postoperative venous thromboembolism following laparoscopic cholecystectomy. Surg Endosc 8:741, 1994.

144. Mayol J, Vincent-Hamelin E, Sarmiento JM et al: Pulmonary embolism following laparoscopic cholecystectomy: Report of two cases and review of the literature. Surg Endosc 8:214, 1994.

145. Iwase K, Takenaka H, Ishizaka T et al: Serial changes in renal function during laparoscopic cholecystectomy. Eur Surg Res 25:203, 1993.

146. Hashikura Y, Kawasaki S, Munakata Y et al: Effects of peritoneal insufflation on hepatic and renal blood flow. Surg Endosc 8:759, 1994.

147. Kubota K, Kajiura N, Teruya M et al: Alterations in respiratory function and hemodynamics during laparoscopic cholecystectomy under pneumoperitoneum. Surg Endosc 7:500, 1993.

148. Chiu AW, Azadzoi KM, Hatzichristou DG et al: Effects of intra-abdominal pressure on renal tissue perfusion during laparoscopy. J Endourol 8:99, 1994.

149. Diebel LN, Dulchavsky SA, Wilson RF: Effect of increased intra-abdominal pressure on mesenteric arterial and intestinal mucosal blood flow. J Trauma 33:45, 1992.

150. Ishizaki Y, Bandai Y, Shimomura K et al: Safe intraabdominal pressure of carbon dioxide pneumoperitoneum during laparoscopic surgery. Surgery 114:549, 1993.

151. Koivusalo A-M, Kellokumpu I, Ristkari S et al: Splanchnic and renal deterioration during and after laparoscopic cholecystectomy: A comparison of the carbon dioxide pneumoperitoneum and the abdominal wall lift method. Anesth Analg 85:886, 1997.

152. Chiche JD, Hamoir E, Joris J et al: CO_2 -pneumoperitoneum induces a transient alteration of splanchnic haemodynamics. Br J Anaesth 74 (suppl S1):A126, 1995.

153. Blobner M, Bogdanski R, Kochs E et al: Effects of intraabdominally insufflated carbon dioxide and elevated intraabdominal pressure on splanchnic circulation: An experimental study in pigs. Anesthesiology 89:475, 1998.

154. Odeberg S, Ljungqvist O, Sollevi A: Pneumoperitoneum for laparoscopic surgery and splanchnic circulation in man. Anesthesiology 83 (suppl 3A):A73, 1995.

155. Thaler W, Frey L, Marzoli GP et al: Assessment of splanchnic tissue oxygenation by gastric tonometry in patients undergoing laparoscopic and open cholecystectomy. Br J Surg 83:620, 1996.

156. Paul A, Troidl H, Peters S, Stuttmann R: Fatal intestinal ischaemia following laparoscopic cholecystectomy. Br J Surg 81:1207, 1994.

157. Dwerryhouse SJ, Melsom DS, Burton PA et al: Acute intestinal ischaemia after laparoscopic cholecystectomy. Br J Surg 82:1413, 1995.

158. Fujii Y, Tanaka H, Tsuruoka S et al: Middle cerebral arterial blood flow velocity increases during laparoscopic cholecystectomy. Anesth Analg 78:80, 1994.

159. Kirkinen P, Hirvonen E, Kauko M et al: Intracranial blood flow during laparoscopic hysterectomy. Acta Obstet Gynecol Scand 74:71, 1995.

160. Josephs LG, Este-McDonald JR, Birkett DH, Hirsch EF: Diagnostic laparoscopy increases intracranial pressure. J Trauma 36:815, 1994.

161. Rosenthal RJ, Hiatt JR, Phillips EH et al: Intracranial pressure. Effects of pneumoperitoneum in a large-animal model. Surg Endosc 11:376, 1997.

162. Uzzo RG, Bilsky M, Mininberg DT et al: Laparoscopic surgery in children with ventriculoperitoneal shunts: Effect of pneumoperitoneum on intracranial pressure--preliminary experience. Urology 49:753, 1997.

163. Lentschener C, Benhamou D, Niessen F et al: Intra-ocular pressure changes during gynaecological laparoscopy. Anaesthesia 51:1106, 1996.

164. Lentschener C, Levecque JP, Mazoit JX et al: Pneumoperitoneum up to 15 mmHg does not adversely affect intraocular pressure in rabbits with alpha-chymotrypsin induced glaucoma.

Anesthesiology 87 (suppl 3A):A510, 1997.

165. Safran D, Sgambati S, Orlando R: Laparoscopy in high-risk cardiac patients. Surg Gynecol Obstet 176:548, 1993.

166. Iwase K, Takenaka H, Yagura A et al: Hemodynamic changes during laparoscopic cholecystectomy in patients with heart disease. Endoscopy 24:771, 1992.

167. Hein HA, Joshi GP, Ramsay MA et al: Hemodynamic changes during laparoscopic cholecystectomy in patients with severe cardiac disease. J Clin Anesth 9:261, 1997.

168. Portera CA, Compton RP, Walters DN et al: Benefits of pulmonary artery catheter and transesophageal echocardiographic monitoring in laparoscopic cholecystectomy patients with cardiac disease. Am J Surg 169:202, 1995.

169. Pepine CL, Lambert CR: Cardiovascular effects of nicardipine. Angiology 41:978, 1990.

170. Aroney CN, Semigran MJ, Dec GW et al: Inotropic effect of nicardipine in patients with heart failure: Assessment by left ventricular end-systolic pressure-volume analysis. J Am Coll Cardiol 14:1331, 1989.

171. Burlew BS, Gheorghiade M, Jafri SM et al: Acute and chronic hemodynamic effects of nicardipine hydrochloride in patients with heart failure. Am Heart J 114:793, 1987.

172. Dhoste K, Lacoste L, Karayan J et al: Haemodynamic and ventilatory changes during laparoscopic cholecystectomy in elderly ASA III patients. Can J Anaesth 43:783, 1996.

173. Joshi GP, Tillmann Hein HA, Ramsay MAE et al: Hemodynamic response to anesthesia and pneumoperitoneum in orthotopic cardiac transplant recipients. Anesthesiology 85:929, 1996.

174. Levecque JP, Benhamou D, Zetlaoui P et al: Laparoscopic cholecystectomy in a patient with a transplanted heart. Anesthesiology 86:1425, 1997.

175. Joris J, Hamoir E, Hartstein G et al: Anesthetic management of laparoscopic adrenalectomy for pheochromocytoma using nicardipine infusion. Anesth Analg 88:16, 1999.

176. Scott DB, Julian D: Observations on cardiac arrhythmias during laparoscopy. Br Med J 1:411, 1972.

177. Desmond J, Gordon RA: Ventilation in patients anaesthetized for laparoscopy. Can Anaesth Soc J 17:378, 1970.

178. Sibbald WJ, Paterson NAM, Holliday RL et al: The Trendelenburg position: Hemodynamic effects in hypotensive and normotensive patients. Crit Care Med 7:218, 1979.

179. Lumb AB, Nunn JF: Respiratory function and ribcage contribution to ventilation in body position commonly used during anesthesia. Anesth Analg 73:422, 1991.

180. Johnston RV, Lawson NW, Nealon WH: Lower extremity neuropathy after laparoscopic cholecystectomy. Anesthesiology 77:835, 1992.

181. Gombar KK, Gombar S, Singh B et al: Femoral neuropathy: A complication of the lithotomy position. Reg Anesth 17:306, 1992.

182. Lydon JC, Spielman FJ: Bilateral compartment syndrome following prolonged surgery in the lithotomy position. Anesthesiology 60:236, 1984.

183. Montgomery CJ, Ready LB: Epidural opioid analgesia does not obscure diagnosis of compartment syndrome resulting from prolonged lithotomy position. Anesthesiology 75:541, 1991.

184. Delaunay L, Bonnet F, Cherqui D et al: Laparoscopic cholecystectomy minimally impairs postoperative cardiorespiratory and muscle performance. Br J Surg 82:373, 1995.

185. Jakeways MSR, Mitchell V, Hashim IA et al: Metabolic and inflammatory responses after open or laparoscopic cholecystectomy. Br J Surg 81:127, 1994.

186. Mealy K, Gallagher H, Barry M et al: Physiological and metabolic responses to open and laparoscopic cholecystectomy. Br J Surg 79:1061, 1992.

187. Karayiannakis AJ, Makri GG, Mantzioka A et al: Systemic stress response after laparoscopic or open cholecystectomy: A randomized trial. Br J Surg 84:467, 1997.

188. Targarona EM, Pons MJ, Balague C et al: Acute phase is the only significantly reduced component of the injury response after laparoscopic cholecystectomy. World J Surg 20:528, 1996.

189. Bessler M, Whelan RL, Halverson A et al: Is immune function better preserved after laparoscopic versus open colon resection? Surg Endosc 8:881, 1994.

190. Trokel MJ, Bessler M, Treat MR et al: Preservation of immune response after laparoscopy. Surg Endosc 8:1385, 1994.

191. Glerup H, Heindorff H, Flyvbjerg A et al: Elective laparoscopic cholecystectomy nearly abolishes the postoperative hepatic catabolic stress response. Ann Surg 221:214, 1995.

192. Senagore AJ, Kilbride MJ, Luchtefeld MA et al: Superior nitrogen balance after laparoscopic-assisted colectomy. Ann Surg 221:171, 1995.

193. McAnema OJ, Austin O, Hederman WP et al: Laparoscopic versus open appendicectomy. Lancet 338:693, 1991.

194. Hotokezata M, Combs MJ, Mentis EP et al: Recovery of fasted and fed gastrointestinal motility after open versus laparoscopic cholecystectomy in dogs. Ann Surg 223:413, 1996.

195. McMahon AJ, Russel IT, Baxter JN et al: Laparoscopic versus minilaparotomy cholecystectomy: A randomised trial. Lancet 343:135, 1994.

196. Kane RL, Lurie N, Borbas C et al: The outcomes of elective laparoscopic and open cholecystectomies. J Am Coll Surg 180:136, 1995.

197. McLauchlan GJ, Macintyre IMC: Return to work after laparoscopic cholecystectomy. Br J Surg 82:239, 1995.

198. Rademaker BM, Ringers J, Odoom JA et al: Pulmonary function and stress response after laparoscopic cholecystectomy: A comparison with subcostal incision and influence of thoracic epidural analgesia. Anesth Analg 75:381, 1992.

199. Donald RA, Perry EG, Wittert GA et al: The plasma ACTH, AVP, CRH and catecholamine responses to conventional and laparoscopic cholecystectomy. Clin Endocrinol 38:609, 1993.

200. Putensen-Himmer G, Putensen C, Lammer H et al: Comparison of postoperative respiratory function after laparoscopy or open laparotomy for cholecystectomy. Anesthesiology 77:675, 1992.

201. McMahon AJ, Russell IT, Ramsay G et al: Laparoscopic and minilap-arotomy cholecystectomy: A randomized trial comparing postoperative pain and pulmonary function. Surgery 115:533, 1994.

202. Calhoun PC, Adams LH, Adams MR: Comparison of laparoscopic and minilap cholecystectomy for acute cholecystitis. Surg Endosc 8:1301, 1994.

203. Wiesel S, Grillas R: Patient-controlled analgesia after laparoscopic and open cholecystectomy. Can J Anaesth 42:37, 1995.

204. Joris J, Hinque VL, Laurent PE et al: Pulmonary function and pain after gastroplasty performed via laparotomy or laparoscopy in morbidly obese patients. Br J Anaesth 80:283, 1998.

205. Bardram L, Funch-Jensen P, Crawford ME et al: Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet 345:763, 1995.

206. Callesen T, Kehlet H: Postherniorrhaphy pain. Anesthesiology 87:1219, 1997.

207. Ure BM, Troidl H, Spangenberger W et al: Pain after laparoscopic cholecystectomy. Intensity and localization of pain and analysis of predictors in preoperative symptoms and intraoperative

events. Surg Endosc 8:90, 1994.

208. Joris J, Thiry E, Paris P et al: Pain after laparoscopic cholecystectomy: Characteristics and effect of intraperitoneal bupivacaine. Anesth Analg 81:379, 1995.

209. Collins KM, Docherty PW, Plantevin OM: Postoperative morbidity following gynaecological outpatient laparoscopy. A reappraisal of the service. Anaesthesia 39:819, 1984.

210. Sharp JR, Pierson WP, Brady CE: Comparison of CO_2 - and NO_2 -induced discomfort during peritoneoscopy under local anesthesia. Gastroenterology 82:453, 1982.

211. Koetsawang S, Srisupandit S, Apimas SJ et al: A comparison study of topical anesthesia for laparoscopic sterilization with the use of the tubal ring. Am J Obstet Gynecol 150:931, 1984.

212. McKenzie R, Phitayakorn P, Uy NTL et al: Topical etidocaine during laparoscopic tubal occlusion for postoperative pain relief. Obstet Gynecol 67:447, 1986.

213. Alexander CD, Wetchler VB, Thompson RE: Bupivacaine infiltration of the mesosalpinx in ambulatory surgical laparoscopic tubal sterilization. Can J Anaesth 34:362, 1987.

214. Narchi P, Benhamou D, Fernandez H: Intraperitoneal local anaesthetic for shoulder pain after day case laparoscopy. Lancet 338:1569, 1991.

215. Loughney AD, Sarma V, Ryall A: Intraperitoneal bupivacaine for the relief of pain following day case laparoscopy. Br J Obstet Gynaecol 101:449, 1994.

216. Rademaker BMP, Kalkman CJ, Odoom JA et al: Intraperitoneal local anaesthetics after laparoscopic cholecystectomy: Effects on postoperative pain, metabolic responses and lung function. Br J Anaesth 72:263, 1994.

217. Scheinin B, Kellokumpu I, Lindgren L et al: Effect of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 39:195, 1995.

218. Raetzell M, Maier C, Schroder D, Wulf H: Intraperitoneal application of bupivacaine during laparoscopic cholecystectomy--risk or benefit? Anesth Analg 81:967, 1995.

219. Alexander JI, Hull MGR: Abdominal pain after laparoscopy: The value of a gas drain. Br J Obstet Gynaecol 94:267, 1987.

220. Fredman B, Jedeikin R, Olsfanger D: Residual pneumoperitoneum: A cause of postoperative pain after laparoscopic cholecystectomy. Anesth Analg 79:152, 1994.

221. Shrivastav P, Nadkarni P, Craft I: Prevention of shoulder pain after laparoscopy. Lancet 339:744, 1992.

222. Smith BE, Suchak M, Siggins D et al: Rectus sheath block for diagnostic laparoscopy. Anaesthesia 43:947, 1988.

223. Comfort VK, Code WE, Rooney ME et al: Naproxen premedication reduces postoperative tubal ligation pain. Can J Anaesth 39:349, 1992.

224. Ding Y, White PF: Comparative effects of ketorolac, dezocine, and fentanyl as adjuvants during outpatient anesthesia. Anesth Analg 75:566, 1992.

225. Gillberg LE, Harsten AS, Stahl LB: Preoperative diclofenac sodium reduces postlaparoscopy pain. Can J Anaesth 40:406, 1993.

226. Van Ee R, Hemrika DJ, Van Der Linden TM: Pain relief following day-case diagnostic hysteroscopy-laparoscopy for infertility: A double-blind randomized trial with preoperative naproxen versus placebo. Obstet Gynecol 82:951, 1993.

227. Liu J, Ding Y, White PF et al: Effects of ketorolac on postoperative analgesia and ventilatory function after laparoscopic cholecystectomy. Anesth Analg 76:1061, 1993.

228. Wilson YG, Rhodes M, Ahmed R et al: Intramuscular diclofenac sodium for postoperative analgesia after laparoscopic cholecystectomy: A randomized, controlled trial. Surg Laparosc Endosc 4:340, 1994.

229. Shapiro MH, Duffy BL: Intramuscular ketorolac for postoperative analgesia following laparoscopic sterilization. Obstet Gynecol 22:22, 1994.

230. Hovorka J, Kallela H, Korttila K: Effect of intravenous diclofenac on pain and recovery profile after day-case laparoscopy. Eur J Anaesthesiol 10:105, 1993.

231. Crocker S, Peach M: Preoperative rectal indomethacin for analgesia after laparoscopic sterilisation. Anaesth Intensive Care 20:337, 1992.

232. Green CR, Pandit SK, Levy L et al: Intraoperative ketorolac has an opioid-sparing effect in women after diagnostic laparoscopy but not after laparoscopic tubal ligation. Anesth Analg 82:732, 1996.

233. Michaloliakou C, Chung F, Sharma S: Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg 82:44, 1996.

234. Mixter CG, Hackett TR: Preemptive analgesia in the laparoscopic patient. Surg Endosc 11:351, 1997.

235. Frazee R, Roberts J, Okeson G: Open versus laparoscopic cholecystectomy: A comparison of postoperative pulmonary function. Ann Surg 213:651, 1991.

236. Freeman J, Armstrong I: Pulmonary function tests before and after laparoscopic cholecystectomy. Anaesthesia 49:579, 1994.

237. Schauer PR, Luna J, Ghiatas AA et al: Pulmonary function after laparoscopic cholecystectomy. Surgery 114:389, 1993.

238. Karayiannakis AJ, Makri GG, Mantzioka A et al: Postoperative pulmonary function after laparoscopic and open cholecystectomy. Br J Anaesth 77:448, 1996.

239. Rothwell BC, Katagiri M, Young RN et al: Costal (cos) and crural (cru) diaphragm function after laparoscopic cholecystectomy (LAPC). Am Rev Respir Dis 145:A152, 1992.

240. Erice F, Fox GS, Salib YM et al: Diaphragmatic function before and after laparoscopic cholecystectomy. Anesthesiology 79:966, 1993.

241. Shulman SM, Chuter T, Weissman C: Dynamic respiratory patterns after laparoscopic cholecystectomy. Chest 103:1173, 1993.

242. Sharma R, Clergue F, Jansson E et al: Diaphragmatic function after laparoscopic cholecystectomy. Br J Anaesth 72(suppl S1):A34, 1994.

243. Tousignant G, Wiesel S, Laporta D et al: The effect of age on recovery of pulmonary function after laparoscopic cholecystectomy. Anesth Analg 74(suppl 2S):S321, 1992.

244. Johnson D, Litwin D, Osachoff J et al: Postoperative respiratory function after laparoscopic cholecystectomy. Surg Laparosc Endosc 2:221, 1992.

245. Joris J, Kaba A, Lamy M: Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures. Br J Anaesth 79:422, 1997.

246. Skacel M, Sengupta P, Plantevin OM: Morbidity after day case laparoscopy: A comparison of two techniques of tracheal anaesthesia. Anaesthesia 41:537, 1986.

247. De Grood PMRN, Habers JBN, van Egmond J et al: Anaesthesia for laparoscopy: A comparison of five techniques including propofol, etomidate, thiopentone and isoflurane. Anaesthesia 42:815, 1987.

248. Bailey PL, Steisand JB, Pace NL et al: Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. Anesthesiology 72:977, 1990.

249. Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment, and prevention. Anesthesiology 77:162, 1992.

250. Beattie WS, Lindblad T, Buckley DN et al: Menstruation increases the risk of nausea and vomiting after laparoscopy. A prospective randomized study. Anesthesiology 78:272, 1993.

251. Green G, Jonsson L: Nausea: The most important factor determining length of stay after ambulatory anaesthesia. A comparative study of isoflurane and/or propofol techniques. Acta Anaesthesiol Scand 37:742, 1993.

252. Okum GS, Colonna-Romano P, Horrow JC: Vomiting after alfentanil anesthesia: Effect of dosing method. Anesth Analg 75:558, 1992.

253. Sukhani R, Vazquez J, Pappas AL et al: Recovery after propofol with and without intraoperative fentanyl in patients undergoing ambulatory gynecologic laparoscopy. Anesth Analg 83:975, 1996.

254. Sukhani R, Lurie J, Jabamoni R: Propofol for ambulatory gynecologic laparoscopy: Does omission of nitrous oxide alter postoperative emetic sequelae and recovery? Anesth Analg 78:831, 1994.

255. Lonie DS, Harper NJM: Nitrous oxide anaesthesia and vomiting. The effect of nitrous oxide anaesthesia on the incidence of vomiting following gynaecologic laparoscopy. Anaesthesia 41:703, 1986.

256. Korttila K, Hovorka J, Erkola O: Nitrous oxide does not increase the incidence of nausea and vomiting after isoflurane anesthesia. Anesth Analg 66:761, 1987.

257. Hovorka J, Korttila K, Erkola O: Nitrous oxide does not increase nausea and vomiting following gynaecological laparoscopy. Can J Anaesth 36:145, 1989.

258. Sengupta P, Plantevin OM: Nitrous oxide and day-case laparoscopy: Effects on nausea and return to normal activity. Br J Anaesth 60:570, 1988.

259. Taylor E, Feinstein R, White PF et al: Anesthesia for laparoscopic cholecystectomy. Is nitrous oxide contraindicated? Anesthesiology 76:541, 1992.

260. Stanton JM: Anaesthesia for laparoscopic cholecystectomy. Anaesthesia 46:317, 1990.

261. Bodner M, White PF: Antiemetic efficacy of ondansetron after outpatient laparoscopy. Anesth Analg 73:250, 1991.

262. Paxton LD, McKay AC, Mirakhur RK: Prevention of nausea and vomiting after day case gynaecological laparoscopy: A comparison of ondansetron, droperidol, metoclopramide and placebo. Anaesthesia 50:403, 1995.

263. McKenzie R, Kovac A, O'Connor T et al: Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. Anesthesiology 78:21, 1993.

264. Grond S, Lynch J, Diefenbach C et al: Comparison of ondansetron and droperidol in the prevention of nausea and vomiting after inpatient minor gynecologic surgery. Anesth Analg 81:603, 1995.

265. Sniadach MS, Alberts MS: A comparison of the prophylactic antiemetic effect of ondansetron and droperidol on patients undergoing gynecologic laparoscopy. Anesth Analg 85:797, 1997.

266. Hitchcock M, Ogg TW: Antiemetics in laparoscopic surgery. Br J Anaesth 72:608, 1994.

267. Declan Fleming RY, Dougherty TB, Feig BW: The safety of helium for abdominal insufflation. Surg Endosc 11:230, 1997.

268. Eisenhauer DM, Saunders CJ, Ho HS et al: Hemodynamic effects of argon pneumoperitoneum. Surg Endosc 8:315, 1994.

269. Roberts MW, Mathiesen KA, Ho HS et al: Cardiopulmonary responses to intravenous infusion of soluble and relatively insoluble gases. Surg Endosc 11:341, 1997.

270. Wolf JS Jr, Carrier S, Stoller ML: Gas embolism: Helium is more lethal than carbon dioxide. J Laparoendosc Surg 4:173, 1994.

271. Lindgren L, Koivusalo A-M, Kellokumpu I: Conventional pneumoperitoneum compared with abdominal wall lift for laparoscopic cholecystectomy. Br J Anaesth 75:567, 1995.

272. McDermott JP, Regan MC, Page R et al: Cardiorespiratory effects of laparoscopy with and without gas insufflation. Arch Surg 130:984, 1995.

273. Rademaker BM, Meyer DW, Bannenberg JJ et al: Laparoscopy without pneumoperitoneum. Effects of abdominal wall retraction versus carbon dioxide insufflation on hemodynamics and gas exchange in pigs. Surg Endosc 9:797, 1995.

274. Woolley DS, Puglisi RN, Bilgrami S et al: Comparison of the hemodynamic effects of gasless abdominal distention and CO_2 pneumoperitoneum during incremental positive end-expiratory pressure. J Surg Res 58:75, 1995.

275. Casati A, Valentini G, Ferrari S et al: Cardiorespiratory changes during gynaecological laparoscopy by abdominal wall elevation: Comparison with carbon dioxide pneumoperitoneum. Br J Anaesth 78:51, 1997.

276. Koivusalo A-M, Kellokumpu I, Scheinin M et al: Randomized comparison of the neuroendocrine response to laparoscopic cholecystectomy using either conventional or abdominal wall lift techniques. Br J Surg 83:1532, 1996.

277. Goldberg JM, Maurer WG: A randomized comparison of gasless laparoscopy and CO_2 pneumoperitoneum. Obstet Gynecol 90:416, 1997.

278. Johnson PL, Sibert KS: Laparoscopy. Gasless vs. CO_2 pneumoperitoneum. J Reprod Med 42:255, 1997.

279. Bouvy ND, Marquet RL, Jeekel H et al: Impact of gas(less) laparoscopy and laparotomy on peritoneal tumor growth and abdominal wall metastases. Ann Surg 224:694, 1996.

280. Watson DI, Mathew G, Ellis T et al: Gasless laparoscopy may reduce the risk of port-site metastases following laparoscopic tumor surgery. Arch Surg 132:166, 1997.

281. Lemaire BMD, van Erp WFM: Laparoscopic surgery during pregnancy. Surg Endosc 11:15, 1997.

282. Hunter JG, Swanstrom L, Thornburg K: Carbon dioxide pneumoperitoneum induces fetal acidosis in a pregnant ewe model. Surg Endosc 9:272, 1995.

283. Barnard JM, Chaffin D, Droste S et al: Fetal response to carbon dioxide pneumoperitoneum in the pregnant ewe. Obstet Gynecol 85:669, 1995.

284. Topel HC: Gasless laparoscopy under epidural anesthesia in a woman with a 14-week gestation. J Am Assoc Gynecol Laparosc 2:S79, 1995.

285. Pelosi MA: Gasless laparoscopy under epidural anesthesia during pregnancy. J Am Assoc Gynecol Laparosc 2:S75, 1995.

286. Liem T, Applebaum H, Herzberger B: Hemodynamic and ventilatory effects of abdominal CO_2 insufflation at various pressures in the young swine. J Pediatr Surg 29:966, 1994.

287. Graham AJ, Jirsch DW, Barrington KJ et al: Effects of intraabdominal CO_2 insufflation in the piglet. J Pediatr Surg 29:1276, 1994.

288. Grunwald Z, Taylor GE, Go L et al: Hemodynamic effects of CO_2 induced pneumoperitoneum in newborn piglets. Anesth Analg 80 (suppl 2S):S164, 1995.

289. Hsing CH, Hseu SS, Tsai SK et al: The physiological effect of CO_2 pneumoperitoneum in pediatric laparoscopy. Acta Anaesthesiol Sin 33:1, 1995.

290. Tobias JD, Holcomb GW, Brock JW et al: Cardiorespiratory changes in children during laparoscopy. J Pediatr Surg 30:33, 1995.

291. Sfez M, Guerard A, Desruelle P: Cardiorespiratory changes during laparoscopic fundoplication in children. Paediatr Anaesth 5:89, 1995.

292. Lejus C, Delile L, Plattner V et al: Randomized, single-blinded trial of laparoscopic versus open appendectomy in children: Effects on postoperative analgesia. Anesthesiology 84:801, 1996.

293. Chapron C, Querleu D, Mage G et al: Complications de la coeliochirurgie gynecologique. Etude multicentrique a partir de 7,604 coelioscopies. J Gynecol Obstet Biol Reprod (Paris) 21:207, 1992.

294. Lehmann-Willenbrock E, Riedel HH, Mecke H, Semm K: Pelviscopy/laparoscopy and its complications in Germany, 1949-1988. J Reprod Med 37:671, 1992.

295. Hulka JF, Peterson HB, Philipps JM et al: Operative laparoscopy. J Reprod Med 38:569, 1993.

296. Hulka JF, Peterson HB, Philipps JM et al: Operative hysteroscopy. J Reprod Med 38:572, 1993.

297. Deziel DJ, Millikan KW, Economou SG et al: Complications of laparoscopic cholecystectomy: A national survey of 4,292 hospitals and an analysis of 77,604 cases. Am J Surg 165:9, 1993.

298. Vincent-Hamelin E, Pallares AC, Felipe JAR et al: National survey on laparoscopic cholecystectomy in Spain. Surg Endosc 8:770, 1994.

299. Schlumpf R, Klotz HP, Wehrli H et al: A nation's experience in laparoscopic cholecystectomy. Surg Endosc 8:35, 1994.

300. Croce E, Azzola M, Golia M et al: Laparocholecystectomy: 6865 cases from Italian institutions. Surg Endosc 8:1088, 1994.

301. McMahon AJ, Baxter JN, O'Dwyer PJ: Preventing complications of laparoscopy. Br J Surg 80:1593, 1993.

302. The Southern Surgeons Club: A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 324:1073, 1991.

303. Strasberg SM, Sanabria JR, Clavien PA: Complications of laparoscopic cholecystectomy. Can J Surg 35:275, 1992.

304. Wolfe BM, Gardiner BN, Leary BF et al: Endoscopic cholecystectomy. An analysis of complications. Arch Surg 126:1192, 1991.

305. Kozarek RA, Sanowski RA, Cintora I: Laparoscopy in a patient with LeVeen shunt: Prevention of air embolism. Gastrointest Endosc 30:193, 1984.

306. Rosen MA, Roizen MF, Eger EI et al: The effect of nitrous oxide on in vitro fertilization success rate. Anesthesiology 67:42, 1987.

307. Jensen AG, Prevedoros H, Kullman E et al: Peroperative nitrous oxide does not influence recovery after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 37:683, 1993.

308. Oikkonen M: Propofol vs isoflurane for gynaecological laparoscopy. Acta Anaesthesiol Scand 38:110, 1994.

309. Jakobsson J, Rane K, Ryberg G: Anaesthesia during laparoscopic gynaecological surgery: A comparison between desflurane and isoflurane. Eur J Anaesthesiol 14:148, 1997.

310. Bailie R, Craig G, Restall J: Total intravenous anaesthesia for laparoscopy. Anaesthesia 44:60, 1989.

311. Marshall CA, Jones RM, Bajorek PK et al: Recovery characteristics using isoflurane or propofol for maintenance of anaesthesia: A double-blind controlled trial. Anaesthesia 47:461, 1992.

312. McClymont C: A comparison of the effect of propofol or thiopentone on the incidence and severity of suxamethonium-induced myalgia. Anaesth Intensive Care 22:147, 1994.

313. Vincent JD, Syrop CH, Van Voorhis J et al: An evaluation of the effect of anesthetic technique on reproductive success after laparoscopic pronuclear stage transfer. Anesthesiology 82:352, 1995.

314. Chassard D, Bryssine B, Golfier F et al: Coelioscopie gynecologique avec ou sans curare [Gynecologic laparoscopy with or without curare]. Ann Fr Anesth Reanim 15:1013, 1996.

315. Chassard D, Berrada K, Tournadre J et al: The effects of neuromuscular block on peak airway pressure and abdominal elastance during pneumoperitoneum. Anesth Analg 82:525, 1996.

316. Goodwin APL, Rowe WL, Ogg TW: Day case laparoscopy. A comparison of two anaesthetic techniques using the laryngeal mask during spontaneous breathing. Anaesthesia 47:892, 1992.

317. Swann DG, Spens H, Edwards SA et al: Anaesthesia for gynaecological laparoscopy--a comparison between the laryngeal mask airway and tracheal intubation. Anaesthesia 48:431, 1993.

318. Brimacombe J, Shorney N: Laparoscopy and the laryngeal mask airway? Anaesth Intensive Care 20:245, 1992.

319. Brimacombe J: Laparoscopy and the laryngeal mask airway. Br J Anaesth 73:121, 1994.

320. Tobias JD, Holcomb GW, Brock JW et al: General anesthesia by mask with spontaneous ventilation during brief laparoscopic inspection of the peritoneum in children. J Laparoendosc Surg 4:379, 1994.

321. Barker P, Langton JA, Murphy PJ et al: Regurgitation of gastric contents during general anaesthesia using laryngeal mask airway. Br J Anaesth 69:314, 1992.

322. Kurer FL, Welch DB: Gynaecological laparoscopy: Clinical experiences of two anaesthetic techniques. Br J Anaesth 54:1207, 1984.

323. Peterson HB, DeStefano F, Rubin GL et al: Deaths attributable to tubal sterilization in the United States, 1977-1981. Am J Obstet Gynecol 146:131, 1983.

324. Verghese C, Brimacombe JR: Survey of laryngeal mask airway usage in 11,910 patients: Safety and efficacy for conventional and nonconventional usage. Anesth Analg 82:129, 1996.

325. Fishburne JI: Anesthesia for laparoscopy: Considerations, complications and techniques. J Reprod Med 21:37, 1978.

326. MacKenzie IZ, Turner E, O'Sullivan GM et al: Two hundred out-patient laparoscopic clip sterilizations using local anaesthesia. Br J Obstet Gynaecol 94:449, 1987.

327. Peterson HB, Hulka J, Spielman FJ et al: Local versus general anesthesia for laparoscopic sterilization. Obstet Gynecol 70:903, 1987.

328. Brady CE, Harkleroad LE, Pierson WP: Alteration in oxygen saturation and ventilation after intravenous sedation for peritoneoscopy. Arch Intern Med 149:1029, 1989.

329. Bridenbaugh LD, Soderstrom RM: Lumbar epidural block anesthesia for outpatient laparoscopy. J Reprod Med 23:85, 1979.

330. Lehtinen AM, Laatikainen T, Koskimies AI et al: Modifying effects of epidural analgesia or general anesthesia on stress hormone response to laparoscopy for in vitro fertilization. J In Vitro Fert Embryo Transf 4:23, 1987.

331. Chilvers CR, Vaghadia H, Mitchell GW et al: Small-dose hypobaric lidocaine-fentanyl spinal anesthesia for short duration outpatient laparoscopy. II. Optimal fentanyl dose. Anesth Analg 84:65, 1997.

332. Lefebvre G, Vauthier-Brouzes D, Darbois Y et al: La coelioscopie sous anesthesie peridurale: technique, indications, resultats a propos de 220 cas. J Gynecol Obstet Biol Reprod (Paris) 20:355, 1991.

333. Galen DI, Jacobson A, Weckstein LN et al: Gasless laparoscopy for gynecology. J Am Assoc Gynecol Laparosc 2:S68, 1995.

334. Topel HC: Gasless laparoscopic assisted hysterectomy with epidural anesthesia. J Am Assoc Gynecol Laparosc 1:S36, 1994.

335. Vergfors M, Cerderholm I, Lennmarken C et al: Should oxygen be administered after laparoscopy in a healthy patient? Acta Anaesthesiol Scand 32:350, 1988.

2024

Chapter 57 - Anesthesia for Obstetrics [*]

Beth Glosten

INTRODUCTION

Important issues when anesthetizing the pregnant woman for labor, vaginal delivery, or cesarean delivery include the physiologic changes of pregnancy, the direct and indirect effects of anesthetics on the fetus and neonate, and the benefits and risks of various anesthetic techniques to the mother. In choosing appropriate anesthetic techniques, the anesthetist must consider any medical or obstetric complications, obstetric requirements, the patient's wishes, and the anesthesiologist's judgment.

PHYSIOLOGIC CHANGES IN THE MOTHER DURING PREGNANCY

Respiratory Changes

The most notable change in maternal lung capacities and volumes occurs in functional residual capacity, which decreases 15 to 20 percent by term (Table 57-1) . [1] [2] [3] [4] [5] Vital capacity remains essentially unchanged throughout pregnancy. The transverse and anteroposterior diameter of the chest increases to compensate for the elevation of the diaphragm from the gravid uterus. The diaphragm moves freely at term; however, as pregnancy progresses, abdominal breathing decreases in favor of thoracic breathing. Measurements of closing volume confirm that in the supine position, one-third of parturients have airway closure during normal tidal ventilation [4] [6] and are therefore at risk for developing atelectasis and an increased oxygen alveolar-arterial gradient. [7] Flow-volume loops, timed forced expiratory volume, and other indicators of respiratory flow during pregnancy do not differ much from their counterparts in nonpregnant women. [3] [5] In addition, diffusing capacity decreases only slightly. [5]

Oxygen uptake increases about 20 percent during pregnancy, owing to increased maternal metabolism and work of breathing and fetal metabolism. [8] [9] Minute ventilation at term is increased about 50 percent, [1] mostly as a result of increased tidal volume, with only a slight increase in respiratory rate. As a result of increased alveolar ventilation at term, arterial carbon dioxide pressure usually decreases to about 32 mm Hg, but arterial pH remains normal because of a compensatory decrease in serum bicarbonate (from 26 to 22 mEq/L) (see Table 57-1 ; Fig. 57-1) (Figure Not Available) . Partial pressure of arterial oxygen is slightly increased from the increased minute ventilation. The oxyhemoglobin dissociation curve shifts to the right during normal pregnancy (increased P50) (Table 57-2) (Table Not Available) , [10] allowing a greater volume of oxygen to be unloaded to the tissues (fetus) at a given arterial oxygen pressure.

This chapter is dedicated to the memory of Sol M. Shnider, who was the senior author of this chapter in all previous editions.

**See Appendix 1, Practice Guidelines for Obstetrical Anesthesia*

TABLE 57-1 -- Maternal Respiratory Changes at Term

VARIABLE	AVERAGE CHANGE
Volumes and capacities	
Total lung capacity	0 to -5%
Inspiratory lung capacity	+5%
Functional residual capacity	-20%
Expiratory reserve volume	-20%
Residual volume	-20%
Vital capacity	No change
Closing volume	No change
Mechanics	
Minute ventilation	+50%
Alveolar ventilation	+70%
Tidal volume	+40%
Respiratory rate	+15%
Dead space	No change
Airway resistance	-36%
Total pulmonary resistance	-50%
Total compliance	-30%
Lung compliance (alone)	No change
Chest-wall compliance (alone)	-45%
FEV_1	No change
Diffusing capacity	-5%
Blood gases	
Arterial P_{CO_2}	-10 mm Hg
Serum bicarbonate	-4 mEq/L
Arterial pH	No change
Arterial P_{O_2}	+10 mm Hg
Oxygen consumption	+20%

During labor, particularly in the late first stage and second stage, the pain from episodic uterine contractions produces corresponding increases in maternal minute ventilation (as much as 300% over that of nonpregnant women) and oxygen consumption. Maternal hypocarbia (arterial carbon dioxide pressure = 20 mm Hg or less), and alkalemia (pH 7.55) results. Hypocarbia can lead to hypoventilation between uterine contractions, resulting in intermittent hypoxemia (particularly in obese patients or those who have received par- enteral opioids) (Fig. 57-2) . Epidural analgesia eliminates these pain-induced increases in oxygen consumption and

Figure 57-1 (Figure Not Available) Progressive changes of alveolar carbon dioxide tensions, pH, alkali reserve throughout pregnancy. *(From Bonica [424])*

TABLE 57-2 -- P50 Values of Nonpregnant, Pregnant, and Preeclamptic Subjects

(Not Available)

From Kambam et al [10]

minute ventilation and the accompanying hyperventilation-hypoventilation cycle (see Fig. 57-2) . [11]

The respiratory and pulmonary changes of pregnancy have notable clinical effects. First, reduced oxygen stores (low functional residual capacity) and increased oxygen consumption lead to pregnant patients' having a much greater and more rapid decline in partial pressure of arterial oxygen when rendered apneic as compared with nonpregnant women. [12] This rapid development of hypoxia can be avoided by administering 100 percent oxygen before induction of anesthesia. In addition, these changes increase the rate at which inhalation anesthesia is induced.

During pregnancy, capillary engorgement of the mucosa occurs throughout the respiratory tract, potentially causing edema in the nasopharynx, oropharynx, larynx, and trachea. Therefore, manipulation of the upper airway requires extreme care. Suctioning of the oropharynx, insertion of airways, and laryngoscopy may cause further edema and bleeding. Because the area of false cords may be swollen, a small, cuffed endotracheal tube (6.5-7.0 mm) is recommended for use when the trachea is intubated. Repeated attempts at laryngoscopy during management of a difficult airway must be minimized to prevent obstructing airway edema.

Cardiovascular Changes

The cardiovascular system is progressively stressed during pregnancy and parturition (Table 57-3 , Figs. 57-3 (Figure Not Available) and 57-4) (Figure Not Available) . Many of the changes appear during the first trimester of pregnancy (increase in cardiac output of 22% and decrease in systemic vascular resistance [SVR] by 30% at 8 weeks' gestation). [13] The changes continue into the second and early third trimester of pregnancy, when cardiac output increases to approximately 30 to 40 percent above nonpregnant values. [14] [15] The increase in cardiac output during pregnancy is primarily a result of an increase in stroke volume (by about 30%), with a more modest increase in heart rate (10-15 beats per minute [bpm]) [13] noted. Arterial blood pressure does not change during normal pregnancy because of a decrease in peripheral vascular resistance. Early reports suggested that cardiac output decreased markedly during the third trimester. These reports, however, studied gravid patients in the supine position.

Figure 57-2 Cyclical changes in maternal transcutaneous (tc) P_{O_2} as a result of hypoventilation between uterine contractions. Epidural analgesia eliminates the decreases in maternal P_{O_2} . *(Modified from Peabody [425])*

Lees and associates [14] [16] and Ueland et al [17] showed that this marked decrease in cardiac output occurring after 28 weeks of pregnancy in subjects in the supine position was caused by obstruction of the inferior vena cava by the gravid uterus. Decreased venous return and reduced cardiac output were not seen in subjects in the lateral position, which eliminates this obstruction.

Maternal blood volume increases markedly during pregnancy (Fig. 57-5) (Figure Not Available) . [18] [19] Near term, blood volume has increased approximately 35 to 40 percent, (i.e., by more than 1,000 mL). Plasma volume increases from 40 mL/kg before pregnancy to 70 mL/kg during late pregnancy, and red blood cell volume increases from 25 to 30 mL/kg. The latter increases at a slower rate than the former, accounting for the relative anemia of pregnancy. Although the dilutional anemia of pregnancy decreases the oxygen-carrying capacity of the blood, several factors compensate for this, including an increase in maternal partial pressure of arterial oxygen (see Table 57-1) , a decrease in blood viscosity, an increase in cardiac output, and a rightward shift in the maternal oxyhemoglobin dissociation curve (see Table 57-2) (Table Not Available) . [10] As a result, transport of oxygen to important organs increases during pregnancy.

The increased blood volume and cardiac output may produce changes in the cardiac examination of the pregnant patient. Auscultation may reveal a wide, loud split first sound and a soft systolic ejection murmur caused by increased blood flow and vasodilation. [20] The position of the heart is usually altered by the elevated diaphragm at term gestation. This displaces the point of maximum impulse to the left and changes the axis of the heart on the electrocardiogram to the left. [20] The electrocardiogram may show minor, nonspecific ST-, T-, and Q-wave changes and benign arrythmias. [20] These normal findings should be differentiated from those indicating heart disease. Signs of significant heart disease in the pregnant woman include true cardiac enlargement, severe arrhythmias, systolic murmur greater than grade 3, or significant diastolic murmur.

TABLE 57-3 -- Hemodynamic Changes in Pregnancy

	NONPREGNANT	PREGNANT	CHANGE (%)
Cardiac output (L/min)	4.3±0.9	6.2±1.0	+43
Heart rate (beats/min)	71.0±10.0	83.0±10.0	+17
Stroke volume (mL)	73.4±9.0	88.3±11.0	+18
Left ventricle change rate (dD/dt), systole	6.7	9.3	+28
Myocardial thickness, end-diastolic (cm)	4.67	4.86	+4
Systemic vascular resistance ($dyne^2/cm/s^{-5}$)	1530±520	1210±266	-21
Pulmonary vascular resistance ($dyne^2/cm/s^{-5}$)	119±47	78±22	-34
Colloid oncotic pressure (mm Hg)	20.8±1	18.0±1.5	-14
Colloid oncotic pressure/Pulmonary capillary wedge pressure gradient (mm Hg)	14.5±2.5	10.5±2.7	-28

D, diameter; t, time

Data from Robson et al [416] and Clark et al [419]

Figure 57-3 (Figure Not Available) Maternal cardiovascular changes during pregnancy and labor from studies on patients in the lateral and supine positions. *(From Mangano [426])*

Figure 57-4 (Figure Not Available) Effects of uterine contractions on cardiac output, stroke volume, and heart rate during labor. Values represent percent increases from control measurements in late pregnancy. *(From Mangano [426])*

The pain and apprehension of labor adds to cardiac work during pregnancy and increases stroke volume and cardiac output by 45 percent over prelabor values. [21] [22] Blood pressure increases during painful labor. Additional stresses are imposed by uterine contractions, which cause, in effect, an autotransfusion. With each uterine contraction, blood from the body of the uterus is pushed into the central circulation, and blood volume and cardiac output increase by 10 to 25 percent. [22] [23] After delivery, the same autotransfusion occurs. In addition to an increase in central blood volume, obstruction of the vena cava is relieved. As a result, there is a marked increase (up to 80% of prelabor values) in stroke volume and cardiac output immediately postpartum. Patients with limited cardiac reserve may experience cardiac

failure at this time.

Despite the increase in blood volume and cardiac output, the parturient at term is susceptible to hypotension when supine. When the patient is supine, the gravid uterus partially or completely compresses the aorta and inferior vena cava, leading to decreased venous return, decreased cardiac output, hypotension, and reduced uterine blood flow (Figs. 57-6 (Figure Not Available) , 57-7 (Figure Not Available) , and 57-8) (Figure Not Available) . [24] [25] [26] [27] [28] Up to 10 percent of pregnant patients near term develop signs of shock (hypotension, pallor, sweating, nausea, vomiting, changes in cerebration) when they assume this position. Compensatory mechanisms include increased sympathetic tone and collateral routes (paravertebral veins to azygos vein) to improve venous return during obstruction of the vena cava. Caval compression also increases uterine venous back pressure, which further decreases uterine blood flow. Compression of the aorta is not associated with maternal symptoms but does cause arterial hypotension in the lower extremities and uterine arteries, which can further decrease uterine blood flow and impair uteroplacental perfusion. [29]

The anesthesiologist must recognize the importance of the aortocaval compression syndrome and the potential for its adverse effects to be exaggerated by anesthesia. Drugs causing vasodilation, such as potent inhaled agents, and particularly anesthetic techniques causing sympathetic blockade (subarachnoid or epidural anesthesia) exacerbate decreased

Figure 57-5 (Figure Not Available) Percent of increase in the volume of plasma, red blood cells (RBC), and total blood during pregnancy, labor, and the puerperium. *(From Bonica [424])*

Figure 57-6 (Figure Not Available) Venogram in the supine position just before cesarean section. (A) Dye has been injected into both femoral veins but does not reach the inferior vena cava, traversing instead the paravertebral veins. (B) Same patient just after cesarean section. The dye now easily reaches the inferior vena cava. *(From Kerr et al [27])*

Figure 57-7 (Figure Not Available) Schematic of lateral angiograms obtained from two women lying in the supine position. In the nonpregnant woman (left), there is a clear gap between the vertebral column and the aorta. Note the uniform width of the aorta. In the pregnant patient near term (right) the aorta is clearly displaced in the dorsal direction, encroaching on the shadow of the spine. The aorta is narrowed at the level of the lumbar lordosis. *(From Bieniarz et al [427])*

Figure 57-8 (Figure Not Available) Serial hemodynamic studies in a patient who exhibited supine hypotension. After the patient had lain supine for 6 minutes, a profound fall in arterial pressure and heart rate was seen. *(From Kerr [26])*

venous return to the heart when the vena cava is obstructed. Aortocaval compression must be prevented. Displacement of the uterus off the great vessels can be accomplished by manually displacing the uterus to the left. During labor, the patient should be positioned either on her side or with a left tilt. During delivery, the operating or delivery table can be tilted laterally to the left, or a small pillow or foam rubber wedge can be used to elevate the patient's right buttock and back about 10 to 15 cm.

The pregnant woman at term is in a hypercoagulable state owing to increases in factors VII, VIII, X, and plasma fibrinogen. [30] Estimates of blood loss at delivery vary but may be around 500 mL for an uncomplicated vaginal delivery. Blood loss during cesarean delivery varies widely, with 500 to 1400 mL being reported. [31] [32]

Hepatic Changes

Levels of alkaline phosphatase, serum transaminases, lactic dehydrogenase, and cholesterol increase slightly during pregnancy and labor. [33] Serum bilirubin levels and hepatic blood flow do not change. Total protein concentration and the albumin-to-globulin ratio decrease. Although plasma cholinesterase activity is reduced during pregnancy and in the immediate postpartum period, [34] moderate doses of succinylcholine and chloroprocaine are usually metabolized easily. [35] [36]

Gastrointestinal Changes

During pregnancy, the secretion of gastric acid increases, possibly owing to markedly elevated levels of the hormone gastrin, which is produced by the placenta. [37] During late pregnancy, gastric emptying is slowed as a result of displacement of the pylorus by the enlarged uterus. Pain, anxiety, and use of opioid analgesia during labor contribute to impaired gastric emptying. When ultrasound was used to examine gastric contents after a test meal, no solid food was detected in healthy nonpregnant volunteers or in pregnant patients not in labor 4 hours after ingestion. However, in pregnant patients in labor, solid food was found in 41 percent of those who had not eaten for 8 to 24 hours before the ultrasound examination. [38] Intragastric pressure is increased during pregnancy, and lower esophageal sphincter pressure is decreased during pregnancy. [39] All these changes increase the risk of regurgitation and aspiration during either general anesthesia or impaired consciousness from any other cause. It remains controversial as to what point in gestation these gastrointestinal changes dictate institution of measures to prevent aspiration pneumonitis during administration of general anesthesia and how long these changes persist in the postpartum period. [40] That aspiration pneumonitis is a greater problem in pregnant versus nonpregnant women is supported by a survey of aspiration pneumonitis in gynecologic and obstetric patients in Norway. This study revealed an incidence of 4 of 3,600 (0.11%) in cesarean section patients

(all four cases received general anesthesia; two were complicated by difficulties with airway management) compared with 0.01 to 0.04 percent in gynecologic patients. [41]

Central Nervous System Changes

Pregnancy reduces anesthetic requirements both during regional and general anesthesia. During spinal or epidural anesthesia, less local anesthetic is required to produce a given level of anesthesia. This reduced anesthetic requirement was thought to be due to the mechanical effects of increased intra-abdominal pressure, causing epidural venous engorgement and a reduction of both the epidural and the subarachnoid spaces. However, Fagraeus et al [42] showed that reduced local anesthetic requirements are seen in early pregnancy (8-12 weeks) before the mechanical effects of the gravid uterus are present. Datta et al [43] compared the effects of bupivacaine on nerve conduction in the isolated vagus nerve from pregnant and nonpregnant rabbits. The onset of block was significantly faster in nerves from pregnant animals. This study indicates that during pregnancy, either nerve fibers have increased sensitivity to local anesthetics or there is enhanced diffusion of the local anesthetic to the membrane receptor site.

Animal studies demonstrate that the requirement for inhaled anesthetics is decreased by up to 40 percent during pregnancy (Table 57-4) (Table Not Available) . [44] Reduced minimum alveolar concentration (MAC) has also been demonstrated in humans during early pregnancy (10-12 weeks' gestation) [45] and in the immediate (24-36 hours) postpartum period. [46] The sedative effects of increased levels of progesterone was proposed as a mechanism, and rabbits given exogenous progesterone show a reduced halothane MAC. [47] However, studies of halothane MAC in nonpregnant, pregnant, and lactating rats showed no correlation between decreased MAC and progesterone levels. [48] Another mechanism for the decrease in MAC during pregnancy was suggested by Gintzler, [49] who found that in pregnant rats there is a progressive increase in pain tolerance, which can be abolished by long-term administration of an opioid antagonist. An increased tolerance to visceral pain conferred by pregnancy in rats is also reversed with naloxone. [50] Thus, a pregnancy-induced activation of the endorphin system is likely a major contributor to the decreased anesthetic requirement observed during pregnancy.

Renal Changes

Renal plasma flow and glomerular filtration rate increase rapidly during pregnancy, reflecting changes in cardiac output. During the third trimester, they slowly return toward normal. Creatinine clearance usually increases, and therefore the upper limits of normal for blood urea nitrogen and serum creatinine are lower in the pregnant

woman.

/das/book/view/29494766/875/629.html

UTERINE BLOOD FLOW

Uterine blood flow in the parturient at term is approximately 700 mL/min and is determined by the following relationship:

There is no autoregulation of uterine blood flow; the vessels are maximally dilated during pregnancy. As such, in the absence of aortic compression, uterine arterial pressure directly reflects maternal blood pressure and cardiac output. Uterine blood flow decreases during maternal hypotension (sympathetic block, hypovolemia, hemorrhage, compression of the inferior vena cava), in circumstances in which uterine venous pressure is increased (compression of the inferior vena cava, abruptio placentae), and with increases in uterine vascular resistance (maternal hypertensive disorders, alpha-agonists, uterine hypercontractility).

Obstetric anesthesia may affect uterine blood flow by changing the perfusion pressure (i.e., by altering the uterine arterial or venous pressure) or by changing uterine vascular resistance, either directly through changes in vascular tone or indirectly by altering uterine contractions or uterine muscle tone. For example, hypotension associated with a sympathetic block or deep general anesthesia decreases perfusion pressure and reduces uterine blood flow in animals. Vasopressors with pure alpha-adrenergic action (e.g., phenylephrine) increase uterine vascular resistance and also decrease uterine blood flow (Fig. 57-9) (Figure Not Available) . Conditions that increase the frequency or duration of uterine contractions (e.g., an overdose of oxytocin or abruptio placentae) also decrease uterine blood flow.

TABLE 57-4 -- MAC Presented as Percent End-Tidal Anesthetic Concentration (Mean ± SE)

(Not Available)

From Palahniuk et al] [44]

Figure 57-9 (Figure Not Available) Mean changes in uterine blood flow at equal elevations of mean arterial blood pressure following administration of ephedrine (0.25, 0.5, 1.0, and 2.0 mg/kg), mephentermine (0.25, 0.5, 1.0, and 2.0 mg/kg), methoxamine (0.025, 0.05, 0.1, and 0.2 mg/kg) and metaraminol (0.025, 0.05, 0.1, and 0.2 mg/kg) to pregnant sheep. Uterine blood flow was not adversely affected by doses of ephedrine which increased maternal blood pressure by up to 50%. *(From Ralston et al* [52] *)*

Ephedrine is the vasopressor of choice for the treatment of hypotension during obstetric anesthesia. Both animal data [51] [52] [53] [54] [55] (see Fig. 57-9 (Figure Not Available) 57-10) (Figure Not Available) and years of clinical use [56] support its beneficial effects of increasing maternal blood pressure, cardiac output, uterine blood flow, and fetal status when used to treat hypotension. The uterine vessels of pregnant sheep do not have the constriction response to ephedrine seen in nonpregnant animals. [55] [57] Thus, when maternal blood pressure and cardiac output is restored with ephedrine therapy, uterine blood flow increases (see Fig. 57-10) (Figure Not Available) . In patients in whom the tachycardic effects of ephedrine should be avoided (e.g., mitral stenosis), it is reassuring that phenylephrine (80- to 100-mug increments) has been used successfully in well-hydrated, healthy cesarean section patients to correct maternal blood pressure during regional anesthesia without adverse effects on neonatal outcome. [58] [59]

PLACENTAL TRANSFER OF ANESTHETICS

Medications administered to the mother enter the fetal circulation primarily by passive diffusion. The Fick law of diffusion determines the rate of transfer across the placenta, which is represented by

where Q/t is the rate of diffusion, K is the diffusion constant of the drug, A is the membrane surface area, Cm is the maternal

Figure 57-10 (Figure Not Available) Changes in maternal and fetal sheep arterial pH following maternal spinal hypotension and subsequent correction with ephe-drine. Numbers identify the eight different maternal-fetal sheep preparations. *(From Shnider et al [51])*

---

drug concentration, Cf is the fetal drug concentration, and D is the membrane thickness.

Passive diffusion is the primary means of placental transfer of drugs. As such, the maternal-fetal concentration gradient, the uterine and umbilical blood flow, and the various factors that determine the diffusion constant of the drug are important in determining fetal exposure to maternally administered anesthetics. Factors producing a high diffusion constant (i.e., rapid diffusion) include low molecular weight (<500 d), low protein binding, high lipid solubility, and low degree of ionization. Almost all drugs used to produce anesthesia, analgesia, or sedation have a molecular weight of less than 500 d, are partially not ionized at physiologic pH, have a relatively high lipid solubility, and are incompletely protein bound in maternal blood and rapidly cross the placenta. Neuromuscular blocking drugs, because of their low lipid solubility and high degree of ionization, are not transferred across the placenta in clinically significant amounts. Factors tending to increase maternal drug concentration are high total doses, use of slowly metabolized drugs, low protein binding, and administration of drugs into highly vascular areas. Once the drug crosses the placenta, fetal pH and protein binding [60] affect the drug disposition. Circumstances of fetal acidosis and low pH favor "trapping" of potentially ionized drugs (e.g., local anesthetics) in the fetal circulation. [61]

The fetal circulation is unique in several ways and greatly modifies drug distribution (Fig. 57-11) (Figure Not Available) . Drugs cross the placenta and enter the fetal circulation via the umbilical vein.

Figure 57-11 (Figure Not Available) Diagram of the fetal circulation. Numbers indicate mean percent oxygen saturation. *(From Born et al [430])*

Umbilical venous blood returning from the placenta either perfuses the liver (40-60%) or bypasses the liver via the ductus venosus. [62] Hepatic drug uptake in the fetus may protect against the occurrence of high drug levels in the fetal heart and central nervous system (CNS). [63] [64] Dilution of umbilical venous blood in the fetal right atrium and shunting of blood across the foramen ovale and ductus arteriosus also modify fetal drug distribution.

Hepatic enzyme activity in the fetus is generally less than that in adults. However, liver microsomes of human fetuses have significant levels of cytochrome P-450 and nicotinamide adenine dinucleotide phosphate-cytochrome C reductase as early as week 14 of gestation. [65] [66] This enzyme activity, even though less than that in adults, suggests that even the premature human fetus has the capacity to metabolize numerous drugs, including most local anesthetics.

EVALUATION OF THE FETUS

The anesthesiologist should include an assessment of the fetus in the preanesthetic evaluation of the parturient. Understanding the means of assessing fetal well-being available to obstetricians also promotes communication in circumstances of emergency delivery for fetal concerns.

Fetal heart rate (FHR) monitoring [67] is commonly used to assess fetal well-being. It is monitored externally with ultrasound or internally with a fetal scalp electrode. Assessing FHR is helpful in confirming fetal well-being (i.e., a normal FHR tracing is consistent with a well-oxygenated fetus) but is an imperfect method to reliably identify fetal asphyxia (an abnormal tracing may reflect conditions other than fetal asphyxia). [68] Under normal conditions, FHR represents a balance of parasympathetic and sympathetic input. A normal FHR is 120 to 160 bpm. An increase in FHR may indicate fetal asphyxia, maternal fever, or drug effects (e.g., ephedrine and terbutaline). A decrease in FHR, particularly if sudden and severe, may represent fetal hypoxia. FHR beat-to-beat variability is an important component of FHR assessment. Normal short-term variability is seen as beat-to-beat FHR differences of two to three beats. This is superimposed on a pattern of long-term variability of five to 20 beats. Normal FHR variability is consistent with a well-oxygenated fetal CNS. FHR variability is decreased from maternally administered opioids or sedatives and fetal sleep. Reduced FHR variability also occurs in fetal hypoxia and acidosis.

The FHR can have periodic patterns related to uterine contractions (measured with a tocodynamometer or an intrauterine pressure catheter placed through the vagina into the uterine cavity). [67] Early decelerations occur with, and mirror, a uterine contraction. The rate rarely drops below 110 bpm. This type of deceleration is thought to represent a vagal reflex in response to fetal head compression and is typically seen during the second stage of labor. Late FHR decelerations begin 20 seconds or more after the onset of a uterine contraction and are worrisome because they represent uteroplacental insufficiency. Late decelerations with normal FHR variability are thought to be due to hypoxia-induced increased vagal discharge. Late decelerations with absent FHR variability are concerning because it is believed that these reflect direct hypoxia-induced myocardial depression.

Variable FHR decelerations are variable in configuration and relationship to uterine contractions and likely represent periodic compression of the umbilical cord. They classically begin with an acceleration in heart rate, followed by a bradycardia, and then return of FHR to normal after the contraction ceases. If persistent through labor, these repetitive variable decelerations can lead to fetal asphyxia and loss of FHR variability.

A nonstress test is used to document fetal well-being during pregnancy. It involves monitoring FHR for 20 minutes and checking for the presence of normal short-term and long-term variability and the absence of decelerations. A contraction stress test similarly evaluates FHR patterns with the added stress of periodic uterine contractions (usually stimulated with an intravenous (IV) infusion of oxytocin). The fetal biophysical profile has been developed to assess fetal well-being. The FHR pattern as well as fetal breathing movements, fetal body movements, fetal tone, and amount of amniotic fluid measured by ultrasound examination are assessed. [69] During labor, fetal scalp capillary blood can be sampled to measure fetal pH. Fetal capillary blood pH has been shown to correlate well with fetal umbilical blood gas values. [70] A fetal scalp blood pH of less than 7.20 indicates significant asphyxia and usually dictates urgent delivery. A value between 7.20 to 7.24 is intermediate and indicates the need for close monitoring and perhaps repeat sampling. A value of greater than 7.24 is reassuring. A positive response (an increase of FHR by 15 bpm lasting 10 seconds) to the less invasive "fetal scalp stimulation test" (tactile stimulation of the fetal scalp) has been shown to correlate with a fetal scalp pH of greater than 7.20. [68]

When abnormal FHR patterns are recognized, means to improve the uterine environment include giving supplemental oxygen to the mother, avoiding aortocaval compression, treating anesthetic (or otherwise)-induced hypotension, altering maternal position (adopting the full lateral or knee-chest position), decreasing uterine activity (discontinuing oxytocin and/or administering terbutaline, 0.25 mg subcutaneously), and/or instituting an amnioinfusion to relieve umbilical cord compression.

NORMAL PROGRESS OF LABOR

"Labor" is the term used to describe the physiologic process by which the products of conception are expelled from the uterus through the vagina. Normal labor requires

Figure 57-12 (Figure Not Available) Composite of the average dilation curve for nulliparous labor based on analysis of the data derived from the patterns traced by a large, nearly consecutive series of gravidas. The first stage is divided into a relatively flat latent phase and rapidly progressive active phase. The active phase has three identifiable component parts--an acceleration phase, a linear phase of maximum slope, and a deceleration phase. *(Modified by Friedman, [428] from Friedman [429])*

uterine contractions and progressive cervical dilation (Fig. 57-12) (Figure Not Available) . Traditionally, labor has been divided into three stages: the first stage extends from the start of regular uterine contractions causing effacement (thinning) and dilation of the cervix until complete cervical dilation, the second stage proceeds from the end of the first stage until delivery of the fetus, and the third stage extends from delivery of the baby until the placenta and membranes are expelled.

At the start of labor, contractions are infrequent and of low intensity. During active labor, uterine contractions occur about every 3 minutes, have a duration of about 1 minute, and achieve an intrauterine pressure of 50 to 70 mm Hg before returning to a resting uterine tone of 10 mm Hg.

Abnormal progress of labor can be classified as follows: slow latent phase, active phase arrest, slow-slope active phase, slow descent, and arrest of descent. Diagnostic features for abnormal progress of labor are listed in Table 57-5 . During the active phase or second stage of labor, cephalopelvic disproportion, malposition, and malpresentation are the most common causes of prolongation. Controversy exists regarding the potential impact of regional analgesic techniques utilized during labor on uterine activity and progress of labor. Retrospective studies assessing the impact

TABLE 57-5 -- Diagnostic Features of Prolonged Labor

FEATURE	NULLIPARAS	MULTIPARAS
Slow latent phase	>20 h	>14 h
Slow-slope active phase	>1.2 cm/h	>1.5 cm/h
Active phase arrest	No cervical dilation for 2 h	
Slow descent of fetus	<1 cm/h	<2 cm/h
Arrest of descent	No descent for 1 h	
	SECOND STAGE	
Nulliparous	More than 2 h without regional analgesia	
	More than 3 h with regional analgesia	
Multiparous	More than 1 h without regional analgesia	
	More than 2 h with regional analgesia	

of regional analgesia on the course of labor and delivery (length and mode of delivery) are difficult to interpret because of selection bias. That is, women with a prolonged, painful labor are more likely to request regional analgesia than women with faster labors. Pain has been suggested as a factor predicting long labor and need for operative vaginal or cesarean delivery. [71] Few prospective, randomized studies of analgesic technique on labor outcome are published, and the results are variable. [72] [73] [74] [75] Although not consistently proved to be important, reasonable principles to follow to minimize any potential effect of obstetric analgesia on outcome of labor and delivery include avoiding maternal hypotension and excessively high or dense blocks with motor impairment. The role of "early" institution of regional analgesia (e.g, at 3-5 cm of cervical dilation) on the outcome of labor (including duration of the first stage of labor and need for cesarean delivery) is also controversial, with some studies indicating an adverse effect of early analgesia and other studies not demonstrating an effect. [75] [76] [77]

ANESTHESIA FOR VAGINAL DELIVERY

Pain Pathways

During the first stage of labor, pain is due primarily to uterine contractions that cause stretching and thinning of the uterine cervix. Pain impulses travel via visceral afferent fibers accompanying the sympathetic nerves and enter the spinal cord at the T10, T11, T12, and L1 spinal segments. This pain is generally poorly localized and described as dull or cramping. In late first stage and in the second stage, stretching of the perineum produces additional pain, more somatic in nature, described as well localized and sharp. These impulses travel via the pudendal nerves from the S2, S3, and S4 spinal segments.

The amount of pain experienced by a woman during labor and delivery can be influenced by many factors, including participation in childbirth preparation classes, parity, and use of oxytocin. A variety of analgesic techniques are available.

Psychologic Techniques

A number of psychologic techniques have been used to assist women with the pain of labor, including hypnosis and psychoprophylaxis. The psychoprophylactic method of Lamaze [78] is the most popular form of psychologic analgesia. This technique relies on positive conditioning and patient education to decrease fear and anxiety regarding the process of childbirth. The patient is taught to focus on a specific object or location away from herself, concentrate on release of muscle tension, maintain a learned breathing rhythm, and listen to reassuring words from her coach. The increased concentration required by these activities distracts from, or inhibits, the painful sensations associated with uterine contractions. Preparation usually begins 6 weeks before delivery and includes instruction in the normal anatomy and physiology of pregnancy, labor, and delivery.

Using the McGill Pain Questionnaire, Melzack and colleagues [79] [80] measured the intensity of labor pain in parturients with and without prepared childbirth training. Those who had received prepared childbirth training had lower pain scores than those who had received no such training (Fig. 57-13) (Figure Not Available) . However, the differences in pain scores were relatively small. Scott and Rose [81] found that although mothers prepared in Lamaze required less analgesia, neonatal outcome in such patients was indistinguishable from that of mothers not prepared in Lamaze. Nevertheless, preparation for the event of childbirth is probably of benefit to almost all women and, regardless of the type of anesthesia used, can make the experience more pleasant. [82]

Acupuncture [83] [84] and transcutaneous electrical nerve stimulation [85] [86] [87] have also been evaluated with varied success.

Systemic Medication

Systemic medications, likely because of their ease of administration, are the most commonly used method to assist women with pain management during labor (Table 57-6) . [88]

Sedatives

Sedative-tranquilizers (Chs. 8 . and 9) may be used, either alone or in combination with an opioid, during the early first stage of labor to promote rest. The use of short-acting or medium-acting barbiturates, such as secobarbital, is no longer popular. The principal objection to the use of barbiturates is their antianalgesic effects in the mother and the prolonged depressant effects on the neonate. [89] Even with small doses that result in no clinical depression ascertainable by the Apgar score, the newborn's attention span may be decreased for 2 to 4 days. [90] The primary indication for the use of barbiturates is as a sedative-hypnotic during the early latent phase of labor when delivery is not anticipated for 12 to 24 hours. The phenothiazine derivatives promethazine and propiomazine seem to be equally effective in relieving anxiety, reducing opioid requirements, and controlling emesis during early labor. [91] Differences among these drugs are relatively minor. Hydroxyzine (Vistaril), although chemically unrelated to the phenothiazines, has similar ataractic properties. [92]

Benzodiazepines are used uncommonly in obstetrics but can be used in small doses for sedation and/or anxiolysis during very early labor or before cesarean delivery. Diazepam has been most extensively studied; it crosses the placenta rapidly, and maternal and fetal blood levels are approximately

TABLE 57-6 -- Analgesia for Labor and Delivery, a Survey of Practice in the United States, 1981 Versus 1992

ANALGESIC TECHNIQUE	1981	1992
None, psychologic techniques	35%	19%
Parenteral opioids	47%	52%
Lumbar epidural	15%	34%
Spinal	0%	4%
Paracervical block	5%	4%

Data from Hawkins et al [88]

Figure 57-13 (Figure Not Available) Comparison of pain scores using the McGill Pain Questionnaire. The figure compares labor pain and pain of other patients in a general hospital pain clinic. *(From Melzack [80])*

equal within minutes of an IV dose. [93] Although the neonate is capable of metabolizing small doses of diazepam, when the total maternal dosage during labor exceeds 30 mg, the drug and its active metabolite persist in pharmacologically active concentrations for at least a week in the neonate. [94] The principal adverse effects of large doses of diazepam are hypotonia, lethargy, decreased feeding, and hypothermia. [94] [95] [96] In small doses, diazepam produces minimal effects on the fetus and neonate, although reduced beat-to-beat variability may be noted on the FHR tracing. [96] [97] Midazolam is a water-soluble benzodiazepine with a rapid onset and a short duration of action. It is most often used for sedation during cesarean delivery (after delivery of the newborn). Rapid IV administration may produce deep sedation and amnesia, [98] and if it is used, it should be administered slowly in increments of 0.5 to 1.0 mg or less with careful observation of the mother. When midazolam (0.3 mg/kg) was used for induction of general anesthesia, more adverse neonatal effects (problems with general body tone and body temperature) were noted when compared with thiopental (4 mg/kg). [99]

Opioids

The most commonly used opioids (Ch. 10) . for labor analgesia include meperidine, morphine, fentanyl, nalbuphine, and butorphanol. No opioid can produce completely effective analgesia for labor and delivery without causing side effects that include some degree of maternal respiratory depression, sedation, and obtundation of reflexes. Therefore, opioids are used to reduce rather than completely eliminate pain. Opioids are most often administered via intermittent intramuscular (IM) or IV injection. Clinical reports describe successful use of patient controlled analgesia to administer opioids (meperidine, nalbuphine, fentanyl) [100] [101] [102] [103] during labor.

Meperidine

Meperidine is a commonly used opioid in obstetrics. The usual IM dose is 50 to 100 mg and the IV dose is 25 to 50 mg. The peak analgesic effect occurs 40 to 50 minutes after IM administration and 5 to 10 minutes after IV administration. The duration of action is 3 to 4 hours. Meperidine used for labor analgesia can produce dose-dependent neonatal depression, [104] as evidenced by prolonged time to sustained respiration, decreased Apgar scores, [89] and abnormal results from neurobehavioral examination. [105] [106] These effects are related to the dose and to the time interval between drug administration in the mother and delivery of the infant. Infants born within 1 hour or more than 4 hours after IM administration of 50 to 100 mg of meperidine to the mother are no more depressed than neonates not receiving meperidine (Fig. 57-14) . [89] Fetal exposure to meperidine is highest 2 to 3 hours after administration of the drug to the mother (Fig. 57-15) (Figure Not Available) . [106] The prolonged changes in neonatal neurobehavior examinations after *in utero* exposure to meperidine are attributed to the prolonged presence of the meperidine metabolite normeperidine in the neonatal circulation. [107] [108]

Figure 57-14 Correlation of the time of administration of meperidine and neonatal depression (defined as Apgar score of 0 to 6). *(From Shnider and Moya [85])*

Figure 57-15 (Figure Not Available) Following maternal administration of meperidine (50 mg IV) during labor, meperidine excretion was measured in the neonate's urine for the first 3 days. The relationship between the drug-delivery interval and the urinary excretion of meperidine by the neonate is shown. For each bar, the mean, standard error, and number or infants are given. Infants whose mothers received meperidine 1 to 2 and 2 to 3 hours prior to delivery excreted more meperidine. *(From Kuhnert et al [431])*

Fentanyl

The usual doses of fentanyl used during labor are 50 to 100 mug IM and 25 to 50 mug IV. After IV administration, the peak effect occurs within 3 to 5 minutes, and the duration is 30 to 60 minutes. Placental transfer is rapid. [109] [110] A dose of 1 mug/kg administered IV to the mother within 15 minutes of cesarean delivery did not produce adverse effects on umbilical cord blood gases or neonatal Apgar scores or neurobehavioral scores. [110] It was concluded that fentanyl might be a useful adjuvant for either regional or general anesthesia for cesarean delivery. Use of fentanyl for intrapartum labor analgesia has also been studied. [101] [111] Temporary analgesia and mild sedation were apparent after administration of 50 or 100 mug. A transient decrease in FHR variability was noted after fentanyl administration. Regardless of the maternal dose (average, 140 ± 42 mug; range, 50-600 mug), newborn drug levels were low and always less than maternal levels. No adverse effects of *in utero* exposure to fentanyl was noted on neonatal examination. [111]

Morphine

The peak analgesic effect of morphine occurs 1 to 2 hours after IM administration and 20 minutes after IV administration. The duration of action is 4 to 6 hours. In equianalgesic doses, morphine produces more respiratory depression of the newborn than does meperidine (Fig. 57-16) (Figure Not Available) . [112] Because of the delayed onset and the prolonged duration of action of morphine in the mother and the greater sensitivity of the newborn's respiratory center to morphine, meperidine and fentanyl have replaced it as obstetric analgesics during active labor. Morphine is usually reserved for use in very early labor.

Butorphanol and Nalbuphine

Butorphanol and nalbuphine are two synthetic agonist-antagonist narcotic analgesics. In nonpregnant patients, analgesic doses of butorphanol (2 mg) and nalbuphine (10 mg) produce respiratory depression equivalent to that caused by 10 mg of morphine. Although larger doses of morphine produce more respiratory depression, larger doses of butorphanol and nalbuphine do not. [113] [114] However, larger doses of these drugs may produce maternal dizziness and somnolence and adverse neonatal neurobehavioral effects. [115] Even with the usual clinical doses, both of these drugs are rapidly transferred across the placenta and have produced sinusoidal FHR patterns. [116] [117] (This heart rate abnormality, which is associated with high-output cardiac failure in the fetus, appears to be benign when it results from medication and does not in itself signify fetal compromise.) The few studies that have been performed with these drugs in obstetrics have not shown significant advantages over other opioids. [103] [118] [119] [120] [121]

Ketamine

Dissociative or amnesia-producing drugs, such as ketamine (Ch. 9) . and scopolamine, are used infrequently during labor. In obstetrics, low-dose IV ketamine (10-25 mg, or 0.25-mg/kg increments) can be used in lieu of inhaled agents to produce analgesia (which can be useful during operative

Figure 57-16 (Figure Not Available) Effect of equianalgesic doses of morphine and meperidine on the CO_2 response curve in the newborn. The standard error of the mean is indicated by the rectangles above each point. *(From Way et al [112])*

vaginal delivery or cesarean delivery). [122] Care must be used to avoid loss of maternal protective reflexes during IV analgesia provided by ketamine.

Inhaled Analgesia

Use of inhaled anesthetics (other than nitrous oxide) for labor analgesia is rare. Methoxyflurane was used in the past to assist with the pain of labor. Now, use of inhalational analgesia is limited but might be used, for example, during operative vaginal delivery. Proper administration of inhaled analgesia in this context requires administration of potent inhaled agents by mask in low concentrations to prevent loss of consciousness and protective airway reflexes. The anesthesiologist must remain in verbal contact with the patient and provide continuous reassurance and encouragement. The major risk of inhaled analgesia is accidental anesthetic overdose with resulting loss of protective reflexes. Vomiting or silent regurgitation may then occur, resulting in aspiration pneumonitis, obstruction, and asphyxia.

Nitrous oxide can be administered for analgesia during labor. It is usually combined by use of a blender apparatus with 50 percent oxygen. These portable machines should be equipped with scavenging devices that reduce the occupational exposure to nitrous oxide for labor room personnel. Reliable analgesia with 50 percent nitrous oxide has not been demonstrated. [123] [124]

Regional Anesthesia

Regional analgesic techniques (Ch. 42) are the most effective means of providing analgesia for labor and vaginal delivery, and their use for analgesia in the United States has increased in the past decade (see Table 57-6) . [88] Regional blocks provide pain relief while allowing the parturient to be awake and able to participate in the labor and delivery process. Epidural analgesia has been shown to reduce levels of catecholamines in the maternal circulation, [125] which may be beneficial to the fetus. [126] Compared with parenteral or inhalational analgesic techniques, regional anesthesia is unlikely to produce drug-induced depression in the fetus or mother. The most common regional anesthetic techniques are lumbar epidural, caudal, and spinal blocks. Paracervical, pudendal, and local perineal infiltration are techniques

usually administered by the obstetrician. Each technique has a specific application and can be used to block some or all of the nerves carrying the pain impulses.

Patient Preparation

Before administering a regional block, an IV infusion should be started, and equipment for resuscitation and treating complications must be immediately available. These include an oxygen delivery system, airways, laryngoscope, endotracheal tubes, suctioning apparatus, thiopental or diazepam for treatment of convulsions, ephedrine for treatment of hypotension, and naloxone for treatment of opioid-induced respiratory depression. A preanesthetic evaluation of the patient, an understanding of the obstetric plan, and an understanding of the fetal status should be performed before a regional block or other anesthetic is administered. Although this is sometimes difficult during the pain of labor, informed consent for the procedure must be obtained. Appropriate monitors (at our institution, maternal blood pressure, electrocardiogram, and FHR are monitored while a regional block is performed) must be in place. Before the block is given, approximately 500 mL of IV balanced saline solution should be infused to decrease the incidence of hypotension from anesthetic-induced sympathetic block.

Lumbar Epidural Analgesia

Lumbar epidural analgesia is the most common regional block performed for labor analgesia. Usually, the block is placed once the patient is in established labor. If augmentation with oxytocin is anticipated, the block can be started earlier. Continuous epidural analgesia provides the ability to

administer analgesics for the duration of labor, with the dose adjusted for desired effect. Low doses of local anesthetics or opioids are often sufficient during the first part of labor to provide an effective T10 to L1 segmental block. As labor progresses, anesthetic dose may need to be increased to cover the increased pain of the late first and second stages of labor and the distribution of the pudendal nerve (S2-S4). The benefits of epidural analgesia include effective pain relief, reduction in maternal catecholamines, and a means to provide surgical anesthesia should that be necessary. There are few absolute contraindications for epidural (spinal or caudal) analgesia; these include patient refusal, infection at the site of needle placement, overt maternal coagulopathy, and maternal hemodynamic instability. Other conditions (e.g., preexisting neurologic disease, prior back surgery, isolated coagulation abnormalities, some cardiac disease) must be considered on a case-by-case basis, with the particular nature of the patient's problem and the risks and benefits of available analgesic techniques being weighed.

The Epidural Test Dose in Obstetrics

Placement of catheters for epidural use may be complicated by IV or subarachnoid placement of the catheter. Initially, aspiration can help identify possible IV or subarachnoid placement of the catheter. Because a negative aspiration does not always ensure against an intravascular or subarachnoid injection, the catheter position must be verified by injecting a test dose. The function of a test dose is to allow recognition of accidental subarachnoid or intravascular catheter location, without causing harm. Injection of a small dose (e.g., 45 mg of lidocaine, 7.5 mg of bupivacaine) can be used to detect subarachnoid injection; evidence of anesthetic block (including sacral analgesia) and possibly leg weakness should be present after 3 to 5 minutes. [127] [128]

Controversy surrounds the best means to detect accidental IV placement of an epidural catheter in obstetric patients. If injected into a blood vessel, epinephrine, 15 mug (i.e., 3 mL of a 1:200,000 solution), has been shown to rapidly produce a transient increase in heart rate of 20 to 30 beats/min in volunteers and surgical patients. [129] However, in the laboring patient, maternal heart rate variability stemming from the pain of uterine contractions may confuse interpretation of the heart rate response after injection of an epinephrine test dose. Further, the pregnant patient may respond less reliably to 15 mug of epinephrine. Leighton et al [130] administered IV either 15 mug of epinephrine or saline to laboring women. When surgical criteria (an increase in heart rate of 25 bpm within 2 minutes of injection) were applied, only five of ten parturients were identified as having received epinephrine. When alternative criteria were applied (an increase in heart rate of >10 bpm over the maximum heart rate observed during the 2 minutes before injection), nine of ten patients had a "positive" response. Another concern with epinephrine is its potential adverse effect on uterine blood flow. Animal data reveal that IV injection of 15 mug epinephrine transiently reduces uterine blood flow. [131] Further, a hypertensive patient may have an exaggerated response to IV epinephrine. Means to improve the reliability of epinephrine include injecting the test dose between uterine contractions when maternal heart rate is stable, repeating test doses when the response is equivocal, and considering only rapid, sudden increases in heart rate to be positive. [132] However, the lack of specificity, sensitivity, and potential adverse effects have led many to avoid this test dose in obstetrics.

Injection of subconvulsant doses of local anesthetics (e.g., 100 mg of lidocaine [133] or chloroprocaine) have also been suggested for use as a test for IV catheter placement. Detection of IV placement relies solely on the subjective responses (tinnitus, perioral numbness) by the mother, which may be unreliable in the anxious or previously medicated parturient. Use of catecholamines other than epinephrine that produce increases in maternal heart rate without adverse effects on uterine blood flow (e.g., isoproterenol, 5 mug [134]) have also been studied, but data from humans are limited. [135] [136] Others have described the injection of 1 to 2 mL of air into the epidural catheter and listening for evidence of IV air with a Doppler monitoring device placed over the maternal precordium. [137] [138]

The safe practice of administering epidural analgesia involves catheter aspiration, testing for possible IV placement (recognizing the limitations of the available tests), testing for possible subarachnoid placement, and injecting the total dose of anesthetic in small increments (
5 mL) while waiting 30 to 60 seconds between injections and constantly observing the patient for evidence of local anesthetic toxicity.

Epidural Agents for Labor and Delivery

The agent or agents used for epidural analgesia must provide effective analgesia and be safe for the mother, fetus, and neonate. When used for labor and vaginal delivery, the agent should produce minimal maternal skeletal muscle relaxation, thereby permitting normal flexion and internal rotation of the fetal head and normal maternal expulsive efforts during the second stage of labor. Epidural opioids, local anesthetics, and their combination are used for labor analgesia.

Epidural Opioids for Labor

Epidural morphine was the first epidural opioid evaluated for labor analgesia. Unfortunately, it has a very long onset time (30-60 minutes), and even with generous doses (7.5 mg), it provides only mediocre pain relief and is often ineffective during the late first and second stages of labor (Fig. 57-17) . [139] Epidural meperidine, 100 mg, provides consistently good analgesia that lasts for about 2.5 hours. [140] Epidural fentanyl, 100 to 200 mug, quickly provides analgesia (5-10 minutes) that lasts 1 to 2 hours with few side effects. [141] In some patients, these doses had to be repeated as often as three times; however, umbilical artery fentanyl levels are low, and in one study, one of 38 neonates was treated for presumed opioid-related depression. [141] Epidural sufentanil, 5 to 50 mug, following a test dose of 45 mg of lidocaine and 15 mug of epinephrine has been reported to provide significant dose-related analgesia for labor. [142] The lower doses, 5 to 15 mug, providedapproximately 1 hour of pain relief, and the larger doses, 40 mug and 50 mug, resulted in a 2-hour analgesic period. Certainly, there is a concern of accidental IV or

Figure 57-17 Pain relief during labor following intrathecal or epidural morphine compared with epidural bupivacaine. *(*Data from Abboud et al [216] ; **data from Hughes et al [139])*

subarachnoid injection of such large doses of sufentanil. Interestingly, epidural administration of 10 mug of sufentanil failed to provide analgesia in patients who did not receive any local anesthetic as a test dose. [143] For meperidine and fentanyl, lower doses (25 mg of meperidine, [144] 80 mug of fentanyl [144]) are effective if combined with a small dose of local anesthetic.

It is not clear what should be considered the maximal total dose of epidural opioid that can be given before birth without affecting the clinical condition of the neonate. Some believe that 30 mug of sufentanil should not be exceeded, [145] although there are data to suggest that 50 mug is safe. [142] One observational study reported decreased neurologic and adaptive capacity scores in neonates whose mothers had received more than 200 mug of fentanyl during labor. [146] Because data clarifying the maximum dose are scarce, if epidural opioids become ineffective for labor analgesia, it makes sense to consider changing to a different epidural analgesic rather

than giving several doses of an opioid.

Epidural Local Anesthetics

Epidural local (Ch. 13) anesthetics are the most commonly used epidural analgesics for labor and delivery. The anesthetics used include bupivacaine, lidocaine, 2-chloroprocaine, and more recently, ropivacaine.

Bupivacaine.

Bupivacaine is the most commonly used local anesthetic for labor analgesia. Its relatively long duration of action and apparent lack of tachyphylaxis [147] are attractive features. Bupivacaine is highly protein bound, and placental passage is low (the umbilical venous:maternal venous concentration ratio is about 0.3). [148] Further, bupivacaine is effective in low concentrations (0.125% alone, or as low as 0.04% when combined with opioid [149]) for early labor. Somewhat higher concentrations (0.25% alone or 0.125% with opioid) may be necessary in late labor. Use of low concentrations minimizes motor block. The 0.5 percent concentration is reserved for use during cesarean delivery.

A concern with the use of bupivacaine is its cardiotoxicity. Bupivacaine-induced seizures from accidental intravascular injection have been associated with cardiac arrests resulting in difficult resuscitation or death. [150] Although these arrests occurred in patients given either 0.5 percent or 0.75 percent bupivacaine, in the early 1980s, the U.S. Food and Drug Administration proscribed the use of the 0.75 percent in obstetrics. (It is important to underscore that cardiac arrests have occurred with concentrations less than 0.75 percent--the total dose and subsequent serum level of bupivacaine determine whether a toxic reaction occurs, not the concentration of the solution. It is, however, easier to give a large dose quickly with the higher concentration.) Animal studies have revealed that bupivacaine appears to be more cardiotoxic than lidocaine. [151] [152] [153] [154] [155] The most likely mechanism for such cardiotoxicity relates to the action of bupivacaine on cardiac sodium channels and the physicochemical properties of bupivacaine. Both lidocaine and bupivacaine block the sodium channels of nerve and heart, an effect that slows or stops conduction. Blockade of cardiac sodium channels by lidocaine appears to be well tolerated by the heart; in fact, the drug is commonly used as an antiarrhythmic agent. When electrophysiologic differences between lidocaine and bupivacaine were compared, lidocaine was found to enter the sodium channel quickly and to leave quickly; bupivacaine was found to be a "fast-in, slow-out" agent. [155] Avid protein binding, particularly at low pH, contributes to this feature and contributes to the difficulties in resuscitating patients in cardiac arrest from bupivacaine toxicity. In addition, the higher lipid solubility of bupivacaine (compared with that of lidocaine) allows the drug to enter the cell more easily. [156]

Most of the reported cases of bupivacaine cardiotoxicity have involved obstetric patients. The reason for the increased

---

incidence and the poor outcome of cardiotoxic reactions to bupivacaine in pregnancy is not clear. It may reflect the more frequent use of bupivacaine for obstetric epidural block or the fact that it is easier to accidentally puncture a dilated epidural vein during parturition. In addition, physiologic changes during pregnancy (low functional residual capacity, high oxygen consumption, and aortocaval compression) make the parturient more difficult to resuscitate than the nonpregnant patient. [157] The hypoxia and acidosis that would be expected to occur rapidly in the pregnant patient contribute to bupivacaine cardiotoxicity. [158] [159] [160] Further animal data suggest that reduced protein binding and higher free bupivacaine levels in pregnancy [161] [162] and progesterone-enhanced bupivacaine (but not lidocaine) cardiac toxicity [163] may contribute to the problem during pregnancy. It is encouraging that an apparent reduction in regional anesthetic-related maternal mortality has been noted since 1984, [164] despite the increased use of regional blocks for labor and cesarean delivery. Perhaps, at least in part, this is a result of the clinical practice of routine testing of epidural catheters for IV or subarachnoid placement and avoiding large bolus injections of local anesthetic.

Lidocaine.

Lidocaine, a local anesthetic commonly used in the operating room, is very popular in obstetrics, particularly for cesarean delivery (1.5-2.0% solutions). For labor, concentrations of 0.75 to 1.0 percent have been used but may not be as effective as bupivacaine. [165] Umbilical venous:maternal venous concentrations are approximately 0.8. [166] [167] However, in 1974, Scanlon et al [168] reported that when used for maternal epidural analgesia during labor, lidocaine compromised neonatal neurobehavioral function. Numerous subsequent studies [169] [170] have either failed to corroborate these findings or found changes so minimal as to be clinically insignificant.

2-Chloroprocaine.

2-Chloroprocaine is an ester-type local anesthetic with a rapid onset and a brief duration of action. Because of its rapid hydrolysis by maternal plasma cholinesterase (the half-life of chloroprocaine in maternal blood is 21 seconds), very little drug crosses the placenta. [171] [172] A disadvantage of 2-chloroprocaine is its apparent antagonism of subsequently injected epidural opioids [173] and bupivacaine. [174] [175] It is particularly useful to rapidly extend a labor epidural block for operative vaginal (2-3% solutions) or cesarean (3% solution) delivery.

In the past, 2-chloroprocaine was thought to be neurotoxic because of reports of arachnoiditis following accidental subarachnoid injection. [176] [177] [178] [179] Subsequent investigations traced the cause of arachnoiditis to the low pH of the anesthetic solution to which sodium bisulfite, an antioxidant, had been added to stabilize the formulation. [176] [180] [181] Replacement of bisulfite by disodium ethylenediaminetetraacetic acid (EDTA) has removed the apparent associated danger of arachnoiditis and exchanged it for the less serious side effect of backache, which tends to accompany large doses (>30 mL) of this formulation. [182]

Ropivacaine.

Ropivacaine is a newer amide local anesthetic similar in structure, potency, and pharmacodynamics to bupivacaine. In animal studies, ropivacaine appears to have a cardiotoxicity that is intermediate between those of lidocaine and bupivacaine. [151] [183] [184] Unlike with bupivacaine, progesterone does not appear to enhance its cardiotoxicity. [185] In pregnant sheep, a more rapid clearance of ropivacaine than that of bupivacaine after IV administration led to a larger dose (but not serum concentration) required to produced toxicity. [186] These findings suggest that there may be a greater margin of safety in pregnant patients with ropivacaine than with bupivacaine, if accidentally injected IV.

Clinical reports find ropivacaine very similar to bupivacaine for labor analgesia. Solutions of either ropivacaine or bupivacaine, 0.25 percent, given as a bolus, followed by an infusion of the same concentration, provided equivalent analgesia. [187] Similarly, 0.125 percent solutions of ropivacaine or bupivacaine delivered comparable analgesia when administered via patient-controlled epidural analgesia. [188] Although an *in vitro* study suggested reduced blockade of motor fibers with ropivacaine compared with bupivacaine, [189] studies in laboring patients have yet to confirm this potential advantage. [187] [188]

Epinephrine as an Adjuvant to Local Anesthetics.

Many investigators recommend that epinephrine be added to local anesthetics to decrease systemic absorption, provide a longer duration of action, and intensify the motor block. Reports of studies questioning whether added epinephrine decreases systemic absorption of epidurally injected local anesthetics in the obstetric patient have been variable. [190] [191] [192] [193] [194] In epidural anesthesia for vaginal delivery, the addition of epinephrine, except for the test dose, is unnecessary because of the small amounts of drug used and the lack of need for motor block. Although the beta-sympathomimetic effects of systemically absorbed epinephrine may produce a transient decrease in uterine contractility, [195] the significance of this finding is unclear. Enhanced analgesia, however, is a potential advantage. [196] For cesarean delivery, in which larger doses of local anesthetic are used and more profound motor block is desired, many favor the addition of epinephrine 1:200,000 to the local anesthetic solution.

Epidural Opioids plus Local Anesthetics

Combining epidural local anesthetics with opioids has become a common practice in obstetric analgesia for labor and delivery. The rationale is that these agents work at two distinct sites--the local anesthetic at the nerve axon and the opioid at the spinal cord receptor--to eliminate pain via a combined and possibly synergistic mechanism. The use of a combination of local anesthetic plus an opioid reduces the total amount of local anesthetic required to produce effective analgesia, and

therefore less motor block occurs, which parturients appreciate.

Mixtures of epidural fentanyl or sufentanil with bupivacaine are commonly used during labor to initiate and maintain analgesia. [145] [149] [175] [197] [198] [199] [200] [201] [202] [203] [204] [205] [206] Addition of 50 mug of fentanyl or 10 mug of sufentanil to 0.04 to 0.25 percent bupivacaine in a 10 mL bolus produces a more rapid onset of more complete labor analgesia than does bupivacaine alone. When continuous infusions are administered after the initial bolus,

TABLE 57-7 -- Suggested Techniques for Lumbar Epidural Anesthesia for Labor and Vaginal Delivery

1. Place epidural catheter in usual manner after maternal informed consent, hydration, and placement of appropriate monitors.
2. Use test dose to rule out accidental intravascular or subarachnoid injection (e.g., 3 mL of lidocaine 1.5% with epinephrine 1:200,000).
3. Initial block--options:
   a. Bupivacaine 0.125-0.25%, lidocaine 1%, or 2-chloroprocaine 2% (8-15 mL)
   b. Sufentanil 10-15 mug in 10 mL of saline
   c. Bupivacaine 0.0625-0.125% + fentanyl 50 mug or sufentanil 10 mug
4. Subsequent analgesia--options:
   a. Intermittent--repeat as above, as necessary, to maintain maternal comfort
   b. Continuous infusions: 8-15 mL/h
      1. Bupivacaine 0.04-0.125% + fentanyl 1-2 mug/mL or sufentanil 0.1-0.3 mug/mL
      2. Bupivacaine 0.125% without opiate
   c. Patient-controlled epidural analgesia (above continuous-infusion drug regimens; background infusion: 4-6 mL/h; option for patient-administered doses: 3-4 mL every 10-20 min) [204] [211] [212] [213]
5. Blood pressure is monitored every 1-2 min for the first 10 min after initial injection of local anesthetic, then every 5-15 min during the infusion and until the block wears off.
6. Careful nursing supervision is mandatory.
7. Patient should be maintained in the lateral position throughout labor to prevent aortocaval compression. Patient should turn from side to side every hour to avoid a one-sided block.
8. Sensory level, adequacy of anesthesia, and motor block should be checked regularly.
9. Adjust infusion rate up or down, depending on dermatome level. Increase concentration of local anesthetic if block is not adequately dense.
10. Diminishing analgesia may indicate intravascular migration. A repeat test dose should be administered before any bolus injections.
11. Development of motor block may indicate subarachnoid migration. Catheter location should be verified by aspiration, careful sensorimotor examination, and if necessary, cautious administration of test dose.
12. If perineal anesthesia is required, administer 10 to 20 mL of local anesthetic, e.g., the bupivacaine infusate, or for denser anesthesia, lidocaine 1.5-2% or chloroprocaine 2-3%.

very low concentrations of bupivacaine (0.04-0.125%) may be combined with fentanyl, 1 to 2.5 mug/mL, or sufentanil, 0.1 to 0.3 mug/mL, at a rate of 8 to 15 mL/h to achieve excellent labor analgesia for the first and often the second stage of labor. One study found the analgesia conferred by an infusion of 0.0625 percent bupivacaine with 2.5 mug/mL of fentanyl at 12 mL/h to be equivalent to that from 0.0625 percent bupivacaine with 0.25 mug/mL of sufentanil. [207] The most significant advantage of combining these opioids with bupivacaine is the lack of motor blockade, [202] which may promote spontaneous vaginal delivery. [145] [203] There appear to be no adverse neonatal effects [198] or loss of beat-to-beat FHR variability when this technique is used. [200]

Suggested drug regimens for initiating lumbar epidural anesthesia for labor and vaginal delivery are presented in Table 57-7 . While an epidural block is being established, the mother should be kept on her side or positioned with left uterine displacement to prevent supine hypotension. Arterial blood pressure should be monitored every 1 to 2 minutes for the first 10 to 20 minutes after injection of local anesthetic until the block is established and stable. During the first 20 minutes after the initial dose and after any additional doses, the patient should be observed continuously and not be left unattended. The FHR and uterine contractions should be continuously monitored electronically before and after an epidural block is instituted. If the initial anesthetic injection does not result in satisfactory analgesia, the anesthesiologist assesses whether or not the epidural catheter is properly situated in the epidural space. If not, the catheter is replaced. If the block is too low or asymmetric, additional volume can be given. Some also advocate withdrawing the epidural catheter 1 cm or so and positioning the patient with the unblocked side dependent to assist with achieving a bilateral block. If labor is progressing rapidly, a more potent analgesic solution may be necessary.

Continuous-Infusion Lumbar Epidural Analgesia

Continuous infusion of low concentrations of local anesthetic into the epidural space provides a continuous stable anesthetic level, thereby avoiding the fluctuations in pain relief found with intermittent epidural injections during labor, and results in improved patient satisfaction. [208] [209] [210] Other potential benefits include less maternal hypotensive episodes from fluctuating levels of sympathetic block and a less labor-intensive anesthetic because there is no need for the time-consuming repeat test doses or the necessary close monitoring of the patient for the first 20 minutes after a reinjection. Because of the dilute local anesthetic solutions used, motor block can be limited. To safely achieve optimum analgesia and patient satisfaction, the anesthesiologist should examine and interview the patient frequently. At these times, the anesthesiologist can make necessary adjustments in the rate of infusion or the concentration of local anesthetic and can note any signs of intravascular or subarachnoid migration of the catheter. Between visits, the patient must be closely supervised by trained nurses. The technique is outlined in Table 57-7 .

The potential complications of this technique are intravascular or subarachnoid migration of the catheter during the infusion or epidural infusion rates that are too high. If the epidural catheter migrates into a blood vessel, the only side effect would probably be loss of analgesia. Significant systemic toxicity is avoided because of the very low rate of infusion of local anesthetic. If the epidural catheter accidentally punctures the dura mater, the onset of motor block from the resulting spinal analgesia would be slow and easily diagnosed. If the infusion rate is too high, the slowly ascending sensory level should be easily recognized.

Another form of continuous-infusion epidural analgesia is

patient-controlled epidural analgesia. [204] [211] [212] [213] [214] [215] After the epidural block is established, a slow rate of infusion is set, with the option for the patient to self-administer a small top-up dose as needed (see Table 57-7) . This form of analgesia requires that the patient understands that she has control over her analgesia. With analgesia being equivalent, one study found overall patient satisfaction with patient-controlled epidural analgesia to be higher than traditional continuous-infusion techniques. [214]

Caudal Analgesia

A caudal block is administered only after labor is well established. Caudal blocks are performed in patients positioned either on their sides or prone with a bolster under the thighs. With the coccyx used as a landmark for the midline, the sacral cornua and the sacrococcygeal ligament are palpated. Once the needle is placed in the canal, the surgical drapes are removed, and a rectal examination is performed to exclude the possibility of accidental puncture of the fetal presenting part and

subsequent anesthetic intoxication of the fetus. [216] After drapes and gloves are replaced, the caudal catheter is introduced through the needle. After aspiration, test doses of local anesthetics (as described for epidural anesthesia) are given. The volume necessary to provide a T10 block varies from 10 to 20 mL.

Lumbar epidural anesthesia is preferable to caudal anesthesia in labor for several reasons: (1) segmental T10-L1 dermatome levels can be achieved in early labor when sacral anesthesia is not required; (2) less drug is needed during labor; (3) pelvic muscles retain their tone, and rotation of the fetal head is more easily accomplished; and (4) despite the increased risk of dural puncture, placement of the lumbar epidural needle is often technically easier for the anesthesiologist and less painful for the patient than caudal anesthesia. Caudal anesthesia administered just before delivery has advantages over lumbar epidural anesthesia in that the onset of perineal anesthesia and muscle relaxation is more rapid. A "double-catheter" technique has been described in which a lumbar epidural catheter is placed for use during the first stage of labor, and a caudal catheter is placed for use during the second stage and delivery. This technique can be used in patients with cardiac disease in whom it is desired to avoid the high anesthetic (and sympathetic) block height that sometimes accompanies attempts to provide complete perineal analgesia with a lumbar epidural catheter.

Spinal Opioid Analgesia

Intrathecal injection of very small doses of opioids (Ch. 69) can produce effective labor analgesia without the usual systemic effects of opioids and without the motor block and sympathectomy that often accompany the use of epidural and spinal local anesthetics. Techniques using opioids alone during labor may be particularly useful in patients who wish to ambulate during early labor or in those with cardiac disease who require analgesia that is adequate to prevent the potentially dangerous increases in heart rate and cardiac output associated with painful labor and in whom anesthesia-related decreases in SVR and cardiac output would not be tolerated (e.g., aortic stenosis and pulmonary hypertension).

Morphine was the first intrathecal opioid studied for the relief of labor pain. Large doses were used initially (0.5-2.0 mg). [217] [218] Although intrathecal morphine provides good analgesia during the first stage of labor for many patients (see Fig. 57-17) , it is often inadequate for the second stage of labor. [218] The latency of analgesia with morphine is long (40-60 minutes), and the side effects, nausea (>50%) and pruritus (80%), are common. [218] Pruritus can be treated with diphenhydramine, nalbuphine, or naloxone. [219] Other side effects include urinary retention, drowsiness, dizziness, and potential respiratory depression. Subsequently, use of a smaller dose of morphine (0.25 mg) combined with fentanyl (25 mug) was reported [220] and found to provide a rapid onset (about 5 minutes) of reasonably good analgesia for the first stage of labor, but side effects remained problematic. Key to the successful use of intrathecal morphine for labor analgesia are recognizing and treating side effects and managing inadequate analgesia. Although respiratory depression is a rare side effect of intrathecal morphine, sedation and drowsiness can occur if women receive systemic analgesics in addition to intrathecal morphine. [221] The side effect profile of intrathecal morphine has led many to abandon its use in laboring patients, but it may be of benefit in patients with significant medical problems in whom it is desired to avoid the effects of epidural local anesthetics. [222] [223]

Sufentanil (10 mug) is commonly administered as an initial analgesic for labor. It has a rapid onset of action which lasts 60 to 180 minutes. Fentanyl (10-25 mug) alone also provides a rapid onset of analgesia lasting 30 to 120 minutes. [224] Fentanyl is used less often than sufentanil because of its shorter duration of action and a clinical impression that sufentanil provides better analgesia. [224] Sufentanil has a faster onset time than epidural bupivacaine (Fig. 57-18) (Figure Not Available) . [225] The addition of a small dose of bupivacaine (2.5 mg) to intrathecal sufentanil has been proposed to improve and increase the duration of the analgesia afforded by sufentanil alone [226] and has been described as being particularly helpful in patients in advanced labor. [227]

There are, however, notable side effects from intrathecal sufentanil. Pruritus is a frequent side effect (>80%). [224] [225] Hypotension (defined as a decrease in systolic blood pressure to <90 mm Hg) has also been reported following intrathecal sufentanil analgesia for labor. [226] Hypotheses to explain this hypotension include (1) a reduction in stress response as a result of analgesia and (2) sympathetic block from a local anesthetic effect of the opioid. Although sensory levels have been measured following intrathecal sufentanil [228] and may at times be quite high, [229] one study found no evidence of sympathetic block following intrathecal sufentanil, [230] suggesting that the observed changes in blood pressure are a result of reduced catecholamine levels and analgesia. Changes in the FHR have also been reported to occur within 40 minutes of injection of intrathecal sufentanil in 14 to 18 percent of patients. [228] [231] The cause of the FHR changes is unknown, but the incidence is similar to that following epidural bupivacaine. [231] Uterine hyperactivity following analgesia has been suggested. [232] It is prudent to monitor maternal blood pressure, uterine contractions, and FHR after intrathecal sufentanil injection. Finally, although rare (estimated incidence, 0.021%), [233] respiratory depression

Figure 57-18 (Figure Not Available) Visual analog pain scores after injection of intrathecal sufentanil (squares) or epidural bupivacaine (circles). Intrathecal sufentanil was injected at -2 minutes. Time 0 is the beginning of the injection of epidural bupivacaine (the times differ because a CSE technique was used for both groups of patients--the epidural bupivacaine patients received intrathecal saline, and the intrathecal sufentanil patients received epidural saline). Each point represents the median ± 25th and 75th percentiles of 25 patients. All time points beyond baseline differ from their respective baseline values. Intrathecal sufentanil provided a more rapid onset of analgesia, even allowing for the different injection times. * $P < .05$ versus sufentanil. *(From D'Angelo et al [225])*

and/or arrest have been reported following the use of intrathecal sufentanil. [234] [235] Proposed risk factors for respiratory depression include large dose (15 mug), repeat doses, and prior administration of parenteral opioids. Patients must be carefully observed for this side effect.

Intrathecal meperidine offers unique features for laboring patients. Intrathecal meperidine has local anesthetic effects, and large doses (60 mg) have been used for surgical anesthesia. Doses of 10 to 20 mg have been used for labor analgesia and have been reported to be particularly effective in patients in advanced labor. [236]

Combined Spinal-Epidural Analgesia

Intrathecal opioids can be administered as a single injection, through a continuous spinal catheter (e.g., an epidural catheter placed via an epidural needle--this technique may be feasible if attempted epidural placement proved difficult and was complicated by dural puncture), or by a combined spinal-epidural (CSE) technique. The CSE technique involves identifying the epidural space with an epidural needle, placing a long spinal needle through the epidural needle, confirming cerebrospinal fluid (CSF) flow, injecting the intrathecal drug, withdrawing the spinal needle, and then placing an epidural catheter to be used later in labor. When the epidural catheter is dosed for labor analgesia, the usual precautions (aspirating, administering a test dose, fractionating the total local anesthetic dose) must be followed. Less epidural local anesthetic may be required for effective analgesia in patients who have received intrathecal opioids, perhaps from an additive or synergistic effect of the previously injected opioid or from leak of the local anesthetic across the dura into the subarachnoid space. [237] [238]

Spinal Anesthesia for Vaginal Delivery

Spinal anesthesia of the sacral nerve roots, often called saddle block, is administered immediately before delivery. A small dose of hyperbaric local anesthetic (e.g., bupivacaine, 5 mg, or lidocaine, 15-20 mg), is injected into the subarachnoid space while the patient is in the sitting position to accomplish sacral anesthesia. More commonly, however, anesthetic distribution to a T10-S5 dermatome level is desired and can be accomplished with slightly larger doses of hyperbaric bupivacaine (6-8 mg) or lidocaine (30-50 mg). Care must be taken not to administer the drug just before or during a uterine contraction lest the accompanying Valsalva maneuver result in an excessively high anesthetic level.

Complications of Regional Analgesia

The most significant complications of regional anesthesia are severe hypotension, convulsions induced by local anesthetics, total spinal anesthesia with resulting respiratory arrest, nerve injury, and headache secondary to dural puncture.

Hypotension

Hypotension remains the most common side effect of major conduction anesthesia for vaginal or cesarean delivery. The incidence and the severity of hypotension depend on the dermatome level of the block, the position of the parturient, the physical status of the parturient, and the prophylactic measures taken to avoid hypotension. Such measures include administration of IV fluids before the block, left uterine displacement, and administration of ephedrine. [239] [240] [241] [242] It is most common after induction of spinal anesthesia for cesarean delivery but can certainly occur in the laboring patient. After administration of any regional block, vigilant monitoring of maternal blood pressure and symptoms (dizziness, shortness of breath, nausea) must be carried out. The FHR must also be evaluated so that any adverse effects on the fetus can be recognized. Hypotension in the obstetric patient can be defined as a systolic blood pressure of less than 90 mm Hg, or a decline

of 20 to 30 percent from baseline. Treatment of hypotension involves ensuring proper maternal position with the uterus displaced off the vena cava, administration of oxygen to the mother, infusion of IV fluids, use of head-down tilt, and administration of ephedrine, 5 to 10 mg IV. If recognized and treated promptly, transient maternal hypotension does not usually cause maternal or neonatal morbidity. [56] [243] [244]

Convulsions Induced by Local Anesthetic

Central nervous system toxicity occurs when the level of local anesthetic in arterial blood (and brain tissue) exceeds a critical level. High blood levels result from accidental intravascular injection, accumulation of local anesthetic after repeated injections, and rapid systemic absorption of local anesthetic from a highly vascular area. Accidental intravascular injection may occur with any regional anesthetic technique, including paracervical and pudendal blocks.

The elimination half-life of amide local anesthetics is 2 to 3 hours. Therefore, systemic accumulation of such anesthetics to near-toxic levels may occur when large doses are given repeatedly or frequently. During properly conducted regional anesthesia, however, the blood level of local anesthetics that occurs as a result of absorption rarely causes symptomatic toxicity, but there is large individual variability, particularly with lidocaine. [245] The risk of systemic accumulation can be minimized by use of the smallest quantity of drug necessary to achieve the desired anesthetic effect and by use of agents that are rapidly metabolized and intrinsically less toxic, such as chloroprocaine.

By talking to the patient frequently and by constantly observing her physical condition and vital signs, the physician not only can recognize incipient toxic reactions but may also mitigate their potential for serious effects as well. Systemic toxicity is usually heralded by sedation and slurred speech, and oxygen is administered. Administering thiopental, 50 to 75 mg, or a benzodiazepine may help prevent a convulsion. Should a seizure occur, the airway is maintained and the patient is ventilated with 100 percent oxygen. Succinylcholine both terminates the skeletal muscle activity (the source of metabolic acidosis after a seizure) and facilitates ventilation and intubation. [246] The maternal circulation is supported with IV fluids and vasopressors as needed. As soon as possible, the condition of the fetus should be assessed and, if necessary, the subsequent course of delivery altered appropriately. Prompt maternal resuscitation usually restores uterine blood flow and fetal oxygenation and permits fetal excretion of local anesthetic to the mother via the placenta.

Treatment of Cardiac Arrest

Cardiac arrest from IV injection of bupivacaine should be treated with external cardiac massage; defibrillation, if necessary; bretylium [247] ; and repeated doses of epinephrine. If the arrest occurs before delivery, all efforts should be made to rapidly deliver the fetus. Not only does this move the fetus to a healthier environment, but it also facilitates maternal resuscitation by relieving aortocaval compression. [157] Maternal blood gases are checked frequently, and any acidosis is corrected. [158] In one case report, cardiopulmonary bypass was used in a nonpregnant patient to support the circulation, minimize metabolic acidosis, and enhance clearance of the bupivacaine from the circulation. [248]

Total Spinal Anesthesia

Total spinal anesthesia usually occurs from an excessive spreading of local anesthetic administered intrathecally. It can occur during intended spinal anesthesia, even when appropriate doses are used. It can also occur if a presumed epidural catheter migrates into the subarachnoid space. [249] A high block can also result from subdural injection of anesthetics. [250] [251] [252] Characteristics of a subdural block include a relatively rapid onset of a high sensory level, sacral sparing, a patchy block, and an incomplete or absent motor block. Although total spinal anesthesia occurs infrequently, the patient must be monitored for it carefully after institution of an epidural or spinal block; severe hypotension and hypoxia from respiratory embarrassment occur quickly, with adverse maternal and fetal effects. Treatment consists of establishing an airway and ventilating with oxygen. Endotracheal intubation should be performed as soon as possible to protect the airway from aspiration. The Trendelenburg position and left uterine displacement should be used to increase venous return to the heart. Fluids and ephedrine should be administered as necessary to maintain blood pressure at a normal level. If accidental injection of a large volume of local anesthetic into the subarachnoid space is suspected, aspiration of the CSF should be considered.

Nerve Injury

Direct nerve injury from spinal or epidural needles and catheters is extremely rare. Pressure on the cord or spinal roots by a needle point produces excruciating pain, and the needle would be withdrawn immediately. Other potential neurologic complications, also very rare, include epidural hematoma; infections, such as epidural and caudal abscess and meningitis; and chemical contamination of the subarachnoid or epidural space. The few instances of reported epidural hematoma associated with regional blocks have occurred mainly in older patients who had defective coagulation capabilities.

In obstetrics, nerve injury in the mother is usually not related to anesthesia but either to compression of the lumbosacral trunk (Fig. 57-19) (Figure Not Available) between the head of the fetus and the sacrum or stretching or compression injuries of the femoral, lateral femoral cutaneous, or peroneal nerves when the patient is in the lithotomy position (Fig. 57-20) (Figure Not Available) . Recovery from these injuries may require 12 to 16 weeks.

Headache After Dural Puncture

Headaches secondary to puncture of the dura mater are caused by leakage of CSF through a patent hole in the dura. Loss of the cerebral CSF "cushion" results in traction on sensitive structures (blood vessels) within the cranium. CSF leak and incidence of headache are related to the size of the needle used (lower with smaller-gauge needles), [253] the number of dural punctures, the patient age, the type of spinal needle (cutting versus noncutting or pencil point), [253] [254] [255] and the direction of the needle bevel (lower with the bevel of a cutting-type needle placed parallel to the dural fibers). [253] [256] [257] About 80 percent of parturients experience a headache after puncture with a 16-gauge epidural needle [256] (i.e., when the dura is accidentally punctured during an attempted epidural block), and about 1 to 4 percent have a significant headache when a 24- to 26-gauge

Figure 57-19 (Figure Not Available) Relationship of the lumbosacral cord to the pelvis and the psoas major muscle. *(From Cole [433])*

Figure 57-20 (Figure Not Available) Common peroneal nerve compressed between lithotomy stirrup and neck of fibula. This can be avoided by padding or having the legs hang away from the stirrup supports. *(From Britt and Gordon [434])*

pencil-point spinal needle is used. [258] [259] Diagnosis is made from clinical history; classically, a postdural puncture headache is postural (worse on standing). Conservative therapy consists of bed rest, analgesics, hydration, and wearing of a tight abdominal binder, which increases epidural pressure and decreases the amount of leaking CSF. Caffeine, perhaps via cerebral vasoconstriction, has also been suggested as therapy for postdural puncture headache. [260] [261]

A blood patch epidural with autologous blood may be performed in patients having severe headaches following dural puncture. Under a rigidly aseptic technique, approximately 10 to 20 mL of blood is withdrawn and immediately placed into the epidural space at the site of the dural rent. If the site of the dural rent is uncertain because of the presence of multiple puncture sites, the lowermost interspace should be used because of the cephalad spread of solutions in the epidural space. [262] The success rate for this procedure is about 90 to 95 percent. [263] [264] Follow-up evaluation has indicated that the epidural blood patch is without serious complication. [265] Although backache is the most common complication, it is seldom severe or incapacitating. The administration of a prophylactic blood patch after accidental dural puncture is controversial. Loeser et al [266] reported a high failure rate for epidural blood patches performed less than 24 hours after dural puncture, but others have found that 15 to 20 mL of autologous blood injected through an epidural catheter after delivery was highly effective in avoiding a subsequent headache. [267] [268] Infusion of epidural saline (10-15 mL/h for 24 hours) after the dural puncture may also limit postdural puncture headache. [269]

Other Blocks in Obstetrics

Paracervical Block

Paracervical block is a relatively simple procedure sometimes used by obstetricians to provide analgesia during labor. Local anesthetic is injected in the submucosa of the fornix of the vagina lateral to the cervix (Fig. 57-21) (Figure Not Available) . The Frankenhauser ganglion, which contains all the visceral sensory nerve fibers from the uterus, cervix, and upper vagina, is anesthetized, but the somatosensory fibers from the perineum are not blocked. Thus, this technique is effective only during the first stage of labor. The major disadvantage of paracervical block anesthesia is the relatively high incidence (8-39%) [270] of fetal bradycardia that occurs after the block. This bradycardia is associated with fetal acidosis, decreased oxygenation,

---

Figure 57-21 (Figure Not Available) Diagram of paracervical area in relation to uteroplacental circulation. From this figure it can be appreciated that the local anesthetic is deposited close to the uterine artery where vasoconstriction or rapid uptake could occur. *(From Asling et al [432])*

and increased likelihood of neonatal depression. Bradycardia usually develops within 2 to 10 minutes of the block and lasts from 3 to 30 minutes. Bradycardia may be related to decreased uterine blood flow, caused by constriction of the uterine artery from closely applied local anesthetics, [271] or it may be related to high levels of local anesthetics absorbed into the fetal circulation (see Fig. 57-21) (Figure Not Available) . [272]

Pudendal Block

Pudendal block and local perineal infiltration anesthesia are usually administered just before delivery and are most commonly performed by the obstetrician through the vagina. During the block, the patient is in the lithotomy position. To give a pudendal block, the physician palpates the ischial spine, places a needle guide under the spine, and introduces a 20-gauge needle through the guide until the point rests on the vaginal mucosa. The needle is advanced approximately ½ inch and pierces the sacrospinous ligament. After negative aspiration, 10 mL of local anesthetic (e.g., 1% lidocaine or mepivacaine and 2% 2-chloroprocaine) is injected. The technique is then repeated on the other side.

General Anesthesia

General anesthesia is rarely needed for vaginal delivery but might be used for emergent operative (forceps or vacuum extraction) vaginal delivery if regional techniques are contraindicated and if other analgesics have proved to be inadequate. General anesthesia can also be used if profound uterine relaxation is needed for intrauterine manipulations for internal podalic version, complete breech extraction, manual removal of the placenta, or replacement of an inverted uterus. The potent inhaled anesthetics isoflurane, enflurane, and halothane cause dose-dependent uterine muscle relaxation and can be used therapeutically. After rapidsequence induction and endotracheal intubation, oxygen and inhaled agent are administered in doses high enough to provide uterine muscle relaxation, while maternal hemodynamics are carefully monitored. As soon as the desired effect is reached and the intrauterine manipulation is complete, the inhaled agent is discontinued to allow the uterus to contract after delivery and to stop bleeding. Uterine muscle relaxation can also apparently be accomplished with IV injection of small (50-100 mug) incremental doses of nitroglycerin. [273] [274] [275] This technique is particularly useful when effective analgesia exists (e.g., with a regional block or IV opioids) because it avoids the need to induce general anesthesia.

ANESTHESIA FOR CESAREAN SECTION

The choice of anesthesia for cesarean section depends on the reason for the operation, the degree of urgency, and the desires of the patient. The anesthesiologist must choose the method that is believed to be safest and most comfortable for the mother and least depressant to the newborn and that provides the optimal working conditions for the obstetrician. Survey data from 1992 from the United States reveal that more than 84 percent of cesarean deliveries are performed with regional anesthesia (spinal, 40%; epidural, 44%; general, 17%). [88] This represents a change since 1981 (spinal, 34%; epidural, 21%; general, 41%). [88]

Regional Anesthesia

Advantages to regional anesthesia include an awake mother, minimal newborn depression, and avoidance of the risks of general anesthesia. These advantages of regional anesthesia (and the risk of general anesthesia) are recognized not only by anesthesiologists but also by the American College of Obstetricians and Gynecologists. In the 1992 Committee Opinion publication "Anesthesia for Emergency Deliveries," [276] the risks of failed intubation and aspiration pneumonitis are recognized as serious complications of general anesthesia. Goals to promote the use of regional anesthesia and minimize the need for general anesthesia are stated and include (1) anesthetic consultation for patients in whom emergency induction of general anesthesia would be particularly hazardous, (2) establishment of IV access and placement and testing of an epidural catheter early in labor in patients at risk for cesarean delivery, and (3) recognition that cesarean delivery for a nonreassuring fetal status does not necessarily preclude the use of regional anesthesia.

Spinal Anesthesia

Advantages of spinal anesthesia include its simplicity, small drug dose, low failure rate (about 3% [277]) and rapid onset.

Figure 57-22 (Figure Not Available) The relationship between height and weight and maximum cephalad spread of block after intrathecal injection of 12 mg hyperbaric bupivacaine to 50 term parturients undergoing cesarean delivery. Symbols: circle, one patient; square, two patients; triangle, three patients; diamond, four patients. There was no predictable relationship between patient height or weight on the extent of spinal block. *(From Norris [435])*

Disadvantages include a higher incidence of hypotension and a finite duration of anesthesia.

Use of hyperbaric bupivacaine limits the significance of the finite duration of spinal anesthesia because its duration (1.5-2 hours) is suitable for the majority of cases. However, the block level with single-shot spinal anesthesia is not predictable. When giving all parturients a set dose (12 mg) of hyperbaric bupivacaine for cesarean delivery, Norris [278] found that anesthetic block levels ranged from T7 to C8. Patient height, weight, or body mass index did not correlate with block height (Fig. 57-22) (Figure Not Available) . On average, increasing the dose of spinal anesthetic increases block height, [279] but the range of block heights is still great. Flexibility limitations of spinal anesthesia can be overcome by use of a continuous spinal anesthetic technique. Continuous spinal anesthesia (using an epidural catheter threaded into the subarachnoid space via an epidural needle) is an option if the initial block attempt was difficult and/or complicated by dural puncture and has been described in a patient with severe kyphoscoliosis [280] and in morbidly obese parturients. [281]

Hypotension occurs more often during spinal (45- 100%) [59] [241] [282] than epidural anesthesia (15-44%). [169] [283] The varied percentage of hypotension in different studies probably stems from varied definitions of hypotension and regimens of prehydration, as well as factors that are difficult to control (completeness of left uterine displacement and preoperative volume status). As previously described, treatment strategies for hypotension include ensuring left uterine displacement, using head-down tilt, administering IV fluids, and administering ephedrine boluses or infusion. [284] [285] Phenylephrine has also been studied for use during cesarean delivery and has been found to be safe and effective in normal parturients. [58] [59] The impact on the fetus of maternal hypotension during spinal anesthesia is controversial. Some have reported decreased umbilical arterial pH in fetuses born of mothers receiving spinal anesthesia compared with those receiving epidural anesthesia for cesarean delivery. [286] [287] Others have not found differences in umbilical cord acid/base status with these two anesthetics. [288] Most studies do not find important differences in newborn vigor or neurologic and adaptive capacity scores with the two anesthetic techniques. [286] [287] [288] The potential impact of hypotension on the fetus must be appreciated.

Analgesia during spinal anesthesia has been reported to be improved when 0.2 mg of epinephrine, [289] 0.2 mg of morphine, [290] epinephrine 0.2 mg plus morphine 0.2 mg, [290] 10 mug of fentanyl, [291] [292] [293] or 10 mug of sufentanil [294] are added to hyperbaric bupivacaine or lidocaine. The addition of opioids to spinal bupivacaine also improves the duration of analgesia after surgery. A suggested technique of spinal anesthesia for cesarean delivery appears in Table 57-8 .

Epidural Anesthesia

Flexibility is probably why epidural anesthesia is used more often than spinal anesthesia for cesarean delivery. [88] Patients with an epidural catheter in place for labor can have the block extended to provide suitable anesthesia for cesarean delivery. An epidural catheter should be placed early and tested for function in patients at risk for cesarean delivery, such as obese parturients. [295] Flexibility for the duration of anesthesia for surgery and control of block height are other advantages of epidural anesthesia.

TABLE 57-8 -- Suggested Technique for Regional Anesthesia for Cesarean Section

1. Administer a nonparticulate oral antacid within 1 h of anesthetic induction.
2. Transport the patient to the operating room in the lateral position. Monitor maternal blood pressure, heart rate, and oxygen saturation throughout surgery. Monitor the FHR during induction of anesthesia, if possible.
3. Administer rapidly 1,000-2,000 mL of dextrose-free balanced salt solution IV. Administer supplemental oxygen to the mother via face mask or nasal prongs.
4. Before starting the block, check resuscitation equipment and drugs: (1) oxygen delivery system in the anesthesia machine; (2) airways; (3) laryngoscope; (4) endotracheal tubes; (5) thiopental or diazepam for possible convulsions; (6) ephedrine for hypotension; and (7) suction apparatus.
5. Administer block.

SPINAL ANESTHESIA

Use smallest needle possible and/or needle with noncutting point (Sprotte, Whitacre, or Gertie Marx).

LOCAL ANESTHETIC OPTIONS:

i. 7-10 mg of hyperbaric tetracaine (tetracaine 1% and equal volumes of 10% dextrose in water)

ii. 60-75 mg of lidocaine (1.2-1.5 mL of lidocaine 5% in 7.5% dextrose in water)

iii. 12-15 mg of bupivacaine (1.6-2.0 mL of bupivacaine 0.75% in 8.25% dextrose in water)

ADDITIVES:

i. Epinephrine, 0.2 mg

ii. Sufentanil, 10 mug

iii. Fentanyl, 10 mug

iv. Morphine 0.1-0.25 mg

v. Fentanyl and morphine in above doses

EPIDURAL ANESTHESIA

Epidural catheter is placed by use of usual technique and tested for possible intravascular or subarachnoid location.

LOCAL ANESTHETIC OPTIONS:

(15-30 mL total dose given in 5-mL increments)

i. 1.5-2.0% lidocaine

ii. 0.5% bupivacaine

iii. 3.0% chloroprocaine

iv. 0.5% ropivacaine

v. Epinephrine may be added to a maximum concentration of 1:200,000.

OPIOID OPTIONS:

i. Fentanyl, 50-100 mug, or sufentanil, 10-20 mug, may be added to above local anesthetics to enhance intraoperative analgesia.

ii. Morphine (3-5 mg) may be administered through the epidural catheter following delivery.

6. Position patient with left uterine displacement and slight (10-degree) Trendelenburg tilt.

7. Monitor arterial blood pressure every minute until birth of the baby, then every 5 min for duration of block.

8. If systolic blood pressure falls by 30% or below 90 mm Hg, ensure left uterine displacement and increase IV infusion rate. If blood pressure is still not restored, administer 5-15 mg of ephedrine IV; repeat if necessary.

9. Treat anxiety and incomplete or "spotty" anesthesia with one or more of the following agents:

a. 0.25-1.0 mg of midazolam IV

b. 0.5-1 mug/kg of fentanyl IV

c. 40-50% nitrous oxide

d. 0.25 mg/kg of ketamine IV

e. 10-20 mL of 0.5% lidocaine intraperitoneally

10. If analgesia is inadequate, proceed to general anesthesia with endotracheal intubation.

11. Postoperative analgesia can be provided with intrathecal or epidural morphine [420] or patient-controlled analgesia. [421] [422] A system for detecting side effects, including excessive sedation and/or respiratory depression, should be in place if intrathecal or epidural morphine is used. [423]

It is notable that despite some decrease in blood pressure during the induction of a surgical level of epidural anesthesia, remarkable stability in maternal cardiac output has been reported. [286] There are maternal conditions that favor the less rapid onset of sympathetic blockade of epidural anesthesia, such as severe hypertension and preeclampsia. [296] With only moderate prehydration (500-750 mL of crystalloid) and a slow onset of anesthetic block, remarkable hemodynamic stability can be maintained. Similarly, patients with mitral or aortic stenosis have been given epidural anesthesia (induced slowly) with appropriate cardiovascular monitoring guiding treatment of hemodynamic perturbations. [297] [298] [299]

The commonly used drugs for epidural anesthesia for cesarean delivery include 2 percent lidocaine ± epinephrine, 1:200,000; 3 percent 2-chloroprocaine; 0.5 percent bupivacaine; and 0.5 percent ropivacaine. Usually, 15 to 30 mL of local anesthetic is required. As such, the possibility of local anesthetic toxicity must be recognized. IV placement of the epidural catheter must be identified, and any epidural local anesthetic must be injected in incremental doses. 2-Chloroprocaine, because of its rapid onset and rapid metabolism, is a good choice for urgent/emergent surgery. Otherwise, lidocaine, which has a longer duration of action and less interference with epidural opioids, is often used. Bupivacaine and ropivacaine have similar characteristics, with a slower onset time and longer duration than lidocaine.

Intraoperative analgesia with lidocaine epidural anesthesia is improved in some patients if fentanyl, 50 to 100

---

mug, [300] [301] or sufentanil, 10 to 20 mug, [302] is added to the local anesthetic. With either spinal or epidural anesthesia, patients undergoing cesarean delivery are most comfortable when regional block height is at least T4. [303] A suggested technique for epidural anesthesia for cesarean delivery appears in Table 57-8 .

CSE Anesthesia

Perhaps the advantages of spinal anesthesia (rapid onset of a dense block) and the advantages of epidural anesthesia (prolonged intraoperative anesthesia and postoperative analgesia) can be obtained with a CSE block. A low or standard dose of local anesthetic is first administered intrathecally, then an epidural catheter is placed. The initial spinal anesthetic can be extended (in height or duration) with epidural local anesthetic. Rawal et al [304] reported improved anesthesia with CSE versus epidural bupivacaine alone. Thoren et al [305] reported CSE to be similar to spinal anesthesia alone. Potential problems of the CSE technique include the inability to "test" the epidural catheter for proper location and the enhanced spread of previously injected spinal drug following the epidural injection. [306]

General Anesthesia

General anesthesia may be necessary for management of cesarean delivery in the obstetric patient in circumstances of severe fetal compromise, maternal hemorrhage or overt coagulopathy, or patient preference. General anesthesia has the advantages of rapid induction, less associated hypotension and cardiovascular instability, and better control of the airway and ventilation. Management of anesthesia for cesarean section is outlined in Table 57-9 . Potential problems during general anesthesia include pulmonary aspiration of gastric contents, failed intubation, maternal hyperventilation, neonatal depression, maternal awareness, and uterine atony.

TABLE 57-9 -- Suggested Technique for General Anesthesia for Cesarean Section

1. Administer a nonparticulate oral antacid within 1 h of induction. A histamine $_2$ blocker and/or metoclopramide can also be given.
2. Position the patient with left uterine displacement. Maternal monitoring includes at least blood pressure, ECG, pulse oximetry, capnography.
3. Preoxygenate with high flow rates of oxygen (>6 L/min).
4. When the surgeon is ready to begin, an assistant applies and maintains cricoid pressure until position of endotracheal tube is verified and trachea is sealed by inflated cuff.
5. Administer 4-5 mg/kg of thiopental and 1.5 mg/kg of succinylcholine, wait approximately 60 s, then intubate trachea.
6. Administer 50% nitrous oxide in oxygen plus either halothane 0.5%, isoflurane 0.75%, or enflurane 1%. Use muscle relaxant as necessary.
7. Avoid maternal hyperventilation.
8. After the umbilical cord is clamped, deepen anesthesia with nitrous oxide, opioid, or benzodiazepine; the halogenated hydrocarbon may be continued in low doses.
9. Extubate when the patient is awake.

Prevention of Pulmonary Aspiration of Gastric Contents

Aspiration of gastric contents during general anesthesia is a major cause of maternal morbidity and mortality. Routine administration of clear antacid, such as sodium citrate, before induction significantly raises gastric pH. [307] [308] However, use of antacids does not diminish the risk of aspiration of particulate matter. Preanesthetic administration of a histamine$_2$ -receptor antagonist, such as ranitidine, [309] [310] has been suggested to decrease gastric acidity and volume; an interval of several hours after oral administration [310] and at least 30 minutes after IV administration are needed for the agent to be effective. [309] Metoclopramide is an antiemetic that increases stomach emptying and raises gastroesophageal sphincter tone. [311] Its efficacy and safety for aspiration prophylaxis in obstetrics have not been fully elucidated. [312] [313] Because of its possible beneficial effects on gastroesophageal sphincter tone and gastric volume, it might be useful in obese parturients or in those who have recently eaten. No adverse fetal or neonatal effects have been described. [312] [313]

A rapid-sequence induction of anesthesia is used for cesarean delivery to minimize the chance of regurgitation before endotracheal intubation. Preoxygenation (either 3-5 minutes of tidal ventilation or four vital capacity breaths) [314] must occur before induction to prevent hypoxia during the apnea before intubation. Positive-pressure ventilation should be avoided, and cricoid pressure should be (Sellick maneuver) used to occlude the esophagus and prevent passive regurgitation. [315] Finally, the patient should be extubated only after she is fully awake and after protective laryngeal reflexes have been restored.

Failed Endotracheal Intubation

A report of anesthesia-related maternal mortality (1979-1990) found that most (106/129; 82%) maternal deaths during anesthesia occur during cesarean delivery. [164] Further, 67 (52%) occurred during general anesthesia, and airway problems accounted for 73 percent of general anesthesia-related deaths. Other reports have found the inability to secure an airway to be a leading cause of anesthesia-related maternal mortality (Ch. 39) . [316] [317] [318] Difficulties with endotracheal intubation occur more commonly in obstetric patients than in general surgical patients. [319] [320] Although maternal deaths resulting from complications of regional anesthesia have decreased over the past decade, the number of deaths resulting from general anesthesia has remained fairly constant. [164] Factors that may contribute to the risk of death during general anesthesia include inadequate time for a thorough airway evaluation, unpredicted airway edema, emergency situations, inadequate skill, and inadequate assessment of proper endotracheal tube position.

Rocke et al [321] looked at factors that were assessed preoperatively that were associated with difficult intubation in 1500 parturients undergoing cesarean delivery with general anesthesia. Mallampati [320] [322] [323] airway classification, short neck, receding mandible, and protruding maxillary incisors emerged as important factors predicting a difficult or failed

Figure 57-23 (Figure Not Available) The probability of experiencing a difficult intubation (defined as either a very difficult intubation requiring mask ventilation, intubating stylet, or different laryngoscope, or the inability to pass a tracheal tube after several attempts or unrecognized esophageal intubation) for the combination of risk factors: Mallampati class I, II, III, or IV, short neck (SN), protruding maxillary incisors (PI), or receding mandible (RM). Data were obtained from 1500 patients undergoing cesarean delivery with general anesthesia. Values in parentheses are the observed incidences of risk factor combinations in the series. *(From Rocke et al [321])*

intubation. However, other airway measures were not assessed, such as mouth opening and atlanto-occipital joint mobility. From their data, an estimated prediction of difficult intubation was calculated from various combinations of these factors (Fig. 57-23) (Figure Not Available) .

Although it is useful to have an index of suspicion about airway problems, airway difficulties may not always be predicted from the preoperative examination. Therefore, a failed intubation drill should be rehearsed by all those providing obstetric anesthesia. The following principles are offered

1. Perform as thorough an airway examination as possible given the clinical circumstances. When a patient has a known or predicted difficult airway, inform the obstetricians that rapid induction of general anesthesia could jeopardize the health of the mother and that you will require time to perform either an awake intubation or a regional anesthetic.
2. Have equipment available (either in the operating room or in a known place that an assistant could quickly find) to help manage the difficult airway. This might include a variety of laryngoscope blades, several sizes of endotracheal tubes, laryngeal mask airway, Combitube, fiberoptic bronchoscope, and a means of transtracheal jet ventilation. Use familiar equipment.
3. If a difficult airway is encountered, call for help and obtain difficult intubation equipment. Inform all operating room personnel and obstetricians of your situation. Prior education of operating room personnel and obstetrics staff helps them assist you.
4. Hypoxia occurs quickly during management of a difficult airway of the parturient. Monitor oxygen saturation during induction of general anesthesia and airway manipulation. Institute mask ventilation if oxygen saturation decreases.
5. Maintain cricoid pressure during induction and attempts at intubation unless cricoid pressure is contributing to difficulties with airway management.
6. Avoid multiple attempts at laryngoscopy. This only contributes to airway edema and increased difficulty oxygenating by mask. Do something different with each attempt at laryngoscopy--do not repeat unsuccessful techniques. Patients die from hypoxia, not the absence of an endotracheal tube.
7. Avoid repeated doses of succinylcholine. Optimize success on the first attempt at intubation by waiting for the onset of complete paralysis before performing laryngoscopy. If intubation is unsuccessful, allow the patient to resume spontaneous ventilation--this helps preserve maternal oxygenation.
8. In nonemergent circumstances, the patient should be awakened, and the surgery should be performed under either regional anesthesia or general anesthesia after the airway is secured with the patient awake. [324]
9. In emergency situations (e.g., severe fetal compromise), make an honest assessment about your ability to oxygenate the mother. This is the priority. If you are able to oxygenate the mother, assess whether or not you can adequately

ventilate and anesthetize the mother. Is maintaining anesthesia by mask a reasonable option? After delivery, the patient may be easier to support (functional residual capacity increases, aortocaval compression is released). An anesthetic technique utilizing spontaneous ventilation, 100 percent oxygen, low-dose inhaled anesthetic, and intermittent IV ketamine or other IV analgesic has been suggested for this situation.

10. In emergent situations in which mask ventilation is difficult or impossible, the priority is still maternal oxygenation. The laryngeal mask airway, although not protecting against aspiration, may be helpful in this circumstance to maintain a patent airway and has been described during the management of the difficult airway in obstetric patients. [325] [326] With the patient breathing spontaneously, the laryngeal mask airway can be used to administer inhaled anesthetics. Further, the laryngeal mask airway provides a conduit to potentially guide placement of a fiberoptic bronchoscope followed by an endotracheal tube. The Combitube, a tube with separate esophageal and tracheal lumens, could also be used to maintain the maternal airway. If oxygenation is not adequate with these techniques, move on to transtracheal jet ventilation or a surgical airway (tracheostomy). [327]

11. Use a method of detecting exhaled carbon dioxide to ensure proper placement of the endotracheal tube.

A diagram of suggested management principles appears in Figure 57-24 .

Adverse Effects of Hyperventilation

Maternal hyperventilation (arterial carbon dioxide pressure < 20 mm Hg) during general anesthesia may be harmful to the unborn fetus. Uterine blood flow is reduced during the institution of positive-pressure ventilation, and hyperventilation causes a leftward shift in the maternal oxygen-hemoglobin dissociation curve and decreases oxygen

Figure 57-24 An algorithm for management of a difficult intubation in the obstetric patient. Means to oxygenate the mother include mask ventilation, laryngeal mask airway, Combitube, transtracheal jet ventilation, or tracheostomy. Alternative anesthetic techniques include regional anesthesia, general anesthesia following awake intubation, or local anesthesia.

availability to the fetus. [328] Hypocarbia may also cause decreased umbilical blood flow from vasoconstriction. [329]

Neonatal Depression

The general anesthetics (nitrous oxide and volatile anesthetics) used for cesarean delivery cross the placenta and can cause neonatal depression (Ch. 58) . Neonatal depression is limited if the time from induction of anesthesia to delivery is less than 10 minutes. [330] Therefore, the duration of anesthesia before delivery should be as brief as possible. This can be accomplished by delaying induction of anesthesia until the patient is prepared and draped and the obstetrician is ready to start. However, although prolonged exposure reduces Apgar scores, the acid/base status of the newborn is not affected provided that maternal hypoxia, excessive hyperventilation, aortocaval compression, and hypotension are avoided and the uterine incision to delivery interval is less than 3 minutes. [331] Retrospective studies associate neonatal depression with the use of general anesthesia; however, these reports are flawed by selection bias. Neonates born of mothers receiving general anesthesia may be more depressed and acidotic and require increased resuscitation not because of general anesthesia per se but because of the reason that general anesthesia was chosen (e.g., severe fetal compromise, maternal hemorrhage). [332] [333] Comparisons of neonatal outcome after elective cesarean delivery with either general or epidural anesthesia do not show important differences in neonatal outcome. [288] [334]

Drugs Used for Induction of Anesthesia

Thiopental

Thiopental is the most commonly used induction agent in obstetrics. Clinical data, in which Apgar scores were used to assess newborn vigor, suggest that the neonate is not depressed following maternal administration of bolus doses of 4 to 7 mg/kg of thiopental [335] [336] to induce general anesthesia. Because thiopental crosses the placenta rapidly, delivery is not possible before the drug is transferred to the fetus (Fig. 57-25) (Figure Not Available) . [63] [335] Fetal brain concentrations of thiopental are limited because blood from the placenta first passes through the liver; most of the thiopental is either cleared by the liver or diluted by blood from the lower extremities and the viscera. [63]

Ketamine

Ketamine is an induction agent that is often used in the asthmatic or potentially hypovolemic patient. Ketamine crosses the placenta rapidly but does not produce neonatal depression unless it is used in doses above 1 to 1.5 mg/kg. [337] [338] At higher doses (>2 mg/kg), neonatal depression has been reported. [339] Because of its sympathomimetic effects, it is usually avoided in patients with hypertension. It has varied effects on uterine contraction frequency, with studies showing an increase postpartum and in early gestation [340] [341] and another study showing no effect at term. [341]

Figure 57-25 (Figure Not Available) The level of thiopental in maternal vein, umbilical vein, and umbilical artery after injection of a single dose of 4 mg/kg for induction of anesthesia. Note the rapid decay of the maternal venous blood level and the rapid transfer to the fetus. *(From Kosaka et al [335])*

Propofol

Propofol has been evaluated for use both as an induction agent and as a maintenance anesthetic during cesarean delivery. For induction, use of 2.0 to 2.5 mg/kg of propofol is not different than thiopental, 4 to 5 mg/kg, in terms of newborn vigor but is associated with less maternal hypertension. [342] [343] [344] [345] [346] Placental transfer of propofol appears to be similar to that of thiopental. Animal studies suggest that an induction dose of propofol does not adversely effect uterine blood flow and placental gas exchange. [347]

Etomidate

Etomidate has also been studied for use in the obstetric patient. When compared with thiopental, 3 to 4 mg/kg, etomidate, 0.3 mg/kg, is associated with a greater hypertensive response to laryngoscopy and intubation. Neonatal outcomes are equivalent. [348] This agent is perhaps best suited for clinical circumstances of maternal hypovolemia or when the myocardial depressant effects of thiopental should be avoided.

Muscle Relaxants

Succinylcholine, pancuronium, atracurium, and vecuronium do not cross the placenta in clinically significant amounts and may be used safely during cesarean section. [349] [350] [351] At this time, no nondepolarizing muscle relaxant matches the rapid onset of succinylcholine. Preliminary studies of rocuronium (0.6 mg/kg) with thiopental (6 mg/kg) or ketamine (1.5 mg/kg) in obstetric patients reveals a favorable profile (onset time, about 1.5 minutes; duration, 30-45 minutes). [352] [353]

Maintenance of Anesthesia

Anesthetic maintenance before delivery must balance neonatal vigor with adequate maternal anesthesia. To ensure adequate fetal oxygenation, an F_{IO_2} of at least 50 percent before delivery is recommended. However, 50 percent nitrous oxide alone does not provide adequate maternal anesthesia. Crawford [354] reported a high incidence (26%) of awareness during surgery if anesthesia was maintained with only 50 percent nitrous oxide and oxygen before delivery. Adding a low dose of potent inhaled agent (e.g., 0.5% halothane, 0.75% isoflurane, 1.0% enflurane) to 50 percent nitrous oxide limits maternal recall without increasing newborn depression. [330] A survey of 3,000 patients who received such a general anesthetic for cesarean delivery reported an overall rate of recall of 0.9 percent and a 6.1 percent rate of dreaming. [355] Clinical trials have also found sevoflurane (1.0% end tidal [ET]) to be equivalent to isoflurane (0.5% ET) [356] and desflurane (3.0% ET) to be equivalent to enflurane (0.6% ET). [357] Halothane, isoflurane, and enflurane decrease uterine contractility and tone in a dose-related fashion. [358] This feature can be advantageous if uterine relaxation is needed during cesarean delivery with general anesthesia. However, after delivery of the fetus, uterine muscle contraction is necessary to stop uterine bleeding. High doses of the volatile anesthetics could contribute to bleeding by inhibiting uterine muscle contraction. However, the uterus contracts in response to oxytocin, provided less than 0.8 to 1.0 MAC of volatile agent is administered. [359]

After delivery of the fetus, nitrous oxide concentrations can be increased as appropriate, and IV opioids or benzodiazepines can be administered in order to maintain adequate maternal anesthesia. Continued use of low doses of inhaled agent can also be used.

/das/book/view/29494766/875/635.html

ANESTHESIA FOR COMPLICATED OBSTETRICS

Emergency Cesarean Delivery

Sudden, unexpected complications occurring during late pregnancy or labor that adversely affect the mother or fetus may necessitate an immediate emergency cesarean delivery. Such complications include massive bleeding, prolapsed umbilical cord, or concerns about fetal status. When the mother or fetus is in immediate jeopardy, general anesthesia is usually selected, but under some circumstances, extension of an existing epidural or administration of a subarachnoid block may be appropriate.

When concerns about the fetus lead to cesarean delivery, the anesthesiologist should help institute measures to improve the uterine environment. If the worrisome fetal condition persists, choice of anesthetic for cesarean delivery must weigh the urgency of the situation against the risk of a specific anesthetic to the mother. Marx et al [360] reported fetal outcome after cesarean delivery for "fetal distress" (defined as severe heart rate abnormalities and a capillary blood pH < 7.20 or decreasing steadily) depending on anesthetic management (general anesthesia [*n* = 71], spinal anesthesia [*n* = 33], or extension of an existing epidural block [*n* = 22]). There were no differences between the groups with regard to fetal biochemical data, but the use of general anesthesia was associated with lower Apgar scores at 1 minute. When faced with providing anesthesia for emergency cesarean delivery, the anesthesiologist communicates with the obstetrician. Choice of anesthetic technique for emergency cesarean delivery for fetal concerns must consider fetal status (estimated degree of acidosis and time before delivery should be accomplished) and condition of the mother (volume status, airway examination).

Preeclampsia and Eclampsia

Preeclampsia, a disease unique to the parturient, complicates 7 to 10 percent of all pregnancies. Preeclampsia is categorized as mild or severe (Table 57-10) . Preeclampsia and other hypertensive disorders are a leading cause of maternal mortality. Causes of maternal death include cerebral vascular accidents, pulmonary edema, and hepatic necrosis/rupture. Obstetric management involves medical management of the disease symptoms; the timing of delivery considers the maternal condition (worsening of disease) and fetal issues (prematurity, intrauterine growth retardation). The disease is cured by delivery.

Pathophysiology

The cause of preeclampsia remains unknown. A proposed theory suggests that an abnormality in placentation results in reduced trophoblastic perfusion. This causes the release of some substance that is cytotoxic to endothelial cells. [361] Endothelial cell damage triggers vasoconstriction (hypertension), platelet activation, and prostacyclin/thromboxane imbalance. [362] The hypertension contributes to ongoing endothelial cell damage. [363] Endothelial cell damage disrupts capillary integrity, resulting in edema. Although classically preeclampsia has been defined as the triad of hypertension, proteinuria, and edema occurring after 20 weeks' gestation, it is clear from consideration of the pathophysiology that preeclampsia is a multisystem disease. Virtually all organ systems can be affected. Anesthetic management of preeclamptic patients starts with an assessment of how the disease affects a particular patient.

Manifestations

Preeclampsia is a state of generalized vasoconstriction and hypoperfusion. Despite retention of sodium and water and generalized edema, the intravascular volume is usually decreased. The cardiac effects of preeclampsia are diverse and reflect the severity of the disease. [296] A spectrum exists from hypertension from a high cardiac output state with a low SVR to relatively low cardiac output with hypertension from a high SVR. Appreciating where a given patient lies on this spectrum helps the anesthesiologist choose appropriate antihypertensive therapy. The high cardiac output state typically exists in younger patients early in the course of the disease. Conversely, an older patient with chronic hypertension

TABLE 57-10 -- Classification of Preeclampsia and Eclampsia

MILD PREECLAMPSIA
Blood pressure >140/90 mm Hg or >30/15 mm Hg increase from baseline
Generalized edema
Proteinuria >300 mg/L (1-2+ dipstick)
SEVERE PREECLAMPSIA
Blood pressure >160/110 mm Hg
Proteinuria >5 g/24 h
Cerebral involvement (headache, visual disturbances)
Oliguria
Increased serum creatinine level
Pulmonary edema
Epigastric pain, right upper quadrant abdominal pain, evidence of hepatic injury (HELLP)
Thrombocytopenia or disseminated intravascular coagulation
ECLAMPSIA
Preeclampsia progressing to seizures

usually has a higher SVR. Patients with high SVR hypertension may experience the largest blood pressure changes with the induction of regional anesthesia. Extra vigilance is required because the fetus of a patient with long-standing hypertension is most vulnerable to changes in maternal cardiac output.

Pulmonary edema may complicate preeclampsia (prevalence, 2-3%). [364] Pulmonary edema can be from cardiac failure, altered capillary permeability, altered hydrostaticoncotic forces, [365] or some combination. [366] Patients at risk for pulmonary edema are those with concomitant medical problems (diabetes, chronic

hypertension) and older maternal age. [364]

Central hemodynamic monitoring has been advocated to assist the management of severe preeclamptic patients, particularly if the disease is complicated by pulmonary edema. Candidates might include patients with pulmonary edema before delivery, patients with severe chronic hypertension who are at risk for cardiac failure, and patients with refractory oliguria who are unlikely to deliver soon. Monitoring central venous pressure or pulmonary artery pressure depends on the clinical situation and the monitoring capabilities. Although a low central venous pressure value is helpful to determine a patient's intravascular volume, a midrange or high value may not be helpful. Data suggest that at these values, correlation with pulmonary capillary wedge pressure is poor. [367]

Uteroplacental perfusion is impaired in the preeclamptic patient, particularly if the patient has underlying chronic hypertension. The placenta may have areas of infarction that limit oxygen delivery to the fetus and cause intrauterine growth retardation. Placental changes contribute to the excess perinatal mortality observed in pregnancies complicated by hypertension. [368] Renal biopsies of patients with preeclampsia demonstrate glomerular endotheliosis and fibrin deposition. Proteinuria is a hallmark of the disease. Renal blood flow and glomerular filtration rate are reduced during preeclampsia, and the normal creatinine of pregnancy (0.4-0.6 mg/dL) may be elevated, as may serum uric acid level. Although acute renal failure is not a common complication of preeclampsia (1%), oliguria may occur in the severely preeclamptic patient and may reflect intravascular volume depletion, poor cardiac output from myocardial failure, or renal artery spasm. Hepatocellular damage, or HELLP (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets) syndrome may present as right upper quadrant pain, elevated liver enzymes, and reduced coagulation factors. Rarely, hepatic rupture complicates preeclampsia. Liver function should be evaluated in patients with abdominal pain.

The normal hematocrit value of pregnant patients is 33 to 34 percent, but preeclamptic patients may have higher hematocrit values (39-40%) because of hemoconcentration. Preeclampsia can be complicated by coagulation problems, the most common being thrombocytopenia. Although disseminated intravascular coagulation can occur, it is rare and usually accompanies the HELLP syndrome. Patients with severe preeclampsia are more likely to have thrombocytopenia. [369] Other abnormalities in coagulation tests were unlikely in the absence of thrombocytopenia. Thrombocytopenia can be progressive, not resolving until 2 to 3 days after delivery. [370] Kelton et al [371] suggested that not only are platelet counts low in patients with preeclampsia but also platelet function may be abnormal. This conclusion was based on a comparison of bleeding times as a function of platelet count in preeclamptic and normal pregnant patients. However, the importance of this finding is unclear because the bleeding time is not necessarily a reliable predictor of abnormal bleeding. The exact platelet count value associated with a negligible risk of abnormal bleeding and epidural hematoma formation remains unknown. Regional anesthesia has been used in patients with unknown thrombocytopenia without problems. [372] The decision to place an epidural block should consider several aspects of a preeclamptic patient's disease. First, what is the patient's presentation? Some patients present with a rapid onset of severe disease with rapid organ function deterioration. Severe thrombocytopenia may occur rapidly in these patients and precludes neuraxial block. Serial platelet counts help assess the patient's course. Second, is there evidence of other coagulation disorders? Finally, the decision to perform any procedure must always weigh risks and benefits of available anesthetic techniques.

The CNS shows increased irritability in preeclampsia that may progress to eclamptic seizures. Early CNS symptoms include headache and visual disturbances. The exact cause of eclamptic seizures is unknown, but vasospasm, hypertensive encephalopathy, and cerebral edema are proposed mechanisms. Should eclamptic seizures occur, maternal oxygenation and proper positioning with left uterine displacement should be ensured. The patient should receive IV magnesium. If the seizure is prolonged or if the patient is unable to control her airway, intubation may be necessary, although this is not usually the case. The fetus may develop bradycardia from the maternal metabolic acidosis resulting from the seizure. The fetus is monitored, and while in utero resuscitation is probably best, if the fetus does not recover from the effects of the seizure, urgent delivery may be necessary.

Pharmacologic Therapy

Pharmacologic therapy of preeclampsia includes blood pressure control and seizure prophylaxis. Parenteral labetalol or hydralazine may be used to control blood pressure. Seizure prophylaxis is accomplished with magnesium therapy. [373] It is usually given IV (4-g load over 15 minutes, followed by a continuous infusion of 1-3 g/h). Therapeutic levels of magnesium are 4 to 6 mEq/L (Table 57-11) . levels

TABLE 57-11 -- Effects of Increasing Plasma Magnesium Levels

OBSERVED CONDITION	mEq/L
Normal plasma level	1.5-2.0
Therapeutic range	4.0-6.0
ECG changes (P-Q interval prolonged, QRS complex widened)	5.0-10
Loss of deep tendon reflexes	10
Sinoatrial and atrioventricular block	15
Respiratory paralysis	15
Cardiac arrest	25

must be monitored closely in a patient with renal dysfunction. Magnesium toxicity is treated with IV calcium. During administration of the bolus dose in preeclamptic patients, magnesium sulfate causes a fall in blood pressure and an increase in cardiac output via a decrease in SVR. [374] At the neuromuscular junction, magnesium sulfate decreases the amount of acetylcholine liberated, diminishes the sensitivity of the endplate to acetylcholine, and depresses the excitability of the muscle membrane. Thus, the pharmacodynamics of muscle relaxants is affected. Animal studies reveal an increased sensitivity to both depolarizing and nondepolarizing muscle relaxants in the presence of magnesium sulfate. [375] However, although one clinical report revealed that the clinical effect of succinylcholine was not altered by magnesium sulfate, [376] the duration of action of vecuronium was prolonged. [376] It is advisable to monitor neuromuscular function during general anesthesia in patients receiving magnesium sulfate therapy. In addition, a small dose of nondepolarizing muscle relaxant (pretreatment) should not be given in order to prevent fasciculations from succinylcholine.

Anesthetic Issues

Anesthetic management of the preeclamptic patient must first include a careful preanesthetic visit in which the manifestations of the disease in the patient is evaluated. Some have raised concerns about the use of regional anesthesia in preeclamptic patients because sympathetic block and maternal hypotension may further compromise uteroplacental circulation. There are also concerns about maternal pulmonary and/or cerebral edema from excessive IV fluid administration [366] in the face of low plasma oncotic pressure. [365] Other investigators have found epidural analgesia to be a valuable technique for the laboring preeclamptic patient. [377] [378] Effective analgesia reduces maternal catecholamines and blood pressure changes as a result of the pain of labor. [125] [379] In addition, provided that hypotension is avoided, epidural analgesia can improve intervillous blood flow. [380] [381] Regional anesthesia can safely be administered to preeclamptic patients and in fact may be beneficial, provided that the pathophysiology of the disease is understood. Blood pressure should be monitored carefully, and any decrease in blood pressure should be treated aggressively to prevent reductions in uterine blood flow. The FHR should be continuously monitored. Only a modest amount of IV fluid as prehydration (e.g., 200-500 mL) should be administered. Anesthesia is induced slowly to allow administration of small boluses of IV fluids or ephedrine to maintain a stable blood pressure. Preeclamptic patients tend to be more sensitive to vasopressors; therefore, only small doses of ephedrine are usually needed. Intrathecal or epidural opioids can also be used in these patients.

In the choice of anesthetic technique for cesarean delivery, maternal physiology and degree of urgency must be considered. Epidural anesthesia is a good anesthetic for cesarean delivery. [378] Modest IV hydration can be administered (about 500-1000 mL of crystalloid) during a slow induction of surgical anesthesia. Any change in maternal blood pressure is treated as previously described. The FHR is monitored continuously while the block is established. Slowly establishing the anesthetic (and sympathetic) block can enable remarkable hemodynamic stability. Although the use of spinal anesthesia for cesarean delivery in preeclamptic patients has been described, [382] the anesthesiologist should be aware of rapid hemodynamic changes with induction.

General anesthesia may be necessary in preeclamptic patients because of overt coagulation problems, maternal hemorrhage, or worrisome fetal status. A concern associated with the use of general anesthesia is the possibility of airway edema complicating intubation. Another problem with induction of general anesthesia in the preeclamptic patient is exaggerated hypertension during laryngoscopy and intubation. [383] Strategies to minimize extreme increases in blood pressure with intubation

include administration of labetalol [384] or small doses of fentanyl before induction and use of a generous dose of thiopental (ketamine should be avoided). Hypertension after intubation can be treated with transient administration of a high dose of volatile anesthetic. IV infusions of nitroprusside, [385] trimethaphan, [386] and nitroglycerin [387] [388] have also been used in this situation (with direct arterial pressure monitoring).

The postpartum preeclamptic patient should be monitored for evidence of uterine atony (magnesium sulfate may contribute to uterine bleeding). The anesthesiologist should be aware that patients with underlying chronic hypertension or diabetes are at risk for developing pulmonary edema in the postpartum period.

Abnormal Fetal Presentation

The usual fetal presentation during vaginal delivery is cephalic in the occiput anterior position. Occasionally, the fetal head is in the occiput posterior presentation. This is a more difficult presentation to deliver vaginally; forceps rotation to the occiput anterior position or forceps assisted delivery may be necessary. Pain, particularly back pain, may be greater when the fetus is in the occiput posterior presentation. Effective regional analgesia can be helpful for these patients.

Breech presentation of the fetus means that the fetal buttocks or lower extremities are the presenting parts. Breech presentation occurs more commonly in the premature fetus. [389] The obstetrician may try to change the fetal position from breech to cephalic presentation by externally manipulating the fetus in the uterus (external cephalic version). If attempted version is not successful, the obstetrician may opt for cesarean delivery of a breech fetus. Vaginal delivery of a term breech fetus may also be attempted. The anesthesiologist should be aware that prolapse of the umbilical cord is more common with breech presentations and may necessitate emergent cesarean delivery. For labor, adequate analgesia, particularly during the second stage, is very helpful. Lumbar epidural analgesia can be titrated to the desired effect to promote perineal relaxation and maternal cooperation during delivery. Rarely, contraction of the lower uterine segment traps the fetal head, precluding vaginal delivery and necessitating rapid uterine muscle relaxation.

Prematurity

Preterm delivery occurs in up to 10 percent of all births and is defined as delivery at 36 weeks of gestation or less.

Prematurity is the major cause of neonatal mortality. [390] These infants are at risk for respiratory distress syndrome and CNS complications from intracranial hemorrhage. To prevent premature delivery, various tocolytic agents are employed when preterm labor occurs. The anesthesiologist should be aware of the maternal and fetal side effects of these tocolytic agents. [391]

Magnesium sulfate reduces uterine contractility and may be the first-line tocolytic employed to stop premature contractions. [392] Serum magnesium levels are maintained between 4.0 and 6.0 mEq/L.

beta-Adrenergic agonists (ritodrine and terbutaline) may be used for tocolysis. Direct stimulation of the beta-adrenergic receptors present in uterine smooth muscle leads to increased intracellular cyclic adenosine monophosphate and uterine muscle relaxation. These drugs have significant side effects. Most women experience tachycardia (either from a direct $beta_1$ effect or in response to $beta_2$ -mediated vasodilation). Hyperglycemia and hypokalemia may also complicate beta-adrenergic agonist therapy. Chest pain and pulmonary edema can also occur. [393] [394] Patients receiving beta-adrenergic agonists are at risk for fluid overload and cardiogenic pulmonary edema as a result of stimulated antidiuretic hormone activity. [395] Further, preterm labor is often precipitated by an infectious process that predisposes to increased capillary permeability and noncardiogenic pulmonary edema. Risk factors for pulmonary edema from beta-adrenergic agonists include anemia, preexisting cardiac disease, multiple gestation, excessive hydration, tachycardia, prolonged tocolytic therapy, and associated infection (e.g., chorioamnionitis).

The anesthesiologist may be required to administer an anesthetic for labor and delivery to a patient who has recently been treated with tocolytic drugs. The respiratory status of patients receiving beta-adrenergic agonist therapy should be closely assessed. Drugs that could exaggerate tachycardia (atropine, pancuronium) should be avoided. Because halothane can sensitize the myocardium to exogenous catecholamines, it may predispose the patient to dysrhythmias and should be avoided. Hydration before regional anesthesia should be modest. If patients receiving magnesium sulfate require general anesthesia, careful neuromuscular blockade monitoring is required, as previously discussed. In addition, uterine atony may occur after delivery.

If vaginal delivery of the preterm fetus is anticipated, effective epidural analgesia provides the advantages of perineal analgesia to facilitate a gentle delivery, perhaps assisted with outlet forceps. If the fetus is in the breech presentation, cesarean delivery is likely because the breech is smaller than the head of the preterm infant, and entrapment of the fetal head behind an incompletely dilated cervix could occur during attempted vaginal delivery. Anesthesia for cesarean delivery considers the usual issues, with epidural, spinal, or general anesthesia being appropriate. The anesthesiologist should be aware that the preterm fetus is particularly susceptible to maternally administered drugs because of immature enzyme systems available for drug metabolism, poorly developed blood-brain barrier, less protein available for drug binding, and competition for drug binding sites from increased levels of bilirubin. After delivery, the preterm infant may require aggressive resuscitation, and appropriate personnel should be available. Anticipated problems include birth asphyxia, respiratory distress, hypoglycemia, and temperature instability.

Multiple Gestations

Important anesthetic considerations of multiple gestations is the high likelihood of prematurity, abnormal presentation (either breech or transverse lie), and need for operative delivery. The anesthesiologist should be aware that the large gravid uterus may be difficult to displace off the inferior vena cava and that hypotension is likely during the induction of regional anesthesia. Further, uterine atony is possible after delivery. Depending on the fetal presentations, twins may be delivered vaginally. During labor and anticipated vaginal delivery, epidural analgesia is useful because it can be titrated to desired effect. After delivery of the first twin, the presentation and status of the second twin can change quickly, possibly necessitating emergent cesarean delivery. Uterine muscle relaxation may be requested to promote gentle cesarean delivery of fetuses in abnormal presentations.

Obstetric Hemorrhage

Obstetric hemorrhage is classified according to timing: antepartum or postpartum. Although most patients tolerate the normal blood loss associated with either vaginal or cesarean delivery, occasionally, blood loss is excessive. Obstetric hemorrhage is an important cause of maternal mortality. [396]

Antepartum Hemorrhage

Antepartum hemorrhage complicates about 4 percent of pregnancies. Important causes include placenta previa, abruptio placentae, and uterine rupture.

Placenta Previa

Placenta previa exists when the placenta lies over the uterine cervix in front of the fetal presenting part (Fig. 57-26) (Figure Not Available) . The diagnosis is suspected from the clinical picture of painless vaginal bleeding and is confirmed by ultrasonography. Vaginal examinations are avoided, and delivery is via cesarean section. Tocolytic therapy may be instituted when premature uterine contractions trigger bleeding. If the gestation is term, delivery may need to proceed urgently. Anesthetic management depends on the degree of urgency and the maternal and fetal status. Regional anesthesia is appropriate for elective surgery, but general anesthesia is appropriate when surgery is prompted by maternal hemorrhage. Excessive bleeding can also occur during surgery because delivery may require cutting through the placenta, and the placental implantation site in the lower segment of the uterus may not contract well after delivery.

Abruptio Placentae

Abruptio placentae is bleeding behind the placenta, causing partial separation (Fig. 57-27) (Figure Not Available) . Both mother and fetus

---

Figure 57-26 (Figure Not Available) Types of placenta previa. (A) Low implantation of the placenta. (B) Partial placenta previa. (C) Total placenta previa. *(From Bonica and Johnson [436])*

Figure 57-27 (Figure Not Available) Abruptio placentae. (A) Internal or concealed hemorrhage. (B) External hemorrhage. (C) Complete placental separation and prolapse. *(From Bonica and Johnson [436])*

can be adversely affected: the mother from acute blood loss and coagulopathy from disseminated intravascular coagulation, and the fetus from reduced uterine blood flow and loss of functional placenta. A large abruption can result in fetal demise. Risk factors for abruptio placentae include chronic hypertension, abdominal trauma, cocaine use, advanced maternal age, multiparity, and history of prior abruption. [397] Abruptio placentae typically presents with painful, frequent uterine contractions and vaginal bleeding. The amount of maternal blood loss can be significant and may not be reflected by the amount of vaginal bleeding because blood can be sequestered behind the placenta. About 10 percent of cases of abruptio placentae are complicated by disseminated intravascular coagulation. Management of patients with abruptio placentae depends on the severity of the abruption and the maternal and fetal condition. A small abruption may trigger labor, which may continue to vaginal delivery if the status of the mother and the fetus is stable. A more significant abruption may lead to emergent cesarean delivery because of maternal and/or fetal instability. The anesthesiologist should be aware that uterine atony can occur because blood extravasated into the myometrium may preclude normal uterine contraction after delivery.

Uterine Rupture

Uterine rupture is a less common (0.4%) but potentially devastating cause of obstetric hemorrhage. It may occur in a previously scarred uterus (particularly after a classical [vertical] uterine incision) or may result from uterine manipulation (forceps, uterine curettage), trauma, or overaggressive

use of IV oxytocin. Other risk factors are uterine anomalies, tumors, and placenta percreta (invasion of the placenta through the uterine wall). Uterine rupture is different than uterine scar dehiscence. Uterine scar dehiscence is a defect in the uterine wall at the site of a previous incision (usually low transverse) that does not result in obstetric hemorrhage. It is reported to occur in about 0.7 percent of patients undergoing vaginal birth after prior cesarean. [398] Uterine rupture is reported to occur in 0.6 to 0.8 percent of vaginal birth-after-cesarean patients. [398] [399] Rupture of an unscarred uterus can result in massive maternal hemorrhage. Symptoms can be nonspecific and include maternal hemodynamic instability, fetal bradycardia, vaginal bleeding, and loss of function of uterine pressure monitors. Treatment requires emergent laparotomy and may require obstetric hysterectomy. [400]

Postpartum Hemorrhage

Postpartum hemorrhage complicates about 10 percent of deliveries and is defined as a blood loss of greater than 500 mL. Important causes include uterine atony, retained placenta, placenta accreta, birth trauma, and uterine inversion.

Uterine Atony

Uterine atony is the most common cause of postpartum hemorrhage. Contraction of the uterine muscle is necessary to stop uterine bleeding after delivery of the placenta. Ineffective uterine muscle contraction leads to hemorrhage. Risk factors for uterine atony include prolonged labor, overdistended uterus (e.g., with twin gestation), grand multiparity, and use of drugs known to decrease uterine muscle contraction (halogenated inhaled anesthetics, beta-adrenergic agonists, and magnesium sulfate). Treatment includes volume resuscitation and administering uterotonic medications. Such medications include oxytocin, carboprost tromethamine, and ergot preparations. Oxytocin is often routinely given as a dilute infusion (20 U/L of IV fluid) after delivery to promote uterine contraction. Bolus doses are avoided because hypotension can result. [391] Carboprost-tromethamine (Hemabate) is the 15-methyl analogue of prostaglandin $F_{2\ alpha}$ and is a potent uterotonic medication given IM (250 mug). Side effects include nausea, vomiting, diarrhea, and bronchoconstriction. [401] The ergot derivatives ergonovine maleate and methylergonovine maleate are effective uterotonic medications. The usual dose is 0.2 mg IM. Hypertension is an important side effect that results from the drug's alpha-adrenergic activity. These medications should be avoided in patients with hypertension or intracranial vascular disease and in those who have recently received vasopressors.

Retained Placenta

Retained placenta exists when all or part of the placenta fails to deliver spontaneously within 1 hour of birth. Hemorrhage results from failure of the uterus to contract where the placenta is adherent. Treatment involves placental removal either manually or via curettage. Anesthetic management involves volume resuscitation, provision of adequate analgesia (with epidural or spinal anesthesia if maternal volume status allows, IV or inhalational analgesia, or general anesthesia), and if necessary, assisting with uterine muscle relaxation to allow uterine manipulation and delivery of the placenta (with halogenated anesthetics administered via an endotracheal tube, or IV nitroglycerin, 50- to 100-mug bolus doses. [402])

Placenta Accreta

Placenta accreta, increta, or percreta (Fig. 57-28) (Figure Not Available) involves invasion of the placenta through the endometrium, into the myometrium, and through the myometrium, respectively. Risk factors include previous uterine surgery or trauma. [403] Normal placental delivery is often precluded and results in hemorrhage perhaps necessitating obstetric hysterectomy. [404] Placenta accreta occurs in about 0.04 percent of pregnancies, but the risk increases markedly in patients with placenta previa (5%) and increases even more dramatically in patients with placenta previa with prior cesarean delivery (24% after one prior cesarean, 40-60% after three to four prior cesareans). [403] The anesthesiologist should be aware of this potential problem when caring for a patient with placenta previa undergoing repeat cesarean delivery and should be prepared to manage massive hemorrhage.

Birth Trauma

Cervical and vaginal lacerations can result in persistent vaginal bleeding postpartum. The anesthesiologist is needed

Figure 57-28 (Figure Not Available) Classification of placenta accreta based on degree of pen-etration of the myometrium. Placenta accreta: adherence of the placenta to the myometrium; placenta increta: invasion of the myometrium; placenta percreta: the placenta erodes through the myometrium to involve the serosa of the uterus and even the surrounding structures. *(From Kamani et al [437])*

to provide the necessary analgesia or anesthesia to allow the obstetrician to visualize and repair the injury. The anesthesiologist should be aware that the amount of blood loss from such lacerations is difficult to assess and is often underestimated.

Uterine Inversion

Uterine inversion is a rare cause of postpartum hemorrhage in which the uterine fundus actually inverts through the cervix into the vagina, precluding uterine contraction. [405] Predisposing factors include retained placenta, prolonged labor, and precipitous labor. Management involves correction of the inversion and may require uterine muscle relaxation. [275] [406]

/das/book/view/29494766/875/636.html

ANESTHESIA FOR SURGERY DURING PREGNANCY

Pregnant women undergoing surgery require special attention in their anesthetic management if injury to the fetus is to be avoided. Goals include maternal safety, avoidance of teratogenic drugs, avoidance of intrauterine fetal asphyxia, and prevention of preterm labor. Many of the physiologic changes of pregnancy are due to hormonal influence and may occur early in pregnancy. Significant changes in minute ventilation, functional residual capacity, cardiac output, and anesthetic requirements occur during the second and third trimesters. Similarly, the hypotensive syndrome associated with the supine position begins to manifest itself early in the third trimester and may lead to decreases in cardiac output, blood pressure, and uterine blood flow.

Most commonly used anesthetic and sedative drugs are teratogenic in some animal species. The applicability of many of these animal studies to human subjects is not clear. Studies in humans have shown an association between increased risk of congenital anomalies and ingestion of minor tranquilizers, such as diazepam (Valium). [407] However, a direct link between the anomaly and the specific drug is difficult to confirm because of confounding issues (including the reason for taking the medication).

Long-term exposure to trace amounts of anesthetic gases or vapors had been suggested as having an adverse effect on reproductive outcome (including spontaneous abortion). However, a review of 14 studies from 1967 to 1982 concluded that no adverse effect of anesthetic gases on reproductive outcome could be accepted on the basis of the retrospective inquiries because of important methodologic problems, including unclear outcomes, poor survey response rates, selection bias, recall bias, and lack of control of confounding variables. [408]

All surveys of women who have received anesthesia for operations during pregnancy have failed to indict any anesthetic as a teratogen. [409] [410] [411] [412] [413] [414] However, in all studies to date, the number of pregnant women receiving an anesthetic for an operative procedure is, in fact, likely too small to state categorically that anesthetics are not teratogenic.

In a large survey, Mazze and Kallen [414] combined data from three Swedish health care registries for the years 1973 to 1981. Adverse outcomes examined were (1) congenital

Figure 57-29 (Figure Not Available) Total number of observed and expected adverse outcomes among women having nonobstetric operations during pregnancy. Incidence of infants with birth weights under 1,500 g and of infants born alive and dying within 168 hours of birth were significantly increased ($P < .05$) in the surgical patients. *(From Mazze and Kallen [414])*

anomalies, (2) stillborn infants, (3) infants dead at 168 hours, and (4) infants with very low and low birth weights. There were 5,405 operations in the population of 720,000 pregnant women (operation rate, 0.75%). Of these, 2,252 operations were performed in the first trimester, and 65 percent received general anesthetics, almost all of which included nitrous oxide. The results are summarized in Figure 57-29 (Figure Not Available) . The incidences of congenital malformations and stillbirths were not increased in the offspring of women undergoing operations. However, the incidences of very low and low-birth-weight infants were increased, as a result of both prematurity and intrauterine growth retardation. The incidence of infants born alive but dying within 168 hours was increased. No specific types of anesthesia or operation were associated with increased incidences of adverse reproductive outcomes.

Some reports have suggested that anesthesia and surgery during pregnancy are associated with the onset of preterm labor. [410] No one agent or technique has been associated with a higher incidence of premature delivery. However, the halogenated anesthetics decrease uterine contractility; if uterine manipulation is anticipated, the use of these agents would theoretically be more likely to minimize the possibility of preterm labor. Alternatively, tocolytic drugs can be given in conjunction with the anesthetic for surgery.

During the anesthetic visit before surgery during pregnancy, great effort should be made to allay maternal anxiety and apprehension. The lack of documented teratogenicity can be presented. The patient should understand that the likelihood of first-trimester miscarriage increases from 5.1 percent without surgery to 8 percent with surgery, [411] and the incidence of premature delivery increases from 5.13 percent without surgery to 7.47 percent with surgery. [414] Although it is clear that there is significant risk to the fetus when an operation is performed during pregnancy, it is not clear whether the hazard is due to the surgery, the pathology for which the surgery was necessary, or the anesthetic.

Elective surgery should be deferred until after delivery when the physiologic changes of pregnancy have returned toward normal. Women of child-bearing age who are scheduled for elective surgery should be carefully queried regarding the possibility of pregnancy. Urgent surgery (i.e., operations that are essential but can be delayed without

Figure 57-30 (Figure Not Available) Effect of electrically induced stress (30-60 seconds) on maternal arterial blood pressure, plasma norepinephrine levels, and uterine blood flow in sheep. All values subsequent to control are given as mean percentage change with standard error. *(From Shnider et al [415])*

increasing the risk of permanent disability) should be deferred until the second or third trimester. Despite the lack of proof that particular drugs should be avoided, we consider it prudent to minimize or eliminate fetal exposure to drugs during the vulnerable first trimester.

Emergency surgery (i.e., operations that cannot be delayed without increasing the risk of maternal morbidity or mortality) may be necessary at any time during pregnancy. The minimal drug exposure conferred by regional anesthesia (particularly spinal anesthesia) makes these techniques theoretically preferable; however, general anesthesia should not be withheld if it will accomplish the best surgical conditions. If general anesthesia is necessary during the first trimester, there is no proof that any well-conducted technique is superior to any other. Adequate oxygenation and avoidance of hyperventilation are mandatory. During pregnancy, patients may be at increased risk of aspiration, and the usual safeguards to prevent aspiration pneumonitis should be observed. Aortocaval compression during the second and third trimesters should be prevented by avoiding the supine position. Ideally, continuous FHR monitoring during surgery should be employed if possible after the middle of the second trimester. This may provide an indication of abnormalities in maternal ventilation or uterine perfusion. Uterine activity should be monitored continuously with an external tocodynamometer during the postoperative period to detect the onset of preterm labor.

/das/book/view/29494766/875/637.html

SUMMARY

A number of anesthetic techniques are safe and effective for facilitating labor, vaginal delivery, and cesarean delivery or for assisting with the management of obstetric complications. The various techniques of obstetric analgesia or anesthesia each has advantages and risks for the mother and the fetus. Whatever the choice of anesthetic, skillful administration and observance of the issues discussed in this chapter is paramount to a safe anesthetic for mother, fetus, and neonate.

In some circumstances, avoidance or inadequate use of analgesia in the name of safety carries its own hazards, in that maternal stress may be left untreated. In pregnant sheep, stress results in maternal hypertension and increased plasma norepinephrine, which is associated with a decrease in uterine blood flow (Fig. 57-30) (Figure Not Available) . [415] In pregnant Rhesus monkeys, psychologic stress results in fetal bradycardia and asphyxia, whereas alleviation of stress with a barbiturate causes an immediate and significant improvement in heart rate and oxygenation. [416] [417] Such studies support the view that skillful anesthesia, coupled with reassurance and emotional support of the parturient, may make birth less stressful not only for the mother but also for the fetus.

References

1. Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. Anesthesiology 26:381, 1965.

2. Russell IF, Chambers WA: Closing volume in normal pregnancy. Br J Anaesth 53:1043, 1981.

3. Baldwin GR, Moorthi DS, Whelton JA et al: New lung functions and pregnancy. Am J Obstet Gynecol 127:235, 1977.

4. Holdcroft A, Bevan DR, O'Sulliivan JC et al: Airway closure and pregnancy. Anaesthesia 32:517, 1977.

5. Weinberger SE, Weiss ST, Cohen SR et al: Pregnancy and the lung. Am Rev Respir Dis 121:559, 1980.

6. Bevan DR, Holdcroft A, Loh L et al: Closing volume and pregnancy. BMJ 1:13, 1974.

7. Awe RJ, Nicotra MB, Newsom TD et al: Arterial oxygenation and alveolar-arterial gradients in term pregnancy. Obstet Gynecol 53:182, 1979.

8. Clapp JF: Oxygen consumption during treadmill exercise before, during, and after pregnancy. Am J Obstet Gynecol 161:1458, 1989.

9. McMurray RG, Katz VL, Berry MJ et al: The effect of pregnancy on metabolic responses during rest, immersion, and aerobic exercise in the water. Am J Obstet Gynecol 158:481, 1988.

10. Kambam JR, Handte RE, Brown WU et al: Effect of normal and preeclamptic pregnancies on the oxyhemoglobin dissociation curve. Anesthesiology 65:1986, 1986.

11. Hagerdal M, Morgan CW, Sumner AE et al: Minute ventilation and oxygen consumption during labor with epidural analgesia. Anesthesiology 59:425, 1983.

12. Archer GW Jr, Marx GF: Arterial oxygen tension during apnoea in parturient women. Br J Anaesth 46:358, 1974.

13. Capeless EL, Clapp JF: Cardiovascular changes in early phase of pregnancy. Am J Obstet Gynecol 161:1449, 1989.

14. Lees MM, Taylor SH, Scott DB et al: A study of cardiac output at rest throughout pregnancy. J Obstet Gynaecol Br Commonw 74:319, 1967.

15. Mashini IS, Albazzaz SJ, Fadel HE et al: Serial noninvasive evaluation of cardiovascular hemodynamics during pregnancy. Am J Obstet Gynecol 156:1208, 1987.

16. Lees MM, Scott DB, Kerr MG et al: The circulatory effects of recumbent postural change in late pregnancy. Clin Sci 32:453, 1967.

17. Ueland K, Novy MJ, Peterson EN et al: Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. Am J Obstet Gynecol 104:856, 1969.

18. Pritchard JA: Changes in blood volume during pregnancy and delivery. Anesthesiology 26:393, 1965.

19. Ueland K: Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. Am J Obstet Gynecol 126:671, 1976.

20. Lang RM, Borow KM: Heart disease. In Barron WM, Lindheimer MD (eds): Medical Disorders During Pregnancy. St. Louis, Mosby Year Book, 1991, p 148.

21. Ueland K, Hansen J: Maternal cardiovascular dynamics. III. Labor and delivery under local and caudal analgesia. Am J Obstet Gynecol 103:8, 1969.

22. Robson SC, Dunlop W, Boys RJ et al: Cardiac output during labour. BMJ 295:1169, 1987.

23. Ueland K, Hansen JM: Maternal cardiovascular dynamics II. Posture and uterine contractions. Am J Obstet Gynecol 103:1, 1969.

24. Eckstein K-L, Marx GF: Aortocaval compression and uterine displacement. Anesthesiology 40:92, 1974.

25. Bierniarz J, Curuchet E, Crottogini JJ: Aortocaval compression by the uterus in late human pregnancy: An arteriographic study. Am J Obstet Gynecol 100:203, 1968.

26. Kerr MG: Cardiovascular dynamics in pregnancy and labor. BMJ Bull 24:19, 1968.

27. Kerr MG, Scott DB, Samuel E: Studies of the inferior vena cava in late pregnancy. BMJ 1:532, 1964.

28. Holmes F: The supine hypotensive syndrome: Its importance to the anaesthetist. Anaesthesia 15:298, 1960.

29. Marx GF: Aortocaval compression: Incidence and prevention. Bull NY Acad Med 50:443, 1974.

30. Letsky E: Hematologic disorders. In Barron WM, Lindheimer MD (eds): Medical Disorders During Pregnancy. St. Louis, Mosby Year Book, 1991, p 272.

31. McCurdy CM, Magann EF, McCurdy CJ et al: The effect of placental management at cesarean delivery on operative blood loss. Am J Obstet Gynecol 167:1363, 1992.

32. Duthie SJ, Ghosh A, Ng A et al: Intra-operative blood loss during elective lower segment caesarean section. Br J Obstet Gynaecol 99:364, 1992.

33. McNair RD, Jaynes RV: Alterations in liver function during normal pregnancy. Am J Obstet Gynecol 80:500, 1960.

34. Shnider SM: Serum cholinesterase activity during pregnancy, labor and the puerperium. Anesthesiology 26:335, 1965.

35. Leighton BL, Cheek TG, Gross JB et al: Succinylcholine pharmacodynamics in peripartum patients. Anesthesiology 64:202, 1986.

36. Blitt CD, Petty WC, Alberternst EE et al: Correlation of plasma cholinesterase activity and duration of action of succinylcholine during pregnancy. Anesth Analg 56:78, 1977.

37. Attia RR, Ebeid AM, Fischer JE et al: Maternal fetal and placental gastrin concentrations. Anaesthesia 37:18, 1982.

38. Carp H, Jayaram A, Stoll M: Ultrasound examination of the stomach contents of parturients. Anesth Analg 74:683, 1992.

39. Brock-Utne JG, Dow TGB, Dimopoulos GE et al: Gastric and lower oesophageal sphincter (LOS) pressures in early pregnancy. Br J Anaesth 53:381, 1981.

40. Jayaram A, Bowen MP, Deshpande S et al: Ultrasound examination of the stomach contents of women in the postpartum period. Anesth Analg 84:522, 1997.

41. Soreide E, Bjornestad E, Steen PA: An audit of perioperative aspiration pneumonitis in gynaecological and obstetric patients. Acta Anaesthesiol Scand 40:14, 1996.

42. Fagraeus L, Urban BJ, Bromage PR: Spread of epidural analgesia in early pregnancy. Anesthesiology 58:184, 1983.

43. Datta S, Lambert DH, Gregus J et al: Differential sensitivities of mammalian nerve fibers during pregnancy. Anesth Analg 62:1070, 1983.

44. Palahniuk RJ, Shnider SM, Eger EI II: Pregnancy decreases the requirement for inhaled anesthetic agents. Anesthesiology 41:82, 1974.

45. Gin T, Chan MT: Decreased minimum alveolar concentration of isoflurane in pregnant humans. Anesthesiology 80:71, 1994.

46. Chan MT, Gin T: Postpartum changes in the minimum alveolar concentration of isoflurane. Anesthesiology 82:1360, 1995.

47. Datta S, Migliozzi RP, Flanagan HL et al: Chronically administered progesterone decreases halothane requirements in rabbits. Anesth Analg 68:46, 1989.

48. Strout CD, Nahrwold ML: Halothane requirement during pregnancy and lactation in rats. Anesthesiology 55:322, 1981.

49. Gintzler AR: Endorphin-mediated increases in pain threshold during pregnancy. Science 210:193, 1980.

50. Iwasaki H, Collins JG, Saito Y et al: Naloxone-sensitive, pregnancy-induced changes in behavioral responses to colorectal distention: Pregnancy-induced analgesia to visceral stimulation. Anesthesiology 74:927, 1991.

51. Shnider SM, deLorimier AA, Holl JW et al: Vasopressors in obstetrics. I. Correction of fetal acidosis with ephedrine during spinal hypotension. Am J Obstet Gynecol 1102:911, 1968.

52. Ralston DH, Shnider SM, deLorimier AA: Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 40:354, 1974.

53. Eng M, Berges PU, Ueland K et al: The effects of methoxamine and ephedrine in normotensive pregnant primates. Anesthesiology 35:354, 1971.

54. James FM, Greiss FC Jr, Kemp RA: An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. Anesthesiology 33:25, 1970.

55. Tong C, Eisenach JC: The vascular mechanism of ephedrine's beneficial effect on uterine perfusion during pregnancy. 76:792, 1992.

56. Brizgys RV, Dailey PA, Shnider SM et al: The incidence and neonatal effects of maternal hypotension during epidural anesthesia for cesarean section. Anesthesiology 67:782, 1987.

57. Li P, Tong C, Eisenach JC: Pregnancy and ephedrine increase the release of nitric oxide in ovine uterine arteries. Anesth Analg 82:288, 1996.

58. Ramanathan S, Grant GJ: Vasopressor therapy for hypotension due to epidural anesthesia for cesarean section. Acta Anaesthesiol Scand 32:559, 1988.

59. Moran DH, Perillo M, LaPorta RF et al: Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. J Clin Anesth 3:301, 1991.

60. Kingston HGG, Kendrick A, Sommer KM et al: Binding of thiopental in neonatal serum. Anesthesiology 72:428, 1990.

61. Brown WU, Bell GC, Alper MH: Acidosis, local anesthetics, and the newborn. Obstet Gynecol 48:27, 1976.

62. Pang LM, Mellins RB: Neonatal cardiorespiratory physiology. Anesthesiology 43:171, 1975.

63. Finster M, Morishima HO, Mark LC et al: Tissue thiopental concentrations in the fetus and newborn. Anesthesiology 336:155, 1972.

64. Finster M, Morishima HO, Boyes RN: The placental transfer of lidocaine and its uptake by fetal tissues. Anesthesiology 36:159, 1972.

65. Yaffe SF: Developmental factors influencing interactions of drugs. Ann NY Acad Sci 281:90, 1976.

66. Yaffe SJ, Juchau MP: Perinatal pharmacology. Annu Rev Pharmacol Toxicol 14:219, 1974.

67. Parer JT: Handbook of Fetal Heart Rate Monitoring. Philadelphia, WB Saunders, 1983.

68. Clark SL, Gimovsky ML, Miller FC: The scalp stimulation test: A clinical alternative to fetal scalp blood sampling. Am J Obstet Gynecol 148:274, 1984.

69. Manning FA, Platt LD, Sipos L: Antepartum fetal evaluation: Development of a fetal biophysical profile. Am J Obstet Gynecol 136:787, 1980.

70. Cohen WR, Schifrin BS: Diagnosis and management of fetal distress during labor. Semin Perinatol 2:155, 1978.

71. Wuitchik M, Bakal D, Lipshitz J: The clinical significance of pain and cognitive activity in latent labor. Obstet Gynecol 73:35, 1989.

72. Sharma SK, Sidawi JE, Ramin SM et al: Cesarean delivery: A randomized trial of epidural versus patient-controlled meperidine analgesia during labor. Anesthesiology 87:487, 1997.

73. Ramin SM, Gambling DR, Lucas MJ et al: Randomized trial of epidural versus intravenous analgesia during labor. Obstet Gynecol 86:783, 1995.

74. Philipsen T, Jensen N-H: Epidural block or parenteral pethidine as analgesic in labour: A randomized study concerning progress in labour and instrumental deliveries. Eur J Obstet Gynecol Reprod Biol 30:27, 1989.

75. Thorp JA, Hu DH, Albin RM et al: The effect of intrapartum epidural analgesia on nulliparous labor: A randomized, controlled, prospective trial. Am J Obstet Gynecol 169:851, 1993.

76. Chestnut DH, McGrath JM, Vincent RD et al: Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are in spontaneous labor? Anesthesiology 80:1201, 1994.

77. Chestnut DH, Vincent RD, McGrath JM et al: Does early administration of epidural analgesia affect obstetric outcome in nulliparous women who are receiving intravenous oxytocin? Anesthesiology 80:1193, 1994.

78. Lamaze F: Painless childbirth: Psychoprophylactic method. London, Burke, 1958.

79. Melzack R, Taenzer P, Feldman P et al: Labour is still painful after prepared childbirth training. Can Med Assoc J 125:357, 1981.

80. Melzack R: The myth of painless childbirth. Pain 19:321, 1984.

81. Scott JR, Rose NB: Effect of psychoprophylaxis (Lamaze preparation) on labor and delivery in primiparas. N Engl J Med 294:1285, 1976.

82. Doering SG, Entwisle DR: Preparation during pregnancy and ability to cope with labor and delivery. Am J Orthopsychiatry 45:825, 1975.

83. Wallis L, Shnider SM, Palahniuk RJ et al: An evaluation of acupuncture analgesia in obstetrics. Anesthesiology 41:596, 1974.

84. Abouleish E, Depp R: Acupuncture in obstetrics. Anesth Analg 54:82, 1975.

85. Robson JE: Transcutaneous nerve stimulation for pain relief in labour. Anaesthesia 34:357, 1979.

86. Stewart P: Transcutaneous nerve stimulation as a method of analgesia in labour. Anaesthesia 34:361, 1979.

87. Augustinsson LE, Bohlin P, Bundsen P et al: Pain relief during delivery by transcutaneous electrical nerve stimulation. Pain 4:59, 1977.

88. Hawkins JL, Gibbs CP, Orleans M et al: Obstetric anesthesia workforce survey, 1981 versus 1992. Anesthesiology 87:135, 1997.

89. Shnider SM, Moya F: Effects of meperidine on the newborn infant. Am J Obstet Gynecol 89:1009, 1964.

90. Irving FC: Advantages and disadvantages of barbiturates in obstetrics. RI Med J 28:493, 1945.

91. Powe CE, Kiem IM, Fromhagen C et al: Propiomaxine hydrochloride in obstetrical analgesia. JAMA 181:290, 1962.

92. Zsigmond EK, Patterson RL: Double-blind evaluation of hydroxyzine hydrochloride in obstetric anesthesia. Anesth Analg 46:275, 1967.

93. Cavanagh D, Condo CS: Diazepam: A pilot study of drug concentrations in maternal blood, amniotic fluid and cord blood. 6:122, 1964.

94. Cree JE, Meyer J, Hailey DM: Diazepam in labour: Its metabolism and effect on the clinical condition and thermogenesis of the newborn. BMJ 4:251, 1973.

95. Owen JR, Irani SF, Blair AW: Effect of diazepam administered to mothers during labour on temperature regulation of neonate. Arch Dis Child 47:107, 1972.

96. Scher J, Hailey DM, Beard RW: The effects of diazepam on the fetus. Br J Obstet Gynaecol 79:635, 1972.

97. Yeh SY, Paul RH, Cordero L et al: A study of diazepam during labor. Obstet Gynecol 43:363, 1974.

98. Kanto J, Aaltonen L, Erkkola R et al: Pharmacokinetics and sedative effect of midazolam in connection with caesarean section performed under epidural analgesia. Acta Anaesthesiol Scand 28:116, 1984.

99. Ravlo O, Carl P, Crawford ME et al: A randomized comparison between midazolam and thiopental for elective cesarean section anesthesia: II. Neonates. Anesth Analg 68:234, 1989.

100. Rosaeg OP, Kitts JB, Koren G et al: Maternal and fetal effects of intravenous patient-controlled fentanyl analgesia during labour in a thrombocytopenic parturient. Can J Anaesth 39:277, 1992.

101. Rayburn W, Leuschen MP, Earl R et al: Intravenous meperidine during labor: A randomized comparison between nursing- and patient-controlled administration. Obstet Gynecol 74:702, 1989.

102. Podlas J, Breland BD: Patient-controlled analgesia with nalbuphine during labor. Obstet Gynecol 70:203, 1987.

103. Frank M, McAteer EJ, Cattermole R et al: Nalbuphine for obstetric analgesia: A comparison of nalbuphine with pethidine for pain relief in labour when administered by patient-controlled analgesia (PCA). Anaesthesia 42:697, 1987.

104. Hodgkinson R, Bhatt M, Wang CN: Double-blind comparison of the neurobehaviour of neonates following the administration of different doses of meperidine to the mother. Can Anaesth Soc J 25:405, 1978.

105. Hodgkinson R, Husain FJ: The duration of effect of maternally administered meperidine on neonatal neurobehavior. Anesthesiology 56:51, 1982.

106. Kuhnert BR, Linn PL, Kennard MJ et al: Effects of low doses of meperidine on neonatal behavior. Anesth Analg 64:335, 1985.

107. Kuhnert BR, Kuhnert PM, Philipson EH et al: Dispostion of meperidine and normeperidine following multiple doses during labor. II. Fetus and neonate. Am J Obstet Gynecol 151:410, 1985.

108. Morrison JC, Whybrew WD, Rosser SI et al: Metabolites of meperidine in the fetal and maternal serum. Am J Obstet Gynecol 126:997, 1976.

109. Craft JB, Coaldrake LA, Bolan JC et al: Placental passage and uterine effects of fentanyl. Anesth Analg 62:894, 1983.

110. Eisele JH, Wright R, Rogge P: Newborn and maternal fentanyl levels at cesarean section. Anesth Analg 61:179, 1982.

111. Rayburn W, Rathke A, Leuschen P et al: Fentanyl citrate analgesia during labor. Am J Obstet Gynecol 161:202, 1989.

112. Way WL, Costley EC, Way EL: Respiratory sensitivity of the newborn infant to meperidine and morphine. Clin Pharmacol Ther 6:454, 1965.

113. Gal TJ: Analgesic and respiratory depressant activity of nalbuphine: A comparison with morphine. Anesthesiology 55:367, 1982.

114. Romagnoli A, Keats AS: Ceiling effect for respiratory depression by nalbuphine. Clin Pharmacol Ther 27:478, 1980.

115. Wilson CM, McClean E, Moore J et al: A double-blind comparison of intramuscular pethidine and nalbuphine in labour. Anaesthesia 41:1207, 1986.

116. Hatjis CG, Meis PJ: Sinusoidal fetal heart rate pattern associated with butorphanol administration. Anesthesiology 67:377, 1986.

117. Feinstein SJ, Lodeiro JG, Vintzileos M: Sinusoidal fetal heart rate pattern after administration of nalbuphine hydrochloride: A case report. Am J Obstet Gynecol 154:159, 1986.

118. Wilson SJ, Errick JK, Balkon J: Pharmacokinetics of nalbuphine during parturition. Am J Obstet Gynecol 155:340, 1986.

119. Quilligan EJ, Keegan KA, Donahue MJ: Double-blind comparison of intravenously injected butorphanol and meperidine in parturients. Int J Gynaecol Obstet 18:363, 1980.

120. Maduska AL, Hajghassemali M: A double-blind comparison of butorphanol and meperidine in labour: Maternal pain relief and effect on the newborn. Can Anaesth Soc J 25:398, 1978.

121. Hodgkinson R, Huff RW, Hayashi RH et al: Double-blind comparison of maternal analgesia and neonatal neurobehaviour following intravenous butorphanol and meperidine. J Int Med Res 1979:224, 1979.

122. Akamatsu TJ, Bonica JJ, Rehmet R et al: Experiences with the use of ketamine for parturition: I. Primary anesthetic for vaginal delivery. Anesth Analg 53:284, 1974.

123. Irestedt L: Current status of nitrous oxide for obstetric pain relief. Acta Anaesthesiol Scand 38:771, 1994.

124. Carstoniu J, Levytam S, Norman P et al: Nitrous oxide in early labor: Safety and analgesic efficacy assessed by a double-blind, placebo-controlled study. Anesthesiology 80:30, 1994.

125. Shnider SM, Abboud TK, Artal R et al: Maternal catecholamines decrease during labor after lumbar epidural anesthesia. Am J Obstet Gynecol 147:13, 1983.

126. Jouppila R, Jouppila P, Hollmen A et al: Effect of segmental extradural analgesia on placental blood flow during normal labour. Br J Anaesth 50:563, 1978.

127. Abraham RA, Harris AP, Maxwell LG et al: The efficacy of 1.5% lidocaine with 7.5% dextrose and epinephrine as an epidural test dose for obstetrics. Anesthesiology 64:116, 1986.

128. Prince GD, Shetty GR, Miles M: Safety and efficacy of a low volume extradural test dose of bupivacaine in labour. Br J Anaesth 62:503, 1989.

129. Moore DC, Batra MS: The components of an effective test dose prior to epidural block. Anesthesiology 55:693, 1981.

130. Leighton BL, Norris MC, Sosis M et al: Limitations of epinephrine as a marker of intravascular injection in laboring women. Anesthesiology 66:688, 1987.

131. Hood DD, Dewan DM, James FM III: Maternal and fetal effects of epinephrine in gravid ewes. Anesthesiology 64:610, 1986.

132. Colonna-Romano P, Salvage R, Lingaraju N et al: Epinephrine-induced tachycardia is different from contraction-associated tachycardia in laboring patients. Anesth Analg 82:294, 1996.

133. Colonna-Romano P, Lingaraju N, Braitman LE: Epidural test dose: Lidocaine 100 mg, not chloroprocaine, is a symptomatic marker of iv injection in labouring parturients. Can Anaesth Soc J 40:714, 1993.

134. Marcus MAE, Vertommen JD, Van Aken H et al: Hemodynamic effects of intravenous isoproterenol versus epinephrine in the chronic maternal-fetal sheep preparation. Anesth Analg 82:1023, 1996.

135. Leighton BL, DeSimone CA, Norris MC et al: Isoproterenol is an effective marker of intravenous injection in laboring women. Anesthesiology 71:206, 1989.

136. Marcus MAE, Vertommen JD, Van Aken H et al: Hemodynamic effects of intravenous isoproterenol versus saline in the parturient. Anesth Analg 84:1113, 1997.

137. Leighton BL, Norris MC, DeSimone CA et al: The air test as a clinically useful indicator of intravenously placed epidural catheters. Anesthesiology 73:610, 1990.

138. Leighton BL, Gross JB: Air: An effective indicator of intravenously located epidural catheters. Anesthesiology 71:848, 1989.

139. Hughes SC, Rosen MA, Shnider SM et al: Maternal and neonatal effects of epidural morphine for labor and delivery. Anesth Analg 63:319, 1984.

140. Baraka A, Maktabi M, Noueihid R: Epidural meperidine-bupivacaine for obstetric analgesia. Anesth Analg 61:652, 1982.

141. Carrie LES, O'Sullivan GM, Seegobin R: Epidural fentanyl in labor. Anesthesia 36:965, 1981.

142. Steinberg RB, Powell G, Hu X et al: Epidural sufentanil for analgesia for labor and delivery. Reg Anesth 14:225, 1989.

143. Camann WR, Denney RA, Holby ED et al: A comparison of intrathecal, epidural, and intravenous sufentanil for labor analgesia. Anesthesiology 77:884, 1992.

144. Brownridge P, Plummer J, Mitchell J et al: An evaluation of epidural bupivacaine with and without meperidine in labor. Reg Anesth 17:15, 1992.

145. Vertommen JD, Vandermeulen E, Van Aken H et al: The effects of the addition of sufentanil to 0.125% bupivacaine on the quality of analgesia during labor and on the incidence of instrumental deliveries. Anesthesiology 74:809, 1991.

146. Brix JL, Yoshi WY, Kotelko DM et al: Effects of cumulative doses of epidural fentanyl in labor on the neuroadaptive capacity of the neonate [abstract]. Anesthesiology 81:A1165, 1994.

147. Crawford JS: Lumbar epidural block in labour: A clinical analysis. Br J Anaesth 44:66, 1972.

148. Belfrage P, Berlin A, Raabe N et al: Lumbar epidural analgesia with bupivacaine in labor. Am J Obstet Gynecol 123:839, 1975.

149. Breen TW, Shapiro T, Glass B et al: Epidural anesthesia for labor in an ambulatory patient. Anesth Analg 77:919, 1993.

150. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 51:285, 1979.

151. Pitkanen M, Feldman HS, Arthur GR et al: Chronotropic and inotropic effects of ropivacaine, bupivacaine, and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. Reg Anesth 17:183, 1992.

152. Lynch C: Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine. Anesth Analg 65:551, 1986.

153. Kotelko DM, Shnider SM, Dailey PA et al: Bupivacaine-induced cardiac arrhythmias in sheep. 60:10, 1984.

154. Moller RA, Covino BG: Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 67:107, 1988.

155. Clarkson CW, Hondeghem LM: Mechanism for bupivacaine depression of cardiac conduction: Fast block of sodium channel during the action potential with slow recovery from block during diastole. 62:396, 1985.

156. de La Coussaye JE, Bassoul B, Albat B et al: Experimental evidence in favor of role of intracellular actions of bupivacaine in myocardial depression. Anesth Analg 74:698, 1992.

157. Kasten GW, Martin ST: Resuscitation from bupivacaine-induced cardiovascular toxicity during partial inferior vena cava occlusion. Anesth Analg 65:341, 1986.

158. Rosen MA, Thigpen JW, Shnider SM et al: Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 64:1089, 1985.

159. Sage DJ, Feldman HS, Arthur GR et al: Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia. Anesth Analg 63:1, 1984.

160. de Jong RH, Ronfeld RA, DeRose RA: Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 61:3, 1982.

161. Santos AC, Pedersen H, Harmon TW et al: Does pregnancy alter the systemic toxicity of local anesthetics? Anesthesiology 70:991, 1989.

162. Wulf H, Munstedt P, Maier C: Plasma protein binding of bupivacaine in pregnant women at term. Acta Anaesthesiol Scand 35:129, 1991.

163. Moller RA, Datta S, Fox J et al: Effects of progesterone on the cardiac electrophysiologic action of bupivacaine and lidocaine. Anesthesiology 76:604, 1992.

164. Hawkins JL, Koonin LM, Palmer SK et al: Anesthesia-related deaths during obstetric delivery in the United States, 1979-1990. Anesthesiology 86:77, 1997.

165. Milaszkiewicz R, Payne N, Loughnan B et al: Continuous extradural infusion of lignocaine 0.75% vs bupivacaine 0.125% in primiparae: Quality of analgesia and influence on labour. Anaesthesia 47:1042, 1992.

166. Kennedy RL, Bell JU, Miller RP et al: Uptake and distribution of lidocaine in fetal lambs. 72:483, 1990.

167. Biehl D, Shnider SM, Levinson G et al: Placental transfer of lidocaine: Effects of fetal acidosis. Anesthesiology 48:409, 1978.

168. Scanlon JW, Brown WJ Jr, Weiss JB et al: Neurobehavioral responses of newborn infants after maternal epidural anesthesia. Anesthesiology 40:121, 1974.

169. Abboud TK, Kim KC, Noueihed R et al: Epidural bupivacaine, chloroprocaine, or lidocaine for cesarean section: Maternal and neonatal effects. Anesth Analg 62:914, 1983.

170. Kuhnert BR, Harrison MJ, Linn PL et al: Effects of maternal epidural anesthesia on neonatal behavior. Anesth Analg 63:301, 1984.

171. Kuhnert BR, Kuhnert PM, Philipson EH et al: The half-life of 2-chloroprocaine. Anesth Analg 65:273, 1986.

172. Philipson EH, Kuhnert BR, Syracuse CD: Fetal acidosis, 2-chloroprocaine, and epidural anesthesia for cesarean section. Am J Obstet Gynecol 151:322, 1985.

173. Camann WR, Hartigan PM, Gilbertson LI et al: Chloroprocaine antagonism of epidural opioid analgesia: A receptor specific phenomenon. Anesthesiology 73:860, 1990.

174. Corke BC, Carlson CG, Dettbarn WD: The influence of 2-chloroprocaine on the subsequent analgesic potency of bupivacaine. Anesthesiology 60:25, 1984.

175. Grice SC, Eisenach JC, Dewan DM: Labor analgesia with epidural bupivacaine plus fentanyl: Enhancement with epinephrine and inhibition with 2-chloroprocaine. Anesthesiology 72:623, 1990.

176. Reisner LS, Hochman BN, Plumer MH: Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 59:452, 1980.

177. Ravindran RS, Bond VK, Tasch MD et al: Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 59:447, 1980.

178. Wang BC, Hillman DE, Spielholz NI et al: Chronic neurological deficits and Nesacaine-CE: An effect of the anesthetic, 2-chloroprocaine, or the antioxidant, sodium bisulfite? Anesth Analg 63:445, 1984.

179. Rosen MA, Baysinger CL, Shnider SM et al: Evaluation of neurotoxicity after subarachnoid injection of large volumes of local anesthetic solutions. Anesth Analg 62:802, 1983.

180. Gissen AJ, Datta S, Lambert D: The chloroprocaine controversy. I. A hypothesis to explain the neural complications of chloroprocaine epidural. Reg Anesth 9:124, 1984.

181. Gissen AJ, Datta S, Lambert D: The chloroprocaine controversy. II. Is chloroprocaine neurotoxic? Reg Anesth 9:135, 1984.

182. Fibuch EE, Opper SE: Back pain following epidurally administered Nesacaine-MPF. Anesth Analg 69:113, 1989.

183. Moller R, Covino BG: Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. Anesthesiology 72:322, 1990.

184. Santos AC, Arthur GR, Pedersen H et al: Systemic toxicity of ropivacaine during ovine pregnancy. Anesthesiology 75:137, 1991.

185. Moller RA, Covino BG: Effect of progesterone on the cardiac electrophysiologic alterations produced by ropivacaine and bupivacaine. Anesthesiology 77:735, 1992.

186. Santos AC, Arthur GR, Wlody D et al: Comparative systemic toxicity of ropivacaine and bupivacaine in nonpregnant and pregnant ewes. Anesthesiology 82:734, 1995.

187. Stienstra R, Jonker TA, Bourdrez P et al: Ropivacaine 0.25% versus bupivacaine 0.25% for continuous epidural analgesia in labor: A double-blind comparison. Anesth Analg 80:285, 1995.

188. Owen MD, D'Angelo R, Gerancher JC et al: 0.125% ropivacaine is similar to 0.125% bupivacaine for labor analgesia using patient-controlled epidural infusion. Anesth Analg 86:527, 1998.

189. Bader AM, Datta S, Flanagan H et al: Comparison of bupivacaine- and ropivacaine-induced conduction blockade in the isolated rabbit vagus nerve. Anesth Analg 68:724, 1989.

190. Abboud TK, David S, Nagappala S et al: Maternal, fetal, and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics. Anesth Analg 63:973, 1984.

191. Brose WG, Cohen SE: Epidural lidocaine for cesarean section: Effect of varying epinephrine concentration. Anesthesiology 69:936, 1988.

192. Ohno H, Watanabe M, Saitoh J et al: Effect of epinephrine concentration on lidocaine disposition during epidural anesthesia. Anesthesiology 68:625, 1988.

193. Reynolds F, Taylor G: Plasma concentrations of bupivacaine during continuous epidural analgesia in labour: The effect of adrenaline. Br J Anaesth 43:436, 1971.

194. Reynolds F, Laishley R, Morgan B et al: Effect of time and adrenaline on the feto-maternal distribution of bupivacaine. Br J Anaesth 62:509, 1989.

195. Matadial L, Cibils LA: The effect of epidural anesthesia on uterine activity and blood pressure. Am J Obstet Gynecol 125:846, 1976.

196. Eisenach JC, Grice SC, Dewan DM: Epinephrine enhances analgesia produced by epidural bupivacaine during labor. Anesth Analg 66:447, 1987.

197. Justins DM, Francis D, Houlton PG et al: A controlled trial of extradural fentanyl in labour. Br J Anaesth 54:409, 1982.

198. Cohen SE, Tan S, Albright GA et al: Epidural fentanyl/bupivacaine mixtures for obstetric analgesia. Anesthesiology 67:403, 1987.

199. Steinberg RB, Dunn SM, Dixon DE et al: Comparison of sufentanil, bupivacaine, and their combination for epidural analgesia in obstetrics. Reg Anesth 17:131, 1992.

200. Viscomi CM, Hood DD, Melone PJ et al: Fetal heart rate variability after epidural fentanyl during labor. Anesth Analg 71:679, 1990.

201. Phillips GH: Epidural sufentanil/bupivacaine combinations for analgesia during labor: Effect of varying sufentanil doses. Anesthesiology 67:835, 1987.

202. Chestnut DH, Owen CL, Bates JN et al: Continuous infusion epidural analgesia during labor: A randomized, double-blind comparison of 0.0625% bupivacaine/0.0002% fentanyl versus 0.125% bupivacaine. Anesthesiology 68:754, 1988.

203. Chestnut DH, Laszewski LJ, Pollack KL et al: Continuous epidural infusion of 0.0625% bupivacaine-0.0002% fentanyl during the second stage of labor. Anesthesiology 72:613, 1990.

204. Lysak SZ, Eisenach JC, Dobson CE: Patient-controlled epidural analgesia during labor: A comparison of three solutions with a continuous infusion control. Anesthesiology 72:44, 1990.

205. Celleno D, Capogna G: Epidural fentanyl plus bupivacaine 0.125 percent for labour: Analgesic effects. Can J Anaesth 35:375, 1988.

206. Phillips G: Continuous infusion epidural analgesia in labor: The effect of adding sufentanil to 0.125% bupivacaine. Anesth Analg 67:462, 1988.

207. Russell R, Reynolds F: Epidural infusions for nulliparous women in labour: A randomized double-blind comparison of fentanyl/bupivacaine and sufentanil/bupivacaine. Anaesthesia 48:856, 1993.

208. Li DF, Rees GAD, Rosen M: Continuous extradural infusion of 0.0625% or 0.125% bupivacaine for pain relief in primigravid labour. Br J Anaesth 57:264, 1985.

209. Bogod DG, Rosen M, Rees GA: Extradural infusion of 0.125% bupivacaine at 10 ml/hr to women during labour. Br J Anaesth 59:325, 1987.

210. Lamont RF, Pinney D, Rodgers P et al: Continuous versus intermittent epidural analgesia. Anaesthesia 44:893, 1989.

211. Gambling DR, Yu P, McMorland GH et al: A comparative study of patient controlled epidural analgesia (PCEA) and continuous infusion epidural analgesia (CIEA) during labor. Can J Anaesth 35:249, 1988.

212. Viscomi C, Eisenach JC: Patient-controlled epidural analgesia during labor. Obstet Gynecol 77:348, 1991.

213. Ferrante FM, Lu L, Jamison SB et al: Patient-controlled epidural analgesia: Demand dosing. Anesth Analg 73:547, 1991.

214. Gambling DR, McMorland GJ, Yu P et al: Comparison of patient-controlled epidural analgesia and conventional intermittent "top-up" injections during labor. Anesth Analg 70:256, 1990.

215. Purdie J, Reid J, Thorburn J et al: Continuous extradural analgesia: Comparison of midwife top-ups, continuous infusions and patient controlled administration. Br J Anaesth 68:580, 1992.

216. Sinclair JC, Fox HA, Lentz JF et al: Intoxication of the fetus by a local anesthetic: A newly recognized complication of maternal caudal anesthesia. N Engl J Med 273:1173, 1965.

217. Baraka A, Noueihid R, Hajj S: Intrathecal injection of morphine for obstetric analgesia. Anesthesiology 54:136, 1981.

218. Abboud TK, Shnider SM, Dailey PA et al: Intrathecal administration of hyperbaric morphine for the relief of pain in labor. Br J Anaesth 56:1351, 1984.

219. Dailey PA, Brookshire GL, Shnider SM et al: The effects of naloxone associated with the intrathecal use of morphine in labor. Anesth Analg 64:658, 1985.

220. Leighton BL, DeSimone CA, Norris MC et al: Intrathecal narcotics for labor revisited: The combination of fentanyl and morphine intrathecally provides rapid onset of profound analgesia. Anesth Analg 69:122, 1989.

221. Herpolsheimer A, Schretenthaler J: The use of intrapartum intrathecal narcotic analgesia in a community-based hospital. Obstet Gynecol 84:931, 1994.

222. Hyde NH, Harrison DM: Intrathecal morphine in a parturient with cystic fibrosis. Anesth Analg 65:1357, 1986.

223. Abboud TK, Raya J, Noueihed R et al: Intrathecal morphine for relief of labor pain in a parturient with severe pulmonary hypertension. Anesthesiology 59:477, 1983.

224. Norris MC, Arkoosh VA: Spinal opioid analgesia for labor. Int Anesthesiol Clin 32:69, 1994.

225. D'Angelo R, Anderson MT, Philip J et al: Intrathecal sufentanil compared to epidural bupivacaine for labor analgesia. Anesthesiology 80:1209, 1994.

226. Campbell DC, Camann WR, Datta S: The addition of bupivacaine to intrathecal sufentanil for labor analgesia. Anesth Analg 81:305, 1995.

227. Abouleish A, Abouleish E, Camann W: Combined spinal-epidural analgesia in advanced labour. Can J Anaesth 41:575, 1994.

228. Cohen SE, Cherry CM, Holbrook RH et al: Intrathecal sufentanil for labor analgesia: Sensory changes, side effects, and fetal heart rate changes. Anesth Analg 77:1155, 1993.

229. Hamilton CL, Cohen SE: High sensory block after intrathecal sufentanil for labor analgesia. Anesthesiology 83:1118, 1995.

230. Riley ET, Walker D, Hamilton CL et al: Intrathecal sufentanil for labor analgesia does not cause a sympathectomy. Anesthesiology 87:874, 1997.

231. Nielsen PE, Erickson JR, Abouleish EI et al: Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: Incidence and clinical significance. Anesth Analg 83:742, 1996.

232. Clarke VT, Smiley RM, Finster M: Uterine hyperactivity after intrathecal injection of fentanyl for analgesia during labor: A cause of fetal bradycardia [letter]? Anesthesiology 81:1083, 1994.

233. Ferouz F, Norris MC, Leighton BL: Risk of respiratory arrest after intrathecal sufentanil. Anesth Analg 85:1088, 1997.

234. Baker MN, Sarna MC: Respiratory arrest after second dose of intrathecal sufentanil [letter]. Anesthesiology 83:231, 1995.

235. Hays RL, Palmer CM: Respiratory depression after intrathecal sufentanil during labor. Anesthesiology 81:511, 1994.

236. Honet JE, Arkoosh VA, Norris MC et al: Comparison among intrathecal fentanyl, meperidine, and sufentanil for labor analgesia. Anesth Analg 75:734, 1992.

237. Abouleish E, Rawal N, Shaw J et al: Intrathecal morphine 0.2 mg versus epidural bupivacaine 0.125% or their combination: Effects on parturients. Anesthesiology 74:711, 1991.

238. Leighton BL, Arkoosh VA, Huffnagle S et al: The dermatomal spread of epidural bupivacaine with and without prior intrathecal sufentanil. Anesth Analg 83:526, 1996.

239. Wollman SB, Marx GF: Acute hydration for prevention of hypotension of spinal anesthesia in parturients. Anesthesiology 29:374, 1968.

240. Gutsche BB: Prophylactic ephedrine preceding spinal analgesia for cesarean section. Anesthesiology 45:462, 1976.

241. Rout CC, Rocke DA, Levin J et al: A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective cesarean section. Anesthesiology 79:262, 1993.

242. Rout CC, Akoojee SS, Rocke DA et al: Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anaesthesia for elective caesarean section. Br J Anaesth 68:394, 1992.

243. Philipson EH, Kuhnert BR, Pimentel R et al: Transient maternal hypotension following epidural anesthesia. Anesth Analg 69:604, 1989.

244. Norris MC: Hypotension during spinal anesthesia for cesarean section: Does it affect neonatal outcome? Reg Anesth 12:191, 1987.

245. Downing JW, Johnson HV, Gonzalez HF et al: The pharmacokinetics of epidural lidocaine and bupivacaine during cesarean section. Anesthesiology 84:527, 1997.

246. Moore DC, Thompson GE, Crawford RD: Long-acting local anesthetic drugs and convulsions with hypoxia and acidosis. Anesthesiology 56:230, 1982.

247. Kasten GW, Martin ST: Bupivacaine cardiovascular toxicity: Comparison of treatment with bretylium and lidocaine. Anesth Analg 64:911, 1985.

248. Long WB, Rosenblum S, Grady IP: Successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary bypass. Anesth Analg 1989:403, 1989.

249. Philip JH, Brown WU: Total spinal anesthesia late in the course of obstetric bupivacaine epidural block. Anesthesiology 44:340, 1976.

250. Lee A, Dodd KW: Accidental subdural catheterisation. Anesthesia 41:847, 1986.

251. Boys JE, Norman PF: Accidental subdural analgesia: A case report, possible clinical implications and relevance to "massive extradurals." Br J Anaesth 47:1111, 1975.

252. Abouleish E, Goldstein M: Migration of an extradural catheter into the subdural space. Br J Anaesth 58:1194, 1986.

253. Ready LB, Cuplin S, Haschke RH et al: Spinal needle determinants of rate of transdural fluid leak. Anesth Analg 69:457, 1989.

254. Halpern S: Postdural puncture headache and spinal needle design. Anesthesiology 81:1376, 1994.

255. Ross BK, Chadwick HS, Mancuso JJ et al: Sprotte needle for obstetric anesthesia: Decreased incidence of post dural puncture headache. Reg Anesth 17:29, 1992.

256. Norris MC, Leighton BL, DeSimone CA: Needle bevel direction and headache after inadvertent dural puncture. 70:729, 1989.

257. Fink BR, Walker S: Orientation of fibers in human dorsal lumbar dura mater in relation to lumbar puncture. Anesth Analg 69:768, 1989.

258. Campbell DC, Douglas MJ, Pavy TJG et al: Comparison of the 25-gauge Whitacre with the 24-gauge Sprotte spinal needle for elective Caesarean section: Cost implications. Can J Anaesth 40:1131, 1993.

259. Mayer DC, Quance D, Weeks SK: Headache after spinal anesthesia for cesarean section: A comparison of the 27-gauge Quincke and 24-gauge Sprotte needles. Anesth Analg 75:377, 1992.

260. Camann WR, Murray RS, Mushlin PS et al: Effects of oral caffeine on postdural puncture headache. Anesth Analg 70:181, 1990.

261. Jarvis AP, Greenawalt JW, Fagraeus L: Intravenous caffeine for postdural puncture headache [letter]. Anesth Analg 65:1986.

262. Szeinfeld M, Ihmeidan IH, Moser MM et al: Epidural blood patch: Evaluation of the volume and spread of blood injected into the epidural space. Anesthesiology 64:820, 1986.

263. DiGiovanni AJ, Galbert MW, Wahle WM: Epidural injection of autologous blood for postlumbar-puncture headache II. Additional clinical experiences and laboratory investigation. Anesth Analg 51:226, 1972.

264. Ostheimer G, Palahniuk RJ, Shnider SM: Epidural blood patch for post-lumbar-puncture headache. 41:307, 1974.

265. Abouleish E, de la Vega S, Blendinger I et al: Long-term follow-up of epidural blood patch. Anesth Analg 54:459, 1975.

266. Loeser EA, Hill GE, Bennett GM et al: Time vs. success rate for epidural blood patch. 49:147, 1978.

267. Cheek TG, Banner R, Sauter J et al: Prophylactic extradural blood patch is effective: A preliminary communication. Br J Anaesth 61:340, 1988.

268. Colonna-Romano P, Shapiro BE: Unintentional dural puncture and prophylactic epidural blood patch in obstetrics. Anesth Analg 69:522, 1989.

269. Crawford JS: The prevention of headache consequent upon dural puncture. Br J Anaesth 44:598, 1972.

270. LeFevre ML: Fetal heart rate pattern and postparacervical fetal bradycardia. Obstet Gynecol 64:343, 1984.

271. Cibils L: Response of human uterine arteries to local anesthetics. Am J Obstet Gynecol 126:202, 1976.

272. Puolakka J, Jouppila R, Jouppila P et al: Maternal and fetal effects of low-dosage bupivacaine paracervical block. J Perinat Med 12:75, 1984.

273. Abouleish AE, Corn SB: Intravenous nitroglycerin for intrapartum external version of the second twin. Anesth Analg 78:808, 1994.

274. Chan ASH, Ananthanarayan C, Rolbin SH: Alternating nitroglycerin and Syntocinon to facilitate uterine exploration and removal of an adherent placenta. Can J Anaesth 42:335, 1995.

275. Altabef KM, Spencer JT, Zinberg S: Intravenous nitroglycerin for uterine relaxation of an inverted uterus. Am J Obstet Gynecol 166:1237, 1992.

276. Anesthesia for emergency deliveries. Washington, DC, American College of Obstetricians and Gynecologists Committee on Obstetrics, 1992.

277. Juhani TP, Hannele H: Complications during spinal anesthesia for cesarean delivery: A clinical report of one year's experience. Reg Anesth 18:128, 1993.

278. Norris MC: Patient variables and the subarachnoid spread of hyperbaric bupivacaine in the term parturient. Anesthesiology 72:478, 1990.

279. De Simone CA, Leighton BL, Norris MC: Spinal anesthesia for cesarean delivery: A comparison of two doses of hyperbaric bupivacaine. Reg Anesth 20:90, 1995.

280. Moran DH, Johnson MD: Continuous spinal anesthesia with combined hyperbaric and isobaric bupivacaine in a patient with scoliosis. Anesth Analg 70:445, 1990.

281. Milligan KR, Carp H: Continuous spinal anaesthesia for caesarean section in the morbidly obese. Int J Obstet Anesth 1:111, 1992.

282. Riley ET, Cohen SE, Rubenstein AJ et al: Prevention of hypotension after spinal anesthesia for cesarean section: Six percent hetastarch versus lactated ringer's solution. Anesth Analg 81:838, 1995.

283. James FM, Dewan DM, Floyd HM et al: Chloroprocaine vs. bupivacaine for lumbar epidural analgesia for elective cesarean section. Anesthesiology 52:488, 1980.

284. Kang YG, Abouleish E, Caritis S: Prophylactic intravenous ephedrine infusion during spinal anesthesia for cesarean section. Anesth Analg 61:839, 1982.

285. Gajraj NM, Victory RA, Pace NA et al: Comparison of an ephedrine infusion with crystalloid administration for prevention of hypotension during spinal anesthesia. Anesth Analg 76:1023, 1993.

286. Robson SC, Boys RJ, Rodeck C et al: Maternal and fetal haemodynamic effects of spinal and extradural anaesthesia for elective caesarean section. Br J Anaesth 68:54, 1992.

287. Roberts SW, Leveno KJ, Sidawi JE et al: Fetal acidemia associated with regional anesthesia for elective cesarean delivery. Obstet Gynecol 85:79, 1995.

288. Abboud TK, Nagappala S, Murakawa K et al: Comparison of the effects of general and regional anesthesia for cesarean section on neonatal neurologic and adaptive capacity scores. Anesth Analg 64:996, 1985.

289. Abouleish EI: Epinephrine improves the quality of spinal hyperbaric bupivacaine for cesarean section. Anesth Analg 66:395, 1987.

290. Abouleish E, Rawal N, Fallon K et al: Combined intrathecal morphine and bupivacaine for cesarean section. Anesth Analg 67:370, 1988.

291. Hunt CO, Datta S, Hauch M et al: Perioperative analgesia with subarachnoid fentanyl-bupivacaine. Anesthesiology 67:A621, 1987.

292. Randalls B, Broadway JW, Browne DA et al: Comparison of four subarachnoid solutions in a needle-through-needle technique for elective caesarean section. Br J Anaesth 66:314, 1991.

293. Connelly NR, Dunn SM, Ingold V et al: The use of fentanyl added to morphine-lidocaine-epinephrine spinal solution in patients undergoing cesarean section. Anesth Analg 78:918, 1994.

294. Courtney MA, Bader AM, Hartwell B et al: Perioperative analgesia with subarachnoid sufentanil administration. Reg Anesth 17:274, 1992.

295. Hood DD, Dewan DM: Anesthetic and obstetric outcome in morbidly obese parturients. Anesthesiology 79:1210, 1993.

296. Chadwick HS, Easterling TR: Anesthetic concerns in the patient with preeclampsia. Semin Perinatol 15:397, 1991.

297. Clark SL, Phelan JP, Greenspoon J et al: Labor and delivery in the presence of mitral stenosis: Central hemodynamic observations. Am J Obstet Gynecol 152:984, 1985.

298. Easterling TR, Chadwick HS, Otto CM et al: Aortic stenosis in pregnancy. Obstet Gynecol 72:113, 1988.

299. Colclough GW, Ackerman WE, Walmsley PM et al: Epidural anesthesia

for a parturient with critical aortic stenosis [letter]. J Clin Anesth 7:264, 1995.

300. Preston PG, Rosen MA, Hughes SC et al: Epidural anesthesia with fentanyl and lidocaine for cesarean section: Maternal effects and neonatal outcome. Anesthesiology 68:938, 1988.

301. Noble DW, Morrison LM, Brockway MS et al: Adrenaline, fentanyl or adrenaline, and fentanyl as adjuncts to bupivacaine for extradural anaesthesia in elective caesarean section. Br J Anaesth 66:645, 1991.

302. Vertommen J: The effect of the addition of epidural sufentanil to bupivacaine 0.5% for elective cesarean section. Anesthesiology 71:A869, 1989.

303. Russell IF: Levels of anaesthesia and intraoperative pain at caesarean section under regional block. Int J Obstet Anesth 4:71, 1995.

304. Rawal N, Schollin J, Wesstrom G: Epidural versus combined spinal epidural block for cesarean section. Acta Anaesthesiol Scand 32:61, 1988.

305. Thoren T, Holmstrom B, Rawal N et al: Sequential combined spinal epidural block versus spinal block for cesarean section: Effects on maternal hypotension and neurobehavioral function of the newborn. Anesth Analg 78:1087, 1994.

306. Blumgart CH, Ryall D, Dennison B et al: Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic. Br J Anaesth 69:457, 1992.

307. Gibbs CP, Spohr L, Schmidt D: The effectiveness of sodium citrate as an antacid. Anesthesiology 57:44, 1982.

308. Gibbs CP, Banner T: Effectiveness of Bicitra as a preoperative antacid. Anesthesiology 61:97, 1984.

309. Rout CC, Rocke DA, Gouws E: Intravenous ranitidine reduces the risk of acid aspiration of gastric contents at emergency cesarean section. Anesth Analg 76:156, 1993.

310. McAuley DM, Moore J, McCaughey W et al: Ranitidine as an antacid before elective Caesarean section. Anaesthesia 38:108, 1983.

311. Koch-Weser J, Schulze-Delrieu K: Drug therapy: Metoclopramide. N Engl J Med 305:28, 1981.

312. Bylsma-Howell M, Riggs KW, McMorland GH et al: Placental transport of metoclopramide: Assessment of maternal and neonatal effects. Can Anaesth Soc J 30:487, 1983.

313. Cohen SE, Jasson J, Talafre ML et al: Does metoclopramide decrease the volume of gastric contents in patients undergoing cesarean section? Anesthesiology 61:604, 1984.

314. Norris MC, Dewan DM: Preoxygenation for cesarean section: A comparison of two techniques. Anesthesiology 62:827, 1985.

315. Sellick BA: Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. Lancet 1:404, 1961.

316. Endler GC, Mariona FG, Sokol RJ et al: Anesthesia-related maternal mortality in Michigan, 1972 to 1984. Am J Obstet Gynecol 159:187, 1988.

317. Hibbard BM, Anderson MM, Drife JO et al: Deaths associated with anaesthesia. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 1988-1990. London, HMSO, 1994, p 80.

318. Hibbard BM, Anderson MM, Drife JO et al: Deaths associated with anaesthesia. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 1991-1993. London, HMSO, 1997.

319. Lyons G: Failed intubation. Anaesthesia 40:759, 1985.

320. Samsoon GL, Young JR: Difficult tracheal intubation: A retrospective study. Anaesthesia 42:487, 1987.

321. Rocke DA, Murray WB, Rout CC et al: Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 77:67, 1992.

322. Mallampati SR: Clinical sign to predict difficult tracheal intubation (hypothesis). Can Anaesth Soc J 30:316, 1983.

323. Mallampati SR, Gatt SP, Gugino LD et al: A clinical sign to predict difficult tracheal intubation: A prospective study. Can Anaesth Soc J 32:429, 1985.

324. Edwards RM: Fibreoptic intubation: A solution to failed intubation in a parturient? Anaesth Intensive Care 22:718, 1994.

325. McClune S, Regan M, Moore J: Laryngeal mask airway for Caesarean section. Anaesthesia 45:227, 1990.

326. Gataure PS, Hughes JA: The laryngeal mask airway in obstetrical anaesthesia. Can J Anaesth 42:130, 1995.

327. Davies JM, Crone LA: Difficult intubation in the parturient. Can J Anaesth 36:668, 1989.

328. Levinson G, Shnider SM, deLorimier AA et al: Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. Anesthesiology 40:340, 1974.

329. Motoyama EK, Rivard G, Acheson F et al: Adverse effect of maternal hyperventilation on the foetus. Lancet 1:286, 1966.

330. Warren TM, Datta S, Ostheimer GW et al: Comparison of the maternal and neonatal effects of halothane, enflurane, and isoflurane for cesarean delivery. Anesth Analg 62:516, 1983.

331. Datta S, Ostheimer GW, Weiss JB et al: Neonatal effect of prolonged anesthetic induction for cesarean section. Obstet Gynecol 58:331, 1981.

332. Gale R, Zalkinder-Luboshitz I, Slater PE: Increased neonatal risk from the use of general anesthesia in emergency cesarean section. J Reprod Med 27:715, 1982.

333. Ong BY, Cohen MM, Palahniuk RJ: Anesthesia for cesarean section: Effects on neonates. Anesth Analg 68:270, 1989.

334. James FM, Crawford JS, Hopkinson R et al: A comparison of general anesthesia and lumbar epidural analgesia for elective cesarean section. Anesth Analg 56:228, 1977.

335. Kosaka Y, Takahashi T, Mark LC: Intravenous thiobarbiturate anesthesia for Cesarean section. Anesthesiology 31:489, 1969.

336. Finster M, Mark LC, Morishima HO et al: Plasma thiopental concentration in the newborn following delivery under thiopental-nitrous oxide anesthesia. Am J Obstet Gynecol 95:621, 1966.

337. Little B, Chang T, Chucot L et al: Study of ketamine as an obstetric anesthetic agent. Am J Obstet Gynecol 113:247, 1972.

338. Dich-Nielsen J, Holasek J: Ketamine as induction agent for Caesarean section. Acta Anaesthesiol Scand 26:139, 1982.

339. Downing JW, Mahomedy MC, Jeal DE et al: Anaesthesia for Caesarean section with ketamine. Anaesthesia 31:883, 1976.

340. Marx GF, Hwang HS, Chandra P: Postpartum uterine pressures with different doses of ketamine. Anesthesiology 50:163, 1979.

341. Oats JN: Effects of ketamine on the pregnant uterus. Br J Anaesth 51:1163, 1979.

342. Moore J, Bill KM, Flynn RJ et al: A comparison between propofol and thiopentone as induction agents in obstetric anaesthesia. Anaesthesia 44:753, 1989.

343. Valtonen M, Kanto J, Rosenberg P: Comparison of propofol and thiopentone for induction of anaesthesia for elective Caesarean section. Anaesthesia 44:758, 1989.

344. Abboud TK, Zhu J, Richardson M et al: Intravenous propofol vs thiamylal-isoflurane for caesarean section, comparative maternal and neonatal effects. Acta Anaesthesiol Scand 39:205, 1995.

345. Gin T, Gregory MA, Chan K et al: Maternal and fetal levels of propofol at Caesarean section. Anaesth Intensive Care 18:180, 1990.

346. Gin T, Gregory MA, Oh TE: The haemodynamic effects of propofol and thiopentone for induction of caesarean section. Anaesth Intensive Care 18:175, 1990.

347. Alon E, Ball RH, Gillie MH et al: Effects of propofol and thiopental on maternal and fetal cardiovascular and acid-base variables in the pregnant ewe. Anesthesiology 78:562, 1993.

348. Downing JW, Buley RJR, Brock-Utne JG et al: Etomidate for induction of anaesthesia at Caesarean section: Comparison with thiopentone. Br J Anaesth 51:135, 1979.

349. Moya F, Kvisselgaard N: The placental transmission of succinylcholine. Anesthesiology 22:1, 1961.

350. Dailey PA, Fisher DM, Shnider SM et al: Pharmacokinetics, placental transfer, and neonatal effects of vecuronium and pancuronium administered during Cesarean section. Anesthesiology 60:469, 1984.

351. Flynn PJ, Frank M, Hughes R: Use of atracurium in caesarean section. Br J Anaesth 56:599, 1984.

352. Abouleish E, Abboud T, Lechevalier J et al: Rocuronium (Org 9426) for Caesarean section. Br J Anaesth 73:336, 1994.

353. Baraka AS, Sayyid SS, Assaf BA: Thiopental-rocuronium versus ketamine-rocuronium for rapid-sequence intubation in parturients undergoing cesarean section. Anesth Analg 84:1104, 1997.

354. Crawford JS: Awareness during operative obstetrics under general anaesthesia. Br J Anaesth 43:179, 1971.

355. Lyons G: Awareness during caesarean section. Anaesthesia 46:62, 1992.

356. Gambling DR, Sharma SK, White PF et al: Use of sevoflurane during elective cesarean birth: A comparison with isoflurane and spinal anesthesia. Anesth Analg 81:90, 1995.

357. Abboud TK, Zhu J, Richardson M et al: Desflurane: A new volatile anesthetic for cesarean section: Maternal and neonatal effects. Acta Anaesthesiol Scand 39:723, 1995.

358. Munson ES, Embro WJ: Enflurane, isoflurane, and halothane and isolated human uterine muscle. Anesthesiology 46:11, 1977.

359. Marx GF, Kim YI, Lin C-C et al: Postpartum uterine pressures under halothane or enflurane anesthesia. Obstet Gynecol 51:695, 1978.

360. Marx GF, Luykx WM, Cohen S: Fetal-neonatal status following caesarean section for fetal distress. Br J Anaesth 56:1009, 1984.

361. Roberts JM: Sera from preeclamptic women specifically activate human umbilical vein endothelial cells in vitro: Morphological and biochemical evidence. Am J Reprod Immunol 27:101, 1992.

362. Walsh SW: Preeclampsia: An imbalance in placental prostacyclin and thromboxane production. Am J Obstet Gynecol 152:335, 1985.

363. Easterling TR, Benedetti TJ: Preeclampsia: A hyperdynamic disease model. Am J Obstet Gynecol 160:1447, 1989.

364. Sibai BM: Pulmonary edema in severe preeclampsia-eclampsia: Analysis of thirty-seven consecutive cases. Am J Obstet Gynecol 156:1174, 1987.

365. Zinaman M, Rubin J, Lindheimer MD: Serial plasma oncotic pressure levels and echoencephalography during and after delivery in severe pre-eclampsia. Lancet 1:1245, 1985.

366. Benedetti TJ, Kates R, Williams V: Hemodynamic observations in severe preeclampsia complicated by pulmonary edema. Am J Obstet Gynecol 152:330, 1985.

367. Cotton DB, Gonik B, Dorman D: Cardiovascular alterations in severe pregnancy-induced hypertension: Relationship of central venous pressure to pulmonary capillary wedge pressure. Am J Obstet Gynecol 151:762, 1985.

368. Naeye RL, Friedman EA: Causes of perinatal death associated with gestational hypertension and proteinuria. Am J Obstet Gynecol 133:8, 1979.

369. Leduc L, Wheeler JM, Kirshon B et al: Coagulation profile in severe preeclampsia. Obstet Gynecol 79:14, 1992.

370. Chandran R, Serra-Serra V, Redman CWG: Spontaneous resolution of pre-eclampsia-related thrombocytopenia. Br J Obstet Gynecol 99:887, 1992.

371. Kelton JG, Hunter DJ, Neame PB: A platelet function defect in preeclampsia. Obstet Gynecol 65:107, 1985.

372. Rasmus KT, Rottman RL, Kotelko DM et al: Unrecognized thrombocytopenia and regional anesthesia in parturients: A retrospective review. Obstet Gynecol 73:943, 1989.

373. Lucas MJ, Leveno KJ, Cunningham FG: A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. N Engl J Med 333:201, 1995.

374. Cotton DB, Gonik B, Dorman KF: Cardiovascular alterations in severe pregnancy-induced hypertension: Acute effects of intravenous magnesium sulfate. Am J Obstet Gynecol 148:162, 1984.

375. Ghoneim MM, Long JP: The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 32:23, 1970.

376. Baraka A: Neuromuscular interaction of magnesium with succinylcholine-vecuronium in the eclamptic patient. Anesthesiology 67:806, 1987.

377. Newsome LR, Bramwell RS, Curling PE: Severe preeclampsia: Hemodynamic effects of lumbar epidural anesthesia. Anesth Analg 65:31, 1986.

378. Moore TR, Key TC, Reisner LS et al: Evaluation of the use of continuous lumbar epidural anesthesia for hypertensive pregnant women in labor. Am J Obstet Gynecol 152:404, 1985.

379. Abboud T, Artal R, Sarkis F et al: Sympathoadrenal activity, maternal, fetal, and neonatal responses after epidural anesthesia in the preeclamptic patient. Am J Obstet Gynecol 144:915, 1982.

380. Jouppila P, Jouppila R, Hollmen A: Lumbar epidural analgesia to improve intervillous blood flow during labor in severe preeclampsia. Obstet Gynecol 59:158, 1982.

381. Ramos-Santos E, Devoe LD, Wakefield ML et al: The effects of epidural anesthesia on the Doppler velocimetry of umbilical and uterine arteries in normal and hypertensive patients during active term labor. Obstet Gynecol 77:20, 1991.

382. Wallace DH, Leveno KJ, Cunningham FG et al: Randomized comparison of general and regional anesthesia for cesarean delivery in pregnancies complicated by severe preeclampsia. Obstet Gynecol 86:193, 1995.

383. Hodgkinson R, Husain FJ, Hayashi RH: Systemic and pulmonary blood pressure during caesarean section in parturients with gestational hypertension. Can Anaesth Soc J 27:389, 1980.

384. Ramanathan J, Sibai BM, Mabie WC et al: The use of labetalol for attenuation of the hypertensive response to endotracheal intubation in preeclampsia. Am J Obstet Gynecol 159:650, 1988.

385. Paull J: Clinical report of the use of sodium nitroprusside in severe pre-eclampsia. Anaesth Intensive Care 3:72, 1975.

386. Poulton TJ, James FM, Lockridge O: Prolonged apnea following trimethaphan and succinylcholine. Anesthesiology 50:54, 1979.

387. Hood DD, Dewan DM, James FM et al: The use of nitroglycerin in preventing the hypertensive response to tracheal intubation in severe preeclampsia. Anesthesiology 63:329, 1985.

388. Snyder SW, Wheeler AS, James FM: The use of nitroglycerin to control severe hypertension of pregnancy during cesarean section. Anesthesiology 51:563, 1979.

389. Morgan HS, Kane SH: An analysis of 16,327 breech births. JAMA 187:262, 1964.

390. Rush RW, Davey DA, Segall ML: The effect of preterm delivery on perinatal mortality. Br J Obstet Gynaecol 85:806, 1978.

391. Spielman FJ, Herbert WNP: Maternal cardiovascular effects of drugs that alter uterine activity. Obstet Gynecol Surv 43:516, 1988.

392. Valenzuela G, Cline S: Use of magnesium sulfate in premature labor that fails to respond to beta-mimetic drugs. Am J Obstet Gynecol 143:718, 1982.

393. Benedetti TJ: Maternal complications of parenteral B-sympathomimetic therapy for premature labor. Am J Obstet Gynecol 145:1, 1983.

394. Benedetti TJ, Hargrove JC, Rosene KA: Maternal pulmonary edema during premature labor inhibition. Obstet Gynecol 59:335, 1982.

395. Schrier RW, Lieberman R, Ufferman RC: Mechanism of antidiuretic effect of beta adrenergic stimulation. J Clin Invest 51:97, 1972.

396. May AE: Editorial: The confidential enquiry into maternal deaths 1988-1990. Br J Anaesth 73:129, 1994.

397. Saftlas AF, Olson DR, Atrash HK et al: National trends in the incidence of abruptio placentae, 1979-1987. Obstet Gynecol 78:1081, 1991.

398. Farmer RM, Kirschbaum T, Potter D et al: Uterine rupture during trial of labor after previous cesarean section. Am J Obstet Gynecol 165:996, 1991.

399. Nielsen T, Ljungblad U, Hagberg H: Rupture and dehiscence of cesarean section scar during pregnancy and delivery. Am J Obstet Gynecol 16:569, 1989.

400. Plauche WC, Von Almen W, Muller R: Catastrophic uterine rupture. Obstet Gynecol 64:792, 1984.

401. Fishburne JI Jr, Brenner WE, Braaksma JT et al: Cardiovascular and respiratory responses to intravenous infusion of prostaglandin F2a in the pregnant woman. Am J Obstet Gynecol 114:765, 1972.

402. DeSimone CA, Norris MC, Leighton BL: Intravenous nitroglycerin aids manual extraction of a retained placenta [letter]. Anesthesiology 73:787, 1990.

403. Clark SL, Koonings PP, Phelan JP: Placenta previa/accreta and prior cesarean section. Obstet Gynecol 66:89, 1985.

404. Read JA, Cotton DB, Miller FC: Placenta accreta: Changing clinical aspects and outcome. Obstet Gynecol 56:31, 1980.

405. Shah-Hosseini R, Evrard JR: Puerperal uterine inversion. Obstet Gynecol 73:567, 1989.

406. Watson P, Besch N, Bowes WA Jr: Management of acute and subacute puerperal inversion of the uterus. Obstet Gynecol 55:12, 1980.

407. Safra MJ, Oakley GP: Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. Lancet 2:478, 1975.

408. Tannenbaum TN, Goldberg RJ: Exposure to anesthetic gases and reproductive outcome. J Occup Med 27:659, 1985.

409. Smith BE: Fetal prognosis after anesthesia during gestation. Anesth Analg 42:521, 1963.

410. Shnider SM, Webster GM: Maternal and fetal hazards of surgery during pregnancy. Am J Obstet Gynecol 92:891, 1965.

411. Brodsky JB, Cohen EN, Brown BW: Surgery during pregnancy and fetal outcome. Am J Obstet Gynecol 138:1165, 1980.

412. Crawford JS, Lewis M: Nitrous oxide in early human pregnancy. Anaesthesia 41:900, 1986.

413. Duncan PG, Pope WD, Cohen MM et al: Fetal risk of anesthesia and surgery during pregnancy. Anesthesiology 64:790, 1986.

414. Mazze RI, Kallen B: Reproductive outcome after anesthesia and operation during pregnancy: A registry study of 5405 cases. Am J Obstet Gynecol 161:1178, 1989.

415. Shnider SM, Wright RG, Levinson G: Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. Anesthesiology 50:524, 1979.

416. Myers RE, Myers SE: Use of sedative, analgesic, and anesthetic drugs during labor and delivery: Bane or boon? Am J Obstet Gynecol 133:83, 1979.

417. Morishima HO, Pederson H, Finster M: The influence of maternal psychological stress on the fetus. Am J Obstet Gynecol 131:286, 1978.

418. Robson SC, Hunter S, Moore M et al: Haemodynamic changes during the puerperium: A Doppler and M-mode echocardiographic study. Br J Obstet Gynaecol 94:1028, 1987.

419. Clark SL, Cotton DB, Lee W et al: Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 161:1439, 1989.

420. Chadwick HS, Ready LB: Intrathecal and epidural morphine sulfate for postcesarean analgesia: A clinical comparison. Anesthesiology 68:925, 1988.

421. Eisenach JC, Grice SC, Dewan DM: Patient-controlled analgesia following cesarean section: A comparison with epidural and intramuscular narcotics. 68:444, 1988.

422. Harrison DM, Sinatra R, Morgese L et al: Epidural narcotic and patient-controlled analgesia for post-cesarean section pain relief. 68:454, 1988.

423. Ready LB, Oden R, Chadwick HS et al: Development of an anesthesiology-based postoperative pain management service. Anesthesiology 68:100, 1988.

424. Bonica JJ: Principles and Practice of Obstetric Analgesia and Anesthesia. Malvern, PA, Lea & Febiger, 1994.

425. Peabody JL: Transcutaneous oxygen measurement to evaluate drug effects. Clin Perinatol 6:109, 1979.

426. Mangano DT: Anesthesia for the pregnant cardiac patient. Shnider SM, Levinson G (eds): Anesthesia for Obstetrics. 3rd ed. Baltimore, Williams & Wilkins, 1993, p 485.

427. Bieniarz J, Crottogini JJ, Curuchet E et al: Aortocaval compression by the uterus in late human pregnancy: II. An arteriographic study. Am J Obstet Gynecol 100:203, 1968.

428. Friedman EA: Labor: Clinical Evaluation and Management. East Norwalk, CT, Appleton Century Crofts, 1978.

429. Friedman EA: Primigravid labor: A graphicostatistical analysis. Obstet Gynecol 6:567, 1955.

430. Born GVR, Dawes GS, Mott JC: Changes in the heart and lungs at birth. Cold Spring Harb Symp Quant Biol 19:102, 1954.

431. Kuhnert BR, Kuhnert PM, Tu ASL: Meperidine and normeperidine levels following meperidine administration during labor. II. Fetus and neonate. Am J Obstet Gynecol 133:909, 1979.

432. Asling JH, Shnider SM, Margolis AJ et al: Paracervical block anesthesia in obstetrics. II. Etiology of fetal bradycardia following paracervical block anesthesia. Am J Obstet Gynecol 107:626, 1970.

433. Cole JT: Maternal obstetric paralysis. Am J Obstet Gynecol 52: 372, 1946.

434. Britt BA, Gordon RA: Peripheral nerve injuries associated with anaesthesia. Can J Anaesth 11:514, 1964.

435. Norris MC: Height, weight, and the spread of subarachnoid hyperbaric bupivacaine in the term parturient. Anesth Analg 67:555, 1988.

436. Bonica JJ, Johnson WL: Placenta praevia, abruptio placentae, or rupture of the uterus. Bonica JJ (ed): Principles and Practice of Obstetric Analgesia and Anesthesia, vol 2. 1st ed. Philadelphia, FA Davis, 1969, p 1164.

437. Kamani AAS, Gambling DR, Christilaw J et al: Anaesthetic management of patients with placenta accreta. Can J Anaesth 34:613, 1987.

Chapter 58 - Resuscitation of the Newborn

George A. Gregory

INTRODUCTION

Profound changes occur in the cardiovascular and respiratory systems at birth. Failure to make these changes may lead to death or central nervous system (CNS) injury. Because of these problems, newborn resuscitation is intensive care of the most complicated type. This chapter discusses the causes and effects of cardiorespiratory insufficiency at birth and discusses currently practiced techniques of resuscitation.

PERINATAL STRESS

During the 1970s, the concept of stress-free birth evolved but was shown to be potentially harmful to patients. Late-term fetuses and neonates are capable of producing large quantities of catecholamines, which help them prepare for birth, adapt to extrauterine life, and cope with hypoxia. Animals who are deprived of a catecholamine surge at birth are less likely to survive hypoxia than those who have a catecholamine surge. Catecholamines initiate clearance of liquid from the lungs before birth, and this improves lung compliance after birth. Catecholamines also release surface-active material (SAM) from alveolar type II cells. During asphyxia, catecholamines maintain cardiac output and redistribute blood flow from the periphery to the heart, brain, and adrenal gland. They also increase arterial blood pressure and slow heart rate, which reduces myocardial oxygen consumption. [1] Catecholamines also are required for breakdown of stored fuels. [2] Infants delivered by cesarean section without maternal labor have lower blood glucose concentrations than those born after labor. Furthermore, blood flow to peripheral organs is higher after vaginal delivery and is related to plasma catecholamine concentrations. Neonates with elevated catecholamine concentrations have higher Apgar scores than those with low concentrations. Thus, stress appears to be an important part of the transition from intra- to extrauterine life.

PERINATAL CARDIORESPIRATORY PHYSIOLOGY

The fetal lung arises from the foregut at 24 days' gestation. By 20 weeks, the airways are lined with cuboidal epithelium and pulmonary capillaries are present. By 26 to 28 weeks, the capillaries are closely approximated to the developing terminal airways. Between 30 and 32 weeks' gestation, the cuboidal epithelium has flattened and thinned, [3] a process that is accelerated by administering steroids to the mother. [4] By 20 weeks' gestation, SAM is present within the alveolar lining cells, [5] and by 28 to 32 weeks' gestation, it is present within the lumen of the airways. Significant amounts of SAM do not appear in terminal airways until 34 to 38 weeks' gestation unless its production and release are stimulated by stress or steroids. At birth, the onset of respiration further increases the concentration of SAM in alveoli. [6] Administration of SAM (calf, human, or artificial) decreases the incidence of hyaline membrane disease and the

Figure 58-1 (Figure Not Available) Intrathoracic pressures during delivery. Note the increased intrathoracic pressure when the mouth and head have been delivered. *(From Gregory [97])*

incidence of serious cardiopulmonary complications in neonates. [7] Administration of these compounds has become a routine part of resuscitation of premature neonates.

At term the fetal lung contains approximately 90 mL (30 mL/kg) of an ultrafiltrate of plasma. About 50 to 150 mL/kg/day [8] [9] of this fluid is produced by the lung and expelled into the mouth, where the fluid is either swallowed or released into the amniotic fluid. Normally, there is no amniotic fluid in lung fluid. If the depth of fetal breathing increases (e.g., during stress), however, amniotic fluid is drawn into the lung. Amniotic fluid in the lung is indicated by the presence of squamous cells and other debris in the lungs of infants in whom gasping occurred *in utero.*[9] Approximately two-thirds of the fluid is expelled from the lungs of a term neonate when the vagina and muscles of the pelvic floor squeeze the fetal chest during the birth process [9] (Fig. 58-1) (Figure Not Available) . The remaining fluid is removed by capillaries, lymphatics, and breathing. Small, preterm neonates, those born rapidly, and those born by cesarean section fail to get this "vaginal squeeze." As a result, these neonates have excess lung water at birth and have more difficulty sustaining respiration than babies whose chests are squeezed effectively during the birth process. Retention of lung fluid results in transient tachypnea of the newborn. [10] Clearance of water from the lung is initiated by labor. Animals born by cesarean section following a period of labor have similar amounts of lung water as animals born vaginally. However, those born by cesarean section without previous labor have increased amounts of lung water. [11] [12]

Neonates normally breathe by 30 seconds of age and sustain respiration by the time they are 90 seconds old. During birth, outward recoil of the compressed chest helps fill the lungs with air. Stimulation of the respiratory centers by mild acidosis, hypercarbia, hypoxia, pain, cold, touch, noise, and clamping of the umbilical cord initiates and sustains rhythmic respiration. [13] [14] Severe acidosis, hypoxia, CNS damage, and maternal drugs (narcotics, barbiturates, local anesthetics, magnesium, alcohol) depress breathing. A few minutes after birth the respiratory rate is 40 to 60 breaths per minute. This rapid respiratory rate removes the increased carbon dioxide produced by the high metabolic rate and helps maintain a normal functional residual capacity.

The circulation of the fetus is in parallel; that of the adult is in series [15] [16] (Fig. 58-2) (Figure Not Available) . The right ventricle ejects two-thirds of the combined ventricular output and the left ventricle ejects one-third. [17] This disparity in output between the two ventricles of fetuses occurs because fetuses have intracardiac and extracardiac shunts, namely, the foramen ovale and ductus arteriosus. Blood returning from the placenta is well oxygenated. As a function of the anatomy, the inferior vena cava and foramen ovale allow oxygenated placental blood to enter into the left atrium. Poorly oxygenated blood from the superior vena cava is directed into the right ventricle and into the pulmonary artery. Of blood entering the pulmonary artery, 95 percent is shunted through the ductus arteriosus into the descending aorta. [16]

The pulmonary vascular resistance (PVR), which is elevated *in utero,* decreases dramatically in response to lung expansion, breathing, increased pH, and the increase in alveolar oxygen tension that occurs at birth. [18] [19] PVR also decreases in the first 5 minutes to 24 hours of life owing to recruitment and dilation of small arteries. During the next few weeks, PVR continues to decrease owing to reduced amounts of arterial muscle. [20] Neonates born by cesarean section have higher pulmonary artery pressures and resistances than those delivered vaginally. [21] Hypoxia, acidosis, hypovolemia, hypoventilation, atelectasis, and cold increase PVR. [18] [22] The combination of hypoxia and acidosis increases PVR more than either hypoxemia or acidosis alone.

The decrease in PVR at birth reduces pulmonary artery pressure and increases pulmonary blood flow. Systemic vascular resistance and left atrial pressure increase, preventing right-to-left shunting of blood through the ductus arteriosus. In fact, left-to-right shunting of blood often occurs. The increased pulmonary blood flow increases the volume of blood returning to the left atrium, which raises left atrial pressure above right atrial pressure and closes the foramen ovale. Closure of the foramen ovale prevents right-to-left shunting of blood through this structure. Anatomic closure of the foramen ovale may not occur for months, if ever. Consequently, if right atrial pressure exceeds left atrial pressure (e.g., in pneumonia, acidosis, or hypoxia) right-to-left shunting of blood will again occur.

The ductus arteriosus of animals born at term gestation closes in response to oxygen, acetylcholine, parasympathetic

Figure 58-2 (Figure Not Available) Diagram of the fetal circulation. The numbers within the circles are percentages of the combined ventricular output. *(From Rudolph and Heymann, [16] with permission from the Annual Review of Physiology, Volume 36, copyright 1974, by Annual Reviews)*

nerve stimulation, and prostaglandins. [23] [24] [25] [26] [27] A Pa O_2 of 60 to 100 mm Hg constricts the ductus arteriosus of term lambs, but a Pa O_2 of 300 to 500 mm Hg fails to constrict the ductus arteriosus of preterm animals. [23] Functionally, the ductus arteriosus closes when the pulmonary arterial pressure is less than systemic arterial pressure. Anatomically, the ductus arteriosus of term neonates may not close completely until the neonate is 10 to 14 days of age. It may take several months for the ductus arteriosus of preterm neonates to close. The parallel circulation of the fetus can be reestablished in term neonates if they become hypoxic, cold, or acidotic during the first 2 weeks of life. It can be reestablished in preterm neonates during the first several weeks of extrauterine life.

/das/book/view/29494766/875/643.html

ASPHYXIA

Asphyxia (decreased Pa O_2 , increased Pa CO_2 and decreased pHa) occurs when gas exchange by the placenta (fetus) and by the lung (neonate) is inadequate. Large quantities of metabolic acids are produced, which are partially buffered by bicarbonate. [28] *In utero,* asphyxia is caused by maternal hypoxia, decreased placental-umbilical blood flow, and fetal heart failure. Maternal hypoxia is caused by maternal cyanotic congenital heart disease, congestive heart failure, or respiratory failure. Asphyxia, caused by maternal hypotension, catecholamine secretion, abruptio placentae, or placental disease (fibrosis, calcification, infarction, infections) reduces placental-umbilical blood flow.

Physiologic Effects

During fetal asphyxia, the Pa O_2 decreases from its normal value of 25 to 40 mm Hg to less than 5 mm Hg in about 2 minutes (Fig. 58-3) (Figure Not Available) . As a result of the severe hypoxia, anaerobic metabolism occurs. The Pa CO_2 rises rapidly. The pH quickly decreases to less than 7.0 because of the combined metabolic and respiratory acidosis. In as little as 5 minutes, the pH may be less than 6.90, the Pa CO_2 greater than 100 mm Hg, and the Pa O_2 unmeasurable. [15] [25] Some of the metabolic acidosis may be due to reduced uptake of lactate by the liver rather than to increased lactate production. [2]

Cardiac output is normal early in the course of asphyxia, but its distribution is altered. [30] [31] [32] Blood flow to the liver, kidney, gut, skin, and muscle is reduced, whereas blood flow to heart, brain, adrenal glands, and placenta is maintained constant or increased. This redistribution of blood flow helps maintain oxygenation and nutrition of the brain and heart, even though the oxygen content of arterial blood is very low. Oxygen extraction by tissues is greatly increased. [33] In part, the function of hypoxemic hearts is maintained by the metabolism of myocardial glycogen and by the metabolism of lactic acid. [34] When these sources of energy fail, as they eventually do, the myocardium fails, and the arterial blood pressure and cardiac output decrease. The myocardium usually fails when the pH is 7.0 or less. If the heart rate decreases to less than 100 beats/min during asphyxia, cardiac output decreases significantly. Central venous pressure rises during asphyxia because the systemic capacitance vessels constrict and increase the central blood volume and

Figure 58-3 (Figure Not Available) The response of newborn monkeys to asphyxia. *(From Dawes [15])*

because the failing myocardium cannot eject the increased volume of blood. Fetuses and newborns may survive severe hypoxia because they have large quantities of endogenous opiates in their blood. [35] These substances, which increase during hypoxia, [36] may reduce oxygen consumption. A normal response to catecholamines is also important for survival from asphyxia (see earlier). Initial systemic circulatory adaptations to hypoxia are mediated on a reflex basis. [37] Normal responses to asphyxia include increased plasma adrenocorticotropic hormone, glucocorticoids, catecholamines, atrial natriuretic factor, renin, arginine vasopressin, and decreased insulin concentrations. [38] [39] Arginine vasopressin causes hypertension, bradycardia, and redistribution of systemic blood flow. [40] Glycogenolysis maintains blood glucose concentrations. [2]

Intrapartum asphyxia can cause either hypervolemia or hypovolemia. [41] Asphyxia during labor usually causes hypervolemia unless (1) umbilical cord compression obstructs the umbilical vein more than it obstructs the umbilical arteries (e.g., cord around the neck, cord compression by the after-coming head during a breech delivery), (2) hemorrhage occurs from the fetoplacental unit (e.g., abruptio placentae, transection of the placenta during cesarean section), (3) maternal hypotension occurs (e.g., shock, trauma, anesthesia), or (4) asphyxia occurs during the latter part of labor and delivery.

ASSESSMENT OF THE FETUS AT BIRTH

The Apgar score, if done properly, is a simple, useful *guide* to neonatal well-being and resuscitation [42] [43] (Table 58-1) . *It is only a guide.* The 1-minute score correlates well with both acidosis and survival. [44] The 5-minute score may be predictive of neurologic outcome. [45] [46] To be of value, each variable encompassed by the score must be evaluated at both 1 and 5 minutes. The Apgar scores of neonates born to women who smoke cigarettes are lower than those of neonates whose mothers do not smoke. [47] The clinician should be well aware that some neonates have relatively normal Apgar scores at 1 and 5 minutes but may be very acidotic. These neonates often have peripheral vasoconstriction and pallor despite relatively normal heart rates and arterial blood pressures.

Heart Rate

The heart rate of normal neonates is 120 to 160 beats/min. Although most neonates tolerate heart rates up to 220 beats/min with little detrimental effect, heart rates below 100 beats/min are often poorly tolerated because they reduce cardiac output and tissue perfusion. Unfortunately, bradycardia is common in asphyxiated neonates. On occasion, bradycardia is associated with congenital heart disease, congenital heart block, and congestive heart failure. Prenatal

TABLE 58-1 -- The Apgar Scoring System[a]

SIGN	SCORE		
	0	**1**	**2**
Heart rate	Absent	Less than 100/min	More than 100/min
Respiratory effort	Absent	Slow, irregular	Good, crying
Color	Blue, pale	Body pink, extremities blue (acrocyanosis)	Completely pink
Reflex irritability (response to insertion of a nasal catheter)	Absent	Grimace	Cough, sneeze
Muscle tone	Limp	Some flexion of extremities	Active motion

[a] Each variable is evaluated individually and scored from 0 to 2 in an infant at both 1 and 5 minutes of age. The total score at each time period is the sum of the scores of the individual variables. A total score of 10 is perfect.

electrocardiogram and echocardiogram allow diagnosis of these problems before birth. If they occur, one must be prepared to treat the bradycardia if there is evidence that the arterial blood pressure and tissue perfusion are compromised (lactic acidosis).

Respiratory Effort

Breathing usually begins by 30 seconds of age and is sustained by 90 seconds of age. Within a few minutes after birth, the respiratory rate of normal neonates is between 30 and 60 breaths/min. There is no pause between inspiration and expiration, which helps to develop and maintain a normal functional residual capacity (FRC). At these rates, the time constants of the lung are too short for the FRC to be exhaled. Apnea and bradypnea prolong exhalation, which reduces FRC and causes hypoxia. Apnea and bradypnea occur with severe acidosis, asphyxia, maternal drugs, infections (meningitis, septicemia, pneumonia), and CNS damage. Tachypnea (>60 breaths/min) occurs with hypoxemia, hypovolemia, acidosis (metabolic and respiratory), CNS hemorrhage, pulmonary gas leaks, pulmonary disease (hyaline membrane disease, aspiration syndromes, infections), pulmonary edema, and maternal drugs (narcotics, alcohol, magnesium, barbiturates).

Muscle Tone

Most neonates, including those who are preterm, are active at birth and move all extremities in response to stimuli. Asphyxia, maternal drugs, CNS damage, amyotonia congenita, and myasthenia gravis decrease muscle tone. Flexion contractures and absent joint creases are signs of CNS damage that occurred *in utero.*

Reflex Irritability

Normal neonates move when an extremity is flicked and grimace or cry when a catheter is inserted into a nostril. Failure to respond occurs with hypoxia, acidosis, sedation by maternal drugs, CNS injury, and congenital muscle disease.

Color

Essentially all neonates have a blue-tinged cast to their skin at the moment of birth. By the time they are 60 seconds old, most neonates are entirely pink, except for their hands and feet, which remain blue (central cyanosis). If central cyanosis persists beyond 90 seconds of age, asphyxia, low cardiac output, pulmonary edema, methemoglobinemia, polycythemia, congenital heart disease, arrhythmias, and pulmonary disorders (respiratory distress, airway obstruction, hypoplastic lungs, diaphragmatic hernia) should be considered, especially when the infant remains cyanotic despite oxygen and controlled ventilation.

Neonates who are pale at birth are often asphyxiated, hypovolemic, acidotic, or anemic or have congenital heart disease (usually left-sided obstructive disease). Neonates whose skin is entirely pink within 2 minutes of birth may be intoxicated with alcohol or magnesium, or they may be alkalotic (pH >7.50). Rubrous neonates are usually polycythemic.

/das/book/view/29494766/875/645.html

RESUSCITATION EQUIPMENT

To ensure that resuscitation proceeds without difficulty, the whereabouts and function of all resuscitation equipment must be known by all delivery room personnel. Before each birth, the equipment should be checked and calibrated to be sure it is functioning properly.

The resuscitation bed should tilt to permit the neonate's head to be positioned below the level of the body. This promotes drainage of lung fluid and reduces the likelihood of aspiration of gastric contents. A servocontrolled infrared heater should be used to maintain the neonate's axillary temperature between 36 and 37°C. A suction device should be included, and the person doing the resuscitation should be able to vary the suction pressure. A second suction device may be required to continuously drain a pneumothorax. The suction pressure should not exceed 100 mm Hg. The resuscitation area should have a bright light with a small focal spot to illuminate catheter insertion sites.

The equipment required for tracheal intubation includes 0 and 00 straight laryngoscope blades; a pencil-type laryngoscope handle; a 2.5-, a 3.0-, and a 3.5-mm Magill-type endotracheal tube; and a suction catheter that easily fits through each size endotracheal tube. Cole tubes reduce the likelihood of an endobronchial intubation but can damage the larynx if enough pressure is applied to force the large portion of the tube into the trachea. [48]

The ventilation system used for resuscitation must permit a positive end-expiratory pressure (PEEP) and ventilatory rates of at least 150 breaths/min to be maintained. The system should not include one-way valves because they often stick in the closed position, especially when high gas flows and respiratory rates are used. If the valve sticks, the patient may develop a pneumothorax. The modified Jackson-Rees or Ayres system shown in Figure 58-4 (Figure Not Available) works well for neonatal resuscitation. It permits controlled ventilation at rapid respiratory rates and maintenance of PEEP. It also has a "pop-off" to reduce the likelihood of creating a pneumothorax. This ventilation system has no valves. The use of Ambu bags may be less effective because the valves can stick closed, it is more difficult to deliver 100 percent oxygen, and it is not possible to maintain a PEEP with these devices. The latter is important when resuscitating neonates who have atelectasis.

As in any intensive care situation, blood gas and pH measurements are mandatory, and the results of these tests must be available within 10 minutes of drawing the blood sample. Insertion of umbilical artery catheters that contain a Pa O_2 electrode or oxygen saturation probe allows Pa O_2 [49] and oxygen saturation [50] to be measured continuously during resuscitation. These catheters (Fig. 58-5) (Figure Not Available) also permit simultaneous measurement of arterial pressure and constant infusion of maintenance fluids. (Oxygen saturation can be measured immediately after birth with a pulse oximeter applied to a hand or foot.)

Because the response time of these catheters is 10 to 15 seconds, the effectiveness of resuscitation efforts in improving oxygenation can be readily ascertained (Fig. 58-6) . Although

Figure 58-4 (Figure Not Available) A modified Ayres T-piece that allows positive end-expiratory pressure and has a "pop-off" to reduce the likelihood of a pneumothorax. *(Modified from Gregory et al, [98] copyright 1971 Massachusetts Medical Society. All rights reserved.)*

Figure 58-5 (Figure Not Available) The oximetric system for measuring arterial oxygen saturation continuously. The catheter contains fiberoptics that transmit light to and from blood passing the catheter tip. *(From Wilkinson [96])*

the level of oxygenation can also be measured transcutaneously, these electrodes take 15 minutes to stabilize after being applied to the skin. Furthermore, the values only correlate with Pa O_2 when the blood pressure is normal and the body temperature is above 35.5°C. [51] Oxygen saturation can also be measured by applying a pulse oximeter probe to the palm of the hand. [52] These devices give good estimates of oxygen saturation when stable, but may give falsely low oxygen saturations with rapid decreases in saturation. [53]

Needle electrodes inserted under the skin provide continuous ECGs and heart rate values. Two pressure transducers are required to measure arterial and central venous pressures. Monitors used in neonatal intensive care units are adequate for use during resuscitation.

PROCEDURE

Someone other than the obstetrician should evaluate and resuscitate the neonate. If intrauterine asphyxia is known to exist or is strongly suspected (Table 58-2) , at least two additional people are required to resuscitate the neonate, one to control ventilation and the other to insert an umbilical artery catheter and correct acid-base and blood-volume abnormalities. A plan for the resuscitation of each neonate should be developed and understood by everyone in the delivery room before the neonate's birth.

Initial Evaluation

The neonate should be observed closely during delivery. As the head is delivered, the mouth and nose are suctioned with a bulb syringe. The neonate is held at the level of the introitus and dried with a towel to stimulate crying and reduce evaporative heat loss. Once breathing is established and the umbilical cord has stopped pulsating, the cord is cut and the neonate taken to the resuscitation table. Holding the neonate below the introitus increases blood volume and

Figure 58-6 The relationship among ventilation, oxygen saturation, Pa $_{O_2}$, and inspired oxygen concentration (F $_{IO_2}$) during neonatal resuscitation.

causes polycythemia. [54] Raising the neonate above the level of the introitus or clamping the umbilical cord early decreases blood volume. [55]

Stripping blood from the umbilical cord to the neonate increases blood volume, [56] respiratory rate, [57] lung water, [58] pulmonary artery pressure, and Pa $_{CO_2}$. [59] Lung compliance, FRC, [60] and Pa $_{O_2}$ [60] decrease. Figure 58-7 (Figure Not Available) shows the effects of early and late cord clamping on placental blood volume. The larger the placental volume, the smaller the neonate's blood volume. Early cord clamping can deprive neonates of up to 30 mL of blood/kg body weight. [55]

If the neonate is flaccid, pale, limp, and/or cyanotic, the umbilical cord should be clamped and cut and the neonate handed off to be resuscitated. It should be remembered that the neonate is probably hypovolemic because the umbilical cord was clamped early.

The neonate should be placed in a radiantly heated resuscitation bed with the head slightly lower than the body, and

Figure 58-7 (Figure Not Available) The effects of early and late cord clamping on placental blood volume. *(From Ogata [55])*

the airway should be cleared of secretions and blood by gently suctioning the mouth and nose with a bulb syringe. In my experience, prolonged suctioning can cause vomiting and arrhythmias, the most common of which is bradycardia, but ventricular arrhythmias occur in 10 to 20 percent of those who are suctioned vigorously while hypoxic.

If the respiratory pattern and color are normal, nothing more needs to be done except to dry the neonate with a towel and quickly insert a suction catheter into the posterior pharynx through each nostril to rule out choanal atresia. The same catheter is then passed through the mouth into the stomach to rule out esophageal atresia and small bowel atresia (see later) and to empty the stomach of its contents. Bilateral choanal atresia may be lethal because the airway will be totally obstructed when the mouth is closed. When the mouth is open, the neonate is pink; when the mouth is closed, the neonate continues to make breathing efforts, but there is no gas movement into or out of the lung. To alleviate the airway obstruction, an oral airway or an endotracheal tube should be inserted. The neonate should be seen by a knowledgeable ear, nose, and throat surgeon, and the bony obstruction should be relieved surgically. The 1-minute Apgar score can be used to guide resuscitation, but it is only a guide. One should not wait until 1 minute has passed before initiating resuscitation. The 5-minute Apgar score may have some predictive value for neurologic outcome.

Apgar Score

Score 8 to 10

Apgar scores of 8 to 10 are achieved by 90 percent of all neonates. Nothing is required except nasal and oral suctioning, drying of the skin, and maintenance of normal body temperature. A careful reevaluation of the neonate's condition should occur at 5 minutes of age because some neonates hypoventilate when stimulation ceases. When stable,

TABLE 58-2 -- Disorders Frequently Associated With Asphyxia at Birth

Maternal conditions
Elderly primigravida (>35 years of age)
Diabetes
Hypertension
Toxemia
Maternal treatment with any of the following:
Glucocorticoids
Diuretics
Antimetabolites
Reserpine, lithium

- Magnesium
- Ethyl alcohol
- beta-Adrenergic drugs (to stop premature labor)

Abnormal estriol levels

Anemia (hemoglobin level less than 10 g/100 mL)

Blood type or group isoimmunization

Previous birth of child with a hereditary disease

Current maternal infection or infection during pregnancy with rubella, herpes simplex, or syphilis

Abruptio placentae

Placenta previa

Antepartum hemorrhage

History of previous infant with jaundice, thrombocytopenia, cardio respiratory distress, or congenital anomalies

Narcotic, barbiturate, tranquilizer, or psychedelic drugs

Ethyl alcohol intoxication

History of previous neonatal death

- Prolonged rupture of membranes

Conditions of labor and delivery

- Forceps delivery other than low elective
- Vacuum extraction delivery
- Breech presentation and delivery or other abnormal presentation
- Cesarean section
- Prolonged labor
- Prolapsed umbilical cord
- Cephalopelvic disproportion
- Maternal hypotension
- Sedative or analgesic drugs given intravenously within 1 hour of delivery or intramuscularly within 2 hours of delivery

Fetal conditions

- Multiple births
- Polyhydramnios
- Meconium-stained amniotic fluid
- Abnormal heart rate or rhythm
- Acidosis (fetal scalp capillary blood)
- Decreased rate of growth (uterine size)
- Premature delivery
- Amniotic fluid surfactant test negative or intermediate within 24 hours of delivery

Neonatal conditions

- Birth asphyxia
- Birth weight (inappropriate for gestational age)
- Meconium-staining of the skin, nails, or umbilical cord
- Signs of cardiorespiratory distress

---

the neonate should be wrapped in a warm blanket and handed to the parents.

Score 5 to 7

Neonates with Apgar scores of 5 to 7 have suffered mild asphyxia just before birth. They usually respond to vigorous stimulation and to oxygen blown over the face. If they are slow to respond and to become pink, they should be ventilated with 80 to 100 percent oxygen via bag and mask. By 5 minutes of age, patients with Apgar scores of 5 to 7 at 1 minute are usually well. At 2 minutes of age, Pa o_2 is usually 50 to 70 mm Hg, Pa co_2 is 40 to 50 mm Hg, and pHa is about 7.15. The base deficit is approximately 12 mEq/L. By 10 minutes of age, the pHa will increase to 7.30 and Pa co_2 will decrease to below 40 mm Hg. The base deficit usually returns to normal (-3.0 to +3.0 mEq/L).

Score 3 to 4

Neonates with Apgar scores of 3 to 4 are moderately depressed at birth. They are usually cyanotic and have poor respiratory efforts, but they usually respond to bag and mask ventilation by breathing and becoming pink. If they have not breathed spontaneously, ventilating the lungs with a bag and mask may be difficult because the airway resistance exceeds that of the esophagus. If so, gas preferentially enters and distends the esophagus, stomach, and gut, which may interfere with ventilation and cause vomiting and regurgitation. Decompressing the stomach makes it easier to ventilate the lungs. If the neonate has not breathed or is breathing ineffectively, an endotracheal tube should be inserted before ventilating the lungs. Umbilical artery and vein blood should be obtained from a double-clamped segment of umbilical cord to measure blood gases and pH. The blood gases are frequently abnormal: a Pa o_2 below 20 mm Hg, Pa co_2 above 60 mm Hg, pHa below 7.15. If the pH and base deficit are unchanged or worse on a sample of blood obtained from a radial or temporal artery, an umbilical artery catheter should be inserted and, if necessary, sodium bicarbonate should be administered (see later).

Score 0 to 2

Neonates with Apgar scores of 0 to 2 are severely asphyxiated and require immediate resuscitation. It is *not* appropriate to stand around and wait to see what the patient will do. The patient's condition will get worse. Get on with the resuscitation! What follows is a discussion of resuscitation of neonates with Apgar scores of 0 to 2.

/das/book/view/29494766/875/647.html

PULMONARY RESUSCITATION

For pulmonary resuscitation, the trachea should be intubated immediately and positive-pressure ventilation should be begun at a rate of 30 to 60 breaths/min. Every fifth breath should be held for 2 to 3 seconds to expand atelectatic lung and to help remove lung fluid. A PEEP of 1 to 3 mm Hg should be maintained. Care must be taken *not* to use excessive pressures to ventilate the lungs of neonates in the delivery room. Recent evidence demonstrates that as few as six large breaths at birth markedly increases the amount of lung injury seen in premature lambs 30 minutes to several hours later and that the response to surfactant is significantly diminished in those ventilated with large breaths. [61]

Tracheal Intubation

The neonate's larynx is located four to six vertebrae more cephalad than the larynx of adults and consequently is more anterior than that of adults. Extension at the head places the larynx in an even more anterior position and makes tracheal

---

Figure 58-8 (Figure Not Available) Laryngoscopy of the newborn infant. See text for details. *(From Gregory [100])*

intubation more difficult. Therefore, the head should be placed in a neutral or "sniffing" position during bag-and-mask ventilation and during tracheal intubation. The laryngoscope should be held with the thumb and index finger and the chin grasped with the ring and middle fingers of the left hand. This "welds" the head and hand into a single unit and reduces the likelihood of pharyngeal lacerations occurring if the neonate's head moves. To improve the view of the larynx, pressure should be applied over the hyoid bone with the small finger of the left hand (Fig. 58-8) (Figure Not Available) . This maneuver moves the larynx posteriorly and exposes the vocal cords. An appropriate-size endotracheal tube should be inserted and the tip of the tube placed 1 to 2 cm below the vocal cords, depending on the size of the neonate. (The appropriate-size endotracheal tube is one that permits a small amount of gas to leak from between the endotracheal tube and trachea when a pressure of 15 to 25 cm H_2O is generated. This usually means a 2.5-mm [internal diameter] tube for neonates weighing less than 1.5 kg, a 3.0-mm tube for those between 1.5 and 2.5 kg, and a 3.5-mm tube for those weighing more than 2.5 kg.)

Adequacy of Ventilation

Adequacy of ventilation is best determined by physical examination and analysis of arterial blood gases. Both sides of the chest should rise equally and simultaneously with inspiration. If one side of the chest rises before the other, the tip of the endotracheal tube may be in a mainstem bronchus, or there may be a pneumothorax or congenital anomaly of the lung. Listening to the breath sounds may be misleading. Because the chest is small, breath sounds are well transmitted within the thorax. Thus, the breath sounds may be normal, even though the neonate has a pneumothorax or congenital anomaly of the lung. A difference in breath sounds between the two sides of the chest should raise suspicion that an endobronchial intubation, a pneumothorax, atelectasis, or a congenital anomaly of the lung is present. Breath sounds are usually heard over the stomach, but these are not as loud as the breath sounds heard over the chest. If they are as loud, it should be determined whether an esophageal intubation has occurred or whether the neonate has a tracheoesophageal fistula. If ventilation is adequate, the neonate will become pink, initiate rhythmic breathing, and have a normal heart rate. Normal blood gases will eventually be restored.

Most asphyxiated neonates do not have lung disease. Therefore, they seldom require more than 25 cm H_2O peak pressure to expand their lungs, even for the first few breaths. Excessive airway pressures cause pulmonary gas leaks and may cause lung injury. [61] Neonates whose lungs are stiff (erythroblastosis fetalis, congenital anomalies of the lung, pulmonary edema, severe meconium aspiration, diaphragmatic hernia) often require much higher inspiratory pressures to ventilate their lungs. If so, they are likely to develop pulmonary gas leaks. To reduce this likelihood, the lungs should first be ventilated with inspiratory pressures of 15 to 20 cm H_2O and rates of 150 to 200 breaths/min. If this low-pressure (low-volume), high-rate ventilation does not improve the blood gases, higher pressures and volumes should be used. One should remember that failure to use adequate pressures (volumes) during controlled ventilation may make hypoxemia worse and lead to CNS damage or even death. However, excessive pressures can be equally problematic. If a pulmonary gas leak occurs and interferes with oxygenation, carbon dioxide removal, or circulation, the gas should be drained with a thoracostomy tube. Pneumopericardia or pneumomediastina seldom requires drainage.

The effects of ventilation should be monitored closely. If the Pa_{O_2} is greater than 80 mm Hg or the oxygen saturation exceeds 94 percent, the inspired oxygen concentration should be reduced in 5 to 10 percent steps until the Pa_{O_2} is between 50 and 80 mm Hg or the oxygen saturation is between 87 and 94 percent. It is especially important to maintain oxygenation within this range when resuscitating neonates of 34 weeks' gestation or less, because they can develop retinopathy of prematurity (retrolental fibroplasia). [62] [63] Although it is not clear what level of Pa_{O_2} (or oxygen saturation) causes retrolental fibroplasia, we know that it can occur in premature neonates with a Pa_{O_2} of about 150 mm Hg for 2 to 4 hours. Furthermore, repeated increases in Pa_{O_2} to these levels may be as dangerous as a constant Pa_{O_2} of 150 mm Hg. The neonate's heart rate should be continuously monitored during endotracheal intubation because arrhythmias are common during this procedure, especially if the neonate is hypoxic at the time of tracheal intubation.

Routine Tracheal Suctioning

In certain situations, the trachea should be suctioned before ventilation of the lungs. These situations include meconium staining of the amniotic fluid or major vaginal bleeding. We found that most meconium is in major airways at birth and that suctioning of the airway after birth removes the majority of this material from the lungs. [64] Meconium aspiration is rare in appropriate-for-gestational age neonates who weigh less than 2,000 g at birth. Meconium aspiration has been reviewed elsewhere. [65]

About 10 percent of pregnant women have meconium staining of their amniotic fluid, and 60 percent of neonates born to mothers with meconium-stained amniotic fluid have meconium in their tracheas at birth. [66] If the airway is not suctioned before or shortly after the onset of breathing,

---

meconium in the airways will move into the alveoli and small airways with the onset of ventilation. About 15 percent of meconium-stained neonates develop respiratory difficulties during the first few days of life, and 10 percent develop a pneumothorax or pneumomediastinum on chest roentgenogram. Most intrathoracic gas leaks are small and cause only tachypnea. However, some large pneumothoraces cause collapse of the cardiovascular system and death if they are unrecognized and untreated.

Because of the seriousness of these complications, "pea soup" or particulate meconium should be removed from the lung before breathing is established to improve

the survival of neonates with meconium aspiration. [67] (Thin, watery meconium does not require suctioning.) Meconium is best removed from the lung by inserting an endotracheal tube, applying a suction device especially designed for this purpose, and sucking on the endotracheal tube as it is withdrawn from the trachea. [68] The laryngoscope should be left in place as the endotracheal tube is removed. If meconium is retrieved from the airway, the endotracheal tube should be quickly reinserted and the airway suctioned again. The lungs should then be gently ventilated with oxygen. The absence of meconium in the mouth and posterior pharynx does not preclude the presence of meconium in the trachea. [66] In one study, 13 percent of neonates had meconium in the trachea but none in the mouth or pharynx. [66] The heart rate should be continuously monitored during laryngoscopy and suctioning and 100 percent oxygen blown over the neonate's face. Suctioning the stomach will remove meconium that might be regurgitated and aspirated later. Chest physical therapy and postural drainage should be done every 30 minutes for 2 hours and hourly thereafter for the next 6 hours to help remove residual meconium from the lung. All neonates born following meconium aspiration should be observed for 24 hours because they can develop persistent fetal circulation (PFC) syndrome, [69] the major cause of death following meconium aspiration. When PFC occurs, blood is shunted right-to-left across the ductus arteriosus and foramen ovale. Little blood perfuses the lung. Of these neonates, 50 percent die during the first few days of life. Recently, extracorporeal membrane oxygenation (ECMO) has been used successfully to treat patients with severe hypoxia from meconium aspiration. [70] [71] Several days are required for pulmonary hypertension to abate and for ECMO to be no longer required. The long-term outcome of children who had meconium aspiration at birth is very good. Unless they had asphyxia in the perinatal period, they are intellectually intact. They also have normal pulmonary function at 6 to 11 years of age. [72] [73]

Other Causes of Respiratory Failure

There are other causes of respiratory failure besides those just described. These must be ruled out if the response to resuscitation is not immediate.

Pneumothorax

Pneumothorax occurs in 1 percent of all vaginal deliveries, in 10 percent of meconium-stained neonates, [66] and in 2 to 3 percent of neonates who require mechanical ventilation in the delivery room. To detect a pneumothorax, the chest should be carefully examined. The hemithorax containing free air is usually hyperexpanded and moves poorly with ventilation. The point of maximum cardiac impulse is shifted toward the chest that does not have a pneumothorax. The heart tones may be muffled.

If a pneumothorax is suspected, a small, high-intensity, cold light should be shone onto the skin of the chest. [74] If a pneumothorax is present, the involved chest will glow. A 22-gauge, relatively blunt needle should be inserted into the second intercostal space in the midclavicular line. The needle should be occluded with a closed stopcock. A "pop" is felt when the needle enters the pleural cavity. Fixing the needle at skin level with a hemostat reduces the likelihood of the needle advancing too far into the chest and accidently damaging the lung. If gas is found in the pleural space, as much gas as possible should be removed with a syringe while a thoracostomy tube is being inserted. The thoracostomy tube should be connected to underwater drainage.

Congenital Anomalies

Congenital anomalies of the airway are relatively common. Choanal atresia is discussed in the section on initial evaluation. Micrognathia (Pierre Robin syndrome) and relative macroglossia cause inspiratory obstruction. If an oral airway can be inserted, the problem is usually temporarily solved. If an oral airway cannot be inserted, a large (10 French) nasogastric tube should be inserted through the nose and the tip of the catheter placed in the stomach. This maneuver prevents the tongue from making a tight seal with the pharyngeal wall, which prevents the neonate from developing large negative pressures in the pharynx and "sucking" the tongue into the pharynx. Grasping the tongue with a towel clip and pulling outward is seldom effective and may cause harm. However, in a life-threatening situation, this maneuver should be tried. The tips of the towel clip should be placed in the sides of the tongue, not in the middle. Neonates with micrognathia should be nursed in the prone position to let the tongue fall forward. It is seldom necessary to do a tracheotomy; however, it is occasionally necessary to intubate the trachea. It is also possible to insert a #1 laryngeal mask; this often provides a good airway. [75] However, the connecting tube is a large deadspace and may significantly increase the Pa CO_2 .

Congenital anomalies of the larynx, such as webs, atresia, and vocal cord paralysis or fusion, are uncommon but when present cause stridor and respiratory distress. On occasion, it may be necessary to force a small endotracheal tube through these lesions. Subglottic stenosis, subglottic webs, and subglottic hemangiomas are also uncommon, but they too cause severe airway obstruction.

Esophageal Atresia and Tracheoesophageal Fistulas

Esophageal atresia and tracheoesophageal fistulas occur in 1 in 2,400 to 4,500 births. Respiratory distress occurs if the neonate aspirates gastric secretions or esophageal pouch

secretions, or if the stomach and gut distend with air and limit movement of the diaphragm. Controlled ventilation may distend the gut further and should be avoided unless it is absolutely necessary. If it is necessary to ventilate the lungs, the tip of the endotracheal tube should first be advanced beyond the fistula. Breath sounds heard over the stomach will diminish in intensity at this time. After ensuring that both lungs are being ventilated equally (i.e., equal chest movement and breath sounds), the endotracheal tube is firmly fixed in place. A sump-type catheter should be placed into the esophageal pouch and the catheter connected to suction to prevent accumulation of secretions in the pouch. The neonate should be nursed in the reverse Trendelenburg position to reduce the likelihood of aspirating the contents of the stomach and pouch.

Diaphragmatic Hernia

Diaphragmatic hernia occurs in 1 in 2,000 births. If the hernia is large, gut fills the involved chest cavity (usually the left) and causes hypoplasia of both lungs. [76] The ipsilateral lung is about 10 to 20 percent of its normal size, and the contralateral lung is about 60 to 70 percent of normal. Because the gut is in the chest cavity, the abdomen is scaphoid. (The abdomen of normal neonates is protuberant.) The breath sounds of the affected chest may or may not be decreased. Acidosis and hypoxia are usually present because of the hypoplastic lungs and because of right-to-left shunting of blood through the patent ductus arteriosus. In addition, many of these patients have pulmonary hypertension. The Pa O_2 of temporal artery or right radial artery blood (which is preductal) is higher than the Pa O_2 of blood from the descending aorta. [77]

The trachea should be intubated and the lungs ventilated rapidly (60-150 times per minute) with small breaths. No attempt should be made to expand the hypoplastic lung, as this may cause a pneumothorax on the side of the "good" lung. Neonates with diaphragmatic hernias are usually hypovolemic and require expansion of their intravascular volume with whole blood or plasma. Overhydration should be avoided because it causes pulmonary edema and makes the Pa O_2 and Pa CO_2 worse. Correction of the acidosis (both respiratory and metabolic) reduces PVR and improves pulmonary blood flow; reduced pulmonary blood flow is the usual cause of death. Hyperventilation (Pa CO_2 20-25 mm Hg) often increases pulmonary blood flow and improves blood gases, [78] but it may reduce cerebral blood flow, especially if the baby is hypotensive.

Recently, ECMO has been used to treat pulmonary hypertension associated with diaphragmatic hernia. [79] The success of this therapy has resulted in the survival of many neonates who otherwise would have died. Nevertheless, the mortality of neonates with a diaphragmatic hernia is still nearly 50 percent.

Administration of Surfactant

Administering surfactant into the lungs of neonates has resulted in significant improvement in the outcome of premature neonates. [80] [81] [82] The incidences of pulmonary gas leaks, hyaline membrane disease, deaths, bronchopulmonary dysplasia, and pulmonary interstitial emphysema are lower following surfactant administration. Frequently, surfactant is given as a liquid (i.e., 5 mL of fluid per kilogram are given into the trachea at birth), which may briefly reduce the oxygen saturation. Subsequently, the arterial oxygen saturation (Sa O_2) increases rapidly in most instances, as does the compliance of the lung. The latter may result in overinflation of the lung and the development of lung injury or a pulmonary gas leak if ventilation is not reduced.

/das/book/view/29494766/875/648.html

VASCULAR RESUSCITATION

Vascular resuscitation is a much neglected aspect of neonatal resuscitation. Few textbooks even mention it, despite the fact that neonates are often hypovolemic at birth. Those who are premature and asphyxiated near the end of labor are especially likely to be hypovolemic.

If the neonate's condition does not improve rapidly with ventilation and tactile stimulation, an umbilical artery catheter should be inserted to measure blood gases and pH, to measure arterial pressure, to expand blood volume, and to administer drugs. Most preterm neonates weighing less than 1,250 g at birth, and 1 to 3 percent of term neonates require an umbilical artery catheter during resuscitation. It also may be helpful to insert a central venous line to determine the adequacy of blood volume replacement.

Insertion of Intravascular Catheters

Umbilical Artery Catheterization

A stopcock should be attached to one end of a 3.5 or 5.0 French umbilical artery catheter and the catheter and stopcock flushed with sterile saline containing 1 to 2 units of heparin per milliliter of fluid. The stump of the umbilical cord is grasped with a clamp and the cord held straight up in the air. The abdomen and umbilical cord are sterilized with an iodine-containing solution and the abdomen is sterilely draped. Next, a sterile umbilical tape is tied loosely around the cord, and the cord is cut cleanly with a scalpel, leaving 2 cm of stump. The stump is firmly grasped with the gloved fingers of one hand, and one of the two thick-walled umbilical arteries is dilated with a curved iris forceps. With the stopcock partially open, a 3.5 French umbilical artery catheter is inserted into the artery if the neonate weighs less than 1,500 g or a 5 French catheter is used if the neonate weighs 1,500 g or more. Some resistance may be encountered when the catheter has been advanced 3 to 5 cm into the vessel, but this resistance can usually be overcome by applying steady pressure to the catheter. If the catheter will not advance, a second catheter should be inserted into the other artery while leaving the first catheter in place. This maneuver often causes one or the other vessel to relax and permits one of the catheters to be advanced into the aorta. When blood appears in the catheter, the stopcock should be closed, blood should be withdrawn from the catheter, and all air should be removed from the system. (The accidental injection of small amounts of air [<0.1 mL] may obstruct blood flow to the legs for several hours.) The catheter should

be attached to a pressure transducer and the arterial pressure measured.

Figure 58-5 (Figure Not Available) shows a catheter (Oximetrix Company, Mountain View, Calif) that is part of a fiberoptic system that makes it possible to measure arterial oxygen saturation and arterial blood pressure simultaneously. Because the catheter is precalibrated, the correct oxygen saturation is measured as soon as the tip of the catheter comes into contact with blood. This device is helpful in resuscitating asphyxiated neonates. [50]

Umbilical Venous Catheterization

The stump of the umbilical cord is prepared, grasped, and tied as described previously. The single, large, thin-walled umbilical vein is grasped with iris forceps and the catheter inserted 3 to 5 cm into the vessel with a twisting motion. The stopcock must be closed to prevent aspiration of air through the catheter if the patient takes a deep breath. The catheter is connected to a pressure transducer, and the intravascular pressure is displayed on an oscilloscope or polygraph. When the catheter tip enters the thoracic vena cava, the pressure tracing deflects negatively with each spontaneous inspiration. When the catheter tip is in an intra-abdominal vein, the deflection is positive during inspiration. Once the catheter tip is in the intrathoracic vena cava, the catheter should be fixed in place and the P_{O_2} of the blood measured. If the P_{O_2} exceeds 40 mm Hg, the catheter tip is probably in the left atrium and should be withdrawn into the right atrium or inferior vena cava. It is imperative that no air be injected through venous catheters because the air may enter the systemic circulation through the foramen ovale and occlude a coronary or cerebral artery. If it does, the neonate may die or suffer CNS damage. If the catheter "tickles" the atrial septum, the neonate may suffer arrhythmias. Withdrawal of the catheter a short distance will solve the problem.

Correction of Acidosis

Respiratory acidosis is corrected by controlling ventilation. Metabolic acidosis is corrected by infusing sodium bicarbonate. Bicarbonate is less expensive and does not cause the severe hypoglycemia, hypocalcemia, hypokalemia, and apnea that can occur with administering tromethamine (Tham). In addition, the volume of sodium bicarbonate required to correct the same amount of acidosis is one-third that of Tham. This reduces the likelihood of inducing hypervolemia with sodium bicarbonate.

Several potentially serious problems are associated with administering sodium bicarbonate:

1. Sodium bicarbonate is hypertonic, about 1,800 mOsm/L. If a large volume of sodium bicarbonate is administered rapidly (more than 1 mEq/kg/min), the intravascular volume may expand rapidly and cause intracranial hemorrhage.
2. The complete reaction of hydrogen ions with 50 mEq of bicarbonate generates approximately 1,250 mL of CO_2. If ventilation is adequate, the CO_2 is quickly exhaled, and the Pa $_{CO_2}$ rises 1 to 3 mm Hg. If ventilation is inadequate, as it is in asphyxiated neonates, the Pa $_{CO_2}$ increases significantly, and, because the CO_2 freely diffuses into cells, may lead to cardiac arrest. Because it dilates cerebral vessels, Pa $_{CO_2}$ increases cerebral blood flow and may cause intracranial hemorrhage. To prevent the rise in Pa $_{CO_2}$, ventilation should be controlled. Alkali should not be infused to correct metabolic acidosis unless ventilation is adequate.
3. Administering bicarbonate may also induce hypotension (Fig. 58-9) (Figure Not Available) . This occurs because acidotic, hypovolemic neonates have intense peripheral vasoconstriction, which preserves their arterial blood pressure. Correcting the acidosis reduces the PVR and induces hypotension because the neonate's blood volume is now inadequate to fill the expanded vascular space.

4. Sodium bicarbonate may also interfere with myocardial function, especially if the acidosis for which it was given is ongoing. [83] [84] This is rare clinically in neonates.
5. Until recently, it was believed that the CO_2 produced by the reaction of bicarbonate with hydrogen ions decreased the intracellular pH of brain. However, this is

not the case. [85]

Figure 58-9 (Figure Not Available) The effects of sodium bicarbonate on aortic blood pressure (P_{AO}), heart rate, and hematocrit level. Note that hypotension occurred following administration of sodium bicarbonate. The hematocrit level decreased as fluid was "pulled" into the intravascular space to compensate for the hypovolemia that was present since birth. Raising pH decreased the peripheral vasoconstriction produced by the preexisting acidosis. Giving albumin increased the aortic pressure to normal. On the basis of the final hematocrit level, the initial blood volume was approximately 30 percent less than predicted. *(From Phibbs. [101] Courtesy of Ross Products Division, Abbott Laboratories Inc., Columbus, OH.)*

Who Requires Alkali Therapy?

Despite the potential problems associated with bicarbonate administration, there are situations in which it is useful. If the Apgar score is 2 or less at 2 minutes or 5 or less at 5 minutes despite tactile stimulation and controlled ventilation with oxygen, the neonate should be given 2 mEq/kg of sodium bicarbonate while the lungs are being ventilated. Bicarbonate should not be infused into a catheter whose tip rests in the liver, because the hypertonic solution may cause hepatic necrosis. Ventilation should be controlled as the drug is infused. Blood gases and pH should be measured. If the pH is below 7.00 and the Pa_{CO_2} is below 35 mm Hg, one-fourth of the base deficit should be corrected with sodium bicarbonate. If the pH is above 7.10, ventilation of the lungs should be continued and arterial pH and blood gases remeasured in 5 minutes. If the pH is 7.15 or above on the repeat measurement, ventilation of the lungs should continue and bicarbonate therapy should be delayed. If the repeat blood gas shows a decrease or no change in pH, one-fourth of the base deficit should be corrected with bicarbonate. Figure 58-10 (Figure Not Available) shows the effects of sodium bicarbonate on the Pa_{O_2} of a group of asphyxiated neonates whose ventilation was held constant. No significant increase in Pa_{O_2} occurred until the pH was above 7.10 to 7.20, the point at which Rudolph and Yuen [18] found their most significant decrease in PVR. It is unclear in the neonates we have treated whether the increase in Pa_{O_2} was due to the increase in pHa or to expansion of blood volume by bicarbonate.

Metabolic acidosis occurs when tissue perfusion is poor. At birth, underperfusion is usually due to hypovolemia or

Figure 58-10 (Figure Not Available) The effects of the rapid infusion of sodium bicarbonate on Pa_{O_2} and pH when ventilation was held constant. The Pa_{O_2} increased when the pH increased above 7.10 to 7.20. *(From Gregory [97])*

heart failure (congenital heart disease, including congenital bradycardia and severe acidosis). Heart failure usually occurs when the pH falls below 7.00. Raising the pH to 7.15 or higher usually improves cardiac output. As a result of this increase, liver perfusion increases and metabolic acids are metabolized. If heart failure is due to cardiac disease (congenital bradycardia from arrhythmias, erythroblastosis fetalis, congenital cardiac anomalies), the cardiac output should be increased with a continuous infusion of isoproterenol (starting with 0.05 mug/kg/min and increasing the dose as necessary) or a transvenous pacemaker should be inserted. In these patients, cardiac output is usually best when the heart rate is raised to 160 to 190 beats/min. Hypoglycemia may also cause heart failure, but hypoglycemia is uncommon in asphyxiated neonates. If it is low, the blood glucose concentration should be increased to normal (50-90 mg/dL) by infusing 5 mL/kg of 10 percent dextrose in water over 3 to 5 minutes. This infusion should be followed with a continuous infusion of enough glucose to maintain a normal glucose concentration.

If the acidosis is due to hypovolemia, as it usually is, the blood volume should be expanded.

Expansion of Intravascular Volume

Approximately 60 percent of asphyxiated preterm neonates weighing less than 1,500 g are hypovolemic at birth because their umbilical cord was clamped and cut earlier than usual (see Fig. 58-7) (Figure Not Available) so that resuscitation could begin. Term neonates are hypovolemic if the umbilical cord is clamped early or if the cord is wound tightly around the neck and must be cut to deliver the neonate. Hypovolemia also occurs with intrauterine asphyxia, with placental abruption, or with transection of the placenta during cesarean section.

Detection of Hypovolemia

Hypovolemia is detected by measuring the arterial blood pressure and by physical examination (skin color, perfusion, capillary refill time, pulse volume, and extremity temperature) (Table 58-3) . After 24 hours of age, urine volume and specific gravity measurements are also helpful.

The arterial pressure can be measured with a Doppler system or an indwelling arterial catheter. Table 58-4 shows the systolic, diastolic, and mean arterial pressures during the first 12 hours after birth. The increase in pressure should be noted with increasing gestational age. If no pressure transducer is available, the umbilical artery catheter can be connected to a venous manometer and the height of the column of water displaced by blood (in centimeters) divided by 13.6 (the density of mercury) to obtain the mean arterial pressure (MAP). MAP is a more useful determinant of the adequacy of intravascular volume than the systolic or diastolic pressure.

Central venous pressure (CVP) measurements are helpful in detecting hypovolemia and in determining the adequacy of fluid replacement. Changes in CVP are more important than a single CVP determination. The venous pressure of normal neonates is 4 to 8 cm H_2O. If the CVP is less than 4 cm H_2O, hypovolemia should be suspected.

TABLE 58-3 -- Relationship of Skin Color, Capillary Refill Time, Pulse Volume, and Extremity Temperature to Hypovolemia

AMOUNT OF VOLUME DEPLETION (%)	SKIN COLOR	CAPILLARY REFILL TIME (SECONDS)	POSTERIOR TIBIAL PULSE VOLUME	SKIN TEMPERATURE
None	Pink	<2	++++	Warm
5	Pale	3-4	++	Cold from midcalf and midforearm out
10	Gray	4-5	0	Cold midthigh and upper arm out
15	Mottled	>5	0	Entire extremity cold

Symbols: ++++, full; ++, moderately full; 0, markedly diminished or absent

Hypovolemic neonates are usually pale and have poor capillary refill and poor perfusion. Their extremities are cold and their pulses (especially the radial and posterior tibial pulses) weak or absent. Those neonates who are intoxicated with alcohol or magnesium are usually pink, peripherally dilated, and hypotensive and may be acidotic.

Treatment of Hypovolemia

The key to treating hypovolemia is intravascular volume expansion. This can best be done with blood; but albumin, plasma, and crystalloid are also used for this purpose. If it is suspected that the neonate will be hypovolemic at birth, maternal blood should be cross matched against one unit of O-negative packed red blood cells and one unit of O-negative whole blood. Both units of blood should be brought to the delivery room in separate "cold packs" (a sealed plastic ice chest containing dry ice) just before the neonate is born. If blood is not needed, it can be returned unopened to the blood bank within 4 hours.

If cross matched blood is not available at the time of delivery, the placenta can be cleansed with iodine and blood can be withdrawn from the umbilical vein and artery with sterile syringes containing 1 to 2 units of heparin per mL of blood collected. These vessels usually contain a large amount of blood, especially if the umbilical cord was clamped immediately after birth. [56] The blood should be passed through a blood filter before it is given to the neonate to eliminate blood clots and debris. There is no concern about incompatibility of blood types because this blood was part of the circulating blood volume of the neonate before the umbilical cord was clamped. We usually reserve transfusing placental blood for emergencies for fear of causing an infection, although this has never occurred. If no source of blood is available (or is not required due to an adequate hematocrit level), the intravascular volume can be expanded with 1 to 2 g/kg of 25 percent albumin, 10 mL/kg of

plasma, or 10 mL/kg of lactated Ringer solution.

On occasion, enormous volumes of blood are required to raise the arterial blood pressure to normal levels. Rarely, more than 50 percent of the blood volume (85 mL/kg) in term neonates and 100 mL/kg in preterm neonates must be replaced (Fig. 58-11). This is especially true if the placenta is transected during a cesarean section. However, in most cases, less than 10 to 20 (Figure Not Available) mL/kg will restore a normal MAP.

Besides indicating the absolute arterial blood pressure, the arterial pressure tracing provides other information helpful to the evaluation of the adequacy of intravascular volume. A decrease in systolic pressure of more than 5 mm Hg with each inspiration suggests that the neonate is hypovolemic (see Fig. 58-11) (Figure Not Available) . It can also be seen that increasing the blood volume eliminates the swings in arterial pressure induced by inspiration.

Care must be taken not to overexpand the intravascular volume and cause hypertension, especially in preterm neonates. Hypertension may disrupt the intracerebral vessels and cause intracranial hemorrhage [86] if cerebrovascular

TABLE 58-4 -- Average Systolic, Diastolic, and Mean Arterial Blood Pressures (mm Hg) During the First 12 Hours of Life in Normal Infants

	HOURS											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Birth weight 1,001-2,000 g												
Systolic	49	49	51	52	53	52	52	52	51	51	49	50
Diastolic	26	27	28	29	31	31	31	31	31	30	29	30
Mean	35	36	37	39	40	40	39	39	38	37	37	38
Birth weight 2,001-3,000 g												
Systolic	59	57	60	60	61	58	64	60	63	61	60	59
Diastolic	32	32	32	32	33	34	37	34	38	35	35	35
Mean	43	41	43	43	44	43	45	43	44	44	43	42
Birth weight >3,000 g												
Systolic	70	67	65	65	66	66	67	67	68	70	66	66
Diastolic	44	41	39	41	40	41	41	41	44	43	41	41
Mean	53	51	50	50	51	50	50	51	53	54	51	50

Figure 58-11 (Figure Not Available) The aortic blood pressure during first 5 hours of life of a premature infant with hypovolemia. P_{AO} equals mean aortic pressures. *(From Gregory [97])*

autoregulation is absent, [87] [88] which it usually is in asphyxiated neonates. [89] [90] [91]

OTHER CAUSES OF HYPOTENSION

Hypoglycemia, hypocalcemia, and hypermagnesemia can also cause hypotension. The hypotension caused by alcohol or magnesium intoxication usually responds to blood-volume expansion, or better still, to an infusion of dopamine. The arterial blood pressure of hypermagnesemic neonates also may increase with a bolus of 100 to 200 mg/kg of calcium gluconate (given over 5 minutes) and a continuous infusion of 100 to 300 mg/kg/d of the drug.

Polycythemia (hematocrit level >65%) may also cause hypotension due to increased PVR and decreased left ventricular filling pressures. Polycythemia occurs with delayed clamping of or with stripping blood from the umbilical cord. The hyperviscosity that accompanies polycythemia also increases PVR, reduces pulmonary blood flow, and increases right-to-left shunting of blood through the ductus arteriosus and foramen ovale. Hyperviscosity also increases the systemic vascular resistance. The combination of hypoxia and increased vascular resistance causes cardiorespiratory failure. Alleviating polycythemia improves the cardiovascular status of the patient. An exchange transfusion with plasma or saline with albumin (4 g albumin/100 mL saline) can be used to reduce the hematocrit level to 50 to 55 percent. Late sequelae of polycythemia include cardiac and renal failure and CNS injury.

CARDIAC MASSAGE

If the heart rate at 1 minute or less of age is below 100 beats/min, the trachea should be intubated, the lungs ventilated with oxygen, and closed chest massage begun. Both thumbs are placed at the junction of the lower and middle third of the body of the sternum, and the fingers, which encircle the chest, should be used to support the back (Fig. 58-12). The sternum is compressed 1 to 2 cm (approximately one-third the distance to the anterior vertebral bodies) at a rate of 100 to 150 (Figure Not Available) times per minute. It is not necessary to interrupt ventilation of the lungs during cardiac massage and vice versa, although the American Heart Association suggests that this be done. [89] Cardiac output is often greater when cardiac massages and ventilation are simultaneous. The effectiveness of cardiac massage is determined by measuring the blood gases and pH and the arterial pressure generated and by examining the pupils. If the cardiac massage and ventilation are effective, the pupils will be in the midposition or constricted. If the pupils are dilated, and no atropine has been given, cerebral blood flow and oxygenation are inadequate.

Ideally, each chest compression should generate a systolic pressure of 80 mm Hg because pressure is related to cardiac output during CPR. [92] This pressure plus a cardiac massage rate of about 120 times per minute will maintain a diastolic pressure of 20 to 25 mm Hg, a level that is adequate to

Figure 58-12 (Figure Not Available) Closed chest massage. For simplification, ventilation is not shown. *(From Gregory [97])*

TABLE 58-5 -- Drugs Used During Resuscitation[a]

DRUG	INDICATION	DOSE	ROUTE	RESPONSE	COMPLICATION
Atropine	Bradycardia	0.03 mg/kg	IV	Increased heart rate	Marked tachycardia, diminished cardiac output
Calcium gluconate	Low cardiac output	100 mg/kg over 5-10 minutes (ECG monitoring)		Improved cardiac arrhythmias	Bradycardia
Epinephrine	"Flat-line" ECG	0.1 mL/kg of a 1:10,000 solution	IV	"Flat-line" ECG converted to some rhythmic response	Hypertension; ventricular fibrillation
Isoproterenol	Bradycardia, hypotension, low cardiac output	4 mg/250 mL of 5 percent dextrose. Start at 0.01 mug/kg/min and increase until heart rate increases	IV	Increased heart rate, improved cardiac output if heart rate output	Arrhythmias, low cardiac more than 180-220/min
Dopamine	Hypotension	40 mg/100 mL. Start at 5 mug/kg/min and increase until desired effect is achieved	IV	Increased arterial pressure; improved cardiac output, perfusion, and urine output	Arrhythmias-- uncommon

ECG, electrocardiogram

[a] Doses given are, in general, starting doses and may have to be increased. Most drugs tend to be more effective when pH > 7.15.

maintain coronary artery perfusion in neonates during diastole. Failure to generate these pressures and rates allows the diastolic pressure to fall below 10 mm Hg, which is inadequate to perfuse the coronary arteries during diastole.

RESUSCITATION DRUGS

Table 58-5 lists drugs and the usual starting doses used during resuscitation of the newborn. Birchfield et al [93] have reviewed the use of drugs in neonatal resuscitation. [93] Severe acidosis (pH <7.0) may decrease the effectiveness of these drugs. Therefore, the pH should be raised above 7.20 as soon as possible. All drugs should be infused in the smallest volume of fluid possible to reduce the risk of inducing hypervolemia. To do so, drugs such as isoproterenol must be administered in high concentrations (16 mug/mL). However, it should be remembered that the dead space of the catheter is filled with the same concentration of the drug. If the contents of the catheter are flushed into the patient by infusing fluid or another drug, serious cardiac arrhythmias or cardiac arrest may occur. To avoid these complications, the dead space of the catheter and stopcock should be cleared by withdrawing 1.5 mL of blood and fluid. It is preferable to infuse potent cardiac and vasoactive drugs into a separate intravenous line.

Hyperglycemia can significantly augment the effects of hypoxia on ischemia. [94] It increases the extent of CNS damage and reduces the survival of patients who can be resuscitated from cardiac arrest. [95] [96] Consequently, glucose should be given only to neonates who are hypoglycemic. The blood glucose concentration should be measured by a glucometer. If the blood glucose concentration is low, one should give a bolus of glucose (0.5-1.0 mL/kg of 10% dextrose) and begin a constant infusion of 5 to 7 mg/kg/min of glucose. Repeat the glucose measurement in 10 minutes and then as necessary.

WHEN TO DISCONTINUE THERAPY

The decision to stop resuscitation is a personal one. It is usually based on one's own experience and the desires of the parents. In making the decision, the physician must consider the probability of neurologic damage and the likelihood of even seminormality. If the chances of a productive, useful life are poor, consideration should be given to discontinuing all resuscitative efforts.

CASE REPORT

This case summarizes the concepts presented in this chapter.

The neonatologists and anesthesiologists at the University of California, San Francisco, were notified of the impending birth of a 1,500 g, appropriate-for-gestational-age neonate by a mother whose membranes had ruptured 24 hours earlier. Labor had progressed despite the use of tocolytic agents. The obstetricians typed and crossmatched the mother's blood against one unit of O-negative packed red blood cells and one unit of whole blood so that blood would be available in the delivery room to transfuse the neonate during resuscitation if the blood volume or hematocrit level were low. Both units of blood were in the delivery room in separate plastic cold packs before the neonate's birth.

Before the neonate was born, arterial and venous pressure transducers and an umbilical Sa_{O_2} catheter were calibrated. A blood-gas machine and a centrifuge were moved into the resuscitation area so that blood gas, pH, and hematocrit data would be available within 2 minutes of obtaining the blood sample.

An anesthesiologist, attending neonatologist, neonatology fellow, pediatric resident, and two neonatal nurses provided care for the patient during resuscitation.

The neonate was born vaginally. Her mouth and nose were suctioned and her umbilical cord clamped and transected. She was handed to a waiting anesthesiologist and dried with a towel as she was quickly taken from the delivery room to the resuscitation room (a distance of 20 feet). The umbilical cord was clamped and cut immediately after birth because the patient was apneic and because her heart rate was about 100 beats/min. Under the assumption that she would be hypovolemic, we were prepared to infuse blood if her MAP was more than 2 standard deviations below the average MAP for a patient of her gestational age.

We weighed the neonate immediately on her arrival in the resuscitation area. This took less than 10 seconds. Knowing her correct weight allowed us to administer the appropriate doses of drugs, fluids, and blood during resuscitation. After weighing the neonate, we placed her on the sterile resuscitation table, inserted needle electrodes under her skin to continuously measure the ECG and heart rate, and intubated her trachea. Ventilation was controlled with 25 cm H_2O pressure and 100 percent oxygen. The first inspiration was held for 2 seconds. After the first breath, ventilation was controlled at a rate of 60 breaths/min; pressures of 20/5 cm H_2O were applied during each breath. Every fifth inspiration was held for 2 seconds in an attempt to improve the distribution of ventilation and increase removal of fluid from the lung. By this time, the neonate was 1.5 minutes old. A pulse oximeter was applied to her hand and her Sa_{O_2} was less than 80 percent.

A nurse held the umbilical cord up in the air while the abdomen and umbilical cord were sterilized with povidone-iodine; then the abdomen was covered with sterile towels. Next, we placed an umbilical tape 1.0 cm above the point where the umbilical cord entered the skin and tied the tape loosely. We were careful not to include the skin of the abdomen in the tie. We then grasped the umbilical cord and tie with the thumb and index finger of one hand to control bleeding, cut off the umbilical cord, and discarded the unwanted portion of the umbilical cord. Next, the artery was dilated with a pair of curved iris forceps; a Shaw umbilical Sa_{O_2} catheter was inserted into one of the thick-walled umbilical arteries. The catheter was advanced until blood flowed back into the catheter. When this occurred, the stopcock was closed and the catheter was advanced an additional 2 cm. The catheter was then connected to the pressure transducer and all air was removed from the system; then the arterial blood pressure was measured.

As the initial Sa_{O_2} was less than 80 percent, we increased the peak inspiratory pressure to 25 cm H_2O and increased the respiratory rate to 80 breaths/min. A sample of blood was obtained for blood gases, pH, hematocrit level, electrolyte determinations, and blood culture and sensitivity of organisms to antibiotics. Because it is often difficult to distinguish hyaline membrane disease from an intrauterine pneumonia, the neonate was given ampicillin (50 mg/kg) and gentamicin (2.5 mg/kg) through the umbilical artery catheter. The neonate was now 5 minutes old.

The neonate's initial MAP was 24 mm Hg and her systolic and diastolic pressures 40/20 mm Hg. Because she was hypotensive, as well as hypoxic and acidotic (Pa_{O_2} 38 mm Hg, Pa_{CO_2} 60 mm Hg, pH 7.02, base deficit 6.0 mEq/L) and because her hematocrit level was adequate (45%), ventilation was kept constant and she was transfused with 5 mL/kg of whole blood. (Hypotension increases right-to-left shunting of blood through the lung, foramen ovale, and ductus arteriosus of hypoxic, acidotic neonates.) The blood transfusion raised the MAP to 26 mm Hg. However, within 2 minutes, the pressure fell to 24 mm Hg. The Sa_{O_2} was 68 percent. Transfusing another 5 mL/kg of whole blood raised the MAP to 28 mm Hg, the lower limits of normal for neonates of this gestational age. Simultaneous with raising the MAP, the Sa_{O_2} rose to 82 percent. A second blood gas measurement showed a Pa_{O_2} of 46 mm Hg, Pa_{CO_2} 53 mm Hg, and pH 7.15. Because the pHa had increased and the Pa_{CO_2} had decreased and because the MAP was stable, we continued to ventilate her lungs rather than administer bicarbonate. Five minutes later, the MAP had increased to 30 mm Hg and 100 percent Sa_{O_2} had been achieved. Another sample of blood was obtained. The Pa_{O_2} was 138 mm Hg, Pa_{CO_2} 37 mm Hg, and pH a 7.27. During the next 10 minutes, the Sa_{O_2} remained above 90 percent despite a progressive reduction of F_{IO_2} to 0.75. On repeat testing, the Pa_{O_2} was 70 mm Hg, Pa_{CO_2} 29 mm Hg, and pH 7.46. Because of the increased pHa and the decreased Pa_{CO_2}, we reduced the ventilatory rate to 60 breaths/min. We continued to reduce the F_{IO_2} as long as the Sa_{O_2} remained between 87 and 94 percent. Fifteen minutes later, when the F_{IO_2} was 0.50, we obtained another blood gas (Pa_{O_2} 68 mm Hg, Pa_{CO_2} 35 mm Hg, pHa 7.42). The MAP was 32 mm Hg and the Sa_{O_2} and F_{IO_2} were stable for the next 15 minutes. A repeat blood gas was similar to the previous one. Consequently, we transferred the patient to the neonatal intensive care unit.

The neonate had mild hyaline membrane disease. By the 3rd day of life, her condition was improved; mechanical ventilation was discontinued and the endotracheal tube removed. She was discharged from the hospital on the 48th day of life and was doing well. Present-day treatment would include giving 5 mg/kg of Exosurf into the endotracheal tube and continuing ventilation. This would improve oxygenation more rapidly once the blood volume was adequate.

This case illustrates several basic points:

1. Resuscitation of severely ill neonates involves all the technology and people required to resuscitate an older child or adult from cardiac arrest. One person cannot do all the things required to resuscitate a neonate. It is essential, therefore, to notify those who are going to resuscitate the patient in time for them to arrive in the delivery room before the patient is born.
2. Neonates who are severely depressed at birth are often hypovolemic and require immediate blood volume expansion. Failure to correct the hypovolemia makes it difficult to correct the hypoxia and acidosis.
3. Blood gases and pHa change rapidly during resuscitation. Therefore, the results of these determinations should be immediately available so that the inspired oxygen concentration and the ventilation pressures and rates can be changed as necessary. Being told the blood-gas results 30 minutes after the blood sample was obtained is of little value, because the blood gases and pH will almost certainly have changed during that time.
4. The equipment required for resuscitation must always be available in the delivery room. One should not wait for an emergency to occur before finding the resuscitation

equipment. The equipment needed includes heating lamps and heating blankets to maintain the neonate's body temperature normal, umbilical arterial catheters, surgical instruments to insert an umbilical artery catheter, pressure transducers and monitors to measure intravascular pressures, and equipment to intubate the trachea and ventilate the lungs.

A hospital that cannot provide the care outlined in this case report should transfer mothers with high-risk pregnancies to a referral hospital early in their course of labor.

References

1. Fisher DJ: Adrenergic influence on increased myocardial oxygen consumption during hypoxemia in awake newborn lambs. Pediatr Res 25:595, 1989.

2. Rudolph CD, Roman C, Rudolph AM: Effect of acute umbilical cord compression on hepatic carbohydrate metabolism in the fetal lamb. Pediatr Res 25:228, 1989.

3. Avery ME: The Lung and Its Disorders in the Newborn Infant. 3rd ed. Philadelphia, WB Saunders, 1974.

4. Platzker ACG, Kitterman JA, Clements JA et al: Surfactant appearance and secretion in the fetal lamb lung in response to dexamethasone. Pediatr Res 6:406, 1972.

5. Platzker ACG, Kitterman JA, Mescher EJ et al: Surfactant in the lung and tracheal fluid of the fetal lamb and acceleration of its appearance by dexamethasone. Pediatrics 56:544, 1975.

6. Lawson EW, Birdwell RL, Huang PS et al: Augmentation of pulmonary surfactant secretion by lung expansion at birth. Pediatr Res 13:611, 1979.

7. Jobe A, Machiko I: Surfactant for the treatment of respiratory distress syndrome. Am Rev Respir Dis 136:1256, 1987.

8. Adams FH, Moss AJ, Fagan L: The tracheal fluid of the foetal lamb. Biol Neonate 5:151, 1963.

9. Karlberg P: The adaptive changes in the immediate postnatal period, with particular reference to respiration. J Pediatr 56:585, 1960.

10. Sundell H, Garrat J, Blankenship WJ et al: Studies on neonates with type II respiratory distress syndrome. J Pediatr 78:754, 1971.

11. Bland RD, Bressack MA, McMillan DD: Labor decreases the lung water content of newborn rabbits. Am J Obstet Gynecol 135:364, 1979.

12. Bland RD, McMillan DD, Bressack MA et al: Clearance of lung liquid from lungs of newborn rabbits. J Appl Physiol 49:171, 1980.

13. Chernick V, Fariday EE, Pagtakhan RD: Role of the peripheral and central chemoreceptors in the initiation of fetal respiration. J Appl Physiol 38:407, 1975.

14. Jansen AH, Chernick V: Site of chemosensitivity in fetal sheep. J Appl Physiol 39:1, 1975.

15. Dawes GS: Foetal and Neonatal Physiology. Chicago, Year Book Medical Publishers, 1968.

16. Rudolph AM, Heymann MA: Fetal and neonatal circulation and respiration. Annu Rev Physiol 36:187, 1974.

17. Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book Medical Publishers, 1974.

18. Rudolph AM, Yuen S: Response of the pulmonary vasculature to hypoxia and H+ ion concentration changes. J Clin Invest 45:1:399, 1966.

19. Cassen S, Dawes GS, Mott JC et al: The vascular resistance of the foetal and newly ventilated lung of the lamb. J Physiol (Lond) 171:61, 1964.

20. Haworth SG, Hislap AA: Adaptation of the pulmonary circulation to extrauterine life in the pig and its relevance to the human infant. Cardiovasc Res 15:108, 1981.

21. Riggs T, Fanaroff A: Neonatal circulating changes following elective cesarean section: An echocardiographic study. Pediatrics 69:374, 1982.

22. Brady JP, Rigatto H: Pulmonary capillary flow in infants. Circulation (suppl) 3:50, 1969.

23. Assali NS, Morris JA, Smith RW et al: Studies on ductus arteriosus circulation. Circ Res 13:478, 1963.

24. Heymann MA, Rudolph AM: Constriction of the ductus arteriosus by acetylcholine in premature infants. Circulation 43:11, 1971.

25. McMurphy DM, Heymann MA, Rudolph AM et al: Developmental changes in constriction of the ductus arteriosus. Responses to oxygen and vasoactive agents in the isolated ductus arteriosus of the fetal lamb. Pediatr Res 6:231, 1972.

26. Clyman RI, Wong L, Heymann MA et al: Responsiveness of the lamb ductus arteriosus to prostaglandins and their metabolites. Prostaglan-dins 15:325, 1978.

27. Boreus LO, Malmfors T, McMurphy DM et al: Demonstration of adrenergic receptor function and innervation in the ductus arteriosus of the human fetus. Acta Physiol Scand 77:316, 1969.

28. Torrance S, Witt-Nick C: The effect of varying arterial oxygen tension on neonatal acid-base balance. Pediatr Res 31:112, 1992.

29. Myers RE: Four patterns of perinatal brain damage and their conditions of occurrence in primates. Adv Neurol 10:223, 1975.

30. Behrman RE, Lees MH, Peterson EN et al: Distribution of circulation in the normal and asphyxiated fetal primate. Am J Obstet Gynecol 108:956, 1970.

31. Yarnell R, Biehl DR, Tweed WA et al: The effect of halothane anesthesia on the asphyxiated foetal lamb in utero. Can J Anaesth 30:24, 1983.

32. Cohn HE, Sacks FJ, Heymann MA et al: Cardiovascular responses to hypokalemia and acidemia in fetal lambs. Am J Obstet Gynecol 120:817, 1974.

33. Boyle DW, Hosk K, Zerbe GO: Fetal fluid limb oxygen consumption and blood flow during acute hypoxia. Pediatr Res 28:94, 1990.

34. Fisher DJ, Heymann MA, Rudolph AM: Fetal myocardial oxygen and carbohydrate consumption during acutely induced hypoxemia. Am J Physiol 242:H657, 1982.

35. Wardlaw SC, Stark RI, Bali C et al: Plasma B-endorphin and B-lipoprotein in the human fetus at delivery: Correlation with arterial pH and PCO2. J Clin Endocrinol Metab 49:888, 1979.

36. Moss IR, Conner H, Yee WFH et al: Human B-endorphin-like immunoreactivity in the perinatal/neonatal period. J Pediatr 101:443, 1982.

37. Iskovitz J, LaGamma EF, Bristow J et al: Cardiovascular responses to hypoxemia in sinoaortic-denervated fetal sheep. Pediatr Res 30:381, 1991.

38. Jones CT, Roebuck MM, Walker DW et al: The role of the adrenal medulla and peripheral sympathetic nerves in the physiological responses of fetal sheep to hypoxia. J Dev Physiol 10:17, 1988.

39. Cheung CY, Brace RA: Fetal hypoxia elevates plasma atrial natriuretic factor concentration. Am J Obstet Gynecol 159:1263, 1988.

40. Perez R, Espinoza M, Riqueline R et al: Arginine vasopressin mediates cardiovascular responses to hypoxia in fetal sheep. Am J Physiol 256:R1011, 1989.

41. Yao AC, Lind J: Blood volume in the asphyxiated term neonate. Biol Neonate 21:199, 1972.

42. Apgar V: A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth 32:260, 1953.

43. Apgar V, James LS: Further observations on the newborn scoring system. Am J Dis Child 104:419, 1962.

44. James LS, Weisbrot IM, Prince CE et al: The acid-base status of human infants in relation to birth asphyxia and onset of respiration. J Pediatr 52:379, 1958.

45. Drage JS, Berendes H: Apgar scores and outcome of the newborn. Pediatr Clin North Am 13:635, 1966.

46. Ruth VJ, Raivio KO: Perinatal brain damage: Predictive value of metabolic acidosis and the Apgar score. BMJ 297:24, 1988.

47. Garn SM, Johnston M, Ridella SA et al: Effect of cigarette smoking on Apgar scores. JAMA 135:503, 1981.

48. Branstater B: Dilation of the larynx with Cole tubes. Anesthesiology 31:378, 1969.

49. Wilkinson AR, Phibbs RH, Gregory GA: Improved accuracy of continuous measurement of arterial oxygen tension in sick newborn infants. Arch Dis Child 54:307, 1979.

50. Wilkinson AR, Phibbs RH, Gregory GA: Continuous measurement of oxygen saturation in sick newborn infants. J Pediatr 93:1016, 1978.

51. Peabody JL, Gregory GA, Willis MM: Transcutaneous oxygen tension in sick infants. Am Rev Respir Dis 118:83, 1978.

52. Jennis MS, Peabody JC: Pulse oximetry: An alternative method for the assessment of oxygenation in newborn infants. Pediatrics 79:524, 1987.

53. Severinghaus JW, Noifeh KH: Accuracy of response of six pulse oximeters to profound hypoxia. Anesthesiology 67:551, 1987.

54.

Yao AC, Moinain M, Lind J: Distribution of blood between infant and placenta after birth. Lancet 2:871, 1969.

55. Ogata ES, Kitterman JA, Phibbs RH et al: The effect of time of cord clamping and maternal blood pressure on placental transfusion with cesarean section. Am J Obstet Gynecol 128:197, 1977.

56. Gunther M: The transfer of blood between baby and placenta in the minutes after birth. Lancet 1:1277, 1957.

57. Oh W, Lind J, Gessner IH: The circulatory and respiratory adaption to early and late cord clamping in newborn infants. Acta Pediatr Scand 55:17, 1966.

58. Cassidy G: Effect of caesarean section on neonatal body water spaces. N Engl J Med 285:887, 1971.

59. Oh W, Arcilla RA, Lind J et al: Arterial blood gases and acid base balance in the newborn infant. Effects of cord clamping at birth. Acta Pediatr Scand 55:593, 1966.

60. Oh W, Wallgreen G, Hanson VS et al: The effects of placental transfusion on respiratory mechanics of normal term infants. Pediatrics 40:6, 1967.

61. Bjorklund LJ, Ingimarsson J, Curstedt T et al: Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. Pediatr Res 42:348, 1997.

62. James LS, Lerman JT: History of oxygen therapy and retrolental fibroplasia. Pediatrics 57(suppl):591, 1976.

63. Kingman JD: Acute retrolental fibroplasia. Arch Ophthalmol 95:39, 1977.

64. Gooding CA, Gregory GA, Tabor P et al: An experimental model for the study of meconium aspiration of the newborn. Radiology 100:137, 1971.

65. Katz VL, Bowes WA Jr: Meconium aspiration syndrome: Reflections on a murky subject. Am J Obstet Gynecol 166:171, 1992.

66. Gregory GA, Gooding C, Phibbs RH et al: Meconium aspiration in infants, a prospective study. J Pediatr 85:848, 1974.

67. Ting P, Brady JP: Tracheal suction in meconium aspiration. Am J Obstet Gynecol 122:767, 1975.

68. Pretlow RA: Hand-powered apparatus for aspiration of meconium from the airway. Pediatrics 79:642, 1987.

69. Goetzman BW, Riemenschnider TA: Persistence of fetal circulation. Pediatr Rev 2:37, 1980.

70. Bartlett R, Gazzaniga AB, Huntable RF et al: Extracorporeal circulation (ECMO) in neonatal respiratory failure. J Thorac Cardiovasc Surg 74:826, 1977.

71. Short BL, Pearson G: Neonatal extracorporeal membrane oxygenation: A review. J Intensive Care Med 1:47, 1986.

72. Macfarlane PI, Heaf DP: Pulmonary function in children after neonatal meconium aspiration syndrome. Arch Dis Child 63:368, 1988.

73. Stevens JC, Eigen H, Wysomiersk D: Absence of long term pulmonary sequalae after mild meconium aspiration syndrome. Pediatr Pulmonol 5:74, 1988.

74. Kuhns LR, Bednarek FJ, Wyman ML et al: Diagnosis of pneumothorax or pneumomediastinum in the neonate by transillumination. Pediatrics 56:355, 1975.

75. Markakis DA, Sayson SC, Schreiner MS: Insertion of the laryngeal mask airway in awake infants with the Robin sequence. Anesth Analg 75:822, 1992.

76. DeLorimier AA, Tierney DF, Parker HR: Hypoplastic lungs in fetal lambs with surgically produced congenital diaphragmatic hernia. Surgery 62:12, 1967.

77. Murdoch AI, Burrington JB, Swyer PR: Alveolar to arterial oxygen tension difference and venous admixture in newly born infants with congenital diaphragmatic herniation through the foramen of Bochdalek. Biol Neonate 16:161, 1971.

78. Drummond W, Gregory GA, Heymann MA et al: The independent effects of hyperventilation, tolazoline and dopamine on infants with persistent pulmonary hypertension. J Pediatr 98:603, 1981.

79. Langham MR, Krummel TM, Greenfield LJ et al: Extracorporeal membrane oxygenation following repair of congenital diaphragmatic hernias. Ann Thorac Surg 44:247, 1987.

80. Jobe A, Ikegami M: Surfactant for the treatment of respiratory distress syndrome. Am Rev Respir Dis 136:1256, 1987.

81. Phibbs RH, Ballard RA, Clements JA: Initial clinical trial on EXOSURF, a protein free synthetic surfactant for the prophylaxis and early treatment of hyaline membrane disease. Pediatrics 88:1, 1991.

82. Hoekstra RE, Jackson JC, Myers TF et al: Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome. Pediatrics 88:10, 1991.

83. Arieff AI, Gertz EW, Park R et al: Lactic acidosis and the cardiovascular system. Clin Sci 64:573, 1983.

84. Arieff AI, Leach W, Park R et al: Systemic effects of $NaHCO_3$ in experimental lactic acidosis. Am J Physiol 11:F586, 1982.

85. Sessler D, Mills P, Gregory G et al: The effects of bicarbonate on arterial and brain intracellular pH in neonatal rabbits recovering from hypoxic lactic acidosis. J Pediatr 111:817, 1987.

86. Lou HC, Lassen NA, Friis-Hansen B: Is arterial hypertension crucial for the development of cerebral hemorrhage in premature infants? Lancet 1:1215, 1979.

87. Lou HC, Lassen NA, Friis-Hansen B: Impaired autoregulation of cerebral blood flow in the distressed newborn infant. J Pediatr 94:118, 1979.

88. Lou HC, Lassen NA, Tweed WA et al: Pressure passive cerebral blood flow and breakdown of the blood-brain barrier in experimental fetal asphyxia. Acta Pediatr Scand 68:57, 1979.

89. Ong BY, Greengrass R, Bose D et al: Acidemia impairs autoregulation of cerebral blood flow in newborn infants. Can J Anaesth 33:5, 1986.

90. Tweed A, Cote J, Lou H et al: Impairment of cerebral blood flow autoregulation in the newborn lamb by hypoxia. Pediatr Res 20:516, 1986.

91. Del TJ, Louis PT, Goddard FJ: Cerebrovascular regulation and neonatal brain injury. Pediatr Neurol 7:3, 1991.

92. Fitzgerald KR, Babbs CF, Frissora HA: Cardiac output during cardiopulmonary resuscitation at various compression rates and durations. Am J Physiol 241:442, 1981.

93. Birchfield DJ, Berkowitz ID, Berg RA: Medications in neonatal resuscitation. Ann Emerg Med 22:435, 1993.

94. Ginsburg MD, Welsh FA, Budd WW: Deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat. Stroke 11:347, 1980.

95. Longstreth WT Jr, Iniu TS: High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. Ann Neurol 15:59, 1984.

96. Lundy EF, Kuhn JE, Kwon JM et al: Infusion of five percent dextrose increases morbidity and mortality following six minutes of cardiac arrest in anesthetized dogs. J Clin Care 2:4, 1987.

97. Gregory GA: Resuscitation of the newborn. Anesthesiology 43:225, 1975.

98. Gregory GA, Kitterman JA, Phibbs RH et al: Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med 284:1333, 1971.

99. Wilkinson A, Phibbs RH, Gregory GA: Continuous in vivo oxygen saturation in newborn infants with pulmonary disease. Crit Care Med 7:232, 1979.

100. Gregory GA: The Anesthesiologist, Mother & Newborn. Baltimore, Williams & Wilkins, 1974.

101. Phibbs RH: Problems of neonatal intensive care units. In Lucey JF: Report on the 59th Ross Conference on Pediatric Research, Columbus, OH, 1969.

Chapter 59 - Pediatric Anesthesia

Charles J. Cote

INTRODUCTION

The provision of safe anesthesia for the pediatric patient depends on a clear understanding of the physiologic, pharmacologic, and psychologic differences between children and adults. Special consideration must be given to premature infants, as well as to those with congenital malformations. This chapter describes how the unique characteristics of pediatric patients influence the safe conduct of anesthesia.

DEVELOPMENTAL PHYSIOLOGY OF THE INFANT

Organogenesis takes place within 8 weeks of conception; organ function develops during the second trimester; and the infant gains weight, primarily muscle and fat, during the third trimester. [1] Therefore, any physiologic or pharmacologic injury or stress during the first trimester may cause abnormal organogenesis; in the second trimester, it may cause abnormal organ functional development, and in the third trimester, smaller organs or reduced muscle and fat mass. [2] Injuries and stress take the form of congenital viral infections, exposure to drugs, nutritional insufficiency (caloric or vascular), or other maternal illness. [3] A genetic predisposition to developmental malformations can also produce adverse effects. Such interruptions in normal growth and development may cause a variety of physiologic abnormalities ranging from simple premature birth to a constellation of congenital malformations.

A premature infant is one born before 37 weeks of gestation; a postmature infant is one born after 42 weeks of gestation. Any infant less than 2,500 g is considered a low-birth-weight infant. Plotting weight against gestational age (GA) allows classification into three general categories: small for GA, appropriate for GA, or large for GA (Fig. 59-1) (Figure Not Available) . Infants who are small or large for GA age often have developmental problems or difficulties associated with maternal disease (Table 59-1) (Table Not Available) . A careful physical and neurologic examination at birth (the Dubowitz scale), modified for extreme prematurity, allows a fairly accurate estimate of GA. [4] [5] The anesthesiologist should be aware of this type of evaluation so that potential problems with the anesthetic regimen can be anticipated. A perinatal history regarding problems in the mother (e.g., maternal drug abuse, maternal infection) is valuable for anesthetic management. In the weeks following birth, measures of weight, height, and head circumference are plotted on standard developmental curves; deviations from the normal (i.e., crossing developmental lines) usually indicate severe physiologic injury. The anesthesiologist should examine the growth chart to evaluate how the child is developing.

Cardiovascular System

The cardiovascular system undergoes dramatic physiologic and maturational changes during the first year of life. *In utero,* most of the cardiac output is directed from the placenta across the foramen ovale into the ascending aorta (oxygenated blood). Superior vena caval blood (deoxygenated)

Figure 59-1 (Figure Not Available) Plotting birth weight against gestational age for neonates determines whether infants are small, appropriate, or large for gestational age. Babies who are either small or large for gestational age are particularly likely to have a variety of problems such as metabolic, developmental, infectious, or structural abnormalities, as well as drug addiction and withdrawal. *(Modified from Battaglia [249])*

is directed to both the pulmonary artery and the ductus arteriosus. Thus, pulmonary blood flow is minimal. At birth, certain events change hemodynamic interactions such that the fetal circulation becomes an adult-type circulation. [6] Specifically, the placenta is removed from the circulation, and exposure of blood entering the ductus arteriosus to oxygen induces ductal closure. As a result of the combined effects of lung expansion and exposure of blood to oxygen, peripheral vascular resistance rises rapidly while pulmonary vascular resistance decreases. The fall in pulmonary vascular resistance occurs rapidly on the first day of life and continues to decrease gradually during the next several years as the architecture of the pulmonary vessels changes. An increase in pressures on the left side of the heart (caused by the increase in peripheral vascular resistance) induces mechanical closure of the foramen ovale. Although closure of the ductus arteriosus probably occurs primarily in response to a rise in arterial oxygen concentration, its successful completion requires arterial muscular tissue. [7] The finding that such tissue is less prevalent in premature infants may account, in part, for the high incidence of patent ductus arteriosus among premature infants. True mechanical closure by fibrosis does not occur until 2 to 3 weeks of age. [6] [7]

During this critical period, the infant readily reverts from the adult circulation to a fetal type of circulation; this state is called transitional circulation. Many factors (hypoxia, hypercarbia, anesthesia-induced changes in peripheral vascular tone) can affect this precarious balance, resulting in a rapid return to fetal circulation. When this reversal occurs, pulmonary artery pressure increases to systemic levels, blood is shunted past the lungs via the patent foramen ovale, and the ductus arteriosus may reopen, allowing blood to shunt at the ductal level. A rapid downhill spiral may occur, causing severe hypoxemia; this explains why hypoxemic events in infants are often prolonged despite adequate pulmonary ventilation with 100 percent oxygen.

Risk factors increasing the likelihood of prolonged transitional circulation include prematurity, infection, acidosis, pulmonary disease resulting in hypercarbia or hypoxemia (aspiration of meconium), hypothermia, and congenital heart disease. Care must be directed to keeping the infant warm, maintaining normal arterial oxygen and carbon dioxide tensions, and minimizing anesthetic-induced myocardial depression.

The myocardial structure of the heart, particularly the volume of cellular mass devoted to contractility, is significantly less developed in the neonate than in the adult. These differences and others produce a leftward displacement of the cardiac function curve and less compliant ventricles. This developmental myocardial immaturity accounts for the tendency toward biventricular failure, sensitivity to volume loading, poor tolerance to increased afterload, and heart rate-dependent cardiac output. [8] [9]

Pulmonary System

The pulmonary system is not capable of sustaining life until both the pulmonary airways and the vascular system have matured sufficiently to allow exchange of oxygen from "air" to the blood stream across the pulmonary alveolar/vascular bed. Independent life is not possible until GA is 24 to 26 weeks. Alveoli increase in number and size until the child is approximately 8 years old [10] ; further growth manifests as an increase in the size of the alveoli and airways. At term, a full complement of surface-active proteins helps maintain patency

---

TABLE 59-1 -- Common Neonatal Problems Associated With Weight and Gestational Age

(Not Available)

Modified from Todres [255]

of the airways. If a child is born prematurely and these proteins are insufficient, respiratory failure (respiratory distress syndrome) may follow.

Several anatomic differences make respiration less efficient for the infant. The small diameter of the airways increases resistance to air flow; resistance is inversely

proportional to the radius raised to the fourth power. The airway of the infant is highly compliant and poorly supported by surrounding structures. The chest wall is also highly compliant, so that the ribs provide little support for the lungs; that is, negative intrathoracic pressure is poorly maintained. Thus, each breath is accompanied by functional airway closure. [11] Dead-space ventilation is similar to that in adults; however, oxygen consumption is two to three times as high as in the adult. In the premature infant, the work of breathing is approximately three times that of the adult, and this work can be increased significantly by cold stress or partial airway obstruction. These differences partially explain the high respiratory rate of the infant and the rapidity with which hemoglobin desaturation can occur. [12]

Another important factor is the composition of diaphragmatic and intercostal muscles. These muscles do not achieve the adult configuration of type 1 muscle fibers until the child is approximately 2 years old [13] (Fig. 59-2) . Because type I muscle fibers provide the ability to perform repeated exercise and because the newborn and the infant are somewhat deficient in type I muscle fibers, any factor that increases the work of breathing contributes to the early fatigue of the respiratory muscles. Fatigue, in turn, leads to apnea or carbon dioxide retention and respiratory failure. Infants have often been described as obligate nasal breathers; however, approximately 8 percent of premature neonates (postconceptual age [PCA], 31-32 wk) and 40 percent of term newborns can convert to oral breathing in the presence of nasal airway obstruction. Nearly all infants can convert to oral breathing by 5 months of age. [14]

Differences in airway anatomy make the potential for technical airway difficulties greater in infants than in teenagers or adults. The airway of the infant differs in five ways [15] [16] : (1) the relatively large size of the infant's tongue in relation to the oropharynx increases the likelihood of airway obstruction and technical difficulties during laryngoscopy; (2) the larynx is located higher in the neck, thus making straight blades more useful than curved blades; (3) the epiglottis is shaped differently, being short and stubby, and is angled over the laryngeal inlet; control with the laryngoscope blade is therefore more difficult; (4) the vocal cords are angled, so that a "blindly" passed endotracheal tube may easily lodge in the anterior commissure rather than slide into the trachea; and (5) the infant larynx is funnel-shaped, the narrowest portion occurring at the cricoid cartilage (Fig. 59-3) (Figure Not Available) . In the adult, an endotracheal tube that passes the vocal cords will readily pass into the trachea, because the glottic opening is the narrowest portion of the larynx. In the infant or young child, an endotracheal tube that easily passes

Figure 59-2 The composition of the diaphragm and intercostal muscles changes markedly during the first 2 years of life. The number of type I muscle fibers is inversely related to age and may account in part for the ease of inducing respiratory fatigue as the work of breathing increases. *(Data from Keens et al [13])*

Figure 59-3 (Figure Not Available) The narrower part of the adult larynx (cylindric shape) (left) occurs at the glottic opening, whereas the narrowest part of the infant larynx (funnel shape) (right) occurs at the level of the cricoid cartilage. The normal adult configuration of the larynx is not achieved until the teenage years. This anatomic difference is one of the reasons why uncuffed endotracheal tubes are preferred for children younger than 10 years of age. A, anterior; cricoid, cricoid cartilage; P, posterior; thyroid cart, thyroid cartilage. *(From Cote and Todres [250])*

the vocal cords may be tight in the subglottic region because of the narrowing at the cricoid cartilage. For this reason, uncuffed endotracheal tubes are the preferred choice for patients younger than 10 years of age.

Kidneys

Renal function is markedly diminished in the neonate because of low perfusion pressure and immature glomerular and tubular function (Fig. 59-4) . Nearly complete maturation of glomerular filtration and tubular function occurs by approximately 20 weeks after birth, although maturation is somewhat delayed in premature infants. Complete maturation of renal function occurs by about 2 years of age. [17] [18] Thus, the ability to handle free water and solute loads may be impaired in the neonate, and the half-life of medications excreted by means of glomerular filtration will be prolonged. [19]

Liver

At term, the functional maturity of the liver is somewhat incomplete. Most enzyme systems for drug metabolism are developed but are not yet induced (stimulated) by the agents they metabolize. As the infant grows, the ability to metabolize medications increases rapidly in two ways: (1) hepatic blood flow increases, and more drug is delivered to the liver; and (2) the enzyme systems develop and are induced. [20] [21] [22] Conjugation reactions are often impaired in the neonate, resulting in jaundice; diminished degradation reactions lead to long drug half-lives. Thus, it is common to have a longer drug elimination half-life in the neonate but a shorter drug half-life in the infant and older child than in the adult.

The premature neonatal liver has minimal glycogen stores and is unable to handle large protein loads. This difference accounts for the tendency to hypoglycemia and acidemia and for the failure to gain weight when the diet contains too much protein. Additionally, plasma levels of albumin and other proteins necessary for binding of drugs are lower in term newborns (and are even lower in premature infants) than in older infants. This condition has clinical implications regarding neonatal coagulopathy (e.g., the need for vitamin K at birth), as well as for drug binding and pharmacodynamics: the lower the albumin value, the less protein binding and the greater the levels of free drug. [23] [24]

Figure 59-4 Glomerular filtration rate is markedly impaired at birth, but it develops rapidly during the first year of life. The ability of the kidney to handle large amounts of solutes and water is also limited during the first several months of life. These developmental changes have significant implications for drug excretion and fluid therapy, particularly during the first 4 weeks of life. Maturation of renal function may be delayed in the sick neonate. *(Data from McCrory [251])*

Gastrointestinal System

At birth, the gastric pH is alkalotic; by the second day of life, pH is in the normal physiologic range for older patients. The ability to coordinate swallowing with respiration does not fully mature until the infant is 4 to 5 months of age. Therefore, the incidence of gastroesophageal reflux in newborns is high. [25] In general, if a developmental problem occurs within the gastrointestinal system, symptoms will occur within 24 to 36 hours of birth. Upper intestinal abnormalities manifest as vomiting and regurgitation, whereas lower intestinal abnormalities produce abdominal distention and failure to pass meconium.

Thermoregulation

The infant is particularly vulnerable to hypothermia because of both the large ratio of body surface area to weight and a limited ability to cope with cold stress (Ch. 37) . The premature infant is even more susceptible because of very thin skin and limited fat stores. The infant may compensate by means of shivering and nonshivering (cellular) thermogenesis. The minimal ability to shiver during the first 3 months of life makes cellular thermogenesis (metabolism of brown fat) the principal method of heat production. [26] These factors underscore the importance of minimizing heat loss. Heat lost by conduction is reduced by placing the baby on a warming mattress and warming the operating room. Heat lost through convection is minimized by keeping the infant in an incubator, covered with blankets. The infant's head should also be covered. Heat lost through radiation is decreased by use of a double-shelled incubator during transport. Heat lost through evaporation is lessened by humidification of inspired gases, the use of plastic wrap to decrease water loss through the skin, and the warming of preparation solutions. Anesthesia also alters the normal thermoregulatory mechanisms, particularly in neonates. [27] [28] [29] Heated air-warming devices are particularly useful in neonates. [30]

/das/book/view/29494766/875/658.html

PHARMACOLOGY AND PHARMACODYNAMICS

The response of the infant and child (and particularly the neonate) to medication is modified by many factors: body composition, protein binding, body temperature, distribution of cardiac output, maturation of the blood-brain barrier, and relative size (as well as functional maturity) of the liver and kidneys. [19] [20] [21] [22] [23] [24] [31]

The body compartments (fat, muscle, water) change with age (Fig. 59-5) . Total body water content is significantly higher in the premature than in the term infant and in the term infant than in the 2-year-old. [1] Fat and muscle content increase with age. These alterations in body composition have several clinical implications for the neonate: (1) a drug that is water soluble has a larger volume of distribution and usually requires a larger initial dose to achieve the desired blood level (e.g., most antibiotics, succinylcholine); (2) because there is less fat, a drug that depends on redistribution into fat for termination of its action has a longer clinical effect (e.g., thiopental); and (3) a drug that redistributes into muscle may have a longer clinical effect (e.g., fentanyl, for which, however, saturation of muscle tissue has not been demonstrated).

In addition to these very basic concepts, other important factors play a role: delayed excretion resulting from the larger volume of distribution, immature hepatic and renal function, and altered drug excretion caused by lower protein binding. Further perturbations in drug pharmacodynamics and pharmacokinetics occur with extreme prematurity and with factors such as sepsis, congestive heart failure, and poor nutritional state. [20] [21] [22] [31]

Older children tend to have mature renal and hepatic function, normal adult values for protein, and fat and muscle content approaching adult values. More of the cardiac output is diverted to the liver and kidneys--which also weigh more in relation to body mass--in older children than in infants. These factors usually mean that most medications have a shorter half-life in children older than 2 years of age

Figure 59-5 Body composition changes rapidly in premature and term infants during the first 12 months of life. Their high water content provides a large volume of distribution for water-soluble medications, whereas their low fat and muscle content provides a small reservoir for drugs that depend on redistribution into these tissues for termination of drug effects. Thus, body composition may significantly affect pharmacokinetics and pharmacodynamics. *(Data from Friis-Hansen [1])*

than in adults. As the child approaches adulthood, the half-life of many drugs lengthens. In general, most medications have a prolonged elimination half-life in premature and term infants, a shortened half-life in children older than 2 years of age up to the early teen years, and a lengthening of half-life in teenagers approaching adulthood.

Inhaled Anesthetics

The expired minimum alveolar concentration (MAC) of inhaled anesthetic required in pediatric patients changes with age (Fig. 59-6) . [32] [33] [34] [35] [36] [37] (Ch. 4) . Carefully controlled studies show that the anesthetic requirement is lower for the premature infant than for the term neonate and lower for the term neonate than for the 3-month-old child. Infants are known to have a greater anesthetic requirement than older

Figure 59-6 The minimum alveolar concentration (MAC) for four commonly used inhalation anesthetics is plotted versus age. Note that MAC is highest in infants 3 to 6 months of age. The reasons for this are not clear. *(Data from a number of studies [32] [34] [36] [37] [60] [252] [253] [254])*

children or adults; the reasons have not been adequately explained. This fact, combined with the need for deeper planes of anesthesia to achieve satisfactory conditions for endotracheal intubation, places the infant in a precarious position between anesthetic overdose (from a cardiovascular standpoint) and inadequate depth of anesthesia (for endotracheal intubation). [38] The early administration of muscle relaxants and narcotics probably decreases this possibility. [39]

The uptake of potent anesthetics is more rapid in children because of increased respiratory rates and cardiac index and a greater proportional distribution of cardiac output to vessel-rich organs. This rapid rise in blood anesthetic levels probably explains in part why it is so easy to give an overdose to infants and small children. Age-related differences in blood/gas partition coefficients may also facilitate a more rapid rise in alveolar concentration in infants. [40] [41] Other factors include the state of hydration (e.g., excessive fasting would make a small infant relatively dehydrated) and the type of anesthesia circuit used. For example, a Mapleson D has a smaller volume than a circle system and therefore less volume to achieve equilibration when the concentration of anesthetic agent exiting the vaporizer increases. With a Mapleson D circuit, the fresh gas flow is introduced into the system at the airway, entering directly into the patient's lungs. These factors facilitate a very rapid rise in blood anesthetic concentration and the potential for anesthetic overdose.

Halothane

Halothane does not have a noxious smell and is still commonly used for the gaseous induction of anesthesia; sevoflurane appears to be slightly less noxious and is being increasingly used for induction with a change to halothane after induction because of cost restraints. Studies of induction and awakening with various anesthetics have found no clinically important differences in rapidity of awakening among

halothane, enflurane, and isoflurane. [42] [43] [44] [45] [46] However, airway-related problems occur less frequently with halothane and sevoflurane than with enflurane, isoflurane, or desflurane. [46] [47] [48] [49] There is nearly always a statistically significant but clinically unimportant difference in the rapidity of awakening when comparing halothane with either desflurane or sevoflurane (usually 3-5 min). [42] [43] [44] [45] [46] I often induce anesthesia with sevoflurane and then use halothane for maintenance in order to reduce costs, to be able to use very low fresh gas flows, and to avoid any unknown issues regarding possible toxic metabolites. Halothane or sevoflurane is the anesthetic of choice for induction of anesthesia by mask or for children with airway problems.

A 1987 report describing seven cases (one fatal) of "halothane hepatitis" concluded that children should not undergo repeated exposure to halothane [50] (Ch. 6) . It is important to place this report in proper perspective. To date, millions of children have been anesthetized with halothane. Perhaps a dozen instances of halothane hepatitis, and one or two deaths, have been reported. This is a remarkable safety record for any medication. If halothane hepatitis were a clinically important issue for

children, dozens--perhaps hundreds--of cases would have been reported. Furthermore, the recommendation to avoid halothane in children was made by internists without the opinion of pediatric anesthesiologists, who would have determined the risk/benefit ratio for halothane. Therefore, it is not in the best interest of the patient or the anesthesiologist to discard this anesthetic until more scientific data are presented. [51] There is little logic in inducing anesthesia with halothane and then changing to enflurane or isoflurane, unless one is particularly interested in the differing effects of anesthetics on the cardiovascular or central nervous system (CNS). It may, however, make some sense to use other anesthetics or techniques in teenage patients and adults.

Another concern with halothane is sensitization of the myocardium to arrhythmias because of exogenous and endogenous catecholamines. Most arrhythmias associated with halothane anesthesia in children are caused by either hypercarbia or an inadequate level of anesthesia. [52] Up to 10 mug of epinephrine per kilogram body weight may be used with minimal risk of cardiac arrhythmias in pediatric patients. [53]

Halothane is a potent myocardial depressant, which can have profound effects on the neonate and on the child with congenital heart disease. [39] [54] Such depression is responsible for the occasional inability to give critically ill patients sufficient concentrations of anesthetics to provide "anesthesia" without inducing severe hypotension. In this circumstance, the liberal use of short-acting narcotics with light concentrations of halothane generally provides the desired response.

Isoflurane

Isoflurane is purported to have some advantages over halothane: less myocardial depression, preservation of heart rate, and greater reduction in cerebral metabolic rate for oxygen. [55] [56] [57] Although these properties may be beneficial in selected patients, clear advantages have yet to be demonstrated, because equivalent depression of the neonatal heart has been demonstrated with both halothane and isoflurane. [58] [59] The major disadvantage of isoflurane is its noxious smell, which is unacceptable to many pediatric patients, and the greater incidence of airway-related events (laryngospasm, coughing). [48] [49]

Desflurane

Desflurane has a gas partition coefficient similar to that of nitrous oxide. [60] Unfortunately, it has been found to cause an unacceptable incidence of coughing, secretions, and laryngospasm during the gaseous induction of anesthesia in children. [47] Gaseous induction of anesthesia with halothane followed by use of desflurane for maintenance of and recovery from anesthesia may be reasonable. This changeover, unlike a similar change to enflurane or isoflurane, may be clinically important, because the gas partition coefficient clearly favors rapid excretion. This difference would appear to be more important for longer cases, in which there is the potential for the accumulation of potent agent within fat, than for brief cases, in which such accumulation is less likely, or for neurosurgical and spinal fusion procedures, in which early assessment of mental and neurologic status is important.

The MAC for desflurane is age-dependent: 9.2 percent for neonates, 9.4 percent for infants 1 to 6 months old, 9.9 percent for infants 6 to 12 months old, 8.7 percent for 1 to 3 year olds, and 8 percent for 5 to 12 year olds. [60] Interestingly, nitrous oxide does not appear to contribute to the MAC of desflurane to the same degree as it does with other potent inhalation agents. [33] There is virtually no hepatic metabolism of this agent, a feature that clearly sets it apart from the other currently available potent anesthetics. The one major concern is the occasional hypertension and tachycardia resulting from sympathetic activation with rapid increases in inspired desflurane concentration. [61] [62] [63] [64] [65] I have observed this effect primarily in teenagers, but I have seen it in infants as well. A further concern is the potential for carbon monoxide poisoning (also possible with isoflurane) [66] ; this can be prevented by rehydration of Baralyme prior to use with desflurane. [67]

Sevoflurane

Sevoflurane is a potent agent that also has a gas partition coefficient similar to that of nitrous oxide. Broad clinical experience has shown that it is less pungent than isoflurane and desflurane; some investigators believe that it is superior or equivalent to halothane for gaseous induction. [42] [68] [69] [70] [71] As with all potent agents, the MAC is highest in infants: 3 percent for neonates, 3.3 percent for infants 1 to 6 months old, and 2.5 percent for children older than 6 months. [32] [34] My personal experience has been very favorable for induction of anesthesia. I generally induce anesthesia with sevoflurane and then change to halothane for maintenance in order to reduce costs. Metabolic breakdown and release of fluoride do not appear to be a significant issue even with prolonged anesthetic regimens. [32] [44] Several concerns have been raised regarding the production of toxic metabolites resulting from interaction with the carbon dioxide absorbant. [72] [73] Compound A appears to be nephrotoxic, at least in animal models [74] ; conflicting data have been presented regarding the clinical importance of this observation. [73] [75] [76] [77] [78] [79] [80] [81] Studies of low flow (2 L/min) and prolonged anesthesia have not demonstrated

significant alteration of the usual markers of renal function. However, there have been reports of altered renal threshold for glucose after prolonged sevoflurane anesthesia as well as transient albuminuria. [82] [83] The clinical importance of these observations remains to be clarified. It would appear for the moment that the more conservative approach would be to limit exposure to sevoflurane, that is, to use it for induction and then change to another agent for maintenance or to use sevoflurane for brief cases.

One further observation is that I have found inadequate suppression of airway reflexes for bronchoscopy performed with spontaneous ventilation; supplementation with intravenous propofol and/or muscle relaxation seems to be required with sevoflurane. Halothane appears to still be a superior inhalation agent for this procedure.

Drugs Used to Induce Anesthesia

Methohexital

Methohexital is generally administered intravenously at a concentration of 1 percent and a dose of approximately 1 to 2 mg/kg [84] (Ch. 8) . Problems associated with intravenous administration include burning, hiccup, apnea, and extrapyramidal-like movement. Methohexital has a shorter elimination half-life than thiopental. Its principal use in my practice has been by rectal administration for induction of anesthesia and for prolonged sedation during radiologic procedures (10% solution). [85] Usually, 25 to 30 mg/kg per rectum produces sleep within 8 to 10 minutes. I normally limit rectal administration to children, up to 20 kg, 10 months to 5 to 6 years of age, who are still in diapers and who are afraid to separate from their parents. This is a reliable drug for induction of anesthesia and has minimal side effects, the most common being soiling. Occasionally, obstructive apnea occurs, so that a means of ventilating the patient must be available; pulse oximetry is recommended. [86] Because it can cause seizures, methohexital is contraindicated in patients with temporal lobe epilepsy. [87] Children receiving seizure medications generally require larger doses.

Thiopental

Intravenous bolus administration of 2.5 percent thiopental, 5 to 6 mg/kg, is sufficient to induce anesthesia in most healthy, unpremedicated pediatric patients [85] [89] (Ch. 8) . Termination of effect occurs through redistribution of the drug in fat; thiopental should be used with caution in children who have low fat stores, such as neonates or malnourished infants. Limiting the total dose to 10 mg/kg or less in older patients minimizes the possibility of prolongation of anesthesia caused by residual barbiturate sedation. Thiopental (30 mg/kg per rectum) may also be administered rectally if methohexital is contraindicated.

Propofol

Propofol is highly lipophilic and rapidly distributes into and out of the vessel-rich organs; its rapid redistribution, hepatic glucuronidation, and high renal clearance account for the rapid termination of its effect. As with barbiturates, the induction dose is higher in younger patients (2.9 mg/kg for infants <2 y) than in older patients (2.2 mg/kg for patients 6-12 y). [90] [91] [92] This may be related in part to a larger central volume and greater clearance in the younger patients. [93] The major drawback of propofol is pain on intravenous administration, particularly through small veins. As little as 0.2 mg/kg lidocaine (mixed with the propofol) has been effective in reducing but not eliminating this discomfort. [94] Another method for minimizing pain is to use a small-gauge (22- to 24-gauge) catheter and to administer the drug through a large antecubital vein. [91] Propofol is particularly useful for the brief and repeated sedation needed for radiotherapy in children with central venous lines; a constant infusion is also a useful means for sedating children undergoing radiologic procedures. [95] A modest reduction in systolic blood pressure often accompanies bolus administration. [96] Propofol has been associated with a reduced rate of postoperative vomiting. [97] [98]

Ketamine

Ketamine, a phencyclidine derivative, causes central dissociation while providing analgesia and amnesia (Ch. 9) . Intravenous administration of doses as low as 1.0 mg/kg produce sedation sufficient for a smooth transition to general anesthesia. Larger doses (10 mg/kg IM) provide sufficient analgesia for insertion of invasive monitoring devices prior to induction of anesthesia (cardiac surgery) or in patients having limited venous access. The patient-to-patient variability in response to this drug is relatively large. A major side effect, increased production of secretions, usually requires administration of an antisialagogue. Other undesirable side effects include vomiting and dreaming; the occurrence of dreaming may be obviated by concomitant administration of a benzodiazepine. Ketamine is useful for induction of anesthesia in the hypovolemic patient.

Contraindications to the use of ketamine in children include the presence of an active upper respiratory tract infection, increased intracranial pressure, open-globe injury, and the presence of a psychiatric or seizure disorder. Ketamine does not preserve the gag reflex and thus should not be used as the sole anesthetic for patients with a full stomach or hiatus hernia. [99] Ketamine may be administered rectally (10 mg/kg), orally (6-10 mg/kg), or intranasally (3-6 mg/kg). [100] [101] [102] [103] [104] The combination of oral ketamine (4-6 mg/kg), oral midazolam (0.4 mg/kg), and oral atropine (0.03 mg/kg) provides a well-sedated patient.

Sedative-Hypnotic Drugs

These drugs are discussed in detail in Chapter 9 .

Droperidol

The primary use of droperidol in pediatrics is as an antiemetic; doses as high as 75 mug/kg have been recommended for patients undergoing surgery for strabismus, although prolonged sedation may result. [105]

Benzodiazepines

Oral absorption of diazepam is more rapid in children than in adults; 0.1 to 0.3 mg/kg orally usually provides excellent sedation within 1 hour. Intravenous administration is painful and is not well tolerated; diazepam may also be administered rectally. Because the liver is the main site of degradation, this medication should be given with caution to any patient with hepatic disease. [106] Diazepam has an extremely long half-life in neonates (80 h) and may be contraindicated until the infant is 6 months of age or until hepatic metabolic pathways have matured. [107]

Midazolam is water soluble and therefore is not painful on intravenous administration. Midazolam is the only benzodiazepine approved by the U.S. Food and Drug Administration for use in neonates. It should be noted that because of its water solubility, midazolam takes three times as long to reach a peak electroencephalographic effect when compared with the more fat-soluble diazepam. The clinical importance of this finding is that one should wait at least 3 minutes between intravenous doses in order to avoid a "stacking" of effect. [108] The short elimination half-life (~2 h) as compared with diazepam (18 h) offers an advantage for use as a premedicant in children. Midazolam is rapidly absorbed after intramuscular (0.1-0.15 mg/kg, maximum 7.5 mg), oral (0.5-0.75 mg/kg, maximum 20 mg), rectal (0.75-1.0 mg/kg, maximum 20 mg), nasal (0.2 mg/kg), or sublingual (0.2 mg/kg) administration. [109] [110] [111] [112] [113] There is less patient upset following sublingual than following nasal administration. [114] The major problem with oral or sublingual administration is the strong aftertaste. A manufactured, flavored oral formulation is now available. The sedation achieved is usually not sleep (even with doses
3.0 mg/kg rectal) [113] but rather it is a compliant, happy state. If sleep occurs, a relative overdose has probably been given. Mid-azolam must always be used with caution when it is administered with narcotics because of the potential for respiratory depression. [115] One important interaction is that erythromycin produces a clinically important delay in midazolam metabolism because of cytochrome P-450 inhibition; either midazolam should be avoided or the dose should be reduced by 50 percent in such patients. [116] One further concern is that, with nasal administration, there is the theoretical possibility of CNS toxicity as a result of drug entering the CNS along neural connections (olfactory nerves). [117] Because neurotoxicity has never been examined and because most children cry with nasal administration, I believe that this route should generally be avoided. [118]

Narcotics

Morphine is the oldest commonly used long-acting narcotic (Ch. 10) . Its use in neonates remains controversial because early studies carried out in newborn infants suggest that morphine produces greater respiratory depression than meperidine. Greater brain levels of morphine were found in neonatal than in adult rats; this finding suggests that permeability of the blood-brain barrier may account in part for the apparent sensitivity of the human neonate to morphine. [119] This rationale led to the common belief that infants are sensitive to the effect of narcotics. More recent studies found age-dependent pharmacokinetics. The newborn has a lower clearance of morphine, and therefore, a lower dose results in higher plasma values because of a longer elimination half-life. [120] Term infants older than 10 days may clear morphine more rapidly than adults.

The issue of respiratory sensitivity and the age at which it decreases in humans has yet to be resolved; animal studies suggest that there appears to be a difference between morphine and fentanyl that may not relate to transport of drug into the brain. [121] Some of these effects may therefore be due to changes in pharmacodynamics rather than to maturation of the blood-brain barrier. Until further studies are carried out, morphine should be administered with caution in the neonate and premature infant who is not in the intensive care unit. Infants older than 6 months probably have a normal adult response to morphine.

Meperidine, a long-acting synthetic narcotic, received great attention when it was found to cause less respiratory depression in newborns than morphine. [122] This difference may be related, in part, to the finding that meperidine is much more lipophilic than morphine and therefore is able to cross the blood-brain barrier more readily. Thus, effects of the blood-brain barrier would be much less significant for meperidine than for morphine. As with all drugs administered to neonates, there is a large patient-to-patient variability in metabolism and response. [123] Meperidine may not be appropriate for long-term administration because of the accumulation of the toxic metabolite normeperidine. [124]

Fentanyl is the most commonly used narcotic in infants and children. [125] Its major advantages relate to its rapid onset and brief duration of action. This narcotic is more lipophilic than meperidine. In essence, the effects of the blood-brain barrier are of no importance with the use of this narcotic. Infants older than 3 months had a lower incidence of apnea than adults given fentanyl [126] ; animal studies further confirm pharmacodynamic differences between fentanyl and morphine. [121] Termination of the effect of low doses of fentanyl results primarily from redistribution, whereas termination of the effect of high doses depends on elimination. High doses of fentanyl achieve properties of long-acting narcotics.

Fentanyl induces a very stable cardiovascular response while providing an anesthetic state. The dosage required to produce anesthesia varies considerably, depending on the patient's age, the surgical procedure, the health of the patient, and the use of anesthetic adjuvants. [127] Neonates having abdominal surgery have a longer fentanyl half-life than neonates undergoing other procedures; hepatic blood flow--and factors that greatly increase or decrease hepatic blood flow--may alter the pharmacokinetics of this drug. [128] Impaired hepatic function may also play a role in altered kinetics with increased intra-abdominal pressure. [129] Therefore, the pharmacokinetic and pharmacodynamic profile is very different and more variable for neonates than for older children. A dose of 12.5 mug/kg produces anesthesia in full-term neonates undergoing abdominal surgery, whereas higher doses (30-100 mug/kg) have been used for cardiac surgery. These doses are safe in children whose ventilation will be controlled postoperatively; much lower doses (2-10 mug/kg) should be used with other anesthetics if ventilation is not to be controlled postoperatively. Because the cardiac output of neonates is determined by heart rate, fentanyl-induced

---

bradycardia may require concomitant administration of a vagolytic drug, such as atropine or pancuronium.

Transoral mucosal administration (5-15 mug/kg) results in reasonably rapid absorption, with peak blood levels achieved within 15 to 30 minutes. [130] Children may

have a lower bioavailability compared with adults. [131] Because vomiting and desaturation have been reported, [132] [133] [134] it is likely that this form of premedication will be of greater use for painful procedures outside the operating room and for postoperative analgesia. [135] [136] Our experience has been that the incidence of serious adverse effects (desaturation, vomiting) prior to anesthetic induction was zero in the 21 children in whom my colleagues and I induced anesthesia within 10 minutes of completion of the Oralet. [137] It is likely that the adverse effects increase with a longer time between completion and induction of anesthesia; these effects may also relate to the dose (mug/kg) administered.

Alfentanil is more rapidly eliminated than fentanyl; its pharmacokinetics is independent of dose. [138] This feature may provide a margin of safety because the greater the administered dose, the greater the elimination. Children may have increased clearance compared with adults. [139] As with any narcotic, there is important patient-to-patient variability in pharmacokinetics and pharmacodynamics in neonates and in patients with impaired hepatic blood flow. [140] [141]

Sufentanil has been used primarily for cardiac anesthesia; age-dependent kinetics is also evident, particularly during the first month of life. [142] Children are able to clear sufentanil more rapidly than are adults. This drug must be administered with caution, because severe bradycardia and asystole have been reported when a vagolytic agent was not administered simultaneously. [143] This narcotic has also been administered nasally as a premedicant (2 mug/kg); however, desaturation may follow. [114]

Muscle Relaxants

These drugs are discussed in detail in Chapter 12 .

Depolarizing Muscle Relaxants

Succinylcholine is highly water soluble and rapidly redistributes into the extracellular fluid volume. For this reason, the dose required for intravenous administration in infants (2.0 mg/kg) is approximately twice that for older patients (1.0 mg/kg). Succinylcholine is the only short acting relaxant that is effective when given intramuscularly. Reliable muscle relaxation occurs within 3 to 4 minutes after 5 mg/kg in infants and 4 mg/kg intramuscularly in children older than 6 months. [144] The skeletal muscle relaxation produced by intramuscular administration may last up to 20 minutes; more rapid onset is not achieved by splitting the dose into two injections or by changing the concentration. In an emergency situation, succinylcholine may be administered intralingually. [145]

Cardiac arrhythmias frequently follow intravenous administration, especially during halothane anesthesia. Intravenous administration of atropine (but not intramuscular administration of the drug as a premedication) reduces the incidence of arrhythmias. Cardiac sinus arrest may follow the first dose of succinylcholine, but it is more common after repeated bolus administration; this may occur in patients of any age. Although the incidence of bradycardia is low in older patients, I have observed one 13-year-old patient who developed asystole for approximately 30 to 45 seconds following a single dose of succinylcholine administered with thiopental but not atropine; this occurred prior to intubation and with 100 percent oxygen saturation. Therefore, atropine probably should be given intravenously just prior to the first dose of succinylcholine in all children, including teenagers.

Succinylcholine has received much attention because of the severity of its possible complications. The potential for rhabdomyolysis, hyperkalemia, masseter spasm, and malignant hyperthermia suggests that routine use of succinylcholine should be abandoned. Two studies, flawed because of their retrospective nature, reported a 1 percent incidence of masseter spasm after administration of succinylcholine during halothane anesthesia. [146] [147] This has not been my experience. Increased jaw muscle tone following succinylcholine has been observed; masseter spasm may be a normal variant. [148] Masseter tetany, which prevents any mouth opening, may represent an extreme variation in increased masseter muscle tone and may be the reaction associated with malignant hyperthermia. I have observed this twice; neither patient developed malignant hyperthermia, but one did have creatine phosphokinase values of more than 20,000 IU the next morning.

With the foregoing cautions in mind, one should not yet abandon succinylcholine, which is the only commercially available short-acting muscle relaxant that provides a dependable, rapid onset of action. However, this drug should be limited to patients who have a full stomach, to treat laryngospasm, and intramuscularly to patients with difficult intravenous access when control of the airway is deemed essential. Until a short-acting nondepolarizing relaxant becomes available, succinylcholine remains the drug of choice when rapid onset of muscle relaxation is needed.

Nondepolarizing Muscle Relaxants

Comparison of infants with older children or adults regarding their response to nondepolarizing muscle relaxants shows that infants are generally more sensitive to these drugs and that their response varies to a greater degree. Although the relationship among volume of distribution, maturation of renal function, and neuromuscular blockade (e.g., actual dose of *d*-tubocurarine per kilogram body weight) is similar for patients of all ages, the greater volume of distribution of the neonate results in a slower rate of excretion and hence a prolongation of the effect. Neuromuscular blockade occurs at a lower blood concentration. [149] This observation is probably true for all nondepolarizing muscle relaxants.

The choice of nondepolarizing muscle relaxant depends on the side effects desired and the duration of muscle relaxation required. If tachycardia is desired (e.g., with fentanyl anesthesia), pancuronium would be the choice. Vecuronium and atracurium are useful for shorter procedures in infants and children or may be administered as a constant infusion. [150] [151] The methods of excretion of atracurium and cisatracurium (Hofmann elimination and ester hydrolysis)

---

make these relaxants particularly useful in newborns. [152] [153] Vecuronium is valuable because no histamine is released; however, the duration of action is prolonged in newborns, a feature that makes it similar to pancuronium. [154]

Mivacurium, a short-acting nondepolarizing relaxant, may offer the advantage of providing satisfactory conditions for endotracheal intubation for brief surgical procedures. A dose of 0.2 to 0.3 mg/kg provides adequate relaxation within 2 minutes; spontaneous 95 percent twitch recovery occurs within 20 minutes. [155] This drug is ideal for administration by constant infusion because there does not appear to be any drug accumulation. Pipecuronium and doxacurium are long-acting, nondepolarizing relaxants; their role has yet to be defined for children, but in general, the duration of action is shorter than in adults. [156] [157]

Rocuronium is the newest intermediate acting nondepolarizing relaxant. It has a clinical profile similar to those of vecuronium and atracurium, [158] [159] but it offers the advantage that it can be administered intramuscularly. One study observed that acceptable conditions for intubation are produced within 3 to 4 minutes following 1,000 mug/kg intramuscular rocuronium in infants and 1,800 mug/kg for children older than 1 year of age; these effects were more dependable with deltoid rather than quadriceps muscle injection. [160] This onset time is similar to that produced with intramuscular succinylcholine; however, the duration of action is approximately 1 hour, a feature that could be a distinct disadvantage for a brief procedure. The onset of neuromuscular blockade is also nearly the same as with succinylcholine when administered intravenously but in very high doses (1,200 mug/kg). I have used this dose with thiopental (5-6 mg/kg) for rapid sequence induction following preoxygenation in patients in whom succinylcholine could present an added risk. Most patients can be intubated at 45 to 60 seconds. The disadvantage is that the duration of action is 60 to 90 minutes, a property that limits its usefulness to either long cases or acceptance that prolonged neuromuscular blockade is more desirable than the potential risk from succinylcholine.

Table 59-2 provides commonly recommended guidelines for dosages. Because of the extreme variability in response, the doses of long-acting muscle relaxants used for infants should be titrated carefully, starting with one-third to one-half the usual dose used in older patients. I recommend antagonism of neuromuscular blockade in all neonates and small infants, even if they have recovered clinically, because any increase in the work of breathing may cause fatigue and respiratory failure. Useful signs of reversal are the ability of the infant to lift the legs and arms and recovery of the train-of-four response to peripheral nerve stimulation. [161]

Premedication

The many published reports on premedication have produced approximately the same results; almost all sedatives are effective. The important issue is effectiveness for individual anesthesiologists at their own institutions. The need for premedication must be individualized according to the underlying medical conditions, the length of surgery, the desired induction of anesthesia, and the psychologic makeup of the child and family. Premedication normally is not necessary for the usual 6-month-old child, but it is warranted for the 10- to 12-month-old who is afraid to be separated from the parents. Induction of anesthesia with a rectally administered

anesthetic (e.g., methohexital) allows the child to fall asleep in a parent's arms. Oral midazolam generally results in a very compliant child who will be separated from the parents without crying. A review of prior anesthetic records is particularly helpful in ascertaining how the child has responded in the past. The most difficult patients are those who have had many surgical procedures. This type of patient may require premedication the night before and the morning of surgery.

TABLE 59-2 -- Recommended Guidelines for Doses of Nondepolarizing Muscle Relaxants and Their Antagonists in Children

	MAINTENANCE DOSE (ED_{95}) (mg/kg) DURING ANESTHESIA WITH		SUGGESTED DOSE (mg/kg) FOR TRACHEAL INTUBATION ($2 \times ED_{95}$)
	N_2O/O_2	*HALOTHANE*	
Muscle relaxant [a]			
d-Tubocurarine	0.60	0.30	0.80
Pancuronium	0.08	0.06	0.10-0.15
Metocurine	0.34	0.15	0.50-0.60
Atracurium	0.30	0.20	0.50-0.60
Cisatracurium	0.10	0.080	0.10
Vecuronium	0.08	0.06	0.10-0.15
Mivacurium	0.10	0.10	0.20-0.25
Doxacurium	0.030	0.030	0.050-0.060
Pipecuronium	0.080	0.080	0.080-0.120
Reversal agents [b]			
Edrophonium	(0.3-1.0 mg/kg) + atropine (0.01-0.02 mg/kg)		
Neostigmine	(0.02-0.06 mg/kg) + atropine (0.01-0.02 mg/kg)		

[a] The response of premature and term neonates (who may be more sensitive to the drugs) to muscle relaxants varies greatly from patient to patient. Therefore, all doses should be titrated to response.
[b] The dose of reversal agent given to antagonize nondepolarizing neuromuscular blockade should be determined by the degree of residual neuromuscular blockade (i.e., dose should be titrated to clinical effect).

Premedications may be administered orally, intramuscularly, intravenously, rectally, sublingually, or nasally. Although most of these routes are effective and reliable, each has drawbacks as well. [162] Oral premedications have a slow onset. Intramuscular medications hurt and may result in sterile abscess. Intravenous medications may hurt during injection or at the start of infusion. Rectal medications sometimes make the patient feel uncomfortable, cause defecation, and occasionally burn. Nasal medications can be irritating, although absorption is rapid. Sublingual medications may provide the best compromise, that is, relatively rapid absorption without causing pain. Drug taste and patient cooperation are the main determinants of success. There is still no ideal premedication or route of administration.

Anticholinergic drugs are not routinely administered intramuscularly to children because these agents are painful on administration and do not significantly reduce laryngeal reflexes during induction of anesthesia. On the other hand, atropine (0.02 mg/kg) administered orally or intramuscularly less than 45 minutes before induction, does reduce the incidence of hypotension during induction with potent inhaled anesthetics, but only in infants younger than 6 months. [163] Oral atropine may be reasonable for these infants.

Histamine$_2$ (H_2)-blocking drugs are frequently used to reduce the potential for pulmonary aspiration of acid gastric contents. Because the true incidence of pulmonary aspiration of gastric contents during routine elective pediatric surgery is approximately 1 in 1,000 cases, histamine blocking agents and metoclopramide should be reserved for patients at greatest risk: those with gastroesophageal reflux, potentially difficult airway problems, endoscopic procedures, a history of previous esophageal surgery, procedures performed in the Trendelenburg position, and urgent but not emergency nonelective procedures. [164]

ANESTHESIA FOR PEDIATRIC AND NEONATAL SURGERY

Preoperative Preparation

The preoperative visit and preparation of the child for surgery are more important than the choice of premedication. [165] During this time, the anesthesiologist evaluates the medical condition of the child, the needs of the planned surgical procedure, and the psychologic makeup of the patient and family. The anesthesiologist also formulates the approach to induction of anesthesia, explains the possibilities regarding induction, and helps to soothe family concerns. Because anxiety felt by the parents may be transferred to the child, any practice that reduces anxiety in the parents may also reduce anxiety in the child. Therefore, the anesthesiologist should explain in great detail what the child and family can expect and what will be done to ensure the utmost safety. The more information the parents and child have, the more easily they will deal with the stress of surgery and hospitalization. Presurgical programs such as videotapes, literature, and hospital tours also help. [162] [166] [167] [168]

After chart review, physical examination, and the furnishing of information regarding the approximate time and length of surgery, the anesthesiologist should describe to the child what anesthesia is and what will be done to ensure good care. The purpose of all monitoring devices should be explained to the patient and family. Children need to understand that none of these devices will hurt and that they can watch during application. If an intravenous line will be started, the child needs to be told that "numbing" medicine will be used. Any special monitoring devices, such as an arterial line, a central venous line, a nasogastric tube or urine catheter, should also be described to the parents, with assurances that these devices will be inserted after induction of anesthesia. Part of this informed consent is also a description of the anesthesiologist's role in the operating room. It is vital to explain to the family that the anesthetic "prescription" will be tailored to meet their child's medical as well as surgical needs. I like to use the phrase "anesthetic prescription" because we are physicians, just like surgeons or pediatricians, and it is important for families to clearly understand that.

Children think in very concrete terms, so care must be taken to avoid misunderstandings. It is important to explain to children that the sleep caused by anesthetic drugs differs from normal sleep. They should know that the anesthesia medicines keep them from awakening during surgery and from remembering the operation. It should also be explained to the children that the anesthesia medicines will be removed at the end of surgery, and that they will then wake up and return to their parents. This type of explanation does not require a significant amount of time and goes a long way toward reassuring the child and family about the quality of care provided.

The issue of pain must not be avoided. Children need to be reassured that everything possible will be done to minimize pain on awakening. Therefore, it should be stressed that pain medications will be administered and that local infiltration nerve blocks, patient-controlled analgesia, or continuous epidural or caudal infusions will be used. Recovery room or intensive care must also be described so that there are no surprises.

Fasting

The approach to preoperative fasting has undergone extensive reevaluation. Several studies have found no difference in gastric residual volume or pH in children allowed to ingest unlimited clear liquids (water, apple juice) up until 2 to 3 hours prior to anesthetic induction compared with standard fasting. [169] [170] This provides a more humane approach for both children and their parents without increasing the risk of pulmonary aspiration of gastric contents. [164] Infants and young children have a higher metabolic rate and a larger ratio of body surface area to weight than adults and become dehydrated more easily than adults. The major advantage of the liberalized fasting guidelines may be a reduced incidence of hypovolemia at the time of anesthetic induction. My approach is to restrict milk and solids after midnight but to allow unlimited clear fluids up to 3 hours prior to induction of anesthesia; if there is a change in the operative schedule, I still feel comfortable with 2 hours of fasting (Table 59-3) . Infants who are breast-fed may have their last breast milk 4 hours prior to anesthetic induction. I consider breast milk to be equivalent to formula because the fat content

TABLE 59-3 -- Fasting Guidelines for Pediatric Patients

AGE	FASTING TIME (h)	
	MILK AND SOLIDS	*CLEAR LIQUIDS*
< 6 mo	4	2
6-36 mo	6	3
> 36 mo	8	3

varies with maternal diet, and delayed gastric emptying may result. [171]

Induction of Anesthesia

The method of inducing anesthesia is determined by a number of factors: the medical condition of the patient, the surgical procedure, the level of anxiety of the child, the ability to cooperate and communicate (because of age, mental handicap, language barrier), the presence or absence of a full stomach, and others. [172]

Inhaled Induction of Anesthesia via Mask

Infants

Mask inductions are usually used in infants younger than 10 to 12 months because this age group readily separates from the parents. Induction by mask is accomplished most easily by holding the end of the anesthesia circuit (a Mapleson D circuit is preferred by some anesthesiologists for patients less than 10 kg) in a cupped hand over the infant's face; the other hand can adjust the concentration of anesthetic. Allowing the neonate and small infant to suck on a rubber nipple or on a finger generally prevents crying during induction of anesthesia. As the infant loses consciousness, the anesthesia mask is added to improve delivery and to decrease operating room pollution. This is the most dangerous time during induction, because it is very easy to misjudge the depth of anesthesia and to depress the heart. Once anesthesia has been induced, it is critical to rapidly reduce the inspired concentration of halothane (1.0-1.5%) or sevoflurane (2-2.5%) and to keep it at this level or lower until an intravenous line is in place. After the intravenous line is inserted, one may either deepen the plane of anesthesia or add a muscle relaxant. *It is*

dangerous to proceed directly to a deep plane of anesthesia without having an intravenous line in place; without this precaution, resuscitation would be difficult.

The second most dangerous point occurs immediately after endotracheal intubation. If the vaporizer has not been closed prior to laryngoscopy, it is easy to forget that a high inspired concentration is being delivered and, during the checking for breath sounds, perhaps to give an overdose of inhaled anesthetics. Therefore, the prudent anesthesiologist discontinues all anesthetics until laryngoscopy and endotracheal intubation have been completed. With a Mapleson D circuit, a high concentration of anesthetic can be delivered more easily because the anesthetic enters directly at the airway. In contrast, changes made at the vaporizer of a circle system take a longer time to achieve equilibration with the circuit; therefore, the inspired concentration of anesthetic rises more gradually. Particular caution should be used when changing from sevoflurane to halothane because the myocardium-depressant effects of these drugs are additive.

Older Pediatric Patients

Successful, psychologically atraumatic induction of anesthesia by mask in the older pediatric patient requires that the patient understand and cooperate. Several different techniques may be employed. One method is to play a game. For example, the smaller child may be asked to "blow up the balloon." The slightly older child (up to adult) may be receptive to hypnotic suggestions during induction. The young child may be susceptible to a suggestion that the anesthesia mask is an "airplane pilot's mask" and that the smell of halothane or sevoflurane is "oxygen" or "aviation fuel." During this type of induction, the operating room must be free of distractions, and the anesthesiologist must be able to communicate with the child. The use of constant conversation and a 0.25 to 0.5 percent increase in the inspired concentration of anesthetic every third or fourth breath usually produce a smooth transition to general anesthesia. Often the patient will breath-hold. If so, one should not attempt to assist respirations, because that action often elicits coughing or laryngospasm. The anesthesiologist must be certain, however, that airway obstruction and laryngospasm can be differentiated from breath-holding. Observing the chest wall and abdomen helps to identify airway obstruction, which creates a rocking-type movement of the chest and abdomen (when the diaphragm descends, the abdomen appears to expand, but the chest does not). As soon as the child loses consciousness, the inspired concentration of anesthetic can be reduced, and an intravenous line can be inserted. Should laryngospasm occur, closing the pop-off valve and creating approximately 10 cm H_2O of positive pressure while allowing the child to breathe spontaneously often allows gas exchange. If this procedure is not effective, administration of rapid positive-pressure breaths, while avoiding inflation of the stomach, often disrupts the laryngospasm. Obviously, administration of a muscle relaxant also breaks the laryngospasm; succinylcholine remains the agent of choice in an emergency situation.

A third method of induction uses flavored masks. Various flavored scents (Loran Oils, Inc., Lansing, Mich) are available to reduce the noxious smell of the anesthetics; the child can select a favorite scent.

The fourth method, the single-breath technique, requires a very cooperative patient who can follow instructions. Using an unattached anesthesia mask, the anesthesiologist should demonstrate the procedure to the child, who then rehearses the following steps: a full inspiration, a full expiration, placement of the mask on the child's face at exactly the end of expiration, another full inspiration held as long as possible, and then normal breathing. Prior to induction, the anesthesia circuit is filled with either 5 percent halothane or 8 percent sevoflurane in 60 percent nitrous oxide. The circuit

bag must be emptied and filled several times so that the entire circuit is filled with 5 percent halothane or 8 percent sevoflurane. If the patient fully cooperates, this procedure generally produces loss of the eyelid reflex in less than 1 minute. Occasionally, a patient does not take a full breath or becomes frightened. If the child is partially anesthetized, induction takes slightly longer, but the child usually does not remember the induction. If the child panics prior to inhalation of anesthetic, induction should not be forced, and an alternative plan should be undertaken.

The Difficult Airway

The child facing a potentially difficult laryngoscopic procedure should have, at most, light sedation before induction of anesthesia by mask in order to maintain spontaneous respiration (Ch. 39) . In this way, breath sounds can be used to guide successful tracheal intubation. When normal airway anatomy cannot be confirmed visually, placing a stylet in the endotracheal tube and bending the tip of the tube acutely allow placement of the tip of the tube in the midline just posterior to the epiglottis. One can then listen for breath sounds exiting from the end of the endotracheal tube. If the patient is not breathing spontaneously, this advantage may be lost. Fiberoptic techniques are also valuable in this circumstance. Generally, the nasal approach, with the child's head flat on the table (no anterior head displacement) is the optimal route and position. The laryngeal mask airway and fiberoptic intubation through the laryngeal mask airway are reasonable alternatives. [173]

The Child With Stridor

The child with intrathoracic airway obstruction has expiratory stridor and prolonged expiration (bronchiolitis, asthma, intrathoracic foreign body). In contrast, the child with extrathoracic upper respiratory obstruction has inspiratory stridor (epiglottitis, laryngotracheobronchitis, laryngeal foreign body). When agitated or crying, such patients have dynamic collapse of the airway (Fig. 59-7) (Figure Not Available) , which can markedly worsen airway obstruction and may lead to respiratory failure and hypoxemia. Therefore, events that can upset the child (drawing of blood gases, venipuncture for blood tests, and separation from the parents) must be minimized.

I have found the following procedure effective for inducing anesthesia in the child with stridor. In order to minimize patient upset, the patient is brought to the operating room with the mother or father, who holds the child during the induction. Induction of anesthesia with halothane or sevoflurane in oxygen by mask is the preferred method, because maintaining spontaneous respiration is critical. As soon as the child loses consciousness, the parent is escorted out of the operating room. With the patient lightly anesthetized and after infiltration of local anesthetic, an intravenous line is inserted. This allows withdrawal of blood samples and deepening of the plane of anesthesia. Hydration is begun with lactated Ringer solution (10-20 mL/kg), and atropine (0.02 mg/kg) is given. If stridor worsens or if mild laryngospasm occurs, the pop-off valve is closed sufficiently to develop 10 cm H_2O of positive end-expiratory airway pressure. This procedure relieves most instances of airway obstruction caused by dynamic collapse of the airway when the child attempts to inspire against an obstructed airway (Fig. 59-8) (Figure Not Available) . As the level of anesthesia deepens, gentle assisting of ventilation may be necessary; however, maintaining spontaneous respiratory efforts is important.

Any child with airway obstruction has a long, slow induction of anesthesia before becoming sufficiently anesthetized to allow laryngoscopy and endotracheal intubation. The issue of a full stomach is secondary to the airway problem; rapid induction of anesthesia is contraindicated in these patients.

The child with laryngotracheobronchitis or epiglottitis usually requires an uncuffed endotracheal tube that is 0.5 to 1.0 mm (internal diameter) smaller than normal; the use of a stylet facilitates its insertion.

Figure 59-7 (Figure Not Available) The infant and young child have highly compliant airway structures. With normal respiration, some dynamic collapse of the extrathoracic upper airway occurs (broken line). When a child has upper airway obstruction, as in epiglottitis, laryngotracheobronchitis, and extrathoracic foreign body (hatched area), and struggles to breathe against this obstruction, dynamic collapse of the trachea increases. This increase in dynamic collapse (dotted line) augments mechanical obstruction of the airway. Therefore, until the airway is secured, it is important to avoid procedures that will upset the child. *(Modified from Cote and Todres [250])*

Figure 59-8 (Figure Not Available) When a child has upper airway obstruction caused by laryngospasm (A) or mechanical obstruction (B), application of approximately 10 cm H_2O of positive end-expiratory pressure (PEEP) (arrows) during spontaneous breathing often relieves obstruction. That is, PEEP helps to keep the vocal cords apart (A) and the airway open (B, broken lines). If this simple maneuver does not relieve obstruction, more vigorous positive-pressure ventilation may be necessary. Airway obstruction caused by the tongue requires insertion of an appropriately sized oral airway. *(Modified from Cote and Todres [250])*

The surgical team should be mobilized and prepared to perform an emergency tracheotomy should total airway obstruction occur and mask ventilation or endotracheal intubation not be possible. A detailed discussion of airway problems is beyond the scope of this chapter, but it is addressed in Chapter 39 .

Rectal Induction

Many different medications may be administered rectally for induction of anesthesia (methohexital, thiopental, ketamine, midazolam). The main advantage of this approach is that the child falls asleep in the parent's arms or, as is the case with midazolam, separates atraumatically from the parents. [85] [113] [174] This technique is no more intimidating than taking a rectal temperature, but it is generally reserved for children still in diapers. Care must be taken not to allow the child to see the rectal catheter or syringe, which would appear very large to the child. My experience has been that rectal administration of 10 percent methohexital (25-30 mug/kg) reliably induces anesthesia within 8 to 10 minutes. [85] Oxygen desaturation is not usually a problem unless the child's head is allowed to flex forward, thereby causing airway obstruction. [86]

Intramuscular Induction

Many medications, such as methohexital (10 mg/kg), ketamine (1-10 mg/kg), or midazolam (0.1-0.15 mg/kg), are administered intramuscularly for premedication or induction of anesthesia. The main advantage of this route of administration is its reliability; the main disadvantage is that it is painful.

Intravenous Induction

Intravenous induction of anesthesia is the most reliable and rapid technique. The main disadvantage is that starting an intravenous line can be painful and threatening for the child. An intravenous induction may be preferable when induction by mask is contraindicated (e.g., in the presence of reflux esophagitis or a full stomach). A two-needle technique using a butterfly-type catheter with a 25-gauge needle is suitable for induction of anesthesia, followed by placement of an intravenous catheter once anesthesia is safely induced. Older children often allow insertion of an intravenous catheter after administration of 50 percent nitrous oxide and local anesthetic. It is important to emphasize to the child that this will not be an excessively painful procedure. Occasionally, children cry with local anesthetic infiltration and become hysterical when they see the intravenous catheter. Two maneuvers help to minimize this response: (1) do not allow the patient to see the catheter; (2) puncture the anesthetized area with a needle, ask the child to look at the needle, and then ask whether there is any sensation. Often the child is astounded at the lack of pain and stops crying. The use of eutectic mixture of local anesthetic (Emla) cream, if time permits, may also provide analgesia without the need for a painful injection. [175]

The Patient With a Full Stomach

The child with a full stomach must be treated the same as an adult with a full stomach; that is, they both should undergo a rapid-sequence induction of anesthesia and application of cricoid pressure. Because oxygen consumption is much greater, hemoglobin desaturation occurs more rapidly in the child than in the adult and more rapidly in the infant

---

than in the child. [12] Additionally, the child may be uncooperative and may refuse to breathe oxygen prior to induction of anesthesia, that is, refuse preoxygenation. In this circumstance, the best that can be done is to enrich the environment with oxygen. Additional equipment that should be available includes two suction catheters (if one becomes blocked, another would be immediately available) and two laryngoscopes with handles (if the bulb, contact, or battery fails, another would be immediately available). While the child is breathing oxygen, atropine (0.02 mg/kg,
0.6 mg) may be administered intravenously to prevent reflexinduced or succinylcholine-induced bradycardia and to delay the bradycardia of hypoxemia should any of these events occur. Because of its rapid onset of neuromuscular blockade, succinylcholine is still the muscle relaxant of choice in this circumstance and should be administered in a dose of 1 to 2 mg/kg immediately after thiopental (5-6 mg/kg). [88] Cricoid pressure is applied gently after the child loses consciousness. Children should be told that they may "feel someone touching you on the neck" as they fall asleep and that this is "normal." In children, the head-up position does not significantly increase protection from pulmonary aspiration of acid gastric contents. [176] In patients in whom succinylcholine is contraindicated, rocuronium (1.2 mg/kg) often provides adequate conditions for intubation within 30 seconds of administration; however, the duration of neuromuscular blockade is 60 to 90 minutes [177] [178] [179] (Ch. 39).

Endotracheal Tubes

For most children, the proper size of endotracheal tube and the proper distance of insertion relative to the alveolar ridge of the mandible or maxilla are moderately constant. Published formulas are estimates that may need to be modified based on physical examination or unusual patient size. Table 59-4 provides a guide to choosing the proper size of endotracheal tube and the recommended distance for insertion. Uncuffed endotracheal tubes are preferred for patients younger than 10 years; a small gas leak should be evident around the tube at peak inflation pressures of 20 to 30 cm H_2O.

Intravenous Fluid and Transfusion Therapy

Intravenous Fluids

The approach to intravenous fluid therapy in the child must consider the high metabolic demands and the high ratio of body surface area to weight (Ch. 45) . The basis for calculating maintenance fluids derives from data by Holliday and Segar, [180] who found that daily fluid requirements depend directly on metabolic demand, specifically, that 100 mL of water is required for each 100 calories of expended energy. Relating this to weight produces hourly fluid requirements of 4 mL/kg for children up to 10 kg, an additional 2 mL/kg for each kilogram above 10 kg up to 20 kg, and an additional 1 mL/kg for each kilogram above 20 kg (Table 59-5) . Thus, a 25-kg child would require 65 mL/h, that is, (10 × 4) + (10 × 2) + (5 × 1) = 65. This amount does not include fluid deficits, third-space losses, modifications because of hypothermia or hyperthermia, or requirements caused by unusual metabolic demands. In general, deficits caused by restriction of food and fluids are calculated

TABLE 59-4 -- Recommended Sizes and Distance of Insertion of Endotracheal Tubes and Laryngoscope Blades for Use in Pediatric Patients

AGE OF PATIENT	RECOMMENDED		
	INTERNAL DIAMETER OF ENDOTRACHEAL TUBE (mm)	*SIZE OF LARYNGOSCOPE STRAIGHT BLADE*	*DISTANCE OF INSERTION[a] (cm)*
Premature (<1,250 g)	2.5	0	6-7
Full term	3.0	0-1	8-10
1 y	4.0	1	11
2 y	5.0	1-1.5	12
6 y	5.5	1.5-2	15
10 y	6.5	2-3	17
18 y	7-8	3	19

[a] Inserting the endotracheal tube this distance from the alveolar ridge of the mandible or maxilla places the distal end of the tube in the midtrachea.

TABLE 59-5 -- Calculation of Maintenance Fluid Requirements for Pediatric Patients

WEIGHT (kg)	HOURLY FLUID REQUIREMENTS (mL)	24-H FLUID REQUIREMENTS (mL)
<10	4 mL/kg	100 mL/kg

11-20	40 mL + 2 mL/kg > 10	1,000 mL + 50 mL/kg > 10
>20	60 mL + 1 mL/kg > 20	1,500 mL + 20 mL/kg > 20

by multiplying the hourly maintenance rate times the number of hours of restriction; 50 percent of the resulting deficit is replaced in the first hour and 25 percent in each of the next 2 hours. Third-space losses are replenished according to the surgical procedure and may vary from 1 mL/kg/h for a minor surgical procedure to as much as 15 mL/kg/h for major abdominal procedures (e.g., surgical repair of an omphalocele).

The composition of the intravenous fluid is also a concern. Because greater hypoxic brain damage was found to occur in animals having high blood glucose levels, some anesthesiologists recommend not using glucose-containing solutions routinely, especially for brief operative procedures. [181] However, a concern about unrecognized hypoglycemia was the motivating factor regarding the routine use of glucose-containing solutions in children, particularly patients who have not had food or fluids for a longer than usual time or those who have diminished glycogen stores. [182] [183] [184] The data are inadequate to eliminate glucose completely, because the relevance of the animal data is not clear, and the true incidence of hypoglycemia is not known in all populations of food-restricted children. This issue is further complicated because there are different values used to define hypoglycemia, which vary with patient age.

Despite limited data, modification of current practice can be proposed for long surgical procedures or for patients believed to be at risk for hypoglycemia. A balanced salt solution (e.g., lactated Ringer solution) should be used for all deficits and third-space losses, and 5 percent dextrose in 0.45 percent normal saline should be administered by "piggyback" infusion at maintenance rates. This procedure minimizes the chance of a bolus administration of glucose and satisfies the concern for unrecognized hypoglycemia or accidental hyperglycemia. The routine use of 5 percent dextrose and lactated Ringer solution as the initial replacement for fluid deficit and for maintenance is discouraged.

The fluid management of the term neonate and premature infant must take into account other variables. The amount of insensible water loss is inversely proportional to GA. The younger and more physically immature the patient is, the higher the skin permeability, the ratio of body surface area to weight, and the metabolic demand. In addition, the use of radiant warmers and phototherapy increases insensible water loss. On the other hand, use of a heated humidifier and warm air mattress preserves body heat and reduces insensible water loss.

The finding that the neonatal kidney is unable to excrete large amounts of excess water or electrolytes must also be considered. As described earlier, the volume of extracellular fluid in the newborn is very large. During the first days of life, some of this excess water is excreted. Therefore, term newborns have reduced fluid requirements for the first week of life. The daily fluid requirements for the term newborn for the following days after birth are: day 1, 70 mL/kg; day 3, 80 mL/kg; day 5, 90 mL/kg; and day 7, 120 mL/kg. Daily fluid requirements would be slightly higher for the premature infant. Sodium and potassium concentrations are usually kept at 2 to 3 mEq/100 mL.

An additional area of concern is the use of 10 percent dextrose in water for newborns. This fluid has been recommended to prevent hypoglycemia and is continued for the first several days of life until glucose values are stable. Infants of diabetic mothers or of mothers given large amounts of glucose just before delivery may require greater concentrations of glucose for protection against rebound hypoglycemia. Infants unable to tolerate oral feeding may continue to receive intravenous 10 percent glucose solutions and may even require peripheral or central alimentation. Some infants have been transferred to our institution with severe and potentially life-threatening hyperglycemia, that is, blood glucose levels of 700 to 900 mg/dL, as the result of overzealous use of this type of glucose therapy. This solution should be used with caution if infants require surgery and it is unclear that 10 percent dextrose in water is still necessary at that time. Every effort should be made to reduce bolus administration of glucose (an infusion pump should be used); blood sugar levels should be monitored and the solution infused at maintenance rates.

Packed Red Blood Cells

The use of blood products in pediatric surgical patients has diminished greatly because of the fear of transmission of disease, particularly the human immunodeficiency virus (HIV), even through blood that has tested negative (estimated to be 1:400,000 units of blood) [185] [186] (Ch. 46) . Because HIV and other disease-causing viruses, such as hepatitis, can be transmitted with as little as 10 mL of packed red blood cells (PRBC), administration of any blood product requires clear, medically defensible clinical indications that preferably are recorded on the anesthetic record.

When caring for children, it is very important to think in terms of blood volumes and portions of blood volumes lost, rather than units, because a unit of blood may constitute several blood volumes in the premature infant but only a fraction of the blood volume of the robust teenager.

These considerations govern calculation of the maximal allowable blood loss (MABL) resulting in an acceptable hematocrit level. The MABL takes into account the effect of patient age, weight, and starting hematocrit level on blood volume. In general, blood volume is approximately 100 to 120 mL/kg for the premature infant, 90 mL/kg for the full-term infant, 80 mL/kg for the child 3 to 12 months old, and 70 mL/kg for the child older than 1 year. These are merely estimates of blood volume. The individual patient's blood volume is calculated by simple proportion by multiplying the patient's weight by the estimated blood volume (EBV) per kilogram. Although several formulas are available, a simple relationship is easiest to remember:

Thus, if a 3-year-old child weighs 15 kg and has a starting hematocrit level of 38 percent and if clinical judgment estimates the desired postoperative hematocrit level to be 25 percent, the calculation would be as follows:

Then MABL would be replaced with 3 mL of lactated Ringer solution per milliliter of blood loss, that is, 3 mL

of lactated Ringer solution times the 359 mL of blood loss = 1,077 mL of lactated Ringer solution. If blood loss is less than or equal to MABL and no further significant blood loss occurs or is anticipated in the postoperative period, there is no need for transfusion of PRBC. If, however, significant postoperative bleeding occurs or is anticipated, discussion of potential transfusion needs with the surgeon is very important. Normally, the child who has had adequate replacement of intravascular volume deficits tolerates anemia very well. There is sufficient time to make the decision to transfuse by observing postoperative urinary output, heart rate, respiratory rate, and overall cardiovascular stability. Unfortunately, no one formula permits a definitive decision. The development of lactic acidosis is a late sign of inadequate oxygen-carrying capacity.

If the child has reached the MABL and significantly more blood loss is expected during surgery, the child should receive PRBC in sufficient quantity to maintain the hematocrit level in the 20 percent range. The entire loss of red cell mass should not be replaced unless clinically indicated if this would expose the child to additional units of blood products. Hematocrit levels in the low 20 percent range are usually well tolerated by most children, the exception being premature infants, term newborns, and patients with cyanotic congenital heart disease or those with respiratory failure who are in need of a high oxygen carrying capacity. Because the incidence of apnea is higher in neonates and premature infants who have hematocrit levels lower than 30 percent, it would be prudent to discuss with both the surgeon and neonatologist the minimal target hematocrit level for such patients and to document the discussion in the patient record. [187] [188] Older children having a history of sickle cell disease may require preoperative transfusion and should be managed in conjunction with their attending hematologist. [189] [190]

Fresh Frozen Plasma

Fresh frozen plasma (FFP) is administered to replenish clotting factors lost during massive blood transfusion (usually defined as exceeding one blood volume), for disseminated intravascular coagulopathy, or for congenital clotting-factor deficit (Ch. 46) . The anesthesiologist initiates and guides therapy with FFP during massive blood loss, whereas the hematologist's advice is sought when either of the other two conditions exists.

Patients with known clotting factor deficits, such as those with massive thermal injury or coagulopathy, may require transfusion of FFP before blood loss exceeds one blood volume. In contrast, healthy patients who do not have coagulation factor deficits at the beginning of surgery do not need FFP until blood loss exceeds one and probably one and one-half blood volumes. [191] This generalization applies to patients given PRBC; patients given whole blood do not need FFP, even when blood loss exceeds several blood volumes. [192] Despite a blood loss of one blood volume, prolongation of the prothrombin time (PT) and the partial thromboplastin time (PTT) is only minor. [191]

Blood loss exceeding one to one and one-half blood volumes (replaced entirely with PRBC and crystalloid, albumin, or other nonblood products), often necessitates transfusion of FFP. However, the decision to administer FFP should be based on observed coagulopathy and documented prolongation of the PT and PTT. Obtaining these test results from the laboratory often takes longer than desired. In this circumstance, a note should be written that blood loss has exceeded one blood volume and that abnormal oozing has occurred in the surgical field. A patient should never be given FFP to correct bleeding that is surgical in nature.

No studies on children have yet clearly defined what values for PT and PTT are associated with pathologic bleeding that require transfusion of FFP to replace clotting factors. However, if associated with abnormal oozing, a PT exceeding 15 seconds or a PTT longer than 60 seconds seems to warrant correction. If these abnormalities exist but oozing does not occur and the surgical field is relatively safe from the complications of hematoma formation, as in orthopedic surgery versus neurosurgery, it seems appropriate to observe the patient and to withhold transfusion of FFP.

The volume of FFP required to correct prolongation of the PT and PTT depends on the severity of the clotting factor deficit and the presence or absence of consumptive coagulopathy. In general, FFP therapy may require replacement of 30 percent or more of the patient's blood volume. Transfusion of FFP at rates exceeding 1.0 mL/kg/min is sometimes followed by severe ionized hypocalcemia, especially if FFP is administered during anesthesia with a potent inhaled anesthetic [193] [194] (Fig. 59-9) (Figure Not Available) . Therefore, exogenous calcium chloride (2.5-5 mg/kg) or calcium gluconate (7.5-15 mg/kg) should be administered during rapid transfusion of FFP. [195] Ionized hypocalcemia occurs very frequently in neonates given FFP, possibly because of their decreased ability to mobilize calcium and to metabolize citrate; patients undergoing liver transplantation or those with compromised hepatic function or perfusion may also be at increased risk because of a decreased ability to metabolize citrate.

Platelets

Thrombocytopenia may occur as a result of disease processes (idiopathic thrombocytopenic purpura, chemotherapy, infection, disseminated intravascular coagulopathy) or as a result of dilution during massive blood loss (Ch. 46) . Children whose platelet count has fallen because of idiopathic thrombocytopenic purpura or chemotherapy generally tolerate platelet counts as low as 15,000/mm ^{3} without need for platelet transfusion. In contrast, patients whose platelet count has decreased because of dilution (massive blood loss) generally require platelet transfusion when the count is 50,000/mm ^{3} or less. [196]

The reason for this disparity is not known. However, in my experience, the preoperative platelet count has been extremely valuable in predicting intraoperative platelet requirements. [196] Children who begin surgery with elevated platelet counts may not require platelet transfusion despite blood loss of four or more blood volumes. Conversely, children who begin surgery with low platelet counts (100,000/mm^3) may require platelet transfusion when blood loss is one or two blood volumes. Children who begin surgery with a normal platelet count (150,000-350,000/mm^3) usually do not require platelet transfusion until two blood volumes or more are lost (Fig. 59-10) .

Figure 59-9 (Figure Not Available) Ionized hypocalcemia always accompanies administration of citrated blood products (fresh frozen plasma, citrated whole blood). Fresh frozen plasma has the highest concentration of citrate per unit volume of any blood product and is the most likely to cause ionized hypocalcemia during rapid infusion. Studies in children with severe thermal injuries suggest that rates exceeding 1.0 mL/kg/min produce severe ionized hypocalcemia. If there is no further administration of citrated blood products, this abnormality will correct itself because of metabolism of the citrate. However, patients with impaired hepatic blood flow (infants, liver transplant patients, trauma patients) may need exogenous calcium therapy. * $P < 0.001$; $P < 0.0021$ compared with baseline. *(From Cote et al [193])*

Whenever platelets are administered, the anesthesia record should document the reason for the transfusion, and every effort should be made to obtain a platelet count before transfusion. Clinical oozing is the desirable indication for platelet transfusion, unless the potential for bleeding would be critical to survival, such as during neurosurgery, cardiac surgery, or major organ transplantation. The initial volume of platelets transfused is approximately 0.1 to 0.3 U/kg; the increase in platelet count obtained with this amount of transfusion varies considerably and depends on the presence or absence of platelet antibodies and on the rate of platelet consumption.

Monitoring the Pediatric Patient

The complexity of monitoring applied to the pediatric patient must be consistent with the severity of the underlying medical condition and the planned surgical procedure.

Figure 59-10 Dilutional thrombocytopenia occurs whenever massive blood loss takes place. The need for platelet transfusion, however, depends on the starting platelet count. Patients who started with low platelet counts developed dilutional thrombocytopenia after blood loss of one or two blood volumes, whereas patients who started with very high platelet counts did not require transfusions of platelets. Broken lines and -O- represent three patients with initial low platelet counts, and broken lines alone represent two children with initial low platelet counts. *(Data from Cote et al [196])*

Routine Monitoring

Minimal monitoring during anesthesia should include a precordial or esophageal stethoscope, a blood pressure cuff, an electrocardiogram (ECG), a temperature probe, a pulse oximeter, and possibly an infrared carbon dioxide and anesthetic agent analyzer. The last three devices provide early warning of impending disaster that may go unobserved until the appearance of late clinical signs such as cyanosis, bradycardia, severe hypotension, or absence of breath sounds. Prospective studies have shown that children younger than 6 months have a higher incidence of critical events. [197] [198] [199] [200] In some studies, these events occurred with greater frequency and severity when oximetry was not available to the anesthesiologist. [197] [198] The incidence of critical events was several times higher in American Society of Anesthesiologists (ASA) physical status III and IV patients than in ASA physical status I and II patients. Several factors may account for these results: the high metabolic rate of small children, the technical difficulty of caring for infants, or the difficulty of estimating actual delivered ventilation when various circuit configurations are available.

The use of the capnograph and pulse oximeter is not without problems, particularly the high incidence of false alarms from movement artifact, light interference, and electrocautery. [201] One of the main drawbacks of capnography in small children is the inaccuracy of the recording obtained when using nonrebreathing circuits. The best method of avoiding artifact is to sample the expired gases at some point within the endotracheal tube [202] [203] or to use the circle system even in small infants. [204] In general, the concentration of carbon dioxide in expired gases is within 2 to 3 mm Hg of that in arterial blood. [203] However, severe pulmonary disease or atelectasis may produce a large difference in these two values. In this type of patient, the gradient between arterial and expired carbon dioxide levels may be used to estimate the severity of the shunting. When such shunts exist, measurement of expired carbon dioxide levels may be used only to monitor trends. Ultimately, the most important monitors are the eyes, ears, and hands of the anesthesiologist, who must gather all the information provided by the patient and by the monitors applied to

the patient, consolidate the information into an accurate picture, and respond accordingly.

Special Monitoring

Arterial and central venous catheters should be used in pediatric patients whenever such monitors contribute to management of safe anesthesia. The anesthesiologist should not alter the decision to place these monitors simply because the patient is small or because the anesthesiologist is uncomfortable applying the technique to a pediatric patient. If these monitors are indicated, they should be inserted by the anesthesiologist, surgeon, cardiologist, or neonatologist. It is critical to pay special attention to the volume of fluid and heparin infused; special care must be taken to avoid introduction of air bubbles. Pulmonary artery flow-directed catheters are rarely indicated in pediatric patients, because right- and left-sided cardiac pressures are almost identical. However, occasionally the occurrence of pulmonary artery hypertension or severe multisystem failure makes this monitor particularly useful.

Multilumen catheters are very valuable in the care of critically ill patients. These devices make possible the simultaneous intravenous administration of a variety of fluids, vasopressors, and antibiotics. The greatest risk from these devices is the false sense of security created by having three intravenous ports. Specifically, if a rapid infusion of colloid or even crystalloid became necessary, the long, narrow lumen would severely limit the rate of infusion and could prevent adequate rapid volume replacement. [205] [206] If the need for rapid volume expansion could possibly arise, a separate large-bore intravenous catheter should be inserted. Short-term cannulation of the femoral or brachiocephalic vein is reasonable and may be lifesaving.

Pediatric Equipment

The anesthesiologist caring for a pediatric patient must be prepared for the unexpected, particularly an undiagnosed congenital malformation or a difficult endotracheal intubation. Having designated pediatric carts containing pediatric equipment is a convenient way of providing optimal care in a variety of locations in and outside the operating room. These carts contain intravenous catheters of various sizes, butterfly needles (scalp vein needles), ECG pads, blood pressure cuffs, precordial stethoscopes, esophageal stethoscopes in both adult and pediatric sizes, arm boards, intravenous fluids in pediatric-size containers, pediatric laryngoscope blades and handles, oral airways, endotracheal tubes, stylets, masks of various sizes, tape, drugs for resuscitation as well as commonly administered medications, and syringes, especially tuberculin syringes, for more precise administration of drugs.

Anesthesia Circuit

Much has been written about the advantages and disadvantages of various anesthesia circuits for use in pediatric patients [207] [208] [209] (Ch. 7) . Most of the attention has been directed to the neonate and ways of reducing the work of breathing while preventing rebreathing. Nonrebreathing circuits provide the advantage of minimal work of breathing because they have no valves to be opened by the patient's respiratory efforts. [208] The rate of induction of anesthesia may be more rapid because the volume of the nonrebreathing circuit is less, because no equilibration with the carbon dioxide canister is required, and because anesthetic gases are delivered immediately at the airway. Additionally, because the volume of the nonrebreathing circuit is small as compared with that of the circle system, the compression and compliance volume will be significantly less. [209] [210] This improves the ability to observe respiratory efforts, as reflected by movement of the anesthesia bag, as well as the ability to estimate pulmonary compliance. Thus, the actual delivered ventilation, when used in conjunction with a ventilator, may be greater with a Mapleson D system than with a circle system (Fig. 59-11) (Figure Not Available) . The Mapleson D circuit is more sensitive to changes in fresh gas flow (i.e., an increase or decrease in minute ventilation) or to the addition of a humidifier

Figure 59-11 (Figure Not Available) Eight types of anesthesia circuits were compared regarding ventilatory losses (circuit efficiency) as a result of compression of anesthetic gases (compression volume) and stretching of the circuit (compliance volume). Compression volume and compliance volume losses vary by as much as a factor of five, depending on the volume of the circuit and the material from which it is constructed. Low-volume, low-compliance circuits (Mapleson D systems) are the most efficient and give the anesthesiologist the greatest amount of tactile feedback regarding tidal volume and lung compliance in small patients. Although large-volume, high-compliance circuits (adult circle systems) can be used in small patients, it is very difficult to estimate tidal volume and lung compliance, because circuit-related losses in compression and compliance volumes are so large. *(From Cote et al [210])*

(decreased minute ventilation) during mechanical ventilation.

The Mapleson D circuit is an excellent circuit and for the foregoing reasons has been recommended for use in children who weigh less than 10 kg. Nevertheless, one must understand the clinical implications associated with this circuit in order to use the system safely. A pediatric circle system is adequate even for neonates as long as one understands the implications: large compression volume losses, longer time to equilibrate, perhaps a decreased ability to determine changes in compliance. [209] [211]

Neonatal Anesthesia

The neonate has unique requirements for equipment, intravenous access, fluid and drug therapy, anesthetic dosage, and environmental control (Ch. 58) . The many neonatal procedures are too numerous to describe in this limited space. However, the basic anesthetic management is the same for all neonates. An understanding of the basic differences in physiology, pharmacologic and pharmacodynamic response, and the underlying pathology of the surgical problem is essential for development of a safe anesthesia plan. Most of the complications that arise are attributable to a lack of understanding of these special considerations prior to induction of anesthesia. The care of neonates is fraught with danger, sudden changes, unexpected responses, and the unknown congenital problem. If anesthesiologists are to deliver optimum pediatric anesthesia care, they must always be prepared for the unexpected, have the proper size and variety of equipment available, and obtain the highest level of support, both in the operating room and in the intensive care unit.

Children younger than 1 year have a higher incidence of complications than older children. [197] [198] [199] [200] [212] [213] These complications relate to oxygenation, ventilation, airway management, and response to anesthetic agents and medications; they occur more frequently in ASA physical status III and IV patients. The neonate, particularly the premature infant, functions on a marginal basis, so that any type of stress is usually poorly tolerated. This vulnerability may relate to the technical difficulty of taking care of small patients, the immaturity of their organ systems (especially the cardiovascular, pulmonary, renal, hepatic, and nervous systems), the high metabolic rate, the large ratio of body surface area to weight, and the ease of miscalculating a drug dose.

When caring for infants and neonates, special attention must be paid to all aspects of anesthesia and surgical management. The anesthesiologist must devote particular care to the calculation of drug dosage and the dilution of drugs. Prevention of paradoxic air emboli requires that all air be vented from intravenous devices and syringes prior to use (aspiration of each intravenous injection port to remove air trapped at these junctions). A volume of air that is clinically unimportant to the adult may prove catastrophic to the infant. Warming of preparation solutions and irrigation fluids prior to application minimizes heat loss. Intravenous fluids should be administered with volume-limiting devices; infusion pumps are particularly helpful in preventing overadministration of intravenous fluid. The composition and infusion rate of flush solutions should be noted and calculated into maintenance fluid therapy.

Every effort must be made to maintain the infant's temperature to minimize thermal stress. The operating room environment should be warmed so that the whole operating room constitutes a giant incubator. In addition, the infant weighing up to 10 kg benefits from a warming blanket, whereas most patients benefit from heated humidification of inspired gases, particularly when a nonrebreathing circuit is used. Heated air mattress devices are particularly useful for maintaining temperature.

Monitoring of expired concentrations of carbon dioxide will be less accurate if the sample is taken at the Y-connector; endotracheal tubes having a built-in sampling port may improve the accuracy of monitoring. Pulse oximetry is definitely of great value, not only in diagnosing hypoxemia, but also in preventing extreme hyperoxia. Maintaining oxygen saturation at 93 to 95 percent keeps the preterm infant on the steep side of the oxygen-hemoglobin dissociation curve. This consideration is important to infants still susceptible to retinopathy of prematurity, that is, those younger than 44 weeks' PCA. Because these infants have the highest oxygen consumption, an oxygen saturation in the 93 to 95 percent range can result in hypoxemia within seconds. When managing such a delicate balance, and bearing in mind the slight inaccuracies of these monitors, [214] the anesthesiologist must

be extremely vigilant and prepared to respond rapidly to changes in oxygen saturation. Keeping arterial carbon dioxide values within the normal range (35-45 mm Hg) may also be important in preventing retinopathy of prematurity. [215] However, many other factors beyond the control of the anesthesiologist often contribute to the development of this condition. [216] [217]

The Stress Response

There is little doubt that the neonate, even the extremely premature infant, is capable of feeling pain and responding to painful stimuli; what actually constitutes a state of "anesthesia" has yet to be proved. [218] [219] No child should be denied analgesia or anesthesia because of size or age. Clearly, the cardiovascular system of the premature infant rarely tolerates the cardiovascular-depressant effects of potent inhaled anesthetics. However, the narcotics (e.g., fentanyl, sufentanil, alfentanil, remifentanil) are usually well tolerated even by critically ill infants. These potent narcotics must be carefully titrated to response, and the anesthesiologist must always be wary of narcotic-induced bradycardia and its consequences on cardiac output. Low concentrations of potent inhaled anesthetics can be used with narcotics, thus providing a way of controlling hemodynamic responses without significantly depressing the myocardium. The relative merits of one anesthetic technique over another are not clear, and the few studies examining this issue are poorly controlled. [220] Narcotics and inhaled anesthetics suppress the hormonal responses to pain. [221] The important result of the provocative studies undertaken to clarify this issue is that they have heightened everyone's awareness of the need to provide adequate anesthesia and analgesia for the neonate.

Special Problems

Meningomyelocele

Meningomyelocele (hernial protrusion of a part of the meninges and spinal cord through a defect in the vertebral column) is a relatively common neonatal abnormality that requires surgery. The following should be considered in addition to the usual concerns for management of the neonate: (1) the possibility of underestimating fluid and blood loss from the defect; (2) the high association of this condition with hydrocephalus; (3) the possibility of cranial nerve palsy, resulting in inspiratory stridor; and (4) the potential for brain-stem herniation. The anesthesiologist must establish adequate intravenous access and invasive monitoring if appropriate, replace all fluid deficits, including loss from the defect (usually with normal saline), and ensure that crossmatched blood is available. Latex allergy precautions should be used with these patients for their first and all subsequent anesthetics. [222]

Pyloric Stenosis

Pyloric stenosis normally presents in the first 3 to 6 weeks of life. The following are major concerns for the anesthesiologist: (1) a full stomach, often filled with barium sulfate; (2) metabolic alkalosis with hypochloremia and hypokalemia; and (3) severe dehydration.

This operation is never a surgical emergency. The patients should be carefully evaluated, and severe metabolic imbalance should be corrected prior to surgery. The stomach should be suctioned with a wide-bore catheter in the supine, right, and left lateral positions immediately before induction of anesthesia, and as much barium as possible should be removed. [223] [224] Patients with pyloric stenosis can be managed with awake endotracheal intubation or rapid-sequence induction of anesthesia. Arguments can be made for either type of induction, and selection depends on the skill and familiarity of the anesthesiologist with that technique.

Omphalocele and Gastroschisis

Omphalocele and gastroschisis are major defects in closure of the abdominal wall, resulting in exposure of viscera that are either covered (omphalocele) or not covered (gastroschisis) by peritoneum. The major problems with these defects include the following: (1) severe dehydration and massive fluid loss, both from the exposed visceral surfaces and from third-space losses caused by partial bowel obstruction; (2) heat loss; (3) the difficulty of surgical closure; and (4) the high association of this condition with prematurity and other congenital defects, including cardiac abnormalities.

These patients must be cared for expeditiously to minimize the potential for infection and the compromise of bowel function and to reverse the loss of fluid and heat. Adequate intravenous access and invasive monitoring are usually necessary. The liberal use of muscle relaxants provides optimal surgical conditions for closure of the defect; hypotension secondary to tension on a major organ (liver) or caval compression is common. If the surgeon is unable to close the defect in one procedure, a staged procedure is planned. In either situation, postoperative ventilation is necessary until the abdominal wall has had time to stretch to accommodate the viscera. Intravenous alimentation may also play a vital role in the rapid recovery of these patients. A small percentage of patients with omphalocele also have Beckwith-Wiedemann syndrome, a condition characterized by profound hypoglycemia, hyperviscosity syndrome, and associated visceromegaly. It should be noted that increased abdominal pressure following closure may compromise hepatic function and may markedly alter drug metabolism. [126] [125]

Tracheoesophageal Fistula Anomaly

The tracheoesophageal fistula anomaly has five or more configurations, most of which present as an inability to swallow because of esophageal atresia (the ending of the esophagus in a blind pouch). Neonates may have aspiration pneumonitis from a distal fistula connecting the stomach to the trachea through the esophagus or from a proximal connection of the esophagus with the trachea. The characteristic diagnostic test is the inability to pass a suction catheter into the stomach. Additionally, this anomaly may be a part of a

---

larger constellation of anomalies known as the VATER syndrome (V, vertebral; A, anal; TE, tracheoesophageal; R, renal). Any patient who presents with tracheoesophageal fistula or esophageal atresia should be suspected of having the other anomalies described earlier, as well as the potential for congenital heart disease.

The major issues for management of safe anesthesia include the following: aspiration pneumonia; overdistention of the stomach because of entry of air directly into the stomach through the fistula; inability to ventilate the patient because of the large size of the fistula; problems associated with other anomalies, particularly a patent ductus arteriosus (shunting); and postoperative intensive care.

For management of anesthesia, the child should not receive any feedings, should have a catheter placed in the esophagus to drain saliva, and should be placed prone in a head-up position. If the child has pneumonia, treatment should be initiated; surgery may be postponed until pneumonitis improves or clears. The child may be a candidate for gastrostomy to provide a means of nutrition during recovery from pneumonitis. Anesthesia evaluation should center around the pulmonary and cardiovascular systems. Generally, an awake intubation is performed, and the endotracheal tube is intentionally passed into the right main stem bronchus; the endotracheal tube is then slowly withdrawn until breath sounds are heard on the left. Often this technique ensures that the tip of the endotracheal tube is placed beyond the origin of the fistula, thus avoiding massive distention of the stomach. Care must be taken to avoid rupturing the stomach; therefore, spontaneous and gently assisted ventilation may be appropriate until gastrostomy is performed. A change in the distance of insertion of the endotracheal tube of as little as 1 to 2 mm may determine whether the anesthesiologist is ventilating both lungs, one lung, or the fistula. Therefore, because a change in oxygen saturation may be the first indication that all is not well, the pulse oximeter is one of the most useful monitors in managing these patients. [225] Taping the stethoscope to the left side of the chest in the axilla also decreases the possibility of unrecognized endobronchial intubation.

Diaphragmatic Hernia

Infants with diaphragmatic hernia usually present on the first day of life with respiratory distress and a scaphoid abdomen. The abnormality is a herniation of the abdominal viscera through a defect in the diaphragm, most commonly the foramen of Bochdalek on the left side. Almost all the abdominal viscera, including the liver and spleen, may be above the diaphragm. The GA at which herniation occurs may determine the degree of lung hypoplasia.

Anesthesia concerns include hypoxemia and hypotension caused by overdistention of the stomach and herniation across the midline, hypoxemia because of primary pulmonary hypoplasia, hypoxemia due to pulmonary hypertension, and systemic hypotension caused by kinking of major blood vessels, particularly those of the liver. In general, the anesthesiologist's ability to control arterial carbon dioxide tension (Pa_{CO_2}) reflects the severity of lung pathology and therefore survival. An inability to

reduce Pa CO_2 is associated with poor prognosis. [226] Extracorporeal membrane oxygenation has reduced the mortality associated with this condition. In addition, the urgency for surgical intervention has diminished, giving way to a desire to stabilize the infant and minimize stress. [227] At some centers, the common practice is to postpone surgery on infants with diaphragmatic hernia until their condition has been stabilized for several days.

Anesthesia management for patients with diaphragmatic hernia includes the following:

1. An awake endotracheal intubation without bag-and-mask-assisted ventilation prevents overdistention of the stomach and herniation across the midline.
2. Insertion of an arterial line and close observation of the surgical field are most helpful in diagnosing impairment of venous return or cardiac output.
3. Blunting of the stress response is accomplished by providing analgesia with narcotics (usually fentanyl) and by controlling respiration with muscle relaxants (usually pancuronium).
4. Careful control of ventilation and oxygenation prevents sudden increases in pulmonary artery pressure (Pa CO_2 is maintained at less than 40 mm Hg and Pa O_2 at more than 100 mm Hg). Pulse oximetry is helpful in diagnosing subclinical episodes of hypoxemia.
5. Hypothermia is avoided in order to decrease the oxygen consumption needed for thermogenesis.
6. Anesthetic agents that could depress the myocardium are avoided until the chest is decompressed.
7. To prevent bowel distention, nitrous oxide is not given.
8. The anesthesiologist should be alert to the development of a barotrauma-induced pneumothorax on the ipsilateral or contralateral side.
9. The anesthesiologist should ensure adequate intravenous access for maintenance of a constant circulating blood volume.
10. Postoperative intensive care should be planned.

The Former Preterm Infant

Since the early retrospective reports noting the high incidence of postoperative apnea in former preterm infants (GA <37 wk), several studies have tried to define the population at risk [187] [228] [229] [230] [231] [232] [233] [234] [235] [236] (Ch. 58) . Most studies have found the majority of infants who develop postanesthesia apnea to be less than 46 weeks' PCA; however, apnea has been reported in infants up to 60 weeks' PCA. [231] The conclusions reached by each of these studies were limited by the relatively small number of patients. I had the opportunity to obtain and analyze the original data from eight prospective studies. [187] [228] [229] [230] [231] [234] [236] [237] A combined analysis examining risk for apnea included only patients undergoing inguinal hernia repair and not receiving special treatment such as caffeine or regional anesthesia. [188] The following risk factors were examined: a history of respiratory distress syndrome, bronchopulmonary dysplasia, neonatal apnea, necrotizing enterocolitis, ongoing apnea at the time of surgery, use of narcotics or long-acting muscle relaxants, anemia (hematocrit level <30%), GA, and PCA. The only two risk factors that stood out across all ages were GA and PCA. The incidence of apnea was inversely related to both GA and PCA.

Figure 59-12 (Figure Not Available) Predicted probability of apnea for all patients, by gestational age and weeks of postconceptual age. Patients with anemia are represented by the horizontal hatched line. Bottom marks indicate the number of data points by postconceptual age. The risk for apnea diminishes for infants born at a later gestational age. The shaded boxes represent the overall rates of apnea for infants within that gestational age range. The probability of apnea was the same regardless of postconceptual age or gestational age for infants with anemia (horizontal hatched line). *(From Cote et al [188])*

For example, if two infants were now 42 weeks' PCA yet one was born at 28 and the other at 36 weeks' GA, the 28-week-GA infant would have approximately twice the potential for apnea (Fig. 59-12) (Figure Not Available) . The incidence of apnea was higher in institutions that collected data with continuous recording devices compared with those that relied on impedance pneumography or nursing observations. Anemia (hematocrit level <30%) is an independent risk factor associated with apnea in former preterm infants (see Fig. 59-12) (Figure Not Available) . What makes this risk factor unique is that the risk of apnea in anemic former preterm infants is not altered by GA or PCA; that is, the risk of apnea would appear to be the same for an anemic 60-week-PCA infant as for an anemic 45-week-PCA infant. Even after eliminating infants with an obvious apnea spell in recovery and infants who were anemic, the risk for apnea does not decrease to less than 1 percent with 95 percent statistical confidence until PCA of 56 weeks with GA of 32 weeks or PCA of 54 weeks with GA of 35 weeks. It would therefore seem prudent to admit all former preterm infants younger than 55 weeks' PCA to monitored beds and all anemic former preterm infants.

Although the risk of apnea may be less with regional anesthesia, apnea may still occur and may even be increased if regional anesthesia is combined with sedation (ketamine, midazolam). [230] [235] [238] [239] There are insufficient numbers of well-controlled studies of regional versus general anesthesia to determine whether the risk is significantly reduced.

Part of the problem of how to treat these children is that we do not know the clinical importance of brief apnea/bradycardia spells that do not require intervention. Because cerebral blood flow is markedly reduced with heart rates lower than 80 beats/min, even brief apnea associated with bradycardia may have adverse effects. [240] The problem faced by the clinician is how to manage former preterm infants scheduled for outpatient procedures. Information concerning the true incidence of postoperative apnea is still very limited because the available data have been collected from so many institutions. Nevertheless, one can conclude that the incidence of apnea is inversely related to PCA and GA, and anemia is also an independent risk factor. [188] More prospective studies need to address whether regional techniques are safer than general anesthesia. Studies must also include methods (nasal thermistry or capnography) for detecting obstructed respiration, which is often missed by chest wall impedance monitoring. Pulse oximetry would help to define the severity of desaturation, and ECG monitoring would help define episodes of bradycardia, which may reduce cerebral blood flow. Kurth and LeBard [234] demonstrated that up to 12 percent of apnea spells are accompanied by desaturation to below 80 percent. It would seem reasonable that the combination of desaturation and bradycardia would be of more physiologic importance than simple documentation of pauses in respiration.

Because the available data are so confusing, it would appear that outpatient anesthesia should be considered only when former preterm infants have had a totally unremarkable neonatal history and are currently healthy. If there is any question, the prudent anesthesiologist will plan on postoperative admission and monitoring. If appropriate facilities are not available, the premature infant who is less than 60 weeks' PCA should be referred to an institution that has such facilities. High-dose caffeine (10 mg/kg) has been recommended. [229] This may be an effective therapy; however, the half-life of caffeine in older former preterm infants is only 6 hours, [241] and the first apnea spells following anesthesia may not manifest until 12 hours. [188] Therefore, one cannot administer caffeine and send the infant home and assume that the problem is treated.

To make the issue even more complex, I have observed a full-term infant who became apneic following general anesthesia. This infant had periodic breathing, which is distinctly unusual in a full-term infant. [242] We still do not know with certainty which patients are truly anesthetized safely on an outpatient basis and at what PCA and GA.

Regional Anesthesia and Analgesia

Most regional anesthesia techniques used in the adult can be administered safely to the pediatric patient as long as strict attention is paid to the dose of local anesthetic, the dose of epinephrine, the route of administration, and the use of proper equipment [243] [244] (Ch. 44) . Perhaps the greatest advance in pediatric anesthesia has been the development of methods producing postoperative analgesia (Chs. 69 and 70) . Miniaturized needles and catheters and infusion pumps have made this feasible. Caudal anesthesia, caudal narcotics, regional blocks, and patient-controlled analgesia have all been accepted by anesthesiologists and patients. Each institution and practitioner must decide which method works best, given each particular practice setting. Obviously, until dosage guidelines and safety standards for monitoring are well established, some of these techniques must be limited to medical centers familiar with their use in children. [245]

It is my practice to supplement the analgesia of either opioid or regional techniques with 40 mg/kg rectal acetaminophen at the beginning of the procedure. A dose-finding study [246] and several others demonstrated that 40 mg/kg rectal acetaminophen places the majority of patients in the therapeutic range for antipyresis (we do not know the plasma levels associated with analgesia in children) within 60 to 180 minutes, hence the need to insert the suppositories at the beginning of the procedure rather than the end of it. [247] [248] It should be noted that suppositories should not be cut because the drug is not evenly distributed within the matrix; combinations of suppository doses are the best means of achieving a dose close to 40 mg/kg.

Regional nerve blocks and direct local infiltration of surgical wounds with long-acting local anesthetics are simple yet very effective methods of providing pain relief for all children. In most institutions, it is now rare for a pediatric patient to awaken from anesthesia without some form of regional block. This practice has been especially helpful in the outpatient population; parents are encouraged to start analgesics when they observe their child becoming irritable but prior to complete dissipation of the block. This approach usually provides a smooth transition from general anesthesia and a pain-free patient.

Chapters 42 to 44 discuss regional anesthesia and analgesia in detail, with Chapter 44 placing special emphasis on pediatrics.

References

1. Friis-Hansen B: Body composition during growth: *In vivo* measurements and biochemical data correlated to differential anatomical growth. Pediatrics 47:264, 1971.

2. Lugo G, Cassady G: Intrauterine growth retardation: Clinicopathologic findings in 233 consecutive infants. Am J Obstet Gynecol 109:615, 1971.

3. Bingol N, Fuchs M, Diaz V et al: Teratogenicity of cocaine in humans. J Pediatr 110:93, 1987.

4. Dubowitz LM, Dubowitz V, Goldberg C: Clinical assessment of gestational age in the newborn infant. J Pediatr 77:1, 1970.

5. Catlin EA, Carpenter MW, Brann BS et al: The Apgar score revisited: Influence of gestational age. J Pediatr 109:865, 1986.

6. Rudolph AM: The changes in the circulation after birth: Their importance in congenital heart disease. Circulation 41:343, 1970.

7. Friedman WF, Hirschklau MJ, Printz MP et al: Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med 295:526, 1976.

8. Romero T, Covell J, Friedman WF: A comparison of pressure-volume relations of the fetal, newborn, and adult heart. Am J Physiol 222:1285, 1972.

9. Kirkpatrick SE, Pitlick PT, Naliboff J et al: Frank-Starling relationship as an important determinant of fetal cardiac output. Am J Physiol 231:495, 1976.

10. Davies G, Reid L: Growth of the alveoli and pulmonary arteries in childhood. Thorax 25:669, 1970.

11. Anthonisen NR, Danson J, Robertson PC et al: Airway closure as a function of age. Respir Physiol 8:58, 1969.

12. Cross KW, Tizard JPM, Trythall DAH: The gaseous metabolism of the newborn infant. Acta Paediatr Scand 46:265, 1957.

13. Keens TG, Bryan AC, Levison H et al: Developmental pattern of muscle fiber types in human ventilatory muscles. J Appl Physiol Respir Environ Exerc Physiol 44:909, 1978.

14. Miller MJ, Carlo WA, Strohl KP et al: Effect of maturation on oral breathing in sleeping premature infants. J Pediatr 109:515, 1986.

15. Negus VE: The Comparative Anatomy and Physiology of the Larynx. New York, Grune & Stratton, 1949.

16. Eckenhoff JE: Some anatomic considerations of the infant larynx influencing endotracheal anesthesia. Anesthesiology 12:401, 1951.

17. Leake RD, Trygstad CW: Glomerular filtration rate during the period of adaptation to extrauterine life. Pediatr Res 11:959, 1977.

18. Jose PA, Fildes RD, Gomez RA et al: Neonatal renal function and physiology. Curr Opin Pediatr 6:172, 1994.

19. van den Anker JN: Pharmacokinetics and renal function in preterm infants. Acta Paediatr 85:1393, 1996.

20. Reed MD, Besunder JB: Developmental pharmacology: Ontogenic basis of drug disposition. Pediatr Clin North Am 36:1053, 1989.

21. Reed MD: Developmental pharmacology: Relationship to drug use. DICP 23(suppl):S21, 1989.

22. Besunder JB, Reed MD, Blumer JL: Principles of drug biodisposition in the neonate. II. A critical evaluation of the pharmacokinetic-pharmacodynamic interface. Clin Pharmacokinet 14:261, 1988.

23. Ehrnebo M, Agurell S, Jalling B et al: Age differences in drug binding by plasma proteins: Studies in human foetuses, neonates, and adults. Eur J Clin Pharmacol 3:189, 1971.

24. Wood M: Plasma drug binding: Implications for anesthesiologists. Anesth Analg 65:786, 1986.

25. Orenstein SR, Orenstein DM: Gastroesophageal reflux and respiratory disease in children. J Pediatr 112:847, 1988.

26. Himms-Hagen J: Cellular thermogenesis. Annu Rev Physiol 38:315, 1976.

27. Sessler DI: Perianesthetic thermoregulation and heat balance in humans. FASEB J 7:638, 1993.

28. Dicker A, Ohlson KB, Johnson L et al: Halothane selectively inhibits nonshivering thermogenesis: Possible implications for thermoregulation during anesthesia of infants. Anesthesiology 82:491, 1995.

29. Ohlson KB, Mohell N, Cannon B et al: Thermogenesis in brown adipocytes is inhibited by volatile anesthetic agents: A factor contributing to hypothermia in infants? Anesthesiology 81:176, 1994.

30. Bissonnette B: Temperature monitoring in pediatric anesthesia. Int Anesthesiol Clin 30:63, 1992.

31. Morselli PL, Franco-Morselli R, Bossi L: Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokinet 5:485, 1980.

32. Lerman J, Sikich N, Kleinman S et al: The pharmacology of sevoflurane in infants and children. Anesthesiology 80:814, 1994.

33. Fisher DM, Zwass MS: MAC of desflurane in 60% nitrous oxide in infants and children. Anesthesiology 76:354, 1992.

34. Katoh T, Ikeda K: Minimum alveolar concentration of sevoflurane in children. Br J Anaesth 68:139, 1992.

35. Taylor RH, Lerman J: Induction, maintenance and recovery characteristics of desflurane in infants and children. Can J Anaesth 39:6, 1992.

36. Nicodemus HF, Nassiri-Rahimi C, Bachman L et al: Median effective doses (ED_{50}) of halothane in adults and children. Anesthesiology 31:344, 1969.

37. Lerman J, Robinson S, Willis MM et al: Anesthetic requirements for halothane in young children 0-1 month and 1-6 months of age. Anesthesiology 59:421, 1983.

38. Yakaitis RW, Blitt CD, Angiulo JP: End-tidal halothane concentration for endotracheal intubation. Anesthesiology 47:386, 1977.

39. Friesen RH, Lichtor JL: Cardiovascular depression during halothane anesthesia in infants: Study of three induction techniques. Anesth Analg 61:42, 1982.

40. Lerman J, Schmitt-Bantel BI, Gregory GA et al: Effect of age on the solubility of volatile anesthetics in human tissues. Anesthesiology 65:307, 1986.

41. Lerman J, Gregory GA, Willis MM et al: Age and solubility of volatile anesthetics in blood. Anesthesiology 61:139, 1984.

42. Rieger A, Schroter G, Philippi W et al: A comparison of sevoflurane with halothane in outpatient adenotomy in children with mild upper respiratory tract infections. J Clin Anesth 8:188, 1996.

43. Sury MR, Black A, Hemington L et al: A comparison of the recovery characteristics of sevoflurane and halothane in children. Anaesthesia 51:543, 1996.

44. Sarner JB, Levine M, Davis PJ et al: Clinical characteristics of sevoflurane in children: A comparison with halothane. Anesthesiology 82:38, 1995.

45. Welborn LG, Hannallah RS, Norden JM et al: Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesth Analg 83:917, 1996.

46. Smiley RM: An overview of induction and emergence characteristics of desflurane in pediatric, adult, and geriatric patients. Anesth Analg 75(suppl):S38, 1992.

47. Zwass MS, Fisher DM, Welborn LG et al: Induction and maintenance characteristics of anesthesia with desflurane and nitrous oxide in infants and children. Anesthesiology 76:373, 1992.

48. Fisher DM, Robinson S, Brett CM et al: Comparison of enflurane, halothane, and isoflurane for diagnostic and therapeutic procedures in children with malignancies. Anesthesiology 63:647, 1985.

49. McAteer PM, Carter JA, Cooper GM et al: Comparison of isoflurane and halothane in outpatient paediatric dental anaesthesia. Br J Anaesth 58:390, 1986.

50. Kenna JG, Neuberger J, Mieli-Vergani G et al: Halothane hepatitis in children. Br Med J 294:1209, 1987.

51. Brown BR Jr, Gandolfi AJ: Adverse effects of volatile anesthetics. Br J Anaesth 59:14, 1987.

52. Rolf N, Cote CJ: Persistent cardiac arrhythmias in pediatric patients: Effects of age, expired carbon dioxide values, depth of anesthesia, and airway management. Anesth Analg 73:720, 1991.

53. Karl HW, Swedlow DB, Lee KW et al: Epinephrine-halothane interactions in children. Anesthesiology 58:142, 1983.

54. Brandom BW, Brandom RB, Cook DR: Uptake and distribution of halothane in infants: *In vivo* measurements and computer simulations. Anesth Analg 62:404, 1983.

55. Wolf WJ, Neal MB, Peterson MD: The hemodynamic and cardiovascular effects of isoflurane and halothane anesthesia in children. Anesthesiology 64:328, 1986.

56. Murray D, Vandewalker G, Matherne GP et al: Pulsed Doppler and two-dimensional echocardiography: Comparison of halothane and isoflurane on cardiac function in infants and small children. Anesthesiology 67:211, 1987.

57. Todd MM, Drummond JC: A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. Anesthesiology 60:276, 1984.

58. Friesen RH, Lichtor JL: Cardiovascular effects of inhalation induction with isoflurane in infants. Anesth Analg 62:411, 1983.

59. Friesen RH, Henry DB: Cardiovascular changes in preterm neonates receiving isoflurane, halothane, fentanyl, and ketamine. Anesthesiology 64:238, 1986.

60. Taylor RH, Lerman J: Minimum alveolar concentration of desflurane and hemodynamic responses in neonates, infants, and children. Anesthesiology 75:975, 1991.

61. Weiskopf RB, Moore MA, Eger EI II et al: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. Anesthesiology 80:1035, 1994.

62. Muzi M, Lopatka CW, Ebert TJ: Desflurane-mediated neurocirculatory activation in humans: Effects of concentration and rate of change on responses. Anesthesiology 84:1035, 1996.

63. Tanaka S, Tsuchida H, Nakabayashi K et al: The effects of sevoflurane, isoflurane, halothane, and enflurane on hemodynamic responses during an inhaled induction of anesthesia via a mask in humans. Anesth Analg 82:821, 1996.

64. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane. Anesthesiology 79:444, 1993.

65. Weiskopf RB: Cardiovascular effects of desflurane in experimental animals and volunteers. Anaesthesia 50(suppl):14, 1995.

66. Fang ZX, Eger EI II, Laster MJ et al: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth Analg 80:1187, 1995.

67. Baxter PJ, Kharasch ED: Rehydration of desiccated Baralyme prevents carbon monoxide formation from desflurane in an anesthesia machine. Anesthesiology 86:1061, 1997.

68. Ariffin SA, Whyte JA, Malins AF et al: Comparison of induction and recovery between sevoflurane and halothane supplementation of anaesthesia in children undergoing outpatient dental extractions. Br J Anaesth 78:157, 1997.

69. Lerman J, Davis PJ, Welborn LG et al: Induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery: A comparison with halothane. Anesthesiology 84:1332, 1996.

70. Sigston PE, Jenkins AM, Jackson EA et al: Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane. Br J Anaesth 78:362, 1997.

71. Naito Y, Tamai S, Shingu K et al: Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia. Br J Anaesth 67:387, 1991.

72. Fang ZX, Kandel L, Laster MJ et al: Factors affecting production of compound A from the interaction of sevoflurane with Baralyme and soda lime. Anesth Analg 82:775, 1996.

73. Frink EJ Jr, Green WB Jr, Brown EA et al: Compound A concentrations during sevoflurane anesthesia in children. Anesthesiology 84:566, 1996.

74. Jin L, Baillie TA, Davis MR et al: Nephrotoxicity of sevoflurane compound A [fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether] in rats: Evidence for glutathione and cysteine conjugate formation and the role of renal cysteine conjugate beta-lyase. Biochem Biophys Res Commun 210:498, 1995.

75. Frink EJ Jr, Isner RJ, Malan TP Jr et al: Sevoflurane degradation product concentrations with soda lime during prolonged anesthesia. J Clin Anesth 6:239, 1994.

76. Gonsowski CT, Laster MJ, Eger EI II et al: Toxicity of compound A in rats: Effect of a 3-hour administration. Anesthesiology 80:556, 1994.

77. Frink EJ Jr, Malan TP, Morgan SE et al: Quantification of the degradation products of sevoflurane in two CO_2 absorbants during low-flow anesthesia in surgical patients. Anesthesiology 77:1064,

1992.

78. Ray DC, Bomont R, Mizushima A et al: Effect of sevoflurane anaesthesia on plasma concentrations of glutathione S-transferase. Br J Anaesth 77:404, 1996.

79. Bito H, Ikeda K: Renal and hepatic function in surgical patients after low-flow sevoflurane or isoflurane anesthesia. Anesth Analg 82:173, 1996.

80. Kharasch ED, Thorning D, Garton K et al: Role of renal cysteine conjugate beta-lyase in the mechanism of compound A nephrotoxicity in rats. Anesthesiology 86:160, 1997.

81. Bito H, Ikeda K: Closed-circuit anesthesia with sevoflurane in humans: Effects on renal and hepatic function and concentrations of breakdown products with soda lime in the circuit. Anesthesiology 80:71, 1994.

82. Eger EI II, Koblin DD, Bowland T et al: Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 84:160, 1997.

83. Iwasaka H, Itoh K, Miyakawa H et al: Glucose intolerance during prolonged sevoflurane anaesthesia. Can J Anaesth 43:1059, 1996.

84. Bjorkman S, Gabrielsson J, Quaynor H et al: Pharmacokinetics of i.v. and rectal methohexitone in children. Br J Anaesth 59:1541, 1987.

85. Liu LMP, Goudsouzian NG, Liu P: Rectal methohexital premedication

in children: A dose comparison study. Anesthesiology 53:343, 1980.

86. Daniels AL, Cote CJ, Polaner DM: Continuous oxygen saturation monitoring following rectal methohexitone induction in paediatric patients. Can J Anaesth 39:27, 1992.

87. Rockoff MA, Goudsouzian NG: Seizures induced by methohexital. Anesthesiology 54:333, 1981.

88. Cote CJ, Goudsouzian NG, Liu LM et al: The dose response of intravenous thiopental for the induction of general anesthesia in unpremedicated children. Anesthesiology 55:703, 1981.

89. Brett CM, Fisher DM: Thiopental dose-response relations in unpremedicated infants, children, and adults. Anesth Analg 66:1024, 1987.

90. Westrin P: The induction dose of propofol in infants 1-6 months of age and in children 10-16 years of age. Anesthesiology 74:455, 1991.

91. Hannallah RS, Baker SB, Casey W et al: Propofol: Effective dose and induction characteristics in unpremedicated children. Anesthesiology 74:217, 1991.

92. Aun CS, Short SM, Leung DH et al: Induction dose-response of propofol in unpremedicated children. Br J Anaesth 68:64, 1992.

93. Murat I, Billard V, Vernois J et al: Pharmacokinetics of propofol after a single dose in children aged 1-3 years with minor burns: Comparison of three data analysis approaches. Anesthesiology 84:526, 1996.

94. Cameron E, Johnston G, Crofts S et al: The minimum effective dose of lignocaine to prevent pain due to propofol in children. Anaesthesia 47:604, 1992.

95. Vangerven M, Van Hemelrijck J, Wouters P et al: Light anaesthesia with propofol for paediatric MRI. Anaesthesia 47:706, 1992.

96. Short SM, Aun CS: Haemodynamic effects of propofol in children. Anaesthesia 46:783, 1991.

97. Watcha MF, Simeon RM, White PF et al: Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. Anesthesiology 75:204, 1991.

98. Hannallah RS, Britton JT, Schafer PG et al: Propofol anaesthesia in paediatric ambulatory patients: A comparison with thiopentone and halothane. Can Anaesth Soc J 41:12, 1994.

99. Carson IW, Moore J, Balmer JP et al: Laryngeal competence with ketamine and other drugs. Anesthesiology 38:128, 1973.

100. Cioaca R, Canavea I: Oral transmucosal ketamine: An effective premedication in children. Paediatr Anaesth 6:361, 1996.

101. Warner DL, Cabaret J, Velling D: Ketamine plus midazolam, a most effective paediatric oral premedicant. Pediatr Anaesth 5:293, 1995.

102. Lin YC, Moynihan RJ, Hackel A: A comparison of oral midazolam, oral ketamine, and oral midazolam combined with ketamine as preanesthetic medication for pediatric outpatients. Anesthesiology 79:A1177, 1993.

103. Malinovsky JM, Servin F, Cozian A et al: Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth 77:203, 1996.

104. Weksler N, Ovadia L, Muati G et al: Nasal ketamine for paediatric premedication. Can J Anaesth 40:119, 1993.

105. Abramowitz MD, Oh TH, Epstein BS et al: The antiemetic effect of droperidol following outpatient strabismus surgery in children. Anesthesiology 59:579, 1983.

106. Klotz U, Avant GR, Hoyumpa A et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 55:347, 1975.

107. Morselli PL, Principi N, Tognoni G et al: Diazepam elimination in premature and full-term infants and children. J Perinat Med 1:133, 1973.

108. Buhrer M, Maitre PO, Crevoisier C et al: Electroencephalographic effects of benzodiazepines. II. Pharmacodynamic modeling of the electroencephalographic effects of midazolam and diazepam. Clin Pharmacol Ther 48:555, 1990.

109. Cray SH, Dixon JL, Heard CM et al: Oral midazolam premedication for paediatric day case patients. Paediatr Anaesth 6:265, 1996.

110. Davis PJ, Tome JA, McGowan FX Jr et al: Preanesthetic medication with intranasal midazolam for brief pediatric surgical procedures: Effect on recovery and hospital discharge times. Anesthesiology 82:2, 1995.

111. Fosel T, Hack C, Knoll R et al: Nasal midazolam in children, plasma concentrations and the effect on respiration. Paediatr Anaesth 5:347, 1995.

112. Malinovsky JM, Populaire C, Cozian A et al: Premedication with midazolam in children: Effect of intranasal, rectal and oral routes on plasma midazolam concentrations. Anaesthesia 50:351, 1995.

113. Spear RM, Yaster M, Berkowitz ID et al: Preinduction of anesthesia in children with rectally administered midazolam. Anesthesiology 74:670, 1991.

114. Karl HW, Keifer AT, Rosenberger JL et al: Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients. Anesthesiology 76:209, 1992.

115. Yaster M, Nichols DG, Deshpande JK et al: Midazolam-fentanyl intravenous sedation in children: Case report of respiratory arrest. Pediatrics 86:463, 1990.

116. Olkkola KT, Aranko K, Luurila H et al: A potentially hazardous interaction between erythromycin and midazolam. Clin Pharmacol Ther 53:298, 1993.

117. Malinovsky JM, Cozian A, Lepage JY et al: Ketamine and midazolam neurotoxicity in the rabbit. Anesthesiology 75:91, 1991.

118. Committee on Drugs American Academy of Pediatrics: Alternate routes of drug administration: Advantages and disadvantages. Pediatrics 100:143, 1997.

119. Kupferberg HJ, Way HJ: Pharmacologic basis for the increased sensitivity of the newborn to morphine. J Pharmacol Exp Ther 141:105, 1963.

120. Lynn AM, Slattery JT: Morphine pharmacokinetics in early infancy. Anesthesiology 66:136, 1987.

121. Bragg P, Zwass MS, Lau M et al: Opioid pharmacodynamics in neonatal dogs: Differences between morphine and fentanyl. J Appl Physiol 79:1519, 1995.

122. Way WL, Costley EC, Way EI: Respiratory sensitivity of the newborn infant to meperidine and morphine. Clin Pharmacol Ther 6:454, 1965.

123. Pokela ML, Olkkola KT, Koivisto M et al: Pharmacokinetics and pharmacodynamics of intravenous meperidine in neonates and infants. Clin Pharmacol Ther 52:342, 1992.

124. Armstrong PJ, Bersten A: Normeperidine toxicity. Anesth Analg 65:536, 1986.

125. Singleton MA, Rosen JI, Fisher DM: Plasma concentrations of fentanyl in infants, children and adults. Can J Anaesth 34:152, 1987.

126. Hertzka RE, Gauntlett IS, Fisher DM et al: Fentanyl-induced ventilatory depression: Effects of age. Anesthesiology 70:213, 1989.

127. Yaster M: The dose response of fentanyl in neonatal anesthesia. Anesthesiology 66:433, 1987.

128. Gauntlett IS, Fisher DM, Hertzka RE et al: Pharmacokinetics of fentanyl in neonatal humans and lambs: Effects of age. Anesthesiology 69:683, 1988.

129. Kuhls E, Gauntlett IS, Lau M et al: Effect of increased intra-abdominal pressure on hepatic extraction and clearance of fentanyl in neonatal lambs. J Pharmacol Exp Ther 274:115, 1995.

130. Feld LH, Champeau MW, van Steennis CA et al: Preanesthetic medication in children: A comparison of oral transmucosal fentanyl citrate versus placebo. Anesthesiology 71:374, 1989.

131. Preston RA, Csontos ER, East KA et al: Plasma fentanyl concentrations after oral transmucosal fentanyl citrate: Children versus adults. Anesthesiology 79:A370, 1993.

132. Epstein RH, Mendel HG, Witkowski TA et al: The safety and efficacy of oral transmucosal fentanyl citrate for preoperative sedation in young children. Anesth Analg 83:1200, 1996.

133. Friesen RH, Lockhart CH: Oral transmucosal fentanyl citrate for preanesthetic medication of pediatric day surgery patients with and without droperidol as a prophylactic anti-emetic. Anesthesiology 76:46, 1992.

134. Ashburn MA, Streisand JB, Tarver SD et al: Oral transmucosal fentanyl citrate for premedication in paediatric outpatients. Can J Anaesth 37:857, 1990.

135. Schutzman SA, Burg J, Liebelt E et al: Oral transmucosal fentanyl citrate for premedication of children undergoing laceration repair. Ann Emerg Med 24:1059, 1994.

136. Schechter NL, Weisman SJ, Rosenblum M et al: The use of oral transmucosal fentanyl citrate for painful procedures in children. Pediatrics 95:335, 1995.

137. Dsida RM, Wheeler M, Birmingham PK et al: Premedication of pediatric tonsillectomy patients with oral transmucosal fentanyl citrate. Anesth Analg 86:66, 1998.

138. Meuldermans W, Van Peer A, Hendrickx J et al: Alfentanil pharmacokinetics and metabolism in humans. Anesthesiology 69:527, 1988.

139. Goresky GV, Koren G, Sabourin MA et al: The pharmacokinetics of alfentanil in children. Anesthesiology 67:654, 1987.

140. Meistelman C, Saint-Maurice C, Lepaul M et al: A comparison of alfentanil pharmacokinetics in children and adults. Anesthesiology 66:13, 1987.

141. Chauvin M, Bonnet F, Montembault C et al: The influence of hepatic plasma flow on alfentanil plasma concentration plateaus achieved with an infusion model in humans: Measurement of alfentanil hepatic extraction coefficient. Anesth Analg 65:999, 1986.

142. Greeley WJ, de Bruijn NP: Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg 67:86, 1988.

143. Starr NJ, Sethna DH, Estafanous FG: Bradycardia and asystole following the rapid administration of sufentanil with vecuronium. Anesthesiology 64:521, 1986.

144. Liu LMP, DeCook TH, Goudsouzian NG et al: Dose response to intramuscular succinylcholine in children. Anesthesiology 55:599, 1981.

145. Mazze RI: Intralingual succinylcholine administration in children: An alternative to intravenous and intramuscular routes? Anesth Analg 47:605, 1968.

146. Carroll JB: Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. Anesthesiology 67:559, 1987.

147. Schwartz L, Rockoff MA, Koka BV: Masseter spasm with anesthesia: Incidence and implications. Anesthesiology 61:772, 1984.

148. van der Spek AF, Fang WB, Ashton-Miller JA et al: The effects of succinylcholine on mouth opening. Anesthesiology 67:459, 1987.

149. Fisher DM, O'Keefe C, Stanski DR, et al: Pharmacokinetics and pharmacodynamics of *d*-tubocurarine in infants, children, and adults. Anesthesiology 57:203, 1982.

150. Meretoja OA: Vecuronium infusion requirements in pediatric patients during fentanyl-N_2O-O_2 anesthesia. Anesth Analg 68:20, 1989.

151. Goudsouzian NG: Atracurium infusion in infants. Anesthesiology 68:267, 1988.

152. Meretoja OA, Taivainen T, Wirtavuori K: Cisatracurium during halothane and balanced anaesthesia in children. Paediatr Anaesth 6:373, 1996.

153. Kisor DF, Schmith VD, Wargin WA et al: Importance of the organindependent elimination of cisatracurium. Anesth Analg 83:1065, 1996.

154. Meretoja OA, Wirtavuori K, Neuvonen PJ: Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. Anesth Analg 67:21, 1988.

155. Goudsouzian NG, Alifimoff JK, Eberly C et al: Neuromuscular and cardiovascular effects of mivacurium in children. Anesthesiology 70:237, 1989.

156. Goudsouzian NG, Alifimoff JK, Liu LM et al: Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane. Br J Anaesth 62:263, 1989.

157. Pittet JF, Tassonyi E, Morel DR et al: Pipecuronium-induced neuromuscular blockade during nitrous oxide-fentanyl, isoflurane, and halothane anesthesia in adults and children. Anesthesiology 71:210, 1989.

158. Meretoja OA, Taivainen T, Erkola O et al: Dose-response and time-course of effect of rocuronium bromide in paediatric patients. Eur J Anaesthesiol Suppl 11:19, 1995.

159. Vuksanaj D, Fisher DM: Pharmacokinetics of rocuronium in children aged 4-11 years. Anesthesiology 82:1104, 1995.

160. Reynolds LM, Lau M, Brown R et al: Intramuscular rocuronium in infants and children: Dose-ranging and tracheal intubating conditions. Anesthesiology 85:231, 1996.

161. Mason LJ, Betts EK: Leg lift and maximum inspiratory force, clinical signs of neuromuscular blockade reversal in neonates and infants. Anesthesiology 52:441, 1980.

162. Cote CJ: Changing concepts in preoperative medication and "NPO" status of the pediatric patient. In Barash PG (ed): ASA Refresher Courses in Anesthesiology. Philadelphia, Lippincott-Raven,

1994, p 101.

163. Miller BR, Friesen RH: Oral atropine premedication in infants attenuates cardiovascular depression during halothane anesthesia. Anesth Analg 67:180, 1988.

164. Cote CJ: NPO after midnight for children: A reappraisal. Anesthesiology 72:589, 1990.

165. Cote CJ: Preoperative preparation of the pediatric patient. In Schwartz AJ (ed): ASA Refresher Courses in Anesthesiology. Philadelphia, Lippincott-Raven, 1997, p 17.

166. American Academy of Pediatrics, Section on Anesthesiology: Evaluation and preparation of pediatric patients undergoing anesthesia. Pediatrics 98:502, 1996.

167. Kain ZN, Mayes LC, Caramico LA: Preoperative preparation in children: A cross-sectional study. J Clin Anesth 8:508, 1996.

168. Karl HW, Pauza KJ, Heyneman N et al: Preanesthetic preparation of pediatric outpatients: The role of a videotape for parents. J Clin Anesth 2:172, 1990.

169. Splinter WM, Schaefer JD: Unlimited clear fluid ingestion two hours before surgery in children does not affect volume or pH of stomach contents. Anaesth Intensive Care 18:522, 1990.

170. Schreiner MS, Treibwasser A, Keon TP: Ingestion of liquids compared with preoperative fasting in pediatric outpatients. Anesthesiology 72:593, 1990.

171. Litman RS, Wu CL, Quinlivan JK: Gastric volume and pH in infants fed clear liquids and breast milk prior to surgery. Anesth Analg 79:482, 1994.

172. Cote CJ: Induction techniques in pediatric anesthesia. In Barash P (ed): ASA Refresher Courses in Anesthesiology 17:43, 1989.

173. Inada T, Fujise K, Tachibana K et al: Orotracheal intubation through the laryngeal mask airway in paediatric patients with Treacher-Collins syndrome. Paediatr Anaesth 5:129, 1995.

174. Lin SM, Liu K, Tsai SK et al: Rectal ketamine versus intranasal ketamine as premedicant in children. Ma Tsui Hsueh Tsa Chi 28:177, 1990.

175. Bjerring P, Arendt-Nielsen L: Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream. Br J Anaesth 64:173, 1990.

176. Salem MR, Wong AY, Fizzotti GF: Efficacy of cricoid pressure in preventing aspiration of gastric contents in paediatric patients. Br J Anaesth 44:401, 1972.

177. Magorian T, Flannery KB, Miller RD: Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. Anesthesiology 79:913, 1993.

178. Wright PM, Caldwell JE, Miller RD: Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. Anesthesiology 81:1110, 1994.

179. Gronert BJ, Brandom BW: Neuromuscular blocking drugs in infants and children. Pediatr Clin North Am 41:73, 1994.

180. Holliday MA, Segar WE: The maintenance need for water in parenteral fluid therapy. Pediatrics 19:823, 1957.

181. Sieber FE, Traystman RJ: Special issues: Glucose and the brain. Crit Care Med 20:104, 1992.

182. Maekawa N, Mikawa K, Yaku H et al: Effects of 2-, 4- and 12-hour fasting intervals on preoperative gastric fluid pH and volume, and plasma glucose and lipid homeostasis in children. Acta Anaesthesiol Scand 37:783, 1993.

183. Aun CS, Panesar NS: Paediatric glucose homeostasis during anaesthesia. Br J Anaesth 64:413, 1990.

184. Graham IF: Preoperative starvation and plasma glucose concentrations in children undergoing outpatient anaesthesia. Br J Anaesth 51:161, 1979.

185. Schreiber GB, Busch MP, Kleinman SH et al: The risk of transfusion-transmitted viral infections: The Retrovirus Epidemiology Donor Study. N Engl J Med 334:1685, 1996.

186. Lackritz EM, Satten GA, Aberle-Grasse J et al: Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. N Engl J Med 333:1721, 1995.

187. Welborn LG, Hannallah RS, Luban NLC et al: Anemia and postoperative apnea in former preterm infants. Anesthesiology 74:1003, 1991.

188. Cote CJ, Zaslavsky A, Downes JJ et al: Postoperative apnea in former preterm infants after inguinal herniorrhaphy: A combined analysis. Anesthesiology 82:809, 1995.

189. Koshy M, Weiner SJ, Miller ST et al: Surgery and anesthesia in sickle cell disease: Cooperative Study of Sickle Cell Diseases. Blood 86:3676, 1995.

190. Vichinsky EP, Haberkern CM, Neumayr L et al: A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease: The Preoperative Transfusion in Sickle Cell Disease Study Group. N Engl J Med 333:206, 1995.

191. Cote CJ: Blood, colloid, and crystalloid therapy. Anesth Clin North Am 9:865, 1991.

192. Miller RD: Complications of massive blood transfusions. Anesthesiology 39:82, 1973.

193. Cote CJ, Drop LJ, Hoaglin DC et al: Ionized hypocalcemia after fresh frozen plasma administration to thermally injured children: Effects of infusion rate, duration, and treatment with calcium chloride. Anesth Analg 67:152, 1988.

194. Cote CJ: Depth of halothane anesthesia potentiates citrate-induced ionized hypocalcemia and adverse cardiovascular events in dogs. Anesthesiology 67:676, 1987.

195. Cote CJ, Drop LJ, Daniels AL et al: Calcium chloride versus calcium gluconate: Comparison of ionization and cardiovascular effects in children and dogs. Anesthesiology 66:465, 1987.

196. Cote CJ, Liu LM, Szyfelbein SK et al: Changes in serial platelet counts following massive blood transfusion in pediatric patients. Anesthesiology 62:197, 1985.

197. Cote CJ, Liu LM, Szyfelbein SK et al: Intraoperative events diagnosed by expired carbon dioxide monitoring in children. Can Anaesth Soc J 33:315, 1986.

198. Cote CJ, Goldstein EA, Cote MA et al: A single-blind study of pulse oximetry in children. Anesthesiology 68:184, 1988.

199. Keenan RL, Shapiro JH, Kane FR et al: Bradycardia during anesthesia in infants: An epidemiologic study. Anesthesiology 80:976, 1994.

200. Keenan RL, Shapiro JH, Dawson K: Frequency of anesthetic cardiac arrests in infants: Effect of pediatric anesthesiologists. J Clin Anesth 3:433, 1991.

201. Rolf N, Cote CJ: Incidence of real and false positive capnography and pulse oximetry alarms during pediatric anesthesia. Anesthesiology 75:A476, 1991.

202. Badgwell JM, McLeod ME, Lerman J et al: End-tidal P_{CC_2} measurements sampled at the distal and proximal ends of the endotracheal tube in infants and children. Anesth Analg 66:959, 1987.

203. Badgwell JM, Heavner JE: End-tidal carbon dioxide pressure in neonates and infants measured by aspiration and flow-through capnography. J Clin Monit 7:285, 1991.

204. Badgwell JM, Swan J, Foster AC: Volume-controlled ventilation is made possible in infants by using compliant breathing circuits with large compression volume. Anesth Analg 82:719, 1996.

205. Beebe DS, Beck D, Belani KG: Comparison of the flow rates of central venous catheters designed for rapid transfusion in infants and small children. Paediatr Anaesth 5:35, 1995.

206. de la Roche MR, Gauthier L: Rapid transfusion of packed red blood cells: Effects of dilution, pressure, and catheter size. Ann Emerg Med 22:1551, 1993.

207. Hatch DJ: Paediatric anaesthetic equipment. Br J Anaesth 57:672, 1985.

208. Nakae Y, Miyabe M, Sonoda H et al: Comparison of the Jackson-Rees circuit, the pediatric circle, and the MERA F breathing system for pediatric anesthesia. Anesth Analg 83:488, 1996.

209. Cote CJ: Pediatric breathing circuits and anesthesia machines. Int Anesthesiol Clin 30:51, 1992.

210. Cote CJ, Petkau AJ, Ryan JF et al: Wasted ventilation measured *in vitro* with eight anesthetic circuits with and without inline humidification. Anesthesiology 59:442, 1983.

211. Stevenson GW, Tobin MJ, Horn BJ et al: The effect of circuit compliance on delivered ventilation with use of an adult circle system for time-cycled volume; controlled ventilation using an infant lung model. Paediatr Anaesth 8:139, 1998.

212. Keenan RL, Boyan CP: Cardiac arrest due to anesthesia: A study of incidence and causes. JAMA 253:2373, 1985.

213. Keenan RL, Boyan CP: Decreasing frequency of anesthetic cardiac arrests. J Clin Anesth 3:354, 1991.

214. Severinghaus JW, Naifeh KH, Koh SO: Errors in 14 pulse oximeters during profound hypoxia. J Clin Monit 5:72, 1989.

215. Wolbarsht ML, George GS, Shearin WA Jr et al: Retinopathy of prematurity: A new look at an old disease. Ophthalmic Surg 14:919, 1983.

216. Flynn JT: Oxygen and retrolental fibroplasia: Update and challenge. Anesthesiology 60:397, 1984.

217. Flynn JT: Retinopathy of prematurity. Pediatr Clin North Am 34:1487, 1987.

218. Anand KJS, Hickey PR: Pain and its effects in the human neonate and fetus. N Engl J Med 317:1321, 1987.

219. Berry FA, Gregory GA: Do premature infants require anesthesia for surgery? Anesthesiology 67:291, 1987.

220. Anand KJS, Hickey PR: Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med 326:1, 1992.

221. Anand KJS, Sippell WG, Schofield NM et al: Does halothane anaesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation? Br Med J 296:668, 1988.

222. Birmingham PK, Dsida RM, Grayhack JJ et al: Do latex precautions in children with myelodysplasia reduce intraoperative allergic reactions? J Pediatr Orthop 16:799, 1996.

223. Cook-Sather SD, Tulloch HV, Liacouras CA et al: Gastric fluid volume in infants for pyloromyotomy. Can J Anaesth 44:278, 1997.

224. Cook-Sather SD, Liacouras CA, Previte JP et al: Gastric fluid measurement by blind aspiration in paediatric patients: A gastroscopic evaluation. Can J Anaesth 44:168, 1997.

225. Rolf N, Cote CJ: Diagnosis of clinically unrecognized endobronchial intubation in paediatric anaesthesia: Which is more sensitive, pulse oximetry or capnography? Paediatr Anaesth 2:31, 1992.

226. Bohn D, Tamura M, Perrin D et al: Ventilatory predictors of pulmonary hypoplasia in congenital diaphragmatic hernia, confirmed by morphologic assessment. J Pediatr 111:423, 1987.

227. Lally KP, Paranka MS, Roden J et al: Congenital diaphragmatic hernia: Stabilization and repair on ECMO. Ann Surg 216:569, 1992.

228. Warner LO, Teitelbaum DH, Caniano DA et al: Inguinal herniorrhaphy in young infants: Perianesthetic complications and associated preanesthetic risk factors. J Clin Anesth 4:455, 1992.

229. Welborn LG, Hannallah RS, Fink R et al: High-dose caffeine suppresses postoperative apnea in former preterm infants. Anesthesiology 71:347, 1989.

230. Welborn LG, Rice LJ, Hannallah RS et al: Postoperative apnea in former preterm infants: Prospective comparison of spinal and general anesthesia. Anesthesiology 72:838, 1990.

231. Kurth CD, Spitzer AR, Broennle AM et al: Postoperative apnea in preterm infants. Anesthesiology 66:483, 1987.

232. Liu LM, Cote CJ, Goudsouzian NG et al: Life-threatening apnea in infants recovering from anesthesia. Anesthesiology 59:506, 1983.

233. Welborn LG, Ramirez N, Oh TH et al: Postanesthetic apnea and periodic breathing in infants. Anesthesiology 65:658, 1986.

234. Kurth CD, LeBard SE: Association of postoperative apnea, airway obstruction, and hypoxemia in former premature infants. Anesthesiology 75:22, 1991.

235. Harnik EV, Hoy GR, Potolicchio S et al: Spinal anesthesia in premature infants recovering from respiratory distress syndrome. Anesthesiology 64:95, 1986.

236. Malviya S, Swartz J, Lerman J: Are all preterm infants younger than 60 weeks postconceptual age at risk for postanesthetic apnea? Anesthesiology 78:1076, 1993.

237. Welborn LG, De Soto H, Hannallah RS et al: The use of caffeine in the control of post-anesthetic apnea in former premature infants. Anesthesiology 68:796, 1988.

238. Webster AC, McKishnie JD, Kenyon CF et al: Spinal anaesthesia for inguinal hernia repair in high-risk neonates. Can J Anaesth 38:281, 1991.

239. Krane EJ, Haberkern CM, Jacobson LE: Postoperative apnea, bradycardia, and oxygen desaturation in formerly premature infants: Prospective comparison of spinal and general anesthesia. Anesth Analg 80:7, 1995.

240. Perlman JM, Volpe JJ: Episodes of apnea and bradycardia in the preterm newborn: Impact on cerebral circulation. Pediatrics 76:333, 1985.

241. Pons G, Carrier O, Richard MO et al: Developmental changes of caffeine elimination in infancy. Dev Pharmacol Ther 11:258, 1988.

242. Cote CJ, Kelly DH: Postoperative apnea in a full-term infant with a demonstrable respiratory pattern abnormality. Anesthesiology 72:559, 1990.

243. Yaster M, Maxwell LG: Pediatric regional anesthesia. Anesthesiology 70:324, 1989.

244. Arthur DS, McNicol LR: Local anaesthetic techniques in paediatric surgery. Br J Anaesth 58:760, 1986.

245. Berde CB: Convulsions associated with pediatric regional anesthesia. Anesth Analg 75:164, 1992.

246. Birmingham PK, Tobin MJ, Henthorn TK et al: Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: An old drug with new recommendations. Anesthesiology 87:244, 1997.

247. Montgomery CJ, McCormack JP, Reichert CC et al: Plasma concentrations after high-dose (45 mg·kg $^{-1}$) rectal acetaminophen in children. Can J Anaesth 42:982, 1995.

248. Houck CS, Sullivan LJ, Wilder RT et al: Pharmacokinetics of a higher dose of rectal acetaminophen in children. Anesthesiology 83:A1126, 1995.

249. Battaglia FC: Intrauterine growth retardation. Am J Obstet Gynecol 106:1103, 1970.

250. Cote CJ, Todres ID: The pediatric airway. In Cote CJ, Ryan JF, Todres ID et al (eds): A Practice of Anesthesia for Infants and Children. Philadelphia, WB Saunders, 1992, p 55.

251. McCrory WW: Developmental Nephrology. Cambridge, Mass, Harvard University Press, 1972.

252. LeDez KM, Lerman J: The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 67:301, 1987.

253. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirements in man. Anesthesiology 30:488, 1969.

254. Katoh T, Ikeda K: The minimum alveolar concentration (MAC) of sevoflurane in humans. Anesthesiology 66:301, 1987.

255. Todres ID: Growth and development. In Cote CJ, Ryan JF, Todres ID et al (eds): A Practice of Anesthesia for Infants and Children, 2nd ed. Philadelphia, WB Saunders, 1993, p 76.

Chapter 60 - Anesthesia for Orthopedic Surgery

Nigel E. Sharrock
John J. Savarese

INTRODUCTION

Perhaps no other subspecialty of anesthesia requires facility with a greater variety of anesthetic techniques than orthopedic anesthesia. As an alternative to general anesthesia, many procedures may perhaps be better managed in orthopedic patients under regional techniques or with combined regional/general anesthetic techniques (Chs. 42 and 43) .

In addition to requiring familiarity with an array of regional anesthetic procedures, orthopedic anesthesia is demanding, requiring a high degree of skill and a facility with other anesthetic techniques such as bronchoscopic intubation for complex airway problems (Ch. 39) , hypotensive anesthesia (Ch. 41) , hemodilution, intraoperative cell saver techniques for minimizing intraoperative blood loss (Ch. 47) , and invasive hemodynamic (Chs. 30 and 31) and evoked potential monitoring (Ch. 35) . Although many of the procedures are short, others are long, necessitating attention to body positioning (Ch. 26) , maintenance of normothermia, fluid balance, and preservation of peripheral blood flow, especially in reimplantation procedures. Factors causing perioperative morbidity and mortality in orthopedics may be different from those of other surgical specialties and thus may demand a different focus of attention.

SPECIFIC PROBLEMS OF THE ORTHOPEDIC PATIENT

Rheumatoid Arthritis

Rheumatoid arthritis is a disease of unknown origin characterized by immune-mediated synovitis. [1] The patients who present the most significant challenge to the anesthesiologist are those with advanced disease having deformity, instability, and destruction of many joints throughout the body. The cervical spine, hips, shoulders, knees, elbows, ankles, wrists, and metacarpophalangeal joints may all be affected. [1] Although cardiac valvular lesions, pericarditis, and pulmonary interstitial fibrosis do occur, these secondary features of the disease are usually not clinically significant. On the other hand, there is an increased incidence of ischemic heart disease (presumably secondary to corticosteroid treatment), cancer (secondary to chemotherapeutic agents), and infections, all of which contribute to only a 50 percent 5-year survival in advanced cases. [2] These patients also have an impaired immune system, wasted musculature, and underlying hypermetabolism. All these factors contribute to an increased rate of postoperative infections and other complications. [3]

TABLE 60-1 -- Orthopedic Patients in Whom Intubation of the Trachea May Be Difficult

DIAGNOSIS	CAUSE(S) OF DIFFICULTY
Ankylosing spondylitis	Fusion of cervical spine
Juvenile rheumatoid arthritis	Ankylosis of cervical spine
	Hypoplasia of mandible
Adult rheumatoid arthritis	Multiple deformity
	Ankylosis and instability of the cervical spine
Prior spine fusion	Ankylosis and limited extension of the cervical spine
Congenital deformities of the cervical spine	
Epiphyseal dysplasia	
Dwarfism (achondroplasia) [245]	
Fractured cervical spine [246]	Limited motion
	Risk of quadriplegia

TABLE 60-2 -- Causes of Atlantoaxial (C1-C2) Instability

Rheumatoid arthritis
Down syndrome
Ankylosing spondylitis
Mucopolysaccharidoses (e.g., Morquio disease)
Note: Patients are stable in extension, but flexion may compress the spinal cord or medulla oblongata.

The anesthesiologist's immediate concerns, however, tend to be technical. Arterial lines may be difficult to place because of small calcific radial arteries that may be inaccessible, owing to flexion deformities of the wrist joint. These patients have a high incidence of carpal tunnel syndrome, which may predispose them to recurrent symptoms postoperatively if radial artery lines are inserted. [4] Central venous lines may be difficult to insert because of fusion and flexion of the neck. The lumbar spine, however, is not often affected in rheumatoid arthritis, so spinal anesthesia and epidural anesthesia are usually straightforward. [5]

Other technical problems of concern are airway management and cervical spine instability. [6] [7] The trachea may be difficult to intubate for a number of reasons (Table 60-1) that are most prominent in those with juvenile rheumatoid arthritis. Atlantoaxial instability (Table 60-2) develops in many patients with adult onset of rheumatoid arthritis. [8] [9] [10] [11] Symptoms include neck pain, headache, or neurologic symptoms in the arms or legs with neck motion. [10] Atlantoaxial subluxation develops from erosion of ligaments by rheumatoid involvement of the bursae around the odontoid process of C2 (Fig. 60-1) . Acute subluxation may result in cord compression and/or compression of the vertebral arteries with quadriparesis or sudden death. Subluxation occurs with flexion of the neck (Fig. 60-2) . Anesthetic management must prevent flexion of the neck and maintain stability of the cervical spine. This may be accomplished by tracheal intubation using a flexible bronchoscope under topical anesthesia and positioning the patient while the patient is still awake. Regional anesthesia with the patient minimally sedated and the neck stabilized is a reasonable perioperative alternative.

Patients with severe rheumatoid arthritis may develop airway obstruction postoperatively from narcotics or sedatives. [12] Therefore, judicious use of narcotics or epidural analgesia for pain relief should be considered postoperatively, together with the administration of nasal oxygen and pulse oximetry if feasible. Cardiopulmonary resuscitation is difficult in rheumatoid patients (Ch. 25) , and emergency tracheotomy is almost impossible in severe cases (Ch. 39) . Jet ventilation by means of a percutaneous catheter through the cricothyroid membrane may be required. [13]

Ankylosing Spondylitis

Ankylosing spondylitis, which is more common in men than women, involves ossification of ligaments at their attachment

Figure 60-1 Magnetic resonance image of a patient with advanced rheumatoid arthritis demonstrating invagination of the odontoid process of C2 (arrow) through the foramen magnum compressing the brain stem. Note the degeneration of C4 and C5, a common problem in rheumatoid arthritis.

Figure 60-2 Computed tomographic scan of the neck demonstrates moderate subluxation of C1 and C2. The odontoid (single arrow) tends to compress the spinal cord (double arrow) against the posterior arch of C1, especially during neck flexion.

to bone. Progressive ossification involves the joint cartilage and disk space of the axial skeleton, with eventual ankylosis. Arthritis and ankylosis may also develop in the hips, shoulders, and costovertebral joints. [14]

Lung function is somewhat impaired from the development of rigidity of the rib cage. Vital capacity is minimally reduced if diaphragmatic activity is preserved. [15] Aortic regurgitation and bundle branch block may develop, necessitating aortic valve replacement or pacemaker insertion. [16] There is an ever-present risk of spine fracture and cervical spine instability in these patients, so careful positioning in the operating room is important [17] (Tables 60-3 and 60-4) .

Anesthetic considerations include (1) use of fiberoptic techniques for tracheal intubation, [13] [18] [19] (2) positioning the patient while the patient is awake, and (3) the choice of axillary rather than interscalene blocks when using regional techniques in the upper extremity. Caudal anesthesia can be readily obtained. The vertebral column is usually fused, making lumbar epidural or spinal anesthesia difficult or impossible. In patients who can still move their neck, fusion of the lumbar spine may be incomplete, [20] enabling epidural or spinal anesthesia to be performed successfully.

POSITIONING FOR ORTHOPEDIC SURGERY

Patients are placed in a variety of positions for orthopedic procedures (Ch. 26) . Improper positioning may result in intraoperative or postoperative problems such as those described below.

Air embolism (Ch. 52) can occur when the operative field is above the level of the heart. This is a potential problem in surgery of the cervical spine or the shoulder in the sitting position, in total hip replacement in the lateral decubitus position, or in lumbar spine surgery in the prone position. Air embolism should be considered if untoward circulatory compromise occurs in any of these settings, although it is rare. [21] [22] [23] [24]

Stretch or malposition of joints may occur during anesthesia and might account for a variety of nonspecific postoperative discomforts in the back or the extremities. Patients with rheumatoid arthritis, osteoporosis, osteogenesis imperfecta, or contractures must be carefully positioned to avoid ligamentous or bony injury.

Direct pressure, especially over bony prominences, may cause tissue ischemia and/or necrosis, particularly after prolonged

TABLE 60-3 -- Anesthetic Problems of the Prone Position

Airway
Endotracheal tube kinking or dislodgement
Edema of upper airway in prolonged cases may cause postoperative respiratory obstruction.
Blood vessels
Arterial or venous occlusion of the upper extremity (check with pulse oximeter on the finger)
Kinking of the femoral vein with marked flexion of the hips; this may predispose to postoperative deep vein thrombosis
During lumbar laminectomy, abdominal pressure increases may cause elevation of epidural venous pressure, contributing to intraoperative bleeding.
Nerves
Brachial plexus stretch or compression
Ulnar nerve compression due to pressure medial to the olecranon
Peroneal nerve compression due to lateral pressure over the head of the fibula
Lateral femoral cutaneous nerve trauma due to pressure over the iliac crest
Head and neck
Gross hyperflexion or hyperextension of the neck [247] [248]
External pressure over the eyes may result in retinal injury due to compression. [26] [249]
Lack of lubrication or coverage of eyes may result in corneal abrasion.
Headrest may cause pressure injury of supraorbital nerve.
Excessive rotation of the neck may contribute to brachial plexus problems or kinking of the vertebral artery. [250]
Lumbar
Excessive lordosis may lead to neurologic injury. [251] [252]

TABLE 60-4 -- Sites of Peripheral Nerve Injury in Orthopedics

NERVE INJURY SITE	CAUSE	COMMENT
Upper extremity		
Brachial plexus	Abduction, external rotation, or extension of shoulder	Usually resolves within several months
	Traction of shoulder	
Ulnar nerve	Pressure at the elbow	Not uncommon
	Traction of C8-T1 dermatomes over the 1st rib	Postoperative palsy results in numbness of ring and fifth fingers
Radial nerve	Pressure behind the arm	Results in wristdrop
Anterior interosseous nerve	Pressure at the distal elbow laterally	Bandages or external pressure [253]
Head		
Supraorbital nerve	Pressure on the supraorbital ridge when lying prone	Results in numbness of forehead
Lower extremity		
Lateral femoral cutaneous nerve of the thigh	Pressure over anterior iliac crest in lateral or prone position or over lateral thigh	Results in numbness of the lateral aspect of the thigh and knee
Femoral nerve	Pressure to the groin of the dependent limb in the lateral decubitus position	Results in numbness of the anterior thigh and medial aspect of lower leg
Common peroneal nerve	Pressure below the head of the fibula	May be due to compartment syndrome
		Results in footdrop

Ankle	Pressure from Esmarch bandage	Pressures beneath Esmarch bandage can be much higher than believed

Checklist:
1. Check for preoperative nerve dysfunction.
2. Check tourniquet problems--duration and pressure.
3. Check postoperative position, splints, tight bandages; rule out compartment syndrome.
4. Check intraoperative surgical factors.
5. Risk of neuropraxia is more common in prolonged surgery.

---

surgery when hypotensive anesthesia is used. Direct pressure on the soft tissues of the orbit when lying prone may lead to retinal artery occlusion, [25] [26] [27] [28] and direct pressure over other peripheral nerves may result in postoperative neurapraxia. [29] [30] [31] [32]

Compression of the veins and/or arteries supplying either the upper or lower extremity may occur. Prolonged venous obstruction at the axillary vein is best alleviated with an axillary roll positioned beneath the upper thorax. Similarly, with patients in the lateral decubitus position, stabilizing posts must be positioned carefully over the groin so as not to interfere with venous return at the level of the femoral vein. Arterial obstruction of a limb may be checked by the use of a pulse oximeter [33] or by palpating the pulse of a distal artery. Venous obstruction may lead to a compartment syndrome with edema, neurapraxia, elevation of creatine phosphokinase level, and myoglobinuria postoperatively. [34]

Positioning of the rheumatoid patient is very important; care must be taken not to flex the neck excessively. Regional anesthesia is particularly suitable for these patients, because neck stability can be maintained by the patients themselves, particularly if only light to moderate sedation is given. In addition, other joints that should not be moved beyond the normal range of motion will be protected by the conscious patient. Excessive motion may occur when these patients are moved in the anesthetized paralyzed state, resulting in neurapraxia, joint dislocation or stretch, or muscle trauma.

The prone position may, in particular, lead to a variety of episodes of minor or major trauma, [35] [36] which are listed in Table 60-3 .

Malpositioning of the extremities may lead to various stretch or compression-induced neurapraxias, [29] [30] [31] [32] as listed in Table 60-4 .

CHOICE OF ANESTHETIC TECHNIQUE

In most cases, the choice of regional or general anesthesia in orthopedics depends on some or all of the following factors: patient preference, state of health of the patient, expertise of the anesthesiologist, duration of the procedure, surgeon's preference, and practice pattern in the hospital. In general, most extremity procedures can be performed using regional anesthesia alone with light sedation. More complicated operations such as allograft replacements, major tumor surgery, reconstructive procedures, and repair of major trauma may be performed using general anesthesia alone. Alternatively, combined techniques using continuous regional anesthesia (e.g., lumbar epidural and axillary or femoral sheath techniques) supplemented with light general anesthesia using a laryngeal mask airway may be particularly useful, incorporating many of the benefits of regional anesthesia with a sedated patient and a "secured" airway. [37]

MAJOR ORTHOPEDIC PROCEDURES

Major operations require special preparation on the part of the anesthesiologist, increased attention to the details of intraoperative monitoring and fluid management, and active participation whenever possible in postoperative pain management.

Management of Blood Loss

Major orthopedic procedures are associated with significant blood loss [38] (Chs. 46 and 47) . Public awareness of the dangers of transfusion has increased dramatically as a result of

---

the acquired immunodeficiency syndrome epidemic as well as a recognition of other risks of transfusion, such as hepatitis, malaria, and, more recently, bovine spongiform encephalitis in Great Britain. [39] [40] [41] A plan to minimize homologous transfusion for all patients undergoing joint replacement, tumor resections, or major spine surgery should be established. This may begin with predonation of autologous blood, [42] preoperative erythropoietin [43] (e.g., in Jehovah's Witnesses [44] or patients with preoperative anemia), intraoperative hemodilution, [45] [46] induced hypotension, [47] conduction anesthesia, use of a cell saver, [48] [49] preservation of normothermia, [50] or by tolerating lower hematocrit values postoperatively (lowering the so-called transfusion trigger [51]) and the use of antifibrinolytic agents. [52] [53] In practice, combination of several of these modalities is most effective in reducing homologous transfusion. At The Hospital for Special Surgery, most patients predonate autologous blood and receive hypotensive anesthesia, and the transfusion trigger has been lowered into the mid 20s. Cell savers, which are expensive and have certain risks, [54] are used selectively in the operating room for major spine surgery for scoliosis. Antifibrinolytic drugs and postoperative cell salvage are probably best used when expected blood loss exceeds 2 L but is unwarranted in more minor procedures due to the risks of aprotinin. [52] [55] [56] [57]

Monitoring Requirements

Optimal intraoperative hemodynamic function requires invasive monitoring and careful fluid management. For these reasons, in longer, more complicated procedures such as those discussed in this chapter, in which major blood loss and massive fluid shifts may be anticipated, the monitoring standards listed in Table 60-5 should be considered.

Total Hip Replacement

Background

Anesthetic management of total hip replacement varies according to the complexity of the surgery, complications that may arise during the surgery, and the medical status of the patient. Complex procedures such as those involving acetabular bone grafting, insertion of a long-stem femoral prosthesis, [58] removal of a prosthesis, revision surgery, or surgery in patients with acetabular protrusion (which entails a risk of entering the pelvic cavity and/or the iliac vessels) complicate the management of the anesthetic.

Anesthetic Management

Monitoring

Because most candidates for total hip replacement have only a limited ability to exercise, their cardiopulmonary function can be difficult to assess. This often elderly population frequently has underlying systemic diseases. Fluid administration must be carefully managed during this type of

TABLE 60-5 -- Suggested Management of Major Orthopedic Procedures

PROCEDURE	AVERAGE DURATION (H)	RANGE OF BLOOD LOSS (UNITS)	SUGGESTED MONITORING OR SPECIAL TECHNIQUES
Total hip	1-4	1-6	Autologous blood donation
			Arterial cannula
			Central venous pressure
			Foley catheter (optional)
			Epidural catheter (optional for postoperative pain treatment)
			Induced hypotension
			Cell saver (revision)
Total knee	1.5-3	0-2 (with tourniquet)	Autologous blood donation
			Arterial cannula
			Foley catheter (optional)
			Epidural catheter (for postoperative analgesia)
Major spinal surgery	3-8	1-10	Autologous blood donation
			Arterial cannula
			Central venous pressure
			Foley catheter
			Induced hypotension
			Evoked potential monitoring
			Wake-up test

Major allograft surgery	2-8	2-10	Autologous blood donation Arterial cannula Central venous pressure Foley catheter Induced hypotension and/or hemodilution Epidural catheter (for postoperative analgesia)
Major pelvic resections	2-8	2-10	Autologous blood donation Arterial cannula Central venous pressure Foley catheter Induced hypotension and/or hemodilution Epidural catheter (for postoperative analgesia) Evoked potential monitoring

extensive surgery. Furthermore, there is an increased likelihood to develop hypoxemia and/or pulmonary edema due to pulmonary endothelial injury from fat or bone marrow emboli [59] and from ventilation/perfusion mismatching (see Positioning and Tables 60-3 and 60-4) . It is, therefore, reasonable to use invasive hemodynamic monitoring periopera- tively in the elderly or medically compromised patient undergoing total hip replacement, especially when this involves complex or revision surgery.

Blood Loss

Extensive studies during and after total hip replacement show that use of either hypotensive or regional (epidural or spinal) anesthesia reduces the blood loss by 30 to 50 percent. [60] [61] Lowering intraoperative mean arterial pressure to 50 mm Hg reduces blood loss more effectively than a mean arterial pressure of 60 mm Hg. [62]

Blood loss during total hip replacement is significantly greater during revision surgery. In these patients, several modalities to reduce the risk of homologous transfusion should be used, including preoperative donation of autologous blood, induced hypotension, or hemodilution. Cell savers can be used if blood loss is expected to be greater than 1 L. With the use of hypotensive epidural anesthesia, intraoperative blood losses of more than 300 mL are unusual, limiting the need for the cell saver or antifibrinolytic agents.

Positioning

The majority of total hip replacements are performed with the patient in the lateral decubitus position. This creates a potential ventilation/perfusion mismatch with resultant hypoxemia, a problem that appears most often in patients with underlying lung disease. The lateral decubitus position can create neurovascular problems as well because the dependent shoulder presses on the axillary artery and brachial plexus, [63] and the anterior stabilizing post compresses the femoral triangle. [33] These problems can be minimized by placing an axillary roll beneath the upper thorax and by careful positioning of the anterior stabilizing post at the dependent groin. Patients who are given hypotensive anesthesia may be at greater risk of neurovascular injury, because less extrinsic pressure is required to compress a less tense vessel. [26]

Cement Fixation

The quality of the cement-bone interface is improved if there is no blood covering the cancellous bone as the cement is applied. Hypotensive anesthesia has been shown radiographically to improve the quality of cement bone fixation, [64] because it reduces bleeding from bone. [62]

Intraoperative Hypotension

Profound hypotension immediately after insertion of cemented femoral prostheses has resulted in cardiac arrest

TABLE 60-6 -- Patients at Risk of Acute Hypotension/Cardiac Arrest During Total Joint Replacement

Long-stem cemented primary total hip replacement
Metastatic cancer [71] [254]
Removal of hardware after intertrochanteric hip fracture [58]
Spiral fracture of femur [58]
Revision of long-stem cemented femoral component
Cemented prosthesis to distal femur
Fracture below femoral component
Cemented long femoral stem total knee replacement [86] [87]

and death [58] [65] [66] [67] (Ch. 41) . These events are not seen with noncemented prostheses. Nowadays, this is distinctly uncommon during elective primary total hip replacement but not uncommon in certain high-risk groups (Table 60-6) . Therefore, it seems likely that hypotension is related in some way to the use of cement (Fig. 60-3) (Figure Not Available) . Two possible explanations are that (1) it may be caused by direct vasodilation and/or cardiac depression from methyl methacrylate or (2) it may be due to the forced entry of air, fat, or bone marrow into the venous system with resultant pulmonary emboli. [65] Large echogenic emboli have been described after insertion of femoral prostheses; this supports the concept that the circulatory collapse is embolic [68] rather than from a toxic effect of the methyl methacrylate. Attempts to minimize this complication have included (1) the use of a plug in the femoral shaft to limit the distal spread of cement in the femur, [69] (2) venting of entrapped air, and (3) waiting for cement to become more viscous before its insertion. These maneuvers minimize the disruption of bone marrow in the distal femur, thereby preventing catastrophic fat/bone marrow pulmonary embolism. Embolization can also be reduced by carefully lavaging the femoral canal. [70] By contrast, in the high-risk group, extensive reaming of the femur occurs, disrupting more bone marrow; and with pressurization with cement, significant marrow is forced into the circulation. This can be seen with transesophageal echocardiography [65] [68] [71] [72] (Fig. 60-4) (Figure Not Available) .

Echogenic material is noted with reaming the femur, after insertion of the cemented femoral component, [65] [68] [71] [72] and with relocation of the hip joint. [73] Large emboli may be observed in the right side of the heart, obstructing the right ventricular outflow tract leading to right-sided heart failure, hypotension, and cardiac arrest. Small emboli traverse the right side of the heart and embolize to the lung. These may increase pulmonary artery pressure but are less likely to cause intraoperative cardiac arrest. In patients with a patent foramen ovale, emboli may pass into the systemic circulation, causing myocardial infarction or stroke. [71] It is curious that although patent foramen ovale is common, severe systemic manifestations of fat emboli are uncommon after total hip replacement even though the majority of patients have evidence of fat embolization during surgery. Fat may also pass through the pulmonary circulation, contributing to systemic manifestation of fat embolism after surgery. [74] Whether this contributes to acute delirium or persistent decline in cognitive function is unclear. [75] [76] [77] [78]

Hypotension may occur with impaction of the femoral component or after relocation of the hip joint (see Fig. 60-3) (Figure Not Available) . With impaction of the

femoral component, the embolic

Figure 60-3 (Figure Not Available) An 85-year-old woman undergoing primary total hip replacement, status post Richard screw with a long side plate. She had a history of chronic obstructive lung disease and osteoporosis. Pulmonary and radial artery pressures were stable until a 200-mm cemented femoral component was inserted (point A). One minute after impaction of the femoral component, pulmonary artery pressure increased acutely (point C) and arterial pressure decreased to 30 mm Hg. Epinephrine, 25 mug, was injected through the distal port of the pulmonary artery catheter (point D). This resulted in a rapid restoration of arterial pressure, a transient tachycardia, and stabilization of the pulmonary artery pressure. The hip was relocated at point B, which resulted in no change in pulmonary artery pressure. *(From Sharrock et al [256])*

material can be forced directly into the venous system. On the other hand, obstruction of the femoral vein occurs during insertion of the femoral component so that fat or bone marrow is usually retained in the femoral vein until the hip joint is relocated. As soon as the obstruction of the vein is relieved, the emboli pass toward the right side of the heart. This process can be monitored with transesophageal echocardiography or by using oximetric pulmonary artery catheters [79] (Fig. 60-5) . An acute decline in mixed venous oxygen saturation occurs in conjunction with a rise in pulmonary artery pressure with release of an obstructed femoral vein containing embolic material.

An effective treatment for the acute hypotension is intravenous epinephrine (4-50 mug) as soon as the hypotension is noted. [56] The dose depends on the degree of hypotension. In the high-risk group, epinephrine (10-20 mug) is injected through the distal port of a pulmonary artery catheter the moment any reduction in arterial pressure is noted after impaction of the long-stem cemented femoral component. If cardiac arrest occurs, much larger doses of epinephrine will be needed to resuscitate the patient.

Hypoxia has been described immediately after insertion of a cemented femoral prosthesis and for up to 5 days into the postoperative period. In the event of hypoxemia, one must first ascertain whether it has a specific cause, such as atelectasis of the dependent lung, hypoventilation, or fluid overload. Even with no specific cause, hypoxemia may persist for some days after hip surgery. [80] It may be a result of the embolic effects of femoral shaft cement or fat embolism. [81] Pulmonary emboli with cement or bone marrow increase pulmonary artery pressures in dogs [82] and humans, [79] but it is unclear whether this is directly responsible for the hypoxemia observed. Postoperative management should include nasal oxygen, pulse oximetry (if necessary for several days), [59] judicious use of narcotics to provide analgesia and yet avoid hypoventilation or airway obstruction, appropriate fluid management, and diuresis. Hypoxia and fluid overload may further increase pulmonary pressures and thus increase the likelihood of pulmonary edema or right-sided heart failure. Postoperative hypoxia is more common in patients who snore. [83]

Total Knee Replacement

Background

Patients who need total knee replacement frequently have severe rheumatoid arthritis, degenerative osteoarthritis, or other significant comorbidities that compound the difficulties of the operation. The average duration of the procedure is 1 to 3 hours (see Table 60-5) .

Anesthetic Management

Unilateral Versus Bilateral Total Knee Replacement

There is considerable debate in the orthopedic literature about the wisdom of performing one-stage bilateral total knee replacement. [84] [85] Knee arthritis is frequently bilateral, and patients appreciate the opportunity to have both replacements performed at the same time so they have only one period of rehabilitation and can "get it over with." On the other hand, patients undergoing bilateral total knee replacement have a higher rate of postoperative complications and require much more perioperative interventions so some selection process is required. However, if patients have appropriate hemodynamic monitoring, postoperative epidural

Figure 60-4 (Figure Not Available) Right atrium during echocardiography. *(A)* Multiple small emboli in the right atrium. *(B)* A large embolus 7 cm in length, which is probably a cast of the femoral vein. *(From Christie et al [73])*

analgesia, and a 24- to 48-hour period of surveillance in a high-dependency unit, the outcome is usually excellent.

Cement

When acrylic cement is applied to the cavities of the tibia, femur, and patella, acute hemodynamic responses seldom follow. Such responses do occur, however, when *long-stem* femoral prostheses are inserted after extensive femoral reaming. [86] [87] Lesser degrees of femoral reaming may reduce the incidence of embolic events, but the significance of these events is unclear. Pressures in the femoral canal of 300 mm Hg or more have been recorded during impaction of the femoral component, [88] although this does not appear to adversely affect arterial oxygen or pulmonary artery pressures. [89]

Figure 60-5 Pulmonary artery oxygen saturation during total hip replacement is recorded from an oximetric pulmonary artery catheter (American Edwards, Baxter Healthcare Corporation, Irvine, Calif). Note the acute fall in pulmonary artery oxygen saturation after relocation of the hip at minute 62 after trial reduction (T) with 8 minutes of potential venous occlusion and minute 74 after final reduction (F) with 12 minutes of potential venous occlusion. *(From Sharrock et al [75])*

On release of the tourniquet after insertion of a cemented total knee replacement, showers of fine emboli are detectable in the right side of the heart. This has been associated with an increase in pulmonary vascular resistance during general anesthesia. [90] Both the severity of metabolic injury [89] and the echogenic material [90] were similar with intramedullary and extramedullary fixation, suggesting that the emboli are thrombi rather than bone marrow. [90] Echogenic material has also been observed during total shoulder replacement. [91]

Blood Loss

The intraoperative use of tourniquets makes blood loss negligible, but postoperative drainage averages 500 to 1,000 mL per knee. [92] Therefore, postoperative monitoring, possibly in the postanesthetic care unit, for 24 hours or more may be necessary in high-risk patients until wound drainage slows. Patients undergoing bilateral procedures are at additional risk of becoming hypovolemic during the first few hours after the operation. Preoperative autologous blood donation can minimize homologous transfusions in this setting.

Fibrinolytic activity increases when the tourniquet is inflated. [93] This observation provided the rationale for the use of antifibrinolytic agents to minimize blood loss after total knee replacement. Although aprotinin has not been clinically proven to be useful in this setting, [94] tranexamic acid is cost effective in unilateral total knee replacement. [53] [95] [96]

Postoperative Pain Management

Total knee replacement is associated with significantly more pain than total hip replacement, and the use of continuous passive motion devices or early mobilization

of the knee increases the pain (Ch. 69) . Epidural analgesia for 24 to 72 hours effectively controls the pain. [97] [98] Femoral/sciatic blocks or intrathecal morphine can be used to provide analgesia for 8 to 24 hours.

Femoral nerve catheter technique can be used for several days. The particular technique depends on the availability of postoperative pain services.

Thoracolumbar Spine Surgery

Major thoracolumbar spine surgery is usually used to correct deformity (e.g., scoliosis), to stabilize fractures, [99] or for resection of tumors. [100]

The basic aim of surgery for scoliosis is to prevent progression of the curvature of the spine, maintain posture, and prevent progression of pulmonary dysfunction. Scoliosis can be congenital or can develop during adolescence or later in life. Comorbidities in adolescent scoliosis include restrictive lung disease, which may lead to pulmonary hypertension, and an increased incidence of malignant hyperpyrexia. Patients with congenital scoliosis may have congenital heart disease, airway abnormalities, and preexisting neurologic deficits. Patients with neuromuscular disease such as Duchenne muscular dystrophy, poliomyelitis, dysautonomia, spinal-cord injury, and neurofibromatosis may also develop scoliosis, which can lead to extremely complex management problems. [101]

Perioperative considerations include intraoperative positioning, spinal-cord monitoring, minimizing of blood loss, and postoperative respiratory care. Many of these patients undergo both anterior and posterior procedures, which may be staged or performed under one anesthetic. The anterior procedure is often performed by thoracotomy. Postoperative ventilatory support and pain management are more complex in patients who have had double procedures and in those with preoperative neuromuscular disorders or dysautonomia.

Problems of surgery and anesthesia in the prone position are listed in Table 60-3 . Particular attention should be focused on positioning of the neck, arms, and eyes to protect pressure points adequately, particularly if hypotensive anesthesia is to be used in longer surgical procedures. Patients may be moved slightly as a result of surgical manipulation after a wake-up test or after alterations in the position of the table. Therefore, reassessment of patient positioning is advisable at regular and pertinent intervals intraoperatively.

Monitoring

Somatosensory Evoked Potentials

Intraoperative spinal-cord function monitoring is important if correction of spinal curvature is to be undertaken. Distraction of the spine may lead to ischemia of the spinal cord because anterior spinal artery flow may be compromised.

There are two approaches to spinal-cord function monitoring: (1) somatosensory evoked potential (SSEP) monitoring [102] (Ch. 35) and (2) the so-called wake-up test. Disruption of spinal cord function results in changes in both amplitude and latency of SSEPs. [103] The SSEPs, however, can also be altered by the use of inhalation agents. On the other hand, they are less disturbed by the nitrous oxide-narcotic-relaxant technique and minimally disturbed by intravenous anesthesia. It is less clear whether deliberate hypotension or moderate hypothermia influences the interpretation of SSEPs, but profound hypotension and shock do cause significant inhibition of the responses. SSEP monitoring may be also used when placing pedicle screws [104] or using other spinal instrumentation or during cervical spine surgery. [105]

Wake-Up Test

SSEPs assess posterior spinal cord function. A reduction in anterior spinal artery blood flow, however, produces ischemia of the anterior regions of the cord, which may result in motor weakness of the lower extremities. In some cases this may occur without observed alterations in SSEPs. For this reason, a wake-up test has been extensively used in many centers in addition to SSEPs during scoliosis surgery. [106]

Patients receive nitrous oxide-narcotic-relaxant anesthesia throughout the procedure. Volatile anesthetics are not

administered. The wake-up test can be performed by discontinuing nitrous oxide and, using peripheral nerve stimulation, ensuring that neuromuscular blockade is relatively shallow (two or three twitches on train-of-four stimulation). Within 3 to 5 minutes from discontinuation of nitrous oxide, patients will usually respond to verbal commands to move their hands and their feet. The presence of motion in the feet suggests that there is not complete ischemia of the spinal cord.

Use of potent anesthetic vapors may delay wake-up for as much as 30 minutes. Intraoperative antagonism of narcosis or of neuromuscular blockade should not be done, because this may cause overly sudden alertness and dangerously excessive movement on the operating table. In the partially paralyzed narcotized state, however, this technique is easy to perform and has worthwhile predictive value regarding the safety of spinal-cord distraction. It is not psychologically traumatic to the patient because amnesia is nearly complete and there is no recollection of pain or discomfort. Anesthesia is reinduced as soon as movement is demonstrated. Motor-evoked potential monitoring has recently been introduced because it should be a better monitor of ischemia in the anterior spinal cord, avoiding the need for a wake-up test. [107] [108]

Conservation of Blood Resources

Because major blood loss is to be expected, autologous blood donation (3 to 4 units if possible), [109] [110] intraoperative hemodilution, use of the cell saver, and induced hypotension should all be considered [102] [110] [112] (Chs. 41 and 47) . Antifibrinolytic agents such as aprotinin reduce blood loss and homologous transfusion in selected cases.

Hemodynamics

Because blood loss during spinal procedures is considerable (2 to 10 units, depending on how many segments are to be fused), moderate levels of hypotension (to a mean of 55 to 60 mm Hg) will effectively reduce blood loss, limiting the likelihood of homologous blood transfusion. Invasive monitoring should be carried out with arterial lines, central venous or pulmonary artery catheters, and Foley catheters for fluid management and replacement therapy.

Postoperative Care

Postoperatively, patients with significant comorbidity should be carefully monitored. [113] Patients with neuromuscular diseases, significant restrictive pulmonary disease, congenital heart disease, or evidence of right-sided heart failure may require ventilation for 24 hours or longer. Admission to an intensive care unit should be planned in advance to ensure precise hemodynamic and fluid monitoring and to allow maximum therapy for pain relief during this time. Intrathecal narcotics [114] [115] or epidural analgesia may also be used for postoperative analgesia. Postoperative hyponatremia sometimes occurs and has been attributed to inappropriate antidiuretic hormone secretion. [116]

Cervical Spine Surgery

Surgery on the cervical spine for trauma, tumor, arthritis, spinal stenosis, or instability has a number of complications. [117] [118] Posterior cervical decompression may be performed in the sitting position, increasing the risk of air embolism, or in the prone position, increasing the risk from external pressure on the eyes. [26] Intubation may be difficult, owing to instability of the spine (as in neck fracture or C1-C2 instability) or to a complex airway due to neck deformity as in rheumatoid arthritis. [8] [11] If any question exists, these patients are best intubated with the aid of a fiberoptic bronchoscope and positioned while they are "awake" (in fact, sedated and amnesic) to be certain that the anesthetic maneuvers have not compromised the spinal cord. An armored endotracheal tube is often preferable to minimize kinking due to retractors or movement during surgery.

Cervical spine surgery may be complicated by injury to the spinal cord during surgery, leading to postoperative quadriplegia with respiratory impairment. [8] For this reason, SSEPs are often used during these procedures to monitor surgical manipulations. Patients with rheumatoid arthritis undergoing cervical spine surgery in the prone position should receive minimal intraoperative fluid, be intubated with the aid of a fiberoptic bronchoscope, and have their neck maintained in a neutral position; and after surgery, they should be kept head up for 3 to 5 hours to minimize the risk of upper airway obstruction after extubation. [119] [120] The potential respiratory difficulty is presumably from upper airway edema secondary to trauma during intubation, excessive fluid, and prolonged dependency. [120] Cervical spine surgery can be performed using local anesthesia to avoid some of these problems. [19] [121]

Lumbar Spine Surgery

Modern lumbar spine surgery ranges from disk excision through tiny incisions to extensive anterior/posterior fusions with allografts, [122] [123] bone grafts, pedicle screws, [124] and so on, which may be associated with excessive blood loss, prolonged dependency, positioning problems, and neurologic monitoring with SSEPs and/or electromyograms. The anesthetic techniques must be adapted to the particular surgery. Although traditionally, these cases have been performed with general anesthesia, spinal or epidural anesthesia is being more commonly performed for simple disk excision. [125] Lumbar spine fusion can be performed with low thoracic epidural anesthesia (usually in combination with general anesthesia). The virtues of epidural anesthesia are less bleeding and improved postoperative epidural analgesia. [126] Epidural catheters can also be placed by either the anesthesiologist or surgeon during scoliosis surgery to facilitate postoperative analgesia.

Major Allograft or Autograft Transplantation Surgery

Background

Major segmental skeletal defects, particularly in the long bones of the extremities, may occur as a result of tumor resection, [127]

Figure 60-6 (Figure Not Available) Three months after en bloc resection and reconstruction with a vascularized fibular graft augmented with autogenous cancellous graft using external fixation for immobilization. *(From Hsu et al [125])*

trauma, or osteonecrosis. Repair of these lesions to eventually permit weight bearing in the legs or restoration of mechanical function to the arms requires bone grafting. Either banked allografts obtained from living or dead donors or vascularized autografts, usually of the fibula, are used to bridge resultant bony gaps [128] [129] (Fig. 60-6) (Figure Not Available) . The duration of these procedures is long (2-10 hours), and many candidates may be debilitated as a result of radiation therapy, chemotherapy, or chronic infection.

Frequently, tumor resection is followed by immediate replacement grafting. The surgical procedure consists of two phases for the anesthesiologist: first, the surgical resection is often bloody, requiring attention to details of fluid management and blood conservation and replacement; second, subsequent fitting of the graft and fixation to adjacent structures followed by wound closure may require several hours of reconstructive surgery. Major anesthetic considerations are monitoring requirements, fluid and transfusion therapy, and postoperative pain relief (see Table 60-5) . In longer procedures, meticulous attention to prevention of pressure necrosis, neurapraxia, joint stiffness, and arthralgia is necessary.

Anesthetic Management

Whatever the choice of anesthetic technique, intraoperative hemodilution combined with deliberate (induced) hypotension should be strongly considered because it is desirable to limit blood loss and to provide as dry a surgical field as possible during the procedure (Chs. 41 and 47) . Preservation of the vascularized graft is vitally important. [130] [131] Patient temperature, circulatory blood volume, and cardiac output must be maintained and, if possible, graft flow augmented by a sympathetic blockade. Other measures include intravenous mannitol and anticoagulation with heparin. Postoperatively, these patients should be kept in special care units so that the wounds can be monitored for graft patency by visual inspection, Doppler flow probe, and pulse oximetry monitoring.

Pelvic and Sacral Resections/Fractures

Background

Major bony resections of the sacrum or pelvis are performed as primary treatment of usually cancerous bone tumors. Major pelvic surgery is also done for repair of complicated pelvic or acetabular fractures. As in major spinal or hip surgery, care in positioning for a long procedure is important, because many of these operations are done in the lateral or prone positions (see Table 60-3) .

Anesthetic Management

Measures for conservation of blood resources and body heat should be carefully followed (Chs. 37 , 41 , and 47) . Invasive monitoring may be essential, and improved postoperative analgesia by means of epidural catheters should be strongly considered [132] (see Table 60-5) .

If the dissection is to involve major pelvic vasculature or nerve roots, the following additional measures might be taken: pulse oximetry in the lower extremity (toe) will aid in judging adequacy of circulation, and SSEP monitoring of L4-L5 to S2 nerve roots may help to lessen the possibility of nerve damage during en bloc dissections of the sacrum (see Table 60-5) or during repair of pelvic fractures. If SSEP monitoring is used, epidural anesthesia and inhalation anesthetics may be contraindicated. Additional large-bore intravenous cannulas may be needed in anticipation of rapid fluid and blood infusion during major resections.

REGIONAL ANESTHESIA OF THE EXTREMITIES

Upper Extremity

Orthopedic procedures in the arm may be performed under a variety of brachial plexus block techniques, with intravenous regional anesthesia, or by using combinations of individual nerve blocks in the arm (Ch. 43) . The selection of a particular technique depends on the need for a tourniquet and on the site of anticipated surgery.

The deep structures of the shoulder are largely innervated by the C5 and C6 dermatomes. This explains why shoulder surgery can be performed under interscalene

block alone, [133] [134] although skin infiltration may be necessary if the skin incision extends toward the axilla. Open-shoulder surgery or arthroscopy performed in the sitting position under interscalene block may be complicated by episodes of bradycardia and/or hypotension in up to 20 percent of cases. [135] These are believed to be vasovagal reactions that are best prevented by fluid loading and pretreatment with intravenous atropine or beta blockers. [136] Excessive absorption of fluid may also occur. [137]

Elbow surgery can be performed by either interscalene or axillary blocks, [138] or by a combination of both. [139] Alkalinization of local anesthetics has been shown to more effectively anesthetize the C8-T1 dermatomes during interscalene blocks. [140] Intercostobrachial blocks (T1-T2) in the axilla may be necessary as a supplement to axillary blocks if medial incisions are performed in the upper arm.

Hand and forearm surgery can be performed with the use of any of the above techniques. Axillary blocks may be preferable for surgery of the medial aspect of the hand and forearm (C7-C8, T1) because this area is sometimes incompletely blocked by the interscalene approach. Continuous axillary blocks may be preferable for prolonged cases. Intravenous regional anesthesia is most applicable for shorter cases.

Peripheral nerve blocks at the wrist or hand can be performed with a long-acting anesthetic such as bupivacaine or ropivacaine to provide postoperative pain relief and facilitate discharge after ambulatory surgery.

Lower Extremity

Essentially, all lower extremity surgery can be performed with spinal, epidural, or combined spinal-epidural anesthesia with variable degrees of sedation (including use of a laryngeal mask airway). Alternatively, nerve blocks can be used alone or in combination with general anesthesia. Knee arthroscopy is usually performed on an outpatient basis with spinal anesthesia using pencil-point needles, [141] with combined spinal-epidural anesthesia, [142] or with femoral block with an intra-articular local anesthetic. Transient radicular irritation is an unresolved problem after outpatient knee arthroscopy under spinal anesthesia. [143]

Surgery of the forefoot can be performed satisfactorily under ankle or midtarsal block [144] or by anesthetizing the branches of the sciatic and femoral nerves proximally. The common peroneal nerve can be anesthetized as it courses superficially below the head of the fibula, or both branches of the sciatic nerve can be blocked in the popliteal fossa. In any surgery involving the medial aspect of the foot, the saphenous branch of the femoral nerve must be anesthetized either at the level of the ankle or perhaps higher up (e.g., inferomedial to the knee). These techniques preclude the use of thigh tourniquets. For ankle blocks, Esmarch bandages or tourniquets applied immediately above the ankle enable at least 2 hours of surgery to be performed without tourniquet pain. [144] [145]

Ankle surgery *cannot* be reliably performed using an ankle block. Epidural anesthesia for ankle surgery is satisfactory, but onset of analgesia may be delayed for up to 30 minutes until complete anesthesia of the L5-S1 nerve roots develops. [146] [147] [148] The addition of an epidural narcotic, epinephrine, clonidine, or bicarbonate [147] [148] to the local anesthetic may also enhance the quality of the anesthesia. Caudal anesthesia is an option in patients with prior lumbar spine surgery, as is spinal anesthesia. Sciatic blocks in combination with femoral or saphenous nerve block are suitable for ankle surgery. The deep structures of the ankle are all innervated by branches of the sciatic nerve, which explains why sciatic or popliteal blocks alone are usually sufficient to reduce ankle fractures and provide excellent postoperative analgesia after ankle surgery. [149]

Femoral and/or sciatic blocks may also be used for surgery of the thigh or the leg. [150] The blocks required depend on the site of the surgery and the necessity for a tourniquet. Three-in-one blocks (femoral plexus block) may be used for knee arthroscopy provided that prolonged tourniquet times can be avoided. A number of sciatic block techniques have been described that are perfectly adequate for surgery below the knee if tourniquets are not used.

Femoral nerve blocks can be performed preoperatively or postoperatively for analgesia. They are particularly effective in providing analgesia for hip or femur fractures [150] [151] and for pain after knee surgery.

POSTOPERATIVE ANALGESIA IN ORTHOPEDICS

Pain after orthopedic surgery depends on the site and extent of surgery and the preoperative use of analgesics by the patient (Ch. 69) . The techniques used are further defined by the facilities available in the hospital. Without a postoperative pain service, systemic narcotics may be the mainstay of therapy. On the other hand, if a postoperative pain service is available, a variety of continuous infusions or patient-controlled analgesia modalities can be used to optimize pain therapy and augment recovery.

Orthopedic surgery lends itself to regional anesthesia. Peripheral blocks with bupivacaine or ropivacaine can provide 12 to 24 hours of significant analgesia, which is often sufficient to eliminate the need for intramuscular or intravenous narcotics. Alternatively, infusions of local anesthetic by means of catheters inserted into the femoral, [152] popliteal, [153] or brachial plexus [154] may provide significant postoperative analgesia. Intra-articular injections of local anesthetic [155] [156] or narcotic [157] [158] can provide effective analgesia, facilitating early discharge after ambulatory surgery.

Epidural analgesia with a combination of low-dose local anesthetic (e.g., 0.05% to 0.1% bupivacaine) in combination with a narcotic (e.g., 2-5 mug/mL fentanyl) provides excellent analgesia after lower extremity surgery. These can be administered as infusions (3-10 mL/h) with patient-controlled analgesia. The rates have to be adjusted to accommodate for changing pain patterns and accumulation of drugs. Nonsteroidal anti-inflammatory drugs can be used to augment the analgesia, [159] [160] although their use is not routinely recommended. [161] Higher doses are required after knee surgery than after hip surgery. Intrathecal infusions of bupivacaine are not recommended for postoperative pain control in orthopedic procedures. [162]

Effective analgesia with epidural infusions or peripheral blockade reduces narcotic requirements, provides better analgesia, reduces catabolism, [163] and results in improved rates of rehabilitation after total knee replacement. [164] [165] To optimize the potential advantage of the analgesia, early rehabilitation should be encouraged. [166]

There are several limitations to the use of catheter techniques for postoperative analgesia after orthopedic surgery. First, as stated earlier, their use is contingent on an effective pain service operating with the cooperation of the nurses and orthopedic surgeons. Second, these modalities must be used in conjunction with the perioperative management of thromboembolism. The risk of epidural catheters is increased when low-molecular-weight heparin is used, [167] [168] whereas there appears to be minimal risk with aspirin or warfarin. [169] At The Hospital for Special Surgery, almost all patients undergoing total hip or knee replacement receive postoperative epidural analgesia for 24 to 72 hours postoperatively. Patients are concurrently given aspirin or warfarin (Coumadin) after surgery in combination with foot pumps, foot exercises, and early ambulation. Low-molecular-weight heparin is not used in conjunction with epidural analgesia. No clinical epidural hematomas have been noted (>2,000 cases are performed annually at The Hospital for Special Surgery).

The final complicating factor relates to persistent lower extremity nerve injury. Patients who are at risk of developing a compartment syndrome should not have epidural infusions of local anesthetic or lower extremity nerve blocks because these may mask the early diagnostic signs (excessive pain, numbness, or muscle weakness). [170] [171] This applies particularly to patients with fractures of the tibia and fibula. [172] A related problem concerns the use of epidural analgesia in patients who are at risk of developing nerve injuries after surgery, particularly peroneal palsy after complicated total knee replacement. [173] [174] Patients with valgus deformities and those undergoing high tibial osteotomy are at risk of developing peroneal palsy after surgery. [175] If the palsy is diagnosed early, the knee can be flexed, bandages changed, and so on to limit injury to the nerve. An epidural infusion can delay the diagnosis, increasing the risk of permanent nerve damage. In these cases, it is preferable to avoid epidural analgesia altogether to avoid confusion and focus on early detection of potential neurologic deterioration. Epidural anesthesia and analgesia can be used to remove an infected prosthesis because the risk of epidural abscess in this setting is negligible. [176]

COMPLICATIONS OF ORTHOPEDIC SURGERY

Tourniquet Problems

Tourniquets are applied around upper or lower extremities to eliminate intraoperative bleeding and thereby provide better operative conditions. Unfortunately, the tourniquet is unphysiologic and is associated with a number of disadvantages (Table 60-7) .

Local Effects of Tourniquet Inflation

Mitochondrial partial pressure of oxygen decreases to zero within 8 minutes of inflating a tourniquet. Anaerobic metabolism then begins. Decrease of nicotinamide adenine dinucleotide and creatine phosphate stores in muscle occurs

TABLE 60-7 -- Physiologic Changes Caused by Limb Tourniquets

Neurologic effects
Abolition of somatosensory evoked potentials and nerve conduction occurs within 30 minutes.
Application for more than 60 minutes causes tourniquet pain and hypertension.
Application for more than 2 hours may result in postoperative neurapraxia.
Evidence of nerve injury may occur at a skin level underlying the edge of the tourniquet.
Muscle changes
Cellular hypoxia develops within 8 minutes.
Cellular creatine declines.
Progressive cellular acidosis occurs.
Endothelial capillary leak develops after 2 hours.
Limb becomes progressively colder.
Systemic effects of tourniquet inflation
Elevation in arterial and pulmonary artery pressures develops. This is usually slight to moderate if only one limb is occluded.
Systemic effects of tourniquet release
Transient fall in core temperature [186]
Transient metabolic acidosis
Transient fall in central venous oxygen tension (but systemic hypoxemia unusual)
Release of acid metabolites into central circulation (e.g., thromboxane)
Transient fall in pulmonary and systemic arterial pressures
Transient increase in end-tidal CO_2
Increased oxygen consumption [255]

over the next 30 to 60 minutes. [177] Cellular acidosis (pH < 6.5) rapidly ensues. [177] [178] Hypoxia and acidosis result in the release of myoglobin, [179] intracellular enzymes, and potassium. [180] Thromboxane is released locally with disruption of endothelial integrity. [181] Tissue edema develops if tourniquets are inflated more than 60 minutes; closure of ankle incisions may then be difficult. [182] The limb loses heat and may approach room temperature with time. Injury to muscle beneath the tourniquet may delay rehabilitation. [183]

Metabolic Response to Tourniquet Release

With deflation of the tourniquet and reperfusion of the extremity, a washout of metabolic byproducts occurs. [184] A decrease in core body temperature of 0.7°C typically occurs within 90 seconds of deflation of a lower limb tourniquet, [185] [186] and venous oxygen saturation [187] may fall 20 percent in 30 to 60 seconds. Increases in end-tidal carbon dioxide are typically noted, [188] but decreases in arterial oxygen saturation are infrequent unless significant pulmonary shunting exists. [189]

Hemodynamic Responses

The causes of hemodynamic responses are the initial inflation of the tourniquet, subsequent prolonged tourniquet inflation, and an immediate response after tourniquet deflation (Fig. 60-7) .

Figure 60-7 The hemodynamic effect of thigh tourniquet inflation (single bar) and deflation (double bar) in an 86-year-old man with hypertension undergoing total knee replacement. Note the changes in pulmonary and systemic artery pressures with both inflation and deflation of the tourniquet. The persistent elevation in pulmonary artery pressure after reinflation of the tourniquet after deflation (after third bar) may represent transient myocardial dysfunction.

Tourniquet Inflation

Inflation of the tourniquet and exsanguination of the limb result in an expansion of central venous blood volume and a theoretical rise in peripheral vascular resistance. In ordinary practice, this results in small increases in central venous or arterial pressures. [190] [191] However, patients with extensive varicose veins or poor ventricular compliance may experience considerable increases in pulmonary artery pressure (see Fig. 60-7) . Bilateral simultaneous tourniquet inflation of the lower extremities may result in significant elevations in central venous pressure. [190] [192]

Tourniquet Deflation

Deflation of the tourniquet with reperfusion of the ischemic limb is frequently associated with decreases in both central venous and arterial pressures. [193] These can be profound (see Fig. 60-7) and have resulted in cardiac arrests. [194] Contributing factors include sudden reduction in peripheral vascular resistance with pooling of blood in the extremity, acute blood loss, and the circulatory effects of the ischemic metabolites (e.g., thromboxane). [181]

Prolonged Inflation

Forty-five to 60 minutes after tourniquet inflation patients under general anesthesia may develop systemic hypertension. [195] The reason for this rather consistent timing is not entirely clear, but it may reflect a critical level of cellular ischemia in the muscle or nerve. Attempts to reduce blood pressure by deepening anesthesia are not always successful, and vasodilators such as hydralazine, nifedipine, or labetalol may be necessary. [195]

Tourniquet Pain

Patients receiving spinal or epidural anesthesia may develop a poorly defined aching or burning sensation in the

distal extremity about 1 hour after tourniquet inflation. [196] [197] Attempts to relieve "tourniquet pain" with intravenous narcotics are not always successful. Tourniquet pain may, however, be relieved by deflating the tourniquet for 10 to 15 minutes and then reinflating it. This correlates with correction of cellular acidosis. [198] Our experience has demonstrated that a complete brachial plexus block using long-acting local anesthetics is not associated with tourniquet pain for as long as 3 to 4 hours. Neither stellate ganglion nor intercostobrachial nerve blocks are effective in relieving tourniquet pain of the upper extremity. [199] These observations taken together suggest that tourniquet pain may be related in some manner to the quality or intensity of somatic neural blockade. [199] Experience with spinal anesthesia also suggests that the intensity of blockade may be more important than the anesthetic level in preventing tourniquet pain, because isobaric spinal anesthesia has a lower incidence of tourniquet pain than hyperbaric spinal anesthesia. [200]

Neurologic Consequences

Neurologic problems may occur when tourniquets are inflated for long periods (>2 hours) or excessive inflation pressures are used. A shear force is applied to nerve trunks at the edges of the tourniquet. [201] Within 30 minutes of inflating a tourniquet, nerve conduction ceases. [202] [203] This may reflect either axonal hypoxia or the direct result of extrinsic pressure on the nerves beneath the tourniquet. [204] In clinical practice, tourniquets should be deflated every 90 to 120 minutes to minimize the risk of postoperative neurapraxias. [178] [198] Alternatively, tourniquet pressure can be lowered to 250 mm Hg while maintaining systolic pressures at 90 to 100 mm Hg. This provides a pressure gradient of 150 mm Hg between the tourniquet and systolic pressure, more than enough to maintain an exsanguinated limb. Anesthesiologists who use regional anesthesia may be implicated when postoperative neurapraxias were in fact secondary to tourniquet injury. Recognition of the adverse effects of tourniquets has led many to perform surgery without a tourniquet [205] [206] [207] or to limit the duration of its use. [208]

Fat Embolism

A certain degree of lung dysfunction occurs in all patients after long bone fractures, but clinically significant fat embolism syndrome as such develops in only 10 to 15 percent of these patients. Signs include hypoxia, tachycardia, mental status changes, and petechiae on the conjunctiva, axilla, or upper thorax. Fat globules in the urine are nondiagnostic, but lung infiltrates seen on chest radiograph confirm the presence of lung injury. [209] [210] [211]

The pathophysiology of fat embolism represents capillary endothelial breakdown causing pericapillary hemorrhagic exudates most apparent in the lungs and brain. Pulmonary edema and hypoxemia occur as a result of pulmonary exudates. Hypoxia and areas of cerebral edema may account for the variable neurologic abnormalities seen.

The more severe cases of fat embolism involve fractures of the femur and tibia. Delays in fixation of bones and extensive reaming of the medullary canals contribute to perioperative morbidity [212] and to the severity of fat embolism syndrome. Efforts to surgically correct fractures early and minimize trauma to the bone marrow lessen the degree of fat/bone marrow embolism. Patients with coexisting lung injury are at additional risk of fat embolism. Evidence suggests that fat may pass to the systemic circulation through a patent foramen ovale [71] [72] or by transpulmonary passage. [74] The chemical composition of the fat may even contribute to this process. [213] For this reason, it is preferable to minimize pulmonary artery hypertension to reduce transpulmonary passage of fat and limit pulmonary endothelial transudation of fluid.

Treatment includes early recognition, oxygen administration, and judicious fluid management. Corticosteroids in large doses shortly after major trauma have been found to minimize the clinical presentation of fat embolism but are probably not necessary in most cases if oxygen therapy is administered. With appropriate fluid management, adequate ventilation, and the prevention of hypoxemia, outcome is usually excellent.

Deep Vein Thrombosis

Deep vein thrombosis is a common problem in orthopedics, [214] and pulmonary embolism is a major cause of postoperative mortality. [215] [216] [217] Rates are low after upper extremity surgery, spine surgery, [218] and knee arthroscopy (3%), [219] but more common after total hip replacement (30-50%), [220] [221] [222] total knee replacement (40-60%), [164] [223] [224] and trauma to the lower extremities (20-50%). Proximal deep vein thrombosis (popliteal femoral or iliac vessels) is more common after total hip replacement (10-20%) [221] [222] [225] and more likely to cause pulmonary embolism.

The emboli form during surgery during periods of venous stasis in the presence of surgical injury. During total knee replacement, there is absolute stasis with the tourniquet inflated, and on release of the tourniquet, acute increases in markers of coagulation can be detected in blood [226] (Fig. 60-8) (Figure Not Available) . Concurrently, thromboemboli can be detected in the right side of the heart on echocardiography. [227] During total hip replacement, obstruction of the femoral vein occurs during surgery on the femur. [79] [228] [229] When obstruction of the vein is relieved when the hip is relocated, an increase in markers of thrombosis is noted (Fig. 60-9) (Figure Not Available) and echogenic material can be seen on echocardiography. Efforts to reduce deep vein thrombosis during surgery should be directed during these phases of venous occlusion. Maneuvers include reducing the duration of surgery (surgeon's responsibility), [225] augmenting lower extremity blood flow during surgery to reduce venous stasis, [230] and finally, administering anticoagulants during this phase of surgery. [79] If 15 to 20 units/kg of unfractionated heparin is administered before surgery on the femur, fibrin formation can be suppressed and deep vein thrombosis rates reduced to 6%. [231]

Epidural or spinal anesthesia reduces deep vein thrombosis rates after total knee replacement by 20% (from 50% to 40%) [164] and after total hip replacement by approximately 40%. [232] [233] Deep vein thrombosis rates during total hip replacement performed with epidural anesthesia can be reduced to 10% with the concurrent use of low-dose epinephrine

Figure 60-8 (Figure Not Available) Fibrinopeptide A in patients receiving general or epidural anesthesia. Determinations were made before the induction of anesthesia (sample 1), 20 minutes after the start of the surgical procedure (sample 2), 45 seconds after deflation of the tourniquet at the end of surgery (sample 3) and 1 hour postoperatively (sample 4). Values are mean ± SEM. Note the increase in fibrinopeptide A after deflation of the tourniquet (sample 3) representing thrombosis in the leg while the tourniquet was inflated. *(From Sharrock et al [226])*

infusions. [225] [234] The mechanism of action of epinephrine is unknown, [235] but it does augment lower extremity blood flow during epidural anesthesia, thereby minimizing venous stasis. [230]

Postoperative epidural analgesia does not appear to provide additional benefit in reducing deep vein thrombosis rates. [223] Epidural infusion of 0.1% bupivacaine does not increase femoral venous blood flow, whereas simple flexion/extension exercises of the foot do increase extremity blood flow. [236] The benefit of epidural analgesia may be that it facilitates early ambulation, which is beneficial in prophylaxis of deep vein thrombosis.

There is a controversy about using epidural anesthesia and heparin. [167] The effects of heparin and epidural anesthesia on deep vein thrombosis prophylaxis are, in fact, additive. [233] [237] Deep vein thrombosis rates of 33% are noted using low-molecular-weight heparin with general anesthesia, whereas rates of 19% are noted with low-molecular-weight heparin and epidural anesthesia. [233] Perioperative anticoagulants are necessary if general anesthesia is used, but the question is whether low-molecular-weight heparin is useful (or in fact dangerous) when used in conjunction with conduction anesthesia. [167]

Postoperative modalities to reduce deep vein thrombosis that can safely be used in conjunction with epidural anesthesia include pneumatic compression boots, [238] foot pumps, [239] [240] foot exercises, [236] early ambulation, aspirin, and low-dose warfarin started the day after surgery. Anticoagulation is not generally recommended after knee arthroscopy or spine surgery. In high-risk cases, vena cava filters may be placed preoperatively.

Figure 60-9 (Figure Not Available) Changes in fibrinopeptide A and D-dimer in patients receiving saline (n = 12) or intravenous heparin (1000 units) (*n* = 11). Determinations were made before the epidural anesthetic (1), after implantation of the acetabular component--1 to 2 minutes before operating on the femur (2), 45 seconds after relocation of hip joint after the cemented femoral component had been inserted (3), and 1 hour postoperatively in the postanesthesia care unit (4). Patients received either intravenous heparin (1000 units) or saline immediately after insertion of the acetabular component (event 2). Note a suppression of fibrinopeptide A after insertion of a cemented femoral component in patients receiving heparin compared to saline (*P* = .006) (event 3), reflecting inhibition of thrombosis with heparin. D-dimer was not affected by heparin administration demonstrating that heparin did not suppress fibrinolysis. Values are mean ± standard error of the mean. *(From Sharrock et al [79])*

The role of the anesthesiologist in the prevention of deep vein thrombosis will change with a recognition of the role of anesthesia in the prevention of thrombosis and a realization that the thrombi form in the operating room rather than after surgery. Because they form during "our watch," anesthesiologists have an opportunity and a responsibility to prevent thrombi from forming.

PEDIATRIC ORTHOPEDIC ANESTHESIA PRACTICE

A subset of pediatric patients may have to undergo repeated hospitalization and orthopedic surgical procedures (Chs. 44 and 59) . These include children with cerebral palsy, congenital spine deformities, juvenile rheumatoid arthritis, osteogenesis imperfecta, epiphyseal dysplasia, and various forms of scoliosis. Many of these patients suffer from pain, disability, and social isolation. They therefore deserve additional care and sympathy as well as excellence of clinical practice to overcome sometimes formidable technical difficulties.

Cerebral Palsy

Children with cerebral palsy may present technical difficulties because of contractures that make intraoperative positioning difficult. Many of these children were born prematurely and suffer the residua of bronchopleural dysplasia with tracheomalacia, irritable airways, and residual lung dysfunction. In addition, they may develop recurrent aspiration due to gastroesophageal reflux. Hypothalamic dysfunction may be a component of the cerebral palsy, making perioperative hypothermia more likely.

The tracheas of patients with certain congenital deformities of the spine may be difficult to intubate for technical reasons (see Table 60-1) . Therefore, fiberoptic laryngoscopy (with pediatric equipment) or regional anesthesia may be necessary. Generalized ligamentous laxity of the cervical spine and atlantoaxial subluxation or stenosis of the foramen magnum may predispose these patients to spinal cord compression with potential quadriparesis during anesthesia.

Juvenile Rheumatoid Arthritis

Children with juvenile rheumatoid arthritis tend to develop fusion of the cervical spine and premature closure of epiphyseal plates, leading to hypoplastic mandible and fixed neck. Oral intubation of the trachea in this setting is essentially impossible. Regional anesthesia can also be complicated in this group because of a characteristic lumbar lordosis and an inability to abduct the shoulder. These factors make lumbar epidural and axillary blocks technically more difficult. Central venous lines may also be difficult to insert because an inability of the child to rotate the head is combined with the forward flexion of the neck. [241]

Regional Anesthesia in Pediatrics

Spinal, caudal, and lumbar epidural anesthesia, transarterial axillary blocks, or lower extremity blocks with the aid of a nerve stimulator may be performed in adequately sedated patients in whom cooperation to define paresthesias is not always obtainable [242] [243] (Chs. 44 and 59) . Regional approaches should be considered when surgery is relatively minor and of shorter duration. [244] Emergence from anesthesia is facilitated by optimal analgesia.

References

1. Firestein GS: Etiology and pathogenesis of rheumatoid arthritis. In Kelly WN, Harris ED Jr, Ruddy S et al (eds): Textbook of Rheumatology. 5th ed. Philadelphia, WB Saunders, 1997, p 851.

2. Pincus T, Callahan LF, Vaughn WK: Questionnaire, walking time and button test measures of functional capacity as predictive markers for mortality in rheumatoid arthritis. J Rheumatol 14:240, 1987.

3. Pellicci PM, Ranawat CS, Tsairis P et al: A prospective study of the progression of rheumatoid arthritis of the cervical spine. J Bone Joint Surg Am 63A:342, 1981.

4. Martin SD, Sharrock NE, Mineo R et al: Acute exacerbation of carpal tunnel syndrome after radial artery cannulation. J Hand Surg 18A:455, 1993.

5. Stevens JM, Kendall BE, Crockard HA: The spinal cord in rheumatoid arthritis with clinical myelopathy: A computed myelographic study. J Neurol Neurosurg Psychiatry 49:140, 1986.

6. Crosby ET, Lui A: The adult cervical spine: Implications for airway management: Review articles. Can J Anaesth 37:77, 1990.

7. Macarthur A, Kleiman S: Rheumatoid cervical joint disease--a challenge to the anaesthetist. Can J Anaesth 40:154, 1993.

8. Popitz MD: Anesthetic implications of chronic disease of the cervical spine. Anesth Analg 84:672, 1997.

9. Santavirta S, Slatis P, Kankaanpaa U et al: Treatment of the cervical spine in rheumatoid arthritis. J Bone Joint Surg Br 70B:658, 1988.

10. Ranawat CS, O'Leary PK, Pellicci PM et al: Cervical spine fusion in rheumatoid arthritis. J Bone Joint Surg Am 61A:1003, 1979.

11. Crockard HA: Surgical management of cervical rheumatoid problems: Spine update. Spine 20:2584, 1995.

12. Gardner DL, Holmes F: Anaesthetic and postoperative hazards in rheumatoid arthritis. Br J Clin Pharmacol 33:258, 1961.

13. Benumof JL: Management of the difficult adult airway: With special emphasis on awake tracheal intubation. Anesthesiology 75:1087, 1991.

14. van der Linden S: Ankylosing spondylitis. In Kelley WN, Harris ED Jr, Ruddy S et al (eds): Textbook of Rheumatology. Philadelphia, WB Saunders, 1997, p 969.

15. Feltelius N, Hedenstrom H, Hillerdall G et al: Pulmonary involvement in ankylosing spondylitis. Ann Rheum Dis 45:736, 1986.

16. Bukley BH, Roberts WC: Ankylosing spondylitis and aortic regurgitation: Description of the characteristic cardiovascular lesion from study of eight necropsy patients. Circulation 48:1014, 1973.

17. Salathe M, Johr M: Unsuspected cervical fracture: A common problem in ankylosing spondylitis. Anesthesiology 70:869, 1989.

18. Sinclair JR, Mason RA: Ankylosing spondylitis: The case for awake intubation. Anaesthesia 39:3, 1984.

19. McMaster MJ: Osteotomy of the cervical spine in ankylosing spondylitis. J Bone Joint Surg Br 79B:197, 1997.

20. Viitanen JV, Kokko M-L, Lehtinen K et al: Correlation between mobility restrictions and radiologic changes in ankylosing spondylitis. Spine 20:492, 1995.

21. Albin MS, Ritter RR, Pruett CE et al: Venous air embolism during lumbar laminectomy in the prone position: Report of three cases. Anesth Analg 73:346, 1991.

22. Frankel AS, Holzman RS: Air embolism during posterior spinal fusion. Can J Anaesth 35:511, 1988.

23. Lang SA, Duncan PG, Dupius PR: Fatal air embolism in an adolescent with Duchenne muscular dystrophy during Harrington instrumentation. Anesth Analg 69:132, 1989.

24. Vavilala MS, O'Donnell RJ, Conrad EU III et al: Paradoxical air embolism after lower limb reconstruction: Case report. Anesth Analg 83:654, 1996.

25. Walkup HE, Murphy JD: Retinal ischemia with unilateral blindness: A complication occurring during pulmonary resection in the prone position. J Thorac Surg 23:174, 1952.

26. Brown RH, Schauble JF, Miller NR: Anemia and hypotension as contributors to perioperative loss of vision. Anesthesiology 80:222, 1994.

27. Roth S, Roizen M: Optic nerve injury: Role of the anesthesiologist? [Letter]. Anesth Analg 82:435, 1996.

28. Roth S, Thisted RA, Erickson JP et al: Eye injuries after nonocular surgery: A study of 60,965 anesthetics from 1988 to 1992. Anesthesiology 85:1020, 1996.

29. Stoelting RK: Postoperative ulnar nerve palsy: Is it a preventable complication? Anesth Analg 76:7, 1993.

---

30. Caplan RA, Posner KL, Cheney FW: Perioperative ulnar neuropathy: Are we ready for shortcuts? Anesthesiology 81:1321, 1994.

31. Kempen PM: Peri- or postoperative ulnar neuropathy. Anesthesiology 82:1538, 1995.

32. Warner MA, Warner ME, Martin JT: Ulnar neuropathy: Incidence, outcome, and risk factors in sedated or anesthetized patients. Anesthesiology 81:1332, 1994.

33. Smith JW, Pellicci PM, Sharrock NE et al: Complications after total hip replacement: The contralateral limb. J Bone Joint Surg Am 71A:528, 1989.

34. Lachiewicz PF, Latimer HA: Rhabdomyolysis following total hip arthroplasty. J Bone Joint Surg Br 73B:576, 1991.

35. Kuperwasser B, Zaid BT, Ortega R: Compartment syndrome after spine surgery and use of the Codman frame. Anesthesiology 82:793, 1995.

36. Ziser A, Friedhoff RJ, Rose SH: Prone position: Visceral hypoperfusion and rhabdomyolysis. Anesth Analg 82:412, 1996.

37. Dyer RA, Llewellyn RL, James MFM: Total I.V. anaesthesia with propofol and the laryngeal mask for orthopaedic surgery. Br J Anaesth 74:123, 1995.

38. Lemos MJ, Healy WL: Blood transfusion in orthropaedic operations. J Bone Joint Surg Am 78A:1260, 1996.

39. Weiskopf RB: More on the changing indications for transfusion of blood and blood components during anesthesia: Editorial views. Anesthesiology 84:498, 1996.

40. Thomas MJG, Desmond MJ, Gillon J: Consensus conference on autologous transfusion: General background paper. Transfusion 36:628, 1996.

41. Landers DF, Hill GE, Wong KC et al: Blood transfusion-induced immunomodulation. Anesth Analg 82:187, 1996.

42. Thomas MJG, Gillon J, Desmond MJ: Consensus conference on autologous transfusion: Preoperative autologous donation. Transfusion 36:633, 1996.

43. Faris PM, Ritter MA, Abels RI, The American Erythropoietin Study Group: The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. J Bone Joint Surg Am 78A:62, 1996.

44. Sparling EA, Nelson CL, Lavender R et al: The use of erythropoietin in the management of Jehovah's Witnesses who have revision total hip arthroplasty. J Bone Joint Surg Am 78A:1548, 1996.

45. Mielke LL, Entholzner EK, Kling M et al: Preoperative acute hypervolemic hemodilution with hydroxyethylstarch: An alternative to acute normovolemic hemodilution? Anesth Analg 84:26, 1997.

46. Gillon J, Thomas MJG, Desmond MJ: Consensus conference on autologous transfusion: Acute normovolaemic haemodilution. Transfusion 36:640, 1996.

47. Sharrock NE, Mineo R, Urquhart B: Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty. Br J Anaesth 67:17, 1991.

48. Desmond MJ, Thomas MJG, Gillon J et al: Consensus conference on autologous transfusion: Perioperative red cell salvage. Transfusion 36:644, 1996.

49. Borghi B, Pignotti E, Montebugnoli M et al: Autotransfusion in major orthopaedic surgery: Experience with 1785 patients. Br J Anaesth 97:662, 1997.

50. Schmied H, Kurz A, Sessler DI et al: Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty. Lancet 347:289, 1996.

51. The American Society of Anesthesiologists Task Force on Blood Component Therapy: Practice guidelines for blood component therapy. Anesthesiology 84:732, 1996.

52. Capdevila X, Calvet Y, Biboulet P et al: Aprotinin decreases blood loss and homologous transfusion in patients undergoing major orthopedic surgery. Anesthesiology 88:50, 1998.

53. Hiippala ST, Strid LJ, Wennerstrand MI et al: Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg 84:839, 1997.

54. Linden JV, Kaplan HS, Murphy MT: Fatal air embolism due to perioperative blood recovery. Anesth Analg 84:422, 1997.

55. Murkin JM, Shannon NA, Bourne RB et al: Aprotinin decreases blood loss in patients undergoing revision or bilateral total hip arthroplasty. Anesth Analg 80:343, 1995.

56. Janssens M, Joris J, David JL et al: High-dose aprotinin reduces blood loss in patients undergoing total hip replacement surgery. Anesthesiology 80:23, 1994.

57. Kasper S-M, Schmidt J, Rutt J: Is aprotinin worth the risk in total hip replacement? Anesthesiology 81:517, 1994.

58. Patterson BM, Healy JH, Cornell CN et al: Cardiac arrest during hip arthroplasty with a cemented long-stem component. J Bone Joint Surg Am 73A:271, 1991.

59. Dyson A, Henderson AM, Chamley D et al: An assessment of postoperative oxygen therapy in patients with fractured neck of femur. Anaesth Intensive Care 16:405, 1988.

60. Thompson GE, Miller RD, Stevens WC et al: Hypotensive anesthesia for total hip arthroplasty: A study of blood loss and organ function (brain, heart, liver, and kidney). Anesthesiology 48:91, 1978.

61. Vazeery AK, Lunde O: An assessment of surgical haemorrhage during sodium nitroprusside infusion. Acta Orthop Scand 50:433, 1979.

62. Sharrock NE, Mineo R, Urquhart B et al: The effect of two levels of hypotension on intraoperative blood loss during total hip arthroplasty. Anesth Analg 76:580, 1993.

63. Owen CA, Murbarak SJ, Hargens AR et al: Intramuscular pressures with limb compression: Clarification of the pathogenesis of the drug-induced muscle-compartment syndrome. N Engl J Med 300:1169, 1979.

64. Ranawat CS, Beaver WB, Sharrock NE et al: Effect of hypotensive epidural anaesthesia on acetabular cement-bone fixation in total hip arthroplasty. J Bone Joint Surg Br 73B:779, 1991.

65. Duncan JA: Intra-operative collapse or death related to the use of acrylic cement in hip surgery. Anaesthesia 44:149, 1989.

66. Adams JH, Graham DI, Mills E et al: Fat embolism and cerebral infarction after use of methylmethacrylate cement. BMJ 3:740, 1972.

67. Hagley SR, Lee FC, Blumbergs PC: Fat embolism syndrome with total hip replacement. Med J Aust 145:541, 1986.

68. Ereth MH, Weber JG, Abel MD et al: Cemented versus noncemented total hip arthroplasty: Embolism, hemodynamics, and intrapulmonary shunting. Mayo Clin Proc 67:1066, 1992.

69. Bulstra SK, Geesink RGT, Bakker D et al: Femoral canal occlusion in total hip replacement using a resorbable and flexible cement restrictor. J Bone Joint Surg Br 78B:892, 1996.

70. Christie J, Robinson CM, Singer B et al: Medullary lavage reduces embolic phenomena and cardiopulmonary changes during cemented hemiarthroplasty. J Bone Joint Surg Br 77B:456, 1995.

71. Christie J, Robinson CM, Pell ACH et al: Transcardiac echocardiography during invasive intramedullary procedures. J Bone Joint Surg Br 77B:450, 1995.

72. Fitzgerald R, Mason L, Kanumilli V et al: Transient cardiac standstill associated with embolic phenomena diagnosed by intraoperative transesophageal echocardiography during cemented total hip arthroplasty. Anesth Analg 79:382, 1994.

73. Christie J, Burnett R, Potts HR et al: Echocardiography of transatrial embolism during cemented and uncemented hemiarthroplasty of the hip. J Bone Joint Surg Br 76B:409, 1994.

74. Byrick RJ, Mullen JB, Mazer CD et al: Transpulmonary systemic fat embolism: Studies in mongrel dogs after cemented arthroplasty. Am J Respir Crit Care Med 150:1416, 1994.

75. Williams-Russo P, Sharrock NE, Mattis S et al: Cognitive effects after epidural vs general anesthesia in older adults: A randomized trial. JAMA 274:44, 1995.

76. O'Keeffe ST, Ni Chonchubhair A: Postoperative delirium in the elderly. Br J Anaesth 73:673, 1994.

77. Parikh SS, Chung F: Postoperative delirium in the elderly. Anesth Analg 80:1223, 1995.

78. Edmonds CR, Barbut D, Hager D et al: Intraoperative cerebral arterial embolization during total hip arthroplasty. Anesthesiology 87:A150, 1997.

79. Sharrock NE, Go G, Harpel PC et al: Thrombogenesis during total hip replacement. Clin Orthop 319:16, 1995.

80. Abraham P, Carter D, Millot JR et al: Prolonged asymptomatic micro-embolism after hip or knee arthroplasty. J Bone Joint Surg Br 79B:269, 1997.

81. Orsini EC, Byrick RJ, Mullen JB et al: Cardiopulmonary function and pulmonary microemboli during arthroplasty using cemented or non-cemented components: The role of intramedullary pressure. J Bone Joint Surg Am 69A:822, 1987.

82. Byrick RJ, Kay JC, Mullen JB: Capnography is not as sensitive as pulmonary artery pressure monitoring in detecting marrow microembolism: Studies in a canine model. Anesth Analg 68:94, 1989.

83. Rosenberg-Adamsen S, Kehlet H, Dodds C et al: Postoperative sleep disturbances: Mechanisms and clinical implications. Br J Anaesth 76:552, 1996.

84. Lynch NM, Trousdale RT, Ilstrup DM: Complications after concomitant bilateral total knee arthroplasty in elderly patients. Mayo Clin Proc 72:799, 1997.

85. Vince KG: Bilateral total knee arthroplasty under one anesthesia: A safe protocol. Mayo Clin Proc 72:883, 1997.

86. Byrick RJ, Forbes D, Wardell JP: A monitored cardiovascular collapse during cemented arthroplasty. Anesthesiology 65:213, 1986.

87. Hall TM, Callaghan JJ: Fat embolism precipitated by reaming of the femoral canal during revision of a total knee replacement. J Bone Joint Surg Am 76A:899, 1994.

88. Fahmy NR, Chandler HP, Danylchuk K et al: Blood-gas and circulatory changes during total knee replacement: Role of the intramedullary alignment rod. J Bone Joint Surg Am 72A:19, 1990.

89. Stern SH, Sharrock NE, Kahn RL et al: Hematologic and circulatory changes associated with total knee arthroplasty surgical instrumentation. Clin Orthop 299:179, 1994.

90. Parmet JL, Horrow JC, Pharo G et al: The incidence of venous emboli during extramedullary guided total knee arthroplasty. Anesth Analg 81:757, 1995.

91. Parmet JL, Horrow JC, Keykhah MM et al: Accumulation of a right ventricular mass during shoulder hemiarthroplasty. Anesth Analg 80:614, 1995.

92. Lotke PA, Faralli VJ, Orenstein EM et al: Blood loss after total knee replacement. J Bone Joint Surg Am 73A:1037, 1991.

93. Sharrock NE, Go G, Sculco TP et al: Changes in circulatory indices of thrombosis and fibrinolysis during total knee arthroplasty performed under tourniquet. J Arthroplasty 10:523, 1995.

94. Thorpe CM, Murphy WG, Logan M: Use of aprotinin in knee replacement surgery. Br J Anaesth 73:408, 1994.

95. Benoni G, Fredin H: Fibrinolytic inhibition with tranexamic acid reduces blood loss and blood transfusion after knee arthroplasty. J Bone Joint Surg Br 78B:434, 1996.

96. Hiippala S, Strid L, Wennerstrand M et al: Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth 74:534, 1995.

97. Anker-Moller E, Spangsberg N, Dahl JB et al: Continuous blockade of the lumbar plexus after knee surgery: A comparison of the plasma concentrations and analgesic effect of bupivacaine 0.250% and 0.125%. Acta Anaesthesiol Scand 34:468, 1990.

98. Dahl JB, Daugaard JJ, Rasmussen B et al: Immediate and prolonged effects of pre- versus postoperative epidural analgesia with bupivacaine and morphine on pain at rest and during mobilization after total knee arthroplasty. Acta Anaesthesiol Scand 38:557, 1994.

99. Akbarnia BA, Crandall DG, Burkus K et al: Use of long rods and a short arthrodesis for burst fractures of the thoracolumbar spine. J Bone Joint Surg Am 76A:1629, 1994.

100. Boriani S, Chevalley F, Weinstein JN et al: Chordoma of the spine above the sacrum: Treatment and outcome in 21 cases. Spine 21:1569, 1996.

101. Rubery PT, Spielman JH, Hester P et al: Scoliosis in familial dysautonomia: Operative treatment. J Bone Joint Surg Am 77A:1362, 1995.

102. Noordeen MHH, Lee J, Gibbons CER et al: Spinal cord monitoring in operations for neuromuscular scoliosis. J Bone Joint Surg Br 79B:53, 1997.

103. Wilber RG, Thompson GH, Shaffer JW et al: Postoperative neurologic deficits in segmental spinal instrumentation: A study using spinal cord monitoring. J Bone Joint Surg Am 66A:1178, 1984.

104. Maguire J, Wallace S, Madiga R et al: Evaluation of intrapedicular screw position using intraoperative evoked electromyography. Spine 20:1068, 1995.

105. Drummond JC, Abitbol J-J, Sanford TJ et al: Transient paraplegia during posterior cervical osteotomy. Anesthesiology 74:628, 1991.

106. Forbes HJ, Allen PW, Waller CS et al: Spinal cord monitoring in scoliosis surgery. J Bone Joint Surg Br 73B:487, 1991.

107. Bernard J-M, Pereon Y, Fayet G et al: Effects of isoflurane and desflurane on neurogenic motor- and somatosensory-evoked potential monitoring for scoliosis surgery. Anesthesiology 85:1013, 1996.

108. Lang EW, Beutler AS, Chestnut RM et al: Myogenic motor-evoked potential monitoring using partial neuromuscular blockade in surgery of the spine. Spine 21:1676, 1996.

109. Moran MM, Kroon D, Tredwell SJ et al: The role of autologous blood transfusion in adolescents undergoing spinal surgery. Spine 20:532, 1995.

110. Siller TA, Dickson JH, Erwin WD: Efficacy and cost considerations of intraoperative autologous transfusion in spinal fusion for idiopathic scoliosis with predeposited blood. Spine 21:848, 1996.

111. Blais RE, Hadjipavlou AG, Shulman G: Efficacy of autotransfusion in spine surgery: Comparison of autotransfusion alone and with hemodilution and apheresis. Spine 21:2795, 1996.

112. Hersey SL, O'Dell NE, Lowe S et al: Nicardipine versus nitroprusside for controlled hypotension during spinal surgery in adolescents. Anesth Analg 84:1239, 1997.

113. Faciszewski T, Winter RB, Lonstein JE et al: The surgical and medical perioperative complications of anterior spinal fusion surgery in the thoracic and lumbar spine in adults: A review of 1223 procedures. Spine 20:1592, 1995.

114. Goodarzi M, Shier N-H, Grogan DP: Effect of intrathecal opioids on somatosensory-evoked potentials during spinal fusion in children. Spine 21:1565, 1996.

115. Karpos PAG, Jones CK, McNamara MJ et al: Persistent leakage of cerebrospinal fluid after intrathecal administration of morphine in an operation on the lumbar spine: A report of two cases. J Bone Joint Surg Am 76A:916, 1994.

116. Brazel PW, McPhee IB: Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients. Spine 21:724, 1996.

117. Malcolm GP, Ransford AO, Crockard HA: Treatment of non-rheumatoid occipitocervical instability. J Bone Joint Surg Br 76B:357, 1994.

118. Oga M, Yuge I, Terada K et al: Tortuosity of the vertebral artery in patients with cervical spondylotic myelopathy: Risk factor for the vertebral artery injury during anterior cervical decompression. Spine 21:1085, 1996.

119. McAfee PC, Bohlman HH, Ducker TB et al: One-stage anterior cervical decompression and posterior stabilization: A study of one hundred patients with a minimum of two years of follow-up. J Bone Joint Surg Am 77A:1791, 1995.

120. Wattenmaker I, Concepcion M, Hibberd P et al: Upper-airway obstruction and perioperative management of the airway in patients managed with posterior operations on the cervical spine for rheumatoid arthritis. J Bone Joint Surg Am 76A:360, 1994.

121. Nygaard OP, Romner B, Thoner J et al: Local anesthesia in posterior cervical surgery. Anesthesiology 86:242, 1997.

122. McDonnell MF, Glassman SD, Dimar JR II et al: Perioperative complications of anterior procedures on the spine. J Bone Joint Surg Am 78A:839, 1996.

123. Fraser RD: Interbody, posterior, and combined lumbar fusions. Spine 20:1675, 1995.

124. Vaccaro AR, Garfin SR: Internal fixation (pedicle screw fixation) for fusions of the lumbar spine. Spine 20:157S, 1995.

125. Jellish WS, Thalji Z, Stevenson K et al: A prospective randomized study comparing short- and intermediate-term perioperative outcome variables after spinal or general anesthesia for lumbar disk and laminectomy surgery. Anesth Analg 83:559, 1996.

126. Joshi GP, McCarroll SM, O'Rourke K: Postoperative analgesia after lumbar laminectomy: Epidural fentanyl infusion versus patient-controlled intravenous morphine. Anesth Analg 80:511, 1995.

127. Alman BA, De Bari AB, Krajbich JI: Massive allografts in the treatment of osteosarcoma and Ewing sarcoma in children and adolescents. J Bone Joint Surg Am 77A:54, 1995.

128. Bishop AT, Wood MB, Sheetz KK: Arthrodesis of the ankle with a free vascularized autogenous bone graft: Reconstruction of segmental loss of bone secondary to osteomyelitis, tumor, or trauma. J Bone Joint Surg Am 77A:1867, 1995.

129. Hsu RW-W, Wood MB, Sim FH et al: Free vascularised fibular grafting for reconstruction after tumour resection. J Bone Joint Surg Br 79B:36, 1997.

130. Aps C, Cox RG, Mayou BJ et al: The role of anaesthetic management of enhancing peripheral blood flow in patients undergoing free flap transfer. Ann R Coll Surg Engl 67:177, 1985.

131. Sigurdsson GH, Banic A, Wheatley AM et al: Effects of halothane and isoflurane anaesthesia on microcirculatory blood flow in musculocutaneous flaps. Br J Anaesth 73:826, 1994.

132. Nolan JP, Dow AAC, Parr MJA et al: Patient-controlled epidural analgesia following post-traumatic pelvic reconstruction: A comparison with continuous epidural analgesia. Anaesthesia 47:1037, 1992.

133. Roch JJ, Sharrock NE, Neudachin L: Interscalene brachial plexus block for shoulder surgery: A proximal paresthesia is effective. Anesth Analg 75:386, 1992.

134. Urmey WF, Grossi P, Sharrock NE et al: Digital pressure during interscalene

block is clinically ineffective in preventing anesthetic spread to the cervical plexus. Anesth Analg 83:366, 1996.

135. Roch J, Sharrock NE: Hypotension during shoulder arthroscopy in the sitting position under interscalene block. Reg Anesth 16:64, 1991.

136. D'Alessio JG, Weller RS, Rosenblum M: Activation of the Bezold-Jarisch reflex in the sitting position for shoulder arthroscopy using interscalene block. Anesth Analg 80:1158, 1995.

137. Ichai C, Ciais JF, Roussel LJ et al: Intravascular absorption of glycine irrigating solution during shoulder arthroscopy: A case report and follow-up study. Anesthesiology 85:1481, 1996.

138. Schroeder LE, Horlocker TT, Schroeder DR: The efficacy of axillary block for surgical procedures about the elbow. Anesth Analg 83:747, 1996.

139. Urmey WF: Combined axillary-interscalene (AXIS) brachial plexus block for elbow surgery. Reg Anesth 18:88, 1993.

140. Sukhani R, Winnie AP: Clinical pharmacokinetics of carbonated local anesthetics: II. Interscalene brachial block model. Anesth Analg 66:1245, 1987.

141. Pittoni G, Toffoletto F, Calcarella G et al: Spinal anesthesia in outpatient knee surgery: 22-gauge versus 25-gauge Sprotte needle. Anesth Analg 81:73, 1995.

142. Urmey WF, Stanton J, Peterson M et al: Combined spinal-epidural anesthesia for outpatient surgery: Dose-response characteristics of intrathecal isobaric lidocaine using a 27-gauge Whitacre spinal needle. Anesthesiology 83:528, 1995.

143. Pollock JE, Neal JM, Stephenson CA et al: Prospective study of the incidence of transient radicular irritation in patients undergoing spinal anesthesia. Anesthesiology 84:1361, 1996.

144. Sharrock NE, Waller JF, Fierro LE: Midtarsal block for surgery of the forefoot. Br J Anaesth 58:37, 1986.

145. Finsen V, Kasseth A-M: Tourniquets in forefoot surgery: Less pain when placed at the ankle. J Bone Joint Surg Br 79B:99, 1997.

146. Galindo A, Hernandez J, Benavides O et al: Quality of spinal extradural anesthesia: The influence of spinal nerve root diameter. Br J Anaesth 47:41, 1975.

147. Benzon HT, Toleikis JR, Dixit P et al: Onset, intensity of blockade and somatosensory evoked potential changes of the lumbosacral dermatomes after epidural anesthesia with alkalinized lidocaine. Anesth Analg 76:328, 1993.

148. Gosteli P, Van Gessel E, Gamulin Z: Effects of pH adjustment and carbonation of lidocaine during epidural anesthesia for foot and ankle surgery. Anesth Analg 81:104, 1995.

149. Singelyn FJ, Gouverneur J-MA, Gribomont BF: Popliteal sciatic nerve block aided by a nerve stimulator: A reliable technique for foot and ankle surgery. Reg Anesth 16:278, 1991.

150. Riou B, Barriot P, Viars P: Femoral nerve block in fractured shaft of femur. Anesthesiology 69:A375, 1988.

151. Haddad FS, Williams RL: Femoral nerve block in extracapsular femoral neck fractures. J Bone Joint Surg Br 77B:922, 1995.

152. Singelyn FJ, Contreras V, Gouverneur JM: Epidural anesthesia complicating continuous 3-in-1 lumbar plexus blockade. Anesthesiology 83:217, 1995.

153. Singelyn FJ, Aye F, Gouverneur JM: Continuous popliteal sciatic nerve block: An original technique to provide postoperative analgesia after foot surgery. Anesth Analg 84:383, 1997.

154. Wajima Z, Shitara T, Nakajima Y et al: Comparison of continuous brachial plexus infusion of butorphanol, mepivacaine and mepivacaine-butorphanol mixtures for postoperative analgesia. Br J Anaesth 75:548, 1995.

155. Sullivan SG, Abbott PJ Jr: Cardiovascular toxicity associated with intraarticular bupivacaine. Anesth Analg 79:591, 1994.

156. Badner NH, Bourne RB, Rorabeck CH et al: Intra-articular injection of bupivacaine in knee-replacement operations: Results of use for analgesia and for preemptive blockade. J Bone Joint Surg Am 78A:734, 1996.

157. Kalso E, Tramer MR, Carroll D et al: Pain relief from intra-articular morphine after knee surgery: A qualitative systematic review. Pain 71:127, 1997.

158. Whitford A, Kealy M, Joshi GP et al: The effect of tourniquet release time on the analgesic efficacy of intraarticular morphine after arthroscopic knee surgery. Anesth Analg 84:791, 1997.

159. Beattie WS, Warriner CB, Etches R et al: The addition of continuous intravenous infusion of ketorolac to a patient-controlled analgesic morphine regime reduced postoperative myocardial ischemia in patients undergoing elective total hip or knee arthroplasty. Anesth Analg 84:715, 1997.

160. Fragen RJ, Stulberg SD, Wixson R et al: Effect of ketorolac tromethamine on bleeding and on requirements for analgesia after total knee arthroplasty. J Bone Joint Surg Am 77A:998, 1995.

161. Feldman HI, Kinman JL, Berlin JA et al: Parenteral ketorolac: The risk for acute renal failure. Ann Intern Med 126:193, 1997.

162. Bachmann M, Laakso E, Niemi L et al: Intrathecal infusion of bupivacaine with or without morphine for postoperative analgesia after hip and knee arthroplasty. Br J Anaesth 78:666, 1997.

163. Carli F, Halliday D: Continuous epidural blockade arrests the postoperative decrease in muscle protein fractional synthetic rate in surgical patients. Anesthesiology 86:1033, 1997.

164. Williams-Russo P, Sharrock NE, Haas SB et al: Randomized trial of epidural versus general anesthesia: Outcomes after primary total knee replacement. Clin Orthop 331:199, 1996.

165. Singelyn FJ, Deyaert M, Joris D et al.: Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesth Analg 87:88, 1998.

166. Kehlet H: Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 78:606, 1997.

167. Horlocker TT, Heit JA: Low molecular weight heparin: Biochemistry, pharmacology, perioperative prophylaxis regimens, and guideline for regional anesthetic management. Anesth Analg 85:874, 1997.

168. FDA Public Health Advisory: Reports of epidural or spinal hematomas with the concurrent use of low molecular weight heparin and spinal/epidural anesthesia or spinal puncture. U.S. Department of Health and Human Resources, December 15, 1997.

169. Horlocker TT, Wedel DJ, Schlichting JL: Postoperative epidural analgesia and oral anticoagulant therapy. Anesth Analg 79:89, 1994.

170. Hyder N, Kessler S, Jennings AG et al: Compartment syndrome in tibial shaft fracture missed because of a local nerve block. J Bone Joint Surg Br 78B:499, 1996.

171. Price C, Ribeiro J, Kinnebrew T: Compartment syndromes associated with postoperative epidural analgesia. J Bone Joint Surg Am 78A:597, 1996.

172. McQueen MM, Christie J, Court-Brown CM: Acute compartment syndrome in tibial diaphyseal fractures. J Bone Joint Surg Br 78B:95, 1996.

173. Horlocker TT, Cabanela ME, Wedel DJ: Does postoperative epidural analgesia increase the risk of peroneal nerve palsy after total knee arthroplasty? Anesth Analg 79:495, 1994.

174. Idusuyi OB, Morrey BF: Peroneal nerve palsy after total knee arthroplasty: Assessment of predisposing and prognostic factors. J Bone Joint Surg Am 78A:177, 1996.

175. Mont MA, Dellon AL, Chen F et al: The operative treatment of peroneal nerve palsy. J Bone Joint Surg Am 78A:863, 1996.

176. Jakobsen KB, Christensen M-K, Carlsson PS: Extradural anaesthesia for repeated surgical treatment in the presence of infection. Br J Anaesth 75:536, 1995.

177. Hampson NB, Piantadosi CA: Near infrared monitoring of human skeletal muscle oxygenation during forearm ischemia. J Appl Physiol 64:2449, 1988.

178. Heppenstall RB, Scott R, Sapega A et al: A comparative study of the tolerance of skeletal muscle to ischemia: Tourniquet application compared with acute compartment syndrome. J Bone Joint Surg Am 68A:820, 1986.

179. Ikemoto Y, Kobayashi H, Usui M et al: Changes in serum myoglobin levels caused by tourniquet ischemia under normothermic and hypothermic conditions. Clin Orthop 234:296, 1988.

180. Lynn AM, Fisher T, Brandford HG et al: Systemic responses to tourniquet release in children. Anesth Analg 65:865, 1986.

181. Lelcuk S, Alexander F, Valeri CR et al: Thromboxane A_2 moderates permeability after limb ischemia. Ann Surg 202:642, 1985.

182. Wilgis EFS: Observations on the effects of tourniquet ischemia. J Bone Joint Surg Am 53A:1343, 1971.

183. Pedowitz RA, Gershuni DH, Schmidt AH et al: Muscle injury induced beneath and distal to a pneumatic tourniquet: A quantitative animal study of effects of tourniquet pressure and duration. J Hand Surg [Am] 16A:610, 1991.

184. Mathru M, Dries DJ, Barnes L et al: Tourniquet-induced exsanguination in patients requiring lower limb surgery: An ischemia-reperfusion model of oxidant and antioxidant metabolism. Anesthesiology 84:14, 1996.

185. Sharrock NE, Mineo R: Body core temperature changes following tourniquet release during total knee arthroplasty under epidural anesthesia. Reg Anesth 13:9, 1988.

186. Estebe J-P, Le Naoures A, Malledant Y et al: Use of pneumatic tourniquet induces changes in central temperature. Br J Anaesth 77:786, 1996.

187. Kahn RL, Sharrock NE, Mineo R: Mixed venous oxygen saturation changes associated with tourniquet deflation under epidural anesthesia for total knee arthroplasty. Anesth Analg 70:S186, 1990.

188. Bourke DL, Silberberg MS, Ortega R et al: Respiratory responses associated with release of intraoperative tourniquets. Anesth Analg 69:541, 1989.

189. Brustowitz RM, Monocorge C, Koka BV: Metabolic responses to tourniquet release in children. Anesthesiology 67:792, 1987.

190. Bradford EMW: Haemodynamic changes associated with the application of lower limb tourniquets. Anesthesiology 24:190, 1969.

191. Valli H, Rosenberg PH: Effects of three anaesthesia methods on hemodynamic responses connected with the use of thigh tourniquet in orthopaedic patients. Acta Anaesthesiol Scand 29:142, 1985.

192. Edfeldt H, Thomson D: Early hemodynamic and respiratory changes following tourniquet release--influence of large doses of methylprednisolone. Acta Chir Scand Suppl S499:45, 1980.

193. Kahn RL, Marino V, Urquhart B et al: Hemodynamic changes associated with tourniquet use under epidural anesthesia for total knee arthroplasty. Reg Anesth 17:228, 1992.

194. Valli H, Rosenberg PH, Kytta J et al: Arterial hypertension associated with the use of a tourniquet with either general or regional anesthesia. Acta Anaesthesiol Scand 31:279, 1987.

195. Kaufman RD, Walts LF: Tourniquet-induced hypertension. Br J Anaesth 54:333, 1982.

196. Rocco AG, Concepcion MA, Desai S et al: The effect of general and regional anesthesia on tourniquet-induced blood pressure elevation. Reg Anesth 12:174, 1987.

197. Bridenbaugh PO, Hagenouw RRPM, Gielen MJM et al: Addition of glucose to bupivacaine in spinal anesthesia increases incidence of tourniquet pain. Anesth Analg 65:1181, 1986.

198. Sapega AA, Heppenstall RB, Chance B et al: Optimizing tourniquet application and release times in extremity surgery: A biochemical and ultrastructural study. J Bone Joint Surg Am 67A:303, 1985.

199. Farah RS, Sebastian T: Sympathetic blockade and tourniquet pain in surgery of the upper extremity. Anesth Analg 66:1033, 1987.

200. Gielen MJM, Stienstra R: Tourniquet hypertension and its prevention: A review. Reg Anesth 16:191, 1991.

201. Ochoa J, Danta G, Fowler TJ et al: Nature of the nerve lesion caused by a pneumatic tourniquet. Nature 233:265, 1971.

202. Dery R, Pelletier J, Jacques A et al: Metabolic changes induced in the limb during tourniquet ischaemia. Can J Anaesth 12:366, 1967.

203. Benzon HT, Toleikis JR, Meagher LL et al: Changes in venous blood lactate, venous blood gases, and somatosensory evoked potentials after tourniquet application. Anesthesiology 69:677, 1988.

204. Korthals JK, Toshiyuki M, Gieron MA: Nerve and muscle vulnerability to ischemia. J Neurol Sci 71:283, 1985.

205. Abdel-Salam A, Eyres K: Effects of tourniquet during total knee arthroplasty: A prospective randomised study. J Bone Joint Surg Br 77B:250, 1995.

206. Maffulli N, Testa V, Capasso G: Use of a tourniquet in the internal fixation of fractures of the distal part of the fibula: A prospective, randomized trial. J Bone Joint Surg Am 75A:700, 1993.

207. Klenerman L: Is a tourniquet really necessary for knee replacement? J Bone Joint Surg Br 77B:174, 1995.

208. Barwell NJ, Anderson G, Hassan A et al: The effects of early tourniquet release during total knee arthroplasty: A prospective randomised double-blind study. J Bone Joint Surg Br 79B:265, 1997.

209. Gossling HR, Pellegrini VD Jr: Fat embolism syndrome: A review of the pathophysiology and physiological basis of treatment. Clin Orthop 165:68, 1982.

210. Hutchins PM, MacNicol MF: Pulmonary insufficiency after long bone fracture. J Bone Joint Surg Br 67B:835, 1985.

211. Lindeque BGP, Schoeman HS, Domisse GF et al: Fat embolism and the fat embolism syndrome: A double-blind therapeutic study. J Bone Joint Surg Br 69B:128, 1987.

212. Zuckerman JD, Skovron ML, Koval KJ et al: Postoperative complications and mortality associated with operative delay in older patients who have a fracture of the hip. J Bone Joint Surg Am 77A:1551, 1995.

213. Djelouah I, Lefevre G, Ozier Y et al: Fat embolism in orthopedic surgery: Role of bone marrow fatty acid. Anesth Analg 85:441, 1997.

214. Lieberman JR, Wollaeger J, Dorey F et al: The efficacy of prophylaxis with low-dose warfarin for prevention of pulmonary embolism following total hip arthroplasty. J Bone Joint Surg Am 79A:319, 1997.

215. Murray DW, Britton AR, Bulstrode CJK: Thromboprophylaxis and death after total hip replacement. J Bone Joint Surg Br 78B:863, 1996.

216. Murray DW, Carr AJ, Bulstrode CJK: Pharmacological thromboprophylaxis and total hip replacement. J Bone Joint Surg Br 77B:3, 1995.

217. Sharrock NE, Cazan MG, Hargett MJL et al: Changes in mortality after total hip and knee arthroplasty over a ten-year period. Anesth Analg 80:242, 1995.

218. Rokito SE, Schwartz MC, Neuwirth MG: Deep vein thrombosis after major reconstructive spinal surgery. Spine 21:853, 1996.

219. Durica S, Raskob G, Johnson C et al: Incidence of deep-vein thrombosis after arthroscopic knee surgery. Thromb Haemost (June suppl):183, 1997.

220. Samama CM, Clergue F, Barre J et al: Low molecular weight heparin associated with spinal anaesthesia and gradual compression stockings in total hip replacement surgery. Br J Anaesth 78:660, 1997.

221. Colwell CW Jr, Spiro TE: Efficacy and safety of enoxaparin to prevent deep vein thrombosis after hip arthroplasty. Clin Orthop 319:215, 1995.

222. Eriksson BI, Ekman S, Kalebo P et al: Prevention of deep-vein thrombosis after total hip replacement: Direct thrombin inhibition with recombinant hirudin, CGP 39393. Lancet 347:635, 1996.

223. Sharrock NE, Hargett MJ, Urquhart B et al: Factors affecting deep vein thrombosis rate following total knee arthroplasty under epidural anesthesia. J Arthroplasty 8:133, 1993.

224. Sharrock NE, Haas SB, Hargett MJ et al: Effects of epidural anesthesia on the incidence of deep-vein thrombosis after total knee arthroplasty. J Bone Joint Surg Am 73A:502, 1991.

225. Sharrock NE, Ranawat CS, Urquhart B et al: Factors influencing deep vein thrombosis following total hip arthroplasty. Anesth Analg 76:765, 1993.

226. Sharrock NE, Go G, Williams-Russo P et al: Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty. Br J Anaesth 79:29, 1997.

227. McGrath BJ, Hsia J, Boyd A et al: Venous embolization after deflation of lower extremity tourniquets. Anesth Analg 78:349, 1994.

228. Warwick D, Martin AG, Glew D et al: Measurement of femoral vein blood flow during total hip replacement: Duplex ultrasound imaging with and without the use of a foot pump. J Bone Joint Surg Br 76B:918, 1994.

229. Planes A, Vochelle N, Fagola M: Total hip replacement and deep vein thrombosis. J Bone Joint Surg Br 72B:9, 1990.

230. Bading B, Blank S, Sculco TP et al: Augmentation of calf blood flow by epinephrine infusion during lumbar epidural anesthesia. Anesth Analg 78:1119, 1994.

231. McCabe JP, Sharrock NE, Salvati EA et al: Intraoperative heparin and hypotensive epidural anesthesia in the prevention of thromboembolism following total hip arthroplasty. Orthop Trans 21:124, 1997.

232. Prins MH, Hirsh J: A critical review of the evidence supporting a relationship between impaired fibrinolytic activity and venous thromboembolism. Arch Intern Med 151:1721, 1991.

233. Eriksson BI, Ekman S, Bauer M et al: Regional block anaesthesia versus general anaesthesia: Are different antithrombotic drugs equally effective in patients undergoing hip replacement? Retrospective analysis of 2354 patients undergoing hip replacement receiving either recombinant hirudin, unfractionated heparin or enoxaparin. Thromb Haemost (June suppl):487, 1997.

234. Lieberman JR, Huo MM, Hanway J et al: The prevalence of deep venous thrombosis after total hip arthroplasty with hypotensive epidural anesthesia. J Bone Joint Surg Am 76A:341, 1994.

235. Sharrock NE, Go G, Mineo R et al: The hemodynamic and fibrinolytic response to low dose epinephrine and phenylephrine infusions during total hip replacement under epidural anesthesia. Thromb Haemost 68:436, 1992.

236. Markel DC, Urquhart B, Derkowska I et al: Effect of epidural analgesia on venous blood flow after hip arthroplasty. Clin Orthop 334:168, 1997.

237. Sharrock NE, Brien WW, Salvati EA et al: The effect of intravenous fixed-dose heparin during total hip arthroplasty on the incidence of deep-vein thrombosis: A randomized, double-blind trial in patients operated on with epidural anesthesia and controlled hypotension. J Bone Joint Surg Am 72A:1456, 1990.

238. Woolson ST: Intermittent pneumatic compression prophylaxis for proximal deep venous thrombosis after total hip replacement. J Bone Joint Surg Am 78A:1735, 1996.

239. Westrich GH, Sculco TP: Prophylaxis against deep venous thrombosis after total knee arthroplasty. Pneumatic plantar compression and aspirin compared with aspirin alone. J Bone Joint Surg Am 78A:826, 1996.

240. Santori FS, Vitullo A, Stopponi N et al: Prophylaxis against deep-vein thrombosis in total hip replacement: Comparison of heparin and foot impulse pump. J Bone Joint Surg Br 76B:579, 1994.

241. McCarthy DJ: Juvenile rheumatoid arthritis. In McCarthy DJ (ed): Arthritis and Allied Conditions, 11th ed. Philadelphia, Lea & Febiger, 1989, p 913.

242. Giaufre E, Dalens B, Gombert A: Epidemiology and morbidity of regional anesthesia in children: A one-year prospective survey of the French-language society of pediatric anesthesiologists.

Anesth Analg 83:904, 1996.

243. Hennrikus WL, Shin AY, Klingelberger CE: Self-administered nitrous oxide and a hematoma block for analgesia in the outpatient reduction of fractures in children. J Bone Joint Surg Am 77A:335, 1995.

244. Dalens B: Regional anesthesia in children. Anesth Analg 68:654, 1989.

245. Berkowitz ID, Raja SN, Bender KS et al: Dwarfs: Pathophysiology and anesthetic implications. Anesthesiology 73:739, 1990.

246. Hastings RH, Marks JD: Airway management of trauma patients with potential cervical spine injuries. Anesth Analg 73:471, 1991.

247. Bernhardt M, Hynes RA, Blume HW et al: Current concepts review: Cervical spondylotic myelopathy. J Bone Joint Surg Am 75A:119, 1993.

248. Deem S, Shapiro HM, Marshall LF: Quadriplegia in a patient with cervical spondylosis after thoracolumbar surgery in the prone position. Anesthesiology 75:527, 1991.

249. Cucchiara RF, Black S: Corneal abrasion during anesthesia and surgery. Anesthesiology 69:978, 1988.

250. Langmayr JJ, Ortler M, Obwegeser A et al: Quadriplegia after lumbar disc surgery: A case report. Spine 21:1932, 1996.

251. Bromage PR: Spinal cord infarction after surgery in a patient in the hyperlordotic position. Anesthesiology 85:429, 1996.

252. Inufusa A, An HS, Lim T-H et al: Anatomic changes of the spinal canal and intervertebral foramen associated with flexion-extension movement. Spine 21:2412, 1996.

253. Casey PJ, Moed BR: Fractures of the forearm complicated by palsy of the anterior interosseous nerve caused by a constrictive dressing. A report of four cases. J Bone Joint Surg Am 79A:122, 1997.

254. Charnley G, Coleman NP, Hashemi-Nejad A: Cardiac arrest during nailing. J Bone Joint Surg Br 76B:506, 1994.

255. Hoka S, Yoshitake J, Arakawa S et al: VO_2 and V CO_2 following tourniquet deflation. Anaesthesia 47:65, 1992.

256. Sharrock NE: Anesthesia. In Callaghan JJ, Rosenberg AG, Rubash HE (eds): The Adult Hip. Philadelphia, Lippincott-Raven, 1998, p 615.

Chapter 61 - Anesthesia for the Elderly

Stanley Muravchick

INTRODUCTION

Although established at the beginning of this century, [1] the specialty of geriatrics has only recently been given the funding and attention appropriate to a medical discipline describing approximately one-fourth of the surgical population. Determining the age at which people, as a group, are considered "elderly" also remains an arbitrary process. Some descriptors of agedness use estimates of life expectancy, an actuarial term describing the average number of years of life members of a specific population may reasonably anticipate, given the environmental and socioeconomic constraints that prevail at time of birth. The determination of the percentage of a population having more or less than a given number of remaining years of life also quantifies the agedness of a population but, similarly, requires an arbitrary subdivision of society into two or more groups. In any case, both methods identify the norm rather than the extreme.

Life span is an idealized biologic standard describing maximal obtainable age. At approximately 110 to 115 years, it is a species-specific value that has not changed throughout history. It is the theoretical maximum lifetime of our biological machinery, a goal realized only when all vital organ systems function optimally in a benign environment. Life expectancy, in contrast, measures typical longevity under more realistic conditions, including the inevitable consequences of malnutrition, environmental pollution, trauma, and disease.

Despite great advances in medical therapeutics, nutrition, and concepts of fitness, a large percentage of our aging population will continue to have chronic disease. These persons will become a major health care burden, especially as life expectancy moves into the 9th decade of life. [2] Surgical intervention and the need for perioperative care and pain control will become even more commonplace in the elderly than it is now. This chapter provides an overview of current concepts regarding age-related physiologic changes in major organ systems, a summary of common age-related disease processes, and a review of the relationship of these factors to the management of anesthesia and perioperative risk.

GERONTOLOGY: THE STUDY OF AGING

For administrative and epidemiologic purposes, it is customary to consider the geriatric era as beginning at 65 years of age. However, some specialized applications classify persons 65 to 74 years of age as "elderly," those 75 to 84 years as "aged," and those 85 years and older as "very old." In the absence of disease, active "elderly" persons maintain adequate normal daily functioning without major changes in lifestyle and with only minor adjustment in the level of activity. As they become "aged," however, limitations in musculoskeletal strength, coordination, and quickness compel them to modify their daily routines dramatically. Favorable environmental, genetic, or perhaps socioeconomic circumstances ultimately determine who will survive to become "very old." In this chapter, however, the terms "elderly" and "geriatric" will be used in their most common sense--as synonyms for persons 65 years of age and older.

Aging is a progressive, universally prevalent physiologic process that produces measurable changes in the structure and decremental alteration of the function of tissues and organs (Table 61-1) . Changes that are not universal or that do not increase in severity or magnitude in proportion to chronologic age are probably not manifestations of aging but, rather, are usually signs or symptoms of age-related disease. Although the mechanism is not yet entirely understood at either a cellular or biochemical level, decreased cellular energy production due to deterioration of the mitochondrial genome, especially in cardiac and neural tissues,

TABLE 61-1 -- Summary of Anatomic and Functional Consequences of Aging on Body Tissues and Major Organ Systems

TISSUE/SYSTEM	ANATOMIC CHANGE	FUNCTIONAL CHANGE
Body composition	Loss of skeletal muscle and other lean tissue components, increased lipid fraction	Prolonged drug effects; decreased metabolism and heat production, decreased resting cardiac output
Nervous system	Loss of neuronal tissue mass, deafferentation, reduced central neurotransmitter activity	Decreased neural plasticity, decreased anesthetic requirement, impaired autonomic homeostasis
Cardiovascular system	Decreased elasticity, reduced beta-adrenergic responsiveness	Decreased cardiac and arterial compliance, decreased maximal heart rate and cardiac output
Pulmonary system	Increased thoracic stiffness, decreased lung recoil, reduced alveolar surface area	Reduced vital capacity, increased work of breathing, impaired efficiency of gas exchange
Renal/hepatic system	Decreased vascularity and perfusion, loss of tissue mass	Decreased drug clearance, inability to withstand salt or water loads
Blood and immune systems	Thymic involution, resorption of bone marrow	Decreased immune competence, loss of hematopoietic reserve

may play a fundamental role in the age-related decline of organ system capacity. [3]

Two general experimental designs have been used to evaluate the effects of aging. Cross-sectional studies investigate young and elderly populations or "cohorts" simultaneously. They are easy to design and execute, but results may be distorted by the subtle manifestations of age-related disease or cohort-specific environmental factors (such as nutritional deficiency or chronic environmental contamination). In effect, cross-sectional studies may demonstrate differences between young and older adults that are real but actually not caused by aging itself. In contrast, longitudinal studies obtain repeated measurements of specific variables over long periods of time in an aging population. Investigators can thereby eliminate from final study those subjects who ultimately show obvious signs of age-related disease. The study group, in effect, acts as its own control because all subjects are from the same cohort. Although longitudinal studies are difficult and expensive to perform and are administratively complex, the data they provide are inherently superior to data obtained from cross-sectional studies.

Analysis of data from the Baltimore Longitudinal Study of Aging, Framingham study, or other longitudinal studies suggests that the difference between maximal and basal organ function inevitably declines, slowly at first during middle adulthood and then more rapidly during the geriatric era (Fig. 61-1) . In fact, most of the recent dramatic improvement in our understanding of the physiology of aging has come from improved experimental design and from the opportunity to review established data and to exclude investigations describing age-related changes due to processes other than aging itself. There are marked differences between individuals with regard to their maximal capacities at somatic maturity, near the end of the 3rd decade of life, as well as in the rate at which those capacities decline. This explains the well-known clinical phenomenon in which some

Figure 61-1 Geriatric individuals who appear to be physiologically "young" or "old" have lesser or greater rates of decline, respectively, than average, but they may also have significantly different maximal capacities than young adults. Organ system functional reserve is defined as the difference between maximal (broken lines) and basal (solid line) function.

elderly patients appear to be "physiologically young" whereas others of the same age seem much less robust because of lesser organ capacity. However, loss of organ system functional reserve, that is, the difference between maximal and basal organ function, remains a constant hallmark of physiologic processes of aging.

Because physicians realize that physiologic or functional age is not always consistent with chronologic age, many attempts have been made to identify specific anatomic or biologic markers such as protein structure that can distinguish the two. However, the primary value of these biologic markers seems to be in quantitating the effectiveness of "antiaging" therapies such as severe restriction of caloric intake or the use of antioxidants to reduce formation of free radicals. Functional variables have also been used, singly or in combination, with inconsistent results in efforts to distinguish between chronologic and physiologic age. For clinical purposes, however, no parameter has been shown to be more valid or more useful than chronologic age in predicting age-related changes in organ systems or the proximity of death. [4]

/das/book/view/29494766/875/675.html

BODY COMPOSITION AND METABOLISM

Drug disposition and excretion are largely determined by body composition and the adequacy of hepatic and renal function. The extent to which aging alters the pharmacokinetics of anesthetic agents and adjuvant drugs reflects, in large part, the changes in the quality and quantity of body tissues that occur after somatic maturity but before complete senescence (approximately the 8th decade). By 60 years of age, for example, body weight is approximately 25 percent higher in men and 18 percent higher in women than in mature young adults. After 60 years of age, however, body weight decreases rapidly, returning to values comparable with, or somewhat below, those of young adulthood. In contrast, body composition changes progressively and irreversibly throughout the middle adult years and into the geriatric era. Aging steadily increases the relative ratio of lipid to aqueous body tissues (Fig. 61-2) and thereby increases the fraction of total body mass functioning as a reservoir for anesthetics and other lipid-soluble drugs.

As they age, women undergo a particularly dramatic increase in total body lipid. Simultaneously, however, osteoporosis produces marked loss of bone and there is a significant reduction of intracellular water that reflects the attrition of metabolically active tissues and other components of lean body mass, with little net overall change in total body weight. Elderly men, on the other hand, undergo a more generalized, multicompartmental loss of tissue mass and experience moderate reductions of both adipose tissue and bone mass. Unlike aging women, aging men also have a dramatic contraction of both intracellular and interstitial water, owing to atrophy (approximately 6 kg) of skeletal muscle mass. However, these changes in total body water in men may be due, at least in part, to subclinical age-related hypertensive disease. [5]

All elderly patients have a virtually universal, progressive decrease in their ability to handle a glucose load. Healthy persons older than 45 years of age require 90 to 95 minutes for return to fasting glucose levels after a 25-g intravenous

Figure 61-2 Body fat increases throughout the middle adult years, but in physically active older men (left) body weight has declined by the geriatric era as a result of the loss of lean tissue mass and subsequent contraction of total body water (cross-hatched areas). In contrast, older women (right) typically experience little change in total body weight because they have a more persistent trend of increasing body fat (diagonal lines) that offsets resorption of skeletal elements (open bars) and loss of lean tissue mass.

glucose challenge; their younger counterparts require, on average, only 65 minutes. The mechanism of glucose intolerance in the elderly is probably insulin antagonism or impairment of insulin function because there is no consistent evidence suggesting decreased rates of insulin secretion or inappropriate timing of insulin release in response to a glucose load. The age-related decrease in lean body mass, tissues that provide storage for carbohydrates, may also be a factor. Although it has not been demonstrated that hyperglycemia is more common or more severe in elderly patients, inability to handle carbohydrate loads, whatever the cause, suggests that elderly patients should not be given large amounts of carbohydrates intravenously as part of perioperative fluid management.

Other functional consequences of loss of muscle tissue are a 30 to 50 percent decrease in maximal oxygen consumption in physically active men and highly significant reductions in resting oxygen consumption in both men and women. There is progressively increasing variability in aerobic capacity between older subjects, although many older athletes are capable of impressive rates of maximal oxygen consumption that in some cases may equal those of sedentary adults 40 years their junior. Nevertheless, basal resting metabolic activity decreases in direct proportion to the age-related attrition of lean tissue mass. Not surprisingly, production of body heat declines in a parallel fashion, contributing to a reduced ability to maintain core temperature in cold environments such as an operating room. [6] In fact, despite normal hypothalamic thermostatic set-points, the intraoperative and postoperative core body temperatures of geriatric patients frequently fall to values below those seen in their young adult counterparts, and rewarming is significantly slower. [7]

Plasma volume is a major determinant of "alpha-phase" pharmacokinetics that describe the molecular aspects of drug redistribution from plasma to various well-perfused compartments immediately after intravenous injection. Plasma volume has long been assumed to decrease with age in a manner similar to that for intracellular water. On the contrary, however, it is now known to be well maintained in healthy and physically active men and women. Many of the classic pharmacokinetic studies of aging demonstrated reduced initial volumes of drug distribution in the elderly because the data were obtained from small numbers of hospitalized patients. Such results are not representative of the elderly population at large, however, although in the perioperative setting many elderly patients indeed have reduced initial distribution volumes for injected drugs because they are bedridden, deconditioned, chronically ill, or hypertensive. Also, they may be receiving diuretics or other drugs having disruptive effects on blood volume homeostasis.

The injection of anesthetic drugs according to a standard dosage schedule based solely on total body weight may explain, at least in part, the higher than expected drug concentrations widely noted during the alpha phase in pharmacologic studies of the elderly. This factor may explain, at least in part, the clinical observation that older adults have an increased sensitivity to anesthetic drugs. [8] Nevertheless, considerable controversy exists as to which drugs commonly used in anesthetic practice truly have altered pharmacodynamics in the elderly and only give the appearance of increased potency because of these age-related changes in early-phase pharmacokinetics. [9] However, with the exception of meperidine, decreases in serum albumin and reduced protein binding clearly have little overall effect on the bioavailability of anesthetic and adjuvant drugs. [10] Similarly, age does not appear to affect absorption of drugs administered orally, a practice growing in frequency because of the increase in outpatient anesthesia.

BLOOD FUNCTIONS

In the absence of disease, aging produces little effect on circulating red blood cell mass, white blood cell count, the number or function of platelets, or coagulation. [11] Hypercoagulability and peripheral thrombosis is common in older adults with vascular and metabolic disease but does not appear to be related to aging itself. Total bone marrow mass and spleen size fall progressively with increasing age, reducing the hematopoietic response to imposed anemia. Erythrocyte fragility increases, although not enough to decrease erythrocyte life expectancy *in vivo.*[12] In any case, clinically significant anemia or disorders of hemostasis in the elderly are always due to disease and not to physiologic processes of aging. In contrast, the obvious susceptibility of even healthy elderly patients to life-threatening infection does imply that aging depresses the selectivity and the effectiveness of immune responses. This decrease in immune responsiveness is almost certainly related to the anatomic involution of the thymus gland that begins during young adulthood and to the altered function of T lymphocytes. [13] Thymic hormones also disappear rapidly after adolescence. However, the few studies of adrenocortical and endocrine functions that have been done indicate that the neuroendocrine response to stress is generally intact or only modestly compromised in geriatric subjects as compared with young adults. [14] [15]

HEPATIC FUNCTION

By the age of 80 years the size of the liver usually declines by as much as 40 percent (Ch. 17) . [16] Because splanchnic blood flow decreases in proportion to the loss of tissue mass, the decrease in hepatic blood flow is significant, even when expressed as a percentage of cardiac output. Thus, aging alters the perfusion patterns of major organs and the relative distribution of cardiac output. Functional indices confirm the assumption that loss of hepatic mass significantly impairs hepatic function. For example, after the 7th decade of life, even healthy older persons who have no other evidence of hepatic dysfunction produce sulfobromophthalein sodium (Bromsulphalein) retention test results in the abnormal range. Although elderly men often have low plasma cholinesterase activity, [17] both microsomal and nonmicrosomal enzyme activity is virtually the same in hepatic tissue specimens (normal liver histology confirmed by biopsy) taken from young and elderly adults. This suggests that in the absence of disease there is probably little qualitative change in hepatocellular enzymatic function with advancing age. [18]

However, some subtle but important gender-specific metabolic changes may occur within this organ system, especially those involved in oxidative phase I forms of drug metabolism, because elderly women maintain normal rates of hepatic clearance for several of the benzodiazepines more frequently than do men. [19] Whatever the true nature of age-related enzymatic effects, it is the quantitative loss of functional hepatic tissue and subsequently reduced liver perfusion that appear to be most important in the marked age-related decrease in the clearance from plasma of opiates, barbiturates, benzodiazepines, propofol, etomidate, most nondepolarizing relaxants, and other drugs requiring hepatic biotransformation.

RENAL FUNCTION

As in virtually all major organs, most of the effects of aging in the kidney are caused by tissue atrophy (Ch. 18) . [20] Maximum young adult bilateral renal tissue mass reaches 270 g, but about 30 percent of that is lost by the 8th decade. There is a parallel decline in the total number of nephron units. Loss of tissue mass would be even greater if parenchymal and cortical atrophy were not offset to some extent by an increase in fat and by diffuse interstitial fibrosis. Aging also compromises renal function through its profound effects on renal vasculature. Total renal blood flow decreases approximately 10 percent per decade in the adult years, although the majority of the loss occurs in the renal cortex and the renal medulla is largely spared. Microscopic examination confirms the disappearance of the kidney's functional units with age: as many as one-half of the glomeruli present in young adults may be gone or rendered nonfunctional by 80 years of age. Glomerular sclerosis also produces anatomic, and perhaps functional, continuity between afferent

Figure 61-3 Data from studies of healthy adult men of various ages show that average serum creatinine concentrations (solid circles, far right axis) stay relatively constant throughout adulthood because they reflect an equilibrium between the declining daily cre-atinine load to be excreted (open diamonds, right axis) and the age-related compromise of glomerular filtration as estimated by the rate of creatinine clearance (solid squares, left axis).

and efferent arterioles, further impairing the efficiency of renal filtration.

Overall, renal plasma flow (RPF) declines more sharply than would be expected solely from the change in renal tissue mass because renal vascular fine structure is especially compromised. However, glomerular filtration rate (GFR) decreases at the rate of 8 mL/min/1.73 m^2 /decade, more slowly than RPF because of compensatory increases in filtration fraction. Creatinine clearance declines about 40 percent between the years of somatic maturity and senescence, yet measurements of serum creatinine concentration remain within normal guidelines in the elderly despite impaired GFR because of the marked atrophy of skeletal muscle mass, particularly in men, that progressively reduces creatinine load (Fig. 61-3) . Although the residual renal function in elderly patients is sufficient to avoid gross azotemia or uremia when demands are basal, the renal functional reserve needed to withstand extreme imposed water and electrolyte imbalance is minimal.

The elderly patient also has a lower responsiveness to antidiuretic hormone, decreased maximal absorption rate for glucose, impaired ability to conserve sodium or concentrate urine, and functional hypoaldosteronism. Loss of lean body mass also reduces total body stores of exchangeable potassium and predisposes to iatrogenic hypokalemia. Elderly surgical patients do not require a special fluid replacement schedule but do require meticulous calculation and monitoring of fluid and electrolyte balance.

Reduced renal vascularity and redistributed cardiac output in the elderly also imply increased susceptibility to renal ischemia. Acute renal failure is, in fact, responsible for at least one-fifth of perioperative deaths among elderly surgical patients. Among geriatric patients who undergo surgery, 30 percent have preexisting renal dysfunction. The prevalence of renal disease not only increases perioperative risk of acute renal insufficiency or failure but also affects the duration of action of many anesthetic and adjuvant drugs. A major pharmacokinetic consequence of age-related changes in renal function is prolongation of the elimination half-time of anesthetic drugs and any metabolites requiring renal clearance (Table 61-2) . In many cases, even though agents such as metocurine are predominantly water soluble and therefore dispersed in a smaller steady-state volume of distribution, the advantage of having a smaller volume to clear is more than offset by the reduction in the rate of clearance. Thus, excretion of these drugs still takes longer in elderly patients than in younger patients.

CENTRAL NERVOUS SYSTEM

Although the age-related changes in both structure and function of the human brain and nervous system are well known, [21] their interrelationship is less well understood (Ch. 19) . As for many organ systems, uncertainty persists because of the inability to distinguish the effects of aging from those of age-related disease. For example, neurofibrillary tangles were once considered the nonspecific manifestations of the aging process within the nervous system. They are now known to be the sequelae of a pathologic deficiency of acetylcholine in the cerebral cortex, clinically manifested as Alzheimer disease. Other "senile" forms of neurologic dysfunction, in particular those with a neurohumoral basis, may also turn out to be age-related diseases rather than inevitable characteristics of the aging nervous system.

Nevertheless, a number of anatomic changes can be considered to be unequivocal hallmarks of aging of the central nervous system (CNS). For one thing, aging reduces brain size. At autopsy, the average weight of the 80-year-old brain is approximately 18 percent lower than that of the 30-year-old brain. Noninvasive, radiographic estimates confirm that the portion of the intracranial volume occupied by brain tissue decreases from 92 to 87 percent over these 5 decades. [22] The most rapid decrease in brain mass (and the greatest

TABLE 61-2 -- Major Effects of Aging on the Pharmacology of Anesthetics and Adjuvant Drugs

	AGE-RELATED CHANGES IN	
	PHYSIOLOGY	***PHARMACOLOGY***
Induction agents	Decreased volumes of distribution	Reduced dose requirement
Thiopental	CNS changes	Prolonged drug effect
Etomidate	Altered distribution of cardiac output	
Propofol		
Opiates	Decreased volumes of distribution	High initial plasma levels
Morphine	Decreased hepatic blood flow	Prolonged drug effect
Fentanyl	CNS changes	Reduced dose requirement
Alfentanil		
Benzodiazepines	Decreased liver mass and blood flow	Prolonged drug effect
Chlordiazepoxide	CNS changes	Reduced dose requirement
Diazepam		
Alprazolam		
Neuromuscular blocking drugs	Disseminated neurogenic atrophy	Same or increased dose requirement
(Nondepolarizers)	Decreased hepatic/renal function	Prolonged drug effect
(Succinylcholine)	Decreased plasma levels of cholinesterase in men	Reduced dose requirement in men
Inhaled anesthetics	CNS changes	Reduced dose requirement

CNS, central nervous system.

compensatory increase in cerebrospinal fluid volume) appears to occur after the 6th decade of life. Whether viewed grossly or radiographically, the cerebral sulci of the very old, even those free of disease, are frequently as much as 35 percent larger than those of young adults. In effect, aging produces a form of low-pressure hydrocephalus.

Most of this tissue shrinkage reflects loss of neurons, not atrophy of the supportive glial cells, which normally constitute almost one-half of total brain mass. Across the entire span of life, the rate of neuronal attrition is 50,000 cells per day, the initial neuron "pool" being approximately 10 billion. This average figure may be misleading, however, because neuronal loss is highly selective by region and by functional role, and the actual rate of loss may vary greatly at different ages. The most highly specialized neuronal subpopulations, particularly those involved with synthesis of neurotransmitter substances, undergo the greatest degree of age-related attrition. Of the neurons in the cerebral and cerebellar cortices, thalamus, locus ceruleus, and basal ganglia, for example, 30 to 50 percent disappear by the end of the 9th decade of life. Age-related loss of neuronal tissue and reduced complexity of synaptic interconnections have been confirmed by microanatomic analysis and radiographically as a decrease in brain tissue radiodensity.

On the other hand, the higher, more complex aspects of "crystallized intelligence" such as language skills, aesthetics, and personality do not appear to decline with increasing age. Despite the long-established bias that aging is associated with an inevitable "senile" deterioration of mental function, most recent studies suggest that storage of information, comprehension, and long-term memory are well maintained in healthy persons through even the 8th decade. However, some decrease in short-term memory, visual and auditory reaction time, and other aspects of "fluid intelligence" that require immediate processing or rapid retrieval of information probably does inevitably occur. In general, throughout the adult life span nervous system functioning is maintained at levels close to those seen at somatic maturity in young adults. Anatomic and functional redundancy compensate for the progressive deterioration of cellular elements and the breakdown of the complex system of neuronal interconnections making up the neuropil.

The intrinsic mechanisms that couple cerebral electrical activity, metabolism, and blood flow remain similarly intact in healthy elderly persons. [23] Although total brain blood flow does decrease approximately 20 percent from maximal values seen in the young adult, this change occurs in proportion to age-related changes in neuronal density. Regional cortical and subcortical adjustments to local metabolic demands occur in the same manner in the elderly as in young adults. Autoregulation of cerebrovascular resistance in response to changes in arterial blood pressure is also well maintained, and the cerebral vasoconstrictor response to hyperventilation remains intact in normal brain tissue. [24] However, patients who have risk factors for stroke and atherogenesis have lower cerebral vasomotor reactivity, especially in response to hypoxia. Still, intentional hyperventilation and the customary relative blood pressure perfusion guidelines used for neurosurgical anesthesia are probably appropriate and effective regardless of patient age, at least for persons free of cerebrovascular disease. Clinically, the rarity of intraoperative stroke despite inevitable marked fluctuations in blood pressure and respiratory parameters supports experimental data indicating that aging is not inevitably associated with "hardening of the

arteries" and inadequate cerebral perfusion. In the healthy elderly individual, decreased cerebral blood flow is a consequence, rather than a cause, of brain tissue atrophy.

Coincident with neuronal loss in specialized areas of the aging brain are generalized depletions of dopamine, norepinephrine, tyrosine, serotonin, and perhaps other neurotransmitters. Simultaneously, there is increased activity of

---

catabolic neurotransmitter enzymes such as monoamine oxidase and catechol *O*-methyltransferase. In the aging brain, the upregulation or increase in number of neurotransmitter receptor sites that appears in young neural tissues in response to any reduction in neurotransmitter activity is less vigorous. CNS "plasticity," the ability to reroute neuronal pathways to compensate for neural injury, is still present but slower and less complete than in children or young adults, and therefore recovery from stroke or traumatic injury is slower and often less complete in the elderly. In addition, receptors for dopamine may have a reduced affinity for neurotransmitter molecules. [25]

PERIPHERAL NERVOUS SYSTEM AND NEUROMUSCULAR FUNCTION

Aging produces a generalized increase in the thresholds for virtually all forms of perception, including vision, hearing, touch, sense of joint position, smell, and peripheral pain and temperature responses (Fig. 61-4) (Ch. 20) . This process of progressive deafferentation may be accelerated by degenerative changes at specialized sense organs. For example, the decrease in the density of pain-sensing Meissner corpuscles in the skin of elderly persons is almost exponential. However, anatomic changes at more central sites are also responsible--specifically, simultaneous attrition of afferent conduction pathways in the peripheral nervous system and spinal cord, as well as reduced velocity and amplitude of electrical transmission in the remaining pathways.

A corresponding deterioration of electrical conduction occurs along motor pathways. The velocity of peripheral motor nerve conduction decreases by approximately 0.15 m/s/y. Impairment of corticospinal transmission may also increase the time between intention and onset of voluntary motor activity. Dynamic muscle strength, control, and the ability to maintain steadiness in the extremities is 20 to 50 percent lower by 80 years of age, although isometric muscle strength is well maintained. Aging skeletal muscle undergoes no dramatic or generalized changes and its enzymatic machinery remains relatively intact, but the neuromuscular junctions show thickening of the postjunctional membrane and spread beyond the usual end-plate areas. [26] Motor end-plate proliferation and the extrajunctional spread of atypical cholinergic receptors are generally regarded as signs of disseminated neurogenic atrophy. This may occur gradually but progressively in older adults because failing proximodistal protoplasmic transport in aging motor neurons reduces the myotrophic support normally provided to skeletal muscle. The increase in the number of cholinergic receptors at the end plate and surrounding areas might compensate for the age-related decline in the number and density of motor end-plate units. However, sensitivity to competitive neuromuscular blocking drugs probably does not decrease significantly. The increased sensitivity to succinylcholine seen in some elderly men is due to reduced plasma cholinesterase enzyme concentrations and not to changes at the neuromuscular junction itself.

AUTONOMIC FUNCTION

Although neurons in sympathoadrenal pathways, as in the rest of the peripheral nervous system, undergo attrition and fibrosis and adrenal mass decreases 15 percent by 80 years of age, plasma levels of norepinephrine, both at rest and in response to exercise-induced stress, are two to four times higher in the elderly than in young subjects (Chs. 14 and 16) . [27] Epinephrine levels are highly variable and do not demonstrate a clear-cut relationship to age itself. In any case, in older adults high catecholamine levels may not be clinically apparent because they are masked by the marked reduction in autonomic end-organ responsiveness associated with aging. Laboratory studies have confirmed that there is a significant impairment of the ability of beta-adrenergic agonists to enhance the velocity and force of cardiac contraction or to increase the rate of electrical discharge of excitable tissues. Elderly human subjects clearly have lower maximal chronotropic responses to isoproterenol, and vascular relaxation mediated by beta-adrenergic receptors decreases in the elderly. [28] Mechanisms possibly accounting for this endogenous beta-blockade of aging include attrition of receptors, reduced affinity for agonist molecules, and impairment of adenylate cyclase activation, perhaps because of decreased cell membrane fluidity. Pharmacologic data demonstrating a decreased affinity of the beta receptors to

Figure 61-4 Aging increases the thresholds, represented here on a logarithmic scale, for the perception of or autonomic response to all forms of sensory and afferent input.

both agonist and antagonist molecules suggest that qualitative, rather than quantitative, changes are responsible.

The complex, integrated autonomic reflex responses that maintain cardiovascular homeostasis in young adults progressively and universally decrease in elderly persons. Baroreflex responsiveness, the vasoconstrictor response to cold stress, and beat-to-beat heart rate responses after postural change are less rapid in onset, smaller in magnitude, and less effective in stabilizing blood pressure in elderly subjects than in young adults. [29] The autonomic nervous system of the elderly patient is, in effect, underdamped and less tightly self-regulated. Therefore, anesthetic agents that disrupt end-organ function or reduce plasma catecholamines, or techniques such as spinal or epidural anesthesia that produce rapid sympathectomy, are more likely to cause hypotension in elderly surgical patients than in young patients. The tendency of this fragile balance to be "disintegrated" will be even more obvious if endogenous autonomic activity has been very high before surgery to compensate for significant end-organ disease, a situation common, for example, in patients with congestive heart failure.

INFLUENCE OF AGE ON DRUG DISTRIBUTION AND METABOLISM

Many drugs used in the practice of anesthesia undergo biotransformation before elimination from the body. Metabolism is extensive for barbiturates, benzodiazepines, narcotic analgesics, and intravenous agents including ketamine, etomidate, and propofol: only minor quantities of such drugs are excreted in their intact form. Enzyme systems responsible for drug metabolism are present in many tissues, the liver being the most important source of those that metabolize drugs used in anesthesia. Of particular significance are the activities of the microsomal mixed function oxidase enzyme system, which catalyzes phase I reactions (e.g., dealkylation and ring hydroxylation) and the enzymes responsible for phase II reactions (conjugation).

Reductions in hepatic blood flow and liver tissue mass would decrease the clearance rates of drugs exhibiting flow-dependent hepatic metabolism. Drugs dependent on hepatic blood flow for metabolism that have high clearance rates include morphine, meperidine, fentanyl, sufentanil, methohexital, ketamine, etomidate, propofol, and possibly midazolam. Although, in theory, clearance of such drugs should decrease dramatically in elderly patients, only limited clinical or experimental evidence exists to support the general conclusion that aging itself inevitably leads to decreased rates of metabolism of such drugs or of other agents used in anesthesia. Several factors are responsible for the lack of consistent information regarding changes in drug metabolism with aging in humans. These include the following:

1. The general problem of wide interindividual variations in rates of drug metabolism, especially those due to gender, race, and ethnic background.
2. Complexities in the metabolic pathways for certain drugs (e.g., benzodiazepines) and the pharmacologic activity of their primary and even secondary metabolites.
3. The difficulty of including the possible role of extrinsic factors (e.g., hormones, alcohol, and tobacco) that also affect drug metabolism.
4. Deficiencies of experimental study design, in particular, a lack of suitable young adult control subjects.

Of even more fundamental concern is the utility of pharmacokinetic data organized in the form of a classic multicompartment model for predicting the clinical effects of anesthetic agents that are given intravenously. It is unclear whether conclusions drawn from studies of the effect of aging on steady-state drug concentrations can reliably anticipate the effects of age on the timing or on the intensity of drug effects within the CNS or at other tissue effector sites. For thiopental, propofol, and perhaps many other drugs used in anesthetic practice, termination of clinical drug effect occurs primarily as a result of the rapid intercompartmental transfer and redistribution rather than as a direct consequence of the eventual molecular biotransformation or excretion of the injected agent. Therefore, rate constants for intercompartmental drug transfer, although these are rarely provided in clinical pharmacokinetic studies, must be compared to predict the behavior of these drugs in a typical clinical setting.

Consequently, traditional pharmacokinetic parameters such as steady-state drug distribution volume or metabolic clearance may be more appropriate for describing the long-term disposition of drug molecules than for analyzing the effect of aging on anesthetic drug effects. There is growing interest in replacing pharmacokinetic parameters derived from simple compartmental models with a more complex but realistic analysis of context-sensitive pharmacokinetics that pays special attention to the movement of drugs between compartments. [30] Little is known about the effect of aging on rate constants for intercompartmental drug transfer, however. There is even controversy as to whether the "correct" number of compartments needed for a useful model can be established. The high plasma concentrations of morphine and fentanyl seen in older adults immediately after intravenous injection [31] were once assumed to be due to decreased plasma volume, but with blood volume now shown to be well maintained in healthy older adults, they may actually reflect more complex age-related changes in alpha-phase pharmacokinetics that determine drug molecule redistribution from the central compartment. [32]

ANALGESIC AND ANESTHETIC REQUIREMENT

Although simple age-related changes in the structure and function of the nervous system are measurable and consistent, their net effect on generalized, pain-related neurologic function in healthy elderly persons is still controversial (Chs. 8 to 10 and 29) . The available data do not support the conclusion that decreasing afferentation in the form of loss of receptors and the dropout of peripheral nerve fibers is necessarily associated with a clinically significant increase in pain threshold or a decreased need for analgesic or local anesthetic agents. The importance of amplification and selectivity of afferent input within the spinal cord, thalamus, and perhaps other sites within the aging nervous system has not been studied adequately. In fact, evidence suggests that

Figure 61-5 With advancing age, anesthetic requirement for unsedated human subjects expressed as relative median effective dose (ED_{50}) or its inhalational equivalent, minimum alveolar concentration (MAC), is progressively and consistently reduced. Despite many differences in chemical structure and clinical pharmacology, anesthetic requirement declines both for inhalational (C,D,H,I,S) and for intravenous (T) anesthetics.

elderly patients have elevated thresholds for discrete, superficial discomfort but reduced thresholds for severe or visceral pain, or for pain associated with illness or with incapacitating injury likely to lead to reduced independence. [33]

The consequences of aging of the nervous system on anesthetic requirements are less complex. Anesthetic requirement is typically quantified by the minimum alveolar concentration (MAC) of an inhaled anesthetic or the median effective dose (ED_{50}) of an intravenously administered anesthetic that is required to abolish response to a stimulus in 50 percent of subjects. With increasing age, the relative MAC or ED_{50} requirement decreases progressively. [34] [35] [36] This decrease occurs for all anesthetic drugs, even the latest inhalational agents such as desflurane and sevoflurane (Fig. 61-5) , and can be as great as 30 percent for those patients who are well into the geriatric era. Although the mechanism for this increasing sensitivity to anesthetic agents is unknown, its remarkable consistency suggests that it is a basically physiologic, rather than pharmacologic, process. In fact, the rate of change in anesthetic requirement parallels the rate of loss of cortical neurons and the reduction in neuronal density within the cortex, the decreases in absolute cerebral metabolic rate and absolute cerebral blood flow, and the age-related reduction in brain neurotransmitter activity.

CARDIOVASCULAR FUNCTION

Analysis of cardiovascular function in the elderly requires careful identification of disease-related conditions. Cardiovascular disease is present in 50 to 65 percent of the elderly, and coronary disease has been found in even completely symptom-free septuagenarians. For the surgical population in general, approximately 10 percent of all perioperative deaths are directly related to cardiovascular abnormalities. Cardiovascular disorders, in fact, account for one-half or more of all the mortality in the geriatric subpopulation (Fig. 61-6) . Geriatric surgical patients have higher rates of both overt and subclinical disease than those found in the surgical patient population as a whole. In one classic study, preoperative pulmonary artery catheterization of deconditioned elderly patients demonstrated that fewer than 15 percent were physiologically normal with respect to hemodynamic and respiratory function, and almost 25 percent had severe and intractable functional abnormalities increasing the likelihood of perioperative death. [37]

In the absence of obvious disease, the major anatomic changes seen in the aging human heart are primarily an increase in ventricular wall thickness and the increasing severity of myocardial fibrosis and valvular fibrocalcification. Therefore, as ventricular compliance decreases, relatively small changes in intravascular volume or venous capacitance become increasingly important determinants of circulatory stability. In effect, aging makes patients volume-dependent yet volume-intolerant because increased cardiac chamber stiffness in elderly patients means that their hemodynamic functioning is optimal only within a narrow range of end-diastolic pressure and volume. Age-related increases in large artery stiffness also increase impedance to the ejection of stroke volume and elevate the aortic systolic pressure associated with any given stroke volume. These higher aortic pressures may then cause reactive hypertrophy and further stiffening of the left ventricular wall. Finally, loss of arterial elasticity also produces a widening of arterial pulse pressure and reduction of the diastolic pressure that largely determines coronary artery perfusion. [38]

However, overall integrated cardiovascular function changes less than would be expected from the structural alterations of the heart that are associated with aging. Classic data indicated a dramatic and progressive decrease in cardiac index that was almost linear with age. However, these data were obtained from deconditioned elderly persons who had a variety of cardiovascular diseases, and therefore, in retrospect, they appear to demonstrate the consequences of age-related disease and not the effects of aging itself on the healthy aging cardiovascular system. There is recent evidence [39] that exercise training can significantly ameliorate the cardiovascular stiffness that is generally thought of as a hallmark of the effects of aging on cardiovascular structure

Figure 61-6 The components of mortality in the elderly population, 1988 data reported in 1991 by the National Center for Health Statistics. Epidemiologic analysis suggests that the probability of death from cardiac, vascular, and pulmonary causes, as well as death from accident, all increase dramatically in the oldest fractions of the geriatric age group, with malignancy and metabolic disorders playing a lesser role.

and function. In fact, more recent studies confirm that the resting cardiac index of fit, active elderly persons is reduced only in direct proportion to their reduced skeletal muscle mass and metabolic rate associated with the inevitable reduction of lean tissue mass.

Exercise-trained older men and women achieve and maintain impressively high levels of cardiac output and maximal oxygen consumption. [40] Nevertheless, aging imposes a ceiling on maximal cardiac output that reflects both reduced maximal heart rate and the age-related prolongation of time required for both myocardial contraction and relaxation. [41] Maximal cardiac output decreases approximately 1 percent per year starting from middle adulthood. Both at rest and at moderate levels of exercise, an increase in left ventricular diastolic volume in response to augmented preload compensate for slower heart rate in elderly persons. Thus, stroke volume, and therefore cardiac output, increases appropriately in response to aerobic demand because of the Frank-Starling mechanism rather than by tachycardia or augmentation of ejection fraction through stimulation of beta-adrenergic agonists characteristic of children and young adults. [42] However, because aging produces ventricular hypertrophy and decreased chamber elasticity, diastolic ventricular filling is slower and more dependent on atrial contraction. Therefore, loss of sinus rhythm and the atrial "kick" it produces severely compromises cardiac output in older adults, and diastolic dysfunction is a far more common cause of hemodynamic insufficiency than in young adults. [43]

VENTILATION AND PULMONARY FUNCTION

The effects of age on the manifold functions of the lung have been comprehensively described (Chs. 15 and 24) . [44] Lung tissue elasticity is the anatomic property most affected by age in this system. With advancing age there is qualitative deterioration of lung elastin rather than simple loss of elastic tissue as had once been thought. In any case, aging is associated with an inevitable and progressive loss of lung recoil, making aging lungs more compliant but unfortunately also reducing the tethering effect that normally maintains patency of the small airways and helps to ensure appropriate and homogeneous distribution of inspired gases. In addition, the breakdown of alveolar septa reduces the total alveolar surface area available to participate in molecular gas exchange. As a result, the elderly patient has progressive increases in both anatomic and alveolar dead space (Fig. 61-7) . The nonuniform loss of elasticity may also explain the progressively more severe mismatching of ventilation and perfusion that occurs in elderly persons. [45]

Calcification decreases chest-wall compliance and makes the thorax of older adults more rigid. Therefore, despite increased lung compliance, total pulmonary compliance changes very little. Within the thorax, loss of lung recoil means that residual volume increases at the expense of expiratory reserve volume. Therefore, with little change in total lung capacity, functional residual capacity (FRC) increases modestly but progressively at the expense of vital capacity (VC) (Fig. 61-8) . Closing volume and closing capacity also increase until they overlap FRC. Thus, in the elderly, small airways may close even during tidal breathing. This condition or the heterogeneous pattern of increased compliance in different areas of the lung may account for the relentless widening of the alveolar-arterial gradient for oxygen that impairs oxygenation and the increased dead-space fraction that reduces the efficiency of carbon dioxide elimination.

Fibrosis and calcification of the chest wall also lessen the effectiveness of the respiratory "bellows" and restrict, to some degree, the pulmonary mechanics of elderly persons. This rigidity, manifested clinically as reductions in forced expiratory volume in 1 second and in midmaximal expiratory flow rate, also increases the work of breathing and ultimately limits maximal breathing capacity. Elderly persons also have marked reduction in the ventilatory response to imposed hypoxia and hypercapnia, [46] although moment-to-moment

Figure 61-7 Alveolar-arterial oxygen gradient (left axis) and dead space fraction (Vd/Vt, right axis) both increase progressively with age but are significantly influenced by body position.

regulation of ventilation appears to be unimpaired. Furthermore, the elderly have increased periodic breathing (i.e., apnea) during sleep, which makes them more likely to have apnea and airway obstruction in the recovery room. [47] The higher incidence of apnea and episodic respiration observed in elderly patients given parenteral narcotics probably reflects the transiently high initial plasma concentrations of these drugs in the elderly rather than a true increase in sensitivity to the respiratory depressant properties of the drugs.

PSYCHOSOCIAL ISSUES

Most surgical patients are psychologically fit but have a variety of concerns, many that are profoundly distressing, about their impending surgery. The elderly do not differ fundamentally in this regard from their younger counterparts, but they are aware that they have decreased functional reserve in many areas. Consequently, they have particularly acute concerns regarding the possibility of irreversible loss of ability to meet the demands of independent normal daily activity and the possibility of long-term institutionalization. Social, financial, and sensory isolation are additional sources of anxiety for elderly surgical patients. At a subconscious or emotional level, they may also sense a greater proximity to, and possibility of, their own death. On the other hand, many older adults seem to face cancer with less anger and with greater equanimity than do young or middle-aged patients.

Competence in the context of patient participation in perioperative decision-making does not specifically require general orientation to time or place, although acute confusion or delirium states due to imposed factors such as sleep deprivation or drug therapy must be medically corrected before assessment of competence. [48] Evaluation of an elderly patient's mental status and competence must be included in virtually every interaction between patient and physician. Unfortunately, "ageism" among physicians makes many of them less likely to take an elderly patient's questions or concerns regarding health care as seriously as those that come from a young adult. Persistent misconceptions that aging somehow necessarily diminishes intellectual or rational capacity, patronizing attitudes toward perceived parent figures, cultural bias, and subconscious emotional reaction to a physician's own fear of aging and disability all combine to reduce the objectivity with which a physician can listen to, and heed, elderly patients' attempts to participate in their own health-care decisions.

In most cases, however, there is no medical reason to expect that an elderly patient does not meet generally accepted legal standards of mental competence. The fundamental ability of the elderly surgical patient to seek, consider, and consent to surgical treatment should be assumed intact. Nevertheless, the standards for assessment of competence by the physicians participating in the perioperative care of an elderly patient may be substantially higher than those used for young adult patients. [49] Although most legal doctrines are generic and therefore do not specifically

Figure 61-8 Aging increases residual volume (RV) at the expense of vital capacity (VC), because total lung capacity (TLC), the sum of all component volumes, remains relatively unchanged unless physical stature is markedly compromised. Functional residual capacity (FRC), the volume of the lung at rest, increases as aging progressively compromises lung elastic recoil and allows residual volume (RV) to expand and closing capacity (CC) to infringe upon normal tidal breathing.

identify the elderly patient as a special subpopulation with unique status, failure to take age-related psychologic, social, economic, and physiologic factors into account when making judgments regarding the patient's decision-making capacity could nevertheless be regarded as a deviation from the "accepted standard of care" imposed on the medical community, especially in the course of legal actions that occur after an adverse outcome.

Before surgery, elderly patients may be increasingly preoccupied with the events of their past. Patient and respectful listening may help the anesthesiologist properly prepare that patient psychologically for surgery in a way that cannot be accomplished pharmacologically. If, however, the elderly patient appears overly fixed on a trivial event or past experience, such preoccupation may indicate endogenous or reactive depression. Endogenous depression is associated with a higher risk of postoperative morbidity and mortality, and recovery from endogenous depression in the elderly is often prolonged. The elderly do have a higher incidence of emotional disturbance and psychologic abnormalities than the surgical population at large. Elderly patients with personality disorders may be particularly manipulative, histrionic, hypochondriacal, demanding, or theatrical.

The compression of the majority of serious illness and disability into the geriatric portion of life span makes decisions regarding continuation of life support and do-notresuscitate (DNR) orders particularly important for geriatric surgical patients. Although accrediting organizations require hospitals to have a DNR policy, to be effective and useful that policy must include provisions for perioperative modification or temporary suspension, on a case-by-case basis, when surgical patients with DNR status require anesthesia for invasive procedures. [50] Evidence from studies of nursing home and hospitalized elderly patients suggest that cardiopulmonary resuscitation (CPR), in fact, is rarely effective in the debilitated patients most likely to receive DNR status. However, the arbitrary assignment of DNR status to those elderly patients believed by their physicians to be "poor candidates for resuscitation" because of a low expected probability of success remains in fundamental conflict with the general principle of patient autonomy. This need not be a significant dilemma, however, because a majority of those elderly patients who are least likely to respond to CPR will, in response to direct and candid discussion of this issue, voluntarily accept DNR status if it is suggested to them. [51]

PERIOPERATIVE RISK AND OUTCOME

As in all forms of epidemiologic investigation, direct comparisons of surveys of perioperative morbidity and mortality should be preceded by careful review to identify any significant differences in methodology and definition of key terms (such as *perioperative* and *morbidity*) (Ch. 22) . [52] Because intraoperative mortality is now rare and because intensive care facilities frequently prolong short-term survival of patients who cannot recover after surgery, the current standard for comparing the rate of perioperative complications should be at least 30 days from the time of surgery.

In the past, some effort was made to distinguish complications due to anesthesia from those not related to anesthesia. Classic studies, from an era in which anesthetic routines were far simpler and postoperative care less intense than now, have suggested that anesthesia-related morbidity probably accounts for approximately 10 percent of complications seen perioperatively. However, the complex interaction between pathophysiologic, pharmacologic, and technical interventions in modern surgery frequently makes it impossible to establish a clear or single cause of perioperative morbidity or death. Therefore, most modern studies simply present data as gross perioperative survival.

Ample and consistent evidence shows that major morbidity and mortality occur more frequently in elderly surgical patients than in younger counterparts undergoing comparable surgery. Current estimates of 30-day perioperative mortality for adequately prepared surgical patients 65 years of age or older are 5 to 10 percent. [53] [54] [55] Although this value is less than one-half that reported 3 or 4 decades ago, it is still three to five times that for young adults. One-year mortality for debilitated geriatric patients approaches 20 percent, although this figure includes many nonsurgical factors. [56]

Three major risk factors appear to determine mortality rates for elderly patients: the need to perform surgery on an emergency basis, the operative site, and the physical status of the patient at the time of surgery. The mechanism by which emergency surgery increases risk 3- to 10-fold is itself probably multifactorial. The personnel, facilities, and time available for emergency surgery are not always equivalent to those normally used for elective surgery. Inadequate preparation and cursory preoperative evaluation, commonplace in elderly patients in general, are likely to be even more haphazard in an emergency. Correctable deficiencies in circulating blood volume, electrolyte imbalance, or impaired oxygen transport may be present in almost two-thirds of the patients having an emergency. In addition, the nature of the surgical lesion and its acute consequences (e.g., as hemorrhage, dehydration, ischemia, and acidosis) may critically reduce already-limited organ system reserve or even injure the elderly patient irreversibly. Finally, infection and sepsis continue to be major causes of death in elderly patients despite vigorous intravenous antibiotic therapies, perhaps because of pervasive age-related deterioration of the vigor and the selectiveness of immune responsiveness in older adults. Whatever the cause, perioperative mortality in elderly patients undergoing emergency surgery remains high.

The importance of the site of surgery as a major determinant of perioperative risk in the elderly applies equally for emergency and elective surgery. Truly superficial operations, such as cataract surgery, incur very few deaths. In contrast, surgical entry into a major body cavity greatly increases the risk of morbidity and mortality. Colon resection and other forms of bowel surgery have mortality rates comparable with those for intrathoracic and major vascular procedures. For the elderly, the risk of death is 10 to 20 times greater for these types of procedures than for inguinal herniorrhaphy or transurethral prostatectomy.

The guidelines of the American Society of Anesthesiologists provide clinical quantification of the severity of disease. In general, the greater the average age of a surgical population, the greater the prevalence of age-related disease, and thus the poorer the physical status of the group. [57] The preoperative physical status of elderly patients clearly correlates with perioperative morbidity (Fig. 61-9) . Therefore, much of the increased risk once ascribed to aging itself--on the vague and theoretical grounds of "decreased vitality"--has now been properly attributed to the impaired physical status associated with age-related disease. Almost one-half of the typical elderly surgical patient population has hypertension, with or without coronary artery disease. Significant portions also have chronic renal, hepatic, pulmonary, and metabolic diseases such as diabetes, which have widespread effects on multiple organ systems and increase the risk of anesthesia despite continuing therapy. In fact, most fatal perioperative myocardial infarctions are not first-time infarcts but reinfarctions in patients with preexisting cardiac disease. Similarly, the most accurate predictor of postoperative pulmonary complications is simply the presence of preoperative pulmonary disease.

Thus, the perception of inevitably increased perioperative morbidity and mortality with advancing age actually reflects the obvious relationship between preoperative physical status and perioperative outcome. Certainly, decreased organ system reserve, especially in very old patients, contributes to the complex interactions by which aging is associated with an increased rate of perioperative mortality (Fig. 61-10) . Adverse drug reactions also play a progressively larger role in perioperative morbidity in older adults who require drug therapy for the treatment of age-related disease (Fig. 61-11) .

ANESTHETIC MANAGEMENT

Debilitated and sickly older patients are particularly prone to perioperative complications, but healthy older surgical patients should do well. In fact, for many types of surgery the likelihood of perioperative morbidity and mortality may not be significantly higher in fit, healthy octogenarians than in young adults undergoing similar procedures. [58] [59] [60] Whatever the age of the patient, a satisfactory and uncomplicated anesthetic course requires (1) an anesthetic plan compatible with the patient's physical status and the type of surgery, (2) consistent monitoring, and (3) careful attention to detail. No additional or unique major principles need to be observed when caring for the elderly patient,

Figure 61-9 Large-scale prospective studies confirm that physical status (PS), here quantified by the American Society of Anesthesiologists (ASA) classification system, is a major determinant of perioperative morbidity. A high prevalence of poor physical status (ASA PS 3 and 4) is largely responsible for the high rate of complications associated with surgery in the elderly.

Figure 61-10 Increased rate of complications and a greater likelihood of perioperative mortality in elderly subjects reflects the interaction of the effects of aging on organ system functional reserve and the consequences of age-related disease and its therapy. Polypharmacy and the need for medical intervention further amplify the likelihood of adverse outcome.

and there is no "best" anesthetic agent or technique for the elderly. Dozens of retrospective and prospective studies have arrived at the same conclusions: no significant difference in outcome can be attributed solely or predominantly to use of any specific anesthetic agent, and no clear and objective benefit can be demonstrated for using regional anesthesia rather than general anesthesia. [61] [62] [63] Peripheral neurologic complications and sequelae such as neurapraxias are more common in older adults after regional anesthesia than in young adults. [64] On the other hand, there is less short-term disruption of postoperative mental functioning when spinal anesthesia, without sedation, is given to elderly patients rather than general anesthesia. [65] Probably only "pure" local infiltration anesthesia given without the addition of intravenous sedation, in those limited circumstances where this approach is practical, can approach the ideal of morbidity-free outcome.

Consequently, selection of anesthetic techniques and specific drugs for elderly patients requires careful review of the patient's physical condition and analysis of the nature and severity of age-related and coexisting disease processes. As in younger patients, administration of an inhaled anesthetic having marked myocardial depressant properties must be done with extreme caution if the patient has intractable congestive heart failure and low cardiac output. Similarly, the acute pharmacologic sympathectomy associated with high thoracic levels of spinal anesthesia is unlikely to be well tolerated in a hypertensive, debilitated elderly person who has reduced circulating blood volume and is being given diuretics. As detailed previously, some loss of renal, cardiac, hepatic, and pulmonary functional reserve is an inevitable consequence of aging even in the healthy, fit patient. Although remaining organ system reserve is adequate to meet small to moderate amounts of imposed stress, complex anesthetic techniques that put a heavy demand on these organs while simultaneously disrupting autonomic function are, at best, difficult to manage and, at worst, a threat to patient survival.

The anesthetic plan for an elderly patient should, however, acknowledge the effect of age on anesthetic requirement. Sensitivity of the cerebral cortex to fentanyl, alfentanil, and midazolam all appear to increase with advancing age. [66] [67] [68] Regardless of whether these observations are due to true age-related alterations of pharmacodynamics or whether they are simply pharmacokinetically produced variations in apparent drug sensitivity due to high initial injected drug concentrations in plasma, dosage of etomidate, barbiturates, propofol, narcotics, or benzodiazepines should be reduced 20 to 40 percent in elderly patients. [69] [70] Increased use of intravenous agents such as remifentanil and cisatracurium that do not require organ-based elimination clearance for the termination of their clinical effects also will facilitate prompt and predictable recovery in older adults.

Segmental dose requirements for epidural anesthetics seem to change in a complex manner with age, perhaps reflecting increased resistance to injection and reduced overall compliance of the epidural space. Dose requirements change insignificantly after injection of small volumes of local anesthetic solutions, whereas injection of large volumes may be followed by markedly exaggerated cephalad spread of the drug in older adults. [71] On the other hand, after subarachnoid injection of local anesthetics or narcotics, there appears to be a somewhat more rapid onset of maximum sensory level and slight prolongation of effective analgesia but not significant change in overall pharmacodynamics. [72]

Traditional nondepolarizing muscle relaxants are required in about the same quantity in elderly as in younger patients to provide equal levels of paralysis, although, in general, their duration of action is prolonged because of decreased rates of clearance from the plasma/extracellular fluid compartment from which they exert their primary effects. [73] [74] Neither the rate of onset nor the peak effectiveness of anticholinesterase drugs used to antagonize neuromuscular blockade (e.g., neostigmine and edrophonium) is altered significantly by processes of aging. However, the incidence of cardiac arrhythmias after neostigmine is higher in elderly patients who have cardiovascular disease. [75] In the elderly, the action of all of these drugs may be prolonged if they require hepatic or renal elimination and/or biotransformation. [76]

Figure 61-11 The incidence of adverse drug reactions rises progressively after early middle age in all modern industrialized societies in which elderly adults have facilitated access to the medical therapy needed to control the symptoms of age-related disease.

The value of consistent cardiac and neuromuscular monitoring arises from the greater variability and unpredictability of the elderly in their response to the complex drug environment inherent in surgery.

The need for increased attention to detail in the perioperative management of elderly surgical patients has already been implied in earlier discussions of intravenous fluid therapy, inspired oxygen concentration, and metabolic support. In addition, reduced skin and soft tissue perfusion make the elderly more prone to ischemic pressure lesions. Agerelated osteoporosis and arthritis may increase the likelihood for iatrogenic injury if positioning for surgery is not done with great care, and decreased lacrimation makes eye protection even more critical than in younger patients. The reduced responsiveness of protective airway reflexes in the elderly [77] may justify routine protection against regurgitation and aspiration of gastric contents. Anesthesiologists must search for and protect prosthetic devices worn or implanted preoperatively and must aggressively conserve body heat intraoperatively to avoid the cardiovascular and metabolic stress of postoperative hypothermia, although decreased skeletal muscle mass and impaired thermoregulation markedly limit the severity of postoperative shivering in elderly adults. [78] Nevertheless,

supplemental oxygen administration should be strongly considered for at least 24 hours after surgery to compensate for the inevitable decrease in efficiency of oxygenation that follows surgery in all patients. This concern is of particular importance to elderly patients, who have impaired efficiency of oxygen extraction and decreased response to hypoxia.

Although nervous system function usually returns quickly and completely after anesthesia, the neurologic examination may be grossly abnormal for up to 40 minutes postoperatively. Subsequent failure of an elderly patient to return spontaneously to preoperative levels of nervous system function almost always reflects prolonged anesthetic effects. Nevertheless, postoperative delirium, disorientation, and acute brain syndromes do occur commonly in older patients and may be due to disordered metabolic states (hypoglycemia or hyperglycemia, hypoxia, hypothermia, or hypercarbia) or expressions of subclinical age-related neurologic disease. [79] Gross nervous system injuries in the elderly patient usually result from cerebral ischemia or embolism. Such injuries are distinguishable from residual drug effects by their severity, focal nature, and the absence of conspicuous improvement in the first few hours after anesthesia and surgery. More subtle forms of residual nervous system dysfunction may, on the other hand, be unique to the geriatric population. Impaired spatial and verbal cognition, as well as memory deficits, may persist beyond the first week after surgery in as many as 25 percent of elderly surgical patients. [80] New electroencephalographic findings appear postoperatively in more than one-third of this surgical subpopulation. In one study, 13 percent of elderly patients had some form of long-term memory loss or "serious mental deterioration."

Although the cause of intermediate- and long-term nervous system dysfunction in the elderly is not known, such dysfunction does not appear to be related to the choice of anesthetic itself. [81] Multiple and complex causes, including isolation and inactivity, anemia, alcoholism, a history of psychologic pathology, or the degree of emotional support provided to the patient and the nature of the surgical outcome, have been suggested. [82] Experimental observations of the inactivation of the enzyme methionine synthase in brain tissue by nitrous oxide suggested that a pharmacologic mechanism is also possible, because this enzyme is essential for memory because it requires the synthesis of nucleic acids. Although permanent nervous system damage is rare, many elderly surgical patients require weeks or months to gain full recovery of all aspects of preoperative mental status, for reasons that remain unknown. [83]

SUMMARY

Rapid recent improvement in our understanding of the physiology and pharmacology of aging has occurred in large part because investigators have been able to separate the effects of aging per se from the consequences of age-related

---

disease. Aging produces progressive atrophy, fibrosis, and loss of elasticity in virtually all tissues and organs. The structural and functional consequences of these changes are measurable from the period of peak somatic maturity, in the 3rd decade of life, through the middle adult years, and then into the period of accelerated senescence during the 8th decade of life. In the absence of disease, organ function remains adequate to meet basal requirements and even moderate demands, but the functional reserve capacity and the maximal capacity of all major organ systems are significantly reduced.

As a group, elderly patients are at greater risk of perioperative morbidity and mortality than their younger counterparts because of the high incidence of coexisting disease. Increased rate and severity of complications may also reflect decreased autonomic homeostasis and a reduced capacity to tolerate or compensate for imposed pathology or surgical stress. Optimal anesthetic management of elderly patients requires adequate diagnosis and treatment of concurrent diseases, meticulous attention to the details of preparation and positioning, and use of monitoring techniques permitting adjustments in dosage appropriate to the altered requirements for anesthetic and adjuvant drugs. Although advanced age (i.e., older than 85 years) is itself a risk factor for patients with severe or multiorgan dysfunction, chronologic age can no longer be considered a contraindication to well-managed anesthesia and surgery in a geriatric subject.

References

1. Nascher IL: Geriatrics. N Y Med J 90:358, 1909.

2. Schneider EL, Reed JD Jr: Life extension. N Engl J Med 312:1159, 1985.

3. Wallace DC: Diseases of the mitochondrial DNA. Annu Rev Biochem 61:1175, 1992.

4. Reff ME, Schneider EI (eds): Biological Markers of Aging. Publication (NIH) 82-221. Bethesda, MD, National Institutes of Health, 1982.

5. Fulop T Jr, Worum I, Csongor J et al: Body composition in elderly people: I. Determination of body composition by multiisotope method and the elimination kinetics of these isotopes in healthy elderly subjects. Gerontology 31:6, 1985.

6. Frank SM, Beattie C, Christopherson R et al: Epidural versus general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothermia. Anesthesiology 77:252, 1992.

7. Vaughan MS, Vaughan RW, Cork RC: Postoperative hypothermia in adults: Relationship of age, anesthesia, and shivering to rewarming. Anesth Analg 60:746, 1981.

8. Berkowitz BA, Ngai SH, Yang JC et al: The disposition of morphine in surgical patients. Clin Pharmacol Ther 17:629, 1975.

9. Homer TD, Stanski DR: The effect of increasing age on thiopental disposition and anesthetic requirement. Anesthesiology 62:714, 1985.

10. Greenblatt DJ, Sellers EM, Shader RI: Drug disposition in old age. N Engl J Med 306:1081, 1982.

11. Hussain S: Disorders of hemostasis and thrombosis in the aged. Med Clin North Am 60:1273, 1976.

12. Detraglia M, Cook FB, Stasiw DM et al: Erythrocyte fragility in aging. Biochim Biophys Acta 345:213, 1974.

13. Hirokawa K, Makinodan T: Thymic involution: Effect on T-cell differentiation. J Immunol 114:1659, 1975.

14. West CD, Brown H, Simons EL et al: Adrenocortical function and cortisol metabolism in old age. J Clin Endocrinol Metab 21:1197, 1961.

15. Snyder PJ, Utiger RD: Response to thyrotropin releasing hormone (TRH) in normal man. J Clin Endocrinol Metab 34:380, 1972.

16. Geokas MC, Haverback BJ: The aging gastrointestinal tract. Am J Surg 117:881, 1969.

17. Shanor SP, Van Hees GR, Baart N et al: The influence of age and sex on human plasma and red cell cholinesterase. Am J Med Sci 242:357, 1961.

18. Woodhouse KW, Mutch E, Williams FM et al: The effect of age on pathways of drug metabolism in human liver. Age Ageing 13:328, 1984.

19. Greenblatt DJ, Abernethy DR, Locniskar A et al: Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 61:27, 1984.

20. MacLachlan MSF: The aging kidney. Lancet 2:143, 1978.

21. Katzman R, Terry RD: Normal aging of the central nervous system. In Katzman R, Terry RD (eds): The Neurology of Aging. Philadelphia, FA Davis, 1983, p 15.

22. Yamamura H, Masatoshi I, Kubota K et al: Brain atrophy during aging: A quantitative study with computerized tomography. J Gerontol 35:492, 1980.

23. Meyer JS, Terayama Y, Takashima S: Cerebral circulation in the elderly. Cerebrovasc Brain Metab Rev 5:122, 1993.

24. Rogers RL, Meyer JS, Mortel KF et al: Age-related reductions in cerebral vasomotor reactivity and the law of initial value: A 4-year prospective longitudinal study. J Cereb Blood Flow Metab 5:79, 1985.

25. Dax EM: Receptors and associated membrane events in aging. Rev Biol Res Aging 2:315, 1985.

26. Tomonaga M: Histochemical and ultrastructural changes in senile human skeletal muscle. J Am Geriatr Soc 25:125, 1977.

27. Ziegler MG, Lake CR, Kopin IJ: Plasma noradrenaline increases with age. Nature 261:333, 1976.

28. Pan HY-M, Hoffman BB, Pershe RA et al: Decline in beta adrenergic receptor-mediated vascular relaxation with aging in man. J Pharmacol Exp Ther 239:802, 1986.

29. Collins KJ, Exton-Smith AN, James MH et al: Functional changes in autonomic nervous responses with ageing. Age Ageing 9:17, 1980.

30. Shafer SL, Stanski DR: Improving the clinical utility of anesthetic drug pharmacokinetics (editorial). Anesthesiology 76:327, 1992.

31. Singleton MA, Rosen JI, Fisher DM: Pharmacokinetics of fentanyl in the elderly. Br J Anaesth 60:619, 1988.

32. Avram MJ, Krejcie TC, Henthorn TK: The relationship of age to the pharmacokinetics of early drug distribution: The concurrent disposition of thiopental and indocyanine green. Anesthesiology 72:403, 1990.

33. Harkins SW, Chapman CR: Detection and decision factors in pain perception in young and elderly men. Pain 2:253, 1976.

34. Gregory GA, Eger EI II, Munson ES: The relationship between age and halothane requirement in man. Anesthesiology 30:488, 1969.

35. Stevens WC, Dolan WM, Gibbons RT et al: Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 42:197, 1975.

36. Munson ES, Hoffman JC, Eger EI II: Use of cyclopropane to test generality of anesthetic requirement in the elderly. Anesth Analg 63:998, 1984.

37. Del Guercio LRM, Cohn JD: Monitoring operative risk in the elderly. JAMA 243:1351, 1980.

38. Weisfeldt ML, Abben R: Presbycardia. Johns Hopkins Med J 149:203, 1981.

39. Vaitkevicius PV, Fleg JL, Engel JH et al: Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation 88(4 part 1):1456, 1993.

40. Heath GW, Hagberg JM, Ehsani AA et al: A physiological comparison of young and older endurance athletes. J Appl Physiol 51:634, 1981.

41. Lakatta EG: Diminished beta-adrenergic modulation of cardiovascular function in advanced age. Cardiol Clin 4:185, 1986.

42. Gerstenblith G, Renlund DG, Lakatta EG: Cardiovascular response to exercise in younger and older men. FASEB J 46:1834, 1987.

43. Wei JY: Age and the cardiovascular system. N Engl J Med 327:1735, 1992.

44. Wahba WM: Influence of aging on lung function--clinical significance of changes from age twenty. Anesth Analg 62:764, 1983.

45. Gunnarsson L, Tokics L, Gustavsson H et al: Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia. Br J Anaesth 66:423, 1991.

46. Kronenberg RS, Drage CW: Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. J Clin Invest 52:1812, 1973.

47. Shore ET, Millman RD, Silage DA et al: Ventilatory and arousal patterns during sleep in normal young and elderly subjects. J Appl Physiol 59:1607, 1985.

48. Appelbaum PS, Grisso T: Assessing patients' capabilities to consent to treatment. N Engl J Med 319:1635, 1988.

49. Kapp MB: Legal aspects of geriatric surgical care. In Katlic MR (ed): Geriatric Surgery. Baltimore, Urban & Schwarzenberg, 1990, pp 29-49.

---

50. Cohen CB, Cohen PJ: Do-not-resuscitate orders in the operating room. N Engl J Med 325:1879, 1991.

51. Wagner A: Cardiopulmonary resuscitation in the aged: A prospective survey. N Engl J Med 310:1129, 1984.

52. Go AS, Browner WS: Cardiac outcomes after regional or general anesthesia. Do we have the answer (editorial)? Anesthesiology 84:1, 1996.

53. Djokovic JL, Hedley-Whyte J: Prediction of outcome of surgery and anesthesia in patients over 80. JAMA 242:2301, 1979.

54. Valentin N, Lomholt B, Jensen JS et al: Spinal or general anaesthesia for surgery of the fractured hip? A prospective study of mortality in 578 patients. Br J Anaesth 58:284, 1986.

55. Davis FM, Woolner DF, Frampton C et al: Prospective, multicentre trial of mortality following general or spinal anaesthesia for hip fracture surgery in the elderly. Br J Anaesth 59:1080, 1987.

56. Edwards AE, Seymour DG, McCarthy JM et al: A 5-year survival study of general surgical patients aged 65 years and over. Anaesthesia 51:3, 1996.

57. Cousin MT: Evaluation of operative risk in the aged. In Conseiller C, Cousin MT (eds): Complications of Anaesthesia Operative Risk: Post Graduate Course. New York, Elsevier, 1982, p 257.

58. Marx GF, Mateo CV, Orkin LR: Computer analysis of postanesthetic deaths. Anesthesiology 39:54, 1973.

59. Tiret L, Desmonts JM, Hatton F et al: Complications associated with anaesthesia--a prospective survey in France. Can J Anaesth 33:336, 1986.

60. Forrest JB, Rehder K, Cahalan MK et al: Multicenter study of general anesthesia: III. Predictors of severe perioperative adverse outcomes. Anesthesiology 76:3, 1992.

61. McKenzie PJ, Wishart HY, Smith G: Long-term outcome after repair of fractured neck of femur: Comparison of subarachnoid and general anaesthesia. Br J Anaesth 56:581, 1984.

62. Christopherson R, Beattie C, Frank SM et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Anesthesiology 79:422, 1993.

63. Bode RH, Lewis KP, Zarich SW et al: Cardiac outcome after peripheral vascular surgery: Comparison of general and regional anesthesia. Anesthesiology 84:3, 1996.

64. Dahlgren N, Tornebrandt K: Neurological complications after anaesthesia: A follow-up of 18,000 spinal and epidural anaesthetics performed over three years. Acta Anaesthesiol Scand 39:872, 1995.

65. Chung F, Meier R, Lautenschlager E et al: General or spinal anesthesia: What is better in the elderly? Anesthesiology 67:422, 1987.

66. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 240:159, 1987.

67. Kanto J, Aaltonen L, Himberg J-J et al: Midazolam as an intravenous injection agent in the elderly: A clinical and pharmacokinetic study. Anesth Analg 65:15, 1986.

68. Jacobs JR, Reves JG, Marty J et al: Aging increases pharmacodynamic sensitivity to the hypnotic effects of midazolam. Anesth Analg 80:143, 1995.

69. Muravchick S: Effect of age and premedication on thiopental sleep dose. Anesthesiology 61:333, 1984.

70. Arden JR, Holley FO, Stanski DR: Increased sensitivity to etomidate in the elderly: Initial distribution versus altered brain response. Anesthesiology 65:19, 1986.

71. Bromage PR: Ageing and epidural dose requirements: Segmental spread and predictability of epidural analgesia in youth and extreme age. Br J Anaesth 41:1016, 1969.

72. Schnider TW, Minto CF, Bruckert H et al: Population pharmacodynamic modeling and covariate detection for central neural blockade. Anesthesiology 85:502, 1996.

73. Matteo RS, Backus WW, McDaniel DD et al: Pharmacokinetics and pharmacodynamics of d-tubocurarine and metocurine in the elderly. Anesth Analg 64:23, 1985.

74. Rupp SM, Castagnoli KP, Fisher DM et al: Pancuronium and vecuronium pharmacokinetics and pharmacodynamics in younger and elderly adults. Anesthesiology 67:45, 1987.

75. Owens WD, Waldbaum LS, Stephen CR: Cardiac dysrhythmia following reversal of neuromuscular blocking agents in geriatric patients. Anesth Analg 57:186, 1978.

76. Cronnelly R, Miller RD: Edrophonium: Dose-response, onset and duration of antagonism in elderly patients (abstract). Anesthesiology 61:A303, 1984.

77. Pontoppidan H, Beecher HK: Progressive loss of protective reflexes in the airway with the advance of age. JAMA 174:2209, 1960.

78. Frank SM, Fleisher LA, Olson KF et al: Multivariate determinants of early postoperative oxygen consumption in elderly patients. Anesthesiology 83:241, 1995.

79. Parikh SS, Chung F: Postoperative delirium in the elderly. Anesth Analg 80:1223, 1995.

80. Muravchick S: Immediate and long-term nervous system effects of anesthesia in elderly patients. Clin Anaesth 4:1035, 1986.

81. Williams-Russo P, Sharrock NE, Mattis S et al: Cognitive effects after epidural vs. general anesthesia in older adults: A randomized trial. JAMA 274:44, 1995.

82. Marcantonio ER, Goldman L, Mangione CM et al: A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 271:134, 1994.

83. Moller JT, JSPOCD Investigators: Long-term postoperative cognitive dysfunction in the elderly: JSPOCD1 study. Lancet 351:857, 1998.

Chapter 62 - Anesthesia for Trauma

John K. Stene
Christopher M. Grande

INTRODUCTION

More than 90,000 Americans die from traumatic causes each year. [1] Injury ranks as the fourth leading cause of death in the United States, following heart disease, cancer, and cerebrovascular disease. Major public health campaigns in this country have successfully reduced mortality from infectious diseases, heart disease, cerebrovascular disease, and, to a limited extent, cancer. Although public health campaigns to combat traumatic injuries have had impact, mostly by reducing mortality from motor vehicle accidents, increasing violent trauma such as gunshot wounds continues to threaten American lives. Currently, for Americans younger than 40 years, trauma is the most common cause of death. However, the mortality rate from trauma is merely the proverbial tip of the iceberg. Because the mortality rate from individual injuries has been decreasing with the organization of trauma centers and improved techniques of trauma care, the total number of injuries has increased faster than the number of trauma deaths. In 1993, approximately 90,000 individuals in the United States died of accidental injuries, for a rate of 34.9 deaths per 100,000 population, the second lowest accidental death rate on record. [1] In the same year there were an estimated 18,200,000 disabling accidental injuries, or about 2,080 injuries every hour, and the 90,000 accidental deaths amounted to 1 every 6 minutes--and these numbers exclude the rising level of intentional injuries caused by attempted or successful suicides and homicides. [1] Thus, anesthesiologists are being faced with anesthetizing an increasing number of trauma patients.

Trauma anesthesia continues to evolve into a distinct area of interest and is one of the fastest growing areas of anesthesia specialization. Interestingly, data compiled from several studies in the United States suggest that an anesthesiologist may be more likely to be in attendance at the arrival of a trauma patient in a hospital that is not a trauma center. This is because a higher portion of trauma patients are triaged to nontrauma centers; therefore, a hospital that is not a trauma center may overall receive more injured patients than a trauma center, especially in urban settings. This emphasizes the implication that all anesthesiologists will likely have significant and unpredictable exposure to trauma patients.

Trauma Centers

Trauma centers have a decided impact on the practice of anesthesia. The regionalization of trauma care into trauma centers not only efficiently utilizes hospital resources, but also provides adequate case experience to develop and sustain the skills of the anesthesia and surgical staff. Trauma center organizations recognize trauma as a specific surgical disease that requires highly trained anesthesia care for optimal outcomes. [2] Table 62-1 outlines the organization of trauma centers. It has been demonstrated that there is a wide variation in the duties of anesthesiologists in trauma care worldwide. Largely in the United States the surgeon concentrates on surgical diagnosis and treatment, and the anesthesiologist provides a secure airway, adequate ventilation, appropriate intravenous fluid management, and required sedation or anesthesia to facilitate the surgical therapy. The trauma anesthesiologist sometimes performs this mission in the field, in the emergency room, or in the critical care unit, as well as in the operating room. In some parts of the world, anesthesiologists are actively involved in prehospital (emergency medical service) care and transportation of trauma patients. [3] [4] Table 62-2 (Table Not Available) lists some of the possible tasks that trauma anesthesiologists assume. Anesthesiologists

TABLE 62-1 -- Trauma Center Organization

	LEVEL 1 : REGIONAL RESOURCE TRAUMA CENTER	LEVEL 2 : COMMUNITY TRAUMA CENTER	LEVEL 3 : RURAL TRAUMA HOSPITAL
Philosophy	Identical community and hospital commitment to excellent care of severe and urgent injuries		Best community commitment to stabilization and transport of severe and urgent injuries
Annual incidence	600-1,000 cases	350-600 cases	----
Facilities			
Emergency room	Lighted heliport 24 h/d with trauma-experienced MD staffing	Lighted heliport 24 h/d with trauma-experienced MD staffing	24 h/d with trauma-experienced MD staffing
Operating room	Staffed and available for trauma 24 h/d	Staffed and available for trauma 24 h/d	Desirable to be staffed and available 24 h/d
Anesthesia personnel	Anesthesiologist with trauma experience 24 h/d	CRNA or anesthesiologist experienced with trauma 24 h/d	In-house anesthesia coverage (MD or CRNA) 24 h/d
Surgery personnel	24 h/d general surgeon and neurosurgeon experienced in trauma; consultants rapidly available	24 h/d general surgeon and neurosurgeon experienced in trauma; consultants rapidly available	Promptly available general surgeon; 24 h/d neurosurgeon availability highly desirable
Surgery case load	At least 50 severe and urgently injured patients per trauma general surgeon per year Level 1 trauma center must make a commitment to trauma training and research	At least 50 severe and urgently injured patients per trauma general surgeon per year	

working in hospitals without trauma centers find their expertise in airway management and monitoring of critically ill patients to be invaluable to the care of the occasional trauma patient.

Scoring Systems

The development of trauma centers has been accelerated by the use of indices of trauma severity [5] (Table 62-3) . The Injury Severity Score, an anatomic scale composed of the sum of squares of the Abbreviated Injury Scale from the three most severely injured body regions, is used retrospectively to compare outcomes in trauma centers. Prospective physiologic scoring systems such as the revised Trauma Score and the Pediatric Trauma Score are used to predict outcome and direct patients to appropriate facilities. [5] [6] The Glasgow Coma Scale (GCS) is a useful prognostic tool for patients with acute head injuries. [7] The American Society of Anesthesiologists Physical Status score has been demonstrated

TABLE 62-2 -- Potential Roles of the Anesthesiologist in the Care of a Trauma Patient

(Not Available)

Courtesy of JP Nolan and PA Oakley, Stoke-on-Trent, England.

to predict mortality from blunt trauma, but it is not very useful for discriminating small differences in severely injured patients. [8]

MECHANISMS OF INJURY

Human physiologic response to injury is uniform enough to justify the term *traumatic disease* despite the myriad causes of trauma. [9] [10] [11] However, the mechanism of injury is important, because it determines the pattern of injury, and this knowledge focuses the treatment priorities for that patient. For example, acute oxygen deprivation from drowning requires immediate attention to restoring oxygen delivery to the cardiopulmonary system, to prevent massive cellular necrosis. Penetrating thoracic trauma requires immediate placement of a chest tube to drain extrapulmonary pleural air and blood. Such a patient may often require no further surgery. Blunt chest trauma requires immediate attention to gas exchange because widespread pulmonary contusion complicates instability of the chest wall. A diagnosis of myocardial contusion and traumatic aneurysm of the thoracic aorta must be immediately excluded.

Blunt Versus Penetration Trauma

The distinction between blunt and penetrating trauma is important because the therapeutic approach is quite different. Blunt trauma, most commonly from motor vehicle accidents or falls, results in widespread energy transfer to the body. When the limits of load tolerance are exceeded, tissues are disrupted. Multiple fractures, soft tissue contusions

or avulsions, and rupture of visceral organs occur, depending on the amount of energy transfer. The physics of the impact determines the sites of energy transfer and thus causes characteristic clusters of injuries. [12]

Penetrating trauma injures tissues as the energy behind the penetrating instrument causes stretching and crushing of tissues. Anatomic injury is confined to the penetration track along which tissues were stretched and crushed. The energy dissipation profiles of different weapons (knives and bullets) determine the anatomic depth and extent of maximum injury. [13]

Trauma patients' deaths demonstrate a trimodal distribution. In the first and largest peak of the distribution curve, death from either blunt or penetrating trauma occurs immediately following widespread laceration of the brain or major blood vessels, including the heart. Such patients can rarely be saved. In the second peak, exsanguination from vascular injuries causes death within a few hours without medical treatment. Victims of penetrating trauma who survive their immediate injury need rapid surgical hemostasis of bleeding arteries and veins within the wound tract. Victims of blunt trauma need careful diagnosis and stabilization prior to surgical correction of hemorrhage from widespread injuries. Frequently, these injuries result in multiple small vessel bleeding, especially from fracture sites. Inadequate or delayed shock resuscitation or surgical treatment leads to late deaths from infection, sepsis, or multiorgan failure. [2] [14]

Neck and Airway Trauma

Penetrating injuries to the neck from gunshot wounds, stab wounds, or penetrating foreign bodies (e.g., construction tools, car parts) are potentially life-threatening because of the anatomic proximity of cardiovascular, aerodigestive, glandular, and neurologic systems in the neck. [15] However, blunt trauma mechanisms can also result in significant injuries to these areas. The anesthesiologist is initially most interested in vascular and airway injuries that need rapid surgical intervention. Knowledge of potential wound tracts, as discussed by Fackler, [13] helps to predict potential injuries. Early airway management with endotracheal intubation is recommended to protect patients from closure of the airway secondary to an expanding hematoma. Anesthetic induction prior to endotracheal intubation is recommended to prevent dislodgement of a hemostatic clot by coughing and straining during intubation. [15] However, when an airway injury is suspected, anesthetic induction and airway control must proceed with caution. [16]

Penetrating injury to the larynx or trachea is diagnosed by air bubbling through the penetration tract, hoarseness, and dysphonia. Distal tracheal injuries may be managed by inserting a cuffed tube through the penetrating wound into the trachea, followed by tracheal repair around the tube, which is left as a tracheostomy tube. Laryngeal injuries require primary repair around a stent with a distal tracheostomy for ventilation. However, these injuries may require lifesaving endotracheal intubation, performed carefully with a small tube, prior to tracheotomy. The laryngotracheal cartilage must be repaired during the initial surgery, with mucosal closure and stent placement for several weeks to prevent stenosis. Cases of complete transection with laryngotracheal separation depend on submucosal elastic tissue to maintain airway patency and approximation of the structures. Disastrous consequences can be suffered with inappropriate attempts at translaryngeal intubation and/or institution of positive pressure ventilation. [16]

All penetrating injuries to the lower or upper neck require preoperative angiography because of the inaccessibility of major arteries. Some surgeons explore midneck injuries before performing arteriography. [15]

The anesthesiologist must be aware of the potential for venous air embolism until injured cervical veins are ligated or repaired. The patient should be kept in a flat or slightly head-down position; positive-pressure ventilation is used to increase venous pressure in the neck.

Thoracic Trauma

Blunt chest trauma, such as commonly occurs when an unbelted driver strikes the steering wheel during an automobile accident (Fig. 62-1) (Figure Not Available) , can directly injure the cardiopulmonary systems. [17] Besides direct injuries affecting

Figure 62-1 (Figure Not Available) Patterns of injury for unbelted driver in head-on collisions. (A) Down-and-under mechanism. (B) Up-and-over mechanism. Note that the patient will exhibit characteristic clusters of injuries, including head and neck, chest, abdomen, and lower extremity fractures, depending on how the body strikes the steering wheel. *(From Parr and Grande [7])*

TABLE 62-3 -- Common Injury Severity Scales

	AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS (ASAPS)	REVISED TRAUMA SCORE (RTS)	GLASGOW COMA SCORE SCALE (GCS)	ABBREVIATED INJURY SCALE (AIS)	INJURY SEVERITY SCORE (ISS)	PEDIATRIC TRAUMA SCORE

Purpose	Assessment of physical status for anesthesia	Physiologic evaluation for triage		Numeric grading scale for coma levels		Anatomic comparison of injury severity	Assessment of combined effects of multiple injuries	Physiologic evaluation of children for triage	
Indicators	Severity of systemic disease: from 1, no disease, to 5, expected to die in 24 h	Systolic blood pressure		Eye opening		Rated by description of injuries in book that assigns number for severity	Sum of squares of 3 worst AIS for following body regions: head and neck, face, chest, abdomen and pelvic contents, extremities and pelvic girdle, external	Weight (lb)	
		89 mm Hg	4	Spontaneous	4			>20	+2
		76-89 mm Hg	3	To voice	3			10-20	+1
		50-75 mm Hg	2	To pain	2			<10	-1
		1-49 mm Hg	1	None	1				
		No pulse	0						
		Weight 0.7326							
				Verbal responses				Airway	
				Oriented	5			Normal	+2
				Confused	4			Maintained	+1
				Inappropriate words	3			Unmaintained	-1
				Incomprehensible words	2				
				None	1				
		Respiratory rate		Motor response				Systolic blood pressure	
		10-29/min	4	Obeys command	6			>90	+2
		>29/min	3					50-90	+1
		6-9/min	2	Localizes pain	5			<50	-1
		1-5/min	1	Withdraws (pain)	4				
		None	0						
		Weight 0.2908		Flexion (pain)	3				
				Extension (pain)	2				
				None	1				
								Central nervous system function	
								Awake	+2
								Obtunded	+1
								Coma	-1
		Glasgow Coma Scale						Open wound	
		13-15	4					None	+2
		9-12	3					Minor	+1
		6-8	2					Major	-1
		4-5	1						
		3	0						
		Weight 0.9368							
Numeric range	1-5	0-7.84		3-15		1--minor injury to	3-75	Skeletal trauma	
	Higher score more serious disease	SBP × Wgt + RR × Wgt + GCS × Wgt = TS		Lower score more serious coma		6--virtually unsurvivable	Any AIS of 6 means automatic 75 ISS	None	+2
						9-- cannot evaluate		Closed	+1
		Lower score more serious injury						Open or multiple	-1
								-6-+12	
Patient example	25-year old man, unhelmeted motorcycle rider, struck by truck: subdural hematoma 100 mL, crushed pelvis, and superficial perforation of bladder. Presented to emergency room with blood pressure 80/40, heart rate 135/min, delayed capillary refill, respirations 30/min with retractive efforts, opens eyes to pain, no verbal response, withdraws all four extremities from pain.								
Score	4E	3 × .7326 = 2.20		2 + 1 + 4 = 7		Subdural AIS4	$4^2 + 4^2 + 3^2 = 41$		
		3 × .2908 = 0.89				Crushed pelvis AIS4			
		2 × .9368 = 1.87				Superficial bladder perforation AIS3			
		4.96							

Glassgow Coma Scale adapted from Teasdale and Jennett, [6ξ] copyright by The Lancet, Ltd.

See Ref. [6] for more detailed discussion.

the cardiopulmonary system, indirect effects of shock and air embolism can affect the central nervous system (CNS) and can complicate anesthetic management. If a traumatic tear of the thoracic aorta is demonstrated, the patient will require an immediate operation. Optimum anesthesia care for repair of a traumatic thoracic aortic

aneurysm requires intra-arterial and pulmonary artery monitoring; therefore, advanced preparation for the surgical anesthetic regimen should start as soon as the diagnosis is suggested by a wide mediastinum on an upright chest roentgenogram prior to arteriographic confirmation. A well-prepared trauma anesthesia care team will be able to appropriately monitor and anesthetize a patient with a traumatic thoracic aortic aneurysm without life-threatening delays of the surgery. Some cardiac surgeons accept transesophageal echocardiographic imaging of an aortic injury as an indication to operate, whereas others require an aortogram revealing the injury.

Other lesions caused by blunt chest trauma that require surgical correction include extensive pulmonary lacerations with a continuous air leak (bronchopleural fistula) and hemorrhage, lacerated intercostal arteries, and traumatic tracheobronchial laceration. These lesions may be surgically corrected following a period of observation with closed thoracostomy drainage. These lesions are diagnosed when a bronchopleural air leak or intrapleural hemorrhage persists following trauma. Hemopericardium or pneumopericardium requires immediate pericardiocentesis to relieve tamponade, followed by a surgical pericardial window to prevent reaccumulation. Traumatic lacerations of the heart either are rapidly fatal or bleed slowly enough to allow careful surgical repair. Arterial air embolism is a complication of blunt as well as penetrating chest trauma. Deep lacerations of the lung from jagged-edged rib fractures allow continuity of the air and vascular spaces. Thus, air can enter the pulmonary venous drainage and the systemic arterial circulation. [18] Long-term care of the patient with multiple rib fractures is enhanced by continuous regional anesthesia to reduce respiratory compromise from splinting. [19] [20] [21]

Closed Head Injury With Open Femur Fracture

Front-seat occupants of modern automobiles with knee bolsters built into the dashboard frequently suffer open femur fractures during an accident that significantly deforms the passenger space (Chs. 35 ,. 52 , and 60). These same victims also frequently suffer head injury if they are not using a seat belt. [12]

Optimum care of an open femur fracture requires operative reduction and fixation within a few hours of the injury. An intramedullary rod provides the most stable internal fixation and allows rapid post-traumatic mobilization of the patient.

High-energy fractures of the femur cause the release of large amounts of bone marrow fat into the circulation. Postfracture hypoxic respiratory failure occurs as the circulating fat released from the fracture collects in the pulmonary vascular system. Early operative stabilization of the fracture under general anesthesia with positive-pressure ventilation prevents mild postfracture hypoxia from developing into severe adult respiratory distress syndrome (ARDS) and fat emboli syndrome. [22]

Prior to anesthetic induction for open reduction with internal fixation of the femur fracture, the patient's closed head injury must be evaluated. Patients with minimal impairment on neurologic examination may have significant brain injury that would cause them to decompensate during anesthesia. Therefore, these patients require a baseline neurologic examination, a computed tomography (CT) scan of the brain, and the placement of an intracranial pressure recording device if there is any question about structural brain injury (Ch. 56) . The prevention of secondary brain injury requires the strict avoidance of hypotension and hypoxia. Therefore, these patients should be monitored by an indwelling arterial catheter. The association of cervical spine fractures with closed head injuries requires a careful evaluation of the patient's cervical spine for fractures and stability.

Postoperative pain management by continuous epidural analgesia is an excellent choice for these patients because analgesia can be provided without depression of consciousness, thus permitting continuous neurologic evaluation.

PREOPERATIVE PREPARATION

The orderly progression of history, physical examination, diagnosis, and treatment must often be abandoned with trauma patients, because resuscitation has priority over diagnosis to ensure a successful outcome (Chs. 23 and 25). Resuscitation protocols, such as outlined in the Advanced Trauma Life Support manual, are designed to identify and correct the most life-threatening problems first. Knowledge of mechanisms of injury is used as described earlier to focus on probable injuries. Following a rapid (30- to 45-second) initial assessment, immediate treatment is initiated. After initial resuscitation is complete, a secondary survey is begun to rule out all occult injuries [23] (Table 62-4) (Table Not Available) .

The anesthesiologist is primarily concerned with preserving CNS function, maintaining adequate respiratory gas exchange, and achieving circulatory homeostasis. [24] CNS function is protected by ensuring an adequate flow of well-oxygenated arterial blood to the brain and by preventing secondary spinal cord damage due to movement of an unstable spinal fracture. Initial evaluation of the patient's GCS, pupil reactivity, and four-extremity motor function provides a baseline of neurologic function prior to extensive therapeutic maneuvers. Intracranial swelling leading to brain death following trauma is a major cause of traumatic death. [25] Endotracheal intubation and mild hyperventilation (Pa CO_2 35 mm Hg) should be initiated on all comatose trauma patients prior to pharmacologic therapy (e.g., with mannitol) aimed at reducing cerebral swelling. The indication for immediate endotracheal intubation and mild hyperventilation varies from trauma center to trauma center, ranging from a GCS of 7 or lower to a GCS of 9 or lower. Intubation in the field prior to transport is most beneficial to comatose patients, because they receive early airway protection from aspiration as well as mild hyperventilation with oxygen. Care must be taken to stabilize the cervical spine during intubation because of the increased association of cervical spine injury with head and facial injuries in blunt trauma. [12] [26]

TABLE 62-4 -- Sequence of Management of Trauma Patients

(Not Available)

From Parr and Grande [69]

Endotracheal Intubation Techniques

Airway control is vital to improve pulmonary gas exchange during resuscitation from hemorrhagic shock, as well as to protect the patient from aspiration (Ch. 39) . [27] Table 62-5 lists the indications for immediate endotracheal intubation of trauma patients. The trauma patient who cannot maintain a patent, protected airway should have a cuffed tube placed in the trachea. Oral or nasal airways have no role in the initial management of the unstable trauma patient, except to maintain a patent airway temporarily during preparation for endotracheal intubation.

Orotracheal intubation facilitated by the use of muscle relaxants is the technique of choice for intubating the trachea of trauma patients. Despite concerns about the unstable cervical spine raised by radiographic postmortem studies of a few victims who died of devastating total-body crush injuries, [28] a well-conducted oral endotracheal intubation can

TABLE 62-5 -- Indications for Endotracheal Intubation

Head injury with Glasgow Coma Scale <9
Shock
Airway obstruction
Combative patient requiring sedation
General anesthesia
Chest trauma with hypoventilation
Postresuscitation hypoxia
Cardiac arrest

be performed without spinal cord damage. Cervical spine stabilization during intubation can be adequately performed with manual immobilization of the head and neck on a long spine board (Fig. 62-2) (Figure Not Available) . An emergency room comparison of muscle relaxant-facilitated oral intubation and blind nasal intubation demonstrated a high rate of complications, including aspiration, in the group receiving blind nasal intubation. [29]

Correctly applied cricoid pressure protects the airway from aspiration of stomach contents (see Ch. 39 and Fig. 62-2) (Figure Not Available) . Cricoid pressure prevents insufflating the stomach with air during mask ventilation prior to intubation in addition to preventing regurgitation of gastric contents into the mouth. [30] The trauma patient with cervical spine stabilization cannot be easily moved to drain gastric contents from the mouth; therefore, prevention of regurgitation is essential. Nonparticulate antacids can be instilled into the stomach to buffer gastric acidity prior to intubation. H_2-histamine antagonists and metoclopramide may be administered intravenously to raise the pH and reduce the volume of gastric contents if these agents are given 0.5 to 1 hour prior to tracheal intubation. [31] Ultimately, the best protection from aspiration for the trauma patient is smooth, well-conducted intubation and extubation delayed until the patient has competent airway reflexes.

Administering oxygen via mask-and-bag ventilation, using cricoid pressure to protect the airway, improves oxygenation prior to endotracheal intubation. In the past, we described this technique as "modified rapid-sequence induction" and believed it to be an important component of difficult airway management for trauma patients. [32] Many trauma patients, on analysis with pulse oximetry or admission blood gas measurements, exhibit significant degrees of oxygen desaturation because of central respiratory dysfunction, deranged chest wall mechanics, or intrapulmonary ventilation/perfusion abnormalities. These considerations become more important in terms of the danger of inducing hypoxic arrhythmias on intubation or during anesthetic induction of the hypermetabolic head-injured patient, who may exhibit deleterious changes from both hypoxia and hypercarbia. Testing the ability to ventilate the airway provides the anesthesiologist with the knowledge that the patient's ventilation can be supported if endotracheal intubation fails. It is our opinion that in many trauma patients these factors, ensuring adequate oxygenation, outweigh the risk of regurgitation through cricoid pressure and possible aspiration pneumonia. Emergency tracheotomy, for a patient whose injuries or preexisting airway anatomy prevent intubation, is best performed while adequate ventilation and oxygenation are maintained. At the minimum, a brief test of the airway with positive-pressure ventilation (with an assistant applying cricoid pressure) is as important in the tense emergency situation as during elective surgery. Table 62-6 summarizes pharmacologic

adjuvants to assist orotracheal intubation for trauma patients.

In patients who cannot be ventilated by a mask, an oral, nasal, or surgical (tracheotomy) approach can be used for awake tracheal intubation. The algorithm developed by the American Society of Anesthesiologists Task Force on Difficult Airway Management [33] is complete and generally applicable. However, in cases of severe trauma, the "rolling thunder" approach to management often precludes retreating

Figure 62-2 (Figure Not Available) The emergency intubation technique for a trauma patient with suspected cervical spine fracture and a full stomach requires keeping the patient supine on a long spine board. An assistant stabilizes the patient's neck by holding a hand over each ear while keeping the patient's shoulders and occiput firmly placed on the board, with the patient's gaze directed straight up. A second assistant maintains cricoid pressure. Well-applied cricoid pressure prevents insufflation of air into the stomach as well as fluid regurgitation from the stomach into the mouth. Thus, the patient can safely be ventilated by mask and bag prior to laryngoscopy and intubation. Manual preoxygenation by face mask increases the margin of safety in potentially difficult intubations because of cervical spine stabilization. *(From Stene [71])*

to or continuing with mask ventilation. In these cases, a definitive airway is achieved by translaryngeal or surgical techniques within the first moments of patient care. In recent years, the laryngeal mask airway has found a niche in providing a rapid route to ventilate difficult-to-intubate trauma patients, whereas a definitive airway is achieved via tracheostomy or intubation through newer versions of the laryngeal mask airway. [34] [35]

Unstable mandibular or maxillofacial fractures may make mask ventilation impossible, and an awake intubation frequently relieves life-threatening airway obstruction. Direct laryngoscopy is frequently superior to fiberoptic bronchoscopic intubation in these patients because the bronchoscope is often not available on an emergency basis, and upper airway bleeding may preclude adequate visualization (Ch. 39) .

Controlled tracheal intubation in the elective setting of a patient with known cervical spine fracture should be performed with the patient awake, having the airway properly prepared with local anesthetics, antisialogogues, etc. with use of a fiberoptic bronchoscope either orally or nasally. Thus, the patient can demonstrate neurologic function before and after intubation.

Tracheotomy is reserved for those patients who cannot be intubated translaryngeally. Massive disruption of the floor of the mouth by penetrating injury and disruption of the larynx or cervical trachea are two indications for emergency tracheotomy. However, it is frequently worth one attempt to intubate patients carefully with a small endotracheal tube prior to tracheotomy unless open laryngeal cartilage is seen during direct laryngoscopy. The cricothyrotomy route is the preferred route for an emergency primary tracheotomy. [23] Although the prolonged care of many patients with maxillofacial injuries and brain trauma is improved by an intraoperative tracheotomy, the presence of highly skilled anesthesiologists in a trauma center will minimize the number of emergency cricothyrotomies needed for airway control. We believe that anesthesiologists working with a high volume of trauma patients should be comfortable with the technique of cricothyrotomy with both a needle and a tracheostomy tube.

Shock Resuscitation

Resuscitation from hemorrhagic shock requires rapid administration of intravenous fluids to ensure the circulation of well-oxygenated blood from the lungs to the brain and other vital organs (Chs. 45 to 47). Initially, intravenous fluids can be introduced into the venous drainage of the bone marrow via an intraosseous needle if all peripheral veins are collapsed. [36] Eventually, large-bore intravenous catheters must be placed either percutaneously or by cutdown. Large-bore introducer sheaths for pulmonary artery catheters can be placed percutaneously in large central veins, reducing the need for cutdowns. [37] Rapid infusion devices using mechanical pumps or gas pressure to force fluid through low-resistance tubing allow adequate resuscitation through only two intravenous catheters. If disruption of either the superior or the inferior vena cava is suspected, intravenous catheters should be placed to provide infusion into the heart through the other vena cava. Therefore, intravenous catheters should be placed above and below the diaphragm in patients with severe trauma to the chest or abdomen. Warming of intravenous

TABLE 62-6 -- Intravenous Anesthetic Drugs for Endotracheal Intubation

CONDITION	HYPNOSIS	MUSCLE RELAXATION	ANALGESIA	AMNESIA
[a] GCS = 3, flaccid, unresponsive	None	None	None	None
Cardiac arrest	None	None	None	None
Shock, syst BP < 80 mm Hg	None	Succinylcholine 1.5 mg/kg or vecuronium 0.28 mg/kg or rocuronium 1.2 mg/kg	Fentanyl 0.5-1 mug/kg as needed or nalbuphine 0.25-0.5 mg/kg	Scopolamine 0.5 mg IV or midazolam 1-2 mg if BP increases
Hypotension, syst BP 80-100 mm Hg	Thiopental 0.3-1 mg/kg (titrate to effect) or midazolam 0.1-0.3 mg/kg (titrate to effect) or ketamine 1 mg/kg or etomidate 0.1-0.2 mg/kg	Succinylcholine 1.5 mg/kg or vecuronium 0.28 mg/kg or rocuronium 1.2 mg/kg	Fentanyl 1-2 mug/kg or nalbuphine 0.5-1.0 mg/kg	Midazolam 1-2 mg if not used for hypnosis
[a] Head injury, GCS 4-9 with hypertension	Thiopental 2-5 mg/kg or etomidate 0.2-0.3 mg/kg	Rocuronium 1.2 mg/kg or vercuronium 0.28 mg/kg or succinylcholine 1.5 mg/kg (if postintubation motor examination needed quickly)	Fentanyl 1-2 mug/kg or sufentanil 0.1-0.2 mug/kg	Midazolam 1-2 mg if not used for hypnosis
Combative, BP normal to elevated	Thiopental 2-5 mg/kg (titrate to effect) or midazolam 0.2-0.3 mg/kg (titrate to effect) or etomidate 0.2-0.3 mg/kg (titrate to effect)	Rocuronium 1.2 mg/kg or vecuronium 0.28 mg/kg or succinylcholine 1.5 mg/kg	Fentanyl 1-2 mug/kg or sufentanil 0.1-0.2 mug/kg or nalbuphine 0.5-1.0 mg/kg (may require frequent redosing)	Midazolam 1-2 mg if not used for hypnosis

GCS, Glasgow Coma Scale; Syst BP, systolic blood pressure

[a] Lidocaine 1.5 mg/kg may be useful to attenuate increases in intracranial pressure with intubation.

fluids is extremely important if the trauma patient requires several exchanges of blood volume (i.e., "massive transfusion"). Hypothermia decreases the effectiveness of hemorrhagic shock resuscitation. Various devices are available to heat fluids prior to administration, the most effective of which use water-perfused heat exchangers similar to cardiopulmonary bypass apparatus. In extreme cases the patient's blood can be circulated, under arterial pressure, through an extracorporeal circuit and heat exchanger to warm profoundly hypothermic patients rapidly. [38]

The choice of the initial administered fluid is based on the priority of first restoring blood volume, next hemoglobin concentration, and finally coagulation. Although lactated Ringer solution and whole blood were used with great success in the Vietnam War, experiments suggest that a colloid-containing fluid improves outcome, especially if packed red blood cells comprise the hemoglobin source. [39] [40] [41] Either albumin or colloidal starch solutions appear effective for traumatic shock resuscitation. [41] [42] Whole blood is superior to packed red cells for replacement of hemorrhagic losses because these losses involved whole blood. However, packed cells are preferred for emergency administration of universal donor (type O) blood to minimize plasma antibodies. Salt and water must be administered along with blood to replace loss of water and electrolytes from the circulatory system, especially to extravascular edema induced by injury and inflammation. [43] The potential for disease transmission by transfusion--human immunodeficiency virus, acquired immunodeficiency syndrome, hepatitis--has caused the formulation of revised guidelines for transfusion of blood and blood products. The tendency is to adopt lower thresholds for triggering replacement. Previously, hematocrits in the range of 28 to 30 percent were favored on the basis of balancing rheologic factors and oxygen-carrying capacity toward optimal oxygen delivery at the cellular level. Currently,

hematocrits in the range of 18 to 22 percent are being accepted in patients who can tolerate such levels. It is not yet clear which patients (especially if they are pregnant, geriatric, or recovering from severe hypovolemic shock) fit within this group.

Proponents of crystalloid use claim that such solutions replace extracellular water more effectively than colloidal solutions. Colloidal solutions preserve intravascular volume and microcirculatory blood flow more efficiently than crystalloids and they increase cardiac output and oxygen delivery, as well as blood pressure, at much lower infused volume than do crystalloid solutions. Crystalloid solutions may merely restore blood pressure without increasing cardiac output. [41] This controversy has been sharpened by a study that suggests that resuscitation of trauma victims with large volumes of crystalloid to achieve high normal blood pressure prior to surgical hemostasis causes excessive hemorrhage and mortality. [44] Current research into shock resuscitation is focused on defining measures of adequate tissue perfusion. This would allow fluid resuscitation to be judiciously administered to maintain tissue perfusion without diluting the patient's hemostatic efforts and causing excessive edema. [45]

Mixtures of hypertonic saline (7.5%) and colloid (dextran) have been used with promising results for resuscitation of trauma patients. [46] Hypertonic saline alone rapidly restored

blood pressure in patients in hemorrhagic shock, but its effect was relatively short-lived; combining the hypertonic saline with a colloid such as dextran prolonged the effective resuscitation. The optimal concentrations are believed to be a 4-mL/kg bolus of 7.5 percent sodium chloride in 12 percent dextran 70. [47] Despite the large quantity of sodium in this resuscitation regimen, hypertonic saline is thought to be beneficial in head injury. [48]

Platelets and coagulation proteins as well as red blood cells are contained in shed blood. Replacement of a patient's blood volume several times over leads to a coagulopathy secondary to thrombocytopenia and possibly consumption of fibrinogen and other coagulation enzymes. [49] Platelet counts lower than 70,000/mm^3 of blood indicate the need for immediate platelet transfusion. Platelet survival in bank blood is limited to a few days. Therefore, in the patient with massive volume replacement, platelet counts rapidly decrease. It is always preferable to wait for surgical hemostasis prior to platelet administration; otherwise, the transfused platelets will merely be lost to further hemorrhage.

Restoration of oxygen consumption to higher than normal levels is currently the best end point of resuscitation after hemostasis is achieved. Accumulative oxygen debt beyond a critical amount is the lethal insult in hemorrhagic shock. [50] Rapid repayment of the oxygen debt by increased oxygen delivery to the tissues with transiently elevated oxygen consumption heralds survival from critical illness. [51]

Practical Intravenous Fluid Management of Trauma Patients

During initial resuscitation, the anesthesiologist estimates the patient's blood loss by evaluating vital signs (Table 62-7) (Table Not Available) . For losses less than or equal to 30 percent of blood volume, crystalloid replacement of three times the volume of shed blood provides adequate resuscitation as long as hemorrhage is controlled. Patients with losses greater than 30 percent of blood volume or with continuing hemorrhage should receive colloid solutions and blood equal to the blood volume lost along with crystalloid equal to one to three times the volume of blood lost. These patients need ventilation with 100 percent oxygen to maximize oxygen delivery to the tissues until hemoglobin can be replaced. Patients with hemorrhage greater than or equal to 40 percent of blood volume require immediate red blood cell transfusion, along with the colloid or crystalloid resuscitation fluids. Type O (universal donor) packed cells can be safely administered to these patients without typing or crossmatch. Rh-negative units are reserved for women of childbearing age. If transfusion is begun with type O blood, it is generally recommended that after two units such transfusions continue with type O blood.

Following initial assessment of blood loss and planned fluid replacements, the anesthesiologist monitors the patient's response to therapy to guide further fluid therapy. Volume of fluid replacement and hemoglobin concentration are prescribed to achieve and maintain a maximal oxygen consumption--a plateau in the curve of oxygen consumption versus oxygen delivery. Normalization of the base excess (deficit) on arterial blood gases is another indicator that oxygen debt has been repaid. Levels of mixed venous lactate have been used in a similar fashion. Coagulation function is monitored, and appropriate replacement therapy is prescribed.

Preanesthetic History

Preanesthetic history includes information from the scene of the accident, either from witnesses or from the patient's own description. Information about how the injury occurred (i.e., "mechanism of trauma") helps the anesthesiologist to prepare for surgical correction of occult injuries. For example, an unbelted driver who sustained bilateral femur fractures in a frontal collision may have a traumatic aneurysm of the thoracic aorta from sudden chest deceleration on the steering wheel.

Preoperative information concerning allergies, preexisting diseases, previous operations, and drug therapy is as important in the trauma patient as in any other surgical patient. Although trauma patients must be treated as patients with full stomachs, careful inquiry into time and type of last oral intake reveals a variable potential for quantity and quality of stomach contents. [31] Self-medication with psychoactive drugs and alcohol is a particular problem with trauma patients. Careful questioning frequently reveals a pattern of substance abuse followed by injury, which is especially prevalent in chronic alcoholics. [52] Besides ethanol, trauma patients frequently are intoxicated with marijuana, cocaine, phencyclidine, and opioids. A history of chronic substance abuse or acute intoxication alerts the anesthesiologist to prepare for unusual responses to anesthetic drugs [53] (Table 62-8) .

Physical Examination

Trauma patients require a physical examination and laboratory testing, as do other surgical patients, but with concentration

TABLE 62-7 -- Changes in Vital Signs with Percent Blood Volume Lost by Hemorrhage

(Not Available)

Modified from American College of Surgeons [23]

TABLE 62-8 -- Common "Street Drugs" Complicating Trauma Anesthesia

DRUG	COMPLICATION
Ethanol	Chronic abusers have frequent serious injuries and require larger doses of many anesthetic drugs. Acute intoxication is additive with anesthetic drugs and reduces anesthesia requirements. Serum osmolarity may be used to estimate blood alcohol level. Delirium tremens from withdrawal may complicate post-traumatic care, and should be covered with benzodiazepine.
Opioids (e.g., heroin)	Chronic abusers have low pain tolerance, require increased doses of opioids, and may acutely withdraw with opioid antagonists. Frequent severe infections, including human immunodeficiency virus, complicate intravenous use. Patients may transmit viral diseases to the anesthesiologist. Acute withdrawal complicates post-traumatic care. Avoid use of antagonists.
Cocaine	Chronic abusers have paranoid delusions, labile blood pressure with extreme hypertension, and difficult vascular access. Acute toxicity causes seizures, ventricular fibrillation, and sudden death. Depression is common following withdrawal.
Marijuana	This drug is frequently mixed with ethanol. Chronic abusers have bronchitis. Acute toxicity is associated with tachycardia hypotension, injected sclera, and somnolence.

Phencyclidine (PCP)	Psychotomimetic effects are long lasting. Bizarre, violent behavior occurs, including apparently painless self-mutilation. Hallucinations are common. Acute intoxication resembles ketamine anesthesia with open-eyed stare, active laryngeal reflexes, hypertension, and tachycardia. Patients need special treatment for extended periods until drug-free.

on the respiratory, circulatory, and nervous systems. The status of the CNS is evaluated with a brief neurologic examination, including level of consciousness (GCS), pupil size, pupil reactivity, and motor function of each extremity. If the trachea is not intubated, the examination includes evaluation of the upper airway for potential intubation problems. Immobilization of the cervical spine increases the difficulty of intubation. The anesthesiologist should examine the patient's chest for signs of pneumothorax, myocardial contusion, and pericardial tamponade. The circulatory system is evaluated for signs of hemorrhagic shock and blood loss. Preexisting blood loss can be quantified according to changes in vital signs, as indicated in Table 62-7 (Table Not Available) . Arterial blood gases, chest radiographs, cervical spine roentgenograms, hemoglobin and hematocrit measurements, serum glucose, urea nitrogen, creatinine, and electrolytes as well as an electrocardiogram (ECG) round out the laboratory analysis.

Monitoring

Trauma patients require at least basic noninvasive monitoring in accordance with the minimal standards for surgical patients of the American Society of Anesthesiologists, [54] regardless of the anesthetizing location--emergency room, diagnostic area, radiology suite, operating room, or critical care unit (Chs. 28 to 38).

More invasive monitoring is indicated to evaluate the patient's response to therapy. Urinary output via an indwelling urethral catheter (Foley catheter) is an important indicator of fluid balance and renal perfusion. The urinary catheter is also a diagnostic tool for trauma to the urinary tract that causes hematuria. Oxygen consumption can be calculated from the pulmonary artery catheter measurements by using the product of cardiac output times the difference between the arterial oxygen pressure (Pa_{O_2}) and pulmonary artery oxygen content. Mortality from trauma varies inversely with post-traumatic oxygen consumption. [55] Therefore, early placement of a pulmonary artery catheter in appropriate patients cannot be overemphasized. Table 62-9 summarizes monitoring choices for the trauma patient.

INTRAOPERATIVE MANAGEMENT

General anesthesia is the technique of choice for patients with multiple injuries. Regional anesthesia may seem attractive because it causes little interference with the patient's cardiopulmonary function and avoids airway manipulation. However, patients with serious trauma benefit from endotracheal intubation and mechanical ventilation and are unlikely to cooperate with lying still during prolonged surgery. Sympathetic blockade from spinal or epidural anesthesia interferes with the homeostatic compensation for hemorrhage. Therefore, regional anesthesia is most useful for isolated limb trauma, for example, brachial plexus block for a forearm fracture.

TABLE 62-9 -- Monitoring Choices for Trauma Patients

Noninvasive	
Essential	ECG for heart rate, noninvasive blood pressure, respiratory rate, temperature, Sa o_2 , ET co_2 with waveform
Optional	Concentrations of anesthetic and respiratory gases (e.g., mass spectrometry, transcutaneous)
Invasive	Foley catheter urine output, intra-arterial pressure catheter, central venous pressure catheter, transesophageal echocardiography
Indications for pulmonary artery catheter	Massive hemorrhage Pretraumatic heart disease Multiple systems injuries/Mechanism of injury Monitoring of cardiac output and oxygen consumption Optimization of fluid therapy in head-injured patient

ECG, electrocardiography; Sa o_2 , arterial oxygen saturation; ET co_2 , end-tidal carbon dioxide pressure

Anesthesia Plan

General anesthesia can be administered safely in the patient with multiple injuries by choosing drugs that minimize cardiovascular depression and intracranial hypertension. Small doses of highly lipophilic drugs such as thiopental, etomidate, and sufentanil can be titrated to desired anesthetic effect without producing profound hypotension. Although pharmacokinetic data during hemorrhagic shock are limited, clinically these patients appear to reach desired drug effects from extremely small intravenous doses. The reduction in blood volume probably concentrates the delivered dose at the active site in the brain, and reduced hepatic blood flow may prolong clearance of the drug. However, normal doses of muscle relaxants need to be used to achieve the rapid paralysis necessary for endotracheal intubation. The drugs outlined in Table 62-6 for induction of anesthesia and endotracheal intubation are useful in the operating room as well as the emergency room.

Because the maintenance of cardiovascular homeostasis with cerebral perfusion by well-oxygenated blood has a higher priority than hypnosis or amnesia in the trauma patient, drug contraindications are extremely important for trauma anesthesia. Contraindicated drugs include ketamine for the head-injured patient, because it increases intracranial pressure as well as arterial pressure (Ch. 52) . Ketamine may actually cause hypotension in patients with high sympathetic tone. [56] Succinylcholine is contraindicated because of exaggerated hyperkalemia more than 24 hours after upper motor neuron (spinal cord) injury and more than 24 hours following major burns (Ch. 12) . The inadvertent use of succinylcholine in these patients can be treated with intravenous calcium, glucose, and insulin as well as cardiopulmonary resuscitation to support the circulation until the serum potassium falls to levels consistent with normal cardiac function. Table 62-10 outlines the adverse effects of succinylcholine. Short-acting, nondepolarizing neuromuscular blocking drugs such as mivacurium have a much longer onset time than succinylcholine, but they do terminate action rapidly. Large doses (several multiples of the ED_{95}) of vecuronium and rocuronium have been used to decrease onset time for neuromuscular blockade. However, this maneuver also prolongs the duration of neuromuscular blockade. Whether this issue is of any clinical significance is

TABLE 62-10 -- Adverse Effects Associated With Succinylcholine

Hyperkalemia, particularly following burns, spinal cord injuries, and generalized major trauma; there has been a single case report of a marked hyperkalemic response to succinylcholine in a patient with a closed head injury without peripheral paralysis
Increased intracranial and intraocular pressures, the practical importance of which is controversial
Increased intragastric pressure, although counterbalanced by the increase in lower esophageal pressure, which reduces or eliminates the increased risk of regurgitation
Muscle pains, more likely to concern the patient with minor injuries who ambulates soon after surgery
Prolonged paralysis in patients with atypical pseudocholinesterase
Cardiac arrhythmias, particularly bradycardiac after repeat doses
Trigger for malignant hyperthermia

debatable, however, as acute trauma patients requiring emergency airway management rarely can be awakened as a failsafe to failed intubation. Rather, management will usually proceed to placement of an LMA, Combitube, or another device, or a surgical airway is performed.

Nitrous oxide is contraindicated in patients with potentially closed air spaces in which this anesthetic will accumulate, such as patients with pneumothorax, pneumocephaly, and gas-filled bowel loops (Ch. 2) . Its use in head-injured patients is controversial, but at low concentrations its contribution to cerebral blood flow/metabolism imbalance is probably minimal. [57] Nitrous oxide has also been demonstrated to decrease cardiac output when combined with opioids. [58] Thus, the use of nitrous oxide should be specifically indicated for trauma patients, not used routinely. Anesthesia machines should be equipped to deliver air, oxygen, and nitrous oxide for use with these patients so that air-oxygen mixtures may be used to decrease the inspired oxygen fraction (F_{IO_2}). Finally, halogenated hydrocarbon vapors should only be used with mild hyperventilation for patients with head injuries.

Common Intraoperative Problems

Despite the complexities of the injuries in a patient with multiple trauma, certain intraoperative problems occur frequently. Some problems--prolonged anesthesia, hypothermia, and massive transfusion--are consequences of long and difficult surgery in a patient with uncontrolled hemorrhage. Other complications, namely, facial

trauma, burns, hypoxia, fever, and malignant hyperthermia (MH), are a result of specific injuries or patient characteristics. The pregnant patient, the very young patient, and the very old patient present special problems for trauma anesthesia. Finally, cardiac arrest (usually electromechanical dissociation) is the terminal event for acute trauma victims who die in the operating room.

Prolonged Surgery

Prolonged operations require prolonged anesthetic regimens. Optimal outcome for an unstable multiply injured patient is achieved if all injuries can be corrected at the time of initial surgery. The victim of blunt trauma with multiple fractures especially benefits from early fracture fixation that reduces ongoing hemorrhage, intravascular release of bone marrow, and postoperative complications of immobilization. [9] [22] The anesthesiologist must treat the operating room as an intensive care unit for these patients. During surgery that approaches or exceeds 24 hours, patients need daily replacement of electrolytes and minerals as well as replacement of blood loss and third-space loss of water.

Hypothermia

Maintenance of temperature homeostasis challenges anesthesiologists caring for multiply injured patients (Chs. 37 and 52). Many patients enter the trauma center with low body temperature, and an inverse relationship between

temperature and trauma score has been noted. [59] Prolonged exposure to a cold operating room, evaporative heat loss from the respiratory tract, infusions of cold fluids, and loss of heat production secondary to shock cause decreased core temperature in most patients. All skin surfaces not in the surgical field should be covered to reduce convective and radiant heat loss. Humidification of inspired gases reduces evaporative heat loss from the lung, and saturation of inspired gases with water heated higher than body temperature produces active warming of the patient. All intravenous fluids should be warmed; modern equipment is available, with heat exchangers capable of warming fluids to 37°C at very rapid infusion rates. Other techniques of temperature maintenance include warming of the operating room to more than 22°C, irrigation of open body cavities with warm saline, and continuous arteriovenous rewarming. [38]

Massive Blood Transfusion

Prolonged surgical attempts to achieve hemostasis may require the anesthesiologist to replace massive amounts of fluids (Chs. 45 and 46). After their blood volume has been replaced several times, patients frequently develop dilutional thrombocytopenia, prolonged clotting times, and transient reductions in calcium ion concentration. Coagulopathy is treated with appropriate factor replacement. Maintenance of normothermia is especially critical to maintain normal hemostatic coagulation function. [60] Temperature correction of prothrombin time and partial thromboplastin time often reveals a hypothermia-induced reversible coagulopathy in cold patients who are clinically coagulopathic but who have normal coagulation studies measured at 37°C in the laboratory. The anesthesiologist should monitor the coagulation status to prescribe replacement therapy accurately. [49] Calcium replacement is initiated when ionized calcium levels decrease secondary to citrate chelation or when hypotension occurs despite adequate volume replacement. [61] The bivalent cation Ca^{2+} is the active form of calcium, and replacement based on calcium concentrations should be based on measured ionized calcium, not total calcium.

Maxillofacial Injuries

Maxillofacial trauma with fractures of the mandible and/or midface frequently compromise the patient's airway and cause difficult tracheal intubation conditions (Ch. 63) . Awake intubation, via either direct laryngoscopy or fiberoptic bronchoscopy, is indicated. Mask ventilation frequently is impossible because of facial skeletal deformity, excessive intraoral bleeding, or basilar skull fractures with cerebrospinal fluid rhinorrhea. Many patients with maxillofacial trauma have associated head and cervical spine injuries. [26] A tracheostomy is the most secure route of tracheal intubation for patients with facial trauma who will require prolonged ventilatory support. Postoperative intramaxillary fixation and nasal packing may make reintubation impossible if the endotracheal tube is dislodged. Because most of these patients can be intubated translaryngeally, it is safer to perform the tracheotomy over an endotracheal tube. A tracheostomy tube with appropriate stay sutures placed next to the stoma can be replaced if required. The laryngeal mask airway or Combitube (Sheridan) can be used to support ventilation and oxygenation during tracheostomy in some patients with maxillofacial injuries that are extremely difficult to intubate.

Fever commonly occurs in patients with panfacial fractures who are undergoing open reduction and fixation of these fractures. This fever is probably secondary to bacteremia from fractures through the paranasal sinuses and can be differentiated from MH by the absence of combined respiratory and metabolic acidosis on blood gas analysis.

Malignant Hyperthermia

MH is a relatively rare complication of anesthesia, which may occur in the trauma patient (Ch. 27) . The pain of trauma, especially fractures, may trigger MH without the presence of anesthetics. [62] The treatment of MH is the same in the trauma patient as in elective surgical patients. However, it may be necessary to complete the operation to save the trauma patient's life. All operating rooms should have an adequate supply of dantrolene to start therapy for a patient with MH.

Thermal Injury

Burns are one of the most severe forms of trauma that a patient can survive. Burn patients present anesthetic challenges, because they have difficult vascular access, fluid and electrolyte imbalances, increased requirements of nondepolarizing muscle relaxants, and temperature regulation problems. Patients with significant full-thickness burns should be managed in a specialized burn center that can cope with the critical care and infection control of burn patients. Circumferential burns may require an immediate escharotomy to retain limb blood flow or chest expansions. [63]

Hypoxia

Intraoperative hypoxia in an acute trauma patient is usually secondary to an occult pneumothorax that has expanded or to pulmonary embolism with bone marrow contents (fat emboli syndrome) (Ch. 72) . Nitrous oxide should be avoided in patients with suspected pneumothorax. Immediate needle decompression followed by chest tube drainage should be started as soon as a pneumothorax is identified. Hypoxia secondary to long-bone fractures responds to mechanical ventilation and early fracture fixation, which reduces continuous seeding of marrow fat into the venous circulation. [22] Prolonged delay in fixation of isolated long-bone fractures while the patient breathes spontaneously frequently causes acute ARDS and classic fat embolism syndrome. [10] [23] Similarly, if patients are extubated immediately following fracture fixation despite evidence of poor oxygenation and a large pulmonary venous admixture, they will develop ARDS and probably the fat emboli syndrome. These patients benefit from mechanical ventilation with positive end-expiratory pressure (PEEP) titrated to reduce the intrapulmonary shunt until the ARDS resolves. [9] [22] [24]

Cardiac Arrest

Cardiac arrest following blunt trauma and hemorrhagic shock carries an abysmal prognosis (Chs. 75 and 76). When the heart finally arrests from low perfusion, significant ischemic damage has already occurred in other organ systems. Cardiac arrest in the operating room during emergency trauma surgery usually occurs with a rapidly falling arterial pressure, electromechanical dissociation, and ventricular standstill. Profound hypothermia usually heralds cardiac demise and may be the result of massive cellular necrosis as well as the cause of cardiac arrest.

Pregnant and Pediatric Trauma Patients

Pregnant women are not excluded from major trauma, which is assuming an increasing role in maternal mortality in recent years [64] (Chs. 57 and 59). Care of the pregnant patient is organized toward saving both mother and fetus. Frequently, however, profound maternal shock kills the fetus, and rapid operative termination of

the pregnancy becomes necessary to save the mother's life. Anesthesia for the pregnant trauma victim must be designed to minimize risk to the fetus. Second- and third-trimester patients should receive fetal heart rate monitoring, with patient positioning (left lateral uterine displacement) to maximize uterine blood flow and fetal heart rate. Teratogenic anesthetic drugs put the fetus at risk in early pregnancy; therefore, intravenous anesthesia is the technique of choice for early pregnancy. [64] Occasionally, a mother receives a devastating brain injury but retains a viable fetus. Artificial life support can maintain the mother until the fetus reaches an age appropriate for delivery. Outcomes of such pregnancies are not uniformly successful, and such life support places a tremendous burden on the intensive care unit staff if continued for more than about 2 days.

Care of the pediatric trauma patient follows the same principles as care of the adult trauma patient. Seriously injured children benefit from early intubation because hypoxia rapidly develops in the hypoventilating child. Accurate fluid replacement is critical in injured children to avoid prolonged ischemia and fluid overload. Well-informed anesthesia care and postoperative pediatric critical care will help to reduce the childhood mortality rate from trauma. Seriously injured children should be transferred to a pediatric trauma center for follow-up care as soon as they are sufficiently stable. [65]

POSTOPERATIVE PERIOD

The seriously injured patient requires major therapeutic interventions postoperatively--both acute critical care and prolonged rehabilitative therapy. The extensive high-technology therapy required to restore the trauma victim to maximum post-traumatic functional levels adds to the high cost of trauma care. [14] Total care of trauma patients is one of the most costly medical endeavors in the United States. Anesthesiologists are especially concerned with the postanesthesia recovery room and the critical care unit.

Postanesthetic Care Unit

Recovery room problems uncommonly seen in the trauma patient include vomiting and aspiration on emergence, delayed recovery from anesthesia, emergence delirium, and incomplete preoperative diagnosis (Ch. 68). Because patients who had eaten just prior to an accident have a high probability of delayed gastric emptying, they may vomit on emergence from anesthesia. Tracheal extubation of trauma patients following emergency surgery should be delayed until the patient has recovered gag and cough reflexes to protect the airway. [31] Criteria for extubating patients following trauma surgery also include the ability to maintain adequate spontaneous respiration, secretion clearance, and oxygenation.

Emergency surgery to correct traumatic injuries frequently must occur so precipitously that a patient does not receive a complete work-up; only the most life-threatening condition is diagnosed and treated. These patients need completion of their surgical diagnosis in the recovery room. One of the most troubling examples of postoperative diagnosis is the patient who does not wake up promptly from anesthesia because of an unsuspected head injury or drug intoxication. The anesthesiologist can assist in the differential diagnosis by demonstrating neuromuscular transmission and end-tidal anesthetic concentrations, possibly administering narcotic and benzodiazopine antagonists (if appropriate; see below), and collecting blood, urine, and gastric contents for toxicologic screening. The patient's family may provide information about the patient's medical or surgical history as well as pretraumatic ingestion of drugs or alcohol.

In contrast to trauma patients with prolonged coma in the recovery room, others emerge from anesthesia in a delirious state. Combative persons who awaken with pain and confusion in a recovery room following emergency surgery that they cannot remember are bound to be agitated. Besides disorientation and fear, drug intoxication or withdrawal may cause emergence delirium. Common approaches to these problems include administration of antagonist drugs such as naloxone, flumazenil, and physostigmine. However, although use of these drugs may be appropriate, it should be remembered that such use can cause complications in trauma patients (e.g., naloxone can trigger acute withdrawal syndrome, cause cardiac arrest, or cause pulmonary edema and may elevate intracranial pressure in head-injured patients). Patients who are disoriented because of their injuries are treated by reassurance and analgesics. Agitation may occur from a head injury or hypoxia, so these diagnoses must be excluded. Delirium from drug abuse requires sedation of the patient and identification of the offending agents for definitive care. [53]

Critical Care Unit

The critical care unit is reserved for the most unstable trauma patients (Ch. 71). Sepsis and multisystem organ failure are the most common causes of postoperative death of trauma victims. [9] [10] [14] Careful attention to metabolic and nutritional support and optimal cardiopulmonary support are necessary to give these patients their best chance of survival. Prophylactically, rapid and complete resuscitation helps to prevent ARDS, sepsis, and multisystem organ failure. [66]

ARDS is a particular problem for anesthesiologists because these patients frequently develop surgical problems while convalescing in the critical care unit and require anesthesia for surgical correction. The anesthetic must be delivered through a ventilator capable of maintaining high minute volumes with elevated airway pressures. Most gas-powered anesthesia ventilators cannot deliver high minute ventilation to a patient who requires high levels of PEEP to maintain oxygenation. Treatment of ARDS is supportive while the lung heals itself. Prevention of ARDS follows the principles of prevention of multisystem organ failure (i.e., prevent prolonged tissue ischemia during resuscitation). Pharmacologic therapy for ARDS has proved to be disappointing. Much developmental work is proceeding on alternate methods of oxygenation to be used in emergency situations. [67]

Transportation

One complication of trauma care is the continuous need to transport critically ill patients throughout the hospital [24] (Ch. 66) . Patients suffering from multiple blunt trauma frequently have associated head injuries and require multiple brain CT scans for diagnosis and follow-up of treatment regimens.

CT, magnetic resonance imaging, and radionuclide imaging techniques are used to outline the extent of injury in other body regions besides the head. Because these imaging techniques require fixed specialized equipment, patients must be moved to the imaging area.

Critically ill patients require portable, battery-operated monitors for intra-arterial, intracranial, and pulmonary artery pressures as well as ECG, pulse oximetry, and, ideally, capnography. The biomedical industry is placing more attention on miniaturizing these monitors and developing patient-sensor interfaces that are resistant to motion artifacts. Ventilation during transportation is more consistent when delivered by a portable ventilator than by hand. At least one critical care ventilator (Siemens 900C) can be powered by an automobile storage battery during transport, so that the patient can be maintained on constant ventilator settings. Patients with head injury who have intracranial pressure that is critically sensitive to Pa CO_2 should be transported with constant ventilation. The development of portable, battery-powered carbon dioxide monitors will facilitate monitoring ventilation during patient transport. Transportation by helicopter or ambulance accentuates all the problems of transportation of critically ill patients and is a frontier of trauma care in which anesthesiologists can have a vital impact.

SUMMARY

Trauma care is becoming an increasingly important part of modern medical practice as advances in care reduce the mortality from other diseases. Organizational changes for the delivery of emergency care have had a tremendous impact on trauma morbidity and mortality. The challenge for the 1990s is to reduce the mortality from trauma for patients who arrive at the hospital alive. The term "golden hour" was coined to describe the window of opportunity to treat a seriously injured patient successfully and is used to accentuate the need for trauma center development. This term emphasizes the need for rapid response to treat traumatic shock and to transport injured patients to definitive treatment centers. The future challenge for anesthesiologists and trauma surgeons is to prevent death from irreversible shock and to extend the treatment window of opportunity to a golden 2 hours by perfecting in-hospital treatment of seriously injured patients. The goal of treatment is to provide cardiopulmonary cerebral resuscitation for the critically injured patient. Such optimum care will give the trauma patient a chance to return to functional life. Efforts are currently underway worldwide to increase the level of involvement of anesthesiologists in clinical traumatology and research. These efforts are being coordinated under the auspices of the International Trauma Anesthesia and Critical Care Society.

References

1. National Safety Council: Accident Facts, 1994 ed. Itasca, Ill, National Safety Council, 1994.

2. Committee on Trauma of the American College of Surgeons: Resources for Optimal Care of the Injured Patient. Chicago, American College of Surgeons, 1990.

3. Grande CM (ed): Textbook of Trauma Anesthesia and Critical Care. St. Louis, Mosby-Year Book, 1993.

4. Schou J: Prehospital Emergency Medicine. Lorrach, Germany, Alix., 1992.

5. MacKenzie EJ: Injury severity scales: Overview and directions for future research. Am J Emerg Med 2:537, 1984.

6. Yates DW: Scoring systems for trauma. BMJ 301:1090, 1990.

7. Jennett B, Teasdale G: Aspects of coma after severe head injury. Lancet 1:878, 1977.

8. Kock JP, McLellan BA, Wortzman D et al: Is the ASA physical status classification adequate in predicting mortality in blunt trauma? Anesthesiology 67:A482, 1987.

9. Booij LHDJ: Pitfalls in anaesthesia for multiply injured patients. Injury 14:81, 1982.

10. Burri C, Kreuzer U, Limmer J: Principles and practice of fracture treatment in the multiply injured patient. Injury 14:44, 1982.

11. Gann DS, Lilly MP: The neuroendocrine response to multiple trauma. World J Surg 7:101, 1983.

12. Feliciano DV, Wall MJ Jr: Patterns of injury. In Moore EE, Mattox KL, Feliciano DV (eds): Trauma, 2nd ed. East Norwalk, Conn, Appleton & Lange, 1991, p 81.

13. Fackler ML: Physics of missile injuries. In McSwain NE Jr, Kerstein MD (eds): Evaluation and Management of Trauma. East Norwalk, Conn, Appleton-Century-Crofts, 1987, p 25.

14. Trunkey DD: Trauma. Sci Am 249:28, 1983.

15. Gens DR: Cervical soft tissue injuries. In Cowley RA, Conn A, Dunham CM (eds): Trauma Care, vol 1: Surgical Management. Philadelphia, JB Lippincott, 1987, p 88.

16. Cicala RS, Kudsk KA, Butts A et al: Initial evaluation and management of upper airway injuries in trauma patients. J Clin Anesth 3:91, 1991.

17. Peters RM: Biomechanics of chest injury. In Nahum AM, Melvin J (eds): The Biomechanics of Trauma. East Norwalk, Conn, Appleton-Century-Crofts, 1985, p 399.

18. Graham JM, Beall AC Jr, Mattox KL et al: Systemic air embolism following penetrating trauma to the lung. Chest 72:449, 1977.

19. Abouhatem R, Hendrickx P, Titeca M et al: Thoracic epidural analgesia in the treatment of rib fractures. Acta Anaesthesiol Belg Suppl 35:271, 1984.

20. Rankin APN, Comber REH: Management of fifty cases of chest injury with a regimen of epidural bupivacaine and morphine. Anaesth Intensive Care 12:311, 1984.

21. Worthley LIG: Thoracic epidural in the management of chest trauma. Intensive Care Med 11:312, 1985.

---

22. Burgess AR, Mandelbaum BR: Acute orthopedic injuries. In Siegel JH (ed): Trauma: Emergency Surgery and Critical Care. New York, Churchill Livingstone, 1987, p 1049.

23. American College of Surgeons: Advanced Trauma Life Support Manual. Chicago, American College of Surgeons, 1993, p 86.

24. Stene JK, Grande CM (eds): Trauma Anesthesia. Baltimore, Williams & Wilkins, 1991.

25. Committee on Trauma Research: Injury in America: A Continuing Public Health Problem. Washington, DC, National Academy Press, 1985.

26. Lewis VL, Manson PN, Morgan RF et al: Facial injuries associated with cervical fractures: Recognition, patterns and management. J Trauma 25:90, 1985.

27. Peters RM: Fluid resuscitation and oxygen exchange in hypovolemia. In Siegel JH (ed): Trauma: Emergency Surgery and Critical Care. New York, Churchill Livingstone, 1987, p 157.

28. Bivins HG, Ford S, Bezmalinovic Z et al: The effect of axial traction during orotracheal intubation of the trauma victim with an unstable cervical spine. Ann Emerg Med 17:25, 1988.

29. Dronen SC, Merigian KS, Hedges JR et al: A comparison of blind nasotracheal and succinylcholine-assisted intubation in the poisoned patient. Ann Emerg Med 16:650, 1987.

30. Lawes EG, Campbell I, Mercer D: Inflation pressure, gastric insufflation and rapid sequence induction. Br J Anaesth 59:315, 1987.

31. Hardy JF: Large volume gastroesophageal reflux: a rationale for risk reduction in the perioperative period. Can J Anaesth 35:162, 1988.

32. Stene JK, Grande CM, Barton CR: Airway management for the trauma patient. In Stene JK, Grande CM (eds): Trauma Anesthesia. Baltimore, Williams & Wilkins, 1991, p 64.

33. American Society of Anesthesiologists: Practice guidelines for management of the difficult airway. Anesthesiology 78:597, 1993.

34. Calder I, Ordman AJ, Jackowski A et al: The brain laryngeal mask airway: An alternative to emergency tracheal intubation. Anaesthesia 45:137, 1990.

35. Pennant JH, White PF: The laryngeal mask airway: Its uses in anesthesiology. Anesthesiology 79:144, 1993.

36. Fiser DH: Intraosseous infusion. N Engl J Med 322:1579, 1990.

37. Millikan JS, Cain TL, Hansbrough J: Rapid volume replacement for hypovolemic shock: A comparison of techniques and equipment. J Trauma 24:428, 1984.

38. Gentillelo LM, Cobean RA, Offner PJ et al: Continuous arteriovenous rewarming: Rapid reversal of hypothermia in critically ill patients. J Trauma 32:316, 1992.

39. Lowery BD, Cloutier CT, Carey LC: Electrolyte solutions in resuscitation in human hemorrhage shock. Surg Gynecol Obstet 133:273, 1971.

40. Modig J: Effectiveness of dextran 70 versus Ringer's acetate in traumatic shock and adult respiratory distress syndrome. Crit Care Med 14:454, 1986.

41. Hankeln K, Radel C, Beez M et al: Comparison of hydroxyethyl starch and lactated Ringer's solution on hemodynamics and oxygen transport of critically ill patients in prospective crossover studies. Crit Care Med 17:133, 1989.

42. Shatney CH, Deepika K, Militello PR et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. Arch Surg 118:804, 1983.

43. Moore FD: The effects of hemorrhage on body composition. N Engl J Med 273:567, 1965.

44. Bickell WH, Wall MJ, Pepe PE et al: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 331:1105, 1994.

45. Dries DJ: Hypotensive resuscitation. Shock 6:311, 1996.

46. Holcroft JW, Vassar MJ, Turner JE et al: 3% NaCl and 7.5% NaCl/dextran 70 in the resuscitation of severely injured patients. Ann Surg 206:279, 1987.

47. Halvorsen L, Gunther RA, Dubick MA et al: Dose response characteristics of hypertonic saline/dextran solutions. J Trauma 31:785, 1991.

48. Battistella FD, Wisner DH: Combined hemorrhagic shock and head injury: Effects of hypertonic saline (7.5%) resuscitation. J Trauma 31:182, 1991.

49. Attar S, Boyd D, Layne E et al: Alterations in coagulation and fibrinolytic mechanisms in acute trauma. J Trauma 9:939, 1969.

50. Crowell JW, Smith EE: Oxygen deficit and irreversible hemorrhagic shock. Am J Physiol 206:313, 1964.

51. Fleming A, Bishop M, Shoemaker W et al: Prospective trial of supranormal values as goals of resuscitation in severe trauma. Arch Surg 127:1175, 1992.

52. Soderstrom CA, Dischinger PC, Smith GS et al: Psychoactive substance dependence among trauma center patients. JAMA 267:2756, 1992.

53. Pavlin EG: Ethanol and substance abuse in trauma patients. In Grande CM: Textbook of Trauma Anesthesia and Critical Care. St. Louis, Mosby-Year Book, 1993, p 744.

54. ASA House of Delegates: Standards for basic intra-operative monitoring. In American Society of Anesthesiologists Directory of Members. Park Ridge, Ill, American Society of Anesthesiologists, 1988, p 590.

55. Shoemaker WC, Appel PL, Kram HR: Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med 16:1117, 1988.

56. White PF, Way WL, Trevor AJ: Ketamine: Its pharmacology and therapeutic uses. Anesthesiology 56:119, 1982.

57. Frost EAM: Central nervous system effects of nitrous oxide. In Eger EI II (ed): Nitrous Oxide/N_2O. New York, Elsevier, 1985, p 157.

58. Eisele JH: Cardiovascular effects of nitrous oxide. In Eger EI II (ed): Nitrous Oxide/N_2O. New York, Elsevier, 1985, p 125.

59. Irving MH, Stone HB: Metabolism and nutrition in trauma. In Carter DC, Polle HC Jr (eds): Surgery, vol. 1: Trauma. London, Butterworths, 1981, p 302.

60. Rohrer MJ, Natale AM: Effect of hypothermia on the coagulation cascade. Crit Care Med 20:1402, 1992.

61. Howland WS: Calcium, potassium and pH changes during massive transfusion. In Nusbacher J (ed): Massive Transfusion. Washington, DC, American Association of Blood Banks, 1978, p 17.

62. Britt BA: Malignant hyperthermia. Can J Anaesth 32:666, 1985.

63. Monafo WW: Initial management of burns. N Engl J Med 335:1581, 1996.

64. Prentice-Berkseth RL, Weinberg RM, Ramanathan S: Anesthesia for obstetric trauma patients. In Grande CM (ed): Textbook of Trauma Anesthesia and Critical Care. St. Louis, Mosby-Year Book, 1993, p 628.

65. Eichelberger MR, Pratsch GL (eds): Pediatric Trauma Care. Rockville, MD, Aspen Publishers, 1988.

66. DeCamp MM, Demling RH: Post-traumatic multisystem organ failure. JAMA 260:530, 1988.

67. High KM, Snider MT, Richard R et al: Clinical trials of an intravenous oxygenator in patients with adult respiratory distress syndrome. Anesthesiology 77:856, 1992.

68. Teasdale G, Jennett B: Assessment of coma and impaired consciousness: A practical scale. Lancet 2:81, 1974.

69. Parr MJA, Grande CM: Concepts of trauma care and trauma scoring. In Grande CM (ed): Textbook of Trauma Anesthesia and Critical Care. St. Louis, Mosby-Year Book, 1993, p 71.

70. Parr MJA, Grande CM: Mechanisms of trauma. In Grande CM (ed): Textbook of Trauma Anesthesia and Critical Care. St. Louis, Mosby-Year Book, 1993, p 325.

71. Stene JK: Anesthesia for the critically ill trauma patient. In Siegel JH (ed): Trauma: Emergency Surgery and Critical Care. New York, Churchill Livingstone, 1987, p 843.

Chapter 63 - Anesthesia for Eye, Ear, Nose, and Throat Surgery

John V. Donlon Jr.

ANESTHESIA FOR EYE SURGERY

Introduction

Anesthetic management can contribute to the success or failure of ophthalmic surgery. A closed-claims analysis by Gild et al [1] found that 30 percent of eye injury claims associated with anesthesia were characterized by patient movement during ophthalmic surgery. Blindness was the outcome in all cases. Although most problems occurred during general anesthesia, one of every four appeared under monitored anesthesia care. Clinical strategies to ensure patient immobility during ophthalmic surgery are essential.

Patient selection, preoperative evaluation, preparation, monitoring, sedation, and local anesthesia techniques are especially important for safe outpatient cataract surgery in the elderly (Chs. 61 and 65) . An understanding of eye anatomy and of the effect of anesthetics on intraocular pressure (IOP) and eye physiology is important when making anesthetic management decisions concerning such situations as strabismus, open eye injuries, performance of local anesthetic techniques, intravitreal gas injections, electroretinographic studies, oculocardiac reflex, and retinopathy of prematurity. [2]

Local Anesthesia

Many ophthalmic procedures, such as cataract extraction, corneal transplants, trabeculectomy, lid surgery, and even vitrectomy or repair of a detached retina, can be performed safely in an outpatient setting, using regional anesthesia and mild sedation. The number of outpatient ophthalmic procedures will increase as health-care costs are contained and the population continues to age. The elderly constitute a large percentage of the 4 million people in the United States who have vision problems related to cataracts. For example, 46 percent of people more than 75 years of age have cataracts. [3]

These elderly ophthalmologic patients frequently also have associated diseases of concern to the anesthesiologist. Congestive heart failure, hypertension, diabetes, angina, chronic lung disease, senility, parkinsonism, and arthritis are all problems that can disrupt a smooth procedure.

Preoperative Evaluation and Preparation

Successful local anesthesia for eye surgery begins with preoperative screening, patient selection, and preparation for anesthesia. Although the general principles of preoperative evaluation and medication are standard (Ch. 23) , specific considerations are important for ophthalmic surgery and anesthesia. Patients with chronic spontaneous cough, shortness of breath while lying flat, parkinsonian head tremor, Alzheimer disease, or claustrophobia may be very difficult to manage with regional anesthesia and light sedation. These patients may best be managed with a general anesthetic. Every effort must be made to help the patient understand the procedure. Hearing aids and dentures should be left in place. Patients are less embarrassed and

may even breathe better with dentures in place. The presence of an interpreter to explain the procedure and the need for cooperation helps to overcome any language barrier. The interpreter should be present at the time of peribulbar block, the most stressful part of the procedure.

Whenever possible, medication regimens should not be interrupted. Treatments for asthma, hypertension, angina, congestive heart failure, or diabetes should be continued throughout the day of surgery. Patients with postnasal drip should be given a drying agent before surgery, and those with gastric esophageal reflux should at least receive metoclopramide (0.15 mg/kg IV).

A thorough explanation of the technique, monitoring, and safety precautions involved in regional anesthesia for eye surgery allays patient anxiety and increases acceptance and cooperation in most cases. Thus, the preoperative anesthesia interview is most important in obtaining cooperation and patient acceptance. Still, premedication can be helpful in lessening anxiety and enhancing amnesia during injection for peribulbar block. The patient must be calm, cooperative, and aware during the operation, and the reflexes should not be obtunded, nor should the airway be obstructed. In the outpatient setting, intramuscular premedication is unnecessary, but proper sedation levels can be achieved by intravenous titration while monitoring effect. The patient should be monitored during the block process and provided with supplemental oxygen.

The ideal sedating drug prior to eye block would ensure amnesia for the block, decrease the discomfort of the injection, and limit patient motion while producing no cardiovascular or significant respiratory side effects. Many agents and combinations have been used for sedation during monitored anesthesia care, including alfentanil, remifentanil, midazolam, and propofol. [4] [5] [6] [7] [8] Benzodiazepines are synergistic with narcotics and increase the risk of apnea. [9] Altered pharmacodynamics with age require decreasing narcotic doses in the elderly. [10]

Propofol in small (20-mg) incremental intravenous doses has been used to achieve amnesia for regional eye blocks. [11] Propofol provides no analgesia for the block needle insertion, and semiconscious patients may have a startle response.

Remifentanil (0.3-0.5 mug/kg IV) has a 90- to 120-second onset time and a 5-minute duration. The patient is calm and cooperative although aware during the eye block but does not move or startle. A small supplement of midazolam (0.5-1.5 mg IV) may be added to this sedation regimen, but it is synergistic and increases the risk of temporary apnea. Midazolam has a 2- to 3-minute onset and 45- to 60-minute duration of action.

Infusions of propofol or narcotic are not necessary during eye surgery. The eye block provides the necessary analgesia and akinesia. The patient should remain awake and aware, but calm and cooperative, during the procedure.

Gold et al [6] noted a 13 percent incidence of nausea and vomiting associated with remifentanil infusion. Low-dose (30 mug IV) bolus injections of remifentanil are not expected to cause nausea or vomiting.

If a narcotic must be used, an antiemetic drug such as droperidol (0.01 mg/kg IV), ondansetron (0.06 mg/kg IV), or dolasetron (0.20 mg/kg IV) may also be given to counteract the tendency of narcotics to cause nausea and vomiting.

Monitoring

Standard monitoring for regional anesthesia for ophthalmic surgery (Chs. 42 and 43) includes observation of arterial blood pressures, the electrocardiogram (ECG),

and the pulse oximeter. If possible, peribulbar block should be performed in a special block area at least 20 minutes before the start of surgery. This interval allows time for the block to become effective, for the use a Honan cuff to lower IOP, and for the patient to begin to recover from sedation. The Honan cuff pressure or the block injection may induce an oculocardiac reflex vagal response that causes bradycardia and nausea. Open eye surgery should not proceed if nausea exists; this complaint should be treated and allowed to subside before proceeding.

Monitoring in the operating room is also standard (Chs. 42 and 43) , but special precautions must be taken because the patient's face is covered by drapes. Respirations may be monitored by direct vision and placing a CO_2 sampler near the mouth. A 4:1, air-oxygen facemask having a total flow rate of at least 10 L/min should be used to supplement oxygen and to prevent accumulation of CO_2 under the drapes surrounding the face. These drapes should be tented away from the patient, to prevent claustrophobia and to permit free flow of air.

Postoperative Care

Postoperative care and discharge are standard (Chs. 65 and 68) . The patient is discharged into the care of a responsible adult who provides help when the patient is walking and eating, as well as home care the night after surgery. Moreover, written instructions from the surgeon are provided. Regional anesthesia for eye surgery is generally safe even for elderly patients having a history of myocardial infarction. [12] However, 26 percent of high-risk (diabetes, hypertension) ambulatory patients having retina surgery under local anesthesia had at least one silent myocardial ischemic event within 18 hours of surgery. [13] These events were usually associated with an increased heart rate. Therefore, the cardiac medication regimen should be continued in the perioperative period, and the use of prophylactic beta-blockers should be considered. [14]

Regional Eye Blocks

Wong [15] and Troll [16] reviewed regional anesthesia techniques for intraocular surgery in detail and presented an excellent description of important orbital anatomy. Techniques for peribulbar/retrobulbar blocks, facial nerve blocks, and choice of anesthetic mixture and types of needles were discussed. Complications associated with retro-bulbar versus peribulbar techniques were discussed and compared. Peribulbar anesthesia carries a lower risk of serious complications. Anesthesiologists can easily acquire expertise in this area on a par with that of ophthalmologists. The importance of a detailed knowledge of orbital anatomy and physiology and attention to detail cannot be overemphasized. [15]

Peribulbar Block

Hamilton et al [17] showed that safe, comfortable, and effective analgesia and akinesia of the eye can be obtained using a peribulbar block; that is, local anesthetic is injected outside the muscle cone. Hamilton and colleagues used their "customized peribulbar block" in more than 10,000 patients without the occurrence of complications (brain-stem anesthesia, retrobulbar hemorrhage, atrophy of the optic nerve, or spread of anesthetic to the contralateral orbit).

Davis and Mandel [18] reviewed 16,225 peribulbar blocks and found them to be effective, with a very low complication rate. Globe perforation occurred in a patient with an eye axial length of 23.5 mm, using a harp needle via a superonasal approach. Akinesia was achieved in 95 percent of patients, and the reinjection rate was about 10 percent. Amaurosis is usually not expected with peribulbar blocks. Disadvantages of peribulbar blocks include the following: large injected volumes (6-8 mL), causing increased IOP [19] ; slower onset (7-12 min); possible globe perforation; myotoxicity of local anesthetic on inferior rectus muscle causing vertical diplopia. [20] [21] [22] [23] [24]

The customized peribulbar block described by Hamilton and coworkers [17] requires attention to detail to maximize patient comfort and good analgesia and to minimize complications. Dull, short-beveled needles are usually recommended to minimize the risk of bleeding and perforation of the globe. Careful placement of the needle and an aspiration check of its contents decrease the risk of vessel perforation. Hamilton and coworkers [17] recommended making the initial injection through the inferior fornix of the conjunctiva, rather than transcutaneously after topical application of 0.5 percent proparacaine. The needle is not inserted beyond 25 mm, because large vessels and the optic nerve are more likely to be encountered with deeper retrobulbar penetration. No attempt is made to pierce the muscle cone.

The traditional practice of having the patient look upward and in, to make the muscle cone more accessible, also brings the optic nerve and vascular structures closer to the tip of the needle, thus increasing the risk of retrobulbar hemorrhage, optic nerve injury, or central nervous system (CNS) tracking of local anesthetic along the optic nerve sheath. A safer maneuver is to have the patient look straight ahead (neutral gaze position) and to avoid entering the cone. All injections should be performed slowly, to ensure patient comfort and to promote the even spread of local anesthetic within the orbit.

Use of an orbital compression balloon facilitates the block by lowering IOP and promoting the periorbital spread of local anesthetic to achieve akinesia of the periorbital muscles. In this way, the need for a separate and painful block of the facial nerve is avoided. Any complications that occur (vasovagal reactions, retrobulbar hemorrhage, spread of the local anesthetic to the CNS) are usually obvious within 10 to 15 minutes of injection.

This procedure is virtually painless because of use of the peribulbar approach, careful placement of fine needles, slow injection of local anesthetic, and avoidance of a separate block of the facial nerve. As a result, the elderly outpatient population usually needs minimal premedication with fewer drug side effects (e.g., somnolence, hypotension, emesis). The local anesthetic mixture advocated by Hamilton and colleagues [17] consists of equal portions of 2 percent lidocaine for rapid onset and penetration and 0.75 percent bupivacaine for prolonged duration and postoperative comfort. The addition of hyaluronidase (3 U/mL) promotes spread of local anesthetic, and the addition of epinephrine (in a final concentration of 1:400,000) reduces bleeding, promotes vasoconstriction, and prolongs orbital akinesia.

The peribulbar technique requires a total of approximately 6 mL of injectate. The total amount of epinephrine injected is small and should pose no problem to patients with angina, hypertension, or irritable myocardia.

Sub-Tenon Block

Direct injection of local anesthetic into the posterior sub-Tenon space using blunt dissection and a blunt probe avoids many of the complications of peribulbar or retrobulbar injections. [25] [26] [27] [28] Tenon capsule is a dense fibrous layer of connective tissue surrounding the globe and extraocular muscles. Local anesthetic in the posterior aspect of this space spreads along the extraocular muscles and diffuses into the retrobulbar space.

This technique uses a blunt probe (curved lacrimal cannula) to instill local anesthetic into the posterior sub-Tenon space, avoiding sharp needles blindly placed in the orbit or retrobulbar space. It is painless and provides reliable anesthesia with minimum risk of serious complications. [26]

Ripart et al [25] have shown computed tomographic (CT) confirmation that a sub-Tenon medial canthus injection is episcleral and allows the local anesthetic to spread over the extraocular muscles and to provide akinesia. A volume of 4 mL is sufficient to surround the globe and to produce analgesia. The sensitivity of the eye is provided by the ciliary nerves, which cross the episcleral space after they emerge from the globe. [25]

Complications

The complications associated with retrobulbar block techniques, although rare (approximately 1 in 500 blocks), usually occur within 15 minutes of injection and are the result of apprehension, pain, oversedation, local anesthetic toxicity, the method of needle placement, or injection of local anesthetic. Hypotension, bradycardia, cardiac arrest, diaphoresis, and nausea are usually responses to fear or pain of injection or to manipulation of the eyeball. Patients should have intravenous oxygen and full monitoring (e.g., ECG, blood pressure, oxygen saturation) during the block procedure.

The oculocardiac reflex (OCR), a vagal response manifested by cardiac arrhythmias and hypotension, may be elicited by pain, pressure, or manipulation of the eyeball. Treatment requires administration of oxygen, Trendelenburg positioning, intravenous administration of crystalloid, discontinuation of pressure or muscle traction at the eyeball (e.g., release of the Honan balloon), and, on occasion, intravenous administration of atropine.

Retrobulbar hemorrhage occurs in 1 of 700 retrobulbar blocks and is usually noted during injection as the eye tenses and pushes forward. Treatment includes the application of

gentle pressure for 20 to 30 minutes and, perhaps, a lateral canthotomy and rescheduling of surgery. This complication is less likely with peribulbar or sub-Tenon blocks.

Direct trauma to the eye (optic nerve damage, scleral perforation) occurs rarely (less than 1 in 1,000 retrobulbar injections). Possible needle penetration risk factors include increased axial length of the needle because of high myopia or previous scleral buckle procedure and poor patient cooperation during the injection. In one study, 70 percent of globe perforations involved sharp, full-beveled needles. Birch et al [29] used ultrasonic localization to show that 56 percent of retrobulbar needle shafts indent the globe. Optic nerve damage and retrobulbar hemorrhage may be minimized by having the patient look straight ahead and by avoiding deep penetration into the orbit. Shivering occurs in approximately 0.64 percent of patients, probably because of the absorption of local anesthetic into the CNS (Chs. 13 and 42 to 44).

Javitt et al [30] reported eight instances of brain-stem anesthesia after retrobulbar block, six of which progressed to apnea requiring mechanical ventilation. The clinical picture of brain-stem anesthesia can include amaurosis, gaze palsy (ductional defects), dysphagia, cardiac arrest, shivering, apnea, tachycardia, hypertension, loss of consciousness, and dilatation of the contralateral pupil. Full recovery from brain-stem anesthesia is the expectation, provided early detection and proper treatment occur. [31]

Nicoll et al [32] found that direct spread of local anesthetic to the CNS along the optic nerve sheath, although infrequent, caused severe, unpredictable, life-threatening complications within 2 to 40 minutes of injection in 1 of 750 retrobulbar blocks. If recognized early and treated promptly, patients usually recover within 60 to 90 minutes and do well. Access to the brain stem can be via direct injection of local anesthesia into the optic nerve sheath during deep retrobulbar approach, tracking retrograde to the midbrain and respiratory area of the brain stem. The effect may be delayed 5 to 15 minutes after injection and lasts for 20 to 90 minutes.

Another mechanism can be an intra-arterial injection with retrograde flow through the ophthalmic artery into the cerebral circulation and midbrain area. Onset is usually immediate and may be associated with seizure activity. Life-threatening complications associated with regional eye blocks can occur quickly and require the anesthesia care team to be prepared and vigilant. Treatment includes oxygen, intravenous fluids and pharmacologic circulatory support, suppression of convulsions, and, if necessary, intubation and cardiopulmonary resuscitation. [33] Javitt et al [30] noted that communication between the optic nerve sheath and subarachnoid space had been demonstrated and that contrast material is able to track along the optic nerve to the optic chiasm and into the subarachnoid space surrounding the pons and midbrain areas. Such an occurrence would be consistent with the signs and symptoms manifested by their patients. Javitt and coworkers also noted that a down-and-out gaze for retrobulbar block injection was safer than the traditional up-and-in gaze. Brain-stem anesthesia has not yet been reported for the peribulbar method of eye anesthesia. Javitt and colleagues concluded that careful monitoring and the presence of an anesthesiologist during administration of anesthesia for the eye are necessary to detect and treat these rare but serious complications.

Postoperative vertical diplopia resulting from muscle fiber degeneration in the inferior rectus muscle has been reported following regional local anesthetic injection for cataract surgery with an incidence of 1.4 percent. [20] Diplopia may be temporary or permanent. Possible causes include traumatic injection, myotoxicity of local anesthetic solution, bridle sutures, surgical trauma, ocular compression, and injectate volume pressure. Carlson and Raimin [22] found muscle degeneration following bupivacaine, mepivacaine, or lidocaine injected near extraocular muscles in rats. Damage reflected diffusion of the anesthetic into the muscle. General recommendations include the following: limiting the injected volume to 6 mL, slowly injected; avoiding injecting into the muscle body; injecting lateral to the inferior rectus muscle [21] ; and avoiding 4 percent xylocaine injectate and adding Wydase to the injection solution.

Postoperative ptosis following cataract surgery is reported with an incidence as high as 13 percent. This usually is associated with the levator palpebrae muscle. Feibel et al [34] found no significant difference in the incidence of ptosis between peribulbar or retrobulbar injections. Injection of a large volume of local anesthetic into the upper lid should be avoided when possible.

Intraocular Pressure

Management of anesthesia for ophthalmic surgery requires control of IOP before, during, and after the procedure. Control of IOP is often important to the success of the procedure. Therefore, the anesthesiologist must understand the physiologic effects of IOP and the implications of anesthetic drugs and maneuvers on IOP. Cunningham and Barry [35] and Murphy [36] thoroughly reviewed the physiologic determinants of IOP and its relation to management of anesthesia.

Physiologic Determinants

Normal IOP is approximately 12 to 20 mm Hg. The most important influences on IOP are movement of aqueous humor, changes in choroidal blood volume, central venous pressure, and extraocular muscle tone. The main physiologic determinant of IOP is the dynamic balance between the production of aqueous humor, a watery, clear fluid in the ciliary body of the posterior chamber, and its eventual elimination into the episcleral venous system via spaces of Fontana and the canal of Schlemm at the iridocorneal angle (Fig. 63-1) (Figure Not Available) .

Most of the aqueous humor is actively secreted at the ciliary process of the posterior chamber and circulates freely around the iris into the anterior chamber. Any increase in venous pressure or decrease in the cross-sectional area of the spaces of Fontana increases resistance to outflow of aqueous humor and increases IOP. Mydriatic drugs relax ciliary muscles, close the iridocorneal angle at Fontana spaces, and thereby increase IOP. Coughing, straining, and Valsalva maneuvers significantly increase central venous pressure, decrease the outflow of aqueous humor from the Schlemm canal into the episcleral venous system, and thus increase IOP.

Figure 63-1 (Figure Not Available) Circulation of the aqueous humor. *(From Aboul-Eish [221])*

Changes in choroidal blood volume (CBV) also affect IOP significantly. The choroid is a vascular meshwork of arterial anastomoses located in the posterior chamber. Choroidal blood flow is usually autoregulated over a range of perfusion pressures to keep IOP stable. Sudden increases in systolic arterial blood pressure cause a transient swelling of CBV; a subsequent temporary outflow adjusts IOP toward normal. Hypotension (systolic arterial blood pressure <90 mm Hg) may reduce IOP as CBV decreases. Sudden increases in CBV can force vitreous gel forward into the anterior chamber during open eye surgery or can increase IOP in the intact eye. Coughing, bucking, emesis, and the Valsalva maneuver increase CBV by increasing central venous pressure and thus increase IOP. Coughing can increase IOP to 30 or 40 mm Hg. CBV, and therefore IOP, will also increase in response to respiratory acidosis and hypercarbia. Choroidal circulation is also sensitive to changes in the partial pressure of oxygen. Hypoxia induces choroidal vasodilation and increases IOP.

When the eye is open during surgery, IOP may be somewhat lower than normal. The transluminal pressure on the choroidal vessels is greater, and a sudden increase in choroidal pressure caused by hypertension, increased venous pressure, or hypercarbia is likely to result in spontaneous bleeding of the choroidal vessels.

The CNS exerts some degree of control over IOP. Experiments with cat diencephalon indicate the areas that affect IOP. Some responses seem to be mediated neurovascularly, whereas others relate to increased extraocular muscle tone. These centers are usually depressed by barbiturates and volatile inhaled anesthetics.

Murphy [36] reviewed factors affecting intraocular blood volume and concluded that, although arterial blood pressure exerts some control over IOP, its effect over a physiologic range of blood pressures is small. A more definite, direct relationship exists between central venous pressure and IOP. A slight head-up tilt during intraocular surgery helps to counteract the effects of central venous pressure.

Intraocular vascular tone is predominantly affected by CO_2 and control areas in the diencephalon. A linear relationship exists between IOP and increasing CO_2 partial pressures. Hypocarbia decreases IOP through vasoconstriction of the choroidal blood vessels and decreases formation of aqueous humor through reduced carbonic anhydrase activity. The increased IOP associated with hypoventilation and hypercarbia occurs as a result of vasodilation of CBV and increases in central venous pressure.

Sudden external pressure on the eyeball initially increases IOP and may induce an oculocardiac vagal reflex. The increased IOP promotes outflow of aqueous humor, thus returning IOP toward normal. The effects of direct external compression of the eyeball on vitreous gel and CBV have not been documented.

Injecting a large volume (8-10 mL) of fluid into the orbit (e.g., peribulbar block [PBB]) may significantly increase IOP. [19] IOP reaching the level of retinal arterial pressure can cause retinal ischemia.

Anesthesia and Intraocular Pressure

Most anesthetics reduce IOP. In general, they relax extraocular muscle tone, depress the CNS (i.e., the diencephalon), improve outflow of aqueous humor, and lower venous and arterial blood pressures (Ch. 12) . Only succinylcholine and ketamine may increase IOP. Laryngoscopy and endotracheal intubation also elevate IOP.

Antisialogogues, such as atropine, scopolamine, and glycopyrrolate, given intramuscularly for premedication, have no significant effects on IOP. However, anticholinergic drugs applied topically to the eye may cause mydriasis and may increase IOP. Combinations using neostigmine and atropine to reverse the effects of nondepolarizing muscle relaxants do not seem to increase IOP. Orally administered diazepam (0.2 mg/kg) has no effect on IOP, whereas intravenously administered diazepam (0.15 mg/kg) and equipotent intravenous doses of midazolam (0.03 mg/kg) significantly lower IOP. Even in patients with glaucoma, narcotic premedication causes no change, or only a slight decrease, in IOP.

In general, CNS depressants lower IOP. Sleep doses of barbiturates such as thiopental and pentobarbital significantly decrease IOP by their central depressive effect on diencephalic control of IOP and by improved outflow of aqueous humor. Two drugs used to induce anesthesia, Althesin (the combination of alfadolone and alfaxalone) and etomidate, also lower IOP. The effect of propofol on IOP during induction of general anesthesia is similar to that of thiopental. [37] During controlled ventilation and normocapnia, volatile inhaled anesthetics reduce IOP in proportion to the depth of anesthesia. Reductions of 14 to 50 percent have been noted. Neuroleptanalgesia produced by mixtures of fentanyl and droperidol decreases IOP 12 percent in normocapnic patients.

The effect of ketamine on IOP varies. Early studies reported an increase in IOP after intramuscular or intravenous administration of ketamine. Ketamine given after premedication with diazepam and meperidine does not affect IOP, and intramuscularly administered ketamine may even lower IOP in children. [35]

The nondepolarizing muscle relaxants decrease IOP. By contrast, succinylcholine causes a transient (4-6 min) but significant increase in IOP of 10 to 20 mm Hg. Although the mechanism is unclear, the increase is not attributable simply to induced muscle fasciculations. Studies on the effects of succinylcholine on IOP were reviewed concisely and thoroughly by Cunningham and Barry. [35]

The increase in IOP after administration of succinylcholine may depend on timing and dose, on the special tonic response of extraocular muscles because of their unique morphologic structure (the Felderstruktur), or on a direct effect of succinylcholine on CBV or formation of aqueous humor. Sectioning the rectus eye muscle does not prevent the increase in IOP after succinylcholine. None of the many attempts at preventing an increase in IOP after succinylcholine has been consistently successful. On the other hand, there are no clinical case reports of further eye damage, loss of vitreous, or other complications in open eye surgery associated with these methods.

The effectiveness of giving a small pretreatment dose of *d*-tubocurarine, diazepam, beta-adrenergic receptor blocking drugs, acetazolamide, or even succinylcholine to attenuate the increase in IOP after succinylcholine has produced contradictory results. These studies have used different timing schedules, doses, anesthetics, and measurement tech-niques. Preventing fasciculations with a pretreatment of *d*- tubocurarine (0.05 mg/kg IV) does not necessarily prevent the increase in IOP following succinylcholine (Ch. 12).

Laryngoscopy and endotracheal intubation are the anesthesia-related practices most likely to increase IOP significantly, that is, at least 10 to 20 mm Hg. [2] [35] [36] The mechanism is not clear, but it probably relates to sympathetic cardiovascular responses to tracheal intubation.

Several pretreatment regimens have been advocated to control sympathetic responses to tracheal intubation; some have been successful in attenuating the IOP response to tracheal intubation. [2] [11] [36] These pretreatments include intravenous administration of lidocaine (1.5 mg/kg) or sufentanil [38] (0.05-0.15 mug/kg) given 3 to 5 minutes before induction. Oral administration of the centrally acting antihypertensive drug clonidine (5 mug/kg) 2 hours before induction of anesthesia blunts the IOP response to intubation. [39] Intranasal administration of nitroglycerin [40] or beta-adrenergic receptor blocking drugs may also be useful in this regard.

Specific Clinical Situations and Complications

Intravitreal Injection of Gas

Ophthalmologists sometimes inject a small bubble of gas into the vitreal cavity during surgical reattachment of the retina. Their goal is to have a long-acting bubble of stable size hold the retina in place. The gases commonly used, sulfur hexafluoride (SF6) and carbon octofluorine (C3F8), are inert, very insoluble in water, and poorly diffusible. Nitrous oxide (N_2O) is 117 times more diffusible than SF6 and rapidly enters the gas bubble. If administration of N_2O continues after injection of gas into the vitreal cavity, the size of the injected gas bubble rapidly increases to 3 times its original size. [41] Within 19 minutes, IOP increases from 14 to 30 mm Hg, and both bubble size and IOP decrease (from 29 to 12 mm Hg) within 18 minutes of discontinuation of N_2O. [42] These rapid and wide variations in bubble size during general anesthesia may adversely affect the outcome of surgery.

Because washout of N_2O from the lung is 90 percent complete within 10 minutes, administration of N_2O should be discontinued at least 20 minutes before an intravitreal injection of gas. Bubble size and IOP should then remain stable. Some anesthetists avoid N_2O altogether when in-travitreal injection gas is planned. Wolf et al [42] noted that SF6 gas bubbles remain for at least 10 days. Other intravitreal gases may remain for as long as 21 to 28 days. N_2O should be avoided in any patient returning for surgery within 3 to 4 weeks of undergoing intravitreal injection of gas. A second exposure to N_2O could cause reexpansion of the bubble and could elevate IOP, resulting in occlusion of the retinal artery and loss of vision. This event is more likely if hypotension occurs during general anesthesia. During experiments in monkeys having intraocular air volumes of only 0.25 mL that were then subjected to pressures simulating those of commercial air travel, IOP rose an average of 42 mm Hg and decreased to lower than normal after return to preflight pressures. Moreover, the retinal artery became temporarily occluded. Therefore, patients with intravitreal gas bubbles may risk ocular damage during air travel.

Penetrating Eye Injuries

Management of emergency anesthesia for a patient having a full stomach and an open eye injury requires balancing the need to prevent aspiration of gastric contents against prevention of sudden significant increases in IOP that may cause further eye damage and loss of vision. [2] [35] [36] [43] If possible, early administration of a histamine (H_2)-receptor antagonist such as cimetidine (2 mg/kg IM) with metoclopramide (0.15 mg/kg IM) decreases gastric acidity and volume, respectively, and provides some protection.

Prior to rapid-sequence induction of anesthesia, several precautions may be taken to blunt the cardiovascular and IOP responses to laryngoscopy and tracheal intubation. Intravenous administration of lidocaine (1.5 mg/kg) and of remifentanil (0.1 mug/kg IV), 3 to 5 minutes before induction, may help to attenuate the increase in IOP after tracheal intubation. A beta-adrenergic receptor blocking drug such as atenolol (0.1 mg/kg IV) or labetalol (0.03 mg/kg IV) may also be useful in blocking

the cardiovascular response to tracheal intubation, especially in patients with angina or hypertension.

A dose of thiopental (6 mg/kg IV) or propofol (2.5 mg/kg IV) ensures adequate depth of anesthesia during tracheal intubation. The effectiveness of using a pretreatmentsuccinylcholine technique in these cases is controversial. [43] Although IOP may increase with this method, no published reports have described further eye damage after rapidsequence induction of anesthesia with *d*-tubocurarine, thiopental, and succinylcholine. In their large clinical experience using this technique to manage open eye injuries, Libonati et al [44] did not encounter the problems of aspiration of gastric contents or extrusion of eye contents (Ch. 12).

Because nondepolarizing muscle relaxants reduce IOP, a modified rapid-sequence technique using preoxygenation, a large dose of nondepolarizing muscle relaxants, [43] thiopental, and application of cricoid pressure for 2 minutes has been advocated for open eye surgery. This technique still requires taking the aforementioned precautions to prevent

increased IOP after laryngoscopy and tracheal intubation. An intermediate-acting or short-acting nondepolarizing muscle relaxant such as vecuronium, mivacurium, or rocuronium can be given in sufficient dose to allow reasonably rapid onset (90-120 s) without prolonged duration of paralysis or excessive cardiovascular effect. Describing a rapid-sequence induction technique using vecuronium (0.2 mg/kg IV), Abbott [45] achieved adequate tracheal intubating conditions at 60 seconds without inducing coughing. If intubation is attempted too early, incomplete relaxation will make laryngoscopy difficult. Moreover, placement of the endotracheal tube may stimulate coughing or bucking, causing a sudden significant increase in IOP.

During general anesthesia for open eye surgery, depth of anesthesia must be adequate to ensure lack of movement [15] or coughing. It is advisable to use neuromuscular blockers and to document full neuromuscular blockade with a train-of-four response to prevent coughing caused by accidental carinal stimulation (Ch. 12).

When there is the possibility of a full stomach, the trachea should be extubated while the patient is awake, breathing spontaneously, and receiving oxygen; the patient's head is to the side. A smooth emergence from anesthesia can be aided by administering an antiemetic drug before or during surgery and by giving lidocaine (1.5 mg/kg IV) or remifentanil (0.5 mug/kg IV) approximately 5 minutes before the patient awakens.

Pediatric Eye Injuries

Management of eye anesthesia in children involves special considerations. [43] [46] [47] Children with eye injuries may also have cranial injuries. If administration of narcotics is necessary to control pain, an antiemetic drug also should be given. Regional anesthesia is not suitable because of the existence of eye trauma and because of the young age and lack of cooperation of the patient. Awake endotracheal intubation, which may increase IOP and is difficult in this age group, should be avoided in children with open eye injuries.

It is usually possible to start an intravenous line gently, using a topical anesthetic cream, and induction of anesthesia may proceed as described for adults. If no intravenous line is reasonably possible, then despite the patient's possibly full stomach, a rapid, gentle induction of anesthesia via mask (with 7-8% sevoflurane) must be performed, avoiding positive pressure and direct mask pressure on the injured eye. An intravenous line is secured as soon as possible.

If the patient has eaten recently, the risk of aspiration of gastric contents can be minimized by delaying these urgent cases a few hours. However, waiting is still no guarantee that the stomach will become empty. Further precautions include using an H_2-receptor antagonist and metoclopramide, as with adults.

The stomach should be decompressed during surgery, and the patient should be extubated awake, with protective airway reflexes intact. To facilitate tolerance of the endotracheal tube and to minimize bucking in the awakening patient, a narcotic may be given 10 to 20 minutes before the end of surgery, with lidocaine (1.5 mg/kg), administered intravenously 5 minutes before extubation of the trachea.

Retinopathy of Prematurity

As a result of improved neonatal care, more than 65 percent of premature infants (750-1,000 g) now survive. More than 50 percent of these survivors have retinopathy of prematurity; therefore, the incidence of this condition is increasing. Although usually associated with hyperoxic periods during neonatal care, retinopathy of prematurity has a complex cause with many origins. Full-term nonhyperoxic infants can also have this condition, as can premature infants who have not had oxygen therapy. The condition may also be associated with factors such as hypoxia, hypercarbia, hypocarbia, sepsis, and apnea. [48] Retinopathy of prematurity occurs despite efforts in neonatal nurseries to control and monitor oxygen delivery. Babies with this condition often have a history of general immaturity, apnea, bradycardia, jaundice, patent ductus arteriosus, intraventricular dysplasia, hypoxia, and developmental delays. [49]

Capillary oxygen tension should be kept at 35 to 40 mm Hg, and arterial oxygen tension should be maintained at 50 to 70 mm Hg in premature infants. The problem for the anesthesiologist giving general anesthesia to a premature infant is to balance the risk of hypoxic damage and respiratory problems frequently encountered in these sick, frail preterm infants [50] (Chs. 58 and 59).

The retina is not completely vascularized at birth. Even at 8 months of age, the temporal retina may remain avascular. Hypoxia causes immature vessels to constrict, leading to peripheral retinal hypoxia. This condition stimulates formation of vascular shunts, vasoproliferative factor, and vessel proliferation. Leaking fluid causes hemorrhages, fibrosis, and scarring. As scars contract, the retina becomes detached. Very early surgical intervention (i.e., at 1-4 wk) with cryotherapy has been advocated to ablate the avascular retina; such surgery eliminates the release of vasoproliferative factor.

Although there is no convincing evidence that retinopathy of prematurity has ever occurred solely because of oxygen given during anesthesia, [48] in addition to the usual anesthesia requirements and precautions for these young, immature patients, [48] [51] prolonged exposure to high intraoperative concentrations of oxygen is best avoided during the period of retinal immaturity (i.e.,
8 mo). Arterial oxygen tensions of 60 to 90 mm Hg may be achieved by giving mixtures of air and oxygen or N_2O and oxygen and by using finger-pulse oximetry to keep arterial oxygen saturations at 90 to 95 percent. [52]

Electroretinography

Halothane, isoflurane, and enflurane can affect visual evoked potentials (VEP). [53] [54] Halothane and isoflurane decrease the amplitude and increase the latency of VEP. A 0.9 percent or higher concentration of isoflurane can prolong the latencies of VEP. [54] Although some studies claim that this relationship is dose-dependent, at least two studies have failed to demonstrate significant differences for various concentrations of anesthetics. Neuroleptanalgesia seems to increase the latency of P2 slightly without changing the amplitude of EP. The effect of isoflurane on VEP may be

minimized by using low concentration, muscle relaxants, if necessary, and supplemental opioids.

Ketamine, a phencyclidine derivative, is a unique anesthetic agent because it increases the electrical activity of the brain. This increased activity could alter the amplitude of VEP and distort the conclusions of testing. Ketamine has been used for anesthesia in rabbits without affecting the electroretinographic response. [55]

Unlike the VEP, which is a complex cortical response, the electroretinographic response is a simple reflex occurring within the eye. Therefore, it is unlikely that such a response would be affected significantly by general anesthetics.

Strabismus

The treatment of poor alignment of the visual axis with amblyopia (strabismus) in children 1 to 6 years of age usually consists of surgery on the extraocular muscles. Surgical intervention must occur by 4 months of age if proper stereoscopic visual development is to proceed. [56] Strabismus repair in the older child is performed for cosmetic purposes. Three problems associated with strabismus are of particular interest for the anesthetist: the possible increased risk of malignant hyperthermia, the high incidence of postoperative nausea and vomiting (PONV), and the likelihood of an OCR.

Strabismus is considered by some to represent an underlying myopathy. These patients are assumed to be at increased risk of malignant hyperthermia. [57] For example, the incidence of isolated masseter spasm after halothane and succinylcholine administration was higher in children with strabismus compared with those without strabismus (2.8 versus 0.72%). [58] Patients with strabismus whose tracheas were intubated with the help of pancuronium did not have isolated masseter spasm. [59] In one study, approximately 50 percent of patients who had malignant hyperthermia had had isolated masseter spasm after induction of anesthesia. [60] Because the overall incidence of malignant hyperthermia in children is only 1 in 15,000, the high incidence of masseter spasm following succinylcholine administration in patients with strabismus suggests that such patients may be more likely to develop malignant hyperthermia.

The risk of malignant hyperthermia may be lessened by avoiding succinylcholine. In addition, because it increases extraocular muscle tone, succinylcholine interferes with the forced duction test (which evaluates muscle tone) for approximately 15 minutes. By contrast, vecuronium, rocuronium, cisatracurium, and mivacurium render the extraocular muscles flaccid, minimizing the afferent stimuli for nausea, vomiting, and OCR. To ensure that a malignant hyperthermia episode is detected promptly, body temperature, ECG, and end-tidal concentrations of CO_2 should be monitored carefully in patients with strabismus (Ch. 27).

The incidence of PONV in children after outpatient strabismus surgery varies from 48 to 85 percent. [61] Persistent PONV delay discharge and may even require overnight admission of the patient. Many regimens have tried to control PONV in these patients without also prolonging recovery time. Droperidol (75 mug/kg IV) successfully reduces PONV to 16 to 22 percent without increasing discharge time (4.6 h). [62] Lower doses of droperidol, usually effective as an antiemetic in adults, do not seem to be effective in children with strabismus. [63] Intravenous administration of lidocaine (1.5 mg/kg) prior to tracheal intubation also reduces the incidence of PONV to 16 to 22 percent. [64]

Wier et al [61] showed a significant decrease in the incidence and frequency (41%) of vomiting in the first 24 hours after strabismus surgery using a propofol infusion and N_2O technique. This incidence was further reduced (24%) when opioids were avoided. Discharge times averaged 2 hours, but postoperative restlessness was more common than in patients receiving an inhalational anesthetic. Splinter and Rhine [65] reduced the incidence of vomiting after strabismus surgery in children to 9 percent using a low-dose ondansetron (50 mug/kg IV) and dexamethasone (150 mug/kg IV) regimen. The emetic symptoms associated with strabismus surgery may be caused by eye muscle manipulation or pain that induces an OCR vagal response. Prophylactic treatment with atropine or glycopyrrolate, however, does not decrease the incidence of PONV. [63] The OCR, commonly elicited in response to traction of the extraocular muscles, is frequently associated with strabismus surgery. Previous studies have noted an increased incidence of OCR during strabismus surgery under propofol infusion. [64]

In addition to the usual practice regarding pediatric management, the following measures should be considered to decrease the incidence of PONV after strabismus surgery:

1. Minimal use of opioids for pain management.
2. The use of propofol to maintain general anesthesia without N_2O supplementing a potent volatile agent.
3. Administration of a serotonin ($5HT_3$) antagonist and metoclopramide (0.15 mg/kg IV) during anesthesia.
4. Insertion and removal of a gastric tube after induction of anesthesia to decompress the stomach.
5. Gentle surgical manipulation of the eye muscles.
6. Adequate hydration of the patient with intravenous crystalloids.
7. Placement of lidocaine near the extraocular muscle by the surgeon, to minimize afferent impulses and postoperative pain on awakening.

Selective $5HT_3$-receptor antagonists such as ondansetron or dolasetron are effective antiemetics as treatment for PONV. [65] [66] [67] [68]

Congenital Syndromes Involving Eye Pathology

The special problems of pediatric ophthalmic anesthesia make it almost a specialty in itself. [69] Congenital syndromes in which eye abnormalities are only one manifestation of a multisystem disorder present problems of overall general anesthesia management.

Patients with homocystinuria, a rare inborn error of amino acid metabolism, may present with subluxation of the lens or glaucoma. These patients are susceptible to thromboembolic complications during general anesthesia. Hyperinsulinemia and hypoglycemic convulsions are also common. Safe anesthesia management requires pretreatment with acetylsalicylic acid and dipyridamole, adequate hydration with glucose or low-molecular-weight dextran, and maintenance of good arterial blood pressure and peripheral

vasodilation. Moreover, to prevent venous stasis, the patient should wear elastic stockings and should walk as soon as possible.

Patients with Marfan syndrome, a disorder of connective tissues, have subluxed lenses and detached retinas. Anesthesia management should consider the possibility of heart valve defects, thoracic aneurysms, and kyphoscoliosis. Children with Down syndrome often have strabismus and cataracts. Of concern to the anesthesiologist are hypotonia, heart defects, hypothyroidism, macroglossia, and seizures, all of which are associated with this syndrome.

Patients with Sturge-Weber syndrome may have secondary glaucoma. This condition consists of cavernous cutaneous angiomas of the face, cerebral cortex, and lower airway. Seizures may occur.

Retinitis proliferans, vitreous hemorrhages, and retinal detachment may occur in patients with homozygous sickle cell disease or thalassemia. Anesthesia management involves the treatment of anemia and avoidance of conditions that trigger sickle cell crisis, such as dehydration, acidosis, hypoxia, infection, venous stasis, and hypothermia.

Patients with craniofacial abnormalities, as in Crouzon disease, Alport syndrome, or Kneist syndrome, may have myopia, detached retinas, exophthalmos, or glaucoma. The trachea can be difficult to intubate in these patients. Chapters 25 and 59 also discuss congenital syndromes involving eye disorders.

Complications

Stead [72] reviewed the mortality and morbidity from coexisting disease in patients having ophthalmic surgery. Wu and Schachat [73] reported that 0.7 percent of ophthalmic patients required transfer to medical service, usually for cardiacrelated conditions. Stead reviewed morbidity from the systemic effects of ophthalmic drugs and complications due to anesthetic techniques; monitored anesthesia care and the risks of regional eye blocks, including optic nerve trauma, ocular penetration, retrobulbar hemorrhage, corneal injury, oculocardiac reflex, and myotoxicity of local anesthetics on extraocular muscles; and discussed general anesthesia, the risk of nausea and vomiting, the results of ophthalmic surgery, and the effect of general anesthesia, intubation, and N_2O on IOP.

Oculocardiac Reflex

The OCR may be induced by pressure on the eyeball, traction on the extraocular muscle, orbital hematoma, ocular trauma, and eye pain. The OCR is a trigeminovagal reflex, manifested by cardiac arrhythmias such as bradycardia, nodal rhythm, ectopic beats, ventricular fibrillation, or asystole. The afferent pathway follows the long and short ciliary nerves to the ciliary ganglion and then to the gasserian ganglion along the ophthalmic division of the trigeminal nerve (the fifth cranial

nerve). These afferent pathways terminate in the main trigeminal sensory nucleus in the floor of the fourth ventricle. The efferent impulses start in the muscles of the vagal cardiac depressor nerve, causing negative inotropic and conduction effects.

The OCR occurs most often during strabismus surgery in children, but it also occurs occasionally during retinal surgery at the time of injection for retrobulbar block, and even during nonophthalmic surgery if pressure is placed on the eyeball. The reported incidence of OCR varies considerably (32-90%), depending on the intensity of observation and the definition of arrhythmias. Transient cardiac arrest may occur as frequently as in 1 in 2,200 cases of strabismus surgery.

The force and type of stimulus seem to influence the incidence of OCR. [70] The more acute the onset and the stronger and more sustained the traction, the more likely OCR is to occur. Although the medial rectus muscle is commonly believed to be the most sensitive in eliciting an OCR, Blanc et al [70] did not find this to be necessarily true. This misconception may result from two lines of reasoning. The medial rectus muscle is less accessible and therefore may require more pulling for exposure. Moreover, the medial rectus is the muscle manipulated most often in strabismus surgery and may therefore be more refractory to fatigue.

Hypoventilation and increased arterial CO_2 partial pressures significantly increase the incidence of bradycardia during strabismus surgery. Intramuscular administration of atropine, gentle manipulation of extraocular muscles, and control of ventilation to maintain normocarbia should reduce the incidence and severity of OCR. [70]

The intravenous administration of atropine to prevent or treat OCR is controversial. Atropine may cause bigeminy and increase ectopic beats, especially when halothane is the primary anesthetic. These arrhythmias are more persistent than the OCR response. Mirakhur et al [71] noted that intramuscular premedication with atropine reduced the incidence of OCR from 90 to 50 percent. However, intravenous administration of atropine or glycopyrrolate was even more effective in preventing OCR. Although the peak effect of glycopyrrolate did not occur for 3 to 4 minutes, glycopyrrolate did not produce as great a tachycardic response as did atropine.

Although bradycardia is the most common manifestation of OCR, other abnormal rhythms (nodal, junctional, ectopic atrial, or even serious ventricular arrhythmias) are possible. Therefore, the ECG should always be monitored continuously during ophthalmic surgery. Because the OCR ceases when stimulation (pressure or traction) ends, the surgeon and anesthesiologist should not hesitate to communicate during procedures involving the possibility of an OCR.

The first step in treating OCR is to stop stimulation by the surgeon before the arrhythmia progresses to sinus arrest. Fortunately, sustained and repeated stimulation usually causes the OCR to fatigue. If arrhythmias persist, treatment with atropine (0.007 mg/kg IV) and a local injection of lidocaine into the eye muscle may be necessary. If the patient still seems unusually sensitive to manipulation of the extraocular muscles, the anesthesiologist should ensure the adequacy of depth of general anesthesia, the existence of normocarbia, and the gentleness of surgical manipulation.

Systemic Effects of Eye Medications

Both the anesthesiologist and the ophthalmologist must be aware that eyedrops are readily absorbed through hyperemic incised conjunctivae. Although small in volume, these

drops contain highly concentrated medication that can produce systemic results. Infants and elderly patients are most susceptible. Systemic effects can be minimized by using lower concentrations, limiting instillation to only one or two drops, and promptly occluding the nasolacrimal duct at the time of instillation. [2] [74] Eye medications that cause systemic effects include phenylephrine, epinephrine, timolol, echothiophate iodide, acetylcholine, cyclopentolate, scopolamine, atropine, and cocaine (Chs. 13 and 14).

Phenylephrine

Phenylephrine eyedrops can cause severe hypertension, arrhythmias, headache, tremulousness, and myocardial ischemia. Because a single drop of 10 percent phenylephrine ophthalmologic solution contains 4 mg of phenylephrine, 2.5 percent solutions are recommended.

Epinephrine

Topical ocular epinephrine (a 2% solution contains 0.8 mg per drop) can cause tachyarrhythmia, premature ventricular beats,

Timolol

Timolol is a beta-adrenergic receptor blocking drug administered as eyedrops to treat glaucoma. Systemic effects include bradycardia, hypotension, congestive heart failure, and exacerbation of asthma and myasthenia gravis.

Echothiophate

Echothiophate iodide eyedrops act systematically to reduce plasma cholinesterase activity significantly. Four to 6 weeks are required for activity to recover after cessation of the drops. Patients treated with these eyedrops may have a prolonged response to succinylcholine or to mivacurium and ester-linked local anesthetics during this time (Chs. 13 and 14).

Acetylcholine

Acetylcholine may be used to produce miosis after cataract surgery. Systemic effects include bradycardia, hypotension, bronchospasm, and increased bronchial secretions and salivation. These undesirable effects may be prevented by the intravenous administration of atropine.

Cyclopentolate

Cyclopentolate eyedrops are used in a 2 percent concentration to dilate the pupils. CNS toxicity, resulting in effects such as disorientation, dysarthria, and seizures, has been reported. Less concentrated (0.5%) solutions are recommended for pediatric use.

Scopolamine

Scopolamine eyedrops can cause disorientation and hallucinations in elderly and very young patients.

Cocaine

Cocaine blocks reuptake of norepinephrine at the nerve terminal and usually produces sympathomimetic effects (Ch. 13) . However, after ocular instillation, very low plasma levels of cocaine can produce severe bradycardia. Topical application of cocaine is no longer recommended for ophthalmic surgery. However, during dacryocystorhinostomy, cocaine is used topically for vasoconstriction and topical anesthesia.

Postoperative Eye Pain

Postoperative eye pain is usually caused by corneal abrasion or acute glaucoma attack, the former being the more common source. During general anesthesia, the blinking reflex is lost, and basal and reflex tear production decreases. A dry, exposed cornea is at high risk for abrasion. Intraoperative measures such as using nonionic petroleum-based eye ointment, avoiding rubbing of the eye, and taping or suturing the eyelids closed are essential in preventing eye injury. Because eye

ointment can cause irritation, it should be used sparingly and only for procedures lasting longer than 60 minutes.

Corneal abrasion pain is a specific eye pain manifesting as the sensation of the presence of a foreign body in the eye, tearing, conjunctivitis, and photophobia. Corneal abrasion pain is made worse by blinking. The abraded section of cornea may be seen directly as a dull nonreflective patch or as a positive area on fluorescein staining. Treatment requires application of antibiotic eye ointment and covering of the eye with a patch for at least 48 hours. Topical application of anesthetic drops and steroids to the cornea is contraindicated because these drugs retard healing. If pain persists more than 24 hours, an ophthalmologist should be consulted.

Acute glaucoma occurs as severe, diffuse, periorbital pain in dry, pale eyes having dilated pupils. No photophobia, tearing, or conjunctivitis occurs. Vision may decrease, and IOP increases. Treatment to reduce IOP includes intravenous administration of either 20 percent mannitol (1 g/kg) over 30 minutes or 500 mg acetazolamide over 5 minutes.

ANESTHESIA FOR NOSE AND THROAT SURGERY

Functional Anatomy of the Larynx

The anesthesiologist confronted with decisions regarding airway management and difficult endotracheal intubations for patients with compromised airways must have a thorough knowledge of the physical and functional anatomy of the larynx. The larynx serves three functions: protection of

the airway, respiration, and vocalization. [75] [76] The protective function occurs primarily through reflex and involuntary processes. The glottic closure reflex activated by swallowing is a basic primitive reflex elicited by many different sensory stimuli that affect the superior laryngeal nerve. The false vocal cords (ventricular folds) can act as a muscular valve that closes because of pressure from below to prevent egress of air. The true vocal cords constitute a one-way entrance valve that resists pressure from above but not from below. [75] Thus, during spasm of the true vocal cords, sudden positive pressure from above may not in itself be sufficient to move air into the lungs.

The nerve supply to the larynx occurs through the vagus nerve (the tenth cranial nerve). Sensory innervation is provided primarily by the superior laryngeal nerve, which arises from the inferior ganglion of the vagus. The internal branch of the superior laryngeal nerve consists mostly of sensory fibers; a few motor fibers lead to the arytenoid muscles. This internal branch further divides into upper and lower branches. The upper branch provides sensory innervation to the mucosa of the lower pharynx, both surfaces of the epiglottis, the vallecula arytenoepiglottic folds, and the laryngeal vestibule. The lower branch passes close under the surface of the mucosa of the pyriform fossa and supplies sensory innervation to the arytenoepiglottic folds and posterior rima glottidis. Sensory innervation below the true vocal cords and into the upper trachea is provided by the recurrent laryngeal nerves. Sensory innervation is denser at the glottic inlet, and there are more touch receptors at the lower half of the true vocal cords; in addition, the epiglottic and supraglottic area contain chemical and thermal receptors. [77] The sensory components of the internal superior laryngeal nerve also include joint, pressure, and stretch receptors from the intrinsic laryngeal muscles. The afferent response impulses from these receptors track back to the tractus solitarius of the brain stem. [75] The recurrent laryngeal nerves provide motor innervation to all the intrinsic laryngeal muscles, except the cricothyroid and inferior pharyngeal constrictors, which receive motor innervation from the external branch of the superior laryngeal nerve.

The intrinsic laryngeal muscles consist of the following:

1. Posterior cricoarytenoids abduct the vocal cords and widen the glottic chink during respiration.
2. Thyroarytenoids and lateral cricoarytenoids adduct the vocal fold (false cords).
3. Interarytenoids close the posterior gap in the glottis (posterior commissure) by abduction.
4. Cricothyroids adduct and tense the true vocal cords.
5. The vocalis muscle also shortens the true vocal cords.
6. Arytenoepiglottis and oblique arytenoids narrow the glottic inlet by adduction of the arytenoepiglottic folds.

The recurrent laryngeal nerve can be injured by endotracheal intubation, neck surgery, or stretching of the neck during surgery. The resulting tone and position of the vocal cords depend on whether the injury is unilateral or bilateral and on whether the external branch of the superior laryngeal nerve (the motor innervation of the cricothyroid muscle, which shortens the vocal cords) is also involved.

Unilateral recurrent laryngeal nerve injury causes the cord on the injured side to assume a paramedian position because the unopposed action of the ipsilateral cricothyroid muscle adducts the cord toward the injured side. If the external branch of the superior laryngeal nerve is also involved, the true vocal cord will be more medial and less tense. The voice is weak and hoarse, and the risk of aspiration increases. Eventually, the muscles compensate somewhat, and the cord becomes positioned more medially.

Laryngospasm

Laryngospasm is an exaggerated prolonged response of the protective glottic closure reflex, mediated by the superior laryngeal nerve in response to irritating glottic or supraglottic stimuli such as the presence of blood, food, vomitus, or a foreign body; instrumentation or manipulation of the endolarynx can all induce laryngospasm.

This strong glottic closure reflex can persist even after irritation of the mucosa ceases. [77] During a fully formed laryngospasm, the false cords and epiglottic body come together firmly. There is no air flow, no vocal sound, and the true vocal cords cannot be seen. The extrinsic muscles of the larynx (especially the thyroid) may also be involved to help create a muscular ball-valve mechanism.

Intravenous administration of lidocaine, topical application of cocaine, and deep levels of anesthesia attenuate the effect of the stimulus and the activity of the superior laryngeal nerve, thereby decreasing the likelihood of prolonged glottic closure. Incremental doses of intravenous fentanyl up to 200 mug depressed the protective airway cough reflex, but not the laryngospasm reflex. [78] Hypoxia and hypercarbia decrease postsynaptic potentials and brain-stem output to the superior laryngeal nerve, resulting in less vigorous glottic closure. [75] Thus, laryngospasm eventually ceases spontaneously as hypoxia and hypercarbia develop. Stimulation of the superior laryngeal nerve may also inhibit medullary inspiratory motoneurons, thereby decreasing phrenic nerve activity and causing a reflex apnea.

Head and Neck Surgery

Major surgery for cancer of the head or neck includes laryngectomy, radical neck dissection, hemimandibulectomy, and radical sinus surgery. Anesthesia management for surgery of malignant tumors of the larynx or pharynx was reviewed in detail by Morrison et al [76] and Daugherty. [79] Joseph et al [80] reviewed the complications and anesthesia considerations for head and neck and reconstructive surgery.

These patients are frequently heavy drinkers and smokers who have bronchitis, pulmonary emphysema, and/or cardiovascular disease. If the tumor interferes with eating, then weight loss, malnutrition, anemia, dehydration, and electrolyte imbalance can be significant. These patients are evaluated and treated as representing difficult endotracheal intubation and potential problems in airway management, as discussed later and in Chapter 39 .

Generally, the use of an inhalation anesthetic dilates the bronchi, depresses airway reflexes, permits the use of high concentrations of oxygen, if necessary, and may produce moderate hypotension (systolic blood pressure 85-90 mm Hg). When a 10- to 15-degree head-up tilt is added, the resulting

moderate hypotension may be sufficient to diminish blood loss without resorting to deliberately inducing hypotension. [57] Induced hypotension is not without risk in debilitated patients and may be unnecessary and dangerous [76] [81] (Ch. 41).

During radical lymph node dissection of the neck for carcinoma, manipulation of the carotid sinus may elicit a vagal reflex that causes bradycardia, hypotension, or even cardiac arrest. Furthermore, trauma to the right stellate ganglion and cervical autonomic nervous system during right radical neck surgery can prolong the QT interval and may lower the threshold for ventricular fibrillation. [82] Severe tachyarrhythmia and cardiac arrest have been reported in these cases, especially in association with hypokalemia.

Although venous air emboli are usually associated with neurosurgical procedures, open neck veins create the possibility of air emboli during head and neck surgery (Ch. 52) . The incidence of air emboli during this type of surgery is low. An end-tidal CO_2 monitor indicates a sudden fall in CO_2 tension, and a precordial Doppler probe picks up the murmur characteristic of venous air embolism. Hypotension and arrhythmias are late signs of air emboli. [76] Treatment includes the following: increasing venous pressure (through the use of positive-pressure ventilation or jugular vein compression); slight Trendelenburg, left lateral positioning; discontinuation of N_2O; use of 100 percent oxygen; and, if possible, aspiration of the air through a central venous catheter.

Postoperative considerations consist of care of the tracheostomy, use of humidified oxygen, institution of chest physical therapy, and the obtaining of a chest radiograph to eliminate the possibility of pneumothorax. The position of the tracheostomy tube should be checked, and possible subcutaneous emphysema and hematoma formation should be sought.

Thyroid Surgery

Perioperative complications of thyroid surgery include airway obstruction secondary to compressing hematoma, hypocalcemic tetany, and recurrent or superior laryngeal nerve paralysis. [80] The recurrent laryngeal nerve (RLN) is at risk for injury during thyroid and parathyroid surgery, resulting in vocal cord paralysis and even airway obstruction. The incidence of permanent nerve injury is 0.2 to 1.0 percent. [80] Spontaneous and evoked electromyography are used to monitor RLN function during surgery. [83] Nerve action potentials can be monitored using a carefully placed special Nerve Integrity Monitor (Xomed-Treace, Jacksonville, Fla) endotracheal tube [84] [85] or surface RLN postcricoid laryngeal electrodes. [86]

Endoscopic Sinus Surgery

The complications of endoscopic sinus surgery are infrequent and are not usually related to the type of anesthesia. Venous air embolism, eye trauma, cerebrospinal fluid leak, excessive bleeding, [87] focal neurologic deficit, and death have been reported. [88]

Trauma

Open and Closed Injuries to the Neck and Larynx

There is no classic or standard presentation of laryngeal trauma (Ch. 62). [89] [90] [91] [92] Often, internal damage is extensive but external signs are absent or only minimal (e.g., mild redness, minor lacerations, hematoma, or subcutaneous emphysema). Stridor and cyanosis may not be present. These injuries most often result from high-speed blunt trauma (motor vehicle accidents, gunshot wounds, or falls). For example, velocity-deceleration accidents can produce severe closed neck injury to the trachea and larynx. [92] Inertia carries the body forward, hyperextends the neck, and forces these vulnerable anterior cervical structures against the fixed cervical vertebrae. Tracheal damage can also be caused by a burst injury that produces simple tears, dislocation of arytenoid cartilages, disruption of the cricothyroid joint (causing a floppy vocal cord), and bleeding (leading to hematoma or edema in the paratracheal/arytenoepiglottic fold space). [92] Unfortunately, more obvious injuries such as a fractured femur can divert the physician's attention from the more subtle signs of airway problems (e.g., hoarseness, weak voice, or tracheal tugging).

The following signs of airway problems may be delayed: increasing stridor, wheezing, coughing, hemoptysis, retractions of the airway, changes in voice (loss of voice, hoarseness, weak voice), and difficulty in speaking or swallowing. Loss of neck prominences and increasing crepitus indicate torn mucosa in the trachea, pharynx, larynx, or esophagus. However, the amount of crepitus does not always correlate with the size of the tear.

An air leak can dissect into the paratracheal space and produce a pneumothorax. Such leakage increases with straining and application of positive-pressure ventilation. Regardless of size, all open neck injuries should be explored, because mortality is as high as 5 percent. Moreover, the possibility of a cervical spine fracture should always be considered when head or neck trauma has occurred.

A review of airway management in a known or suspected cervical spine injury indicated that early neck immobilization followed by orotracheal intubation, while an assistant applied in-line stabilization, had the lowest incidence of adverse events. There is no evidence that nasotracheal intubation is necessarily safer. [93]

Certain age-related differences in anatomy may determine the type of injury and the ability to tolerate a compromised airway. The larynx of the infant and young child is positioned high in the neck and is shielded by the mandible. Cartilage is more elastic and flexible in the child, who is therefore less likely to sustain a fracture than is an adult. However, because of weaker connecting membranes, the child is more vulnerable to intercartilage rupture. [89] Moreover, because their airways have a small diameter at the subglottic region of the cricoid cartilage, young children do not tolerate edema or compromise of the airway as well as do adults.

There are many vital structures at risk in the neck (e.g., the recurrent laryngeal nerve, the carotid or inferior thyroid arteries, and major veins). Thus, mismanagement of neck

---

and laryngeal injuries has the potential for acute disaster. Airway problems are dynamic. Mild stridor can worsen an air leak, aggravating subcutaneous emphysema and, in turn, increasing airway obstruction and stridor. The onset of cyanosis may be followed in rapid succession by myocardial ischemia, hypotension, hypercarbia, and loss of consciousness. Therefore, the anesthesiologist needs as much information as possible when attending to the problem airway. Monitoring of these patients from the emergency department to the operating room should include an ECG, pulse oximeter, and observation of the state of consciousness.

Blind passage of an endotracheal tube can increase damage or obstruction, induce laryngospasm, or create a false passage through a tear in the mucosa. Whenever possible, when dealing with laryngeal trauma, the trachea should be intubated under direct vision using a laryngoscope, rigid bronchoscope, or fiberoptic laryngoscope. A careful mask induction of anesthesia with no application of positive pressure, followed by bronchoscopic examination, may be safe in selected cooperative patients (i.e., those with no full stomach or bleeding in the airway). Tracheostomy using local anesthesia is frequently a safe approach to laryngeal trauma and is the only guarantee of establishing an airway when dealing with a possible laryngotracheal disruption.

Facial Injuries

The evaluation and anesthetic management [92] [94] [95] of maxillofacial injuries have been discussed extensively. The most common fractures involve the mandible and midface (Le Fort I, II, and III fractures of the maxilla). Because of the presence of loose teeth, blood, and displaced fragments, all these fractures may be accompanied by some degree of compromised airway. A first priority is to secure the airway by placing the patient in the lateral position, pulling the mandible or maxilla forward, and clearing the oropharynx of blood or loose teeth. If this action is not successful, endotracheal intubation or emergency tracheostomy should be considered. These patients may also have head trauma or fractures of the cervical spine.

Mandible fractures, if unilateral, remain stable. Bilateral mandibular fractures are unstable. The posterior fragment may be pulled medially and upward, causing the base of the tongue to obstruct the pharynx. Trismus and lingual hematoma or edema may contribute to respiratory obstruction. [92] If no trismus or mechanical problem

exists, a routine rapid-sequence induction of anesthesia and tracheal intubation may proceed. Otherwise, induction of anesthesia with an inhaled anesthetic, or awake endotracheal intubation, is indicated. Although the possibility of interdental fixation may seem to make use of a nasotracheal tube preferable, the easiest route of intubation should be chosen. Later, during surgery, the oral tube can be removed and a nasal tube inserted. Patients undergoing interdental fixation should be given an antiemetic drug, undergo awake tracheal extubation, and be placed on their side with scissors/wire cutter at the bedside.

Midface fractures (Le Fort fractures of the maxilla) [92] often present difficult clinical problems. A Le Fort I fracture is a simple horizontal fracture of the lower maxilla that produces only a mobile palate. A Le Fort II fracture, a triangular extension of the Le Fort I fracture, involves two oblique fracture lines along the malarmaxillary suture to the floor of the orbit and the base of the tongue. The maxillae are displaced backward and may be free floating. The Le Fort III fracture is a high-level transverse fracture above the malar bone and through the orbits. It is characterized by complete separation of the maxilla from the craniofacial skeleton, epistaxis, and a flat dish-face deformity. Tears in the dura occur in 25 percent of all Le Fort II and III fractures, as evidenced by leakage of cerebrospinal fluid. Orotracheal intubation is necessary when intranasal damage is a possibility. Attempted passage of a nasogastric or nasotracheal tube may cause bleeding, mucosal dissections, and further damage. The course of these tubes is uncertain; they can enter the maxillary antrum, the orbit, the base of the skull, or even the cranium.

Special Clinical Problems Involving the Airway

Microlaryngoscopy

Many different anesthesia techniques have been advocated for microlaryngeal endoscopic surgery (Ch. 39) . The common goal of these techniques is to provide the surgeon with a clear view, immobile field, and sufficient room in which to work. The anesthesiologist's objectives are to protect the trachea, to ensure good ventilation and oxygenation, to minimize secretions and reflexes, and to promote rapid awakening and return of protective airway reflexes. Morrison et al [76] described the advantages and disadvantages of these techniques.

Because of the varying degrees of upper airway disorder and the need for rapid awakening in these brief (30-40 min) procedures, routine premedication should be avoided. An antisialogogue, such as glycopyrrolate, which facilitates drying of oral secretions, may be helpful. If sedation is necessary to decrease anxiety, intravenous titration of 1-mg increments of a benzodiazepine such as midazolam may be given with monitoring in the preinduction area.

Special attention must be devoted to understanding the extent of the upper airway disorder that brings these patients to surgery. For example, preoperative decisions about tracheal intubation and anesthesia management depend on whether the abnormality is a small lesion (e.g., a vocal cord polyp or carcinoma *in situ*), a large and potentially obstructing lesion such as a papillomatosis, or a large and friable supraglottic tumor that will completely obstruct the glottic opening. If there is any question about the airway, direct laryngoscopic examination should be performed (after topical laryngeal block) [96] [97] in the awake patient to assess the difficulty of intubation.

In only approximately 5 percent of microsurgical procedures on the larynx do the pathologic conditions involve the lower third of the vocal cords or the posterior commissure area. Therefore, for 95 percent of these procedures, a small, long (5 mm × 31 cm) endotracheal tube having a highvolume low-pressure cuff can be used without obscuring

the surgeon's view. [76] [98] The posterior commissure area may then be inspected at extubation or by moving the tube aside. Adequate oxygenation and ventilation can be monitored in adults by controlled ventilation through a small (4.5-5.0-mm ID) endotracheal tube. [99] The use of a small endotracheal tube allows for application of positive-pressure ventilation, ensures the absence of gastric distention, facilitates control of oxygenation and elimination of CO_2, protects the trachea, and allows for a variety of general anesthesia regimens and an indefinite time period for the surgeon.

Another method of providing anesthesia for microlaryngoscopy places a small catheter between the vocal cords for insufflation of anesthetic gases at high flows. This technique does not protect the trachea or allow for use of positive-pressure ventilation. High concentrations of the inhaled anesthetic must be used to overcome atmospheric dilution, and, unfortunately, exhaled gas is blown back at the surgeon and into the operating room. There may also be motion of the vocal cords.

Jet ventilation using the Venturi entrainment effect provides anesthesia and ventilation without the use of an endotracheal tube. [76] [100] The surgeon has an unobstructed view of the larynx. Keeping the tip of the jet within the laryngoscope avoids airway barotrauma and provides a clear view. Alignment of the laryngoscope with the tracheal axis is essential. The vocal cords need to be relaxed fully, and pathologic conditions in the airway must not be so large as to obstruct airflow into the trachea. The jetted gas must have free egress, and motion of the chest wall must be monitored at all times. Ventilation begins at low pressures (30-50 psi). Inspiration is 1.5 seconds, passive expiration is 6 seconds, and ventilatory rate is 6 to 7 breaths/min. [76] The jet Venturi technique is contraindicated in children, obese patients, and patients with bullous emphysema. When large tumors are present in the upper airway, debulking of the tumor using general anesthesia and a tracheal tube should be accomplished first, [76] because the jet technique may force blood or tumor tissue into the lungs and gas into the stomach.

An apneic technique using alternate tracheal intubation and no tube during endoscopic removal of papillomas in children has been used successfully by Weisberger and Miner. [101] Moreover, Babinski et al [102] described the use of high-frequency positive-pressure ventilation during anesthesia for laryngoscopy. Small tidal volumes provide good gas exchange at low airway pressures. Respiratory rates of 60 breaths/min at 60 to 100 psi are used by means of a stiff 3.5-4.0-mm catheter placed through the vocal cords. The risk of barotrauma and pneumothorax is lower, especially in patients with obstructive airway disease.

Good muscle relaxation is an essential part of anesthesia management for microsurgery of the larynx. A succinylcholine drip infusion may be considered for very brief cases. If the procedure is expected to last at least 30 minutes, use of a neuromuscular blocking drug such as vecuronium, rocuronium, or mivacurium for tracheal intubation allows return of muscle strength and spontaneous respiration for safe extubation.

Stimulation of the larynx can induce many reflex responses that produce hypertension, tachycardia, and arrhythmias. Intravenous administration or topical application of lidocaine and small doses of fentanyl (1-2 mug/kg IV) will help to moderate the sympathetic response. beta-Adrenergic receptor blocking drugs may also be helpful.

Propofol induction (2 mg/kg IV) and infusion (10 mg/kg/h) combined with fentanyl (1-2 mug/kg IV) supplementation, topical anesthesia of the larynx, and appropriate muscle relaxation have been used for microlaryngoscopy procedures. [103] Monitoring (pulse oximeter, ECG, blood pressure, and end-tidal concentrations of CO_2) is especially important, because the incidence of myocardial infarction or ischemia after microlaryngoscopic procedures has been reported to be 1.5 to 4.0 percent. [104]

Laser Surgery of the Upper Airway

CO_2 and neodymium-yttrium aluminum garnet (Nd:YAG) lasers are frequently used for microsurgery of the upper airway and trachea (Ch. 64). The surgical advantages of using lasers include less bleeding, the ability to coagulate small vessels, maintenance of sterile conditions, less tissue reaction, increased precision of dissection, preservation of normal tissue, and, in the case of Nd:YAG lasers, the ability to transmit the beam by fiberoptics. Excellent articles by Van der Spek et al [105] and Hermens et al [106] reviewed the physics and medical uses of lasers, including safety and implications for anesthesia management.

The American Society for Testing and Material (ASTM) Subcommittee F29.02.10 of the Anesthesia Patient Safety Foundation developed guidelines for the provision of safe anesthesia during laser surgery for the upper airway. These guidelines compare and comment on the advantages and disadvantages of several anesthetic techniques and laserresistant endotracheal tubes. [107]

Light amplification by stimulated emission of radiation (LASER) produces a beam of light that is monochromatic (of the same wavelength) and "coherent" (all the photons are moving in the same direction). Lasers exist in the infrared, visible, and ultraviolet regions of the electromagnetic spectrum. Depending on the emission medium used, such light can be focused into an extremely small point, thereby achieving a very high-power density. This beam of high-power density is capable of vaporizing biologic tissue. Each laser medium emits radiation of a specific wavelength, which determines how the beam will interact with biologic tissue. Lasers are operated in short pulses, long pulses, or continuously. The continuous-wave CO_2 laser, which produces radiation having a wavelength of 10 mm, is strongly absorbed by water, damaging tissue surfaces to a depth of 200 mm. For this reason, the CO_2 laser is suitable for removing lesions on the vocal cords and in the larynx.

The Nd:YAG laser, a short-pulsed, high-powered glass laser producing light with a wavelength of 1.06 m, can be transmitted by fiberoptics. Energy from Nd:YAG or

argon (wavelength of 0.5 mm) lasers is absorbed preferentially by hemoglobin and pigmented tissue, has deep, penetrating effects, and is useful in treating detached retinas.

Reflection and scatter of laser beams can cause immediate or delayed injury (perforation, hemorrhage, pneumothorax) to normal tissue. The CO_2 laser reacts at the surface, causing corneal damage, whereas lasers of shorter wavelength (argon, Nd:YAG) can pass through the cornea and damage the retina. Therefore, the patient's eyes must be

taped closed and covered with moist gauze. Nontarget tissue should be protected by moist gauze covering; in addition, alignment of the laser should be checked, and immobility of the patient should be ensured. Operating room personnel should wear appropriately colored glasses or goggles to absorb the wavelength emitted by the laser in use. Laser hits on the skin cause a pinpoint burn. Instruments used with lasers should have a dull matte finish, to decrease reflection. The energy density of reflected beams decreases greatly as the distance from the focal point increases.

Fire is a major hazard. As a source of intense heat, lasers can ignite various materials used in anesthesia practice (endotracheal tubes). The CO_2 laser beam can penetrate an endotracheal tube and ignite a fire, which would then be supported by oxygen and N_2O. [108] [109] The subglottic, epiglottic, and oropharyngeal areas are the regions usually involved. Furthermore, inhalation of smoke can cause chemical injury, bronchospasm, edema, and respiratory failure. Red rubber tubes char, melt, and then burn, producing carbon monoxide gas. Polyvinyl chloride tubes burn more vigorously, producing hydrogen chloride, a pulmonary toxin.

In 1979, the reported incidence of airway fires during CO_2 laser surgery was 0.4 percent. [106] [110] However, with the use of modern equipment, techniques, and gas mixtures according to the Anesthesia Patient Safety Foundation guidelines for anesthesia for laser surgery, [107] the incidence of airway fires during laser surgery should be negligible.

To reduce the hazard of fire during laser surgery on the airway, not more than 30 percent oxygen in nitrogen or helium should be used in the gas mixture. N_2O supports combustion, as does oxygen. Sixty percent helium is an effective fire quencher if the CO_2 laser is used at an energy level of 10 watts or less. [111] The use of selected, protected endotracheal tubes reduces the risk of fire. [112] Commercially available laser-safe endotracheal tubes should be used. These may be metal, aluminum, or copper foil [113] -wrapped, laser-resistant materials [114] or double-cuffed silicone-coated metal tubes. These tubes may be recommended as resistant to the CO_2 laser but not to the Nd:YAG laser. [115]

An alternative is to use a Venturi ventilation technique with no endotracheal tube. [100] However, fire in the airway can still be a risk, because tissue may dry up, carbonize, and ignite in the high jet flow of oxygen.

Treatment of airway fires requires temporary discontinuation of oxygen, removal of the burning endotracheal tube, reintubation of the trachea, and flushing of the pharynx with cold saline. Later, a rigid bronchoscope should be used to check for damage and the presence of foreign bodies (e.g., pieces of burned tube). Administration of humidified gas, steroids, and antibiotics, the use of controlled ventilation, and even tracheostomy may be necessary. Monitoring includes the use of chest radiographs, pulse oximetry, ECG, and analysis of arterial blood gases (Ch. 64).

Laser surgery of the tracheobronchial tree is performed with CO_2 or Nd:YAG lasers by means of a rigid bronchoscope. This instrument allows better visualization, access, control of bleeding, suctioning, and irrigation. [116] The literature on ventilation and anesthesia technique for bronchoscopic laser surgery is not consistent. Reviewing many techniques, Van der Spek et al [105] discussed advantages and disadvantages and described their own successful clinical practices.

The management of subglottic laser surgery presents challenges for the anesthesiologist. Bargainner et al [117] analyzed these challenges and outlined safe methods using a ventilating laryngoscope and jet ventilation, as well as discussing potential complications (Ch. 68).

Either a CO_2 laser or an Nd:YAG laser is used in subglottic laser surgery. The Nd:YAG laser penetrates tissue (4-5 mm), has hemostatic properties, and can be conducted by a single optic fiber. Even foil-wrapped and special laser-shielded endotracheal tubes have been perforated and ignited within 12 seconds during continuous Nd:YAG laser exposure. [118]

Postoperative considerations include head-up positioning to decrease edema, careful observation for bleeding and edema, and administration of humidified oxygen. If a Venturi jet technique has been used, complications such as pneumothorax or respiratory failure (from the forcing of blood or tissue particles into air passages) may occur within the first 2 hours. Steroids and racemic epinephrine mist may be helpful in controlling laryngeal edema.

Tonsillectomy

Improved monitoring and postanesthesia care have reduced mortality from tonsillectomy to almost zero (Ch. 59) . However, management of the airway during this procedure can still present a challenge to the anesthesiologist. The goal of anesthesia for elective tonsillectomy is to provide deep general anesthesia that prevents reflex-induced hypertension, tachycardia, or arrhythmias. Muscle relaxation is required to allow easy placement of the mouth gag and to prevent bucking, coughing, or straining. Rapid recovery to consciousness and the return of protective airway reflexes are also desirable. The safest practice is probably to extubate the trachea when the patient is awake. The use of the reinforced, flexible laryngeal mask airway for tonsillectomies, [119] [120] [121] adenoidectomies, [122] and nasal surgery [123] provides excellent airway protection and good field exposure with less eventful recovery, cough, or airway obstruction on emergence.

Postextubation stridor and laryngospasm following adenotonsillectomy can be minimized by applying topical 2 percent lidocaine (maximum 3 mg/kg) to the glottic and supraglottic areas before intubation. This proved as effective as giving intravenous lidocaine (1 mg/kg) just prior to extubation, but without higher sedation scores. [124]

Preoperative evaluation includes checking for loose teeth (especially in the 4- to 7-year-old patient), ensuring there has been no recent ingestion of aspirin, and determining coagulation variables. Premedication is usually not necessary. Barbiturates are of little use in brief upper airway surgical procedures, which require rapid return of protective airway reflexes and may render the larynx more susceptible to laryngospasm during a slow awakening from the effects of barbiturates.

A technique using fentanyl and a short-acting muscle relaxant with a volatile inhaled anesthetic is satisfactory. A topical spray of 4 percent lidocaine on the tonsil area will help to decrease the anesthetic requirement, the incidence of arrhythmias, and postoperative stridor and laryngospasm. [124] [125] These patients should be well hydrated with a solution of balanced crystalloid (3-5 mL/kg/h). Blood loss during tonsillectomy is difficult to estimate and may reach

5 percent of estimated blood volume. Blood loss should be replaced if it exceeds 10 to 15 percent of blood volume.

Patients with sickle cell disease are at a higher risk for postoperative complications such as pneumonia, atelectasis, and vaso-occlusive crises. Children with sickle cell disease presenting for elective tonsillectomy should be given a transfusion to reduce the hemoglobin S ratio to less than 40 percent. [126] Children with chronic adenotonsillar hypertrophy may also have associated undiagnosed obstructive sleep apnea syndrome and are at increased risk for respiratory complication in the immediate recovery period. [127] Patients with Down syndrome may have large tongues and unstable atlanto-occipital joints and require more careful perioperative airway management for tonsillectomy. [128]

Tracheal extubation usually occurs in the operating room when the patient is awake and protective airway reflexes are present. Some coughing should not interfere with surgical closure of the tonsillar bed. Intravenous administration of lidocaine (1.5 mg/kg) has been used to decrease laryngospasm after extubation.

Pediatric tonsil patients are placed in the "tonsil position" (i.e., on one side, with the head slightly down) in the recovery area to allow blood or secretions to drain out

rather than flow back onto the vocal cords and are observed closely for bleeding or airway obstruction. One hundred percent oxygen mist is given by facemask; pulse oximeter, arterial blood pressure, and ECG are monitored routinely. Patients should be kept in the recovery room for at least 60 minutes; the pharynx should be rechecked directly for bleeding before discharge from the recovery room.

Intraoperative complications from tonsillectomy consist of arrhythmias caused by increased levels of endogenous epinephrine from light general anesthesia, sensitization of the myocardium to catecholamines by halothane, and perhaps hypercarbia. Postoperative complications consist of poor respiratory function and continued bleeding. Patients with a history of obstructive sleep apnea must be extubated awake and observed closely in the recovery room for depressed respiratory function or apneic periods. [129] [130]

Increasingly, tonsillectomy is being performed as an outpatient procedure. Although postoperative bleeding is the most serious complication, persistent vomiting and poor oral intake are the most common reasons for unscheduled overnight admission after ambulatory surgery. The incidence of PONV can be as high as 70 percent during the first 24 hours after tonsillectomy. [131] Many different antiemetic regimens have been advocated to minimize PONV following tonsillectomy surgery. [132] [133] [134] Pappas et al [135] noted that a single, large (1 mg/kg, maximum 25 mg) preoperative dose of dexamethasone significantly decreased the incidence of PONV after tonsillectomy in children.

Although metoclopramide may help to empty the stomach, it does not seem to have specific antiemetic properties compared with ondansetron in preventing PONV after tonsillectomy. [136] Withholding oral fluids postoperatively from children undergoing day surgery reduces the incidence of vomiting. [137]

It is important to develop anesthetic techniques and to use appropriate antiemetics and recovery protocol to minimize vomiting after tonsillectomy (e.g., avoid meperidine, decompress stomach of air and blood, discontinue N_2O, [138] administer an antiemetic regimen prophylactically, keep patient well hydrated intravenously, and do not force oral food or fluid intake). [137]

Bleeding Tonsil Management

The incidence of post-tonsillectomy bleeding that requires surgery is 0.3 to 0.6 percent. This complication usually occurs within 6 hours of surgery [139] and can be a difficult anesthesia problem. Management of anesthesia for these patients should include the following considerations. The extent of blood loss may not be obvious and is usually underestimated. Before the patient is transported to the operating room, no premedication should be given, and coagulation variables should be checked, if possible. Moreover, blood should be typed and crossmatched for blood replacement, and the patient should be well hydrated via a reliable intravenous line. Most problems before induction of anesthesia for bleeding tonsil are caused by unsuspected hypo-volemia, full stomach, and airway obstruction.

At induction of anesthesia, an additional person should be available to provide good suctioning of blood. A rapid-sequence induction of anesthesia with application of cricoid pressure and slight head-down positioning of the patient will protect the trachea and glottis from aspiration of blood. After induction, a nasogastric tube may be placed and removed. As with elective tonsillectomy, extubation is safest with the patient awake.

Abscesses

A peritonsillar abscess extending to the soft palate can cause severe pain, trismus, dysphagia, and respiratory obstruction. Often, the abscess can be drained or decompressed by incision or needle aspiration using local anesthesia. The risks of general anesthesia include further respiratory obstruction, difficult endotracheal intubation because of continued trismus and distorted anatomy, and spontaneous rupture of the abscess, with subsequent spilling of pus into an unprotected airway.

Planning general anesthesia for a peritonsillar abscess may include preoperative decompression of the abscess by needle aspiration to minimize the risk of rupture. A difficult intubation should be expected because of distorted anatomy, edema, and incomplete resolution of trismus. Although difficult, endotracheal intubation must be performed slowly, carefully, and gently. If the abscess is right-sided, a left-sided approach for laryngoscopy may be indicated. If airway obstruction is expected, one of three options should be selected: careful intubation of the trachea under direct vision, with the patient awake; induction of anesthesia by mask, with the patient breathing spontaneously; or elective tracheostomy.

Ludwig angina is a cellulitis of the submandibular and sublingual spaces that may include the floor of the mouth and anterior compartments of the neck. Visualization of the glottic opening is frequently impossible because of trismus, edema, and distorted anatomy. General anesthesia is contraindicated if stridor occurs at rest. Therefore, tracheostomy using local anesthesia through the cellulitis, although not ideal, may be the safest way to secure the airway.

Adult Epiglottitis

Adult epiglottitis occurs in 1 per 100,000 adults per year. [140] Causes include infection, trauma, and radiation. Symptoms are typically sore throat, dysphagia, a muffled "hot potato" voice and respiratory distress. This respiratory distress can be immediate, severe, and progress rapidly, requiring airway management in the operating room. A careful inhalation induction and titrated intravenous sedation prior to a rigid bronchoscopy or endotracheal intubation are the recommended techniques. [141] [142] The use of steroids is controversial, but it may help in cases of angioedema. [143] Racemic epinephrine is not necessarily useful.

Foreign Body in the Airway

Aspiration of a foreign body into the trachea is a common cause of sudden onset of obstructive breathing, croupy cough, hoarseness, or wheezing in young children. Several reviews have described in detail the problems and precautions of managing anesthesia during retrieval of a foreign body from air passages. [76] [95] Care must be taken not to convert partial obstruction into total obstruction by dislodging the foreign body into the upper trachea.

During severe airway obstruction, the anesthesiologist should consider either direct laryngoscopy in an awake patient or a rigid bronchoscopic examination without application of positive pressure. Most of these cases occur in children. Usually, a gentle mask induction without cricoid pressure or positive-pressure ventilation is the preferred induction technique, [144] [145] although Kosloske [146] routinely used muscle paralysis and controlled ventilation. Removal of foreign bodies from the trachea and larynx is a hazardous procedure. The surgeon must be prepared to perform an emergency tracheostomy or cricothyrotomy if partial obstruction suddenly becomes complete.

Laryngeal and subglottic edema may last for 24 hours after removal of a foreign body. Close observation and use of humidified oxygen are suggested during this recovery period.

Difficult Airways: Causes and Classification

Difficult airways include both difficult intubations and compromised airways (Ch. 39) . Difficult intubations are usually caused by anatomic abnormalities such as micrognathia, limited jaw motion, or congenital syndromes (cra-niofacial dysostoses). Other causes of difficult intubations include obesity, acromegaly, cervical spine problems, rheumatoid arthritis, and even gastric reflux. [147] These patients usually have intact, clear airways, but abnormal anatomy prevents adequate visualization of the glottis and may inhibit easy passage of an endotracheal tube.

A preoperative evaluation of the head, neck, mandible, tongue, teeth, and oropharynx using specific assessment techniques may help to predict a potentially difficult intuba-tion. Various strategies have been devised and modified to assess the airway. [148] [149] [150] [151] [152] They often have a high sensitivity, but low predictive value, and may fail to predict difficult intubations accurately. Compromised airway implies partial obstruction to air flow and the risk of total obstruction if tumor, infection, or disease further narrows the airway. Pathologic conditions above the glottis may prevent a clear view of the glottic opening, whereas subglottic lesions permit a good view of the vocal cords, but they require careful placement of a small endotracheal tube or bronchoscope. All compromised airways are difficult intubations, but not all difficult intubations are in patients with compromised airways. A large percentage of serious anesthesia accidents involves some aspect of airway mismanagement. Caplan et al [153] reported that the majority of respiratory complications involve inability to intubate, unrecognized esophageal intubation, or inadequate ventilation. The American Society of Anesthesiologists (ASA) developed a specific practice algorithm for safe management of the difficult airway. [154] Several reviews of the causes,

techniques, necessary equipment, and problems associated with difficult airways are available. [155] Benumof [154] [158] reviewed the specific management of the difficult adult airway with emphasis on awake tracheal intubation techniques [96] and the use of transtracheal jet ventilation (TTJV). [159] The intubating laryngeal mask airway [160] [161] [162] is a recent development. Benumof noted that the incidence of "cannot ventilate-cannot intubate" situations may be as high as 1 per 5,000 anesthesics. [158] Proper responses to these emergency situations involve use of the intubating laryngeal mask airway, Combitube (Kendall-Sheridan, Argyle, NY), TTJV, or immediate surgical tracheostomy. [154] Sofferman et al [163] discussed alternatives for management of lost airway during anesthesia inductions in head and neck surgery, including use of the laryngeal mask airway and Combitube. A combined technique using an anterior commissure laryngoscope and gum elastic bougie is preferred for the special circumstances of patients requiring otolaryngologic surgery.

Laryngeal Block

Topical and regional nerve blocks of the nasal oropharynx, larynx, and glottis may be used to facilitate awake endotracheal intubation (Chs. 39 and 43) . Sanchez et al [96] and Donlon [97] reviewed in detail the preparation of patients for awake intubation, including premedication, topicalization techniques, and specific nerve blocks from nasal cavity to trachea. These include sphenopalatine nerve and blocks of the glossopharyngeal and superior laryngeal nerves. [96] [156] [164] [165] The glossopharyngeal nerve (the ninth cranial nerve) supplies sensory innervation for the posterior third of the tongue, the oropharynx, the tonsillar area, and the gag reflex. This nerve can be blocked by infiltration of 3 mL of 2 percent lidocaine posterior to the palatopharyngeal fold at its midpoint, 1 cm deep to the mucosa of the lateral pharyngeal wall. Paralysis of the pharyngeal muscles and relaxation of the base of the tongue may cause some respiratory obstruction. [166] [167] Therefore, if a glossopharyngeal nerve block is used with blockade of the superior laryngeal nerve for awake intubation, the latter procedure should be performed first to avoid respiratory obstruction.

The internal branch of the superior laryngeal nerve lies just below the mucosa in the depth of the pyriform fossa. A topical block of this nerve can be performed by applying local

anesthetic for 3 to 5 minutes onto the pyriform fossa mucosa. [96]

In the absence of neck tumor or infection, an external approach to block the superior laryngeal nerve may be used. A 23-gauge needle is placed 1 cm medial to the superior cornu of the hyoid bone and is directed caudad to pierce the thyrohyoid membrane. After aspiration, 2 mL of local anesthetic is injected. Block of the superior laryngeal nerve anesthetizes all laryngeal mucous membranes above the rima glottidis, including epiglottic and arytenoepiglottic folds. Because it removes some protective reflexes, this block should be used with caution in patients with a full stomach. A maxillary nerve block can interrupt sensory innervation to the nasal cavity in preparation for nasotracheal intubation. The mandibular nerve can be blocked from an external approach. This block eliminates masseter muscle tone, relaxes the jaw, and minimizes biting by an awake but uncooperative patient. The loss of masseter tone may cause partial upper airway obstruction.

The trachea and vocal cord area can be anesthetized either by atomizer from above or by transtracheal injection. The sensory innervation is supplied by the vagus nerve via the RLN. These nerves run along the tracheoesophageal groove and supply both sensory fibers and motor fibers (intrinsic muscles of larynx). Bilateral, specific RLN blocks could result in bilateral vocal cord paralysis and airway obstruction.

A combination of these regional blocks used in conjunction with topical anesthesia of the pharynx and larynx is simple and often very effective in dealing with difficult tracheal intubations or compromised airways. [51] Direct laryngoscopy, bronchoscopy, or tracheal intubation can be performed in the awake patient with minimal discomfort or risk after a topical laryngeal block. Lidocaine is absorbed rapidly into the systemic circulation from the trachea; therefore, the maximum safe dose of topical lidocaine in the trachea is 4 mg/kg.

Management Techniques: Difficult Intubations

These situations can occur unexpectedly in otherwise healthy patients, despite preoperative airway evaluation, and they usually involve the inability to visualize the glottic opening or even the epiglottis. Crosby et al [155] reviewed the literature and made recommendations for the safe management of unexpected difficult airways. Parmet et al [168] found that, over a 2-year period, the laryngeal mask airway provided rescue ventilation without complications in 94 percent of cases of unanticipated difficult intubation and ventilation. Difficult direct laryngoscopy occurs in 1.5 to 8.5 percent of general anesthetics. Failed intubation occurs in 0.13 to 0.3 percent of general anesthetics. [155] Current techniques for predicting difficult intubations have a low predictive value. Simple initial methods for dealing with these unexpected situations include the following: manipulation of the cricoid cartilage by the optimal external laryngeal manipulation [169] or backward, upward, rightward laryngeal displacement [170] maneuver to bring the glottis into view; use of a stylet in the endotracheal tube; repositioning of the head in a more-or-less flexed position; change (in size or shape) of the laryngoscope blade; and use of special blades. [171] A flexion-flexion (chin to chest) position of the head and neck may be ideally suited to achieve optimal glottal exposure in cases of difficult direct laryngoscopic intubations. The flexion-flexion position aligns the oral and pharyngeal cavities to facilitate direct view of the vocal cords. Extension of the head at the atlanto-occipital joint leads to backward displacement of the tongue base into the airway. If these actions are ineffective, further options include the intubating laryngeal mask airway, [154] [160] [162] [172] use of a flexible fiberoptic scope, various rigid fiberoptic laryngoscopes, [173] [174] or nasotracheal intubation with general anesthesia, spontaneous respiration, and as much visualization of the mouth as possible. Fewer than 50 percent of blind nasotracheal intubations succeed on the first attempt. Furthermore, bleeding and trauma often occur after several attempts.

Other methods use a light wand, [175] [176] a rigid bronchoscope, Combitube, [177] or a retrograde catheter technique. [171] [175] The Combitube has been associated with esophageal rupture and should be inserted carefully, under direct vision whenever possible. [178] Practice and skill should be attained in routine cases before relying on these methods for a difficult intubation. Fiberoptic equipment must be used often enough in routine situations to be reliable during intubation of abnormal airways. [179] [180] The fiberoptic scope has been useful during nasotracheal intubations in rheumatoid arthritis patients who have trismus or spondylosis. Fiberoptic visualization may also be difficult when the larynx has pathologic conditions or abnormal supraglottic anatomy. Chapter 39 also discusses difficult endotracheal intubations.

Compromised Airway

Several investigators have provided guidelines for the safe evaluation and management of patients with compromised airways. [92] [154] [155] [156] [157] [158] [171] [172] [181] [182] Often, the extent of the limitation of airflow is not obvious. Although clinical signs and symptoms (stridor, tachypnea, cyanosis, anxiety, sternal retractions, diaphoresis, and tachycardia) are usually present, patients with chronically abnormal airways learn to adapt their breathing and vocalization to limited airflow. Before attempting any method of intubating the compromised airway, as much information as possible should be gathered concerning the airway problem. Such information consists of radiographs, CT, or magnetic resonance imaging (MRI) scans, old records, history, and physical examinations.

Unlike difficult intubations in normal airways, patients with compromised airways must not be given general anesthesia or muscle relaxants unless control of the airway is ensured. Attempts at awake intubation should not be done "blindly" in patients with uncertain pathologic processes. Safe techniques for managing compromised airways include awake direct laryngoscopy after careful topical laryngeal block [96] [97] ; spontaneous breathing using an inhaled anesthetic; awake fiberoptic evaluation of the airway [183] ; tracheostomy under local anesthesia; and, if necessary, lifesaving TTJV through a cricothyroid puncture with a large-caliber (14-gauge) needle, or an emergency cricothyrotomy. [184]

The efficacy and importance of TTJV in the management of the difficult airway were reviewed by Benumof. [159] [185] Inadequate oxygenation and ventilation were reported to be responsible for as many as 75 percent of cardiac arrests following the administration of anesthesia. TTJV is a quick, easy, safe solution to the problem of "cannot ventilate/ intubate." Various methods of providing TTJV are possible, and it is recommended that TTJV be available for every anesthetizing location. The incidence of serious complications resulting from elective use of TTJV is relatively low and is usually related to tissue emphysema or pneumothorax. The risk of barotrauma, gas trapping, and lung hyperexpansion from TTJV is greatly increased in cases in which total upper airway obstruction limits the ability to expel TTJV gas from the lungs. [159]

Emergency Tracheostomy

Tracheostomy may be necessary for upper airway obstruction caused by marked edema, large supraglottic tumors, laryngeal trauma, or impacted foreign bodies, as well as for loss of protective airway reflexes owing to muscle weakness, unconsciousness, or chronic aspiration caused by vocal cord paralysis (Chs. 62 and 72). [186] Other reasons for tracheostomy are that endotracheal intubation is not feasible, stridor is present at rest, patency of the airway is lost on attempts to induce anesthesia by mask, or an unstable foreign body is present in the airway. Moreover, a tracheostomy after major head and neck surgery sometimes ensures a smoother postoperative recovery.

Ideally, a tracheostomy performed using general anesthesia provides the surgeon with an immobile, cooperative patient and allows a less-hurried procedure. When possible, general anesthesia may be provided by means of a small endotracheal tube, a rigid bronchoscope, a facemask, a glottic aperture seal airway, or a laryngeal mask airway. [187] Intubation may be accomplished with the aid of a fiberoptic bronchoscope or an intubating laryngeal mask airway. An expectation of airway obstruction warrants consideration of avoidance of muscle relaxants. Careful direct laryngoscopy with the patient awake may be possible to evaluate the airway fully before deciding a safe course of action.

Tracheostomy using local anesthesia is safe but requires some patient cooperation. Infiltration of local anesthetic may be supplemented with a bilateral superficial cervical plexus block. Patient cooperation is best achieved through the anesthetist's confident demeanor and verbal reassurance, and not through heavy sedation of the patient. During the procedure, the anesthesiologist must attend to airway management, giving 100 percent oxygen and following vital signs with full monitoring (i.e., ECG, blood pressure, end-tidal concentrations of CO_2, and pulse oximeter).

Coughing may be decreased by giving lidocaine (1.5 mg/kg IV) approximately 2 minutes before placement of the tracheostomy tube. Often, the sudden reestablishment of a good airway results in rapid correction of hypercarbia, resolution of stress, a decrease in endogenous catecholamines, and subsequent hypotension. Postobstructive pulmonary edema can also occur and has been reported in a young adult with coronary artery disease subsequent to relief of airway obstruction (intubated for epiglottitis). [188] A major early complication of tracheostomy, especially in children, is malpositioning of the tube. As soon as a tracheostomy tube is placed, end-tidal concentrations of CO_2, breath sounds, and oxygen saturation must be checked. As soon as feasible, a chest radiograph should be obtained to verify correct tube placement and the absence of pneumothorax. Other early complications of tracheostomy include bleeding and local emphysema, which are usually exacerbated if the patient coughs and struggles.

The most important of the late complications of long-term tracheostomy is tracheal stenosis at the cuff site or stoma. [189] The use of high-volume low-pressure (15-20 mm Hg) cuffs inflated only when necessary and checked every 4 hours sometimes minimizes this complication. During general anesthesia, N_2O diffuses into tracheal cuffs within 60 to 90 minutes, causing increased cuff pressure.

A Montgomery T-tube [190] or Olympic tracheal button must be carefully placed without tension. These devices have the advantages of having no cuff, producing less tracheal irritation and airway resistance, and allowing air to pass through the mouth for speech. On the other hand, they provide no protection from aspiration for the area above the device, and application of positive-pressure ventilation is difficult. In an emergency, the button is easily removed and replaced with a small endotracheal tube, which can then seal the airway and allow for use of positive-pressure ventilation, if necessary.

Postoperative care after tracheostomy requires administration of humidified oxygen, careful intermittent suctioning of secretions, attention to sterile precautions, and adjustment of cuff pressure to maintain 15 to 20 mm Hg. Prolonged tracheal suctioning not preceded or followed by oxygenation can result in arrhythmias secondary to hypoxia. Moreover, the tract from stoma to trachea is not fully established for 5 days. Therefore, changing the tube within 5 days of tracheostomy runs the risk of losing this tract. Under these circumstances, a pediatric laryngoscope may be helpful in holding the tissue apart and facilitating visualization of the trachea. For emergency airway management, a laryngoscope and small endotracheal tube should be at the bedside of all patients who have recently undergone tracheostomy.

Cricothyrotomy is another method of establishing an airway quickly (within 1-2 min) in an emergency, life-threatening situation. The complication rate of 8.6 percent is less than that for emergency tracheostomy. [191] The trachea is entered directly through an incision in the cricothyroid membrane at the third tracheal ring, just below the vocal cords. Disadvantages include damage to the cricoid cartilage that leads to tracheal collapse or stenosis, bleeding, and the need for insertion of a small tube. Emergency cricothyrotomy is a temporary procedure that secures an airway until a definitive tracheostomy can be established.

No patient should undergo injury or death because of upper airway obstruction. At the very least, the cricothyroid membrane can be punctured using a 12- to 14-gauge needle to provide temporary oxygenation until a proper airway can be established. This method of transtracheal ventilation through a large needle has been effective in preventing hypoxia and respiratory acidosis. [159] [192] Oxygen is provided by flushing oxygen at the rate of 15 L/min or by jet ventilation (40 psi) at a slow, intermittent rate of 6 breaths/min and an inspiratory, expiratory respiratory cycle of 14. This ratio allows

time for passive expiration through a narrow channel. Otherwise, high airway pressure results, thereby decreasing venous return and arterial blood pressure and increasing the risk of pneumothorax.

Complications of Endotracheal Intubation

The perioperative complications of endotracheal intubation have been reviewed by many investigators [193] [194] [195] [196] (Chs. 39 and 72) . Fortunately, the more common complications are minor; however, some of the less frequent complications can be serious.

Injury during intubation is more likely in children, female patients, patients with poor dentition, and those undergoing difficult tracheal intubation. Blanc and Tremblay [194] listed more than 30 possible acute problems associated with intubation and extubation of the trachea, such as broken teeth, lacerations and perforations of the pharynx, subluxation of arytenoid cartilage, hoarseness, sore throat, paralysis of the vocal cords, and nerve damage. The overall incidence of laryngeal injury after short-term intubation is 6.2 percent, [197] the most common injury being hematoma of the vocal cord (4.5%). Mucosal lacerations occur in approximately 1 in 1,000 intubations.

Perforations of the trachea usually occur during difficult intubations using a stylet. If subcutaneous emphysema is noted after a difficult intubation, the patient must be evaluated for mediastinitis and pneumothorax.

Reflex responses to laryngoscopy and tracheal intubation are frequently minor, but they may be serious. Sympathetic responses are hypertension, tachycardia, and tachyarrhythmias. Vagal responses are laryngospasm, bradycardia, hypotension, cardiac arrest, and apnea. These responses are most likely during light levels of anesthesia and, in association with hypoxia, during periods of hypercarbia and acidosis. These reflexes may be diminished by pretreatment with lidocaine (intravenous or topical administration), narcotics, or beta-adrenergic receptor blocking drugs and by ensuring an adequate depth of anesthesia at the time of laryngoscopy.

Pharyngitis and sore throat after tracheal intubation are not uncommon. Even patients undergoing only anesthesia by mask may complain of postoperative sore throat. This complication usually resolves within 72 hours. Causes include the use of dry gases, reaction to the lubricant, increased cuff size and pressure, patient motion (coughing, bucking) while the tube is in place, difficult intubation requiring repeated attempts, and excessive tube size. Hoarseness, indicating vocal cord injury, is another postintubation problem associated with tube size. Usually, mild postoperative hoarseness resolves within 5 to 7 days. Hoarseness that worsens or persists beyond 7 days requires evaluation by an otolaryngologist.

Vocal cord paralysis secondary to damage to the recurrent laryngeal nerve is a rare but more serious cause of hoarseness. This complication may occur because the endotracheal tube cuff presses the recurrent laryngeal nerve between the thyroid lamina and the arytenoid cartilage [193] or because of direct injury during head and neck surgery. Unilateral injury causes some change in voice and mild aspiration, but no respiratory obstruction. Bilateral recurrent nerve injury is more serious and may result in respiratory distress, stridor, and complete obstruction, as both true vocal cords become motionless and adducted. A tracheostomy may be required

during the 6-week recovery period.

The use of the laryngeal mask airway does not necessarily avoid complications. Sore throats and even unilateral right hypoglossal nerve paralysis have been reported. [198] Inadvertent intubation of the esophagus or bronchi can be avoided by the following practices: observation of the tube as it passes through the vocal cords; checking the distance indicator at the teeth (21 cm for female patients and 23 cm for male patients); listening for equal bilateral breath sounds and for the absence of gastric sounds; checking for symmetric chest motion synchronous with squeezing of the ventilator bag; and noting the sustained presence of exhaled CO_2 on a capnometer. CO_2 may temporarily effuse from the stomach, having been forced there during the application of positive-pressure ventilation by mask. Adequate oxygenation, as evidenced by monitoring of the pulse oximeter, does not necessarily indicate proper endotracheal intubation. If the patient has breathed 100 percent oxygen for 4 to 5 minutes, oxygen desaturation following intubation of the esophagus may not occur for at least 2 to 3 minutes. Moreover, the presence of breath sounds does not always indicate a successful endotracheal intubation. A spontaneously breathing patient whose esophagus has been intubated can still produce valid breath sounds.

Cocaine

Cocaine is a naturally occurring alkaloid of the *Erythroxylon coca* plant. It is an ester of benzoic acid and the methylated base ecgonine. In addition to its local anesthetic effects on mucous membranes, cocaine is an excellent vasoconstrictive agent. For these reasons, it is used in intranasal surgery to provide anesthesia, to decrease bleeding, and to shrink congested mucous membranes. [199] Cocaine also has sympathomimetic effects, sensitizing organs to epinephrine and blocking the reuptake of released epinephrine at peripheral nerve terminals. [200] Therefore, cocaine should be avoided in hypertensive patients, especially those taking monoamine oxidase inhibitors.

In one study, intranasally applied cocaine (1.5 mg/kg) was absorbed rapidly, reaching peak levels in 30 to 45 minutes; these levels remained elevated for at least 120 minutes. [201] No important cardiovascular effects occurred during general anesthesia with halothane. Smaller intranasal doses (0.5-1 mg/kg) have been found to increase heart rate 10 beats/min and to raise both systolic and diastolic blood pressures approximately 10 mm Hg. [202] Higher doses (2 mg/kg) sensitize the myocardium to the arrhythmogenic effect of epinephrine, whereas even higher doses (5-10 mg/kg) depress the heart.

The response to cocaine varies. In some patients, even small doses of 0.4 mg/kg may cause ventricular fibrillation, cardiac arrest, hypertension, tachycardia, respiratory depression, or restlessness. The median lethal dose (LD_{50}) for orally administered cocaine is approximately 500 mg. [203] For intranasal administration of a 4 percent solution, the safe recommended maximum dose is approximately 1.5 mg/kg.

Each drop of a 4 percent solution contains about 3 mg of cocaine.

Cocaine is absorbed from the laryngeal tracheal mucosa as rapidly as if it were injected intravenously. It is metabolized primarily through ester hydrolysis by plasma pseudocholinesterase and is also slowly detoxified in the liver and excreted unchanged by the kidney. Patients with pseudocholinesterase deficiency may be sensitive to cocaine. The practice of adding epinephrine to cocaine is hazardous, and there is no evidence that this addition produces less bleeding at the site of surgery.

ANESTHESIA FOR EAR SURGERY

Safe, comfortable operating conditions can be provided for ear surgery by infiltration of local anesthetic or by administration of general anesthesia. [204]

Local Anesthesia

Surgical otologic procedures such as premeatal operations, stapedectomy, and uncomplicated middle ear surgery of less than 2 hours' duration can be performed on selected patients using infiltration of local anesthetic and carefully titrated sedation. Patients should be able to understand, communicate, and be cooperative (i.e., remain still, especially during microscopic surgery of the middle ear). During the preoperative visit, the anesthesiologist should perform the same thorough medical evaluation as for general anesthesia. The goal of preoperative sedation is to render the patient calm, cooperative, and comfortable but not overmedicated (i.e., with obtunded reflexes) or out of touch with surroundings. Light sedation can be achieved by titrating intravenous propofol (0.5-0.7 mg/kg) during the injection of local anesthetic and, if necessary, by adding midazolam (0.02-0.04 mg/kg IV) during the procedure.

Nerve Block

Four nerves provide sensory innervation of the ear. The auriculotemporal nerve (the mandibular division of the trigeminal nerve) supplies the outer auditory meatus and can be blocked by injection of 2 mL of local anesthetic into the anterior wall of the external auditory meatus. The great auricular nerve (the cervical plexus nerve) supplies the medial-lower aspect of the auricle and part of the external auditory meatus. The auricular branch of the vagus runs between the mastoid process and the external auditory meatus to supply the concha and external auditory meatus. The great auricular and auricular (vagus) nerves can be blocked by injection of 2 to 3 mL of local anesthetic posterior to the ear canal (great auricular nerve). The tympanic nerve (the glossopharyngeal nerve) supplies the tympanic cavity and can be blocked topically by instillation of sterile 4 percent lidocaine. When a large perforation of the tympanic membrane has occurred, care must be taken not to place toxic substances into the auditory canal, lest they enter and damage the middle ear cavity.

Addition of epinephrine to the local anesthetic increases the intensity and duration of the effect and provides some local vasoconstriction, thereby decreasing bleeding. A safe dose of epinephrine is 0.1 mg (10 mL of 1:100,000 concentration) and may be repeated after 20 minutes, if necessary.

General Anesthesia

General anesthesia for ear surgery requires attention to preservation of the facial nerve, the effect of N_2O in the middle ear, extremes of head positioning, the possibility of air emboli, blood loss, and, during microsurgery of the ear, control of bleeding, and prevention of nausea and vomiting.

Positioning of the Patient During Ear Surgery

When positioning the patient's head for surgery under general anesthesia, one must avoid extremes of neck extension or head torsion. Injuries can occur to the brachial plexus (stretch injuries) or cervical spine (Ch. 26) . Patients with limited carotid artery blood flow are especially vulnerable to further decreases in blood flow from exaggerated neck positions.

Preservation of the Facial Nerve

Surgical identification and preservation of the facial nerve are essential during many ear operations. The goal is more easily accomplished and confirmed if the patient is not totally paralyzed. If a narcotic muscle relaxant technique must be used, the effects of the muscle relaxant should be monitored to ensure that at least 10 to 20 percent of muscle response remains. Otologic surgical procedures are associated with a 0.6 to 3.0 percent incidence of facial nerve paralysis. Intraoperative monitoring of evoked facial electromyographic activity may assist in functional preservation of the facial nerve during surgery in the mastoid/temporal bone area. [205]

Nitrous Oxide and Middle Ear Pressure

The middle ear and paranasal sinuses are normal body air cavities that consist of open, nonventilated spaces (Ch. 4) . The middle ear space is vented intermittently when the eustachian tube is opened. Expansion of these air spaces by replacing nitrogen with N_2O reflects the 34-fold difference between the blood/gas coefficients of the two gases (0.013 for nitrogen versus 0.46 for N_2O). Specifically, when inhaled in high concentrations, N_2O enters the air cavities faster than nitrogen can leave. In a fixed cavity such as the middle ear, the result is an increase in pressure. [206] Normally, passive venting by the eustachian tube occurs at a pressure of approximately 200 to 300 mm H_2O. If eustachian tube function decreases because of surgical trauma, disease, or acute inflammation and edema, middle ear pressure can reach 375 mm H_2O within 30 minutes of the start of N_2O.

In addition, after discontinuation of N_2O, the gas is rapidly reabsorbed, and sustained, marked, negative middle ear pressure may develop. When eustachian tube function is abnormal, negative ear pressure of -285 mm H_2O can occur within 75 minutes of discontinuation of N_2O. Such pressure may contribute to the development of serous otitis, disarticulation of the stapes, and impaired hearing. [196] Demonstrating these marked changes in middle ear pressure associated with N_2O, Patterson and Bartlett [207] also noted hearing impairment caused by hematotympanum and disarticulation of stapes struts. These investigators believe that N_2O anesthesia may be hazardous to hearing in patients who have had previous reconstructive middle ear surgery.

Transient worsening of middle ear function, rapid increases in middle ear pressures proportional to the inhaled concentration of N_2O, nausea and vomiting, and rupture of the tympanic membrane have all been associated with elevated middle ear pressure and abnormal eustachian tube function during N_2O anesthesia in susceptible patients. Susceptible patients include those with previous otologic surgery, acute or chronic otitis media, sinusitis, upper respiratory tract infection, enlarged adenoids, and pathologic conditions of the nasopharynx. Decreased compliance, increased resistance, and conductive hearing loss have also been observed in patients given N_2O anesthesia for adenotonsillectomy.

A bulging eardrum and "lifting off" of the tympanic membrane graft can occur during tympanoplasty surgery. There is no evidence that using N_2O (50%) for general anesthesia for type 1 tympanoplasties will interfere with the graft placement or outcome of the surgical procedure. [208] To avoid complications, however, the anesthetist should limit the concentration of N_2O to 50 percent and should discontinue administration 15 minutes before closure of the middle ear. The

subsequent decrease in subatmospheric pressure can be avoided by flushing the middle ear cavity with air prior to closure of the tympanic membrane.

Microsurgery of the Ear

During microsurgery of the ear, the technique selected for anesthesia should help to provide good operative conditions for the surgeon. A 10- to 15-degree head-up tilt increases venous drainage, keeps venous pressure low, and decreases venous bleeding. The use of a volatile anesthetic agent helps to control arterial blood pressure. Microsurgery of the ear may require additional local vasoconstriction to control bleeding. Local infiltration of 0.1 mg of epinephrine (10 mL of a 1:100,000 concentration), repeated within 20 minutes, is a safe practice in a well-ventilated patient given halothane anesthesia. Isoflurane does not sensitize the myocardium to catecholamines to the same extent as does halothane. Topical application of epinephrine in the ear usually requires only a few drops. Concentrations higher than 150,000 do not provide any additional vasoconstrictive effects.

The need for deliberately induced hypotension during microsurgery of the ear is questionable [81] [209] (Ch. 41) . The goal should be diminished bleeding, rather than an absolutely bloodless field. Inducing hypotension for ear, nose, or throat procedures, Condon [81] concluded that, even when precautions were taken, controlled hypotension was not free of complications. These complications, however uncommon, are usually major problems involving the heart or CNS. Furthermore, in a blind study on the use of controlled hypotension for ear surgery, Eltringham et al [210] found no correlations between blood pressure and quality (i.e., dryness) of the operative field. Modified hypotensive techniques based on controlled ventilation with halothane have been reported to provide successful general anesthesia for ear surgery. Multidrug combinations of nitroglycerin, hydralazine, propranolol, droperidol, and others can lead to excessive hypotension in which rapid reversal is not possible. In this author's experience, satisfactory conditions for microsurgery of the ear can be provided by placing the patient in a 15-degree head-up position, maintaining systolic blood pressure at approximately 85 mm Hg, using controlled ventilation with a volatile agent, and adding narcotic and local infiltration of topical application of epinephrine, if necessary.

In summary, general anesthesia using a volatile agent is the first choice for microsurgery of the ear. No muscle relaxation is required. Moreover, if the administration of N_2O must be discontinued, the effects of the potent anesthetic agent remain, identification of the facial nerve is not impeded, and relative hypotension (systolic blood pressure 80-85 mm Hg) can easily be maintained.

Middle Ear Surgery: Nausea and Vomiting

Procedures on the middle ear are likely to cause postoperative emesis (Ch. 65) . PONV can undo the results of the delicate middle ear reconstruction. The anesthetic management of middle ear surgery should include a plan to minimize PONV. Many regimens have been shown effective, including propofol infusion, [211] granisetron, [212] transdermal scopolamine, [213] ondansetron, [214] droperidol, and eliminating N_2O. [138] [215] Splinter et al [216] were unable to demonstrate that N_2O induces vomiting in children after the brief general anesthetic for myringotomy. PONV may be controlled with intravenous doses of a potent antiemetic drug (e.g., droperidol, 0.01/kg; ondansetron, 0.05 mg/kg; or dolasetron, 0.20 mg/kg) given during surgery.

Myringotomy

Bilateral myringotomy with tube placement is the second most frequently performed pediatric surgical procedure. [216] [217] Some form of analgesia is required in most children after this brief outpatient procedure. [218] Derkay et al [217] found that when intraoperative ear drops mixed with 4 percent lidocaine were used, the preoperative oral analgesics were of little added benefit. Preoperative oral acetaminophen, [219] or acetaminophen with codeine, [218] and even intranasal butorphanol [220] have been recommended as effective.

References

1. Gild WM, Posner KL, Caplan RA et al: Eye injuries associated with anesthesia. Anesthesiology 76:204, 1992.

2. Donlon JV Jr: Anesthesia for ophthalmic surgery. In Barash P (ed): ASA Refresher Course Lectures, vol 16. Philadelphia, JB Lippincott, 1988, p 81.

---

3. Kahn HA, Leibowitz HM, Ganely JP et al: The Framingham Eye Study. I. Outline and major prevalence findings. Am J Epidemiol 106:17, 1977.

4. Smith I, Avramov MN, White PF: A comparison of propofol and remifentanil during monitored anesthesia care. J Clin Anesth 9:148, 1997.

5. Wong HW, Merrick PM: Intravenous sedation prior to peribulbar anesthesia for cataract surgery in elderly patients. Can J Anaesth 43:1115, 1996.

6. Gold MI, Watkins D, Sung YF et al: Remifentanil versus remifentanil/midazolam for ambulatory surgery during monitored anesthesia care. Anesthesiology 87:51, 1997.

7. Yee JB, Burns TA, Mann JM, et al: Propofol and alfentanil sedation during retrobulbar block for cataract surgery. J Clin Anesth 8:623, 1996.

8. Mingus ML, Monk TG, Gold MI et al: Remifentanil versus propofol as adjuncts to regional anesthesia. J Clin Anesth 10:46, 1998.

9. Vinik HR, Bradley EC, Kissin I: Triple anesthetic combination: Propofol, alfentanil, midazolam. Anesth Analg 78:354, 1994.

10. Scott JC, Pongaris KV, Stanski DR: EEG quantitation of narcotic effect: Comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 62:234, 1985.

11. Ferrari LR, Donlon JV: Comparison of propofol, midazolam and methohexital for sedation during retrobulbar and peribulbar block. J Clin Anesth 4:93, 1992.

12. Backer CL, Tinker JH, Robertson DM et al: Myocardial reinfarction following local anesthesia for ophthalmic surgery. Anesth Analg 59:257, 1980.

13. Gozal Y, Drenger B, Robertson JE et al: ST segment changes following retinal surgery. J Clin Anesth 10:297, 1998.

14. Wallace A, Layug B, Tateo I et al: Prophylactic atenolol reduces postoperative myocardial ischemia. Anesthesiology 88:7, 1998.

15. Wong DHW: Regional anesthesia for intraocular surgery: A review. Can J Anaesth 40:635, 1993.

16. Troll G: Regional ophthalmic anesthesia: Safe techniques and avoidance of complications. J Clin Anesth 7:163, 1995.

17. Hamilton RC, Gimbel HV, Strunin L: Regional anesthesia for 12,000 cataract extraction and intraocular lens implantation procedures. Can J Anaesth 35:615, 1988.

18. Davis DB, Mandel MR: Efficacy and complication rate of 16,224 consecutive peribulbar blocks: A prospective multicenter study. J Cataract Refract Surg 20:327, 1994.

19. Morgan JE, Chandra A: Intraocular pressure after peribulbar anesthesia: Is Honan balloon necessary? Br J Ophthalmol 79:46, 1995.

20. Corboy JM, Jiang X: Postanesthesia hypotropia: A unique syndrome in left eyes. J Cataract Refract Surg 23:1394, 1997.

21. Hamilton SM, Elsas FJ, Dawson TL: A cluster of patients with inferior rectus restriction following local anesthesia for cataract surgery. J Pediatr Ophthalmol Strabismus 30:288, 1993.

22. Carlson BM, Raimin EA: Rat extraocular muscle regeneration: Repair of local anesthetic damage. Arch Ophthalmol 103:1373, 1985.

23. Raimin EA, Carlson BM: Post operative diplopia and ptosis: A clinical hypothesis based on the myotoxicity of local anesthetics. Arch Ophthalmol 103:1337, 1995.

24. Rao VA, Kavatra VK: Ocular myotoxic effects of local anesthetics. Can J Ophthalmol 23:171, 1988.

25. Ripart J, Metge L, Prat-Brandal D et al: Medial canthus single injection episcleral sub-tenon anesthesia: CT imaging. Anesth Analg 87:42, 1998.

26. Guise PA: Single quadrant Sub-Tenons block: Evaluation of a new local anesthetic technique for eye surgery. Anaesth Intensive Care 24:241, 1996.

27. Anderson CJ: Circumferential perilimbal anesthesia. J Cataract Refract Surg 22:1009, 1996.

28. Fukasa KH, Marron M: Pin point anesthesia: A new approach for local ocular anesthesia. J Cataract Refract Surg 20:468, 1994.

29. Birch AA, Evans M, Redembo E: The ultrasonic localization of retrobulbar needles during retrobulbar block. Ophthalmology 102:824, 1995.

30. Javitt JC, Addiego R, Friedberg HL et al: Brain stem anesthesia after retrobulbar block. Ophthalmology 94:714, 1987.

31. Gomez RS, Andrade LOF, Costa JR: Brainstem anesthesia after peribulbar anesthesia. Can J Anaesth 44:732, 1997.

32. Nicoll JMV, Kacharya PA, Ahlen K et al: Central nervous system complications after 6000 retrobulbar blocks. Anesth Analg 66:1298, 1987.

33. Hamilton RC: Brainstem anesthesia as a complication of regional anesthesia for ophthalmic surgery. Can J Ophthalmol 27:323, 1992.

34. Feibel RM, Custer PL, Grodon MO: Post cataract ptosis: A randomized double masked comparison of peribulbar and retrobulbar anesthesia. Ophthalmology 100:660, 1993.

35. Cunningham AJ, Barry P: Intraocular pressure: Physiology and implications for anaesthetic management. Can J Anaesth 33:195, 1986.

36. Murphy DF: Anesthesia and intraocular pressure. Anesth Analg 64:520, 1985.

37. Deramoudt V, Gaudon M, Malledant Y et al: Effect of propofol on IOP in strabismus surgery in children. Ann Fr Anesth Reanim 9:1, 1990.

38. Badrinath SK, Braverman B, Ivankovich AD: Alfentanil and sufentanil prevent the increase in IOP from succinylcholine and intubation. Anesth Analg 67:S5, 1988.

39. Ghignone M, Noe C, Calvillo O et al: The effects of clonidine on intraocular pressure. Anesthesiology 68:707, 1988.

40. Mahajan RP, Grover V, Sharma SL et al: Intranasal nitroglycerin and intraocular pressure during general anesthesia. Anesth Analg 67:631, 1988.

41. Stinson T, Donlon JV: Interaction of intraocular sulfur hexafluoride and nitrous oxide. Anesthesiology 56:49, 1982.

42. Wolf GL, Capuano C, Hartung J: Nitrous oxide increases IOP after intravitreal sulfur hexafluoride injection. Anesthesiology 59:547, 1983.

43. Hall SC, Lerman J: Should succinylcholine be used in the child with an open eye injury and full stomach? Anesth Rev 20:98, 1993.

44. Libonati MM, Leahy JJ, Ellison N: The use of succinylcholine in open eye surgery. Anesthesiology 62:637, 1985.

45. Abbott MA: The control of IOP during the induction of anesthesia for emergency eye surgery: High dose vecuronium. Anaesthesia 42:1008, 1987.

46. Daitch JS: The child with open eye injury. Anesthesiol News 3:12, 1988.

47. McGoldrick KE: Pediatric ophthalmic surgery: Anesthetic considerations. In McGoldrick KE (ed): Anesthesia for Ophthalmic and Otolaryngologic Surgery. Philadelphia, WB Saunders, 1992, p 190.

48. Steward DJ: Anesthetic considerations for neonates and the premature infant. In Barash PG (ed): ASA Refresher Course Lectures, vol 20. Philadelphia, JB Lippincott, 1992, p 213.

49. Lucey JF, Dangman B: A reexamination of the role of oxygen in retrolental fibroplasia. Pediatrics 73:82, 1988.

50. McGoldrick KE: Anesthesia for retinopathy of prematurity. In Bruce RA, McGoldrick KE (eds): Anesthesia for Ophthalmology. Birmingham, Ala, Aesculapius, 1982, p 203.

51. Liu LMP, Cote J, Goudsouzian NG et al: Life-threatening apnea in infants recovering from anesthesia. Anesthesiology 59:506, 1983.

52. Wasunna A, Whitelaw AGL: Pulse oximetry in preterm infants. Arch Dis Child 62:957, 1987.

53. Sebel PS, Ingram DA, Flynn PJ et al: Evoked potentials during isoflurane anaesthesia. Br J Anaesth 58:580, 1986.

54. Chi OZ, Field C: Effects of isoflurane on visual evoked potentials during isoflurane anaesthesia. Br J Anaesth 58:580, 1986.

55. Sasovetz DS: Ketamine: An effective anesthetic for use in electroretinography. Ann Ophthalmol 10:1510, 1978.

56. Kelley SD: Anesthetic considerations for pediatric strabismus surgery. SAMBA Newslett 3:5, 1988.

57. Lewandowski KB: Strabismus as a possible sign of subclinical muscular dystrophy. Can J Anaesth 29:372, 1982.

58. Carroll JB: Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. Anesthesiology 67:559, 1987.

59. Schwartz L, Rockoff MA, Koka BV: Masseter spasm with anesthesia: Incidence and implications. Anesthesiology 61:772, 1984.

60. Rosenberg H, Fletcher JE: Masseter muscle rigidity and malignant hyperthermia. Anesth Analg 65:161, 1986.

61. Wier PM, Munro HM, Reynolds PI et al: Propofol infusion and the incidence of emesis in pediatric outpatient strabismus surgery. Anesth Analg 76:760, 1993.

62. Christensen S, Farrow-Gillespie A, Lerman J: Postanesthetic vomiting in children after strabismus repair: A comparison of droperidol and lidocaine. Anesth Analg 67:S30, 1988.

63. Hardy JF, Charest J, Girouard G et al: Nausea and vomiting after strabismus surgery in preschool children. Can J Anaesth 33:618, 1988.

64. Watcha MF, Simeon RM, White PF et al: Effect of propofol on the incidence of postoperative vomiting after pediatric outpatient strabismus surgery. Anesthesiology 75:204, 1991.

65. Splinter WM, Rhine EJ: Low-dose ondansetron with dexamethasone decreases vomiting after strabismus surgery. Anesthesiology 88:72, 1998.

66. Figueredo ED, Canosa LG: Ondansetron in the prophylaxis of postoperative vomiting: A meta-analysis. J Clin Anesth 10:211, 1998.

67. Kovac AL, Scuderi PE, Boerner TF et al: Treatment of postoperative nausea and vomiting with single intravenous doses of dolasetron. Anesth Analg 85:546, 1997.

68. Kortell K, Clerque F, Leeser J et al: Intravenous dolasetron and ondansetron in prevention of postoperative nausea and vomiting. Acta Anaesthesiol Scand 41:914, 1997.

69. McGoldrick KE: Anesthetic implications of congenital diseases. In Bruce RA, McGoldrick KE (eds): Anesthesia for Ophthalmology. Birmingham, Ala, Aesculapius, 1982, p 139.

70. Blanc VF, Hardy J-F, Milot J et al: The oculocardiac reflex: A statistical analysis in children. Can J Anaesth 30:360, 1983.

71. Mirakhur RK, Jones CJ, Dundee JW et al: IM or IV atropine or glycopyrrolate for prevention of oculocardiac reflex in children during squint surgery. Br J Anaesth 54:1059, 1982.

72. Stead SW: Complications in ophthalmic anesthesiology. Semin Anesth 15:171, 1996.

73. Wu WCS, Schachat AP: Transfer from ophthalmology to medical service. Ophthalmic Surg 22:7, 1991.

74. McGoldrick KE: Anesthetic ramifications of ophthalmic drugs. In McGoldrick KE (ed): Anesthesia for Ophthalmic and Otolaryngologic Surgery. Philadelphia, WB Saunders, 1992, p 227.

75. Sasaki CT, Isaacson G: Dynamic anatomy of the larynx in physiology and consequences of intubation. In Bishop MJ (ed): Problems in Anesthesia, vol 2. Philadelphia, JB Lippincott, 1988, p 163.

76. Morrison JD, Mirakhur RK, Craig HJL: The larynx. In Anaesthesia for Eye, Ear, Nose and Throat Surgery. 2nd ed. Edinburgh, Churchill Livingstone, 1985, p 21.

77. Suzuki M, Sasaki CT: Laryngospasm: A neurophysiologic redefinition. Ann Otol Rhinol Laryngol 86:150, 1977.

78. Tagaito Y, Isono S, Nishino T: Upper airway reflexes during a combination of propofol and fentanyl anesthesia. Anesthesiology 88:1459, 1998.

79. Daugherty TM: Anesthesia management for head and neck surgery. J Clin Anesth 6:74, 1994.

80. Joseph MM, Kaufman WA, Shindo ML: Complications of anesthesia for head-neck and reconstructive surgery. Semin Anesth 15:203, 1996.

81. Condon HA: Deliberate hypotension in ENT surgery. Clin Otolaryngol 4:241, 1979.

82. Otteni JC, Pottecher T, Bronner G et al: Prolongation of the QT interval and cardiac arrest following right radial neck dissection. Anesthesiology 59:358, 1983.

83. Khan A, Pearlman RC, Bianchi DA et al: Experience with two types of electromyography monitoring electrodes during thyroid surgery. Am J Otolaryngol 18:99, 1997.

84. Maloney RW, Muriek BW, Steehler KW et al: A new method for intraoperative recurrent laryngeal nerve monitoring. Ear Nose Throat 73:30, 1994.

85. Eisele DW: Intraoperative electrophysiologic monitoring of the recurrent laryngeal nerve. Laryngoscope 106:443, 1996.

86. Rice DH, Cone-Wesson B: Intraoperative recurrent laryngeal nerve monitoring. Otolaryngol Head Neck Surg 105:372, 1991.

87. Vleming M, Middelward RJ, Vries ND: Complications of endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg 118:617, 1992.

88. Rheinhart DJ, Anderson JS: Fatal outcome during endoscopic sinus surgery. Anesth Analg 77:188, 1993.

89. Alonso W, Holliday J: Injuries of the lower respiratory tract. In Bluestone CD, Stool SE (eds): Pediatric Otolaryngology, vol 2. Philadelphia, WB Saunders, 1980, p 1285.

90. Seed RF: Traumatic injury to the larynx and trachea. Anaesthesia 26:55, 1971.

91. Flood LM, Astley B: Anesthetic management of acute laryngeal trauma. Br J Anaesth 54:1339, 1982.

92. Morrison JD, Mirakhur RK, Craig HJL: Trauma to the face and neck. In Anaesthesia for Eye, Ear, Nose and Throat Surgery. 2nd ed. Edinburgh, Churchill Livingstone, 1985, p 90.

93. Wood PR, Lawler PGP: Management of the airway in cervical spine injury: A review. Anaesthesia 47:792, 1992.

94. Davis RM, Scott JG: Anaesthesia for major oral and maxillofacial surgery. Br J Anaesth 40:202, 1968.

95. Gotta AW, Sullivan CA: Anesthetic management of maxillofacial trauma. In McGoldrick KE (ed): Anesthesia for Ophthalmic and Otolaryngologic Surgery. Philadelphia, WB Saunders, 1992, p 90.

96. Sanchez T, Trivedi NS, Morrison DE: Preparation of the patient for awake intubation. In Benumof JL (ed): Airway Management: Principles and Practice. St. Louis, CV Mosby, 1996, p 166.

97. Donlon JV: Anesthetic and airway management of laryngoscopy and bronchoscopy. In Benumof JL (ed): Airway Management: Principles and Practice. St. Louis, CV Mosby, 1996, p 682.

98. Keen RI, Kotak PK, Ramsden RT: Anesthesia for microsurgery of the larynx. Ann R Coll Surg Engl 64:111, 1982.

99. Torres LE, Reynolds RC: Experience with a new endotracheal tube for microlaryngeal surgery. Anesthesiology 52:347, 1980.

100. Weeks DB: Use of jet Venturi ventilation during microsurgery of the glottis and subglottis. Anesth Rev 12:32, 1985.

101. Weisberger EC, Miner J: Apneic anesthesia for endoscopic removal of laryngeal papillomatosis. Laryngoscope 98:693, 1988.

102. Babinski M, Smith RB, Klain M: High frequency jet ventilation for laryngoscopy. Anesthesiology 52:178, 1980.

103. Ewalenko P, Deloof T, Gerin M et al: Propofol infusion with fentanyl supplementation for microlaryngoscopy. Acta Anaesthesiol Belg 41:297, 1990.

104. Strong MS, Vaughn CW, Mahler DL et al: Cardiac complications of microsurgery of the larynx. Laryngoscope 84:908, 1974.

105. Van der Spek AL, Spargo M, Norton ML: The physics of lasers and implications for their use during airway surgery. Br J Anaesth 60:709, 1988.

106. Hermens JM, Bennett MJ, Hirshman CA: Anesthesia for laser surgery. Anesth Analg 62:218, 1993.

107. Pashayan AG, Wolf G, Gottschalk A et al: Anesthetic management guidelines for laser airway surgery: ASTM subcommittee. Anesth Patient Safety Found Newslett 8:13, 1993.

108. Gaba DM: More on nitrous oxide and laser surgery (letter and reply). Anesth Analg 67:488, 1988.

109. Pashayan AG, Gravenstein N: More on nitrous oxide and laser surgery (letter). Anesth Analg 67:489, 1988.

110. Burgess GE, LeJeune FE: Endotracheal tube ignition during laser surgery of the larynx. Arch Otolaryngol 105:561, 1979.

111. Pashayan AG, Gravenstein JS, Cassisi NJ et al: The helium protocol for laryngotracheal operations with CO_2 laser: A review of 523 cases. Anesthesiology 68:801, 1988.

112. Sosis M, Heller S: A comparison of five metallic tapes for endotracheal tube protection during CO_2 laser surgery. Can J Anaesth 35:S63, 1988.

113. Sosis MB: Which is the safest endotracheal tube for use with CO_2 laser: A comparative study. J Clin Anesth 4:217, 1992.

114. Green JM, Gonzalez RM, Sonbolian N et al: The resistance to carbon dioxide laser ignition of a new endotracheal tube: Xomed Laser Shield II. J Clin Anesth 4:89, 1992.

115. Sosis MB, Braverman B, Caldarelli DD: Evaluation of a new laserresistant fabric and copper foil wrapped endotracheal tube. Laryngoscope 106:842, 1996.

116. Rontal E, Rontal M, Wenokur ME et al: Anesthetic management for tracheobronchial laser surgery. Ann Otol Rhinol Laryngol 95:556, 1986.

117. Bargainner DR, Hasnian JV, Matjasko MJ: How do you manage the patient requiring subglottic laser surgery? Surv Anesthesiol 37:53, 1993.

118. Jackson KA, Marland MH: Anesthesia for resection of lesions of the trachea using Nd-YAG laser. Anaesth Intensive Care 18:69, 1990.

119. Williams PJ, Baily PM: Comparison of the reinforced laryngeal mask airway and tracheal intubation for adenotonsillectomy. Br J Anaesth 70:30, 1993.

120. Boisson-Bertrand D: Tonsillectomies and the reinforced laryngeal mask. Can J Anaesth 42:857, 1995.

121. Webster AC, Morely-Forster PK, Dain S et al: Anesthesia for adenotonsillectomy: A comparison between tracheal intubation and the armoured laryngeal mask airway. Can J Anaesth 40:1171, 1993.

122. Ruby RR, Webster AC, Morely-Forster PK: Laryngeal mask airway in pediatric otolaryngologic surgery. J Otolaryngol 24:288, 1995.

123. Williams PJ, Thomsett C, Bailey PM: Comparison of the reinforced laryngeal mask airway and tracheal intubation for nasal surgery. Anaesthesia 50:987, 1995.

124. Koc C, Kozaman F, Aygem E et al: The use of preoperative lidocaine to prevent stridor and laryngospasm after tonsillectomy and adenoidectomy. Otolaryngol Head Neck Surg 118:880, 1998.

125. Staffel JG, Weissler MC, Tyler EP et al: Prevention of postoperative stridor and laryngospasm with topical lidocaine. Arch Otolaryngol Head Neck Surg 117:1123, 1991.

126. Halvorson DJ, McKie V, McKie K et al: Sickle cell disease and tonsillectomy: Preoperative management and postoperative complications. Arch Otolaryngol Head Neck Surg 123:689, 1997.

127. Warwick JP, Mason DG: Obstructive sleep apnea syndrome in children. Anaesthesia 53:571, 1998.

128. Goldstein NA, Armfield DR, Kingsley LA et al: Postoperative complications after tonsillectomy and adenoidectomy in children with Down syndrome. Arch Otolaryngol Head Neck Surg 124:171, 1998.

129. Biro P, Kaplan V, Bloch KE: Anesthetic management of a patient with obstructive sleep apnea syndrome and difficult airway access. J Clin Anesth 7:417, 1995.

130. Strollo PJ, Rogers RM: Obstructive sleep apnea. N Engl J Med 334:99, 1996.

131. Ferrari LR, Donlon JV: Metoclopramide reduces the incidence of vomiting after tonsillectomy in children. Anesth Analg 75:351, 1992.

132. Splinter WM, Rhine EJ: Prophylaxis for vomiting by children after tonsillectomy. Ondansetron compared with perphenazine. Br J Anaesth 80:155, 1998.

133. Hamid SK, Selby IR, Sikich N et al: Vomiting after adenotonsillectomy in children: A comparison of ondansetron, dimenhydrinate and placebo. Anesth Analg 86:496, 1998.

134. Fuji Y, Saitoh Y, Tamaka H et al: Comparison of granisetron and droperidol in the prevention of vomiting after strabismus surgery or tonsillectomy in children. Paediatr Anaesth 8:241, 1998.

135. Pappas AL, Sukhani R, Hotaling AJ et al: Preoperative dexamethasone and postoperative morbidity in children undergoing adenotonsillectomy. Anesth Analg 87:57, 1998.

136. Stene FN, Seay RE, Young LA et al: Prospective comparison of metoclopramide and ondansetron for prevention of posttonsillectomy emesis. J Clin Anesth 8:540, 1996.

137. Kearney R, Mack C, Entwistle L: Withholding oral fluids from children undergoing day surgery reduces vomiting. Paediatr Anaesth 8:331, 1998.

138. Pandit UA, Malviya S, Lewis IS: Vomiting after outpatient tonsillectomy in children: Role of nitrous oxide. Anesth Analg 80:230, 1995.

139. Crysdale WS, Russel D: Complications of tonsillectomy and adenoidectomy in 9409 children. Can Med Assoc J 135:1139, 1981.

140. Wurtule P: Acute epiglottitis in children and adults: A large scale incidence study. Otolaryngol Head Neck Surg 103:902, 1990.

141. Baxter FJ, Dunn RD: Acute epiglottitis in adults. Can J Anaesth 35:428, 1988.

142. Crosby E, Reid D: Acute epiglottitis in the adult: Is intubation mandatory? Can J Anaesth 38:914, 1991.

143. Andreassen UK, Baer S, Nielsen TG et al: Acute epiglottitis: 25 year experience, current management, future trends. J Otolaryngol 106:1072, 1992.

144. Woods AM: Pediatric endoscopy. In Berry FA (ed): Anesthetic Management of Difficult and Routine Pediatric Patients. 2nd ed. New York, Churchill Livingstone, 1990.

145. Kain ZN, O'Connor TZ, Berde CB: Management of tracheo-bronchial and esophageal foreign bodies in children. J Clin Anesth 6:28, 1994.

146. Kosloske AM: Bronchoscopic extraction of aspirated foreign bodies in children. Am J Dis Child 136:924, 1982.

147. Cantillo J, Cybel D, Schaffer SR et al: Difficult intubation from gastro-esophageal reflux disease (GERD) in adults. J Clin Anesth 10:235, 1998.

148. El-Ganzouri AR, McCarthy RJ, Thurma KJ et al: Preoperative airway assessment: Predictive value. Anesth Analg 82:1197, 1996.

149. Saava D: Prediction of difficult intubation. Br J Anaesth 73:149, 1994.

150. Tse JC, Rimm EB, Hussain A: Predicting difficult intubations: A prospective blind study. Anesth Analg 81:254, 1995.

151. Butler PJ, Dhara SS: Prediction of difficult laryngoscopy: Assessment of thyromental distance and Mallampati tests. Anaesth Intensive Care 20:139, 1992.

152. Cobley M, Vaughan RS: Recognition and management of difficult intubation. Br J Anaesth 68:90, 1992.

153. Caplan RA, Benumof JL, Berry FA et al: Practical guidelines for management of the difficult airway. Anesthesiology 78:597, 1993.

154. Benumof JL: Laryngeal mask airway and the ASA difficult airway algorithm. Anesthesiology 84:686, 1996.

155. Crosby ET, Cooper RM, Douglas MJ et al: The unanticipated difficult airway with recommendation for management. Can J Anaesth 45:757, 1998.

156. Latto IP, Vaughn RS: Difficulties in tracheal intubation, 2nd ed. London, WB Saunders, 1997.

157. Ovassapian A: Management of the difficult airway. In Ovassapian A (ed): Fiberoptic Endoscopy and the Difficult Airway, 2nd ed. New York, Lippincott-Raven, 1996, p 201.

158. Benumof JL: Management of the difficult airway: A review. Anesthesiology 75:1087, 1991.

159. Benumof JL, Scheller MS: The importance of transtracheal jet ventilation in the management of the difficult airway. Anesthesiology 71:769, 1989.

160. Brimacombe JR: Difficult airway management with the intubating laryngeal mask. Anesth Analg 85:1173, 1997.

161. Brain AJ, Verghese C, Addy EV et al: The intubating laryngeal mask: A new device for the intubation of the trachea. Br J Anaesth 79:699, 1997.

162. Kapila A, Addy EV, Verghese C et al: The intubating laryngeal mask: Preliminary clinical reports. Br J Anaesth 79:704, 1997.

163. Sofferman RA, Johnson DL, Spencer RF: Lost airway during anesthesia induction: Alternatives for management. Laryngoscope 107:1476, 1997.

164. Gotta AW, Sullivan CA: Anesthesia of the upper airway using topical anesthetic and superior laryngeal nerve block. Br J Anaesth 53:1055, 1981.

165. Barton S, William JD: Glossopharyngeal nerve block. Arch Otolaryngol 93:186, 1971.

166. Bean-Lijewski JD: Glossopharyngeal nerve block after pediatric tonsillectomy: Two cases of life threatening upper airway obstruction. Anesth Analg 84:1232, 1997.

167. Sher MH, Laing DI, Brands E: Airway obstruction after glossopharyngeal block: Due to large dose of bupivacaine (letter)? Anesth Analg 86:678, 1998.

168. Parmet JL, Colonma-Romano P, Harrow JC et al: The laryngeal mask airway reliably provides rescue ventilation in cases of unanticipated difficult intubations. Anesth Analg 87:661, 1998.

169. Benumof JL, Cooper SD: Quantitative improvement in laryngoscopic view by optimal external laryngeal manipulation. J Clin Anesth 8:136, 1996.

170. Takahata O, Kubata M, Mamiya K et al: The efficacy of the BURP maneuver during a difficult laryngoscopy. Anesth Analg 84:419, 1997.

171. Latto IP: Management of difficult intubation. In Latto IP, Rosen M (eds): Difficulties in Tracheal Intubation. Philadelphia, Bailliere Tindall, 1985, p 99.

172. Pennant JH, White PF: The laryngeal mask airway: Its uses in anesthesiology. A review. Anesthesiology 79:144, 1993.

173. Cooper SD, Benumof JL, Ozaki GT: Evaluation of the Bullard laryngoscope with a new intubating stylet. Anesth Analg 79:965, 1994.

174. Watts AD, Gelb AW, Bach DB et al: Comparison of the Bullard and Macintosh laryngoscopes for intubation in patients with cervical spine injury. Anesthesiology 87:1335, 1997.

175. Hung OR, Al-Qatari M: Light guided retrograde intubation. Can J Anaesth 44:877, 1997.

176. Hung OR, Stewart RD: Lightward intubation. Can J Anaesth 42:820, 1995.

177. Frass M, Franzer R, Zahler J et al: Ventilation via esophageal Combitube in a case of difficult intubation. J Cardiothorac Anesth 1:565, 1987.

178. Klein H, Williamson M, Surlong HM et al: Esophageal rupture associated with the Combitube. Anesth Analg 85:937, 1997.

179. Ovassapian A, Mesnick PS: The art of fiberoptic intubations. Anesthesiol Clin North Am 13:395, 1995.

180. Ovassapian A: The difficult airway. In Ovassapian A (ed): Fiberoptic Endoscopy and the Difficult Airway. 2nd ed. New York, Lippincott- Raven, 1996, p 185.

181. Amment R: A systematic approach to the difficult intubation. Anesth Rev 5:12, 1978.

182. Donlon JV: Anesthetic management of patients with compromised airways. Anesth Rev 7:22, 1980.

183. Ovassapian A: Flexible bronchoscopic intubation of awake patients. J Bronchol 1:240, 1994.

184. Melker R, Florete O: Cricothyrotomy: A review and debate. Anesthesiol Clin North Am 13:565, 1995.

185. Benumof JL: Percutaneous transtracheal jet ventilation. In Benumof JL (ed): Airway Management: Principles and Practice. St. Louis, CV Mosby, 1995, p 455.

186. Morrison JD, Mirakhur RK, Craig HJL: The trachea and bronchi. In Anaesthesia for Eye, Ear, Nose and Throat Surgery, 2nd ed. Edinburgh, Churchill Livingstone, 1985, p 52.

187. Benumof JL: The glottic aperture seal airway. Anesthesiology 88:1219, 1998.

188. Weisel S, Gutman JBL, Kliman SJ: Adult epiglottis and postobstructive pulmonary edema in a patient with coronary artery disease. J Clin Anesth 5:158, 1993.

189. Kirchner JA, Astrahan DI: Tracheostomy, an alternative to prolonged intubation. In Bishop MJ (ed): Physiology and Consequences of

Tracheal Intubation: Problems in Anesthesia, vol 2. Philadelphia, JB Lippincott, 1988, p 262.

190. Lane GA, Steude GM, Pashley N: Anesthesia for a patient with a tracheal T-tube stent. Anesth Analg 60:218, 1981.

191. Boyd AD, Ronita MC, Conlon AA: A clinical evaluation of cricothyrotomy. Surg Gynecol Obstet 149:365, 1979.

192. Thomas TC, Zornow MH, Scheller MS et al: Efficacy of three different modes of percutaneous trans-tracheal ventilation in hypoxic, hypercarbic swine. Can J Anaesth 35:S61, 1988.

193. Stout DM, Bishop MJ: Perioperative laryngeal and tracheal complications of intubation. In Bishop MJ (ed): Physiology and Consequences of Tracheal Intubation: Problems in Anesthesia, vol 2. Philadelphia, JB Lippincott, 1988, p 255.

194. Blanc V, Tremblay N: Complications of tracheal intubation: A new classification and review of the literature. Anesth Analg 53:202, 1974.

195. Harmer M: Complications of tracheal intubation. In Latto IP, Rosen M (eds): Difficulties in Tracheal Intubation. Philadelphia, Bailliere Tindall, 1985, p 36.

196. Steen SN, Canas LM, Zelman V: Complications: Rare and unusual. Semin Anesth 15:238, 1996.

197. Peppard SB, Dickens JH: Laryngeal injury following short term intubation. Ann Otol Rhinol Laryngol 92:327, 1983.

198. Nagai K, Sakuramoto C, Goto F: Unilateral hypoglossal nerve paralysis following the use of laryngeal mask airway. Anaesthesia 49:603, 1994.

199. Schenk NL: Cocaine: Its use and misuse in otolaryngology. Trans Am Acad Ophthalmol Otol 80:343, 1975.

200. Smith RB: Cocaine and catecholamines interaction. Arch Otolaryngol 98:139, 1973.

201. Barash PG, Kopriva CJ, Langou R et al: Is cocaine a sympathetic stimulant during general anesthesia? JAMA 243:1437, 1980.

202. Van Dyke C, Byck R: Cocaine. Sci Am 246:128, 1982.

203. Gay GR, Inaba DS, Rappolt RT et al: An ho ho baby, take a whiff on me: La dama blanca cocaine in current perspective. Anesth Analg 55:582, 1976.

204. Donlon JV: Anesthesia for ear surgery. In: Albert PW, Ruben RJ (eds): Otologic Medicine and Surgery. New York, Churchill Livingstone, 1988, p 995.

205. Leonetti JP, Smith PG, Matz GJ: Facial nerve monitoring in otologic surgery. Ann Otol Rhinol Laryngol 99:911, 1990.

206. Chinn K, Brown OE, Manning SC et al: Middle ear pressure variation: Effect of nitrous oxide. Laryngoscope 107:357, 1997.

207. Patterson ME, Bartlett PC: Hearing impairment caused by intratympanic pressure changes during general anesthesia. Laryngoscope 85:399, 1976.

208. Katayama M, Bernardi GEC, Pashool JR et al: Nitrous oxide and the middle ear. Braz J Anesthesiol Int Issue 3:1, 1992.

209. Washburn MC, Hyer RL: Deliberate hypotension for elective major maxillofacial surgery. J Maxillofac Surg 10:50, 1982.

210. Eltringham RJ, Youna PN, Fairbairn ML et al: Hypotensive anesthesia for microsurgery of the middle ear. Anaesthesia 37:1028, 1982.

211. Jellish WS, Leonetti JP, Murdoch JR et al: Propofol based anesthesia for middle ear surgery. J Clin Anesth 7:292, 1995.

212. Fuji Y, Toyooka H, Tanaka H: Granisetron reduces nausea and vomiting after middle ear surgery. Br J Anaesth 79:539, 1997.

213. Reinhart DJ, Klein KW, Schroff E: Transdermal scopolamine for the reduction of PONV in outpatient ear surgery. Anesth Analg 79:281, 1994.

214. Jellish WS, Thalji Z, Fluter E et al: Ondansetron versus droperidol prophylactically to prevent PONV in patients undergoing middle ear procedures. J Clin Anesth 9:451, 1997.

215. Kenny GN: Risk factors for postoperative nausea and vomiting: A review. Anaesthesia 49 (suppl 6):10, 1994.

216. Splinter WM, Roberts DJ, Rhine EJ et al: Nitrous oxide does not increase vomiting in children after myringotomy. Can J Anaesth 42:274, 1995.

217. Derkay CS, Wadsworth JV, Darrow DH et al: Tube placement: A prospective randomized double blind study. Laryngoscope 108:97, 1998.

218. Tobias JD, Love S, Hersey S et al: Analgesia after bilateral myringotomy: Acetaminophen vs. acetaminophines with codeine. Anesth Analg 81:496, 1995.

219. Bean-Lijewski JD, Stinson JC: Acetaminophen or ketorolac for postmyringotomy pain in children? Paediatr Anaesth 7:131, 1997.

220. Bennie RE, Boehringer LA, Dierdorf S et al: Intranasal butorphanol is effective for postoperative pain relief in children undergoing myringotomy. Anesthesiology 89:385, 1998.

221. Aboul-Eish E: Physiology of the eye pertinent to anesthesia. Int Ophthalmol Clin 13:1, 1973.

Chapter 64 - Anesthesia for Laser Surgery

Ira J. Rampil

INTRODUCTION

The word *laser* is an acronym for light amplification by stimulated emission of radiation, and laser technology is one consequence of Nobel prize-winning developments in quantum mechanics, which are among the most important in 20th century physical sciences. In essence, lasers provide the ability to transfer large quantities of energy rapidly to remote locations. Applications in medicine have been sought since the laser's creation. Now, some 30 years later, lasers are an accepted, often preferred member of the surgical armamentarium. The rapid proliferation of this technology has, however, been accompanied by occasionally severe complications, making it imperative that anesthesiologists understand the potential threat to their patients and themselves and be prepared to respond properly. This chapter reviews relevant highlights of the fundamental physics of lasers and laser light, rationales for the variety of lasers in clinical use, and important anesthesia-related concerns during laser surgery. A glossary of terms relevant to this topic is presented in Table 64-1 .

PHYSICS OF LASER LIGHT

Visual light is electromagnetic radiation, as are radio waves, x-rays, and gamma rays. These different classes of electromagnetic radiation are similar phenomena that occur at very different wavelengths. In 1864, Maxwell [1] explained that light is an electromagnetic wave with combined electrical and magnetic oscillations that propagates at 299,792,458 m/s. Max Planck [2] subsequently discovered the photoelectric effect: that is, light of a certain color (e.g., blue) causes metal to eject electrons at a rate proportional to the brightness of the light, whereas intense light at other wavelengths (e.g., red, orange, or yellow) cannot. Planck's discovery was the first step toward laser physics, because explaining it required a new conceptual framework. Einstein [3] developed this framework, quantum mechanics, in 1905, establishing the theoretical basis for laser action. He explained that all electromagnetic radiation (e.g., light, radio, x-ray) consists of photons, which may be described as follows:

1. Their properties are consistent with both particles and waves.
2. They propagate in a vacuum without diminishing, at a constant speed of 299,792,458 m/s.
3. Their energy is proportional to their vibrational frequency:

   v

   where h is the Planck constant, 6.63×10^{-34} (jouleseconds) and v is the frequency of the photon in hertz.
4. Their wavelength (lambda) can be calculated as follows:

Wavelengths of visible light range from 385 to 760 nm (nanometers, 10^{-9} m); shorter wavelengths are ultraviolet, and longer wavelengths are infrared.

Einstein also explained that the photoelectric effect is independent of the number of photons present, occurring even if only one photon at a time struck the metal surface. Energy is the key; that is, only photons of high enough energy

TABLE 64-1 -- Glossary of Laser Terminology

Ablation: Removal of tissue by vaporization

Absorption: The transformation, by interaction with matter, of radiant energy to a different form of energy.

Active medium: A material that acts as a laser with the proper excitation

Aiming beam: A very low-powered laser beam that is collimated with the high-powered, often invisible therapeutic beam to illuminate the target site

A **ngstrom unit** (A) **:** 10^{-10} m

Anode: The positive terminal in a gas discharge laser

Attenuation: The reduction in beam energy by absorption or scattering as it passes through matter

Brewster windows: Transparent windows at the ends of a gas laser discharge tube set at such an angle to the optical axis of the tube (Brewster angle) as to provide maximum light transmission

Coherent light: Light in which the photons all have the same wavelength and maintain a constant in-phase relationship with each other

Collimation: The property of a light beam that describes the degree to which the constituent photons move in a single direction; highly collimated beams do not spread in diameter as they move away from the source

Continuous wave (CW) mode: A mode of operation in which the laser discharge is continuous

Diffraction: The modulation in intensity and apparent bending exhibited by photons as they pass through an opaque body

Dopant: A chemical added to a crystal matrix to serve as an active laser constituent

Energy density: The amount of energy per unit area arriving at a surface, usually expressed in joules per square centimeter

Excimer: Excited dimer; a type of laser based on the transition states of a diatomic molecule (e.g., ArF, KrF, or XeCl); these lasers produce photons of very high energy

Extinction length: The thickness of a specified medium that absorbs 98 percent of the incident beam intensity (expressed as wave number in cm^{-1})

Infrared: Electromagnetic radiation whose wavelengths lie in the band 0.7 mum to 1.0 mm (i.e., longer than visible light, but shorter than microwave or radio waves)

Interference: The phenomenon in which photons of like wavelength but different phase combine constructively and destructively to modulate the resulting intensity

Joule (J): A unit of energy (1 joule = 1 watt-second)

Micrometer (mu **m):** 10^{-6} m

Mode: A description of the intensity cross-section of a laser beam

Monochromatic light: Light of a single wavelength or color

Nanometer (nm): 10^{-9} m

Neodymium (Nd): A rare earth metal, frequently chosen as a laser material within a substrate of glass or yttrium aluminum garnet (YAG)

Output power: Rate of energy discharge, usually measured in watts or joules per second

Photon: A quantum of electromagnetic energy possessing both wave-like and particle-like properties; photons travel at a constant speed of approximately 300,000,000 m/s

Power density: The amount of power (energy per second) per unit area arriving at a surface, usually expressed in watts per square centimeter

Pulsed mode: A mode of operation in which the laser delivers discrete (usually quite brief) bursts of photons

Pump: The means of inducing an electron population inversion so that stimulated emission might occur

Resonator: The combination of laser material and mirrors necessary to support laser activity

Spontaneous emission: The emission of a photon when an excited orbital electron decays back to its ground-state energy

Stimulated absorption: The process by which an orbital electron captures the energy of a colliding photon and is boosted to a higher energy orbital

Stimulated emission: The process by which an electron in a high-energy orbital will, if struck by an appropriate photon, emit a new photon of wavelength, phase, and direction equal to that of the original, colliding photon

Tunable laser: A laser that can be adjusted so as to provide a selected output wavelength from a range of possibilities

Ultraviolet: Electromagnetic radiation having wavelengths shorter than visible light, in the range between 0.01 and 0.38 mum

YAG: A synthetic crystalline matrix composed of yttrium, aluminum, and garnet, with the chemical formula $Y_3 Al_5 O_{12}$

Wavelength: The distance from peak to peak of a photon wave, the usual units for light waves are nanometers (nm) or micrometers (mum)

(high enough frequency) can provide the energy necessary to stimulate electron emission; lower-energy photons, even arriving in large numbers at a given time (brightness), cannot. These findings precipitated the development of laser light.

Some additional aspects of quantum physics provide greater insight into the origin and nature of laser light. For example, electrons circling the nuclei of atoms are constrained to a few specific orbital patterns and radii (Fig. 64-1) . Each orbital is associated with a specific energy level; the only way an electron can move from one orbital to another of higher or lower energy is to absorb or emit, respectively, an amount of energy exactly equal to the difference in energy between the two orbitals. The process by which a photon's energy is captured by an electron, thereby vaulting the electron into a higher energy orbital, is called *stimulated absorption* (Fig. 64-2) ; the converse process by which an electron drops to a lower orbital, in the process, sending out a photon to carry away the excess energy, is called *spontaneous emission.* In 1917, Einstein predicted that *stimulated emission,* the key to laser action, [4] also could occur. For this process, a photon of a particular wavelength (energy) must collide with an atom ready for spontaneous emission at that wavelength (i.e., having an electron already in the higher energy orbital), stimulating immediate photon emission and electron descent to a lower orbital. The colliding photon leaves the electron with the emitted photon, both photons having the identical wavelength, phase, and direction.

The energy differences between electron orbitals are specific to different atoms and are responsible for the fingerprint-like emission or absorption spectra used in chemical identification. Under normal circumstances of thermodynamic equilibrium, most of a substance's electrons are in the lowest available (ground-state) energy orbitals. Normally, an electron is much more likely to engage in spontaneous than in stimulated emission (by a factor of 10^{33}:1). The key to the creation of the laser was the achievement of a *population inversion,* in which many electrons are "pumped up" to the higher orbital, waiting for a photon to come along and start a chain reaction (or amplification) of stimulated emission. In 1958, the technology for pumping up electrons to achieve stimulated emission was introduced. [4] A method was found

---

Figure 64-1 Electronic orbitals and energy levels are shown in this schematic diagram of the Bohr model of the hydrogen atom. The circular electron orbitals are a simplification of the probabilistic electron cloud structure. Superimposed on the electron orbitals are the energy transitions responsible for two of the line series in the emission spectrogram of hydrogen. The Lyman series of spectral lines occurs when electrons release photons as they jump down to the lowest energy orbital; the Balmer series of lines represents jumps to an orbital just above the lowest. The wavelength of the resulting photons are inversely proportional to the size of the jump: for example, in the Balmer series the jump from the n = 3 orbital to the n = 2 orbital releases a photon of wavelength 656.3 nm, whereas the jump from n = 5 to n = 2 is more energetic, releasing a 434-nm photon.

for enclosing the laser medium between parallel mirrors, so that laser frequency photons could traverse the medium repeatedly and maximize the number of stimulated emissions. If one of the mirrors is partly transparent, a beam of laser light will eventually exit through that mirror.

Laser light differs from ordinary light in three ways. First, it is highly monochromatic; that is, it consists of photons that have a well-defined, very narrow band of wavelengths, whereas ordinary light contains a wide spectrum of wavelengths. Second, laser light is coherent, a property that implies that the electromagnetic fields of all photons in the laser beam oscillate synchronously, in identical phase. In ordinary light, the electromagnetic fields are phased randomly even at the same wavelength. Third, directed beams of laser light are collimated (i.e., have minimal dispersion). The light remains in a narrow, collimated beam, whereas ordinary light beams spread out in all directions from a point source. These three characteristics allow lasers to generate intense light beams, to send such beams efficiently and accurately through lenses, and to deliver intense energy to small target sites.

LASER SYSTEM HARDWARE

The essential components of a laser system include a laser medium containing the atoms whose electrons create the laser light, resonating mirrors to boost laser efficiency, and an energy source to excite or (pump) the atoms of the laser medium into producing laser light (Fig. 64-3) .

Figure 64-2 Absorption, emission, and stimulated emission. Photons may interact with orbital electrons in three ways. (A) A photon striking an electron may transfer its energy to the electron, pushing the electron into a higher energy orbit. This interaction is known as absorption. (B) An electron in an orbit higher than the ground (minimal energy) state may spontaneously lose energy in the form of an emitted photon. (C) An incoming photon may interact with an electron that is already in a high-energy orbit, with the result that two perfectly coherent, collimated photons leave the electron; this is known as stimulated emission.

The different types of lasers applied in clinical practice use a variety of laser media and energy pumps. Some clinical lasers use a gaseous medium such as CO_2, argon, krypton, or helium-neon and are pumped by electric discharge through the gas. Gas lasers may produce either a continuous or an intermittently pulsed beam output. Other lasers use solid rods of laser-passive material containing small quantities of ionic impurities, known as *dopants,* which are the actual laser materials. Dopants commonly used for their laser potential include chromium (as in the ruby laser), neodymium (Nd), and holmium (Ho). A synthetic gem crystal known as YAG (yttrium aluminum garnet) is commonly used as a passive host matrix, but even glass has been used. Solid lasers usually are pumped by high-energy photons from a xenon flash lamp and therefore produce a pulsed beam. Lasers also can be made from liquid dyes and semiconductors, but these technologies have yet to appear to a significant extent in surgical practice. Some medically relevant laser media and their respective output wavelengths are listed in Table 64-2 .

Because lasers are not very efficient at converting electricity into light, they require a large power supply. For example, a laser with a 10-W output requires in excess of 1,000 W of alternating current from a wall socket; consequently, some laser systems may require special wiring for the high current load. This electrical energy is converted to very high voltages (5,000-30,000 V) to drive the gas discharge or a xenon flash lamp. Many laser systems also require running water for cooling. Some power supply units contain nonmedical compressed gas (e.g., argon, krypton, or CO_2) either as a laser medium or as a coolant.

Frequency doublers convert laser light to a different wavelength, enhancing therapeutic flexibility. A beam of laser light passed through a crystal of KTP (potassium titanium

Figure 64-3 Generic laser hardware. A laser system consists of several components, regardless of whether the laser is solid-, liquid-, or gas-based. The central component is the laser medium itself, which may, for example, be a solid crystal of YAG with a small concentration of neodymium as dopant or may be a tube containing CO_2. The energy pump provides the means of obtaining a population inversion (see text) of orbital electrons; it may consist of a xenon flash lamp or an electric spark generator. A pair of axial mirrors allows repeated passes of collimated photons through the medium, allowing maximum amplification by stimulated emission. The mirror on the right is not 100 percent reflective, allowing the beam to escape eventually. The optional Q switch increases the efficiency of pulsed lasers by allowing a small delay to increase the pumping.

phosphate) emerges with a mixture of light of the original wavelength and light of a wavelength that is half of the original (double the original frequency). In medical lasers, KTP is most often used with Nd:YAG. Truly "tunable" or frequency-adjustable lasers exist, but they are still relatively low-powered devices.

A *light guide* directs the laser beam to the surgical site, as illustrated in Figure 64-4 . Fiberoptic bundles provide a convenient, flexible conduit for visible and near-infrared wavelengths. Wavelengths outside this range, such as the long infrared from a CO_2 laser, require either an articulated arm containing front-surface mirrors at each joint or newly developed exotic materials in a fiberoptic bundle. Once the laser beam is delivered in proximity to the surgical site, either

TABLE 64-2 -- Laser Media Wavelengths

LASER MEDIUM	COLOR	WAVELENGTH (nm)	TYPICAL APPLICATION
CO_2	Far infrared	10,600	General, cutting
Erbium-YAG	Infrared	2,930	Dental, arthroscopy
Holmium-YAG	Infrared	2,060	Angioplasty
Neodymium-YAG	Near infrared	1,064	General, coagulation, via fiberoptics
Ruby	Red	694	Tattoos, nevi
Krypton	Red	647	
Helium-neon	Red	632	Aiming beam
Gold (vapor)	Red	632	
Organic dye (liquid)	Red	632	Phototherapy
Organic dye (liquid)	Yellow	585	Dermatology, ophthalmology
Copper (vapor)	Yellow	578	
Organic dye (liquid)	Yellow	577	
Krypton	Yellow	568	Retina
KTP:neodymium-YAG	Green	532	General, pigmented lesions
Krypton	Green	521	

Argon	Green	514	Vascular, pigmented lesions
Copper (vapor)	Green	510	
Organic dye (liquid)	Green	504	
Argon	Blue	488	Vascular, pigmented lesions
Xenon fluoride	Ultraviolet	351	Cornea, angioplasty
Xenon chloride	Ultraviolet	308	Cornea, angioplasty
Krypton fluoride	Ultraviolet	248	Cornea, angioplasty
Krypton chloride	Ultraviolet	222	Cornea, angioplasty
Argon fluoride	Ultraviolet	193	Cornea, angioplasty

KTP, potassium titanium phosphate; YAG, yttrium aluminum garnet

Figure 64-4 Light guides. (A) Schematic representation of a CO_2 laser guide such as may be found in either an operating microscope or a hand-held wand. The guide consists of rigid hollow tubes with hinged, aligned mirrors, which reflect the beam from its source through the focusing lens. (B) Schematic of a flexible fiberoptic guide with a sapphire contact scalpel and a coaxial cooling system.

ther it is focused to the site by the lens of an operating microscope or the shape of the beam is intentionally altered by passing it through a contact probe directly on the tissue to be ablated.

An operating microscope accurately aims a laser by directing a low-powered (about 1-mW) visible beam (usually from a low-powered helium-neon gas laser) through the same optical path as the surgical laser. Some surgical lasers can be focused to a spot size of 30 mum (0.030 mm), creating very high-power densities.

For surgical procedures that do not require a "no-touch" technique, there are special heat-resistant (sapphire) direct-contact probes [5] (see Fig. 64-4) that are interchangeable and whose shapes can be designed for sharp cutting or diffuse coagulation, as needed. However, these probes require active cooling in the form of a compressed gas or liquid jet, a feature that has become responsible for a significant contribution to laser-related morbidity and mortality. [6] The mechanism of action of the contact probe is probably a combination of thermal conversion of most of the laser energy within the sapphire (heating the surface to >800°C) and transmission of perhaps 20 percent of the near-infrared energy to the surrounding tissue. [7]

CLINICAL APPLICATIONS

Lasers are now used as scalpels and electrocoagulators with some unique advantages. For example, lasers allow highly precise microsurgery, even in confined or difficult-to-reach sites. Two examples of a laser system's ability to reach remote sites effectively include percutaneous diskectomy [8] and endovascular angioplasty. [9]

The ability to focus laser beams on small target areas concentrates the intensity or power per area enormously. For example, a 10-W beam, originally 1 cm^{-2} in area, would have a power density of 10,000 W/cm^{2} when focused on a target area of 0.001 cm^{-2} . This power density delivers approximately 2,500 cal/s to the target site, producing heating at a rate of many thousand degrees per second, depending on the volume of energy absorption. This allows precise, rapid vaporization of tissue or indeed most materials except metals and ceramics. Lasers do not increase the energy of a particular photon, but simply place more photons at a given place and time than do other light sources. Laser surgery is relatively "dry," providing near-instantaneous sealing of small blood vessels and lymphatics, even in the presence of clotting abnormalities. However, early claims for faster than normal healing and lower infection rates have not yet been convincingly validated. [10]

BIOLOGIC EFFECTS OF LASER LIGHT

Living tissue is a complex aqueous solution containing a variety of molecules that absorb light. When an atom interacts with a photon whose energy does not exactly match a possible electron transition, the photon's energy may be translated into atomic vibrations we recognize as heat. The degree to which a particular wavelength of light is absorbed and converted to heat in the target tissue determines its effect on that tissue.

Long infrared wavelengths are absorbed with great efficiency by water, the main constituent of tissue. Long-wavelength laser light, like that from CO_2 (operating at 10,600 nm), is therefore completely absorbed by water in the first few layers of cells. With powerful, focused CO_2 beams, this results in explosive vaporization of the surface tissue of the target with surprisingly little damage to underlying cells.

Excimer lasers have an extremely precise effect because they produce ultraviolet light that is absorbed more intensely by water and other molecules. Near-infrared light from an Nd:YAG laser at 1,064 nm is less absorbed by water, and the beam diffuses through several millimeters, scattering through a volume of tissue perhaps 100 to 1,000 times the volume through which a CO_2 beam diffuses. Consequently, the energy of an Nd:YAG beam is more widely disseminated (Fig. 64-5) , producing less vaporization and more thermal coagulation (i.e., a cooking effect). Some of the effects of this bulk coagulation may not be apparent for hours or days following exposure. The red light produced by a ruby laser (694 nm) is poorly absorbed, except by cells containing dark pigment. The green and blue light produced by argon (514, 488 nm) or krypton (476, 521, 568 nm) gas lasers is transmitted by water but is intensely absorbed by hemoglobin, providing the ability to penetrate skin or ocular structures and selectively coagulate vascular or pigmented regions. Although lasers that produce infrared or

Figure 64-5 Different wavelength laser light causes different patterns of tissue destruction. The actual destructive effect of laser light on tissue depends on both laser parameters and tissue factors.

visible light have exclusively thermal effects on tissue, the photons produced by ultraviolet excimer lasers are energetic enough to disrupt chemical bonds directly and cause ionization, which can result in mutation and carcinogenesis.

RISKS OF LASER USE

Standards and Regulations

Because lasers are potentially dangerous technologic devices, their clinical use is subject to some degree of federal regulation and to voluntary consensus standards to minimize possible risks. The U.S. Food and Drug Administration (FDA) controls the manufacture and marketing of medical laser equipment. Currently, however, there are no mandatory federal safety precautions or regulations governing the clinical use of lasers. Institutions using lasers clinically should subscribe to the standards published in the *American National Standard for the Safe Use of Lasers in Health Care Facilities* (Z136.3-1988) by the American National Standards Institute (ANSI). [*] These standards reflect a consensus of governmental, industrial, and professional opinions on the methods used to define and control the risks of laser use, define and standardize training, and assess and ensure safety. The FDA also has suggested a set of regulations that have been adopted and modified by several states. [11] The safety guidelines proposed by both ANSI and the FDA should be followed to the maximal extent possible. Although it is patients who are at most risk from the surgical use of lasers, injuries to staff have not been rare. Accordingly, the U.S. Occupational Safety and Health Administration (OSHA) is empowered to intervene if the medical use of lasers threatens the health of employees.

Data regarding the true incidence of laser-related injury are limited. Manufacturers are required to report unusual incidents or injury as they become aware of them. However, clinical reporting has, until recently, been voluntary, except when complications of laser use occur in the course of a premarketing testing protocol. The passage by Congress of the Safe Medical Devices Act of 1990 now requires reporting by clinicians of all serious injuries and should provide more accurate data regarding the prevalence of such injuries.

LASER HAZARDS

The hazards associated with laser use can be divided into 4 major categories: atmospheric contamination, perforation of a vessel or structure, embolism, and inappropriate energy transfer. There were 21 injuries reported to the FDA between January 1989 and June 1990: 2 minor, 12 serious, and 7 fatal. [12] The distribution by type of injury is illustrated in Figure 64-6 .

Atmospheric Contamination: Laser Plume

Vaporization of tissue, whether by electrosurgery or laser radiation, produces a plume of smoke and fine particulates (mean size, 0.31 mum; range of sizes, 0.1-0.8 mum[13]), sized within the range that is efficiently transported and deposited in the alveoli. Many individuals find the odor of this plume objectionable, and sensitive individuals have described headaches, tearing, and nausea as a consequence of inhalation. Deposition of laser plume particulates in rat lung appears capable of producing interstitial pneumonia, bronchiolitis, reduced mucociliary clearance, inflammation, and emphysema. [14] [15]

Potentially, laser plume also may be mutagenic, [16] [17] teratogenic, or a vector for viral infection. *In vitro,* the mutagenic

Figure 64-6 Distribution of laser injury type reported to the U.S. Food and Drug Administration, from January 1989 to June 1990. *(Data from U.S. Food and Drug Administration [12])*

*ANSI Z136.3-1988 is available from the American National Standards Institute, Inc., 1430 Broadway, New York, NY 10018, or from the Laser Institute of America, 5151 Monroe St., 102W, Toledo, Ohio 43623

potential of laser condensate is half that of electrocautery, [17] and the total mutagenic potential from 1 g of tissue is comparable with that from smoking three to six cigarettes. The role of the smoke plume as a viral vector is controversial: viral DNA has been detected in plume from condylomas [18] [19] and skin warts, [20] but not from laryngeal papillomas. [21] Human immunodeficiency virus (HIV) was not detected in electrosurgical smoke plume [22] in one study, and only noninfectious DNA fragments were found in a CO_2 laser plume from HIV-infected tissue pellets. [23] Competent transmission of any viral infection via smoke plume has yet to be demonstrated. [24] Laser plume does not appear to contain viable eukaryotic cells (i.e., tumor cells [25] [26]) but it may contain viable bacterial spores. [27] [28]

CO_2 lasers seem to produce the most smoke due to the vaporization of tissue, and Nd:YAG contact probes produce much less. The most effective means of preventing dissemination of the plume is to use an efficient smoke evacuator at the surgical site. [29] [30] Ordinary surgical masks efficiently filter particles only down to 3.0 mum, and therefore, special high-efficiency masks (e.g., The Protector II, Anago, Fort Worth, Tex) are required to catch laser plume particulates. However, the high-efficiency masks are less effective when wet and may need to be changed periodically.

Tissue/Vessel Perforation

Misdirected laser energy may perforate a viscus [31] [32] [33] [34] or a large blood vessel (vessels >5 mm are not coagulable by laser). Laser-induced pneumothorax has been reported following a laryngeal procedure. [35] With an Nd:YAG system, the depth of damage is impossible to assess accurately or immediately, and perforation and bleeding may not occur until edema and necrosis have become maximal several days postoperatively.

Embolism

The Nd:YAG laser system has been associated with venous gas embolism. Embolization has been a particular problem during hysteroscopic surgery with Nd:YAG contact probes when the gas coolant for the sapphire probe tip has accidentally inflated the uterine cavity. In 1989, this technique was reported to have resulted in five widely publicized cases involving four deaths. [6] In another report, uterine insertion of a sheathed quartz fiber (with coaxial coolant gas running) produced an immediate massive and fatal gas embolism. [36] The laser and its contact probe per se were not directly responsible for the injury. Therefore, a liquid (saline) coolant is strongly preferred during hysteroscopy. If a coolant gas must be used, CO_2 will produce less damage following embolization than either nitrogen or air. If uterine distention is achieved with saline rather than with gas, a fluid overload similar to that seen during transurethral prostate surgery is possible. [37]

Venous gas embolization also has been reported during Nd:YAG resection of tumor in the trachea [38] [39] and during various types of laparoscopic and endoscopic procedures. [40] [41] A laser coolant malfunction during laparoscopic ablation of endometriosis lesions at the University of California, San Francisco resulted in complete subcutaneous air emphysema, from which the patient recovered following a benign course. During laparoscopic surgery with CO_2 insufflation, mechanical hyperventilation should be instituted and adjusted to compensate for intra-abdominal CO_2 absorption and cephalad displacement of the diaphragm. Continuous airway CO_2 monitoring is highly recommended for detection of either embolization or hypercapnia.

Energy Transfer to an Inappropriate Location

All currently available medical laser wavelengths are transmitted transparently through air and are well reflected by smooth metal surfaces. Pressing the laser control trigger at the wrong time can deliver damaging laser light across the wound to sites at which surgical ablation was not desired or across the operating room into colleagues' eyes. Potentially tragic situations include laser ignition of surgical drapes [42] [43] and, of special concern for anesthesiologists, accidental irradiation of an endotracheal tube during airway surgery.

EYE PROTECTION

The ANSI standards as well as common sense dictate that the eyes of the operating room staff and the patient be protected during the conduct of laser surgery. Errant infrared energy from a CO_2 laser can quickly cause a serious corneal injury, [44] whereas argon, (KTP) Nd:YAG, or ruby lasers may burn the retina. [45] The lids of patients' (nonoperated) eyes should be taped closed, then covered with an opaque, saline-soaked knit or metal shield. [46] [47] [48] Operating room personnel must wear safety goggles or lenses specific for the laser wavelength in use. Safety goggles should provide wraparound protection from reflected light. For CO_2 lasers, any clear glass or plastic lenses will suffice because they are opaque to far infrared. Regular eyeglasses may be sufficient, but contact lenses are not. Other lasers require color filters whose wavelength specificity and optical density are regulated. Nd:YAG lasers require either special green-tinted goggles, which make assessment of patient skin color difficult, or clear lenses (Nd:YAG Protection Glass, Surgical Laser Technologies, Malvern, Pa), which have a special coating opaque to near infrared. Argon or krypton lasers require an amber-orange lens filter, and KTP:Nd:YAG lasers require a red filter. Because lasers other than the far-infrared CO_2 produce beams that pass through glass, all windows into the operating room should be covered during laser procedures and specific, specially designed warning signs should be posted as described in ANSI Z136.3.

ENDOTRACHEAL TUBE FIRES

A feared complication of laser use during airway surgery is endotracheal tube fire. The estimated incidence of this complication during such operations is 0.5 to 1.5 percent. [49] [50] Although a survey of otolaryngologists did not provide an incidence for fires, it did demonstrate that laser-induced ignition of endotracheal tube, cuff, or cottonoids

Figure 64-7 (Figure Not Available) Blowtorch ignition of an endotracheal tube. *(From Emergency Care Research Institute [107])*

was responsible for most (41%) perioperative complications, followed by postoperative laryngeal web (19%) and laser-related or laser-induced facial burn (11%). [51] The largest published (retrospective) series of CO_2 laser airway procedures documented 6 airway fires in 4,416 cases (0.14% incidence), [52] confirming it as the most frequent laser-related complication in patients undergoing this type of procedure. Given the proximity of the endotracheal tube to surgical sites around the larynx, the potential for fire or other airway complications is clear. Many of these fires, when appropriately handled, result in minimal or no harm to the patient, [49] [53] [54] , 54 but catastrophic consequences are possible. [55] [56]

With the energy delivery rates described earlier, any hydrocarbon material, including tissue, plastic, or rubber, can ignite and burn, particularly in an oxygen-enriched atmosphere. Fires can result from direct laser illumination, reflected laser light, or incandescent particles of tissue blown from the surgical site. [57] Initially, most fires are located solely on the external surface of the endotracheal tube, where they can cause local thermal destruction. If a fire is unrecognized and burns through to the interior of the tube, the oxygen-enriched gas combined with the to-and-fro gas flow due to ventilation will produce a blowtorch-like flame, blowing heat and toxic products of combustion down to the pulmonary parenchyma (Fig. 64-7) (Figure Not Available) . Puncture and unrecognized deflation of the tube cuff may also permit oxygen-enriched gas to flood the operative site and increase the chance of a devastating fire following a subsequent laser burst.

Two strategies have been developed to reduce the incidence of airway fire: (1) reduce the flammability of the endotracheal tube, and (2) remove flammable materials from the airway by using a metallic venturi jet ventilation cannula or intermittent extubation with or without apnea. Each of these is discussed later.

Relative Flammability: Effect of Tube Composition

Given that all common endotracheal tubes are potentially flammable, the relative risks of the various types of construction material have been well studied. For many years, reusable red rubber tubes were commonplace, but these were supplanted by clear polyvinylchloride (PVC) plastic tubes. Modern PVC strongly absorbs far-infrared light and is thus very sensitive to CO_2 laser energy. PVC tubes appear to be much more easily ignited by CO_2 lasers than red rubber tubes [52] [58] [59] and to produce more toxic combustion products. *In vitro,* PVC is transparent and thus is immune to Nd:YAG and visible laser light; however, a thin coating of mucus or blood *in vivo* will absorb energy and restore the hazard. [60] Commercially available tubes fabricated of PVC without opaque lettering or barium stripe make claims of laser resistance based on the *in vitro* tests--however, caveat emptor ("let the buyer beware").

Two studies of the effects of Nd:YAG laser energy on common types of tubes, including those designed to be resistant to laser irradiation, revealed that endotracheal tubes of all materials are, in fact, quite vulnerable. [61] [62] Ossoff et al [58] compared the extent of acute damage to the trachea from blowtorch-type ignitions in dogs ventilated with 1 percent halothane and 70 percent nitrous oxide (balance oxygen) through PVC, rubber, or silicone endotracheal tubes. PVC ignited and developed intense flame the soonest, resulting in widespread deposit of carbonaceous debris and significant ulceration and inflammation of the trachea on postmortem analysis. Red rubber tubes were more resistant to ignition and produced less debris and inflammation. Silicone tubes were the most resistant to ignition, but they produced copious white silica ash, suggesting the potential for late development of silicosis. Ossoff [63] subsequently measured the time to intraluminal ignition during exposure to CO_2 laser energy to determine resistance to ignition and reversed the ranking of silicone and red rubber, PVC remaining the most vulnerable. He also found that addition of 2 percent halothane vapor retarded ignition. Once ignition occurs, the index of flammability is the minimum inspired oxygen fraction (F_{IO_2}) necessary to maintain combustion. Wolf and Simpson [64] reported that PVC is actually less flammable than silicone or red rubber, having a flammability index of 0.26 versus 0.19 for silicone and 0.19 for red rubber. When nitrous oxide was used as the oxidant, PVC retained the highest index (0.46), followed by silicone (0.41) and red rubber (0.37).

Despite the conflicting data, many authors recommend the use of red rubber endotracheal tubes during laser surgery of the aerodigestive tract and base this suggestion on criteria of resistance to ignition and least toxic combustion products. However, at the University of California, San Francisco, one surgeon has performed more than 4,000 microdirect laryngoscopies using a CO_2 laser, incurring only 2 fires (0.005%) and no significant fire-related morbidity (H.H. Dedo, personal communication, 1992), with aluminum-taped PVC endotracheal tubes and moistened pledgets (see later). Regardless of the tube substrate, there are additional safety considerations and maneuvers to consider, as outlined later.

Effect of Respiratory Gas Mixture

The mixture of airway gases becomes an important issue when any type of potentially flammable endotracheal tube is

used. Combustion is more vigorous when excess oxidizer is present, and most clinicians recognize the need to reduce the F_{IO_2} to less than 0.40 or to the minimum concentration consistent with patient oxygenation. That nitrous oxide also is a powerful oxidizer is less well recognized, but adding nitrous oxide as a diluent for oxygen is just as dangerous as having a high F_{IO_2} . [64] Use of an air-oxygen mixture appears to be acceptable. Some investigators prefer helium as a diluent to nitrogen because helium has a higher thermal conductivity and may delay the ignition of an endotracheal tube for a few seconds. [63] [65] However, the index of flammability is reduced by only 1 to 2 percent when oxygen-helium is substituted for oxygen-nitrogen. [66] Helium also has a lower density and allows the use of a smaller endotracheal tube without turbulence and high flow resistance. [67] [68] [69]

The volatile anesthetics currently used in clinical practice are nonflammable and nonexplosive in clinically relevant concentrations. [70] [71] During an airway fire, however, they may undergo pyrolysis to potentially toxic compounds. [72] Thus, the ANSI Z136.3 standard recommends not using volatile anesthetics during airway laser surgery. This is an extremely conservative stance given the low concentration of anesthetic gas as compared with the products of combustion from an endotracheal tube and the lack of evidence of toxicity due to the pyrolytic products. When venturi ventilation is used, administration of volatile agents usually is not

practical.

Protection of the Endotracheal Tube

Once the possibility of endotracheal tube ignition was raised, extrinsic protection of the tubes was suggested. [73] Patil and colleagues [74] suggested wrapping tubes with moistened muslin. However, if allowed to dry, muslin becomes flammable. Kumar and Frost [75] suggested coating the vulnerable portion of the exterior of the tube with dental acrylic. This approach, however, renders the tube rigid with a rough surface, which may traumatize the mucosal surfaces. The most popular approach to the problem has been wrapping the tube with metallized foil tape. [50] [59] [61] [63] [73] [76] [77]

Three types of tape have been used: aluminum foil with adhesive backing, copper foil with adhesive backing, and plastic tape thinly coated with metal on one side and adhesive on the other. These tape products are widely available from electronics, arts and crafts, and building supply shops. Lead foil (commonly used on windows for burglar alarms) is similar in appearance but is toxic and should never be used in the airway.

The aluminum and copper tapes have been evaluated for protection of different types of endotracheal tubes with various lasers. Although taping does not provide protection of the inflatable cuff portion of an endotracheal tube, these metal tapes do offer a measure of protection against inadvertent, brief, or unfocused far-infrared CO_2 laser hits to the taped portion of the tube shaft. Metallic tapes, however, are a less certain shield against the near-infrared beam from Nd:YAG. The solid copper (1-mil foil from Venture Tape Corp., Rockland, Mass) or aluminum (No. 425 or 433 from 3M Corp., Industrial Tape Division, St. Paul, Minn) tapes were able to withstand at least 60 seconds of direct Nd:YAG laser exposure without penetration or ignition. [77] An Emergency Care Research Institute (ECRI) study [78] found that the 3M aluminum tape provided protection against CO_2 and KTP:Nd:YAG, but it did allow ignition of a PVC tube at the highest power setting of an Nd:YAG laser. Copper tape (No. 1181, 3M Corp., Electrical Products Division, St. Paul, Minn) provided ignition protection from all three lasers. Sosis and Dillon [77] found that metallized plastic tape (Radio Shack No. 44-1155) was actually more easily ignited by Nd:YAG than an unwrapped red rubber tube, with a time to ignition of 6 seconds versus 13 seconds for the unwrapped control. ECRI [78] also found that although the metallized plastic tape was most pliant and least likely to abrade the larynx, it provided protection only against CO_2 lasers, not against Nd:YAG or KTP:Nd:YAG.

Applying a protective metal foil wrap to an endotracheal tube requires some care. A clean tube should be wiped with alcohol to remove residue that could interfere with adhesion, then optionally wiped lightly with Mastisol or tincture of benzoin. The end of the tape should be cut at an angle of about 60 degrees and the cut edge aligned with the proximal end of the cuff junction (Fig. 64-8) . Tape should be wrapped in a spiral, with about 30 percent overlap, to the exit point of the cuff pilot tube. Wrinkles should be eliminated to avoid abrading the tracheal mucosa. The result should eliminate bare tubing or areas of exposed tape adhesive (which is quite flammable). Rewiping the wrapped tube with alcohol will provide a degree of cleanliness prior to tracheal intubation.

Figure 64-8 Cuff wrapping technique. If a wrapped endotracheal tube is the chosen method for laser protection, the technique for wrapping is critical in ensuring protection from both ignition and foil-induced mucosal abrasions. It is often helpful first to paint the tube sparingly with a medical adhesive such as benzoin or Mastisol. The end of the tape should be cut with a scalpel to approximately 60 degrees. Wrapping is begun by aligning the cut end of the tape with the junction of the tube and the proximal end of the cuff and is done in a spiral with a 30 to 50 percent overlap between layers. Wrapping should include the inflation tube for the cuff and should be continued until just short of the pilot balloon, with care taken not to wrinkle the tape at any point.

Although this use is well supported in the medical literature, none of these metal foils currently has FDA approval because their manufacturers have not sought it. Thus, physicians who devise a wrapped endotracheal tube using such tapes incur some product liability risk as a noncertified "manufacturer" should injury occur, especially because there now are FDA-approved commercial products.

The Merocel Laser Guard (Merocel Corp., Mystic, Conn) is a commercial, FDA-approved endotracheal wrap consisting of an adhesive metal foil laminated to a synthetic sponge surface. Properly placed on an endotracheal tube and kept moist, the Merocel product provides protection against CO_2, argon, and KTP:Nd:YAG but not YAG lasers. [79] However, it adds almost 2 mm to the diameter of the endotracheal tube. Like the nonapproved tapes, Laser Guard can be applied only to the shaft of the tube and provides no protection for the cuff.

The FDA also has approved the use of an integral laser-resistant coating in the manufacture of endotracheal tubes. The commercially available Xomed Laser Shield tube (Xomed-Treace, Jacksonville, Fla.) is fabricated from silicone with an outer layer of finely divided aluminum powder in silicone; the aluminized layer extends over the inflatable cuff. However, this tube is specified for use only with CO_2 lasers, a beam power density of less than 4,900 W/cm_2, and an F_{IO_2} of less than 25 percent. Although more resistant to far-infrared radiation than either PVC or red rubber tubing, [79] [80] the Laser Shield nonetheless burns vigorously once ignited *in vitro,* [63] producing friable silica dust. It also may ignite under typical surgical conditions (thus failing the ECRI flammability test). [78] In at least one case, an airway fire involving this tube occurred, [56] resulting in serious injury attributed to an intraluminal fire secondary to laser penetration of the cuff; the laser power settings were within specified limits, but the respiratory gas mixture included an excessive F_{IO_2} and nitrous oxide. A newer version, the Laser Shield II, is approved for use with either CO_2 or KTP lasers. The construction of this version includes a silicone-based tube, which is smoothly wrapped by a coated aluminum tape. The cuff is made of unshielded silicone elastomer, designed to be expanded with saline, and includes methylene blue dye to tint the saline. The tube wrap is specified to withstand *(in vitro)* 35,000 W/cm_2 of CO_2 laser energy or 11,000 W/cm_2 of KTP energy for up to 3 minutes. Blood or mucus on the tube can be expected to reduce its tolerance to laser irradiation by approximately 60 percent.

Protection of the Endotracheal Tube Cuff

The thin plastic envelope of a standard high-volume, low-pressure endotracheal cuff is extremely susceptible to misdirected laser energy. Although combustion is possible, simple puncture may be more common. Unrecognized cuff punctures lead to oxygen enrichment of the gas surrounding the surgical site and endotracheal tube and increase the likelihood of a catastrophic airway fire. Cuffs with significant laser resistance that maintain the mechanical properties necessary to minimize tracheal trauma are not available. Many authors recommend filling the standard Hi-Lo cuff with colored saline both to signal a puncture more clearly and potentially to quench a small cuff fire. The cuff should be placed as far distal in the trachea as possible, and the surgeon should completely cover the visible cuff with moistened cotton pledgets. The cotton strings attached to the pledgets should be replaced by uninsulated wire, and the pledgets should be remoistened as needed. The utility of moistened pledgets in preventing or delaying cuff ignition from CO_2 laser exposure has been confirmed. [81]

Metal Endotracheal Tubes

In 1978, Norton and De Vos [82] introduced a nonflammable endotracheal tube constructed as an interlocking stainless steel spiral coil, resembling electrical cable armor (Baxter Healthcare Corp., Niles, Ill). The manufacture of this endotracheal tube has been discontinued. Its walls were not airtight, and although this property allowed a cooling gas flow to the exterior surface, it could make ventilation difficult in patients with relatively noncompliant lungs, particularly because the tube had no inflatable cuff. Jet ventilation with a modified Sanders venturi coupler was suggested as a means to overcome this problem, [83] as was the use of a separate, slide-on cuff, but these are all flammable and thus pose an ignition risk.

Two other metal endotracheal tubes are commercially available and are approved for use with specific lasers. The Laser Flex tube (Mallinckrodt Inc., St. Louis, Mo) is an airtight stainless steel spiral with two distal, saline-inflatable PVC cuffs (redundant in case of puncture of the proximal cuff). This tube is resistant to CO_2 and KTP laser energy, [84] but not to the Nd-YAG laser. [78] The Bivona Fome-Cuf (Bivona Inc., Gary, Ind) is an aluminum spiral tube with an outer covering of silicone and a unique, self-inflating foam sponge-filled cuff, which prevents deflation following puncture. This feature allows continued positive-pressure ventilation and segregation of airway gases from the operative site, but it may lead to injury if a puncture of the cuff or of the filling tube prevents deflation prior to removal. The Fome-Cuf is approved for use only with pulsed CO_2 lasers.

The use of laser-resistant endotracheal tubes requires particular care to prevent mucosal abrasions, because these tubes tend to be bulkier and more rigid than conventional tubes. Surgeons must ensure that laser energy is not reflected from smooth metal surfaces and directed at sensitive structures. Finally, use of a metal

endotracheal tube does not imply absolute protection from ignition; 50 W of an Nd:YAG beam focused to 0.68 mm has been reported to ignite a Laser Flex tube in 6 seconds. [85]

Jet Ventilation

Some authors contend that optimal surgical conditions and patient safety can be obtained with "jet" ventilation. This technique takes advantage of Bernoulli's venturi principle to augment the ventilation produced by a narrow, high-speed gas stream. In practice, jet ventilation uses an intermittent high-pressure oxygen supply, directed at the glottis through a small metal tube, such as a ventilating bronchoscope, or even a 12-gauge blunt needle. [86] [87] [88] [89] [90] [91] A retrospective review of 942 cases of microdirect laryngoscopy using endolaryngeal jet

---

Figure 64-9 Complications of laser airway surgery. Pneumothorax was relatively common with jet ventilation, but potentially lethal airway fires occurred with endotracheal intubation. *(Based on data by Cozine et al [97])*

ventilation found only four complications. [92] Jet ventilation with air also has been used via a bronchoscope when resecting distal tracheal and bronchial tumors. [93] [94] [95] [96] It has been suggested that patients undergoing laser resections of airway tumors during jet ventilation may absorb carbon monoxide from entrained laser smoke in the pharynx. The carbon monoxide, in turn, can result in an overestimate of arterial oxygen saturation by pulse oximetry. Goldhill and colleagues [95] found neither a significant increase in carboxyhemoglobin during Nd:YAG bronchoscopy nor a difference in pulse oximetry reading versus *in vitro* co-oximeter measurement of arterial oxygen saturation. Although jet ventilation generally provides adequate ventilation without introducing flammable material or a large obstacle to the surgical field, potential disadvantages include the following: the risk of barotrauma, pneumothorax, or crepitus; the restriction to intravenous agents; gastric distention; and the relative requirement for compliant lungs. In the presence of papillomas, a common indication for laryngeal laser surgery, jet ventilation could cause distal bronchial seeding with active virus. However, Shikowitz and colleagues [92] found no evidence of this phenomenon in 96 patients who had multiple laser procedures and were followed over time. Cozine et al, [97] in a survey of 58 institutions (15,701 cases) performing CO_2 laser airway surgery, found a higher rate of ventilatory complications with jet ventilation than with a standard endotracheal tube (Fig. 64-9) , but the only fatality was due to an endotracheal tube fire. [97] The authors concluded that no single mode of ventilation proved superior during laser surgery.

To reduce obstruction of the surgical field by ventilatory instrumentation even further, several authors have advocated complete removal of such instrumentation combined with the technique of spontaneous ventilation or intermittent apnea, with general anesthesia provided by nasal insufflation or bronchoscopic delivery of a potent inhaled anesthetic [47] [72] [98] [99] or use of an intravenous anesthetic. [100] Cohen et al [101] and Hawkins and Joseph [102] have advocated modest hyperventilation followed by intermittent tracheal extubation by the surgeon for periods of 90 to 120 seconds, during which the laser is used. Pulse oximetry adds a measure of safety by confirming adequate oxygenation from a denitrogenated pulmonary residual capacity during apnea.

Other Considerations

Although not specifically related to laser procedures in the airway, vagal hyperactivity often occurs during instrumentation of the trachea. Immediate recognition and treatment are important. In addition, the paraneoplastic syndrome occasionally observed in small cell and other types of endobronchial tumors may lead to prolonged weakness after administration of neuromuscular relaxants. [103]

AIRWAY FIRE PROTOCOL

Should an airway fire or explosion occur, the surgeon and anesthesiologist must act quickly, decisively, and in coordinated fashion. This may not be easy following an explosion, because the event may be so traumatic as to incapacitate the operating room staff temporarily. Clear communication and emergency practice (at least a mental drill of the emergency procedure) are key to managing such a crisis. Schramm and colleagues [104] have provided a useful review of the ensuing pathologic features and have suggested emergency management.

A surgeon who detects an endotracheal or other source of airway fire should as quickly as possible remove the source and simultaneously inform the anesthesiologist, who should immediately, despite reflexive training to the contrary, stop ventilation. Temporarily disconnecting the breathing circuit from the anesthesia machine may be useful. These maneuvers remove the flame and the retained heat in the tube and stop the flow of oxygen-enriched gas. The flaming material should be extinguished in a bucket of water, which should always be available during laser surgery. Ventilation with 100 percent oxygen should then be provided by mask, and anesthesia should be continued.

Direct laryngoscopy and rigid (venturi-ventilating) bronchoscopy should then be performed to survey damage and to remove debris. If the fire was of the "interior blowtorch" type, gentle bronchial lavage may be indicated, followed by fiberoptic assessment of the more distal airways. If any airway damage is apparent, the patient should be reintubated. Fortunately, small fires involving only the exterior of the tube may not cause appreciable damage. If the damage is severe, a low tracheotomy may be indicated.

The pattern of damage in interior fires tends to be worst in the upper airway and diminishes as one approaches and passes the carina. The patient's oropharynx and face should be assessed, and a chest radiograph should be obtained. Pulmonary damage due to heat and/or smoke inhalation may necessitate prolonged intubation and mechanical ventilation. A brief course of high-dose steroids may be helpful. [105] [106]

Lasers provide a useful tool in the surgical armamentarium, one for which anesthesiologists must, with increasing frequency, prepare their patients and themselves. Although some of the potential threats posed by clinical lasers are unique, most are simply extensions of the risks posed by the previous generation of surgical tools. As with most potentially dangerous procedures, the risks of laser use can be minimized by common sense and preconsidered contingency plans.

References

1. Maxwell JC: A Treatise on Electricity and Magnetism. Oxford, Clarendon, 1873 (Landmarks of Science Series Microfiche, New York, Readex, 1967).

2. Planck M: Verh Dtsch Phys Ges 2:202, 1900.

3. Einstein A: Zur Electrodynamik bewegter Korper. Ann Physik 17:132, 1905.

4. Schawlow AL, Townes CH: Infrared and optical masers. Phys Rev 112:1940, 1958.

5. Daikuzono N, Joffe SN: Artificial sapphire probe for contact photocoagulation and tissue vaporization with the Nd:YAG laser. Med Instrum 19:173, 1985.

6. Baggish MS, Daniell JF: Catastrophic injury secondary to the use of coaxial gas-cooled fibers and artificial sapphire tips for intrauterine surgery: A report of five cases. Lasers Surg Med 9:581, 1989.

7. Shirk GJ: Use of the Nd:YAG Laser with Sapphire Scalpels. Philadelphia, JB Lippincott, 1991.

8. Quigley MR, Shih T, Elrifai A et al: Percutaneous laser discectomy with the Ho:YAG laser. Lasers Surg Med 12:621, 1992.

9. Ahn SS, Eton D, Moore WS: Endovascular surgery for peripheral arterial occlusive disease: A critical review. Ann Surg 216:3, 1992.

10. Allendorf JD, Bessler M, Huang J et al: Helium-neon laser irradiation at fluences of 1, 2, and 4 J/cm ^{2} failed to accelerate wound healing as assessed by both wound contracture rate and tensile strength. Lasers Surg Med 20:340, 1997.

11. U.S. Food and Drug Administration: Suggested State Regulations for Control of Radiation, vol 2: Lasers. Washington, DC, U.S. Government Printing Office, 1983.

12. U.S. Food and Drug Administration: Special report: Laser safety. Laser Nurs 4:3, 1990.

13. Nezhat C, Winer WK, Nezhat F et al: Smoke from laser surgery: Is there a health hazard? Lasers Surg Med 7:376, 1987.

14. Baggish MS, Elbakry M: The effects of laser smoke on the lungs of rats. Am J Obstet Gynecol 156:1260, 1987.

15. Freitag L, Chapman G, Sielczak M et al: Laser smoke effect on the bronchial system. Laser Surg Med 7:283, 1987.

16. Kokosa J, Eugene J: Chemical composition of laser-tissue interaction smoke plume. J Laser Appl 2:59, 1989.

17. Tomita Y, Mihashi S, Nagata K et al: Mutagenicity of smoke condensates induced by CO_2 -laser and electrocauterization. Mutat Res 89:145, 1981.

18. Ferenczy A, Bergeron C, Richart RM: Human papillomavirus DNA in CO_2 laser-generated plume of smoke and its consequences to the surgeon. Obstet Gynecol 75:114, 1990.

19. Ferenczy A, Bergeron C, Richart RM: Carbon dioxide laser energy disperses human papillomavirus deoxyribonucleic acid onto treatment fields. Am J Obstet Gynecol 163:1271, 1990.

20. Sawchuk WS, Weber PJ, Lowy DR et al: Infectious papillomavirus in the vapor of warts treated with carbon dioxide laser or electrocoagulation: Detection and protection. J Am Acad Dermatol 21:41, 1989.

21. Abramson AL, DiLorenzo TP, Steinberg BM: Is papillomavirus detectable in the plume of laser-treated laryngeal papilloma? Arch Otolaryngol Head Neck Surg 116:604, 1990.

22. Johnson GK, Robinson WS: Human immunodeficiency virus-1 (HIV-1) in the vapors of surgical power instruments. J Med Virol 33:47, 1991.

23. Baggish MS, Poiesz BJ, Joret D et al: Presence of human immunodeficiency virus DNA in laser smoke. Lasers Surg Med 11:197, 1991.

24. Wisniewski PM, Warhol MJ, Rando RF et al: Studies on the transmission of viral disease via the CO_2 laser plume and ejecta. J Reprod Med 35:1117, 1990.

25. Voorhies RM, Lavyne MH, Strait TA et al: Does the CO_2 laser spread viable brain-tumor cells outside the surgical field? J Neurosurg 60:819, 1984.

26. Oosterhuis JW: Tumor Surgery With the CO_2 Laser: Studies With the Cloudman S91 Mouse Melanoma. Groningen, Netherlands, Veenstra-Visser, 1977.

27. Walker NP, Matthews J, Newsom SW: Possible hazards from irradiation with the carbon dioxide laser. Lasers Surg Med 6:84, 1986.

28. Byrne PO, Sisson PR, Oliver PD et al: Carbon dioxide laser irradiation of bacterial targets *in vitro.* J Hosp Infect 9:265, 1987.

29. Smith JP, Moss CE, Bryant CJ et al: Evaluation of a smoke evacuator used for laser surgery. Lasers Surg Med 9:276, 1989.

30. Smith JP, Topmiller JL, Shulman S: Factors affecting emission collection by surgical smoke evacuators. Lasers Surg Med 10:224, 1990.

31. Faintuch JS: Endoscopic laser therapy in colorectal carcinoma. Hematol Oncol Clin North Am 3:155, 1989.

32. D'Hallewin MA, Clays K, Persoons A et al: Large-bowel perforation: A rare complication of intravesical Nd-YAG laser irradiation of bladder tumors. Urol Int 44:373, 1989.

33. Radford CM, Ahlquist DA, Sarr MG et al: Endoscopic gastric vagotomy: A feasibility study using laser in dogs. Gastrointest Endosc 35:419, 1989.

34. Dittrich K, Armbruster C, Hoffer F et al: Nd:YAG laser treatment of colorectal malignancies: An experience of 4½ years. Lasers Surg Med 12:199, 1992.

35. Ganfield RA, Chapin JW: Pneumothorax with upper airway laser surgery. Anesthesiology 56:398, 1982.

36. Challener RC, Kaufman B: Fatal venous air embolism following sequential unsheathed (bare) and sheathed quartz fiber Nd-YAG laser endometrial ablation. Anesthesiology 73:548, 1990.

37. Jamieson WM, Chamberlain JA: Patient response to endometrial ablation with the Nd:YAG laser. Lasers Surg Med 7:37, 1989.

38. Peachey T, Eason J, Moxham J et al: Systemic air embolism during laser bronchoscopy. Anaesthesia 43:872, 1988.

39. Ross DJ, Mohsenifar Z, Potkin RT et al: Pathogenesis of cerebral air embolism during neodymium-YAG laser photoresection. Chest 94:660, 1988.

40. Greville AC, Clements EA, Erwin DC et al: Pulmonary air embolism during laparoscopic laser cholecystectomy. Anaesthesia 46:113, 1991.

41. Golish JA, Pena CM, Mehta AC: Massive air embolism complicating Nd-YAG laser endobronchial photoresection. Lasers Surg Med 12:338, 1992.

42. Bauman N: Laser drape fires: How much of a risk? Laser Med Surg News Adv 7:2, 1989.

43. Berg P: Laser starts fire in operating room. Washington Post, Feb. 2, WH:5, 1988.

44. Liebowitz HM, Peacock GR: Corneal injury produced by carbon dioxide laser radiation. Arch Ophthalmol 52:993, 1980.

45. Wolbarski M, Fligster KE, Hayes JR: Pathology of neodymium and ruby laser burns. Science 150:1453, 1965.

46. Garry BP, Bivens HE: Anesthetic technique for safe laser use in surgery. Semin Surg Oncol 6:184, 1990.

47. Keon TP: Anesthetic considerations for laser surgery. Int Anesthesiol Clin 26:50, 1988.

48. Spiess BD, Ivankovich AD: Anesthetic management of laser airway surgery. Semin Surg Oncol 6:189, 1990.

49. Snow JC, Norton ML, Salvja TS et al: Fire hazard during CO_2 laser microsurgery on the larynx and trachea. Anesth Analg 55:146, 1976.

50. Hermens JM, Bennett MJ, Hirschman CA: Anesthesia for laser surgery. Anesth Analg 62:218, 1983.

51. Fried MP: A survey of the complications of laser laryngoscopy. Arch Otolaryngol 110:31, 1984.

52. Healy GB, Strong MS, Shapshay S et al: Complications of CO_2 laser surgery of the aerodigestive tract: Experience of 4,416 cases. Otolaryngol Head Neck Surg 92:13, 1984.

53. Burgess GEI, Le Juene FEJ: Endotracheal tube ignition during laser surgery of the larynx. Arch Otolaryngol Head Neck Surg 105:561, 1979.

54. Meyers A: Complications of CO_2 laser surgery of the larynx. Ann Otol Rhinol Laryngol 90:132, 1981.

55. Cozine K, Rosenbaum LM, Askanazi J et al: Laser-induced endotracheal tube fire. Anesthesiology 55:583, 1981.

56. Sosis MB: Airway fire during CO_2 laser surgery using a Xomed laser endotracheal tube. Anesthesiology 72:747, 1990.

57. Hirschman CA, Smith J: Indirect ignition of the endotracheal tube during carbon dioxide laser surgery. Arch Otolaryngol Head Neck Surg 106:639, 1980.

58. Ossoff RH, Duncavage JA, Eisenman TS et al: Comparison of tracheal damage from laser-ignited endotracheal tube fires. Ann Otol Rhinol Laryngol 92:333, 1983.

59. Patel KF, Hicks JN: Prevention of fire hazards associated with the use of carbon dioxide lasers. Anesth Analg 60:885, 1981.

60. Sosis M, Dillon F: Hazards of a new, clear, unmarked polyvinylchloride tracheal tube designed for use with the Nd-YAG laser. J Clin Anesth 3:358, 60, 1991.

61. Sosis MB: What is the safest endotracheal tube for Nd-YAG laser surgery? A comparative study. Anesth Analg 69:802, 1989.

62. Geffin B, Shapshay SM, Bellack GS et al: Flammability of endotracheal tubes during Nd-YAG laser application in the airway. Anesthesiology 65:511, 1986.

63. Ossoff RH: Laser safety in otolaryngology--head and neck surgery: Anesthetic and educational considerations for laryngeal surgery. Laryngoscope 99:1, 1989.

64. Wolf GL, Simpson JI: Flammability of endotracheal tubes in oxygen and nitrous oxide enriched atmosphere. Anesthesiology 67:236, 1987.

65. Pashayan AG, Gravenstein JS: Helium retards endotracheal tube fires from carbon dioxide lasers. Anesthesiology 62:274, 1985.

66. Simpson JI, Schiff GA, Wolf GL: The effect of helium on endotracheal tube flammability. Anesthesiology 73:538, 1990.

67. Lu T, Ohmura A, Wong KC et al: Helium-oxygen treatment of upper airway obstruction. Anesthesiology 45:678, 1976.

68. Pashayan AG, Gravenstein JS, Cassisi NJ et al: The helium protocol for laryngotracheal operations with CO_2 laser: A retrospective review of 523 cases. Anesthesiology 68:801, 1988.

69. Rampil IJ: Helium and gas flow (in response). Anesth Analg 76:453, 1993.

70. Brown TA, Morris G: The ignition risk with mixtures of oxygen and nitrous oxide with halothane. Br J Anaesth 38:164, 1966.

71. Leonard PF: The lower limits of flammability of halothane, enflurane, and isoflurane. Anesth Analg 54:238, 1975.

72. Hunton J, Oswal VH: Anaesthetic management for carbon dioxide laser surgery in tracheobronchial lesions. Anaesthesia 42:1222, 1987.

73. Snow JC, Kripke BJ, Strong MS et al: Anesthesia for carbon dioxide microsurgery on the larynx and trachea. Anesth Analg 53:507, 1974.

74. Patil V, Stehling LC, Zauder HL: A modified endotracheal tube for laser microsurgery (letter). Anesthesiology 51:571, 1979.

75. Kumar A, Frost E: Prevention of fire hazard during laser microsurgery (letter). Anesthesiology 54:350, 1981.

76. Sosis MB: Evaluation of five metallic tapes for protection of endotracheal tubes during CO_2 laser surgery. Anesth Analg 68:392, 1989.

77. Sosis M, Dillon F: What is the safest foil tape for endotracheal tube protection during Nd-YAG laser surgery? A comparative study. Anesthesiology 72:553, 1990.

78. Emergency Care Research Institute: Laser-resistant endotracheal tubes and wraps. Health Devices 19:112, 1990.

79. Fontenot RJ, Bailey BJ, Stiernberg CM et al: Endotracheal tube safety during laser surgery. Laryngoscope 97:919, 1987.

80. Hayes DM, Gaba DM, Goode RL: Incendiary characteristics of a new laser-resistant endotracheal tube. Otolaryngol Head Neck Surg 95:37, 1986.

81. Sosis MB: Saline soaked pledgets prevent carbon dioxide laser-induced endotracheal tube cuff ignition. J Clin Anesth 7:395, 1995.

82. Norton ML, De Vos P: New endotracheal tube for laser surgery of the larynx. Ann Otol Rhinol Laryngol 87:554, 1978.

83. Woo P, Strong MS: Venturi ventilation through the metal endotracheal tube: A nonflammable system. Ann Otol Rhinol Laryngol 92:405, 1983.

84. Fried MP, Mallampati SR, Liu FC et al: Laser resistant stainless steel endotracheal tube: Experimental and clinical evaluation. Lasers Surg Med 11:301, 1991.

85. Sosis MB: What is the safest endotracheal tube for Nd-YAG laser surgery? A comparative study. Anesth Analg 69:802, 1989.

86. Anand VK, Herbert J, Robbett WF et al: Safe anesthesia for endoscopic laryngeal laser surgery. Lasers Surg Med 7:275, 1987.

87. Herbert JT, Berlin I, Eberle R: Jet ventilation via a copper endotracheal tube for CO_2 laser surgery of the oropharynx. Laryngoscope 95:1276, 1985.

88. Borland LM, Reilly JS: Jet ventilation for laser laryngeal surgery in children: Modification of the Saunders jet ventilation technique. Int J Pediatr Otorhinolaryngol 14:65, 1987.

89. Crockett DM, McCabe BF, Shive CJ: Complications of laser surgery for recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 96:639, 1987.

90. Gussack GS, Evans RF, Tacchi EJ: Intravenous anesthesia and jet ventilation for laser microlaryngeal surgery. Ann Otol Rhinol Laryngol 96:29, 1987.

91. Paes ML: General anaesthesia for carbon dioxide laser surgery within the airway: A review. Br J Anaesth 59:1610, 1987.

92. Shikowitz MJ, Abramson AL, Liberatore L: Endolaryngeal jet ventilation: A 10-year review. Laryngoscope 101:455, 1991.

93. Blomquist S, Algotsson L, Karlsson SE: Anaesthesia for resection of tumours in the trachea and central bronchi using the Nd-YAG-laser technique. Acta Anaesthesiol Scand 34:506, 1990.

94. George PJ, Garrett CP, Nixon C et al: Laser treatment for tracheobronchial tumours: Local or general anaesthesia? Thorax 42:656, 1987.

95. Goldhill DR, Hill AJ, Whitburn RH et al: Carboxyhaemoglobin concentrations, pulse oximetry and arterial blood-gas tensions during jet ventilation for Nd-YAG laser bronchoscopy. Br J Anaesth 65:749, 1990.

96. Jackson KA, Morland MH: Anaesthesia for resection of lesions of the trachea and main bronchi using the neodymium yttrium aluminum garnet (Nd YAG) laser: A report of 75 treatments in 52 patients. Anaesth Intensive Care 18:69, 1990.

97. Cozine K, Stone JG, Shulman S et al: Ventilatory complications of carbon dioxide laser laryngeal surgery. J Clin Anesth 3:20, 1991.

98. Talmage EA: Safe combined general and topical anesthesia for laryngoscopy and bronchoscopy. South Med J 66:455, 1973.

99. Johans TG, Reichert TJ: An insufflation device for anesthesia during subglottic carbon dioxide laser microsurgery in children. Anesth Analg 63:368, 1984.

100. Aun CS, Houghton IT, So HY et al: Tubeless anaesthesia for microlaryngeal surgery. Anaesth Intensive Care 18:497, 1990.

101. Cohen SR, Herbert WI, Thompson JW: Anesthesia management of microlaryngeal laser surgery in children: Apneic technique anesthesia. Laryngoscope 98:347, 1988.

102. Hawkins DB, Joseph MM: Avoiding a wrapped endotracheal tube in laser laryngeal surgery: Experiences with apneic anesthesia and metal laser-flex endotracheal tubes. Laryngoscope 100:1283, 1990.

103. Hanowell LH, Martin WR, Savelle JE et al: Complications of general anesthesia for Nd:YAG laser resection of endobronchial tumors. Chest 99:72, 1991.

104. Schramm VLJ, Mattox DW, Stool SE: Acute management of laser-ignited intratracheal explosion. Laryngoscope 91:1417, 1981.

105. Demling RH: Smoke inhalation injury. Postgrad Med 82:63, 1987.

106. Dressler DP, Skornik WA, Kupersmith S: Corticosteroid treatment of experimental smoke inhalation. Ann Surg 183:46, 1976.

107. Emergency Care Research Institute: Airway fires: Reducing the risk during laser surgery. Health Devices 19:109, 1990.

Chapter 65 - Outpatient Anesthesia *

Janet M. van Vlymen
Paul F. White

INTRODUCTION

In the early 1900s, a legendary American anesthesiologist, Ralph Waters, opened his Downtown Anesthesia Clinic in Sioux City, Iowa. [1] This facility, which provided care for dental and minor surgery cases, is generally regarded as the prototype for the modern freestanding ambulatory unit. However, there was little further interest in ambulatory surgical care until the 1960s, when the first hospital-based ambulatory surgery units were developed. Over the past 3 decades, outpatient surgery has grown at an exponential rate, progressing from the practice of performing simple procedures on healthy patients in a physician's office to encompass a broad spectrum of patient care in freestanding ambulatory surgery centers and offices. The formal development of ambulatory anesthesia as a subspecialty occurred with the establishment of the Society for Ambulatory Anesthesia (SAMBA) in 1984 and with the evolution of postgraduate subspecialty training programs.

By 1985, 7.3 million elective operations in the United States (34% of all elective surgical procedures) were performed on an ambulatory basis. Today, more than 60 percent of all elective surgery is performed in the outpatient surgical setting, and by the end of the century, it is expected that this number will increase to more than 70 percent. [2] This rapid growth in ambulatory surgery would have not been possible without the changing role of the anesthesiologist and the development of more highly titratable anesthetic drugs and less invasive surgical techniques. [3] The availability of rapid, shorter-acting anesthetic, analgesic, and muscle-relaxant drugs has facilitated the recovery process, allowing more extensive procedures to be performed on a wide variety of outpatients. [4] Future studies of new drugs need to focus not only on subjective improvement during the immediate perioperative period, but also on the overall cost-effectiveness and quality of care being provided. These studies should emphasize meaningful outcomes such as time to resume normal activities or return to work. [5]

The range of acceptable ambulatory surgical patients and procedures continues to expand. Because patients presenting for outpatient surgery may have increasingly complex medical conditions, the anesthesiologist must play an active role in their preoperative assessment and preparation in order to avoid costly delays and cancellations. [6] In modern outpatient facilities, surgical procedures may be safely performed without sacrificing quality while minimizing hospital resources. [7] In this era of cost containment, the savings inherent in providing ambulatory services ensure that the number of outpatient procedures will continue to grow into the 21st century.

BENEFITS OF AMBULATORY SURGERY

Ambulatory surgery can offer a number of advantages for patients, health-care providers, third-party payers, and even hospitals (Table 65-1) . Many patients, especially children and the elderly, prefer to have their surgical procedures performed as outpatients because it decreases separation from

* *See Appendix 1, Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists*

TABLE 65-1 -- Benefits of Ambulatory Surgery

Patient preference, especially children and elderly
Lack of dependence on availability of hospital beds
Greater flexibility in scheduling operations
Low morbidity and mortality
Lower incidence of infection
Lower incidence of respiratory complications
Higher volume of patients (greater efficiency)
Shorter surgical waiting lists
Lower overall procedural costs
Less preoperative testing and postoperative medication

their familiar home environment. One survey of patient satisfaction reported that 97 percent of respondents would choose day surgery again. [8] Unlike inpatient surgery, ambulatory surgery does not depend on the availability of a hospital bed, and thus there is a greater degree of flexibility for patients to schedule the timing of their operation. Outpatient surgery may be performed very safely with a low incidence of both minor and major morbidity. [9] Studies have shown that unanticipated admission to the hospital occurs in only 1 percent of patients, and return visits to the hospital occur in only 3 percent of patients following ambulatory surgical procedures. [10] [11] [12] The lower infection rate associated with outpatient surgery is particularly beneficial to pediatric and immunocompromised patients. [13] Finally, there is evidence that the incidence of respiratory complications (i.e., pulmonary embolus and pneumonia) may also be decreased. [14]

There are economic benefits associated with ambulatory surgery. The efficiency of ambulatory centers appears to be significantly increased, with shorter operating room times and faster turnaround times. [7] The ability to care for high volumes of patients may considerably reduce surgical waiting lists. Compared with similar procedures in hospitalized patients, there is less preoperative laboratory testing and a reduced demand for postoperative medications after ambulatory surgical procedures. These factors all contribute to the 25 to 75 percent reduction in overall costs for most operations performed in the outpatient setting. [15] However, procedures requiring specialized postoperative care (e.g., extensive physical therapy or pain management) may actually be more costly when performed on an outpatient basis. [16] Patients requiring blood transfusions or intravenous antibiotics may best be handled as same-day (23-hour) admissions, although modern home nursing and physical therapy may soon enable most of these services to be performed in the patient's home. Assuming that the number of available hospital beds declines in the future, the continued growth of ambulatory surgery should increase the return on increasingly limited health-care dollars.

FACILITY DESIGN AND SAFETY

Ambulatory surgical facilities need to be well designed in order to ensure optimal delivery of surgical services at reduced cost. In the late 1960s, it was proposed that a facility for performance of general anesthesia and minor surgical procedures did not need to be affiliated with a hospital. The first freestanding outpatient surgical facility was built and managed by a group of anesthesiologists in Phoenix, Arizona to provide surgical care to patients whose operations were too demanding for a surgeon's office yet did not require overnight hospitalization. [17] Since that time, outpatient surgical facilities have continued to grow and evolve. [18] Today, these facilities are found in a wide variety of different environments that reflect their association with other health-care facilities. There are four basic designs of a prototypical ambulatory surgical unit [19] :

1. *Hospital-integrated:* Ambulatory surgical patients are managed through the same surgery facility as inpatients. The outpatients may have separate preoperative preparation and second-stage recovery areas.
2. *Hospital-based:* There is a separate ambulatory surgical facility located within a hospital that handles only outpatients.
3. *Freestanding:* These facilities may be associated with hospitals but are housed in separate buildings that share no space or patient care functions. The preoperative evaluation, surgical care, and recovery occur within this unit.
4. *Office-based:* The operating suites are managed in conjunction with physicians' offices for the convenience of the surgeons.

There are many specific requirements to consider when planning an ambulatory surgical facility. The patient volume, types of patients and procedures, organizational structure, and radiologic and laboratory testing must all be considered during the initial planning of a new facility. To be optimally efficient, it is necessary to assemble all the outpatient services in one dedicated area. Designs that place the waiting room, preanesthesia room, operating suites, and recovery areas in proximity have many advantages. [20] Surgeons are able to visit the patient and family before and after the operation without losing time in transit. Patient transportation time is reduced to a minimum, and extra personnel are unnecessary because the circulating nurse or anesthesiologist can transport the patient to the operating room (Fig. 65-1) (Figure Not Available) .

Quality assurance and total quality improvement are necessary to maintain high standards for outpatient care and to ensure safety. Quality standards are set and enforced either by government regulation, through a licensing process, or by accreditation by private organizations such as the Accreditation Association for Ambulatory Health Care, Inc (AAAHC). [21] The AAAHC is an independent accreditation organization whose principal activities are the development of standards, the conduct of surveys, and the conferring of accreditation on ambulatory health-care providers. In the United States and Canada, hospital-based ambulatory surgical facilities receive accreditation through the Joint Commission on Accreditation of Health Care Organizations (JCAHO), which is the primary accreditation agency for hospitals.

The American Society of Anesthesiologists (ASA) also provides guidelines for ambulatory surgical facilities (Appendix 1). The availability of personnel and equipment for unexpected emergencies or a delayed return to the operating room is essential. In-service training of all staff regarding skills that are infrequently required should be given regularly, including advanced cardiac life support, drills for airway complications, emergency tracheotomy, and treatment of malignant hyperthermia (MH). [19] Depending on the size and range of surgical services, a formal cardiac arrest team

Figure 65-1 (Figure Not Available) Essential components related to patient flow in an ambulatory surgery facility. *(Modified from Snyder and Pasternak [15])*

may be needed, and all facilities require a portable crash cart and suction device. General support services for routine laboratory tests, a portable electrocardiography (ECG) machine, and access to a blood supply should be available. A permanent on-site MH kit is required for any location where general anesthesia is performed.

As ambulatory surgery continues to expand, dedicated outpatient facilities will be developed in a variety of settings (e.g., medical centers, surgical clinics, and physicians' offices). Anesthesiologists need to be involved in the initial planning and organization of these facilities to ensure safe, efficient, and economic patient care.

PATIENT SELECTION

Selection of Procedures

Surgical procedures suitable for ambulatory surgery should be accompanied by minimal postoperative physiologic impairment and uncomplicated recovery. [22] [23] With advances in surgical technologies and the rapid growth of minimally invasive surgery, a wide variety of operations may now be performed on an outpatient basis (Table 65-2) . Consequently, published reports have begun to appear regarding the advantages of minimally invasive outpatient thyroidectomy, vaginal hysterectomy, ectopic tubal pregnancy removal, ovarian cystectomy, and laparoscopic cholecystectomy. A report in the *New England Journal of Medicine* suggested that laparoscopic-assisted herniorrhaphy offered significant advantages over conventional open repair with respect to late recovery. [3]

Patients undergoing procedures that are likely to have postoperative surgical complications should be admitted to hospital. Although autologous blood transfusions are used for more extensive outpatient plastic surgery (e.g., reduction mammoplasty, liposuction), procedures associated with excessive fluid shifts are more appropriately handled in an overnight recovery facility. Similarly, operative procedures requiring prolonged immobilization or parenteral analgesic therapy are not ideally suited to ambulatory care. The availability of newer analgesic therapies (e.g., nonopioid, nonpharmacologic) and ambulatory patient-controlled analgesia (e.g., subcutaneous, transcutaneous) may alter the latter recommendation in the near future. [24] [25] [26]

Duration of Surgery

The duration of ambulatory surgery was originally limited to procedures lasting less than 90 minutes. A retrospective review by Meridy [27] showed no correlation between the duration of anesthesia and recovery time, and he concluded that an arbitrary upper limit on the duration of anesthesia was not warranted. More recently, other investigators have demonstrated that surgical time longer than 60 minutes is an independent predictor of unanticipated admission to the hospital [10] [28] and is associated with a higher perioperative complication rate. [14] Nevertheless, longer surgical procedures are regularly performed on outpatients, and with careful preoperative selection and postoperative management (e.g., home health care), hospital admission may be avoidable.

Patient Characteristics

In successful ambulatory surgical facilities, patients are properly selected and prepared for surgery. Most patients

TABLE 65-2 -- Operative Procedures Suitable for Ambulatory Surgery

SPECIALTY	TYPES OF PROCEDURES
Dental	Extraction, restoration, facial fractures
Dermatology	Excision of skin lesions
General	Biopsy, endoscopy, excision of masses, hemorrhoidectomy, herniorrhaphy, laparoscopic procedures, varicose vein surgery
Gynecology	Cone biopsy, dilatation and curettage, hysteroscopy, laparoscopy, polypectomy, tubal ligation, vaginal hysterectomy
Ophthalmology	Cataract extraction, chalazion excision, nasolacrimal duct probing, strabismus repair, tonometry
Orthopedic	Anterior cruciate repair, arthroscopy, bunionectomy, carpal tunnel release, closed reduction, hardware removal, manipulation under anesthesia
Otolaryngology	Adenoidectomy, laryngoscopy, mastoidectomy, myringotomy, polypectomy, rhinoplasty, tonsillectomy, tympanoplasty
Pain Clinic	Chemical sympathectomy, epidural injection, nerve blocks
Plastic	Basal cell cancer excision, cleft lip repair, liposuction, mammoplasty, otoplasty, scar revision, septorhinoplasty, skin graft
Urology	Bladder surgery, circumcision, cystoscopy, lithotripsy, orchiectomy, prostate biopsy, vasovasotomy

TABLE 65-3 -- Relationship Between American Society of Anesthesiologists Physical Status Classification and Morbidity and Mortality

(Not Available)

From Warner et al, [9] copyright 1993 American Medical Association

seen in ambulatory surgical facilities are classified as ASA physical status I or II. However, because of improved anesthesia care, increasing numbers of medically stable patients of ASA status III are able to undergo operations away from conventional medical centers. [2] In a large, prospective outcome study by Warner et al, [9] 24 percent of ambulatory surgical patients were ASA physical status III, and these patients had a similarly low incidence of morbidity when compared with ASA I and II patients (Table 65-3) (Table Not Available) . Other studies showed that patients with preexisting medical conditions do not have an increased incidence of perioperative complications. [29] This was attributed to prudent patient selection involving thorough preoperative evaluation and close communication among surgeon, anesthesiologist, and primary care physician. However, a multicenter study found an increased risk of perioperative complications in patients who had preexisting cardiovascular disease. [14] The risk of complications was reduced when symptoms were under good control for at least 3 months before the operation. Therefore, ASA physical status should not be considered in isolation because the type of surgical procedure, anesthetic technique, and a multitude of social factors can also influence decisions regarding patient suitability. [30]

Malignant Hyperthermia Susceptibility

MH-susceptible patients can be successfully managed with nontriggering anesthetics in the outpatient setting (Ch. 27) . The decision to admit a patient postoperatively should be based on clinical criteria, because admission solely on the basis of MH susceptibility is no longer warranted. [31] If anesthesia and surgery have been uneventful, MH-susceptible patients should be observed for at least 4 hours postoperatively and may then be safely discharged. [32] Patients and their families should be advised about the signs and symptoms of MH in addition to the usual postoperative instructions.

Extremes of Age

Although acceptability of patients at the extremes of age (i.e., <6 months and >70 years) has been questioned by some ambulatory centers, age alone should not be considered a deterrent in the selection of patients for ambulatory surgery (Chs. 59 and 61) . Most studies have failed to demonstrate an age-related increase in recovery time or incidence of complications following outpatient anesthesia. [27] However, recovery of fine motor skills and cognitive function is slowed with increasing age. Therefore, elderly outpatients may require a greater degree of supervision after discharge than their younger counterparts. Social factors, including lack of transportation, a responsible escort, or caretaker at home may make it difficult for some elderly patients to undergo ambulatory procedures.

By contrast, ex-premature infants (gestational age <37 wk) recovering from minor surgical procedures after general anesthesia have an increased risk of developing postoperative apnea. [33] Controversy exists regarding the postconceptual age after which no further risk remains. [34] Most studies suggest that the risk is greatest in premature infants younger than 46 weeks' postconceptual age. [35] [36] However, some authors have reported that the risk of apnea may persist until as late as 60 postconceptual weeks. [37] Anemia, with a hematocrit level less than 30 percent, independently increases the risk of postoperative apnea in former preterm infants less than 60 weeks' postconceptual age. [38] Treatment with high-dose caffeine may prevent prolonged apnea and desaturation in these patients, but postoperative monitoring is still recommended. [39] A combined analysis determined the following: (1) apnea was strongly and inversely related to both gestational and postconceptual age; (2) an associated risk factor was continuing apnea at home; (3) infants who were small for gestational age seemed to be somewhat protected from apnea; (4) anemia was a significant independent risk factor, particularly for patients less than 43 weeks' postconceptual age; and (5) no relationship between apnea and a history of necrotizing enterocolitis, respiratory distress syndrome, bronchopulmonary dysplasia, or intraoperative use of opioid analgesics or muscle relaxants could be demonstrated. [40]

Contraindications to Outpatient Surgery

With ever improving anesthetic and surgical techniques, the types of surgical procedures and patient populations undergoing ambulatory surgery continue to grow. Patients with more complex medical conditions are having longer and more complicated surgical procedures on an ambulatory basis. However, patients with the following conditions appear to be at increased risk for postoperative complications and should be offered the option of overnight hospitalization [23] :

1. Serious, potentially life-threatening diseases that are not optimally managed (ASA III and IV): brittle diabetes, unstable angina, symptomatic asthma
2. Morbid obesity complicated by hemodynamic or respiratory problems
3. Drug therapy: monoamine oxidase inhibitors (e.g., pargyline, tranylcypromine); acute substance abuse (active cocaine abuse increases the risk of intraoperative cardiorespiratory complications)
4. Ex-premature infants less than 60 weeks' postconceptual age
5. Lack of a responsible adult at home to care for the patient on the evening after surgery

PREOPERATIVE VISIT

The preoperative assessment of outpatients has become increasingly important because patients are presenting for ambulatory surgery with more complex medical conditions (Ch. 23) . It is essential to develop a method of screening these patients preoperatively in order to avoid costly delays and last-minute cancellations. [6] This may be accomplished by means of a telephone screening interview [41] or through a visit to a preoperative evaluation clinic. [42] [43] The use of computerized questionnaires before preoperative evaluation by the anesthesiologist can be timesaving and efficient. Modern computerized questionnaires are more accurate in listing positive and negative historical information than a physician interview and can be used to predict the need for preoperative laboratory testing. [44] A laptop computer-type device (HealthQuiz, Nellcor, Hayward, Calif), has been developed that asks patients yes/no questions. The answers are then printed out with the suggested laboratory tests. Clinical trials suggest that this computerized device is readily usable and is accepted by a wide range of patients, thus allowing for more appropriate and cost-effective use of preoperative laboratory testing in the future.

Preoperative Assessment

The preoperative assessment attempts to identify patients who have concurrent medical problems requiring further diagnostic evaluation or treatment. Patients requiring specific anesthetic techniques (e.g., difficult airway, MH susceptibility) or those with a high risk for anesthetic and surgical complications are also identified. Of the three key components of a preoperative assessment (history, physical examination, and laboratory testing), the medical history is clearly the most valuable. [45] Studies of medical ambulatory consultations showed that 86 percent of diagnoses depend entirely on information obtained from patients' histories. A further 6 percent of diagnoses were discovered by physical examination, and only 8 percent were determined by laboratory investigations or radiographs. [46] Routine preoperative testing of all patients prior to elective surgery is unjustified and expensive. [47]

Studies have suggested that 60 percent of routinely ordered preoperative screening tests could be eliminated if testing were based solely on recognizable indications, and only 0.2 percent of the abnormalities reported would have

TABLE 65-4 -- Laboratory Test Recommendations for Asymptomatic Healthy Patients Scheduled to Undergo Non-Blood Loss Peripheral Procedures Under General Anesthesia

(Not Available)

From Roizen [294]

influenced perioperative care. [48] Inappropriate tests may even be harmful to patients because of unnecessary follow-up of false-positive test results or lack of appropriate follow-up from false-negative results. The commonly used guidelines for ordering screening laboratory tests were developed by Roizen (Table 65-4) (Table Not Available) , and further specific testing should be governed by information obtained from the patient's history and physical examination. [49]

For healthy, active outpatients undergoing superficial surgical procedures (e.g., biopsy, dilatation and curettage, herniorrhraphy, vein stripping), no laboratory tests appear to be indicated in males, and only a hemoglobin (or hematocrit) test may be necessary for females. Obviously, patients with chronic diseases (e.g., hypertension, diabetes) require additional laboratory studies (e.g., electrolytes, glucose). Patients with an unexplained hemoglobin concentration of less than 10 g/dL should undergo further evaluation prior to elective outpatient surgery because a low hemoglobin level may be associated with many diseases that could influence perioperative mortality and morbidity.

In addition to the anesthesiologist's evaluation, the preoperative visit should be used by the nursing staff to assess, prepare, and teach the patient and by the hospital business office to perform a financial interview and to familiarize the patient and family with the center. To avoid unexpected delays resulting from incomplete assessment, all paperwork, including the consent form, history and physical examination, and laboratory test results should be reviewed before arrival for surgery. A well-planned and smooth-functioning ambulatory surgery program can yield many benefits to patients and their families, as well as to surgeons. In summary, thorough patient preparation prior to the day of surgery can

prevent unnecessary delays, absences, last-minute cancellations, and inadequate patient management.

Preoperative Preparation

Optimal preoperative preparation of outpatients makes ambulatory surgery both safer and more acceptable for patients and hospital staff (Ch. 23) . The preparation process is aimed at reducing the risks inherent in ambulatory surgery, improving patient outcome, and making the surgical experience pleasant for the patient and family. Preparation should minimize patient anxiety through pharmacologic and nonpharmacologic means and should reduce potential postoperative problems by use of appropriate premedication.

Nonpharmacologic Preparation

The anticipation of undergoing anesthesia can cause psychologic stress, which is manifested as anxiety. Preoperative anxiety has been shown to rise at least 1 week before surgery and return to normal levels in the postoperative period only after the patient is assured of uneventful recovery. [50] The cause of patients' preoperative anxiety is multifactorial, but most commonly it is related to concerns about intraoperative awareness, not awaking after surgery, or postoperative pain and nausea. High levels of stress preoperatively, which are associated with slower recovery and greater analgesic and antiemetic requirements, can be effectively reduced with preoperative preparation (Fig. 65-2) (Figure Not Available) . [51] Overall, well-informed patients tend to recover faster and experience less pain.

Nonpharmacologic preparation has many desirable characteristics. These methods are economical, lack undesirable side effects, and are associated with high patient acceptance and motivation. More than 30 years ago, Egbert et al [52]

Figure 65-2 (Figure Not Available) Preoperative psychologic preparation reduces stress prior to and up to 1 week after surgery, as measured by the Spielberger state anxiety score. * $P < .05$. *(Modified from Wallace. [51] Reprinted with permission of the Helen Dwight Reid Educational Foundation. Published by Heldref Publications, 1319 Eighteenth St., Washington, D.C. 20036-1802. Copyright 1984.)*

demonstrated that the anesthetist's visit was more effective than a sedative premedicant in relieving preoperative anxiety. Postoperative pain has been similarly reduced by preoperative instruction. [52] The timing of the preoperative interview is also important, because anxiety is only significantly decreased when the interview

takes place outside the operating room immediately prior to surgery. [53] Many centers have shown encouraging results using instructional preoperative videotapes that offer a complete explanation of the events surrounding surgery. [54]

The use of play-oriented preoperative teaching, books, pamphlets, and video programs may be particularly beneficial for pediatric patients. [55] Separation anxiety and postoperative behavioral changes, prominent with children 1 to 4 years of age, may be diminished with such preparation programs. [56] In the modern ambulatory surgery center, both psychologic and pharmacologic means should be used to alleviate patients' anxiety and to decrease postoperative morbidity. Proper preoperative preparation should also include written and verbal instructions regarding arrival time and place, fasting instructions, and information concerning the postoperative course, limitations in driving abilities, and the need for a responsible adult to escort and accompany the patient during the postoperative period.

Pharmacologic Preparation

The use of premedication in the outpatient setting has been a subject of considerable interest and debate. The primary indications for preoperative medications in the outpatient setting are similar to those for patients undergoing inpatient procedures. These indications include anxiolysis, sedation, analgesia, amnesia, vagolysis, and prophylaxis against postoperative emesis and aspiration pneumonia. [57] Despite these well-recognized indications, premedication is not routinely used in most ambulatory surgery facilities in the United States. [2] An important concern in outpatient anesthesia is prompt recovery, and many anesthesiologists avoid using centrally active depressant premedicants because of concerns that these drugs will prolong the recovery period. Interestingly, most prospective studies have not found a prolonged recovery following the use of premedication in the outpatient setting. [58] [59] Proper choice of the premedication may actually facilitate the discharge of outpatients because the anesthetic and analgesic requirements, as well as the degree of postoperative emesis, are decreased.

Anxiolysis and Sedation

When administered for premedication, sedative-hypnotic drugs can allay anxiety and can reduce the overall anesthetic requirements, thereby improving recovery. Traditionally, the most widely used anxiolytic-sedative-hypnotic premedications have been barbiturate and benzodiazepine drugs. With increased dose, these drugs produce anxiolysis, sedation, and even unconsciousness. Barbiturates are not commonly used as premedicants in the outpatient setting because of their adverse effects on postoperative recovery, effects that make them less cost-effective than the newer sedative drugs. [60]

TABLE 65-5 -- Use of Anxiolytic-Sedative Drugs as Premedication of Adult Outpatients

(Not Available)

Modified from Shafer [66]

Benzodiazepines.

The use of benzodiazepines for premedication is a well-established practice. Not surprisingly, the amnesic and anxiolytic properties of these drugs are also useful in the outpatient setting (Table 65-5) (Table Not Available) . Although diazepam was the most commonly used benzodiazepine, midazolam has become the drug of choice because its relatively short elimination half-life and lack of significant side effects contribute to a rapid recovery after ambulatory surgery. [61] [62] One study showed that midazolam, administered immediately before anesthetic induction with propofol, did not decrease the dose of propofol necessary for hypnosis or the maintenance of surgical anesthesia in patients undergoing diagnostic dilatation and curettage. [63] To achieve the benefit of administering midazolam for premedication, it should be administered at least 5 minutes before induction. Although larger doses of midazolam are required because of first-pass metabolism, oral midazolam has been reported to be highly effective in both adults and children. [56] [64] When given in doses of 0.5 mg/kg, oral midazolam allowed children to be separated from their parents as early as 15 minutes after ingestion, without prolonging recovery even after brief surgical procedures. [64] [65] Temazepam has also been reported to be an effective oral premedicant for outpatient surgery. [64] Although oral triazolam can produce effective sedation and amnesia, it may be less effective than diazepam or midazolam in decreasing anxiety. Lorazepam, because of its long duration of action, is not routinely used in ambulatory surgery. If a patient expresses significant anxiety during the preoperative interview, diazepam may be prescribed to be taken at home in the evening and in the morning 60 to 90 minutes before surgery. However, a responsible adult must accompany the patient to the surgery center. If significant anxiety becomes apparent after admission to the day surgery center, intravenous midazolam (1-3 mg IV) is the drug most often administered.

alpha$_2$ -Adrenergic Agonists

alpha$_2$ -Adrenergic agonist drugs reduce dose requirements for anesthesia and analgesia, produce sedation, and decrease heart rate and blood pressure under anesthesia. Oral clonidine, the prototypic alpha $_2$ -agonist, has been utilized for ambulatory premedication; however, residual postoperative sedation may be a problem for elderly outpatients. Dexmedetomidine, however, is a more highly selective alpha $_2$ -agonist with a shorter duration of action compared with clonidine. [66] Because of its high potency and selective agonist action on alpha $_2$ -receptors, dexmedetomidine may gain more widespread acceptance in outpatient anesthesia. Although the profound hemodynamic effects of these drugs may limit their use as premedicants, they may prove to be valuable adjuncts during surgery because of their anesthetic and analgesic-sparing effects. The adverse clinical effects of clonidine and dexmedetomidine can be readily reversed with the antagonist atipamezole.

Analgesics

Opioid Analgesics.

The routine use of narcotic analgesics for premedication has been criticized unless the patient is experiencing acute or chronic pain (Ch. 10) . Use of opioid premedicant combinations can increase the incidence of postoperative nausea and vomiting (PONV) and may result in a delayed discharge after ambulatory surgery. Opioid analgesics may be beneficial if given intravenously prior to induction because they provide acute control of preoperative anxiety, decrease anesthetic drug requirements at induction, and provide postoperative pain relief. [67] When sufentanil was given intravenously 15 to 30 minutes before induction of general anesthesia, anxiety was decreased without prolonging recovery times or increasing postanesthetic morbidity. [68] However, if reduction of anxiety is the primary goal, it is better achieved with sedative-hypnotic drugs. Oral transmucosal fentanyl can provide for effective preoperative sedation and analgesia, but it is also associated with a high incidence of pruritus and emetic sequelae. [69] The use of agonist-antagonists such as butorphanol and nalbuphine as premedicants increases sedation and is associated with an increased incidence of postoperative anxiety, confusion, and dreaming. [70]

Nonopioid Analgesics.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) during the perioperative period has been extensively studied. These drugs are clearly less efficacious than opioid compounds at controlling acute postoperative pain. [71] However, NSAIDs have proven to be valuable adjuvants because of their long-lasting opioid-sparing actions. [72] When administered as part of a balanced analgesia technique in combination with narcotic analgesics and

local anesthetics, NSAIDs can facilitate early recovery, decrease side effects, and result in faster discharge times. [4] For many minor outpatient procedures, NSAIDs can eliminate the need for opioid analgesics postoperatively. [73]

Prevention of Nausea and Vomiting

PONV are common problems after general anesthesia. They are particularly disturbing in outpatients, because they can delay discharge and may result in unplanned

overnight hospital admissions. [10] [27] [74] [75] As early as 1916, it had been suggested that the anesthetic agent, the type of surgery, and opioid analgesics can all influence PONV. More recently, additional factors have been identified that influence the incidence of PONV. These include the patient's body habitus and medical condition, gender, pregnancy, phase of menstrual cycle, type of surgery, anesthetic and analgesic medications, postoperative hypotension, and age (Table 65-6) (Table Not Available) . [76] [77] [78] The incidence of emesis is very low in infants and gradually increases toward adulthood (Fig. 65-3) (Figure Not Available) . [79] [80] [81] The phase of the menstrual cycle influences the incidence of PONV most prominently during the ovulatory and luteal phases of the cycle (Fig. 65-4) (Figure Not Available) . This information should be considered when scheduling a patient for surgery who has a significant history of PONV. It is doubtful whether a single drug will ever be effective in treating emesis in all conditions. Thus, a combination of medications may be required to treat some patients successfully. [82] [83] Because of the low

TABLE 65-6 -- Risk Factors for Postoperative Nausea and Vomiting

(Not Available)

From Kallar, [295] copyright 1992, with permission from Elsevier Science

Figure 65-3 (Figure Not Available) Incidence (percentage) of postoperative nausea and vomiting as a function of age. *(From Lerman [76])*

incidence of PONV and the cost, potential side effects, and variable efficacy of antiemetic medications, routine prophylactic use of these drugs is recommended only in susceptible (high-risk) patients who have a previous history of postoperative vomiting and in patients with other significant risk factors for postoperative nausea.

Butyrophenones.

Droperidol is a butyrophenone neuroleptic drug with antiemetic properties as a result of its antagonistic effects at dopamine receptors. It is used predominantly for the treatment and prevention of PONV. Outpatient studies involving both children and adults indicate that droperidol is a highly effective antiemetic. [74] [84] Large doses of droperidol, greater than 20 mug/kg, enhance postoperative sedation and may significantly prolong recovery and discharge in ambulatory surgical patients. [85] Low doses of droperidol, less than 10 mug/kg, may be as effective as higher doses without delaying recovery. [86] One study showed that low-dose droperidol in combination with metoclopramide was more effective than ondansetron in preventing postoperative nausea after laparoscopic cholecystectomy. [87] Larger doses of droperidol (>1 mg) may result in unwanted side effects, including dyskinesia, restlessness, and dysphoric reactions, which may last up to 24 hours after surgery. This morbidity limits the use of droperidol as a routine premedication for outpatients. To limit these side effects, the lowest effective doses are recommended.

Phenothiazines.

The antiemetic action of phenothiazines also results from their ability to block dopamine receptors in the chemoreceptor trigger zone. Chlorpromazine and promethazine have been used for many years to treat nausea and vomiting, particularly caused by opioid use. [77] Phenothiazines can produce hypotension along with significant sedation during recovery, thus delaying discharge, and

Figure 65-4 (Figure Not Available) Incidence of postoperative nausea and vomiting correlated to the day of menstrual cycle. *(From Beattie and Buckley [81])*

may produce extrapyramidal effects ranging from restlessness to oculogyric crisis. [88]

Gastrokinetic Drugs.

Metoclopramide and domperidone are gastrokinetic agents that facilitate gastric and small bowel motility and increase lower esophageal sphincter tone. Metoclopramide (20 mg IV or 0.2 mg/kg IV) seems to be effective in the prevention of PONV. Because of its short half-life, metoclopramide should be given near the end of surgery to ensure efficacy in the early postoperative period. [77] The combination of metoclopramide, 10 to 20 mg IV, and low-dose droperidol, 0.5 to 1.0 mg IV, appears to be more effective than droperidol (1 mg) alone. [83]

Anticholinergics.

Anticholinergic drugs (e.g., atropine, glycopyrrolate, and scopolamine) have traditionally been used because of their antisialagogic and vagolytic actions. Transdermal scopolamine, a centrally acting anticholinergic, is effective in controlling motion sickness. Preoperative placement of a patch can reduce the incidence of severe PONV but it must be in place at least 8 hours before surgery and is associated with an unacceptably high incidence of adverse effects. Side effects, including dry mouth, somnolence, mydriasis, and dizziness, limit its usefulness in the outpatient setting. [66]

Antihistamines.

Dimenhydrinate and hydroxyzine are antihistamines that act on the vomiting center and vestibular pathways to prevent PONV. They are particularly useful in the prophylaxis and treatment of motion sickness and for outpatients undergoing middle-ear surgery. Dimenhydrinate has been shown to be successful in decreasing vomiting after strabismus surgery. When given in doses of 0.5 mg/kg at induction of anesthesia, dimenhydrinate significantly reduced vomiting for up to 24 hours postoperatively and did not delay discharge from the ambulatory facility. [89]

Serotonin Antagonists.

The discovery of the role of 5-hydroxytryptamine (5-HT) in the pathophysiology of cytoxic drug-induced emesis, as well as the discovery of the 5-HT antagonists, has generated considerable interest in the use of these compounds in the treatment and prevention of PONV. Ondansetron, granisetron, dolasetron, and tropisetron are all highly selective 5-HT_3 -receptor antagonists that lack the sedative, dysphoric, and extrapyramidal effects of other commonly used antiemetics. [90] [91] Ondansetron, by blocking both central and peripheral 5-HT_3 receptors, is effective in preventing PONV after ambulatory surgery. [90] [91] [92] [93] [94] [95] It has also been shown to be effective in the treatment of established postoperative emesis. [96] Because ondansetron has a short elimination half-life, it is more effective in reducing the need for rescue antiemetics in the recovery room when it is administered at the end of longer surgical procedures. [97] The use of small, 1- to 2-mg doses of ondansetron has not been found to be as effective as 4- and 8-mg doses in preventing PONV after discharge. [92] This is important to consider when treating patients with ondansetron, because the cost of the drug is substantial. In comparison, droperidol, 0.625 mg, and ondansetron, 4 mg, had equal antiemetic prophylaxis and discharge times, but droperidol was more cost-effective. [84] [98] Thus, the cost of these agents prohibits their routine use in the prevention of PONV in the outpatient setting.

Nonpharmacologic Techniques.

Acupuncture and acupressure have been used for the prevention of PONV with varying degrees of success. [77] [99] [100] In a study of minor gynecologic procedures with opioid premedication, P-6 acupuncture point stimulation with a needle resulted in a significant reduction in emesis postoperatively. [100] More recent reports comparing the use of P-6 acupressure to placebo or sham (non-P-6 location) treatment have also shown beneficial effects. [101] [102] Future studies comparing acupressure to traditional antiemetic drugs should include a pharmacoeconomic analysis. [103]

Prevention of Aspiration Pneumonitis

A controversial aspect of premedication in outpatients relates to the need for prophylactic medication to decrease the risk of pulmonary injury from aspiration of gastric contents. Early studies suggested that outpatients may be at a theoretically increased risk for aspiration based on the finding that a larger percentage of patients had a residual gastric volume greater than 25 mL with a pH less than 2.5. [104] However, more recent work showed no difference in the risk of aspiration in outpatients compared with inpatients. Several studies suggested that 40 to 60 percent of outpatients meet the criteria to be at risk for aspiration. [105] [106] [107] Despite this finding,

the incidence of pulmonary aspiration is very low (<1/35,000) in elective surgical patients with no specific risk factors. [108] Therefore, routine prophylaxis for acid aspiration is not recommended.

Using medications prophylactically in all patients to decrease the risk of pulmonary aspiration is costly and may be associated with unwanted side effects. Unfortunately, many practicing anesthesiologists feel compelled to use these drugs as routine premedicants because of the prevailing environment for malpractice litigation. Nevertheless, in outpatients with predisposing factors for pulmonary aspiration (i.e., pregnancy, scleroderma, hiatal hernia, nasogastric tubes, morbid obesity), use of the H_2 -receptor blocking drugs for premedication may be appropriate.

TABLE 65-7 -- Prophylactic Regimens Used to Decrease Gastric Volume and to Increase pH in Outpatients

MEDICATION/DOSE	DOSING INTERVAL (MIN)[a]	GASTRIC VOLUME (ML)[a]	GASTRIC PH	PATIENTS WITH PH < 2.5 AND VOL > 25 ML (%)	UNTREATED CONTROLS WITH PH < 2.5 AND VOL > 25 ML (%)[b]	REFERENCES
Ranitidine 150 mg PO	113	1	5.2	0	35	Sutherland et al (1986) [107]
	154	10	6.4	5	60	Manchikanti et al (1985) [296]
With 150 mL H_2O	144	8	5.5	0	46	Maltby et al (1986) [109]
With 150 mL H_2O	159	10	6.2	0	48	Maltby et al (1988) [112]
With 150 mL coffee	160	14	5.7	6	38	Maltby et al (1988) [112]
With 150 mL juice	142	15	5.4	8	42	Maltby et al (1988) [112]
Cimetidine 300 mg PO	146	13	5.0	4	48	Manchikanti and Roush (1984) [105]
Sodium citrate (Bicitra) 15 mL PO and metoclopramide 10 mg IV	50	22	3.4	4	36	Manchikanti et al (1985) [113]
Sodium citrate (Bicitra) 30 mL PO and metoclopramide 10 mg IV	50	26	3.7	8	36	Manchikanti et al (1985) [113]
Sodium citrate (Bicitra) 15 mL PO	45	32	3.2	12	36	Manchikanti et al (1985) [113]
Sodium citrate (Bicitra) 30 mL PO	46	58	3.7	12	36	Manchikanti et al (1985) [113]
Cimetidine 400 mg PO	105	13	5.0	12	35	Stock and Sutherland (1985) [297]

[a] Mean values
[b] Average duration of fasting 12 to 14 hours

H_2 -Receptor Antagonists.

The H_2 -receptor antagonists are effective in increasing gastric pH and in decreasing gastric volume by reducing gastric acid secretion (Table 65-7) . Ranitidine offers the advantages of a prolonged period of protection and fewer side effects than cimetidine. [106] [107] [109] If given intravenously, ranitidine has a faster onset of action and better protection than cimetidine. [110] Cimetidine is more cost-effective, but it may cause sedation or confusion and may interfere with drugs metabolized by cytochrome P-450. Compared with fasted patients who did not receive ranitidine, patients who received fluids plus oral ranitidine 2 to 3 hours before induction of anesthesia had lower residual gastric volumes, higher pH values, and a decreased incidence of thirst. [111] [112]

Antacids.

Sodium citrate is a nonparticulate antacid, which rapidly increases gastric fluid pH. It is commonly used in obstetric and emergency anesthesia because it reduces the consequences of aspiration of gastric contents in these high-risk patients. Because ingestion of this antacid increases gastric volume, the addition of a gastrokinetic agent is necessary when it is administered in the outpatient setting. [113] Disadvantages include the potential for emesis resulting from unpleasant taste, variable duration of effect, and decreased efficacy compared with H_2 -receptor antagonists. [114] Its use should be restricted to a select outpatient population (e.g., diabetic or morbidly obese patients) at the highest risk for complications from aspiration of acidic gastric contents.

Gastrokinetic Agents.

Metoclopramide, a dopamine antagonist, reduces gastric volume by stimulating gastric emptying time without altering pH. The use of effective doses of metoclopramide in combination with an H_2 -receptor blocking drug has been advocated to decrease postoperative emesis and further reduce the potential risk of aspiration pneumonitis. [115] Other studies failed to demonstrate a significant advantage of this drug combination over an H_2 -receptor antagonist alone. [106] However, metoclopramide may offer an additional protective effect as a result of its ability to increase lower esophageal sphincter tone.

Nothing-by-Mouth Guidelines

Because prolonged fasting does not guarantee an empty stomach at the time of induction, several investigators have questioned the value of even a 4- to 5-hour fast prior to elective surgery. [109] [116] [117] [118] This is logical, because the half-life of clear fluids in the stomach is 10 to 20 minutes, and residual gastric volume after 2 hours is less in patients ingesting small amounts of clear fluids than in fasted patients. [119] After an overnight fast, 50 and 44 percent of outpatients complained of moderate-to-severe hunger and thirst, respectively. [107] It was postulated that these symptoms contributed significantly to preoperative anxiety. More important, 14 percent of young female outpatients presenting to the operating room in the afternoon after an overnight fast had a serum glucose concentration of less than 45 mg/dL. [120] Ingestion of

150 mL of water as late as 2 hours before surgery significantly decreased the severity of thirst without increasing gastric volume in fasted outpatients. [109] Furthermore, ingestion of 150 mL of either coffee or orange juice 2 to 3 hours before induction of anesthesia had no significant effect on residual gastric volume or pH in adults. [121] Similarly, preoperative ingestion of apple juice, 3 mL/kg, decreased gastric volume, thirst, and hunger in children and had no adverse effect on gastric contents. [122] Thus, arbitrary restrictions (e.g., nothing by mouth [NPO] after midnight) dictating when outpatients may drink fluids before an elective operation appear to be unwarranted. A national survey in the United States demonstrated that 69 percent of anesthesiologists had changed their NPO guidelines to allow ingestion of clear fluids for children, and 41 percent had changed their guidelines for adults. [123] Unless outpatients scheduled for late morning or early afternoon surgery have

delayed gastric emptying or receive a narcotic premedicant, the requirement for a 10- to 16-hour fast is not justified. Prolonged fasting causes discomfort to outpatients without any apparent benefit.

ANESTHETIC TECHNIQUES

Quality, safety, efficiency, and the cost of drugs and equipment are important considerations in choosing an anesthetic technique for outpatient surgery. The ideal outpatient anesthetic should have a rapid and smooth onset of action and it should produce intraoperative amnesia and analgesia, good surgical conditions with a short recovery period, and no side effects. Outpatient surgery requires the same basic equipment as inpatient surgery for delivery of anesthetic drugs, monitoring, and resuscitation. Standard intraoperative monitoring equipment for outpatient operations includes a precordial stethoscope, ECG, blood pressure cuff, pulse oximeter, and capnograph.

The choice of anesthetic technique depends on both surgical and patient factors. For many ambulatory procedures, general anesthesia remains the most popular technique with both patients and staff. Although central neuroaxis blockade has been traditionally popular for peripheral procedures, its use in ambulatory anesthesia can delay discharge because of residual sympathetic blockade. Peripheral nerve blocks, however, may facilitate the recovery process by minimizing the use of opioid analgesics, which can produce nausea or sedation. There are an increasing number of cases now being performed with a combination of local nerve blocks and intravenous sedation as part of a so-called monitored anesthesia care technique. Although there is no ideal anesthetic agent or technique for outpatients, there is a vast array of pharmacologically active drugs that, when combined in a rational manner and carefully titrated, can produce the desired anesthetic conditions with an acceptable recovery profile and cost.

General Anesthesia

The ability to deliver a safe and cost-effective general anesthetic with minimal side effects and rapid recovery is critical in a busy outpatient surgery unit. General anesthesia remains the most widely used anesthetic technique for managing ambulatory surgery patients because of its popularity with patients, surgeons, and anesthesiologists. In addition to intraoperative anesthetic conditions, the anesthesiologist must consider the recovery characteristics of the anesthetic as well as the management of postoperative pain and PONV when making the anesthesia care plan.

The question whether to start an intravenous line in outpatients arises in pediatric patients undergoing brief surgical procedures. For procedures lasting less than 15 minutes that do not require intravenous administration of drugs or fluid (e.g., myringotomies and eye examinations under anesthesia), an intravenous line is not essential. Preoperative fasting for periods of 10 to 15 hours does not result in hypoglycemia in healthy 5-year-old outpatients. However, for longer cases or situations in which the patient has been without oral intake for longer than 15 hours, an intravenous line is useful for the maintenance of fluid balance and glucose homeostasis, as well as for facilitating the administration of drugs during the perioperative period. [120] In addition, postoperative morbidity, such as drowsiness, dizziness, and thirst, may be associated with poor hydration status. Outpatients who received 20 versus 2 mL/kg of intravenous hydration had less minor postoperative morbidity, including PONV (Fig. 65-5) (Figure Not Available) . [124] Use of heated humidifiers, as well as passive heat and moisture exchangers, will further decrease fluid losses and conserve heat during longer outpatient procedures. [125] However, in procedures lasting less than 2 hours, these devices are unlikely to be cost-effective in adult ambulatory surgery.

Airway Management

Endotracheal intubation causes a high incidence of postoperative airway-related complaints including sore throat, croup, and hoarseness (Ch. 39) . Many outpatients undergoing

Figure 65-5 (Figure Not Available) Preoperative hydration of 20 versus 2 mL/kg decreases postoperative morbidity in outpatients. *(Modified from Yogendran et al [124])*

peripheral procedures under general anesthesia do not require endotracheal intubation unless they are at high risk for aspiration. The laryngeal mask airway (LMA) was first described by Brain in 1983 as an alternative to endotracheal intubation or a facemask. Its use has grown rapidly for outpatient surgery since that time. [126] When compared with anesthesia with a mask and oral airway, patients with an LMA had fewer desaturation episodes, fewer intraoperative airway manipulations, and fewer difficulties in maintaining an airway. [127] The LMA frees the anesthesiologist's hands for record-keeping, monitoring, and drug administration. Fatigue from maintaining the airway with mask is also eliminated.

The LMA can be positioned easily without direct visualization or neuromuscular blocking agents, and the patient can be allowed to ventilate spontaneously throughout the procedure. Compared with endotracheal intubation, insertion of the LMA causes minimal cardiovascular response and is better tolerated at lighter levels of anesthesia. [128] The incidence of sore throat is markedly reduced when the LMA is used. In a large survey, 47 percent of intubated patients complained of sore throat postoperatively versus only 7 percent with patients having the LMA. [129] [130]

The LMA does not protect the airway from foreign material and should not be used in patients at high risk of regurgitation, aspiration, or upper airway bleeding. Furthermore, if a high positive airway pressure is required for maintaining the airway or ventilation, the risk of gastric dilatation and subsequent aspiration may be increased. [131] An alternative to the LMA is the cuffed oropharyngeal airway (COPA) device. [132] Although the COPA is easy to insert after induction without muscle relaxants, its ability to maintain an obstruction-free airway must compared with the currently used airway devices. Furthermore, the ability to assist ventilation with the COPA must be further evaluated.

Intravenous Anesthetic Drugs

Induction of general anesthesia is usually accomplished with a rapid-acting intravenous anesthetic (Chs. 8 and 9) . The increased availability of intravenous, inhaled, analgesic, and muscle-relaxant drugs with a rapid onset and short duration of action has made brief surgical procedures safer and more pleasant for outpatients (Table 65-8) (Table Not Available) . Propofol has virtually replaced barbiturates and benzodiazepines for induction of anesthesia because of its favorable recovery profile. [133] The most popular technique for maintenance of anesthesia is the combination of a volatile anesthetic agent with nitrous oxide. The extremely low solubility of nitrous oxide and the newer less soluble volatile agents contribute to a more rapid onset and recovery from general anesthesia. Although some investigators have suggested that there is an association between nitrous oxide and PONV, more recent studies question the clinical importance of nitrous oxide in producing this side effect. [134] [135] [136] [137]

Barbiturates

Thiopental (3-6 mg/kg) is the prototypic intravenous induction agent with a rapid onset and a short duration of action resulting from redistribution of the drug (Ch. 8) . However, thiopental impairs fine motor skills for several hours after surgery and produces a "hangover" sensation. Methohexital appears to be associated with slightly

shorter awakening time, but recovery of fine motor skills may still require 6 to 8 hours after an induction dose. [138] [139] Compared with thiopental, methohexital is associated with a higher incidence of pain on injection, involuntary muscle movements, and hiccoughing. The use of small doses of a rapid-acting opioid analgesic (e.g., sufentanil 5-10 mug IV) can minimize side effects during the induction period. Furthermore, methohexital compared favorably with propofol when used for induction only in outpatient procedures lasting longer than 2 hours. [140]

Benzodiazepines

Studies with the water-soluble benzodiazepine, midazolam (0.2-0.4 mg/kg IV) indicate that it is also an adequate induction agent in outpatients (Ch. 9) . However, its onset of action is slower and recovery is prolonged compared with the barbiturate compounds and propofol. [141] If combined with nitrous oxide and sufentanil or alfentanil, midazolam, in doses of 0.1 to 0.15 mg/kg, will induce general anesthesia. When midazolam was used for induction and flumazenil, a specific benzodiazepine antagonist, was administered at the end of surgery, prompt recovery was achieved after outpatient arthroscopy. However, compared with propofol, recovery after flumazenil antagonism of midazolam anesthesia was still significantly slower. [142]

TABLE 65-8 -- Comparison of Currently Available Intravenous Anesthetics for Use During Ambulatory Anesthesia

(Not Available)

From White [163]

Etomidate

Etomidate (0.2-0.3 mg/kg) has also been used for induction and maintenance (1-3 mg/min) of general anesthesia during short outpatient procedures (Ch. 9) . Recovery tends to be faster than after thiopental administration and compares favorably with methohexital. Disadvantages of etomidate include pain on injection, high incidence of PONV, myoclonic movements, and transient suppression of adrenal steroidogenesis. [143] Because of its side-effect profile, the use of etomidate is best restricted to those clinical situations in which its hemodynamic stability offers an advantage over other available induction agents (e.g., elderly outpatients with coronary artery or cerebrovascular disease).

Ketamine

Ketamine compares unfavorably with barbiturates and opioid compounds for minor gynecologic procedures because of its prominent psychomimetic effects and high incidence of PONV during the early postoperative period (Ch. 9) . Premedication with a benzodiazepine (e.g., midazolam 0.05-0.1 mg/kg IV) decreases the incidence of ketamineinduced emergence reactions. [144] Investigators have reported that low doses of ketamine (10-20 mg IV) may be a useful alternative to opioid analgesics during induction of anesthesia.

Propofol

Propofol is an intravenous anesthetic agent that has a metabolic clearance ten times faster than that of thiopental (Ch. 9) . [145] Recovery after propofol anesthesia compares favorably with that of most other anesthetics in the outpatient setting. This is particularly important because the cost of propofol is higher than that of many other commonly used anesthetics. [146] [147] [148] However, when the total patient costs are calculated, the use of propofol may contribute to significant savings. [60] For example, compared with an isoflurane-based anesthetic, patients who had a propofol-based anesthetic were discharged earlier from the hospital and returned to work significantly sooner. [149] Recovery following induction of anesthesia with propofol is faster than with the commonly used barbiturate compounds, irrespective of the maintenance agent used (Fig. 65-6) (Figure Not Available) . [133] [139] [150] Compared with methohexital, the use of propofol was associated with fewer side effects (hiccoughing, nausea, and vomiting) intraoperatively and postoperatively and faster recovery times. [139] Faster intermediate recovery with propofol-based anesthetics may also yield significant savings in nursing hours. For example, a 15-minute reduction in phase I recovery room stay could save 1,000 nursing hours in a 4,000-case per year ambulatory surgical facility. [149] Early experience with propofol in the United Kingdom suggested a reduction in the need for overtime nursing personnel.

Propofol is associated with less PONV and decreased use of antiemetic medications. [146] [151] [152] [153] [154] There is evidence that propofol may possess inherent antiemetic activity, and it has been successfully used to treat refractory nausea and vomiting in patients undergoing chemotherapy. [155] When propofol

Figure 65-6 (Figure Not Available) Comparison of mean changes in choice reaction time (CRT) postoperatively in untreated controls and outpatients who received thiopental, methohexital, or propofol for induction of anesthesia. * $P < .05$. *(From MacKenzie and Grant [150])*

was administered in subhypnotic doses (10-20 mg IV) to treat PONV, 81 percent of patients showed improvement versus 35 percent of the lipid emulsion control group. [156] Unfortunately, 28 percent of patients experienced a relapse of their symptoms within 30 minutes. For propofol to be clinically useful as an antiemetic, it would need to be given as a continuous infusion because of its rapid clearance. Subhypnotic concentrations of propofol have also shown other central effects, including perioperative mood alterations. Patients emerging from propofol anesthesia were more likely to exhibit sensation-seeking tendencies (e.g., adventurous, daring, energetic) and to report feeling elated and euphoric. [157] Intravenous administration of propofol is associated with a high incidence of venous pain and discomfort. Lidocaine (40 mg IV) immediately before propofol injection reduces the incidence and severity of pain when it is injected into small hand veins, whereas thiopental (50 mg IV) has also been shown to reduce only the severity of the pain. [158]

Inhaled Anesthetic Drugs

Volatile anesthetics are convenient to use in ambulatory anesthesia (Chs. 4 and 5) . Changes in the depth of anesthesia can be made readily because of the rapid uptake and elimination of these anesthetics. [159] [160] The rapid elimination of anesthetic vapors provides for a fast patient recovery and potentially earlier discharge from the outpatient facility. Although a similar spectrum of pharmacologic activity is produced by the three traditionally used volatile agents (halothane, enflurane, and isoflurane), isoflurane has been the most commonly used for maintenance of general anesthesia. Studies involving outpatients undergoing brief procedures have shown no significant clinical differences in recovery

TABLE 65-9 -- Comparison of Currently Available Inhaled Anesthetics for Use During Ambulatory Anesthesia

(Not Available)

From White [163]

TABLE 65-10 -- Recovery Times After Discontinuation of Isoflurane or Desflurane

(Not Available)

From Ghouri et al [169]

times among the three potent inhaled anesthetics. For procedures lasting longer than 90 minutes, recovery times after isoflurane seem to be faster when compared with enflurane. [161] Despite its lower solubility, isoflurane may not offer any significant advantages over enflurane for short ambulatory procedures. Interestingly, adult outpatients receiving isoflurane during minor gynecologic surgery had a higher incidence of postoperative complications than those receiving enflurane. [160]

Most studies of pediatric patients have reported that halothane is associated with the lowest incidence of perioperative complications. [162] Isoflurane is associated with

several disadvantages when it is used for induction of anesthesia in children (e.g., coughing, laryngospasm). However, ventricular arrhythmias are more likely to occur during halothane anesthesia.

The newer volatile anesthetics, sevoflurane and desflurane, are proving to be extremely useful in the outpatient setting because of their more favorable pharmacokinetic profiles (Table 65-9) (Table Not Available) . [163] [164] [165] [166] [167] [168] In outpatients, the immediate recovery (emergence) after desflurane was significantly faster compared with isoflurane (Table 65-10) (Table Not Available) . [169] However, intermediate and late recovery after desflurane is similar to that after isoflurane and propofol (Fig. 65-7) (Figure Not Available) . [170] [171] In fact, propofol anesthesia may offer some advantages because the incidence of nausea and vomiting is less than with desflurane (Fig. 65-8). (Figure Not Available) The solubility of desflurane (0.42) is lower than that of nitrous oxide (0.46), and clinical studies suggest that recovery of cognitive and psychomotor function occurs very rapidly following discontinuation of this agent. [170] [172] [173] [174] [175] [176] [177] [178] Despite its shorter elimination kinetics and recovery characteristics, the introduction of desflurane in one center did not result in faster operating room exit times. [179] Other studies have showed a greater incidence of postoperative agitation and excitement in patients recovering from desflurane and significant autonomic stimulation may result from rapid adjustments in inspired concentration. [174] [175] [180] [181] The pungency of desflurane results in respiratory tract irritation and coughing, breath-holding, and laryngospasm when administered at high concentrations for induction of anesthesia. [182] Thus, desflurane's usefulness as a drug to induce anesthesia in children and adults is limited.

Sevoflurane has a relatively low solubility and an impressive lack of airway irritation that makes it very useful for inhalation induction of anesthesia. [183] [184] [185] [186] Even at high concentrations, inhalational induction is well tolerated because of its lack of pungent odor, and it is more pleasant for rapid inhalational

Figure 65-7 (Figure Not Available) Intermediate recovery after propofol, desflurane (±N_2O), or propofol-desflurane anesthesia. *(From Van Hemelrijck et al [171])*

Figure 65-8 (Figure Not Available) Postoperative nausea after propofol, desflurane (±N_2O), or propofol-desflurane anesthesia. *(From Van Hemelrijck et al [171])*

induction than halothane. [187] These features make sevoflurane popular for pediatric outpatient anesthesia. [188] [189] [190] [191] [192] [193] Controversy still exists regarding the significance of the breakdown products of sevoflurane. [194] Sevoflurane can be degraded in carbon dioxide absorbents to compound A, which can produce renal toxicity in rats. [195] [196] [197] The production of compound A is related to the concentration of sevoflurane, the temperature of the absorbent, the fresh gas flow rate, and the duration of administration. Although the U.S. Food and Drug Administration has recommended that sevoflurane not be used at total gas flow rates less than 2 L/min, studies have failed to demonstrate any change in renal or hepatic function when sevoflurane was used at total gas flows of 1 L/min or during closed-circuit anesthesia. [194] [197]

Use of nitrous oxide as an adjuvant to the anesthetic management of outpatients significantly reduces the requirements for the volatile agents during the maintenance period. Therefore, recovery is rapid and the cost of the anesthesia less when nitrous oxide is used. Nitrous oxide can increase postoperative nausea by increasing the pressure in the middle ear, thereby stimulating the vestibular system, and by increasing gastrointestinal pressure. Nevertheless, the role of nitrous oxide in causing PONV remains controversial and is not clinically significant when considering the overall ratio of cost to benefit to the health-care system. [135] [137] [198] [199]

Analgesics

Opioid and nonopioid analgesics are frequently administered in the immediate preinduction period to suppress the autonomic responses to endotracheal intubation and during maintenance of general anesthesia to prevent autonomic responses to painful stimuli (Ch. 10) . Opioids can reduce the requirement for sedative-hypnotic drugs, thereby decreasing recovery times. In addition, opioids have been shown to decrease the incidence of pain on injection and involuntary motor activity associated with methohexital, etomidate, and propofol.

Although morphine (and its more lipid-soluble derivatives) and meperidine can be used in outpatient anesthesia, they are not as popular as the more potent, rapid, and shorter-acting opioid analgesics (e.g., fentanyl, sufentanil, and alfentanil). A recent study comparing morphine and fentanyl in ambulatory surgical patients found higher pain scores and more oral analgesic use in the fentanyl group. Morphine produced better quality analgesia, but it was associated with increased nausea and vomiting especially after discharge. There was no difference in recovery times or discharge times despite the shorter duration of action of fentanyl. [200]

Use of small doses of potent opioids (e.g., fentanyl, 1-2 mug/kg; alfentanil, 15-30 mug/kg; sufentanil, 0.15-0.3 mug/kg) can effectively attenuate the cardiostimulatory response to laryngoscopy and intubation, and these drugs are useful supplements to inhaled anesthetics during the maintenance period. Compared with a standard inhaled anesthetic, most investigators have demonstrated improved intraoperative conditions and a more rapid emergence from anesthesia when fentanyl or one of its newer analogues was administered as part of a balanced anesthetic technique. [201] [202] When a sufentanil infusion was compared with fentanyl for maintenance of general anesthesia with nitrous oxide, its use was associated with less nausea and postoperative pain. [203] Alfentanil has a rapid onset and a short duration of action. These characteristics make it particularly useful in the outpatient setting. Although one study found no significant difference in awakening times after anesthesia maintained with alfentanil compared with fentanyl, most investigators have reported a faster emergence and recovery of psychomotor function after an alfentanil-based anesthetic technique. [202]

Remifentanil is an ultrashort-acting opioid analgesic with an analgesic potency similar to that of fentanyl. It is metabolized by nonspecific esterases, a process that allows for rapid systemic elimination. [204] [205] Remifentanil has a half-life of 8 to 10 minutes and a context-sensitive half-life (the time for a 50% decrease in its effect-site concentration after the infusion is stopped) of 4 minutes regardless of the duration of infusion (Fig. 65-9) (Figure Not Available) . [206] This is in contrast to alfentanil, which has a context-sensitive half-life of 58 minutes and depends on its small volume of distribution for rapid termination of its clinical effect. [207] When remifentanil was compared with alfentanil as part of a total intravenous anesthesia technique, remifentanil provided more effective suppression of intraoperative responses but prolonged awakening and recovery room stay. [208] There was an earlier need for analgesics postoperatively with remifentanil, and both groups had similar discharge times. Studies involving the use of remifentanil in

Figure 65-9 (Figure Not Available) Computer simulation of the "context-sensitive" half-life time (CSHT) for remifentanil (3.65 min), alfentanil (58.5 min), sufentanil (240 min), and fentanyl (262.5 min). Note that remifentanil's CSHT is independent of the duration of infusion. *(Modified from Egan et al [206])*

combination with the less-soluble volatile anesthetics suggest that a low-dose infusion (0.05-0.2 mug/kg/min) can produce a significant anesthetic-sparing effect. [209] Furthermore, a 1-mug/kg bolus dose of remifentanil was more effective than a similar dose of fentanyl in suppressing the acute hemodynamic responses to laryngoscopy and tracheal intubation in patients undergoing outpatient laparoscopy. [210]

The semisynthetic opioid agonist-antagonist compounds (i.e., butorphanol, nalbuphine, dezocine) may offer advantages as adjuvants to general anesthesia over the potent opioid compounds in the outpatient setting because of their more limited potential to produce ventilatory depression. Unfortunately, there is a "ceiling effect" with respect to analgesic efficacy. Dezocine is a short-acting opioid with high mu-receptor activity. Compared with alfentanil, intraoperative dezocine provided significantly longer postoperative analgesia. However, dezocine increased postoperative nausea and delayed discharge from the hospital compared with fentanyl and ketorolac. [211] When nalbuphine (0.3-0.5 mg/kg) was compared with fentanyl (1.5 mug/kg) during outpatient anesthesia, it was found to produce more unpleasant dreaming during surgery and greater postoperative anxiety, drowsiness, and PONV. [70]

Muscle Relaxants

Many outpatient surgical procedures require no neuromuscular relaxation (Ch. 12) . Muscle relaxants are required in outpatient anesthesia to facilitate tracheal intubation and to optimize the surgical conditions during intra-abdominal procedures. In addition, their use can decrease anesthetic requirements and recovery time. Although it has been suggested that controlled ventilation with muscle relaxants may decrease postoperative emesis, this was not verified when controlled ventilation (versus spontaneous) was compared in outpatients undergoing strabismus repair. [212]

Before the introduction of intermediate-acting nondepolarizing muscle relaxants, an infusion of succinylcholine was the most frequently used muscle relaxant technique during outpatient anesthesia. Unfortunately, the administration of succinylcholine may be associated with hyperkalemia, arrhythmias, MH, and muscle pains lasting up to 4 days after surgery. Nevertheless, succinylcholine is indicated when a rapid onset of neuromuscular block is required. Factors other than succinylcholine may also contribute to the occurrence of myalgias following outpatient surgery. For example, the use of vecuronium (versus succinylcholine) did not lower the incidence or severity of muscle pain after laparoscopy. [213]

With the availability of intermediate-acting nondepolarizing muscle relaxants (e.g., atracurium, vecuronium, and mivacurium), reversal of neuromuscular blockade can be achieved even after brief surgical procedures. [214] Atracu- rium, vecuronium, and mivacurium are each metabolized through distinctly different pathways. [215] Intubating doses of atracurium and mivacurium cause histamine release, which may prove to be disadvantageous in certain situations. In outpatients, the primary consideration in choosing one of these agents is the duration of surgery and the costeffectiveness of the drug. After the recommended intubating doses of atracurium and vecuronium, the duration of action (time to 95% spontaneous recovery) is approximately 1 hour. An intubating dose of mivacurium (0.15-0.20 mg/kg) has approximately twice the duration of succinylcholine (20-30 min) and a significantly more rapid spontaneous recovery profile than atracurium, vecuronium, or rocuronium. [216] [217] [218] A continuous infusion of mivacurium or small (4-8-mg) bolus doses can further improve titration and thereby can ensure a prompt spontaneous recovery, decreasing the need for muscle relaxant reversal agents.

Reversal of Drug Effects

Pharmacologic antagonists, drugs that compete with agonists at the receptor site, may be useful in outpatient anesthesia by facilitating the recovery process. However, antagonists may also have unwanted side effects that should be considered before using these agents. Because their duration of action is sometimes shorter than that of the agonists, (e.g., naloxone, flumazenil, and edrophonium), a rebound of the agonist effect may follow their use.

Although severe opioid side effects, such as rigidity and respiratory depression, can be treated with incremental boluses of naloxone (20-40 mug), this drug is not recommended for routine reversal of opioid effect because of its own intrinsic side effects (nausea and vomiting, pulmonary edema, and arrhythmias). [219] It is preferable to titrate the opioid carefully to achieve the desired effect during surgery. Butorphanol, nalbuphine, and dezocine combine the properties of opioid agonists and antagonists such as naloxone. These drugs can be used to treat such opioid-related side effects as pruritus without adversely affecting the analgesia.

The central effects of benzodiazepines (excessive sedation, amnesia, and dysphoria) can be promptly reversed with flumazenil (0.1-0.2-mg increments). Although flumazenil is a specific benzodiazepine antagonist with few side effects, it is too costly for routine use. As with opioids, it may be more

cost-effective to titrate the benzodiazepines to the desired clinical effect, rather than relying on flumazenil to reverse residual effect. Relapses of sedation (rebound) can occur, because the half-life of flumazenil is shorter than that of most benzodiazepine agonists.

Intermediate-acting neuromuscular agents usually require reversal of their action, and neostigmine and edrophonium are the two most widely used anticholinesterase drugs. The choice of the reversal agent may influence the frequency of PONV. When compared with patients receiving no reversal agents or reversal with edrophonium, patients receiving neostigmine have an increased frequency of PONV. [220] [221] [222] Mivacurium may be advantageous in this regard because reversal is seldom required if the drug is carefully titrated during the maintenance period. The ability to avoid reversal drugs may prove cost-effective because of a reduction of the costly treatment of PONV.

Special Pediatric Considerations

In unruly, frightened, or mentally retarded children, preoperative sedation is often required prior to taking the patient into the operating room (Ch. 59) . In general, sedative premedication is not offered for patients less than 9 to 12 months old and is most often used for toddlers or preschool-aged children. Because of the aversion of these patients to intramuscular injections, oral or rectal premedicants are more popular with children. Midazolam is the most common anxiolytic premedication used at present. After receiving 0.5 mg/kg of midazolam orally, children can be easily separated from their parents within 10 to 20 minutes without prolonging discharge time. [65] [223] When rectal methohexital is administered (20-30 mg/kg) prior to halothane anesthesia, the recovery time may be prolonged significantly compared with halothane alone. Rectal etomidate (6 mg/kg) or ketamine (5-10 mg/kg) can also produce a rapid onset of hypnosis without cardiorespiratory depression in children undergoing minor outpatient procedures. [224] Intramuscular ketamine (2-4 mg/kg) can also be an extremely useful drug for induction of the uncooperative child; however, home-readiness may be delayed when larger doses of ketamine (>5 mg/kg) are combined with a volatile anesthetic. [225] In addition, recurrent illusions and flashbacks have been reported several weeks after ketamine administration to children. [226]

Although controversial, the practice of allowing parents to be present during the induction of anesthesia is becoming more common. An informal survey indicated that 50 percent of pediatric anesthesiologists allow parents to be present during induction. [227] Studies have shown that most parents are calm and supportive, and the number of very upset or turbulent children during preinduction and induction is significantly decreased. [228] Appropriate selection and education of parents is essential. Parents must be told exactly what to expect and must agree to leave immediately if asked to do so by the anesthesiologist. Unduly anxious or hysterical parents should not be encouraged to be present for induction because they may increase the child's anxiety. [229] With proper preparation, parents can help to decrease the need for sedative premedication and can avoid a traumatic separation.

Regional Anesthesia

Regional anesthesia can offer many advantages for the ambulatory patient (Chs. 42 to 44) . In addition to limiting the anesthetized area to the surgical site, common side effects of general anesthesia (e.g., nausea, vomiting, dizziness, lethargy) can be avoided. [230] Furthermore, the risks of aspiration pneumonitis and the side effects of tracheal intubation are minimized, postanesthesia nursing care and patient recovery time may be decreased, and effective analgesia is provided in the early postoperative period. [231] [232] A large retrospective study by Meridy [27] showed a shorter recovery room stay and a lower unanticipated hospital admission rate in patients with local or regional anesthesia compared with general anesthesia. Proper patient selection along with the skill and enthusiasm of the surgical and anesthesia teams will allow a wider variety of procedures to be performed with regional anesthetic techniques.

Epidural and Spinal Anesthesia

There is renewed interest in the use of regional anesthesia in the outpatient setting because of the lower incidence of side effects and improved recovery compared with general anesthesia. [233] Spinal anesthesia is the simplest and most reliable regional anesthetic technique; however, the incidence of side effects is surprisingly high. [234] The most troublesome complications of outpatient spinal anesthesia are postdural puncture headache (PDPH) and backache. Although the incidence of PDPH can be minimized by the use of small-bore, 25-gauge, pencil-point needles, the incidence of failed blocks is higher. [235] The use of these needles results in a low incidence of PDPH (1-2%), few failed blocks, low incidence of backache, and high patient acceptance. [233]

Short-acting local anesthetics, such as lidocaine, are preferable for use in outpatients to ensure predictable recovery. However, the use of 5 percent hyperbaric lidocaine has become controversial because of numerous reports of transient radicular irritation. [236] [237] As a result, investigators are recommending the use of isobaric lidocaine (2% lidocaine) as well as combinations of low-dose hypobaric lidocaine and fentanyl. The addition of fentanyl (10-20 mug) prolongs sensory but not motor block and appears to decrease the time to voiding and full recovery. In a study involving outpatients undergoing laparoscopy, a small-dose hypobaric solution of 1 percent lidocaine (25 mg) with 25 mug of fentanyl caused significantly faster recovery and less intraoperative hypotension compared with 75 mg of hyperbaric lidocaine alone. [238] [239] [240] However, the addition of the opioid analgesic increased the incidence of pruritus. Intrathecal bupivacaine has been used in ambulatory surgical patients, but it should be reserved for procedures of anticipated long duration (2-3 hours) because of the prolonged recovery times. [238] [241] [242] Outpatients should be allowed to recover motor function fully prior to discharge. Following complete recovery of motor function, residual sympathetic blockade and orthostatic hypotension are rarely a problem on ambulation. [243] [244]

Epidural anesthesia is technically more difficult, has a slower onset time and a risk of potential intravascular or intrathecal

injection, and a greater chance of an incomplete sensory block compared with spinal anesthesia. The main advantage of epidural anesthesia is the ability to extend the duration of anesthesia for procedures with a variable surgical time. Some studies have shown a faster recovery time with epidural versus spinal anesthesia, whereas the incidence of PDPH and patient satisfaction were similar. [233] The use of chloroprocaine for outpatient epidural anesthesia is associated with a high incidence of back pain resulting from muscle spasm thought to be related to the preservative ethylenediaminetetra-acetic acid (EDTA). [233]

The use of combined spinal-epidural anesthesia has also been studied in ambulatory surgical patients. [245] [246] [247] The combined technique allows for the reliability of spinal anesthesia with the flexibility of continuous epidural anesthesia. [233] Patients receive an initial small dose of intrathecal local anesthetic via a needle-through-needle technique, and then an epidural catheter is placed. The small initial dose of intrathecal drug results in lower sensory levels, reduced side effects, and faster recovery from the sensory-motor blockade. If necessary, the epidural catheter could be used to extend the block beyond the duration of the spinal anesthetic.

Intravenous Regional Anesthesia

For short superficial surgical procedures (<60 min) limited to a single extremity, the intravenous regional (Bier) block with lidocaine, 0.5 percent, is a simple and reliable technique (Ch. 43). [233] This procedure, which can be used for either upper or lower extremity surgery, uses a double tourniquet to decrease tourniquet pain. Intravenous regional anesthesia also facilitates the outpatient treatment of upper extremity injuries in children.

Peripheral Nerve Blocks

If more profound and prolonged anesthesia of the upper extremity and shoulder is required, a regional block of the brachial plexus can be used (e.g., axillary block or interscalene block) (Ch. 43) . [248] Peripheral nerve blocks are also useful for surgery on the leg. The "three-in-one block" (femoral, obturator, and lateral femoral cutaneous nerves) using a perivascular technique is useful for outpatient knee arthroscopy and anterior cruciate ligament repairs, providing excellent postoperative analgesia with a high degree of patient acceptance. Ankle blocks are also simple and effective techniques for surgery on the foot. Popliteal sciatic nerve blocks have been shown to provide excellent postoperative analgesia after foot surgery. [249]

Pediatric Patients

In pediatric patients, regional blocks can be performed immediately after induction of general anesthesia to reduce the anesthetic requirement, to provide profound postoperative analgesia, and to facilitate early recovery after surgery (Ch. 44) . [243] Historically, caudal anesthesia has been the most popular technique to reduce postoperative pain in children undergoing lower abdominal, perineal, and lower extremity procedures. Other useful techniques include blockade of the ilioinguinal and iliohypogastric nerves to minimize postherniorrhaphy pain and the use of caudal, dorsal nerve block, subcutaneous ring block, or topical lidocaine ointment for postcircumcision pain. [250] Interestingly, simple wound infiltration with local anesthetics may be as effective as a caudal or ilioinguinal nerve block in reducing pain after inguinal hernia repair. [251] Studies suggest that systemic ketorolac (1 mg/kg) is as efficacious as caudal blockade, with a lower incidence of side effects. [252]

Local Infiltration Techniques

Of all the anesthetic techniques suitable for outpatients, local infiltration of the operative site with dilute solutions of local anesthetics may be the simplest and safest. Outpatient urologic procedures (e.g., vasovasostomy, orchiopexy, and hydrocele and spermatocele repairs) performed using local anesthesia can significantly decrease the overall cost compared with inpatient procedures. [15] Outpatient knee arthroscopy is commonly performed using local anesthesia (e.g., bupivacaine 0.5%, 30 mL). [253] Inguinal herniorrhaphy has also been performed using local anesthesia, with excellent patient acceptance and minimal postoperative complications. [254] A combination of local infiltration and intercostal nerve blocks can be used for lithotripsy. [255] Careful patient selection is required for operations performed with local infiltration or a field block because patient cooperation is necessary. Local anesthetic supplementation (e.g., infiltration with bupivacaine 0.25-0.5%) may decrease incisional pain in the recovery room, and the use of topical local anesthetics (e.g., lidocaine creams and aerosols, Emla cream) may be beneficial for analgesia after selected procedures.

Monitored Anesthesia Care

The combination of local anesthetics with intravenous analgesic and sedative drugs is gaining popularity, particularly for ambulatory procedures (Ch. 40) . This technique was introduced by the American Dental Association to describe the care of patients requiring sedative or analgesic drugs during dental procedures and was called "conscious sedation." [256] As the term implies, conscious sedation is a minimally depressed level of consciousness that retains the patient's ability to maintain an airway independently and continuously and to respond appropriately to physical stimulation and verbal commands. The ASA avoids this term in their *Practice Guidelines of Sedation and Analgesia by Non-anesthesiologists* because it is imprecise. [257]

Monitored anesthesia care is the term used when an anesthesiologist monitors a patient receiving local anesthesia and/or administers anesthetic drugs to patients undergoing diagnostic or therapeutic procedures. [258] The standard of care of patients receiving monitored anesthesia care should be the same as for patients undergoing general or regional anesthesia and should include a complete preoperative assessment, intraoperative monitoring, and postoperative recovery. Vigilant monitoring is required because patients may rapidly progress from a light level of sedation to deeper sedation or unconsciousness and thus may be at risk for airway

---

TABLE 65-11 -- Relation of Anesthetic Technique to the Incidence of Postoperative Complications After Outpatient Surgery

(Not Available)

From Federated Ambulatory Surgery Association [14]

obstruction, oxygen desaturation, and aspiration. In fact, a Federated Ambulatory Surgery Association survey found a higher overall complication rate after ambulatory surgery with combined local anesthesia and intravenous sedation compared with general, regional, or local anesthesia alone (Table 65-11) (Table Not Available) . [14]

Anesthetic drugs administered during monitored anesthesia care procedures should provide analgesia, sedation, and anxiolysis, which is easily titratable and provides for a rapid recovery with few side effects. Systemic analgesics are used to reduce discomfort during injection of local anesthesia and from prolonged immobilization or where effective local anesthesia is difficult to achieve (e.g., endoscopy). [259] However, the primary method of treating pain should be supplemental local or regional infiltration with local anesthetics. Sedative drugs make procedures more tolerable for patients by reducing anxiety and by providing a degree of intraoperative amnesia. During longer surgical procedures, patients may become restless, bored, or uncomfortable from remaining immobile, and sedative-hypnotic drugs may be beneficial in allowing patients to rest. [260] Patients' anxiety may also be substantially reduced by simple measures, including good preoperative communication, keeping the patient warm and covered, and allowing the patient to listen to music during the procedure. [261] Many different sedative drugs have been used during monitored anesthesia care procedures (including barbiturates, benzodiazepines, ketamine, and propofol) using different delivery systems (e.g., intermittent boluses, variable-rate infusion, target-controlled infusion, patient-controlled sedation). [262] [263] The most commonly used sedative drugs are midazolam and propofol, either alone or in combination. [264] [265] [266] However, the careful titration of these agents to achieve the desired level of sedation and to ensure prompt recovery is more important than the choice of the drug. [258]

/das/book/view/29494766/875/723.html

SPECIAL CONSIDERATIONS

Office-Based Anesthesia

Office-based anesthesia is a variant of ambulatory anesthesia, which has attracted growing interest for short surgical procedures. It is currently estimated that 3 to 5 percent of outpatient surgical procedures are performed in the office setting, and this number is anticipated to be at least 15 percent by the year 2000. [267] As efforts to reduce the overall cost of surgical procedures continue to increase, surgeons and anesthesiologists are moving cases to facilities where they have more direct control over costs. Because office-based facilities have lower overhead than hospital or freestanding ambulatory surgical centers and are comfortable and convenient for patients, interest in office-based surgery centers continues to grow. It is important to select patients appropriately and to adhere to the usual guidelines for safe anesthetic care (Appendix 1). The optimal anesthetic techniques for office-based surgical procedures are not known. The effect of nitrous oxide with propofol anesthesia was studied in outpatients having short procedures in an office setting. [268] Nitrous oxide was shown to decrease the propofol requirements and to allow patients to be discharged within 30 minutes after the procedure without increasing the incidence of PONV. The availability of newer anesthetics associated with a faster emergence as well as improved surgical technology should facilitate the growth of office-based anesthesia in the future.

Although the practice of office-based anesthesia is relatively new in the United States, a similar practice of office-based dental anesthesia has been in place for several decades in the United Kingdom. Following a review of several anesthetic deaths in dental offices, it was recommended that all anesthetics be administered by an accredited anesthesiologist whose training included specific experience in dental anesthesia. [269] There were also recommendations regarding resuscitation equipment and the availability of drugs needed for emergency use. In the years following publication the Poswillo report, the number of dental offices offering general anesthesia for office-based procedures significantly decreased. [270] The high cost required to equip and maintain such locations was the main reason for this change of practice in the United Kingdom. Based on the British experience, it is obvious that if office-based anesthesia is going to be successful in North America, issues other than cost must be considered.

Anesthesia for Procedures Outside the Operating Room

Anesthesiologists are being called upon to provide anesthetic care for an increasing number of procedures in remote locations (Ch. 66) . The most common of these are electroconvulsive therapy (ECT), extracorpeal shock wave lithotripsy (ESWL), and neuroradiologic procedures including magnetic resonance imaging (MRI) and computed tomography (CT). The anesthetic machines and monitors used in these locations are frequently old or unfamiliar models, and the monitoring equipment and supplies are often limited. Experienced assistants may be unavailable, and nursing staff members in these locations are frequently unaccustomed

to the anesthetic equipment or procedures. Consequently, the anesthesiologist must be vigilant when checking the anesthetic machine and must know where to locate emergency resuscitation drugs and equipment.

As with any ambulatory surgical procedure, patients must be carefully selected and evaluated prior to the procedure. The anesthetic techniques used for these procedures should provide for a prompt recovery with minimal side effects. Patients undergoing general anesthesia, regional anesthesia, or monitored anesthesia care must fulfill the same discharge criteria as patients having procedures in an operating room facility.

Many of these procedures have specific anesthetic considerations and potential complications, which may require careful management. The anesthetic techniques used for ESWL have changed dramatically over the past several years. With the development of new-generation lithotriptors, a water bath may no longer be required, and the targeting is more precise so fewer shocks are required. These improvements have essentially eliminated the routine use of general or regional anesthesia, and most of these procedures can be performed with intravenous sedation and analgesia techniques. [271] [272] Intercostal nerve blocks may improve patient comfort during ESWL. [255] However, the topical use of eutectic mixture of local anesthetics (Emla cream) did not have a significant opioid-sparing effect during immersion lithotripsy. [273]

The use of ECT is expanding, particularly in the elderly population, in whom antipsychotic drug therapy is poorly tolerated because of side effects. Because the clinical efficacy of ECT depends on the duration of the seizure, the anesthetic drug that allows for the longest seizure is preferred. The effects of methohexital, propofol, and etomidate on seizure duration have been compared. [274] Both methohexital and propofol produce dose-dependent decreases in motor and electroencephalographic seizure duration compared with etomidate. The awakening times and recovery profiles were similar in all groups. The administration of adjuvant medications may be necessary to blunt the hypertensive response to electrical stimulation. The use of beta-blockers (e.g., labetalol, esmolol) is usually adequate to control the acute hyperdynamic response following the electrical stimulus. In hypertensive patients, nicardipine (1.25-2.5 mg IV) may be a useful adjunct to the beta-blocking drugs. [275]

DISCHARGE CRITERIA

There are three stages of recovery following ambulatory surgery, namely, early, intermediate, and late (Ch. 68) . Early and intermediate recovery stages occur in the ambulatory surgical facility, whereas late recovery refers to the resumption of normal daily activities and occurs after discharge. Early recovery is the time interval during which patients emerge from anesthesia, recover their protective reflexes, and resume motor activity. During this phase of recovery, patients are cared for in a phase I postanesthesia care unit (PACU), where their vital signs and oxygen saturation are carefully monitored and supplemental oxygen, analgesics, or antiemetics may be administered. The Aldrete score is commonly used to assess the fitness of patients to be transferred to the phase II recovery area (or to a hospital bed in the case of hospital inpatients). [276]

During the intermediate recovery period, patients are cared for in a reclining chair and progressively begin to ambulate, drink fluids, void, and prepare for discharge. Most ambulatory surgical facilities have a separate phase II recovery area for the intermediate recovery of outpatients to a home-ready state (see Fig. 65-1) (Figure Not Available) . The choice of anesthetic technique as well as postoperative analgesic and antiemetic drugs may have an impact on the duration of the intermediate recovery period. A prolonged early and intermediate recovery will significantly increase the cost of the patient's operation. [277] The late recovery period starts when the patient is discharged home and continues until full, functional recovery is achieved and the patient is able to return to work. The anesthetics, analgesics, and antiemetics may have an effect on the patient's recovery during the first 24 to 48 hours. However, the surgical procedure itself has the highest impact on the patient's full functional recovery.

"Fast Tracking" After Ambulatory Surgery

The availability of rapid and short-acting anesthetic drugs for the maintenance of general anesthesia (e.g., propofol, desflurane, and sevoflurane) has facilitated the early recovery of outpatients after ambulatory surgical procedures. [278] Patients may be completely awake and oriented, breathing comfortably, with stable vital signs at the time they leave the operating room after brief ambulatory surgical procedures performed using general anesthesia. A faster early recovery may not necessarily correlate with a reduction of overall costs because the major determinant of PACU costs is personnel. [279] [280] However, significant cost savings may be achieved by bypassing the PACU and transferring patients directly to a more economical phase II (step-down) recovery area. There is a growing interest in this process known as "fast tracking" after ambulatory surgery. [281]

A newer study examined the effects of three maintenance anesthetics (propofol, desflurane, and sevoflurane) on the fast-track eligibility of outpatients after laparoscopic tubal ligation. [282] Compared with propofol, desflurane and sevoflurane caused a higher percentage of outpatients to be judged fast-track eligible (89 and 75% versus 26%). There was no evidence of respiratory depression with any of the anesthetic techniques. Further outcome studies are needed to ensure patient safety before widespread implementation of fast tracking after ambulatory surgery can be recommended.

Assessment of Home-Readiness

Guidelines for safe discharge from an ambulatory surgical facility include stable vital signs, return to baseline orientation, ambulation without dizziness, minimal pain and PONV, and minimal bleeding at the surgical site. [31] The major accreditation bodies in the United States and Canada require that all ambulatory surgical patients have an escort to transport them home, and they must receive written postoperative instructions including advice on whom to contact in case

a problem develops. A discharge scoring system has been developed to evaluate and document patient's readiness for discharge objectively. [283] [284] The Post-Anesthetic Discharge Scoring System (PADSS) is a simple cumulative index that measures patient's home-readiness and is based on five major criteria: (1) vital signs, including blood pressure, heart rate, respiratory rate, and temperature; (2) ambulation and mental status; (3) pain and PONV; (4) surgical bleeding; (5) fluid intake/output. [283] Patients achieving a score of 9 or greater and have an adult escort are considered fit for discharge. The requirement for patients to drink and to void prior to discharge may not be necessary. A modified PADSS score was developed that eliminated input and output as discharge criteria and resulted in earlier discharge for 20 percent of patients (Table 65-12) (Table Not Available) . [31]

Delays in discharge are typically related to persistent symptoms such as pain, PONV, hypotension, dizziness, unsteady gait, or, frequently, the lack of an escort. [285] Excessive postoperative pain is a common surgery-related cause of delayed discharge from ambulatory surgical facilities and of unexpected hospital admission of outpatients. [286] One prospective study of 10,008 ambulatory surgical patients found a 5.3 percent incidence of severe pain in the PACU after ambulatory surgery. [287] Outpatients with severe postoperative pain often had more prolonged surgical procedures, a longer stay in the PACU and step-down unit, and a longer time to discharge compared with patients without severe pain. Outpatients undergoing orthopedic surgery had the highest incidence of pain (16.1%) followed by urologic (13.4%) and general surgical procedures (11.5%). The ability to identify outpatients at risk for severe postoperative pain allows the anesthesiologist to formulate an appropriate prophylactic analgesic plan.

Discharge After Regional Anesthesia

Patients recovering from regional anesthesia must meet the same discharge criteria as patients recovering from general

TABLE 65-12 -- Modified Postanesthesia Discharge Scoring System

(Not Available)

From Chung, [31] copyright 1993, with permission of Elsevier Science

anesthesia. However, these outpatients must also fulfill additional criteria to ensure safe ambulation after central neuroaxis blockade. With spinal or epidural anesthesia, it is generally accepted that motor and sensory function return before sympathetic nerve function. [243] Residual blockade of the sympathetic nerve supply to the bladder and urethra may cause urinary retention. Because it is necessary after ambulatory regional anesthesia for patients to be able to void, long-acting local anesthetics (e.g., bupivacaine, tetracaine) should be avoided. [238] The use of shorter-acting local anesthetics (e.g., lidocaine) with the addition of fentanyl can provide adequate anesthesia without prolonging recovery. [239] [240] Prior to ambulation, patients should have normal perianal (S4-S5) sensation, the ability to plantarflex the foot, and proprioception of the big toe. [243] Thus, discharge criteria after spinal and epidural anesthesia should include the return of normal sensation, muscle strength, and proprioception, as well as the return of sympathetic nervous function.

Controversies Related to Discharge Criteria

There is considerable controversy surrounding the requirement for all outpatients to drink fluids and void prior to discharge from an ambulatory surgical facility. It is clearly unacceptable to discharge a patient who is actively vomiting and unable to tolerate oral fluids. However, Schreiner and Nicolson [119] found that requiring children to drink prior to discharge increased the rate of vomiting by more than 50 percent and delayed discharge. Children are more likely to vomit after discharge than during their stay at the surgical facility, and, therefore, tolerating clear fluids prior to discharge does prevent vomiting and dehydration at home. At the Children's Hospital of Philadelphia, more than 20,000 day-surgery patients have been discharged without requiring intake of oral fluids with no readmissions for dehydration. [119] All patients (except those having myringotomy tubes placed) received the equivalent of 8 hours of intravenous maintenance fluids during their hospital stay. Thus, wellhydrated outpatients have been discharged home safely without necessarily demonstrating an ability to tolerate oral fluids.

The requirement to void prior to discharge is also controversial. The inability to void and urinary retention may be caused by pain (which inhibits normal bladder detrusor function), administration of drugs with anticholinergic effects, or prolonged blockade of the autonomic innervation to the bladder. [31] Patients may be discharged earlier if voiding is not a discharge requirement; however, there must be appropriate measures in place if the inability to void persists after discharge. [284]

Prior to leaving the outpatient facility, patients should have their dressings checked and should be given both verbal and written instructions regarding their postoperative care. Most postoperative symptoms (e.g., pain, PONV, dizziness, headache, and myalgias) resolve within 24 hours. However, if these symptoms persist, the patient should be encouraged to contact the facility regarding appropriate follow-up care. All patients must leave in the company of a responsible adult and must be aware of the recommendations

regarding appropriate activities after discharge. Patients should be warned not to operate machinery, drive a car, or make important decisions for at least 24 hours following outpatient anesthesia. [288]

It is important to have an efficient mechanism in place for admitting outpatients to the hospital. Most well-organized outpatient facilities have an overall hospital admission rate of less than 1 percent. [10] [14] However, transfer rates are higher in ambulatory centers with a larger proportion of neonates, the elderly, and ASA physical status III outpatients. The Federated Ambulatory Surgery Association multicenter study showed that 69 percent of all perioperative complications occurred after discharge from the ambulatory surgery center. [14] This finding emphasizes the importance of providing clear, written discharge instructions and the availability of a responsible adult to monitor the patient at home. Most practitioners recommend that out-of-town patients spend their first postoperative night within a reasonable distance from the outpatient facility. All outpatient facilities should have a mechanism in place for collecting follow-up information regarding patient well-being after discharge. For example, nurses at many outpatient facilities telephone the patient the day after discharge to determine the progress of recovery from surgery and anesthesia, whereas other facilities use postcard questionnaires for postoperative follow-up.

OUTCOME MEASURES AFTER OUTPATIENT SURGERY

As outpatient surgery continues to grow and the types of surgical procedures become more complex, ambulatory surgical centers must develop methods to evaluate patient outcome during both early and late recovery periods (Chs. 21 and 22) . [289] The overall risk of major morbidity and mortality is very low following ambulatory surgery. A large, retrospective study of more than 45,000 ASA I to III outpatients found that only 31 patients (1:1455) experienced major morbidity. [9] Four patients died, 2 as passengers in automobile accidents within the first 48 hours and 2 of myocardial infarctions more than 48 hours after surgery. The Federated Ambulatory Surgery Association performed a multicenter study in 1987 that found an increased risk of perioperative complications in patients who had preexisting cardiovascular diseases and after procedures with a duration longer than 1 hour (Table 65-13) (Table Not Available) . [14] A similar Canadian 4-center prospective study of 6,914 outpatients showed that patients with underlying medical conditions (e.g., hypertension, diabetes, and gastrointestinal disorders) were at higher risk for adverse events in the perioperative period, even if they were optimally managed preoperatively. [290] There were no deaths during the study period, and major morbid events were rare.

Although there is a low incidence of major morbidity, minor complications remain problematic after ambulatory surgery. PONV remains a "big little problem." [291] One study showed that 35 percent of outpatients discharged from ambulatory surgical centers experienced PONV severe enough to prevent their return to normal daily activities. [292] Most of these patients had not experienced PONV in the recovery room and only became symptomatic several hours after discharge.

TABLE 65-13 -- Predisposing Factors to Complications During and After Outpatient Anesthesia

(Not Available)

From Federated Ambulatory Surgery Association [14]

Other postoperative symptoms may persist for more than 24 hours after outpatient surgery. Incisional pain, PONV, drowsiness, dizziness, headache, and fever are the most frequent minor symptoms that occur after patients are discharged home. [293] The type of surgical procedure also influences the incidence of symptoms, with laparoscopic, general, and orthopedic surgical procedures having a high incidence and dilatation and curettage and ophthalmologic procedures having a low incidence of postoperative symptoms. As with PONV, patients experiencing other postoperative symptoms had a delay in returning to their usual daily activities compared with a similar population not experiencing postoperative symptoms. Despite the frequent occurrence of minor sequelae of ambulatory surgery, there is remarkably high patient satisfaction, and most would choose to have their surgery on an outpatient basis in the future. [8]

Unexpected hospital admission following outpatient surgery is an easily identifiable and important outcome measure in ambulatory anesthesia. Not only does hospital admission add to the expense of the procedure, but also it is disruptive for the patient and the surgical facility. Most facilities have admission rates of less than 1 percent. [10] [11] However, freestanding and office-based units tend to have lower transfer rates compared with hospital-based units. This may reflect the relative ease of admission of the latter or possibly a difference in the criteria for patient and procedure selection. [11] The most common causes for unexpected admission are pain, bleeding, intractable vomiting, surgical misadventure (e.g., bowel or uterine perforation), more extensive surgery, urinary retention, or lack of an escort. [10]

The likelihood of admission is related more to the type of anesthesia and surgical procedure than to specific patient characteristics. The frequency of return hospital visits after discharge from ambulatory units is another useful outcome measure. One published study found that 3 percent of patients returned to the same hospital after discharge following ambulatory surgery. [12] Bleeding at the surgical site was

the most common reason (41.5%) for patients to seek medical attention and occurred with greatest frequency after dilatation and curettage. Patients undergoing varicocelectomy and hydrocelectomy were eight times more likely to return to hospital and most commonly were diagnosed with an infection at the surgical site. Most outpatients (76.5%) who sought medical attention in the emergency room were treated and discharged, a finding indicating that better preoperative and postoperative education may have prevented an unnecessary hospital visit.

SUMMARY

Ambulatory anesthesia is continuing to evolve and has now become a recognized anesthesia subspecialty with formal postgraduate training programs. It is clear that the number of operations performed on an outpatient basis will continue to expand in the 21st century. Increasing evidence suggests that arbitrary limits placed on the type of surgery, the age of the patient, the duration of the operation, and the preoperative fasting period may be unwarranted. The ability to provide adequate pain management following outpatient surgery has become a major limiting factor in determining the types of operative procedures that can be performed in this setting. The expansion of home health-care services creates the potential for newer analgesic modalities to be used in the home (e.g., ambulatory patient-controlled analgesia, nonpharmacologic techniques).

Many controversies remain unresolved. [163] Questions regarding the optimal anesthetic technique, airway management device, need for prophylactic antiemetics, and type of postoperative pain management remain to be answered. With growing limitations on health-care resources, anesthesiologists must carefully reevaluate clinical practice. The focus in future studies of new anesthetic drugs should emphasize overall cost-effectiveness, as well as quality of patient care and improvement in outcome.

In conclusion, the rational use of combinations of anesthetic drugs will provide for rapid and smooth induction, excellent intraoperative conditions, and fast recovery with minimal adverse effects. The incidence of anesthetic-related side effects may be altered depending on the premedication, the anesthetic technique, and the skill of the anesthesiologist. Further studies are needed to determine the origin of the adverse effects caused by anesthesia and surgery, as well as the optimal therapeutic modalities. With the availability of more rapid-acting and shorter-acting anesthetic, analgesic, and muscle relaxant drugs as well as improved administration and monitoring techniques, and highly specific intravenous adjunctive drugs, anesthetic care will continue to improve into the next century.

References

1. Waters RM: The downtown anesthesia clinic. Am J Surg 33:71, 1919.

2. White PF, Smith I: Ambulatory anesthesia: Past, present, and future. Int Anesthesiol Clin 32:1, 1994.

3. Liem MS, van der Graaf Y, van Steensel CJ et al: Comparison of conventional anterior surgery and laparoscopic surgery for inguinalhernia repair. N Engl J Med 336:1541, 1997.

4. Michaloliakou C, Chung F, Sharma S: Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg 82:44, 1996.

5. White PF, Smith I: Impact of newer drugs and techniques on the quality of ambulatory anesthesia. J Clin Anesth 5:3S, 1993.

6. Pollard JB, Zboray AL, Mazze RI: Economic benefits attributed to opening a preoperative evaluation clinic for outpatients. Anesth Analg 83:407, 1996.

7. Kitz DS, Slusarz-Ladden C, Lecky JH: Hospital resources used for inpatient and ambulatory surgery. Anesthesiology 69:383, 1988.

8. Philip BK: Patients' assessment of ambulatory anesthesia and surgery. J Clin Anesth 4:355, 1992.

9. Warner MA, Shields SE, Chute CG: Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. JAMA 270:1437, 1993.

10. Gold BS, Kitz DS, Lecky JH et al: Unanticipated admission to the hospital following ambulatory surgery. JAMA 262:3008, 1989.

11. Fancourt-Smith PF, Hornstein J, Jenkins LC: Hospital admissions from the Surgical Day Care Centre of Vancouver General Hospital 1977-1987. Can J Anaesth 37:699, 1990.

12. Twersky R, Fishman D, Homel P: What happens after discharge? Return hospital visits after ambulatory surgery. Anesth Analg 84:319, 1997.

13. Natof HE: Complications associated with ambulatory surgery. JAMA 244:1116, 1980.

14. Federated Ambulatory Surgery Association: Special Study 1. 1986.

15. Caldamone AA, Rabinowitz R: Outpatient orchiopexy. J Urol 127:286, 1982.

16. Pineault R, Contandriopoulos AP, Valois M et al: Randomized clinical trial of one-day surgery: Patient satisfaction, clinical outcomes, and costs. Med Care 23:171, 1985.

17. Ford JL, Reed WA: The surgicenter: An innovation in the delivery and cost of medical care. Ariz Med 26:801, 1969.

18. Calcinai CJ, Barrett JC: Five years' experience in a free-standing outpatient surgical clinic. Aust N Z J Surg 56:55, 1986.

19. Snyder DS, Pasternak LR: Facility design and procedural safety. In White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 61.

20. Reed WA, Ford JL: Development of an independent outpatient surgical center. Int Anesthesiol Clin 14:113, 1976.

21. Pender JW, Jamplis RW: Free-standing outpatient surgical facilities. Aust N Z J Surg 56:2, 1986.

22. McTaggart RA: Selection of patients for day care surgery. Can Anaesth Soc J 30:543, 1983.

23. Duncan PG: Day surgical anaesthesia: Which patients? Which procedures? Can J Anaesth 38:881, 1991.

24. Lehmann KA, Einnolf C, Eberlein HJ et al: Transdermal fentanyl for the treatment of pain after major urological operations: A randomized double-blind comparison with placebo using intravenous patient-controlled analgesia. Eur J Clin Pharmacol 41:17, 1991.

25. Eriksson H, Tenhunen A, Korttila K: Balanced analgesia improves recovery and outcome after outpatient tubal ligation. Acta Anaesthesiol Scand 40:151, 1996.

26. Benedetti F, Amanzio M, Casadio C et al: Control of postoperative pain by transcutaneous electrical nerve stimulation after thoracic operations. Ann Thorac Surg 63:773, 1997.

27. Meridy HW: Criteria for selection of ambulatory surgical patients and guidelines for anesthetic management: A retrospective study of 1553 cases. Anesth Analg 61:921, 1982.

28. Mingus ML, Bodian CA, Bradford CN et al: Prolonged surgery increases the likelihood of admission of scheduled ambulatory surgery patients. J Clin Anesth 9:446, 1997.

29. Natof HE: Pre-existing medical problems: Ambulatory surgery. Ill Med J 166:101, 1984.

30. Rudkin GE, Osborne GA, Doyle CE: Assessment and selection of patients for day surgery in a public hospital. Med J Aust 158:308, 1993.

31. Chung F: Are discharge criteria changing? J Clin Anesth 5:64S, 1993.

32. Yentis SM, Levine MF, Hartley EJ: Should all children with suspected or confirmed malignant hyperthermia susceptibility be admitted after surgery? A 10-year review. Anesth Analg 75:345, 1992.

33. Hannallah RS: Selection of patients for paediatric ambulatory surgery. Can J Anaesth 38:887, 1991.

34. Fisher DM: When is the ex-premature infant no longer at risk for apnea? Anesthesiology 82:807, 1995.

35. Liu LM, Cote CJ, Goudsouzian NG et al: Life-threatening apnea in infants recovering from anesthesia. Anesthesiology 59:506, 1983.

36. Malviya S, Swartz J, Lerman J: Are all preterm infants younger than 60 weeks postconceptual age at risk for postanesthetic apnea? Anesthesiology 78:1076, 1993.

37. Kurth CD, LeBard SE: Association of postoperative apnea, airway obstruction, and hypoxemia in former premature infants. Anesthesiology 75:22, 1991.

38. Welborn LG, Hannallah RS, Luban NL et al: Anemia and postoperative apnea in former preterm infants. Anesthesiology 74:1003, 1991.

39. Welborn LG, Hannallah RS, Fink R et al: High-dose caffeine suppresses postoperative apnea in former preterm infants. Anesthesiology 71:347, 1989.

40. Cote CJ, Zaslavsky A, Downes JJ et al: Postoperative apnea in former preterm infants after inguinal herniorrhaphy: A combined analysis. Anesthesiology 82:809, 1995.

41. Patel RI, Hannallah RS: Preoperative screening for pediatric ambulatory surgery: Evaluation of a telephone questionnaire method. Anesth Analg 75:258, 1992.

42. Fischer SP: Development and effectiveness of an anesthesia preoperative evaluation clinic in a teaching hospital. Anesthesiology 85:196, 1996.

43. Conway JB, Goldberg J, Chung F: Preadmission anaesthesia consultation clinic. Can J Anaesth 39:1051, 1992.

44. Tompkins BM, Tompkins WJ, Loder E et al: A computer-assisted preanesthesia interview: Value of a computer-generated summary of patient's historical information in the preanesthesia visit. Anesth Analg 59:3, 1980.

45. Arvidsson S: Preparation of adult patients for anaesthesia and surgery. Acta Anaesthesiol Scand 40:962, 1996.

46. Hampton JR, Harrison MJ, Mitchell JR et al: Relative contributions of history-taking, physical examination, and laboratory investigation to diagnosis and management of medical outpatients. BMJ 2:486, 1975.

47. Charpak Y, Blery C, Chastang C et al: Prospective assessment of a protocol for selective ordering of preoperative chest x-rays. Can J Anaesth 35:259, 1988.

48. Kaplan EB, Sheiner LB, Boeckmann AJ et al: The usefulness of preoperative laboratory screening. JAMA 253:3576, 1985.

49. Roizen MF: Cost-effective preoperative laboratory testing. JAMA 271:319, 1994.

50. Johnston M: Anxiety in surgical patients. Psychol Med 10:145, 1980.

51. Wallace LM: Psychological preparation as a method of reducing the stress of surgery. J Hum Stress 10:62, 1984.

52. Egbert LD, Battit GE, Turndorf H: The value of the preoperative visit by an anesthetist. JAMA 185:553, 1963.

53. Arellano R, Cruise C, Chung F: Timing of the anesthetist's preoperative outpatient interview. Anesth Analg 68:645, 1989.

54. Klafta JM, Roizen MF: Current understanding of patients' attitudes toward and preparation for anesthesia: A review. Anesth Analg 83:1314, 1996.

55. Hain WR: Peer modelling and paediatric anaesthesia. Anaesthesia 38:158, 1983.

56. Feld LH, Negus JB, White PF: Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 73:831, 1990.

57. Kanto J, Watanabe H, Namiki A: Pharmacological premedication for anaesthesia. Acta Anaesthesiol Scand 40:982, 1996.

58. Shafer A, White PF, Urquhart ML et al: Outpatient premedication: Use of midazolam and opioid analgesics. Anesthesiology 71:495, 1989.

59. Jakobsen H, Hertz JB, Johansen JR et al: Premedication before day surgery: A double-blind comparison of diazepam and placebo. Br J Anaesth 57:300, 1985.

60. Kain ZN, Gaal DJ, Kain TS et al: A first-pass cost analysis of propofol versus barbiturates for children undergoing magnetic resonance imaging. Anesth Analg 79:1102, 1994.

61. Richardson MG, Wu CL, Hussain A: Midazolam premedication increases sedation but does not prolong discharge times after brief outpatient general anesthesia for laparoscopic tubal sterilization. Anesth Analg 85:301, 1997.

62. Miller DR, Blew PG, Martineau RJ et al: Midazolam and awareness with recall during total intravenous anaesthesia. Can J Anaesth 43:946, 1996.

63. Oxorn D, Ferris LE, Harrington E et al: The effects of midazolam on propofol-induced anesthesia: Propofol dose requirements, mood profiles, and perioperative dreams. Anesth Analg 85:553, 1997.

64. Hargreaves J: Benzodiazepine premedication in minor day-case surgery: Comparison of oral midazolam and temazepam with placebo. Br J Anaesth 61:611, 1988.

65. Levine MF, Spahr-Schopfer IA, Hartley E et al: Oral midazolam premedication in children: The minimum time interval for separation from parents. Can J Anaesth 40:726, 1993.

66. Shafer A: Preoperative medication: Adults and children. In White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 173.

67. Horrigan RW, Moyers JR, Johnson BH et al: Etomidate vs. thiopental with and without fentanyl: A comparative study of awakening in man. Anesthesiology 52:362, 1980.

68. Pandit SK, Kothary SP: Should we premedicate ambulatory surgical patients? (abstract). Anesthesiology 65:A352, 1986.

69. Feld LH, Champeau MW, van Steennis CA et al: Preanesthetic medication in children: A comparison of oral transmucosal fentanyl citrate versus placebo. Anesthesiology 71:374, 1989.

70. Garfield JM, Garfield FB, Philip BK et al: A comparison of clinical and psychological effects of fentanyl and nalbuphine in ambulatory gynecologic patients. Anesth Analg 66:1303, 1987.

71. Souter AJ, Fredman B, White PF: Controversies in the perioperative use of nonsteroidal antiinflammatory drugs. Anesth Analg 79:1178, 1994.

72. Liu J, Ding Y, White PF et al: Effects of ketorolac on postoperative analgesia and ventilatory function after laparoscopic cholecystectomy. Anesth Analg 76:1061, 1993.

73. Watcha MF, Ramirez-Ruiz M, White PF et al: Perioperative effects of oral ketorolac and acetaminophen in children undergoing bilateral myringotomy. Can J Anaesth 39:649, 1992.

74. Abramowitz MD, Oh TH, Epstein BS et al: The antiemetic effect of droperidol following outpatient strabismus surgery in children. Anesthesiology 59:579, 1983.

75. Korttila K, Ostman P, Faure E et al: Randomized comparison of recovery after propofol-nitrous oxide versus thiopentone-isoflurane-nitrous oxide anaesthesia in patients undergoing ambulatory surgery. Acta Anaesthesiol Scand 34:400, 1990.

76. Lerman J: Surgical and patient factors involved in postoperative nausea and vomiting. Br J Anaesth 69:S24, 1992.

77. Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment, and prevention. Anesthesiology 77:162, 1992.

78. Cohen MM, Duncan PG, DeBoer DP et al: The postoperative interview: Assessing risk factors for nausea and vomiting. Anesth Analg 78:7, 1994.

79. Honkavaara P, Lehtinen AM, Hovorka J et al: Nausea and vomiting after gynaecological laparoscopy depends upon the phase of the menstrual cycle. Can J Anaesth 38:876, 1991.

80. Beattie WS, Lindblad T, Buckley DN et al: The incidence of postoperative nausea and vomiting in women undergoing laparoscopy is influenced by the day of menstrual cycle. Can J Anaesth 38:298, 1991.

81. Beattie WS, Buckley DN: Influence of menstrual cycle on postoperative nausea and vomiting after propofol anaesthesia (abstract). Anesthesiology 77:A29, 1992.

82. McKenzie R, Uy NT, Riley TJ et al: Droperidol/ondansetron combination controls nausea and vomiting after tubal banding. Anesth Analg 83:1218, 1996.

83. Doze VA, Shafer A, White PF: Nausea and vomiting after outpatient anesthesia: Effectiveness of droperidol alone and in combination with metoclopramide. Anesth Analg 66:S41, 1987.

84. Tang J, Watcha MF, White PF: A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. Anesth Analg 83:304, 1996.

85. Melnick B, Sawyer R, Karambelkar D et al: Delayed side effects of droperidol after ambulatory general anesthesia. Anesth Analg 69:748, 1989.

86. Rita L, Goodarzi M, Seleny F: Effect of low dose droperidol on postoperative vomiting in children. Can Anaesth Soc J 28:259, 1981.

87. Steinbrook RA, Freiberger D, Gosnell JL et al: Prophylactic antiemetics for laparoscopic cholecystectomy: Ondansetron versus droperidol plus metoclopramide. Anesth Analg 83:1081, 1996.

88. Watcha MF, White PF: New antiemetic drugs. Int Anesthesiol Clin 33:1, 1995.

89. Vener DF, Carr AS, Sikich N et al: Dimenhydrinate decreases vomiting after strabismus surgery in children. Anesth Analg 82:728, 1996.

90. Sung YF, Wetchler BV, Duncalf D et al: A double-blind, placebo-controlled pilot study examining the effectiveness of intravenous ondansetron

in the prevention of postoperative nausea and emesis. J Clin Anesth 5:22, 1993.

91. Bodner M, White PF: Antiemetic efficacy of ondansetron after outpatient laparoscopy. Anesth Analg 73:250, 1991.

92. Scuderi P, Wetchler B, Sung YF et al: Treatment of postoperative nausea and vomiting after outpatient surgery with the 5-HT3 antagonist ondansetron. Anesthesiology 78:15, 1993.

93. Zahl K: The role of ondansetron and other antiemetics in ambulatory anesthesia. J Clin Anesth 5:52S, 1993.

94. Kovac AL, Pearman MH, Khalil SN et al: Ondansetron prevents postoperative emesis in male outpatients: S3A-379 Study Group. J Clin Anesth 8:644, 1996.

95. Khalil SN, Kataria B, Pearson K et al: Ondansetron prevents postoperative nausea and vomiting in women outpatients. Anesth Analg 79:845, 1994.

96. Khalil S, Rodarte A, Weldon BC et al: Intravenous ondansetron in established postoperative emesis in children: S3A-381 Study Group. Anesthesiology 85:270, 1996.

97. Sun R, Klein KW, White PF: The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. Anesth Analg 84:331, 1997.

98. Sniadach MS, Alberts MS: A comparison of the prophylactic antiemetic effect of ondansetron and droperidol on patients undergoing gynecologic laparoscopy. Anesth Analg 85:797, 1997.

99. Dundee JW, Ghaly RG, Bill KM et al: Effect of stimulation of the P6 antiemetic point on postoperative nausea and vomiting. Br J Anaesth 63:612, 1989.

100. Dundee JW, Chestnutt WN, Ghaly RG et al: Traditional Chinese acupuncture: A potentially useful antiemetic? BMJ 293:583, 1986.

101. Stein DJ, Birnbach DJ, Danzer BI et al: Acupressure versus intravenous metoclopramide to prevent nausea and vomiting during spinal anesthesia for cesarean section. Anesth Analg 84:342, 1997.

102. Fan CF, Tanhui E, Joshi S et al: Acupressure treatment for prevention of postoperative nausea and vomiting. Anesth Analg 84:821, 1997.

103. White PF: Are nonpharmacologic techniques useful alternatives to antiemetic drugs for the prevention of nausea and vomiting? Anesth Analg 84:712, 1997.

104. Ong BY, Palahniuk RJ, Cumming M: Gastric volume and pH in out-patients. Can Anaesth Soc J 25:36, 1978.

105. Manchikanti L, Roush JR: Effect of preanesthetic glycopyrrolate and cimetidine on gastric fluid pH and volume in outpatients. Anesth Analg 63:40, 1984.

106. Manchikanti L, Roush JR, Colliver JA: Effect of preanesthetic ranitidine and metoclopramide on gastric contents in morbidly obese patients. Anesth Analg 65:195, 1986.

107. Sutherland AD, Stock JG, Davies JM: Effects of preoperative fasting on morbidity and gastric contents in patients undergoing day-stay surgery. Br J Anaesth 58:876, 1986.

108. Olsson GL, Hallen B, Hambraeus-Jonzon K: Aspiration during anaesthesia: A computer-aided study of 185,358 anaesthetics. Acta Anaesthesiol Scand 30:84, 1986.

109. Maltby JR, Sutherland AD, Sale JP et al: Preoperative oral fluids: Is a five-hour fast justified prior to elective surgery? Anesth Analg 65:1112, 1986.

110. Morison DH, Dunn GL, Fargas-Babjak AM et al: A double-blind comparison of cimetidine and ranitidine as prophylaxis against gastric aspiration syndrome. Anesth Analg 61:988, 1982.

111. Sandhar BK, Goresky GV, Maltby JR et al: Effect of oral liquids and ranitidine on gastric fluid volume and pH in children undergoing outpatient surgery. Anesthesiology 71:327, 1989.

112. Maltby JR, Reid CR, Hutchinson A: Gastric fluid volume and pH in elective inpatients. II. Coffee or orange juice with ranitidine. Can J Anaesth 35:16, 1988.

113. Manchikanti L, Grow JB, Colliver JA et al: Bicitra (sodium citrate) and metoclopramide in outpatient anesthesia for prophylaxis against aspiration pneumonitis. Anesthesiology 63:378, 1985.

114. Foulkes E, Jenkins LC: A comparative evaluation of cimetidine and sodium citrate to decrease gastric acidity: Effectiveness at the time of induction of anaesthesia. Can Anaesth Soc J 28:29, 1981.

115. Rao TL, Madhavareddy S, Chinthagada M et al: Metoclopramide and cimetidine to reduce gastric fluid pH and volume. Anesth Analg 63:1014, 1984.

116. Eriksson LI, Sandin R: Fasting guidelines in different countries. Acta Anaesthesiol Scand 40:971, 1996.

117. Cote CJ: NPO after midnight for children: A reappraisal. Anesthesiology 72:589, 1990.

118. Goresky GV, Maltby JR: Fasting guidelines for elective surgical patients. Can J Anaesth 37:493, 1990.

119. Schreiner MS, Nicolson SC: Pediatric ambulatory anesthesia: NPO--before or after surgery? J Clin Anesth 7:589, 1995.

120. Doze VA, White PF: Effects of fluid therapy on serum glucose levels in fasted outpatients. Anesthesiology 66:223, 1987.

121. Hutchinson A, Maltby JR, Reid CR: Gastric fluid volume and pH in elective inpatients. I. Coffee or orange juice versus overnight fast. Can J Anaesth 35:12, 1988.

122. Splinter WM, Stewart JA, Muir JG: The effect of preoperative apple juice on gastric contents, thirst, and hunger in children. Can J Anaesth 36:55, 1989.

123. Green CR, Pandit SK, Schork MA: Preoperative fasting time: Is the traditional policy changing? Results of a national survey. Anesth Analg 83:123, 1996.

124. Yogendran S, Asokumar B, Cheng DC et al: A prospective randomized double-blinded study of the effect of intravenous fluid therapy on adverse outcomes on outpatient surgery. Anesth Analg 80:682, 1995.

125. Conahan TJ, Williams GD, Apfelbaum JL et al: Airway heating reduces recovery time (cost) in outpatients. Anesthesiology 67:128, 1987.

126. Benumof JL: Laryngeal mask airway: Indications and contraindications. Anesthesiology 77:843, 1992.

127. Smith I, White PF: Use of the laryngeal mask airway as an alternative to a face mask during outpatient arthroscopy. Anesthesiology 77:850, 1992.

128. Pennant JH, White PF: The laryngeal mask airway: Its uses in anesthesiology. Anesthesiology 79:144, 1993.

129. Joshi GP, Inagaki Y, White PF et al: Use of the laryngeal mask airway as an alternative to the tracheal tube during ambulatory anesthesia. Anesth Analg 85:573, 1997.

130. Alexander CA, Leach AB: Incidence of sore throats with the laryngeal mask. Anaesthesia 44:791, 1989.

131. Wittmann PH, Wittmann FW: Laryngeal mask and gastric dilatation. Anaesthesia 46:1083, 1991.

132. Sesay M, Cros AM, Nouette K et al: Use of COPA versus LMA during anesthesia for magnetic resonance imaging (abstract). Anesthesiology 87:A958, 1997.

133. Johnston R, Noseworthy T, Anderson B et al: Propofol versus thiopental for outpatient anesthesia. Anesthesiology 67:431, 1987.

134. Hovorka J, Korttila K, Erkola O: Nitrous oxide does not increase nausea and vomiting following gynaecological laparoscopy. Can J Anaesth 36:145, 1989.

135. Fisher DM: Does nitrous oxide cause vomiting? Anesth Analg 83:4, 1996.

136. Sukhani R, Lurie J, Jabamoni R: Propofol for ambulatory gynecologic laparoscopy: Does omission of nitrous oxide alter postoperative emetic sequelae and recovery? Anesth Analg 78:831, 1994.

137. Splinter WM, Roberts DJ, Rhine EJ et al: Nitrous oxide does not increase vomiting in children after myringotomy. Can J Anaesth 42:274, 1995.

138. Korttila K, Linnoila M, Ertama P et al: Recovery and simulated driving after intravenous anesthesia with thiopental, methohexital, propanidid, or alphadione. Anesthesiology 43:291, 1975.

139. Doze VA, Westphal LM, White PF: Comparison of propofol with methohexital for outpatient anesthesia. Anesth Analg 65:1189, 1986.

140. Sun R, Skrivanek G, Stool L et al: Use of methohexital for induction of outpatient anesthesia: A cost-effective alternative to propofol? (abstract) Anesth Analg 84:S29, 1997.

141. Berggren L, Eriksson I: Midazolam for induction of anaesthesia in outpatients: A comparison with thiopentone. Acta Anaesthesiol Scand 25:492, 1981.

142. Forrest P, Galletly DC: Comparison of propofol and antagonised midazolam anaesthesia for day-case surgery. Anaesth Intensive Care 15:394, 1987.

143. Wagner RL, White PF: Etomidate inhibits adrenocortical function in surgical patients. Anesthesiology 61:647, 1984.

144. White PF: Ketamine update: Its clinical uses in anesthesia. Semin Anesth 7:113, 1988.

145. Smith I, White PF, Nathanson M et al: Propofol: An update on its clinical use. Anesthesiology 81:1005, 1994.

146. Korttila K: Recovery from propofol: Does it really make a difference? J Clin Anesth 5:443, 1993.

147. Korttila K, Nuotto EJ, Lichtor JL et al: Clinical recovery and psychomotor function after brief anesthesia with propofol or thiopental. Anesthesiology 76:676, 1992.

148. Doze VA, Shafer A, White PF: Propofol-nitrous oxide versus thiopental-isoflurane-nitrous oxide for general anesthesia. Anesthesiology 69:63, 1988.

149. Sung YF, Reiss N, Tillette T: The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental sodium-isoflurane-nitrous oxide anesthesia. J Clin Anesth 3:391, 1991.

150. Mackenzie N, Grant IS: Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. Br J Anaesth 57:725, 1985.

151. Hannallah RS, Britton JT, Schafer PG et al: Propofol anaesthesia in paediatric ambulatory patients: A comparison with thiopentone and halothane. Can J Anaesth 41:12, 1994.

152. Weir PM, Munro HM, Reynolds PI et al: Propofol infusion and the incidence of emesis in pediatric outpatient strabismus surgery. Anesth Analg 76:760, 1993.

153. Ved SA, Walden TL, Montana J et al: Vomiting and recovery after outpatient tonsillectomy and adenoidectomy in children: Comparison of four anesthetic techniques using nitrous oxide with halothane or propofol. Anesthesiology 85:4, 1996.

154. Reimer EJ, Montgomery CJ, Bevan JC et al: Propofol anaesthesia reduces early postoperative emesis after paediatric strabismus surgery. Can J Anaesth 40:927, 1993.

155. Scher CS, Amar D, McDowall RH et al: Use of propofol for the prevention of chemotherapy-induced nausea and emesis in oncology patients. Can J Anaesth 39:170, 1992.

156. Borgeat A, Wilder-Smith OH, Saiah M et al: Subhypnotic doses of propofol possess direct antiemetic properties. Anesth Analg 74:539, 1992.

157. Oxorn D, Orser B, Ferris LE et al: Propofol and thiopental anesthesia: A comparison of the incidence of dreams and perioperative mood alterations. Anesth Analg 79:553, 1994.

158. Haugen RD, Vaghadia H, Waters T et al: Thiopentone pretreatment for propofol injection pain in ambulatory patients. Can J Anaesth 42:1108, 1995.

159. Carter JA, Dye AM, Cooper GM: Recovery from day-case anaesthesia: The effect of different inhalational anaesthetic agents. Anaesthesia 40:545, 1985.

160. Tracey JA, Holland AJ, Unger L: Morbidity in minor gynaecological surgery: A comparison of halothane, enflurane and isoflurane. Br J Anaesth 54:1213, 1982.

161. Valanne JV, Korttila K: Recovery following general anesthesia with isoflurane or enflurane for outpatient dentistry and oral surgery. Anesth Prog 35:48, 1988.

162. Kingston HG: Halothane and isoflurane anesthesia in pediatric outpatients. Anesth Analg 65:181, 1986.

163. White PF: Ambulatory anesthesia and surgery: Past, present, and future. In White PF (ed): Ambulatory Anesthesia and Surgery. London, WB Saunders, 1997, p 3.

164. Eger EI: New drugs in anesthesia. Int Anesthesiol Clin 33:61, 1995.

165. Young CJ, Apfelbaum JL: Inhalational anesthetics: Desflurane and sevoflurane. J Clin Anesth 7:564, 1995.

166. Brown BJ: Sevoflurane: Introduction and overview. Anesth Analg 81:S1, 1995.

167. Smith I, Nathanson M, White PF: Sevoflurane: A long-awaited volatile anaesthetic. Br J Anaesth 76:435, 1996.

168. White PF: Studies of desflurane in outpatient anesthesia. Anesth Analg 75:S47, 1992.

169. Ghouri AF, Bodner M, White PF: Recovery profile after desflurane-nitrous oxide versus isoflurane-nitrous oxide in outpatients. Anesthesiology 74:419, 1991.

170. Rapp SE, Conahan TJ, Pavlin DJ et al: Comparison of desflurane with propofol in outpatients undergoing peripheral orthopedic surgery. Anesth Analg 75:572, 1992.

171. Van Hemelrijck J, Smith I, White PF: Use of desflurane for outpatient anesthesia: A comparison with propofol and nitrous oxide. Anesthesiology 75:197, 1991.

172. Nathanson MH, Fredman B, Smith I et al: Sevoflurane versus desflurane for outpatient anesthesia: A comparison of maintenance and recovery profiles. Anesth Analg 81:1186, 1995.

173. Lebenbom-Mansour MH, Pandit SK, Kothary SP et al: Desflurane versus propofol anesthesia: A comparative analysis in outpatients. Anesth Analg 76:936, 1993.

174. Welborn LG, Hannallah RS, Norden JM et al: Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesth Analg 83:917, 1996.

175. Davis PJ, Cohen IT, McGowan FXJ et al: Recovery characteristics of desflurane versus halothane for maintenance of anesthesia in pediatric ambulatory patients. Anesthesiology 80:298, 1994.

176. Gupta A, Kullander M, Ekberg K et al: Anaesthesia for day-care arthroscopy: A comparison between desflurane and isoflurane. Anaesthesia 51:56, 1996.

177. Graham SG, Aitkenhead AR: A comparison between propofol and desflurane anaesthesia for minor gynaecological laparoscopic surgery. Anaesthesia 48:471, 1993.

178. Apfelbaum JL, Lichtor JL, Lane BS et al: Awakening, clinical recovery, and psychomotor effects after desflurane and propofol anesthesia. Anesth Analg 83:721, 1996.

179. Patel N, Smith CE, Pinchak AC et al: Desflurane is not associated with faster operating room exit times in outpatients. J Clin Anesth 8:130, 1996.

180. Weiskopf RB, Eger EI, Daniel M et al: Cardiovascular stimulation induced by rapid increases in desflurane concentration in humans results from activation of tracheopulmonary and systemic receptors. Anesthesiology 83:1173, 1995.

181. Weiskopf RB, Moore MA, Eger EI et al: Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. Anesthesiology 80:1035, 1994.

182. Eger EI: New inhalational agents: Desflurane and sevoflurane. Can J Anaesth 40:R3, 1993.

183. Piat V, Dubois MC, Johanet S et al: Induction and recovery characteristics and hemodynamic responses to sevoflurane and halothane in children. Anesth Analg 79:840, 1994.

184. Sloan MH, Conard PF, Karsunky PK et al: Sevoflurane versus isoflurane: Induction and recovery characteristics with single-breath inhaled inductions of anesthesia. Anesth Analg 82:528, 1996.

185. Greenspun JC, Hannallah RS, Welborn LG et al: Comparison of sevoflurane and halothane anesthesia in children undergoing outpatient ear, nose, and throat surgery. J Clin Anesth 7:398, 1995.

186. Black A, Sury MR, Hemington L et al: A comparison of the induction characteristics of sevoflurane and halothane in children. Anaesthesia 51:539, 1996.

187. Sigston PE, Jenkins AM, Jackson EA et al: Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane. Br J Anaesth 78:362, 1997.

188. Sarner JB, Levine M, Davis PJ et al: Clinical characteristics of sevoflurane in children: A comparison with halothane. Anesthesiology 82:38, 1995.

189. Kataria B, Epstein R, Bailey A et al: A comparison of sevoflurane to halothane in paediatric surgical patients: Results of a multicentre international study. Paediatr Anaesth 6:283, 1996.

190. Rieger A, Schroter G, Philippi W et al: A comparison of sevoflurane with halothane in outpatient adenotomy in children with mild upper respiratory tract infections. J Clin Anesth 8:188, 1996.

191. Lerman J: Sevoflurane in pediatric anesthesia. Anesth Analg 81:S4, 1995.

192. Sury MR, Black A, Hemington L et al: A comparison of the recovery characteristics of sevoflurane and halothane in children. Anaesthesia 51:543, 1996.

193. Johannesson GP, Floren M, Lindahl SG: Sevoflurane for ENT-surgery in children: A comparison with halothane. Acta Anaesthesiol Scand 39:546, 1995.

194. Mazze RI, Jamison RL: Low-flow (1 l/min) sevoflurane: Is it safe? Anesthesiology 86:1225, 1997.

195. Bito H, Ikeda K: Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. Br J Anaesth 74:667, 1995.

196. Cunningham DD, Huang S, Webster J et al: Sevoflurane degradation to compound A in anaesthesia breathing systems. Br J Anaesth 77:537, 1996.

197. Bito H, Ikeda K: Degradation products of sevoflurane during low-flow anaesthesia. Br J Anaesth 74:56, 1995.

198. Heath KJ, Sadler P, Winn JH et al: Nitrous oxide reduces the cost of intravenous anaesthesia. Eur J Anaesthesiol 13:369, 1996.

199. Hartung J: Twenty-four of twenty-seven studies show a greater incidence of emesis associated with nitrous oxide than with alternative anesthetics. Anesth Analg 83:114, 1996.

200. Claxton AR, McGuire G, Chung F et al: Evaluation of morphine versus fentanyl for postoperative analgesia after ambulatory surgical procedures. Anesth Analg 84:509, 1997.

201. Ghouri AF, White PF: Effect of fentanyl and nitrous oxide on the desflurane anesthetic requirement. Anesth Analg 72:377, 1991.

202. White PF, Coe V, Shafer A et al: Comparison of alfentanil with fentanyl for outpatient anesthesia. Anesthesiology 64:99, 1986.

203. Phitayakorn P, Melnick BM, Vicinie AF: Comparison of continuous sufentanil and fentanyl infusions for outpatient anaesthesia. Can J Anaesth 34:242, 1987.

204. Glass PS: Remifentanil: A new opioid. J Clin Anesth 7:558, 1995.

205. Michelsen LG, Hug CCJ: The pharmacokinetics of remifentanil. J Clin Anesth 8:679, 1996.

206. Egan TD, Lemmens HJ, Fiset P et al: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 79:881, 1993.

207. Burkle H, Dunbar S, Van AH: Remifentanil: A novel, short-acting, mu-opioid. Anesth Analg 83:646, 1996.

208. Philip BK, Scuderi PE, Chung F et al: Remifentanil compared with alfentanil for ambulatory surgery using total intravenous anesthesia: The Remifentanil/Alfentanil Outpatient TIVA Group. Anesth

Analg 84:515, 1997.

209. Song D, White PF, Johnson ER: Use of remifentanil during desflurane anesthesia facilitates early recovery in outpatients undergoing laparoscopic tubal ligation procedures (abstract). Anesthesiology 89:A15, 1998.

210. Song D, White PF: Optimal dose of remifentanil for maintaining hemodynamic stability during anesthetic induction and tracheal intubation: A comparison with fentanyl (abstract). Anesth Analg 86:S105, 1998.

211. Ding Y, White PF: Comparative effects of ketorolac, dezocine, and fentanyl as adjuvants during outpatient anesthesia. Anesth Analg 75:566, 1992.

212. Walsh C, Smith CE, Ryan B et al: Postoperative vomiting following strabismus surgery in paediatric outpatients: Spontaneous versus controlled ventilation. Can J Anaesth 35:31, 1988.

213. Zahl K, Apfelbaum JL: Muscle pain occurs after outpatient laparoscopy despite the substitution of vecuronium for succinylcholine. Anesthesiology 70:408, 1989.

214. Pearce AC, Williams JP, Jones RM: Atracurium for short surgical procedures in day patients. Br J Anaesth 56:973, 1984.

215. Apfelbaum JL: Muscle relaxants for outpatient surgery: Old and new. J Clin Anesth 4:2S, 1992.

216. Tang J, Joshi GP, White PF: Comparison of rocuronium and mivacurium to succinylcholine during outpatient laparoscopic surgery. Anesth Analg 82:994, 1996.

217. Savarese JJ, Ali HH, Basta SJ et al: The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): A short-acting nondepolarizing ester neuromuscular blocking drug. Anesthesiology 68:723, 1988.

218. Goldberg ME, Larijani GE, Azad SS et al: Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. Anesth Analg 69:93, 1989.

219. Partridge BL, Ward CF: Pulmonary edema following low-dose naloxone administration. Anesthesiology 65:709, 1986.

220. King MJ, Milazkiewicz R, Carli F et al: Influence of neostigmine on postoperative vomiting. Br J Anaesth 61:403, 1988.

221. Ding Y, Fredman B, White PF: Use of mivacurium during laparoscopic surgery: Effect of reversal drugs on postoperative recovery. Anesth Analg 78:450, 1994.

222. Watcha MF, Safavi FZ, McCulloch DA et al: Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. Anesth Analg 80:713, 1995.

223. Weldon BC, Watcha MF, White PF: Oral midazolam in children: Effect of time and adjunctive therapy. Anesth Analg 75:51, 1992.

224. Saint-Maurice C, Laguenie G, Couturier C et al: Rectal ketamine in paediatric anaesthesia. Br J Anaesth 51:573, 1979.

225. Hannallah RS, Patel RI: Low-dose intramuscular ketamine for anesthesia pre-induction in young children undergoing brief outpatient procedures. Anesthesiology 70:598, 1989.

226. Meyers EF, Charles P: Prolonged adverse reactions to ketamine in children. Anesthesiology 49:39, 1978.

227. Hannallah RS: Who benefits when parents are present during anaesthesia induction in their children? Can J Anaesth 41:271, 1994.

228. Hannallah RS, Rosales JK: Experience with parents' presence during anaesthesia induction in children. Can Anaesth Soc J 30:286, 1983.

229. Hannallah RS: Pediatric ambulatory anesthesia: Role of parents. J Clin Anesth 7:597, 1995.

230. Philip BK: Regional anaesthesia for ambulatory surgery. Can J Anaesth 39:R3, 1992.

231. Mingus ML: Recovery advantages of regional anesthesia compared with general anesthesia: Adult patients. J Clin Anesth 7:628, 1995.

232. Bridenbaugh LD: Regional anaesthesia for outpatient surgery: A summary of 12 years' experience. Can Anaesth Soc J 30:548, 1983.

233. Greenberg CP: Practical, cost-effective regional anesthesia for ambulatory surgery. J Clin Anesth 7:614, 1995.

234. Vloka JD, Hadzic A, Mulcare R et al: Femoral and genitofemoral nerve blocks versus spinal anesthesia for outpatients undergoing long saphenous vein stripping surgery. Anesth Analg 84:749, 1997.

235. Pittoni G, Toffoletto F, Calcarella G et al: Spinal anesthesia in outpatient knee surgery: 22-gauge versus 25-gauge Sprotte needle. Anesth Analg 81:73, 1995.

236. Pollock JE, Neal JM, Stephenson CA et al: Prospective study of the incidence of transient radicular irritation in patients undergoing spinal anesthesia. Anesthesiology 84:1361, 1996.

237. Pinczower GR, Chadwick HS, Woodland R et al: Bilateral leg pain following lidocaine spinal anaesthesia. Can J Anaesth 42:217, 1995.

238. Mulroy MF, Wills RP: Spinal anesthesia for outpatients: Appropriate agents and techniques. J Clin Anesth 7:622, 1995.

239. Vaghadia H, McLeod DH, Mitchell GW et al: Small-dose hypobaric lidocaine-fentanyl spinal anesthesia for short duration outpatient laparoscopy. I. A randomized comparison with conventional dose hyperbaric lidocaine. Anesth Analg 84:59, 1997.

240. Chilvers CR, Vaghadia H, Mitchell GW et al: Small-dose hypobaric lidocaine-fentanyl spinal anesthesia for short duration outpatient laparoscopy. II. Optimal fentanyl dose. Anesth Analg 84:65, 1997.

241. Ben-David B, Levin H, Solomon E et al: Spinal bupivacaine in ambulatory surgery: The effect of saline dilution. Anesth Analg 83:716, 1996.

242. Liu SS, Ware PD, Allen HW et al: Dose-response characteristics of spinal bupivacaine in volunteers: Clinical implications for ambulatory anesthesia. Anesthesiology 85:729, 1996.

243. Pflug AE, Aasheim GM, Foster C: Sequence of return of neurological function and criteria for safe ambulation following subarachnoid block (spinal anaesthetic). Can Anaesth Soc J 25:133, 1978.

244. Alexander CM, Teller LE, Gross JB et al: New discharge criteria decrease recovery room time after subarachnoid block. Anesthesiology 70:640, 1989.

245. Urmey WF, Stanton J, Peterson M et al: Combined spinal-epidural anesthesia for outpatient surgery: Dose-response characteristics of intrathecal isobaric lidocaine using a 27-gauge Whitacre spinal needle. Anesthesiology 83:528, 1995.

246. Joshi GP, McCarroll SM: Evaluation of combined spinal-epidural anesthesia using two different techniques. Reg Anesth 19:169, 1994.

247. Joshi GP: Combined spinal/epidural anesthesia for outpatient surgery. Anesthesiology 84:481, 1996.

248. D'Alessio JG, Rosenblum M, Shea KP et al: A retrospective comparison of interscalene block and general anesthesia for ambulatory surgery shoulder arthroscopy. Reg Anesth 20:62, 1995.

249. Singelyn FJ, Aye F, Gouverneur JM: Continuous popliteal sciatic nerve block: An original technique to provide postoperative analgesia after foot surgery. Anesth Analg 84:383, 1997.

250. Vater M, Wandless J: Caudal or dorsal nerve block? A comparison of two local anaesthetic techniques for postoperative analgesia following day case circumcision. Acta Anaesthesiol Scand 29:175, 1985.

251. Reid MF, Harris R, Phillips PD et al: Day-case herniotomy in children: A comparison of ilio-inguinal nerve block and wound infiltration for postoperative analgesia. Anaesthesia 42:658, 1987.

252. Splinter WM, Reid CW, Roberts DJ et al: Reducing pain after inguinal hernia repair in children: Caudal anesthesia versus ketorolac tromethamine. Anesthesiology 87:542, 1997.

253. Trieshmann HWJ: Knee arthroscopy: A cost analysis of general and local anesthesia. Arthroscopy 12:60, 1996.

254. Ben-David B, Baune-Goldstein U, Goldik Z et al: Is preoperative ketorolac a useful adjunct to regional anesthesia for inguinal herniorrhaphy? Acta Anaesthesiol Scand 40:358, 1996.

255. Malhotra V, Long CW, Meister MJ: Intercostal blocks with local infiltration anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 66:85, 1987.

256. McCarthy FM, Solomon AL, Jastak JT: Conscious sedation: Benefits and risks. J Am Dent Assoc 109:546, 1984.

257. Task Force on Sedation and Analgesia by Non-anesthesiologists: Practice guidelines for sedation and analgesia by non-anesthesiologists. A report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Anesthesiology 84:459, 1996.

258. Sa Rego MM, Watcha MF, White PF: The changing role of monitored anesthesia care in the ambulatory setting. Anesth Analg 85:1020, 1997.

259. Ramirez-Ruiz M, Smith I, White PF: Use of analgesics during propofol sedation: A comparison of ketorolac, dezocine, and fentanyl. J Clin Anesth 7:481, 1995.

260. Smith I: Monitored anesthesia care: How much sedation, how much analgesia? J Clin Anesth 8:76S, 1996.

261. Cruise CJ, Chung F, Yogendran S et al: Music increases satisfaction in elderly outpatients undergoing cataract surgery. Can J Anaesth 44:43, 1997.

262. Newson C, Joshi GP, Victory R et al: Comparison of propofol administration techniques for sedation during monitored anesthesia care. Anesth Analg 81:486, 1995.

263. White PF: Intravenous anesthesia and analgesia: What is the role of target-controlled infusion? J Clin Anesth 8:26S, 1996.

264. White PF, Negus JB: Sedative infusions during local and regional anesthesia: A comparison of midazolam and propofol. J Clin Anesth 3:32, 1991.

265. Pratila MG, Fischer ME, Alagesan R et al: Propofol versus midazolam for monitored sedation: A comparison of intraoperative and recovery parameters. J Clin Anesth 5:268, 1993.

266. Taylor E, Ghouri AF, White PF: Midazolam in combination with propofol for sedation during local anesthesia. J Clin Anesth 4:213, 1992.

267. Boysen PG: Ancillary site and office-based anesthetic care. 48th Annual ASA Refresher Course Lectures 154.1, 1997.

268. Tang J, Chen L, White PF et al: Use of propofol for office-based anesthesia: Effect of nitrous oxide (abstract). Anesthesiology 87:A9, 1997.

269. James DW: General anaesthesia, sedation and resuscitation in dentistry. Br Dent J 171:345, 1991.

270. Macpherson LM, Binnie VI: A survey of general anaesthesia, sedation and resuscitation in general dental practice. Br Dent J 181:199, 1996.

271. Monk TG, Rater JM, White PF: Comparison of alfentanil and ketamine infusions in combination with midazolam for outpatient lithotripsy. Anesthesiology 74:1023, 1991.

272. Monk TG, Boure B, White PF et al: Comparison of intravenous sedative-analgesic techniques for outpatient immersion lithotripsy [published erratum appears in Anesth Analg 74:324, 1992]. Anesth Analg 72:616, 1991.

273. Monk TG, Ding Y, White PF et al: Effect of topical eutectic mixture of local anesthetics on pain response and analgesic requirement during lithotripsy procedures. Anesth Analg 79:506, 1994.

274. Avramov MN, Husain MM, White PF: The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. Anesth Analg 81:596, 1995.

275. Avramov MN, Thomas JA, Luke SJ et al: Effect of nicardipine on seizure duration and hemodynamic responses during ECT (abstract). Anesth Analg 82:S14, 1996.

276. Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 49:924, 1970.

277. Watcha MF, White PF: Economics of anesthetic practice. Anesthesiology 86:1170, 1997.

278. Korttila K: Recovery from outpatient anaesthesia: Factors affecting outcome. Anaesthesia 50 (suppl):22, 1995.

279. White PF, Watcha MF: Are new drugs cost-effective for patients undergoing ambulatory surgery? Anesthesiology 78:2, 1993.

280. Dexter F, Tinker JH: Analysis of strategies to decrease postanesthesia care unit costs. Anesthesiology 82:94, 1995.

281. Lubarsky DA: Fast track in the postanesthesia care unit: Unlimited possibilities? J Clin Anesth 8:70S, 1996.

282. Song D, Joshi GP, White PF: Fast-track eligibility after ambulatory anesthesia: A comparison of desflurane, sevoflurane, and propofol. Anesth Analg 86:267, 1998.

283. Chung F, Chan VW, Ong D: A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 7:500, 1995.

284. Chung F: Discharge criteria: A new trend. Can J Anaesth 42:1056, 1995.

285. Chung F: Recovery pattern and home-readiness after ambulatory surgery. Anesth Analg 80:896, 1995.

286. Joshi GP: Postoperative pain management. Int Anesthesiol Clin 32:113, 1994.

287. Chung F, Ritchie E, Su J: Postoperative pain in ambulatory surgery. Anesth Analg 85:808, 1997.

288. Korttila K: Recovery and driving after brief anaesthesia. Anaesthesist 30:377, 1981.

289. Orkin FK, Cohen MM, Duncan PG: The quest for meaningful outcomes. Anesthesiology 78:417, 1993.

290. Duncan PG, Cohen MM, Tweed WA et al: The Canadian four-centre study of anaesthetic outcomes. III. Are anaesthetic complications predictable in day surgical practice? Can J Anaesth 39:440, 1992.

291. Kapur PA: The big "little problem." Anesth Analg 73:243, 1991.

292. Carroll NV, Miederhoff P, Cox FM et al: Postoperative nausea and vomiting after discharge from outpatient surgery centers. Anesth Analg 80:903, 1995.

293. Chung F, Un V, Su J: Postoperative symptoms 24 hours after ambulatory anaesthesia. Can J Anaesth 43:1121, 1996.

294. Roizen MF: Preoperative laboratory testing: "What do we need?" 48th Annual ASA Refresher Course Lectures 1997:142.1, 1997.

295. Kallar SK: New modalities in postoperative nausea and vomiting. J Clin Anesth 4:16S, 1992.

296. Manchikanti L, Colliver JA, Roush JR et al: Evaluation of ranitidine as an oral antacid in outpatient anesthesia. South Med J 78:818, 1985.

297. Stock JG, Sutherland AD: The role of H_2 receptor antagonist premedication in pregnant day care patients. Can Anaesth Soc J 32:463, 1985.

Chapter 66 - Anesthesia at Remote Locations *

Ronald A. Mackenzie
Peter A. Southorn
Paul E. Stensrud

INTRODUCTION

When called on to provide care to patients undergoing diagnostic or therapeutic procedures outside the surgical or obstetric suites, anesthesiologists should strive to maintain their high standards of anesthesia care. [1] The anesthetic implications of the patient's medical condition do not vary with anesthetizing location, but the logistics in providing anesthesia services frequently differ. Physical constraints imposed by the environment, different paramedical personnel, and often a lack of the full array of monitoring and equipment available in the surgical suite challenge the anesthesiologist to tailor provision of anesthesia services to the special requirements posed by the situation.

Standards have been developed by the Harvard Medical School for anesthetizing in locations outside the operating rooms. [2] The American Society of Anesthesiologists (ASA) 1994 Guidelines For Nonoperating Room Anesthetizing Locations include recommendations for (1) oxygen source, (2) suction, (3) scavenging, (4) necessary equipment, drugs, and monitors, (5) electrical outlets, (6) illumination, (7) space, (8) emergency equipment, (9) communications, and (10) building and safety codes. [3]

Monitoring

Appropriate patient monitoring is a universal requirement (Chs. 28 to 37) . The ASA standards for basic anesthetic monitoring (originally published in 1986 and updated in 1996) [4] require the following: (1) the continuous presence of qualified anesthesia personnel in an anesthetizing location throughout the conduct of all anesthetic regimens; and (2) during all anesthetic regimens, patients' oxygenation, ventilation, circulation, and temperature must be continually evaluated. Oxygenation should be measured by monitoring inspired oxygen and pulse oximetry. [5] Adequacy of ventilation should be evaluated by clinical examination and expired gas analysis, endotracheal tube positioning must be verified, and disconnection alarms must be used with mechanical ventilators. Circulation should be evaluated by continuous display of the electrocardiogram (ECG) and by frequent determination of arterial blood pressure and heart rate and other measurements (e.g., auscultation of heart sounds). In addition, there should be readily available a means to measure the patient's temperature continuously.

---

* *See Appendix 1, Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists*

Facilities and Equipment

Potential problems for the anesthesiologist providing care for patients in remote locations can be due to the physical layout of the facility, to unfamiliar or outdated anesthesia equipment, to the anesthetic implications of the procedure performed, to working with personnel who are less familiar with the anesthetic aspects of patient care in these settings, and to the remoteness from available help. [6] [7] [8]

Delivery of anesthetic care for diagnostic or therapeutic procedures in a room not originally designed for such work frequently means that access to the patient may be compromised by diagnostic or therapeutic equipment (e.g., x-ray tubes, C-arms, angiographic equipment, extracorporeal lithotripter) (Figs. 66-1 and 66-2) . Achieving and maintaining adequate access to the patient, anesthesia equipment, and monitors often require advance planning.

Piped-in gases, suction, and isolated power or grounded plugs are not always available. Electrical equipment posing an increased risk to the patient or electrical interference with monitors frequently is present. Lack of an isolated power system mandates proper grounding of electrical equipment. Since 1962, the National Electrical Code requires installation of three-contact grounding-type electrical receptacles in new construction. Retrofitting of outlets in existing buildings, however, was not required. Patient and personnel safety dictates that grounding of electrical equipment via three-wire cords, three-pronged plugs, and grounded three-contact outlets be a minimum requirement in anesthetizing locations.

Anesthesia personnel used to working with anesthesia machines supplied by piped-in gases need to maintain familiarity with gas cylinder-supplied machines. Proper function of the anesthetic machine and the availability of an adequate supply of gas cylinders must be confirmed prior to beginning the anesthetic administration. Older anesthesia machines with features that do not meet recent standards for new machines may have been relegated to the remote area; anesthesia personnel need to be familiar with all equipment prior to its use. A mechanism to prevent contamination of one calibrated vaporizer by the output from another vaporizer

Figure 66-1 The surgeon and radiotherapist align the operative site and accelerator port prior to treatment. Bulky equipment and the sterile field restrict the anesthesiologist's access to the patient.

Figure 66-2 Anesthetized patient undergoing magnetic resonance imaging. Another example of limited accessibility to the patient.

is required. An oxygen analyzer is required by Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards. The oxygen flush valve must have only one function and cannot be integrated with a vaporizer on/off valve. The practice of using obsolete equipment in remote locations is to be condemned. [9]

Personnel

Nonanesthesia personnel involved in the care of patients in areas remote from the operating suite may be less familiar with the overall management of anesthetized patients than are their counterparts who work in surgical or obstetric suites. This lack of familiarity, combined with geographic remoteness from the surgical suite, may mean that less ancillary help will be available to the anesthesiologist. Education programs for these nonanesthesia personnel regarding care of anesthetized patients are both beneficial and appreciated. The presence of an adequate number of fully trained anesthesia personnel is vital.

Medications

Monitored anesthesia care (MAC) (incorporating the usual noninvasive hemodynamic and respiratory monitoring, oxygen administration as indicated, intravenous sedation/analgesia in adults, and oral, intramuscular, intravenous, or rectal administration of sedatives/analgesics in children) or general anesthesia may be required. [10] Benzodiazepines and opioids frequently are used for intravenous sedation and analgesia in patients receiving MAC for diagnostic or therapeutic procedures. Midazolam's advantages of water solubility, minimal discomfort on intravenous injection, comparable effects on cerebral metabolism and blood flow, shorter half-life, and lack of active metabolites have rendered it preferable to diazepam. In doses generally used, midazolam usually does not produce significant cardiovascular

depression. Midazolam dosage requirements are reduced

in older patients. [11] Midazolam is associated with a depression of the central respiratory drive that is related to both dose and rate of administration. [12] In analgesic doses, fentanyl has minimal cardiovascular effects, even in patients with compromised left ventricular function. [13] The combination of fentanyl and a benzodiazepine, however, can produce cardiovascular depression. [14]

Opioids that stimulate mu receptors cause a dose-dependent depression of the ventilatory response to CO_2 by a direct effect on medullary respiratory centers. [15] Analgesic doses of fentanyl (e.g., 2 mug/kg) can result in respiratory depression that peaks at approximately 5 to 10 minutes after injection and can last longer than the analgesic effect. Higher doses of fentanyl can result in chest wall rigidity.

Evaluation of the patient's respiratory status throughout the procedure and during the recovery period is essential. A methodology for this evaluation was described in the ASA practice guidelines for sedation and analgesia by nonanesthesiologists (Table 66-1) (Table Not Available) . [16] Both during the procedure and in the recovery period, patients are asked to respond verbally to a series of questions, are encouraged to take a deep breath periodically, and are monitored with a pulse oximeter. Respiratory depression usually can be avoided by following these guidelines.

The assistance of the anesthesiologist frequently is sought when verbal reassurance and sedation administered by the radiology team have failed. [17] Midazolam (0.5 mg/kg), in concentrated grape-flavored Kool-Aid (with sugar added to counter the bitter taste) given orally 30 minutes prior to the procedure, can be an effective sedative for small children. Ketamine can be administered by a variety of routes: intramuscular, intravenous, rectal, [18] or oral. [19] [20] Propofol has become a popular intravenous anesthetic for use in remote areas. [21] [22] [23] Tachyphylaxis to propofol [24] and ketamine [25] has been reported.

Rectal administration of thiopental or methohexital can be used to sedate children [7] [26] (Ch. 59) . Prolonged sedation for up to 2 to 3 hours can follow rectal administration of barbiturates. Rectal mucosal injury can occur with this technique, and proctitis and colitis have been reported following repeated use of rectal thiopental in some children [27] (e.g., children who require repeated therapeutic radiation sessions). General anesthesia may be preferable to sedation in certain patients (e.g., infants and mentally impaired adults.)

TABLE 66-1 -- Sedation Guidelines Summary[a]

(Not Available)

Modified from the American Society of Anesthesiologists [16]

[a] This is a summary of the guidelines. The body of the document should be consulted for complete details.

Patient Transport and Postanesthesia Care

The patient's medical condition should be stable before initiating transport (Ch. 68) . In some situations, it may be preferable to keep the patient sedated or anesthetized during transport and then recover him or her in the postanesthesia care unit (PACU) or other recovery area. The anesthesiologist responsible for the patient's welfare during transport should be accompanied by an assistant responsible for moving the transport cart.

During transportation to the PACU following the procedure, appropriate monitoring related to the patient's anesthetic management and medical condition should be continued. Following general anesthesia, such monitoring includes arterial blood pressure, heart rate, ECG, and pulse oximetry. A transport stretcher that has facilities for supplying supplemental oxygen and appropriate resuscitative drugs and equipment for airway management is useful (Fig. 66-3) . For patients with significant cardiovascular disease who are being transported to or from remote anesthetizing areas, the transport stretcher also should include a portable defibrillator. Following monitored anesthesia care, a transport stretcher with those components appropriate for the patient's medical condition is used. The importance of monitoring oxygen saturation and providing supplemental oxygen

Figure 66-3 A transport stretcher with oxygen tanks, a self-inflating bag with valve for ventilating the patient, an electrocardiographic/hemodynamic monitor, a pulse oximeter, an intravenous pole, and brackets for strain gauges and flush bag. To this type of cart can be added infusion pumps, a defibrillator, equipment for chest compression, medication storage, and other essential equipment and supplies.

as indicated in both children and adults has been well documented. [28] [29] [30] [31] [32]

RADIOLOGY SUITE

Technical advances in radiologic imaging in the last few years and, in particular, the realization of the full potential of ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have both dramatically improved the ability to detect and diagnose disease and increased the demand for this expertise. These developments go hand in hand with the greater use of minimally invasive surgery and demands to control health-care costs. They have also opened new diagnostic and therapeutic options. For example, it has become possible for radiologists, using their imaging techniques, to place biopsy needles precisely in various organs to obtain tissue for pathologic diagnosis. Even more recently, two other important types of interventional radiology have evolved. Cancer treatment may be revolutionized by one of these techniques, percutaneous ultrasound-guided tissue ablation. [33] In the other field, interventional neuroradiology, high-speed digital subtraction angiography is used to guide endovascular treatment of various life-threatening, sometimes inoperable, cerebrovascular lesions. [34] This realization of the potential for radiology, together with these advances, has increased the need for the anesthesiologist's involvement in the radiology suite, both to provide general anesthesia and to advise and assist management of patients who need to be sedated during examinations.

General Considerations

In both diagnostic and therapeutic radiology procedures, patients must often remain immobile for long periods. For many studies, radiologists ideally require patient cooperation, but in numerous instances this may not be possible, such as when studies are performed in obtunded individuals, in those with seizures or tremors, and in children too young to understand. Patients also may not be able to tolerate the procedure by virtue of anxiety, claustrophobia, or confused mental status. Certain aspects of these procedures, for example, inserting needles, urinary catheterization, and the discomfort associated with injection of contrast dye also can affect the patient's ability to cooperate and to lie still.

The anesthesia provider called on to sedate or anesthetize patients in the radiology suite confronts several problems in addition to those found when managing patients in other locations outside the operating room. It is unfortunate that, to date, many radiology studies have been regarded as minor procedures in which anesthesia and sedation, if required, can be given with little risk. This clearly is not the case, particularly in those patients who are a poor anesthetic risk because of their age or coexisting medical conditions such as coronary artery disease, respiratory disease, diabetes, and obesity. In addition to the patient's comorbid conditions, often he or she has already been sedated by the radiologist, but this has not produced the desired effect of immobilizing the patient. These patients also may have received oral contrast media that places them at risk of aspiration when their

airway reflexes are impaired. The work environment in the radiology suite confronting the anesthesiologist often is ill adapted to safe care of patients, particularly in older facilities. Radiology rooms tend to be crowded, the presence of bulky radiology equipment impedes patient access, and poor lighting combined with other impediments to monitoring the patient such as are found in the MRI suite can all potentially adversely affect the delivery of anesthesia care. The patient is often deliberately moved during the radiologic examination, a factor that can, unless carefully guarded against, cause dislodgement or obstruction of airway devices and loss of monitoring capability or vascular access. Given the use of high-voltage equipment, there is a risk that leakage current will be conducted down electrically conductive leads used for monitoring the patient. Finally, it is also worth noting that many radiology suites have poor air circulation, and effective scavenging of waste anesthetic gases in them is difficult.

A unique hazard encountered in the radiology suite is radiation exposure. This is potentially harmful, both in terms of its somatic effects during a person's lifetime (e.g., producing leukemia) and in causing genetic injury resulting in fetal abnormality due to damage to the gonadal cells. Although it has been found that anesthesia personnel working in the operating room do not face a significant radiation danger, [35] this may not be the case when working in the cardiac catheterization, CT, and interventional radiology suites. In these latter environments, anesthesia personnel should take precautions to avoid such exposure from the radiation source and that scattered from the patient and should monitor this exposure by wearing dosimeters. The maximum permissible radiation dose for occupationally exposed persons is 50 milliSieverts (mSv) annually, 10 mSv × age lifetime cumulative dose, and 0.5 mSv monthly exposure for pregnant women. [36] Radiation exposure can be reduced by wearing appropriate lead aprons and thyroid shields, employing movable lead-lined glass screens, and innovative techniques to allow patient monitoring to be conducted remote from the patient's immediate contact, for example, with the use of microphones and closed-circuit television.

Administering safe anesthesia care in this environment is not to be undertaken lightly. Ideally, the anesthesiology department should be involved in planning for such care with the building of each new radiology suite. The safe delivery of anesthesia care requires not only employing trained and experienced anesthesia personnel, but also ensuring that the equipment for administering anesthesia and for monitoring and resuscitating the patient, if needed, are up to the standard used in the operating room.

Sedation Practices Used in the Radiology Suite

Sedation is frequently employed in various radiologic examinations to improve patient comfort, to allay anxiety, and to permit theprocedure to be performed while the patient remains immobile (Chs. 40 and 65) . Traditionally, anesthesiologists have rarely been involved in the provision of such sedation and have acted only in an advisory capacity. The altruistic goal of ensuring the maximum patient benefit without harm suggests that the special expertise of anesthesiologists should be employed in this activity. The JCAHO has mandated such involvement by our specialty. [37] [38]

Even though sedation during radiology procedures is a field of active ongoing study, with most modern potent intravenous anesthetics currently being evaluated, there is little consensus to date about the most appropriate sedation practice for a particular patient or procedure. Various gradations of sedation are described. The most common is "conscious sedation," a state in which a patient can respond appropriately to verbal command and other stimuli, can retain protective airway reflexes, and can independently maintain the airway. "Deep sedation" is a state in which the patient is not easily aroused, and airway reflexes and patency of the airway may be lost. Deep sedation appears to be more akin to general anesthesia. Currently, the most popular sedative used by radiologists for very young children remains chloral hydrate. Pentobarbital is commonly used for older children, and the benzodiazepines with or without fentanyl supplementation are first-line drugs used to sedate adults (Table 66-2) .

The American Academy of Pediatrics first published its comprehensive guidelines on the sedation and anesthesia of children in 1985. [39] Recommendations made included obtaining informed consent for sedation, employing NPO (nothing by mouth) standards prior to sedation, continuously observing the deeply sedated child, and monitoring and documenting vital signs. A large national study of sedation practices used for children undergoing CT examinations, however, revealed considerable variability in practice patterns among centers, with many of them not following these guidelines. [40] A survey of adults undergoing sedation for interventional radiologic procedures found similar variability in terms of the lack of universality in obtaining preoperative patient assessment and the lack of consistent availability of trained nursing staff to monitor the patient's welfare during sedation. [41]

Newer anesthetics, for example, propofol, are currently being examined for possible use in sedating patients undergoing

TABLE 66-2 -- Sedation Medication Guidelines

PATIENT AGE	DRUG	COMMENTS
<1 mo	--	Avoid sedation if possible
4 mo	Chloral hydrate PO	25-50 mg/kg
Older children/toddlers	Chloral hydrate PO	50-75 mg/kg (begin 50 mg/kg)
Children >12 mo	Pentobarbital IV	2-3 mg/kg over 1-2 min (repeat 10-15 min if needed, max 7 mg/kg)
Adults	Diazepam IV	2 mg/5 min (max 20 mg/max 10 mg with narcotics)
	Midazolam IV	1 mg (max 5 mg)
	Fentanyl	50-100 mug (max 200 mug)

As used in Radiology Department, Mayo Clinic, Rochester, Minn, 1997

radiologic procedures. [42] Such use was, however, criticized in a radiologic journal editorial because arterial oxyhemoglobin desaturation secondary to airway obstruction has been documented to occur occasionally in such studies. This situation is not necessarily managed optimally by the radiologist performing the imaging procedure, but rather it necessitates the presence of an individual trained in airway management. [43]

The Department of Anesthesia at Harvard Medical School has published its guidelines for sedation by nonanesthesiologists, [44] and recently, the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists also published similar practice guidelines (see Table 66-1 (Table Not Available)). [16] These guidelines, together with the recommendations by the American Academy of Pediatrics, which were updated in 1992, [45] will be helpful to anesthesiologists seeking to counsel and assist their radiologic colleagues involved in the sedation of patients. Such involvement by anesthesiologists is now mandated by the JCAHO. This body considers sedation to be a component of anesthesia services and mandates that hospitals have training programs, policies and procedures, and monitoring systems for their safe provision, that there be collaboration between departments and services providing and supporting surgical and anesthesia services, and, finally, that the director of anesthesia has a specific responsibility to ensure the quality and appropriateness of anesthesia care provided by individuals in any department or service in the hospital. [37] [38]

Side Effects of Iodinated Contrast Media

The radiopacity of contrast media is based on their containing substances with a high atomic number to absorb x-rays. Soluble contrast media utilize iodine (atomic number 53) for this purpose. Side effects used to be common with the older, relatively toxic, ionized contrast media, in part because of their hyperosmolarity. [46] More recently, nonionized contrast media, which have a much lower osmolarity, have been increasingly utilized despite their higher cost. [47] [48] [49] [50] [51] The use of such agents is associated with a much lower incidence and severity of adverse side effects. Indeed, it has been suggested that their higher cost is offset by the reduced cost of managing the adverse reactions associated with the older agents. [47] Examples of the newer agents used in intravascular studies include iohexol, iopamidol, iopromide, and ioversol.

Adverse reactions encountered with these drugs comprise toxic, idiosyncratic, and allergic side effects. Their incidence and severity depend on which agent is used, the type of investigation performed, the total dose and speed of injection, and, importantly, patient susceptibility. Most organ systems can be affected, but cardiovascular and respiratory system adverse reactions are potentially of greatest risk (Table 66-3) . These reactions usually occur in the first 5 or 10 minutes following the injection of the contrast media. It is advisable, therefore, to keep the patient under close observation for 20 minutes following such an injection.

Minor cardiovascular complications include hypertension or hypotension, bradycardia, various arrhythmias, and serious life-threatening manifestations are hypotensive shock, ventricular fibrillation, and cardiac arrest. Disseminated intravascular coagulation can follow hypotensive shock. Most of these cardiotoxic adverse reactions respond to treatment if it is prompt. It has been suggested that such complications are more common in patients undergoing CT because these patients are inaccessible during this examination. [47] Respiratory complications include bronchospasm, which may be particularly induced in patients with preexisting asthma. Pulmonary edema has occurred, especially in patients with incipient cardiac failure. Adult respiratory distress syndrome is also reported. Hypotension induced by a contrast media reaction can render the patient unconscious, and convulsions have been reported in patients with a history of epilepsy. Nausea and vomiting are frequent antecedents of such severe complications. Diarrhea and various other manifestations affecting the gastrointestinal tract have also been reported. Renal failure is a well-documented association with the use of contrast media, particularly in patients with preexisting renal disease or other factors predisposing to renal failure; for example, diabetes, jaundice, severe cardiovascular disease associated with diminished renal blood flow, and multiple myeloma. [47] [52] In these particular patients, radiologic studies employing contrast media should, if possible, be avoided. If renal failure is induced in diabetic patients taking metformin, lactic acidosis could occur. It is recommended that this particular drug be withheld for 48 hours before performing a radiologic study employing contrast media. [53]

Patients who have experienced previous reactions to contrast material have a higher incidence of potentially severe repeat reactions if they are exposed to these agents again. This increased prevalence and severity can, in part, be reduced by pretreatment with prednisolone, 50 mg the night

TABLE 66-3 -- Reactions to Soluble Contrast Media

MILD	SEVERE	LIFE-THREATENING
Nausea, retching	Vomiting	Glottic edema/bronchospasm
Perception of warmth	Rigors	Pulmonary edema
Headache	Feeling faint	Life-threatening arrhythmias
Itchy skin rash	Chest pain	Cardiac arrest
Mild urticaria	Severe urticaria	Seizures/unconsciousness
	Bronchospasm, dyspnea	
	Chest pain	
	Abdominal pain/diarrhea	
	Arrhythmias	
	Renal failure	

before and the morning of the procedure, and diphenhydramine, 50 mg intravenously immediately before the procedure. [47] [54]

The mechanisms of these adverse drug reactions are often unclear. [47] [55] Some of the effects are immunologically based, but this is not universal. The treatments referred to earlier for patients who have previously experienced adverse reactions with these agents will reduce the frequency and severity of such reactions, but they will not necessarily eliminate the risk. When the reaction does occur, it is treated with intravenous steroids, oxygen as needed, and management directed at specific components of the patient's reaction. For example, shock and hypotension would be treated with fluid replacement and vasopressors. Clearly, all radiology suites

should have immediately available the medications and resuscitation equipment required to manage these reactions.

Magnetic Resonance Imaging

MRI can reveal subtle differences between areas of different anatomy, physiology, and pathology not possible with other imaging techniques. Other advantages include the following:

1. Unlike conventional x-rays and CT, MRI can obtain images in any plane (transverse, sagittal, coronal, or oblique).
2. It provides excellent soft tissue contrast (Fig. 66-4) .
3. It may provide intravascular contrast without the need for intravenous contrast media (Fig. 66-5) .
4. It requires very little patient preparation.
5. It does not produce ionizing radiation, is noninvasive, and does not in itself produce biologically deleterious effects.

Figure 66-4 Detailed soft tissue contrast of brain is possible with magnetic resonance imaging.

Figure 66-5 Cerebral angiogram obtained with magnetic resonance imaging.

Principles

Detailed discussions on the physics and technical aspects of MRI are addressed elsewhere. [56] [57] [58] Briefly, atomic nuclei with an odd number of protons or neutrons have the potential to act as magnetic dipoles. This property is possessed by all paramagnetic elements (^{1}H, ^{13}C, ^{19}F, ^{23}Na, and ^{31}P). In biologic tissues with their high water content, hydrogen, which contains a single proton, is the most important element in this context, and its detection is the basis of MRI. Outside a magnetic field, these hydrogen protons are oriented randomly and do not exhibit any net magnetic field. If, however, biologic tissue containing them is placed in a strong external magnetic field, some of the hydrogen protons will align themselves parallel or antiparallel to the applied magnetic field (like a compass), and the tissue itself will exhibit slight net magnetism. This tissue magnetism results from the nuclei that are aligned antiparallel to the external magnetic field, being in a slightly higher energy state than those aligned parallel to the field. This energy difference increases with the strength of the applied magnetic field. In MRI, tissue so magnetized by a powerful static magnetic field is suddenly also exposed transiently to a second magnetic field aligned perpendicular to this static field. This transient second magnetic field is generated by a pulse of radio frequency (RF) energy sent through an RF coil that

closely surrounds the patient. These events cause the tissue nuclei to flip away from their previous longitudinal alignment and into a higher energy state. When the transient RF pulse is subsequently terminated, the nuclei return to their original alignment and equilibrium in the static magnetic field and simultaneously induce a weak transient RF signal that is picked up by the RF coil, which now acts as a receiver. This energy release is related to the proton quantity, their chemical identity, and their relationship with surrounding tissue. The characteristics of the decay of the emergent signal, which is called "relaxation," provide most of the information for generating the MRI image. The latter is constructed with sophisticated computers that control the timing, strength, and sequencing of the RF pulse and also analyze the transmitted RF signal from the tissue.

The magnetic field strength employed in MRI scanners is measured in tesla units. One tesla unit equals 10,000 gauss, with the strength of the earth's magnetic field at its surface being between 0.5 and 1.0 gauss. Field strengths used in most clinically used MRI vary from 0.05 to 2.0 tesla, but the use of 3 tesla units is currently being studied. The advantage of weaker-field MRI scanners is that they allow better patient access, and the advantage of those with stronger fields is that they produce better image quality. Stronger-field MRI scanners usually employ cryogenic magnets with superconductivity coils operating in liquid helium (4° Kelvin).

Hydrogen proton density and relaxation dynamics as detected by MRI vary in different tissues, reflecting the tissue's physical and chemical properties. Because the differences in water content and proton environment in gray and white matter are greater than differences in electron densities as measured by CT, the MRI can produce better resolution between gray and white matter (see Fig. 66-4), and the same is also applicable to soft tissue examinations. MRI permits evaluation of blood flow (see Fig. 66-5), cerebral spinal fluid flow, contraction and relaxation of organs, and, because calcium does not emit a signal in the MRI, images of tissues surrounded by bone. This lack of a calcium signal, however, prevents MRI from detecting pathologic calcification in tumors of soft tissue and pathologic changes in cortical bone. [59]

The RF signal obtained during MRI scanning is of very low intensity and is subject to interference from stray high-frequency, electronic radiation (e.g., FM radio signals) and that arising from electronic equipment or monitoring devices. [56] For this reason, the scanning area is enclosed in the RF shield, which is incorporated usually into the fabric of the MRI imaging suite (Fig. 66-6) . Monitoring devices situated outside the monitoring field can conduct interference to the scanner unless appropriate filters are employed. Preventing interference from monitors situated within the RF field is often challenging, with attempts to overcome this problem made by using isolated power sources or battery power, filtering, and sometimes enclosing the monitor in its own small RF shield.

Limitations and Hazards

MRI scanning has a number of limitations and one major hazard. A relatively long time is required to obtain images; individual scans may take up to 20 minutes, and an entire examination may take more than 1 hour. Any patient movement

Figure 66-6 View of a magnetic resonance imaging scanner from control desk, showing the radio frequency shield in the window.

and that resulting from physiologic motion (e.g., cardiac and vascular flow pulsations, cerebrospinal fluid flow and pulsation, respiratory excursion, and peristalsis in the gastrointestinal tract) can produce artifacts. To optimize information when imaging the cardiovascular system, the signal acquisition is synchronized or "gated" with phases of the cardiac cycle (ECG R wave) in order to freeze cardiac motion. Anxiety and claustrophobia are experienced by some patients when they have to lie in the small-diameter, hollow bore of the magnet (typically 50-65 cm in diameter) and are exposed to the loud pulsing noises, caused by the switching on and off of the RF coils. Obese patients cannot be examined in this small magnetic bore. Heating due to RF energy of nonferromagnetic prosthetic devices has not proved to be a problem. [60] Body surfaces do absorb this RF energy, but it is unlikely that the patient's temperature will increase by more than 1°C.

The most significant risk posed to the patient and workers in the MRI scanning suite is the attraction of ferromagnetic objects to the magnet. [56] [59] [60] Such metallic objects (e.g., scissors, pens, keys, ferromagnetic stethoscopes, and oxygen cylinders) brought into the vicinity of the magnet can literally fly into it and may cause severe injury to the patient and bystanders. Dislodgement and malfunction of implanted biologic devices or other objects containing ferromagnetic material is also a real possibility. Such items include shrapnel, vascular clips and shunts, wire spiral endotracheal tubes, pacemakers, automatic implantable cardiac defibrillators, and implanted biologic pumps. Potential problems with cardiac pacemakers include possible reed switch closure or damage, pacemaker inhibition, or reversion to an asynchronous mode. Programming changes, torque on the pacemaker itself, or development of voltage across the pacemaker inhibiting its discharge may also occur. [57] Implanted automatic cardiac defibrillators may be deactivated. Patients with such devices should not undergo MRI examinations. Manufacturers of some biologic devices, for example, the clips used in vascular surgery and neurosurgery, are now trying to employ alloys that have low ferromagnetic properties and are safe in the MRI suite. Detailed lists of each manufacturer's implantable devices and their ferromagnetic properties

Figure 66-7 Patient screening form for magnetic resonance imaging.

have been published and should be consulted. [61] [62] A particular item from one manufacturer may be unsafe, whereas a similar product from another manufacturer may pose no danger to the patient in the MRI suite. Some eye makeup products and tattoos can cause artifacts in the scan, and some permanent eyeliners may produce eye irritation. Many departments have found it useful to develop a checklist to review with patients to ensure that they do not possess a potentially harmful metallic object that would make MRI scanning dangerous (Fig. 66-7) . [63]

Anesthetic Management

Patient acceptance is generally high. Most adults and small babies (if recently fed and well wrapped up) tolerate the procedure without sedation. Sedation may be required in older children and in adults who cannot cooperate. Such sedation is usually administered by the radiologists, nurses, and technical staff in the MRI suite. This generally works well, although, as previously discussed, concern has been expressed for the patient's safety in this situation. The likelihood that a child can undergo the examination successfully under such sedation is enhanced if he or she is sleep deprived for several hours the previous night. All patients receiving such sedation need supplemental oxygen and close monitoring. Anesthesia personnel become involved in these patients' care in the MRI suite when sedation fails, when it is impossible to control patient movement without general anesthesia, and when it is necessary to protect the patient's airway and to control ventilation, for example, in patients who are critically ill.

Several thoughtful reviews have been published regarding the anesthetic management of patients undergoing MRI. [64] [65] [66] [67] [68] [69] Anesthesia and monitoring in the MRI suite pose several unique problems. These include the following:

1. Limited patient access and visibility.
2. The need to exclude ferromagnetic components.
3. The interference/malfunction of monitoring equipment produced by the changing magnetic field and RF currents.
4. The potential degradation of the imaging caused by the stray RF currents produced by the monitoring equipment and leads.
5. The necessity to not move the anesthetic and monitoring equipment once the examination has started so as to prevent degradation of the magnetic field homogeneity.

To overcome these problems, ideally, anesthesiology departments called on to take care of patients in MRI suites should be involved in the suites' planning and construction. Satisfactory performance of the anesthetic and monitoring equipment and ensuring that this equipment does not interfere with the scanning need to be confirmed prior to clinical use. One solution adopted by some MRI units and their anesthesiologists is to keep the anesthetic and monitoring equipment outside the MRI suite. [69] The disadvantage of this approach includes the need for extralong monitoring leads, breathing tubing, and other connections to the patient with the risk of disconnection, and the need to have extra personnel resources simultaneously with the patient and with monitoring equipment. A more common approach is to induce anesthesia in the induction area adjacent to the MRI suite outside the magnetic field using conventional equipment with the patient on a stainless steel dedicated MRI transport table, which is nonferromagnetic (unlike the normal hospital cart). This transport table is used to bring the patient into the MRI suite, where anesthesia and monitoring are continued using MRI-compatible devices. This MRI transport table is also used to remove the patient rapidly from the scanner should an emergency arise. This is important because the ferromagnetic equipment employed for patient resuscitation by the code team and others cannot be brought into the MRI room.

Various techniques for modifying anesthesia machines, for identifying appropriate ventilators, using the Bain and other breathing circuits, and other measures to permit satisfactory equipment function and monitoring and avoid image degradation have been described. [64] [65] [66] [67] [68] [69] Locating this anesthetic and monitoring equipment beyond the 100-gauss line limits artifact and projectile risk. We have used custom-made, wall-mounted, and secured anesthetic machines equipped with pipe gases and suction located approximately 3 m from the scanner to anesthetize our patients (Fig. 66-8) . The fixed location of this machine permitted adjustment of the magnetic field when the magnet was brought on-line. Temperature-compensated specific-anesthetic vaporizers operate satisfactorily when exposed to a magnetic field. [70] We have also employed portable anesthetic machines that are constructed of nonmagnetic material, utilize aluminum gas cylinders, and have an MRI-compatible oxygen analyzer. Several manufacturers make these MRI-compatible anesthetic machines. Various breathing circuits have been used successfully in the MRI suite. They can be used to deliver breaths generated by a nonmagnetic pressure-generator mechanical ventilator or

Figure 66-8 Wall-mounted anesthesia machine, nonrebreathing bag and circuit, wall-mounted suction equipment, anesthesia storage cart with automatic blood-pressure measuring device, and pulse oximeter.

by manual inflation of an anesthesia bag. Because the patient's airway is not easily accessed during the MRI scan, many centers routinely intubate the anesthetized patient to control the airway. Other centers utilize a laryngeal mask for this purpose. Endotracheal tubes and laryngeal masks and the connections to the breathing circuit must contain no ferromagnetic material. Because conventional zinc batteries are strongly ferromagnetic, if a laryngoscope is needed in the MRI suite, it should be of plastic construction and equipped with lithium batteries and aluminum spacers.

Given the patient's inaccessibility in the MRI scanner and limitations of physical examination usually to only observing chest expansion and palpating the dorsalis pedis artery pulse, additional monitoring is essential (see Fig. 66-2) . In this environment, monitoring each physiologic parameter poses its own distinct unique problems, and in addition, there is a potential risk of patient burns resulting from current induction in the monitoring leads induced by oscillating RF fields. The latter risk can be minimized by removing any electrically conductive material from the magnetic core that is not required and by ensuring that leads are properly insulated, that they do not form loops within the magnetic core, and that they are separated from the patient's skin by thermal insulating padding. [64]

In general, cathode ray displays are distorted by magnetic fields, whereas those based on liquid crystal technology are

preserved. This is one modification employed by equipment manufacturers in designing monitoring equipment for use in the MRI environment.

Specific problems and solutions for monitoring each physiologic parameter in the MRI environment can be summarized as follows [64] :

1. ECG: Voltage induced by blood flow in the aorta when the patient is in a static magnetic field produces T- and ST-wave abnormalities. In addition, the rapid changing magnetic fields can induce artifacts in the ECG trace. Twisting the ECG leads and placing them as close as possible to the center of the magnetic field help to minimize the latter artifacts.
2. Pulse oximetry: This has proven very difficult to use. Technologies employed by manufacturers to address the problem include incorporating RF filters, ECG-locking facilities, and fiberoptic signal linking between the sensor and monitor.
3. Noninvasive blood pressure monitoring: This can be successfully accomplished, provided the metal connections of the blood pressure cuff and hoses are changed to plastic.
4. Precordial and esophageal stethoscopes: These do not function well because of the interference created by the noise of the scanner when it is in operation.
5. Capnography: This monitor usually functions satisfactorily, but the length of the sample tube may cause a significant time delay in signal transduction.
6. Temperature: This is not generally a problem if temperature probes employing RF filters are utilized.

It is prudent to test each monitoring device in the specific location and room where it is to be used to make sure that it functions appropriately. Magnetic field strength

and RF may vary between two supposedly identical MRI systems. It has been documented that one specific manufacturer's pulse oximeter functioned satisfactorily in one MRI room, whereas in another, supposedly identical adjacent room, it produced a significant artifact in the MRI image. This problem was subsequently shown to be due to differences in the RF employed by the two MRI systems. [71]

It is our practice to secure the patient's airway routinely with endotracheal intubation and to control ventilation mechanically. Although some centers permit the patient to breathe spontaneously, we believe that neuromuscular blockade and controlled ventilation are preferable, not only in terms of producing satisfactory gas exchange, but also in avoiding excessive head and neck movement that may interfere with the imaging process. Some patients benefit from sedative premedication prior to being anesthetized, but this may compromise seriously ill patients, including those who have increased intracranial pressure. Airway secretions cannot be removed during the examination, and when secretions are perceived to be a potential problem, glycopyrrolate can be administered to reduce the volume. The MRI examination is not painful, and we normally avoid nitrous oxide and excess opioids. Anesthesia is usually maintained with a volatile anesthetic, rather than an intravenous agent, given the potential problems associated with the use of drug infusion pumps in this environment. Following the procedure, the patient is transferred to an adjacent induction room and then is taken to the postoperative recovery room, where recovery from anesthesia can be closely monitored.

Computed Tomography

CT produces a two-dimensional, cross-sectional image by rotating an x-ray beam around the area of the patient's anatomy of interest. Each cross-section requires a few seconds of radiation exposure, and the typical scan comprises 20 such sections. Patient immobility is required during each exposure to produce a high-quality image, but the patient can move between sections, provided alignment with the imaging equipment is not changed. The x-ray tube and detectors are housed in a circular scanning tunnel in which the patient lies during the study. The scanning procedure is noisy, some heat is generated, and the patient can become claustrophobic and frightened. Although small children often sleep through an examination if they have been recently fed, older children commonly and some adults need to be sedated to tolerate this examination. As previously discussed, the administration of these sedatives and the care of the patient receiving them have not traditionally involved anesthesiologists.

CT is commonly used for diagnostic purposes, for example, to evaluate the status of a neoplastic process in the thorax or abdomen. It has proved valuable in studies of vascular malformations and tumors. Caregivers involved in imaging the patients undergoing this examination should be mindful that some patients have limited reserve because of their disease process, (e.g., compression of the upper airway or vena cava by a neoplastic process). The CT is occasionally also used for invasive therapeutic procedures instead of fluoroscopy, for example, for visualized drainage of a liver abscess. Contrast media are often used in conjunction with the CT to enhance the quality of the image. If contrast media are to be given into the gastrointestinal system in patients who are sedated or anesthetized, it is usually given via nasogastric tube. When the airway is not protected in this situation, there is a risk of aspiration. [40] It has also been suggested that there is a higher incidence of adverse sequelae associated with the use of contrast media in patients undergoing CT compared with other types of radiologic studies because of limited access to the patient and consequent compromised monitoring and treatment if reactions do occur. [47]

Many of the issues confronting anesthesiologists requested to anesthetize patients undergoing CT are similar to those previously identified as occurring in the MRI suite, such as inaccessibility of the patient and control of movement artifact. Monitoring interference is not a problem in CT, however. With anesthetized patients, care needs to be taken to ensure that the side walls of the scanning tunnel do not occlude or dislodge the breathing circuit or monitoring leads. Cautions need to be taken against ionizing radiation exposure that occurs during CT scans. The patient can be monitored visually through a lead glass window, supplemented if necessary by closed-circuit television.

Ultrasound-Guided Percutaneous Tissue Ablation

Percutaneous ethanol injection performed under ultrasound (or CT) guidance has become widely used in the treatment of early stages of hepatocellular carcinoma. [33] [72] [73] [74] For appropriate patients with this malignant disease, ablation by

injection of absolute alcohol into the tumor is associated with lower morbidity and mortality compared with surgery, can be performed at significantly lower costs, and has high patient acceptance.

The ideal patient has good liver function and a single neoplasm smaller than 3 cm in diameter. Now that experience has been gained, patients with multiple neoplasms or larger ones are also being treated. The procedure is usually performed on an outpatient basis with the patient fasted. Total calculated dose of absolute alcohol required to ablate the tumor is given in divided doses in two to three sessions over a 1-week period. This alcohol is injected into the tumor using 21- or 22-gauge spinal needles, which are sometimes modified to have multiple holes at their distal end. The procedure takes 20 minutes to perform, and the patient is kept under observation for 3 hours afterward. Injection of alcohol is associated with mild to moderate pain, probably because the alcohol tracks back into the peritoneum through the hole created by the needle. This discomfort can be effectively treated with sedation and analgesics. Some centers have started giving the total ablating dose of alcohol in one treatment session. [75] [76] Patients undergoing such single-session treatments are usually anesthetized because the larger ethanol injection is associated with significant pain. A conventional anesthetic regimen employing muscle relaxants, control of the airway, and mechanical ventilation has been found to be successful in this situation. During injection of the ethanol, periods of controlled apnea and respiratory standstill with partial pulmonary inflation are required.

Complications associated with this procedure are uncommon and are usually minor. They include the pain already mentioned, a fever lasting several days associated with destruction of the tumor, and acute alcohol intoxication. A severe persistent fall in blood pressure requiring vasopressor therapy has been occasionally documented with ethanol injection. [77] This is presumed usually due to systemic vasodilation induced by the alcohol metabolite, acetaldehyde acetate, and possibly direct alcohol-induced pulmonary vasoconstriction and negative inotropic effect. Intraperitoneal hemorrhage must also be considered in the differential diagnosis. Rarely, when the lesion is subdiaphragmatic, the pleural cavity has been entered and has resulted in pneumothorax, pleural hemorrhage, and pleural effusion.

Liver metastases are more common than hepatocellular carcinoma in the United States. Ethanol injection ablation is usually ineffective with such liver metastases because their firm texture prevents adequate perfusion of the ethanol in the neoplasm. [78] [79] Cryoablation has been used when patients cannot undergo surgical resection or receive adequate chemotherapy to treat such a metastasis. The relatively large size of the liquid nitrogen cryoprobes has limited this technique to the operating room. An alternative to cryoablation now being employed to treat these metastases in the radiology suite is RF ablation. In this technique, high-frequency alternating current is sent through an insulated electrode inserted through a percutaneously placed needle into the tumor. Patients need to be anesthetized for this treatment. A 5- to 10-minute electrocautery burn is employed that usually needs to be repeated once to complete the patient's treatment. The results of RF tissue ablation appear to be comparable to those of surgery, but it has the advantage of minimal side effects and easy repeatability if tumor recurs. [33] Percutaneously inserted ultrasound-guided laser therapy is another related technique that holds great promise for the future. In it, optical fibers are inserted through percutaneously placed needles to deliver lasers that cause photocoagulation by heating the tissue. Finally, ultrasound can also be used to guide the injection of substances, such as chemotherapeutic and immunochemical therapeutic agents, into the tumor. It is indeed possible that ultrasound-guided tissue ablation techniques will revolutionize cancer treatment in the future.

Because of its success in treating liver tumors, percutaneous ultrasound-guided ethanol injection has also been used to ablate hepatic and renal cysts, parathyroid adenomas, thyroid nodules, and ovarian cysts. [33] This imaging technology has been used to facilitate percutaneous neurolysis of the celiac plexus via the anterior approach in patients with malignancy or chronic pancreatitis. [80] [81]

Interventional Neuroradiology

Neuroradiologists and neurosurgeons are currently making rapid strides in employing an endovascular approach to treat various cerebrovascular disorders. [34] [82] [83] [84] [85] [86] [87] [88] [89] This advance has been made possible by the simultaneous development of new imaging technology, catheter systems that can gain access to the distal cerebral and spinal cord vasculatures through use of this imaging, [90] and the use of a variety of detachable balloons, coils, and other vascular embolic agents, therapeutic materials, and drugs that can be placed through these catheters. Many conditions for which there were formerly no effective therapies can now be managed using these techniques, either by themselves or as adjuncts to planned neurosurgery. This field has proven to be particularly useful in the management of unclippable cerebral aneurysms, [34] [91] [92] complex arteriovenous malformations and fistulas, [93] [94] and the vasospasm that can follow aneurysmal subarachnoid hemorrhage, [95] [96] in applying superselective thrombolysis for acute strokes, [97] [98] [99] and as an alternative to carotid endarterectomy. Reducing the vascularity of central nervous system tumors prior to surgery is another application. In the future, there will undoubtedly be other conditions that benefit from this rapidly evolving

therapeutic modality.

This complex field, by its very nature, can be associated with significant morbidity and benefits from expert anesthesiology involvement. [100] [101] [102] Relieving any patient stress and discomfort is essential because patients have to remain immobile for extended periods, often for several hours. Successful treatment of some lesions requires monitoring the patient's neurologic status, particularly at certain critical junctures and, for this, the patient's level of consciousness often needs to be modified on demand. Elevating or lowering the blood pressure is also often needed at certain critical times, both as part of the treatment of the lesion and to treat any complication that arises.

Methods

High-resolution fluoroscopy and high-speed digital subtraction angiography are combined to obtain a real-time

---

"road map" of the patient's vascular anatomy through which the catheter can be manipulated. [103] [104] This map is made by initially injecting contrast through the catheter and then superimposing the resulting angiogram onto a live fluoroscopy image in which the interference produced by bone and other overlying structures has been simultaneously subtracted. The vascular system is usually accessed via the femoral vessels, and then, following anticoagulation with heparin, a catheter system is advanced under fluoroscopic control into the carotid or vertebral arteries, where, finally, a microcatheter is superselectively advanced into the vessels supplying the lesion or the lesion itself (Fig. 66-9) (Figure Not Available) . This superselective microcatheter is used to deliver the therapeutic device, embolic material, or drug therapy required to treat the lesion. The rapidly expanding variety of embolic agents includes detachable balloons, silk suture material, polyvinyl alcohol particles, thrombogenic platinum coils (Fig. 66-10) (Figure Not Available) , and cyanoacrylate, a monomer that polymerizes to a solid form on contact with blood. [105] [106] [107] The use of

Figure 66-9 (Figure Not Available) Diagramatic representation of catheter system used in interventional neuroradiology. *(From Young and Pile-Spellman [100])*

balloons allows neurologic testing before permanent occlusion.

Neurologic assessment of the awake patient remains the most sensitive measure used to assess the effects of distal ischemia induced by the embolization procedure. Once the superselective catheter is believed to be correctly placed, to ensure further that such embolization will not impair the function of critical brain areas adjoining the lesion, provocative testing of the cerebral circulation may be performed. [108] [109] [110] [111] This testing entails injecting 30 mg of sodium amylbarbital through the superselective catheter and then assessing its effect on involved or adjacent brain by observing the patient's awake neurologic status. This test is generally reliable, but it does have false-positive and false-negative results. Lidocaine, 15 mg, has been similarly used to assess cranial nerve function and the integrity of white matter tracts, especially in the spinal cord. [112]

The interventional neuroradiology angiography suite in which these procedures are performed should be equipped similarly to the neurosurgical operating room. This includes having an anesthetic machine with piped gases and suction, a refrigerator for drugs, cardiopulmonary resuscitation equipment, and adequate lighting. Caution needs to be followed to prevent undue radiation exposure. The ability to summon help immediately, including that of a neurosurgeon, is vital.

Anesthetic Management

Patients undergoing aneurysm ablation usually do not require awake neurologic assessment during the procedure and can be managed with general anesthesia given in a fashion similar to that used to treat these lesions surgically. Awake intraprocedure assessment is more commonly employed during the embolization of arteriovenous malformations, fistulas, and tumors. Such patients must remain immobile, usually for several hours, yet they must be rapidly arousable for neurologic assessment. This state is usually achieved by reversible intravenous sedation aiming to alleviate anxiety, pain, and discomfort. Small children and uncooperative adults who cannot tolerate such sedation need to have a general anesthetic. With these latter patients, the neurologic status may be monitored by using the electroencephalogram, somatosensory and motor-evoked potentials, transcranial Doppler ultrasound, or cerebral blood flow monitoring.

When awake neurologic assessments during the procedure are planned, it is useful, during the preoperative preparation, to train patients in what to expect. In evaluating such patients preoperatively, one should also make sure that they can lie supine for extended periods and that they are not prone to airway obstruction when sedated in this position. A history of past reactions to contrast media needs to be solicited in all patients. Likewise, because management of patients' blood pressure is often an important part of the procedure, one should ensure that patients are normotensive or that their preexisting hypertension is well controlled.

Because the procedure lasts many hours, and multiple treatments often are needed, it is important to position the patient comfortably. Air and foam mattresses are employed, and a pillow is placed under the knees. Two intravenous

---

Figure 66-10 (Figure Not Available) Occlusion of an aneurysm with a Guglielmi detachable coil. (A) Aneurysm of the basilar artery before treatment. (B) A microcatheter has been placed inside the aneurysm, and the first coil has been delivered inside the aneurysm but not yet detached. The arrow depicts the junction between the guide wire and the coil. (C) The coil has been detached, and the guide wire has been withdrawn proximally into microcatheter (arrow). (D) Appearance of the aneurysm after completion of treatment. The aneurysm is filled and is excluded from intracranial circulation by a combination of thrombus and multiple coils. The microcatheter is being withdrawn from the basilar artery (arrow). *(From Nichols et al [34])*

lines are placed, one for drug infusions and the other for administering fluids and drug boluses. Invasive arterial pressure monitoring is essential, accessed via the side port of the femoral artery catheter inserted by the neuroradiologist. Because contrast media are osmotic diuretics and significant quantities are utilized in these procedures, it is essential to catheterize the patient's bladder. The patient's respiratory rate is monitored with a capnograph sampling tube connected to the nasal cannula through which oxygen is given to the patient. The ECG, pulse oximetry, and temperature are monitored. It is also useful to have a pulse oximeter on one of the toes of the patient's leg that has the femoral artery cannulated. This device gives an early warning of distal thromboembolism in that leg. Because it is essential for the patient to avoid shivering, which causes movement and image degradation, heating devices are employed.

Various analgesic and sedative combinations have been used to manage these patients. Currently, we titrate small intravenous doses of fentanyl and midazolam, aiming to produce an easily arousable, lightly sedated patient with a patient airway and adequate spontaneous ventilation. In addition to these medications, ondansetron is commonly administered to reduce the risk of postprocedure nausea and vomiting.

To prevent thromboembolic complications, most patients are heparinized throughout these procedures. Following determination of a baseline activated clotting time, the patient is given 60 U heparin/kg, and activated clotting times are repeated half-hourly, with subsequent heparin doses being adjusted to keep the activated clotting time two to two and one-half times its baseline value (Ch. 49) .

Deliberate hypotension may be employed to decrease blood flow through a feeding artery to the arteriovenous malformation prior to injection of cyanoacrylic glue, to prevent this material from being embolized distally beyond the malformation (Ch. 41) . Such hypotension is also useful to test the cerebrovascular reserve in patients undergoing trial balloon occlusion of the carotid artery. Esmolol with, if necessary,

---

labetalol works well for this purpose, and sodium nitroprusside has also been used. Deliberate hypertension is required when the patient experiences cerebral ischemia resulting from either a planned or an inadvertent vascular occlusion, with the goal of increased perfusion via collateral vessels to the area of ischemia on a temporary basis. For this situation, phenylephrine, 1 mug/kg bolus intravenously, followed by an infusion of this drug, is used to increase mean blood pressure 30 to 40 percent higher than baseline. With such therapeutic hypertension, it is important to monitor the ECG for signs of myocardial ischemia.

Interventional neuroradiology, by its nature, can be associated with significant morbidity. Complications, if they occur, tend to be rapid in onset, and to prevent them from producing permanent brain damage requires established prior planning and teamwork. [113] Emergency neurosurgical intervention may occasionally be required. The primary responsibility of anesthesia personnel in such emergencies is to secure the patient's airway and to ensure that the patient has good gas exchange. This situation usually necessitates rapid induction of general anesthesia with sodium thiopental and use of a muscle relaxant to facilitate endotracheal intubation. Temporizing measures employed to treat vascular occlusion-induced ischemia are to improve collateral blood flow to the ischemic area by elevating systemic vascular pressures using phenylephrine with or without direct thrombolysis. If the problem is hemorrhagic, immediate reversal of the heparin with protamine combined with induced hypotension is indicated. Rupture and perforation of blood vessels can sometimes be treated using balloons, coils, or glue.

NONSURGICAL CARDIOVASCULAR PROCEDURES

Nonsurgical cardiovascular procedures include arteriography, coronary angiography and cardiac catheterization, electrophysiologic studies, and cardioversion. These procedures, both diagnostic and therapeutic, can benefit from the involvement of anesthetic personnel, in terms of both procedural outcome and patient comfort. Anesthesiologists caring for these patients, in order to develop a coherent anesthetic plan, must be familiar with the patient's medical condition as well as with the planned procedure.

The environment of the cardiac catheterization laboratory is not optimized for anesthetic management (see Fig. 66-1) . The rooms are frequently darkened to allow better visualization of fluoroscopic images, and they are crowded with equipment and personnel. It is critical that the requirements for anesthetic equipment and monitoring discussed earlier are met and that the anesthesiologist remains vigilant for rapid changes in the patient's condition, which frequently occur in this distracting environment.

Arteriography

Arteriography permits radiologic visualization of blood vessels by injection of contrast media through a catheter inserted into proximal vasculature. The arteries of the viscera and lower extremities may be accessed via the femoral arteries, although arterial occlusive disease may require a translumbar approach to the aorta. The gaining of vascular access and the injection of contrast media may result in patient discomfort. Many patients benefit from judicious administration of analgesics and sedatives. Some patients requiring translumbar aortography may require general anesthesia and endotracheal intubation, because the procedure is performed in the prone position. Alternatively, transvenous aortography may be performed with a larger amount of contrast media injected via the venous circulation. This approach is much less invasive and requires only minimal, if any, sedation. Patients undergoing arteriography to determine the extent of vascular occlusive disease have a high incidence of serious comorbid conditions, including diabetes mellitus and coronary and cerebral vascular disease, and appropriate monitoring and precautions must be taken when caring for this group of patients.

Coronary Angiography

The coronary vasculature may be visualized using radiographic contrast media, allowing determination of coronary anatomy, precise determination of the presence and location of coronary artery stenoses, and detection of coronary vasospasm. [114] Although other procedures, such as rapid CT and MRI, may allow determination of the presence of coronary artery disease, coronary angiography remains the "gold standard" for this diagnosis. In addition, interventional procedures to improve coronary blood flow may be performed as part of the same procedure. [115] Some patients undergoing this procedure may be inpatients, but many are outpatients, and the anesthetic plan must take this possibility into account. Information obtained from coronary angiography is used to determine further treatment, which may range from medication to transvascular interventional procedures performed in the coronary catheterization laboratory to coronary artery bypass grafting (CABG). Increasingly, interventions are performed in the coronary catheterization laboratory.

Coronary angiography is performed by passing a catheter in retrograde fashion through the arterial tree to the aortic root for the selective injection of contrast media into the ostia of the coronary arteries. Usually, the catheter is inserted via the femoral artery, but arterial occlusive disease may necessitate access via the brachial or radial arteries. Local anesthesia is used at the catheter insertion site, to limit patient discomfort related to vascular access. Peripheral intravenous access is necessary for the administration of cardiac medications and analgesics and sedatives. Anesthetic agents used include fentanyl and midazolam, sometimes supplemented with propofol. Sedation and analgesia are helpful in reducing the discomfort of contrast injection and of remaining motionless and supine during long procedures. Supplemental oxygen is administered via nasal cannula. Sublingual and intravenous nitroglycerin should be readily available for administration, if the patient develops myocardial ischemia. Standard anesthetic monitoring [4] is used during the procedure. Arterial blood pressure can be directly transduced from the arterial introducer during femoral or brachial catheterization. The ECG must be scrutinized and the patient closely watched for the presence of angina or heart failure,

all while anesthetic personnel are shielded from exposure to radiation. Complications are more common in patients with severe coronary artery disease and include arrhythmias, heart failure, and stroke. [116] Finally, the patient must be observed closely following the procedure for bleeding or hematoma at the catheter site. Discharge criteria for outpatients are the same as for outpatient surgical procedures.

Interventional Transvascular Coronary Arterial Procedures

Once the presence and location of coronary artery stenosis are confirmed, interventional cardiologists can use a variety of methods to improve myocardial blood flow directly. Access to the coronary arteries is via the femoral, brachial, or radial arteries using local anesthesia, combined with intravenous analgesia and sedation. [117] Heparin is administered prior to the procedure. Percutaneous transluminal coronary angioplasty (PTCA) involves traversing the stenotic area with a balloon-tipped catheter and compressing the stenosis with the balloon, thus opening the coronary artery. [118] Transient coronary artery occlusion occurs during balloon inflation, and the patient's hemodynamic status must be closely monitored. Further analgesia may be necessary because angina may develop during this time. The obligate ischemia limits the stenosis sites that may be treated with this technique to the distal coronary vasculature and, usually, to one- or two-vessel coronary artery disease. These limitations are changing as technology of angioplasty, coronary stents, and extracorporeal circulation allows treatment of more severely affected patients in the catheterization laboratory, as discussed later. More recently, PTCA has been supplemented by various techniques that remove, rather than compress, the atheromatous plaques causing coronary arterial stenosis. Coronary atherectomy may be performed using either atherectomy catheters that "shave" the plaque or excimer laser. [119]

During ischemia, and frequently during reperfusion following dilation of the stenotic coronary artery, ventricular arrhythmias may develop and may require treatment. Hemodynamically significant premature ventricular contractions and nonsustained ventricular tachycardia should be initially treated with lidocaine. More severe arrhythmias may require cardioversion with the patient under general anesthesia. Rupture of the coronary artery may result in hemopericardium and pericardial tamponade. Tamponade must be treated with emergency pericardiocentesis and may require operative intervention. Another rare complication of PTCA is coronary artery occlusion, which may result from coronary artery dissection, thrombus within the coronary artery, or vascular spasm due to dysfunctional coronary artery endothelium. Vascular spasm often may be relieved by the injection of 200 mug of nitroglycerin via the coronary artery. Thrombosis of the coronary artery may require multiple therapeutic approaches. [120] Thrombus formation is retarded by the prior administration of heparin. Once thrombus has formed, intracoronary injection of thrombolytic agents, such as urokinase, may dissolve the thrombus. Bleeding complications may result from thrombolytic therapy, especially if the patient requires an emergent surgical procedure. Abciximab, a platelet IIb/IIIa receptor antagonist, has been demonstrated to reduce the rate of acute ischemic complications associated with PTCA markedly. Abciximab is increasingly administered as an intravenous infusion during these procedures. [121] [122] Again, bleeding disorders may result, complicating postprocedural management and management during emergency operation. These patients may require relatively massive autologous platelet

transfusions. It should be anticipated that further developments will occur in regulation of the hemostatic system to reduce acute and chronic occlusion. [123]

Acute coronary occlusion may not respond to transluminal treatment in the catheterization laboratory and may require emergency CABG. The patient may have angina, hypotension, and arrhythmias and may benefit from the insertion of an intra-aortic balloon pump. In addition, the patient may require inotropic support and endotracheal intubation. Nitroglycerin is administered in an effort to improve collateral coronary flow and to reduce preload. Adequate preload must be ensured, and monitoring of central pressures may be helpful. If the stenotic or dissected area can be traversed with a guide wire, the cardiologist may be able to leave a perfusing catheter in place, allowing some coronary blood flow and limiting myocardial ischemia pending surgical revascularization. [124] Great care must be taken in transport in order not to dislodge this catheter.

Time is critical when the patient requires emergency CABG in this situation. The patient must be expeditiously transported to the operating suite and placed on cardiopulmonary bypass as soon as possible for maximal myocardial salvage. Multidisciplinary examination of institutional systems may result in streamlining of the procedure for rapid transport of the patient to the operating suite, thus improving patient outcomes. [125] Because these patients may be very hemodynamically unstable, their cardiovascular and respiratory status must be continuously monitored.

Results obtained from PTCA and atherectomy procedures are initially excellent. However, the rate of restenosis of the dilated coronary arteries is as high as 30 to 40 percent and is at least partially due to dysfunctional coronary endothelium. [126] Increasingly, expandable metallic stents are used to maintain coronary artery patency. The stents are placed across the area of stenosis following PTCA or atherectomy and remain in place following the procedure. [127] The anesthetic implications are similar to those for PTCA. The spectrum of treatment administered in the cardiac catheterization laboratory is constantly changing, and various combinations of the described procedures may be performed on each individual patient, depending on the severity and location of lesions and the practice at each individual institution. [128]

Patients with evolving myocardial infarction benefit from thrombolytic therapy and, possibly, from PTCA and/or coronary artery stenting to restore myocardial blood flow. [129] [130] Such treatment must be administered within 6 to 12 hours to maximize myocardial viability and to reduce morbidity and mortality. These patients may have full stomachs and may be hemodynamically unstable. General anesthesia has been successful in such patients who cannot tolerate the procedure because of pain, anxiety, or dyspnea. [131]

Developments in perfusion technology have increased the portability of the cardiopulmonary bypass machine. It is now

feasible to perform extracorporeal circulation in the cardiac catheterization laboratory. This procedure maintains hemodynamic stability during procedures that would otherwise result in unacceptable amounts of myocardial ischemia, such as PTCA and stenting of stenoses of the left main coronary artery. Currently, this is most frequently done on patients who are not otherwise candidates for CABG surgery, such as those with unacceptably poor ventricular function or distal coronary artery disease that would preclude CABG. [132] Extracorporeal circulation is established via the femoral artery and vein following induction of general anesthesia and systemic heparinization. Monitoring is as for CABG in the operating suite. Following the procedure, extubation is perform-ed as soon as the patient's condition allows. The anesthetic technique chosen must provide hemodynamic stability and the potential for early extubation. A balanced anesthetic regimen of fentanyl and a volatile agent, with neuromuscular blockade, provides these conditions. The patients must be closely monitored for bleeding complications because heparinization is frequently continued following the procedure. Abciximab and other medications affecting hemostasis are frequently administered. Should complications occur in these patients, who are supported by extracorporeal circulation but who are not surgical candidates, ethical dilemmas may occur. The possibility of complications and the potential treatment options, or lack thereof, must be clearly understood by the patient and by all medical personnel caring for the patient prior to undertaking such procedures. Clear and open communication is essential in this setting.

Cardiac Catheterization

Placement of transvenous and transarterial catheters into the heart and great vessels (cardiac catheterization) allows determination of cardiac anatomy, ventricular function, valvular anatomy, and pulmonary vascular anatomy (Ch. 49) . Pressure measurements in cardiac chambers and vascular structures may be made via these catheters. Injection of contrast media allows radiologic visualization of various structures, and indicator injection with distal sampling allows flow determination using the Fick principle. In addition, blood samples may be withdrawn from various areas for determination of oxygen saturation to detect the presence and location of shunts. Although much (but by no means all) of this information can be obtained with echocardiography, cardiac catheterization remains the gold standard for detailed diagnosis of complex cardiac anatomic anomalies. [133] It must be noted that, because multiple measurements and samples are necessary for the complete cardiac catheterization procedure, the measurements cannot be performed simultaneously. In order for the hemodynamic and shunt calculations to be valid, a relatively constant cardiovascular and respiratory state is necessary. [134] [135] Arterial pressures of oxygen (Pa $_{O_2}$) and of CO_2 (Pa $_{CO_2}$) must be "normal" for the patient being studied and must remain so during the measurement periods. The anesthetic techniques used in a given institution should be consistent in order that the cardiologist not have to account for differences in anesthetic techniques in interpreting diagnostic data. These constraints can make anesthetic management of these patients extremely difficult.

Adult Cardiac Catheterization

Cardiac catheterization in adults is frequently performed in conjunction with coronary angiography (Ch. 49) . Access to the right heart (pulmonary circulation) is via the venous system, usually involving catheter placement in the femoral vein. The left heart (systemic circulation) is accessed as the coronary arteries are accessed, via the brachial, radial, or, more commonly, femoral arteries. Complications related to vascular access are similar to those outlined for coronary angiography. Because catheters are placed within the cardiac chambers, supraventricular and ventricular arrhythmias are common during this procedure. The procedure is usually performed using local anesthesia, but patients benefit from systemic analgesia and sedation. Medications frequently used for this purpose include fentanyl and midazolam, sometimes supplemented with propofol. Oxygen is administered as needed, but care must be taken to maintain "normal" (for the patient) arterial blood gases if pulmonary hemodynamics are to be measured during the procedure. As with coronary angiography, the anesthesiologist must be prepared to deal with acute hemodynamic and respiratory instability in patients who may have severe valvular and myocardial dysfunction.

Pediatric Cardiac Catheterization

Anesthetic management for cardiac catheterization in pediatric patients can be uniquely challenging (Ch. 50) . These patients range in age from premature neonates to the upper limits of the pediatric age group. Cardiac anomalies vary from relatively simple atrial septal defects to complex congenital cardiac anomalies such as hypoplastic left heart syndrome. Shunts may be present at multiple levels, and the patients may be profoundly cyanotic. Ventricular dysfunction may be severe. Patients may also have coexisting noncardiac congenital abnormalities. In addition, these young patients may be uncooperative, and their parents may be severely stressed and thus of limited assistance. Neonatal studies are frequently performed on an emergency basis, and these patients are often deeply cyanotic and critically ill. The diagnosis of the cardiac anomaly is usually made prior to cardiac catheterization by echocardiography, but the determination of surgical treatment or possible catheter-based intervention is dependent on the results of the cardiac catheterization.

Anesthetic techniques used in these cases range from sedation and analgesia to general anesthesia. Again, it must be remembered that a "steady state" must be maintained for diagnostic accuracy. In general, older, cooperative patients are readily managed with intravenous sedation and analgesia. Even in cyanotic patients, supplemental oxygen is not administered unless oxygen saturation falls below baseline levels. Care must be taken to maintain ventilation and Pa $_{CO_2}$ within normal physiologic limits to avoid alterations in pulmonary vascular resistance. [136] Medications administered for sedation include fentanyl, midazolam, propofol, and ketamine. Premedication with midazolam, 0.5 mg/kg by mouth dissolved in grape Kool-Aid with sugar added for increased palatability, can be particularly helpful. There is some evidence that ketamine can increase oxygen consumption, and

care must be taken to ensure that this does not impair diagnostic accuracy. [137] Even small infants have been sedated in this manner for these procedures.

Infants and small children frequently cannot tolerate the procedure under intravenous sedation and are more readily managed with a general anesthetic regimen. As with intravenous sedation for these procedures, premedication with oral midazolam, 0.5 mg/kg, can be very helpful. If intravenous access is not present, an inhalation induction with nitrous oxide, oxygen, and a volatile anesthetic, such as sevoflurane, is performed, and intravenous access is obtained after the patient is anesthetized. Alternatively, intravenous induction using thiopental, ketamine, etomidate, or propofol is performed. A nondepolarizing neuromuscular relaxant is administered, and endotracheal intubation is performed when the patient is fully relaxed. Correct endotracheal tube position is confirmed by end-tidal CO_2 measurement, and position above the carina is readily confirmed using fluoroscopy. Anesthesia is maintained with volatile anesthesia and controlled ventilation using room air, as long as the oxygen saturation does not fall below baseline levels. Controlled ventilation avoids the increases in Pa $_{CO_2}$ frequently seen with levels of intravenous sedation adequate to allow performance of this invasive procedure in pediatric patients. Controlled ventilation has not been found to affect the diagnostic accuracy of cardiac catheterization. [134] Minute ventilation and respiratory rate are adjusted to maintain normal Pa $_{CO_2}$, based on analysis of arterial blood gases drawn by the cardiologist from the arterial catheter. The end-tidal CO_2 determination can be used to adjust ventilation subsequently, but it must be remembered that the physiologic dead space is highly variable in such patients. Infiltration of local anesthetic at vascular access sites limits postprocedural discomfort. Small amounts of an opioid such as fentanyl may be administered to provide for postprocedure sedation, thus allowing the patient to remain still and to avoid bleeding complications at the femoral vascular access sites. As an alternative to a volatile anesthesia-based technique, the patient can be managed with total intravenous anesthesia using various combinations of opioids, benzodiazepines, propofol, and ketamine. [138] [139] [140] [141] [142] [143] Again, steady-state conditions are essential, and the anesthetic plan at any institution should be consistent from patient to patient to provide reproducible patient conditions for the cardiologists who must interpret the diagnostic data.

Close monitoring of these patients is required. Especially in neonates, deterioration can be rapid. These patients may be very sensitive to anesthetics, and hemodynamic instability may ensue. Repeated blood gas analysis is necessary, because metabolic acidosis may be the initial sign of low cardiac output state. Even mild degrees of metabolic acidosis should be treated in critically ill patients, and inotropic therapy may be necessary. Hypocalcemia and hypoglycemia may develop in neonates and may require treatment. Hypothermia can be a problem in young patients, especially those under general anesthesia. The room may need to be warmed. In addition, inspired gases may need to be warmed and humidified, and a warming blanket or forced air warming system should be available. Rectal temperature may need to be monitored in small patients, because an esophageal or axillary probe may intrude into the cardiologist's imaging area. Blood loss during the procedure is less well tolerated than in larger patients, because the loss may represent a significant fraction of a smaller patient's blood volume. Hematocrit must be monitored carefully, and anemia must be treated appropriately. Deeply cyanotic patients tend toward polycythemia, and sufficient fluids must be administered to balance the osmotic effects of contrast media, which could result in hemoconcentration and microembolic events.

Complications of cardiac catheterization include arrhythmias, bleeding at vascular access sites, perforation of cardiac chambers or great vessels by catheters, vascular dissection or hematoma, and embolic phenomena. Arrhythmias are the most frequent complication. [144] Supraventricular tachycardias are most common, often related to catheter tip placement, in which case the arrhythmias usually resolve with withdrawal of the catheter. Occasionally, vagal maneuvers, intravenous medication, or cardioversion may be necessary to terminate the arrhythmia. Second- or third-degree heart block may also be seen. Sinus bradycardia may require treatment with atropine. Profound bradycardia may require temporary ventricular pacing if hemodynamic instability results.

Pericardial tamponade can be detected by characteristic hemodynamic alterations, as well as by a widened mediastinum and reduced cardiac motion on fluoroscopy. The definitive diagnosis of tamponade is best made by echocardiography, which should be readily available and can be used to guide emergency pericardiocentesis. The pericardiocentesis catheter can cause arrhythmias by mechanical irritation. These arrhythmias can be either supraventricular or ventricular, and they may be poorly tolerated in critically ill patients. As with coronary angiography, emergency surgical procedures may be necessary, and hospital systems must allow rapid, safe transport of these patients to the operating suite.

Interventions During Cardiac Catheterization

Balloon Atrial Septostomy

Balloon atrial septostomy (Rashkind procedure) is performed in infants requiring communication between the pulmonary and systemic circulations for survival (e.g., transposition of the great vessels) (Ch. 49) . A balloon-tipped catheter is placed across the atrial septum. The balloon is inflated to rupture the septum, thus creating an atrial septal defect and allowing shunting at the atrial level. In the case of transposition of the great vessels, oxygenated blood flowing from the lungs to the left atrium would mix in the right atrium with venous return blood and flow into the systemic circulation via the right ventricle. Neonates presenting for this procedure are usually receiving intravenous prostaglandin E_1 to maintain a patent ductus arteriosus. It is critical to maintain this infusion to keep the ductus patent until the atrial septostomy is complete and is determined to be of adequate size to maintain systemic oxygenation. Anesthesia for the procedure is otherwise as described earlier.

Balloon Valvuloplasty

Balloon-tipped catheters have been used to dilate stenotic heart valves and great vessels. The procedure has been used

to dilate congenital pulmonary valvular stenosis, [145] stenotic pulmonary arteries, and aortic coarctation. Balloon valvuloplasty has also been used to ameliorate acquired stenosis of the tricuspid, pulmonary, mitral, and aortic valves. [146] The procedure is usually reserved for patients regarded as very high-risk surgical candidates. [147] During balloon inflation, the circulation is blocked, and severe hypotension may result that, because of the tenuous condition of the patient, may not resolve immediately on deflation of the balloon. Inotropic and antiarrhythmic therapy may be necessary, and preload may need to be optimized with intravenous fluid administration. Complications of the procedure are similar to those of cardiac catheterization. In addition, valvular insufficiency may develop.

Older patients usually tolerate this procedure when local anesthetics are infiltrated at the site of catheter entry. Intravenous sedation with fentanyl, midazolam, and propofol attenuates discomfort related to the environment and to balloon inflation. When the aortic valve is to be dilated, two intravenous catheters are inserted. Valvuloplasty of other valves requires only a single intravenous catheter. If the patient becomes hemodynamically unstable, the balloon must be immediately deflated. Vagal stimulation can occur with balloon inflation and may require treatment with atropine. Should major complications ensue, prompt surgical intervention may be necessary.

Electrophysiologic Studies and Catheter Ablation of Abnormal Conduction Pathways

Electrophysiologic studies involve placement of special multipolar catheters within cardiac chambers to define the mechanism, origin, and pathways of arrhythmias and to determine the best therapeutic options. [148] Vascular access is usually via the femoral artery and vein, and frequently additional catheters are placed via the internal jugular vein. Programmed electrical stimulation is performed near the bundle of His, in the right ventricular apex, and sometimes in the left ventricular apex, using standard transvascular catheterization techniques. Using specifically timed electrical impulses, the arrhythmia is reproduced under controlled conditions and is monitored through both the catheters and the surface ECG leads. Electrical energy delivered through appropriately positioned catheters can then be used to ablate arrhythmogenic foci or accessory pathways. Another intervention that also may be employed in the laboratory is to place the electrodes precisely for subsequent connection to an implantable defibrillator.

Antiarrhythmic drugs are stopped prior to these studies and are avoided during the procedure, because they may prevent the detection of accessory conducting pathways and arrhythmogenic foci. These studies use multiple catheters and often take several hours to perform. To ensure patient comfort, adults and older children are usually sedated with midazolam and receive analgesics such as fentanyl. Total administered doses of these drugs may seem quite high at the end of the procedure, but the procedures are prolonged, and the pain resulting from the ablation current may be severe. Brief periods of general anesthesia using thiopental or propofol may be needed during ablation, [149] or if cardioversion is required for supraventricular arrhythmias that cannot be terminated by overdrive pacing via the catheters. Care must be taken during mask ventilation so that the internal jugular venous catheters are not moved and the operative site is not contaminated. Electrophysiologic studies in younger children are usually performed using general anesthesia, as outlined in the section on cardiac catheterization. Intravenous and volatile anesthetic techniques have both been used successfully in electrophysiologic testing, [150] [151] but, as for cardiac catheterization, consistent anesthetic techniques should be used in a given institution to ensure diagnostic accuracy.

Pacemaker and Implantable Cardioverter-Defibrillator Implantation

Permanent pacemakers and permanent cardioverter-defibrillators are increasingly placed in the cardiac catheterization laboratory. Implantation of both devices involves placement of transvenous leads into the cardiac chambers (usually right atrium and/or ventricle) with tunneling of the leads to a subcutaneous pocket in which the device is placed. Although the discomfort of the procedure can be reduced with local anesthesia, these procedures are most readily performed with the patient under general anesthesia, with endotracheal intubation or laryngeal mask airway. General anesthesia is necessary during testing of the permanent cardioverter-defibrillator. Patients with severely impaired ventricular function are best managed with direct arterial pressure monitoring.

Elective Cardioversion

Cardioversion is used to convert supraventricular and ventricular arrhythmias to sinus rhythm. When these arrhythmias are not causing hemodynamic instability or when the arrhythmia is of long standing and has not responded to drug therapy, the cardioversion can be performed on an elective, possibly outpatient, basis. The patient's cardiovascular status and medical therapy are optimized prior to elective cardioversion. In contrast, emergency cardioversion is often required when the arrhythmia causes hemodynamic instability and when time pressure and the patient's condition may not allow for full evaluation or administration of anesthesia.

Elective cardioversion is uncomfortable, and general anesthesia is required. Many medications, including barbiturates, propofol, etomidate, and benzodiazepines, have been used. [152] [153] [154] [155] The patient should be fasting. In the case of chronic atrial fibrillation, echocardiography is performed prior to cardioversion in order to rule out the presence of left atrial thrombus, which could cause stroke. Monitoring includes ECG, blood pressure cuff, and pulse oximetry. When all is in readiness for the cardioversion, the patient is preoxygenated and then is given small incremental doses of anesthetic agent until the eyelid reflex is abolished. Immediately prior to the countershock, the mask is removed, and it is confirmed that no person is touching the patient. More than one shock may be required to restore sinus rhythm, and it is important to keep the patient anesthetized until the

procedure is successful or the attempt is terminated. Following the countershocks, the patient is ventilated with 100 percent oxygen until he or she regains consciousness and is able to maintain the airway. It should be noted that muscle relaxants are not typically required for this procedure. If cardioversion is required on an urgent basis, it must be remembered that the patient may not have been fasting prior to the procedure. To prevent aspiration during anesthesia in this situation, it is appropriate to intubate the trachea using a rapid-sequence induction technique employing cricoid pressure.

THERAPEUTIC RADIATION

Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT) involves the delivery of radiation during exposure of a tumor or tumor bed at the time of a planned operative procedure. In its broadest sense, this includes brachytherapy with temporary or permanent implantation of radioactive seeds. [156] As discussed in this section, IORT refers to the intraoperative application of electron beams. Radiation therapy plays a major role in the management of many malignant diseases. The usual method by which radiation is delivered is external-beam treatment with high-energy photons. The external-beam doses required to achieve local tumor control can exceed the radiation tolerance of some normal organs and other structures of the body. [157] IORT with variable-energy electrons can effectively be used as a supplemental boost to external-beam treatments. By delivering the radiation therapy during surgery, it is possible to remove normal structures away from the radiation beam or to shield them with lead. [158]

This method of treatment is appealing, particularly for locally advanced malignant lesions, when conventional modalities are unlikely to produce local tumor control. Theoretical advantages over conventional external radiotherapy are the ability to increase tumor dose with less damage to adjacent healthy tissues and more accurate localization of the radiation field. Disadvantages of this technique are that an operation is needed, optimal dose combinations of external-beam and radiation and IORT are complex to calculate, [157] and complications are not infrequent. These complications include pelvic abscess, small bowel obstruction, ureteral obstruction, [159] and peripheral neuropathy. [160] All patients treated with IORT at Mayo Clinic in Rochester, Minnesota, are specifically told about possible nerve-related side effects. [161] In most patients treated with IORT, surgery alone would not achieve local control, and external radiation doses needed for local control would exceed normal tissue tolerance. [162]

The largest clinical experience with IORT has been with gastrointestinal cancers in adults. Of patients treated with IORT at Mayo Clinic, the most frequent diagnosis is locally advanced colorectal cancer. [161] Moderate experience has also been obtained with locally advanced retroperitoneal sarcomas, [156] as well as with recurrent genitourinary and gynecologic cancers. [163]

Most of the advances in the use of radiation have been achieved by an improved dose distribution and better differentiation of dose delivered to tumor and normal tissue. Delivering the radiation during the surgical procedure permits direct observation of tumor size and density and of tissue at risk for microscopic spread of tumor. Shielding of nearby sensitive structures from the intense local radiation field is possible by surgical manipulation. [164] By moving normal and noninvolved tissue out of the path of the electrons, the radiation

Figure 66-11 Intraoperative radiation therapy room. Anesthesia, incision, radiation, and closure occur in this dedicated area.

Figure 66-12 A sterile Lucite cylinder is adjusted to isolate the tumor mass and displace surrounding normal structures.

is confined to the cancer, and the therapeutic ratio can be maximized. [165] Patient selection for IORT should include no contraindications to surgery and the belief that surgical intervention alone will not result in local tumor control. The tumor should be a localized focus of disease, and no distant metastasis should be apparent [156] ; therefore, the treatment is seen as potentially curative. [164] Clotting parameters should be checked preoperatively, particularly in patients with obstructive jaundice. [166]

Ideally, anesthesia, incision, radiation, and closure occur in a single dedicated IORT room (Fig. 66-11) . At the Mayo Clinic, both the operative procedure and delivery of IORT are performed in a dedicated IORT room within the operating suite. [100] [162] [167] A dedicated IORT room has the advantages of allowing surgery and radiation therapy to be accomplished in a single setting without moving the patient through a nonsterile environment. Other advantages of a dedicated IORT room within the surgical suite include the close proximity of other ancillary facilities (e.g., blood bank) and the immediate availability of additional anesthesia and surgical personnel and/or equipment.

Alternatively, induction of anesthesia, surgical incision, and tumor isolation can be accomplished in a modified operating room within the radiation oncology area. [163] This alternative allows the linear accelerator room to be used without interruption for treating other patients while the patient who is to undergo IORT is being prepared. Following preparation, the anesthetized and surgically draped patient is transported a short distance to the accelerator treatment room. Following radiation treatment, the patient is returned to the modified operating room for closure of the incision.

Patients typically receive a conventional general anesthetic regimen with endotracheal intubation. After surgical incision and exploration, the tumor is exposed and isolated. A sterile Lucite cylinder then is inserted to cover the tumor mass, to define the radiation beam, and to displace normal structures outwardly circumferentially around its perimeter [166] (Fig. 66-12) . Radiation therapy may then be focused directly on the isolated tumor.

During IORT, the patient is ventilated automatically. Monitoring includes devices customarily used for any major surgical procedure (e.g., ECG, blood pressure, heart rate, pulse oximetry, gas analysis, temperature, and neuromuscular function). During the actual radiation treatment period, all personnel must leave the treatment room to avoid receiving high radiation exposure, and the patient, anesthesia equipment, and monitors are observed continuously by closed-circuit television (Fig. 66-13) . Following treatment, the patient is transported to the recovery room.

Patients who undergo IORT may present special challenges to anesthesiologists. The patient's physical status may be compromised by the malignant disease process or by chemotherapy and surgery may involve advanced resection of tumor and considerable blood loss. [168] Nutritional support is important in these patients, many of whom will have lost 20 percent or more of their body weight because of the malignant disease and may have been subjected to multiple operations. A feeding-tube jejunostomy frequently is inserted selectively during the IORT procedure to facilitate nutritional support during convalescence. Perioperative deaths due to intraoperative cerebrovascular accidents, postoperative hemorrhage, hepatorenal syndrome, and aspiration have been reported. [169]

External-Beam Radiation of Cancer in Children

Optimal treatment of essentially all children with cancer uses planned combined modality therapy incorporating chemotherapy, surgery, and radiotherapy (Ch. 59) .

Figure 66-13 Patient chest movements and pulse oximeter, electrocardiographic, and arterial blood pressure monitors are remotely observed on closed-circuit television screens.

solid tumors; either resection or radiation is needed for local tumor control. [170] Children with radiosensitive malignant tumors typically require radiation therapy for a number of sessions over several weeks. Although the treatments are painless, young children cannot be depended on to remain absolutely motionless in the strange and frightening surroundings of radiation therapy rooms. Because immobility during treatment is mandatory, sedation or general anesthesia usually is necessary. [171]

Anesthetizing locations within the therapeutic radiology department should have facilities and monitors that satisfy, or exceed, the current standards promulgated by the ASA. [3] Sedative medication doses required to produce predictable immobility may be associated with unwanted side effects (e.g., loss of airway in unattended patients, respiratory and cardiovascular depression, [172] and prolonged recovery). General anesthesia may be preferable when potential airway problems exist or when control of intracranial pressure is critical. [173]

Anesthetic regimens for external-beam radiation in children should provide brief periods of anesthesia at a depth that ensures immobility and minimal time to recovery. [174] Airway management should be appropriate in whatever body position the patient requires for the radiation. Because all personnel must leave the room during the actual delivery of radiation, the anesthetic technique should facilitate remote monitoring of the patient, thus allowing continuous assessment of the patient. [174] During the actual radiation treatment period, the patient, anesthesia equipment, and monitors are observed continuously by closed-circuit television.

General anesthesia may be indicated. The anesthesia team occasionally is asked to provide general anesthesia in a location where there is no means to scavenge waste anesthetic gases. Scavenging of waste gases is desirable and has been recommended by the National Institute of Occupational Safety and Health [175] and the American Society of Anesthesiologists. [3] A modified stethoscope has been developed that allows remote auscultation of heart and breath sounds during the radiation period. [176]

Typically, patients require a series of treatments and hence a series of anesthetic regimens. It is therefore desirable to avoid repeated invasive procedures to the degree feasible [174] and to keep the anesthesia technique as simple as possible. The laryngeal mask airway has proved to be a simple and safe airway device for use in children undergoing general anesthesia for external-beam radiation. [177] [178] Other techniques for administering general anesthesia for external-beam radiation in children without use of an endotracheal tube have been described. [174] Intravenous propofol infusion can also be used satisfactorily in these children. [23] [179] If the patient does not have an intracranial mass lesion, intramuscular administration of ketamine can provide satisfactory conditions. [180] A need to increase the ketamine dose gradually with successive radiation treatments (tachyphylaxis) may be observed. [25] Similar increasing dose requirements have been noted with propofol. [24] The anesthesiologist must watch for excessive salivation and postoperative vomiting. [180] Others have described the use of oral ketamine as a satisfactory induction technique. [19] [20]

When overt or potential intracranial hypertension is a concern, ketamine should not be used (Ch. 52) . Hypercarbia should be avoided, and moderate hypocarbia should be achieved prior to the introduction of a volatile agent. Induction of anesthesia may be satisfactorily achieved with intravenous thiopental or propofol, plus some short-acting narcotic if indicated.

We recommend that skeletal muscle response to tracheal intubation be abolished with a nondepolarizing muscle relaxant. Pharmacologic blunting of the hemodynamic response to intubation also helps to prevent an increase in intracranial pressure. End-tidal CO_2 may be monitored. In

the absence of initial intravenous access, an inhalation induction can be accomplished safely, with conversion to, or supplementation with, intravenous agents that decrease cerebral metabolic rate and cerebral blood flow as soon as the child is anesthetized sufficiently to allow insertion of an intravenous cannula.

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) was introduced in the 1930s as a treatment for schizophrenia. [181] Although use of this therapy declined through the 1970s because of negative publicity, interest in and use of ECT increased through the 1980s and 1990s. Current acceptance of this procedure is in part due to the use of general anesthesia to reduce the physical and psychologic trauma associated with ECT.

ECT consists of programmed electrical stimulation of the central nervous system to initiate seizure activity. The precise mechanism of therapeutic effect of ECT remains unknown, despite increasing research into this area. The electrical stimulus results in generalized tonic activity for approximately 10 seconds, followed by generalized clonic activity for a variable period ranging from a few seconds to more than 1 minute. It has been generally believed that overall seizure duration is a primary determinant of treatment efficacy, but this view is changing. [182] [183] [184] However, seizure durations of less than 25 seconds are believed to be ineffective. Seizure duration depends on many factors, including patient age, energy of stimulus delivered, electrode placement, seizure threshold, and medications administered, including anesthetics. [185] [186] Electrodes may be placed bilaterally or unilaterally. Bilateral placement is more effective, but it results in greater cognitive side effects. [187] The seizure threshold varies among patients, and the initial ECT treatment may require several stimulations as the stimulus energy is titrated upward to a point where the energy delivered is higher than the patient's seizure threshold. Excessive energy delivery increases cognitive side effects of the treatment. ECT is administered as a series of treatments, usually two to three times per week initially, and continued until the patient improves or the treatment is deemed ineffective. Some patients may benefit from "maintenance" ECT delivered every several weeks, especially if their psychiatric disorder is severe or if they have a history of relapse. [188]

Indications and Contraindications

Indications for ECT include severe major depression (especially patients with delusions and psychomotor retardation), acute schizophrenia, acute mania, and catatonia. [189] ECT is the treatment of choice in those patients requiring a rapid response to treatment, such as patients with catatonia or who are clearly suicidal. Pheochromocytoma is a contraindication to ECT. Relative contraindications include increased intracranial pressure, recent cerebrovascular accident, cardiovascular conduction defects, high-risk preg-nancy, and aortic and cerebral aneurysms. [181] [190] In these conditions, the risk of the patient's psychiatric illness and side effects of antidepressant medications must be weighed against the risk from ECT and anesthesia.

Physiologic Effects

Seizure activity causes initial parasympathetic discharge, manifested by bradycardia, occasional asystole, and/or premature atrial and ventricular contractions. Hypotension and salivation may be noted. The parasympathetic discharge is followed by sympathetic discharge, associated with tachycardia, hypertension, premature ventricular contractions, and rarely ventricular tachycardia. The tachycardia peaks at 2 minutes after stimulus and is normally self-limited. [191] [192] ECG changes including ST-segment depression and T-wave inversion may also be seen following ECT, without myocardial enzyme changes consistent with myocardial infarction. These ECG changes are presumed to be secondary to the sympathetic discharge. [193] [194] ECT has been found to be relatively safe even in high-risk cardiac patients, provided careful management is provided. [195] [196]

Neurologic side effects noted frequently include headache, confusion, agitation following ECT, and cognitive impairment, which is generally transient. [183] [197] [198] [199] Cerebrovascular changes include initial increases in cerebrovascular resistance followed immediately by increased cerebral blood flow and cerebral metabolic rate. This situation can be problematic in patients with increased intracranial pressure or intracranial mass lesions, and caution must be exercised in these cases, although successful treatment with ECT has been reported in such patients. [200] [201] [202] The electroencephalogram demonstrates seizure activity, which is generally more prolonged than the peripheral clonic activity. Following the treatment, electroencephalographic depression is noted. [181]

Neuroendocrine responses to ECT include increased levels of stress hormones, including adrenocorticotropic hormone, cortisol, and arginine vasopressin, and of prolactin and growth hormone. [181] [203] Norepinephrine and epinephrine increase immediately after ECT, and epinephrine levels decrease more rapidly thereafter. Glucose homeostasis may be variably affected by ECT. Improvement is generally noted in control of non-insulin-dependent diabetes, whereas hyperglycemia may be seen when diabetes is insulin dependent. A single report noted hyperglycemia in a patient with no prior history of diabetes. [204]

Antidepressant Drug Therapy

Most patients presenting for ECT are receiving tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), and/or lithium carbonate. Tricyclic antidepressants block the reuptake of norepinephrine, serotonin, and dopamine into presynaptic nerve terminals, thus increasing central sympathetic tone. [205] [206] Tricyclic antidepressants have antihistamine, anticholinergic, and sedative properties and also slow cardiac conduction. [207] These side effects are less common with newer types of antidepressant agents such as trazodone, bupropion, and fluoxetine. [207] Combination of centrally acting anticholinergics, such as atropine, with tricyclic antidepressants can increase postprocedural delirium. [208]

Clinical use of MAOI is increasing. These drugs inhibit monoamine oxidase by irreversibly combining with it to form a stable complex, thus blocking the metabolism of norepinephrine, serotonin, and dopamine. Use of indirectly acting

sympathomimetics in patients receiving MAOI can result in hypertensive crises. [205] [206] An exaggerated response to direct-acting sympathomimetics may also be seen. Hypotension in these patients should be treated with reduced doses of direct-acting sympathomimetic agents. MAOI can inhibit hepatic microsomal enzymes. MAOI may interact with opioid analgesics and may cause excessive depression. Used concomitantly with meperidine, MAOI may result in severe, possibly fatal, excitatory phenomena. [209]

Lithium carbonate prolongs the action of neuromuscular blocking agents. [210] Elevated lithium levels, higher than the therapeutic range, can prolong the action of benzodiazepines and barbiturates. Patients receiving lithium may demonstrate more cognitive side effects following ECT.

Anesthetic Technique

Anesthesia and neuromuscular blockade are necessary during ECT to prevent psychologic and physical trauma. Rapid recovery is desirable. Careful preoperative evaluation is necessary, with particular attention paid to coexisting neurologic and cardiac disease, osteoporosis and other causes of bone fragility, and medications the patient may be receiving. The patient may be a poor historian because of the psychiatric condition, and accompanying caregivers may provide necessary history and assurance of fasting status. Standard monitors include ECG, noninvasive blood pressure measurement, and pulse oximetry. Pretreatment with glycopyrrolate,

which does not cross the blood-brain barrier, can reduce the occurrence of bradycardia and the amount of oral secretions associated with ECT, as discussed later. Following preoxygenation, anesthesia is administered via peripheral intravenous catheter, and neuromuscular blockade is induced. When relaxation is adequate and satisfactory mask ventilation with oxygen is ensured, a bite block is placed, and the stimulus is delivered to induce the seizure. If the patient has a hiatal hernia and gastroesophageal reflux, rapid sequence induction and endotracheal intubation with cricoid pressure may be a reasonable approach. Adequate ventilation is ensured during the procedure because, among other detrimental effects, hypoxia and hypercarbia decrease seizure duration. [211] [212] The peripheral seizure is monitored by electromyogram, and the central seizure is monitored by electroencephalogram. It must be remembered that central seizure duration may outlast peripheral clonic manifestations. A blood pressure cuff inflated on the leg to isolate the limb prior to neuromuscular block administration can assist in monitoring of peripheral seizure. If this is the initial ECT treatment, more than one stimulus may be necessary, and additional anesthesia and/or neuromuscular blockade may need to be administered. Following the procedure, ventilation with oxygen via mask is continued until the patient awakens and is breathing adequately. During this time, tachycardia and hypertension, if persistent and/or of hazardous magnitude, may require treatment. The patient is monitored (ECG, pulse oximetry, and blood pressure) in the recovery area following the procedure until routine discharge criteria are met. Some patients demonstrate significant oxygen desaturation following ECT, and we routinely administer oxygen by nasal cannula until the patient is fully awake. [213]

Certain intravenous anesthetic agents have been used to induce anesthesia for ECT, including methohexital, thiopental, propofol, and ketamine. Propofol was found to reduce seizure duration, and this was believed to decrease the efficacy of ECT. However, more recent studies demonstrated no difference in outcome when propofol was compared with methohexital. [214] [215] [216] Methohexital, as well as propofol, administration is associated with pain on injection, which may be poorly tolerated by psychiatrically fragile patients. Use of thiopental avoids pain on injection, but it is associated with more hypertension and tachycardia than propofol. [217] Etomidate may prolong seizures and recovery. [218] Benzodiazepines result in undesirably short seizure duration. [219] Ketamine has been demonstrated not to increase seizure length or to produce excessive postprocedural agitation. [220]

Complete neuromuscular blockade is not necessary for ECT and may not be desirable because monitoring of peripheral seizure duration would be impeded. Partial neuromuscular blockade is necessary, however, to reduce the peripheral manifestations of the seizure and to prevent trauma to the patient. Succinylcholine has been used most frequently for neuromuscular blockade during ECT, because of its short duration of action and low frequency of side effects. An initial dose of 0.5 mg/kg is administered and is adjusted for subsequent treatments based on the patient's response. Mivacurium has been suggested as an alternative to succinylcholine, but it may not be as effective as succinylcholine at preventing tonic-clonic muscle contractions, which could result in traumatic injury to the patient. [221] [222] Mivacurium also necessitates prolonged postprocedural ventilatory support, thus increasing anesthetic requirements. [223] Both succinylcholine and mivacurium are metabolized by plasma cholinesterase, and alternative nondepolarizing muscle relaxants may need to be used for patients with plasma cholinesterase deficiency. Prolonged neuromuscular blockade may need to be accepted in such patients in order to avoid trauma from the seizure.

Prophylactic medications have been advocated to avoid various side effects of ECT. Transient asystole is rare during ECT, but it may be prevented with anticholinergic pretreatment. Glycopyrrolate is preferred to atropine because glycopyrrolate has no central anticholinergic side effects. In addition, glycopyrrolate is an effective antisialagogue. Both esmolol and labetalol have been successfully used to control hypertension and tachycardia following ECT. [224] There is some evidence that esmolol reduces seizure duration. [225] [226] Routine treatment with esmolol or labetalol is not recommended because the hypertension and tachycardia are usually self-limited, as are premature ventricular contractions.

Anesthetics and neuromuscular blocking agents administered to each patient should, as in other anesthetic cases, be accurately recorded. This is especially important with ECT, because the treatment is repeated over several weeks to months, and consistent patient conditions must be provided for predictable ECT stimulus response. In addition, patients' responses, such as development of arrhythmias or agitation, to previous treatment and additional medications, such as beta-antagonists or benzodiazepines, that were required should be noted, so that additional precautions can be taken at subsequent treatments. Proper anesthetic care allows for safe administration of ECT in patients with multiple

coexisting medical complaints, even in very elderly patients. [227]

References

1. Eichhorn JH, Cooper JB, Cullen DJ et al: Standards for patient monitoring during anesthesia at Harvard Medical School. JAMA 256:1017, 1986.

2. Eichhorn JH, Cooper JB, Cullen DJ et al: Anesthesia practice standards at Harvard: A review. J Clin Anesth 1:55, 1988.

3. Guidelines of the American Society of Anesthesiologists: Directory of Members, American Society of Anesthesiologists. Park Ridge, Ill, American Society of Anesthesiologists, 1997, p 404.

4. Guidelines of the American Society of Anesthesiologists: Directory of Members, American Society of Anesthesiologists. Park Ridge, Ill, American Society of Anesthesiologists, 1997, p 394.

5. Council on Scientific Affairs, American Medical Association: The use of pulse oximetry during conscious sedation. JAMA 270:1463, 1993.

6. Gallagher TJ: Anesthesia outside the operating room. Adv Anaesth 4:25, 1987.

7. Forestner JE: Anesthesia for radiologic procedures. In Murphy C, Murphy M (eds): Radiology for Anesthesia and Critical Care. New York, Churchill Livingstone, 1987, p 239.

8. Greenberg DJ, Romanoff ME: Anesthesia outside of the operating room. p 302. In Kirby RR, Brown DL (eds): Problems in anesthesia, vol 6, no. 3. Philadelphia, JB Lippincott, 1992, p 302.

9. Forbes RB: Anesthesia for nonsurgical procedures. In Longnecker DE, Tinker JH, Morgan GE (eds): Principles and Practice of Anesthesiology. St. Louis, CV Mosby, 1998, p 2288.

10. ASA: Position on monitored anesthesia care. In Directory of Members, American Society of Anesthesiologists, Park Ridge, Ill, American Society of Anesthesiologists, 1997, p 413.

11. Jacobs JR, Reves JG, Marty J et al: Aging increases pharmacodynamic sensitivity to hypnotic effects of midazolam. Anesth Analg 80:143, 1995.

12. Alexander C, Teller L, Gross J: Slow injection does not preclude midazolam induced ventilatory depression. Anesth Analg 74:260, 1992.

13. Stanley TH, Philbin DM, Coggins CH: Fentanyl-oxygen anesthesia for coronary artery surgery: Cardiovascular and antidiuretic hormone responses. Can Anaesth Soc J 26:168, 1979.

14. Reves JG, Kissin I, Fournier SE et al: Additive negative inotropic effect of a combination of diazepam and fentanyl. Anesth Analg 63:97, 1984.

15. Keats AS: The effect of drugs on respiration in man. Annu Rev Pharmacol Toxicol 25:41, 1985.

16. American Society of Anesthesiologist's Task Force on Sedation and Analgesia by Non-Anesthesiologists: Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 84:459, 1996.

17. Holzmann RS: Anesthesia and sedation for procedures outside the operating room. In Motoyama EK, Davis PJ (eds): Smith's Anesthesia for Infants and Children, 6th ed. St. Louis, CV Mosby 1996, p 695.

18. Idvall J, Holasek J, Stenberg P: Rectal ketamine for induction of anaesthesia in children. Anaesthesia 38:60, 1983.

19. Tobias JD, Phipps S, Smith B: Oral ketamine premedication to alleviate the distress of invasive procedures in pediatric oncology patients. Pediatrics 90:537, 1992.

20. Petros AJ: Oral ketamine. Its use for mentally retarded adults requiring day care dental treatment. Anaesthesia 46:646, 1991.

21. Vangerven M, Van Hemelrijck J, Wouters P et al: Light anesthesia with propofol for pediatric MRI. Anaesthesia 47:706, 1992.

22. Levati A, Colombo, N, Arosio EM et al: Propofol anaesthesia in spontaneously breathing paediatric patients during magnetic resonance imaging. Acta Anaesthesiol Scand 40:561, 1996.

23. Martin LD, Pasternak LR, Pudimat MA: Total intravenous anesthesia with propofol in pediatric patients outside the operating room. Anesth Analg 74:609, 1992.

24. Deer R, Rich GF: Propofol tolerance in a pediatric patient. Anesthesiology 77:828, 1992.

25. Byer DE, Gould AB: Development of tolerance to ketamine in an infant undergoing repeated anesthesia. Anesthesiology 54:255, 1981.

26. Glasier CM, Stark JE, Brown R et al: Rectal thiopental sodium for sedation of pediatric patients undergoing MR and other imaging studies. Am J Neuroradiol 16:111, 1995.

27. Hinkle JA, Weinlander CM: Rectal mucosal injury after rectal premedication with methohexital (abstract). Anesthesiology 61:A436, 1984.

28. Morris RW, Buschman A, Warren DL et al: The prevalence of hypoxemia detected by pulse oximetry during recovery from anesthesia. J Clin Monit 4:16, 1988.

29. Patel R, Norden J, Hannallah RS: Oxygen administration prevents hypoxemia during post-anesthetic transport in children. Anesthesiology 69:616, 1988.

30. Soliman IE, Patel RI, Ehrenpress MD et al: Recovery scores do not correlate with postoperative hypoxemia in children. Anesth Analg 67:53, 1988.

31. Murray RS, Raemer DB, Morris RW: Supplemental oxygen after ambulatory surgical procedures. Anesth Analg 67:967, 1988.

32. Bailey P, Pace N, Ashbury M et al: Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 73:826, 1990.

33. Reading CC: Ultrasound-guided percutaneous ethanol ablation of solid and cystic masses of the liver, kidney, thyroid and parathyroid. Ultrasound Q 12:67, 1994.

34. Nichols DA, Meyer FB, Piepgras DG et al: Endovascular treatment of intracranial aneurysms. Mayo Clin Proc 69:272, 1994.

35. McGowan C, Heaton B, Stephenson RN: Occupational x-ray exposure of anaesthetists. Br J Anaesth 76:868, 1996.

36. National Council on Radiation Protection and Measurements: Limitations of exposure to ionizing radiation. Report 116. Washington, DC, National Council on Radiation Protection and

Measurements, 1993.

37. Joint Commission on Accreditation of Healthcare Organizations (JCAHO): Accreditation Manual for Hospitals. Oak Brook, Ill, JCAHO, 1993, p 165.

38. Joint Commission on Accreditation of Healthcare Organizations: Accreditation Manual for Hospitals. Oak Brook, Ill, JCAHO, 1991, p 269.

39. Committee on Drugs, Section on Anesthesiology: Guidelines for the effective use of conscious sedation, deep sedation, and general anesthesia in pediatric patients. Pediatrics 76:317, 1985.

40. Keeter S, Benator RM, Weinberg SM et al: Sedation in pediatric CT: National survey of current practice. Radiology 175:745, 1990.

41. Mueller PR, Wittenberg KH, Kaufman JA et al: Patterns of anesthesia and nursing care for interventional radiology procedures: A national survey of physician practices and preferences. Radiology 202:339, 1997.

42. Bloomfield EL, Masaryk TJ, Caplin A et al: Intravenous sedation for MR imaging of the brain and spine in children: Pentobarbital versus propofol. Radiology 186:93, 1993.

43. Cauldwell CB, Fisher DM: Sedating pediatric patients: Is propofol a panacea? Radiology 186:9, 1993.

44. Holzman RS, Cullen DJ, Eichhorn JH et al: Guidelines for sedation by nonanesthesiologists during diagnostic and therapeutic procedures. J Clin Anesth 6:265, 1994.

45. American Academy of Pediatrics Committee on Drugs: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 89:1110, 1992.

46. Goldberg M: Systemic reactions to intravascular contrast media. Anesthesiology 60:46, 1984.

47. Dukes MNG: Radiological contrast media and radiopharmaceuticals. In Dukes MNG (ed): Meyler's Side Effects of Drugs, vol 13. New York, Elsevier, 1996, p 1382.

48. Thomsen HS, Dorph S: High-osmolar and low-osmolar contrast media: An update on frequency of adverse drug reactions. Acta Radiol 34:205, 1993.

49. Siegle RL: Rates of idiosyncratic reactions: Ionic versus nonionic contrast media. Invest Radiol 28:S95, 1993.

50. Bettman MA: Contrast agent use, regulation and adverse events: Safety and efficacy of iodinated contrast agents. Invest Radiol 29(suppl 1):S33, 1994.

51. McClennan BL: Adverse reactions to iodinated contrast media: Recognition and response. Invest Radiol 29(suppl 1):46, 1994.

52. Goldfarb S, Spinler S, Berns JS et al: Low-osmolality contrast media and the risk of contrast-associated nephrotoxicity. Invest Radiol 28(suppl 5):S7 (discussion S11), 1993.

53. Sirtori GR, Pasik C: Re-evaluation of a biquanide, metformin: Mechanisms of action and tolerability. Pharmacol Res 30:187, 1994.

54. Marshall Jr GD, Lieberman PL: Comparison of three pretreatment protocols to prevent anaphylactoid reactions to radiocontrast media. Ann Allergy 67:70, 1991.

55. Almen T: The etiology of contrast medium reactions. Invest Radiol 29(suppl 1):S37, 1994.

56. Menon DK, Peden CJ, Hall AS et al: Magnetic resonance for the anaesthetist. Part I: Physical principles, applications, safety aspects. Anaesthesia 47:240, 1992.

57. Gadian DG: Nuclear magnetic resonance theory. In Nuclear Magnetic Resonance and Its Applications to Living Systems. Oxford, Clarendon, 1982, p 143.

58. Council on Scientific Affairs: Fundamentals of magnetic resonance imaging. JAMA 258:3417, 1987.

59. Consensus Conference: Magnetic resonance imaging. JAMA 14:2132, 1986.

60. Kanal E, Shellock FG, Talagala L: Safety considerations in MR imaging. Radiology 76:593, 1990.

61. Shellock FG, Curtis JS: MR imaging and biomedical implants, materials and devices: An updated review. Radiology 180:541, 1991.

62. Shellock FG, Morisoli S, Kanal E: MR procedures and biomedical implants, materials, and devices: 1993 update. Radiology 189:587, 1993.

63. Elster AD, Link KM, Carr JJ: Patient screening prior to MR imaging: A practical approach synthesized from protocols at 15 U.S. medical centers. AJR Am J Roentgenol 162:195, 1994.

64. Peden CJ, Menon DK, Hall AS et al: Magnetic resonance for the anaesthetist. Part II: Anaesthesia and monitoring in the MR units. Anaesthesia 47:508, 1992.

65. Karlik SJ, Heatherley T, Pavan F et al: Patient anesthesia and monitoring at a 1.5-T MRI installation. Magn Reson Med 7:210, 1988.

66. Holshouser BA, Hinshaw DB Jr, Shellock FG: Sedation, anesthesia, and physiologic monitoring during MR imaging: Evaluation of procedures and equipment. J Magn Reson Imaging 3:553, 1993.

67. Patteson SK, Chesney JT: Anesthetic management for magnetic resonance imaging: Problems and solutions. Anesth Analg 74:121, 1992.

68. Rao CC, Krishna G: Anaesthetic considerations for magnetic resonance imaging. Ann Acad Med Singapore 23:531, July, 1994.

69. Zorab JSM: A general anaesthesia service for magnetic resonance imaging. Eur J Anaesthesiol 12:387, 1995.

70. Kross J, Drummond JC: Successful use of a Fortec II vaporizer in the MRI suite: A case report with observations regarding magnetic field-induced vaporizer aberrancy. Can J Anaesth 38:1065, 1991.

71. Jorgensen NH, Messick JM Jr, Gray J: ASA monitoring standards and magnetic resonance imaging. Anesth Analg 79:1141, 1979.

72. Livraghi T, Giorgio A, Marin G et al: Hepatocellular carcinoma and cirrhosis in 746 patients: Long-term results of percutaneous ethanol injection. Radiology 197:101, 1995.

73. Shiina S, Niwa Y, Omata M: Percutaneous ethanol injection therapy for liver neoplasms. Semin Intervent Radiol 10:57, 1993.

74. Livraghi T, Solbiati L: Percutaneous ethanol injection in liver cancer: Method and results. Semin Intervent Radiol 10:69, 1993.

75. Livraghi T, Lazzaroni S, Pellicano S et al: Percutaneous ethanol injection of hepatic tumors: Single-session therapy with general anesthesia. AJR Am J Roentgenol 161:1065, 1993.

76. Giorgio A, Tarantino L, Francica G et al: One-shot percutaneous ethanol injection of liver tumors under general anesthesia: Preliminary data on efficacy and complications. Cardiovasc Intervent Radiol 19:27, 1996.

77. Gelczer RK, Charboneau JW, Hussain S et al: Complications of percutaneous ethanol ablation: A report of 2 cases. J Ultrasound Med 17:531, 1998.

78. Lee MJ, Mueller PR, Dawson SL et al: Percutaneous ethanol injection for the treatment of hepatic tumors: Indications, mechanism of action, technique, and efficacy. AJR Am J Roentgenol

164:215, 1995.

79. Charboneau JW: Image-guided liver tumor ablation: Freeze it, fry it, inject it, or forget it. Radiology grand rounds, Brigham & Womens Hospital, Boston, MA, April 14, 1998.

80. Wiersema MJ, Wiersema LM: Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc 44:656, 1996.

81. Caratozzolo M, Lirici MM, Consalvo M et al: Ultrasound-guided alcoholization of celiac plexus for pain control in oncology. Surg Endosc 11:239, 1997.

82. Barnwell SL: Interventional neuroradiology. West J Med 158:162, 1993.

83. Martin NA: Neurosurgery and interventional neuroradiology. In Vinuel FF, Halbach VV, Dion JD (eds): Interventional Neuroradiology: Endovascular Therapy of the Central Nervous System. New York, Raven Press, 1992, p 193.

84. Setton A, Berenstein A: Interventional neuroradiology. Curr Opin Neurol Neurosurg 5:870, 1992.

85. Brown MM: Surgery, angioplasty, and interventional neuroradiology. Curr Opin Neurol Neurosurg 6:66, 1993.

86. Hopkins LN: Endovascular approach: Role of neurosurgery. Semin Intervent Radiol 10:189, 1993.

87. Halbach VV, Higashida RT, Hieshima GB: Interventional neuroradiology. AJR Am J Roentgenol 153:467, 1989.

88. Eskridge JM: Interventional neuroradiology. Radiology 172:991, 1989.

89. Luessenhop AJ: Interventional neuroradiology: A neurosurgeon's perspective. Am J Neuroradiol 11:625, 1990.

90. Berenstein A, Kricheff II: Catheter and material selection for transarterial embolization: Technical considerations. Radiology 132:619, 1979.

91. Berenstein A, Ransohoff J, Kupersmith M et al: Transvascular treatment of giant aneurysms of the cavernous carotid and vertebral arteries: Functional investigation and embolization. Surg Neurol 21:3, 1984.

92. Vasquez Anon V, Aymard A, Gobin YP et al: Balloon occlusion of the internal carotid artery in 40 cases of giant intracavernous aneurysm: Technical aspects, cerebral monitoring, and results. Neuroradiology 34:245, 1992.

93. Debrun GM, Vinuela F, Fox AJ et al: Indications for treatment and classification of 132 carotid-cavernous fistulas. Neurosurgery 22:285, 1988.

94. Horton JA, Latchaw RE, Gold LHA et al: Embolization of intramedullary arteriovenous malformations of the spinal cord. Am J Neuroradiol 7:113, 1986.

95. Kaku Y, Yonekawa Y, Tsukahara T et al: Superselective intra-arterial infusion of papaverine for the treatment of cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg 77:842, 1992.

96. Kassell NF, Helm G, Simmons N et al: Treatment of cerebral vasospasm with intra-arterial papaverine. J Neurosurg 77:848, 1992.

97. Del Zoppo GJ, Ferbert A, Otis S et al: Local intra-arterial fibrinolytic therapy in acute carotid territory stroke: A pilot study. Stroke 19:307, 1988.

98. Wardlaw JM, Warlow CP: Thrombolysis in acute ischemic stroke: Does it work? Stroke 23:1826, 1992.

99. Newell DW, Eskridge JM, Mayberg MR et al: Angioplasty for the treatment of symptomatic vasospasm following subarachnoid hemorrhage. J Neurosurg 71:654, 1989.

100. Young WL, Pile-Spellman J: Anesthetic considerations for interventional neuroradiology. Anesthesiology 80:427, 1994.

101. O'Mahony BJ, Bolsin SNC: Anaesthesia for closed embolisation of cerebral arteriovenous malformations. Anaesth Intensive Care 16:318, 1988.

102. Manninen PH, Gignac EM, Gelb AW et al: Anesthesia for interventional neuroradiology. J Clin Anesth 7:448, 1995.

103. Osborn AG: Technical aspects of cerebral angiography. In Introduction to Cerebral Angiography. Philadelphia, Harper & Rowe, 1980, pp 1-31.

104. Weinstein MA, Modic MT, Furlan AJ et al: Digital subtraction angiography. In Wilkins RH, Rengashary SS (eds): Neurosurgery, vol 1: San Francisco, McGraw Hill, 1985, p 280-288.

105. Guglielmi G, Vinuela F, Dion J et al: Electrothrombosis of saccular aneurysms via endovascular approach. J Neurosurg 75:8, 1991.

106. Purdy PD, Batjer HH, Risser RC et al: Embolic materials to enhance arteriovenous malformation of the brain: Choosing embolic materials to enhance safety and ease of excision. J Neurosurg 77:217, 1992.

107. Guglielmi G, Vinuela F, Duckwiler G et al: Endovascular treatment of posterior circulation aneurysms by electrothrombosis using electrically detachable coils. J Neurosurg 77:515, 1992.

108. Purdy PD, Batjer HH, Samson D et al: Intraarterial sodium amytal administration to guide preoperative embolization of cerebral arteriovenous malformations. J Neurosurg Anesth 3:103, 1991.

109. Rauch RA, Vinuela F, Dion J et al: Preembolization functional evaluation in brain arteriovenous malformations: The ability of superselective amytal test to predict neurologic dysfunction before embolization. Am J Neuroradiol 13:309, 1992.

110. Wada J, Rasmussen T: Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. J Neurosurg 17:266, 1960.

111. Deveikis JP: Sequential injections of amobarbital sodium and lidocaine for provocative neurologic testing in the external carotid circulation. Am J Neuroradiol 17:1143, 1996.

112. Doppman JL, Girton M, Oldfield EH: Spinal Wada test. Radiology 161:319, 1986.

113. Purdy PD, Batjer HH, Samson D: Management of hemorrhagic complications from preoperative embolization of arteriovenous malformations. J Neurosurg 74:205, 1991.

114. Judkins MP: Selective coronary arteriography. Part 1. A percutaneous transfemoral technique. Radiology 89:815, 1967.

115. Kimmel SE, Berlin JA, Hennessy S et al: Risk of major complications from coronary angioplasty performed immediately after diagnostic coronary angiography: Results from the Registry of the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol 30:193, 1997.

116. Kennedy JW, Chairman, and the Registry Committee of the Society for Cardiac Angiography: Complications associated with cardiac catheterization and angiography. Cathet Cardiovasc Diagn 8:5, 1982.

117. Kiemeneij F, Laarman GJ, Odekerken D et al: A randomized comparison of percutaneous transluminal angioplasty by the radial, brachial, and femoral approaches: The access study. J Am Coll Cardiol 29:1269, 1997.

118. Vlietstra RE, Holmes DR, Smith HC, et al: Percutaneous Transluminal Coronary Angioplasty: Initial Mayo Clinic experience. Mayo Clin Proc 56:287, 1981.

119. Holmes DR Jr, Garratt KN, Isner JM et al: Effect of subintimal resection on initial outcome and restenosis for native coronary lesions and saphenous vein graft disease treated by directional

coronary atherectomy: A report from the CAVEAT I and II investigators. Coronary Angioplasty Versus Excisional Atherectomy Trial. J Am Coll Cardiol 28:645, 1996.

120. Neuhaus KL, Zeymer U: Prevention and management of thrombotic complications during coronary interventions. Combination therapy with antithrombins, antiplatelets, and/or thrombolytics: Risks and benefits. Eur Heart J 16(suppl L):63, 1995.

121. The EPILOG investigators: Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 336:1689, 1997.

122. Califf RM, Lincoff AM, Tcheng JE: An overview of the results of the EPIC trial. Eur Heart J 16(suppl L):43, 1995.

123. Adgey AA: Bleeding complications with new antithrombotics used in ischaemic heart disease. Haemostasis 26:237, 1996.

124. Heikkinen L, Virtanen K, Heikkila J et al: Surgical treatment of acute myocardial ischaemia related to coronary angioplasty with special reference to use of perfusion balloon catheter and long-term outcome. J Cardiovasc Surg 38:101, 1997.

125. Berger PB, Stensrud PE, Daly RC et al: Time to reperfusion and other procedural characteristics of emergency coronary artery bypass surgery after unsuccessful coronary angioplasty. Am J Cardiol 76:565, 1995.

126. Meurice T, Vallet B, Bauters C et al: Role of endothelial cells in restenosis after coronary angioplasty. Fundam Clin Pharmacol 10:234, 1996.

127. Umans VA, Melkert R, Foley DP et al: Clinical and angiographic comparison of matched patients with successful directional coronary atherectomy or stent implantation for primary coronary artery lesions. J Am Coll Cardiol 28:637, 1996.

128. Hasdai D, Berger PB, Bell MR et al: The changing face of coronary interventional practice: The Mayo Clinic experience. Arch Intern Med 157:677, 1997.

129. Lange RA, Hillis LD: Immediate angioplasty for acute myocardial infarction (editorial). N Engl J Med 328:726, 1993.

130. Gibbons RJ, Holmes DR Jr, Reeder GS et al: Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 328:685, 1993.

131. de-Bruijn NP, Hlatky MA, Jacobs JR et al: General anesthesia during percutaneous transluminal coronary angioplasty for acute mocardial infarction: Results of a randomized controlled clinical trial. Anesth Analg 68:201, 1989.

132. Shawl FA, Baxley WA: Role of percutaneous cardiopulmonary bypass and other support devices in interventional cardiology. Cardiol Clin 12:543, 1994.

133. D'Orsogna L, Sandor GGS, Patterson MWH et al: Influence of echocardiography in preoperative cardiac catheterization in congenital heart disease. Int J Cardiol 24:19, 1989.

134. Manners JM, Codman VA: General anesthesia for cardiac catheterization in children: The effect of spontaneous or controlled ventilation on the evaluation of congenital abnormalities. Anaesthesia 24:541, 1969.

135. Korten K: Anesthesia for diagnostic procedures. Am Fam Physician 15:103, 1977.

136. Manners JM: Anaesthesia for diagnostic procedures in cardiac disease. Br J Anaesth 43:276, 1971.

137. Berman W Jr, Fripp RR, Rubler M et al: Hemodynamic effects of ketamine in children undergoing cardiac catheterization. Pediatr Cardiol 11:72, 1990.

138. Reich DL, Silvay G: Ketamine: An update on the first 25 years of clinical experience. Can J Anaesth 36:186, 1989.

139. Coppel DL, Dundee JW: Ketamine anaesthesia for cardiac catheterization. Anaesthesia 27:25, 1972.

140. Faithfull NS, Haider R: Ketamine for cardiac catheterization: An evaluation of its use in children. Anaesthesia 26:318, 1971.

141. Lebovic S, Reich DL, Steinberg LG et al: Comparison of propofol versus ketamine in pediatric patients undergoing cardiac catheterization. Anesth Analg 74:490, 1992.

142. Rautiainen P: Alfentanil infusion for sedation in infants and small children during cardiac catheterization. Can J Anaesth 38:980, 1991.

143. Meretoja OA, Rautiainen P: Alfentanil and fentanyl sedation in infants and small children during cardiac catheterization. Can J Anaesth 37:624, 1990.

144. Stanger P, Heymann MA, Tarnoff H et al: Complications of cardiac catheterization of neonates, infants, and children: A three-year study. Circulation 50:595, 1974.

145. Kan JS, White RI Jr, Mitchell SE et al: Percutaneous balloon valvuloplasty: A new method for treating congenital pulmonary-valve stenosis. N Engl J Med 307:540, 1982.

146. Balloon valvuloplasty. Mayo Clinic Update 3:1, 1987.

147. Cribier A, Savin T, Saoudi N, et al: Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: An alternative to valve replacement? Lancet 1:63, 1986.

148. Hammill SC, Sugrue DD, Gersh BJ et al: Clinical intracardiac electrophysiologic testing: Technique, diagnostic indications, and therapeutic uses. Mayo Clin Proc 61:478, 1986.

149. Davis J, Scheinman MM, Ruder MA et al: Ablation of cardiac tissues by an electrode catheter technique for treatment of ectopic supraventricular tachycardia in adults. Circulation 74:1044, 1986.

150. Lavoie J, Walsh EP, Burrows FA et al: Effects of propofol or isoflurane anesthesia on cardiac conduction in children undergoing radiofrequency catheter ablation for tachydysrhythmias. Anesthesiology 82:884, 1995.

151. Sharpe MD, Dobkowski WB, Murkin JM et al: Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction in Wolff-Parkinson-White syndrome during alfentanil/midazolam anesthesia. Anesthesiology 82:888, 1995.

152. Sternlo JE, Hagerdal M: Anaesthesia for cardioversion: Clinical experience with propofol and thiopentone. Acta Anaesthesiol Scand 35:606, 1991.

153. Conessa R, Lema G, Urzua J et al: Anesthesia for elective cardioversion: A comparison of four anesthetic agents. J Cardiothorac Vasc Anesth 5:566, 1991.

154. Ford SR, Maze M, Gaba DM: A comparison of etomidate and thiopental anesthesia for cardioversion. J Cardiothorac Vasc Anesth 5:563, 1991.

155. Fennelly ME, Powell H, Galletly DC et al: Midazolam sedation reversed with flumazenil for cardioversion. Br J Anaesth 68:303, 1992.

156. Gunderson LL: Rational for and results of intraoperative radiation therapy. Cancer 74:537, 1994.

157. Ritchey ML, Gunderson LL, Smithson WA et al: Pediatric urological complications with intraoperative radiation therapy. J Urol 143:89, 1990.

158. Tepper JE, Gunderson LL, Orlow E et al: Complications of intraoperative radiation therapy. Int J Radiat Oncol Biol Phys 10:1831, 1984.

159. Suzuki K, Gunderson LL, Devine RM et al: Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. Cancer 75:939, 1995.

160. Shaw EG, Gunderson LL, Martin JK et al: Peripheral nerve and ureteral tolerance to intraoperative radiation therapy: Clinical and dose-response analysis. Radiat Oncol 18:247, 1990.

161. Gunderson LL, Nelson H, Martenson JA et al: Locally advanced primary colorectal cancer: Intraoperative electron and external beam irradiation. Int J Radiat Oncol Biol Phys 37:601, 1997.

162. Gunderson LL, Dozois RR: Intraoperative irradiation for locally advanced colorectal carcinomas. Perspect Colon Rectal Surg 5:1, 1992.

163. Gunderson LL, Martin JK, Earle JD et al: Intraoperative and external beam irradiation with or without resection: Mayo pilot experience. Mayo Clin Proc 59:691, 1984.

164. Wolff BG, Gunderson LL: Intraoperative radiation therapy for rectal carcinoma. Semin Colon Rectal Surg 1:44, 1990.

165. Tepper JE: Intraoperative radiation therapy. In Perez CA, Brady LW (eds): Principles and Practice of Radiation Oncology. Philadelphia, JB Lippincott, 1987, p 310.

166. Gunderson LL, Tepper JE, Biggs PJ et al: Intraoperative external beam irradiation. Curr Probl Cancer 7:1, 1983.

167. Gunderson LL, Willett CG, Harrison LB et al: Intraoperative irradiation: Current and future status. Semin Oncol 24:715, 1997.

168. Friesen RH, Morrison JE, Verbrugge JJ et al: Anesthesia for intraoperative radiation therapy in children. J Surg Oncol 35:96, 1987.

169. Tuckson WB, Goldson AL, Ashayeri E et al: Intraoperative radiotherapy for patients with carcinoma of the pancreas. Ann Surg 207:648, 1988.

170. Donaldson SS. Lessons from our children. Int J Radiat Biol Phys 26:739, 1993.

171. Cronin MM, Bousfield JD, Hewett EB et al: Ketamine anaesthesia for radiotherapy in small children. Anaesthesia 27:135, 1972.

172. Mitchell AA, Louik C, Lacouture P et al: Risks to children from computed tomographic scan premedication. JAMA 247:2385, 1982.

173. Wolfson B, Hetrick WD, Dastur KJ: Neuroradiologic procedures. In Newfield P, Cottrell JE (eds): Handbook of Neuroanesthesia. Boston, Little, Brown, 1983, p 390.

174. Glauber DT, Audenaert SM: Anesthesia for children undergoing craniospinal radiotherapy. Anesthesiology 67:801, 1987.

175. National Institute for Occupational Safety and Health (NIOSH). Criteria for a recommended standard: Occupational exposure to waste anesthetic gases and vapors. Pub. no. 77B140. Cincinnati, Ohio, U.S. Department of Health, Education, and Welfare, Public Health Service, Center For Disease Control, NIOSH, 1977.

176. Henneberg S, Nilsson A, Persoon MP: Anesthesia and monitoring during whole body radiation in children. J Clin Anesth 2:76, 1990.

177. Grebenik CR, Ferguson C, White A: The laryngeal mask airway in pediatric radiotherapy. Anesthesiology 72:474, 1990.

178. Schulman SR: Anesthesia for external-beam radiotherapy. In Halperin EC, Constine LS, Tarbell NJ et al (eds): Pediatric Radiation Oncology, 2nd ed. New York, Raven Press, 1994, p 576.

179. Setlock MA, Palmisano BW: Propofol for radiation therapy in small children. Anesth Analg 75:860, 1992.

180. Edge WG, Morgan M: Ketamine and paediatric radiotherapy. Anaesth Intensive Care 5:153, 1977.

181. Selvin BL: Electroconvulsive therapy: 1987. Anesthesiology 67:367, 1987.

182. Holden C: A guarded endorsement for shock therapy. Science 228:1510, 1985.

183. Sackeim HA, Prudic J, Devanand DP et al: Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 328:839, 1993.

184. Lalla FR, Milroy T: The current status of seizure duration in the practice of electroconvulsive therapy. Can J Psychiatry 41:299, 1996.

185. Swartz CM: Anesthesia for ECT. Convuls Ther 9:301, 1993.

186. Fink M: Prolonged seizures (editorial). Convuls Ther 9:87, 1993.

187. Sackeim HA, Long J, Luber B et al: Physical properties of the ECT stimulus. I. Basic principles. Convuls Ther 10:93, 1994.

188. Fink M, Abrahms R, Bailine S et al: Ambulatory electroconvulsive therapy: Report of a task force of the Association for Convulsive Therapy. Convuls Ther 12:42, 1996.

189. Potter WZ, Rudorfer MV: Electroconvulsive therapy: A modern medical procedure (editorial). N Engl J Med 328:883, 1993.

190. Walker R, Swartz CM: Electroconvulsive therapy during high-risk pregnancy. Gen Hosp Psychiatry 16:348, 1994.

191. McCall WV: Asystole in electroconvulsive therapy: Report of four cases. J Clin Psychiatry 57:199, 1996.

192. Ring BS, Parnass SM, Shulman RB et al: Cardiogenic shock after electroconvulsive therapy. Anesthesiology 84:1511, 1996.

193. Dec GW, Stern TA, Welch C: The effects of electroconvulsive therapy on serial electrocardiograms and serum cardiac enzyme values. JAMA 253:2525, 1985.

194. Cockey GH, Conti CR: Electroconvulsive therapy-induced transient T-wave inversions on ECG. Clin Cardiol 18:418, 1995.

195. Rice EH, Sombrotto LB, Markowitz JC et al: Cardiovascular morbidity in high-risk patients during ECT. Am J Psychiatry 151:1637, 1994.

196. Zielinski RJ, Roose SP, Devanand DP et al: Cardiovascular complications of ECT in depressed patients with cardiac disease. Am J Psychiatry 150:904, 1993.

197. Folkerts H: Migraine after electroconvulsive therapy. Convuls Ther 11:212, 1995.

198. Fink M: Post-ECT delirium. Convuls Ther 9:326, 1993.

199. Weiner SJ, Ward TN, Ravaris CL: Headache and electroconvulsive therapy. Headache 34:155, 1994.

200. Maltbie AA, Wingfield MS, Volow MR et al: Electroconvulsive therapy in the presence of a brain tumor: Case reports and an evaluation of risk. J Nerv Ment Dis 168:400, 1980.

201. Tsuang MT, Tidball JS, Geller D: ECT in a depressed patient with a shunt in place for normal pressure hydrocephalus. Am J Psychiatry 136:1205, 1979.

202. Husum B, Vester-Andersen T, Buchmann G et al: Electroconvulsive therapy and intracranial aneurysm: Prevention of blood pressure elevation in a normotensive patient by hydralazine and propranolol. Anaesthesia 38:1205, 1983.

203. Weinger MB, Partridge BL, Hauger R et al: Prevention of the cardiovascular and neuroendocrine response to electroconvulsive therapy. II. Effects of pretreatment regimens on catecholamines, ACTH, vasopressin, and cortisol. Anesth Analg 73:563, 1991.

204. Reddy S, Nobler MS: Dangerous hyperglycemia associated with electroconvulsive therapy. Convuls Ther 12:99, 1996.

205. Gaines GY, Rees DI: Electroconvulsive therapy and anesthetic considerations. Anesth Analg 65:1345, 1986.

206. Janowsky EC, Risch C, Janowsky DS: Effects of anesthesia on patients taking psychotropic drugs. J Clin Psychopharmacol 1:14, 1981.

207. Potter WZ, Rudorfer MV, Manji H: The pharmacologic treatment of depression. N Engl J Med 325:633, 1991.

208. Pritchett JT, Bernstein HJ, Kellner CH: Combined ECT and antidepressant drug therapy. Convuls Ther 9:256, 1993.

209. Stack CG, Rogers P, Linter SPK: Monoamine oxidase inhibitors and anaesthesia. Br J Anaesth 60:222, 1988.

210. Murkherjee S: Combined ECT and lithium therapy. Convuls Ther 9:274, 1993.

211. Chater SN, Simpson KH: Effect of passive hyperventilation on seizure duration in patients undergoing electroconvulsive therapy. Br J Anaesth 60:70, 1988.

212. Rasanen J, Martin DJ, Downs JB et al: Oxygen supplementation during electroconvulsive therapy. Br J Anaesth 61:593, 1988.

213. McCormick ASM, Saunders DA: Oxygen saturation of patients recovering from electroconvulsive therapy. Anaesthesia 51:702, 1996.

214. Malsch E, Gratz I, Mani S et al: Efficacy of electroconvulsive therapy after propofol and methohexital anesthesia. Convuls Ther 10:212, 1994.

215. Martensson B, Bartfai A, Hallen B et al: A comparison of propofol and methohexital as anesthetic agents for ECT: Effects on seizure duration, therapeutic outcome, and memory. Biol Psychiatry 35:179, 1994.

216. Fear CF, Littlejohns CS, Rouse E et al: Propofol anesthesia in electroconvulsive therapy: Reduced seizure duration may not be relevant. Br J Psychiatry 165:506, 1994.

217. Boey WK, Lai FO: Comparison of propofol and thiopentone as anaesthetic agents for electroconvulsive therapy. Anaesthesia 45:623, 1990.

218. Trzepacz PT, Weniger FC, Greenhouse J: Etomidate anesthesia increases seizure duration during ECT: A retrospective study. Gen Hosp Psychiatry 15:115, 1993.

219. Loimer N, Hofmann P, Chaudry HR: Midazolam shortens seizure duration following electroconvulsive therapy. J Psychiatr Res 26:97, 1992.

220. Rasmussen KG, Jarvis MR, Zorumski CF: Ketamine anesthesia in electroconvulsive therapy. Convuls Ther 12:217, 1996.

221. Kelly D, Brull SJ: Neuroleptic malignant syndrome and mivacurium: A safe alternative to succinylcholine? Can J Anaesth 41:845, 1994.

222. Fredman B, Smith I, d'Etienne J et al: Use of muscle relaxants for electroconvulsive therapy: How much is enough? (letter) Anesth Analg 78:190, 1994.

223. Janis K, Hess J, Fabian JA et al: Substitution of mivacurium for succinylcholine for ECT in elderly patients. Can J Anaesth 42:612, 1995.

224. Castelli I, Steiner LA, Kaufmann MA et al: Comparative effects of esmolol and labetalol to attenuate hyperdynamic states after electroconvulsive therapy. Anesth Analg 80:557, 1995.

225. Howie MB, Black HA, Zvara D et al: Esmolol reduces autonomic hypersensitivity and length of seizures induced by electroconvulsive therapy. Anesth Analg 71:384, 1990.

226. Kovac AL, Goto H, Pardo MP et al: Comparison of two esmolol bolus doses on the hemodynamic response and seizure duration during electroconvulsive therapy. Can J Anaesth 38:204, 1991.

227. Tomac TA, Rummans TA, Pileggi TS et al: Safety and efficacy of electroconvulsive therapy in patients over age 85. Am J Geriatr Psychiatry 5:126, 1997.

Chapter 67 - Clinical Care at Altered Environmental Pressure

Richard E. Moon
Enrico M. Camporesi

INTRODUCTION

The modern clinical application of hyperbaric oxygen (HBO) began in the late 1950s, in parallel with an increased understanding of blood gas analysis and gas exchange physiology. Use of O_2 at high pressure for the treatment of decompression sickness had previously been documented, [1] but it remained an isolated medical curiosity. Exposure of patients to hyperbaric pressures for therapeutic purposes had been introduced in several large facilities even decades before, following the principles elucidated by Paul Bert. These early applications, however, based on vague pathophysiologic principles, suffered from an overoptimistic view of the results. Hyperbaric spas flourished in the early 1900s on the North American continent and in Europe. Lack of a firm physiologic basis and poor choice of indications caused scientific stasis in the field for many subsequent years. [2] [3]

In the early 1960s, two institutions preeminently pursued the clinical aspects of high-pressure oxygenation. In the surgical department of the University of Amsterdam, Boerema, followed by Bakker, developed the use of intermittent HBO for the treatment of gas gangrene. The second major focus of interest in this area was the Royal Infirmary in Glasgow, where various anesthetic and surgical applications were developed (treatment of necrotizing infection, anesthesia under hyperbaric conditions). In 1968, Duke University in North Carolina expanded a long-standing program of environmental physiology with the construction of interconnected multiplace hyperbaric chambers. From the outset, this facility was intended for patient care in addition to providing an experimental facility, and various clinical protocols were developed.

Since about 1970, several large hyperbaric systems of similar nature and many more single-chamber facilities have been installed worldwide. Instructional courses are continuously organized, often under the guidance of the Undersea and Hyperbaric Medical Society (headquarters in Kensington, Md). This medical organization publishes an extensive bibliography with a list of indications for hyperbaric oxygenation, updated every 2 to 3 years. [4]

TABLE 67-1 -- Partial List of Conditions for Which Hyperbaric Oxygen Has Been Used

Gas-bubble disease
Air embolism [53] [54] [182]
Decompression sickness [53] [54]
Poisoning
Carbon monoxide [29] [33] [183]
Cyanide [29] [184]
Carbon tetrachloride [185] [186]
Hydrogen sulfide [29] [187] [188]
Infections
Clostridial myonecrosis [58] [59] [189] [190]
Other soft tissue necrotizing infections [60] [61] [190]
Refractory chronic osteomyelitis [191] [192]
Mucormycosis [193] [194]
Acute ischemia
Crush injury [195]
Compromised skin flaps [11] [12] [196] [197]
Chronic ischemia
Radiation necrosis (soft tissue, radiation cystitis, an osteoradionecrosis) [198] [199] [200] [201] [202]
Ischemic ulcers, including diabetic ulcers [203] [204]
Central nervous system edema [205]
Acute hypoxia
Support of oxygenation during therapeutic lung lavage [65] [66]
Exceptional blood-loss anemia (when transfusion delaye unavailable) [67]
Thermal injury (burns) [206] [207] [208] [209]
Brown recluse spider envenomation [210] [211]

The still limited number of facilities providing well-integrated care within medical centers may explain the varied perception among physicians of HBO as a poorly defined therapeutic modality. Nevertheless, clear evidence exists for efficacy of HBO in a variety of acute and chronic illnesses (Table 67-1) , and anesthesiologists are often called on to provide care of patients in this unusual environment.

Interest in the physiologic and medical aspects of altitude originated because of mountaineering and high-altitude balloon exploits in the 19th century. This body of knowledge has been increasingly useful, as ever-increasing numbers of people fly in aircraft, travel from low to high altitude, and live or work at higher elevations (Table 67-2) . Exposure to altitude is accompanied by well-known physiologic changes and often unique clinical syndromes. Significant effort has been devoted to techniques for prophylaxis and treatment of these illness in recent years. In addition, increasingly sensitive methods of monitoring oxygenation during anesthesia have led to the recognition that routine anesthetic care at even moderate altitudes may require some modifications in order to avoid hypoxia in normal individuals. Moreover, millions of individuals are exposed acutely to high altitude during commercial aircraft flight. The effects of the small reduction in inspired O_2 pressure (P_{O_2}) may be clinically significant for individuals with cardiorespiratory or cerebrovascular disease.

/das/book/view/29494766/875/737.html

PHYSIOLOGIC EFFECTS OF INCREASED GAS PRESSURE

Increased Barometric Pressure

Some effects of altered ambient pressure are summarized in Figure 67-1 . An increase in environmental pressure is accompanied by significant adiabatic heat production, whereas decompression generates cooling. This results in an increase in chamber temperature during compression and significant cooling and precipitation of water droplets during decompression. These phenomena may limit the rate of compression in manned chambers in order to maintain temperature within a comfortable range.

Additionally, the pockets of trapped gas within body cavities either contract or expand on compression or decompression.

TABLE 67-2 -- Range of Terrestrial Altitudes

ALTITUDE[a]		AMBIENT PRESSURE		
(ft)	*(m)*	*(ATA)*	*(mm H g)*	*COMMENTS*
		0.32	246*	Lowest pressure to which volunteers have been continuously exposed (hypobaric chamber study: Operation Everest I) [212]
29,028	8,848	0.35	263*	Mt. Everest, Nepal: highest point on earth
19,521	5,950	0.49	373*	Aucanquilcha mine, Chile: highest altitude continuously inhabited by humans [213]
14,110	4,301	0.58	444	Pike's Peak, Colorado, USA [143]
13,796	4,205	0.60	460*	Mauna Kea, Hawaii
		(0.57-0.63)	(433-479)	(Keck Observatory) [214]
11,910	3,630	0.64	485	La Paz, Bolivia
10,500	3,200	0.67	513	Alta Ski Resort, Utah, USA
10,430	3,179	0.67	511	Leadville, Colorado, USA (highest altitude incorporated city in North America; population 3,000) [215]
9,321	2,841	0.71	536	South Pole Station, Antarctica
9,249	2,819	0.71	538	Quito, Equador
7,546	2,300	0.76	574	Mexico City, Mexico
5,280	1,609	0.81	616	Denver, Colorado; Zermatt, Switzerland
4,500	1,372	0.85	644	Banff, Alberta, Canada; Kathmandu, Nepal
0	0	1.00	760	Sea level

[a] Altitudes and barometric pressures are shown for Mt. Everest and several locations inhabited at least part time. Barometric pressures have been obtained from the International Civil Aviation Organization standard atmosphere table, [216] except for values with an asterisk (*), which were obtained by direct measurement. [213]

Figure 67-1 Ambient pressure as a function of altitude and water depth. Whereas ambient pressure increases linearly with depth, pressure and altitude are not linearly related. As air is inspired and humidified, there is a small and usually insignificant drop from atmospheric P_{O_2} to inspired P_{O_2} . At altitude, however, this decrease comprises a greater proportion of the total ambient pressure. The O_2 partial pressure line in the water is shown for a constant F_{IO_2} of 21 percent. At increasing depth the inspired P_{O_2} eventually exceeds the pulmonary toxic limit (14 m depth) and the central nervous system toxic limit (70 m depth). The threshold for high-pressure nervous syndrome and pressure reversal of anesthesia (observed in nonnarcotic atmospheres) is around 150 to 200 m depth. The shaded red bars represent the depth or altitude ranges over which the risk progresses from low (light shading) to high (dark shading).

These pockets include gas in the middle ear and paranasal sinuses, intestinal gas, pneumothorax, and gas pockets within monitoring and life-support systems. The changes in gas volume occur according to Boyle's law:

such that a doubling of environmental pressure (P) causes the volume (V) of a gas-filled cavity to decrease by half. This effect also underlies one of the major beneficial effects of hyperbaric treatment of pathologic gas, as in arterial gas embolism or decompression sickness (see later). A comparison of pressure units used clinically with those in common use in hyperbaric environments is shown in Table 67-3 .

Increased Partial Pressure of Oxygen

Breathing O_2 at increased ambient pressure leads to elevation of alveolar O_2 tension (P_{AO_2}), which can be calculated according to the alveolar gas equation for O_2 :

where P_{IO_2} and F_{IO_2} are the inspired partial pressure and fractional O_2 concentration, respectively; P_{ACO_2} is alveolar P_{CO_2} , assumed to equal arterial P_{CO_2} (Pa_{CO_2}); and R is the respiratory quotient (usually 0.8). Typical values are shown in Table 67-4 . From these values of Pa_{O_2} , arterial P_{O_2} (Pa_{O_2}) has been estimated,

assuming that the arterial/alveolar P O_2 ratio remains constant. [5] Whereas at 1 atmosphere absolute (ATA) the fraction of O_2 in arterial blood that is carried dissolved in the plasma is minimal, it can be seen that at elevated Pa O_2 in the range of 1,000 to 2,000 mm Hg, significant quantities of O_2 may exist in dissolved form (Fig. 67-2)

Increased Pa O_2 has at least four pharmacologic effects: (1) increased blood O_2 content; (2) vasoconstriction; (3) antibacterial action, particularly against anaerobic bacteria; and (4) inhibition of endothelial neutrophil adhesion in injured tissue. The increased arterial O_2 content underlies the rationale for administering HBO for the treatment of ischemic conditions, for example ischemic, nonhealing wounds. The elevation in Pa O_2 leads to an increase in tissue P O_2, which can be estimated using transcutaneous P O_2 electrodes, even in ischemic tissue. [6] The second effect is an explanation for the effectiveness of HBO in the treatment of traumatic edema (e.g., crush injury). The mechanism of

TABLE 67-3 -- Units of Pressure

ATMOSPHERES ABSOLUTE (ATA)	ABSOLUTE PRESSURE (mm Hg)	GAUGE PRESSURE (mm Hg)	FEET OF SEA WATER (fsw)	METERS OF SEA WATER (msw)
1	760	0	0	0
2	1,520	760	33	10
3	2,280	1,520	66	20
6	4,560	3,800	165	50

TABLE 67-4 -- Expected[a] Gas Tensions and Arterial Blood O_2 Content at Various Ambient Pressures in a Normal Individual (Hemoglobin 14 g/dL)

PRESSURE (ATA)	Fio_2	INSPIRED Po_2 (mm Hg)	Pao_2 (mm Hg)	Pao_2 (mm Hg)	Cao_2 (TOTAL) (mL/dL)	Cao_2 (DISSOLVED) (mL/dL)	$Paco_2$ (mm Hg)
1	0.21	150	102	87	18.7	0.3	40
1	1.0	713	673	572	21.2	1.7	40
2	1.0	1,473	1,433	1,218	23.1	3.7	40
3	1.0	2,233	2,193	1,864	25.1	5.6	40

[a] Assuming constant Pa O_2 /Pa O_2 ratio [5]

Figure 67-2 Blood O_2 content versus P O_2. Virtually complete saturation of hemoglobin (Hb) with O_2 occurs at a P O_2 of 100 mm Hg. Further increases in P O_2 do not alter the quantity of O_2 bound to Hb. However, there is a linear increase in total blood O_2 content with P O_2 due to increasing quantities of O_2 dissolved in plasma.

HBO-induced vasoconstriction appears to be inactivation of nitric oxide because of increased production of superoxide [7] and possibly decreased release of nitric oxide from circulating S-nitrosohemoglobin. [7] [8]

These two effects, increased O_2 content and vasoconstriction, lead to hemodynamic changes that have been described by Whalen et al [9] and are shown in Table 67-5 . The elevation in Pa O_2 that occurs while breathing 100 percent O_2 at 3.06 ATA results in a drop in cardiac output and heart rate and an increase in total peripheral resistance. There is also a slight increase in mean arterial pressure.

The other major pharmacologic effect of increased Pa O_2 is the inhibition of toxin production and growth of certain anaerobic bacteria. Additionally, increased Pa O_2 has been shown to return phagocytic ability and the ability of aminoglycosides to kill aerobic bacteria in ischemic tissue to normal. These bacteriologic effects of HBO have been reviewed by Park et al. [10]

HBO also has some poorly characterized microcirculatory and cellular effects. Zamboni et al [11] [12] [13] have described a reduction in blood flow occurring on reperfusion of ischemic myocutaneous tissue flaps. This decrease in flow appears to be due to leukocyte adherence to the capillary endothelium mediated by leukocyte adhesion glycoprotein CD18, [14] an effect that is prevented and ameliorated by HBO treatment. [11] [12] [13] In an animal model, timely administration of HBO also appears to decrease the lipid peroxidation in the brain that occurs after treatment of carbon monoxide (CO) poisoning. [15]

Elevation of Inert Gas Partial Pressure

Elevation of the partial pressure of the inert gas (usually nitrogen) present in a breathing mixture is associated with a narcotic effect, predictable by the Meyer-Overton hypothesis. Based on its olive-oil solubility, nitrogen has approximately 0.03 to 0.05 times the narcotic potency of nitrous oxide. At 3 ATA (breathing air), most people experience mild euphoria. At 6 ATA, there may be memory loss and poor judgment. At 10 ATA, some individuals lapse into unconsciousness. Nitrogen narcosis has been compared with alcoholic intoxication, an increase in ambient pressure of 1.5 ATA resulting in an effect that is said to be similar to drinking one martini. Argon and to a lesser degree, hydrogen, are narcotic, whereas helium has minimal if any narcotic effect.

Elevation of Absolute Pressure

High-Pressure Nervous Syndrome

High pressure induces a constellation of symptoms consisting of tremor, ataxia, nausea, and vomiting, known as the high-pressure nervous syndrome. [16] It occurs at an ambient pressure greater than 15 to 20 ATA and was first described during the compression phase of deep dives with a helium-O_2 atmosphere. This syndrome is ameliorated by slow compression and addition of a narcotic gas (e.g., nitrogen) to the breathing mix. [17]

Pressure Reversal of Anesthesia

High pressure has the tendency to reverse general anesthesia. Elevations in partial pressure in the absence of a narcotic inert breathing gas tend to decrease the effectiveness of both inhaled and intravenous anesthetics. At 50 ATA, approximately a 20 percent increase in the 50 percent effective dose (ED_{50}) has been observed in mice for a variety of inhaled anesthetics. At this same ambient pressure, the effective dose of thiopental increases approximately 30 percent in rats and mice. Winter et al [18] demonstrated a reversal of phenobarbital anesthesia in rats under high pressure, with a 63 percent increase in ED_{50} at 103 ATA as compared with 1

TABLE 67-5 -- Mean Blood Acid-Base and Cardiovascular Responses to Hyperbaric Oxygenation in Ten Normal Subjects

ATMOSPHERIC PRESSSURE (ATA)	*INSPIRED GAS*	ARTERIAL BLOOD			VENOUS BLOOD[a]			CARDIAC OUTPUT (L min^{-1})	HEART RATE (min^{-1})	STROKE VOLUME (mL)	MEAN ARTERIAL PRESSURE(mm Hg)	TOTAL PERI[HERAL RESISTANCE (dyne· s· cm^{-5})
		Po_2 (mm Hg)	*pH*	*Pco_2 (mm Hg)*	*Po_2 (mm Hg)*	*pH*	*Pco_2 (mm Hg)*					
1	Air	89	7.45	37	41	7.42	41	6.1	75	81	89	1,224
1	100% O_2	507	7.46	37	57	7.42	42	5.8	71	82	90	1,280
3.06	Air	402	7.45	39	68	7.41	44	5.7	68	85	88	1,264
3.06	100% O_2	1,721	7.47	37	424	7.40	45	5.3	63	86	92	1,424

Data from Whalen et al [9]

[a] Obtained from a catheter with tip at the junction of the superior vena cava and right atrium

ATA. At 31 ATA, the effective concentration for half maximal effect (EC_{50}) of propofol for loss of righting reflex in tadpoles is increased by 19 percent and at 61 ATA, 38 percent. [19] Using the same technique, the EC_{50} for dexmedetomidine at 31 ATA is nearly double the value at 1 ATA, and it is increased 2-fold at 61 ATA. [20] This effect of pressure reversal of general anesthesia has been reviewed by Wardley-Smith and Halsey [21] and Wann and Macdonald [22] (Ch. 3) .

Effects of Hyperbaric Exposure on Drug Disposition

A few studies have examined the disposition of drugs and drug effects at increased environmental pressures. Studies in awake dogs at pressures up to 6 ATA and ambient P_{O_2} up to 2.8 ATA have shown that liver plasma flow decreased when either ambient pressure or P_{O_2} was raised. There was an apparent increase in plasma volume at 1.3 ATA and a return toward 1 ATA values at higher pressures. In the same studies, plasma volume was inconsistently affected by ambient pressure, but it was reduced by increases in P_{O_2} . [23]

Major pharmacokinetic or pharmacodynamic differences for most drugs up to pressures used for most clinical purposes (6 ATA) would not be expected. Indeed, up to 6 ATA, the pharmacokinetics of meperidine [24] and of pentobarbital [25] are unchanged under hyperbaric and hyperoxic conditions in the dog. No significant effects of hyperoxia or increased ambient pressure were demonstrated on the total plasma clearance, volume of distribution, or elimination half-life of these two drugs. Canine studies have also demonstrated no alteration in either theophylline [26] or salicylate [27] kinetics at ambient pressures to 6 ATA and inspired P_{O_2} up to 2.8 ATA.

Stoudemire et al [28] described the use of benzodiazepines, chlorpromazine, and lithium carbonate for the treatment of agitation, auditory and visual illusions, agitation, and paranoia in a previously normal subject participating in an experimental dive to 650 m (66 ATA). The symptoms, poorly controlled with diazepam 120 mg and temazepam 60 mg per day, ultimately responded to chlorpromazine 300 mg per day. Lithium carbonate subsequently administered in conventional doses appeared to display normal pharmacokinetics. Although the effect of chlorpromazine appeared clinically to be appropriate, the authors were uncertain whether the failure of benzodiazepines to elicit a desired therapeutic response was due to the diver's condition or to a pressure-reversal phenomenon. In summary, clinical experience and the published literature indicate that for a variety of drugs, conventional parenteral drug dosing schedules may be used safely under hyperbaric conditions.

RATIONALE FOR THE TREATMENT OF SPECIFIC SYNDROMES

Carbon Monoxide Poisoning

Hemoglobin (Hb) binds CO with an affinity much higher (by a factor of about 200) than that for O_2. This binding of CO with Hb to form carboxyhemoglobin (COHb) has two

TABLE 67-6 -- Carbon Monoxide Elimination Half-Times While Breathing Air or 100 Percent Oxygen at 1 and at 2.5 Atmospheres Absolute

BREATHING GAS (ATA)	MEAN HALF-LIFE (MIN)[a]	NO. SUBJECTS
Air: 1	214	10
Oxygen: 1	43	15
Oxygen: 2.5	19	10

[a] Mean values from data of Pace et al [183]

major effects. First, that proportion of Hb that is occupied by CO molecules is unavailable for O_2 transport, resulting in a functional anemia. Second, the avidity with which the remaining Hb binds O_2 is increased (shift to the left of the Hb-O_2 dissociation curve). The result of this is a decreased ability to unload O_2 from blood to tissue at the capillary. Previously, it was believed that these effects were totally responsible for the toxicity of CO. However, evidence has since been presented to show that the binding of CO to intracellular pigments (e.g., cytochrome, myoglobin) may contribute significantly to the toxicity of CO. This intracellular toxicity of CO has been reviewed by Piantadosi. [29] These mechanisms result in toxicity to multiple organ systems, including brain and heart. [30] Late neurologic sequelae remain an important secondary toxic effect, often after a clear window of lucidity. [31]

High P_{O_2} hastens the removal of CO from blood, such that the half-life of COHb is greatly reduced by HBO therapy (Table 67-6) . Additionally, the increased dissolved O_2 in plasma may support tissue oxygenation pending removal of CO from Hb and other proteins important for O_2 transport. Although the treatment of CO poisoning with HBO remains somewhat controversial, there is mounting evidence that for poisoning in which neurologic symptoms occur, HBO treatment may decrease both early and late morbidity from this condition. Two comparable series containing relatively large numbers of patients have been published since 1985, one group (115 patients) having been treated with HBO, [30] the other (79 patients) with 100 percent O_2 at 1 ATA. [32] In those patients who had impaired consciousness, mortality in the group administered HBO was 15 percent, versus 30 percent of those treated with normobaric O_2. In a randomized, prospective trial of HBO versus normobaric O_2, Thom et al [33] demonstrated that HBO treatment results in a significant reduction in neurologic sequelae.

The diagnosis of CO poisoning is made by a history of exposure (internal combustion engine exhaust, fire, improperly adjusted gas or oil heating, charcoal or gas grills, or exposure to paint stripper containing methylene chloride, which is metabolized by the liver to CO). Confirmation of the diagnosis is made by finding an elevated COHb in either arterial or venous blood. COHb concentration in anticoagulated blood samples is stable for several days. Therefore, if COHb determination is not available at a referring facility, the diagnosis can be confirmed using a blood sample obtained at the time of initial evaluation and transported with the patient. Fetal Hb (HbF) produces a falsely elevated reading for COHb on certain four-wavelength laboratory co-oximeters. In the first few weeks of life, blood from normal

infants' measurements may therefore falsely indicate 7 to 8 percent COHb.

Actual COHb levels measured on arrival in the emergency room correlate poorly with clinical status and should not be used as the sole criterion to determine the need for treatment. Because of the lower intracellular P_{O_2}, elimination of CO from intracellular binding sites occurs more slowly. Significant mental obtundation, vomiting, and headache may remain even in the face of a normal COHb level.

Brain CT imaging may reveal a variety of abnormalities, including hypodensities in the globus pallidus and subcortical white matter, cerebral cortical lesions, cerebral edema, hippocampal lesions, and loss of gray-white differentiation. Except to exclude other disorders, brain imaging is not useful for determining who should receive HBO, but it may provide prognostic information. CT scans in a group of 40 patients who had received HBO for CO poisoning were systematically reviewed by Pracyk et al. [34] Twenty of 23 patients (87%) with a normal scan had a favorable clinical outcome, in contrast to only 6 of 17 patients (35%) with an abnormal scan.

Supportable guidelines for the application of HBO therapy in CO poisoning include the following: a history of neurologic impairment (including loss of consciousness); symptoms or evidence of cardiac abnormalities (ischemia, arrhythmias, ventricular failure); and a COHb level that has been higher than 25 percent. Fetuses are particularly susceptible to CO toxicity. Pregnant women who fulfill the foregoing criteria or cases of fetal distress should be treated with HBO. Case reports, [35] [36] [37] published series, [38] [39] and a critical review [40] support the concept that inadequately treated CO poisoning is a serious risk to the mother and fetus, and the benefits of HBO outweigh the theoretical risks to the fetus of HBO treatment. Potential adverse effects of currently implemented HBO treatment protocols are extremely rare in clinical practice.

Gas Embolism and Decompression Illness

Introduction of gas into the arterial circulation (arterial gas embolism [AGE]) has traditionally been associated with scuba divers and has been attributed to pulmonary barotrauma during ascent from a dive while breathing compressed gas. However, it may also occur iatrogenically in several clinical circumstances, such as during cardiopulmonary bypass or as a result of inadvertent injection of air during a diagnostic arteriogram or hemodialysis. Additionally, large amounts of gas may enter the venous system, for example, during neurosurgical procedures with the patient in the sitting position, hemodialysis, Harrington rod insertion, total hip replacement, cesarean section, laparoscopy, intrauterine laser surgery, arthroscopy (from air escaping from a faulty air-powered drill) and hydrogen peroxide irrigation or oral ingestion (from elaboration of gaseous oxygen from tissue and blood catalase). Venous gas embolism (VGE) can also occur when a central venous catheter is opened to air. Severe VGE has also occurred during orogenital sex after blowing air intravaginally. [41] VGE has also been reported in patients with adult respiratory distress syndrome (ARDS) who were ventilated with positive end-expiratory pressure. [42] VGE in sufficient quantity may overwhelm the ability of the pulmonary vasculature to filter the gas, thus allowing bubbles to pass into the arterial circulation. Even small amounts of venous gas (e.g., VGE due to decompression from

diving) have been implicated in neurologic syndromes in scuba divers because of transatrial passage through a patent foramen ovale. [43]

The effects of gas embolism are not solely due to vessel obstruction by bubbles. Bubble-endothelial interaction causes increased capillary permeability and extravasation of fluid. [44] [45] Another effect has been demonstrated in a model of AGE in anesthetized rabbits by Helps et al, [46] [47] who showed that small doses of intracarotid air may pass through the cerebral microcirculation yet produce sustained vasodilatation, delayed reduction of cerebral blood flow, and neurophysiologic impairment. Leukocytes are required for this effect, because inducing neutropenia prior to the experiment abolishes the effect. [48] This phenomenon of delayed reduction of cerebral blood flow may be responsible for the clinical observation of initial neurologic improvement after AGE, followed by delayed deterioration. [49]

A related syndrome that results from pathologic effects of tissue and blood gas bubbles is decompression sickness, seen in aviators and compressed gas divers. The gas bubbles in these situations occur because of a decrease in ambient pressure at rate sufficient to induce local inert gas supersaturation, resulting in formation of bubbles *in situ* from tissue stores.

Symptoms of AGE classically consist of impaired consciousness, hemiparesis, or seizures, but they may be less severe. Decompression sickness most commonly presents with any combination of joint pain, paresthesias, motor weakness, bladder or bowel sphincter dysfunction, vertigo, tinnitus, or hearing loss. Additional details regarding the clinical presentation of decompression illness can be found in Elliott and Moon [50] and in the annual report of the Divers Alert Network. [51]

Treatment principles for both forms of gas bubble disease, AGE and decompression sickness, are the same and consist of fluid resuscitation, administration of a high inspired O_2 concentration, and increasing the ambient pressure. Increasing arterial P_{O_2} by administering supplemental O_2, even at ambient pressure as a first aid measure, results in an increased rate of resolution of gas bubbles because of the resulting higher partial pressure gradient for diffusion of inert gas from the interior of the bubble into the surrounding tissue or blood. Fluid resuscitation replenishes intravascular volume, reduces hemoconcentration, and helps to maintain microcirculatory flow, principles that have been confirmed by both animal [52] and human clinical data. [44]

Hyperbaric therapy causes a diminution in gas volume according to Boyle's law and hastens resolution further. The usefulness of hyperbaric treatment of diving-related or aerospace-related gas embolism associated with rapid decompression is well documented. [53] [54] Less recognized but equally documented is the use of HBO in the treatment of iatrogenic embolism. In the authors' experience in treating iatrogenic AGE, HBO may affect neurologic improvement even after a significant delay between the embolic event and treatment. A retrospective review of the authors' experience in 14 patients revealed no relationship between outcome

and delay of HBO for up to 42 hours, [55] although severe abnormalities are unlikely to resolve unless treated promptly. Treatment of AGE is usually performed at ambient pressures from 2.8 to 6 ATA (see the later discussion of treatment schedules).

The morbidity of recompression treatment for gas bubble disease is extremely low, and the efficacy is high. Therefore, whenever adequate recompression facilities are available, it is usually appropriate for all symptomatic individuals with gas embolism or decompression illness to receive hyperbaric treatment. In addition, most physicians who administer HBO recommend treatment even for asymptomatic patients who have experienced gas embolism to the central nervous system (CNS), in expectation that delayed effects of bubble-endothelium interaction [46] [47] [49] an be prevented.

The decision to administer recompression treatment should be based on clinical evaluation. The only appropriate role for brain or spinal imaging (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) is to exclude other disorders such as hemorrhage, and only if there is a high degree of suspicion that bubbles are not the cause of a patient's symptoms. It has been suggested by Dexter and Hindman [56] that patients with AGE should only be treated with HBO if CT of the brain reveals air. In the authors' experience, brain imaging of patients who respond clinically to HBO shows abnormalities in a minority of cases. Furthermore, HBO-responsive phenomena, besides occlusion of vessels by macrobubbles, such as edema or delayed reduction in cerebral blood flow, may not be detectable using currently available imaging techniques. Unless there is a strong clinical suspicion of disease other than AGE that requires urgent exclusion, performing CT, MRI, or other imaging prior to recompression serves only to delay appropriate treatment. Neither single photon emission tomography (SPECT) nor positron emission tomography (PET) has yet been demonstrated to provide clinically useful information in the management of patients with gas bubble disease. Further details of treatment of AGE and decompression illness have been described by Moon and Gorman [53] and Moon and Sheffield. [54]

Acute Infections

Anaerobic bacteria are especially sensitive to increased tissue P_{O_2}, as mentioned previously, probably because of the lack of antioxidant defenses such as superoxide dismutase in these bacteria. Inhibition of exotoxin production, especially the alpha-toxin by *Clostridium* species, by high O_2 tensions has been demonstrated. [57] Because the systemic manifestations of clostridial infection are largely attributable to the production of toxin, the clear beneficial effects of HBO in this type of infection are attributed to this mechanism. A large clinical series of clostridial myonecrosis was published by Bakker and van der Kleij, [58] [59] and it appears that the early treatment of disease with HBO, in addition to antibiotics and appropriate surgical debridement, can be limb-saving and probably lifesaving. Immediate clinical response to HBO may often be seen in these patients, with reduction in tissue crepitus and decreased heart rate, cardiac output, and other signs of sepsis. Hyperbaric treatment should not be delayed and may be used beneficially prior to surgery to preserve viable infected tissue and to allow better demarcation for surgical debridement. [58] [59]

Typical treatment schedules for clostridial myonecrosis are up to 3.06 ATA for 90 minutes while the patient breathes 100 percent O_2. Commonly, three HBO treatments are administered within the first 24 hours, five times within the first 48 hours, and then twice daily for a total of seven to nine treatments, by which time the clinical course of the infection is usually evident.

The rationale for treatment of nonclostridial soft tissue necrotizing infections is that high tissue P_{O_2} inhibits the growth of anaerobic bacteria. Initially, it may be difficult to differentiate clostridial from nonclostridial infections, and there is evidence that such patients benefit from HBO in a manner similar to that of documented clostridial infection. HBO also appears to offer a significant reduction in morbidity and mortality in nonclostridial necrotizing infections, as documented in a controlled trial. [60] [61] A meta-analysis of 554 published cases indicated a mortality of 44 percent in patients not treated with HBO versus 20 percent in HBO-treated patients. [62] Because many of these infections are indolent, treatment beyond the first 3 or 4 days may be beneficial.

Support of Arterial Oxygenation

For circumstances in which patients may otherwise be severely hypoxemic, such as cyanotic heart disease, HBO may offer a margin of safety during anesthesia. Smith [63] reported 45 cases of surgical correction of cyanotic heart disease in children operated on under HBO. Although most of these patients had Pa_{O_2} around 25 mm Hg or less while breathing 100 percent O_2 at 1 ATA, the Pa_{O_2} values increased to 50 mm Hg or greater in the majority of patients at ambient pressures up to 4 ATA. Halothane anesthesia was used in most cases. No complications were reported, and it was concluded that HBO was useful to maintain Pa_{O_2} in these critically ill infants. There was no evidence that increased concentrations of anesthetic were required to maintain anesthesia at the pressures used.

Li et al [64] reported a series of 48 patients with open heart surgery under HBO at 3 ATA, anesthetized with intravenous fentanyl. In several of the patients, the blood Hb concentration was reduced by phlebotomy to 3 to 4 g/dL during HBO. It is pointed out that a major advantage of this technique is a reduction in transfusion requirements.

HBO has been reported to be a safe and effective method of supporting arterial oxygenation while therapeutic lung lavage is performed under general anesthesia using one-lung ventilation. [65] [66] In the authors' experience of more than 60 procedures, arterial oxygenation has been satisfactorily maintained with no resulting complications (Fig. 67-3) . A reversible simulation of pulmonary gas exchange during the lavage procedure can be provided by temporarily ventilating the lung to be lavaged with 5 percent O_2. This reduces P_{AO_2} in that lung to approximately the level of mixed venous P_{O_2}, thereby confining O_2 exchange to the contralateral lung. If, during a 5-minute period of unilateral hypoxic ventilation, the patient's arterial Hb-O_2 saturation drops below 90 percent, then it is likely that lavage at 1 ATA will be accompanied by arterial hypoxemia.

Figure 67-3 Pa O_2 during unilateral lung lavage under hyperbaric conditions. The open circles represent measured Pa O_2 at various ambient pressures (abscissa). The solid circles represent the predicted Pa O_2 at 1 ATA, calculated on the assumption of a constant Pa O_2 /P AO_2 ratio. [5] It can be seen that six of the eight patients would have had Pa O_2 values lower than 50 mm Hg had the procedure been performed at atmospheric pressure.

Maintenance of Oxygen Transport in Severe Anemia

The ability of HBO to increase arterial O_2 content in plasma to clinically useful levels may allow support of tissue O_2 delivery even in the absence of Hb. This finding has led to the application of HBO for temporary support of severely anemic patients pending availability of definitive therapy in the form of crossmatched blood. Hart et al [67] reported the use of this technique in 26 patients. The mean hematocrit of all patients was 12.9 percent. Mean heart rate decreased from 124 to 98 beats/min after 30 minutes of breathing 100 percent O_2 at 2 ATA. Although the indication for this treatment is extremely uncommon, the temporary use of HBO to support the patient pending appropriate blood crossmatching may be lifesaving.

THERAPEUTIC SYSTEMS

The traditional method of administering hyperbaric therapy is with a multiplace chamber, which accommodates two or more persons (Fig. 67-4) . Size may vary from a small, portable two-person chamber used for transporting patients in the field to one 20 ft or more in diameter, in which up to a dozen patients may be comfortably admitted, in addition to tenders. The largest multiplace chamber ever built was a 20-m-diameter sphere, which could be compressed to 3 ATA. [3] Multiplace chambers are compressed with air, while the patient breathes O_2 with a head tent (Fig. 67-5) , face mask, or endotracheal tube. Because of the immediate access to the patient by accompanying nursing personnel or physicians, monitoring is relatively straightforward. Intravenous lines can be inserted during treatment, and airway control may be exercised. Surgery has even been performed inside multiplace hyperbaric chambers. The operation of these chambers is complex. They have a large space requirement for installation and are costly.

The other type of chamber is the monoplace, which is large enough to accommodate only one patient (Fig. 67-6) ; a tender can only be used with a child. The chamber wall in many types is manufactured of Plexiglas, facilitating close observation of the patient. The chamber is usually compressed with 100 percent O_2 . The advantage of monoplace chambers is their relatively low cost and ease of installation. The chamber may be put into use merely by connecting the O_2 inlet to the hospital supply, although some modification may be required of the main supply piping to accommodate

Figure 67-4 Multiplace hyperbaric chamber, which is large enough for one or more patients and tenders. Chamber atmosphere is compressed air. The patient receives 100 percent O_2 via mask, head tent, or endotracheal tube. Monitors are usually kept outside the chamber because of electrical safety considerations. Monitoring is possible through a porthole. Personnel lock and transfer lock allow physicians, nurses, or other personnel, in addition to medications, food, and blood samples, to be moved into and out of the chamber without repeated compression and decompression of the patient.

Figure 67-5 Head-tent circuit for use in a multiplace chamber. Fresh gas (100% O_2) flows at a constant rate (>30 L/min) through the head tent. Exhaust gas may be either vented outside the chamber or recirculated through a CO_2 scrubber. The sample line attached to the exhaust hose allows monitoring of the patient breathing gas.

large flow rates. Operation of the chamber is relatively simple, but it has the disadvantage of lower flexibility. The patient inside the chamber at pressure cannot be evaluated "hands on," monitoring is somewhat more remote, and emergency care of the airway cannot be provided. Development of a pneumothorax, particularly a tension pneumothorax, although rare, can be fatal because of the impossibility of inserting a chest tube prior to decompression. The other major disadvantage of these chambers is that the ambient

Figure 67-6 Monoplace chamber. This type of chamber has room for one patient or a tender with a small child. Chamber atmosphere is 100 percent O_2 . The chamber is constructed of transparent plastic to allow easy observation. Through-hull penetrators (not shown) near the head of the patient allow monitoring and intravenous fluid administration and control of a ventilator inside the chamber.

pressure limit is 3 ATA, and for practical reasons treatment times are limited. Moreover, intermittent periods of air breathing, in order to decrease the risk of O_2 toxicity (see later), require installation of an additional gas-delivery system. Nevertheless, monoplace technology now permits intravenous fluid administration from the outside of the chamber, invasive intravascular monitoring, mechanical ventila- tion, and utilization of pleural drainage systems incorporating regulated suction. Additional details can be found in a monograph available from the Undersea and Hyperbaric Medical Society. [68] Many chambers are now equipped additionally with mask systems from which the patient may intermittently breathe air (called "BIBS" for built-in breathing system), permitting the administration of U.S. Navy treatment tables for decompression illness (see later).

HYPERBARIC TREATMENT SCHEDULES

Ideally, a patient who has therapeutic indication for hyperbaric O_2 would be exposed for an unlimited time until the condition resolves. Unfortunately, several factors limit the dose and duration of HBO: O_2 toxicity; decompression obligation for nursing staff (or other tenders) accompanying patient; difficulty of monitoring; and patient discomfort.

Treatment schedules have been developed that are compromises between O_2 partial pressure and exposure time on one hand and O_2 toxicity and other practical limiting factors listed on the other. The original schedules (or "tables") were developed by the various navies of the world to treat decompression sickness and gas embolism in divers. Two U.S. Navy tables are shown in Figure 67-7 .

U.S. Navy Table 6 (see Fig. 67-7) prescribes an initial exposure to 2.8 ATA (60 ft of sea water [fsw], equivalent to 18 m of sea water [msw]), followed by slow decompression to 1.9 ATA (30fsw). Periods of O_2 breathing are interspersed with 5- or 15-minute periods of air breathing to decrease O_2 toxicity (see later). This schedule remains the mainstay of treatment for decompression illness in multiplace chambers throughout the world. Patients who remain symptomatic during treatment may have their exposure extended in time at both 2.8 and 1.9 ATA. U.S. Navy Table 6A (see Fig. 67-7) is occasionally used for the treatment of air embolism, in which larger amounts of intravascular gas may be present. In Table 6A, the Table 6 schedule is preceded by a period of 30 minutes at 6 ATA while breathing air (see Fig. 67-7). More recently, 40 or 50 percent O_2 has been advocated during this period in order to hasten the elimination of nitrogen bubbles and to increase O_2 delivery to ischemic tissue. In practice, patients are treated once according to either of these schedules and then are reassessed. Incomplete relief of signs or symptoms may be treated with repeated applications of the protocols of these tables on a daily basis. An alternative method of treating severe gas bubble disease is saturation treatment. The principle is that the patient is subjected to elevated pressure (e.g., 2.8 ATA) and is allowed to remain at that ambient pressure until symptoms have stabilized. Periodic O_2 breathing is given according to a recommended schedule as tolerated. Because saturation treatment results in a much larger degree of nitrogen uptake in both the patient and the tender, decompression must occur

Figure 67-7 U.S. Navy treatment tables. (A) U.S. Navy Table 6A. This schedule is designed for the treatment of arterial gas embolism. A 30-minute period at 6 ATA breathing air was designed to compress gas bubbles to one-sixth of their original volume. Subsequent periods at 2.8 and 1.9 ATA breathing 100 percent O_2 allow for oxygenation of ischemic tissue and faster resolution of intravascular gas than would occur if the patient were breathing air. Short periods of air breathing (air breaks) diminish the rate of occurrence of pulmonary O_2 toxicity (see Fig. 67-9 (Figure Not Available)). (B) U.S. Navy Table 6. This table was designed for the treatment of decompression sickness. Both tables may be extended, with additional periods of O_2 breathing at both 2.8 and 1.9 ATA. Stippled areas, O_2 breathing; clear background, air breathing. When Table 6 or 6A is extended, additional safety for the tender can be provided by administering 100 percent O_2 for the last 30 to 90 minutes at 30 fsw (1.9 ATA) according to the number of extensions at 60 fsw (2.8 ATA): 30 minutes (no extensions), 60 minutes (1 extension), 90 minutes (2 extensions); 100 percent O_2 is breathed by the tender for the entire period of decompression from 30 fsw (1.9 ATA) to "surface" (1 ATA). Further details can be found in the U.S. Navy Diving Manual. [85]

much more slowly, usually over 24 to 36 hours. [69] [70] Although this therapy avoids the theoretical disadvantage of intermittent treatment--failure of resolution of gas bubbles, it is also considerably more labor intensive. Because hyperbaric chambers used for saturation treatments require additional hardware (e.g., CO_2 scrubbing capability) and personnel, the application of this method outside the military and commercial diving has been limited.

A schedule used for treatment of patients with clostridial myonecrosis or other life-threatening anaerobic infections is shown in Figure 67-8 . This schedule consists of 85 minutes at 3.06 ATA, followed by a 33-minute decompression stop for the tenders at 1.3 ATA. This stop may be omitted for the patient if a second team is available to lock in and decompress with the patient. The original tenders can then remain at 1.3ATA for the required decompression time. This treatment schedule was designed to maximize Pa_{O_2} (and hence tissue bactericidal activity due to O_2) without an undue risk of hyperoxic seizures.

Administration of HBO to patients with chronic diseases (e.g., radionecrosis) is usually performed using shorter tables at lower ambient pressure. The most commonly employed schedule is 1.5 to 2 hours at 2 to 2.5 ATA (see Fig. 67-8). Because of the lower ambient pressure, the risk of O_2 toxicity is minimal and an exposure of this duration is not particularly onerous for the patient on a repetitive basis once or twice daily.

SIDE EFFECTS OF HYPERBARIC THERAPY

Oxygen Toxicity

A major toxic effect of HBO therapy is due to the O_2 itself. In fact, O_2 toxicity is the factor that limits the maximum allowable P_{O_2} and duration of a hyperbaric treatment. Current opinion is that O_2 toxicity is caused by excessive production of oxygen free radicals (e.g., superoxide, hydroxyl radicals, and singlet oxygen). Mechanisms within the body to scavenge these free radicals may be overcome by increased rates of free-radical production at high O_2 partial pressures. [71] With the use of supplemental O_2 at 1 ATA, the manifestations of O_2 toxicity are almost exclusively confined to the lung. Because of the close proximity of pulmonary tissue cells to gas-containing spaces, tissue P_{O_2} within the lung may increase nearly 5-fold while the patient is breathing 100 percent O_2. Despite the corresponding elevation in Pa_{O_2}, tissue P_{O_2}

Figure 67-8 Clinical hyperbaric O_2 treatment schedules. (A) The patient breathes 100 percent O_2 for 2 hours at an ambient pressure of 2 ATA. Usually this schedule is used for repetitive treatments for chronic conditions (e.g., osteoradionecrosis). (B) Therapeutic schedule for the treatment of clostridial myonecrosis. The patient spends 85 minutes at an ambient pressure of 3.06 ATA and breathes 100 percent O_2, with the exception of two 5-minute air breaks to minimize pulmonary and central nervous system O_2 toxicity. A decompression stop is made at 1.3 ATA, according to the U.S. Navy standard air decompression table. This decompression stop is designed to prevent decompression sickness in the tenders, who breathe air throughout the period at 3.06 ATA.

Figure 67-9 (Figure Not Available) Decrease in vital capacity (VC) as a function of time breathing 100 percent O_2 at 2 ATA in humans. The diagram illustrates the value of intermittent O_2 (20 min O_2, 5 min air) versus continuous O_2 administration in the prevention of pulmonary O_2 toxicity in humans. The numbers in parentheses represent the number of subjects tested. *(From Clark [217])*

in other organs may not be substantially elevated at 1 ATA.

O_2 toxicity during HBO therapy principally affects mainly three organ systems: the lung, the CNS, and the eye. Pulmonary toxicity in the conscious patient is heralded by symptoms of tracheobronchial irritation, namely, cough and burning chest pain. Prolonged exposure may result in a decrease in vital capacity (VC), ARDS, and, ultimately, in pulmonary fibrosis. The rate of development of pulmonary O_2 toxicity may be slowed by intermittent air-breathing periods ("air breaks"). Data supporting the use of air breaks are shown in Figure 67-9 (Figure Not Available) .

The degree to which O_2 is toxic is related to the P_{O_2} of the inspired gas. At 1 ATA, 100 percent O_2 is as toxic as 16.7 percent O_2 at 6 ATA or 2 percent O_2 at 50 ATA. An attempt to quantify O_2 exposure was made by Clark and Lambertsen. [72] In this system (uni pulmonary toxic dose, or UPTD) the number of UPTD units (U) is calculated by the following formula:

where t is the exposure time in minutes; P is the inspired P_{O_2} in ATA, and m is a slope constant that has an empiric value of 1.2. After 1,425 UPTD units of O_2 exposure, there is an average 10 percent decrease in VC; After 2,190 UPTD units, there is an associated decrease of 20 percent. Complete reversal of VC decrements as large as 40 percent of control has been observed after extended O_2 exposure at 2 ATA. [72]

Although the UPTD system may be useful as a rough guide to safe O_2 exposures, particularly in intubated patients who may be unable to report symptoms, its use as an accurate guide to the development of pulmonary O_2 toxicity is limited. Reanalysis of a larger data set than the one used for the UPTD model, which included those data, resulted in a different prediction equation:

where P and t are the same as for equation 1. [73] Interindividual variability may be substantial, however. In a study 12 healthy men who breathed gas containing a P_{O_2} = 0.3 ATA for 12 hours and then a P_{O_2} of 1.05 ATA for 48 hours experienced decrements in VC ranging from 0 to nearly 30 percent. [74] Furthermore, O_2 toxicity can be modified by humidity, [75] circulating catecholamine and corticosteroid levels, leukocyte accumulation in the lungs (e.g., with pneumonia), and circulating endotoxin. A more useful guide in practice is the patient's symptoms. Asymptomatic persons usually have minimal or no change in VC.

Some of the effects of pulmonary O_2 toxicity can be cumulative. Patients given supplemental O_2 to breathe between hyperbaric treatments often complain of burning chest pain. Therefore, in patients receiving multiple HBO treatments, between hyperbaric exposures it is best to use the minimum inspired O_2 compatible with clinical safety (e.g., in the intensive care unit).

Some antineoplastic agents, such as bleomycin [76] and mitomycin C, [77] [78] appear to predispose to fatal pulmonary O_2 toxicity (ARDS and respiratory failure) from what should otherwise have been well-tolerated doses of supplemental O_2. The risk of pulmonary O_2 toxicity due to HBO therapy in patients with previous exposure to such agents is unknown, although the authors have treated several such individuals with a remote history of bleomycin treatment with repetitive doses of HBO. The protocol has been a longer than usual interval between HBO exposures during the initial phase of treatment (e.g., daily instead of the usual twice daily therapy) and close monitoring of spirometry, CO transfer factor, and arterial blood gases. Patients are instructed to seek immediate medical evaluation if they develop progressive dyspnea or cough after an HBO session. If after 1 week of daily therapy there have been no O_2 toxicity symptoms or pulmonary mechanical or gas exchange deterioration, then

the frequency of therapy is increased to twice daily. Some of these individuals have developed mild pulmonary O_2 toxicity symptoms such as retrosternal chest tightness, but none have developed severe O_2 toxicity using a treatment schedule of 2 ATA for 2 hours.

CNS O_2 toxicity is manifested in its most severe form as nonfocal tonic-clonic seizures. This toxicity may occur without warning, but it is sometimes preceded by premonitory signs or symptoms (e.g., nausea, facial numbness, facial twitching, bradycardia, unpleasant olfactory or gustatory sensations, or acoustic symptoms). The probability of seizures increases with increasing Pa_{O_2} and time of exposure. In a study of 36 divers breathing 100 percent O_2 at 3.7 ATA, all experienced one or more of these symptoms within 100 minutes or less. [79] [80] In clinical practice, convulsions are rare at 2 ATA. In the authors' experience, hyperoxic convulsions occur in less than 0.02 percent of HBO treatments at 2 ATA for 2 hours. The probability of a convulsion is greater at higher P_{O_2}, but it is less than 5 percent even at ambient pressures of 3 ATA. Metabolic factors may reduce the seizure threshold, such as the administration of high-dose penicillin (e.g. for clostridial infection), sepsis, and hypoglycemia.

The treatment of hyperoxic seizures is easily accomplished by immediately decreasing the inspired O_2 concentration. In a multiplace chamber, the head tent or face mask should be removed. An intubated patient should be removed from the ventilator and manually ventilated with compressed air using a bag-valve system until the seizure has stopped. In a monoplace chamber, 100 percent O_2 in the chamber atmosphere may be replaced by air. The chamber should not be decompressed while the patient is actively having a seizure because airway closure and failure to exhale during this period may result in pulmonary barotrauma such as pneumothorax or AGE. Seizure threshold may be elevated with benzodiazepines or with therapeutic serum concentrations of phenytoin or phenobarbital. Some physicians routinely administer an anticonvulsant such as phenobarbital, phenytoin, or a benzodiazepine after a hyperoxic seizure, although others do not believe this is necessary. Other than pulmonary barotrauma (which can occur if chamber decompression is performed during a seizure, as noted earlier), hyperoxic seizures have no sequelae and rarely recur despite continuation of HBO, particularly if anticonvulsant prophylaxis is used. Thus, hyperoxic CNS symptoms should not be a reason to discontinue a series of HBO treatments.

Hyperoxic effects on the eye may be acute (narrowing of the visual fields) or chronic (change in the refractive index of the lens resulting in myopia). Myopia may occur during the course of intermittent HBO therapy over several weeks and usually resolves in a similar period. However, some patients may be left with residual myopia, particularly the elderly. [81] It has been suggested that hyperbaric therapy may promote nuclear cataract formation. [82] However, the population of patients most likely to require hyperbaric treatment (elderly people with peripheral vascular disease and diabetes) also have a high prevalence of cataracts. Moreover, cataractous lenses tend to progress without hyperbaric exposure, and the changes are difficult to quantify, as pointed out by Anderson and Shelton. [81] Therefore, more definitive data are required before the hypothesis that HBO may result in cataracts can be accepted. Additional toxic effects of O_2 on the neonatal retina have been well described and may result in retrolental fibroplasia. Concern has been raised about the risk of this complication in the unborn child of a woman who may require acute HBO therapy during pregnancy. Although many pregnant women have been treated with single exposures to HBO (e.g., for CO poisoning), the authors are not aware of any incidents of retrolental fibroplasia in the child after birth. The authors therefore recommend that pregnant women with acute, symptomatic illness for which HBO is indicated (e.g., CO poisoning) be treated with HBO because the risk to the fetus of the underlying condition is usually much greater. O_2 toxicity of other organs has been suggested or demonstrated in experimental animals, but its clinical importance has not become evident, at least not with currently used HBO schedules.

Inert Gas Uptake

Breathing air at high ambient pressure may result in two "toxic" effects that are due to the nitrogen. The first is a dose-dependent decrement in cerebral performance known as nitrogen narcosis, which is due to the anesthetic properties of nitrogen. This often becomes apparent to an outside tender trying to communicate with a nurse inside the chamber, for whom actions requiring fine motor control (e.g., starting an intravenous line) and rapid decision-making may be more difficult. This is particularly true at 6 ATA; however, most therapeutic recompressions are limited to 3 ATA, at which narcotic effects are usually tolerable. Narcosis may be avoided entirely by using helium-O_2 (heliox) as the chamber atmosphere rather than nitrogen-O_2. However, this is expensive and engenders communication difficulties because the speech of people inside the chamber becomes relatively unintelligible in a helium atmosphere ("Donald Duck voice"). Heliox recompression is usually reserved for saturation treatment of helium-breathing divers. Although there is anecdotal evidence that helium-O_2 may be more efficacious than nitrogen-O_2 mixtures for the treatment of nitrogen-induced decompression sickness, [83] [84] this contention has yet to be supported by a systematic trial.

The second major adverse effect of nitrogen is that it is taken up by body tissues and must therefore be released during and after decompression. Overly rapid decompression may result in the formation of bubbles within the tissues and blood, leading to decompression sickness manifested by joint pains or neurologic symptoms referable to the spinal cord. Neither this nor nitrogen narcosis is a problem for the patient, who breathes O_2 throughout most of the therapeutic hyperbaric exposure. However, the tender in a multiplace chamber breathes compressed air in the atmos-phere. Therefore, decompression schedules must be designed to minimize the risk of decompression sickness in tenders. Most hyperbaric facilities use U.S. Navy compressed air decompression tables (see Fig. 67-7). [85] Additional safety for the tender can be provided by requiring the tender to breathe 100 percent O_2 for a period immediately prior to and during decompression (Table 67-7) . O_2 breathing results in increased nitrogen elimination because of the resulting rapid lowering of tissue partial pressure of nitrogen.

TABLE 67-7 -- Duke Modifications of the U.S. Navy Air Decompression Tables

Standard air decompression time calculation for tenders
Within 2 ft of standard Navy depth divisions, use the next greatest depth
Within 2 min of standard Navy time divisions, use the next greatest time
During decompression of the chamber after a compressed air dive, breathe 100% O_2 from an equivalent depth of 50 fsw (2.5 ATA) to the surface or for 15 min, whichever is shorter
Time for decompression
68-30 fsw (3.06-1.9 ATA): 3 min
30-20 fsw (1.9-1.6 ATA): 1 min
20-10 fsw (1.6-1.3 ATA): 1 min
10 fsw (or last stop)-"surface" (1.3-1.0 ATA): 5 min
For decompression from USN treatment tables, see legend for Figure 67-7 .

Rare episodes of decompression sickness in tenders are usually minor, generally consisting of mild joint pain.

Exposure to Trace Gases

Because the chamber is an enclosed environment, there is a possibility for build-up of other gases that may be toxic. CO_2 is produced by the patient and tender, and significant accumulation in the atmosphere may result in elevated Pa_{CO_2}, which may augment nitrogen narcosis as well as CNS O_2 toxicity. The chamber atmosphere must therefore be carefully monitored, and action must be taken to lower individual gas concentrations if threshold limits are exceeded. Most hyperbaric facilities require that the atmospheric P_{CO_2} not rise above 4 mm Hg. Other potentially toxic gases may be produced from smoldering or burning of electrical components or may be released from batteries. All batteries produce small quantities of hydrogen. Lithium- sulfur dioxide batteries, although hermetically sealed with an interior pressure of 4.5 ATA, may vent sulfur dioxide in the event of a seal failure. (Minimization of these risks is discussed later.) CO is released into the atmosphere in a closed chamber by body metabolism and by other environmental factors, and during saturation dives (prolonged chamber exposures at a constant pressure) it may accumulate unless converted to CO_2 by catalysis. Because monoplace chambers are continuously ventilated with 100 percent O_2 at high flow rates, this issue pertains mostly to multiplace chambers.

Barotrauma

As the ambient pressure is altered, the pressure within gas-containing spaces in the body must equalize with the ambient pressure or must undergo a change in volume. Volume change can easily occur in compliant compartments such as the gastrointestinal tract, but if free flow of gas into and out of containing spaces surrounded by a rigid shell, such as the lung, paranasal sinuses, and middle ear, is impeded, then tissue disruption and hemorrhage can occur (see later). Despite the number of potential adverse effects of HBO therapy, major complications are extremely rare.

PRACTICAL ASPECTS OF HYPERBARIC THERAPY

Middle Ear Pressure Equilibration

Probably the most common patient side effect of hyperbaric chamber use is the difficulty that some patients experience in equilibrating the pressure in the middle ear. This is manifested by acute pain, tympanic membrane stretching or tearing, and hemorrhage into the middle ear (referred to as ear "squeeze"). Difficulty in equilibrating middle ear pressure may also result in labyrinthine window (round or oval window) rupture. [86] Equilibration may be accomplished using several techniques, such as performing intermittent Valsalva maneuvers, swallowing while the nose is pinched, thrusting the jaw forward, or simply swallowing intermittently during compression. Children can often be induced to equalize their ear pressure adequately by having them drink small amounts of liquid during compression. Most patients can learn the technique; however, others may be unable to clear their ears, sometimes because of acute respiratory tract infection. In these patients, equilibration can sometimes be aided by application of a topical nasal vasoconstrictor (e.g., oxymetazoline 0.05% [Afrin]), which may shrink the nasopharyngeal mucosa and increase the patency of the eustachian tube. Myringotomy is usually reserved for patients who cannot equalize the pressure despite these measures or for obtunded or intubated patients. For patients who cannot equalize the pressure and who require hyperbaric therapy beyond 2 or 3 days, placement of tympanostomy tubes will ensure a patent opening into the middle ear. Squeeze may occasionally also affect the sinuses, resulting in acute pain. Despite the common occurrence of middle ear or sinus squeeze on compression, symptoms on decompression, because of inability of gas to exit via the eustachian tubes or sinus ostia (reverse squeeze), are extremely rare.

Pulmonary Pressure Equilibration

Areas of poor ventilation within the lung must also reach equilibration during compression and, more important, during decompression in order to prevent pulmonary barotrauma, which may result in pneumothorax, pneumomediastinum, or AGE. Patients with bullae on a chest radiograph could therefore be disqualified from hyperbaric therapy. Patients with obstructive pulmonary disease should have bronchodilator therapy optimized prior to commencement of HBO. However, despite the relatively frequent occurrence of pulmonary barotrauma in scuba divers (
100 cases/ yr from the continental United States reported to the Divers Alert Network [51]), pulmonary barotrauma during HBO therapy is increasingly rare. The authors are aware of only one case of AGE resulting from decompression of a patient inside a hyperbaric chamber. This finding is perhaps surprising, given that many such patients have been heavy smokers and therefore frequently have some degree of obstructive lung disease. Possibly, the reason is that immersion in water elevates pulmonary closing volume (CV), which may result in areas of lung that are pneumatically isolated from the tracheobronchial

tree. Incomplete emptying of these areas during decompression from the dive may result in alveolar rupture. Prefaut et al [87] measured the relationship of closing volume to expiratory reserve volume in air and during immersion in water. In six healthy volunteers in air, expiratory reserve volume was larger than closing volume; in four of six of these persons, however, immersion in water caused closing volume to exceed expiratory reserve volume. This finding implies that, in these persons, immersion in water resulted in closure of lung units at lung volumes higher than functional residual capacity. In addition, rates of ascent in hyperbaric chambers can be much more accurately controlled and are generally slower (5 to 6 fsw/min, as compared with up to 60 fsw/min in divers).

Although a pneumothorax would be expected to diminish in size and to resorb more quickly after compression, continuing leakage of air from the lung may result in tension pneumothorax during decompression. Pneumothorax detected prior to treatment is usually treated by insertion of a chest tube and water seal or Heimlich-type valve. Caution must be exercised when using certain commercially available pleural suction regulators, which can exert high negative pleural pressures during chamber compression. [88] Such excessive suction can be relieved by an attendant inside a multiplace chamber by using the manual pressure-relief valve.

Patient Monitoring

Despite the changes in the acoustic properties of compressed air, blood pressure measurement may be performed without difficulty with a standard sphygmomanometer and stethoscope. It is recommended that aneroid pressure gauges be used rather than mercury columns because of the risk of atmospheric contamination due to spillage of mercury in the chamber. More detailed monitoring of the electrocardiogram and of intravascular pressures requires some planning and engineering. It is advisable to minimize the number of electronic devices inside the chamber. Electrocardiographic and pressure transducer cables can be plumbed through the chamber wall to the preamplifiers kept outside. Provision of appropriate cable connectors inside the chamber will minimize the delay necessary in connecting a patient to the monitors after being placed in the chamber. Two simultaneous displays should be available, one for viewing by an outside observer and one facing through a porthole for use by the inside attendant. Standard intensive care monitors can be used to provide simultaneous measurement of arterial and pulmonary artery pressures and intermittent measurement of cardiac output by thermodilution. Occasionally, the increase in ambient temperature induced by chamber compression may alter the zero offset of pressure transducers, with the older nondisposable type exhibiting greater drift than the newer, disposable ones, which have smaller diaphragms. The authors therefore recommend that transducers be zeroed again immediately after compression. Additionally, if pressure bags are used to drive continuous-flow systems for vascular monitoring, it is necessary to repressurize the bags during compression. Similarly, intermittent venting of pressure bags will be necessary as the chamber is decompressed. This minor inconvenience can be solved by using a spring-loaded system to compress the flush bag.

Pulmonary artery catheter balloon ports should be vented to chamber pressure (i.e., remove the balloon inflation syringe from the port and ensure that the gate valve is open) prior to compression and decompression, to avoid forceful implosion and breakage during compression and hyperexpansion and rupture during decompression. Although general recommendations suggest the filling of tracheal tube cuffs with water (see later) to avoid loss of seal with compression, pulmonary artery catheter balloons should never be inflated with liquid, which may cause balloon rupture.

Because of increased fire hazard in a hyperbaric chamber and the possibility of electrical sparking during defibrillation, this procedure must be accomplished in an extremely careful manner and only in a multiplace chamber. Flammable materials, including tape that may have been used to secure the head tent to the patient's torso, must be removed from the immediate area of the defibrillator paddles. An adequate conductive bridge must be obtained between the electrode paddle and the skin by using gel designed for the purpose. A low-resistance gel is recommended, because it has been suggested that high-resistance gels may pose a fire risk because of the increased amount of heat generated at the paddle-skin interface during defibrillation. [89] An alternative, possibly safer, approach from the point of view of sparking employs preapplied conductive disposable ("R-2") pads. [90] Control of the defibrillator by an outside person minimizes the risk that the device will be unintentionally fired.

Intravenous Fluid Administration

In multiplace chambers, there is no intrinsic difficulty in giving fluid intravenously, because the intravenous fluid container and the patient are at the same ambient pressure. The only practical difficulty is that the meniscus within the drip chamber moves upward as the air volume is compressed during the compression phase of

the HBO treatment and downward due to expansion during decompression. Careful adjustment of the fluid level in the drip chamber during decompression prevents air infusion into the patient. Abbott Lifecare "Plum" Infusion Systems (Abbott Critical Care Products, Morgan Hill, Calif.) do not require an air-filled interface to regulate flow, and they work well in multiplace chambers. Particular care must also be taken if glass bottles are used for the fluid because large pressure gradients across the glass wall of a bottle containing fluid and air may cause fracture, unless the bottle is vented with a tube passing from the gas pocket within the bottle directly to the outside. Use of glass bottles in hyperbaric chambers is best avoided entirely.

In monoplace chambers, administration of fluids is technically more difficult because most intravenous infusion devices must be used outside the chamber. Therefore, fluids must be pumped in against the pressure within the chamber (up to 3 ATA or 1,500 mm Hg pressure gradient across the chamber wall). This may be accomplished by a variety of standard intravenous fluid pumps. It is recommended that

intravenous tubing with check valves be used, in order to prevent inadvertent backflow of blood from the patient in the event of disconnection of the pump while the intravenous line is unclamped. Because it is impossible to manipulate intravenous tubing within the monoplace chamber during treatment, the tubing should be arranged to minimize the possibility of a kink. The use of rigid arterial-pressure transducer tubing can prevent this problem.

Blood Gas Assessment and Ventilator Management

The therapeutic administration of O_2 in most hospital settings is guided by measurement of arterial blood gases. Because elevation of tissue P_{O_2} is usually the major therapeutic aim with the use of HBO, it would be preferable if blood gases could be used in exactly the same way in this setting. However, there are several practical reasons that make it difficult to attain this goal. First, blood gas values in a sample taken from a patient in the hyperbaric chamber may not remain stable. In any sample of arterial blood, there is a tendency of gas to diffuse from the blood into the small bubbles that inevitably exist within the syringe unless extremely careful technique is employed to remove them. Under normal clinical conditions, the diffusion of O_2 and CO_2 from blood into a small bubble in a syringe results in only minor changes in blood gas tensions. The reason is that partial pressure changes are buffered by the relatively large contents of O_2 (because of Hb binding) and CO_2 (because of the relatively high solubility of CO_2 in plasma). It is obvious that relatively large changes in P_{O_2} may result from delay in measurement of an arterial blood sample, changes that are compounded if the measurement is to be made outside the chamber. In that situation, small bubbles present in the syringe prior to decompression would be correspondingly increased in size after decompression to 1 ATA. Furthermore, at an ambient pressure of 760 mm Hg, the O_2 in the blood sample will be supersaturated and will tend to move rapidly out of solution into small bubbles, as the CO_2 in carbonated beverages tends to do when the cap is removed from the bottle. Finally, it is impossible to calibrate blood gas machines accurately for gas tensions higher than ambient barometric pressure. Therefore, ideally blood gas tension measurement should be performed inside the hyperbaric chamber, which requires a dedicated analyzer and a skilled technician.

If these facilities are not available, there are two approaches to estimate Pa_{O_2}. The first is simply to draw the arterial blood sample, extrude bubbles as carefully as possible, decompress the sample to 1 ATA, and measure the sample as quickly as possible. Modern blood gas analyzers can produce a Pa_{O_2} estimate by extrapolating the calibration curve obtained from lower O_2 tensions. Weaver and Howe [91] demonstrated that O_2 tension in blood samples obtained at 3 ATA in a hyperbaric chamber can be measured accurately at 1 ATA if analysis is performed immediately after decompression of the blood sample.

Another approach is to estimate the Pa_{O_2} based on measurements obtained at 1 ATA. Gilbert and Keighley [5] demonstrated that at 1 ATA the ratio of arterial/alveolar P_{O_2} (Pa_{O_2}/P_{AO_2}, or $a/_A$ ratio) is relatively constant over a wide range of inspired O_2 concentrations. The authors have examined this ratio over a range of inspired O_2 concentrations, from 0.21 to 1.0, and ambient pressures from 1 to 3 ATA. Arterial blood gases were obtained at 1 ATA, from which the $a/_A$ ratio was calculated. Predicted values for Pa_{O_2} were then calculated for breathing air or 100 percent O_2 at elevated ambient pressure and were correlated with actual measurements of Pa_{O_2} inside the chamber. There was reasonable agreement between predicted and actual values (Fig. 67-10) (Figure Not Available) up to Pa_{O_2} values of 1,700 mm Hg. The following equations may be used to predict Pa_{O_2} at pressure.

The alveolar gas equation (Equation 2) is required to calculate P_{AO_2}:

where Pb and P_{H_2O} are, respectively, ambient and saturated water vapor pressures. If $F_{IO_2} = 0.2$, R = 0.8, and body temperature = 37°C, Equation 5 can be simplified to the following:

Having calculated P_{AO_2} and measured Pa_{O_2}, the $a/_A$ ratio can then be obtained at 1 ATA. The predicted Pa_{O_2} at increased ambient pressure while breathing 100 percent O_2 may then be obtained from Equation 6:

where ATA is the chamber pressure in atmospheres absolute. Although as yet there are no dose-response curves

Figure 67-10 (Figure Not Available) Measured versus predicted Pa_{O_2} at increased ambient pressure. Predicted Pa_{O_2} is calculated from room air arterial blood gases, assuming arterial/alveolar PO_2 ratio (Pa_{O_2}/P_{AO_2}, or $a/_A$ ratio) is a constant. Data are shown both for persons with normal lungs ($a/_A$ ratio 0.75) and for patients with gas exchange abnormalities ($a/_A$ ratio <0.75). It is evident that Pa_{O_2} predicted in this way is close to the actual measured Pa_{O_2}. *(From Moon et al [216])*

TABLE 67-8 -- Hemodynamic and Oxygen Data in a 77-Year-Old Woman With Necrotizing Fasciitis

	AMBIENT PRESSURE (ATA)	F_{IO_2}	Pao_2 (mm Hg)	Pv^-o_2 (mm Hg)	Sv^-o_2 (%)	CARDIAC OUTPUT[a] ($L \cdot min^{-1}$)	HEART RATE (min^{-1})
A	1	2 $L \cdot min^{-1}$	130	33	61	3.7	102
B	2.5	1.0	>1,000	45	79	2.6	95
C	2.5	1.0	>1,000	56	88	3.6	101

[a] Note the decrease in cardiac output and heart rate with hyperbaric oxygenation (A, B). There was a significant increase in $Pv^-_{O_2}$, which increased further when cardiac output was increased because of a reduction in afterload with sodium nitroprusside infusion (C). At pressure, $Pv^-_{O_2}$ and $Sv^-_{O_2}$ are significantly higher than usually observed at 1 ATA.

for HBO, the authors arbitrarily aim to raise Pa_{O_2} to more than 1,000 mm Hg for routine long-term therapy and to as high a level as possible consistent with patient

safety for treatment of acute necrotizing infections.

A better monitor of tissue oxygenation may be mixed venous P_{O_2} ($P_{\bar{v}O_2}$), which, in the absence of shunts, may be a reasonably accurate estimate of mean tissue P_{O_2}. [92] In critically ill patients with pulmonary artery catheters, routine measurement of $P_{\bar{v}O_2}$ is a convenient method of estimating the degree to which HBO therapy is delivering additional O_2 to tissue. A low value usually indicates insufficiently high oxygen delivery. An example is shown in Table 67-8 .

Normal values for pH and P_{CO_2} under hyperbaric conditions are the same as they are at 1 ATA. This has been shown up to an ambient pressure of 66 ATA. [93] P_{CO_2} (and hence pH) should not be expected to change significantly in blood samples that are decompressed, as noted earlier. Therefore, values of P_{CO_2} and pH measured in a blood gas laboratory at 1 ATA on samples of blood decompressed from a chamber can be relied on for clinical purposes.

Mechanical ventilation in a hyperbaric environment presents a variety of challenges. The ideal requirements for ventilation include small size, no electrical requirement, no use of flammable lubricants, ability to operate on a volume-cycled basis over a wide range of tidal volumes and respiratory rates, minimal modification requirement for installation, and ability to provide positive end-expiratory pressure, as well as to ventilate in intermittent mandatory ventilation and assist/control modes. [94] Additionally, the ideal gas source to actuate the ventilator should minimize the risk of combustion caused by build-up of static electricity.

As ambient pressure increases, gas density is proportionately raised, whereas there is relatively little change in gas viscosity. Therefore, in regions of turbulent flow (i.e., in the large airways), airway resistance would be expected to increase. Indeed, Anthonisen et al [95] found that lung conductance (the reciprocal of resistance) during tidal breathing changed with gas density according to the following formula:

where G is lung conductance at gas density rho; G_0 is the conductance at gas density 1.1 g/L (1 ATA); and kappa is a constant that was found to have a mean value of -0.39. At 6 ATA, this equation would predict that lung conductance would decrease by 50 percent, which is equivalent to a doubling of pulmonary resistance. A similar decrement in maximum voluntary ventilation has been observed at gas densities up to 25 times greater than at atmospheric pressure. [93] [96] The effect of increased gas density in raising flow resistance also applies to ventilator circuits.

These findings are of importance when mechanically ventilating healthy persons, because a higher peak inspiratory pressure is expected. They are of considerably greater importance when ventilating a person with high airway resistance. A patient requiring mechanical ventilation at a minute volume close to that individual's maximum voluntary ventilation at 1 ATA may not be adequately ventilated in a hyperbaric chamber, with resulting hypercapnia because of pulmonary mechanical limitation. This problem may be compounded by an increase in physiologic dead space, which has been observed in saturation divers while breathing gas with density 8 to 17 times greater than sea level air. [93] The cause of this is unknown; however, its result is an increased ventilatory requirement. Clinical experience suggests that it is not a major factor at 3 ATA; however, there is insufficient clinical experience at higher ambient pressures used clinically (e.g., up to 6 ATA) to estimate its effect. The probability of hypercapnia during mechanical ventilation of patients undergoing hyperbaric therapy can be minimized by routine measurement of Pa_{CO_2} and appropriate ventilatory adjustment.

Several types of ventilators have been used and tested in hyperbaric chambers. Pressure-cycled devices such as the Bird ventilator have been used with some success, because their compactness admirably fulfills the requirement for small size. However, continual adjustment of rate and cycling pressure is necessary with changes in ambient pressure. Systematic evaluation of two Bird (Bird Products Corp., Palm Springs, Calif. http://www.birdprod.com) ventilator models and a Mark 2 model modified for hyperbaric use by adding inspiratory and expiratory flow cartridges was performed by Gallagher et al. [97] Two of the Bird ventilators failed at 3 ATA, and one failed at 4 ATA. All the devices tested varied their tidal volumes and ventilatory rates with changes in ambient pressure. Several volume-cycled ventilators have been tested and found to be superior. The pneumatic Emerson ventilator (JH Emerson Co., Cambridge, Mass. http://www.jhemerson.com) functioned satisfactorily up to 6 ATA. [97] The disadvantages are that this ventilator was designed only to be used in control mode, and its leather bellows are lubricated with mineral oil, which violates most hyperbaric safety standards. The Penlon Oxford ventilator

(Penlon Ltd., Abingdon, Oxon, UK) has been tested to 6 ATA in a compressed-air environment and to 31 ATA in heliox. [98] It delivered 800-mL tidal volume at stable rates and expired volume over its entire pressure range. The Monaghan 225 ventilator (Monaghan Medical Corp., Plattsburgh, New York) works well in the hyperbaric environment, delivering up to 18 L/min at 6 ATA over a range of tidal volumes from 0.2 to 2 L. [94] Its main disadvantages are its tendency to decrease cycling rate with increasing pressure, requiring some adjustment of rate during compression, and the requirement of its standard mode of operation to be supplied with compressed O_2 rather than with air. However, a simple modification allows it to be powered with compressed air (Fig. 67-11). (Figure Not Available) The authors have used this ventilator for hundreds of hours without malfunction. Another ventilator that has been used in a hyperbaric environment is the Siemens 900C [99] (Siemens Medical Systems Inc., Danvers, Mass http//www.siemens.vents.com). This ventilator is widely used in critical care units and would be an excellent clinical tool in the hyperbaric setting because of its flexibility and compactness. However, tidal volume measured by the ventilator is inaccurate at increased ambient pressure because of the use of screen-type pneumotachographs, which have density-dependent characteristics. Other ventilators used in the hyperbaric environment include the Bennett PR-2, [100] Drager Hyperlog [101] (Dragerwerk, Lubeck, Germany http://www.draeger.com), LAMA-RCH (Laboratoires de Mechanique Appliquee, Egly, France), [102] Logic-03, [103] Penlon Nuffield 200 (Penlon Ltd., Abingdon, Oxon, UK), [104] Pneumatic Emerson (JH Emerson Co., Cambridge, Mass., http://www.jhemerson.com) [97] PneuPAC variant HB (Pneupac Ltd., Luton, Bedfordshire, UK), [105] and Sechrist 500A (Sechrist Industries Inc., Anaheim, Calif. http://www.sechristind.com). [100]

Two safety considerations are worthy of mention. First, in any ventilator delivering enriched O_2, there is a potential for O_2 build-up within the housing. A fire hazard may exist if electrical components surrounded by high O_2 concentration overheat or spark. Moreover, leakage of O_2 from the housing into the chamber may cause rapid O_2 build-up in the chamber atmosphere. The O_2 leakage rate of the Monaghan 225 specified by the manufacturer is on the order of 18 to 20 L/min at 1 ATA. At 2.8 ATA, this was estimated to be close to 60 L/min, [94] a rate that may be inconveniently high in a small chamber. The effect of this leakage on chamber O_2 concentration may be minimized in practice by inserting scavenging tubing into the ventilator cowling, thus removing a large proportion of the leakage O_2 through the chamber overboard dump system. Modification of this ventilator to compressed air actuation [94] eliminates O_2 leakage other than from the patient's expired gas. The other safety consideration is the reliability and safety of electrical components. Large sealed components such as power transistors, Nixie tube displays and cathode ray tubes are inherently fragile at high ambient pressure. Integrated circuit chips, light-emitting diode displays, and discrete components such as resistors

Figure 67-11 (Figure Not Available) Monaghan 225 ventilator modified for use in hyperbaric chamber. A gas-mixing system with two ball rotameters has been added to provide the inspired gas, which enters the ventilator via a conduit attached to the air intake. The F_{IO_2} setting has been permanently set at 21 percent in order to force the ventilator to use the externally mixed gas as the breathing gas. The F_{IO_2} adjustment knob has been removed. A 5-L reservoir bag is attached to the patient gas circuit. A reservoir relief valve prevents overpressurization of the reservoir bag. A subambient pressure-relief valve allows entrainment of room air if insufficient gas is provided to the reservoir bag. *(From Moon et al [94])*

and capacitors are relatively resistant to changes in ambient pressure. Nevertheless, whenever there is a risk of overheating of a component, purging the device with an inert gas will likely prevent ignition (see later).

Air-filled endotracheal tube cuffs tend to lose volume during compression and reexpand during decompression. Therefore, either continuous adjustment of the air pressure within the cuff manually or the easier measure of filling the cuff with water obviates these difficulties.

Atmosphere Control

Careful control of the chamber atmosphere is essential to provide a safe environment for the patient and tender. The major components of atmosphere quality control

are O_2 , CO_2 , and trace gases.

In a multiplace chamber, it is essential that the patient breathe as high a concentration of O_2 as possible (usually 98%) and that the O_2 concentration within the chamber be maintained at close to 21 percent in order to minimize fire hazard. In some hyperbaric units, head-tent O_2 concentration is routinely monitored. In others, the concentration is assumed to be high because of a high rate of O_2 flow through the head tent. Leakage of O_2 from head tents, masks, and ventilators tends to raise the atmospheric O_2 concentration. Typically, an upper limit of around 23 percent is used as a criterion for ventilating the chamber with air or 100 percent nitrogen until the O_2 concentration decreases. Monoplace chambers are continuously ventilated at 85 to 240 L/min, a rate that usually keeps the O_2 content close to 100 percent.

CO_2 control, particularly within a head tent, is important because significant elevations of inspired CO_2 concentration potentiate O_2 toxicity, as noted earlier. Some physicians believe that a small amount of CO_2 in the inspired gas may be beneficial in order to vasodilate ischemic tissue and increase O_2 delivery. No data are available to recommend one approach over the other. A typical standard for the upper limit for head-tent CO_2 is 1 percent "surface equivalent" CO_2 , equal to a partial pressure of 7.6 mm Hg. Chamber CO_2 is usually limited to around 0.5 percent surface equivalent (ambient P_{CO_2} 4 mm Hg), although in nonsaturation dives, it is very unlikely that CO_2 would approach this value except in a very small chamber. Using a nonscrubbing (open-circuit) system, head-tent O_2 flow rates of 40 to 60 L/min (measured at chamber pressure) are usually adequate to keep CO_2 levels appropriately low.

Trace gases that may enter the environment include CO and hydrocarbons from improperly functioning compressors or from automobile exhaust that may be near the compressor air intake. Volatile gases such as alcohol vapor from skin disinfectant solutions and mercury vapor from spillage of sphygmomanometer columns may also pollute the atmosphere. Trace gases become extremely important in hyperbaric chambers because of the increase in partial pressure that occurs with increasing ambient pressure. For example, although a CO concentration of 50 ppm is acceptable for a short time at 1 ATA, the same concentration at 6 ATA is equivalent to 300 ppm, a level that is clearly unacceptable. Compressed air from the chamber banks should be submitted periodically for analysis of trace gases. Nonvolatile skin preparation solutions such as benzalkonium or iodine compounds minimize pollution of the chamber atmosphere. It is recommended that mercury in any form should be excluded from hyperbaric chambers. There is at least one chamber in the United States that had to be decommissioned because of pervasive mercury vapor contamination due to spillage. Acute mercury poisoning has also occurred in occupants of a hyperbaric chamber when mercury from a broken thermometer fell on the floor and remained undetected.

Considerations of battery use may have implications for chamber atmosphere control as well as fire hazards. All batteries release small quantities of hydrogen, although not usually in amounts that would be hazardous. As mentioned previously, lithium-sulfur dioxide batteries carry a theoretical risk of sulfur dioxide discharge. Similarly, there is an objection to the use of mercury cells. Release of inert gas taken up by the battery during the dive may theoretically result in leakage of mercury into the atmosphere. The risk of this must be weighed against the potential benefits (e.g., of using mercury cell-powered temporary pacemakers). Alkaline cells are considered safe, although temporary failure has been observed at extremely high ambient pressures (40-60 ATA). The only battery that has been specifically tested at increased ambient pressure is the lead-acid, gelled electrolyte battery, which has been specifically tested up to 8 ATA. [106] After pressure compensation with mineral oil, these batteries in fact may operate satisfactorily to an ambient pressure of 680 ATA.

Fire Hazards

Although fires in hyperbaric chambers are rare, they are usually lethal. The effects of fire at elevated ambient pressure can be devastating so fast that the fire extinguisher system may not be activated until all occupants of the chamber have died. The very real risk of fire in hyperbaric chambers has been illustrated by accidents in which chamber fires were started by a hand warmer, a sparking toy, and other sources of ignition carried into the chamber in the patient's clothing. Minimization of these risks involves the following: control of chamber O_2 concentrations (irrelevant in a monoplace chamber); minimizing the use of combustible materials within the chamber; controlling sources of heat and spark; and chamber fire extinguisher system.

The geometric increase in burning rate with increases in O_2 concentrations mandates careful monitoring of chamber O_2 , as already noted. At increased ambient pressure, burning occurs more rapidly, even when the O_2 concentration is 21 percent. It is important to ensure that patients do not carry cigarette lighters, matches, battery-operated devices, or other sources of combustion into the chamber. Cotton garments, which tend not to result in build-up of static charges, are generally considered safest. Flame-retardant materials may be of benefit, but in a monoplace chamber, they will probably burn nearly as quickly as untreated material. Hair grease should be removed. Humidification of the O_2 within the head tent helps to minimize the risk of static electricity build-up in hair. Hydrocarbon lubricants (e.g., for stretcher wheels) should be scrupulously avoided because they may spontaneously ignite on contact with aluminum in the presence of high O_2 tensions. Nonflammable fluorocarbon lubricants are recommended.

Sources of sparks from electrically powered equipment should be minimized. Plugging and unplugging electrical cables during hyperbaric treatments are sources of sparking that can be eliminated by taping all electrical plugs onto female receptacles prior to compression. In multiplace chambers, the flammability of electrically powered devices (e.g., intravenous controllers) can be reduced by purging with 100 percent nitrogen or helium via ports drilled in the covering, at a rate sufficient to keep O_2 concentration at a level that does not support combustion, typically at a flow rate of two to three times the internal volume per minute. Electrical systems used in monoplace chambers must comply with specific codes, which specify the types of switches, grounding, and insulation that can be used. [68]

Fluorinated anesthetics can be combustible at 1 ATA in high concentrations. Brown and Morris [107] observed that, in 100 percent O_2 , halothane up to saturation (33%) in an open tube was nonflammable. In a closed-tube concentrations of 20 to 22.5 percent would allow propagation of ignition. Lower halothane concentrations propagated ignition when nitrous oxide was used as the diluent gas. Electrical sparking did not result in ignition of enflurane at concentrations up to 5 percent in 100 percent O_2 or nitrous oxide in a closed tube at 3 ATA. [108] Isoflurane and sevoflurane Drager vaporizers have been tested up to 3 ATA using 100 percent O_2 , with no evidence of spontaneous combustion at room temperature. Given the experience with halothane under hyperbaric conditions, without any reported fires, and the resistance to combustion in 100 percent O_2 at 1 ATA, in the absence of a source of ignition, it is not likely that any of the modern fluorinated anesthetics pose a fire safety hazard in the hyperbaric environment.

Evaluation of a Patient for Safety of Hyperbaric Oxygen Treatment

In addition to ensuring that HBO is indicated for the disease process in question, it is important to assess the patient in terms of general effectiveness and safety of HBO. The following issues should be addressed: whether a sufficient elevation in Pa_{O_2} can be obtained; whether the patient can equilibrate middle ear pressure; adequacy of control of seizure disorders; optimization of reversible obstructive lung disease and the presence of pulmonary bullae or blebs; whether hyperoxic myopia may critically affect vision; and whether claustrophobia may occur during treatment.

Predicted Pa_{O_2} in the hyperbaric chamber may be calculated by Equation 7. It can easily be predicted, for example, that a patient who has sufficient lung disease or injury such that Pa_{O_2} during treatment would not exceed 1,000 mm Hg would probably obtain marginal benefit from HBO unless the reason for HBO is gas bubble disease.

The ability to vent the middle ears may be estimated by observing directly the tympanic membrane while the patient holds his or her nose or performs a Valsalva maneuver. Movement of the eardrums indicates a patent eustachian tube and the ability to equilibrate middle ear pressure. If otic barotrauma is unlikely to be avoided (e.g., with mental obtundation or the presence of an endotracheal tube) or because of a condition that may render the patient susceptible to inner ear injury (e.g., stapedectomy), myringotomy or tube placement is often performed.

The presence of pulmonary bullae or blebs should be considered relative contraindications to HBO treatment. The low risk of pulmonary barotrauma must be weighed against the urgency or efficacy of HBO for treatment of the patient's disease process.

Because hyperoxia may result in generalized seizures, it is prudent to ensure that anticonvulsant medication has been optimized. It should be noted that HBO will

accelerate existing pulmonary O_2 toxicity. Therefore, significant pre-HBO exposure of the patient to high levels of inspired O_2 may also be a relative contraindication to HBO therapy, depending on the urgency of treatment.

For patients requiring more than 20 to 30 HBO treatments, periodic checks of visual acuity may be helpful to determine the onset of hyperbaric myopia. Consultation with an ophthalmologist may be required to advise the patient with impaired vision and in whom myopia due to HBO may further reduce vision. Because most hyperbaric chamber systems are small and cramped, patients who cannot tolerate enclosed spaces may require anxiolytic therapy to facilitate toleration of the HBO therapy.

Delivery of Anesthesia at Increased Pressure

A review of the problems of anesthesia under HBO was published as a report to a committee of the American Society of Anesthesiologists. [109] The report explored various issues, including the potential for nitrous oxide to be used as a sole anesthetic.

Anesthesia may be required as a procedure incidental to the hyperbaric exposure. Ross et al [110] considered the problems of anesthesia up to 35 ATA, in order to provide care for injured divers while in a saturation diving system (e.g., in North Sea oil fields). They suggested using intravenous agents for general anesthesia rather than gaseous anesthetics because of the problems of pollution of the chamber environment with the latter. Regional anesthesia was recommended whenever possible. The authors noted that muscle relaxants should be titrated to effect because some degree of pressure reversal at around 10 ATA has been reported.

Since the 1960s, anesthesia has been performed at increased ambient pressure using a variety of agents to facilitate surgery for carotid stenosis, [111] to perform cesarean section for fetal distress in a hypoxic patient, [112] to allow therapeutic lung lavage for patients with alveolar proteinosis, [65] [66] to perform emergency surgery in a saturation dive, [113] to increase oxygenation in open heart surgery, [63] and to enhance the effectiveness of irradiation of carcinoma. [114]

Inhaled Anesthesia

Nitrous Oxide

The increased ambient pressure in a hyperbaric chamber allows nitrous oxide to be used at partial pressures exceeding its minimum alveolar concentration (MAC). [115] Russell et al [116] observed that it was a less than ideal anesthetic during studies in normal volunteers administered 75 percent nitrous oxide in O_2 for 2 to 4 hours in a hyperbaric chamber at

an ambient pressure of 2 ATA. Hornbein et al performed a similar study at 1.87 ATA (82% nitrous oxide). Although in both studies induction of anesthesia by nitrous oxide was rapid (<60 s), it was accompanied by tachypnea, tachycardia, hypertension, diaphoresis, muscle rigidity, catatonic jerking of the extremities, eye opening, and opisthotonos. After 2 to 4 hours of anesthesia, subjects emerged rapidly from the anesthetic; however, the majority subsequently experienced nausea and vomiting, which was often severe. In a study of two volunteers briefly anesthetized with nitrous oxide at pressures up to 2 ATA, Smith et al [115] observed unexpectedly prolonged recovery in one subject.

A potential problem associated with nitrous oxide anesthesia at high ambient pressures is the possibility that tissues could become supersaturated during decompression, thus allowing bubbles to form (decompression illness). This was not observed by Russell et al, [116] who used an empirical staged decompression schedule with a decompression stop for 30 minutes at 1.3 ATA while the patients breathed 100 percent O_2. Bubble formation can occur without decompression if the patient breathes one gas while surrounded by an atmosphere of another gas that is more soluble. For example, breathing air while in a helium-O_2 environment at 5 to 7 ATA can lead to urticaria and vestibular dysfunction [117] because of rapid diffusion of helium into tissues, causing local inert gas pressure to exceed ambient pressure (isobaric gas counterdiffusion). This phenomenon can even occur at normal atmospheric pressure if a person breathes nitrous oxide-O_2 while surrounded by helium. [118] Therefore, it is imperative that nitrous oxide never be administered in a helium atmosphere.

If a rapid decompression procedure is implemented while the patient continues to breathe a nitrous oxide-O_2 mixture, large amounts of dissolved nitrous oxide will move from the tissues and blood into the lungs, possibly causing a significant degree of diffusion hypoxia. Therefore, an O_2-enriched breathing mix should be administered for several minutes prior to decompression.

Inhaled anesthesia of any type will pollute the enclosed chamber atmosphere with anesthetic gases. Russell et al [116] reported nitrous oxide concentrations in chamber air of 2,500 ppm; ventilation of the chamber with air at a high rate (3,500 L/min of air) was required to reduce the concentration to 25 to 75 ppm. Contamination of the chamber atmosphere may exert pharmacologic effects on medical personnel inside the chamber, particularly at high ambient pressures.

In patients who have recently engaged in scuba diving or have suffered decompression illness, nitrous oxide should be avoided even at 1 ATA, because its administration may result in tissue or blood bubble growth and recrudescence of pain or neurologic symptoms. Such a case, in a patient who developed neurologic symptoms after a nitrous oxide anesthetic regimen following apparent spontaneous resolution of decompression illness, has been reported by Acott and Gorman. [119]

Volatile Anesthetics

Halothane, the most commonly administered volatile agent, has been found both safe and effective in the hyperbaric environment. Although the effect of increased ambient pressure in reversing anesthesia is minimal at 6 ATA, there are effects of increased ambient pressure on the behavior of vaporizer systems.

The effect of a volatile anesthetic on a patient is proportional to the partial pressure of that anesthetic, not to the alveolar concentration. For example, the effect of 1 percent halothane at 1 ATA (with a partial pressure of 7.6 mm Hg) is equivalent to a 0.5 percent concentration at 2 ATA (with the same partial pressure).

Consider the behavior of a traditional copper kettle vaporizer system, in which oxygen saturated with anesthetic vapor is blended with fresh gas. The percentage concentration of an anesthetic in the gas leaving the system is given by the following formula:

where P_v and P_b are the anesthetic vapor pressure and barometric pressures, respectively, and V_k and V_b are the kettle and bypass gas flows. Multiplication of the right side of this equation by P_b gives the partial pressure of the anesthetic:

Calculation of partial pressures of halothane leaving the vaporizer system at 1, 2, and 3 ATA, using bypass gas flow of 5 L/min, kettle flow of 0.1 L/min, and vapor pressure of halothane 243 mm Hg, produces values of 6.94, 5.65, and 5.92 mm Hg, respectively. Despite the 300 percent increase in ambient pressure from 1 to 3 ATA, there is only a 23 percent change in delivered halothane partial pressure at constant flow settings. Therefore, one can estimate delivered anesthetic potency using the same rules of thumb regarding flow rates at any clinically useful ambient pressure. One caveat is that rotameter flowmeters calibrated at 1 ATA indicate falsely high values in the chamber because of the increased gas density. McDowell [120] reported the following relationship for rotameter flow:

where $Flow_{actua}$ and $Flow_{read}$ are the actual and scale reading flows, and rho_1 and rho_P are the gas densities at 1 ATA and P ATA, respectively. This inaccuracy in rotameter performance up to 4 ATA has been confirmed by others [109] (Fig. 67-12) (Figure Not Available) . Although both V_b and V_k are indicated inaccurately by a rotameter, the ratio of flow rates, (V_b /V_k), should be indicated within tolerable clinical accuracy. Therefore Equation 10 remains valid within clinically acceptable limits.

As discussed previously, copper kettle systems should deliver anesthetic partial pressures that are relatively unchanged at varying ambient pressures. The behavior of an anesthetic-specific calibrated vaporizer also should theoretically deliver a constant partial pressure of anesthetic if the ratio of gas flow through the vaporizer to bypass the flow remains the same (Fig. 67-13) (Figure Not Available) . Because of the effect of increased gas density on this flow ratio, in practice the delivered

Figure 67-12 (Figure Not Available) Performance of anesthetic vaporizer system at increased ambient pressure. (A) Flow characteristics of a rotameter system as shown. At 4 ATA the actual delivered flow is less than 60 percent of the flow indicated by the rotameter. (B) Fluotec vaporizer output in partial pressure of halothane as a function of ambient pressure. A small increase in delivered partial pressure is evident at 3 ATA, particularly at 2 and 3 percent settings. *(From Committee on Hyperbaric Oxygenation, [219] copyright 1966, by the National Academy of Science. Courtesy of the National Academy Press, Washington, D.C.)*

partial pressure is somewhat dependent on ambient pressure. A slightly increased partial pressure of halothane delivered by a Fluotec vaporizer at 3 ATA has been observed [109] (see Fig. 67-12 (Figure Not Available)). Drager isoflurane and sevoflurane vaporizers deliver constant vapor partial pressures with acceptable accuracy at ambient pressures up to 3 ATA.

Intravenous Anesthesia

Intravenous agents behave similarly and are unlikely to be affected within the usual clinical range of ambient pressure. There is no evident alteration in the pharmacokinetics of either meperidine [24] or pentobarbital [25] at ambient pressures up to 6 ATA. For therapeutic lung lavage, the authors have provided anesthesia at ambient pressures up to 3 ATA using conventional doses of ketamine and benzodiazepines or propofol and narcotics with nondepolarizing muscle relaxants.

Regional Anesthesia

Regional anesthesia is likely to be both safe and effective in a hyperbaric environment by avoiding the requirement for mechanical ventilation. A bowel resection has been performed at an ambient pressure 6.75 ATA in a helium-O_2 environment using local injection of lidocaine supplemented with parenteral meperidine. [113] When administering intravenous solutions or spinal or epidural anesthesia at increased ambient pressure, care should be taken to avoid injecting air bubbles, which would then expand during decompression and could cause symptoms. Extreme care should be taken to ensure sterile technique because of the

Figure 67-13 (Figure Not Available) Behavior of an ideal Fluotec vaporizer at 1 and 3 ATA. If the ratio of the O_2 flows (anesthetic vaporizer flow/bypass flow) is unchanged at different ambient pressures, it can be seen that the partial pressure of halothane delivered at the exit of the vaporizer is constant. *(From Smith [65])*

propensity for enhanced bacterial growth in the warm, humidified environment of a hyperbaric chamber, particularly during saturation chamber exposures.

EFFECTS OF ALTITUDE

There are approximately 40 million people worldwide living permanently at altitudes higher than 2,439 m and possibly an equal number who visit high altitudes each year, [121] many of whom will require medical care. There is therefore clearly a need for anesthesia and critical care practitioners to understand the physiology of this environment.

Unlike the relationship between ambient pressure and water depth, the relationship between pressure and altitude is nonlinear (see Fig. 67-2 .) The physiologic effects of altitude exposure are mainly attributable to reduction in the following three variables: inspired P_{O_2}, ambient pressure, and gas density. Extreme or prolonged altitude exposure may be accompanied by additional factors, which may modulate physiologic responses, such as hypothermia, exertion, dehydration, and polycythemia.

Hypoxia

Physiologic Changes

O_2 partial pressures from inspired to venous, at various altitudes, are shown in Figure 67-14 (Figure Not Available) . The major mechanism resulting in hypoxia at altitude is the reduction in inspired P_{O_2}. However, an additional reason for arterial hypoxemia is the failure of erythrocytes in the pulmonary circulation to equilibrate fully with alveolar gas (diffusion nonequilibrium). [122] This is especially likely to be important during exercise, when increased pulmonary blood flow reduces capillary transit time. In addition, there is increased ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch, believed to be related to pulmonary hypertension. [123]

The effects of hypoxia on normal physiology have been reviewed by Kafer and Sugioka [124] and by West. [125] The responses to acute hypoxia include increased heart rate and cardiac output. There is a corresponding increase in organ blood flow, including cerebral blood flow. Hypoxia also induces hyperpnea (because of increased breathing rate), to a degree that varies considerably among individuals. End-tidal P_{CO_2} measured in one subject breathing air at the summit of Mt. Everest (barometric pressure 263 mm Hg) was 7.5 mm Hg, whereas P_{AO_2} was 37.6 mm Hg. [126] This hypocapnia has several effects. It results in an increased affinity of Hb for O_2 (leftward shift of the Hb-O_2 dissociation curve), which enhances oxygenation of blood at the lung while simultaneously interfering with transport of O_2 from tissue capillary to mitochondrion. The overall effect on O_2 transport is beneficial. [127]

Hypoxemia may be particularly accentuated during sleep. Figure 67-15 (Figure Not Available) depicts continuous ear oximetry during sleep at an altitude of 4,400 m, demonstrating the severe degree of arterial Hb-O_2 desaturation that can occur. [128]

Acute exposure to altitudes in the range of 4,000 to 5,000 m results in arterial hypoxemia (Pa_{O_2} 40 mm Hg) and an arterial Hb-O_2 saturation of approximately 75 percent. Although

Figure 67-14 (Figure Not Available) Oxygen tension at rest and during exercise, from inspired air to mixed venous blood. Circles indicate sea level (P_{IO_2} 149 mm Hg); upward triangles signify P_{IO_2} 80 mm Hg; squares indicate P_{IO_2} 63 mm Hg; downward triangles represent P_{IO_2} 49 mm Hg; diamonds represent P_{IO_2} 43 mm Hg (equivalent to the inspired O_2 tension at the summit of Mount Everest). Data were obtained from Operation Everest II, in which normal male volunteers underwent decompression over 40 days to simulate a climb to the peak of Mount Everest. *(From Sutton et al [220])*

colors may be perceived as somewhat less bright than normal, other than limitation of exercise capacity, at these altitudes there are no other major temporary or permanent impairments of performance. Acute exposure to mild hypoxia appears not to result in any permanent ill effect. Crow and Kelman [129] found no detriment on test of free recall and visual scanning when healthy subjects were exposed to a simulated altitude of 3,658 m (inspired P_{O_2} 92 mm Hg). One measure of performance during hypoxia that is used in aviation physiology is the effective performance time, defined as the amount of time the individual is able to perform useful flying duties. [130] In an unacclimatized person at 5,500 m altitude, the effective performance time is 20 to 30 minutes, which is reduced to 2.5 to 3 minutes at 8,500 m and 1 to 2 minutes at 9,100 m.

Gradual exposure to altitude or long-term exposure results in a series of adaptive changes, allowing individuals to function extremely well and to do substantial physical work at altitudes at which newcomers can barely function. For instance, Mt. Everest has been climbed without the benefit of supplemental O_2, whereas acute exposure to such an altitude would result in rapid loss of consciousness. Subjects exposed to a progressively lower barometric pressure, reaching to simulated altitude of 8,848 m in a hypobaric chamber

Figure 67-15 (Figure Not Available) Ear oximetry in a subject at an altitude of 4,400 m on Mt. McKinley. The subject had no symptoms on the evening of the study, but the next day developed severe acute mountain sickness when he attempted to ascend to a higher altitude. He exhibited no increase in ventilation when exposed to hypoxia (absent hypoxic ventilatory response). *(From Hackett and Roach [126])*

over the course of 40 days, were able to work on an exercise ergometer at 120 watts while their mean Pa_{O_2} was only 30 mm Hg (arterial Hb-O_2 saturation 58%). [131] In the same study, blood Hb concentration increased from 13.5 to 17.0 g/dL (hematocrit, 40.4-51.9%). The development of polycythemia is perhaps one mechanism by which tolerance to hypoxia occurs. However, the mechanisms of adaptation are still incompletely understood.

One of the adaptive mechanisms is a gradual reduction in plasma bicarbonate, [131] preceded by a decrease in cerebrospinal fluid bicarbonate, [132] tending to offset the initial respiratory alkalosis. After a 40-day simulated climb of Mt. Everest in a hypobaric chamber, resting serum bicarbonate had decreased from 22.2 to 9.9 mmol/L, whereas pH had increased from 7.43 to 7.56. [131] Other adaptive changes include increases in hematocrit and capillary density, as well as undoubtedly other mechanisms as yet undiscovered.

Despite the adaptive mechanisms, careful neuropsychologic testing of subjects before and after mountaineering expeditions to altitudes of 7,000 m or greater have shown evidence of mild persistent performance impairment. [133] [134] Although it is not certain that these abnormalities on for-mal testing are of any functional significance, investigators have reported that impairments may last for up to several months after exposure. Individuals who have the most vigorous hypoxic ventilatory response, and who therefore hyperventilate the most, usually tolerate altitude exposure the best. However, Hornbein et al [133] have shown that neuropsychologic impairment after prolonged extreme altitude exposure is correlated with a brisk hypoxic ventilatory response. These authors hypothesized that despite a higher Pa_{O_2} in individuals with a vigorous hypoxic ventilatory response, brain O_2 delivery may be lower because of hypocapnic cerebral vasoconstriction.

Support for this hypothesis is provided by a study in which hypocapnia was shown to result in a reduction in brain blood volume and cytochrome redox. [135]

Effect of Maternal Hypoxia on the Fetus

Data on the fetal effects of maternal hypoxia are sparse. However, using changes in fetal heart rate as an end point, the fetus appears to be relatively resistant to moderate degrees of maternal hypoxia. Administration of 15 percent O_2 (inspired P_{O_2} = 108 mm Hg, equivalent to 2,500 m altitude) for 4 minutes to 5 primigravid women at 36 to 38 weeks' gestation resulted in an increase in fetal heart rate of only 2 to 3 beats/min. [136] The same investigator observed no change in fetal heart rate after administration of mixtures as low as 10 percent O_2 (inspired P_{O_2} = 71 mm Hg, equivalent to 5,300 m altitude) for 20 minutes in 8 of 28 pregnant women. Polvi et al [137] administered 10 percent O_2 for 10 minutes to pregnant women at 35 to 41 weeks' gestation. Fetal heart rate, heart rate variability, and Doppler velocimetry in the umbilical and middle cerebral arteries of the fetus were unchanged from baseline. Acute hypoxia of this magnitude appears to exert no detectable effects on the healthy fetus, because of augmentation of uterine blood flow. It is therefore unlikely that acute exposure to altitudes up to 2,500 to 3,000 m would adversely affect the fetus.

Additional adaptations to long-term altitude exposure specific to pregnant women include an increase in placental capillary volume and a reduction in villous membrane thickness. [138] Babies born at altitude, even as high as 4,329 m, have scalp vein O_2 tensions similar to values obtained from babies born at sea level. [139] Consequently, a significant reduction in maternal O_2 delivery can be tolerated without any impact on fetal O_2 consumption.

Mountain Sickness

Acute exposure to altitude often results in a constellation of signs and symptoms known as acute mountain sickness (AMS). The most common symptoms are headache, decreased appetite, nausea and vomiting, insomnia, and peripheral edema. [140] AMS can occur after several hours of exposure to elevations higher than 2,500 to 3,000 m, although there is interindividual variation in susceptibility. Approximately 25 percent of visitors to ski resorts in the American Rockies (altitude 1,920-2,960 m) develop AMS. [141] Parenthetically, it is tempting to speculate that the headache that frequently occurs in patients receiving narcotic analgesia after surgery may be due to a form of "AMS" caused by mild hypoxemia. Effective prophylactic measures against AMS in mountaineers include slow ascent (300 m/d) or "staging" in which several days are spent at an intermediate altitude of around 2,000 m. [140] Pharmacologic prophylactic measures include the administration of acetazolamide, [142] which is believed to work by augmenting the ventilatory response to hypoxia because of the metabolic acidosis that occurs following its administration. A dose of 250 mg orally twice daily begun the day before ascent is effective. Dexamethasone has also been shown to be effective in a dose of 4 mg every 6 hours, although symptoms may occur as soon as it is discontinued. [143] [144] Despite its value in preventing HAPE (see later), nifedipine does not prevent AMS symptoms. [145]

Less frequent complications of hypoxia are high-altitude pulmonary edema (HAPE) and high-altitude cerebral

edema (HACE). [146] [147] [148] A hemodynamic pathophysiology for HAPE is suggested by its tendency to occur when pulmonary vascular flows or pressures are particularly high, such as in individuals with an exaggerated pulmonary hypertensive response to hypoxia and in the lung contralateral to a unilateral absence of the pulmonary artery. [149] In addition, in HAPE-susceptible individuals, the probability of a recurrence can be reduced by administration of slow-release nifedipine, 20 mg every 8 hours. [150] On the other hand, bronchopulmonary lavage in subjects with HAPE has revealed that the protein content of the edema fluid is high, implicating an increase in permeability. [151] [152] Paradoxically, measurement of transcapillary escape rate of albumin has revealed no altitude-related increase. [153] A hypothesis that connects mechanical forces in the pulmonary circulation with increased pulmonary capillary permeability suggests that HAPE may be caused by stress failure of pulmonary capillaries resulting from the acute elevation of pulmonary artery pressure. [154]

Most individuals recover from AMS after several days at altitude. However, patients with severe cases, in which there is HAPE or HACE, require treatment, the most efficacious of which is descent or administration of supplemental O_2 . Descent can be simulated by placing the patient inside a commercially available lightweight collapsible bag (Gamow bag), which can be pressurized to about 120 mm Hg higher than ambient pressure with either a foot-powered or an electric pump. Kasic et al [155] have reported that the Gamow bag is as effective as supplemental O_2 for the treatment of AMS at an altitude of 2,850 m. Acetazolamide has also been reported to be effective; when 250 mg was given orally and repeated 8 hours later, symptoms of AMS at 4,200 m were eliminated in five of six climbers within 24 hours. [156] Dexamethasone 4 mg every 6 hours is also effective [157] ; in a randomized, controlled trial at an altitude of 4,559 m, dexamethasone, 8 mg orally followed by 4 mg every 6 hours, provided more sustained improvement, although less rapid relief of symptoms, than 1 hour of compression in a Gamow bag to a gauge pressure of approximately 0.2 atm. [158] The headache may respond to aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs or small doses of a narcotic such as codeine. Sumatriptan, 100 mg orally, also appears to provide temporary relief of the headache associated with AMS. [159] Pulmonary artery pressure can be lowered in patients with HAPE with nifedipine, hydralazine, or phentolamine. [160] Scherrer et al [161] administered 40 ppm nitric oxide (inspired O_2 concentration 20%) by inhalation to individuals with HAPE at 4,559 m altitude (barometric pressure 440 mm Hg) and observed a reduction in pulmonary artery pressure and improvement in arterial Hb-O_2 saturation (67% preinhalation to 73%) after breathing nitric oxide for 15 minutes. When treating a patient with HAPE, if descent or treatment with O_2 are not immediately possible, then pharmacologic reduction in PA pressure should be initiated. Nifedipine, 10 mg sublingually followed by 20 mg of a slow-release preparation administered orally every 6 hours, was successful in treating six patients with HAPE. [162]

A few high-altitude residents develop symptoms consisting of headaches, bone pain, confusion, sleeplessness, and a sensation of congestion in the head, often accompanied by extreme polycythemia, a constellation of findings known as Monge's syndrome. [163] Clinical improvement and increased work capacity often result from phlebotomy, and descent to lower altitudes relieves the symptoms completely.

Reduction in Ambient Pressure

Acute ascent to altitude can cause bubbles to form within tissues as a result of local supersaturation of inert gas. Symptoms of decompression illness rarely occur unless a rapid ascent occurs from sea level to an altitude of 5,000 to 6,000 m, [164] although symptoms have rarely occurred after ascent to only 2,437 m. [165] After scuba diving, exposure to even lower altitudes (2,400 m) within 12 to 24 hours can precipitate decompression illness. [166] In order to reduce the risk of decompression illness, it is the practice of individuals planning a rapid decompression to low ambient pressure (e.g., military pilots, astronauts) to denitrogenate their tissues by prebreathing 100 percent O_2 for periods ranging from a few minutes to several hours, depending on the altitude of the planned exposure.

Reduction in Gas Density

Reduction in gas density results in lower breathing resistance. Varene et al [167] examined the effect of ambient pressure from 0.5 to 5 ATA on airway resistance in healthy persons. Their data can be summarized by either of the following equations:

or:

where P_{ATA} is ambient pressure in ATA, R_P is airway resistance at ambient pressure; and R_0 is airway resistance at 1 ATA. For example, at an ambient pressure of 0.5 ATA (5,486 m), airway resistance is reduced by approximately 20 percent. Under resting conditions, differences in breathing pattern during altitude exposure,

compared with a similar degree of hypoxia at sea level, are minor. [168]

Other Environmental Stresses at Altitude

Individuals at altitude are subjected to low temperature, wind, and ultraviolet radiation. The effects of hypoxia may therefore be compounded by hypothermia, dehydration, frostbite, and sunburn.

Anesthesia at Altitude

General Principles

Because of the reduced ambient P_{O_2} at high altitudes, the risk of perioperative hypoxia is likely to magnified. Newcomers

to altitude are likely to be particularly susceptible. Opiates depress both the tachycardia and hyperpnea that normally occur in response to acute hypoxemia. Slow recovery of consciousness and postanesthetic headache have been reported after anesthesia using thiopental with air or nitrous oxide. [169] When ventilation was assisted or controlled during the anesthetic regimen and when postoperative supplemental O_2 was administered, these complications did not occur, a finding that suggests that intraoperative or postoperative hypoxemia may be a pathophysiologic factor. On the other hand, long-term residents at altitude may be more tolerant of hypoxemia; in such individuals, other considerations may be important, including the higher baseline hematocrit, pulmonary hypertension, and lower Pa_{CO_2} and bicarbonate concentrations. [131] [170] In order to prevent renal retention of bicarbonate, which reduces ventilatory drive, patients requiring controlled ventilation should have the Pa_{CO_2} maintained at its baseline value rather than in the traditionally normal range. Similarly, maintenance of Pa_{O_2} within the sea level normal range results in loss of adaptation and difficulty in readapting the patient to room air breathing.

Increased oozing of blood from surgical wounds at altitude has been reported. [146] This has been attributed to higher venous pressure, blood volume, vasodilatation, and increased capillary density. Camporesi [171] reviewed the topic of anesthesia at both high and low ambient pressures.

Anesthesia Equipment

James and White [172] tested Fluotec Mark II and Drager Vapor halothane vaporizers at sea level and at 5,000 ft (1,524 m), and 10,000 ft (3,048 m) of altitude. At any given setting, the delivered percentage of halothane increased with altitude; however, its partial pressure remained constant. Therefore, when these devices are used at a given vaporizer setting, anesthetic is delivered at a constant potency regardless of altitude.

The same authors [172] also examined the effect of altitude on floating-bobbin or floating-ball gas flowmeters. At 10,000 ft (3,048 m) of simulated altitude, both nitrous oxide and O_2 flowmeters underread the actual flow rate. The percentage error progressively increased up to 4 L/min, at which point both flowmeters were approximately 20 percent in error. A hazard may therefore arise when a low flow of O_2 is mixed with a higher flow of nitrous oxide. Unless an O_2 analyzer is available, the delivered percentage of O_2 may be significantly lower than that calculated on the basis of the flowmeter readings. Venturi-type gas mixing devices tend to deliver higher concentrations of O_2 at altitude than they do at sea level [172] ; at 10,000 ft (3,048 m) of altitude, a mask designed to deliver 35 percent O_2 at sea level actually delivered 41 percent O_2 .

General Anesthesia

The potency of anesthetic gases is proportional to their partial pressure. Therefore, as barometric pressure is reduced, fixed concentrations of inhaled anesthetics have lower potency. Cleaton-Jones et al [173] reported insignificant differences in the effect of nitrous oxide at sea level and at 1,700 m altitude. On the other hand, at an altitude of 3,300 m, James et al [174] showed a significant reduction in efficacy of 50 percent nitrous oxide in reducing pain threshold in normal volunteers (Table 67-9) . Because of this reduced effectiveness and the errors in administered gas concentration, which can occur because of altered gas flowmeter performance (see later), in the absence of accurate inspired gas monitoring, the risks associated with use of nitrous oxide at altitudes higher than about 2,000 m may exceed the benefit.

Because supplemental O_2 may not be available in some mountain locations, it may be imperative to choose an anesthetic technique that is least likely to suppress ventilation. Pederson and Benumof [175] reported using ketamine anesthesia with spontaneous ventilation in 23 patients requiring general anesthesia at an altitude of 1,830 m. Two patients developed significant, though brief, desaturation, which resolved quickly. The authors concluded that this form of anesthesia is a practical method in a rural hospital setting at altitude without access to supplemental O_2 . Nunn [176] reported successful induction of general anesthesia using halothane in a hypobaric chamber at a barometric pressure of 375 mm Hg (equivalent altitude = 5,490 m). A standard halothane vaporizer (Fluotec Mark II) was used, with an inspired O_2 concentration of 60 percent. Recovery was rapid and uneventful.

Regional Anesthesia

Spinal anesthesia has been reported to result in unacceptably high incidence of dural puncture headache. [169] Possible causes include chronically increased cerebrospinal fluid pressure, dehydration, and altered sensitivity of the altitude resident's CNS to intracranial pressure changes. [169] Headaches

TABLE 67-9 -- Effect of 50 Percent Nitrous Oxide on Pain Threshold in Normal Volunteers at High Altitude [a]

ALTITUDE (m)	BAROMETRIC PRESSURE (mm Hg)	INCREASE IN PAIN THRESHOLD (%)	SIDE EFFECTS
0	760	71.5	3 subjects, nausea; 2 subjects, semicomatose
1,460	636	40.0	None
3,300	517	19.0	None

Data from James et al [174]

[a] Pain threshold was measured in 20 subjects at each altitude by applying pressure to the anterior aspects of the tibia using a spring balance. Simulated altitude exposures were in a hyperbaric chamber. At increasing altitudes, a fixed concentration of nitrous oxide is progressively less effective.

were not reported in 20 young native mountain dwellers in whom Severinghaus obtained cerebrospinal fluid samples with 25-gauge needles. [169]

Perioperative Supplemental Oxygen

At high altitude, alveolar P_{O_2} is normally increased by hyperventilation induced by the hypoxic ventilatory drive. Administration of anesthetics or narcotic analgesics, both of which types of drugs blunt the hypoxic ventilatory drive, may therefore precipitate hypoxia. The resulting hypoxic symptoms of irritability, confusion, and restlessness may be misinterpreted as due to pain, and misguided administration of additional narcotics would only compound the problem. Nunn [176] refers to analgesic-induced respiratory depression as a likely cause of death in a Sherpa who had debridement of frostbitten fingers at 4,300 m altitude. Therefore, if analgesia

is necessary, supplemental O_2 may be required to prevent fatal hypoxia.

Effects of Commercial Air Travel

Cotrell [177] and Aldrete and Aldrete [178] recorded actual cabin altitude during commercial pressurized aircraft flights at 2,700 m, at which Pa o_2 in healthy individuals is likely to be around 50 to 55 mm Hg. This degree of mild hypoxemia (Sa o_2
90%) is well tolerated by healthy individuals. However, in a group of patients with chronic obstructive pulmonary disease (mean sea level Pa o_2 , 68 mm Hg), Pa o_2 at an altitude of 2,250 m was reduced to a mean of 44.7 mm Hg (lowest 25 mm Hg). [179] Arterial desaturation of this magnitude may be expected to cause symptoms. Indeed, Dillard et al [180] reported 44 patients with chronic obstructive pulmonary disease who had traveled by commercial aircraft. Of the 44 patients, 8 had experienced one or more of the following symptoms during flight: dyspnea, edema, wheezing, cyanosis, and chest pain.

It has been recommended that patients with baseline hypoxemia be considered for in-flight O_2 administration. Gong et al [181] described a high-altitude simulation test in which subjects were given hypoxic concentrations of O_2 in order to simulate the inspired P o_2 at altitude. The authors derived the following prediction equation for Pa o_2 at altitude:

SUMMARY

Increasingly widespread use of HBO to treat critically ill patients has created a demand for individuals skilled in using this technology. Planning and design of monitoring capabilities will enable optimal control of hemodynamics and oxygenation. Careful attention to detail will maximize patient safety in this environment. Optimized treatment schedules will evolve from further studies of mechanism of action. Advances in prevention and treatment of O_2 toxicity may allow more prolonged therapy than can currently be safely administered and hence a more aggressive approach to ischemic and infectious syndromes.

The reduction in ambient pressure and ensuing hypoxia associated with acute altitude exposure result in well-described physiologic changes, often associated with clinical symptoms. Methods for prophylaxis and treatment have been described. Safe anesthesia at altitude requires some modification of sea level techniques, not only because of the hypoxia and reduced ambient pressure, but also because suboptimal equipment may be available in mountain conditions.

References

1. Yarbrough OD, Behnke AR: The treatment of compressed air illness using oxygen. J Ind Hyg Toxicol 21:213, 1939.

2. Cunningham OJ: Oxygen therapy by means of compressed air. Anesth Analg 6:64, 1927.

3. American Medical Association Bureau of Investigation: The Cunningham "tank treatment:" The alleged value of compressed air in the treatment of diabetes mellitus, pernicious anemia and carcinoma. JAMA 90:1494, 1928.

4. Hampson NB (ed): Hyperbaric oxygen therapy: 1999 Committee Report. Kensington, Md. Undersea and Hyperbaric Medical Society, 1999.

5. Gilbert R, Keighley JF: The arterial-alveolar oxygen tension ratio: An index of gas exchange applicable to varying inspired oxygen concentrations. Am Rev Respir Dis 109:142, 1974.

6. Mathieu D, Neviere R, Pellerin P et al: Pedicle musculocutaneous flap transplantation: Prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. Plast Reconstr Surg 91:329, 1993.

7. Demchenko IT, Boso AE, Natoli MJ et al: Nitric oxide is involved in the mechanism of HBO-induced cerebral vasoconstriction. Undersea Hyperb Med 25 (suppl):54, 1998.

8. Stamler JS, Jia L, Eu JP et al: Blood flow regulation by S-nitrosohemoglobin in the physiological oxygen gradient. Science 276:2034, 1997.

9. Whalen R, Saltzman H, Holloway D et al: Cardiovascular and blood gas responses to hyperbaric oxygenation. Am J Cardiol 15:638, 1965.

10. Park MK, Muhvich KH, Myers RAM et al: Effects of hyperbaric oxygen in infectious diseases: Basic mechanisms. In Kindwall EP (ed): Hyperbaric Medicine Practice. Flagstaff, Ariz, Best Publishing, 1995, p 141.

11. Zamboni WA, Roth AC, Russell RC et al: The effect of acute hyperbaric oxygen therapy on axial pattern skin flap survival when administered during and after total ischemia. J Reconstr Microsurg 5:343, 1989.

12. Zamboni WA, Roth AC, Russell RC et al: The effect of hyperbaric oxygen on reperfusion of ischemic axial skin flaps: A laser Doppler analysis. Ann Plast Surg 28:339, 1992.

13. Zamboni WA, Roth AC, Russell RC et al: Morphological analysis of the microcirculation during reperfusion of ischemic skeletal muscle and the effect of hyperbaric oxygen. Plast Reconstr Surg 91:1110, 1993.

14. Zamboni WA, Stephenson LL, Roth AC et al: Ischemia-reperfusion injury in skeletal muscle: CD 18-dependent neutrophil-endothelial adhesion and arteriolar vasoconstriction. Plast Reconstr Surg 99:2002, 1997.

15. Thom S: Antagonism of carbon monoxide-mediated brain lipid peroxidation by hyperbaric oxygen. Toxicol Appl Pharmacol 105:340, 1990.

16. Bennett PB, Towse EJ: The high pressure nervous syndrome during a simulated oxygen-helium dive to 1500 ft. Electroencephalogr Clin Neurophysiol 31:383, 1971.

17. Bennett PB, Coggin R, Roby J: Control of HPNS in humans during rapid compression with trimix to 650 m (2132 ft). Undersea Biomed Res 8:85, 1981.

18. Winter PM, Smith RA, Smith M et al: Pressure antagonism of barbiturate anesthesia. Anesthesiology 44:416, 1976.

19. Tonner PH, Poppers DM, Miller KW: The general anesthetic potency of propofol and its dependence on hydrostatic pressure. Anesthesiology 77:926, 1992.

---

20. Tonner PH, Scholz J, Koch C et al: The anesthetic effect of dexmedetomidine does not adhere to the Meyer-Overton rule but is reversed by hydrostatic pressure. Anesth Analg 84:618, 1997.

21. Wardley-Smith B, Halsey MJ: Recent molecular theories of general anesthesia. Br J Anaesth 51:619, 1979.

22. Wann KT, Macdonald AG: Actions and interactions of high pressure and general anaesthetics. Prog Neurobiol 30:271, 1987.

23. Gross DR, Kramer WG, Gentile BJ et al: Plasma volume and estimated liver plasma flow during hyperbaric and hyperoxic exposures in awake dogs. Aviat Space Environ Med 56:1203, 1985.

24. Kramer WG, Gross DR, Moreau PM et al: Drug disposition under hyperbaric and hyperbaric-hyperoxic conditions: Meperidine in the dog. Aviat Space Environ Med 54:410, 1983.

25. Kramer WG, Welch DW, Fife WP et al: Pharmacokinetics of pentobarbital under hyperbaric and hyperbaric hyperoxic conditions in the dog. Aviat Space Environ Med 54:1005, 1983.

26. Kramer WG, Gross DR, Fife WP et al: Theophylline pharmacokinetics during hyperbaria and hyperbaric hyperoxia in the dog. Res Commun Chem Pathol Pharmacol 34:381, 1981.

27. Kramer WG, Welch DW, Fife WP et al: Salicylate pharmacokinetics in the dog at 6 ATA in air and at 2.8 ATA in 100% oxygen. Aviat Space Environ Med 54:682, 1983.

28. Stoudemire A, Miller J, Schmitt F et al: Development of an organic affective syndrome during a hyperbaric diving experiment. Am J Psychiatry 141:1251, 1984.

29. Piantadosi CA: The role of hyperbaric oxygen in carbon monoxide, cyanide and sulfide intoxication. Probl Respir Care 4:215, 1991.

30. Norkool DM, Kirkpatrick JN: Treatment of acute carbon monoxide poisoning with hyperbaric oxygen: A review of 115 cases. Ann Emerg Med 14:1168, 1985.

31. Shillito FH, Drinker CK, Shaughnessy TJ: The problem of nervous and mental sequelae in carbon monoxide poisoning. JAMA 106:669, 1936.

32. Krantz T, Thisted B, Strom J et al: Acute carbon monoxide poisoning. Acta Anaesthesiol Scand 32:278, 1988.

33. Thom S, Taber R, Mendiguren I et al: Delayed neuropsychologic sequelae after carbon monoxide poisoning: Prevention by treatment with hyperbaric oxygen. Ann Emerg Med 25:474, 1995.

34. Pracyk JB, Stolp BW, Fife CE et al: Brain computerized tomography after hyperbaric oxygen therapy for carbon monoxide poisoning. Undersea Hyperb Med 22:1, 1995.

35. Hollander DI, Nagey DA, Welch R et al: Hyperbaric oxygen therapy for the treatment of acute carbon monoxide poisoning in pregnancy: A case report. J Reprod Med 32:615, 1987.

36. Van Hoesen KB, Camporesi EM, Moon RE et al: Should hyperbaric oxygen be used to treat the pregnant patient for acute carbon monoxide poisoning? A case report and literature review (published erratum appears in JAMA 1990:273, 2750). JAMA 261:1039, 1989.

37. Brown DB, Mueller GL, Golich FC: Hyperbaric oxygen treatment for carbon monoxide poisoning in pregnancy: A case report. Aviat Space Environ Med 63:1011, 1992.

38. Elkharrat D, Raphael JC, Korach JM et al: Acute carbon monoxide intoxication and hyperbaric oxygen in pregnancy. Intensive Care Med 17:289, 1991.

39. Mathieu D, Wattel F, Neviere R et al: Carbon monoxide poisoning: Mechanism, clinical presentation and management. In Oriani G, Marroni A, Wattel F (eds): Handbook on Hyperbaric Medicine. New York, Springer-Verlag, 1996, p 281.

40. Camporesi EM: Hyperbaric oxygen therapy for CO intoxication during pregnancy. In Oriani G, Marroni A, Wattel F (eds): Handbook on Hyperbaric Medicine. New York, Springer-Verlag, 1996, p 305.

41. Kaufman BS, Kaminsky SJ, Rackow EC et al: Adult respiratory distress syndrome following orogenital sex during pregnancy. Crit Care Med 15:703, 1987.

42. Morris WP, Butler BD, Tonnesen AS et al: Continuous venous air embolism in patients receiving positive end-expiratory pressure. Am Rev Respir Dis 147:1034, 1993.

43. Moon RE, Camporesi EM, Kisslo JA: Patent foramen ovale and decompression sickness in divers. Lancet 1:513, 1989.

44. Brunner F, Frick P, Buhlmann A: Post-decompression shock due to extravasation of plasma. Lancet 1:1071, 1964.

45. Boussuges A, Blanc P, Molenat F et al: Haemoconcentration in neurological decompression illness. Int J Sports Med 17:351, 1996.

46. Helps SC, Parsons DW, Reilly PL et al: The effect of gas emboli on rabbit cerebral blood flow. Stroke 21:94, 1990.

47. Helps SC, Meyer-Witting M, Rilley PL et al: Increasing doses of intracarotid air and cerebral blood flow in rabbits. Stroke 21:1340, 1990.

48. Helps SC, Gorman DF: Air embolism of the brain in rabbits pre-treated with mechlorethamine. Stroke 22:351, 1991.

49. Pearson RR, Goad RF: Delayed cerebral edema complicating cerebral arterial gas embolism: Case histories. Undersea Biomed Res 9:283, 1982.

50. Elliott DH, Moon RE: Manifestations of the decompression disorders. In Bennett PB, Elliott DH (eds): The Physiology and Medicine of Diving. Philadelphia, WB Saunders, 1993, p 481.

51. Divers Alert Network: Report on Decompression Illness and Diving Fatalities. Durham, NC, Divers Alert Network, 1999.

52. Merton DA, Fife WP, Gross DR: An evaluation of plasma volume expanders in the treatment of decompression sickness. Aviat Space Environ Med 54:218, 1983.

53. Moon RE, Gorman DF: Treatment of the decompression disorders. In Bennett PB, Elliott DH (eds): The Physiology and Medicine of Diving. Philadelphia, WB Saunders, 1993, p 506.

54. Moon RE, Sheffield PJ: Guidelines for treatment of decompression illness. Aviat Space Environ Med 68:234, 1997.

55. Massey EW, Moon RE, Shelton D et al: Hyperbaric oxygen therapy of iatrogenic air embolism. J Hyperb Med 5:15, 1990.

56. Dexter F, Hindman BJ: Recommendations for hyperbaric oxygen therapy of cerebral air embolism based on a mathematical model of bubble absorption. Anesth Analg 84:1203, 1997.

57. Van Unnik AJM: Inhibition of toxin production in *Clostridium perfringens in vitro* by hyperbaric oxygen. Antonie Van Leeuwenhoek 31:181, 1965.

58. Bakker DJ, van der Kleij AJ: Soft tissue infections including clostridial myonecrosis: Diagnosis and treatment. In Oriani G, Marroni A, Wattel F (eds): Handbook on Hyperbaric Medicine. New York, Springer-Verlag, 1996, p 343.

59. Bakker DJ, van der Kleij AJ: Clostridial myonecrosis. In Oriani G, Marroni A, Wattel F (eds): Handbook on Hyperbaric Medicine. New York, Springer-Verlag, 1996, p 362.

60. Riseman JA, Zamboni WA, Curtis A et al: Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery 108:847, 1990.

61. Zamboni WA, Kindwall EP: Author's reply to: Still unproved in necrotising fasciitis. BMJ 307:936, 1993.

62. Moon RE, Dear GDL, Stolp BW: Hyperbaric oxygen in critical care. In Ayres SM et al (eds): Textbook of Critical Care. Philadelphia, WB Saunders, 1999.

63. Smith RM: Anesthesia during hyperbaric oxygenation. Ann N Y Acad Sci 117:768, 1965.

64. Li W, Zhang Z, Liao C et al: Open heart surgery with extracorporeal circulation under hyperbaric oxygenation at 3 ATA. In Kindwall EP (ed): Proceedings of the Eighth International Congress on Hyperbaric Medicine. San Pedro, Calif, Best Publishing, 1987, p 177.

65. Camporesi EM, Moon RE: Hyperbaric oxygen as an adjunct to therapeutic lung lavage in pulmonary alveolar proteinosis. In Bove AA, Bachrach AJ, Greenbaum LJ Jr (eds): Underwater and Hyperbaric Physiology. IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda, Md, Undersea and Hyperbaric Medical Society, 1987, p 955.

66. Jansen HM, Zuurmond WW, Roos CM et al: Whole-lung lavage under hyperbaric oxygen conditions for alveolar proteinosis with respiratory failure. Chest 91:829, 1987.

67. Hart GB, Lennon PA, Strauss MD: Hyperbaric oxygen in exceptional acute blood-loss anemia. J Hyperb Med 2:205, 1987.

68. Weaver LK, Strauss MB (eds): Monoplace Hyperbaric Chamber Safety Guidelines. Kensington, Md, Undersea and Hyperbaric Medical Society, 1997.

69. Miller JN, Fagraeus L, Bennett PB et al: Nitrogen-oxygen saturation therapy in serious cases of compressed air decompression sickness. Lancet 2:169, 1978.

70. Davis P, Piantadosi CA, Moon RE: Saturation treatment of decompression illness in a hospital based hyperbaric facility. In Moon RE, Sheffield PJ (eds): Treatment of Decompression Illness. Kensington, Md, Undersea and Hyperbaric Medical Society, 1996, p 294.

71. Yusa T, Beckman JS, Crapo JD et al: Hyperoxia increases H_2 O_2 production by brain *in vivo.* J Appl Physiol 63:353, 1987.

72. Clark JM, Lambertsen CJ: Rate of development of pulmonary oxygen toxicity in man during oxygen breathing at 2.0 ATA. J Appl Physiol 30:739, 1971.

73. Harabin AL, Homer LD, Weathersby PK et al: An analysis of decrements in vital capacity as an index of pulmonary oxygen toxicity. J Appl Physiol 63:1130, 1987.

74. Eckenhoff RG, Dougherty JH Jr, Messier AA et al: Progression and recovery of pulmonary oxygen toxicity in humans exposed to 5 ATA air. Aviat Space Environ Med 58:658, 1987.

75. Miller JN, Camporesi EM, McLeod M et al: Studies of early pulmonary oxygen toxicity in man. Anesthesiology 55(suppl):A369, 1981.

76. Mathes DD: Bleomycin and hyperoxia exposure in the operating room. Anesth Analg 81:624, 1995.

77. Bilfinger TV, Hartman AR: Acute pulmonary failure with neoadjuvant protocol including mitomycin C and surgical therapy. J Thorac Cardiovasc Surg 102:935, 1991.

78. Thompson CC, Bailey MK, Conroy JM et al: Postoperative pulmonary toxicity associated with mitomycin C therapy. South Med J 85:1257, 1992.

79. Donald KW: Oxygen poisoning in man. I. Br Med J 1:667, 1947.

80. Donald KW: Oxygen poisoning in man. II. Br Med J 1:712, 1947.

81. Anderson B Jr, Shelton DL: Axial length in hyperoxic myopia. In Bove AA, Bachrach AJ, Greenbaum LJ Jr (eds): Underwater and Hyperbaric Physiology. IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda, Md, Undersea and Hyperbaric Medical Society, 1987, p 607.

82. Palmquist BM, Philipson B, Barr PO: Nuclear cataract and myopia during hyperbaric oxygen therapy. Br J Ophthalmol 68:113, 1984.

83. Kol S, Adir Y, Gordon CR et al: Oxy-helium treatment of severe spinal decompression sickness after air diving. Undersea Hyperb Med 20:147, 1993.

84. Goldenberg I, Shupak A, Shoshani O: Oxy-helium treatment for refractory neurological decompression sickness: A case report. Aviat Space Environ Med 67:57, 1996.

85. U.S. Navy Department: US Navy Diving Manual, vol 1, revision 3: Air Diving. NAVSEA 0994-LP-001-9110. Best Publishing, Flagstaff, Ariz, 1993.

86. Farmer JC Jr: Otological and paranasal sinus problems in diving. In Bennett PB, Elliott DH (eds): The Physiology and Medicine of Diving. Philadelphia, WB Saunders, 1993, p 267.

87. Prefaut C, Dubois F, Roussos C et al: Influence of immersion to the neck in water on airway closure and distribution of perfusion in man. Respir Physiol 37:312, 1979.

88. Simonson SG, Pritchard RJ, Moon RE et al: Evaluation of two chest tube drainage systems at 2 ATA and 3 ATA. Undersea Hyperb Med 23(suppl):124, 1996.

89. Hummill RS III, Ornato JP, Weinberg SM et al: Spark-generating properties of electrode gel used during defibrillation. JAMA 260:3021, 1988.

90. Martindale LG, Milligan M, Friese P: Test of an R-2 defibrillator adaptor in a hyperbaric chamber. J Hyperb Med 2:15, 1987.

91. Weaver LK, Howe S: Normobaric measurement of arterial oxygen tension in subjects exposed to hyperbaric oxygen. Chest 102:1175, 1992.

92. Tenney SM: A theoretical analysis of the relationship between venous blood and mean tissue oxygen pressures. Respir Physiol 20:283, 1974.

93. Salzano JV, Camporesi EM, Stolp BW et al: Physiological responses to exercise at 47 and 66 ATA. J Appl Physiol 57:1055, 1984.

94. Moon RE, Bergquist LV, Conklin B et al: Monaghan 225 ventilator use under hyperbaric conditions. Chest 89:846, 1986.

95. Anthonisen NR, Bradley ME, Vorosmarti J et al: Mechanics of breathing with helium-oxygen and neon-oxygen breathing mixtures in deep saturation diving. In Lambertsen CJ (ed): Underwater Physiology. IV. Proceedings of the Fourth Symposium on Underwater Physiology. New York, Academic Press, 1971, p 339.

96. Lambertsen CJ, Gelfand R, Peterson R et al: Human tolerance to He, Ne, and N_2 at respiratory gas densities equivalent to He-O_2 breathing at depths to 1200, 2000, 3000, 4000, and 5000 feet of sea water (Predictive Studies III). Aviat Space Environ Med 48:843, 1977.

97. Gallagher TJ, Smith RA, Bell GC: Evaluation of mechanical ventilators in a hyperbaric environment. Aviat Space Environ Med 49:375, 1978.

98. Saywood AM, Howard R, Goad RF et al: Function of the Oxford Ventilator at high pressure. Anaesthesia 37:740, 1982.

99. Holcomb JR, Matos-Navarro AY, Goldmann RW: Critical care in the hyperbaric chamber. In Davis JC, Hunt TK (eds): Problem Wounds: The Role of Oxygen. New York, Elsevier, 1988, p 187.

100. Weaver LK: Air breaks with the Sechrist 500A monoplace hyperbaric ventilator. J Hyperb Med 3:179, 1988.

101. Pelaia P, Volturo P, Rocco M et al: La ventilazione meccanica in ambiente iperbarico: Valutazioni sperimentali del Draeger Hyperlog. Minerva Anestesiol 56:1371, 1990.

102. Le Masson Y, Le Pechon J-C, Barratt M et al: Ventilator for space station freedom. In Schmutz J, Wendling J (eds): Proceedings of the Joint Meeting on Diving and Hyperbaric Medicine. Basel, Foundation for Hyperbaric Medicine, 1992, p 78.

103. Degauque C, Lamy M, Stas M: Use of the Logic 03 for controlled ventilation in hyperbaric oxygen therapy. Acta Anaesthesiol Belg 28:251, 1977.

104. Lewis RP, Szafranski J, Bradford RH et al: The use of the Penlon Nuffield 200 in a monoplace hyperbaric oxygen chamber: An evaluation of its use and a clinical report in two patients requiring ventilation for carbon monoxide poisoning. Anaesthesia 46:767, 1991.

105. Spittal MJ, Hunter SJ, Jones L: The pneuPAC hyperbaric variant HB: A ventilator suitable for use within a one-man hyperbaric chamber. Br J Anaesth 67:488, 1991.

106. Briggs WD: Performance of lead-acid gelled electrolyte batteries in the deep ocean environment. Technical Note N-1526. Washington, DC, Naval Material Command, 1978.

107. Brown TA, Morris G: The ignition risk with mixtures of oxygen and nitrous oxide with halothane. Br J Anaesth 38:164, 1966.

108. Baker AB, Unsworth IP: No ignition risk with hyperbaric enflurane. Anaesth Intensive Care 6:157, 1978.

109. Severinghaus JW: Hyperbaric oxygenation: Anesthesia and drug effects. Anesthesiology 26:812, 1965.

110. Ross JAS, Manson HJ, Shearer A et al: Some aspects of anaesthesia in high pressure environments. In Smith G (ed): Proceedings of the Sixth International Congress on Hyperbaric Medicine. Aberdeen, Scotland, Aberdeen University Press, 1977, p 449.

111. Jacobson I, Bloor K, McDowall DG et al: Internal carotid endarterectomy at two atmospheres of pressure. Lancet 2:546, 1963.

112. Ledingham IM, McBride TI, Jennett WB et al: Fatal brain damage associated with cardiomyopathy of pregnancy, with notes on caesarean section in a hyperbaric chamber. BMJ 4:285, 1968.

113. Carter LH, Goldsmith GA: The ordeal of Donald Boone. Nutr Today Autumn:2, 1970.

114. Holt JAG: The principles of hyperbaric and anoxic radiotherapy. Br J Radiol 48:819, 1975.

115. Smith WDA, Mapleson WW, Siebold K et al: Nitrous oxide anaesthesia induced at atmospheric and hyperbaric pressures. I. Measured pharmacokinetic and EEG data. Br J Anaesth 46:3, 1974.

116. Russell JB, Snider MT, Richard RB et al: Hyperbaric nitrous oxide as a sole anesthetic agent in humans. Anesth Analg 70:289, 1990.

117. Blenkarn GD, Aquadro C, Hills BA et al: Urticaria following the sequential breathing of various inert gases at a constant ambient pressure of 7 ATA: A possible manifestation of gas-induced osmosis. Aviat Space Environ Med 42:141, 1971.

118. Lambertsen CJ, Idicula J: A new gas lesion syndrome in man, induced by "isobaric gas counterdiffusion." J Appl Physiol 39:434, 1975.

119. Acott CJ, Gorman DF: Decompression illness and nitrous oxide anaesthesia in a sports diver. Anaesth Intensive Care 20:249, 1992.

120. McDowell DG: Anaesthesia in a pressure chamber. Anaesthesia 19:321, 1964.

121. Moore LG: Altitude-aggravated illness: Examples from pregnancy and prenatal life. Ann Emerg Med 16:965, 1987.

122. Wagner PD, Gale GE, Moon RE et al: Pulmonary gas exchange in humans exercising at sea level and simulated altitude. J Appl Physiol 61:260, 1986.

123. Gale GE, Torre-Bueno JR, Moon RE et al: Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude. J Appl Physiol 58:978, 1985.

124. Kafer ER, Sugioka K: Respiratory and cardiovascular responses to hypoxemia and the effects of anesthesia. Int Anesthesiol Clin 19:85, 1981.

125. West JB: Tolerance to severe hypoxia: Lessons from Mt. Everest. Acta Anaesthesiol Scand 94(suppl):18, 1990.

126. West JB, Hackett PH, Maret KH et al: Pulmonary gas exchange on the summit of Mount Everest. J Appl Physiol 55:678, 1983.

127. Bencowitz HZ, Wagner PD, West JB: Effect of change in P50 on exercise tolerance at high altitude: A theoretical study. J Appl Physiol 53:1487, 1982.

128. Hackett PH, Roach RC: Medical therapy of altitude illness. Ann Emerg Med 16:980, 1987.

129. Crow TJ, Kelman GR: Psychological effects of mild acute hypoxia. Br J Anaesth 45:335, 1973.

130. Sheffield PJ, Heimbach RD: Respiratory physiology. In DeHart RL (ed): Fundamentals of Aerospace Medicine. Baltimore, Williams & Wilkins, 1996, p 69.

131. Sutton JR, Reeves JT, Wagner PD et al: Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. J Appl Physiol 64:1309, 1988.

132. Severinghaus JW, Mitchell RA, Richardson BW et al: Respiratory control at high altitude suggesting active transport regulation of CSF pH. J Appl Physiol 18:1155, 1963.

133. Hornbein TF, Townes BD, Schoene RB et al: The cost to the central nervous system of climbing to extremely high altitude. N Engl J Med 321:1714, 1989.

134. Cavaletti G, Tredici G: Effects of exposure to low oxygen pressure on the central nervous system. Sports Med 13:1, 1992.

135. Hampson NB, Camporesi EM, Stolp BW et al: Cerebral oxygen availability by NIR spectroscopy during transient hypoxia in man. J Appl Physiol 69:907, 1990.

136. John AH: The effect of maternal hypoxia on the heart rate of the foetus *in utero.* Br J Anaesth 37:515, 1965.

137. Polvi HJ, Pirhonen JP, Erkkola RU: The hemodynamic effects of maternal hypo- and hyperoxygenation in healthy term pregnancies. Obstet Gynecol 86:795, 1995.

138. Reshetnikova OS, Burton GJ, Milovanov AP: Effects of hypobaric hypoxia on the fetoplacental unit: The morphometric diffusing capacity of the villous membrane at high altitude. Am J Obstet Gynecol 171:1560, 1994.

139. Sobrevilla LA, Cassinelli MT, Carcelen A et al: Human fetal and maternal oxygen tension and acid-base status during delivery at high altitude. Am J Obstet Gynecol 111:1111, 1971.

140. Johnson TS, Rock PB: Acute mountain sickness. N Engl J Med 319:841, 1988.

141. Honigman B, Theis MK, Koziol-McLain J et al: Acute mountain sickness in a general tourist population at moderate altitude. Ann Intern Med 118:587, 1993.

142. Larson EB, Roach RC, Schoene RB et al: Acute mountain sickness and acetazolamide: Clinical efficacy and effect on ventilation. JAMA 248:328, 1982.

143. Rock PB, Johnson TS, Cymerman A et al: Effect of dexamethasone on symptoms of acute mountain sickness at Pikes Peak, Colorado (4,300 m). Aviat Space Environ Med 58:668, 1987.

144. Johnson JS, Rock PB, Fulco CS et al: Prevention of acute mountain sickness by dexamethasone. N Engl J Med 310:683, 1984.

145. Hohenhaus E, Niroomand F, Goerre S et al: Nifedipine does not prevent acute mountain sickness. Am J Respir Crit Care Med 150:857, 1994.

146. Dickinson JG: Severe acute mountain sickness. Postgrad Med J 55:454, 1979.

147. Sutton JR: Mountain sickness. Neurol Clin 10:1015, 1992.

148. Bartsch P: High altitude pulmonary edema. Respiration 64:435, 1997.

149. Rios B, Driscoll DJ, McNamara DG: High altitude pulmonary edema with absent right pulmonary artery. Pediatrics 75:314, 1985.

150. Bartsch P, Maggiorini M, Ritter M et al: Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med 325:1284, 1991.

151. Schoene RB, Hackett PH, Henderson WR et al: High altitude pulmonary edema: Characteristics of lung lavage fluid. JAMA 256:63, 1986.

152. Schoene RB, Swenson ER, Pizzo CJ et al: The lung at high altitude: Bronchoalveolar lavage in acute mountain sickness and pulmonary edema. J Appl Physiol 64:2605, 1988.

153. Kleger GR, Bartsch P, Vock P et al: Evidence against an increase in capillary permeability in subjects exposed to high altitude. J Appl Physiol 81:1917, 1996.

154. West JB, Mathieu-Costello O: Stress failure of pulmonary capillaries: Role in lung and heart disease. Lancet 340:762, 1992.

155. Kasic JF, Yaron M, Nicholas RA et al: Treatment of acute mountain sickness: Hyperbaric versus oxygen therapy. Ann Emerg Med 20:1109, 1991.

156. Grissom CK, Roach RC, Sarnquist FH et al: Acetazolamide in the treatment of acute mountain sickness: Clinical efficacy and effect on gas exchange. Ann Intern Med 116:461, 1992.

157. Hackett PH, Roach RC, Wood RA et al: Dexamethasone for prevention and treatment of acute mountain sickness. Aviat Space Environ Med 59:950, 1988.

158. Keller HR, Maggiorini M, Bartsch P et al: Simulated descent v dexamethasone in treatment of acute mountain sickness: A randomised trial. BMJ 310:1232, 1995.

159. Bartsch P, Maggi S, Kleger GR et al: Sumatriptan for high-altitude headache (letter). Lancet 344:1445, 1994.

160. Hackett PH, Roach RC, Hartig GS et al: The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: A comparison. Int J Sports Med 13(suppl 1):S68, 1992.

161. Scherrer U, Vollenweider L, Delabays A et al: Inhaled nitric oxide for high-altitude pulmonary edema. N Engl J Med 334:624, 1996.

162. Oelz O, Maggiorini M, Ritter M et al: Nifedipine for high altitude pulmonary oedema. Lancet 2:1241, 1989.

163. Winslow RM, Monge CC: Hypoxia, Polycythemia, and Chronic Mountain Sickness. Baltimore, The Johns Hopkins University Press, 1987.

164. Kumar KV, Waligora JM, Calkins DS: Threshold altitude resulting in decompression sickness. Aviat Space Environ Med 61:685, 1990.

165. Rudge FW: A case of decompression sickness at 2,437 m (8,000 feet). Aviat Space Environ Med 61:1026, 1990.

166. Vann RD, Denoble P, Emmerman MN et al: Flying after diving and decompression sickness. Aviat Space Environ Med 64:801, 1993.

167. Varene P, Timbal J, Jacquemin C: Effect of different ambient pressures on airway resistance. J Appl Physiol 22:699, 1967.

168. Borel C, Simonds D, Guy J et al: Effect of hypobaricity on hypoxic ventilatory response in humans. Anesthesiology 85(suppl):A1121, 1996.

169. Safar P, Tenicela R: High altitude physiology in relation to anesthesia and inhalation therapy. Anesthesiology 25:515, 1964.

170. Groves BM, Reeves JT, Sutton JR et al: Operation Everest II: Elevated high-altitude pulmonary resistance unresponsive to oxygen. J Appl Physiol 63:521, 1987.

171. Camporesi EM: Anesthesia at different environmental pressures. In Ehrenwerth J, Eisenkraft JB (eds): Anesthesia Equipment. St. Louis, Mo, Mosby-Year Book, 1993, p 588.

172. James MFM, White JF: Anesthetic considerations at moderate altitude. Anesth Analg 63:1097, 1984.

173. Cleaton-Jones P, Moyes DG, Whittaker AM: Clinical effects of nitrous oxide and oxygen mixtures at sea-level and at 1,700 meters altitude. Anaesthesia 34:859, 1979.

174. James MFM, Manson EDM, Dennett JE: Nitrous oxide analgesia and altitude. Anaesthesia 37:285, 1982.

175. Pederson L, Benumof J: Incidence and magnitude of hypoxaemia with ketamine in a rural African hospital. Anaesthesia 48:67, 1993.

176. Nunn JF: Anaesthesia at altitude. In Ward MP, Milledge JS, West JB (eds): High Altitude Medicine and Physiology. London, Chapman and Hall Medical, 1989, p 481.

177. Cotrell JJ: Altitude exposures during aircraft flight: Flying higher. Chest 93:81, 1988.

178. Aldrete JA, Aldrete LE: Oxygen concentrations in commercial aircraft flights. South Med J 76:12, 1983.

179. Schwartz JS, Bencowitz HZ, Moser KM: Air travel hypoxemia with chronic obstructive pulmonary disease. Ann Intern Med 100:473, 1984.

180. Dillard TA, Beninati WA, Berg BW: Air travel in patients with chronic obstructive pulmonary disease. Arch Intern Med 151:1793, 1991.

181. Gong H Jr, Tashkin DP, Lee EY et al: Hypoxia-altitude simulation test: Evaluation of patients with chronic airway obstruction. Am Rev Respir Dis 130:980, 1984.

182. Leitch DR, Green RD: Pulmonary barotrauma in divers and the treatment of cerebral arterial gas embolism. Aviat Space Environ Med 57:931, 1986.

183. Pace N, Strajman E, Walker E: Acceleration of carbon monoxide elimination in man by high pressure oxygen. Science 111:652, 1950.

184. Litovitz TL, Larkin RF, Myers RAM: Cyanide poisoning treated with hyperbaric oxygen. Am J Emerg Med 1:94, 1983.

185. Truss CD, Killenberg PG: Treatment of carbon tetrachloride with hyperbaric oxygen. Gastroenterology 82:767, 1982.

186. Berk RF, Lane JM, Patel K: Relationship of oxygen and glutathione in protection against carbon tetrachloride-induced hepatic microsomal lipid peroxidation and covalent binding in the rat: Rationale for the use of hyperbaric oxygen to treat carbon tetrachloride ingestion. J Clin Invest 74:1996, 1984.

187. Whitcraft DD, Bailey TD, Hart GB: Hydrogen sulfide poisoning treated with hyperbaric oxygen. J Emerg Med 3:23, 1985.

188. Smilkstein MJ, Bronstein AC, Pickett HM et al: Hyperbaric oxygen

therapy for severe hydrogen sulfide poisoning. J Emerg Med 3:27, 1985.

189. Demello FJ, Haglin JJ, Hitchcock CR: Comparative study of experimental *Clostridium perfringens* infection in dogs treated with antibiotics, surgery and hyperbaric oxygen. Surgery 73:936, 1973.

190. Moon RE, Dear GDL, Stolp BW: Hyperbaric oxygen in critical care. In Ayres SM et al (eds): Textbook of Critical Care. Philadelphia, WB Saunders, 1995, p 953.

191. Mader JT, Brown GL, Guckian JC et al: A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 142:915, 1980.

192. Davis JC, Heckman JD, DeLee JC et al: Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. J Bone Joint Surg Am 68:1210, 1986.

193. Price JC, Stevens DL: Hyperbaric oxygen in the treatment of rhinocerebral mucormycosis. Laryngoscope 90:737, 1980.

194. Yohai RA, Bullock JD, Aziz AA et al: Survival factors in rhino-orbital-cerebral mucormycosis. Surv Ophthalmol 39:3, 1994.

195. Bouachour G, Cronier P, Gouello JP et al: Hyperbaric oxygen therapy in the management of crush injuries: A randomized double-blind placebo-controlled clinical trial. J Trauma 41:333, 1996.

196. Nemiroff PM: Synergistic effects of pentoxifylline and hyperbaric oxygen on skin flaps. Arch Otolaryngol Head Neck Surg 114:977, 1988.

197. Zamboni WA, Wong HP, Stephenson LL: Effect of hyperbaric oxygen on neutrophil concentration and pulmonary sequestration in reperfusion injury. Arch Surg 131:756, 1996.

198. Hart GB, Mainos EG: The treatment of radiation necrosis with hyperbaric oxygen. Cancer 37:2580, 1976.

199. Farmer JC Jr, Shelton DL, Angelillo JD et al: Treatment of radiation-induced tissue injury with hyperbaric oxygen. Ann Otol Rhinol Laryngol 87:707, 1978.

200. Ferguson BJ, Hudson WR, Farmer JC: Hyperbaric oxygen therapy for laryngeal radionecrosis. Ann Otol Rhinol Laryngol 96:1, 1987.

201. Norkool DM, Hampson NB, Gibbons RP et al: Hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis. J Urol 150:332, 1993.

202. Bevers RF, Bakker DJ, Kurth KH: Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. Lancet 346:803, 1995.

203. Hammarlund C, Sundberg T: Hyperbaric oxygen reduced size of chronic leg ulcers: A randomized double-blind study. Plast Reconstr Surg 93:829, 1994.

204. Zamboni WA, Wong HP, Stephenson LL et al: Evaluation of hyperbaric oxygen for diabetic wounds: A prospective study. Undersea Hyperb Med 24:175, 1997.

205. Sukoff MH, Ragatz RE: Hyperbaric oxygenation for the treatment of acute cerebral edema. Neurosurgery 10:29, 1982.

206. Hart GB, O'Reilly RR, Broussard ND et al: Treatment of burns with hyperbaric oxygen. Surg Gynecol Obstet 139:693, 1974.

207. Niu AKC, Yang C, Lee HC et al: Burns treated with adjunctive hyperbaric oxygen therapy: A comparative study in humans. J Hyperb Med 2:75, 1987.

208. Cianci P, Lueders HW, Lee H et al: Adjunctive hyperbaric oxygen therapy reduces length of hospitalization in thermal burns. J Burn Care Rehabil 10:432, 1989.

209. Niezgoda JA, Cianci P, Folden BW et al: The effect of hyperbaric oxygen therapy on a burn wound model in human volunteers. Plast Reconstr Surg 99:1620, 1997.

210. Broughton G 2nd: Management of the brown recluse spider bite to the glans penis. Mil Med 161:627, 1996.

211. Maynor ML, Moon RE, Klitzman B et al: Brown recluse spider envenomation: A prospective trial of hyperbaric oxygen therapy. Acad Emerg Med 4:184, 1997.

212. Riley RL, Houston CS: Composition of alveolar air and volume of pulmonary ventilation during long exposure to high altitude. Am J Physiol 3:526, 1951.

213. West JB: Tolerable limits to hypoxia: On high mountains. In Sutton JR, Houston CS, Coates G (eds): Hypoxia. The Tolerable Limits. Indianapolis, Ind, Benchmark Press, 1988, p 353.

214. Forster PJG: Health and work at high altitude: A study at the Mauna Kea observatories. Publ Astronom Soc Pacific 96:478, 1984.

215. Scoggin CH, Hyers TM, Reeves JT et al: High-altitude pulmonary edema in the children and young adults of Leadville, Colorado. N Engl J Med 297:1269, 1977.

216. Harding RM: The earth's atmosphere. In Ernsting J, King P (eds): Aviation Medicine. London, Butterworths, 1988, p 3.

217. Clark JM: Oxygen toxicity. In Bennett PB, Elliott DH (eds): The Physiology and Medicine of Diving. Philadelphia, WB Saunders, 1993, p 121.

218. Moon RE, Camporesi EM, Shelton DL: Prediction of arterial P_{O_2} during hyperbaric treatment. In Bove AA, Bachrach AJ, Greenbaum LJ Jr (eds): Underwater and Hyperbaric Physiology. IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology, Bethesda, Md, Undersea and Hyperbaric Medical Society, 1987, p 1127.

219. Committee on Hyperbaric Oxygenation: Fundamentals of Hyperbaric Medicine. Publication no. 1298. Washington, DC, National Academy Press, 1966.

220. Sutton JR, Reeves JT, Wagner PD et al: Tolerable limits of hypoxia for the lungs: Oxygen transport. In Sutton JR, Houston CS, Coates G (eds): Hypoxia: The Tolerable Limits. Indianapolis, Ind, Benchmark Press, 1988, p 123.

Chapter 68 - The Postanesthesia Care Unit

Thomas W. Feeley
Alex Macario

INTRODUCTION

Recovery from anesthesia is, for most patients, a smooth, uneventful emergence from an uncomplicated anesthetic regimen and operation. However, for a significant number of patients, recovery from anesthesia can be a life-threatening process best managed by prompt intervention delivered by skilled medical and nursing personnel. For anesthesiologists, involvement in optimizing recovery from anesthesia is one component of perioperative medicine. The postanesthesia care unit (PACU) often faces the task of simultaneously caring for patients waking up from routine surgery, patients recovering from regional anesthesia, critically ill postoperative patients, and children emerging from the frightening world of anesthesia and surgery. The facilities and staff must be experienced and flexible to deal with these diverse situations as well as meet the requirements of various users including surgeons and patients. Each user values the PACU differently. Patients may value adequate analgesia, a friendly staff, and prompt relief of nausea and vomiting, whereas surgeons and anesthesiologists value skilled nursing care.

HISTORY

Although methods of general anesthesia have been available for more than 150 years, PACU have only become common in the past 40 years. The first description is from 1801 at the Newcastle Infirmary in England and predates modern anesthesia. There were two five-bed rooms adjacent to the operating room that were reserved for patients who were seriously ill or who had just undergone a major operation. [1] Another early description came in 1863, when Florence Nightingale [2] wrote: "It is not uncommon, in small country hospitals, to have a recess or small room leading from the operating theater in which the patients remain until they have recovered, or at least recovered from the immediate effects of the operation."

The first description of a recovery room in the United States was from 1873 at the Massachusetts General Hospital. Charles Tomes, a British dental surgeon, was invited to deliver the graduation address to dental students at Harvard. There he observed ether being administered in an induction room separate from the operating room as well as the use of a recovery room: "Also, patients were apt to be noisy after recovery, so they are, at this hospital, temporarily placed in a small ward, whence, after complete recovery, they are transferred to their own wards." [3]

In the 1920s and 1930s, the complexity of surgical procedures increased, and several PACUs were opened in the United States and abroad. In 1923, a three-bed neurosurgical unit was opened at Johns Hopkins Hospital by Dandy and Firor. [4] [5] It was not until World War II, however, that a large increase in the number of PACUs occurred. The major reason for the increase was the shortage of nurses that existed in the United States. PACUs were created so that an adequate level of nursing care could be provided for the immediate postsurgical patient. [6] PACUs were opened at the Mayo Clinic in 1942, at New York Hospital in 1944, and at the Ochsner Clinic in 1945. [7]

In addition to conserving nursing facilities, postoperative care saved lives. In 1947, the Anesthesia Study Commission of the Philadelphia County Medical Society issued a report

---

that further stimulated growth of PACUs. [8] The Commission found that, in an 11-year period, nearly one-half of the deaths that occurred during the first 24 hours of surgery were preventable. They also found that at least one-third of those deaths could have been prevented by improved postoperative nursing care. [5] [7] Following this report, many U.S. hospitals opened postanesthesia care units. [9] [10] [11] In 1949, the Operating Room Committee for New York Hospital [12] stated: "Today it can be stated categorically that an adequate recovery room service is a necessity to any hospital undertaking modern surgical therapy."

During the 1950s, the uses of these units expanded even further. This increase allowed for a better understanding of the nature and course of the more common postanesthetic complications. The 1950s and 1960s also witnessed the rapid growth of surgical intensive care and postoperative respiratory support. This resulted in an ever-increasing number of complex surgical procedures and increased numbers of patients who required postoperative mechanical ventilation. In many hospitals, the original intensive care unit (ICU) proved too small to handle the large number of cases requiring intensive postoperative care. Many PACUs were therefore forced to serve as short-term ICU for surgical patients. The increased use of invasive monitoring techniques in the 1970s, as well as a continued trend toward providing prophylactic postoperative ventilatory support, required many PACUs to manage both routine recovery from anesthesia and critically ill postoperative patients receiving respiratory and circulatory support. The late 1980s and 1990s have seen the emergence of outpatient surgery. The PACU staff must now manage patients who will be going home following anesthetic recovery and not to a hospital ward.

ECONOMICS

With the increased prevalence of prepaid care, hospitals and operating room suites are reducing costs as a primary strategy for managing profitability. This approach has transformed the operating room suite, including the PACU, from revenue centers to cost centers. This means that minimizing costs replaces maximizing revenue as the financial objective.

In a study of 715 inpatients undergoing diskectomy, prostatectomy, appendectomy, or laparoscopic cholecystectomy, 3.85 percent of the total costs for a patient's hospitalization was allocated to the PACU. [13] However, PACU charges (as they appeared on the patient's hospital bill) were 3.2 percent of the overall hospital charge. The mean cost-to-charge ratio for the PACU is 0.54 (Table 68-1) (Table Not Available) . The differing cost-to-charge ratios result when hospitals mark up the charges for services in one area (i.e., PACU) to invest in other unreimbursed hospital departments (i.e., medical records) or to pay for development of new clinical programs.

The PACU has a high fixed (does not change in proportion to number of patients treated) cost component. Variable costs, or labor and supplies directly involved in producing a specific patient service, account for 33 percent of overall PACU cost. [13] Because the remaining two-thirds of PACU costs are fixed, even if a patient spends an extra 20 minutes in the recovery room, institutional costs may not be affected significantly. This is not an argument for avoiding drugs with better recovery profiles or avoiding more costly antiemetics because patient satisfaction with care may be higher with the use of these agents. Mathematic modeling of PACU time and cost data suggest that what is most likely to produce cost savings in the PACU is optimizing the timing of the arrival of patients into the PACU to reduce peak requirements of nursing personnel. [14]

A survey at a university hospital revealed that recovery room nurses consider 60 minutes to be a minimum period of time to check the patient in, process the paperwork, and prepare the patient for transfer to the floor. [15] Because of this requirement and the high fixed cost structure of the PACU, reasonably achievable decreases in the times to PACU discharge by improvements in anesthesia practice are unlikely to reduce PACU costs substantially. More rapid awakening after anesthesia may be associated with decreased PACU costs if the patient bypasses the recovery room entirely, or if fewer staff members are required. Identifying anesthetics that can allow the patient to bypass the PACU is under investigation at both academic centers and community hospitals. Appropriate patients receiving monitored anesthesia care or regional anesthesia may not need to recover in the PACU. For example, deciding whether to leave a patient in the PACU until a motor block wears off from a conduction anesthetic deserves further study. Independent predictors of PACU length of stay include complexity and length of the surgical procedure, anesthetic type, and American Society of Anesthesiologists (ASA) status. [16] Some patients may need to remain in the PACU for monitoring and treatment of surgical problems, not anesthesia-related issues. Instead of requiring a minimum PACU stay for all patients, PACU stay can be adjusted according to patient and surgical factors--sicker patients having extensive surgery require extended recovery.

TABLE 68-1 -- Cost Ratios for Selected Hospital Departments

(Not Available)

Modified from Macario et al [13]

DESIGN AND STAFFING

Location and Size

The PACU should be located close to the operating suite to permit anesthesiologists and surgeons to be nearby and to permit rapid return of the patient to the operating room if necessary. The PACU should have good access to immediate roentgenographic, blood bank, blood gas, and other clinical laboratory services. Having the PACU located near the ICU is also useful, especially because nursing staff is shared between the units.

The size of the unit is determined by the surgical caseload of the institution. Approximately 1.5 PACU beds per operating room utilized are usually adequate. This is roughly equivalent to two beds for every four procedures performed in a 24-hour period. [17] [18] An open ward is optimal for patient observation; however, at least one isolation room is a helpful addition to every PACU for the management of those patients with either contaminated wounds or severe immunosuppression. A separate pediatric PACU is also useful when the volume of pediatric cases is high (Ch. 59) .

Facilities

The ward itself should have large doors, adequate lighting, efficient environmental control, and sufficient electrical and plumbing facilities. In addition to the bed spaces, there should be a central nursing station and physician station, as well as storage and utility rooms (Fig. 68-1) (Figure Not Available) . Each bed space should have piped-in oxygen, air, and vacuum for suction (both intermittent pressure for gastric suction and high pressure for airway and chest suction).

Equipment

There should be an automated blood pressure device or sphygmomanometer and intravenous supports by each bed. Pulse oximetry is an essential monitoring technique in the PACU. An area for charting and storage of bedside supplies is also necessary, with sterile suction catheters, needles, syringes, gloves, and face-mask oxygen available at every bedside. Electrocardiographic monitoring is routinely available for all patients. The capability for direct interarterial monitoring of blood pressure and of intracranial pressure is also required in hospitals where critically ill postoperative patients use the PACU.

A supply of immediately available emergency equipment should also be located in the PACU. This should include an airway cart consisting of the following: oral and nasal airways; orotracheal, nasotracheal, and tracheostomy tubes; laryngoscopes; bronchoscopes; and hand-ventilating devices. Self-inflating bags with positive end-expiratory pressure (PEEP) valves are also useful. A defibrillator capable of synchronized defibrillation should be available, as well as an electrocardiogram (ECG), pacemaker, and pacing wires. Equipment for pulmonary artery catheterization should be available. This includes an introducer set, [19] pulmonary artery catheters, transducers and flushing system, and a cardiac output computer. A "crash cart" containing cardiopulmonary resuscitation equipment and emergency drugs should be available and fully stocked at all times. Chest-tube trays, cutdown trays, and tracheostomy trays are necessary. A wide variety of intravenous solutions should also be available.

A new technology becoming increasingly prevalent is an automated patient-tracking system that uses computers to provide real-time information on the location and status of

Figure 68-1 (Figure Not Available) The postanesthesia care unit should be well lighted, spacious, and equipped to deal with any possible postanesthetic emergency. A central nursing and physician station is useful. Each bedside should be fully equipped with air, oxygen, and suction. *(Courtesy of Dr. Fred Mihm)*

surgical patients in the operating room suite. These systems provide video displays in which real-time surgical case information is available. The information is maintained by the use of bar-code scanners, magnetic readers, or common keyboard-based input terminals. Patient flow is tracked using bar-coded charts and bar-coded identification bracelets. Automated patient tracking systems can provide the PACU with information regarding room utilization, delays and cancellation, transit times, and expected arrival to the recovery room. This information may facilitate staffing. Whether this technology improves staff efficiency and operating room utilization deserves study.

Personnel

The personnel required will vary somewhat from unit to unit, but a nursing ratio of one nurse to every three patients is usually sufficient. If critically ill patients are admitted, the ratio is increased to one nurse to two patients (and occasionally, as high as two nurses to one patient). [17] [18] A charge nurse should oversee nursing care. Most PACUs are under the medical direction of the anesthesia department; however, few provide continual physician coverage with a full-time physician in the PACU. In most hospitals, the anesthesiologist responsible for the surgical anesthetic regimen remains responsible for the patient in the PACU and intervenes when necessary. The anesthesiologist is usually responsible for patient discharge to the postsurgical ward, ICU, or home.

Efficient staff scheduling is important in minimizing the costs of running a PACU. The two factors that affect the actual number of patients in the PACU at a given time of day are the hourly admission rates and the times to discharge. Because personnel costs are a major component of PACU costs, hospitals are creating a lower-cost team of personnel who can provide the same quality of service. To maintain an efficient recovery room, employees must possess multiple skills to cover various assignments because the type and amount of work fluctuate. Cross-training of nurses to care for patients in the preoperative area in the morning and in the postoperative area at midday and in the afternoon may increase efficiency. In addition, substitution of higher-cost labor with technicians, along with flexible work schedules, may better match supply and demand. A ward clerk and an orderly are helpful members of a busy PACU staff. In addition, structural changes in facilities, such as having nearby office facilities for surgeons to see patients between cases or a separate base adjacent to the PACU where family members can aid in caring of the patient, may improve cost efficiency. Because the major determinant of PACU cost is the distribution of admissions, PACU costs are unlikely to change without a decline in peak census. [14]

/das/book/view/29494766/875/751.html

ROUTINE RECOVERY

Factors Influencing Awakening

The recovery of a patient following an uncomplicated anesthetic regimen and operation is often routine. The recovery process actually begins in the operating room when the operation and anesthetic are completed and the trachea is extubated. [20] The time to recovery from inhaled anesthetics is a function both of the solubility coefficient of the agent and of the level of alveolar ventilation of the patient [21] (Ch. 4) . Some forms of premedication can delay recovery, such as high doses of rectally administered midazolam (2 mg/kg). [22] Alveolar hypoventilation is a common reason for delay in awakening from inhaled anesthetics. Administration of high concentrations of inhaled anesthetics for a long procedure is another common cause of delayed awakening. Recovery from morphine-based anesthetics is often a function of the dose administered and of postoperative renal function [23] (Ch. 10) . Propofol-based anesthesia is associated with a quicker return to normal activities than thiopental-isoflurane anesthesia in patients undergoing outpatient procedures. [24]

The introduction of sevoflurane has resulted in several studies that have examined its recovery characteristics. Although one study demonstrated a significantly faster time to eye opening as compared with time with isoflurane, [25] another did not, but the patients in the latter study felt less clumsy than those who received isoflurane. [26] Despite more rapid time to eye opening, patients receiving sevoflurane were not ready for discharge home any faster than patients receiving isoflurane. [25] When compared with those patients who received propofol-based anesthesia, patients who received sevoflurane had more rapid eye opening and were extubated sooner in one study, [27] but not in another. [28] However, the sevoflurane-treated patients had a higher incidence of vomiting. [26] When compared with desflurane, sevoflurane had a slower time to emergence and extubation. There were no differences in time to recovery of cognitive functions or time to discharge. [29]

Recovery from neuromuscular blockade is a function of the agent given, the dose, and the presence or absence of renal or hepatic disease (Ch. 12) . In addition, the dose of reversing agent, the patient's temperature, acid-base status, and the presence of drugs that increase neuromuscular blockade are also important. [30] The introduction of mivacurium, with its short duration of action, into clinical practice has led some anesthesiologists to omit reversal of the drug. If this is done, some adults exhibit residual neuromuscular blockade in the PACU and may require reversal there. [31] In addition, there have been two case reports of prolonged neuromuscular blockade following mivacurium in patients with low plasma cholinesterase levels. [32] [33]

Transportation

After tracheal extubation, the patient is transferred from the operating room table to a stretcher with side rails that can be moved into both Trendelenburg and head-up positions, if necessary. The patient should be transported from the operating room in the lateral position to minimize the risk of airway obstruction or aspiration of gastric contents from vomiting.

Report

When the patient arrives in the PACU, the anesthesiologist should give the nurse a full report of the events during

surgery. This report should include the patient's name, age, surgical procedure, medical problems, preoperative medications, allergies, anesthetic drugs and methods, fluid and blood replacement, blood loss, urinary output, gastric output, and surgical or anesthetic complications encountered.

Care

Following major surgical procedures, all patients should receive oxygen therapy via a face mask or nasal prongs. Healthy patients, following a brief minor surgical procedure, may not require oxygen therapy and can be guided by pulse oximetry. The routine administration of oxygen in the PACU is mildly controversial in the modern PACU equipped with a pulse oximeter. [34] [35] The nurse should be informed of any special medications, tests, or procedures that will be necessary in the PACU. Vital signs should be recorded at least every 15 minutes during the first postoperative hour. The nurse should also encourage the patient to wake up, cough, breathe deeply, and move about, if possible.

Discharge Considerations

Some patients may meet discharge criteria on arrival to the recovery room. Neither an arbitrary time limit nor a discharge score can be used to define a medically appropriate length of stay in the recovery room accurately.

The patient should be seen again by the anesthesiologist before being discharged from the PACU, and the patient's condition should be recorded in the chart. Before discharge, the patient who has undergone general anesthesia should be arousable and oriented, have stable vital signs for at least the prior hour, and be comfortable. Patients who have had recent large doses of narcotic analgesics should be observed for at least 30 minutes. The patient should be able to obtain nursing help while in the surgical ward if necessary. Patients discharged without supplemental oxygen need to have their arterial oxygen saturation measured by pulse oximetry while they are breathing room air.

Discharge of the patient from the recovery room following regional anesthesia depends on the type of block used and sedation administered. Nerve blocks of the upper extremities do not need to have resolved completely prior to discharge. However, patients should be able to ambulate if necessary in a ward (Chs. 42 to 44) . A full description of the patient's course should then be given by the recovery room nurse to the ward nurse before the patient is transferred.

Various system-based, nonmedical factors (i.e., no available bed, waiting for test results, transport delay, lack of physician release) account for many delayed discharges from the PACU. In the ambulatory setting, even after discharge criteria are satisfied, most patients have delayed discharge because of the unavailability of escorts or the lack of their discharge medications. Delays longer than 30 minutes for nonmedical reasons occur in 54 percent of outpatients, most commonly because the patient's companions are not immediately available. [36]

/das/book/view/29494766/875/752.html

STANDARDS

The ASA has the following standards for postanesthesia care, updated in October, 1994, by the ASA House of Delegates [37]:

```
These Standards apply to postanesthesia care in all locations. These
Standards may be exceeded based on the judgment of the responsible
anesthesiologist. They are intended to encourage quality patient care, but
cannot guarantee any specific patient outcome. They are subject to revision
from time to time as warranted by the evolution of technology and practice.
Under extenuating circumstances, the responsible anesthesiologist may waive the
requirements marked with an asterisk (*); it is recommended that when this is
done, it should be so stated (including the reasons) in a note in the
patient's medical record.
```

Standard I

All patients who have received general anesthesia, regional anesthesia or monitored anesthesia care shall receive appropriate postanesthesia management.

1. A Postanesthesia Care Unit (PACU) or an area which provides equivalent postanesthesia care shall be available to receive patients after anesthesia care. All patients who receive anesthesia care shall be admitted to the PACU or its equivalent **except** by specific order of the anesthesiologist responsible for the patient's care.
2. The medical aspects of care in the PACU shall be governed by policies and procedures which have been reviewed and approved by the Department of Anesthesiology.
3. The design, equipment and staffing of the PACU shall meet requirements of the facility's accrediting and licensing bodies.

Standard II

A patient transported to the PACU shall be accompanied by a member of the Anesthesia Care Team who is knowledgeable about the patient's condition. The patient shall be continually evaluated and treated during transport with monitoring and support appropriate to the patient's condition.

Standard III

Upon arrival in the PACU, the patient shall be re-evaluated and a verbal report provided to the responsible PACU nurse by the member of the Anesthesia Care Team who accompanies the patient.

1. The patient's status on arrival in the PACU shall be documented.
2. Information concerning the preoperative condition and the surgical/anesthetic course shall be transmitted to the PACU nurse.
3. The member of the Anesthesia Care Team shall remain in the PACU until the PACU nurse accepts responsibility for the nursing care of the patient.

Standard IV

The patient's condition shall be evaluated continually in the PACU.

1. The patient shall be observed and monitored by methods appropriate to the patient's medical condition. Particular attention should be given to monitoring oxygenation, ventilation, circulation and temperature. During

recovery from all anesthetics, a quantitative method of assessing oxygenation such as pulse oximetry shall be employed in the initial phase of recovery.* This is not intended for application during the recovery of the obstetrical patient in whom regional anesthesia was used for labor and vaginal delivery.
2. An accurate written report of the PACU period shall be maintained. Use of an appropriate PACU scoring system is encouraged for each patient on admission, at appropriate intervals prior to discharge and at the time of discharge.
3. General medical supervision and coordination of patient care in the PACU should be the responsibility of an anesthesiologist.
4. There shall be a policy to assure the availability in the facility of a physician capable of managing complications and providing cardiopulmonary resuscitation for patients in the PACU.

Standard V

A physician is responsible for the discharge of the patient from the PACU.

1. When discharge criteria are used, they must be approved by the Department of Anesthesiology and the medical staff. They may vary depending upon whether the patient is discharged to a hospital room, to the Intensive Care Unit, to a short stay unit or home.
2. In the absence of the physician responsible for the discharge, the PACU nurse shall determine that the patient meets the discharge criteria. The name of the physician accepting responsibility for discharge shall be noted on the record.

/das/book/view/29494766/875/753.html

QUALITY IMPROVEMENT AND CLINICAL PATHWAYS

The Joint Commission on Accreditation of Health Care Organizations requires continuous quality improvement of hospitals. Quality improvement is the effort to measure the level of current performance, to find ways to improve that performance, and to implement new and better methods. [38]

Teams of physicians, nurses, and other staff members may have little knowledge of the practice of others. Clinical pathways, also called care pathways or critical pathways, put providers caring for a patient "on the same page." Clinical pathways are an application of continuous quality improvement to health care. Hospitals are using clinical pathways to cut costs and to reduce unnecessary variation in care. These scientifically grounded, continuously reviewed treatment strategies facilitate multidisciplinary communication, data collection, data analysis, and feedback with a goal of quality outcomes at low cost. In nonmedical sectors, simplification and standardization of production processes to eliminate waste and duplication of effort have reduced costs.

The effect of clinical pathways on the PACU is largely unknown. Hospitals have tried to reduce anesthesia drug costs through written guidelines. Limiting neuromuscular blocking drug use, for instance, increased the average time from end of surgery to PACU arrival by an average of 3 minutes. [39] Although this finding was statistically significant, the economic effect of this change may be limited.

Institutional differences in clinical practice and cost may make it difficult for some cost-saving interventions to succeed. For example, if institutional policy requires a minimal period of PACU observation following all surgical procedures, the economic benefits to the PACU of completing a higher fraction of surgical procedures using monitored anesthesia care instead of general anesthesia may not be obtained.

Many studies of recovery room care compare intermediate end points such as early awakening or return to baseline on psychometric test. Although fewer patients are required to establish significant differences in these end points in clinical studies, comprehensive PACU outcome measures need to include other outcomes including patient satisfaction, incidence of unplanned hospital admissions, and ability to begin postoperative rehabilitation.

COMPLICATIONS

Survey Results

Until recently, studies of complications in the PACU were rare in the anesthesia literature. During the past 4 years, four separate groups have performed large surveys of complications occurring in the PACU. The first was a survey from Yale. Hines and colleagues [40] studied 18,473 PACU admissions in a university hospital. These investigators found that the incidence of PACU complications was high, with significant events occurring in nearly 24 percent of all patients. The most common complications were nausea and vomiting (9.8%), need for airway support (6.9%), hypotension (2.7%), dysrhythmia (1.4%), hypertension (1.1%), altered mental status (0.6%), rule out myocardial infarction (0.3%), and major cardiac events (0.3%) (Fig. 68-2) (Figure Not Available) . A survey of 120 anesthesia-related incidents from Australia found that nearly two-thirds of the reported incidents were respiratory. [41]

Figure 68-2 (Figure Not Available) Complications in the postanesthesia care unit (PACU). Two studies examined the frequency of PACU complications. Among inpatients, 24 percent of patients had a complication, whereas among outpatients, only 8 percent of patients had a complication. Nausea and vomiting were the most common in both studies. Life-threatening cardiovascular and respiratory complications were rare among outpatients. Nausea and vomiting accounted for 90 percent of the complications in outpatients. Dotted bars, outpatients *(data from Duncan et al [43])*; lined bars, inpatients *(data from Hines et al [40])*; CNS, central nervous system; CV, cardiovascular; N & V, nausea and vomiting. *(Redrawn from Hines et al [40] and Duncan et al [43])*

Figure 68-3 (Figure Not Available) Soft tissue roentgenograms of the head and neck of an awake patient show that with the head in the neutral position in a supine patient, the air clearance at the base of the tongue is about 3 mm. When the patient is unconscious, this small opening is often lost, and airway obstruction results. *(From Ruben et al [46])*

The factors that appeared to have the greatest influence on the complication rate in the Yale study were ASA class II, a duration of anesthesia between 2 and 4 hours, emergency procedures, and the type of surgical procedure, with abdominal and orthopedic procedures having the highest incidence of complications. Hypothermia also prolonged the recovery room stay. [40] A history of smoking also results in longer stays in the PACU. [42]

The complications in an ambulatory surgical PACU are similar, but they follow a different distribution. Duncan et al [43] found that because cardiac and respiratory events were infrequent, nausea and vomiting emerged as the major complication in outpatients (Fig. 68-2) (Figure Not Available) .

Respiratory Complications

The major respiratory complications encountered in the PACU are airway obstruction, hypoxemia, hypercapnia, and aspiration. Prompt recognition and treatment of these life-threatening problems are crucial in good postanesthesia care. Rose et al [44] defined these events as a critical respiratory event (CRE). In an evaluation of 24,157 consecutive PACU admissions over a 33-month period, these investigators found that for patients receiving a general anesthetic, the risk of a CRE was 1.3 percent (hypoxemia 0.9%, hypoventilation 0.2%, and airway obstruction 0.2%). A wide variety of factors increased the risk of a CRE such as increased age, obesity, long or emergency operations, use of opioids, and use of thiopental in contrast to propofol. Patients who did have a CRE had longer PACU stays and more cardiac problems, and they were more likely to require ICU admission. [44]

Airway Obstruction

The most common cause of postoperative airway obstruction is pharyngeal obstruction from a sagging tongue in the unconscious patient [45] (Fig. 68-3) (Figure Not Available) (Ch. 39) . Laryngeal obstruction can also occur secondary to laryngeal spasm or direct airway injury. [46] [47] [48] The most effective method of dealing with airway obstruction due to pharyngeal obstruction is a combination of backward tilt of the head with anterior displacement of the mandible (Figs. 68-4 (Figure Not Available) and 68-5) (Figure Not Available) . The proper position for each patient depends on trial and error until one has a completely patent airway. If the obstruction is not immediately reversible, a nasal or oral airway can be inserted. The nasal airway is preferred because it is better tolerated by patients. The oral airway may stimulate gagging and vomiting as well as laryngeal spasm. If the airway obstruction

Figure 68-4 (Figure Not Available) A combination of backward head tilt and anterior mandibular displacement is most effective in relieving airway obstruction resulting from pharyngeal blockade by the tongue. This maneuver is also helpful in relieving obstruction due to laryngeal spasm. *(From Ruben et al [46])*

Figure 68-5 (Figure Not Available) Radiographs of the head and neck of an anesthetized patient show that combining backward head tilt with anterior mandibular displacement results in an increased clearance at the tongue base to 22 mm (see Fig. 68-3) (Figure Not Available) . *(From Ruben et al [46])*

is due to laryngeal spasm, this sometimes can be relieved with similar airway maneuvers. If the obstruction cannot be relieved by simple maneuvers, 10-mg dexamethasone intravenously may reopen the airway. Small doses of succinylcholine, 10 to 20 mg intravenously, have been used, but this practice is risky owing to the nonspecific relaxation of all muscles, including the diaphragm. All patients with airway obstruction should receive oxygen via face mask. (F_{IO_2}, 1.0). When the airway cannot be opened by physical means, positive-pressure ventilation with a bag, mask, and 100 percent oxygen is indicated. If succinylcholine has been given, assisted ventilation should be continued for at least 5 to 10 minutes, even if the obstruction has been relieved. [49] For all cases of airway obstruction, if an adequate airway cannot be established by simple physical or pharmacologic means, one must be established via orotracheal intubation using direct laryngoscopy. The laryngeal mask airway may be useful in certain patients and has even been used to provide pressure support ventilation in the PACU. [50] In the very rare case in which the trachea cannot be intubated, an emergency cricothyroidotomy will relieve the obstruction. This procedure is probably safer than emergency tracheostomy, because excessive bleeding is common with the latter procedure done under emergency conditions. Prompt action is crucial in airway obstruction because the partial arterial carbon dioxide pressure (Pa_{CO_2}) increases 6 mm Hg during the first minute of total obstruction and then at a rate of 3 to 4 mm Hg per minute thereafter. In such cases, there is also a progressive fall in Pa_{O_2}, owing to the continuously falling alveolar P_{O_2}.

Patients with obstructive sleep apnea are at high risk of airway obstruction when they are sedated. Nasal continuous positive airway pressure can be very useful in these patients from the time of tracheal extubation onward. [51]

Hypoxemia

Hypoxemia is a common and potentially serious postoperative complication. [52] [53] [54] The pulse oximeter has allowed for more careful evaluations of the incidence of

postoperative hypoxemia than ever before in the history of the PACU. In a survey performed in Denmark, 55 percent of patients had one or more episodes of hypoxemia (Sa_{O_2} < 90%) often despite the presence of routine supplemental oxygen. Ninety-five percent of those episodes went unrecognized by the PACU staff. Factors predisposing to these incidents were duration of anesthesia, use of general anesthesia, and a history of smoking. [55] The same group performed a randomized, blinded study of the effects of oximetry and found that episodes of extreme hypoxemia (Sa_{O_2} < 80%) were not seen in patients in whom the PACU staff had access to the pulse oximetry data but were encountered when they did not. Interestingly, the overall complication rates in the two groups were not different. [56]

Hypoxemia following anesthesia and surgery can be caused by many factors. Evaluation of the hypoxemic postoperative patient should include consideration of each of the classic causes of hypoxemia: (1) low inspired concentration of oxygen; (2) hypoventilation; (3) areas of low ventilation-to-perfusion relations; and (4) an increased intrapulmonary right-to-left shunt. Situations such as increased age, postanesthetic shivering, and a lowered cardiac output may worsen the degree of hypoxemia in postsurgical patients when an intrapulmonary shunt is present. [57] [58] [59]

Low inspired concentrations of oxygen (F_{IO_2} < 0.21) is fortunately a rare cause of significant postoperative hypoxemia; however, the delivery of hypoxic gas mixtures to postoperative patients is possible. Crossing of nitrous oxide and oxygen pipelines during hospital construction resulted in the loss of more than 30 lives in a Canadian hospital. Pipelines have crossed in hospital modernization projects. Switching of all adapters can also lead to delivery of the wrong gas, as can purging the system with nitrogen for pipeline repairs [60] (Ch. 7) .

The most common cause of postoperative hypoxemia is an increase in the right-to-left intrapulmonary shunt. Increases in the intrapulmonary shunt can be caused by many processes. Atelectasis is the most common cause of an increased right-to-left shunt. Atelectasis occurs as the result of collapse of an entire lung, lobe, or lung segment, or it can occur in a diffuse pattern. Bronchial obstruction from secretion or blood is a frequent cause of atelectasis. Lobar and segmental collapses often result from bronchial obstruction with secretions and are best managed by providing adequate humidification of the inspired gases, coughing, deep breathing, and postural drainage. Endobronchial intubation with collapse of the opposite lung is a serious complication and should be avoided.

Pneumothorax is a cause of hypoxemia that can have serious sequelae. Pneumothorax causes hypoxemia due to atelectasis and an intrapulmonary shunt. Pneumothorax occurs as a result of direct lung or airway injury from trauma, rib fractures, or attempts at percutaneous vascular cannulation. Pneumothoraces resulting from mechanical ventilation per se are rare unless airway pressures are high. [61] [62] Treatment depends on the size of the pneumothorax and the patient's condition. A 10 to 20 percent pneumothorax in a spontaneously breathing patient can be observed with frequent upright chest roentgenograms. A pneumothorax of more than 20 percent in a spontaneously breathing patient or any pneumothorax in a mechanically ventilated patient should be treated by insertion of a chest tube for drainage. This is usually done in the second intercostal space in the midclavicular line. A tension pneumothorax occurs when the pleural cavity fills with air and compresses the mediastinum, resulting in circulatory compromise. Tension pneumothorax is treated in the same manner; however, one should not await roentgenographic confirmation of the diagnosis if tension pneumothorax with circulatory depression is diagnosed. A 14-gauge needle inserted in the second intercostal space can relieve the tension prior to chest-tube insertion.

Arterial hypoxemia may be present in postoperative patients who have no discernible change in the chest roentgenogram. These patients may have an increased right-to-left intrapulmonary shunt due to diffuse airway collapse. The relationship between the functional residual capacity (FRC) of the lung and closing capacity is a prime determinant of this effect. [63] [64] When the closing capacity exceeds FRC, airways collapse during tidal breathing and an intrapulmonary shunt develops. Any situation that results in either increased closing capacity (e.g., increasing age) or reduced FRC (pulmonary edema, infection, aspiration,

Figure 68-6 (Figure Not Available) In a study of 40 cases of postoperative pulmonary edema, the cumulative incidence of pulmonary edema (percentage) is plotted with respect to the end of the operation (minutes). Most cases occurred within the first 30 minutes, and most were preceded by hypertension. *(From Cooperman and Price [66])*

obesity) places the patient at increased risk for hypoxemia. Difficulties in interpreting the closing capacity led some investigators to question the FRC/closing capacity relationship as being the sole determinant of impaired gas exchange during the perioperative period. [65]

Pulmonary edema can result in hypoxemia in the postoperative period. Although pulmonary edema has been well studied in patients with left ventricular failure, [66] [67] studies of this process in the immediate postoperative period are rare. Cooperman and Price [68] examined 40 cases of perioperative pulmonary edema and found one-half of the patients to have preoperative evidence of cardiovascular disease. [68] The most common time of appearance of pulmonary edema was observed within 60 minutes of completion of surgery (Fig. 68-6) (Figure Not Available) . More than one-half of these cases were preceded by hypertension, a finding suggesting that this problem may be related to the high pulmonary vascular pressures seen in acute, postoperative hypertension. Detection was made frequently by the presence of wheezing. Elevation of the central venous pressure and neck vein distention were not common findings. Patients develop pulmonary edema postoperatively because of high hydrostatic pressure in the pulmonary capillaries, increased capillary permeability, or sustained reductions in the interstitial hydrostatic pressure. The last-named type of pulmonary edema is seen following prolonged airway obstruction. [69] [70] Patients with a permeability injury can have their pulmonary edema exacerbated by increases in hydrostatic pressure. High-pressure pulmonary edema is usually caused by ischemic or valvular heart disease. Pulmonary edema characterized by a permeability injury is seen following a wide variety of serious clinical situations such as disseminated intravascular coagulation, shock, trauma, massive transfusion, sepsis, and anaphylaxis. This type of pulmonary edema is frequently called the adult respiratory distress syndrome and is characterized by hypoxemia, diffuse pulmonary infiltrates on roentgenogram, and reduced lung compliance. A common early pathologic finding is neutrophil accumulation in the lung vasculature and tissue. There is increasing evidence that activation of arachidonic acid metabolites, the prostaglandins and the leukotrienes, may be responsible for the permeability injury seen in humans. [71] Experimentally, leukotriene D_4 increases pulmonary permeability. [72] Because more is being learned about these substances, future breakthroughs in the adult respiratory distress syndrome probably will center around the use of naturally occurring inhibitor substances of key reactions.

Current treatment of both forms of pulmonary edema centers around lowering the hydrostatic pressure in the lungs to the lowest possible level consistent with adequate perfusion of all organ systems. This is done with diuretics, fluid restriction, vasodilators, or dialysis if there is associated renal failure. Positive-pressure ventilation is useful if there is severe hypoxemia or respiratory acidosis. Ventilation with end-expiratory pressure improves oxygenation by increasing lung volume, not by decreasing lung water. [73] Monitoring with a pulmonary artery catheter is often helpful. Monitors of extravascular lung water employing double-indication dilution techniques are available and accurate, but they are probably too technically demanding for routine clinical use. [74] [75] Respiratory support with oxygen and mechanical ventilation are frequently necessary while the patient receives definitive treatment. Vomiting and aspiration of gastric contents during and after anesthesia can produce a severe permeability injury resulting in pulmonary edema and hypoxemia.

Pulmonary embolism occurring in the immediate postoperative period is a serious event that can lead to profound hypoxemia. The exact physiologic explanation of the hypoxemia is unclear. Patients at bed rest for prolonged periods prior to surgery are very susceptible to emboli. The diagnosis is suspected in a patient with sudden pleuritic chest pain, shortness of breath, pleural effusion, or tachypnea. Evidence of right heart strain can sometimes be seen on the ECG. Massive emboli result in hypotension, pulmonary hypertension, and an elevated central venous pressure. Because the treatment of choice is anticoagulation, the establishment of an accurate diagnosis is imperative so that patients in the immediate postsurgical period are not needlessly exposed to the risks of anticoagulation. The only certain way to make the diagnosis is pulmonary angiography. This is often the procedure of choice for this type of patient. Once the diagnosis is made, heparin is given via continuous intravenous infusion to keep the patient's partial thromboplastin time 2 to 2.5 times control. If emboli recur or if bleeding develops with adequate heparinization, vena caval obstruction by percutaneously placed umbrella may be indicated.

Posthyperventilation hypoxemia and diffusion hypoxemia can occur but are rarely seen in clinical practice because oxygen administration prevents the clinical manifestations of the events. Following anesthetic techniques that use hyperventilation, the body's supplies of carbon dioxide are restored from endogenous carbon dioxide production and ventilation. P_{AO_2} is reduced accordingly. The top solid line in Figure 68-7 (Figure Not Available) illustrates the theoretic drop in P_{AO_2} that would occur. Diffusion hypoxia occurs when nitrous oxide is replaced with air at the end of the anesthetic. Because nitrous oxide is 31 times more soluble than nitrogen, there is dilution of the inspired

Figure 68-7 (Figure Not Available) Posthyperventilation hypoxia and diffusion hypoxia. The upper (dashed) line represents normal P_{AO_2} during breathing of air. Posthyperventilation hypoxia is indicated by the upper solid line, assuming that the patient hyperventilated for an hour was then allowed to accumulate CO_2 for 10 minutes before zero time. Diffusion hypoxia (following equilibration

with 79% nitrous oxide [N_2 O]) was added to posthyperventilation hypoxia as described earlier, except the inspired gas was changed to air at zero time. *(From Marshall and Wyche [57])*

air with nitrous oxide and the P_{AO_2} falls. The combination of hyperventilation and nitrous oxide can result in the drop in P_{AO_2} seen in the bottom line of Figure 68-7 (Figure Not Available) . [59]

The type of anesthetic and the site of operation influence the reduction in Pa_{O_2} seen following anesthesia and surgery. Abdominal operations are associated with the most prolonged reductions in Pa_{O_2} . Although the Pa_{O_2} may be normal during the immediate postoperative period, abdominal operations under regional anesthesia are associated with the greatest reduction in Pa_{O_2} after 24 hours. [57] This is likely because of the reduced vital capacity seen following upper abdominal surgery. A shift from diaphragmatic to rib cage breathing probably accounts for this well-recognized decrease in postoperative vital capacity. [76]

Reductions in cardiac output can contribute to large decreases in Pa_{O_2} in patients with existing intrapulmonary shunts. This is due to the effect of the lowered mixed venous P_{O_2} , which is added directly to the arterial circulation through the right-to-left shunt [59] (Fig. 68-8) (Figure Not Available) . Postoperative shivering can result in increases in oxygen consumption of as much as 500 percent; however, this only rarely contributes to arterial hypoxemia. [58] Shivering also reduces the Pa_{O_2} in patients with an intrapulmonary shunt by lowering of the mixed venous oxygen tension. Significant increases in postoperative oxygen consumption also occur following anesthesia for burn treatment leading to inadequate oxygen delivery. [77]

Recognition of hypoxemia can be difficult during the recovery from anesthesia if pulse oximetry is not used. Lowered hemoglobin concentrations may prevent the detection of peripheral cyanosis. The ventilatory and circulatory responses to hypoxemia may also be attenuated in elderly patients. Currently, the best method of assessing hypoxemia during anesthetic recovery is with a pulse oximeter. [78] Comparisons of the measured with the oximeter correlate closely with measurements made from samples of arterial blood. The system provides information about early reductions in oxygen saturation that serves as an early warning, so that therapeutic intervention can be made before life-threatening hypoxemia develops. The device is useful for monitoring patients at high risk of developing postoperative hypoxemia during recovery from anesthesia. [79] The response time for this device is faster than that using transcutaneous techniques. [80]

The ability to evaluate Pa_{O_2} continuously during and following anesthesia has led to some interesting results. Monitoring during transport to the PACU without supplemental oxygen has demonstrated that about one-third of adult and pediatric patients develop hypoxemia (Sa_{O_2} < 90%) during transport to the recovery room. [81] [82] During a patient's stay in the recovery room, arterial desaturation is not an uncommon event. In children, hypoxemia does not correlate with wakefulness. [83] In adults, the risk factors for postoperative hypoxemia are age, obesity, length of surgery, and ASA physical status. In one study, the most common time hypoxemia

Figure 68-8 (Figure Not Available) Relationship between cardiac index and arterial oxygenation with shunt fractions (Q_{VA}/Q_T) ranging from 5 to 30 percent. With large intrapulmonary shunts, a small drop in cardiac index results in a large fall in arterial oxygenation. *(From Philbin et al [59])*

Figure 68-9 (Figure Not Available) Relationship between shunt fraction and arterial oxygen tension (Pa_{O_2}) for varying inspired concentrations of oxygen (P_{AO_2} 100-680 mm Hg). Patients with small shunt fractions have large increases in Pa_{O_2} with increasing inspired oxygen, whereas patients with high shunt fractions have a small response to increasing oxygen concentration. *(From Pontoppidan et al [85] ; graph courtesy of Dr. M.A. Duvelleroy)*

was observed was just prior to transfer to the postsurgical ward. [84] The findings of these studies suggest that all patients should have oxygen saturation assessed during their stay in the PACU and that a measurement of the arterial oxygen saturation should be made in every patient prior to discharge.

Treatment of hypoxemia by face-mask oxygen is effective in restoring the Pa_{O_2} in many cases. The Pa_{O_2} response to oxygen breathing depends on the degree of intrapulmonary shunt. Increasing the F_{IO_2} from room air to 100 percent results in a large increase in Pa_{O_2} when the shunt fraction is small; however, oxygen has little effect on the Pa_{O_2} in patients with a large shunt fraction [85] (Fig. 68-9) (Figure Not Available) . If hypoxemia persists (Pa_{O_2} <60 mm Hg) despite maximal oxygen therapy (F_{IO_2} , 1.0), tracheal intubation and mechanical ventilation should be initiated. In such patients, ventilation with PEEP increases the functional residual capacity and improves arterial oxygenation. Ventilation with PEEP eventually permits a reduction in F_{IO_2} without a fall in Pa_{O_2} .

Continuous positive airway pressure (CPAP) by an external mask (mask or nasal CPAP) is increasingly used for treatment of patients with severe hypoxemia who have adequate carbon dioxide elimination [86] (Ch. 72) . Certainly, patients have avoided tracheal intubation because of the use of mask or nasal CPAP. However, many patients who have a trial of mask or nasal CPAP fail that trial and need to receive tracheal intubation and mechanical ventilation. Good candidates for mask or nasal CPAP are patients with severe hypoxemia requiring more than 80 percent oxygen to have a Pa_{O_2} higher than 60 mm Hg. They must have a normal or low Pa_{CO_2} and not have severe respiratory distress. They must be awake and alert. Mask or nasal CPAP is most useful when the cause of hypoxemia can be quickly corrected, such as cardiogenic pulmonary edema, because the mask becomes very uncomfortable for the patient even after several hours of use. Newer mask designs have improved on this problem, but they have not eliminated it.

Hypoventilation

Hypoventilation is defined as reduced alveolar ventilation resulting in an increase in Pa_{CO_2} . During the postoperative period, hypoventilation occurs as a result of poor respiratory drive, poor respiratory muscle function, a high production rate of carbon dioxide, or acute or chronic lung disease.

Central respiratory depression is seen with any anesthetic. Narcotic anesthetics produce respiratory depression that is detectable by a shift of the carbon dioxide curve downward and to the right (Ch. 10) . Neuroleptic anesthetic techniques can produce a biphasic respiratory depression with respiratory depression intraoperatively, which dissipates on arrival in the recovery room, only to be followed by a second period of respiratory depression [87] (Fig. 68-10) (Figure Not Available) .

Figure 68-10 (Figure Not Available) Slopes of CO_2 response curves are expressed as percentage of control slopes at the time of the last dose of fentanyl or Innovar (time = 0) at the end of operation, at the time they are steepest, flattest, and at the end of the operation. Patients receiving neuroleptic agents as supplements to nitrous oxide (N_2O) anesthesia exhibit biphasic respiratory depression. *(From Becker et al [87])*

Narcotic-induced respiratory depression can be reversed by use of narcotic antagonists. [88] When small doses are used, these agents can reverse the narcotic-induced respiratory depression without altering pain relief; however, the duration of action of currently available antagonists is shorter than most narcotics and the dose has to be repeated at least once. Larger doses of these agents reverse the analgesic effects of the narcotics and result in a patient in severe pain who often develops profound increases in heart rate and blood pressure. These increases in rate pressure product (heart rate × systolic blood pressure) signify large increases in myocardial oxygen consumption and can result in ischemia in patients with coronary artery disease. An inadequate central respiratory drive can also be seen after certain neurosurgical procedures, such as cervical cordotomy.

Poor respiratory muscle function occurs following surgery and often contributes to hypoventilation. The site of the incision affects the ability to take a large breath, as measured by the vital capacity. Nearly all patients have reductions in vital capacity that are the greatest on the day of surgery. Patients undergoing upper abdominal surgery have the greatest reduction in vital capacity, showing as much as a 60 percent reduction on the day of surgery [89] (Fig. 68-11) (Figure Not Available) . This problem, secondary to diaphragmatic impairment, results in problems with both carbon dioxide elimination and oxygenation. [76]

Failure of reversal of neuromuscular blocking agents may result in inadequate respiratory muscle function postoperatively. This can be due to inadequate excretion of the drug, as in renal failure, or to the presence of other drugs that accentuate neuromuscular blockade, such as gentamicin, neomycin, clindamycin, or furosemide [90] [91] (Ch. 12) . Hypermagnesemia potentiates neuromuscular blockade, as does hypothermia. [30]

Obesity, gastric dilation, tight dressings, and body casts also inhibit respiratory muscle function and can predispose

Figure 68-11 (Figure Not Available) Change in vital capacity seen following surgical procedures in various sites. All patients manifest the lowest vital capacity on the day of surgery. Upper abdominal surgery is associated with the greatest reduction in vital capacity, and spinal surgery is associated with the least. *(From Ali et al [85])*

to carbon dioxide retention. A high level of carbon dioxide production from sepsis or shivering can result in carbon dioxide retention, especially if the patient cannot increase minute ventilation. [49]

The direct measurement of Pa CO_2 is the best method of detecting hypoventilation in the postoperative period. Although hypertension and tachycardia commonly occur during carbon dioxide retention, they may not be seen in postsurgical patients and the elderly, who have an attenuated response to increased levels of carbon dioxide (Ch. 61) . Transcutaneous electrodes can continuously monitor the CO_2 tension and are useful in high-risk patients. Measurements of the vital capacity and maximum inspiratory force are good guides to the ability of the postsurgical patient to breathe spontaneously in the postoperative period. [49] The vital capacity should be at least 10 mL/kg body weight, and the inspiratory force should be numerically greater than -20 cm H_2O. [92] If these minimum values cannot be maintained, the patient should receive controlled mechanical ventilation until he or she is awake enough to generate adequate respiratory muscle function. End-tidal carbon dioxide measurements can be used in the patient whose trachea is intubated whether breathing spontaneously or with mechanical ventilation. [93]

Treatment of serious respiratory failure necessitates emergency tracheal intubation. The need to perform reintubation is rare, occurring in 0.2 percent of about 13,000 patients studied in one series. [94] In that series, 77 percent of the reintubations occurred within the first hour in the PACU and were more common in children and the elderly. Many of the cases were believed to be preventable and related to excessive anesthetic and sedative drugs, excessive fluid administration, persistent effects of muscle relaxants, and upper airway obstruction.

Circulatory Complications

Critical cardiovascular events in the PACU are the second major group of life-threatening complications for patients in this setting. The risk factors for and the ultimate outcome were evaluated by Rose et al [95] in a study of 18,380 patients following general anesthesia in Toronto. These investigators found that patients who developed hypertension or tachycardia in the PACU had more unplanned critical care admissions and had a higher mortality rate than those who did not. In contrast to respiratory events, anesthetic factors only contributed in a minor way to the development of cardiovascular problems in the PACU, whereas patient and surgical factors were more important risk factors. [95]

Hypotension

Hypotension in the recovery phase of anesthesia usually signifies decreased ventricular preload, reduced myocardial contractility, or a profound reduction in systemic vascular resistance. Decreased ventricular preload is caused by intravascular volume depletion due to blood loss, excessive third-space fluid loss, unreplaced urinary losses, or septicemia with vasodilatation and capillary leakage of fluid (Chs. 45 46 and 62) . Acute, massive pulmonary embolism

produces hypotension by blocking the flow of blood to the left heart. Reductions in myocardial contractility occur because of continued effects of anesthetic drugs, preexisting ventricular dysfunction, or the development of a perioperative myocardial infarction. Profound reductions in systemic vascular resistance usually occur with septicemia, but they are also seen in chronic liver failure.

Prompt diagnosis and treatment are important, because prolonged hypotension can result in hypoperfusion of vital organs and subsequent ischemic damage. Quickly assess whether the hypotension is real or an artifact of the measurement system. If the hypotension is real, ventricular preload can be increased by elevation of the patient's legs and administration of intravenous fluids. Physiologic saline and lactated Ringer solution are effective and inexpensive choices. The surgical wound area is examined for evidence of rapid blood loss, and a hematocrit determination is ordered. If hypotension persists despite attempts to restore intravascular volume, ventricular preload must be further assessed. In patients with normal left ventricular function, the central venous pressure estimates ventricular preload. In the presence of left ventricular dysfunction, the central venous pressure is not an accurate guide to ventricular filling pressure, and a flow-directed pulmonary artery catheter should be inserted (Ch. 30) . During this time, administration of a vasopressor prevents a prolonged period of hypotension while hemodynamic monitoring is established. Following insertion of the pulmonary artery catheter, ventricular preload can be assessed by examining the pulmonary artery occlusion pressure. The pulmonary artery catheter also allows for bedside measurement of the cardiac output by the thermodilution technique. With skilled personnel, this type of catheterization can be carried out in the PACU in less than 30 minutes. With the pulmonary artery catheter, various forms of shock can be assessed.

Despite the widespread acceptance of the pulmonary artery catheter to enable the clinician to diagnose the etiology of shock states and the state of the intravascular volume accurately, carefully controlled trials evaluating its use have been absent from the literature. One study suggests that patients who are treated in critical situations with a pulmonary artery catheter have a higher mortality rate, use more costly resources, and have a longer length of hospital stay than patients treated without a pulmonary artery catheter. [96] This study was done in ICU patients and not in patients undergoing anesthesia or in the PACU; however, the implications of the study suggest that anesthesiologists should reexamine their use of this device in the perioperative period. It has been suggested that specific uses of the pulmonary artery catheter be subject to randomized, controlled clinical trials, or that the U.S. Food and Drug Administration (FDA) ban their use entirely. [97]

Hypovolemic shock is characterized by a low pulmonary artery occlusion pressure (PAOP <5-10 mm Hg) with a normal low cardiac index (normal, 2.5-4.0 L/min/m^2) and a normal or elevated systemic vascular resistance:

Normal = 900 to 1,400 dynes/s/cm^{-5} , where SVR is systemic vascular resistance, MAP is mean arterial pressure, CVP is central venous pressure, and CO is cardiac output (Chs. 16 and 30) .

Cardiogenic shock is characterized by increased PAOP (>15 mm Hg) with a low cardiac index and elevated systemic vascular resistance. Patients in whom left ventricular failure is suspected should have an ECG and chemical analysis of the cardiac enzymes, especially a fractionated creatinine phosphokinase (CPK) to rule out a myocardial infarction. Elevation of the myocardial fraction of the CPK (CPK-MB) in the first 24 hours is a specific test for myocardial muscle death and provides prompt, accurate evidence of infarction in the postsurgical patient. Examination of the total CPK alone is of no use in the surgical patient because it is elevated frequently secondary to skeletal muscle damage. Newer methods of measuring the CPK-MB have made this test rapid, and results can be available in less than 1 hour.

In *septic shock* PAOP is usually low with a very high cardiac output and low systemic vascular resistance. The patient often has fever, an elevated white blood cell count, and some other sign of systemic infection.

Treatment of such prolonged hypotension is now guided by following the variable of ventricular preload, cardiac output, and urinary output. Hypovolemic shock is treated by intravenous administration of blood and crystalloid. The role of albumin replacement in this setting is controversial but widely used (Chs. 45 and 46) . Albumin is no more effective than crystalloid in restoring intravascular volume and can cause deterioration of renal function when used for hypovolemic resuscitation. [98] Albumin is also far more expensive than crystalloid. Comparison of the use of albumin versus crystalloid for hypovolemia shows that the only difference in the two groups of patients was a more costly resuscitation in the albumin-resuscitated group. [99] Starch solutions are a less expensive and an effective alternative to albumin and saline. [100] When lung injury exists, resuscitation with crystalloid, albumin, or starch solutions will not further damage the lung if resuscitation is not performed with increased pulmonary hydrostatic pressure. [101]

Cardiogenic shock is managed by first optimizing the ventricular preload. Although the heart normally functions with a low preload (PAOP 3-8 mm Hg), when the left

ventricle fails, it often functions best when the preload is elevated. Therefore, one should attempt to give fluid or blood intravenously to increase the preload and follow the cardiac output (CO) and stroke volume (SV):

where HR is heart rate.

Most patients have an optimal cardiac output when the PAOP is increased to 15 to 20 mm Hg (Chs. 16 and 30) . Occasional patients with severe, long-standing ventricular failure require PAOP of 20 to 25 mm Hg to maintain cardiac output. In addition to an optimal preload, these patients also require inotropic support with dopamine in the range of 3 to 10 mug/kg/min. Dopamine in that dosage acts as a beta-adrenergic-receptor agonist as well as acting on dopaminergic receptors in the kidney, thus increasing renal blood flow. This effect is most prominent in the lower dosage range (1-3 mug/kg/min), but it also is present to some degree up to 10 mug/kg/min. At a higher dose, an alpha-adrenergic effect

Figure 68-12 (Figure Not Available) The normal Starling relation of the heart is depicted on the upper line, where increasing left ventricular filling pressure (LVFP) increases stroke volume (SV). In the presence of ventricular dysfunction, this curve is shifted downward and to the right. The depressed curve can be shifted toward normal by inotropic drugs (I) or vasodilator drugs (V). Infusion of both (V + I) produces a synergistic effect. Diuretics (D) reduce filling pressure without increasing output. The dashed line suggests that SV may rise later. *(From Cohn and Franciosa, [102] copyright 1977 Massachusetts Medical Society. All rights reserved.)*

dominates. Some patients with left ventricular failure still have a low cardiac output and high systemic vascular resistance despite optimal preload and inotropic support. In that situation, careful addition of a peripheral vasodilator such as sodium nitroprusside or hydralazine lowers the outflow impedance to ventricular ejection (lowered vascular resistance and increased stroke volume). Combined inotropic and vasopressor support often restores cardiac output to near-normal values [102] (Fig. 68-12) (Figure Not Available) . In this setting, vasodilator therapy should not be abruptly terminated because a rebound rise in vascular resistance often results in worse ventricular function than was present before the drug was begun [103] (see Ch. 14 for a detailed discussion of these autonomic drugs). Vasodilator therapy should not be used without first increasing preload and increasing the inotropic state of the heart. Vasodilators can only be used in this setting if the hypotension has been first reversed with fluid and inotropic therapy.

Septic shock is managed by replacing the fluid lost from capillary endothelial leak with crystalloid. Use of albumin in this situation is possibly harmful, because the albumin can leak out into the interstitium and may draw intravascular fluid with it. [104] An inotropic agent such as dopamine is often necessary to increase cardiac output further and to raise the arterial blood pressure. On occasion, patients with severe sepsis remain hypotensive with a high cardiac output and lowered vascular resistance despite infusion of fluids and an inotropic drug. In this situation, prolonged lowered diastolic pressure results in insufficient coronary blood flow and myocardial ischemia. This usually manifests itself as a sudden and irreversible ventricular dysrhythmia. To prevent this problem, an alpha-adrenergic agonist, such as norepinephrine or phenylephrine, could be introduced. Use of these agents is successful only if the septic process can be brought under control. Use of vasoconstrictors for more than 24 hours may result in renal and gastrointestinal ischemia.

Hypertension

When hypertension develops in the PACU, it is often due to pain, hypercapnia, hypoxemia, or excessive intravascular fluid volume. Any patient who manifests hypertension in the PACU should have those causes investigated and treated. Severe hypertension can lead to left ventricular failure, myocardial infarction, or a dysrhythmia from a sharp increase in myocardial oxygen consumption. Acute hypertension may also precipitate acute pulmonary edema or a cerebral hemorrhage.

Preexisting hypertension is present in more than one-half of the patients who develop hypertension in the recovery room. [105] Such hypertension can be made worse if antihypertensive medications have to be abruptly withdrawn preoperatively. [106] When hypertension does develop during recovery from anesthesia, it usually begins within 30 minutes of the end of the operation [105] (Fig. 68-13) (Figure Not Available) .

Treatment of acute hypertension involves first treating pain, hypercapnia, hypoxemia, or fluid overload. If hypertension is still present, an antihypertensive drug is necessary. Because most postoperative hypertension is resolved within 4 hours of surgery, long-acting antihypertensive drugs are unnecessary. Most patients without preexisting hypertension do not need prolonged treatment. [105] A rapid-acting drug such as sodium nitroprusside is effective in treating postoperative hypertension because its onset is prompt and its effects can be quickly reversed by discontinuing the drug. Nitroprusside is a vasodilator that acts directly on the vessel walls, both of the arterioles and venules. Nitroprusside is administered as a continuous infusion beginning at 0.5 to 1.0 mug/kg/min and titrating the blood pressure to acceptable

Figure 68-13 (Figure Not Available) Time of onset of hypertension in 60 patients in whom hypertension developed after surgery. More than one-half had a history of hypertension. Pain, emergence excitement, hypercapnia, hypoxemia, and volume overload were common causes. *(From Gal and Cooperman [105])*

levels. Nitroprusside should be used in conjunction with close monitoring of the arterial blood pressure, preferably using direct intra-arterial monitoring. An automatic blood pressure device is an adequate alternative that can provide frequent, accurate information about the mean arterial pressure. [107] The dose should not exceed 5 mug/kg/min or a total of 3 mg/kg in 24 hours, because nitroprusside is metabolized to cyanide, which may result in general blockade of oxidative phosphorylation resulting in diffuse cellular injury. This complication is best prevented by close observation of the dose administered. The best sign of cyanide toxicity is the finding of progressive metabolic acidosis [108] (Chs. 14 and 41) , which, if present, dictates discontinuation of the nitroprusside and substitution of another antihypertensive drug.

An alternative to nitroprusside is trimethaphan, which produces a decreased arterial blood pressure resulting from ganglionic blockade. Trimethaphan is also given as a continuous infusion. Advantages to trimethaphan are that it prevents the reflex tachycardia seen with nitroprusside by virtue of its ganglionic blockade and it prevents reflex increase in pulse pressure sometimes seen when nitroprusside is given to patients with a hyperdynamic circulation such as patients with aortic dissection or atherosclerotic cardiovascular disease. The major disadvantage is that it produces ileus and urinary retention secondary to ganglionic blockade. Tachyphylaxis to the drug is common after 12 to 24 hours of use. Hydralazine is another vasodilator that can be given intravenously for acute hypertension as a 5- to 10-mg injection. The onset is delayed 15 to 30 minutes and does not permit prompt control. In addition, tachycardia is a common complication of its use as an antihypertensive.

Beta-blocking drugs such as propranolol, labetalol, and esmolol are all effective in treating hypertension during recovery. Labetolol, a combined alpha and beta blocking agent, is commonly used in the PACU. When used for treatment of postoperative hypertension, its beta effects predominate, and the reduction in blood pressure results from its negative inotropic effects. [109] When used in the PACU, its effects are prompt and no further treatment is needed in most cases. Labetalol can be given in intravenous 5-mg increments, with the effect on blood pressure apparent in several minutes. [110] Labetalol is also effective in neurosurgical patients already receiving high doses of nitroprusside. [111] Esmolol is an ultrashort-acting beta blocker that is effective in treating postoperative hypertension and tachycardia. Its short half-life means it must be given as a continuous infusion at rates of 25 to 300 mug/kg/min [112] (Ch. 14) .

Dysrhythmias

The factors predisposing to development of postoperative dysrhythmias are electrolyte imbalance (especially hypokalemia), hypoxia, hypercapnia, metabolic alkalosis and acidosis, and preexisting heart disease (Chs. 23 32 and 49) . When a dysrhythmia occurs in the PACU, it is often a sign of some metabolic or perfusion problem. Dysrhythmias appearing in the PACU rarely need long-term treatment. The most common dysrhythmias are sinus tachycardia, sinus bradycardia, ventricular premature beats, ventricular tachycardia, and supraventricular tachyarrythmias. These are discussed in Chapter 32 .

Failure to Regain Consciousness

The evaluation of the patient who does not regain consciousness following general anesthesia requires a careful evaluation of the patient. Preoperative factors such as drug or alcohol intoxication should be sought. The most common reason for persistent somnolence is residual effects of anesthetics, sedatives, and preoperative medications. [113] In most such cases, some level of responsiveness should be achieved within 90 minutes following the completion of the anesthetic regimen. Initial management should include pharmacologic reversal agents aimed at the most likely sedative drug. Naloxone in small doses (0.2 mg IV) will increase ventilatory rate if narcotic sedation is the problem. Physostigmine (1.25 mg IV) can reverse the effects of some sedatives and inhalation anesthetics. [114] The sedative and amnestic effects of the benzodiazepines can be reversed by the use of flumazenil (up to 1.0 mg IV). [115] [116] Because profound neuromuscular blockade can make a patient appear unconscious, this should also be considered. This cause is unlikely, however, in the absence of significant respiratory compromise as well as unconsciousness. Once pharmacologic causes are ruled out, metabolic and structural origins must be sought. Profound hypothermia (temperature <33°C) can produce unconsciousness, as can profound abnormalities of serum glucose such as hyperglycemia or hypoglycemia. Blood glucose, electrolytes, and blood gases should be evaluated in all such cases. If there is reason to suspect hypoglycemia, 50 percent dextrose should be administered immediately, and a blood glucose determination should not be awaited. If the diagnosis remains unclear, a structural neurologic abnormality should be sought. Raised intracranial pressure may occur following head trauma or neurosurgery. Thromboembolic cerebrovascular accidents can occur in the postoperative period, but they are uncommon. [117] [118] Intraoperative cerebral hypoxia from hypoxemia or poor cerebral perfusion can produce diffuse encephalopathy. Emergency computed tomography scanning can be used to evaluate the presence of raised intracranial pressure or an acute intracranial hemorrhage as the cause of the delayed emergence. Rarely, overdose with lidocaine can present as unconsciousness. [119] Old age per se does not account for delayed emergence from general anesthesia. [120]

Postoperative Agitation and Pain

Postoperative pain and agitation are common problems. Pain can usually be simply controlled using small doses of intravenous narcotics; however, certain patients need large doses of narcotics to control severe pain. In addition, patients occasionally awaken from anesthesia in a violent, agitated state, often requiring manual restraint to prevent them doing harm to themselves or PACU personnel. Although this type of exaggerated response may be due to pain, several other important factors could be involved. Hypoxemia, hypercapnia, gastric distention, and urinary retention with bladder distention can all result in marked agitation. These problems can be easily managed, usually with resolution of the agitated state. The use of scopolamine, phenothiazines, and barbiturates as premedicants without narcotics increases the incidence of postoperative excitement. [121] The

administration of 3 to 4 mg of physostigmine reverses the agitation associated with scopolamine. [122] [123] Agitation also occurs in young patients who are apprehensive about the findings at operation, as well as in persons who fear pain.

Management of the agitated patient involves ascertaining the adequacy of blood gas exchange, evaluating possible urinary or gastric distention, and administering a small dose of intravenous narcotic. Restraints are sometimes needed. Often a change in the patient's position in bed is helpful.

Pain is one of the most common problems requiring recovery room management. Many factors influence the onset, incidence, and severity of postoperative pain. The age of the patient is important. The very young and very old seem to experience less pain than do people in the middle years of life. Preoperative neurotic personality traits tend to increase postoperative pain, as does the fear of pain itself. The way in which a patient is prepared for the experience of pain preoperatively can markedly alter the perception of postoperative pain [124] (Fig. 68-14) (Figure Not Available) . Preoperative medication is important in that agents such as scopolamine and barbiturates given alone appear to worsen postoperative pain. The use of a narcotic as a premedicant delays the first postoperative request for pain, but it does not affect the total dose required (see Ch. 23 for different premedication suggestions). The site of the operation certainly influences the severity of pain. Thoracotomy appears to be, in general, the most painful operation, with upper abdominal surgery a close second. Lower abdominal surgery is less painful. Patients who receive

Figure 68-14 (Figure Not Available) Ninety-seven patients having abdominal surgery were divided into two groups. The control group had a preoperative visit in which the anesthetist discussed the patient's medical condition but did not explain postoperative events. The special-care group had a careful preoperative explanation about postoperative pain, including its character, intensity, and management, stressing that it was a normal occurrence. The special-care group required significantly less morphine for pain relief than the control group, stressing the importance of the preoperative visit in postoperative care. *(From Egbert et al [124])*

no narcotic preoperatively or during the operation need a narcotic sooner during the postoperative period than those patients who do receive a narcotic. The type of anesthetic, however, does not seem to influence the total amount of narcotic analgesic required. [125] Most cases of postoperative pain can be managed by giving small intravenous doses of narcotics. Narcotics for pain relief result in a decreased respiratory rate, decreased tidal volume, and a regularization of the pattern of respiration. The presence of pain does not prevent narcotic-induced respiratory depression. [126] Patients need encouragement to cough and to breathe deeply. This maneuver is better tolerated by a patient who has received a narcotic; however, narcotics do not completely eliminate the pain associated with coughing and deep breathing. The use of small intravenous doses of narcotic in the PACU permits titration of the dose needed for adequate pain relief while carefully observing for the respiratory- and circulatory-depressant effects. Maximal narcosis does not occur for 30 minutes. Patients in pain can be given 1 to 3 mg of morphine (or the equivalent amount of meperidine) every 15 to 30 minutes with careful observation of the degree of pain relief and the amount of respiratory depression. Careful titration often results in more prompt pain relief than with intramuscular administration, as well as a smaller total dose. [126] [127] The continuous infusion of narcotic analgesics may result in a smoother course when these agents are used for postoperative pain relief. Such an infusion requires careful monitoring and titration. Patients receiving narcotics by continuous infusion maintain constant blood levels of analgesic and receive less total drug. [128] Patient-controlled analgesia allows the patient to determine the timing of analgesic doses and allows for improved titration of analgesia. It also minimizes patient anxiety. Patients receiving this form of pain therapy should have it begun in the PACU. [129] Although morphine has been the standard for this form of therapy, patients who use hydromorphone are in a better mood; however, they have decreased cognitive function when compared with patients receiving patient-controlled analgesia with morphine. [130] Some institutions have eliminated patient-controlled analgesia with meperidine because of reports of central nervous system toxicity and seizures in patients receiving high doses.

The use of narcotics in the epidural space to control postoperative pain is a very effective approach (Ch. 69) . Morphine, 2 to 4 mg diluted to 10 mL, provides prompt analgesia with a duration of action of about 12 hours. Complications include respiratory depression, which is dose related and can occur as long as 6 hours after injection of the morphine. Significant respiratory depression occurs in less than 1 percent of patients receiving epidural narcotics and can be reversed with naloxone. Synthetic narcotics have also been used successfully for epidural analgesia. [131] [132] About 15 to 20 percent of patients complain of pruritus. Nausea and urinary retention have also been reported. One case of paresis occurring during epidural morphine treatment was thought to be secondary to anterior spinal artery thrombosis. The technique is most useful when used for patients undergoing major thoracic or abdominal surgery who are at high risk for complications of parenteral analgesic therapy. [133] [134] [135] [136] [137]

Other methods of narcotic administration have been used, such as transdermal administration and intra-articular administration following knee surgery. Studies do not

demonstrate any apparent benefits of giving narcotics by these routes. [138] [139] Addition of bupivacaine to morphine in intra-articular administration may provide better pain relief than either agent used separately. [140] Bupivacaine plus morphine has a longer duration of action than bupivacaine plus fentanyl. [141]

Regional anesthesia has been used for the relief of postoperative pain to avoid narcotic-induced respiratory depression (Ch. 42 to 44 and 69) . Intercostal nerve blocks, when used for relief of pain of cholecystectomy, result in less fluctuation in arterial blood gases, in earlier ambulation, and in earlier hospital discharge than in narcotic-treated patients. [142] The availability of longer-acting local anesthetics makes this method possible for managing postoperative pain; however, the placement and the repetition of the block do take time, and there is always the risk of pneumothorax. Nevertheless, intercostal nerve blocks can be effective in patients with severe lung disease in whom narcotic analgesics may provide too little analgesia and too much respiratory depression and who have a contraindication to placement of an epidural catheter for narcotic administration. Bilateral intrapleural use of bupivacaine also reduces the need for narcotic analgesics when it is used in patients undergoing major thoracic and upper abdominal surgery. [143] Finally, instillation of local anesthetic into a wound can be very efficacious and is simple to perform. [144]

Continuous epidural block can provide good postoperative analgesia and, when administered in the thoracic space, can permit early postoperative ambulation [145] (Ch. 69) . Use of epidural analgesia probably results in somewhat better arterial oxygenation; however, the incidence of postoperative respiratory complications appears no better than with narcotics. [146] Patients having epidural pain relief can ambulate earlier, and this permits earlier hospital discharge. [147] Hypotension

requiring treatment is still a problem. The use of regional anesthesia for postoperative pain relief appears to be best suited for the patient with preexisting lung disease in whom narcotics would be hazardous and in whom a regional technique could relieve pain without adversely affecting respiration. [148] Although this technique has been used extensively, we find the use of epidural narcotics safer and far less complicated than the use of postoperative regional anesthesia in most patients.

Nonnarcotic analgesics are being used increasingly for postoperative pain. The most common agents used are the nonsteroidal anti-inflammatory agents. Ketorolac was among the first to be available for parenteral administration and is free of respiratory-depressant effects. Although ketorolac is not as potent as the narcotics, it can be an effective alternative to narcotic analgesics without major complictions. [149] [150] Anecdotal concerns about ketorolac center around the possibility of increased bleeding in patients receiving this agent; however, well-controlled evaluations of this potential problem are lacking at this time. Finally, ibuprofen has been suggested as a reasonable alternative to narcotic analgesics in patients undergoing laparoscopic surgery. [151]

Nausea and Vomiting

Postoperative nausea and vomiting are common complications that result in patient discomfort, prolonged stay in the PACU, and, rarely, one of the pulmonary aspiration syndromes. Postoperative nausea and vomiting are often multifactorial in origin. [152] There is little strong evidence that any one anesthetic technique has a lower incidence of nausea and vomiting than others, with the exception that propofol appears to have an inherent antiemetic effect. [153] [154] Propofol-based anesthetic regimens consistently have lower incidence of postoperative nausea and vomiting than other techniques, even when potent antiemetics such as ondansetron are combined with inhalation agents. [155] [156] The use of nitrous oxide does appear to increase the incidence of nausea and vomiting. [157] Even though occasional studies have been unable to implicate nitrous oxide in postoperative nausea and vomiting, [158] [159] one survey of the literature reviewed 27 publications and found that all but 3 contained evidence implicating nitrous oxide in postoperative nausea and vomiting. [157] This finding is not meant to imply that nitrous oxide should be abandoned but that its use must be evaluated carefully when attempting to design an anesthetic regimen with a lower incidence of nausea and vomiting. [160]

The type of surgical procedure has an important influence on the occurrence of nausea and vomiting. Patients having laparoscopic surgery and strabismus surgery are at increased risk for nausea and vomiting. After laparoscopy for tubal ligation, patients who are menstruating have a higher risk of nausea and vomiting, which is not prevented by droperidol. [161]

Antiemetics can be given postoperatively. Droperidol (75 mug/kg IV) can be very effective for patients who develop nausea and vomiting. Droperidol combined with propofol, however, increases the incidence of nausea and vomiting. [162] Metoclopramide has also been shown to be an effective and safe antiemetic for both the prevention and the treatment of postoperative nausea and vomiting. [163] [164] Transdermal scopolamine patches can be very effective in reducing the incidence of nausea associated with epidural narcotics if the patches are applied several hours preoperatively [165] ; however, in many places, they are no longer available. Although these patches are effective in reducing nausea, side effects can include blurring of vision and mental confusion in elderly patients.

The approval by the FDA of the serotonin antagonist ondansetron for treatment of postoperative nausea and vomiting has caused great interest among anesthesiologists because of the high incidence of the problem and its effects on patients undergoing anesthesia and surgery. The serotonin antagonists have been known for many years; however, they have only recently been used for treatment of nausea and vomiting due to chemotherapy for cancer. [166] [167] [168]

Ondansetron is more effective than placebo in preventing postoperative nausea and vomiting in gynecologic surgery. [169] It was also found to be more effective in preventing nausea and vomiting than both droperidol and metoclopramide. [170] When used to treat nausea and vomiting after it develops, ondansetron was also more effective than placebo in two separate studies. [171] [172] Although droperidol and ondan- setron are equally efficacious, droperidol prolongs the PACU stay. [173] [174] The usual dose is 4 mg intravenously. Ondansetron can be given orally to children as an effective premedication (0.1 mg/kg). [175]

Granisetron, a newer serotonin antagonist, is currently being evaluated. It appears that a dose of 40 mug/kg is an effective

prophylactic agent as well as a treatment. [176] [177] The combination of granisetron with dexamethasone in one study produced a striking reduction in the frequency of nausea and vomiting even when compared with the serotonin antagonist alone. [178] Further studies of combined serotonin antagonist-steroid therapy seem warranted.

Hypothermia and Shivering

Inadvertent hypothermia is a common occurrence following major surgical procedures (Ch. 37) . The major adverse effects are patient discomfort, vasoconstriction, and shivering. Full recovery sometimes takes many hours. [179] Shivering increases metabolic rate and hence the need to increase cardiac output and minute ventilation. Not all patients who shiver postoperatively are hypothermic, a finding suggesting that the mechanism of this event may be related to inadequate descending control of spinal reflexes following inhalation of anesthesia. [180] Longer anesthetic regimens are associated with a higher frequency of shivering. [181] Prevention is important, and the use of a heated humidifier results in higher patient temperature when the patient arrives in the PACU. [182] Patients who have had propofol have a lower incidence of shivering than those receiving thiopental. [183] Once in the PACU, hypothermic patients should have supplemental oxygen, warm intravenous fluids and blood, and external warming. External warming can be accomplished with thermal blankets or thermal ceilings, which lower oxygen consumption. [184] Patients who develop shivering should receive supplemental oxygen. Although many drugs have been used to treat postanesthetic shivering, meperidine (25-30 mg IV) is very effective in both stopping the shivering and decreasing oxygen consumption. In some patients, a second dose is necessary. [185] Fentanyl is also effective, but for a shorter interval. [186]

OUTPATIENT SURGERY

Increasing numbers of surgical procedures are being done without admitting the patient to the hospital (Ch. 65) . Surveys indicate that more than 50 percent of all surgical procedures are performed on an outpatient basis. This approach is safe and effective for properly chosen patients. These patients need to be able to leave the hospital shortly after discharge from the PACU. Once awake, the outpatient attempts to ambulate with assistance. After 1 to 3 hours of observation, stable vital signs, and satisfactory ambulation, the patient may leave, with provision for follow-up as necessary. Patients should always be accompanied by another person. Because virtually all anesthetic techniques impair psychomotor skills, driving or operating machinery should not be attempted for 8 to 24 hours. [187] [188] [189]

References

1. Zuck D: Anaesthetic and postoperative recovery rooms: Some notes on their early history. Anaesthesia 50:435, 1995.

2. Nightingale F: Notes on Hospitals, 3rd ed. London, Longman, Green, Longman, Roberts and Green, 1863.

3. Tomes CS: The administration of ether in America. BMJ 1:297, 1873.

4. Harvey AM: Neurosurgical genius: Walter Edward Dandy. Johns Hopkins Med J 135:358, 1974.

5. Hilberman M: The evolution of intensive care units. Crit Care Med 3:159, 1975.

6. Dunn FE, Shupp MG: The recovery room, a war time economy. Am J Nurs 43:279, 1943.

7. Carahan JM: Recovery room for patients. Am J Nurs 49:581, 1949.

8. Ruth HS, Haugen FP, Grave DD: Anesthesia Study Commission: Findings of eleven years of activity. JAMA 135:881, 1947.

9. Conboy CE: A recovery room. Am J Nurs 47:686, 1947.

10. Anderson CD, Miller EG: Postanesthesia unit in private hospitals. Anesthesiology 10:351, 1949.

11. Charbon GA, Livingston HM: Planning recovery room for adequate care. Hospitals 23:35, 1949.

12. Wiklund PE: Intensive care units: Design, location, staffing ancillary areas, equipment. Anesthesiology 31:122, 1969.

13. Macario A, Vitez T, Dunn B et al: What does perioperative care really cost? Analysis of hospital costs and charges for inpatient surgical care. Anesthesiology 83:1138, 1995.

14. Dexter F, Tinker J: Analysis of strategies to decrease post anesthesia costs. Anesthesiology 82:94, 1995.

15. Lubarsky DA: Fast track in the post anesthesia care unit: Unlimited possibilities? J Clin Anesth 8:70S, 1996.

16. Waddow J, Piccirillo J, Evers A: Inappropriate length of stay in the postanesthesia care unit: What is it and how often does it occur? Anesth Analg 82:S472, 1996.

17. Snow JC: Manual of Anesthesia. Boston, Little, Brown, 1977.

18. Drain CB, Shipley SB: The Recovery Room. Philadelphia, WB Saunders, 1979.

19. Turnbull AD, Carlon G, Makowsky M et al: Multipurpose central venous access using the Cordis sheath introducer system. Crit Care Med 7:30, 1979.

20. Smith RM: Normal recovery. In Smith RM (ed): Anesthesia for Infants and Children. St. Louis, CV Mosby, 1968, p 184.

21. Stoelting RK, Eger EI II: The effects of ventilation and anesthetic solubility on recovery from anesthesia: An in-vivo and analog analysis before and after equilibrium. Anesthesiology 30:290, 1969.

22. Spear RM, Yaster M, Berkowitz ID et al: Preinduction of anesthesia in children with rectally administered midazolam. Anesthesiology 74:670, 1991.

23. Stanley TH, Lathrop GD: Urinary excretion of morphine during and after valvular and coronary-artery surgery. Anesthesiology 46:166, 1969.

24. Sung YF, Reiss N, Tillette T: The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus sodium thiopental-isoflurane-nitrous oxide anesthesia. J Clin Anesth 3:391, 1991.

25. Eriksson H, Haasio J, Korttila K: Recovery from sevoflurane and isoflurane anaesthesia after outpatient gynaecological laparoscopy. Acta Anaesthesiol Scand 39:377, 1995.

26. Sloan MH, Conard PF, Karsunky PK et al: Sevoflurane versus isoflurane: induction and recovery characteristics with single-breath inhaled inductions of anesthesia. Anesth Analg 82:528, 1996.

27. Wandel C, Neff S, Bohrer H et al: Recovery characteristics following anaesthesia with sevoflurane or propofol in adults undergoing out-patient surgery. Eur J Clin Pharmacol 48:185, 1995.

28. Fredman B, Nathanson MH, Smith I et al: Sevoflurane for outpatient anesthesia: A comparison with propofol. Anesth Analg 81:823, 1995.

29. Nathanson MH, Fredman B, Smith I et al: Sevoflurane versus desflurane for outpatient anesthesia: A comparison of maintenance and recovery profiles. Anesth Analg 81:1186, 1995.

30. Miller RD: Antagonism of neuromuscular blockade. Anesthesiology 44:318, 1976.

31. Bevan DR, Kahwaji R, Ansermino JM et al: Residual block after mivacurium with or without edrophonium reversal in adults and children. Anesthesiology 84:362, 1996.

32. Fox MH, Hunt PC: Prolonged neuromuscular block associated with mivacurium. Br J Anaesth 74:237, 1995.

33. Sockalingam I, Green DW: Mivacurium-induced prolonged neuromuscular block. Br J Anaesth 74:234, 1995.

34. DiBenedetto RJ, Gravenstein N: Against routine postoperative oxygen administration in the PACU. J Clin Monit 11:408, 1995.

35. Gravenstein D: For routine postoperative oxygen administration in the PACU. J Clin Monit 11:406, 1995.

36. Chung F: Recovery pattern and home readiness after ambulatory surgery. Anesth Analg 80:896, 1996.

37. American Society of Anesthesiologists: Standards for Postanesthesia Care. Directory of Members. American Society of Anesthesiologists, Park Ridge, Ill, 1996, p 395.

38. Berwick DM: Continuous improvement as an ideal in health care. N Engl J Med 320:53, 1989.

39. Lubarsky D, Gan T, Glass P et al: PACU clinical outcomes and financial savings following a pharmaceutical cost containment program in anesthesia using practice guidelines. Anesth Analg 82:S285, 1996.

40. Hines R, Barash PG, Watrous G et al: Complications occurring in the postanesthesia care unit: A survey. Anesth Analg 74:503, 1992.

41. Van der Walt JH, Webb RK, Osborne GA et al: The Australian incident monitoring study: Recovery room incidents in the first 200 incident reports. Anaesth Intensive Care 21:650, 1993.

42. Handlin DS, Baker T: The effects of smoking on postoperative recovery. Am J Med 93:32S, 1992.

43. Duncan PG, Cohen MM, Tweed WA et al: The Canadian four-centre study of anaesthetic outcomes. III. Are anaesthetic complications predictable in day case practice? Can J Anaesth 39:440, 1992.

44. Rose DK, Cohen MM, Wigglesworth DF: Critical respiratory events in the postanesthesia care unit: Patient, surgical and anesthetic factors. Anesthesiology 81:410, 1994.

45. Morikawa S, Safer P, De Carlo J: Influence of head-jaw position on upper airway patency. Anesthesiology 22:265, 1961.

46. Ruben HM, Elam JO, Ruben AM et al: Investigation of upper airway problems in resuscitation. Anesthesiology 22:271, 1961.

47. Komorn RM, Smith CP, Irwin JR: Acute laryngeal injury with short-term endotracheal anesthesia. Laryngoscope 82:683, 1973.

48. Jaffe BF: Postoperative hoarseness. Am J Surg 123:432, 1972.

49. Cullen DJ, Cullen BL: Postanesthetic complications. Surg Clin North Am 55:987, 1975.

50. Groudine SB, Lumb PD, Sandison MR: Pressure support ventilation with the laryngeal mask airway: A method to manage severe reactive airway disease postoperatively. Can J Anaesth 42:34, 1995.

51. Rennotte MT, Baele P, Aubert G et al: Nasal continuous positive airway pressure in the perioperative management of patients with obstructive sleep apnea submitted to surgery. Chest 107:367, 1995.

52. Parfrey PS, Harte PI, Quinlan JP: Pulmonary function in the early postoperative period. Br J Surg 64:384, 1977.

53. Nunn JF, Payne JP: Hypoxia after general anesthesia. Lancet 2:631, 1962.

54. Katamur AH, Sawa T, Ikezono E: Postoperative hypoxemia: The contribution of age to the mal-distribution of ventilation. Anesthesiology 36:244, 1972.

55. Moller JT, Wittrup M, Johansen SH: Hypoxemia in the postanesthesia care unit: An observer study. Anesthesiology 73:890, 1990.

56. Moller JT: Anesthesia related hypoxemia: The effect of pulse oximetry monitoring on perioperative events and postoperative complications. Dan Med Bull 41:489, 1994.

57. Marshall BE, Wyche MQ: Hypoxemia during and after anesthesia. Anesthesiology 37:178, 1972.

58. Bay I, Nunn JF, Prys-Roberts C: Factors influencing arterial P_{C_2} during recovery from anesthesia. Br J Anaesth 40:398, 1968.

59. Philbin DM, Sullivan SF, Bowman FO et al: Postoperative hypoxemia: Contribution of cardiac output. Anesthesiology 32:136, 1970.

60. Feeley TW, Hedley-Whyte J: Bulk oxygen and nitrous oxide delivery system. Anesthesiology 44:301, 1976.

61. Cullen DJ, Caldera DL: The incidence of ventilator-induced pulmonary barotrauma in critically ill patients. Anesthesiology 50:185, 1979.

62. Hamilton WK: Atelectasis, pneumothorax, and aspiration as postoperative complications. Anesthesiology 22:708, 1961.

63. Don HF, Wahba WM, Craig DB: Airway closure, gas trapping, and the functional residual capacity during anesthesia. Anesthesiology 36:533, 1972.

64. Alexander JI, Horton PA, Miller WT et al: The effect of upper abdominal surgery on the relationship of airway closing point to end-tidal position. Clin Sci 43:137, 1972.

65. Rehder K, Marsh HM, Rodarte JR et al: Airway closure. Anesthesiology 47:40, 1977.

66. Robin ED, Cross CE, Zelis R: Pulmonary edema. I. N Engl J Med 288:239, 1973.

67. Robin ED, Cross CE, Zelis R: Pulmonary edema. II. N Engl J Med 288:292, 1973.

68. Cooperman LH, Price HR: Pulmonary edema in the operative and postoperative period: Review of 40 cases. Ann Surg 172:883, 1970.

69. Weissman C, Damask MC, Yang J: Noncardiogenic pulmonary edema following laryngeal obstruction. Anesthesiology 60:163, 1984.

70. Jackson FN, Rowland V, Corssen G: Laryngospasm induced pulmonary edema. Chest 78:819, 1980.

71. Crandall ED, Staub NE, Goldberg HS et al: Recent developments in pulmonary edema. Ann Intern Med 99:808, 1983.

72. Shapiro JM, Mihm FG, Trudell JR et al: Leukotriene D_4 increases extravascular lung water in the dog. Circ Shock 21:121, 1987.

73. Saul GM, Feeley TW, Mihm FG: Effect of graded administration of PEEP on lung water in noncardiogenic pulmonary edema. Crit Care Med 10:667, 1982.

74. Mihm FG, Feeley TW, Rosenthal MH et al: Measurement of extravascular lung water in dogs using the thermal-green dye indicator dilution method. Anesthesiology 57:116, 1982.

75. Lewis FR, Elings VB, Hill SL et al: The measurement of extravascular lung water by thermal-green dye indicator dilution. Ann N Y Acad Sci 384:411, 1982.

76. Ford GT, Whitelaw WA, Rosenal TW et al: Diaphragm function after upper abdominal surgery in humans. Am Rev Respir Dis 127:431, 1983.

77. Demling RH, Lalonde C: Oxygen consumption is increased in the postanesthesia period after burn excision. J Burn Care Rehabil 10:381, 1989.

78. Tremper KK, Barker SJ: Pulse oximetry. Anesthesiology 70:98, 1989.

79. Yelderman MH, New W: Evaluation of pulse oximetry. Anesthesiology 59:349, 1983.

80. Eberhard P, Mindt W, Schafter R: Cutaneous blood gas monitoring in the adult. Crit Care Med 9:702, 1981.

81. Pullerits J, Barrows FA, Roy WL: Arterial desaturation in healthy children during transfer to the recovery room. Can J Anaesth 34:470, 1987.

82. Tyler IC, Tantisira B, Winter PM et al: Continuous monitoring of arterial oxygen saturation with pulse oximetry during transfer to the recovery room. Anesth Analg 64:1108, 1985.

83. Soliman IE, Patel RI, Ehronpreis MB et al: Recovery scores do not correlate with postoperative hypoxemia in children. Anesth Analg 67:53, 1988.

84. Morris RAW, Buchman A, Warren DL et al: The prevalence of hypoxemia detected during recovery from anesthesia. J Clin Monit 4:16, 1988.

85. Pontoppidan H, Laver MB, Geffin B: Acute respiratory failure in the surgical patient. Adv Surg 4:163, 1970.

86. Smith RA, Kirby RR, Gooding JM et al: Continuous positive airway pressure (CPAP) by face mask. Crit Care Med 8:483, 1980.

87. Becker LD, Paulson BA, Miller RD et al: Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. Anesthesiology 44:291, 1976.

88. Longnecker DE, Grazis PA, Eggers GWN: Naloxone for antagonism of morphine induced respiratory depression. Anesth Analg 52:447, 1973.

89. Ali J, Weisel RD, Layug AB et al: Consequences of postoperative alterations in respiratory mechanics. Am J Surg 128:376, 1974.

90. Miller RD, Cullen DJ: Renal failure and postoperative respiratory failure: Recurarization? Br J Anaesth 48:253, 1976.

91. Fogdall RP, Miller RD: Prolongation of pancuronium-induced neuromuscular blockade by clindamycin. Anesthesiology 41:407, 1974.

92. Feeley TW, Hedley-Whyte J: Weaning from controlled ventilation and supplemental oxygen. N Engl J Med 292:903, 1975.

93. Skoog RE: Capnography in the postanesthesia care unit. J Post Anesth Nurs 4:147, 1989.

94. Mathew JP, Rosenbaum SE, O'Connor T et al: Emergency tracheal intubation in the postanesthesia care unit: Physician error or patient disease? Anesth Analg 71:691, 1990.

95. Rose DK, Cohen MM, DeBoer DP: Cardiovascular events in the postanesthesia care unit: Contribution of risk factors. Anesthesiology 84:772, 1996.

96. Connors AF, Speroff T, Dawson NV et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 276:889, 1996.

97. Dalen JE, Bone RC: Is it time to pull the pulmonary artery catheter. JAMA 276:916, 1996.

98. Siegel DC, Cochin A, Goocaris T et al: Effects of saline and colloid resuscitation on renal function. Ann Surg 177:51, 1973.

99. Loewe RJ, Moss GS, Jilek T et al: Crystalloid vs. colloid in the etiology of pulmonary failure after trauma: A randomized trial in man. Surgery 81:676, 1977.

100. Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. Crit Care Med 9:833, 1981.

101. Halperin BD, Pearl RC, Rosenthal MH et al: Lung water following resuscitation with colloid and crystalloid solutions. Anesth Analg 63:227, 1984.

102. Cohn JN, Franciosa JA: Vasodilator therapy of cardiac failure. N Engl J Med 297:27, 1977.

103. Packer M, Maller J, Medina N et al: Rebound hemodynamic effects after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. N Engl J Med 301:1193, 1979.

104. Holcroft JW, Trunkey DD, Carpenter MA: Sepsis in the baboon: Factors affecting resuscitation and pulmonary edema in animals resuscitated with Ringer's lactate versus Plasmanate. J Trauma 17:600, 1977.

105. Gal TJ, Cooperman LH: Hypertension in the immediate postoperative period. Br J Anaesth 47:70, 1975.

106. Katz JD, Cronau LH, Barash PG: Postoperative hypertension: Hazard of abrupt cessation of antihypertensive medication in preoperative period. Am Heart J 92:79, 1976.

107. Yelderman M, Ream AK: Indirect measurement of mean blood pressure in the anesthetized patient. Anesthesiology 50:253, 1979.

108. Tinker JH, Michenfelder JK: Sodium nitroprusside. Anesthesiology 45:340, 1976.

109. Le Bret F, Coriat P, Gosgnach M et al: Transesophageal echocardiographic assessment of left ventricular function in response to labetalol for control of postoperative hypertension. J Cardiothorac Vasc Anesth 6:433, 1992.

110. Leslie JB, Kalayjian RW, Sargo MA et al: Intravenous labetalol for treatment of postoperative hypertension. Anesthesiology 67:413, 1976.

111. Orlowski JP, Shiesles D, Vidt DG et al: Labetolol to control blood pressure after cerebrovascular surgery. Crit Care Med 16:765, 1988.

112. Gray RJ, Bateman TM, Czer LSC et al: Esmolol: A new ultra-short acting beta blocking agent. J Am Coll Cardiol 5:2451, 1985.

113. Denlinger JK: Prolonged emergence and failure to regain consciousness. In Orkin FK, Cooperman LH (eds): Complications in Anesthesiology. Philadelphia, JB Lippincott, 1983, p 368.

114. Bourke DL, Rosenberg M, Allen PD: Physostigmine: Effectiveness as an antagonist of respiratory depression and psychomotor effects caused by morphine or diazepam. Anesthesiology 61:523, 1984.

115. Jensen S, Knudsen L, Kirkegaard L et al: Flumazenil used for antagonizing the central effects of midazolam and diazepam in outpatients. Acta Anaesthesiol Scand 33:26, 1989.

116. Ghoneim MM, Dembo JB, Block RI: Time course of antagonism of sedative and amnestic effects of diazepam by flumazenil. Anesthesiology 70:899, 1989.

117. Larsen SF, Zaric D, Boysen G: Postoperative cerebrovascular accidents in general surgery. Acta Anaesthesiol Scand 32:698, 1988.

118. Oliver SB, Cucchiara RF, Warner MA et al: Unexpected focal neurologic deficit on emergence from anesthesia: A report of three cases. Anesthesiology 67:823, 1987.

119. Douglas JH, Ross JD, Bruce DL: Delayed awakening due to lidocaine overdose. J Clin Anesth 2:126, 1990.

120. Chung F, Seyone C, Dyck B et al: Age-related cognitive recovery after general anesthesia. Anesth Analg 71:217, 1990.

121. Eckenhoff JE, Kneale DH, Dripps RD: The incidence and etiology of postanesthetic excitement. Anesthesiology 22:667, 1961.

122. Smiler BG, Bartholomew EG, Sivak BJ et al: Physostigmine reversal of scopolamine delirium in obstetric patients. Am J Obstet Gynecol 116:326, 1973.

123. Hill GE, Stanley TH, Sentker CR: Physostigmine reversal of postoperative somnolence. Can Anaesth Soc J 24:707, 1977.

124. Egbert LD, Battit GE, Welsch CE et al: Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med 270:825, 1964.

125. Henderson JJ, Parbrook GD: Influence of anaesthetic technique on postoperative pain. Br J Anaesth 48:587, 1976.

126. Keats AS, Girgis KZ: Respiratory depression associated with relief of pain by narcotics. Anesthesiology 29:1006, 1965.

127. Swerdlow M: General analgesics used in pain relief: Pharmacology. Br J Anaesth 39:699, 1967.

128. Austin KL, Stapleton JV, Mather LW: Pethidine clearance during continuous intravenous infusions in postoperative patients. Br J Clin Pharmacol 1:25, 1981.

129. White P: Use of patient controlled analgesia for management of acute pain. JAMA 259:243, 1988.

130. Rapp SE, Egan KJ, Ross BK et al: A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 82:1043, 1996.

131. Kreitzer JM, Kirschenbaum LP, Eisenkraft JB: Epidural fentanyl by continuous infusion for relief of postoperative pain. Clin J Pain 5:283, 1989.

132. Sinatra RS, Sevarino FB, Chung JH et al: Comparison of epidurally administered sufentanyl, morphine, and sufentanyl-morphine combination for postoperative analgesia. Anesth Analg 72:522, 1991.

133. Behar M, Olshwang D, Magora F et al: Epidural morphine in the treatment of pain. Lancet 1:527, 1979.

134. Ebert J, Varner PD: The effective use of epidural morphine sulfate for postoperative orthopedic pain. Anesthesiology 53:257, 1980.

135. Chayen MS, Rudick V, Borvine A: Pain control with epidural injection of morphine. Anesthesiology 53:338, 1980.

136. Glynn CJ, Mather LE, Cousins MJ et al: Peridural meperidine in humans: Analgesic response, pharmacokinetics, and transmission to CSF. Anesthesiology 55:520, 1981.

137. Mehnert JH, Dupont TJ, Rose DH: Intermittent epidural morphine instillation for control of postoperative pain. Am J Surg 146:145, 1983.

138. Sevarino FB, Naulty JS, Sinatra R et al: Transdermal fentanyl for postoperative pain management in patients recovering from abdominal gynecologic surgery. Anesthesiology 77:463, 1992.

139. Heard SO, Edwards WT, Ferrari D et al: Analgesic effect of intraarticular bupivacaine or morphine after arthroscopic knee surgery: A randomized, prospective, double-blind study. Anesth Analg 74:822, 1992.

140. Khoury GF, Chen ACN, Garland DE et al: Intraarticular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. Anesthesiology 77:263, 1992.

141. Uysalel A, Kecik Y, Kirdemir P et al: Comparison of intraarticular bupivacaine with the addition of morphine or fentanyl for analgesia after arthroscopic surgery. Arthroscopy 11:660, 1995.

142. Bridenbaugh PO, Du Pen SL, Moore DC et al: Postoperative intercostal nerve block analgesia versus narcotic analgesia. Anesth Analg 52:81, 1973.

143. el-Naggar MA: Bilateral intrapleural regional analgesia for postoperative pain control: a dose-finding study. J Cardiothorac Anesth 3:574, 1989.

144. Casey WF, Rice LJ, Hannallah RS et al: A comparison between bupivacaine instillation versus ilioinguinal/iliohypogastric nerve block for postoperative analgesia following inguinal herniorrhaphy in children. Anesthesiology 72:637, 1990.

145. Bromage PR: Extradural analgesia for pain relief. Br J Anaesth 39:721, 1967.

146. Muneyuke M, Ueda Y, Urabe N et al: Postoperative pain relief and respiratory function in man: Comparison between intermittent intravenous injections of meperidine and continuous lumbar epidural anesthesia. Anesthesiology 29:304, 1968.

147. Pflug AE, Murphy TM, Butler SH et al: The effects of postoperative peridural analgesia in pulmonary therapy and pulmonary complication. Anesthesiology 41:8, 1974.

148. Shuman RL, Peters RG: Epidural anesthesia following thoracotomy in patients with chronic obstructive airway disease. J Thorac Cardiovasc Surg 71:82, 1976.

149. Ding Y, White PF: Comparative effects of ketorolac, demonic, and fentanyl as adjuvants during outpatient anesthesia. Anesth Analg 75:566, 1992.

150. Watcha MF, Jones MB, Lagueruela RG et al: Comparison of ketorolac and morphine as adjuvants during pediatric surgery. Anesthesiology 76:368, 1992.

151. Rosenblum M, Weller RS, Conard PL et al: Ibuprofen provides longer lasting analgesia than fentanyl after laparoscopic surgery. Anesth Analg 73:255, 1991.

152. Watcha MF, White PF: Postoperative nausea and vomiting: Its etiology, treatment, and prevention. Anesthesiology 77:162, 1992.

153. Borgeat A, Wilder-Smith OH, Saiah M et al: Subhypnotic doses of propofol possess direct antiemetic properties. Anesth Analg 74:539, 1992.

154. Ostman PL, Faure E, Glosten B et al: Is the antiemetic effect of the emulsion formulation of propofol due to the lipid emulsion? Anesth Analg 71:536, 1990.

155. Eriksson H, Korttila K: Recovery profile after desflurane with or without ondansetron compared with propofol in patients undergoing outpatient gynecological laparoscopy. Anesth Analg 82:533, 1996.

156. Barst SM, Markowitz A, Yossefy Y et al: Propofol reduces the incidence of vomiting after tonsillectomy in children. Paediatr Anaesth 5:249, 1995.

157. Hartung J: Twenty-four of twenty seven studies show a greater incidence of emesis associated with nitrous oxide. Anesth Analg 83:114, 1996.

158. Muir JJ, Warner MA, Offord KP et al: Role of nitrous oxide and other factors in postoperative nausea and vomiting: A randomized and blinded prospective study. Anesthesiology 66:513, 1987.

159. Splinter WM, Roberts DJ, Rhine EJ et al: Nitrous oxide does not increase vomiting in children after myringotomy. Can J Anaesth 42:274, 1995.

160. Fisher DM: Does nitrous oxide cause vomiting? Anesth Analg 83:4, 1996.

161. Beattie WS, Lindbald T, Buckley DN et al: Menstruation increases the risk of nausea and vomiting after laparoscopy: A prospective randomized study. Anesthesiology 78:272, 1993.

162. Wagner BK, Berman SL, Devitt PA et al: Retrospective analysis of postoperative nausea and vomiting to determine antiemetic activity of droperidol added to propofol: A possible drug interaction. Pharmacotherapy 14:586, 1994.

163. Ferrari LR, Donlon JV: Metoclopramide reduces the incidence of vomiting after tonsillectomy in children. Anesth Analg 75:351, 1992.

164. Broadman LM, Ceruzzi W, Patane PS et al: Metoclopramide reduces the incidence of vomiting following strabismus surgery in children. Anesthesiology 72:245, 1990.

165. Loper KA, Ready LB, Dorman BH: Prophylactic transdermal scopolamine reduces nausea in postoperative patients receiving epidural morphine. Anesth Analg 68:144, 1989.

166. Freeman AJ, Cunningham KT, Tyers MB: Selectivity of 5-HT $_3$ receptor antagonists and anti-emetic mechanisms of action. Anticancer Drugs 3:79, 1992.

167. Legaha SS, Hodges C, Ring S: Efficacy of ondansetron against nausea and vomiting caused by dacarbazine-containing chemotherapy. Cancer 70:2018, 1992.

168. Koulu M, Sjoholm B, Lappalainen J et al: Effects of acute GR38032f (ondansetron), a 5-HT $_3$ receptor antagonist on dopamine and serotonin metabolism in mesolimbic and nigrostriatal dopaminergic neurons. Eur J Pharmacol 169:321, 1989.

169. McKenzie R, Kovac A, O'Connor T et al: Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. Anesthesiology 78:21, 1993.

170. Alon E, Himmelseher S: Ondansetron in the treatment of postoperative vomiting: A randomized, double-blind comparison with droperidol and metoclopromide. Anesth Analg 75:561, 1992.

171. Scuderi P, Wetchler B, Sung YF et al: Treatment of postoperative nausea and vomiting after outpatient surgery with the 5-HT $_3$ antagonist ondansetron. Anesthesiology 78:15, 1993.

172. Bodner M, White PF: Antiemetic efficacy of ondansetron after outpatient laparoscopy. Anesth Analg 73:250, 1991.

173. Davis PJ, McGowan FX Jr, Landsman I et al: Effect of antiemetic therapy on recovery and hospital discharge time: A double-blind assessment of ondansetron, droperidol, and placebo in pediatric patients undergoing ambulatory surgery. Anesthesiology 83:956, 1995.

174. Grond S, Lynch J, Diefenbach C et al: Comparison of ondansetron and droperidol in the prevention of nausea and vomiting after inpatient minor gynecologic surgery. Anesth Analg 81:603, 1995.

175. Splinter WM, Baxter MR, Gould HM et al: Oral ondansetron decreases vomiting after tonsillectomy in children. Can J Anaesth 42:277, 1995.

176. Fujii Y, Tanaka H, Toyooka H: Optimal anti-emetic dose of granisetron for preventing postoperative nausea and vomiting. Can J Anaesth 41:794, 1994.

177. Mikawa K, Takao Y, Nishina K et al: The antiemetic efficacy of prophylactic granisetron in gynecologic surgery. Anesth Analg 80:970, 1995.

178. Fujii Y, Tanaka H, Toyooka H: Granisetron-dexamethasone combination reduces postoperative nausea and vomiting. Can J Anaesth 42:387, 1995.

179. Kurz A, Sessler DI, Narzt E et al: Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia. J Clin Anesth 7:359, 1995.

180. Sessler DI, Israel D, Pozos RS et al: Spontaneous postanesthetic tremor does not resemble thermoregulatory shivering. Anesthesiology 68:843, 1988.

181. Harwood RJ, Singh P, Cartwright DP et al: The effect of different end-tidal volatile agent and carbon dioxide concentrations upon the incidence of postoperative shivering. Anaesthesia 50:786, 1995.

182. Goldberg ME, Epstein R, Rosenblum F et al: Do heated humidifiers and heat and moisture exchangers prevent temperature drop during lower abdominal surgery? J Clin Anesth 4:16, 1992.

183. Singh P, Harwood R, Cartwright DP et al: A comparison of thiopentone and propofol with respect to the incidence of postoperative shivering. Anaesthesia 49:996, 1994.

184. Henneberg S, Eklun A, Joachimsson PO et al: Effects of a thermal ceiling on postoperative hypothermia. Acta Anaesthesiol Scand 29:602, 1985.

185. Macintyre PE, Paulin EG, Dworsteg JF: Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in postanesthesia shivering. Anesth Analg 66:751, 1987.

186. Alfonsi P, Hongnat JM, Lebrault C et al: The effects of pethidine, fentanyl and lignocaine on postanaesthetic shivering. Anaesthesia 50:214, 1995.

187. Epstein BS: Recovery from anesthesia. Anesthesiology 43:285, 1975.

188. Kortilla K, Linnoila M, Ertama P et al: Recovery and simulated driving after anesthesia with thiopental, methohexital, propanidid, or alphadione. Anesthesiology 43:291, 1975.

189. Kortilla K, Tammisto T, Ertama P et al: Recovery, psychomotor skills, and simulated driving after brief inhalation anesthesia with halothane or enflurane combined with nitrous oxide and oxygen. Anesthesiology 46:220, 1977.

Chapter 69 - Acute Perioperative Pain *

L. Brian Ready

FUNDAMENTAL CONSIDERATIONS

Past Deficiencies and Current Directions in the Treatment of Perioperative Pain

Many millions of patients worldwide undergo surgery each year and benefit from knowledge, skills, and sophisticated technology that characterize most aspects of modern surgical treatment. Although effective pain control is essential for optimal care of surgical patients, [1] [2] [3] and despite advances in knowledge of pathophysiology, pharmacology of analgesics, and the development of more effective techniques for perioperative analgesia, many patients continue to experience distressing pain. [1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18]

The concept of perioperative pain management by anesthesiologists is now established in North America and in many other parts of the world. [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] Basic changes in long-established practices such as pain management have received attention not only from clinicians, but also from economists and politicians. One manifestation of this attention in the United States is a clinical practice guideline entitled *Acute Pain Management: Operative or Medical Procedures and Trauma.*[3] This document was commissioned, published, and distributed by the Office of the Forum for Quality and Effectiveness in Health Care, of the Agency for Health Care Policy and Research, U.S. Department of Health and Human Services. The text of the guideline is extensive. Important elements include recognition of historic inadequacies in perioperative pain management, clear acknowledgment of the importance of good pain control, and a statement of the need for the involvement of specialists in appropriate cases. The guideline also emphasizes a need for a process of accountability for adequate provision of perioperative analgesia by health care institutions. It recommends placing responsibility for that activity in the hands of those with the greatest knowledge and interest in perioperative pain.

In the United States the American Society of Anesthesiologists (ASA) has developed clinical practice guidelines for acute pain management in the perioperative period. [36] That document is based on an extensive literature search and meta-analysis as well as on the collective opinions of many experts (see Appendix for full text of this guideline). It offers recommendations that, if followed, will result in a variety of improved outcomes for surgical patients. It also provides a number of templates that may be useful to practitioners who wish to begin providing improved pain relief to their surgical patients.

There is currently a great deal of interest in redefining the role of the specialty of anesthesiology. The popular term "perioperative physician" reflects the physician anesthetist as a consultant and therapist throughout an institution as well as a highly skilled expert in the operating room. The provision of effective analgesia for surgical (and other) patients is an important component of this vision for the future.

Pain Pathways

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience

---

* *See Appendix I, Practice Guideliness for Acute Pain Management in the Perioperative Setting*

associated with actual or potential tissue damage, or described in terms of such damage." [37] Surgery produces local tissue damage with consequent release of algesic substances (prostaglandins, histamine, serotonin, bradykinin, 5-hydroxytryptamine, substance P) and generation of noxious stimuli that are transduced by nociceptors and transmitted by A delta and C nerve fibers to the neuraxis. Further transmission is determined by complex modulating influences in the spinal cord. Some impulses pass to the anterior and anterolateral horns to provoke segmental reflex responses. Others are transmitted to higher centers via the spinothalamic and spinoreticular tracts, where they produce suprasegmental and cortical responses.

Segmental reflex responses associated with surgery include increased skeletal muscle tone and spasm with associated increases in oxygen consumption and lactic acid production. Stimulation of sympathetic neurons causes tachycardia, increased stroke volume, cardiac work, and myocardial oxygen consumption. Tone is decreased in the gastrointestinal and urinary tracts. Suprasegmental reflex responses result in further increased sympathetic tone and hypothalamic stimulation. Metabolism and oxygen consumption are further increased.

Cortical responses in awake, unanesthetized patients after surgery are provoked by nociceptive impulses reaching the highest brain centers where complex systems concerned with integration and perception of pain are activated. Apprehension and anxiety may accompany pain resulting in additional hypothalamic stimulation. [38] [39] [40] [41] [42] [43] [44]

Adverse Effects of Perioperative Pain

Physiologic Responses

Physiologic responses to injury and stress include the following: pulmonary, cardiovascular, gastrointestinal, and urinary dysfunction; impairment of muscle metabolism and function; and neuroendocrine and metabolic changes as components of the stress response. Many of these responses can be eliminated or reduced with currently available analgesic techniques.

Respiratory Effects

Surgery involving the upper abdomen or thorax produces a number of pulmonary changes including reduced vital capacity, tidal volume, residual volume, functional residual capacity, and forced 1 second expiratory volume (FEV_1). These changes and their significance are discussed in Chapter 15 . Painful surgical incisions involving the upper abdomen result in a reflex-mediated increase in tone in the abdominal muscles during expiration [45] and a decrease in diaphragmatic function. [46] The result is reduced pulmonary compliance, muscle splinting, inability to breathe deeply or to cough forcefully, and in some cases, hypoxemia, hypercarbia, retention of secretions, atelectasis, and pneumonia. Increased muscle tone is a contributing cause of increased oxygen consumption and lactic acid production. Distended bowel associated with postoperative ileus or tight binders or dressings may further impair ventilation, and fear of producing or aggravating pain can cause patients to avoid breathing deeply or coughing. Opioids administered by a variety of routes to relieve pain and improve pulmonary function can themselves induce or contribute to respiratory failure. [47] [48] [49] [50] [51] [52] [53] [54] Nonopioid analgesics can also cause respiratory system morbidity. [55]

Cardiovascular Effects

Pain causes stimulation of sympathetic neurons and subsequent tachycardia, increased stroke volume, cardiac work, and myocardial oxygen consumption. The risk of

myocardial ischemia or infarction may be increased, as is the risk of deep vein thrombosis when fear of aggravating pain results in reduced physical activity, venous stasis, and platelet aggregation. [56] Some of these sequelae may be reduced by using effective perioperative analgesic therapy. [57] [58] [59]

Gastrointestinal and Urinary Effects

Ileus, nausea, and vomiting following surgery can occur for a number of reasons that include nociceptive impulses from viscera and somatic structures. Pain can also cause hypomotility of the urethra and bladder and consequent difficulty with urination. [2] [60] These effects can be very unpleasant for patients and, especially in the case of ileus, may prolong hospital stay. Postoperative epidural analgesia has been shown to speed the return of bowel function following a variety of abdominal surgical procedures. [61] [62] [63] [64] [65] [66]

Stress Response: Neuroendocrine and Metabolic Effects

The stress response has been termed "the integrated, adaptive living web of neuroendocrine, immunologic, and intercellular biochemical signals evoked by tissue injury." [67] The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical and sympathoadrenal interactions. Suprasegmental reflex responses to pain result in increased sympathetic tone, hypothalamic stimulation, increased catecholamine and catabolic hormone secretion (cortisol, adrenocorticotropic hormone, antidiuretic hormone, growth hormone, cyclic adenosine monophosphate, glucagon, aldosterone, renin, angiotensin II), and decreased secretion of anabolic hormones (insulin, testosterone). [68] The effects of these changes include sodium and water retention and increased blood glucose, free fatty acids, ketone bodies, and lactate. Metabolism and oxygen consumption are increased, and metabolic substrates are mobilized from storage depots. A catabolic state and negative nitrogen balance result if the process continues. There is considerable current interest in the endocrine-metabolic stress response in the surgical patient, its possible consequences, and inhibition by various anesthetic and analgesic methods. The interested reader can review this subject further. [67] [69] [70]

Psychologic Responses

Not surprisingly, perioperative pain can be a major source of fear and anxiety in hospitalized patients. When prolonged,

---

it can lead to anger, resentment, and adversarial relationships with doctors and nurses who are perceived to be withholding pain relief. Insomnia may accompany the process, with further detriment to recovery. In some cases, increased pain reporting may represent patients' attempts to obtain pharmacologic relief for these problems.

Factors that Modify Perioperative Pain

A number of factors may influence the intensity, quality, and duration of perioperative pain. [2] The most important of these are as follows: (1) the site, nature, and duration of surgery; (2) the type and extent of the incision and other surgical trauma; (3) the physiologic and psychologic makeup of the patient; (4) the preoperative psychologic, physiologic, and pharmacologic preparation of the patient; (5) the presence of complications related to the surgery; (6) the anesthetic management before, during, and after surgery; (7) the quality of perioperative care; and, as discussed in the next section (8) preoperative treatment to eliminate painful stimuli prior to surgery. By considering how each of these factors applies to individual patients, optimal care becomes more likely.

Preemptive Treatment of Perioperative Pain

The traditional approach to postoperative analgesia is to begin therapy when surgery is completed and pain is experienced. Preemptive analgesia has been defined as "antinociceptive treatment that prevents the establishment of altered central processing, which amplifies postoperative pain." [71] Intense noxious stimulation can sensitize portions of the central nervous system (CNS) to subsequent input. [72] Such stimulation, in the form of a surgical incision, may lead to functional changes in the dorsal horn of the spinal cord (sometimes called "windup") and other consequences that later cause postoperative pain to be perceived as more "painful" than it would otherwise have been. [73] Although the rationale for clinically useful preemption of surgical pain seems sound, the reported results are mixed. Some investigators have found benefit, [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90] whereas others have not. [91] [92] [93] [94] [95] [96] [97] [98] In-depth reviews of the subject have been written, [99] [100] [101] and thoughtful commentary has been offered bearing both on the complexity of the subject and on factors to consider in reconciling differences in the findings of various studies. [71]

It is possible that preemptive analgesia, in addition to reducing acute perioperative pain arising from surgical wounds, may also offer prophylaxis against certain pathologic chronic pain states. Amputees have been found less likely to experience phantom limb pain if they were rendered pain-free with epidural blockade for a period of time prior to surgery. [75] [84] [102] In these populations of amputees, the incidence of phantom limb pain may have been reduced by decreasing the amount of CNS sensitization present at the time of amputation. The amount of acute pain experienced immediately after thoracotomy appears to predict the probability of subsequent chronic post-thoracotomy pain. [90]

Multimodal Approaches

For purposes of this discussion, multimodal therapy is defined as two or more analgesic agents or techniques used in combination. The ASA "Practice Guidelines for Acute Pain Management in the Perioperative Setting" [36] (Appendix) contains the following statement:

> During the administration of anesthetics for surgery, the needs of many patients may best be met by taking advantage of the combined effects of a number of agents. Similarly, there is growing conviction that a multimodality approach to providing perioperative analgesia has advantages over the use of a single modality. The literature supports the efficacy of two or more analgesic techniques (including non-pharmacologic methods) used in combination for the control of perioperative pain, especially when different sites and/or mechanisms of action are involved and/or when synergy of effect is achieved. In addition, the literature indicates that multimodality approaches are associated with side effects no greater than those resulting from single analgesic techniques for perioperative pain management.

Examples of how multimodal therapy may be applied include using an opioid and a nonsteroidal anti-inflammatory drug (NSAID) together, combining two or more agents in an epidural infusion, and providing therapy for perioperative anxiety as well as for pain. The terms "multimodal" and "balanced analgesia" are sometimes used interchangeably. [100]

Postoperative Rehabilitation

Effective treatment of perioperative pain is, in itself, an important goal. However, comfort after surgery should be used to facilitate other desirable outcomes. A comprehensive and integrated approach to the accelerated recovery of the postoperative patient has been termed *postoperative rehabilitation.* Key elements in this approach include early mobilization and return to enteric nutrition, prevention of postoperative fatigue and impairment of pulmonary function, and early discharge from hospital. [103] Such an approach appears to hold much promise for the future.

/das/book/view/29494766/875/759.html

TREATMENT METHODS

Systemic Opioids

Opioids produce analgesia primarily as a result of their agonist effects on opioid receptors in the CNS. Effective doses of appropriate drugs can be administered by the oral, rectal, transdermal, or sublingual route or by subcutaneous, intramuscular, or intravenous injection or infusion (Ch. 10) . Of these options, intramuscular opioids have been the most common treatment choice for patients after surgery. This practice has been based on the apparent simplicity and universal applicability of the technique. A dose of an opioid is ordered to be given as often as the physician or nurse considers it necessary and safe. Unfortunately, the orders frequently provide for a "standard dose" that is optimal for only a small proportion of patients, and the "as needed" part of the order is often interpreted to mean "as little as possible."

There is typically little flexibility in doses or injection intervals for individual patients. The resulting conservative prescriptions result in inadequate analgesia for many patients.

Highly variable pharmacodynamic and pharmacokinetic dose-response curves for individual patients have been demonstrated. A standard dose of intramuscular opioid can result in 5-fold differences in peak blood levels among different patients, the time to reach peak levels may vary as much as 7-fold, and serum opioid levels required to produce analgesia in different patients vary as much as 4-fold. [104] [105] There does not appear to be a significant correlation between gender and analgesic requirement, and there is no scientific justification for the calculation of analgesic doses on the basis of body weight or surface area. [106] Although intramuscular injections are generally considered safe and require no special precautions, apnea and abnormal respiratory patterns may occur, and oxygen desaturation may be more severe than with some newer methods of opioid administration. [51] [107] Because the intramuscular route is such an unpredictable delivery system, using it effectively and safely requires careful ongoing assessment of patients, with adjustments in doses and frequency of administration until individual care is optimized.

Intravenous opioid infusions can abolish wide swings in drug concentration and may permit prompt titration of drug to the needs of individual patients. Accumulation may occur using drugs having an intermediate or long half-life, so that ongoing assessment and adjustment of dose to meet changing needs are a necessity. Respiratory depression of life-threatening severity has been reported, [108] and concern for this risk has limited the widespread use of continuous opioid infusions for perioperative pain. Intravenous administration during general anesthesia of a single dose of 20 mg of methadone, an opioid with a long half-life and low clearance, can produce postoperative analgesia that lasts many hours. [109] At the other end of the spectrum, the analgesic effects of remifentanil, a very short-acting synthetic opioid, last only a few minutes after discontinuing an intravenous infusion. [110] [111] Termination of the analgesic effect must be anticipated to avoid periods of severe pain after surgery.

Transdermal delivery of fentanyl after surgery has been demonstrated to be effective. [112] This method of opioid administration avoids the discomfort of injections and offers a useful alternative for patients unable or unwilling to swallow oral medications. Therapeutic blood levels are achieved, and the usual side effects associated with opioid administration (including respiratory depression) are seen. As with other routes of administration, dosing must be individualized under medical supervision.

Oral opioids in appropriate doses are remarkably effective. They can frequently be used in place of parenteral drugs 12 to 24 hours after superficial surgery and, after some intra-abdominal procedures, as soon as oral intake is possible. Placing oral opioids (and other analgesics) at the bedside can improve analgesia by permitting patients to choose the dose and frequency of administration best suited to their individual needs. The concept of patient-controlled analgesia (PCA), as discussed in the following section, is not limited to parenteral administration. A detailed discussion of the pharmacology and use of oral opioids is beyond the scope of this chapter.

Tramadol (Ultram) has been in use in a number of European countries for many years and has been approved by the Food and Drug Administration (FDA) in the United States. The drug's analgesic effects are thought to result from a combination of weak opioid receptor binding and norepinephrine and serotonin reuptake inhibition. Early studies [113] [114] found a lack of association with development of dependence, tolerance, and respiratory depression. However, subsequent domestic reports to the FDA resulted in March 1996 in labeling changes warning physicians of a risk of drug abuse, seizures, and anaphylactoid reactions. This development raises questions about the risk-to-benefit ratio of tramadol as a routine analgesic for surgical patients.

Traditionally, opioids are administered for the purpose of producing analgesia through their actions within the CNS. There is evidence of analgesic effects that result from activation of opioid receptors outside the nervous system following topical application, intravenous regional injection, or perineural injection in the vicinity of nerve trunks. Clinical studies have investigated peripheral analgesic effects of opioids on postoperative pain with demonstration of significant analgesia [115] and with contrasting findings of no significant analgesia. [116] [117]

Patient-Controlled Analgesia

PCA, the self-administration of small doses of opioids by patients when they experience pain, was originally conceived and developed to minimize the effects of pharmacokinetic and pharmacodynamic variability among individual patients. [118] [119] [120] It is based on the premise that a negative feedback loop exists: when pain is experienced, analgesic medication is demanded; when the pain is reduced, there are no further demands. The loop fails and risks are increased if nurses, relatives, or parents assume responsibility for drug administration. As discussed later in this chapter, the loop also fails if patients choose to self-administer drugs for reasons other than pain relief.

Most intravenous PCA devices consist of a microprocessor-controlled pump triggered by depressing a button. When the pump is triggered, a preset amount (incremental dose) of opioid is delivered into the patient's intravenous line. A timer in the pump prevents administration of an additional bolus until a specified period (lockout interval) has elapsed. Thus, individual patients titrate opioids to their own needs within safe clinical parameters. Many commercially available devices for this purpose are now available.

The safety of PCA, especially in relation to respiratory depression, has been addressed by a number of investigators. In two studies, serial blood gas analyses showed normal values in patients using PCA. [121] [122] No differences in respiratory mechanics (FEV_1 , functional residual capacity, peak flow rates) were found between patients using PCA and those using intramuscular opioids. [123] [124] However, cases of respiratory depression during PCA use have been reported. [122] [125] [126] Advanced age, hypovolemia, large incremental doses, and use of a background continuous-infusion mode were thought to be contributing factors by some investigators. Some investigators reported the incidence of respiratory depression among PCA patients managed by an anesthesiology-based acute pain service (Table 69-1) . [127] [128] [129] [130] Included in the table is the unpublished experience of the

TABLE 69-1 -- Respiratory Depression With Patient-Controlled Analgesia

AUTHOR	PATIENTS RECEIVING PATIENT-CONTROLLED ANALGESIA	INCIDENCE OF RESPIRATORY DEPRESSION (%)
Fleming and Coombs [127]	1,122	0.7
Schug and Torrie [128]	1,947	0.56
Ashburn et al [129]	3,785	0.37
Etches [130]	1,600	0.50
Ready et al, 1996	15,000	0.31

University of Washington Medical Center obtained from the pain-service database.

Quality of analgesia with PCA has been consistently reported as superior or equal to that with intramuscular opioids. Less PCA opioid use compared with intramuscular control groups is sometimes observed, [131] and satisfaction of patients and nurses is high. The principal advantages of PCA to patients are high-quality analgesia, autonomy, elimination of delay in decisions to medicate for pain, and freedom from painful intramuscular injections. It may take nurses less time to provide for the analgesic needs of postoperative patients using PCA.

Optimal efficacy and safety using PCA, as with other forms of treatment for perioperative pain, require careful planning, establishment of appropriate policies and procedures, education of physicians and nurses, and frequent medical assessment of individual patients (Table 69-2) (Table Not Available) . Preoperative patient teaching further facilitates optimal results. A number of opioid analgesics can be self-administered by patients. Those best suited are potent opioids with rapid onset and intermediate duration of action. Morphine, meperidine, and hydromorphone are widely used in North America. Table 69-3 lists suggested starting incremental doses and lockout intervals for these and other opioids. Initial PCA therapy should be preceded by a titrated opioid loading dose if severe pain is present. The PCA pump should be available as soon after surgery as the patient is capable of using it--often in the postanesthesia care unit. If adequate analgesia is not achieved with initial pump settings, the incremental dose should be increased and/or the lockout interval decreased.

Most PCA pumps offer the option to add a continuous background infusion to the basic patient-controlled mode. Theoretic advantages include the following: (1) a more constant opioid serum level; (2) improved analgesia, especially during sleep; and (3) modulation of the final opioid dose by patients, to achieve optimal analgesia. Theoretic disadvantages include the following: (1) difficulty predicting the optimal infusion rate for individual patients and thus the possibility of a prescribed overdose; (2) loss of an important safety element because sleeping patients continue to be medicated; and (3) more human errors in PCA pump programming because more steps are involved. Findings from controlled studies show that, compared with the PCA mode used alone, with addition of the continuous-infusion mode, patients receive more opioid, pain relief is unchanged, and dangerous pump-programming errors may occur. [126] [132] [133] [134] [135] [136] [137] [138] [139] [140] Recommendations for use of the background continuous-infusion mode are as follows: (1) avoid routine use of continuous-infusion mode; (2) add the continuous-infusion mode

TABLE 69-2 -- Elements of Intravenous Patient-Controlled Analgesia Daily Care by Anesthesiologists

(Not Available)

Modified from Ready et al [36]

TABLE 69-3 -- Guidelines for Patient-Controlled Intravenous Opioid Administration [a]

DRUG (CONCENTRATION)	SIZE OF BOLUS (mg)	LOCK-OUT INTERVAL (min)
Morphine (1 mg/mL)	0.5-2.5	5-10
Meperidine (10 mg/mL)	5-25	5-10
Hydromorphone (0.2 mg/mL)	0.05-0.25	5-10
Methadone (1 mg/mL)	0.5-2.5	8-20
Oxymorphone (0.25 mg/mL)	0.2-0.4	8-10
Fentanyl (0.01 mg/mL)	0.010-0.020	3-10
Sufentanil (0.002 mg mL)	0.002-0.005	3-10
Alfentanil (0.1 mg/mL)	0.1-0.2	5-8
Pentazocine (10 mg/mL)	5-30	5-15
Nalbuphine (1 mg/mL)	1-5	5-15
Buprenorphine (0.03 mg/mL)	0.03-0.1	8-20

[a] Precede with titrated intravenous loading dose if necessary to establish initial analgesia. Individual patient requirements vary widely. Small doses should be used initially for elderly or compromised patients.

for specific indications (e.g., pain during sleeping hours); (3) base the rate of infusion on established need (e.g., 30-50% of what a patient self-administered with the demand mode); (4) decide whether the continuous-infusion mode is needed only at night or around the clock; (5) provide regular in-service education to ward nurses on PCA pump-programming procedures.

There are times (difficult intravenous access, no option for enteric analgesics) when the use of PCA delivery systems via the subcutaneous route can be of value. [141] [142] [143] [144] [145] Additional experience has been reported in treating cancer pain. [146] [147] [148] [149] [150] A standard PCA pump attached to an administration set is all the equipment necessary. The administration set can be a small-gauge "butterfly" needle or a special device designed for the purpose (Baxter Sub-Q-Set) (Hooksett, NH). Choice of opioids is the same as for the intravenous PCA route (see Table 69-3) . The concentration of the opioid solutions should be increased 5-fold to reduce their volume. The same incremental doses and lockout intervals as for the intravenous route are programmed into the pump, and a continuous background infusion can be used, if needed. No basic intravenous solution is infused into the subcutaneous tissue.

Side effects (nausea, vomiting, itching) resulting from PCA can be treated by changing the opioid in the pump or by using drugs that provide symptomatic relief. Monitoring of vital signs should be according to protocols established to suit the needs of the patients and practices in each institution. A preprinted set of standard orders used throughout an institution can facilitate a uniform standard of care (Fig. 69-1) .

The PCA paradigm has been used to provide intranasal analgesia with meperidine [151] and fentanyl. [152] Intravenous patient-controlled midazolam has been provided to treat postoperative anxiety. [153] [154]

Regional Anesthetic Techniques

Regional anesthetic techniques used for surgery produce the following: positive respiratory, cardiovascular, and neuroendocrine effects; reduced thromboembolic complications and blood loss; and reduced convalescence (Chs. 42 to 44) . A variety of neural blockade techniques continued into the postoperative period can result in effective and safe analgesia. These include local infiltration of incisions with long-acting local anesthetics, peripheral nerve or plexus blocks, and continuous block techniques at various sites in the periphery or neuraxis.

A single injection of 0.25 percent bupivacaine into incisions after inguinal hernia repair produces effective analgesia for outpatients, [155] whereas repeated subcutaneous injections of a 0.5 percent solution through an epidural catheter provide sustained benefit. [156] Long-acting local anesthetics used for nerve or plexus anesthesia during surgery also eliminate early postoperative pain. Interscalene brachial plexus blocks for surgery on the shoulder can provide total comfort for 12 to 24 hours. [157] Sciatic and femoral nerve blocks can produce similar results after surgery on the ankle and foot, whereas intercostal blocks produce effective and safe analgesia for 6 to 12 hours after thoracic and upper abdominal surgery. [158]

Following thoracic or upper abdominal surgery, administration of long-acting local anesthetics through a catheter placed in the interpleural space can produce unilateral analgesia with little or no evidence of sensory block. The effect is presumably a result of multiple intercostal nerve blocks caused by spread of the local anesthetic through the parietal pleura. [159] [160] [161] Although the technique appears to provide effective analgesia in some situations, its use is controversial. The reported doses of local anesthetic required to produce analgesia vary among investigators and in some cases result in serum levels traditionally thought to be associated with signs and symptoms of toxicity. Clamping of chest tubes with each local anesthetic administration following thoracotomy may be necessary to avoid loss of the drug, and analgesia may be positional, with loss of effect in sitting or ambulating patients. Tension pneumothorax has been reported, [162] as have bronchospasm [163] and intrapulmonary catheter placement. [164]

Postoperative local anesthetic infusions into the axillary sheath, [165] femoral sheath, [166] and the vicinity of the sciatic nerve [167] have been used to maintain analgesia and sympathetic blockade after a variety of surgical procedures. These techniques may be particularly useful to facilitate perfusion

Figure 69-1 Pain service intravenous patient-controlled analgesia (PCA) physician orders.

after extensive revascularization or reimplantation surgery, to maintain a normal range of motion following joint surgery, and to administer to anticoagulated patients in whom spinal or epidural block may be considered with caution.

Spinal anesthesia can provide pain relief for several hours after the completion of surgery if long-acting agents containing vasoconstrictors are used. Continuous epidural anesthesia through a catheter offers several options for perioperative

analgesia. Local anesthetic boluses or infusions can provide profound analgesia, with advantages over parenteral opioids that include earlier ambulation, improved bowel function, higher arterial oxygen tension, and fewer pulmonary complications. [168] [169] For optimal results with the least amount of local anesthetic, the epidural catheter tip should be near the segments innervating the incision. Placement of thoracic or cervical epidural catheters should only be considered by those experienced in the use of lumbar catheters.

Intraspinal Analgesia

Opioids

Following the initial reports in 1979 of clinical efficacy of intrathecal [170] and epidural opioids, [171] these drugs have been used to control pain following a wide variety of surgical procedures. [172] Intrathecal opioids have the appeal of ease of administration, either at the time of spinal local anesthetic injection for surgical anesthesia or as a separate technique when general anesthesia is administered. Many patients remain comfortable for 24 hours or more after a single injection of intrathecal morphine. It is possible that in the future, sustained-release preparations of morphine may further extend that duration of analgesia. [173]

The epidural route has been used much more extensively for perioperative pain control. Reasons include popularity of the technique alone or in combination with light general anesthesia during surgery, willingness to leave an epidural catheter in place for extended periods to maintain analgesia, familiarity with perioperative analgesia using epidural local anesthetics, and freedom from the risk of post-lumbar-puncture headache. Several reports regarding the use of epidural opioids for postoperative pain control are of special note. Stenseth et al [174] published a prospective study reporting the efficacy and side effects of epidural morphine in 1,085 patients after thoracic, abdominal, urologic, or orthopedic surgery. This large experience from a single institution provides a wealth of observations that are instructive to the clinician contemplating the use of epidural opioids.

In a randomized double-blinded study by Rawal et al [62] of obese patients undergoing gastroplasty for weight reduction, the effects of intramuscular and epidural morphine were compared with respect to analgesia, ambulation, gastrointestinal motility, early and late pulmonary function, duration of hospitalization, and occurrence of deep vein thrombosis in the postoperative period. With a protocol designed to provide adequate analgesia by either route, the average dose of intramuscular morphine was up to seven times higher than that required by the epidural route. Patients receiving epidural morphine reported superior analgesia, ambulated sooner, had fewer pulmonary complications, had earlier return of bowel function, and were discharged from hospital earlier than patients receiving intramuscular morphine.

Yeager et al [175] randomized high-risk surgical patients to two groups: the first received general anesthesia and conventional postoperative analgesia (i.e., intramuscular or intravenous opioids), whereas the second group received combined epidural/general anesthesia and epidural opioids for postoperative pain. [175] Mortality rate, overall complication rate, infection rate, time to extubation, and hospital costs were significantly lower in the group receiving epidural therapy.

Although not as effective as regional analgesia with local anesthetics for controlling pain associated with vaginal delivery, intraspinal opioids for control of pain following cesarean section are widely used. These drugs may be offered when spinal or epidural anesthesia is chosen for surgery. Although most reports focus on the latter application, good results have also been reported using the intrathecal route. [176] Pain after vaginal delivery originating from a large episiotomy or a perineal tear may also be managed with intraspinal opioids.

Table 69-4 lists a number of opioids used for intraspinal analgesia, suggested dose ranges, expected latency, and duration of analgesia. Doses necessary to produce analgesia and their duration of effect vary considerably from one patient to another, depending on age, medical condition, site of injection, type of pain, and other factors. Incorporating some of these factors, Table 69-5 suggests starting doses of epidural morphine, the most widely used opioid for incisional pain. The recommended doses are only guidelines. A dynamic ongoing assessment of adequacy of pain relief for individual patients with changes in dose or frequency of injection as necessary is the logical approach. Preservative-free morphine preparations have been used in a wide range of concentrations with no apparent difference in efficacy. The commercially available 0.1 percent solution is satisfactory without dilution. The addition of epinephrine to morphine is not recommended. Although most experience with morphine has involved intermittent injection, the drug has been used with success as a continuous infusion. Effective doses may range from less than 0.1 to 1.0 mg/h.

Elderly patients may require remarkably small doses of epidural morphine. In evaluating women after abdominal hysterectomy, a significant inverse relationship has been found between age and effective total dose of epidural morphine needed each 24 hours to achieve analgesia. The relationship can be expressed by the following equation:

[177]

A lipophilic drug such as fentanyl is useful when rapid onset of epidural analgesia is important. Intermittent epidural boluses of 50 to 75 mug can be used to achieve analgesia promptly in the immediate postoperative period if an initial epidural morphine dose is not adequate. Used as the sole opioid, a 25- to 100-mug epidural bolus can be followed by a continuous infusion of 25 to 100 mug/h. Epidural meperidine is widely used in some parts of the world and is gaining popularity in North America. [178] As with other opioids, respiratory depression can occur. [53]

Although not widely used in North America, epidural opioids with mixed agonist-antagonist actions (e.g., buprenorphine) are popular in some places. [179] [180] [181] It is not likely that this family of drugs offers significant benefits over pure opioid agonists for most postoperative patients.

Until it is possible to identify and eliminate the factors that occasionally lead to severe respiratory depression in patients receiving intraspinal opioid analgesia, it must be assumed

TABLE 69-4 -- Intraspinal Opioids for the Treatment of Perioperative Pain

DRUG	SINGLE DOSE[a] (mg)	INFUSION RATE[b] (mg/h)	ONSET (min)	DURATION OF SINGLE DOSE[c] (h)
Epidural				
Morphine	1-6	0.1-1.0	30	6-24
Meperidine	20-60	10-60	5	4-8
Methadone	1-8	0.3-0.5	10	6-10
Hydromorphone	1-2	0.1-0.2	15	10-16
Diamorphine	4-6	?	5	12
Fentanyl	0.025-0.1	0.025-0.1	5	1.5-3
Sufentanil	0.01-0.06	0.01-0.05	5	2-4
Alfentanil	0.5-1	0.2	15	1-3
Subarachnoid				
Morphine	0.1-0.3	--	15	8-24+
Meperidine	10-30	--	?	10-24+
Diamorphine	1-2	--	?	20
Fentanyl	0.005-0.025	--	5	3-6

[a] Low doses may be effective when administered to the elderly or when injected in the cervical or thoracic region.
[b] If combining with a local anesthetic, consider using 0.0625-0.125 percent bupivacaine.
[c] Duration of analgesia varies widely; higher doses produce longer duration.

that all patients offered these techniques are at risk. To prevent serious injury or death, there is no substitute for a high level of vigilance. This may be provided by a nurse trained to check the rate and depth of respiration as well as general status and level of consciousness at frequent intervals. Respiratory monitors that sound an alarm if ventilation is not detected may augment this process, but they should not be viewed as substitutes for alert, well-trained human observers.

Intensive care facilities are well suited to this level of monitoring and should be used for patients at special risk (advanced age, serious underlying conditions, extensive surgery). However, the expense and limited availability of these facilities render them impractical for routine use. A "step-down unit," intermediate between intensive care and a regular ward, is an appealing alternative. It has been demonstrated that with extensive nursing education, careful patient selection, frequent monitoring of ventilation, protocols for immediate treatment of complications, and immediate availability of medical personnel, this care can safely be offered in conventional hospital wards. [182] A preprinted set of standard orders used throughout an institution can facilitate a uniform high standard of care (Fig. 69-2) . Delegation of all responsibility for pain control to one group of physicians within an institution can minimize errors of conflicting or duplicated orders or inadvertent administration of parenteral opioids to patients receiving intraspinal opioids.

Early respiratory depression occurring in the first 2 hours following epidural opioid injection is the result of vascular uptake and redistribution (i.e., the same mechanism that follows intramuscular injection). Delayed respiratory depression occurring between 6 and 12 hours following spinal or epidural injection is likely the consequence of rostral spread of opioid in cerebrospinal fluid (CSF). The target site is thought to be the respiratory center located superficially in the floor of the fourth ventricle. The actual incidence of this event is not known and is dependent on a number of factors including the population studied, how they are monitored, and the definition of respiratory depression that is chosen. In a large, multi-institutional Swedish questionnaire

TABLE 69-5 -- Initial Dose of Epidural Morphine for Perioperative Pain [a]

PATIENT AGE (y)	NONTHORACIC SURGERY	THORACIC SURGERY	
	(LUMBAR OR CAUDAL CATHETER) (mg)	*THORACIC CATHETER (mg)*	*LUMBAR CATHETER (mg)*
15-44	4	4	5
45-65	3	3	4
66-75	2	2	3
76+	1	1	2

[a] These doses should only be considered as guidelines. They are based on the use of undiluted 0.1 percent preservative-free morphine. Safe and effective doses for individual patients may vary considerably.

Figure 69-2 Pain service epidural analgesia physician orders.

survey, the incidence of "depression requiring naloxone" was 0.25 to 0.40 percent. [50] In a questionnaire survey of 74 U.S. institutions, the incidence of "respiratory insufficiency" was 1.9 to 2.3 percent, [183] and in a prospective study of 1,085 patients in a single institution, the incidence of "respiratory depression" was 0.9 percent. [174] At the University of Washington Medical Center in Seattle, the incidence was found to be 0.2 percent. [182]

It is not known whether the risk of severe respiratory depression is greater after intraspinal opioids than following opioid administration by more conventional routes. It has been reported that 860 hospitalized patients receiving morphine orally or parenterally (intravenously, intramuscularly, subcutaneously) demonstrated a 0.9 percent incidence of "life-threatening" respiratory depression. [47]

The risk of delayed respiratory depression after intraspinal opioid administration appears to be greatest early in the course of therapy. There are no reported cases of this complication occurring later than 24 hours after administration of the initial dose of drug. Consistently impressive among predisposing risk factors in reported cases are advanced age, concomitant use of systemic opioids or other CNS depressants, and extensive surgery. Therefore, large parenteral doses of perioperative opioids or long-acting sedatives should be avoided, as should perioperative parenteral opioids in patients receiving epidural opioid analgesia.

Respiratory rate alone is not an adequate indicator of ventilatory status in postoperative patients receiving epidural opioids. [19] [184] A more global assessment is necessary, particularly during the first 24 hours of treatment. This should include assessment of level of consciousness because increasing sedation (presumably due to central drug effect and CO_2 narcosis) has been noted with advanced respiratory depression. Healthy volunteers breathing CO_2 mixtures have been observed to lose consciousness at CO_2 pressure (P_{CO_2}) levels of about 80 mm Hg. [185] Every patient receiving intraspinal opioids whose level of consciousness deteriorates unexpectedly should be assumed to have respiratory depression until disproved by arterial blood gas analysis.

The immediate treatment of severe respiratory depression is support of ventilation. Equipment to deliver oxygen with positive pressure must be readily available, and personnel in the area must be familiar with its use. Naloxone titrated in small doses (0.1 mg) intravenously usually restores adequate spontaneous ventilation promptly, but repeated doses are sometimes necessary. This drug should be readily available for immediate use.

Pruritus is common in patients receiving intraspinal opioids. The incidence is particularly high in obstetric patients. Itching may be generalized or localized, with the face being a common site. This side effect is seen both with opioids containing preservatives and with preservative-free preparations. Although the pruritus is probably not due to histamine release, antihistamines often provide symptomatic relief. Nalbuphine may also be of value. [186] [187] [188] Naloxone is consistently effective, but repeated doses or infusions may sometimes be necessary.

The incidence of urinary retention is higher in volunteers than in patients, and it is higher in males. Naloxone may help to prevent or reverse urinary retention, but doses approaching those that antagonize analgesia may be needed. Some patients require bladder catheterization. On the other hand, most patients with indwelling urinary catheters in place following surgery are able to void spontaneously when the catheters are removed, even when epidural opioid therapy is continued.

Nausea and vomiting are believed to be the result of rostral spread of opioid in CSF to the vomiting center and the chemoreceptor trigger zone located superficially in the floor of the fourth ventricle. Relief is frequently possible with antiemetics, but these may also produce unwanted sedation or may even contribute to the risk of respiratory depression. [189] Transdermal scopolamine patches applied to the mastoid area have been found to be effective. [190] [191] At the University of Washington Medical Center, they are commonly used in combination with intravenous metoclopramide. Intravenous droperidol in small doses is used as second-line therapy, whereas ondansetron is also sometimes considered (Fig. 69-2) .

Sedation produced by intraspinal opioids, rarely a significant problem with moderate drug doses, may be the result of spread of the drug in CSF to receptors in the thalamus, limbic system, or cortex. Hypercarbia and associated CO_2 narcosis can augment the clinical picture of sedation. [185] Epidural buprenorphine 0.15 mg has been shown to produce prolonged depression of the CO_2 response that lasted 8 to 12 hours. A similar observation was made after 2 to 4 mg doses of epidural butorphanol. [192]

Opioid-Local Anesthetic Mixtures

The rationale for combining epidural opioids and local anesthetics is to use lower doses of each agent, to preserve effective analgesia, and to reduce the side effects and problems associated with the use of the individual drugs. Some degree of blunting of the stress response may also be possible. Whereas the opioid in the mixture acts by inhibiting the release of substance P in the dorsal horn of the spinal cord, the local anesthetic blocks transmission of impulses at the level of the nerve axonal membrane. These two distinctive actions may contribute to the synergy of analgesic effect that has been demonstrated.

Bupivacaine is the most widely used local anesthetic for perioperative analgesia because of its tendency to block sensory fibers preferentially, with relative sparing of motor fibers. Dilute bupivacaine solutions can therefore provide analgesia while preserving the ability of some patients to ambulate. Even dilute solutions can lead to some degree of sympathetic, sensory, and motor block. Associated unwanted effects are listed in Table 69-6 . In Table 69-7 , two commonly used concentrations of bupivacaine (0.0625% and 0.125%) are compared with regard to these effects. Figure 69-3 shows the frequency of bupivacaine-related motor block limiting ambulation using either lumbar or thoracic epidural catheters at the University of Washington Medical Center. It is possible that dilute ropivacaine infusions will provide analgesia equivalent to that provided by bupivacaine with less impact on motor function.

TABLE 69-6 -- Unwanted Effects With Epidural Local Anesthetic Techniques

FUNCTION BLOCKED	POSSIBLE PROBLEM
Sympathetic	Hypotension (thoracic > lumbar)
Proprioception	Difficulty ambulating
Sensory	Pressure injury
	Mask a complication
Motor	Loss of function (cough, ambulation)

TABLE 69-7 -- Comparison of Two Common Bupivacaine Concentrations

BUPIVACAINE CONCENTRATION	0.0625%	0.125%
Hypotension	Absent	Rare
Loss of proprioception	Subtle effect (lumbar > thoracic)	Marked effect (lumbar > thoracic)
Sensory block	Variable	Common
Motor block	Variable	Common
Clinical application	High-volume infusion	Low-volume infusion (segmental block)

Various opioids are commonly combined with bupivacaine. The most common in the United States are fentanyl and morphine, with concentrations of both varying widely among different users. Monitoring of patients receiving epidural mixtures of opioids and local anesthetics should include strategies to detect side effects or problems associated with both components (see Fig. 69-2) .

Epidural opioids used alone in effective doses for relief of perioperative pain do not appear to mask certain postoperative complications, in particular compartment syndrome in the lower extremity. [193] It is not known whether this is also true using epidural infusions that contain local anesthetics. Because there is a possibility of producing dense sensory block that could mask the pain associated with this complication, epidural local anesthetic solutions may best be avoided or used with special monitoring precautions in patients at high risk of developing a compartment syndrome.

Ketamine

Ketamine is a phencyclidine derivative with analgesic properties probably mediated by several mechanisms including interactions with cholinergic, adrenergic, and serotonergic systems. Some clinical studies show satisfactory analgesic efficacy of epidural ketamine [194] [195] [196] [197] whereas others do not. [198] [199] [200] [201] Intrathecal administration is also reported. [202]

Side effects such as sedation, blurred vision, tachycardia, hypertension, and hallucinations have been reported following epidural administration of ketamine. [198] [203] [204] [205] It should be noted that there has been a lack of consensus regarding the neurotoxic potential of the drug. In one study, intrathecal administration in baboons showed no neurotoxic

Figure 69-3 Motor block impairing ambulation using epidural bupivacaine infusions.

changes [206] whereas in another, the same authors observed focal degeneration with loss of myelin and axoplasm in monkeys. [207] Histologic changes in rats have also been seen. [208] The routine use of epidural or intrathecal ketamine in humans cannot be recommended at this time.

Clonidine

The alpha$_2$ -adrenergic agonist clonidine has been extensively studied and is currently in clinical use as an intraspinal agent in some parts of the world. Clonidine administered by the oral route can augment spinally mediated opioid analgesia [209] whereas epidural or intrathecal clonidine can provide effective analgesia alone. [210] [211] [212] [213] [214] [215] [216] [217] [218] [219] [220] [221] [222] [223] [224] [225] [226] Intrathecal clonidine does not provide surgical anesthesia. [227]

Neostigmine

Neostigmine represents a novel approach to providing analgesia. Unlike with local anesthetics, unwanted axonal blockade does not occur, and unlike alpha $_2$ -adrenergic agonists, neostigmine is not a direct agonist stimulating all receptors of a certain type. Intrathecal neostigmine provides analgesia by inhibiting breakdown of acetylcholine, an endogenous spinal neurotransmitter. Early studies involving its administration to humans are promising, [228] [229] [230] [231] [232] but determining the possible role of this agent in clinical practice will require further study. Analgesia and side effects associated with intrathecal neostigmine were found to be dose-dependent. [228] A single dose through a no. 19.5 needle of 50 mug showed no measurable effect. A dose of 150 mug caused mild nausea, and 500 to 750 mug produced subjective leg weakness, decreased deep tendon reflexes, and sedation. The 750-mug dose was associated with anxiety, increased blood pressure and heart rate, and decreased end-tidal CO_2 .

Intraspinal Analgesia in Patients Receiving Anticoagulants

Thromboembolic complications following major surgery can be catastrophic. Many surgeons seek to minimize this risk through the prophylactic use of a variety of anticoagulants. These include unfractionated heparin, low-molecular-weight heparin (LMWH), and oral anticoagulants such as

coumarins. Higher heparin doses are required during surgery when major cardiac or vascular surgery is performed. Platelet aggregation-inhibiting drugs (aspirin and NSAIDs) are also commonly administered in the perioperative period. Thrombolytic agents (e.g., streptokinase, urokinase) are also used in some patients facing surgery. The development of spinal hematomas is a rare event. Such hematomas have been reported spontaneously in "normal" patients exposed neither to anticoagulants nor to neuraxial blocks. They have also been reported during the use of either low-dose anticoagulants or neuraxial blocks alone, and they have been reported when these forms of therapy have been combined. (There are no studies evaluating epidural catheter insertion in fully anticoagulated patients.) What can one learn from published reports on this subject?

Evidence of Safety

Tryba [233] reviewed 13 case series totaling more than 850,000 patients having epidural block. Three spinal hematomas occurred. Using statistical analysis with a 95 percent confidence interval, the estimated incidence was 1:150,000. Seven other case series involved 650,000 intrathecal blocks without a bleeding complication (estimated incidence, 1:220,000). Another review by Vandermeulen et al [234] documented 18 case series from 1952 to 1989 that found no spinal hematomas after epidural or intrathecal anesthesia. The large aggregates in these and other major reviews [235] [236] [237] [238] offer considerable reassurance about the overall safety of intraspinal analgesic techniques. Further, at least 25 prospective reports involving a total of more than 30,000 patients document the safe utilization of epidural and intrathecal anesthesia in the presence of anticoagulants. Notable among these are the reports of Rao and El-Etr [239] and Odoom and Sih. [240]

There is wide variation in response to subcutaneous low-dose heparin. Yet Lowson and Goodchild [241] and Allemann et al [242] reported no cases of spinal hematoma in a combined total of 204 epidural and 119 spinal anesthetic regimens in patients who received 5,000 U of unfractionated subcutaneous heparin 2 hours prior to needle placement. Schwander and Bachmann [243] noted no spinal hematomas in 5,528 patients who received varying doses of subcutaneous heparin in combination with spinal or epidural anesthesia. Spinal hematomas in patients undergoing major conduction block while receiving low-dose heparin are very rare; there are only 3 cases reported. [244] [245] [246]

Various preparations of LMWH have been widely used for a number of years in Europe. In a literature review, Bergqvist et al [247] identified 44 articles on LMWH for thromboprophylaxis. At least 9,013 of the patients received spinal or epidural anesthesia during LMWH treatment. There were no reported cases of spinal hematoma with neurologic dysfunction in these patients. Schwander and Bachmann [243] reported no spinal hematomas after epidural or intrathecal blocks in 13,917 patients receiving LMWH. Although the actual number of patients who have received LMWH in combination with central neural blockade is not known, pharmaceutical companies estimate it to be at least one million.

Few data exist regarding the risk of spinal hematoma in patients with indwelling spinal or epidural catheters who are subsequently anticoagulated with coumarins. Odoom and Sih [240] performed 1,000 continuous lumbar epidural anesthetics in 950 patients undergoing vascular procedures and who received oral anticoagulants preoperatively. There were no neurologic complications. In another study, there were no reported spinal hematomas in 192 patients receiving postoperative epidural analgesia in conjunction with low-dose warfarin after total knee arthroplasty. [248]

Although epidural or spinal needle and catheter placement with subsequent heparinization appears relatively safe, the risk of spinal hematoma in patients who receive thrombolytic therapy is less well defined. Two cases of spinal hematoma have been reported in patients with indwelling epidural catheters who received thrombolytic agents. [249] [250]

A number of studies of patients receiving aspirin or NSAID showed no spinal hematomas following epidural or intrathecal anesthesia. [251] [252] [253] Of additional note is the Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP), in which 1,422 high-risk obstetric patients who received 60 mg of aspirin daily underwent epidural anesthesia without any neurologic sequelae [254] (Ch. 57).

Evidence of Risk

Groen and Ponssen [255] reviewed 199 patients who suffered "spontaneous" spinal epidural hematomas. A coagulopathy (drug-induced, acquired, or congenital) was present in 25 percent of these patients. Vandermeulen et al [234] published details of reported cases of spinal hematoma after epidural or intrathecal block. In their retrospective search spanning the years from 1906 to 1994, 61 cases were found. Thirty-two patients had received epidural blocks; 29 had received intrathecal blocks. It is notable that 42 of the 61 spinal hematomas (68%) occurred in patients with impaired coagulation (either on the basis of anticoagulant therapy or disease). Technical difficulties (bleeding, multiple attempts, difficult needle placement) were also commonly noted. In 15 of 32 patients (47%) receiving an epidural catheter, spinal bleeding occurred shortly after catheter removal.

Conclusions

Whether the use of anticoagulants in patients receiving epidural and intrathecal anesthesia increases the risk of spinal hematoma is not known (Ch. 42) . In their review article, Vandermeulen et al [234] concluded: "The presence of anticoagulants (mainly therapeutic levels of heparin, and to a lesser degree, low-dose thromboprophylaxis with UH [unfractionated heparin] or LMWH) . . . must be considered critical in the formation of a spinal bleeding complication."

Whenever possible, it is desirable to correct defects in coagulation status before proceeding with epidural or intrathecal anesthetic/analgesic techniques (and before removing intraspinal catheters). However, it is likely that the risk of fatal pulmonary embolus because of an omitted

thromboprophylactic treatment is higher than the risk of spinal hemorrhage when unfractionated heparin or LMWH is combined with epidural or intrathecal block. In a fully anticoagulated patient, it is recommended that the necessity of the anticoagulation be determined, as well as whether it may be reversed during the period of epidural catheter placement and use. Central neural block should probably be avoided in patients who must remain fully anticoagulated or who may receive thrombolytic therapy.

When intrathecal anesthesia/analgesia is used in a patient with abnormal coagulation, frequent neurologic examination is essential. Opioid-based epidural analgesia or the use of dilute local anesthetics can facilitate frequent neurologic examination. If spinal hematoma develops, the treatment of choice is immediate decompressive laminectomy.

Decisions to combine epidural or intrathecal anesthesia with anticoagulant therapy should be made on a caseby-case basis after careful evaluation of the possible risks and benefits (including risks and benefits of alternative options).

Patient-Controlled Epidural Analgesia

There is currently considerable interest in attempting to combine the potent analgesic effects of drugs delivered into the epidural space with the advantages of patient participation associated with the PCA concept. [178] [179] [256] [257] [258] [259] [300] [301] The technique involves epidural catheter placement in standard fashion, establishment of comfort with a loading dose (opioid, local anesthetic, or both), setting of the PCA pump to define the size of patient-activated bolus doses and lockout interval between doses, and usually a continuous background epidural infusion rate.

Patient-controlled epidural analgesia (PCEA) based on morphine has been described by several investigators. Chrubasik et al [257] compared the effectiveness of several epidural opioids administered on demand. They found that the self-administered dose of morphine required to provide analgesia was significantly less than amounts required by continuous epidural infusion or by intravenous PCA. Sjostrom et al [259] also reported the use of morphine via PCEA (bolus, 1 mg; lockout 30 min). Average utilization was 0.5 mg/h. Walmsley [278] reported effective and safe PCEA morphine in more than 4,000 postoperative patients using a 2- to 3-mg loading dose, bolus dose of 0.2 mg, lockout of 10 to 15 minutes, and continuous infusion of 0.4 mg/h. The maximum dose was limited to 1.2 mg/h.

PCEA fentanyl has been used successfully. However, some investigators have shown that drug requirements, pain levels, and plasma fentanyl levels were no different when compared with intravenous PCA fentanyl administration. [279]

Hydromorphone as a PCEA opioid is reported by some therapists. [272] [276] Drug requirements following cesarean section were 4- to 5-fold less than in patients receiving intravenous PCA hydromorphone. [272] Additional observations included more rapid return of bowel function and a shorter hospital stay.

Although PCEA appears to have great future potential, there has been little systematic comparison of different drugs and dosing regimens. There appear to be almost as many formulas as there are publications on the subject, and many of the clinical reports to date relate to use of the technique in obstetric patients. Considerable further research will be needed to establish criteria for patient selection, optimal drugs or drug mixtures, and PCA pump settings. Table 69-8 includes a few examples of the many recommended protocols. Dose schedules are generally those recommended for use through lumbar epidural catheters. Doses should be reduced when a thoracic epidural catheter is used.

Combined Spinal-Epidural Technique

Combined spinal-epidural analgesia/anesthesia has become popular in obstetrics (Ch. 57) and has also been used in the operating room setting. With this technique, an epidural needle is first placed in the epidural space. A small-bore spinal needle is then advanced through the epidural needle until the subarachnoid space is entered. An intrathecal dose of opioid and/or local anesthetic is injected, and the spinal needle is removed. Finally, a catheter is threaded into the epidural space prior to removal of the epidural needle. It has been claimed that an advantage of the spinal-epidural technique in the operating room is rapid onset of surgical anesthesia obtained with an initial subarachnoid local anesthetic injection followed by the

TABLE 69-8 -- Examples of Patient-Controlled Epidural Analgesia Regimens [a]

DRUG	CONCENTRATION	LOADING DOSE	INCREMENTAL DOSE	LOCKOUT (min)	CONTINUOUS INFUSION/h
Morphine	50 mug/mL	2-4 mg	100-200 mug	10-15	300-600 mug
Hydromorphone [b]	10 mug/mL	0.5-1.5 mg	20-30 mug	6-8	80-120 mug
Fentanyl	5 mug/mL	75-100 mug	10-15 mug	6	30-75 mug
Sufentanil	2 mug/mL	30-50 mug	4-6 mug	6	5-10 mug
Meperidine	5 mg/mL	30 mg	30 mg	30	None
Bupivacaine plus fentanyl	0.625% + 2 mug/mL	0.5% bupivacaine	3 mL	6	6 mL

[a] Doses for use with lumbar epidural catheters; consider reductions if thoracic catheters are used.
[b] Bupivacaine 0.031% was added in most cases.

availability of an epidural catheter for ongoing postoperative analgesia.

There are at least three significant issues relevant to postoperative analgesia in choosing this technique. First, when an initial spinal anesthetic is initiated, it becomes impossible to test the function of the subsequently placed epidural catheter adequately. A conventional epidural test dose of local anesthetic that contains epinephrine may help to exclude an intravascular catheter placement, but that test provides no assurance that the catheter will provide effective postoperative analgesia when it is needed. An untested epidural catheter in a surgical patient in severe pain can represent a real diagnostic and therapeutic problem.

Second, it is possible that the hole in the meninges produced by a spinal needle will increase spread of subsequently injected or infused epidural solutions. [302] If so, the risk of respiratory depression (from epidural opioids) or extensive block (from epidural local anesthetics) may increase.

Third, following an intrathecal dose of a hydrophilic opioid such as morphine, analgesia is likely to be present for many hours. When analgesia recedes, however, often in the middle of the night, alternative measures are needed, and the smooth transition from intrathecal morphine to another analgesic technique can be challenging. There is also potential additional risk because one may be faced with administering systemic opioids while substantial residual intrathecal effects are still present. This combination of opioid administration routes has been noted as a common feature in many of the reported cases of respiratory depression during intraspinal opioid therapy. With these issues in mind, it is the preference of the writer to avoid combined spinal-epidural techniques under most circumstances when superior postoperative analgesia is expected to be necessary for more than a few hours.

Role of the Anesthesiologist in Providing Intraspinal Analgesia

Whatever intraspinal agents are used, anesthesiologists offering intraspinal analgesia in the perioperative period should provide regular bedside assessment and should be prepared to meet the changing needs of individual patients. A list of suggested functions and responsibilities involved in meeting this obligation is presented in Table 69-9 (Table Not Available) .

Intra-Articular Analgesia

Small doses of intra-articular morphine have been administered in an attempt to provide analgesia following arthroscopic and other joint surgery. [303] [304] [305] [306] [307] [308] [309] From these conflicting

TABLE 69-9 -- Elements of Intraspinal Analgesia Daily Care by Anesthesiologists

(Not Available)

Modified from Ready et al [36]

reports, the presence of peripheral opioid-mediated analgesia remains controversial. Following arthroscopic surgery in outpatients, a combination of systemic ketorolac and intra-articular bupivacaine decreased analgesic requirements and pain. Ketorolac alone or in combination with bupivacaine did not alter the recovery time. [310]

Nonopioid Analgesics

Nonsteroidal Anti-Inflammatory Drugs

Although parenteral opioids have historically been the primary form of therapy for patients experiencing severe postoperative pain, in a number of studies this approach has been found to lack efficacy. Attempts to improve analgesia have included the addition of a second agent such as a phenothiazine derivative or hydroxyzine. The result has frequently been unwanted sedation and other side effects associated with the additive with little improvement in comfort. The concept of combining an opioid with a nonsedating, nonopioid analgesic is a simple form of multimodal therapy and has been used to advantage for many years in drug combinations available for administration by the oral route (e.g., codeine or oxycodone plus acetaminophen). Although a detailed discussion of the pharmacology of NSAIDs is beyond the scope of this chapter, brief reference is made to ketorolac tromethamine, an NSAID used primarily as an analgesic and the first injectable NSAID available in the United States.

NSAIDs act principally through inhibition of prostaglandin synthesis. Advantages over opioids include a reduction in opioid-related side effects, especially respiratory depression, absence of tolerance or addiction potential, and less sedation. Most evaluations of NSAIDs for postoperative pain relief have involved comparison with opioids in "either/or" protocols. With an improved understanding of perioperative pain and its consequences, there is growing emphasis on the advantages of combined pharmacologic approaches to therapy (i.e., multimodal therapy). [311] [312] Systemic opioids with centrally mediated actions and concurrent NSAIDs with peripheral sites of action appear to have advantages over either class of drug used alone.

It is unlikely that NSAIDs can completely replace opioids in most patients suffering moderate and severe postoperative pain immediately after surgery. [313] Under such conditions, NSAIDs are best considered as adjuncts to opioid therapy with benefits that include a reduction in opioid requirements. There is evidence that later in the postoperative period, as pain begins to subside, NSAIDs alone can provide adequate analgesia. In a single-dose comparison between intramuscular ketorolac and morphine postoperatively, it was found that both 10 and 30 mg of ketorolac were equal in analgesic effect to 12 mg of morphine on postoperative day 1 or 2. [314] In a comparison of intramuscular ketorolac 30 mg and morphine 10 mg for pain relief after cholecystectomy, it was concluded that, compared with morphine, ketorolac alone provided poor pain relief in the immediate postoperative period. The next day, the analgesic effects of the two drugs were similar. [315]

The concurrent use of PCA opioids and supplemental parenteral ketorolac after surgery has been reported. In a study of women using PCA opioids after abdominal hysterectomy, no difference in the incidence of common side effects was seen in a group who received ketorolac intraoperatively and postoperatively compared with controls. However, opioid requirements, time to return of bowel function, and time to hospital discharge were reduced. [316] Another study evaluated women using PCA morphine after intra-abdominal gynecologic surgery. Pain scores were comparable in each treatment group, but there was a ketorolac dose-related reduction in morphine use. [317]

As with all drugs, ketorolac may cause side effects. These include bronchospasm, [55] [318] gastrointestinal bleeding, [319] [320] alteration in platelet function and possibly associated perioperative bleeding, [321] [322] [323] [324] [325] [326] and impairment of renal function. [319] In balance, ketorolac and other NSAIDs can be used safely to provide perioperative analgesia by therapists who thoroughly understand the pharmacology of these drugs.

Nitrous Oxide

Under some circumstances, N_2O can be a useful (Ch. 4) analgesic, especially for acutely painful experiences of short duration. [327] [328] Examples include repeated postoperative dressing changes or superficial wound debridement. The low solubility of N_2O provides rapid onset of analgesia and rapid elimination on cessation of inhalation. N_2O in concentrations of 30 to 50 percent delivered through an anesthetic apparatus or a calibrated mixer is said to be as potent as 10 mg of intramuscular morphine.

Care must be exercised using N_2O in combination with other CNS depressants because "anesthesia" and its associated risks may occur. In particular, the risk of aspiration of gastric contents should be considered. With chronic administration of N_2O, bone marrow depression leading to leukopenia may occur secondary to impairment of methionine synthetase. This is reversible when detected early. Trace gas exposure of medical personnel can be minimized with scavenging devices attached to the N_2O delivery apparatus. N_2O use is widespread in the United Kingdom, where it is available as a commercial 50 percent mixture with oxygen (Entonox).

Ketamine

Ketamine was originally introduced as a dissociative anesthetic and has been widely used, especially in burn surgery (Ch. 9) . It has also been found to be useful in "subdissociative" doses as an analgesic. [81] [329] [330] [331] [332] [333] [334] [335] Suggested typical infusion rates are 3 to 4 mg/kg/h following an initial bolus of 1 mg/kg. Ketamine has been used in combination with morphine [336] [337] and self-administration of ketamine by patients has been reported. [336] [338] Epidural ketamine is discussed in an earlier section of this chapter.

Although systemically administered ketamine may have a place as a short-term analgesic, some concerns have limited its widespread acceptance. Little analgesia is possible without sedation and unpleasant emergence delirium, and hallucinations are common following both anesthetic and analgesic doses. Their incidence and intensity may be reduced

---

with opioid and scopolamine premedication, concomitant administration of physostigmine, or small doses of barbiturates, benzodiazepines, or droperidol. Ketamine may have a role in providing analgesia in patients with extreme degrees of opioid tolerance. [339]

Cryoanalgesia

Cooling peripheral nerves to temperatures between -5 and -20°C causes disintegration of axons and breakdown of myelin sheaths while the perineurium and epineurium remain intact. Interruption of conduction is prolonged, lasting an average of several weeks. [340] Recovery of function is dependent on the rate of nerve regeneration and the distance of the lesion from the end organ. A typical cryoanalgesia instrument includes a regulating system to deliver compressed gas (N_2O or CO_2) to a probe where expansion through a small orifice results in cooling. The probe contains a thermocouple and a nerve stimulator to facilitate nerve localization. Cryoprobes small enough to be used percutaneously are available.

Cryoanalgesia applied directly to intercostal nerves through the parietal pleura at the time of thoracotomy has been shown to be beneficial. [341] [342] The treatment resulted in less reported pain and fewer analgesic requirements. The pain that persisted was frequently not incisional, but rather was related to chest tubes. Lesions applied to the ilioinguinal nerves in patients having hernia repairs also reduced postoperative analgesic requirements. [343] Residual neuropathic pain has been seen following cryoanalgesia.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) (Ch. 70) , widely used to manage chronic pain, can also be used to provide perioperative analgesia. Advantages include absence of opioid-induced side effects such as respiratory depression, sedation, nausea and vomiting, and urinary retention. The technique is simple, noninvasive, and free of toxicity. An element of patient participation and control is provided.

Patients receive information and instruction in the use of the stimulator preoperatively. Using a stimulator that generates an asymmetric, biphasic wave form, initial settings for current output (range, 12-20 mA), stimulus frequency (range, 10-100 Hz), and pulse width (range, 60-150 mus) are selected to produce a vibrating, tingling, soothing sensation that itself is not painful. Immediately after wound closure, sterile adhesive electrodes are applied to the skin on either side of the incision. The wound is dressed, and the electrodes are connected to the stimulator. Stimulation is started using the predetermined settings, with subsequent adjustments on a trial-and-error basis to produce maximum benefit.

The mechanism by which analgesia is produced with TENS is not known. It may be the result of modulation of nociceptive impulses in the spinal cord as predicted by the gate-control theory postulated by Melzack and Wall, [344] activation of inhibitory reflex areas in the brain stem, [345] stimulation of the release of endorphins, or a combination of these and other mechanisms. A placebo effect may also play a role.

Although TENS remains promising, controversy exists regarding its efficacy in relieving perioperative pain, its effect on opioid requirements, and its ability to attenuate expected decrements in pulmonary function. [346] [347] It may facilitate rehabilitation after knee surgery, [348] and it has been reported to benefit patients with protracted ileus after abdominal surgery or trauma. [349] Complications are uncommon. Skin irritation from gel or adhesives at the electrode sites may occur, but it is rarely serious. The presence of cardiac pacemakers and pregnancy in the first trimester are considered contraindications by some clinicians. [346] TENS has been widely used for managing the pain of labor.

Perioperative TENS has been used for purposes other than treatment of incisional pain. TENS applied to the arms of women following total abdominal hysterectomy resulted in approximately 50 percent less vomiting compared with a group having an inactive TENS unit. The two groups were not significantly different after TENS discontinued. [350] Patients with high-intensity TENS reported a 50 percent reduction in mean pain levels compared with controls during distention shoulder arthrography. [351]

Psychologic and Other Methods

Following surgery, patients may suffer "discomfort" from causes unrelated to their incisions. Some of these causes may be physical such as headaches or sensations arising from nasogastric tubes, surgical drains, and intravenous catheters. Others may be the result of nonorganic causes such as anxiety, fear, or insomnia. Therapy for these latter problems can enhance patients' overall sense of well-being and, in some cases, may result in reporting of less "pain." One novel approach involved allowing postoperative patients to self-administer midazolam from a PCA pump. [153] [154]

Some studies have shown that psychologic support in the form of preoperative discussion, reassurance, and provision of information results in less anxiety, less opioid use after surgery, and a shorter hospital stay compared with control groups. [38] [39] [40] Relaxation tapes used by patients prior to surgery also result in reduced analgesic use and a smoother recovery. [352] Hospitals are usually designed for the convenience of the staff and sometimes leave patients feeling "depersonalized" and helpless. Measures that restore freedom, control, and participation in care, even involving simple self-care tasks, are likely to be beneficial. [353] The use of psychologic and other nonpharmacologic methods in combination with conventional analgesics is one approach to multimodal therapy.

PERIOPERATIVE ANALGESIA IN SPECIAL POPULATIONS

Pediatric Patients

As is the case for adults, the treatment of perioperative pain in infants and children may often be inadequate [354] [355] [356] (Ch. 59) . Misconceptions about pain in children are common. They include the belief that children do not feel pain, and that if it is felt it is not remembered. There is no

scientific basis for these attitudes. Pain causes suffering and physiologic abnormalities in children similar to those that occur in adults. This is also true for neonates [357] and for the preterm infant undergoing surgery. [358]

Compared with adults, pediatric surgical patients present some unique problems. In the neonate, safe methods for providing analgesia have been lacking. Opioid clearance is prolonged compared with older children, and infants are apparently more prone to opioid-induced respiratory depression. Because of developmental, cognitive, and emotional differences, the assessment of pain in pediatric patients can be more difficult. Special scales are available to assist young children in self-reporting of pain. In preverbal children, or in those who cannot or will not self-report, the interpretation of behavior must be used to estimate pain intensity. Frequently, these observations are unstructured and are open to misinterpretation. When clear evidence of pain is not seen, the tendency has been to assume that it is not present and to defer treatment.

Fear of needles makes intramuscular injection of opioids less acceptable to children than to adults. Children may choose to suffer in silence knowing that an expression of pain will result in a dreaded injection. In an effort to overcome these problems and to improve the quality of analgesia for pediatric patients, alternatives are being sought to the intramuscular opioid approach. Sublingual, rectal, and transdermal routes are under investigation. With availability of well-trained nurses and structured, medically supervised programs, many of the techniques now available for adults may have a place in pediatric populations.

Carefully titrated intravenous opioid boluses or infusions avoid unpleasant intramuscular injections and produce rapid pain relief, [359] whereas self-administration of small intravenous opioid boluses (PCA) has proved effective in children and adolescents. [360] [361] [362]

Epidural opioid analgesia using a caudal approach can be used to provide effective perioperative analgesia in children. [363] The risks and side effects of this technique are similar to those seen in adults.

Regional anesthetic techniques in some circumstances can offer effective and safe analgesia for pediatric patients after surgery. Dorsal nerve block of the penis or application of lidocaine jelly or aerosol spray provide comfort after circumcision. [364] Emla cream, in addition to providing postoperative analgesia, has been used to provide anesthesia for circumcision. Iliohypogastric and ilioinguinal nerve blocks performed with bupivacaine by the surgeon through the open wound reduce pain after herniorrhaphy or orchiopexy. [365] Infusion of bupivacaine through pleural catheters in children can be effective in controlling post-thoracotomy pain. [366] Other nerve blocks that have been effective after surgery in adults may also have applications in pediatric practice.

Parenteral [367] and oral [368] NSAIDs for postoperative analgesia in pediatric patients have been evaluated. As in adults, these agents are best considered as adjuncts rather than as primary agents for the treatment of moderate or severe postoperative pain.

Elderly Patients

Geriatric patients represent the most rapidly growing segment of the U.S. population (Ch. 61) . The chance of developing surgically treatable disease also increases with age. Thus, it can be expected that the average age of surgical patients will increase in the future and that a higher proportion of patients seen in an operating room will fall into the geriatric category.

Older patients facing surgery can generally be expected to have more complex cases than their younger counterparts. They have more systemic diseases (e.g., cardiac, pulmonary, endocrine), and usually those diseases have advanced to more serious stages. These patients may suffer disability, both physical and mental, and they frequently bring different attitudes and expectations about their treatment to the hospital with them. For example, some older patients are likely to be reluctant to play an active role in their own therapy, thus making some contemporary forms of analgesia (e.g., PCA, PCEA) ineffective. Communication in some elderly patients may present challenges. In the confused or speech-deprived patient, or in the patient displaying a high degree of stoicism, assessment of pain relief therapy becomes more difficult.

Physicians and nurses treating geriatric patients tend to have an unfounded level of fear of complications associated with treating perioperative pain. Although it is known that inadequate analgesia may delay recovery, the treatment of perioperative pain in the geriatric patient remains inadequate, even relative to younger patients. [369] [370] It is known that pain is reported less in the elderly. However, do older patients have a different pain threshold than young patients? Limited information derived under experimental and clinical conditions is available to address this question. [371] [372] [373] [374] [375]

It is well established that there is increased responsiveness to the effects of opioids in the elderly. This may mean that the risk of respiratory depression is increased. [51] The risk of nausea may not increase. [376] Increased sensitivity of older patients to systemic opioids probably involves both pharmacokinetic factors (changes in drug distribution) and pharmacodynamic factors (increased response at opioid receptor sites). Although the mechanisms causing differences in the elderly may be complex, the clinical implications are not. They include slow titration of opioids to allow for long circulation times, lower total doses because of increased sensitivity, and expectation of a longer duration of action because of reduced clearance.

NSAIDs may have benefits for some elderly patients after surgery just as they do for younger patients. These benefits include a peripheral site of action that may be more effective than opioids for some types of pain, opioid sparing when they are used in conjunction with an opioid, and an additional anti-inflammatory effect. However, elderly patients may also be at additional risk for side effects based on decreased renal clearance. It is therefore prudent to decrease the doses of NSAIDs in elderly patients as recommended by the manufacturers and also to limit the duration of use.

As discussed earlier in this chapter, dose requirements for epidural morphine [177] (and probably other opioids) are reduced. Possible reasons for these reduced requirements in older patients include increased responsiveness of spinal cord opioid receptors, higher CSF morphine levels, [377] decreased effectiveness of neural barriers, and overall decline in function of the CNS with age.

Regional anesthesia offers a number of advantages to many patients, particularly the elderly, during and after surgery. These advantages include minimizing physiologic trespass, pharmacologic simplicity, reduced blood loss, fewer thromboembolic complications, reduced endocrine-metabolic stress response, less confusion, and less postoperative pain. The response to local anesthetics in geriatric patients differs from that in the young. Most of these differences can be explained by progressive changes in the nervous system with age. Several clinical studies confirm that dose requirements for local anesthetics decline as age increases. [378] [379] [380]

In the elderly patient, postoperative delirium (POD) is a common complication associated with negative outcomes. [381] It is also a reliable marker for acute onset of underlying medical problems and possibly for underlying dementia. POD has been defined as a transient organic mental syndrome characterized by a global disorder of attention and cognition, a reduced level of consciousness, abnormally increased or decreased psychomotor activity, and a disturbed sleep-wake cycle. The main aspects of cognition, perception, and memory are all distorted, hence the term *global disorder.*

The reported incidence of postoperative delirium in the elderly varies between 7 and 61 percent. It appears to be more common after orthopaedic surgery than after general or cardiovascular surgery. It most commonly appears on postoperative day 3 or 4. Hallucinations are present in about 40 percent of patients and are commonly visual and frightening. Negative outcomes associated with POD include increased length of hospital stay, increased demands on treatment resources, poorer postdischarge functional outcome, and increased risks associated with patients' noncompliance with postoperative care. It is obvious that approaches to postoperative analgesia in the elderly that minimize the risk of POD have the potential to improve outcome. Many causes of POD have been identified, including a collection of metabolic, toxic, environmental, or infectious insults.

Patients With Chronic Pain and/or Chronic Opioid Use

Over the past decade, there has been an increase in the interest of anesthesiologists in the management of perioperative pain (Ch. 70) . However, as has been true in the past, many fewer in the specialty wish to participate in the treatment of chronic pain. Those who already manage perioperative pain realize that it is not always possible, even if it were desirable, to separate these areas of practice completely. Patients with underlying cancer pain commonly face surgery. The patient with chronic low back pain may require relief of surgical pain following a laminectomy. Such examples represent some of the potentially most complex and challenging patients the therapist treating postoperative pain will encounter. It is of practical importance to distinguish basic differences between acute and chronic pain (Table 69-10) . In particular, it should be noted that perioperative pain is usually of short duration and in general is appropriately and effectively treated with opioid analgesics.

TABLE 69-10 -- Comparison of Acute and Chronic Pain

ACUTE PAIN	CHRONIC PAIN
Signal of organic disease process	No useful function served
Cause usually obvious	Cause often unclear
Disappearing with treatment of the cause	Often unresponsive to many forms of therapy
Opioids typically indicated and effective	Opioids rarely indicated or effective
Usually no secondary gains	Secondary gains common

When perioperative pain is encountered in patients with underlying chronic pain, standard approaches to assessment and therapy may be inadequate. Although each patient is a unique human being, a number of general principles involving pain assessment and treatment can be applied: (1) expect high self-reported pain scores; these are common in patients with chronic pain; (2) base treatment decisions primarily on objective pain assessment (ability to deep breath, cough, ambulate); (3) recognize and treat nonnociceptive sources of suffering (e.g., provide an anxiolytic for anxiety); (4) and when opioids are used, continue them for as long as is appropriate for acute pain; avoid extended therapy if it is not appropriate for a concomitant chronic condition.

Any patient with chronic pain can be difficult to manage when acute pain is experienced. The difficulty can be expected to increase when, in addition, patients have been chronic users of opioids, whether for legitimate reasons (e.g., control of cancer pain) or for illegitimate reasons. Greatest difficulty can be expected in the street drug user who requires surgery. In dealing with chronic opioid use, several pharmacologic terms are commonly misused. This practice can lead to misunderstanding and inappropriate treatment decisions. The following definitions should be familiar to all therapists managing pain.

Tolerance is a pharmacologic property of many opioids (and other drugs). It can be defined as less susceptibility to the effects of the drug as a consequence of its prior administration. Clinically, in relation to the treatment of pain with opioids, tolerance is manifested as a pattern of increasing dose requirement to maintain a given level of analgesia. Special caution is needed in dealing with "incomplete cross-tolerance" seen in patients with cancer pain when one opioid is replaced with another. [382] After calculating the equivalent dose of the replacing opioid, therapy should begin with about 50 percent of that amount. The same caution is likely warranted in patients using substantial doses of opioids chronically for noncancer pain.

Physical dependence is another pharmacologic property of opioids characterized by the occurrence of an abstinence syndrome after abrupt discontinuation of the drug or administration of an antagonist. Although it is often associated with signs of tolerance, the emergence of a withdrawal syndrome alone is sufficient reason to use this term. The labels of pharmacologic tolerance and physical dependence do not imply the aberrant psychologic state or behaviors of the addicted patient. *Addiction* is a chronic disorder characterized by the compulsive use of a substance resulting in physical,

psychologic, or social harm to the user and continued use despite that harm.

Patients with a background of chronic opioid use may or may not be clinically obvious. [383] [384] The clinician should consider the possibility of these conditions when the following clinical triad is seen: (1) high self-reported pain scores compared with other patients having similar procedures; (2) high opioid use compared with other patients having similar procedures; (3) a relative absence of opioid-induced side effects. [385]

A number of principles can be applied to the treatment of perioperative pain in patients with chronic opioid use:

1. Recognize the need to identify and treat two major problems: maintenance of a basal opioid requirement and control of incisional pain.
2. Discuss the treatment plan with the patient early (before surgery, if possible); repeat it often.
3. Make it clear that the patient will receive basal opioid replacement unconditionally and irrespective of pain reports.
4. Add appropriate short-term therapy for acute pain.
5. Choose a non-opioid-based approach (e.g., local anesthetic, NSAID) to treat the acute pain whenever possible.
6. Expect high subjective pain scores. Do not rely on them to guide therapy.
7. Recognize that detoxification is usually not an appropriate goal in the perioperative period.

Is there a role for PCA in patients with chronic opioid use? Probably not for the purpose of providing basal opioid replacement. This is usually better accomplished by fixed oral doses or intravenous infusions controlled by the therapist. There probably is a role for short-term PCA in selected patients to provide extra opioids needed for postoperative pain. It is worth recalling that the central premise for successful PCA therapy is based on a simple assumption: that a feedback loop exists such that when pain is present, the patient will self-administer opioids; when pain is relieved, self-administration will cease. It is worth considering, on a patient-by-patient basis, whether this loop is likely to be intact. The advantages of placing "control" in the hands of opioid-naive patients with postoperative pain become liabilities if the basic loop does not exist. Under such circumstances, it is probably best to retain "control" of all analgesic administration in the hands of the therapist.

/das/book/view/29494766/875/761.html

ROLE OF THE ANESTHESIOLOGIST IN PERIOPERATIVE PAIN MANAGEMENT

Anesthesiologists are a logical choice to provide perioperative pain relief. They are familiar with the pharmacology of analgesics and local anesthetics, are aware of the short- and long-term effects of drugs given intraoperatively, are knowledgeable about pain pathways and their interruption, and are skilled in techniques available to provide superior pain control. Management of postoperative pain by anesthesiologists can be professionally rewarding. Expressions of gratitude from patients free from pain can contribute to feelings of self-esteem and job satisfaction. Additional contact with patients, nurses, other physicians, and administrators helps to define anesthesiologists as valued consultants outside the operating room. Provision of perioperative analgesia is highly compatible with the emerging identity of anesthesiologists as "perioperative physicians."

PERIOPERATIVE PAIN MANAGEMENT SERVICES

Although dedicated individuals can improve perioperative pain control for a few patients, more comprehensive programs developed specifically to treat this problem can provide for the needs of all patients within an institution. Such programs, developed and administered by anesthesiologists, are now widely reported. [19] [20] [21] [22] [23] [24] [26] [27] [28] [29] [30] [31] [32] [34] [35] [386] [387] [388] [389] [390]

The organizational aspects of such comprehensive services are considerable but necessary for effective, safe care (Table 69-11) (Table Not Available) . In-service training for nursing staff is essential before the introduction of new pain-relieving techniques or equipment (e.g., PCA pumps, epidural analgesic infusions). Written nursing protocols and procedures, appropriate preprinted standard orders, and didactic and practical teaching sessions require time, but they are necessary for effective, safe care. Most hospital systems support nursing educators who can assist in this work. By involving nurses early and by inviting their participation in the development of a perioperative pain program, enthusiasm and support are likely to be strong.

Surgeons may be reluctant to allow other physicians to assume responsibility for pain management. Departmental

TABLE 69-11 -- Organizational Aspects of an Anesthesiology-Based Perioperative Pain Program

(Not Available)

Modified from Ready et al [36]

conferences and individual discussion are useful to inform them of the potential benefits to their patients of a perioperative pain service. To avoid potentially dangerous duplication, it is necessary to establish that all pain-related orders, including orders for sedatives, hypnotics, and other CNS depressants, become the responsibility of the pain service.

It is essential that human resources within an anesthesiology department are available at all times to provide coverage for perioperative pain management. The condition of patients after major surgery can change rapidly, requiring reevaluation of many aspects of care including pain relief. It is difficult to meet such needs if the individuals providing care are concurrently assigned to operating rooms.

When professional time is committed to a new clinical activity, financial compensation for that time must be considered. There is a strong medical tradition to support the concept that professional fees for services should be provided to specialists whose knowledge and skills are necessary to treat complex medical problems optimally. Just as critical care anesthesiologists collect professional fees for managing patients on mechanical ventilators after surgery, it is also reasonable to collect professional fees for perioperative pain management. It is the responsibility of those who treat perioperative pain to develop fair and reasonable charges for the care they provide and perhaps in the future to find creative ways to include perioperative pain management in comprehensive health care packages.

Various interactions characterize the daily operation of an in-hospital perioperative pain service. In addition to those already discussed, they include meetings with pharmacists, hospital administrators, suppliers of special equipment and drugs, health care providers, and government agencies. Additional details are contained in the ASA practice guidelines for acute pain management in the perioperative setting. [36] It is gratifying to note that in a survey of 500 institutions of 100 or more beds in the United States, 73 percent of respondents indicated that they had an anesthesiology-based acute pain service. [35] An international view of anesthesiology-based acute pain services is available to interested readers. [390]

References

1. Nageman J: Measurement and control of postoperative pain. Ann R Coll Surg Engl 6:419, 1979.

2. Bonica JJ: Current status of postoperative pain therapy. In Yokota T, Dubner R (eds): Current Topics in Pain Research and Therapy. Amsterdam, Excerpta Medica, 1983, p 169.

3. Carr DB, Jacox AK, Chapman RC et al: Clinical Practice Guideline: Acute Pain Management: Operative or Medical Procedures and Trauma. Rockville, Md, Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, 1992.

4. Papper EM, Brodie BB, Rovenstine EA: Postoperative pain: Its use in the comparative evaluation of analgesics. Surgery 32:107, 1952.

5. Cronin M, Redfern PA, Utting JE: Psychometry and postoperative pain complaints in surgical patients. Br J Anaesth 45:879, 1973.

6. Cohen FL: Postsurgical pain relief: Status and nurses' medication choices. Pain 9:269, 1980.

7. Donovan BD: Patient attitudes to postoperative pain relief. Anaesth Intensive Care 11:125, 1983.

8. Sriwatanakul K, Weiss OF, Alloza JL et al: Analysis of narcotic analgesic usage in the treatment of postoperative pain. JAMA 250:926, 1983.

9. Weiss OF, Sriwatanakul K, Alloza JL et al: Attitudes of patients, housestaff, and nurses toward postoperative analgesic care. Anesth Analg 62:70, 1983.

10. Wilder-Smith CH, Schuler L: Postoperative analgesia: Pain by choice? The influence of patient attitudes and patient education. Pain 50:257, 1992.

11. Wilson JF, Brockopp GW, Kryst S et al: Medical students' attitudes toward pain before and after a brief course on pain. Pain 50:251, 1992.

12. Abbott FV, Gray-Donald K, Sewitch MJ et al: The prevalence of pain in hospitalized patients and resolution over six months. Pain 50:15, 1992.

13. Rose DK, Cohn MM, Yee DA: Postoperative pain control: How are we doing? Anesth Analg 76:S355, 1993.

14. Warfield CA, Kahn CH: Acute pain management: programs in U.S. hospitals and experiences and attitudes among U.S. adults. Anesthesiology 83:1090, 1995.

15. Green CR, Cross R, Tait A: Anesthesiology house officers' attitudes regarding the management of acute postoperative pain: Results of a pilot survey. Anesth Analg 80-S1:S159, 1995.

16. Finley GA, McGrath PJ, Forward SP et al: Parents' management of childrens' pain following 'minor' surgery. Pain 64:83, 1996.

17. McGrath PJ, Frager G: Psychological barriers to optimal pain management in infants and children. Clin J Pain 12:135, 1996.

18. Breitbart W, Rosenfeld BD, Passik SD et al: The undertreatment of pain in ambulatory AIDS patients. Pain 65:243, 1996.

19. Ready LB, Oden R, Chadwick HS et al: Development of an anesthesiology-based postoperative pain management service. Anesthesiology 68:100, 1988.

20. Ramsey DH: Perioperative pain: establishing an analgesia service. In Brown DL (ed): Problems in Anesthesia: Perioperative Analgesia. Philadelphia, JB Lippincott, 1988, p 321.

21. Berde C, Sethna NF, Masek B et al: Pediatric pain clinics: Recommendations for their development. Pediatrician 16:94, 1989.

22. Macintyre PE, Runciman WB, Webb RK: An acute pain service in an Australian teaching hospital: The first year. Med J Aust 153:417, 1990.

23. Cartwright PD, Helfinger RG, Howell JJ et al: Introducing an acute pain service: Department of Anaesthesia, Princess Royal Hospital, Telford. Anaesthesia 46:188, 1991.

24. Wenrich J: Acute pain service in a community hospital. J Post Anesth Nurs 6:324, 1991.

25. Rawal N: Postoperativ Smarta Och Dess Behandling. Orebro, Kabi Pharmacia, 1991.

26. VadeBoncouer TR, Ferrante FM: Management of a postoperative pain service in a teaching hospital. In Ferrante FM, VadeBoncouer TR (eds): Postoperative Pain Management. New York, Churchill Livingstone, 1993, p 625.

27. Zimmermann DL, Stewart J: Postoperative pain management and acute pain service activity in Canada. Can J Anaesth 40:568, 1993.

28. Salomaki TE, Laitinen JO, Nuutinen LS: Postoperative pain management on wards: Finnish experience. Acta Anaesthesiol Scand Suppl 37:9, 1993.

29. Schug SA, Haridas RP: Development and organizational structure of an acute pain service in a major teaching hospital. Aust N Z J Surg 63:8, 1993.

30. Delilkan AE, Vijayan R: Experience with an acute pain service in a developing country. In Abstracts of the 7th World Congress on Pain. Seattle, Wash, IASP Publications, 1993, p 395.

31. Judge M, Merry AF: The assessment of the impact of the introduction of an acute pain management service. Abstracts of the 7th World Congress on Pain. Seattle, Wash, IASP Publications, 1993, p 398.

32. Breivik H, Hogstrom H, Curatoto M et al: Developing a hospital-wide postoperative pain service. Acta Anaesthesiol Scand Suppl 37:223, 1993.

33. Mackey DC, Ebener MK, Howe BL: Patient-controlled analgesia and the acute pain service in the United States: health-care financing administration policy is impeding optimal patient-controlled analgesia management (letter). Anesthesiology 83:433, 1995.

34. Rawal N: Acute pain services in Europe: A 17-country survey. Reg Anesth 20(suppl 2):85, 1995.

35. Ready LB: How many acute pain services are there in the United States and who is managing patient-controlled analgesia? (letter). Anesthesiology 82:322, 1995.

36. Ready LB, Ashburn M, Caplan RA et al: Practice guidelines for acute pain management in the perioperative setting: A report by the American Society of Anesthesiologists task force on pain management, acute pain section. Anesthesiology 82:1071, 1995.

37. Merskey H, Albe-Fessard DG, Bonica JJ: Pain terms: A list with definitions and notes on usage. Pain 6:249, 1979.

38. Egbert LD, Battit GE, Turndorf H et al: The value of the preoperative visit by an anesthesiologist. JAMA 185:553, 1963.

39. Egbert LD, Battit GE, Welch CE et al: Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med 270:825, 1964.

40. Schmitt FE: Psychological preparation in surgical patients. Nurs Res 22:108, 1973.

41. Johnson M: Anxiety in surgical patients. Psychol Med 10:145, 1980.

42. Chapman CR: Psychological factors in postoperative pain and their treatment. In Covina B, Smith G (eds): Acute Pain. London, Butterworth International Medical Reviews, 1985, p 22.

43. Egan KJ: Psychological issues in postoperative pain. In Oden RV (ed): Anesthesiology Clinics of North America. Philadelphia, WB Saunders, 1989, p 183.

44. Badner NH, Nielson WR, Munk S et al: Preoperative anxiety: Detection and contributing factors. Can J Anaesth 37:444, 1990.

45. Duggan J, Drummond GBF: Activity of lower intercostal and abdominal muscle after surgery in humans. Anesth Analg 66:852, 1987.

46. Ford GT, Whitelaw WA, Rosenal TW: Diaphragm function after upper abdominal surgery in humans. Am Rev Respir Dis 127:431, 1983.

47. Miller RR, Greenblatt DJ: Drug Effects in Hospitalized Patients. New York, John Wiley & Sons, 1976.

48. Reiz S, Westberg M: Side-effects of epidural morphine. Lancet 2:203, 1980.

49. Catley DM, Thornton C, Jordan C et al: Postoperative respiratory depression associated with continuous morphine infusion. Br J Anaesth 54:235, 1982.

50. Gustafsson LL, Schildt B, Jacobsen KJ: Adverse effects of extradural and intrathecal opiates: Report of a nationwide survey in Sweden. Br J Anaesth 54:479, 1982.

51. Catley DM, Thornton C, Jordon C et al: Pronounced, episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. Anesthesiology 63:20, 1985.

52. Turner K, Sandler AN, Vosu H et al: Respiratory pattern in post-caesarean patients after epidural or intramuscular morphine. Anesth Analg 68:S296, 1989.

53. Rosaeg OP, Suderman V, Yarnell RW: Early respiratory depression during cesarean section following epidural meperidine. Can J Anaesth 39:71, 1992.

54. Cohn SE, Labaille T, Benhamou D et al: Respiratory effects of epidural sufentanil after cesarean section. Anesth Analg 74:677, 1992.

55. Zikowski D, Hord AH, Haddox JD et al: Ketorolac-induced bronchospasm. Anesth Analg 76:417, 1993.

56. Modig J: Thromboembolism and blood loss: continuous epidural versus general anesthesia with controlled ventilation. Reg Anesth 7:S84, 1982.

57. Beattie WS, Buckley DN, Forrest JB: Epidural morphine reduces the risk of postoperative myocardial ischaemia in patients with cardiac risk factors. Can J Anaesth 40:532, 1993.

58. Kock M, Blomberg S, Emanuelsson H et al: Thoracic epidural anesthesia improves global and regional left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease. Anesth Analg 71:625, 1990.

59. Kowalewski RJ, MacAdams CL, Eagle CJ et al: Anaesthesia for coronary artery bypass surgery supplemented with subarachnoid bupivacaine and morphine: A report of 18 cases. Can J Anaesth 41:1189, 1994.

60. Bonica JJ: The Management of Pain. Philadelphia, Lea & Febiger, 1953.

61. Gelman S, Feigenberg Z, Dintzman M et al: Electroenterography after cholecystectomy. Arch Surg 112:580, 1977.

62. Rawal N, Sjostrand U, Christoffersson E et al: Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: Influence on postoperative ambulation and pulmonary function. Anesth Analg 63:583, 1984.

63. Scheinin B, Asantila RRO: The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. Acta Anaesthesiol Scand 31:161, 1987.

64. Thoren T, Sundberg A, Wattwil M et al: Effects of epidural bupivacaine and epidural morphine on bowel function and pain after hysterectomy. Acta Anaesthesiol Scand 33:181, 1989.

65. Borkowski RG, Mekhail N: Advantages of epidural analgesia in upper abdominal surgery. Reg Anesth 20(suppl 2):49, 1995.

66. Liu SS, Carpenter RL, Mackey DC et al: Effects of perioperative analgesic technique on rate of recovery after colon surgery. Anesthesiology 83:757, 1995.

67. Cepeda MS, Carr DB: The stress response and regional anesthesia. In Brown DL (ed): Regional Anesthesia and Analgesia. Philadelphia, WB Saunders, 1996, p 108.

68. Kehlet H: Pain relief and modification of the stress response. In Cousins MJ, Phillips GD (eds): Acute Pain Management. New York, Churchill Livingstone, 1986, p 49.

69. Stevens RA, Beardsley D, White JL et al: Does the choice of local anesthetic affect the catecholamine response to stress during epidural anesthesia? Anesthesiology 79:1219, 1993.

70. Harukuni I, Yamaguchi H, Sata S et al: The comparison of epidural fentanyl, epidural lidocaine, and intravenous fentanyl in patients undergoing gastrectomy. Anesth Analg 81:1169, 1995.

71. Kissin I: Preemptive analgesia: Why its effect is not always obvious (editorial). Anesthesiology 84:1015, 1996.

72. Woolf CJ: Recent advances in the pathophysiology of acute pain. Br J Anaesth 63:139, 1989.

73. McQuay HJ, Dickenson AH: Implications of nervous system plasticity for pain management. Anaesthesia 45:101, 1990.

74. McQuay HJ, Carroll D, Moore RA: Postoperative orthopaedic pain: The effect of opiate premedication and local anaesthetic blocks. Pain 33:291, 1988.

75. Bach S, Noreng MF, Tjellden NU: Phantom limb in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 33:297, 1988.

76. Tverskoy M, Cozacov C, Ayache M et al: Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. Anesth Analg 70:29, 1990.

77. Kavanagh BP, Katz J, Sandler AN et al: Pain and narcotic use following thoracic surgery are reduced by preemptive lumbar epidural fentanyl: A randomized, prospective, double-blind crossover

study. Can J Anaesth 39:A79, 1992.

78. Ejlersen E, Andersen HB, Eliasen K et al: A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. Anesth Analg 74:495, 1992.

79. Katz J, Kavanaugh BP, Sandler AN et al: Preemptive analgesia: Clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology 77:439, 1992.

80. Seltzer J, Greek R, Maurer P et al: The preemptive analgesic effect of regional anesthesia for shoulder surgery. Anesthesiology 79:A815, 1993.

81. Roytblat L, Korotkoruchko A, Katz J et al: Postoperative pain: The effect of low-dose ketamine in addition to general anesthesia. Anesth Analg 77:1161, 1993.

82. Katz J, Clairoux M, Kavanagh BP et al: Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient-controlled morphine consumption after lower abdominal surgery. Pain 59:395, 1994.

83. Negre I, Gueneron JP, Jamali SJ et al: Preoperative analgesia with epidural morphine. Anesth Analg 79:298, 1994.

84. Jahangiri M, Jayatunga AP, Bradley JW et al: Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. Ann R Coll Surg Engl 76:324, 1994.

85. Shir Y, Raja SN, Frank SM: The effect of epidural versus general anesthesia on postoperative pain and analgesic requirements in patients undergoing radical prostatectomy. Anesthesiology 80:49, 1994.

86. Code WE, Yip RW, Rooney ME et al: Preoperative naproxen sodium reduces postoperative pain following arthroscopic knee surgery. Can J Anaesth 41:98, 1994.

87. Gwirtz KH, Beckes KA, Maddock RP et al: Subarachnoid opioid analgesia reduces long-term postsurgical pain after nephrectomy. Reg Anesth 19:89, 1994.

88. Salcedo E, Shay P, Berrigan M et al: The pre-emptive analgesic effect of interscalene block prior to shoulder surgery. Reg Anesth 21, 2S:107, 1996.

89. Pasqualucci A, De Angelis V, Contardo R et al: Preemptive analgesia: Intraperitoneal local anesthetic in laparoscopic cholecystectomy. Anesthesiology 85:11, 1996.

90. Katz J, Jackson M, Kavanagh BP et al: Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 12:50, 1996.

91. Clairoux M, Katz J, Kavanagh B et al: Does the timing of a high lumbar epidural local anaesthetic before or after incision for abdominal surgery have any effects on post-operative pain or analgesic requirements? Anesthesiology 79:A911, 1993.

92. Victory RA, Gajraj N, Van Elstraete A et al: Pre-emptive analgesia fails to decrease pain following hysterectomy. Anesthesiology 79:A902, 1993.

93. Johansson B, Glise H, Hallerback B et al: Preoperative local infiltration with ropivacaine for postoperative pain relief after cholecystectomy. Anesth Analg 78:210, 1994.

94. Abdulatif M, Al-Ghambi A, Gyamfi YA et al: Can pre-emptive interpleural block reduce perioperative anesthetic and analgesic requirements? Reg Anesth 20:296, 1995.

95. Fassoulaki A, Sarantopoulos C, Zotou M: Preemptive opioid analgesia does not influence pain after abdominal hysterectomy. Can J Anaesth 42:109, 1995.

96. Taguchi N, Watanabe S, Sato Y et al: Epidural morphine neither 2 mg nor 4 mg provides pre-emptive analgesic effect for post abdominal hysterectomy pain. Anesth Analg 80(suppl 1):S488, 1995.

97. Dakin MJ, Osinubi OYO, Carli F: Preoperative spinal bupivacaine does not reduce postoperative morphine requirement in women undergoing total abdominal hysterectomy. Reg Anesth 21:99, 1996.

98. Sarantopoulos C, Fassoulaki A: Sufentanil does not preempt pain after abdominal hysterectomy. Pain 65:273, 1996.

99. Coderre TJ, Katz J, Vaccarino AL et al: Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 52:259, 1993.

100. Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 77:1048, 1993.

101. Woolf CJ, Chong M-S: Preemptive analgesia: Treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:362, 1993.

102. Schug SA, Burrell R, Payne J et al: Pre-emptive epidural analgesia may prevent phantom limb pain (letter). Reg Anesth 20:256, 1995.

103. Moiniche S, Dahl JB, Rosenberg J et al: Colonic resection with early discharge after combined subarachnoid-epidural analgesia, preoperative glucocorticoids, and early postoperative mobilization and feeding in a pulmonary high-risk patient. Reg Anesth 19:352, 1994.

104. Austin KL, Stapleton JV, Mather LE: Relationship between blood meperidine concentrations and analgesic response. Anesthesiology 53:460, 1980.

105. Austin KL, Stapleton JV, Mather LE: Multiple intramuscular injections: A major source of variability in analgesia response to meperidine. Pain 8:47, 1980.

106. Belville JW, Forrest WH, Miller E et al: Influence of age on pain relief from analgesics. JAMA 217:1835, 1971.

107. Brose WG, Cohn SE: Oxyhemoglobin saturation following cesarean section in patients receiving epidural morphine, PCA, or IM meperidine analgesia. Anesthesiology 70:948, 1989.

108. Catling JA, Pinto DM, Jordan C et al: Respiratory effects of analgesia after cholecystectomy: Comparison of continuous and intermittent papaveretum. BMJ 281:478, 1980.

109. Gourlay GK, Wilson PR, Glynn CJ: Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology 57:485, 1982.

110. Derchwitz M, Randel GI, Rosow CE et al: Initial clinical experience with remifentanil, a new opioid metabolized by esterases. Anesth Analg 81:619, 1995.

111. Hogue CW, Bowdle TA, O'Leary C et al: A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery. Anesth Analg 83:279, 1996.

112. Caplan RA, Ready LB, Oden RV et al: Safety and efficacy of transdermal fentanyl for postoperative pain management: A double-blind study. JAMA 261:1036, 1989.

113. Preston KL, Jasinki DR, Testa M: Abuse potential and pharmacological comparison of tramadol and morphine. Drug Alcohol Depend 27:7, 1991.

114. Houmes R-JM, Voets MA, Verkaaik A et al: Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg 74:510, 1992.

115. Mays KS, Lipmann JJ, Schnapp M: Local analgesia without anesthesia using peripheral neural morphine injections. Anesth Analg 66:417, 1987.

116. Bullingham RES, O'Sullivan G, McQuay HJ et al: Peripheral injection of morphine fails to relieve postoperative pain in humans. Anesth Analg 62:164, 1983.

117. Dahl JB, Daugaard JJ, Kristoffersen E: Perineural morphine: A comparison with epidural morphine. Anaesthesia 43:463, 1988.

118. Forrest WH, Smethurst PWR, Kienitz ME: Self-administration of intravenous analgesics. Anesthesiology 33:363, 1970.

119. Sechzer PH: Studies in pain with the analgesic-demand system. Anesth Analg 50:1, 1971.

120. Keeri-Szanto M: Apparatus for demand analgesia. Can J Anaesth 18:581, 1971.

121. White WD, Pearce DJ, Norman J: Postoperative analgesia: A comparison of intravenous on-demand fentanyl with epidural bupivacaine. BMJ 2:166, 1979.

122. Tamsen A, Hartvig P, Fagerlund C: Patient-controlled analgesic therapy: Clinical experience. Acta Anaesthesiol Scand suppl 26:157, 1982.

123. Ellis R, Haines D, Shah R: Pain relief after abdominal surgery: Comparison of i.m. morphine, sublingual buprenorphine and self-administered i.v. pethidine. Br J Anaesth 54:421, 1982.

124. Welchew EA: On-demand analgesia: A double-blind comparison of on-demand intravenous fentanyl with regular intramuscular morphine. Anaesthesia 38:19, 1983.

125. Gibbs MM, Johnson HD, Davis FM: Patient administration of i.v. buprenorphine for postoperative pain relief using the Cardiff demand analgesia apparatus. Br J Anaesth 54:279, 1982.

126. White PF, Parker RK: Is the risk of using "basal" infusion with patient-controlled analgesia therapy justified? (letter) Anesthesiology 76:489, 1992.

127. Fleming BM, Coombs DW: A survey of complications documented in a quality-control analysis of patient-controlled analgesia in the postoperative patient. J Pain Symptom Manage 7:463, 1992.

128. Schug SA, Torrie JJ: Safety assessment of postoperative pain management by an acute pain service. Pain 55:387, 1993.

129. Ashburn MA, Love G, Pace NL: Respiratory-related critical events with intravenous patient-controlled analgesia. Clin J Pain 10:52, 1994.

130. Etches RC: Respiratory depression associated with patient-controlled analgesia: A review of eight cases. Can J Anaesth 41:125, 1994.

131. White PF: Use of patient-controlled analgesia for management of acute pain. JAMA 259:243, 1988.

132. Owen H, Szekely SM, Plummer JL et al: Variables of patient-controlled analgesia. II. Concurrent infusion. Anaesthesia 44:11, 1989.

133. Vinik HR, Hammonds W, Lett A et al: Patient controlled analgesia (PCA) combined with continuous infusion (CI). Anesth Analg 70:S418, 1990.

134. Sinatra R, Chung KS, Silverman DG: An evaluation of morphine and oxymorphone administered via patient-controlled analgesia (PCA) or PCA plus basal infusion in postcesarean-delivery patients. Anesthesiology 71:502, 1989.

135. Kerr IG, Sone M, DeAngelis C: Continuous narcotic infusion with patient-controlled analgesia for chronic cancer pain in outpatients. Ann Intern Med 108:554, 1988.

136. Parker RK, Holtman B, White PF: Effects of "basal" opioid infusion on the postoperative analgesic requirement. Anesthesiology 71:A256, 1990.

137. Hansen LA, Noyes MA, Lehman ME: Evaluation of patient-controlled analgesia (PCA) versus PCA plus continuous infusion in postoperative cancer patients. J Pain Symptom Manage 6:4, 1991.

138. Silverman DG, Preble LM, Paige D et al: Basal infusion as supplement to PCA in orthopedic patients. Anesth Analg 72:S256, 1991.

139. Parker RK, Holtmann B, White PF: Effects of a nighttime opioid infusion with PCA therapy on patient comfort and analgesic requirements after abdominal hysterectomy. Anesthesiology 76:362, 1992.

140. Parker RK, Holtmann B, White PF: Patient-controlled analgesia: Does a concurrent opioid infusion improve management after surgery? JAMA 266:1947, 1991.

141. Urquhart ML, Klapp K, White PF: Patient-controlled analgesia: A comparison of intravenous versus subcutaneous hydromorphone. Anesthesiology 69:428, 1988.

142. White PF: Subcutaneous-PCA: An alternative to IV-PCA for postoperative pain management. Clin J Pain 6:297, 1990.

143. Bruera E, MacMillan K, Hanson J et al: The Edmonton Injector: A simple device for patient-controlled subcutaneous analgesia. Pain 44:167, 1991.

144. Shipton EA, Beeton AG, Minkowitz HS: Introducing a patient-controlled analgesia-based acute pain service. S Afr Med J 83:501, 1993.

145. Shipton EA, Minkowitz HS, Becker PJ: PCA in burn injuries: the subcutaneous route (letter). Can J Anaesth 40:898, 1993.

146. Bruera E, Brenneis C, Michaud M et al: Patient-controlled subcutaneous hydromorphone versus continuous infusion for the treatment of cancer pain. J Natl Cancer Inst 80:1152, 1988.

147. Bruera E: The use of subcutaneous patient-controlled analgesia. J Pain Symptom Manage 4:97, 1989.

148. Swanson G, Smith J, Bulich R et al: Patient-controlled analgesia for chronic cancer pain in the ambulatory setting: A report of 117 patients. J Clin Oncol 7:1903, 1989.

149. Citron ML, Kalra J, Seltzer VL et al: Patient-controlled analgesia for cancer pain: A long-term study of inpatient and outpatient use. Cancer Invest 10:335, 1992.

150. Vanier MC, Labrecque G, Lepage-Savary D et al: Comparison of hydromorphone continuous subcutaneous infusion and basal rate subcutaneous infusion plus PCA in cancer pain: A pilot study. Pain 53:27, 1993.

151. Striebel HW, Bonillo B, Schwagmeier R et al: Self-administration of intranasal meperidine for postoperative pain management. Can J Anaesth 42:287, 1995.

152. Striebel HW, Oelmann T, Spies C et al: Patient-controlled intranasal analgesia: A method for noninvasive postoperative pain control. Anesth Analg 83:548, 1996.

153. Loper KA, Ready LB, Brody M: Patient-controlled anxiolysis with midazolam. Anesth Analg 67:1118, 1988.

154. Egan KJ, Ready LB, Nessly M et al: Self-administration of midazolam for postoperative anxiety: A double blinded study. Pain 49:3, 1992.

155. Ryan JA, Adye BA, Jolly PC et al: Outpatient inguinal herniorrhaphy with both regional and local anesthesia. Am J Surg 148:313, 1984.

156. Hashemi K, Middleton MD: Subcutaneous bupivacaine for postoperative analgesia after herniorrhaphy. Ann R Coll Surg Engl 65:38, 1983.

157. Ready LB: Anesthesia for shoulder procedures. In Rockwood CA, Matsen FA (eds): The Shoulder. Philadelphia, WB Saunders, 1990, p 247.

158. Moore DC: Intercostal nerve block for postoperative somatic pain following surgery of the thorax and upper abdomen. Br J Anaesth 47:284, 1975.

159. Reiestad F, Stromskag KE: Intrapleural catheter in the management of postoperative pain: A preliminary report. Reg Anesth 11:89, 1986.

160. Baxter AD, Jennings FO, Harris RS et al: Continuous intercostal blockade after cardiac surgery. Br J Anaesth 59:162, 1987.

161. Stromskag KE, Reistad F, Holmqvist ELO et al: Interpleural administration of 0.25%, 0.375% and 0.5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg 67:430, 1988.

162. Gomez MN, Symrent T, Johnson B et al: Intrapleural bupivacaine for intraoperative analgesia: A dangerous technique? Anesth Analg 67:S78, 1988.

163. Shantha TR: Unilateral bronchospasm after interpleural analgesia. Anesth Analg 74:291, 1992.

164. Lefever EB, Rosenthal RM, Ramamurthy S: Intrapulmonary placement of a pleural catheter. Reg Anesth 17:107, 1992.

165. Selander D: Catheter technique in axillary plexus block. Acta Anaesthesiol Scand 21:324, 1977.

166. Rosenblatt RM: Continuous femoral anesthesia for extremity surgery. Anesth Analg 59:631, 1980.

167. Smith BE, Fischer HBJ, Scott PV: Continuous sciatic nerve block. Anaesthesia 39:155, 1984.

168. Modig J: Lumbar epidural nerve blockade versus parenteral analgesics. Acta Anaesthesiol Scand (suppl) 70:30, 1978.

169. Cuschieri RJ, Morran CG, Howie JC et al: Postoperative pain and pulmonary complications: Comparison of three analgesic regimens. Br J Surg 72:495, 1985.

170. Wang JK, Nauss LA, Thomas JE: Pain relief by intrathecally applied morphine in man. Anesthesiology 50:149, 1979.

171. Behar M, Olshwang D, Magora F et al: Epidural morphine in the treatment of pain. Lancet 1:527, 1979.

172. Cousins MJ, Mather LE: Intrathecal and epidural administration of opiates. Anesthesiology 61:276, 1984.

173. Kim T, Murdande S, Gruber A et al: Sustained-release morphine for epidural analgesia in rats. Anesthesiology 85:331, 1996.

174. Stenseth R, Sellevold O, Breivik H: Epidural morphine for postoperative pain: Experience with 1085 patients. Acta Anaesthesiol Scand 29:148, 1985.

175. Yeager MP, Glass DD, Neff RK et al: Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 66:729, 1987.

176. Chadwick HS, Ready LB: Intrathecal and epidural morphine sulfate for postcesarean analgesia: A clinical comparison. Anesthesiology 68:925, 1988.

177. Ready LB, Chadwick HS, Ross B: Age predicts effective epidural morphine dose after abdominal hysterectomy. Anesth Analg 66:1215, 1987.

178. Yarnell RW, Polis T, Reid GN et al: Patient-controlled analgesia with epidural meperidine after elective cesarean section. Reg Anesth 17:329, 1992.

179. Cohn S, Amar D, Pantuck C et al: Epidural patient-controlled analgesia after cesarean section: Buprenorphine-0.015% bupivacaine with and without epinephrine. Anesth Analg 74:226, 1992.

180. Miwa Y, Yonemura E, Fukushima K: Epidural administered buprenorphine in the perioperative period. Can J Anaesth 43:907, 1996.

181. Inagaki Y, Mashimo T, Yoshiya I: Mode and site of analgesic action of epidural buprenorphine in humans. Anesth Analg 83:530, 1996.

182. Ready LB, Loper KA, Nessly M et al: Postoperative epidural morphine is safe on surgical wards. Anesthesiology 75:452, 1991.

183. Mott JM, Eisele JH: A survey of monitoring practices following spinal opiate administration. Anesth Analg 65:S170, 1986.

184. Rawal N, Wattwil M: Respiratory depression after epidural morphine: An experimental and clinical study. Anesth Analg 63:8, 1984.

185. Sechzer PH, Egbert LD, Linde HW et al: Effects of CO_2 inhalation on arterial pressure, ECG and plasma catecholamines and 17-OH corticosteroids in normal man. J Appl Physiol 15:454, 1960.

186. Davies GG, From RF: A blinded study using nalbuphine for prevention of pruritus induced by epidural fentanyl. Anesthesiology 69:763, 1988.

187. Penning JP, Samson B, Baxter AD: Reversal of epidural morphine-induced respiratory depression and pruritus with nalbuphine. Can J Anaesth 35:599, 1988.

188. Cohn SE, Ratner EF, Kreitzman TR et al: Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. Anesth Analg 75:747, 1992.

189. Cohen SE, Rothblatt AJ, Albright GA: Early respiratory depression with epidural narcotic and intravenous droperidol. Anesthesiology 59:559, 1983.

190. Loper KA, Ready LB, Dorman HB: Prophylactic transdermal scopolamine reduces nausea in postoperative patients receiving epidural morphine. Anesth Analg 68:144, 1989.

191. Kotelko DM, Rottman RL, Wright WC et al: Transdermal scopolamine decreases nausea and vomiting following cesarean section in patients receiving epidural morphine. Anesthesiology 71:675, 1989.

192. Murphy DF, MacEvilly M: Pain relief with epidural buprenorphine after spinal fusion: A comparison with intramuscular morphine. Acta Anaesthesiol Scand 28:144, 1984.

193. Montgomery CJ, Ready LB: Epidural morphine analgesia does not obscure diagnosis of compartment syndrome resulting from prolonged lithotomy position. Anesthesiology 75:541, 1991.

194. Islas J, Astorga J, Laredo M: Epidural ketamine for control of postoperative pain. Anesth Analg 64:1161, 1985.

195. Klimscha W, Brinkmann H, Plattner O et al: Epidural ketamine and clonidine after lower limb surgery. Anesthesiology 79:A805, 1993.

196. Lehmann LJ, Moffat EC, Bikhazi GB: Epidural ketamine versus fentanyl for postoperative pain after c-section. Reg Anesth 21(suppl 2):84, 1996.

197. Naguib M, Sharif AM, Seraj M et al: Ketamine for caudal analgesia in children: Comparison with caudal bupivacaine. Br J Anaesth 67:559, 1991.

198. Ravat F, Dorne R, Baechle J et al: Epidural ketamine or morphine for postoperative analgesia. Anesthesiology 66:819, 1987.

199. Kawana Y, Sato H, Shimada H et al: Epidural ketamine for postoperative pain relief after gynecologic operations: A double-blind study and comparison with epidural morphine. Anesth Analg 66:735, 1987.

200. Mori K, Shingu K: Epidural ketamine does not produce analgesia (letter). Anesthesiology 68:296, 1988.

201. Peat SJ, Bras P, Hanna MH: A double-blind comparison of epidural ketamine and diamorphine for postoperative analgesia. Anaesthesia 44:555, 1989.

202. Yang C-Y, Wong C-S, Chang J-Y et al: Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth 43:379, 1996.

203. Brock-Utne JG, Rubin J, Mankowitz E: Epidural ketamine for control of postoperative pain: Two comments (letter). Anesth Analg 65:990, 1986.

204. Schneider I, Diltoer M: Continuous epidural infusion of ketamine during labor (letter). Can J Anaesth 34:657, 1987.

205. Van der Auwera D, Verborgh C, Camu F: Epidural ketamine for postoperative analgesia (letter). Anesth Analg 66:1340, 1987.

206. Brock-Utne JG, Kallichurum S, Mankowitz E et al: Intrathecal ketamine with preservative: Histological effects on spinal nerve roots of baboons. S Afr Med J 61:440, 1982.

207. Brock-Utne JG, Kallichurum S, Mankowitz E et al: Effects of intrathecal saline and ketamine with and without preservative on the spinal nerve roots of monkeys. S Afr Med J 61:360, 1982.

208. Ahuja BR: Analgesic effect of intrathecal ketamine in rats. Br J Anaesth 55:991, 1983.

209. Goyagi T, Nishikawa T: Oral clonidine premedication enhances the quality of postoperative analgesia by intrathecal morphine. Anesth Analg 1996:1192, 1996.

210. Kalia PK, Madan R, Batra RK et al: Clinical study on epidural clonidine for postoperative analgesia. Indian J Med Res 83:550, 1986.

211. Gordh T Jr: Epidural clonidine for treatment of postoperative pain after thoracotomy: A double-blind placebo-controlled study. Acta Anaesthesiol Scand 32:702, 1988.

212. Petit J, Oksenhendler G, Colas G et al: Comparison of the effects of morphine, clonidine, and a combination of morphine and clonidine administered epidurally for postoperative analgesia. Anesthesiology 71:A647, 1989.

213. Bonnet F, Boico O, Rostaing S et al: Postoperative analgesia with extradural clonidine. Br J Anaesth 63:465, 1989.

214. Lund C, Qvitzau S, Greulich A et al: Comparison of the effects of extradural clonidine with those of morphine on postoperative pain, stress responses, cardiopulmonary function and motor and sensory block. Br J Anaesth 63:516, 1989.

215. Eisenach JC, Lysak SZ, Viscomi CM: Epidural clonidine analgesia following surgery: Phase I. Anesthesiology 71:640, 1989.

216. Mendez R, Eisenach JC, Kashtan K: Epidural clonidine analgesia after cesarean section. Anesthesiology 73:848, 1990.

217. Bonnet F, Boico O, Rostaing S et al: Clonidine-induced analgesia in postoperative patients: Epidural versus intramuscular administration. Anesthesiology 72:423, 1990.

218. Penon C, Ecoffey C, Cohn SE: Ventilatory response to carbon dioxide after epidural clonidine injection. Anesth Analg 72:761, 1991.

219. Smith BD, Baudendistel LJ, Gibbons JJ et al: A comparison of two epidural alpha $_2$ -agonists, guanfacine and clonidine, in regard to duration of antinociception, and ventilatory and hemodynamic effects in goats. Anesth Analg 74:712, 1992.

220. Filos KS, Goudas LC, Patroni O et al: Intrathecal clonidine as a sole analgesic for pain relief after cesarean section. Anesthesiology 77:267, 1992.

221. Rockemann MG, Goertz A, Seeling W et al: Epidural clonidine causes hemodynamic instability mainly by reduction of heart rate and cardiac output. Anesthesiology 79:A808, 1993.

222. Eisenach J, Detweiller D, Hood D: Hemodynamic and analgesic actions of epidurally administered clonidine. Anesthesiology 78:277, 1993.

223. De Kock M, Crochet B, Morimont C et al: Intravenous or epidural clonidine for intra- and postoperative analgesia. Anesthesiology 79:525, 1993.

224. Bernard J-M, Kick O, Bonnet F: Comparison of intravenous and epidural clonidine for postoperative patient-controlled analgesia. Anesth Analg 81:706, 1995.

225. De Kock M, Famenne F, Deckers G et al: Epidural clonidine or sufentanil for intraoperative and postoperative analgesia. Anesth Analg 81:1154, 1995.

226. Eisenach JC, De Kock M, Klimscha W: alpha $_2$ -Adrenergic agonists for regional anesthesia: A clinical review of clonidine (1984-1995). Anesthesiology 85:655, 1996.

227. Malinovsky J-M, Bernard J-M: Spinal clonidine fails to provide surgical anesthesia for transurethral resection of the prostate. Reg Anesth 21:419, 1996.

228. Hood DD, Eisenach JC, Tuttle R: Phase I safety assessment of intrathecal neostigmine methylsulfate in humans. Anesthesiology 82:331, 1995.

229. Hood DD, Mallak KA, Eisenach JC et al: Interaction between intrathecal neostigmine and epidural clonidine in human volunteers. Anesthesiology 85:315, 1996.

230. Lauretti GR, Reis MP, Prado WA et al: Dose-response study of intrathecal morphine versus intrathecal neostigmine, their combination, or placebo for postoperative analgesia in patients undergoing anterior and posterior vaginoplasty. Anesth Analg 82:1182, 1996.

231. Lauretti GR, Eisenach JC, Hood DD et al: Intrathecal neostigmine for postoperative analgesia: Dose response. Reg Anesth 21, 2S:74, 1996.

232. Hood DD, Krukowski JA, Eisenach JC et al: Intrathecal neostigmine for post cesarean section analgesia: Dose response. Reg Anesth 21, 2S:78, 1996.

233. Tryba M: Epidural regional anesthesia and low molecular heparin: Pro (German). Anasthesiol Intensivmed Notfallmed Schmerzther 28:179, 1993.

234. Vandermeulen EP, Van Aken H, Vermylen J: Anticoagulants and spinal-epidural anesthesia. Anesth Analg 79:1165, 1994.

235. Owens EL, Watson GW, Hessel EA: Spinal subarachnoid hematoma after lumbar puncture and heparinization: A case report, review of the literature, and discussion of anesthetic implications. Anesth Analg 65:1201, 1986.

236. Louville Y, Cazalaa J-B: Spinal anesthesia and heparin antithrombotic prevention (French). Agressologie 31:160, 1990.

237. Sage DJ: Epidural, spinals and bleeding disorders in pregnancy: A review. Anaesth Intensive Care 18:319, 1990.

238. Schmidt A, Nolte H: Subdural and epidural hematomas following spinal, epidural, or caudal anaesthesia (German). Anaesthesist 41:276, 1992.

239. Rao TLK, El-Etr AA: Anticoagulation following placement of epidural and subarachnoid catheters: An evaluation of neurologic sequelae. Anesthesiology 55:618, 1981.

240. Odoom JA, Sih IL: Epidural analgesia and anticoagulant therapy: Experience with one thousand cases of continuous epidurals. Anaesthesia 38:254, 1983.

241. Lowson SM, Goodchild CS: Low-dose heparin therapy and spinal anesthesia. Anaesthesia 44:67, 1989.

242. Allemann BH, Gerber H, Gruber UF: Ruckenmarksnahe anaesthesie und subkutan verabreichtes low-dose heparin-dihydergot zur thromboembolieprophylaxe (Peri-spinal anesthesia and subcutaneous administration of low-dose heparin for prevention of thromboembolism). Anaesthetist 32:80, 1983.

243. Schwander D, Bachmann F: Heparin and spinal or epidural anaesthesia: Clinical decision making (French). Ann Fr Anesth Reanim 10:284, 1991.

244. Darnat S, Guggiari M, Grob R: Lumbar epidural haematoma following the setting-up of an epidural catheter. Ann Fr Anesth Reanim 5:550, 1986.

245. Dupeyrat A, Dequire PM, Merouani A et al: Subarachnoid hematoma and spinal anesthesia. Ann Fr Anesth Reanim 9:560, 1990.

246. Metzger G, Singbartl G: Spinal epidural hematoma following epidural anesthesia versus spontaneous spinal subdural hematoma (French). Acta Anaesthesiol Scand 35:105, 1991.

247. Bergqvist D, Lindblad B, Matzsch T: Low molecular weight heparin for thromboprophylaxis and epidural/spinal anaesthesia: Is there a risk? Acta Anaesthesiol Scand 36:605, 1992.

248. Horlocker TT, Wedel DJ, Schlichting JL: Postoperative epidural analgesia and oral anticoagulant therapy. Anesth Analg 79:89, 1994.

249. Dickman CA, Shedd SA, Spetzler RF: Spinal epidural hematoma associated with epidural anesthesia: Complications of systemic heparinization in patients receiving peripheral vascular

thrombolytic therapy. Anesthesiology 72:947, 1990.

250. Onishchuk JL, Carlsson C: Epidural hematoma associated with epidural anesthesia: Complications of anticoagulant therapy. Anesthesiology 77:1221, 1992.

251. Benzon HT, Brunner EA, Vaisrub N: Bleeding time and nerve blocks after aspirin. Reg Anesth 9:86, 1984.

252. Horlocker TT, Wedel DJ, Offord KP: Does preoperative antiplatelet therapy increase the risk of hemmorrhagic complications associated with regional anesthesia? Anesth Analg 70:631, 1990.

253. Horlocker TT, Wedel DJ, Schroeder DR et al: Preoperative antiplatelet therapy does not increase the risk of spinal hematoma associated with regional anesthesia. Anesth Analg 80:303, 1995.

254. CLASP: CLASP: A randomized trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9,364 pregnant women. Lancet 343:619, 1994.

255. Groen RJ, Ponssen H: The spontaneous spinal epidural hematoma: A study of the etiology. J Neurol Sci 98:121, 1990.

256. Chrubasik J, Wiemers K: Continuous-plus-on-demand epidural infusion of morphine for postoperative pain relief by means of a small, externally worn infusion device. Anesthesiology 62:263, 1985.

257. Chrubasik J, Wust H, Schulte-Monting J et al: Relative analgesic potency of epidural fentanyl, alfentanil and morphine in treatment of postoperative pain. Anesthesiology 68:929, 1988.

258. Gambling DR, Yu P, Cole C et al: A comparative study of PCEA and CIEA during labor. Can J Anaesth 35:249, 1988.

259. Sjostrom S, Hartvig D, Tamsen A: Patient controlled analgesia with extradural morphine or pethidine. Br J Anaesth 60:358, 1988.

260. Lysak SZ, Eisenach JC, Dobson CE: Patient controlled epidural analgesia during labor: A comparison of three solutions with a continous infusion control. Anesthesiology 72:44, 1990.

261. Gambling DR, McMorland GH, Yu P et al: Comparison of patient controlled epidural analgesia and conventional "top-up" injections during labor. Anesth Analg 70:256, 1990.

262. Grass JA, Zuckerman RL, Tsao H et al: Patient controlled epidural analgesia results in shorter hospital stay after cesarean section. Reg Anesth 15:S26, 1991.

263. Gambling DR, Huber C, Howell P et al: Patient-controlled epidural analgesia during labor: The effects of varying bolus size and lock-out intervals. Reg Anesth 15:S40, 1991.

264. Ferrante FM, Barber M, Segal M et al: 0.0625% bupivacaine/0.0002% fentanyl via patient controlled epidural analgesia for pain of labor and delivery. Anesthesiology 75:A738, 1991.

265. Walmsley P, Vandeveer B, Littrell R et al: Experience with 894 cases of patient controlled epidural analgesia. Reg Anesth 15:S26, 1991.

266. Price RL, Fortinot RF, Weinger MB et al: Double-blind patient evaluation of patient controlled epidural analgesia during labor. Anesthesiology 75:A836, 1991.

267. Welchew EA, Breen DP: Patient controlled on-demand epidural fentanyl. Anaesthesia 46:438, 1991.

268. Viscomi C, Eisenach JC: Patient-controlled epidural analgesia during labor. Obstet Gynecol 77:348, 1991.

269. Boudreault D, Brasseur L, Samii K et al: Comparison of continuous epidural bupivacaine infusion plus either continuous epidural infusion or patient-controlled epidural injection of fentanyl for postoperative analgesia. Anesth Analg 73:132, 1991.

270. Ferrante FM, Lu L, Jamison S et al: Patient-controlled epidural analgesia: Demand dosing. Reg Anesth 15:S36, 1991.

271. Paech MJ: Patient controlled epidural analgesia in labour: Choice of solution. Reg Anesth 17:59, 1992.

272. Parker RK, White PF: Epidural patient-controlled analgesia: An alternative to intravenous patient-controlled analgesia for pain relief after cesarean delivery. Anesth Analg 75:245, 1992.

273. Vercauteren M, Van De Put D, Geernaert K et al: Epidural PCA (demand + continuous rate) with sufentanil in post-cesarean section patients: The influence of epinephrine addition. Reg Anesth 17:58, 1992.

274. Vercauteren MP: PCA by epidural route (PCEA). Acta Anaesthesiol Belg 43:33, 1992.

275. Bustamante J, Sawaki Y, White PF: Comparison of IV-PCA versus epidural PCA following major vascular surgery. Anesth Analg 74:S39, 1992.

276. Parker RK, Sawaki Y, White PF: Epidural patient-controlled analgesia: Influence of bupivacaine and hydromorphone basal infusion on pain control after cesarean delivery. Anesth Analg 75:740, 1992.

277. Prados W, Spruill W: PCEA fentanyl-bupivacaine: effect of decreasing basal rates on the cumulative dose. Reg Anesth 17:138, 1992.

278. Walmsley PNH: Patient controlled epidural analgesia. In Sinatra RS, Hourd A, Ginsberg B et al (eds): Acute Pain: Mechanisms and Management. St. Louis, Mosby-Year Book, 1992, p 312.

279. Glass PSA, Estok P, Ginsberg B et al: Use of PCA to compare the efficacy of epidural to IV fentanyl administration. Anesth Analg 74:345, 1992.

280. Domsky M, Tarantino D: Patient-controlled spinal analgesia for postoperative pain control. Anesth Analg 75:453, 1992.

281. Grant R, Dolman J, Harper J et al: Patient controlled lumbar epidural fentanyl compared with patient controlled intravenous fentanyl for post-thoracotomy pain. Can J Anaesth 39:214, 1992.

282. Cohn S, Amar D, Pantuck C et al: Post C/S epidural PCA: Fentanyl-bupivacaine 0.01%-epinephrine versus sufentanil-bupivacaine 0.1%-epinephrine. Anesth Analg 74:S46, 1992.

283. Cohen S, Amar D, Pantuck CB et al: Postcesarean delivery epidural patient-controlled analgesia: Fentanyl or sufentanil? Anesthesiology 78:486, 1993.

284. Bush DJ, Kramer DP: Intravascular migration of an epidural catheter during postoperative patient-controlled epidural analgesia. Anesth Analg 76:1150, 1993.

285. Yu PY, Gambling DR: A comparative study of patient-controlled epidural fentanyl and single dose epidural morphine for post-caesarean analgesia. Can J Anaesth 40:416, 1993.

286. Grass JA, Sakima NT, Valley M et al: Assessment of ketorolac as an adjuvant to fentanyl patient-controlled epidural analgesia after radical retropubic prostatectomy. Anesthesiology 78:642, 1993.

287. Nolan JP, Dow AA, Parr MJ et al: Patient-controlled epidural analgesia following post-traumatic pelvic reconstruction: A comparison with continuous epidural analgesia. Anaesthesia 48:736, 1993.

288. Gambling DR, Huber CJ, Berkowitz J et al: Patient-controlled epidural analgesia in labour: Varying bolus dose and lockout interval. Can J Anaesth 40:211, 1993.

289. Geller E, Chrubasik J, Graf R et al: A randomized double-blind comparison of epidural sufentanil versus intravenous sufentanil on epidural fentanyl analgesia after major abdominal surgery. Anesth Analg 76:1243, 1993.

290. Swenson JD, Hullander RM, Bready RJ et al: A comparison of patient controlled epidural analgesia with sufentanil by the lumbar versus thoracic route after thoracotomy. Anesth Analg 78:215, 1994.

291. Ferrante FM, Rosinia FA, Gordon C et al: The role of continuous background infusions in patient-controlled epidural analgesia for labor and delivery. Anesth Analg 79:80, 1994.

292. Grass JA, Zuckerman RL, Sakima NT et al: Patient-controlled analgesia after cesarean delivery. Reg Anesth 19:90, 1994.

293. Lubenow TR, Tanck EN, Hopkins EM et al: Comparison of patient-assisted epidural analgesia with continuous-infusion epidural analgesia for postoperative patients. Reg Anesth 19:206, 1994.

294. Rosaeg OP, Lindsay MP: Epidural opioid analgesia after cesarean section: A comparison of patient-controlled analgesia with meperi-dine and single bolus injection of morphine. Can J Anaesth 41:1063, 1994.

295. Paech MJ, Moore JS, Evans SF: Meperidine for patient-controlled analgesia after cesarean section: Intravenous versus epidural administration. Anesthesiology 80:1268, 1994.

296. Bouchard F, Drolet P: Thoracic versus lumbar administration of fentanyl using patient-controlled epidural after thoracotomy. Reg Anesth 20:385, 1995.

297. Ferrante FM, Barber MJ, Segal M et al: 0.0625% Bupivacaine with 0.0002% fentanyl via patient-controlled epidural analgesia for pain of labor and delivery. Clin J Pain 11:121, 1995.

298. Vercauteren MP, Coppejans HC, Broecke PW et al: Epidural sufentanil for postoperative patient-controlled analgesia (PCA) with or without background infusion: A double-blind comparison. Anesth Analg 80:76, 1995.

299. Steude GM, Hasselbach N, Urbanski B: Complications associated with bupivacaine-fentanyl epidural infusions with PCEA for pain control in postoperative patients. Anesth Analg 80-S1:S473, 1995.

300. Etches RC, Gammer T-L, Cornish R: Patient-controlled epidural analgesia after thoracotomy: A comparison of meperidine with and without bupivacaine. Anesth Analg 83:81, 1996.

301. Smet IGG, Vercauteren MP, De Jongh RF et al: Pressure sores as a complication of patient-controlled epidural analgesia after cesarean section. Reg Anesth 21:338, 1996.

302. Suzuki N, Koganemaru M, Onizuka S et al: Dural puncture with a 26-gauge spinal needle affects spread of epidural anesthesia. Anesth Analg 82:1040, 1996.

303. Khoury GF, Chen ACN, Garland DE et al: Intraarticular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. Anesthesiology 77:263, 1992.

304. Joshi GP, McCarroll SM, O'Brien TM et al: Intraarticular analgesia following knee arthroscopy. Anesth Analg 76:333, 1993.

305. Joshi GP, McCarroll SM, McSwiney M et al: Effects of intraarticular morphine on analgesic requirements after anterior cruciate ligament repair. Reg Anesth 18:245, 1993.

306. Allen GC, St. Amand MA, Lui ACP et al: Postarthroscopy analgesia with intraarticular bupivacaine/morphine: A randomized clinical trail. Anesthesiology 79:475, 1993.

307. Joshi GP, McCarroll SM: Intraarticular morphine for the management of "frozen shoulder." Anesthesiology 79:A816, 1993.

308. Dalsgaard J, Felsby S, Juelsgaard P et al: Low-dose intra-articular morphine analgesia in day case knee arthroscopy: A randomized double-blinded prospective study. Pain 56:151, 1994.

309. Reuben SS, Connelly NR: Postarthroscopic meniscus repair analgesia with intraarticular ketorolac or morphine. Anesth Analg 82:1036, 1996.

310. Smith I, Shively RA, White PF: Effects of ketorolac and bupivacaine on recovery after outpatient arthroscopy. Anesth Analg 75:208, 1992.

311. Kehlet H: Surgical stress: The role of pain and analgesia. Br J Anaesth 63:189, 1989.

312. Dahl JB, Rosenberg J, Dirkes WE et al: Prevention of postoperative pain by balanced analgesia. Br J Anaesth 64:518, 1990.

313. Ready LB, Brown CR, Stahlgren LH et al: Evaluation of intravenous ketorolac administered by bolus or infusion for treatment of postoperative pain: A double-blind, placebo-controlled, multi-center study. Anesthesiology 80:1277, 1994.

314. O'Hara DA, Fragen RJ, Kinzer M et al: Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 41:556, 1987.

315. Power I, Noble DW, Douglas E et al: Comparison of i.m. ketorolac trometamol and morphine sulphate for pain relief after cholecystectomy. Br J Anaesth 65:448, 1990.

316. Parker RK, White PF: Effect of ketorolac on the postoperative opioid requirement and recovery profile. Anesthesiology 75:A758, 1991.

317. Sevarino FB, Ning T, Sinatra RS et al: The efficacy of ketorolac 15 mg or 30 mg in combination with morphine PCA in postoperative gynecological surgery patients. Anesthesiology 75:A1090, 1991.

318. Haddow GR, Riley E, Isaacs R et al: Ketorolac, nasal polyposis, and bronchial asthma: A cause for concern. Anesth Analg 76:420, 1993.

319. Buckley MM, Brogden RN: Ketorolac: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 39:86, 1990.

320. Steinberg RB, Tessier EG: Gastrointestinal bleeding after administration of ketorolac (letter). Anesthesiology 79:1146, 1993.

321. Conrad KA, Fagan TC, Mackie MJ et al: Effects of ketorolac tromethamine on hemostasis in volunteers. Clin Pharmacol Ther 43:542, 1988.

322. Spowart K, Greer IA, McLaren M et al: Haemostatic effects of ketorolac with and without concomitant heparin in normal volunteers. Thromb Haemost 60:382, 1988.

323. Greer IA: Effects of ketorolac tromethamine on hemostasis. Pharmacotherapy 10:71S, 1990.

324. Fleming BM, Coombs DW: Bleeding diathesis after perioperative ketorolac. Anesth Analg 73:235, 1991.

325. Splinter WM, Rhine EJ, Roberts DW et al: Preoperative ketorolac increases bleeding after tonsillectomy in children. Can J Anaesth 43:560, 1996.

326. Thwaites BK, Nigus DB, Bouska GW et al: Intravenous ketorolac tromethamine worsens platelet function during knee arthroscopy under spinal anesthesia. Anesth Analg 82:1176, 1996.

327. Baskett PJ, Bennett JA: Pain relief in hospital: The more widespread use of nitrous oxide. BMJ 1:509, 1971.

328. Kripke BJ, Justice RE, Hechtman HB: Postoperative nitrous oxide analgesia and the functional residual capacity. Crit Care Med 11:105, 1983.

329. Sadove MS, Shulman M, Hatano S: Analgesic effects of ketamine administered in subdissociative doses. Anesth Analg 50:452, 1971.

330. Ito Y, Ichiyanagi K: Post-operative pain relief with ketamine infusion. Anaesthesia 29:222, 1974.

331. Slogoff S, Allen G, Wessels JV: Clinical experience with subanesthetic ketamine. Anesth Analg 53:354, 1974.

332. Clausen L, Sinclair DM, Van Hasselt CH: Intravenous ketamine for postoperative pain. S Afr Med J 49:1437, 1975.

333. Clements JA, Nimmo WS: Pharmacokinetics and analgesic effects of ketamine in man. Br J Anaesth 53:27, 1981.

334. Rubin J, Mankowitz E, Brock-Utne JG: Ketamine and postoperative pain. S Afr Med J 63:433, 1983.

335. Jahangir SM, Islam F, Aziz L: Ketamine infusion for postoperative analgesia in asthmatics: A comparison with intermittent meperidine. Anesth Analg 76:45, 1993.

336. Javery KB, Colclough GW, Sutterlin J et al: IVPCA: Morphine vs morphine plus ketamine. A double blind comparison (abstract). Can J Anaesth 40:A48, 1993.

337. Javery KB, Ussery TW, Steger HG et al: Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 43:212, 1996.

338. Nimmo WS, Clements JA: Ketamine on demand for postoperative analgesia. Anaesthesia 36:286, 1981.

339. Johnstone RE, Smith DJ: Complete tolerance to opioids (letter). Anesth Analg 75:467, 1992.

340. Katz J, Nelson W, Forest R et al: Cryoanalgesia for post-thoracotomy pain. Lancet 1:512, 1980.

341. Glynn CJ, Lloyd JW, Barnard JDW: Cryoanalgesia in the management of pain after thoracotomy. Thorax 35:325, 1980.

342. Joucken K, Michel L, Schoevaerdts J et al: Cryoanalgesia for post-thoracotomy pain relief. Acta Anaesthesiol Belg 38:179, 1987.

343. Wood GJ, Lloyd JW, Evans PJ et al: Cryoanalgesia and day care herniorrhaphy. Lancet 2:479, 1979.

344. Melzack R, Wall PD: Pain mechanisms: A new theory. Science 150:971, 1965.

345. Melzack R: Prolonged relief of pain by brief, intense, transcutaneous somatic stimulation. Pain 1:357, 1975.

346. Tyler E, Caldwell C, Ghia JN: Transcutaneous electrical nerve stimulation: An alternative approach to the management of postoperative pain. Anesth Analg 61:449, 1982.

347. Coleman DL: Control of postoperative pain: Nonnarcotic and narcotic alternatives and their effect on pulmonary function. Chest 92:520, 1987.

348. Harvie KW: A major advance in the control of postoperative knee pain. Orthopedics 2:26, 1979.

349. Perdkis P: Transcutaneous nerve stimulation in the treatment of protracted ileus. S Afr J Surg 15:81, 1977.

350. Fassoulaki A, Papilas K, Sarantopoulos C et al: Transcutaneous electrical nerve stimulation reduces the incidence of vomiting after hysterectomy. Anesth Analg 76:1012, 1993.

351. Morgan B, Jones AR, Mulcahy KA et al: Transcutaneous electric nerve stimulation (TENS) during distention shoulder arthrography: A controlled study. Pain 64:265, 1995.

352. Wilson JF: Behavioral preparation for surgery: Benefit or harm? Behav Med 4:79, 1981.

353. Taylor SE: Hospital patient behavior: Reactance, helplessness of control? In Friedman HS, Dimatteo MR (eds): Interpersonal Issues in Health Care. New York, Academic Press, 1982, p 453.

354. Eland JM, Anderson JE: The experience of pain in children. In Jacox AK (ed): Pain: A Source Book for Nurses and Other Health Care Professionals. Boston, Little, Brown, 1977, p 453.

355. Beyer JE, DeGood DE, Ashley LC et al: Patterns of postoperative analgesic use with adults and children following surgery. Pain 17:71, 1983.

356. Mather L, Mackie J: The incidence of postoperative pain in children. Pain 15:271, 1983.

357. Anand KJS, Hickey PR: Pain and its effects on the neonate and fetus. N Engl J Med 317:1321, 1987.

358. Anand KJS, Sippell WG, Aynsley-Green A: Randomized trial of fentanyl anaesthesia in preterm babies undergoing surgery. Lancet 1:243, 1987.

359. Lynn AM, Opheim KE, Tyler DC: Morphine infusion after pediatric cardiac surgery. Crit Care Med 12:863, 1984.

360. Tyler DC: Patient controlled analgesia in adolescents. Pain 4:S236, 1987.

361. Rogers BM, Webb CJ, Stergios D et al: Patient-controlled analgesia in pediatric surgery. J Pediatr Surg 23:259, 1988.

362. Brown RE, Broadman LM: Patient-controlled analgesia (PCA) for postoperative pain control in adolescents. Anesth Analg 66:S22, 1988.

363. Krane EJ, Jacobson LE, Lynn AM: Caudal morphine for postoperative analgesia in children: A comparison with caudal bupivacaine and intravenous morphine. Anesth Analg 66:647, 1987.

364. Tree-Trakarn T, Pirayavaraporn S: Postoperative pain relief for circumcision: Comparison among morphine, nerve block, and topical anesthesia. Anesthesiology 62:519, 1985.

365. Shandling B, Steward DJ: Regional analgesia for postoperative pain in pediatric outpatient surgery. J Pediatr Surg 15:477, 1980.

366. McIlvaine WB, Knox RF, Fennessey PV et al: Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 69:261, 1988.

367. Maunuksela E-L, Olkkoa KT, Kokki H: Pharmacokinetics of intravenous ketorolac and its efficacy in relieving postoperative pain in children. J Pain Symptom Manage 6:143, 1991.

368. Watcha MF, Ramirez-Ruiz M, White PF et al: Perioperative effects of oral ketorolac and acetaminophen in children undergoing bilateral myringotomy. Can J Anaesth 39:649, 1992.

369. Faherty BS, Grier MR: Analgesic medication for elderly people post-surgery. Nurs Res 33:369, 1984.

370. Portenoy RK, Kanner RM: Patterns of analgesic prescription and consumption in a university-affiliated community hospital. Arch Int Med 145:439, 1985.

371. Chapman WP, Jones CM: Variations in cutaneous and visceral pain sensitivity in normal subjects. J Clin Invest 23:81, 1944.

372. Harkins SW, Kwentus J, Price DD: Pain and suffering in the elderly. In Bonica JJ (ed): Management of Pain. Philadelphia, Lea & Febiger, 1990, p 552.

373. Heft MW, Cooper BY, O'Brien KK et al: Age differences in the perception of painful and nonpainful thermal stimuli in humans (abstract). In Abstracts of the 7th World Congress on Pain. Seattle, Wash, IASP Publications, 1993, p 98.

374. Porter FL, Miller JP, Morris J et al: Pain in aging: Attention, cognitive performance, perception, and physiologic response (abstract). In Abstracts of the 7th World Congress on Pain. Seattle, Wash, IASP Publications, 1993, p 99.

375. Tremblay N, Allard N, Veillette Y: Effect of age on pain perception: Preliminary results (abstract). In Abstracts of the 7th World Congress on Pain. Seattle, Wash, IASP Publications, 1993, p 98.

376. Burtles R, Pecket BW: Postoperative vomiting: Some factors affecting its incidence. Br J Anaesth 29:114, 1957.

377. Gustafsson LL, Grell AM, Garle M et al: Kinetics of morphine in cerebrospinal fluid after epidural. Acta Anaesthesiol Scand 28:535, 1984.

378. Bromage PR: Ageing and epidural dose requirements: Segmental spread and predictability of epidural analgesia in youth and extreme age. Br J Anaesth 41:1016, 1969.

379. Sharrock NE: Epidural anesthetic dose responses in patients 20 to 80 years old. Anesthesiology 49:425, 1978.

380. Veering BT, Burm AG, van Kleef JW et al: Epidural anesthesia with bupivacaine: Effects of age on neural blockade and pharmacokinetics. Anesth Analg 66:589, 1987.

381. Fisher BW, Gilchrist DM: Postoperative delirium in the elderly. Ann R Coll Physicians Surg Can 26:358, 1993.

382. Crews JC, Sweeney NJ, Denson DD: Clinical efficacy of methadone in patients refractory to other mu-opioid receptor agonist analgesics for management of terminal cancer pain: Case presentations and discussion of incomplete cross-tolerance among opioid agonist analgesics. Cancer 72:2266, 1993.

383. Ready LB, Hare B: Drug problems in chronic pain patients. Anesthesiol Rev 6:28, 1979.

384. Turner JA, Calsyn DA, Fordyce WE et al: Drug utilization patterns in chronic pain patients. Pain 12:357, 1982.

385. Rapp SE, Ready LB, Nessly ML: Acute pain management in patients with prior opioid consumption: A case-controlled retrospective study. Pain 61:195, 1995.

386. Shapiro BS, Cohen DE, Covelman KW et al: Experience of an interdisciplinary pediatric pain service. Pediatrics 88:1226, 1991.

387. Wheatley RG, Madej TH, Jackson IJB et al: The first year's experience of an acute pain service. Br J Anaesth 67:353, 1991.

388. O'Connor M, Warwick P, Culpeper VEA: Evaluation of the effectiveness of an acute pain team. Abstracts of the 7th World Congress on Pain. Seattle, Wash, IASP Publications, 1993, p 394.

389. Brenn BR, Rose JB: Pediatric pain services: Monitoring for epidural analgesia in the non-intensive care unit setting (letter). Anesthesiology 83:432, 1995.

390. Ready LB, Rawal N: Anesthesiology-based acute pain services: a contemporary view. In Brown DL (ed): Textbook of Regional Anesthesia and Analgesia. Philadelphia, WB Saunders, 1996, p 632.

Chapter 70 - Chronic Pain *

John C. Rowlingson
Terence M. Murphy

INTRODUCTION

Pain is a sensory and emotional experience associated with actual tissue damage or described in terms of such damage. [1] The blend of the physical and nonphysical components varies depending on whether the pain is acute or chronic in nature *and* with the patient in whom the pain is occurring. The patient's understanding of and attitude about the meaning of the pain influence compliance with treatment and its success. Acute pain is a signal of ongoing or impending tissue damage that provokes the patient to escape from the injurious event or seek treatment. [2] [3] This condition is now referred to as inflammatory pain. When pain persists in spite of therapy (and becomes chronic or neuropathic, in modern-day terminology), it loses its distinct signal function and is entangled by aspects of physical, emotional, and psychosocial disarray as well as neural imprinting that markedly influence its perceived severity. [4] [5] [6] [7] Chronic pain can linger even when the original source is gone because physical deconditioning, behavioral consequences, and/or neurophysiologic disruption may persist. A primary research focus now is the induced changes in neurophysiologic response based on alterations in neural threshold, chemistry, and modulation that are due to the adverse effects of the repetitive bombardment of the central nervous system (CNS) with nociceptive input. [8]

The protocol for patient evaluation must be systematic and thorough, it must encompass the physical and behavioral components, *and* it must respect the neurophysiologic mechanisms that are operative. Pain assessment with tools more scientific than the Visual Analogue Scale (VAS) remains a supreme challenge, as does outcome-based and evidence-based therapy. The wisdom that management of chronic pain demands the coordination of multidisciplinary input with attention to the psychologic, vocational, and rehabilitation aspects, as advocated by such pioneers as Bonica, Beecher, and Fordyce, has been repeatedly borne out over time. [5] [6] [9] This chapter aims to provide insight into the significant issues in the management of chronic (neuropathic) pain and to impart the modalities for treatment based on an appreciation for the rationale of their use.

Given the leadership of anesthesiology in raising awareness about the issues of (chronic) pain management and the enormous effort put forth over the past 5 decades to create pain clinics and pain-management centers as convenient instruments by which to incorporate and proliferate the practice of pain medicine, our specialty has created a certificate of special qualification in pain management. [10] Now, other specialties are recognizing the importance of pain medicine and are considering doing the same. In contemporary practice, not only has the academic domain of the anesthesiologist had to increase, but so has the respect for knowledge about business and practice management principles.

Even single practitioners who are contemplating "adding some pain management" to their practice face many significant challenges: how to gain access to patients with pain problems, how to blend their evaluation and management into the established practice of operating room-based anesthesia, how to prevent being overwhelmed by referrals and subsequent patient demands, and how to be available when questions and aftercare needs arise. These tasks become more daunting as the practice grows in size, the number of physicians and nonphysician health-care professionals and

---

* *See Appendix 1, Practice Guidelines for Chronic Pain Management*

This chapter was originally written by Dr. Murphy. As a tribute to his contributions to the field of pain medicine following his untimely death in 1996, his chapter has been updated rather than rewritten.

support personnel increases, the geographic area covered expands, and the complexity of the patients seen evolves. A pain-management center embodies the fundamental concept that patients with complex acute or chronic pain problems will be best served by a synchronized, integrated team of specialists who have different backgrounds. [4] [5] [6] [7] This structure is more likely to guarantee the comprehensive evaluation of such patients as well as to provide access to reputable, contemporary pain-management philosophy and techniques. It is from pain-management centers that new understanding about the nature of pain and pain-related behavior is being derived. It is important to consider information that is not only physical but also psychosocial, biochemical, ethnocultural, cognitive, affective, and environmental, as it relates to the patient. The data gathered need to be shared freely with all practitioners involved in the care of the patient because the multidimensional workup sequence *must* lead to an accurate diagnosis, one that encompasses the physical as well as the psychosocial contributors to the "pain." Only after achieving this objective can a realistic treatment prescription follow. Dworkin [11] has initiated a movement that identifies risk factors for patients to develop chronic pain.

In the United States, Bonica [5] calculated that as much as one-third of the population has chronic pain conditions, and the estimated annual cost of chronic pain in the United States was at least 80 billion dollars because of the millions of days of lost work, the costs of necessary health care, and the consequences of pain in terms of compensation and litigation. Headaches remain the number 1 chronic pain problem. [12] Back pain is ubiquitous in society and ranks as the second most chronic pain problem. [5] [13] It causes otherwise healthy, productive individuals to lose time from work, recreation, and family pursuits and contributes mightily to health care costs. Statistics reveal that approximately 10 percent of patients with acute low back pain complaints do not improve after 4 to 6 weeks, and a majority will redevelop symptoms within a few years. [13] [14] [15] [16]

MECHANISMS OF PAIN

Comprehension of "pain" is enhanced by appreciating the mechanisms for pain. Physicians have long understood acute pain because the tissue damage is usually obvious, such as a laceration or a broken bone, and the intensity of the pain is perceived to be correlated with the severity of the injury. [1] [3] Physicians readily acknowledge how various mediators are released at the damage site to initiate the blood clotting cascade, to activate the immune system, and to provoke the nervous system response. In the usual conception of pain, tissue-damaging or tissue-threatening stimuli send neurophysiologic messages directly from the peripheral receptors to the sensory cortex via specific pathways in the peripheral and central nervous systems. In this scheme, the greater the stimulation of the peripheral receptor, the more severe the pain. Experience and research indicate that this concept of such direct transmission of pain is naive, especially regarding chronic pain, and that the mechanisms are in fact much more complex. [1] [8] [17] Although specific pathways for transmission of nociceptive nerve impulses do exist (classically, A delta and C fibers) in peripheral nerves, it is now proven that when this information synapses in the dorsal horn of the spinal cord, it is modified, dampened, or augmented, depending on many factors existing within and outside the organism. [18]

Algesic mediators, such as serotonin, histamine, potassium, prostaglandins, and components of the arachidonic acid cascade, such as leukotrienes and thromboxanes, are released from tissues at *and near* the site of injury. Injury can be thermal (heat or cold), the result of direct noxious mechanical stimulation such as intense pressure, or chemical. Various kinins, such as bradykinin and neurokinin, are activated in plasma and substances in the nerves, such as substance P, are elaborated to influence the transmission of impulses from the site of injury to the CNS. The spinal cord is a site at which an extremely complex system of neurochemicals, interneurons (relay neurons), and neuromodulators interplays to determine what subsequent neural response will occur. Traditionally, C fibers (called C polymodal nociceptors because they respond to noxious thermal, mechanical, or chemical stimuli) represent a large number of fibers in peripheral nerves, are unmyelinated, transmit sensations that are perceived as dull, aching, burning, and poorly localized, have large receptive fields, and have input that does not fatigue or extinguish with repeated stimulation. A delta fibers (called high-threshold mechanoreceptors because they increase their firing rate with increased stimulus intensity) are myelinated. Thus, they transmit neural signals faster than C fibers, are associated with pain that is sharp, specific, and well-localized, have more specific representation on the skin (smaller receptive fields), and demonstrate lessening activity with repeated stimulation, although they can become sensitized and increase the frequency of their discharge.

When chemical mediators sensitize and/or stimulate the peripheral nociceptors, sensitization is said to occur. This implies that less stimulation will be necessary to trigger an adverse response in the nervous system. *Allodynia* is the term used to describe the phenomenon that a nonpainful stimulus provokes a painful response. [1] *Hyperesthesia* refers to the condition in which a lower threshold for nonpainful stimuli causes a response, and *hyperalgesia* means that a lower threshold to noxious stimulation provokes an enhanced pain response. [1] These conditions arise in the peripheral and central nervous systems when injury occurs, mediators are elaborated, and the consequences of the neural response become manifest at the dorsal root ganglion (DRG) and within the spinal cord. [18] These mechanisms are best studied in superficial peripheral tissues, but how they relate to pain from deeper tissues such as bone, joints, muscles, and visceral structures is not entirely clear. Free nerve endings, the stimulation of which triggers activity in A delta and C fibers, are present in all these tissues. Exactly how the sympathetic nervous system interplays with the somatic nerves is not perfectly defined. Further confusion comes from the reality that A delta and C fibers innervate visceral organs and travel with sympathetic afferent fibers, leading some to say that blockade of sympathetic afferent fibers blocks visceral pain. [19]

The DRG represents a passageway for much of the sensory input into the spinal cord. The DRG is subject to the enormous influences of chemical mediators, so sensitization and amplified responses are common even at this level. [20]

There can be a number of axon projections from one DRG into various levels of the spinal cord. Particular attention has focused on the layering of axon termination in the lamina of the dorsal horn of the spinal cord, the pharmacology of which is increasingly being determined. [18] Much of the A-delta and C-fiber input terminates in layers I, II (the substantia gelatinosa), and V. Peptides such as substance P, somatostatin, cholecystokinin, enkephalins, glutamate, aspartate, and vasoactive intestinal polypeptide (VIP) act as neurotransmitters; their release continues the propagation of the neural response *and* provides the opportunity for interruption thereof with selective blocking agents or antagonists. Wide dynamic range neurons (located primarily in layers I and V) are an important group of neurons in that they receive input from nociceptive specific *and* nonspecific afferent fibers.

When repetitive stimulation of dorsal horn neurons involved in the pain response occurs, the frequency of discharge can be shown with neurophysiologic techniques to increase. [2] [3] [21] This phenomenon is called sensitization or "wind-up." The clinical correlate is that less peripheral stimulation is required to activate a "pain response" in the nervous system. Thus, stimuli that are not normally painful, such as lightly stroking the skin, cause patients agony because the nervous system response is augmented by maladaptive changes in the processing of sensory input; the touch hurts *and* the pain lingers even after the direct stimulation is stopped because of the hyperirritability of the nervous system and the failure of the usual modulatory systems to dampen the reactivity.

What happens in the more central projections of the nervous system from the spinal cord is still not well understood. Input travels in the spinothalamic tract (STT) from laminae I, V, VII, and VIII and crosses the midline to ascend in the anterolateral quadrant of the spinal cord to nuclei in the thalamus and brain stem. [1] [8] Near the thalamus, the STT divides into a lateral portion, often called the neospinothalamic tract (which is associated with sensory/discriminative aspects of pain perception), and a medial portion, called the paleospinothalamic tract (which is associated with the affective/motivational aspects of pain perception). The paleospinothalamic tract has numerous synapses with the reticular formation of the brain stem, the medial thalamus, the periaquaductal gray matter, and the hypothalamus. Sensory input is processed in the thalamus and passes to the cerebral cortex.

Some contemporary therapy has evolved from the understanding of neural systems that descend from intracranial sites and that can exert a modifying effect on incoming noxious input. [1] [8] [22] That such sites existed was predicted by the gate-control theory of pain proposed by Melzack and Wall in 1965. [23] Many such sites, such as the periaquaductal gray matter, have high concentrations of endogenous opioid neurotransmitters. [1] [8] [22] These areas project to the rostroventral medulla and, via the reticulospinal tracts and the dorsal lateral funiculus, to laminae I, II, and V. Other neurochemicals such as norepinephrine and serotonin are implicated in these inhibitory/modulatory circuits. [8] This knowledge provides abundant opportunity for therapeutic interventions that provoke or intensify the descending modulating systems.

In the past, it was common to classify pain as acute or chronic. Contemporary nomenclature is more mechanism-oriented, and the terms now used are *inflammatory* or *neuropathic pain,* respectively. The implication is that chronic pain is more entrenched because it induces marked changes in the CNS. Previously, alternate terms included *central pain* and *deafferentation pain.* The newer term emphasizes the fact that contributory sources to the ongoing pain actually involve the neuroadaptive process, and it connotes the pervasive changes that occur within the nervous system to complicate the clinical situation: the induction of A alpha and A beta fibers to transmit nociceptive input, the utilization of neurotransmitters that are distinct from those involved in the acute pain response, an increase in receptive fields, remodeling in the CNS and the sensitization of the CNS by the constant bombardment with noxious input.

In its more refractory forms, chronic pain can be influenced by the intensity of the stimulus, the interaction between the stimulus and afferent modulating systems

within the CNS, and, most important, by a variety of behavioral and learned strategies that enhance/intensify or suppress the resulting neurophysiologic event. Thus, it is possible to have at one end of the spectrum a patient who has severe tissue injury yet who shows no sign of pain (i.e., the athlete, a soldier in combat) and at the other end a patient who has no apparent tissue damage or source of injury, yet is debilitated by chronic pain.

The modern-day concept that pain is a mixture of sensory and emotional phenomena precludes anyone from concluding that a patient's pain is "all in his or her head." [1] [4] [6] [6] [7] [9] [11] [24] In the past, this was termed *psychogenic pain.* This was said to be present when patients mislabeled psychologic distress, such as anxiety and depression, and described it using both the language and behavior of tissue damage. Although a peripheral nociceptive source may have existed, the core problem was deemed actually to be a psychologic event. It is creative now to hypothesize that many patients diagnosed as having psychogenic pain had genuine symptoms that only appeared to be exaggerated, when actually, the sensitized status of the neurophysiologic response was the explanation.

Psychogenic pain is *not* synonymous with the common behavioral aspects of acute and chronic pain. Pain is commonly communicated via behavior, because it is only by word, grimace, posture, and other such signals that we know that another person is in pain. [9] [11] For some patients, a precipitating nociceptive event results in appropriate pain behavior at first, but that behavior receives such reinforcement from the psychosocial environment that it persists beyond the healing of tissue damage and contributes to the generation of a chronic pain state. [9] In other instances, pain behavior may persist even when it is not directly reinforced because "well behavior" is aversive; that is, for some patients, normal social and occupational activities are perceived as not being possible, nor do the expectations of family, friends, and coworkers overcome the advantages of having chronic pain. These patients may be using a pain-based lifestyle as a rationale for the inability to cope mentally with the demands of work, recreation, or family activities. The management of pain due to mostly psychologic factors is profoundly distinct from that associated with obvious physical causes, so gaining as complete an understanding as possible about the origin of the "pain" is crucial. It is clinically useful to accept the reality that all pain, be it acute (inflammatory)

or chronic (neuropathic), involves physical and psychological factors, emphasizing again that the causes of chronic pain are complex. Thus, patients with chronic degenerative joint disease may become quite depressed at their inability to hold a job or to function domestically. Such depression could exacerbate nociceptive pain from joints injured by arthritis or trauma. In addition, an overly attentive and sympathetic spouse may reinforce "pain behavior" (i.e., by encouraging staying away from work, resting, assuming the invalid role). In this way, patients may add behavioral aspects to their chronic pain problems. These patients make more progress with therapy that not only is based in a conventional orientation, but also that avails them of additional psychological support, strategies to embolden coping with pain, and behavioral modification, all in order to help them regain more normal functioning.

EVALUATION OF THE PATIENT

From the outset, pain should be acknowledged to be a real problem for the patient. Challenging the authenticity of the patient's pain only provokes more dramatic pain behaviors that cannot help but to impede the diagnostic evaluation and the subsequent therapeutic milieu. The thrust of contemporary pain medicine is *not* to determine whether the patient has organic (real) or psychogenic (unreal) pain because the operative definition of pain now obviates the importance of this distinction. Equally true is that an exact source for every complaint of pain may not be discovered. Still, the patient should feel that the physician does believe that he or she has pain and is suffering. Suffering is not the same as "the pain"; rather, it is a composite of the patient's ability to accept the disease/diagnosis/condition and to cope with it or not. Because all practitioners who interact with patients who have chronic pain now endorse the vast influence that countless psychosocial factors can have on complaints of physical pain, [4] [5] [6] [7] [11] [25] patient evaluation by psychologists and psychiatrists is no longer a terminal event, obtained only after all medical technologies have been tried. This pattern of referral only fostered the opinion that the patient had "imaginary pain." This impression contaminated the productivity of the subsequent evaluation and provoked patients to continue to search for "the" correct diagnosis, maintaining the anguish of friends and family members and greatly increasing the cost of the chronic pain. Homage must be shown by recognizing that patients with chronic pain need (and deserve) a thorough and systematic workup.

Protocols for patient evaluation *must* include attention to factors that influence the patient's presentation of complaints and symptoms as well as compliance with therapy. The clinician must discriminate between those patients who need aggressive intervention and those who need time and observation. The disease of chronic pain involves far more than the physical factors of the original problem. Innumerable psychosocial factors come into play to complicate the evaluation and management of the patient. [4] [5] [6] [7] [25] For the patient, diminishing satisfaction and self-esteem become manifest because endless workups do not reveal "what's wrong," expensive tests fail to explain (or document) the intractable pain, doctors project suspicion about the frequency and intensity of the professed symptoms and alleged disability, and participation in vocational, recreational, and social activities declines.

The history of the pain must include information about the pain onset, location, radiation, quality, characteristics, constancy, and response to previous therapy, whether simple, such as ice or rest, or complicated, such as surgery or spinal cord stimulation. In patients with acute pain, this brief history, in addition to assessment of the general medical condition including such items as medications and allergies, plus findings from the physical examination, and the emotional reaction to this injury (worry, anxiety, frustration at plans being interrupted), may allow the establishment of a differential diagnosis and the choice of a likely diagnosis. When patients have chronic symptoms, the occupational, social, psychologic, emotional, past surgical, cultural, and economic realms of their life *must* also be investigated. [26] Given the enormity of this task, this portion of the history taking is best addressed with the use of questionnaires, whether manual or computerized. It may be advantageous to have the patient fill out this form before the actual office evaluation. Many patients appreciate the thoroughness reflected in the listing of questions and perceive that "here is someone who really understands and cares." A wealth of crucial information becomes available from the questionnaire in a familiar, systematic, usable format. Pain diaries and various scales of pain, distress, and suffering can be included. [27] Records about all the patient's previous episodes of pain and general medical condition should be reviewed. In so doing, one can gauge the magnitude of change in the patient's current signs and symptoms. Furthermore, these records facilitate the clinician's creation of a chronologic outline of the patient's complaints. This imposes an organizational pattern to the history taking and, most important, allows time for the patient to answer the doctor's questions genuinely. Patients are more satisfied when they believe that they were given a chance to "tell their story" to an unhurried, understanding physician. [28] The benefits of this crucial step in establishing an effective and resilient doctor-patient relationship are often incalculable. Therefore, the physician *must* develop an efficient information-gathering routine from which the essence of the patient's problems can be distilled.

Past records assist the clinician in a comparative way when they contain physical examination findings. The data from physical examination are largely subjective, meaning that they can be influenced by the patient's cooperation and motivation (emphasizing again the importance of comparison with previous examination results). In a patient with complaints of low back pain, for example, the patient should be observed for gait and the use of appliances while ambulating from the waiting room to the examination area. Limping, grabbing at walls, grimacing, and the use of canes or walkers are all observable behaviors that help the clinician to formulate an opinion about the intensity and the severity of the patient's complaints. The purpose of the examination is to define the correlation between the patient's complaints and the anatomic possibilities. It is important to remember that the back is a complex machine and rarely is one structure or tissue responsible for all the pain complaints. Tailored neurologic and musculoskeletal examinations confirm or refute the working hypothesis that the practitioner has formulated. Sensory and/or motor abnormalities in dermatomal

areas or in particular nerve distributions suggest a specific anatomic location of the problem. Avoid tests early in the examination sequence that are likely to cause the patient discomfort because the subsequent pain, muscle spasm, and guarding will influence the further cooperation of the patient. For purposes of thorough patient evaluation and for documentation for billing, the more complete the examination process, the better.

How much use to make of laboratory tests in a particular patient is a perpetual and contemporary challenge. Again, using patients with low back pain as an example, both the Quebec Task Force on Spinal Disorders and the more recent U.S. Agency for Health Care Policy and Research (AHCPR) Guidelines for acute back pain encourage little or no diagnostic testing for most patients for the first 4 to 6 weeks of symptoms. [13] [29] Rewards for financial conservatism in managed medical care clearly will elevate the significance of history taking and physical examination skills in the present day. Not accounted for in the AHCPR treatise on acute low back pain (which provides a general outline for the use of laboratory tests, and includes a "red flag" section) is the necessary sensitivity that must be shown to the patient in explaining the findings. As pain becomes more chronic, patients put more hope into a test providing "the answer" for the endless pain. Negative laboratory test results must *not* be presented with the implication that there is no real or significant pain. Laboratory findings have significance for the practitioner who is contemplating invasive therapies, because the results may indicate the presence of blood-borne infection, altered coagulation, metabolic disarray, metastatic disease, or anatomic perturbations. Deyo [30] predicted the difficulty in the evaluation of patients with low back pain by noting "... up to 85 percent of patients with low back pain cannot be given a definitive diagnosis because of the poor association among symptoms, pathologic findings and imaging results."

The clinician should be aware that even positive laboratory studies may not always explain the patient's pain. The patient with chronic pain experiences an expanding frustration with a triad of persistent symptoms (that are often perceived as disabling), changing physical condition, and nonrevealing tests. Thus, attention must be paid to the impact of myriad psychosocial factors that influence the patient's complaints. [4] [5] [6] [7] [9] [11] [25] This domain can be so influential that it is routine in pain medicine for patients to have a psychologic assessment and occasionally a psychiatric evaluation. The appropriateness of selected therapeutic interventions in a given patient, such as nerve blocks, surgery, or long-term opioid therapy, can be more accurately assessed when one entirely understands the patient's attitude about the pain, who he or she believes is to blame for it, the behaviors associated with the pain, the nature of lifestyle accommodations to the pain made by the patient, and the patient's very understanding of and beliefs about the pain. Accurate decisions about the need for neuropsychologic testing can also be made. Most patients with chronic pain do not manifest psychiatric illness. Rather, they experience frustration, despair, anger, anxiety, and depression as they try to deal with the impotence of the health-care system in diagnosing and treating their problem. [31] These feelings can be exacerbated by the compensation/disability system that scrutinizes patients severely and attempts to steal their independence and direct their every move. When previously supportive relationships become contaminated by the patient's chronic pain, self-esteem and self-confidence are replaced by innuendo and doubt. This patient benefits from concurrent therapy that restores his or her feelings of self-worth and the effectiveness of interpersonal skills while the important physical rehabilitation ensues.

/das/book/view/29494766/875/768.html

PRACTICE STYLES FOR PAIN MANAGEMENT

Once it was obvious that no single practitioner could or should be responsible for the comprehensive evaluation of patients with complex chronic pain syndromes such as complex regional pain syndrome (CRPS), headaches, back pain, and postherpetic neuralgia, the concept of coordinated practices emerged. The solo practitioner with only a referral network in his or her community may struggle to establish multidisciplinary alliances. Larger practices likely incorporate the necessary specialists in the same building, thereby facilitating access to each other and enhancing the cohesiveness of the practice. The facility may be freestanding or hospital based, and there are advantages and disadvantages to each style. [32] Pain centers associated with teaching hospitals have extensive programs with physicians and painmanagement specialists from every possible interest available, as are research opportunities and inpatient services. Inpatient services are expensive in terms of time and resources and may serve only a limited number of patients, yet they are necessary when advanced techniques for pain management, such as spinal cord stimulation and implanted intrathecal pumps, are becoming more prevalent. Additionally, inpatient care is excellent for patients needing concurrent drug therapy manipulation, extensive psychologic and/or behavioral therapy, guided physical therapy, and nonambulatory care while the pain treatment program benefits evolve. Those for whom outpatient therapy has failed and those who have such global life disruption and are entrenched in a detrimental home situation that they need to refocus their lives away from the pain also profit from inpatient care.

Outpatient patient therapy costs far less and theoretically puts the burden for improvement squarely on the patient's shoulders because he or she must cooperate with and apply the recommended treatment amid distractions in the home and work environment. On the other hand, activities of daily living such as driving and working can be incorporated into the therapy program and utilized while the patient continues to rehabilitate. Outpatient management demands that local and/or referring physicians be thoroughly educated about the patient's program and become actively involved in the implementation of the treatment plan so that a consistent ideologic approach is provided to the patient even when he or she is away from the pain center. The challenge of outpatient pain management to the physician is establishing a highly efficient, service-oriented office practice. [33]

Patients with chronic pain can stymie and frustrate their referring physician to the point of ineffectiveness. A comprehensive, second-opinion approach to referred patients becomes essential because patients who have been disappointed by uncertain diagnoses and unsuccessful treatment

---

also suffer with anxiety, depression, and desperation. The pain-center staff has an experienced attitude about such complex patients. Staff members apply established protocols for patient evaluation and generate a program of options for pain management that is continually upgraded and adjusted to meet the unique needs of the individual patient. The abundant and broad expertise available at a multidisciplinary center encourages the necessary consideration of emotional, psychosocial, family, and occupational consequences of the patient's pain, critical factors that can be overlooked in the chain of single, subspecialty evaluations. The comprehensive body of data obtained paves the way for the development of a treatment plan that addresses all aspects of the patient's "pain."

The primary care provider must discriminate between patients who need more time to heal and those who need a more thorough workup or referral to a pain center. Some would argue that the pain-center personnel should be the group that differentiates patience from the pursuit of more information. A practical problem is that patients may be viewed adversely early in their course as they act out the personal importance of their pain, or they may receive treatments that may be inappropriate. These adverse or negative experiences taint their consideration of similar therapy in the future, such as another surgical procedure or another nerve block, at a time when more inclusive modalities are also made available and greater appreciation of the extent of the pain problem is demonstrated.

As the practice plan is formulated, consideration must be given to both the medical mission and the business organization. The medical issues are perhaps the easiest to resolve. Physicians are familiar with record and laboratory review, history taking, and performing a physical examination. These data must be condensed into a cohesive differential diagnosis and a treatment plan. What most physicians find far more intimidating is winding their way through the essential business of medicine demands--marketing and advertising, defining the business mission statement and goals, creating a referral system receptive to the needs of the patients and their referring physicians, functioning as a provider of service, communicating with the patient's primary physician and other health care suppliers, maintaining a competitive identity, and being reimbursed fairly for the time spent and the services provided. [32] [33]

STANDARDIZATION OF FACILITIES

Attempts at establishing standardization of facilities and services represent a natural facet of the evolution of pain centers. The leader in this field has been the Commission for Accreditation of Rehabilitation Facilities. [5] As one could anticipate, there is an expectation for any pain center so accredited to match the standards of a rehabilitation facility, which not all pain centers necessarily strive to emulate. Therefore, other organizations, such as the International Association for the Study of Pain, have generated standards for interdisciplinary pain treatment units run by those of many specialties, such as psychology, psychiatry, neurosurgery, physiatry, and anesthesiology. The American Society of Regional Anesthesia has also created standards for facilities that are run primarily by anesthesiologists. By and large, all the standards address the following: the number of specialists involved in patient care; their experience, education, and degree of participation in the subspecialty of pain medicine, such as continuing medical education programs; the breadth of pain problems evaluated in the unit; the variety of therapeutic modalities offered; and the hours the facility functions.

TREATMENT OF CHRONIC PAIN

The aim of the treatment of acute (inflammatory) pain is to eliminate it and to return the patient to a premorbid functional level. [3] The practical goals of chronic pain management are effecting a maximal reduction in pain, helping the patient to cope with the residual pain, and increasing the patient's functional capacity. It is essential to respect the patient's expectations when presenting the treatment plan and to foster an appreciation of how "chronic" pain is entirely different from "acute" pain. When any of the available treatment modalities for pain management is applied in singular fashion, it may decrease the patient's chronic pain by a seemingly insignificant amount. If these same treatments are used *together* in a coordinated program, a significant reduction in chronic pain may be manifested. When clinicians avoid treating all pain in the same way and address the needs of the patient, successful management becomes more likely, as it will if the patient understands the rationale for the chosen therapy and is active in the treatment process. [4] Practitioners must acknowledge, however, that just taking the physical pain away does not instantly eliminate the environmental, cognitive, behavioral, emotional, biochemical, neurophysiologic, and social consequences of the chronic pain. [5] [6] [7] Because of the neuroadaptive changes, the treatment of chronic pain must continue well past the presumed healing period of the patient's injury. [8]

Just as the thrust in the evaluation scheme is multidisciplinary, so must the treatment planning for chronic pain be creative and expansive in consideration yet individualized in application. A limited-scope approach may deny the patient the combination of modalities necessary to achieve pain reduction. Advertisements make many common modalities sound miraculous, and a growing public interest in the alternative/complementary therapies encourages an open-minded attitude about any such therapy. Nevertheless, one physician's survey revealed that when treating low back pain, many physicians expressed "... ignorance or rejection of existing scientific evidence, excessive commitment to a particular mode of therapy or a tendency to discount the efficacy of competing treatments." [34] Guidelines such as those published by the AHCPR will help the practitioner in managing patients. [13] The Quebec Task Force on Spinal Disorders expressed the opinion that, after 3 months of conservative therapy or accumulated time missed from work, the patient with back pain should be sent to a multidisciplinary pain center. [29] The benefits of such a referral are documented by a number of authors. [4] [5] [7] [26] [29] [35] Flor et al [36] and Cutler et al [37] used meta-analysis to document that treatment at pain centers does restore the majority of patients with chronic low back pain to a greater functional status.

It is imperative that the health care professional discuss the conclusions from the assessment *and* the proposed plan

---

of action with the patient. A patient who understands why he or she is having pain and who helps to design the treatment program is more likely to adhere to the therapy. [38] [39] Von Korff et al [40] showed that patients with back pain who were *involved by education* in their care achieved equivalent therapeutic results but with *less* medication, *less* bed rest, and *lower* costs than a comparative group receiving more traditional conservative therapy. Treatment options can be divided into surgical and conservative categories. In the latter group are medications, stimulation techniques, complementary therapies, regional analgesic interventions, physical therapy, and psychologic strategies. Because chronic pain alters the neurochemistry of *both* pain transmission and nervous system processing of noxious information, valid complaints of pain can persist even when the original cause of the pain is gone. In pain treatment, this implies that the adaptive changes in the nervous system do not "heal" as fast as the primary generator.

Medications

Because medication prescription is so easy for the health care provider and so commonly expected by the patient, and because medications are so widely available, so simple to use, and so various in form and effect, medications are the most frequently chosen modality for pain management. Many preparations are available to patients in an over-the-counter form. Although mundane, it is fundamental to understand that medications are but one component of the more comprehensive pain-management plan. Their use can provoke annoying side effects or life-threatening reactions, so cautious choice must be guided by the identified mechanisms for the pain and appreciation for the patient's concurrent physical condition and medical history. [41] Primary analgesics do *not* effectively treat pain that has a strong psychosocial basis. Because chronic pain is a dynamic disease, and because responses to therapy as well as the patient's needs change, follow-up evaluation of the patient with chronic pain who is taking prescribed medications is essential.

Nonnarcotic Analgesics

For most chronic pain of nonmalignant origin, nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the most useful analgesics. [42] [43] Perhaps more important than the specific agent is the manner in which the medicines are administered. [41] For chronic pain problems unlikely to resolve within a short time, analgesics should be taken *before* the pain becomes a problem, rather than after. The original purpose of giving analgesics on an "as-needed" basis was to reduce the amount of medication taken. In fact, administration of medicine based on time rather than on symptoms usually results in less medication use and better pain relief. Therefore, analgesics such as the NSAIDs or acetaminophen should be taken at specific time intervals and on a regular basis without regard to the current intensity of the pain. For some patients, a once-a-day or a sustained-released preparation that minimizes drug-taking is preferred. On the other hand, some patients lack faith in such formulations, so alternating therapeutic doses of an NSAID with acetaminophen throughout the day is perceived as being more efficacious.

NSAIDs have potent anti-inflammatory properties and are very useful for bone pain associated with metastatic cancer. These drugs are readily available, mostly inexpensive, and do not generally create physiologic depression. They do have a ceiling effect. Common side effects such as gastric irritation and fluid retention can be troublesome, but complications such as gastrointestinal hemorrhage or renal failure are very worrisome. When NSAIDs are poorly tolerated or contraindicated, acetaminophen is an acceptable alternative drug that lacks the peripheral anti-inflammatory effects of the NSAIDs. It does block spinal hyperalgesia induced by *N*-methyl- D-aspartate (NMDA) and substance P. [44]

Opioid Analgesics

The narcotic analgesics have traditionally been sanctioned for use in acute pain because of its limited duration or for the pain associated with terminal malignant disease, for which such drug administration is also perceived to be relatively finite. [42] [43] Concern has been expressed that patients taking narcotic analgesics, especially patients with chronic, noncancer pain, will develop tolerance to the drug, the first sign of which is decreased analgesic effect from the same dosage. Increased dose requirements and, potentially, physical dependence result. The anticipated clinical situation is complete when drug-seeking behavior becomes a major problem of ongoing patient management. Unfortunately, in the early years of pain management, many patients with chronic pain had already become dependent on narcotics and/or sedative-hypnotic drugs before referral to pain centers, given the overemphasis on the use of these drugs by physicians who believed that they had little more to offer than ongoing prescriptions; thus, initial management also needed to include detoxification. [7] However, as the attitudes about the use of opioids as a *part of an otherwise comprehensive pain-management program* have liberalized, it has become obvious that a majority of *selected* patients can achieve a stable dosing regimen and do not routinely escalate their narcotic usage without a major change in the pathophysiology of the primary disease. [45] [46] [47]

In acute pain circumstances and when patients with otherwise stable chronic pain have a flare-up, NSAID therapy may not be adequate. Consideration is then given

to using opioids for pain relief. Practitioners fear triggering an investigation by regulatory authorities and/or being tricked by the patient who is abusing or selling the prescription drugs while seeming to continue such therapy. These pressures all too frequently result in the prescription of inadequate doses of opioids, if any at all. When the patient asks for more, drug-seeking behavior is suspected, and the opioid trial is summarily stopped. Fortunately, as pain medicine has developed and research has been reported, data show that selected patients can use opioids responsibly on a long-term basis and that physicians' attitudes about such use are changing. [45] [46] [47] Patients receiving opioid therapy should be carefully screened, and documentation of a change in their functional status while continuing these drugs *must be* reported at each follow-up visit. The use of a signed narcotic

agreement details the duties and responsibilities of both the prescribing physician and the patient. This arrangement does not eliminate all attempts at misusing this privilege, but it does clearly establish the guidelines for conduct and places ultimate accountability on the patient. The long-term administration of potent opioids in the absence of other therapy is usually unsuccessful in the management of chronic pain of nonmalignant origin. However, most pain centers have a number of carefully selected and functional patients whose pain seems best controlled by the long-term administration of narcotic analgesics in the absence of other options. [7] Guidelines for the long-term use of opioids are being created (see appendix to this chapter).

Although all narcotics are equally potent at equivalent doses (Table 70-1) , individual variation exists among patients, in that one narcotic may provide more effective relief than another. [42] [43] Undertreatment of cancer pain is *still* common because of inadequate knowledge about the drugs that are already available and their proper use, negative attitudes about patients who take or need "large" doses, state and federal drug regulations that intimidate the wellmeaning physician, and the costs of some medications. [48] [49] The World Health Organization (WHO) and other authorities offer that 70 to 90 percent of cancer patients should be able to achieve comfort through the judicious use of medications. [42] [48] The analgesic ladder method advocates titrating medications to effect: prescribing nonopioid analgesics combined with adjuvant analgesics for mild to moderate pain, then adding oral opioids for moderate pain, and finally administering narcotics "by the clock" for severe pain with permission also to use rescue dosing. [42] [50] This concept bases treatment more on pain intensity than using the most contemporary approach of treating pain based on its cause.

Narcotics have a specific and well-accepted role in the management of pain caused by advanced terminal cancer. [42] [43] [48] [49] [50] Morphine is the gold standard, and longacting oral morphine preparations are very useful for establishing a daily narcotic foundation on which fine-tuning with additional opioids or other therapy can occur. The oral route of administration is preferred because it is the most convenient and cost-effective. Collin et al [51] pointed out that apparent tolerance is more frequently due to progression of

TABLE 70-1 -- Analgesic Equivalents to Methadone

DRUG (TRADEMARK OR SYNONYM)	DOSE	
	ORAL (mg)	*INTRAMUSCULAR (mg)*
Methadone (Dolophine)	10.0	8.8
Alphaprodine (Nisentil)	--	45.0
Buprenorphine (Stadol)	--	2.0
Codeine	200.0	130.0
Diacetylmorphine (heroin)	--	3.0
Fentanyl	--	0.1
Hydromorphone (Dilaudid)	7.5	1.5
Meperidine (Demerol)	200.0	50.0
Morphine	60.0	10.0
Oxycodone (Percodan)	30.0	15.0
Oxymorphone (Numorphan)	--	1.5
Pentazocine (Talwin)	180.0	60.0
Propoxyphene HCl (Darvon)	260.0	--
Propoxyphene napsylate (Darvon-N)	400.0	--

the primary disease than pharmacologic acceptance in patients with cancer pain. The synthetic narcotic methadone has advantages associated with continuous oral administration including being inexpensive and well absorbed orally (in comparison with morphine), having a prolonged effect of 6 to 8 hours, and exhibiting a low side-effect profile even with ongoing use. When methadone is administered orally, four times a day, an excellent plateau of analgesia can be achieved. [52] [53] In some patients with cancer pain, opioids effectively treat the pain, but excessive sedation interferes with their desired participation in activities with family and friends. The combination of dextroamphetamine with narcotics has been claimed to provide better analgesia and to leave the patient more alert. [54] This combination or methylphenidate has been used with success as a means of combating the depressing effects of opioids in patients with terminal cancer. [55] Patient-controlled analgesia (PCA) technology may be used by patients accurately to identify the ideal 24-hour narcotic need, but such patients may require a number of days to become used to the concept of selfdosing, to overcome sleep deprivation secondary to intense pain, and to eliminate other drugs from their body. [42]

Transdermal Systems

There has been some clinical success in administering drugs through the skin. [56] This route has distinct advantages for patients whose gastrointestinal tract is nonfunctional, as in patients with cancer pain or those with sporadic dysfunction, such as patients with nausea and vomiting secondary to chronic pancreatitis. Transdermal fentanyl has achieved significant use, although most experience has been acquired with such nonanalgesics as scopolamine for motion sickness, nitroglycerin for angina prophylaxis, capsaicin for neuropathic pain, and clonidine for hypertension. [57]

Sedative-Hypnotic Drugs

In the past, sedative-hypnotic drugs (primarily the barbiturates and benzodiazepines) were administered frequently by physicians and were misused by patients with chronic pain. [7] The hypnotic effect of many of the drugs used is of relatively short duration, and the risk of physical dependency is well recognized. Prescribing practices have become more appropriate because of an increasing awareness of the hazards of these drugs and more so because of the abundance of knowledge about pain-management strategies that are much more effective. The antihistamines diphenhydramine (Benadryl) and hydroxyzine (Vistaril) in doses of 25 to 100 mg, respectively, may be more useful as sedative medications than long-term administration of barbiturates or benzodiazepines. [7] These antihistamines do not lead to dependency or withdrawal on discontinuation of the drug. Of the benzodiazepines, clonazepam (Klonopin) has a reputation for being the most useful in patients with chronic pain because of its chloride channel blockade. Indirect muscle relaxant drugs, which have sedative effects, may be prescribed to interrupt pain-initiated reflex muscle spasm. These same sedative qualities may limit the daytime use of these drugs, but they can be of benefit with evening dosing

to manage pain-related insomnia in a gentler way than stronger medications. Occasionally, the gamma-aminobutyric acid (GABA) agonist baclofen is prescribed in daily oral doses of 30 to 90 mg to achieve greater muscle spasm control, although it, too, can be sedating. [58]

Anticonvulsants

Neuropathic pain is caused by an area of damage within the nervous system that creates an additional pain generator to other, more external sources. [1] [7] [8] [18] The

consequence is that neural output resembles abnormal epileptiform activity on the sensory input side of the nervous system that requires specific drug therapy. Examples of neuropathic pain states are tic douloureux (trigeminal neuralgia), postherpetic neuralgia, phantom limb pain, and denervation dysesthesias. In these conditions, if a patient has pain in parts of the body lacking an intact nervous supply, such as occurs in paraplegia, amputation, and peripheral nerve injury, conventional analgesics and sedatives will provide little relief.

The most appropriate medications for neuropathic pain states seem to be the anticonvulsants. [8] [57] [59] In the past, phenytoin (Dilantin) and carbamazepine (Tegretol) were popular. A trial of phenytoin, 100 mg three times a day, was not uncommon. However, more refractory pain may require carbamazepine at initial doses of 200 mg per day. Because carbamazepine is a potent drug with significant side effects such as ataxia, disorientation, and nausea, the therapeutic dose is gradually obtained by increasing the dose by one 200-mg tablet per day to a daily maximum of 1500 mg. If distressing side effects occur, the dose is decreased to the previously well-tolerated level, is kept at this level for several days, and then gradually is increased again. This method precisely establishes the therapeutic dose, which, if administered initially, would have produced intolerable side effects. The drug also has a reputation for depressing hematopoiesis, and the patient should be advised to report sore throat or signs of developing anemia. Long periods of carbamazepine (Tegretol) therapy warrant periodic checks of hemoglobin, white blood cell counts, and liver function tests.

Contemporary pain management now centers around the use of new-generation anticonvulsants such as gabapentin (Neurontin) [60] [61] and lamotrigine (Lamictal). [62] These drugs have a milder side-effect profile and are well tolerated by most patients, even those taking significant doses of other medications. Sedation with gabapentin is minimized by gradual upward titration of the drug. Doses start at 100 mg three times daily. Lamotrigine (Lamictal) has a 10 percent incidence of skin rash, so the starting dose of 25 mg at bedtime is continued for a week of observation before the daily dose is increased. Intravenous lidocaine infusion also decreases central pain and provides good temporary relief. [57] Some patients subsequently respond well to mexiletine, an oral form of lidocaine, and other sodium channel blockers have been found to produce significant reduction in pain as compared with placebo. [59]

Calcitonin appears to have significant analgesic activity, [63] [64] although the mechanisms are not fully understood. Calcitonin's actions may involve the modulation of descending pain perception control pathways. It is used in the treatment of osteoporosis and has been demonstrated to have significant pain-relieving effects in those individuals with osteoporotic vertebral compression fractures, [63] as well as phantom limb pain and even reflex sympathetic dystrophy (RSD). [64]

Antidepressant Drugs

One of the earliest assumptions about patients with chronic pain was that they were depressed because depression seemed to accompany chronic pain. [4] [5] [6] [7] [11] [65] [66] Successful treatment of depression was found to be followed by pain relief. Tricyclic antidepressant drugs that blocked serotonin reuptake, such as amitriptyline and doxepin, gained a reputation for helping a significant percentage of patients who had chronic pain. [57] These drugs appear to be tolerated by most patients, and, in oral doses of 25 to 100 mg at bedtime (doses that do not necessarily treat depression), they often effectively modulate the pain complaints, improve mood, and provide a boost in nocturnal sedation in patients with pain-related insomnia. [67] The newer selective serotonin reuptake inhibitors (SSRI) most directly utilize increasing CNS serotonin as a specific therapeutic intervention. [57] However, not all SSRIs have been demonstrated to be effective adjunct analgesics. [68] Our contemporary understanding is that an effect on particular subclasses of serotonin receptors is the significant mechanism involved in the augmentation of analgesia by antidepressants. There is now a wellrecognized discontinuation syndrome associated with this whole class of drugs. [69]

Nerve Blocks

Nerve blocks are often highly successful in controlling acute pain, such as that related to trauma and surgery. [3] Enthusiasm for the use of nerve block therapy in relation to chronic pain has waxed and waned as the role of interventional techniques has come under repeated scrutiny in the search for scientific documentation of undeniable benefits. Caution about the interpretation of nerve blocks traditionally viewed as clearly of value has been raised most recently by Hogan and Abram. [70] Their contention is that few studies exist to verify or to substantiate the diagnostic or prognostic value of most nerve blocks because of the vagaries of anatomy, the varying strengths of the solutions injected, and the bias the practitioner has toward achieving a positive benefit.

Chronic pain states have multiple causes, [1] [4] [5] [6] [7] [25] [71] and it is intuitive that nerve blocks have their greatest therapeutic value in pain problems in which nociceptive stimulation dominates. When chronic pain results from behavioral or psychiatric problems, a nerve block is unlikely to relieve symptoms because there will be multiple, more significant, nonsomatic contributions to the "pain," and one should be concerned about the high possibility of inducing complications that are at least perceived to be related to nerve block therapy. Establishing the source of a pain generator is crucial to appropriate, effective pain treatment. Nerve blocks may be used diagnostically to determine whether an afferent nociceptive stimulus exists and perhaps can aid in establishing which neuropathways are involved. [72] [73] When such information is at hand, prognostic nerve blocks may predict

whether surgical or neurolytic or thermal (radiofrequency [RF] or cryotherapy) interruption of the specific nerve path would be warranted or whether a series of therapeutic nerve blocks should be undertaken. These interventions are exceedingly common and run the gamut from simple infiltration of myofascial trigger points to injection of alcohol or phenol into a major nerve plexus for relief of pain, as in terminal cancer. [72] [73] [74] As the subspecialty of pain medicine grows, the proper place for nerve blocks in patient management will be elucidated, as will the risks of acquired infection for practitioners. [75] As more nonanesthesiologists enter the field, greater emphasis will be placed on the use of treatment modalities other than nerve blocks, a change that will enhance the likelihood that the necessary comparative studies will be done.

General Principles and Patient Assessment

A workup of the patient must precede the use of any nerve blocks, because it is necessary to determine that there are no major medical contraindications to the application of such therapies (including blood-borne infection, infection at the proposed needle insertion site, major anticoagulation, or the patient's or surrogate's refusal). [72] Even when these objections are not found, the crucial question to answer in preparation for nerve block therapy is whether a nerve block is appropriate for *this* patient at *this* time. Just because one can provide the therapy does not mean that it is indicated. The patient must provide written, informed consent following a concise presentation of the risks and benefits and the rationale for the planned procedure. [72] The ability to manage the side effects and complications of any blocks performed is requisite for the safe practice of regional analgesia in contemporary pain medicine.

Because it is of little use to perform diagnostic nerve blocks on patients who have no pain on the day of the procedure, the patient should affirm the intensity of the pain on a verbal 0 to 10 scale, in which 0 equals no pain and 10 is pain so severe that the patient is desperate. [7] [26] Alternately, the patient could make a mark on a VAS. The conventional medical examination preceding any nerve block must include a neurologic examination with particular attention to documenting the preexisting sensory and motor deficits. [26] [72] Often, very nonspecific information is obtained from patients undergoing diagnostic nerve blocks. [7] For example, the response to minor inconveniences (positioning, fitting of the blood pressure cuff, placing an intravenous catheter) gives an important perspective on the patient's demeanor. Some patients describe their pain in dramatic tones and as being of incredible severity, yet they manifest florid pain complaints on assertion of a 25-gauge needle. They may also claim that this pain is more severe than the chronic pain they hope to have relieved. Conversely, patients who tolerate quite uncomfortable needling procedures with great stoicism also provide insight into the reserved nature of their complaints. Relevant studies, such as radiographs, may need to be reviewed, as will the records of any preceding interventional therapy. Large doses of analgesic or sedative drugs may interfere with the patient's feedback about the immediate benefit of the nerve block or a painful complication, so careful consideration should be given to medicating such patients.

Assessment of the response to nerve blocks is both subjective and objective. The rating of the pain on a VAS should be repeated after the block is done. One must relate any reported pain relief to the onset of analgesia and recovery of function in the blocked nerves to the drugs used. The practitioner should check both the dermatomal and myotomal extent of the nerve block and should assess the impact on autonomic function. [72] [73] The extended response of the patient to the nerve block (in addition to his or her verbal report) should be further accentuated by appraisal of changes in the functional activity level, sleep patterns, gait, and medication requirements. The duration of side effects of the nerve blocks should be noted, and the positive effects should be correlated with the subjective and objective results. Repeated nerve blocks, using agents of different duration, will help to confirm the validity of initial impressions about their benefit and to dispel concerns regarding a placebo effect. [76] One must be careful in interpreting the duration of clinical improvement following even short-acting local anesthetics because decreasing the degree of CNS sensitization may result in pain relief that exceeds the expected duration of the drug used. [1] [2] [3] [8] [21] In addition, blocks performed with plain local anesthetics may have profound effects even though the actual period of pain impulse transmission blockade is relatively short because the patient sees, finally, that something really can be done about the pain. With the patient's attitude so affected, benefit from and compliance with other therapy increase. Nerve block therapy is

rarely provided in isolation, so the patient's cooperation with other components of the treatment program must also be assessed.

Nerve blocks can confirm the presence or absence of nociceptive stimulation as the cause of pain and thus may give a clue as to whether pain originates from a peripheral site, the CNS, or psychologic/behavioral sources. [72] [73] Furthermore, nerve blocks can isolate the specific nociceptive pathway by showing that a specific nerve block, such as a median dorsal branch block for facet pain, [77] repeatedly abolishes pain. In this way, nerve blocks can be used in a prognostic fashion to suggest the effects of longer-term procedures such as RF denervation, cryotherapy, neurolytic blocks, or even surgery. Unfortunately, the satisfactory shorter-term effects of nerve blocks performed with local anesthetics are not always manifested when a more permanent nerve block procedure is done. Therefore, destructive nerve blocks are often reserved for carefully selected patients and those with terminal cancer. [74] [78]

The differential (or graduated) spinal anesthetic is of historical interest as a diagnostic tool in pain evaluations. This technique makes use of the fact that different concentrations of local anesthetics can almost selectively block sympathetic, somatic, and motor fibers. [7] [70] [73] [79] Investigators have used differential spinal techniques to diagnose common and obscure pain problems. On the other hand, differential spinal techniques are one of the best examples of the cautions raised by Hogan and Abram [70] concerning the absolute certainty of conclusions drawn from diagnostic and prognostic blocks.

Myofascial Pain and Fibromyalgia

Myofascial pain may be a primary cause of pain after injury to muscles, bones, or joints, or it may be a secondary consequence of pain from a distant site that causes subsequent postural alterations and stress/strain of muscles and supporting tissues over time. [80] [81] [82] Thus, myofascial pain may persist long after the original injury has healed and may be associated with referred pain. This condition must be distinguished from fibromyalgia; characteristic symptoms include complaints of widespread, chronic, nondermatomal musculoskeletal pain (described as being steady, deep, aching, and often associated with reflex muscle spasm), morning stiffness, decreased range of motion of joints, sleep disturbance, activity compromise, fatigue, and multiple areas that are tender. [80] [81] [82] This is a diagnosis made over time and generally without the aid of specific laboratory tests. The disease is characterized by exacerbations and remissions, and no single psychologic profile is associated with it. Criteria for diagnosis are published. [83]

Treatment is based on establishing a *program* of options and educating the patient about the mechanical factors that aggravate the symptoms, such as repetitive motions in unsteady positions. [81] Medications that decrease inflammation (NSAIDs), decrease muscle spasm (cyclobenzaprine, 10 mg tid; baclofen, 10-20 mg PO tid) and enhance stage IV, non-rapid eye movement (REM) sleep (amitriptyline, 25-100 mg PO qhs; sertraline 50-100 mg qd) are beneficial. Exercises that stretch muscles and then restore normal posture have the most lasting effect on the patient's life.

Myofascial Trigger Points

Trigger points are tender areas in the muscles or their supporting tissues that are believed to be caused by trauma from a specific accident or chronic occupational positioning, such as from typing or poor posture. [81] A trigger point can be found by applying pressure that reproduces the patient's pain, which may have a nondermatomal but consistent referral pattern. Several pain areas and trigger points may exist in the same patient, and there is great debate over how many trigger point injections should be provided at one visit and over time. On examination, [81] the painful areas have been described as feeling "rope-like." A positive "jump sign" is said to be present when the trigger point is palpated and the patient "jumps" away from the pain.

Anesthesiologists are frequently asked to perform trigger point injections at the site of maximal tenderness. [7] [81] Dry needling techniques without injecting any drug are said to be successful in relieving pain, a finding suggesting that mechanical stimulation of the trigger point may be more important than the actual injectate. [84] As with most chronic pain states, the earlier such intervention takes place, the better the prognosis. Topical application of vapocoolant spray can precede the actual injection of local anesthetics such as 0.5 to 1 percent lidocaine or 0.125 to 0.25 percent bupivacaine, or saline, all with or without steroids. [81] Follow-up evaluation of the localized analgesic effect is necessary. Trigger point therapy is relatively benign and well tolerated. The ultimate goal is to assist the patient in achieving analgesia such that they can participate in active and passive physical therapy.

Sympathetic Nerve Blocks

Sympathetic nerve blocks have been a traditional modality for diagnosing and treating patients with RSD and causalgia, [70] [72] [73] [79] now referred to as CRPS type I and type II, respectively. [1] The global term sympathetically maintained pain (SMP) has been coined to classify these problems for which chronic pain appears to be associated with sympathetic nervous system dysfunction. [1] This title then refers to syndromes that characterize the effects on the body (usually on an extremity) that are thought to be mediated by sympathetic nervous system dysfunction after trauma such as fractures, lacerations, ligamentous strains/sprains, infections, and surgical incisions or resulting from visceral or CNS diseases. No single theory has exactly explained sympathetic nervous system dysfunction after such varied injuries, and the pathophysiology of SMP is poorly understood. Roberts [85] proposed that input from myelinated lowthreshold mechanoreceptors (LTM) sensitized WDR neurons in the spinal cord, and this triggered atypical CNS processing of noxious *and* non-noxious sensations (allodynia). Eventually, sympathetic nervous system efferent activity can stimulate the peripheral sensory receptors in the absence of cutaneous stimulation. Raja et al [86] postulated that norepinephrine at the site of injury activates alpha$_1$ -adrenoreceptors on the nociceptive afferent fibers and/or causes the release of algesic amines (prostaglandin E, serotonin, and bradykinin) from reactive cells. There is evidence that nerve injury induces the acquisition of an abnormal excitatory response to the presence of norepinephrine in the periphery and at the level of the dorsal horn. This explains the lack of correlation between sympathetic tone and temperature, [87] why sympathetic blocks do not relieve all symptoms, and why sufficient blockade is so difficult to verify. [70] Harden et al [88] measured norepinephrine and epinephrine levels from the extremities of patients with SMP. Rather than reaffirming the traditional concept of sympathetic nervous system hyperactivity in the affected limb, they showed upregulation of peripheral nociceptors that manifested a pathologic response to *circulating* catecholamines. Other proposed mechanisms for SMP include activation of an inflammatory process in the sympathetic ganglion, the release of sympathotropic factors (such as nerve growth factor), increased vascular permeability, and a failure of the "usual" opioid modulation of regional sympathetic ganglia. [89] [90]

Clinically, the degree of inciting trauma bears *no* correlation with the severity of the SMP syndrome. RSD and causalgia are the two most common types of SMP. In RSD (CRPS-type 1), the history of a specific *nerve* injury is *not* always elicited (but *tissue* injury is common), and the original injury does not result in demonstrable neurologic deficits. The incidence of RSD following traumatic brain injury and stroke is in the 12 to 25 percent range, and the treating clinician should maintain a high index of suspicion when caring for such patients. [89] In causalgia (CRPS-type II), there is always at least partial nerve damage as the apparent inciting event. Common to the CRPS syndromes are burning pain, allodynia,

TABLE 70-2 -- History, Signs, and Symptoms of Complex Regional Pain Syndrome

CRPS type 1 (RSD)
Initial noxious event
Distal aspect of extremity involvement
Pain, allodynia, or hyperalgesia
Pain disproportionate to injury
Pain not limited to a single nerve
Associated edema, changes in skin blood flow, abnormal sudomotor activity
What is not CRPS type 1 (RSD)
Pain in an area of decreased sensation

	No cutaneous hyperalgesia or allodynia
	Pain only in a specific nerve distribution
	Proximal symptoms only
CRPS type 2 (causalgia)	
	Burning pain
	Allodynia
	Hyperpathia
	Hand and foot involvement
	Sequela of injury to nerve or major branch
	More discrete localization than type 1 CRPS
	Most common nerves: median, sciatic, tibial, and ulnar

CRPS, complex regional pain syndrome; RSD, reflex sympathetic dystrophy

and hyperesthesia/hyperpathia (which can be thought of as exquisite sensitivity to stimulation). Table 70-2 summarizes the pertinent historical findings, but much variation in patient description and physical presentation is common. The onset of pain after the injury is variable pain and can spread from an initial area of involvement in an extremity to the trunk and even to the contralateral limb. [7] Laboratory studies are frequently not necessary, and tests that detect alterations of blood flow may not be of essential use in the patient's workup or in the documentation of improvement with treatment. Sherman et al [87] showed that videothermography is not an appropriate tool to use alone for either singlesession diagnosis or multisession tracking of RSD. Because of the possible alpha-adrenergic chemosensitivity, 1-10 mg phentolamine given intravenously over 5 to 10 minutes may be useful in distinguishing SMP from neuropathic pain [86] and in predicting the usefulness of Bier block therapy. [91] A decrease in the VAS for *both* the ongoing rest pain and the evoked pain is necessary to view the test as predictive.

The most common treatment for the sympathetically maintained component of the CRPS syndromes has been to provide interruption of the apparent pathologic somatic-sympathetic interaction by means of sympathetic blocks, although the absolute rationale for this approach is challenged at least by consideration of the contemporary mechanisms for SMP. [70] [72] [73] [74] [79] A positive response to a block may relieve only some of the pain and indicates that the patient responded at that time. Treating the cause of the CRPS does *not* constitute its management. The therapeutic or diagnostic effect of the specific techniques of sympathetic blockade should not be confounded by additional sensory or motor block.

Stellate Ganglion Blocks

Because humans do not possess a stellate ganglion per se, the more accurate anatomic term is "cervicothoracic sympathetic block." [72] Up to 15 mL of local anesthetic is injected into the lower cervical sympathetic chain region at the C6 level. [7] [71] [72] [79] The caudad spread in the appropriate prevertebral fascial plane anesthetizes the lower cervical and upper thoracic sympathetic ganglia and effectively blocks transmission of impulses from the ganglia to the ipsilateral upper extremity. Ready et al [92] and Galindo [93] used a side-port needle for cervicothoracic block to ensure the stability of the needle and injection of drug into the proper tissue plane because in so doing one can keep the point of the needle in contact with the Chassaignac turbercle. Satisfactory sympathetic blockade results without the need to withdraw the needle from its bony end point.

Cervicothoracic blocks are usually performed using an anterior paratracheal approach with the patient in the supine position, but other techniques are described in Chapter 43 . The regional anatomy predicts the potential side effects and complications from both the needle and the drugs with these techniques. Spread of the solution into the groove between the esophagus and the trachea blocks the ipsilateral recurrent laryngeal nerve, leaving the patient with a hoarse voice for the duration of the local anesthetic effect. If the solution is administered deep to the prevertebral fascia, the local anesthetic will spread posteriorly and laterally and will involve the somatic components of the brachial plexus. Some or all of the roots of the brachial plexus may then be anesthetized. If local anesthetics are used, this is not a serious problem; however, if neurolytic agents are injected, this complication can be catastrophic.

A serious complication occurs when the local anesthetic solution is injected unexpectedly into the vertebral artery. The vertebral artery is posterior to the anterior tubercle of C6 and runs in the foramina transversaria in the transverse processes of the upper six cervical vertebrae. If the exploring needle passes between these processes and rests on the posterior rather than the anterior tubercle, withdrawal of the needle could leave the tip of the needle in the lumen of the vertebral artery. Small-volume injections (<1 mL) of local anesthetic solution into this vessel can produce convulsions. Therefore, careful aspiration is mandatory, and not more than 1 mL of local anesthetic solution should be administered as a test dose. [94] Treatment of a convulsion consists of oxygen by mask and/or positive-pressure ventilation plus the intravenous administration of a short-acting sedative-hypnotic, i.e., thiopental (Pentothal), midazolam, or propofol. Spread of the local anesthetic solution to the epidural and/or subarachnoid spaces producing profound anesthesia for a variable period of time is conceivable, although uncommon, as is motor blockade of the cervical plexus, leading to phrenic nerve paralysis.

Lumbar Sympathetic Blocks

As the sympathetic chain leaves the thoracic area, it lies alongside the lumbar vertebrae, anterior to the psoas major muscle and its fascia and posterior to the aorta on the left and the inferior vena cava on the right. Because of this positioning, the sympathetic chain can be successfully blocked from a posterior approach (Ch. 43) .

Figure 70-1 shows the approach for a lumbar sympathetic block. [7] In the traditional method, three needles inserted

Figure 70-1 Lumbar sympathetic block. This figure shows the relation of the lumbar sympathetic chain on the anterolateral aspect of the lumbar vertebral bodies to the large vessels and somatic nerves. Inset diagram shows how the needle must traverse and, in its final position, be anterior to the psoas major muscle and its sheath to block the sympathetic chain satisfactorily. If injections are made within the psoas major muscle, its sheath will prevent diffusion of the drug to the sympathetic chain, and somatic nerve block of the lumbar plexus will result. The 10-cm needle is introduced at an angle of 45 degrees, approximately 8 cm lateral to the cephalad end of the L3 vertebral spine, as shown in Figure 70-4 . The block can also be performed with a single needle at the L2 or L4 vertebral level.

at L2, L3, and L4 are advanced through the paravertebral space to the sympathetic chain. It is more common now to insert just one needle at the L2 or L3 level to produce an effective block. [7] [72] [73] [79] [95] This more lateral approach is often more comfortable for the patient (Fig. 70-2) . In the lateral approach, the needle is inserted 8 to 10 cm lateral to the L2 spine. [95] Through a local anesthetic skin wheal, the 10-cm, 22-gauge needle is advanced at a 45-degree angle toward the vertebral body. Injection of a 1-mL bolus of local anesthetic relieves the discomfort felt by the

Figure 70-2 Needle positions for lumbar sympathetic block and celiac plexus block. Although the specific site of entry for the needle may vary, the intent is for the point of the needle to reach the target area of the anterolateral aspect of the L2, L3, or L4 vertebra for the lumbar sympathetic block. The celiac plexus block is usually a bilateral maneuver in which needles approach the celiac plexus, which lies anterior to the T12-L1 junction, from either side. The lateral approach to a celiac plexus block is shown on the left. The needle enters below the 12th rib. An approach angling cephalad ensures correct placement. For lumbar sympathetic block, the needle is inserted as shown on the right at a similar distance from the midline, that is, four finger-breadths. Here, however, the approach of the needle is more horizontal.

patient as the needle passes through the lumbar fascia. As the needle advances through the psoas major muscle, paresthesia may occur in the distribution of the

lumbar plexus and usually over the anterior aspect of the thigh (the genitofemoral nerve distribution). If this occurs, the needle should be redirected until only the vertebral body is contacted. The needle is then withdrawn slightly, and the angle progressively increased until the needle is advanced and slips just anterolateral to the vertebral body. At this point and after an aspiration test is negative, a test dose of local anesthetic with radiographic dye is administered. When accurate location of the needle is confirmed, a 10- to 15-mL bolus of local anesthetic (0.25% bupivacaine or 1% lidocaine) is injected. The patient maintains the prone position to prevent the local anesthetic from tracking back between the origins of the psoas muscle and into the paravertebral space where the lumbar somatic nerves could be anesthetized, thus confounding the effect of the trial block. Extensive infiltration of local anesthetic during needle insertion can anesthetize components of the lumbar plexus (usually the L2 and L3 dermatomes and/or myotomes in the anterior thigh). The use of higher concentrations of local anesthetic can produce motor block and impairment of the ability to walk, necessitating supervision of the patient until this dissipates.

As in the cervicothoracic ganglion block, complications of the lumbar sympathetic block consist of spread of the solution to the neuraxis and somatic nerves (lumbar plexus) and unexpected injection of the solution into a blood vessel. [7] [72] [73] [79] [95] If the transverse process is mistakenly identified as the vertebral body, and a large volume of drug is injected then into the intervertebral foramen, an ipsilateral lumbar plexus block and/or epidural spread of the solution may occur. Therefore, concentrations of drugs that do not produce motor blockade should be used. If the needle is advanced so far that it is sitting in either the aorta or the inferior vena cava, injections of local anesthetic could easily produce systemic toxicity (Ch. 43) .

Neurolytic lumbar sympathetic blockade [74] [78] [95] has been recommended for persistent ischemia of the lower extremity and some forms of persistent pain, because the afferent pathways involved in such problems are believed to pass through the lumbar sympathetic ganglia. For neurolysis with 6 to 10 percent aqueous phenol or 50 to 100 percent alcohol, the needle position *must be* confirmed radiographically prior to injection. Small quantities (2-4 mL) of drug should be injected through two needles placed at L3 and L4, as opposed to the single bolus injection technique used in diagnostic and other therapeutic blocks with local anesthetics, to decrease the dose of neurolytic drug placed at any one site. Minor groin anesthesia occurs in about 8 to 10 percent of these patients for up to 3 to 5 weeks (genitofemoral neuralgia).

With sympathetic block therapy, a staircase pattern of improvement is sought with serial blocks with local anesthetics, meaning that pain is reduced more and for a longer period of time for each block. Wang et al [96] [97] have shown that not all patients treated conservatively or with blocks improve. If benefits are not progressive but have definitive, albeit temporary effects, consideration may be given to RF ablation or thoracoscopic or surgical sympathectomy. [74] Brachial plexus blocks or continuous epidural blocks with solutions of local anesthetics with or without opioids may enhance pain relief and may allow for concurrent physical therapy. The therapeutic benefit of the blocks will be enhanced if physical therapy is provided to restore range of motion and to improve functional recovery of the affected extremity.

Intravenous Regional Sympathetic Blocks

In 1974, Hannington-Kiff [98] produced prolonged sympathetic blockade by the intravenous regional administration of guanethidine. He wanted to provide sympathetic blockade for weeks at a time and to avoid repeated cervicothoracic or lumbar sympathetic blocks using conventional needle techniques. Regional intravenous administration of guanethidine was found to produce a 3-day sympathetic block of dystrophic pain of the upper extremity, whereas a cervicothoracic block with bupivacaine lasted approximately only 10 hours. Bonelli et al [99] reported similar lengths of sympathetic blockade with guanethidine. In another study, [100] reported pain and blood flow were significantly lower, and skin temperature was significantly higher, when this block was compared with placebo injections of saline. Because injectable guanethidine is not available in North America, nor is its replacement, reserpine, other drugs have been sought. Ford et al [101] and Hord et al [102] reported on the use of bretylium in an intravenous regional (IVR) technique. Poplawski et al [103] reported using an IVR technique with local anesthetic and 80 mg methylprednisolone (Solu-Medrol), and Vanos et al [104] reported the successful addition of 60 mg ketorolac to the injectate.

Because anesthesiologists practice pain medicine while providing sympathetic blocks, they should be aware of additional modalities that will enhance the patient's response to treatment: ongoing physical therapy, transcutaneous electrical nerve stimulation (TENS) over vascular channels, NSAIDs, oral steroids, alpha- and beta-adrenergic or calcium channel blocking medications, and self-regulation techniques. [105] Epidural clonidine infusion (10-50 mug/h) in patients who responded to a bolus injection was proposed by Rauck et al. [106] Neurostimulation techniques are showing success in some chronic cases, and implanted narcotic pumps are also finding utility in some selected cases. Topical treatment with Emla, clonidine, or capsaicin is being investigated further. The admixture between SMP syndromes and neuralgic pain suggests that some patients with chronic cases will need management as for neuralgic pain.

Celiac Plexus, Hypogastric Plexus, and Ganglion Impar Blocks

Celiac plexus block is another of the sympathetic block techniques that has been especially useful for patients with intractable pain due to cancer of the pancreas or other upper abdominal viscera. [72] [73] [74] [75] [78] [107] [108] [109] Successful block of the celiac plexus denervates the abdominal organs from the gastroesophageal junction to the splenic flexure of the large colon. Although permanent neurolytic blocks work well for cancer of the pancreas, they are much less successful for nonmalignant pain, such as that due to chronic pancreatitis, because the pain relief lasts only a few months. The technique,

more fully described in Chapter 43 , is strikingly similar to that for lumbar sympathetic block, except an additional 45-degree angle is used to place the needle at the level of L1 rather than at L2 or L3. Figure 70-2 shows the needle position for this block.

The most frequently encountered complication of celiac plexus block is postural hypotension. Because blockade of the vasoconstrictor fibers to the viscera hinders rapid compensation for changes in posture, blood pools in the viscera when the patient assumes the upright position. This problem is usually transient, lasting only a few days after neurolytic blockade. During this period, the patient must learn to assume the vertical position in a slow and deliberate fashion, because rapid movement can cause fainting. The spread of local anesthetic or neurolytic agent to somatic nerves is particularly pertinent because of the large volumes normally required for celiac plexus block. Spread of the agent to the upper lumbar nerves can impair motor power or hip flexion and the ability to walk. This complication is especially problematic if neurolytic agents are used with the technique in patients with nonmalignant disease. Therefore, neurolytic celiac plexus blocks require radiographic confirmation of correct needle placement before the injection of large quantities of neurolytic agents. Because of the proximity of the needle tip to the aorta and the inferior vena cava, aspiration tests and the administration of test doses are necessary to minimize the distinct risk of intravascular injection.

It is possible to perform celiac plexus blocks with alternative approaches to the classic prone position, such as with the patient in a decubitus position. [110] Montero-Matamala et al [111] claimed that the anterior approach is better tolerated by all patients, but in particular by terminally ill, heavily sedated patients and by all those who would have difficulty tolerating the lateral or prone positions. Ultrasound was used to locate the celiac arterial trunk. Claims are made that this technique is faster and more convenient than the lateral or posterior approaches and that a single-needle technique is sufficient. Jain and Ketchedjian [112] more recently wrote about the anterior approach. Boas [113] described a "retrocrural" technique for blocking the splanchnic nerves in an effort to improve the success with this block. Although these different approaches have been described, [114] there is no apparent difference with regard to pain relief. Most techniques appear to be safe when practiced appropriately, which usually means neurolytic procedures are done under radiologic control and with the use of a test dose with local anesthetic prior to the use of neurolytic agents through the same needle.

Sharfman and Walsh [115] challenged the efficacy of neurolytic blocks in patients with pancreatic cancer. The celiac plexus block is a percutaneous technique that interrupts afferent and efferent traffic in the celiac plexus. Brown et al [107] documented the definitive and sustained benefit of this technique when used in selected patients. They also showed that the incidence of side effects and complications was low, but not zero. Eisenberg et al [108] provided meta-analysis of the literature concerning neurolytic celiac plexus block. Eighty-nine percent of patients had good to excellent relief for the first 2 weeks after neurolytic celiac plexus block; partial to complete analgesia was maintained in about 90 percent of patients who were alive at 3 months, and 70 to 90 percent of patients surviving longer than 3 months continued to have partial or complete pain relief as well. The complication rate was 2 percent and included such incidents as intravascular injection, epidural or subarachnoid injection resulting in paraplegia, or needle trauma to the kidney, lung, or intestine. Side effects including localized pain at the injection site, diarrhea, and hypotension occurred as well.

There has been an awakening concerning the effectiveness of blocks of the sympathetic nervous system at many levels to provide cancer-related analgesia. An example is superior hypogastric plexus block. [116] [117] [118] This bilateral, retroperitoneal plexus is located at the L5-S1 area (the sacral promontory), close to the bifurcation of the common iliac vessels. It is the continuation of the celiac and lumbar sympathetic chains on each side of the vertebral column, and it innervates the pelvic viscera via the hypogastric nerves. The first description of blockade of this plexus was provided by Plancarte et al in 1990. [117] Twenty-eight patients with

cancers of the cervix, prostate, or testicle who had had a positive response to local anesthetic blocks were given 10 percent aqueous phenol under radiographic guidance. A mean decrease in pain of 70 percent was achieved, and additional therapy increased the analgesia to 90 percent reduction of pain, with these benefits sustained until the patient's death over the ensuing 3 to 12 months in 26 of 28 patients. There were no complications reported, although the potential exists for injury to sacral nerves, bladder or bowel perforation, incontinence, and intravascular injection. Others who have reported benefits with this technique include deLeon-Casasola [116] and Waldman et al. [118]

The union of the bilateral sympathetic chains into a single, retroperitoneal plexus (the ganglion of Walther or the ganglion impar) is located anterior to the coccyx at the sacrococcygeal junction. This can be blocked with local anesthetic and then with neurolytic agents to denervate the lower pelvic structures and the perineum. Plancarte et al [119] presented the first use of this technique in 16 patients with advanced pelvic cancer. From 70 to 90 percent pain relief was achieved in all patients, with a remarkably low incidence of side effects and complications.

Back Pain and Epidural Injection of Steroids

Back pain is a most common and complex type of chronic pain. [14] [15] [16] [29] [77] [120] [121] [122] [123] [124] Many chronic back and extremity pain problems are thought to arise from musculoskeletal sources. A subset of patients with low back pain will have phospholipase A_2 (PLA-2) leaked from the nucleus pulposus as a plausible explanation for their radicular pain. [125] Because it has been shown that corticosteroids can counteract the subsequent inflammatory reaction in the nerve roots and surrounding tissues, several investigators have injected steroids, with or without local anesthetic agents, into the epidural space. [126] The technique consists of injecting 40 to 80 mg methylprednisolone acetate (Depo-Medrol) or 25 to 50 mg triamcinolone diacetate (Aristocort) in 5 to 10 mL of local anesthetic or saline into the epidural space at the level of the suspected pathologic process. In the past, similar doses of steroids, but in smaller volumes of only 1 to 2 mL diluent, had been injected into the subarachnoid space when spinal pain was refractory to epidural administration.

This procedure fell by the wayside years ago when concerns about the tissue toxicity of the corticosteroid preparations was paramount. [127] [128] Subsequent research did not identify that the commercial preparations of corticosteroids are indeed toxic when injected into the subarachnoid space. [129] [130] More to the point, when one understands that radicular pain is believed to originate from inflammatory reactions in the nerve roots in the epidural space, the logic of depositing drugs in the subarachnoid space to manage this pathologic process is lacking.

The significant analgesic effect of epidurally administered opiates in postsurgical and trauma-related pain resulted in their addition to corticosteroids given in the epidural space to treat chronic low back pain more thoroughly. Although initial reports were enthusiastic, subsequent studies were unable to duplicate those results. [131] Intraspinal opiates alone can provide significant pain relief for chronic low back pain caused by nociceptive stimulation from the low back area. [132] Therefore, some patients with chronic low back pain may benefit from ongoing therapy with continuousdelivery systems for administering long-term neuraxial narcotics. The most stable location for the long-term perispinal delivery of opiates is the subarachnoid space, and contemporary therapy includes an intrathecal catheter attached to an implanted pump (after a positive response to a trial of percutaneous intrathecal injections with opiates has been documented). [77]

The true place of steroids in subarachnoid and epidural analgesic blocks is still not completely clarified. [126] Controversy rages with regard to this widely used therapy. Specific guidelines and indications are awaited. Neither the optimal number nor the volume of injections is known, nor is it established whether corticosteroids should be injected with or without local anesthetics or other diluents. Benzon [133] reviewed this controversial topic more than 10 years ago, and many of the essential technique-based queries remain unanswered. Steroids are probably best reserved for instances in which conservative therapy for acute radicular back pain has been ineffective after 4 to 6 weeks or when the patient is suffering a flare-up of chronic back pain that has radicular features. [12] [29] [72] [73] [77] [79] [124] [126] [134] Steroids are used by some clinicians for intra-articular facet joint injections. [77]

Neurolytic Nerve Blocks

Intractable pain of malignant origin may warrant nerve destruction with neurolytic agents by procedures other than those mentioned earlier. [43] [47] This is most commonly considered when life expectancy is short and when chronic pain has a malignant source. It is fair to admit that clinicians still do not have all of the data relevant to deciding the exact indications for nerve blocks or which patients need them and when. Clinicians must carefully select patients for neurolytic procedures, by considering their coagulation and immune status, and must be technically meticulous so as not to obviate the advantages of nerve block therapy (outpatient procedures with less risk than surgery, repeatability, ready availability, and decrease in the need for other therapies [135] [136] [137] [138]). Factors that should influence the decision to use neurolytic regional analgesic techniques include the patient's general medical condition, the location and rapidity of growth of the pain generator, the type of pain, the patient's life expectancy, the risks of the proposed procedure, the patient's tolerance for narcotics and previous conservative therapy measures, the response to a diagnostic block and the tolerance for any related side effects, and access to other specialists. The use of neurolytic blocks represents the ultimate in clinical judgment, rapport, and technical precision. Criteria that must be applied in consideration of such a procedure include a localized source of pain, pain that is diminished with a diagnostic block, pain that is poorly responsive to other more conservative therapy modalities, the absence of coagulopathy, the absence of localized infection or tumor at the proposed site of injection, the patient's tolerance for potential sensory/ motor/continence impairment, and the patient's understanding of the risks. [139]

Because peripheral nerve destruction with alcohol or phenol is frequently followed by denervation/dysesthetic (neuropathic) pain that may be as severe, if not worse, than the original pain, most anesthesiologists access the subarachnoid or epidural spaces for neurolytic injection. [140] The more extensive block provided by these routes of administration is often desirable because of possible growth of the tumor and a subsequent increase in nociceptive stimulation.

The relative merits of the different neurolytic agents are a matter of controversy. Alcohol and phenol are the most widely used agents. [7] The injection of alcohol is very painful, whereas that of phenol, which is usually mixed with saline or glycerin, is painless. The neurolytic effects of alcohol are more intense, and the effect with the block can be evaluated immediately. Phenol has a biphasic action, because it behaves both as a local anesthetic and as a neurolytic agent. Therefore, the extent of the block immediately after the procedure, which may reflect the local anesthetic action, decreases over the ensuing 24 hours to reveal a block of lesser extent. These blocks are not truly permanent; sensation and pain return within weeks or months. Therefore, these procedures are most often suggested to patients whose life expectancy is shorter than this time interval.

Somatic nerve blocks are performed with 50 to 100 percent alcohol, as are blocks of the sympathetic nerves. Alcohol is readily available and is easily stored. For peripheral nerves, 5 to 20 percent phenol is usually diluted with saline or water. For subarachnoid injection of phenol, it is mixed with glycerin (which makes its specific gravity greater than that of cerebrospinal fluid) for use in a hyperbaric technique.

Subarachnoid Neurolytic Nerve Blocks

Neurolytic subarachnoid blocks are best suited for patients with cancers involving the cranial nerves or for tumors involving somatic nerves lying between the limb plexus (i.e., tumors of the breast, chest, abdominal wall, or abdominal viscera). [140] For hypobaric subarachnoid neurolytic nerve blocks, the patient is positioned on the operating room table with the dermatomes to be blocked positioned uppermost. This configuration requires considerable finesse with positioning of the table and appropriate padding and other support to ensure patient comfort and stability during the block. If more than one spinal segment needs to be blocked, needles are inserted at the appropriate spinal levels. Small, discrete

aliquots (0.10-0.25 mL) of absolute alcohol are injected at each level until the desired analgesic effect is obtained. It is usually safer not to try to spread the alcohol over more than a single spinal level. When the desired analgesic effect has been achieved and correlated with appropriate dermatomal analgesia, the patient is left in this position for at least 20 minutes for consolidation of the block.

Hyperbaric subarachnoid neurolytic block is performed with phenol mixed in 10 percent glycerin. This mixture is not commercially available and must be prepared immediately before the block by the hospital pharmacy department. [7] Because glycerin is very viscid, wide-bore needles (18-21 gauge) are used for injection.

Positioning of the patient places the affected side down and the appropriate segmental levels in the most dependent position. The spinal puncture is performed at the appropriate level, and discrete 0.5 mL aliquots of the phenol-glycerin solution are injected until the desired pain relief and dermatomal analgesia have been obtained. As mentioned earlier, treatment of several segmental levels is accomplished more safely by using needles at each level rather than by injecting a larger bolus at a single level.

As an alternative to the traditional neurolytic agents alcohol and phenol, Korsten et al [141] demonstrated, in a small series of 12 terminally ill cancer patients with intractable pain, the effectiveness of a highly lipid-soluble congener of benzocaine, which appeared to afford satisfactory analgesia without creating compromise of motor or bladder/bowel function. Protocols for the clinical use of this agent are in development.

Epidural Neurolytic Nerve Blocks

Epidural nerve block is not widely performed using neurolytic agents. [72] [74] [140] However, epidural injection of 5 or 10 percent phenol in saline has been used successfully for some types of chronic cancer pain. This technique is particularly useful for bilateral pain and is not associated with major motor blockade; it therefore may be appropriate in the region of the limb plexus. It is difficult to detect any evidence of nerve deficits within a day or so of the block, although pain relief often persists considerably longer after this procedure. [7] This is a relatively safe neurolytic procedure, but it carries the theoretical risks of postinjection neuritis, excessive spread, and accidental subarachnoid placement with possible catastrophic paralysis.

Complications

The most frustrating problem with such procedures is usually failure to relieve pain after an apparent satisfactory block. [7] Involvement of nerve structures other than the intended neural elements can lead to unplanned sensory or motor deficits. [7] [74] [78] [107] [108] [109] [116] [140] [142] Thus, establishing the likely diagnosis for the cause of the pain and feeling confident that it can be approached with regional analgesic techniques will go a long way in avoiding these realities. In addition, many cancer pain patients use the intensity of their pain as an index of the activity of their disease. Thus, offers to eliminate the pain must be very clearly understood to guarantee satisfaction on both ends of the needle. Many cancer patients find comfort just in knowing what will be available when needed and will choose not to have all their pain relieved. One must be careful not to exchange tolerable pain for weakness, numbness, incontinence, and/or neuropathic pain. Sphincter disturbance is a very real concern with neurolytic blocks, especially those performed in the lumbar or caudal areas. [7] [140] Retention of urine with overflow incontinence is one of the most common complications. This condition is treated with an indwelling urinary catheter until such time as recovery occurs and the patient can be trained to urinate at regular intervals. These complications usually resolve with days to weeks. Obviously, patients must be thoroughly forewarned of the possibilities, informed consent must be obtained, and preexisting neural deficits must be documented. It is unlikely that a neurolytic block will eliminate all the patient's pain, even when the procedure is performed perfectly. Thus, a compassionate treatment program that blends medication and nonmedication modalities, as in hospice care, will still be needed [135] [136] [138] [143] [144] (Fig. 70-3) .

Neuraxial Administration of Narcotics and Other Drugs

The profound analgesia produced by administration of opioids at spinal cord receptors has led to tremendous interest in the clinical applications of this technique (Ch. 43) . Wang et al [145] initially demonstrated therapeutic feasibility using subarachnoid injections of morphine in patients with terminal cancer. Since then, increasingly sophisticated delivery systems have been used for providing such therapy. [135] [136] [139] [144] [146] [147] [148] It is possible that the patient will have the postoperative epidural catheter left in place so that analgesia can be provided on a continuous basis into the extended in-hospital recovery period or even after discharge from the hospital. [135] [149] [150] [151] Narcotics delivered by indwelling catheters can provide analgesia for patients on an outpatient basis, [152] so patients with terminal cancer can now receive pain relief at home, where home health practitioners provide an increasing array of sophisticated care options. The ability to tunnel these catheters subcutaneously so that they emerge at an anterior abdominal wall site has helped to make this application possible. Automated external and implantable pumps are now also available. [146] [147] [148] Morphine has been the most widely used drug for epidural administration of narcotics for chronic pain. The side effects of its long-term administration (pruritus, urinary retention, mental status change, respiratory depression) occur only rarely and are manageable in patients with terminal cancer. [139] [143] [146] [147] [148]

Hogan et al [153] studied the use of epidural opioids and local anesthetics in referred patients with cancer pain. Of 1,205 patients, these investigators identified 16 who needed perispinal drugs. Six of the 16 patients obtained relief with just morphine, whereas the remaining 10 needed local anesthetic added. Common components of an epidural infusion could include opioids, local anesthetics, clonidine, and, occasionally, steroids. [146] [147] [148] Local anesthetics have been suggested as adjuncts in most infusions for chronic pain because one generally wants to avoid inducing weakness, numbness, and/or postural hypotension, which are the primary pharmacologic effects of the drugs. When patients

Figure 70-3 A daily diary kept by the patient can be very helpful in determining the nature and cause of chronic pain. The patient records all daily activity (sitting, walking/standing, and reclining). The right side of the diary documents the time and doses of medication; and the last column, the level of pain (on a scale of 0 to 10). If pain "switches off" at night, as in this example, pain may well be caused by environmental factors, rather than tissue damage. In this patient, the record of medication does not indicate drug dependence. Also significant is the inordinate amount of downtime. Specifically, the patient is active for only 2¼ hours a day, the rest of the time being spent reclining or sitting. This fact suggests that a behavior-modification program to improve the level of activity would be appropriate.

show refractoriness to the opioid infusion, local anesthetics have been used to "rest" the opioid receptors and to restore their effectiveness during a brief hospitalization.

Detractions from epidural opioid infusions other than tolerance include the lack of expertise for initiation of such treatment and/or its maintenance in the patient's home area, the labor intensiveness of the follow-up care, and the cost. Sjoberg et al [156] [157] provided an important study that addressed the safety of long-term intrathecal injections of drugs for the treatment of refractory cancer pain. They detailed the neuropathic changes in 15 patients with infusions of morphine and bupivacaine for a median of 81 days (range, 4-274 d). [156] No patient had neuropathic changes correlated with the duration or cumulative doses of the intrathecal

therapy. This group also refined the recommendations about specific drugs one could infuse in patients with intractable cancer pain. [157] Fifty-three patients had VAS scores decreased from 6 to 7 of 10 to 0 to 2 of 10 during an infusion duration of 7 to 334 days while receiving a continuous infusion of morphine and bupivacaine in roughly a 1:10 ratio. Reported side effects were associated with bupivacaine and included urinary retention, paresthesias, gait impairment, and, occasionally, orthostatic hypotension.

The search for "new" analgesics will continue. DuPen et al [150] demonstrated the feasibility of combining morphine with low-dose bupivacaine to maximize analgesia even in a home-based setting. Steroids may be beneficial in decreasing the consequences of inflammatory neuropathy, as when cancer invades neural structures in the epidural space. Clonidine, an alpha $_2$ -adrenergic agonist, has become available for general use as a modality in neuropathic pain control. [154] [155] Through actions at presynaptic and postsynaptic alpha $_2$ -receptors of the spinal cord, 30 mug hourly can augment opioid-based analgesia with a low profile of side effects. [146] [147] [148] [154] [155] A central effect of benzodiazepines that is less dramatic for C fiber stimulation than it is for A-delta stimulation has been demonstrated, so these drugs may find utility in the future, as may NMDA antagonists, ion channel blockers, NSAIDs, and cholinesterase inhibitors. [147] Even with these valuable additions to the pharmacologic armamentarium, more modalities must be at hand. Unique techniques for regional analgesia other than neuraxial blockers, [158] [159] neuroablative procedures, [160] and neurosurgical treatments [161] [162] [163] represent such diversity.

Anesthesiologists have guided the subspecialty of pain management for years and have advocated the rational administration of drugs and the performance of nerve blocks to treat chronic pain. They have recognized, too, that other therapies are necessary. Because the treatment of patients with chronic pain has now become the practice of pain medicine, all health care workers must acknowledge the need for a treatment *program,* one that incorporates a number of therapeutic modalities (in addition to medications) used concurrently, regards all the discovered contributors to the "pain," and fosters routine follow-up so that the therapeutic plan can be

modified to include only those treatments that are contributing positively to the patient's quality of life.

/das/book/view/29494766/875/771.html

PSYCHOLOGIC ASPECTS OF PATIENTS WITH CHRONIC PAIN

Patients with chronic pain, who may have had unsatisfactory treatment at the hands of the medical profession, often interpret a referral for psychologic evaluation as an indication that their pain is "all in their head," "imaginary," or "not real." One may ask, how can a patient who is so desperate for improvement be closed-minded about any therapeutic option that has potential for diminishing some of the pain? It is vitally important to introduce patients (and family members) to the idea of psychologic evaluation at a very early point in the comprehensive evaluation scheme. [1] [4] [5] [6] [7] [9] [11] [25] [26] [38] The assessment aims to explore the breadth of the patient's emotional reaction range, identifies behaviors that are being reinforced, and investigates the reality of the patient's expectations about treatment. It may be optimal to accomplish both medical and psychologic evaluations simultaneously, as is most frequently done in contemporary practice. Patients with chronic pain cannot deny the presence of anxiety, depression, or frustration, for example, which they attribute to the agony of their chronic pain. (This testimony fulfills the operative definition of pain, that it is both a sensory and an emotional experience). The incidence of depression in chronic low back pain patients is approximately three to four times greater than in the general population. [164] [165]

Behavioral Analysis

Because of the influential importance of behavioral factors in many patients with chronic pain, a form of behavioral analysis by a clinical psychologist or psychiatrist should be considered. [9] [166] [167] Numerous formalized, standardized tests are used including the classic Minnesota Multiphasic Personality Inventory (MMPI) and the newer Symptom Checklist 90 (SCL-90). Behavioral analysis usually has little application in pain problems caused by acute tissue damage, except when the disruption of the patient's lifestyle provokes excessive anxiety or anger that obstructs therapeutic progress, or it occurs in a patient with preexisting chronic pain whose subsequent symptoms seem disproportionate to the injury or circumstances. The patient should have objective documentation of the relationship between daily activities and pain. This is frequently accomplished with the use of a diary, [26] which lists specific activities such as sitting, reclining, or standing and the accompanying level of pain as well as the nature and timing of medication (see Fig. 70-3) .

Behavioral evaluation should identify those factors that increase or decrease pain behavior. Evidence of how the patient has handled stress in the past and the presence of dependent personalities, external locus of control, or a tendency to misuse substances are established during this interview. Reinforcing factors that enable pain behavior are identified, as are patients who are blatantly psychotic and who thus deserve appropriate therapy directed at this significant aspect of their illness. [168] Patients with neuropsychologic deficits are identified, and proper action is taken.

When environment and behavioral factors are paramount in chronic pain, patients may benefit more from inpatient management, especially if dependence on medications is excessive, family members are strongly reinforcing pain behavior, or structured physical exercise is also necessary. [165] [166] [167] There is no evidence that chronic pain resolves with bed rest. [7] These three factors can be very difficult to attend to consistently on an outpatient basis. The primary goal of inpatient care is to reduce specific pain behaviors. This is a relatively easy goal to reach, particularly over the short term, and therapy often produces extremely effective results. [7]

Reduction of medications and an increase in physical activity are two very important goals of inpatient operant conditioning for behavior modification in patients with chronic pain. [9] [166] The difficult task is to substitute a "well-behavior" lifestyle for the previous pain-oriented lifestyle. A main goal is usually to increase the level of activity, because most people with chronic pain have considerable "down time"; that is, bed rest and inactivity have almost inevitably become part of the problem, rather than part of the solution. Most patients

---

with chronic pain are somewhat more mobile than implicated earlier and can cooperate with a graded aerobic exercise/conditioning program that is an integral part of most pain-management programs. Increasing endurance is a measurable parameter of behavioral change and can, in fact, be quantified. [169] [170]

Retraining the family is also vitally important. The family must learn to not reinforce pain behavior but to encourage nonpain behavior. [9] [166] The patient must be impelled to develop self-care and pain-coping strategies to deal with the pain more realistically. The patient will manifest less reliance on external resources and will begin to retake control of the pain when this is accomplished. Before attempting behavioral modification of a patient's pain problem, one should be sure that the desired behavioral changes are within the patient's capabilities. It is obviously inappropriate to attempt to rehabilitate an individual for a given task or skill if that person would be incapable of that activity even without the pain complaint. [7]

Pain-management programs contribute substantially to the rehabilitation of chronic pain sufferers, and there is evidence that the more intensive the program, the greater the improvement. [171] Objective measures such as activity and work status are desirable, whereas control groups left to rely on conventional medical support "languish or deteriorate." [171] Behavior modification programs using operant conditioning are very effective in reversing pain behavior, reducing dependence on medications, and decreasing use of health care resources. [7] [166] [172]

Disability Associated With Chronic Pain

Physicians who work in pain centers are often asked to rate the degree of disability in the case of injured workers. This is an exceedingly complex and controversial problem without easy solutions and one in which distress between medical and nonmedical issues is often intertwined. [173] One of the strongest predictors of developing disabling back pain on the job is work dissatisfaction. [174] Thus, pain and disability become woven; "it is hard to get well if you have to prove that you are sick." [175] Although often far removed from the anatomy and physiology of nociception, the issues of disability, such as wage replacement and job satisfaction, become pivotal in the assessment and management of disabled workers. [176] Because the data submitted on various physical capability forms are so crucial to the realistic rehabilitation of patients, completing such paperwork should not be done in a cavalier fashion. Many practitioners become certified in declaring disability or use the professional services of colleagues trained in the application and interpretation of functional capacity evaluation methods. Ergonomic evaluation analyzes the patient in his or her total work environment and is an additional, sometimes crucial, but often neglected, arena for investigation.

Biofeedback Techniques

Biofeedback is a self-regulation technique used for controlling normally unconscious or involuntary bodily activity, such as a heart rate, through conscious mental control. [12] [24] In theory, this goal becomes possible when some type of signal is used to make such activity perceptible to the individual's senses. Biofeedback has had its best results in the control of the muscle contraction component of head and neck pain and in migraine headaches. Muscle contractions are recorded with a surface electromyographic electrode, and the patient then learns how to make dial readings or tones change, reflecting a lessening of muscle contraction and, therefore, tension. For migraine headaches, the signal used may be the skin temperature of a digit. The patient learns to improve blood flow to the digits as manifested by a rise in local skin temperature while reducing headache symptoms.

Controversy exists as to whether biofeedback techniques produce better results than simple relaxation training. [12] [24] On the one hand, biofeedback does constitute a safe and benign therapy for muscle contraction conditions, head and neck pain, and migraine headaches and has a success rate of 30 to 60 percent. [7] On the other hand, biofeedback techniques alone are much less successful for low back pain and other pain syndromes, although many pain centers use the method as an adjunct therapy in patients with multiple pain syndromes. A critical review by Zitman [177] described the difficulty of evaluating current studies using this form of therapy and confirmed that relaxation training, because it is most easily applied and is less expensive, is probably the treatment of choice. Further critical evaluation may produce more selective recommendations regarding thermal and electromyographic feedback techniques. [178]

STIMULATION OF THE NERVOUS SYSTEM

Transcutaneous Electrical Nerve Stimulation

When great advances in the understanding of the mechanisms of pain were first being made, one of the earliest applications of this new knowledge pertained to TENS. [23] The use of stimulation techniques for the nervous system was originally based on the reality that hyperstimulation of the nervous system could "drown out" pain. [23] [179] [180] Our contemporary understanding acknowledges that stimulation may also provoke the outpouring of inhibitory neurotransmitters or may manipulate the normal physiologic inhibition or facilitation of afferent input. [179] [180] Stimulators consist of small, battery-powered, portable units that can be worn undetected under clothing (Fig. 70-4) . The corresponding stimuli are administered through flat electrodes applied to the skin. Because TENS has few, if any, side effects, it is highly recommended as an adjunct treatment for patients with chronic pain. The advantages of such therapy are numerous, but the fact that TENS is patient controlled (frequency and strength of stimulation, frequency of use, duration of use), noninvasive, and portable enhances its utility. As with other forms of stimulation-produced analgesia, such as acupuncture and massage, the TENS electrodes are usually placed near the painful area. The stimulators provide low-intensity stimuli of 5 to 200 Hz, which produces a tingling or vibration sensation. Transcutaneous nerve stimulators appear to work best in patients

Figure 70-4 One of the many transcutaneous stimulator units available commercially. Most units use a rechargeable battery pack. The electrodes consist of soft conductive rubber; they conform well to most anatomic sites of application, held in place by tape. Contact is facilitated by conductive jelly placed between the electrode and the skin.

with myofascial syndromes, peripheral nerve injuries, phantom limb pain, and stump pain. [7] These stimulators are less effective in low back pain and cervical spine pain, especially if the patient has had surgery. TENS appears to be unsatisfactory in patients with chronic pain that has no peripheral nociceptive cause (such as central pain states or psychosocial-based pain) and in patients with a physiologic and/or psychologic dependence on drugs. [7]

Many innovative methods to deliver electrical stimulation to the neuraxis and deep brain sites have been tried. [181] [182] [183] [184] The use of deep brain stimulation has been reviewed, and as yet the true place of this invasive technique for controlling chronic pain has not been exactly clarified. [183] Electrical stimulation of central brain-stem sites, such as the nucleus raphe magnus and the periventricular gray matter, can produce profound analgesia in both animals and human beings, but the relation of these findings to TENS is not well defined. Electrical stimulation of the dorsal columns of the spinal cord has now been virtually abandoned as an open, operative procedure. Dorsal column stimulation via percutaneously placed epidural electrodes is a technologic advance that is becoming more popular for patients with chronic spinal pain. [181] [182] [184] Careful selection of patients by their meeting specific criteria for both the implantation procedure and the trial period and by passing psychologic screening [185] can result in an admirable success rate in a group of patients for whom other, more conservative, therapies have not resulted in satisfactory analgesia or adequate return to functional status. North et al [186] established that the trial stimulation should decrease pain by at least 50 percent, decrease concurrent medication use, and result in a very low incidence of side effects. Other reviews echo the experience of most clinicians who use spinal cord stimulation in chronic pain management; mainly, that at best the success rate is approximately 40 percent over the long term. [184] [187]

Acupuncture

Acupuncture is a minimally invasive technique founded in Asian medicine that has neurophysiologic consequences probably related to augmentation of neural input or the provocation of modulating influences. [188] [189] A distracting focus of input is created by the insertion of needles into specific points around the body, as described in historical charts. Newer variations of the traditional technique that use needling of the painful area and sometimes add electrical stimulation through the needles are in vogue. Such treatments do seem to influence pain perception, but they produce relatively weak analgesia and may be more effective in acute pain than in chronic pain. The added expense and the need for a therapist make acupuncture less available than TENS as a therapy for chronic pain, yet the public demand for it and for the many complementary therapies is high. [190] [191] Studies have shown that headache frequency and analgesic consumption are significantly decreased during a course of both acupuncture and placebo treatments. [192] Reviews have been most critical of acupuncture, yet it has been endorsed by the National Institutes of Health for a few, nonpain applications (nausea and vomiting associated with pregnancy, chemotherapy, and the postoperative period) and postoperative dental pain. [193]

Neurosurgical Techniques

Surgery has been performed on almost every conceivable part of the nervous system--from peripheral nerves to the frontal lobes of the brain--in an attempt to control pain. [163] [194] Even though neurosurgical procedures often produce good pain relief on a short-term basis, as with other neurodestructive procedures, pain often returns over time. Therefore, neurosurgical ablation techniques may be best

reserved for patients with terminal cancer and, ideally, those having a life expectancy of only several months. Dorsal rhizotomies, much used in the past, do not consistently provide the desired long-lasting pain relief. Some cranial neuralgias resistant to carbamazepine arise from intracranial arterial compression of the trigeminal or glossopharyngeal nerves, for which operative relief of this compression has been successful in eliminating pain in some patients. [7]

Percutaneous Cordotomy

Percutaneous cordotomy has been used by several practitioners in specialized centers throughout the world. Although it requires special skills and equipment, it appears to be an effective way of interrupting the lateral spinothalamic tract of the spinal cord in which a majority of sensory input ascends to higher CNS levels. Although percutaneous cordotomy initially produces a 95 percent success rate in relieving pain, this rate decreases to 25 percent after 1 year. [7] [194] Therefore, as with most neurodestructive procedures, percutaneous cordotomy is more successful in the patient with terminal illness and a short life-span than in the patient with pain of nonmalignant origin. As with open cordotomy, it is difficult to produce analgesia in the cervical and upper thoracic dermatomes using percutaneous techniques. Postoperative mortality in percutaneous cordotomy, resulting from sleep apnea, occurs in fewer than 1 percent of patients having unilateral procedures but in as many as 10 percent of patients having bilateral procedures. Nashold et al [195] described a new technique for neurosurgical ablation of the dorsal root entry zone (DREZ) in the management of refractory deafferentation pain problems, such as nerve plexus avulsion. [196]

Deep Brain Stimulation

Over the past decade, invasive neurosurgical implantation of electrodes has been used by enthusiasts to treat chronic pain of both malignant and nonmalignant nociceptive origin with mixed success. [163] [194] In a large series of 141 such patients, pain relief occurred in approximately 30 percent. [183] Nociceptive pain is treated usually by stimulation of the periaqueductal or periventricular gray matter, whereas deafferentation pain is treated usually by stimulation of the sensory thalamus. In this series, greater success was achieved in patients believed to have a nociceptive source of pain. Long-term follow-up evaluation of patients undergoing deep brain stimulation indicates that 60 percent of patients with nociceptive sources do obtain pain relief, whereas fewer than 50 percent of those with deafferentation pain achieve lasting results. The rate of complications with this therapy was significant. [183] [194] As experience grows, fewer technical problems should occur while the exact place of this therapy in the armamentarium of pain management is clarified.

Neurolytic Surgical Procedures

Heat lesioning with RF techniques [194] [197] and cold lesioning with cryotherapy techniques [198] have been used to interrupt pain-carrying nerve fibers. Thermocoagulation of the gasserian ganglion has been most effective in the 15 percent of patients with trigeminal neuralgia who do not respond adequately to carbamazepine. [194] Because of its effectiveness and low incidence of side effects, this technique has replaced alcohol block of the gasserian ganglion for these refractory cases. The patient is thereby spared hemifacial numbness, with its conjunctival inflammatory problems. Most series attest to the benign nature of thermocoagulation, which can be repeated if necessary. RF lesions of the DRG of cervical nerves (C4, C5, or C6) in patients with chronic cervical neck pain have the expected 75 percent success during the first month or so after surgery, but pain recurs 3 to 9 months after treatment. [199]

Nerves can be "frozen" with a cryoprobe, [198] [200] the lesion of which disrupts sensory nerve functions for several weeks and may have a lower incidence of denervation neuralgias that often follow the destruction of nerves with neurolytic drugs such as alcohol. Cryoprobes have been shown to control the time-limited pain after thoracotomy. [201] They have also been used for control of chronic pain, mainly on superficial trigeminal nerve branches, and for lumbar facet nerves. [198]

SUMMARY

Because of the tremendous growth in interest in the disease of pain and its subsequent management and the proliferation of facilities for treating patients with pain, the opportunities and demands for clinicians in many specialties to become involved in pain management are increasing. Practitioners need not only technical ability in a variety of nerve blocks, but also the general diagnostic, management, and clinical skills necessary to provide ongoing care for these often complicated and difficult-to-manage patients. Traditionally, these skills have not been part of most anesthesia training programs, although increasing numbers of fellowship positions are now available that permit more formal acquisition of the necessary skills.

Wilson et al [202] stressed the importance of integrating clinical and basic science experience for medical students, but why be so limited in focusing on this group of neophytes? The blending of such data is important for all practitioners, to influence long-term clinical attitudes and to produce lasting changes in practice behavior in a state of affairs whereby health care providers (as well as students) perceive only the negative characteristics of patients with chronic pain, and believe that working with them is "too difficult." By introducing the students at an early stage in their curriculum to the known facts concerning acute and chronic pain and the treatment spectrum, one can develop an understanding that all pain is very real and can also convey the message that working with these patients can be rewarding. [202]

Currently, it seems that pain-management programs are the treatment of choice for those patients disabled by chronic nonmalignant pain. Although added expense is involved, such programs appear to be cost-effective because the alternatives of conventional therapy and repeated operations may be even more expensive. Clinicians' efforts in pain medicine should initially be directed toward prevention. When injury occurs, rapid remobilization of the injured

---

worker and identification of those patients destined to have chronic pain needing the long conservative therapy model are now appreciated. Because so many of the more chronic varieties of pain are accompanied by a significant array of nonphysical influences, it is unlikely that simple therapy for these long-standing entities will be discovered. Anesthesiologists should mobilize the analgesic and anesthetic resources and skills they have to maximize the control of pain at its onset while realizing that a comprehensive, diversified program of therapy is most likely to benefit the patient with chronic pain. Taking this leadership role will honor the rich tradition that anesthesiology enjoys and will propel the fledgling specialty of pain medicine in its natural evolution.

References

1. Sidall PJ, Cousins MJ: Introduction to pain mechanisms: Implications for neural blockade. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 675.

2. Rowlingson JC: Pain relief before pain starts. Am Pain Soc J 2:125, 1993.

3. Sinatra RS: Acute pain management and acute pain services. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 793.

4. Turk DC, Okifuji A: Interdisciplinary approach to pain management: Philosophy, operations, efficacy. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 235.

5. Haddox JD, Bonica JJ: Evolution of the specialty of pain medicine and the multidisciplinary approach to pain. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 113.

6. Ready LB, Laird D: The interface between acute and chronic pain. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 613.

7. Murphy TM: Chronic pain. In Miller RD (ed): Anesthesia, 4th ed. New York, Churchill Livingstone, 1994, p 2345.

8. Yaksh TL: Physiologic and pharmacologic substrates of nociception and nerve injury. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 727.

9. Fordyce WF: Behavioral Methods for Chronic Pain and Illness. St. Louis, CV Mosby, 1976.

10. Jacobson L, Mariano AJ, Chabal C et al: Beyond the needle: Expanding the role of anesthesiologists in the management of chronic non-malignant pain. Anesthesiology 87:1210, 1997.

11. Dworkin RH: Which individuals with acute pain are most likely to develop a chronic pain syndrome? Pain Forum 6:127, 1997.

12. Mauskop A: Head pain. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 249.

13. Bigos S, Bowyer O, Braen G et al: Acute low back problems in adults. Clinical Practice Guidelines: Quick Reference Guide No. 14. Agency for Health Care Policy and Research, AHCPR Pub. No. 95-0643. Rockville, Md, U.S. Dept. of Health and Human Services, Public Health Service.

14. Deyo RA, Loeser JD, Bigos SJ: Herniated lumbar intervertebral disk. Ann Intern Med 112:598, 1990.

15. Frymoyer JW, Cats-Baril WL: An overview of the incidence and costs of low back pain. Orthop Clin North Am 22:263, 1991.

16. Osti OL, Cullum DE: Occupational low back pain and intervertebral disc degeneration: Epidemiology, imaging and pathology. Clin J Pain 10:331, 1994.

17. Raja SN, Meyer RA, Campbell JN: Peripheral mechanisms of somatic pain. Anesthesiology 68:571, 1988.

18. Sluka KA, Willis WD, Westlund KN: The role of dorsal root reflexes in neurogenic inflammation. Pain Forum 4:141, 1995 (see commentaries on pp 150-162).

19. Mayer EA, Gebhart GF: Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 107:271, 1994.

20. Byrod G, Olmarker K, Konno S et al: A rapid transport route between the epidural space and the intraneural capillaries of the nerve roots. Spine 20:138, 1995.

21. Woolf CJ, Chong MS: Preemptive analgesia: Treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 77:362, 1993.

22. Basbaum AI, Fields HL: Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci 7:309, 1984.

23. Melzack R, Wall PD: Pain mechanisms: A new theory. Science 150:971, 1965.

24. Doleys DM, Murray JB, Klapow JC et al: Psychological assessment. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 27.

25. Melzack R: Psychological aspects of pain. Implications for neural blockade. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 781.

26. Longmire DR: Evaluation of the pain patient. In Raj PP (ed): Pain Medicine: A Comprehensive Review. St. Louis, CV Mosby, 1996, p 26.

27. Follick MJ, Ahein DK, Laser-Wolston N: Evaluation of a daily activity diary for chronic pain patients. Pain 19:373, 1984.

28. Marple RL, Kroenke K, Lucey CR et al: Concerns and expectations in patients presenting with physical complaints. Arch Intern Med 157:1482, 1997.

29. Spitzer WO, LeBlanc FE, Dupuis M: Scientific approach to the assessment and management of activity related spinal disorders: a monograph for clinicians. Report of the Quebec Task Force on Spinal Disorders. Spine 12(Suppl):S1, 1987.

30. Deyo RA: Fads in the treatment of low back pain. N Engl J Med 325:1039, 1991.

31. Fernandez E, Turk DC: The scope and significance of anger in the experience of chronic pain. Pain 61:165, 1995.

32. Waldman SD: Providing pain management services. II. Special considerations. Am J Pain Med 4:132, 1994.

33. Abram SE, Gillespie BM: Standards of care and reimbursement issues in pain management. In Raj PP (ed): Practical Management of Pain, 2nd ed. St. Louis, Mosby-Year Book, 1992, p 40.

34. Elam K, Cherkin D, Deyo R: How emergency physicians approach low back pain: choosing costly options. J Emerg Med 13:143, 1995.

35. Lanes T, Gauron E, Spratt K et al: Long-term follow-up of patients with chronic low back pain treated in a multidisciplinary rehabilitation program. Spine 20:801, 1995.

36. Flor H, Fydrich T, Turk DC: Efficacy of multidisciplinary pain treatment centers: A meta-analytic review. Pain 49:221, 1992.

37. Cutler RB, Fishbain DA, Rosomoff HL et al: Does nonsurgical pain center treatment of chronic pain return patients to work? Spine 19:643, 1994.

38. Burton A, Tillotson K, Main C et al: Psychosocial predictors of outcome in acute and subchronic low back pain trouble. Spine 20:722, 1995.

39. Deyo RA, Diehl AK: Patient satisfaction with medical care in low-back pain. Spine 11:28, 1986.

40. von Korff M, Barlow W, Cherkin D et al: Effects of practice style in managing back pain. Ann Intern Med 121:187, 1994.

41. Egan TD: Modern clinical pharmacology concepts and pain management. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 75.

42. Zuckerman LA, Ferrante FM: Nonopioid analgesia. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 111.

43. Katz JA: Opioids and nonsteroidal anti-inflammatory analgesics. In Raj PP (ed): Pain Medicine: A Comprehensive Review. St. Louis, CV Mosby, 1996, p 126.

44. Bjorkman R, Hallman K, Hedner J et al: Acetaminophen blocks spinal hyperalgesia induced by NMDA and substance P. Pain 57:259, 1994.

45. Portenoy RK, Foley KM: Chronic use of opioid analgesics in nonmalignant pain: Report of 38 cases. Pain 25:171, 1986.

46. Turk DC, Brody MC, Okifuji EA: Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. Pain 59:201, 1994.

47. Turk DC, Okifuji A: What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? Clin J Pain 13:330, 1997.

---

48. Bonica JJ: Cancer pain. In Bonica JJ (ed): Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 400.

49. Jacox A, Carr DB, Payne R et al: Management of Cancer Pain: Clinical Practice Guidelines No. 9. AHCPR Publication No. 94-0592. Rockville, Md, Agency for Health Care Policy and Research, U.S. Dept. of Health and Human Services, Public Health Service, 1994.

50. Grond S, Zech D, Schug SA et al: Validation of World Health Organization Guidelines for Cancer Pain Relief during last days and hours of life. J Pain Symptom Manage 6:411, 1991.

51. Collin E, Poulain P, Gauvain-Piquard A: Is disease progression the major factor in morphine "tolerance" in cancer treatment? Pain 5:319, 1993.

52. Paalzow L, Nilsson L, Stenberg P: Pharmacokinetic basis for optimal methadone treatment of pain in cancer patients. Acta Anaesthesiol Scand Suppl 74:55, 1982.

53. Hansen J, Ginman C, Hartvig P et al: Clinical evaluation of oral methadone in treatment of cancer pain. Acta Anaesthesiol Scand Suppl 74:124, 1982.

54. Forrest WIT: Dextroamphetamines with morphine for the treatment of postoperative pain. N Engl J Med 296:712, 1977.

55. Bruera E, Fainsinger R, MacEachern T: The use of methylphenidate in patients with incident cancer pain receiving regular opiates: A preliminary report. Pain 50:75, 1992.

56. Streisand JB, Ashburn MA: Noninvasive drug delivery systems. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 187.

57. Lipman AG: Pharmacological approaches to pain management: Nontraditional analgesics and analgesic adjuvants. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 99.

58. Dapas F, Hartmann SF, Martinez LB: Baclofen for the treatment of acute low-back syndrome. Spine 10:345, 1985.

59. Tanalian DL, Brose WG: Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: Lidocaine, carbamazepine, and mexiletine. Anesthesiology 74:949, 1991.

60. Rosner H, Rubin L: Gabapentin adjunctive therapy in neuropathic pain states. Clin J Pain 12:56, 1996.

61. Field MJ, Oles RJ, Lewis AS et al: Gabapentin (neurontin) and S -(+)-3 isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol 121:1513, 1997.

62. Fitton A, Goa KL: Lamotrigine: An update on its pharmacology and therapeutic use in epilepsy. Drugs 50:691, 1995.

63. Pecile A: Calcitonin and the relief of pain. Bone Mineral 16:187, 1992.

64. Goblet C, Waldburger M, Meier JL: The effect of adding calcitonin to physical treatment of reflex sympathetic dystrophy. Pain 48:171, 1992.

65. Mauni G: On the relationship between chronic pain and depression when there is no organic lesion. Pain 31:1, 1987.

66. Ahles TA, Yunus MB, Masi AT: Is chronic pain a variant of depressive disease? The case of primary fibromyalgia syndrome. Pain 29:105, 1987.

67. Frazier A: Antidepressants. J Clin Psychiatry 58:9, 1997.

68. McQuay HJ, Tramer M, Nye BA: A systematic review of antidepressants in neuropathic pain. Pain 68:217, 1996.

69. Lejoyeux M, Ades J: Antidepressant discontinuation: A review of the literature. J Clin Psychiatry 58:11, 1997.

70. Hogan QH, Abram SE: Neural blockade for diagnosis and prognosis: A review. Anesthesiology 86:216, 1997.

71. Abram SE: Pain mechanisms in lumbar radiculopathy. Anesth Analg 67:1135, 1988.

72. Bonica JJ, Buckley FP: Regional analgesia with local anesthetics. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 1883.

73. Hogan QH: Neural blockade for diagnosis and treatment of painful conditions. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 275.

74. Patt RB, Cousins MJ: Technologies for neurolytic neural blockade. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 1007.

75. Berry AJ, Greene ES: The risk of needle stick injury and needle stick-transmitted diseases in the practice of anesthesiology. Anesthesiology 77:1007, 1992.

76. Benson H, Friedman R: Harnessing the power of the placebo effect and renaming it "remembered wellness." Annu Rev Med 47:193, 1996.

77. Manning DC, Rowlingson JC: Back pain and the role of neural blockade. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 879.

78. Ditonto ED, de Leon-Casasola OA: Neurolytic blockade for the management of pain associated with cancer. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 489.

79. Hogan QH, Abram SE: Diagnostic and prognostic neural blockade. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 837.

80. Goldenberg DL: Fibromyalgia syndrome: An emerging controversial condition. JAMA 257:2782, 1987.

81. Sola AE, Bonica JJ: Myofascial pain syndromes. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 352.

82. Boissevain MD, McCain CA: Toward an integrated understanding of fibromyalgia syndrome. I. Medical and pathophysiological aspects. Pain 45:227, 1991.

83. Wolfe F, Smythe HA, Yunus MB: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee. Arthritis Rheum 33:160, 1990.

84. Lewitt K: The needle effect in the relief of myofascial pain. Pain 6:83, 1979.

85. Roberts WJ: An hypothesis on the physiological basis for causalgia and related pains. Pain 24:297, 1986.

86. Raja SN, Treede R-D, Davis KD et al: Systemic alpha-adrenergic blockade with phentolamine: A diagnostic test for sympathetically maintained pain. Anesthesiology 74:691, 1991.

87. Sherman RA, Karstetter KW, Damiano M: Stability of temperature asymmetries in reflex sympathetic dystrophy over time and changes in pain. Clin J Pain 10:71, 1994.

88. Harden RN, Duc TA, Williams TR et al: Norepinephrine and epinephrine levels in affected versus unaffected limbs in SMP. Clin J Pain 10:324, 1994.

89. Janig W: Experimental approach to reflex sympathetic dystrophy and related syndromes. Pain 46:241, 1991.

90. Gellman H, Keenan MAE, Stone L et al: Reflex sympathetic dystrophy in brain injured patients. Pain 51:307, 1993.

91. Arner S: Intravenous phentolamine test: Diagnostic and prognostic use in reflex sympathetic dystrophy. Pain 46:17, 1991.

92. Ready LB, Kozody R, Barsa JE et al: Side-port needles for stellate ganglion block. Reg Anesth 7:160, 1982.

93. Galindo A: Special needles for nerve blocks. Reg Anesth 5:12, 1980.

94. Kozody R, Ready LB, Barsa J et al: Dose requirements of local anesthetics to produce grand-mal seizures during stellate ganglion block. Can Anaesth Soc J 29:489, 1982.

95. Rowlingson JC: Lumbar ganglion. In Hahn MB, McQuillan PM, Sheplock GJ (eds): Regional Anesthesia: An Atlas of Anatomy and Techniques. St. Louis, CV Mosby, 1996, p 183.

96. Wang JK, Erickson RP, Ilstrup DM: Repeated stellate ganglion blocks for upper extremity reflex sympathetic dystrophy. Reg Anesth 10:125, 1985.

97. Wang JK, Johnson KA, Ilstrup DM: Sympathetic blocks for reflex sympathetic dystrophy. Pain 23:13, 1985.

98. Hannington-Kiff JG: Intravenous regional sympathetic block with guanethidine. Lancet 1:1019, 1974.

99. Bonelli S, Conoscente F, Movilia PG et al: Regional intravenous guanethidine vs stellate ganglion block in reflex sympathetic dystrophies: A randomized trial. Pain 16:297, 1983.

100. Glynn CJ, Basedow RW, Walsh JA: Pain relief following postganglionic sympathetic blockade with IV guanethidine. Br J Anaesth 53:1297, 1981.

101. Ford SR, Forrest WH Jr, Eltherington L: The treatment of reflex sympathetic dystrophy with intravenous regional bretylium. Anesthesiology 68:137, 1988.

102. Hord AH, Rooks MD, Stephens DO et al: Intravenous regional bretylium and lidocaine for treatment of reflex sympathetic dystrophy: A randomized double-blind study. Anesth Analg 74:818, 1992.

103. Poplawski ZJ, Wiley AM, Murray JF: Post-traumatic dystrophy of the extremities. J Bone Joint Surg Am 65:642, 1983.

104. Vanos DN, Ramamurthy S, Huffman J: Intravenous regional block using ketorolac: Preliminary results in the treatment of reflex sympathetic dystrophy. Anesth Analg 74:139, 1992.

105. Raj PP: Reflex sympathetic dystrophy. In Raj PP (ed): Pain Medicine: A Comprehensive Review. St. Louis, CV Mosby, 1996, p 466.

106. Rauck RL, Eisenach JC, Jackson K et al: Epidural clonidine treatment for refractory reflex sympathetic dystrophy. Anesthesiology 79:1163, 1993.

107. Brown DL, Bulley CK, Quiel EL: Neurolytic celiac plexus block for pancreatic cancer pain. Anesth Analg 66:869, 1987.

108. Eisenberg E, Carr DB, Chalmers TC: Neurolytic celiac plexus block for treatment of cancer pain: A meta-analysis. Anesth Analg 80:290, 1995.

109. Wong GY, Brown DL: Celiac plexus block for cancer pain. Tech Reg Anesth Pain Manage 1:18, 1997.

110. Cherry DA, Rao DM: Lumbar sympathetic and coeliac plexus block: An anatomical study in cadavers. Br J Anaesth 54:1037, 1992.

111. Montero-Matamala A, Lopez FV, Sanchez JL et al: Percutaneous anterior approach to the coeliac plexus using ultrasound. Br J Anaesth 62:637, 1989.

112. Jain S, Ketchedjian AG: Anterior approach to the celiac plexus block. Pain Digest 5:264, 1995.

113. Boas RA: The sympathetic nervous system and pain relief. In Swerdlow M (ed): Relief of Intractable Pain. New York, Elsevier, 1983, p 215.

114. Ischia S, Ischia A, Poliati E et al: Three posterior percutaneous celiac plexus block techniques. Anesthesiology 76:534, 1992.

115. Sharfman WH, Walsh TD: Has the analgesic efficacy of neurolytic celiac plexus block been demonstrated in pancreatic cancer pain? Pain 41:267, 1990.

116. deLeon-Casasola OA: Superior hypogastric block and ganglion impar neurolysis for pain associated with cancer. Tech Reg Anesth Pain Manage 1:27, 1997.

117. Plancarte R, Amescula C, Patt R et al: Superior hypogastric plexus blocks for pelvic cancer pain. Anesthesiology 73:236, 1990.

118. Waldman SD, Wilson WL, Kreps RD: Superior hypogastric plexus block using a single needle and computed tomography guidance: Description of a modified technique. Reg Anesth 16:286, 1991.

119. Plancarte R, Amescula C, Patt R et al: Presacral blockade of the ganglion of Walther (ganglion impar). Anesthesiology 73:A751, 1990.

120. Borenstein D: Low back pain: Epidemiology, etiology, diagnostic evaluation, and therapy. Curr Opin Rheumatol 3:207, 1991.

121. McCowin PR, Borenstein D, Wiesel SW: The current approach to the medical diagnosis of low back pain. Orthop Clin North Am 22:315, 1991.

122. Frank A: Low back pain: Review. BMJ 306:901, 1993.

123. McCulloch J: Differential diagnosis of low back pain. In Tollison C, (ed): Handbook of Chronic Pain Management. Williams & Wilkins, Baltimore, 1994, p 347.

124. Rowlingson JC, Keifer RB: Low back pain. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 261.

125. Saal JS, Franson RC, Dobson R et al: High levels of inflammatory phospholipase A_2 activity in lumbar disc herniations. Spine 15:674, 1990.

126. Rowlingson JC: Epidural steroids: Do they have a place in pain management? Am Pain Soc J 3:20, 1994.

127. Abram SE: Subarachnoid corticosteroid injection following inadequate response to epidural steroids for sciatica. Anesth Analg 57:313, 1978.

128. Nelson DA: Further warnings from Australia concerning intraspinal steroids. Arch Neurol 48:259, 1991.

129. Wilkinson HA: Intrathecal Depo-Medrol: A literature review. Clin J Pain 8:49, 1992.

130. Abram SE, Marsala M, Yaksh TL: Analgesic and neurotoxic effects of intrathecal corticosteroids in rats. Anesthesiology 81:1198, 1994.

131. Dallas TL, Lin RL, Wu WH et al: Epidural morphine and methylprednisolone for low back pain. Anesthesiology 67:408, 1987.

132. Murphy TM, Hinds S, Cherry DC: Intraspinal narcotics for nonmalignant pain. Acta Anaesthesiol Scand Suppl 31:75, 1987.

133. Benzon HT: Epidural steroid injections for low back pain and lumbosacral radiculopathy. Pain 24:277, 1986.

134. Spaccarelli KC: Lumbar and caudal epidural corticosteroid injections. Mayo Clin Proc 71:169, 1996.

135. Ferrer-Brechner T: Anesthetic techniques for the management of cancer pain. Cancer 63:2343, 1989.

136. Lipton S: Pain relief in active patients with cancer: The early use of nerve blocks improves the quality of life. BMJ 298:37, 1989.

137. Rowlingson JC, Hamill RJ, Patt RB: Comprehensive assessment of the patient with cancer pain. In Patt RB (ed): Cancer Pain. Philadelphia, JB Lippincott, 1993, p 23.

138. Ashburn MA, Lipman AG: Management of pain in the cancer patient. Anesth Analg 76:702, 1993.

139. Waldman SD, Feldstein GS, Allen M et al: Selection of patients for implantable intraspinal narcotic delivery systems. Anesth Analg 65:883, 1986.

140. d'Amours RH, Ferrante FM: Subarachnoid and epidural neurolysis. Tech Reg Anesth Pain Manage 1:32, 1997.

141. Korsten HHM, Ackerman EW, Grouls RJE et al: Long-lasting epidural sensory blockade by *n*-butyl- *p*-aminobenzoate in the terminally ill intractable cancer pain patient. Anesthesiology 75:950, 1991.

142. Jain S, Patt RB: Complications of invasive procedures. In Patt RB (ed): Cancer Pain. Philadelphia, JB Lippincott, 1993, p 443.

143. Ventafridda V: Continuing care: A major issue in cancer pain management. Pain 36:137, 1989.

144. Watling CJ, Payne R: Management strategies for pain in the cancer patient. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 473.

145. Wang JK, Nauss LE, Thomas JE: Pain relief by intrathecally applied morphine in man. Anesthesiology 50:149, 1979.

146. Waldman SD, Leak DW, Kennedy LD et al: Intraspinal opioid therapy. In Patt RB (ed): Cancer Pain. Philadelphia, JB Lippincott, 1993, p 285.

147. Carr DB, Cousins MJ: Spinal route of analgesia: opioids and future options. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 915.

148. Rauck RL: Intraspinal therapy in the management of refractory cancer pain. Tech Reg Anesth Pain Manage 1:38, 1997.

149. de Leon-Casasola OA, Myers DP, Donaparthi S et al: A comparison of postoperative epidural analgesia between patients with chronic cancer pain taking high doses of oral opioids versus opioid-naive patients. Anesth Analg 76:302, 1993.

150. DuPen SL, Kharasch ED, Williams A: Chronic epidural bupivacaine-opioid infusion in intractable cancer pain. Pain 49:293, 1992.

151. Lubenow TR, Ivankovich AD: Intraspinal narcotics for treatment of cancer pain. Sem Surg Oncol 6:173, 1990.

152. Downing J, Busch EH, Stedman PM: Epidural morphine delivered by a percutaneous epidural catheter for outpatient treatment of cancer pain. Anesth Analg 67:1159, 1988.

153. Hogan Q, Haddox JD, Abram SE: Epidural opiates and local anesthetics for the management of cancer pain. Pain 46:271, 1991.

154. Eisenach JC, DuPen S, Dubois M: The Epidural Clonidine Study Group: Epidural clonidine analysis for intractable cancer pain. Pain 61:391, 1995.

155. Eisenach JC, DeKock M, Klimscha W: Alpha 2-adrenergic agonists for regional anesthesia: A clinical review of clonidine (1984-1995). Anesthesiology 85:655, 1996.

156. Sjoberg M, Karlsson P-A, Nordborg C et al: Neuropathic findings after long-term intrathecal infusion of morphine and bupivacaine for pain treatment in cancer patients. Anesthesiology 76:173, 1992.

157. Sjoberg M, Nitescu P, Applegren L et al: Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain. Anesthesiology 80:284, 1994.

158. Sist T: Head and neck nerve blocks for cancer pain management. Tech Reg Anesth Pain Manage 1:3, 1997.

159. O'Leary KA, Myers DP: Interpleural analgesia and neurolysis. Tech Reg Anesth Pain Manage 1:11, 1997.

160. Saberski L, Ligham D: Neuroblative techniques for cancer pain management. Tech Reg Anesth Pain Manage 1:53, 1997.

161. Sundaresan N, DiGiacinto GV, Hughes JEO: Neurosurgery in the treatment of cancer pain. Cancer 63:2365, 1989.

162. Tasker RR: Neurosurgical and neuroaugmentative intervention. In Patt RB (ed): Cancer Pain. Philadelphia, JB Lippincott, 1993, p 471.

163. Silvers J, Campbell JN, North RB: Neurosurgical modalities for pain management. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 519.

164. Sullivan MJL, Reesor K, Mikail S et al: The treatment of depression in chronic low back pain: Review and recommendations. Pain 50:5, 1992.

165. Ward NG: Pain and depression. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 310.

166. Fordyce WE: Learned pain: Pain as behavior. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 291.

167. Pilowsky I: Pain and chronic illness behavior. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 300.

168. Merskey H: Chronic pain and psychiatric illness. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 320.

169. Manniche C, Lundberg E, Christensen I et al: Intensive dynamic back exercises for chronic low back pain: A clinical trial. Pain 47:53, 1991.

170. Linchitz RM, Capulong E, Battista DF et al: Physical modalities for pain management. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 401.

171. Peters J, Large RG, Elkind G: Follow up results of a randomized control trial evaluating in and out patient management programs. Pain 50:41, 1992.

172. Linton SJ: Behavioral remediation of chronic pain: A status report. Pain 24:125, 1986.

173. Brena SF, Meacham AM: Evaluation of function and disability. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 641.

174. Bigos SJ, Battie MC, Spengler DN et al: A prospective study of work perceptions and psychosocial factors affecting the report of back injury. Spine 16:1, 1991.

175. Hadler NM: Backache and humanism. In Frymoyer J (ed): The Adult Spine. New York, Raven Press, 1991, p 55.

176. Sullivan MD, Loeser JD: The diagnosis of disability: Treating and rating disability in a pain clinic. Arch Intern Med 152:1829, 1992.

177. Zitman FG: Biofeedback and chronic pain. In Bonica JJ (ed): Advances in Pain Research and Therapy, vol 5. New York, Raven Press, 1983, p 795.

178. Flor H, Haag G, Turk DC: Long-term efficacy of EMG biofeedback for chronic rheumatic back pain. Pain 27:195, 1986.

179. Myerson BA: Electrostimulation procedures: effects, presumed rationale, and possible mechanisms. In Bonica JJ (ed): Advances in Pain Research and Therapy, vol 5. New York, Raven Press, 1983, p 495.

180. Sjolund BH, Erikkson M, Loeser JD: Transcutaneous and implanted electric stimulation of peripheral nerves. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 1852.

181. North RB, Kidd DH, Zahurak M et al: Spinal cord stimulation for chronic intractable pain: Experience over two decades. Neurosurgery 32:384, 1993.

182. Root TM, Weaver MA, Hahn MB: Implantation therapy for pain management. In Ashburn MA, Rice LJ (eds): The Management of Pain. New York, Churchill Livingstone, 1998, p 419.

183. Levy RN, Lamb S, Adams JE: Treatment of chronic pain by deep brain stimulation: Long-term follow-up and review of the literature. Neurosurgery 21:885, 1987.

184. Shetter A: Spinal cord stimulation in the treatment of chronic pain. Curr Rev Pain 1:213, 1997.

185. Nelson DV, Kennington M, Novy DM et al: Psychological selection criteria for implantable spinal cord stimulators. Pain Forum 5:93, 1996.

186. North RB, Kidd DH, Lee MS et al: A prospective, randomized study of spinal cord stimulation versus reoperation for failed back surgery syndrome: Initial results. Stereotact Funct Neurosurg 62:267, 1994.

187. De La Porte C, Van de Kelft E: Spinal cord stimulation in failed back surgery syndrome. Pain 52:55, 1993.

188. Chapman CR, Gunn CC: Accupuncture. In Bonica JJ (ed): The Management of Pain, 2nd ed. Philadelphia, Lea & Febiger, 1990, p 1805.

189. Raj PP, Evans D: Accupuncture. In Raj PP (ed.): Pain Medicine: A Comprehensive Review. St. Louis, CV Mosby, 1996, p 309.

190. Eisenberg DM, Kessler RC, Foster C et al: Unconventional medicine in the United States: Prevalence, costs, and patterns of use. N Engl J Med 328:246, 1993.

191. Paramore LC: The use of alternative therapies: Estimates from the 1994 Robert Wood Johnson Foundation National Access to Care Survey. J Pain Symptom Manage 13:83, 1997.

192. Tavola T, Galla G, Conte G et al: Traditional Chinese accupuncture in tension type headache: A control study. Pain 48:325, 1992.

193. National Institutes of Health (NIH): NIH Consensus Development Conference on Accupuncture. Bethesda, Md, NIH, 1997.

194. Tasker RR: Neurostimulation and precutaneous neural destructive techniques. In Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia, Lippincott-Raven, 1998, p 1063.

195. Nashold BS, Aosdahl RH, Bullite E et al: Dorsal root entry root zone lesions: A new neurosurgical therapy for deafferentation pain. In Bonica JJ (ed): Advances in Pain Research and Therapy, vol 5. New York, Raven Press, 1983, p 739.

196. Wynn Parry CB: Management of pain in avulsion lesions of the brachial plexus. In Bonica JJ (ed): Advances in Pain Research and Therapy, vol 5. New York, Raven Press, 1983.

197. Noe CE, Racz GB: Radiofrequency. In Raj PP (ed): Pain Medicine: A Comprehensive Review. St. Louis, CV Mosby, 1996, p 305.

198. Arthur JM, Racz GB: Cryolysis. In Raj PP (ed): Pain Medicine: A Comprehensive Review. St. Louis, CV Mosby, 1996, p 297.

199. van Kleef M, Spaans F, Dingemans W et al: Effects and side effects of a percutaneous thermal lesion of the dorsal root ganglion in patients with cervical pain syndrome. Pain 52:49, 1993.

200. Evans PJD: Cryoanalgesia: The application of low temperature to nerves to produce anaesthesia or analgesia. Anaesthesia 36:1003, 1981.

201. Rooney SM, Subhash J, McCormack et al: A comparison of pulmonary function tests for post-thoracotomy pain using cryoanalgesia and transcutaneous nerve stimulation. Ann Thorac Surg 41:204, 1986.

202. Wilson JF, Brockopp GW, Kryst S et al: Medical student attitudes toward pain before and after a brief course of pain. Pain 50:251, 1992.

/das/book/view/29494766/875/775.html

Appendix-GUIDELINES FOR THE USE OF OPIOIDS IN THE TREATMENT OF CHRONIC, NON-CANCER PAIN

THE MEDICAL SOCIETY OF VIRGINIA

Report of the MSV Pain Management Subcommittee

Preface

Recently, there has been increasing interest on the part of physicians, regulatory agencies, legislators, the public and patients for the proper diagnosis, timely workup and state of the art treatment for acute, cancer and non-cancer chronic pain conditions. While there is widespread agreement among health care providers concerning the treatment of acute and cancer pain with opioids (also known as narcotics)--as exemplified by Federal Clinical Practice Guidelines published by the Agency for Health Care Policy and Research, U.S. Department of Health and Human Services--there has been a lack of consensus, misunderstanding and hesitation among health care providers (physicians, nurses, pharmacists), regulatory agencies, patients and third party providers concerning the use of these same agents in the management of chronic, non-cancer pain.

Inadequate understanding about issues such as addiction, tolerance, physical dependence and abuse has led to unfounded stigma against proper opioid prescription. Fears of legal and regulatory sanctions or discipline from local, state and federal authorities often result in inappropriate and inadequate treatment of chronic pain patients. Undertreatment or avoidance of appropriate opioid therapy increasingly has been reported by physicians, patients, and other health care team members.

The discipline of pain medicine has produced a new awareness about the necessity of proper diagnosis, history and physical examination and treatment planning for the patient with chronic pain. Unfortunately, the paucity of specially trained physicians in the field of pain management often precludes patient access to specialized pain treatment facilities. The treatment for these patients will appropriately fall within the realm of the primary care or specialty physician. Until adequate guidelines are made for prescribers of opioids for patients with chronic noncancer pain, episodes of undertreatment of this deserving population will continue.

As a result of the efforts and recommendations of the Governor's Joint Subcommittee studying pain, the Medical Society of Virginia's House of Delegates, at the 1996 annual meeting of its legislative body, recognized the lack of national consensus as well as the need for parameters concerning the proper use of opioids for patients with intractable pain of non-cancer origin within the Commonwealth of Virginia. The following guidelines are presented with the hope that they will attenuate fears about professional discipline, encourage adequate and proper treatment of chronic pain with all appropriate therapies, and educate about and protect patients as well as the general public from unsafe or inappropriate prescribing patterns or abuses.

The Society believes that physicians have an obligation to treat patients with intractable pain and to lessen suffering and that opioids may be appropriately and safely prescribed for many acute, cancer and chronic pain conditions as long as acceptable protocols and standards are closely followed. The Society feels that physicians should be encouraged to prescribe, dispense and administer opioids when there is demonstrated medical necessity and proper indication for these agents without fear of discipline, excessive scrutiny or remunerative or restrictive legal penalties.

These guidelines should not be interpreted as absolute standards of care in the treatment of chronic pain patients, nor are they absolute directives for clinical practice. Rather, they are guidelines by which all physicians may more safely and comfortably evaluate and treat this very problematic and needy group of patients.

Guidelines for the Use of Opioids in the Treatment of Chronic, Non-Cancer Pain

For the purposes of this document the following terms shall have the following definitions:

Addiction is a disease process involving use of opioid(s) wherein there is a loss of control, compulsive use, and continued use despite adverse social, physical, psychological, occupational, or economic consequences.

Substance abuse is the use of any substance(s) for non-therapeutic purposes; or use of medication for purposes other than those for which it is prescribed.

Physical dependence is a physiologic state of adaptation to a specific opioid(s) characterized by the emergence of a withdrawal syndrome during abstinence, which may be relieved in total or in part by re-administration of the substance. Physical dependence is a predictable sequelae [sic] of regular, legitimate opioid or benzodiazepine use, and does not equate with addiction.

Tolerance is a state resulting from regular use of opioid(s) in which an increased dose of the substance is needed to produce the desired effect. Tolerance may be a predictable sequelae of opiate use and does not imply addiction.

Withdrawal syndrome is a specific constellation of signs and symptoms due to the abrupt cessation of, or reduction in, a regularly administered dose of opioid(s).

Opioid withdrawal is characterized by three or more of the following symptoms that develop within hours to several days after abrupt cessation of the substance: (a) dysphoric mood, (b) nausea and vomiting, (c) muscle aches and abdominal cramps, (d) lacrimation or rhinorrhea, (e) pupillary dilation, piloerection, or sweating, (f) diarrhea, (g) yawning, (h) fever, (i) insomnia.

Acute pain is the normal, predicted physiological response to an adverse (noxious) chemical, thermal, or mechanical stimulus. Acute pain is generally time limited and is historically responsive to opioid therapy, among other therapies.

Chronic pain is persistent or episodic pain of a duration or intensity that adversely affects the function or well-being of the patient, attributable to any non-malignant etiology.

Assessment, Documentation and Treatment

A. History and Physical Examination

The physician must conduct a complete history and physical exam of the patient prior to the initiation of opioids. At a minimum the medical record must contain documentation of the following history from the chronic pain patient:

1. Current and past medical, surgical, and pain history including any past interventions and treatments for the particular pain condition being treated.
2. Psychiatric history and current treatment.
3. History of substance abuse and treatment.
4. Pertinent physical examination and appropriate diagnostic testing.
5. Documentation of current and prior medication management for the pain condition, including types of pain medications, frequency with which medications are/were taken, history of prescribers (if possible), reactions to medications, and reasons for failure of medications.
6. Social/work history.

B. Assessment

A justification for initiation and maintenance of opioid therapy must include at a minimum the following initial workup of the patient:

1. The working diagnosis (or diagnoses) and diagnostic techniques. The original differential diagnosis may be modified to one or more diagnoses.
2. Medical indications for the treatment of the patient with opioid therapy. These should include, for example, previously tried (but unsuccessful) modalities/medication regimens, diverse reactions to prior treatments, and other rationale for the approach to be utilized.
3. Updates on the patient's status including physical examination data must be periodically reviewed, revised, and entered in the patient's record.

C. Treatment Plan and Objectives

The physician must keep detailed records on all patients, which at a minimum include:

1. A documented treatment plan.
2. Types of medication(s) prescribed, reason(s) for selection, dose, schedule administered and quantity.
3. Measurable objectives such as:
   a. social functioning and changes therein due to opioid therapy.
   b. activities of daily living and changes therein due to opioid therapy.
   c. adequacy of pain control using standard pain rating scale(s) or at least statements of the patient's satisfaction with the degree of pain control.

D. Informed Consent and Written Agreement for Opioid Treatment

Written documentation of both physician and patient responsibilities must include:

1. Risks and complications associated with treatment using opioids
2. Use of a single prescriber for all pain related medications.
3. Use of a single pharmacy, if possible.
4. Monitoring compliance of treatment:
   a. Urine/serum medication levels screening (including checks for non-prescribed medications/substances) when requested.
   b. Number and frequency of all prescription refills.
   c. Reason(s) for which opioid therapy may be discontinued (e.g. violation of written agreement item(s)).

E. Periodic Review

Intermittent review and comparison of previous documentation with the current medical records are necessary to determine if continued opioid treatment is the best option for a patient. Each of the following must be documented at every office visit:

1. Efficacy of Treatment
   a. Subjective pain rating (e.g. 0 & shy; 10 verbal assessment of pain)
   b. Functional changes.
      i. Improvement in ability to perform activities of daily living (ADLs).
      ii. Improvement in home, work, community or social life.
2. Medication side effects.
3. Review of the diagnosis and treatment plan.
4. Assessment of compliance (e.g. counting pills, keeping record of number of medication refills, frequency of refills and disposal of unused medications/prescriptions).
5. Unannounced urine/serum drug screens and indicated laboratory testing, when appropriate.

F. Consultation

Most chronic non-cancer patients, like their cancer pain counterparts can be adequately and safely managed by most physicians without regard for specialty. However, the treating physician must be cognizant of the availability of pain management specialists to whom the complex patient may be referred. The physician must be willing to refer the patient to a physician or a center with more expertise when indicated or when difficult issues arise. Consultations must be documented. The purpose of this referral should not necessarily be to prescribe the patient opioids.

G. Medical Records

Accurate medical records must be kept, including, but not limited to documentation of:

1. All patient office visits and other consultations obtained.
2. All prescriptions written including date, type(s) of medication, and number (quantity) prescribed.
3. All therapeutic and diagnostic procedures performed.
4. All laboratory results.
5. All written patient instructions and written agreements.

Summary/Concluding Remarks

The treatment of patients with chronic, non-cancer pain should not be limited to pain specialists only. Because of complex social, regulatory, ethical and legal issues surrounding the use of opioids in these patients, the physician who elects to help treat these patients may find it useful to utilize the guidelines and examples outlined in this document. While these guidelines do not define standard of care, it is the hope of the Medical Society of Virginia, working in close conjunction with the Virginia Board of Medicine, and the Commonwealth of Virginia's Joint Subcommittee to Study the Commonwealth's Current Laws and Policies Related to Chronic, Acute and Cancer Pain Management, that physicians who do treat this very difficult and deserving patient population will find significant clinical benefit from this document and will be enlightened by the suggestions offered herein.

This document is the product of the Medical Society of Virginia's Ad Hoc Subcommittee on the Treatment of Chronic Non-Cancer Pain and is the result of many

months of deliberation and study. Members of this committee were Stephen P. Long, MD, Chairman; John Barsanti, MD; Edwin Harvie, MD; Joanne Hudson, MD; Albert Jones, MD; Katherine Maurath, MD; Randolph Merrick, MD; John Rowlingson, MD; Paul Spector, DO; John Tietjen, MD; Thomas Wash, MD. Ex Officio members were Senator Jane Woods; Delegate Vincent Behm; Warren Koontz, MD (Executive Director, Virginia Board of Medicine); Karen Perrine, Esquire (Virginia Board of Medicine); Norma Szakal, Esquire (Division of Legislative Services).

The Medical Society of Virginia.
4205 Dover Road, Richmond VA 23221
(804) 353-2721.

Section 5 - Critical Care Medicine

Chapter 71 - Overview of Anesthesiology and Critical Care Medicine

Robert R. Kirby
Cheri A. Sulek
Michael J. Banner

INTRODUCTION

In October 1979, the Society of Critical Care Medicine listed 882 physician members, of whom 386 (44%) were anesthesiologists. By March 1984, 2,351 physicians were members, 643 (27%) of whom were anesthesiologists. In June 1988, the physician membership had increased to 2,835 and included 679 (24%) anesthesiologists. As of May 1992, the physician membership was 5,411, of whom 916 (17%) were anesthesiologists, and in 1996, physician membership was 6,905, of whom 1,150 were anesthesiologists (17%) (Table 71-1) . Thus, in absolute terms, the rate of increase of anesthesiologists in the Society of Critical Care Medicine slowed, and the percentage of anesthesiologist members declined substantially from 1979 to 1996 (Table 71-1) . At the same time, surgeons (1,850) and internists (2,801) increased their membership and in 1996 outnumbered anesthesiologists by a significant margin. [1]

In view of the illustrious contributions by anesthesiologists to the inception and development of critical care medicine over the past 45 years, the reasons for the decline can only be surmised. The practicalities of modern medicine cannot be ignored. In anything other than an academic setting, anesthesiologists can find employment in an intensive care unit (ICU) but have difficulty being reimbursed. Often, they must work in the operating room, at least on a part-time basis, in order to be able to afford the "luxury" of practicing critical care. Third-party payers seem more likely to reimburse them for administering anesthetics (albeit at an increasingly reduced rate) than for the time they spend in the ICU. This situation seems unlikely to change in the near future and may be the primary reason that fewer anesthesiologists enter critical care medicine than entered a few years ago.

THE ANESTHESIOLOGIST'S ROLE IN CRITICAL CARE

Techniques that anesthesiologists employ daily in the operating room--airway management, including tracheal intubation and manual or mechanical ventilation; intravenous administration of potent and rapidly acting pharmacologic agents; blood and fluid infusion; and cardiorespiratory monitoring--are the mainstays of intensive therapy and critical care medicine. No other specialty provides similar day-to-day experience in these areas, as a result of which anesthesiologists have the oppe the opportunity to become highly proficient and technically competent. They are well suited to assume an important role in critical care if they so choose.

Profound pathophysiologic changes occur in ICU patients, often with little or no warning. Rapid diagnosis and treatment on a minute-to-minute basis are essential if intact survival is to result. Implementation of therapy requires knowledge of physiologic, biochemical, and pharmacologic principles, augmented by sound clinical experience. Critical care medicine represents the ultimate in clinically applied basic science, and no specialty training provides a stronger background in the basic sciences than anesthesiology.

The relationship of the physical and life sciences on the one hand to the art of medicine on the other has been integral to the growth of anesthesiology and to the role of its specialists in the development of techniques including mechanical ventilation, [2] [3] [4] [5] [6] [7] cardiovascular monitoring, [8] [9] positive end-expiratory pressure (PEEP) and continuous positive airway pressure (CPAP), [10] [11] [12] [13] cardiopulmonary resuscitation, [14] resuscitation of the acutely brain-injured patient, [15] and parenteral nutrition. [16] [17] By 1985, noninvasive monitoring techniques, including pulse oximetry and capnography, were commonplace in anesthesiology [18] [19] and are now published standards of care. [20] They are regularly employed in the ICU, augmenting (and often supplanting) more invasive, and hence potentially more dangerous, methods. [21]

TABLE 71-1 -- Membership in the Society of Critical Care Medicine (1979-1996)

YEAR	ANESTHESIOLOGISTS		ALL OTHER PHYSICIANS	
	NO.	*% TOTAL PHYSICIANS*	*NO.*	*%*
1979	386	44	496	56
1984	643	27	1,708	73
1988	679	24	2,156	76
1992	916	17	5,411	83
1996	1,150	17	6,905	83

New methods of ventilatory support were introduced in attempts to improve the outcome and to decrease the untoward effects of mechanical ventilation. [7] [22] [23] [24] [25] [26] [27] [28] [29] Lessons learned in the ICU have been translated into the design of new anesthesia ventilators that are significantly improved compared with their earlier counterparts. [30] [31] This example also highlights the parallel, yet interdependent, development of modern anesthesiology and critical care medicine.

MAJOR PROBLEM AREAS

Problems in critical care medicine are so numerous that one chapter cannot possibly discuss them in any meaningful fashion. However, some, by their ubiquitous nature, impact, and expense, may transcend the rest. Every intensivist can prepare a similar list, and each probably would attach different importance to individual items. Our list is summarized in Table 71-2 . With a few exceptions, it is similar to the one published in the second edition of this text.

Monitoring

Prevention of Cardiac Arrest

Davis [32] addressed the history of intraoperative monitoring. Most of what he said appears applicable to the ICU. In the early 1950s, interest in abrupt and unexpected cardiac arrest was heightened as allegations that it was increased during anesthesia were disseminated. Subsequently, improved methods of resuscitation were developed, [14] culminating in today's well-known basic and advanced cardiac life support. Emphasis was placed on the early detection of circulatory abnormalities and rapid restoration of hemodynamic stability because cerebral damage or death could occur if oxygenation was interrupted for more than a few minutes. In the operating room, this interest translated into increased use of simple physical assessment of heart rate, arterial blood pressure, and skin color.

In 1947, however, Comroe and Botelho [33] described the unreliability of detecting cyanosis visually, even by trained physiologists and anesthesiologists. Similarly, indirect measurements of blood pressure and pulse rate long have been known to be poor indicators of cardiovascular function under many conditions of anesthesia and surgery. As a result, increasing reliance has been placed on electronic surveillance and vascular cannulation to evaluate cardiopulmonary function, with the expectation that improved monitoring will translate into improved patient care. However, this expectation has not been realized.

Taylor et al [34] reviewed 41 cases of intraoperative cardiac arrest detailed in malpractice claims between 1956 and 1971. Thirty-one of the patients were healthy and were undergoing elective surgical procedures. Resuscitation was prompt, yet all but three of the survivors sustained permanent brain damage. In these cases of cardiac arrest resulting from respiratory dysfunction and hypoxemia, the cardiovascular monitoring detected cardiac dysfunction too late to prevent brain damage.

Similar data were presented by Davis. [32] Of 18 cases in which cardiac arrest was the heralding event signaling an intraoperative circulatory catastrophe, 15 patients were resuscitated, but all sustained permanent brain injury. The other three patients died. Nineteen additional cases of unsuspected brain damage occurred, only one of which had any premonitory signs of circulatory inadequacy. Davis concluded that the central nervous system was damaged before recognizable cardiovascular distress signals were detected.

Caplan et al [35] reported similar findings in a study of 14 cases of cardiac arrest in healthy patients undergoing spinal anesthesia for elective or emergency operative procedures. A detailed retrospective analysis suggested that applicable standards of anesthesia care were employed and that observation and monitoring were appropriate. Nevertheless, 10 of the 14 patients never regained consciousness, whereas three of the four who did sustained permanent brain damage. Objective criticism of the techniques of resuscitation, including an inordinate delay in the use of epinephrine, was provided in an accompanying editorial. [36] These observations no doubt played a role in the changes of guidelines and standards for intraoperative monitoring that have been published by the American Society of Anesthesiologists. [20]

TABLE 71-2 -- Major Critical Care Problems

MANAGEMENT
Monitoring
Invasive
Noninvasive
Cost-effectiveness
Respiratory
Equipment
Techniques
Complications
Resuscitation
Fluids and electrolytes
Cardiopulmonary
Drugs
Central nervous system
OUTCOME
Predictive indices
MISCELLANEOUS CONSIDERATIONS
Renal, hepatic function
Nutrition
Bleeding
Ethical
Acquired immunodeficiency syndrome
Transplantation

Invasive Techniques

The response to this problem was an escalation of invasive monitoring in both the operating room and the ICU (Chs. 30, 31, and 35) . With increased invasive monitoring, however, came new problems. Catheter-related thrombosis, embolization, infection, and sepsis were well known and well documented. More ominous, however, was the possibility of mortality directly related to, or resulting from, the technique employed. Robin [37] suggested that the overall mortality associated with pulmonary artery (PA) catheterization was 1 percent. In 1986, he estimated that 500,000 of these catheters were inserted in the United States. Hence, by his analysis, some 5,000 patients may have died as a result of the monitoring used to assess their well-being.

Some corroboration for Robin's viewpoint was expressed by Connors et al, [38] who studied 5,735 patients, 2,179 (38%) of whom underwent PA catheterization. In this group, 1,354 (62%) were still alive 30 days later, compared with 2,463 (69%) of the 3,566 noncatheterized patients. The two study groups allegedly were similar with respect to age and severity of illness. Of perhaps equal significance was the failure to identify any patients who appeared to benefit from PA catheterization. In this regard, even widely standardized noninvasive techniques have not been demonstrated to reduce morbidity and mortality. [32] [35] [39] In view of the $2 billion estimated cost associated with the use of PA catheters, the findings of Robin [37] and Connors et al [38] warrant further assessment, as suggested in an editorial commentary by Dalen and Bone [40] and a 1997 consensus statement. [41]

To improve the quality and the quantity of information obtained, new technology incorporated a fiberoptic sheath that allows PA catheter reflectance spectrometry determination of mixed venous oxygen saturation (Sv O_2). In general, Sv O_2 correlates directly with cardiac output if oxygen consumption remains unchanged. Continuous monitoring of Sv O_2 in critically ill patients now is thought by many to represent a satisfactory means to assess cardiac outputent a satisfactory means to assess cardiac output that is similar to intermittent Sv O_2 assessment in the past. [11] Other PA catheters utilize a fast-response thermistor and two intracardiac

TABLE 71-3 -- Proposed Etiologic Factors in Acute Respiratory Failure

Thoracic trauma
Sepsis
Acute pancreatitis
Aspiration of gastric contents
Acid pH < 1.5-2.0
Food
Meconium (newborn)
Necrotizing pneumonia (viral, bacterial)
Near-drowning
Oxygen (F_{IO_2} > 0.6)
Brain injury (hypothalamic dysfunction)
Altitude
Fat embolization, pulmonary thromboembolization
Amniotic fluid embolization
Inhalation of toxic gases, vapors, smoke
Fluid overload (doubtful in absence of congestive heart failure)
Hyaline membrane disease (newborn)
Disseminated intravascular coagulation
Prolonged cardiopulmonary bypass
Acquired immunodeficiency syndrome

electrocardiographic electrodes for measurement of cardiac output, right ventricular ejection fraction, right ventricular end-diastolic and end-systolic volumes, and stroke volume in conjunction with a single-purpose ejection fraction cardiac output computer. Efficacy in conjunction with transesophageal echocardiography and radionuclide techniques has been demonstrated.

Two other PA catheters also warrant mention: one incorporates a 10-MHz ultrasound transducer proximal to the catheter tip that measures instantaneous and continuous cardiac output with Doppler-shifted ultrasound [42] ; the other employs a filamentous element in the right ventricle that is heated intermittently in pseudorandom fashion. Heat transfer to the blood results in a downstream temperature change in the PA. [43] This stochastic identification technique thus uses a warm thermal indicator to provide continuous cardiac output data.

Respiratory Care

Basic Concerns

Causes of acute respiratory failure are variable (Table 71-3) , but the acute manifestations are sufficiently similar to be considered as a single entity--the acute respiratory distress syndrome (ARDS) (Ch. 72) . Although simplified, this method of classification has merit. Assuming that a major error in diagnosis has not been made, standardized therapy may be applied. If one accepts the premise that severe, uncorrected cellular hypoxia ultimately is lethal, a simplified concept of therapeutic priorities can be created. These include improvement of gas exchange, particularly oxygen transfer, optimization of oxygen transport from the lungs to the tissues, and enhancement of oxygen use by the cells.

Patients who are unable to breathe spontaneously require some form of ventilatory support. However, many are able to maintain effective alveolar ventilation but are hypoxemic because of ventilation/perfusion abnormalities and intrapulmonic shunting. The primary goal of therapy is restoration of satisfactory oxygenation through the use of PEEP/CPAP. Full support of ventilation (carbon dioxide removal) is not required. Intermittent and synchronized intermittent mandatory ventilation are useful techniques that allow a combination of spontaneous breathing with controlled or assisted mechanical ventilation, respectively. [2] [3] As long as sufficient PEEP/CPAP is used to maintain lung inflation and to increase pulmonary compliance, these techniques work very well. [11] [12]

Large tidal volume (V_T) and high peak inflation pressure are often used to effect adequate ventilation in severe cases of ARDS. Pulmonary barotrauma and depression of cardiovascular function, particularly in hypovolemic patients, may result. Interest has been directed toward low V_T and pressure delivered at a rapid rate (
60 breaths per minute) in an attempt to decrease or eliminate these problems and to improve ventilation and oxygenation. [4] [5] The techniques are referred to collectively as high-frequency ventilation. High-frequency ventilation is useful in diagnostic and therapeutic laryngoscopy and bronchoscopy, some cases of bronchopleurocutaneous fistula, newborn diaphragmatic hernia, and persistent pulmonary hypertension of the newborn. Results

in ARDS are equivocal, and widespread application in adult critical care, despite more than 30 years of development, has not occurred.

To achieve similar goals, permissive hypercapnia has been advocated. [44] A reduction of V_T and minute ventilation delivered by conventional techniques (as opposed to high-frequency ventilation) is deliberately employed, allowing partial pressure of arterial carbon dioxide (Pa_{CO_2}) to increase. Lower peak inflation pressures and V_T are thought to reduce barotrauma (volutrauma) and other complications of conventional therapy. Markedly improved survival in ARDS is reported, [44] but the technique has not been validated in controlled trials. [45]

V/Q Inequalities in Respiratory Failure

Reductions in both partial pressure of arterial oxygen (Pa_{O_2}) and Pa_{CO_2} are characteristic of the early stage of ARDS. Later, Pa_{CO_2} increases, and in the terminal stage of the disease, it cannot be returned to normal by even the most vigorous attempts at mechanical ventilation. Hypoxemia results from continued perfusion of lung regions with decreased-to-absent ventilation.

Poliomyelitis, Guillain-Barre syndrome, and other neuromuscular diseases produce respiratory insufficiency because of a failure of mechanical or neural control of ventilation. ARDS, in contrast, represents a failure of gas exchange that is related primarily to parenchymal involvement. Both neuhough exceptions, such as flail chest associated with an underlying pulmonary contusion, do occur. Even in this case, the musculoskeletal abnormality is of secondary importance to the underlying pulmonary contusion.

A mechanical ventilator is a satisfactory device to sustain ventilation when neuromuscular and musculoskeletal dysfunction predominate. When a decrease in alveolar volume is present--whether associated with surfactant depletion, partial airway obstruction, interstitial and alveolar pulmonary edema, or a combination of these factors--a mechanical ventilator can have salutary effects only during inspiration. During expiration, when airway pressure is reduced, alveolar volume is again decreased, and oxygen exchange is impaired (Fig. 71-1) . Thus, when used alone, a ventilator does not alter the basic pathophysiologic changes of ARDS, and severe hypoxemia frequently persists.

Positive End-Expiratory Pressure and Continuous Positive Airway Pressure

Because decreased lung volume is a predominant feature of ARDS, therapy in most instances includes some form of expiratory positive airway pressure. PEEP maintains an increased volume of gas within the lungs and tends to prevent atelectasis. Improvement in oxygen transfer to the pulmonary capillary blood throughout the entire respiratory cycle usually results, with a concomitant increase in Pa_{O_2}.

Many spontaneously breathing patients with ARDS can maintain satisfactory carbon dioxide elimination; they do not

Figure 71-1 (A) Inspiration. With positive-pressure ventilation, a collapsed or fluid-filled lung area can be inflated following careful adjustment of pressure volume and flow. (B) Expiration. When gas is exhaled and airway pressure decreases, whatever forces predisposed to collapse of fluid accumulation are unopposed; either or both forces then recur.

require intermittent positive-pressure ventilation. CPAP applied through either an endotracheal tube or a face mask is often sufficient in mild-to-moderately severe cases of respiratory distress. In general terms, CPAP maintains a higher mean airway pressure, is associated with less work of breathing, and is potentially more depressing to venous return at a given setting than the same level of PEEP in spontaneously breathing patients. However, the distinctions are not always clear. For example, even though the configuration of a given circuit may suggest that it delivers CPAP, if the gas delivery from the flowmeter and reservoir bag (or demand valve) is inadequate to meet the patient's peak inspiratory demand, airway pressure changes characteristic of PEEP result.

Ventilator Modes

Intermittent Mandatory Ventilation/Synchronized Intermittent Mandatory Ventilation

Intermittent and synchronized mandatory ventilation are commonly used techniques for ventilatory support. Their advantages, although clearly evident in the clinical setting, are difficult to establish on the basis of scientifically valid studies. These techniques have been subjected to rigorous criticism by investigators who allege that significant disadvantages are associated with their use, including increased work of breathing, respiratory muscle fatigue, prolongation of weaning if the intermittent or synchronized mandatory ventilation rate is decreased too slowly, and increasedittent or synchronized mandatory ventilation rate is decreased too slowly, and increased likelihood of cardiac decompensation during weaning. [25] [45] Despite such criticism, they persist as mainstays of respiratory care.

Mandatory Minute Volume

Minute ventilation with intermittent or synchronized mandatory ventilation ventilators is variable because only

the ventilator rate and V_T are programmable. In 1977, Hewlett et al [6] proposed that a preselected minute volume might be more physiologic. The original concept incorporated a known constant flow of gas from which the patient could breathe spontaneously. Any gas greater than that breathed by the patient accumulated in a bellows; when a certain volume was reached, the ventilator cycled, delivering this volume to the patient. If spontaneous ventilation decreased, the bellows accumulated gas more rapidly, and more frequent ventilator breaths were delivered. Conversely, if the spontaneous component increased, gas collected in the bellows more slowly, and the number of mechanical breaths decreased. In both cases, minute ventilation remained constant; only the proportion breathed spontaneously by the patient or provided by the ventilator changed.

Pressure Support Ventilation

Operational Principles

Pressure support ventilation (PSV) is used to relieve the respiratory muscles of their workload in patients with decreased lung and chest wall compliance, increased airway resistance, or both. It utilizes the ventilator to reduce patient work to a more tolerable level, known as partial unloading, [46] [47] [48] [49] or may provide all the work of breathing by total unloading of the respiratory muscles. [46] [47] [48] [49] The technique is useful in overcoming endotracheal tube resistance and that of the ventilator circuitry. [47] [48] When a spontaneous breath is initiated, the ventilator responds to the decrease in airway pressure and delivers a high flow of gas into the circuit, raising the pressure to a preselected maximum level (e.g., 20 cm H_2O). This pressure is maintained until the patient's total flow falls to 25 percent of the initial peak value. At that point, the ventilator cycles off, and circuit flow ceases.

Work of Breathing

Pressure support ventilation levels may be adjusted to provide optimal muscle load, taking into account both the imposed work, caused by the endotracheal tube and ventilator circuitry, and the physiologic work. Until recently, such determinations were difficult or impossible. [49] Conventional methods used to assess respiratory muscle load (e.g., rate of respiration, breathing pattern, and use of accessory muscles) are unreliable and inexact. [50] Today, however, the amount of PSV necessary to achieve graded reductions or increases of spontaneous work can be determined by directly and simultaneously measuring the patient's spontaneous work and the ventilator's mechanical work. [49] A computerized, portable respiratory monitor (Bicore Monitoring systems, Allied, Riverside, CA) provides a real-time display of the pressure-volume (work) loops and calculates the imposed work of the circuit, ventilator components, and endotracheal tube. Differentiation of the physiologic work (related to changes of compliance, resistance, and inertial forces) from the imposed work is thus possible. If imposed work is excessive, an increase of PSV offsets it, thereby reducing the total work of breathing to an acceptable range. Using this approach, one may avoid respiratory muscle fatigue (not enough PSV) on one hand and muscle atrophy (too much PSV) on the other.

Banner et al [46] studied the utility of real-time measurements of work of breathing obtained from the Bicore respiratory monitor to set PSV levels for partial and total

respiratory muscle unloading. Work of breathing was obtained for 30 adult patients with acute respiratory failure. All patients were intubated transorally or had a tracheostomy tube in place and were breathing spontaneously with CPAP. The first measurements were taken while the patients breathed spontaneously with CPAP and PSV set to 0 cm H_2 O. PSV was then increased until the patient's work of breathing corresponded to a normal range of physiologic work (i.e., partial respiratory muscle unloading). Subsequently, it was increased so that the ventilator provided all the work of breathing, thereby totally unloading the respiratory muscles.

Intraesophageal pressure, tidal volume, and airway pressure were entered into the monitor's computer, which constructed a Campbell diagram [46] and calculated the work of breathing performed by the patient and the ventilator. As PSV increased, patient work of breathing decreased, and ventilator work of breathing increased. The respiratory muscles were totally unloaded at PSV of 31 ± 8 cm H_2 O. Investigators concluded that real-time measurement of work of breathing can serve as a goal-oriented approach for applying PSV to decrease the workload to appropriate levels.

Pressure Augmentation

Pressure augmentation provides a guaranteed tidal volume per breath during PSV. This mode is available only with the BEAR 1000 ventilator. When PSV is used as a stand-alone mode or is combined with CPAP, decreases in tidal and minute volume may occur as a result of decreases in the level of consciousness, inspiratory effort, and pulmonary mechanics. Hypoxemia, hypercapnia, acidemia, and their associated sequelae may occur secondary to inappropriately low minute volume.

Operational Principles

Pressure augmentation may be available in the "background" or may be actively operating during PSV to protect the patient from hypoventilation. The PSV level is preselected. Next, a minimum V_T and a back-up inspiratory flow rate are chosen. If the V_T during the PSV breath is greater than the minimum V_T setting, no augmentation of pressure above PSV occurs; the breath is terminated or flow-cycled "off" in the usual manner. If V_T is less than the minimum volume setting after the initial phase of the pressure-supported breath, a constant flow rate of gas (back-up inspiratory flow setting) is directed to the patient until the minimum V_T is delivered. As a result, airway pressure is augmented above the PSV level, and the breath is volume-cycled "off." With pressure augmentation, the breath looks like a conventional PSV breath; the volume feature is activated only when necessary.

Pressure augmentation guarantees V_T during PSV and represents a sensible safety precaution. Future ventilator

designs will, in all likelihood, incorporate pressure augmentation or a similar mode to prevent hypoventilation. In addition to setting a minimum V_T and back-up inspiratory flow rate, a back-up respiratory rate setting is recommended to protect the patient in case of apnea.

Proportional Assist Ventilation

Pressure support ventilation, when properly adjusted, optimizes the relationship between respiratory muscle workloads and ventilatory response. This optimal relationship applies for only one specific set of physiologic conditions. If patient work of breathing changes as a result of changes in airway resistance (Raw), elastance of the respiratory system (E_{RS}), inspiratory flow rate demand (V_T), or V_T, the clinician must increase or decrease the level of PSV to maintain an optimal and nonfatiguing respiratory muscle workload. Because one or more of these parameters may change frequently, maintaining the precise level of PSV required to optimize respiratory muscle workload is sometimes difficult.

Operational Principles

A favorable relationship between respiratory muscle workload and alveolar ventilation is an important therapeutic objective. Proportional assist ventilation (PAV), an experimental technique, [28] [29] may eventually prove superior to PSV in accomplishing this objective. A ventilator capable of PAV continuously manipulates the level of PSV applied to the airway throughout the course of each spontaneous inhalation. In contrast, conventional PSV applies a single rway throughout the course of each spontaneous inhalation. In contrast, conventional PSV applies a single pressure level through the inspiratory phase. During PAV, airway pressure (Paw) varies in response to the patient's respiratory muscle pressure or effort, which is affected by Raw (change in pressure/flow rate), E_{RS} (change in pressure/change in volume), V_T, and V_T. The relationship between these variables and the ventilator's response is described by the following equation of motion for the respiratory system:

To use PAV (and solve the equation of motion), the clinician must first accurately measure the patient's Raw and E_{RS}. Two ventilator controls are then adjusted. One, the resistive gain control, is based on the measured Raw; the other, the elastic gain control, is based on the measured E_{RS}. With this information and real-time feedback from airway pressure, flow rate, and volume sensors positioned in the breathing circuit, the ventilator automatically adjusts the applied PSV up or down to maintain the specific relationship defined by the equation of motion.

Consider an adult whose E_{RS} increases to 50 cm H_2 O/L (normal = approximately 10 cm H_2 O/L) and whose Raw increases to 10 cm H_2 O/L/s (normal = approximately 2 cm H_2 O/L/s). To "normalize" this particular patient, the elastic gain control would be set to 40 cm H_2 O/L (measured E_{RS} - normal E_{RS}), thereby causing the ventilator to assume the extra work resulting from the increase in E_{RS}. The resistive gain control would be set to approximately 8 cm H_2 O/L/s (measured Raw - normal Raw). The total resistive work, or pressure drop, the patient must generate across the airways and breathing apparatus to achieve a desired inspiratory flow rate would thereby decrease.

During PAV, the patient interacts with the pressure-supported breath and retains control over V_T, inspiratory time, breathing frequency, V_T, and minute ventilation. Unlike PSV, the patient regulates the applied airway pressure level as well, thus retaining control over *all* ventilatory parameters during PAV.

Clinical Applications

With PAV, the elastic and resistive gain controls can be set in many different ways, based on a patient's needs. Chronically fatigued respiratory muscles can be totally unloaded to allow a period of rest simply by adjusting the gain controls to assume the total work of breathing. The respiratory muscles may be partially unloaded by adjusting the gain to allow only the work that the patient can tolerate. Finally, the gain can be adjusted to exercise the patient's respiratory muscles by periodically forcing a greater normal work of breathing.

Potential Problems

As with other ventilatory approaches, PAV has shortcomings. It requires real-time airway pressure, flow rate, and volume signals from the "Y" piece of the breathing circuit. Loss or alteration of any or all of these signals can jeopardize the patient. Accurate determinations of Raw and E_{RS} also are necessary. Just as levels must be set for PSV, the gain controls must be readjusted whenever Raw or E_{RS} changes in PAV.

Potential problems include dependence on the patient's spontaneous effort (without spontaneous effort, PAV cannot function) and pressure "runaway" (e.g., a leak in the breathing circuit that causes the ventilator to provide inappropriately high flow rates in response to the leak rather than to patient effort). Finally, PAV controls neither V_T nor breathing rate and, therefore, has no direct control over a patient's breathing pattern.

Airway Pressure Release Ventilation

Airway pressure release ventilation allows spontaneous ventilation with CPAP but differs from conventional ventilatory modes because peak inspiratory pressure never exceeds the level of CPAP. [7] Airway pressure decreases rather than increases when a mechanically controlled tidal volume is delivered (Fig. 71-2) (Figure Not

Available) . The risk of pulmonary barotrauma and adverse hemodynamic effects associated with conventional positive-pressure ventilation may be decreased because of the lower peak inspiratory and mean airway pressures. This technique appears useful for patients who do well at low-rate intermittent or synchronized mandatory ventilation but are unable to effect the transition to totally spontaneous breathing with CPAP.

Figure 71-2 (Figure Not Available) Airway pressure release ventilation circuitry and its clinical application. (A) A high-flow air/oxygen gas mixture passes continuously into a continuous positive airway pressure (CPAP) system, which is bifurcated at its distal end. When the electronically controlled solenoid valve is closed, all gas passes through the CPAP valve, and an airway pressure of 10 cm H_2O results. Typical airway pressure tracings are shown. (B) When the solenoid valve is opened transiently, all the gas flows through the portal, and airway pressure falls to zero. A larger exhalation results. (C) The solenoid valve is again closed, with an immediate restoration of airway pressure back to 10 cm H_2O. Depending on how many times the system is depressurized and repressurized (cycles per minute), an increase or decrease of ventilation can be superimposed on the patient's spontaneous component. Note that the highest pressure is the CPAP value. Other forms of positive-pressure ventilation are associated with an increase of airway pressure above the level of CPAP. *(Courtesy of M.E. Banner, PhD.)*

Resuscitation

Fluid and Electrolyte Therapy

Appropriate intravascular fluid resuscitation (Chs. 45 and 75) in shock and cardiovascular insufe occurs in skeletal muscle cellular transmembrane potential and in peak amplitude of the evoked potential. A progressive increase in intracellular sodium and water and extracellular potassium occurs with an associated decrease in extracellular water (Table 71-4) . The increase in intracellular water occurs at the expense of extracellular fluid, presumably accounting for the loss of functional extracellular fluid volume demonstrated by radioactive isotope dilution techniques.

In severe or long-standing shock, the restoration of intravascular volume alone is insufficient for successful resuscitation. Until restoration of the functional extracellular fluid volume is completed, normal oxygen and nutrient delivery to the cells and removal of waste products from them cannot occur. Provided that cellular damage is reversible, the administration of extracellular fluid substitutes, such as lactated Ringer's solution, is useful.

Critics of such therapy argue that the large volumes of electrolyte solution that may be required to offset a functional extracellular fluid volume deficit of several liters predispose to the formation of pulmonary edema and an increased incidence of ARF. They suggest that dilution of plasma by balanced electrolyte solutions decreases the colloid oncotic pressure and enhances water flux into the pulmonary interstitium. [51] Staub [52] noted, however, that "a decrease in plasma protein concentration, even to low levels, should not produce pulmonary edema because it would be accompanied by similar decreases in perimicrovascular protein concentration of the pulmonary interstitium."

The common practice of administering plasma, albumin, or colloidal suspensions, such as hydroxyethyl starch, to offset possible decreases in plasma oncotic pressure may be deleterious. Holcroft et al [53] reported that the increased albumin extravasation and edema that occur in the lungs, heart, brain, and liver of septic animals cannot be prevented by plasma protein infusion. In septic animals, Sturm et al [54] showed that the administration of plasma solutions is associated with an increased flux of albumin into the pulmonary interstitium compared with that occurring during crystalloid resuscitation. This albumin flux is accompanied by an increase of extravascular lung water (interstitial pulmonary edema).

TABLE 71-4 -- Changes in Skeletal Muscle Fluid and Electrolyte Composition During Hemorrhagic and Septic Shock

COMPONENT	INTRACELLULAR	EXTRACELLULAR
Water		
Na^+		NS
	,	
K^+		
		,

, increases;
, decreases; NS, no significant changes

Colloids and Crystalloids

Much of the controversy concerning the administration of colloid and crystalloid solutions (Ch. 45) to shock/trauma patients appears to be based on misinterpretation or incomplete knowledge of the factors governing fluid exchange in the lung. Absolute values for pulmonary microvascular pressure and plasma colloid oncotic pressure are relatively unimportant in pulmonary edema formation. Rather, as Staub [52] suggested, it is the gradient of hydrostatic and oncotic pressures between the intravascular and pulmonary interstitial spaces that is the important determinant.

Analysis of lung lymphatic drainage showed that normal pulmonary interstitial albumin content is at least 50 percent that of plasma and is altered directly with changes in plasma albumin. [52] [54] An attempt to increase plasma oncotic pressure with colloid solutions in order to prevent pulmonary edema is not based on sound physiologic observations. If an increase in pulmonary capillary permeability occurs, interstitial albumin concentration and oncotic pressure approach that of the plasma.

The most comprehensive assessment of colloid therapy was presented in a workshop on the assessment of plasma volume expanders. [55] All pertinent clinical trials involving albumin, dextran, and hydroxyethyl starch were evaluated in terms of efficacy, cost, indications, and complications. Little evidence supported short-term or long-term benefits associated with colloid administration for burns, blood loss, cardiopulmonary bypass, treatment of pulmonary edema, trauma, or nutritional supplementation. Serum albumin levels as low as 3 g/dL were not deleterious. Even values as low as 2 g/dL were not clearly problematic.

Hypertonic Saline

Therapeutic Implications

Peripheral edema is one of the consequences of balanced electrolyte solutions administered in large quantities. Patients' weight often increases several kilograms during resuscitation. Although adverse cardiopulmonary effects generally do not occur in patients without preexisting cardiopulmonary disease, the edema can cause problems in patients who have sustained major burns and may predispose to anastomotic leaks in general and vascular surgical patients. Here, lesser volumes of hypertonic saline solutions may be of value to reduce or eliminate the requirement for escharotomy; eliminate large, weeping surface areas, which are susceptible to infection; and maintain anastomotic integrity. Renal, cardiovascular, and pulmonary function are supported in a satisfactory manner with such therapy.

Physiologic Effects

Hypertonic saline solutions also have proved to be beneficial in resuscitation from shock/trauma. [56] [57] [58] [59] [60] [61] [62] [63] Compared with isotonic solutions, such as lactated Ringer's, the lesser volumes are associated with equivalent or improved systemic blood pressure, cardiac output, and survival in experimental animals. A positive inotropic effect has been consistently noted. Restoration of normal cellular transmembrane potential is enhanced, indicating a reversal of the cellular abnormalities induced by hemorrhagic shock. As long as 24 hours after the shock episode, blood pressure is maintained more effectively than with lactated Ringer's

solution alone or a combination of lactated Ringer's solution with added mannitol.

Traverso et al [58] found that 7.5 percent saline was more effective with respect to survival than 0.9 percent, 5 percent, or 10 percent saline solutions. They believed that improved tissue perfusion occurred as indicated by reduced lactate values. Improvement in myocardial contractility and reduction in systemic vascular resistance were probably contributory. Early increase in urine output, less fluid retention, and better late pulmonary function are also demonstrable. [59] Hypertonic saline solutions appear equally efficacious, whether administered peripherally (cephalic and femoral veins) or centrally (superior vena cava). Gross and histologic inspection demonstrates no vascular damage. [60]

Infusion of hypertonic lactated Ringer's solution in rabbits was accompanied by a reduction in the percentage of water in all cerebral and extracerebral tissues, an increase in their specific gravity, and a reduction of intracranial pressure (ICP). [61] Cerebral blood flow concomitantly was increased. Although normal animals were studied, the approach may have some advantages over the use of isotonic fluids in the resuscitation of head-injured patients. Similar findings also were reported by Gunnar et al [62] and Suarez et al. [63] In a simulated closed-head injury model, hypertonic saline infusion was accompanied by lower ICP and less cerebral edema than occurred with isotonic saline or colloid. [62]

The findings in experimental animals have been substantiated in humans. Holcroft et al [64] noted that 7.5 percent saline in combination with 4.2 percent dextran 70, administered during air ambulance transport, improved hemodynamic function and appeared to enhance survival in 20 severely injured patients compared with lactated Ringer's solution. The volumes infused were 700 ± 500 mL and 1,300 ± 900 mL, respectively.

Potential Problems

Replacement of the chloride anion with acetate has been suggested to avoid the risk of hyperchloremia and acidosis associated with hypertonic saline. To test this hypothesis, Frey et al [65] compared hypertonic sodium ssed. The study demonstrated that both hypertonic solutions effectively restored cardiac index and oxygen consumption and that sodium acetate dextran offered no advantages over sodium chloride/dextran, although the serum pH was improved.

Despite impressive experimental results, many anesthesiologists seem reluctant to employ hypertonic solutions. Few, if any, studies report deleterious effects, including hyperosmolar states, as long as careful monitoring is employed. Certainly additional experimental and clinical work in this area is warranted. A comprehensive review of the subject has been published by McGough. [66] The composition of various intravenous fluids is summarized in Table 71-5 .

TABLE 71-5 -- Composition of Selected Fluids

SOLUTION	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Mg^{2+} (mEq/L)	Ca^{2+} (mEq/L)	LACTATE (mEq/L)	OTHER	APPROX pH	mOsm/L (CALCULATED)
D_5 W							Dextrose, 5 g/dL	5.0	253
0.9 NaCl	154	154						4.2	308
Lactated Ringer's	130	109	4.0		3.0	28		6.5	273
Plasmalyte	140	98	5.0	3.0	-	-	Acetate, 27 mEq/L; gluconate, 23 mEq/L	7.4	294
Hespan	154	154	-	-	-	-	Hetastarch, 6 g/dL	5.5	310
Dextran 70	154	154	-	-	-	-		5.5	308
5% Albumin	145	145	-	-	-	-	Albumin, 5.0 g/dL		308
3% NaCl	513	513	-	-	-	-		5.0	1,027
5% NaCl	855	855						5.6	1,710

D_5 W, 5% dextrose in water; NaCl, sodium chloride

Cardiopulmonary Resuscitation

Historical Considerations

In 1921, Dr. Ralph M. Waters [67] presented the following narrative:

> On November 21, 1920, a woman died during tonsillectomy....
> Forty-five minutes after apparent death I used high pressure (200 mm Hg) in inflating the lungs with pure oxygen .... (using) a McKesson anesthesia apparatus which allows of sudden complete inflation of the lungs....
> Beginning with a dead color of the skin, after fifteen minutes the skin gradually took on a normal color.... This condition was maintained over two hours, in fact until the surgeons convinced me, by opening the diaphragm through the abdomen .... that there was absolutely no heart activity.
>
> By inflating the lungs with oxygen under high pressure .... it would seem reasonable to assume that pressure compression of the heart and large vessels of the chest would result in at least some movement of the bloodstream.

This report predated modern cardiopulmonary resuscitation (CPR) by almost 40 years (Ch. 75) . Since 1961, CPR has been a widely accepted therapeutic procedure. Initially, enthusiasm was high for this new technique that combined artificial ventilation with closed-chest cardiac compression. [68] This noninvasive technique was predicted to replace open-chest cardiac massage as the treatment of choice in cardiac arrest and to improve survival rates. It was estimated that 70 percent of out-of-hospital victims of witnessed primary cardiac arrest in ventricular fibrillation or tachycardia would be saved if effective bystander CPR and paramedic response time were less than 4 minutes. [69] Eighty percent of cardiac arrest patients admitted to a coronary care unit were thought to be salvageable with the immediate availability of a defibrillator and adequately trained personnel.

Survival rates in both prehospital [70] and in-hospital settings have, in fact, been dramatically lower. [71] [72] This discrepancy is due, in large part, to the fact that both prehospital and in-hospital resuscitations are frequently performed on victims with preexisting comorbid conditions and noncardiac causes of arrest. Prehospital survival is determined primarily by the cause of arrest. Critical determinants ofre frequently performed on victims with preexisting comorbid conditions and noncardiac causes of arrest. Prehospital survival is determined primarily by the cause of arrest. Critical determinants of success for ventricular fibrillation or ventricular tachycardia include whether the arrest is witnessed and how much time elapses from arrest to arrival of a defibrillator (Table 71-6) (Table Not Available) . [69] Survival rates for cardiac arrest from other causes (i.e., near-drowning, drug overdose, trauma) remain low and have not changed significantly in the almost 3 decades since the introduction of emergency medical systems. Likewise, survival rates for both noncritically ill (floor) [71] [73] and critically ill (intensive care) [72] hospitalized patients have not improved significantly since the introduction of CPR.

Determinants of Survival

Several factors affect in-hospital survival rates. Rates differ from study to study, depending in large part on the patient population and the diagnostic mix (Table 71-7) (Table Not Available) . Unwitnessed arrest is associated with a dismal outcome. Patients who are intubated, are septic, are in cardiogenic shock, have acute renal failure, have metastatic disease uniformly do poorly, and few survivors are reported. [72] Successful resuscitation must occur quickly; prolonged resuscitation (>30 min) has a similarly poor prognosis. Asystole or pulseless electrical activity usually signifies a delay in identifying arrest and is also associated with poor outcome. Age greater than 70 years has been correlated with poor survival in some studies but not in others. Survival in children generally is no higher than in adults, although some studies suggest that children in ICUs respond more to high-dose epinephrine than do adults. [74] High-dose epinephrine has been shown to be of no value in prehospital pediatric arrest. [75]

Cardiopulmonary arrest is the final pathway to death, and critically ill patients often die. The question is how to identify patients who have a good prognosis for meaningful survival and might benefit from CPR from the considerable number with poor expected outcome in whom CPR can be withheld. Early involvement of the patient's family and, when possible, the patient in decision making precludes unnecessary resuscitative attempts. [76] The neurologic status of successfully resuscitated patients is of predictive value and can be used in decision making about whether further resuscitative efforts will be withheld.

TABLE 71-6 -- Relationships of Patient and Cardiopulmonary Resuscitation Variables to Outcome

(Not Available)

Adapted from Erb and Nowak [71]

TABLE 71-7 -- Outcome of Inpatient Resuscitation Attempts Reported in the Literature

(Not Available)

Adapted from Landry et al [72]

Cerebral Perfusion

A major determinant of intact survival is the adequacy of cerebral perfusion. Traditionally, carotid arterial blood flow has been used to gauge the adequacy of cerebral blood flow. Various methods to enhance cardiac output and cerebral blood flow include maintenance of positive-pressure inspiration during cardiac compression (using Waters' [67] original observation) and combinations of abdominal thoracic binding to maximize pleural pressure. [77] [78] Significant improvement in blood pressure and carotid flow using these techniques can result compared with conventional CPR. How- ever, only the internal carotid portion of total carotid flow is involved in cerebral perfusion. Hence, overall carotid flow cannot be equated with CBF. This fact is clearly evident in brain-dead patients with good carotid artery pulsation but with absent cerebral blood flow documented by perfusion scans. An increase of pleural pressure to augment forward flow in the arterial system also increases venous and hence ICP by a potentially equal amount. The result can actually be a zero increase in cerebral perfusion pressure, which is equal to the mean arterial pressure minus the mean ICP.

High-Dose Epinephrine

Interest has focused on the use of high-dose epinephrine for CPR. However, in an unpublished trial of doses as high as 0.07 to 0.2 mg/kg in more than 2,450 cases of cardiac arrest, no statistically significant improvement in survival was found when patients who received the high doses were compared with those who were treated with standard doses (i.e., 0.5-1.0 mg). Accordingly, the latest American Heart Association guidelines list higher doses of epinephrine as class IIb (they are acceptable but are neither recommended nor discouraged). [79]

Neurosurgical Critical Care

The scope of neurosurgical critical care has evolved rapidly (Chs. 35 and 52) . Improved outcome can be attributed in part to improvements in initial resuscitation that increase the probability of survival after an acute neurologic insult; advances in microsurgical techniques that allow the surgical treatment of complex disease processes; improvements in neurologic monitoring modalities; and recognition of the role of secondary neuronal injury and treatment directed toward its prevention. Care of neurologically injured patients requires an understoptimize treatment in the ICU and the operating room in order to improve overall patient outcome.

Improvement in initial resuscitative measures; immobilization procedures; acute therapeutic interventions, such as high-dose steroid therapy after acute spinal cord injury; and rapid transit to tertiary care centers has increased initial survival of neurologically injured patients and has contributed positively to final neurologic outcome. The availability of multiple medical disciplines, trained personnel, and advanced imaging techniques in tertiary care centers expedites early diagnosis and acute surgical intervention when warranted and postoperative care after complicated neurosurgical procedures.

Intracranial Contents

The intracranial contents consist of brain tissue, blood, cerebrospinal fluid (CSF), and meninges and communicate with the spinal axis via the foramen magnum. The calvarium is a nondistensible, semiclosed container that limits intracranial volume expansion. Volume of the intracranial contents remains constant unless a pathophysiologic change is introduced. When a new volume is added (i.e., hematoma) or expansion of an existing volume occurs (i.e., tumor), a reciprocal reduction in volume of one or more of the intracranial components must occur to maintain normal ICP. [80] [81] [82]

Intracranial Pressure

Intracranial pressure measurement utilizes subarachnoid bolts, ventriculostomy catheters, and subdural or epidural catheters. Each method has advantages and disadvantages.

Figure 71-3 Intracranial pressure-volume curve. Points A-B represent spatial compensation with expanding intracranial volume. Elastance is low. At C, spatial exhaustion occurs. From C-D, elastance is increased; small changes in volume produce large changes in intracranial pressure.

Normal ICP is less than 15 mm Hg. Values above 29 mm Hg, if sustained, are associated with a reduction in cerebral perfusion pressure and a poor prognosis. An intracranial mass and reduced compliance can be associated with major damage from relatively small changes in pressure. A normal ICP does not exclude a mass lesion.

The intracranial pressure-volume curve (Fig. 71-3) [82] [83] depicts the relationship between intracranial volume expansion and ICP in the presence of a pathologic process. The effect of intracranial volume expansion on ICP depends on the chronicity of the underlying pathologic process and the adequacy of the buffering capacity of the intracranial system. During the period of spatial compensation, even large changes in intracranial volume result in minimal alterations in ICP. Normal ICP is maintained by a displacement of predominantly venous blood from the vasculature, an increase in the rate of CSF absorption, and occasionally by a loss of

water and electrolytes from brain tissue. The greatest buffering capacity is afforded by the CSF; decompensation occurs when maximal CSF absorption occurs.

Cerebral blood volume is the intracranial content most easily manipulated through alterations in ventilation and drug therapy. When the buffering capacity of the intracranial space is exhausted, small increases in intracranial volume result in dramatic rises in ICP. If a mass expands rapidly (i.e., epidural hema most easily manipulated through alterations in ventilation and drug therapy. When the buffering capacity of the intracranial space is exhausted, small increases in intracranial volume result in dramatic rises in ICP. If a mass expands rapidly (i.e., epidural hematoma), compensation cannot occur, and ICP rises abruptly.

Aneurysmal Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is the result of primary bleeding into the subarachnoid space or direct extension from an intraparenchymal hemorrhage. Intracranial aneurysms are present in over 5 million North Americans, and approximately 28,000 cases of SAH occur each year. [84] The peak age for aneurysm rupture is 40 to 50 years. [84] SAH in patients younger than 20 years is usually secondary to an arteriovenous malformation. The female/male ratio for SAH is 1.6:1 for patients older than 40 years of age. [85] A linear relationship between risk of rupture and aneurysm size appears to exist; however, giant aneurysms (>2.5 cm) do not appear to have a higher risk of bleeding per year, probably because of thrombosis and calcification of the aneurysm wall. [86] Aneurysm rupture also has been associated with the last trimester of pregnancy, excluding delivery; during the postpartum period; and following cocaine use.

Rebleeding

Neurologic complications of SAH include rebleeding, acute hydrocephalus, and seizures. Cerebral vasospasm is a late complication of SAH but warrants early preventive measures in high-risk patients. The risk of rebleeding poses one of the greatest dangers if aneurysm clipping is delayed or conservative management is elected. Fifty percent of patients treated conservatively experience a rebleed within 6 months of initial hemorrhage, ultimately declining to 2 to 3 percent per year. [84] The greatest risk of rebleeding is within 24 hours of hemorrhage (approximately 4% on day 1) and peaks again between days 14 to 21. Aneurysm rebleeding is associated with a 50 percent mortality; of the 50 percent who survive, outcome is often poor.

Hydrocephalus

Acute hydrocephalus is detected by computed tomography (CT) in 15 percent of patients after SAH; of these, 40 percent are clinically symptomatic. [87] Hydrocephalus may contribute to the initial poor clinical grade, or its development may manifest as an acute decline in mental status. The development of hydrocephalus after SAH has been correlated with posterior aneurysms, intraventricular hemorrhage or thick subarachnoid clot, cerebral vasospasm, altered level of consciousness on admission, hyponatremia, advanced age, and hypertension. Acute hydrocephalus manifests with impairment of CSF flow through the ventricular system or impedance of CSF absorption at the arachnoid granulations. CT demonstrates enlargement of the ventricles. Ventriculostomy may be warranted even in the absence of ventriculomegaly if ICP elevation is suspected.

Cerebral Vasospasm

Pathogenesis

The pathogenesis of cerebral vasospasm is poorly understood but is likely complex and multifactorial in origin. It is characterized acutely by smooth muscle contraction, but chronically, structural and morphologic damage to the endothelium becomes evident. [89] Oxyhemoglobin has potent spasmogenic properties and likely plays a vital role in the development of cerebral vasospasm. [89] [90] As oxyhemoglobin is autoxidized, superoxide ion is released and initiates a cascade

of events that lead to endothelial damage, lipid peroxidation, and calcium influx. [88] Superoxide dismutase converts superoxide anion to hydrogen peroxide, and the interaction between the two results in the production of free radicals. [91] Free radicals probably are responsible for the initiation of lipid peroxidation and endothelial damage. Elevated levels of lipid peroxides, which are inherently potent vasoconstrictors, have been detected in animal models and in humans with vasospasm. [88] [92]

Platelet-activating factor, which is produced by inflammatory cells and neurons, may also be contributory via its link to prostaglandins and leukotrienes and by promotion of an inflammatory reaction and platelet aggregation. [93] Under ischemic conditions, glutamate, the predominant excitatory amino acid in the central nervous system, increases platelet-activating factor production. [94]

An imbalance between endothelin-1 and endothelium-derived relaxing factor may play a role in the development of vasospasm. Hemoglobin and oxyhemoglobin stimulate endothelin-1 synthesis and concurrently inhibit endothelium-derived relaxing factor activity. [95] Endothelin-1 is a potent vasoconstrictor that in the absence of endothelium-derived relaxing factor promotes arterial constriction in animal models. [96] Elevated levels of endothelin-1 have been detected in ischemic tissue in animals after global or focal cerebral ischemia; in humans, elevated CSF levels have been documented after stroke and SAH. [96] [97]

Treatment

The primary treatment for established cerebral vasospasm is hypertensive, hypervolemic, hemodilution therapy to augment cerebral blood flow in an effort to reverse or improve isvhemic neurologic deficits achieve a good outcome with this therapy. [98] Intravenous volume expansion is commonly achieved with crystalloid, colloid, or packed red blood cells, if the hematocrit value is low, in conjunction with PA catheter monitoring. Hypertension is induced with fluid infusion, vasopressors, or both, to improve cerebral perfusion and collateral blood flow. In our institution, systolic blood pressure is increased to 180 mm Hg or greater. An optimal hematocrit value is 30 to 32 percent. CBF is increased by a reduction in blood viscosity.

Calcium channel antagonists, specifically nimodipine and nicardipine, are routinely administered from the time of diagnosis and continued for 21 days. Their neuroprotective role may be the result of prevention of calcium influx and cell death. Clinical trials utilizing nimodipine or nicardipine report a decreased severity of symptomatic vasospasm but no difference in overall outcome at 3 months when compared with placebo. [99] [100] [101]

Tirilazad (U74006F or Freedox) is the most promising investigational drug in large clinical trials worldwide for the prophylactic treatment of cerebral vasospasm. It inhibits iron-mediated lipid peroxidation and in animal models attenuates chronic vasospasm after SAH. [92] [102] [103] Patients receiving tirilazad (6 mg/kg/d) had a reduced mortality and an increased frequency of good neurologic outcome compared with their counterparts receiving placebo or lower doses of drug. [104] Men appeared to benefit more than women in this trial.

Superoxide dismutase, platelet-activating factor antagonist, and anti-platelet-activating factor immunoglobulin M for cerebral vasospasm have been investigated in animal models only, with promising results in some trials and no benefit in others. Aspirin use before or after SAH was correlated with a decreased incidence of permanent neurologic deficits and cerebral infarction detected by CT. [105]

Head Injury

Glasgow Coma Scale

The Glasgow Coma Scale (GCS) [106] is used to evaluate level of consciousness after head injury (Chs. 35 and 52) and is not designed to assess focal neurologic deficits (Table 71-8) (Table Not Available) . A separate scale should be used to evaluate children younger than 4 years of age (Children's Coma Scale). The maximal obtainable score is 15, and a separate notation (t) is designated for intubated patients. Severe head injury is commonly defined as a GCS of less than 8. The initial GCS is used to determine the need for ICP monitoring and has been used to predict outcome in head-injured patients.

Radiographic Presentation

Computed tomography is the radiographic imaging study of choice for the diagnosis of acute intracranial pathology associated with head injury. It is a highly sensitive study for the detection of acute hemorrhage, mass lesions, or osseous injury and is ideal for hemodynamically unstable patients who benefit from rapid imaging time. CT documentation of midline shift and compressed ambient cisterns strongly correlates with ICP el sensitive study for the detection of acute hemorrhage, mass lesions, or osseous injury and is ideal for hemodynamically unstable patients who benefit from rapid imaging time. CT documentation of midline shift and compressed ambient cisterns strongly correlates with ICP elevation. [107] Magnetic resonance imaging can be employed to detect subacute collections of blood and to evaluate chronic intracranial pathology; it is more sensitive than CT scanning for the diagnosis of diffuse axonal damage.

TABLE 71-8 -- Modified Glasgow Coma Score

(Not Available)

Adapted from Jannett and Teasdale, [106] copyright by The Lancet, Ltd.

Indications for Intracranial Pressure Monitoring

The need for ICP monitoring is dictated by a combination of factors, including severity of head injury, age, neurologic examination, hypotension, and CT findings. Patients with severe head injury (GCS of 3-8) and abnormal CT scan require ICP monitoring. Monitoring also should be initiated in severely head-injured patients with a normal CT scan if two of the following conditions are also present at admission: age greater than 40 years, unilateral or bilateral motor posturing, or systolic blood pressure less than 90 mm Hg. Eisenberg et al [107] documented intracranial hypertension in 10 to 15 percent of patients with evidence of severe head injury and relatively normal admission CT scan. O'Sullivan et al [108] also documented intracranial hypertension during hospitalization in seven of eight severely head-injured patients (GCS
8) with normal admission CT scan.

Clinical Diagnosis of Brain Death

The diagnosis of brain death is made by assessment of brain-stem reflexes and is often corroborated with radiologic findings, electroencephalography, transcranial Doppler studies, multimodality-evoked potential monitoring or ^{99m}Tc blood flow scans. The diagnosis of death requires the irreversible cessation of cardiopulmonary or brain function (including the brain stem). [109] A recent history of severe brain injury must be deemed irreversible, and the clinical picture must not complicated by hypothermia, severe hypotension (systolic blood pressure <90 mm Hg), metabolic abnormalities, or medications that may confound the neurologic examination. Medications such as barbiturates, atropine, and narcotics preclude the diagnosis of brain death until drug levels are subtherapeutic. After prolonged administration of barbiturates (i.e., treatment of refractory intracranial hypertension), elimination may take several days.

The following conditions must be met for a diagnosis of brain death to be made: (1) pupils fixed and dilated with absent light reflex, (2) absent corneal reflexes, (3) absent oculocephalic or oculovestibular reflexes, (4) absent gag reflex, (5) apnea, and (6) absent motor response to deep central pain [109] (not to be confused with spinal cord-mediated reflex movements).

OUTCOME

Predictive Indices

A laudable, but thus far unattained, goal in critical care is the prediction of outcome for ICU patients early in the course of disease (Ch. 21) . In theory, resources could then be directed to those patients with the greatest potential for intact survival and, just as important, would not be spent on those for whom survival is unlikely. This concept originates from mass casualty situations in the military, during which resources are limited.

Predictive indices are based on patient-disease interactions, physician perceptions, and requirements for nursing care (Table 71-9) . The basic goal of each system is to amass

TABLE 71-9 -- Predictive Indices for Patient Outcome in the Intensive Care Unit

Patient-disease interactions	Frequency distribution of cardiorespiratory variables. Results from survivors applied to critically ill patients.
	Complications Impact Index: Age plus observable diagnoses and complications classified by eight organ systems
	Condition Index Score: Weight assigned to each of 225 complications
	Mortality Prediction Model[113] : Multivariate statistical analysis of easily derived admission variables; results expressed as probability rather than score.
Physician perceptions	*Therapeutic Intervention Scoring System (TISS):* Patients classified from I to IV; sickest patients require the most interventions
	Acute Physiology and Chronic Health Evaluation (APACHE): Weighted sum of 34 potential physiologic measurements in the first 24 hours of ICU admission, plus four- category designation of preadmission health status.
	APACHE II: Weighted sum of 12 physiologic measurements, plus age and previous health status.
	APACHE III
Requirements for nursing care	Based on the number of nursing hours per patient per 24 hour period: Class 1 12 hours; class 2 > 13 < 24 hours; class 3 > 24 hours. Generally equivalent to TISS classes II, III, and IV, respectively.

data that when subjected to appropriate statistical analyses, will determine the severity of illness and the prospects for recovery more accurately and precisely than clinical judgment alone.

Severity of Illness

Severity of illness is usually a major consideration in determining the need for critical care. However, patients are often admitted to an ICU for overnight observation after elective surgery and are discharged within 24 hours, whereas other patients who are extremely ill when admitted die within 24 hours. The first group may be "too well" to require an ICU admission, whereas the second group is "too sick" to benefit. In one study, these two groups constituted 34 percent of all surgical ICU admissions but were responsible for only 5 percent of ICU days and 8 percent of the total charges. [110] [111] Thus, the seemingly paradoxical fact is that the sickest and healthiest patients use the same amount of ICU resources. All predictive scoring systems can distinguish between these two extremes, but so can clinical judgment. It is the majority of patients in between that present the major difficulties.

Common Problems

No predictive index score generated at the time of ICU admission improves on the approximately 15 percent misclassification

rate inherent to each scoring system. For long-term patients, the factors that ultimately determine outcome either are not known or are normal on admission. [110] [112] Pneumothorax, myocardial infarctie, or shock that occurs on the sixth ICU day cannot be taken into account on day 1. Yet, that initially unknown event may be the final determinant of survival, independent of all the predictive factors present on admission.

Mortality Probability Models

The problem of mortality prediction for patients in the ICU for more than 24 hours was addressed by Lemeshow et al [113] in 1994. Using data from a prospective, multicenter study, the authors developed models to estimate mortality at 48 and 72 hours. Their models--the MPM_{48} and the MPM_{72} --are based on the Mortality Probability Model (MPM II) system. The MPM II system consists of the MPM_0 and the MPM_{24} models, which are used to estimate hospital mortality probability for patients at ICU admission and at 24 hours. The MPM_{48} and MPM_{72} models contain the same 13 variables and coefficients as the MPM_{24} ; however, the two new models differ from the MPM_{24} in their constant terms.

The authors also tested whether the MPM_{24} could be used to predict mortality beyond 24 hours. They studied 6,290 consecutive admissions to ICUs in Massachusetts and New York. Of these admissions, 4,485 patients were still in the ICU at 24 hours, 3,023 patients remained at 48 hours, and 2,233 patients remained at 72 hours. The investigators first tested the MPM_{24} model to determine whether it could estimate mortality probability for patients remaining in the ICU at 48 and 72 hours. For both time periods, the model consistently underestimated the probability of mortality. In every patient group, the number of deaths predicted by the MPM_{24} model was lower than the actual number.

Taking into account the underestimates produced by the MPM_{24} model for the longer time periods, the authors generated a new $beta_0$ value for the 48- and 72-hour models, using the 13 coefficients from the MPM_{24} model as a fixed offset variable. After the adjustment, both the MPM_{48} and the MPM_{72} provided a validated probability of hospital mortality in the ICU, at 48 and 72 hours, respectively. The investigators concluded that models developed for specific time periods cannot be successfully used for other time periods. They also noted that although the two new models provided a validated index of severity of illness for patients in the ICU for more than 24 hours, they are not appropriate tools for defining guidelines for allocation of limited resources or for transfer of patients out of the ICU.

Intensive Care Unit Discharge

Noting that there has been little study to determine when it is safe to transfer an ICU patient to an intermediate care unit, Zimmerman et al [114] set out to devise a method to assist physicians in making daily ICU discharge decisions for individual patients. They developed a series of multivariate equations to provide daily estimates of the probability that an ICU patient will receive life-support treatment within the following 24 hours. The equations were based on demographic, physiologic, and treatment data obtained at the time of admission to the ICU and during the first 7 days in the ICU. The authors noted that an ICU patient who has a high probability of receiving life-support treatment during the following 24 hours can be given this treatment most efficins were based on demographic, physiologic, and treatment data obtained at the time of admission to the ICU and during the first 7 days in the ICU. The authors noted that an ICU patient who has a high probability of receiving life-support treatment during the following 24 hours can be given this treatment most efficiently in the ICU. On the other hand, a low probability of next-day active treatment is a major indication for ICU discharge.

Among 13,787 ICU patients who remained for 2 days or more, 4,898 were predicted to have a less than 10 percent risk of requiring life support treatment during the second ICU day; 4,648 of these patients did *not* receive next-day life support treatment (Table 71-10) . Of those 8,860 patients in the ICU for 3 or more days, 2,718 were predicted to have a less than 10 percent risk of requiring life support during the third ICU day; 2,579 of these patients did *not* receive next-day active treatment. The study identified two major determinants of next-day risk for life support treatment: the current day's therapy and physiologic abnormalities, as reflected by the Acute Physiology Score of APACHE III.

Limitations

Zimmerman et al [114] acknowledged at least three limitations to these predictions: (1) factors that influence triage decisions are not considered, (2) the predictions are not 100 percent accurate, and (3) some patients predicted to be at low risk actually receive multiple life support treatments. Moreover, the effect of missing physiologic data on predictive accuracy has to be taken into account. Because unmeasured physiologic data generate an Acute Physiology Score of zero, the probability of next-day active treatment is underestimated. The authors concluded that the probability estimates can be used to supplement the physician's clinical judgment, facilitating ICU discharge decisions.

Daily Prognostic Estimates

Wagner et al [115] developed daily prognostic estimates for risk of death during each of the first 7 days of ICU care. Their goal was to create a single probability estimate that would represent the patient's current prognosis. The study was a prospective, multicenter, inception cohort analysis involving 17,440 consecutive ICU admissions. A series of multivariate equations was developed on the basis of primary reasons for ICU admission, age, chronic health status, treatment before ICU admission, Acute Physiology Score on admission, current-day Acute Physiology Score, and change between the current and previous day's Acute Physiology Score. The equations were used to create day-to-day risk predictions.

The percentage of cases with cross-validated predicted risks greater than 90 percent increased from 2.3 percent on day 1 to 8.8 percent (of patients still in the ICU) on day 7. The 1,033 patients who had a daily risk estimate of greater than 90 percent during any of their initial 7 days in the ICU had a 90 percent mortality rate and represented 47 percent of all ICU deaths (Table 71-11) . The authors concluded that daily physiologic measurements provide a high degree of explanatory

TABLE 71-10 -- Classification Tables Using a Cut-Point of 10% for Comparing Predicted and Actual Next-Day Active Treatment

	PREDICTED RISK	
	HIGH RISK (10%)	***LOW RISK (< 10%)***
ICU DAY 1		
Observed Active Treatment		
Actively treated	6,080	250
Not actively treated	2,809	4,648
[a] Sensitivity, 96%; [b] specificity, 62%; predicted to be at low (<10%) risk but received next-day active treatment (false negative), 5.1%.		
ICU DAY 2		
Observed Active Treatment		
Actively treated	4,147	139
Not actively treated	1,995	2,579
[a] Sensitivity, 97%; [b] specificity, 56%, predicted to be at low (<10%) risk but received next-day active treatment (false negative), 5.1%.		
ICU DAY 3		
Observed Active Treatment		
Actively treated	3,100	93
Not actively treated	1,064	1,627
[a] Sensitivity, 97%; [b] specificity, 60.4%; predicted to be at low (<10%) risk but received next-day active treatment (false negative), 5.4%.		

Data from Zimmerman et al [114]

[a] Defined as those predicted to be at >10% risk of life support divided by all cases receiving active treatment on target day

[b] Defined as those predicted to be at <10% risk of life support divided by all cases not actively treated on target day

power for hospital mortality rate. They further concluded that these daily prognostic estimates may help improve clinical decision making.

Summary and Critique

Survival, although easy to measure and of fundamental importance, is not the only determinant of outcome. [116] Some patients improve enough to leave the ICU only to die before hospital discharge. Other patients survive hospitalization but require nursing home placement or undergo

TABLE 71-11 -- Hospital Death Rate for Patients Predicted to be at 90% Risk of Death on ICU Days 1 to 7

	PATIENTS		
ICU DAY	***n*** [a]	**%**	**OBSERVED HOSPITAL DEATH RATE(%)**
1	406	2.3	90.6
2	399	2.8	92.5

3	348	3.9	92.8
4	330	5.5	91.8
5	271	6.5	93.0
6	240	7.7	92.5
7	218	8.8	91.7

Data from Wagner et al [115]

[a] Among the 17,440 patients in the APACHE III database, there were 2,212 such predictions in 1,033 patients. These 1,033 patients accounted for 47% of the total 1,681 ICU deaths and 933 (31%) of the total 3,030 hospital deaths.

subsequent long-term hospitalization for severe physical and mental impairments. Thus, life and death are not the only important outcome determinants. Rational choices among treatments depend on patients' and families' personalized assessments of specific risks and benefits.

Three groups of patients need ICU care, each with distinctly different goals: physiologically stable patients who are admitted for intensive observation; physiologically stable patients who require extensive nursing care and monitoring (frequently of an invasive nature); and physiologically unstable patients who need constant nursing and physician care. Patients admitted to most ICUs include those who might otherwise be considered "too sick" or "too well." Those who are too well (could survive without intensive care) often are given observation and intensive nursing care and consume a small portion of ICU bed days. Those who are severely ill often die rapidly and also use few bed days. Some patients, however, may respond favorably to intensive treatment and survive, an outcome that would not be possible if all of them were to be excluded from unit admission. Control can be achieved by evaluating and lowering expenditures while patients are in the ICU.

Quantitative indices are thought by many clinicians to provide more precise and accurate tools to evaluate the degree of illness and the likelihood of recovery. Outcome can be accurately predicted in approximastems that were functioning

normally at the time of ICU admission. Most predictive indices are weighted for acute physiologic changes, predominantly of cardiorespiratory and oxygen transport functions. In multiple organ system failure, these indicators often are close to normal, even moments before death. [117]

Cullen and Chernow [118] commented that society may move toward limiting care for critically ill patients sooner than we can perfect the science of risk prediction. They concluded

> Those persons who now believe that risk prediction models intrude on the many variables that caring clinicians use to make decisions about continuing or discontinuing intensive care may find themselves supporting risk prediction models in order to counter the inevitable drive toward limiting care for purposes of cost containment and rationing.

References

1. Society of Critical Care Medicine: Membership Committee Report, May 1996.

2. Downs JB, Klein EF, Modell JH et al: Intermittent mandatory ventilation: A new approach to weaning patients from mechanical ventilation. Chest 64:331, 1975.

3. Kirby RR, Robison E, Schulz J et al: Continuous flow ventilation as an alternative to assisted or controlled ventilation in infants. Anesth Analg 51:871, 1972.

4. Sjostrand U: High frequency positive pressure ventilation (HFPPV). Acta Anesthesiol Scand Suppl 64:1, 1977.

5. Carlon GC, Ray C Jr, Pierce MK et al: High frequency jet ventilation: Theoretical considerations and clinical observation. Chest 81:350, 1982.

6. Hewlett AM, Platt AS, Terry VG: Mandatory minute volume: A new concept in weaning from mechanical ventilation. Anaesthesia 30:163, 1977.

7. Rasanen J, Cane RD, Downs JB et al: Airway pressure release ventilation during acute lung injury: A prospective multicenter trial. Crit Care Med 19:1234, 1991.

8. Civetta JM, Gabel JC, Laver MB: Disparate ventricular function in surgical patients. Surg Forum 22:252, 1971.

9. Gregory GA, Kitterman JA, Phibbs RH et al: Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med 284:1333, 1971.

10. Gallagher TJ, Civetta JM: Goal-directed therapy of acute respiratory failure. Anesth Analg 59:831, 1980.

11. Kirby RR, Downs JB, Civetta JM et al: High-level positive end-expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 67:156, 1975.

12. Kirby RR, Perry JC, Calderwood HW et al: Cardiorespiratory effects of high positive end-expiratory pressure. Anesthesiology 43:533, 1975.

13. Suter PM, Fairley HB, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:248, 1975.

14. Kouwenhoven WB, Longworthy OR: Cardiopulmonary resuscitation: An account of forty-five years of research. JAMA 226:887, 1973.

15. Breivik H, Safar P, Sands P et al: Clinical feasibility trials of barbiturate therapy after cardiac arrest. Crit Care Med 6:228, 1978.

16. Askanazi J, Nordenstrom J, Rosenbaum SH et al: Nutrition of the patient with respiratory failure: Glucose vs. fat. Anesthesiology 54:373, 1981.

17. Askanazi J, Weissman C, Rosenbaum SH et al: Nutrition and the respiratory system. Crit Care Med 10:163, 1982.

18. Gravenstein JS, Paulus DA: Clinical Monitoring Practice. Philadelphia, JB Lippincott, 1987.

19. Gravenstein N (ed): Monitoring. Probl Anesth. Philadelphia, JB Lippincott, 1(1):1988.

20. American Society of Anesthesiologists: Standards for Basic Anesthetic Monitoring. Oct 21, 1986; amended Oct 21, 1998 (effective January 1, 1999).

21. Niehoff J, Del Guercio C, La Morte W et al: Efficacy of pulse oximetry and capnometry in postoperative ventilatory weaning. Crit Care Med 16:701, 1988.

22. MacIntyre NR: Pressure support ventilation: Effects on ventilatory reflexes and ventilatory muscle workloads. Respir Care 32:447, 1987.

23. Stock MC, Downs JB: Airway pressure release ventilation: A new approach to ventilatory support during acute lung injury. Respir Care 32:517, 1987.

24. Kirby RR, Smith RA, Desautels D: Mechanical ventilation. In Burton GC, Hodgkin JE (eds): Respiratory Care: A Guide to Clinical Practice. Philadelphia, JB Lippincott, 1984, p 556.

25. Weisman IM, Rinaldo JE, Rogers RM et al: Intermittent mandatory ventilation. Am Rev Respir Dis 127:641, 1983.

26. Hasten RW, Downs JB, Heenan TJ: A comparison of synchronized and non-synchronized intermittent mandatory ventilation. Respir Care 27:554, 1980.

27. Groeger JS, Levinson MR, Carlon GC: Assist control vs. synchronized intermittent mandatory ventilation during acute respiratory failure. Crit Care Med 17:607, 1989.

28. Younes M: Proportional assist ventilation: A new approach to ventilatory support. Am Rev Respir Dis 145:114, 1992.

29. Younes M, Puddy A, Roberts D et al: Proportional assist ventilation. Am Rev Respir Dis 145:121, 1992.

30. Kacmarek RM, Meklaus G: Microprocessor-controlled mechanical ventilators. In Banner MJ (ed): Positive Pressure Ventilation: Problems in Critical Care. Philadelphia, JB Lippincott, 1990, p 161.

31. Banner MJ, Blanch PB: Respiratory care. In Miller RD (ed): Atlas of Anesthesia, vol 1: Critical Care. Philadelphia, Current Medicine, 1997, pp 1.1-1.20.

32. Davis DA: An analysis of anesthetic mishaps from medical liability claims. Int Anesthesiol Clin 22(2):31, 1984.

33. Comroe JH, Botelho S: The unreliability of cyanosis in the recognition of arterial anoxemia. Am J Med Sci 214:1, 1947.

34. Taylor G, Larson CP, Prestwich R: Unexpected cardiac arrest during anesthesia and surgery. JAMA 236:2758, 1976.

35. Caplan RA, Ward RJ, Posner K et al: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

36. Keats A: Anesthesia mortality: A new mechanism [editorial]. Anesthesiology 68:2, 1988.

37. Robin ED: Iatroepidemics: A probe to examine systematic preventable errors in (chest) medicine. Am Rev Respir Dis 135:1152, 1987.

38. Connors AF Jr, Speroff T, Dawson NV et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 276:889, 1996.

39. Moller JT, Pedersen T, Rasmussen L et al: Randomized evaluation of pulse oximetry in 20,802 patients (parts I and II). Anesthesiology 78:436, 1993.

40. Dalen JE, Bone RC: Is it time to pull the pulmonary artery catheter? [editorial]. JAMA 276:916, 1996.

41. Pulmonary artery catheter consensus conference: Consensus statement. New Horiz 5:175, 1997.

42. Segal J, Pearl RG, Ford AJ et al: Instantaneous and continuous cardiac output obtained with a Doppler pulmonary artery catheter. J Am Coll Cardiol 13:6, 1989.

43. Yelderman M: Continuous measurement of cardiac output with the use of stochastic system identification techniques. J Clin Monit 6:322, 1990.

44. Hickling KG, Walsh J, Henderson S et al: Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia. Crit Care Med 22:1568, 1994.

45. Stewart TE, Meade MO, Cook DJ et al: Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med 338:355, 1998.

46. Banner MJ, Kirby RR, Gabrielli A et al: Partially and totally unloading respiratory muscle based on real-time measurements of work of breathing: A clinical approach. Chest 106:1835, 1994.

47. Banner MJ, Blanch PB, Kirby RR: Imposed work of breathing and methods of triggering a demand-flow continuous positive airway pressure system. Crit Care Med 21:183, 1993.

48. Banner MJ, Kirby RR, Blanch PB et al: Decreasing imposed work of the breathing apparatus to zero using pressure support ventilation. Crit Care Med 21:1333, 198:1338, 1995.

49. Banner MJ, Kirby RR, MacIntyre NR: Patient and ventilator work of

breathing and ventilatory muscle load at different levels of pressure support ventilation. Chest 100:531, 1991.

50. Banner MJ, Kirby RR, Kirton OC et al: Breathing frequency and pattern are poor predictors of work of breathing in patients receiving pressure support ventilation. Chest 108:1338, 1995.

51. Shoemaker WC, Hauser CJ: Critique of crystalloid versus colloid therapy in shock and shock lung. Crit Care Med 7:117, 1979.

52. Staub NC: "State of the art" review: Pathogenesis of pulmonary edema. Am Rev Respir Dis 109:358, 1974.

53. Holcroft JW, Trunkey DD, Carpenter MA: Extravasation of albumin in tissues of normal and septic baboons and sheep. J Surg Res 26:341, 1979.

54. Sturm JA, Carpenter BA, Lewis FR et al: Water and protein movement in the sheep lung after septic shock: Effect of colloid versus crystalloid resuscitation. J Surg Res 26:233, 1979.

55. Workshop on Assessment of Plasma Volume Expanders. Center for Biologics, Food and Drug Administration and National Heart, Lung, Blood Institute, Division of Blood Diseases and Resources, Bethesda, Maryland, March 25-26, 1991.

56. Nakayama S-I, Kramer GC, Carlsen RC et al: Infusion of very hypertonic saline to bleed rate: Membrane potentials and fluid shifts. J Surg Res 38:180, 1985.

57. Peters RM, Shackford SR, Hogan JS et al: Comparison of isotonic and hypertonic fluids in resuscitation from hypovolemic shock. Surg Gynecol Obstet 163:219, 1986.

58. Traverso LW, Bellamy RF, Hollenbach SJ et al: Hypertonic sodium chloride solutions: Effects of hemodynamics and survival after hemorrhage in swine. J Trauma 27:32, 1987.

59. Cone JB, Wallace BH, Caldwell FT Jr et al: Beneficial effects of a hypertonic solution for resuscitation in the presence of acute hemorrhage. Am J Surg 154:585, 1987.

60. Hands R, Holcroft JW, Perron PR et al: Comparison of peripheral and central infusions of 7.5% NaCl/6% dextran 70. Surgery 103:684, 1988.

61. Todd MH, Tommasino C, Moore S: Cerebral effects of isovolemic hemodilution with a hypertonic saline solution. J Neurosurg 63:944, 1985.

62. Gunnar W, Jonasson O, Merlotti G et al: Head injury and hemorrhagic shock: Studies of the blood brain barrier and intracranial pressure after resuscitation with normal saline solution, 3% saline solution, and dextran-40. Surgery 103:398, 1988.

63. Suarez JI, Qureshi AI, Bhardwaj A et al: Treatment of refractory intracranial hypertension with 23.4% saline. Crit Care Med 26:1118, 1998.

64. Holcroft JW, Vassar MJ, Turner JE et al: 3% NaCl and 7.5% NaCl/dextran 70 in the resuscitation of severely injured patients. Ann Surg 206:279, 1987.

65. Frey L, Kesel K, Pruckner S et al: Is sodium acetate dextran superior to sodium chloride dextran for small volume resuscitation from traumatic shock? Anesth Analg 79:517, 1994.

66. McGough EK: Resuscitation in shock, trauma, and burns. In Kirby RR (ed): Problems in Critical Care. Philadelphia, JB Lippincott, 1991, p 346.

67. Waters RM: Resuscitation: Artificial circulation by means of intermittent high pressure chest inflations with oxygen: A preliminary report. Joint Meeting of the Canadian, Interstate and New York Anesthetists with the Ontario Medical Association. Niagara Falls, Canada, June 1-3, 1921.

68. Kouwenhoven WB, Judge JR, Knickerbocker GG: Closed-chest cardiac massage. JAMA 173:1064, 1960.

69. Eisenberg M, Hollstrom A, Bergner L: The ACLS score: Predicting survival from out-of-hospital cardiac arrest. JAMA 246:50, 1981.

70. Becker LB, Ostrander MP, Barrett J et al: Survival from cardiopulmonary resuscitation in a large metropolitan area: Where are the survivors? Ann Emerg Med 20:355, 1991.

71. Erb D, Nowak RM: Resuscitation in the in-hospital setting: Special considerations. In Paradis NA, Halperin HR, Nowak RM (eds): Cardiac Arrest: The Science and Practice of Resuscitation Medicine. Baltimore, Williams & Wilkins, 1996, p 597.

72. Landry FJ, Parker JM, Phillips YY: Outcome of cardiopulmonary resuscitation in the intensive care setting. Arch Intern Med 152:2305, 1992.

73. Berger R, Kelley M: Survival after in-hospital cardiopulmonary arrest of noncritically ill patients: A prospective study. Chest 106:872, 1994.

74. Goetting MG, Paradis NA: High-dose epinephrine improves outcome from pediatric cardiac arrest. Ann Emerg Med 20:22, 1996.

75. Dieckmann RA, Vardia R: High-dose epinephrine in pediatric out-of-hospital cardiopulmonary arrest. Pediatrics 95:901, 1995.

76. Sorum PC: Deciding about cardiopulmonary resuscitation: The contributions of decision analysis. Arch Intern Med 155:513, 1995.

77. Weisfeldt ML: Augmentation of cerebral perfusion by simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. Lancet 1:175, 1980.

78. Chandra N, Rudikoff M, Weisfeldt ML: Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. Lancet 1:175, 1980.

79. Emergency Cardiac Care Committee and Subcommittee: American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiac care. III. Adult advanced cardiac life

support. JAMA 268:2208, 1992.

80. Kellie G: An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the 3D, and whose bodies were discovered in the vicinity of Leith on the morning of the 4th November 1821 with some reflections on the pathology of the brain. Trans Med Chir Sci Edinb 1:84, 1824.

81. Marmarou A, Shulman K, LaMorgese J: Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. J Neurosurg 43:523, 1975.

82. Lofgren J, von Essen C, Zwetnow NN: The pressure-volume curve of the cerebrospinal fluid space in dogs. Acta Neurol Scand 49:557, 1973.

83. Langfitt TW, Weinstein JD, Kassell NF: Cerebral vasomotor paralysis produced by intracranial hypertension. Neurology 15:622, 1965.

84. Day AL, Salcman M: Subarachnoid hemorrhage. Am Fam Physician 40:95, 1989.

85. Kassell NF, Torner JC, Haley EC et al: The International Cooperative Study on the Timing of Aneurysm Surgery. Part I. Overall management results. J Neurosurg 73:18, 1990.

86. Juvela S, Porras M, Heiskanen O: Natural history of unruptured intracranial aneurysms: A long-term follow-up study. J Neurosurg 79:174, 1993.

87. Graff-Radford NR, Torner J, Adams HP et al: Factors associated with hydrocephalus after subarachnoid hemorrhage. Arch Neurol 46:744, 1989.

88. MacDonald RL, Weir BK: Cerebral vasospasm and free radicals. Free Radic Biol Med 16:633, 1994.

89. Otsuji T, Endo S, Hirashima Y et al: An experimental model of symptomatic vasospasm induced by oxyhemoglobin in rabbits. Stroke 25:657, 1994.

90. Vollrath BAM, Weir BKA, MacDonald RL et al: Intracellular mechanisms involved in the responses of cerebrovascular smooth-muscle cells to hemoglobin. J Neurosurg 80:261, 1994.

91. Shishido T, Suzuki R, Qian L et al: The role of superoxide anions in the pathogenesis of cerebral vasospasm. Stroke 25:864, 1994.

92. Zuccarello M, Marsch JT, Schmitt G et al: Effect of the 21-aminosteroid U-74006F on cerebral vasospasm following subarachnoid hemorrhage. J Neurosurg 71:98, 1989.

93. Hirashima Y, Endo S, Otsuji T et al: Platelet-activating factor and cerebral vasospasm following subarachnoid hemorrhage. J Neurosurg 78:592, 1993.

94. Feuerstein G, Yue T, Lysko PG: Platelet-activating factor: A putative mediator in central nervous system injury? Stroke 21(suppl III):III90, 1990.

95. Cosentino F, Katusic ZS: Does endothelin-1 play a role in the pathogenesis of cerebral vasospasm? Stroke 25:904, 1994.

96. Baykaner MK: Evidence for the participation of vascular endothelium originated humoral factors to cerebral vasospasm. Acta Neurochir (Wien) 124:135, 1993.

97. Barone FC, Globus MYT, Price WJ et al: Endothelin levels increase in rat focal and global ischemia. J Cereb Blood Flow Metab 14:337, 1994.

98. Origitano TC, Wascher TM, Reichman OH et al: Sustained increased cerebral blood flow with prophylactic hypertful in cerebral aneurysmal surgery? A retrospective study. Neurosurgery 34:30, 1994.

99. Haley EC, Kassell NF, Torner JC et al: A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. J Neurosurg 78:537, 1993.

100. Mercier P, Alhayek G, Rizk T et al: Are the calcium antagonists really useful in cerebral aneurysmal surgery? A retrospective study. Neurosurgery 34:30, 1994.

101. Ohman J, Servo A, Heiskanen O: Long-term effects of nimodipine on

cerebral infarcts and outcome after aneurysmal subarachnoid hemorrhage and surgery. J Neurosurg 74:8, 1991.

102. Matsui T, Asano T: Effects of new 21-aminosteroid tirilazad mesylate (U74006F) on chronic cerebral vasospasm in a "two-hemorrhage" model of beagle dogs. Neurosurgery 34:1035, 1994.

103. Kanamaru K, Weir BKA, Findlay JM et al: A dosage study of the effect of the 21-aminosteroid U74006F on chronic cerebral vasospasm in a primate model. Neurosurgery 27:29, 1990.

104. Kassell NF, Haley EC, Apperson-Hansen C et al: Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: A cooperative study in Europe, Australia and New Zealand. J Neurosurg 84:221, 1996.

105. Juvela S: Aspirin and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. J Neurosurg 82:945, 1995.

106. Jannett B, Teasdale G: Aspects of coma after severe head injury. Lancet 1:878, 1977.

107. Eisenberg HM, Gary HE, Aldrich EF et al: Initial CT findings in 753 patients with severe head injury: A report from the NIH Traumatic Coma Data Bank. J Neurosurg 73:688, 1990.

108. O'Sullivan MG, Statham PF, Jones PA et al: Role of intracranial pressure monitoring in severely head-injured patients without signs of intracranial hypertension on initial computerized tomography. J Neurosurg 80:46, 1994.

109. President's Commission for the Study of Ethical Problems in Medicine: Guidelines for the Determination of Death. JAMA 246:2184, 1981.

110. Kirby RR, Civetta JM: Critical care. In Brown DL (ed): Risk and Outcome in Anesthesia, 2nd ed. Philadelphia, JB Lippincott, 1992, pp 235-257.

111. Civetta JM: Prediction and definition of outcome. In Civetta JM, Taylor RW, Kirby RR (eds): Critical Care, 2nd ed. Philadelphia, JB Lippincott, 1992, pp 1873-1898.

112. Lemeshow S, Teres D, Avrunin JS et al: Refining intensive care outcome prediction by using changing probabilities of mortality. Crit Care Med 16:470, 1988.

113. Lemeshow S, Teres D, Pastides H et al: A method for predicting survival mortality of ICU patients using objectively derived weights. Crit Care Med 13:519, 1985.

114. Zimmerman JE, Wagner DP, Draper EA et al: Improving intensive care unit dialog decision: Supplementing physician judgement with predictions of next day risk for life support. Crit Care Med 22:1373, 1994.

115. Wagner DP, Knaus WA, Harrell FE et al: Daily prognostic estimates for critically ill adults in intensive care units: Results from a prospective multicenter inception cohort analysis. Crit Care Med 22:1359, 1994.

116. Civetta JM: Prediction and definition of outcome. In Civetta JM, Taylor RW, Kirby RR (eds): Critical Care, 3rd ed. Philadelphia, Lippincott-Raven, 1997, pp 127-148.

117. Civetta JM, Kirby RR: ICU outcome. In Miller RD (ed): Atlas of Anesthesia, vol 1: Critical Care. Philadelphia, Current Medicine, 1997nter inception cohort analysis. Crit Care Med 22:1359, 1994.

118. Cullen DJ, Chernow B: Predicting outcome in critically ill patients. Crit Care Med 22:1345, 1994.

/das/book/view/29494766/875/782.html

Chapter 72 - Respiratory Care

Barry A. Shapiro
William T. Peruzzi

Chronic Obstructive Pulmonary Disease

/das/book/view/29494766/875/783.html

INTRODUCTION

The knowledge and skills required to provide safe and effective respiratory care were pioneered and developed by anesthesiologists. Acute respiratory care includes both ambient-pressure and positive-pressure therapies applied via the airway. Appropriate and timely application of ambient-pressure modalities (oxygen therapy, bronchial hygiene therapy, and aerosol therapy) often avoids or shortens the time course of positive-pressure therapy. Ventilator management has become complex as basic knowledge, clinical experience, and technologic capabilities expand. Interestingly, advances in respiratory care have been so successful in supporting cardiorespiratory function that clinicians now must be able to support parenchymal lung disease of such severity that the airway pressure therapy itself must be limited to avoid further lung injury. This situation demands training of intensive care specialists with a sophisticated level of knowledge and skill, much of which is an integral part of anesthesiology.

Anesthesiology is the only medical specialty that requires the consistent application of cardiopulmonary supportive

techniques. The anesthesiologist must be prepared to provide patient care outside the operating room, where cardiopulmonary knowledge and skill are needed for reasons other than induction of the anesthetic state and performance of surgery. This chapter concentrates on the principles of respiratory support in which the anesthesiologist is most commonly involved outside the operating room theater.

OXYGEN THERAPY

Tissue oxygenation is primarily dependent on the milliliters of oxygen per minute delivered to the tissues. This oxygen delivery (D_{O_2}) is usually expressed as follows:

Oxygen content is determined by the concentration of hemoglobin [Hb] in the blood (g/dL), the percentage of the hemoglobin saturated with oxygen [percent S_{O_2}], and the milliliters of oxygen dissolved in 1 dL of plasma:

When fully saturated, 1 g of Hb combines with 1.34 mL of oxygen. The solubility coefficient for oxygen dictates that for each mm Hg partial pressure of oxygen (P_{O_2}), 1 dL of plasma will contain 0.003 mL of oxygen in the gaseous state.

Hypoxemia is clinically defined as a relative deficiency of oxygen in the arterial blood. Assuming normal Hb content,

Figure 72-1 (Figure Not Available) Alveolar oxygen tension (P_{AO_2}) is determined from the dynamic equilibrium established between the alveolar oxygen delivery (arrow A) and the alveolar oxygen extraction (arrow B). Alveolar oxygen delivery is a function of the minute ventilation (V_E) and the inspired oxygen fraction (F_{IO_2}). Alveolar oxygen extraction is a function of the pulmonary arterial oxygenation status (Sv_{O_2}) and the capillary blood flow (Q_C). *(From Shapiro et al [1])*

an arterial P_{O_2} (Pa_{O_2}) measurement of less than 80 mm Hg signifies hypoxemia. Hypoxia is clinically defined as an inadequate oxygen tension at the cellular level and cannot be directly measured.

The physiologic responses to either arterial hypoxemia or tissue hypoxia are to improve Ca_{O_2} by primarily increasing cardiac output and secondarily increasing ventilation. The clinical goal of oxygen therapy is to increase the alveolar oxygen content (C_{AO_2}), which is essentially equivalent to increasing the alveolar P_{O_2} (P_{AO_2}). An increase in the C_{AO_2} may result in an increase in the Ca_{O_2}, thereby decreasing the work of breathing and myocardial work required to attain a given arterial oxygen content. [1]

Oxygen therapy is clinically referred to as the fraction of inspired gas that is oxygen (F_{IO_2}). As schematically illustrated in Figure 72-1 (Figure Not Available), inhalation of oxygen concentrations of more than 20.9 percent will increase the P_{AO_2} because there is an increase in the amount of oxygen delivered to the alveolus per unit time. When hypoxemia is secondary to low P_{AO_2} values, increasing the F_{IO_2} increases the Pa_{O_2}, often diminishing both myocardial and ventilatory work. The clinically effective range of F_{IO_2} for prolonged oxygen administration is from 0.24 to 0.50. Prolonged administration of 1.0 F_{IO_2} to patients with diseased lungs often has detrimental physiologic (denitrogenation absorption atelectasis) and cytotoxic (oxygen toxicity) effects. [2] [3]

Oxygen Delivery Systems

Outside the operating room setting, where gases are administered by rebreathing systems that include a CO_2 absorber, oxygen therapy is provided by either partial rebreathing or nonrebreathing delivery systems that do not require a CO_2 absorber. A partial rebreathing system allows for the initial portion of the expired gases containing little or no CO_2 to be collected in a reservoir while the remaining expiratory gases are vented to the atmosphere. Most oxygen delivery systems are intended to function as nonrebreathing systems in which all exhaled CO_2 is vented to the atmosphere and only fresh inspiratory gases are inhaled. Nonrebreathing systems are divided into *high-flow* (fixed performance) and *low-flow* (variable performance) systems.

A high-flow oxygen delivery system provides the total inspired atmosphere so that a premixed F_{IO_2} is consistently and predictably delivered. To accomplish this goal, the inspiratory gas flows must be three to four times the measured minute ventilation. [4] [5] [6] So-called venturi devices (Fig. 72-2) (Figure Not Available) are the most commonly used high-flow oxygen devices for nonintubated patients. The physical behavior of these air-entrainment devices is best explained by the principle of constant-pressure jet mixing, where viscous shearing forces distal to the orifice entrain room air in a specific ratio. [7] Variation in orifice or entrainment port size changes F_{IO_2}, whereas variation of the oxygen flow rate determines the total volume of gas provided by the device. F_{IO_2} values of 0.24 to 0.40 are readily provided by air-entrainment mask systems, whereas higher F_{IO_2} values are best provided by large-volume nebulizers with wide-bore tubing leading to a mask or endotracheal tube. The intubated patient should breathe close to 100 percent humidified 37°C gas, to avoid drying of the tracheobronchial mucosa. This is safely and

Figure 72-2 (Figure Not Available) Principle of an air entrainment device. Pressurized oxygen is forced through a constricted orifice; the increased gas velocity distal to the orifice creates a shearing effect that causes room air to be entrained through the entrainment ports. The high flow of gas fills the mask; holes allow both exhaled and delivered gases to escape. A and B show that the size of the entrainment ports (EP) determines the amount of room air to be entrained. OS, oxygen source. Large ports (A) result in relatively low inspired oxygen fraction (F_{IO_2}); small ports (B) result in relatively higher F_{IO_2}. For any size EP, the F_{IO_2} is stable; however, the total gas flow varies with the pressurized oxygen flow. *(From Shapiro et al [1])*

economically accomplished by placing a reservoir tubing on the distal limb of the endotracheal T-connection so that inspiring room air is avoided.

A low-flow oxygen delivery system requires that the patient inspire some room air to meet inspiratory demands. These systems are popular because of their simplicity, patient comfort, and economics. The use of a low-flow oxygen delivery system does not imply delivery of low oxygen concentrations. As shown in Figure 72-3 (Figure Not Available), the F_{IO_2} is determined by the size of the oxygen reservoir, the oxygen flow rate, and the breathing pattern. For example, a nasal cannula at an oxygen flow rate greater than 6 L/min accomplishes minor increases in F_{IO_2} because the nasopharyngeal reservoir is filled with 100 percent oxygen at a 6 L/min flow rate. An oxygen reservoir must be increased (placing a mask over the nose and mouth) to achieve an F_{IO_2} greater than 0.40. Assuming a normal breathing pattern, Table 72-1 lists the approximate F_{IO_2} at various flow rates for the common low-flow oxygen delivery systems. With abnormal ventilatory patterns (Table 72-2) (Table Not Available), the larger the tidal volume (V), or the faster the respiratory rate, the lower the F_{IO_2}.

/das/book/view/29494766/875/785.html

BRONCHIAL HYGIENE THERAPY

Mucociliary activity and the cough mechanism are major factors that ensure spontaneous clearance of pulmonary secretions (bronchial hygiene). Bronchial hygiene therapy is primarily intended to mobilize retained secretions and to reinflate atelectatic lung regions. Normal pulmonary secretions form the mucus lining the airways that normally moves toward the larynx at 1 to 2 cm/min propelled by ciliary activity. This normal mucus blanket is capable of transporting a foreign particle from a respiratory bronchiole to the larynx in 20 minutes. When the properties of the mucus blanket and ciliary activity become abnormal, the cough mechanism is invoked to mobilize secretions. An effective cough mechanism requires an intact glottis, functional abdominal and intrathoracic musculature, and an adequate inspiratory capacity.

Table 72-3 provides an overview of the goals of bronchial hygiene therapy. Although the maintenance of bronchial hygiene is of recognized importance, the criteria for application of bronchial hygiene therapy are controversial. [8] The essential factors involved in bronchial hygiene therapy can be discussed in five general categories: (1) humidification of the airways, (2) incentive spirometry, (3) chest physical therapy, (4) positive-pressure techniques, and (5) invasion of the tracheal tree.

Humidification

Absolute humidity is the weight of water vapor in 1 L of gas (mg/L). Relative humidity is the absolute humidity expressed as a portion of the maximum absolute humidity. Table 72-4 lists the relationships between absolute and relative humidity at body temperature and at room air temperature.

Figure 72-3 (Figure Not Available) Reservoirs in low-flow oxygen therapy. The anatomic reservoir consists of the nose, the nasopharynx, and the oropharynx. This reservoir is estimated to be approximately one-third of the anatomic dead space. The appliance reservoir consists of (1) the mask: 100- to 200-mL volume, depending on the appliance; and (2) the reservoir bag: 600 to 1,000 mL of added volume. *(From Shapiro et al [1])*

Alveolar air is normally 100 percent humidified at 37°C, having a water vapor content of 44 mg/L and exerting a partial pressure of 47 mm Hg. Standard "room air" conditions (21°C, 50% relative humidity) have water vapor contents of less than 10 mg/L. The difference between alveolar water vapor content and that of room air is termed the *humidity deficit.* The nose normally restores most of the humidity deficit; however, the tracheobronchial mucosa must warm and humidify the inspired gas when the nose is bypassed. The tracheobronchial mucosa is more readily dehydrated than the nasal mucosa, a feature resulting in impairment of mucociliary activity and mucosal inflammation.

TABLE 72-1 -- Guidelines for Estimating Inspired Oxygen Concentrations With Low-Flow Oxygen Devices

100% O_2 FLOW RATE[a] (L)	F_{IO_2}
Nasal cannula or catheter	
1	0.24
2	0.28
3	0.32
4	0.36
5	0.40
6	0.44
Oxygen mask	
5-6	0.40
6-7	0.50
7-8	0.60
Mask with reservoir bag	
6	0.60
7	0.70
8	0.80
9	0.80
10	0.80

F_{IO_2} , inspired oxygen concentration

From Shapiro et al [1]

[a] Normal ventilatory pattern is assumed

The administration of dry oxygen lowers the water content of the inspired air, and placement of tracheal airways bypasses the nasopharynx and oropharynx, where the humidification of inspired gases primarily takes place. If adequate humidification of inspired gases is not provided prior to gas entry into the trachea, the deficit of humidity is provided by moisture from the mucus blanket of the tracheobronchial tree. This situation can result in drying of the tracheobronchial tree, ciliary dysfunction, impairment of mucus transport, inflammation and necrosis of the ciliated pulmonary epithelium, retention of dried secretions, atelectasis, bacterial infiltration of the pulmonary mucosa, and pneumonia.

To prevent these complications, a humidifier or nebulizer should be used to increase the water content of inspired gases. A humidifier increases the water vapor in a

gas without producing particulate water. A humidifier can prevent water loss from the pulmonary system, but it cannot add water to the system. Humidifiers are designed to increase water

TABLE 72-2 -- Variability in Inspired Oxygen Concentrations With Low-Flow Oxygen-Delivery Systems and Variable Patterns of Ventilation

(Not Available)

Modified from Vender JS, Spices BD: Post Anesthesia Care. Philadelphia, WB Saunders, 1992.

TABLE 72-3 -- Goals of Bronchial Hygiene Therapy

I. Goals of aerosol therapy
  A. Aid bronchial hygiene
    1. Restore and maintain mucus blanket continuity
    2. Hydrate dried, retain secretions
    3. Promote expectoration
  B. Humidify inspired gases
  C. Deliver medication
II. Goals of intermittent positive-pressure breathing
  A. Improve and promote cough mechanism
  B. Improve distribution of ventilation
  C. Deliver medication
III. Goals of chest physical therapy
  A. Aid bronchial hygiene
    1. Prevent accumulation of bronchial secretions
    2. Promote mobilization of bronchial secretions
    3. Improve cough mechanism
  B. Improve efficiency and distribution of ventilation
IV. Goals of sustained maximum inflation therapy
  A. Optimize lung inflation
    1. Prevent atelectasis
    2. Prevent accumulation of bronchial secretions
  B. Optimize cough mechanism
  C. Detect acute pulmonary disease early

vapor by passing gas over heated water (heated-passover humidifier), by fractionating gas into tiny bubbles as gas passes through water (bubble humidifiers), by allowing gas to pass through a chamber that contains a heated, water-saturated wick (heated-wick humidifier), or by vaporizing water and selectively allowing the vapor to mix with the inspired gases (vapor-phase humidifier). A nebulizer increases the water content of the inspired gas by generating aerosols (small droplets of particulate water) of uniform size that become incorporated into the delivered gas stream and then evaporate into the inspired gas as it is warmed in the respiratory tract. Pneumatic nebulizers operate from a pressurized gas source, and electric nebulizers are powered by an electrical source and are referred to as "ultrasonic." There are several varieties of the foregoing nebulizers that depend more on design differences than on power source.

Incentive Spirometry

The incentive spirometer is an effective and inexpensive prophylactic bronchial hygiene tool that provides a visual

TABLE 72-4 -- Relationships of Humidity and Temperature

TEMPERATURE (° C)	ABSOLUTE HUMIDITY (mg H_2 O/L GAS)	RELATIVE HUMIDITY (%)
37	44	100
37	22	50
37	18	40
21	18	100
21	9	50

goal or "incentive" for the patient to achieve and sustain a maximal inspiratory effort. When performed on an hourly basis, this modality provides optimal lung inflation, distribution of ventilation, and an improved cough. The hope is to prevent atelectasis and the retention of bronchial secretions. Incentive spirometry can also be helpful in the diagnosis of acute pulmonary disease in that a sudden decrease in the ability of a patient to perform at a previously established level may herald the onset of severe atelectasis, pneumonia, or other pulmonary disorders. For incentive spirometry to be effective, the patient must be cooperative, motivated, and well instructed in the technique (by the respiratory therapist, nurse, or physician); a vital capacity of more than 15 mL/kg or an inspiratory capacity of more than 12 mL/kg should be obtainable; the patient should not be tachypneic or receiving a high F_{IO_2} .

Chest Physical Therapy

Chest physical therapy techniques can be classified into those that promote bronchial hygiene, those that improve breathing efficiency, and those that promote physical reconditioning. The techniques considered here are those concerned with bronchial hygiene.

Postural drainage is a technique that utilizes different body positions to facilitate gravitational drainage of mucus from various lung segments (Fig. 72-4) . Common diseases that are amenable to postural-drainage therapy include cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease (COPD), acute atelectasis, and lung abscess. In hospitalized patients, the basilar lung regions can often benefit from postural drainage because most hospital bed positions do not permit adequate drainage of these lung segments. Of course, patients with increased intracranial pressure or congestive heart failure may not tolerate head-down positioning. In patients with unilateral lung disease, it is best also to provide drainage of the contralateral lung because cross-contamination of the nondiseased lung is always a possibility.

External manipulation of the thorax, in the form of percussion and vibration, is a technique used to loosen and mobilize secretions that are adherent to bronchial walls. [9] The percussion is intended to apply kinetic energy intermittently to the chest wall and lung. This is accomplished by rhythmically striking the thorax with cupped hands or a mechanical device placed directly over the lung segment to be drained. This procedure generates a mechanical energy wave that is transmitted through

the chest wall to the lung tissue and loosens adherent mucus. [9] [10] Mechanical percussion devices are available and have some theoretic advantages in that they apply vibratory/percussive forces in a more consistent, uniform fashion, and they are not subject to fatigue. However, no convincing evidence demonstrates the superiority of one method over the other. [11] Vibration normally follows percussion and involves the application of a fine tremorous action that is manually performed by pressing in the direction of the patient's ribs and soft tissue of the chest. Chest vibration is accomplished by placing the hands on the patient's chest wall and generating a rapid vibratory motion in the arms, from the shoulders, and gently compressing the chest wall in the direction in which the ribs normally move during

Figure 72-4 Common postural drainage positions for (A) posterior basilar segments; (B) middle lobe and ligula; and (C) apical segments of upper lobes.

exhalation. [9] [12] [13] Vibrations should be delivered during expiration over the draining area for optimal effect.

Positive-Pressure Techniques

Compared with spontaneous efforts in a patient with compromised pulmonary function, intermittent positive-pressure breathing (IPPB) can provide a significantly larger V_T and a physiologically advantageous inspiratory-to-expiratory pattern. IPPB therapy is most useful when inspiratory capacity is limited. Although widely applied in the past, this type of therapy is very expensive and should only be utilized when reasonable alternatives are not available. It is suggested that the patient's vital capacity (VC) should be less than 15 mL/kg, the IPPB treatment should augment this by at least 100 percent, and there is an identifiable end point for the therapy. The use of IPPB should be limited to patients with a reversible disease process.

Invasive Tracheal Techniques

Tracheal suction can be accomplished safely through endotracheal or tracheostomy tubes because adequate preoxygenation can be provided. Most commonly, the patient is hyperventilated with a high F_{IO_2} for three to five breaths to minimize the hypoxemia induced by removal of the patient from an oxygen source and the application of suction to the airways. A sterile suction catheter less than half the diameter of the tracheal tube should be advanced without the application of a vacuum until it can no longer be easily advanced. The catheter should then be withdrawn slightly, and intermittent suction should be applied while the catheter is withdrawn with a rotating motion. The duration of the entire procedure should not exceed 20 seconds. The patient should be immediately ventilated with an oxygen-enriched atmosphere to ensure adequate lung reexpansion and oxygenation. The patient must be closely observed for signs of distress, bronchospasm, hemodynamic instability, or cardiac arrhythmias throughout the entire procedure. In conjunction with a ventilator, a closed-system suction catheter may be of benefit to minimize contamination of both patient and health care professional. [14] [15]

Suctioning of the tracheobronchial tree without an established tracheal tube (i.e., nasotracheal suctioning) is common, but it is associated with significant risk because the patient cannot be adequately ventilated and "preoxygenated" prior to the procedure. [15] [16] In addition, passing the suction catheter through the vocal cords can result in laryngospasm or vocal cord injury with subsequent airway obstruction. Nasotracheal suction should be limited to patients who have reasonable ventilatory reserves and are free of coronary artery disease. "Routine" suctioning of the airway should be discouraged, except in neonates, whose small airway diameters can be acutely obstructed by a small accumulation of secretions.

Bronchoscopy for removal of secretions and reinflation of atelectasis is indicated when there is radiographic evidence of segmental or lobar atelectasis and the patient's clinical condition requires urgent intervention, or the atelectasis is persistent despite aggressive postural drainage, percussion, and vibration, and it is likely to result in detrimental sequelae such as pneumonia and lung abscess.

AEROSOL THERAPY

An aerosol is a suspension of fine particles of a liquid in a gas. Particle size should be 5 mum or less for deposition in the pulmonary tree. [17] Aerosols are used in respiratory care to aid bronchial hygiene, to humidify inspiratory gases, and to deliver medications.

Bland Aerosol Therapy

Aerosols of water or salt solutions are considered "bland" if they do not contain medications. Bland aerosol therapy can be used in the hydration of dried, retained secretions and the restoration and maintenance of the mucus blanket. However, bland aerosols are known to increase airway resistance (bronchospasm) or to cause dry secretions to swell, resulting in clinical deterioration that worsens hypoxemia. [18] These detrimental effects may be ameliorated by the administration of a bronchodilator. Although bland aerosol therapy is widely used, the practice is controversial because clear scientific evidence to support the utility of such therapy is not available. [19] [20] The administration of high-volume aerosolized saline (hypertonic, isotonic, or hypotonic) for 30 minutes via a continuous ultrasonic aerosol is appropriate to achieve sputum induction, provided the patient has a strong, effective cough and there is sputum in the airways that can be mobilized and expectorated. Complications associated with ultrasonically nebulized aerosols are wheezing or bronchospasm, infection, overhydration, patient discomfort, and the potential for exposure to droplet nuclei of *Mycobacterium tuberculosis* or other airborne contagion produced as a consequence of coughing, particularly during sputum induction.

Medication by Aerosol

Numerous drugs have been investigated for delivery by aerosol. In most instances, the drug was intended to have a topical or direct effect on the airways or lung tissue while minimizing its systemic effects.

Several antibiotic agents are currently used. There is a high incidence of bronchospastic reactions associated with the administration of aerosolized antibiotics. Either pretreatment or concurrent treatment with an aerosolized beta-agonist is recommended. Aerosolized pentamidine has been shown to be effective for *Pneumocystis carinii* pneumonia. [21] [22] However, pentamidine must be administered with an aerosol device that produces particles with a mass median aerodynamic diameter of less than 3.0 mum to ensure adequate penetration to the lung parenchyma and to minimize bronchospasm. Aerosolization and inhalation of amphotericin B have been investigated as a method to provide prophylaxis against pulmonary fungal infections while minimizing the adverse side effects of the drug. [23] The best reported results are against pulmonary aspergillosis. [24] Aerosolized antibiotic therapy for infections associated with cystic fibrosis was also explored, but it was found to be of equivocal efficacy. [25] Ribavirin has been recommended for the treatment of respiratory syncitial virus in children, especially those with congenital heart disease, immunodeficiency, or bronchopulmonary dysplasia. [25] The U.S. Food and Drug Administration (FDA) recommends an aerosol device that will generate particles with a mass median aerodynamic diameter of less than 1.5 mum.

Table 72-5 (Table Not Available) lists the most commonly used aerosolized pharmacologic agents. The beta-agonists and anticholinergic agents act primarily by enhancing bronchodilation through increases in intracellular cyclic adenosine monophosphate (cAMP) levels or decreases in intracellular cyclic guanosine monophosphate (cGMP) levels. The anti-inflammatory agents have gained popularity in the treatment of bronchospastic disorders because the disease processes have been demonstrated to be of an inflammatory nature.

Small-Volume Nebulizers

The delivery of medications via small-volume nebulizers (SVN) is the standard in clinical practice for aerosol medication delivery. Although the SVN is small and relatively easy to use, it requires a gas source that can produce a flow of 5 to 10 L/min. Either a respiratory therapist or a nurse must spend significant time for the aerosolized medication to be administered via a SVN, thus making these processes expensive and inefficient. [26]

Metered-Dose Inhaler

A functional alternative to the SVN is the metered-dose inhaler (MDI). The MDI is a device that permits rapid, self-administration of an inhaled drug by the patient. With appropriate use, delivery of drug to the lower airways has been demonstrated to be approximately 10 percent of the total dose and is comparable to that attained with the SVN. [27] [28] However, in contrast to the SVN, with which 66 percent of the drug is deposited in the apparatus, MDI administration results in only 5 to 10 percent of drug deposition in the apparatus. [27] [29] MDI and SVN modes of therapy have been clinically compared with respect to bronchodilator administration, and no differences were found between peak expiratory flow rates or severity of symptoms in stable patients treated with either modality. [30] In addition to equal clinical efficacy, administering bronchodilator therapy with MDI devices requires less personnel time and offers significant cost savings to the hospital. [31]

The effective use of an MDI requires that the patient meet certain clinical criteria. The patient must be able to position and actuate the device appropriately, to inspire deeply, and to coordinate the inspiratory effort with the device actuation. [32] [33] To ameliorate some of the problems associated MDI use, "spacer devices" have been developed. As shown in Figure 72-5 , a spacer acts as a reservoir into which the drug is discharged, and the device eliminates the need for significant coordination of hand, mouth, and breathing functions and improves delivery of the drug to the airways. [34] Patients can be expected to benefit from MDI-spacer therapy if they meet the following criteria: [35]

1. Respiratory rate less than 25 breaths/min.
2. Ability to breath-hold for 5 seconds or more.
3. VC greater than 15 mL/kg.
4. Ability to understand verbal and visual instructions.
5. Appropriate hand-mouth-inspiratory coordination.
6. Peak expiratory flow rates greater than or equal to 150 L/min for females and greater than or equal to 200 L/min for males.

Bronchodilators and Ventilators

The use of SVN to deliver bronchodilation during mechanical ventilation can result in bacterial contamination of

TABLE 72-5 -- Aerosolized Bronchodilators and Antiasthmatic Drugs

(Not Available)

From Peruzzi WT, Shapiro BA: Respiratory care. In Murray MJ, Coursin DB, Pearl RG et al (eds): Critical Care Medicine: Perioperative Management. Philadelphia, Lippincott-Raven, 1997, p 467.

Figure 72-5 Illustration of a spacer with a metered-dose inhaler. (A) Aerosol suspension dispersing equally in the gas volume within the spacer following ejection from the inhaler. (B) The patient takes a deep, slow inhalation of the medication.

the ventilator circuit, alteration in the delivered V_T, increased work of breathing during patient-initiated modes of ventilation, and damage to flow-measurement devices incorporated into some ventilator circuits. [34] Administration of aerosols via an endotracheal tube is known to reduce penetration to the lower airways. [36] MDI have been shown to be comparable to SVN delivery systems without the associated problems in ventilator-dependent patients. [34]

PRINCIPLES OF POSITIVE-AIRWAY PRESSURE THERAPY

Positive-airway pressure therapy refers to the application of higher than ambient airway pressures during inspiration and/or exhalation for the purpose of improving pulmonary and respiratory function. Positive pressures applied during inspiration are usually referred to as positive-pressure ventilation (PPV). Positive pressures applied during exhalation are usually referred to as positive end-expiratory pressure (PEEP). Positive airway pressure is an essential component of critical care medicine and represents the single most important area demanding the unique skills and knowledge of the anesthesiologist.

The application of positive-airway pressure therapy to critically ill patients is confusing and controversial because of the following: (1) the physics, physiology, and technology are complex; (2) the terminology is inconsistent and at times contradictory; and (3) prospective conclusive human studies are rare because of multiple variables and the multidisciplinary clinical setting. This discussion is intended to provide a cohesive overview for all anesthesiologists irrespective of involvement in critical care medicine. Table 72-6 lists the definitions used in this chapter. These definitions are as acceptable as any others and are compatible with the published standards of the American College of Chest Physicians, the American Thoracic Society, and the American Association for Respiratory Care.

Physiology Associated With Positive-Pressure Ventilation

The need for PPV arises when one of three abnormal cardiopulmonary conditions is clinically evident: (1) apnea or any ventilatory pattern inconsistent with sustaining life; (2) acute ventilatory failure (acute respiratory acidosis), which is a condition in which the lungs fail to excrete adequate volumes of CO_2 [37]; and (3) impending ventilatory failure, in which clinical assessment of cardiopulmonary work suggests that the work of breathing is detrimental to maintaining respiratory homeostasis. [38]

Pathogenesis of Ventilatory Failure

Respiration is the exchange of oxygen and CO_2 across permeable membranes. Respiratory failure traditionally refers to inadequate molecular gas exchange at the pulmonary level. Because pulmonary gas exchange involves both bulk flow of gas in and out of the lungs (ventilation) and molecular gas exchange across the alveolar-capillary membrane (external respiration), ventilatory failure is a component of respiratory failure. Acute respiratory failure (ARF) can be conceptualized as resulting from either lung or pump failure (Fig. 72-6) .

Figure 72-6 Schematic representation of the pathogenesis of acute respiratory failure (ARF). The ventilatory pump is composed of the chest cage, the ventilatory muscles, and the nervous system elements involved in respiration. The pump primarily affects carbon dioxide excretion (CO_2). The lung involves the elements that allow inspired gas to exchange with pulmonary blood flow and primarily affects blood oxygenation (O_2). The large arrow from lung to pump represents the finding that lung disease often increases the work of the pump.

TABLE 72-6 -- Definitions

TERM	DEFINITION
Positive-airway pressure therapy	Positive pressure applied to the airway during any phase of the breathing cycle for the purposes of supporting or improving respiratory function
Positive-pressure ventilation (PPV)	Positive pressure applied to the airway for the purpose of providing or augmenting inspiratory tidal volume
Full ventilatory support (FVS)	Provision of PPV in a manner ensuring that the patient is *not obligated* to contribute to the work of breathing required for maintenance of CO_2 homeostasis
Partial ventilatory support (PVS)	Provision of PPV in a manner that *obligates* the patient to provide some of the work of breathing required for maintenance of CO_2 homeostasis
Ventilator mode	A combination of mechanisms that governs the ventilator's function and determines the potential interactions between patient and ventilator
Inverse-ratio ventilation (IRV)	PPV intended to result in an inspiratory time equal to or greater than the expiratory time
Volume-preset modes [a]	
Control-mode ventilation (CMV)	A volume-preset mode in which the patient is not allowed to participate in any phase of breathing cycle (time initiated, volume limited, volume/time cycled)
Assist-mode ventilation (AMV)	A volume-preset mode in which the ventilator frequency is determined by the patient's inspiratory efforts (pressure initiated, volume limited, volume/time cycled)
Assist/control mode ventilation (A/CMV)	Assist mode in which the ventilator frequency is determined by the patient's inspiratory efforts only when the patient's respiratory rate exceeds a preset control-mode rate (pressure or time initiated, volume limited, volume/time cycled)
Intermittent mandatory ventilation (IMV)	A ventilator system that allows spontaneous breathing via a continuous-flow device. Machine breaths are delivered at preset time intervals (time initiated, volume limited, volume/time cycled + spontaneous breathing)
Synchronized IMV (SIMV)	A ventilator system that allows spontaneous breathing via a demand-flow device. Machine breaths are delivered in synchrony with a spontaneous inspiratory effort occurring within a preset time interval (time/pressure initiated, volume limited, volume/time cycled)
Volume variable modes [b]	
Pressure-support ventilation (PSV)	A volume-variable mode in which the ventilator frequency is determined by the patient's inspiratory efforts; a preset system pressure is rapidly achieved and is maintained throughout inspiration by adjustment of machine inspiratory flow, and inspiration ends when the inspiratory flow falls below a preset minimal value (pressure initiated, pressure limited, flow cycled)

Pressure-control ventilation (PCV)	A volume-variable mode in which inspiration is time initiated; a preset system pressure is rapidly achieved and is maintained throughout inspiration by adjustment of machine inspiratory flow; and inspiration ends at a predetermined time (time initiated, pressure limited, time cycled)
Airway pressure-release ventilation (APRV)	A volume-variable mode in which inspiration is time initiated; a preset system pressure is maintained throughout inspiration by a continuous flow (threshold-resistor device), and inspiration ends at a predetermined time (time initiated, pressure limited, time cycled + spontaneous breathing)
Positive end-expiratory pressure (PEEP) [c]	
Continuous positive-pressure ventilation (CPPV)	PEEP in conjunction with positive pressure breaths (CMV + PEEP, A/CMV + PEEP)
Continuous positive airway pressure (CPAP)	PEEP in conjunction with a spontaneous breath through an apparatus designed to maintain airway pressure fluctuations above and below the baseline to no greater extent than would be present with normal spontaneous breathing
Expiratory positive airway pressure (EPAP)	PEEP in conjunction with a spontaneous breath through an apparatus designed to allow inspiratory flow only when inspiratory airway pressures descend below atmospheric

[a] Positive-pressure modes that deliver a specified tidal volume unless predetermined safety limits are exceeded--volume-limited modes
[b] Positive-pressure modes that deliver varying tidal volumes determined both by preset ventilator limits and patient factors--pressure, flow, or time limited
[c] Maintenance of a positive airway pressure at the end of exhalation

Ventilation is the movement of gas in and out of the pulmonary system. The pulmonary system is a to-and-fro valveless pump consisting of the chest cage, ventilatory muscles, and those nervous system components that regulate and influence muscular performance. Failure of the ventilatory pump occurs secondary to (1) fatigue of the ventilatory muscles (primarily the diaphragm); (2) abnormalities or major infringement on chest wall movement (e.g., flail chest, kyphoscoliosis, peritonitis, hemothorax, or after thoracoabdominal operations); (3) myoneural junction abnormality (e.g., myasthenia gravis, pharmacologic blockade); (4) motor nerve deficits (e.g., spinal cord trauma, poliomyelitis, polyneuritic diseases [Guillain-Barre syndrome], amyotrophic lateral sclerosis); and (5) central nervous system (CNS) depression or dysfunction. Acute or impending ventilatory failure is a consequence of a compromised ventilatory pump. The most common clinical manifestation of impending ventilatory failure is respiratory distress due to ventilatory muscle fatigue.

Ventilatory Muscle Fatigue

The energy required for muscle contraction is largely determined by the combination of workload and system efficiency; ventilatory workload is determined by minute ventilation, airway resistance, and lung compliance; and system efficiency is determined by such factors as stability of the chest wall, freedom of movement of the chest wall and abdomen, intrathoracic gas volume, nutritional status, and energy storage within the muscles. For any required degree of muscular work, onset of fatigue is best conceptualized as a situation in which energy demand exceeds energy supply.

Figure 72-7 (A) The work of breathing in relation to the minute volume. Solid line, normal; dashed line, lung disease. (B) The work of breathing in relation to vital capacity. Point "a" represents a tidal volume of 500 mL with a vital capacity to 5 L; point "b" represents a tidal volume of 500 mL with a vital capacity of 1 L.

Increased energy demand is a common reason for ventilatory muscle fatigue. The efficiency of ventilatory muscle activity is the primary determinant of energy demands. In healthy persons at rest, oxygen utilization of the ventilatory muscles (O_{2ven}) accounts for 2 to 5 percent of the total body oxygen consumption (O_{2tot}). Even in this optimal physiologic condition, the efficiency with which energy is transformed into mechanical work is astoundingly poor. [39] As minute ventilation increases, O_{2ven} increases at a faster rate than the increase in O_{2tot}, [40] resulting in the relationship depicted in the solid line in Figure 72-7 A.

In patients with cardiorespiratory disease (see Fig. 72-7, dashed line), resting O_{2ven} is 20 to 25 percent of O_{2tot}. [41] This increased resting O_{2ven} is only partly due to recruitment of postural and synergistic accessory muscles that do not directly contribute to ventilation. Because minute ventilation is increased in patients with cardiopulmonary disease, the O_{2ven}/O_{2tot} ratio has been reported to increase at an exponential rate. [42] It is reasonable to conclude that as ventilation increases, an ever greater proportion of the additional oxygen uptake is diverted to the ventilatory muscles. If this is at the expense of oxygen available for nonventilatory work, further increases in ventilation may be detrimental to vital tissue oxygenation.

In severe cardiopulmonary disease states, the ventilatory pump may become so inefficient that any oxygen potentially gained from increased ventilation is completely consumed by the increased work of the ventilatory muscles. This situation may progress to the point at which the work of breathing is so costly that an increase in ventilation results in a net oxygen loss to the patient.

Decreased oxygen supply is another common reason for ventilatory muscle fatigue. Energy substrates such as glucose are stored within skeletal muscle, so that during limited periods when demand increases over supply (e.g., during exercise), the muscles consume stored energy substrates to avoid fatigue. However, skeletal muscles have no significant ability to store oxygen, so that decreases in oxygen delivery may result in anaerobic metabolism that adversely affects the biochemical reactions involved in muscle contraction.

In the absence of hypoxemia, the oxygen supply available to ventilatory muscles is essentially related to blood flow, which is capable of increasing in proportion to O_{2ven} over a wide range of minute ventilation. [43] [44] Although it has been suggested that the diaphragm may differ to some degree, [45] most investigators agree that the respiratory rate and inspiratory/expiratory (I:E) ratio have potential implications for ventilatory muscle perfusion, because anything that significantly shortens expiratory time potentially diminishes blood flow to the muscles. In either case, a normal cardiopulmonary system is capable of increasing both cardiac output and ventilatory muscle blood flow to allow 3- to 4-fold increases in minute ventilation without fatigue.

When blood flow is limited, increased ventilatory demands may result in anaerobic metabolism of the ventilatory muscles, creating a lactic acidosis. [46] Under these circumstances, a significant portion (25-30%) of the limited cardiac output perfuses the ventilatory muscles, resulting in even lesser flow to other skeletal muscles and vital organs, which may result in a further increase in blood lactate. [47] When diminished arterial oxygen availability exists (e.g., hypoxemia or anemia), as much as 30 to 40 percent of the cardiac output may perfuse the diaphragm at the expense of brain, kidney, and other essential organs. [48] [49] The increase in O_{2tot} is almost entirely due to increased O_{2ven}. If possible, the cardiovascular system increases cardiac output above normal to satisfy total body oxygen requirements.

The clinical relevance of this physiology is that PPV ablates or diminishes detrimental work of breathing. In hyperdynamic states, application of ventilatory support significantly reduces O_{2ven}, and thereby O_{2tot}, resulting in a diminishing cardiac output toward normal and often an improvement in the arterial oxygenation status. It is suggested that such beneficial physiologic responses to PPV are due to decreased ventilatory muscle oxygen demands. [50] Allowing the patient to breathe to whatever extent the ventilatory

muscles can efficiently function, while providing the remainder of the work of breathing with a ventilator, is the best means of eliminating the detrimental work of breathing while optimizing hemodynamic function. [51]

Lung Failure Versus Pump Failure

Lung failure results from pathologic processes that cause inadequate exchange between alveolar gas and pulmonary blood, usually manifested clinically as an arterial oxygenation deficit. Increased work of breathing invariably accompanies lung failure secondary to one or a combination of (1) hypoxemia resulting in increased ventilatory drive, (2) increased airway resistance, (3) decreased lung compliance, or (4) increased physiologic dead space. Pump failure occurs when the work of breathing exceeds reserve capability, usually manifest clinically as respiratory distress and/or hypercapnia. As illustrated in Figure 72-6 , a reasonable generalization is that lung disease primarily results in oxygenation deficits and secondarily may cause inadequate CO_2 elimination; ventilatory pump failure primarily threatens CO_2 excretion and secondarily oxygenation.

Oxygenation

Hypoventilation creates arterial hypoxemia during breathing of room air. Such hypoxemia is reversed when adequate ventilation is restored spontaneously or with a ventilator. Hypoxemia coincident with adequate alveolar ventilation (hypoxemic respiratory failure) is seldom improved by the institution of PPV, except when decreasing O_{2ven} will significantly diminish O_{2tot} , as with impending ventilatory failure.

Most primary arterial oxygenation deficits are best supported by means of oxygen therapy, cardiovascular therapy, bronchial hygiene therapy, PEEP therapy, or combinations of these techniques. Although any or all of these therapies may be administered in conjunction with the ventilator, none of them requires the use of a ventilator. PPV must be considered a tool for directly relieving or diminishing the work of breathing, while indirectly having the potential to improve oxygenation in some clinical circumstances.

Increased Physiologic Dead Space

Minute ventilation is the sum of alveolar ventilation (V_A) and dead-space ventilation (V_D). The adequacy of V_A is clinically reflected by measurement of the Pa_{CO_2} . Normally, ventilation/perfusion relationships (V/Q) are largely determined by pulmonary blood flow preferring gravitydependent lung and spontaneous inspiration favoring similar distribution of ventilation. PPV tends to result in non- gravity-dependent gas distribution in part because of a lack of decreased pleural pressures during inspiration. Additionally, non-gravity-dependent lung normally has less airway resistance and higher compliance than that of gravity-dependent lung, which also favors gas distribution to areas with less perfusion. The resultant increase in V/Q with PPV is generally referred to as an increase in V_D (ventilation in excess of perfusion). This is the major reason why a greater minute ventilation is usually required to maintain a normal Pa_{CO_2} with a ventilator than with spontaneous ventilation.

Decreased Cardiac Output

Diminishment of cardiac output due to embarrassment of venous return to the right heart was the first documented disadvantage of PPV. [52] Appropriate vascular space expansion with intravenous fluid administration restores the cardiac output to pre-PPV levels. Too often, hypotension following the establishment of an airway and PPV is assumed to be due to such factors as (1) stress of intubation, (2) delay in accomplishing successful intubation, (3) use of pharmacologic agents to facilitate intubation, and (4) inappropriate support of ventilation. Although any of these factors is possible, hypotension often occurs in their absence.

Increased sympathetic activity is common in patients requiring initiation of ventilatory support because of factors such as hypoxemia, hypercapnia, acidemia, and increased work of breathing. This sympathetic activity causes contraction of the venous space (venoconstriction) and myocardial stimulation. Initiation of ventilator support usually relieves the work of breathing and reverses hypercapnia, acidemia, and hypoxemia, thereby decreasing sympathetic activity. Most often, the hypotension seen with initiation of PPV is secondary to a decrease in sympathetic tone, creating a relative hypovolemia with resultant decreases in venous return to the right heart. When hypotension is severe, the patient should immediately have both lower extremities elevated 20 to 30 degrees from the horizontal position. The transient increase in "core" blood volume should improve venous return to the right heart. The eventual correction of the relative hypovolemia is accomplished by appropriate intravenous fluid administration. The patient must not be allowed to "fight" the positive-pressure breath to avoid unduly increasing intrathoracic pressures.

Spontaneous Breathing

In the process of initiating PPV, the first priority is to establish the airway and manually to support ventilation, to take over ventilation gradually and to vary the breathing pattern in conjunction with patient efforts. This technique should allow a smooth transition to the ventilator. It is not uncommon for patients to demonstrate cardiovascular instability during this process. Often, delays in establishing the airway, stress of intubation, sedative drugs, and inappropriate support are condemned for this occurrence. However, such instability often occurs in the absence of any of the previously mentioned factors, as a result of the following: (1) the relief of respiratory distress, causing a decrease in circulating catecholamine, with subsequent vasodilatation and decreased cardiac output; (2) decreased venous return related to the positive airway pressure; or (3) a combination thereof.

Principles of anesthesia care apply outside the operating room and must be followed. Vascular access and appropriate monitors must be established as soon as possible. Appropriate analgesia and sedation are necessary to achieve a comfortable and stable patient on a ventilator.

Modes of Positive-Pressure Ventilation

The functions of a positive-pressure ventilator must involve four physical factors: volume, flow, pressure, and time. As shown in Figure 72-8 , three mechanical factors regulate the inspiratory phase, and each must be governed by a physical factor: (1) a mechanism to begin the inspiratory cycle (initiation) must be governed by a physical factor; (2) a generator provides the driving force, and the power of the generator must be governed by a physical factor (limit); and (3) a mechanism for ending inspiration (cycle off) must be governed by a physical factor. Positive-pressure ventilators are traditionally classified by the physical factor that ends the inspiratory cycle.

Volume-Preset Modes

Volume-preset modes are either time initiated (controllers) or pressure initiated (assisters). Volume-preset modes possess several advantages: (1) the volume of gas delivered to the patient is reliably controlled; (2) volume delivery remains constant despite pathophysiologic changes in the patient's condition; (3) reliable monitoring devices are readily adaptable; (4) variations in airway pressure waveforms are readily accomplished; and (5) a consistent oxygen atmosphere can be easily maintained.

Figure 72-9 illustrates the airway pressure curves for the four common volume-preset modes. Control mode delivers positive-pressure breaths to the patient at predetermined time intervals. In the conscious patient, lack of available gas for spontaneous breathing between ventilator cycles may create a sensation of breathlessness and may result in "fighting

Figure 72-8 Airway pressure curves illustrating the three mechanical functions: IN, initiation of the cycle; LIM, a preset limit imposed on the positive-pressure cycle; CYC, ending the cycle. Each mechanical function is preset to be governed by one of three physical factors: volume, pressure, or flow time. (A) Time-initiated, volume-limited, volume-cycled mode. (B) Pressure-initiated (intended to be a sub-baseline pressure secondary to the patient's effort to initiate a breath), volume-limited, volume-cycled mode. (C) Time-initiated, volume-limited, time-cycled mode that extends inspiration

beyond the time the volume is delivered.

Figure 72-9 Airway pressure tracings of the four standard volumepreset modes. Thick solid lines represent ventilator breaths and thick dotted lines represent spontaneous breaths. The thin dotted lines refer to what the spontaneous pattern would have been without the ventilator breaths. IMV, intermittent mandatory ventilation; SIMV, synchronized IMV.

the ventilator." The control mode is seldom used outside the operating room. Assist/control mode initiates a positive-pressure cycle when the ventilator senses a circuit pressure lower than baseline. Because there is no source for fresh gas flow between cycles, circuit pressure must decrease when the patient initiates a spontaneous breath. A minimal back-up rate is set below which the ventilator will initiate breaths at an assigned time interval independent of patient effort. Assist/control mode eliminates the sensation of breathlessness often observed with control mode and usually diminishes requirements for sedation and paralysis. Although respiratory alkalemia may complicate assist/control mode in some patients, generally assist/control greatly improves clinical care when compared with the control mode. It has been shown that the energy expenditure required to initiate the ventilator cycle with assist/control continues throughout the entire inspiratory cycle. [53] [54] This energy expenditure may be significant in patients with extremely limited cardiopulmonary reserves.

Intermittent mandatory ventilation (IMV) is essentially a control mode in conjunction with circuitry that provides a fresh gas flow for spontaneous breaths. The positive-pressure cycle is completely independent of the patient's spontaneous ventilatory pattern. An adequate fresh gas source at least four times the patient's spontaneous minute volume is required to minimize the work of breathing imposed by the ventilator circuit. An appropriately functioning continuous-flow system providing the inspired gas for spontaneous breathing should cause inspiratory airway pressures to drop no more than 2 to 3 cm H_2O below baseline. [55] [56]

Synchronized IMV (SIMV) is essentially an assist/control mode in conjunction with a demand-valve system that provides a fresh gas flow for spontaneous breaths. Originally described as intermittent demand ventilation, [57] SIMV allows spontaneous breathing with positive-pressure cycles triggered by the patient's inspiratory effort at predetermined intervals. The patient will be mechanically ventilated at a

Figure 72-10 Schematic representation of a demand-flow system. DV, demand valve device; EXV, exhalation valve; Initial Spon Inspiration, gas flow at the moment the demand-valve mechanism opens; OWV, one-way valve to minimize tubing that must be decompressed to create sub-baseline pressure; PPV, gas flow during positive-pressure ventilation; PSD, pressure-sensing device that cycles ventilator and demand-valve mechanism; Spon Inspiration, gas flow after the flow has reached the patient; VOWV, ventilator one-way valve.

preset rate if insufficient spontaneous efforts are absent within a prescribed period. The resultant airway pressure pattern synchronizes spontaneous and mechanical breaths (see Fig. 72-9) .

Figure 72-10 schematically illustrates a ventilator demand-flow system. A pressure-sensing device is located near the patient's airway and detects a fall in baseline pressure, activating either the positive-pressure cycle or the demand-flow device. The major disadvantage of demand-flow systems is the delay in providing adequate inspiratory gas flow to the airway, especially when reasonably large V_T or rapid inspiratory flow rates are required. These factors result in an imposed work of breathing significantly greater than that associated with continuous-flow systems. [58] When spontaneous breathing is providing most of the required minute ventilation, the imposed work of breathing coincident with demand-flow systems may be detrimental in patients with significantly limited ventilatory reserves. [59]

Volume-Variable Modes

Pressure-limited ventilators were widely used during the 1940s and 1950s because they confined the pressure applied to the airway. They were clinically unacceptable for ventilator support because they did not provide consistent V_T, and

TABLE 72-7 -- Modes of Mechanical Ventilation and the Factors Controlling the Ventilatory Cycle

VENTILATOR MODE	INITIATED	LIMITED	CYCLED
Control-mode	Time	Volume	Volume/time
Assist/control-mode	Pressure	Volume	Volume/time
Intermittent mandatory	Time	Volume	Volume/time
Synchronized intermittent mandatory	Pressure	Volume	Volume/time
Pressure-support	Pressure	Pressure	Flow
Pressure-control	Time	Pressure	Time
Airway pressure-release	Time	Pressure	Time

monitors to ensure consistent ventilation were not available. Such technologic limitations led to the preference for volume-preset ventilators in acute respiratory care. The availability of microprocessor technology in the 1980s allowed development of pressure-preset (volume-variable) modes with finite inspiratory flow variability, finite control of the preset airway pressure, and extensive monitor and alarm systems. This technologic advance has led to a general acceptance of volume variable modes.

Pressure-preset modes are initiated by time or pressure. Table 72-7 compares currently available volume-preset modes with the standard volume-variable modes. Figure 72-11 schematically illustrates the mechanics of the pressure-support mode. A sub-baseline pressure near the proximal airway activates the demand-flow system. A rapid flow enters the circuitry and continues until a predetermined pressure is achieved. Constant microprocessor analysis of the delivered flow and circuit pressure determines the required variation of flow necessary to maintain the predetermined circuit pressure. Assuming that no leaks are present in the system, the flow entering the circuitry to maintain the preset pressure should be the same as that entering the patient's pulmonary system. When the delivered flow reaches some predetermined minimum set by the manufacturer, flow stops entering the system, and the exhalation valve is opened.

Pressure support was initially developed to surmount the imposed work of breathing associated with demand-flow systems. [60] Three to 8 cm H_2O pressure support has been shown comparable to a continuous-flow system in reference to imposed work of breathing during spontaneous ventilation. [61] Using the continuous positive-airway pressure (CPAP) mode of a demand-flow ventilator imposes work of breathing. Provision of 3 to 5 cm H_2O pressure support allows the CPAP mode to impose no more work of breathing than a continuous-flow CPAP system. [62]

The routine use of 3 to 5 cm H_2O pressure support with SIMV should be considered no different from IMV with a properly functioning continuous-flow system. [63] Combining SIMV with pressure support higher than 10 cm H_2O constitutes the simultaneous application of two ventilating modes. Pressure support greater than 10 cm H_2O should be considered an independent mode for positive-pressure support. Most patients demonstrate an increase in V_T when the pressure-support level

exceeds 10 cm H_2O, and most demonstrate a decrease in respiratory rate by 20 cm H_2O. [64] Despite claims of shorter ventilator time and faster weaning, [65] there are no prospective studies comparing pressure-support

Figure 72-11 Schematic illustration of pressure-support mechanics. IN, initiation; LIM, limit; CYC, cycle; EX, exhalation.

Figure 72-12 Airway pressure tracings of (A) pressure support and (B) pressure control. IN, initiation; LIM, limit; CYC, cycle.

systems with other modes. Observations of lower peak airway pressure, higher mean airway pressure, and subjective comfort during pressure support as compared with SIMV appear valid. [66]

The pressure-control mode is schematically illustrated in Figure 72-12 . The inspiratory gas flow is determined in the same manner as pressure support, but the pressure-control mode is initiated by time and is cycled off by time. The number of ventilatory cycles per minute is preset and determines the time intervals at which a new inspiratory cycle will begin. The positive pressure is cycled off when a predetermined time has elapsed from the start of inspiration. Therefore, the mode allows for any desired inspiratory/expiratory ratio.

The pressure-release mode (Fig. 72-13) consists of a continuous-flow system with a release valve situated in the expiratory limb that determines which of two paths will be open to the gas flow. The release valve is driven by a timing device that allows adjustment of the extent, length, and frequency of pressure release. Closing of the release valve by a timing mechanism initiates the inspiratory phase. During this phase (Fig. 72-13 A), the continuous gas flow exits through a threshold resistor with a preset pressure greater than that during expiration. Opening of the release valve by a timing mechanism cycles the mechanism from inspiration to expiration. This process allows the continuous gas flow to exit through a threshold resistor with a lower preset pressure (Fig. 72-13 B). Thus, airway pressure falls rapidly, and gas exits the lungs. The lung volume at end-inspiration is primarily determined by the preset pressure and the pulmonary compliance. The end-exhalation lung volume is determined by lung compliance, airway resistance, release time, and the gradient between the inspiratory and expiratory preset pressures. Unlike pressure-control mode, the pressure-release mode allows spontaneous breathing without imposed work of breathing.

High-Frequency Ventilation

High-frequency ventilation (HFV) provides V_T less than the anatomic dead space at rates significantly more rapid than normal. Frequencies are stated as cycles per minute or cycles per second (Hz). For purposes of simplicity and clarity, only the three major techniques with the greatest potential for clinical applicability are discussed. More complete discussions are available. [67] [68]

High-frequency positive-pressure ventilation refers to the delivery of small V_T through an insufflation catheter or endotracheal tube with circuitry having a minimal internal compressible volume. The characteristic rate is 60 to 100 per minute, with inspiration taking 20 to 30 percent of the cycle. [69] High-frequency oscillation delivers gas to a reciprocating pump that actively transports the gas both into and out of the lungs. Oscillators are distinct from other high-frequency

Figure 72-13 Schematic representation of airway pressure-release ventilation. (A) Inflation pressure generated by a continuous-flow system with a threshold resistor set at +30 cm H_2O. Flow into the lungs is determined by the inflation pressure and the forces impeding flow (resistance and compliance). The inspiratory lung volume is determined by the inflation pressure and the pulmonary compliance. (B) Release valve positioned to allow flow through the threshold resistor set at +10 cm H_2O. The resultant release pressure in the circuit allows exhalation.

devices because active expiration is an intrinsic part of their design, and oscillators are much less likely to result in hyperinflation because the device actively pulls gas out of the system during the expiratory phase. [70] Commonly used frequencies of 10 to 15 Hz have evolved empirically. High-frequency jet ventilation is the technique most widely used in North America. The technique refers to the delivery of a pulse of gas from a high-pressure source (5-50 psi) through a small-bore cannula with an interposed cycling mechanism allowing high frequencies. Gas entrainment can occur around the jet and may contribute significantly to inspiratory flow. The optimal catheter gauge and positioning within the endotracheal tube have not been established. [71] Inadequate humidification of delivered gas remains a major problem during high-frequency jet ventilation, resulting in tracheal mucosal damage and thickened secretions blocking the airways. Attempts at humidification have included nebulization of a saline infusion by the jet stream, entrainment of humidified gases, and humidification of the jet gases. [68]

Despite numerous anecdotal reports of clinical utility, there is little evidence that HFV has distinct advantages over more traditional approaches. The least controversial indication for use of HFV is with massive air leaks through fistulous tracts. [72] [73] [74] Because the fistula effectively represents a region of high compliance, much of the V_T is lost through the fistulous tract during conventional ventilation. At higher frequencies, the distribution of ventilation depends more on resistance, whereas compliance becomes relatively unimportant. [68] [75] Patients with a massive air leak from a fistulous tract can be ventilated and oxygenated with HFV when conventional techniques have failed. [72] [73] Although randomized prospective studies comparing conventional ventilation with HFV in the management of patients with airway rupture are lacking, crossover animal studies support these clinical observations. [74]

Any purported advantages of HFV must be considered in relation to the potential hazards of massive barotrauma, injection injury, and alveolar overdistention. Injection injury occurs when a high-pressure jet of gas is directed against the tracheal mucosa and results in submucosal dissection and even perforation of the wall. Tension pneumothorax occurs more readily with HFV than with conventional ventilation, owing to the "stacking" of breaths that so rapidly occurs if insufficient time or space for gas escape is allowed.

Positive End-Expiratory Pressure Devices

The safety and efficacy of adult CPAP/PEEP therapy are greatly dependent on the appropriate technical application of threshold devices to avoid increased expiratory airway pressures, increased work of breathing, diminished cardiac output, and an increased incidence of barotrauma. An ideal threshold resistor exerts a constant force that will not impede flow in any way until the system pressure is less than the pressure at which the constant force will completely stop flow. When placed in the exhalation limb of an adult breathing circuit, a threshold resistor stops exhalation at a preset pressure higher than ambient pressure. There are no commercially available threshold resistors that are totally free of flow-resistive properties that increase pressure when flow is high. Additionally, if the cross-sectional area available for gas to exit the device is smaller than the cross-sectional area of the expiratory circuit, or if gas is routed through a convoluted path, flow resistance is created.

Gravity-dependent threshold-resistor devices demonstrate the lowest degree of flow-resistor characteristics, but they require an upright and stable position that severely limits portability and safety. The water-column threshold resistor, very popular before the microprocessor-driven ventilators were introduced, is now only of historical importance. The weighted-ball valve device creates a threshold resistance by the weight of a precision-ground ball atop a calibrated orifice; the heavier the ball, the greater the expiratory pressure. These devices are so gravity dependent that even a 10-degree tilt from vertical may cause changes in end-expiratory pressure level.

Non-gravity-dependent devices are the most popular type of threshold resistors. Spring-loaded valves are available in which expiratory pressure is maintained by the

compression of a spring below its no-load length. The flow-resistance properties of these valves depend on the surface area available at the point of seating of the valve diaphragm. Balloon-type devices (Fig. 72-14) establish PEEP by maintaining a force in the balloon that must be exceeded in order for exhalation to occur.

Continuous Positive Airway Pressure Systems

The application of positive airway pressure at end-exhalation, in conjunction with PPV, is referred to PEEP therapy. [76] When used in conjunction with spontaneous ventilation, the designation CPAP is applied. [1] [77] A CPAP system must provide inspiratory gas flow sufficient to meet the patient's spontaneous inspiratory flow demands. As discussed earlier, the inspiratory gas flow can be provided by either a continuous-flow or a demand-flow system (see Fig. 72-10) . The considerable manufacturing advantages of a demand-flow system are offset by the clinical problem of the imposed work of breathing. [58] [59] As schematically illustrated in Figure 72-15 , changes in pressure during spontaneous ventilation are reflections of the work of breathing. Normal work of breathing causes fluctuations of approximately 2 cm H_2O from baseline (Fig. 72-15 A). Fluctuations of greater magnitude during inspiration (Fig. 72-15 B) may be corrected by increasing system flow in a demand-flow system or increasing the size of the circuit reservoir in a continuous-flow system. Changes in baseline pressure during exhalation (Fig. 72-15 C) are primarily affected by the flow-resistance properties of the threshold resistor employed to produce the end-expiratory pressure.

Physiology Associated With Continuous Positive Airway Pressure/Positive End-Expiratory Pressure

PEEP exists whenever the airway pressure is greater than ambient pressure prior to the next inspiratory cycle. The

Figure 72-14 Schematic representation of a balloon-type exhalation valve, with balloon connected to ventilator pressure line. (A) Pressure (+10 cm H_2O) is applied to the balloon during exhalation. When the exhalation line (EL) pressure exceeds +10 cm H_2O, the balloon will be displaced and gas will flow to the outlet port (OP). There is a potential restriction to flow resulting from the partially expanded balloon. This may be a clinically significant factor at relatively greater flow rates. (B) When the exhalation line pressure is equal to or less than +10 cm H_2O, the balloon will occlude the exhalation line and will stop flow.

acronym PEEP generally refers to positive end-expiratory pressure in conjunction with a positive-pressure inspiration; the acronym CPAP usually refers to PEEP in conjunction with a spontaneous inspiration. To avoid controversy and confusion, we use the acronym CPAP/PEEP in reference to the end-expiratory phenomena independent of the inspiratory dynamics.

Pulmonary Effects

Two universal pulmonary effects of CPAP/PEEP are redistribution of extravascular water and increased functional residual capacity (FRC). Several other mechanisms have been proposed to explain the beneficial pulmonary effects of

Figure 72-15 (A-C) Continuous positive-airway pressure (CPAP) airway pressure curves.

CPAP/PEEP, but these appear to be important only when specific pulmonary disease is present. For example, CPAP/PEEP has been shown to have a favorable effect on the relationship between the closing volume (lung volume at which dependent small-airway closure occurs) and FRC, thereby decreasing the degree of low V/Q that occurs in anesthetized human patients with severe COPD and morbid obesity. [78] The extent to which this phenomenon is clinically significant in nonanesthetized human patients with acute restrictive lung disease is, at best, marginal.

Redistribution of extravascular lung water is a major mechanism by which CPAP/PEEP improves lung function. It has been established that CPAP/PEEP therapy does not decrease total lung water [79] [80] ; on the contrary, it appears that CPAP/PEEP directly increases the accumulation of extravascular lung water. [81] [82] However, the application of CPAP/PEEP to patients with either cardiogenic or noncardiogenic pulmonary edema improves oxygenation and pulmonary mechanics largely because of the effects on the distribution of lung water. As shown in Figure 72-16 , the application of CPAP/PEEP to the edematous lung decreases intra-alveolar fluid volume and facilitates the movement of water from the less compliant interstitial spaces (between the alveolar epithelium and pulmonary capillary endothelium) where gas exchange occurs to the more compliant interstitial spaces (peribronchial and hilar regions). [83] [84] [85] This

Figure 72-16 (A and B) Redistribution of extravascular lung water with positive end-expiratory pressure.

Figure 72-17 (A-C) Increasing alveolar volumes with +10 and +20 cm H_2O positive end-expiratory pressure. Black arrows represent elastic forces; white arrows represent distending forces.

redistribution of interstitial water improves oxygenation, lung compliance and V/Q matching.

CPAP/PEEP results in an increased FRC by two distinct mechanisms: (1) 10 cm H_2O or less is primarily responsible for increasing the volume of patent alveoli, and (2) 10 cm H_2O or more is generally responsible for alveolar recruitment. [86]

As schematically illustrated in Figure 72-17 , incidence light photomicrography studies on normal lung demonstrate that (1) alveolar diameters increase linearly with 0 to 10 cm H_2O CPAP/PEEP; (2) end-expiratory diameters increase to a greater degree than end-inspiratory diameters; (3) at levels higher than 10 cm H_2O CPAP/PEEP, increases in alveolar diameters progressively diminish and reach a plateau at approximately 15 cm H_2O; and (4) at levels higher than 15 cm H_2O CPAP/PEEP, alveolar pressure increases without measurable increase in alveolar diameters. [87] These data suggest that there are upper limits to the distensibility of normal alveoli and that, within these limits, the application of CPAP/PEEP can increase FRC simply by increasing alveolar size. Increased alveolar volumes result in a greater surface-area exposure of alveolar gas and capillary blood secondary to elongation of juxta-alveolar vessels (see Fig. 72-17) . This has been proposed as the primary mechanism by which CPAP/PEEP affects gas exchange in the normal lung, a hypothesis consistent with available clinical data. [86] [88]

Alveolar recruitment is a term commonly used to refer to

Figure 72-18 Schematic representation of alveolar recruitment at +10 cm H_2O positive end-expiratory pressure. External arrows represent elastic forces; internal arrows represent distending forces.

an increase in FRC secondary to inflation of previously collapsed alveoli (Fig. 72-18) . [89] [90] Studies of the effects of CPAP/PEEP on volume-pressure curves during ARDS have demonstrated an inflection point that is thought to represent the critical pressure necessary to reopen or "recruit" closed peripheral airways and/or collapsed alveolar units. [91] [92] [93] Computed tomography (CT) scanning techniques have been applied to correlate the physiologic changes observed in volume-pressure relationships with morphologic changes noted on CT scans in ARDS patients during PEEP therapy. [94] [95] Using this technique, Figure 72-19 (Figure Not Available) B demonstrates a classic inflection point (P_{flex}) in the gas-to-tissue (g/t) ratio curve, at a critical PEEP level, which is consistent with alveolar recruitment; Figure 72-19 (Figure Not Available) C demonstrates no increase in the g/t ratio with increasing PEEP, a finding that indicates no additional lung inflation and is consistent with a consolidative process.

The response to CPAP/PEEP titration varies not only with the type of lung disease, but also in relation to gravity. [94] [95] More gravity-dependent lung regions appear to undergo greater degrees of alveolar recruitment, whereas less gravity-dependent lung regions tend to experience greater increases in alveolar volume without recruitment. It has also been radiographically confirmed that the application of PEEP to ARDS-affected lungs results in a redistribution of tidal ventilation from the less dependent (upper) regions of lung to the more dependent (lower) regions of the lung. [96] Further, the cyclic alveolar collapse and recruitment that occur with normal tidal ventilation, primarily in the middle lung fields, is reduced with the application of PEEP. [96]

Intrapulmonary shunting (Q_{SP}/Q_T) is a mathematic reflection of all lung factors affecting arterial oxygenation and is often used as a means of quantifying the lung response to CPAP/PEEP therapy in terms of arterial oxygenation. Oxygen tension indices, such as Pa_{O_2}/F_{IO_2}, are popular, but they are sometimes misleading in reflecting the status of Q_{SP}/Q_T. [97] Comprehending the importance of the intrapulmonary shunt is important because whenever perfusion exceeds ventilation to an alveolus (low V/Q), the blood leaving that alveolus has a lower oxygen content than blood leaving a well-matched alveolar capillary unit. The resultant hypoxemia is responsive to oxygen therapy, because the increased F_{IO_2} increases the Pa_{O_2}. Perfusion to a collapsed alveolus (0 V/Q) is termed a true shunt unit, and the hypoxemia it creates is not responsive to oxygen therapy because the blood does not come in contact with alveolar gas. The application of CPAP/PEEP therapy to a lung with appropriate pathologic

Figure 72-19 (Figure Not Available) Curves of gas-tissue ratios at various positive end-expiratory pressure (PEEP) levels as determined by computed tomographic scanning. (A) linear gas-tissue ratio curve indicative of alveolar expansion; (B) biphasic gas-tissue ratio curve with classic inflection point (P_{flex}) indicative of alveolar recruitment; (C) insignificant or unchanging gas-tissue ratio curve indicative of alveolar consolidation. *(From Gattinoni et al [88])*

features may result in alveolar distention of poorly ventilated alveoli and the recruitment of collapsed alveoli. As a result, the Q_{SP}/Q_T is decreased, leading to a hypoxemia that is more responsive to oxygen therapy. [98]

V_D is defined as the portion of ventilation that does not respire with pulmonary capillary blood. The application of excessive CPAP/PEEP to lungs with nonuniform pathologic features can overdistend normal alveoli, compressing surrounding capillaries and diminishing perfusion to those alveoli (increased V_D). When the appropriate level of CPAP/PEEP is applied to a relatively diffuse disease, alveolar recruitment and distention should improve V/Q without a significant increase in V_D.

Cardiovascular Effects

A diminishment in cardiac output with CPAP/PEEP therapy is attributable to at least three mechanisms: (1) decreased venous return to the right heart, (2) right ventricular dysfunction, and (3) alterations in left ventricular distensibility. Because oxygen delivery to the tissues is determined by the arterial oxygen content and the cardiac output, oxygen delivery may be compromised if reductions in cardiac output occur to a greater degree than improvement in arterial oxygen content.

The primary mechanism responsible for reduction in cardiac output appears to be decreased venous return resulting from increased intrathoracic pressure. The increase in mean airway pressure associated with CPAP/PEEP increases the pleural and pericardial pressure, decreasing the cardiac transmural pressure, which may significantly decrease the end-diastolic volume and stroke volume of both ventricles. [99] [100] This reduced stroke volume can be restored by preload augmentation. [101]

A secondary mechanism responsible for reduction in cardiac output is right ventricular dysfunction. CPAP/PEEP increases right ventricular afterload because of increased pulmonary vascular resistance. In the normal heart, this results in a diminished right ventricular end-diastolic volume (RVEDV), whereas the right ventricular ejection fraction (RVEF) remains unchanged. [102] [103] At higher levels of CPAP/PEEP, a greater increase in RVEDV results, which may reduce RVEF if myocardial contractility is less than optimal. In patients with preexisting right ventricular dysfunction, even small amounts of CPAP/PEEP have the potential to cause significant changes in RVEDV and RVEF. [104]

Alterations in left ventricular function during CPAP/ PEEP appear to be ventricular septal shifting and cardiac compression. Increases in RVEDV have been associated with a leftward shift in the intraventricular septum, [105] thereby limiting the distensibility of the left ventricle. Decreased distensibility of the left ventricle during CPAP/ PEEP is directly related to the transmission of elevated pressures to the heart from the lung. [103] [106] [107]

In patients with underlying left ventricular dysfunction and elevated filling pressures, CPAP/PEEP may improve cardiac function by improvement in coronary arterial oxygen content, by augmentation of systolic contraction, or by reduction of venous return. [108] The reduction in venous return may actually produce a salutatory effect by shifting the end-diastolic volumes to a position on the Starling curve associated with improved myocardial function.

Application of CPAP/PEEP is known to have effects on hemodynamic measurements because the intrapleural and mediastinal pressures are increased. Normally, more than one-half the elevated alveolar pressure is dissipated by the lung's elastic forces. [109] Less than one-half the elevated alveolar pressure is transmitted when the lungs are poorly compliant; conversely, extremely compliant lungs transmit a greater degree of pressure, which can lead to significant adverse hemodynamic consequences. Pulmonary venous pressure affects pulmonary capillary pressure and is therefore a major factor determining fluid flux in the lung. The pulmonary artery occlusion pressure (PAOP) is commonly used to reflect pulmonary venous pressures. Although acceptable correlation between PAOP and left atrial pressures up to 10 cm H_2O CPAP/PEEP has been demonstrated, at higher levels of CPAP/PEEP, the PAOP may bear no correlation to the actual left atrial pressure. [110] There is no advantage to removing CPAP/PEEP before measuring PAOP because that maneuver has been demonstrated to give consistently unreliable data. [111]

The reduction in aortic blood flow that occurs within one respiratory cycle after applying CPAP/PEEP [112] is related to a decrease in pulmonary flow during exhalation. The reduction in pulmonary blood flow is considerably less with spontaneous breathing (CPAP) than with positive-pressure ventilation (PEEP), and this finding explains why CPAP requires less fluid loading to maintain cardiac output and enhances the transpulmonary pressure gradient resulting from any level of end-expiratory pressure.

Physiologic Alterations due to Airway-Pressure Therapy

Undesirable physiologic alterations attributable to a therapeutic entity are not necessarily complications because they may not contribute directly to mortality or morbidity. In addition to the pulmonary and cardiovascular factors just discussed, there are physiologic alterations attributable to positive airway pressure that affect renal function and water metabolism, hepatic and gastrointestinal function, and psychologic changes.

Positive airway-pressure therapy affects renal function by reducing urine volume, glomerular filtration rate, sodium excretion, and free water clearance. [113] The direct effects on renal function appear to be due to a decrease in renal perfusion, although redistribution of intrarenal blood flow has also been suggested as a mechanism. [114] There appears to be a significant relationship between the degree of renal dysfunction and the intravascular volume, because volume replacement returns renal

function to baseline before the cardiac function returns to baseline. [115] The direct renal effects of positive airway pressure can be minimized with prior intravascular volume expansion or the administration of low-dose dopamine. [116] Positive airway-pressure therapy causes antidiuresis and antinatriuresis by increasing renal sympathetic activity and by increasing release of antidiuretic hormone and renin and angiotensin. [117] [118] Clinical observation and available data suggest that there is increased water retention with increased levels of positive airway pressure.

Gastrointestinal bleeding is common in all critically ill patients. It has been estimated that without prophylactic therapy, as many as 40 percent of patients requiring airwaypressure therapy for more than 3 days would manifest gastrointestinal bleeding; one-half of these patients would require blood transfusion. [119] Most gastrointestinal bleeding in patients receiving airway-pressure therapy is due to multiple acute ulcerations of the gastric and bowel mucosa. [120] The institution of antacid regimens that maintain the gastric fluid pH higher than 5.0 was demonstrated essentially to abolish major gastrointestinal bleeding caused by multiple acute ulcerations. [121] Histamine (H_2) blockers and other agents that reduce secretion of gastric acid appear to be equivalent to traditional antacid regimens in preventing gastrointestinal bleeding. Ileus is common in patients receiving airway-pressure therapy. Although narcotic sedation is often implicated, there is little evidence that nonnarcotic sedation regimens decrease the incidence or severity of ileus.

There may be a higher incidence of liver dysfunction in patients receiving airway-pressure therapy than other critically ill patients, a circumstance widely attributed to the decreased portal blood flow associated with airway-pressure therapy. [122] The decrease of mesenteric blood flow appears to be greater to the stomach than to the small intestine.

Critically ill patients are often conscious, apprehensive, depressed, and exposed to a significant amount of emotional stress. Dependence on mechanical breathing devices limits self-sufficiency and self-image. The concerns of dependency and the threat of machinery malfunction are a constant source of fear for the ventilator-dependent patient. If a mishap occurs, this fear is magnified dramatically. A concerted effort by the staff is necessary to enhance the limited lines of communication. Calm explanations of all interventions help to meet the intellectual and emotional needs of the patient.

CONVENTIONAL VENTILATOR MANAGEMENT

The basic principles of PPV were first developed in the operating room to facilitate anesthesia and thoracic surgery. When postanesthesia recovery rooms began to develop and evolve into intensive care units (ICU) in the 1950s, anesthesiologists' concepts of PPV, endotracheal intubation, sedation/analgesia, and neuromuscular blockade were introduced and accepted. By 1960, there was widespread acceptance that the delivery of a preset V_T was the safest and most predictable means by which to support patients with respiratory failure. [123]

Initiation of Positive-Pressure Ventilation

As all anesthesiologists know, the first priority must be to establish a patent and protected airway through which PPV can be readily administered. It is not uncommon for patients with respiratory failure to demonstrate cardiovascular instability when tracheal intubation is accomplished and PPV is applied. It is common for other physicians to attribute the cardiovascular instability to delays in establishing the airway, stress of intubation, and sedative drugs. However, such instability often occurs in the absence of any of the previously mentioned factors for the following reasons: (1) relief of respiratory distress, causing a decrease in circulating catecholamine, with subsequent vasodilatation and decreased cardiac output; (2) decreased venous return related to the positive airway pressure; or (3) a combination thereof.

Initiating ventilator management in a critically ill patient is no different from the process of induction of anesthesia. Principles of anesthesia care apply outside the operating room and must be followed. Vascular access and appropriate monitors must be established as soon as possible. Vascular volume resuscitation must be timely. Appropriate analgesia and sedation must be instituted at the earliest possible time consistent with patient safety.

Sedation and Analgesia

Increases in intercostal muscle tone, abdominal muscle tone, or abdominal pressure or contents decrease chest compliance. In conjunction with PPV, any factor that decreases chest compliance results in higher intrathoracic pressures, diminished venous return to the right heart, and

diminished V_A. When a ventilated patient actively attempts to impede flow during the inspiratory cycle, the process is referred to as fighting the ventilator. Patients often make breathing efforts during the ventilator's expiratory cycle, a phenomenon that has little detrimental effect in most patients. The most common reasons for fighting the ventilator are (1) inadequate ventilation (hypercapnia), (2) acidemia, (3) inadequate oxygenation, (4) CNS dysfunction, and (5) pain or anxiety. Assisting the patient with a hand ventilator for a short time often "settles the patient down." However, these maneuvers should not replace adequate evaluation and treatment of the underlying cause of fighting the ventilator.

Sedation and analgesia are necessary for more than human compassion. It is well known that the neurohumoral response to stress can be detrimental in critically ill patients. [124] [125] The anesthesiologist is often consulted in these matters and must appreciate how the ICU milieu differs from the operating room. It is important for anesthesiologists to remember that, unlike providing anesthesia in the operating room, they are not going to be in constant attendance. Therefore, anesthesiologists must work within the established protocols of the ICU. They must be flexible and accommodating to the medications and philosophies that are familiar to the health care personnel caring for the patient.

The Society for Critical Care Medicine (SCCM) published practice parameters for intravenous sedation and analgesia in adults in the ICU. [126] Although there are many acceptable ways to accomplish adequate analgesia and sedation, it is helpful to be familiar with these national guidelines. They recommend that morphine sulfate should be the basic analgesic agent because it is an effective analgesic, reasonable sedative, good euphoric, familiar to nursing staff, and inexpensive. Relatively large doses of morphine have little cardiovascular effect other than venodilation in the well-ventilated, well-oxygenated, acid-base-balanced patient. [127] The patient should have reasonable arterial blood gas values, and the airway should be established prior to administration of large doses of morphine. In adults with adequate vascular volume, up to 80 mg may be administered intravenously during the first hour, and up to 20 mg/h thereafter without untoward effects. Fentanyl is recommended [126] if there is concern about the patient's cardiovascular stability.

A benzodiazepine is recommended to provide anxiolysis, sedation, and amnesia: midazolam is suggested for patients in whom less than 24 hours of PPV support is anticipated; lorazepam is recommended for longer-term use. Propofol in subanesthetic doses may replace the benzodiazepine as long as it is anticipated the drug will not be used for longer than 36 hours. [126]

Neuromuscular blocking agents are often the only alternative when preventing a patient from fighting the ventilator, ablating the work of breathing, or protecting the patient from harm and allowing necessary care. Muscle relaxants are required for the low-volume techniques that are becoming widely used for patients with severely diseased lungs. Neuromuscular blockade should be a last resort rather than a first-line alternative. Sedation, analgesia, and amnesia must be provided for paralyzed ICU patients. The SCCM practice parameters [128] recommend pancuronium as the agent of choice. They recommend atracurium for patients with cardiovascular instability; however, cisatracurium [129] became available since the guidelines were published and is less expensive than atracurium while possessing all the same pharmacokinetic advantages.

Traditional Goals of Positive-Pressure Ventilation

Eucapnic ventilation was universally accepted as a basic goal of ventilator management. In a previously healthy patient, eucapnia means maintaining a Pa_{CO_2} between 30 and 50 mm Hg consistent with an arterial pH between 7.30 and 7.50. [130] A patient who chronically retained CO_2 would be considered eucapnic at the established hypercapnic baseline. The reasons for maintaining eucapnea are primarily acid-base and electrolyte considerations. Acute deviation from a baseline Pa_{CO_2} results in alkalemia or acidemia, to which the kidneys respond by retaining or excreting bicarbonate ion. Healthy kidneys can compensate for a Pa_{CO_2}-induced pH change in 24 to 36 hours. This altered acid-base status can be responsible for difficulties in weaning the patient from the ventilator.

In adults with normal or mildly diseased lungs, the clinical propriety of relatively large V_T (10-15 mL/kg), [131] [132] delivered within 1 second, [133] [134] at rates of 8 to 12 per minute, was reinforced by data showing that: (1) consistent use of large V_T maintained near-normal compliance and arterial oxygenation without intermittent larger sigh breaths [135] [136] ; (2) large V_T reduced the incidence of atelectasis when compared with smaller V_T [137] ; (3) large V_T were advantageous in compensating for the increased V_D caused by positive-pressure ventilation [138] [139] ; and (4) large V_T were better tolerated by the conscious and mildly sedated patient. [140] It is important to note that there are no data refuting the safety and efficacy of relatively large V_T (10-15 mL/kg) at relatively slow ventilator rates (8-12/min), except when severe restrictive or obstructive pulmonary disease exists.

End-inspiratory pause (inflation hold) is a ventilator maneuver in which exhalation is delayed for a specific period after the preset inspiratory volume has been delivered. The longer the time from gas delivery to end-inspiration, the greater will be the distribution of gas to areas of low V/Q because of regional airway-resistance variance. [141] Manual inflation hold has long been used by anesthetists to reexpand retracted lung at the end of an open chest procedure. This principle was first applied in respiratory care following suctioning procedures to ensure expansion of a collapsed lung. Whether the naturally occurring yawn has a similar function is still being debated; however, many investigators believe that the constant-volume hypoventilation of the sleep state leads to miliary atelectasis that is reexpanded on awakening by a "natural inflation hold," the yawn. [142] This reasoning led to applying intermittent larger V_T ("sigh breaths") with the earlier volume-preset ventilators.

Appropriate Levels of Continuous Positive Airway Pressure/Positive End-Expiratory Pressure Therapy

The level of CPAP/PEEP required is primarily determined by pulmonary pathology and secondarily by cardiac

pathology. Although a major effect of CPAP/PEEP therapy is to improve lung compliance, the most readily identifiable goal is to achieve adequate arterial oxygenation with an F_{IO_2} of 0.5 or less without impairing tissue perfusion. The degree of CPAP/PEEP therapy that provides the greatest benefit while producing the fewest nonbeneficial effects is difficult to define and complex to monitor clinically. Proper interpretation of the available information necessitates consideration of the data on which various concepts of clinical end points have been based.

Seven factors are commonly considered when monitoring CPAP/PEEP therapy:

1. Pa_{O_2}.
2. Cardiac output.
3. Arteriovenous oxygen content difference: This calculation represents the volume of oxygen extracted from 100 mL of blood and is not necessarily reflective of total body oxygen extraction per minute (V_{O_2}). Normal ($Ca\text{-}VO_2$) values are 4.5 to 6.0 mL/dL; however, acute stress has been demonstrated to result commonly in cardiac output increases in excess of increased oxygen demand, producing ($Ca\text{-}VO_2$) values of 3 to 4 mL/dL. [143]
4. Oxygen delivery (D_{O_2}): This calculation is cardiac output multiplied by the arterial oxygen content multiplied by 10. It is expressed as milliliters per minute and represents the total oxygen volume presented to the tissues per minute.
5. Intrapulmonary shunt fraction (Q_{SP}/Q_T): This calculation requires blood gas analysis of both arterial and pulmonary artery blood samples, and the F_{IO_2}.
6. V_D: This parameter can be quantified by calculation of V_D/V_T or monitored by noting changes in the difference between the arterial and the end-tidal P_{CO_2}.
7. Lung compliance (C_L).

Extrapolation of available data in both animal and human studies allows for the foregoing seven factors to be placed in the general schema depicted in Figure 72-20. The graphs represent pre-lung injury levels, post-lung injury stabilized levels, and levels after incremental applications of CPAP/PEEP therapy. It is assumed that the F_{IO_2} remains at 0.5, the pH and P_{CO_2} remain acceptable, and appropriate fluid therapy is administered.

Optimum PEEP (most commonly referred to as "best PEEP") was defined in the animal model as the level at which the Q_{SP}/Q_T is lowest without a detrimental drop in cardiac output. [144] Because cardiac output increases and $Ca\text{-}VO_2$ decreases in humans, a $Ca\text{-}VO_2$ of less than 3.5 mL/dL under most circumstances should reflect an adequate cardiac output for the oxygen demands. Optimal PEEP was defined as that which provided maximum oxygen delivery and the lowest V_D/V_T. [145] This was found to be coincident with significant improvement in lung compliance and prior to a decrease in lung compliance. Figure 72-21 illustrates that these commonly used end points were simply different ways of looking at the same circumstances.

It is reasonable to state that expansion of collapsed alveoli and avoidance of alveolar hyperoxia create an advantageous milieu for lung repair. These factors must be accomplished while maintaining adequate perfusion and adequate oxygen content. It has been suggested that, regardless of the specific factors measured to make the assessments, the clinically appropriate level of CPAP/PEEP is the least amount

Figure 72-20 Graphic depiction of seven factors used as clinical monitors to determine the required level of positive end-expiratory pressure (PEEP) therapy in humans with acute respiratory distress syndrome. Although anesthetized animal models show a decreased cardiac output (Q_T) postinjury, available data and clinical experience demonstrate that humans respond with a significantly increased cardiac output. A-V, the arterial mixed-venous oxygen content difference. The horizontal gray band represents 3 to 4 vol%. O_2 Del, oxygen delivery expressed as milliliters per minute (cardiac output × arterial oxygen content × 10). C_L, lung compliance; Q_{SP}/Q_T, physiologic intrapulmonary shunt; V_D, deadspace ventilation.

that will result in adequate perfusion and a Pa_{O_2} of 60 mm Hg or greater with adequate Hb concentration at an F_{IO_2} of less than 0.5. [86]

Barotrauma and Airway Pressure

Pulmonary barotrauma is classically defined as extra-alveolar air from lung damage secondary to changes in intrathoracic pressure. The common clinical manifestations of pulmonary barotrauma are listed in Table 72-8 (Table Not Available). [119] Tension pneumothorax refers to pleural air under greater than ambient pressure, displacing mediastinal structures and potentially decreasing venous return to the heart. In the extreme, tension pneumothorax can cause cardiovascular collapse and inability to ventilate. Pneumothorax in conjunction with PPV necessitates decompression because 60 to 90 percent of these conditions are radiologically reported to be under tension. [146] Although a needle inserted into the chest confirms the diagnosis, it may not adequately decompress the

Figure 72-21 Graphic depiction of the factors governing best positive end-expiratory pressure ("best PEEP") and "optimal PEEP." Definitions of abbreviated terms are as in Figure 72-20.

tension immediately. Tube thoracostomy is the recommended therapy for decompression and lung re-expansion.

Bronchopleural fistula is suspected when there is persistent air leak for more than 24 hours after tube thoracostomy. [147] This can be due to several conditions in addition to airway-pressure therapy, but management is greatly compromised by the continued application of positive airway pressure. Efforts to minimize airway pressure without compromising gas exchange should be attempted. HFV can be used for this purpose, but it has not been associated with improved outcome. The same is true of independent lung ventilation.

Barotrauma is associated with a significant increase in morbidity and mortality. Because high airway pressures correlate with the incidence of barotrauma, most practitioners assume a cause-and-effect relationship. The incidence of pulmonary barotrauma is unclear, with reports ranging from 0.5 percent to more than 50 percent. [148] [149] Discrepancies are attributable to differences in patient populations, retrospective

TABLE 72-8 -- Manifestations of Pulmonary Barotrauma

(Not Available)

From Vender [119]

versus prospective studies, and diagnostic methods. Most centers report a 7 to 10 percent incidence of barotrauma in ICU patients receiving positive-airway pressure therapy; the incidence is higher among patients with severe lung disease.

Peak inspiratory pressure (PIP) greater than 60 to 80 cm H_2O is associated with an increased incidence of barotrauma. [150] A prospective study evaluating the effect of high-frequency jet ventilation on the incidence of barotrauma showed no significant reduction despite low PIP and low mean airway pressure. [151] Another study comparing various modes of ventilation showed the group with the highest PIP to have the lowest incidence of barotrauma. [152] A higher incidence of barotrauma has been demonstrated with CPAP/PEEP levels greater than 15 mm Hg (18 cm H_2O), [153] [154] yet there are no data to suggest that limiting PEEP to 15 mm Hg decreases or changes the incidence of barotrauma. [155] It appears that the high-airway-pressure therapy observed to correlate with barotrauma reflects the severity of lung disease and has no direct effect on the incidence of barotrauma.

The association of barotrauma and positive airway pressure is an obvious concern. Available data overwhelmingly favor the concept that when eucapnia is maintained, the risk of barotrauma increases as the severity of lung disease increases, regardless of the ventilator technique applied. [156] [157] The observed correlation between high airway pressures and barotrauma incidence is due to the common denominator of the severity of lung disease; the nature and degree of lung disease appear to be the most significant factors in the genesis of barotrauma (Fig. 72-22) . There is no conclusive evidence that manipulating airway pressures while maintaining eucapnic ventilation diminishes the incidence of barotrauma.

Figure 72-22 The relationship between barotrauma and the severity of lung disease is direct; the relationship between barotrauma and airway pressures is indirect. MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

Full and Partial Ventilator Support

As listed in Table 72-9 , full ventilator support infers that all the work of breathing necessary to maintain eucapnia is provided by the ventilator; partial ventilator support infers that both the patient and the ventilator provide essential portions of the required work of breathing to maintain eucapnia. [158] The concept of partial ventilator support is predicated on the finding that spontaneous breathing is normally beneficial for cardiopulmonary homeostasis, whereas energy expenditure that exceeds cardiopulmonary reserves is detrimental work of breathing and should be avoided. [38]

Ventilator modes designed to provide partial support permit the patient to breathe spontaneously to whatever extent desirable without physiologic detriment, whereas the ventilator supplies the remaining work of breathing. [56] The first mode capable of providing partial support was IMV, which provided a continuous-flow system to allow spontaneous breathing between the volume-preset cycles. [159] Because of difficulties in manufacturing continuous-flow systems, SIMV was introduced. Essentially, SIMV is an assist/control volume-preset ventilator in conjunction with a demand-flow system for spontaneous breathing. The major disadvantage of demand-flow systems was a delay in providing adequate inspiratory gas flow to the patient, resulting in an imposed work of breathing that was significantly greater than that associated with continuous-flow systems. However, SIMV became almost universally utilized because demand-flow systems

TABLE 72-9 -- Definitions of the Three Levels of Ventilator Support

LEVEL	DEFINITION
Total ventilator support	Patient rendered unable to contribute work of breathing for the purpose of avoiding ventilator-induced lung injury
Full ventilator support	Patient not obligated to contribute work of breathing for the purpose of maintaining eucapnic ventilation
Partial ventilator support	Patient obligated to contribute work of breathing for the purpose of maintaining eucapnic ventilation

were preferable to continuous-flow systems from a manufacturing viewpoint.

In comparison with full ventilator support, techniques of partial ventilator support have been demonstrated to enhance cardiac output in patients with normal left ventricular function, [160] to cause less hemodynamic compromise in conjunction with CPAP/PEEP therapy, [161] and to allow for significantly greater urine output and renal blood flow. [162] However, not all patients do better with partial ventilator support. For example, patients with severe ventilatory muscle fatigue, usually those with COPD, may be treated more successfully with full ventilator support. [163] Another example is a patient with cardiogenic shock and poor left ventricular reserve, who maintains better left ventricular function and has improved peripheral perfusion when all the work of breathing is supplied by the ventilator. [164]

Guidelines for Conventional Ventilator Management

Although there are many acceptable ways to provide conventional ventilator care, it is always helpful to have a "prototype" approach that is consistent with the preponderance of available data and has been time tested in clinical practice. The following suggestions are intended to provide such a prototype and are not intended to define a standard of care or to describe the only way to accomplish good care.

Simply stated, the primary purpose for utilizing conventional ventilator management in the ICU is to provide all or a portion of the work of breathing for maintenance of adequate respiratory gas exchange. The challenge is related to how that support can be provided in a manner that minimizes physiologic insult and avoids lung injury. Conventional ventilator management encompasses all matters pertaining to the safe and effective application of positive-airway pressure therapy. Assuming due diligence is provided to essential factors such as airway management, cardiovascular support, Hb content, analgesia and sedation, we submit that the following guidelines represent a scientifically justified and clinically practical approach to ventilator management in the surgical ICU.

Most ventilator-dependent patients in the surgical ICU require oxygen supplementation and CPAP/PEEP therapy. Inspired oxygen concentrations greater than 50 percent are best avoided for more than several hours. CPAP/PEEP levels of 5 to 20 cm H_2O seldom interfere significantly with cardiovascular function when the therapy is titrated to the minimum level that accomplishes redistribution of extravascular lung water and alveolar recruitment.

1. When the primary concern is diminished arterial oxygenation, one should apply the minimum level of endexpiratory pressure that provides a Pa_{O_2} greater than or equal to 60 mm Hg at a nontoxic F_{IO_2} (0.5).
2. When the primary concern is diminished lung compliance, one should apply the minimum level of end-expiratory pressure that provides optimal V_T delivery.

Full ventilator support connotes an approach in which the patient is *not obligated* to contribute work of breathing to maintain eucapnia (see Table 72-9 ; Table 72-10) . With most patients, it is prudent to initiate full ventilator support and then to consider either partial or total support when the patient

TABLE 72-10 -- Essential Factors Differentiating the Three Levels of Ventilator Support

	FULL	PARTIAL	TOTAL
Clinical goal	Eucapnia	Eucapnia	Avoidance of volutrauma

Recommended modes	SIMV	SIMV or pressure-support	Pressure-control or pressure-release
Neuromuscular blockade	Usually not	Never	Required

SIMV, synchronized intermittent mandatory ventilation

is stabilized and the circumstances are better appreciated.

1. The use of the SIMV mode with 10 to 15 mL/kg V_T and rates of 8 to 12/min in conjunction with 5 to 20 cm H_2O CPAP/PEEP is the most predictable and versatile approach to full ventilator support. In conjunction with appropriate sedation and analgesia, spontaneous breathing efforts should be ignored unless the patient is fighting the ventilator to a degree that there is (1) interference with the distribution of ventilation, (2) cardiovascular instability, or (3) significant expenditure of energy.
2. The assist/control mode in association with appropriate levels of PEEP is usually acceptable, but ventilator rates greater than or equal to 16/min are associated with auto-PEEP and are best avoided. Further, unlike SIMV, theassist/control mode necessitates changing to another mode when partial support is required.
3. Pressure-support mode at 30 to 50 cm H_2O in conjunction with appropriate levels of CPAP is acceptable if the patient's breathing rate is less than 20/min. However, we prefer volume-preset modes for full ventilator support because they allow greater latitude for deep sedation and analgesia without undue demands on nurses, therapists, and physicians.

Partial ventilator support connotes an approach in which the patient is *obligated* to contribute some work of breathing to maintain eucapnia (see Tables 72-9 and 72-10) . This approach is appropriate for relatively stable patients who are capable of providing a significant portion of the work of breathing without physiologic detriment, and for patients requiring a prolonged weaning process. The advantages to this approach are that spontaneous breathing improves V/Q, increases venous return to the right heart, improves cardiac function, diminishes CPAP/PEEP requirements, decreases intravenous fluid and vasopressor requirements, and reduces the need for sedation requirements.

1. Partial ventilator support is easily and effectively provided for most patients with the SIMV mode. V_T of 10 to 15 mL/kg with 5 to 15 cm H_2O CPAP/PEEP at rates of 2 to 8/min are recommended unless the patient has significant permanent lung volume deficits (partial or total pneumonectomy, pulmonary fibrosis), in which case smaller V_T may be indicated.
2. SIMV should always be administered in conjunction with 3 to 5 cm H_2O pressure support to ensure that the work of breathing imposed by the demand-flow system is sufficiently compensated. SIMV rates of 2/min or less with 5 cm H_2O CPAP/PEEP and 5 cm H_2O pressure support are almost always compatible with spontaneous breathing after extubation.
3. Pressure support may be the best available mode for providing partial ventilator support in those patients in whom a difficult or prolonged weaning process is predicted. Pressure support, in conjunction with appropriate CPAP/PEEP levels, should be titrated between 10 to 30 cm H_2O to attain breathing rates less than 20/min with V_T of 8 to 12 mL/kg. Rapid breathing rates should initially be assumed to reflect the patient's inability to provide the required work of breathing rather than anxiety or inadequate sedation. As the patient improves, eucapnia and breathing rates lower than 20/min can be maintained at lower levels of pressure support (usually, 2.5-5 cm H_2O increments are best).
4. A pressure-support level of 5 cm H_2O in conjunction with 5 cm H_2O CPAP/PEEP is usually compatible with spontaneous breathing after extubation.

ACUTE LUNG INJURY

Conventional volume-preset techniques for ventilator management are undeniably appropriate for most surgical patients requiring ventilator assistance. Nonetheless, volume-preset modes have not been judged favorably for patients with severely diminished pulmonary compliance resulting from acute restrictive lung disease. New technologies and more complete knowledge of alveolar pathophysiology make it mandatory to consider approaches to ventilator management that are specifically oriented to patients with severe acute restrictive lung disease.

Pathogenesis

Critically ill patients commonly manifest a diffuse cellular malfunction of lung parenchyma secondary to primary pulmonary disease as well as severe systemic insults such as sepsis, [165] hypoperfusion, [166] and multiple trauma. [167] This pathologic process was first described as the adult respiratory distress syndrome (ARDS) [168] [169] manifesting a clinical picture of hypoxemia, decreased lung compliance, increased work of breathing, bilateral and diffuse pulmonary infiltrates on chest radiograph, and pulmonary hypertension. It is now agreed that ARDS is part of a clinical and pathologic spectrum termed acute lung injury (ALI) with noncardiogenic pulmonary edema at the least severe end of the spectrum and ARDS at the more severe end of the spectrum (Fig. 72-23) (Figure Not Available) . [170] [174] It has been suggested that the term "acute" replace "adult" in the ARDS acronym, [172] to reflect the severe manifestations of ALI more appropriately. Regardless of the acronyms used to refer to this pathophysiologic spectrum, specific therapy must be directed at underlying disease processes because there is currently no direct therapeutic

---

Figure 72-23 (Figure Not Available) Major pathophysiologic manifestations comprising the spectrum of acute lung injury (ALI) from mild to severe disease. *(From Shapiro and Peruzzi[174])*

means by which to reverse the lung parenchymal dysfunction. [172] Although there is ample evidence that appropriate application of conventional ventilator-management techniques improves survival in patients with mild to moderate ALI, [157] [175] [176] these techniques have not changed the outcome in patients with severe ARDS. [176] [179] [182]

Prevailing knowledge of ALI supports the concept of a spectrum of disease as depicted in Figure 72-23 (Figure Not Available) . [171] [172] [178] *Mild ALI,* often referred to as "noncardiogenic pulmonary edema," involves diminished lung volume and compliance secondary to vascular endothelial cell damage. The subsequent changes in endothelial permeability increase water and colloid transductance from blood to interstitium that results in accumulation of extravascular lung water. At this stage of the pathologic spectrum, there is little alveolar epithelial cell abnormality and therefore minimal accumulation of alveolar fluid. Although abnormalities in endothelial permeability occur early in the ALI process, metabolic endothelial dysfunction occurs and progresses at later stages of the lung injury process. This partially accounts for the association of multiple organ system failure seen with ALI because the pulmonary vascular endothelium is normally responsible for production and metabolism of numerous circulating substances essential for appropriate immune responses and tissue repair. [179] [182]

Moderate ALI, often referred to as "early ARDS," entails significant diminishment of lung compliance secondary to both the sloughing of type 1 alveolar epithelial cells, resulting in diminished hysteresis, and hypermitosis of type 2 cells, resulting in insufficient or abnormal production of the surfactant complex. [183] [185] Because the interstitial edema accumulates in gravity-dependent lung, the geometrically unstable alveoli in those areas more readily collapse. [95] These atelectatic alveoli are potentially recruitable with appropriate CPAP/PEEP therapy. In addition to alveolar collapse and interstitial edema, the disorder includes some accumulation of alveolar fluid and an inflammatory response. [183]

Severe ALI, often referred to as "late or severe ARDS," involves extensive atelectasis and consolidation secondary to dysfunctional type 2 epithelial cells. [183] The consolidated lung is not recruitable and results in a significantly diminished number of alveoli that can be ventilated. This disorder has been described as the "baby lung syndrome" [95] because the adult patient has no more lung tissue available for ventilation than a small baby. The severity of type 2 cell dysfunction appears to be correlated with the extent of lung consolidation and fibrotic repair. [183]

The original concept that ARDS was a homogeneous pathologic process has been refuted by CT studies demonstrating gravitational distribution of disease and heterogeneous involvement of alveoli. [94] [95] [96] The anatomic evidence of a heterogeneous distribution of pathologic features ranging from overdistention to collapsed and consolidated alveoli is supported by multiple inert gas studies showing a mixture of high, low, and normal V/Q matching. [186] The recognition of this unique pathologic heterogenicity underscores the complexities inherent with the achievement of optimal distribution of V/Q in such a diseased lung.

Oxygen-Induced Lung Injury

High concentrations of oxygen have long been known to be toxic to cells and tissues. Oxygen toxicity is believed to be in part related to the generation of oxygen-derived free radicals, which are extremely reactive and can cause severe cellular injury. [187] The toxicity is related to both the oxygen concentration and the duration of exposure. It has been demonstrated that diffuse alveolar damage results when healthy mice breathe 100 percent oxygen for several days. [187] Animal and human data demonstrate that high alveolar oxygen concentrations can aggravate and accelerate a preexisting lung injury process. [188] It is now generally agreed that inspired oxygen concentrations of less than 50 percent are reasonably safe and concentrations of more than 60 percent are potentially deleterious. [89] [157] [189]

Although it is debatable whether high inspired oxygen concentrations are toxic to patients without lung injury, the data supporting the statement that patients with ALI are oxygen sensitive and should not receive an F_{IO_2} greater than 0.6 are overwhelming. It is known that lung injury causes release of oxygen-derived free radicals at rates that exceed the ability of the lung to reduce or scavenge them, resulting in cellular destruction, increased permeability, and organ dysfunction. [190] Further, there is evidence that depletion of the pulmonary antioxidant abilities reduces survival in animals exposed to increased oxygen concentrations, [189] increasing antioxidant potential appears to prolong survival despite high oxygen concentrations, [38] [158] and antioxidant therapy can blunt these responses and may minimize tissue damage. [56] In light of such data, inspired oxygen concentrations should be minimized as much as possible in patients with ALI.

Ventilator-Induced Lung Injury (Volutrauma)

LaPlace's law dictates that when the alveolar gas volume falls below some prescribed limit (hypodistention), elastic forces become overwhelming, and alveolar collapse ensues. The same physical law states that above the critical volume, as volume increases, the elastic forces diminish. As the alveolar volume approaches the limit of distensibility (hyperdistention), the contiguous epithelial, interstitial, and endothelial structures are subject to mechanical distortions and stresses that may

induce or exacerbate lung injury. [183] [191]

Pathologic features associated with alveolar hyperdistention are referred to as ventilator-induced lung injury. As illustrated in Figure 72-24 (Figure Not Available) , hyperdistention-induced lung injury can be produced in baby pigs or rats with normal lungs when they are mechanically ventilated at tidal volumes that generate alveolar pressures greater than 40 cm H_2O. [191] [192] In young rabbits and rats, artificial restriction of the chest cage and ventilation at nonhyperdistending V_T results in alveolar pressures greater than 40 cm H_2O but does not result in hyperdistention-induced lung injury. [191] [193] Although high alveolar pressures may not always be associated with alveolar hyperdistention, tidal volumes that produce hyperdistention of alveoli are always associated with high airway pressures when delivered with positive-pressure ventilation. [191] [194]

Figure 72-24 (Figure Not Available) Illustration of animal data indicating that it is hyperdistending alveolar volumes rather than airway pressure that are responsible for ventilator-induced lung injury. A shows animals (pigs, rabbits, rats) ventilated with low airway pressures and normal or low tidal volumes. B shows animals (pigs, rabbits, rats) ventilated with high airway pressure and high tidal volumes without chest wall restriction. C shows animals (rabbits, rats) ventilated with low tidal volumes resulting in high airway pressure attributable to chest wall restriction. D shows animals (rats) ventilated with low airway pressures (negative pressure ventilation; i.e., iron lung) and high tidal volumes. *(From Peruzzi WT, Franklin ML, Shapiro BA: New concepts and therapies of adult respiratory distress syndrome. J Cardiovasc Anesth 11:771, 1997)*

In addition, hyperdistending alveolar volumes in subatmospheric conditions also produce ALI. [194]

Alveolar hyperdistention has been termed "volutrauma," [195] to emphasize that the damage is directly attributable to excessive alveolar volume rather than to excessive alveolar pressure. Preset-pressure modes ordain that alveolar gas volumes are determined by the preset airway pressure and the compliance of individual alveoli, thereby providing the technical means to apply a concept of ventilator management in which the primary goal is the avoidance of ventilator-induced lung injury.

ASSESSMENT OF AIRWAY AND ALVEOLAR PRESSURES

Because one must be concerned with alveolar volume and pressure, it is essential to interpret the available airway-pressure measurements correctly.

Physical Principles

The pressures measured at the Y-piece resulting from a positive-pressure inspiration delivered through the tracheal tube, tracheobronchial tree, and lung parenchyma are determined by inspiratory flow rate, airway resistance, and the compliance factors (lung and chest wall) that impede the flow. For any given V_T delivery, the pressure resulting from compliance factors is essentially independent of flow (static), whereas the pressure resulting from resistance factors is directly dependent on flow (dynamic). Under dynamic conditions, upstream pressures are greater than downstream

---

pressures, and this difference is augmented by increases in either resistance or flow. Under static conditions (essentially zero flow), pressures must be essentially equal throughout the pulmonary system and the ventilator circuit.

Dynamic Airway-Pressure Measurement

Airway-pressure measurements coinciding with high inspiratory gas flows, such as PIP, provide little information concerning alveolar pressures. [196] In fact, the point of greatest resistance and lowest compliance in the entire ventilator-patient circuit is the tracheal tube. The PIP can increase with increased flow rates, increased V_T, airway secretions, or tracheal tube narrowing without any predictable relation to changes in alveolar pressure.

Static Airway-Pressure Measurement

When near zero flow conditions exist, a pressure measurement anywhere in the ventilator-patient circuit should bear a predictable relationship to alveolar pressures. Figure 72-25 (Figure Not Available) illustrates delivery of a fixed V_T in 1 second followed by the inflation-hold (or inspiratory pause) maneuver in which exhalation is delayed for 1 second. During the inflation-hold maneuver, the pressure gradient between the proximal airway and alveoli results in continued flow toward the alveoli, resulting in a *plateau* pressure in the proximal airway. * When near-zero flow exists for at least 0.5 second, usually requiring at least a 1-second inflation-hold, the plateau pressure should reflect the average peak alveolar pressure. [157] [197] It is common practice to measure the inspiratory plateau pressure at the end of a 0.5-second inflation-hold maneuver, a circumstance that *approaches* zero flow (see Fig. 72-25) (Figure Not Available) but still somewhat overestimates the average peak alveolar pressure.

Assessing Alveolar Pressures

It is reasonable to infer from numerous animal studies that *alveolar* pressures exceeding 35 cm H_2O may induce or proliferate lung injury. [157] [172] [191] When applying volume-preset modes, one must develop a scheme to utilize the inspiratory plateau pressure as a means by which to assess the alveolar pressures and thereby to assess the risks of volutrauma.

Clinical observations demonstrate that when delivering 12 to 15 mL/kg V_T, neuromuscular blockade often reduces the plateau pressure by 5 to 10 cm H_2O simply by diminishing the chest wall and abdominal muscle tone. Because inspiratory plateau pressure measurements commonly overestimate alveolar pressures, concern for potential volutrauma is likely justified when the inspiratory plateau pressure approaches 40 cm H_2O in the paralyzed patient or 50 cm H_2O in the nonparalyzed patient.

Figure 72-25 (Figure Not Available) Schematic illustration of inspiratory cycle for volume preset (1,000 mL) tidal volume delivered by square wave generator in 1 second, followed by a 1-second inflation-hold maneuver. The inspiratory cycle is 2 seconds, although tidal volume is delivered by ventilator in 1 second. Normal compliance and resistance are assumed. Proximal airway pressure is shown as a solid line, alveolar pressure as a dashed line, and gas flow in airways as a dotted line. Peak airway pressure is achieved near end of tidal volume delivery, at which point there is considerable gradient between peak airway pressure and alveolar pressure that results in continued flow to lung. Airway pressure rapidly diminishes as flow continues toward the alveoli. Measurable flow in the system has essentially ceased 0.5 seconds after the ventilator has delivered tidal volume; however, a gradient remains between airway and alveolar pressures. To attain true plateau pressure, at which airway pressure reflects average peak alveolar pressure, an additional 0.5 seconds of inflation hold is required after the absence of measurable flow in the system. *(From Shapiro and Peruzzi [174])*

Patients in the surgical ICU commonly have conditions that decrease thoracic compliance independent of alveolar disease, such as abdominal distention, fractured ribs, and surgical wounds. Such circumstances can result in significantly increased inspiratory plateau pressures without suggesting hyperdistended alveoli.

PRESSURE-PRESET VENTILATION FOR TOTAL VENTILATOR SUPPORT

Table 72-9 defines three levels of ventilator support. As previously presented, the clinical goal for full and partial support is to achieve eucapnic ventilation while minimizing potentially detrimental physiologic alterations.

Defining Total Ventilator Support

The term *total ventilator support* describes the concept of applying pressure-preset modes to establish a constant inspiratory pressure, lower than some crucial level, for the purpose of avoiding volutrauma. Total ventilator support is an appropriate term because total control of the ventilatory pattern (neuromuscular blockade) is imperative to optimize ventilation and oxygenation. Microprocessor-controlled ventilators have provided the capability to establish a constant inspiratory pressure reliably and predictably.

Pressure-control and pressure-release modes have been

* When the airway is occluded at the end of exhalation, any pressure gradient between the alveoli and the proximal airway results in flow, and the proximal airway pressure increases. The difference between the end-expiratory occlusion pressure and the baseline pressure (atmospheric pressure or PEEP) is referred to as auto-PEEP.

discussed previously. Briefly, the pressure-control mode provides inspiratory gas flow in the same manner as the pressure-support mode, but the cycle is both initiated and ended by preset time factors. The pressure-release mode consists of a continuous-flow system with a solenoid valve situated in the expiratory limb that determines which of two paths will be open to gas flow. During the inspiratory phase, the continuous gas flow exits through a threshold resistor with a preset pressure greater than that present during exhalation. As illustrated in Figure 72-26 (Figure Not Available) , both pressure-control and pressure-release modes begin inspiration at preset time intervals, rapidly achieve the preset circuit pressure, maintain the preset inspiratory pressure while inspiratory flow varies, and end the inspiratory cycle at a preset time interval. Assuming an adequate inspiratory time, the delivered V_T will be determined by the preset airway pressure and the pulmonary compliance.

The concept of applying pressure-preset modes for the purpose of avoiding ventilator-induced lung injury is based on data and logic specifically pertaining to patients with severe acute restrictive lung disease. [157] [172] [198] No data exist to justify the application of total ventilator support techniques to patients without severe acute lung disease.

Using Volume Preset Modes?

It has been suggested that volutrauma can be avoided using volume-preset modes by decreasing the V_T so that inspiratory plateau pressures are maintained at 35 to 40 cm H_2O. [199] Although this is a superficially appealing concept, it does not logically follow the dictates of physics and airway mechanics. Because airway pressures exceed 40 cm H_2O during most of inspiration, it is probable that some alveoli achieve higher pressures and are transiently overdistended. Further, distribution of ventilation is unpredictable in a lung that has contiguous alveoli of varying compliances. In other words, suboptimal ventilation is imposed without a reasonable expectation that alveolar hyperdistention will be avoided. This is in contrast to the pressure-preset mode wherein by limiting the airway pressure to 40 cm H_2O throughout inspiration and ensuring a near no-flow state at end-inspiration, not a single alveolar pressure can be predicted to exceed 40 cm H_2O at any time while optimal volumes can be predicted to be delivered to every open alveolus. [174]

Permissive Hypercapnia

Three major clinical liabilities of total ventilator support are as follows: (1) hemodynamic instability is commonly encountered when the technique is initiated; (2) neuromuscular blockade must be initiated and maintained; and (3) eucapnic ventilation may not be maintained. Perhaps the greatest clinical concern related to total ventilator support is relinquishing eucapnia as a clinical goal.

Purposefully permitting an arterial blood gas value to transcend traditional limits of acceptability has been sanctioned for many years in relation to the Pa_{O_2} in critically ill patients. Although an Pa_{O_2} greater than or equal to 60 mm Hg is traditionally considered acceptable in critically ill patients, [1]

Figure 72-26 (Figure Not Available) Schematic illustration of a pressure-preset (40 cm H_2O), time-initiated, time-cycled ventilator mode set to provide a 4-second cycle (rate of 15/min) with a 1:1 inspiration-to-expiration (I:E) ratio. Significantly diminished pulmonary compliance with relatively normal airway resistance is assumed. Proximal airway pressures are shown as a solid line, alveolar pressures as a dashed line, and flow in airways as a dotted line. Inspiration (Inspir.): Proximal airway pressure rapidly attains a preset pressure limit of 40 cm H_2O, which is maintained throughout a 20-second inspiratory cycle. Alveolar pressures equalize with proximal airway pressure before the end of the inspiratory cycle. Flow delivery by the ventilator is variable and rapidly approaches 100 L/min. Flow consistently decreases as alveolar pressures approach airway pressure. Ventilator flow ceases before alveolar pressures equal proximal airway pressure. Expiration (Expir.): Airway pressure reaches baseline and flow ceases before the end of the expiratory cycle. *(From Shapiro and Peruzzi [174])*

when severe lung disease is present, there are few who would argue with tolerating an Pa_{O_2} of 50 to 59 mm Hg to avoid use of a potentially deleterious F_{IO_2} or CPAP/PEEP level. [123] Thus, "permissive hypoxemia" (Table 72-11) has been an acceptable clinical concept for decades. The degree of arterial hypoxemia that is tolerated is determined by each clinician's judgment concerning the risk-to-benefit ratio between accelerating potentially harmful respiratory support and maintaining adequate cellular oxygenation.

Permissive hypercapnia (see Table 72-11) is the purposeful act of allowing the Pa_{CO_2} to increase acutely be-yond the point traditionally considered acceptable for the maintenance of homeostasis. Most clinicians agree that an acute Pa_{CO_2} increase to 60 mm Hg is not life-threatening provided the arterial pH is greater than 7.30; in fact, an arterial pH greater than or equal to 7.25 is usually well tolerated by patients who are free of preexisting cardiac disease. [174]

When lung compliance is significantly diminished, total ventilator support administered with a pressure limit of 40 cm H_2O could be expected to result in an Pa_{CO_2} greater than 60 mm Hg. This hypercapnia may be considered permissible provided the clinician judges that the hazards of volutrauma are potentially more deleterious than the potential hazards of cellular acidosis. Although permissive hypercapnia has been safely applied in limited studies, it is premature to assume that this practice is either beneficial or without risk. Reliable criteria and guidelines for permissive hypercapnia await further investigation.

Inverse-Ratio Ventilation

Pressure-control and pressure-release modes of ventilation can provide any desired I:E ratio because the beginning

TABLE 72-11 -- Demarcation of Permissive Hypercapnia and Hypoxemia

PERMISSIVE HYPOXEMIA	PERMISSIVE HYPERCAPNIA
Pa o_2 60 mm Hg, acceptable (normoxia)	Pa co_2 50 mm Hg, acceptable (eucapnia)
	Pa co_2 51-60 mm Hg, acceptable if increasing tidal volume risks lung injury
Pa o_2 50-59 mm Hg, acceptable if cardiovascular function adequate and advancing F $_{IO_2}$ or PEEP risks lung injury	Pa co_2 >60 mm Hg, acceptable if pH_a 7.25, cardiovascular function adequate, advancing pressure limit risks lung injury
Pa o_2 <50 mm Hg, acceptable if advancing F $_{IO_2}$ or PEEP deemed a greater risk to survival than the risks of inducing tissue hypoxia	Pa co_2 >60 mm Hg, pH_a <7.25 acceptable if risks of inducing lung injury deemed a greater risk to survival than the risks of inducing tissue acidosis

F $_{IO_2}$, inspired oxygen concentration; Pa $_{CO_2}$ and Pa $_{O_2}$, arterial partial pressures of carbon dioxide and oxygen; PEEP, positive end-expiratory pressure

and end of the inspiratory cycle occur at preset time intervals. The use of an inverse I:E ratio (inspiration longer than exhalation) was initially noted to improve oxygenation and ventilation in neonates with severe infant respiratory distress syndrome and was later reported to be useful in ARDS. [200] Figure 72-27 (Figure Not Available) illustrates that a 2-second inspiratory time is usually associated with a near no-flow state at end-inspiration. [201] A ventilator rate of 15/min results in a ventilatory cycle of 4 seconds, allowing for a 2-second inspiratory time while a 1:1 I:E ratio is maintained. As illustrated in Figure 72-27 (Figure Not Available) , a rate greater than 15/min requires an inverse I:E ratio to achieve a 2-second inspiratory time.

Available data suggest that inverse-ratio ventilation serves to enhance alveolar recruitment primarily by creating auto-PEEP, [202] as shown in Figure 72-27 (Figure Not Available) . Those who prefer to avoid prescribing extrinsic PEEP levels in excess of 15 cm H_2O, but who also embrace the concept of inverse I:E ratios for support of oxygenation, must realize that the total PEEP level (auto-PEEP plus extrinsic PEEP) is the determinant of the extent of alveolar recruitment. When applying

Figure 72-27 (Figure Not Available) Schematic illustration of a pressure-preset (40 cm H_2O), time-initiated, time-cycled ventilator mode set to provide a 3-second cycle (rate of 20/min) with a 1:1 inspiration-to-expiration (I:E) ratio. Significantly diminished pulmonary compliance with relatively normal airway resistance is assumed. Proximal airway pressures are shown as a solid line and flow in airways as a dotted line. Inspiration (Inspir.): See Figure 72-26 (Figure Not Available) . Expiration (Expir.): Flow has not reached zero at the end of the expiratory cycle (1 s); therefore, alveolar pressure is greater than baseline. The figure shows an airway pressure greater than baseline, but this may not be the case. To show an airway pressure equal to alveolar pressure may require a delay of next inspiratory cycle (expiratory occlusion pressure). Therefore, auto-positive end-expiratory pressure (auto-PEEP) (intrinsic PEEP) is detected either by measuring airway pressure after an exhalation pause or noting that flow has not ceased at the end of the expiratory cycle. *(From Shapiro and Peruzzi[174])*

total ventilator support, there are no data to suggest that inverse-ratio ventilation has any advantage over a 1:1 I:E ratio (at a ventilator rate 15/min) as long as the appropriate extrinsic PEEP levels are prescribed. There is no evidence to suggest that high Pa $_{CO_2}$ levels are significantly diminished by inverse ratios as compared with 1:1 ratios and appropriate extrinsic PEEP.

Extrapulmonary Gas Exchange

A technique permitting exchange of oxygen and CO_2 at sites other than the lung should allow total ventilator support at 40 cm H_2O while allowing the maintenance of eucapnia. To be considered for routine use, an extrapulmonary gas exchange device should be (1) readily initiated at the bedside by an intensive care specialist, (2) readily maintained by routine ICU personnel, and (3) safe enough to be utilized as an alternative to exposure of the lungs to excessive gas volumes and oxygen concentrations. [203]

Extracorporeal membrane oxygenation (ECMO) is known to be capable of completely replacing the gas exchange functions of the lung. [204] [205] Although ECMO failed to demonstrate a decreased mortality rate in adults with severe ARF in the 1970s, [206] interest in this technique continues as a means of limiting lung damage resulting from airway pressure therapy. The significant costs of personnel and equipment associated with ECMO have prevented widespread availability in this era of cost containment.

Extracorporeal CO_2 removal ($ECCO_2R$) is a simple venovenous technique introduced in 1980 to provide significant CO_2 removal in adults. [207] Although $ECCO_2R$ effectively removes CO_2 so that significantly reduced V_T can be applied while maintaining eucapnia, there is limited evidence suggesting that this technique decreases mortality in adults with severe ARF. [208] Although $ECCO_2R$ requires fewer resources than ECMO, current $ECCO_2R$ techniques still demand facilities and personnel beyond the capabilities of the average ICU.

Inhaled Nitric Oxide

Nitric oxide (NO) is an endogenous substance whose primary function appears to be vascular smooth muscle relaxation. [209] The concept of inhaled NO as a practical means by which to achieve selective and therapeutic pulmonary vasodilation [210]

is based on the presumption that NO is so rapidly inactivated in blood that diffusion into a pulmonary capillary can produce local vasodilation without systemic effects. [211] Available data suggest that inhalation of NO by patients with severe ALI reduces pulmonary artery pressures in ventilated lung areas, improves blood flow to these areas, and subsequently improves arterial oxygenation without producing systemic vasodilation. [212] Although this is a promising concept, further investigation is required to define better appropriate dosage, effect on clinical outcome, and the types and incidence of associated toxicity.

Guidelines for Total Ventilator Support

In total ventilator support, the patient is *rendered unable* to contribute any work of breathing, secondary to neuromuscular blockade, for the expressed purpose of avoiding ventilator-induced lung injury (see Tables 72-9 and 72-10) .

1. Total ventilator support should be considered when volume-preset tidal volumes of 12 mL/kg, in conjunction with appropriate CPAP/PEEP levels, display plateau pressures exceeding 40 cm H_2O in the paralyzed patient or 50 cm H_2O in the nonparalyzed patient provided, of course, that there are no significant extrapulmonary factors decreasing thoracic compliance.
2. It is essential first to establish appropriate monitoring systems, cardiovascular stabilization, adequate sedation/analgesia, neuromuscular blockade, and optimal PEEP/F $_{IO_2}$ levels with the patient on full ventilator support with a volume-preset mode. We suggest initial settings for pressure-control or pressure-release at a 1:1 ratio, a rate of 15/min (4-s cycle); the same PEEP/F $_{IO_2}$ levels as required with full ventilator support, and a pressure limit equal to the plateau pressure exhibited with full ventilator support. Within a reasonable time period and with prudent vasopressor and intravenous fluid manipulation, the patient is usually hemodynamically stable, with arterial blood gases similar to those associated with full ventilator support.
3. The pressure limit is then decreased (usually in increments of 2.5-5 cm H_2O) as rapidly as possible until 40 cm H_2O is achieved. The continuous presence of a knowledgeable and experienced physician is required for the safe initiation of total ventilator support.
4. It is essential that the patient remain deeply sedated with adequate analgesia and a level of neuromuscular blockade that ensures complete absence of chest wall and abdominal muscle tone.
5. The pressure limit of 40 cm H_2O is continued while PEEP is incrementally adjusted (5-20 cm H_2O) to establish the minimum level that produces an optimal V_T

delivery; in most cases, this will also be the PEEP level that provides the optimal P_{O_2} at an F_{IO_2} no greater than 0.5.

6. The use of flow graphics is suggested, especially when inverse I:E ratios are applied, to facilitate detection of a no-flow state at end-inspiration or auto-PEEP. This approach may allow more accurate control of ventilator support, but it must be guided by an experienced physician.
7. Hypercapnia to 60 mm Hg should be readily permitted, provided the pH is higher than 7.25 and cardiovascular stability is present. Allowing Pa_{CO_2} values to rise higher than 60 mm Hg, or the pH_a to fall lower than 7.25, requires a clinical judgment about which situation poses the best risk-to-benefit ratio--worsening hypercapnia/acidemia or escalating alveolar volumes.

Does Total Support Improve Outcome?

There are data showing that patients with severe ALI have improved outcomes when total ventilator support is incorporated within a computerized patient care protocol that includes the availability of $ECCO_2R$ or ECMO. [209] [213] Such information must not be interpreted as testimony that simply replacing volume-preset modes with pressure-preset modes will improve outcome or diminish morbidity. [214] [215] More importantly, there is no evidence to indicate that this approach to ventilator management is appropriate for patients with normal or mildly to moderately diseased lungs or that this approach justifies the abandonment of established principles of CPAP/PEEP and oxygen therapy.

VENTILATOR DISCONTINUANCE AND WEANING

Because PPV ventilation is initiated to normalize acute respiratory dysfunction, it is reasonable that reversal of that acute pathologic process should be the major factor considered prior to discontinuance of the therapy. Although the correct definition of the word wean is simply "to withdraw," the common connotation of the term is "to tease away gradually." This gradual concept is unfortunate when applied to ventilator management because most ventilator-dependent patients can be rapidly removed from the ventilator when the disease process has been adequately reversed. In this discussion, the term weaning is used only in reference to the minority of patients who cannot be discontinued from ventilatory support without gradual maneuvers taking more than 8 hours.

Mechanical ventilation should be discontinued at the earliest time consistent with patient safety. Premature attempts to discontinue ventilator support usually result in unnecessary cardiopulmonary stress without shortening the ventilator course. Ventilator discontinuance should be attempted only when (1) the underlying indication for ventilatory support is reversed or significantly improved, (2) measurements of the cardiopulmonary reserves are judged adequate for spontaneous ventilation, and (3) general clinical examination and laboratory measurements suggest no factors that significantly increase ventilatory demand.

Assessment of Cardiopulmonary Reserves

1. VC greater than 15 mL/kg reflects an adequate ventilatory muscle reserve. One should not rule out a trial of ventilator discontinuance for a patient with a VC of 10 to 15 mL/kg because the VC often improves dramatically over

several hours of spontaneous breathing. Patients with chronic diseases (e.g., COPD, chronic heart failure, quadriplegia) adapt in many ways and can be independent of ventilatory support with an extremely limited VC.
2. V_T: Immediate spontaneous V_T of greater than 2 mL/kg are encouraging. V_T is often difficult to evaluate before the patient is breathing spontaneously for a period of time.
3. Tachypnea: Spontaneous ventilatory rates of less than 25/min are encouraging; tachypnea demands reevaluation.
4. Tachycardia: Significant tachycardia on the ventilator is discouraging because the assumption of the work of breathing demands a significant increase in myocardial work. Partial ventilatory support may prove a helpful step in evaluation.
5. Hypotension/hypertension: Hypotension on the ventilator is discouraging; hypertension must be carefully evaluated.
6. Arrhythmia: Cardiac arrhythmia must be evaluated. The increased myocardial work associated with the work of breathing may be significant.
7. Hb: Oxygen-carrying capacity greatly affects the extent of increased myocardial work resulting from the assumption of the work of breathing.
8. Ventilatory demand: Factors that increase ventilatory demand (e.g., acidemia, hypoxemia, and high metabolic rates) should be corrected.

The respiratory status is best assessed by blood gas evaluation before attempting removal from the ventilator: (1) arterial blood gas measurements must be acceptable on the ventilator; (2) no evidence of acute increased V_D should be present; and (3) intrapulmonary shunt measurement should be less than 30 percent, preferably less than 20 percent (Pa_{O_2}/F_{IO_2} 150).

Ventilatory Challenge

The method of withdrawal from the ventilator support is of little significance in patients with adequate ventilatory reserves. [216] In such patients, ventilator discontinuance is mainly a matter of a smooth transition from PPV to spontaneous breathing.

Following is the scientific rationale for a procedure that makes clinical common sense, the ventilatory challenge. There must be adequate stimulation of central chemoreceptors that are sensitive to decreased cerebrospinal fluid (CSF) pH. Because the CSF does not contain appreciable buffering capabilities, small changes in Pa_{CO_2} will result in relatively large pH changes. In apneic patients who are well oxygenated, anesthetized, and paralyzed, the mean rate of rise in Pa_{CO_2} is 13.5 mm Hg in the first minute and 3.5 mm Hg each minute thereafter. [217] With an initial arterial pH of 7.40 and Pa_{CO_2} of 40 mm Hg, the Pa_{CO_2} can be expected to rise 25 to 30 mm Hg after 5 minutes of apnea, resulting in an arterial pH of approximately 7.25. The CSF pH would be expected to change from a baseline of 7.36 to less than 7.10 in response to an increase in P_{CO_2} from 40 to 70 mm Hg, a change that should provide a maximal stimulus to the central chemoreceptors. [218] When a minimum of two positive-pressure breaths per minute is applied to an apneic patient with a clinically apparent basal metabolic rate, the Pa_{CO_2} rise is seldom greater than 15 to 20 mm Hg in 5 minutes. [219]

Clinical assessment begins with notation of baseline values and a pulse oximeter applied. A positive-pressure breath synchronized with the patient's spontaneous pattern is provided every 30 seconds with a manual ventilator delivering 50 to 80 percent oxygen. If the patient manifests significant detrimental changes in vital signs or clinical appearance, the ventilator is reinstituted. Most patients do not require any positive-pressure breaths after several minutes and make a smooth transition to spontaneous ventilation. Patients with chronic CO_2 retention may require Pa_{O_2} values lower than 70 mm Hg to maintain adequate spontaneous ventilation. In such cases, the manual ventilator should be used with an appropriate F_{IO_2}, to avoid relative hyperoxemia.

The patient is allowed to assume the work of breathing, while the Sp_{O_2}, pulse rate, blood pressure, ventilatory pattern, and breathing efforts are closely monitored. The spontaneous ventilatory rate may dramatically change toward normal as the work of breathing is assumed. Breathing rates approaching 20 to 25/min should not cause concern so long as the rate stabilizes, the pattern is acceptable, and the effort is not distressing to the patient. Spontaneous work of breathing is often accompanied by blood pressure and cardiac rate increases up to 10 percent from baseline; this should not be considered a problem in the absence of dysrhythmia or distress. Mild diaphoresis is a common feature and should not cause concern unless it is accompanied by other signs of increased sympathetic discharge or physiologic stress.

Difficult-to-Wean Patients

A ventilatory challenge is applied to patients deemed capable of maintaining respiratory homeostasis without ventilatory support or to patients who appear borderline. When the ventilatory challenge fails, there must be a complete reevaluation of residual sedation, narcosis, and neuromuscular blockade. Most weaning problems are due to (1) attempts to discontinue ventilation too early in the disease course, (2) improper ventilator maintenance, or (3) preexisting chronic disease or malnutrition that severely limits reserves.

Even though there are no data suggesting that specific weaning techniques have any inherent advantage, [220] biases are rampant. IMV, SIMV with pressure support, and pressure-support modes have the advantage of allowing the patient to assume more work of breathing gradually. However, these modes are misused when they

are routinely chosen to provide a prolonged weaning process to patients capable of spontaneous breathing. Improved knowledge of ventilatory muscle function has led to the development of techniques (isocapnic hyperpnea, inspiratory resistive breathing) specifically designed to increase ventilatory muscle strength and endurance. [221] Further study of these techniques as weaning aids is required.

There are circumstances in which the use of 5 to 10 cm H_2O CPAP aids in the ability to maintain spontaneous ventilation. Theoretic benefits include the maintenance of an improved FRC, improved lung compliance, and a subjective "sensation" of better lung inflation. As a general rule, patients

already receiving CPAP/PEEP therapy should be maintained on 5 to 10 cm H_2O CPAP during ventilator discontinuance and extubated from that level. [222]

An inadequate nutritional status impairs ventilatory muscle efficiency and strength and has been assumed to be a potential cause of failure to wean from the ventilator. Although this assumption remains controversial, it is well documented that parenteral hyperalimentation can significantly increase CO_2 production, which may produce weaning difficulties. [223] Parenteral regimens with high-carbohydrate diets are associated with the greatest increases in CO_2 production; fat energy sources added to the diet are recommended to minimize CO_2 production.

Patients Receiving Long-Term Ventilation

Most patients legitimately requiring lengthy weaning programs are those lacking adequate reserves because of chronic lung or heart disease. Often, inordinate time, energy, and emotion are spent to remove the patient from the ventilator for several days and to discharge the patient from the ICU, only to have the patient return in need of ventilatory support without identifiable acute insult. No one disagrees that all patients deserve reasonable attempts to be free of the ventilator. However, after a reasonable trial period, it becomes evident (although difficult to accept) that patients are at least intermittently in need of prolonged ventilator support. Quality of life is best served by early acceptance of these facts and preparation of the patient and family for long-term ventilator support.

OBSTRUCTIVE DISEASE AND RESPIRATORY FAILURE

Two of the most common respiratory abnormalities encountered by anesthesiologists are COPD and asthma. These disease processes are responsible for significant morbidity and mortality, both in the perioperative period and during acute exacerbations of the chronic disease process.

Asthma

Bronchospasm is the most readily reversible pulmonary pathologic process encountered during the perioperative period. Table 72-5 (Table Not Available) outlines some of the various drugs used for the treatment of bronchospasm. First-line therapy for bronchospastic disease consists of inhaled beta-agonists. These drugs are used differently depending on the severity of the patient's disease. Some patients may use them intermittently depending on symptoms, whereas others may require a regular regimen. However, in the perioperative period, the use of beta-agonists on a regular schedule (i.e., q9h) for prophylaxis is recommended. [224] Anticholinergic agents are also considered first-line therapy, especially in older patients or those with a significant smoking history. [225] Asthma has been recognized as an inflammatory process affecting the airways. As such, inhaled and systemic corticosteroids have become a mainstay of therapy in many patients, [226] and they should be continued throughout the perioperative period. Preventive therapy with cromolyn sodium is most effective in younger patients with a strong allergic basis for their asthma. [227] Although this drug also should be continued throughout the perioperative period, if possible, cromolyn has no place in the treatment of acute bronchospastic episodes.

Second-line therapy for bronchospastic disorders consists of oral theophylline and/or sympathomimetics (i.e., albuterol and terbutaline). [227] The use of theophylline for treatment of bronchospastic disorders is controversial; however, if the patient is already being treated with the drug, and there are no signs of toxicity (i.e., tremulousness, tachycardia, nausea, vomiting, seizures), then it should be continued throughout the perioperative period, and drug levels should be checked as indicated. If the patient is being treated with oral sympathomimetics, they can usually be discontinued in the perioperative period, but inhaled agents should be substituted on a scheduled administration basis.

If general anesthesia is utilized, the choice of anesthetic agents may affect the patient's clinical course. In terms of the effects of intravenous induction agents on reactive airways, ketamine [228] [229] and propofol [230] are the only ones that have bronchodilatory effects; however, virtually any agent is acceptable, provided an adequate depth of anesthesia is obtained prior to airway manipulation. Inhalational agents all have bronchodilatory effects. Although some inhalational agents may be more potent in this regard than others, no clinically significant difference has ever been demonstrated. Histamine release is also a concern in patients with bronchospastic disease processes, and, whenever possible, drugs that cause significant histamine release should be avoided. However, the potential for histamine release is not an absolute contraindication to the use of any specific drug in the appropriate clinical situation.

It is important to restart any aerosolized bronchodilator medications as soon as possible in the postoperative period. Frequently, it is necessary to administer aerosolized bronchodilators via a hand-held nebulizer or a face mask until the patient has the ability to properly use an MDI, with or without a spacer device. Contrary to popular belief, there is no clinical advantage to the administration of bronchodilators with a hand-held nebulizer over an MDI if the patient is able to use an MDI properly. [31] Therefore, it is not surprising that the most cost-effective method of aerosolized drug administration has been demonstrated to be via an MDI. [231]

Acute asthmatic exacerbations are occurring more commonly and with greater severity. The anesthesiologist may become involved in the care of the acutely asthmatic patient when ventilator management becomes necessary. The traditional means of estimating the severity of acute asthma in relation to maintaining respiratory homeostasis is to categorize the arterial blood gases into four stages:

1. Stage 1: Mild hypoxemia with normal pH and Pa $_{CO_2}$.
2. Stage 2: Mild hypoxemia with respiratory alkalosis(pH > 7.45 and Pa $_{CO_2}$ < 35 mm Hg breathing room air.
3. Stage 3: Severe hypoxemia (requires 0.4 F $_{IO_2}$) with normalizing pH and Pa $_{CO_2}$.
4. Stage 4: Acute respiratory acidosis (pH < 7.30, Pa $_{CO_2}$ 55 mm Hg) with severe hypoxemia.

Positive airway-pressure therapy applied to patients with acute asthma is associated with a high incidence of barotrauma,

which is the largest contributor to morbidity and mortality in these patients. [232] [233] The first case reports of permissive hypercapnia were attempts to avoid barotrauma in patients with acute asthma by limiting V_T. Although everyone agrees that alveolar overdistention must be avoided, there is controversy about how this is best accomplished. The traditional approach utilizing volume-preset modes is to deliver reasonable V_T (8-10 mL/kg) at rates of 4 to 6/min, allowing extremely prolonged expiratory times. This requires very heavy sedation (even anesthesia) with neuromuscular blockade to ensure that there is no coughing or ventilatory dyssynchrony. A newer approach is to use pressure-preset modes and airway graphics to avoid hyperinflation and barotrauma. [234]

The anesthesiologist is often consulted to intubate the patient with severe acute asthma. Although there is no clear evidence linking the worsening of bronchospasm to the placement of an endotracheal tube, virtually all anesthesiologists have encountered clinical situations in which this has occurred. The most important factor in dealing with an acute asthma exacerbation requiring intubation and mechanical ventilatory support is to induce an adequate state of anesthesia during airway manipulation and initiation of mechanical ventilation. Following this, treatment of the underlying processes can progress with appropriate medications (i.e., inhaled or parenteral beta-agonists, anticholinergics, steroids).

Chronic Obstructive Pulmonary Disease

COPD is an imprecise term encompassing a wide variety of chronic respiratory conditions, including chronic bronchitis, emphysema, chronic asthma, cystic fibrosis, and bronchiolitis. Regardless of type or degree of underlying disease, all patients with COPD demonstrate several common characteristics: (1) chronically increased airway resistance resulting in increased work of breathing, (2) decreased efficiency of inspiratory muscles secondary to chronic thoracic hyperinflation, and (3) impaired pulmonary gas exchange. Although the incidence of chronic hypercapneia rises as the severity of COPD increases, some patients become hypercapneic with moderate lung disease, whereas others remain eucapnic despite severe obstructive processes. A baseline blood gas analysis can be very helpful in determining the patient's chronic status. This is especially important when mechanical ventilatory support is anticipated during the perioperative period. It is imperative that mechanical ventilation be titrated according to the patient's baseline status if optimal outcomes are to be achieved. This applies not only to patients requiring mechanical ventilation during the perioperative period, but also to those experiencing acute exacerbations of their chronic disease.

Although ARF in a patient with COPD can be a catastrophic event, appropriate therapy is often lifesaving. A 2-year survival greater than 70 percent may be expected when mechanical ventilation can be avoided; these patients have a life expectancy comparable to that of stable outpatients with the same severity of COPD who have not experienced ARF. [235] Immediate therapy to decrease airway resistance and to improve pulmonary gas exchange is essential, regardless of precipitating events. Airway resistance is diminished by bronchodilator therapy and removal of secretions (bronchial hygiene therapy); gas exchange is improved by oxygen therapy and ventilator assistance if required.

Bronchodilators have been demonstrated to be beneficial to most patients with COPD, especially those with impending or respiratory failure or ARF. Optimal bronchodilator therapy has been the subject of much clinical research. Although beta-agonists remain the first-line therapy in asthma, [236] the use of inhaled anticholinergic agents has been demonstrated to have equal efficacy compared with beta-agonists in patients with COPD. [237] The combination of an inhaled anticholinergic compound (i.e., ipatroprium bromide) and a beta-agonist appears to have clinical advantages over the administration of beta-agonists alone in patients with COPD, [238] [239] [240] [241] in critically ill mechanically ventilated patients, [242] and in pediatric patients. [243] Current evidence indicates that anticholinergic bronchodilators have emerged as the treatment of first choice in patients with COPD and as a significant adjunctive therapeutic modality in patients with acute asthma. [244] Fortunately, the arrhythmia potential of ipotroprium bromide in patients with COPD and ischemic heart disease appears to be negligible. [245]

The various agents used to achieve bronchodilation often have beneficial effects other than bronchodilation. For example, theophylline may improve diaphragmatic contractility [246] in patients with COPD. [247] [248] Additionally, inhaled beta-agonists, in addition to causing bronchodilation, may improve the ciliary action in the tracheobronchial tree and may enhance the clearance of mucus. [249] [250]

Corticosteroids have been claimed to be useful in reducing air-flow resistance in patients with COPD with acute exacerbations not caused by pneumonia. Intravenous methylprednisolone sodium succinate (Solu-Medrol), 0.5 mg/kg every 6 hours for the initial 72 hours of hospitalization, has been shown to produce significant improvements in air flow. [251] Interestingly, although these beneficial effects have been noted, questions have been raised regarding the ability of inhaled steroid therapy to improve the quality of life in patients with asthma or COPD. [252]

All patients with COPD and ARF require oxygen therapy. The goal is to restore the patient's arterial oxygenation status to a level that ensures adequate Hb saturation while approximating the patient's stable baseline. This usually requires a Pa_{O_2} of 50 to 60 mm Hg. The classic explanation for CO_2 retention with oxygen administration has been "suppression of the hypoxic drive." In its simplest form, this situation is thought to result from a central CO_2 response that is blunted by chronic CO_2 retention, leaving only hypoxiasensitive peripheral chemoreceptor mechanisms intact to drive ventilation. When an increased F_{IO_2} results in augmentation of the Pa_{O_2}, a decrease in hypoxic stimulation occurs, causing hypoventilation. Experience in acute respiratory care resulted in abandonment of that traditional wisdom in favor of a more complex concept in which additional factors such as changes in the work of breathing, hypoxic vasoconstriction, denitrogenation, and Hb-oxygen affinity relationships are potentially involved. Suffice it to say that oxygen administration, although clinically necessary, has the risk of augmenting CO_2. Thus, it is best to administer precise and consistent inspired oxygen concentrations with high-flow oxygen systems; however, the risk of CO_2 retention

is still present even with precisely controlled inspired oxygen concentrations.

References

1. Shapiro BA, Peruzzi WT, Templin R: Arterial oxygenation. In Clinical Application of Blood Gases, 5th ed. Chicago, Mosby-Year Book, 1994, pp 33-53.

2. Markello R, Winter P, Olszowka A: Assessment of ventilationperfusion inequalities by arterial-alveolar nitrogen differences in intensive care patients. Anesthesiology 37:4, 1972.

3. Deneke SM, Fanberg BL: Normobaric oxygen toxicity of the lung. N Engl J Med 303:76, 1980.

4. Schacter EN, Littner MR, Luddy P et al: Monitoring of oxygen delivery systems in clinical practice. Crit Care Med 8:405, 1980.

5. Shapiro BA, Kacmarek RM, Cane RD et al: Oxygen therapy. In Clinical Application of Respiratory Care, 4th ed. Chicago, Mosby-Year Book, 1991, p 123.

6. Shapiro BA, Kacmarek RM, Cane RD et al: Limitations of oxygen therapy. In Clinical Application of Respiratory Care, 4th ed. Chicago, Mosby-Year Book, 1991, p 135.

7. Scacci R: Air entrainment masks: Jet mixing is how they work; the Bernoulli and Venturi principle is how they don't. Respir Care 24:928, 1979.

8. Shapiro BA, Cane RD, Peterson J et al: Authoritative medical direction can assure cost beneficial bronchial hygiene therapy. Chest 93:1038, 1988.

9. Hardy AK: A review of airway clearance: New techniques, indications, and recommendations. Respir Care 39:440, 1994.

10. Eid N, Buchheit J, Neuling M et al: Chest physiotherapy in review. Respir Care 36:270, 1991.

11. Maxwell M, Redmond A: Comparative trial of manual and mechanical percussion technique with gravity-assisted bronchial drainage in patients with cystic fibrosis. Arch Dis Child 54:542, 1979.

12. Shapiro BA, Kacmarek RM, Cane RD et al: Applying and evaluating bronchial hygiene therapy. In Clinical Application of Respiratory Care, 4th ed. Chicago, Mosby-Year Book, 1991, p 85.

13. AARC clinical practice guidelines: Postural drainage therapy. 36:1418, 1991.

14. Sloan HE: Vagus nerve in cardiac arrest. Surg Gynecol Obstet 91:257, 1950.

15. Crimlisk JT, Paris R, McGonagle EG et al: The closed tracheal suction system: Implications for critical care nursing. Dimensions Crit Care Nurs 13:292, 1994.

16. Shim C, Fine N, Fernandez R et al: Cardiac arrhythmias resulting from tracheal suctioning. Ann Intern Med 71:1149, 1969.

17. Consensus Conference of Aerosol Delivery: Aerosol consensus statement. Chest 100:1106, 1991.

18. Kuo CD, Lin SE, Wang JH: Aerosol, humidity and oxygenation. Chest 99:1352, 1991.

19. Hess D: The open forum: Reflections on unanswered questions about aerosol therapy delivery techniques (editorial). Respir Care 33:19, 1988.

20. Ward JJ, Helmholz HF: Applied humidity and aerosol therapy. In Burton GG, Hodgkin JE, Ward JJ (eds): Respiratory Care: A Guide to Clinical Practice, 3rd ed. Philadelphia, JB Lippincott, 1991, p 355.

21. Leoung GS, Hopewell PC: *Pneumocystis carinii* pneumonia: Therapy and prophylaxis. In The AIDS Knowledge Base, 2nd ed. Boston, Little, Brown, 1994, p 617.

22. Myers SE, Devine SM, Topper RL et al: A pilot study of prophylactic aerosolized amphotericin B in pathetists at risk for prolonged neutropenia. Leuk Lymphoma 8:229, 1992.

23. Hertenstein B, Kern WV, Scmeiser T et al: Low incidence of invasive fungal infections after bone marrow transplantation in patients receiving amphotericin B inhalations during neutropenia. Ann Hematol, 68:21, 1994.

24. Schmitt HJ: New methods of delivery of amphotericin B. Clin Infect Dis 17(suppl):S501, 1993.

25. Ziment I: Drugs used in respiratory therapy. In Burton GG, Hodgkin JE, Ward JJ (eds): Respiratory Care: A Guide to Clinical Practice, 3rd ed. Philadelphia, JB Lippincott, 1991, p 411.

26. Newman SP: Aerosol deposition considerations in inhalation therapy. Chest 88:152S, 1985.

27. Kacmarek RM, Hess D: The interface between patient and aerosol generator. Respir Care 36:952, 1991.

28. Newman SP, Pavia D, Moren F et al: Deposition of pressurized aerosols in the human respiratory tract. Thorax 36:52, 1981.

29. Lewis RA, Fleming JS: Fractional deposition from a jet nebulizer: How it differs from a metered dose inhaler. Br J Dis Chest 79:361, 1985.

30. Jenkins SC, Heaton RW, Fulton TJ et al: Comparison for domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. Chest 91:804, 1987.

31. Bowton DL, Goldsmith WM, Haponik EF: Substitution of metered-dose inhalers for hand-held nebulizers: Success and cost savings in a large, acute-care hospital. Chest 101:305, 1992.

32. Roberts RJ, Robinson JD, Doering PL et al: A comparison of various types of patient instruction in the proper administration of metered inhalers. Drug Intell Clin Pharm 16:53, 1982.

33. Armitage JM, Williams SJ: Inhaler technique in the elderly. Age Aging 17:275, 1988.

34. Hess D: Inhaled bronchodilators during mechanical ventilation: Delivery techniques, evaluation of response, and cost-effectiveness. Respir Care 39:105, 1994.

35. Leiner GC, Abramowitz S, Small MJ, et al: Expiratory peak flow rate standard values for normal subjects: Use as a clinical test of ventilatory function. Am Rev Respir Dis 88:644, 1963.

36. Ahrens RC, Ries RA, Popendorf W et al: The delivery of therapeutic aerosols through endotracheal tubes. Pediatr Pulmonol 2:19, 1986.

37. Shapiro BA, Peruzzi WT, Templin R: Respiratory acid-base balance. In Clinical Application of Blood Gases, 5th ed. Chicago, Mosby-Year Book, 1994, p 25.

38. Shapiro BA: When is an increase in work of breathing clinically significant? Crit Care Med 18:681, 1990.

39. Peters R: The energy cost (work) of breathing. Ann Thorac Surg 7:51, 1969.

40. Robertson CH, Pagel MA, Johnson RI: The distribution of blood flow, oxygen consumption and work output among the respiratory muscles during unobstructed hyperventilation. J Clin Invest 59:43, 1977.

41. Field S, Kelly SM, Maclem PT: The oxygen cost of breathing in patients with cardiorespiratory disease. Am Rev Respir Dis 126:9, 1982.

42. Fritts HW, Filler J, Fishman AP et al: The efficiency of ventilation during ventilatory hypernea: Studies in normal subjects and in dyspneic patients with either chronic pulmonary emphysema or obesity. J Clin Invest 38:1339, 1959.

43. Riley RL: The work of breathing and its relation to respiratory acidosis. Ann Intern Med 41:172, 1954.

44. Robertson CH, Foster GH, Johnson RL: The relationship of respiratory failure to the oxygen consumption and lactate production by, and distribution of blood flow among, respiratory muscles during increasing inspiratory resistance. J Clin Invest 59:31, 1977.

45. Roussos CH, Fixley M, Gross D et al: Fatigue of inspiratory muscles and their synergistic behavior. J Appl Physiol 46:897, 1979.

46. Eldridge F: Anaerobic metabolism of the respiratory muscles. J Appl Physiol 421:853, 1966.

47. Aubier M, Viires N, Syllie G et al: Respiratory muscle contribution to lactic acidosis in low cardiac output. Am Rev Respir Dis 126:648, 1982.

48. Cherniak RM: The oxygen consumption and efficiency of the respiratory muscles in health and emphysema. J Clin Invest 38:494, 1959.

49. Rochester DG, Pradel Guena M: Measurement of diaphragmatic blood flow in dogs from xenon 133 clearance. J Appl Physiol 34:68, 1973.

50. Bjork VO, Grenvik A, Holmdahl MH et al: Cardiac output and oxygen consumption during respiratory treatment. Acta Anesthesiol Scand Suppl 15:158, 1964.

51. Bartlet R: Oxygen cost of breathing. J Appl Physiol 12:413, 1958.

52. Cournand A, Motley HL, Werko L: Physiologic studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152:162, 1948.

53. Marini JJ, Capps JS, Culver BH: The inspiratory work of breathing during assisted mechanical ventilation. Chest 87:612, 1985.

54. Marini JJ, Rodriquez RM Lamb V: The inspiratory workload of patient-initiated mechanical ventilation. Am Rev Respir Dis 134:902, 1986.

55. Kacmarek RM, Wilson RS: IMV systems: Do they make a difference? Chest 87:557, 1985.

56. Cane RD, Shapiro BA: Mechanical ventilatory support. JAMA 254:87, 1985.

57. Shapiro BA, Harrison RA, Walton RJ et al: Intermittent demand ventilation (IDV): A new technique for supporting ventilation in critically ill patients. Respir Care 21:521, 1976.

58. Gibney RTN, Wilson RT, Pontoppidan H: Comparison of work of breathing on high gas flow and demand valve continuous positive airway pressure breathing systems. Chest 82:692, 1982.

59. Marini JJ, Smith TC, Lamb VJ: External work output and force generation during synchronized intermittent mechanical ventilation. Am Rev Respir Dis 138:1169, 1988.

60. Norlander O: New concepts of ventilation. Acta Anaesthesiol Belg 33:221, 1982.

61. Kacmarek RM: The role of pressure support ventilation in reducing work of breathing. Respir Care 33:99, 1988.

62. Katz JA, Kraemer RW, Gjerde GE: Inspiratory work and airway pressure with continuous positive airway pressure delivery systems. Chest 88:519, 1985.

63. Sassoon CS, Light RW, Lodia R et al: Pressure-time product during continuous positive airway pressure, pressure support ventilation, and T-piece during weaning from mechanical ventilation. Am Rev Respir Dis 143:469, 1991.

64. MacIntyre NR: Respiratory function during pressure support ventilation. Chest 89:677, 1986.

65. Prakash O, Meij S: Cardiopulmonary response to inspiratory pressure support during spontaneous ventilation vs conventional ventilation. Chest 88:403, 1985.

66. MacIntyre NR: Pressure support ventilation (editorial). Respir Care 31:189, 1986.

67. Froese AB, Bryan AC: State of the art: High frequency ventilation. Am Rev Respir Dis 135:1363, 1987.

68. McCulloch PR, Froese AB: High frequency ventilation. Anesthesiol Clin North Am 5:873, 1987.

69. Sjostrand U: High-frequency positive-pressure ventilation (HFPPV): A review. Crit Care Med 8:345, 1980.

70. Carlon GC, Ray C Jr, Griffin J et al: Tidal volume and airway pressure on high frequency jet ventilation. Crit Care Med 11:83, 1983.

71. Gallagher TJ, Klain MK, Carlon CG: Present status of high frequency ventilation. Crit Care Med 10:613, 1982.

72. Turnbull AD, Carlon GC, Howland WS et al: High frequency jet ventilation in major airway or pulmonary disruption. Ann Thorac Surg 32:468, 1981.

73. Carlon GC, Kahn RC, Howland WS et al: Clinical experience with high frequency jet ventilation. Crit Care Med 9:1, 1981.

74. Mayers I, Long R, Breen PH et al: Artificial ventilation of a canine model of bronchopleural fistula. Anesthesiology 64:739, 1986.

75. Drazen JM, Kamm RD, Slutsky AS: High-frequency ventilation. Physiol Rev 64:505, 1984.

76. A report of the ACCP-STS Joint Committee on Pulmonary Nomenclature. Chest 67:583, 1975.

77. Duncan AW, Oh TE, Hillman DR: PEEP and CPAP. Anaesth Intensive Care 14:236, 1986.

78. Hedenstierna G, Santesson J, Norlander O: Airway closure and distribution of inspired gas in the extremely obese, breathing spontaneously and during anesthesia with intermittent positive pressure ventilation. Acta Anaesthesiol Scand 20:334, 1976.

79. Bredenberg CE, Kazui T, Webb WR: Experimental pulmonary edema: The effect of positive end-expiratory pressure on lung water. Ann Thorac Surg 26:62, 1978.

80. Hopewell PC: Failure of positive end-expiratory pressure to decrease lung water content in alloxan-induced pulmonary edema. Am Rev Respir Dis 120:813, 1979.

81. Demling RH, Staub NC, Edmonds LH: Effect of end-expiratory airway pressure on accumulation of extravascular lung water. J Appl Physiol 38:907, 1975.

82. Goldberg HS, Mitzner W, Batra G: Effect of transpulmonary and vascular pressures on rate of pulmonary edema formation. J Appl Physiol 43:14, 1977.

83. Miller WC, Rice DL, Unger KM et al: Effect of PEEP on lung water content in experimental noncardiogenic pulmonary edema. Crit Care Med 9:7, 1981.

84. Malo J, Jameel A, Wood LDH: How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? J Appl Physiol 57:1002, 1984.

85. Pare PD, Warriner B, Baile EM et al: Redistribution of pulmonary extravascular water with positive end-expiratory pressure in canine pulmonary edema. Am Rev Respir Dis 127:590, 1983.

86. Shapiro BA, Cane RD, Harrison RA: Positive end expiratory pressure therapy on adults with special reference to acute lung injury: A review of the literature and suggested clinical correlations. Crit Care Med 12:127, 1984.

87. Daly BDT, Edmonds CH, Norman JC: *In vivo* alveolar morphometrics with positive end expiratory pressure. Surg Forum 24:217, 1973.

88. Gattinoni L, D'Andrea L, Pelosi P et al: Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. JAMA 269:2122, 1993.

89. Kumar A, Falke KI, Geffin B et al: Continuous positive-pressure ventilation in acute respiratory failure: Effects on hemodynamics and lung function. N Engl J Med 238:1430, 1970.

90. McIntyre RW, Laws AK, Ramachandran PR: Positive expiratory pressure plateau: Improved gas exchange during positive-pressure ventilation. Can Anaesth Soc J 16:477, 1969.

91. Matamis D, Lemaire F, Hart A et al: Total respiratory pressure-volume curves in the adult respiratory distress syndrome. Chest 86:58, 1984.

92. Benito S, Lemaire F: Pulmonary pressure-volume relationship in acute respiratory distress syndrome in adults: Role of positive endexpiratory pressure. J Crit Care 5:27, 1990.

93. Ranieri VM, Eissa NT, Corbeil C et al: Effects of positive endexpiratory pressure on alveolar recruitment and gas exchange in patients with adult respiratory distress syndrome. Am Rev Respir Dis 144:544, 1991.

94. Gattinoni L, Pesenti A, Bombino M et al: Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology 69:824, 1988.

95. Gattinoni L, Pesenti A, Avalli L et al: Pressure-volume curve of total respiratory system in acute respiratory failure: CT scan study. Am Rev Respir Dis 136:730, 1987.

96. Gattinoni L, Peolsi P, Crotti S et al: Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807, 1995.

97. Cane RD, Shapiro BA, Templin R et al: The unreliability of oxygen tension based indices in reflecting intrapulmonary shunting in the critically ill. Crit Care Med 12:1243, 1988.

98. Shapiro BA, Peruzzi WT, Templin R: Responsive and Refractory Hypoxemia. In Clinical Application of Blood Gases, 5th ed. Chicago, Mosby-Year Book, 1994, p 138.

99. Leithner C, Podolsky A, Globits S et al: Magnetic resonance imaging of the heart during positive end-expiratory pressure ventilation in normal subjects. Crit Care Med 22:426, 1994.

100. Huemer G, Kolev N, Kurz A et al: Influence of positive end-expiratory pressure on right and left ventricular performance assessed by Doppler two-dimensional echocardiography. Chest 106:67, 1994.

101. Qvist J, Pontoppidan H, Wilson RS et al: Hemodynamic responses to mechanical ventilation with PEEP. Anesthesiology 42:45, 1975.

102. Robotham JL, Lixfield W, Holland L et al: The effects of positive end expiratory pressure on right and left ventricular performance. Am Rev Respir Dis 121:677, 1980.

103. Pinsky MR, Desmet JM, Vincent JL: Effect of positive end-expiratory pressure on right ventricular function in humans. Am Rev Respir Dis 146:681, 1992.

104. Brooks H, Kirk ES, Vokonas C et al: Performance of the right ventricle under stress. J Clin Invest 50:2176, 1971.

105. Jardin F, Farcot J, Boisante L et al: Influence of positive end expiratory pressure on left ventricular performance. N Engl J Med 304:387, 1981.

106. Dorinsky PM, Whitcomb ME: The effects of PEEP on cardiac output. Chest 84:210, 1983.

107. Terai C, Uenishi M, Sugimoto H et al: Transesophageal echocardiographic dimensional analysis of four chambers during positive endexpiratory pressure. Anesthesiology 63:640, 1985.

108. Grace MP, Greenbaum DM: Cardiac performance in response to PEEP in patients with cardiac dysfunction. Crit Care Med 10:358, 1982.

109. Nunn J: Positive end-expiratory pressure. Int Anesthesiol Clin 22:149, 1984.

110. Davidson RD, Parker M, Harrison RA: The validity of determinations of pulmonary wedge pressure during mechanical ventilation. Chest 73:352, 1978.

111. Downs JB, Douglas ME: Assessment of cardiac filling pressure during CPPV. Crit Care Med 8:285, 1980.

112. Pershau RA, Pepine CJ, Nichols WW et al: Instantaneous blood flow responses to positive end-expiratory pressure with spontaneous ventriculation. Circulation 59:1313, 1979.

113. Berry AJ: Respiratory support and renal function. Anesthesiology 55:685, 1981.

114. Hall SV, Johnson EE, Hedley-Whyte J: Renal Hemodynamics and function with continuous positive pressure ventilation in dogs. Anesthesiology 41:452, 1974.

115. Priebe HJ, Heimann JL, Hedley-Whyte J: Mechanism of renal dysfunction during positive end expiratory pressure ventilation. J Appl Physiol 50:643, 1981.

116. Hemmer M, Suter PM: Treatment of cardiac and renal effects of PEEP with dopamine in patients with acute respiratory failure. Anesthesiology 50:399, 1979.

117. Fewell JE, Bond GC: Role of sinoaortic baroreceptors in initiating the renal response to continuous positive pressure ventilation in the dog. Anesthesiology 52:408, 1980.

118. Annat G, Viale JP, Xuan BB et al: Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins, urinary ADH and prostaglandins. Anesthesiology 58:136, 1983.

119. Vender JS: Complications and physiologic alterations of positive airway pressure therapy. Anesthesiol Clin North Am 5:807, 1987.

120. Lucas CE, Sugawa C, Riddle J: Natural history and surgical dilemma of "stress" gastric bleeding. Arch Surg 102:266, 1971.

121. Harris SK, Bone RC, Ruth WE: Gastrointestinal hemorrhage in respiratory intensive care unit. Chest 72:301, 1977.

122. Bredenberg CE, Paskanik A, Fromm D: Portal hemodynamics in dogs during mechanical ventilation with positive end expiratory pressure. Surgery 90:87, 1981.

123. Shapiro BA: A historical perspective on ventilator management. New Horiz 2:8, 1994.

124. Lewis KS, Whipple JK, Michael KA et al: Effect of analgesic treatment in the physiological consequences of acute pain. Am J Hosp Pharm 51:1539, 1994.

125. Rosenfield BA, Beattie C, Christopherson R et al: The effects of different anesthetic regimens on fibrinolysis and the development of postoperative arterial thrombosis. Anesthesiology 79:415, 1993.

126. Shapiro BA, Warren J, Egol AB et al: Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: An executive summary. Crit Care Med 23:1596, 1995.

127. Lowenstein E: Morphine "anesthesia": A perspective. Anesthesiology 35:563, 1971.

128. Shapiro BA, Warren J, Egol AB et al: Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: An executive summary. Crit Care Med 23:1601, 1995.

129. Prielipp RC, Coursin DB, Scuderi PE et al: Comparison of the infusion requirements and recovery profiles of vecuronium and cisatracurium 51W89 in intensive care unit patients. Anesth Analg 81:3, 1995.

130. Pontoppidan H, Hedley-Whyte J, Bendixen HH et al: Ventilation and oxygenation requirements during prolonged artificial ventilation in patients with respiratory failure. N Engl J Med 273:401, 1965.

131. Bergman NA: Effects of varying waveforms on gas exchange. Anesthesiology 28:390, 1967.

132. Suter PM, Fairley HB, Isenberg MD: Effect of tidal volume and positive end expiratory pressure on compliance during mechanical ventilation. Chest 73:158, 1978.

133. Motley HL, Cournand A, Werko L et al: Intermittent positive pressure breathing, a means of administering artificial respiration in man. JAMA 137:370, 1948.

134. Astrup P, Gotzche H, Neukirch F: Laboratory investigations during treatment of patients with poliomyelitis and respiratory paralysis. Br Med J 1:780, 1954.

135. Levine M, Gilbert R, Auchincloss JH: A comparison of the effects of sighs, large tidal volumes, and positive end-expiratory pressure in assisted ventilation. Scand J Respir Dis 53:101, 1972.

136. Sykes MK, Young WE, Robinson BE: Oxygenation during anesthesia with controlled ventilation. Br J Anaesth 37:314, 1965.

137. Bendixen HH, Bullwinkel B, Hedley-Whyte J et al: Atelectasis and shunting during spontaneous ventilation in anesthetized patients. Anesthesiology 25:297, 1964.

138. Laver MB, Morgan J, Bendixen HH et al: Lung volume, compliance and arterial oxygen tension during controlled ventilation. J Appl Physiol 19:725, 1964.

139. Fairley HB, Blenkarn GD: Effect of pulmonary gas exchange of variations in inspiratory flow rate during intermittent positive pressure ventilation. Br J Anaesth 38:320, 1966.

140. Morch ET: History of mechanical ventilation. In Kirby RR, Banner MJ, Downs JB (eds): Clinical Applications of Ventilatory Support. New York, Churchill Livingstone, 1990.

141. Dammann JF, McAslan TC: Optimal flow pattern for mechanical ventilation of the lungs. Crit Care Med 5:128, 1977.

142. Bartlett RH, Hanson EL, Moore RD: Physiology of yawning and its application to postoperative care. Surg Forum 22:222, 1970.

143. Harrison RA, Davison RD, Shapiro BA et al: Reassessment of the assumed A-V oxygen content difference in the shunt calculation. Anesth Analg 54:198, 1975.

144. Downs JB, Modell JH: Patterns of respiratory support aimed at pathophysiologic conditions. In Hershey SG (ed): ASA Refresher Courses in Anesthesiology, vol 7. Philadelphia, JB Lippincott Co, 1977, p 71.

145. Suter PM, Fairley HB, Isenberg MD: Optimum end-expiratory pressure in patients with acute pulmonary failure. N Engl J Med 292:284, 1975.

146. Albeloa SM, Gefter WB, Kelley MA et al: Ventilator induced subpleural air cysts: Clinical, radiographic and pathologic significance. Am Rev Respir Dis 127:360, 1983.

147. Pierson DJ: Persistent bronchopleural air leak during mechanical ventilation: A review. Respir Care 27:408, 1982.

148. Cullen DJ, Caldera DL: The incidence of ventilator induced pulmonary barotrauma in critically ill patients. Anesthesiology 50:185, 1979.

149. Moylan FMB, Walker AM, Kramer SS et al: The relationship of bronchopulmonary dysplasia to the occurrence of alveolar rupture during positive pressure ventilation. Crit Care Med 6:140, 1978.

150. Petersen GW, Baier H: Incidence of pulmonary barotrauma in medical ICU. Crit Care Med 11:67, 1983.

151. Carlon GC, Howland WS, Ray C et al: High frequency jet ventilation: A prospective randomized evaluation. Chest 84:551, 1983.

152. Mathru M, Roat K, Venus B: Ventilator induced barotrauma in controlled mechanical ventilation versus intermittent mandatory ventilation. Crit Care Med 11:359, 1983.

153. Downs JB, Chapman RL: Treatment of bronchopleural fistula during continuous positive pressure ventilation. Chest 69:363, 1976.

154. Kirby RR, Downs JB, Civetta JM et al: High level end expiratory pressure in acute respiratory failure, Chest 67:156, 1975.

155. Kirkpatrick BV, Felman AH, Eitzman DV: Complications of ventilatory therapy in respiratory distress syndrome. Am J Dis Child 128:496, 1974.

156. Haake R, Schlichtig R, Ulstad DR et al: Barotrauma: Pathophysiology, risk factors, and prevention. Chest 91:608, 1987.

157. Slutsky SS: Mechanical Ventilation ACCP Consensus Conference. Chest 104:1833, 1993.

158. Shapiro BA, Cane RD: The AMV-IMV controversy: A plea for clarification and redirection. Crit Care Med 12:472, 1984.

159. Downs JD, Klein EF Jr, Desutels D et al: Intermittent mandatory ventilation: A new approach to weaning patients from mechanical ventilators. Chest 64:331, 1973.

160. Mathru M Rao TL, El-Etr AA et al: Hemodynamic response to change in ventilatory patterns in patients with normal and poor left ventricular reserve. Crit Care Med 10:423, 1982.

161. Shah DM, Newell JAC, Dutton RE et al: Continuous positive airway pressure versus positive end expiratory pressure in respiratory distress syndrome. J Thorac Cardivasc Surg 75:557, 1977.

162. Steinhoff HH, Kolhoff RJ, Falke KJ: Facilitation of renal function by intermittent mandatory ventilation. Intensive Care Med 10:59, 1984.

163. Roussos C, Macklem PT: Diaphragmatic fatigue in man. J Appl Physiol 43:189, 1977.

164. Tokioka H, Saito S, Kosaka F: Effect of pressure support ventilation on breathing patterns and respiratory work. Intensive Care Med 15:491, 1989.

165. Anderson RR, Holliday RL, Driedger AA et al: Documentation of pulmonary capillary permeability in the adult respiratory distress syndrome accompanying human sepsis. Am Rev Respir Dis 119:869, 1979.

166. Anderson RW, De Vries WC: Transvascular fluid and protein dynamics in the lung following hemorrhagic shock. J Surg Res 20:281, 1976.

167. Webb WR: Pulmonary complications in non-thoracic trauma: Summary of the National Research Council Conference. J Trauma 9:7000, 1959.

168. Petty TL, Ashbaugh DG: The adult respiratory distress syndrome:

Clinical features, factors influencing prognosis and principles of management. Chest 60:233, 1971.

169. Ashbaugh DG, Bigelow DB Petty TL et al: Acute respiratory distress in adults. Lancet 60:233, 1967.

170. Solliday NH, Shapiro BA, Gracey DR: Adult respiratory distress syndrome. Chest 69:207, 1976.

171. Shapiro BA, Cane RD: Metabolic malfunction of lung: Noncardiogenic edema and adult respiratory distress syndrome. Surg Ann 13:271, 1981.

172. Bernard GR, Artigas A, Brigham KL et al: The American-European consensus conference on ARDS: Definitions, mechanisms, relevant outcomes and clinical trial coordination. Am J Respir Crit Care Med 149:818, 1994.

173. Petty TL: The acute respiratory distress syndrome: Historical perspective. Chest 105:44S, 1994.

174. Shapiro BA, Peruzzi WT: Changing practices in ventilator management: A review of the literature and suggested clinical correlations. Surgery 117:121, 1995.

175. Suchyta MR, Clemmer TP, Orme JF et al: Increased survival of ARDS patients with severe hypoxemia: ECMO criteria. Chest 99:951, 1991.

176. Montgomery AB, Stager MA, Carrico CJ et al: Causes of mortality in patients with adult respiratory distress syndrome. Am Rev Respir Dis 132:485, 1985.

177. Morris AH, Wallace CJ, Clemmer TP et al: Extracorporeal CO_2 removal therapy for adult respiratory distress syndrome patients. Respir Care 35:224, 1990.

178. Shapiro BA, Cane RD, Harrison RA: Positive end-expiratory pressure in acute lung injury. Chest 83:558, 1983.

179. Bone RC, Balk R, Slotman G et al: Adult respiratory distress syndrome: Sequence and importance of development of multiple organ failure. Chest 101:320, 1992.

180. Pinsky MR, Matuschak GM: Multiple organ system failure: Failure of host defense homeostasis. Crit Care Clin 5:199, 1989.

181. American College of Chest Physicians: Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101:1644, 1992.

182. Abraham E (ed): Sepsis: Cellular and physiologic mechanisms. New Horiz 1:1, 1993.

183. Demling RH: Adult respiratory distress syndrome: Current concepts. New Horiz 1:388, 1993.

184. Edelson JD: Epithelial dysfunction in acute lung injury. New Horiz 3:229, 1995.

185. Lewis JF, Jobe AH: Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis 147:218, 1993.

186. Ralph DD, Robertson HT, Weaver LJ et al: Distribution of ventilation and perfusion during positive end expiratory pressure in the adult respiratory distress syndrome. Am Rev Respir Dis 131:54, 1985.

187. Goode HF, Webster NR: Free radicals and trace element metabolism in sepsis and injury. Br J Intensive Care 2:312, 1992.

188. Katzenstein AA, Bloor CM, Leibow AA: Diffuse alveolar damage: The role of oxygen, shock, and related factors. A review. Am J Pathol 85:210, 1976.

189. Fulmer JD: ACCP-NHLBI National Conference on Oxygen Therapy. Chest 86:234, 1984.

190. Hackney JD, Evans MJ, Spier CE et al: Effect of high concentrations of oxygen on reparative regeneration of damaged alveolar epithelium in mice. Exp Mol Pathol 34:338, 1981.

191. Parker JC, Hernandez LA, Peevy KJ: Mechanics of ventilator-induced lung injury. Crit Care Med 21:131, 1993.

192. Tsuno K, Miura K, Takeya M et al: Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. Am Rev Respir Dis 143:1115, 1991.

193. Hernandez LA, Peevy KJ, Moise AA et al: Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol 66:2364, 1989.

194. Dreyfuss D, Soler P, Basset G et al: High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume and positive end expiratory pressure. Am Rev Respir Dis 137:1159, 1988.

195. Zapol WM: Volutrauma and the intravenous oxygenator in patients with adult respiratory distress syndrome. Anesthesiology 77:847, 1992.

196. Manning HL: Peak airway pressure: Why the fuss? Chest 105:242, 1994.

197. Kacmarek RM: Management of the patient-mechanical ventilator system. In Piersson DJ, Karmarek RM (eds): Foundations of Respiratory Care. New York, Churchill Livingstone, 1992, p 973.

198. Marini JJ, Kelsen SG: Re-targeting ventilatory objectives in adult respiratory distress syndrome: New Treatment prospects-persistent questions. Am Rev Respir Dis 146:2, 1992.

199. Zimmerman JL: Problem-solving approach to adult respiratory distress syndrome. New Horiz 1:578, 1993.

200. Ravizza AG, Caruga D, Cerchiari EL et al: Inverse ratio and conventional ventilation: Comparison of the respiratory effects. Anesthesiology 59:A523, 1983.

201. Munoz J, Guerrero JE, Escalante JL et al: Pressure-controlled ventilation versus controlled mechanical ventilation with decelerating inspiratory flow. Crit Care Med 21:1143, 1993.

202. Marcy TW, Marini JJ: Inverse ratio ventilation in ARDS: Rationale and implementation. Chest 100:494, 1991.

203. Shapiro BA, Peruzzi WT: Intracorporeal respiratory support: A potential supplement to airway pressure therapy? Chest 103:1, 1993.

204. Davis WB, Rennard SI, Bitterman PB et al: Pulmonary oxygen toxicity: Early reversible changes in human alveolar structures induced by hyperoxia. N Engl J Med 309:878, 1983.

205. Hill JD, O'Brien TG, Murray JJ et al: Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock lung syndrome). N Engl J Med 286:629, 1972.

206. Zapol WM, Snider MT, Hill JD et al: Extracorporeal membrane oxygenation in severe acute respiratory failure. JAMA 242:2193, 1979.

207. Gattinoni L, Agnostoni A, Pesenti A et al: Treatment of acute respiratory failure with low frequency positive pressure ventilation and extracorporeal CO_2 removal. Lancet 2:292, 1980.

208. Morris AH, Wallace CJ, Menlove RL et al: Final report: A computerized protocol controlled randomized clinical trial of new therapy that includes LFPPV-ECCO $_2$ R. Am Rev Respir Dis 145:A184, 1992.

209. Moncada A, Higgs A: The L-arginine-nitric oxide pathway. N Engl J Med 329:2002, 1993.

210. Frostell CG, Blomquist H, Hedenstierna G et al: Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. Anesthesiology 78:427, 1993.

211. Oda H, Nogami H, Kusomoto S et al: Long-term exposure to nitric oxide in mice. J Jpn Soc Air Pollut 11:150, 1976.

212. Rossaint R, Falke KJ, Lopez F et al: Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 328:399, 1993.

213. Rossaint R, Slama K, Falke KJ: Therapy of acute pulmonary failure. Dtsch Med Wochenschr 116:1635, 1991.

214. Lessard MR, Guerot E, Lorino H et al: Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. Anesthesiology 80:983, 1994.

215. Marini JJ: Ventilation of the acute respiratory distress syndrome: Looking for Mr. Goodmode. Anesthesiology 80:972, 1994.

216. Tomlinson JR, Miller S Lorch DG et al: A prospective comparison of IMV and T-piece weaning from mechanical ventilation. Chest 96:348, 1989.

217. Stock MC, Schisler JQ, McSweeney TD: The Pa CO_2 rate of rise in anesthetized patients with airway obstruction. J Clin Anesth 1:328, 1989.

218. Shapiro BA: The apnea-Pa CO_2 relationship: Some clinical and medicolegal considerations. J Clin Anesth 1:323, 1989.

219. Shapiro BA, Kacmarek RM, Cane RD et al: Positive pressure ventilation. In Clinical Application of Respiratory Care, 4th ed. Chicago, Mosby-Year Book, 1991, p 299.

220. Schacter EN, Tucker D, Beck GJ: Does intermittent mandatory ventilation accelerate weaning? JAMA 246:1210, 1981.

221. Pardy RI, Leigh DE: Ventilatory muscle training. Respir Care 29:278, 1984.

222. Gilmour I, Burnham M, Craig DB: Closing capacity measurement during general anesthesia. Anesthesiology 45:477, 1976.

223. Askanazi J, Weissman C, Rosenbaum SH et al: Nutrition and the respiratory system. Crit Care Med 10:163, 1982.

224. Lee DKP, Ingbar DH: Aerosol delivery: What's best for your patient? J Respir Dis 10:97, 1989.

225. Braun SR, McKenzie WN, Copeland C et al: A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive disease. Arch Intern Med 149:544, 1989.

226. Jacobs M: Maintenance therapy for obstructive lung disease: How to achieve the best response with the fewest agents. Postgraduate Med 95:87, 93, 99, 1994.

227. Siefkin AD: Perioperative care of the asthmatic patient. In Hanowell LH, Junod FL (eds): Pulmonary Care of the Surgical Patient. Mount Kisco, NY, Futura, 1994, p 1.

228. Corssen G, Gutierrez J, Reves JG et al: Ketamine in the anesthetic management of asthmatic patients. Anesth Analg 51:588, 1972.

229. Sarma VJ: Use of ketamine in acute severe asthma. Acta Anaesthesiol Scand 36:106, 1992.

230. Conti G, DellUtri D, Vilardi V et al: Propofol induces bronchodilation in mechanically ventilated chronic obstructive pulmonary disease (COPD) patients. Acta Anaesthesiol Scand 37:105, 1993.

231. Turner MO, Gafni A, Swan D et al: A review and economic evaluation of bronchodilator delivery methods in hospitalized patients. Arch Intern Med 156:2113, 1996.

232. Mansel JK, Stogner SW, Peterini MF et al: Mechanical ventilation in patients with acute severe asthma. Am J Med 89:42, 1990.

233. Williams TJ, Tuxen DV, Scheinkestel CD et al: Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. Am Rev Respir Dis 146:607, 1992.

234. Tuxen DV, Williams TJ, Scheinkestel CD et al: Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with acute severe asthma. Am Rev Respir Dis 146:1136, 1992.

235. Martin RT, Lewis SW, Albert FK: The prognosis of patients with chronic obstructive pulmonary disease after hospitalization for acute respiratory failure. Chest 82:310, 1982.

236. Siefkin AD: Optimal pharmacologic treatment of the critically ill patient with obstructive airways disease. Am J Med 100:54S, 1996.

237. Blosser SA, Maxwell SL, Reeves-Hoche MK et al: Is an anticholinergic agent superior to a beta 2-agonist in improving dyspnea and exercise limitation in COPD? Chest 108:730, 1995.

238. Tashkin DP, Bleecker E, Braun S, et al: Results of a multicenter study of nebulized inhalant bronchodilator solutions. Am J Med 100:62S, 1996.

239. Levin DC, Little KS, Laughlin KR et al: Addition of anticholinergic solution prolongs bronchodilator effect of beta 2 agonists in patients with chronic obstructive pulmonary disease. Am J Med 100:40S, 1996.

240. COMBIVENT Inhalation Aerosol Study Group: In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone: An 85-day multicenter trial. Chest 105:1411, 1994.

241. Friedman M: A multicenter study of nebulized bronchodilator solutions in chronic obstructive pulmonary disease. Am J Med 100:30S, 1996.

242. Fernandez A, Munoz J, de la Calle B et al: Comparison of one versus two bronchodilators in ventilated COPD patients. Intensive Care Med 20:199, 1994.

243. Rubin BK, Albers GM: Use of anticholinergic brochodilation in children. Am J Med 100:49S, 1996.

244. Chapman KR: An international perspective on anticholinergic therapy. Am J Med 100:2S, 1996.

245. Seider N, Abinader EG, Oliven A: Cardiac arrhythmias after inhaled bronchodilators in patients with COPD and ischemic heart disease. Chest 104:1070, 1993.

246. Gayan-Ramirez G, Decramer M: Inotropic effects of theophylline on foreshortened canine diaphragm. Am J Respir Crit Care Med 149:920, 1994.

247. Mulloy E, McNicholas WT: Theophylline improves gas exchange during rest, exercise, and sleep in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 148:1030, 1993.

248. McKay SE, Howie CA, Thomson AH et al: Value of theophylline treatment in patients handicapped by chronic obstructive lung disease. Thorax 48:227, 1993.

249. Yang B, Schlosser RJ, McCaffrey TV: Dual signal transduction mechanisms modulate ciliary beat frequency in upper airway epithelium. Am J Physiol 270:L745, 1996.

250. Tamaoki J, Chiyotani A, Sakai N et al: Stimulation of ciliary motility mediated by atypical beta-adrenoceptor in canine bronchial epithelium. Life Sci 53:1509, 1993.

251. Albert RK, Martin TR, Lewis SK: Controlled clinical trials of methylprenisolone in patients with chronic bronchitis and acute respiratory insufficiency. Ann Intern Med 92:753, 1980.

252. Van Schayck CP, Dompeling E, Rutten MP et al: The influence of an inhaled steroid on quality of life in patients with asthma or COPD. Chest 107:1199, 1995.

Chapter 73 - Pediatric and Neonatal Intensive Care

W. Daniel Kovarik
P. Pearl O'Rourke

PARENT/FAMILY SUPPORT

/das/book/view/29494766/875/796.html

INTRODUCTION

The major objective of pediatric intensive care is to provide maximum surveillance and support of vital systems in infants and children with acute, reversible, life-threatening disease. In contrast to adult patients, few children admitted to a pediatric intensive care unit (PICU) suffer from chronic or degenerative organ system disorders. Most of these children have a potentially reversible life-threatening illness or injury that, if successfully treated, will restore the child to a normal, productive life. [1]

Although the principles of intensive care for children are similar to those for adult intensive care, the age spectrum from infancy through adolescence requires that the intensive care staff have special expertise in developmental physiology and psychology. The pediatric intensive care team must be familiar with fetal and neonatal cardiopulmonary physiology as well as with the physiologic and psychological aspects of growth and development to adulthood. All critically ill children, regardless of diagnosis or subspecialty category, should be placed in units dedicated exclusively to children, whenever possible. Specific guidelines describing minimum criteria for PICUs and services have been published. [2] Beginning in 1985, the American Board of Pediatrics officially recognized the subspecialty of pediatric critical care medicine.

When matched for severity of illness, there is decreased mortality in pediatric patients cared for in PICUs as compared with those cared for by physicians without pediatric intensive care training in nontertiary care facilities. [3] Hospitals without sufficient numbers of pediatric patients to provide specialized facilities for pediatric intensive care should consider transferring critically ill children to a regional PICU. It is the obligation of regional PICUs to develop

transport systems that will facilitate the safe and timely transport of critically ill children to the referral center. In addition, the regional center should provide medical education in emergency and critical care pediatrics to primary care and referring physicians and nurses.

ORGANIZATION OF THE PEDIATRIC INTENSIVE CARE UNIT

The PICU should be represented in the hospital by a multidisciplinary committee of the professional staff, including the medical and nursing directors, hospital administrators, and representatives from pediatric medicine, anesthesia, surgery, and the pediatric subspecialties. This committee should be responsible for policy and procedures pertaining to the PICU and should make recommendations regarding personnel staffing, equipment purchases, and structural and design changes within the unit.

The PICU staff should include a medical director whose special expertise and training in pediatric critical care qualify that person to oversee the quality of care provided to all patients in the unit. Additional responsibilities include patient triage, implementation of policy and procedures, in-service education, and coordination of multiple consultants. Physician coverage should be full-time geographic at the resident, fellow, or attending staff level. The medical director also functions as arbiter and patient advocate.

The nursing director should have special skills in pediatric intensive care, education, and personnel management. The medical director and nursing director must collaborate as a team. The registered nursing staff must be trained in all aspects of pediatric critical care and resuscitation, and staffing needs to be flexible enough to provide one-on-one coverage when necessary. A multidisciplinary in-service program for continuing education and orientation is essential.

Other team members should include respiratory therapists, physical therapists, nutritionists, social workers, psychiatrists, and psychologists for both patients and staff, as well as laboratory technologists. All support personnel are essential to the team effort and should be included in rounds and team meetings whenever possible.

The physical facility for the PICU should be self-contained and spacious enough to provide adequate work area around each bed space and enough storage to keep life-support equipment within reach. Because the PICU staff practically live in the environment, space for reading, meeting, sleeping, and showering should be available. Parent and visitor space is essential to permit parents to sleep overnight. Facilities should be designed to encourage constant parental participation, because parents are such an essential part of the therapeutic plan of any critically ill child.

Each bed space should be standardized so that the level of support and monitoring can be escalated. Distance between bed spaces should be adequate to ensure privacy and to minimize nosocomial infection. Complete precaution or isolation rooms should be available within the confines of the unit.

Along with life-support equipment, devices for diversion and entertainment should be available for children who are conscious. Children's television programs can often replace heavy sedation when patient cooperation is essential. On the other hand, there is no substitute for parental and nursing involvement at the bedside in preventing accidental self-extubations or other inadvertent, potentially self-destructive behavior. Because of the need for close personal observation, centrally monitored nursing stations have little place in the PICU.

CARDIOVASCULAR SYSTEM

Circulation

Circulatory well-being in infants and children is dependent on the progression of structural and functional maturation (Chs. 58 and 59) . An understanding of this agedependent process is essential for the diagnosis and treatment of circulatory failure in infants and children.

Structural and Functional Development

The external shape of the heart is complete by 6 weeks' gestation, but an increase in myofibrillar density and maturation continues at least through the first year of postnatal life. [4] During this time, myocytes are engaged in rapid protein synthesis and rapid cell growth, which require a high intracellular concentration of nuclei, mitochondria, and endoplasmic reticulum. This greater number of nonelastic and noncontractile elements makes the neonatal myocardium stiffer (less compliant) and less efficiently contractile than the adult. [5] In the fetus and newborn infant, because of this decreased ventricular compliance, even small changes in end-diastolic volume cause large changes in end-diastolic pressure. In addition, augmentation of stroke volume by the Frank-Starling mechanism is less effective in the newborn; this necessitates a greater, but not exclusive, dependence on heart rate for maintenance of cardiac output. [6] [7]

Development of the Circulation

Adult and fetal circulation differ in many ways. Fetal circulation is distinguished by (1) the placenta as the organ of respiration, (2) high pulmonary vascular resistance, (3) low systemic vascular resistance, and (4) the fact that the fetal ventricles pump in parallel with a dominant right ventricle. [8] In addition, the fetus exists in a remarkably hypoxic environment compensated for by a relatively high cardiac output and a hemoglobin with a high affinity for oxygen. [9] The fetus compensates for the placement of the placenta in the systemic circulation by several shunts: the ductus arteriosus, ductus venosus, and the foramen ovale. When the fetus becomes an extrauterine being, the following important changes occur to bring the circulation to an adult form:

1. With the first breath, the increase in oxygen saturation, as well as other potential neurohumoral mediators and nitric oxide (NO), [10] relaxes the pulmonary vasospasm that existed *in utero.* Pulmonary blood flow then increases. [11]
2. The placenta separates from the uterine wall, the placental blood vessels constrict, and systemic vascular resistance

(SVR) and left ventricular afterload increase. As the pulmonary vascular resistance (PVR) decreases and SVR increases, left atrial pressures rise above the right atrium, and the "flap valve" of the foramen ovale [12] functionally closes.
3. The ductus arteriosus closes as the arterial oxygen tension (Pa O_2) increases. Mediators such as the prostanoids and kinins, as well as changes in autonomic vascular tone, promote closure of the ductus arteriosus. The ductus is usually functionally closed during the first 24 to 96 hours of life, and anatomic obliteration follows during the next several weeks. [13] [14]
4. The ductus venosus passively closes with the removal of the placental circulation and readjustment of the portal pressure relative to inferior vena cava pressure. [15]
5. There is a further gradual decline in PVR because of a structural remodeling of the muscular layer of pulmonary blood vessels. During fetal life, the central pulmonary vascular bed has a relatively thick muscle layer. After birth, this muscle coat thins and extends to the periphery of the lung, a process that takes months and years to complete. [16]

Development of Autonomic Control of the Circulation

There is still considerable speculation regarding the functional integrity of autonomic circulatory control during fetal and perinatal development. It has been shown in several species that the fetal heart has a reduced store of catecholamines and an increased sensitivity to exogenously administered norepinephrine. [5] The sympathetic nerves first develop in the atria and grow into the ventricles toward the apex at a variable and species-specific rate. [17]

In fetal lambs, resting alpha-adrenergic tone begins at approximately 0.6 gestation and is nearly complete at birth, but resting beta-adrenergic control does not begin until 0.8 gestation and is incompletely developed at birth. [18] Adrenergic innervation of the human myocardium may be complete between 18 and 28 weeks' gestation. However, low cardiac stores of norepinephrine, as well as a lack of fluorescence of sympathetic nerves, have been demonstrated in humans after birth. Adrenergic responses are apparently present but diminished in the newborn human. [19]

Development of cholinergic (vagal) control of the heart is also variable and is species specific. In human newborn infants, the cholinergic system appears completely developed at birth, and the heart is sensitive to vagal stimulation. [20] This provides for a relative vagal predominance of neural cardiovascular control, making bradycardia a more likely response to any increase in autonomic tone.

The chemoreceptor and baroreceptor reflexes have important developmental implications in the infant and child; the baroreceptor reflex is present but is incompletely developed at term in the human. In preterm infants, postural changes elicit no change in heart rate, but there is an increase in peripheral vascular resistance, illustrating an incomplete and attenuated baroreceptor response. [21] The chemoreceptor response seems to be well developed *in utero.* Fetal bradycardia in response to hypoxia is thought to be mediated through the chemoreceptors and may be similar to the oxygen-conserving mechanisms of diving animals. [22]

Myocardial Metabolism

Adult cardiac muscle is almost exclusively dependent on oxygen for its metabolism, with an efficiency of oxygen extraction greater than in other organs. Anaerobic metabolism is nearly nonexistent in adult cardiac muscle, so that the heart is extremely sensitive to hypoxia or ischemia. Either of these conditions, however brief, alters the energy supply and affects the mechanical response of the adult heart.

The metabolic characteristics of the fetal myocardium are different. Relative hypoxia is normal *in utero,* and the infant's heart has been shown to tolerate hypoxia better than the adult's. [23] [24] This difference may be partly due to high concentrations of glycogen in fetal myocardial tissue and the finding that the hypoxic fetal myocardium produces lactate, suggesting anaerobic metabolism. [25] In addition, fetal hemoglobin is more efficient than adult hemoglobin in hypoxic environments. These mechanisms make the fetal/newborn heart relatively resistant to the destructive effects of hypoxia, provided oxygenation and perfusion are reestablished within a reasonable period of time.

Myocardial demands change significantly in the first month of life. Oxygen consumption increases precipitously after birth, presumably owing to thermogenesis. The full-term infant's oxygen consumption in a neutral thermal setting is approximately 5 mL/kg/min and increases to 7 mL/kg/min and 8 mL/kg/min at 10 days and 4 weeks, respectively. Over the ensuing months, oxygen consumption and cardiac output gradually decline. [26] [27] [28]

Age-Related Circulatory Variables

Common Cardiovascular Disease States

Congenital Heart Disease

Although a complete discussion of congenital heart disease is not possible here, various abnormalities that produce significant alterations in oxygenation, perfusion, and myocardial function after birth are worthy of attention (Table 73-1 (Table Not Available) ; Ch. 50). The more common lesions include obstruction to systemic outflow (i.e., congenital aortic stenosis and coarctation of the aorta) and lesions that alter the adequacy of pulmonary blood flow (i.e., tricuspid or pulmonary atresia or tetralogy of Fallot). Many of these lesions are associated with other abnormalities that facilitate mixing or diversion of blood flow from one circuit to the other, in order to permit even marginal survival. Patent fetal conduits such as the ductus arteriosus or foramen ovale may exist in isolation or in association with other "shunt" lesions, and, in some circumstances, rather than helping survival, they may become a source of cardiac decompensation. [6]

Newborns with significant congenital heart disease commonly present with either cyanosis or congestive heart failure (CHF). It is important to recognize that the degree of dysfunction changes during the first 2 to 3 months of life because the PVR decreases to adult levels. [29] As this resistance falls, left-to-right shunts can increase, and the symptoms of CHF become more apparent. In the newborn, the usual signs and symptoms of CHF include poor feeding, irritability,

TABLE 73-1 -- Age-Related Circulatory Variables [a]

(Not Available)

From Crone [383]

[a] Chs. 50 , 58 , and 59

TABLE 73-2 -- Common Congenital Heart Lesions in the Newborn

Cyanotic congenital heart lesions
Tetralogy of Fallot
Transposition of the great arteries
Hypoplastic left heart syndrome
Pulmonary atresia with intact ventricular septum
Single ventricle
Total anomalous pulmonary venous return
Tricuspid atresia
Congenital heart lesions presenting with congestive heart failure
Ventricular septal defect
Patent ductus arteriosus
Hypoplastic left heart syndrome
Critical aortic stenosis
Coarctation of the aorta

sweating, tachycardia, tachypnea, decreased peripheral pulses, poor cutaneous perfusion, and hepatomegaly. Cyanosis may indicate structural cardiac disease; however, respiratory disease, neurologic disease, PVR (persistent pulmonary hypertension), and methemoglobinemia must also be considered [6] (Table 73-2) .

The diagnosis of congenital heart disease can be made on the basis of the physical examination, the electrocardiogram (ECG), chest radiograph, and the echocardiogram. Cardiac catheterization may be performed after initial stabilization and prior to either definitive or palliative cardiac surgery.

The initial medical treatment of congenital heart disease is aimed at relieving CHF, improving systemic perfusion, and maintaining pulmonary blood flow. In some situations (i.e., hypoplastic left heart syndrome, aortic stenosis, or atresia), the patency of the ductus arteriosus may be crucial to provide perfusion to the body. In these cases, prostaglandin E_1 (PGE_1) infusion has proved useful in maintaining the patency of the ductus arteriosus until definitive surgical correction can be performed [30] [31] (see the discussion of pharmacology later in this chapter).

Acute Circulatory Failure in Children

Acute circulatory failure is defined as any clinical condition in which systemic blood flow is inadequate to meet the metabolic demands of the body. [32] The clinical syndrome of shock includes the signs and symptoms of both an inadequate circulation and an attempt to compensate for circulatory failure. The child has a remarkable ability to compensate for an inadequate circulation, with both endogenous catecholamine release and increased peripheral autonomic tone. The signs of compensation are often the earliest clinical clues that a child is in shock. Anxiety or irritability, cool, pale extremities, and unexplained tachycardia are usually the earliest signs. Tachypnea, moderate metabolic acidosis, oliguria, and somnolence are signs of inadequate tissue perfusion, whereas obtundation, periodic breathing, and apnea are signs of impending cardiopulmonary arrest. Arterial blood pressure is not usually a good indicator of the adequacy of perfusion in children. The child's ability to constrict the peripheral circulation is so efficient that central blood pressure may be normal despite impending circulatory collapse. Circulatory failure can result from pump failure or from intravascular hypovolemia. Intravascular hypovolemia is a consequence of either true volume loss (blood, plasma, water) or an alteration in peripheral vascular resistance (Table 73-3) (Table Not Available) .

In children, the most common cause of circulatory failure is hypovolemia from excessive volume loss. This condition produces decreased ventricular preload that reduces stroke volume and cardiac output. The causes of acute hypovolemia are (1) blood loss (trauma, gastrointestinal bleeding), (2) plasma loss (capillary leak syndrome associated with sepsis, hypoproteinemia, burns, peritonitis), and (3) water loss (most commonly vomiting and diarrhea, glycosuric diuresis in diabetic ketoacidosis). Patients with acute hypo-volemia usually have extreme peripheral vasoconstriction with cool, poorly perfused extremities. Peripheral pulses may be thready, and the capillary refill time may be prolonged.

Intravascular hypovolemia can also result from decreased peripheral vascular resistance associated with anaphylaxis, septic or endotoxic shock, and the ingestion of

vasodilating drugs. In these cases, peripheral perfusion is usually maintained with warm extremities. [32] [33]

Cardiogenic shock is a relatively uncommon cause of circulatory failure in the pediatric patient when compared with the incidence in adults. In the neonate, the usual cause is congenital heart disease with outflow obstruction or systemic-to-pulmonary shunting, although viral and bacterial sepsis also is a common cause. In any child, extrinsic inflow or outflow obstruction associated with tension pneumothorax, hemopericardium, or pneumopericardium, as well as pericardial effusion, must also be considered. Last, primary pump failure associated with viral or infiltrative cardiomyopathies,

TABLE 73-3 -- Circulatory Failure: Hypotension

(Not Available)

Modified from Crone [32]

collagen vascular or Kawasaki disease, [31] [32] metabolic derangements such as hypoglycemia, sepsis, or uremia can produce circulatory failure that is refractory to treatment. [34] [35] [36] [37] Arrhythmias such as paroxysmal atrial tachycardia or atrioventricular block can also precipitate circulatory failure in children.

Treatment

The cause and functional physiologic features of shock can frequently be identified from a history and physical examination. Specific therapy may differ in various clinical conditions, but immediate therapy should include assessment of the airway, administration of oxygen, establishment of adequate ventilation, and obtaining vascular access. A peripheral venous site may be cannulated percutaneously, but impaired perfusion may reduce the possibility of success. The intraosseous (IO) route for fluid and drug bolus or infusion is now routine in emergency settings. [38] A stiff, short-beveled trocar needle is placed into the proximal third of the tibia (Fig. 73-1) or the distal femur. Specific needles are manufactured for this purpose, but 18-gauge spinal needles and bone marrow aspirate needles also function well. Care must be given to avoid the epiphysis. When the IO needle is properly positioned, its shaft is anchored in the cortex, with the needle tip in the marrow cavity. The cortex supports the needle solidly, blood and bone spicules can usually be aspirated, and the infusion of fluids is easy without distorting the soft tissues of the leg. The IO line is then used to obtain blood samples for laboratory analysis, to deliver fluids, and to administer all resuscitation medications traditionally given intravenously. The IO line provides rapid, safe, emergent vascular access. Standard intravenous access should be achieved as soon as possible because IO placement degrades with time. Percutaneous cannulation of the jugular [39] and subclavian veins carries the risk of carotid puncture, hemothorax, pneumothorax, and perforation of the superior vena cava or right atrium. The smaller size of the child increases the risks [40] of any vessel cannulation.

Specific therapy for circulatory failure is directed toward increasing cardiac output and normalizing peripheral organ perfusion. Because the determinants of cardiac output are

Figure 73-1 Intraosseous cannulation technique.

heart rate and stroke volume, an increase in either may be beneficial. If tachycardia does not already exist, heart rate may be increased either by vagolysis or by cardiac beta-stimulation (positive chronotropy). The principal vagolytic agent is atropine (0.02 mg/kg), and the most commonly used positive chronotropic agents are isoproterenol or epinephrine. In children, a 30 to 50 percent increase in heart rate over control levels is well tolerated and usually increases cardiac output substantially. [7] [8] Stroke volume is increased by (1) increasing preload, (2) decreasing afterload, or (3) improving contractility.

Because most children in shock are hypovolemic, preload augmentation is the usual initial therapy. Once vascular access is obtained, the blood volume should be augmented with an infusion of isotonic crystalloid or colloid solution. Hypertonic resuscitation fluids have been utilized, but there is inadequate information available to justify their use. The amount and rate of infusion of an isotonic solution depend on the clinical condition. A good starting point is 10 mL/kg of estimated body weight rapidly infused over a few minutes. The bolus should be repeated until improvement in perfusion is observed. If no improvement has occurred by the fourth bolus, ongoing losses or a different cause of shock should be suspected, and further diagnoses should be pursued. [32] [33] Intravascular volume can be assessed by physical examination, chest radiography, echocardiography, or placement of a central venous pressure catheter.

Echocardiography has the advantage of being rapid and noninvasive, but it requires the immediate availability of sophisticated equipment and personnel skilled in interpreting pediatric echocardiograms. In addition, structural cardiac abnormalities can be ruled out, and myocardial function may be qualitatively assessed in real time. [41] Most infants and children who need ongoing assessment and cardiovascular support require a central venous catheter. Although a central venous pressure (CVP) value of 5 mm Hg is a reasonable estimate for adequate intravascular volume, there is no single optimal CVP; only with careful incremental infusions of volume (10 mL/kg per bolus) can the effect on cardiac output be assessed. Several extracardiac factors, including lung compliance, the level of positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), and increasing abdominal pressure, affect CVP or right ventricular filling pressure; thus, each patient's optimal CVP may differ considerably. Once a reasonable CVP has been obtained, if there is no improvement in blood pressure, cutaneous perfusion, or urine output, cardiogenic causes of circulatory failure must be considered. Arterial blood gases, hematocrit, serum electrolytes, glucose, and calcium levels should be determined. Correction of acidosis, hypoxemia, or metabolic derangement is essential. Blood and other appropriate sites must be cultured, and broad-spectrum parenteral antibiotic coverage must be begun, if sepsis is a possibility.

Urine output can be an important indicator of the adequacy of the circulation. A urine output of greater than 1 mL/kg/h usually indicates an adequate renal blood flow and cardiac output. Patients with an output less than 0.5 mL/kg/h should be evaluated for circulatory failure, renal failure, or obstruction to urine flow.

Myocardial contractility can be improved by correcting existing metabolic derangements (hypoxia, acidosis, hypoglycemia) and by administering positive inotropic agents

such as sympathomimetic amines (beta-agonists), xanthines, and cardiac glycosides.

In clinical practice, the pulmonary artery catheter is used less frequently in children than in adult patients. In contrast to the adult with preexisting coronary artery disease, most conditions causing circulatory failure in children are associated with biventricular failure. In these cases, left ventricular filling pressures are reflected by the right atrial pressure, and the CVP is an adequate indicator of left- and right-sided filling pressures. The pulmonary artery catheter in children is usually used for continuous measurement of pulmonary artery pressure or for intermittent measurement of cardiac output by thermodilution technique. [42] [43] [44]

Pulmonary artery catheters are available in two sizes: the "adult" 7 French and the "pediatric" 5 French. The CVP port is 30 cm and 15 cm proximal to the tip in the 7- and 5-French catheters, respectively. Children who weigh less than 8 to 10 kg are too small for even the 5-French catheter.

Afterload reduction may be indicated specifically when "pump failure" coexists with an elevated SVR. [45] Under these circumstances, there may be an advantage to reducing afterload and ventricular work in order for the ventricle to pump more efficiently with an increase in stroke volume. Afterload reduction may be effected with a direct vasodilator such as sodium nitroprusside, a beta-agonist (isoproterenol), or an alpha-antagonist (phentolamine or tolazoline). Afterload reduction is frequently unpredictable, and the associated hypotension may reduce coronary perfusion to such a degree that it reduces cardiac efficiency rather than improves it. Vasodilators should be used with extreme caution, and vasoconstricting agents (phenylephrine or norepinephrine) should be available for immediate use.

Pharmacologic vasoconstriction is used when hypotension results from an inappropriately low SVR such as in anaphylaxis and warm septic shock. [32] The major complication of this therapy is that vasoconstricting agents produce an increase in the myocardial work and myocardial oxygen consumption, with the result that any

primary myocardial decompensation may be worsened.

Cardiovascular Pharmacology in Children

Pharmacologic support of the circulation includes positive inotropic and chronotropic agents, vasoconstrictors and vasodilators (afterload reduction), and antiarrhythmics (Chs. 14 and 59). Most drugs currently used have not been adequately studied in children, so that dosage recommendations and anticipated effects are extrapolated from studies in adults, as well as from anecdotal clinical experience in children.

Positive inotropic drugs are often used in children, to augment cardiac output in a variety of situations associated with circulatory failure. Most inotropic agents also affect heart rate and vasomotor tone. Tachycardia is often a deleterious side effect in the adult with limited myocardial oxygen reserve, whereas in the child, an increase in heart rate is usually well tolerated and is often beneficial. [32] Particularly in the neonate, whose ventricles are relatively noncompliant and in whom stroke volume is less variable, [6] tachycardia is an important component of cardiac output augmentation. Because all drugs that increase heart rate or contractility also increase myocardial oxygen consumption, it is imperative to ensure adequate arterial oxygenation and adequate supply of metabolic substrate during their administration. In addition, it is important to note that the cardiovascular response to the sympathomimetic amines is attenuated in the presence of acidosis and possibly sepsis; higher infusion rates of these drugs are required and need readjustment as acidosis improves.

Commonly used inotropes are listed in Table 73-4 . Brief comments regarding their use in pediatric intensive care are provided.

Epinephrine

Epinephrine is primarily used for children with cardiac arrest or children with profound myocardial depression and hypotension. Epinephrine is preferably used for initial stabilization, with the hope of switching to another inotrope with less peripheral vasoconstriction as soon as possible. [46] [47]

Dopamine

Dopamine is the most commonly infused inotrope in pediatrics. The physiologic effects are very dose dependent, with activity in low doses, beta activity in intermediate doses, and some alpha activity in higher doses. Specific doses can be patient dependent, but as a rule, young children require higher doses than an adult to produce the same effect. [48] In one study, an infusion of 15 mug/kg/min was needed to increase the cardiac output higher than control in a group of infants after cardiac surgery. [49] This finding may reflect the decreased releasable stores of norepinephrine in the myocardium of immature ventricles. [50]

Isoproterenol

Isoproterenol is a pure beta-agonist medication with very strong chronotropic effects that are often better tolerated in the child than in the adult. Even though a strong inotrope, it causes vasodilation, which may be problematic for the patient who is volume depleted.

Dobutamine

Dobutamine was designed to provide positive inotropy with afterload reduction, without the chronotropy of isoproterenol. However, clinical experience with this drug has demonstrated an associated tachycardia. [51] [52]

Norepinephrine

Norepinephrine, an alpha- and beta-agonist drug, is rarely used in the child except in situations of near-normal cardiac function and extreme peripheral vasodilation. Examples are warm septic shock, anaphylaxis, and sympathetic blocks associated with regional anesthesia. [46] [47]

TABLE 73-4 -- Vasoactive and Inotropic Agents in Pediatrics

DRUG	EFFECT		DOSE[a]	INOTROPY	CHRONOTROPY	VASODILATION	VASOCONSTRICTION
Epinephrine (Adrenalin)	alpha, beta		0.05-2.0	++	++		++
Isoproterenol (Isuprel)	beta (1, 2)		0.05-2.0	++	++	+	
Dopamine (Intropin)	delta		1-3			+Renal splanchnic	
	beta > alpha		5-15	+	+		+/-
	beta, alpha		>15	+	+		+
Amrinone		Bolus	3-4.5 mg/kg divided	+		+	
		Infusion					
		neonates	3-5	+		+	
		infants	10	+		+	
		adults	5-10	+		+	
Milrinone		Bolus	50 mug/kg over 10 min	+		+	
		Infusion	0.375-0.75 mug/kg/min				
Norepinephrine	alpha >> beta		0.05-1.0	sl+	+		++
Nitroprusside			0.5-10			++ Art > venous	
Nitroglycerin			1-20			++	

[a] All infusions are mug/kg/min.

Amrinone and Milrinone

Amrinone and milrinone are noncatecholamine, nonglycoside inotropes and vasodilators. As phosphodiesterase III inhibitors, they increase cyclic adenosine monophosphate (cAMP). These drugs are frequently used for treatment of CHF and postoperative low cardiac output states. [53] [54] [55] In adults, a serum amrinone level of 4 mug/mL has been correlated with a 50 percent increase in cardiac index. [56] In adults, these serum levels are attained with a 0.75-mg/kg loading dose, and they are maintained with an infusion of 5 to 10 mug/kg/min. In infants and neonates, a higher loading dose is required to reach the same therapeutic levels. Lawless et al [57] suggested that infants receive a loading dose of 3 to 4.5 mg/kg in divided doses followed by an infusion of 10 mug/kg/min. Neonates should receive the same bolus, with an infusion of 3 to 5 mug/kg/min. Milrinone is administered as a loading dose of 50 mug/kg over 10 minutes and a maintenance infusion of 0.375 to 0.750

mug/kg/min. This recommendation is extrapolated from adult data, and initial studies suggest the need for a higher loading dose and lower infusion rate in neonates. [58] Medication risks include hypotension, especially during loading doses, and a dose-related thrombocytopenia that may occur with amrinone.

Digitalis

Digitalis is an excellent medication for the long-term treatment of myocardial failure in children. The long half-life and the unpredictability of digitalis toxicity in patients who demonstrate changing levels of serum potassium, calcium, and pH make this drug inappropriate in the unstable, acutely ill patient. More rapid-acting titratable inotropes should be used. [59]

Calcium

Calcium is an often overlooked inotrope. When serum ionized calcium levels are low, the administration of calcium produces a positive inotropic effect; if ionized calcium levels are normal, however, the inotropic effect is much less marked. Low ionized calcium levels are most commonly documented in patients with DiGeorge syndrome or septic shock, after massive volume replacement with citrated blood, and in neonates with relatively unstable calcium metabolism. [60] [61] Calcium can also have a number of effects on the conduction system. In children with a normal ionized calcium level, the rapid administration of calcium through a central venous catheter can cause severe bradycardia or asystole. This effect can be exaggerated in the presence of hypokalemia and digitalis. There have also been reports of calcium precipitating malignant ventricular arrhythmias in adult patients with coronary artery disease; the relative absence of coronary artery disease in children minimizes this complication in the pediatric patient. The vasomotor effects of calcium are somewhat controversial, but most reports show an increase in SVR. Increased PVR has also been documented. [62]

Bicarbonate Therapy

Acidosis profoundly depresses myocardial function and is a sensitive indicator of inadequate tissue perfusion. Initial correction with 1 to 2 mEq/kg of sodium bicarbonate is indicated for a pH of less than 7.20 after establishment of adequate ventilation (P_{CO_2} < 40 mm Hg). The circulatory system is refractory to sympathomimetic amines in the presence of severe acidosis; thus, inotropic agents, even in massive doses, are rendered ineffective unless acidosis is corrected. After initial correction of the pH, the persistence or reappearance of metabolic acidosis suggests a return to an underperfused state and is cause for immediate alarm and therapeutic action. Sodium bicarbonate therapy can only be used as a stopgap measure to render the circulation amenable to pharmacologic support. Repeat infusions of sodium bicarbonate rapidly lead to hypernatremia and hyperosmolarity and cannot neutralize the ongoing lactic acidosis associated with inadequate tissue perfusion.

Vasodilators

Vasodilators are used in children for four main purposes: (1) to control systemic hypertension, (2) to increase cardiac output by decreasing afterload, (3) to control pulmonary hypertension, and (4) to attempt to control cardiac shunting. The use of vasodilators for control of systemic hypertension and for increasing cardiac output in children with CHF has been quite successful. By contrast, the treatment of pulmonary hypertension and cardiac shunting with vasodilators has shown mixed results. The primary problem is that most available vasodilators work on the systemic circulation as well as on the pulmonary circulation. Systemic hypotension and increases in left-to-right shunting have resulted from attempts to treat pulmonary hypertension with vasodilators. The identification of NO as a selective pulmonary vasodilator shows considerable promise in the treatment of pulmonary hypertension.

Sodium Nitroprusside.

This vasodilator relaxes arteriolar and venous smooth muscle, producing a decrease in the afterload and possibly a decrease in the preload. The half-life is only minutes; as such, it is very safe to titrate infusions of this drug to a desired effect. Most common indications for its use are to control severe systemic hypertension, to precipitate an intraoperative episode of controlled hypotension in an attempt to decrease blood loss, and to increase cardiac output in children with low output syndromes [63] (myocarditis, postcardiac surgery). Sodium nitroprusside can be used for days without problems. Potential difficulties include cyanide and thiocyanate poisoning. Cyanate is an intermediate metabolite of nitroprusside; thiocyanate is the final metabolite and is slowly cleared via renal excretion. Thiocyanate toxicity is more common than cyanate toxicity. Thiocyanate levels of 10 mg/dL are associated with weakness, hypoxia, nausea, muscle spasms, and disorientation. Treatment involves discontinuing the administration of nitroprusside. [46] [64]

Nitroglycerin.

Intravenous nitroglycerin is similar in effect to sodium nitroprusside, except nitroglycerin has a relatively

stronger vasodilating effect on the venous capacitance system than on the arterial bed. [65]

Hydralazine.

This vasodilator is routinely used to control systemic hypertension. It produces vascular smooth muscle relaxation in the arterial system much more than in the venous system. There have also been some preliminary reports of hydralazine therapy for treatment of pulmonary hypertension. [66] [67] Certain unpleasant effects of hydralazine therapy (i.e., headache, nausea, dizziness, sweating, tremors) have been described. The most important acute side effect is the cardiovascular effect of reflex tachycardia, with possible increased cardiac output: a beta-antagonist (i.e., propranolol) is often used as adjunctive therapy to counteract this effect.

Tolazoline and Phentolamine.

These competitive alpha-adrenergic blockers have been used in the treatment of pulmonary hypertension. The success of this therapy is not uniform, and these drugs are now rarely used. [68] Serious side effects of these drugs include tachycardia, ventricular arrhythmias, hypotension, and tissue edema.

Prostaglandin E_1 .

Although classified as a vasodilator, PGE_1 is a unique drug that has greatly improved the care of neonates with heart disease. PGE_1 acts directly on vascular smooth muscle; infused at a rate of 0.1 mug/kg/min, it maintains patency of the ductus arteriosus or even reopens the ductus in neonates. This response is dependent on such factors as age and the state of contraction of the ductus. Side effects of apnea, hypotension from systemic vasodilation, or central nervous system (CNS) excitability should be anticipated. This drug is indispensable in patients with ductus-dependent cardiac lesions such as interrupted aortic arch, critical aortic stenosis, or hypoplastic left heart syndrome, in which systemic flow is supplied through the ductus. [30] It is equally indispensable in pulmonary atresia and critical pulmonic stenosis, in which pulmonary blood flow is supplied by the ductus. [31] It has also been used to treat pulmonary hypertension with varying degrees of success.

Nitric Oxide.

With the discovery of NO as one of the endothelium-derived relaxation factors, it appears that we now have a drug that is capable of selectively vasodilating the pulmonary vasculature. [69] NO can be administered by inhalation to patients with pulmonary hypertension, in whom it reduces PVR. [70] It diffuses across the alveoli, dilates the pulmonary vascular bed, and is inactivated by binding with hemoglobin prior to delivery at the systemic vasculature. Extensive clinical testing of inhaled NO is occurring in PICU and neonatal ICU. NO does not appear to cause systemic vasodilation or clinically significant methemoglobinemia in the doses administered (5-80 ppm). [71] Initial studies have shown it to be effective in reducing PVR and in improving outcome in children with reactive pulmonary hypertension. [72]

Arrhythmias

Arrhythmias are less common in children than in adults, most likely reflecting the relative lack of atherosclerosis in the pediatric age group (Chs. 32 and 50). However, a few categories of arrhythmias should be considered.

Perhaps the most common pediatric arrhythmia is sinus bradycardia caused by hypoxemia. Hence, the primary antiarrhythmic agent of childhood is oxygen. Heart block is seen in children after surgical repair of congenital heart disease. If the block persists for more than 2 weeks postoperatively, a pacemaker is generally indicated. [73] Another cause of heart block is connective tissue disease; in fact, infants born to mothers with systemic lupus erythematosus have been diagnosed with heart block *in utero.*[74]

Sick sinus syndrome is usually associated with surgery, myo-carditis, or myocardiopathy. [75] Prolonged QT syndrome, an abnormality of ventricular repolarization, is a familial disorder that can result in sudden cardiac death. Other than sinus bradycardia, the most common arrhythmia is supraventricular tachycardia (SVT), a narrow QRS complex with a regular RR interval. In infants and neonates, the rate can be 200 to 300 beats/min; in the older child, 150 to 250 beats/min. SVT causes a slow myocardial decompensation. The older patient with SVT will frequently complain of palpitations or a racing heart rate and seek medical care long before CHF ensues. By contrast, the younger child is unable to verbalize the sensation of palpitations and will most likely present with CHF. Treatment includes vagal maneuvers, adenosine (0.1-0.2 mg/kg, with maximum single dose 12 mg) IV rapid bolus and direct current cardioversion (0.25-1 J/kg). [76] [77]

Hypertension

Essential hypertension is not a common problem in children. When hypertension does occur, it is secondary (Table 73-5) and is often more difficult to control. The acute onset of severe systemic arterial hypertension constitutes a medical emergency because of the potential for cardiovascular decompensation, as well as the CNS complications of encephalopathy, seizures, or intracranial hemorrhage. In older children, the neurologic manifestations of hypertension are more likely to precede cardiovascular decompensation. By contrast, severe hypertension in the neonate often presents with the nonspecific cardiorespiratory symptoms of CHF. Treatment of hypertension is tailored to the disease process, the absolute degree of hypertension, and the presence of cardiovascular or neurologic symptoms. [78] [79]

The classes of drugs are listed in Table 73-6 . In the ICU, moderate hypertension often accompanies and complicates other disease processes; therefore, familiarity with all these drugs is necessary. However, if malignant hypertension is the admitting diagnosis, an aggressive approach is mandated. This includes close monitoring with a cardiac monitor and an arterial line. In emergency situations, diazoxide is often given. This potent vasodilator reduces blood pressure rapidly, but it has a short half-life and must be followed by other agents of longer duration. Nitroprusside infusions are also beneficial in the acute setting. [80]

Specific Pediatric Diseases

Kawasaki Disease

Kawasaki disease, also known as mucocutaneous lymph node syndrome, was first described in 1967. This disease is a

TABLE 73-5 -- Causes of Severe Hypertension in Children

Renal
Acute glomerulonephritis (e.g., poststreptococcal, Henoch-Schonlein)
Hemolytic uremic syndrome
Chronic glomerulonephritis (all types)
Acute and chronic pyelonephritis
Congenital malformations (dysplasia, hypoplasia, cystic diseases)
Tumors (e.g., Wilms, leukemic infiltrate)
Postrenal transplantation: also rejection
Oliguric renal failure
Trauma
Obstructive uropathy
After genitourinary surgery
Blood transfusions in children with azotemia
Cardiovascular
Coarctation of the aorta
Renal artery abnormalities (e.g., stenosis, thrombosis)
Takayasu disease
Endocrine
Pheochromocytoma
Neuroblastoma
Adrenogenital disease
Cushing syndrome
Hyperaldosteronism
Hyperthyroidism
Hyperparathyroidism
Iatrogenic
Intravascular volume overload
Sympathomimetic administration (e.g., epinephrine, ephedrine)
Corticosteroid administration
Rapid intravenous infusion of methyldopa
Miscellaneous
Immobilization (e.g., fractures, burns, Guillain-Barre syndrome)
Hypercalcemia (e.g., hypervitaminosis D, metastatic disease, sarcoidosis, some immobilized patients)
Hypernatremia
Stevens-Johnson syndrome
Increased intracranial pressure (any cause)

panvasculitis whose victims are primarily children (>80% < 4 y of age). Kawasaki disease is divided into three stages: the acute febrile stage (1-2 wk); the subacute phase; and finally, the convalescent stage (usually 6 wk after onset). The cause is uncertain but presumed infectious. The diagnosis is made when patients fulfill five of six criteria: (1) cervical lymphadenopathy with one node larger than 1.5 cm; (2) mucosal changes, usually the oropharynx, with red, cracked lips; (3) more than 5 days of fever of 101 to 105°F; (4) conjunctival edema and injection; (5) erythema of the palms and soles, often with desquamation after 2 weeks; and (6) an erythematous rash.

Although the disease affects many organ systems, cardiovascular involvement is the usual cause for an ICU admission. Forty percent of patients have cardiac involvement with myocarditis, effusion, and arrhythmias. Twenty percent develop coronary aneurysms with and without thrombosis. Acute myocardial infarction causes death in 3 to 4 percent of patients.

Laboratory tests reveal an elevated leukocyte count with a left shift, increased acute-phase reactants, and, after the first few weeks, a platelet count that is often grossly elevated. An echocardiogram must be done in any child with this presumed diagnosis for assessment of the coronary arteries.

TABLE 73-6 -- Antihypertensive Medications

I. Converting enzyme inhibitors, decrease angiotensin II
Caution in the face of renovascular disease
Captopril
Enalapril
II. Calcium channel blockers, usually type II blockers
Caution: Myocardial decompensation
Nifedipine
Nimodipine
III. Diuretics, usually as an adjunct
IV. beta-Adrenergic blockers
Caution: Reactive airway disease
Propranolol
Esmolol
V. alpha$_2$ -Antagonists
Prazosin
VI. Central alpha-agonist
Clonidine
VII. alpha- and beta-adrenergic blockers
Labetalol
VIII. Dilators
Hydralazine
Diazoxide

Treatment at present is intravenous gamma globulin, 1 to 2 g/kg administered as a 6- to 8-hour infusion. Some patients require inotropic support, and there is much controversy regarding the use of anticoagulation in the face of thrombosis in coronary aneurysms. Survivors of this disease often have resolution of their aneurysms, although some require coronary artery bypass surgery to maintain adequate myocardial perfusion. [81] [82]

Anomalous Origin of Coronary Arteries

Vascular causes of myocardial ischemia are extremely uncommon in pediatric patients. Anomalous origin of the left coronary artery is one rare exception (incidence 1:300,000). In this congenital disease, the coronary artery originates from the pulmonary artery. During the first weeks to months of life, when the PVR is elevated, there can be adequate coronary perfusion. As the PVR decreases, however, coronary perfusion falls and, in fact, can become retrograde. These infants usually present with overwhelming myocardial failure at the age of 2 to 6 months. In the presence of large collateral vessels, these patients can survive into adulthood. The treatment is surgical. [83]

RESPIRATORY SYSTEM

Age-Dependent Respiratory Variables: Structural and Functional Development

Airways and Alveoli

The main fetal organs, including the lungs, appear in the 4th to 8th weeks of gestation [4] (Table 73-7 (Table Not Available) ; Chs. 58 and 59) . At 4 weeks, the endodermal lung buds have divided into the

TABLE 73-7 -- Age-Dependent Respiratory Variables: Normal Values [a]

(Not Available)

From O'Rourke and Crone [384]

[a] Ch. 59

main-stem bronchi; by 6 weeks, all subsegmental bronchi can be identified, and by 16 weeks, the number of airway generations arising from axial pathways is similar to that in the adult. When this airway development is complete, the terminal airways remodel and multiply to form a cluster of large saccules, which are alveolar precursors capable of supporting gas exchange. True alveoli appear before and after birth, when the respiratory saccules become thinner and septated during postnatal growth. [84]

At birth, children have 24 million alveoli; by 8 years, this number has increased to 300 million. After this age, further lung growth reflects an increase in the size of the alveoli. Collateral ventilation between airways (Lambert canals) and between alveoli (Kohn pores) is not present at birth, but it develops by age 8. [85]

The neonatal lung has a decreased amount of elastic tissue, with elastin extending only to the level of the alveolar duct. Elastin progresses to the level of the alveolus, reaching maximal levels by 18 years of age, then over the next 5 decades, it slowly deteriorates. [86] Lung compliance is integrally related to the amount of elastin, and, hence, compliance peaks in adolescence and is relatively low in the very young and the very old. [87]

Pulmonary Circulation

The main axial arteries are present at 14 weeks' gestation, and by 20 weeks, the pattern of branching is similar to that seen in the adult. By 20 weeks' gestation, collateral supernumerary vessels are present in an adult pattern. During fetal life, additional arteries develop to accompany respiratory airways and saccules. Bronchial arteries appear between the 9th and 12th weeks of gestation. [87] The arterial wall develops a fine elastic lamina by 12 weeks' gestation, and muscle cells develop as early as 14 weeks. [88] By 19 weeks, the elastic structure extends to the seventh generation of arterial branching and muscularization extends distally. In the fetus, muscularization of the arteries ends at a more proximal level than in childhood or adulthood. However, the arteries that are muscularized have thicker walls than the arteries of similar size in the adult. The pattern of development of the pulmonary venous system is similar to that of the arterial system. [84] Studies of blood flow to the lungs of fetal lambs suggest that the pulmonary arteries are in a state of active vasoconstriction until the latter part of gestation. In the fetal lamb, pulmonary blood flow at 0.4 to 0.7 gestation is only 3.5 percent of combined ventricular output, increasing to 7 percent near term. [89]

The pulmonary arteries continue to develop after birth; new artery formation follows airway branching up to 19 months of age, and supernumerary arteries continue to grow until the 8th year. [90] As alveolar size increases, the acinar branching pattern becomes more extensive and complex. [84] The arterial structure also changes, preexisting arteries increase in size, and during the first year of life, the thickness of the muscular arteries decreases to adult levels.

Biochemical Development

In the developing lung, two cellular types become obvious by 24 weeks' gestation as alveolar cuboidal epithelium flattens: type I pneumocytes, which become lining and supporting cells for alveoli, and the larger type II cells, which manufacture and store surfactant. [91] Surfactant initially appears at 23 to 24 weeks' gestation in the human and increases in concentration during the last 10 weeks of gestational life. [92] The maturation of the surfactant system is partly controlled by the neuroendocrine system. [93]

Respiratory Transition: Placenta to Lung

By approximately 24 weeks' gestation, the lungs are capable of extrauterine gas exchange. However, several important circulatory and mechanical changes must occur soon after birth for pulmonary gas exchange to be adequate.

Ventilation begins to match perfusion within the first hours of life. Initially, there is right-to-left intrapulmonary shunting through atelectatic areas in the lung, as well as possible extrapulmonary shunting through the ductus arteriosus and foramen ovale. The resultant Pa_{O_2} of 50 to 70 mm Hg in the newborn infant indicates a right-to-left shunt three times that seen in normal adults. [94] [95]

The transition from fetal to neonatal respiration and circulation is dynamic. Postnatally, the pulmonary vascular bed can continue to constrict in response to physiologic stresses such as acidosis or hypoxia. If constriction does occur, the extrapulmonary right-to-left shunting of desaturated blood through the foramen ovale and the ductus arteriosus increases, thus decreasing pulmonary blood. [96] Persistence of this active pulmonary vasoconstriction is called persistent pulmonary hypertension of the newborn or persistent fetal circulation. This syndrome is an important consideration when treating infants with congenital diaphragmatic hernia, meconium aspiration, and sepsis. [97]

Mechanics of Breathing

In order to ventilate the lungs with fresh gas, the respiratory muscles must overcome static-elastic and dynamic-resistive forces intrinsic to the lungs themselves. Changes in these opposing forces during postnatal development affect lung volume, pattern of respiration, and the work of breathing. [98]

Lung Compliance Versus Age

Lung compliance changes with age, as a function of the changing alveolar structure, amount of elastin, and amount of surfactant. [99] At birth, compliance is low secondary to the presence of thick-walled alveolar precursors and decreased amounts of elastin. A deficiency of surfactant as seen in hyaline membrane disease further decreases compliance. Compliance improves over the first years of life with continuing development of alveoli and elastin.

Chest Wall

The thoracic cage of the newborn is mechanically different from that of the adult. The chest wall in the infant is less rigid because ribs are cartilaginous and not bony. In addition, the boxlike configuration of the infant's thorax permits less elastic recoil than does the dorsoventrally flattened thoracic cage of the adult. [100] There are also age-related differences in the intercostal and diaphragmatic muscle fibers. The adult has a high proportion of slow-twitch, high-oxidative, fatigue-resistant fibers: 65 percent of the intercostal fibers and 60 percent of the diaphragmatic fibers. The neonate has fewer: 19 to 46 percent of the intercostal fibers and 10 to 25 percent of the diaphragmatic fibers. [101] Therefore, the infant is more vulnerable to muscle fatigue, which may further decrease the stability of the chest wall. As a result of all these factors, the infant's chest wall is extremely compliant. The net effect of the compliant chest wall and the poorly compliant lungs should be alveolar collapse with lower resting lung volume or passive functional residual capacity (FRC). Despite this tendency to collapse, the child maintains a larger dynamic FRC by a number of active mechanisms, including incomplete exhalation secondary to a rapid respiratory rate, laryngeal breaking, and stabilization of the chest wall with increased intercostal tone during exhalation. [102] [103] [104] [105]

Upper Airway

There are numerous anatomic differences in the upper airway of the child versus the adult, differences that must be considered before any airway manipulation is attempted. The more anterior and cephalad position of the larynx in the child explains the advantage of the "sniffing position" for either mask ventilation or endotracheal intubation. Extreme neck extension can actually obstruct the airway. In addition, whereas the narrowest part of the adult airway is at the level of the vocal cords, the child's airway is narrowest at the level of the cricoid cartilage. An endotracheal tube (ETT) that passes easily through the vocal cords may cause ischemic damage to the airway more distally. The cricoid narrowing and the very pliant tracheal cartilage provide an adequate seal around an uncuffed ETT. Children younger than 10 years of age rarely require a cuffed ETT. [106]

Closing Capacity

The elastic properties of the lung are also closely correlated with closing capacity. Closing volume is the lung volume at which terminal airways begin to collapse, creating discontinuity between trapped gas and conducting airways. [107] Large closing volumes increase dead-space ventilation and can lead to atelectasis and shunting. It is postulated that the elastic tissue helps to keep the airways open, so that the greater the elastic stroma in the small airways, the lower the lung volume required before gravitational forces can close small, noncartilaginous airways. Therefore, closing volume is small in the late adolescent and relatively large in the elderly and the very young. [108] Children overcome the complications of large closing volumes and secondary atelectasis by keeping their lungs expanded through constant activity and crying. However, closing volume becomes a significant problem in the infant who is inactive or sedated because of illness.

Resistive Forces

Poiseuille's law defines resistance during laminar flow through a tube:

where *l* is the length of the tube, r is the radius, and eta is gas viscosity. Because air flow in the lung is generally not laminar, resistance is underestimated by this calculation. However, the Poiseuille law does emphasize the dependence on the radius of the airway. [109]

Not surprisingly, neonates have small airways with high

resistance or low conductance (conductance = 1/resistance). Of interest, the caliber of the small airways does not significantly increase until after the age of 5 years; hence, young children have elevated resistance at baseline and are particularly vulnerable to diseases that cause further narrowing of the airways (i.e., smooth muscle constriction, airway edema/inflammation). [110]

Control of Breathing

Respiratory control in the newborn infant may be unique. Hypoxia in the newborn produces an initial increase, followed by a sustained decrease in ventilation. [111] This response is more exaggerated in the preterm newborn and disappears rapidly in the full-term infant after several weeks. Irregular respiration, known as periodic breathing, is also more common in infants, particularly in the preterm, a finding suggesting incomplete development of the medullary respiratory centers. [112]

Oxygen Transport: Oxygen Loading and Unloading

Oski and others have shown that fetal hemoglobin does not bind with 2,3-diphosphoglycerate (DPG), so that the P_{50} of fetal hemoglobin is lower than that of adult hemoglobin in the presence of 2,3-DPG. [113] This gives the fetus the teleologic advantage of loading more oxygen at low fetal oxygen tensions (fetal Pa_{O_2}, 20-30 mm Hg). As fetal hemoglobin is replaced by adult hemoglobin, the young infant's P_{50} approximates the adult's, enhancing oxygen delivery. At 3 to 4 months of age, infants have higher levels of 2,3-DPG than do adults. [114] The resultant higher P_{50} may compensate for the relative anemia at this age, when the hemoglobin concentration commonly falls below 10 g percent.

The infant is a very metabolically active organism: oxygen consumption at birth is 6 to 8 mL/kg/min and falls to 5 to 6 mL/kg/min over the first year of life. [115] The decreased ventilation/perfusion ratio, the decreased P_{50} of fetal hemoglobin, and the physiologic anemia characteristic of infants can make adequate oxygen delivery difficult. The infant compensates for this by having a high cardiac output up to 250 mL/kg/min, which remains elevated until 4 to 5 months of age. [116] When oxygen delivery to the tissues is inadequate, the cells shift to anaerobic metabolism through the Embden-Meyerhof glycolytic pathway. Byproducts of this pathway are lactic and pyruvic acid, which produce a net acid load. Thus, the arterial pH (pH_a) becomes a very sensitive indicator of the adequacy of oxygen transport. Particularly in young infants and children, metabolic acidosis indicates inadequate oxygen transport until proven otherwise.

Respiratory Failure

Respiratory failure may be defined as inadequate oxygenation resulting in systemic arterial hypoxemia or as inadequate ventilation resulting in systemic arterial hypercarbia (Ch. 58). Because it is impossible to ascribe specific arterial blood gas (ABG) values to this definition without knowledge of the clinical situation, respiratory failure is best described by an integration of historical, clinical, and laboratory observations. These observations must be tailored to the pediatric patient.

A complete family history and medical history characterizing the severity and chronicity of the respiratory dysfunction help to formulate a differential diagnosis and a therapeutic approach. Specific data should include history of prematurity, previous airway instrumentation, previous mechanical ventilation, nonpulmonary organ dysfunction, and family history of any respiratory disease. A detailed feeding history and up-to-date growth chart can provide valuable information.

The clinical examination of lung function includes close visual observation as well as auscultation. The color of the skin and mucous membranes as well as the frequency, pattern, and depth of respiration should be documented. The presence of any end-expiratory grunting, nasal flaring, and intercostal or subcostal retractions can be used to estimate the work of breathing. The profound compliance of the infant's chest wall can exaggerate the severity of retractions. The symmetry of chest movement should be visually noted: because of the small thoracic volume with easy transmission of sounds, auscultation is not always the best way to ascertain symmetry of air entry. Abdominal distention should also be assessed: because children are abdominal breathers and have very compliant chest walls, abdominal distention can dramatically impede adequate air entry. The sounds produced by air movement through the airways can be examined by naked ear as well as by stethoscope.

Radiologic evaluation of the nasopharynx, neck, and thorax can often provide meaningful information regarding the cause and severity of the respiratory dysfunction. Fluoroscopy can be used as an adjunct in evaluating the uncooperative child.

Pulmonary function tests are frequently useful for assessing respiratory function, but secondary to children's lack of cooperation, these tests are difficult to perform in any child younger than 5 years of age. There are numerous maneuvers for evaluating the unintubated child; most of these require a tight-fitting mask, which in itself can be problematic. [117] In the intubated child, lung volumes, expiratory flow rates, compliance, and inspiratory forces can be measured; in fact, most ventilators routinely provide these measurements.

The measurement of ABG (Ch. 38) is an objective indicator of the adequacy of gas exchange. The Pa_{O_2} is helpful, but it is most useful when considered in relation to the inspired oxygen content. Two ways of evaluating this relationship are the gradient difference between the partial pressure of inspired oxygen and the Pa_{O_2} and the calculation of shunt of desaturated blood across the lung.

The elimination of CO_2 from the arterial blood is another indicator of lung function. The specific importance of the Pa_{CO_2} must always be considered in light of the finding that CO_2 is more diffusible than oxygen and that any increase in minute ventilation can often compensate for inefficiency of CO_2 excretion.

Various invasive as well as noninvasive techniques permit measurement of alveolar P_{O_2} (P_{AO_2}), Pa_{O_2}, P_{ACO_2}, and Pa_{CO_2} in even the smallest infants and children. ABG sampling can be thought of as the gold standard. When numerous or repeat analyses are required, blood sampling can be facilitated by an indwelling arterial cannula.

Umbilical artery cannulation is still a popular technique in the newborn; these catheters are relatively simple to insert and, once in place, are easy to maintain. They are most commonly used in the very-low-birthweight infant of less than 1,000 g or in the larger infant during an initial resuscitation prior to transport to an intensive care nursery. To reduce the risk of thromboembolic complications to the renal and splanchnic circulations, the tip of the catheter should be in the aorta either at the level of the diaphragm or at the level of the aortic bifurcation. Extreme caution must be used because all intra-arterial catheters carry the risk of distal thromboembolic disease, and a catheter in the aorta has the potential for distal infarction of extremities or vital organs. [118] Insertion of an arterial catheter as distal from the central circulation as possible would seem to offer the potential advantage of minimal embolic damage. In fact, peripheral arterial cannulation has become the most common technique for repeat ABG sampling in infants and children. [119] The arteries most commonly used are the radial, dorsalis pedis, and posterior tibialis. These arteries are superficial, are easily palpated, and can be cannulated percutaneously in the smallest of infants.

With proper insertion and maintenance, serious complications of arterial lines can be avoided. Although many arteries cannulated on a long-term basis are occluded after removal of the cannula, these arteries tend to recanalize within a short period. [120]

Less invasive techniques for monitoring gas exchange have also been developed. Transcutaneous electrodes designed to measure oxygen and CO_2 have been in use for more than a decade. The main advantage is the ease of application and noninvasive nature, but there are numerous problems. These electrodes are inaccurate during hypoperfusion states, and transcutaneous monitors require a warm-up time that makes "spot-checks" difficult. They are better used as trend monitors after correlating the value with a measured arterial sample. Absolute values can be misleading; this is particularly true with the CO_2 electrode. [121] [122]

Pulse oximeters have become routine in the care of critically ill children. They are accurate, require no warm-up time, and require no skill for application. Unlike fingertip or toe placement on the larger patient, the probe is usually wrapped around the child's entire hand or foot. [123]

End-tidal CO_2 monitoring allows continuous assessment of CO_2 elimination and the capnogram (CO_2 excretion recorded through time) provides information about gas flow in the small and large airways. There are limitations of this technology in the small child. The dead space is increased. The weight of the monitor on the end of the endotracheal tube can result in accidental extubations. The volume of gas withdrawn for sampling can alter the inspired volume and inspired oxygen fraction (F_{IO_2}) in the extremely small child. [124]

Causes

The cause of respiratory failure can be differentiated by the age of the patient at presentation. Respiratory failure in the newborn often reflects a congenital abnormality or immaturity. Congenital abnormalities can include airway malformations, lung dysgenesis, or nonpulmonary organ dysgenesis or malfunction, all of which impair ventilation. Lesions of immaturity include both apnea of prematurity and hyaline membrane disease, a biochemical immaturity of the surfactant system. In addition, the perinatal period is characterized by specific infections, insults, and stress reactions. One particular problematic reaction is persistent pulmonary hypertension, which can complicate neonatal pulmonary and nonpulmonary problems. These and other important causes of respiratory failure in the newborn are listed in Table 73-8 . A wide variety of disorders can cause respiratory failure in the older child (Table 73-9) . Regardless of specific cause, respiratory failure can be categorized as hypoventilation syndromes in patients with normal lungs, intrinsic alveolar and interstitial disease, and obstructive airways disease.

Hypoventilation Syndromes in Children With Normal Lungs

Clinical conditions that produce hypoventilation include neuromuscular disease, central hypoventilation on the basis of reduced CNS efferent activity, and structural/anatomic impairment of lung expansion (i.e., upper airway obstruction, massive abdominal distention). These clinical conditions are characterized by inadequate lung expansion, which secondarily results in progressive atelectasis (intrapulmonary right-to-left shunt) with systemic hypoxia. Atelectasis and the resultant decreased FRC also increase the work of breathing. The child's response to this increased work of breathing at lower lung volumes is to breathe faster with reduced tidal volume at lower lung volumes, a pattern that causes further atelectasis and shunting. As a result, children with intrinsically normal lungs but with hypoventilation syndromes present with shallow tachypnea and possible evidence of increased work of breathing and cyanosis. Their radiographs reveal small lung volumes with miliary or lobar atelectasis. Lung reexpansion with intermittent positive-pressure ventilation (IPPV) and PEEP quickly reverses the pathologic process.

Primary Pulmonary Alveolar or Interstitial Disorders

Intrinsic lung disease involving alveoli or pulmonary interstitium affects respiratory function by decreasing lung compliance and increasing airway closure, both resulting in an increased work of breathing and atelectasis. Edema or inflammation of the alveoli and edema, inflammation, or fibrosis of the interstitium decrease the compliance of the lung or make the lung stiffer. In a stiffer lung, a greater negative intrapleural pressure is required to generate air movement, thus increasing the work of breathing.

In addition, the normal developmental physiology of large closing volumes with a tendency to airway closure is exaggerated, resulting in airway closure, increasing atelectasis and shunting. The principal pathophysiologic feature in the child with intrinsic alveolar or pulmonary interstitial disease is atelectasis. This child may

clinically and radiographically resemble the child with normal lungs and a hypoventilation syndrome, but with a different response to therapeutic maneuvers.

TABLE 73-8 -- Classification of Causes of Neonatal Respiratory Failure

	CONGENITAL ABNORMALITIES	DEVELOPMENTAL IMMATURITY	SPECIFIC NEONATAL " STRESS"
Impaired control of ventilation	Central nervous system dysgenesis Ondine's curse	Apnea of prematurity Intracranial hemorrhage	Drug intoxication (note maternal drugs) Sepsis Central nervous system infections Seizures
Neuromuscular disorders Structural impairment	Congenital myopathies Thoracic deformities Lung hypoplasia Diaphragmatic hernia Potter syndrome Abdominal malfunction Gastroschisis Omphalocele		High cervical cord injuries Severe abdominal distention Pneumothorax or other air leak
Airway obstruction Upper airway	Choanal atresia Pierre Robin syndrome Laryngeal web/cleft Congenital tracheal/laryngeal stenosis Recurrent laryngeal palsy Hemangioma Lymphangioma		Massive meconium aspiration Vocal cord paralysis secondary to myelodysplasia
Lower airway	Tracheoesophageal fistula Lobar emphysema		Meconium/blood aspiration
Alveolar disorders Cardiovascular disorders	Congenital cardiac malformations Congestive heart failure (critical coarctation or aortic stenosis) Total anomalous pulmonary venous return	Respiratory distress syndrome	Bronchopulmonary dysplasia Persistent pulmonary hypertension

Obstructive Airways Disease

Obstruction of the airways can be extrinsic, such as lower tracheal and upper bronchial compression by vascular structures or neoplasms, or intrinsic, caused by intraluminal obstruction or by the airway wall itself. Intrinsic small airways obstruction is commonly seen in bronchiolitis, bronchopneumonia, asthma, and bronchopulmonary dysplasia.

The decreased conductance or increased resistance increases the work of breathing. The degree of airway obstruction ranges from partial to complete. Partial obstruction impedes air outflow more than air inflow, resulting in trapped gases or regional emphysema. Complete airway obstruction results in atelectasis. In small airways disease, there is usually a mixture of total and partial obstruction throughout the airways that results in an inhomogeneous picture of collapse and overdistention. The areas of collapse contribute to an intrapulmonary right-to-left shunt, and the areas of overdistention contribute to dead space. If overdistention is the predominant feature, overdistention of the entire lung can occur, resulting in decreased compliance and increased work of breathing. The key to small airways disease is the inhomogeneity of the pathophysiology; the clinical and radiographic picture will vary with different degrees of collapse and overdistention.

In summary, all causes of respiratory failure share similar pathophysiology, namely, atelectasis with decreased FRC and intrapulmonary right-to-left shunting and/or alveolar overdistention with increased dead-space volume and decreased CO_2 elimination. The concept of increased work of breathing is important to all causes of respiratory dysfunction: any clinical disease that causes increased work of breathing (i.e., decreased compliance or increased dead-space volume) can result in fatigue and a breathing pattern that further complicates the initial process.

Treatment

The standard therapeutic approach to respiratory failure includes (1) maximizing the child's position, (2) increasing the ambient oxygen, (3) relieving an obstruction by either airway instrumentation or pharmacotherapy, (4) treating infection, (5) correcting fluid overload, (6) maximizing all nonpulmonary systems, and (7) instituting either negative-pressure or positive-pressure mechanical ventilation. More specialized and investigational forms of therapy should also be considered. Exogenous surfactant, high-frequency ventilation, and extracorporeal membrane oxygenation are accepted standards of care, whereas liquid ventilation and inhalation of NO are currently undergoing clinical trials.

The child's position must be guarded. Unlike the adult or older child, the infant may require help maintaining optimal positioning. Specific maneuvers may include keeping the

TABLE 73-9 -- Causes of Respiratory Failure in Children

Impaired control of ventilation
Head trauma
Intracranial hemorrhage
Increased intracranial pressure secondary to tumor, edema, hydrocephalus, Reye syndrome, etc.
CNS infections
Ondine's curse
Drug intoxication
Status epilepticus
Neuromuscular disorders
High cervical cord injury
Poliomyelitis
Guillain-Barre syndrome
Neurodegenerative diseases (e.g., Werdnig-Hoffmann syndrome)

- Muscular dystrophies and myopathies
- Myasthenia gravis
- Botulism
- Tetanus
- Phrenic nerve injury

Structural impairment
- Severe kyphoscoliosis
- Flail chest
- Large intrathoracic tumor
- Pneumothorax or pneumomediastinum
- Large pleural effusion, hemothorax, empyema
- Severe abdominal distention
- Severe obesity (pickwickian syndrome)

Airway obstruction
- Upper airway
  - Congenital anomalies
  - Tumor--intrinsic or extrinsic
  - Epiglottitis
  - Croup (laryngotracheobronchitis)
  - Foreign body
  - Postintubation edema, granulation tissue, or scarring
  - Vocal cord paralysis
  - Burns
  - Vascular ring
- Lower airway
  - Asthma
  - Bronchiolitis
  - Foreign body
  - Lobar emphysema
  - Cystic fibrosis

Alveolar disorders
- Pneumonia
  - Infectious--bacterial, viral, fungal, pneumocystis
  - Chemical--aspiration, hydrocarbon, smoke inhalation
- Pulmonary edema--cardiogenic, near drowning, capillary leak syndrome

Massive atelectasis

Oxygen toxicity

Pulmonary contusion

Pulmonary hemorrhage

---

child in a semi-upright position to avoid aspiration or gastroesophageal reflux as well as to minimize the effects of abdominal distention. At times, the upper airway must be supported by keeping the head in a midline position and minimizing excessive neck flexion.

An increase in inspired oxygen can be accomplished in a number of ways. Tight-fitting anesthesia masks and nasal prongs may agitate the child and may negate any beneficial effects. Blow-by oxygen, space masks, croup tents, and head boxes are alternative, less invasive maneuvers.

Relief of an upper airway obstruction can be lifesaving. Instrumentation of the airway includes placement of an ETT, a tracheostomy, or a nasopharyngeal tube to stent open the posterior oropharynx. Pharmacology can decrease airway obstruction as well: inhaled racemic epinephrine and intravenous steroids decrease subglottic edema, [125] [126] antibiotics decrease infectious swelling, and beta-agonists and inhaled anticholinergic medications relax bronchial smooth muscle. [127] Patients with pneumonitis should be evaluated for bacterial, viral, or fungal pathogens and treated with appropriate antibiotics. Excessive intravascular fluid from inappropriate fluid administration and/or cardiac failure should be corrected by limiting fluid intake and by administering diuretics and cardiotonic or vasoactive drugs. Nonpulmonary systems must also be closely monitored. Good nutrition, fluid and electrolyte balance, and adequate cardiovascular and renal function are required for maximal pulmonary support.

Mechanical ventilation is the mainstay in the treatment of respiratory failure and provides respiratory support for nonpulmonary disease as well. There are several nonpulmonary reasons for instituting respiratory support, as follows:

1. *Resuscitation from circulatory collapse.* In virtually any situation in which the cardiovascular system is unstable, it is safest to support ventilation. In the event of cardiac arrest, respiratory support is mandatory. During the immediate postoperative cardiac surgical period, ensuring stable gas exchange and normal ABG afforded by mechanical ventilation minimizes the risk of untoward cardiovascular decompensation.
2. *Respiratory assistance for supranormal gas exchange.* Intentional hyperoxia or, more commonly, hypocarbia is used primarily to treat disorders unrelated to respiratory failure. One example is persistent pulmonary hypertension in which relative hyperoxia and hypocarbia, with resultant alkalosis, may dilate the pulmonary vascular bed in some newborns. [68] A second example is intracranial hypertension: intentional hyperventilation may reduce increased intracranial pressure (ICP) in some patients by reducing cerebral blood volume (CBV). [128] Postoperatively, some children are at risk of developing respiratory failure because of their underlying disease and the nature of their surgery. Underlying conditions that predispose children to respiratory failure include morbid obesity, sepsis, nutritional debilitation, and kyphoscoliosis with respiratory compromise.
3. *Reduced work of breathing.* In addition, reducing the oxygen cost of breathing in some patients may improve the patient's ability to overcome a major physiologic insult. The child with bronchopulmonary dysplasia may need to conserve the energy expended during breathing on a long-term basis in order to grow. [129]

Ventilatory Therapy

Mechanical respiratory assistance can be given by a variety of methods, including continuous positive airway pressure (CPAP), IPPV, and negative-pressure ventilation [130] (Ch. 72). Positive pressure is applied almost exclusively by way of an intratracheal artificial airway, either an ETT or a tracheostomy tube. Oral intubations are easier to perform than nasal intubations and should be used in emergency situations. Although nasal endotracheal intubations can be

more difficult to perform in children, a nasal tube is more comfortable and more easily secured for long-term management.

The size of the ETT should be carefully selected. One formula that estimates the required size of the tube for children over age 2 years is as follows:

which gives the size by internal diameter. If the ETT size is correct, there should be a slight air leak when a positive pressure of 20 to 30 cm H_2O is applied to the airway. [131] Serious lifelong laryngeal and subglottic damage can result from insertion of an inappropriately large ETT; this is particularly important in inflammatory lesions of the upper airway such as laryngotracheobronchitis. Because of the more flexible tracheal cartilage and the relative subglottic narrowing in children, uncuffed ETTs generally provide an adequate seal in children younger than 8 years of age.

After endotracheal intubation, the position of the tube within the trachea should be assessed. Physical examination should reveal symmetric chest movement and symmetric breath sounds on auscultation. An electronic or colorimetric CO_2 detection system should be available to confirm endotracheal position of the tube. On chest radiography, the tip of the ETT should be midway between the vocal cords and the carina. In small infants, this leaves a very small margin of error before the tube has either progressed down one main-stem bronchus or migrated above the vocal cords; extreme care should be given to verify the position of the tube. It is important to realize that movement of the child's head and neck can affect the placement of the tube. Flexion of the neck advances the tube farther into the trachea, and extension pulls the tube higher into the airway, making it important to avoid extreme flexion or extension of the neck during patient care.

In recent years, ETTs have been left in place in infants and children for increasing periods of time. It is not uncommon to leave a child's trachea intubated for more than 2 weeks and up to 12 weeks without performing a tracheostomy. This approach has been possible because of proper humidification and improved techniques of nursing care in both endotracheal suctioning as well as patient surveillance.

Despite these improved techniques, any child with an ETT in place must be constantly monitored for the complications of ETT obstruction with secretions and accidental extubation or accidental intubation of a main-stem bronchus. Tracheostomy is indicated in those children who require a long-term artificial airway for mechanical ventilation or endotracheal suctioning or to bypass obstruction of the upper airway. A potentially life-threatening complication of tracheostomy is accidental dislodgement of the tracheostomy tube soon after surgery before a well-healed track is formed. Reinsertion of the tube can be very difficult during these first 72 hours after surgery, and forceful blind reinsertion of a tracheostomy tube through a fresh tracheostomy site can result in blunt dissection between the tissue planes. The complications of airway obstruction, pneumomediastinum, and pneumothoraces can result.

Continuous Positive Airway Pressure and Positive End-Expiratory Pressure

With CPAP, the child breathes spontaneously with a constant specified positive pressure applied to the airway. With PEEP, the child is ventilated with constant specified PEEP. Positive pressure during spontaneous inspiration is maintained by either placing a pressurized reservoir bag into the system or increasing the fresh gas flow to exceed the inspiratory flow rates (gas flow rates of at least two to three times the patient's minute ventilation are required just to avoid rebreathing from the circuit). Exhalation occurs against a water column adjusted to deliver the desired pressure resistance.

CPAP is applied by way of an ETT, nasal cannulas, or face mask. Because newborns are obligate nose breathers, relatively low levels of CPAP can be produced with nasal cannulas. This method has had variable success, depending on the size and activity of the infant; crying and mouth breathing reduce the efficiency of the system. Gaseous distention of the abdomen is a common complication, and an orogastric tube is often required as a continuous vent. [132] CPAP via face mask can be applied effectively to adults as well as infants and children for short periods of time. Mask CPAP has also been associated with the complications of gastric distention and pressure necrosis of the face and eyes. [130]

Low to moderate levels of PEEP can be maintained in children with uncuffed ETT. If leakage around the ETT precludes a stable level of PEEP, there are two options: the ETT can be upsized to a larger internal diameter tube, or a cuffed ETT can be used.

The goals and risks of CPAP and PEEP are the same in the child and adult. The optimal level of CPAP or PEEP can be difficult to ascertain for each clinical situation. Too little may afford no beneficial effect, whereas too much may cause overdistention of the lung and dead-space ventilation. Low levels of CPAP or PEEP (2-5 cm H_2O) are often considered homeopathic and have been advocated by some authors for any child with an artificial airway in order to maintain FRC at preintubation levels. [133]

In children with lung disease, the goal of optimal CPAP or PEEP is to maximize improvement while minimizing side effects. A conservative approach to choosing pressure is to limit CPAP to levels sufficient to improve oxygenation, decreasing the F_{IO_2} to 0.6 or less while the patient experiences no cardiovascular changes. A second approach is to increase pressure levels until maximal improvement in compliance is achieved. A bedside measurement of compliance can be calculated in ventilated patients to assess the effect of the PEEP. Airway pressure is measured at the end of a 3- to 5-second inspiratory hold. Compliance is then estimated by subtracting the end-expiratory pressure from this end-inspiratory hold pressure and then dividing by the measured expired tidal volume. End-inspiratory hold pressure is used rather than peak airway pressure because it is a more accurate assessment of inflating pressure, without the influence of mechanical flow characteristics or flow-resistance factors. This calculation can be performed at various end-expiratory pressures in order to determine optimal PEEP. [134]

Suter et al [135] proposed that optimal or best PEEP (or CPAP) is the level of pressure associated with the maximal oxygen transport, defined as the product of cardiac output

---

and arterial oxygen content. This concept accounts for both the beneficial effect of improved oxygenation and the complication of decreased cardiac output. This is important in view of the finding that once a patient is higher than optimal PEEP, airway pressure is more directly transmitted to the cardiovascular system and may decrease the cardiac output and, hence, oxygen transport. To apply the concept of Suter et al of best PEEP, repeated cardiac output determinations are required, necessitating a Swan-Ganz thermodilution catheter. The indications and risks of pulmonary artery catheterization must be weighed against the benefits of accurately determining best PEEP and the risks of high levels of pressure. Most clinicians accept that an approximation of optimal CPAP or PEEP can be safely determined by clinical trial and compliance estimates, as long as the level of CPAP or PEEP is less than 20 cm H_2O. If more than 20 cm H_2O is considered, thermodilution catheters are often inserted.

Another alternative for estimating the CPAP or PEEP level is the use of an esophageal pressure monitor. Ideally, esophageal pressure should change only slightly until optimal intrathoracic pressure is reached. Once the maximal improvement in lung compliance is attained, increasing CPAP will result in greater transmission of pressure to the esophagus.

Positive-Pressure Ventilation

Positive-pressure mechanical ventilators can be classified according to their method of control as (1) volume preset, (2) pressure preset, and (3) time-flow preset. [136] As a general rule, time-flow- or pressure-preset ventilators are more convenient to use in infants and young children (<10 kg), whereas volume-preset ventilators are most commonly used in older children (>10 kg) and adults. The time-flow pressure-preset ventilators have several advantages in ventilatory assistance in infants and young children. Most commonly, infants and young children are intubated with an uncuffed ETT, so a variable amount of leak is produced around the ETT. This leak, along with the relatively large compression volume factor in relation to tidal volume in infants, makes the volume-preset determination on volume ventilators unreliable. [137] [138] The main problem of using any pressure-preset or time-flow-preset ventilator is that delivered volume depends on the child's total thoracic and lung

compliance. This may result in overventilation and an increased risk of alveolar rupture as compliance increases. Alternatively, it may cause hypoventilation should compliance decrease.

Intermittent mandatory ventilation (IMV) is available on pressure-, time-flow-, and volume-preset ventilators. [139] [140] In the IMV system, the child may breathe spontaneously from a fresh gas source at low resistance while receiving active inflations from the mechanical ventilator at preset intervals with the same level of end-expiratory pressure. This allows the child additional breaths at the same F_{IO_2}, and PEEP. IMV is produced either by a continuous-flow circuit or by a series of demand valves. Continuous-flow IMV circuits are simpler and do not require additional patient effort during spontaneous breathing. Thus, continuous-flow circuits may have an advantage over demand-valve systems in children with relatively high respiratory rates, in which valve sensitivity and response time are potentially important during weaning from mechanical ventilation. Pressure-support ventilation is an innovation of the assist/control mode of ventilation. In pressure-support ventilation, each spontaneous breath is augmented by the delivery of gas at a preset pressure. The patient determines the respiratory rate and the inspiratory time. The pressure support increases the delivered tidal volume and may decrease the work of breathing and improve patient comfort. This mode is most commonly used while weaning a patient from mechanical ventilation. Because it depends on the patient's own initiation of a breath, pressure support cannot be used in a patient who has abnormal respiratory drive. [141] [142]

The pressure pattern of ventilation is dependent on the inspiratory and expiratory flow rates, the tidal volume, the duration of inspiration and expiration (I:E ratio), and the respiratory rate. The optimal ventilatory pattern varies from patient to patient from one disease state to another.

Insights into the pathophysiology of pulmonary interstitial or alveolar disease represented by the acute respiratory distress syndrome (ARDS) have led to a better understanding of the implications of ventilator management. Table 73-10 outlines the salient features of the pathophysiology of ARDS. This has led to a change in therapy, using ventilator strategies that employ relatively long inspiratory times, high end-expiratory pressures, and low tidal volumes. This technique results in lower minute ventilation and elevated Pa_{CO_2}. Termed *permissive hypercapnia,* this strategy decreases the shear forces acting on the terminal airways and recruits lung units that have dropped below closing volumes. [143] Acid-base status must be maintained with a compensatory metabolic alkalosis that occurs gradually through renal retention of bicarbonate. This process can be assisted with the administration of sodium bicarbonate or tromethamine, allowing time for equilibration of blood tissue pH.

By contrast, the optimal pattern of ventilation for patients with obstructive airway disease is different. In these patients, using a faster inspiratory flow rate with a shorter inspiratory time and prolonged expiratory time allows for better ventilation of relatively normal parts of the lung while still permitting exhalation of gas in obstructed portions of the lung. Unlike treating patients with alveolar collapse, mechanical ventilation in patients with small airways disease should be considered supportive care only, because it is rarely therapeutic. Pharmacologic bronchodilation is the principal therapy in this disease. Barotrauma and alveolar rupture are common complications of ventilatory support in patients with small airways disease.

TABLE 73-10 -- Pathophysiology of Acute Respiratory Distress Syndrome

Disruption of endothelial barriers with leakage of protein-containing fluids and inflammatory cells into the alveoli
Inactivation of surfactant resulting in increased surface tension of the alveolar lining layer
Atelectasis and lung volume loss
Shunting of blood through nonventilated areas of lung resulting in hypoxemia and tissue hypoxia
Decreased pulmonary compliance

Although there is no specific formula for initiating mechanical ventilation, some general principles can be followed. In our experience, the human hand is still the best mechanical ventilator. After a patient has been intubated and stabilized, hand ventilation with a Mapleson-type anesthesia circuit with an airway-pressure manometer in line is useful in determining the approximate pressures required to inflate the chest. In patients with alveolar or interstitial disorders, a prolonged I:E ratio of 1.51 or 11 is frequently useful, using a relatively slow frequency of less than 24 cycles/min in the infant and less than 16 cycles/min in the child.

When initiating mechanical ventilation with a volume-preset ventilator, choosing an arbitrary tidal volume of 10 to 15 mL/kg (using the higher number in the smaller child) while observing peak airway pressures is commonly employed. Regardless of the type of ventilator, the most important variables in initiating mechanical ventilation are the adequacy of chest expansion and gas exchange by clinical observation and auscultation and the adequacy of alveolar ventilation by measuring the Pa_{CO_2}. The peak airway pressure should be measured frequently as close to the ETT as possible.

PEEP should begin at 3 to 4 cm H_2O until arterial oxygenation is maximized. It is unusual in our experience to require end-expiratory pressure above 20 cm H_2O in pediatric patients.

With the initiation of positive-pressure ventilation, it is not uncommon to see systemic arterial hypotension, which usually responds to a volume infusion of 10 to 20 mL/kg of crystalloid or colloid. However, it is strongly recommended that CVP be measured in any patient requiring mechanical ventilation with a PEEP of 10 cm H_2O or greater. These data are helpful in determining the effects of mechanical ventilation and positive airway pressure on the cardiovascular system.

Adjunctive Pharmacologic Therapy: Sedatives and Analgesics

At least initially, some degree of sedation is required for conscious children to cooperate with mechanical ventilation. The amount of sedation depends on the child's age, size, underlying disease, and degree of respiratory support required. Occasionally, an infant in respiratory failure may be initially severely depressed and may not require any sedation. Sedation facilitates the patient's breathing "in phase" with the ventilator, so that minimum peak airway pressure can be maintained without the child's coughing and straining. It is not unusual to find that once the child accommodates to the mechanical ventilator, the amount of sedation required can be reduced. Various combinations of sedatives have been advocated for children, with probably equal success. The drug we usually administer is fentanyl (1-2 mug/kg/h), given intravenously as a constant infusion after an initial bolus. If additional sedation is required, one may use lorazepam (0.1-0.3 mg/kg), administered intravenously every 4 to 6 hours, midazolam (0.05-0.2 mg/kg/h), given as an infusion, or chloral hydrate (30-50 mg/kg), administered rectally or by nasogastric tube every 4 to 6 hours. These drugs have minimal cardiovascular effects, provided intravascular volume is adequate. [144]

There is no perfect pharmacologic recipe for chronic sedation in the ICU. Unfortunately, because children experience tachyphylaxis to many of these drugs, the dosage is continuously increased and/or other agents are added. The result can be a polypharmacy of extremely high drug doses, and weaning from this sedation adds to the patient's problems. Some children develop symptoms of withdrawal and require very slow drug taper, which is often accomplished by switching to oral agents such as methadone and lorazepam.

Neuromuscular blocking drugs are used to increase chest wall compliance, to reduce oxygen consumption, [145] and more commonly, to facilitate mechanical ventilation by preventing patient-ventilator dyssynchrony. These drugs should always be used in combination with medications that provide amnesia and anxiolysis. Adequate analgesia should be provided to patients to ensure that pain is well controlled.

Pancuronium and vecuronium are employed most commonly in the PICU. The usual dose of pancuronium is 0.1 mg/kg administered intravenously every 1 to 1½ hours, or 40 to 100 mug/kg/h as an infusion. Although tachycardia with pancuronium is an undesired side effect [146] in adults, this is rarely of clinical significance in infants and children. Vecuronium and cisatracurium are competitive blocking agents with shorter durations of action than pancuronium. Vecuronium (0.08-0.2 mg/kg, followed by an infusion of 60-150 mug/kg/h) causes less tachycardia than pancuronium: cisatracurium (0.1-0.2 mg/kg, followed by an infusion of 60-120 mug/kg/h) is not dependent on renal or hepatic function for elimination. Neuromuscular blocking agents need to be titrated using a peripheral nerve stimulator or observing movement with regular drug holidays.

Weaning From Mechanical Ventilation

The criteria for weaning are ill-defined clinical factors. In general, weaning from respiratory support should begin only when the child has a stable cardiovascular system and is awake and alert. It is unwise to begin reducing respiratory support in a child who is still at risk of acute cardiac decompensation. It is also best to wait until other major metabolic abnormalities have been corrected. Severe anemia, hypoglycemia, hypernatremia, hypochloremia, or malnutrition may severely impair a child's ability to be weaned from mechanical ventilation. The chest wall and diaphragm must be intact, and the child should be able to generate at least 20 cm H_2O pressure at the airway (inspiratory force) and be able to move at least 10 mL/kg of air with maximal effort (vital capacity). The parameters that can then be weaned include rate, F_{IO_2}, peak inspiratory pressures, and CPAP/PEEP.

On pressure-limited or time-flow-limited ventilators, the peak inspiratory pressure must be reduced, because compliance improves during the weaning process. The best indicators of a change in compliance are the degree of chest expansion seen clinically and the Pa_{CO_2} decrease as alveolar ventilation increases. If peak inspiratory pressure is not reduced, there is a significant risk of alveolar rupture and resultant pneumothorax and/or pneumomediastinum.

Ventilator rates should not be weaned until the ABG is stable with a required inspired oxygen concentration of less than 0.5, a required PEEP of less than 10 cm H_2O, and a peak airway pressure of less than 30 to 35 cm H_2O.

One must also be certain that all residual effects of neuromuscular blocking drugs have disappeared and that a reduced level of sedation is ordered. Neuromuscular blockade can be reversed with the intravenous administration of neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg); a peripheral nerve stimulator can confirm the presence of acceptable neuromuscular function. [147] Weaning is then begun by gradually decreasing the ventilator rate over a period of hours to days.

Weaning should continue as long as ABGs remain within an acceptable range and as long as the child's clinical condition tolerates weaning. As the amount of effective spontaneous ventilation increases, the increased work of breathing may cause the child's overall condition to change before blood gases begin to deteriorate. Tachycardia, hypertension or hypotension, tachypnea and increased work of breathing, and anxiety are danger signs. Weaning should be discontinued, and additional ventilatory support should be reinstated. Frequent assessment of ABGs and observation of the child's clinical condition are essential throughout the weaning process. If a child has any residual lung disease with decreased lung compliance, there may be a tendency for the development of decreased FRC with atelectasis and decreased lung volumes. These potential problems can be minimized by weaning on moderate levels of CPAP or PEEP (5-10 cm H_2O).

Once the child is completely weaned from mechanical ventilation, it is wise to observe his or her spontaneous ventilation on CPAP alone for a period of at least several hours before reducing the level of CPAP. Once CPAP has been reduced in a stepwise fashion to 2 to 3 cm H_2O without a deterioration in the child's clinical condition or ABGs, it is reasonable to extubate the trachea. Extubation should be performed by an individual skilled in laryngoscopy, should gas exchange deteriorate and reintubation be required. Once tracheal extubation has occurred, it is not unusual for the patient to require a 20 percent increase in F_{IO_2} by face mask or Oxy-Hood oxygenator. It is essential that the patient be encouraged to cough and clear secretions, while taking slow, deep breaths as often as possible. Incentive spirometry, early mobilization, and chest physical therapy play a significant part in recovering from respiratory failure. [147] [148]

It should be emphasized that weaning from mechanical ventilation requires close clinical observation, frequent assessment of blood gases, and good clinical judgment. The rate of weaning depends on the child's overall clinical condition, as well as on the underlying pathologic process. The child who is ventilated postoperatively overnight may be weaned very rapidly (over an hour or two), whereas the child recovering from severe interstitial pneumonia may require days to weeks to be weaned successfully. In chronically ventilated patients, meticulous attention must be paid to other system problems. Intravascular fluid balance must be excellent, with the patient kept relatively "dry." Serum bicarbonate and chloride should be kept in the normal range to prevent compensatory hypercarbia. The hematocrit must be maintained in the high-normal range to minimize cardiovascular stress. Caloric intake should be maximized with enteral or intravenous alimentation. Infection must be under control, and it is best if the child can be alert and cooperative. If the weaning process is stressful, rest periods of full-time mechanical ventilation, particularly at night, may be helpful. We all find a difficult task more easily handled after a good night's sleep.

Before tracheal extubation is considered, careful assessment of the quality and volume of endotracheal secretions is essential. Large, thick secretions may cause extubation to fail if the child is unable to cough and to clear them adequately. Extubation should be planned carefully and should preferably be performed in the morning while a full staff is available for careful observation. If the weaning and extubation process has been carefully planned and executed, reintubation should be a very rare occurrence.

Negative-Pressure Ventilation

Body-type negative-pressure ventilators, first described by Drinker and Shaw in 1929 [149] and used extensively during the polio epidemic of the 1950s, [150] have achieved renewed popularity. Reports of these devices in children and adults with chronic respiratory insufficiency have rekindled interest in the mechanics and physiology of negative-pressure ventilation. Patients with severe neuromuscular disabilities, such as Duchenne muscular dystrophy, and those with chronic obstructive pulmonary disease (COPD), such as cystic fibrosis, have been reported to have sustained improvement in their gas exchange and general clinical condition when subjected to chronic or nighttime home ventilation. Measurements of vital capacities, inspiratory force, and force of diaphragmatic muscle contraction suggest in a preliminary way that this therapy will improve gas exchange, reduce the complications of chronic hypoxemia and hypercarbia, and prolong life. [151]

Several negative-pressure ventilators are available commercially. The iron lung is most commonly employed in the hospital setting. Its large size and weight, as well as its cost, are limitations to home use. The portable body cuirass and raincoat have achieved popularity for home use. An intermittent vacuum pump provides suction, producing a negative pressure within the body shell or cuirass. Although portable and reasonably affordable, these devices are less efficient and noisy and require closer attention, owing to the difficulty in achieving a tight seal and the likelihood of developing air leaks with body movement. Continued use and future critical study will be important in determining the role of negative-pressure ventilation in the treatment of respiratory failure.

The main advantage of negative-pressure ventilation is that the airway does not have to be instrumented with an ETT or a tracheostomy tube. Unfortunately, there are numerous serious clinical limitations. For example, patient size and patient deformity can make the patient-machine interface both difficult and uncomfortable, and the ability to provide basic and specialized patient care can be compromised. Any degree of upper airway obstruction (anatomic/structural or massive secretions) decreases the effectiveness of gas flow in negative-pressure ventilation. Finally, negative-pressure ventilation is not effective in patients with very poor lung compliance; maximal respiratory pressure is 30

cm H_2O, and it is not possible to sustain a reliably constant distending airway pressure (CPAP equivalent). The ideal candidate for negative-pressure ventilation is one who is cooperative, who has normal lungs and upper airway, and who needs intermittent support for neuromuscular disability.

High-Frequency Ventilation

High-frequency ventilation describes a pattern of ventilation characterized by smaller than anatomic dead-space volumes delivered at high respiratory rates (>150 breaths/ min). High-frequency ventilation can be generated by a number of different types of ventilators: the high-frequency jet ventilator, the high-frequency oscillating ventilator (HFOV), and the flow interrupter. Each of these machines differs in technical design and in clinical application and most likely differs in the mechanics of gas exchange. [152]

Use of the HFOV has become accepted practice for neonatal patients with respiratory failure. There is impressive evidence that use of the HFOV has successfully supported infants who previously would have required extracorporeal membrane oxygenation (ECMO) or who would have died. [153] [154] The HFOV used for neonates has been approved by the U.S. Food and Drug Administration (FDA) for the support of patients up to 35 kg. There has been success with HFOV to treat children with

acute homogeneous interstitial and alveolar disease. [155] The use of the HFOV in large children and in adults has been less successful to date, because of physical limitations of the equipment; however, ongoing research suggests that the utility of this mode will be expanded. Jet ventilation is used in some centers for multiple causes of respiratory failure, although the main indication remains the patient with barotrauma.

Exogenous Surfactant

The administration of exogenous surfactant is now routine therapy for the surfactant-deficient premature infant. Numerous preparations are available that have clearly improved the survival of these children and decreased their need for aggressive mechanical support. [156] Exogenous surfactant has not enjoyed the same success in older children and adults. The primary problem is the nature of the lung disease. Whereas the premature infant has an inadequate amount of surfactant, the older patient has surfactant dysfunction or inhibition rather than absolute decrease in amount. Therefore, exogenous surfactant is vulnerable to the same inhibition.

Liquid Ventilation

Perfluorochemical (PFC) liquids are clear, colorless fluids approximately twice as dense as water with one-fourth its surface tension, 16 times the oxygen solubility, and 3 times greater CO_2 solubility. PFC liquid was first used as a respiratory medium in the 1960s [157] and was popularized in the 1989 movie *The Abyss.* The first human trials of tidal PFC liquid ventilation involved 3 preterm infants "at the point of death" because of severe respiratory failure. They were successfully ventilated for two 3- to 5-minute cycles using PFC liquid tidal volumes exchanged by gravity. [158]

More recent approaches have employed PFC liquid-filled lungs and gas ventilation using a conventional mechanical ventilator. This therapy is referred to as partial liquid ventilation (PLV) or perfluorocarbon-associated gas exchange. [159] The PLV technique has been shown to produce significant improvements in lung function and viability in numerous animal studies of diseased or injured lungs. The decreased surface tension of the perfluorocarbon gas interface enables recruitment of atelectatic alveoli with lower ventilator pressures. This allows reduced oxygen settings, and the combined effect of lower oxygen toxicity and barotrauma can apparently minimize lung damage. PLV is now undergoing clinical trials in the treatment of pediatric respiratory failure. The first published report of PLV in humans involved six children being treated with extracorporeal live support for respiratory failure. They underwent PLV for periods ranging from 3 to 7 days. All six patients survived to hospital discharge. [160]

Extracorporeal Membrane Oxygenation

ECMO is standard of care for term (34 weeks' gestation) neonates with acute respiratory failure (ARF). More than 11,000 infants with an 80 percent predicted mortality receiving conventional management have received ECMO support, 81 percent of whom survived. [161] Although neonatal ECMO is successful, the technology and the patient populations are constantly changing. The majority of ECMO is venoarterial (VA), in which blood is drained from the venous system and is returned to the ascending aorta, supporting not only respiratory but cardiac function as well. Venovenous (VV) ECMO is less efficient than VA ECMO, but it preserves pulmonary flow and avoids cannulation of the arterial system. VV ECMO is rapidly gaining popularity, and many clinicians believe that VV ECMO will be more commonly used than VA ECMO. [162] In addition to these technical changes, the target neonatal ECMO populations are also changing. Exogenous surfactant and new modes of ventilation such as HFOV are "saving" children from ECMO. In fact, most ECMO centers report that their ECMO candidates are a sicker group of infants, with a greater preponderance of sepsis and multiorgan system failure. ECMO support for premature infants is also being evaluated in some centers with phase I studies. [163]

ECMO support for the older child/adult with ARF continues to pique interest. Approximately 500 pediatric ARF ECMO patients have been reported to the Extracorporeal Life Support Organization. All were patients who had a presumed 80 to 100 percent predicted mortality. With ECMO support, 52 percent have survived. [161] These data are difficult to evaluate in this population because of the extreme heterogeneity of age, diagnoses, conventional management, and criteria for ECMO. In addition, whereas the neonatal causes of ARF generally have reversible pathophysiologic features, reversibility of ARF in the older patient population is uncertain. [164] [165]

Common Respiratory Disorders

Laryngotracheobronchitis (Croup)

Croup is the most common cause of acute upper airway obstruction in the otherwise healthy child (Ch. 59) . This viral infection (parainfluenza, influenza, adenovirus) produces swelling and edema of the tissues in the upper airway, particularly in the immediate subglottic region. Croup occurs most commonly in young infants and children between the ages of 3 months and 3 years. Children usually present with a few days' history of an upper respiratory infection followed by the development of hoarseness, a croupy cough, and possibly stridor. [166] These children are nontoxic. The degree of respiratory distress and the child's ability to compensate for the increased work of breathing are best assessed by clinical examination.

Infants are initially treated with mist and aerosolized racemic epinephrine to reduce local mucosal swelling. [167] The use of steroids is both common and controversial. [125] Intubation is required when the infant can no longer sustain the necessary work of breathing. The child is intubated with the smallest possible ETT (usually 3.0 mm in a child <2 y or 3.5 mm in a child aged 2-4 y) that will permit suctioning of secretions. Spontaneous resolution in 3 to 7 days is common. In our experience, the average duration of intubation is 4 to 5 days. As the trachea grows, laryngotracheobronchitis becomes an uncommon cause of significant airway obstruction in children older than 3½ or 4 years of age.

Epiglottitis

Epiglottitis is an inflammation of the mucosa of the supraglottic structures usually caused by *Haemophilus influenzae* type B. [168] It is a true pediatric emergency: the rapid progression has the potential for unpredictable and fatal airway obstruction. Restoration of a secure airway is the first priority. Epiglottitis is usually easily differentiated from laryngotracheobronchitis in that patients with epiglottitis are usually older (4-6 y), there is rarely an antecedent upper respiratory illness, and the child is quite toxic with the fulminant onset of fever and respiratory distress. Expectant intubation under anesthesia is the most common treatment until antibiotic therapy (ampicillin and chloramphen-icol or ceftriaxone) is initiated and signs of systemic toxicity subside. The incidence of epiglottitis is dependent on contact with *H. influenzae,* which occurs most commonly in the early school-age population. [169] The introduction of *H. influenzae* vaccine has dramatically decreased the incidence of this disease, as well as that of other *H. influenzae* processes. [170]

Bronchiolitis

Bronchiolitis is an acute viral infection of the lower respiratory tract, frequently occurring in the first 2 years of life, when small airways have the lowest specific conductance. The signs and symptoms are air trapping, wheezing, mild to moderate systemic hypoxemia, and a considerable increase in the work of breathing because of increased airway resistance. The cause is viral, usually attributed to respiratory syncytial virus. [171] Bronchiolitis is epidemic in nature and variable in severity.

Although the disease is self-limited, patients at high risk of respiratory failure include the very young and infants with a history of prematurity, chronic lung disease, or congenital heart disease. In the very young, apnea is often the first sign of decompensation, frequently occurring before significant hypercarbia. Clinical signs of fatigue are often more important than ABG sampling in determining whether mechanical ventilation is indicated. Therapy is primarily supportive, with endotracheal intubation and mechanical ventilation when the child can no longer support gas exchange. [172]

Ribavirin is a virostatic drug currently available for use in children with respiratory syncytial viral infection. Infants and young children with complicated congenital heart disease, underlying immunosuppressive diseases, or multiple congenital anomalies who develop respiratory syncytial viral disease and are at high risk of serious complications should be considered for ribavirin aerosol therapy. Because of concerns about its safety, benefit, and cost, definitive recommendations for ribavirin therapy are not possible at this time. [170]

Status Asthmaticus

Asthma, a disease of airway hyperreactivity, is the most common chronic respiratory disorder of childhood and is often the most frequent admission diagnosis to a pediatric medical service. Acute attacks are generally associated with intercurrent viral infections, allergen exposures, stress, or noncompliance of therapy. [173]

The chronic treatment of asthma emphasizes inhaled aerosolized beta-agonists and steroids. [174] Of concern, the number of asthmatic patients and the mortality rate of asthma have been increasing. High mortality is associated with a number of risk factors: teen age, black race, history of previous life-threatening episodes, hospitalization within the last year, poor long-term medical care, and psychologic and psychosocial problems. [173]

Some children with extremely severe asthma are now being treated with methotrexate, with improvement in some. Some pulmonologists and allergists believe that the risk-to-benefit ratio of methotrexate favors the use of this drug in some patients with severe asthma. [175]

Most episodes of status asthmaticus respond to emergency department management with oxygen, nebulized/inhaled beta-agonists, anticholinergic agents, and steroids. A few children, however, fail to improve, or even worsen, despite this therapy. Signs of respiratory failure develop, including tachypnea and tachycardia, very poor aeration with a prolonged expiratory phase, marked retractions, and nasal flaring, increased pulsus paradoxus, anxiety, or depressed mental status. Despite the increased minute ventilation, Pa $_{CO_2}$ is either normal or elevated, and moderate to severe hypoxemia is present. Treatment of this impending respiratory failure is to maximize conservative therapy and to start an intravenous terbutaline infusion, beginning at a rate of 0.1 mug/kg/min and increasing until clinical improvement occurs

or until heart rate exceeds 180 to 200 beats/min. If the patient is being treated with aminophylline, levels should be closely monitored. It is important to note that both phosphodiesterase inhibitors and adrenergic agonists share the serious side effects of increased myocardial oxygen consumption, potential myocardial ischemia, and ventricular arrhythmias [176] ; hence, it is important to prevent hypoxia and to monitor closely with a continuous ECG. Children tolerate these drug groups better than do their adult counterparts, most likely because children have relatively normal coronary arteries and better myocardial reserve.

Tracheal intubation and mechanical ventilation are considered a last resort. Pa $_{CO_2}$ values in excess of 70 or 80 mm Hg are tolerated as long as the patient is cardiovascularly and neurologically stable. [177] Intubation is only rarely required in the pediatric patient with asthma, and intubation is avoided if possible, because the ETT serves as an irritant in the airway and may cause further bronchoconstriction. In addition, mechanical ventilation is usually inefficient in the patient with small airways disease, and the complications of barotrauma in all its forms are common. Inhalation anesthetic agents such as halothane and isoflurane have been used as bronchodilators in mechanically ventilated patients with asthma and with severe respiratory failure who are unresponsive to maximal conventional therapy. [178] ECMO could also be used in these patients if gas exchange cannot be achieved with conventional ventilators.

Cystic Fibrosis

Cystic fibrosis is becoming an increasingly common diagnosis of children and young adults in the PICU. It is a fatal autosomal recessive disease carried on chromosome 7. Although it manifests with pancreatic, hepatic, pulmonary, gastrointestinal, and reproductive abnormalities, 90 percent of the reported morbidity and mortality is pulmonary. [179] The pulmonary pathology is severe obstructive disease with bronchiectasis, emphysema, and, ultimately, terminal respiratory failure.

Survival has improved dramatically over the past 30 years. More than one-third of patients survive beyond the age of 30 years. [180] This change reflects improved antibiotic therapy, nutritional adjuncts, and a more aggressive approach to the complications of the disease. This aggressive approach often involves extensive surgical procedures such as pleural stripping and pulmonary lobectomies. The success of these procedures necessitates a program of careful preoperative, intraoperative, and postoperative pulmonary care. This can often require a lengthy ICU admission for respiratory support and management. Lung transplants are being offered to these patients with chronic respiratory failure. [181]

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease seen in young patients who survive severe neonatal lung disease. The etiology is uncertain, but patients usually share the common history of prematurity, hyaline membrane disease, and a requirement of prolonged aggressive respiratory support with high levels of inflating and distending pressures and high F $_{IO_2}$ values. Children with BPD have a decreased dynamic compliance, increased airway resistance, increased physiologic dead space, and a markedly increased work of breathing. On examination, these children are hyperinflated with retractions, nasal flaring, and wheezing. Chest radiographs show large lung volumes, fibrosis, and cystic and atelectatic areas. ABG show a chronic hypercarbia and varying degrees of hypoxemia. [182] [183]

Therapy for BPD includes maximal nutritional supplementation to support the large energy expenditure for the increased work of breathing in addition to varying degrees of respiratory support. Some children have been treated with chronic mechanical ventilation and chronic increased ambient oxygen. Diuretics and bronchodilators are often adjunctive therapies. Most children are long-term survivors with subjectively normal pulmonary function. However, there is evidence [184] [185] demonstrating chronic physiologic changes in this population. During the first years of life, any extraneous pulmonary infection or embarrassment may necessitate acute or chronic intensive respiratory support or may in fact prove to be a fatal event.

Much effort is being made to prevent the development of BPD. Because the trauma of mechanical ventilation on the immature lung is identified as the major cause, alternate modes of ventilatory support are being evaluated. These include exogenous surfactant, high-frequency ventilation (especially HFOV), [153] ECMO, and liquid ventilation. [182] [186]

Sleep Apnea

Normal ventilation during sleep depends on normal upper airway anatomy and a number of intact reflexes, including central response to hypercarbia and hypoxia, response to airway irritation, and dynamic phasic contraction of the pharyngeal and hypopharyngeal muscles, which maintain a patent airway. Sleep apnea usually results from an abnormality of one or more of these normal protective responses.

In infancy, central sleep apnea is not uncommon. Numerous potential causes have been postulated, but perhaps the most attractive is immaturity of the medullary chemoreceptors. Central sleep apnea can be complete, as in the Ondine curse, or it may be some lesser degree of hypoventilation related to the group of disorders causing sudden infant death syndrome (SIDS). Treatment consists of respiratory stimulants (theophylline), cardiorespiratory monitoring during sleep, and, in complete sleep apnea, tracheotomy and nighttime mechanical ventilation. [187]

Obstructive sleep apnea can occur in any age child. It can be associated with an identifiable anatomic disorder (e.g., tonsils, adenoids, and Pierre Robin) or with the more obscure dynamic abnormalities of lax pharyngeal musculature. Signs and symptoms include loud snoring, obstructive episodes with constant arousal, behavior disorders associated with sleep deprivation, and cor pulmonale. Diagnosis is made by history, ECG, and formal sleep studies.

Treatment includes any maneuver that helps to remove or to bypass the obstruction. Tonsillectomy and adenoidectomy are usually performed to maximize the patent airway. Rarely does a child require a tracheostomy for definitive therapy.

Foreign Body Aspiration

Foreign body aspiration is a relatively common and often catastrophic event in children. Although it can occur at any age, the peak incidence is 6 months to 3 years. Materials aspirated range from vegetable matter (peanuts) and other foodstuffs (hot dogs) to coins and small pieces of toys; of interest to the clinician is that most of

these objects are radiolucent. Presenting symptoms are a function of both the location of the foreign body within the airway and the time of presentation. Acute symptoms may include total airway obstruction, stridor, wheezing, or acute onset of cough, whereas more chronic symptoms are bloody sputum, chronic cough, or wheezing. The diagnosis is made on the basis of history and examination. Specific radiologic imaging can be useful (plain films or fluoroscopy).

Treatment is controversial. There is much argument about the comparative efficacy and safety of abdominal thrusts, Heimlich maneuvers, and back slaps, all of which are reserved for the acute upper airway obstruction in which there is no air movement. Treatment of less acute or lower airway foreign body aspiration includes bronchoscopy, postural drainage, chest physical therapy, bronchodilators, and surgical removal. [188]

Upper Airway Obstruction and Meningomyelocele

Stridor from bilateral vocal cord abductor paralysis is a reported complication of myelodysplasia. The vocal cord paralysis is secondary to brain-stem abnormalities. Children with meningomyelocele have associated Arnold-Chiari malformations with a caudally displaced medulla, abnormally long cranial nerve tracts, and abnormal arterioarchitecture of the brain stem.

The vocal cord paralysis may be secondary either to pressure on the brain stem (i.e., with hydrocephalus) or to focal infarcts. Treatment entails decompressing any degree of hydrocephalus and, if the paralysis persists, performing a high cervical decompression. Despite these surgical maneuvers, some children require a tracheotomy for long-term care.

CENTRAL NERVOUS SYSTEM

CNS dysfunction secondary to systemic illness occurs quite commonly in infants and children. Seizures, head trauma, CNS infections, and hypoxic or metabolic encephalopathy are the common causes of acute neurologic dysfunction in the PICU. Assessment of neurologic function depends on an understanding and awareness of the age-dependent progression of motor and cognitive skills. Table 73-11 (Table Not Available) lists the developmental milestones.

Functional Postnatal Neurologic Development

Motor function in the newborn is dependent on gestational, rather than postnatal, age. [189] That is, an infant born at 28 weeks' gestation who is 3 months old exhibits motor responses similar to those of a full-term newborn. Motor function and tone as well as reflex behavior serve as the basis for assessing gestational age in the newborn. Although potentially modifiable by cortical influence, most neonatal motor behavior is subcortically controlled, [190] permitting normal motor behavior in newborn infants with severe cortical damage.

Intellectual development is difficult to assess in the newborn; initially, it is predicated on the loss of some newborn reflexes and on the acquisition of new motor skills. Adaptive

TABLE 73-11 -- Normal Ages for Major Developmental Milestones

(Not Available)

Modified from Crone [30C]

or interactive behavior is first seen with accommodation to repeated stimuli and eye contact. The infant's intellectual development depends on the presence of significant external stimulation and social interaction, preferably from one or a few individuals. This has important implications for the infant and child requiring long-term intensive care.

Monitoring of Neurologic Function

The most important aspect of assessing neurologic function is the clinical examination. In the awake child, interactions with the examiner and caretakers are all sensitive indicators of high or integrative cortical function. When the child's cognitive function is depressed from disease or pharmacologic agents, examinations of gross motor function, general level of activity, and peripheral and brain-stem reflexes become important, albeit crude, measures of CNS function. The Glasgow coma scale (GCS) has been used to quantitate the level of function in neurologically impaired patients [191] (Table 73-12) (Table Not Available) . A pediatric GCS has been developed to obviate the problems in a child without language skills (Table 73-13) (Table Not Available) .

Laboratory Assessment of Neurologic Function

The electroencephalogram (EEG) is useful in identifying seizure activity, in diagnosing isoelectric brain death, and in monitoring therapy during therapeutic barbiturate coma. Otherwise, in most neurologic diseases, the EEG is so nonspecific as to be uninterpretable. Brain-stem-evoked potentials (auditory, visual, and somatosensory) have gained acceptance as a means of neurologic assessment in the comatose patient. Evoked potentials define marginally functioning neurons that cannot be detected by the clinical examination. Asymmetry, abnormality, or absence of conduction of auditory, visual, or tactile stimuli through the brain stem to the cortex can provide useful information regarding the progress of neurologic injury or recovery. Although evoked potentials are only mildly affected by barbiturates, a

TABLE 73-12 -- Glasgow Coma Score[a]

(Not Available)

Modified from Teasdale and Jennett [191]

[a] Chs. 35 and 52

TABLE 73-13 -- Modified Coma Score for Infants

(Not Available)

From Ramondi, [385] *reproduced with permission of S.Karger AG, Basel*

flat response during therapeutic coma cannot be used as diagnostic of brain death.

Computed tomography (CT) remains an invaluable tool for rapid evaluation of the neurologically impaired child for surgical lesions, extent of structural injury, and noninvasive assessment of ICP. Cranial ultrasound is an effective bedside method of assessing ventricular size and intracranial anatomy in the infant whose cranial sutures have not yet fused. Magnetic resonance imaging (MRI) plays an increasingly important role in the evaluation of acute brain injury. Qualities that make the MRI invaluable in the examination of intraorbital and ocular injuries and brain-stem and spinal cord disorders are its multiplanar imaging capabilities, exquisite soft tissue contrast resolution, and lack of bone interference. [192] The major drawbacks of MRI are the length of time required to complete the examination and the relative inaccessibility of the patient in the scanner. The logistics of safely obtaining an MRI scan for a patient who has significant cardiorespiratory compromise are formidable.

Doppler ultrasound is gaining popularity as a method of assessing cerebral blood flow velocity in the ICU. Although incapable of measuring cerebral blood flow (CBF) directly, it is proving useful as a noninvasive bedside tool for guiding therapy to effect cerebral perfusion. Cerebral angiography plays an increasingly smaller role with the introduction and development of these less invasive tests. CBF scans remain the gold standard for the diagnosis of brain death during barbiturate coma.

Methods of ICP monitoring include placement of a catheter in a lateral ventricle, a subarachnoid screw, a transducer in the epidural space, or cerebral parenchyma. The ventricular catheter is inserted through a drill hole placed in the area of the coronal suture in line with the ipsilateral pupil. If the ventricle is large enough, a

catheter can be placed easily, by penetrating brain substance. It produces an accurate waveform and has the advantage that cerebrospinal fluid (CSF) can be removed as a treatment of raised ICP.

The subarachnoid screw is placed transcranially via a drill hole through which the dura and arachnoid have been incised. Although placement is technically easier than with the intraventricular catheter, the pressure tracing is easily damped and is possibly inaccurate when the brain is soft and swollen. The subarachnoid screw cannot be placed in children

---

under 1 year of age, because the bony structure cannot support the appliance.

The epidural transducer is placed by way of a bur hole or through a formal craniotomy incision at surgery. It is relatively easy to place and does not require incising the dura; once placed, however, it cannot be recalibrated and is therefore only of relative value.

Pathophysiology of Neurologic Disease

The pathophysiology of critical neurologic disease includes increased ICP, abnormal electrical discharge (status epilepticus), and focal loss of functioning neurons (Ch. 52) .

Increased Intracranial Pressure

Increased ICP has been implicated as a potential source of morbidity and mortality in severe neurologic diseases such as head trauma, Reye syndrome, hypoxic ischemic encephalopathy, metabolic encephalopathies, intracranial space-occupying lesions, and hydrocephalus. Increased ICP occurs with an increase in intracranial volume: CSF, blood, brain, or supporting tissues. An increase in one compartment can only occur at the same ICP by displacing another compartment. When displacement is no longer possible, ICP rises proportionate to volume. [193] In older children and adults with closed sutures and rigid calvaria, the cranial cavity is a closed receptacle whose contents are incompressible.

Intracranial Compliance Curve

Recognition of increased ICP is important. In addition to the underlying pathology, intracranial hypertension causes further neurologic injury by two mechanisms: (1) if ICP is sufficiently high to reduce the arteriovenous pressure gradient or cerebral perfusion pressure (CPP), brain ischemia occurs; and (2) ICP can cause compression and herniation of the brain stem or other vital structures if a pressure differential exists. This compression alters brain function acutely and may cause ischemia or infarction of the brain stem. During the past several years, monitoring of ICP and anticipatory treatment of intracranial hypertension have led to claims of improved outcome, particularly in patients with head trauma.

Head Trauma

Significant percentages of adult patients with head injury and altered level of consciousness have abnormal ICP. In one study of 160 head-injured patients, the ICP on admission was greater than 20 mm Hg in 44 percent of cases and greater than 10 mm Hg in 82 percent. All patients whose ICP could not be reduced by therapy to less than 20 mm Hg died. [194] Other studies have confirmed that sustained intracranial hypertension following head injury is associated with poor outcome. Although these trends are impressive, it is important to recognize that the acceptable upper limit of ICP is unknown and may vary with age and disease. [195]

As many as 50 percent of patients who die of head injury are conscious at admission, yet many succumb as increasing ICP impairs CPP. CBF studies done acutely after head trauma have demonstrated that an increased CBF and CBV (hyperemia) are frequent, although unexplained, findings in children. Thus, this common early increase in intracranial volume is usually due to an increase in blood volume, not cerebral edema. In children who die a few days after sustaining head trauma, the most common neuropathologic finding is a swollen brain with little, if any CSF. CT scans confirm in the first days after injury that ventricular size frequently decreases as cerebral swelling increases. [196]

Adults with head injuries and GCS scores (see Table 73-12 (Table Not Available)) of 7 or less (i.e., not spontaneously verbalizing or responsive to pain) have an approximately 55 percent incidence of significantly elevated ICP. It is noteworthy that the incidence of abnormal ICP is similar in patients following evacuation of a hematoma compared with patients without surgical lesions. [197] In children, intracranial hypertension did not occur with GCS scores higher than 6, but it was present in 81 percent of those with GCS scores of 3 or 4. [195]

It is important to reiterate that intracranial hypertension is frequently not detectable by clinical examination. Although certainly not a substitute for careful neurologic assessment, ICP monitoring may provide evidence that further intervention is necessary. In head-injured patients, intracranial hypertension may occur with or without a surgical lesion, or it may only develop after a hematoma is evacuated. Although children have better outcomes than adults after similar head injuries, significant damage frequently occurs. [198] Evidence is accumulating that prompt recognition and treatment of increased ICP increase survival and improve neurologic outcome. [199]

Hypoxic-Ischemic Encephalopathy

There is little documented experience on the incidence of increased ICP in this group or on the ability to alter outcome. However, general clinical impressions suggest the following: (1) outcome is less favorable in this group than in those with trauma or metabolic encephalopathy; (2) aggressive management of ICP, at best, prevents further damage; and (3) the GCS provides a reasonable assessment of initial neurologic function in these patients.

Hydrocephalus

A massive increase of the CSF component of the intracranial volume can result in increased ICP. The most common causes of hydrocephalus are obstructed ventricular shunts or aqueductal stenosis/compression from congenital malformations, infection, posterior fossa tumors, or intracranial bleeds. Decompression of the system by either external or internal shunts can be lifesaving.

Tumors

Brain tumors in children are common. They are characteristically found in the posterior fossa, which is a relatively clinically silent area. The initial presentation may be focal

---

deficits, ataxia, or symptoms of increased ICP either from tumor mass or from secondary obstructive hydrocephalus.

Guidelines for Intracranial Pressure Monitoring

A patient with a diagnosis of head trauma, Reye syndrome, or metabolic encephalopathy is a candidate for ICP monitoring if the following criteria are met: a GCS score of 7 or less, clinical signs of increased ICP, and evidence of increased ICP on CT scan.

Coagulopathies must be corrected before any ICP monitor is placed.

Treatment of Increased Intracranial Pressure

Once intracranial hypertension is documented, prompt therapy must be initiated. Increases in pressure must be interpreted within the context of the clinical situation. While treating increased ICP, it is important to expedite the treatment of the underlying condition, which may also be therapeutic for the intracranial hypertension (i.e., evacuation of a hematoma, drainage of CSF in hydrocephalus, or antibiotics). The general approach to increased ICP includes the following maneuvers:

1. *Positioning.* The head is elevated to 15 to 30 degrees and is kept in midline position to enhance cerebral venous outflow and to maximize CPP.
2. *Adequate oxygenation.* The airway is secured and oxygenation is maintained with the Pa o_2 at 100 mm Hg or greater. Elevated airway pressures should be avoided if possible.
3. *Hyperventilation.* Elevated Pa co_2 decreases cerebrovascular resistance and increases CBF, CBV, and ICP. Conversely, reducing Pa co_2 decreases CBF, CBV, and ICP. [200] [201] Overvigorous hyperventilation could reduce CBF to such a degree as to produce ischemia; a Pa co_2 of approximately 25 mm Hg is generally effective and safe for the acute management of intracranial hypertension. Prolonged hyperventilation has not been demonstrated effective and may be deleterious in patients with severe head injury. [202] Mild hyperventilation with a Pa co_2 of 30 to 35 mm Hg should be maintained in the child recovering from head trauma.
4. *Osmotic agents and diuretics.* Mannitol reduces ICP by decreasing blood viscosity, transiently increasing CBF and improving oxygen transport, which results in a decreased adenosine level. The drop in adenosine causes cerebral vasoconstriction in areas of the brain that have intact autoregulation. [203] CBF remains constant with a decrease in CBV and ICP. Mannitol will have little effect if autoregulation is impaired or CPP is elevated and cerebral vasoconstriction is already maximal. Mannitol should be administered only when necessary to control ICP. Serum osmolarity should be measured and should not exceed 320 mOsm/L. Furosemide reduces ICP by causing the preferential excretion of water over solute in the distal renal tubule. [204] Serum electrolytes should be monitored, and hypovolemia with decreased cardiac output should be avoided.

Steroids

Steroids have been proven efficacious in decreasing vasogenic edema surrounding a brain tumor and reducing 8th nerve swelling and associated hearing loss from bacterial meningitis. [205] [206] It has become increasingly clear that steroids play no role in the treatment of global cerebral edema. Precautions to avoid gastric ulceration should be undertaken if steroids are used.

Temperature Control

Hyperthermia is to be avoided in all patients with brain injury. Cerebral metabolic rate is proportional to body temperature increasing 5 to 7 percent/°C. Antipyretic agents (acetaminophen) and cooling devices should be employed for temperatures higher than 37°C. By contrast, hypothermia reduces cerebral metabolic rate. At 30°C, the cerebral metabolic rate is 50 percent of control. [207] [208] There is evidence that induction of hypothermia prior to a cerebral ischemic insult can permit prolonged periods of inadequate CBF, but there is no reliable evidence that hypothermia induced after an insult improves neurologic outcome. Theoretically, there may be a rationale for decreasing the metabolic rate with hypothermia of 30 to 35°C. Practically, temperatures lower than 33°C are associated with a number of multisystem complications that may increase morbidity and mortality. Hypothermia should not be induced unless the patient is paralyzed and anesthetized to prevent shivering.

Glucose Control

Poor neurologic outcome has been associated with hyperglycemia following head injury in adults and children. [209] [210] Several investigators have demonstrated in animal models that hyperglycemia in the setting of incomplete cerebral ischemia leads to enhanced anaerobic glycolysis and lactic acidosis. [211] [212] [213] The ensuing acidosis in at-risk tissue results in extension of the initial injury. When insulin is used to maintain normoglycemia during temporary cerebral ischemia in rats, fewer neurologic deficits are seen than in their hyperglycemic counterparts. [214] Blood glucose levels should be checked. Hypoglycemia should be avoided, but the routine administration of dextrose-containing intravenous solutions in the setting of head injury should also be avoided.

Seizure Control

Seizures cause an increase in metabolic requirements, resulting in increases in CBF, CBV, and ICP. In the paralyzed patient, an EEG should be obtained to document any seizure activity, and all seizures should be aggressively treated with anticonvulsants.

Muscle Relaxants

Neuromuscular paralysis may reduce ICP in patients with intracranial hypertension by reducing increased intrathoracic

---

and venous pressure associated with coughing, straining, or "bucking" the ventilator.

Sedation

Fear, anxiety, and response to painful stimuli (surgical procedures, intubation, neurologic examination) increase CBF and ICP. Although sedating unconscious patients may appear incongruous and can even obscure the neurologic examination, under some circumstances the benefits may outweigh the risk. Most intravenous sedatives, including benzodiazepines, butyrophenones, and barbiturates, are efficacious and frequently decrease CBF and ICP. Ketamine increases CBF and should be avoided. Opioids can be used if the patient has responses to painful stimuli and respirations are controlled.

Barbiturates

Barbiturates induce the greatest reduction in CBF and cerebral metabolism. [215] Thiopental, 1 to 5 mg/kg, as an intravenous bolus, acutely reduces ICP for 5 to 10 minutes. For a more prolonged effect, pentobarbital (Nembutal), 3 to 30 mg/kg, as an intravenous loading bolus followed by a maintenance dose of 1 to 2 mg/kg/h, is effective in reducing ICP. Blood levels of 20 to 40 mg/L are generally effective, although higher levels may be necessary to achieve burst suppression on EEG monitoring and lower ICP. In these doses, barbiturate metabolism and excretion may be altered; and levels must be monitored closely. Because myocardial depression and hypotension are significant complications of barbiturate therapy, cardiovascular function must be closely followed with specialized monitoring (e.g., Swan-Ganz catheter), if high levels of drugs (30 mg/L) are required or if cardiac decompensation is evident. [216] Although barbiturate administration decreases ICP, it has not been demonstrated conclusively that barbiturates improve survival or neurologic outcome. [217] [218] [219]

Lidocaine

An intravenous bolus of 1 to 1.5 mg/kg may be helpful in minimizing ICP increases that occur with noxious airway stimulation (i.e., endotracheal suctioning).

Status Epilepticus in Children

Status epilepticus is defined as continuous motor seizure activity for more than 20 minutes or as repeated episodes without intercurrent awakening. [220] It occurs in children with a history of seizures, as well as in children previously thought to be neurologically normal. Although it is not unusual for no cause to be found, the most common identifiable causes are infections such as meningitis or encephalitis, metabolic abnormalities or toxins, head trauma, and hypoxic and ischemic injury. Because seizure activity increases both brain and skeletal muscle metabolism and oxygen consumption, status epilepticus may place the child at risk of cellular hypoxia. During a seizure, airway obstruction and ineffective chest wall and diaphragmatic excursion are common such that arterial hypoxemia and hypercarbia are

the rule.

Treatment begins with reestablishing an airway, administering oxygen, and ensuring adequate ventilation. Specific treatment is aimed at stopping the seizure activity by the administration of anticonvulsant drugs, preferably by the intravenous route. Especially in the newborn, intravenous administration of metabolic substrate, including glucose and calcium, is important specific, as well as supportive, treatment. Commonly employed anticonvulsants include lorazepam, phenobarbital, paraldehyde, and phenytoin.

Lorazepam is a rapid and reliable drug for stopping seizures. It is administered in small intravenous boluses of 0.1 mg/kg, or it can be given rectally if intravenous access is unobtainable. Phenobarbital is also used, 5 to 10 mg/kg, up to a total dose of 20 mg/kg. The main complication is respiratory depression, which can occur with high levels. This respiratory depression is exaggerated when phenobarbital is used in combination with lorazepam. Phenytoin can also be given intravenously in doses up to 20 mg/kg, but it should be given slowly to avoid cardiovascular depression. Paraldehyde may be given rectally in a dose of 0.3 mL/kg. Last, sodium thiopental in an intravenous dose of 1 to 4 mg/kg stops the most intractable seizures; however, apnea almost invariably occurs, and the risk of vomiting and aspirating may be high. Once the seizures are under control, a cause should be established, with care taken to maintain an adequate airway and ventilation.

Brain Death

The longest-standing criterion for death is irreversible cessation of cardiorespiratory function (Ch. 76) . Today, death has become less well defined as modern technology of organ system support allows clinicians to maintain cardiopulmonary function indefinitely, even after brain function has permanently ceased. These medical advances have necessitated a reassessment of the definition of death; brain death is a clinical and legal definition of death that describes a permanent cessation of brain function.

The clinical criteria of brain death include irreversibly absent cerebral and brain-stem functions. Absent cerebral function is recognized when there is no cortically mediated receptivity or responsivity to external stimuli. [221] Absent brain-stem function is recognized when brain-stem reflexes cannot be elicited: absent pupillary response to light, corneal, oculocephalic, oculovestibular, oropharyngeal, and respiratory reflexes.

Irreversibility is determined when the cause of coma is sufficient to account for the loss of brain function and when the possibility of recovery is excluded by clinical observation and/or laboratory studies. Laboratory studies that should be considered include analysis of blood and urine for toxic substances, EEG, radionuclide brain scans, cerebral angiography, and brain-stem-evoked potentials. These laboratory functions should be considered confirmatory in nature and supplementary to the clinical history and physical examination. It is important to identify any factors that can simulate the clinical and/or laboratory criteria of absent brain function; severe hypothermia (core temperature < 30°C) and elevated

barbiturate levels present the most common situation. Both hypothermia and the presence of barbiturates can significantly depress electrical activity in the brain and may render an EEG meaningless. In such cases, the technetium 99m (^{99m}Tc) radionuclide angiogram is useful. In patients with brain death, there is no arterial blood flow to the anterior and middle cerebral arteries and no venous flow in the sagittal sinus; blood flow to the extracranial tissues is preserved. This study is independent of the patient's core temperature or barbiturate level. It is usually helpful to have at least two physicians concur on the clinical and/or laboratory diagnosis of brain death. All evidence must be clearly documented in the patient's record.

Whenever a patient is declared brain dead, the family should be approached for the possibility of solid organ donation. Tissue donation (e.g., eyes and heart valves) can also be offered to families after the child has had a cardiovascular death. Regional procurement agencies can provide protocols and support to the ICU staff as well as to families.

RENAL SYSTEM

Structural and Functional Development of the Excretory System

The embryologic development of the renal system begins in the middle of the third week of gestation with the development of the pronephric tubule, which undergoes further development and regression through the stages of pronephric duct, mesonephros, and ultimately the metanephric kidney. By 10 weeks' gestation, a functioning kidney and collection system exist, and fetal urine is discharged into the bladder. At 32 to 36 weeks' gestation, nephron induction is complete, and the full complement of nephrons per kidney is present. [222] Table 73-14 (Table Not Available) presents the normal values for pediatric renal function.

Functional Development of the Kidney

Because the placenta is the major excretory organ of the fetus, renal growth is not governed by functional requirements. Renal growth during the third trimester increases

TABLE 73-14 -- Normal Values for Pediatric Renal Function

(Not Available)

Modified frin Goldsmith [227]

linearly with body weight and body surface area. [223] Glomerular filtration rate (GFR) increases rapidly from 28 to 35 weeks' gestation--the period of greatest nephron growth and functional maturation. At term birth, GFR is 10 mL/min/m^2 and increases to 20 mL/min/m^2 by 2 weeks of age. Although GFR is lower in the premature infant, the rate of increase is at the same rate as in the term infant. [224] Tubular functions are not fully mature in the full-term newborn at birth. The newborn kidney is sensitive to antidiuretic hormone (ADH), or vasopressin, but the urine osmolarity can only vary from 50 mOsm/L up to 780 mOsm/L. [225] The tubular function of premature infants is less mature; they can concentrate their urine only to 600 to 700 mOsm/L.

The renal threshold for bicarbonate in the newborn is about 20 mEq/L (
4-6 mEq/L less than that of the adult). This means that standard acid-base nomograms do not apply to infants, because a serum bicarbonate concentration of 20 mEq/L is normal and does not indicate metabolic acidosis. The renal tubular glucose threshold is at adult levels in the term infant, but it is reduced to approximately 150 mg/dL in the premature infant. The full-term infant handles sodium well, with 1 percent or less fractional excretion by the third day of life. Fractional excretion of sodium can be as high as 5 percent in the premature infant. [226] Renin, angiotensin, and aldosterone levels are high in the newborn and decrease over the first few weeks of life. Table 73-14 (Table Not Available) presents the normal values for pediatric renal function. [227]

Renal Failure

Acute renal failure is an abrupt, often temporary, loss of renal function following an insult that may or may not be evident on presentation (Chs. 51 and 55) . Oliguria is the rule, polyuria the exception, and anuria uncommon. Urine volume and composition are altered, and fluid, electrolyte, and acid-base disorders are commonly associated. Therapy is directed at maintaining normal metabolic and fluid homeostasis, supporting nutrition, and exhibiting patience. Acute renal failure is caused by prerenal, postrenal (obstructive), or intrinsic renal disorders. Prerenal causes are related to the adequacy of renal blood flow. Reducing systemic cardiac output, or renal blood flow specifically, reduces urine output and ultimately causes azotemia and ischemic renal damage. Measurement of the adequacy of the circulating blood volume by central venous pressure and cardiac output and assessment of renal blood flow with Doppler flow studies or nuclear imaging techniques are useful in differentiating prerenal from renal causes of azotemia. [228]

Postrenal obstruction to urine flow can occur anywhere within the collecting system. Chronic partial obstruction at the level of the bladder neck or the ureterovesical or ureteropelvic junction is a common form of congenital malformation. Posterior urethral valves are frequently demonstrated in males. All these malformations can cause mechanical obstructive nephropathy and renal injury or renal failure. Signs of obstruction may be subtle and may require radiologic, ultrasonic, or endoscopic evaluation. Recurrent urinary tract infections are frequently the clinical presentation of obstructive lesions. [229]

Intrinsic renal failure may be due to disorders of the renal

glomeruli, tubules, or blood vessels. Glomerular diseases include hemolytic uremic syndrome, poststreptococcal glomerulonephritis, Henoch-Schonlein purpura, and other inflammatory and immune complex diseases. Acute tubular injury is most commonly caused by hypoxia and ischemia; other causes are rhabdomyolysis, sepsis, hyperthermia, hemolysis, and myriad nephrotoxins, such as mercury, carbon tetrachloride, and ethylene glycol. [230] Vascular disease, including arterial embolus and venous thrombosis, as well as congenital malformations, can lead to acute renal failure.

Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS) is one of the most commonly acquired causes of acute renal failure in children. This syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury. In North America, HUS is most often associated with infection by cytotoxin-producing *Escherichia coli* 0157, but other serotypes and other Shiga-like toxin-producing bacteria have been implicated. [231]

E. coli 0157 is an inhabitant of the intestinal tract of cattle and can contaminate the surface of beef during processing. [232] The bacterium is killed on cooking, but it survives in uncooked meat or inside undercooked hamburger. Secondary infections can occur as a result of person-to-person spread in day care centers, institutions, and the military. There also appears to be a familial form of this disease that accounts for a small percentage of the total. [233]

HUS predominates in children from 6 months to 4 years of age, but it ranges from the neonatal period through adulthood. [234] It shares many laboratory and clinical features with the adult disease thrombotic thrombocytopenic purpura. In fact, some investigators consider the two disorders to represent a continuum of the same disease. The abnormalities that develop in HUS are believed to be caused by cytotoxins and lipopolysaccharide, a bacterial endotoxin. The toxins damage endothelial cells in the kidney, vasculature, and other organs directly or indirectly by the activation of leukocytes. [235] Cytokines such as interleukin-1 and tumor necrosis factor, prostaglandin I_2 , thromboxane A_2 , and von Willebrand factor multimeres are also released and probably play a role in the pathogenesis of this disease. [236]

The time from exposure to presentation varies from 3 to 12 days, and symptoms last for about a week. Patients usually present with abdominal cramping, bloody diarrhea, tenesmus, and vomiting. [237] On average, about 10 percent of children with *E. coli* 0157 bloody diarrhea progress to HUS. Mildly affected patients exhibit anemia, thrombocytopenia, azotemia, decreased urine output, and an uncomplicated course. In severely affected patients, anuria is common, hypertension and seizures may occur, and the duration of illness is protracted. A small number of children will exhibit progressive and permanent renal insufficiency, severe and recurrent hemolysis, thrombocytopenia, and neurologic impairment.

Hematologic abnormalities include hemolysis and thrombocytopenia. The Coombs-negative microangiopathic hemolysis can result in hyperbilirubinemia, and, despite reticulocytosis, anemia with hemoglobin concentrations as low as 4 to 5 g/dL can also occur. Thrombocytopenia is caused by platelet destruction and sequestration in liver and spleen. [238] The remaining platelets demonstrate impaired aggregation. [239] Disseminated intravascular coagulation (DIC) is not uncommon. Glomerular capillary endothelial injury is the most consistent renal finding in HUS. Acute renal failure with oliguria or anuria usually lasts less than a week, but it can last more than 10 weeks. [240] Glomerular and/or arterial injury may predominate, depending on the presence and extent of renal insufficiency (glomerular injury) and hemolysis and hypertension (arterial injury). CNS abnormalities are manifested by decreased levels of consciousness, seizures, irritability, ataxia, hypotonia, hemiparesis, hyperreflexia, and hallucinations. CNS complications may be due to severe hypertension, electrolyte disturbances, microthrombi, or cerebral edema and increased ICP. [241] Abdominal cramping is common, and vigilance is required to distinguish colitis from intussusception, intestinal stricture or perforation, colonic gangrene, or other surgical emergencies. [242] Pancreatitis is common in patients with HUS. CHF may be a result of fluid overload, hypertension, anemia, or myocardial depression secondary to circulating endotoxins.

Treatment is primarily supportive, with meticulous attention paid to volume status, electrolyte and acid-base balance, nutrition, antisepsis, and treatment of hypertension and coagulopathies as required. Enteric isolation is mandatory to prevent secondary spread. Accurate fluid intake and output records, weights, and frequent clinical assessments of volume status are the pillars of good management. A central venous catheter can be used for pressure measurements and blood sampling and also as a route for intravenous medications and nutrition. In children with cardiac dysfunction, a pulmonary artery catheter can be useful for assessing changes in volume and function. Nephrotoxic drugs should be avoided if possible, or their dose should be modulated with serum levels closely monitored. [243] Daily fluids should be restricted to replacing insensible losses, urine output, and any ongoing losses. Fluids should be used that reflect the electrolyte content of the losses. Caloric support is essential. Enteral feedings are preferred, but ileus often makes parenteral nutrition necessary. No specific treatment has demonstrated to be effective to date. Antidiarrheal medications prolong the duration of colitis and increase the risk of HUS. [244] Heparin, fibrinolytic agents, aspirin, dipyridamole, corticosteroids, vitamin E, and furosemide are not proven to affect the outcome of HUS. [245] Immunoglobulin therapy and infusions of fresh frozen plasma have had mixed results; no therapeutic benefit has been demonstrated.

Dialysis, improved nutrition, and supportive care have decreased the mortality rate from 100 percent in the original report to less than 12 percent in the last decade. [246] Mortality rates in developing countries and in those children who exhibit a genetic predisposition for HUS remain high.

The technique for peritoneal dialysis includes the placement of a soft catheter with multiple holes into the peritoneal cavity through an anterior abdominal wall incision. This procedure can be performed in the ICU with the use of local anesthesia. Once the placement and patency of the catheter are confirmed, a commercially available dialysate solution is infused into the peritoneal cavity, where it equilibrates with the plasma and extracellular fluids, using the parietal and visceral surfaces as semipermeable dialysis membranes. [247] The period of fluid instillation (dwell time) for equilibration can

be varied, depending on clinical conditions. The composition of the dialysis fluid tends to be similar to that of plasma, containing approximately 130 mEq/L of sodium, 100 mEq/L of chloride, 35 mEq/L of acetate or lactate as a buffer, 3.5 mEq/L of calcium, and 1.5 mEq/L of magnesium. The glucose concentration can be varied to be either isosmotic, with 1.5 percent glucose, or hyperosmotic, with 4.25 percent glucose. The latter concentration allows for additional intravascular and extracellular fluid to equilibrate with the dialysate fluid, so that this fluid, as well as electrolytes, can be removed when the peritoneal cavity is evacuated. Complications occur with peritoneal dialysis. Respiratory compromise from increased abdominal pressure during dwell time may require intubation and mechanical ventilation in children with impaired preexisting respiratory function. Peritonitis from bacterial or fungal agents from contamination of the dialysis catheter or dialysate can occur in a patient whose host defenses are not normal. [248] Severe dehydration, including circulatory collapse and metabolic derangements, can occur if peritoneal dialysis is too rapidly or improperly performed. The principles of hemodialysis are essentially the same as those of peritoneal dialysis, using the blood compartment to interface with a semipermeable membrane rather than the peritoneum. Some investigators argue that hemodialysis is more efficient than peritoneal dialysis and therefore is more appropriate for the acute setting.

More recently, the technique of hemofiltration or ultrafiltration has gained popularity. This is an extracorporeal process in which uremic blood is cleansed by a technique based solely on the principle of convective solute transport. During this procedure, an ultrafiltrate of the plasma is created by hydrostatic pressure exerted across a highly permeable membrane. Simultaneously, the blood volume is replaced by a modified lactated Ringer solution. [249]

Outcome

The prognosis in acute renal failure depends on the patient's age, underlying disease, and the extent of the precipitating insult (Ch. 21) . In general, children tend to have a better outcome than adults; in fact, they usually recover completely from a renal insult of hypoxia or ischemia within a short time, provided other organ systems are not involved. [250] In children who develop chronic renal failure, long-term outpatient peritoneal dialysis or long-term hemodialysis is necessary for survival until a renal transplant can be performed. [251]

ENDOCRINE SYSTEM

Certain endocrine disorders cause chronic disease in the pediatric patient (Ch. 25) . It is beyond the scope of this chapter to discuss these in detail, but some acute disorders frequently encountered in the PICU are highlighted in the following sections.

Adrenal

Abnormalities of the adrenal axis result in either deficient or excessive production of glucocorticoids and/or mineralocorticoids. Many of these disorders are diagnosed and treated as they are in the adult. Special reference should be made to the problems of congenital adrenal hyperplasia, pheochromocytoma, and iatrogenic chronic adrenal insufficiency.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is an autosomal recessive disorder that describes deficiencies in either 21-, 11-, or 17-hydroxylase enzymes. 21-Hydroxylase deficiency is the most common disorder, causing problems from cortisol and aldosterone deficits as well as from the build-up of active intermediary metabolites. [252] 21-Hydroxylase deficiency found in children can either be partial (simple virilizing form) or more complete (salt-losing form); at birth, affected children demonstrate masculinization of the external genitalia, and those with the more complete deficiency show a progressive salt-losing state (i.e., loss of sodium and elevation of potassium). Presentation is usually in the first few weeks of life, with a history of feeding difficulty, vomiting, and failure to thrive--a clinical and historical course suggestive of pyloric stenosis. If these children are not diagnosed and treated early in life, they can present with severe cardiovascular collapse.

Treatment is aggressive support of the intravascular volume and myocardial function and replacement of the deficient hormones. Cortisol can be replaced with oral administration of hydrocortisone at a dose of 25 mg/m^2 /d divided into three doses; if the child is unable to tolerate oral medication, cortisone acetate can be administered intramuscularly in a dose of 37.5 mg/m^2 /d given every 3 days. For emergency therapy, when the oral route is not possible and the perfusion of the muscle bed is poor, hydrocortisone acetate can be used intravenously at a dose of 1.5 to 2.0 mg/kg bolus, then 25 to 250 mg/d in divided doses. Mineralocorticoid is replaced with fludrocortisone acetate 0.05 to 0.2 mg/d orally; these patients usually require the addition of salt to their daily diet. [253] [254] Deficiencies of 11- and 17-hydroxylase do not result in salt wasting; masculinization and hypertension are the common presenting signs. [254]

Pheochromocytoma

Fewer than 5 percent of pheochromocytomas are diagnosed in children. As a rule, these tumors are more often confined to the adrenal medulla, but they can occur anywhere throughout the sympathetic chain. [255] The clinical signs and symptoms of excessive catecholamines are the same as those in the adult.

Iatrogenic Chronic Adrenal Insufficiency

The long-term daily use of steroids for the treatment of asthma, nephrotic syndrome, and malignancies is common. It is important to remember that a hypoadrenal state can result that produces potential risk during severe illness and stress crises. [256] In children, it is also important to remember

that topical steroids have been reported to depress the production of adrenocorticotropic hormone (ACTH). Replacement of stress-level steroids (three times the daily replacement dose) is required.

Anterior Pituitary

Panhypopituitarism can be a problem in the pediatric patient, usually secondary to tumor or to aggressive dissection of tumor. [257] Acute ICU problems that result include the support of the adrenal axis and abnormalities of ADH.

Diabetes Insipidus

Diabetes insipidus can have a central, renal, or psychogenic origin. The central mechanism is the most common form found in ICU patients. The absence of ADH results in polyuria and polydipsia; the patient with a critical disease may not be able to meet the thirst requirement and may then develop severe hypovolemia. Diabetes insipidus can be precipitated by brain tumor, head trauma, neurosurgery, and clinical brain death. [258] [259] Treatment in the setting of the ICU is fluid replacement, or, if this is unwieldy, replacement of hormone with the following: aqueous Pitressin, 0.1 to 1.0 mL IM (duration, 4-6 h); Pitressin tannate in oil, 0.25 to 1.0 mL IM (duration, 24-72 h); desmopressin acetate intranasal, 2.5 to 10 mug bid (duration, 10-11 h). [260] The clinical syndrome may be transient or chronic, and close supervision of fluid intake and output is essential.

Syndrome of Inappropriate Secretion of Antidiuretic Hormone

The syndrome of inappropriate secretion of ADH describes hyponatremia and hypo-osmolality from inappropriate urinary losses of sodium and free water in patients with normal kidneys. Urine osmolality is greater than serum osmolality. This syndrome can be precipitated by a number of mechanisms, including head trauma, neurosurgery, meningitis, hypoxia, and any major surgical procedure with large volumes of fluid shifts and fluid replacement. [261] [262]

This disease is usually self-limited, and the only real problem occurs if the diagnosis is not considered and the level of hyponatremia is low enough to cause CNS dysfunction. Seizures are rare until the serum sodium is less than 120 mEq/dL. Care should be taken to raise serum sodium levels slowly. This syndrome is treated by fluid restriction and, in severe cases, with the infusion of hypertonic or isotonic saline.

Pancreas/Insulin

Hypoglycemia

Hypoglycemia is routinely anticipated as a potential problem in ICU patients. In children, hypoglycemia has been defined by a number of investigators. The definition suggested by Cornblath and Schwartz [263] is generally accepted: premature infants: blood sugar less than 20 mg/dL; term infants up to 3 days: blood sugar less than

30 mg/dL; and children older than 3 days: blood sugar less than 40 mg/dL.

The usual symptoms of hypoglycemia include the early changes of tachycardia, diaphoresis, and weakness, followed by mental clouding, seizures, and coma. [263] In children, hypoglycemia can be precipitated by a number of specific diseases not commonly encountered in the adult. Causes can be subdivided into disorders of increased utilization and disorders of decreased production. Transient hypoglycemia of the newborn from decreased or immature hepatic gluconeogenesis is a condition that self-corrects within hours to days. If the hypoglycemia persists, hepatic enzyme deficiencies, endocrine problems, or hyperinsulinism (i.e., pancreatic cell abnormalities, infants of diabetic mothers) must be considered. Other causes of hypoglycemia in the neonatal period include sepsis, hypothermia, hypoxia, and transplacental exposure to maternal hypoglycemic drugs.

In the older child, hypoglycemia is associated with ketotic hypoglycemia, [264] hepatic enzyme abnormalities, hyperinsulinism, hepatic failure, and Reye syndrome and as a side effect of certain drugs. [265] Regardless of cause, the initial treatment of hypoglycemia is the administration of adequate glucose. The initial emergency dose is 0.5 g/kg given as 50 percent or 25 percent dextrose in water. This should be followed by a dextrose infusion that meets the metabolic requirements of the child (see the later section on gastrointestinal system).

Diabetic Ketoacidosis

The most serious acute complication of diabetes mellitus is diabetic ketoacidosis (DKA), a syndrome of glucose and ketone overproduction and underutilization that results in hyperglycemic ketoacidosis. The clinical syndrome includes dehydration and hypovolemic shock resulting from the forced hyperglycemic osmotic diuresis, compensatory hyperventilation (Kussmaul pattern), life-threatening electrolyte depletion, and, in cases of severe metabolic imbalance, neurologic obtundation and coma. [266] The laboratory evaluation demonstrates elevated blood glucose concentrations, severe metabolic acidosis despite a compensatory hypocarbia, increased osmolality, hyperlipidemia, and a normal or low sodium level (usually fictitiously low because of the hyperlipidemia). There is total body depletion of potassium and possibly phosphate, but levels may be falsely normal because of the metabolic acidosis.

Treatment of DKA requires careful correction of the metabolic derangements with meticulous monitoring of the multisystem complications of DKA, as well as the complications of therapy. Adequate intravascular volume is restored with the administration of an isotonic glucose-free solution. Regular insulin is given as an intravenous infusion of 0.1 U/kg/h. The goal is to decrease the blood glucose at a rate of 75 to 100 mg/dL/h. This infusion is continued until the blood glucose reaches 250 to 300 mg/dL, at which time D_5 W is added to the infusate. [266] This regimen of simultaneous glucose and insulin infusion can be continued until the patient is able to tolerate oral nutrient intake and routine subcutaneous insulin administration. Most clinicians continue the insulin infusion until the acidosis is nearly corrected.

During any fluid administration, potassium should be closely monitored. These children have total-body potassium depletion, and potassium should be added to any infusion as soon as urine output is demonstrated. The addition of phosphate to the intravenous infusion is controversial. [267] The need for phosphate may be more theoretic than real, but in most situations, one-half the potassium is given as a phosphate salt. The severe metabolic acidosis is usually corrected with volume and insulin administration.

The use of bicarbonate is usually avoided because of concern of precipitating or worsening the patient's neurologic status. [268] In severe DKA, there is a tendency for brain cells to reduce their intracellular volume as the patient becomes dehydrated and hyperosmolar. In an attempt to maintain their normal size, brain cells generate osmotically active idiogenic osmoles. These particles attract more water into the intracellular compartment to help the cells retain their size. As systemic rehydration and correction of the hyperosmolar state begin, the brain cells tend to swell until the added idiogenic osmoles are metabolized or cleared. Consequently, rapid osmolar correction can lead to significant brain edema. [269] In addition, rapid correction of the metabolic acidosis may produce worsening neurologic dysfunction. The pH of the brain is determined by the CSF bicarbonate level as well as by the CO_2 content; the CSF CO_2 content equilibrates much more rapidly than the bicarbonate does with the vascular space. Therefore, with systemic correction of the acidosis, respiratory hyperventilation decreases, causing a rise in the Pa_{CO_2}; if this rise is precipitous, there could be a worsening of the CSF acidosis until the increased bicarbonate equilibrates with the CSF space. Because rapid correction of pH is problematic, bicarbonate administration is not advocated in DKA unless there is cardiovascular instability. Even then, the doses administered are small. Unfortunately, despite very careful and slow correction of the hyperosmolar and acidotic state, hyperosmolar coma with fulminant brain edema can occur. [270] The pathophysiology of brain swelling in DKA is poorly understood. There is radiographic evidence that subclinical brain swelling may in fact be relatively common in children with DKA. [271] If the swelling is significant, the therapeutic approach is to administer mannitol immediately and to begin therapy for intracranial hypertension.

GASTROINTESTINAL SYSTEM

Gastrointestinal (GI) problems in the ICU include organ dysfunction and organ failure from acquired disease as well as congenital anatomic malformations and dysfunction. In addition, delivery of adequate nutrition is perhaps the most critical concern in the care of the critically ill patient.

Structural and Functional Development of the Intestine

An understanding of fetal midgut development makes it easier to understand a number of severe congenital anomalies. Although the intestine begins as a hollow tube that is occluded by rapidly growing epithelial cells by 7 to 10 weeks' gestation, this central lumen is later reconstituted when vacuoles within the epithelial cells coalesce. Some of the neonatal intestinal atresias result from abnormalities of this recanalization process. At 3 to 10 weeks' gestation, the midgut lies outside the abdominal cavity, with only the hindgut fixed in the left side of the abdomen. The gut rotates 270 degrees counterclockwise and reenters the abdominal cavity at 10 weeks' gestation. If the midgut fails to migrate back into the abdominal cavity, an omphalocele results. Abnormalities of midgut rotation result in abnormal intra-abdominal relationships, the most important being malrotation volvulus of the intestine. [272]

Development of the Liver

The liver begins as an outgrowth of the foregut ectoderm at approximately 3 weeks' gestation. During fetal life, the liver is relatively large compared with the adult liver. Although the fetus relies on the maternal liver and placenta for detoxification and excreting function *in utero,* the fetal liver is necessary for both prenatal and postnatal survival. As early as 10 to 12 weeks' gestation, the fetal liver is involved in glucose regulation, protein synthesis, lipid synthesis, and some drug metabolism.

Fetal stored hepatic glycogen is approximately three times that of the adult, but it is nearly completely released within several hours of birth to compensate for interruption of the placental supply of nutrients. [273] It takes several weeks for the newborn to restore the liver's stores of glycogen, thus putting the infant at risk of hypoglycemia if any stressful event occurs during this vulnerable period.

Congenital Malformations

Gross anatomic malformations are usually diagnosed during the first few days of life. Some are apparent on initial physical examination, such as omphalocele, gastroschisis, diaphragmatic hernia, and imperforate anus. Others present in the first few days of life as enteral feeding failures, intestinal atresias, microcolon, tracheoesophageal fistula, and meconium ileus. Other malformations present difficult diagnostic and therapeutic dilemmas after the neonatal period. Specific clinical problems are discussed in the following sections.

Intestinal Malrotation and Midgut Volvulus

Malrotation of the intestine is related to the incomplete rotation of the fetal midgut during migration into the abdominal cavity. This abnormal rotation can lead to either partial or complete duodenal obstruction by peritoneal (Ladd) bands or, more important, to volvulus of the midgut. [274] The midgut (duodenum to transverse colon) and its vascular supply hang on a single pedicle; if this twists, vascular infarction of the entire midgut can result. [275] Infants with omphalocele almost invariably have associated malrotation. Symptomatic infants and children usually present with signs of high intestinal obstruction (bilious vomiting) or signs of an acute abdomen, intestinal perforation, and sepsis.

Treatment is surgical reduction and fixation of the volvulus with resection of nonviable bowel. Postoperative respiratory support and total parenteral nutrition are often required in those infants who were severely compromised before surgery.

Meckel Diverticulum

Meckel diverticulum represents a persistence of the omphalomesenteric or vitelline duct that clinically comes to attention as a cause of painless lower GI bleeding. [276] The site of bleeding is an ulceration in the bowel mucosa caused by secretion of gastric acid. Although these hemorrhages are usually self-limited, massive and life-threatening hemorrhages have been reported. [277] The diagnosis is often one of exclusion and can be difficult to make. The technetium-pertechnetate isotope scan is helpful only if there is gastric mucosa in the diverticulum. Therapy is supportive, with particular attention paid to blood replacement. The definitive therapy is surgical resection.

Hirschsprung Disease

Hirschsprung disease (congenital aganglionic megacolon) is characterized by absence of the parasympathetic ganglion cells in varying distal lengths of the rectum and colon. [278] The lack of these ganglion cells produces a relatively narrowed segment of bowel: the normal proximal bowel becomes distended. The resultant clinical symptoms can be relatively minor, with abdominal distention and stool retention, or severe, with toxic megacolon, peritonitis, and perforation. Toxic megacolon usually presents in the younger child; reported mortality rates are as high as 75 percent. [279]

The diagnosis of Hirschsprung disease can sometimes be made on the basis of history and physical examination. Barium enema should reveal a narrowed segment with ballooning of the proximal bowel. The definitive diagnosis is made by rectal/colon biopsy with observation for the presence or absence of ganglion cells. Treatment of toxic megacolon is both supportive, with meticulous volume reexpansion and antibiotic coverage, and definitive, with surgical decompression by creating a colostomy in the region of normal bowel.

Other Intestinal Disorders

Intestinal disorders can produce bleeding, obstruction, or inflammation with secondary problems of malabsorption and bowel perforation. GI bleeds in children are caused by inflammatory diseases (gastritis), ulcers, varices, or vascular malformations. Although ulcer disease is an uncommon presenting complaint in the pediatric patient, the problem of stress ulcer or stress gastritis must be anticipated in any critically ill child. Prophylactic antacids or a histamine II antagonist should be considered. Bowel obstruction can occur from intussusception, twisting of the bowel around congenital or postsurgical bands, and twisting of the bowel on itself (volvulus). Intussusception is relatively common in the pediatric age group and usually occurs in the distal ileum. Only in a few cases can a leading point be identified, such as a polyp or localized edema, as seen in Henoch-Schonlein purpura. The treatment of intussusception can be surgical, or, if there is no evidence of necrotic

bowel, many lesions can be successfully decompressed with a carefully manipulated barium enema. [280] Inflammatory bowel diseases include Crohn disease and regional enteritis. [281] [282] Infectious agents that must also be considered include *Salmonella, Shigella,* and *Yersinia.*[283] These patients can present with diarrhea, evidence of malabsorption, especially with lactose intolerance, and bloody diarrhea. They can also present with a toxic acute abdomen.

Necrotizing Enterocolitis

A specific disease that merits separate discussion is necrotizing enterocolitis, commonly referred to as NEC. This fulminant neonatal disease is characterized by ulceration and necrosis of the small bowel and colon. It has been reported to occur in 2.4 per 1,000 live births. [284] The cause is unknown, but most hypotheses suggest bowel ischemia as the main precipitating factor. Umbilical artery catheters, perinatal asphyxia, respiratory distress syndrome, and persistent patent ductus arteriosis have all been implicated. [285] Most children have had enteral feedings before clinical NEC develops: some investigators suggest that specific pre-existing bowel flora carries a risk of the disease. [286] Feeding intolerance, abdominal distention, and bloody stools are the most common presenting signs. Intestinal obstruction, perforation, and sepsis may follow. Treatment consists of withholding enteral feedings, administering appropriate antibiotics, and surgical exploration if an acute abdomen with free air is evident. Total parenteral nutrition is often required for several weeks, and intestinal obstruction can occur weeks to months after a relatively benign course. [287] [288]

Hepatic Failure

Hepatic failure can occur in patients with chronic or acute liver disease. The causes and clinical presentations differ: chronic liver failure can be caused by biliary atresia, inborn errors of metabolism (tyrosinosis, Wilson disease, galactosemia, cystic fibrosis), or chronic inflammatory hepatitis. Children with chronic disease often present with the signs and symptoms of synthetic dysfunction (malnutrition, hypoalbuminemia, abnormal coagulation), degradation dysfunction (icterus and hyperammonemia), and portal hypertension (hypersplenism and varices). Acute liver failure is most commonly caused by infectious hepatitis, types A and B. Toxic hepatic failure is a close second. [289]

The physical examination is important for the identification of liver and spleen size and for evidence of bleeding, edema, and other organ dysfunction. The laboratory evaluation should include a screen of the synthetic function (albumin, prothrombin [PT], partial thromboplastin time [PTT]), a degradation screen (bilirubin, ammonia), and values of all the liver enzymes. Hepatic ultrasound, radiographic contrast studies, and liver biopsy are indicated on an individual basis.

The life-threatening complications of liver failure include acute bleeding, cardiovascular compromise secondary to

massive intravascular hypovolemia from fluid shifts, and intracranial hypertension from the toxic encephalopathy. Treatment is expectant and supportive. A 10 percent dextrose infusion is used to guarantee an adequate carbohydrate supply. Low-protein diets tend to minimize ammonia production. Coagulation is supported with the administration of vitamin K, fresh frozen plasma, and platelets as required. Plasmapheresis with fresh frozen plasma and platelets can be used to improve coagulation while maintaining normovolemia. Oral lactulose and neomycin enemas are given in an attempt to decrease the enterohepatic cycle of ammonia production and absorption. [290] Cardiovascular and respiratory function should be closely monitored and supported as required.

It is important to anticipate the complication of intracranial hypertension. Serum ammonia levels are often used to monitor or track the neurologic dysfunction, [290] [291] but it is important to remember that it is unknown whether the ammonia is the primary CNS toxin or is just one of many chemical markers. There are other specific and controversial therapies as well. Steroids have been proposed for some forms of inflammatory hepatitis. Exchange transfusions and plasmapheresis have been advocated to decrease the toxin load, [290] and although they have had variable results, to date no strong evidence indicates that morbidity and mortality are changed with these interventions. Patients with certain forms of acute hepatic failure, including that resulting from toxic as well as infectious causes, may be considered candidates for liver transplantation. [292]

Extrahepatic Biliary Atresia

Extrahepatic biliary atresia occurs once in every 8,000 to 10,000 live births. [293] The atresia differs from patient to patient, involving variable degrees of obstruction or discontinuity of the biliary tree between the duodenum and the proximal branches of the hepatic ducts. The treatment is surgical (jejunal Roux-en-Y, and portoenterostomy) and is tailored to the amount of extrahepatic bile duct architecture present. These Kasai procedures are most successful in patients operated on at an early age (before 6-9 mo). [294] There are many acute and chronic complications of this surgery, including hepatic failure, ascending cholangitis, and cirrhosis with portal hypertension and varices. Despite these complications, the Kasai procedure persists because of the scarcity of suitable donor organs.

Liver Transplants

Improved immunosuppressive drugs and surgical technique have increased interest in and the success of liver transplantation. The perioperative and postoperative periods require a coordinated approach of many disciplines: surgery, gastroenterology, anesthesia, immunology, and ICU staff. Reports to date suggest that although these children are critically ill, they do not pose unique clinical problems. Most of the clinical issues that arise can be anticipated. These children experience large blood losses and require massive replacement therapy in the operating room. Because of this situation, the intravascular volume status, renal status, and hematology/coagulation profiles must be closely monitored, and basic liver failure therapy is indicated. The immunosuppression required for graft survival puts the patient at risk of infection, with both "normal" and opportunistic organisms. Surveillance cultures and early aggressive antibiotic therapy are indicated. Perhaps the only unanticipated complication has been systemic hypertension, which appears unrelated to elevated CVP or pulmonary capillary wedge pressure. Many patients have required aggressive therapy (hydralazine, diazoxide, captopril). [295] [296]

Nutritional Support in the Critically Ill Child

Adequate nutritional support of the child with critical disease is of paramount importance because it can decrease morbidity and mortality (Ch. 74) . It is essential to try to meet the caloric and mineral requirements of these patients. The nutritional requirements for healthy children have been defined, but the requirements of critically ill children are less well understood; the measurements of oxygen consumption and nitrogen balance are not easy bedside maneuvers.

Even when caloric needs can be ascertained, it can be difficult to deliver adequate amounts because of extenuating circumstances, such as bowel compromise, severe fluid restriction for either renal or CNS disease, and glucose intolerance. Therefore, all avenues of nutrition (enteral and parenteral) must be explored, and nutritional intervention must be implemented early, before a catabolic state ensues.

The use of the GI tract for alimentation is usually the safest and most efficient approach. Numerous commercial formulas with variable sources and quantities of protein, fat, and carbohydrate are available. Protein requirements can be met by using whole protein, protein hydrolysates, or individual amino acids. Whole protein, which has the least osmotic effect, allows for greater nutrient density. However, it can only be used in children with normal pancreatic function and no allergy. Children with protein allergy, pancreatic deficiency, or severe intestinal mucosal disease may benefit from a protein hydrolysate. However, these formulas have high osmolarity. Free amino acid formulas are also available and are used in chemically defined diets restricted by specific requirements or intolerances.

The high caloric density of fat makes it an important component in nutritional support. A long-chain triglyceride (LCT) yields approximately 9 kcal/g, whereas a medium-chain triglyceride (MCT) yields 8.3 kcal/g. Although of greater caloric density, LCTs are less readily absorbed. MCTs are hydrolyzed more rapidly and are converted almost exclusively into free fatty acids and glycerol. MCTs are absorbed even in the absence of lipase, because of their relative water solubility and emulsification properties. However, there are drawbacks. For example, MCTs may cause osmotic diarrhea, and they contain no essential fatty acids, so that linoleic acid must be added to the diet separately. [297]

Secondary disaccharidase deficiency is a common carbohydrate absorption problem in the critically ill child. Lactase function is easily impaired by hypoxia and ischemia, as well as by infection and malnutrition. [298] In these situations, lactose should be avoided and replaced with sucrose or polycose,

which have the least osmotic effect. Enteral feedings can be delivered orally, through a nasogastric tube or a gastrostomy tube. Children with ETT in place can be safely fed through a nasogastric tube; the risk of aspiration is minimized by using continuous infusion of formula rather than bolus feedings and by placing the child in an upright semisitting position. Opioid analgesics and muscle relaxants hinder enteral feeding; if possible, these groups of drugs should be avoided.

Parenteral Alimentation

Parenteral nutrition is used in children who cannot tolerate enteral feedings. It is used as supportive therapy in the critically ill child with acute respiratory or GI disease and as primary treatment in children with chronic short bowel syndrome, Crohn disease, and renal failure.

Procedure for Implementation of Parenteral Nutrition in Children

When intravenous alimentation is considered, $D_{10}W$ is administered at 1 to 1.5 maintenance for 24 hours. The patient is closely monitored for glycosuria, hyperglycemia, and edema. If glucose load is tolerated, a $D_{10}W$ solution with amino acids (PN-10) can then be initiated. Administration of $D_{10}W$ with or without amino acids can be done safely through either a central or a peripheral catheter. Any more concentrated formula causes sclerosis of peripheral veins and therefore must be given through a centrally placed line. If a central line has been placed and the patient is tolerating the relatively high glucose loads of 1.5 maintenance with PN-10 or $D_{10}W$, one may switch to PN-20 and simultaneously decrease the fluid rate to maintenance, to permit accommodation to the higher glucose load. The PN-20 is then advanced over 2 days, to the 1.5 maintenance rate. The patient should gain relatively little weight until 1.5 maintenance with PN-20 is achieved. [299] In general, if a patient is malnourished (<0.80 weight for height), fluid rates must be adjusted downward to roughly 80 percent of those for children of the same weight. After 1 week of nutritional rehabilitation, regular maintenance fluids may be used (Table 73-15) .

Often, the physician has determined a different maintenance fluid rate for a particular patient on the basis of previous intake/output data. If this is the case, the patient should be started on $D_{10}W$ at the low side of the maintenance rate and advanced to the maximum tolerable rate. When switching

TABLE 73-15 -- Maintenance Fluid Rates in Pediatric Patients on Parenteral Nutrition

BODY WEIGHT	REGULAR MAINTENANCE (mL/kg/d)	MALNOURISHED MAINTENANCE (mL/kg)
1st 10 kg	100	80-90
2nd 10 kg	50	40
Wt > 20 kg	20	20

to $D_{20}W$, the low rate is again used, and the advance in rates is repeated. Initial fluid and electrolyte deficits and ongoing losses (e.g., diarrhea) should not be repleted with parenteral nutrition solutions. A separate intravenous solution and line should be used for these extra losses. It should be adjusted every 8 hours to equal the patient's output. If a patient has severe hypoalbuminemic or edematous malnutrition, or both, great care must be exercised in the management of fluid status. Edema, hypervolemia, and hypovolemia may develop rapidly in these patients. [300]

Intravenous Lipid Alimentation

Lipid in Central Intravenous Alimentation

With central intravenous alimentation, lipid is necessary only to prevent essential fatty acid deficiency and should be given at 5 to 10 percent of the total calories. [301] The following fluid rate permits rough determination of the lipid rate necessary to prevent essential fatty acid deficiency during central intravenous alimentation: 5 to 10 mL/kg for the first 10 kg, 2.5 to 5 mL/kg for the second 10 kg, and 1.25 to 2.5 mL/kg for weight greater than 20 kg. Lipids are usually introduced a number of days after parenteral nutrition has been started. There are multiple reasons for withholding lipid during the initiation of intravenous alimentation. First, the tolerance of lipid products is improved if the patient has been primed by a period of adequate caloric intake. Second, fatty acids may impair the patient's tolerance of the large dextrose load. When increasing dextrose administration, the simultaneous introduction of fat products may confuse the interpretation and treatment of glycosuria. Lipemia checks should be done whenever lipid is used.

Lipid in Peripheral Intravenous Alimentation

With peripheral intravenous alimentation (10% concentration), the lipid product must constitute a major component of the caloric intake, because it is the only isomolar product of sufficient caloric density to provide significant caloric intake by peripheral vein. Thus, once the patient receiving peripheral alimentation has reached a maximum rate of PN-10, Intralipid may be added at a rate of 10 mL/kg/d and advanced by 10 mL/kg/d, to a maximum of 40 mL/kg/d. However, lipid calories must not exceed 60 percent of the total calories. [302] Lipid clearance may be facilitated by administering lipid continuously over 24 hours. Serum lipemia is monitored daily during lipid administration. For calculations, the caloric densities shown in Table 73-16 may be used.

Peripheral Versus Central Alimentation: Energy Considerations

Peripheral intravenous alimentation is a stopgap measure that rarely permits caloric intakes in excess of maintenance requirements. Therefore, there are few extra calories for growth and repletion. Peripheral intravenous alimentation should be limited to 2 weeks' duration. By contrast, central

TABLE 73-16 -- Calculated Caloric Density of Lipid Products Used in Pediatric Peripheral Intravenous Alimentation

LIPID PRODUCT	CALORIC DENSITY
Amino acids	3.33 cal/g
10% dextrose	0.34 cal/mL
20% dextrose	0.68 cal/mL
PN-10	0.39 cal/mL
PN-20	0.73 cal/mL
Lipid 10%	1.1 cal/mL
Lipid 20%	2.0 cal/mL

alimentation can provide caloric and nitrogen requirements for both growth and maintenance. However, an increased risk of infection is associated with the prolonged use of indwelling catheters. [303]

Caloric requirements represent the energy intake necessary for maintenance, growth, and activity. Whatever net energy is left after allowance for maintenance and activity is available for growth. The caloric cost of growth is at least 5 cal/g weight. Normal growth is approximately 25 to 30 g/d for the first 6 months of life, 10 to 15 g/d for the next 6 months, and roughly 7 to 10 g/d thereafter. Representative maintenance energy requirements for the nonstressed state are listed in Table 73-17 . Using these data, intravenous alimentation can be adjusted to produce normal or moderate catch-up growth rates. Weight gain in the face of inadequate caloric intake

(less than maintenance) inevitably means edema. If the goal of nutritional therapy is merely supportive over 1 to 2 weeks, growth may not be necessary, and peripheral alimentation may therefore be adequate. If significant catch-up growth or long-term support is required, the child's growth and activity requirements should be met. [300]

Monitoring of Children on Total Parenteral Nutrition

Careful assessment of intake, output, and body weight should be made on a daily basis. The site of alimentation, either peripheral or central, should be evaluated regularly for signs of obstruction, extravasation, or occlusion. Skin and mucous membranes should be evaluated regularly for evidence of trace metal deficiency. Liver size and function must be monitored: intrahepatic cholestasis, excessive fat and glycogen deposition, and elevated liver function tests have been documented in patients receiving parenteral nutrition.

TABLE 73-17 -- Maintenance Energy Requirements for Nonstressed Patients

AGE (y)	MAINTENANCE ENERGY (kcal/kg/d)
<2	75-80
2-5	70-75
5-10	55-70
10-17	40-55
Adult	40

Other metabolic studies should include routine screening of electrolytes, glucose, blood urea nitrogen, and creatinine, as well as ammonia. A serum lipemia check should be done daily. Total protein, albumin, hemoglobin, and triglycerides should be checked regularly but less frequently. [302]

Outcome

A child's survival obviously depends on adequate nutritional intake. It has been shown that an infant with a nonfunctioning gastrointestinal tract can survive on total parenteral nutrition for years, but this is clearly a stopgap measure. [304] The risk of complications from central vein cannulation increases with time, and vascular access in the child becomes increasingly limited as sites are used. Attention to alimentation has improved outcome in the ICU. Although difficult to quantify, it is our impression that children with any critical illness benefit from improved nutritional intake, with faster recovery and decreased morbidity.

HEMATOLOGY

Hematologic emergencies in the ICU include abnormalities of coagulation, immunity, and the red blood cell (RBC) mass. These abnormalities can be primary isolated defects, or they can be secondary to multiorgan system failure. The immune system is discussed in the section on infectious disease.

Coagulation System

Normal clotting includes an initial phase of platelet hemostatic plug formation and a second stage of fibrin production that occurs by either the intrinsic or extrinsic pathways (Fig. 73-2) (Figure Not Available) . For both phases to occur, platelets, coagulation factors, and an intact blood vessel are essential. [305] Neonates have a number of measurable coagulation abnormalities that rarely have clinical manifestations. Term infants and most preterm infants show normal platelet-vessel interaction, but platelet aggregation is transiently impaired. In addition, many coagulation factors are decreased in activity or concentration in the fetus and in the newborn. Of greatest importance are the vitamin K-dependent factors: factors II, VII, IX, and X. These are low at birth and fall to even lower levels during the first week of life unless vitamin K is administered. Factors V and VIII are close to adult levels in all but the most premature infants. Although routine screening tests for coagulation activity are prolonged in infants, the newborn's blood clots more rapidly *in vitro,* owing to a deficiency of naturally occurring protease inhibitors, principally antithrombin III. [305]

Diagnosis of Hemostatic Disorders

Coagulation disorders are diagnosed on the basis of history, physical examination, and laboratory data. It is important to elicit any history of easy bleeding, bruising, drug ingestion,

Figure 73-2 (Figure Not Available) Scheme of blood coagulation. The suffix a denotes the activated factor with enzyme activity. PK, prekallikrein; HMWK, high-molecular-weight kininogen. *(Modified from Hathaway [305])*

associated illnesses, or a family history of bleeding. The patient should be closely examined for evidence of petechiae or bruises, bleeding gums, or hepatosplenomegaly. Any sites of bleeding or venipuncture should be observed for fresh clot or oozing. The laboratory evaluation of PTT, PT, thrombin time, platelet count, and bleeding time gives valuable information on the nature of the hemostatic defect.

Specific Coagulation Disorders

Congenital Disorders

Hereditary deficiencies of most of the coagulation factors are described, but classic hemophilia (factor VIII) and Christmas disease (factor IX) account for the majority (Ch. 25) . Since the advent of modern factor replacement therapy, these disorders only rarely cause life-threatening hemorrhage requiring ICU management. [306]

Factor VIII Deficiency or Hemophilia A.

Factor VIII deficiency or hemophilia A is transmitted by sex-linked recessive inheritance and occurs in 1 in 10,000 male infants. The severity of the clinical disease is determined by the amount of circulating factor: severe disease is associated with less than 1 percent of normal levels, moderately severe disease with 1 to 5 percent, and very mild disease with 5 to 30 percent of normal levels. The most common sites of bleeding are the joint spaces, but hemorrhage may also occur in the peritoneal cavity, gastrointestinal tract, muscle, skin, or CNS. Severe trauma or surgery can cause extensive bleeding. The diagnosis is made by demonstrating an elevated PTT and decreased levels of factor VIII. Treatment requires administration of factor VIII in the form of plasma-derived or recombinant proteins. There is a wide variety of products available for the treatment of hemophilia A. [307]

von Willebrand Disease.

von Willebrand disease occurs nearly as commonly as hemophilia A and is transmitted to both sexes by an autosomal dominant inheritance. It is characterized by abnormalities of the factor VIII molecule, as well as by qualitative platelet dysfunction. Skin and mucous membrane bleeding, particularly nosebleeds and menorrhagia, are the most frequent clinical problems. The PTT and bleeding time are prolonged in this disorder, as are some tests of platelet function. Desmopressin can be used to increase plasma von Willebrand factor and factor VIII concentrations 2- to 5-fold. Cryoprecipitate or other plasma derivatives of von Willebrand factor can be used in patients unresponsive to desmopressin and in patients in whom severe bleeding occurs. [308]

Hereditary Thrombocytopenia.

Hereditary thrombocytopenia is an uncommon congenital defect. Most cases are associated with the familial sex-linked immunodeficiency diseases such as Wiskott-Aldrich syndrome. [309] Platelet transfusions are given to control clinical bleeding.

Acquired Disorders

A variety of circumstances can impair the production of coagulation factors. The vitamin K-dependent factors are the most commonly affected. [310] These factors are decreased in the presence of liver disease, warfarin therapy, and malabsorption syndromes secondary to either bowel disease or altered bowel flora with long-term antibiotic therapy. In addition, untreated vitamin K deficiency in the neonatal period results in hemorrhagic disease of the newborn. In these disorders, the PT is prolonged, and specific assays demonstrate low levels of factors II, VII, IX, and X. The administration of vitamin K usually reverses these deficiencies unless synthetic function of the liver is markedly compromised.

Acquired platelet abnormalities include problems of decreased production, increased destruction, and decreased function. Decreased production or hypoproliferative states include marrow diseases such as leukemia and aplastic anemia and, perhaps most commonly, side effect of chemotherapeutic

agents. Increased destruction can be immune mediated (i.e., idiopathic thrombocytopenic purpura [311]) or from consumption (i.e., microangiopathic states, HUS, or thrombotic thrombocytopenic purpura [312]). Finally, platelet dysfunction has been demonstrated in the presence of uremia and chronic polycythemia seen in patients with cyanotic heart disease. [309] [313]

Treatment of all the acquired thrombocytopenias includes platelet transfusions and, if possible, correction of the underlying disorder. Therapeutic splenectomy has been used to increase platelet survival in some of the severe immune-mediated diseases.

DIC is characterized as a consumptive coagulopathy with decreased platelets and fibrinogen, increased PT, PTT, and thrombin time, and an elevation of fibrin degradation products. DIC complicates a number of nonspecific conditions: sepsis, anaphylaxis, shock, acidosis, massive tissue trauma, sickle cell disease, and certain malignancies, particularly acute myelogenous leukemia in childhood. [314] Purpura fulminans is a particularly severe type of DIC associated with ecchymosis and thrombosis of the skin, subcutaneous tissue, and distal extremities. This condition is seen with acute meningococcemia as well as with other bacterial, viral, and fungal septicemias. Purpura fulminans is associated with a high morbidity and mortality; the main morbidity is the ischemic loss of distal extremities. [315]

Treatment of DIC consists of removing the triggering event whenever and as soon as possible. General support of the vascular volume and oxygen transport is essential. When active bleeding is present, transfusion of platelets (0.2 U/kg) and fresh frozen plasma (10 mL/kg) every 4 to 6 hours as a bolus or continuous infusion will replenish platelet and clotting factors, as well as coagulation antagonists such as antithrombin III. Heparin has been advocated by some clinicians; however, it has not been shown to improve outcome and may enhance clinical bleeding. Transfusion with factor concentrates may be helpful when fresh frozen plasma therapy is limited by intravascular hypervolemia. Occasionally, exchange transfusion with fresh whole blood or plasma exchange/plasmapheresis with fresh frozen plasma and platelets may be necessary to treat severe DIC effectively. [316] [317] [318]

Red Blood Cell Abnormalities

RBC abnormalities include either a decrease in the RBC mass or the presence of abnormally functioning RBC. The RBC mass is reduced by either decreased production or increased loss. Decreased RBC production is associated with factor deficiencies (iron, folate, vitamin B_{12}), bone marrow disease (aplastic anemia, leukemia), chronic diseases (infection, neoplasm, renal disease), and rarely, a congenital deficiency of RBC precursors (Diamond-Blackfan syndrome). [319] RBC loss is either extracorporeal blood loss (hemorrhage) or cell destruction (hemolysis). Hemolysis can be caused by intrinsic RBC abnormalities or by extrinsic factors. Intrinsic anomalies include membrane defects (spherocytosis, elliptocytosis), enzyme defects (glucose-6-phosphate dehydrogenase, pyruvate kinase deficiencies), and hemoglobinopathies (hemoglobin S, C, D, E, and thalassemia). The extrinsic abnormalities can be immune mediated or infection and toxin mediated, or they may occur secondary to microangiopathic destruction. [320]

Regardless of cause of RBC mass decrease, the signs, symptoms, and therapy depend on the acuity and severity of the blood loss. The acute loss of massive amounts of blood (hemorrhage) can cause hypovolemic shock. Treatment consists of oxygen and emergency intravascular volume reexpansion and ultimately replacement of RBC. In the absence of hypovolemia, acute and chronic RBC loss is tolerated until there is a critical loss of oxygen-carrying capacity, which results in high-output cardiac failure. Treatment of these severe anemias includes oxygen and replacement of the RBC mass, which should be done cautiously and slowly in an attempt to avoid the complications of fluid overload. Partial exchange transfusions are sometimes necessary to deliver an adequate RBC load safely.

The main functional abnormality of the RBC is an inability to carry oxygen; sulfhemoglobinemia and methemoglobinemia are the most common of these abnormalities. Methemoglobinemia and sulfhemoglobinemia can be either congenital or acquired disorders that produce hemoglobin that cannot bind oxygen. The congenital forms are usually asymptomatic and require no therapy, but the acquired or toxic forms may be fatal. Treatment includes oxygen, intravenous administration of methylene blue, and occasionally exchange transfusion. [321]

Complications of Transfusion Therapy

Although the administration of blood products can be lifesaving, a number of potential complications should be anticipated (Ch. 46) . Whenever massive transfusion therapy is employed, the risks of citrate toxicity, transfusion reactions, and leukocyte and platelet sensitization must be kept in mind. In addition, depending on the age and type of blood component being employed, electrolyte disturbances such as hypocalcemia, hyperkalemia, and hypernatremia can occur. Whenever in doubt, a sample of the infusate should be sent for electrolyte analysis, and the patient's serum values of electrolytes and ionized calcium should be followed during therapy. [322] Transfusion-acquired infections, including hepatitis, cytomegalovirus, and acquired immunodeficiency syndrome (AIDS), have decreased with improvements in the screening of blood donors and extensive testing of units of blood. [323]

Finally, hemochromatosis complicates the care of those patients who require long-term transfusion therapy for the treatment of an RBC abnormality. Efforts designed to decrease this often lethal complication include aggressive iron chelation therapy and the selective transfusion of young RBCs in an attempt to increase the time interval between required transfusions. [324] [325]

In addition to RBC loss and abnormal oxygen binding, grossly deformed RBCs can cause vaso-occlusive disease. Sickle cell anemia is the best example of this pathophysiology. Sickle cell anemia is a hemoglobinopathy. The major ICU complication is vaso-occlusive disease that can present as a painful crisis; if the vaso-occlusion occurs in the cerebral

---

vessels or in another vital organ supply, it can present as a stroke or infarction. [326] Vaso-occlusive disease of the lung is referred to as acute chest syndrome and presents clinically as ARDS. Treatment consists of hydration, oxygen, and, when severe, exchange transfusion and mechanical ventilation. [327] The other potentially fatal crisis of sickle cell disease is splenic sequestration, which occurs in infants and young children who have not undergone autosplenectomy. Splenic sequestration presents with severe anemia and hypovolemic shock. The treatment is aggressive supportive therapy with emergency surgical splenectomy. [328] Other children with sickle cell disease have usually had a functional autosplenectomy from multiple splenic infarcts. These "splenectomized" children are at risk of severe infection from encapsulated organisms. Routine pneumococcal vaccine is administered as a precaution. [329]

ONCOLOGY

Neoplastic disease in the child usually involves the hematopoietic system, the CNS and sympathetic nervous system, and soft tissue, bone, and kidney. Although much of oncology has become an outpatient subspecialty, some clinical situations do require hospitalization and intensive care.

Blast Crisis in Leukemia

Children who present with an initial WBC count of more than 100,000 are at a high risk of two potentially lethal complications: leukostasis and metabolic crisis (tumor lysis syndrome).

Leukostasis

Leukostasis is a syndrome of vascular obstruction caused by the high viscosity of elevated cell counts or by the WBC themselves. This syndrome should be anticipated in acute lymphoblastic leukemia patients with presenting WBC counts of more than 500,000 and in acute myelogenous leukemia (AML) patients with WBC counts of more than 200,000. The leukemic cell in AML is less deformable than the lymphoblast; therefore, in AML, a relatively lower WBC can produce the same syndrome. [330]

The two major target organs for leukostasis are the brain and the lung; the pathophysiologic feature is vascular plugging, causing infarct. Presenting symptoms include tachypnea, cyanosis, increased work of breathing, altered mental status, and focal neurologic deficits. In addition to supportive therapy, the goal is to decrease the circulating tumor load and thereby to decrease the viscosity. Leukophoresis and exchange transfusion transiently lower the tumor mass. Cranial radiation may reduce the CNS load, and chemotherapy interrupts cell production and possibly destroys circulating cells. The initial chemotherapy is aimed at stopping cell production without a large amount of cell lysis; this gives the advantage of halting a continually growing tumor load without causing a huge metabolic crisis before adequate perfusion is reestablished. [331] [332] [333]

Tumor Lysis Syndrome

Tumor lysis syndrome is a metabolic crisis precipitated by acute lysis of a large tumor load. The main abnormalities that result are elevations in uric acid, potassium, and phosphate; the elevated phosphate results in hypocalcemia. The hyperkalemia and hypocalcemia can be life-threatening; the increased uric acid causes acute renal failure, which further exacerbates the other metabolic imbalance. [334]

Specific therapy is anticipatory monitoring with alkalinization of the urine and diuresis. Before any chemotherapy is administered, the patient's renal function should be assessed and allopurinol therapy should begin. In most cases, this conservative approach of a forced diuresis and allopurinol is adequate, but occasionally dialysis must be used. Basic indications at our institution for the initiation of dialysis include the following:

1. Potassium > 6 mEq/L and rising despite resin exchange
2. Uric acid > 19 mg/L
3. Creatinine > 10 mg/L
4. Phosphorus > 10 mg/L or rapidly rising
5. Volume overload
6. Symptomatic hypocalcemia

If dialysis is necessary, it is usually only needed for a few days until tumor lysis is nearly complete.

Respiratory Distress and Mediastinal Mass

Children with a mediastinal mass and respiratory distress present a difficult therapeutic and diagnostic dilemma. These children often complain of cough, difficulty in breathing, stridor, and shortness of breath. They prefer to sit upright and cannot tolerate supine positioning. The chest radiograph usually shows a large mediastinal mass, often with obliteration or obscuring of the tracheal air column. These tumors can be either malignant (87% Hodgkin's and non-Hodgkin's lymphoma) or benign; the prognosis and therapy rely on an adequate diagnosis. The diagnosis is best made by tissue sampling prior to any therapy. [335] However, a problem may result because tissue sampling of a mediastinal mass requires anesthesia and surgery; by necessity, the airway must be manipulated and instrumented.

The obstructed intrathoracic trachea presents a major anesthetic risk; it is often impossible to maintain such an airway with the patient supine, deeply anesthetized, or receiving muscle relaxants. [336] Care of these patients clearly requires individualized and creative approaches. If the airway compromise is severe, blind tumor therapy at the expense of obscuring the tissue diagnosis must precede any diagnostic procedure. Mediastinal radiation and systemic steroids are the two modes of emergency therapy most commonly administered. Sometimes, this diagnostic dilemma can be circumvented; peripheral nodes or masses can undergo biopsy using local anesthesia or, if the tumor mass is very large, some of the tumor may remain outside the radiation field. In summary, although diagnosis is the key to neoplastic disease, mediastinal mass is one situation

in which the risk may far outweigh the benefit of tissue diagnosis.

Fever and Neutropenia

The most common admission diagnoses for children with neoplastic disease are fever and neutropenia. The neutropenic immunocompromised state caused by chemotherapy is a high-risk period for life-threatening infections.

/das/book/view/29494766/875/806.html

INFECTIOUS DISEASE: LIFE-THREATENING INFECTIONS IN THE INFANT AND CHILD

Infections in the Newborn

The newborn has an increased susceptibility to infection as a result of a number of developmental immunologic deficiencies. Depressed cell-mediated immunity renders the fetus and infant more susceptible to viral and fungal infection. In addition, infants have depressed B-cell function with diminished production of immunoglobulins. One protective compensatory mechanism is the active transplacental transfer of maternal immunoglobulin G (IgG), which gives neonates a reasonable amount of IgG at term. At 2 to 3 months of age, however, the level of maternal antibodies reaches a nadir before the infant adequately assumes antibody production. [337] This time of relatively low levels of circulating antibody is a time of increased risk.

A discussion of perinatal infections can be divided into congenitally acquired and postnatally acquired infections. Congenital infections result from prenatal exposure to viral, protozoal, or, rarely, bacterial pathogens. Common diseases are the TORCH infections: *Toxoplasma gondii* (T); "other" (O) including human immunodeficiency virus (HIV), syphilis, and tuberculosis; rubella (R); cytomegalovirus (C); and herpes simplex virus type II (H). Only rarely do these infections produce a picture of overwhelming sepsis, but they can sometimes be confused with bacterial infection when profound CNS depression, circulatory collapse, or thrombocytopenia are presenting signs. When these infections occur in the first trimester, they can result in fetal wastage or major organ malformations. [338]

The incidence of acute infections in the newborn is highest in the premature child. However, regardless of gestational age, the signs and symptoms of infection are often subtle. Therefore, a very low threshold for diagnosing and treating infection is important. [339] Table 73-18 lists the common signs and symptoms of neonatal sepsis.

The most common acquired pathogens are the organisms that colonize the mother's genital tract, group B *Streptococcus, E. coli, Listeria monocytogenes,* and herpesvirus. Herpes is a particularly fulminant infection in the neonate; the presence of active lesions in the birth canal is an indication for a cesarean birth. The most common bacterial pathogen of sepsis in the neonate is group B *Streptococcus.* During the immediate perinatal period, group B *Streptococcus* presents with severe cardiorespiratory instability and meningitis (in 30% of cases). In contrast, the later presentation of this

TABLE 73-18 -- Common Signs and Symptoms of Neonatal Sepsis

Temperature instability (hypothermia and hyperthermia)
Lethargy and poor feeding
Respiratory distress and apnea
Hypoglycemia and metabolic acidosis
Poor cutaneous perfusion, hypotension
Skin rashes or petechiae
Seizures

pathogen at 2 to 3 weeks of age is associated with a higher incidence of meningitis and a lower incidence of pulmonary disease. [340]

Whenever sepsis is suspected, bacterial cultures should be obtained from blood, urine, and CSF. It is important to perform a complete septic workup because it is difficult for both the infant and the physician to localize an infection. After appropriate cultures are obtained, broad-spectrum treatment with ampicillin and an aminoglycoside such as gentamicin is usually begun until specific bacteriologic information becomes available.

The Older Child: Sepsis and Septic Shock

The infectious diseases that require intensive care include sepsis with organ dysfunction and septic shock. Children can develop sepsis from virtually any bacterial or viral pathogen. Sepsis in the previously well child is often accompanied by an obvious primary local site or source of infection. Although older children can usually localize an infection as well as an adult, the younger child does not localize infections well. Of particular note, CNS infections can be difficult to diagnose in children who are younger than 2 years of age, because they are unable to give an adequate history of headache, and also because meningismus or other signs of meningeal irritation are not reliable findings.

The most common clinical manifestations of sepsis in the neonatal age group include fever or hypothermia, tachypnea and tachycardia, poor cutaneous perfusion, altered level of neurologic function (agitation and irritability followed by apnea or coma), petechiae, purpura or other rashes, DIC, and the metabolic abnormalities of metabolic acidosis, hypoglycemia, and hypocalcemia. Sepsis can also be associated with septic shock. In septic shock, endotoxin, exotoxin, or other endogenously liberated vasoactive substances produce an endothelial lesion that results in a syndrome of increased vascular permeability with resultant ARDS, increased utilization of metabolic substrate, depressed myocardial function, and profound DIC. [341]

The mainstay of therapy for any infection and particularly for septic shock is eradication of the infection. Parenteral broad-spectrum antibiotic coverage should begin according to the specific clinical situation, and any septic foci or abscess should be surgically drained. The child in septic shock requires early, and possibly massive, cardiorespiratory support. Endotracheal intubation and positive-pressure ventilation with increased levels of PEEP are used to support the child with ARDS. Inotropic agents are often needed to

maintain adequate cardiac output and tissue perfusion. A Swan-Ganz catheter can provide useful information in this situation. Because coagulopathies, including thrombocytopenia and generalized factor deficiencies, are common in septic shock, fresh frozen plasma and platelet transfusions may be required. In the past, high-dose steroids, although controversial, were commonly suggested for use in septic shock. [342] Clinical studies have shown steroids to have at the least no effect and possibly a deleterious effect in septic shock. [343] The use of these drugs is not advocated, except in the situation of steroid replacement in purpura fulminans with possible Waterhouse-Friderichsen syndrome.

The immunocompromised host differs from the previously healthy child. These children often lack a specific primary focus of infection; in addition, they suffer from attacks from different pathogens, *Pseudomonas aeruginosa, E. coli, Klebsiella, Staphylococcus aureus,* and coagulase-negative *Staphylococcus,* as well as fungi *(Candida albicans* and *Aspergillus).*[344] Immunocompromised children may also suffer polymicrobial sepsis with bacterial seeding from the GI tract. These children may

have few if any premonitory signs or symptoms before developing septic shock. Fever is probably the most common and often the earliest sign of opportunistic infection. Bacterial, fungal, and viral cultures should be obtained, and broad-spectrum antimicrobial therapy should be started. Antifungal agents should also be considered in these patients. Granulocyte transfusions have been reported in neutropenic patients with overwhelming sepsis--usually with a gram-negative organism. [345] Table 73-19 (Table Not Available) lists the most common predisposing causes of immunosuppression, along with the most commonly associated opportunistic organisms. [346]

Human Immunodeficiency Virus

HIV infections are increasing in the pediatric age group. HIV in the young child is secondary to vertical transmission from a seropositive mother. Adolescents with HIV infection are also increasing in number; unsafe sexual practices and intravenous drug use are the most common causes of infection. The adolescent presents in much the same way as the adult; therefore, this discussion is limited to HIV in the younger child.

Perinatal HIV is the primary issue. A mother with HIV infection has a 25 to 35 percent chance of infecting her child. The diagnosis of perinatal infection is problematic in that most infants have passively acquired maternal IgG antibody, preventing serodiagnosis. With current nucleic acid-based detection methods, a diagnosis can be confidently made by 4 months. The usual clinical presentation in the very young includes failure to thrive, hepatosplenomegaly, and chronic interstitial pneumonitis. The toddler age group has a higher incidence of lymphadenopathy, recurrent bacterial infections, neurologic delay, and progressive encephalopathy. Some children may be asymptomatic for years.

Pneumocystis carinii pneumonia (PCP) is seen in all age groups, but it is more common and is associated with a higher mortality in children younger than 1 year of age. The mainstay of treatment remains trimethoprim-sulfamethoxazole and support care.

Lymphocytic interstitial pneumonitis (LIP) is a slowly progressive interstitial disease with chronic cough and slight to moderate hypoxemia seen more commonly in children older than 1 year of age. The radiographic findings are small nodules and fine reticular densities. Treatment of LIP is supportive; the efficacy of steroids remains uncertain.

Children with HIV infection are most commonly admitted to an ICU for pulmonary disease, usually PCP. At this time, aggressive care is provided in the absence of other organ system failure. Survival after respiratory failure from PCP has improved during the past few years. [347] [348]

PEDIATRIC TRAUMA

Prenatal and Perinatal Injuries

Perinatal trauma is sustained by the fetus or newborn before, during, or immediately after birth. The most common prenatal injuries are due to maternal gunshot wounds and maternal blunt trauma. The fetal mortality in either case is greater than twice that of the mother, [349] with fetal death attributable to maternal shock and fetal oxygen deprivation rather than to direct injury. Birth injuries occur more commonly in large full-term infants and in infants with breech presentation. [350] Injuries to the head include linear or depressed skull fractures, cephalohematomas that result from subperiosteal hemorrhage, subdural or subarachnoid hematomas, and intraparenchymal or intraventricular hemorrhage. Intracranial injuries can lead to increased ICP, cerebral ischemia, neurologic injury, and death. Neck trauma can result in torticollis from injury to the sternocleidomastoid muscle and, rarely, cervical cord transection during a difficult breech extraction. [351] This latter tragedy leads to lifelong quadriplegia. Less devastating nerve injuries, also resulting from cervical traction, are phrenic nerve paralysis and Erb or Klumpke palsies from brachial plexus injury.

Perinatal bone fractures occur commonly in the clavicles and humeri from shoulder dystocia; femoral shaft fractures are more common in breech deliveries. Abdominal injuries to the liver, spleen, adrenal glands, and kidneys can produce life-threatening hemorrhage or thrombosis. [351] Thrombosis can cause vaso-occlusion with distal tissue loss in the cerebral, coronary, or renal vascular beds. Finally, emergency instrumentation of the airway in the delivery room can cause tracheal and esophageal perforations, particularly in the premature infant.

Trauma in Children

The leading causes of death among children aged 1 to 14 years are accidents and trauma. [352] The nature of the trauma is different from that in adults; children are usually victims of drops or falls, drowning, near drowning, motor vehicle accidents (pedestrian), ingestions, and burns. The types of bodily damage a child experiences also differ. Head injuries are more common, especially in younger children, who have disproportionately large heads with relatively poor neck muscle support. [353] Children are less likely to be victims of gunshot or knife attacks, causing penetrating injuries; instead, blunt injuries are more usual. Blunt trauma to the abdomen causes solid organ injury (liver and spleen) rather

TABLE 73-19 -- Opportunistic Infection in Inherited and Acquired Disorders

(Not Available)

From Feigin and Matson [346]

than a perforated viscus. [354] Hypothermia is more frequently encountered as a complication of the initial trauma; heat loss is very rapid in children because of their relatively large ratio of body surface area to volume. Although drowning and near drowning are the prototypical hypothermic injuries, hypothermia must be considered in all pediatric trauma victims.

Similar to adult trauma, the management of pediatric trauma requires an organized approach that combines diagnosis and treatment. Most preventable deaths in pediatric trauma are a result of airway obstruction, pneumothorax, shock secondary to inadequately treated bleeding, or secondary brain injury due to an expanding intracranial hematoma. [355] The American College of Surgeons recommends a four-step approach: (1) the primary survey, (2) resuscitation, (3) secondary survey, and (4) definitive care. [356] The primary survey requires rapid assessment of the airway, breathing, and circulation. A disproportionately large tongue in relation to a narrow oropharynx easily obstructs the airway in an unconscious child. A patent airway can often be established by proper jaw positioning, enabling bag-and-mask ventilation until intubation can be accomplished. Cervical spine injuries are less common in children surviving injuries than in their adult counterparts, but the neck of these patients should be immobilized until spinal damage is excluded. [357] Following establishment of an airway, adequacy of respiration should be verified by observation of symmetric chest wall movement, auscultation of normal and equal breath sounds, and an early chest radiograph. Tension hemopneumothoraces can be diagnosed clinically and treated by needle aspiration at the second thoracic interspace in the midclavicular line. This alleviates the tension and permits stabilization until a chest tube can be placed. The circulation can be quickly assessed in children. Hypovolemia is manifested first by tachycardia, poor peripheral perfusion, weak peripheral pulses, and, finally, hypotension, which may not occur until the child has lost more than 25 percent of the circulating blood volume. [358] The severely hypovolemic child requires venous access quickly. If a peripheral venous catheter cannot be placed expeditiously, an IO cannula should be placed until central venous access is established. [359] The degree of volume resuscitation is dictated by the clinical condition of the child and the estimated volume of blood or plasma loss.

During the secondary survey, a thorough head-to-toe examination is done, and a plan of definitive treatment is developed. Diagnostic measures in the pediatric trauma patient are similar to those in the adult patient with consideration to special problems. Because of the higher incidence of solid organ injury and a more conservative approach to management, diagnostic peritoneal lavage is less helpful in children. Most intra-abdominal injuries that require laparotomy are recognized clinically because they produce peritonitis or involve increasing abdominal girth. [360] Diagnostic peritoneal lavage may be helpful in children who are hemodynamically unstable despite fluid resuscitation with greater than 40 mL/kg of blood. It can be used to locate the site of occult bleeding in a child too unstable to undergo CT scan, or it can be used to evaluate abdominal injury in a child about to undergo emergency nonabdominal surgery. The indications for surgical intervention for abdominal trauma include free peritoneal air, evidence of a ruptured viscus, and acute uncontrolled bleeding greater than 40 mL/kg. A ruptured spleen or liver laceration is not an indication for surgery; preferred treatment is supportive therapy with aggressive blood volume replacement. [361]

A careful head and neurologic examination yields rapid information regarding intracranial trauma. The most important indicator of intracranial bleeding is a decrease in the level of consciousness. Rapid diagnosis and treatment of intracranial mass lesions can reduce ICP and may prevent secondary brain injury.

Child Abuse

Children have been subjected to violence, neglect, abandonment, slavery, and murder since time and events were recorded. Child abuse was brought to medical attention in 1962 by Kempe et al, [362] who coined the term *battered child syndrome.* The diagnosis of child abuse is often supported by the presence of an acute injury that may have a plausible explanation, along with signs of past trauma, including healing bruises, contusions, and fractures. Child abuse may also take the form of psychologic or sexual abuse, as well as the parents' failure to meet a child's need for food, clothing, shelter, hygiene, medical care, education, or supervision. [363] In

the ICU setting, physical abuse is the primary concern; however, emotional abuse and neglect can be independent or contributing factors.

Suspicion of child abuse often begins with a history of inappropriate or inadequate explanations for injuries or when the degree of trauma exceeds the historical cause. Multiple hospital admissions, emergency department visits, doctor or hospital "shopping," and a history of previous trauma are all of potential concern. Often, the story regarding the injury changes over time. [364] Certain clinical features are common to child abuse, but they are by no means pathognomonic. Most abused children are younger than 3 years of age and may have poor hygiene and delayed somatic or psychologic development. Injuries seen most commonly include bruises, welts, lacerations, scalds, and burns from cigarettes, stoves, heating grates, or irons. Long-bone fracture, often of varying ages, and abdominal injuries, signs of smothering, and multiple soft tissue or genital bruises are also common. Head injuries are reported; shaking a crying infant can cause neck injuries and intracranial hemorrhage, without necessarily producing external manifestations of trauma. The approach to a suspected victim of child abuse includes a meticulous and nonjudgmental history, written in detail on the chart, stating all allegations and documenting any change in the reported history. The physical examination should include growth parameters, descriptions of soft tissue bruising or burns, and diagrams or preferably photographs of all injuries. The color, shape, placement, and estimated age of all injuries should be catalogued. Laboratory studies should include the following: a skeletal survey of all long bones, ribs, and skull; a coagulation profile, including hematocrit, platelet count, PT, and PTT; and genital and throat cultures for venereal disease if sexual abuse is suspected.

Ingestion Injury

Despite the success of various preventive public health programs, poisoning in the pediatric population continues to be a common occurrence. Fortunately, the vast majority of presumed poisonings in young children can be managed at home by telephone consultation with a regional poison-control center. In one study, acute poisoning accounted for approximately 5 percent of all medical admissions to a PICU. [365] In this study, approximately one-half were accidental ingestions, and one-half were suicidal overdoses. The median age for the accidental group was 2 years, and for the suicidal group it was 15 years. Although many different toxic substances are ingested by children and adolescents, the approach to therapy is routine. Management has three main goals: (1) identifying, decontaminating, and eliminating the toxic agents [366] ; (2) minimizing the toxic effects to the host; and (3) providing close observation and organ system support until detoxification is complete. Procedures for drug elimination include emesis, gastric lavage, activated charcoal, and magnesium citrate. Minimizing toxic effects can be done with specific antidotes when available, with hemodialysis, or with charcoal hemoperfusion. Examples of specific antidotes are deferoxamine for iron ingestion, ethanol infusion for methanol ingestion, naloxone for narcotic overdose, and *N*-acetylcysteine for acetaminophen ingestion. Because many ingestions, particularly the suicidal ones, include multiple drugs, specific antidote therapy is only occasionally successful. Organ system surveillance and support usually include airway protection and mechanical ventilation, intravenous fluids, cardiovascular monitoring for arrhythmias and myocardial depression, and anticonvulsive therapy when seizures occur. Consultation with clinical pharmacologists or with the regional poison-control center and contacting a social worker or psychiatrist are essential aspects of the care of the acutely toxic child. Common complications of ingestions and their therapy include aspiration pneumonia from hydrocarbon ingestions or loss of glottic function, sepsis, respiratory depression, myocardial depression, arrhythmias, seizures, and coma. Although it is important to treat the specific ingestion, the psychosocial environment that allowed or precipitated the ingestion must also be considered. Families should be counseled about proper supervision and "childproofing" their home. Psychiatric intervention should be introduced early; unsuccessful suicide attempts are often repeated.

Transporting the Critically Ill Infant or Child

With regionalization first of neonatal intensive care and later of pediatric intensive care, emergency interhospital transport systems were developed to provide rapid, safe, and effective transfer of critically ill children from community hospitals to regional intensive care facilities. More recently, *in utero* transfer of women with identifiable high-risk pregnancies to regional obstetric perinatal centers has been instituted to provide maximal surveillance and support at the time of delivery. The philosophy of transport systems is not only to provide a means of transferring a sick patient to a more appropriate facility, but also to institute appropriate intensive care monitoring and treatment to the patient before leaving the referring hospital. This begins as soon as the referring physician telephones the intensive care physician at the referral hospital. The patient is presented to the ICU physician, who offers advice regarding immediate treatment and then mobilizes the transport team and alerts the appropriate consultants and hospital resources required for the incoming patient. The transport team usually consists of a physician and nurse who are specially trained in neonatal or pediatric intensive care and transport. Support personnel may include respiratory therapists, anesthesiologists (particularly in the case of a pediatric upper airway problem), emergency medical technicians, or additional nursing or physician trainees. Portable intensive care equipment must include cardiovascular monitoring devices, an infant transport device to maintain a neutral thermal environment during transport, resuscitation equipment (including airway and breathing devices), and additional equipment to institute intensive care on arrival at the referral hospital.

Problems that may arise during transport must be anticipated and treated before the patient is transported. This usually requires a careful assessment of the airway, breathing, and the adequacy of gas exchange along with monitoring the adequacy and stability of the circulation. Because procedures are so difficult to perform in transit, such interventions as intubation and placement of venous or arterial catheters are completed at the referring hospital if there is any question that they will be required. Possible medications required during transport should be anticipated and made immediately available. Transport can be carried out by ambulance, helicopter, or fixed-wing aircraft, depending on local circumstances. In general, the environment provided by helicopter transport is the most difficult one in which to provide surveillance and treatment because of poor temperature and noise control, as well as limited operating space. Communication with the transport team and regional center is essential in order to facilitate consultation with senior staff members and to help the accepting ICU anticipate the nature and degree of illness. The most serious flaws in the transport system are usually the response time of the transport team once a referral call is made and the availability of on-call transport team members who are adequately trained. An institutional commitment of funds, personnel, and equipment, along with excellent organization, can ensure that neonatal and pediatric transport systems have a significant impact on patient care, community physician education, and regional hospital referrals. [367] [368]

SUDDEN INFANT DEATH SYNDROME

Sudden infant death syndrome (SIDS) describes unexplained and sudden death in an infant younger than 1 year of age. It is a major cause of death and morbidity, with an incidence of 2 to 3 victims per 1,000 live births. The incidence peaks at 3 to 4 months of age and can be temporally, but not causally, associated with an intercurrent event such as an upper respiratory tract infection, recent immunization and, rarely, anesthesia and surgery. [369] Potential causes of SIDS include abnormalities to the cardiac conduction system such as the prolonged QT interval syndrome and Wolff-Parkinson-White syndrome and abnormalities of the respiratory

---

system such as central and/or peripheral chemoreceptor abnormalities, upper airway obstruction, and central hypoventilation associated with sleep. [370] [371] When the publication of epidemiologic studies from New Zealand, Britain, and the Netherlands linked the prone sleeping position to SIDS, the American Academy of Pediatrics issued a statement recommending that infants be placed on their back or side. This "back to sleep" recommendation was associated with a decrease in the SIDS rate in the United States. [372] Southall [373] suggested a syndrome of expiratory apnea characterized by severe hypoxemia in the face of continued respiratory effort. For unknown reasons, these children develop sudden severe intrapulmonary right-to-left shunting. [373] In most cases, SIDS appears to be a "quiet" death, in that breathing appears to stop without evidence of arousal or struggle. Occasionally, an infant is observed to be apneic and cyanotic and responds to tactile stimulation or to more vigorous resuscitative efforts. These near-miss SIDS infants are often admitted to PICU for intensive monitoring and observation. Those infants who are discovered close to death may require treatment for multiorgan system hypoxic-ischemic injury.

Future treatment and monitoring of survivors of near-miss SIDS remain controversial, but most authorities recommend cardiorespiratory monitoring at home and that all caretakers be thoroughly instructed in infant cardiopulmonary resuscitation (CPR) techniques. Families of infants who are monitored at home require a variety of home support services, including technical expertise, constant physician availability, and respite care personnel. In addition, parent groups and the National Foundation for Sudden Infant Death have proved helpful to some families, regardless of outcome.

THE ASPHYXIATED CHILD

The asphyxiated patient, whether an older child or an infant with aborted SIDS or birth asphyxia, poses an important challenge for the intensive care pediatrician. Asphyxia produces injury to a number of target end organs.

Asphyxial Injury to Organ Systems

Cardiovascular System

Asphyxia produces hypoxia with mixed metabolic and respiratory acidosis. The resultant hypoxia produces a fall in cardiac output by depression of the medullary cardiac regulation center, with bradycardia and decreased myocardial contractility. [25] As compensation for this decreased cardiac output, there is preferential blood flow to the cerebral and coronary circulations at the expense of shunting blood away from the kidneys and gastrointestinal tract. Clinically asphyxiated children are cold and mottled, with evidence of a low-output shock state. The specific therapy of cardiovascular dysfunction secondary to asphyxia consists of correction of the respiratory abnormality, correction of the acidosis, and chronotropic and inotropic pharmacologic support. (Appropriate monitoring and general treatment of circulatory failure are discussed in the section on acute circulatory failure in children.)

Respiratory System

Respiratory decompensation following an asphyxiation is commonly characterized by pulmonary edema. This may be secondary to increased microvascular pressure from hypoxic myocardial failure, or it may reflect capillary endothelial damage with a resultant capillary leak. [374] Treatment of both conditions includes cardiovascular support and the use of CPAP or PEEP with positive-pressure ventilation. Respiratory support is effected by the establishment of a patent airway, supplementation of inspired oxygen, CPAP, and mechanical ventilation.

Central Nervous System

CNS complications of asphyxia include intraventricular hemorrhage, cortical infarction, and cerebral edema. Intraventricular hemorrhage is a problem in premature infants and is thought to occur as a consequence of hypoxic-ischemic necrosis of the paraventricular germinal matrix. This area undergoes liquefaction and ruptures into the ventricular system several hours to days after the initial asphyctic injury. [375]

Cortical infarction occurs in children of all ages. This condition usually occurs in a "watershed pattern," affecting the motor cortex controlling the upper extremities and the visual cortex. [376]

Cerebral edema is a relatively late consequence of asphyxia, occurring 8 to 72 hours after injury. Because the ultimate neurologic outcome principally depends on the degree of cortical injury occurring at the time of asphyxia, aggressive management of cerebral edema can only be expected to prevent or reduce the amount of additional damage resulting as a late complication. Measures that ensure adequate oxygenation and hemodynamic stability should be instituted. Patients who demonstrate purposeful movements and normal brain-stem examination 24 hours after their hypoxic insult have a good neurologic recovery. Children without these findings at 24 hours are more likely to suffer severe neurologic deficits or death. [377] (The treatment of cerebral edema is discussed in the CNS section.)

Renal and Metabolic Effects

Asphyxia may cause renal ischemia, producing tubular or glomerular necrosis, as well as thrombosis of the renal vein or glomerular capillary bed. Metabolic complications in the asphyxiated infant and child may include hypoglycemia, hypocalcemia, hypomagnesemia, and metabolic acidosis, all of which produce profound myocardial depression and systemic hypotension. [378] Hypervolemia and hypo-osmolality are common problems associated with fluid resuscitation, water absorbed from mechanical ventilator systems, and syndrome of inappropriate ADH. Every attempt should be made to minimize free water overload.

Hematologic System

The major hematologic complication of asphyxia is the development of DIC. In the newborn, as well as in the older

child, levels of vitamin K-dependent factors (II, VII, IX, X) may be low, related to asphyctic hepatic dysfunction; these conditions may respond to vitamin K supplementation.

Gastrointestinal System

Splanchnic ischemia may produce necrosis of the intestinal mucosa, with ulceration or perforation anywhere within the GI tract. [379] Monitoring is difficult and consists mainly of testing all nasogastric secretions and stool for blood, monitoring bowel sounds and abdominal girth, and evaluating abdominal radiographs for intraluminal, intramural, intraportal, or extraluminal air. NEC is a common postasphyctic consequence in the premature infant. In severe cases bowel perforation, peritonitis, and sepsis can lead to death. Treatment consists mainly of minimizing the osmotic load of feedings until the GI tract has fully recovered. This treatment may require avoiding any oral or gastric alimentation for several days to several weeks after injury. When feedings are initiated, low-osmolality solutions should be used. During GI recovery, intravenous alimentation should be maintained through a central venous catheter. The gastric pH should be monitored and treated with antacids or an H_2-blocker. Hypoxia and hypoperfusion to the liver produce hepatocellular damage. The extent of pathophysiologic injury is a direct function of the duration and severity of the insult. Elevated transaminases, abnormal coagulation, elevated bilirubin, and unstable carbohydrate metabolism may all result, but all functional and laboratory abnormalities should be corrected unless there is underlying liver disease. [380]

Approach to Death Due to Asphyxia

Because the CNS is most sensitive to asphyxia, it is not uncommon to see full cardiovascular recovery in combination with profound CNS damage or even brain death. In situations in which meaningful, neurologic recovery is hopeless or when brain death has occurred, life support may have to be terminated. Parents who have lost a child in such a manner need a great deal of support, counseling, and understanding. Parents often react with guilt, denial, or hostility once confronted with the unexpected loss. Particularly in the case of SIDS, parents may react with guilt for not having been more vigilant. These issues must be addressed directly by trained

professionals.

/das/book/view/29494766/875/810.html

CARDIOPULMONARY RESUSCITATION

Pediatric cardiopulmonary arrests differ from adult arrests in a number of ways. Adults usually experience cardiac arrest secondary to coronary artery disease with severe ischemia and precipitation of a malignant arrhythmia. Children, on the other hand, have relatively normal coronary arteries, and it is uncommon for them to experience a primary arrhythmia. The more usual situation in pediatrics is initial respiratory compromise or arrest followed by secondary cardiac arrest. Another difference is the character of the terminal arrhythmia. Adults generally display ventricular arrhythmias, whereas children are more likely to demonstrate a bradyarrhythmia that degenerates into asystole.

In any PICU, there are patients who were victims of cardiopulmonary arrest and successful resuscitation; the treatment of these patients is described in the section on the asphyxiated patient. In addition to caring for successfully resuscitated patients, the PICU staff must be prepared to provide CPR for their own patients. Identifying patients at risk before they have a full cardiopulmonary arrest is as important as providing good CPR. This requires constant clinical surveillance and identification of risk factors. Critically ill patients are frequently placed at risk at various times during the day. Problems can be avoided by increasing everyone's attentiveness to these high-risk periods--during airway manipulation, during any change of therapy, during patient and bed manipulation, and at the change of doctor and nursing shifts.

The basic ABCs of resuscitation are a sequence that must be so familiar that little or no thought is required to begin the initial resuscitative efforts. Despite the evolving literature regarding new CPR, the standard American Heart Association CPR is still advocated as the appropriate method.

Once ventilation has begun, if there is no evidence of a pulse, external cardiac compressions should be started. (The establishment and maintenance of an airway are discussed elsewhere.) A rhythm is very important: five sternal compressions are given for each breath. A pause is given after each five compressions to allow for adequate lung inflation. The rate of compressions should be at least 100 per minute in infants and 80 to 100 per minute in children and adults. Hand positioning can be done in a number of ways. For CPR in an infant, there are two correct hand placements: (1) both thumbs can be placed over the sternum while the fingers are curved around the back over the spine; or (2) one hand can be placed behind the back for support while sternal compressions are done with two fingers of the other hand. This second procedure can also be used in toddlers. The adult-style two-handed massage is preferable in older children, with the patient placed on a cardiac board. Pressure should always be completely released between forceful compressions to permit filling of the heart chambers, and a pulse should be palpated to assess the adequacy of the compressions.

Vascular access is important, but in the child, attaining it may be difficult or impossible. Although a number of medications (atropine, epinephrine, lidocaine) can be given via the ETT, bicarbonate, calcium, fluid, and pressors require vascular access. New CPR guidelines include IO lines (18-gauge spinal or IO needle inserted in the tibia 2 to 3 cm below the tibial tuberosity). Common drugs used for CPR include the following:

1. *Atropine* is used for treatment of bradycardia; the dose in children is 0.02 mg/kg with a minimum dose of 0.1 mg and a maximum of 1.0 mg.
2. *Sodium bicarbonate* corrects the metabolic component of the acidosis. The recommended dose is 1 mEq/kg, followed by 0.5 mEq/kg. The usual acidosis is primarily respiratory, and in the event of inadequate ventilation, administration of bicarbonate may increase the Pa CO_2 and thereby may decrease the pH. In addition, overzealous use of bicarbonate has complications: lowered threshold for ventricular

fibrillation and left shift of the oxygen dissociation curve. The present guidelines suggest that bicarbonate administration be tailored to ABG values.
3. *Calcium* is a positive inotrope and peripheral vasoconstrictor. Caution should be exercised during the administration of calcium in an adult with cardiopulmonary arrest, because calcium has been implicated in decreasing the threshold for ventricular arrhythmias. In pediatrics, because ventricular arrhythmias are rarely a problem, calcium administration is relatively safer. The dose of calcium is 10 mg elemental calcium per kg. The present recommendation is to use calcium only to treat hypocalcemia, hyperkalemia, and calcium channel blocker overdose.
4. *Dextrose* is given to correct hypoglycemia that may be a precipitating or a complicating feature of the arrest. The dose of dextrose is 0.5 to 1.0 g/kg. It is available as D_{50} W (dose, 1-2 mL/kg) and D_{25} W (dose, 2-4 mL/kg). In cardiovascular arrest, D_{50} W and D_{25} W also act as osmotic diuretics. Dextrose is also used in combination with insulin to treat hyperkalemia: dextrose (0.5 g/kg) and insulin (0.1 U/kg). Hyperglycemia should be avoided during resuscitation for fear of increasing CNS damage.
5. *Epinephrine,* an adrenergic agonist, is usually given by intravenous or IO route, but it can also be administeredvia the ETT. Epinephrine is supplied as a 1:10,000 solution (0.1 mg/mL); the dose is 0.1 mL/kg. There has been some success with "high-dose" epinephrine. The newer recommendations include epinephrine 0.2 mg/kg after failure of two standard doses of epinephrine to increase perfusion pressure satisfactorily within 5 minutes. [381]
6. *Lidocaine* is used to decrease ventricular irritability and to help maintain a normal rhythm following defibrillation. It is also a myocardial depressant that decreases myocardial contractility and should therefore be given only when absolutely necessary (i.e., stable rhythm cannot otherwise be maintained). The dose is 1 mg/kg as a single dose; this may be repeated several times, or it can be given as an infusion of 1 to 2 mg/kg/h.

During resuscitation, a constant infusion of an inotrope or chronotrope is commonly used. Countershock therapy (cardioversion) is indicated if the patient presents with or develops ventricular fibrillation or ventricular tachycardia. The dose used in pediatrics is 1 to 3 W-sec/kg or 10 to 15 W-sec/year of life. The synchronized mode is selected for ventricular tachycardia, and the nonsynchronized mode is used for fibrillation. If small paddles are not immediately available for small children, the adult paddles are most easily used in an anteroposterior placement. If resuscitation efforts prove unsuccessful, the primary event that precipitated the arrest should be evaluated for correctable mechanical and/or metabolic insults. Possible reasons for an unsuccessful resuscitation include tension pneumothorax/hemothorax, disruption of the major vessels, cardiac tamponade, profound hypovo-lemia, profound metabolic imbalance, toxin ingestion, and hypothermia. Hypothermia presents a considerable problem: a patient with a core temperature of less than 30°C may appear dead and/or unresponsive to pharmacologic management, and it is important to rewarm the patient as part of the resuscitation. A hypothermic patient can be pronounced dead only if there is no electrical activity on ECG with a core temperature of at least 30°C, or if the person cannot be warmed to 30°C with aggressive methods (including peritoneal dialysis for rewarming).

There are also iatrogenic complications that may make resuscitation unsuccessful. These include traumatic pneumothorax from attempted vascular cannulation, pericardial tamponade from intracardiac injections, splenic or hepatic rupture from closed-chest compressions, pneumothorax from overzealous positive-pressure ventilation, and placement of the ETT into the esophagus. A patient in cardiorespiratory distress or arrest has excellent chances of full recovery with adequate resuscitation. Speed, orderly direction, cooperation of all personnel, and continuous assessment of the effectiveness of resuscitation are key to the successful restoration of adequate heart rate, blood pressure, ventilation, and, most important, brain function. Keeping the brain alive must be the objective of every resuscitative effort and, with rapid institution and maintenance of ventilation and cardiac massage, patients can be neurologically normal after periods of cardiac arrest.

/das/book/view/29494766/875/811.html

PARENT/FAMILY SUPPORT

Numerous unavoidable stresses are encountered in any intensive care setting. In a PICU, the difficulty of dealing with the illness and/or death of a child often tends to magnify this normal stress. In order to support the ICU staff, children, and families adequately, these potential problems should be discussed and understood. The population in an ICU includes a permanent nurse, physician, and technical staff, a rotating group of residents, and an ever-changing cadre of patients and families. Together, these people are exposed to extremes of frustration and success; this exposure has an emotional and psychologic impact on everyone. Constantly available support systems for patients, parents, and staff are a necessity.

The pediatric patient ranges from a premature infant to an adult, and each patient must be approached in an age-appropriate manner. Diseases, procedures, and treatments should be discussed with the patient; each child should participate in his or her own care to the degree that limits of age, sedation, and disability permit. Parents of a child with a critical illness often progress through the stages of grief reaction described by Kubler-Ross. [382] Their interaction with the ICU staff and with their child is dramatically influenced by the character of their grief reaction. In addition, the ICU may be very confusing. The hectic pace and the numbers of physicians and nurses often leave parents feeling a lack of control and direction. ICU are also very intimidating and isolating. They are usually geographically isolated with a separate dedicated staff, a level of technology not seen in other parts of the hospital, and a terminology of numbers and abbreviations that can render conversations uninterpretable. All these factors make it difficult for a parent to maintain a parenting role. Too often, parents assume a role of the absent or passive parent, the angry critical parent, or the parent who wants to assume the role of physician. Some parents can never be directed into a more productive role, but often careful explanations of ICU operational procedures and generous use of social and clerical services can help parents to retain their parenting roles. Other members of the family, especially the patient's siblings, should also be

considered. Many parents need help and encouragement before they can involve their children at home in the events taking place at the hospital. Visiting should be encouraged and supported by the ICU staff.

There are numerous potentially troublesome interfaces among various members of the ICU staff. The permanent ICU staff members have developed a credibility of their intensive care skills and knowledge. Often, residents in training have never been exposed to intensive care medicine; these physicians may find the ICU and ICU staff overwhelming and intimidating. For the permanent staff, it is frustrating to have to retrain yet another group of residents. These constantly changing levels of expertise may produce antagonism. It is important for supervisors to be aware of these problems and to address them frequently.

Death is a frequent and complicated subject in the ICU. With the explosive growth of technology, the ability to support life often exceeds the ability to cure diseases. Basic definitions of death are being challenged in the medical, legal, and political arenas. The concepts of irreversible disease, chronic vegetative state, and meaningful versus meaningless life are under constant discussion and consideration. This lack of definitive guidelines increases the stress and frustration of families as well as of ICU staff members. By definition, intensive care is a fast-moving, stressful situation. Psychosocial supports are a necessity for patients and for parents as well as for staff members.

References

1. Butt W, Shann F, Tibballs J et al: Long-term outcome of children after intensive care. Crit Care Med 18:961, 1990.

2. Committee on Hospital Care and Pediatric Section of the Society of Critical Care Medicine: Guidelines and levels of care for pediatric intensive care units. Pediatrics 92:166, 1993.

3. Pollack MM, Alexander SR, Clarke N et al: Improved outcomes from tertiary center pediatric intensive care: A statewide comparison of tertiary and nontertiary care facilities. Crit Care Med 19:150, 1991.

4. England MA: Color Atlas of Life Before Birth: Normal Fetal Development. Chicago, Year Book, 1983.

5. Friedman WF: Intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 15:87, 1972.

6. Rudolph AM: Congenital Diseases of the Heart. Chicago, Year Book, 1974.

7. Crone RK: The cardiovascular effects of isoproterenol in the preterm newborn lamb. Crit Care Med 12:33, 1984.

8. Rudolph AM, Heymann MA: Circulatory changes with growth in the fetal lamb. Circ Res 26:298, 1970.

9. Nelson NM, Prod'hom LS, Cherry RB et al: A further extension of the in vivo oxygen-dissociation curve for the blood of the newborn infant. J Clin Invest 43:606, 1964.

10. Luscher TF: Endothelium-derived nitric oxide: The endogenous nitrovasodilator in the human cardiovascular system. Eur Heart J 12 (suppl E):2, 1991.

11. Arcilla RA, Oh W, Wallgren G et al: Quantitative studies of the human neonatal circulation. II. Hemodynamic findings in early and late clamping of the umbilical cord. Acta Paediatr Scand Suppl 179:23, 1967.

12. Dawes GS, Mott JC, Widicombe JG: Closure of the foramen ovale in newborn lambs. J Physiol (Lond) 128:384, 1955.

13. Moss AJ, Emmanouilidies G, Duffie ER: Closure of the ductus arteriosus in the newborn infant. Pediatrics 32:25, 1963.

14. Gentile R, Stevenson G, Dooley T et al: Non-invasive determination of time of ductal closure in normal newborn infants. Pediatr Cardiol 1:177, 1979.

15. Smith CA, Nelson NM: The Physiology of the Newborn Infant, 4th ed. Springfield, Ill, Charles C Thomas, 1976.

16. Hislop A, Beid L: Pulmonary arterial development during childhood: Branching pattern and structure. Thorax 28:129, 1973.

17. Friedman WF, Pool PE, Jacobowitz D et al: Sympathetic innervation of the developing rabbit heart: Biochemical and histochemical comparison of fetal, neonatal, and adult myocardium. Circ Res 23:25, 1968.

18. Liebowitz EA, Novick JS, Rudolph AM: Development of myocardial sympathetic innervation in the fetal lamb. Pediatr Res 6:887, 1972.

19. Gennser G, Studnitz WV: Noradrenaline synthesis in human fetal heart. Experientia 31:1422, 1975.

20. Schifferli PY, Caldero-Barcia B: Effects of atropine and beta adrenergic agents on the heart rate of the human fetus. In Barens L (ed): Fetal Pharmacology. New York, Raven Press, 1973, p 259.

21. Waldman S, Krauss AN, Auld PAM: Baroreceptors in preterm infants: Their relationship to maturity and disease. Dev Med Child Neurol 21:714, 1979.

22. Daly M de B, Angell-James JE, Elsner R: Role of carotid-body chemoreceptors and their reflex interactions in bradycardia and cardiac arrest: Lancet 1:764, 1979.

23. Enhoring G, Westin B: Experimental studies of the human fetus in prolonged asphyxia. Acta Physiol Scand 31:359, 1954.

24. Mott JC: The ability of young animals to withstand total oxygen lack. Br Med Bull 17:145, 1961.

25. Penefsky ZJ: Perinatal development of cardiac contractile mechanisms. In Gootman N, Gootman P (eds): Perinatal Cardiovascular Function. New York, Marcel Dekker, 1983, p 188.

26. Wood C, Beard RW: Temperature of the human fetus. J Obstet Gynaecol Br Commonw 71:768, 1964.

27. Dawes GS: Fetal and Neonatal Physiology. Chicago, Year Book, 1973.

28. Rudolph AM, Heyman MA: Fetal and neonatal circulation and respiration. Annu Rev Physiol 36:187, 1974.

29. Rudolph AM: The changes in the circulation after birth: Their importance in congenital heart disease. Circulation 41:343, 1970.

30. Clyman RI, Neymann MA, Rudolph AM: Ductus arteriosus response to prostaglandin E1 at high and low oxygen concentrations. Prostaglandins 13:219, 1977.

31. Freed MA, Neymann MA, Lewis AB et al: Prostaglandin E1 in infants with ductus arteriosus-dependent congenital heart disease. Circulation 64:899, 1981.

32. Crone RK: Acute circulatory failure in children. Pediatr Clin North Am 27:525, 1980.

33. Perkin RM, Levin DL: Shock in the pediatric patient. J Pediatr 101:319, 1982.

34. Leung DY: New developments in Kawasaki disease. Curr Opin Rheumatol 3:46, 1991.

35. Gersony WM: Diagnosis and management of Kawasaki disease. JAMA 265:2699, 1991.

36. World Health Organization Report: Report of WHO/IFSC task force on the definition and classification of cardiac myopathies. Br Heart J 44:672, 1980.

37. Aretz HT, Billingham ME, Edwards WD et al: Myocarditis: A histopathologic definition and classification. Am J Cardiovasc Pathol 1:3, 1986.

38. Wagner MB, McCabe JB: A comparison of four techniques to establish interosseous infusion. Pediatr Emerg Care 4:87, 1988.

39. Cote C, Schwartz A, Jobes D et al: Two approaches to cannulation of the child's internal jugular vein. Anesthesiology 50:371, 1979.

40. Puri VK, Carlson RW: Complications of vascular catheterization in the critically ill: A prospective study. Crit Care Med 9:157, 1981.

41. Colan SD: Assessment of ventricular and myocardial performance. In Fyler DC (ed): Nadas' Pediatric Cardiology. Philadelphia, Hanley and Belfus, 1992, p 225.

42. Todres ID, Crone RK, Rogers MC et al: Swan Ganz catheterization in the critically ill newborn. Crit Care Med 7:330, 1979.

43. Pollack MM, Reed TD, Holbrook PR et al: Bedside pulmonary artery catheterization in pediatrics. J Pediatr 96:274, 1980.

44. Moodie DS: Measurement of cardiac output by thermodilution in pediatric patients. Pediatr Clin North Am 27:513, 1980.

45. Dillon TR, Janos CC, Meyer RA et al: Vasodilator therapy for congestive heart failure. J Pediatr 96:623, 1980.

46. Hug CC: Making a choice of inotropes and vasodilators in clinical situations. J Card Surg 5 (suppl):272, 1990.

47. Luchessi BR: Inotropic agents and drugs used to support the failing heart. In Antonaccio M (ed): Cardiovascular Pharmacology. New York, Raven Press, 1977, p 337.

48. Outwater KM, Treves S, Tang P et al: Renal and hemodynamic effects of dopamine in infants following corrective cardiac surgery. Anesthesiology 61:A130, 1984.

49. Outwater K, Treves ST, Lang P et al: Renal and hemodynamic effects of dopamine in infants following cardiac surgery. J Clin Anesth 2:253, 1990.

50. Lagercrantz H, Bristoletti P: Catecholamine release in the newborn after birth. Pediatr Res 11:889, 1973.

51. Martinez AM, Padbury JF, Thio S: Dobutamine pharmacokinetics and cardiovascular responses in critically ill neonates. Pediatrics 89:47, 1992.

52. Perkin RM, Levin DL, Webb R et al: Dobutamine: A hemodynamic evaluation in children with shock. J Pediatr 100:977, 1982.

53. Hines R: Clinical applications of amrinone. J Cardiothorac Anesth 3(suppl 2):24, 1989.

54. Barton P, Garcia J, Kovatli A et al: Hemodynamic effects of IV milrinone lactate in pediatric patients with septic shock. Chest 109:1302, 1996.

55. Sorensen GK, Ramamoorthy C, Lynn AM et al: Hemodynamic effects of amrinone in children after Fontan surgery. Anesth Analg 82:241, 1996.

56. Edelson J, LeJemtel TH, Alousi AA et al: Relationship between amrinone plasma concentration and cardiac index. Clin Pharmacol Ther 29:723, 1981.

57. Lawless S, Burckart G, Diven W et al: Amrinone in neonates and infants after cardiac surgery. Crit Care Med 17:751, 1989.

58. Ramamoorthy C, Williams GD, Bratton SL et al: Pharmacodynamics of milrinone in children following open heart surgery. Anesth Analg 82:SCA 19, 1996.

59. Soyka LF: Clinical pharmacology of digoxin. Pediatr Clin North Am 19:241, 1972.

60. Stanley TH, Amaral JI, Liu WS et al: Peripheral vascular versus direct cardiac effects of calcium. Anesthesiology 45:46, 1976.

61. Tsang RC, Donovan EF, Steichen JJ: Calcium physiology and pathology in the neonate. Pediatr Clin North Am 23:611, 1976.

62. Drop LJ, Geffen GA, O'Keffe DD et al: Relation between ionized calcium concentration and ventricular pump performance in the dog under hemodynamically controlled conditions. Am J Cardiol 47:1041, 1981.

63. Beekman RN, Rocchini AP, Rosenthal A: Hemodynamic effects of nitroprusside in infants with a large ventricular septal defect. Circulation 64:553, 1981.

64. Davies DW, Greiss L, Steward DJ: Sodium nitroprusside in children: Observations on metabolism during normal and abnormal responses. Can J Anaesth 122:553, 1975.

65. Rosenthal MN, Pearl RB, Schroeder JS et al: Nitroglycerine versus nitroprusside in pulmonary hypertension. Anesthesiology 55:A79, 1981.

66. Brent B, Berger H, Mahler D et al: Acute effects of hydralazine on the pulmonary circulation and right ventricular function in chronic lung disease and pulmonary hypertension. Clin Res 30:4A, 1982.

67. Rubin LJ, Peter RN: Oral hydralazine for primary pulmonary hypertension. N Engl J Med 302:69, 1980.

68. Drummond WH, Gregory GA, Neymann MA et al: The independent effects of hyperventilation, tolazoline and dopamine on infants with persistent pulmonary hypertension. J Pediatr 98:603, 1981.

69. Palmer RMJ, Ferrige AG, Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived releasing factors. Nature 325:524, 1987.

70. Frostell CG, Bloomquist H, Hedenstierna G et al: Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. Anesthesiology 78:427, 1993.

71. Zapol WM, Hurford WE: Inhaled nitric oxide in the adult respiratory distress syndrome and other lung diseases. New Horiz 4:638, 1993.

72. Kinsella JP, Abman SH: Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. J Pediatr 126:853, 1995.

73. Hofshire PJ, Nicoloff DM, Moller JH: Postoperative heart block in 64 children treated with and without cardiac pacing. Am J Cardiol 39:559, 1977.

74. McCue CM, Mantakas ME, Tingelstad JB et al: Congenital heart block in newborns of mothers with connective tissue disease. Circulation 56:82, 1977.

75. Walsh EP, Saul JP: Cardiac arrhythmias. In Fyler DC (ed): Nadas' Pediatric Cardiology. Philadelphia, Hanley and Belfus, 1992, p 377.

76. Camm AJ, Garratt CJ: Adenosine and supraventricular tachycardia. N Engl J Med 326:1621, 1991.

77. Flynn PA, Engle MA, Ehlers KH: Cardiac issues in the pediatric emergency room. Pediatr Clin North Am 39:955, 1992.

78. Stapleton FB, Jones DP, Green RS: Acute renal failure in neonates: Incidence, etiology and outcome. Pediatr Nephrol 1:314, 1987.

79. Sinaiko AR: Pharmacologic management of childhood hypertension. Pediatr Clin North Am 409:195, 1993.

80. Ferguson RK, Vlasses PH: Hypertensive emergencies and urgencies. JAMA 225:1607, 1986.

81. Newburger JW, Takahashi M, Beiser AS et al: A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 324:1633, 1991.

82. American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease: Diagnostic guidelines for Kawasaki disease. Am J Dis Child 144:1218, 1990.

83. Menahem S, Venables AW: Anomalous left coronary artery from the pulmonary artery: A 15 year sample. Br Heart J 58:378, 1987.

84. Hislop A, Reid L: Growth and development of the respiratory system. In Davis J, Dobbling J (eds): Scientific Foundation of Paediatrics. Philadelphia, WB Saunders, 1974, p 226.

85. Davies GM, Reid L: Growth of alveoli and pulmonary arteries in childhood. Thorax 25:669, 1970.

86. Turner J, Mead J, Wohl M: Elasticity of the human lungs in relation to age. Appl Physiol 25:664, 1968.

87. Bryan AC, Mansell AL, Levison H: Development of the mechanical properties of the respiratory system. In Hodson WA (ed): Development of the Lung. New York, Marcel Dekker, 1977, p 446.

88. Reid L: Structural and functional reappraisal of the pulmonary arterial system. In The Scientific Basis of Medicine Annual Reviews. London, Athlone, 1968, p 289.

89. Rudolph AM, Heymann MA: Pulmonary circulation in fetal lambs. Pediatr Res 6:341, 1972.

90. Hislop A, Reid L: Intrapulmonary arterial development during childhood: Branching pattern and structure. Thorax 28:129, 1973.

91. Meyrich B, Reid L: Ultrastructure of alveolar lining. In Hodson WA (ed): Development of the Lung. New York, Marcel Dekker, 1977, p 139.

92. Clements IA, Nellenbogen J, Trahan H: Pulmonary surfactant and evolution of the lungs. Science 69:603, 1970.

93. Chisurch M, Ahmed A, Jack P et al: Control of fetal lung development in the rabbit. Arch Dis Child 48:709, 1973.

94. Nelson NM: Neonatal pulmonary function. Pediatr Clin North Am 13:769, 1966.

95. Nourse CH, Nelson NM: Uniformity of ventilation in the newborn infant: Direct assessment of the arterial-alveolar N_2 difference. Pediatrics 43:226, 1969.

96. Campbell ACM, Cockburn F, Dawes CS et al: Pulmonary vasoconstriction in asphyxia during cross circulation between twin fetal lambs. J Physiol (Lond) 192:111, 1967.

97. O'Rourke PP: Pulmonary hypertension of the newborn: medical treatment and extracorporeal membrane oxygenation (ECMO). In Weir EK, Archer SL, Reeves JT (eds): The Diagnosis and Treatment of Pulmonary Hypertension. Mount Kisco, NY, Futura, 1992, p 139.

98. Agostini E, Mead I: Statistics of the respiratory system. In Fenn WO, Rahn H (eds): Handbook of Physiology. Section 3: Respiration, vol 1. Washington, DC, American Physiological Society, 1964, p 287.

99. Loosli CG, Potter EL: Pre- and post-natal development of the respiratory portion of the human lung. Am Rev Respir Dis 80:5, 1959.

100. Krahl VE: Anatomy of the mammalian lung. In Fenn WO, Rahn H (eds): Handbook of Physiology. Section 3: Respiration, vol 1. Washington, DC, American Physiological Society, 1964.

101. Keens TG, Bryan AC, Levison H et al: Developmental patterns of muscle fiber types in human ventilatory muscles. J Appl Physiol 44:909, 1978.

102. Olinsky A, Bryan MN, Bryan AC: Influence of lung inflation on respiratory control in neonates. J Appl Physiol 36:426, 1974.

103. Fisher JT, Mortola JP, Smith JB et al: Respiration in newborns: Development of the control of breathing. Am Rev Respir Dis 56:650, 1985.

104. Agostini E: Volume-pressure relationships of the thorax and lung in the newborn. J Appl Physiol 14:909, 1959.

105. Avery ME, Cook CD: Volume-pressure relationships of lungs and thorax in fetal, newborn and adult goats. J Appl Physiol 16:1034, 1961.

106. Cote CJ, Todres ID: The pediatric airway. In Cote CJ, Ryan JF, Todres

ID et al (eds): A Practice of Anesthesia for Infants and Children. Philadelphia, WB Saunders, 1986, p 69.

107. Dolfuss R, Milic-Emili J, Bates D: Regional ventilation of the lung studied with boluses of (133)xenon. Respir Physiol 2:234, 1967.

108. Mansell A, Bryan AC, Levison H: Airway closure in children. Appl Physiol 33:711, 1972.

109. Ferris BC, Mead J, Opie LH: Partitioning of respiratory flow resistance in man. J Appl Physiol 19:653, 1964.

110. Hogg J, Williams J, Richardson J et al: Age as a factor in the distribution of lower airway conductance in the pathologic anatomy of obstructive lung disease. N Engl J Med 283:1283, 1970.

111. Rigatto H, Brady J, de la Torre Verduzco R: Chemoreceptor reflexes in preterm infants: The effect on gestational age and postnatal age on ventilatory response to inhalation of 100% and 15% oxygen. Pediatrics 55:604, 1975.

112. Rigatto H, Brady JP: Periodic breathing and apnea in preterm infants. I. Evidence for hypoventilation possibly due to central respiratory depression. Pediatrics 50:202, 1972.

113. Delworia-Papadapoulos M, Ronceric NP, Oski FA: Postnatal changes in oxygen transport of term, premature and sick infants: The role of red cell 2,3 diphosphoglycerate and adult hemoglobin. Pediatr Res 5:235, 1971.

114. Motoyama EK, Zigas CJ, Troll C: Functional basis of childhood anemia (abstract). Am Soc Anesth 41:283, 1974.

115. Cross KW, Tizard JPM, Trythall DAH: The gaseous metabolism of the newborn infant. Acta Paediatr Scand 46:265, 1957.

116. Oski FA: Designation of anemia on a functional basis. J Pediatr 83:353, 1973.

117. O'Rourke PP: Assessment and monitoring of respiratory function. In Fuhrman BP, Zimmerman JJ (eds): Pediatric Critical Care. St Louis, CV Mosby, 1992, p 411.

118. Cochran WD, Davis HT, Smith CA: Advantages and complications of umbilical artery catheterization in the newborn. Pediatrics 42:769, 1968.

119. Todres ID, Rogers MC, Shannon DC et al: Percutaneous catheterization of the radial artery in the critically ill neonate. J Pediatr 87:273, 1975.

120. Gardner RU, Schwartz R, Wong HC et al: Percutaneous indwelling radial artery catheters for monitoring cardiovascular function: Prospective study of the risk of thrombosis and infection. N Engl J Med 290:1227, 1974.

121. Stock MC: Non-invasive carbon dioxide monitoring. Crit Care Clin 4:522, 1988.

122. Brown M, Vender JS: Non-invasive oxygen monitoring. Crit Care Clin 4:499, 1988.

123. Barker SJ, Tremper KK: Advances in oxygen monitoring; pulse oximetry: Applications and limitations. Int Anesthesiol Clin 15:3, 1987.

124. Hoffman RA, Krieger BP, Kramer MR et al: End-tidal carbon dioxide in critically ill patients during changes in mechanical ventilation. Am Rev Respir Dis 140:1265, 1989.

125. Westly CR, Cotton EK, Brooks JG: Nebulized racemic epinephrine by IPPB for the treatment of croup. Am Dis Child 132:484, 1978.

126. Leipzig B, Oski FA, Cummings CW et al: A prospective randomized study to determine the efficacy of steroids in treatment of croup. J Pediatr 94:194, 1979.

127. Fuglksang G, Pedersen S, Borgstrom L: Dose-response relationships of intravenously administered terbutaline in children with asthma. J Pediatr 114:315, 1989.

128. Shapiro NM: Intracranial hypertension: Therapeutic and anesthetic considerations. Anesthesiology 43:445, 1975.

129. Kazzi NJ, Brans YW, Poland RL: Dexamethasone effects on the hospital course of infants with bronchopulmonary dysplasia who are dependent on artificial ventilation. Pediatrics 86:722, 1990.

130. Crone RK: Assisted ventilation in children. In Gregory GA (ed): Respiratory Failure in the Child. New York, Churchill Livingstone, 1981, p 17.

131. Pascucci RC: Pediatric intensive care. In Gregory GA (ed): Pediatric Anesthesia. New York, Churchill Livingstone, 1989, p 1316.

132. Johnson B, Ahlstrom H, Lindroth M et al: Continuous positive airway pressure: Modes in relation to clinical application. Pediatr Clin North Am 27:687, 1980.

133. Venus B, Copiozo GB, Jacobs K: Continuous positive airway pressure: The use of low levels in adult patients with artificial airways. Arch Surg 115:824, 1980.

134. Chatburn RL: Evaluation of pediatric pulmonary function: theory and application. Respir Care 34:597, 1989.

135. Suter PM, Fairley HB, Isenberg MD: Optimal end expiratory pressure in patients with acute pulmonary failure. N Engl J Med 292:248, 1975.

136. Downes JJ, Goldberg AI: Airway management, mechanical ventilation and cardiopulmonary resuscitation. In Scarpelli EM, Auld PAM, Goldman HS (eds): Pulmonary Disease of the Fetus, Newborn and Child. Philadelphia, Lea & Febiger, 1978, p 99.

137. Haddad D, Richards CC: Mechanical ventilation of infants: significance of compression volume and elimination of compression volume. Anesthesiology 29:365, 1968.

138. Robins L, Crocker D, Smith RM: Tidal volume losses of volume limited ventilators. Anesth Analg 46:294, 1967.

139. Downs JB, Klein EF, Desautels DA: Intermittent mandatory ventilation: A new approach to weaning patients from mechanical ventilation. Chest 64:331, 1973.

140. Kirby RR, Robinson O, Schultz J: Continuous flow ventilation as an alternative to assisted or controlled ventilation in infants. Anesth Analg 51:871, 1972.

141. MacIntyre NR: Respiratory function during pressure support ventilation. Chest 89:677, 1986.

142. Fiastro JF, Habib MP, Quan SF: Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest 93:499, 1988.

143. Ring JC, Stidham GL: Novel therapies for acute respiratory failure. Pediatr Clin North Am 41:1325, 1994.

144. Marx CM, Rosenberg DJ, Ambuel B et al: Pediatric intensive care sedation: Survey of fellowship training programs. Pediatrics 91:369, 1993.

145. Crone RK, Favoritol J: The effects of pancuronium bromide on infants with hyaline membrane disease. J Pediatr 97:991, 1980.

146. Anderson EF, Rosenthal M: Pancuronium bromide and tachyarrhythmias. Crit Care Med 3:13, 1975.

147. Craven JL, Evans GA, Davenport PJ: The evaluation of incentive spirometry in the management of postoperative pulmonary complications. Br J Surg 61:793, 1974.

148. Mellins RB: Pulmonary physiotherapy in the pediatric age group. Am Rev Respir Dis 110:137, 1974.

149. Drinker P, Shaw LA: An apparatus for the prolonged administration of artificial respiration. J Clin Invest 7:229, 1929.

150. Plum F, Lukas DS: An evaluation of the cuirass respirator in acute poliomyelitis respiratory insufficiency. Am J Med 221:417, 1951.

151. Rochester DF, Braun NM: The diaphragm and dyspnea. Am Rev Respir Dis 119:77, 1979.

152. O'Rourke PP, Crone RK: High frequency ventilation. JAMA 250:2845, 1983.

153. Abbasi S, Bhutani VK, Spitzer AR et al: Pulmonary mechanics in preterm neonates with respiratory failure treated with high-frequency oscillatory ventilation compared with conventional mechanical ventilation. Pediatrics 87:487, 1991.

154. Clark RH, Gertsmann DR, Null DM et al: Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 89:5, 1992.

155. Arnold JH, Hanson JH, Toro-Figuero LO et al: Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. Crit Care Med 22:1530, 1994.

156. Merritt TA, Soll RF, Hallman M: Overview of exogenous surfactant replacement therapy. J Intensive Care Med 8:205, 1993.

157. Clark LC, Gollan F: Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. Science 152:1755, 1966.

158. Greenspan JS, Wolfson MR, Rubenstein SD et al: Liquid ventilation of human preterm neonates. J Pediatr 117:106, 1990.

159. Fuhrman BP, Paczan PR, De Francisis M: Perfluorocarbon-associated gas exchange. Crit Care Med 19:712, 1991.

160. Gauger PG, Pranikoff T, Schreiner RJ et al: Initial experience with partial liquid ventilation in pediatric patients with the acute respiratory distress syndrome. Crit Care Med 24:16, 1996.

161. Extracorporeal Life Support Organization (ELSO) Registry, Ann Arbor, Mich, ELSO, 1997.

162. Keszler M, Kolobow T: Venovenous ECMO. In Arensman RM, Cornish JD (eds): Extracorporeal Life Support. Boston, Blackwell Scientific, 1993, p 2623.

163. Bui KC, LaClair P, Vanderkerkhove J et al: ECMO in premature infants: Review of factors associated with mortality. ASAIO Trans 37:54, 1991.

164. Rivera RA, Butt W, Shann F: Predictors of mortality in children with respiratory failure: Possible indications for ECMO. Anaesth Intensive Care 18:385, 1990.

165. Timmons OD, Dean JM, Vernon DD: Mortality rates and prognostic variables in children with adult respiratory distress syndrome. J Pediatr 119:896, 1991.

166. Newth CJL, Levison H, Bryan AC: The respiratory status of children with croup. J Pediatr 81:1068, 1972.

167. Taussig LM, Castro O, Beaudry PH et al: Treatment of laryngotracheobronchitis (croup). Am J Dis Child 129:790, 1975.

168. Sell SHW: The clinical importance of *Haemophilus influenzae* infections in children. Pediatr Clin North Am 17:415, 1970.

169. Kimmons HC, Peterson BM: Management of acute epiglottitis in pediatric patients. Crit Care Med 14:278, 1986.

170. American Academy of Pediatrics: *Haemophilus influenzae* infections. In Peter G (ed): 1997 Red Book: Report of the Committee on Infectious Diseases, 24th ed. Elk Grove Village, Ill, American Academy of Pediatrics, 1997, p 220.

171. Wohl MEB, Chernick V: Bronchiolitis. Am Rev Respir Dis 118:759, 1978.

172. Nicolai T: Acute viral bronchiolitis in infancy: Epidemiology and management. Lung 168s:396, 1990.

173. Larsen LG: Asthma in children: Review article. N Engl J Med 326:1540, 1992.

174. Bentur L, Canny GJ, Shields MD et al: Controlled trial of nebulized albuterol in children younger than 2 years of age with acute asthma. Pediatrics 89:133, 1992.

175. Guss S, Portnoy J: Methotrexate treatment of severe asthma in children. Pediatrics 89:635, 1992.

176. Szczeklik A, Nizankowski R, Mruk J: Myocardial infarction in status asthmaticus. Lancet 1:658, 1977.

177. Darioli R, Perret C: Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 129:385, 1984.

178. O'Rourke PP, Crone RK: Halothane in status asthmaticus. Crit Care Med 10:341, 1982.

179. Shwachman H: Cystic fibrosis. In Kendig E, Chernick V (eds): Disorders of the Respiratory Tract in Children, 4th ed. Philadelphia, WB Saunders, 1984, p 640.

180. David TS: Cystic fibrosis. Arch Dis Child 65:152, 1990.

181. Smyth RL: Cystic fibrosis: The current state of lung transplantation for cystic fibrosis. Thorax 46:213, 1991.

182. Truog WE, Jackson JC: Alternative modes of ventilation in the prevention and treatment of bronchopulmonary dysplasia. Clin Perinatol 19:621, 1992.

183. Parker RA, Lindstrom DP, Cotton RB: Improved survival accounts for most, but not all, of the increase in bronchopulmonary dysplasia. Pediatrics 90:663, 1992.

184. Bader D, Ramos AD, Lew CD et al: Childhood sequellae of infant lung disease: Exercise and pulmonary function abnormalities after bronchopulmonary dysplasia. J Pediatr 110:693, 1987.

185. Gerhardt T, Hehre D, Feller R et al: Serial determination of pulmonary function in infants with chronic lung disease. J Pediatr 110:448, 1987.

186. Greenspan JS, Wolfson MR, Rubenstein D et al: Liquid ventilation of human preterm neonates. J Pediatr 117:106, 1990.

187. American Academy of Pediatrics Task Force on Prolonged Apnea: Prolonged infantile apnea: 1985. Pediatrics 76:129, 1985.

188. Weissberg D, Schwartz J: Foreign bodies in the tracheobronchial tree. Chest 91:730, 1987.

189. Amiel-Tison C: Neurologic examination of the maturity of newborn infants. Arch Dis Child 43:89, 1968.

190. Schulte FJ: The neurologic development of the neonate. In Davis J, Dobbing J (eds): Scientific Foundations of Paediatrics. Philadelphia, WB Saunders, 1974, p 596.

191. Teasdale G, Jennett B: Assessment of coma and impaired consciousness: A practical scale. Lancet 2:81, 1974.

192. Gentry LR: Facial trauma and associated brain damage. Radiol Clin North Am 27:435, 1989.

193. Shapiro HM: Intracranial hypertension: therapeutic and anesthetic considerations. Anesthesiology 43:445, 1975.

194. Miller JD, Becker DP, Ward JD et al: The outcome of severe head injury with early diagnosis and intensive management. J Neurosurg 47:491, 1977.

195. Bruce DA, Schut L, Bruno LA et al: Outcome following severe head injury in children. J Neurosurg 48:679, 1978.

196. Bruce DA, Schut L: The value of CAT scanning following pediatric head injury. Clin Pediatr 19:719, 1980.

197. Marshall LF, Smith RW, Shapiro HM: The outcome with aggressive treatment in severe head injuries. J Neurosurg 48:679, 1978.

198. Levin HS, Aldrich EF, Saydjari C et al: Severe head injury in children: Experience of the traumatic coma data bank. Neurosurgery 31:435, 1992.

199. Mahoney WJ, D'Souza BJ, Haller JA et al: Long term outcome of children with head trauma and prolonged coma. Pediatrics 71:756, 1983.

200. Kjallquist A, Siesjo BK, Zwetnow N: Effects of increased intracranial pressure in cerebral blood flow and on cerebral venous P_{O_2}, P_{CO_2} pH, lactate and pyruvate in dogs. Acta Physiol Scand 75:267, 1969.

201. Reivich M: Arterial P_{CO_2} and cerebral hemodynamics. Appl Physiol 206:25, 1964.

202. Muizelaar JP, Marmarou A, Ward JD et al: Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 75:731, 1991.

203. Muizelaar JP, Lutz HA, Becker DP: Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head injured patients. J Neurosurg 61:700, 1984.

204. Pollay M, Fullenwider C, Roberts PA et al: Effect of mannitol and furosemide on blood-brain osmotic gradient and intracranial pressure. J Neurosurg 59:945, 1983.

205. Reuben HJ, Schurmann K (eds): Steroids and Brain Edema. New York, Springer-Verlag, 1972.

206. American Academy of Pediatrics: Dexamethasone therapy for bacterial meningitis in infants and children. In Peter G (ed): 1997 Red Book: Report of the Committee on Infectious Diseases, 24th ed. American Academy of Pediatrics, Elk Grove Village, Ill, 1997, p 6.

207. Rosomoff HL: Pathophysiology of the central nervous system during hypothermia. Acta Neurochir Suppl (Wien) 13:11, 1964.

208. Lafferty JJ, Kekhah MM, Shapiro HM et al: Cerebral hypometabolism obtained with deep pentobarbital anesthesia and hypothermia (30°C). Anesthesiology 49:159, 1978.

209. Lam AM: Hyperglycemia and neurological outcome in patients with head injury. J Neurosurg 75:545, 1991.

210. Michaud LJ: Elevated initial blood glucose levels and poor outcome following severe brain injuries in children. J Trauma 31:1356, 1991.

211. Marsh RW: Effect of hyperglycemia on brain pH levels in areas of focal incomplete cerebral ischemia in monkeys. J Neurosurg 65:693, 1986.

212. deCourten-Myers G: Hyperglycemia enlarges infarct size in cerebrovascular occlusion in cats. Stroke 19:623, 1988.

213. Chopp M: Global cerebral ischemia and intracellular pH during hyperglycemia and hypoglycemia in cats. Stroke 19:1383, 1988.

214. LeMay DR: Insulin administration protects neurologic function in cerebral ischemia in rats. Stroke 19:1411, 1988.

215. Pierce EC, Lambertsen CJ, Deutch S et al: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. J Clin Invest 41:1664, 1962.

216. Swedlow DB, Raphaelly RC, Kettrick RG et al: Cardiovascular performance with hypothermia and deep pentobarbital coma in children. Crit Care Med 8:236, 1980.

217. Miller JD, Becker DP, Ward JD et al: Significance of intracranial hypertension in severe head injury. J Neurosurg 47:503, 1977.

218. Miller JD: Barbiturates and raised intracranial pressure. Ann Neurol 6:189, 1979.

219. Rockoff M, Marshall L, Shapiro L: High dose barbiturate therapy in humans: A clinical review of 60 patients. Ann Neurol 6:194, 1979.

220. Aicardi J, Chevrie JJ: Convulsive status epilepticus in infants and children. Epilepsia 11:187, 1970.

221. Guidelines for the Determination of Death: Report of the Medical Consultants on the Diagnosis of Death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA 246:2184, 1981.

222. McCory WM: Embryonic development and prenatal maturation of the kidney. In Edelman CM Jr (ed): Pediatric Kidney Disease. Boston, Little, Brown, 1978, p 3.

223. Shulz DM, Giordano DA, Shulz DH: Weights of organs of fetuses and infants. Arch Pathol Lab Med 74:244, 1962.

224. Guignard JP: Renal function in the newborn infant. Pediatr Clin North Am 29:777, 1982.

225. Aviles DH, Fildes RD, Jose PA: Evaluation of renal function. Clin Perinatol 19:69, 1992.

226. Oh W: Renal function and clinical disorders in the neonate. Clin Perinatol 8:215, 1981.

227. Goldsmith DI: Clinical and laboratory evaluation of renal function. In Edelman CM Jr (ed): Pediatric Kidney Disease. Boston, Little, Brown, 1978, p 213.

228. Ellis D, Gartner JC, Galvis AG: Acute renal failure in infants and children: Diagnosis, complications, and treatment. Crit Care Med 9:607, 1981.

229. Warshaw BL, Edelbrock HH, Ettenger RB et al: Progression to end stage renal disease in children with obstructive uropathy. J Pediatr 100:183, 1982.

230. Hollenberg NK, Adams DF, Oken DE et al: Acute renal failure due to nephrotoxins. N Engl J Med 282:1329, 1970.

231. Karmali MA: Infection by verocytotoxin-producing *Escherichia coli.* Clin Microbiol Rev 2:15, 1989.

232. Riley LW: The epidemiologic, clinical, and microbiologic features of hemorrhagic colitis. Annu Rev Microbiol 41:383, 1987.

233. Kaplan BS: Hemolytic uremic syndrome in families. In Kaplan BS (ed): Hemolytic Uremic Syndrome/Thrombotic Thrombocytic Purpura. New York, Marcel Dekker, 1992, p 213.

234. Kaplan BS: The hemolytic uremic syndrome: The most important cause of acute renal failure in infants and children. In Strauss J (ed): Acute Renal Disorders and Renal Emergencies. Boston, Martinus Nijhoff, 1984, p 3.

235. Kaplan BS: Recent advances in understanding the pathogenesis of the hemolytic uremic syndromes. Pediatr Nephrol 4:276, 1990.

236. Forsyth KD: Neutrophil-mediated endothelial injury in haemolytic uremic syndrome. Lancet 2:411, 1989.

237. Riley LW, Remis RS, Helgerson SD et al: Hemorrhagic colitis associated with a rare *Escherichia coli* serotype. N Engl J Med 308:681, 1983.

238. Fong JSC: Hemolytic uremic syndrome: Current concepts and management. Pediatr Clin North Am 29:835, 1982.

239. Fong JSC: Impairment of platelet aggregation in hemolytic uremic syndrome: Evidence for platelet "exhaustion." Blood 60:564, 1982.

240. Sieniawska M: Prognostic significance of certain factors in the haemolytic-uraemic syndrome. Pediatr Nephrol 4:213, 1990.

241. Hahn JS: Neurological complications of hemolytic-uremic syndrome. J Child Neurol 4:108, 1989.

242. Robson WLM: Gastrointestinal complications of hemolytic uremic syndrome. J R Soc Med 84:383, 1991.

243. Bennett WM, Singer I, Golper T et al: Guidelines for drug therapy in renal failure. Ann Intern Med 86:754, 1977.

244. McCarron DA: Clinical use of antihypertensive drugs in renal disease patients. Dial Transplant 8:45, 1979.

245. Parker S, Carlon GC, Isaacs M et al: Dopamine administration in oli-guria and oliguric renal failure. Crit Care Med 9:630, 1981.

246. Frishberg Y, Obrig TG, Kaplan BS: Hemolytic uremic syndrome. In Holliday MA, Barratt TM, Avner ED (eds): Pediatric Nephrology. Baltimore, Williams & Wilkins, 1994, p 885.

247. Chan JCM, Campbell RA: Peritoneal dialysis in children: A survey of its indications and applications. Clin Pediatr 12:131, 1973.

248. Hyams PJ, Smithivas T, Matalon R et al: The use of gentamicin in peritoneal dialysis. II. Microbiologic and clinical results. J Infect Dis 124:884, 1971.

249. Pascual JF, Lopez JD, Molina M: Hemofiltration in children with renal failure. Pediatr Clin North Am 34:803, 1987.

250. Adams AJ: Renal Disease in Childhood, 3rd ed. St. Louis, CV Mosby, 1976, p 274.

251. Salusky IB, Lucullo L, Nelson P et al: Continuous ambulatory peritoneal dialysis in children. Pediatr Clin North Am 29:1005, 1982.

252. Bongiovanni AM, Root AW: The adrenogenital syndrome. N Engl J Med 268:1283, 1963.

253. Hansen JW, Loriaux DL: Variable efficacy of glucocorticoids in congenital adrenal hyperplasia. Pediatrics 57:952, 1976.

254. Kaplan SA: Diseases of the adrenal cortex. II. Congenital adrenal hyperplasia. Pediatr Clin North Am 26:77, 1979.

255. Robinson MJ, Kent M, Stocks J: Pheochromocytoma in childhood: Report of 3 cases. Arch Dis Child 48:137, 1973.

256. Axelrod L: Glucocorticoid therapy. Medicine (Baltimore) 55:39, 1976.

257. Hoffman HJ, Hendrick EB, Humphreys RP et al: Management of craniopharyngioma in children. J Neurosurg 47:218, 1977.

258. Perkin RM, Levin DL: Common fluid and electrolyte problems in the pediatric intensive care unit. Pediatr Clin North Am 27:567, 1980.

259. Outwater KM, Rockoff MA: Diabetes insipidus accompanying brain death in children. Neurology 34:1243, 1984.

260. Becker DS, Foley TP: 1-Deamino-8-arginine vasopressin in the treatment of central diabetes insipidus in childhood. J Pediatr 92:1011, 1978.

261. Robertson GL, Aycinena P, Zerbe RL: Neurogenic disorders of osmoregulation. Am J Med 72:339, 1982.

262. Burrows FA, Shutack JG, Crone RK: Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. Crit Care Med 11:527, 1983.

263. Cornblath M, Schwartz R: Carbohydrate Metabolism in the Neonate, 2nd ed. Philadelphia, WB Saunders, 1977.

264. Dahlquist G, Gentz J, Hagenfeldt L et al: Ketotic hypoglycemia of childhood: A clinical trial of several unifying etiological hypotheses. Acta Paediatr Scand 68:649, 1979.

265. Pagliara AS, Karl IE, Haymond MW et al: Hypoglycemia in infancy and childhood. I, II. J Pediatr 82:365, 558, 1973.

266. Hochman HI, Grodin MA, Crone RK: Dehydration, diabetic ketoacidosis, and shock in the pediatric patient. Pediatr Clin North Am 26:803, 1979.

267. Kreisberg RA: Diabetic ketoacidosis: New concepts and trends in pathogenesis and treatment. Ann Intern Med 88:681, 1978.

268. Kaye R: Diabetic ketoacidosis the bicarbonate controversy. J Pediatr 93:883, 1978.

269. Feig PU, McCurdy DK: The hypertonic state. N Engl J Med 297:1444, 1977.

270. Rosenbloom AL, Riley WI, Weber FT et al: Cerebral edema complicating diabetic ketoacidosis in childhood. J Pediatr 96:357, 1980.

271. Krane EJ, Rockoff MA, Wallman JK et al: Subclinical brain swelling in children during treatment of diabetic ketoacidosis. N Engl J Med 312:1147, 1985.

272. Arey LB: Developmental Anatomy. Philadelphia, WB Saunders, 1974.

273. Delaiglesia FA, Sturgess M, McGuire EI et al: Quantitative microscopic evaluation of endoplasmic reticulum in developing human liver. Am J Pathol 82:62, 1976.

274. Rees JR, Redo SF: Anomalies of intestinal rotation and fixation. Am J Surg 116:834, 1968.

275. Bill A II: Malrotation of the intestine. In Ravitch MM, Welch KJ, Benson CD (eds): Pediatric Surgery, 3rd ed. Chicago, Year Book, 1979, p 912.

276. DeBartolo HM, van Heerden JA: Meckel's diverticulum. Ann Surg 183:30, 1976.

277. Mackey WC, Dineen P: A fifty year experience with Meckel's diverticulum. Surg Gynecol Obstet 156:56, 1983.

278. Silverman A, Roy CC (eds): Congenital aganglionic megacolon (Hirsch-sprung's disease). In Pediatric Clinical Gastroenterology, 3rd ed. St Louis, CV Mosby, 1983, p 399.

279. Swenson O, Sherman JO, Fisher JH et al: Diagnosis of congenital megacolon: An analysis of 501 patients. J Pediatr Surg 8:587, 1973.

280. Wayne ER, Campbell JB, Barrington JD et al: Management of 344 children with intussusception. Radiology 107:597, 1973.

281. Ament ME: Inflammatory disease of the colon: Ulcerative colitis and Crohn's colitis. J Pediatr 86:321, 1975.

282. Poley JR: Chronic inflammatory bowel disease in children and adolescents. South Med J 171:935, 1978.

283. Kohl S, Jacobson JA, Nahmias A: *Yersinia enterocolitica* infections in children. J Pediatr 89:77, 1976.

284. Ryder RW, Shelton JD, Guinan ME: Necrotizing enterocolitis: A prospective multicenter investigation. Am J Epidemiol 112:113, 1980.

285. Brown EG, Sweet AY: Neonatal necrotizing enterocolitis. Pediatr Clin North Am 29:1149, 1982.

286. Kliegman RM: Neonatal necrotizing enterocolitis: Implications for an infectious disease. Pediatr Clin North Am 26:327, 1979.

287. Bell MJ, Ternberg JL, Askin FB et al: Intestinal stricture in necrotizing enterocolitis. J Pediatr Surg 11:319, 1970.

288. Schwartz MZ, Richardson CJ, Hayden CK et al: Intestinal stenosis following successful medical management of necrotizing enterocolitis. J Pediatr Surg 15:890, 1980.

289. Trey C: Acute hepatic failure. In Smith CA (ed): The Critically Ill Child. Philadelphia, WB Saunders, 1972, p 104.

290. Rogers EL, Rogers MC: Fulminant hepatic failure and hepatic encephalopathy. Pediatr Clin North Am 27:701, 1980.

291. Walker CO, Schenkers S: Pathogenesis of hepatic encephalopathy

with special reference to the role of ammonia. Am J Clin Nutr 23:619, 1970.

292. Paradis KJ, Freese DK, Sharp HL: A pediatric perspective on liver transplantation. Pediatr Clin North Am 35:409, 1988.

293. Weber TR, Grosfeld JL: Contemporary management of biliary atresia. Surg Clin North Am 61:1079, 1981.

294. Howard ER, Mowat AP: Extrahepatic biliary atresia: Recent developments in management. Arch Dis Child 52:825, 1977.

295. Riegle CM, Thompson AE, Gartner JC: Intensive care unit course following pediatric hepatic transplantation. Crit Care Med 12:220A, 1984.

296. Cienfuegos JA, Dominguez RM, Tamelchaff LW et al: Surgical complications in the postoperative period of liver transplants in children. Transplant Proc 16:1230, 1984.

297. LeLeiko NS, Murray C, Munro HN: Enteral support of the hospitalized child. In Suskind RM (ed): Textbook of Pediatric Nutrition. New York, Raven Press, 1981, p 357.

298. Lloyd-Still J: Gastroenteritis with secondary disaccharide intolerance. Acta Paediatr Scand 58:147, 1969.

299. Filler RM: Parenteral support of the surgically ill child. In Suskind RM (ed): Textbook of Pediatric Nutrition. New York, Raven Press, 1981, p 341.

300. Crone RK: Pediatric critical care: Supporting the developing organ system. In Shoemaker WC (ed): Critical Care: State of the Art, vol 5. Fullerton, Calif, Society of Critical Care Medicine, 1984, p D1.

301. Postuma R, Pease PWB, Watts R et al: Essential fatty acid deficiency in infants receiving parenteral nutrition. J Pediatr Surg 13:393, 1978.

302. Reimer SL, Michener WM, Steiger E: Nutritional support of the critically ill child. Pediatr Clin North Am 27:647, 1980.

303. Sanders RA, Sheldon GF: Septic complications of total parenteral nutrition: A 5 year experience. Am J Surg 132:214, 1976.

304. Jeejeebhoy KN, Langer B, Tsallas G et al: Total parenteral nutrition at home: Studies in patients surviving 4 months to 5 years. Gastroenterology 71:943, 1976.

305. Hathaway WE: Hemostasis. In Rudolph AM (ed): Pediatrics, 17th ed. East Norwalk, Conn, Appleton-Century-Crofts, 1982, p 1110.

306. Briggs R: Recent advances in the management of haemophilia and Christmas disease. Clin Haematol 8:95, 1979.

307. DiMichele D: Hemophilia 1996. Pediatr Clin North Am 43:709, 1996.

308. Werner EJ: von Willebrand disease in children and adolescents. Pediatr Clin North Am 43:683, 1996.

309. Weiss HJ: Platelet physiology and abnormalities of platelet function. I, II. N Engl J Med 293:531, 580, 1975.

310. Prydz H: Vitamin K dependent clotting factors. Semin Thromb Hemost 4:1, 1977.

311. Medeiros O, Buchanan GR: Current controversies in the management of idiopathic thrombocytopenic purpura during childhood. Pediatr Clin North Am 43:757, 1996.

312. Ridulfi RL, Bell WR: Thrombotic thrombocytopenic purpura: Report of 25 cases and review of the literature. Medicine (Baltimore) 60:413, 1981.

313. Maurer HM, McCue CM, Caul J et al: Impairment in platelet aggregation in congenital heart disease. Blood 40:207, 1972.

314. Preston FE: Disseminated intravascular coagulation. Br J Hosp Med 28:129, 1982.

315. Toews WH, Bass JW: Skin manifestations of meningococcal infection: An immediate indicator of prognosis. Am J Dis Child 127:173, 1974.

316. Deykin D: The clinical challenge of disseminated intravascular coagulation. N Engl J Med 283:686, 1970.

317. Heene DL: Disseminated intravascular coagulation: Evaluation of therapeutic approaches. Semin Thromb Hemost 3:291, 1977.

318. Haak HL, Stolk JC, Gratama JW: Use of antithrombin concentrate in stable diffuse intravascular coagulation. Acta Haematol 68:28, 1982.

319. Diamond LK, Wang WC, Alter BP: Congenital hypoplastic anemia. Adv Pediatr 22:349, 1976.

320. Miller DR: Hemolytic anemia: Metabolic defects. In Miller DR, Pearson HA (eds): Smith's Blood Diseases of Infancy and Childhood, 4th ed. St. Louis, CV Mosby, 1978, p 1948.

321. Finch CA: Methemoglobinemia and sulfhemoglobinemia. N Engl J Med 239:470, 1948.

322. Zauder HL: Massive transfusion. Int Anesthesiol Clin 20:157, 1982.

323. Manno CS: What's new in transfusion medicine? Pediatr Clin North Am 43:793, 1996.

324. Nienhuis AW: Safety of intensive chelation therapy. N Engl J Med 296:114, 1977.

325. Propper RD, Bulton LN, Nathan DG: New approaches to the transfusion management of thalassemia. Blood 55:55, 1980.

326. Leikin SL, Gallagher D, Kinney TR et al: Mortality in children and adolescents with sickle cell disease. Pediatrics 84:500, 1989.

327. Castro O, Brambilla DJ, Thorington B et al: The acute chest syndrome in sickle cell disease: Incidence and risk factors. Blood 84:643, 1994.

328. Seeler RA, Shwiaki MZ: Acute splenic sequestration crisis (ASSC) in young children with sickle cell anemia. Clin Pediatr 11:701, 1972.

329. Cowan MJ, Ammann AJ, Wara DW et al: Pneumococcal polysaccharide immunization in infants and children. Pediatrics 62:721, 1978.

330. Vernant JP, Brun B, Mannoni P: Respiratory distress of hyperleukocytic granulocytic leukemias. Cancer 44:264, 1979.

331. Dearth J, Salter M, Wilson E et al: Early deaths in acute leukemia in children. Med Pediatr Oncol 11:225, 1983.

332. Wald BR, Heisel MA, Ortega JA: Frequency of early death in children with acute leukemia with hyperleukocytosis. Cancer 50:150, 1982.

333. Kamen BA, Summers CP, Pearson HA: Exchange transfusion as a treatment for hyperleukocytosis, anemia, and metabolic abnormalities in a patient with leukemia. J Pediatr 96:1045, 1980.

334. Cohen LF, Balow JE, Magrath IT et al: Acute tumor lysis syndrome: A review of 37 patients with Burkitt's lymphoma. Am J Med 68:486, 1980.

335. King RM, Telander RL, Smithson WA: Primary mediastinal tumors in children. J Pediatr Surg 17:512, 1982.

336. Halpern S, Chatten J, Meadows AT: Anterior mediastinal masses: Anesthetic hazards and other problems. J Pediatr 102:407, 1983.

337. Wilson CB: Immunologic basis of increased susceptibility of the neonate to infection. J Pediatr 108:1, 1986.

338. Pass RF: Viral infections in the fetus and neonate. In Long SS, Pickering LK, Prober CG (eds): Pediatric Infectious Diseases. New York, Churchill Livingstone, 1997, p 614.

339. Harris MC, Polio RA: Neonatal septicemia. Pediatr Clin North Am 30:243, 1983.

340. Baker C: Summary of the workshop on perinatal infections due to Group B *Streptococcus.* J Infect Dis 136:137, 1977.

341. Bone RC: Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: What we do and do not know about cytokine regulation. Crit Care Med 24:163, 1996.

342. Schumer W: Steroids in the treatment of clinical septic shock. Ann Surg 184:333, 1976.

343. Slotman GJ, Fisher CJ, Bone RC et al: Detrimental effects of high-dose methylprednisolone sodium succinate on serum concentrations of hepatic and renal function indicators in severe sepsis and septic shock: The methylprednisolone study group. Crit Care Med 21:191, 1993.

344. Hughes WT, Tufenkeji H, Bartley DL: The immune compromised host. Pediatr Clin North Am 30:103, 1983.

345. Herzig RH, Herzig GP, Graw KG et al: Successful granulocyte transfusion therapy for gram negative septicemia. N Engl J Med 296:70, 1977.

346. Feigin RD, Matson DO: Opportunistic infections: The compromised host. In Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases, vol 1, 2nd ed. Philadelphia, WB Saunders, 1987, p 1013.

347. Caldwell MB, Rogers MF: Epidemiology of pediatric HIV infection. Pediatr Clin North Am 38:1, 1991.

348. Burroughs MH, Edelson PJ: Medical care of the HIV infected child. Pediatr Clin North Am 38:45, 1991.

349. Rothenberger D, Quattleebaum FW, Perry JF et al: Blunt maternal trauma: A review of 103 cases. J Trauma 18:173, 1978.

350. Bianco AJ, Schlein AP, Kruse RL et al: Birth fractures. Minn Med 55:471, 1972.

351. Tank ES, Davis R, Holt JF et al: Mechanisms of trauma during breech delivery. Obstet Gynecol 38:761, 1971.

352. Eichelberger MR, Randolph JG: Pediatric trauma: An algorithm for diagnosis and therapy. J Trauma 23:91, 1983.

353. Rivara FP: Epidemiology of childhood injuries. Am J Dis Child 136:399, 1982.

354. Levy JL, Linder LH: Major abdominal trauma in children. Am J Surg 120:55, 1970.

355. Dykes EH, Spence LJ, Bohn DJ et al: Evaluation of pediatric trauma care in Ontario. J Trauma 29:724, 1989.

356. Subcommittee of Advanced Trauma Life Support of the American College of Surgeons Committee on Trauma: Advanced Trauma Life Support Student Manual. Chicago, American College of Surgeons, 1989.

357. Hubbard DD: Injuries of the spine in children and adolescents. Clin Orthop 100:546, 1974.

358. Kissoon N, Dreyer J, Walia M: Pediatric trauma: Differences in pathophysiology, injury patterns, and treatment compared with adult trauma. Can Med Assoc J 142:27, 1990.

359. Fiser DH: Intraosseous infusion. N Engl J Med 322:1579, 1990.

360. Breaux CW Jr, Smith G, Georgeson KE: The first two years' experience with major trauma at a pediatric trauma center. J Trauma 30:37, 1990.

361. Hoelzer DJ, Brian MB, Balsava VJ et al: Selection and nonoperative management of pediatric blunt trauma patients: The role of quantitative crystalloid resuscitation and abdominal ultrasonography. J Trauma 26:57, 1986.

362. Kempe CH, Silverman FN, Steele BF et al: The battered-child syndrome. JAMA 181:17, 1962.

363. McNeese MC, Hebeler JR: The abused child: A clinical approach to identification and management. Clin Symp 29:35, 1977.

364. Kempe CH: Sexual abuse, another hidden pediatric problem: The 1977 C. Anderson Aldrich Lecture. Pediatrics 62:283, 1978.

365. Fazen LE, Lovejoy FH, Crone RK: Acute poisoning in a general pediatric hospital. Pediatrics 77:144, 1986.

366. Lovejoy FH, Gellis SS: Acute poisoning. In Gellis SS, Kagan BM (eds): Current Pediatric Therapy, 9th ed. Philadelphia, WB Saunders, 1980.

367. Black RE, Mayer T, Walker ML et al: Air transport of pediatric emergency cases. N Engl J Med 307:1465, 1982.

368. Simon JE, Smookler S, Guy B: A regionalized approach to pediatric emergency care. Pediatr Clin North Am 28:677, 1981.

369. Shannon DC, Kelly DH: SIDS and near-SIDS. I. N Engl J Med 306:959, 1982.

370. Shannon DC, Kelly DH: SIDS and near-SIDS. II. N Engl J Med 306:1022, 1982.

371. Southall J, Richards JM, Arrowsmith WA et al: Identification of infants destined to die unexpectedly during infancy: Evaluation of predictive importance of prolonged apnea and disorders of cardiac rhythm or conduction. BMJ 286:1092, 1983.

372. American Academy of Pediatrics Task Force on Infant Positioning and SIDS: Positioning and sudden infant death syndrome (SIDS). Pediatrics 98:1216, 1996.

373. Southall DP: Role of apnea in sudden infant death syndrome: A personal view. Pediatrics 80:73, 1988.

374. Safar P, Grenvik A, Smith J: Progressive pulmonary consolidation: Review of cases and pathogenesis. J Trauma 12:955, 1972.

375. Tarby TJ, Volpe JJ: Intraventricular hemorrhage in the premature infant. Pediatr Clin North Am 29:1077, 1982.

376. Nemoto EM: Pathogenesis of cerebral ischemia-anoxia. Crit Care Med 6:203, 1976.

377. Bratton SL, Jardine DS, Morray JP: Serial neurologic examinations after near drowning and outcome. Arch Pediatr Adolesc Med 148:167, 1994.

378. Barnes JL, McDowell EM: Pathology and pathophysiology of acute renal failure: A review. In Cowley RA, Trump BF (eds): Pathophysiology of Shock, Anoxia and Ischemia. Baltimore, Williams & Wilkins, 1982, p 324.

379. Bunton G, Durbin GM, McIntosh N et al: Necrotizing enterocolitis. Arch Dis Child 52:772, 1977.

380. Cowley RA, Hankins JR, Jones RT et al: Pathology and pathophysiology of the liver. In Cowley RA, Trump BF (eds): Pathophysiology of Shock, Anoxia, and Ischemia. Baltimore, Williams & Wilkins, 1982, p 285.

381. Goetting MG, Paradis NA: High-dose epinephrine improved outcome from pediatric cardiac arrest. Ann Emerg Med 20:22, 1991.

382. Kubler-Ross E: On Death and Dying. New York, Macmillan, 1969.

383. Crone RK: Pediatric intensive care. ASA Refresher Courses in Anesthesiology, vol 9. Philadelphia, JB Lippincott, 1981.

384. O'Rourke PP, Crone RK: The respiratory system. In Gregory G (ed): Pediatric Anesthesia, 2nd ed. New York, Churchill Livingstone, 1989, p 63.

385. Ramondi AJ: Head injury in the infant and toddler. Childs Brain 11:12, 1984.

386. American Heart Association: Textbook of Pediatric Advanced Life Support. Dallas, American Heart Association, 1994, p 5.

Chapter 74 - Nutritional Aspects

John K. Stene
Thomas C. Vary

INTRODUCTION

Nutrition has an important impact on the quality of human protoplasm and ultimately on a patient's fitness for surgery. Thus, anesthesiologists need a fundamental knowledge of nutritional principles to develop a logical approach to nutritional support for the surgical patient during the perioperative period. Changes in energy use induced by starvation (fasting), trauma, and critical illness also have implications for anesthesia care. Amino acid patterns in plasma that vary with dietary changes and in certain pathologic conditions affect plasma binding of drugs and alter neurotransmitter precursor availability. [1] Furthermore, the choice of anesthetic technique may affect the patient's use of energy substrates and nutritional needs. [2]

This chapter concentrates on the perioperative nutritional care of the surgical patient both in the intensive care unit and in the operating room. Although much of the information in this chapter is derived from studies on centrally administered total parenteral nutrition (TPN), perioperative nutritional support may also be administered by peripheral veins and is increasingly being administered enterally through the gut. Physiologic principles for nutritional support are stressed in the chapter. Such physiologic knowledge will help the anesthesiologist decide who will benefit from nutritional support, whether to provide parenteral or enteral nutrition, how to monitor the patient's response to nutritional support, and what prescription to write for nutritional support.

NUTRITIONAL REQUIREMENTS OF SURGICAL PATIENTS

Knowledge of basic substrate-endocrine relationships is essential for the rational planning of perioperative nutritional support. Failure to consider these relationships leads to the use of empirical therapy, to the use of inappropriate intravenous solutions, and to the development of complications, such as hyperglycemia, hypoglycemia, metabolic acidosis, and fatty infiltration of the liver.

Normal organ function depends on normal cellular function. Proper nutrient substrates must be delivered to the cells to maintain healthy cells and normal organ function. The ultimate aim of guidelines for nutritional support therapy should be to maintain cellular homeostasis. Besides uptake of appropriate nutritional substrates, use by the cells depends on substrate delivery by cardiac output and on microcirculatory blood flow.

The choice of appropriate nutrient solutions depends on the knowledge of changes in the energy substrate-endocrine relationships that occur in the perioperative period. [3] These changes are effected by starvation, trauma, anesthesia, and excess glucose administration.

General Principles

The role of nutrition in the posttrauma or surgical patient is generally overlooked. Often, concern with the physical injuries and surgical procedures causes one to forget what is actually occurring within the individual. Healthy people eat to replenish energy stores and to maintain health and well-being. Although there are charts and suggestions for proper nutrition, most healthy adults consume enough (sometimes too much) food to maintain normal structure and function of their organs. This implies that the nutrients delivered by the circulatory system are sufficient to meet the individual organ's needs. Nutrients provide both structural building blocks for cells and fuels for the production of energy. Both functions are vital to the maintenance of normal cell structure and function.

In the normal individual, a balance between those processes involved in anabolism and catabolism is maintained such that the concentration of plasma metabolites remains fairly constant over a wide range of physiologic insults. After meals, anabolism predominates with the storage of energy substrates, which include glycogen, to sequester excess glucose mainly in liver and muscle, triglycerides from both ingested fatty acids and de novo synthesis from glucose and stored in adipose tissue, and proteins necessary for normal function of all tissues (Fig. 74-1) . Between meals and under pathologic conditions, the body draws on these energy stores to maintain normal structure and function (Table 74-1) (Table Not Available) . The resulting catabolism is a normal response in periods in which nutrient intake could be compromised. However, although it is a normal response to starvation, in trauma and sepsis, this catabolic phase leads to further complications unless it is corrected. Although trace elements, vitamins, and minerals are also nutrients that contribute to the overall well-being of the organism, this discussion concentrates on the macronutrients (i.e., carbohydrate, fat, and amino acids). The state of nutritional assessment is based more on empirical anecdotes rather than on scientific fact. As such, the role of nutritional support in the critically ill patient is evolving rather than static. For an appreciation of the changes in nutritional assessment and required support, a solid understanding of the changes in these nutrients in various

TABLE 74-1 -- Body Fuels in Adult Man

(Not Available)

From Hawkins and Vina [190]

disease states is required. Unfortunately, not all the alterations are well defined. This chapter addresses the metabolic and nutrient requirements of the critically ill patient.

Starvation

A lack of food has profound effects on the normal flow of nutrients in the body. The immediate result of food deprivation is decreased intake of glucose. Glucose is vital to the animal for survival because certain cells, such as erythrocytes, cells of the renal medulla, and cells of the central nervous system, have an absolute requirement for glucose, amounting to approximately 180 g/d (Fig. 74-2) (Figure Not Available) . Despite reduced sugar intake, the circulating blood glucose concentration varies little. This is because humans adapt to decreased glucose intake during starvation by two mechanisms that serve to maintain the plasma glucose concentration. First, fatty acids mobilized from triglyceride stores in adipose tissue are used as an alternative fuel to glucose in those tissues that can oxidize fats. This use of alternative fuel for energy production lowers the requirements for glucose, thereby decreasing the demand for more glucose at a time when input via feeding is not available. Second, several adaptations in intracellular glucose metabolism occur that result in an inhibition of glucose-utilizing pathways and a stimulation of glucose-producing pathways (Fig. 74-3) . Initially, to maintain the plasma glucose concentration, glycogen is broken down. The loss of glycogen is rapid and significant. Within

Figure 74-1 Flow of nutrients in the fed state.

Figure 74-2 (Figure Not Available) General scheme of fuel metabolism in normal fasted humans, emphasizing the central position of the liver as a metabolic transformer. Two primary fuel sources are shown: muscle and adipose tissue, and three types of fuel consumer: (1) nerve (including brain), (2) pure glycolyzers producing lactate (red blood cells and white blood cells), and (3) the remainder of the body (heart, kidney, and muscle) that can use fatty acids and ketones. The brain can also use ketone bodies after injury and starvation. *(Modified from Cahill* [194] *)*

48 hours of starvation, rats show a 99.5 percent loss of liver glycogen and a 70.3 percent loss of carcass glycogen. However, the amount of glucose released by glycogenolysis is insufficient to sustain the energy needs of the whole body for more than a short period of time. The liver, and to a certain extent, the kidneys have the ability to synthesize glucose from different carbon sources via the process of gluconeogenesis (Fig. 74-4) (Figure Not Available) . Glucose is synthesized primarily from glycerol, lactate, pyruvate, and certain amino acids, particularly alanine. Lactate and pyruvate are released by peripheral tissues, particularly skeletal muscle. Lactate provides 60 to 70 percent of the glucose carbon used for gluconeogenesis. Glycerol is derived from adipose tissue after the breakdown of triglycerides. Amino acids are derived from the breakdown of proteins in both liver and peripheral tissues.

More than 35 years ago, an interorgan cycle (Cori cycle) accounting for the flow of glucose carbon during starvation was proposed. Glucose taken up by peripheral

organs is converted to lactate, which enters the blood and is returned to liver. The lactate is taken up by the liver and is synthesized to glucose (Fig. 74-5) .

The amount of lactate that can be produced and cleansed by the liver may be extremely high. The normal liver can clear up to 400 g of lactate per day. Lactate production by skeletal muscle must increase to provide the necessary gluconeogenic precursors for the maintenance of sustained rates of gluconeogenesis in starvation or diabetes. Lactate arises from the reduction of tissue pyruvate.

Lactate production occurs whenever the rate of pyruvate production from glycolysis exceeds glucose oxidation by the mitochondria. Therefore, for increased lactate production to be important physiologically, mitochondrial glucose oxidation must decrease under conditions known to result in increased gluconeogenesis. In humans, whole-body glucose oxidation is inhibited 90 percent in starvation, 70 percent in type 1 diabetes mellitus, and 40 percent in non- insulin-dependent

Figure 74-3 Adaptations in glucose metabolism during starvation. M, muscle; L, liver; K, kidney; AT, adipose tissue; CNS, central nervous system.

Figure 74-4 (Figure Not Available) Diagram of pathway of gluconeogenesis from various precursors. Shown are the stages in which amino acids (alanine), glycerol, and lactate join the pathway of gluconeogenesis. The reactions common to gluconeogenesis and glycolysis are those indicated by the straight arrows; the downward arrows show the direction of gluconeogenesis, the upward arrows the direction of glycolysis. The curved arrows represent the reactions (pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose 1,6-diphosphatase, glucose 6-phosphatase) circumventing the energy barriers obstructing the direct reversal of glycolysis. *(Modified from Biebuyck [195])*

(type 2) diabetes mellitus. Each of these conditions is associated with enhanced rates of gluconeogenesis (Ch. 25) .

At the enzymatic level, the pyruvate dehydrogenase (PDH) complex catalyzes the first irreversible reaction in the mitochondrial oxidation of glucose. Pyruvate is oxidized by the PDH complex in the presence of the oxidized form of nicotinamide adenine dinucleotide (NAD^+) and coenzyme A (CoA) to form acetyl-CoA, the reduced form of NAD (NADH), and CO_2 . As such, the PDH complex is the primary regulator of glucose oxidation in mammalian cells. [4] [5] [6] Regulation by this complex is important to glucose homeostasis because the oxidation of pyruvate results in the net loss of body glucose carbon sources since glucose cannot be synthesized from acetyl-CoA and the PDH reaction is physiologically irreversible. Thus, the activity of the PDH complex determines whether pyruvate is oxidized to CO_2 and water or is converted to lactate via lactate dehydrogenase. The decreased activity of the PDH complex is caused by several mechanisms, the most prominent of which is reversible phosphorylation (Fig. 74-6) (Figure Not Available) .. Increased phosphorylation results in a decreased flux of glucose through the PDH complex (Fig. 74-7)

Release of amino acids from skeletal muscle is intimately related to glucose homeostasis because amino acids represent an important precursor for gluconeogenesis. Most amino acids are released from muscle in proportion to their concentration in muscle proteins. [7] However, the exceptions are alanine and glutamine, which are released in excess of their concentration in muscle proteins. These observations implied that de novo synthesis of alanine and glutamine occur in skeletal muscle. Because alanine is utilized by the liver and kidney as a major substrate for gluconeogenesis, Felig et al [8] proposed a glucose-alanine cycle as a means of transferring amino nitrogen from muscle to liver and kidney. According to this hypothesis, glucose taken up by muscle is metabolized to pyruvate. Pyruvate, instead of being oxidized via the PDH complex, serves as a nitrogen acceptor, with alanine being formed through transamination from glutamate. The alanine released from muscle recirculates to the liver, where it is taken up and reconverted to glucose.

Although the proposed glucose-alanine cycle allows for the transfer of nitrogen groups derived from amino acid catabolism to liver, it does not account for a net flow of carbon from protein to carbohydrate. Both alanine and glutamine are also synthesized from other amino acids. In the postabsorptive state, about 40 percent of the circulating plasma alanine is derived from endogenous proteins, whereas 60 percent is derived from de novo synthesis in humans. [9] In addition, at least 20 percent of the nitrogen required for the de novo alanine synthesis comes from leucine. [10] Leucine (isoleucine and valine) nitrogen is incorporated into alanine through a series of reversible transamination reactions involving the nitrogen transfer from leucine to glutamate via the branched-chain aminotransferase and the subsequent transamination of glutamate with pyruvate forming alanine. The rate of alanine synthesis is determined by (1) the rate of leucine appearance and (2) the rate of pyruvate availability.

If requirements for glucose carbon continued unabated, protein breakdown would result in a severe depletion of vital proteins. However, ketone body concentrations rise in long-term starvation or diabetes mellitus. Ketone bodies are derived from the incomplete oxidation of fatty acids in the liver. The brain adapts to using alternative fuels such as ketone bodies as a primary energy source, rather than glucose. Thus, by utilizing alternative fuels, the demand for glucose is further reduced (Table 74-2) (Table Not Available) . An important consequence of this adaptation is that the breakdown of muscle is no longer required to maintain the flow of alanine to the liver for gluconeogenesis (Fig. 74-8) (Figure Not Available) . The net result is that muscle proteins are spared further degradation. The adaptive ability of the organism to use alternative fuels instead of glucose is of fundamental importance to the survival of the animal because otherwise, protein function would eventually be compromised.

These adaptive processes are under hormonal control, which serves to regulate the flow of glucose carbon to ensure adequate levels of glucose in the blood. These hormones can be broadly categorized into two groups: anabolic hormones and catabolic hormones. At any given time, the net effect of the hormones, whether to break down or to store fuels, depends on the ratio of concentrations of each of the hormones to each other, as well as on their absolute concentration. The principal anabolic hormone is insulin. Insulin is of major importance in fuel storage, promoting the deposition of glycogen, triglycerides, and proteins. At basal levels, insulin has an important anticatabolic role in restraining glycogenolysis, gluconeogenesis, and lipolysis. Growth hormone is also anabolic, but only with respect to protein

Figure 74-5 Role of inhibition of skeletal muscle glucose oxidation in starvation and diabetes. OAA, oxaloacetic acid; CoA, coenzyme A; NAD, oxidized form of nicotin-amide adenine dinucleotide; NADH, reduced form of nicotinamide adenine dinucleotide.

Figure 74-6 (Figure Not Available) Site of action of dichloroacetate (DCA) in mammalian cells; DCA activates pyruvate dehydrogenase, thereby increasing the flux of C_3 compounds into the tricarboxylic acid cycle and decreasing the release of lactate, pyruvate, and alanine into the circulation. *(Modified from Blackshear et al [196])*

Figure 74-7 Mechanism regulating pyruvate dehydro-genase (PDH) complex activity in starvation and diabetes. FA, fatty acid; KAP, kinase activator protein.

metabolism, in which growth hormone stimulates amino acid transport and protein synthesis. Some studies have suggested that parts of the anabolic effects of growth hormone are mediated by a faster-term insulin-like growth factor-1. [11] The major catabolic hormones are glucagon, cortisol, and catecholamines. Individually, none of these hormones totally opposes the action of insulin; instead, they act together to counterbalance insulin action. Glucagon has its major effects on the liver, promoting gluconeogenesis, amino acid uptake, ureogenesis, and protein catabolism. Cortisol enhances extrahepatic protein catabolism, thereby increasing the release of amino acids, and promotes hepatic utilization of the mobilized amino acids for gluconeogenesis. Catecholamines stimulate lipolysis and glycogenolysis in both hepatic and extrahepatic tissues.

Stress Response to Surgery and Trauma

The body responds to trauma or surgical stress in a characteristic fashion (Fig. 74-9) (Ch. 10) . Monitoring of the

TABLE 74-2 -- Fuels in Circulation in Man

(Not Available)

From Hawkins and Vina [190]

Figure 74-8 (Figure Not Available) Use of metabolic fuels during fasting. The energy fuel substrate flux shown in terms of calories per day has been calculated from experimental data. Protein loss would be equal to approximately 16.6 g of nitrogen. Aa, amino acid; ADP, adenosine diphosphate; ATP adenosine triphosphate; FFA, free fatty acid; Glc, glucose; KB, ketone body; RQ, respiratory quotient; Tg, triglyceride. *(Modified from Blackburn and Phinney* [197] *)*

stressed surgical or trauma patient has demonstrated a pattern of physiologic adaptations designed to return the host to normal function. [12] [13] The pattern reflects the adequacy of the host defense system and arises out of the interorgan fuel metabolism and immunologic response mechanisms. The normal stress response is characterized by a neurohormonal sympathetic response mediated by a rise in norepinephrine, epinephrine, glucagon, and cortisol levels. Hemodynamically, heart rate, contractility, and cardiac index increase. Oxygen consumption is augmented. Metabolically, in the first few days after trauma injury, the normal balance between anabolic and catabolic processes is altered in the direction of catabolic metabolism. The catabolic response is mediated primarily by a rise in the catabolic hormones. Glucose turnover increases at least 2-fold. The rate of glucose production can be matched by an increased rate of utilization such that euglycemia is maintained. Within days, this sympathetic stress response abates, and lean muscle mass is restored. This pattern of host response is the normal response to a posttraumatic stress. The failure to achieve this state or to deviate from this course represents an abnormal physiologic response in the posttrauma or surgical patient.

Respiratory Muscle Function After Trauma

Respiratory muscle power is reduced during starvation, and respiratory muscles probably are not preferentially spared in the nitrogen losses after trauma (Ch. 62) . The effects of the prolonged use of muscle relaxant drugs and of the enforced immobilization of respiratory muscles on recovery of ventilatory strength and chest-wall coordination have not been adequately investigated. Specific deficiency states may contribute to reduced muscle power; for example, acute areflexic paralysis with respiratory failure resulting from hypophosphatemia has been described. [14] As the malnourished patient with an associated hypermetabolic disease process becomes more depleted, strength is diminished, which can lead to use of the accessory muscles of respiration as well as compromised pulmonary function (Fig. 74-10) (Figure Not Available) . Minute ventilation and ventilatory response to CO_2 breathing are increased in spontaneously breathing patients who receive an amino acid-enriched nutritional formula. [15] Thus, nutritional support with high nitrogen loads leads to improved respiratory muscle strength and ventilatory response.

GLUCOSE HOMEOSTASIS DURING PARENTERAL NUTRITION

Normally, the concentration of plasma glucose is kept within close limits. There is a constant requirement for glucose by glucose-dependent tissues (brain, erythrocytes). Equally, there are detrimental effects of extreme hyperglycemia (e.g., hyperosmolar coma). [16] [17] The mechanisms responsible for the regulation of plasma glucose levels are of fundamental importance to the entire metabolic response to hyperalimentation. [18]

Figure 74-9 Interorgan substrate fluxes in response to trauma or surgery.

Figure 74-10 (Figure Not Available) Effects of semistarvation on metabolic rate and hypoxic and hypercapnic ventilatory responses. The hypoxic response is quantitated by A, defined in the equation $V_E = V_0 + A/(Pa_{O_2} - 32)$, where V_E is minute ventilation, Pa_{O_2} is alveolar oxygen tension, and V_0 is the asymptote for ventilation obtained by extrapolation. The hypercapnic response is quantitated by S, defined in the equation $V_E = S(Pa_{CO_2} - B)$, where Pa_{CO_2} is end-tidal CO_2 tension, and B is the extrapolated intercept on the abscissa (Pa_{CO_2} axis). V_{O_2} and V_{CO_2} declined, reaching the lowest level by the 10th day, as did the hypoxic response. The hypercapnic response declined slightly but not significantly. Asterisk (*) denotes significantly different from control ($P < .05$). Brackets indicate ± SEM. *(From Doekel et al [145])*

During intravenous infusion of glucose, two processes can minimize changes in plasma glucose concentration: (1) reduction in the rate of glucose production and (2) enhanced ability to clear glucose from the blood stream. Wolfe et al [19] demonstrated that when glucose was infused into normal volunteers at the rate of 1 mg/kg/min (84 mL/h of 5% dextrose in water in a 70-kg patient), endogenous glucose production was suppressed. One of the principal reasons whereby infused glucose is of nutritional benefit is that the suppression of glucose production resulting from glucose infusion spares amino acids that would otherwise be catabolized to provide gluconeogenic precursors. The rate of glucose infusion that provides the maximal benefit depends on the condition of the patient. [20]

From a clinical point of view, the justification for administering glucose at rates in excess of 3 to 4 mg/kg/min must therefore reside in the ability of the body to oxidize the infused glucose. Table 74-3 (Table Not Available) shows that even during a 4-mg/kg/min infusion, less than one-half the infused glucose was directly oxidized, and that at an infusion rate of 9 mg/kg/min, approximately one-third of the glucose was directly oxidized. [21] At this high level of glucose infusion, however, only 61.6 percent of CO_2 was attributed to direct oxidation of glucose. Thus, even at these levels of glucose supply, other substrates are being oxidized.

The percentage of CO_2 from glucose infusion also reaches a plateau at around 60 percent in burn patients, regardless of the infusion rate. [22] Importantly, and against all previous reasoning, apparently, if insulin is infused simultaneously with glucose, the glucose clearance rate increases, but the rate of glucose oxidation is unaltered. Perhaps 22 percent of carbon dioxide that is coming from fat oxidation can be attributed to the conversion of excess infused glucose to fat.

RESPONSE TO SEPSIS

The major cause of an abnormal physiologic stress response in surgical intensive care is sepsis (Chs. 55 and 71) . Sepsis is the host's response to infection, which imposes another stress to the host in addition to the stress imposed by trauma alone. As can be expected, this leads to a continuum of responses with increasing severity. Ultimately, the patient either improves and returns to the normal stress response or continues to deteriorate. The complications of sepsis leads to a condition described clinically as a sequential failure of the major organ systems of the body. [13] [23] [24] [25] [26] In operations for intra-abdominal sepsis, multiple system organ failure (MSOF) occurs in 30 to 50 percent of cases and is the major cause of death in patients with sepsis.

Initially, the conditions leading to sepsis-induced MSOF are clinical episodes of shock, resuscitation, and postresuscitation hypermetabolism. The shock state is usually short lived, and the patient is adequately resuscitated with fluids and cardiotrophic support. Clearly, during the shock episode, alterations in hemodynamics and metabolism are driven by the degree of hypoperfusion. This problem can be corrected by increasing the oxygen delivery via augmentation of fluid resuscitation and cardiac output. The end point for resuscitation should be the absence of flow-dependent increase in oxygen consumption, and this should be the cornerstone of therapy. [27] [28]

Three to 4 days after the septic episode, patients enter a phase characterized by persistent hypermetabolism, which can last weeks. These patients are hemodynamically stable, demonstrating an increased cardiac output at 10 to 12 L/min. In contrast to the stress response, the total peripheral resistance falls, indicative of a hyperdynamic cardiovascular state. The oxygen consumption rises approximately

TABLE 74-3 -- Glucose Oxidation During Total Parenteral Nutrition in Postoperative Patients (*n* = 5)

(Not Available)

From Wolfe et al [191]

2-fold above normal (Fig. 74-11) (Figure Not Available) . The respiratory gas quotient falls to 0.8 to 0.85, indicative of a greater reliance on fats for oxidative energy production. In general, there is marked increase in metabolic demand and work relative to the resting, fasting human. The plasma lactate level is increased

Figure 74-11 (Figure Not Available) Cardiovascular and metabolic responses after trauma and sepsis, in 10 septic and 16 nonseptic patients. Mean values over postinjury course for cardiac index (CI) and oxygen consumption (V_{O_2}) are shown for trauma patients who developed sepsis (ST) and compared to those who had nonseptic courses. Note increase in CI and V_{O_2} in ST patients as sepsis becomes established between 5 and 7 days after injury. *(From Sganga et al, [82] copyright 1985, American Medical Association)*

into the 2 to 3 mg/dL range. However, this rise in lactate is not accompanied by a metabolic acidosis. In fact, the plasma pyruvate concentrations also rise such that the lactate/pyruvate ratio in the arterial and femoral vein plasma is within normal limits, implying a normal cytosolic redox potential. [29] Without any overt injury to specific organ systems, the level of plasma enzymes used as indicators of ischemic injury (serum glutamic oxaloacetic transaminase, creatine phosphokinase, lactate dehydrogenase, and ornithine transcarbamylase) are not increased. Biopsies of skeletal muscle reveal adequate levels of high-energy phosphates, also indicative of adequate blood flow. Under this condition, energy production and utilization are consistent with adequate oxygen supply, and metabolically insignificant amounts of hypoxia-driven metabolic alterations are observed. Instead, other mechanisms or abnormalities besides inadequate oxygen delivery are involved in the regulation of plasma metabolites and fluxes in sepsis.

As the septic processes progress, hemodynamic and metabolic dysfunction are observed. [12] In particular, the increase in oxygen delivery begins to fall such that the hyperlactatemia becomes associated with acidosis. Oxygen consumption decreases as organ systems fail. Respiratory dysfunction at this stage leads to the retention of CO_2 , and respiratory acidosis is observed. Eventually, cardiac organ failure leads to a profound myocardial insufficiency in which the hyperdynamic cardiovascular state develops into a hypodynamic state. At this stage, the alterations induced by profound hypoper-fusion outweigh any changes induced by altered metabolism.

It is in the setting of the stable hyperdynamic cardiovascular condition that patients need the maximal nutritional support to prevent sustained starvation from limiting recovery. [30] The septic insult results in pathologic alterations in glucose, fatty acid, and amino acid (protein) metabolism (Fig. 74-12) . Virtually no organ system is spared from the metabolic alterations in sepsis. The pattern of alterations in the plasma level of these fuels is superimposed on changes in the plasma level of hormones. Changes in carbohydrate metabolism after severe trauma and during sepsis include hyperglycemia, increased gluconeogenesis with an increased output of glucose from the liver, hyperlactatemia, and insulin resistance. The metabolic alterations that occur in sepsis are numerous, and all probably contribute to a cascade of secondary alterations that result from the initial traumatic or septic episode. Collectively, these changes lead to the observed plasma alteration in hormones and substrates in the critically ill patient. The metabolic changes observed are likely to result from changes in hormone concentrations and/or expression of inflammatory or immunologic mediators.

Figure 74-12 Interorgan substrate fluxes in response to sepsis.

Sepsis increases glucose turnover by stimulating hepatic glucose production and by augmenting peripheral glucose utilization. [31] [32] Gluconeogenesis represents the major pathway for lactate clearance, and enhanced rates of gluconeogenesis are associated with a 2-fold to 3-fold increase in net lactate extraction by the liver during sepsis. [33] [34] In injured patients, endogenous glucose production is elevated 2-fold to 3-fold above the normal basal level. Therefore, as much as two or three times as much infused glucose may be required to suppress glucose production in the injured patient. By contrast, sepsis appears to minimize the effectiveness of exogenous glucose in suppressing glucose production. The response to glucose in any patient can be determined by recording the infusion rate at which the glucose level begins to rise rapidly. The ability of tissues to clear glucose increases with time on hyperalimentation (Fig. 74-13) (Figure Not Available) . This increase in clearance apparently is not due to insulin mechanisms. [21]

Sepsis also increases glucose utilization, as measured by lactate and alanine production. However, the increased glucose uptake is not accompanied by a corresponding increase in glucose oxidation. Instead, the glucose carbon is released from peripheral tissues into the venous blood as lactate, pyruvate, and alanine. [31] [34] Because the rates of pyruvate, lactate, and alanine production are normal or increased, it appears that glucose uptake and glycolysis are normal or accelerated

in sepsis. Thus, glucose carbon is conserved by the body because oxidation would deplete the body stores of glucose carbon. The lactate, pyruvate and alanine released by skeletal muscle are returned to the liver and kidney, where glucose is synthesized from these C_3 precursors by the process of gluconeogenesis. This interorgan relationship probably accounts for the increased rate of glucose carbon recycling observed in sepsis (Fig. 74-14) (Figure Not Available) . Furthermore, it is a futile cycle in that the overall process consumes energy with no net energy production. Thus, it is not necessary to invoke an uncoupling of oxidative metabolism to account for the increased oxygen demands during sepsis. In fact, this futile cycle may account in part for the increased hepatic oxygen consumption.

An impairment in glucose oxidation in conjunction with normal or increased lactate, alanine, and/or pyruvate production suggests a specific inhibition of the pyruvate dehydrogenase reaction. This impairment can be due either to the decreased formation of pyruvate or to the entry of glucose carbon into the tricarboxylic acid (TCA) cycle. Estimates of glucose recycling [31] [32] [33] [34] suggest that the rate of pyruvate formation from glucose is probably not rate limiting for

Figure 74-13 (Figure Not Available) Glucose concentration and glucose clearance (glucose uptake/glucose concentration) in postoperative patients on total parenteral nutrition. There is a progressive rise in glucose clearance such that after 6 days of infusion, the glucose concentration is significantly lower than at 2 hours of infusion, even though the infusion rate is much higher at 6 days. Glucose production is suppressed in normal volunteers by exogenous glucose infusion. During the first 2 hours of glucose infusion, suppression of glucose production appears to be of predominant importance in maintaining normal blood glucose concentration. Maximal suppression can be obtained at glucose infusion rates well below rates conventionally administered in total parenteral nutrition. *(Modified from Wolfe [196])*

Figure 74-14 (Figure Not Available) Gluconeogenic response to trauma in 10 septic and 16 nonseptic patients, mean values for plasma glucose and alanine in patients with sepsis after trauma (ST) compared to those with nonseptic post-trauma courses (NST). Note early rise in plasma glucose associated with increase in plasma alanine in ST patients with progressive increase as the septic course evolves. *(From Vary and Siegal [12])*

glucose oxidation. Thus, entry of glucose carbon into the TCA cycle may be limiting for glucose oxidation in sepsis. Some studies have identified a specific inhibition of the pyruvate dehydrogenase complex in sepsis.

Endotoxin administration and bacterial infusions stimulate glucose uptake and phosphorylation in skeletal muscle. [35] [36] [37] The increased glucose uptake and phosphorylation is associated with a 2-fold increase in the glucose 6phosphate content. [38] The mechanisms responsible for these changes are unknown. Glucose entry into muscle is facilitated by specific transport proteins. At least five isoforms of the facultative glucose transporter have been described, of which two of these isoforms, GLUT-1 and GLUT-4, are present in skeletal muscle. The GLUT-1 isoform is present in a wide variety of tissues and mediates basal glucose uptake. [39] In contrast to GLUT-1, the GLUT-4 isoform is expressed only in those tissues in which glucose uptake is facilitated by insulin. [39] In skeletal muscle, glucose uptake is the rate-limiting step in glucose utilization. Sustained increases in glucose transport activity result from an increase in the number of cell surface glucose transporters. [39] Some studies have demonstrated an increased amount (approximately 70%) of GLUT-1 protein in skeletal muscle from septic animals compared with controls. [38] The increased GLUT-1 transporter expression correlates with enhanced basal (non-insulin-stimulated) glucose transport after endotoxin administration or sepsis. [40] [41] The significance of this observation is that non-insulin-mediated glucose uptake accounts for 75 to 85 percent of the total glucose disposal in the basal postabsorptive state. [35] Therefore, the increased glucose transport in sepsis may result in part from an increased GLUT-1 transporter protein content.

There is a specific inhibition of the PDH complex in sepsis, and the degree of impairment is dependent on the severity of the septic episode. [42] [43] Because decreased PDH activity is associated with decreased pyruvate oxidation, the inhibition of the complex during sepsis may provide a biochemical explanation for the shift in skeletal muscle glucose metabolism in sepsis. The inhibition of the PDH complex results from an increased phosphorylation, catalyzed by the PDH kinase. The effect of sepsis to increase PDH kinase activity is mediated by an increase in the acetyl-CoA/CoA concentration ratio. [42] In muscle tissue, the acetyl-CoA/CoA concentration is a sensitive index of the availability of metabolic fuels to be oxidized by the TCA cycle. The ratio is increased when noncarbohydrate fuels are the major oxidative substrate. Because the acetyl-CoA/CoA ratio is increased in skeletal muscle from septic rats, the skeletal muscle may have become more dependent on noncarbohydrate fuels. The net effect of an increased dependence on noncarbohydrate fuels for energy production would be a decreased rate of glucose oxidation and a conservation of glucose carbon. Analysis of respiratory quotients [44] [45] and of indirect calorimetry data [46] in septic patients has demonstrated an increased dependence on fatty acid oxidation, supporting the concept of altered fuel utilization in sepsis. Sepsis also increases the activity of the PDH kinase by mechanisms that are independent of the acetyl-CoA/CoA ratio. Rate constants for PDH kinase activity are increased more than 2-fold in sepsis. [47]

The regulation of the PDH complex makes a significant contribution to glucose homeostasis during sepsis. In experimental septic animal models, activation of the PDH complex with dichloroacetate decreases skeletal muscle, liver, and plasma lactate, pyruvate, and alanine concentrations [48] [49] [50] [51] [52] (Fig. 74-15) (Figure Not Available) . Concomitant with the fall in plasma gluconeogenic precursors, the rates of glucose production and glucose turnover were reduced to nonseptic values. [49]

Hormonal Changes in Sepsis

Typically sepsis is characterized by a decrease in the thyroid hormone, triiodothyronine, whereas the levels of the other stress hormones, namely cortisol, epinephrine, and glucagon, are elevated. Glucagon levels rise to an extraordinarily high level. Although the rise in glucagon is accompanied by a rise in immunoassayable insulin, the insulin-to-glucagon ratio is reversed compared with the postabsorptive state. This reversal of the insulin-to-glucagon ratio may be responsible in part for the accelerated rate of glucose production by the liver in sepsis. Both insulin and

Figure 74-15 (Figure Not Available) Effect of dichloroacetate in skeletal muscle. *(Modified from Vary and Siegal [12])*

glucagon have immediate and delayed effects on hepatic glucose metabolism. The immediate effects of glucagon on hepatic glucose production are seen within seconds and are mediated by alterations in the level of cyclic adenosine monophosphate (cAMP). Somewhat surprisingly, the action of cAMP acts not on the gluconeogenic enzymes directly but rather by restraining phosphofructokinase and pyruvate kinase activity, which are both regulators of glycolysis in liver. Longer-term effects of glucagon on liver metabolism usually appear within hours of glucagon stimulation and involve changes in the synthesis or degradation of enzymes in the metabolic pathway of glucose production. In addition to stimulating the enzymes necessary for gluconeogenesis, glucagon also stimulates the breakdown of intracellular proteins. Although the precise mechanism of action of glucagon responsible for this is unknown, glucagon does enhance the formation of autophagic vacuoles, which engulf and digest intracellular proteins via lysosomes. The stimulation of autophagic vacuole formation occurs secondary to a reduction in the amino acid glutamine levels in the liver, and glucagon reduces hepatic glutamine levels. By increasing the degradation of hepatic proteins, the action of glucagon on protein metabolism ensures that adequate substrate, in the form of amino acids, is available for gluconeogenesis.

Catecholamines also stimulate both glycogenolysis and gluconeogenesis. Plasma catecholamines levels of epinephrine and norepinephrine have been demonstrated to rise progressively with increasing severity of injury. Both epinephrine and norepinephrine rise to levels considered high enough to produce metabolic changes. In this regard, plasma epinephrine concentrations are more important for stimulating hyperglycemia than is the severity of the injury itself. The stimulation of hepatic output of glucose by epinephrine involves the breakdown of glycogen with the release of glucose. It appears that catecholamines activate glycogenolysis more effectively through a cAMP-alpha independent mechanism involving alpha-receptors, rather than through cAMP production by stimulation of beta-receptors. The alpha-adrenergic activation of glycogenolysis is due to an increase in phosphorylase a, secondary to stimulation of a Ca^{2+} -sensitive phosphorylase kinase. However, changes in the hormonal milieu are not solely responsible for enhanced gluconeogenesis in sepsis. Unlike other pathologic conditions, such as starvation and diabetes, in sepsis, gluconeogenesis is not suppressed by infusion of glucose. [31] [53] The failure of glucose to limit hepatic gluconeogenesis has been proposed to occur as a result of enhanced and continual delivery of gluconeogenic precursors from peripheral tissues.

Metabolic Changes in Sepsis

Skeletal Muscle Protein Metabolism

In addition to its role in locomotion, skeletal muscle (by virtue of its mass in relationship to body weight) represents the major reservoir of amino acids. Some of these amino acids, including alanine, serine, and glycine, are important substrates for gluconeogenesis in liver and kidney. Protein wasting is a general feature of trauma, sepsis, and burns. The earliest recognizable disturbance in protein metabolism in the injury process is excessive urea excretion, resulting in a loss of nitrogen from

the body. [12] [30] [31] [54] [55] Much of this nitrogen loss originates from protein in skeletal muscle. This catabolic phase is an intrinsic response to trauma and sepsis, with the loss of muscle protein exceeding that simply resulting from bed rest. In trauma patients, the catabolic phase is short lived, and restoration of normal nitrogen balance and lean body mass follows. In contrast to trauma, the catabolic phase continues unabated in sepsis and accounts for the massive loss of body protein observed in septic patients. [30] The loss of protein arises from an imbalance in protein turnover in skeletal muscle (Fig. 74-16) (Figure Not Available) .

The rate of muscle protein breakdown increases to a greater degree than that of the whole body, with the contribution of muscle proteolysis to whole-body protein degradation nearly doubling. The measurement of nitrogen excretion by the kidney can be used as an estimate of protein breakdown because the nitrogen excreted is derived from amino acids released by proteolysis. The increased proteolysis results in the release of amino acids from structural protein stores, particularly in skeletal muscle. The rate of release of amino acids across the lower extremities increases 2-fold to 5-fold in trauma or septic patients, compared with healthy volunteers after an overnight fast. Although the protein economy of the whole body can be estimated by monitoring the nitrogen balance, the contribution of muscle tissue can be monitored by measuring the rate of 3-methylhistidine production. 3-Methylhistidine is a component of actin-myosin proteins and is released from muscle in proportion to its concentration in muscle protein (both skeletal and smooth). [56] [57]

The increased rate of net catabolism in sepsis can result from a rise in protein degradation, or a decrease in protein synthesis, or both. The relative importance of protein synthesis versus degradation in the induction of the negative nitrogen balance during sepsis is unresolved. The increased net catabolism after trauma uncomplicated by sepsis results from an inhibition of protein synthesis rather than a change in protein degradation. [54] [58] [59] In contrast, sepsis accelerates muscle proteolysis. [56] [60]

The rate of protein synthesis in mixed hindlimb muscles is not altered in nonseptic inflammation, whereas sepsis produces

Figure 74-16 (Figure Not Available) Effect of sepsis on rate of protein synthesis (A), RNA concentration (B), and translational efficiency (C) in gastrocnemius (gastroc), psoas, soleus, and heart. Open bars represent control animals, shaded bars animals with septic abscess (5 days after fecal-agar pellet infected with *Escherichia coli* + *Bacteroides fragilis* implanted intraperitoneally.) *(Modified from Vary and Kimball [61])*

a 50 percent inhibition of protein synthesis. [61] [62] This reduction did not result from a decreased RNA content. Instead, the translational efficiency, expressed as protein synthesis/RNA, was significantly reduced by 50 percent in skeletal muscle of septic animals compared with controls. The effect of sepsis to lower protein synthesis was further examined by use of individual muscles containing different fiber types. [61] Gastrocnemius and psoas muscles were chosen to represent fast-twitch muscles, whereas soleus and heart muscles represented slow-twitch muscles. Sepsis caused a decrease in the muscle weight of all four muscles. Furthermore, both the protein concentration and the protein synthetic rate in fast-twitch muscle were reduced by sepsis, whereas neither of these parameters was affected in slow-twitch or heart muscles. The sepsis-induced inhibition of protein synthesis in fast-twitch muscles resulted from a restraint in peptide-chain initiation because sepsis caused a 1.6-fold increase in free ribosomal subunits. [55] [61]

Amino Acid Metabolism

The net catabolic state in skeletal muscle is characterized by changes in the intracellular amino acid concentrations. Postoperatively, there are rises in the concentrations of branched chain amino acid, phenylalanine, tyrosine, and methionine compared with preoperative values. Although the basic amino acids show small reductions, the overriding feature of injury is a depletion of glutamine concentrations.

The concentration of glutamine in human muscle is extremely high (20 mM) and is equivalent to 715 g of nitrogen in the adult. Glutamine, which represents as much as 65 percent of the total free amino acids in muscle, decreases by up to 50 percent immediately after trauma. [49] [63] [64] The muscle glutamine constitutes a labile pool that could influence changes in whole-body nitrogen balance. Furthermore, this fall in glutamine cannot be rectified by administration of total parental nutrition (TPN) support because most TPN solutions do not contain glutamine. Glutamine is unique among the amino acids because muscle glutamine concentrations are inversely related to rates of protein synthesis. [65] In liver, a decrease in glutamine concentrations is associated with increased rates of protein degradation.

Glutamine arises both from de novo synthesis and from release from protein stores. Glutamine is synthesized from alpha-ketoglutarate, a citric acid cycle intermediate, via glutamate and transamination reactions. Glutamine synthase, a multienzyme complex, catalyzes this reaction, and its concentration is particularly high in skeletal muscle and kidney. After amination of glutamate to glutamine, glutamine is released into the blood stream. It is the most important carrier for removal of nitrogen from peripheral tissues to the splanchnic area.

The role of this labile pool of glutamine in skeletal muscle has not been fully elucidated. Possible functions of increased glutamine release by muscle are to serve as (1) a labile store of fuel for both intestinal cells and lymphocytes and (2) a source of ammonia for utilizing acid-base imbalances. As a fuel, cells use glutamine for two major processes. First, it can be used as an energy source. Cells of the small intestine use glutamine for oxidative energy metabolism. The output of ammonia, protein, alanine, glutamate, and citrulline from gut cells depends on the supply of glutamine to the gut. Second, glutamine is a donor of nitrogen in de novo purine and pyridine biosynthesis. Hence, glutamine is essential for cellular proliferation. Therefore, an intraorgan relationship between glutamine release by skeletal muscle and utilization by splanchnic organs exists.

Decreased skeletal muscle glutamine concentrations postoperatively could result from decreased glutamine synthase activity, decreased release of glutamine from protein stores, increased release of glutamine from muscle through accelerated transport activity, and/or increased breakdown of glutamine via glutaminase. It is unlikely that increased glutaminase activity is responsible for the decrease in muscle glutamine in sepsis because functional hepatectomy

causes a significant accumulation of glutamine in the blood. [51] Furthermore, it argues against decreased glutamine synthase activity. Glutamine synthase activity in skeletal muscle traumatized by 1-carrageenan is markedly increased, not decreased. [66]

Inhibition of glutamine synthase with methionine sulfoximine attenuates glutamine release by 50 percent, suggesting that release of glutamine from protein stores is also an important mechanism in glutamine production. [52] Despite increased production of glutamine by de novo synthesis and increased proteolysis, the skeletal muscle glutamine concentrations are reduced. Therefore, an increase in glutamine transport must also occur.

To determine whether decreased glutamine is critical in posttraumatic skeletal muscle protein catabolism, glutamine has been administered as part of TPN. In this regard, Kapadia et al [67] reduced the postoperative efflux of amino acids from dog hindlimb by infusing an amino acid mixture supplemented with glutamine. However, commercially available amino acid supplements do not contain glutamine, because it is considered a nonessential amino acid and is unstable in aqueous solutions. Consequently, it must be added immediately before use. A more convenient method of supplying glutamine in TPN solutions is to use stable dipeptides, such as alanyl-glutamine and glycyl-glutamine. Both dipeptides are hydrolyzed in the body, releasing glutamine. Furthermore, administration of these dipeptides as part of TPN counteracts the decrease in muscle glutamine and improves nitrogen balance in the immediate postoperative period (Fig. 74-17) (Figure Not Available) .

In addition to provision of dipeptides, plasma and skeletal muscle glutamine concentrations can be augmented by the provision of ornithine-alpha-ketoglutarate or alpha-ketoglutarate. Supplementation of TPN with either of these compounds maintains nitrogen balance and decreases cumulative urea excretion after abdominal surgery. [68] In addition, the rate of protein synthesis is maintained, and the characteristic increase in several essential amino acids in skeletal muscle is also attenuated.

Mediators of Metabolic Changes in Sepsis

The stimulus for enhanced muscle catabolism during sepsis is unknown. A certain amount of catabolic response in trauma patients can be attributed to direct injury to the muscle. However, the enhanced catabolism in the septic patient occurs without any overt signs of direct tissue trauma. The amount of catabolism observed in

septic patients is far in excess of what would be expected simply because these patients are bedridden and inactive.

In burn patients, cortisol is a major determinant of the catabolic response. [69] The catabolic effects of cortisol have been confirmed in healthy volunteers subjected to cortisol infusions to levels seen in burn patients. Cortisol administration in animals reduces the rate of protein synthesis in fast-twitch muscles but not in slow-twitch fibers and heart. The fall in protein synthesis results from a loss of total tissue RNA and to an impairment of translation. [70]

Besides cortisol, epinephrine concentrations are elevated in sepsis. In contrast to cortisol, the catecholamines may not have as a dramatic effect on protein turnover. [71] Isoproterenol does not alter protein synthesis but does reduce protein

Figure 74-17 (Figure Not Available) Day-to-day and cumulative nitrogen balance in patients receiving 1-alanyl-1-glutamine dipeptide-supplemented (black columns) or conventional amino acid total parenteral nutrition (TPN) (open columns). These results clearly illustrate a beneficial effect of increasing glutamine concentration on maintaining nitrogen balance. *** $P < .001$; ** $P < .01$. *(From Stehle et al [199])*

degradation by 20 percent. The decreased proteolysis is sufficient to prevent the release of alanine, threonine, phenylalanine, tyrosine, lysine, arginine, leucine, and valine.

Insulin conserves muscle protein both by stimulating protein synthesis and by inhibiting protein degradation. [72] [73] However, in sepsis, the breakdown of muscle protein, as measured by 3-methylhistidine release, is increased despite increased insulin concentrations. [56] These observations also suggest that additional factors resulting from the septic episode accelerate muscle catabolism or that injury itself renders the muscle resistant to insulin action.

The factors responsible for the septic-induced metabolic alterations are unknown. Although the cause of potential mediators may be multifactorial, a frequent common denom-inator of organ dysfunction and organ failure is alterations in the release of cytokines, particularly by the macrophage. In particular, tumor necrosis factor, interleukin-1, and interleukin-6 have been demonstrated to play a pivotal role in mediating some of the metabolic responses to sepsis. As a mediator of the septic process, tumor necrosis factor triggers neutrophils to degranulate, lymphocytes to divide, and other cytokines (including interleukin-1 and interleukin-6) to be released. The natural induction of tumor necrosis factor during inflammation is protective, but overproduction, as occurs in sepsis, is detrimental to the host. There are essentially two approaches to delineating the role of these cytokines in sepsis. First, several metabolic disturbances present in infectious diseases have been reproduced by administration of recombinant monokines. Second, it is possible to attempt to block the cytokine response to sepsis. There are several potential mechanisms to block cytokine function. Cytokine synthesis or release can be inhibited as well as inhibit the cytokine action by blocking, for example, cytokine receptors.

Branched-Chain Amino Acid Metabolism

In addition to the role of leucine in de novo alanine synthesis, the branched-chain amino acids are of special importance because some reports have suggested that administration of branched-chain amino acids is beneficial in septic patients, improving the survival in surgical patients with multiple organ failure. [74] [75] [76] Administration of branched-chain amino acids as part of the nutritional support in traumatized or septic animals results in decreased weight loss, reduced negative nitrogen balance, decreased protein catabolism, and increased protein synthesis. In surgical patients, nitrogen retention was greater in those patients receiving TPN with 45 percent of the amino acids as branched-chain amino acids than those patients receiving TPN with 24 percent of the amino acids as branched-chain amino acids. One hypothesis for their efficacy is that they provide a fuel for skeletal muscle and liver energy metabolism at a time when glucose oxidative metabolism may be inhibited.

Branched-chain amino acids are among the few amino acids oxidized in muscle tissues. In healthy animals and humans, there appears to be a differential pattern of branched-chain amino acid metabolism in muscle and liver. In muscle tissues, the aminotransferase activity is high, and the oxidative decarboxylation of the corresponding alpha-ketoacid is rate-limiting for leucine oxidation. Only about 50 percent of the leucine undergoing transamination is oxidized. The corresponding alpha-ketoacids are released into the blood. The concentration of all three alpha-ketoacids of branched-chain amino acids in human plasma is approximately 0.1 to 0.04 mM. In contrast to muscle, in hepatic tissue, the activity of the branched chain dehydrogenase is higher than that of the transaminase, and alpha-ketoacids are readily oxidized. The reason for differential pattern may lie in the differential regulation of the branched-chain amino acid dehydrogenase in muscle and liver. The branched-chain alpha-ketoacid dehydrogenase is also regulated by a phosphorylation/dephosphorylation cycle, analogous to the PDH complex. [77] The branched-chain alpha-ketoacid dehydrogenase is inactived in muscle tissue through phosphorylation but is protected in some way from inactivation in liver. This affords a mechanism whereby alpha-ketoacids released by extrahepatic tissues are taken up and used by the liver with the possible formation of glucose and ketone bodies.

The absolute contribution of branched chain amino acids to the overall energy metabolism (adenosine triphosphate generation) is still debatable. In the absence of any other exogenous substrate, leucine oxidation in cardiac muscle could only account for about 5 percent of the total oxygen consumption, even at supraphysiologic levels of leucine. [78] Furthermore, leucine could not provide sufficient energy to maintain normal cardiac function. Hence, it is doubtful that leucine represents a significant energy fuel.

Alternatively, the branched-chain amino acids, and leucine in particular, are unique in that they stimulate protein synthesis. [79] [80] The stimulatory effect of branched chain amino acids on protein synthesis was associated with a facilitated efficiency of translation. However, the response is not as great as that produced by insulin. Therefore, the protein-sparing effects of branched-chain amino acids are more likely a result of modulation of protein metabolism.

Hepatic Protein Metabolism

While it is clear that net proteolysis occurs in skeletal muscle in sepsis, in liver, protein synthesis after trauma or infection is increased (Ch. 17) . The increased rates of protein synthesis coincide with enhanced hepatic uptake (or clearance) of amino acids. Thus, the increased hepatic protein synthesis has been suggested to be caused by or dependent on an increased supply of amino acids from the peripheral tissues. Liver is unique in that it synthesizes proteins for its own use (i.e., structural proteins essential for normal cell function), as well as proteins that are secreted into the blood (i.e., secretory proteins, e.g., albumin). The synthesis of secreted and nonsecreted proteins was stimulated in inflammation and sepsis (Table 74-4) (Table Not Available) . [81] There was a preferential stimulation of proteins destined for secretion, the acute phase proteins.

Distinct and coordinated changes in the concentration of individual plasma proteins, called acute phase proteins, occur within 24 hours after injury. [82] The acute phase proteins maximize immune responsiveness to the foreign body and repair to damaged tissues. These functions include complement activation and opsonization needed for bacterial killing (C-reactive protein), coagulation, surface structure,

TABLE 74-4 -- Effect of Sterile Inflammation and Sepsis on Rates of Protein Synthesis in Perfused Livers

(Not Available)

From Vary and Kimball [81]

and support lattice formations needed for leukocyte entrapment of foreign material (fibrinogen), superoxide scavenging (ceruloplasmin), and inactivation of excess proteases needed to prevent damage to viable cells (alpha $_1$ -antitrypsin) (Fig. 74-18) (Figure Not Available) . A differential pattern in the plasma acute phase protein profile has been demonstrated in trauma and septic patients. The presence of sepsis, whether clinically evident or not, modifies the posttraumatic acute phase protein response, so as to favor the increase of some acute phase proteins, while effecting a decrease in the concentration of other proteins that may not be as critical for survival. In both nonseptic and septic patients during the first 2 to 3 days after injury, there is a rise in C-reactive protein, fibrinogen, alpha $_1$ -antitrypsin, and

ceruloplasmin concentrations. After 3 days, the concentrations of C-reactive protein, fibrinogen, and ceruloplasmin all return toward normal values in nonseptic trauma patients, whereas alpha$_1$ -antitrypsin concentrations remain elevated. In contrast, in trauma patients who show clinical signs of sepsis, C-reactive protein, fibrinogen, alpha$_1$ -antitrypsin, and ceruloplasmin concentrations all remain elevated. There is an early decrease in transferrin, but alpha $_2$ -macroglobulin and albumin

Figure 74-18 (Figure Not Available) Hepatic acute phase (AP) protein response after trauma in 10 septic and 16 nonseptic patients. Mean values for C-reactive protein (CRP) (A), fibrinogen (B), alpha$_1$ -antitrypsin (C), and ceruloplasmin (D). Patients with sepsis developing after trauma are compared to patients with nonseptic post-trauma courses. Note early rise of CRP and alpha $_1$ -antitrypsin in patients who later become clinically septic at 5 to 7 days. The fibrinogen response and ceruloplasmin response tend to be increased in sepsis, but only after the fully developed septic clinical picture is demonstrated. *(From Sganga et al, [82] copyright 1985, American Medical Association)*

concentrations do not change in nonseptic trauma patients. The plasma concentrations of these latter proteins decrease as the septic episode progresses.

Because the liver is responsible for the synthesis of these acute phase proteins, hepatic protein synthesis is accelerated by a wide variety of acute inflammatory insults. Despite the accelerated rate of hepatic protein synthesis during inflammation and sepsis, the mechanisms responsible for this stimulation have not been fully elucidated. The synthesis of specific proteins is probably regulated transcriptionally during inflammation. For example, messenger RNA concentrations for the acute phase proteins are elevated, [83] [84] [85] whereas albumin messenger RNA is decreased. [86] However, increased messenger RNA concentrations may not wholly account for the overall increased rates of protein synthesis. Instead, the translation phase of the protein synthetic pathway is also increased. [81] Interleukin-6 appears to be responsible for the changes in acute phase messenger RNA levels in trauma and sepsis. [87]

Fatty Acid Metabolism

The metabolic course of the traumatized or septic patient shows that fatty acids become the preferred fuel for oxidative metabolism. The same dependence on fatty acid metabolism is observed under conditions of starvation and diabetes, in which the conservation of glucose carbon becomes pathologic (Fig. 74-19) (Figure Not Available) .

The release of fatty acids from adipose tissue in sepsis is variable, with some reports of an increased release and other reports of a decreased release. Despite unaltered arterial fatty acid concentrations, fatty acids are continually released into the blood stream and are delivered to the liver. After removal from plasma, fatty acids may either undergo oxidation for energy and ketone body production, or esterification to triglycerides. Increased hepatic triglyceride levels are a characteristic feature of sepsis, giving rise to the histologic observations of increased lipid droplets in liver tissue at autopsy. The increased triglyceride levels may be partly due to reesterification. This increased reesterification may be responsible in part for the increased secretion of triglycerides as very-low-density lipoproteins. Administration of monokines, either tumor necrosis factor or interleukin-1, increases hepatic lipogenesis in fed rats, but not in fasted rats. [89] [89]

Lipogenesis

Although ketogenesis may be inhibited during sepsis, lipogenesis appears to be accelerated. In septic patients receiving only glucose in excess of 800 cal/m ^{2} body surface area, the respiratory quotient (RQ) rises above 1.0, a value

Figure 74-19 (Figure Not Available) Septic alteration of metabolic regulation of hepatic fatty acid oxidation, ketogenesis, fatty acid synthesis, and carbohydrate metabolism. Malonyl-CoA (...) derived from citrate and cytosolic acetyl-CoA inhibits carnitine:acyl CoA transferase I. (Carnitine:acyl CoA transferases [I and II] are bound to inner mitochondrial membrane in vivo, but for clarity, the reactions are shown away from membrane.) The effects of hormones (insulin or glucagon) and of small and large septic abscesses to increase (+), or inhibit (-) particular synthetic pathways or oxidation of specific substrates are shown. FFA, long-chain fatty acids; FA-CoA, long-chain fatty acyl-CoA; FACarn, long-chain fatty acyl carnitine; CoA, coenzyme A; OAA, oxaloacetate; PYR, pyruvate; LACT, lactate; TCA, tricarboxylic cycle; TG, triglycerides; PL, phospholipids; CAT-1, carnitine:acyl-CoA transferase I; II, carnitine:acyl transferase II; PDH, pyruvate dehydrogenase complex; MITO, mitochondria; HMG-CoA, beta-hydroxy-beta-methyl glutaryl-CoA; cholesterol esters, CE. *(Modified from Vary et al [200])*

that is indicative of net lipogenesis. [44] [45] The capacity to synthesize lipids is increased, suggesting an increased flow of acetyl groups toward fatty acid synthesis and away from ketone body formation. These observations support the concept of a reciprocal relationship between lipogenesis and ketogenesis, thus preventing both fatty acids and ketone bodies from being synthesized simultaneously, which would result in an energy-wasting futile cycle.

The potential site of hepatic fatty acid oxidation regulation, and therefore ketone body formation, is the carnitine:acyl transferase-1. This enzyme is competitively inhibited by malonyl-CoA, resulting in decreased formation of long-chain fatty acyl carnitine. Malonyl-CoA is the first committed intermediate in the conversion of glucose carbon into fat, and its concentration is known to fluctuate in parallel with the rate of fatty acid synthesis. The physiologic role of malonyl-CoA is to provide unidirectional flow of glucose carbon to fatty acid synthesis by preventing the futile oxidation of newly synthesized fatty acids via the carnitine:acyl transferase system to beta oxidation. The malonyl-CoA concentration is elevated 2-fold in livers from septic animals. [90] The rise in malonyl-CoA concentration is in the range reported for maximal inhibition of the carnitine:acyl transferase-1. Therefore, the increased malonyl-CoA concentrations would be expected to inhibit the carnitine:acyl transferase-1 during sepsis.

Progressive sepsis increases plasma triglycerides as the septic process worsens. Besides an increase in hepatic triglyceride synthesis, an impairment in the peripheral triglyceride disposal mechanisms may exist. Lipoprotein lipase activity, the enzyme responsible for clearance of plasma triglycerides, is reduced in both adipose tissue and muscle from septic animals. Concomitant with the lowered lipoprotein lipase activity, plasma triglyceride concentrations are increased. It appears that a monokine or several monkines acting synergistically act to downregulate lipoprotein lipase activity.

Ketone Bodies

The normal response of the liver to increased delivery of fatty acids is the synthesis of ketone bodies (3- $_L$-hydroxybutyrate and acetoacetate). In addition, reversal of the insulin-to-glucagon ratio enhances the ketogenic capacity of the liver. In sepsis, there is a rise in the glucagon-to-insulin ratio, but the plasma ketone body concentrations are lower than expected given the hormonal environment, and septic animals and patients undergoing a total fast do not demonstrate ketonemia. The lack of elevated plasma ketones does not indicate a lack of fatty acid oxidation, because these patients have an RQ of 0.75, which is indicative of fat oxidation. Thus, sepsis appears to induce changes in hepatic fatty acid metabolism that prevent or reverse maximal rates of ketogenesis.

The failure of hepatic tissue to enhance ketogenesis may be important to the clinical outcome of the septic episode, because survival is dependent on normal liver function. A decrease in the circulating ketone body concentrations would be expected to increase the dependence of peripheral tissues on alternative substrates for energy production when cellular metabolism is accelerated by sepsis. The failure of similar increases in plasma ketone bodies in nondiabetic septic patients may be an additional factor in the markedly increased rates of proteolysis in septic patients. Of considerable interest is the observation that enhanced muscle catabolism in response to injury is not observed if the blood concentration of ketone bodies is increased. However, it would be impractical to simply supply ketone bodies as nutritional support. To replace 5 percent glucose, one would require 125 g ketones/d. That amount of ketone bodies presents few problems, because ketone bodies are readily soluble in saline. The problem is that accompanying the ketone body infusion would be approximately 1,200 mEq of a positive ion (Na^+). Such a salt load on the kidneys is certainly not advised in healthy persons and is probably devastating in the septic patient, who may have complicating renal dysfunction.

Insulin Resistance in Sepsis

The effects of sepsis on glucose production in liver are well characterized, but very little information is available concerning the effect of sepsis on peripheral glucose utilization. Abnormal glucose tolerance tests are commonly observed following traumatic injury, burn, shock, or sepsis despite normal or accentuated insulin secretion. Despite the responsiveness of the pancreatic beta cells to secrete insulin in response to a glucose load, glucose intolerance and hyperglycemia persist, suggesting that certain target organs in the injured or septic patient are relatively insensitive to the effects of circulating insulin. Because glucose consumption by central and peripheral nervous tissue, renal medulla, bone marrow, erythrocytes, and leukocytes is not insulinsensitive, the primary sites of insulin resistance are in peripheral tissues, particularly skeletal muscle and adipose tissue, where insulin stimulates glucose uptake. Because only a small percentage (1%) of the glucose load is taken

up by adipose tissue, the major effect of insulin appears to be in muscle tissue.

In the case of sepsis, insulin resistance is manifested by either an abnormal glucose tolerance test or simply an elevated plasma glucose concentration for a given insulin concentration. This insulin resistance could occur by alterations at one of three levels: (1) before the interaction of insulin with the receptor, (2) at the receptor level, or (3) at steps distal to the insulin-receptor interaction, namely, cellular metabolism. Insulin concentration is the same or increased in sepsis, and no anti-insulin antibodies have been detected. At the receptor level, the sensitivity of the receptor to circulating insulin appears to be normal. [91] Hence, it appears that insulin resistance in sepsis may be related to an intracellular defect in glucose metabolism.

MEASUREMENTS OF ENERGY REQUIREMENTS FOR PARENTERAL NUTRITION

Kinney [92] pointed out that surgical weight loss can be rapid and can result in massive depletion of up to 20 percent of normal body weight within 3 weeks of multiple injuries, despite the resumption of some oral intake within the first

week. Surgeons have tried to explain this large tissue loss and increased nitrogen excretion on the following basis: a major injury produces a very large increase in the rate of resting energy expenditure (REE) [a] that exceeds the energy availability from fat mobilization; muscle protein is progressively broken down, the resulting amino acids deaminated, and the carbon chains oxidized for energy. The preceding sections have outlined the theoretical basis of catabolic response to sepsis as attempts to compensate for decreased peripheral oxidation of glucose and the need for increased hepatic protein synthesis. Partial starvation in the perioperative period aggravates the catabolic loss of lean body mass. Therefore, it is imperative to consider a nutritional prescription to the septic or stressed patient.

Nutritional Assessment

Four factors have been used to assess the need for nutritional support: [93] (1) history of unexplained weight loss of 10 percent of body weight, (2) serum albumin concentration of less than 0.34 g/dL, (3) anergy to a battery of four or five standard skin-test antigens, and (4) abnormally low total lymphocyte count. A patient who manifests all four indexes is severely malnourished. However, the efficacy of preoperative parenteral nutrition in reducing operative morbidity and mortality is still open to question. Serum transferrin and prealbumin are better markers than albumin for rapid changes in nutritional status because they have shorter half-lives than albumin. The excretion of 3-methylhistidine (primarily from muscle actin) also has been used as a marker for muscle breakdown. [94] However, the MM band of creatine phosphokinase isoenzyme is also elevated after skeletal muscle trauma.

Estimating Energy Expenditure

For severely ill patients, indirect calorimetry seems the most feasible method. The measurement of four independent quantities is required for this procedure: [95] (1) daily intake of fat, carbohydrate, and protein; (2) daily nitrogen excretion; (3) daily oxygen consumption (DV $_{O_2}$); (4) daily CO_2 production (DV $_{CO_2}$). For bedridden patients who are completely at rest during the entire 24 hours, three to five measurements of REE (40-60 minutes' duration) may be extrapolated to obtain a reasonably good estimate of total energy expenditure (TEE) for the 24-hour period. Van Lanschot et al [96] investigated the Harris-Benedict equation versus the accurate measurement of TEE by continuous indirect calorimetry. Despite the overestimation of TEE when caloric needs were calculated by formula, they remarked that the difficulties associated with continuous indirect calorimetry left "unresolved, whether or not indirect calorimetry is actually to be preferred in daily clinical practice." [96]

The usual approach is to measure DV $_{O_2}$, DV $_{CO_2}$, and nitrogen excretion. Energy requirements must be adjusted for variations resulting from difference in body size. The basal metabolic rate refers to energy expenditure at a specific time in the morning, soon after awakening and approximately 14 hours after the last meal, measured at thermal neutrality. This discussion refers to basal energy expenditure (BEE) instead of basal metabolic rate.

Harris-Benedict Equation

Heat production per square meter of body surface area per unit time decreases steadily as humans approach puberty; then energy expenditure more gradually decreases as age increases. This decrease is approximately 1 to 2 percent per decade in adults (20-75 years of age). [97]

The Harris-Benedict equation is an empirically derived equation with variables that reflect the relative contributions to overall heat production per square meter body surface area of activity, age, sex, and body size:

For males:

For females:

BEE equals basal energy expenditure in kilocalories per day.

To apply this equation to nutritional requirements, the BEE is multiplied by activity and injury factors to arrive at a daily nutrition requirement in kilocalories per day, or TEE. Activity factors vary from 1 for a patient on bed rest to 1.3 for an ambulatory patient. Injury factors vary from 1 to 1.2 for minor surgery to 1.8 for major sepsis (Table 74-5) (Table Not Available) . For each degree above 37.2°C, the daily nutrition requirement is multiplied by 1.07. An important reason for excessive energy administration is using TEE based on weight and on estimates

TABLE 74-5 -- Energy Expenditures Measured in Different Clinical Conditions

(Not Available)

From Popp and Brennan [192]

[a] REE is defined as the mean daily value obtained from measurements of gas exchange at rest. It includes the specific dynamic action of foods and is about 10 percent greater than the basal metabolic rate.

of BEEs rather than on measured metabolic expenditures. [96] [98] Lean tissue repletion is maximal at 4 to 6 g/d of nitrogen in the malnourished, nonstressed patient receiving energy at 1.75 × BEE (estimated BEE) and protein at 1.5 g/kg/d. [99] Any positive energy balance beyond this is used in fat synthesis. In the past, nutritional support was used with very high multiples of BEE to attempt to force positive nitrogen balance. Current practice is to prescribe energy (glucose, lipids) to meet measured energy requirements and separately prescribe proteins (amino acids) to meet measured nitrogen excretion. [100]

Calculation of Energy Metabolism from Gaseous Exchange

Energy expenditure is more accurately assessed by measuring DV O_2 and DV CO_2 (Ch. 15) . When urinary nitrogen (UN) is measured, the formula described by Weir [101] can be used to calculate the amount of nonprotein energy expended in kilocalories: [b]

Energy expenditure/unit of time

where DV O_2 and DV CO_2 are in L/24 h STPD (standard temperature and pressure, dry).

The technique of indirect calorimetry has been used to measure metabolic rate. Furthermore, it has long been recognized that these measurements also can give information on the type and the rate of fuel oxidation within the body. This latter information is based on a number of assumptions, which may not hold in the presence of two metabolic processes: gluconeogenesis and lipogenesis. [102]

Resting energy expenditure includes BEE and the thermal effect resulting from food intake as well as nonshivering thermogenesis in response to environmental temperature alterations. Infusing amino acids increases energy expenditure by 10 percent over 24 hours in normal subjects and in postoperative patients, whereas glucose and lipid infusions have little effect. [103] [104] Increased energy expenditure, however, is noted when carbohydrates are given in excess of energy requirements. REE can be initially estimated from the following formula [105] after indirect calorimetry measurements of oxygen consumption and carbon dioxide production:

Resting energy expenditure can then be adjusted for protein metabolism by measuring the UN in grams per day.

The adjusted metabolic expenditure equals REE - 2.17 × UN. A 2-hour UN measurement can be substituted for a 24-hour collection. [106] UN excretion is calculated from

TABLE 74-6 -- Assessment of Daily Nitrogen Losses and Requirements

(Not Available)

From Lee [193]

measured urinary urea measurements as outlined in Table 74-6 (Table Not Available) .

The REEs of a hospitalized patient are usually a balance between the decrease that normally occurs in association with any weight loss and nutritional depletion from partial starvation and any increase that results from disease or injury. An average increase of 13 percent in energy expenditure is associated with each degree centigrade of fever.

Respiratory Quotient

The RQ is the ratio of DV CO_2 divided by DV O_2 (DV CO_2 /DV O_2). Normally, the RQ ranges between 0.7 (lipid oxidation) and 1.0 (glucose oxidation) and varies with substrate oxidation. The RQ moves toward 1 with dietary carbohydrate loading and decreases to 0.7 with prolonged fasting, demonstrating almost complete fat oxidation during the starved state. With lipogenesis from excess caloric intake, RQ becomes greater than 1.0. The RQ measurement also reflects gas exchange from protein metabolism. UN excretion is therefore determined, and the contribution of protein combustion to gas exchange is calculated. This correction yields the "nonprotein RQ."

Thus, measurement of DV O_2 , DV CO_2 , and UN excretion permits determination of individual fuel sources oxidized as well as calculation of the total quantity of heat produced. [107]

The RQ for metabolism of carbohydrates equals 1:

In oxidation of fat, the RQ is less than 1:

[b] Food energy values are usually given in kilocalories. One kilocalorie is the amount of heat necessary to raise 1 kg of water from 15° to 16°C. Energy conversion factors generally used are 4.1 kcal/g of food protein or carbohydrate and 9.3 kcal/g of food fat. The energy expenditure to nitrogen loss for a 70-kg man receiving no nitrogen intake would be 1,800 kcal/3.7 g/d of nitrogen. The minimal nitrogen intake, however, has been set at 5.2 g/d in the form of high-quality protein.

Cells can oxidize multiple substrates concurrently and can convert glucose into both fat and glycogen. Therefore, an RQ derived from gas analysis cannot provide precise information concerning the metabolic pool. However, the RQ estimates the relative contributions of glucose, lipids, and proteins as well as lipogenesis from overfeeding.

Methods of Measuring Respiratory Quotient

The most common methods for measurement of the respiratory quotient use a closed-circuit or open-circuit technique. The closed-circuit method uses a spirometer, filled with oxygen with a CO_2 absorber placed in the circuit. The rate of disappearance of oxygen from the spirometer equals the oxygen consumption, and mean expired CO_2 concentration times the minute volume equals the CO_2 production. The open-circuit method uses a set of one-way valves to direct expired air into a collecting container (usually a Douglas bag or a Tissot spirometer). At the end of a carefully timed collecting period, both the volume and the composition of the

expired air are measured, and the rate of DV $_{O_2}$ and DV $_{CO_2}$ are determined by the difference between the concentrations of inspired gas and the expired gas collected. A correction (Haldane) is used to account for the difference between inspired and expired volumes. Because the Haldane correction depends on a conservation of nitrogen between inspired and expired gas, it becomes inaccurate at low inspired nitrogen (high fraction of inspired oxygen [F $_{IO_2}$]) levels.

Kinney et al [108] designed a noninvasive system for nonintubated patients that consisted of a clear plastic head canopy (with no attachment to the face or airway) ventilated with air that is continuously analyzed for measurement of DV $_{O_2}$ and DV $_{CO_2}$. REE of hospitalized patients can be determined by obtaining average gas-exchange measurements from five 30- to 45-minute canopy runs during each waking day (Fig. 74-20) (Figure Not Available) .

Commercial instruments with attached CO_2 and oxygen analyzers that have been developed to measure DV $_{O_2}$ and DV $_{CO_2}$ in patients in the operating room and intensive care unit are now available. Several problems are associated with validation of these instruments and in performing gas exchange measurements during mechanical ventilation. [109] [110] The closed-circuit devices function well on mechanically ventilated patients because they are not effected by F $_{IO_2}$. The open circuit devices can be utilized for patients either breathing spontaneously through their native airways or breathing through an endotracheal tube and ventilator but are limited to an F $_{IO_2}$ value of 0.6 or less.

NUTRITIONAL PRESCRIPTION

Prescribing intravenous nutritional support for surgical patients during the perioperative period requires a knowledge of the patient's requirements for calories and protein nitrogen. To accurately predict a patient's protein-calorie requirements, one must know the patient's current state of nutritional health and current predicted calorie requirements. The previous sections discussed the assessment of nutritional defects measuring caloric use with indirect calorimetry

Figure 74-20 (Figure Not Available) Alterations in gas exchange secondary to total parenteral nutrition (TPN) are shown (mean ± SD). Glucose was the primary source of nonprotein calories. Clearly, two different responses are seen. Depleted patients show a respiratory quotient (RQ) above 1.0 with a small increase in V_{O_2}, while hypermetabolic patients have an RQ less than 1.0 with a marked increase in V_{O_2}. Both groups show a large increase in V_{CO_2}. *(From Askanazi et al [126])*

and the calculation of REE and measurement of protein requirements by nitrogen balance studies.

Parenteral Versus Enteral Nutrition

Nutritional requirements for perioperative surgical patients can be administered either enterally through the gut or parenterally via a central or peripheral vein. [111] [112] [113] All three routes have their indications and advocates. Enteral feeding either through a fine-bore nasogastric tube or bypassing the stomach with a feeding enterostomy tube in the distal gastrointestinal tract has the advantage of the use of normal routes for nutrient absorption as well as a decreased risk of infection. Although enterostomy tubes provide a convenient simple route for nutrition, they must be carefully monitored for function. If the stoma breaks down or the tube becomes misplaced, the patient is at risk for peritonitis from leakage of gut contents or tube feedings into the peritoneal space.

It has been demonstrated that enteral feeding decreases the atrophy of the luminal brush border of the gut and may decrease bacterial translocation from the intestinal lumen to the blood stream. [114] However, enteral feeding intolerance was associated with an increased mortality in a study by Chang and colleagues. [115] This complication was aggravated by delayed recognition of enteral feeding intolerance and a period of starvation before the commencement of intravenous nutrition. Enteral feeding intolerance is manifested by diarrhea, bowel distention from unabsorbed feedings, high residual volume aspirated from the catheter, and failure to reverse signs of malnutrition. It is not immediately apparent whether the route of nutrition caused the mortality

noted by Chang et al [115] or merely heralded a more profound systemic disease. Because the efficacy of perioperative nutritional support is generally effective only to reverse specific nutritional deficits, [116] [117] [118] [119] it is unlikely that any route of nutrition would reverse an otherwise inexorable, downhill clinical course.

Perioperative starvation impairs wound healing [120] [121] and causes excessive protein catabolism, but routine TPN to all surgical patients is not cost-effective because well-nourished surgical patients with brief perioperative fasting periods do not demonstrate a therapeutic effect of TPN. [121] [122] [123] [124] Cancer patients frequently represent a group of patients who benefit from TPN [125] [126] to replace specific nutritional deficits. The use of enteral feedings placed through a tube distal to the pylorus allows an increasing use of nutrition support for surgical patients, including cancer patients. Enteral feeding is associated with fewer complications and less expense than TPN, but it must be monitored carefully to avoid the complications noted by Chang et al. [115] Appropriately monitored enteral feedings can be successfully administered into the small bowel of most postsurgical and trauma patients, including those who have undergone abdominal surgery. Parenteral nutrition via a peripheral vein or a central vein provides nutritional support in patients with a nonfunctioning gastrointestinal tract.

Substrate Requirements for Total Parenteral Nutrition

A caloric source and an amino acid source are required for adequate nutrition (Fig. 74-21) (Figure Not Available) . When glucose is given as the sole caloric source, 1 dL/wk of 10 percent fat solution prevents essential fatty acid deficiency. However, a balanced daily energy supply of fat and glucose is commonly used for TPN. This approach may decrease the problems in hepatic and pulmonary function that occur with high glucose loads. [127] [128]

If the total energy requirements are not met with a total dextrose intake of 5 to 6 mg/kg/min (or about 2.5 L of 25% dextrose for a 70-kg adult), consideration should be given to providing extra calories as fat emulsions--not only to prevent fatty infiltration of the liver and glucose intolerance but also to avoid excessive production of CO_2. An excess of CO_2 resulting from administration of too much parenteral glucose can compromise weaning of hypermetabolic patients from mechanical ventilation or can precipitate respiratory failure in patients with severe obstructive pulmonary diseases. Infusion of 1 L of solution containing 4 to 5 percent amino acids and only 15 percent dextrose (1,400 mOsm/L), combined with 5 dL of a 20 percent fat emulsion may be indicated in these situations. [129] This combination provides the same amount of amino acids and calories as regular central formulations; however, 50 percent of the calories are derived from dextrose and 50 percent from fat emulsions.

The provision of 5 dL of a 20 percent fat emulsion has been shown to have no adverse effects on hemodynamic status or pulmonary diffusing capacity in critically ill patients. [130] [131] Medium-chain triglycerides may be substituted for long-chain triglycerides, with improved patient tolerance of fat infusions. [132] [133]

All solutions should contain the daily requirements of essential electrolytes. Zinc, copper, selenium, and chromium are increasingly being used to prevent abnormalities associated with trace-metal deficiency. Daily vitamin supplementation is required. [134] Figure 74-21 (Figure Not Available) illustrates a worksheet/ order sheet for parenteral nutritional support prescription writing.

Administration

Peripheral Administration

When the need for parenteral supplementation is limited (approximately 1,500 kcal/d), TPN may be delivered through a peripheral vein. A solution containing 3 to 4 percent amino acids (e.g., Travasol, FreAmine, or Aminosyn) mixed with 5 to 10 percent dextrose and given simultaneously with fat emulsion (Intralipid or Liposyn) delivers 1,100 to 1,800 kcal and 0.8 to 1 g/kg/d of amino acids. Fat emulsions supply essential fatty acids and a concentrated source of energy (1.1 kcal/mL). With an osmolarity of 280 mOsm, they can be infused through a peripheral vein.

Central Administration

When 2,000 kcal or more is required daily, a central catheter should be inserted (subclavian vein). A 15 percent dextrose (1,400 mOsm/L) solution containing 4 to 5 percent amino acids can be combined with 5 dL of fat emulsion. This provides balanced parenteral nutrition by administration of 50 percent of the nonprotein calories

as fat and 50 percent as dextrose.

Central venous catheter complications (Table 74-7) (Table Not Available) limit the usefulness of intravenous nutrition administered by this method. Catheter-related sepsis is a common complication of any central venous catheter left in place longer than 72 hours. Therefore, a device (Vitacuff) that consists of silver ion-impregnated collagen to seal the subcutaneous and intravascular catheter tract from the environment appears very promising for central vein-administered nutritional support. [135] [136] This device has significantly reduced the number of catheter-related infections for catheter durations of up to 10 days. Multilumen catheters for central venous insertion are also attractive for parenteral nutrition because one lumen may be dedicated to the nutritional media, which is highly bacteriophilic, and other lumens may be used for pressure monitoring or drug administration. The combination of the subcutaneous, sealed cuff with a multilumen catheter is attractive because there is concern that multilumen catheters may lead to an increased incidence of catheter-related sepsis. [137] Other complications of TPN are outlined in Table 74-8 (Table Not Available) .

Complications

Depression of Serum Folate Concentration

Tennant et al [138] reported acute depression of serum folate concentrations in patients fed preoperatively with parenteral nutrition solutions. Their studies seem to indicate

Figure 74-21 (Figure Not Available) Adult total parenteral nutrition order form. *(Courtesy of Pennsylvania State University, Hershey, Pa.)*

that the amino acid component of the solutions may be at least partially responsible for the fall in serum folate level, as suggested by Krebs and coworkers. [139] Tennant and colleagues [140] cautioned that further investigation may be indicated in patients receiving postoperative parenteral nutrition after anesthesia exposure to nitrous oxide, which may alter serum methionine and folate concentrations. [141] [142]

The most common errors are underestimating phosphate needs (40-100 mEq/d) and overestimating calcium requirements (3-8 mEq/d). The most common abnormality in patients receiving TPN is a mild-to-moderate elevation in results of liver function tests. This may be a result of fatty infiltration of the liver that occurs with excess glucose administration. In a patient who begins with normal indexes of liver function, 2-fold elevations in serum glutamic oxaloacetate (SGOT) and serum glutamic pyruvate transaminase (SGPT) levels and a progressive mild rise in alkaline phosphatase level are not uncommon. If an increase in bilirubin

TABLE 74-7 -- Potential Catheter Complications of Total Parenteral Nutrition

(Not Available)

From Dudrick [93]

occurs and SGOT and SGPT levels continue to rise, a cause other than the TPN infusion should be sought. Unfortunately, maintenance or restoration of lean body mass in hypercatabolic patients can be difficult because of the inevitable increased breakdown of muscle protein supplying amino acids for gluconeogenesis. An attempt to induce anabolism by infusing large amounts of carbohydrate increases the metabolic rate, the conversion of carbohydrate into fat, and the rate of DV $_{CO_2}$; it does not promote increased protein synthesis, and thus, it results in self-defeating hypermetabolism. [143] Hypercatabolic patients must be given adequate amino acids to achieve nitrogen equilibrium. Patients with persistent negative nitrogen balance should have the ratio of nitrogen to calories increased without increasing nonprotein calories beyond their use capabilities. [119] [143] [144]

Respiratory Complications of Total Parenteral Nutrition and Relative Starvation

In 1976, Doekel et al [145] reported that normal volunteers fed 400 kcal/d of carbohydrate orally for 10 days experienced a decrease in ventilatory response to hypoxia, a measure of respiratory drive (Fig. 74-10) (Figure Not Available) . Weissman et al [146] observed that 7 days of infusion of 400 kcal/d of 5 percent dextrose resulted in a reduced mean inspiratory flow, another measure of neuromuscular drive.

Arora and Rochester [147] found that chronically ill, nutritionally depleted patients had significant reductions in respiratory muscle strength, as measured by maximal inspiratory and expiratory pressures; endurance, as measured by maximal voluntary ventilation; and vital capacity. High-protein nutritional support improves respiratory muscle strength and ventilatory drive. [118] [148]

Excessive glucose administration leads to an increase in minute ventilation that is proportional to an increase in DV $_{CO_2}$ caused by oxidation of carbohydrate (RQ = 1) or lipogenesis (RQ = 8). [149] Thus, infusion of glucose as a sole energy source can lead to increased respiratory work because ventilation increases in response to added CO_2 .

In summary, Weismann and Askanazi [149] recommended that nonprotein calories be administered as 50 percent carbohydrate and 50 percent lipid. They recommended this balanced supply of energy sources both for patients with poor respiratory function and for those who are septic and hypermetabolic. This approach leads to less DV $_{CO_2}$ than occurs with methods supplying 100 percent of the nonprotein calories as glucose. Furthermore, the combined substrate technique causes less increase in energy expenditure and norepinephrine secretion in the septic and hypermetabolic patient [150] and prevents essential fatty acid deficiency. [116]

Hypoglycemia

The most common cause of hypoglycemia is a slowing or a cessation of infusion. The increased secretion of insulin that accompanies TPN when suddenly unopposed by exogenous glucose results in hypoglycemia. For this reason, TPN solutions should never be abruptly discontinued in the operating room without being replaced with a concentrated glucose solution, such as 10 percent dextrose solution.

Complications of Intravenous Fat Emulsions

Extended TPN using lipid emulsions may injure the bilirubin-transfer mechanism in the liver and lead to progressive

TABLE 74-8 -- Potential Metabolic Complications of Total Parenteral Nutrition

(Not Available)

From Dudrick [93]

cholestasis. This is usually a benign, readily reversible state, but continued TPN without a change in the constituents can cause liver injury with hepatocyte necrosis and periportal fibrous changes. In a study by Allardyce, [151] patients with a high lipid intake had significant elevations of the serum bilirubin and alkaline phosphate levels at the completion of parenteral nutrition. Cholestatic jaundice is associated with administration of lipid emulsion in a dose of 3 g/kg/d in patients fed intravenously for more than 3 weeks. The condition improves, with a return of liver function to normal, when the dose of lipid emulsion is reduced or when intravenous feeding is discontinued. Lipid emulsion might be limited to 1 g/kg/d, and liver function may be evaluated twice weekly. It appears that the dose of lipid emulsion should be reduced if a progressive rise in serum alkaline phosphatase level occurs.

Disorders of Water Metabolism

Bistrian et al [99] pointed out that the tendency to retain water is characteristic of many of the disease states for which TPN is employed, including postoperative states, shock resuscitation, congestive heart failure, oliguric renal failure,

hepatic insufficiency, and severe malnutrition. The antinatriuresis that results from the hyperinsulinemia seen with glucose-based TPN can lead to serious water overload in a brief period. This can be minimized or avoided by matching total fluid losses plus 5 dL, by limiting sodium intakes to less than 40 mEq of sodium beyond loss replacement, and by limiting insulin response by the use of a mixed-fuel system.

EFFECTS OF NUTRITION ON DRUG METABOLISM

Pantuck et al [152] showed that TPN can alter rates of hepatic drug oxidation in divergent ways, depending on the type of nutrition furnished. After six healthy young male volunteers had their total nutrition provided parenterally for 4 days with 5 percent dextrose followed by an isocaloric amount of amino acids (Aminosyn, 3.5%) for 1 day, disposition of the model drug antipyrine changed significantly. Compared with antipyrine clearance values obtained on their home diet, the 4 days on dextrose significantly decreased antipyrine clearance. By contrast, after only 1 day on parenteral amino acids, antipyrine clearance increased markedly. Thus, dextrose retarded, whereas amino acids enhanced, rates of antipyrine elimination. This and other studies led Vesell and Biebuyck [153] to suggest that anesthesiologists should consider that the doses of many drugs given to surgical patients may need to be changed on commencement of TPN. Drugs eliminated primarily by hepatic metabolism may especially require dosage adjustment.

These effects also occur from enteral feeding. In general, high-protein diets significantly enhance drug clearance (Fig. 74-22) (Figure Not Available) . [154] [155] [156] [157] [158] Patients on a low-protein diet had delayed drug clearance, regardless of the lipid/carbohydrate ratio of their diets. These changes occurred without changes in volume of distribution or plasma protein binding. The effect of protein is also seen in vegetarians; high-protein vegetarian diets significantly enhance drug clearance. [159] This effect is so pronounced in experimental studies that variations in dietary protein intake probably explain the otherwise

Figure 74-22 (Figure Not Available) A comparison of theophylline half-life results during test diet periods. Bars represent means ± SD. *(From Feldman et al [201])*

inscrutable interpatient variation in response to intravenously administered anesthetics. Furthermore, starvation during a period of critical illness retards clearance of many intravenous drugs. Enteral feedings directly inhibit the absorption of enterally administered phenytoin; thus, tube feedings must be discontinued for an hour before and an hour after phenytoin dosing. The total volume of tube feedings must compensate for the period of discontinuation.

PERIOPERATIVE NUTRITIONAL SUPPORT IN SPECIAL SITUATIONS

Modifications of the standard adult formula are required for the treatment of patients with congestive cardiac failure, hepatic failure, and renal failure. Modifications of the solution are often necessary, depending on the patient's metabolic response. It is essential for the anesthesiologist to recognize that no single intravenous nutrient solution can be ideal for all situations. Nutritional support services are becoming a feature of modern critical care units. These consulting services, which may employ critical care anesthesiologists among their medical staff, must consider the following special situations for nutritional support.

The Neurosurgical Patient

Three cautions should be remembered when TPN is being considered for the brain-injured patient (Ch. 52) :

1. Severe head injury is associated with hyperglycemia, and administration of large amounts of glucose could worsen this abnormality. [16] [160]
2. Free water administration is usually restricted after brain trauma to prevent severe hyponatremia.
3. The greatest hazard of TPN is sepsis. This risk should not be underestimated in critically ill patients bearing numerous catheters and multiple possible foci for infection.

Animal experiments employing controlled degrees of cerebral ischemia have demonstrated that elevated blood-brain glucose concentrations greatly enhance the extent and the degree of subsequent brain damage. [161] Pulsinelli et al [162] have examined the effect of hyperglycemia versus normoglycemia in nondiabetic patients with stroke. These workers reported that stroke-related deficits among nondiabetic patients appeared to be more severe when the admission blood glucose level was above 120 mg/dL than when it was below this level. The precise mechanism of the adverse effects of hyperglycemia in ischemic brain is unknown. Myers [163] suggested that increased cerebral lactic acidosis, which results from the anerobic glycolysis of increased brain glucose stores, is directly or indirectly responsible for the adverse effect. Because the blood's oxygen reserve is substantially less than its glucose reserve (especially in hyperglycemia), areas of brain experiencing severe but incomplete reduction of blood flow would be particularly affected by such a mechanism. Thus, hypoxic areas of brain receiving continued delivery of glycolytic substrate would be subject to higher levels of accumulation of lactic acid. [164] Pulsinelli et al [162] concluded that hyperglycemia can accentuate ischemic brain damage in humans and suggested that blood

glucose levels be maintained in the near-normal range in diabetic patients with a high risk of stroke. Similarly, they suggest that glucose-containing infusions should be avoided in the immediate treatment of patients with acute or progressive stroke, in patients undergoing surgery that could affect cerebral blood flow (e.g., carotid endarterectomy, extracranial-intracranial bypass, cardiac bypass), or in those who have had a cardiac arrest.

Renal Failure

The principle that endogenous urea can be converted to nonessential amino acids if an adequate amount of carbohydrate is provided underlies one nutritional approach to patients with acute renal failure (Chs. 34 53 and 55) . The Giordano [165] -Giovanetti [166] diet contains a high carbohydrate load with limited protein, abundant in its percentage of essential amino acids. The use of commercially available essential amino acids (NephrAmine) with hypertonic glucose has served to facilitate control of electrolyte balance, to lower blood urea nitrogen levels, to decrease or eliminate the need for dialysis, and to speed recovery of patients with acute tubular necrosis.

Patients with acute tubular necrosis are treated by parenteral nutrition with essential amino acids and hypertonic dextrose, now commercially available as NephrAmine (McGraw Laboratories: 12.7 g of eight L-essential amino acids and 350 g of dextrose, insulin, and vitamins, in a total of 750 mL). The total glucose concentration thus reaches 47 percent, and the osmolarity of the solution is 2,100 mOsm/L. The high concentrations of glucose in a small volume enable even an oliguric patient to receive a substantial amount of calories.

Because urinary glucose is notoriously unreliable in renal failure, the blood glucose level should be checked at least twice daily when therapy is started. Insulin is added to the solution as necessary, according to blood glucose levels. Hypokalemia, hypomagnesemia, and hypophosphatemia occur regularly, sometimes as soon as 8 hours after the initiation of renal failure fluid infusion. Reduced amounts of standard amino acid formula can be utilized just as successfully in most renal failure patients.

Feinstein [167] demonstrated a novel approach to providing amino acids to patients with hemodialysis-dependent renal failure by adding the amino acids to the dialysate. There was a substantial, although slow, uptake by the patient of amino acids from the dialysis bath. Patients with large wounds and acute renal failure require increased protein for wound healing and dialysis for the control of excessive plasma urea.

Hepatic Failure

Nutritional support is highly desirable for many surgical patients with cirrhosis, in the perioperative management of bleeding esophageal varices, and in postshunt encephalopathy. Intravenous solutions for patients with liver failure (Chs. 54 and 55) should essentially fulfill the following requisites [168] :

1. Provide adequate amounts of calories and nitrogen for protein synthesis.
2. Neither produce nor aggravate plasma amino acid imbalance.
3. Do not produce electrolyte or acid/base imbalance.
4. Neither produce nor aggravate neurologic or encephalopathic symptoms.
5. Provide sufficient calories in a volume tolerated by patients with hepatic failure.

Hepatic Encephalopathy

Hepatic disease may lead to symptoms of brain malfunction or encephalopathy ranging from subtle behavioral changes to deep coma (Ch. 54) . Such patients often have shunting of blood around the liver, either produced surgically or occurring spontaneously. Increases in brain ammonia and glutamine have been demonstrated in hepatic encephalopathy. A current hypothesis of the cause of hepatic encephalopathy is that an imbalance of neurotransmitters, specifically monoamines, occurs in the brain. [169] This is based on the finding of an increased content of the amino acids tryptophan, tyrosine, and phenylalanine in the brain [170] ; these are precursors for the synthesis of serotonin and the catecholamines.

In the case of catecholamines, the excess precursor material in the brain in hepatic encephalopathy may cause inhibition of the normal synthetic pathway, leading to a reduced content of dopamine and norepinephrine and to increased amounts of trace amines, such as octopamine and phenylethanolamine.

Plasma amino acid profiles are characteristically changed when hepatic failure is present. A common finding is elevation of phenylalanine and methionine levels. The plasma levels of the branched-chain amino acids leucine, isoleucine, and valine are generally decreased in patients with hepatic failure, possibly because of peripheral use of these amino acids in muscle. The levels of plasma amino acids in liver disease relate to competition between some of the same neutral amino acids--phenylalanine, tyrosine, and tryptophan--and of the branched-chain amino acids in penetrating the blood-brain barrier. The neurotransmitter profile is markedly deranged in hepatic encephalopathy. There is increased serotonin, decreased norepinephrine, and to a lesser extent, decreased dopamine in the brain. Octopamine, a known false transmitter that may replace dopamine and norepinephrine in the central nervous system, is markedly increased in the brains of animals and in the blood of patients in hepatic coma.

Tyrosine is thought to be the normal precursor of the catecholamines dopamine and norepinephrine. Profound depletion of norepinephrine has been demonstrated in hepatic coma. [171] Phenylalanine may compete with tyrosine-3- hydroxylase and decrease the conversion of tyrosine to dopa in hepatic encephalopathy. Tyrosine then accumulates and becomes decarboxylated to tyramine and then to octopamine.

Aims of Total Parental Nutrition in Liver Failure

If the amino acid levels in plasma are abnormal in hepatic encephalopathy, and if these have a role in the pathophysiology

of the disease, a reasonable starting point in therapy would be the normalization of the plasma amino acid patterns (Chs. 54 and 55) . Therapeutic efforts have been directed at attempting to normalize the brain amino acid concentrations during TPN with specific "hepatic failure" solutions. The amino acids tryptophan, tyrosine, and phenylalanine compete with other large neutral amino acids (including the branched-chain amino acids) for passage across the blood-brain barrier. There has therefore been increasing interest in therapeutically altering plasma amino acid concentrations in patients with liver disease by infusing branched-chain amino acid mixtures. The results obtained with these treatments have been ambiguous. Several uncontrolled studies have reported clinical improvement. [172] Controlled studies have not clarified these situations: for example, Wahren et al [173] concluded that no effect on encephalopathy could be attributed to the amino acid infusion.

An experimental solution has been developed that appears to be well tolerated by patients with hepatic insufficiency and encephalopathy. [174] The solution is now commercially available as HepatAmine. The solution with reduced aromatic amino acids and increased amounts of branched-chain amino acids was devised to normalize plasma amino acid patterns and to improve encephalopathy.

Sepsis

The nutritional support of septic patients is designed to reduce glucose administration because plasma glucose levels are high and peripheral tissues cannot use glucose. [175] Lipid emulsions are used to provide calories because fatty acids and ketone bodies are preferred fuel for many organs during sepsis. Amino acid mixtures are enriched with branched-chain amino acids to provide another nonglucose fuel source for skeletal muscle and to prevent extensive muscle autocatabolism. Marked improvement of indexes of nutritional competence has been demonstrated in stressed patients in surgical intensive care units who were given branched-chain amino acid-enriched mixture. [176]

Intraoperative Management for Patients Receiving Total Parenteral Nutrition

Whether TPN is temporarily discontinued or unchanged during the operative period, the anesthesiologist must monitor blood glucose levels meticulously to avoid hypoglycemia or hyperglycemia. Hyperosmolar, nonketotic, hyperglycemic coma has been reported in patients who fail to regain consciousness after anesthesia. [17] [177] [178]

Hagerdal et al [179] pointed out the effect of even 5 percent glucose intraoperatively on the RQ seen in the recovery room in patients after anesthesia. They demonstrated a 20 percent greater DV CO_2 during the first hour in the recovery room in patients who had received 5 percent dextrose intraoperatively compared with those who had received isotonic saline.

The anesthesiologist should also be meticulous about ensuring the presence of normal serum phosphate levels in the patient receiving TPN. Hypophosphatemia has been associated with several clinical conditions of interest to the anesthesiologist. Newman et al [180] described two cases of acute respiratory failure associated with hypophosphatemia. These patients, both with a history of alcoholism, developed profound areflexic muscle weakness such that mechanical ventilation became necessary. Serum phosphate levels were 500 and 400 mg/dL. Muscle strength returned quickly after phosphate administration.

Preoperative Anesthetic Considerations

A preoperative check should include the following evaluations [181] :

1. Serum sodium, potassium, chloride, and bicarbonate levels
2. Chest roentgenogram showing infusion catheter position
3. Serum phosphate level
4. Serum calcium level
5. Serum magnesium level
6. Urinary phosphate and magnesium level
7. Blood urea nitrogen and creatinine level
8. Forced vital capacity
9. Blood and urine glucose levels
10. Blood acid/base status and blood gases
11. Liver function tests
12. RQ (if measured)

Details of the duration and the type of TPN solutions and additives should include the following:

1. Incidence of hyperglycemia or hypoglycemia
2. Addition of insulin to regimen
3. History of chronic alcoholism
4. Presence of sepsis
5. Central catheter functioning
6. Site for additional intravenous infusion during anesthesia

A decision must be made whether to continue TPN [182] or to replace TPN by 10 percent dextrose for the perioperative period. [183] In either event, special precautions and monitoring are essential. In most instances, it is safer to continue the patient's TPN during the operation, especially with mixed glucose/lipid solutions. The anesthesiologist must remember that the TPN volume is added to the total intravenous intake. It is important to monitor plasma glucose level, potassium level, and pH.

Intraoperative Anesthetic Management

In theory, it is possible to lessen the stress hormone response to surgery by using either opioid-based anesthesia or spinal or epidural anesthesia (Chs. 10 42 and 43) . [184] [185] [186] [187] [188] One study could not demonstrate a consistent reduction in stress response to surgery when regional anesthesia was used. [189]

SUMMARY

Perioperative nutritional support is indicated for malnourished patients, severely catabolic patients (trauma, burns, sepsis), cancer patients, and patients with organ failure. Special nutritional support is not indicated for well-nourished surgical patients with uncomplicated surgery who will have a limited period of fasting (2-4 days). If nutritional support is indicated, it should be initiated as soon as possible. Many patients tolerate enteral nutritional support via gastric or jejunal feeding tubes. In the absence of contraindications for enteral feeding, it should be attempted with a willingness to rapidly switch to parenteral nutrition if the enteral route fails. Patients with modest caloric requirements (<1,800 kcal/d) may receive adequate nutritional support through a peripheral vein with amino acid, glucose, and lipid solutions. Central venous administration of nutrition should be reserved for patients with high caloric requirements and a nonfunctioning gastrointestinal tract because of increased complications of central venous catheterization.

The optimal nutritional prescription includes adequate protein intake (as amino acid solutions) in aiming to keep the patient in nitrogen equilibrium as well as calories in the form of glucose and fat (each supplying 50% of the total calories) to meet measured daily energy expenditure. Protein and energy requirements should be considered separately and monitored individually: nitrogen balance for protein, indirect calorimetry for energy. A convenient starting point for protein administration is 1.0 to 1.5 g/kg/d, with glucose and lipids adjusted to each provide 50 percent of calculated or measured nonprotein calories per day. The prescription must also include vitamins, minerals, and trace elements. Markers of muscle protein metabolism, such as serum 3-methylhistidine, transferrin, and prealbumin, are monitored to rule out extensive catabolic activity. Water balance is followed by daily weighing, and serum electrolyte levels, liver enzyme levels, and renal function test results are also monitored frequently. Properly administered, perioperative nutritional support can markedly enhance the care of selected surgical patients.

References

1. Pardridge WM: Brain metabolism: A perspective from the blood-brain barrier. Physiol Rev 63:1481, 1983.

2. Shaw JHF, Galler L, Holdaway IM et al: The effect of extradural blockage upon glucose and urea kinetics in surgical patients. Surg Gynecol Obstet 165:260, 1987.

3. Biebuyck JF: Effects of anesthetic agents on metabolic pathways: Fuel utilization and supply during anesthesia. Br J Anaesth 45:263, 1973.

4. Randle PJ, Kerbey AL, Espinal J: Mechanisms of decreasing glucose oxidation in diabetes and starvation: Role of lipid fuels and hormones. Diabetes Met Rev 4:623, 1988.

5. Sugden MC, Holness MJ, Palmer TN: Fuel selection and carbon flux during the starved-to-fed transition. Biochem J 263:313, 1989.

6. Yeaman SJ: The 2-oxo acid dehydrogenase complexes: Recent advances. Biochem J 257:625, 1989.

7. Ruderman N, Berger M: The formation of glutamine and alanine in skeletal muscle. J Biol Chem 249:5500, 1974.

8. Felig P, Wahran J, Raf L: Evidence of inter-organ amino acid transport by blood cells in humans. Proc Natl Acad Sci U S A 70:1775, 1973.

9. Haymond MW, Miles JM: Branched chain amino acids as a major source of alanine nitrogen in man. Diabetes 31:86, 1982.

10. Robert JJ, Bier DM, Zhao XH et al: Glucose and insulin effects on de novo amino acid synthesis in young men. Metabolism 31:1210, 1982.

11. Daughaday WH, Hall K, Raben MS et al: Somatomedin: Proposed designation for sulfation factor. Nature 235:107, 1972.

12. Vary TC, Siegel JH: Sepsis, abnormal metabolic control and multiple organ failure syndrome. In Siegel JH (ed): Trauma: Emergency Surgery and Critical Care, New York, Churchill Livingstone, 1987, p 411.

13. Bone RC, Balk RA, Cerra FB et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101:1644, 1992.

14. Furlan AJ, Hanson M, Cooperman A: Acute areflexic paralysis associated with hyperalimentation and hypophosphatemia. Arch Neurol 32:696, 1975.

15. Askanazi J, Weissman C, LaSala PA et al: Effect of protein intake on ventilatory drive. Anesthesiology 60:106, 1984.

16. Sieber FE, Smith DS, Traystman RJ et al: Glucose: A reevaluation of its intraoperative use. Anesthesiology 67:72, 1987.

17. Seki S: Clinical features of hyperosmolar hyperglycemic nonketotic diabetic coma associated with cardiac operation. J Thorac Cardiovasc Surg 91:867, 1986.

18. Wolfe RR: Regulation of glucose metabolism. In Burke JF (ed): Surgical Physiology. Philadelphia, WB Saunders, 1983, p 75.

19. Wolfe RR, Allsop JR, Burke JF: Glucose metabolism in man: Response to intravenous glucose infusion. Metabolism 28:210, 1979.

20. Nordenstrom J, Persson E: Energy supply during total parenteral nutrition: How much and what source. Acta Anesthesiol Scand 29:95, 1985.

21. Wolfe RR, Burke JF: Glucose and lactate metabolism in experimental septic shock. Am J Physiol 235:R219, 1978.

22. Burke JF, Wolfe RR, Mullany C et al: Glucose requirements following burn injury. Ann Surg 190:274, 1979.

23. Baue AE: Multiple progressive, or sequential organ systems failure. Arch Surg 110:779, 1975.

24. Carrico CJ, Meakins JL, Marshall JC et al: Multiple organ failure syndrome. Arch Surg 121:196, 1986.

25. Fry DE, Pearlstein L, Fulton RL et al: Multiple system organ failure: The role of uncontrolled infection. Arch Surg 115:136, 1980.

26. Manship L, McMillin RD, Brown JJ: The influence of sepsis and multiorgan organ failure on mortality in surgical intensive care unit. Ann Surg 50:94, 1984.

27. Shoemaker WC, Appel PL, Kram HB: Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med 16:1117, 1988.

28. Vincent JL, Dufaye P, Beru J et al: Serial lactate determination during circulatory shock. Crit Care Med 11:449, 1983.

29. Cerra FB: Hypermetabolism-organ failure: A metabolic response to injury. Crit Care Clin 5:289, 1989.

30. Cerra FB, Siegel JH, Coleman B et al: Septic autocatabolism: A failure of exogenous nutritional support. Ann Surg 192:570, 1980.

31. Shaw JHF, Klein S, Wolfe RR: Assessment of alanine, urea and glucose interrelationships in normal subjects and subjects with sepsis with stable isotopes. Surgery 97:557, 1985.

32. Lang CH, Bagby GJ, Spitzer JJ: Glucose kinetics and body temperature after lethal and non-lethal doses of endotoxin. Am J Physiol 248:R471, 1985.

33. Keller DL, Puinno PA, Fang BC et al: Glucose and lactate kinetics in septic rats. Metabolism 31:252, 1982.

34. Wolfe RR, Burke JF: Glucose and lactate metabolism in experimental septic shock. Am J Physiol 235:R219, 1978.

35. Meszaros K, Bagby GJ, Lang CH et al: Increased uptake and phosphorylation of 2-deoxyglucose by skeletal muscle in endotoxin-treated rats. Am J Physiol 253:E33, 1987.

36. Lee MD, Zentella A, Pekala PH et al: Effect of endotoxin-induced monokines on glucose metabolism in the muscle cell line L6. Proc Natl Acad Sci U S A 84:2590, 1987.

37. Lang CH, Dobrescu C, Meszaros K: Insulin-mediated glucose uptake by individual tissues during sepsis. Metabolism 39:1096, 1990.

38. Vary TC, Drnevich D, Brennan WA Jr: Molecular mechanisms regulating skeletal muscle glucose metabolism in sepsis. Am J Physiol, in press.

39. Klip A, Paquet MR: Glucose transport and glucose transporters in muscle and their metabolic regulation. Diabetes Care 13:228, 1990.

40. Lang CH, Dobrescu C: In vivo insulin resistance during nonlethal hypermetabolic sepsis. Circ Shock 28:165, 1989.

41. Lang CH, Dobrescu C: Gram-negative infection increases noninsulin-mediated glucose disposal. Endocrinology 128:645, 1991.

42. Vary TC, Siegel JH, Nakatani T et al: Effects of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. Am J Physiol 250:E634, 1986.

43. Vary TC, Siegel JH, Tall D et al: Role of anaerobic bacteria in intraabdominal septic abscess in mediating septic control of skeletal muscle glucose oxidation and lactic acidosis. J Trauma 29:1003, 1989.

44. Nanni G, Siegel JH, Coleman B et al: Increased lipid fuel dependence in the critically ill septic patient. J Trauma 24:14, 1984.

45. Sganga G, Siegel JH, Coleman B et al: The physiologic meaning of respiratory index in various types of critical illness. Circ Shock 17:179, 1985.

46. Stoner HB, Little RA, Frayn KN et al: The effect of sepsis on the oxidation of carbohydrate and fat. Br J Surg 70:32, 1983.

47. Vary TC: Increased pyruvate dehydrogenase kinase activity in response to sepsis. Am J Physiol 260:E669, 1991.

48. Vary TC, Siegel JH, Tall BD, et al: Metabolic effect of partial reversal of pyruvate dehydrogenase activity by dichloroacetate in sepsis. Circ Shock 24:3, 1988.

49. Vary TC, Siegel JH, Zechnich A et al: Pharmacological reversal of abnormal glucose regulation, BCAA utilization and muscle catabolism in sepsis by dichloroacetate. J Trauma 28:1301, 1988.

50. Vary TC, Siegel JH, Placko R et al: Effect of dichloroacetate on plasma and hepatic amino acids in sterile inflammation and sepsis. Arch Surg 124:1071, 1989.

51. Vary TC, Murphy JM: Role of extra-splanchnic organs in the metabolic response to sepsis: Effect of insulin. Circ Shock 29:41, 1989.

52. Vary TC, Plack R, Siegel JH: Pharmacologic modulation of increased release of gluconeogenic precursors from extra-splanchnic organs in sepsis. Circ Shock 29:59, 1989.

53. Long CL, Kinney JM, Geiger JW: Non-suppressibility of gluconeogenesis by glucose in septic patients. Metabolism 25:193, 1975.

54. Crane CW, Picou D, Smith R et al: Protein turnover in patients before and after elective orthopedic operations. Br J Surg 64:129, 1977.

55. Wernerman J, von der Decken A, Vinnars E: Protein synthesis in skeletal muscle in relation to nitrogen balance after abdominal surgery: The effect of total parenteral nutrition. J Parenter Enteral Nutr 10:578, 1986.

56. Long CL, Birkhahn RH, Geiger JW et al: Urinary excretion of 3-methylhistidine: An assessment of muscle protein catabolism in adult normal subjects and during malnutrition, sepsis and skeletal trauma. Metabolism 30:765, 1981.

57. Rennie MJ, Bennegard K, Eden E et al: Urinary excretion and efflux from the leg of 3-methylhistidine before and after major surgical operation. Metabolism 33:250, 1984.

58. Rennie MJ: Muscle protein turnover and the wasting due to injury and disease. Br Med Bull 41:257, 1985.

59. Rennie MJ, Edwards RHT, Emery PW et al: Depressed protein synthesis is the dominant characteristic of muscle wasting and cachexia. Clin Physiol 3:387, 1983.

60. Clowes GHA, George BC, Villee C et al: Muscle proteolysis induced by a circulating peptide in patients with sepsis and trauma. N Engl J Med 308:545, 1983.

61. Vary TC, Kimball SR: Sepsis-induced changes in protein synthesis: Differential effects on fast- and slow-twitch muscles. Am J Physiol 262:C1513, 1992.

62. Jepson MM, Pell JM, Bates PC et al: The effects of endotoxaemia on protein metabolism in skeletal muscle and liver of fed and fasted rats. Biochem J 235:329, 1986.

63. Vinnars E, Bergstrom J, Furst P: Influence of postoperative state in the intracellular free amino acids in human muscle tissue. Ann Surg 163:665, 1975.

64. Askanazi J, Carpenter YA, Michelsen CB et al: Muscle and plasma amino acids following injury. Ann Surg 192:78, 1980.

65. MacLennon PA, Brown RA, Rennie MJ: A positive relationship between protein synthetic rate and intracellular glutamine concentration in perfused rat skeletal muscle. FEBS Lett 215:187, 1987.

66. Albina JE, Henry W, King PA et al: Glutamine metabolism in rat skeletal muscle wounded with L-carrageenan. Am J Physiol 252:E49, 1987.

67. Kapadia CR, Colpoys MF, Jiang Z-M et al: Maintenance of skeletal muscle intracellular glutamine during standard surgical trauma. J Parenter Enteral Nutr 9:583, 1985.

68. Wernerman J, Hammarkvist K, Ali MR et al: Glutamine and ornithine-ketoglutarate but not branched chain amino acids reduce the loss of glutamine after surgical trauma. Metabolism 38(suppl 1):63, 1989.

69. Wilmore DW, Aulick LH, Mason AP et al: Influence of burn wound on local and systemic response to injury. Ann Surg 186:444, 1977.

70. Rannels SR, Jefferson LS: Effects of glucocorticoid on muscle protein turnover in perfused rat hemicorpus. Am J Physiol 238:E564, 1980.

71. Li JB, Jefferson LS: Effect of isoproterenol on amino acid levels and protein turnover in skeletal muscle. Am J Physiol 232:E243, 1977.

72. Hasselgren P-O, Fischer JE: Regulation by insulin of muscle protein metabolism during sepsis and other catabolic conditions. Nutrition 8:434, 1992.

73. Jefferson LS: Role of insulin in the regulation of protein synthesis. Diabetes 20:487, 1980.

74. Bower RH, Muggia-Sullan M, Vallgren S et al: Branched chain amino acid-enriched solutions in septic patients. Ann Surg 203:13, 1986.

75. Cerra FB, Mazuki JE, Chute E et al: Branched chain metabolic support. Ann Surg 199:286, 1984.

76. Freund HR, Ryan JA, Fischer JE: Amino acid derangements in patients with sepsis: Treatment with branched chain amino acid rich effusions. Ann Surg 188:423, 1978.

77. Lau KS, Fantania HR, Randle PJ: Inactivation of rat liver and kidney branched chain 2-oxoacid dehydrogenase complex by adenosine triphosphate. FEBS Lett 126:66, 1981.

78. Ichihara K, Neely JR, Siehl DL et al: Utilization of leucine by working rat heart. Am J Physiol 239:E430, 1980.

79. Buse MG, Atwell R, Mancusi V: In vitro effect by branched chain amino acids on the ribosomal cycles in muscles of fasted rats. Horm Metab Res 11:289, 1979.

80. Li JB, Jefferson LS: Influence of amino acid availability on protein turnover in perfused skeletal muscle. Biochim Biophys Acta 544:351, 1978.

81. Vary TC, Kimball SR: Regulation of hepatic protein synthesis in chronic inflammation and sepsis. Am J Physiol 262:C445, 1992.

82. Sganga G, Siegel JH, Brown G et al: Reprioritization of hepatic plasma protein release in trauma and sepsis. Arch Surg 120:187, 1985.

83. Princeton GMG, Nieuwenhuizen W, Mol-Backx GPBM et al: Direct evidence of transcriptional control of fibrinogen and albumin synthesis in rat liver during the acute-phase response. Biochem Biophys Res Commun 102:717, 1981.

84. Ricca GA, Hamilton RW, McLean JW et al: Rat 1-acid glycoprotein mRNA: Cloning of double-stranded cDNA and kinetics of induction of mRNA levels following acute inflammation. J Biol Chem 256:10362, 1981.

85. Schreiber G, Howlett G, Hagashima M et al: The acute-phase response of plasma protein synthesis during experimental inflammation. J Biol Chem 257:10271, 1982.

86. Liao WS, Jefferson LS, Taylor JM: Changes in plasma albumin concentration, synthesis rate, and mRNA level during acute inflammation. Am J Physiol 251:C928, 1986.

87. Heinrich PC, Castell JV, Andus T: Interleukin 6 and acute phase response. Biochem J 265:621, 1990.

88. Blackham M, Cesar D, Park O-J et al: Effects of recombinant monokines on hepatic pyruvate dehydrogenase, pyruvate dehydrogenase kinase, lipogenesis de novo and plasma triacylglycerols. Biochem J 284:129, 1992.

89. Feingold KR, Soued M, Serio MK et al: The effect of diet on tumor necrosis stimulation of hepatic lipogenesis. Metabolism 39:623, 1990.

90. Vary TC, Siegel JH, Nakatani T et al: A biochemical basis for depressed ketogenesis in sepsis. J Trauma 26:419, 1986.

91. Black PR, Brooks BC, Bessley PQ et al: Mechanism of insulin resistance following injury. Ann Surg 196:420, 1982.

92. Kinney JM: The application of indirect calorimetry to clinical studies. In Kinney JM (ed): Assessment of Energy Metabolism in Health and Disease. Columbus, Ohio, Ross Laboratories, 1980, p 42.

93. Dudrick SJ: Parenteral nutrition. In Dudrick SJ, Baue AE, Eiseman B et al (eds): Manual of Preoperative and Postoperative Care. Philadelphia, WB Saunders, 1983, p 86.

94. Antonas KN, Curtas MS, Meguid MM: Use of serum CPK-MM to monitor response to nutritional intervention in catabolic surgical patients. J Surg Res 42:219, 1987.

95. Elwyn DH, Kinney JM: A unique approach to measuring total energy expenditure by indirect calorimetry. In Kinney JM (ed): Assessment of Energy Metabolism in Health and Disease. Columbus, Ohio, Ross Laboratories, 1980, p 54.

96. Van Lanschot JJB, Feenstra BWA, Looijen R et al: Total parenteral nutrition in critically ill surgical patients: Fixed vs tailored caloric replacement. Intensive Care Med 13:46, 1987.

97. Keys A, Taylor HL, Grande F: Basal metabolism and age of adult man. Metabolism 22:579, 1973.

98. Biebuyck JF: Total parenteral nutrition in the perioperative period: A time for caution? Anesthesiology 54:360, 1981.

99. Bistrian BR, Bothe A Jr, Blackburn GL: Complications of total parenteral nutrition. In Clin Anaesthesiol 1:693, 1983.

100. Grimble GK, Payne-James JJ, Silk DBA: Advances in nutrition in the critically ill. Baillieres Clin Anaesthesiol 6:213, 1992.

101. Weir JBV: New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol (Lond) 109:1, 1949.

102. Frayn KN: Calculation of substrate oxidation rate in vivo from gaseous exchange. J Appl Physiol 55:628, 1983.

103. Lowry SF, Horowitz GD, Brennan MF: Body protein kinetics during perioperative intravenous nutritional support. Surg Gynecol Obstet 163:303, 1986.

104. Elwyn DH, Kinney JM, Jeevanandam M et al: Influence of increasing carbohydrate intake on glucose kinetics in injured man. Ann Surg 191:117, 1979.

105. Brennan MF, Horowitz GD: Total parenteral nutrition in surgical patients. Adv Surg 17:1, 1984.

106. Quandt CM, Horst HM, Obeid FN et al: Accuracy of two-hour urine urea nitrogen determinations in critically ill patients. Clin Pharm 3:408, 1984.

107. Wilmore DW: The Metabolic Management of the Critically Ill. New York, Plenum, 1977.

108. Kinney JM, Morgan AP, Domingues FJ et al: A method for continuous measurement of gas exchange and expired radioactivity in acutely ill patients. Metabolism 13:205, 1964.

109. Damask MC, Forse RA, Kinney JM: Clinical applications of gas exchange measurements. Clin Anaesthesiol 1:599, 1983.

110. Bursztein S, Elwyn DH, Apleanazi J et al: Energy Metabolism, Indirect Calorimetry, and Nutrition. Baltimore, Williams & Wilkins, 1989.

111. Wilson A, Goode AW, Kirk CJC et al: Parenteral nutrition via peripheral veins: A feasibility study. J R Soc Med 80:430, 1987.

112. Adams S, Dellinger EP, Wertz MJ et al: Enteral versus parenteral nutritional support following laparatomy for trauma: A randomized prospective trial. J Trauma 26:882, 1986.

113. Moore EE, Jones TN: Benefits of immediate jejunostomy feeding after major abdominal trauma: A prospective, randomized study. J Trauma 26:874, 1986.

114. Fong Y, Macano MA, Barber A et al: Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. Ann Surg 210:449, 1989.

115. Chang RWS, Jacobs S, Lee B: Gastrointestinal dysfunction among intensive care unit patients. Crit Care Med 15:909, 1987.

116. Aldin PB, Svingen BA, Johnson SB et al: Partial correction by exogenous lipid of abnormal patterns of polyunsaturated fatty acids in plasma phospholipids of stressed and septic surgical patients. Surgery 100:671, 1986.

117. Helms RA, Dickerson RN, Ebbert ML et al: Retinol-binding protein and prealbumin: Useful measures of protein repletion in critically ill, malnourished infants. J Pediatr Gastroenterol Nutr 5:586, 1986.

118. Robin AP, Nordenstrom J, Askanazi J et al: Influence of parenteral carbohydrate on fat oxidation in surgical patients. Surgery 95:608, 1984.

119. Wilmore DW: Catabolic illness: Strategies for enhancing recovery. N Engl J Med 325:695, 1991.

120. Anonymous: Effects of TPN on wound healing. Nutr Rev 45:331, 1987.

121. Askanazi J, Hensle TW, Starker PM et al: Effect of immediate postoperative nutritional support on length of hospitalization. Ann Surg 203:236, 1986.

122. Cooper JK: Does nutrition affect surgical outcome? J Am Geriatr Soc 35:229, 1987.

123. Twomey PL, Patching SC: Cost-effectiveness of nutritional support. J Parenter Enterol Nutr 9:3, 1985.

124. Detsky AS, Jeejeebhoy KN: Cost-effectiveness of preoperative parenteral nutrition in patients undergoing major gastrointestinal surgery. J Parenter Enterol Nutr 8:632, 1984.

125. Meguid MM, Meguid V: Preoperative identification of the surgical cancer patient in need of postoperative supportive total parenteral nutrition. Cancer 55:258, 1985.

126. Fasth S, Hulten L, Magnusson O et al: Postoperative complications in colorectal surgery in relation to preoperative clinical and nutritional state and postoperative nutritional treatment. Int J Colorectal Dis 2:87, 1987.

127. Lowry SF, Brennan MF: Abnormal liver function during parenteral nutrition: Relation to infusion excess. J Surg Res 26:300, 1979.

128. Askanazi J, Carpentier YA, Elwyn DH et al: Influence of total parenteral nutrition on fuel utilization in injury and sepsis. Ann Surg 191:40, 1980.

129. Michel L, Serrano A, Malt RA: Nutritional support of hospitalized patients. N Engl J Med 19:1147, 1981.

130. Greene BL, Hazlett D, Demaree R: Relationship between intralipid-induced hyperlipidemia and pulmonary function. Am J Clin Nutr 29:127, 1976.

131. Jarnberg PO, Lindholm M, Eklund J: Lipid infusion in critically ill patients. Crit Care Med 9:27, 1981.

132. Wolfram G: Medium-chain triglycerides (MCT) for total parenteral nutrition. World J Surg 10:33, 1986.

133. Ball MJ, White K: Metabolic effects of intravenous medium- and long-chain triacylglycerols in critically ill patients. Clin Sci 76:165, 1989.

134. Phillips GO: Total parenteral nutrition in acute illness. Anaesth Intensive Care 13:288, 1985.

135. Maki DG, Cobb L, Garman JK et al: An attachable silver-impregnated cuff for prevention of infection with central venous catheters: A prospective randomized multicenter trial. Am J Med 85:307, 1988.

136. Flowers RH, Schwenzer KJ, Kopel RF et al: Efficacy of an attachable subcutaneous cuff for the prevention of intravascular catheter-related infection. JAMA 261:878, 1989.

137. Lee RB, Buckner M, Sharp KW: Do multi-lumen catheters increase central venous catheter sepsis compared to single-lumen catheters? J Trauma 28:1472, 1988.

138. Tennant GB, Smith RC, Leinster SJ et al: Acute depression of serum folate in surgical patients during preoperative infusion of ethanol-free parenteral nutrition solutions. Scand J Haematol 27:327, 1981.

139. Krebs HA, Hems R, Tyler B: The regulation of folate and methionine metabolism. Biochem J 158:341, 1976.

140. Tennant GB, Smith RC, Leinster SJ et al: Amino-acid infusion induced depression of serum folate after cholecystectomy. Scand J Haematol 27:333, 1981.

141. Amess JAL, Burman JF, Rees GM et al: Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 2:339, 1978.

142. Chanarin I, Deacon R, Lumb M et al: Vitamin B 12 regulates folate metabolism by the supply of formate. Lancet 2:505, 1980.

143. Cerra FB, Siegel JH, Coleman B et al: Septic autocannibalism: A failure of exogenous nutritional support. Ann Surg 192:570, 1980.

144. Cerra FB, Hirsh JB, Mullen K et al: The effect of stress level amino acid formula, and nitrogen dose on nitrogen retention in traumatic and septic stress. Ann Surg 205:282, 1987.

145. Doekel RC, Jr, Zwillich CW, Scoggin CH et al: Clinical semistarvation: Depression of hypoxic ventilatory response. N Engl J Med 295:358, 1976.

146. Weissman C, Askanazi J, Rosenbaum SH et al: Amino acids and respiration. Ann Intern Med 98:41, 1983.

147. Arora NS, Rochester DF: Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis 126:5, 1982.

148. Delafosse B, Bouffard Y, Bertrand O et al: Effects of protein intake on pulmonary gas exchange and ventilatory drive in postoperative patients. Anesthesiology 70:404, 1989.

149. Weissman C, Askanazi J: Respiratory complications of nutritional support. Clin Anaesthesiol 1:707, 1983.

150. Nordenstrom J, Jeevanandam M, Elwyn D et al: Increasing glucose intake during parenteral nutrition increases norepinephrine excretion in trauma and sepsis. Clin Physiol 1:1, 1981.

151. Allardyce DB: Cholestasis caused by lipid emulsions. Surg Gynecol Obstet 154:641, 1982.

152. Pantuck EJ, Pantuck CB, Weissman C et al: Effects of parenteral nutrition regimens on oxidative drug metabolism. Anesthesiology 60:534, 1984.

153. Vesell ES, Biebuyck JF: New approaches to assessment of drug disposition in the surgical patient. Anesthesiology 60:529, 1984.

154. Kappas A, Anderson KE, Conney AH et al: Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. Clin Pharmacol Ther 20:643, 1976.

155. Feldman CH, Hutchinson VE, Pippenger CE et al: Effect of dietary protein and carbohydrate on theophylline metabolism in children. Pediatrics 66:956, 1980.

156. Fagan TC, Walle T, Oexmann MJ et al: Increased clearance of propranolol and theophylline by high-protein compared with highcarbohydrate diet. Clin Pharmacol Ther 41:402, 1987.

157. Juan D, Worwag EM, Schoeller DA et al: Effects of dietary protein on theophylline pharmacokinetics and caffeine and aminopyrine breath tests. Clin Pharmacol Ther 40:187, 1986.

158. Anderson KE: Influences of diet and nutrition on clinical pharmacokinetics. Clin Pharmacokinet 14:325, 1988.

159. Brodie MJ, Boobis AR, Toverud E-L et al: Drug metabolism in white vegetarians. Br J Clin Pharmacol 9:523, 1980.

160. Gadisseux P, Ward JD, Young HF et al: Nutrition and the neurosurgical patient. J Neurosurg 60:219, 1984.

161. Pulsinelli WA, Waldman S, Rawlinson D et al: Moderate hyperglycemia augments ischemic brain damage: A neuropathological study in the rat. Neurology 32:1239, 1982.

162. Pulsinelli WA, Levy DE, Sigsbee B et al: Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 74:540, 1983.

163. Myers RE: A unitary theory of causation of anoxic and hypoxic brain pathology. Adv Neurol 26:195, 1979.

164. Nordstrom C-H, Siesjo BK: Effects of phenobarbitol in cerebral ischemia. Part 1. Cerebral energy metabolism during pronounced, incomplete ischemia. Stroke 9:327, 1978.

165. Giordano C: Use of exogenous and endogenous urea for protein synthesis in normal and uremic subjects. J Lab Clin Med 62:231, 1963.

166. Giovanetti S, Neaggiore Q: A low nitrogen diet with protein of high biological value for severe chronic uremia. Lancet 1:1000, 1964.

167. Feinstein EI: Nutrition in acute renal failure. Adv Exp Med Biol 212:297, 1987.

168. Aguirre A, Funovics J, Wesdorp RI et al: Parenteral nutrition in hepatic failure. In Fischer JE (ed): Total Parenteral Nutrition. Boston, Little, Brown, 1976.

169. Munro HN, Fernstrom JD, Wurtman RJ: Insulin, plasma amino acid imbalance and hepatic coma. Lancet 1:722, 1975.

170. Mans AM, Biebuyck JF, Shelley K et al: Regional blood-brain barrier permeability to amino acids after portacaval anastamosis. J Neurochem 38:705, 1982.

171. Fischer JE, Baldessarini RJ: False neurotransmitters and hepatic failure. Lancet 2:75, 1971.

172. Freund H, Dienstag J, Lehrich J et al: Infusion of branched-chain enriched amino acid solution in patients with hepatic encephalopathy. Ann Surg 196:209, 1982.

173. Wahren J, Denis J, Desurmont P et al: Is intravenous administration of branched-chain amino acids effective in the treatment of hepatic encephalopathy? A multicenter study. Hepatology 3:475, 1983.

174. Fischer JE, Rosen HM, Ebeid AM et al: The effect of normalization of plasma amino acids on hepatic encephalopathy in man. Surgery 80:77, 1976.

175. Siegel JH, Vary TC: Sepsis, abnormal metabolic control, and the multiple organ failure syndrome. In Siegel JH (ed): Trauma: Emergency Surgery and Critical Care. New York, Churchill Livingstone, 1987, p 411.

176. Cerra FB, Mazuski JE, Chute E et al: Branched-chain metabolic support. Ann Surg 199:286, 1984.

177. Toker P: Hyperosmolar hyperglycemic nonketotic coma, a cause of delayed recovery from anesthesia. Anesthesiology 41:284, 1974.

178. Wulfsen HD, Dalton B: Hyperosmolar hyperglycemic nonketotic coma in a patient undergoing emergency cholecystectomy. Anesthesiology 41:286, 1974.

179. Hagerdal M, Caldwell C, Gross JB: Intraoperative fluid management influences carbon dioxide production and respiratory quotient. Anesthesiology 59:48, 1983.

180. Newman JH, Neff TA, Ziporin P: Acute respiratory failure associated with hypophosphatemia. N Engl J Med 296:1101, 1977.

181. Schneider AJL, Biebuyck JF: Intraoperative management of patients receiving total parenteral nutrition. Clin Anaesthesiol 1:697, 1983.

182. Newmark SR, Key JC, Roberts J: Perioperative stabilization of glucose levels in patients supported with total parenteral nutrition. J Parenter Enterol Nutr 4:494, 1980.

183. Dudrick SJ, MacFadyen BV Jr, VanBuren C et al: Parenteral hyperalimentation: Metabolic problems and solutions. Ann Surg 176:259, 1972.

184. Kehlet H, Brandt MR, Prange-Hansen A et al: Effect of epidural analgesia on metabolic profiles during and after surgery. Br J Surg 66:543, 1979.

185. George JM, Reier CE, Canese RR et al: Morphine anaesthesia blocks cortisol and growth hormone response to surgical stress in humans. Clin Endocrinol Metab 38:736, 1974.

186. Brandt MR, Korshin J, Prange-Hansen A et al: Influence of morphone anaesthesia on the endocrine-metabolic response to open heart surgery. Acta Anaesthesiol Scand 22:400, 1978.

187. Cooper GM, Paterson JL, Ward ID et al: Fentanyl and the metabolic response to gastric surgery. Anaesthesia 36:667, 1981.

188. Walsh ES, Paterson JL, O'Riordan JB et al: Effect of high-dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. Br J Anaesth 53:1155, 1981.

189. Watters JM, March RJ, Desai D et al: Epidural anaesthesia and analgesia do not affect energy expenditure after major abdominal surgery. Can J Anaesth 40:314, 1993.

190. Hawkins RA, Vina JR: Lipid and ketone body metabolism in man. Clin Anaesthesiol 1:559, 1983.

191. Wolfe RR, O'Donnell TF, Stone MD et al: Investigation of factors determining the optimal glucose infusion rate in total parenteral nutrition. Metabolism 29:892, 1980.

192. Popp MB, Brennan MF: Metabolic response to trauma and infection. In Fischer JE (ed): Surgical Nutrition. Boston, Little, Brown, 1983, p 492.

193. Lee HA: Fluid balance and parenteral feeding. In Nunn JF, Utting JE, Brown BR (eds): General Anaesthesia. London, Butterworth, 1989, p 1213.

194. Cahill GJ Jr: Starvation in man. N Engl J Med 282:668, 1970.

195. Biebuyck JF: Anaesthesia and hepatic metabolism: Current concepts of carbohydrate homeostasis. Anesthesiology 39:188, 1973.

196. Blackshear PJ, Fang LST, Axelrod L: Treatment of severe lactic acidosis with dichloroacetate. Diabetes Care 5:391, 1982.

197. Blackburn GL, Phinney SD: Lipid metabolism in injury. In Burke JF (ed): Surgical Physiology. Philadelphia, WB Saunders, 1983, p 113.

198. Wolfe RR: Regulation of glucose metabolism. In Burke JF (ed): Surgical Physiology. Philadelphia, WB Saunders, 1983, p 75.

199. Stehle P, Zander J, Mertes N et al: Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. Lancet 1:231, 1989.

200. Vary TC, Siegel JH, Nakatani T et al: A biochemical basis for depressed ketogenesis in sepsis. J Trauma 26:419, 1986.

201. Feldman CH, Hutchinson VE, Pippenger CH et al: Effect of dietary protein and carbohydrate on theophylline metabolism in children. Pediatrics 66:956, 1980.

Chapter 75 - Cardiopulmonary Resuscitation: Basic and Advanced Cardiac Life Support

Roger D. White

INTRODUCTION

Although the history of resuscitation can be dated at least to biblical times, [1] contemporary approaches to cardiopulmonary resuscitation (CPR) go back to 1966, when a National Academy of Sciences National Research Council conference generated consensus standards for the performance of CPR. [2] Since that time, successive conferences have reviewed the practice of CPR in light of available experimental and clinical data and have prepared revisions of previous standards. [3] [4] [5] [6] [7] The most recent such conference was held in 1992, and from it emerged the current guidelines for CPR and emergency cardiac care (ECC). [6] [7] This conference in particular experienced the benefit of considerable information relative to resuscitation, although it was still hampered by a disquieting lack of substantive data. Despite this limitation, both basic life support (BLS) and advanced cardiac life support (ACLS) have been established on credible foundations and have enjoyed widespread acceptance in the ECC community. Indicative of this acceptance is the widespread popularity of the American Heart Association (AHA) BLS and ACLS training programs and related training materials. The intent of this chapter is to review the premise, rationale, and techniques for the performance of both BLS and ACLS in light of current understanding and as incorporated in the 1992 guidelines [6] and AHA textbooks on BLS [8] and ACLS. [9] It is not the intent of this chapter to restate the performance steps and rationale for all the BLS CPR procedures, which can be reviewed in the guidelines and also in the AHA BLS text. [8] Rather, both BLS and ACLS are reviewed within the context of their application by anesthesiologists in operating rooms and intensive care units (ICU) or other in-hospital areas.

BASIC LIFE SUPPORT

It is well accepted that effective CPR is based on the artificial delivery of oxygenated blood to systemic circulatory beds at rates that are sufficient to preserve vital organ function and at the same time providing the physiologic substrate for the rapid return of spontaneous circulation. The mechanisms for provision of this adequate blood flow have undergone intensive scrutiny, and the result has been both insightful and controversial. Both components of CPR (ventilation and perfusion) are reviewed in light of current understanding.

Airway Control and Ventilation

Anesthesiologists know well that ventilation is critical for the restoration of a spontaneous circulation and organ preservation in cardiac arrest (Ch. 39) . The AHA ACLS training program has conveyed effectively this treatment priority. [9] The techniques employed are obviously dependent on the clinical situation. In out-of-hospital or hospital ward settings, initial airway control and ventilation usually are accomplished by mouth-to-mouth or mask-to-mouth techniques. [9] The head tilt-chin lift is recommended for initial airway control. [8] [10] [11] The epiglottis rather than the tongue is the major cause of obstruction of the upper airway in unconscious humans. [12] Because of its ligamentous attachments to the hyoid bone, the epiglottis can be lifted by manual maneuvers that displace the hyoid anteriorly. These observations provide anatomic confirmation of the efficacy of the head tilt-chin lift for opening an obstructed airway. The head tilt-jaw thrust accomplishes the same purpose in restoring airway patency. [13]

In order to minimize high airway pressures and thereby reduce the likelihood of exceeding esophageal opening pressures, [14] emphasis is placed on a slow inspiratory phase

(1.5-2.0 seconds) in the nonintubated patient receiving CPR, and during two-person CPR, a deliberate pause is incorporated after every fifth chest compression in order to provide time for safe and effective ventilation at relatively low inspiratory pressures.

Because anesthesiologists employ advanced life support procedures and devices early in resuscitation, whether in the operating room or elsewhere, these procedures are reviewed here within the context of early control of the airway and ventilation. In the traditional BLS/ACLS format, these procedures are all considered as ACLS techniques and adjuncts.

Endotracheal intubation is the usual and expected standard of airway control in critical care settings. [15] There are alternative devices that may be useful to gain rapid control of the airway and ventilation and to protect the patient at risk of aspiration. These include the esophageal obturator airway, esophageal gastric-tube airway, pharyngotracheal airway, and combination esophageal-tracheal tube. [16] All these devices are classified in the 1992 guidelines as acceptable and possibly helpful. [6] Although they may be helpful as temporizing devices, endotracheal intubation remains the optimal technique for controlling the airway and ventilating the lungs during CPR.

Confirmation of proper placement of an endotracheal tube can be difficult in the patient who has undergone cardiac arrest. Observation of rise and fall of the thorax and auscultation of lung fields in this situation can be misleading. Likewise, because of the very low pulmonary blood flow during CPR, end-tidal carbon dioxide ($E_{T}CO_2$) detection devices may not readily distinguish tracheal from esophageal tube position. For these reasons, esophageal detector devices, based on the description by Wee, [17] have been introduced and advocated for use in emergency situations such as cardiac arrest. Both a syringe and a self-inflating bulb (SIB) have been used. The efficacy of these devices in distinguishing esophageal from tracheal intubation is based on the principle that the trachea remains patent during aspiration of air, whereas the esophagus collapses because of its fibromuscular structure. The effectiveness of the SIB in distinguishing esophageal from tracheal tube position has been documented. [18] [19] [20] It has also been effective in confirming proper position of the esophageal-tracheal tube (Combi-tube, Sheridan Catheter Corp., Argyle, NY). [21] In an emergency patient population, an esophageal detector device as described by Wee was observed to be more accurate than $E_{T}CO_2$ detection because of its greater accuracy in patients in cardiorespiratory arrest. [22] Nevertheless, false-negative results occur with the SIB more frequently in emergency intubations than reported in anesthetized patients undergoing elective procedures. Causes include partial tube obstruction with secretions, atelectasis, bronchospasm, and endobronchial intubation. [23] A high incidence of false-negative results was observed in morbidly obese patients. [24] In these patients, reduced functional residual capacity and large airway collapse secondary to invagination of the membranous posterior tracheal wall with application of subatmospheric pressure with the SIB were identified as the cause of the false-negative results. [24] With these limitations in mind, however, the SIB or syringe-type esophageal detector device should be considered a very useful device in emergency situations such as cardiac arrest.

Despite extensive experience with the laryngeal mask airway (LMA) in fasted patients undergoing general anesthesia, its role during CPR remains somewhat controversial. [25] [26] [27] [28] [29] In anesthetized patients, positive-pressure ventilation with the LMA has been observed to be safe and effective, but concern was expressed that gastric inflation could be a problem in the presence of increased inflation pressures. [30] This, of course, is a common problem in patients who sustain cardiorespiratory arrest, who typically have a full stomach and frequently require high inflation pressures during ventilation. The LMA has been used successfully in arrested patients who have no evidence of regurgitation or aspiration. [31] It may be particularly useful in trauma victims with possible cervical spinal injury in whom direct laryngoscopy and intubation cannot be accomplished; likewise, in arrested patients in whom endotracheal intubation is not possible, the LMA may offer the best available alternative to control the airway and to ventilate the patient. [27]

If these devices and techniques are unsuccessful in securing an airway, an immediate cricothyroidotomy may be necessary. A 12-, 13-, or 14-gauge catheter-over-needle can be inserted quickly into the trachea through the cricothyroid membrane. Equipment permitting transtracheal jet ventilation from a 50-psi oxygen source via such a catheter should be available in the operating room and the ICU. [32] [33] Benumof and Scheller [33] provided specific guidelines for acceptable transtracheal jet ventilation systems. These guidelines should be consulted for the implementation of an effective jet ventilation system in operating rooms or ICUs. Ventilation of the arrested patient can be accomplished with a variety of devices, including anesthesia bags, self-inflating bags, oxygen-powered manually cycled demand valves with peak flow rates of 40 L/min, and time-cycled, constant inspiratory flow rate generators, known as automatic transport ventilators.

Chest Compression

Delivery of oxygenated blood during cardiac arrest and CPR is critically dependent on the effectiveness of chest compressions. The major thrust of current CPR research has been directed toward optimizing blood flow by means of variations in compression techniques. The AHA-recommended chest compression rate is 80 to 100/min with a depth (
1.5-2 inches) sufficient to generate a palpable carotid or femoral pulse. A compression/relaxation ratio of 50:50 is advocated. During one-person CPR, the recommended compression/ ventilation ratio is 15:2, whereas for two-person CPR, it is 5:1. In both instances, the compression rate is 80 to 100/min.

Physiologic Considerations

Since the early 1960s, when CPR became a widespread clinical technique, it has been assumed that blood is ejected as a direct result of actual compression of the heart between the sternum and the vertebral column. This is commonly referred to as the *cardiac pump mechanism.* Echocardiographic and hemodynamic measurements obtained during experimental porcine CPR demonstrated that both mitral and tricuspid valves opened during the upstroke phase of external

Figure 75-1 (Figure Not Available) (A) Schematic representation of the cardiac compression pump. (B) The intrathoracic pressure pump. C, collapse of airways and venous structures; LV, left ventricle; RV, right ventricle. *(Modified from Halperin [274])*

compressions and closed during the downstroke. A reduction in left ventricular area occurred during the downstroke. [34] These observations support direct cardiac compression as the mechanism producing forward blood flow during CPR. Transesophageal echocardiography in arrested humans provides an opportunity to assess changes in cardiac dimensions and valve positions during chest compressions, as well as directional blood flow. Using this method of assessment, it has been confirmed that, at least in some patients, direct cardiac compression is the predominant mechanism of blood flow during external chest compressions. [35] [36] [37] Right and left ventricular compression, mitral valve closure during the downstroke of the compression phase, and opening of the mitral valve during the upstroke or relaxation phase are all consistent with direct cardiac compression, or the cardiac pump mechanism [35] [36] (Fig. 75-1 (Figure Not Available) .A)

The finding that repeated, forceful coughing (cough CPR) can sustain consciousness during ventricular fibrillation (VF) for as long as 100 seconds suggests that mechanisms other than direct compression of the heart may account for forward blood flow during cardiac arrest in some circumstances. [38] Indeed, vigorous coughing produces an arterial pressure pulse associated with forward blood flow and opens the aortic valve during pressure and flow generation. [39] These findings support the proposal that increases in intrathoracic pressure generate forward blood flow. [40] This is commonly referred to as the *thoracic pump mechanism* for movement of blood (Fig. 75-1 (Figure Not Available) B). The increasing intrathoracic pressure during chest compression equalizes intravascular pressures within the thorax. On the venous side, valves and venous collapse at the thoracic inlet limit transmission of retrograde pressure or flow. The arterial system, which is relatively resistant to collapse, transmits pressure and flow into the extrathoracic arterial tree. A peripheral arteriovenous pressure difference is thus established that permits blood to flow forward in the extrathoracic vascular system. Some studies suggest that, during compression or vigorous coughing, the left side of the heart may act as a passive conduit for the transfer of pulmonary venous blood out into the peripheral arterial circulation. During compression, blood flows from the lungs through the left ventricle and toward the periphery. The pulmonary valve is closed and the mitral and aortic valves are open during periods of high intrathoracic pressure when the chest is compressed. [41]

Interposed abdominal counterpulsation (IAC) is a form of CPR in which the abdomen is compressed during the upstroke of the chest compression phase in an attempt to sustain aortic diastolic pressure and thus to improve coronary perfusion pressure, a critical determinant of successful restoration of a spontaneous circulation. There is experimental evidence that carotid blood flow [42] and end-diastolic arteriovenous pressure differences, [43] indexes of coronary perfusion pressure, are increased with this IAC CPR. A randomized controlled trial comparing IAC CPR with standard CPR in humans in asystolic and electromechanical dissociation arrest indicated that IAC CPR conferred a significantly higher rate of return of spontaneous circulation, but no patient in either the IAC CPR group or the standard CPR group survived to hospital discharge. [44]

Active compression-decompression (ACD) CPR accomplishes compression and active decompression of the thorax by means of a device containing a suction header, bellows, and a compression area within the bellows. Preliminary data in arrested humans comparing ACD CPR with standard CPR provided evidence of hemodynamic benefit, with higher systolic arterial pressure and $E_T CO_2$ concentrations

and echocardiographic demonstration of increased velocity time integral, an analogue of cardiac output. Transesophageal echocardiographic imaging during ACD CPR disclosed that the atrioventricular (AV) valves were closed during chest compression but open during active decompression. [45] During the compression phase, direct compression of right and left ventricles occurs, with ejection of blood into the pulmonary artery and aorta, whereas ventricular filling from right and left atria occurs during the decompression, or relaxation, phase. [46] In a study of 16 patients with out-of-hospital cardiac arrest, peak $E_T CO_2$ pressure was significantly higher during ACD CPR compared with that during standard manual CPR (27.6 ± 3 mm Hg versus 15.6 ± 2.2 mm Hg). [47] This finding was interpreted to reflect a higher cardiac output with ACD CPR. In a porcine model of VF arrest, intermittent impedance to inspiratory gas flow during ACD CPR improved coronary perfusion pressure and blood flow to brain and heart. [48] This finding was attributed to enhanced equilibration of the negative intrathoracic pressure generated by active chest wall expansion, with increased venous return the result.

In humans studied during implantation of cardioverterdefibrillators, ACD CPR increased systemic arterial pressure, coronary perfusion pressure, and minute ventilation when compared with standard CPR. [49] Although these observations provided clinical support for experimental studies, indicating improved hemodynamic (and perhaps ventilatory) function with ACD CPR compared with standard CPR, still lacking was evidence of patient outcome benefit. Several studies have been undertaken to address this critical question. In one such study of patients experiencing inhospital cardiac arrest, initial return of spontaneous circulation was higher with ACD CPR compared with standard manual CPR, but there was no statistically significant improvement in survival to hospital discharge. [50]

Several studies of ACD CPR have been carried out in patients with out-of-hospital cardiac arrest. [51] [52] [53] None of these has demonstrated an improvement in patient outcome in terms of hospital discharge when ACD CPR was compared with standard CPR. The largest and most recent study comparing ACD CPR with standard CPR includes 1,784 adults with in-hospital and prehospital cardiac arrest. This study, like its predecessors, concluded that ACD CPR does not improve survival or neurologic outcomes. [54] Thus, despite the earlier experimental and clinical evidence that ACD CPR may confer benefit to victims of cardiac arrest by virtue of enhanced hemodynamic variables, no evidence to date supports the hypothesis that ACD CPR improves outcome from cardiac arrest in humans when compared with standard manual CPR.

Circumferential compression of the chest employing a pneumatic vest (vest CPR) has been described as a mechanism for generating intrathoracic pressure fluctuations and thereby improving blood flow [55] [56] (Fig. 75-2) (Figure Not Available) . The increased intrathoracic pressure fluctuations are apparently mediated through increased chest compression force and increased airway collapse during chest compression, trapping air in the lungs. The latter may also increase the effectiveness of transmission of vest pressure to the intrathoracic space. The increased intrathoracic pressure with vest CPR is the presumed major mechanism of hemodynamic benefit. As with ACD CPR, vest CPR has been shown in a preliminary study to increase both aortic and coronary perfusion pressures, [57] but no data are yet available relative to its impact on survival, the ultimate determinant of benefit.

Much more information is needed before any of these observations can be extended to modification of currently recommended CPR practice as described earlier. It is likely that both direct cardiac compression and intrathoracic pressure changes contribute to forward blood flow and that they are not mutually exclusive. In some patients, the cardiac pump may be primarily operative, whereas in others, the thoracic pump may predominate. [58] [59] Continued transesophageal echocardiographic observations in human victims of cardiac arrest may provide the insight into definition of which mechanism of blood flow is functional in which patients. Most important, until the clinical relevance of any of these observations is established, standard CPR techniques as described earlier are recommended. What is certain is that CPR, regardless of mechanism of blood flow and technique, is only a temporizing procedure in need of rapid supplementation with ACLS, most critically rapid defibrillation of the fibrillating heart.

Monitoring CPR Performance

Until recently, palpation of the carotid or femoral pulse and observation of pupillary size were the standard and very indirect measures for assessing the apparent adequacy of CPR. Obviously, a palpable large-artery pulse indicates only the transmission of a pressure wave into the arterial tree during chest compression and provides no objective evidence of the effectiveness of cardiac output. Initial pupillary size and changes during CPR are of some prognostic value. [60] Persistently contracted or initially dilated but subsequently contracting pupils are associated with a greater likelihood of successful resuscitation and neurologic recovery than

persistently dilated or subsequently dilating pupils. [61]

As already discussed, monitoring the systemic arterial pressure directly, as can usually be done during in-hospital CPR, is helpful. [62] Aortic diastolic pressure in particular, as an index of coronary perfusion pressure, should be monitored whenever possible and optimized with appropriate changes in manual compression technique and with early and repeated injection of epinephrine prior to restoration of a spontaneous circulation.

In 1978 Kalenda [63] described use of the capnogram as a guide to the effectiveness of external chest compressions. He demonstrated the value of $E_T CO_2$ monitoring in three patients in cardiac arrest and confirmed changes in $E_T CO_2$ with changes in external chest compression technique. He also observed a rapid increase in $E_T CO_2$ with restoration of a spontaneous circulation. He proposed that when ventilation is constant, as during controlled mechanical ventilation, "the expired CO_2 is a precise and continuous mirror of lung perfusion and hence of cardiac output." [63]

Despite the potential clinical importance of Kalenda's well-documented observations and conclusions, it was several years before $E_T CO_2$ monitoring during cardiac arrest and CPR was explored further. In 1984, using a porcine model of cardiac arrest, Grundler et al [64] demonstrated the rapid decrease in $E_T CO_2$ with onset of arrest and its immediate increase with resuscitation. Based on these preliminary

Figure 75-2 (Figure Not Available) A comparison of the thoracic vest system (A) for cardiopulmonary resuscitation (vest CPR) with standard manual CPR (B). The vest contains a bladder that is inflated and deflated by the pneumatic system. The lower panels show schematic representations of transverse sections of the midthorax during vest CPR and manual CPR. The thoracic size during chest relaxation is shown by the solid lines. The arrows indicate force applied to the thorax during chest compression. With vest inflation, there is a relatively uniform decrease in the dimensions of the thorax. With manual CPR, the sternum is displaced during compression (arrow) and the lateral thorax can bulge, thereby increasing thoracic volume and reducing the intrathoracic pressure generated during compression. *(Modified from Halperin et al. [57] Copyright 1993 Massachusetts Medical Society. All rights reserved.)*

experimental observations, this group suggested that $E_T CO_2$ monitoring may be a relatively simple and noninvasive guide to advanced life support interventions during CPR. [64] [65] Severe reductions in pulmonary blood flow during cardiac arrest and CPR, and therefore an acute failure in CO_2 delivery to the lungs, explained the observed very low $E_T CO_2$ and the increased venous CO_2 pressure ($P CO_2$) (see the discussion of sodium bicarbonate later). [66] Subsequent studies in dogs provided confirmation of this possible utility of $E_T CO_2$ in that expired $P CO_2$ correlated very closely with coronary perfusion pressure, which itself was shown to be a determinant of survival from cardiac arrest in this model. [67] [68] In a porcine model of VF, onset of VF was associated with a rapid decline in $E_T CO_2$ from a mean (±SEM) of 4.0 ± 0.2 percent to less than 0.7 ± 0.2 percent. [69] With external chest compression and constant-volume mechanical ventilation, $E_T CO_2$ increased to 1.9 ± 0.3 percent, with an immediate increase to 4.9 ± 0.3 percent after successful defibrillation following 12 minutes of CPR. There was a close correlation between changes in cardiac output and $E_T CO_2$ during both closed-chest and open-chest CPR. [69]

$E_T CO_2$ pressure monitoring has been reported in arrested humans undergoing CPR. [70] [71] [72] [73] In a study of ten patients in whom spontaneous circulation returned, the $E_T CO_2$ increased immediately on restoration of a spontaneous circulation, from a mean (±SD) of 1.7 ± 0.6 to 4.6 ± 1.4 percent. [70] The rapid increase in $E_T CO_2$ was often the first clinical evidence of resumption of spontaneous circulation.

In ten critically ill patients, nine of whom were in septic or cardiogenic shock at the onset of cardiac arrest, the $E_T CO_2$ decreased from a mean (±SD) of 1.4 ± 0.9 to 0.4 ± 0.4 percent shortly after the onset of cardiac arrest. [72] The very low prearrest value is indicative of a low cardiac output and therefore low pulmonary blood flow. During external chest compressions, this value increased to 1.0 ± 0.5 percent. In seven patients in whom circulation was restored, the $E_T CO_2$ rapidly increased from 1.3 ± 0.5 to 3.7 ± 2.1 percent, then it declined to a stable volume of 2.4 ± 1.8 percent 4 minutes after resumption of a spontaneous circulation. In patients in whom resuscitation failed to restore spontaneous circulation, the $E_T CO_2$ remained at 0.7 ± 0.4 percent. [72]

There is increasing evidence that $E_T CO_2$ measurements obtained during cardiac arrest and CPR may have predictive value relative to the likelihood that spontaneous circulation will be restored. [71] [73] [74] In one study, patients who later developed a pulse had a mean $E_T CO_2$ of 19 ± 14 (SD) mm Hg at the beginning of resuscitation, whereas those who never regained a spontaneous pulse had a mean $E_T CO_2$ of 5 ± 4 mm Hg ($P < .0001$). [73] Other investigations have observed similar significant differences in $E_T CO_2$ during CPR between those patients who develop spontaneous circulation and those who do not. [74] [75] [76] Two of these studies were conducted in patients in out-of-hospital cardiac arrest. [75] [76] The $E_T CO_2$ was significantly higher during CPR in these patients who subsequently regained spontaneous circulation than in those who did not. For example, 1 minute after initiation of measurement, the $E_T CO_2$ was 23.0 ± 17.4 mm Hg in those who regained pulses and 13.2 ± 14.7 mm Hg in those who did not ($P = .0002$) (Table 75-1) (Table Not Available) . Differences of similar magnitude were noted at 2 minutes as well as with the maximum value observed during the resuscitation. [75] Although more such data are needed to quantitate the predictive power of these differences, it seems certain that $E_T CO_2$ measurements during cardiac arrest and CPR will become an objective index to predict the likelihood that persistent resuscitative efforts will result in restoration of spontaneous circulation.

The major determinants of $E_T CO_2$ are CO_2 production, alveolar ventilation, and pulmonary blood flow. [77] [78] [79] [80] In the presence of constant-volume ventilation and apparently unchanged CO_2 production immediately after cardiac arrest, the changes in $E_T CO_2$ observed both experimentally and clinically during cardiac arrest and CPR and resumption of spontaneous circulatory function indicate that $E_T CO_2$ reflects pulmonary blood flow and therefore cardiac output. [70] [71] [72] [73] [74] Monitoring of both systemic arterial pressure via arterial catheter and $E_T CO_2$ with controlled ventilation should provide optimal hemodynamic assessment of the adequacy of the resuscitative effort and response to interventions such as changes in depth, rate, and location of manual chest compressions, as well as response to drugs such as epinephrine. [62]

TABLE 75-1 -- End-Tidal Carbon Dioxide in Cardiopulmonary Resuscitation

(Not Available)

From Asplin and White [75]

ADVANCED CARDIAC LIFE SUPPORT

Although it is commonly understood and accepted that all physicians, regardless of specialty, should be able to perform CPR, it must be emphasized that CPR almost invariably necessitates rapid interventional follow-up care with ACLS procedures. It is essential that anesthesiologists be capable of rendering such follow-up definitive intervention, whether in the operating room, ICU, emergency department, delivery room, or hospital ward. In the operating room, cardiac arrest is rare; during a 15-year period, a cardiac arrest incidence of 1.7 per 10,000 anesthetic regimens was identified. [81] As Vandam [82] stated in an accompanying editorial, the fact that cardiac arrest occurs at all is terrifying. [82] The somewhat reassuring observation that intraoperative cardiac arrest is a rare occurrence does not dismiss the need for anesthesiologists to be thoroughly acquainted with ACLS equipment and interventions, because when these methods are needed, they must be executed skillfully and decisively. The need for skillful and knowledgeable ACLS intervention in intraoperative cardiac arrest is recognized. [83] Failure to intervene rapidly with ACLS pharmacologic therapy was identified as a major cause of poor outcome in these intraoperative cardiac arrests. [83] [84] It is evident that ACLS is a body of knowledge and skill with which anesthesiologists must be thoroughly familiar.

In a study using a computer program that simulates critical patient incidents such as cardiac arrest, it was observed that only 30 percent of participants, consisting of anesthesiology residents, faculty, and private practitioners, managed a simulated cardiac arrest in accordance with AHA ACLS guidelines. [85] Time since the last ACLS training was noted to be an important predictor of proper management of simulated cardiac arrest. Of those trained in ACLS within 6 months preceding the assessment, 71 percent managed simulated cardiac arrests successfully, whereas successful management decreased to about 30 percent by those whose ACLS training occurred from 6 months to 2 years earlier. No participant who had been trained in ACLS longer than 2 years prior to the assessment used ACLS guidelines correctly in simulated cardiac arrest management. [85] This experience supports the position that some form of training and periodic retraining in ACLS are necessary to enable anesthesiologists, as well as other physicians, to maintain the level of knowledge and skill essential for management of cardiorespiratory arrest in accord with contemporary principles as incorporated in the ACLS training program. Because advanced airway control and ventilation have already been discussed, this section presents the remaining components of ACLS as they directly pertain to anesthesiologic practice.

Monitoring and Arrhythmia Recognition

Prompt recognition and treatment of potentially life-threatening (prearrest) cardiac arrhythmias are essential components of ACLS (also see Ch. 32). [86] Early recognition and immediate pharmacologic intervention frequently can prevent the onset of fatal arrhythmias necessitating the full application of BLS and ACLS. In this context, supraventricular arrhythmias that may cause hemodynamic compromise are discussed first, followed by recognition and management of those that are ventricular in origin.

Supraventricular Bradyarrhythmia

Supraventricular bradyarrhythmias may be sinus or junctional in origin, or they may be caused by second-degree (types I and II) or third-degree AV block. Sinus (or junctional) bradycardia and type I (AV nodal) second-degree AV block are usually manifestations of increased vagal tone. Sinus bradycardia and type I second-degree AV block (Wenckebach phenomenon) may be observed during high-dose narcotic anesthesia. During spinal anesthesia, reduced venous return and unopposed vagal tone may produce bradycardia and hypotension of sufficient severity to progress to cardiac arrest. [87] Treatment is indicated whenever the bradycardia, regardless of type, leads to a significant fall in systemic arterial pressure, produces clinical signs of reduced cardiac output (or a fall in measured output), or is accompanied by

ventricular ectopic depolarizations. Any of these signs should be taken as evidence of hemodynamic or electrophysiologic deterioration with the propensity to progress to lethal arrhythmias, either bradyasystole or VF. Initial treatment is with atropine, 0.5 to 1.0 mg intravenously and repeated as needed at 3- to 5-minute intervals to 0.04 mg/kg. [88] If this treatment is ineffective in producing an increase in heart rate and in hemodynamic (increased systemic pressure and/or cardiac output) or electrophysiologic (elimination of ventricular ectopy) improvement, alternatives include external or transvenous pacing or, during spinal anesthesia, small (0.2 mg) intravenous doses of epinephrine. [89] The availability of intraoperative cardiac pacing equipment and techniques has diminished the need for isoproterenol for treatment of brady-arrhythmias. The increase in myocardial oxygen demand imposed by isoproterenol makes its use potentially hazardous in the presence of acute myocardial ischemia. If transvenous or transcutaneous pacing is not available to treat atropine-refractory bradyarrhythmias, an infusion of dopamine (5-20 mg/kg/min) or epinephrine (2-10 mg/min) would be a better choice than isoproterenol.

Pulmonary artery catheters that permit the insertion of ventricular or atrial pacing probes are available. If such a catheter is in place, emergency pacing can be instituted rapidly. Pacing probes can be advanced into position quickly to permit rapid control of cardiac rate via ventricular, atrial, or AV sequential pacing.

External transcutaneous pacing can be used rapidly to treat atropine-resistant symptomatic bradyarrhythmias. The safety and effectiveness of these devices have been described, as has favorable intraoperative experience. [90] [91] Their greatest therapeutic benefit is likely to be in atropine-resistant bradyarrhythmias, and these devices should be available for emergency use along with a defibrillator. External pacing has not yet been shown to be useful in bradyasystolic cardiac arrest.

Transesophageal atrial pacing has been shown to be effective in treating intraoperative supraventricular bradyarrhythmias such as sinus or junctional bradycardia. [92] [93] In its present configuration, it cannot be used to pace the ventricles, and therefore it is not useful in the management of any form of bradycardia caused by AV conduction disturbances. An esophageal pacing probe modified to enable ventricular pacing has been described, but it is not available for clinical use. [94]

Supraventricular Tachyarrhythmia

Supraventricular tachyarrhythmias include atrial flutter, atrial fibrillation, AV junctional tachycardia, multifocal atrial tachycardia, paroxysmal reentrant tachycardias, and other much less frequent arrhythmias. Paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation (or flutter) with rapid ventricular rates, and multifocal atrial tachycardia are discussed here because not only can they produce hemodynamic compromise, but also they can present diagnostic and therapeutic challenges.

An example of PSVT is shown in Figure 75-3 . If such a tachyarrhythmia produces hemodynamic deterioration, cardioversion is the treatment of choice, beginning at 50 joules (J) and progressing to 100, 200, 300, and 360 J if needed. If the patient is hemodynamically stable, vagal maneuvers can be tried (e.g., Valsalva maneuver in awake patients). Adenosine is the drug of choice for termination of such arrhythmias, for which it is highly effective. [95] [96] [97] The drug is also of diagnostic usefulness in revealing the underlying mechanism in tachyarrhythmias of uncertain origin by inducing transient block of AV nodal conduction [98] [99] [100] (Fig. 75-4) . Adenosine can be used initially in a dose of 6 mg given rapidly through an antecubital venous catheter; if necessary, a second dose of 12 mg can be given in 1 to 2 minutes. If a central venous catheter is used, these doses can be reduced to 3 and 6 mg, respectively. [101] Because of rapid cellular uptake and metabolism, adenosine must be injected rapidly into a venous catheter proximal enough to the heart to ensure delivery of a sufficient concentration of the drug at the AV node to

induce AV nodal conduction block. If the drug is injected more distally and slowly (e.g., into a small-bore dorsal hand vein catheter), not only may therapeutic failure result, but also transient acceleration of the tachyarrhythmia may occur [102] (Fig. 75-5) (Figure Not Available) . This paradoxic acceleration of the rate is a manifestation of the increase in sympathetic venous traffic induced by adenosine in the presence of inadequate AV nodal blockade. Likewise, conversion of 2:1 to 1:1 conduction in atrial flutter has been observed. [103] [104] [105] This adverse effect indicates that an attempt to establish the diagnosis of atrial flutter should be made electrocardiographically, using vagal maneuvers if necessary to unmask the flutter waves. Rate acceleration also has been observed after adenosine administration in patients with atrial fibrillation and preexcitation (Wolff-Parkinson-White syndrome). [106] As with verapamil in this setting, the rate acceleration is a result of the AV nodal block with diversion of fibrillation wavefronts through the accessory connection. Even though the short half-life of adenosine may reduce this hazard, it seems prudent to avoid adenosine as well as other AV nodal-blocking drugs in patients with atrial fibrillation and preexcitation.

Adenosine induces slowing of AV nodal conduction and prolongation of refractoriness and therefore is very effective in terminating PSVT, the most common cause of which is reentry within the AV node. [107] [108] [109] Its very short half-life

Figure 75-3 Paroxysmal supraventricular tachycardia. The rate is 250 beats/min with no clearly identifiable P waves.

Figure 75-4 A supraventricular tachycardia at a rate of 180 beats/min is present; the origin of the tachycardia is not evident (A). Following injection of 6 mg adenosine, atrial flutter waves are clearly visible, establishing the diagnosis (B).

Figure 75-5 (Figure Not Available) (A) Atrial fibrillation with a ventricular response of 190 beats/min. (B) Following injection of 6 mg adenosine, the ventricular response increased to 240 beats/min. *(From White [102])*

(<5 seconds) is both advantageous and disadvantageous: side effects such as flushing, dyspnea, and chest pain are short-lived, but the tachyarrhythmia may recur, necessitating use of another drug. The AV nodal-blocking action of adenosine is antagonized by theophylline or related methylxanthines and is potentiated by dipyridamole and carbamazepine [95] [96] [97] [110] [111] (Fig. 75-6) (Figure Not Available) . A suggested scheme for the use of adenosine, including dosage adjustments, is shown in Table 75-2 .

Bronchospasm also has been described after injection of adenosine, including intraoperatively. [112] [113] [114] [115] This complication has occurred in patients with bronchial asthma or chronic obstructive pulmonary disease (COPD). The mechanism is unknown, but it may result from stimulation of bronchial smooth muscle adenosine receptors or stimulation of mast cell-derived mediators of bronchoconstriction. Aminophylline, an adenosine receptor antagonist, has been used successfully intraoperatively to treat adenosineinduced bronchospasm. [115] In light of this experience, adenosine should not be used, or used with caution, in patients with a history of bronchial asthma or COPD with a bronchospastic component.

If the PSVT does not respond to adenosine, or if it recurs, verapamil is the drug of choice. A dose of 5 mg produces a more sustained block of AV nodal conduction. Verapamil can also be used to slow the ventricular response in atrial fibrillation or flutter. [116] However, it should not be used in patients with Wolff-Parkinson-White syndrome who develop atrial fibrillation or flutter. In this setting, verapamil-induced increases in conduction over the accessory pathway may produce alarming acceleration of the ventricular rate or VF. [117] [118] [119] If atrial flutter or fibrillation results in hemodynamic deterioration because of the rapid ventricular response, cardioversion is the treatment of choice. Atrial flutter

Figure 75-6 (Figure Not Available) The cardiac adenosine system is composed of three components: (1) formation; (2) receptor complex effects; and (3) degradation. (1) Adenosine (ADO) can be formed intracellularly via the adenosine triphosphate (ATP) or *S*-adenosylhomocysteine (SAH) pathway, or extracellularly via breakdown of adenosine nucleotides. (2) The adenosine receptor (ADO-R) is coupled to ion channels via the guanine binding regulatory proteins (G i). Theophylline (THEO) derivatives act as competitive antagonists for the adenosine receptors. (3) ADO can be transported into the cell and then degraded via deamination to inosine or phosphorylated to adenosine monophosphate (AMP). Dipyridamole can block the cellular uptake of ADO, thus prolonging its effect. ADP, adenosine diphosphate; cAMP, cyclic AMP; GTP, guanosine triphosphate. *(Modified from Bertolet and Hill [275])*

TABLE 75-2 -- Administration of Adenosine

Peripheral (antecubital): 6 mg, then 12 mg if needed
Central: 3 mg, then 6 mg if needed
If taking theophylline-containing drugs: 9 mg peripherally, 6 mg centrally
If taking dipyridamole: 2 mg peripherally, 1 mg centrally
Use with caution in asthmatic patients
Caution in patients taking carbamazepine

can be terminated with low-energy synchronized shocks (e.g., 25-50 J).

Atrial fibrillation or atrial flutter with rapid ventricular response can cause rate-related hemodynamic compromise, manifest perioperatively as hypotension and/or decreased cardiac output. In hemodynamically unstable patients, cardioversion should be used. Recent-onset atrial flutter is typically very sensitive to low-energy shocks (e.g., 50 J) (Fig. 75-7) (Figure Not Available) . For atrial fibrillation, the initial energy dose should be 100 J and increased as needed to 200, 300, and 360 J. Atrial flutter also can be terminated by overdrive pacing using external generators with this capability.

In hemodynamically stable patients with rapid ventricular rates secondary to atrial fibrillation or flutter, treatment is pharmacologic. With recent onset of these tachyarrhythmias (<45 days), ibutilide given intravenously has been successful in restoring sinus rhythm. [120] Ibutilide is a recently approved class III antiarrhythmic drug that prolongs action potential duration and effective refractory period without effects on action potential upstroke. The dose is 1 mg over 10 minutes. A second dose can be given 10 minutes after the first, if necessary. Conversion of atrial flutter is more frequent in atrial flutter than in atrial fibrillation (63% versus 31%), and more frequent in atrial fibrillation with shorter arrhythmia duration. [120] Prolongation of the QT interval reflects the pharmacologic action of the drug; polymorphic ventricular tachycardia accompanied by increases in the QT interval has been reported in 8.3 percent of patients receiving ibutilide, so clinicians should be prepared to manage this arrhythmia [120] (see the discussion of ventricular tachyarrhythmias).

Alternative options include diltiazem or verapamil to control ventricular rate or digoxin for rate control and procainamide for conversion of the tachyarrhythmias. Diltiazem is given as a loading dose of 0.25 mg/kg over 2 minutes, followed, if needed, in 10 to 15 minutes by 0.35 mg/kg. An infusion at a rate of 10 mg/h can be used to maintain rate control. If verapamil is used, 5 mg can be given initially, then 7.5 to 10 mg in 15 to 30 minutes if needed. Rate control also can be achieved with beta blocking drugs such as esmolol or propranolol if there is no contraindication to their use.

Multifocal (multiform) atrial tachycardia (MAT) is a quite common tachyarrhythmia often misdiagnosed as atrial fibrillation. [121] [122] [123] It is usually described as occurring in patients with COPD, especially during exacerbations necessitating ICU management. However, it occurs in other settings as well, such as hypokalemia, catecholamine administration, and acute myocardial ischemia. [124] [125] MAT is diagnosed by observing the presence of at least three morphologically different P waves in the same lead with a rate greater than 100 beats/min (Fig. 75-8) . Misdiagnosis as atrial fibrillation is a concern because it can lead to ineffective and even hazardous therapy. Digitalization and cardioversion, both useful in management of patients in atrial fibrillation, are ineffective in MAT. Digitalis toxicity or repeated and

futile attempts at cardioversion can follow misdiagnosis. Verapamil has been useful in rate control and in some cases in termination of MAT while the underlying cause, such as hypoxia or hypokalemia, is corrected if possible. [126] [127]

Ventricular Bradyarrhythmia

Within the setting of ECC, the bradyarrhythmia arising within the ventricles in need of urgent treatment is complete heart block with a very slow idioventricular escape rhythm (e.g., 15-30 beats/min) (Fig. 75-9) . In this situation, atropine can be tried, but the treatment of choice is external or transvenous pacing as soon as it can be accomplished. If an external pacemaker is available, pacing can be instituted quickly.

Figure 75-7 (Figure Not Available) Electrical cardioversion algorithm (with the patient not in cardiac arrest). *(Modified from American Heart Association, [6] copyright 1992, American Medical Association)*

Ventricular Tachyarrhythmia

In this category of potentially life-threatening, and sometimes prearrest, arrhythmias, ventricular tachycardia (VT) (Fig. 75-10) is commonly in need of urgent intervention. VT that produces cardiac arrest (pulseless VT) is discussed with VF. Treatable causes of VT should always be sought before or during pharmacologic or electrical interventions. Hypoxemia, hypercarbia, hypokalemia and/or hypomagnesemia, digitalis toxicity, and acid-base derangements are obvious considerations.

Treatment of VT is dependent on the degree of hemodynamic compromise induced by the tachycardia. If a patient remains stable, lidocaine is the drug of choice. [128] It is given initially in a dose of 1.0 to 1.5 mg/kg and is repeated in a dose of 0.5 to 0.75 mg/kg every 5 to 10 minutes, until the arrhythmia is suppressed or a total of 3 mg/kg has been given. If this treatment is ineffective, procainamide can be administered in a dose of 20 to 30 mg/min until the tachycardia is controlled or a total of 17 mg/kg has been injected. With constant monitoring of systemic arterial pressure and the electrocardiogram (ECG) for QRS widening more than 50 percent of control width as an end point, procainamide can be used very safely and effectively. If these measures fail to control the arrhythmia, bretylium can be administered in a dose of 5 to 10 mg/kg over 8 to 10 minutes. [128] If a conversion is effected with this drug, an infusion at a rate of 1 to 2 mg/min can be started.

For VT refractory to this approach, intravenous amiodarone may be effective, providing a new therapeutic option.

Figure 75-8 Multifocal atrial tachycardia. P waves with several different morphologic identities are evident.

Figure 75-9 Slow (14 beats/min) idioventricular escape rhythm in a patient with carotid sinus hypersensitivity. External or transvenous pacing is the treatment of choice for bradyarrhythmias such as this.

Figure 75-10 Ventricular tachycardia. The rate is 280 beats/min, QRS width is 160 ms, and three consecutive capture/fusion beats are seen.

[129] [130] [131] [132] The mechanism of action is unclear, but it probably includes antisympathetic and calcium channel blocking actions. It exerts antiarrhythmic action within an hour of intravenous administration. The initial dose is 150 mg in 100 mL dextrose in water given over 10 minutes, followed by a loading infusion of 1 mg/min for 6 hours. The loading infusion is prepared by adding 100 mg to 500 mL dextrose in water. If breakthrough VT/VF occurs, supplemental 150-mg infusions over 10 minutes can be given. Because the intravenous form of amiodarone has only recently become available, it is not included in the AHA ACLS algorithms.

In unstable patients (e.g., in the presence of systemic hypotension, pulmonary edema, or clinical or ECG signs of acute ischemia or infarction), cardioversion is the treatment of choice, with energy doses of 100, 200, 300, and 360 J in progressive increments as needed. An algorithm for cardioversion of a variety of tachyarrhythmias, including VT, is shown in Figure 75-7 (Figure Not Available) .

There is an atypical form of VT known as *torsades de pointes* ("twisting of the points") originally described in 1966, characterized by a twisting of the QRS axis around the baseline and a polymorphic appearance. [133] [134] [135] [136] [137] The underlying electrophysiologic derangement in this arrhythmia is a marked and nonuniform delay in repolarization, manifested as a prolonged QT interval on the ECG. It typically begins with a characteristic long-short initiating sequence (Fig. 75-11) . It can be induced by drugs such as quinidine, procainamide, disopyramide, and phenothiazines and also by bradycardia, hypokalemia, hypomagnesemia, or acute ischemia or infarction. [138] Even though amiodarone produces marked prolongation of repolarization, it rarely causes torsades de pointes. This may be because the drug-induced prolonged repolarization is uniform (nondispersed), in contrast to the repolarization abnormality induced by other drugs. [139] Closely related to torsades de pointes is polymorphic ventricular tachycardia (PVT) (Fig. 75-12) (Figure Not Available) . The description of the tachycardia as PVT rather than as torsades de pointes implies that there is no evident cause of prolonged repolarization and the QT interval is not prolonged. [140] [141] [142] [143] Because both PVT and torsades de pointes can be life-threatening, a correct diagnosis is required. The critical therapeutic distinction is based on the presence or absence of QT-interval prolongation. If QT prolongation is present, therapy is directed toward shortening the repolarization time (after withdrawal of offending drugs listed earlier or correction of abnormalities such as hypokalemia). In the past, drugs such as isoproterenol were used for this purpose, but definitive short-term therapy is overdrive ventricular

Figure 75-11 Torsades de pointes ventricular tachycardia. The Qtc interval is 450 mg during the sinus rhythm preceding the tachycardia. This arrhythmia occurred in a patient expressing an acute myocardial infarction.

Figure 75-12 (Figure Not Available) Polymorphic ventricular tachycardia. The QRS complexes have varying morphology, but without the "twisting of the points" torsades morphology seen in Figure 75-11 . The tachycardia terminated spontaneously. *(From White and Wood [143])*

Figure 75-13 (Figure Not Available) Tachycardia algorithm. *(Modified from the American Heart Association, [6] copyright 1992, American Medical Association)*

or atrial pacing, preferably the latter, if AV conduction is intact. Magnesium sulfate has also been used successfully in the treatment of torsades de pointes, and some clinicians recommend it as the first line of emergency treatment. [144] [145] [146] [147] If PVT is present (i.e., without evident QT prolongation), standard antiarrhythmic therapy as outlined earlier for VT can be tried, although magnesium sulfate should be considered early in the treatment of this form of PVT as well, particularly if torsades de pointes is suspected by history but QT prolongation cannot be confirmed on the ECG. In fact, a 12-lead ECG is often needed to identify QT lengthening. If hemodynamic deterioration occurs with PVT, defibrillation should be used as initial treatment.

An algorithm for the treatment of tachyarrhythmias, encompassing those of supraventricular and ventricular origin, is shown in Figure 75-13 (Figure Not Available) . This algorithm makes provision for intervention in a patient with a wide-QRS complex tachycardia of indeterminate origin, beginning with lidocaine, then, if unresponsive, moving to adenosine for either therapeutic or diagnostic purposes. Catecholaminemediated VT sensitive to adenosine is well documented, [148] [149] [150] including an intraoperative event [151] (Fig. 75-14) (Figure Not Available) . If a wide-QRS complex tachycardia is accompanied by clinical evidence of catecholamine

excess, adenosine should be considered as a possibly therapeutic drug after a trial of lidocaine, as recommended in the section of the tachycardia algorithm for wide-complex tachycardia of unknown origin (see Fig. 75-13 (Figure Not Available) .)

Verapamil should be avoided in any wide-QRS complex tachycardia, unless it is known with certainty that the tachycardia is supraventricular in origin; if VT is present, verapamil can induce severe hypotension or cardiovascular

Figure 75-14 (Figure Not Available) Wide-QRS complex tachycardia at a rate of 160/min. (A) Precordial lead 5; (B) lead 2. Atrioventricular dissociation is present, evident by the P wave preceding the third QRS complex, confirming this to be ventricular tachycardia. *(From Wagner et al [151])*

Figure 75-15 Adverse response to verapamil. Tachycardia thought to be atrial flutter was present initially (A). After injection of 5 mg verapamil, the rate accelerated, and the patient became unresponsive, necessitating cardioversion (B). The first rhythm was ventricular tachycardia. Cardiovascular collapse is a potential complication of verapamil injection when the tachycardia is ventricular in origin.

collapse in as many as 87 percent of such misdiagnosed episodes (Fig. 75-15) . Any wide-complex tachycardia of uncertain origin (despite careful scrutiny of the ECG for all helpful clues) should be assumed to be VT and treated accordingly. If the patient is hemodynamically deteriorating, cardioversion should be used initially, without a prior trial of drug therapy.

Management of Cardiac Arrest

This section reviews the interventions, both electrical and pharmacologic, utilized in the treatment of the various forms of cardiorespiratory arrest. Included is a discussion of the major beneficial and adverse actions of the drugs used in ACLS. Clinical applications of some of these drugs have already been presented in the review of recognition and management of "prearrest" or potentially life-threatening events.

Pulseless Ventricular Tachycardia or Ventricular Fibrillation

For therapeutic purposes, it is reasonable to consider pulseless VT and VF as the same entity in need of the same interventions. It is fortunate that this is the most common form of cardiac arrest because it is the most treatable one, and it is the arrhythmia that yields the greatest likelihood of immediate and long-term survival, both in hospital and out of hospital. [152] This finding has accelerated the extension of early intervention in VF to levels of out-of-hospital emergency care lower than emergency medical technicianparamedics to basic emergency medical technicians and even first responders with minimal training. [153] This likelihood of significant salvage by early defibrillation also accounts for the growing interest in, and application of, automated external defibrillators [6] and the rapid increase in implantation of implantable cardioverter-defibrillators [154] [155] [156] [157] [158] [159] in patients at risk of cardiac arrest from VF. It is obvious that physicians involved in caring for patients in hospital are assumed to know how to intervene in the event of cardiac arrest, how to operate defibrillators, and how to administer drugs rationally, especially in the presence of VT/VF, when survival is likely with rapid and correct treatment.

Despite rare reports of apparently spontaneous termination of VF, the required and definitive intervention is rapid defibrillation. Two practical and important considerations enter into every attempt to defibrillate patients in VF. The first is the energy output of the defibrillator. [160] Termination of VF is critically dependent on the amount of energy available from a defibrillator, and therefore it is necessary that output be checked at regular intervals. Guidelines for proper maintenance of defibrillators are available. [161]

The second practical consideration is the resistance to current flow during shock delivery. Current flow is inversely related to resistance; excessive resistance because of poor technique can impede the transthoracic flow of adequate current to permit defibrillation to occur. [160] The major operator-controllable variables that can reduce impedance during defibrillation are proper electrode position, firm pressure against each hand-held paddle, and an optimal electrode-chest wall coupling medium such as electrode paste or the use of self-adhesive electrode pads. [160] Preapplied electrode pads are particularly advantageous in the operating room when patient position precludes rapid access to the chest for standard paddle placement.

In the operating room or ICU, in which the cardiac arrest is witnessed and a monitor reveals the mechanism to be pulseless VT or VF and where a defibrillator is immediately available, a 200-J shock should be delivered immediately; if this shock is unsuccessful, a second shock of 200 to 300 J, and, if necessary, a third shock of 360 J should be administered. Thus, for persistent VF, a series of three shocks (200, 200-300, and 360 J) should be delivered in rapid succession. If a cardiac arrest is witnessed but not monitored and a defibrillator is not available, a single precordial thump can be applied before beginning CPR and while awaiting the arrival

of the monitor-defibrillator. If at any time VF recurs following successful conversion, the series of up to three shocks should be repeated. This sequence of rapidly repeated defibrillatory shocks for persistent VF underscores the primacy of this treatment of VF over all other interventions. If VT persists despite this initial treatment, pharmacologic therapy becomes necessary. It is assumed that the airway and ventilation are already controlled by the anesthesiologist with endotracheal intubation and ventilation with 100 percent oxygen.

Drug therapy at this point begins with epinephrine. Assuming that a peripheral intravenous line is present, initial drug injections can be given by this route, but if cardiac arrest persists, a central venous catheter should be inserted to ensure more rapid drug delivery and attainment of higher peak arterial concentrations more quickly than with peripheral injection. [85] Because of evidence that glucose administration during global cerebral ischemia can worsen neurologic outcome in survivors, [162] [163] [164] [165] lactated Ringer's solution or normal saline should be used instead of glucose-containing solutions. If for some reason an intravenous line is not pres-ent or cannot be inserted promptly, epinephrine can be injected into the tracheobronchial tree, a site from which it is absorbed rapidly to produce prompt pharmacologic effects. [166] [167] [168] If this route is used, a dose of 2 to 2.5 times the intravenous dose is recommended. [85]

Previous clinical impressions regarding the beneficial effects of epinephrine during cardiac arrest, regardless of the underlying rhythm, have been substantiated. [169] [170] [171] [172] [173] The drug increases both cerebral and myocardial blood flow in experimental cardiac arrest. [169] [170] [171] The mechanisms responsible for enhanced cerebral and myocardial blood flow appear to be based on prevention of arterial collapse and intense vasoconstriction in other vascular beds, thus preventing runoff of blood into noncritical tissues and preferentially increasing cerebral and myocardial perfusion pressures and flow. [169] Because of the critical role of potent vasoconstriction in the beneficial action of epinephrine, phenylephrine has been studied as well. [170] [174] [175] Comparison of phenylephrine and epinephrine in experimental cardiac arrest has shown no evident benefit gained from using phenylephrine in terms of changes in blood flow, [170] [175] somatosensory evoked potentials, [170] or neurologic or cardiovascular outcome. [172] In human victims of cardiac arrest, epinephrine has been shown to produce increases in both peak aortic and coronary perfusion pressures, further attesting to its vasoconstrictive properties in a clinical setting. [176] Thus, epinephrine remains the drug of choice at this time.

The recommended dose of epinephrine is 1.0 mg (10 mL of a 1:10,000 dilution). This dose should be repeated every 3 to 5 minutes as long as cardiac arrest persists to ensure sustained blood flow benefit.

Based on experimental observations of apparent hemodynamic benefit from large doses of epinephrine (up to 0.2 mg/kg), [177] [178] numerous clinical reports and studies have assessed the impact of high-dose epinephrine (HDE) on such end points as restoration of a spontaneous circulation (ROSC) and discharge from the hospital. [179] [180] [181] [182] [183] [184] [185] Although some investigators have observed an increased frequency of ROSC after HDE compared with standard 1-mg doses, [183] most have not, and no study has yet confirmed benefit in terms of discharge survival. Therefore, the currently recommended (standard) dose is 1 mg given every 3 to 5 minutes. Alternative doses are considered acceptable and possibly helpful if an initial trial with standard doses is not effective. These additional dosing regimens are intermediate (2-5 mg every 3-5 minutes), escalating (1 mg, 3 mg, 5 mg at 3-minute intervals), and high (0.1 mg/kg every 3-5 minutes). [186]

Following the initial injection of epinephrine after the third shock, defibrillation should be attempted again, using 360 J. If VF persists, it is necessary to use a drug with antifibrillatory actions. Lidocaine is the drug of choice for this purpose. [128] Lidocaine has been shown to enhance intraoperative ventricular defibrillation in cardiac surgery, permitting defibrillation with fewer shocks of lower energy and current. [187] This concept is controversial, however, because other investigators have observed an elevation of defibrillation threshold with blood concentrations of lidocaine that may occur during cardiac arrest and resuscitation. [188] [189] [190] In persistent pulseless VT and VF, lidocaine is given initially in a dose of 1.5 mg/kg, followed by a 360-J shock. If VF persists, lidocaine can be repeated in a dose of 1.5 mg/kg in 3 to 5 minutes, with a total loading dose of 3 mg/kg. Lidocaine, like epinephrine and atropine, can be injected into the tracheobronchial tree via an endotracheal tube, but data on absorption from this site in cardiac arrest are not available. [85] Until this issue is resolved, it is not certain that therapeutic benefit can be expected from endotracheally administered lidocaine in human victims of cardiac arrest.

If lidocaine is apparently ineffective in terminating VF, bretylium can be used. It has been shown to possess both antiarrhythmic and antifibrillatory properties. [191] [192] [193] In acute ischemia, depressed conduction and shortening of the refractory period are electrophysiologic substrates for reentrant excitation and thus to both VT and VF. Bretyliuminduced improvement in conduction along with prolongation of the refractory period would tend to extinguish these reentrant mechanisms during ischemia. [193] The drug also elevates the VF threshold. [191] Bretylium can be given in a dose of 5 mg/kg, followed by a 360-J shock. If VF remains, a second dose of 10 mg/kg can be given in 5 minutes, followed by another shock. If necessary, a third dose of 10 mg/kg can be given.

VF or pulseless VT that remains refractory to repeated shocks, epinephrine, lidocaine, and bretylium poses a major therapeutic dilemma. If an electrolyte disorder, such as hypokalemia, hyperkalemia, or hypomagnesemia, is suspected or documented, correction may permit shocks to restore a sustained conversion (Fig. 75-16) . There is increasing evidence that magnesium plays a critical role in maintenance of a stable cardiac rhythm. [194] [195] [196] [197] [198] [199] [200] Hypomagnesemia should be suspected and treated when refractory VT or VF is present. Even in the absence of documented hypomagnesemia, magnesium sulfate, 1 to 2 g over 1 to 2 minutes, can be used to treat refractory VT or VF. [201] [202] Its benefit in terminating torsades de pointes has already been discussed. Procainamide, 30 mg/min to a total of 17 mg/kg, can also be used in refractory VT or VF. Intravenous amiodarone is likely to become a part of the therapeutic approach for refractory VF as well as for refractory VT, as discussed earlier. The same dosage scheme can be used for VF as that outlined for VT.

Figure 75-16 (A and B) Hyperkalemic ventricular tachycardia with a sine-wave morphologic pattern. The serum potassium was 7.8 mEq/L.

In cardiac arrest that does not respond to the initial measures (intubation, ventilation with 100% oxygen, defibrillation, epinephrine, and antiarrhythmic drugs), sodium bicarbonate can be considered. If hyperkalemia is known or suspected to be present, sodium bicarbonate should be administered promptly. Recommendations for the use of this drug in cardiac arrest have changed substantially. Despite its long history of early and frequent administration in cardiac arrest, there is still no convincing evidence that it confers any benefit in survival from VF. [203] [204] By contrast, its adverse effects are well documented, including severe plasma hyperosmolality, [205] [206] paradoxic cerebrospinal fluid acidosis, [207] and CO_2 generation. [205] [208] It is this last effect that has been primarily responsible for renewed concern.

During cardiac arrest, with severely reduced pulmonary blood flow and therefore CO_2 transport and elimination, CO_2 is retained in mixed-venous blood and tissues, producing a disparity between pH and P_{CO_2} in arterial and mixed-venous blood. [208] Sodium bicarbonate is a rapid and potent CO_2 generator, which can be observed in arterial blood, as well as in expired air, after intravenous injection. Sodium bicarbonate would only add to the CO_2 load and could worsen mixed-venous (and presumably tissue) acidosis. Myocardial hypercarbic acidosis has been confirmed to exist during experimental cardiac arrest and resuscitation, [209] and it is not reversed with sodium bicarbonate or other buffer agents. [210] At least with regard to the heart, increases in tissue P_{CO_2} produce progressive decreases in the performance of ischemic myocardium. Clinically, one may infer that intractable electromechanical dissociation (EMD) could be a consequence, even if VF were removed. Myocardial hypercarbic acidosis decreases the success of restoration of spontaneous circulatory function and survival. [211]

In light of all these observations, sodium bicarbonate should not be used routinely in the treatment of cardiac arrest. It can be considered after the foregoing electrical and pharmacologic measures have been instituted, if preexisting metabolic acidosis is present, or if severe documented metabolic acidosis develops during the arrest. [212] A review of acid-base derangements during cardiac arrest [213] [214] suggests that sodium bicarbonate may be beneficial in restoring spontaneous circulation after prolonged (15 minutes) VF cardiac arrest, based on experimental observations. Clinically, if this drug is used, an initial dose of 1 mEq/kg can be given, followed at 10-minute intervals by 0.5 mEq/kg. Of course, if a base deficit is documented on blood gas analysis, the drug can be given based on that measurement. Other antacids, such as sodium carbonate, [212] carbicarb, [212] [215] and tribonat, [212] [216] have been studied, but none has been shown to be superior to sodium bicarbonate in clinical cardiac arrest. Monitoring both arterial and mixed-venous blood gases and pH during cardiac arrest helps to define the derangements in acid-base equilibrium occurring in arrested humans and thereby leads to more rational antacid therapy.

Pulseless Electrical Activity

The term "pulseless electrical activity" (PEA) is now applied to a heterogeneous group of cardiac rhythm disorders, all characterized by pulselessness in the presence of some type of electrical activity other than VT or VF. Thus, included in this designation are the traditional EMD, in which pulseless but organized electrical activity is present; idioventricular rhythms, ventricular escape rhythms, postdefibrillation idioventricular rhythms, and bradyasystole.

High priority must be given to identification of a possibly correctable cause of any form of PEA. For example, when EMD is present, the clinician should immediately consider severe hypovolemia. In a traumatized patient, in addition to hypovolemia, cardiac tamponade and tension pneumothorax with hypoxemia are possible causes. Intraoperatively or postoperatively, acute massive pulmonary thromboembolism should be considered. Idioventricular rhythms may accompany such derangements as severe hyperkalemia, acidosis, hypothermia, or overdose with such drugs as digitalis, beta blockers, calcium channel blockers, and tricyclic antidepressants.

In any of these forms of PEA, the most important point is that although initial temporizing measures such as injection of epinephrine or pacing may be needed to "tide the patient over," an immediate diagnostic assessment and redirection of treatment in a disorder-specific direction may permit salvage of many patients with PEA.

Asystole

The complete and sustained absence of electrical activity is most often an irreversible and therefore terminal event, caused by such derangements as uncorrected persistent hy-poxia, severe hyperkalemia, massive drug overdose, myocardial infarction, or hypothermia. In most of these conditions, asystole is irreversible and terminal, but at least a brief trial of intervention may be warranted in some patients. In specific instances, such as hyperkalemia, known metabolic acidosis, or tricyclic antidepressant overdose, sodium bicarbonate should be administered early in the effort. Pacing has not been shown to improve survival from asystolic cardiac arrest, but if it is tried, it should be done as early as possible in the attempted resuscitation.

Outcome Following In-Hospital Resuscitation

Discharge survival rates following in-hospital cardiac arrest and resuscitation range from 8 to 21 percent, with most reports demonstrating an average survival rate of approximately 14 percent. [217] [218] [219] [220] [221] [222] [223] [224] [225] [226] [227] These reports usually include cardiac arrests in both ICUs and general wards. In a retrospective review of 668 cardiac arrests over a 3-year period, discharge survival was 3.3 percent in ICU patients and 14.0 percent in non-ICU patients. [225] In a small retrospective study of 24 consecutive patients who had an intraoperative cardiac arrest between 1986 and 1994, the survival rate was 38 percent. [228] A primary cardiac event was presumed causative in 50 percent. An accompanying invited commentary pointed out that much of the credit for these favorable outcomes is attributable to advances in intraoperative management by anesthesiologists. In any case, it is certain that anesthesiologists well trained in resuscitation can play a

decisive role in the management of patients with intraoperative cardiac arrest.

The most favorable outcome, as in out-of-hospital cardiac arrest, is observed with VF or VT. [217] [219] [220] [222] [223] In a study comparing CPR techniques in 143 hospitalized patients experiencing asystolic or EMD arrest, there were no survivors to hospital discharge with intact neurologic function. [44] Duration of resuscitative attempts is a determinant of survival [222] [224] [225] [226] [227] [228] ; in one study, none of 179 patients in whom resuscitative efforts lasted longer than 30 minutes survived to be discharged. [222] Other variables that limit survival from in-hospital cardiac arrest include unwitnessed arrest, [224] sepsis, [224] cancer, [222] [224] renal failure, [222] and prearrest hypotension. [217] [222] Age is a major determinant of outcome. [224] In one study, no patients 70 years of age or older who experienced cardiac arrest and resuscitative attempts survived to discharge. [224] These data were obtained in a hospitalized population of relatively sick, aged, male patients, and it is not possible to extrapolate these observations to a different hospital population. Nevertheless, these observations have provoked open and candid discussion and reappraisal in an attempt to define the appropriate application of CPR in hospitalized patients as well as in patients in long-term care institutions. [229] [230] Certainly, age alone should not preclude patients from receiving CPR. [222] [230] At the same time, the presence of sepsis or cancer in an elderly patient who experiences an unwitnessed bradyarrhythmic cardiac arrest would be an example of a clinical circumstance in which resuscitative efforts would be unwarranted. As CPR becomes increasingly available, sophisticated clinical and ethical discussions and decision-making must assume a more dominant role in defining the appropriate application of resuscitation in hospitalized patients.

Do-Not-Resuscitate Orders

The increasing application of do-not-resuscitate (DNR) orders in hospitalized patients has necessitated development of specific guidelines for the management of such patients. The CPR and ECC guidelines [6] addressed this issue in a section entitled "Ethical Considerations in Resuscitation," and the American Medical Association Council on Ethical and Judicial Affairs developed guidelines for use of DNR orders. [231] These documents provide helpful assistance in the utilization of DNR orders in hospitalized patients and should be consulted.

In an analysis of DNR orders in ICUs comparing practice in the period 1988 to 1990 with that in 1979 to 1982, it was observed that DNR orders were written earlier and more frequently in the more recent time period. [232] These practice changes preceded implementation of the Patient SelfDetermination Act, a finding suggesting that improved understanding and acceptance of the limitations of treatment by both physicians and families resulted in more frequent and earlier application of DNR policies.

A unique aspect of application of DNR orders is posed by the patient with such orders who comes to the operating room, for example, for a palliative procedure. Should DNR orders be suspended for this period, or should they be modified in some way? These are difficult questions with no definitive answers that can be applied uniformly to all patients in the same manner. Many authors have addressed these issues and have proposed approaches that give due consideration to patients' wishes and ethical concerns of both anesthesiologist and surgeon. [233] [234] [235] [236] [237] [238] [239] [240] Some investigators have recommended continuing all DNR orders during the perioperative period after discussion of this option with the patient. Guidelines published by the American Society of Anesthesiologists in 1993 recognize that automatic suspension of DNR orders may not honor a patient's rights to self-determination, but that such a suspension is respectful of a patient's wishes if it is explicitly discussed with the patient or surrogate. [241] For the anesthesiologist, an immediate question in such a setting is what constitutes resuscitation, because the monitoring and life support measures accompanying the administration of anesthesia could be taken to be a component of resuscitation in another context. An institutional policy that uniformly suspends all DNR orders for the intraoperative period would seem to be unduly restrictive and probably not respectful of a patient's wishes. The most acceptable position for such a patient coming to the operating room is to engage the patient or designated surrogate in a detailed and explicit discussion that assesses the patient's wishes after he or she has been informed of the usual interventions taken in the administration of anesthesia and what therapeutic options are available in the event of cardiorespiratory failure. Suggested guidelines for the acquisition of this type of informed consent have been proposed. [233] One specific focus of this patient-physician discussion should be whether or not an effort should be made to restore spontaneous circulation in the event of cardiac arrest in any of the forms discussed earlier, such as VF, asystole, or any type of pulseless electrical activity. In this context, attempted restoration of spontaneous circulation from pulselessness in any form would be the ultimate criterion of application of a DNR order intraoperatively. All other forms of life support interventions would be applied as in any other circumstance. Whatever decisions are made during the patient-physician discussion must be documented by the physician in the patient's record.

PEDIATRIC RESUSCITATION

It is now well understood and accepted that pediatric resuscitation is an area of knowledge and skill with specific diagnostic

and therapeutic considerations. No longer is it acceptable to treat pediatric patients as "little adults." [242] [243] Recognition of this change is evident in the new guidelines and in the AHA BLS instructor's manual [8] and the ACLS textbook, [9] both of which devote specific sections to pediatric BLS and ACLS. In addition, training programs incorporating this body of knowledge and skill have been developed with *Textbook of Pediatric Basic Life Support,*[244] *Instructor' s Manual for Pediatric Basic Life Support,*[245] and *Textbook of Pediatric Advanced Life Support.*[246] This discussion highlights the major areas of essential information, again, as in the previous portion of this chapter, with specific regard to application by anesthesiologists in the operating rooms or ICU settings. The AHA textbooks should be consulted for further specific details.

Basic Life Support

Primarily for convenience and uniformity in teaching, infants are considered to be 0 to 1 years of age and children are aged 1 to 8 years. Table 75-3 (Table Not Available) depicts similarities and differences in the performance of CPR in these two groups. In infants, the brachial pulse is often more easily located and palpated than the carotid, and therefore it is recommended for assessment of pulselessness. The tips of two fingers can be used for chest compressions over the lower half of the patient's sternum, with a compression depth of one-third to one-half the depth of the chest (
0.5-1.0 inch), a compression rate of at least 100/min, and a compression/ventilation ratio of 5:1. The 5:1 ratio is used whether one or two rescuers are performing CPR. In children, the heel of one hand can be used to deliver chest compressions over the lower half of the patient's sternum at a rate of 100/min, a depth of one-third to one-half the depth of the chest (
1.0-1.5 inches), and a compression/ventilation ratio of 5:1. Chest radiographs and right heart angiograms in infants, children, and young adults ages 1 day to 19 years have confirmed that the heart lies under the lower sternum in all age groups [247] [248] ; therefore, this is the proper location for external chest compression.

Advanced Cardiac Life Support

Generally speaking, unlike adults, infants and children predominantly experience cardiorespiratory arrest secondary to respiratory arrest, rarely secondary to a primary cardiac event. [6] [242] [243] [249] [250] [251] [252] This is a critical observation because ACLS interventions directed primarily toward the restoration of cardiac function may cause the physician to delay properly directed therapy. For example, a progressive decline in cardiac rate leading to bradycardiac arrest is likely to be an ominous sign of hypoxia in infants and children. Treatment with atropine in a futile attempt to increase heart rate would be tragically misdirected therapy. Furthermore, VF and VT, so common in adults, are uncommon cardiac arrest arrhythmias in infants and small children, [249] [250] although there is evidence that VF is not rare in children and adolescents experiencing prehospital cardiac arrest. [253] Thus, the application of ACLS is indeed different in this patient population. Because the cause of cardiac arrest in children is most commonly respiratory and not cardiogenic, the ensuing pathophysiologic events and mode of presentation of the cardiac arrest state are different, and the subsequent initial efforts at resuscitation must be directed toward respiratory support maneuvers. In addition, of course, equipment, techniques, and drug dosages are of necessity different. All these facts mandate that physicians caring for infants and children have a clear understanding of the role of ACLS interventions in these patients.

Airway Control and Ventilation

The foregoing discussion underscores what is well known to anesthesiologists: definitive control of the airway and oxygenation and ventilation are the most decisive, pivotal, and critical ACLS interventions in pediatric cardiac arrest. As in adults, anesthesiologists ordinarily intubate the trachea for this purpose, then ventilate with such devices as anesthesia bags or bag-valve units with supplemental oxygen. [254] It should be noted that alternative devices such as esophageal obturator airways, esophageal gastric-tube airways, or

TABLE 75-3 -- Summary of Basic Life Support Maneuvers in Infants and Children

(Not Available)

From the American Heart Association, [6] copyright, American Medical Association.

esophageal-tracheal Combitubes referred to earlier for use in adults are not available in sizes for pediatric application. [254] It should also be noted that with the evolution of experience with LMAs, these devices have been successfully utilized for neonatal resuscitative efforts in the delivery room setting. [255] [256] [257] However, as with the esophageal adjuncts mentioned earlier, the LMA should be viewed as an adjunct in this setting, with a secured airway via an endotracheal tube the gold standard during resuscitation.

Monitoring and Arrhythmia Recognition

ECG monitoring permits immediate recognition of the arrest rhythm or, more likely in infants and children, the "prearrest" rhythm. Prompt intervention and correction in the latter event prevent cardiac arrest that, if induced by unrecognized hypoxia and manifested by progressive bradycardia, may be irreversible. With this in mind, potentially life-threatening arrhythmias are discussed first, followed by cardiac arrest.

Supraventricular Bradyarrhythmia

As already discussed, the appearance and progression of slowing of the heart rate in infants and children demand immediate assessment of the cause, ruling out first the most likely culprit--hypoxia. The bradycardia at this point (before cardiac arrest) is most commonly sinus or junctional in origin. Second- or third-degree heart block may ensue if corrective treatment is not applied. If hypoxia has been ruled out and if the bradycardia is accompanied by clinical evidence of impaired perfusion, usually with systemic hypotension, the patient should be treated with epinephrine in a dose of 0.01 mg/kg intravenously, repeated if necessary every 3 to 5 minutes. The 1:10,000 dilution of epinephrine is used for intravenous injections. If the drug is injected into the tracheobronchial tree via an endotracheal tube, 0.1 mg/kg

(1:1,000 dilution) is recommended. The intraosseous route also can be used if necessary (see later).

Epinephrine is the first choice in treating bradyarrhythmias in infants and children. If the rate does not increase with this drug, atropine can be used in a dose of 0.02 mg/kg and repeated once. An algorithm depicting recommended interventions in pediatric bradyarrhythmias is shown in Figure 75-17 (Figure Not Available) .

Supraventricular Tachyarrhythmia

In infants and children, supraventricular tachycardia (SVT) may represent ectopic atrial rhythms, atrial flutter or fibrillation, or paroxysmal reentrant tachycardia. [258] Standard pediatric cardiology texts should be referred to for specific diagnostic and therapeutic details. Although SVT is usually well tolerated in most infants and older children, immediate cardioversion may be necessary when heart rates in the range of 240 to 300 beats/min are reached, rates that may result in severe and rapid hemodynamic compromise. In this emergency setting in which rapid SVT causes cardiovascular instability, [259] synchronized cardioversion is the treatment of choice. The initial energy dose is 0.5 J/kg body weight; if necessary, the energy dose is doubled. [246] If conversion to sinus rhythm still does not occur, the diagnosis of SVT should be reconsidered.

In hemodynamically stable children with SVT, adenosine is the drug of choice, as with adults. The drug can be given as a rapid bolus in a dose of 0.1 mg/kg intravenously, ideally injected into the closest port to the hub of the catheter and flushed with 2 to 3 mL of saline. If the SVT persists or recurs, a second dose of 0.2 mg/kg intravenously can be given in 1 to 2 minutes. [6] [246] [260] [261] [262] The maximum single dose should not exceed 12 mg.

Verapamil is not recommended for SVT in an emergency setting because it may induce systemic hypotension and a state of depressed myocardial contractility. [263] [264] [265] Specifically, it is not recommended in this setting for infants less than 1 year of age, for children with congestive heart failure or myocardial depression, for children receiving beta-adrenergic-blocking drugs, or for children who may have a bypass tract. [246]

Ventricular Bradyarrhythmia

As with supraventricular bradyarrhythmias, a slow idioventricular rhythm that has not yet produced pulselessness must be considered indicative of severe hypoxia (Fig. 75-18) (Figure Not Available) , and treatment must be directed accordingly. Only after this condition has been addressed should rateaccelerating therapy as discussed for supraventricular bradycardia be invoked.

Ventricular Tachyarrhythmia

Despite a common misconception, VT is not always associated with severe hemodynamic compromise. Slow ventricular rates (e.g., 150-200 beats/min) may be well tolerated, as defined by the presence of palpable pulses, but they should nonetheless be converted to a normal rhythm. In this setting, synchronized cardioversion is the indicated treatment, beginning with 0.5 J/kg and increasing to progressively higher doses (up to 4 J/kg) if needed. Lidocaine, 1 mg/kg intravenously, can be given before or after cardioversion. If VT recurs, an infusion should be begun after a loading bolus dose of lidocaine. An infusion can be prepared by adding 120 mg lidocaine (40 mg/mL) to 97 mL 5 percent dextrose in water and infusing it at a rate of 20 to 50 mug/kg/min (1.0-2.5 mL/kg/h). [246] However, if the tachycardia is very rapid, as with rates of 300/min or more, and if it is associated with frank cardiovascular collapse (i.e., no palpable pulses), then this situation should be treated like VF.

Management of Cardiac Arrest

Once pulselessness ensues, therapy must be directed not only at correcting the underlying rhythm disorder, but also at maintaining organ viability during the period of cardiorespiratory arrest. Meticulous attention must be paid to ensuring proper CPR technique and the administration of drugs

Figure 75-17 (Figure Not Available) The bradycardia decision tree. *(From Chameides. [246] Reproduced with permission. Copyright American Heart Association.)*

Figure 75-18 (Figure Not Available) (A-D) Serial ECGs in a 5-year-old victim of fatal smoke inhalation. Note the progressive slowing of the heart rate from sinus tachycardia (A) to a terminal very slow idioventricular rhythm (D). *(From Walsh and Krongrad, [249] with permission of Excerpta Medica Inc.)*

that appear to help support perfusion pressures during cardiac arrest and resuscitation.

In the great majority of pediatric cardiac arrests, bradyasystole is the terminal cardiac electrical activity (see Fig. 75-18 (Figure Not Available)). Early dominance of the parasympathetic nervous system and alpha-adrenergic activity may, in part, explain this dominance of bradyasystolic mechanisms as the terminal events in infants. [249] In addition, ventricular tachyarrhythmias (VT/VF) are most commonly seen in infants and children with congenital heart disease. [249] Such children may have cardiac hypertrophy and increased ventricular muscle mass sufficient to provide an anatomic substrate for reentrant wavefronts that initiate and sustain VT or VF.

PEA and Asystole

PEA, as in adults, includes disorders in which some form of cardiac electrical activity is present, but without palpable pulses. In infants and children, this most commonly is an idioventricular rhythm at a very slow and irregular rate (bradyasystole) and is the usual predecessor to ventricular asystole. When PEA is present in the form of organized electrical activity (EMD), or even when any electrical activity is still present, an immediate and aggressive effort should

be made to identify correctable causes. As in adults, diagnoses to be considered immediately include hypovolemia, tension pneumothorax, cardiac tamponade, hypoxemia and/or acidosis, or hypothermia. Immediate consideration of these possibilities and corresponding direction of therapeutic efforts may avoid pursuing with drugs what will inevitably become a terminal situation if an underlying potentially reversible catastrophe is present.

For both PEA and asystole, epinephrine is the drug of choice, given initially in a dose of 0.01 mg/kg (0.1 mL/kg of 1:10,000 solution) intravenously. Subsequent doses of 0.1 mg/kg (0.1 mL/kg of 1:1,000 solution) repeated every 3 to 5 minutes are recommended because there is some evidence that high doses of epinephrine may be beneficial. Second and subsequent doses as high as 0.2 mg/kg (0.2 mL/kg of 1:1,000 solution) can be tried. [266] [267] It is also recommended that defibrillation at 4 J/kg be administered 30 to 60 seconds following each second and subsequent dose of epinephrine. [246]

If vascular access has not been achieved, initial treatment with epinephrine can be given via an endotracheal tube. For this purpose, the recommended dose is 0.1 mg/kg using a 1:1,000 solution. The dose should be repeated at 3- to 5-minute intervals, as long as arrest persists. Epinephrine is presumed to have the same beneficial actions in elevating perfusion pressure as discussed earlier in management of adult arrest. In an infant animal model (infant piglets), epinephrine increases cerebral and myocardial blood flow, a finding suggesting that it may have a similar beneficial action in infants and children. [268]

If venous cannulation cannot be achieved quickly, the intraosseous route, preferred over the endotracheal tube route, can be used. This access route is preferred for children 6 years old or younger, although it has been successfully used for older children. Figure 75-19 (Figure Not Available) outlines the current algorithm recommended for priorities for vascular access during resuscitation. Alternatives to peripheral venous access should be considered in this setting if reliable access cannot be achieved in three attempts or 90 seconds, whichever comes first. [6] [246]

There are two main types of devices currently available for intraosseous cannulation: the intraosseous infusion needle and the Jamshidi-type bone marrow aspiration needle. If either of these is not available in the emergency setting, then an 18-gauge spinal needle with a stylet may be considered for this use. Several publications describe the history, technique, and application of intraosseous infusion in the resuscitation of infants and children. [269] [270] [271] [272] Whichever needle is used, it is

inserted perpendicularly to the skin into the tibia approximately one finger-breadth below the tubercle on the anteromedial surface. The needle is advanced with a boring-type motion until the marrow cavity is entered, as evidenced by a distinct loss of resistance as the needle passes through the bony cortex. [272] The stylet is removed, and bone marrow is aspirated into a saline-filled syringe. The needle is then flushed with saline and is connected to an intravenous administration set. Any fluid or drug needed for resuscitation can be administered by this route. Whereas fluid should flow freely through the needle, administration of fluid with an intravenous pump can be considered if care is taken to ensure absence of subcutaneous infiltration.

In cardiorespiratory resuscitation of infants and children, it is recommended that a rapid glucose test be obtained and glucose injected if hypoglycemia is present. [6] [246] For those

Figure 75-19 (Figure Not Available) Priorities for vascular access. *(Modified from Chameides. [246] Reproduced with permission. Copyright American Heart Association.)*

Figure 75-20 (Figure Not Available) Asystole and pulseless arrest decision tree. *(Modified from Chameides. [246] Reproduced with permission. Copyright American Heart Association.)*

infants and children who do not respond to resuscitative therapy, glucose administration should also be considered. However, as expressed earlier in the discussion of adult cardiac arrest, routine use of glucose-containing solutions should be avoided because of a potentially adverse impact on the neurologic outcome and because glucose administration may result in hyperglycemia and secondary osmotic diuresis. If glucose is necessary, the dose is 0.5 to 1.0 g/kg intravenously in a solution of 25 percent dextrose in water (2-4 mL/kg) for infants and children, preferably given as a continuous infusion rather than as a bolus to avoid a sudden increase in serum osmolality. [6] [246] The commercially available 50 percent dextrose in water solution can be diluted 1:1 with sterile water for this purpose. For the neonate, in general, the concentration of glucose administered should not exceed 12.5 percent, thus necessitating a further dilution of the 50 percent dextrose solution.

The same concerns discussed earlier regarding sodium bicarbonate therapy in adults also apply in pediatric patients. If it is used, 1 mEq/kg can be given initially, and 0.5 mEq/kg at 10-minute intervals thereafter, unless arterial blood measurements of pH, Pa CO_2 , and base deficit are available and indicate a different dosage scheme. [246] Likewise, there is no available evidence to support the continued use of calcium salts in cardiac arrest in infants and children. The use of calcium chloride should be reserved for the acute treatment of hyperkalemia, hypermagnesemia, hypocalcemia, or calcium channel-blocking drug toxicity. In these clinical situations, 0.2 to 0.25 mL/kg of 10 percent calcium chloride (5-7 mg/kg elemental calcium) can be given and repeated once in 10 minutes. [246]

Pulseless Ventricular Tachycardia or Ventricular Fibrillation

As indicated earlier, this is a relatively uncommon form of cardiac arrest in infants and children and is most likely to be seen when congenital heart disease and increased cardiac muscle mass are present to provide the anatomic and electrophysiologic milieu for maintaining reentrant wavefronts. Defibrillation should be done as soon as possible, and all defibrillators should be equipped with electrode paddles suitable for pediatric age groups. Pediatric defibrillator paddles, approximately 4.5 cm diameter, are recommended for infants weighing less than 10 kg. For those who weigh more, at approximately 1 year of age, adult paddles of 8 to 13 cm diameter should be used. [160] [273] The initial energy dose is 2 J/kg;

TABLE 75-4 -- Drugs Used in Pediatric Advanced Life Support

(Not Available)

From the American Heart Association, [6] copyright, American Medical Association.

if VT or VF is not terminated, 4 J/kg should be used and rapidly repeated twice if needed. For pulseless VT or VF persistent beyond these shocks, antiarrhythmic therapy is necessary, along with assessment of ventilation, oxygenation, and acid-base balance if feasible.

As long as pulseless VT or VF persists, epinephrine should be given in doses described for pulseless electrical activity-related cardiac arrest in an attempt to increase cerebral and myocardial perfusion pressure during CPR. A decision tree for intervention in cardiorespiratory arrest in infants and children is presented in Figure 75-20 (Figure Not Available) .

Lidocaine is the antiarrhythmic drug of choice, given in an initial intravenous dose of 1 mg/kg. In this situation, a continuous infusion, as outlined earlier for VT, can be begun after bolus injection. Alternatively, bretylium, in a dose of 5 mg/kg, can be injected, followed by a 4 J/kg shock. If VF persists, 10 mg/kg can be given followed by another defibrillatory shock.

One of the most difficult aspects of pediatric resuscitation is determination of correct drug dosages in the midst of the crisis, especially if one deals with cardiac arrests in infants and children infrequently. Various schemes have been proposed for simplifying this need. Table 75-4 (Table Not Available) incorporates a convenient scheme for selecting the proper dose of drug to be injected, based on body weight. It includes the major resuscitative drugs (i.e., epinephrine, atropine, lidocaine), along with additional drugs that could be used in some cardiac arrests or other pediatric emergencies.

ACKNOWLEDGMENTS

I wish to acknowledge the assistance of Scott E. LeBard, M.D., for reviewing and updating the section on pediatric resuscitation and Kimberly D. Sankey for her secretarial work in preparation of the manuscript.

References

1. 2 Kings 4:33-35, King James Version.

2. National Academy of Sciences National Research Council: Cardiopulmonary resuscitation. JAMA 198:373, 1966.

3. American Heart Association and the National Academy of Sciences National Research Council: Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 227(suppl):833, 1974.

4. American Heart Association: Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 244(suppl):453, 1980.

5. American Heart Association: Standards and guidelines for cardiopulmonary resuscitation and emergency cardiac care. JAMA 255(suppl):2841, 1986.

6. American Heart Association Emergency Cardiac Care Committee and Subcommittees: Guidelines for cardiopulmonary resuscitation and emergency cardiac care. JAMA 268:2135, 1992.

7. Emergency Cardiac Care Committee and Subcommittees, American Heart Association: Proceedings of the 1992 National Conference on Cardiopulmonary Resuscitation and Emergency Cardiac Care. Ann Emerg Med 22:275, 1993.

8. Subcommittee on Basic Life Support: Instructor's Manual for Basic Life Support. Dallas, American Heart Association, 1994.

9. Subcommittee on Advanced Cardiac Life Support: Textbook of Advanced Cardiac Life Support. Dallas, American Heart Association, 1994.

10. Elam JO, Greene DG, Schneider MA et al: Head-tilt method of oral resuscitation. JAMA 172:812, 1960.

11. Greene DG, Elam JO, Dobkin AB et al: Cinefluorographic study of hyperextension of the neck and upper airway patency. JAMA 176:570, 1961.

12. Boidin MP: Airway patency in the unconscious patient. Br J Anaesth 57:306, 1985.

13. Safar P: Recognition and management of airway obstruction. JAMA 208:1008, 1969.

14. Ruben H, Knudsen EJ, Carugati G: Gastric inflation in relation to airway pressure. Acta Anaesthesiol Scand 5:107, 1961.

15. Hee MKJ, Plevak DJ, Peters SG: Intubation of critically ill patients. Mayo Clin Proc 67:569, 1992.

16. Pepe PE, Zachariah BS, Chandra NC: Invasive airway techniques in resuscitation. Ann Emerg Med 22:393, 1993.

17. Wee MYK: The oesophageal detector device: Assessment of a new method to distinguish oesophageal from tracheal intubation. Anaesthesia 43:27, 1988.

18. Zaleski L, Abello D, Gold MI: The esophageal detector device: Does it work? Anesthesiology 79:244, 1993.

19. Salem MR, Wafai Y, Joseph NJ et al: Efficacy of the self-inflating bulb in detecting esophageal intubation: Does the presence of a nasogastric tube or cuff deflation make a difference? Anesthesiology 80:42, 1994.

20. Salem MR, Wafai Y, Baraka A et al: Use of the self-inflating bulb for detecting esophageal intubation after "esophageal ventilation." Anesth Analg 77:1227, 1993.

21. Wafai Y, Salem MR, Baraka A et al: Effectiveness of the self-inflating bulb for verification of proper placement of the esophageal tracheal Combitube®. Anesth Analg 80:122, 1995.

22. Bozeman WP, Hexter D, Liang HK et al: Esophageal detector device versus detection of end-tidal carbon dioxide level in emergency intubation. Ann Emerg Med 27:595, 1996.

23. Czinn EA, Wafai Y, Salem MR et al: Efficacy of the self-inflating bulb for confirmation of emergency tracheal intubation in critically ill patients. Anesthesiology 83:A266, 1995.

24. Lang DJ, Wafai Y, Salem R et al: Efficacy of the self-inflating bulb in confirming tracheal intubation in the morbidly obese. Anesthesiology 85:246, 1996.

25. Reed AP: Current concepts in airway management for cardiopulmonary resuscitation. Mayo Clin Proc 70:1172, 1995.

26. Brimacombe J, Berry A, Verghese C: The laryngeal mask airway in critical care medicine. Intensive Care Med 21:361, 1995.

27. Sasada MP, Gabbott DA: The role of the laryngeal mask airway in pre-hospital care. Resuscitation 28:97, 1994.

28. Samarkandi AH, Seraj MA, El Dawlatly A et al: The role of laryngeal mask airway in cardiopulmonary resuscitation. Resuscitation 28:103, 1994.

29. Bailey AR, Hett DA: The laryngeal mask airway in resuscitation. Resuscitation 28:107, 1994.

30. Devitt JH, Wenstone R, Noel AG et al: The laryngeal mask airway and positive-pressure ventilation. Anesthesiology 80:550, 1994.

31. Kokkinis K: The use of the laryngeal mask airway in CPR. Resuscitation 27:9, 1994.

32. Benumof JL: Management of the difficult adult airway. Anesthesiology 75:1087, 1991.

33. Benumof JL, Scheller MS: The importance of transtracheal jet ventilation in the management of the difficult airway. Anesthesiology 71:769, 1989.

34. Deshmukh HG, Weil MH, Gudipati CV et al: Mechanism of blood flow generated by precordial compression during CPR. I. Studies on closed chest precordial compression. Chest 95:1092, 1989.

35. Higano ST, Oh JK, Ewy GA et al: The mechanism of blood flow during closed chest cardiac massage in humans: Transesophageal echocardiographic observations. Mayo Clin Proc 65:1432, 1990.

36. Kuhn C, Juchems R, Frese W: Evidence for the "cardiac pump theory" in cardiopulmonary resuscitation in man by transesophageal echocardiography. Resuscitation 22:275, 1991.

37. Redberg RF, Tucker KJ, Cohen TJ et al: Physiology of blood flow during cardiopulmonary resuscitation: A transesophageal echocardiographic study. Circulation 88:534, 1993.

38. Harada Y, Fuseno H, Ohtomo T et al: Self-administered hyperventilation cardiopulmonary resuscitation for 100 s of cardiac arrest during Holter monitoring. Chest 99:1310, 1991.

39. Criley JM, Niemann JT, Rosborough JP et al: Modifications of cardiopulmonary resuscitation based on the cough. Circulation 74(suppl IV):IV-42, 1986.

40. Halperin HR, Chandra NC, Levin HR et al: Newer methods of improving blood flow during CPR. Ann Emerg Med 27:553, 1996.

41. Cohen JM, Chandra N, Alderson PO et al: Timing of pulmonary and systemic blood flow during intermittent high intrathoracic pressure cardiopulmonary resuscitation in the dog. Am J Cardiol 49:1883, 1982.

42. Einagle V, Bertrand F, Wise RA et al: Interposed abdominal compressions and carotid blood flow during cardiopulmonary resuscitation: Support for a thoracoabdominal unit. Chest 93:1206, 1988.

43. Lindner KH, Ahnefeld FW, Bowdler IM: Cardiopulmonary resuscitation with interposed abdominal compression after asphyxial or fibrillatory cardiac arrest in pigs. Anesthesiology 72:675, 1990.

44. Sack JB, Kesselbrenner MB, Jarrad A: Interposed abdominal compression-cardiopulmonary resuscitation and resuscitation outcome during asystole and electromechanical dissociation. Circulation 86:1692, 1992.

45. Cohen TJ, Tucker KJ, Lurie KG et al: Active compression-decompression: A new method of cardiopulmonary resuscitation. JAMA 267:2916, 1992.

46. Pell ACH, Pringle SD, Guly UM et al: Assessment of the active compression-decompression device (ACD) in cardiopulmonary resuscitation using transesophageal echocardiography. Resuscitation 27:137, 1994.

47. Orliaguet GA, Carli PA, Rozenberg A et al: End-tidal carbon dioxide during out-of-hospital cardiac arrest resuscitation: Comparison of active compression-decompression and standard CPR. Ann Emerg Med 25:48, 1995.

48. Lurie KG, Coffeen P, Shultz J et al: Improving active compressiondecompression cardiopulmonary resuscitation with an inspiratory impedance valve. Circulation 91:1629, 1995.

49. Schultz JJ, Coffeen P, Sweeney M et al: Evaluation of standard and active compression-decompression CPR in an acute human model of ventricular fibrillation. Circulation 89:684, 1994.

50. Tucker KJ, Galli F, Savitt MA et al: Active compression-decompression resuscitation: Effect on resuscitation success after in-hospital cardiac arrest. J Am Coll Cardiol 24:201, 1994.

51. Lurie KG, Shultz JJ, Callaham ML et al: Evaluation of active compression-decompression CPR in victims of out-of-hospital cardiac arrest. JAMA 271:1405, 1994.

52. Schwab TM, Callaham ML, Madsen CD et al: A randomized clinical trial of active compression-decompression CPR vs standard CPR in out-of-hospital cardiac arrest in two cities. JAMA 273:1261, 1995.

53. Luiz T, Ellinger K, Denz C: Active compression-decompression cardiopulmonary resuscitation does not improve survival in patients with prehospital cardiac arrest in a physician-manned emergency medical system. J Cardiothorac Vasc Anesth 10:178, 1996.

54. Stiell IG, Hebert PC, Wells GA et al: The Ontario trial of active compression-decompression cardiopulmonary resuscitation for in-hospital and prehospital cardiac arrest. JAMA 275:1417, 1996.

55. Beattie C, Guerci AD, Hall T et al: Mechanisms of blood flow during pneumatic vest cardiopulmonary resuscitation. J Appl Physiol 70:454, 1991.

56. Halperin HR, Chandra NC, Levin HR et al: Newer methods of improving blood flow during CPR. Ann Emerg Med 27:553, 1996.

57. Halperin HR, Tsitlik JE, Gelfand M et al: A preliminary study of cardiopulmonary resuscitation by circumferential compression of the chest with use of a pneumatic vest. N Engl J Med 329:762, 1993.

58. Hackl W, Simon P, Mauritz W et al: Echocardiographic assessment of mitral valve function during mechanical cardiopulmonary resuscitation in pigs. Anesth Analg 70:350, 1990.

59. Chandra NC: Mechanisms of blood flow during CPR. Ann Emerg Med 22:281, 1993.

60. Sobotka P, Gebert E: Effect of complete brain ischaemia on pupillary changes. Acta Anaesthesiol Scand 16:112, 1972.

61. Steen-Hanson JE, Hansen NN, Vaagenes P et al: Pupil size and light reactivity during cardiopulmonary resuscitation: A clinical study. Crit Care Med 16:69, 1988.

62. Ornato JP: Hemodynamic monitoring during CPR. Ann Emerg Med 22:289, 1993.

63. Kalenda Z: The capnogram as a guide to the efficacy of cardiac massage. Resuscitation 6:259, 1978.

64. Grundler WG, Weil MH, Bisera J et al: Observations on end-tidal carbon dioxide during experimental cardiopulmonary arrest. Clin Res 32:672A, 1984.

65. Trevino RP, Bisera J, Weil MH et al: End-tidal CO_2 as a guide to successful cardiopulmonary resuscitation: A preliminary report. Crit Care Med 13:910, 1985.

66. Grundler W, Weil MH, Rackow EC: Arteriovenous carbon dioxide and pH gradients during cardiac arrest. Circulation 74:1071, 1986.

67. Sanders AB, Ewy GA, Bragg S et al: Expired P_{CO_2} as a prognostic indicator of successful resuscitation from cardiac arrest. Ann Emerg Med 14:948, 1985.

68. Sanders AB, Atlas M, Ewy GA et al: Expired P_{CO_2} as an index of coronary perfusion pressure. Am J Emerg Med 3:147, 1985.

69. Gudipati CV, Weil MH, Bisera J et al: Expired carbon dioxide: A noninvasive monitor of cardiopulmonary resuscitation. Circulation 77:234, 1988.

70. Garnett AR, Ornato JP, Gonzalez ER et al: End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. JAMA 257:512, 1987.

71. Sanders AB, Kern KB, Otto CW et al: End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation: A prognostic indicator for survival. JAMA 262:1347, 1989.

72. Falk JL, Rackow EC, Weil MH: End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. N Engl J Med 318:607, 1988.

73. Callaham M, Barton C: Prediction of outcome of cardiopulmonary resuscitation from end-tidal carbon dioxide concentration. Crit Care Med 18:358, 1990.

74. Steedman DJ, Robertson CE: Measurement of end-tidal carbon dioxide concentration during cardiopulmonary resuscitation. Arch Emerg Med 7:129, 1990.

75. Asplin BA, White RD: Prognostic value of end-tidal carbon dioxide pressures during out-of-hospital cardiac arrest. Ann Emerg Med 25:756, 1995.

76. Wayne MA, Levine RL, Miller CC: Use of end-tidal carbon dioxide to predict outcome in prehospital cardiac arrest. Ann Emerg Med 25:762, 1995.

77. Isserles SA, Breen PH: Can changes in end-tidal P CO_2 measure changes in cardiac output? Anesth Analg 73:808, 1991.

78. Shibutani K, Muraoka M, Shirasaki S et al: Do changes in end-tidal P CO_2 quantitatively reflect changes in cardiac output? Anesth Analg 79:829, 1994.

79. Trillo G, von Planta M, Kette F: ETCO $_2$ monitoring during low flow states: Clinical aims and limits. Resuscitation 27:1, 1994.

80. Idris AH: End-tidal carbon dioxide physiology and monitoring during resuscitation. Anesthesiol Clin North Am 13:785, 1995.

81. Keenan RL, Boyan CP: Cardiac arrest due to anesthesia: A study of incidence and causes. JAMA 253:2373, 1985.

82. Vandam LD: Cardiac arrest: Signal of anesthetic mishap. JAMA 253:2415, 1985.

83. Caplan RA, Ward RJ, Posner K et al: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

84. Keats AS: Anesthesia mortality: A new mechanism. Anesthesiology 68:2, 1988.

85. Schwid HA, O'Donnell DO: Anesthesiologists' management of simulated critical incidents. Anesthesiology 76:495, 1992.

86. White RD: Pharmacologic management of arrhythmias during advanced cardiac life support. Anesthesiol Clin North Am 13:849, 1995.

87. Mackey DC, Carpenter RL, Thompson GE et al: Bradycardia and asystole during spinal anesthesia: A report of three cases without morbidity. Anesthesiology 70:866, 1989.

88. Gonzalez ER: Pharmacologic controversies in CPR. Ann Emerg Med 22:317, 1993

89. Brown DL, Carpenter RL, Moore DC et al: Cardiac arrest during spinal anesthesia. III. Anesthesiology 68:971, 1988.

90. Falk RH, Zoll PM, Zoll RH: Safety and efficacy of noninvasive cardiac pacing: A preliminary report. N Engl J Med 309:1166, 1983.

91. Berliner D, Okun M, Peters RW et al: Transcutaneous temporary pacing in the operating room. JAMA 254:84, 1985.

92. Smith I, Monk TG, White PF: Comparison of transesophageal atrial pacing with anticholinergic drugs for the treatment of intraoperative bradycardia. Anesth Analg 78:245, 1994.

93. Atlee JL 3d, Pattison CZ, Mathews EL et al: Transesophageal atrial pacing for intraoperative sinus bradycardia or AV junctional rhythm: Feasibility as prophylaxis in 200 anesthetized adults and hemodynamic effects of treatment. J Cardiothorac Vasc Anesth 7:436, 1993.

94. Cochrane DJ, McEneaney DJ, Dempsey GJ et al: An esophageal and gastric approach to ventricular pacing. PACE 18:28, 1995.

95. Rankin AC, Brooks R, Ruskin JN et al: Adenosine and the treatment of supraventricular tachycardia. Am J Med 92:655, 1992.

96. Camm AJ, Garratt CJ: Adenosine and supraventricular tachycardia. N Engl J Med 325:1621, 1991.

97. DiMarco JP, Sellers TD, Lerman BB et al: Diagnostic and therapeutic use of adenosine in patients with supraventricular tachyarrhythmias. J Am Coll Cardiol 6:417, 1985.

98. Rankin AC, Oldroyd KG, Chong E et al: Value and limitations of adenosine in the diagnosis and treatment of narrow and broad complex tachycardias. Br Heart J 62:195, 1989.

99. Griffith MJ, Linker NJ, Ward DE et al: Adenosine in the diagnosis of broad complex tachycardia. Lancet 1:672, 1988.

100. Sharma AD, Klein GJ, Yee R: Intravenous adenosine triphosphate during wide QRS complex tachycardia: Safety, therapeutic efficacy, and diagnostic utility. Am J Med 88:337, 1990.

101. McIntosh-Yellin NL, Drew BJ, Scheinman MM: Safety and efficacy of central intravenous bolus administration of adenosine for termination of supraventricular tachycardia. J Am Coll Cardiol 22:741, 1993.

102. White RD: Acceleration of the ventricular response in paroxysmal lone atrial fibrillation following the injection of adenosine. Am J Emerg Med 11:245, 1993.

103. Slade AKB, Garratt CJ: Proarrhythmic effect of adenosine in a patient with atrial flutter. Br Heart J 70:91, 1993.

104. Brodsky MA, Allen BJ, Grimes JA et al: Enhanced atrioventricular conduction during atrial flutter after intravenous adenosine. N Engl J Med 330:288, 1994.

105. Brodsky MA, Hwang C, Hunter D et al: Life-threatening alterations in heart rate after the use of adenosine in atrial flutter. Am Heart J 130:564, 1995.

106. Shen W-K, Kurachi Y: Mechanisms of adenosine-mediated actions on cellular and clinical cardiac electrophysiology. Mayo Clin Proc 70:274, 1995.

107. DiMarco JP, Sellers TD, Berne RM et al: Adenosine: Electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. Circulation 68:1254, 1983.

108. Belardinelli L, Linden J, Berne RM: The cardiac effects of adenosine. Prog Cardiovasc Dis 32:73, 1989.

109. Lerman BB, Belardinelli L: Cardiac electrophysiology of adenosine: Basic and clinical concepts. Circulation 83:1499, 1991.

110. Lerman BB, Wesley RC, Belardinelli L: Electrophysiologic effects of dipyridamole on atrioventricular nodal conduction and supraventricular tachycardia: Role of endogenous adenosine. Circulation 80:1536, 1989.

111. German DC, Kredich NM, Bjornsson TD: Oral dipyridamole increases plasma adenosine levels in human beings. Clin Pharmacol Ther 45:80, 1989.

112. DeGroff CG, Silka MJ: Bronchospasm after intravenous administration of adenosine in a patient with asthma. J Pediatr 125:822, 1994.

113. Drake I, Routledge PA, Richards R: Bronchospasm induced by intravenous adenosine. Hum Exp Toxicol 13:263, 1994.

114. Bennett-Guerrero E, Young CC: Bronchospasm after intravenous adenosine administration. Anesth Analg 79:386, 1994.

115. Aggarwal A, Farber NE, Warltier DC: Intraoperative bronchospasm caused by adenosine. Anesthesiology 79:1132, 1993.

116. Waxman HL, Myerburg RJ, Appel R et al: Verapamil for control of ventricular rate in paroxysmal supraventricular tachycardia and atrial fibrillation or flutter: A double-blind randomized cross-over study. Ann Intern Med 94:1, 1981.

117. McGovern B, Garan H, Ruskin JN: Precipitation of cardiac arrest by verapamil in patients with Wolff-Parkinson-White syndrome. Ann Intern Med 104:791, 1986.

118. Gulamhusein S, Ko P, Carruthers SG et al: Acceleration of the ventricular response during atrial fibrillation in the Wolff-Parkinson-White syndrome after verapamil. Circulation 65:348, 1982.

119. Garratt C, Antoniou A, Ward D et al: Misuse of verapamil in preexcited atrial fibrillation. Lancet 1:367, 1989.

120. Stambler BS, Wood MA, Ellenbogen KA et al: Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Circulation 94:1613, 1996.

121. Scher DL, Arsura EL: Multifocal atrial tachycardia: Mechanisms, clinical correlates, and treatment. Am Heart J 118:574, 1989.

122. Varriale P, David W, Chryssos BE: Multifocal atrial arrhythmia--a frequent misdiagnosis? A correlative study using the computerized ECG. Clin Cardiol 15:343, 1992.

123. Schwartz M, Rodman D, Lowenstein SR: Recognition and treatment of multifocal atrial tachycardia: A critical review. J Emerg Med 12:353, 1994.

124. White RD: Prehospital recognition of multifocal atrial tachycardia: Association with acute myocardial infarction. Ann Emerg Med 21:753, 1992.

125. Strickberger SA, Miller CB, Levine JH: Multifocal atrial tachycardia from electrolyte imbalance. Am Heart J 115:680, 1988.

126. Salerno DM, Anderson B, Sharkey PJ et al: Intravenous verapamil for treatment of multifocal atrial tachycardia with and without calcium pretreatment. Ann Intern Med 107:623, 1987.

127. Levine JH, Michael JR, Guarnieri T: Treatment of multifocal atrial tachycardia with verapamil. N Engl J Med 312:21, 1985.

128. Jaffe AS: The use of antiarrhythmics in advanced cardiac life support. Ann Emerg Med 22:307, 1993.

129. Naccarelli GV, Jalal S: Intravenous amiodarone: Another option in the acute management of sustained ventricular tachyarrhythmias. Circulation 92:3154, 1995.

130. Kowey PR, Levine JH, Herre JM et al: Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. Circulation 92:3255, 1995.

131. Schienman MM, Levine JH, Cannom DS et al: Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. Circulation 92:3264, 1995.

132. Levine JH, Massumi A, Scheinman MM et al: Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. J Am Coll Cardiol 27:67, 1996.

133. Dessertenne F, Fabiato A, Coumel P: A new chapter of electrocardiography: The progressive variations in the amplitude of the electrocardiogram. Cardiovasc Drugs Ther 5:171, 1991.

134. Dessertenne F, Coumel P, Fabiato A: Ventricular fibrillation and torsades de pointes. Cardiovasc Drugs Ther 4:1177, 1990.

135. Priori SG, Napolitano C, Schwartz PJ: Electrophysiologic mechanisms involved in the development of torsades de pointes. Cardiovasc Drugs Ther 5:203, 1991.

136. Napolitano C, Priori SG, Schwartz PJ: Torsade de pointes: Mechanisms and management. Drugs 47:51, 1994.

137. Tan HL, Hou CJY, Lauer MR et al: Electrophysiologic mechanisms of the long QT interval syndromes and torsade de pointes. Ann Intern Med 122:701, 1995.

138. Kay GN, Plumb VJ, Arciniegas JG et al: Torsade de pointes: The long-short initiating sequence and other clinical features: Observations in 32 patients. J Am Coll Cardiol 2:806, 1983.

139. Hohnloser SH, Klingenheben T, Singh BN: Amiodarone-associated proarrhythmic effects: A review with special reference to torsade de pointes tachycardia. Ann Intern Med 121:529, 1994.

140. Nguyen PT, Scheinman MM, Seger J: Polymorphous ventricular tachycardia: Clinical characterization, therapy, and the QT interval. Circulation 74:340, 1986.

141. Soffer J, Dreifus LS, Michelson EL: Polymorphous ventricular tachycardia associated with normal and long Q-T intervals. Am J Cardiol 49:2021, 1982.

142. Wolfe CL, Nibley C, Bhandari A et al: Polymorphous ventricular tachycardia associated with acute myocardial infarction. Circulation 84:1543, 1991.

143. White RD, Wood DL: Out-of-hospital pleomorphic ventricular tachycardia and resuscitation: Association with acute myocardial ischemia and infarction. Ann Emerg Med 21:1282, 1992.

144. Keren A, Tzivoni D: Torsades de pointes: Prevention and therapy. Cardiovasc Drugs Ther 5:509, 1991.

145. Tzivoni D, Keren A, Cohen AM et al: Magnesium therapy for torsades de pointes. Am J Cardiol 53:528, 1984.

146. Tzivoni D, Banai S, Schuger C et al: Treatment of torsade de pointes with magnesium sulfate. Circulation 77:392, 1988.

147. Perticone F, Adinolfi L, Bonaduce D: Efficacy of magnesium sulfate in the treatment of torsade de pointes. Am Heart J 112:847, 1986.

148. Lerman BB, Belardinelli L, West GA et al: Adenosine-sensitive ventricular tachycardia: Evidence suggesting cyclic AMP-mediated triggered activity. Circulation 74:270, 1986.

149. Lerman BB: Response of nonreentrant catecholamine-mediated ventricular tachycardia to endogenous adenosine and acetylcholine: Evidence for myocardial receptor-mediated effects. Circulation 87:382, 1993.

150. Wilber DJ, Baerman J, Olshansky B et al: Adenosine-sensitive ventricular tachycardia: Clinical characteristics and response to catheter ablation. Circulation 87:126, 1993.

151. Wagner SR IV, Johnson SS, White RD: Intraoperative ventricular tachycardia responsive to adenosine. Anesth Analg 82:1086, 1996.

152. White RD: Out-of-hospital intervention in sudden cardiac death. In Brandenburg RO, Fuster V, Giuliani ER et al (eds): Cardiology: Fundamentals and Practice. Chicago, Year Book, 1994.

153. Eisenberg MS, Cummins RO: Defibrillation performed by the emergency medical technician. Circulation 74(suppl IV):IV-9, 1986.

154. Kelly PA, Cannom DS, Garan H et al: The automatic implantable cardioverter-defibrillator: Efficacy, complications and survival in patients with malignant ventricular arrhythmias. J Am Coll Cardiol 11:1278, 1988.

155. Akhtar M, Garan H, Lehmann MH et al: Sudden cardiac death: Management of high-risk patients. Ann Intern Med 114:499, 1991.

156. Fromer M, Brachmann J, Block M et al: Efficacy of automatic multimodal device therapy for ventricular tachyarrhythmias as delivered by a new implantable pacing cardioverter-defibrillation: Results of a European multicenter study of 102 implants. Circulation 86:363, 1992.

157. Naccarelli GV: Implantable cardioverter/defibrillators. In Willerson JT, Cohn JN (eds): Cardiovascular Medicine. New York, Churchill Livingstone, 1995, p 1441.

158. Saksena S, Diaz ML, Varanasi S et al: Third- and fourth-generation implantable cardioverter defibrillators: Current status and future development. J Intervent Cardiol 7:427, 1994.

159. Pinski SL, Trohman RG: Implantable cardioverter-defibrillators: Implications for the nonelectrophysiologist. Ann Intern Med 122:770, 1995.

160. Kerber RE: Electrical treatment of cardiac arrhythmias: Defibrillation and cardioversion. Ann Emerg Med 22:296, 1993.

161. White RD: Maintenance of defibrillators in a state of readiness. Ann Emerg Med 22:302, 1993.

162. Longstreth WT Jr, Diehr P, Inui TS: Prediction of awakening after out-of-hospital cardiac arrest. N Engl J Med 308:1378, 1983.

163. Longstreth WT Jr, Inui TS: High blood glucose level on hospital admission and poor neurologic recovery after cardiac arrest. Ann Neurol 15:59, 1984.

164. Lanier WL, Stangland KJ, Scheithauer BW et al: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. Anesthesiology 66:39, 1987.

165. Nakakimura K, Fleischer JE, Drummond JC et al: Glucose administration before cardiac arrest worsens neurologic outcome in cats. Anesthesiology 72:1005, 1990.

166. Chernow B, Holbrook P, D'Angona DS et al: Epinephrine absorption after intratracheal administration. Anesth Analg 63:829, 1984.

167. Roberts JR, Greenberg MI, Baskin SI: Endotracheal epinephrine in cardiorespiratory collapse. JACEP 8:515, 1979.

168. Roberts JR, Greenberg MI, Knaub MA et al: Blood levels following intravenous and endotracheal epinephrine administration. JACEP 8:53, 1979.

169. Michael JR, Guerci AD, Koehler RC et al: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. Circulation 69:822, 1984.

170. Schleien CL, Koehler RC, Gervais H et al: Organ blood flow and somatosensory-evoked potentials during and after cardiopulmonary resuscitation with epinephrine or phenylephrine. Circulation 79:1332, 1989.

171. Schleien CL, Dean JM, Koehler RC et al: Effect of epinephrine on cerebral and myocardial perfusion in an infant animal preparation of cardiopulmonary resuscitation. Circulation 73:809, 1986.

172. Paradis NA, Koscove EM: Epinephrine in cardiac arrest: A critical review. Ann Emerg Med 19:1288, 1990.

173. Brown CG, Werman HA: Adrenergic agonists during cardiopulmonary resuscitation. Resuscitation 19:1, 1990.

174. Brillman J, Sanders A, Otto CW et al: Comparison of epinephrine and phenylephrine for resuscitation and neurologic outcome of cardiac arrest in dogs. Ann Emerg Med 16:11, 1987.

175. Brown CG, Werman HA, Davis EA et al: The effect of high-dose phenylephrine versus epinephrine on regional cerebral blood flow during CPR. Ann Emerg Med 16:743, 1987.

176. Swenson RD, Weaver WD, Niskanen RA et al: Hemodynamics in humans during conventional and experimental methods of cardiopulmonary resuscitation. Circulation 78:630, 1988.

177. Brown CG, Werman HA, Davis EA et al: The effects of graded doses of epinephrine on regional myocardial blood flow during cardiopulmonary resuscitation in swine. Circulation 75:491, 1987.

178. Berkowitz ID, Gervais H, Schleien CL et al: Epinephrine dosage effects on cerebral and myocardial blood flow in an infant swine model of cardiopulmonary resuscitation. Anesthesiology 75:1041, 1991.

179. Martin D, Werman HA, Brown CG: Four case studies: High-dose epinephrine in cardiac arrest. Ann Emerg Med 19:322, 1990.

180. Koscove EM, Paradis NA: Successful resuscitation from cardiac arrest using high-dose epinephrine therapy: Report of two cases. JAMA 259:3031, 1988.

181. Paradis NA, Martin GB, Rosenberg J et al: The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation. JAMA 265:1139, 1991.

182. Barton C, Callaham M: High-dose epinephrine improves the return of spontaneous circulation rates in human victims of cardiac arrest. Ann Emerg Med 20:722, 1991.

183. Callaham M, Madsen CD, Barton CW et al: A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. JAMA 268:2667, 1992.

184. Stiell IG, Hebert PC, Weitzman BN et al: High-dose epinephrine in adult cardiac arrest. N Engl J Med 327:1045, 1992.

185. Brown CG, Martin DR, Pepe PE et al: A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. N Engl J Med 327:1051, 1992.

186. Ornato JP: Use of adrenergic agonists during CPR in adults. Ann Emerg Med 22:411, 1993.

187. Lake CL, Kron IL, Mentzer RM et al: Lidocaine enhances intraoperative ventricular defibrillation. Anesth Analg 65:337, 1986.

188. Dorian P, Fain ES, Davy J-M et al: Lidocaine causes a reversible, concentration-dependent increase in defibrillation energy requirements. J Am Coll Cardiol 8:327, 1986.

189. Chow MSS, Kluger J, Lawrence R et al: The effect of lidocaine and bretylium on the defibrillation threshold during cardiac arrest and cardiopulmonary resuscitation. Proc Soc Exp Biol Med 182:63, 1986.

190. Ujhelyi MR, Schur M, Frede T et al: Differential effects of lidocaine on defibrillation threshold with monophasic versus biphasic shock waveforms. Circulation 92:1644, 1995.

191. Koch-Weser J: Drug therapy: Bretylium. N Engl J Med 300:473, 1979.

192. Cardinal R, Sasyniuk BI: Electrophysiological effects of bretylium tosylate on subendocardial Purkinje fibers from infarcted canine hearts. J Pharmacol Exp Ther 204:159, 1978.

193. Nishimura M, Watanabe Y: Membrane action and catecholamine release action of bretylium tosylate in normoxic and hypoxic canine Purkinje fibers. J Am Coll Cardiol 2:287, 1983.

194. Iseri LT: Role of magnesium in cardiac tachyarrhythmias. Am J Cardiol 65:47K, 1990.

195. DiCarlo LA, Morady F, de Buitleir M et al: Effects of magnesium sulfate on cardiac conduction and refractoriness in humans. J Am Coll Cardiol 7:1356, 1986.

196. Nattel S, Turmel N, MacLeod R et al: Actions of intravenous magnesium on ventricular arrhythmias caused by acute myocardial infarction. J Pharmacol Exp Ther 259:939, 1991.

197. Tzivoni D, Keren A: Suppression of ventricular arrhythmias by magnesium. Am J Cardiol 65:1397, 1990.

198. England MR, Gordon G, Salem M et al: Magnesium administration and dysrhythmias after cardiac surgery: A placebo-controlled, double-blind, randomized trial. JAMA 268:2395, 1992.

199. Tso EL, Barish RA: Magnesium: Clinical considerations. J Emerg Med 10:735, 1992.

200. Levine SR, Crowley TJ, Hai HA: Hypomagnesemia and ventricular tachycardia. Chest 81:244, 1982.

201. Tobey RC, Birnbaum GA, Allegra JR et al: Successful resuscitation and neurologic recovery from refractory ventricular fibrillation after magnesium sulfate administration. Ann Emerg Med 21:92, 1992.

202. Craddock L, Miller B, Clifton G et al: Resuscitation from prolonged cardiac arrest with high-dose intravenous magnesium sulfate. J Emerg Med 9:469, 1991.

203. Guerci AD, Chandra N, Johnson E et al: Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs. Circulation 74(suppl IV):IV-75, 1986.

204. Weil MH, Trevino RP, Rackow EC: Sodium bicarbonate during CPR: Does it help or hinder? Chest 88:487, 1985.

205. Matter JA, Weil MH, Shubin H et al: Cardiac arrest in the critically ill. II. Hyperosmolal states following cardiac arrest. Am J Med 56:162, 1974.

206. Bishop RL, Weisfeldt ML: Sodium bicarbonate administration during cardiac arrest: Effect on arterial pH, P_{CO_2}, and osmolality. JAMA 235:506, 1976.

207. Berenyi KJ, Wolk M, Killip T: Cerebrospinal fluid acidosis complicating therapy of experimental cardiopulmonary arrest. Circulation 52:319, 1975.

208. Weil MH, Rackow EC, Trevino R et al: Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 315:153, 1986.

209. von Planta M, Weil MH, Gazmuri RJ et al: Myocardial acidosis associated with CO_2 production during cardiac arrest and resuscitation. Circulation 80:684, 1989.

210. Kette F, Weil MH, von Planta M et al: Buffer agents do not reverse intramyocardial acidosis during cardiac resuscitation. Circulation 81:1660, 1990.

211. Maldonado FA, Weil MH, Tang W et al: Myocardial hypercarbic acidosis reduces cardiac resuscitability. Anesthesiology 78:343, 1993.

212. von Planta M, Bar-Joseph G, Wiklund L et al: Pathophysiologic and therapeutic implications of acid-base changes during CPR. Ann Emerg Med 22:404, 1993.

213. Bircher NG: Acid-base physiology during advanced cardiac life support. Anesthesiol Clin North Am 13:799, 1995.

214. Vukmir RB, Bircher NG, Radovsky A et al: Sodium bicarbonate may improve outcome in dogs with brief or prolonged cardiac arrest. Crit Care Med 23:515, 1995.

215. Gazmuri RJ, von Planta M, Weil MH et al: Cardiac effects of carbon dioxide-consuming and carbon dioxide-generating buffers during cardiopulmonary resuscitation. J Am Coll Cardiol 15:482, 1990.

216. Wiklund L, Ronquist G, Stjernstrom H et al: Effects of alkaline buffer administration on survival and myocardial energy metabolism in pigs subjected to ventricular fibrillation and closed-chest CPR. Acta Anaesthesiol Scand 34:430, 1990.

217. Saphir R: External cardiac massage: Prospective analysis of 123 cases and review of the literature. Medicine 47:73, 1968.

218. Lemire JG, Johnson AL: Is cardiac resuscitation worthwhile? A decade of experience. N Engl J Med 286:970, 1972.

219. Wildsmith JAW, Dennyson WG, Myers KW: Results of resuscitation following cardiac arrest. Br J Anaesth 44:716, 1972.

220. Eltringham RJ, Baskett PJF: Experience with a hospital resuscitation service including an analysis of 258 calls to patients with cardiorespiratory arrest. Resuscitation 2:57, 1973.

221. Jeresaty RM, Liss JP, Basu SK: Long-term follow-up of 122 patients who survived cardiac arrest. Resuscitation 2:191, 1973.

222. Bedell SE, Delbanco TL, Cook EF et al: Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 309:569, 1983.

223. Sowden GR, Robins DW, Baskett PJ: Factors associated with survival and eventual cerebral status following cardiac arrest. Anaesthesia 39:39, 1984.

224. Taffet GE, Teasdale TA, Luchi RJ: In-hospital cardiopulmonary resuscitation. JAMA 260:2069, 1988.

225. Karetzky M, Zubair M, Parikh J: Cardiopulmonary resuscitation in intensive care unit and non-intensive care unit patients. Arch Intern Med 155:1277, 1995.

226. Berger R, Kelley M: Survival after in-hospital cardiopulmonary arrest of noncritically ill patients: A prospective study. Chest 106:872, 1994.

227. Ballew KA, Philbrick JT, Caven DE et al: Predictors of survival following in-hospital cardiopulmonary resuscitation: A moving target. Arch Intern Med 154:2426, 1994.

228. Gerardi LN, Barie PS: Improved survival after intraoperative cardiac arrest in noncardiac surgical patients. Arch Surg 130:15, 1995.

229. Murphy DJ: Do-not-resuscitate orders: Time for reappraisal in long-term-care institutions. JAMA 260:2098, 1988.

230. Youngner SJ: The decision to forgo CPR in the elderly patient. JAMA 260:2096, 1988.

231. Council on Ethical and Judicial Affairs, American Medical Association: Guidelines for the appropriate use of do-not-resuscitate orders. JAMA 265:1868, 1991.

232. Jayes RL, Zimmerman JE, Wagner DP et al: Do-not-resuscitate orders in intensive care units: Current practices and recent changes. JAMA 270:2213, 1993.

233. Martin RL, Soifer BE, Stevens WC: Ethical issues in anesthesia: Management of the do-not-resuscitate patient. Anesth Analg 73:221, 1991.

234. Keffer MJ, Keffer HL: Do-not-resuscitate in the operating room: Moral obligations of anesthesiologists. Anesth Analg 74:901, 1992.

235. Truog RD: "Do-not-resuscitate" orders during anesthesia and surgery. Anesthesiology 74:606, 1991.

236. Cohen CB, Cohen PJ: Do-not-resuscitate orders in the operating room. N Engl J Med 325:1879, 1991.

237. Walker RM: DNR in the OR: Resuscitation as an operative risk. JAMA 266:2407, 1991.

238. Clemency MV, Thompson NJ: "Do not resuscitate" (DNR) orders in the perioperative period: A comparison of the perspectives of anesthesiologists, internists, and surgeons. Anesth Analg 78:651, 1994.

239. Margolis JO, McGrath BJ, Kussin PS et al: Do not resuscitate (DNR) orders during surgery: Ethical foundations for institutional policies in the United States. Anesth Analg 80:806, 1995.

240. Layon AJ, Dirk L: Resuscitation and DNR: Ethical aspects for anaesthetists. Can J Anaesth 42:134, 1995.

241. American Society of Anesthesiologists: Ethical guidelines for the anesthesia care of patients with do-not-resuscitate orders or other directives that limit treatment. In 1996 Directory of Members, 61st ed. Park Ridge, Ill, American Society of Anesthesiologists, 1996, p 400.

242. Ludwig S, Kettrick RG, Parker M: Pediatric cardiopulmonary resuscitation: A review of 130 cases. Clin Pediatr 23:71, 1984.

243. Torphy DE, Minter MG, Thompson BM: Cardiorespiratory arrest and resuscitation of children. Am J Dis Child 138:1099, 1984.

244. Subcommittee on Pediatric Resuscitation: Textbook of Pediatric Basic Life Support. Dallas, American Heart Association, 1994.

245. Chameides L (ed): Instructor's Manual for Pediatric Basic Life Support. Dallas, American Heart Association, 1994.

246. Chameides L (ed): Textbook of Pediatric Advanced Life Support. Dallas, American Heart Association, 1994.

247. Finholt DA, Kettrick RG, Wagner HR et al: The heart is under the lower third of the sternum: Implications for external cardiac massage. Am J Dis Child 140:646, 1986.

248. Phillips GW, Ziderman DA: Relation of infant heart to sternum: Its significance in cardiopulmonary resuscitation. Lancet 1:1024, 1986.

249. Walsh CK, Krongrad E: Terminal cardiac electrical activity in pediatric patients. Am J Cardiol 51:557, 1983.

250. Gillis J, Dickson D, Rieder M et al: Results of inpatient pediatric resuscitation. Crit Care Med 14:469, 1986.

251. Friesen RM, Duncan P, Tweed WA et al: Appraisal of pediatric cardiopulmonary resuscitation. Can Med Assoc J 126:1055, 1982.

252. Kuisma M, Suominun P, Korpela R: Paediatric out-of-hospital cardiac arrests: Epidemiology and outcome. Resuscitation 30:141, 1995.

253. Mogayzel C, Quan L, Graves JR et al: Out-of-hospital ventricular fibrillation in children and adolescents: Causes and outcomes. Ann Emerg Med 25:484, 1995.

254. Todres ID: Pediatric airway control and ventilation. Ann Emerg Med 22:440, 1993.

255. Paterson SJ, Byrne PJ, Molesky MG et al: Neonatal resuscitation using the laryngeal mask airway. Anesthesiology 80:1248, 1994.

256. Baraka A: Laryngeal mask airway for resuscitation of a newborn with Pierre-Robin syndrome. Anesthesiology 83:645, 1995.

257. Brimacombe J, Berry A: The laryngeal mask airway: A consideration for the Neonatal Resuscitation Programme guidelines? Can J Anaesth 42:88, 1995.

258. Garson A Jr, Gillette PC, McNamara DG: Supraventricular tachycardia in children: Clinical features, response to treatment, and long-term follow-up in 217 patients. J Pediatr 98:875, 1981.

259. Gikonyo BM, Dunnigan A, Benson DW Jr: Cardiovascular collapse in infants: Association with paroxysmal atrial tachycardia. Pediatrics 76:922, 1985.

260. Overholt E, Rheuban K, Gutgesell H et al: Usefulness of adenosine for arrhythmias in infants and children. Am J Cardiol 61:336, 1988.

261. Ralston MA, Knilans TK, Hannon DW et al: Use of adenosine for diagnosis and treatment of tachyarrhythmias in pediatric patients. J Pediatr 124:139, 1994.

262. Kugler JD, Danford DA: Management of infants, children, and adolescents with paroxysmal supraventricular tachycardia. J Pediatr 129:324, 1996.

263. Epstein M, Kiel E, Victorica B: Cardiac decompensation following verapamil in infants with supraventricular tachycardia. Pediatrics 75:737, 1985.

264. Garson A Jr: Medicolegal problems in the management of cardiac arrhythmias in children. Pediatrics 79:84, 1987.

265. Zaritsky A: Pediatric resuscitation pharmacology. Ann Emerg Med 22:445, 1993.

266. Goetting MG, Paradis NA: High dose epinephrine in refractory pediatric cardiac arrest. Crit Care Med 17:1258, 1989.

267. Goetting MG, Paradis NA: High-dose epinephrine improves outcome from pediatric cardiac arrest. Ann Emerg Med 20:22, 1991.

268. Koehler RC, Michael JR, Guerci AD et al: Beneficial effect of epinephrine infusion on cerebral and myocardial blood flows during CPR. Ann Emerg Med 14:744, 1985.

269. Berg RA: Emergency infusion of catecholamines into bone marrow. Am J Dis Child 138:810, 1984.

270. Kanter RK, Zimmerman JJ, Strauss RH et al: Pediatric emergency intravenous access. Am J Dis Child 140:132, 1986.

271. Rosetti VA, Thompson BM, Miller J et al: Intraosseous infusion: An alternative route of pediatric intravascular access. Ann Emerg Med 14:885, 1985.

272. Smith RJ, Keseg DP, Manley LK et al: Intraosseous infusions by prehospital personnel in critically ill pediatric patients. Ann Emerg Med 17:491, 1988.

273. Atkins DL, Kerber RE: Pediatric defibrillation: Current flow is improved by using "adult" electrode paddles. Pediatrics 94:90, 1994.

274. Halperin HR: Mechanisms of forward flow during external chest compression. In Paradis NA, Halperin HR, Nowak RM (eds): Cardiac Arrest: The Science and Practice of Resuscitation Medicine. Baltimore, Williams & Wilkins, 1995, p 252.

275. Bertolet BD, Hill JA: Adenosine: Diagnostic and therapeutic uses in cardiovascular medicine. Chest 104:1860, 1993.

Chapter 76 - Brain Death

Kenjiro Mori
Koh Shingu
Shin-ichi Nakao

INTRODUCTION

Because advancements in medicine have changed the definition and concept of death, legislation must also change accordingly. This issue results from progress in organ transplantation and the increasing number of patients who have a living body but a nonfunctioning brain. The latter circumstance results from new discoveries in resuscitative and life-support techniques. Such refinements in critical care medicine mean that not only neurologists and neurosurgeons but also anesthesiologists must now more than ever be able to make an appropriate diagnosis of "death."

HISTORY

In 1902, Cushing [1] first reported cessation of cerebral circulation when intracranial pressure exceeded arterial blood pressure in monkeys. He also described the use of artificial ventilation to prolong cardiac function for 23 hours after cessation of spontaneous respiration in a patient with a brain tumor. [1] In 1959, Bertrand et al [2] reported the maintenance of respiration by mechanical means for 3 days after death of a patient with otitis media who underwent circulatory collapse. Repeated convulsions in this patient had preceded a deep coma. Autopsy revealed extensive brain necrosis of the cerebral and cerebellar cortices, basal ganglia, and brain-stem nuclei, attributed to cessation of cerebral circulation during artificial ventilation. Also in 1959 appeared the first description of cessation of brain functions using a concept similar to today's definition of brain death, "le coma deasse" by Mollaret and Goulon. [3]

These historical reports support the argument that the concept of brain death is independent of, and was established before, the start of organ transplantation from brain-dead patients. However, there is still dispute whether brain death is or is not directly related to organ transplantation. Actually, the heated discussion on brain death started after the first heart implantation by Barnard in 1967. One year later, Harvard Medical School [4] published its criteria for brain death, followed by numerous other publications and criteria. [5] [6] [7] [8] [9]

TRADITIONAL CONCEPT OF DEATH OF AN ORGANISM

All living organisms take in oxygen by respiration, distribute the oxygen to peripheral tissues through circulation, and then excrete metabolites by means of both circulation and

respiration. Therefore, both respiration and circulation are vital to the living organism. Respiration is the functional expression of the brain stem, and cessation of brain-stem functions leads to the cessation of respiration. Furthermore, because the brain stem maintains its function through its supply of oxygen and nutrients, cessation of circulation ultimately leads to cessation of respiration. The functions of the brain, heart, and lungs are thus mutually dependent and share the basic role of maintaining life. An organism dies when one of these life-sustaining organ systems ceases to function.

The traditional concept of death of an organism emphasized the cessation of either respiration or circulation, without consideration for the role of the brain. This was so simply because assessment of brain function was not easy to accomplish. Furthermore, when mechanical ventilation was not widely used, cessation of brain functions related directly to cessation of respiration, and assessment of brain-stem functions was unnecessary.

CONCEPT OF BRAIN DEATH

"Brain death" represents death of the organism and not merely death or necrosis of the brain in a living body. The organism is an aggregation of living cells. However, a simple aggregation of living cells does not necessarily constitute an organism. An organism exists only when the cell aggregation is put under the control of modulating systems such as the central nervous system (CNS), the endocrine system, and the immune system. [10] [11] [12] Once any one of these systems ceases to function, death is inevitable unless artificial measures can be taken. The physiologic significance of brain death and of cardiac death is essentially equal; both types of death represent an irreversible loss of communication between the control center and peripheral cells and tissues and/or loss of modulation of an aggregation of cells. Without these systems, harmonious functioning of the individual cells as constituents of the whole organism ceases. Because total and irreversible elimination of immune or endocrine function is not a phenomenon of reality, in contrast to the CNS, the concept of endocrine or immune death does not exist.

Previously, cessation of respiration was equivalent to immediate death of the organism. Artificial ventilation is able to prolong the life of a body for a certain period of time. Until several years ago, cessation of brain functions inevitably led to cessation of cardiac function within 10 to 14 days. [13] [14] [15] [16] [17] Various functions are believed to reside in the hypothalamus and brain stem--endocrine, autonomic, and immune functions, as well as others that are currently unknown. The brain stem also contains the main tracts for neural communication between the control center and peripheral tissues. All the motor outputs from the hemispheres have to travel through the brain stem, as do all the sensory inputs to the brain (except sight and smell). Each of these functions of hypothalamus and brain stem can be monitored precisely and provided artificially. At present, autonomous respiratory function of the lower brain stem constitutes the border between life and death, and the need for mechanical devices to supply respiratory functions is defined as representing death of the individual. Possibly, most of the brain functions vital to life could be replaced with computers and drugs, and the circulatory functions could be maintained for months and years. However, the only function advance technology cannot provide is that constituting "humanity" or "personality," both of which are possibly products of the telencephalon.

The traditional concept of death has used the cessation of cardiac and respiratory functions as its basis, owing to acceptance of simple and nonmedical concepts: that life begins with the first inspiration after birth, that death comes with the last expiration, and that cardiac activity ceases within a few minutes of the last expiration. By contrast, today's concept of brain death adopts the conclusions of modern biologic science: (1) the CNS, including the brain stem, is the control center for the living organism; (2) cessation of CNS functions represents cessation of the harmony of life; and (3) without CNS control, the living organism is nothing more than a simple aggregation of living cells.

MECHANISM OF BRAIN DEATH

Brain injury has a number of sources, such as traumatic or cerebrovascular injury and generalized hypoxia, all of which produce brain edema. Based on the pathologic mechanisms involved, brain edema is classified as either vasogenic or cytotoxic. [18] [19] [20] Because it is rare that only one mechanism operates exclusively, the label "vasogenic" or "cytotoxic" is only relative.

Vasogenic edema is induced by an increase in cerebrovascular permeability after leaking of serum proteins into the brain parenchyma (i.e., after destruction of the blood-brain barrier). Chemical mediators such as histamine, serotonin, angiotensin, bradykinin, and prostaglandins are believed to induce destruction of the blood-brain barrier. [21]

Cytotoxic brain edema occurs in hypoxia and ischemic conditions and results from disturbance of cellular osmoregulation, a process that depends primarily on energydependent functioning of ionic pumps. The disturbance of osmoregulation increases entry of water into brain parenchyma. Although in a pure form of cytotoxic edema the blood-brain barrier would remain basically intact, cytotoxic edema would nevertheless disturb blood flow and thus would induce hypoxia and vasogenic edema.

Brain edema may be focal at first, but then it spreads throughout the whole brain in the following sequence. Because the brain is covered by a rigid bony skull, its edema is accompanied by an increase in intracranial pressure, which, if sufficiently high, exceeds arterial blood pressure. When cerebral circulation ceases, aseptic necrosis of the brain ensues. Within 3 to 5 days, the brain becomes a liquefied mass, a condition known as "respirator brain." [22] Such increased intracranial pressure compresses the entire brain, including the brain stem, and "total brain infarction" follows. [23]

NEUROPHYSIOLOGIC BASIS OF BRAIN DEATH

Areas of the Brain Involved

By definition, brain death is a total irreversible cessation of functioning of the brain. "Brain" includes all the CNS

structures except the spinal cord. However, the definition used by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology includes the first cervical spine segment. [6] It is generally agreed that brain death does not include lower portions of the spinal cord (caudal from C2), because their location outside the skull spares them from compression during brain edema. Histologic studies of human spinal cord in brain death revealed divergent pathologic findings ranging from histologically intact tissues to complete destruction. [22]

The United Kingdom [9] and Belgium [24] adopted, and the Eurasian Neurosurgical Academy [24] supported, a rather exceptional criterion for brain death, one that excludes involvement of the bilateral cerebral cortices. [25] This state, known as "brain-stem death," does not require recording of an electroencephalogram (EEG) for its diagnosis. The rationale for excluding the cerebral cortices is that the brain stem, and not the cerebral cortices, plays the major role in controlling whole-body vital activities such as respiration, circulation, and other homeostatic functions. Furthermore, we believe that if the cerebral cortices were excluded, assessment of brain-stem functions would be more careful, and the danger of mistaking the vegetative state for brain death could be avoided.

Consciousness and the Electroencephalogram

Bremer [26] and Moruzzi and Magoun [27] demonstrated the essential role of the brain-stem reticular core in activating the cortical EEG. Segundo et al [28] showed that destruction of the brain-stem reticular core leads to loss of consciousness in laboratory animals. In brain death, the patient is believed to have no consciousness, no intellectual activity, and thus no true "humanity." This state is defined as "deep coma" and is the basis for the concept of brain-stem death.

Since the 1960s, laboratory studies have shown that the control mechanisms for the sleep-wake cycle are located in the lower brain stem (i.e., the pontine and medullary reticular formation). [29] Animals subjected to resection of the cerebral cortices and diencephalon still underwent a sleep-wake cycle, took a sphinx position, and responded to auditory stimuli. [29] This animal model represents the complete Apallic syndrome in humans. However, the psychophysiology of the Apallic syndrome has not been studied sufficiently in humans, and no information is available on the state of consciousness, personality, and intellectual activities of such patients.

Hockaday et al [30] and Schwab et al [31] studied the EEG of 550 comatose patients, analyzed EEG for 26 cases of sudden cardiac arrest and 13 cases of respiratory arrest, and classified abnormalities on EEG into five grades according to final outcome (Table 76-1) (Table Not Available) . The prognosis for patients belonging to grade I was favorable. The determination of the prognosis for grade II and III patients required repeated recording of the EEG. When the EEG showed improvement on the day 2 or 3 recording session, the prognosis was favorable. When the EEG tended to deteriorate, the prognosis was poor. In this system, grade Vb represented the EEG for brain death.

TABLE 76-1 -- Arbitrary Classification of Abnormalities on Encephalogram, With Two Subdivisions, Based on Final Outcome for 550 Comatose Patients

(Not Available)

From Hockaday et al, [30] with permission from Elsevier Science.

Significant EEG changes occur when blood flow is less than 18 mL/100 g/min [32] and becomes isoelectric when blood flow is in the range of 12 to 15 mL/100 g/min. [33] Paolin et al [34] reported that 7 of 15 patients with a clinical diagnosis of brain death showed persistent electrical activity, although both cerebral blood flow measurements with xenon-133 (^{133} Xe) and selective cerebral angiography showed intracranial circulatory arrest.

Respiration

The primary respiratory center, consisting of the inspiratory and expiratory neurons, is located in the reticular core of the medulla oblongata. Although the other respiratory neurons distributed in the pons are believed to affect the activities of these neurons, [35] [36] this theory is undergoing modification. [37] [38] Various abnormal patterns of respiration (e.g., gasping, apneusis, and irregular shallow respirations) are observed in laboratory animals and humans having brain-stem lesions. In brain death, spontaneous respiration does not occur in patients even when arterial carbon dioxide partial pressure (Pa $_{CO_2}$) reaches 55 to 60 mm Hg. The presence or absence of respiration is assessed by visual observation of movement of the thorax or the respiratory bag connected to the endotracheal tube. Mechanical stimulation of the carina to induce the cough reflex may be helpful in detecting residual functioning of the medullary respiratory neurons.

Cardiovascular Functions

The central neurons that control the circulatory system distribute diffusely in the pontine and medullary reticular core. [39] Of these neurons, the vasomotor and cardioaccelerating

neurons undergo negative feedback control through the carotid and aortic sinus nerves, which relay at the nucleus solitarius. Activation of these cells induces sympathetic nervous outflow, thereby increasing heart rate and arterial blood pressure. Hypertension then suppresses these cells through the feedback mechanism, and circulation returns to preactivation levels.

During the process of brain death after head injury or intracranial bleeding, intracranial pressure increases, and compression of the brain stem leads to marked hypertension (Cushing syndrome). When intracranial pressure is elevated, arterial blood pressure suddenly decreases (Fig. 76-1) . This sudden decrease is the sign of "tonsillar herniation" (herniation of the cerebellar tonsils) through the foramen magnum on the cervical spinal cord, in which outflow of the cardioaccelerating and vasomotor neurons to the spinal cord suddenly ceases. This is one typical onset for brain death. Such dramatic changes in arterial blood pressure are not observed in

other types of brain death such as that induced by hypoxia or those involving other intricate factors. The vasomotor and cardioaccelerating neurons of the spinal cord (located in the lateral horn) obtain automaticity within several days of disconnection from the supraspinal structures, and arterial blood pressure returns to normal without supplementation with vasopressors. [40] This situation is familiar to anesthesiologists, because background arterial blood pressure is usually normal in tetraplegic patients.

After the establishment of brain death, different types of autonomic spinal cord reflexes develop, such as elevation of arterial blood pressure because of bladder distention. Extreme elevation by noxious stimulation is well known in patients with chronic tetraplegia, but it has not been reported for brain death. Although the cardioaccelerating and vasomotor neurons are located in the brain stem, changes in arterial blood pressure are not used as an index of brain-stem function. That is, the condition of the circulatory system changes greatly in brain death, making precise interpretation of the meaning of changes in arterial blood pressure therefore very difficult, if not impossible.

Regulation of Body Temperature

Rodbard [41] suggested that the neural mechanisms governing homeostatic temperature control developed in the hypothalamus from circulatory control neurons in the course of evolution from reptile to mammal. The heat-sensitive center consists of both the heat-loss center in the anterior hypothalamus and the heat-producing center in the posterior hypothalamus. [42] [43] [44] Body temperature is regulated when changes in blood temperature stimulate heat-sensitive receptors in the hypothalamus. Nerve impulses from cold receptors in the skin can also activate heat-producing neurons. The most important heat producers are the skeletal muscles, brain, liver, and heart. The greatest heat radiator is the skin, especially that on the hands. Local electrical stimulation of the heat-producing center induces shivering and constriction of blood vessels in the skin, thus activating vasomotor nerves and decreasing blood flow. Warming of the heat-loss center suppresses vasomotor nerve activity and in this way increases blood flow through the skin.

In brain death, the neural connection between the temperature-regulating center and peripheral body tissues is lost, and the patient becomes poikilothermic. When criteria from the National Institute of Neurological Diseases and Stroke were applied to establish brain death, such patients showed only a "tendency for the temperatures to be subnormal." [22] By contrast, when brain death was established using the criterion of cessation of all brain stem functions, "poikilothermia was found in all patients later than 24 hours after brain death." [45] Even if infection occurs, fever should not develop in brain death, because the temperature-regulating centers no longer function. After brain death, body temperature tends to be hypothermic, even with vigorous application of external heat.

Figure 76-1 The representative time course of arterial blood pressure and heart rate before and after brain death. The patient was an 18-year-old man involved in a traffic accident. Sustained hypertension was followed by a sudden and marked decrease in blood pressure. Dopamine was administered to increase blood pressure, which gradually became stable. Doses of dopamine were tapered and finally became unnecessary.

Hypothalamic-Pituitary Endocrine Functions

Not all the criteria used to establish brain death attempt to determine whether functions of the hypothalamus are preserved. Clinical studies have indicated that hypothalamic and anterior pituitary functions are preserved to a certain degree for a certain period of time after the onset of brain death. Hall et al [46] and Schrader et al [47] reported normal levels of anterior pituitary hormones, half-lives of which are less than 1 hour, such as thyroid-stimulating hormone, prolactin, growth hormone, and luteinizing hormone, as well as positive tests for the hypothalamic hormones luteinizing-hormone releasing hormone and thyrotropin-releasing hormone for 2 to 24 hours after determination of brain death. Sugimoto et al [48] confirmed that concentrations of these hormones were normal for more than 1 week. By contrast, vasopressin, a hormone produced in the hypothalamus and stored in the posterior pituitary, decreased sharply after brain death. [48] The occurrence of diabetes insipidus is variable. In one study, many patients did not have diabetes insipidus after brain death. [49] Another study said that diabetes insipidus did not develop in 23 percent of 31 patients with brain death. [50] Both results indicate sustained secretion of vasopressin. It has become evident that when arginine vasopressin is added to the infusion in cases of brain death with diabetes insipidus, the heartbeat can be maintained for several months. [51]

The diaphragma sellae protects the pituitary gland from compression caused by swelling of the brain. Blood supply to the pituitary gland comes mostly from the superior, middle, and inferior hypophyseal arteries and the capsular arteries. The portal venous system is another source of blood supply to the anterior lobe. In brain death, blood supply through the superior hypophyseal artery and the portal vein would be easily blocked. However, blood supply through the cavernous portion of the internal carotid artery and its branches, such as the inferior hypophyseal artery and the capsular artery, may possibly be spared. [48] [52] [53] Morphologic studies of brain death indicate that damage to the anterior lobe is incomplete but severe, whereas the posterior lobe is relatively preserved. [48] However, because antidiuretic hormone (ADH) is synthesized in the hypothalamus and is transferred to the posterior lobe of the pituitary through axoplasmic flow along the long axon, depletion of this hormone may be greater than one would expect from the only slight morphologic damage seen in the posterior lobe.

In studies on brain death, the hypothalamic hormones, such as growth hormone-releasing hormone, corticotropin-releasing hormone, thyroxine-releasing hormone, and luteinizing hormone-releasing hormone were at trace to subnormal levels. [48] [54] Schrader et al [47] reported a normal growth hormone response to hypoglycemic stimulation. Arita et al [55] also demonstrated that insulin and arginine increased growth hormone in brain-dead patients. Hypoglycemia affects glucoreceptors in ventromedial nucleus to stimulate release of growth hormone- and corticotropinreleasing hormones and finally stimulates growth hormone or corticotropin release, indicating that some hypothalamic function is preserved.

The origin of the hypothalamic hormones released in brain death cannot be identified. Results from morphologic studies of the hypothalamus are controversial. Walker et al [22] reported that the neurons with lytic changes were intermingled with relatively normal cells, a result that may account for the sustained secretion of hypothalamic hormones. Sugimoto et al [48] observed extensive necrosis of the hypothalamus after day 6 of brain death and postulated a nonbrain supply of these hormones, such as the pancreas, intestine, or adrenal gland. The hypothalamus receives its blood supply through the branches of the superior hypophyseal and posterior communicating arteries (Fig. 76-2) (Figure Not Available) . Blood flow to the hypothalamus, at least its basal part, may be preserved in relatively mild instances of intracranial hypertension. The survival of the hypothalamus after brain death is an issue for future study.

Immune System

The immune system is also under the control of the CNS. Even if the immune system is intact, its response to stimulation is modified considerably after total irreversible loss of CNS functions. No information is available as to whether brain death entails vulnerability to infection. Amado et al [56] investigated interleukin-1 beta, tumor necrosis factor-alpha, and interleukin-6 in brain-dead patients and reported that although interleukin-1 and tumor necrosis factor levels were within the normal range, interleukin-6 levels were clearly higher than the normal range in all patients.

Brain-Stem Reflexes

Various brain-stem reflexes are used to diagnose brain death, such as pupillary, oculocephalic, oculovestibular, and cough reflexes. Preservation of the cough reflex indicates preservation of the brain-stem respiratory center. All the brain-stem reflexes (except those of the respiratory centers) need not be present for the organism to be said to be alive, but they are tested simply to confirm the preservation of brain-stem functions.

/das/book/view/29494766/875/838.html

CRITERIA AND TESTS FOR DETERMINING BRAIN DEATH

Determination of brain death confirms the irreversible cessation of all functions of the entire brain, including the brain stem (Table 76-2) (Table Not Available) . [8] Irreversibility means that no treatment may reasonably be expected to change the condition. The responsible disorder may be thought of as structural, and it is not due to such functional, potentially reversible, causes as drug intoxication, hypothermia, and metabolic or endocrine disturbance. The passage of time is also an essential component in determining that a lesion is irremediable. Although testing all functions of the brain is conceptually impossible, the cessation of all functions of the brain is practically determined by (1) loss of consciousness, (2) loss of brain-stem responses, (3) lack of EEG activity, and (4) apnea. The absence of EEG activity is not a required criterion in the United Kingdom [9] and Belgium, [24] because loss of functions in the brain stem but not the entire brain is defined as the criterion for death of individuals in these nations.

Figure 76-2 (Figure Not Available) This illustration of the arterial blood supply to the human pituitary gland shows that small branches from the posterior communicating artery and the superior hypophyseal artery supply the hypothalamus. *(Modified from McConnell. [53] Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)*

TABLE 76-2 -- Criteria for Determination of Death

(Not Available)

From Medical Consultants on the Diagnosis of Death, [8] copyright 1981, American Medical Association

Loss of Consciousness and Unresponsiveness

The patients should be in coma and should score 3 on the Glasgow Coma Scale. Motor responses of the limbs or facial muscles to painful supraorbital pressure should be absent. Motor responses (Lazarus sign) may occur spontaneously during apnea testing [57] and are considered of spinal origin. This sign is often observed during hypoxic or hypotensive episodes. Other spontaneous movements of spinal origin are observed.

Pupils

The shape of the pupils can be round, oval, or irregular. The size of the pupils may vary from 4 to 9 mm, but most are 4 to 6 mm. [58] Sympathetic cervical pathways can be intact in the state of brain death, connect with the radially arranged fibers of the dilator muscle, and dilate the pupils.

Brain-Stem Responses

The tests for brain-stem responses vary in different countries. The 1995 criteria of the American Academy of Neurology [59] include light reflex, oculocephalic reflex, caloric (vestibular) test, corneal reflex, jaw reflex, pharyngeal reflex, and cough reflex.

Apnea Test

Ever since equipment for measuring blood gas analysis became generally available, the importance of the value of Pa co_2 rather than the time for observation of apnea has been confirmed. During the apnea test, dramatic changes in vital signs, marked hypotension, and severe cardiac arrhythmias may be shown, and the intracranial pressure can increase markedly. Therefore, the apnea test should be performed as the last test after other tests fulfill the criteria of brain death. Further, the following prerequisites are suggested: [59] (1) core temperature higher than or equal to 36.5°C, (2) systolic blood pressure higher than or equal to 90 mm Hg, (3) euvolemia, (4) eucapnia (option: Pa co_2
40 mm Hg), and (5) normoxemia (option: Pa o_2
200 mm Hg). During the testing, blood pressure, electrocardiogram, and Sp o_2 should be monitored. Testing proceeds as follows: (1) the patient is mechanically ventilated with pure oxygen for 10 minutes; (2) the ventilator is disconnected; (3) 100 percent oxygen is delivered at 6 L/min through a catheter in the tracheal tube; (4) the clinician looks closely for respiratory movements; and (5) arterial blood gas analysis is performed occasionally (e.g., at 3, 5, 8, and 10 min) and confirms the increase in Pa co_2 to be greater than 60 mm Hg.

Controversy in the Apnea Test

The level of Pa co_2 to be achieved in the apnea test is controversial. Increase in Pa co_2 decreases pH in the cerebrospinal fluid, which stimulates the medullary respiratory chemical center. The ventilatory response to the increase in Pa co_2 rises lineally to 80 mm Hg, and then the slope become less steep and peaks at about 150 mm Hg in dogs. [60] The proposed levels of Pa co_2 to be achieved are 44 mm Hg, [61] 50 to 55 mm Hg, [62] 60 mm Hg, [63] and 80 to 90 mm Hg. [64] Ropper et al [61] investigated the levels of Pa co_2 at which spontaneous respiration resumed in 36 patients who fulfilled the other criteria for brain death. Results were between 41 and 51 mm Hg. Damage in the medullary respiratory center may affect the level of Pa co_2 for development of spontaneous respiration. Further, the level of Pa co_2 at which spontaneous respiration resumes is modified by Pa o_2 . The exact level of Pa co_2 to be achieved in the apnea test is unknown, but the generally accepted level is 60 mm Hg. [59]

Electroencephalographic Recording

Electrocerebral inactivity or electrocerebral silence is defined as no EEG activity of more than 2 muV when recording from scalp electrode pairs 10 cm or more apart with interelectrode impedances less than 10,000 ohm, but more than 100 ohm. Ten guidelines for EEG recordings are recommended: [65]

1. A minimum of eight scalp electrodes should be utilized.
2. Interelectrode impedances should be less than 10,000 ohm but more than 100 ohm.
3. The integrity of the entire recording system should be tested.

4. Interelectrode distances should be at least 10 cm.
5. Sensitivity must be increased from 7 muV/mm to at least 2 muV/mm for at least 30 minutes of the recording, with inclusion of appropriate calibrations.
6. Filter settings should be appropriate for the assessment of electrocerebral silence.
7. Additional monitoring techniques should be employed when necessary.
8. There should be no EEG reactivity to intense somatosensory, auditory, or visual stimuli.
9. Recordings should be made only by a qualified technologist.
10. A repeat EEG should be performed if there is doubt about electrocerebral silence.

PREREQUISITES TO DIAGNOSING BRAIN DEATH

Several disorders mimic brain death and can lead to an erroneous diagnosis. The absence of these conditions must be confirmed and the following factors considered before the criteria for brain death are applied.

Deep Coma and Its Cause

The patient must be in a deep coma, and the cause of the coma must be identified; that is, irremediable organic brain damage must be confirmed. Certainly, drug intoxication, intracranial hematomas, and other common treatable disorders should be ruled out, especially if the diagnosis is uncertain. However, it may be obvious within hours of a primary intracranial event such as head injury or spontaneous intracranial hematoma, or after neurosurgery, that brain damage is irremediable. [9]

Body Temperature

After cessation of brain-stem and hypothalamic functions, and after complete disconnection of the spinal cord from supraspinal brain structures, the patient becomes poikilothermic, and body temperature tends to be hypothermic, even with vigorous warming. [45] Because hypothermia suppresses CNS function and leads to misdiagnosis of brain death, body temperature must be within normal range (i.e., hypothermia must be corrected) before the criteria for brain death are applied.

Absence of Cardiovascular Collapse

When intracranial pressure increases, systemic hypertension occurs as a result of Cushing syndrome. This is followed by a sudden decrease in blood pressure because of sudden interruption of vasomotor output from the brain stem and hypothalamus to the spinal cord. Hypotension usually resolves spontaneously within several days because of restoration of spontaneous activity of the spinal cord vasomotor neurons. Because hypotension not only suppresses cerebral

---

blood flow but perhaps EEG activity and can thus promote a spurious diagnosis, administration of vasopressor is required. Vasopressor occasionally restores EEG activity for the determination of brain death.

SPECIAL CONSIDERATIONS

Cerebral Death ("Persistent Vegetative State")

Cerebral death, the so-called persistent vegetative state, refers to cessation of the functions of the cerebral cortices. Brain-stem functions governing the respiratory centers, autonomic nervous system, endocrine system, and immune system, which are vital for maintaining life, are preserved. Although the cortical EEG is flat, it is usually contaminated by electromyographic activity of the forehead, a sign of preservation of function of the facial nerve in the brain stem.

The persistent vegetative state represents irreversible loss of consciousness, but not irreversible loss of life or the mechanism of life; patients in this state can survive for months and years. The term cerebral death is occasionally used erroneously to indicate brain death, which includes the brain stem.

Cerebral death has not been accepted traditionally as equivalent to death. [66] However, some investigators have advocated that cerebral death should be accepted as the death of individuals because the critical elements of life are the organized cognition and "personhood" as the unique feature of human life, which originate from the cerebrum. [67] [68] The problems of this notion are that the permanence of cerebral dysfunction cannot be easily predicted in most clinical circumstances and would threaten the extremely senile and profoundly retarded, who could have severely damaged high-brain functions. [68] [69] The shortage of infant organs available for transplantation worldwide has promoted a growing recognition of the potential use of anencephalic infants, who are born without a forebrain and a cerebrum but with a rudimentary functional brain stem, as a donor. [70] [71] Their natural course is that half of the fetuses die *in utero* and about 95 percent of those born live usually die within 7 days. [71] The American Medical Association Council on Ethical and Judicial Affairs has changed its previous position and supports the use of live anencephalic infants as organ donors. [70] It claimed that anencephalic neonates are definitely different from individuals who are in a persistent vegetative state, infants with profound neurologic injury, and elderly adults with severe dementia, because they have no history of consciousness and no possibility of ever being conscious. In 1961, a kidney transplantation was first performed with an anencephalic newborn as a donor, [72] followed by other such attempts. [73] [74] However, Western countries, except Germany, consider anencephalic infants to be legally alive as long as the brain stem is functioning. [75] [76] This issue is still controversial. [70] [71] [77] [78] [79]

Spinal Cord Reflexes and Surgery

The CNS structures essential to the definition of brain death do not include the spinal cord. Histologic studies have shown that the spinal cord is the best preserved part of the CNS, and results have ranged from grossly normal histologic features to edema, neuronal loss, neurolysis, and, on rare occasion, infarction. [22] However, in brain death, the first cervical segment of the spinal cord (C1) or the junction of C1 and the caudal medulla oblongata is the most severely damaged. Because this is the site of herniation of the cerebellar tonsils, the blood supply is easily cut off by compression of the anterior and posterior spinal cord and vertebral arteries. [80]

Jorgensen [45] reported retention of spinal reflexes for 50 of 63 cases of brain death, and Ivan [80] observed spinal reflexes for 52 of more than 80 cases. The so-called flexor reflex, induced by stimulation of the skin and expressed by flexion of the extremities, was always confirmed when spinal cord reflexes were preserved. Ropper [57] reported bizarre, seemingly purposeful movements of the upper extremities in 5 of 25 cases of brain death. The movements were observed several minutes or more after cessation of ventilatory support, when the ventilator was removed permanently, or during apnea testing. It is important to remember that the patient moves in response to noxious stimulation, and that full curarization is thus required for surgical procedures involving brain death.

Considerations Regarding Children

The brain of infants and young children has greater resistance to damage. On neurologic examination, infants and young children may recover substantial brain functioning after periods of unresponsiveness that are longer than those from which adults could recover. [8] It is generally assumed that the brain of infants and children is more resistant to injury leading to death, although this issue is controversial and lacks convincing clinical documentation. [81] [82] However, the presence of open fontanelles and open sutures in young children makes the skull an expandable chamber. Therefore, intracranial pressure does not exceed mean arterial blood pressure, and cerebral blood flow continues.

There had been an increased need for facilitation of end-of-life decision and organ procurement in infants and children. In 1987, the Task Force for the Determination of Brain Death in Children endorsed the Determination of Death Act and offered the "Guidelines for the Determination of Brain Death in Children" [83] (Table 76-3) (Table Not Available) . The distinctions from the criteria for adults are three separate longer observation periods depending on the child's age and the necessity for two corroborating EEG or one EEG with corroborating radionuclide angiography. Farrell and Levin [84] claimed, in their review of brain death in pediatric patients, that the issues of the determination of brain death in children are as follows: (1) Do the adult criteria apply to infants and children? (2) Are ancillary tests necessary or even capable of establishing the criteria? (3) Are there appropriate time intervals between triggering events, the physical examination of death, the ancillary tests, and the pronouncement of death? (4) Is the whole-brain death definition of death the only acceptable one? It is generally agreed that except in very immature, preterm newborns, the same criteria of brain death can apply to full-term newborns, infants older than 7 days of age, children, and adults, [85] [86] [87] [88] [89] [90] [91] [92] [93] although there have been some reports criticizing this notion. [94] [95] [96] The Special

TABLE 76-3 -- Brain Death Guidelines in Children

(Not Available)

From Task Force for the Determination of Brain Death in Children [83]

Task Force excluded infants younger than 7 days old from its guideline. [83] Volpe [96] addressed the issues of diagnosis of brain death in newborns: (1) if the injury occurred *in utero,* the duration of the insult and severity may be difficult to establish; (2) normal systemic arterial pressure of newborn is not determined; (3) EEG and transcranial Doppler sonography (TCD) may not be 100 percent reliable; and (4) the clinical examinations cannot be reliable because of immaturity. Ashwal and Schneider, [93] [97] however, suggested that in infants younger than 1 week of age, the diagnosis of brain death can be made after observation over a 2-day period and in the preterm infant over a 3-day period, and that the developmental reflexes necessary to ascertain cranial nerve functions are present in the preterm infant by 34 weeks. Farrell and Levin [84] emphasized that no ancillary test is absolutely confirmatory of brain death except a four-vessel cerebral angiography test showing the lack of cerebral blood flow. Scher et al [98] reported that 15 of 20 neonates who showed isoelectric EEG preserved partial clinical brain function. The issues of brain death in pediatric patients concern not only how to diagnose but how to practice. Mejia and Pollack [99] investigated the variability in practices for determining brain death and organ procurement in pediatric intensive care units. Contrary to their expectation, there was great variability. Although apnea testing has been considered the most important criterion for brain death, [100] apnea testing was not carried out in 23 of 93 brain-dead patients (25%), and the methods of apnea testing were not

consistent with the Task Force guidelines for determination of brain death in children in 20 patients (22%). Four of 30 patients younger than 1 year of age did not have a confirmatory test. The investigators concluded that the variability in brain-death determination practices may reflect differences in documentation, lack of knowledge of the guidelines, or disagreement with them.

/das/book/view/29494766/875/841.html

ANCILLARY TESTS FOR BRAIN DEATH

Some ancillary tests are recommended and are adopted when applying the criteria for brain death (Table 76-4) . However, any ancillary test should be used in conjunction with appropriate clinical judgment.

Evoked Responses

Somatosensory evoked potentials (SSEP) are usually recorded as indicators of cerebral activity, whereas brain-stem auditory evoked potentials (BAEP) are considered indicators of the functional integrity of the brain stem.Although several studies describe the importance of recording sensory evoked potentials in the diagnosis of brain death, [101] [102] the need for special equipment and experts limits this practice.

BAEP are signals generated in the auditory nerves and brain stem following an acoustic stimulus. BAEP consist of five identifiable waves generated from specific brain-stem structures along the auditory pathways. Wave I represents the eighth nerve compound action potential; wave II, the eight nerve and cochlear nerves; wave III, the lower pons including the superior olive; waves IV and V, the upper pons and the midbrain, as high as the inferior colliculus. [103]

TABLE 76-4 -- Ancillary Tests for Brain Death

A. Electrophysiology
   1. Electroencephalography (EEG)
   2. Steady (DC) potentials
   3. Sensory evoked potentials
      a. Somatosensory evoked potentials (SEP)
      b. Auditory evoked potentials (AEP)
      c. Visual evoked potentials (VEP)
   4. Others (electroretinogram, electrocochleogram, blink reflex)

B. Cerebral blood flow
   1. Angiography
      a. Conventional (aortocranial, four-vessel)
      b. Digital subtraction
      c. Radioisotope
         (1) Intravenous (bolus technique)
         (2) Intracarotid
      d. Enhanced (dynamic) computed tomography (CT)
   2. Quantitative measurement
      a. N_2O inhalation
      b. Intracarotid injection
      c. Intracerebral injection
      d. Xenon computed tomography (Xe CT)
      e. Single photon emission computed tomography (SPECT)
      f. Positron emission computed tomography (PET)
   3. Echoencephalography
   4. Doppler ultrasonography (cervical, transcranial)
   5. Cerebral perfusion pressure and intracranial pressure

C. Cerebral metabolism
   1. Cerebral metabolic rate of oxygen (CMR_{O_2})
   2. Arteriovenous oxygen difference (AVD_{O_2})
   3. Jugular venous oxygen tension (Pjv_{O_2})
   4. Jugular venous oxygen saturation (Sjv_{O_2})
   5. Lactic acid content of the cerebrospinal fluid
   6. Single photon emission tomography (SPECT)
   7. Positron emission tomography (PET)
   8. Magnetic resonance spectroscopy (MRS)

D. Pathomorphology
   1. Computed tomography (CT)
   2. Magnetic resonance imaging (MRI)
   3. Cytology of the cerebrospinal fluid

Therefore, brain-stem abnormalities can be detected with BAEP. The loss of waves III to V, II to V, or no reproducible BAEP on both sides are usually regarded as brain death, [104] [105] although wave I sometimes remains. [106] [107] Previous deafness or severe peripheral auditory system damage must be checked, because it may lead to a false-positive diagnosis. Some cases with a loss of waves II to V or III to V in spite of maintained spontaneous breathing have been reported. [106] [108]

Following electrical stimulation of peripheral nerve, waves of SSPE are generated from the neural structures along the afferent somatosensory pathways: the brachial plexus, the upper cervical cord, the dorsal column nuclei, the ventroposterior thalamus, and the sensory cortex. [103] "Practice Parameters for Determining Brain Death in Adults," published in *Neurology,* recommended bilateral absence of N20-P22 responses with median nerve stimulation as a confirmatory laboratory test. [59] Facco et al [107] reported that the absence of components later than N13, which represents postsynaptic activity in the central gray matter of the cervical cord, or N13/P13 dissociation was reliable to confirm brain death. These investigators also recommended the combined use of BAER and SSEP for determining brain death. [109] Wagner et al [110] reported a comatose patient who showed apnea and brain-stem areflexia with preserved cortical SSEP.

Measurement of Cerebral Blood Flow

Possible mechanisms for brain death include an obstruction of circulation by cerebral swelling. Therefore, the demonstration of absent intracranial circulation would indicate irreversible cerebral damage. Adopting this concept, Scandinavian nations have taken the stance that total brain infarction constitutes brain death. [23] [111] [112] The following methods are used to measure cerebral blood flow.

Angiography

Contrast Angiography

Absence of blood flow to the brain leads to destruction of brain tissue. Cessation of cerebral blood flow confirmed by angiography is required for the diagnosis of brain death in Sweden and Norway. [111] [112] The greatest advantage of angiography for the determination of brain death is that it is influenced neither by CNS-depressant drugs nor by hypothermia. Therefore, this method has been recommended to confirm brain death. [34] [105] [116] [114] [115] [116] An article published in *Neurology* recommended the following criteria as a confirmatory test: [59] no intracerebral filling at the level of the carotid bifurcation or circle of Willis; patent external carotid circulation; and possibly delayed filling of the superior longitudinal sinus. Drawbacks of this method are that the patients need to be transported to the radiology suite, and the cost is relatively high. Furthermore, in conventional angiography, the contrast medium can be artifactually injected into the brain-supplying artery by pressure. [112] [116] Aortic arch or intravenous digital subtraction angiography has been shown to be as effective as conventional four-vessel angiography, less invasive, and easier to perform. [105] [112] [114] [115] These tests can be performed even at the patient's bedside.

Radionuclide Angiography

Confirmation of brain death using conventional dynamic radionuclide angiography with blood pool agents has been used for a long time. [117] [118] [119] [120] [121] Such investigations are carried out at the patient's bedside using a mobile scintillation camera. Technetium-99m (^{99m}Tc)-pertechnetate, ^{99m}Tc-diethylenetriaminepenta-acetic acid (DTPA), or ^{99m}Tc-glucoheptonate, which do not penetrate the blood-brain barrier, are administered as an intravenous bolus. The absence of intracranial arterial flow is considered a criterion for brain death. These agents, however, are not reliable indicators of posterior fossa and brain-stem blood flow, [122] and persistent filling of venous sinuses has been reported. [121] [123] [124] [125] [126] Lee et al [126] reported that the mere presence of a sagittal venous sinus in the absence of demonstrable cerebral arterial flow activity is not clinically significant and does not contradict the diagnosis of brain death. In recent years, the use of newer radioligands such as ^{99m}Tc-hexamethyl-propyleneamine-oxime (HMPAO) and *N*-isopropyl- *p*- [123] I-iodoamphetamine, which cross the blood-brain-barrier and are picked up and held by viable cells for several hours, have been recommended to confirm brain death. [127] [128] [129] [130] [131] [132] [133] [134] The lack of uptake of isotope in brain parenchyma ("hollow skull phenomenon") is characteristic of brain death. [59] These tests can be of value for patients who have no viable neurons in spite of preserved brain perfusion resulting from artifactual cerebral perfusion pressure or whose perfusion scans are inconclusive. ^{99m}Tc-HMPAO is also used for tomographic functional imaging (single photon emission computed tomography [SPECT]) to confirm the diagnosis of brain death, [135] [136] [137] [138] which allows much more precise regional information.

Computed Tomography

Dynamic CT has been thought to be useful as noninvasive tests to confirm brain death. [139] [140] [141] [142] [143] After intravenous bolus injection of iodinated contrast medium, time-density analysis in specific area can be obtained with a CT scanner equipped with a special software program, which can evaluate blood flow. This technique also has the advantage of demonstrating underlying intracranial disorders that may cause coma. Xe CT cerebral blood flow techniques have also been developed and applied to a wide variety of clinical problems including the confirmation of brain death. [34] [144] [145] [146] [147] This technique is accurate in quantifying low cerebral blood flow, the information of which can be directly coupled to CT anatomy. Pistoria et al [145] suggested that an average global flow of less than 5/mL/100 mL/min is confirmatory of brain death.

Magnetic Resonance

Magnetic resonance (MR) imaging (MRI) and MR angiography have been used for the confirmation of brain

death with the advent of MRI-compatible ventilators. [148] [149] [150] [151] [152] MRI allows an assessment of intracranial contents and is particularly helpful in defining abnormalities in the posterior fossa, which may be obscured by bone artifact inherent in CT. Orrison et al [151] reported that "carotid artery enhancement (intravascular enhancement sign)" and "prominent nasal and scalp enhancement (MR hot nose sign)" as well as "transtentorial and foramen magnum herniation," "absent in intracranial vascular flow void," "poor gray matter/white matter differentiation," and "no intracranial contrast enhancement" in MR findings provided additional imaging support in the clinical diagnosis of brain death.

Phosphorus and proton MR spectroscopy (MRS) has also been used for the determination of brain death. [153] [154] [155] [156] Total absence of high-energy phosphorus compound (including adenosine triphosphate) leaving only one single peak of inorganic phosphate in phosphorus-31 (^{31}P)-MRS and massive lactate concentration in hydrogen-1 (^{1}H)-MRS was demonstrated. However, this technique unfortunately lacks the information of regional brain condition.

Transcranial Doppler Sonography

This technique uses a 2-MHz ultrasonic probe affixed to the temporal area above the zygomatic arch, and usually the flow velocity of middle cerebral artery is monitored. However, it can also insonate the anterior cerebral artery and the posterior cerebral artery from the temporal window, the basilar and vertebral arteries from the occipital window, and the intracranial internal carotid artery and the ophthalmic arteries through the orbital window. Its merit is that it is noninvasive and inexpensive, and it can be performed at the patient's bedside without known risk to the patient. With an intracranial pressure increase, the mean flow velocity decreases, and the pulsatility index ([peak velocity - enddiastolic velocity]/mean velocity) increases. [157] When intracranial pressure reaches levels approaching the mean arterial pressure (brain death), TCD demonstrates systolic spikes, undetectable flow (no signal), or reversal of blood flow in diastole ("to-and-fro" or oscillating waveform). [158] [159] [160] [161] Feri et al [160] reported that these patterns were highly specific (100%) for brain death. Petty et al [161] also reported that these patterns were highly specific (100%) and sensitive (91.3%) for brain death. However, Paolin et al [34] addressed that "no signal" cannot be considered an expression of circulatory arrest unless it is confirmed by cerebral angiography or is the end point of deteriorating intracranial hemodynamics in patients submitted to serial TCD investigations. These TCD signals should be recorded from multiple intracranial arteries (both middle cerebral arteries or at least one middle cerebral artery and basilar artery) to be considered confirmatory of brain death without any other test [161] to rule out the possibility of the occlusion of a single artery.

Positron Emission Tomography

Positron emission tomography (PET) imaging involves intravenous injection of radiotracers labeled with positron-emitting nuclides (e.g., oxygen-15 [^{15} O], carbon-11 [^{11} C], nitrogen-13 [^{13} N]). These radionuclides are incorporated into organic compounds that are chemically similar to those present in the body, and several physiologic parameters can be measured. There have been some reports of the use of PET in the setting of brain death, a few of which indicated the utility of PET in the confirmation of brain death. No detectable glucose metabolism was reported using fluorine-18 fluorodeoxyglucose (^{18} F-FDG) in brain-dead patients. [162] [163] However, cerebral blood flow and cerebral glucose metabolism were reported in brain-dead children. Altman et al [164] reported two clinically brain-dead neonates with electrocerebral silence who demonstrated intact cerebral blood flow on a PET scan using ^{15} O-labeled water, although preservation of cerebral blood flow detected by other means in clinically brain-dead children is common. Medlock et al [165] reported a clinically brain-dead 2-month-old infant with no cerebral electrical activity who demonstrated the persistence of glucose metabolism. These investigators speculated that the preservation of glucose metabolism seems partly due to glial cells, which are more resilient than neurons. The use of PET in the investigation of comatose and/or brain-dead patients is still in an early stage of development, and it is limited by its high cost and need for special facilities. However, the capability of PET to measure diverse physiologic parameters accurately will make it a potentially powerful method of brain death.

References

1. Cushing H: Some experimental and clinical observations concerning states of increased intracranial tension: The Mutter lecture for 1901. Am J Med Sci 124:375, 1902.

2. Bertrand I, Lhermitte F, Antoine B et al: Necroses massives du systeme nerveux central dans une survie artificielle. Rev Neurol (Paris) 101:101, 1959.

3. Mollaret P, Goulon M: Le coma depasse (Memoire preliminaire). Rev Neurol (Paris) 101:3, 1959.

4. Ad Hoc Committee of the Harvard Medical School: A definition of irreversible coma: Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA 205:337, 1968.

5. Mohandas A, Chou SN: Brain death: A clinical and pathological study. J Neurosurg 35:211, 1971.

6. International Federation of Societies for Electroencephalography and Clinical Neurophysiology: Report of the Committee on Cessation of Cerebral Function. Electroencephalogr Clin Neurophysiol 37:521, 1974.

7. Black PM: Brain death (first of two parts). N Engl J Med 299:338, 1978.

8. Medical Consultants on the Diagnosis of Death: Guidelines for the determination of death: Report of the Medical Consultants on the Diagnosis of Death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA 246:2184, 1981.

9. Conference of Medical Royal Colleges: Diagnosis of brain death: Statement issued by the honorary secretary of the Conference of Medical Royal Colleges and Their Faculties in the United Kingdom on 11 October 1976. BMJ 2:1187, 1976.

10. Weissman C: The metabolic response to stress: An overview and update. Anesthesiology 73:308, 1990.

11. Hopkins SJ, Rothwell NJ: Cytokines and the nervous system. I. Expression and recognition. Trends Neurosci 18:83, 1995.

12. Rothwell NJ, Hipkins SJ: Cytokines and the nervous system. II. Actions and the mechanisms of action. Trends Neurosci 18:130, 1995.

13. Ouaknine G, Kosary IZ, Braham J et al: Laboratory criteria of brain death. J Neurosurg 39:429, 1973.

14. Korein J, Maccario M: On the diagnosis of cerebral death: A prospective

---

study on 55 patients to define irreversible coma. Clin Electroencephalogr 2:178, 1971.

15. Ibe K: Clinical and pathophysiological aspects of the intravital brain death (abstract). Electroencephalogr Clin Neurophysiol 30:272, 1971.

16. Ingvar DH, Widen L: Hjarndod: Sammanfattning av ett symposium. Lakartidningen 69:3804, 1972.

17. Pallis C: ABC of brain stem death: Prognostic significance of a dead brain stem. BMJ 286:123, 1983.

18. Klatzo I: Presidential address: Neuropathological aspects of brain oedema. J Neuropathol Exp Neurol 26:1, 1967.

19. Klatzo I: Brain oedema following brain ischaemia and the influence of therapy. Br J Anaesth 57:18, 1985.

20. Klatzo I: Pathophysiological aspects of brain edema. Acta Neuropathol (Berl) 72:236, 1987.

21. Wahl M, Unterberg A, Baethmann A et al: Mediators of blood-brain barrier dysfunction and formation of vasogenic brain edema. J Cereb Blood Flow Metab 8:621, 1988.

22. Walker AE, Diamond EL, Moseley J: The neuropathological findings in irreversible coma: A critique of the "respirator brain." J Neuropathol Exp Neurol 34:295, 1975.

23. Ingvar DH: Brain death-total brain infarction. Acta Anaesthesiol Scand Suppl 45:129, 1971.

24. Brihaye J, Walker AE: Academia Eurasiana Neurochirurgica: Brain death. Acta Neurochir (Wien) 105:85, 1990.

25. Pallis C: Further thoughts on brainstem death. Anaesth Intensive Care 23:20, 1995.

26. Bremer F: L'activite cerebrale au cours du sommeil et de la narcose: Contribution a l'etude du mecanisme du sommeil. Bull Acad R Med Belg 2:68, 1937.

27. Moruzzi G, Magoun HW: Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1:455, 1949.

28. Segundo JP, Arana A, French JD: Behavioral arousal by stimulation of the brain in the monkey. J Neurosurg 12:601, 1955.

29. Jouvet M: Paradoxical sleep-a study of its nature and mechanisms. Prog Brain Res 18:20, 1965.

30. Hockaday JM, Potts F, Epstein E et al: Electroencephalographic changes in acute cerebral anoxia from cardiac or respiratory arrest. Electroencephalogr Clin Neurophysiol 18:575, 1965.

31. Schwab RS, Potts F, Bonazzi A: EEG as aid in determining death in the presence of cardiac activity (ethical, legal and medical aspects) (abstract). Electroencephalogr Clin Neurophysiol 15:147, 1962.

32. Sharbrough FW, Sundt TM Jr: The value of simultaneous EEG and blood flow monitoring during carotid endarterectomy. Electroencephalogr Clin Neurophysiol 37:423, 1979.

33. Sundt TM Jr, Sharbrough EW, Anderson RE et al: Cerebral blood flow measurements and electroencephalograms during carotid endarterectomy. J Neurosurg 41:310, 1974.

34. Paolin A, Manuali A, Di Paola F et al: Reliability in diagnosis of brain death. Intensive Care Med 21:657, 1995.

35. Lumsden T: Observations on the respiratory centres in the cat. J Physiol (Lond) 57:153, 1923.

36. Pitts RF, Magoun HW, Rason SW: The origin of respiratory rhythmicity. Am J Physiol 127:654, 1939.

37. Hoff HE, Breckenridge CG: The medullary origin of respiratory periodicity in the dog. Am J Physiol 158:157, 1949.

38. Hukuhara T Jr: Neuronal organization of the central respiratory mechanisms of the brain of the cat. Acta Neurobiol Exp (Warsz) 33:219, 1973.

39. Alexander RS: Tonic and reflex functions of medullary sympathetic cardiovascular centers. J Neurophysiol 9:205, 1946.

40. Brooks CM: Reflex activation of the sympathetic system in the spinal cat. Am J Physiol 106:251, 1933.

41. Rodbard S: Body temperature, blood pressure, and hypothalamus. Science 108:413, 1948.

42. Magoun HW, Harrison F, et al: Activation of heat loss mechanisms by local heating of the brain. J Neurophysiol 1:101, 1938.

43. Strom G: Influence of local thermal stimulation on the hypothalamus of the cat on cutaneous blood flow and respiratory rate. Acta Physiol Scand Suppl 20:47, 1950.

44. Strom G: Effect of hypothalamic cooling on cutaneous blood flow in the unanesthetized dog. Acta Physiol Scand 21:271, 1950.

45. Jorgensen EO: Spinal man after brain death: The unilateral extension-pronation reflex of the upper limb as an indication of brain death. Acta Neurochir (Wien) 28:259, 1973.

46. Hall GM, Mashiter K, Lumley J et al: Hypothalamic-pituitary function in the "brain-dead" patient. Lancet 2:1259, 1980.

47. Schrader H, Krogness K, Aakvaag A et al: Changes of pituitary hormones in brain death. Acta Neurochir (Wien) 52:239, 1980.

48. Sugimoto T, Sakano T, Kinoshita Y et al: Morphological and functional alterations of the hypothalamic-pituitary system in brain death with long term bodily living. Acta Neurochir (Wien) 115:31, 1992.

49. Zaloga GP: Endocrine function after brain death. Crit Care Med 18:785, 1990.

50. Keogh AM, Howlett TA, Perry L et al: Pituitary function in brain-stem dead organ donors: A prospective survey. Transplant Proc 20:729, 1988.

51. Yoshioka T, Sugimoto H, Uenishi M et al: Prolonged hemodynamic maintenance by the combined administration of vasopressin and epinephrine in brain death: A clinical study. Neurosurgery 18:565, 1986.

52. Leclercq TA, Grisoli F: Arterial blood supply of the normal human pituitary gland: An anatomical study. J Neurosurg 58:678, 1983.

53. McConnell EM: The arterial blood supply of the human hypophysis cerebri. Anat Rec 115:175, 1953.

54. Yokota H, Nakazawa S, Shimura T et al: Hypothalamic and pituitary function in brain death. Neurol Med Chir (Tokyo) 31:881, 1991.

55. Arita K, Uozumi T, Oki S et al: The function of the hypothalamopituitary axis in brain dead patients. Acta Neurochir (Wien) 123:64, 1993.

56. Amado JA, Lopes-Espadas F, Vazquez-Barquero A et al: Blood levels of cytokines in brain-dead patients: Relationship with circulating hormones and acute-phase reactants. Metabolism 44:812, 1995.

57. Ropper AH: Unusual spontaneous movements in brain-dead patients. Neurology 34:1089, 1984.

58. Wijidicks EFM: Determining brain death in adults. Neurology 45:1003, 1995.

59. Quality Standards Subcommittee of the American Academy of Neurology: Practice parameters for determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 45:1012, 1995.

60. Nunn JF: Control of breathing. In Applied Physiology, 3rd ed. London, Butterworths, 1987, p 72.

61. Ropper AH, Kennedy SK, Russell L: Apnea testing in the diagnosis of brain death: Clinical and physiological observations. J Neurosurg 55:942, 1981.

62. Nelson RF: Determination of brain death. Can J Neurol Sci 13:355, 1986.

63. Schafer JA, Caronna JJ: Duration of apnea needed to confirm brain death. Neurology 28:661, 1978.

64. Pitts LH, Kaktis J, Caronna J et al: Brain death, apneic diffusion oxygenation, and organ transplantation. J Trauma 18:180, 1978.

65. Guideline Three: Minimum technical standards for EEG recording in suspected cerebral death. J Clin Neurophysiol 11:10, 1994.

66. Power DJ, Darby JM, Grenvik A: Controversies in brain death certification. Ayres SM, Grenvik A, Holbrook PR et al (eds): In Textbook of Critical Care, 3rd ed. Philadelphia, WB Saunders, 1995, p 1579.

67. Grandford RE, Smith DR: Consciousness: The most critical moral (constitutional) standard for human personhood. Am J Law Med 13:233, 1987.

68. Lizza JP: Persons and death: What's metaphysically wrong with our current statutory definition of death? J Med Philos 18:351, 1993.

69. Young B, Blume W, Lynch A: Brain death and the persistent vegetative state: Similarities and contrasts. Can J Neurol Sci 16:388, 1989.

70. Council on Ethical and Judicial Affairs, American Medical Association: The use of anencephalic neonates as organ donors. JAMA 1995; 273:1614, 1995.

71. Diaz JH: The anencephalic organ donor: A challenge to existing moral and statutory laws. Crit Care Med 21:1781, 1993.

72. Goodwin WE, Kaufman JJ, Mims MM et al: Human renal transplantation. I. Clinical experiences with six cases of renal homotransplantation. J Urol 89:13, 1963.

73. Kantrowitz A, Haller JD, Joos H et al: Transplantation of the heart in an infant and an adult. Am J Cardiol 22:782, 1968.

74. Cabasson J, Blanc WA, Joos HA: The anencephalic infant as a possible donor for cardiac transplantation. Clin Pediatr 8:86, 1969.

75. Steiberg A, Katz E, Sprung CL: Use of anencephalic infants as organ donors: Commentary. Crit Care Med 21:1787, 1993.

76. Holzgrave W, Beller RK, Buchholz B et al: Kidney transplantation from anencephalic donors. N Engl J Med 316:1069, 1987.

77. Sytsma SE: Anencephalics as organ sources. Theor Med 17:19, 1996.

78. McQuillen MP: Anencephalic infants as organ donors (letter; comment). JAMA 274:1758, 1995.

79. Khan JH: Anencephalic infants as organ donors (letter; comment). JAMA 274:1758, 1995.

80. Ivan LP: Spinal reflexes in cerebral death. Neurology 23:650, 1973.

81. Schwartz JA, Baxter J, Brill DR: Diagnosis of brain death in children by radionuclide cerebral imaging. Pediatrics 73:14, 1984.

82. Moshe SL, Alvarez LA: Diagnosis of brain death in children. J Clin Neurophysiol 3:239, 1986.

83. Task Force for the Determination of Brain Death in Children: Guidelines for the determination of brain death in children. Neurology 37:1077, 1987.

84. Farrell MM, Levin DL: Brain death in the pediatric patients: Historical, sociological, medical, religious, cultural, legal, and ethical considerations. Critical Care Med 21:1951, 1993.

85. Freeman JM, Ferry PC: New brain death guidelines in children: Further confusion. Pediatrics 81:301, 1988.

86. Rowland TW, Donnelly JH, Jackson AH et al: Brain death in the pediatric intensive care unit. Am J Dis Child 137:547, 1083.

87. Crone RK: Brain death. Am J Dis Child 137:545, 1983.

88. Ashwal S, Schneider S: Brain death in children. I. Pediatr Neurol 3:5, 1987.

89. Ashwal S, Schneider S: Brain death in children. II. Pediatr Neurol 3:69, 1987.

90. Fackler JC, Rogers MC: Is brain death really cessation of all intracranial function? J Pediatr 110:84, 1987.

91. Coulter DL: Special article: Neurologic uncertainty in newborn intensive care. N Engl J Med 316:840, 1986.

92. Watchko JF: Neurologic uncertainty in newborn intensive care. N Engl J Med 317:960, 1987.

93. Ashwal S, Schneider S: Brain death in the newborn. Pediatrics 84:429, 1969.

94. Scewmon DA: Brain death in children. Neurology 38:1813, 1988.

95. Toffol GJ, Lansky LL, Hughes JR et al: Pitfalls in diagnosing brain death in infancy. J Child Neurol 2:134, 1987.

96. Volpe JJ: Commentary: Brain death determination in the newborn. Pediatrics 80:293, 1987.

97. Ashwal S: Brain death in early infancy. J Heart Lung Transplant 12:S176, 1993.

98. Scher MS, Barabas RE, Barmada MA: Clinical examination findings in neonates with the absence of electrocerebral activity: An acute or chronic encephalopathic state? J Perinatol 16:455, 1996.

99. Mejia RE, Pollack MM: Variability in brain death determination practices in children. JAMA 274:550, 1995.

100. Ashwal S, Schneider S: Pediatric brain death: Current perspectives. Adv Pediatr 38:181, 1991.

101. Goldie WD, Chiappa KH, Young RR et al: Brainstem auditory and short-latency somatosensory evoked responses in brain death. Neurology 31:248, 1981.

102. Hall JW III, Mackey-Hargadine JR, Kim EE: Auditory brain-stem response in determination of brain death. Arch Otolaryngol 111:613, 1985.

103. Ciappa KH, Hock DB: Electrophysiologic monitoring. In Ropper AH (ed): Neurological and Neurosurgical Intensive Care. New York, Raven Press, 1993, p 147.

104. Stohr M, Trost E, Ullrich A et al: Significance of early acoustic evoked potentials in the diagnosis of brain death. Dtsch Med Wochenschr 111:1515, 1986.

105. Nau R, Prange HW, Klingelhoefer J et al: Results of four technical investigations in fifty clinically brain dead patients. Intensive Care Med 18:82, 1992.

106. Buchner H, Ferbert A, Bruckmann H et al: Validity of four technical investigations in fifty clinically brain dead patients. EEG EMG Z Elektroenzephlogr Verwandte Geb 17:117, 1986.

107. Facco E, Casartelli-Liviero M, Munari M et al: Short latency evoked potentials: New criteria for brain death? J Neurol Neurosurg Psychiatry 53:351, 1990.

108. Biniek R, Ferbert A, Buchner H et al: Loss of brainstem acoustic evoked potentials with spontaneous breathing in a patient with supratentorial lesion. Eur Neurol 30:38, 1990.

109. Facco E, Munari M, Baratto F: Multimodality evoked potentials (auditory, somatosensory and motor) in coma. Neurophysiol Clin 23:237, 1993.

110. Wagner W, Ungersbock K, Perneczky A: Preserved cortical somatosensory evoked potentials in apnoeic coma with loss of brain-stem reflexes: Case report. J Neurol 240:243, 1993.

111. Swedish Ministry of Health and Social Affairs: The concept of death: Report of the Swedish Committee on Defining Death. Stockholm, Swedish Ministry of Health and Social Affairs, 1984.

112. Vatne KP, Nakstad P, Lundar T: Digital subtraction angiography (DSA) in the evaluation of brain death: A comparison of conventional cerebral angiography with intravenous and intraarterial DSA. Neuroradiology 27:155, 1985.

113. Louvier N, Combes JC, Nicolas F et al: Cerebral angiography must have medicolegal value for brain death confirmation in France. Transplant Proc 28:377, 1996.

114. Gomes A, Hallinan J: Intravenous digital subtraction angiography in the diagnosis of brain death. AJNR Am J Neuroradiol 4:21, 1983.

115. VanBunnen Y, Delcour C, Wery D et al: Intravenous digital subtraction angiography: A criterion of brain death. Ann Radiol 32:279, 1989.

116. Kricheff II, Pint RS, George AE et al: Angiographic findings in brain death. Ann N Y Acad Sci 315:168, 1978.

117. Schwartz JA, Baxter J, Brill D et al: Radionuclide cerebral imaging confirming brain death. JAMA 249:246, 1983.

118. Tsai SH, Cranford RE, Rockswold GL et al: Cerebral radionuclide angiography: Its application in the diagnosis of brain death. JAMA 248:591, 1982.

119. Korein J, Braunstein P, Kricheff I et al: Radioisotopic bolus technique as a test to detect circulatory deficit associated with cerebral death: 142 studies on patients demonstrating the bedside use of an innocuous IV procedure as an adjunct in the diagnosis of cerebral death. Circulation 51:924, 1975.

120. Korein J, Braunstein P, George A et al: Brain death. I. Angiographic correlation with the radioisotopic bolus technique for evaluation of critical deficit of cerebral blood flow. Ann Neurol 2:195, 1977.

121. Patel YP, Gupta SM, Batson R et al: Brain death: Confirmation by radionuclide cerebral angiography. Clin Nucl Med 13:438, 1988.

122. Monsein LH: The imaging of brain death. Anaesth Intensive Care 23:44, 1995.

123. Goodman JM, Heck LL, Moore BD: Confirmation of brain death with portable isotope angiography: A review of 204 consecutive cases. Neurosurgery 16:492, 1985.

124. Brill DR, Schwarts JA, Baxter JA: Variant flow pattern in radionuclide cerebral imaging performed for brain death. Clin Nucl Med 10:346, 1985.

125. Coker SB, Dellehy GL: Radionuclide cerebral imaging for confirmation of brain death in children: The significance of dural sinus activity. Pediatr Neurol 2:43, 1986.

126. Lee VW, Hauck RM, Morrison MC et al: Scintigraphic evaluation of brain death: Significance of sagittal sinus visualization. J Nucl Med 28:1279, 1987.

127. Spieth ME, Ansari AN, Kawada TK et al: Direct comparison of Tc-99m DTPA and Tc-99m HMPAO for evaluating brain death. Clin Nucl Med 19:867, 1994.

128. Mrhac L, Zakko S, Parikh Y: Brain death: The evaluation of semi-quantitative parameters and other signs in HMPAO scintigraphy. Nucl Med Commun 16:1016, 1995.

129. Muttini P, Dagnino N: ^{99m}Tc-HMPAO and mobile gamma-camera in the diagnosis of brain death. J Nucl Biol Med 38:14, 1994.

130. Wilson K, Gordon L Selby JB: The diagnosis of brain death with Tc-99m HMPAO. Clin Nucl Med 18:428, 1993.

131. de la Riva A, Gonzales FM, Llamas Elvira JM et al: Diagnosis of brain death: Superiority of perfusion studies with ^{99m}Tc-HMPAO over conventional radionuclide cerebral angiography. Br J Radiol 65:289, 1992.

132. Roine RO, Launes J, Lindroth L et al: ^{99m}Tc-hexamethylpropyleneamine oxime scans to confirm brain death (letter). Lancet 2:1223, 1986.

133. Galaske RG, Schober O, Heyer R: ^{99m}Tc-HM-PAO and ^{123}I-amphetamine cerebral scintigraphy: A new, non invasive method in determination of brain death in children. Eur J Nucl Med 14:446, 1988.

134. Reid RH, Gulenchyn KY, Ballinger JR: Clinical use of technetium-99m HM-PAO for determination of brain death. J Nucl Med 30:1621, 1989.

135. Soricelli A, Mainenti PP, Leone D: Evaluation of brain perfusion with high resolution single photon emission tomography in the diagnosis of brain death. Minerva Anestesiol 62:209, 1996.

136. Bonetti MG, Ciritella P, Valle G et al: ^{99m}Tc HM-PAO brain perfusion SPECT in brain death. Neuroradiology 37:365, 1995.

137. Wieler H, Marohl K, Kaiser KP: Tc-99m HMPAO cerebral scintigraphy:

A reliable, noninvasive method for determination of brain death. Clin Nucl Med 18:104, 1993.

138. Valle G, Ciritella P, Bonetti MG et al: Consideration of brain death on SPECT cerebral perfusion study. Clin Nucl Med 18:953, 1993.

139. Handa J, Matsuda M, Matsuda I et al: Dynamic computed tomography in brain death. Surg Neurol 17:417, 1982.

140. Rappaport ZH, Brinker RA, Rovit RL: Evaluation of brain death by contrast-enhanced computerized cranial tomography. Neurosurgery 2:230, 1978.

141. Walker AE: Ancillary studies in the diagnosis of brain death. Ann N Y Acad Sci 315:228, 1978.

142. Tan WS, Wilbur AC, Jafar JJ et al: Brain death: Use of dynamic CT and intravenous digital subtraction angiography. Am J Neuroradiol 1987; 8:123, 1987.

143. Arnold H, Kuhne D, Rohr W et al: Contrast bolus technique with rapid CT scanning: A reliable diagnostic tool for the determination of brain death. Neuroradiology 22:129, 1981.

144. Johnson DW, Stringer WA, Marks MP et al: Stable xenon CT cerebral blood flow imaging: Rationale for and role in clinical decision making. Am J Neuroradiol 12:201, 1991.

145. Pistoria F, Johason DW, Darby JM et al: The role of xenon CT measurements of cerebral blood flow in the clinical determination of brain death. Am J Neuroradiol 12:97, 1991.

146. Darby J, Yonas H, Brenner RP: Brainstem death with persistent EEG activity: Evaluation by xenon-enhanced computed tomography. Crit Care Med 15:519, 1987.

147. Latchaw RE, Yonas H, Darby JM et al: Xenon/CT cerebral blood flow determination following cranial trauma. Acta Radiol Suppl 369:370, 1986.

148. Matsumura A, Meguro K, Tsurushima H et al: Magnetic resonance imaging of brain death. Neurol Med Chir (Tokyo) 36:166, 1996.

149. Ishii K, Omura T, Kinoshita T et al: Brain death: MR and MR angiography. Am J Neuroradiol 17:731, 1996.

150. Lee DH, Nathanson JA, Fox AJ et al: Magnetic resonance imaging of brain death. Can Assoc Radiol J 46:174, 1995.

151. Orrison WW Jr, Champlin AM, Kesterson OL et al: MR "hot nose sign" and "intravascular enhancement sign" in brain death. Am J Neuroradiol 15:913, 1994.

152. Jones KM, Barnes PD: MR diagnosis of brain death. Am J Neuroradiol 13:65, 1992.

153. Grade K, Mortensen AC, Toft PB et al: Phosphorus and proton spectroscopy in relation to near incarceration and incarceration of the human brain. Acta Radiol 35:197, 1994.

154. Aichner F, Felber S, Bribamer G et al: Magnetic resonance: A noninvasive approach to metabolism, circulation, and morphology in human brain death. Ann Neurology 32:507, 1992.

155. Terk MR, Gober JR, DeGiorgio C et al: Brain death in the neonate: Assessment with P-31 MR spectroscopy (letter; comment). Radiology 182:582, 1992.

156. Kato T, Tokumaru A, O'uchi T et al: Assessment of brain death in children by means of P-31 MR spectroscopy: Preliminary note. Work in progress. Radiology 179:95, 1991.

157. Klingelhofer J, Conrad B, Benecke R et al: Evaluation of intracranial pressure from transcranial Doppler studies in cerebral disease. J Neurol 235:159, 1988.

158. Yoneda S, Nishimoto A, Nukada T et al: To-and-fro movement and external escape of carotid arterial blood in brain death cases: A Doppler ultrasonic study. Stroke 5:707, 1975.

159. Hassler W, Steinmets H, Gawlowski J: Transcranial Doppler ultrasonography in raised intracranial pressure and intracranial circulatory arrest. J Neurosurg 68:745, 1988.

160. Feri M, Ralli L, Felici M et al: Transcranial Doppler and brain death diagnosis. Crit Care Med 22:1120, 1994.

161. Petty GW, Mohr JP, Pedley TR et al: The role of transcranial Doppler in confirming brain death: Sensitivity, specificity, and suggestion for performance and interpretation. Neurology 40:300, 1990.

162. Momose T, Nishikawa J, Watanabe T et al: Clinical application of ^{18}F-FDG-PET in patients with brain death. Kaku Igaku 29:1139, 1992.

163. Meyer MA: Evaluation brain death with positron emission tomography: Case report on dynamic imaging of ^{18}F-fluorodeoxyglucose activity after intravenous bolus injection. J Neuroimaging 6:117, 1996.

164. Altman DI, Perlman JM, Powers WJ et al: Preservation of brain stem and cerebral blood flow (CBF) in two asphyxiate newborn infants with clinical brain death. Pediatr Res 21:487A, 1987.

165. Medlock MD, Hanigan WC, Cruse RP: Dissociation of cerebral blood flow, glucose metabolism, and electrical activity in pediatric brain death. J Neurosurg 79:752, 1993.

Section 6 - Ancillary Responsibilities and Problems

Chapter 77 - Scope of Modern Anesthetic Practice

Fredrick K. Orkin
Stephen J. Thomas

INTRODUCTION

Turbulent, mercurial, exciting, challenging, and uncertain describe the specialty of anesthesiology during the 5 years since the last edition of this text. This undoubtedly reflects the volatile nature of our times--economic boom at home while the President fights impeachment, the Pacific Rim recovers from recession, and Russia fights economic and political meltdown. Scientifically, it has been the time of nitric oxide--meriting the Nobel Prize in Medicine, availability in our operating rooms (ORs) and intensive care units (ICUs) for the treatment of pulmonary hypertension, and the development and marketing of sildenafil citrate (Viagra).

However, it is the financing of health care, experiencing its most tumultuous changes since the inception of Medicare, that has affected medicine and anesthesiology so critically. The defeat of the Clinton Health Plan ushered in the "market solution" to health care--managed care--a cost-containment method of funding and delivering the "commodity" known as health care. [1] Major legislative, rather than market-based, reform of health care financing in the United States, where we currently spend 13 percent of the gross domestic product (GDP) yet still manage to leave 16 percent of the population uninsured, must await the millennium and the election of a new president.

The term "scope of practice" has multiple meanings. Medically, anesthesiology now encompasses the entire perioperative experience from preoperative evaluation to intraoperative regional or general anesthesia (given almost anywhere--hospital, ambulatory care center, procedure room, doctor's office) to the postanesthesia care unit (PACU) or ICU. It also now includes many types of management, both clinical--pain, PACU, ICU--and now administrative--the operating room (Ch. 82) . Scientifically, our scope of practice still includes the development of new, faster-acting drugs of short duration but expands now to molecular biologic techniques investigating issues from the adrenergic system to mechanisms of anesthesia and to outcome studies looking at the medical and economic effects of our actions. In fact, both the journals *Anesthesia and Analgesia* and *Anesthesiology* now have separate sections devoted to economics. This is important because of both physicians' concerns about their futures and the fact that the economics of our specialty--or at least the perceived economics--resulted in a precipitous decline in interest by American medical students, which only now is rebounding as the original perceptions and assumptions prove incorrect (and, perhaps, because the initial zeal for primary care on the part of managed care organizations and deans of medical schools proves misguided).

To better define the scope of the specialty, it is useful to review the definition of anesthesiology as defined by the American Board of Anesthesiology [2] :

> Anesthesiology and perioperative management is defined as a continuity of patient care involving preoperative evaluation, intraoperative and postoperative care and the management of systems and personnel that support these activities. It is the practice of medicine dealing with but not limited to: the assessment of, consultation for and preparation of patients for anesthesia; the provision of insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures, and the management of patients so affected; the monitoring and restoration of homeostasis during the perioperative period, as well as homeostasis in the critically ill injured, or otherwise seriously ill patient; the diagnosis and treatment of pain; the clinical management and teaching of cardiac and pulmonary resuscitation; the evaluation of respiratory function and application of respiratory therapy in all its forms; the conduct of research at the clinical and basic science levels to explain and improve the care of patients; the management of patient care delivery systems and the supervision, teaching and evaluation of performance of personnel, both medical and paramedical, involved in perioperative care; the administrative involvement in hospitals, medical schools, and outpatient facilities necessary to implement these responsibilities.

Scope of practice also has a distinct political interpretation, encompassing the questions of who can practice anesthesiology and under whose direction. The traditional approaches to delivery of anesthesia, either by the

anesthesiologist alone or as part of a care team [3] --including residents and/or Certified Registered Nurse Anesthetists (CRNA) and/or anesthesia assistants--is under increasing political pressure as CRNAs join other advance-practice nurses in seeking independent privileges to practice. [4] The Health Care Financing Administration and the Congress, as well as state legislators and judiciaries, are being asked to adjudicate this question. There is hope, however, that scientific inquiry into anesthetic outcomes will more appropriately decide these vexing and persistent issues. [5]

PREOPERATIVE EVALUATION

It is ironic that as our interest, expertise, and knowledge concerning preoperative evaluation increase, our abilities to meet and talk with patients directly appears to be decreasing (Ch. 23) . The emphasis on ambulatory surgery (see later) (also see Ch. 65) and same-day admissions, regardless of type of surgery, often makes personal contact with patients, whether in urban or rural settings, difficult. Despite such difficulties (as well as those relating to staffing, patient scheduling, and reimbursement), preoperative clinics appear to be increasing. Patients are seen, histories and physical examinations are reviewed, appropriate (and only appropriate) laboratory tests are ordered, and additional consultations, if indicated, are requested. [6] [7] Explanations of the anesthetic and surgical plans and options for postoperative pain relief decrease patient anxiety and give him or her a modicum of control over his or her own destiny. [8] Evaluation of comorbid conditions is not only directed to "getting the patient ready for surgery" but also focuses on the long-term prognosis of specific diseases. Diagnostic and therapeutic interventions are then ordered from that perspective. This is especially true in the area of cardiac disease. [9] [10]

Undoubtedly, new options for familiarizing patients about anesthesia and surgery will emerge in the ensuing years. These might, and in some cases already do, include supplemental videotapes, in-hospital on-demand television, and departmental or hospital-based Web sites accessible from any patient's home. [8] These sites will likely become interactive and a source for data input directly by the patient.

OPERATING ROOM

The OR continues to be the focus of the anesthetic practice. Whereas the anesthesiologist is comfortable in the operating room setting, it can be seen as a hostile environment both to patients and to other medical personnel. The use of various volatile anesthetics and the contamination of the environment by those gases are concerns that must be recognized by the anesthesiologist and appropriately monitored. Because anesthesiologists use needles and are constantly exposing themselves and others to blood and other body fluids, appropriate consideration and thought must be given to how to prevent injury, both to the anesthesia personnel and to others who work in the OR. [11] Unfortunately, not only are physician and nursing personnel subjected to needlestick injuries, but also housekeeping personnel are at risk because of potential inattention by anesthesia personnel. Certainly, it is in the best interest of the anesthesiologist to look at creative new ways to administer drugs and monitor patients that will decrease the incidence of contamination of personnel in the OR by body fluids from patients.

It is well recognized that the OR is a major consumer of hospital, physician, and patient resources. It is equally apparent that efficient management of ORs can minimize costs and at the same time maximize patient through-put, though not without extraordinary effort and continuing education. [12] Whereas few doubt the wisdom of these observations, fewer still have developed the ideal administrative and operational structure to effect the efficiencies needed in today's cost-constrained environment. [13] Nevertheless, the effort continues, and anesthesiologists, by their temperament, availability, and interest, will be some of the principal players in the game (Ch. 79) .

Triage is another important aspect of the anesthesiologist's role in the OR. Urgent or emergent cases need to be inserted into operative schedules during normal working hours, and often emergency cases vie for available resources during the off-hours. The anesthesiologist must have the broad medical and surgical knowledge to allocate resources and maximize treatment of patients in an orderly progression. If this triage responsibility is abdicated, patient care suffers. The anesthesiologist usually has the best overview of the surgical, nursing, and anesthesia personnel necessary to care for the patient.

AMBULATORY CARE

Arguably among the most significant trends affecting health care in the last quarter of the 20th century has been the development of ambulatory surgery. Indeed, two-thirds of U.S. surgery has already moved out of the hospital, with that fraction expected to reach almost three-quarters by the millennium (Fig. 77-1) . [14] Many factors contribute to this trend, including consumerism, especially because the public is increasingly eager to have an ever-larger decision-making role in its medical care; new technologies in anesthesia (rapidly acting, short-lasting anesthetic drugs and adjuvants) and surgery (tools for minimally invasive surgery, such as endoscopic devices and lasers); and changes in health-care economics. However, judging from the temporal aspects of the transition depicted in Figure 77-1 , economic factors are by far the pivotal factor.

The phase-in of Medicare's prospective payment system, beginning in 1983, limited payments for hospital inpatient care to predetermined amounts associated with the surgical procedure's diagnosis-related group. Suddenly, there was a potent financial incentive to move as much surgery (and other care) away from the hospital to escape the limitations imposed by these fixed rates. Thus, an increasing amount of surgery was shifted to the hospital's outpatient surgery facilities, where payment was based on the former, uncapped, cost-based system, thus allowing the hospital flexibility in setting charges. Shortly thereafter, noting both the safety and cost savings associated with outpatient surgery, Medicare (and then other insurers) covered an increasing array of procedures in hospital-independent, freestanding surgery centers, providing substantial incentive for a further shift of hospital cases into the ambulatory setting. More recently, increasing cost-consciousness has encouraged the movement

Figure 77-1 The growth of U.S. surgical procedures by site, 1981 to 2000. *(Hospital data through 1993 from the American Hospital Association; freestanding and office data through 1993 and all estimates after 1993 provided by SMG Marketing Group, Inc., Chicago.)*

of surgery to the setting with the lowest costs, the surgeon's office. What was once the only site for biopsies and dental extractions has matured into what might be termed freestanding single-specialty (e.g., hand and cosmetic surgery, cataract extractions, hernia repair) surgery centers. Indeed, the surgeon's office is now the most rapidly growing surgical site, expected to capture about 14 percent of the U.S. surgical caseload in the year 2000. Anecdotes describe a similar movement of pain management to freestanding offices.

Although economics, enhanced technology, and a ready and willing public account for the development and flourishing of this ambulatory care, what fosters this transition in care is its apparent safety. That is, the shift in the locus of care could not have occurred unless patient outcomes were at least comparable to those associated with inpatient care. The corollary is that it behooves anesthesiologists practicing in these various ambulatory sites to maintain the same procedural and institutional safeguards required for highquality care--including policies and procedures regarding patient and procedure selection, as well as practice standards--as pertain to inpatient care.

OTHER SITES

The need to provide anesthetics in non-operating room locations continues to increase at a furious pace (Ch. 66) . As procedures become "less invasive" and do not need the facilities of an operating room, it is now easier to bring the anesthesia to the patient than the converse. Areas qualifying for the label "off the floor" or "in the outfield" encompass almost every specialty and include in vitro fertilization laboratories, lithotripsy suites, electroshock therapy, and cardioversions. These environments require special knowledge, equipment, and preparation. Strict adherence to quality standards is important. The American Society of Anesthesiologists has developed a number of standards of care. In this instance, "Guidelines for Nonoperating Room Anesthetizing Locations" (approved in 1994) is the appropriate guide.

Interventional neuroradiology, the cardiac catheterization and electrophysiologic laboratories are areas where new procedures seem to appear on a monthly basis. The radiology equipment, the need for shielding, and the fact that many of these laboratories were designed neither for the anesthesiologist nor the necessary anesthesia equipment often make these procedures an event. An exception to this is the fact that when new cardiac catheterization laboratories are constructed, many are designed with the ability to become a complete operating room. However, the magnetic resonance imaging suite continues to be a less-thanhospitable place, whether we are called to care for a child, a trauma victim, or an inconsolable claustrophobic.

The electrophysiologic (EP) laboratory is a continual source of requests for care. Increasing knowledge of conducting systems of the heart permits electrical ablation of specific areas to control arrhythmias. Such procedures are extremely lengthy, and patients often become restless. Providing sedation and/or general anesthesia to these patients may be required. Additionally, the placement of implantable cardioverter-defibrillators, previously performed via a thoracotomy in the OR, is now carried out via the percutaneous route in the EP laboratory. Patients undergoing these procedures often have limited myocardial reserve and are being treated with a variety of antiarrhythmic drugs. Extensive knowledge of drug interactions for these patients is necessary, and the ability to support the circulation may be required.

POSTANESTHESIA CARE UNIT

PACUs have flourished. Requirements for medical direction, nursing education, and the quality of services provided in these units are discussed in Chapter 68 . It is now recognized that the same degree of vigilance that occurs in the OR must occur in the PACU. The evolution of new surgical procedures means that special consideration for patients is crucial. For example, the widespread use of laparoscopic procedures requires increased vigilance for unrecognized hemorrhage or bowel perforation (Ch. 56) .

In the past, management of postoperative patients and the resources of the PACU was ill-defined. Now, a medical director must be designated, and it is his or her responsibility to ensure the delivery of appropriate standards of care. This responsibility is gaining importance because of the increasing regulations and severity of illness seen in these areas. The anesthesiologist can effectively manage the PACU so as to maximize the efficiency of that unit while providing the best possible care.

The use of shorter-acting drugs and the prompt institution of effective pain relief, combined with acknowledged standards for PACU admission *and* discharge, have altered the approach to anesthetic recovery. [15] If a patient meets both anesthetic and surgical PACU discharge criteria to a second-stage unit, there is no reason not to go directly to the secondary recovery area immediately from the operating room. Dexter and Tinker [16] have shown that this type of flexibility, much more than anesthetic drug costs, can influence labor costs crucial to cost containment in the PACU.

CRITICAL CARE MEDICINE

Bendixen and colleagues, [17] in 1965, reviewed the pathophysiology of respiratory failure and detailed methods of mechanical respiratory support in their seminal book, *Respiratory Care.* (Also see Chs. 71 and 72 .) This documented the beginning of anesthesiology's involvement with critically ill patients outside the operating room. Initially, our role was to provide adequate ventilation for a patient and to determine when weaning from mechanical ventilation was feasible. It became obvious that respiratory function was only one aspect of care of the critically ill; therefore, the anesthesiologist became knowledgeable in cardiovascular support, nutrition, infection, and various diagnostic procedures needed for these patients.

In 1986, the Residency Review Committee (RRC) for Anesthesiology began to accredit programs training in critical care medicine (CCM) in departments that already had core residency training programs. At the same time, the American Board of Anesthesiology began examinations in CCM leading to subspecialty certification. It is worth noting that this followed fruitless negotiations with the specialties of surgery and pulmonary medicine in an attempt to define CCM jointly and to issue only one type of certification. Figure 77-2 demonstrates the fact that there is interest in CCM by anesthesiology residents, but it also confirms that CCM is not their overwhelming favorite. The number of CCM programs remains stable at around 50, with the number of trainees approximating 90. This is in marked contrast to the response following development of programs in pain management. This is unfortunate, because hospitals, given the transition to ambulatory care described previously, are devoting more and more of their bed space to intensive care. Pronovost and colleagues demonstrated improved outcomes in patients undergoing abdominal aneurysm resection where postoperative care was directed by an ICU physician who made daily rounds. [17A]

Some hospitals are taking a global approach and forming ICU administration groups that include all relevant physician specialties and jointly decide medical and administrative policies.

Critical care, however, is practiced not only in critical care units. More and more frequently, PACUs are substituting for the inadequate number of critical care beds. Appropriate resources and personnel must therefore be available in the PACU to serve these patients in a manner that is similar to what would be available in the ICU.

PAIN MANAGEMENT

John Bonica, the former chair of the anesthesiology department at the University of Washington, deserves credit for devoting time, effort, and interest in the understanding,

Figure 77-2 The number of critical care medicine programs in departments of anesthesiology and the number of residents in these programs for the years 1989-1997. As of December 1998, the American Board of Anesthesiology had awarded 855 certificates in critical care medicine. This number is greater than the number of trainees, because initially many candidates took the examination using temporary or practice criteria. *(Data provided by the American Board of Anesthesiology.)*

diagnosis, and treatment of pain (Chs. 69 and 70). Despite his entreaties, most departments devoted few resources--human, financial, or otherwise--to this area. Obviously, the turnabout has been remarkable; today almost every department--private, academic, or governmental--has the ability to treat acute, chronic, and cancer pain.

The recent development of acute pain services is yet another example of the expanding role of anesthesiologists in the medical center. We can now offer patients the prospect of a surgical experience that is totally (or almost totally) pain-free. The availability of intravenous patient-controlled analgesia, followed by other modalities--intrathecal, epidural, and intrapleural infusions, continuous nerve blocks--mandated that acute pain services be developed.

As society changes, the demands for health care change as well. The anesthesiologist's role in limiting postoperative pain by the appropriate use of drugs and devices is a very positive aspect of our specialty.

Interest in training in pain management continues to increase (Fig. 77-3) . There are now 250 to 300 residents taking an additional year of training in about 100 pain programs. As of December 1998, the American Board of Anesthesiology had awarded 2,238 certificates in pain management.

ANESTHESIA WORKFORCE

The workforce for anesthesia services continues to undergo dramatic change relating to its supply, diversity, and function. Historically an undersupplied specialty, unable to meet clinical demands in even the surgical operating room, anesthesiology has grown increasingly rapidly during the past 20 years. [18] Diverse trends account for this growth, including the increasing of sophistication of anesthesia care, itself related to maturation of subspecialty surgery (e.g., transplantation, cardiothoracic surgery); increasing incomes of physician specialists; and a doubling of the number of U.S. medical students graduated each year. As a result (and as described previously), anesthesiologists now work in sites well beyond the surgical operating room as well as sites outside the hospital, including the freestanding ambulatory surgery center, pain management office, and surgeon's office. Indeed, by 1990, anesthesiologists devoted the majority of their professional time to recognized subspecialties (e.g., ambulatory, cardiothoracic, obstetric, and pediatric anesthesia, critical care medicine, and pain management). Clearly, anesthesiology has entered a period of maturation if not sophistication in its professional development.

The growth in the supply of anesthesiologists--109 percent during the period between 1980 and 1996, compared with 58 percent for the total physician supply [19] --has markedly altered the mix of U.S. anesthesia care providers. Whereas there were two nurse anesthetists for every anesthesiologist 30 years ago, [20] by the latter 1980s, the two provider groups had equal numbers. In 1991, there were about 21,000 nurse anesthetists and 25,000 anesthesiologists [20] ; at the end of 1996, there were 33,318 anesthesiologists. [19] Approximately 500 anesthesiologists' assistants have also been trained since the two training sites opened in the early 1970s. These personnel are deployed in a highly variable array of configurations across the United States, even in the same community. Most anesthesia care is delivered by an anesthesia care team comprising an anesthesiologist medically directing nurse anesthetists and anesthesiology residents, with differing ratios among the provider types reflecting the composition of the care delivered. However, in much of the West, anesthesiologists tend to provide direct care, without nurse anesthetists, and in rural areas, nurse anesthetists often work in the absence of anesthesiologists. [18] [20] [21] Overall, there is an almost 6-fold variation in the per capita presence of the anesthesiologist across the United States (Fig. 77-4) (Figure Not Available) .

As dramatic as these workforce changes have been, they constitute merely a preface to future changes. The marked growth in the supply of anesthesiologists peaked by the mid-1990s, when the rate of production of new practitioners was about three times that of attrition. As a result, coupled with marketplace changes related to accelerating growth of managed care, graduates experienced difficulty finding jobs, medical students shunned the specialty, and new trainee cohorts more closely approximated attrition (currently, about 600 per year); now professional opportunities again seem adequate. However, looming on the horizon are diverse factors that are likely to alter the equilibrium if not the practice of anesthesiology. Among factors that may encourage more

Figure 77-3 The number of pain management programs in departments of anesthesiology and the number of residents in these programs for the years 1993-1997. *(Data provided by the American Board of Anesthesiology.)*

Figure 77-4 (Figure Not Available) The geographic distribution of anesthesiologists per 100,000 population, by hospital referral region in 1996, ranged from 4.3 (Harlingen, Texas) to 25.5 (Hinsdale, Illinois). *(From Wennberg and Cooper. [24] Copyright, the Trustees of Dartmouth College, 1997.)*

students to opt for anesthesiology are the emerging recognition that the shortage of primary care physicians proclaimed early in the decade was either quickly treated or a forecasting error; further expansion of the anesthesiologist's role and practice sites; and increasing sophistication of surgery. Certain factors may dissuade students, though the extent to which these factors will occur is still conjectural. They include the continued political fight to alter Medicare regulations (that would be adopted by other insurers) fostering independent practice by nurse anesthetists; further decreases in federal support of graduate medical education, especially specialist training; continued increases in students' already high loan indebtedness coupled with potential reductions in anesthesiologists' income relative to those of other specialties; and continued managed-care-related contraction of professional opportunities. Clearly, the anesthesia workforce continues to change subject to a most dynamic marketplace.

VALUE-BASED ANESTHESIA CARE

A feast-and-famine U.S. health-care marketplace had developed by the early 1990s. Several decades of runaway health-care cost escalation at two to three times the general economy's inflation rate, coupled with a large uninsured segment of the population and health indices (e.g., life-span, infant mortality) below those of countries with lower per capita health-care spending, increasingly suggested misallocation of resources in the U.S. health-care system. When federal reform failed in 1994, the marketplace accelerated the fundamental restructuring of health-care financing and delivery that had begun. What has resulted is a payer-dominated, constrained, increasingly competitive health-care marketplace that seeks greater *value,* which may be represented as

Value-based anesthesia care is a neologism advanced to encourage anesthesiologists to look beyond widely misunderstood concepts, such as cost-effectiveness, to focus on meeting the challenge of enhancing the value of care by providing the best patient outcome achievable at reasonable cost. [22] Given a large literature documenting that perhaps 25 percent of care is inappropriate [23] and large variations in resource use for similar care exist across small geographic areas, [24] it has become clear that quality and cost are not tightly linked: Better quality is not necessarily associated with higher cost, nor does spending less (by doing less) necessarily lead to lower quality.

Insights into the relationship between patient outcome (or benefit) and cost may be gleaned by noting the relationship between overall health benefit and incremental inputs to health care (Fig. 77-5 (Figure Not Available) A). As in other productive endeavors, the anesthesiologist should continue to add resources (e.g., newer and more costly drugs; special patient monitoring; adjunctive pain management protocols) to care as long as positive benefit results. Beyond "the top of the curve," the point of maximal benefit and thus optimal investment, further investment merely results in *negative* benefit (e.g., complications, higher cost without patient benefit). Whereas it is commonly believed that the U.S. health-care system has passed the top of the curve, we may "rationalize" our decision-making by reducing investment and moving back to the point of maximal benefit (Fig. 77-5 (Figure Not Available) B).

Seemingly arcane, this economic construct applies well to most decisions anesthesiologists face, including drug choice, equipment acquisition, and administrative policies. Common to each decision is choosing the appropriate technology or using technology appropriately. (We must acknowledge that *medical technology* is not limited to devices such as patient

Figure 77-5 (Figure Not Available) (A) The hypothetical relationship between inputs to a productive process and the benefits derived describes a *production function.* As investment continues, the net benefit, segment $DeltaB_n$, progressively decreases, then becomes negative, illustrating the law of diminishing return. (B) Rationalizing rather than rationing health-care technology achieves maximal benefit at "the top of the curve," a level of investment associated with the optimal investment. *(Panel A is reproduced from Orkin. [25] Panel B is modified from Orkin [25] and Reinhardt. [26])*

monitors, but, according to the congressional Office of Technology Assessment, also includes drugs, medical and surgical procedures, protocols, support systems, and organizational systems through which health-care professionals deliver care. [27]) The challenge of knowing when we are doing what is "appropriate" (and no more or less) is especially difficult, because our knowledge of the effectiveness of our clinical practices, among other complex issues, is incomplete. [23] The quandary is further complicated because of our rudimentary understanding of outcomes and economics, which extend well beyond the purely clinical and financial, to include quality of life, patient preferences, and patient-based assessment of care, among other seemingly subjective topics. [28] Although general [29] [30] and anesthesia-specific [28] [31] [32] guidance is available, few anesthesiologists will have sufficient time or expertise to undertake this outcomes-related research. Yet, anesthesiologists must develop an appreciation of the considerations when evaluating or planning value-based comparisons of care (Table 77-1) (Table Not Available) .

Once a potential, value-enhancing practice change is

TABLE 77-1 -- Considerations in Value-Based Comparisons of Care

(Not Available)

Modified from Orkin [22]

identified from the work of others (e.g., article in a professional journal) or through research in one's own institution, the next challenge is implementation. In truth, there is no shortage of good ideas, but putting them into action is often difficult. A major problem is inertia within the institution (e.g., "We always do it this way"). Moreover, even when an improved practice is implemented, the improvement is usually short-lived, due to regression to former practice patterns. For example, a new departmental policy dictates use of specified lower-cost drugs with similar patient outcomes in each drug class, but if the full array of drugs remain readily available, backsliding often occurs. Maintenance of the desired improvement requires fundamental change in the system of processes comprising practice patterns. Indeed, an authority on achieving improvement in institutions notes, "Every system is perfectly designed to get the results it gets." [33] Thus, lasting improvement requires modifying systems and related care processes to sustain desired practice patterns that enhance the value of care.

A recent report documented substantial cost savings without apparent adverse outcomes consequent to adoption of department-defined pharmaceutical practice guidelines for limiting the use of several high-cost drugs. [34] Acceptance ("buy in") of the guidelines was achieved in part through soliciting comments from all anesthesia care providers and including among the guideline committees ardent proponents of particular drugs. Compliance was maintained by several mechanisms, including widely publicizing the *department*' *s* successes, periodic feedback to each provider on his or her practice patterns, making compliance with the guidelines more convenient than noncompliance, and permitting departures from the guidelines for appropriate circumstances.

Ideally, we want to concentrate our improvement efforts where they would have greatest effect; however, in many situations we have only vague impressions, in part because the processes of care are themselves so complicated and outcomes are not tracked. A variety of sources can guide the focus of improvement efforts: patient complaints, staff suggestions, critical incident reports, accreditation survey results, benchmarking (i.e., comparison with similar institutions), statewide databases, peer review organization results, and articles in professional journals. Once a focus is chosen, Figure 77-6

Figure 77-6 General schema for improving the value of health care by applying the clinical value compass model. *(Modified from Nelson et al. [35])* Underlying this framework are several assumptions: Health is composed of biologic, physical, mental, and social aspects; the aim of health care is to reduce or limit the burden of illness by restoring or improving health functioning; quality health care provides care processes most likely to achieve the health outcomes desired by the patient at a price representing value for that patient; and the value of health care is a function of quality, costs, and volume.

provides a framework for conceptualizing the improvement effort. Improving the care requires that we understand the underlying processes, particularly where there may be wasted time and resources. Flowcharting the core processes by a team comprising representatives of the personnel involved intimately in the care aids in identifying likely opportunities for improvement. An initiative is adopted and pilot-tested in the care setting, and appropriate outcomes are tracked. Besides the purely clinical, other outcomes include patient satisfaction (e.g., wait times, delays, adequacy of instructions) and cost (including institutional performance). If improvement is documented, the relevant processes are modified to "hold the gain"; regardless of whether improvement occurs, the team moves on to other improvement opportunities. Although superficially resembling what institutions have been doing to satisfy external requirements (e.g., accreditation) for clinical tracking on a limited number of indicators, this measurement approach is more flexible and serves the need to enhance the value of care.

EDUCATION

Resident training is governed by the Resident Review Committee for Anesthesiology. It is charged by the Accreditation Council on Graduate Medical Education with developing standards for residency education, which are reviewed and revised every 5 years, and with inspecting and evaluating all residency programs, both core and subspecialty. The parent organizations for the anesthesia RRC are the American Board of Anesthesiology, the American Society of Anesthesiologists, and the American Medical Association. In 1998, for the first time a resident member was added to the RRC bringing the unique and welcome view of the trainee to the discussions.

As mentioned previously and depicted in Figure 77-7 , American medical student interest declined dramatically secondary to the perception that there were few practice opportunities. Anesthesia programs followed this trend. In 1988, there were 161 anesthesia residency programs; the number fell to 136 in 1998

The American Board of Anesthesiology, similar to most other specialty boards, will issue time-limited primary certificates beginning January 1, 2000. The time limit is 10 years.

RESEARCH

The Congress ending in 1998 did one spectacular thing for medicine; it increased the budget for the National Institutes of Health (NIH) by 15 percent. The exact proportion of the money that will go to anesthesiology is unknown, but hopefully it will stimulate more effort to secure a treasured R-01 grant from NIH. It would be presumptuous to attempt to detail the myriad domains in which anesthesiologists are asking questions, seeking answers. The 84 chapters in this text can be a starting point for the interested scientific traveler.

FUTURE

Predicting the future is hazardous business. One is safe in saying that the period until the next edition of this book will be just as tumultuous and challenging for the specialty as the 5 years since the last edition.

Because economic influences were so predominant in explaining our current situation, it might be useful to review some predictions that have been made. Smith and colleagues from the HCFA [36] have ventured a few guesses concerning medical expenses for the next 10 years. In 1998, total

Figure 77-7 Number of first-year residents in anesthesiology registered with the American Board of Anesthesiology over the years 1989-1998. *(Data provided by the American Board of Anesthesiology.)*

health-care dollars amounted to $1.1 trillion (~14% of GDP). They predict this will double to $2.1 trillion (16.6% of GDP) by the year 2007. This increase will be concentrated in the private sector, will be triggered by technology and longevity (the baby boomers will definitely have arrived), and will be fostered by the fact that managed care as we currently know it already enrolls 85 percent of the workforce and cannot be expected to effect substantial new savings.

The aging of the population combined with technological advance should make many positions available for anesthesiologists. Our expansion into new areas should do the same. The renaissance of interest among medical students is exhilarating to all involved in medical education. Our techniques in pain management will make the operative experience less frightening and less of a physiologic trespass.

References

1. Angell M: The American health care system revisited--A new series. N Engl J Med 340:48, 1999.

2. American Board of Anesthesiology: Booklet of Information. Raleigh, North Carolina, American Board of Anesthesiology, 1998.

3. Abenstein JP, Warner MA: Anesthesia providers, patient outcomes, and costs. Anesth Analg 82:1273-1283, 1996.

4. Zambricki CS: "Anesthesia providers, patient outcomes, and costs": The AANA responds to the Abenstein and Warner article in the June 1996 *Anesthesia and Analgesia.* AANA J 64:413-463, 1996.

5. Silber JH, Kennedy SK, Koziol LF et al: Do nurse anesthetists need direction by anesthesiologists? Anesthesiology 89:1184A, 1998.

6. Roizen MF: Cost-effective preoperative laboratory testing. J Am Med Assoc 271:319-320, 1994.

7. Roizen MF: Preoperative evaluation: A shared vision for change. J Clin Anesth 9:435-463, 1997.

8. Klafta JM, Roizen MF: Current understanding of patients' attitudes toward and preparation for anesthesia: A review. Anesth Analg 83:1314-1321, 1996.

9. Eagle KA, Brundage BH, Chaitman BR et al: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery. Circulation 93:1278-1317, 1996.

10. Fleisher LA: Preoperative cardiac evaluation before noncardiac surgery. Anesth Analg (suppl):20-27, 1998.

11. Needlestick-prevention devices. Focus on blood collection devices and catheters. Health Devices 27:184-232, 1998.

12. Overdyk FJ, Harvey SC, Fishman RL, Shippey F: Successful strategies for improving operating room efficiency at academic institutions. Anesth Analg 86:896-906, 1998.

13. Truong A, Tessler MJ, Kleiman SJ, Bensimon M: Late operating room starts: Experience with an education trial. Can J Anaesth 43:1233-1236, 1996.

14. Orkin FK: Ambulatory anesthesia: Past, present, and future. Anesthesiol Clin North Am 14:595-608, 1996.

15. Apfelbaum JL: Bypassing PACU: A cost effective measure. Can J Anaesth 45:R91-4, 1998.

16. Dexter F, Tinker JH: Analysis of strategies to decrease postanesthesia care unit costs [see comments]. Anesthesiology 82:94-101, 1995.

17. Bendixen HH, Egbert L, Hedley-Whyte J, et al: Respiratory Care. St. Louis, Mosby, 1965.

17A. Pronovost PJ, Jenckes MW, Dorman T, et al: Organizational characteristics of intensive care units related to outcomes. JAMA 281:1310, 1999.

18. Orkin FK: Work force planning for anesthesia care. Int Anesthesiol Clin 33:101, 1995.

19. Randolph L (ed): Physician Characteristics and Distribution in the US, 1997-98 ed. Chicago, American Medical Association, 1999.

20. Rosenbach M, Cromwell J: A profile of anesthesia practice patterns. Health Affairs 7:118-131, 1988.

21. Orkin FK: Rural realities. Anesthesiology 88:568-571, 1998.

22. Orkin FK: Moving toward value-based anesthesia care. J Clin Anesth 5:91-98, 1993.

23. Naylor CD: What is appropriate care? N Engl J Med 338:1918-1920, 1998.

24. Wennberg JE, Cooper MM (eds): The Dartmouth Atlas of Health Care. Chicago, American Hospital Publishing, 1998.

25. Orkin FK: Practice standards: The Midas touch or the emperor's new clothes? (editorial). Anesthesiology 70:567-571, 1989.

26. Reinhardt U: Health Care Quality Management for the 21st Century. Tampa, Florida, American College of Physician Executives, 1991.

27. Office of Technology Assessment, U.S. Congress: Strategies for Medical Technology Assessment, 3rd ed. Washington, DC, US Government Printing Office, 1982.

28. Orkin FK: Outcomes research in anesthesia. Adv Anesthes 16:99-128, 1999.

29. Eisenberg JM: Clinical economics: A guide to the economic analysis of clinical practices. J Am Med Assoc 262:2879-2886, 1989.

30. Drummond MF, O'Brien B, Stoddart G et al: Methods for the Economic Evaluation of Health Care Programmes, 2nd ed. New York, Oxford University Press, 1997.

31. Sperry RJ: Principles of economic analysis. Anesthesiology 86:1197- 1205, 1997.

32. Watcha MF, White PF: Economics of anesthetic practice. Anesthesiology 86:1170-1196, 1997.

33. Berwick DM: A primer on leading the improvement of systems. Br Med J 312:619-622, 1996.

34. Lubarsky DA, Glass PSA, Ginsburg B et al: The successful implementation of pharmaceutical practice guidelines: Analysis of associated outcomes and cost savings. Anesthesiology 86:1145-1160, 1997.

35. Nelson EC, Batalden PB, Ryer JC (eds): The Clinical Improvement Action Guide. Oak Brook, Illinois, Joint Commission on Accreditation of Healthcare Organizations, 1998.

36. Smith S, Freeland M, Heffler S, McKusick D: The next ten years of health spending: What does the future hold? The Health Expenditures Project Team. Health Aff 17:128-140, 1998.

Chapter 78 - Finding Professional Information on the Internet

Ira J. Rampil

INTRODUCTION

An interconnection of computers known as the Internet is changing the nature of information dissemination. Information on every conceivable topic has become instantaneously accessible by telephone or even satellite anywhere in the world. Publishing information on the Internet has spurred a revolution that may come to be seen as significant as the development of the printing press because the impediment to instant, global publication has essentially disappeared. Public and private professional agencies, commercial interests, universities, and private citizens have all taken advathe Internet to publish medical information. Subsequently, as the corpus of medical literature moves to electronic form, it is also being transformed from its classical, controlled, peer-reviewed, article-based format to a more free form with variable provenance. This review focuses on sites that serve as key depots of information and on strategies for efficiently locating anesthesia-related information of the highest quality. Although every effort has been made to use current Internet addresses, the dynamic nature of the Internet ensures that some of these addresses will change over time.

The information content within the Internet is packaged by its provider or publisher in one of several ways. Each type of package provides a different "look and feel" or interface to the end user, and each is transmitted by a different software protocol. At present, the most widely used protocols are electronic mail (E-mail), World Wide Web pages (WWW, or Web), bulletin boards (USENET), and simple file transfer protocol (FTP).

The development of hypertext technology is probably the dominant alluring feature of the Web. The basic concept of hypertext was originated by Vannevar Bush [1] and was developed by Theodore Nelson. [2] [3] Simply put, text can be annotated or cross-referenced by marking key words. If activated by the reader with a mouse click, these "hot word links," or simply, "links" in text bring the reader to a new text that expands on the original linked words. Reading is thus converted from a sequential or linear process to a readercontrolled nonlinear experience, with the reader skipping around ("surfing") as interest or mood strikes. The concept of hypertext has been expanded for two-way communication between the reader and the publisher by way of data entry forms. Forms are presented to the reader as an area of a Web page with blank boxes that await reader-entered text as well as buttons, check boxes, and other elements of the common graphical user interfaces.

In the 1960s, when computers filled special air-conditioned rooms and communicated by exchanging magnetic tapes, the Internet began as an experiment in direct, wired, communication. With funding from the U.S. Department of Defense Advanced Research Projects Agency (ARPA), the Internet developed into a matrix of computers that could pass data around the country, even if part of the matrix was disabled. Through the early 1990s, the Department of Defense funded the expansion of the network for military and scientific research purposes. During this time, computer scientists developed a variety of uses for the network in addition to the original transfer of data files. These ancillary Internet services grew in popularity, eclipsing the original research intent, and eventually convinced the government to commercialize the Internet. The Internet continues to expand, as it has from its inception, with more than 18 million computers assigned network addresses and more than 100 million daily users worldwide as of the summer of 1997.

The rapid expansion of public and commercial use of the Internet has to some extent "clogged its arteries," slowing data transfer rates for the research community. Therefore, the National Science Foundation has helped fund the creation of Internet II, which has much higher capacity than the original; at present, it is only open to certain research universities and industrial users.

When the government of the United States relinquished control over access to the Internet, the demographics of Internet

publishers shifted dramatically from university-based academics to a population composed predominantly of commercial interests and average citizens. The nearly absolute freedom to publish material on the Internet has led to the present situation, in which valuable medical and scientific information must compete for attention with advertising, hucksterism, quackery, and fringe opinion. Nevertheless, the Internet remains a valuable resource that can be efficiently mined for medical information, if the user knows where to look.

SOURCES OF TRUSTWORTHY MEDICAL INFORMATION

Peer-Reviewed Literature

The National Library of Medicine (NLM), a branch of the National Institutes of Health (NIH) in the United States, has been collecting a bibliographic database of the world's serial literature of biomedical science since 1966. This database, known as MEDLINE, has citation information and author abstracts from roughly 3,800 journals and more than 9 million papers and is widely considered the premier source of peer-reviewed medical information. [4] Once the domain of librarian-specialists and expensive subscription services, the NLM now provides free MEDLINE access to all on the World Wide Web. MEDLINE is available through two different styles of user interface.

Internet Grateful Med (http://igm.nlm.nih.gov) is the free continuation of an old fee-based subscription service. Grateful Med is a Web page that has a data entry form containing many fields with which the user may control the search process. Grateful Med allows searches by subject word, author name, or title word. At the top of the search form, a button labeled "Find MeSH/Meta Terms" is the link to the NLM metathesaurus that allows the user to convert arbitrary or common English language phrases or concepts into precise MeSH (medical subject heading) search terms. For example, the metathesaurus suggests converting "mad cow" into "encephalopathy, bovine spongiform." Use of the metathesaurus is highly recommended to ensure that all relevant citations are retrieved. A set of pop-up menus limit parameters for the search, including publication type (e.g., clinical trials, editorials, reviews), gender of study subjects, age groups, dates of publication, and language of publication. An asterisk appended to the start of a subject word informs the search engine that the subject must be a major component of the citation. Once a search has been performed, the resulting citations are listed, eight at a time, in an abbreviated format. The short format has the full title and author list, the affiliated institution, the journal citation, and a note as to whether an abstract is available. Each citation in this list also has a checkbox that selects the citation for more detailed secondary display that includes abstract and MeSH headings. Grateful Med has an option to save the detailed search results to the user's local disk. This feature is particularly useful for filling a bibliographic database used in conjunction with a word processor. Users who choose to use non-Web-based access software to Grateful Med must still pay a subscription fee, but they are entitled to order (for an additional fee) reprints of articles they find in a search.

PubMed (http://nlm.nih/gov) is a simpler, but still powerful, alternative interface to the MEDLINE database. The entry screen to PubMed uses only a single field in which one may enter subject words and authors. The grammar for basic searching is relaxed compared with that of Grateful Med: list the words of interest, separated by spaces. For example pulmonary vasodilation nitric oxide locates all articles with these terms as MeSH subjects, title words, or abstract words. When more than one search term is entered in the simple entry field, the terms are presumed to be ANDed together. If a multiword phrase is sought, it can be enclosed in quotation marks. Author names may be entered as only surnames or with initials. When initials are added, they should be delimited with a comma. The entries Hamilton WK, anesth* find all the publications of W.K. Hamilton that contain a root or MeSH term that starts with "anesth." The asterisk is a wild card that allows a match to all subjects and MeSH terms starting with "anesth," including anesthesia, anesthetic, anesthesiologist, and anesthesiology. Advanced users may employ a more sophisticated search grammar that includes Boolean expressions (AND, OR, NOT) and specific search fields (Table 78-1) . For example: clonidine[majr] AND anesthesiology[ta] AND 1996[pdat] locates the eight papers that appeared in *Anesthesiology* in 1996 with a major subject of clonidine. Note that the Boolean operator words must be capitalized, whereas the search field descriptors (abbreviations) are lower case. PubMed has an advanced search page that prompts the user with pop-up menus for the search field descriptors and Boolean operators. In advanced mode, a search may be incrementally refined by adjusting terms and limits after each search. A powerful feature of PubMed is the "see Related Articles" link, which appears next to each citation in the short display list. This feature uses a complex algorithm to compare both the text and the MeSH terms of articles when they are entered into the system to define "neighbors" on the basis of similarity of content. The list of related articles is sorted by degree of similarity. As with the Grateful Med interface, PubMed can save the results of a search in a variety of formats for later use. PubMed provides direct links in citations to that small number of journals (currently <100) whose publisher provided the full text of articles on-line. Although detailed discussion of search strategies within MEDLINE is beyond the scope of this review, it is important to note that the quality of the search results is very sensitive to the approach the user takes to searching. One example was provided by two different searches for randomized controlled trials in epilepsy. [5] In this case, one search strategy located 103 papers, and the other strategy, 275 of 308 known relevant papers. The long-term solution for users of these databases is the evolution of database search software to automatically translate vocabularies of disciplines and to efficiently extract core semantic concepts from the archived manuscripts. [6] A database user may then rely on the search engine to find the right citations, even if they do not include the exact wording sought.

Computer database search results are frequently plagued by the inclusion of irrelevant citations. Nonspecific citations are a particular problem for clinicians who seek efficiency. The NLM has taken some steps to solve this problem with the Clinical Queries system. In Clinical Queries, the user enters

TABLE 78-1 -- PubMed Database Search Fields[a]

FIELD	ABBREVIATION	DESCRIPTION
Affiliation	AD	Contains the institutional affiliation and address of the primary author and sometimes of other authors.
All fields	ALL	Covers all searchable PubMed fields.
Author name	AU	Contains the list of authors for a paper in the literature. The format for author names is the last name, followed by a space and the first initial(s), without periods, e.g., David J. Lipman would be Lipman DJ; James Ostell would be Ostell J. Initials may be omitted when searching.
E.C. number	RN	Is a number assigned by the Enzyme Commission to designate a particular enzyme. This field also includes Chemical Abstract Service registry numbers.
Journal title	TA	Is the name of the journal where the record was published. Journal names are stored in the database in abbreviated form, e.g., the *Journal of Biological Chemistry* is stored as J Biol Chem. If one is not sure how a journal name is abbreviated, one uses "List Terms" mode to browse the journal titles. One may also enter the complete journal name or the ISSN number in this field. A "Journal Browser" is also available to look up the full name, abbreviation, and ISSN number of a journal.
Language	LA	Is the language in which the article was published. Note that many non- English articles, however, do have English abstracts.
MeSH major topic	MAJR	Includes all MeSH terms that are marked as being of major importance to this record by the National Library of Medicine indexers for MEDLINE.

MeSH terms	MH	Includes all of the terms in the MeSH terms, a controlled vocabulary of terms used to index MEDLINE. Each MEDLINE citation is given a group of MeSH terms that relate to the subject of the paper from which it is drawn. Frequently, MeSH terms have an additional term, called a "subheading," that further defines how the MeSH term relates to the article it is associated with. This subheading is appended to the MeSH term, e.g., "pneumonia/diagnosis." Searching on the MeSH term (here, "pneumonia") retrieves all of the articles that use that MeSH term, whether they have subheadings or not. One uses the subheading terms if one requires more specificity than the MeSH term alone allows. *Note:* MeSH terms searched for using the MeSH or MeSH major topic fields are automatically "exploded" by PubMed, i.e., all terms that are logical subsets of the term entered are included. For instance, "vision disorders" includes "blindness." MeSH terms found using the "All Fields" search, however, are *not* exploded.
Modification date	MDAT	Contains the date that the record was placed into PubMed, in the format year/month/day, As for publication date, see below.
Page number	PG	Is the number of the first journal page that the article appears on.
Publication date	DP	Contains the date that the article was published in the format year/month/ day, e.g., 1984/10/06. Entry of a year alone (e.g., "1984") retrieves all articles for that year; entry of a year and month (e.g., "1984/03") retrieves all articles for that month. Journals vary in the way the date appears, some including only year, some year plus month, some year plus month plus day. PubMed takes the date as it appears in the journal.
Publication type	PT	Refers to the form of presentation of an article or other work. Examples include review articles, clinical trials, randomized controlled trials, and retracted publications. (See Table 78-2.)
Substance	NM	Contains the names of any chemicals associated with this record from the Chemical Abstract Service (CAS) registry and the MEDLINE "Name of Substance" field.
Text words	TW	Includes all words in the title and abstract, plus individual words from MeSH terms and chemical substance names.
Title words	TI	Includes only those words found in the title of a record.
Volume	VI	Is the number of the journal volume in which this article is published.
MEDLINE ID	UI	Is the MEDLINE unique identifier of a given citation.
PubMed ID	PMID	Is the PubMed unique identifier of a given citation.

[a] *Derived from http://www.ncbi.nlm.nih.gov/PubMed/pubmedhelp.html#SearchFields. Partial listing only.*

the usual search terms plus a category: therapy, diagnosis, etiology, or prognosis. The system will then report only the most relevant papers. See Table 78-2 .

The NLM has coordinated a program with local medical libraries to deliver copies of full articles on request. Fees and form of delivery depend on the local library.

Besides MEDLINE, the NLM has other databases that contain a wealth of information for the researcher, the practitioner, and the public. These databases are listed in Table 78-3 . The NLM provides a Web page (www.nlm.nih.gov/ databases/alerts/clinical alerts.html) that lists NIH "Clinical Alerts." These alerts are a public service tAlerts." These alerts are a public service that reviews the outcomes

TABLE 78-2 -- Publication Types (Partial List)

Bibliography	Journal article
Biography	Letter
Classical article	Meeting abstact
Clinical trial	Meta-analysis
Congress	Multicenter study
Controlled clinical trial	Newsletter article
Randomized clinical trial	Practice guideline
Comment	Published erratum
Consensus development conference	Retracted publication
	Review
Editorial	Review, tutorial
Festschrift	Technical report
Historical article	Twin study

TABLE 78-3 -- National Library of Medicine Databases

BROWSER INTERFACE	
GRATEFUL MED	***PUBMED***
AIDSLine	MEDLINE
AIDSDrugs	GenBank DNA Sequences
AIDSTrials	GenBank Protein Sequences
DIRLine	Biomolecule 3D Structures
HealthSTAR	Complete Genomes
HISTLine	
HSRPro	
MEDLINE	
OldMEDLINE	
PreMEDLINE	
SDILine	

of major NIH-funded clinical trials and provides notice of results that are believed by the NIH to have the potential for major impact on medical practice.

Other useful sources of information include the drug nomograph database at cponline.gsm.com and the government's consumer guide to health care at www.healthfinder.gov.

Journals

Many traditional peer-reviewed journals have developed electronic outposts on the World Wide Web. These Web sites are in varying states of evolution, and thus, each provides a different set of features. Most provide a set of contact addresses for the respective editorial offices and manuscript preparation instructions for authors. Many provide timely search access to published article abstracts, and a few provide access to published full papers with illustrations. Although successful economic models of paperless publishing have yet to be developed, the trend away from paper publishing and third-class mailing seems clear. Table 78-4 provides a small sample of the medical journals now on the Web. A more complete, updated list is available at www. yahoo.com/Health/Medicine/journals.

Textbooks and Patient Care Protocols

Many of the major textbooks of anesthesiology and medicine in general now have electronic counterparts. To date, these works have been commercial and proprietary and are available for sale only on a CD-ROM rather than on the Internet. At least two groups of volunteer authors have therefore started to produce Web-based texts. The first, *Global Textbook of Anesthesiology* (http://gasnet.med.yale.edu/gta), has a structure similar to that of traditional texts with major sections and chapters. At present, the 26 available chapters tend to be narrowly focused and together cover perhaps 5 to 10 percent of the field of anesthesiology. The chapters have been neither reviewed nor edited. The second effort is called the *Virtual Anaesthesia Textbook* (http://www.usyd.edu.au/ su/anaes/VAT/VAT.html). This site is actually an organized compendium of preexisting anesthesia-related Web pages. Volunteer chapter organizers seek out Web pages with appropriate key words and list them within the framework of a "chapter." Although this is certainly an interesting experiment in electronic collaboration, the results are predictably

TABLE 78-4 -- A Sample of Peer-Reviewed Journals Available on the Web

JOURNAL	URL	SEARCH CONTENT	ABSTRACT	FULL TEXT
Anesthesia and Analgesia	anesthesia.ucsf.edu/webdocs/aa/aa.html	Y	Y	N
Anesthesiology	www.anesthesiology.org	Y	Y	N
Annals of Internal Medicine	www.acponline.org/journals/annals/annaltoc.htm	Y	Y	P
Chest	journals.chestnet.org/chest/first.html	Y	Y	N
Journal of the American College of Cardiology	www-east.elsevier.com/jac/	Y	Y	P
Journal of the American Medical Association	www.ama-assn.org/public/journals/jama/jamahome.htm	Y	Y	N
Nature Medicine	medicine.nature.com	Y	Y	N
New England Journal of Medicine	www.nejm.org	Y	Y	N
Science	www.sciencemag.org	Y	Y	Y

N, no; P, partial; Y, yes

TABLE 78-5 -- Resident Teaching Materials and Patient Care Protocols on the Web

TITLE	AUTHOR	URL
Redbook (Resident Handbook)	University of Basel	www.medana.unibas.ch/redbook
Educational Research Lab	Cleveland Clinic Foundation	www.anes.ccf.org/pilot/
Electronic Case Conferences	Penn State University	www.anes.hmc.psu.edu/caseconferencefolder/caseconferencetoc.html
Neuroanesthesia Basics	New York University	mcns10.med.nyu.edu/research/basicneuro.html
Anesthesia for the Pregnant Patient	University of Chicago	dacc.bsd.uchicago.edu/library/manuals/obstetric/obanesthesia.html
Didactic Materials	University of California, San Francisco	anesthesia.ucsf.edu/anesthweb/didactics/didacthome.html

uneven. Some of the linked pages are of high quality, others of marginal quality or relevance, and the thematic coverage is spotty and subject to the organizers' ability to track down what other people have written.

Some of the pages linked by the *Virtual Anaesthesia Textbook* were written as teaching handouts. A small number of academic departments, professional societies, and individuals have placed resident-oriented teaching materials on the Internet. These include electronic versions of lecture notes and local protocols for the anesthetic conduct of certain types of cases. These pages often provide useful insight into case management and are a reminder to the variability in approach across institutions. However, this type of Web page is not reviewed by the Food and Drug Administration or even peer reviewed in general. Therefore, suggestions regarding pharmacology, especially off-label use of drugs, must be considered only advisory. A few examples of patient care protocols that have been published on the Internet are listed in Table 78-5 .

Grants and Funding Information

In the present competitive funding environment, access to the current NIH Requests for Proposals (RFP) and other Institute news and offerings can be quite useful. The NIH provides several means by which investigators may stay abreast of funding opportunities. The NIH Guide is available on the World Wide Web (http://www.nih.gov/grants/ guide/index.html). Versions of the NIH application forms that can be downloaded are also available at http:// www.nih.gov/grants/forms.htm. Each institute maintains its own Web site as well. The RAMS-FIE company offers a free E-mail notification system (FEDIX Opportunity Alert). This system allows subscribers to note their fields of interest, and the system then notifies them periodically to relevant funding opportunities across all federal funding agencies. FEDIX Opportunity Alert may be subscribed to at www.rams-fie.com/opportunity.html.

The NIH maintains a database (CRISP) of funded research projects that may be searched via the Web. CRISP contains project abstracts and investigator and institutional information. The CRISP search engine may be accessed at http://www-commons.cit.nih.gov/crisp.

Politics and News

The impact of political and social forces on the practice of medicine has never been greater. Changing social policy regarding access to health care and the ascendancy of competitive he is therefore as important in this area as it is in the scientific arena.

Professional organizations, including the American Society of Anesthesiologists (http://www.asahq.org) and the American Medical Association (http://www.ama-assn.org), have Web sites that offer practice news and commentary in addition to membership-oriented services. The American Society of Anesthesiologists Web site also maintains a library of downloadable practice guidelines that have been reviewed and approved by the organization. Several anesthesia-related subspecialty organizations have developed a presence on the Internet (Table 78-6) . These organizations provide newsletters, information regarding scientific and professional meetings, and some access to subspecialty journals. For those with an interest in the latest alterations in regulations, reimbursement, and enforcement issues, the Department of Health and Human Services Health Care Financing Administration maintains a Web site at www.hcfa.gov.

General news is available from many Internet sources. Daily newspapers and weekly magazines are available at Web sites or via subscription E-mail. Reputable

news organ-izations like the *New York Times* (www.nyt.com) and CNN (www.cnn.com) often have timely coverage of major medical stories. A current listing of general news sources may be obtained from a Web directory, such as Yahoo (www. yahoo.com/news).

Departments of Anesthesia

Many academic and private departments of anesthesia have Web sites. These sites provide information on the faculty; the residency program, if present; and in some cases, descriptions of special clinical services for prospective patients. Up-to-date lists of links to anesthesia departments can be found at http://www.yahoo.com/Health/Medicine/

TABLE 78-6 -- Anesthesia-Related Subspecialty Web Sites

ORGANIZATION	URL
American Society of Critical Care Anesthesiologists	gasnet.med.yale.edu/ascca
American Society of Regional Anesthesia	www.asra.com
Anesthesia Patient Safety Foundation	apsf.med.yale.edu
Society for Ambulatory Anesthesia	www.samba.org
Society for Intravenous Anesthesia	siva.org
Society for Neuroanesthesia & Critical Care	anesthesia.ucsf.edu/snaccweb/snacc.html
Society for Obstetric Anesthesia and Perinatology	www.anes.ccf.org/soap/index.htm
Society for Pediatric Anesthesia	www.uams.edu/spa/spa.htm
Society for Technology in Anesthesia	gasnet.med.yale.edu/wsta/sta/

Anesthesiology/Institutes/ or http://www.asahq.org/anes links.html.

Discussion Groups

A popular means of professional communication on the Internet is known as the discussion group. In essence, a group of interested people sends their E-mail addresses to a central party known as a host or list server, creating a list of recipients. A member of that list may then send an E-mail message to the host, which in turn rebroadcasts the message to all members of the list. The message traffic on these lists may be rare or dozens of messages per day. The content of the messages ranges from the seeking and rendering of clinical advice, discussion of cases, or even frank commercial Spam (unsolicited junk E-mail). Many busy discussion groups provide a digest service as an alternative to receiving dozens of individual messages. The largest anesthesiarelated discussion group is GASNet (http://gasnet.med. yale.edu/maillist/). A current list of more than 50 anesthesia-related groups with their electronic contact addresses can be obtained at www.eur.nl/cgi-bin/wrt4.pl.

A service known as USENET provides another variant of the discussion group. Instead of using E-mail to communicate with a fixed list of subscribers, USENET uses a public bulletin board format. In USENET, there are topical boards, also known as newsgroups, where anyone may read or post messages. At present, USENET has almost 33,000 separate newsgroups, although none relate directly to the practice of anesthesia or critical care at present. Newsgroups are named to place themselves within a subject hierarchy. For example, comp.sys.mac.digest is a newsgroup within the computers group (comp) related to Macintosh computers (.sys.mac) that contains summaries of news, commentary, and new file postings (.digest). Another example is rec.auto.bmw, a newsgroup in which hobbyists and enthusiasts (rec = recreation) discuss the minutiae of BMW automobiles. Topics of general medical interest may be found within the sci.med hierarchy, such as sci.med, sci.med.cardiology, sci.med.pharmacy, and sci.med.informantics.

On-Line Journals

Early in the genesis of the Internet, the ability to instantly and inexpensively disseminate information proved tempting to investigators eager to get their message out. The physicists were first, creating in the 1980s an on-line archive of preprint manuscripts, followed by an on-line peer review system for both traditional and purely electronic publications. There has been an effort to create a similar venue for the field of anesthesiology. A purely electronic, peerreviewed journal, the *Internet Journal of Anesthesiology,* now appears at http://www.ispub.com/journals/ija.htm. This journal provides a venue for publications that include multimedia (video, sound, and color pictures) and interactive features. Eventually, mainstream paper-based journals can be expected to move to a predominantly Web-based existence.

General Information

With more than 70 million Web pages and millions more FTP and gopher sites, as well as many hundred thousand USENET messages per week, some information is available on almost any conceivable topic. A hallmark of this collection of information is that there is absolutely no central control or official index. Finding relevant information is almost always an uncertain venture. Because of the great popularity of the Web, several commercial ventures have arisen that index the Internet and provide free searches to the public in exchange for providing advertising banners. Each of these services has different characteristics; some are presented as primarily search engines, such as Alta-Vista and Open Text, whereas others, like Excite, Infoseek, Lycos, and Yahoo, are designed for use as directories, although they have some search capability. Search engines usually locate more Web pages than directories, but the directory results are usually more relevant. Most of these services search the newsgroups of USENET as well as the Web. The Alta-Vista search engine is the most complete Web database. It catalogs more than 50 million Web pages and 8 billion words. Other services range from nearly that large to lists of only several hundred thousand Web sites that have been selected for content or, in some cases, commercial consideration. These indexes of the Web are dynamic, with new entries constantly being fed into the databases by so-called Web spiders. Spiders are software programs that aggressively map the World Wide Web by reading all the text and links on a page, then following up on the found links in an iterative process that tries to find all available Web pages. Because the Web is so large, a complete traversal by a spider program can take months. Therefore, some fraction of the Web sites found in a search or a directory are no longer available at the listed universal resource locator (URL). Most searches find pages that do not really relate to the search subject. Many of the search services allow the user to refine with Boolean terms, a search that may produce a massive number of listings. The Alta-Vista site also has a unique graphical approach to refining

a search. Efficiently finding the Web pages that are truly interesting requires knowing the "grammar" of each search engine because they are all different. Most of these services provide a tutorial page for their system's search request grammar.

Often, a URL is rendered obsolete by a rearrangement of files in the disk of the server, rather than an actual deletion. In such cases, there is no harm in removing the file directory information in the URL, leaving just the domain name. Reading the top Web page of the server often provides a path or at least a clue to the missing pages. When using a search or directory services for medical information, one must remember that random Web pages resulting from a search may well have a random probability of containing accurate information. The power and failing of the Internet is that it provides a medium for true freedom of the press, but when one is seeking professional medical information, it is prudent to exercise judgement and to rely on sources of known provenance.

/das/book/view/29494766/875/861.html

References

1. Bush V: As we may think, Atlantic Monthly July 176:106-107, 1945.

2. Nelson TH: Computer Lib/Dream Machines. Sausalito, CA, Mindful Press, 1974.

3. Nelson TH: As we will think. On-line 72 Conference Proc 1:439-454, 1972.

4. McCarn DB, Leiter J: On-line services in medicine and beyond. Science 181:318-324, 1973.

5. Marson AG, Chadwick DW: How easy are randomized controlled trials in epilepsy to find in MEDLINE? The sensitivity and precision of two MEDLINE searches. Epilepsia 37:377-380, 1996.

6. Schatz BR: Information retrieval in digital libraries: Bringing search to the net. Science 275:327-334, 1997.

Appendix 1-Glossary [a]

Address
: Every computer on the Internet is assigned a unique numerical (IP) address that must be used to direct communications. Most computers also have an alphabetic (domain) name that is easier to remember.

Applet
: A small JAVA program embedded within a Web page.

ASCII
: American standard code for information interchange. The numeric code by which computers represent alphabetic letters, numbers, and symbols.

Bandwidth
: The speed rating of a communications link. Usually measured in bits per second, in which an ASCII character is eight bits and a full page of text is about 16,000 bits. Standard modems provided a band width of 28,800 bits per second.

Domain name
: An alphabetic name that is assigned to the IP number address.

FAQ
: Frequently asked questions. A list of common questions and answers. Usually an unreviewed volunteer effort.

FTP
: File transfer protocol.

HTTP
: Hypertext transfer protocol. The communications protocol that drives the World Wide Web.

HTML
: Hypertext markup language. A system of markup or formatting tags used to create Web pages.

IP
: Internet protocol number. A numeric address unique to each computer on the Internet. An IP address consists of four 8-bit numbers separated by periods, e.g., 128.218.173.143. Each IP can have a domain name.

JAVA
: A computer programming language designed to create programs downloaded as part of a Web page and executed on the user's computer.

MeSH
: Medical subject heading. A controlled hierarchical vocabulary used to index MEDLINE.

Modem
: Modulator-demodulator. A device that converts binary computer data into sound signals for transmis- sion across a telephone network.

MIME
: Multipurpose Internet mail extensions. A protocol to convert binary data to ASCII so that it may be E- mailed through the Internet.

NNTP
: Network news transfer protocol.

PKI
: Public key infrastructure. A means of providing secure, private communications between two parties. PKI creates two coding keys for each party, one key is held secret, the other made public.

RFC
: A request for comment document. The documents are the actual technical description and specifica- tions for Internet protocols. They are published by a group known as the Internet Engineering Task Force (IETF). RFCs may be read via the Internet at http://ds.internic.net/ds/dspg1intdoc.html.

Spam
: Unsolicited electronic junk mail.

TCP
: Transmission control protocol. The underlying data transmission schemes that move data across the Internet.

URL
: Uniform resource locator. An expanded address to define the location of information on the World Wide Web. Each URL contains a protocol, an IP address (or its equivalent domain name), and a file ad- dress within the remote computer. The protocol is separated from the actual IP address by a colon and two forward slashes, e.g., http://www.anesthesiology.org.

UUEncode
: Unix-to-Unix encoding. A protocol to convert binary files into a format by which they may be trans- ferred via E-mail or USENET.

[a] For a larger glossary, see www.matisse.net/files/glossary.html.

Appendix 2-Computer Network Protocols

Each type of computer network service makes use of a different computer protocol. These protocols set certain limits on how information is available by use of that service.

E-MAIL

E-mail is a service designed to transmit a message privately from one party to another. The transmission process moves the message from one computer host to another until the message arrives at the computer from which the recipient can retrieve the message. The transmission process is not secure, and messages may be intercepted and read with little effort at any point along the transmission route unless the message is encrypted. (PKI encryption is most widely used.) E-mail may include binary data as well as text. The binary data are translated into a form of ASCII by use of UUEncode or MIME for transmission across the network, but the translation process is usually invisible to both the sender and the receiver.

FTP

FTP is a file transfer protocol that requires its own server software on a server computer. When a document is transmitted via FTP, it is moved directly from the host's hard disk to the client's hard disk without being displayed on the screen. Long documents or raw data files are usually transferred by FTP. Web spiders do not access the contents of FTP documents, and so Web directories can index files at an FTP server site only by file name, if they are indexed at all. FTP services require that the client or user log into the host computer. Those FTP sites that allow public access commonly grant that access to users who enter the name "anonymous" or "guest" as the log-in name with a password of "guest" or the user's actual E-mail address.

GOPHER

Gopher is a protocol similar to FTP except that it does not require the user to log in to read the files being served. Gopher sites are not indexed by spiders; instead, there is a separate system that uses search software known as JUGHEAD or VERONICA (www.yahoo.com/computers and internet/ internet/gopher/searching/). Gopher, like FTP, requires only a text-based user interface, which was the common mode of Internet access before inexpensive personal computers and graphical Web browser software replaced them.

USENET

USENET is a distributed message passing system. The actual messaging protocol is known as network news transfer protocol (NNTP). NNTP uses the "pouring water" technique to pass messages, which implies that a message "poured" into a host spreads horizontally. Specifically, a user may "post" a message on a particular newsgroup through a local host; the message is then broadcast to neighboring NNTP servers in the network. The neighbors in turn pass the message to their neighbors until all NNTP servers get the message. Individual USENET users may then retrieve the message from their local server.

HTTP

Hypertext transfer protocol (HTTP) is the basic communication service used by the World Wide Web. Its purpose is to provide a means by which remote clients (Web browsers) may request downloads of files. Web page files are written in a document description language known as Hypertext markup language (HTML). HTML pages are ASCII text that declares the actual readable text, the formatting for the text, and URLs for whatever embedded objects may be in the page, e.g., pictures, applets, hypertext links. There are now many software products that allow creation of HTML Web pages in a process akin to word processing. An individual may then "publish" these pages on the World Wide Web by transferring the files to their Internet service provider.

Appendix 3-Access to the Internet

An individual user may access the Internet easily from most of the developed world. To use the Internet, one must first have a personal computer with Web browsing software installed. Most personal computers sold today have this software and a modem preinstalled. Several browsers are available; all are roughly comparable in features required for professional information gathering. The other necessary component is a connection to the network. From the hospital work environment, this often is as simple as plugging into the medical center information network. Some hospitals that have an information infrastructure do not allow access to the Internet because of security concerns for patient and financial data. From home, there are several possible ways to attach to the Internet. At present, the most common is via a telephone line with a computer-attached modem. A connection is then made to a remote computer, which mediates the Internet conversation. The remote computer may belong to a national information carrier like American Telephone & Telegraph (ATT), a private computer network like America On-Line (AOL), or a local Internet Service Provider (ISP). All of these services offer Internet connections for a monthly fee in the range of $20.00 with unlimited connect time. Alternative connections that are more popular in the areas served by them include cable television modems, DSL (telephone-based Digital Subscriber Line) wireless modems in urban areas, and direct satellite links. These technologies offer much higher bandwidth (communication speed), but they have limited availability and higher cost.

Chapter 79 - Quality Assurance/Quality Improvement

Barbara A. Dodson

INTRODUCTION

The practice of medicine in the United States is undergoing profound changes. Advances in medical technology have raised to new heights the public's expectations of and demands for health care. However, the costs for these advance also continue to increase. Indeed, the Health Care Financing Administration (HCFA) has predicted that more than 16 percent of every dollar spent in the year 2007 will be spent on health care. Cost containment and reduction have become major issues in the current era of health care. Clinicians are faced with the difficult task of significantly reducing costs and resource utilization while maintaining quality of care and patient satisfaction with an aging and increasingly sicker patient population. In this economic environment, the need to monitor and ensure quality health care has become increasingly important. This has been recognized by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), professional organizations, government agencies, and the health-care industry. Changing terminology reflects changing in the field of quality of health care. Following the 1995 shift from quality assurance to quality improvement activities in the JCAHO accreditation process, the term *quality assurance* was replaced by *quality improvement.*[1] Recently, with the increasing emphasis on performance/outcome measurements in quantifying quality in health care, the terminology has begun to shift from *quality improvement* to *performance improvement* or *value improvement.* Although types of programs (and their terminology) change, the goal for any quality improvement process in anesthesia continues to be improving health care. This chapter discusses the basic concepts in quality improvement as well as some of the methods used to monitor quality as they relate to health care in general and the practice of anesthesiology in particular.

DEFINITION OF QUALITY

Quality is a concept embodied with positive connotations whose definition subjectively depends on the definer. [2] The Institute of Medicine defines quality of patient care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current knowledge." [3] Others have developed similar and complementary definitions, including "that kind of care which is expected to maximize an inclusive measure of patient welfare, after one has taken account of the balance of expected gains and losses that attend the process of care in all its parts." [4] To the health-care consumer, quality in health care is that which produces the best health with the fewest complications for the least amount of money in the most timely fashion. The confusion caused by this lack of a single definition has led to defining quality in terms of its attributes or components. Quality in health care has been defined in terms of seven attributes requiring assessment: safety, provider competence, acceptability, accessibility, efficiency, appropriateness, and effectiveness. In a similar fashion, the JCAHO has identified nine components in defining quality in patient care (Table 79-1) (Table Not Available) . [5] A model by Donabedian [6] widely used in the health-care industry defines quality of care in terms of three elements or indicators: structure, process, and outcome. *Structure* is the setting in which care is provided and includes the personnel, equipment, and physical plant used to provide health care. Included in structure are the qualification and licensing of personnel, ratio of health-care personnel to patients, standards for medical equipment and facilities, and the organizational structure in which health care is delivered. *Process* refers to a goal-directed interrelated series of actions, events, mechanisms, or steps, including the sequence, coordination, and

TABLE 79-1 -- Components of Quality Performance

(Not Available)

From the Joint Commission on Accreditation of Healthcare Organizations [5]

delivery of patient care activities. [5] A *function* is a goaldirected group of interrelated processes. [7] *Outcome* is the effect of care or the result of the performance or nonperformance of a function or process [5] ; that is, what is accomplished for patients with regard to their health status following the delivery of care. [4] For an organization to function properly, the structure must be adequate to perform its mission, the processes must be workable and efficient, and both must be effective in improving outcomes. As such, much of the focus of quality improvement programs has been on evaluating and quantifying these three elements in an attempt to measure and improve the quality of health care.

WHY MONITOR QUALITY OF HEALTH CARE

Quality in today's health care is not driven solely by the professional integrity of health-care providers. It has also developed a strong economic component. Quality is being defined and demanded by health-care consumers. Indeed, in a 1998 *Wall Street Journal*/NBC News poll, 23% of those surveyed placed quality as the most important issue in health care, as compared with 8 percent in 1993. [8] Employers, providers, and third-party payers also are demanding accountability in health-care outcomes. Therefore, to survive within the competitive health-care market, quality and its quantification must become a priority for health-care organizations.

QUALITY ASSURANCE PROGRAMS

The goal of traditional quality assurance programs has been to identify deviations from the norm. To this end, quality assurance programs have focused on defining the norm (i.e., standards of care), determining whether adverse events were caused by deviations from the norm, and preventing their occurrences.

Peer Review

Peer review is the oldest method for evaluating quality in medical care. With peer review, diagnostic and therapeutic decisions and professional behavior are reviewed by other physicians; that is, one's peers. The basic premise of peer review is that the medical profession is best equipped to govern and police itself. Peer review may take many forms, including informed consultation with colleagues and chart reviews. The most well-known form of the peer review process is the morbidity and mortality review conference.

An example of a departmental peer review program, based on a clinical competence model, was published by the American Society of Anesthesiologists (ASA) Committee on Peer Review. [9] [10] The program contains three major concepts:

1. Peer review should be used to determine a practitioner's competence.
2. The best indication of competence is outcome.
3. Although people are inherently fallible, one error does not necessarily imply incompetence.

Both peer review and quality improvement techniques are used in the evaluation. At the core of the program is an ongoing collective outcomes analysis. Error analysis is used to judge competence. The database consist of anesthesiarelated adverse events, either self-reported or reported by others. The departmental quality improvement committee evaluates blinded reports with respect to (1) relationship to anesthesia care, (2) grading with a negative outcome score, (3) identification and classification of the type of error, (4) conclusions with explanations and references, and (5) recommendations for future prevention. The report is then presented to the entire department. If there is departmental concurrence, the report become part of the practitioner's "error profile." This profile is compared to minimal performance levels and to the departmental aggregate profile. The program is based on the principle that incompetent practitioners will have error patterns markedly different from those of competent practitioners (approximately one to two important errors per year [10]). This approach to peer review is not without its limitations. Two major criticisms are its reliance on self-reported (see subsequent discussion) and its individual-based rather than process-based focus.

Medical staff credentialing, clinical privileging, performance reviews, and reappointments are also part of the peer review process. Anesthesia privileges must be officially granted, delineated in writing, and renewed annually or biannually. Medical staff committees have traditionally performed peer review for a hospital. In cases of quality issues

or professional behavior, the appropriate medical staff committee reviews, investigates, and recommends action to the service chief, medical board, chief medical officer, and/or hospital governing body. Medical staff credentialing has expanded in recent years from a hospital-based function to a process required by many other health care sectors, including insurers, health maintenance organizations, preferred provider organizations, medical groups, and independent practice associations. Recognized accreditation bodies such as the JCAHO, National Committee for Quality Assurance (NCQA), and American Accreditation Health Care Commission/Utilization Review Accreditation Committee have all set standards for the credentialing of health-care providers. Indeed, a credentials verification industry has developed in an attempt to make the process of medical staff credentialing more consistent, efficient, faster, and less expensive. [11]

The HCFA of the federal government has used the peer review process in its Professional Review Organizations (PROs) to monitor quality of care rendered to patients under the Medicare program. Physician surveyors reviewed hospital charts to assess quality of care as well as Medicare utilization review. Anesthesia-related categories in the Generic Quality Screens of PROs include deaths during or following elective surgery, deaths following return to an intensive care unit within 24 hours of transfer, life-threatening complications of surgery, and a life-threatening transfusion error or reaction. A major criticism of this peer review process is its lack of universally accepted definitions and standards for quality health care. This has frequently led to individual reviewers using their personal knowledge and experience to judge whether the process of care and its outcome was appropriate. [6] There is considerable debate as to the reliability and validity of unstructured judgments by a single reviewer. [12] Goldman [13] found that the degree of physician agreement regarding the quality of care was only slightly better than chance in an analysis of 12 studies of the peer review. In contrast, Caplan et al [14] found significant agreement ($P < .0001$) with respect to judgments on appropriateness of clinical care, presence or absence of human error, and role of better monitoring in the prevention of mishap in a study of peer reviewer agreement in evaluating major anesthetic mishaps. Furthermore, differences in practice type, time in practice, and previous experience with adverse event review did not appear to influence agreement.

In its 1992 Health Care Quality Improvement Initiative, HCFA changed the methodology of its PROs from using local criteria for evaluating individual clinical events to using more specific and explicit nationally uniform criteria called Uniform Clinical Data Sets to examine outcome trends. [15] [16] With this initiative, HCFA hopes that by focusing on differences between observed and achievable outcomes rather than on specific deficiency occurrences and by helping providers identify problem areas, PROs will both monitor and improve quality of care.

The use of multiple reviewer procedures and structured assessment instruments, particularly for reviews that have major consequences for patients and health care providers, has been proposed because of questions as to the reliability and validity of unstructured, single-reviewer judgments. [17] [18] Bias must also be addressed in peer review processes. For example, in a study of anesthesiologists assessing identical case scenarios but with different outcomes, Caplan et al [19] found a significant inverse relationship between severity of outcome and judgments of appropriateness of care. That is, care was judged appropriate if the injury was temporary and inappropriate if the injury was permanent. Because of outcomes biases, attention must also be given to critical events resulting in both negative outcomes and/or no injury. All adverse events should be analyzed for areas of improvement.

Another limitation in the peer review process is the reluctance of physicians to testify against a colleague. Reasons for this reluctance include the desire to protect colleagues and to not publicize intraprofessional problems. Another reason is fear of reprisal by the reviewers, with respect to both their own potential adverse outcomes and possible legal actions by the health-care provider against whom they testified. This potential for liability in the peer review process was addressed by the federal government with the Health Care Quality Improvement Act of 1986, which shields medical staff from suits brought about by peer review actions. Part A of the Act provides peer review board members with qualified state and federal immunity from private suits. [20]

Despite its limitations, the peer review process remains an important method for reviewing the appropriateness, adequacy, and effectiveness of medical care. Department-wide peer review incorporates an educational component into a quality improvement program. It also provides a basis for analysis of critical incidents,

trends in measured outcomes, possible causes for such occurrences, and potential directions for improvement. In addition, it is the main mechanism for disciplinary action toward individual physicians by departments, hospital boards, and state licensing authorities.

Risk Management

Risk management is a term developed by the insurance industry in the 1960s in relation to funding and control of predictable business losses. In health care, risk management is the process for preventing accidents and their consequences--specifically, the risk and cost of litigation to the health-care system. [21] All large health-care organizations have risk managers who are responsible for identifying potential litigation, investigating the sequence of events, assessing potential liability, and, if necessary, aiding in the defense of the institution in case of malpractice proceedings. Another, more proactive aspect of a risk-management program is to reduce risks by preventing similar injury to other patients, thus reducing the number and costs of legal suits. This latter function is a quality-management tool, because identifying ways of reducing the risks of suits often provides opportunities to improve care and outcome. [22] [23]

National Practitioner Data Bank

The National Practitioner Data Bank (NPDB) was formed as part of the Health Care Quality Improvement Act of 1986. It is an aggregate (since September 1990) database of physicians' malpractice payments by insurers and adverse actions by state medical boards and hospitals regarding medical privileges as well as membership actions by medical

societies that have formal peer review processes. [24] NPDB reports are now required information in the process for acquiring staff privileges, professional credentials, and licenses. Despite attempts to define a minimum dollar amount necessary to report, at present any payment made on behalf of a health-care professional in response to a written complaint or claim must be reported. This has made clinicians increasingly reluctant to settle nuisance suits because of the resultant inclusion of their names in the NPDB files.

A physician is notified when a report is submitting to the NPDB and has 60 days from the date of NPDB report processing to dispute it. The reporting body may also correct or void the form during this time. The physi-cian also has the option of filing a brief statement with the report or appealing to the Secretary of Health and Human Services, who may also correct or void the form, or both. Once a form is entered into the data bank, it cannot be removed.

American Society of Anesthesiologists Closed Claims Project

The most clinically relevant aspects of risk management are prevention of patient injury, adherence to standards of care, documentation, and attention to patient relations. To this end, the ASA has developed the ASA Committee on Professional Liability's Closed Claims Project (CCP) (Ch. 22) . The ASA CCP is an ongoing, in-depth investigation of closed anesthesia malpractice claims designed to identify major areas of loss, patterns of injury, and strategies for prevention. Closed claims are examined by trained anesthesiologist reviewers using standardized, objective, dataabstracting procedures. [14] This standardized collection of case summaries of anesthesia-related adverse outcomes was started in 1985 and now contains about 4,000 claims from 35 insurance companies that insure approximately 14,500 anesthesiologists.

A recent data analysis by the ASA CCP suggests that severe anesthesia-related adverse events (e.g., death and brain damage) have become less frequent in the past 20 years (56% versus 31%, 1975-1979 versus 1990+). [25] The most common source of these claims is ventilation-related adverse events, with the most frequent events being inadequate ventilation, esophageal intubation, and difficult intubation (Ch. 39) . However, claims for death or brain damage for this subset have also decreased significantly in this same 20-year period, with the greatest reduction in claims for inadequate ventilation (22% versus 7%). In contrast, claims for severe cardiovascular-related adverse events have increased from 12% to 24% over the same period. There was also a slight decrease in equipmentrelated claims for death and brain damage. [26] One possible explanation for the decreases in ventilation-related claims for death or brain damage is the increased use of pulse oximetry (Sp O_2) and end-tidal CO_2 (ET CO_2) capnography (Chs. 28 to 35). [27] These two monitors came into use in the latter part of the 1980s and became ASA standards of practice in the early 1990s. Interestingly, claims for severe ventilation/respiration-related events began to decrease even before the widespread use of pulse oximetry. Furthermore, a large study of 20,000 surgical patients found that the use of pulse oximetry had no effect on decreasing postoperative complications. [28] However, claims for injury due to inadequate ventilation and esophageal intubation have decreased in the 1990s, whereas those for difficult intubation have not, supporting the benefit of increased monitoring on outcomes. In an attempt to decrease injuries due to difficult intubation, the ASA has developed evidence-based practice guidelines for the management of difficult airways (i.e., the difficult airway algorithm). [29] The ASA CCP Subcommittee is currently evaluating all new closed claims to determine whether the guidelines are being followed clinically, and, if so, what their effects have been on the incidence of claims for difficult intubation mishaps.

Other major areas of loss have been identified using from ASA CCP database. For example, closed claims analysis suggests that, despite opinion to the contrary, monitored anesthesia care poses significant risk, especially for elderly and chronically ill patients (Ch. 61) . [30] A high percentage of claims involving MAC were associated with death and brain damage (34% and 19%, respectively). Eye injuries, especially those caused by patient movement, also were common (12%). Indeed, eye injuries alone, including corneal abrasion and those secondary to patient movement, account for 3% of all closed claims. [31] With respect to obstetric claims, the most frequent causes for claims were death (22%), newborn brain damage (20%), and headache (12%), as compared with death (39%), nerve damage (16%), and brain damage (13%) in the nonobstetric group (Ch. 57) . [32] Obstetric claims involving general anesthesia were more frequently associated with severe injuries and higher payments than those involving regional anesthesia. [32] Anesthesia-related nerve injuries represent approximately 17% of all claims, with the ulnar nerve injury accounting for 25% of total nerve injuries (Ch. 22) . [33] The mechanism of the injury was unknown in many cases, leading to the observation that "in certain susceptible patients, nerve injury may occur in spite of conventionally accepted methods of positioning and padding." [34] The ASA CCP also found that ventilationrelated adverse events were more common (43% versus 30%), the mortality rate was higher (50% versus 35%), and anesthetic care more frequently was determined less than appropriate (54% versus 44%) in pediatric than in adult claims. [35] With regard to regional anesthetics, the ASA CCP identified inadequate recognition of level of sedation and inadequate treatment with alpha-agonists to counteract sympathetic blockade as the two major factors associated the poor outcome (Chs. 42 and 43). [36]

The ASA CCP reports have been helpful in delineating areas requiring further attention to reduce anesthesiarelated adverse events and, consequently, liability claim. However, the ASA CCP database reflects only closed claims and not all patient injuries. The decrease in claims in the last 20 years may reflect changes in litigation practices rather than increase in quality of anesthetic care. Nevertheless, the database suggests that fewer claims for death or brain damage are being successfully pursued. ASA CCP Subcommittee findings are published on a regular basis both in *Anesthesiology* and in the ASA newsletter and are also available on the Web at http://depts.washington.edu/~asaccp/.

Practice Guidelines and Standards of Care

Practice parameters were originally designed to both define standard of care and provide clinical guidelines in an effort to decrease adverse events. In recent years, these practice parameters have become increasingly important in providing a basis for quality/performance assessments. [37] Although practice parameters can be used for many purposes, they roughly fall into four major categories: (1) medicolegal standards of care, (2) voluntary guidelines to clinical management, (3) guidelines for reimbursement decisions by third-party payers, and (4) measurement tools in the quality improvement process. Standards are defined as absolute minimum requirements for patient care. They specify what is always expected without exception. An example would be the ASA Standard for Basic Anesthesia Monitoring. [38] In contrast, practice guidelines are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." [39] Generally, guidelines are recommendations that identify specific patient management strategies. Guidelines differ from standards in that they specify what is usually recommended or expected while allowing for exceptions or modifications to fit specific clinical circumstances. Guidelines can be precepts, boundaries, or clinical algorithms. [9] *Precepts* are general principles with few specifics; *boundaries* define limits of appropriate care; and *algorithms* are very detailed decision trees. A similar concept, care plans, has become part of nursing practice. These plans consist of a group of procedures designed to optimize the process of care. More recently, practice guidelines and care plans have been combined to form critical pathways. These are series of guidelines and care plans that guide patient care throughout an illness or hospitalization. An example of a critical pathway with considerable anesthesia input and involvement is the perioperative

management of cardiac patients (Ch. 49) . [40]

The federal government, health-care organizations, and third-party payers view practice parameters as mechanisms for reducing care variability, improving quality, measuring outcomes, and reducing costs and malpractice litigation. [41] In 1989, The Agency for Health Care Policy and Research (AHCPR), a Department of Health and Human Services agency, was established, in part, to develop and periodically review and update clinically relevant guidelines, standards of care, performance measures, and medical review criteria. [42] Examples of federal practice guidelines are the HCFA Uniform Clinical Data Sets used in Medicare reimbursement. [15] [16] Private organizations, including accreditation agencies, are also issuing practice parameters with significant implications for clinical anesthesia. Although accreditation by the JCAHO is theoretically voluntary, reimbursement for hospital services is contingent on its accreditation, thus making it, in reality, mandatory. [43] Therefore, JCAHO standards are extremely important and frequently define health-care delivery. Table 79-2 (Table Not Available) contains examples of specific JCAHO standards regarding anesthesia care. [44] [45]

Some clinicians see practice parameters as regulatory tools imposed by nonphysicians resulting in a further erosion of clinical autonomy. Indeed, the application of nonmedical

TABLE 79-2 -- Joint Commission on the Accreditation of Healthcare Organizations Standards Regarding Anesthesia Care

(Not Available)

From the Joint Commission on Accreditation of Healthcare Organizations. [44]

values combined with intense economic pressures can create an environment for guideline misuse. [46] Others believe that practice parameters can provide health-care providers with valuable medical information, improve objectivity in medical decision-making, and provide a way of maintaining if not improving quality of health care in an era of cost containment. Many medical organizations, including the American Medical Association, and specialty associations have been actively developing practice policies. An example of a nonanesthesia guideline with significant anesthetic implications is the American College of Cardiology/ American Heart Association guidelines for perioperative cardiovascular evaluation for noncardiac surgery. [47]

The ASA has been a leader among medical specialty groups in developing practice parameters. [38] (Because of their importance, all ASA practice parameters are published in this text; see appropriate chapters.) The ASA developed its first practice guidelines in 1968 and published its first set of stricter practice standards in 1986. An impetus for ASA practice parameter development is the belief that physicians should develop their own standards rather than have them imposed by nonphysician third parties. [48] These practice parameters have had a significant impact on clinical anesthesia, especially with regard to perioperative physiologic monitoring (Chs. 28 to 38). [48] These standards originated in part from the Harvard Medical School's Anaesthesia Practice Standards [49] and include criteria for minimal monitoring, requirements for anesthetizing locations outside the operating room, apparatus checkout, and postanesthesia care. [38] ASA guidelines regarding specific areas of practice have been published for acute pain management in the perioperative setting, [50] blood component therapy, [51] cancer pain management, [52] chronic pain management, [53] management of the difficult airway, [54] perioperative transesophageal echocardi-ography, [55] pulmonary artery catheterization, [56] and sedation and analgesia by nonanesthesiologists. [57] Guidelines for preoperative fasting and obstetric anesthesia are under development and should be published shortly. These guidelines were developed by the ASA to assist in the practice of anesthesiology with the proviso that they may be adopted, modified, or rejected according to clinical needs and constraints. ASA practice policies (Table 79-3) (Table Not Available) undergo frequent modifications and amendments and should be reviewed on a regular basis. The ASA Standards of Practice, Guidelines and Statements are published yearly in the ASA Directory of Members and are available from the ASA on the Web at http://www.asahq.org/.

Development of Practice Guidelines

According to the Institute of Medicine, good guidelines have eight attributes: validity, reliability, clinical applicability, clinical flexibility, clarity, multidisciplinary process of development, scheduled review for warranted revision, and documentation. [58] Guidelines must be based on the best available information and be developed through a rigorous, standardized process that ensures that all of the available evidence is examined and considered, including cost/benefit information, if they are to be accepted by physicians. [59] They

TABLE 79-3 -- American Society of Anesthesiologists Standards, Guidelines, and Statements

(Not Available)

Adapted from the American Society of Anesthesiologists. [36]

must be specific enough to be useful in delineating what particular course of action is indicated in a specific circumstance, but not be so complex as to be difficult to use. They should be comprehensive enough to encompass all of the nuances of a particular clinical situation, but be limited so as to prevent unsubstantiated inferences to topics not expressly covered. Furthermore, the development of practice guidelines must be open, honest (both ethically and intellectually), and unbiased. [37]

Several methods have been described for developing practice guidelines. [60] [61] [62] The AHCPR has outlined a five-step process: process definition, clinical benefits and harm assessment, assessment of health policy issues, preparation of practice guideline, and evaluation of its effect. [63] An example of the process is the AHCPR guidelines for acute postoperative pain management. [64] Initially, a multidisciplinary panel of pain experts reviewed current and emerging practices, principles, technologies, and costs as well as the need for guidelines in this area. This review included examination of existing guidelines and standards and expert opinion from consultants, panel discussions, and open forums. The panel then reviewed the published scientific literature. Topics included pain assessment, pharmacologic and nonpharmacologic treatments, complications, patient satisfaction, and cost information. The information obtained was also analyzed using meta-analysis or best evidence synthesis. [65] [66] A draft document was then developed and subjected to both external peer review and beta testing by the intended users. Comments elicited from both groups relative to the clarity, clinical applicability, flexibility, resources and training needed for implementation, and cost implications of the guidelines were incorporated into the document. Finally, the guidelines were issued.

The process of developing practice guidelines must be considered a dynamic process. Once released, the validity of the guidelines should be verified by examining the relationship of the guidelines to outcomes. [9] [67] Mechanisms must be provided for review of the clinical experience with the guidelines and for revision, if warranted, based either on clinical experience or on new evidence produced by ongoing research. [39]

Implementation of Guidelines

Although methods for producing guidelines are relatively well understood and continue to improve, implementation has proven difficult for a variety of reasons. [68] [69] Most attempts at implementation rely on provider education. This has often failed because physicians frequently viewed guidelines as a form of "cookbook" medicine. [70] Critics have emphasized that often, little attention is paid to guideline quality (i.e., scientific validity), goals, impact, implementation, and evaluation. [39] [71] Recommendations are often worded in highly specific language that achieves clarity at the expense of scientific validity, resulting in guidelines that do not represent accepted medical practice. As discussed earlier, physicians also worry that guidelines will decrease their clinical autonomy and income and increase medicolegal liability. A particular concern relates to the expansion of enforcement programs that require clinicians to follow guidelines or face financial or other penalties. Rigid enforcement of such guidelines could harm patients, interfere with the individualization of care, increase costs, and promote unfair judgments against clinicians who deviate from them for good reasons. [70]

There are relatively few studies examining the clinical impact of practice parameter implementation. [72] [73] [74] For example, Worrall et al [72] found in a review of 13 trials of clinical practice guidelines that only 5 of the 13 trials improved patient outcomes. In contrast, Wachtel and O'Sullivan [75] found significantly less frequent use of laboratory tests, radiographs, and electroencephalograms by physicians participating in a guideline initiative than in those not participating (Ch. 23) . [75] The use of

clinical practice guidelines in outcome studies is discussed in more detail later.

In general, practice guidelines will not be rapidly implemented into clinical practice unless they are (1) directed toward problems that would have substantial impact if improved, (2) perceived to be of high scientific quality by clinicians, (3) well publicized and readily available, (4) integrated into clinical decision-making and practice patterns of the clinicians, and (5) linked with incentives for use that are powerful enough to motivate compliance (e.g., financial, medicolegal, or quality improvement incentives). [76] [77] [78] Implementation will occur only if the guidelines are perceived by the front-line health-care providers to improve patient care and outcomes while not adding time-consuming tasks of no immediate help to either the providers or their patients. [79] [80] Ultimately, acceptance is fostered by peer pressure, which requires institutional or medical professional and administrative leadership to support the concept of practice guidelines. [79]

Standards, Guidelines, and Litigation

Lack of adherence to standards of care is a frequent basis for litigation following adverse events and has significant implications with respect to the likelihood and amount of financial recovery by the plaintiff. However, expert medical witnesses often rely on implicit (unstated, personal) criteria rather than explicit (published) criteria in determining standard of care. This frequently results in divergent opinions as to whether appropriate care was given. [81] Furthermore, there is still a greater than 40 percent chance that payment will be made for a malpractice claim even if an anesthesiologist can support the assertion of appropriate care. [82]

Guidelines have developed medicolegal implications. Even though practice guidelines are meant as clinical recommendations rather than standards or absolute requirements, they can be interpreted as establishing the relevant standard of care in medical malpractice. [74] [83] This is unfortunate, because interpreting guidelines as constituting express legal standards of care would limit creative initiatives to discover methods of patient care that result in good outcomes but do not conform to traditional medical practice. Physicians would likely feel both limited in their clinical choices and reluctant to deviate from the guidelines except under the auspices of carefully controlled research protocols. [83] The legal implications of clinical practice guidelines are not well defined and promise to be a topic of considerable debate in the future.

For better or worse, practice parameters will have an increasing role in clinical anesthesia. Practice parameters can

provide a powerful tool in resolving the complexity of medical decisions by freeing health-care providers from weighing the pros and cons of each decision. They can also provide a method for dissemination of research information and professional consensus as to appropriate and current clinical practices. [37] Continuous quality improvement programs can provide a mechanism for implementing and monitoring practice guidelines, analyzing their effects on outcomes, and involving health-care providers in the assessment and revision of guidelines. [84]

QUALITY IMPROVEMENT PROGRAMS

Continuous Quality Improvement

Traditional quality assurance programs focused on identifying the outliers, or "bad apples." Adverse events were interpreted to be a function of individual or "operator" error, and, as such, problems were addressed on the individual level. Unfortunately, this method did little besides document the incident, assign blame, and repeat the refrain that such an event would not happen again. Although numerous studies suggested that most adverse events (up to 80% in anesthesia) are secondary to human error, it has become increasingly recognized that the individual involved in an event is a single element in the complex system that constitutes health-care delivery. [85] [86] [87] This has led to a conceptual change in the philosophy underlying quality of care programs from defining and ascertaining deviations from the norm to constant testing and improving--that is, continuous quality improvement (CQI). [88] CQI programs focus on the health-care system itself, where the system is defined to be all the components involved in health-care delivery including health-care professionals, patients and their families, material management, administration, and so on. In the CQI process, adverse events are considered a function of system errors and, therefore, represent opportunities for identifying underlying causes for such incidents and developing methods for improving the structure and process for patient care. [89]

The CQI process involves identification of processes for improvement by continuous monitoring of important aspects of patient care. Identification can be by peer review processes or by the use of specific standards and indicator measurement systems. Once a problem area is identified and documented and its current performance measured, the structures and processes leading to the problem areas are analyzed. If changes that may result in improved care are identified, they are implemented into the system. After a specified length of time, the problem area is remeasured to determined effectiveness of the changes. The CQI process is then directed either to continued improvement in the problem area or to identify other areas and different processes for improvement. [90] As with practice parameters, it is important for anesthesiologists to actively participate in the development and application of these projects to ensure the delivery of quality anesthetic care. [91] [92]

The CQI method has been extended into the concept of total quality management (TQM), where TQM encompasses all aspects of health-care delivery including operating room scheduling, clinical care, medical records, material management, billing, and so on. [89] [93] CQI/TQM processes are being examined as programs to reconcile cost/quality conflicts, increase patient satisfaction, and improve hospitals' competitiveness and operational and financial performance. [94] [95] They are also required as part of the JCAHO accreditation process. [96] However, although CQI/TQM is excellent in theory, there is still debate as to its overall effectiveness in improving patient care. [97] [98] [99] As with practice guidelines and for similar reasons, CQI/TQM implementation into health-care organizations has been difficult. [100] CQI/TQM administrators are rarely clinicians, which leads to conflicts over loss of clinical autonomy. Physicians consider many of the CQI/TQM issues to be clinically irrelevant. Data collection, review, and analysis in CQI/TQM can be costly and time-consuming. Finally, CQI/TQM administrators often become process-oriented rather than outcome-oriented, resulting in organizational changes with little clinical or economic advantage. Modifications suggested to improve compliance in the CQI/TQM process include involving physicians in the change process, building an infrastructure that promotes clinical leadership, ensuring that the clinical information and data analyses used to generate the changes are scientifically sound, and reliably measuring the clinical and economic impact of the changes on patient care. [69] [94] [95]

To be successful, continuous quality improvement activities must become integral parts of the routine activities of medical departments. [101] The observations, recommendations, and plans of the department quality improvement program should be reported and discussed at departmental meetings. Medical staff should receive training as to how to participate in quality improvement activities and should be asked to suggest topics for improvement. Cooperation is also predicated on a constructive aim to the process. Physician cooperation is most likely if positive clinical results are achieved and the medical and hospital leadership is to actually committed to changes.

JCAHO Requirements for Quality Improvement Programs

Anesthesiology departments are required to have comprehensive quality/performance assessment and improvement programs that comply with institutional bylaws and JCAHO, federal (e.g., HCFA, Food and Drug Administration, Occupational Safety and Health Administration), state, and local health department regulations and guidelines. JCAHO requirements for quality improvement programs are updated on an annual basis. All areas of departmental involvement (e.g., postanesthesia care unit, pain management program, critical care units) need to be included in the departmental CQI program. Departmental involvement is also needed in other hospital medical staff committees, including medical records review, blood and blood component usage review, drug usage evaluation, and infection control. The department head is ultimately responsible for both providing quality anesthetic care and assessing and improving this care as outlined by JCAHO and government directives.

A department's CQI program, formally documented and approved by both the department's and the institution's

medical staff leadership, must outline the evaluation process, identify the individuals responsible, and detail the communication pathway to the departmental and hospital medical staffs and hospital leadership. Policies and procedures for credentialing and continuing staff education should also be included. A manual containing information on anesthesia CQI programs, including a checklist of steps in the CQI process and sample charts, is available from the ASA. [102]

The JCAHO has specifically identified anesthesia care as a function critical to patient care, where anesthetic care is defined as "the administration (in any setting, by any route, for any purpose) of general, spinal, or other major regional anesthesia or sedation with or without analgesia for which there is a reasonable expectation that, in the manner used, the sedation or analgesia will result in the loss of protective reflexes for a significant percentage of a group of patients." [44] Policies and procedures for the administration of anesthesia are required to be consistent (i.e., standard of care) for all anesthetizing locations within a health-care facility. During its accreditation and review process, the JCAHO will focus on an organization's performance, using, in part, its standards for anesthesia (see Table 79-2 (Table Not Available)). [44] [45]

QUANTIFYING QUALITY IMPROVEMENT

One of the chief characteristics of the CQI process is quantification of CQI activities, both baseline and ongoing, that can be used to benchmark performance, track and validate performance measures or indicators, and identify problems in the health delivery system. The CQI database can provide information on type, frequency, and length of procedures performed, patient acuity, complication rates, blood utilization, and so on. Information in such CQI databases is necessary for any cost/benefit analysis. The question is what variables are important, how to collect and store them, and how to analyze the data to obtain useful information. Examples of volume statistics important to anesthesia CQI programs include total number of anesthetics, the number of patients who received general or regional anesthesia or monitored anesthesia care, the number of intraoperative deaths, the number of unplanned hospital admissions, the number of emergency versus elective cases, the number of patients seen for acute and chronic pain treatment, and the number of intensive care unit admissions, length of stay, and daily census. Volume statistics (i.e., number of cases or patients) allow department and hospital administrators to both assess departmental activity and track trends and changes in practice. These statistics may also be used as the denominators for evaluating clinical indicators. Volume statistics are usually tallied on a monthly basis, with an annual summary.

Another method of collecting CQI data is the retrospective medical record review. Important considerations in data collecting include triggers or thresholds for reporting, standards definitions, and appropriate sampling techniques. Chart review is especially advantageous in quantifying adequacy of documentation. Quality assessment should be restricted to information normally included on an anesthetic record (e.g., blood loss, blood pressure, temperature). Quality issues need to be explicitly defined and the definitions standardized. For example, hypotension maybe defined as an absolute (systolic blood pressure <75 mm Hg) or relative (<80% of baseline for >5 minutes) measurement. If possible, definitions should be contextualized. For example, excessive blood loss should be defined with respect to both total blood loss and type of surgical procedure.

Reduction in adverse outcomes is a commonly used variable in documenting and quantifying improvements in patient care. However, adverse outcomes (resulting in mortality or serious mortality) are relatively rare for patients undergoing surgical procedures. Recent studies conservatively estimated the rates of deaths due to anesthesia to be 1:20,000 to 1:65,000. [103] [104] [105] [106] Such low occurrences make improvement measurements statistically extremely difficult. Therefore, other CQI measures, such as incident reporting and indicator systems, have been developed to monitor patient care.

Incident Reporting

The monitoring of patient care and departmental operations involves the evaluation of adverse events, including deaths, life-threatening or unusual complications, equipment problems, and adverse drug reactions (these must also be reported to the pharmacy). Some state health codes require that certain types of clinical incidents be reported to the state health department. All adverse events should be evaluated. Equipment involved in an incident should be sequestered, medical records reviewed, and involved personnel debriefed as soon as possible. A confidential investigation should attempt to determine the cause of the event. Corrective CQI actions may include counseling and educating an individual or group of practitioners, changing policy, or revising procedures. The actual policies and procedures by which an anesthesia department systematically investigates adverse events should be a documented part of the department's quality improvement program. An example of such procedures are the Harvard Medical School's Anaesthesia guidelines for response to an adverse event. [107]

Self-reporting of anesthesia-related adverse events is frequently used for for CQI data collection and analysis. [10] [108] Many self-reporting systems use a checklist of adverse events and outcomes that is completed by the clinician for each anesthetic. Other systems have general guidelines for adverse event reporting without specific check-off items. Posner et al [108] described one such CQI program that uses a dichotomous (yes/no) response on the anesthesia record with immediate case investigations providing data for systematic peer review. In a study of 10,740 cases, they found a doubling (537 cases) in reporting of problems related to anesthesia management as compared with the previously used checklist system (5% versus 2.7% of all anesthetics).

Self-reporting of adverse events can be extremely useful in monitoring patient care. Australia has used such as system for the last 30 years and has shown a substantial decrease in anesthetic mortality. [105] [109] Unfortunately, self-reporting of adverse events appears to be, at best, an incomplete method of data acquisition. For example, in a comparison of an automated anesthesia system to a voluntary, manual-entry, electronic reporting system, Sanborn et al [110] found that only 4.1 percent of deviations from predefined limits of vital signs

identified by the automated system were also voluntarily reported. Similarly, Cullen et al [111] reported that only 6 percent of hospital adverse drug events were voluntarily reported through health-care organizations incident report system. Part of the problem lies within the culture of medicine in the United States. Both the medical community and the public expect medical care to be error-free and assume that any adverse event must be secondary to negligence on the part of the health-care provider. [112] Therefore, to report an adverse event would be to admit an error in management, which could lead to both professional censure and litigation. Improvement in self-reporting depends on continuing to change the focus of analysis of adverse events from assignment of individual blame to fixing system problems. Better incentives, such as demonstration of the usefulness of reporting on patient care and protection from unwarranted public scrutiny, are needed to improve self-reporting. [113]

Sentinel Events

The JCAHO requires that all adverse events or patterns of adverse events be intensively assessed. Of particular significance are those adverse events that the JCAHO defines as "sentinel events"; that is, "an unexpected occurrence or variation involving serious physical or psychological injury, or risk thereof." [114] This includes adverse events that lead to an "unanticipated death or permanent loss of function, ... is associated with a significant deviation from the usual process(es) ....; or has undermined, or has the potential to undermine, the public's confidence in the hospital." [114] The event is called *sentinel* because it sends an alarm or signal that requires immediate attention. The health-care organization must take immediate corrective action whenever such an event occurs. However, what specific adverse events a health-care organization defines as sentinel events remains somewhat vague. Furthermore, as of October 1998, the mandatory reporting of sentinel events to the JCAHO (the accreditation watch process) has been suspended because of confidentiality and liability concerns. [115]

Indicator Monitoring and Evaluation

An important component of a health-care organization's CQI program is the monitoring and evaluation process mandated by the JCAHO. [5] This involves (1) identifying the most important aspect of care and service provided by an organization, department, or service, (2) using quantitative measures called indicators to systematically monitor specific aspects of care and service in an ongoing way, (3) evaluating the care or service when predetermined thresholds or trigger points are reached to identify opportunities to improve services or care, and (4) taking actions to improve care or service, to solve problems, and to evaluate the effectiveness of those actions. The monitoring and evaluation process has two major elements: measuring what is happening (quality/performance measurement and assessment), and using these data to improve care (quality/performance improvement). It can be performed in a variety of ways analogous to the development and implementation

of practice guidelines. One of the most popular methods is the JCAHO's ten-step process. [116] In CQI programs, these standards and indicators focus on patient processes and outcomes, with standards furnishing the basis for measuring and guaranteeing quality.

The main component of this process is the tracking of indicators, where indicators are defined as quantitative measures of an aspect of patient care. They are not direct measures of quality but rather screens or flags indicating areas for more detailed review. [117] That is, the occurrence of an indicator, like an adverse event, should trigger a quality improvement review of the circumstances under which it occurred. Indicators should monitor important, preferably high-risk, high-volume aspects of care (e.g., the incidence of pneumonia in postoperative patients). [118] Indicators may monitor single or multiple components of care as well as desirable or undesirable events. For example, the indicator "unplanned postoperative admissions to ICU" may monitor patient selection, scheduling procedures, and intraoperative anesthetic management. [119] Indicators can be single or combined event measures. Combined data indicators involve collection and aggregation of data about many events. Indicators can also be continuous or rate-based measures. [120] Continuous variable indicators measure variables that can fall anywhere along a continuous scale (e.g., weight change during nutritional support). Rate-based (or discrete variable) indicators monitor an event for which a certain proportion of the events that occur are expected. An example would be mortality rate.

It is extremely important in indicator tracking that both the number of indicators or events recorded (numerator) and population at risk (denominator) be defined and measured. [121] This is necessary to establish the rate of a specific event as well as determine whether an occurrence is common or random. Exclusions from the denominator population must also be defined. Most importantly, it is necessary to collect reliable data and to use appropriate statistical analysis so that valid conclusions can be reached.

It is also important in indicator tracking to define an evaluation trigger or threshold. [21] For rate-based indicators, triggers can be set by review of clinical literature, internal or external expert opinion, evaluation of trends, or by using statistical analysis. This has been referred to as *benchmarking,* where a benchmark is defined as a point of reference or standard by which something can be measured or judged. [7] Internal benchmarking occurs within an organization, whereas external benchmarking occurs between institutions. [7] [122] However, it is extremely important when using external benchmarks to ascertain that conditions, such as patient populations and surgical techniques, are comparable. Often it is necessary to perform a preliminary retrospective or prospective study to determine the institutional rate. Another way to evaluate indicator data and establish thresholds is to analyze trends (e.g., to compare current performance to that of a previous period of time). Statistical analysis can also be used to identify triggers.

The exact data and method of collection must be considered in great detail prior to initiation of collection. The sources of the data must be reliable and valid. [123] Prospective data collection may be more appropriate because medical records frequently do not contain the required data. [124]

Concurrent data collection is the preferred method, because it permits rapid review and hasty retrieval of missing data. [125] If a sample, rather than entire population, is being examined, the sample size and sample selection must be defined. Preferably, data should be entered directly into a computer to facilitate rapid analysis. Data may also be obtained from computerized patient information systems, such as anesthesia record-keeping systems or hospital information systems. [110] [126] [127]

PERFORMANCE MEASUREMENTS

Performance measurements are rapidly becoming a way of life for health-care providers. With the incorporation of CQI processes including performance measurement into its review and accreditation process, the JCAHO has shifted from defining specific expectations for each discipline and department to describing functions that it defines as critical to patient care. The JCAHO expects health-care organizations to use indicators in their interdisciplinary quality/ performance improvement activities to systematically measure and assess the level at which the organization carries out these functions. The specific 1995 JCAHO requirement is that "the organization designs processes well and systematically measures, assesses, and improves its performance to improve patient health outcomes." [128] Proof of such activities is a prerequisite for JCAHO accreditation. [44] The general format for this recurrent CQI performance evaluation is the design of a process or function, measurement of its performance, assessment of performance measurements through statistical analysis or comparison to other data sources, and improvement of the process or function. The focus is on the systems and processes of the health-care organization rather than on individuals.

Examples of indicators that can be tracked by an anesthesia department include (1) causes of canceled surgery; (2) incidence of postoperative nausea, vomiting, and hypothermia; (3) causes of delays in beginning anesthesia; and (4) incidence of reintubation in the postanesthesia care unit (PACU). In addition, under its Indicator Measurement System (IMS), the JCAHO is developing its own quality improvement indicators for all medical specialties, with a gradual phase-in of these specific clinical and organizational performance indicators into its reaccreditation and review processes. [5] [44] [117] Under the IMS, health-care organizations will submit indicator data (without patient or health-care provider identifiers) to the JCAHO for analysis. JCAHO will provide organizations with information, including comparative data from other health-care organizations, that they can then use to monitor and improve their performance, while helping meet external needs for performance measurement. [117] In addition, after risk stratification, information relative to complications will be made available to health-care consumers to allow them to make health-care purchasing decisions. Each institution will track the same indicators and the data will be collated and analyzed by the JCAHO. It is hypothesized that this will permit continuous collection of objective data to provide comparative data among institutions, identify patterns within institutions, and develop a national database for health services research. One of its first sets of indicators developed by the JCAHO involved anesthesia (Table 79-4) (Table Not Available) . [5] All cases will be screened and the occurrence of any one of these events will trigger a quality improvement review of the particular circumstances of the case. Other indicators have been identified or are under development for obstetric care, oncology, cardiovascular disease, trauma, infection control (including an indicator that focuses on postoperative pneumonia that occurs within 10 postoperative days), medication use (including timing of intravenous prophylactic antibiotics within 2 hours before first surgical incision), and home infusion therapy. JCAHO standards will likely play an even greater role in clinical anesthesia in the future.

TABLE 79-4 -- Joint Commission on the Accreditation of Healthcare Organizations Anesthesia Indicators

(Not Available)

From the Joint Commission on Accreditation of Healthcare Organizations [1] [5]

Outcome Measures

An increasingly important way by which performance/ quality improvement is quantified is by measuring changes in outcomes. Outcomes have been called "the paramount criterion of good quality either by themselves or as related to costs if efficiency and optimality are to be determined." [4] Measuring outcomes has become an essential part of any quality improvement effort. This trend toward outcome measurement is driven in part by economics. [129] For example, health maintenance organizations are interested in outcomes such as hospital mortality, complication rates, complications after discharge, patient satisfaction, and level of daily function in negotiating contracts with health-care organizations.

In general, outcome measures fall into four main categories: [130]

1. *Financial outcomes.* These include utilization of health-care services for specific patient cohorts and cost for providing these services. Outcomes are measured as costs per service rendered, overall cost, and utilization rates. Total cost is usually quantified on a per patient rather than a per usage basis.
2. *Performance outcomes.* These include internal measures of institutional performance and external evaluations based on patient, third-party provider, and payer satisfaction. Patient satisfaction surveys are used extensively in performance outcome studies.
3. *Clinical outcomes.* These include the quantification of appropriateness and effectiveness of different types of treatment and care. Specific surgical procedures are also being examined in both large-scale, multicenter clinical trials and smaller, perioperative re-engineering projects in attempts to ascertain predictive factors for outcomes. Examples of surgical procedures that have undergone large-scale clinical outcome trials include coronary artery bypass surgery and carotid endarterectomy.
4. *Perceived health outcomes.* These include outcome measurements that attempt to quantify patients' perceptions of their health status and quality of life. Two widely used measures of health-related quality of life are the Short Form-36 Health Survey (SF-36) and the Quality of Wellbeing Scale (QWB). Both have been used extensively in characterizing health outcomes over time in patients having serious illnesses, including cancer and acquired immunodeficiency syndrome. [131]

A major strength of outcome measures is that they are integrative (i.e., they measure the effects of all causes within and outside the system). Other reasons that outcomes measures are important include (1) being of immediate interest to practitioners, patients, and payers of health-care services; (2) directing organizational attention to the processes that contribute or lead to the outcome; (3) setting priorities for improvement of processes; and (4) measuring effects of implementing one or more process changes. [7] Outcomes allow for both intrainstitutional and interinstitutional performance comparisons.

As discussed earlier, it is quite difficult to monitor changes in clinical outcomes where outcome is defined in terms of mortality or serious mortality. These adverse events are relatively rare for patients undergoing surgical procedures, and large sample sizes are required to demonstrate tangible differences. Edsall estimated that a denominator of 230,000 cases would be needed to detect a 50 percent difference in mortality rates between groups of patients treated by two anesthesiologists. [132] This requirement for large sample sizes for statistical significance necessitates the use of large, multicenter, prospective studies to determine both risk factors and effect of therapies on outcomes. [133] When mortality and morbidity are used as outcome measures, they must be stratified for such factors as age, sex, physical status score, case mix, disease severity and comorbidity, length of operation (as an index of surgical severity), and emergency status. [134] Because differences in adjusted rates are often assumed to reflect differences in "quality," [135] severity adjustment must be rigorously performed and results must be interpreted with caution. [136] [137] Temporal change factors that may alter outcomes (e.g., change in patient population, surgical and/or anesthetic technique, type of anesthetic practitioner) must also be continuous re-evaluated.

Much of the focus of anesthesia outcome research has been on the differences between specific techniques (e.g., epidural versus general anesthesia [138]), anesthetics (e.g., intravenous versus inhalational agents [139]), adjunct drugs (e.g., antiemetics [140] [141] [142]), and types of surgical patients (e.g., obstetric [143] [144] or

cardiac versus noncardiac [145] [146] [147] [148]). Of increasing importance for future anesthesia outcomes studies will be the inclusion of patient satisfaction issues (e.g., nausea, vomiting, headache, hypothermia, ease of admis-sion and discharge from outpatient facilities) into their analysis. [149] [150]

Proponents of practice parameters contend that practice guidelines improve patient outcomes by reducing practice variations, controlling unnecessary care, reducing health-care cost, and improving the quality of patient care. [151] [152] These assertions have been supported in the development and implementation of "fast-track" protocols for cardiac surgery. [40] [153] Nevertheless, caution must be taken in interpreting outcome data. It is particularly important to monitor the effect of cost containment on other aspects of patient outcomes. For example, Weingarten et al [154] found that implementation of guidelines for reducing hospital stay after hip or knee surgery did resulted in reduction in total length of stay (Ch. 60) . However, very short lengths of stay for patients undergoing hip surgery were associated with increased intensity of care following discharge, suggesting both cost shifting and total cost increases. That is, the cost incurred by transferring patients to rehabilitation facilities may have been greater than the cost of the patients' remaining in the acute care hospital for an additional 1 or 2 days and then sent directly home.

Outcome studies examining ways to reduce anesthetic drug costs have become increasingly popular. Two major reasons for this popularity are that drug costs are visible and easy to quantify. [155] [156] However, anesthesia drugs constitute only small percentage (5-6%) of total perioperative costs, with staff salaries making up the largest allotment of costs. [157] This can also lead to potential cost shifting. For example, Lubarsky et al [158] found that implementation of pharmaceutical guidelines on anesthetic drug usage reduced drug cost from $56 per case to $32 per case. However, they also found an increase in both time from end of surgery to arrival in the PACU and admission of inpatients receiving

MAC to the PACU as compared with directly admitted to the floors (11 ± 7 minutes versus 14 ± 8 minutes, $P < .0001$ and 6.5 versus 12.9%, $P < .02$, respectively). [158] Changes in patient outcomes such as these could potentially increase rather than decrease total perioperative costs. Overall, considerably more savings could be actualized by improving perioperative efficiency (better scheduling of cases, more efficient processing of patients into and out of the PACU, and so on) than on reducing anesthetic-related drug costs. [91] Nevertheless, as with all new technologies, careful evaluations of all new anesthesia drugs should be performed to assess all associated costs and benefits, including patient personal preferences and patient satisfaction, for subsets of patients undergoing different types of surgical procedures. [159]

There are still relatively few studies that have evaluated the effect of different practice parameters on outcomes. [72] To address this lack of relevant outcome data, the AHCPR has increased financial support for outcomes research. [42] In 1993, AHCPR budgeted $48.2 million for the establishment of Patient Outcome Research Teams. The 14 comprehensive 5-year studies currently underway are composed of four elements: a review and synthesis of available research data; data collection and analysis to identify practice variations and outcome differences; the development of recommendations regarding the effectiveness and appropriateness of the various management techniques; and the dissemination of the information to health-care providers. The AHCPR will continue to play a leading role in funding the development of practice guidelines and outcomes research. [42] However, additional funds will be necessary to expand the field of outcomes research, especially with respect to large-scale outcome studies. [133]

Health-Care Report Cards

Recently, performance data have been used to generate health-care report cards, which are defined as any effort that quantifies or qualifies specific health-care indicators or criteria to established comparative estimations of quality of health care. [160] The indicators used in report cards include items such as length of hospital stay, cost of services, morbidity and mortality rates, and patient satisfaction. NCQA and JCAHO both use report card systems in their accreditation processes in an effort to measure the quality of care provided by health-care organizations. NCQA reviews and accredits health maintenance organizations as well as point-of-service health plans and certain physician-hospital organizations. NCQA's Health Plan Employer Data and Information Set (HEDIS) was created to standardize the way in which health plans calculate and report information about their performance, thereby enabling comparisons among plans. In the future, health plans will be required to submit HEDIS data as part of the NCQA survey process. In 1997, JCAHO began phasing in requirements for performance/ outcome data as part of its accreditation process. [161] As part of JCAHO's ORYX initiative, by the end of 1998, health-care organizations were required to select a sufficient number of clinical indicators to evaluate 25 percent of its patient population or eight performance measures, with data to be submitted by July 1999. [162] [163] These required measurements are scheduled to increase in number and will in the future contain patient satisfaction measures. ORYX was designed as a report card system to provide health-care organizations objective feedback to be used internally for performance improvement projects and externally to demonstrate accountability to the public, third-party payers, and other stakeholders in the organization. [163] In terms of health report cards, JCAHO accreditation decisions are available to the public. In addition, HCFA publishes individual hospital mortality rates, while the New York State Department of Health annually releases the adjusted adult cardiac surgery mortality rate of surgeons performing more than 200 such operations per year.

Health-care report cards are purported to provide accountability to the health-care consumer interested in finding the best medical care, both clinically and economically. However, there has been considerable debate as to the usefulness of such performance data. [164] [165] The four main issues of debate are the quality of the data sources, [166] [167] methods of risk adjustment and stratification, [168] development of outcome "standards" or benchmarks, and data and report standardization. [93] [169] [170] Despite these problems, health-care report cards will most likely play an increasingly important role in defining comparative performances in an increasingly competitive health-care market. For example, hospitals and surgeons with better outcomes reported in the New York State Cardiac Surgery Reports experience a relative increase in their market share and prices. [171] Therefore, increasing effort must be made in defining performance indicators, verifying and standardizing the collection and reporting of data, and demonstrating the improvement of health care from the release of such data. [170]

SUMMARY

Health-care reforms have resulted in profound changes in the practice of medicine. Governmental directives and corporate imperatives continue to have significant consequences on health-care delivery. JCAHO now requires a multidisciplinary rather than individual or department focus in quality improvement programs. Individual departments constitute a single element in CQI/TQM focus on the system-wide processes involved in patient care. Measurement and assessment of performance and outcome will become increasingly important in evaluating the consequences of CQI/TQM programs. Anesthesiologists will have to be able to justify their practices, as well as be capable of quantifying the effects of reforms on their patients' outcomes. By necessity, CQI has become an integral part of clinical anesthesia. [37] Professional societies will need to maintain their leadership in developing guidelines and standards while continuing to educate their members in the safe and effective practice of anesthesia.

References

1. Joint Commission on Accreditation of Healthcare Organizations: Comprehensive Accreditation Manual for Hospitals, Oakbrook Terrace, Illinois, JCAHO, 1994.

2. Eagle CJ, Davies JM: Current models of "quality": An introduction for anaesthetists. Can J Anaesth 40:851, 1993.

---

3. Lohr KN, Grossman JH, Cassel CK: From the Institute of Medicine. JAMA 270:1911, 1993.

4. Donabedian A: The role of outcomes in quality assessment and assurance. QRB Qual Rev Bull 18:356, 1992.

5. Joint Commission on Accreditation of Healthcare Organizations: Development and application of indicators for continuous improvement in surgical and anesthetic care. Oakbrook Terrace, Illinois, JCAHO, 1991.

6. Donabedian A: The quality of care. How can it be assessed? JAMA 260:1743, 1988.

7. Joint Commission on Accreditation of Healthcare Organizations: The measurement mandate: On the road to performance improvement in healthcare. Oakbrook Terrace, Illinois, JCAHO, 1993.

8. Hunt AR: Politicians risk voter backlash this autumn if they ignore call for action. Wall Street Journal, New York, June 25, 1998.

9. American Society of Anesthesiologists: Peer Review in Anesthesiology. Park Ridge, Illinois, American Society of Anesthesiologists, 1991.

10. Vitez TS: A model for quality assurance in anesthesiology. J Clin Anesth 2:280, 1990.

11. Hernandez AM: Trends in health care practitioner credentialing. J Health Care Finance 24:66, 1998.

12. Rubin HR, Rogers WH, Kahn KL et al: Watching the doctorwatchers. How well do peer review organization methods detect hospital care quality problems? JAMA 267:2349, 1992.

13. Goldman RL: The reliability of peer assessments of quality of care. JAMA 267:958, 1992.

14. Caplan RA, Posner K, Ward RJ, Cheney FW: Peer reviewer agreement for major anesthetic mishaps. QRB Qual Rev Bull 14:363, 1988.

15. Calhoun T: Peer review and risk management. J Natl Med Assoc 85:692, 1993.

16. Jencks SF, Wilensky GR: The health care quality improvement initiative. A new approach to quality assurance in Medicare. JAMA 268:900, 1992.

17. Posner KL, Sampson PD, Caplan RA et al: Measuring interrater reliability among multiple raters: An example of methods for nominal data. Stat Med 9:1103, 1990.

18. Goldman RL, Ciesco E: Improving peer review: Alternatives to unstructured judgments by a single reviewer. Jt Comm J Qual Improv 22:762, 1996.

19. Caplan RA, Posner KL, Cheney FW: Effect of outcome on physician judgments of appropriateness of care. JAMA 265:1957, 1991.

20. Horner SL: The Health Care Quality Improvement Act of 1986: Its history, provisions, applications and implications. Am J Law Med 16:455, 1990.

21. Davies JM: On-site risk management. Can J Anaesth 38:1029, 1991.

22. Walker JS, Wilson M: Clinical risk management in anaesthesia. Qual Health Care 4:115, 1995.

23. Kravitz RL, Rolph JE, McGuigan K: Malpractice claims data as a quality improvement tool. I. Epidemiology of error in four specialties. JAMA 266:2087, 1991.

24. Johnson EK: Reports to the National Practitioner Data Bank. JAMA 265:417, 1991.

25. Cheney FW: Anesthesia patient safety and professional liability continue to improve. ASA Newsletter 61:18, 1997.

26. Caplan RA, Vistica MF, Posner KL, Cheney FW: Adverse anesthetic outcomes arising from gas delivery equipment: A closed claims analysis. Anesthesiology 87:741, 1997.

27. Tinker JH, Dull DL, Caplan RA et al: Role of monitoring devices in prevention of anesthetic mishaps: A closed claims analysis. Anesthesiology 71:541, 1989.

28. Moller JT, Johannessen NW, Espersen K et al: Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. Anesthesiology 78:445, 1993.

29. Caplan RA, Benumof JL, Berry FA et al: Practice guidelines for management of the difficult airway: A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 78:567, 1993.

30. Domino KB: Trends in anesthesia litigation in the 1990's: Monitored anesthesia care claims. ASA Newsletter 61:15, 1997.

31. Gild WM, Posner KL, Caplan RA, Cheney FW: Eye injuries associated with anesthesia. A closed claims analysis. Anesthesiology 76:204, 1992.

32. Chadwick HS, Posner K, Caplan RA et al: A comparison of obstetric and nonobstetric anesthesia malpractice claims. Anesthesiology 74:242, 1991.

33. Cheney FW: Perioperative ulnar nerve injury: A continuing medical and liability problem. ASA Newsletter 62:10, 1998.

34. Kroll DA, Caplan RA, Posner K et al: Nerve injury associated with anesthesia. Anesthesiology 73:202, 1990.

35. Morray JP, Geiduschek JM, Caplan RA et al: A comparison of pediatric and adult anesthesia closed malpractice claims. Anesthesiology 78:461, 1993.

36. Caplan RA, Ward RJ, Posner K, Cheney FW: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. Anesthesiology 68:5, 1988.

37. Shomaker TS: Practice policies in anesthesia: A foretaste of practice in the 21st century. Anesth Analg 80:388, 1995.

38. American Society of Anesthesiologists: ASA Standards, Guidelines, and Statement. Park Ridge, Illinois, American Society of Anesthesiologists, 1997.

39. Audet AM, Greenfield S, Field M: Medical practice guidelines: Current activities and future directions. Ann Intern Med 113:709, 1990.

40. Cohn LH, Rosborough D, Fernandez J: Reducing costs and length of stay and improving efficiency and quality of care in cardiac surgery. Ann Thorac Surg 64:S58, 1997.

41. Holzer JF: The advent of clinical standards for professional liability. QRB Qual Rev Bull 16:71, 1990.

42. Gaus CR: Future directions for the Agency for Health Care Policy and Research. Am J Med Qual 11:S26, 1996.

43. Bergman R: No accreditation, no contract, say most managed care plans. Hosp Health Netw 68:64, 1994.

44. Joint Commission on Accreditation of Healthcare Organizations: Comprehensive Accrediation Manual for Hospitals. Oakbrook Terrace, Illinois, JCAHO, 1998.

45. Cohen JA, Philips BK: How to prepare for a Joint Commission survey. Am Soc Anesthesiol Newslett 62:22, 1998.

46. Berger JT, Rosner F: The ethics of practice guidelines. Arch Intern Med 156:2051, 1996.

47. Eagle KA, Brundage BH, Chaitman BR et al: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Am Coll Cardiol 27:910, 1996.

48. Goldsmith MF: Anesthesiology led in establishing standards of care, now plans practice parameter strategies. JAMA 267:1575, 1992.

49. Eichhorn JH, Cooper JB, Cullen DJ et al: Standards for patient monitoring during anesthesia at Harvard Medical School. JAMA 256:1017, 1986.

50. Practice guidelines for acute pain management in the perioperative setting. A report by the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section. Anesthesiology 82:1071, 1995.

51. Practice guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 84:732, 1996.

52. Practice guidelines for cancer pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section. Anesthesiology 84:1243, 1996.

53. Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Anesthesiology 86:995, 1997.

54. Practice guidelines for management of the difficult airway. A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology 78:597, 1993.

55. Practice guidelines for perioperative transesophageal echocardiography. A report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. Anesthesiology 84:986, 1996.

56. Practice guidelines for pulmonary artery catheterization. A report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Anesthesiology 78:380, 1993.

57. Practice guidelines for sedation and analgesia by non-anesthesiologists. A report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Anesthesiology 84:459, 1996.

58. Field MJ, Lohr KW: Clinical practice guidelines: Directions for a new program. Washington, DC, National Academy Press, 1990.

59. Leape LL: Practice guidelines and standards: An overview. QRB Qual Rev Bull 16:42, 1990.

60. Kelly JT, Swarthart JE: Development of practice parameters by physicians organizations. QRB Qual Rev Bull 16:54, 1990.

61. Eddy DM: Clinical decision making: from theory to practice. Practice policies--guidelines for methods. JAMA 263:1839, 1990.

62. Ellrodt G, Cook DJ, Lee J et al: Evidence-based disease management. JAMA 278:1687, 1997.

63. Nash DB, Markson LE, Howell S, Hildreth EA: Evaluating the competence of physicians in practice: From peer review to performance assessment. Acad Med 68:S19, 1993.

64. Agency for Healthcare Policy and Research: Acute pain management: Operative or medical procedures and trauma. US Department of Health and Human Services, Washington, DC, 1992.

65. Cook DJ, Mulrow CD, Haynes RB: Systematic reviews: Synthesis of best evidence for clinical decisions. Ann Intern Med 126:376, 1997.

66. Mosteller F, Colditz GA: Understanding research synthesis (meta-analysis). Annu Rev Public Health 17:1, 1996.

67. Dickinson E: Clinical effectiveness for health care quality improvement. J Qual Clin Pract 18:37, 1998.

68. Mittman BS, Tonesk X, Jacobson PD: Implementing clinical practice guidelines: Social influence strategies and practitioner behavior change. QRB Qual Rev Bull 18:413, 1992.

69. Greco PJ, Eisenberg JM: Changing physicians' practices. N Engl J Med 329:1271, 1993.

70. Woolf SH: Practice guidelines: A new reality in medicine. III. Impact on patient care. Arch Intern Med 153:2646, 1993.

71. Fletcher RH, Fletcher SW: Clinical practice guidelines. Ann Intern Med 113:645, 1990.

72. Worrall G, Chaulk P, Freake D: The effects of clinical practice guidelines on patient outcomes in primary care: A systematic review. CMAJ 156:1705, 1997.

73. Grimshaw JM, Russell IT: Effect of clinical guidelines on medical practice: A systematic review of rigorous evaluations. Lancet 342:1317, 1993.

74. Huttin C: The use of clinical guidelines to improve medical practice: Main issues in the United States. Int J Qual Health Care 9:207, 1997.

75. Wachtel TJ, O'Sullivan P: Practice guidelines to reduce testing in the hospital. J Gen Intern Med 5:335, 1990.

76. Sonnad SS, Foreman SE: An incentive approach to physician implementation of medical practice guidelines. Health Econ 6:467, 1997.

77. Wise CG, Billi JE: A model for practice guideline adaptation and implementation: Empowerment of the physician. Jt Comm J Qual Improv 21:465, 1995.

78. Ball JR: Practice guidelines and their role in quality assurance and cost effectiveness. Qual Assur Health Care 2:31, 1990.

79. Woolf SH: Practice guidelines, a new reality in medicine. II. Methods of developing guidelines. Arch Intern Med 152:946, 1992.

80. Dickinson E: Clinical effectiveness for health care quality improvement. J Qual Clin Pract 18:37, 1998.

81. Posner KL, Caplan RA, Cheney FW: Variation in expert opinion in medical malpractice review. Anesthesiology 85:1049, 1996.

82. Cheney FW, Posner K, Caplan RA, Ward RJ: Standard of care and anesthesia liability. JAMA 261:1599, 1989.

83. Hirshfeld E: Use of practice parameters as standards of care and in health care reform: A view from the American Medical Association. Jt Comm J Qual Improv 19:322, 1993.

84. Burns LR, Denton M, Goldfein S et al: The use of continuous quality improvement methods in the development and dissemination of medical practice guidelines. QRB Qual Rev Bull 18:434, 1992.

85. Galletly DC, Mushet NN: Anaesthesia system errors. Anaesth Intensive Care 19:66, 1991.

86. Kumar V, Barcellos WA, Mehta MP, Carter JG: An analysis of critical incidents in a teaching department for quality assurance. A survey of mishaps during anaesthesia. Anaesthesia 43:879, 1988.

87. Lagasse RS, Steinberg ES, Katz RI, Saubermann AJ: Defining quality of perioperative care by statistical process control of adverse outcomes. Anesthesiology 82:1181, 1995.

88. Berwick DM: Continuous improvement as an ideal in health care. N Eng J Med 320:53, 1989.

89. Deming WE: Quality, Productivity and Competitive Position. Cambridge, Massachusetts, Massachusetts Institute of Technology, 1982.

90. Juran JM: Juran on Planning Quality. New York, Free Press, 1988.

91. Watcha MF, White PF: Economics of anesthetic practice. Anesthesiology 86:1170, 1997.

92. Buccini EP: Total quality management in the critical care environment. A primer. Crit Care Clin 9:455, 1993.

93. Ruark-Hearst M: Cornerstones of health care in the nineties: Key constituencies debate propositions for collaborating in the quality revolution. QRB Qual Rev Bull 17:60, 1991.

94. Carman JM, Shortell SM, Foster RW et al: Keys for successful implementation of total quality management in hospitals. Health Care Manage Rev 21:48, 1996.

95. Kaluzny AD, McLaughlin CP, Simpson K: Applying total quality management concepts to public health organizations. Public Health Rep 107:257, 1992.

96. McCabe WJ: Total quality management in a hospital. QRB Qual Rev Bull 18:134, 1992.

97. Bigelow B, Arndt M: Total quality management: Field of dreams? Health Care Manage Rev 20:15, 1995.

98. Gustafson DH, Hundt AS: Findings of innovation research applied to quality management principles for health care. Health Care Manage Rev 20:16, 1995.

99. Shortell SM, O'Brien JL, Carman JM et al: Assessing the impact of continuous quality improvement/total quality management: Concept versus implementation. Health Serv Res 30:377, 1995.

100. Wakefield DS, Wakefield BJ: Overcoming the barriers to implementation of TQM/CQI in hospitals: Myths and realities. QRB Qual Rev Bull 19:83, 1993.

101. Caldwell C: Accelerators and inhibitors to organizational change in a hospital. QRB Qual Rev Bull 19:42, 1993.

102. Manual for Anesthesia Department Organization and Management. Park Ridge, Illinois, American Society of Anesthesiologists, 1997.

103. Wu KH, Rau RH, Lin CF, Chan YL: Cardiac arrest during anesthesia in a teaching hospital. A 4 years survey. Int Surg 82:254, 1997.

104. Eagle CC, Davis NJ: Report of the Anaesthetic Mortality Committee of Western Australia 1990-1995. Anaesth Intensive Care 25:51, 1997.

105. Warden JC, Borton CL, Horan BF: Mortality associated with anaesthesia in New South Wales, 1984-1990. Med J Aust 161:585, 1994.

106. Tikkanen J, Hovi-Viander M: Death associated with anaesthesia and surgery in Finland in 1986 compared to 1975. Acta Anaesthesiol Scand 39:262, 1995.

107. Cooper JB, Cullen DJ, Eichhorn JH et al: Administrative guidelines for response to an adverse anesthesia event. The Risk Management Committee of the Harvard Medical School's Department of Anaesthesia. J Clin Anesth 5:79, 1993.

108. Posner KL, Kendall-Gallagher D, Wright IH et al: Linking process and outcome of care in a continuous quality improvement program for anesthesia services. Am J Med Qual 9:129, 1994.

109. Staender S, Davies J, Helmreich B et al: The anaesthesia critical incident reporting system: An experience based database. Int J Med Inf 47:87, 1997.

110. Sanborn KV, Castro J, Kuroda M, Thys DM: Detection of intraoperative incidents by electronic scanning of computerized anesthesia records. Comparison with voluntary reporting. Anesthesiology 85:977, 1996.

111. Cullen DJ, Bates DW, Small SD et al: The incident reporting system does not detect adverse drug events: A problem for quality improvement. Jt Comm J Qual Improv 21:541, 1995.

112. Leape LL: Error in medicine. JAMA 272:1851, 1994.

113. Cooper JB: Is voluntary reporting of critical events effective for quality assurance? Anesthesiology 85:961, 1996.

114. Joint Commission on Accreditation of Healthcare Organizations: Sentinel Events: Evaluating Cause and Planning Improvement. Oakbrook Terrace, Illinois, JCAHO, 1998.

115. Deffenbaugh JH: The joint commission's revised sentinel-event policy. Am J Health Syst Pharm 55:1112, 1998.

116. Joint Commission on Accreditation of Healthcare Organizations: An introduction to quality improvement in health care. Oakbrook Terrace, Illinois, JCAHO, 1991.

117. Nadzam DM, Turpin R, Hanold LS, White RE: Data-driven performance improvement in health care: The Joint Commission's Indicator Measurement System (IMSystem). Jt Comm J Qual Improv 19:492, 1993.

118. Angaran DM: Selecting, developing, and evaluating indicators. Am J Hosp Pharm 48:1931, 1991.

119. Downey GB, O'Connell AJ: Audit of unbooked paediatric postanaesthesia admissions to intensive care. Anaesth Intensive Care 24:464, 1996.

120. Characteristics of clinical indicators. QRB Qual Rev Bull 15:330, 1989.

121. Everett WD: An epidemiological approach to quality assurance in the hospital. Health Care Manage Rev 18:91, 1993.

122. Johnson DI: Using external data and databases: Issues and sources. J Nurs Care Qual 10:31, 1995.

123. McGhee TD: Observations on database design for improving clinical care. Int J Clin Monit Comput 13:143, 1996.

124. Weissman C: Can hospital discharge diagnoses be used for intensive care unit administrative and quality management functions? Crit Care Med 25:1320, 1997.

125. Sanazaro PJ, Mills DH: A critique of the use of generic screening in quality assessment. JAMA 265:1977, 1991.

126. Edsall DW: Quality assessment with a computerized anesthesia information management system (AIMS). QRB Qual Rev Bull 17:182, 1991.

127. Davies AR, Doyle MA, Lansky D et al: Outcomes assessment in clinical settings: a consensus statement on principles and best practices in project management. Jt Comm J Qual Improv 20:6, 1994.

128. Kelvin JF, Houston K: Improving organizational performance: An introduction to the 1995 Joint Commission on Accreditation of Healthcare Organizations Standard. Cancer Pract 4:88, 1996.

129. al-Assaf AF: Healthcare outcomes management and quality improvement. J R Soc Health 116:245, 1996.

130. Bernstein AB: Ready or not, here it comes; Medical practice in the new millennium. Semin Med Pract 1:2, 1998.

131. Anderson JP, Kaplan RM, Coons SJ, Schneiderman LJ: Comparison of the Quality of Well-being Scale and the SF-36 results among two samples of ill adults: AIDS and other illnesses. J Clin Epidemiol 51:755, 1998.

132. Edsall DW: Computerization of anesthesia information management: Users' perspective. J Clin Monit 7:351, 1991.

133. Mangano DT: Adverse outcomes after surgery in the year 2001: A continuing odyssey. Anesthesiology 88:561, 1998.

134. Lee A, Lum ME: Measuring anaesthetic outcomes. Anaesth Intensive Care 24:685, 1996.

135. Dubois RW, Brook RH, Rogers WH: Adjusted hospital death rates: A potential screen for quality of medical care. Am J Public Health 77:1162, 1987.

136. Cohen MM, Duncan PG, Pope WD et al: The Canadian four-centre study of anaesthetic outcomes: II. Can outcomes be used to assess the quality of anaesthesia care? Can J Anaesth 39:430, 1992.

137. Silber JH, Williams SV, Krakauer H, Schwartz JS: Hospital and patient characteristics associated with death after surgery. A study of adverse occurrence and failure to rescue. Med Care 30:615, 1992.

138. Christopherson R, Beattie C, Frank SM et al: Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Anesthesiology 79:422, 1993.

139. Strauss RA, Silloway KA, Perkins D: Comparison of morbidity of outpatient general anesthesia administered by the intravenous or inhalation route. J Oral Maxillofac Surg 56:1035, 1998.

140. Sanderson JH, Blades JF: Multicentre study of propofol in day case surgery. Anaesthesia 43(Suppl):70, 1988.

141. Tang J, Wang B, White PF et al: The effect of timing of ondansetron administration on its efficacy, cost-effectiveness, and cost-benefit as a prophylactic antiemetic in the ambulatory setting. Anesth Analg 86:274, 1998.

142. Jakobsson J, Oddby E, Rane K: Patient evaluation of four different combinations of intravenous anaesthetics for short outpatient procedures. Anaesthesia 48:1005, 1993.

143. Chestnut DH: Epidural analgesia and the incidence of cesarean section. Anesthesiology 87:472, 1997.

144. Willatts S: Anaesthetic lessons to be learnt from confidential inquiries into maternal death. Acta Anaesthesiol Scand Suppl 110:25, 1997.

145. Badner NH, Knill RL, Brown JE et al: Myocardial infarction after noncardiac surgery. Anesthesiology 88:572, 1998.

146. Forgosh LB, Movahed A: Assessment of cardiac risk in noncardiac surgery. Clin Cardiol 18:556, 1995.

147. Ellison N, Pierce EC Jr: Risk management in cardiac anesthesia: Analysis of critical issues. Introduction. J Cardiothorac Vasc Anesth 12:1, 1998.

148. Silber JH, Rosenbaum PR, Schwartz JS et al: Evaluation of the complication rate as a measure of quality of care in coronary artery bypass graft surgery. JAMA 274:317, 1995.

149. Using patient input in a cycle for performance improvement. Jt Comm J Qual Improv 21:87, 1995.

150. Fung D, Cohen MM: Measuring patient satisfaction with anesthetic care: A review of current methodology. Anesth Analg 87:1089, 1998.

151. Hohmann SF, Lockowitz PA: Clinical risk management: Measuring practices and outcomes to change behavior and reduce liability. J Health Care Finance 21:66, 1994.

152. Cohen MM, Rose DK, Yee DA: Changing anesthesiologists' practice patterns. Can it be done? Anesthesiology 85:260, 1996.

153. Cheng DC: Fast-track cardiac surgery: Economic implications in postoperative care. J Cardiothorac Vasc Anesth 12:72, 1998.

154. Weingarten S, Riedinger MS, Sandhu M et al: Can practice guidelines safely reduce hospital length of stay? Results from a multicenter interventional study. Am J Med 105:33, 1998.

155. Dexter F, Lubarsky DA, Gilbert BC, Thompson C: A method to compare costs of drugs and supplies among anesthesia providers: A simple statistical method to reduce variations in cost due to variations in case mix. Anesthesiology 88:1350, 1998.

156. McNitt JD, Bode ET, Nelson RE: Long-term pharmaceutical cost reduction using a data management system. Anesth Analg 87:837, 1998.

157. Macario A, Vitez TS, Dunn B, McDonald T: Where are the costs in perioperative care? Analysis of hospital costs and charges for inpatient surgical care. Anesthesiology 83:1138, 1995.

158. Lubarsky DA, Glass PS, Ginsberg B et al: The successful implementation of pharmaceutical practice guidelines. Analysis of associated outcomes and cost savings. SWiPE Group. Systematic Withdrawal of Perioperative Expenses. Anesthesiology 86:1145, 1997.

159. Boldt J, Jaun N, Kumle B et al: Economic considerations of the use of new anesthetics: A comparison of propofol, sevoflurane, desflurane and isoflurane. Anesth Analg 86:504, 1998.

160. Hanchak NA: Managed care, accountability, and the physician. Med Clin North Am 80:245, 1996.

161. O'Malley C: Quality measurement for health systems: Accreditation and report cards. Am J Health Syst Pharm 54:1528, 1997.

162. Joint Commission on Accreditation of Healthcare Organizations: ORYX Outcomes: The Next Evolution in Accreditation. Oakbrook Terrace, Illinois, JCAHO, 1997.

163. Koss RG, Bowie MK, Sprenger SL, Loeb JM: ORYX: The next evolution in accreditation. JCOM J Clin Outcomes Manag 4:16, 1997.

164. Green J, Wintfeld N, Krasher M, Wells C: In search of America's best hospitals. The promise and reality of quality assessment. JAMA 277:1152, 1997.

165. Epstein A: Performance reports on quality: Prototypes, problems, and prospects. N Engl J Med 333:57, 1995.

166. Boscarino JA, Chang J: Commentary: Inaccurate data on the quality of care may do more harm than good--an alternative approach is required. Am J Med Qual 12:196, 1997.

167. Cleves MA, Golden WE: Assessment of HCFA's 1992 Medicare hospital information report of mortality following admission for hip arthroplasty. Health Serv Res 31:39, 1996.

168. Iezzoni LI: The risks of risk adjustment. JAMA 278:1600, 1997.

169. Epstein AM: Rolling down the runway: The challenges ahead for quality report cards. JAMA 279:1691, 1998.

170. Swamidoss CP, Brull SJ, Watrous G, Barash PG: Health-care report cards and implications for anesthesia. Anesthesiology 88:809, 1998.

171. Mukamel DB, Mushlin AI: Quality of care information makes a difference: An analysis of market share and price changes after publication of the New York State Cardiac Surgery Mortality Reports. Med Care 36:945, 1998.

Chapter 80 - Human Work Environment and Simulators

David M. Gaba

/das/book/view/29494766/875/876.html

INTRODUCTION

The safe conduct of anesthesia depends on the appropriate application by the skilled anesthetist of knowledge concerning the physiology of patients during and after anesthesia, the characteristics of anesthetic and adjuvant drugs, and the means of monitoring the patient and the life-support equipment throughout the perioperative period. In this chapter, the term *anesthetist* refers to any anesthesia practitioner, whether a physician or a certified nurse anesthetist.

Traditionally, it has been assumed that an adequately trained anesthetist automatically performs appropriately. Deviations from optimal outcomes were understood to be due to imperfections in the art and science of anesthesia, leading to a heavy emphasis on the scientific and technical part of anesthesia training and care. More rarely, adverse outcomes were ascribed to negligence or incompetence on the part of the anesthetist.

Today, there is a more complete understanding that anesthetists themselves, both as a profession and as individuals, have strengths and vulnerabilities pertaining to their work environment. The performance of human beings is incredibly flexible and powerful (no computer can match human beings in this regard), but at the same time it is vulnerable to distractions, biases, and errors. This chapter surveys some of the human characteristics that define the performance parameter of the anesthetist. The domain of the anesthetist is very challenging, being every bit the equal of domains, such as aviation, that more readily capture the public's imagination. The last 10 years have seen new research concerning the nature and limitations of professional judgment and decision making in this dynamic and complex world. The second section of this chapter explores developments in simulation technology that have contributed to this research and that may open new opportunities to prepare anesthetists to handle the challenges that they will face in their work.

The literature related to human performance is vast (standard reference works are available [1] [2]), and this chapter only samples a portion of it as it most closely relates to the work of anesthetists. Moreover, this chapter does not deal to any great extent with human-machine interactions and the physical design of the work environment. These aspects of human factors or ergonomics in anesthesia have considerable importance in their own right. The reader is referred to several publications that review these issues in detail. [3] [4] [5] [6]

Study of Human Performance

The study of human performance involves research paradigms that are different from those usually considered in the science of anesthesia. There are many obstacles to obtaining hard, statistically valid data on human performance. There are no animal models for expert human performance, no "Sprague Dawley anesthesiologists" to be studied in detail, nor can studies of professional performance be conducted using the psychologist's typical experimental subject, the university undergraduate student. Recruiting expert anesthetists to be the subjects of study is difficult, raising issues of selection bias concerning those who do volunteer. Especially if conducted during actual patient care, investigations of human performance are strongly influenced by concerns about litigation, credentialing, and confidentiality, thus making it difficult to execute optimal studies. Furthermore, the variability among individual anesthetists is quite striking, because different anesthetists respond to the same situation in different ways, and each individual may act differently on different days or at different times of the same day. The magnitude of this *intra*individual variability is often nearly the same as the *inter*individual variability.

"Performance" itself is an intuitively meaningful concept that is difficult to define precisely. There are no gold standards for the clinical decisions and actions of anesthetists. They depend heavily on the context of specific situations. In addition, determining how anesthetists perform their job, whether successfully or unsuccessfully, means delving into their mental processes. These cannot be measured easily. On the one hand, one can use experimental designs that involve artificial laboratory tasks, for which performance can be objectively measured. These tasks will then be far removed from the real world of administering anesthesia. On the other hand, investigating the actual performance of trained practitioners in the real world yields primarily subjective and indirect data. Understanding the anesthetist's performance must be seen as analogous to solving a jigsaw puzzle. Pieces of the puzzle likely come from a variety of sources, none of which by itself captures the entire picture. These pieces include objective data from artificial laboratory tasks, prospective observation of routine patient care, analysis of retrospective reports of near misses or anesthetic mishaps, and prospective observation of the response to simulated events. To achieve the best possible understanding of the situation, it is necessary to accept many data that seem uncomfortably subjective to the physical or biologic scientist. Because the research methodologies may be unfamiliar to anesthetists, the key studies of anesthetist performance are described in detail in this chapter.

Why Study Human Performance in Anesthesia?

How can an improved understanding of the human performance of anesthetists help them to provide patient care more safely, in a wider variety of clinical situations, with greater efficiency, and with increased satisfaction to both patients and practitioners? The possibilities include the following:

1. *Improved operational protocols and enhanced training of anesthetists.* The way in which individuals conduct anesthesia is based, in part, on knowing the limits of their performance envelope. Anesthetic techniques and operating room (OR) practices should draw on anesthetists' abilities and should mitigate their weaknesses. Anesthetists' abilities are strongly affected by training. Understanding the required performance characteristics and inherent human limitations will lead to improved training, which will develop most fully the strengths and counter the existing vulnerabilities of the anesthetist. This process should make patient care safer, less stressful, and more efficient to provide.
2. *A more rational view of professional work and legal responsibility (Ch. 85) .* Modern medicine, especially in the United States, is strongly influenced by medicolegal concerns. The litigation system has a major selection bias in that every case that comes before it involves an adverse outcome for a patient. The duty of the practitioner is to render care as a "reasonable and prudent" specialist in the area of anesthesia. What is reasonable and prudent? What type of performance is to be expected from appropriately trained human beings in a complex and dynamic environment? By understanding human performance, it may be possible to generate a more rational view of what is, and is not, within the standard of care.

3. *A more effective work environment (Ch. 81).* Anesthetists now perform their tasks using an array of technology, most of which has not been designed to support the anesthetist's work most optimally. By understanding the anesthetist's tasks and performance requirements, the workspace and tools could be improved to support the most difficult tasks better. This, too, can lead to greater safety and to greater efficiency and work satisfaction.
4. *A more efficient organizational system (Ch. 82).* Anesthesia is embedded within a larger system of organizedmedical care that involves interactions among numerous institutions, organizations, and professional domains. Understanding how the anesthetist's work relates to the larger system may enable the development of more rational and efficient flows of information and organizational control.

/das/book/view/29494766/875/877.html

ANALYZING THE ANESTHETIST'S DOMAIN: THE OPERATIONAL WORLD VERSUS THE ORGANIZATIONAL WORLD

Psychologists and cognitive engineers who study people at work refer to each field of work as a domain. Each domain has specific characteristics that set it apart from others, including the nature of the tasks to be performed, the relationships among the tasks, the time scale over which they must be executed, and the criteria for their successful performance. This chapter deals primarily with the operational domains in which anesthesia care is delivered, primarily the OR, the postanesthesia care unit (PACU), and the intensive care unit (ICU). However, as pointed out by Reason, [7] [8] as well as by Woods and Cook and colleagues, [9] [10] [11] [12] what goes on in the operational domain is extensively shaped by the organizational and managerial environment in which it is located, even to the point that operational personnel believe themselves to be the "victims" of problematic decisions further back in the system.

In everyday practice, these distinctions are hidden or blurred. The positive and negative contributions of the organizational and management elements are often so embedded in the normal routine that they are difficult to isolate. The most interesting information about the system often comes from considering abnormal situations, accidents, or near misses, instead of normal events. Traditionally, one speaks of errors arising in decisions and actions that led to a mishap. The term *error* is increasingly considered an inappropriate way to categorize behaviors (being a judgment of attribution and blame) and should be thought of merely as a way to identify behaviors at the locus of a critical situation. Some errors are actively produced in the operational domain (active errors), and others are introduced by the organizational environment. James Reason, a psychologist at the University of Manchester, England, introduced the concept of "latent errors" [7] [8] :

> errors whose adverse consequences may lie dormant within the system
> for a long time, only becoming evident when they combine with other factors to
> breach the system's defenses. [They are] most likely to be spawned by
> those whose activities are removed in both time and space from the direct
> control interface: designers, high-level decision makers, construction workers,
> managers and maintenance personnel.

Latent errors probably exist in all complex systems, and Reason has adopted a medical metaphor to describe them as "resident pathogens." Like microorganisms in the body, the resident pathogens remain under control until sets of local circumstances "combine with these resident pathogens in subtle and often unlikely ways to thwart the system's defenses and bring about its catastrophic breakdown" [8] (Fig. 80-1) (Figure Not Available) .

A complementary analysis of complex systems by the organizational theorist Charles Perrow [13] called attention to two features that make a system particularly vulnerable to the occurrence of accidents: (1) the complexity of interactions among the system's elements; and (2) the presence of tight coupling among the system's elements. When these characteristics coexist, abnormal sequences of events can sometimes be hidden, and they can have complex and unpredictable consequences. Typically, active errors in the system do not result in an accident because they are trapped at some point by the system's multiple layers of checks and defenses (see Fig. 80-1 (Figure Not Available)). In the presence of latent errors, even a minor active error can cause normal system behaviors to become out of control because of complex interactions and tight coupling. Perrow called this a "normal accident" because it arises out of apparently normal system operations. He suggested that attention should be directed at strengthening the recovery pathways by which small events can be properly handled before they evolve to a serious accident. Perrow also emphasized the effects of the "larger system" on operational mishaps and the ways in which the incentives offered by the system could influence safety-related decisions.

Complexity and Tight Coupling: Latent Errors in Anesthesia

Clearly, the anesthesia domain involves complex interactions with tight coupling. [14] The complexity stems to some degree from the variety of devices in use and their interconnections, but these are, in truth, vastly simpler than those

Figure 80-1 (Figure Not Available) James Reason's model of accident causation. Latent failures at the organization level may combine with psychologic precursors and event triggers at the operational level to initiate the accident sequence. Most accident sequences are trapped at one or more layers of the system's defenses. The defenses can fail either because of organizational failure or because of performance failures of the operators. *(From Reason [6])*

found in an oil refinery, a 747 aircraft, or the space shuttle. A more important source of complexity is the "uncertainty complexity" of the patient. [14] The human body is an incredibly complex system containing numerous components the interactions of which are only vaguely understood. Because many body systems affect each other, the patient is a major site of tight couplings. Furthermore, the anesthetic state tends to ablate the buffers among some of these interconnected systems, thus strengthening the coupling among them and between the patient and external mechanical supports. Galletly and Mushet [15] studied anesthesia "system errors" and observed tight coupling associated with "the use of neuromuscular blocking drugs, the presence of cardiorespiratory disease, certain types of surgical procedure, and from the effect of the general anesthetic agents. Looser coupling was observed with the use of high concentrations of oxygen and air mixtures, preoxygenation, and spontaneous breathing techniques."

A variety of latent failures can exist in the anesthesia environment. They may include such issues as how surgical cases are booked, how cases are assigned to specific anesthetists, what provisions are made for preoperative evaluation of outpatients, and what relative priority is given to rapid turnover between cases or avoiding the cancellation of cases as opposed to the avoidance of risk. Latent errors can also result from the design of anesthesia equipment and its user interfaces. Manufacturing defects and failures of routine maintenance are also sources of latent failures.

Eagle and Davies [16] described a number of active failures and latent failures in a case report concerning a severely ill patient who died 6 days after suffering aspiration of gastric contents during general anesthesia for cystoscopy. The initial urologist in this case made an active error by booking the case inappropriately to be performed under local anesthesia. This active error interacted with other latent features of the system. For example, the OR scheduling system improperly allowed the urologist to be assigned to two different cases simultaneously, which led to the surgical procedure's being transferred to another urologist who was unfamiliar with the patient. The second urologist requested a general anesthetic, at which point an anesthetist, who was equally unfamiliar with the patient, was brought into the situation. Through this combination of events, the seriously ill patient did not receive a thorough evaluation in advance of his surgery. Specifically, the anesthetist was not aware that the patient had suffered an episode of projectile vomiting at 4 AM on the day of surgery. This information was available in the hospital's computerized record-keeping system, but there was no computer terminal in the OR. The information was not contained on the patient's chart. The nursing notes in the chart indicated that the patient had been fasting for 24 hours. The second urologist and the anesthetist believed that the case was an urgent addition to the OR list. They decided to go ahead with the case despite their cursory evaluation of the patient.

The analysis of Eagle and Davies reinforced the concept that investigation of untoward events must address both latent and active failures and both the organizational and managerial environment and the operational domain. One risk of focusing solely on active failures is that the operational personnel believe

themselves to be victims of the system, making them defensive and uncooperative. Rasmussen, [17] as well as Cook and Woods et al, [9] [11] [12] [18] pointed out that if one looks at the chain of events in an accident sequence, one can always find a failure on the part of an operator. If the analysis stops at this point, the operator (i.e., the anesthetist) may be wrongly blamed for a failure the real roots of which go back to latent failures in the organization.

One trend in the study of several high-hazard industries attempts to define the important organizational elements that promote or inhibit safety. One school of thought, which is sometimes contrasted with the approach of Perrow, focuses on successful high-risk activities (such as aircraft carrier flight operations) involving "high-reliability orga-nization." [19] [20] [21] [22] [23] The key elements of a high-reliability organization are as follows:

1. Priority of safety and reliability as a goal by political elites and organizational leadership.
2. High levels of redundancy in personnel and technical safety measures.
3. Development of "high-reliability culture" in decentralized and continually practiced operations (with high proceduralization).
4. Sophisticated forms of trial and error organizational learning.

Anesthesiology in most institutions contains some elements of a high-reliability organization, particularly technical safety measures. However, many elements are not as fully realized as they are in classic high-reliability organizations in the military and in commercial aviation. Another analysis of the impact of the organization on safety comes from sociologist Diane Vaughan's book *The Challenger Launch Decision.*[24] Vaughan's main thesis is that the Challenger exploded *not* because "risk-taking" managers "broke the rules," but because the system evolved to make excessive risk a part of "following the rules." This occurred because of four key organizational elements she identified:

1. A culture of production (ingrained production pressure).
2. Risk as a social construction.
3. Normalization of deviance (explaining away abnormal findings).
4. Structural secrecy.

These same features can also be identified in many medical environments including anesthesiology. I am currently conducting a 2-year comprehensive comparison, funded by the Robert Wood Johnson Foundation, of the organizational, system, and safety-cultural aspects of tertiary care medicine versus other high-risk industries.

Nature of the Operational Domain of Anesthesiology

Accepting the important caveat that the performance of anesthetists is strongly affected by organizational factors and by latent failures present in the work environment, it is still in the operational domain of actual patient care in which anesthetists put their skills on the line. Thus, this chapter examines the operational environment and the anesthetist's performance in more detail.

The operational domain of anesthesia is a complex, dynamic world [25] that presents a cognitive profile common to

many real-world task domains. The analysis of complex dynamic worlds in the last decade has departed sharply from previous conceptions of decision making. [26] Classic decision-making approaches, such as decision theory and multiattribute utility theory, were mathematic techniques that were traditionally used as the dominant framework for understanding human performance. They worked well in simplified laboratory experiments on decision making and action, yet a number of investigators had significant difficulty in applying them to real-world decision and action settings. [26] Orasanu and Connolly [26] identified eight factors that characterize such naturally occurring complex dynamic worlds. They apply to anesthesia as follows:

1. *Ill-structured problems.* Unlike in traditional decision experiments, there is not a single decision to be made. There are a variety of interrelated decisions to be made by the anesthetist and the surgeon. The patient's physiologic behavior is not an independent random variable but is causally linked to previous decisions and actions.
2. *Uncertain dynamic environment.* Dynamism stems from the frequency of routine and anomalous changes or events, the rapidity with which they evolve, and the unpredictability of the patient's physiology and response to interventions. The anesthetized patient during surgery is in a constant state of change, with many events outside the anesthetist's control. Although preventive measures can reduce the likelihood of some events, others cannot be avoided because they are inevitable side effects of medically necessary procedures (e.g., surgical blood loss). Unpredictable and dynamic occurrences compete with the preplanned aspects of the case driving the anesthetist's actions. The true state of the patient cannot usually be measured directly. It must be inferred from ambiguous patterns of clinical observations and data from electronic monitors. These data are imperfect because, unlike industrial systems that are designed and built with sensors in key areas to measure the most important variables, patients are typically instrumented to measure the variables that are easiest to monitor, predominantly using noninvasive methods. Most physiologic functions are observed indirectly through weak signals available at the body surface and thus are prone to various types of electrical and mechanical interference. Invasive measurements are also vulnerable to artifacts and uncertainties of interpretation. Even if the anesthetist knew the exact state of the patient, the patient's response to interventions would be unpredictable.
3. *Time stress.* Because the OR is a scarce resource, there is an incessant overall time pressure to use it efficiently. There is an even more intense immediate time stress within each case, generated by dynamic situations that evolve rapidly and that must be dealt with in a timely fashion.
4. *Shifting, ill-defined, or competing goals.* Multiple goals of case management (e.g., hemodynamic stability, good operating conditions for the surgeon, rapid emergence from anesthesia) may compete with each other. The surgeon's goals may sometimes compete with those of the anesthetist. All these goals shift as the patient's situation shifts dynamically throughout the case.
5. *Action/feedback loops.* The time constants of actions and their effects are very short, on the order of seconds to minutes. There is a complete intermixing of decision-making and action; these functions are not performed in separate cycles. Most decisions and actions are implemented and evaluated incrementally with the effect of one cycle assessed before deciding on further possible actions.
6. *High stakes.* The stakes are high because, even for elective surgery in healthy patients, there is an ever-present and very real risk of injury, brain damage, or even death. A catastrophe is often the end result of many pathways that begin with seemingly innocuous triggering events. Each intervention, even if appropriate, is associated with side effects, some of which are themselves serious. Some risks cannot be avoided. Unlike a commercial flight, which can be delayed or aborted if a problem occurs, immediate surgery may be necessary to treat a medical problem that is itself life-threatening. Balancing the risks of the anesthesia and surgery against that of the underlying surgical disease is often extremely difficult.
7. *Multiple players.* The anesthesia domains involve multiple players from different professional backgrounds. Each individual has a set of goals, abilities, and limitations. In some situations, interpersonal interactions dominate the work environment.
8. *Organizational goals and norms.* The anesthetist works within the stated and unstated norms of the OR suite, the anesthesia department, the institution, and the profession as a whole. Decisions are sometimes made to conform to these norms that are not wholly subscribed to by the anesthetist.

Although many of these features apply to other domains of medicine, anesthesiology is unique in that all eight factors are prominent. In particular, what sets anesthesia apart from clinic-based or ward-based medicine is the intensity of dynamism, time pressure, and uncertainty. Each of these factors exacerbates the difficulties posed by the others.

ANESTHETIST'S TASKS

The investigation of a complex work environment typically starts with a task analysis. One type is an abstract analysis of the work procedures and the tasks required to perform them. A second technique is to observe what skilled practitioners actually do in their work and to classify these actions into task elements. In this section, the anesthetist's task is examined in the abstract. In the following section, the empirical task analysis approach is reviewed.

There are two distinct phases of anesthetic care: (1) preoperative evaluation, planning, and preparation; and (2) conduct of the anesthetic regimen and immediate postoperative care.

Preoperative Evaluation and Planning

There are few data on how well anesthetists identify important patient conditions through history-taking and physical examination (Ch. 23) . A frequent organizational obstacle to the anesthetist's evaluation task is the inability to obtain the patient's previous medical records. The performance of

anesthetists in selecting appropriate laboratory tests has been found to be relatively poor. Roizen [27] (Ch. 25) states that:

> Even when physicians agree to reduce testing by using specific, agreed upon criteria for selectively ordering tests based on history and physical examination, they still make a surprising number of mistakes when ordering tests. Approximately 30 to 40 percent of patients who should have certain tests ... do not get them, and 20 to 40 percent of patients who should not have tests are subjected to them.

Roizen has argued for the automation of routine patient questioning and selection of laboratory tests and has participated in the development of commercial devices to do so. Whether these devices, in combination with human follow-up for patients with medical problems, will improve the efficiency and accuracy of preoperative evaluation remains to be determined. The performance of anesthetists at interpreting electrocardiograms (ECG) [28] and chest radiographs [29] also appears to be poor relative to specialists in these fields. The extent to which this factor influences the design of anesthetic plans or patient outcomes is unknown.

Anesthetic Plan

In constructing the plan, the anesthetist uses the preoperative evaluation of the patient to match the technical requirements of the surgical procedure and the physiologic characteristics of the patient to the mental, physical, and technologic resources available. A typical anesthetic plan contains several elements. For example, the plan for general anesthesia includes choices for the means of inducing anesthesia, securing the airway and ensuring proper ventilation, maintaining anesthesia, conducting emergence from anesthesia, and postoperative pain control. Skilled planning is as critical to safe patient care as is skilled execution. If a significant feature of the situation is missed in formulating the plan, it can leave the patient vulnerable, regardless of how adeptly the plan is implemented.

The technical requirements of most surgical procedures are well known. Most patients do not have medical problems that could significantly alter the anesthetic plan, although Gibby et al [30] found that 20 percent of outpatients, most of them with American Society of Anesthesiologists (ASA) physical status 1 or 2, had conditions identifiable through an anesthetist's history and examination that required changes from a "standard" anesthetic plan. When a procedure is new or challenging, when the patient has significant underlying disease, or when needed resources are not available, creative planning may be needed to identify a set of physiologic goals for the anesthetic regimen. Routine anesthetic plans can be modified or combined to produce a compromise plan that best fits the goals and constraints of the situation.

Although faculty anesthetists routinely critique the anesthetic plans of residents, and planning is explicitly probed during the oral examination of the American Board of Anesthesiologists, the process of constructing anesthetic plans has been studied very little. Most of the existing literature on preoperative planning concentrates only on the medical and physiologic aspects of underlying diseases and their anesthetic ramifications.

Pre-Use Preparation and Checkout of Equipment

After the plan is established, the anesthetist must prepare the work environment (Chs. 7 and 11). This involves obtaining necessary equipment and supplies, assembling infusions, preparing syringes of needed drugs, and conducting pre-use checkouts of life support equipment. The performance of anesthetists at these tasks is not optimal. Buffington et al [31] demonstrated that only 3 percent of anesthetists examining an anesthesia machine could identify all five faults with which it had been rigged; most practitioners found only two of the five. Nearly 30 percent missed such major faults as the complete absence of both unidirectional valve disks in a circle anesthesia breathing system or a swap of the nitrous oxide and oxygen cylinders (made possible by a fault in the pin-indexing system).

The U.S. Food and Drug Administration (FDA), in cooperation with the ASA, the Anesthesia Patient Safety Foundation (APSF), and experts from academics and industry, developed a set of recommendations for the checkout of anesthesia apparatus. [32] This checklist was widely disseminated by the ASA and the APSF. However, it was found that use of the checkout procedure was minimal and that the extent of pre-use checkout by practitioners was extremely variable. A newer study [33] was conducted to compare the checkout of anesthesia machines by practitioners with and without the use of the FDA checkout procedure. Most of the faults were detected by 50 percent or fewer of participants, regardless of the checkout procedure used. Only for one fault, the failure of the oxygen/nitrous oxide ratio protection system, did the FDA checklist offer significant advantages; when using it, the detection rate went up to 65 percent. Interestingly, 34 percent of faults that were not detected occurred for practitioners who correctly answered three out of three written test questions concerning that fault. This suggests that although some of the performance deficit may be related to a lack of knowledge, a substantial proportion is due to the inability to apply abstract knowledge to the practical performance of equipment checkout. There were many criticisms of the original checklist, particularly of its complexity. [34] A streamlined version of the original checklist was published by the FDA in 1993. [35] There are no data at this time as to whether the new checklist will assist clinicians to detect machine faults better than the original checklist.

Execution and Adaptation of Plans

Anesthetic plans are dynamic. The anesthetist must monitor the plan as it is executed and must adapt it in response to dynamically changing events. The key features of this task are (1) checking for the achievement of milestones and (2) reactive plan adaptation. These are shown schematically in Figure 80-2 (Figure Not Available) . At various points of a case, there are critical milestones that must be achieved in order to keep the original plan unaltered. If a milestone is not achieved, the anesthetist must decide whether to delay the next action in the sequence, to modify the plan, or to suspend or abort the case. On some occasions, the milestones are

explicitly identified in advance, whereas in other cases, the milestones are implicit.

Figure 80-2 (Figure Not Available) Schematic diagram of the dynamic adaptation of preoperative plans. The anesthetist begins the anesthetic with an intravenous induction as planned (top left). On achieving the milestone of successful induction of anesthesia, the blood pressure is checked before proceeding with laryngoscopy and intubation (lower left). If it is not satisfactory, the next step may be delayed and the plan amended to optimize the blood pressure. If necessary, the case could even be aborted at this stage. Throughout the case, the anesthetist is vigilant for the occurrence of new problems (the "police cars"). If a problem is detected, a process of reactive problem solving takes place, which may result in new adaptations to the plan (in this case, treatment of bronchospasm). *(From Gaba [10])*

The anesthetist must also react to a large number of other contingencies, some of which can be predicted in advance, based on the patient's history and the type of surgery, whereas others cannot be anticipated. Incoming data streams must be constantly scrutinized (see the "police cars" in Fig. 80-2 (Figure Not Available)), to determine whether an expected or unexpected contingency is occurring. If so, the existing plan may have to be modified. As plans are changed, actions may be taken that invalidate other aspects of the previous plan, requiring further adaptation of the plan. In some cases, even the original goals of the anesthetic plan may need to be adapted.

Frequency of Events Requiring Active Intervention by the Anesthetist

This abstract analysis suggests that anesthetists must be prepared to react dynamically to changing events. How frequent is this requirement? In the Multicenter Study of General Anesthesia, [36] 17,201 patients received general anesthesia under specific protocols with random stratification to receive one of four anesthetic techniques (each of the three common volatile anesthetic drugs or narcotics plus nitrous oxide). The anesthetists observed the patients for the occurrence of any of a large variety of carefully defined perioperative outcomes, which were adverse events ranging from minor events such as sore throat or hypotension (i.e., systolic blood pressure reduced more than 20% from baseline), to serious events such as myocardial infarction or death. There were 34,926 observed outcomes in the 17,201 patients. Clearly, some patients had more than one outcome, whereas others had none, but 86 percent of patients had at least one undesirable outcome. Although most events were minor and caused no injury to the patient, more than 5 percent of patients had one or more severe events requiring "significant therapy, with or without full recovery." This incidence is probably a lower limit for severe events because the entry criteria of the study precluded the enrollment of critically ill patients or emergency surgeries for which the likelihood of severe problems requiring intervention would be expected to be high.

In another study by Cooper et al, [37] impact events, defined as "undesirable, unexpected, and which could cause at least moderate morbidity," occurred in 18 percent of patients either

---

in the OR or in the PACU. Three percent of all cases involved a "serious" event. These figures are also probably lower limits because, for technical reasons, the study excluded patients going directly from surgery to an ICU.

Moller et al [38] reported on a Danish randomized evaluation of the effect of pulse oximetry on patient outcome. In the oximetry group (which most closely resembled current U.S. practices), 10,312 patients underwent anesthesia and surgery with pulse oximetry in use in addition to all other case-appropriate monitoring modalities. Patients were carefully observed for cardiovascular, pulmonary, and neurologic occurrences that met the criteria of "impact event" as in the study cited earlier. There were 4,439 events detected in these patients either in the OR (2,441) or in the PACU (1,998). Here again, some patients had several events, whereas others had none. The investigators did not compute the frequency of severe events, but overall, these data appear to be consistent with the earlier studies.

Model of Event Evolution

These findings, as well as the larger system issues raised by Reason and Perrow, can be summarized in a model of event evolution [14] [39] [40] [41] (Fig. 80-3) (Figure Not Available) . Similar models incorporating some of the same features have also been described. [15] [42] [43] Underlying aspects of the system can generate latent failures. Either by random chance or because of interactions between the latent failures, an event may be triggered in one of four components of the operational system in the OR--the anesthetist, the surgeon, the patient, or the equipment. Anesthetists have traditionally been most interested in events they triggered themselves (such as esophageal intubation), but, in fact, most events are initiated by a combination of underlying patient disease and another of the triggering factors. Most problems are not directly harmful to the patient unless they evolve further. The possibilities for problem evolution include the following:

1. A single problem worsens and by itself evolves into an adverse outcome.
2. The problem begins to evolve but remains self-limited without any intervention.
3. Multiple small problems combine to trigger a problem that can evolve into an adverse outcome; the original problems by themselves would not have evolved further.
4. A single problem triggers another problem that evolves into an adverse outcome.
5. An evolving problem should be able to be stopped, but the recovery pathway is faulty.

The system has a variety of interruption points at which the occurrence of problems can be prevented (preoperative evaluation of patients and pre-use checkout of equipment) or at which the process of accident evolution can be thwarted before an adverse patient outcome actually occurs. The interruption of accident evolution corresponds to the "defense-in-depth" in Reason's model (see Fig. 80-1 (Figure Not Available)) and to recovery from a normal accident in Perrow's paradigm.

In the prospective studies of intraoperative events cited earlier, there was a surprisingly high incidence of undesirable situations, whereas the rate of actual patient harm was quite low. The patient's safety was frequently protected only

Figure 80-3 (Figure Not Available) Chain of accident evolution in anesthesia. As in Reason's model, underlying latent failures predispose to the triggering of an accident sequence by equipment, the patient, the surgeon, or the anesthesiologist. This sequence can be prevented by prophylactic measures such as preoperative evaluation and treatment of patient diseases or pre-use checkout of life support equipment. Once a problem occurs, it may remain self-limited, or it may evolve further down the accident chain. Using dynamic decision making, the anesthetist must detect and correct problems that do occur at the earliest possible point in the chain of evolution. The interruption of the accident chain is made more difficult when there is tight coupling within the system, when there are multiple interacting problems, or when problems disrupt recovery processes. *(From Gaba et al [41])*

---

by the skilled intervention of a trained anesthetist. Note that this is a markedly different picture from that in commercial aviation. Although the accident rate in aviation is very low (for both commuter and major airlines, the 1995 accident rate was approximately 0.4 per 100,000 departures, according to the National Transportation Safety Board World Wide Web page), adverse events in aviation matching the "impact event" criteria given earlier are relatively unusual and come nowhere near to approaching 1 event every 5 flights. The actual number of aviation "impact events" is not known, but it is probably at least 100 times greater than the number of accidents, but even so, this would still make aviation impact events far less frequent than the 3 to 5 percent rate of significant impact events in anesthesia. Based on these data, it is clear that the intraoperative management of dynamically changing events remains the critical locus of anesthesia skill.

Empirical Studies of the Anesthetist's Tasks

Over the past 20 years, there have been a number of studies [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [54] of the anesthetist's intraoperative activities. The earliest studies used time-lapse photography of a handful of anesthetic cases with a frame-by-frame analysis of tasks. One major finding of the first task analysis, by Drui et al in 1973 [44] was that "the anesthesiologist's attention was often directed away from the patient-surgical field." In subsequent studies, [45] [46] [47] [48] it was found that about 40 to 50 percent of the time, the anesthetist's gaze was directed away from the patient or surgical field. McDonald and Dzwonczyk, [47] studying cases from 1981, classified a direct patient activity as "one during which the anesthetist had contact with the patient and a view of the surgical field." These investigators explicitly noted "observation of skin color," "palpation of pulse," and "auscultation of heart and breath sounds" as direct patient activities. Observing the arterial pressure or ECG and

observing or adjusting the anesthesia machine or intravenous infusions were classified as indirect patient activities. In this study, 83 percent of the anesthetist's time was spent on activities that were not direct patient activities. The same group [48] repeated its study in 1985 and demonstrated a much higher rate of direct patient monitoring than obtained in 1981 (44.8 versus 16.8%). This group attributed this difference to the change from manual ventilation in 1981, which took up much of the anesthetist's visual attention, to the use of mechanical ventilators in 1985, which freed the anesthetist to watch the patient.

It has become a truism that looking at the patient and at the surgical field is a hallmark of an excellent clinician. Opponents of technology decry the degree to which monitors and therapeutic devices distract the anesthetist's gaze from the patient. However, an important distinction has to be made between the anesthetist's attention, which surely must be directed to the patient's needs, and the anesthetist's gaze, which, in fact, may best serve the patient by being directed elsewhere. Many of the tasks cited in the McDonald and Dzwonczyk study [47] were highly related to the management of the patient, even though they did not involve direct visualization of or contact with the patient. The critical question, which task analysis by itself cannot answer, is this: When anesthetists gaze at the surgical field, how often are they gathering information, and how often are they just "watching the scenery"? Put more generally, what is the information content of the various observations being made and what is their relation to action tasks and to the goals of conducting a safe anesthetic regimen?

Intriguingly, Drui et al [44] had asked physicians who were helping to code their films to consider "what information, if any, do you gain from the direct performance of this activity?" However, these investigators never described what information was available from each activity, although they seem to have assumed that turning the anesthesiologist's gaze away from the patient and surgical field was bad. Boquet et al [45] not only studied the gaze of anesthetists (using a sophisticated eye tracking system), but they also asked consultant anesthetists to grade the importance of different visual targets and manual tasks. "The patient" was assigned the maximal importance on the scale. However, "the surgical field," which occupied 25 percent of the anesthetist's time (
10 s/gaze), was apparently not listed by the consultants. Perhaps, in their minds, the surgical field was lumped together with the patient.

Another key finding of the study by Drui et al [44] was that 40 percent of the anesthetist's time was coded as "idle," meaning that no obvious task was seen on that frame of film. In 1988, McDonald and Dzwonczyk [47] stated that this and other "studies showed that the anaesthetist spends most time performing tasks that are either secondary or unrelated to patient care." However, in their original article, Drui et al [44] correctly recognized that the absence of visually apparent activity did not mean that the anesthetist was truly idle; in fact, they hypothesized that this time was used by anesthetists to make the decisions on which the observable tasks were based.

The most detailed task analyses have taken place in a series of studies [49] [50] [51] [52] [53] [54] carried out by a collaboration of investigators from the University of California San Diego (UCSD, primarily involving Weinger and Herndon) and from the Department of Veterans Affairs (VA) and Stanford University (Gaba). These analyses have used progressively more task categories (11 to 28 to 32) to analyze the activities of novice and experienced anesthetists in day surgery cases and of senior residents during cardiac surgery. These studies have shown that a small number of tasks, repeated frequently, occupy the majority of case time. In one study, four tasks (observing monitors, recording, conversing with attending staff for novice residents, and adjusting monitors) accounted for 50.1 percent of total case time. Specific activities such as airway management (e.g., bag ventilation, laryngoscopy) occurred in brief, but intense clusters (Fig. 80-4) . Given the larger number of task categories, the anesthetist was rarely seen to be idle.

These studies have attempted to determine whether there is a difference between the task patterns of novice versus experienced anesthetists. Confirming a priori expectations, these investigators found that novices perform many of the same tasks as do experienced personnel at specific phases of an anesthetic regimen, but the novices had a longer dwell time, on average, for each task. These investigators also found that experienced providers had a lower heterogeneity of tasks and greater efficiency of tasks per unit time. [53]

Of note (but also not unexpected), novice residents spent more time speaking to their attending staff (
11% of preintubation

Figure 80-4 Distribution of the anesthetist's tasks during an actual ambulatory surgery procedure. The anesthetist was directly observed by an investigator who recorded a code number for each task as it was performed (there were 28 task codes). Certain tasks, such as bag ventilation, were clustered in specific phases of the case, whereas others, such as observing monitors, were repeated frequently throughout the case.

time) than did experienced residents or certified registered nurse anesthetists (CRNA). Interestingly, experienced personnel observed the surgical field more than did the novices by roughly the same proportion of time. Again, the implications of this finding are not clear. Novices did take longer to complete patient preparation and anesthesia induction, but it appeared that some of the extra time taken by novices working under supervision was offset by the efficiency of off-loading concurrent other tasks to the attending anesthesiologist, such that preintubation time was increased by only 6 minutes for novices. [53] This group also reported that as the density of tasks per unit time increased, the dwell time on each task decreased, and vice versa. This finding has important implications for how anesthetists allocate their attention (see *Management and Coordination of the Core Process*).

Automation

The early task analyses identified repetitive tasks that did not appear to offer substantial information content or therapeutic benefit as candidates for automation. Drui et al [44] identified filling out anesthesia records, measuring the blood pressure, and adjusting intravenous infusions. Kennedy et al [46] identified data display and trend plotting. Many of these tasks have, in fact, been automated in the last 20 years. Loeb, [55] from the University of California, Davis (UCD), showed that anesthesiologists typically observed monitors for about 1 to 2 seconds every 10 to 20 seconds, and they usually took several observing cycles before detecting a subtle cue on the monitor. Gurushanthaiah et al [56] studied the effect of more sophisticated display modalities on the signal detection of anesthesiologists and found that histogram and polygon formats improved response latency in the laboratory setting compared with formats using raw numbers only. However, the applicability of this laboratory finding to the more complex signal detection that must occur in the midst of patient care is uncertain. Incidentally, the experience in aviation suggests that automation of both monitoring and therapeutic devices produces its own problems in human-machine interactions and may well be a causative or contributing factor in some adverse anesthetic events. Some of the same types of automation-related adverse events seen in aviation [57] [58] are now being observed in anesthesiology. [59] [60]

The impact of automation on task distribution is uncertain. The change to mechanical ventilation did affect the analyses of McDonald and Dzwonczyk, [47] as detailed earlier. A study by Dzwonczyk et al [61] showed no reduction in time spent recording when automated record-keeping devices were used. However, the UCSD/VA-Stanford collaboration published data demonstrating a 20 percent reduction in the time spent record-keeping when automated record-keeping was in use during cardiac anesthesia. [52] [54] There was a slight, but not significant, increase in time spent on direct patient care activities when electronic record-keeping was in use. Thus, there is no clear evidence that electronic record-keeping will yield a marked enhancement of the anesthetist's ability to perform other patient care tasks, although automated record-keeping may yield other benefits. Both the UCD and UCSD/VA-Stanford groups demonstrated that electronic automated record-keeping does not significantly reduce the vigilance of anesthetists. [54] [62]

Mental Workload of Administering Anesthesia

The observable tasks do not tell the whole story of what the anesthetist is doing. As Drui et al [44] suggested, there is mental activity going on even when the anesthetist appears idle. What, then, is the mental workload of administering anesthesia? Mental workload is another concept that is readily understood but difficult to define precisely. There are various ways to measure workload, none of which is ideal. The primary task performance measure assesses the subject's performance on the standard work tasks as they are

made progressively more difficult by increasing the number of tasks, the task density, or the task complexity. At first, the subject is able to keep up with the increasing task load, but at some point, the workload exceeds the ability to manage it, and performance on the standard tasks decreases. The disadvantage of the primary task performance measure is that, in many complex task domains, there is no accepted way to measure objectively the subject's performance on the primary work tasks except by loading to the point of catastrophic performance failure, which is easily detected. In actual high-risk domains, one cannot allow primary task performance to

degrade, and certainly not to fail catastrophically. Although experiments of this type are in principle feasible using anesthesia simulators, they have not yet been attempted.

Secondary Task Probing

A more useful technique, secondary task probing, tests the subject with a minimally intrusive secondary task that is added to the primary work tasks. The secondary task is a simple one for which performance can be objectively measured, and the subject is instructed that the primary tasks of patient care take absolute precedence over the secondary task. [63] Therefore, assuming that the secondary task requires some of the same mental resources as the primary task, the performance of the subject on the secondary task is an indirect reflection of the spare capacity available to deal with it, and thus it is an inverse measure of primary task workload (the greater the spare capacity, the lower the primary workload). Secondary tasks such as reaction time (with or without choice), finger tapping, and mental arithmetic have been used for this technique in the psychology laboratory, in high-fidelity simulators, and in some field studies of actual work situations. [63]

Gaba and Lee [64] presented two-digit addition problems on a computer screen placed in the anesthesia workspace at random approximately every 45 seconds. The delay in responding to problems and the number of problems skipped were logged over time and were correlated with a concurrent six-category task analysis. The dynamic ebb and flow of mental workload during cases of varying complexity was documented. For example, cardiopulmonary bypass was confirmed as a time of very low workload for the anesthetist, whereas the induction of anesthesia was confirmed as a period of high workload. Manual tasks and conversing with the attending were correlated with a delayed or absent response to the secondary task.

Subsequent studies by the UCSD/VA-Stanford group [53] [54] and the UCD group [55] [62] [65] used the reaction time to a changing display in or around the clinical monitors as a secondary task to assess mental workload and/or vigilance. For the UCSD/VA-Stanford group, the display was a red light placed next to the main physiologic monitor. This secondary task was analogous to, but totally separate from, the standard tasks of clinical work. When the secondary task was embedded in the regular work tasks, it was called an *embedded task.* The UCD group used a secondary task involving recognition of changes in the alphanumeric display of an unused channel of an actual clinical monitor (a parameter labeled "Vig" on the monitor changed values from "5" to

Figure 80-5 Test of the anesthetist's vigilance. The figure shows the mean reaction time of novice residents and experienced anesthetists to the illumination of a red light placed next to the electrocardiogram monitor display during actual ambulatory surgery procedures. For both groups, reaction was faster in the maintenance phase than during induction of anesthesia. Novices reacted significantly more slowly than did experienced anesthetists. Because the distribution of reaction times was asymmetric and nongaussian, error bars are not shown, and nonparametric statistics were used for hypothesis testing.

"10"). This task was only partially "embedded" because although it did involve an actual clinical monitor, it displayed on an otherwise unused channel and was not of clinical significance. The VA-Stanford group has been experimenting with fully embedded secondary tasks during simulator anesthetic cases, in which the values of actual clinical variables can be manipulated at will to evaluate the subject's response time to the excursion of data values beyond predefined reporting thresholds.

The mean response time to the red light used by UCSD/VA-Stanford was markedly less than 60 seconds for experienced subjects in both the induction and postinduction (maintenance) phases, but it was much higher for novice residents during the induction phase (Fig. 80-5) . The probe was not given frequently enough to track the ebb and flow of workload. The response to the UCD task typically (56%) occurred within 60 seconds, but 16 percent of stimuli overall (27% during the induction period) were not responded to within 5 minutes. The conclusion was that spare capacity may be limited by the workload of the case during certain periods of anesthesia care.

There are several problems with these workload studies. One is interference with the "response channel." If responding to the probe requires manual activity with a mouse or keyboard (as for the studies of Gaba and Lee and UCD), it cannot be performed whenever the subject is occupied with a manual task. This is especially true during a sterile procedure. Thus, it may be impossible to distinguish between a high primary task load (i.e., no spare capacity to address the secondary task) and a low primary task load that happens to usurp the manual response channel. However, in the Gaba and Lee study, [64] 37 percent of the problems that were skipped for lack of spare capacity did not occur during a manual task. The UCSD/VA-Stanford studies have all allowed

multiple response channels (manual, voice, and gesture), so there was no response channel interference, but the potential for interference remains in the UCD studies. An additional problem with all these studies is that even these simple secondary tasks were intrusive when repeated frequently. Thus, there was a tradeoff between the temporal resolution of the measurement and its intrusiveness. There is also controversy about whether these probes measure "vigilance" or "workload," although the same techniques probably measure both aspects of performance. When probes occur infrequently, are subtle, have multiple response channels, and are performed with a low level of existing workload, they are more likely to measure "vigilance," whereas when they are frequent, readily detectable, require manual response, and are performed during a high workload period, they probably are more indicative of spare capacity and workload.

Subjective Measures

A third modality of workload assessment consists of subjective measures in which individuals are asked, either in retrospect or in real time, how much load they were or are under during actual work situations. Subjective measures complement objective measurements because the subjective perceptions of the anesthetist may be an important source of stress and anxiety; conversely, an anesthetist may subjectively underestimate the workload in settings in which objective measurements demonstrate a marked reduction in spare capacity.

Various scales have been proposed to measure dimensions of mental workload that are, in theory, different. [63] However, Gaba and Lee [64] adapted a set of workload scales from those used at the National Aeronautics and Space Administration (NASA) [66] and showed that workload ratings on each of the scales were highly correlated. In subsequent studies by the UCSD/VA-Stanford group [53] a single dimension of overall load was assessed using an asymmetric numeric scale that minimized biases caused by a tendency to group responses at the middle and extremes of symmetric scales. This group demonstrated that a neutral observer can estimate the subjective workload of the anesthetist in real time with a high correlation to the self-rated workload of the subject. Again, as could be expected, subjective workload was highest during induction and emergence from anesthesia, especially for novices.

Physiologic Measures

The final set of techniques for assessing workload consists of physiologic measures. Visual or auditory evoked potentials have been used successfully to assess mental workload, but this technique can only be used in a static laboratory environment. Heart rate is a relatively easily measured variable that may be altered by mental workload. Toung et al [67] [68] showed that the anesthetist's heart rate increases at the time of intubation, and the amount of increase is inversely related to the amount of overall medical training. Azar et al [69] found that anesthesia faculty members' heart rate and blood pressure increased during induction of anesthesia, and one individual developed significant ST-segment depression. Bitetti et al [70] confirmed that heart rate changes occurred during anesthesia, but these did not always correlate with contemporaneous self-recordings of "stress."

Because of the many factors that affect heart rate, the beat-to-beat variability of heart rate is thought to be a better indicator of mental workload. [63] The frequency components of heart variability can be separated by spectral analysis; a component at 0.1 Hz has been linked to mental workload. Although several groups have acquired heart rate data on anesthesiologists, none has reported an analysis of the workload-related frequency components.

Applications of Task Analysis and Workload Methodologies

The results of the task analyses and workload measurements have primarily provided objective confirmation for a number of intuitive beliefs about anesthesia practice. The real importance of these studies is that a coherent methodology has been developed that may be useful for studying a variety of interesting questions. The question of the impact of electronic automated record-keeping systems is addressed earlier. Another question concerns transesophageal echocardiography (TEE). This new monitoring modality has become commonplace during cardiac anesthesia and anesthesia for other patients with cardiovascular disease who undergo

complex operations. It is widely recognized that evaluating TEE images and manipulating the TEE probe require substantial visual and mental attention.

The UCSD/VA-Stanford group published data suggesting that vigilance (as measured by response latency to illumination of a red light) was substantially lower when the anesthesiologist was involved with manipulating, adjusting, or examining the TEE compared with other patient care tasks [54] (Fig. 80-6) (Figure Not Available) . This may be due, in part, to the layout of the workspace. The TEE machine is large and is often placed near the left side of the head of the OR table, whereas the anesthesia machine and attendant monitors, by convention, are typically placed near the right side of the head of the table. Remote displays slaved to the primary monitor are also more likely to be on the patient's right side. This arrangement makes it difficult physically to glance from one modality to another. The degree to which the mental concentration required to use TEE itself detracts from vigilance for other signals remains to be determined explicitly. Furthermore, it is important to differentiate the different uses of TEE. When it is used to answer specific clinical questions triggered by events or milestones during the procedure, the value of the information may be worth an investment of effort, even with a reduction in overall vigilance. When it is used as a continuous monitor for myocardial ischemia, or when conducting a detailed routine examination, the reduction of vigilance must be considered when evaluating the potential benefits of the technology. Some practitioners describe special ways to handle the attention requirements of TEE, including tightening alarm thresholds (to provide audio warnings of changed values) or assigning specific patient monitoring functions to another individual while conducting the initial TEE placement and examination.

Figure 80-6 (Figure Not Available) Vigilance test data during anesthetic tasks with and without automated record-keeping. The figure depicts the range of data for each of four task categories for electronic automated record-keeping (EARK) and for manual record-keeping (MAN). Each box contains 50 percent of the data for that subgroup (upper limit of box is 75th percentile; lower limit is 25th percentile), whereas the maximum and minimum are shown by the upper and lower bars. The response latency during record-keeping was not significantly different between EARK and MAN. In both record-keeping groups, subjects had significantly slower responses when observing or adjusting the transesophageal echocardiogram (TEE) when compared with record-keeping, observing monitors, or adjusting intravenous lines* ($P < .05$). Subjects in both groups had faster response latency when observing the monitoring array, which contained the red light; $P < .05$ compared with all three other tasks. *(From Weinger et al [54])*

There remain many other interesting questions concerning the performance of anesthetists that can be addressed with the techniques of task analysis and workload and vigilance assessment, including the following:

1. How do the task load and task density differ between private practice settings and academic settings?
2. How do the work patterns of novices change to become those of "experts"? How can the training of novices be focused to support these changes best? Is suboptimal performance of novices detectable through analysis of task distributions and mental workload?
3. How much task load can the average, single anesthetist handle? How are tasks distributed among personnel (i.e., between resident and faculty, between CRNA and supervisor, or among staff anesthetists) during the high-workload periods of patient care? This question is just beginning to be addressed (by the UCSD/VA-Stanford study) by applying the task-analysis techniques described earlier to videotapes of actual anesthetic cases. Using the tape, the task sequences of multiple anesthesia personnel can be elicited separately, as can the communications used to coordinate their activities.

OTHER STUDIES OF "VIGILANCE" AND DECISION-MAKING BY ANESTHETISTS

Studies of "Vigilance"

The dominant metaphor for the mental activity of the anesthetist has been that of a vigilance task. "Vigilance" is the motto on the seal of the ASA. What is vigilance, and to what degree does it capture the complex nature of the anesthetist's work? "Vigilance, or sustained attention refers to the ability of observers to maintain their focus of attention and to remain alert to stimuli for prolonged periods of time" (J. Warm, presentation at the Panel on Vigilance, ASA annual meeting, 1992). There is an enormous literature concerning vigilance. Many laboratory studies have demonstrated vigilance decrements during prolonged vigilance tasks, which are exacerbated or ameliorated by a variety of factors. These studies have generated considerable controversy. Some psychologists believe that the results of laboratory studies of vigilance have little application to complex real-world task domains. [71] [72] Certainly, the anesthetist's work involves vigilance as a necessary component, because if new stimuli are not perceived, no meaningful work can be accomplished. However, the anesthetist's task is much more complex than just vigilant alertness to stimuli. Therefore, vigilance is a necessary but not sufficient condition for appropriate performance. [14]

Several studies have attempted to quantitate the vigilance of anesthetists to changes in clinically important variables using low-fidelity simulation. Beatty et al [73] had anesthetists watch for changes in displays of six vital signs on a video monitor. Denisco et al [74] used videotapes containing abnormal changes of anesthesia flowmeter settings and physiologic monitor displays. The raw reaction times were not reported, only the "vigilance scores." These studies purported to demonstrate a degradation of performance for sleep-deprived and fatigued residents, but there were methodologic flaws. For example, in the study of Denisco et al, [74] the subjects were never told the threshold of change for them to report. In addition, the work environment of the anesthetist is much more complex than that presented in these low-fidelity simulations. Although it could be argued that complexity would worsen vigilance performance, this is not necessarily the case. Complexity can combat boredom, which is a distinct possibility in vigilance experiments. In addition, the real work environment often provides redundant data cues of changes, offering multiple possibilities for their detection.

A study of rested anesthetists [75] using a realistic anesthesia simulator (see the section on simulators later) measured detection

times (first awareness of a problem) for a variety of intraoperative events embedded within a realistic case situation. Interestingly, an event that caused alarms to sound immediately, such as ventricular tachycardia/fibrillation, was detected in 10 seconds or less (confirming its veracity and acting on it took longer in many instances, however). Another event, occlusion of the intravenous line, was detectable only by visual observation in the direction opposite from the anesthesia machine and monitors. This event took several minutes (on average) to detect, but it was corrected quickly after detection. The redundancy of cues in the task domain was confirmed in that 6 different observational modalities were used by at least 1 of the 19 residents studied to detect an endobronchial intubation initially.

Other vigilance studies have focused on detecting the loss of an existing monitoring modality during actual patient care. In one study, [76] the esophageal stethoscope was occluded with a clamp following a staged distraction (conversation or a loud noise). Subjects most commonly detected the occlusion by observing the clamp, rather than by noting a loss of sound. Although this study purported to show a difference in vigilance related to the use of automatic blood pressure measurement devices, the artificial distraction could have biased the results, the subjects typically failed to hear the loss of sounds, and there was a significant result only for one group of residents, arbitrarily stratified by length of training. Another study [77] that evaluated reaction time to loss of esophageal stethoscopy more carefully showed that 13 percent of occlusions were detected after 1 minute. However, this study required a manual response, and the investigators noted that in some instances of delay, the subject was involved in a manual clinical activity such as administering blood or drugs.

Apparent reductions in vigilance could be due either to a reduction of "spare capacity" to attend to the stimuli immediately or to a reduction in the overall alertness of the anesthetist. Enhancements in the display and annunciation of relevant information would be a useful ameliorative strategy in the first case, whereas this strategy would not be useful if the anesthetist's overall alertness is impaired, as by sleep deprivation or illness.

Empirical Studies of Complex Decision-Making and Action by Anesthetists

Traditional concepts of decision-making in medicine have concentrated on relatively static, well-structured decisions. For example, should patient A with an elevated blood pressure be treated for hypertension with drug X, or should no treatment be started? [78] Other investigators have looked only at "diagnosis" as an isolated task (specifically "diagnostic explanation") both in internal medicine [79] [80] [81] and in radiology. [82] These approaches to decision-making have not captured the unique aspects of dynamism, time pressure, and uncertainty seen in anesthesiology. Over the past decade, a paradigm has emerged concerning decision-making and action in complex real-world situations. [8] [17] [25] [26] [83] [84] [85] [86] [87] [88] Several teams both from inside the anesthesiology profession and from the human performance community have been striving to develop a more comprehensive understanding of the complex performance of anesthetists. Their work has been based on a small number of new experiments (often involving medium- or high-fidelity anesthesia simulators), the reinterpretation of previous experiments, direct and indirect observation of the conduct of anesthesia, and extrapolations from other industries to anesthesiology. Because each experiment has probed several aspects of decision-making and action, these results are described first, before describing cognitive models that synthesize the results.

Responding to Simulated Critical Incidents

Using a realistic hands-on anesthesia simulator, Gaba and DeAnda [75] [89] [90] studied the response of anesthesia trainees and experienced anesthesia faculty and private practitioners to six preplanned critical incidents of differing type and severity: (1) breathing hoses too short to turn the table 180 degrees, as requested by the surgeon; (2) endobronchial intubation (EI) resulting from surgical manipulation of the tube; (3) intravenous tubing occlusion; (4) atrial fibrillation (AF) with rapid ventricular response and hypotension; (5) disconnection between the endotracheal tube and the breathing circuit; and (6) ventricular tachycardia/fibrillation. These investigators measured both the detection time (as described in the section on vigilance) and the correction time (the time from the event's onset until any one of a predefined set of corrective actions was first taken). They assessed the information sources by which subjects detected the incidents and then confirmed and diagnosed the problem. They asked subjects to "think aloud," to allow subjective analysis of their decision-making strategies. A summary of the data is shown in Figure 80-7 (Figure Not Available) . Major findings from this set of studies included the following:

1. *Events differed from each other in their inherent ease of solution.* Some events (airway disconnection) were rapidly detected and corrected. Some problems (intravenous occlusion) were difficult to detect, but once they were detected, the diagnosis and therapy were rapidly achieved. Other problems (EI, AF) were easy to detect, using one of several redundant information sources as the first clue (six for EI, four for AF), but they required additional time (7-8 minutes for EI; 1.5-4.5 minutes for AF) to confirm the abnormality, to establish a diagnosis, and to initiate appropriate therapy. Diagnosis and the planning and monitoring of therapy used a large number of information sources (11 for EI; 9 for AF).
2. *For each incident, there was considerable interindividual variability in detection and correction times, in information sources used, and in the actions taken.* In

each experience group, there were some who required excessive time to solve the problem or who never solved it. In each experience group, at least one individual made major errors that could have had a substantial negative impact on a patient's clinical outcome. For example, one faculty member never used electrical countershock to treat ventricular fibrillation. One private practitioner treated the EI as if it were "bronchospasm" and never assessed the symmetry of ventilation. One resident never found the airway disconnection.

3. *The average performance of the anesthetists tended to*

improve with experience, although this varied by incident. The performance of the experienced groups was not definitively better than that of the second-year residents (who were in their final year of training at that time). Many (but not all) novice residents performed indistinguishably from more experienced subjects.

4. *The elements of suboptimal performance were both technical and cognitive.* Technical problems included choosing defibrillation energies appropriate for internal paddles when using external paddles, ampule swap, and failure to inflate the endotracheal tube cuff, resulting in a leak. Cognitive problems included failure to allocate attention to the most critical problems and fixation errors.

Figure 80-7 (Figure Not Available) Response times of anesthesiologists with different levels of experience to four simulated critical incidents: (A) Endobronchial intubation, (B) intravenous occlusion, (C) atrial fibrillation, and (D) airway disconnection. Detection time is shown with open circles, and correction time is shown with filled circles (see text for definitions of these times). Unless there is overlap between response times, each circle represents a single individual. The scale of response times is different for each event. There is substantial variability among incidents and among individuals. Although there was a trend to better performance with increased experience, major errors were made by individuals in all groups. *(From DeAnda and Gaba [90])*

Schwid and O'Donnell, [91] from the University of Washington, used the Anesthesia Simulator Consultant (ASC) screen-only simulator to perform an experiment similar to those of Gaba and DeAnda using a realistic simulator. This method enabled them to evaluate some elements of anesthetist behavior more carefully, albeit with the limitations imposed by presenting the OR "on the screen." After working on several practice cases without critical incidents, each subject was asked to manage three or four cases involving a total of four serious critical events (esophageal intubation, myocardial ischemia, anaphylaxis, and cardiac arrest). The progression of each event was mediated by the interaction of physiologic and pharmacologic models with the actions taken by the subject. The anesthesiologists studied had varying experience levels. One group was made up of ten anesthesia residents with at least 1 year of anesthesia training, whereas the other two groups contained ten anesthesia faculty members and ten private practitioners, respectively.

Major findings of the study included the following:

1. Significant errors in diagnosis or treatment were made in every experience group (Table 80-1) (Table Not Available) . The errors occurred

for both diagnosis of problems and for deciding on and implementing appropriate treatment. For example, 60 percent of subjects did not make the diagnosis of anaphylaxis despite available information on heart rate, blood pressure, wheezing, increased peak inspiratory pressure, and the presence of a skin rash. In managing myocardial ischemia, there were multiple failures (Table 80-2) (Table Not Available) .

2. Thirty percent of subjects did not compensate for severe abnormalities while considering diagnostic maneuvers.
3. Fixation errors were frequent in which initial diagnoses and plans were never revised, even when they were clearly wrong.

TABLE 80-1 -- Incidence of Totally Correct Diagnosis or Treatment of Simulated Critical Incidents Using the Anesthesia Simulator Consultant

(Not Available)

From Schwid and O'Donnell [91]

Westenskow et al [92] used a test lung and remotely activated faults in the breathing circuit to test the anesthetist's ability to identify faults related to ventilation and the anesthesia breathing circuit after hearing an alarm. One group of subjects used standard alarms, set to factory defaults, of an Ohmeda Modulus II anesthesia machine, which included a capnograph. The other group used the same anesthesia machine with the alarms disabled along with a neural network-based intelligent alarm and fault identification system. The mean "human response time," which was the time between the sounding of the first alarm and the time of event identification, ranged from approximately 15 seconds for airway disconnection to approximately 90 seconds for an endotracheal tube cuff leak. The 10 anesthesiologists tested with the standard alarm setup were unable to identify the fault within 2 minutes on 11 occasions--5 cuff leaks, 3 airway obstructions, and 3 stuck-open expiratory valves. However, in such circumstances, they did take appropriate compensatory actions while continuing to search for the cause (e.g., increasing the fresh gas flow to compensate for a cuff leak).

The intelligent alarm apparatus used data from three sensors (in-line capnograph, spirometer, and airway pressure). A neural network determined whether any of seven faults was present, and if so, displayed a text message specifying the fault as well as an animated diagram of the lung, airway, and anesthesia breathing circuit with the faulty component highlighted in red. Interestingly, the smart alarm system took slightly longer on average to detect a fault than did the conventional alarm system (25 versus 21 seconds), but the human response time was markedly reduced for three of the seven faults. There were no statistically significant differences between anesthesia residents and faculty members using either alarm system.

The investigators suggested that the more specific alarm messages in their intelligent alarm system could direct the attention of the anesthetist to the occurrence of specific problems and in so doing would decrease workload and reduce the likelihood of fixating on inappropriate information. They stated that such a system's advantages would be even greater in a more realistic clinical environment in which the anesthetist has multiple complex tasks, not just the detection and identification of ventilation-related events.

Complex, Multiple Personnel Simulations of Anesthetic Crises

In the process of evaluating a new type of training for anesthetists concerning crisis management, Howard et al [93] collected anecdotal data on the responses of teams of anesthetists, surgeons, and nurses to planned (and unplanned) critical events. These experiments largely confirmed the results of the studies described earlier and extended them to

TABLE 80-2 -- Failure Rate in the Management of Simulated Myocardial Ischemia Using the Anesthesia Simulator Consultant

(Not Available)

From Schwid and O'Donnell [91]

include more complex management issues and team interactions. Howard and coworkers found a substantial incidence of difficulties in managing multiple problems simultaneously, applying attention to the most critical needs, acting as team leader, and communicating with personnel and using all available OR resources to best advantage.

Botney et al [94] [95] analyzed similar videotapes from 18 different simulator training sessions on crisis management. In one event, a volatile anesthetic vaporizer had been left on at 4 percent and was hidden beneath a printout from the noninvasive blood pressure monitor. Simultaneously, there was a mechanical failure of the capnograph, making it impossible to confirm endotracheal intubation using CO_2 measurements. This event purposefully presented an invitation to become fixated on the endotracheal tube while ignoring other relevant information. Five of 18 subjects never discovered the volatile anesthetic overdose despite catastrophic effects on blood pressure and heart rate and clear evidence that the endotracheal tube was correctly placed. Of those who did detect the vaporizer setting, the average time to

detection was nearly 4 minutes, with some subjects taking more than 12 minutes.

In the second event studied, there was a loss of pipeline O_2 supply while an anesthetist was assuming the care of a critically ill patient who required an inspired O_2 fraction (F_{IO_2}) of 100 percent to achieve satisfactory blood oxygenation. The O_2 cylinder on the machine was empty (i.e., it had not been checked by the initial anesthetist, who left the case after becoming ill). The pipeline failure was quickly detected (19 seconds), but the responses to it were extremely variable and showed a variety of problems. Five of 18 anesthetists closed the anesthesia circuit (which preserves the existing oxygen in the circuit), but all 5 subsequently switched to ventilation with a self-inflating bag using room air or to mouth-to-tube ventilation. Five of 18 could not open the reserve oxygen cylinder because they could not locate the tank wrench attached to the machine (it tended to rest between two gas cylinders). Several teams had trouble in mounting a new oxygen tank on the anesthesia machine; problems with the gasket disk were frequent. The individuals did not appear to have a well-formulated plan for managing this event, and they did not optimally coordinate their actions with their assistants or with the other OR personnel.

Indirect Observation of Anesthetists Involved in Difficult Cases

An unusual approach involving indirect observation of actual cases was used by Cook et al [9] at the Ohio State University. Rather than collecting data on the case itself, these investigators transcribed the discussions of interesting cases occurring at a weekly quality assurance conference. They argued that this approach allowed them to apply a "neutral observer criterion" to the behavior of the anesthetist. The investigators acknowledged the risks of hindsight bias and selection bias of this methodology, but they suggested that their technique provided a unique window on human performance issues.

Fifty-seven cases were analyzed, of which 21 had a full cognitive analysis for the final report. From the presentation and discussion of a case, the investigators classified the evolution of the events into one of five categories: acute incident, going-sour incident, inevitable outcome incident, difficult airway incident, and no-incident incident. For each case, the cognitive analysis was "based on using knowledge about the cognitive demands of the task domain and data about practitioner activities to analyze practitioner's information processing strategies and goals, given the resources and constraints of the situation." The investigators postulated a cognitive cycle described by Neisser [96] as a component of data-driven activation of knowledge and knowledge-driven observation and action.

Cook et al [9] called attention to several issues that surfaced in their cognitive analysis of these cases. These include the following:

1. *Multiple themes.* Many cases involved several lines of concern simultaneously, each of which could have interacted with another (e.g., tight coupling). Each theme had multiple means available to deal with it. Maintaining "situation awareness" was important. The multiple themes sometimes generated competing or conflicting goals. Adaptive planning (as described in the section on the abstract task analysis) was sometimes required.
2. *Unusual situations.* The greatest expertise was seen with infrequent or unusual situations, rather than with typical situations.
3. *Allocation of attention.* The allocation of attention to relevant stimuli or to the most important "theme" was an important issue. The attentional shifts were not always well supported by existing alarm and display technologies.
4. *Cognitive workload.* Anesthetists attempted to reduce their cognitive workload whenever possible.
5. *Team interaction.* Cooperative work, team interaction, and communications issues were problems in several cases. These stemmed from both individual and organizational failures to coordinate information and efforts from different organizational components (e.g., ICU and OR, or surgeons and anesthesiologists).

Direct Observation of Anesthetists

A team of cognitive scientists and anesthesiologists at the University of Toronto [97] [98] conducted direct observations of anesthesiologists and obtained verbal "think aloud" protocols during actual case management. Their work centered on the active management of workload and is discussed later in this chapter.

Video Analysis of Actual Trauma Resuscitations and Anesthetics

Mackenzie et al [99] [100] [101] pioneered the analysis of actual clinical care of anesthetists captured on videotape, focusing on trauma resuscitations and anesthesia of trauma patients at the Maryland Shock Trauma Unit. The sophisticated recording system captures audio, video, and vital signs data and only requires the clinicians to insert a videotape to start the whole system. Analyses of these cases have revealed inadequacies in the availability and arrangement of monitoring

equipment, nonexistent or ambiguous communication, and weak interactions between the anesthesia care team and the surgical team. [101]

Problems faced by all investigators are the lack of an accepted standard for objective or subjective evaluation of anesthetist performance and the absence of an agreed-on methodology for analyzing and describing anesthetist performance. Several of the previously mentioned groups are working on methodologies for evaluating both technical and behavioral aspects of performance. [102] [103] [104] [105] [106] [107] The measurement of complex performance is a difficult problem, and it is likely to be some time until there is a well-established metric for performance assessment (see the later section on performance evaluation using patient simulators).

COGNITIVE PROCESS MODEL OF THE ANESTHETIST

The empirical data can best be interpreted in accordance with an explicit model of the cognition involved in the anesthetist's performance. Several investors [9] [10] [14] [39] [40] [41] [60] [97] [98] [108] [109] [110] [111] [112] [113] [114] have written about the cognitive elements in anesthesiology. The model I have developed is explicit, comprehensive, and specific to anesthesia. It is described in detail as a framework for understanding the empirical data and provides a vocabulary for discussing the elements of both successful and unsuccessful performance by anesthetists. However, this model draws heavily from the work of Woods and Cook and from a number of other investigators [8] [9] [18] [83] [84] [85] [86] [87] [115] [116] [117] [118] [119] [120] [121] [122] [123] studying human performance in a variety of complex, dynamic worlds.

Decision-Making Involves Multiple Levels of Mental Activity

The model (Fig. 80-8) (Figure Not Available) depicts the anesthetist as working at five different interacting cognitive levels to implement and control a core process of observation, decision, action, and reevaluation. The core process must then be integrated with the behavior of other team members and with the constraints of the work environment.

The division of mental activities into levels follows the work of Rasmussen [17] [86] [124] and Reason. [8] [125] [126] Having multiple levels supports parallel processing (performing more than one task at a time) and multitasking (performing only one task at a time, but switching very rapidly from one task to another). The anesthesia task analyses [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [54] and the direct observations of anesthetists in Toronto [97] [98] have provided clear evidence for the occurrence of parallel processing and multitasking.

At the sensorimotor level, activities involving sensory perception or motor actions take place with minimal conscious control; they are smooth, practiced, and highly integrated

Figure 80-8 (Figure Not Available) Cognitive process model of the anesthetist's real-time problem-solving behavior (see text for detailed description). Five levels of cognition operate in parallel. The core process involves a main loop (heavy black arrows) of observation, decision, action, and reevaluation. The core process is managed by two levels of metacognition, involving supervisory control, allocation of attention, and resource management (above the core process). Each component of the model requires different cognitive skills, and each component is vulnerable to a different set of performance failures or "errors." BP, blood pressure; CO, cardiac output; MAP, mean arterial pressure; SVR, systemic vascular resistance. *(From Gaba et al [41])*

patterns of behavior. At the procedural level, the anesthetist performs regular routines in a familiar work situation. These routines have been derived and internalized from training and from previous work episodes. A level of abstract reasoning is used during preoperative planning, and intraoperatively it is used in unfamiliar situations for which no well-practiced expertise or routine is available from previous encounters.

Dynamic Adaptation of the Anesthetist's Thought Processes

Rasmussen's model [17] [86] [124] was extended by the explicit addition of two additional levels of mental activity that provide for dynamic adaptation of the anesthetist's own thought processes. This ability to "think about thinking" in order to control one's own mental activities strategically is called *metacognition* by psychologists, [83] [121] and it is thought to be an important component of working in complex, dynamic domains. Supervisory control is concerned with dynamically allocating finite attention between routine and nonroutine actions, among multiple problems or themes, and among the five cognitive levels. Resource management deals with the command and control of available resources, including teamwork and communication. [127] [128]

Core Process

Observation

Management of rapidly changing situations requires the anesthetist to assess a wide variety of information sources. These include visual observation of the patient and the surgical field, visual inspection of a multitude of displays from electronic monitors, visual observation of the activities of nurses and the contents of suction cannisters and sponges, listening for normal and abnormal sounds from the patient and equipment; interpreting radiographs, and the reading of reports of laboratory test results. Because the human mind can only attend closely to one or two items at a time, the anesthetist's supervisory control level must decide what information to attend to and how frequently to observe it.

The multitasking involved in observing multiple data streams was probed by the experiments measuring secondary task performance and vigilance. The realistic simulation studies demonstrated the large number of information sources actually used during the response to a critical event. Routine parts of the core process operate primarily at the sensory motor and procedural levels and are executed repetitively throughout the course of an anesthetic. The results from the UCSD/VA-Stanford group concerning the vigilance of experienced anesthetists compared with novices suggest that the novices had not fully developed their core process as a highly automated function, requiring them to devote more mental resources to routine activities.

Verification

In the OR environment, the available information is not always reliable. Most monitoring is noninvasive and indirect and is therefore susceptible to artifacts (false data). Even direct clinical observations such as vision or auscultation can be ambiguous. Brief transients (true data of short duration) can occur that quickly correct themselves. To prevent them from triggering precipitous actions that may have significant side effects, critical observations must be verified before the clinician acts on them. Verification uses a variety of methods:

1. Repeating the observation or observing the short-term trend.
2. Observing an existing redundant channel (e.g., invasive arterial pressure and cuff pressure are redundant).
3. Correlating multiple related (but not redundant) variables (e.g., heart rate, heart rhythm, and blood pressure).
4. Activating a new monitoring modality (e.g., placing a pulmonary artery catheter).
5. Recalibrating an instrument or testing its function.
6. Replacing an entire instrument with a back-up device.
7. Asking for a second opinion from other trained personnel.

Knowing when and how to verify data is a good illustration of strategic knowledge (metacognition). For example, the anesthetist must decide under what conditions it

is useful to invest time, attention, and energy in establishing a new information source (e.g., a pulmonary artery catheter) in the middle of a case, rather than relying on more indirect information sources that are already in place.

Problem Recognition

Whereas anesthetists are taught the importance of scanning their instruments and environment, they must use these observations to decide whether the patient's course is "on track" or whether a problem is occurring. If a problem is found, a decision must be made as to its identity and its importance. This process of problem recognition (also known as situation assessment) is a central feature of several theories of cognition in complex, dyna-mic worlds. [88] [110] [123] [129] [130] [131] Problem recognition involves matching sets of environmental cues to patterns that are known to represent specific types of problems. Given the high uncertainty seen in anesthesia, the available information sources cannot always disclose the existence of a problem, and even if they do, they may not specify its identity or origin. Westenskow's [92] experiment with the intelligent alarm system mainly probed these parts of problem recognition. In this experiment, subjects were already alerted to the existence of a problem by an alarm, so they could immediately focus their attention specifically on information sources concerning ventilation. In 11 cases, the fault could not be identified, but there was successful compensation for the fault, as described in the next paragraphs.

The supervisory control level mediates the decision when a clear-cut match or "diagnosis" cannot be made. Anesthetists and other dynamic decision-makers use approximation strategies to handle these ambiguous situations; psychologists term such strategies *heuristics.*[132] One heuristic is to categorize what is happening as one of several "generic" problems, each of which encompasses many different underlying conditions. Another is to gamble on a single diagnosis

(frequency gambling [125]), initially choosing the single most frequent candidate event. During preoperative planning, the anesthetist may adjust a mental "index of suspicion" for recognizing certain specific problems anticipated for that particular patient or surgical procedure. The anesthetist must also decide whether a single underlying diagnosis explains all the data, or whether these data could be due to multiple causes. [9] [11] [115] This decision is important because excessive attempts to refine the diagnosis can be very costly in terms of allocation of attention. By contrast, a premature diagnosis can lead to inadequate or erroneous treatment. [133]

The use of heuristics is typical of expert anesthetists and often results in considerable time savings in dealing with problems. However, it is a two-edged sword. Both frequency gambling and inappropriate allocation of attention solely to expected problems can seriously derail problem solving when these gambles do not pay off if the reevaluation component of the core process does not correct the situation.

Prediction of Future States

Problems must be assessed in terms of their significance for the future states of the patient. [88] [110] Those problems that are already critical or that can be predicted to evolve into critical incidents receive the highest priority. Prediction of future states also influences action planning by defining the time frame available for required actions. Cook and Woods [9] described "going sour" incidents in which the future state of the patient was not adequately taken into account when early manifestations of problems were apparent.

Precompiled Responses and Abstract Reasoning

Having recognized a problem, how does the expert anesthetist respond? The classic paradigm of decision-making posits a careful comparison of the evidence with various causal hypotheses that can explain them. [26] This is then followed by a careful analysis of all possible actions and solutions to the problem. This approach, although powerful, is relatively slow and does not work well with ambiguous or scanty evidence. In complex, dynamic domains such as anesthesia, many problems require quick action to prevent a rapid cascade to a catastrophic adverse outcome. For these problems, deriving a solution through formal deductive reasoning from "first principles" is too slow.

In complex, dynamic domains, the initial responses of experts to the majority of events stem from precompiled rules or response plans for dealing with a recognized event. [8] [17] [125] This method is referred to as *recognition-primed decision-making,*[85] [134] because once the event is identified, the response is well known. In the anesthesia domain, these responses usually are acquired through personal experience alone, although there is a growing realization that critical response protocols need to be codified explicitly and taught systematically. [41] Experienced anesthetists have been observed to rearrange, recompile, and rehearse these responses mentally based on the patient's condition, the surgical procedure, and the problems to be expected. [9] [97] Ideally, precompiled responses to common problems are retrieved appropriately and are executed rapidly. When the exact nature of the problem is not apparent, a set of generic responses appropriate for the overall situation may be invoked. For example, if a problem with ventilation is detected, the anesthetist may switch to manual ventilation using a higher F_{IO_2} while considering further diagnostic actions.

However, the experiments involving screen-only [91] and realistic [90] [93] [94] [95] [104] simulators have demonstrated that even experienced anesthetists show great variability in their use of response procedures to critical situations. This finding has led these investigators to target simulator-based training on the systematic training in responses to critical events.

Even the ideal use of precompiled responses is destined to fail when the problem does not have the suspected cause or when it does not respond to the usual actions. Anesthesia cannot be administered purely by precompiled "cookbook" procedures. Abstract reasoning about the problem utilizing fundamental medical knowledge still takes place in parallel with precompiled responses even when quick action must be taken. This seems to involve a search for high-level analogies [8] [125] or true deductive reasoning using deep medical and technical knowledge and a thorough analysis of all possible solutions. Anesthetists managing simulated crises have linked their precompiled actions to abstract medical concepts. [91] It is unclear whether this represented merely self-justification, as opposed to true abstract reasoning, in part because the particular simulated crises they faced did not require novel abstract solutions. At this time, the degree to which abstract reasoning is necessary for optimal intraoperative crisis management is unknown.

Action Implementation

A hallmark of anesthesia practice is that anesthetists do not just write orders in a patient's chart; they are directly involved in implementing the desired actions. Action implementation can usurp a large amount of the anesthetist's attention. In addition, anesthetists engaged in a manual procedure are strongly constrained from performing other manual tasks, as demonstrated in several of the mental workload and vigilance studies described earlier.

Errors in executing a task are termed *slips,* as distinguished from errors in deciding what to do, which are termed *mistakes.*[117] [135] Slips are actions that do not occur as planned, such as turning the wrong switch or making a syringe swap. Thus, when critical incident [136] [137] and quality assurance studies described "technical errors" in using equipment, they were referring to slips, whereas "judgment errors" referred to mistakes. One particular type of execution error, termed a *mode error,*[117] is becoming more frequent in all domains with the increased use of microprocessor-based instrumentation and devices. [58] [59] [60] [138] In a mode error, actions appropriate for one mode of a device's operation are incorrect for another mode. An example in anesthesiology is the "bag/ventilator" selector valve in the anesthesia breathing circuit, which selects between two modes of ventilation. Failing to activate the ventilator when in the "ventilator mode" can be catastrophic. Mode errors can also occur

for monitoring or drug delivery devices if they assign different functions to the same displays or switches depending on the mode of operation selected.

Particularly dangerous slips of execution can be addressed through the use of *engineered safety devices*[13] that physically prevent incorrect actions. For example, newer anesthesia machines have interlocks that physically prevent the simultaneous administration of more than one volatile anesthetic drug. Other interlocks physically prevent the selection of a gas mixture containing less than 21 percent O_2 .

Certain very complex issues concerning human-machine interactions and the ways in which technology affects behavior in complex patient care environments are

beyond the scope of this chapter. Other publications address these issues. [3] [4] [5] [6] [59] [60] [135]

Reevaluation

In order to cope with the rapid changes and the profound diagnostic and therapeutic uncertainties seen during anesthesia, the core process must include repetitive reevaluation of the situation. Thus, the reevaluation step returns the anesthetist to the observation phase of the core process, but with the following specific assessments in mind:

1. Was the initial situation assessment or diagnosis correct?
2. Did the actions have any effect? (e.g., did the drug reach the patient?)
3. Is the problem getting better, or is it getting worse?
4. Are there any side effects resulting from previous actions?
5. Are there any new problems or other problems that were missed before?

The process of continually updating the situation assessment and of monitoring the efficacy of chosen actions is termed *situation awareness.*[88] [123] [129] [130] [131] There has been a review of situation awareness issues in anesthesiology. [110]

Fixation Errors

Faulty reevaluation, inadequate plan adaptation, or loss of situation awareness can result in a type of human error termed a *fixation error.*[116] [140] A fixation error is the persistent failure to revise a diagnosis or plan in the face of readily available evidence that suggests that a revision is necessary. This type of error is extremely common in dynamic situations. There are three main types of fixation errors [116] [140] .

1. This and only this:

   Persistent failure to revise a diagnosis or plan despite plentiful evidence to the contrary.

   Available evidence interpreted to fit the initial diagnosis.

   Attention allocated to a minor aspect of a major problem.

2. Everything but this:

   Persistent failure to commit to the definitive treatment of a major problem.

   Extended search for information made without ever addressing potentially catastrophic conditions.

3. Everything is OK:

   Persistent belief that no problem is occurring in spite of plentiful evidence that it is.

   Abnormalities attributed to artifacts or transients.

   Failure to declare an emergency or accept help when facing a major crisis.

Fixation errors have been described by all the investigators conducting experimental studies of anesthetist responses to abnormal situations. [90] [91] [94] [111]

Management and Coordination of the Core Process

The empirical studies have clearly demonstrated that attention sharing is needed among cognitive levels, among tasks, and often among problems. The intensive demands on the anesthetist's attention could easily swamp the available mental resources. Therefore, the anesthetist must strike a balance between acting quickly on every small perturbation (which requires a lot of attention) and adopting a more conservative "wait-and-see" attitude. This balance must be constantly shifted between these extremes as the situation changes. However, during simulated crisis situations, some practitioners showed a great reluctance to switch from "business as usual" to "emergency mode" even when serious problems were detected. Erring too far in the direction of "wait and see" is an error that can be particularly catastrophic.

In addition to the attentional demands of the anesthetist's core tasks, the OR environment is full of distractions. Routine events, such as turning the OR table or repositioning the patient, distract attention from the main process of conducting the anesthetic. Noise is prevalent, with peak levels exceeding that of a freeway. [141] [142] Practitioners find false auditory alarms from monitors or other equipment to be extremely distracting. [143] [144] [145] [146] [147] Other distractions include teaching in progress, [148] incoming telephone calls, background music, and conversation with OR personnel. Expert anesthetists modulate the distractions, eliminating them when the workload is high while allowing them to occur when workload is low (in order to improve morale and team building).

One major aspect of strategic control of attention is the active management of workload. Rather than passively dealing with rising or falling workload, the anesthetist actively manages it. Schneider and Detweiler [149] and Gopher (position paper, Conference on Human Error in Anesthesia, Asilomar, Calif, 1991) described the theoretical basis for a variety of strategies of workload management. These strategies have been addressed specifically for anesthesiology by several investigators. [9] [40] [41] [97] The anesthetist actively manages workload by the following techniques.

1. *Avoiding high workload situations:* Experts may choose techniques and plans that reduce the workload (especially when their individual and team resources are limited), even when those plans are marginally inferior from a technical standpoint. For example, a single anesthetist may choose not to use a high-technology, high-workload monitor such as TEE, because of the high workload required to use it properly.
2.

   Distributing workload over time: The anesthetist can prepare for future tasks when the current load is low (preloading) and can delay or shed low-priority tasks when the workload is high (offloading). Resources that require a significant amount of workload to prepare, such as intravenous infusions, are often made ready before the case starts. Multitasking is also a way to distribute work over time. Each task is made up of several subtasks, each of which has a finite duration. Because close attention may not be required during each of these subtasks, they can be interleaved with a fixed amount of attention (multiplexing). Multiplexed tasks must be scheduled and coordinated in real time by the supervisory control level.
3. *Distributing workload over personnel:* When workload cannot be distributed over time, and when additional resources are available, tasks can be distributed to them. Some resources are internal to the individual anesthetist, whereas others require additional personnel. For example, a single anesthetist can simultaneously ventilate the patient by hand, assess the cardiac rhythm, and discuss patient care with the surgeon. The single anesthetist cannot simultaneously insert a pulmonary artery catheter and ventilate the patient's lungs by hand. If these tasks are to be performed at the same time, they must be assigned to different individuals.
4. *Changing the nature of the task:* The nature of a task is not fixed. Surgery and anesthesia can be postponed or aborted. Tasks can be executed to different standards of performance; as the standards are loosened, the workload required to perform them is reduced. For example, during periods of massive blood loss, the anesthetist focuses primarily on administering blood and fluids and on monitoring the blood pressure. In such cases, less critical tasks such as writing on the

anesthesia record are offloaded to lessen the workload. The acceptable limits of blood pressure will also be widened.

Special rules may be adopted to help manage tasks. Xiao et al [96] cited the example of an anesthetist who always left his hand on the ventilator power switch when turning it off transiently as a reminder to turn it back on again. Such a technique helps to prevent this critical subtask from becoming forgotten during high workload periods or when unanticipated events usurp attention from planned tasks.

Action Selection and Scheduling

At any time during an anesthetic regimen, there may be multiple things to do, each of which is intrinsically appropriate, yet they cannot all be done at once. The simulator experiments have shown that anesthetists sometimes have difficulty in selecting, planning, and scheduling actions optimally. The anesthetist must consider the following factors:

1. Preconditions are necessary for carrying out the actions (e.g., it is impossible to measure a thermodilution cardiac output if there is no pulmonary artery catheter in place).
2. Constraints are placed on the proposed actions (some actions are incompatible with other aspects of the situation; e.g., it is impossible to check the diameter of the pupils when the head is fully draped in the surgical field).
3. Side effects of the proposed actions often play a controlling role in choosing among possible drug therapies.
4. Rapidity and ease of implementation of proposed actions are factors; those that are easily and rapidly performed are preferred over those that require more time, attention, and skill.
5. Certainty of success of the actions is often traded off against rapidity and ease of implementation (under some circumstances, the higher certainty of success of a set of actions justifies the investment of time, attention, and resources needed to implement them).
6. Reversibility of the action and the cost of being wrong are considered, with rapidly reversible actions preferred over those that cannot be reversed, especially when potential side effects are significant.
7. Cost of the action in terms of attention, resources, and money is taken into account.

Experts in other complex, dynamic domains (specifically tank commanders and fire chiefs) have been observed [85] to conduct a mental simulation of the actions they are contemplating to determine whether there are hidden flaws in their plans. Anesthetists have been observed [9] [97] [98] to rehearse a plan mentally in advance of a case, but the degree to which this is done in real time is not known. Because most actions can be executed incrementally, as in titrating a drug in small aliquots, adverse consequences can often be discovered through repetitive reevaluation.

Resource Management

The ability of the anesthetist to command and control all the resources at hand to execute the anesthetic regimen as planned and to respond to problems that arise is termed *resource management* (another concept first described in aviation that applies equally well to anesthesiology). This involves translating the knowledge of what needs to be done into effective team activity, taking into account the limitations of the complex and ill-structured OR, PACU, or ICU domain. Resource management explicitly requires teamwork and crew coordination. It is not enough for the anesthetist to know what to do or even to be able to do each task alone. The anesthetist can only accomplish so much in a given time, and there are some tasks that can only be performed by other skilled personnel (e.g., laboratory tests, taking radiographs). When the task load exceeds the resources available, the anesthetist must mobilize help and must distribute the tasks among those present. Many issues concerning optimum resource management and crew coordination are not yet well understood and are the focus of active research by cognitive scientists and experts in many complex and dynamic domains. [150] [151] Research in aviation has already demonstrated that a large proportion of aircraft accidents was linked to failures on the part of crews with appropriate technical skills to manage the flight deck effectively. [83] [127] [152] [153] [154] The hallmarks of resource management derived from these studies include the following:

1. Prioritization of tasks.
2. Distribution of workload.
3. Leadership and crew coordination.
4. Communication.

5. Mobilization and use of all available resources.
6. Monitoring, cross-checking, and utilization of all available data.

Complex multiple personnel simulations of anesthetic crises addressed these issues. Although the data from these sessions are still preliminary, it appears that poor supervisory control and resource management were substantial components of suboptimal management of the simulated crises. [94] [95] In other words, like the pilots, anesthetists had the knowledge and technical skill to manage the patient, but they failed to manage their environment properly to achieve success.

Resource management is now taught systematically to crew members of all major U.S. airlines through training programs in Crew (originally "cockpit") Resource Management (CRM). [151] A similar program in anesthesiology is described in the section of this chapter dealing with anesthesia simulators.

SOCIAL PSYCHOLOGY AND ANTHROPOLOGY OF THE OPERATING ROOM ENVIRONMENT

Unlike teams in aviation, the military, or police and fire services, the OR team is unusual in that there is an ambiguous command structure. The physicians (surgeon and anesthesiologist) are nominally superior to nursing and technical staff, but the physicians are coequally responsible for the patient during the immediate perioperative period. Each physician, as well as the nurses and technicians, has a primary territory of knowledge, skill, and responsibility, but there is considerable overlap among them.

Strictly speaking, a team is defined as "a distinguishable set of two or more people who interact, dynamically, interdependently, and adaptively toward a common and valued goal/objective/mission, who have each been assigned specific roles or functions to perform, and who have a limited life-span of membership." [122] A team is distinct from a group in that a group is an ad hoc collection of individuals without a specific mission and without specific roles. [122] In the OR, all team members have the common goal of a good outcome for the patient. However, there can be considerable disagreement on how to achieve this goal and which elements of patient care have the highest priority. These differences are probably traceable to the fact that the OR team is itself made up of several crews (i.e., surgery, anesthesiology, nursing, perfusionist, radiology), each of which has its own command hierarchy, its own global properties (professional standing, culture, traditions, and history), and its own set of local goals and objectives for management of the patient. The differences among the crews can be so striking that some investigators refer to them as separate tribes (transcript of Conference on Human Error in Anesthesia, Asilomar, Calif, 1991).

Crew members work together to form a crew, and crews work together to form a team. A critical component of the success of this process is the establishment and maintenance of a shared mental model of the situation. [121] To the degree that this can be accomplished, the different individuals will be able to tailor their efforts toward a common goal. Experience working together as a crew or team will improve the likelihood of generating a shared mental model.

As yet, there are few data about these issues in the OR, concerning both the interactions within the anesthesia crew and the interaction between the anesthesia and surgical crews. Gild and Posner led a team at the University of Washington investigating the relationships between cardiac anesthetists and cardiac surgeons in and out of the OR using ethnographic (anthropologic) techniques. These investigators tentatively identified several areas for more intensive study, including coordination between perfusionists and anesthesiologists during cardiopulmonary bypass (CPB), sharing of control during weaning from CPB, and methods used by anesthetists and surgeons to resolve conflicts (presented at the annual meeting of the Society for Technology in Anesthesia, 1993).

A more recent study of crew and team behaviors in operating rooms was carried out in Basel, Switzerland. [103] [155] The authors found that "communication at the interface between anesthesia and surgical teams was classified as unacceptable/absent in approximately 20 percent of the observations." These communications were rated "within the lower half of the scale" in 70 percent of observations.

Status and Hierarchy Effects

Status and hierarchy effects are important in team performance. Especially in crisis situations, the lower-status crew member tends to defer to the higher-status individual, even if that individual is performing poorly. In aviation, some airplane crashes have occurred in which overbearing captains were combined with unassertive subordinates (first officer copilot and flight engineers). The team was not able to respond effectively, even when the subordinates knew that something was wrong. [156]

In aviation, as in academic anesthesia, training is an ongoing activity in the domain. Although the captain is in charge of the flight, the captain and the first officer (who is essentially in training to become a captain) traditionally alternate the roles of "pilot flying" and "pilot not flying" on each leg of a flight. Each of these roles is carefully defined and involves separate but interrelated tasks (the pilot flying handles the flight controls, whereas the pilot not flying handles radio communications and other tasks). In anesthesiology, the roles of the trainee and the faculty member during patient care are rarely made explicit. The trainee is often expected to do all tasks with only occasional assistance from the supervisor (part of a training method known as *cognitive scaffolding*). The exact responsibility for different tasks in a crisis is not predefined. Interestingly, two factors frequently found to be associated with critical incidents in anesthesia have been "teaching in progress" and "inadequate supervision." [148]

Production Pressure

The social and organizational environment may also act as a source of production pressure on anesthetists. Production pressure encompasses the economic and social pressures on workers to place production, not safety, as their primary priority. [13]

In anesthesiology, this typically means keeping the OR schedule moving speedily, with few cancellations and minimum time between cases. When anesthetists succumb to these pressures, they may skip appropriate preoperative evaluation and planning, or they may fail to perform adequate pre-use checkout of equipment. Even when preoperative evaluation does take place, overt or covert pressure from surgeons (or others) can cause anesthetists to proceed with elective cases despite the existence of serious or uncontrolled medical problems. Production pressures can cause anesthetists to choose techniques that they otherwise believe to be inadvisable.

Gaba et al [157] reported on a randomized survey of California anesthesiologists concerning their experience with production pressures. They found that 49 percent of respondents had witnessed a situation in which patient safety was compromised by pressure on the anesthesiologist. Thirty percent reported strong to intense pressure from surgeons to proceed with a case they wished to cancel. Notably, 20 percent agreed with the statement that "If I cancel a case, I might jeopardize working with that surgeon at a later date." The economic pressures are obvious. Production pressure also leads to haste by the anesthetist, a psychologic precursor to the commission of unsafe acts. In the survey, 20 percent of respondents answered "sometimes" to the statement "I have altered my normal practices in order to speed the start of surgery," whereas 5 percent answered "often" to this statement. Twenty percent of respondents rated pressure by surgeons to hasten anesthetic preparation or induction as strong or intense. Repeated exposure to these conflicts can cause the anesthetist to internalize pressures; 38 percent of survey respondents felt strong to intense internal pressure to "get along" with surgeons, and 48 percent reported strong internal pressures to avoid delaying cases. They may then feel impelled to go ahead with cases against their better judgment, even in the absence of overt pressure. Investigating these aspects of the work environment is difficult because these relationships are driven by economic considerations as well as by the complex organizational and interpersonal networks linking the different medical cultures. Changing the environment will be equally challenging.

/das/book/view/29494766/875/882.html

PERFORMANCE-SHAPING FACTORS

With a few exceptions, the foregoing discussion of the performance of skilled anesthetists has assumed that they are normally fit, rested, and acting in a standard working environment. Experience in human performance in the laboratory and other domains suggests that there are profound effects on the abilities of even highly trained personnel from internal and external performance-shaping factors. The degree to which performance-shaping factors affect the overall performance of anesthetists and the outcomes for patients is highly uncertain. In extreme cases, such as profound fatigue, there is no question that these factors can result in severe degradation of the anesthetist's performance or even complete incapacitation. However, these extreme conditions are quite unusual, and it is unclear whether the levels of performance decrement likely to be induced in typical work situations have any significant effect. Although the practice of anesthesia does require an attentive and skilled individual, it does not require peak human performance. It would be unrealistic to expect peak performance for every anesthetic regimen because there are on the order of 60,000 anesthetic regimens administered each day in the United States by a total of approximately 40,000 to 60,000 anesthetists.

With these caveats in mind, however, there are several performance-shaping factors that are potentially of sufficient magnitude to be of concern. Ambient noise, music, fatigue and sleep deprivation, aging, illness, drug use, and attitudes are discussed later. Several other factors that are not discussed include the level of illumination and environmental temperature. These can be shown to have a performance-shaping effect in the laboratory, [2] [158] but it is uncertain how much they affect performance in the OR.

Ambient Noise and Music in the Operating Room

The OR is a relatively noisy work environment. [141] [142] [159] [160] Mean sound levels are considerably higher than in most offices or control rooms (continuous air movement through an open surgical suction tip is a common source of continuous noise), whereas peak sound levels can be quite high. Some sources of noise are uncontrollable, such as surgical drills, monitor alarms, or inadvertently dropped instrument pans; other sources are controllable, such as conversation and music (see later). There is evidence in the general literature that noise can adversely affect human performance. [161] [162] Furthermore, studies by Murthy et al [163] demonstrated that volume-accurate replay of recordings of OR noise significantly interfered with the speech-discrimination ability of anesthesia residents during laboratory testing. The OR noise also caused a significant reduction in residents' performance on psychometric tests of mental efficiency and short-term memory. [164] The potential interference of noise with communication among personnel in the OR is particularly worrisome to those concerned with optimizing teamwork in this complex work environment.

The use of music in the OR is now widespread. Many health-care professionals believe that music enlivens the work day and can build team cohesiveness when all team members enjoy the music. A controversial study by two social psychologists, Allen and Blascovich, [165] suggested that surgeon-selected music improved surgeons' performance on a serial subtraction task and reduced their autonomic reactivity (i.e. "relaxed" them) when compared with control conditions with experimenter-selected music or no music at all. The methodology of the study has been criticized. [166] Anesthesiologists Swamidoss et al [167] presented preliminary data from a study of anesthesiologists' autonomic reactivity and problem-solving performance using a screen-based anesthesia simulator. They did not find any significant effect of "least enjoyed" music compared with either "most enjoyed" music or no music at all for autonomic reactivity or recognition and correction of simulated critical incidents.

In response to Allen and Blascovich, several anesthesiologists challenged the notion that the surgeon's preference for type or volume of music can or should override the needs of the other members of the team. [166] [168] This issue generates considerable controversy among surgeons and anesthesiologists. In a reply to some of the letters to the editor generated by their study, Allen and Blascovich [169] stated: "The letters here suggest that not everyone on the surgical team always

appreciates the type of music chosen by the surgeon, and anesthesiologists in particular appear to prefer silence in surgery. When we asked the surgeons in our study about this issue, we were told that the environment of surgery does not lend itself to the democratic process, and music was part of the environment in which they felt most comfortable."

There is no simple answer to the question of the proper role of music in the OR. Clearly, optimal patient care is the primary goal. Some surgical or anesthesia personnel explicitly forbid any type of music in the OR. A more common approach of many OR teams is to allow any team member to veto the choice or volume of music if they believe that it interferes with their work.

Reading in the Operating Room

The observation that some anesthetists were observed to read journals or books casually during patient care [170] led to a vigorous debate of the appropriateness of such an activity. [171] Although it is indisputable that reading *can* distract attention from patient care, there are no data at present to determine the degree to which reading *does* distract attention, especially if the practice is confined to low-workload portions of a case. Furthermore, many anesthetists pointed out that reading as a distraction is not necessarily any different from many other kinds of activities not related to patient care that are routinely accepted, such as idle conversation among personnel. [171] Many comments about the issue related not to the actual vigilance decrement induced by reading, but rather the impact of the negative perception of the practice (and of those who do it) by surgeons, and by patients (were they to be aware of it).

A noted researcher on human performance in anesthesia, Matt Weinger, was asked to comment on the practice of reading in the OR. [172] He pointed out that reading can combat boredom, which can be a significant distractor in its own right. He concluded that, in the absence of data specifically on the topic, it would be unscientific to condemn the practice outright, but that reading--like all other distractions--should not be allowed to impair vigilance and patient care. My colleagues and I teach, in our training course on anesthesia CRM, that the anesthetist is responsible for modulating *all* controllable distractions, for example, allowing music during routine work (if all agree) but eliminating it when the situation becomes complex or urgent. Similarly, although our own institution does not have a policy against reading in the OR (or against casual conversation for that matter), we *do* expect the anesthetist to terminate all incidental activities when necessary and to have a very low threshold for abandoning any potential distractions.

Sleep Deprivation and Fatigue *

General Principles

Scientists are discovering the importance of adequate sleep to allow normal human performance. A consensus report by the leaders in the field of sleep medicine stated that:

> [we] evaluated scientific and technical reports on the distribution throughout the 24-h day of medical incidents (such as heart attack and stroke) and performance failures (such as vehicular accidents and human errors in industrial and technical operations that can affect public safety). We found that these events occur most often at times of day coincident with the temporal pattern of brain processes associated with sleep. It thus appears that the occurrence of a wide range of catastrophic phenomena are influenced by sleep-related processes in ways heretofore not fully appreciated. <refref refref="r080010173" refnum="173">

This report goes on to give many examples of catastrophes that have occurred at least in part because of the effects of sleep deprivation and fatigue. Investigations in other complex industries (aviation, nuclear power, maritime, long-haul trucking) have identified fatigue as the probable cause, or a contributing factor, in many accidents. The National Transportation Safety Board (NTSB) determined that fatigue was a probable cause of the Exxon *Valdez* accident, one of the most visible and costly transportation accidents in history. Other disasters in which fatigue has been identified as causal or contributory include the nuclear disasters at Three Mile Island and Chernobyl and the space shuttle Challenger explosion.

Based on these findings, it is likely that chronic sleep dep-rivation, circadian rhythm abnormalities, and fatigue can be blamed for some iatrogenic adverse patient outcomes. However, it is difficult to determine the degree to which this is true. These factors have long been minimized or ignored by health-care professionals, and we believe that an understanding of them is critical to maximize patient safety.

Normal Sleep

Carskadon and Dement [174] referred to sleep as a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment that is usually accompanied by postural recumbancy, quiescence, closed eyes, and other indicators commonly associated with sleeping. Sleep can be thought of as a physiologic drive state similar to hunger or thirst and is necessary for the maintenance of alertness, performance, and overall well-being. The intensity of this drive can be inferred from noting how quickly an individual falls asleep. Just as eating and drinking satiate hunger and thirst states, sleeping reverses the desire to sleep.

The amount of sleep *required* by any individual is that which allows him or her to be awake and alert throughout the day. The average sleep time for young adults is 7 to 8 hours in a 24-hour period, with an approximately 15 percent interindividual variation. These sleep requirements are not constant and can vary over time.

Sleep is studied with a polysomnograph. Electrodes are placed on the scalp to monitor the electroencephalogram (EEG), near the eyes to monitor eye movements (extraoculogram [EOG]), and on the chin to monitor muscle tone (electromyogram [EMG]). Sleep is scored in 30-second epochs using standardized criteria to determine the particular sleep state and stage. [175] There are two states of sleep that can be distinguished from analysis of the EEG. The states are referred to as *non-rapid eye movement* (NREM) sleep

* This section was cowritten by Steven K. Howard, M.D., staff anesthesiologist, VA Palo Alto Health Care System, and assistant professor, Stanford University School of Medicine, Stanford, Calif.

and *rapid eye movement* (REM) sleep. NREM is further broken down into four stages (1, 2, 3, 4) based on the form of the EEG signal, in which stages 3 and 4 are sometimes combined together and referred to as delta sleep or slow-wave sleep (SWS). REM sleep is the state in which dreams occur most frequently, and it is characterized by EEG activation similar to the awake EEG, reversible muscle atonia, and rapid eye movements.

Sleep in normal individuals begins through an initial period of NREM sleep followed by the first REM period 80 to 110 minutes after sleep onset. NREM and REM sleep then cyclically alternate throughout the night approximately every 90 to 110 minutes. In young, healthy adults, SWS predominantly occurs during the first third of the night, whereas longer REM periods occur during the latter third. In healthy young adults without sleep complaints, NREM sleep accounts for 75 to 80 percent of sleep, whereas REM comprises 20 to 25 percent of sleep. SWS decreases dramatically as we age, whereas the percentage of time spent in REM sleep stays approximately the same. Brief awakenings (both reportable and nonreportable by the individual), which can fragment sleep and greatly diminish its quality, also increase in frequency with age. Elderly sleepers exhibit the greatest interindividual variability, making it particularly difficult to make broad generalizations regarding sleep-related issues for this population.

Sleep Debt

Individuals have their own particular sleep requirement in a 24-hour period. If adequate sleep is not obtained for whatever reason, daytime sleepiness and impaired performance ensue. Sleep loss is cumulative, resulting in what is referred to as a *sleep debt.* The individual who has obtained an optimal amount of sleep is better prepared to perform long periods of sustained work compared with one who is operating from a sleep debt.

Even minor sleep loss on a nightly basis can insidiously accumulate into a substantial sleep debt. [176] Importantly, the *only* way to pay back a sleep debt is with sleep. After accruing a sleep debt, the recovery sleep shows a particular pattern. SWS predominates over REM sleep. REM sleep rebound or recuperation follows after the body has recovered SWS. The reason for this prioritization of SWS over REM sleep is not known, but it may be due to a "restoring" effect of SWS.

Chronic sleep debts are commonplace in our culture. Shift work, long and irregular work hours, and the demands of family and recreation lead to irregular sleep patterns and prevent restful sleep. This may be particularly true for physicians, who often work in shifts, have long duty periods, and must frequently care for patients beyond normal working hours.

Fatigue

Fatigue is defined technically as a diminished ability to perform work, and it is caused by excessive physical or cognitive work. [177] Physical fatigue is usually produced by excessive muscular work. It is accompanied by a diminished ability of the muscles to respond, feeling of muscle tiredness, and a decrease in physical performance. Physicians are exposed to periods of physical fatigue during duty periods where they are asked to care for patients for long periods of time. For example, surgeons who participate in prolonged operations stand in the same position for many hours, leading to muscle fatigue.

There are also cognitive components to physical fatigue such as when the mind succumbs before the muscles. Mental fatigue is accompanied by subjective feelings of tiredness after periods of sustained performance on predominantly cognitive tasks. Nonstimulating environments also bring about feelings of boredom that can compound feelings of mental fatigue. Sleep deprivation accentuates the feelings of mental fatigue and probably also decreases an individual's motivation to perform during these periods. Mood, initiative, and enthusiasm all decline as fatigue progresses. Fatigue can also result from disturbed circadian rhythms.

Circadian Rhythms

Rhythms that fluctuate on a 24-hour time scale are known as *circadian rhythms,* from the Latin *circa,* meaning "about," and *dies,* meaning "day." The biologic clock that is responsible for these rhythms is located in the suprachiasmatic nucleus in the human brain. The best-known circadian rhythms are those of body temperature, hormone secretion, metabolism, and the sleep/wake cycle. The circadian system is synchronized to the 24-hour day by external stimuli referred to as *zeitgebers,* the most influential of which is the light/dark cycle of day and night.

The circadian system is biphasic, producing a state of increased sleep tendency and decreased performance capacity during two periods throughout the 24-hour day--from 2 AM to 6 AM and from 2 PM to 6 PM. These periods are sometimes referred to as *circadian lulls.* The circadian clock is very resistant to alterations, and it does not adjust rapidly to changes such as that produced by jet lag or shift work. Disruption of the normal circadian rhythm or incomplete circadian adaptation leads to acute and chronic sleep deprivation, decreased alertness, increased subjective fatigue, and decreased physical and mental performance. [178]

Sleepiness and Alertness

Sleepiness and alertness are at opposite ends of a continuum. The most obvious effect of failing to obtain adequate sleep is sleepiness at times when the body should be awake, most commonly referred to as *daytime sleepiness.* Healthy adults are maximally alert by midmorning. This is sequentially followed by a circadian lull in the early afternoon (causing some cultures to incorporate an afternoon "siesta"), increased alertness in the early evening, and finally increased sleepiness that normally results in falling asleep at night.

Patients often present to sleep disorder clinics with complaints of excessive sleepiness. Such patients have an increased incidence of automobile accidents and of accidents on the job or of being fired from employment because of sleepiness. The most extreme periods of sleepiness become

---

manifest when one is required to remain awake when one would normally be asleep (2 AM to 6 AM). Data from the NTSB reveal that the greatest numbers of single-vehicle accidents take place during the early morning hours when people are at a circadian lull of alertness. These accidents are thought to be due to inadvertent lapses in driver attention brought about by extremes of sleepiness.

Determinants of Sleepiness

Knowing what determines the level of daytime sleepiness may allow the development of measures to minimize its effects. [179] The major factors causing sleepiness are decreased quantity of sleep, poor quality of sleep (sleep fragmentation resulting from multiple awakenings or abnormal progression of sleep states and stages), disrupted circadian rhythms, and the use of certain medications. The amount of sleep obtained is directly related to daytime sleepiness. If sleep is restricted in healthy adults, daytime sleepiness can be demonstrated the following day. [176] [180] If one is allowed to extend sleep beyond the usual sleep time, increased alertness can be demonstrated in the laboratory. [181] Sleep quality is affected by many things. Sleep fragmentation affects the elderly and patients with sleep disorders such as sleep apnea and periodic limb movements. Sleep fragmentation commonly occurs in young physicians who are awakened from sleep to care for children at home or to care for patients while in the hospital.

Different drugs can either delay or hasten sleep onset, but in either case, they may disrupt normal sleep structure, which can be detrimental even if total sleep time is increased. For example, depressant drugs such as barbiturates, benzodiazepines, ethanol, clonidine, and certain antihistamines do hasten sleep onset, but they have been shown to cause hangover effects the morning after ingestion that can alter the individual's sleepiness and performance the following day. [182] These effects may not be readily apparent to the individual or to others. Depressant drugs also act in conjunction with the level of preexisting sleepiness so that the central nervous system (CNS) depressant effect is likely to be even more profound if it is superimposed on a chronic sleep debt.

Caffeine is used frequently to increase alertness temporarily, but there are caveats to its use. [183] [184] Caffeine and other stronger stimulants are known to reduce nocturnal sleep if ingested close to bedtime, hence decreasing sleep quantity and quality. Potent stimulants such as amphetamines do produce increased alertness, but they have significant side effects, and the individual must undergo a substantial amount of recovery sleep ("crash") after their effect is gone.

Mood

Long work hours, fatigue, and sleep deprivation have also been shown to bring about dramatic changes in mood and emotions. [185] [186] Depression, anxiety, irritability, anger, and depersonalization have all been shown to increase during testing of chronically fatigued house staff. These emotions are an obvious source of stress between anesthetists and their coworkers, patients, and families.

Vigilance

Vigilance, the centerpiece of the ASA logo, is defined as "the ability to remain alertly watchful especially to avoid danger." [187] Vigilance is critical, although studies of the performance of anesthesiologists make it clear that vigilance is not the only key characteristic of the careful anesthesiologist. [40] Vigilance is a necessary but not sufficient condition to permit the safe passage of a patient through the perioperative period. If vigilance and other aspects of decisionmaking are impaired by performance-shaping factors such as sleep deprivation and fatigue, there will be a greater likelihood of an adverse patient outcome.

Monitoring slowly changing stimuli is a classic vigilance task, which makes up a significant proportion of the anesthetist's work. This type of task is the most sensitive to the degrading effects of sleepiness and fatigue. During the performance of lengthy vigilance tasks, the most common types of decrements include increased reaction time, lapses (a transient period of unawareness), and a reduction in the probability of detecting an alarm. [188] This type of performance impairment has been documented after as little as 30 minutes of time on task, and the decrement is even more pronounced if the individual is physiologically sleepy at the beginning of the vigilance task.

Microsleep Events

The most extreme cause of impaired vigilance is the occurrence of actual sleep episodes *(microsleeps)* encroaching into periods of wakefulness. Microsleep events, as measured by the EEG, typically last a few seconds to a few minutes. They are intermittent in onset, and their impending occurrence is difficult for the individual to predict. Most individuals underestimate their level of sleepiness when they can be objectively shown to be extremely sleepy, thus making this problem even more insidious. In other words, one can fall asleep and not be perceptually aware of it.

Microsleeps are a sign of extreme sleepiness and are harbingers of the onset of true sleep. Microsleeps typically occur during periods of low workload or stimulation and when the individual is maximally sleepy. In addition, the individual's performance between microsleep episodes is also impaired. Frequent and longer microsleeps increase the number of errors of omission.

If a truck driver is driving down the interstate at 70 mph and has a brief microsleep, there is a high likelihood that the driver will have an accident, possibly killing himself or others. Although the anesthetist's work environment does not (usually) evolve as fast as that of the truck driver, the safety implications of falling asleep while providing anesthesia care are obvious.

Studies reveal that a significant proportion of shift workers actually do fall asleep on the job. Akerstedt et al [189] [190] conducted ambulatory EEG studies of train engineers demonstrating microsleep episodes during periods of train operation. Are similar events occurring nightly in ORs around the world?

Scientists at the NASA Ames Research Center studied the occurrence of microsleep episodes on pilots during transmeridian flights. [191] These flights involve multiple time

---

zone changes with long, irregular work schedules and a resultant disruption of circadian rhythms. This situation causes fatigue, sleepiness, and decreased performance, which are believed to have an impact on flight safety. The protocol compared two pilot groups flying equivalent flights: a control group and a nap group. This experimental study had to be cleared by the Federal Aviation Administration (FAA), whose rules do not normally allow sleep on the flight deck. EEG monitoring of the pilots was performed to determine the extent of microsleep episodes and also to document whether pilots were actually able to nap if given the opportunity. In brief, the study revealed that (1) crew members were able to nap if given the opportunity, (2) the non-nap crew had significantly more microsleep episodes during critical phases of flight when compared with the crew that had napped, and (3) performance on a standardized test of visual reaction time was impaired in the non-nap group when compared with the group that had napped. This study demonstrated that microsleeps do occur even in a work environment in which sleep is strictly forbidden and (as detailed in a later section) in which work hours are tightly regulated. Napping appears to be a reasonable countermeasure to decrease the likelihood of microsleeps, and that improves performance. Results from this study and others may be used to make major changes to regulations governing scheduled

rest on the flight deck.

Do anesthetists suffer microsleep events? The answer almost certainly is yes. Anecdotal evidence as well as unpublished reports from our own surveys suggest that these events do occur from time to time. No formal study of anesthesia care providers has been completed, although I am in the process of collecting these data. Anesthetists should realize that they are vulnerable to these dangerous episodes, which can strike without warning.

Shift Work

Because very long duty periods are problematic, shift work is a common method for providing 24-hour coverage in various work environments. It is estimated that 20 to 30 percent of the U.S. work force engages in some type of shift work. Comparisons of male shift workers versus nonshift workers reveal that men working irregular shifts report higher rates of alcohol use, job stress, and emotional problems. The many difficulties caused by shift work suggest that it is not a perfect solution for 24-hour duty requirements.

The ability to cope well with shift work depends on the interaction of three factors on the individual: circadian rhythms, sleep-related issues, and social factors. The circadian system often takes days to change to an altered work shift. Once circadian realignment to an evening or night shift is achieved, it is very difficult to maintain this schedule because our society is structured strongly on a day-night basis. It is socially "abnormal" to sleep during the day, and shift workers often adopt a nocturnal orientation during the week but revert back to the more normal diurnal orientation during the weekend and on days off from work. In this situation, a worker never fully adjusts to working on the night shift, and the circadian system is constantly disordered. [178]

The normal human circadian system runs on a cycle of approximately 25 hours. This fact and data from studies of jet lag provide an explanation for the finding that some work schedule changes are easier to adjust to than others. Because the circadian cycle is slightly longer than the 24-hour day, it is usually easier for workers to adjust to shifts in a forward direction (day shift to evening shift to night shift), thereby stretching the work schedule to conform to the body's natural rhythm. This is the same reason that jet lag is typically less severe flying westward when compared with flying eastward.

Sleep-related factors play an important role in shift work adjustment. For a variety of reasons, night shift workers average less sleep than those who work during the day. It is very difficult to screen out all environmental stimulation and noise that take place during the daytime. Even when screened from sunlight and noise, people do not sleep as well during the day because their circadian system is not reset sufficiently to command sleep at this time. This situation leads to chronic sleep deprivation, which becomes increasingly prevalent as night work is maintained. Sleep lost during the week can be partially recovered on days off and during the weekend, but sleep is often not given sufficient priority when compared with the demands of family and recreation.

Social factors also play a major role in the quantity and quality of sleep that shift workers are able to obtain during the day. Many household duties can only be performed during daytime "working hours," a factor that obviously decreases the likelihood of obtaining adequate sleep. In our society, the female shift worker is often expected by her significant other to continue to manage the household and to be the primary caregiver to the children. This situation diminishes daytime sleep for the woman, and it also can be a source of stress in the relationship because mood can be dramatically altered as sleep deprivation ensues.

From a practical standpoint, shift work will remain a common method to provide 24-hour care in the hospital setting. Workers and managers should learn how circadian factors, sleep-related factors, and social factors affect the lives of workers and their families. Organizations should make it a priority to establish that workers are appropriately rested, just as they try to ensure that workers are not impaired by drugs or alcohol on the job. However, given current knowledge concerning shift work and the many factors that affect an individual's ability to cope, there is no single "best" schedule for shift work. Some workers tolerate systems that others find excessively onerous. If given a choice, many workers choose suboptimal shiftwork rotations when doing so gives them increased pay or more time off from work.

An example of physiologically based shift work scheduling was studied by Czeisler et al [192] in a potash mining and processing facility. [192] These investigators intervened by changing the workers' rotating shifts in ways that allow for better circadian adjustment (phase delay to later shifts, every 3 weeks). These shift changes were associated with an improvement in health indexes, a reduction in personnel turnover, and a marked increase in the productivity of the workers.

Methodologies for Assessing Sleepiness

There are various ways in which to assess an individual's level of sleepiness. These include behavioral indicators, subjective

measures, and physiologic measures. Behavioral indicators of sleepiness include yawning, ptosis, decreased social interaction, and microsleep events. Many of these behaviors are difficult to quantify. Subjective measures include various types of numeric or visual analogue scales that attempt to measure how sleepy the individual *feels.* These methods are used frequently in studies of sleepiness because they are very easy to implement. Subjective feelings of fatigue and sleepiness are often underestimated by individuals in comparison with their level of physiologic sleepiness. Both behavioral and subjective sleepiness can be masked by a stimulating environment, even though the individual remains physiologically sleepy. When environmental stimuli wane, physiologic sleepiness manifests itself as an overwhelming need to fall asleep. A person who is physiologically alert does not experience sleepiness as environmental stimuli decreases. For example, without physiologic sleepiness, an individual becomes bored during a boring lecture, but does not fall asleep.

Physiologic (objective) measures of sleepiness have been used extensively in sleep research and sleep medicine. Carskadon and Dement and colleagues [193] [194] [195] developed the Multiple Sleep Latency Test (MSLT), which is now thought of as the standard method for quantifying daytime sleepiness. The MSLT tests the propensity of an individual to fall asleep in a sleep-inducing environment (dark, temperature-controlled room, minimal noise, comfortable bed). Once again, the level of daytime sleepiness reflects acute and cumulative sleep loss, circadian disruption, and fatigue and correlates with performance. The MSLT is performed in a standard sleep laboratory setting and consists of five opportunities to fall asleep every 2 hours over the course of the day, usually from 10 AM to 6 PM. To determine precisely when sleep onset occurs, the EEG (central positions), EOG (outer canthi), and submental EMG are measured. These variables are scored according to standardized and accepted criteria. [194] Sleep latency is measured from the beginning of the test (lights out) until sleep onset. A *short* sleep latency (i.e., falling asleep quickly) is a sign of *increased* sleepiness, and a *long* sleep latency (i.e., falling asleep slowly) is a sign of *decreased* sleepiness. For research purposes, sleep is not allowed to accrue during the test; therefore, if the subject falls asleep, he or she is awakened after 1.5 minutes of continuous sleep. If the subject does not fall asleep within 20 minutes, the test is terminated. The MSLT score is the average of the five sleep latencies measured over the course of the day. A normal MSLT score is greater than 10 minutes, whereas a pathologic score is less than or equal to 5 minutes. The pathologic level corresponds to the daytime sleepiness typically seen in patients with narcolepsy, sleep apnea, or in healthy individuals deprived of sleep for 24 hours.

Sleep Deprivation and Fatigue in Medical Personnel

Human error represents a significant risk to hospitalized patients, [196] [197] and it has been estimated to play a role in more than 70 percent of anesthesia mishaps. [148] This is similar to the error rate seen in cognitively similar work environments such as aviation. [152] Clearly, the physiologic capabilities and limitations of the human operator in complex work environments remain central to safe and productive performance. The 24-hour demands of medical care parallel the physiologic challenges present in other operational domains, yet minimal data are available to quantify the fatigue-related risk to performance and alertness in medical personnel.

Providing quality health care requires physicians to attend to life-critical details such as the monitoring of changing vital signs, administering the correct type and dose of medications, and in general, making crucial decisions to achieve optimal patient care. Physicians, like other workers, are affected by all the physiologic, psychologic, and behavioral demands that characterize work environments requiring continuous, around-the-clock operation. However, whereas much of the health-care system (e.g., nursing) relies on multiple work shifts to cover the 24-hour day, physicians more typically work long duty periods and frequently experience sleep loss, circadian disruption, and fatigue. Even minimal levels of sleep loss, for example, obtaining as little as 2 hours less sleep than an individual requires, can lead to lapses in performance, increased physiologic sleepiness during the daytime (including microsleeps), and altered moods. This level of degraded performance and alertness almost certainly contributes to medical error and health-care mishaps.

Resident physicians, in particular, work long, grueling hours, often for years at a time. On-call duty periods commonly last 24 to 36 hours, occasionally even longer, and some resident groups work 100 to 120 hours per week. [198] These schedule demands cannot help but lead to acute and chronic sleep loss, circadian disruption, and fatigue with subsequent adverse effects on performance, alertness, and mood. Therefore, individuals who administer life-sustaining care are *at risk* for making

fatigue-related mistakes and causing costly medical errors.

A case of an intraoperative death occurring when the anesthesiologist was described by witnesses as being asleep received considerable media attention (*Dateline NBC,* prime-time news magazine, October, 1995). [199] The patient apparently suffered from an episode of malignant hyperthermia. If the witnesses' statements are correct, the anesthesiologist's sleep state may have had a profound impact on his suboptimal response to this crisis.

How Long Are the Work Hours of Anesthesiologists?

Berry and Hall [200] reported on the work hours of residents in seven anesthesiology programs. They found that the programs surveyed were within current guidelines of the Accreditation Council for Graduate Medical Education (ACGME) for overall resident work hours. The ACGME Special Requirements for Residency Training in Anesthesiology further state that, "while the actual number of hours worked by residents may vary, residents should have sufficient off-duty time to avoid undue fatigue and stress. Residents should be allowed to spend, on average, at least 1 full day out of 7 away from the hospital, and participate in on-call duty in the hospital no more frequently than on average every third night." These guidelines also call for an 80-hour work week that comprises the total duty time of the house officer in the hospital (including sleep during on-call periods).

In this survey, residents within clinical anesthesia years 1 to 3 spent an average of 64 to 66 hours per week in the hospital. This survey did not address the sleep habits of the survey respondents, thus making it impossible to assess the impact that these work hours had on the subjects' sleep cycle, complaints of fatigue, alteration in mood, or impairment of performance.

In a survey of California anesthesiologists (residents, faculty, and private practitioners), Gaba et al [157] reported that respondents worked an average of 52±16 hours per week and were on call approximately 5 nights and 2 weekend days per month. Those surveyed slept an average of approximately 7 hours when not on call and 5 hours when they were on call. Gravenstein et al [201] reported on the work hours of different categories of anesthesia caregivers. In their survey, professional hours in the typical work week were 56 hours for an anesthesiologist, 48 hours for a CRNA, and nearly 70 hours for a resident. From the surveys described earlier, the average work week for anesthetists as a whole ranges from 50 to 70 hours.

Residents, who receive a fixed salary, are unlikely to want to work after a 24-hour on-duty period. Most anesthesia residency programs provide for residents to be relieved from clinical work after such an on-call period. This is clearly not the case for many anesthesiologists in practice, who often receive compensation on a fee-for-service basis. In their survey of California anesthesiologists, Gaba et al [157] found that 41 percent of respondents were expected at least "sometimes" (21% "often" or "always") to "do cases the day after being awake most of the night on call." The majority of all survey respondents reported feeling fatigued at work, and that this had increased in recent years. Approximately 20 percent of anesthesiologists in this survey felt a significant amount of production pressure to work while fatigued. [157]

Do Anesthesiologists Perceive Fatigue as a Problem?

The survey by Gaba et al [157] also revealed that more than 50 percent of respondents believed that they had made an error in clinical management that *they* thought was related to fatigue. In another survey of anesthesiologists and CRNAs, the majority (61%) of respondents recalled having made an error in the administration of anesthesia that they attributed to fatigue. [201] Data from these surveys reveal that issues of sleepiness and fatigue *are* perceived by anesthesia practitioners as being important causative factors in reducing anesthesia-related patient safety.

Sleep and Performance

Previous studies addressed the effects of sleep deprivation and fatigue on physician performance and well-being. Major reviews of this literature identified little consensus. [202] [203] Some of the published studies showed sleep deprivation to have negative effects on physician performance, whereas other studies showed no statistically significant effects. There are several methodologic flaws in the existing literature: (1) the degree of acute sleep deprivation of subjects was poorly defined, and no assessment of chronic fatigue was made; typically, studies relied on only the previous night's sleep as a level of "fatigue," and subjects could well have been chronically fatigued during baseline (control) trials, which could mask the degree of impairment resulting from the acute fatigue of being on call; (2) measuring actual clinical performance is difficult and was not attempted; most studies had to rely on simple cognitive tasks that probed only short-term memory, immediate recall, and simple reaction time; the validity of using such simple tests to probe complex performance has been challenged because these simple tests do not assess the higher-level cognitive functions most critical to skilled medical care [71] ; (3) most of the performance tests were of very short duration (3-5 minutes); studies have shown that, if sufficiently motivated, even fatigued subjects can perform well on short-duration tasks; and (4) practice effects were not adequately accounted for; if subjects have not learned a particular performance test sufficiently to achieve maximum performance, subsequent trials will almost certainly show performance improvement because of further learning of the task.

Some studies requiring subjects to perform sustained vigilance tasks of long duration have, in fact, shown a performance impairment in fatigued physicians. [74] [204] [205] Tasks of this type that require sustained attention to detail are highly relevant to the anesthetist's tasks, and they are the most sensitive to sleep loss and fatigue.

Evaluation of Physiologic Sleepiness in Anesthesia Residents

Howard et al [206] evaluated physiologic daytime sleepiness (using the MSLT as described earlier) of anesthesia residents in three different conditions. The conditions studied were (1) "baseline" (daytime shift, no on-call duty period in previous 48 hours); (2) "post-call" (immediately after a 24-hour work and in-house on-call period); and (3) "sleep satiated." The sleep-satiated condition requires further explanation. Residents were told to maximize sleep, and they were allowed to arrive for work at 10 AM (3 hours later than normal) for 4 consecutive days prior to testing. They were not on call during this time. The sleep-satiated condition was studied to provide a true control state of maximal rest and optimum alertness. Studies of adolescents have demonstrated that sleep extension improves daytime alertness. [181]

In this study, the anesthesia residents had an MSLT score of 5.9±2.7 minutes in the "baseline" condition and 6.1±4.7 minutes in the "post-call" condition, both scores revealing nearly pathologic levels of daytime sleepiness seen in patients with narcolepsy or sleep apnea. The "baseline" group slept an average of 6.6±0.98 hours per night, whereas the "post-call" group reported an average of 6.2±0.64 hours of sleep during their night on call. Ironically, although the on-call periods were during rotations that often have very busy call nights, only a few subjects were, in fact, awake most of the night. In the "sleep-satiated" condition, when subjects were allowed to extend their sleep to an average of over 9 hours per night, the MSLT score was in the normal range (13±5.1 minutes).

Figure 80-9 shows MSLT profiles for anesthesia residents studied in these three conditions. The two lower curves demonstrate physiologic sleepiness that is in the pathologic

Figure 80-9 Average sleep latency profiles for residents in different work conditions. Both the baseline and post-call groups show a low sleep latency and no decrease in the afternoon. The sleep-satiated group shows a normal sleep latency, with a characteristic circadian lull. Error bars represent the standard error of the mean.

range (<5-minute sleep latency). These individuals were less alert and were prone to falling asleep at this level of physiologic sleepiness. These results clearly demonstrate that medical personnel who have not been on call *cannot* be assumed to be "rested" when compared with "fatigued" post-call residents. These data also support that, under normal working conditions, the resident physicians studied were physiologically sleepy to near pathologic levels. This finding documents a previously unknown level of chronic sleep deprivation in this population. Importantly, these data cast substantial doubt on previous studies of the performance of medical personnel that have relied on the assumption that individuals working under "normal" conditions are truly rested. However, preliminary data from this study on the performance of these residents on a 10-minute task of visual reaction time (psychomotor vigilance task [PVT]) show no clear significant reduction in performance

in the post-call state or of an increase in performance in the sleep-satiated state. Ironically, although the on-call residents in this study were expected (by the nature of their call duties) to lose considerable sleep, their average on-call sleep in the study was higher than expected. Those who did lose considerable sleep were too few to permit statistical analysis.

Geer et al [207] studied performance of residents on the same PVT reaction time test, before and after a 24-hour on-call period. Results of their study showed that residents obtained less sleep while on call (3.2 versus 7.6 hours) and had self-reported sleepiness ratings that were significantly higher after being on call. Post-call data from the vigilance task revealed that the fastest 10 percent of response times (a measure of peak performance) was slower and the number of lapses was greater, when compared with the subjects' own performance before the on-call period.

Building on this study, the same group evaluated both residents and faculty members before and after a 24-hour call period. [208] Performance on the PVT was significantly worse (slower mean and fastest reaction times and more and longer lapses) after call for residents, but not for faculty members. Although residents reported more sleep than faculty before being on call, the residents lost more sleep on call than did faculty members (resident mean sleep loss, 4.8 hours; faculty mean sleep loss, 2.1 hours).

Thus, even using standard laboratory tests of reaction times (which have been shown by sleep researchers to be sensitive to sleep loss), performance tests of anesthesiologists after an on-call period show conflicting results. Furthermore, how the laboratory test correlates with more complex anesthestic performance remains an unanswered question. Geer et al [209] measured the performance of residents before and after being on call by constructing several clinical management scores based on the subjects' handling of different critical incidents using a "screen-based" anesthesia simulator (the ASC). Overall, there was no significant difference in the clinical management scores of residents between the pre-call and post-call conditions. However, these were short (20-minute) simulations, and the screen-based simulator is far from the reality of actual OR work.

Lichtor et al [210] used a realistic anesthesia simulator as well as standard psychomotor tests to study the effects of fatigue on medical personnel. In one study, these investigators found that "fatigued" individuals had impaired performance on a coordination task and a vision test (Maddox Wing) similar to the impairment seen when under the influence of a low dose of alcohol (0.5 g/kg). "Performance" in the realistic simulator was not significantly impaired after a 24- to 36-hour on-call period. However, the details of this experiment have never been published, and the assessment of clinical performance depends heavily on the duration and intensity of the simulation, as well as on the complexity of the behaviors to be measured.

Weinger et al [211] at UCSD conducted task analyses of residents performing matched-difficulty general anesthesia cases during the daytime and at night. Residents reported higher workloads during nighttime cases (although cases were matched for difficulty), and the task analyses showed lower task efficiency at night. However, reaction time to the red light secondary task (see the earlier section on secondary tasks) was no different at night than during the day.

Howard et al (VA-Stanford) is conducting a complex assessment of the occurrence of microsleeps and of multiple measures of performance (including PVT, multiple types of secondary task probes, and response to clinical events) in highly rested versus highly fatigued anesthesia residents conducting long (4-hour) anesthetic regimens using a realistic patient simulator.

Evaluation of Subjective Sleepiness

Howard et al [212] also investigated the degree of discrepancy between the residents' subjective sleepiness (how sleepy they *felt*) and their physiologic sleepiness (how easily they fell asleep). Subjective sleepiness was measured using a validated numeric scale (Stanford Sleepiness Scale [213] [214]), whereas physiologic sleepiness was measured using the MSLT as described earlier. Subjects' self-reported sleepiness immediately prior to each sleep opportunity during the MSLT did not, in general, correlate with their MSLT score. As in previous studies, subjective sleepiness correlated better with physiologic sleepiness when subjects were extremely alert or extremely sleepy.

Furthermore, we also found that subjects demonstrated little ability to determine whether they had actually fallen asleep during the MSLT sleep opportunities. For example, in 51 percent of trials in which the EEG/EOG measurements showed that the subject had fallen asleep, the subjects thought they had remained awake throughout. The same data can also be expressed as follows: in 68 percent of trials in which subjects thought that they had remained awake, they were wrong. These results support the contention that medical personnel *are* physiologically vulnerable to degraded alertness *yet are unable to perceive this decrement.* Thus, an anesthetist could in fact fall asleep during a case, awaken, and be totally unaware of the lapse in vigilance.

Countermeasures

Studies such as the ones described previously are just beginning to establish the true picture of sleepiness and fatigue in medical personnel. From our knowledge of the performance of fatigued individuals in other domains, we know that professionals become increasingly vulnerable to the degrading effects of sleepiness as the sleep debt accumulates. It may be very difficult to determine a causal relationship between anesthetist fatigue and patient outcome. However, it is clear that if the anesthetist is not awake, he or she cannot possibly be aware. Such a lapse in vigilance is unacceptable. Furthermore, the anesthetist cannot prevent sleep by willpower alone, because it is a fundamental physiologic drive. Demands for clinical services must be balanced against the potential for reduced vigilance and error by seriously fatigued practitioners, anesthetists, and surgeons alike. Because fatigue is such a widespread and insidious problem, it is important to determine ways to counteract its effects. *Countermeasures* are methods that institutions or practitioners can use to minimize the negative effects of sleepiness and fatigue on performance. Countermeasures include the following:

1. Education.
2. Sleep hygiene.
3. Rest breaks at work.
4. Strategic napping.
5. Medications.
6. Light therapy.

Education

The first step in addressing sleepiness and fatigue of medical personnel is to educate health-care professionals and the administrators of health-care institutions about the impact of sleep issues on work performance, mood, job satisfaction, and health. Education is a relatively simple and inexpensive countermeasure that can be implemented immediately. Educational programs covering sleep deprivation, circadian disruption and fatigue, and countermeasures have been enthusiastically adopted by an increasing fraction of the aviation community. [215] [216] Similar programs should be developed for the health-care community. Education alone is sufficient for some individuals and institutions to change their work and sleep habits or their organizational and scheduling procedures. However, it is likely that education will not be sufficient to address this issue fully.

Sleep Hygiene

Sleep hygiene is defined as the conditions and practices that promote sufficient quantity and quality of sleep for each individual. Good sleep hygiene includes the following: regularity of bedtime and wake-up time; sufficient time for sustained and individually adequate sleep; restriction of alcohol, caffeine, and nicotine prior to bedtime; and employment of exercise, nutrition, and environmental factors so that they enhance rather than disturb sleep. [217] A regular sleep schedule is an important part of optimal sleep hygiene, but it is often not possible for medical personnel, given the requirement to cover clinical needs on a 24-hour basis. Medical personnel should make greater efforts to maintain as constant a sleep schedule as possible and to maximize sleep opportunities prior to and after periods of reduced sleep.

Social drug use can have profound effects on sleep. Physicians often use caffeine to help stay awake during on-call periods. Caffeine produces an increase in awakenings and decreases the total nocturnal sleep time. These effects can last as long as 12 hours after ingestion. Individuals who ingest large amounts of caffeine and who have nocturnal sleep disturbances should limit or cease their caffeine intake. Nicotine is a stimulant that produces effects similar to those of caffeine. Alcohol

is often used successfully to initiate sleep, but its effect on sleep architecture after sleep onset can be devastating. After ingestion of alcohol, frequent awakenings from sleep occur that can be associated with increased sympathetic nervous system activity, often manifested by headache, sweating, and tachycardia. Clearly, use of these substances should be restricted near bedtime.

Physicians often lack good nutritional habits, especially during long duty periods. Meals may be skipped or ingested quickly whenever there is adequate time. If one is hungry prior to bedtime, it is best to avoid eating or drinking heavily because this, too, can disturb sleep.

The effects of age can make optimum sleep hygiene difficult to achieve. The number of awakenings per night rises after the age of 45 years, corresponding to decreased sleep efficiency (time in bed versus total sleep time) and increased sleep fragmentation. The ability to initiate sleep at any time during a 24-hour day is diminished after the age of 25 years, and "sleeping in" to make up for lost sleep is more difficult as individuals grow older. Sleep-related disorders such as breathing disruptions (obstructive sleep apnea) and periodic limb movements also become more common with age.

The sleep setting should ideally be a dark, quiet room devoid of interruptions such as pets, telephones, pagers, and children. Sleeping surface and environmental temperature should be comfortable. Psychologic stressors increase baseline physiologic arousal and can impair the quality and quantity of sleep. For example, reviewing the previous day's events or attempting to plan tomorrow's activities while trying to fall asleep is not conducive to sleep. An effort should be made to separate the work of the day with a period of relaxation prior to attempting to initiate sleep.

Rest Breaks at Work

Other industries have openly recognized the reality of vigilance decrements resulting from fatigue and sleepiness. The health-care system has not. Rest breaks and rotation of task duties are mandatory for air traffic controllers and are part of naval ship command procedures as an attempt to prevent potential lapses in vigilance. Short breaks have been shown to increase productivity and job satisfaction, and they probably also help to alleviate boredom. [218] In anesthesia training programs, residents are often given rest breaks during the daytime, but this is often not the case with private practitioners. Private practice anesthesia typically does not provide the mechanisms for rest breaks or task duty rotation, in part because of fiscal concerns. An "extra" anesthetist would be necessary to provide for these opportunities on a regular basis.

The optimal timing and length of breaks are unknown, but a periodic relief from duty should be taken when possible. Cooper et al [219] [220] studied the effects of intraoperative exchange of anesthesia personnel. Although in some cases the process of relieving OR personnel caused a problem, it more frequently was associated with the discovery of a preexisting problem. The positive effect of relief of personnel probably depends on the quality of the handover briefing conducted by the anesthetists.

If anesthetists are unable to obtain a break during long work periods, there are measures that they can take to remain alert. They can engage other OR personnel in conversation (although this, too, can be distracting), thereby increasing the level of stimulation in the environment. Walking around or standing up are both techniques that decrease subjective but not physiologic sleepiness. If the anesthetist is having microsleep events, which may be noticed by other personnel rather than by the anesthetist, fatigue is already very severe, and complete sleep is imminent. In such a situation, the practitioner must secure additional assistance in surveillance of the patient and, if necessary, obtain relief to allow him or her to sleep. The patient should not pay the price for the anesthetist's bravado.

Strategic Napping

If adequate sleep during the night cannot be obtained, naps can be utilized to decrease sleepiness and to improve performance. Based on circadian physiology, there are two times during the 24-hour day that are optimal for naps. These are the periods when the body is already physiologically prepared for sleep, corresponding to the two circadian lulls (approximately 2 PM to 6 PM and 2 AM to 6 AM). Napping at times when circadian rhythms are instructing wakefulness is not easily accomplished and can be counterproductive. [221] [222]

The optimal nap length for most individuals is around 45 to 60 minutes, because this acutely improves alertness and allows for improved performance, but it minimizes the possibility of *sleep inertia* on awakening. Sleep inertia corresponds to the period of reduced ability to function optimally immediately on awakening. This phenomenon usually occurs when individuals are awakened out of SWS and is manifested by grogginess and impaired performance lasting as long as 15 to 30 minutes after awakening. Sleep inertia can also occur after being awakened from normal sleep and is most common during the early morning circadian trough (2-6 AM). Depending on the preexisting level of sleepiness, individuals who take naps longer than 40 minutes are at a greater risk for sleep inertia on awakening. Sleep inertia can be important to health-care professionals who may be awakened out of deep sleep to provide emergency care to patients (e.g., emergency cesarean section or emergency intubation). If urgent work can be anticipated, the sleeping individual should be awakened in time (at least 15 minutes) to minimize the fogginess and performance decrement associated with sleep inertia. If sleep inertia is unavoidable, it would be wise for the affected person to ask for help until the grogginess dissipates.

Napping may alter regular nocturnal sleep. Depending on the timing and length of the nap, sleep initiation and maintenance may be more difficult. Increased sleep latency and decreased total sleep time are commonly seen in people who have taken long (2-hour) naps during the day.

Therefore, the decision whether to nap is complex. Data from NASA studies of flight crews (described earlier) demonstrate that, on the whole, napping is a useful countermeasure to fatigue and sleep deprivation. [191] However, no single recommendation can be made for the use of naps in any work environment, and there are as yet no data on the use of naps in the health-care domain.

Further complicating the appropriate use of napping by medical professionals is the finding that physicians have had an individual and cultural tendency to ignore or to minimize the effect of fatigue and sleep deprivation. The culture of medicine views work breaks and naps as signs of weakness. The military has addressed similar attitudes with the concept of "power napping." Troops are strongly encouraged to take naps of 10 minutes to 1 hour when the situation permits, in order to increase their strength and performance. [177] This approach appropriately presents the idea of napping in a positive light as a sign of wisdom and strength, rather than one of cowardice and frailty.

Medications

A few studies have evaluated the effects of sedative-hypnotics for promotion of sleep during nonduty hours of nonmedical personnel (e.g., to assist in daytime sleep after a night shift). [184] Many questions remain unanswered regarding the quality of sleep obtained after using hypnotics, the severity of hangover effects, and the potential risks of abuse. Melatonin, which is a hormone secreted from the pineal gland, may have promise as a nonaddictive daytime sleepinducing agent, but the results of existing studies are controversial.

Stimulants may have a role in the maintenance of alertness during periods of extreme sleepiness. Caffeine is frequently used in this manner. Amphetamines have been used to increase alertness in extreme situations in the military, but their use is contraindicated for normal (even high-risk) civilian work situations because of the many concerns regarding their use. Some of these concerns involve issues such as perceptual distortions, the intensity of poststimulant recovery sleep, medical side effects of use, and the potential

for addiction and abuse. The use of sedatives and potent stimulants to manipulate sleep is *not* considered an appropriate option for anesthetists.

Light Therapy

Properly timed cycles of bright light and darkness have been used in certain circumstances to facilitate adaptation to shift work. Exposure to bright light

(>7,000-12,000 lux) and darkness at the appropriate points in the circadian cycle has been shown to be able to reset the circadian pacemaker by 12 hours over 2 to 3 days. [223] This is an important finding that demonstrates the ability to make significant changes in the circadian system relatively quickly. However, this resetting of the circadian timekeeper is *critically* dependent on the timing, intensity, and duration of the exposures to light and to "total" darkness. Being off by only an hour can prevent the desired effect. Adhering to such time-critical schedules for this treatment is probably impractical for anesthetists, given the many work-related and social factors that affect their activities. Research on light treatment continues and may eventually result in more practical treatment regimens.

Regulations Concerning Work Hours

The work hours of personnel in nearly every other high-risk industry, including aviation, trucking, railroads, shipping, and nuclear power, are regulated by legislation or by rules of statutory regulatory agencies. [224] Although the duty limits are of similar magnitude in all these industries, the most comprehensive regulations are for air transport pilots operating under Part 121 of the FAA Regulations, which affects aircraft with more than 30 seats or greater than 7,500 payload-pound capacity. Currently, these include daily, weekly, and monthly limits on flight duty hours (time operating the aircraft). [225] [226] Limits on total duty (time at work with or without operation of the aircraft) have been proposed, [226] because total duty time for a pilot may be double that qualifying as flight duty per se. The current limits are worded in a complicated fashion. For example, the daily limit is expressed as no more than "8 hours between required rest periods," the required rest being (approximately) 10 consecutive hours of rest per 24-hour period. [225] The weekly limit is 30 flight duty hours, and the monthly limit is 100 flight hours. New recommendations for limits on pilot work hours are 10 hours per day of flight duty (more in multiperson crews and when crew members are allowed opportunities to sleep in the aircraft), 14 hours of total duty per day, and at least 36 continuous hours off duty per 7-day period. [226] Anesthesiologists and other medical professionals frequently violate these limits by a wide margin. In fact, nearly every on-call day for an anesthesiologist violates these limits. In 1989, the Libby Zion case in New York City brought the issue of resident fatigue to national attention. Although the details of the case are complicated, the patient's death was believed to be due to suboptimal medical care in the middle of the night, and many concluded that resident fatigue played a major role. [227] The degree to which resident fatigue was the proximate cause is open to debate, but regulatory changes dealing with house staff supervision and resident work hours did follow in New York State. Other jurisdictions have considered similar rules. These changes cap resident work hours for continuous duty (24 hours) as well as for duty hours averaged over time (80 h/wk, averaged over a 4-week period). It is not clear whether working conditions now allowed under the average weekly cap are significantly better than those previously in force, although it does seem likely for the house officers who were previously at the highest end of the spectrum (120 h/wk). These reforms were very costly to implement, and it is not clear that the regulations are being followed. Of note, even the 80-hour work week still allows for chronic sleep deprivation to ensue. It is still legal for a resident to work more hours in 1 to 2 weeks than an airline pilot can legally work in a month.

Aging

Every person understands that his or her abilities cannot be maintained indefinitely as he or she ages. On average, performance on laboratory tests of discrete sensory-motor and cognitive skills can be shown to decrease with increasing age. [228] However, there are large differences among individuals. Again, except at extreme points of performance failure (e.g., severe impairment of vision or hearing), the contribution of isolated changes in physiologic or cognitive performance is difficult to relate to real work situations. [229] [230] For one thing, the work environment is often rich with redundant cues involving multiple sensory modalities. For another, technologic compensation may be possible, as with the use of hearing aids or glasses. Finally, along with possible physiologic changes of age typically comes greater experience with a variety of situations. For many individuals, the lessons learned from experience more than offset the modest degree of physiologic impairment they face as they grow older. This compensation has, in fact, been documented for skilled typists, chess players, and bridge players. [231] Middle-aged individuals can utilize their experience to solve everyday problems better than young individuals, but for the elderly (on average), compensation by experience is no longer sufficient to offset cognitive slowing. [229] Age takes a toll on short-term (or "working") memory, [232] [233] [234] and there is evidence that aged workers are more sensitive to the interruptions of attention that are so prevalent in dynamic environments. [235] However, few of these deficits have been documented in complex work settings, largely because it is so difficult to measure performance in these domains. The issue of the aging anesthesiologist has raised considerable controversy among anesthesiologists. [236] [237] [238]

What do other industries do about this issue? There is an FAA regulation in the United States (colloquially known as the "Age 60 Rule") that bans pilots older than 60 years of age from flying under Part 121 of the FAA regulations, described earlier. This rule may soon be extended to pilots of commuter aircraft (<30 seats) regulated under Part 135, as part of an overall thrust to increase safety in commuter air transport. There are no such regulations for business or general aviation pilots operating under other regulations. The Age 60 Rule has been in force since 1959, the rationale being that "increased speeds and passenger loads of commercial airliners placed greater demands on pilots with respect

to their physical fitness and piloting skills." [239] Some may argue that the increasingly challenging nature of anesthesia practice also places greater demands on anesthetists than ever before.

The Age 60 Rule has been the topic of much debate, and the U.S. Congress mandated a review of the rule in 1979, resulting in several studies by a variety of investigators and agencies. [239] [240] [241] [242] [243] [244] The conclusions of these studies are in part contradictory. However, the most recent analysis of available data indicates no increase in accidents per hours flown as pilots approach their 60th year and only a slight hint that class III medical certificate pilots (i.e., "private pilots") have an increased accident rate when they are older than 63 years of age. [239] However, the issue is very complex, and the regulators are extremely conservative. FAA regulations do require air transport pilots (encompassing all Part 121 pilots) to pass "class I" medical examinations every 6 months. However, the medical examination process appears to be largely aimed at identifying individuals with chronic medical conditions that put them at risk for sudden incapacitation (such as significant coronary heart disease). Pilot incapacitation during high-workload phases of flight has been shown in simulator testing [245] to lead to a significant rate of crashes, even when there is a second pilot at the controls. These physical examinations should weed out pilots with severe cognitive or sensory-motor deficiencies, but they are not designed to assess subtle aspects of performance change resulting from age. Of course, there are no requirements for medical examination or certification of anesthesiologists.

It is likely that age alone does not independently cause a significant performance decrement, but age correlates with other factors that are likely to affect performance. The concern about aging professionals revolves more around the loss of knowledge and skill as one gets farther from initial training, rather than the loss of fundamental mental capacities. Thus, the originally well-trained practitioner who keeps abreast of the changing standard of care, and who exercises emergency skills frequently, is less likely to be affected by advancing age than is the marginal practitioner whose knowledge and skills were frozen immediately after completion of training and who practices in a low-complexity environment. The FAA regulations deal with this issue for air transport pilots by requiring frequent (every 6 months) evaluations of performance by FAA-certified check pilots. These evaluations are performed both during actual flights and in realistic simulators, and they, in essence, check fitness for duty regardless of age. There is currently no similar program in anesthesia to assess the competency of practitioners at any age, except for initial board certification, which is voluntary. Periodic recertification will be required by the American Board of Anesthesiology after the year 2000, but it is not mandatory to be Board-certified to practice anesthesia, and the recertification examinations are not likely to be as intense, as thorough, or as frequent as those performed by air transport pilots.

Illness and Drug Use

Every anesthetist is vulnerable to transient illnesses, which in some cases probably reduce performance ability. All personnel are vulnerable to chronic medical conditions, which could directly or indirectly affect their fitness and performance capabilities. The culture of the caring professions often leads individuals to continue to work with illnesses that would cause other professionals to stay at home or to seek medical advice. The performance-shaping effects of the illness can be exacerbated by the use of either over-the-counter or prescribed medications. The degree to which illness and medications affect anesthetist performance is unknown.

A serious problem for anesthetists is that of drug abuse (Ch. 84) . [246] [247] [248] [249] [250] [251] It is estimated that up to 8 percent of physicians should be classified as alcoholics. In an anonymous survey of anesthesia personnel from one institution, 75 percent of respondents reported drinking alcohol on a regular basis. [252] They reported drinking an average of 1.6 drinks per day on 2.7 days per week. Just less than 10 percent of subjects reported having been hung over while conducting anesthesia, and 40 percent reported having given anesthesia within 12 hours of alcohol consumption; 84 percent stated that alcohol use never adversely affected their clinical performance.

The degree to which small doses of alcohol or hangovers affect performance on complex, real-world tasks is uncertain. Some studies of general aviation or navy pilots [182] [244] [253] [254] suggested that hangover effects can degrade performance even when more than 8 hours have elapsed since alcohol consumption and there is no

detectable blood alcohol level. However, although statistically significant, the performance changes seen in these studies may not have been functionally significant. These studies [244] [253] [254] also suggested an interaction among age, workload, and hangover in causing performance decrements. However, the "aged" cohort was defined as 31 years of age or older and was compared with a cohort of young pilots in their early 20s. Extrapolating these results to the anesthesia domain is difficult.

Nonetheless, the natural history of serious abuse of alcohol, cocaine, sedatives, or narcotics by anesthetists is such that cognitive performance will at some point be seriously compromised. However, addiction specialists frequently report that job performance is one of the last areas of life to become impaired. [250] For this reason, the period of time in which the addicted anesthetist's performance in the OR is significantly impaired is a relatively small fraction of the total time during which drugs are abused. Although this in no way excuses the practice of conducting anesthesia while under the influence of drugs, it may account for the fact that reports of addicted anesthesiologists are, unfortunately, common, whereas reports of overt patient risk or harm resulting from an addicted physician's errors are unusual.

Anesthesiology has been at the forefront of dealing with impaired medical personnel. The management of those discovered with drug impairment is fairly standardized, [246] [248] but the question whether to return these individuals to anesthesia practice is increasingly controversial, even when they return under carefully monitored reentry protocols. [251] The main risk appears to be to the addict's own safety, although questions about patient safety can never be eliminated.

Ultimately, the responsibility rests with the anesthetist to ensure that his or her own performance level is sufficient for the work at hand. Pilots utilize a mnemonic checklist to review the effects of potential performance-shaping factors

TABLE 80-3 -- Examples of Hazardous Attitudes and Their Antidotes

(Not Available)

Modified from Federal Aviation Administation [256]

and are instructed not to fly if they are impaired for any reason. The difficulty in anesthesiology (and to some degree in aviation) is that the real-world organization and incentives of many practice settings do not provide mechanisms for personnel to excuse themselves if they are temporarily impaired. Ironically, there may now be better means to identify and support the practitioner with a serious addiction than there are for the more common occurrences of profound sleep deprivation or impairment by a transient or chronic illness.

Hazardous Attitudes

Attitudes are an important component of ability, which can affect performance as strongly as physiologic performance-shaping factors. [255] Psychologists studying judgment in aviators have identified five attitude types as being particularly hazardous, and they have developed specific antidote thoughts for each hazardous attitude. [256] These attitudes as related to anesthesia are shown in Table 80-3 (Table Not Available) . The aviation psychologists instruct pilots physically to verbalize the antidote thought whenever they find themselves thinking in a hazardous way.

The invulnerable and macho attitudes are particularly hazardous for anesthetists. They are compounded by production pressures to do more cases in less time with fewer cancellations and with less opportunity for preoperative evaluation. The feeling that a catastrophe "cannot happen to me" and that perfect performance can always be called on to avert a disaster can lead to cavalier behavior and poor planning. It can alter thresholds for believing that abnormal data represent a problem, thereby leading to the fixation error of "everything's OK." In 1984, Cooper et al [148] wrote about their studies of critical incidents in anesthesia:

> Perhaps the most insidious hazard of anesthesia is its relative
> safety. The individual anesthetist rarely, on average, will be responsible for
> a serious iatrogenic complication. It is our impression from the process of
> collecting incidents, that most seemingly minor errors are not taken seriously
> and that risk management depends almost solely on the anesthetist's
> ability to react instinctively and flawlessly every time a problem arises.

Expert human performance is the anesthetist's most powerful tool to safeguard the patient. Planning to avoid catastrophe is likely to be more successful than battling to avert it, however.

SIMULATORS

The preceding discussion of human performance in anesthesia rests heavily on data acquired using computer-based simulators in anesthesia. Anesthesia simulation is an emerging field. In this section, the history of the development of anesthesia simulation is presented, as well as the current status of the field.

Simulation refers to the artificial replication of sufficient elements of a real-world domain to achieve a stated goal. The goals can include understanding the domain better, training personnel to deal with the domain, or testing the capacity of personnel to work in the domain. The fidelity of a simulation refers to how closely it replicates the domain and is determined by the number of elements that are replicated and the error between each element and the real world. The fidelity required depends on the stated goals. Some goals can be achieved with minimal fidelity, whereas others require very high fidelity.

Simulation has probably been a part of human activity since prehistoric times. The rehearsal of hunting activities and of warfare was a likely occasion for simulating the behavior of prey or enemy warriors. Technologic simulation probably dates back to the dawn of technology itself. Good and Gravenstein [257] point to the Roman quintain as a technologic device that crudely simulated the behavior of an opponent during sword fighting. If the swordsman did not duck at the appropriate time after striking a blow, he would be hit by a component of the quintain. In modern times, preparation for warfare has been an equally powerful spur to the development of simulation technologies especially for aviation, shipping, and the operation of armored vehicles. These technologies have been adopted by their civilian counterparts, but they have reached their most extensive use in commercial aviation.

Aviation Simulation History

Although some aircraft simulators were built between 1910 and 1927, none of them could provide the proper feel of the aircraft because they could not dynamically reproduce its behavior. [258] In 1930, Edwin Link filed a patent for a pneumatically driven aircraft simulator. The "Link Trainer" was a standard for flight training before World War II, but

TABLE 80-4 -- Use of Simulators in Complex Work Environments

(Not Available)

From Singleton [259]

the war accelerated its use and the further development of flight simulators. In the 1950s, electronic controls replaced pneumatic ones through analogue, digital, and hybrid computers. The aircraft simulator achieved its modern form in the late 1960s, but it has been continuously refined. Aviation simulators are so realistic now that pilots with experience flying one airliner are routinely certified to fly totally new or different aircraft having never flown the actual aircraft without passengers on board. Similar stories of the development of simulators can be told for a number of other industries.

Uses of Simulators

Although simulators were originally used to provide basic instruction in the operation of aircraft controls, [258] the variety of uses of simulators in general has expanded greatly in the last 30 years. Singleton [259] outlined the possible uses of simulators in all types of complex work situations (Table 80-4) (Table Not Available) .

Thus, simulation can be seen as a powerful generic tool for dealing with human performance issues (training, testing, and research), for investigating human-machine interactions, and for the design and validation of equipment. As delineated later in this chapter, each of these uses is potentially relevant to anesthesiology.

Classification of Patient Simulators

There is no accepted classification scheme for patient simulators for use in anesthesia. Any classification involves some overlaps and gray areas. The following classification and definitions are used in this chapter. In addition to simulators, there are also computer-assisted instruction programs and computer-based training devices. Although the training devices may replicate certain portions of the anesthesia domain, they do not attempt to replicate the bulk of the work environment. Some individuals consider the screen-only simulator as a training device and not as a simulator. Computer-assisted instruction programs and training devices are not reviewed in this chapter. A patient "simulator" is a system that presents the clinical work environment (e.g., operating room, PACU, ICU) in one of the following ways:

1. In actual physical reality, defined as a realistic simulator or a hands-on simulator.
2. On a computer screen only, defined as a screen-only simulator or microsimulator.
3. Using virtual reality, defined as a virtual reality simulator.

Virtual reality refers to a set of techniques in which one interacts with a synthetic ("virtual") environment that exists solely in the computer. [260] In the typical conception of virtual reality, the representation of the synthetic environment is fed fairly directly to the eyes and ears through goggles or visors and headphones (i.e., there is no "screen"). The actions of the user in the environment are translated directly from typical physical activities, *not* through manipulating a special pointing device. There is a continuum of realizations of this ideal, involving compromises on these input/output modalities. At one end of the continuum, which I call a "complete virtual reality simulation," the participant is immersed in a virtual world that fully replicates at least three sensory inputs--vision, hearing, and touch (more technically known as a haptic/kinesthetic system) [260] --and allows complete physical interaction with the world. At the other extreme of the continuum is a screen-based simulator, which generates a limited virtual world, but it restricts its output to a screen display and provides interaction with the virtual world only through a pointing device. The screen-based simulator provides an interface to the human sensory system that is very far from physical reality, whereas a complete virtual reality simulation may be, in its most advanced form, nearly indistinguishable from the real world. A "partial" virtual reality simulator would replicate fewer senses (or less complete replication) and/or could restrict physical interaction with the world. Finally, one can imagine hybrids of realistic simulators and virtual reality simulators in which the virtual reality representation is overlaid onto a real physical environment.

A complete virtual reality patient simulator would be very complicated because it requires the following:

1. A complete computer model of the patient, the environment, and the *function* of every object in the environment that could be utilized (e.g., monitoring devices, carts).
2. A means of tracking visual, audio, and touch fields of the user to determine what is to be displayed and to identify what physical actions are being performed.

3. Appropriate display hardware for every sensory modality and appropriate input hardware for each action pathway (e.g., touch, speech).
4. Hardware to compute all the models, to conduct the tracking, and to produce all the outputs to the display hardware *in real time.*

Virtual reality is a rapidly developing field. There is intense interest in virtual reality in a number of domains, particularly the military and entertainment. Although the potential of this approach is very exciting, practical virtual reality simulators are currently quite limited in capability or extremely expensive to produce, or in many cases, they are both limited and expensive.

Components of a Patient Simulator

An anesthesia patient simulator system contains several components (Fig. 80-10) . A set of outputs make up a representation

Figure 80-10 A schematic diagram of the generic architecture of patient simulator systems. The simulator generates a representation of the patient and the work environment using appropriate interface hardware and/or display technologies. The representation is perceived by the anesthesiologist, whose actions are then input to the simulator through physical actions or input devices. The behavior of the simulated patient is determined through sets of interlinked physiologic models and control logic that are manipulated by the instructor or operator through a workstation that allows selection of different patients, abnormal events, and other features of the simulation.

of the patient, the OR environment, and diagnostic and therapeutic equipment. For screen-only simulators, this representation is generated graphically on the computer screen. For realistic simulators, the representation is generated on actual clinical equipment and on a patient mannequin in an actual OR-like setting. The clinical equipment and the mannequin are stimulated or actuated by interface hardware. Realistic simulators often use physical stimulation of clinical equipment in addition to electronic stimulation. For example, the mannequin can actually be ventilated with any desired mix of inspired gases. Carbon dioxide and other gases can be introduced by the simulator into the mannequin's lungs physically to provide the desired elements of gas exchange. A real respiratory gas analyzer can thus be used to measure the inspired and expired gases.

The simulator must have control logic by which changes in the simulated patient's condition can be generated, to be sent to the appropriate output of the representation. Originally, the control logic was embedded in the software as a fixed sequence of events, or it required continuous inputs from the instructor working from a script. Newer simulators incorporate a more sophisticated technique using mathematical differential equation models of a patient's physiology and pharmacology to provide the bulk of the control logic. These models can be tailored to represent different patients with different pathophysiologic abnormalities. However, not all states or changes in a patient can be modeled using differential equations. For example, ventricular fibrillation is a totally different state of heart rhythm that does evolve continuously from normal rhythms. No model can predict *exactly* when a patient will suffer a myocardial infarction or when an ischemic heart will begin to fibrillate. A model can only predict those factors that increase the likelihood of such events. Thus, most simulators incorporate other modeling techniques in addition to the basic physiologic and pharmacologic mathematical equations, including finite-state models, instructor initiation of abnormal events, and even manual modulation of modeled parameters. In finite-state models, different underlying clinical states are defined, each of which has appropriate entry conditions as well as transition conditions to other states. When an entry or transition condition is met, a new state becomes active, which may directly trigger new observable phenomena (e.g., ventricular fibrillation) or may alter constants in the mathematical models that then evolve in time. [261] [262] [263]

The control logic of realistic simulators is manipulated via an *instructor/operator' s station (IOS)* that allows the instructor to create specific patients, select and implement abnormal events and faults, and monitor the progress of the simulation session. There may also be a remote-control hand-held IOS in addition to the main IOS. The IOS typically provides logs of physiologic changes and the anesthesiologist's response and may provide graphics to support the analysis of a simulation run. Some screen-based simulators provide advice and tutorials linked to the management of simulated events. With realistic simulators, detailed records of the simulation and the actions taken may also be made using video and audio recording of the anesthesiologist working in the simulator.

Sim One: An Anesthesia Simulator Before Its Time

The potential of simulators for training anesthetists was recognized 30 years ago. In the late 1960s, an electromechanical

TABLE 80-5 -- Clinical Features Supported by Sim One[a]

Spontaneous ventilation as well as ability to be ventilated by external bag or ventilator
Palpable pulses with appropriate pulse amplitude
Bucking
Pupillary dilation and constriction
Laryngospasm
Regurgitation of gastric contents
Frowning
Variable jaw tension
Fasciculation
Force-sensitive teeth
Force-sensitive lower lips
Abdominal distention (esophageal intubation)

[a] Sim One, product of the Sierra Engineering Company, Sierra Madre, Calif.

realistic anesthesia simulator was developed (Sim One). [264] [265] Sim One was produced by the Sierra Engineering Company based on specifications from physicians and medical educators from the University of Southern California. [264] [265] The goal was to construct a simulated patient for learning the skill of endotracheal intubation, along with the induction of anesthesia. The system consisted of a patient mannequin comprising the head, neck, thorax, upper abdomen, and arms. The mannequin and the table on which it was permanently mounted contained electromechanical and pneumatic actuators for a variety of clinical features (Table 80-5) . Appropriately for the late 1960s (but not for today), Sim One provided outputs only for clinical cues such as heart sounds and peripheral pulses; it did not provide outputs to any electronic monitors.

Sim One could electronically sense a variety of clinical actions. Placement of the mask on the mannequin's face was sensed by tiny reed relays embedded in the plastic flesh of the face. A special magnetic endotracheal tube was constructed with iron molded into the plastic. Its position could be determined by magnetic sensors. Sim One could automatically recognize the identity and amount injected of four drugs: thiopental, succinylcholine, methoxamine, and ephedrine. This system depended on each drug's being administered using a specific size of needle, and thus it could not be expanded to identify a larger number of drugs. A standard anesthesia machine was specially instrumented to report gas flow rates (but not the concentration) of volatile anesthetic.

A computer program provided the control logic. For example, the program responded to drugs based on the dose-time-effect curves for those drugs. However, there was no true modeling of pharmacokinetics or pharmacodynamics. The Sim One IOS provided readouts of the system's internal status and external outputs. Chart

recordings of multiple variables could be produced. The IOS provided toggle switches or buttons to actuate a variety of preprogrammed events, including cardiac arrest, bucking, increased and decreased blood pressure or heart rate, changes in respiratory rate, and occlusion of the mainstem bronchus.

Produced in 1968, Sim One was a technologic marvel, costing approximately $100,000 (on the order of $450,000 today) to design and build a single hand-crafted unit. It incorporated many features of today's simulators, and it even included a number of desirable features that are not currently implemented. Sim One was used for several training purposes, of which only a few involved anesthesiologists. The investigators used the simulator to speed the training of anesthesia residents in endotracheal intubation. [264] [266] Ten novice residents were randomly allocated to receive either no additional training or special training in intubation using Sim One (5.5-9.5 hours of training over a 2-week period). The investigators attempted to measure the proficiency of the ten residents at intubation by scoring blinded copies of the residents' anesthetic records. [266] The scoring for each record was a binary decision ("plus" or "minus") whether "On the basis of what you see on this chart, would you be willing to trust the anesthesiology resident in an operating room without supervision?" Performance criteria were set as (1) four consecutive plus ratings, (2) seven of eight consecutive cases with a plus rating, and (3) nine of ten consecutive cases with a plus rating. There was a statistically significant difference between the groups in the number of cases (and the number of days) to achieve the nine-out-of-ten criterion, but there was no difference in the time to achieve the other criteria. It took the simulator-trained residents 45.6 days to reach this criterion, whereas the control group took 77.0 days.

Although the investigators' intent was admirable, this study was seriously flawed. The simulator group received special one-on-one attention that the control group did not receive. The scoring system for the anesthetic records was poorly defined and ambiguous. The performance criteria established were completely arbitrary. Appropriate statistical techniques were not utilized to evaluate the results. In another publication, [267] the investigators stated that residents cut their number of errors in anesthesia induction by half and reduced the average time to perform an induction by one-third after training with Sim One; however, no details of these experiments were provided. These investigators also listed other training uses including teaching nurses to perform "ventilator application" (perhaps this referred to intermittent positive-pressure breathing treatments), intramuscular injection, recovery room care, and pulse and respiration measurement. They discussed the cost effectiveness of Sim One in terms of decreased faculty time to impart specific skills, improvements in student performance, and potential reduction in patient discomfort and risk. In many ways long before their time, they stated that:

> the effectiveness of simulation depends on the instructional method with which simulation is being compared. For example, if there is no alternative training method available ... the effectiveness of a simulation device probably depends on the simple fact that the device provides some kind of learning experience as opposed to none. When a simulation device is compared with conventional on-the-ward training, however, the device's effectiveness seems related to the degree to which learning a given task is facilitated by systematic presentation of that task. Systematic presentation is not easily achieved on the wards, whereas simulation devices can provide a number of systematic patterns, such as graduation of difficulty level or complexity.

The Sim One project drifted into oblivion (a planned Sim Two was never built) for a number of reasons. [268] It was clearly ahead of its time technologically, although changes in techniques of anesthesia and of monitoring have outstripped

Sim One's ability to replicate important aspects of the anesthesia work environment. For example, only four drugs could be used, and there were no outputs for electronic monitors. Sim One was costly, and many anesthetists of the time viewed computers and technology with suspicion. Finally, I believe that both the investigators and the profession as a whole did not have sufficient understanding of the relevant issues of human performance for which simulator training, testing, and research would be an ideal tool. Thus, although we can now see that Sim One had great potential for teaching personnel about the management of a variety of challenging perioperative situations, its use in anesthesia then was focused primarily on standard inductions and endotracheal intubation. We now know that, although simulator training in intubation can be helpful (and simulator training in complex airway management may be even more useful), most residents rapidly acquire reasonable skill at intubation through clinical experience. To be truly useful, the simulator must be targeted at a different set of skills. Thus, for these and for many other reasons lost in time, the legacy of Sim One essentially disappeared.

Reinvention of Anesthesia Simulators

Several anesthesia simulators were developed and introduced in the mid to late 1980s (see later). Each was an independent development, and none had any connection with the Sim One project. Several factors led to these developments. Most prominent was the new availability of powerful (compared with advanced minicomputers of a decade earlier) personal computers at a relatively cheap price. The popularity of a variety of simulators for personal computers (e.g., flight simulators, driving simulators) demonstrated that simulation of complex systems was possible using a personal computer, and a screen-based simulator could give users some degree of "feel" that they had been in the environment. For realistic simulators, inexpensive clinical waveform generators became available. These produced typical clinical signals for ECG and invasive pressure monitors, and the waveforms produced could be selected by an external computer. On the applications side, the public and the anesthesia profession had become more aware of the utility of simulation-based training for military and commercial aviation, space flight, automobile driving, shipping, military command and control, and operation of nuclear power plants. Media coverage of the space program and the corrective responses to the Three Mile Island nuclear accident highlighted the role of simulators. Another pivotal factor was a growing interest within anesthesiology in studying the anesthetist's performance and the human factors and ergonomics of the anesthesia work environment. [4] [14] [39] [148]

By the time of this writing, nearly every system has evolved through several generations of improvements. I briefly describe each of the systems and its evolution. Although several "homemade" simulators are still in use in the United States (University of Alabama) and in Europe (see later), two systems are being offered commercially. Commercialization has enabled many institutions to acquire simulators without having to invest in the engineering and clinical expertise to develop a system from scratch. The descriptions given in the following sections are very brief, and the introduction of new or upgraded features in all the simulation systems continues steadily. For up-to-date information about any of the current systems, the reader is advised to contact the manufacturers or authors directly.

Screen-Only Simulators: SLEEPER and BODY Simulation

In San Diego, Smith and associates [269] [270] [271] continued a long series of work concerning the modeling of the cardiopulmonary systems and of drug distribution. The group developed a set of linked physiologic and pharmacologic models that accurately reproduced major elements of the patient's clinical behavior. The early work used analogue and hybrid computers, [269] [270] [271] but for the last 10 years, the evolving systems have used standard personal computers. When the models were combined with an appropriate graphic representation of the patient and clinical data on the computer screen, and a graphic user interface for the input of clinically relevant actions, the system became a complete screen-only simulator known originally as SLEEPER. [272] SLEEPER used a complex transport model to deal with gas exchange and drug distribution. This model provided the opportunity to create "drugs" with characteristics unlike those of any existing drug, as well the ability to predict the concentration of drugs in specific anatomic regions (e.g., myocardium or gray matter).

In collaboration with Marquette Electronics, Inc., (Milwaukee, Wis) the SLEEPER software has evolved into a program called BODY Simulation. In addition to extensions to the original transport and physiologic models, a unique feature of BODY is that the monitoring equipment and anesthesia delivery equipment are high-resolution computer-screen replicas of actual or prototype Marquette Electronics equipment. This lends additional realism to the system as well as allowing it to be used to test the usability of the user interface of the clinical equipment.

Anesthesia Simulator Recorder and Anesthesia Simulator Consultant

At the University of Washington, Seattle, physician Howard Schwid, (formerly a research fellow with Ty Smith) and programmer Daniel O'Donnell developed a screen-based simulator originally called the Anesthesia Simulator Recorder (ASR, AneSoft Corporation, Bellevue, Wash). [261] [262] [263] This then evolved into the ASC. It was specifically geared to training anesthetists in managing patients, with more emphasis than SLEEPER (or BODY Simulation) on critical incidents and less emphasis on pharmacologic and physiologic plotting. This system provides graphic representations of mock monitoring displays and clinical equipment, as well as photographs to display the patient and actions taken on the patient (Fig. 80-11) (Figure Not Available) . Interaction with this system also uses a desktop pointing device. The ASC uses traditional pharmacokinetic and pharmacodynamic models drawn from the pharmacology literature to track drug levels and effects of more than

70 drugs, as opposed to the physical transport models used in SLEEPER and BODY Simulation.

Figure 80-11 (Figure Not Available) Computer screen display of the Anesthesia Simulator Consultant (ASC). The actual screen is in full color. Additional information and actions can be selected using a pointing device ("mouse") and menus. *(Courtesy of Howard Schwid, M.D., with permission)*

A unique feature of the ASC is that 80 cases have been contributed by nationally recognized experts. A number of critical events can be preselected by the user or selected at random by the system.

Schwid and his collaborators conducted evaluations of the original ASR with 44 anesthesia residents and faculty members at several teaching institutions in the United States. [262] The results showed that the ASR was easy to learn to use, was reasonably realistic, and was rated as an outstanding teaching device. More than 3,000 copies of ASR or ASC have been distributed throughout the world (H. Schwid, personal communication).

Realistic Simulators

Comprehensive Anesthesia Simulation Environment

In 1986, Gaba and DeAnda began developing the Comprehensive Anesthesia Simulation Environment (CASE) series of anesthesia simulators with a primary goal of conducting research into decision-making by anesthetists (the first transcript of an anesthetist responding to a simulated intraoperative crisis was obtained in spring, 1986). The architecture of the first-generation CASE 1.2-1.3 simulator [273] used commercially available clinical waveform generators to provide signals to actual clinical instruments. Other devices, such as the automated noninvasive blood pressure cuff were "simulated" as a virtual instrument using a computer program on a Macintosh Plus computer acting as a virtual instrument.

The CASE 1.2-1.3 mannequin was modified to enable occlusion of the left mainstem bronchus, infusion of CO_2, and the insertion of intravenous lines. This mannequin allowed mask ventilation, intubation, and auscultation of breath sounds, but it did not have palpable pulses or spontaneous ventilation. The behavior of all of the waveform generators and actuators was coordinated using a central control computer. The control logic of CASE 1.2 was provided by an operator typing commands at the IOS based on a written simulation script describing the appropriate changes for a variety of anticipated actions on the part of the subject in the simulation. An experienced anesthesiologist observed the activities of the subject and directed the simulator operator using a private headset intercom. This control logic and IOS enabled the simulator to respond to any actions on the part of the subject, not just those that were previously anticipated.

The CASE 1.2 system was evaluated by residents [273] (and later faculty and private practitioners) and was rated as very realistic, except for the plastic mannequin. The success of such a crude system, which lacked physiologic and pharmacologic models, lies in the exceptional variability of patients and in the ability of anesthetists to "suspend disbelief" if placed into a plausible clinical situation. No anesthetist can

predict the exact behavior of a *specific patient* in response to drugs and actions. The responses of the simulator only have to be plausible for the situation to appear very realistic. This is especially true for critical event training situations in which plausible but unusual events are presented. On the other hand, physiologic and pharmacologic models do offer substantial advantages, including greater consistency and reproducibility of situations, the ability to handle multiple physiologic changes simultaneously, and greater automation of the simulation process.

In 1989, CASE 2.0 was unveiled. This was a major redesign of the system that incorporated a physiologic model of the cardiovascular system. [274] Waveforms and electronic data streams, including heart sounds, were generated directly from the cardiovascular model. CASE 2.0 was used extensively in the conduct of the Anesthesia CRM (ACRM) training program described in a subsequent section of this chapter.

Commercialization

In 1992 to 1993, the CAE-Link Corporation (now called Medsim Eagle Simulation, Inc., Binghamton, NY), a manufacturer of military aviation and space flight simulators, licensed technology from Gaba's simulator group and from Schwid's group as part of its development of a commercial anesthesia simulator system. *

This simulator was originally called the Virtual Anesthesiology Training Simulator System, but the name was later changed to the Eagle Patient Simulator. Version 2.0 of this device was introduced in late 1995 (Fig. 80-12) (Figure Not Available) . It is completely operated by physiologic, pharmacologic, and finite-state models. The Eagle Patient Simulator contains complete models of cardiovascular, pulmonary, fluid, acid-base-electrolyte, and thermal physiology. It includes computer-controlled electromechanical lungs with dynamically changeable compliance, embedded totally within the mannequin's thorax, so that the patient mannequin can be moved onto an OR table, ICU bed, or emergency room gurney. The interface components are housed in a rolling cart that can be placed underneath or beside the patient's bed. The airway of the mannequin allows mask ventilation, endotracheal intubation, use of the laryngeal mask and the Sheridan Combitube (Kendall, Mansfield, Mass), and cricothyrotomy or transtracheal jet ventilation. The mannequin provides electronically generated heart sounds and breath sounds, dynamically changeable airway anatomy, palpable pulses, and a thumb twitch responding to stimulation by actual nerve stimulators.

Some variants of the mannequin provide eyelids that open and close, eyes that move, and pupils that constrict or dilate and respond to light. Arm movements support decerebrate or decorticate posturing. Traumatic injuries can be simulated, and procedures common in trauma settings (such as placement of a chest tube) are possible.

Quantitative physical elimination of CO_2 through the lungs is provided, so that a clinical gas analyzer can be used in its usual fashion. Other gases wash in and wash out appropriately but there is no uptake and distribution of O_2, nitrous oxide, or volatile agents in the standard unit.

The IOS in the Eagle Patient Simulator uses a graphic user interface (Fig. 80-13) (Figure Not Available) to provide a rich set of tools for the instructor to choose and implement different *events* (up to five events can run simultaneously), different simulated *patients,* and complete *scenarios.* The instructor can tailor each event in advance, altering features such as the onset time, severity, or manifestations of the event. Tailored events can be saved under different names, allowing the creation of a library of events or situations. A new drug editor allows alteration of drug kinetic and dynamic parameters.

Many inputs to the device are automatic. A gas analyzer recognizes all inspired gases and passes their values to the pharmacologic models. An automated drug recognition system detects and identifies the drug administered and its dose of drug administration through an electromagnetic

Figure 80-12 (Figure Not Available) The Eagle Patient Simulator (version 2.0) mannequin and interface cart. The mannequin rests on a standard operating room table. Interface and linkage hardware is contained in the rolling cart below the table. The simulator is shown in a re-creation of an operating room at the Veterans Affairs Palo Alto/Stanford University Simulation Center, Palo Alto, Calif. *(Courtesy of Medsim Eagle Simulation, Inc., Binghamton, NY)*

* The author and his partner received a payment from CAE-Link to license their simulator technology and the author and his partner receive a small royalty on the sale of each anesthesia simulator by Medsim Eagle Simulation, Inc. The author is periodically a paid consultant to Medsim Eagle Simulation, Inc., on anesthesia simulator development.

Figure 80-13 (Figure Not Available) The instructor/operator's station (IOS) of the Eagle Patient Simulator (version 2.0). This screen provides complete control of patients, events, and physiologic parameters. The right-hand window is an "event tailoring" window in which the characteristics of a critical event to be simulated can be modified and stored in a library of different events. *(Courtesy of Medsim Eagle Simulation, Inc., Binghamton, NY)*

coding object affixed to each stopcock and detected by an instrumented stopcock manifold. Like the ASC, the system can track the kinetics and dynamics of more than 70 different drugs. The Eagle Patient Simulator also logs simulator outputs, state changes, and actions by the subject that are input to the simulator.

Other features include a model of CPB, so that cardiac surgical situations can be presented, including weaning from bypass. The bypass model can also be used to teach clinicians about the physiology and technical issues of CPB.

Gainesville Anesthesia Simulator

Shortly after the CASE simulator was developed, a similar simulator was produced at the University of Florida, Gainesville, by a team headed by Good and Gravenstein. [257] This system, called the Gainesville Anesthesia Simulator (GAS), also used commercially available waveform generators under the control of a central computer, along with a mannequin and real OR equipment. GAS could stimulate noninvasive blood pressure measurement devices and also provided palpable pulses. Unlike CASE, it was capable of spontaneous ventilation using a mechanical lung placed inside the operating table on which the mannequin was mounted. An interesting component of GAS was an anesthesia machine that was modified to incorporate a variety of mechanical faults that could be triggered electronically.

Over time, other important features have been added to GAS, including a complex quantitatively accurate physical simulation of multiple gas exchange. The lung concentrations of O_2 , nitrous oxide, N_2 , and one volatile anesthetic could be physically made to match the alveolar gas content predicted by a mathematical model of gas exchange and anesthetic uptake and distribution. Another added feature is a moving thumb that responds appropriately to stimulation from a nerve stimulator, based on the level of neuromuscular blockade. The Gainesville group then developed a simulator control system using physiologic and pharmacologic models.

Commercialization

The GAS was also commercialized, initially with Loral Data Systems, and later via an independent spinoff company, with Loral Data Systems as a minority shareholder, Medical Education Technologies, Inc. (METI, Sarasota, Fla). The METI Human Patient Simulator (Fig. 80-14) (Figure Not Available) also uses full physiologic and pharmacologic mathematic models. Its mannequin supports numerous clinical cues and interventions such as pulses, breath sounds, heart sounds, and invasive airway management. It provides outputs for nearly all modalities of invasive and noninvasive monitoring. Like its predecessor GAS, it continues to provide quantitative physical modeling of uptake and distribution of several gases. The newest version of the Human Patient Simulator

---

Figure 80-14 (Figure Not Available) The METI Human Patient Simulator. The mannequin rests on a standard operating room table. Interface and linkage hardware is contained in the tall cart behind the table. *(Courtesy of Medical Education Technologies, Inc., Sarasota, Fla)*

has moved the lung system to a remote interface cart, thus freeing the mannequin from its table and allowing for full-force cardiopulmonary resuscitation chest compressions.

The IOS of the Human Patient Simulator runs on a personal computer and allows real-time control of parameters and situations. A pen-based remote personal computer can be used as the IOS. The user interface primarily involves selection of files from menus and is less of a traditional graphic user interface than on the Eagle Patient Simulator.

Some unique features of the Human Patient Simulator include a genital/urinary system that allows user selectable urine output and Foley catheterization (the mannequin contains interchangeable genitals to provide for either patient gender), and an automatic drug-recognition system that uses a bar code scanner embedded in the stopcock manifold assembly (a design first sketched but not implemented for CASE 3.0).

Leiden Anesthesia Simulator

At the 1992 World Congress of Anesthesiologists, a group from Leiden, the Netherlands, led by Chopra and Bovill, unveiled the Leiden Anesthesia Simulator. [275] This simulator used the same architecture as CASE 1.2 and replicated many of its features as well as some of those of GAS. (In fact, the Leiden simulator was derived in part from technical information provided to the Leiden group by the Stanford investigators.) Like GAS, the Leiden simulator incorporated a mechanical lung capable of spontaneous ventilation. A new control logic IOS allowed the instructor to select from a number of scripted critical events and to control different physiologic variables directly. The addition of physiologic and pharmacologic models to the Leiden simulator was planned.

Anaesthesia Simulator SOPHUS

The Anaesthesia Simulator SOPHUS was developed by a group of anesthesiologists and scientists in Denmark (Herlev Hospital, Roskilde University, and Riso National Laboratory). All necessary physiologic parameters are animated and controlled by signals from the computer. Simulation of human response to anesthesia is based on detailed mathematic models of pharmacokinetic/dynamic processes and the cardiovascular system. However, the Anaesthesia Simulator SOPHUS does not appear to be quite as comprehensive as the Eagle Patient Simulator or the Loral Human Patient Simulator. The SOPHUS simulator is also in use at the University of Basel, where it has been adapted to form the Wilhelm Tell simulator. A unique feature of the Wilhelm Tell simulator is the addition of perfused bovine or porcine organs from a slaughterhouse, on which surgeons can perform laparoscopic procedures while anesthesiologists manage the patient.

Other "Homemade" Realistic Patient Simulators

A simulator apparently roughly equivalent to CASE 1.2 has been developed at Stavanger College, Stavanger, Norway (Stavanger College World Wide Web page). A less realistic simulator (ACCESS), which is a screen-based simulator with the addition of a nonintubatable mannequin as a "prop," was developed at the University of Wales. [276]

Virtual Reality Simulators

A prototype virtual reality anesthesia simulator has been under development by a commercial firm (headed by British anesthetists at the University of Nottingham) called Virtumed Limited. In a prototype discussed in the *Sunday Times of London,* [277] the display apparently uses an off-the-shelf visor display to depict slightly cartoonish renditions of the OR, the patient, and certain pieces of clinical equipment (e.g., anesthesia machine, a mock-monitor screen). As of this writing, there is no published experience with this system.

Although virtual reality simulators have many theoretical advantages over screen-based and realistic simulators (e.g., realism, virtual "hands-on" interaction, instantaneous reset of the environment), these advantages are currently offset

---

by the immaturity of the field. In spite of considerable hype about virtual reality, such systems are now either very limited in capability or very expensive, or in most cases, they are both limited and expensive. A true virtual reality "immersion" experience in a patient care setting comparable to that obtainable using a realistic simulator is not yet on the horizon.

Nonetheless, it is likely that virtual reality techniques will eclipse other types of simulators within 10 to 20 years. [278] In the interim, I believe that virtual reality will be used primarily to augment the display representation of current screen-based simulators.

Experience With Patient Simulators in Anesthesia

The new patient simulators have been in use in anesthesia for more than 10 years, and there has already been considerable collective experience with the devices. Their use for research on decision-making has been covered in preceding sections of this chapter. This section and those that follow cover the use of simulators for training, evaluation, and for future research in decision-making and human factors.

Training

Medical Students

Many simulation centers have used their devices for medical student training. Several curricula exist:

1. Educational sessions and demonstrations concerning basic cardiopulmonary physiology or pharmacology; in some institutions, these sessions replace animal laboratory exercises. [279]
2. Introduction to the integrated management (i.e., interleaving of diagnosis and therapy) of the critically ill patient; this training is offered to immediate preclinical medical students as part of their preparation for clinical medicine course.
3. Anesthesia practicum for clinical students during anesthesia clerkship. [280]

Anesthesia Residents

The ASR/ASC was highly rated by residents and faculty and is now available as a voluntary resource at approximately 50 percent of U.S. anesthesia training institutions. When asked, the vast majority of residents at the University of Washington expressed recognition of their own need for additional training in handling critical incidents and the likelihood that the ASC exercises would help them. Nonetheless, it was found that only 20 percent of residents completed the prescribed set of 12 simulations on a voluntary basis. Thus, the University of Washington program has made these exercises mandatory. The printed log of each simulated case is reviewed by a faculty member, who critiques the case management of the resident (H. Schwid, personal communication).

Good et al [281] reported on a randomized study of the effect of simulator-based training on novice resident performance. Twenty-six beginning residents, matched for previous training and gender, were randomized to receive either daily simulator training sessions or daily lectures on 10 predefined learning objectives during weeks 2 and 3 of the residency. Resident performance was assessed both by a written test and by evaluations of clinical ability by supervisors at weeks 1, 3, 8, and 13 of training. There was no difference in performance on the written test. Although there was a trend of improvement in the overall raw clinical ability scores for the simulator group at weeks 3 and 8, this was not statistically significant. However, the change in clinical score was significantly greater for the simulator group than for the lecture group at weeks 3 and 8, but not at week 13, by which time the change in clinical score was identical for the two groups. This study suggests that there may have been somewhat faster improvement in clinical ability when simulator-based training was used, but that by 3 months of anesthesia experience, all residents had improved their ability by the same amount. It was noted that additional work is needed to refine and coordinate the clinical and simulator curricula and also that continuing simulator exercises may have benefits over the single "bolus" of training over 2 weeks.

The Leiden group [282] reported that simulator-based training and practice in the management of malignant hyperthermia led to a significant improvement in handling of malignant hyperthermia when participants were tested in the simulator 4 months later. All participants had been given simulator training, but only half were trained concerning malignant hyperthermia. This design partially controlled for effects resulting solely from familiarity with the simulator environment. Gonzalez and Schaefer [283] reported training residents (and others) in the ASA difficult airway management algorithm using an Eagle Patient Simulator.

Anesthesia Crisis Resource Management

In 1989, based on the cognitive process model presented in the preceding section, Gaba, Fish, and Howard of the VA-Stanford group identified gaps in the training of anesthesiologists concerning several critical aspects of decision-making and crisis management that were not systematically taught during standard residency or postgraduate education. These gaps were as follows: (1) inadequate learning of precompiled plans for dealing with perioperative events; (2) inadequate skills of metacognition and allocation of attention; and (3) inadequate skill at resource management behaviors, including leadership, communication, workload management, monitoring, and cross-checking of all available information. Historically, it had been assumed that anesthetists would acquire these plans and skills "by osmosis," solely by experience and by observing role models who had these qualities. As indicated in a previous section, the aviation domain had learned that such skills were not acquired unless specifically taught, and CRM training was created to address these issues for flight crews. The VA-Stanford group modeled their ACRM training [93] after CRM. To target the identified gaps in anesthesia training, approximately 40 percent of the emphasis of ACRM training is on the medical and technical management of specific high-risk perioperative situations,

and 60 percent of the emphasis is on generic principles of crisis management that apply to nearly every complex patient care situation.

The ACRM curriculum used several teaching modalities to achieve these goals:

1. A comprehensive textbook on anesthesia crisis management (*Crisis Management in Anesthesiology*[41]). This includes didactic material on ACRM principles as well as a comprehensive catalog of critical incidents in anesthesia that provides in a uniform format guidelines for preventing, recognizing, and managing 83 perioperative situations. The catalog section of the text is intended to provide study material to increase anesthetist's stock of precompiled response plans to common and uncommon situations.
2. A brief presentation reviewing the principles of ACRM and anesthesia safety.
3. Analysis of a videotape of an aviation accident.
4. Small group exercises analyzing a videotape of an actual anesthetic mishap.
5. Several hours of complex multifaceted realistic simulations in which training participants rotate through different roles, including primary anesthesiologist, first responder (called "cold" with no knowledge of the situation), and scrub nurse. Other personnel play the roles of surgeons, nurses, and technicians as in a real OR. Each situation is followed by a detailed debriefing (lasting about the same amount of time as the situation itself) in which an experienced instructor leads the group to apply ACRM principles in analyzing their own performance.

There have been several publications detailing the response of participants of varying levels of experience to ACRM training. [93] [284] [285] Participants have been extremely positive about their experience in the ACRM course, and most believe that it contributes to their safe practice of anesthesia (Table 80-6) (Table Not Available) .

In addition to the inventors of ACRM at the VA-Stanford Simulation Center, several other simulation centers have adopted ACRM as a major focus of their training (Boston Center for Medical Simulation; Canadian Simulation Centre, Toronto; Washington University, St. Louis; Referral Hospital System, Edmonton, Alberta, Canada). Several variant curricula similar to ACRM have been developed based on the textbook *Crisis Management in Anesthesiology* and on the original ACRM experiences. These include the crisis management training at the University of Pittsburgh, the Rational Anesthesia curriculum in Denmark, and simulation training courses in Brussels, Belgium, and Fukuoka, Japan. Interest in ACRM is growing, but because it is very complex, special training for ACRM instructors has been developed by the Working Group on Crisis Management Training in Health Care (composed of the three pioneering centers in the development of ACRM: VA-Stanford Simulation Center, the Boston Anesthesia Simulation Center, and the Canadian Simulation Centre). This working group has developed and tested a 3-day ACRM Instructor Training Course, [286] and it has produced a 150-page training manual for ACRM Instructor candidates. Experience with the instructor training course suggests that the most difficult aspect of ACRM instructing is "debriefing," and new instructors require a significant period of experience, preferably under supervision by more senior instructors, before being ready to be fully independent ACRM instructors. ACRM instructor training continues at these three centers under the auspices of the working group.

Team-Oriented Medical Simulation

In 1994, a simulator-based CRM-oriented curriculum was developed independently by Helmreich, Schaefer, and colleagues at the University of Basel (Robert

Helmreich is a social psychologist who has long investigated aerospace crew performance issues and is one of the originators of CRM in aviation). [287] Although both ACRM and Team Oriented Medical Simulation (TOMS) share many features, and both derive from the model of CRM in aviation, the TOMS approach has somewhat more emphasis on the social psychology of team interactions in the OR, whereas ACRM has somewhat more emphasis on the cognitive psychology of the anesthesiologist in the context of team interactions. Using the Wilhelm Tell variant of the SOPHUS simulator (in which perfused animal organs are provided to allow laparoscopic surgery), the TOMS group conducts true combined team training of complete OR teams. An OR team of surgeons, nurses, anesthetists, and orderlies is assigned to the TOMS operating room on a given day instead of to their normal OR and conducts routine operative patient care of

TABLE 80-6 -- Evaluation of Anesthesia Crisis Resource Management Course in the Harvard Anesthesia Simulation Training

(Not Available)

Modified from Holzman et al, [284] with permission from Elsevier Science

the simulated patient just as they would of actual patients. During surgery, one or more adverse events may be triggered by the instructors. As in ACRM, a debriefing session using videotapes of the simulation follows. The TOMS approach emphasizes self-debriefing by the entire OR team and exploration of team communication and interaction issues. All subgroups of the OR team rated the simulations and debriefing sessions as highly realistic and valuable, suggesting to the investigators that "all groups benefited equally from training." [287]

Continuing Medical Education

Most simulation centers offer continuing medical education for experienced practitioners, and nearly all aspects of simulation training for residents (except novice training) can be expanded for this purpose.

Uses of Patient Simulation in Support of Biomedical Industries

Various simulation activities have related to the pharmaceutical or medical equipment industries. Numerous centers (perhaps Gainesville was the first) offer training to executives and sales representatives of equipment and pharmaceutical manufacturers. The simulator allows these individuals to gain some understanding of the clinician's task demands during patient care and of the situations in which their company's drugs or devices could be useful. At the Boston Center for Medical Simulation, this course is dubbed "Anesthesia for Amateurs." Other industrial uses include training personnel in the use of novel pharmaceuticals. Simulators have featured in a multifaceted approach to the launch of the opioid remifentanil. Simulators were used to train the manufacturer's representatives and clinicians in safe use of the drug. Besides offering important educational benefits, the industrial activities are an important source of income for simulation centers that helps to defray the costs of training students and residents.

Simulators have been used to conduct research on human factors issues in the development of new monitoring and therapeutic devices. [288] The simulator also provides a unique test bed and demonstration modality for the preprocurement evaluation of the usability of medical devices from different manufacturers. In my own hospital, this enabled us to conduct an evaluation of a prototype monitoring system that was not yet approved for clinical use and thus could not be evaluated in a preprocurement clinical trial.

Use of Patient Simulation for Training Health-Care Personnel Outside Anesthesia

At different centers, simulators have been used to train diverse groups of personnel in a wide spectrum of health-care domains. Many of the applications of simulation training in anesthesiology, particularly the CRM approach, can be translated to other high-dynamism, high-criticality areas such as ICU, PACU, emergency room, and obstetrics. The extension of CRM training to these areas has been under way at several centers, especially the University of Pittsburgh and at the Boston Anesthesia Simulation Center, which changed its name to Center for Medical Simulation to reflect their "growing interest in simulation among a wide-range of medical specialties" (D. Raemer, personal communication). Such training applications can be geared primarily to physicians in these areas or, better yet, to entire teams of personnel including physicians, nurses, orderlies, and clerks. The simulator can be particularly useful to nursing personnel for conducting in-service training on clinical skills or on the use of clinical equipment.

Other Uses

Other unique applications of simulators have surfaced. Some centers use simulators for conducting "outreach" programs with high school or college students interested in health care. Simulators have been used to help produce educational videotapes concerning various patient safety issues. It has even been suggested that a "Legislator Day" could be held in a simulator center to familiarize legislators with the demands of dynamic patient care.

Other Questions Regarding Simulator-Based Training in Anesthesia and Other Health-Care Domains

Effectiveness

The most important question concerning simulator-based training in anesthesia is its cost effectiveness. This is a complicated question that has two relatively independent components. The first component is: What are the impact and benefit of the training on the performance abilities of participants? The second component is: What does it cost to achieve that impact? In principle, simulation has many advantages as a training tool [273] :

1. There is no risk to a patient.
2. Exercises in routine procedures can be repeated intensively, whereas situations and events involving uncommon but serious problems can be presented at will.
3. Participants can learn to use actual complex devices (with a hands-on simulator).
4. The same situation can be presented independently to multiple subjects for evaluating individual or group performance.
5. Errors can be allowed to occur that in a clinical setting would require immediate intervention by a supervisor.
6. The simulation can be frozen to allow discussion of the situation and its management, and it can be restarted or begun anew to demonstrate alternative techniques.
7. Recording, replay, and critique of performance are facilitated, because there are no issues of patient safety or confidentiality.

The fidelity required of the simulator and thus the choice between screen-only and realistic simulators is dependent on the intended goals of the training and the relevant target

population. A spectrum of computer-based training is possible. Computer-assisted instruction programs and part-task trainers can be used to teach basic concepts and technical material, such as the uptake and distribution of inhaled anesthetics or pharmacokinetics of intravenous drugs. These are appropriate for students, novices, advanced residents, and experienced practitioners. Screen-only simulators are inexpensive and easy to use. They allow the presentation of and practice with the concepts and procedures involved in managing normal and abnormal case situations. They, too, are useful for a large number of user populations. Realistic simulators can be used to capture the full complexity of the real task domain including the human-machine interactions and the complications of working with multiple personnel. They are most appropriately used for residents and experienced practitioners. Regardless of the device used, the simulator is only a teaching tool that must be coupled with an effective curriculum for its use.

The evaluations conducted so far suggest that simulator-based training is a powerful technique that both novice and experienced anesthetists believe to be highly beneficial and that participants and instructors alike believe may improve clinical performance. As the developers of Sim One pointed out, when simulation provides an opportunity to teach material that cannot be taught in another way, as for the systematic instruction of anesthesiologists in handling severe critical events such as

cardiac arrest, anaphylaxis, or malignant hyperthermia, there is *nothing* with which to compare the simulator. Assessing whether the actual outcome of patients can be affected by this or any other training modality will be extremely difficult and expensive. Those investigating simulator-based training do not believe that such an outcome study is logistically feasible. [285] Determining the impact of a given type of simulator training on the intermediate variables of "performance" and "ability" is feasible, but it will not be easy. The Leiden group provided data supporting the contention that simulation training improves performance on handling a malignant hyperthermia situation. However, there is a potential for substantial bias when attempting to measure the impact of the simulator training by using performance in the simulator as a criterion. The control procedures as used by the Leiden group alleviate this bias, but they cannot eliminate it. [282]

Perhaps of even greater importance, there is currently no accepted methodology for measuring the clinical performance of anesthetists either in the simulator or in actual practice. Ironically, the simulator itself provides a tool for presenting the same calibrated situation to multiple anesthetists and may thus be a crucial tool in developing such performance measures.

Evaluation of Clinical Performance During Simulation Situations

Several research groups have been investigating performance assessment tools for use during simulation sessions. The VA-Stanford group has divided performance into two components: technical performance, which is the appropriateness and thoroughness of the medical and technical response to the critical event, and behavioral performance, which is the appropriate use of sound crisis management behaviors (such as leadership, communications, distribution of workload). [104] Simulation offers some benefits in assessing technical performance. Because the nature and cause of the critical incident are known, one can, in advance, construct a list of essential or appropriate technical activities with relative weights of importance. For example, in assessing technical performance in managing malignant hyperthermia, terminating the trigger agent and administering intravenous dantrolene would be essential items, whereas cooling measures, hyperventilation, and bicarbonate therapy would be among many appropriate (but less critical) technical responses. One can also predict in advance specific technical pitfalls. For malignant hyperthermia, these could include diluting dantrolene with the wrong diluent (not sterile water) or an insufficient quantity of diluent. These are pitfalls known to plague those unfamiliar with malignant hyperthermia therapy.

The behavioral component of crisis management must be assessed in a subjective fashion. Two research groups (VA-Stanford and University of Basel) are studying adaptations of the anchored subjective rating scales developed by the NASA/University of Texas Aerospace Crew Performance Project. The VA-Stanford group published preliminary data reviewing the interrater reliability of subjective ratings of behaviors on 5-point anchored scales. [104] Using a fairly stringent test of interrater reliability (the topic is quite complex in the statistical literature), they found only moderate reliability when 5 trained raters scored 14 anesthesia teams, each managing 2 different complex critical events (malignant hyperthermia and cardiac arrest) using a 5-point scale. Although there was some difficulty in agreement on the operational definitions of each type of behavior, the investigators stated that the largest problem in achieving agreement was the high variability of each behavior over the course of a simulation. For example, an anesthesia crew could show evidence of good communication at one instant, only to be shouting ambiguous orders into thin air at the next instant. Aggregating these behaviors into a single rating was extremely difficult, even for bounded time segments of the scenario. These data demonstrate the importance of evaluating performance by more than one rater, who, no matter how well trained, may produce scores that differ significantly from another single rater. The investigators suggested combining scores from a minimum of a pair of raters, showing that the mean of scores from two raters had a very low probability of differing from the mean of five raters by more than a single rating point.

The University of Toronto (Canadian Simulation Centre) demonstrated good interrater reliability between two raters of a simplified performance assessment rating scale. This was tested using scripted, role-played variants of standardized scenarios containing multiple anesthetic problems that were acted out for videotape using the simulator. [105] A subsequent analysis of the rating system showed that there was poor internal consistency among the different anesthetic problems presented in the scenarios. This suggests that the items acted "independently, reflecting different aspects of anesthesia care." When aggregated across the five problems, the results were affected by the "level of importance placed on each problem by individual subjects." [106] The Danish group also gave a preliminary report on their attempts to validate subjective and objective evaluation parameters, a

technique they named "PEANUTS" (Performance Enhancement in Anesthesia Using the Training Simulator). [107]

Can the "clinical" outcome of the simulator's mathematical physiology predict how a real patient would have fared under that individual's care? In extreme cases, this is likely to be true. A subject who demonstrates *totally* erroneous decision-making (e.g., failure to defibrillate a simulated patient with ventricular fibrillation) quickly allows the patient's state to deteriorate unmistakably. However, the mathematical models are not sufficient to predict what would happen to any actual patient after complex sequences of therapy and more subtle patient care judgments.

Thus, the clinical outcome of the simulated patient is one datum that can be used to assess the performance of the anesthetist on a simulation scenario, but for the forseeable future, any credible performance measurement technique *must* involve subjective and semiobjective judgments by clinical experts. The results from the various simulation groups suggest that it will be very difficult to develop a robust set of performance measures of anesthetists' skill, even using the simulator as a tool to present standardized patient scenarios. The data on performance show both a high interrater variance and a high interindividual (and interteam) variability. [53] [90] [91] [93] [104] [282] A definitive study is in principle possible, but it would require a very large number of subjects rated by multiple raters and would thus be complex and costly. Still other factors complicate the assessment of the effectiveness of simulator-based training. Studying the impact of a single session of a course that uses a new technology and a new approach to training may underestimate the course's impact when it is used on a regular and repetitive basis. For example, it is widely believed in commercial aviation that CRM training must begin with the initial training of pilots and must be continued throughout their career. Social psychologists Robert Helmreich and H. Clayton Foushee, two of the main architects of CRM training, have written [128] : "Data indicate that even intensive initial CRM training constitutes only an awareness phase and introduction to the concepts, and that continuing reinforcement is essential to produce long-term changes in human factors practice." Similarly, United Airlines states in its CRM manual [290] : "Command/Leadership/Resource management [United's terminology for CRM] cannot be a one-shot approach. It has to be a coordinated long range program. It must therefore be an integral part of the entire training effort: new hire training, transition and upgrade programs, and recurrent training." Finally, the principles and procedures taught in training must be reinforced within the operational environment. Simulator-based safety training can be totally negated if production pressures or latent failures in the workplace make it impossible to implement its teachings effectively.

Costs

What are the costs of simulator-based training? The costs of simulator-based training depend on many of the same factors that determine the curriculum:

1. Types of training involved, ranging from technology in-service to training in basic anesthesia skills, critical incidents management, or CRM.
2. Target populations for the training, whether equipment technicians, medical students, novice residents, experienced residents, nurse anesthetists, teaching faculty, or private practitioners.
3. Organizational and financial characteristics of the institution.

The hardware and software costs of the screen-only simulator are quite low (as low as $1,500), whereas the equivalent cost of a complete hands-on simulator is relatively high (the prices of commercial simulators are more than $175,000 depending on features; one should contact the manufacturers for detailed information) and do not include the necessary clinical equipment and space. However, even these large expenditures do not dominate in the cost equation because the capital equipment can be amortized over a relatively long useful life, with appropriate provisions for service and upgrades. The dominant cost is likely to be the salaries of expert instructors. An expert must oversee the curriculum, but the type of training and the target population will determine the amount of expert instruction that is required. For example, a single faculty member can review the summaries of exercises performed by residents on a screen-only simulator in a few hours per resident per year. A single instructor can use the simulator to demonstrate pulmonary or cardiovascular physiology to a whole class of medical students. When training novice residents in basic anesthesia skills, it may be possible to have senior residents or fellows conduct the sessions at a low marginal cost. However, when training experienced residents and practitioners in complex material, such as the handling of critical events, there is likely to be no substitute for expert instructors. The cost of expert instruction depends on the organizational arrangements of the institution.

Another organizational factor that affects the cost has to do with making trainees available for what can be complex, exhausting, and lengthy training sessions. Removing residents from revenue-producing work for training purposes is expensive. On the other hand, if simulator training could allow residents or other anesthetists to work more safely and more efficiently, the benefit would outweigh the cost. Some residency programs are restructuring to make the residency supernumerary to the demands of the clinic. In such cases, residents are nearly always available for educational activities, but faculty time may be even more scarce.

As anesthesiology has become less popular as a choice for graduating medical students, many programs have used simulation training as a recruiting tool. These factors support the belief that if simulator-based training is deemed to be desirable, innovative changes in organization will evolve to allow it to occur.

Simulation Centers

Although one can install a simulator in a laboratory or conference room, many institutions have equipped complete simulation centers. Typically, these centers provide a separate control room to allow complex simulations to be presented without an instructor intruding on the simulated case. The center also provides a debriefing room where videotapes of the simulation session can be reviewed. Some centers have elaborate computer-controlled audio-video

systems allowing the recording of multiple views with real-time annotation of the tapes and rapid search to marked portions of the tape. Dedicated centers facilitate all types of research and training applications of simulators, but they are especially important for intensive activities such as ACRM. Typically, a technician, an anesthesia fellow, or an administrator manages the center, coordinating scheduling and logistics, as well as assisting the experienced clinicians conduct training and research.

The costs of a simulator training program can be shared among the anesthesia departments of multiple institutions, as was the case at the Boston Anesthesia Simulation Center. The cost can also be shared among departments within a single institution because the simulator can be a resource tool for other training in other areas besides anesthesia. The anesthesia simulator is really a simulator of the critically ill patient, which can be a suitable platform for training of physicians, nurses, technicians, and other medical and technical personnel. Multiple different simulator-based curricula have been developed at the various simulation sites.

Proliferation of Simulation Centers

At this time, despite the lack of definitive cost-effectiveness data, training with realistic simulators is under way in more than 100 sites around the world, with many of them choosing to conduct fairly "high-end" crisis-management and critical-incident training sessions. These programs have already "voted with their feet" on the issue of cost versus benefit. With so many centers exploring the realities of simulation training, we can expect to see some data on efficacy and cost within the next few years.

Therefore, it is too early to make definitive statements about either the benefits or the costs of simulator-based training in anesthesia. To some extent, a catch-22 is involved. One cannot attempt to determine the true costeffectiveness until simulation is widespread enough for complex and expensive studies to be undertaken and until there is more experience concerning the different organizational aspects of providing the training. On the other hand, many institutions will shy away from taking the risk until the cost-effectiveness is proven.

Uses of Patient Simulation for Research

The utility of simulators for studying the cognitive processes of anesthetists has already been discussed. Simulators will be important tools for addressing numerous questions concerning the fundamental limitations of the human performance envelope in the anesthesia domain. A sampling of these questions is listed in Table 80-7 .

Can Simulators Be Used for the Evaluation and Testing of Residents or Practitioners?

As discussed previously in this chapter, patient simulators should be useful tools for evaluating the performance of

TABLE 80-7 -- Research Issues That Can Be Addressed Using Anesthesia Simulators

Cognitive science of dynamic decision-making
What is the interaction of precompiled procedural knowledge versus deep medical knowledge and abstract reasoning?
How does supervisory control of observation relate to vigilance, data overload, and visual scanning patterns?
What is the information content of watching the surgical field?
How are optimum action planning and scheduling implemented?
How does reevaluation fail, resulting in fixation errors?
Human-machine interactions
What is the distraction penalty of false alarms?
Is there an advantage to integrated monitors and displays versus multiple stand-alone devices and displays?
How easy to use are the controls and displays of existing anesthesia equipment in standard case situations and in crisis situations? Do they invite mode errors?
What is the mental workload imposed by a new diagnostic device such as transesophageal echocardiography?
Teaching anesthesia in the operating room
How much teaching can be accomplished in the operating room without sacrificing the anesthesia crew's vigilance?
How well can faculty detect and categorize the performance of anesthesia trainees?
What teaching styles are best integrated with case management in the operating room?
Teamwork
How does the anesthesia crew (attending plus resident or CRNA pair) interact during case and crisis management? How is workload distributed among individuals? How do crew members communicate with each other, and how do they communicate with other members of the operating room team?
Effects of performance-shaping factors on anesthetist performance
How do sleep deprivation, fatigue, aging, or the carryover effects of over-the-counter medications, coffee, or alcohol affect the performance of anesthetists?
Intelligent decision support
Can smart alarm systems or artificial intelligence provide correct and clinically meaningful decision support in the operating room or intensive care unit?

trainees and others. However, scoring or certifying competence using the simulator is more problematic than is using it as a teaching tool.

Anesthetists have discussed the possibility of using the simulator as a tool for examinations, either for graduation from a residency or for the American Board of Anesthesiologists. This use would require independent evaluation of the simulation scenarios and of the predictive power of the subjective judgments made by experts scoring the examinee. Here, too, an obstacle is the lack of any well-accepted gold standard for performance evaluation. Another difficulty with using simulation for Board certification testing is that the OR equipment would rarely be the same as that used by the candidate, and the OR staff's operational protocols could differ from those familiar to the candidate. In the training situation, these difficulties can be overlooked as part of the global "suspension of disbelief" needed to maximize the benefits of simulator training. In the test situation, these differences could potentially skew the results.

Despite these difficulties, it is likely that if the use of anesthesia simulators does become more widespread, anesthetists will become more interested in using them to assist in evaluating performance. The existing system of performance evaluation that uses a relatively haphazard system of subjective judgments of clinical competency in residency

along with written and oral examinations has itself never been validated. Many believe that the written examination does not correlate well with clinical ability, and the degree to which the oral examination process tests actual clinical skill is unknown. Simulation could offer candidates the ability to demonstrate the clinical abilities in a controlled clinical domain, while still demonstrating their consulting and language skills through oral examination.

The first trials of evaluation using simulators may occur in situations for which the evaluation is a nonthreatening critique or is graded "pass/fail." Another situation would be for the evaluation of residents who have been placed on probation or for whom dismissal from the residency program is already a distinct possibility. For these residents, the burden of proof is on them to demonstrate their skills. The simulator could offer a more controlled environment for them to do so. The same could be true for practitioners who wish to return to clinical work after a hiatus.

Future of Patient Simulation in Anesthesia

Although past its first decade of consistent development, the field of anesthesia simulation is still new. Simulators have become more sophisticated, and users can now choose from different models offered by multiple manufacturers. Improvements in simulators will depend on the demand for the devices and on the tradeoff between fidelity and cost. Many otherwise desirable improvements may be too costly for the impact that they can be expected to produce.

The physiologic and pharmacologic models used in the simulators have become more sophisticated, supported by ever-improving computer hardware. However, medical simulators will remain far behind those used in aviation. Unlike aeronautical engineers, physicians do not design and build the system they wish to model. The fundamental differential equations of fluid mechanics and aerodynamics are firmly established, allowing supercomputers to provide technically meaningful simulations as replacements for many wind tunnel tests. Furthermore, there still are wind tunnel tests as well as test flights of actual prototype aircraft. Sophisticated instrumentation can be built into test structures to define their behaviors accurately. Physicians will never have this type of knowledge about the human body.

A profound milestone will be the development of virtual reality simulators that will eventually allow the subject to be completely immersed in a simulated situation without physically replicating the OR environment. Hardware and software will soon be released for consumer-level virtual reality games. As the field expands and matures, the tools will become available to convert screen-only simulators or realistic simulators to virtual reality. For some time, however, realistic simulators will offer some advantages over virtual reality. A virtual reality system would have to contain computer models of all available monitoring equipment. The realistic simulator deals with this by simulating actual clinical equipment. Realistic simulators will have an advantage for simulation scenarios involving multiple personnel such as ACRM and other combined team training until the technology is available for complex linking of multiple individual virtual reality simulators. The early 21st century will probably see virtual reality simulations take over from computer screen and realistic simulations. Virtual reality will become the norm for training in many complex work fields, and virtual reality technology is likely to change the nature of work itself.

Patient simulators have emerged from their purely experimental phase to become an accepted, although still new, component of research and training in health care. It is highly likely that simulators will become a regular part of the initial and recurrent training of most anesthetists and of many other clinicians. The anesthesia community can be proud of its pioneering role in developing patient simulation technology and simulation-based training curricula. As this process continues, it is also likely that anesthetists will continue to lead the rest of health care in the evolution of this technology and of its educational, research, and evaluation applications.

References

1. Boff KR, Kaufman L, Thomas JP: Handbook of Perception and Human Performance. New York, Wiley-Interscience, 1986.

2. Salvendy G: Handbook of Human Factors. New York, Wiley-Interscience, 1987.

3. Weinger MB, Smith NT: Vigilance, alarms, and integrated monitoring systems. In Ehrenwerth J, Eisenkraft JB (eds): Anesthesia Equipment: Principles and Applications. St. Louis, Mosby-Year Book, 1993, p 351.

4. Weinger MB, Englund CE: Ergonomic and human factors affecting anesthetic vigilance and monitoring performance in the operating room environment. Anesthesiology 73:995, 1990.

5. Loeb RG, Weinger MB, Englund CE: Ergonomics of the anesthesia workspace. In Ehrenwerth J, Eisenkraft JB (eds): Anesthesia Equipment: Principles and Applications. St. Louis, Mosby-Year Book, 1993, p 385.

6. Botney RI, Gaba DM: Human factors issues in monitoring. In Blitt C (ed): Monitoring in Anesthesia and Intensive Care, 3rd ed. New York, Churchill Livingstone, 1994, p 23.

7. Reason J: The contribution of latent human failures to the breakdown of complex systems. Philos Trans R Soc Lond B Biol Sci 327:475, 1990.

8. Reason JT: Human Error. Cambridge, Cambridge University Press, 1990.

9. Cook RI, Woods DD, McDonald JS: Human Performance in Anesthesia: A Corpus of Cases. Columbus, Ohio, Cognitive Systems Engineering Laboratory, Department of Industrial and Systems Engineering, Ohio State University, 1991.

10. Cook RI, Woods DD, McDonald JS: On attributing critical incidents to factors in the environment (letter). Anesthesiology 71:808, 1989.

11. Woods DD, Cook RI: Dynamic Problem Solving in Anesthesiology: Expertise and Error. Columbus, Ohio, Cognitive Systems Engineering Laboratory, Department of Industrial and Systems Engineering, Ohio State University, 1991.

12. Woods DD, Johannesen LJ, Cook RI et al: Behind Human Error: Cognitive System, Computers, and Hindsight. Dayton, Ohio, Crew Systems Ergonomics Information Analysis Center, Wright Patterson Air Force Base, 1994.

13. Perrow C: Normal Accidents. New York, Basic Books, 1984.

14. Gaba DM, Maxwell M, DeAnda A: Anesthetic mishaps: Breaking the chain of accident evolution. Anesthesiology 66:670, 1987.

15. Galletly DC, Mushet NN: Anaesthesia system errors. Anaesth Intensive Care 19:66, 1991.

16. Eagle CJ, Davies JM: Accident analysis of large-scale technological disasters applied to an anaesthetic complication. Can J Anaesth 39:118, 1992.

17. Rasmussen J: Information Processing and Human-Machine Interaction: An Approach to Cognitive Engineering. New York, Elsevier Science, 1986.

18. Woods DD: Modeling and predicting human error. In Elkind JI, Card SK, Hochberg J et al (eds): Human Performance Models for Computer-Aided Engineering. Boston, Academic Press, 1990, p 248.

19. Rochlin GI, La Porte TR, Roberts KH: The self-designing high reliability organization: Aircraft carrier flight operations at sea. Naval War Coll Rev 42:76, 1987.

20. Roberts KH, Rousseau DM: Research in nearly failure-free, high reliability organizations: Having the bubble. IEEE Trans Eng Manage 36:132, 1989.

21. Roberts KH: New challenges in organizational research: High reliability organizations. Industrial Crisis Q 3:111, 1989.

22. Sagan SD: The Limits of Safety. Princeton, NJ, Princeton University Press, 1993.

23. La Porte TR, Perrow C, Rochlin G et al: Systems, organizations, and the limits of safety: A symposium. J Conting Crisis Manage 2:205, 1994.

24. Vaughan D: The Challenger Launch Decision. Chicago, University of Chicago Press, 1996.

25. Hollnagel E, Mancini G, Woods DD: Cognitive Engineering in Complex Dynamic Worlds. San Diego, Academic Press, 1988.

26. Orasanu J, Connolly T: The reinvention of decision making. In Klein G, Orasanu J, Calderwood R et al (eds): Decision Making in Action: Models and Methods. Norwood, NJ, Ablex Publishing, 1993, p 3.

27. Roizen MF: Preoperative Evaluation. In Miller RD (ed): Anesthesia, 4th ed. New York, Churchill Livingstone, 1994, p 827.

28. Wolman RL, Lasecki M, Shapiro JH et al: Should preoperative EKG's be officially interpreted by cardiologists prior to anesthesia? (abstract). Anesthesiology 73:A1026, 1990.

29. Mohamed S, Kaplan T, Mangar D et al: Interpretation of chest radiographs by anesthesiologists (abstract). Anesth Analg 76:S268, 1993.

30. Gibby GL, Gravenstein JS, Layon AJ et al: How often does the preoperative interview change anesthetic management? (abstract). Anesthesiology 77:A1134, 1992.

31. Buffington CW, Ramanathan S, Turndorf H: Detection of anesthesia machine faults. Anesth Analg 63:79, 1984.

32. Anesthesia Apparatus Checkout Recommendations. Fed Register 52:36, 1987.

33. March MG, Crowley JJ: An evaluation of anesthesiologists' present checkout methods and the validity of the FDA checklist. Anesthesiology 75:724, 1991.

34. Lees DE: FDA preanesthesia checklist being evaluated, revised. APSF Newslett 6:25, 1991.

35. FDA publishes final version of Revised Apparatus Checkout. APSF Newslett 9:35, 1994.

36. Forrest JB, Cahalan MK, Rehder K: Multicenter Study of General Anesthesia. II. Results. Anesthesiology 72:262, 1990.

37. Cooper JB, Cullen DJ, Nemeskal R et al: Effects of information feedback and pulse oximetry on the incidence of anesthesia complications. Anesthesiology 67:686, 1987.

38. Moller JT, Johannessen NW, Espersen K et al: Randomized evaluation of pulse oximetry in 20,802 patients. II. Perioperative events and postoperative complications. Anesthesiology 78:445, 1992.

39. Gaba DM: Human error in anesthetic mishaps. Int Anesthesiol Clin 27:137, 1989.

40. Gaba DM: Dynamic decision-making in anesthesiology: Cognitive models and training approaches. In Evans DA, Patel VL (eds): Advanced Models of Cognition for Medical Training and Practice. Berlin, Springer-Verlag, 1992, p 122.

41. Gaba DM, Howard SK, Fish KJ: Crisis Management in Anesthesiology. New York, Churchill Livingstone, 1994.

42. Philip JH, Raemer DB: Selecting the optimal anesthesia monitoring array. Med Instrum 19:122, 1985.

43. Harrison GG: Deaths attributable to anesthesia: Its incidence and the commoner causes. In Zorab JSM (ed): Lectures in Anesthesiology. Oxford, Blackwell Scientific Publications, 1985, p 15.

44. Drui AB, Behm RJ, Martin WE: Predesign investigation of the anesthesia operational environment. Anesth Analg 52:584, 1973.

45. Boquet G, Bushman JA, Davenport HT: The anaesthetic machine, a study of function and design. Br J Anaesth 52:61, 1980.

46. Kennedy PJ, Feingold A, Wiener EL et al: Analysis of tasks and human factors in anesthesia for coronary artery bypass. Anesth Analg 55:374, 1976.

47. McDonald JS, Dzwonczyk RR: A time and motion study of the anaesthetist's intraoperative time. Br J Anaesth 61:738, 1988.

48. McDonald JS, Dzwoncyzk R, Gupta B et al: A second time-motion study of the anesthetist's intraoperative period. Br J Anaesth 64:582, 1990.

49. Dallen L, Nguyen L, Zornow M et al: Task analysis/workload of anesthetists performing general anesthesia (abstract). Anesthesiology 73:A498, 1990.

50. Gaba DM, Herndon O, Zornow M et al: Task analysis, vigilance, and workload in novice residents (abstract). Anesthesiology 75:A1060, 1991.

51. Herndon O, Weinger M, Paulus M et al: Analysis of the task of administering anesthesia: Additional objective measures (abstract). Anesthesiology 75:A47, 1991.

52. Herndon OW, Weinger MB, Zornow MH et al: The use of automated record keeping saves time in complicated anesthetic procedures (abstract). Anesth Analg 76:S140, 1993.

53. Weinger MB, Herndon OW, Zornow MH et al: An objective methodology for task analysis and workload assessment in anesthesia providers. Anesthesiology 80:77, 1994.

54. Weinger MB, Herndon BW, Gaba DM: The effect of electronic record keeping and transesophageal echocardiography on task distribution, workload, and vigilance during cardiac anesthesia. Anesthesiology 87:144, 1997.

55. Loeb RG: Monitor surveillance and vigilance of anesthesia residents. Anesthesiology 80:527, 1994.

56. Gurushanthaiah K, Weinger MB, Englund CE: Visual display format affects the ability of anesthesiologists to detect acute physiologic changes: A laboratory study employing a clinical display simulator. Anesthesiology 83:1184, 1995.

57. Wiener EL: Cockpit automation. In Wiener EL, Nagel DC (eds): Human Factors in Aviation. San Diego, Academic Press, 1988, p 433.

58. Sarter NB, Woods DD: "How in the world did we ever get into that mode?" Mode error and awareness in supervisory control. Hum Factors 37:5, 1995.

59. Gaba DM: Automation in anesthesiology. In Mouloua M, Parasuraman R (eds): Human Performance in Automated Systems: Current Research and Trends. Hillsdale, NJ, Lawrence Erlbaum, 1994, p 57.

60. Cook RI, Woods DD: Implications of automation surprises in aviation for the future of total intravenous anesthesia (TIVA). J Clin Anesth 8:29, 1996.

61. Dzwonczyk R, Allard J, McDonald JS et al: The effect of automatic record keeping on vigilance and record keeping time (abstract). Anesth Analg 74:S79, 1992.

62. Loeb RG: Manual record keeping is not necessary for anesthesia vigilance. J Clin Monit 11:9, 1995.

63. O'Donnell RD, Eggemeier FT: Workload assessment methodology. In Boff KR, Kaufman L, Thomas JP (eds): Handbook of Perception and Human Performance. New York, Wiley Interscience, 1986, p 42.

64. Gaba DM, Lee T: Measuring the workload of the anesthesiologist. Anesth Analg 71:354, 1990.

65. Loeb RG: A measure of intraoperative attention to monitor displays. Anesth Analg 76:337, 1993.

66. Foushee HC, Lauber JK, Baetge MM et al: Crew Factors in Flight Operations. III. The Operational Significance of Exposure to Short-Haul Air Transport Operations. NASA Technical Memorandum 88322. Washington, DC, National Aeronautics and Space Administration, 1986.

67. Toung TJK, Donham RT, Rogers MC: The stress of giving anesthesia on the electrocardiogram (ECG) of anesthesiologists (abstract). Anesthesiology 61:A465, 1984.

68. Toung TJK, Donham RT, Rogers MC: Effect of previous medical training on the stress of giving anesthesia (abstract). Anesthesiology 65:A473, 1986.

69. Azar I, Sophie S, Lear E: The cardiovascular response of anesthesiologists during induction of anesthesia (abstract). Anesthesiology 63:A76, 1985.

70. Bitetti J, Hartwell P, Chin ML et al: Stress in the attending anesthesiologist (abstract). Anesthesiology 73:A1004, 1990.

71. Mackie RR: Vigilance research: Are we ready for countermeasures? Hum Factors 29:707, 1987.

72. Adams JA: Criticisms of vigilance research: A discussion. Hum Factors 29:737, 1987.

73. Beatty J, Ahern SK, Katz R: Sleep deprivation and the vigilance of anesthesiologists during simulated surgery. In Mackie RR (ed): Vigilance: Theory Operational Performance, and Physiological Correlates. New York, Plenum, 1977, p 511.

74. Denisco RA, Drummond JN, Gravenstein JS: The effect of fatigue on the performance of a simulated anesthetic monitoring task. J Clin Monit 3:22, 1987.

75. Gaba DM, DeAnda A: The response of anesthesia trainees to simulated critical incidents. Anesth Analg 68:444, 1989.

76. Kay J, Neal M: Effect of automatic blood pressure devices on vigilance of anesthesia residents. J Clin Monit 2:148, 1986.

77. Cooper JO, Cullen BF: Observer reliability in detecting surreptitious random occlusions of the monaural esophageal stethoscope. J Clin Monit 6:271, 1990.

78. Schwartz S, Griffin T: Medical Thinking: The Psychology of Medical Judgment and Decision Making. New York, Springer-Verlag, 1986.

79. Patel VL, Groen GJ, Frederiksen CH: Differences between medical students and doctors in memory for clinical cases. Med Educ 20:3, 1986.

80. Patel VL, Evans DA, Kaufman DR: Reasoning strategies and the use of biomedical knowledge by medical students. Med Educ 24:129, 1990.

81. Patel VL, Groen GJ, Arocha JF: Medical expertise as a function of task difficulty. Mem Cognit 18:394, 1990.

82. Lesgold AM, Feltovich PJ, Glaser R et al: The Acquisition of Perceptual Diagnostic Skill in Radiology. Technical Report Number PDS-1. University of Pittsburgh Learning Research and Development Center, Pittsburgh, Pa., 1981.

83. Orasanu JM: Decision making in the cockpit. In Wiener E, Kanki B, Helmreich R (eds): Cockpit Resource Management. San Diego, Academic Press, 1993, p 137.

84. Klein G, Orasanu J, Calderwood R: Decision Making in Action: Models and Methods. Norwood, NJ, Ablex Publishing, 1993.

85. Klein GA: Recognition-primed decisions. Adv Man-Machine Sys Res 5:47, 1989.

86. Rasmussen J: Skills, rules, and knowledge: Signals, signs, and symbols, and other distinctions in human performance models. IEEE Trans Systems Man Cybernet 13:257, 1983.

87. Woods DD: Coping with complexity: The psychology of human behavior in complex systems. In Goodstein LP, Andersen HB, Olsen SE (eds): Tasks, Errors, and Mental Models. London, Taylor & Francis, 1988, p 128.

88. Sarter NB, Woods DD: Situation awareness: A critical but ill-defined phenomenon. Int J Aviat Psychol 1:45, 1991.

89. DeAnda A, Gaba DM: Unplanned incidents during comprehensive anesthesia simulation. Anesth Analg 71:77, 1990.

90. DeAnda A, Gaba DM: The role of experience in the response to simulated critical incidents. Anesth Analg 72:308, 1991.

91. Schwid HA, O'Donnell D: Anesthesiologists' management of simulated critical incidents. Anesthesiology 76:495, 1992.

92. Westenskow DR, Orr JA, Simon FH et al: Intelligent alarms reduce anesthesiologist's response time to critical faults. Anesthesiology 77:1074, 1992.

93. Howard SK, Gaba DM, Fish KJ et al: Anesthesia crisis resource management training: Teaching anesthesiologists to handle critical incidents. Aviat Space Environ Med 63:763, 1992.

94. Botney R, Gaba DM, Howard SK et al: The role of fixation error in preventing the detection and correction of a simulated volatile anesthetic overdose (abstract). Anesthesiology 79:A1115, 1993.

95. Botney R, Gaba DM, Howard SK: Anesthesiologist performance during a simulated loss of pipeline oxygen (abstract). Anesthesiology 79:A1118, 1993.

96. Neisser U: Cognition and Reality: Principles and Implications of Cognitive Psychology. San Francisco, WH Freeman, 1976.

97. Xiao Y, Milgram P, Doyle DJ: Off-loading, prevention, and preparation: Planning behaviors in complex system management. In Proceedings of the 25th Annual Conference of the Human Factors Association of Canada, 1992, p 193.

98. Xiao Y, Milgram P, Doyle DJ: Incident evolution and task demands: An analysis and a field study of "going sour" incidents (abstract). In Proceedings of the Human Factors Society 36th Annual Meeting, Atlanta, Ga, 1992, p 1279.

99. Mackenzie CF, Craig GR, Parr MJ: Video analysis of two emergency tracheal intubations identifies errors in decision making (abstract). J Clin Monit 9:227, 1993.

100. Mackenzie CF, Hu PF, Horst RL et al: An audio-video system for automated data acquisition in the clinical environment. J Clin Monit 11:335, 1995.

101. Mackenzie CF, Martin P, Xiao Y: Video analysis of uncorrected esophageal intubation. Anesthesiology 84:1494, 1996.

102. Schafer HG: How Do We Communicate in the Induction Room? Basel, Department of Anaesthesia, University of Basel, 1993.

103. Sexton B, Marsch S, Helmreich R et al: Jumpseating in the operating room (abstract). Presented at the Rochester Conference on Anesthesia Simulation, Rochester, NY, 1996.

104. Gaba DM, Botney R, Howard SK et al: Interrater reliability of performance assessment tools for the management of simulated anesthetic crises (abstract). Anesthesiology 81:A1277, 1994.

105. Devitt JH, Kurrek MM, Cohen MM: Testing the raters: Interrater reliability during observation of simulator performance (abstract). Can J Anaesth 43:A51, 1996.

106. Devitt H, Kurrek M, Cohen M et al: Testing the instrument: Internal consistency during evaluation of performance in an anesthesia simulator (abstract). Anesthesiology 85:A931, 1996.

107. Jacobsen J, Jensen PF, Osterfaard D et al: Performance enhancement in anesthesia using the training simulator Sophus (PEANUTS) (abstract). Presented at the Rochester Conference on Anesthesia Simulation, Rochester, NY, 1996.

108. Gaba DM: Human performance issues in anesthesia patient safety. Probl Anesth 5:329, 1991.

109. Gaba DM: Human error in dynamic medical environments. In Bogner MS (ed): Human Error in Medicine. Hillsdale, NJ, Lawrence Erlbaum, 1994, p 197.

110. Gaba DM, Howard SK, Small S: Situation awareness in anesthesiology. Hum Factors 37:20, 1995.

111. Cook RI, McDonald JS: Cognitive tunnel vision in the operating room: Analysis of cases using a frame model (abstract). Anesthesiology 69:A497, 1988.

112. Cook RI, Potter SS, Woods DD et al: Evaluating the human engineering of microprocessor-controlled operating room devices. J Clin Monit 7:217, 1991.

113. Cook RI, Woods DD, Howie MB et al: Unintentional delivery of vasoactive drugs with an electromechanical infusion device. J Cardiothorac Anesth 6:238, 1992.

114. Sonenberg EA, Lawrence JA, Zelcer J: Modeling disturbance management in anesthesia: A preliminary report. Artif Intell Med 4:447, 1992.

115. Woods DD: Cognitive activities and aiding strategies in dynamic fault management. II. The cognitive demands of disturbance management. Columbus, Ohio, Cognitive Systems Engineering Laboratory, Department of Industrial and Systems Engineering, Ohio State University, 1992.

116. DeKeyser V, Woods DD, Masson M et al: Fixation Errors in Dynamic and Complex Systems: Descriptive Forms, Psychological Mechanisms, Potential Countermeasures. Technical Report for NATO Division of Scientific Affairs, 1988.

117. Norman DA: Categorization of action slips. Psychol Rev 88:1, 1981.

118. Norman DA: The Psychology of Everyday Things. New York, Basic Books, 1988.

119. Norman DA: Turn Signals Are the Facial Expressions of Automobiles. Reading, Mass, Addison-Wesley, 1992.

120. Norman DA: Things That Make Us Smart. Reading, Mass, Addison-Wesley, 1993.

121. Orasanu J: Shared Mental Models and Crew Decision Making. Princeton University Cognitive Science Laboratory, Princeton, NJ, 1990.

122. Salas E, Dickinson TL, Converse SA et al: Toward an understanding of team performance and training. In Swezey RW, Salas E (eds): Teams: Their Training and Performance. Norwood, NJ, Ablex Publishing, 1992, p 3.

123. Tenney YJ, Adams MJ, Pew RW et al: A Principled Approach to the Measurement of Situation Awareness in Commercial Aviation. NASA Contractor Report 4451. Washington, DC, National Aeronautics and Space Administration, 1992.

124. Rasmussen J: Cognitive control and human error mechanisms. In Rasmussen J, Duncan K, Leplat J (eds): New Technology and Human Error. Chichester, England, John Wiley & Sons, 1987, p 53.

125. Reason J: Generic error-modeling system (GEMS): A cognitive framework for locating common human error forms. In Rasmussen J, Duncan K, Leplat J (eds): New Technology and Human Error. Chichester, England, John Wiley & Sons, 1987, p 63.

126. Reason J: Modelling the basic error tendencies of human operators. Reliabil Eng System Safety 20:137, 1988.

127. Lauber JK: Cockpit resource management: Background and overview. In Orlady HW, Foushee HC (eds): Cockpit Resource Management Training. NASA Conference Publication 2455. Washington, DC, National Aeronautics and Space Administration, 1986, p 5.

128. Helmreich RL, Foushee HC: Why crew resource management? In Weiner EL, Kanki BG, Helmreich RL (eds): Cockpit Resource Management. San Diego, Academic Press, 1993, p 3.

129. Fracker ML: A theory of situation assessment: Implications for measuring situation awareness. In Proceedings of the Human Factors Society 32nd Annual Meeting. Santa Monica, Calif, Human Factors Society, 1988, p 102.

130. Hartman BO, Secrist GE: Situational awareness is more than exceptional vision. Aviat Space Environ Med 62:1084, 1991.

131. Secrist GE, Hartman BO: Situational awareness: The trainability of the near-threshold information acquisition domain. Aviat Space Environ Med 64:885, 1993.

132. Tversky A, Kahneman D: Judgement under uncertainty: Heuristics and biases. Science 185:1124, 1974.

133. Woods DD, Roth EM, Pople H Jr: Cognitive Environment Simulation: An Artificial Intelligence System for Human Performance Assessment. Washington, DC, U.S. Nuclear Regulatory Commission, 1987.

134. Klein GA: A recognition-primed decision (RPD) model of rapid decision making. In Klein G, Orasanu J, Calderwood R et al (eds): Decision Making in Action: Models and Methods. Norwood, NJ, Ablex Publishing, 1993, p 138.

135. Reason JT, Mycieslka K: Absent-Minded? The Psychology of Mental Lapses and Everyday Errors. Englewood Cliffs, NJ, Prentice-Hall, 1982.

136. Cooper JB, Newbower RS, Long CD et al: Preventable anesthesia mishaps: A study of human factors. Anesthesiology 49:399, 1978.

137. Cooper JB: Toward prevention of anesthetic mishaps. Int Anesthesiol Clin 22:167, 1984.

138. Woods DD, Cook RI, Sarter N et al: Mental models of anesthesia equipment operation: Implications for patient safety (abstract). Anesthesiology 71:A983, 1989.

139. Cook RI, Woods DD: Operating at the sharp end: The complexity of human error. In Bogner MS (ed): Human Error in Medicine. Hillsdale, NJ, Lawrence Erlbaum, 1994, 255.

140. De Keyser V, Woods DD: Fixation errors: Failures to revise situation assessment in dynamic and risky systems. In Colombo AG, Saiz de Bustamonte A (eds): Systems Reliability Assessment. Boston, Kluwer Academic Publishers, 1990, p 231.

141. Shapiro R, Berland T: Noise in the operating room. N Engl J Med 287:1236, 1972.

142. Lewis P, Staniland J, Cuppage A et al: Operating room noise (abstract). Can J Anesth 37:S79, 1990.

143. McIntyre JWR: Ergonomics: Anaesthetists' use of auditory alarms in the operating room. Int J Clin Monit Comput 2:47, 1985.

144. Quinn M: A philosophy of alarms. In Gravenstein JS, Newbower RS, Ream AK et al (eds): The Automated Anesthesia Record and Alarm Systems. Boston, Butterworth, 1987, p 169.

145. Stanford LM, McIntyre JWR, Hogan JT: Audible alarm signals for anaesthesia monitoring equipment. Int J Clin Monit Comput 1:251, 1985.

146. Stanford LM, McIntyre JWR, Nelson TM et al: Affective responses to commercial and experimental auditory alarm signals for anaesthesia delivery and physiological monitoring equipment. Int J Clin Monit Comput 5:111, 1988.

147. Griffith RL, Raciot BM: A survey of practicing anesthesiologists on auditory alarms in the operating room. In Hedley-White (ed): Operating Room and Intensive Care Alarms and Information Transfer. ASTM STP 1152. Philadelphia, American Society for Testing and Materials, 1992, p 10.

148. Cooper JB, Newbower RS, Kitz RJ: An analysis of major errors and equipment failures in anesthesia management: Considerations for prevention and detection. Anesthesiology 60:34, 1984.

149. Schneider W, Detweiler M: The role of practice in dual-task performance: Toward workload modeling in a connectionist/control architecture. Hum Factors 30:539, 1988.

150. Swezey RW, Salas E: Teams: Their Training and Performance. Norwood, NJ, Ablex Publishing, 1992.

151. Wiener E, Kanki B, Helmreich R: Cockpit Resource Management. San Diego, Academic Press, 1993.

152. Billings CE, Reynard WD: Human factors in aircraft incidents: Results of a 7-year study. Aviat Space Environ Med 55:960, 1984.

153. Jensen RS, Biegelski CS: Cockpit resource management. In Jensen RS (ed): Aviation Psychology. Aldershot, U.K. Gower Technical, 1989, p 176.

154. Helmreich RL: Theory underlying CRM training: Psychological issues in flight crew performance and crew coordination. In Orlady HW, Foushee HC (eds): Cockpit Resource Management Training. NASA Conference Publication 2455. Washington, DC, National Aeronautics and Space Administration, 1986, p 15.

155. Helmreich RL, Schaefer HG: Team performance in the operating room. In Bogner MS (ed): Human Error in Medicine. Hillsdale, NJ, Lawrence Erlbaum, 1994, p 225.

156. Foushee HC, Helmreich RL: Group interaction and flight crew performance. In Wiener EL, Nagel DC (eds): Human Factors in Aviation. San Diego, Academic Press, 1988, p 189.

157. Gaba DM, Howard SK, Jump B: Production pressure in the work environment: California anesthesiologists' attitudes and experiences. Anesthesiology 81:488, 1994.

158. Hancock PA: Environmental stressors. In Warm JS (ed): Sustained Attention and Human Performance. Chichester, England, John Wiley & Sons, 1984, p 103.

159. Hodge B, Thompson JF: Noise pollution in the operating theatre. Lancet 335:891, 1990.

160. Wallace MS, Ashman MN, Matjasko MJ: Hearing acuity of anesthesiologists and alarm detection. Anesthesiology 81:13, 1994.

161. Miles C, Auburn TC, Jones DM: Effects of loud noise and signal probability on visual vigilance. Ergonomics 27:855, 1984.

162. Hockey GRJ: Effects of noise on human work efficiency. In May D (ed): Handbook of Noise Assessment. New York, Van Nostrand Reinhold, 1978, p 335.

163. Murthy VSSN, Malhotra SK, Bala I et al: Auditory functions in anaesthesia residents during exposure to operating room noise. Indian J Med Res 101:213, 1995.

164. Murthy VSSN, Malhotra SK, Bala I et al: Detrimental effects of noise on anaesthetists. Can J Anaesth 42:608, 1995.

165. Allen K, Blascovich J: Effects of music on cardiovascular reactivity among surgeons. JAMA 272:882, 1994.

166. Weinger M: Cardiovascular reactivity among surgeons: Not music to everyone's ears (letter). JAMA 273:1090, 1995.

167. Swamidoss C, Bell C, Sevarino F et al: Effects of music on simulated task performance by anesthesiologists. In Society for Technology in Anesthesia Annual Meeting, San Diego, 1996, p 17.

168. Stevenson GW, Hall SC: Cardiovascular reactivity among surgeons: Not music to everyone's ears (letter). JAMA 273:1090, 1995.

169. Allen K, Blascovich J: Cardiovascular reactivity among surgeons: Not music to everyone's ears: In reply (letter). JAMA 273:1091, 1995.

170. Bostek CC: Is it OK to read during OR cases? (letter). APSF Newslett 9:45, 1994.

171. Question on reading in OR sparks debate. APSF Newslett 10:1, 1995.

172. Weinger MB: In my opinion: Lack of outcome data makes reading a personal decision. APSF Newslett 10:13, 1995.

173. Mitler MM, Carskadon MA, Czeisler CA et al: Catastrophes, sleep, and public policy: Consensus report. Sleep 11:100, 1988.

174. Carskadon MA, Dement WC: Normal human sleep: An overview. In Kryger MH, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine, 2nd ed. Philadelphia, WB Saunders, 1994, p 16.

175. Rechtschaffen A, Kales A: A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles, UCLA Brain Information Service/Brain Research Institute, 1968.

176. Carskadon MA, Dement WC: Cumulative effects of sleep restriction on daytime sleepiness. Psychophysiology 18:107, 1981.

177. Krueger GP: Fatigue, performance, and medical error. In Bogner MS (ed): Human Error in Medicine. Hillsdale, NJ, Lawrence Erlbaum, 1994, p 311.

178. Comperatore CA, Krueger GP: Circadian rhythm desynchronosis, jet lag, shift lag, and coping strategies. Occup Med 5:323, 1990.

179. Carskadon MA, Dement WC: Nocturnal determinants of daytime sleepiness. Sleep 5:S73, 1982.

180. Carskadon MA, Harvey K, Dement WC: Sleep loss in young adolescents. Sleep 4:299, 1981.

181. Roehrs T, Timms V, Zwyghuizen-Doorenbos A et al: Sleep extension in sleepy and alert normals. Sleep 12:449, 1989.

182. Yesavage JA, Leirer VO: Hangover effects on aircraft pilots 14 hours after alcohol ingestion: A preliminary report. Am J Psychiatry 143:1546, 1986.

183. Lumley M, Roehrs T, Asker D et al: Ethanol and caffeine effects on daytime sleepiness/alertness. Sleep 10:306, 1987.

184. Johnson LC, Freeman CR, Spinweber CL et al: Subjective and objective

measures of sleepiness: Effect of benzodiazepine and caffeine on their relationship. Psychophysiology 28:65, 1991.

185. Engel W, Seime R, Powell V et al: Clinical performance of interns after being on call. South Med J 80:761, 1987.

186. Friedman RC, Kornfeld DS, Bigger TJ: Psychosocial problems associated with sleep deprivation in interns. J Med Educ 48:436, 1973.

187. Webster's New Twentieth Century Dictionary. New York, Simon & Schuster, 1979.

188. Mackie RR: Vigilance: Theory, Operational Performance, and Physiological Correlates. New York, Plenum, 1976.

189. Torsvall L, Akerstedt T: Sleepiness on the job: Continuously measured EEG changes in train drivers. Electroencephalogr Clin Neurophysiol 66:502, 1987.

190. Akerstedt T, Torsvall L, Gillberg M: Sleepiness and shift work: Field studies. Sleep 5:S95, 1982.

191. Rosekind MR, Graeber RC, Dinges DF et al: Crew Factors in Flight Operations. IX. Effects of Preplanned Cockpit Rest on Crew Performance and Alertness in Long-Haul Operations. Moffett Field, Calif, NASA Ames Research Center, 1995.

192. Czeisler CA, Moore-Ede MC, Coleman RM: Rotating shift work schedules that disrupt sleep are improved by applying circadian principles. Science 217:460, 1982.

193. Carskadon MA, Dement WC: The multiple sleep latency test: What does it measure? Sleep 8:S67, 1982.

194. Carskadon MA, Dement WC, Mitler MM et al: Guidelines for the multiple sleep latency test (MSLT): A standard measure of sleepiness. Sleep 9:519, 1986.

195. Richardson GS, Carskadon MA, Flagg W et al: Excessive daytime sleepiness in man: Multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr Clin Neurophysiol 45:621, 1978.

196. Leape LL, Brennan TA, Laird N et al: The nature of adverse events in hospitalized patients: Results of the Harvard Medical Practice Study II. N Engl J Med 324:377, 1991.

197. Brennan TA, Leape LL, Laird NM et al: Incidence of adverse events and negligence in hospitalized patients: Results of the Harvard Medical Practice Study I. N Engl J Med 324:370, 1991.

198. Daugherty SR, Baldwin DC: Sleep deprivation in senior medical students and first-year residents. Acad Med 71:S93, 1996.

199. Pankratz H: Witness: doctor dozed. Denver Post, p 1, September 15, 1995.

200. Berry AJ, Hall JR: Work hours of residents in seven anesthesiology training programs. Anesth Analg 76:96, 1993.

201. Gravenstein JS, Cooper JB, Orkin FK: Work and rest cycles in anesthesia practice. Anesthesiology 72:737, 1990.

202. Asken MJ, Raham DC: Resident performance and sleep deprivation: A review. J Med Educ 58:382, 1983.

203. Samkoff JS, Jacques CHM: A review of studies concerning effects of sleep deprivation and fatigue on residents' performance. Acad Med 66:687, 1991.

204. Friedman J, Globus G, Huntley A et al: Performance and mood during and after sleep reduction. Psychophysiology 14:245, 1977.

205. Jacques CHM, Lynch JC, Samkoff JS: The effects of sleep loss on cognitive performance of resident physicians. J Fam Pract 30:223, 1990.

206. Howard SK, Gaba DM, Rosekind MR: Evaluation of daytime sleepiness in resident anesthesiologists (abstract). Anesthesiology 83:A1007, 1995.

207. Geer R, Jobes D, Gilfor J et al: Reduced psychomotor vigilance in anesthesia residents after 24-hour call (abstract). Anesthesiology 83:A1008, 1995.

208. Geer RT, Jobes DR, Dzien K et al: Psychomotor vigilance performance in anesthesia faculty compared to residents: Effects of an on-call cycle (abstract). Anesthesiology 85:A930, 1996.

209. Geer RT, Etzioni DA, Gilfor J et al: Use of a computer simulation to measure anesthesia resident fatigue (abstract). Anesthesiology 83:A1006, 1995.

210. Lichtor JL, Zacny J, Lanes BS et al: Research grant report: How does night call affect next-day performance in anesthesia? APSF Newslett 10:30, 1995.

211. Weinger MB, Vora S, Herndon OW et al: Performance may be impaired in on-call residents doing nighttime cases (abstract). Anesthesiology 85:A932, 1996.

212. Howard SK, Gaba DM, Rosekind MR: Subjective assessment of sleepiness and sleep onset perception of resident anesthesiologists (abstract). Anesthesiology 83:A1009, 1995.

213. Hoddes E, Zarcone V, Smythe H et al: Quantification of sleepiness: A new approach. Psychophysiology 10:431, 1973.

214. Hoddes E, Dement WC, Zarcone V: The development and use of the Stanford Sleepiness Scale (SSS). Psychophysiology 9:150, 1972.

215. Rosekind MR, Gander PH, Miller DL et al: NASA Fatigue Countermeasures Program. FAA Aviation Safety J 3:20, 1993.

216. Rosekind MR, Gander PH, Gregory KB, et al: Managing fatigue in operational settings I. Physiological considerations and countermeasures. J Behav Med 21:157, 1996.

217. Walsh JK, Hartman PG, Kowall JP: Insomnia. In Chokroverty S (ed): Sleep Disorders Medicine. Boston, Butterworth-Heinemann, 1994, p 219.

218. Krueger GP: Sustained work, fatigue, sleep loss, and performance: A review of the issues. Work Stress 3:129, 1989.

219. Cooper JB, Long CD, Newbower RS et al: Critical incidents associated with intraoperative exchanges of anesthesia personnel. Anesthesiology 56:456, 1982.

220. Cooper JB: Do short breaks increase or decrease anesthetic risk? J Clin Anesth 1:228, 1989.

221. Dinges DF: Differential effects of prior wakefulness and circadian phase on nap sleep. Electroencephalogr Clin Neurophysiol 64:224, 1986.

222. Dinges DF, Orne MT, Whitehouse WG et al: Temporal placement of a nap for alertness: Contributions of circadian phase and prior wakefulness. Sleep 10:313, 1987.

223. Czeisler CA, Johnson MP, Duffy JF et al: Exposure to bright light and darkness to treat physiologic maladaptation to night work. N Engl J Med 322:1253, 1990.

224. U.S. Congress Office of Technology Assessment: Biological Rhythms: Implications for the Worker (OTA-BA-463). Washington, DC, U.S. Government Printing Office, 1991.

225. Airline Pilots Association: Guide to Flight Time Limitations and Rest Requirements, 3rd ed. Washington, DC, Air Line Pilots Association, 1985.

226. Dinges DF, Graeber, RC, Rosekind MR, et al: Principles and guidelines for duty and rest scheduling in commercial aviation. (NASA Technical Memorandum No.110404) Moffett Field, Calif, NASA Ames Research Center, 1996.

227. McCall TB: The impact of long work hours on resident physicians. N Engl J Med 318:775, 1988.

228. Craik FIM, Salthouse TA (eds): The Handbook of Aging and Cognition. Hillsdale, NJ, Lawrence Erlbaum, 1992.

229. Denney NW: Everyday problem solving: Methodological issues, research findings, and a model. In Poon LW, Rubin DC, Wilson BA (eds): Everyday Cognition in Adulthood and Later Life. Cambridge, Cambridge University Press, 1989, p 330.

230. Hartley AA: The cognitive ecology of problem solving. In Poon LW, Rubin DC, Wilson BA (eds): Everyday Cognition in Adulthood and Later Life. Cambridge, Cambridge University Press, 1989, p 300.

231. Salthouse TA: A Theory of Cognitive Aging. Amsterdam, North Holland, 1985.

232. Birren JE, Livingston J: Cognition, Stress, and Aging. Englewood Cliffs, NJ, Prentice-Hall, 1985.

233. Birren JE, Schaie KW: Handbook of the Psychology of Aging. San Diego, Academic Press, 1990.

234. Leirer VO, Yesavage JA, Morrow DG: Marijuana, aging, and task difficulty effects on pilot performance. Aviat Space Environ Med 60:1145, 1989.

235. Park DC: Applied cognitive aging research. In Craik FIM, Salthouse TA (eds): The Handbook of Aging and Cognition. Hillsdale, NJ, Lawrence Erlbaum, 1992, p 449.

236. Travis KW: What to do with the older anesthesiologist (letter). APSF Newslett 8:21, 1993.

237. Lees DE: Are "older" anesthesiologists necessarily incompetent, as says "callow youth" (letter). APSF Newslett 9:12, 1994.

238. Travis KW: Duty fitness outweighs question of aging (letter). APSF Newslett 9:34, 1994.

239. Kay EJ, Harris RM, Voros RS et al: AGE 60 PROJECT Consolidated Database Experiments Final Report. Technical Report 8025-3C(R2). Oklahoma City, Okla, Civil Aeromedical Institute, 1993.

240. Airline Pilot Age, Health, and Performance: Scientific and Medical Considerations. Washington, DC, National Academy Press, 1981.

241. Office of Technology Assessment: Medical Risk Assessment and the Age 60 Rule for Airline Pilots. Washington, DC, U.S. Government Printing Office, 1990.

242. Guide PC, Gibson RS: An analytical study of the effects of age and experience on flight safety (abstract). In Proceedings of the Human Factors Society 35th Annual Meeting. Santa Monica, Calif,

Human Factors Society, 1991, p 180.

243. Johnson MM: Age differences in decision making: A process methodology for examining strategic information processing. J Gerontol 45:8, 1990.

244. Morrow D, Leirer V, Yesavage J et al: Alcohol, age, and piloting: Judgement, mood, and actual performance. Int J Addict 26:669, 1991.

245. O'Hare DO, Roscoe S: Flightdeck Performance: The Human Factor. Ames, Iowa, Iowa State University Press, 1990.

246. Talbott GD: Treating impaired physicians: Fourteen keys to success. Va Med Q 113:95, 1986.

247. Talbott GD, Wright C.: Chemical dependency in health care professionals. State Art Rev Occup Med 2:581, 1987.

248. Talbott GD, Gallegos KV, Wilson PO et al: The Medical Association of Georgia's Impaired Physicians Program: Review of the first 1000 physicians: Analysis of specialty. JAMA 257:2927, 1987.

249. Talbott GD, Gallegos KV: The Pilot Impaired Physicians Epidemiologic Surveillance System. QRB Qual Rev Bull 14:133, 1988.

250. Spiegelman WG, Saunders L, Mazze RI: Addiction and anesthesiology. Anesthesiology 60:335, 1984.

251. Menk EJ, Baumgarten RK, Kingsley CP et al: Success of reentry into anesthesiology training programs by residents with a history of substance abuse. JAMA 263:3060, 1990.

252. Herndon OW, Weinger MB, Englund C: Indices of substance abuse and psychological disturbances in a population of anesthesia providers (abstract). Anesthesiology 77:A1047, 1992.

253. Morrow D, Leirer V, Yesavage J: The influence of alcohol and aging on radio communications during flight. Aviat Space Environ Med 61:12, 1990.

254. Morrow D, Yesavage J, Leirer V et al: Influence of aging and practice on piloting tasks. Exp Aging Res 19:53, 1993.

255. Prince C, Chidester TR, Bowers C et al: Aircrew coordination: Achieving teamwork in the cockpit. In Swezey RW, Salas E (eds): Teams: Their Training and Performance. Norwood, NJ, Ablex Publishing, 1992, p 329.

256. Federal Aviation Administration: Aeronautical Decision Making. Advisory Circular Number 60-22. Washington, DC, Federal Aviation Administration, 1991.

257. Good ML, Gravenstein JS: Anesthesia simulators and training devices. Int Anesthesiol Clin 27:161, 1989.

258. Rolfe JM, Staple KJ: Flight Simulation. Cambridge, Cambridge University Press, 1986.

259. Singleton WT: The Mind at Work. Cambridge, Cambridge University Press, 1989.

260. Kalawsky RS: The Science of Virtual Reality and Virtual Environments. Workingham, England, Addison-Wesley, 1993.

261. Schwid HA: A flight simulator for general anesthesia training. Comput Biomed Res 20:64, 1987.

262. Schwid HA, O'Donnell D: The Anesthesia Simulator-Recorder: A device to train and evaluate anesthesiologists' responses to critical incidents. Anesthesiology 72:191, 1990.

263. Schwid HA, O'Donnell D: Educational computer simulation of malignant hyperthermia. J Clin Monit 8:201, 1992.

264. Denson JS, Abrahamson S: A computer-controlled patient simulator. JAMA 208:504, 1969.

265. Carter DF: Man-made man: Anesthesiological medical human simulator. J Assoc Adv Med Instrum 3:80, 1969.

266. Abrahamson S, Denson JS, Wolf RM: Effectiveness of a simulator in training anesthesiology residents. J Med Educ 44:515, 1969.

267. Hoffman KI, Abrahamson S: The "cost-effectiveness" of Sim One. J Med Educ 50:1127, 1975.

268. Good ML, Gravenstein JS: Training for safety in an anesthesia simulator. Semin Anesth 12:235, 1993.

269. Smith NT, Zwart A, Beneken JE: Interaction between the circulatory effects and the uptake and distribution of halothane: Use of a multiple model. Anesthesiology 37:47, 1972.

270. Zwart A, Smith NT, Beneken JE: Multiple model approach to uptake and distribution of halothane: The use of an analog computer. Comput Biomed Res 5:228, 1972.

271. Fukui Y, Smith NT: Interactions among ventilation, the circulation, and the uptake and distribution of halothane: Use of a hybrid computer multiple model. II. Spontaneous vs. controlled ventilation and the effects of CO_2 . Anesthesiology 54:119, 1981.

272. Smith NT, Sebald AV, Wakeland C et al: Cockpit simulation: Will it be used for training in anesthesia? In Anesthesia Simulator Curriculum Conference, Rockville, Md, 1989, SLEEPER p 1.

273. Gaba DM, DeAnda A: A comprehensive anesthesia simulation environment: Re-creating the operating room for research and training. Anesthesiology 69:387, 1988.

274. Gaba DM, Williams JD: CASE simulation system status report 9/89. In Anesthesia Simulator Curriculum Conference, Rockville, Md, 1989, CASE p 1.

275. Chopra V, Engbers FHM, Geerts M et al: The Leiden anesthesia simulator: A high fidelity system for anesthesia training (abstract). In Tenth World Congress of Anesthesiologists, the Hague, 1992, p 115.

276. Byrne AJ, Hilton PJ, Lunn JN: Basic simulations for anaesthetists. Anaesthesia 49:376, 1994.

277. Anaesthetists learn to operate in virtual reality. Sunday Times (London), London, April 16, 1995.

278. Gaba DM: Anesthesia simulators: A virtual reality. ASA Newslett 57:20, 1993.

279. Ohrn MAK, van Meurs WL, Good ML: Laboratory classes: Replacing animals with a patient simulator (abstract). Anesthesiology 83:A1028, 1995.

280. Fish MP, Flanagan B: Use of a realistic patient simulator to teach anesthesia medical students (abstract). Anesthesiology 85:A1041, 1996.

281. Good ML, Gravenstein JS, Mahla ME et al: Can simulation accelerate the learning of basic anesthesia skills by beginning anesthesia residents (abstract). Anesthesiology 77:A1133, 1992.

282. Chopra V, Gesink BJ, De Jong J et al: Does training on an anaesthesia simulator lead to improvement in performance? Br J Anaesth 73:293, 1994.

283. Gonzalez RM, Schaefer JJ: A new method for teaching the ASA difficult airway management algorithm using a full-scale human simulator (abstract). Anesthesiology 85:A933, 1996.

284. Holzman RS, Cooper JB, Gaba DM et al: Anesthesia crisis resource management: Real-life simulation training in operating room crises. J Clin Anesth 7:675, 1995.

285. Kurrek MM, Fish KJ: Anaesthesia crisis resource management training: An intimidating concept, a rewarding experience. Can J Anaesth 43:430, 1996.

286. Kurrek MM, Small S, Feinstein D et al: Anaesthesia crisis resource management (ACRM) instructor course: Teaching the teachers (abstract). Anesth Analg 82:S256, 1996.

287. Sexton B, Marsch S, Helmreich R et al: Participant evaluation of team-oriented medical simulation (abstract). In Rochester Conference on Anesthesia Simulation, Rochester, NY, 1996.

288. Chopra V, Bovill JG: Evaluation of a patient monitor using an anaesthesia simulator (abstract). Anesthesiology 83:A1064, 1995.

289. Gaba DM: Improving anesthesiologists' performance by simulating reality (editorial). Anesthesiology 76:491, 1992.

290. Orlady HW: Airline pilot training today and tomorrow. In Wiener EL, Kanki BG, Helmreich RL (eds): Cockpit Resource Management. San Diego, Academic Press, 1993, p 447.

Chapter 81 - Teaching Anesthesia

Alan Jay Schwartz

"Pedantic" is a description teachers wish to avoid. In the interest of doing this, I offer a fifth grader's biography of the great teacher Socrates: [1]

```
Socrates was a man.

Socrates was a Greek.

Socrates went around telling people what to do.

They poisoned him!
```

INTRODUCTION

This chapter on anesthesia education is not intended in such a manner that I risk Socrates' fate but rather is intended to be provocative, to give cause for thought to an important subject not often reflected on. All of anesthesia education can be easily considered in the following question (Greenhow DE: personal communication, 1982):

> How shall who teach what to whom for what purpose now and in the future?!

Anesthesia education is presented using this question as the framework for consideration. This chapter provides a philosophy of teaching anesthesia rather than a detailed account of the many aspects of anesthesia education (e.g., operating room anesthesia versus critical care medicine versus cardiopulmonary resuscitation versus chronic pain management).

TEACHING AND EDUCATION

Teaching, in a narrow sense, the way most of us think about it, is an activity by an individual aimed at causing another person to know some new fact or to know how to accomplish some new task. The focus appears to rest on the teacher and the activity of teaching. It does not take long to realize, however, that this way of looking at the teaching/learning activity has misplaced emphasis. If not with the teaching activity, where does the emphasis belong? The answer to this question lies in understanding the definition of education.

Education is an all-encompassing process (not merely a specific activity) resulting in a change in behavior on the part of the student/learner. The focus of education is the learner, not the teacher. It is the student who is educated by interacting with an environment that provides experience(s). *Education is a change in behavior based on experiences.* The experiences most often include the student's interacting with a teacher but are almost never limited to that alone. The entire milieu defines the total experience (Fig. 81-1) (Figure Not Available) . When the milieu changes, so may the education; that is, the change in behavior exhibited by the student may vary dramatically if the milieu is varied.

Picture the educational setting in which an anesthesiology resident is learning how to use epinephrine when weaning a patient from cardiopulmonary bypass. The knowledge and skills that must be learned include application of the pharmacologic principles of catecholamines to the pathophysiology of cardiovascular disease by turning on a mechanical infusion pump to deliver the indicated dose of a medication while technically monitoring for dose response and toxicity. Learning these facts and the skills sufficient to employ them is much different when done from a textbook or a preoperative conference with a staff preceptor than when done during the operating room interaction between the surgeon and anesthesiologist, where varied opinions may consider dopamine a more sound physiologic choice or intermittent boluses a better administration technique. The interposition of the concerned surgeon and real-time patient setting between the student and the knowledge and skills to be learned changes the learning environment and, hence, the educational experience for the resident. More is learned than the facts and psychomotor skills. As the attitudes of both the anesthesiologist and the surgeon are displayed during the resolution of the questions about the "best" drug to use and the "right" way to give it, the resident learns how these two types of practitioners are supposed to relate to one another.

It seems obvious, therefore, that there is more to consider than just teaching. What more is there to the anesthesiologist's responsibility than just teaching those around him or

Figure 81-1 (Figure Not Available) Diagrammatic representation of the educational experience. The two major components are the plan for teaching and the process of education that actually occurs. At the core is the content (cognitive, psychomotor, and/or affective) to be taught and learned. Growing out of the content are the planned goals of education, the methods and the program of instruction, and the environment in which the teaching and learning will occur. In the diagram, each building block of the plan is added to the previous one in an all-encompassing fashion. What is planned as education and what is experienced may or may not be the same. As represented by the diagram, the educational process that actually occurs includes all of the plan and layers on it, both the real environment and teacher/student interactions that provide the education, that is, the experiences on which the student's behaviors ultimately change. *(Modified from Atkins [43])*

her? The answer is provided by answering the component parts of the question posed at the beginning of this chapter.

```
Teach to whom?

Why teach?

Who teaches?

What to teach?

How to teach?
```

THE STUDENTS

The simplest answer to the question "Who learns anesthesiology?" is "those who will provide anesthetic care to patients." Included are the anesthesiologist, nurse anesthetist, and dentist who administers anesthesia for dental procedures. [2] [3] Also to be included are the many varied paramedical personnel who participate in patient care activities related to primary anesthetic care; the anesthesia technician, anesthesia aide, postanesthesia recovery room nurse, physician assistant, surgeon assistant, respiratory therapist and aide, intensive care/critical care/emergency room/trauma nurse, perfusionist, emergency medical technician/paramedic, cardiopulmonary technologist, pulmonary function technician, and blood gas laboratory technician. [2] [3] Each of these occupations is intimately related in some way to the body of knowledge that constitutes the practice of anesthesiology.

In a much broader sense, the entire medical community can be considered appropriate learners of anesthesiology. Medical students, for example, are appropriate candidates for learning a core of anesthetic knowledge and skills, specifically those that are essential for the training of all physicians. Basic central nervous system, cardiovascular, and pulmonary diagnostic monitoring, as well as emergency airway management and the clinically applied pharmacology of local anesthetics, are some of these essentials. Medical students, graduate physicians, and paramedical personnel of many types are appropriate learners because all are often faced with the task of educating the lay public about anesthesiology. Who learns anesthesiology, therefore, are those who practice it or perform related duties that require some understanding of the subject.

Another way to address the question of who learns anesthesiology is to answer, adult learners. *What describes an adult learner?*[4] How are adult learners unique? Adult learners are those with strong *motivation* to participate in a set of experiences, for example, a curriculum, to learn a specific discipline. The discipline they want to learn is one they are interested in and/or need to know. The resident actively seeks out education in anesthesiology. The sixth grader (a child learner) in contrast does not seek out education in arithmetic. Adult learners participate in *life-centered* situational learning in the area(s) in which relevance is most likely.

Adult learners enter the learning activity with a wealth of *prior experiences.* They therefore view the current educational experiences in light of their background. The internist who enters an anesthesiology residency in preparation for a career in intensive care medicine has a rich resource background in medical practice. Adult learners can capitalize on this prior learning. At the same time, however, the previous learning may color how the current learning takes place. The key for the teacher is to acknowledge the adult learner's expertise and build the new education on it, rather than downplay it and in essence, "reject" the adult learner.

Working together in a mutual peer relationship with the teacher, adult learners are *self-directed.* Where the child learners need a set of directions that originate from the teacher, the adult learners initiate their own activities. Because adult learning is goal oriented toward relevant life-centered needs, the adult learner tends to pick and choose some, not necessarily all, of the educational activities available.

Strong commitment and specific intentional attachments uniquely characterize adulthood. Marriage and child rearing are examples of such commitments and attachments. At the same time that adults make commitments, their lives are evolving and they pass through many *critical life stages* (e.g., assuming financial responsibility, coping with the illness or death of a parent). These strategic choice points in life impact

---

adult learning. The decision by an anesthesiology resident, for example, to extend his or her education an additional year to learn a subspecialty or to participate in research training may be based on the total financial debt incurred for medical education up to the time of residency and the need to repay that, weighed against the acuteness of the family financial needs.

Inherent differences among people tend to increase with aging. Adult education must provide for the difference in style, time, place, and pace of learning among adult learners. The time factor for learning is especially crucial for adults. Adults perceive that time passes more rapidly, that is, there is *less time available* to learn, or do anything, for that matter. With time perceived to be in short supply, adult learners tend to be selective in their learning in order to use what time they have more efficiently. The anesthesiology resident may devote time to learning in the operating room and weekly departmental case conference but may choose to skip the journal club to spend time with the family.

Recognition of the special traits that adult learners possess allows the anesthesiology educator to provide an educational program acceptable to the student rather than one that is rejected. Assessing the needs of the adult learner and using this as a springboard from which a curriculum is designed is more likely to result in a good educational outcome than to impose on the learner what the teacher alone thinks is right.

THE REASONS

An obvious reason for teaching anesthesiology is that we as a specialty have defined this as part of our identity [5] (Ch. 1) :

> The American Board of Anesthesiology, representing the medical specialty of anesthesiology and perioperative management, exists in order to: ... maintain the highest standards of practice by fostering educational facilities and training in anesthesiology and perioperative management which the ABA defines as the practice of medicine dealing with but not limited to: ... teaching of cardiac and pulmonary resuscitation. ... supervision, teaching and evaluation of performance of personnel, both medical and paramedical, involved in perioperative care.

In addition to our own description, others define anesthesiology in similar terms [2] :

> [An anesthesiologist] may instruct medical students and other personnel in characteristics and methods of administering various types of anesthetics, signs and symptoms of reactions and complications, and emergency measures to employ.

Teaching anesthesiology is clearly one component of an anesthesiologist's daily activities. In some instances, this means providing the experiences necessary so physician trainees can achieve consultant anesthesiologist status. In other settings, this means providing the experiences necessary so other medical and paramedical professionals can achieve a level of expertise appropriate to their required competencies: for example, for an internist, the ability to understand anesthesiology sufficiently to relate to anesthesiologists and educate patients about anesthesiology; for a postanesthesia recovery room nurse, the ability to understand anesthesiology sufficiently to care appropriately for patients emerging from anesthesia and to be versed in the critical care aspects of the preanesthesia and postanesthesia periods to provide life support if necessary.

Another major purpose for teaching anesthesiology is to provide a common set of learning experiences that when mastered by students will lead to relatively standardized behaviors. These standards (minimum standards though they may be) become the criteria by which a student candidate can be evaluated for entry into a specified mastery level. [5] [6]

Becoming a consultant anesthesiologist certified by the American Board of Anesthesiology (ABA), for example, depends on being able to demonstrate that one possesses a minimum standard of knowledge and skills in, and attitudes about, anesthesiology. [5] The public trust is gained by this process of specialty certification because this ensures that the certified specialist has met the defined standards of anesthesia practice. [5] Although specialty certification culminates in evaluation mechanisms (achieving clinical competence as attested to by the training program and successfully passing written and oral examinations), the certification process is driven by the educational activities focused at teaching the resident how to become a consultant anesthesiologist. [5] [6] A key part of this is the establishment by the ABA of the training curriculum or continuum of education in anesthesiology. [5]

The resident trainee in anesthesiology voluntarily enrolls in a training program and accepts the ABA's approved curriculum and evaluation (testing) protocol. Coupled with the physician candidate certification process is the residency training accreditation process. [7] Training program accreditation is a voluntary process whereby an institution applies for recognition of its anesthesiology residency as meeting a minimum set of teaching standards. Such recognition is achieved from the Accreditation Council for Graduate Medical Education (ACGME). The ACGME represents the combined "wisdom" of all specialty residency review committees in its publication of *Institutional Requirement of Accredited Residencies.*[7] The more focused training guidelines published as *Program Requirements* are defined by the Anesthesiology Residency Review Committee, a group representing the ABA, the American Society of Anesthesiologists, and the American Medical Association. [7] These include Program Requirements for Residency Education in (1) Anesthesiology, (2) Anesthesiology Critical Care Medicine, (3) Pain Management, and (4) Pediatric Anesthesiology. [7] [8]

The teaching responsibilities addressed by the candidate certification and residency training accreditation processes are clearly articulated by the ABA [5] :

> Establish and maintain criteria for the designation of a Board-certified anesthesiologist.
>
> Inform the ACGME concerning the training required of individuals seeking certification as such requirements relate to residency training programs in anesthesiology.
>
> Establish and conduct those processes by which the Board may judge whether a physician who voluntarily applies should be issued a certificate indicating that the required standards for certification or recertification as a diplomate of the ABA have been met.
>
> A Board-certified anesthesiologist is a physician who provides medical management and consultation during the perioperative period, in pain management and in critical care medicine. A diplomate of the Board must possess knowledge, judgment, adaptability, clinical skills, technical facility and personal characteristics sufficient to carry out the entire scope of anesthesiology practice. An ABA diplomate must logically organize and effectively present rational diagnoses and appropriate treatment protocols to peers, patients, their families, and others involved in the medical community. A diplomate of the Board can serve as an expert in matters related to anesthesiology, deliberate with others, and provide advice and defend opinions in all aspects of the specialty of anesthesiology. A Board-certified anesthesiologist is able to function as the leader of the anesthesiology care team.

Because of the nature of anesthesiology,
the ABA diplomate
must be able to manage emergent life-threatening situations in an independent and timely fashion. The ability to independently acquire and process information in a timely manner is central to assure individual responsibility for all aspects of anesthesiology care. Adequate physical and sensory faculties, such as eyesight, hearing, speech and coordinated function of the extremities, are essential to the independent performance of the Board-certified anesthesiologist. Freedom from the influence of or dependency on chemical substances that impair cognitive, physical, sensory or motor function also is an essential characteristic of the Board-certified anesthesiologist.

Establish and conduct those processes by which the Board
may judge whether a physician who voluntarily applies should be issued a certificate indicating that the required standards for subspecialty certification or recertification in an ABA designated subdiscipline of anesthesiology have been met.

The ABA-ACGME model addresses the purpose of education in anesthesiology and clearly outlines the anesthesiologist's responsibilities in teaching colleagues. Other organizational models similar to the ABA-ACGME example serve the same function for teaching physician anesthesiologists outside of the United States.

Meeting the teaching responsibilities for nurse anesthesia is standardized in similar fashion to the ABA-ACGME model. For nurses, the Council on Accreditation of Nurse Anesthesia Educational Programs and the Council on Certification of Nurse Anesthetists serve similar functions to the ABA-ACGME model. In 1996 to 1997, 85 nurse anesthesia educational programs of 24 to 36 months' duration educated nearly 2,200 students in approximately 700 clinical training sites using 2,737 certified registered nurse anesthetists and 1,416 anesthesiologists as faculty (Council on Accreditation of Nurse Anesthesia Educational Programs: personal communication, 1998). After the first 2 years of certification, certified registered nurse anesthetists are required to achieve biennial recertifications under the auspices of the Council on Recertification of Nurse Anesthetists. Education for other health care professionals is coordinated by 13 agencies accrediting training programs in 40 professions. [9] These agencies provide the guidelines for education in a standardized fashion so that professionals in 40 allied health occupations can gain certification in their respective disciplines. [9] Forty-eight professional organizations (including, for example, the American Society of Anesthesiologists), serve as experts in their fields, working hand-in-hand with the 13 agencies to accredit the educational programs for the health professions. [9] The magnitude of this teaching responsibility becomes clear when one realizes that in 1997 to 1998, 2,094 institutions sponsoring nearly 5,000 accredited programs trained approximately 150,000 students. [9]

Occupations that are related to anesthesiology and for which standardized educational programs have been defined, benefiting from the Commission on Accreditation of Allied Health Education Program's (one of the 13 accrediting agencies referred to earlier) blending of experts' guidance about teaching, include anesthesiologist's assistant, cardiovascular technologist, emergency medical technician- paramedic, perfusionist, physician assistant, respiratory therapist, respiratory therapy technician and surgical technologist. [9] These occupations are taught in 834 accredited programs. [9] Students enrolled in these training programs during the 1995 to 1996 academic year numbered 31,820. [9] This teaching responsibility for other health care professionals compares with the commitment to educate 3,708 resident anesthesiologists in 147 accredited American anesthesiology residency programs in 1997. [10] Adding the tasks of teaching medical and allied health care students, participating in continuing education for anesthesiologists, and teaching other practicing physicians and allied health care professionals increases the educational responsibilities of anesthesiologists in an exponential fashion.

One reason we teach anesthesiology is that we recognize the need to provide uniform educational experiences so students participating in these activities can reach a goal; that is, they will be acknowledged as competent in the discipline. So important is this process that it has been incorporated into the very definition that we use to describe ourselves. Now more than ever, competence and physician performance are concepts that are key in the minds of the public consuming medical care, the agencies paying for medical care, and the institutions and individuals providing medical education. [11] [12] [13] The United States has a system designed to assess medical competence by defining and ensuring the processes of education, licensing, accreditation, and certification. [11] [12] More and more, recredentialing is being added to this list.

To address the multitude of questions that have been posed about recredentialing and continued "competence" of physicians initially certified as consultants, especially questions related to the public trust, in 1989 the ABA established a mechanism for revalidation of the primary certificate called continued demonstration of qualifications (CDQ). [5] [14] [15] This program allowed anesthesiologists to demonstrate their continuing qualifications through a voluntary recredentialing program that had been years in development. [15] The first implementation of CDQ, with its two components--(1) documentation of an anesthesiologist's approved practice credentialing and (2) administration of a secure written examination to assess an anesthesiologist's current knowledge of anesthesia practice--took place in 1993. The CDQ certificate allowed anesthesiologists a means to accomplish recredentialing for needs defined by governmental, health care finance reimbursement, hospital, or other regulatory bodies.

Since the development of the voluntary CDQ recredentialing mechanism, the ABA has developed a more formal recertification process. In 1994 and 1995, the ABA adopted time-limited certification, that is, all specialty (anesthesiology) certificates issued by the board on or after January 1, 2000 will be valid for 10 years from the time of completion of the examination for the initial certification. [5] [16] To complement this, in 1996, the ABA converted the CDQ mechanism

into the recertification process containing the same two components described earlier. Anesthesiologists who are Board certified in the next century and wish to remain so after the end of the time limit on their certification will be required to formally recertify and obtain a new Board certificate rather than revalidate the primary certificate. [5] [16]

Since 1985, the ABA has had a certification process for the subspecialty of critical care medicine. As of December 1997, the ABA has not deemed the critical care certification process time-limited. In 1991, the ABA began certification of pain management subspecialists. The ABA pain management certificate is time-limited, that is, it is valid for 10 years from successful completion of the examination for pain management certification. Recertification in pain management, therefore, will be operative in a fashion similar to that described earlier for recertification in anesthesiology. Similar models for continuing medical education and documentation of physician competence are being developed in other countries as well as the United States. [17] [18]

Anesthesiology education for physicians and other health care professionals is, as described earlier, a specific application of assessing medical competence by process evaluation. An equal and perhaps even more important question is how to evaluate the outcome of the education rather than the process by which it is achieved. [11] [12] The question of why we teach medicine, specifically anesthesiology, is best answered by saying that we want physicians and other health care professionals to perform the activities of anesthesia practice at a specific level of achievement. Although we are very good at evaluating knowledge, outcome assessment of practice is not easily measured. Outcome assessment, that is, evaluation of the practice aspects of anesthesiology, represents the greatest challenge for the future. [11] [12]

One such assessment demonstrates the value of the ABA-ACGME model of educating and certifying physician anesthesiologists. Silber et al, [19] in their study of almost 6,000 patients undergoing prostate or gallbladder surgery in multiple hospitals, demonstrated that patient recovery or "rescue" from an adverse event correlated with the proportion of Board-certified anesthesiologists in the hospital.

Outcome analysis is also becoming a part of the training process for anesthesiologists. [20] An example of this type of approach in an educational setting, employing quality improvement concepts developed in industry, has been described. [20] This is also appearing in posttraining practice settings as a form of continuing medical education as well as a quality assessment tool. [21] We will undoubtedly see more of this type of approach as the pressures of health care economics help restructure

our clinical practice.

/das/book/view/29494766/875/890.html

THE TEACHERS

Anesthesiology is taught by physician anesthesiologists, the experts in the field, and other expert individuals in related disciplines, examples of whom include pharmacologists, physiologists, biomedical engineers, pediatricians, and neurosurgeons. Full-time anesthesiology faculty positions in United States medical schools in 1997 to 1998 numbered 4,860. [22] The majority (96.5%) of these budgeted positions were filled. [22] Anesthesiologists represent approximately 6 percent of the clinical teachers and 5 percent of all American medical school teaching faculty. [22] The 4,860 anesthesia faculty in medical schools bear the major responsibility for teaching some or all of the more than 66,700 enrolled undergraduate medical students, the 3,708 graduate trainees in anesthesiology residency training programs, as well as many of the approximately 98,100 other physician house-staff trainees. [10] [22]

Clinical care, teaching, research, and administration are major roles assumed by faculty. For anesthesia faculty, clinical care is the prime activity for obvious reasons. The other functions are attended to as time and resources permit. For this reason, teaching is often relegated to a lower level of priority, not always adequately acknowledged in career advancement decisions. Junior faculty are frequently expected to take on a large part of the teaching load. This expectation, however, could be viewed as a case of reversal of the proper roles for the junior and senior faculty. [23] Junior faculty have the heavy teaching load during the phase of their career when they lack experience. [23] Senior faculty, on the other hand, are responsible for departmental, institutional, and/or specialty roles that limit their availability for teaching, though these same individuals have vast experience and could teach much. [23] The extreme example of this dichotomy is the expectation that house staff teach the more junior of their ranks and/or medical students. Perhaps the teaching role for house staff would be best accomplished by making the resident a teaching apprentice who not only receives general medical and anesthesiology specialty education but also is educated about education.

Little specific information exists about the teaching credentials or qualities of anesthesiologists. These have been described for other physician groups. [24] [25] These descriptions can be used to infer what does or could characterize anesthesiology teachers. Physician teachers in general are not trained as educators. [24] They have not had formal training in educational psychology or methodology. [24] Physicians who teach do not use the educational resources available. [24] When faced with a new or difficult educational assignment, physician teachers rarely read the medical education journals, nor do they consult educational experts as they might seek help, for example, from a cardiologist when treating a difficult patient. [24] Physician teachers, for the most part, mimic their own teachers, who also had little or no formal training as educators. [24] Although we would not trust a general surgical resident to perform a complicated neurosurgical dissection and achieve a good outcome for the patient, we do entrust an anesthesiology trainee to faculty who have limited educational expertise, hoping for a good learning outcome.

What characterizes a good teacher? Effective clinical teachers, who are able to succeed at the bedside teaching encounter, display specific actions noted by their students and themselves. [25] Table 81-1 (Table Not Available) presents a schema that was developed by observing internists teaching internal medicine residents and medical students. The similarity of the attending anesthesiologist teaching at the bedside in the intensive care unit and/or in the operating room is striking.

A teaching responsibility that anesthesiology faculty might consider is how to blend their "expert" status as anesthesiologists with their "novice" status as teachers. As the experts, teachers of anesthesiology can define educational objectives based on the competencies they believe newly

TABLE 81-1 -- Traits of Effective Clinical Teachers

(Not Available)

Adapted from Mattern et al [25]

trained anesthesiologists need. Having set the objectives, the teacher can direct the educational process by selecting the appropriate learning activities and then designing tests that assess the learning. As described, the "authoritarian" teacher, the expert, determines the educational ends that must be met, defines the means to those ends, and requires conformity to these ends by the student.

Although anesthesiology faculty provide education using this type of curriculum design, few if any know they are employing Tyler's model, nor do they realize that there might be equally good alternatives. [26] Dewey's progressive education offers one such alternative. [27] The philosophy of education elevates students to a level where they can join in a partnership with the teacher. For students of anesthesiology, the adult learners described previously, this type of student-teacher relationship may make good sense.

An example of these two philosophies put into action clarifies their differences. Let us consider teaching/learning how to manage a patient who is being mechanically ventilated in the operating room. The Tyler teacher might lecture to the residents on how to use the ventilator. It is hoped that the residents will remember what they heard and be able to put what they learned into action. In contrast, the teacher using Dewey's approach might create a patient simulation exercise in which residents can "experiment" with differing ventilator setups to infer what might occur clinically. A much more meaningful learning environment might be provided by the simulation--coupled with the anesthesiologist faculty member's reactions to and guidance about how the residents tinkered with the ventilator--than might be provided by the lecture format. In addition, the teacher using Dewey's philosophy might be more likely to encourage the student with prior experience, like residents who used different types of ventilators during their internship, to share their know-how with other, less experienced, peers.

This chapter is discussing the component parts of the question "How shall who teach what to whom for what purpose now and in the future?" It should be obvious that individually studying the component parts of the question is an artificial separation for teaching purposes. To fully understand the question, its parts must be linked to one another. The consideration "Who teaches anesthesiology?" is an example of how the blending of the individual parts of the total picture of anesthesia education must occur. It is virtually impossible to talk about the teacher without bringing the student and the educational needs into the discussion. This key concept, that is, the importance of knowing not only the component parts of education but how they interrelate, is essential for understanding and implementing anesthesiology education.

THE CURRICULUM

The table of contents from any standard anesthesiology textbook provides a broad outline of what to teach in anesthesiology. Similar to a medical school course outline, anesthesiology is a mix of the fundamental basic sciences applied to clinical practice as they relate to specific pathophysiologic disease entities. Patients with these problems present in preoperative, intraoperative, and postoperative settings; therefore, the content is taught as it specifically applies to these different patient environments. This framework of basic and clinical science is used for teaching anesthesiology to all health professionals with particular emphasis placed on those areas most pertinent to the particular group being taught (e.g., detailed teaching about the mechanics and clinical application of ventilators is provided to student respiratory therapy technicians).

An accepted uniform content outline that has been agreed on for teaching physician anesthesiologists has been updated. [28] The major outline headings are listed in the Appendix. Few teachers would be at a loss to define the content of anesthesiology teaching. Anesthesiology education, however, is not limited to content teaching alone.

There are three major areas for teaching/learning all subjects: cognitive, psychomotor, and affective. For anesthesiology, it appears that the *cognitive teaching/learning* area is well defined. It is the responsibility of the anesthesiology teacher, however, to go further than just listing the content topics. Teaching in the content area requires attention to increasingly complex cognitive functions. Described by Bloom, [29] teaching/learning in the cognitive domain for any topic addresses the following:

1. Knowledge--recall
2. Comprehension--understanding
3. Application--use of abstractions
4. Analysis--break down; seeing the relationship of parts
5. Synthesis--put together; creating a new entity
6. Evaluation--judgment of value

Knowing the facts about pulmonary function is obviously much more basic than being able to apply them to the management of a multiple trauma patient on a ventilator. The teacher of anesthesiology serves the students well by considering the more complex aspects of cognitive learning.

A general taxonomy of *psychomotor skill teaching/learning* for universal application to all educational settings does not exist because of the great variability of this type of domain among disciplines. A broadly accepted, standardized outline of psychomotor skill learning for anesthesiology also does not exist. There are many psychomotor skills that anesthesiologists and other related health-care professionals need to learn. Perhaps a major challenge for the teachers of anesthesiology is to codify the fundamental and supplemental

---

psychomotor skills that must be taught and learned. This is beginning to occur with the introduction of practice parameters or practice guidelines developed by medicine in general and anesthesiology in particular. [30] [31] [32] [33] [34] [35] [36]

Affective teaching/learning deals with feelings or emotions. The taxonomy of affective learning addresses the following [37] :

1. Receiving
2. Responding
3. Valuing
4. Organizing
5. Value complexing

While we actively and consciously teach in the cognitive and psychomotor areas, we are much less aware of our affective teaching. Even though we may not be aware of it, however, we are constantly teaching in the affective arena by therole modeling we perform. Earlier in this chapter an example of how affective teaching and learning takes placewas described. In the real-life setting, the aggressive,passive-aggressive, or passive posture of the anesthesiology teacher interacting with the surgeon provides a lasting lesson in the affective domain for the resident anesthesiology learner.

Thinking about affective learning results in arriving at the goals for such learning, which permits development of teaching plans to achieve the goals. Only if we decide how we believe we as anesthesiologists and health-care professionals in related fields need to behave in relation to others, will we be able to teach professionalism and these psychosocial skills to our students. [38]

Another example of the importance of affective learning concerns our approach to the teaching task. When our students sense our own enthusiasm about and commitment to a particular topic, their attitudes about it follow suit. In similar fashion, if we as teachers are negative about some aspect of learning, we can expect our students to mimic these feelings.

The charge that teachers of anesthesiology must accept is that they must be conscious of the emotions they display and prospectively decide on the values they wish to teach because affective teaching and learning occurs all of the time.

Defining the areas of learning (i.e., what to teach) makes it possible for the teacher to devise methods to evaluate the success of the teaching endeavor. For anesthesiology education of physicians, the ABA examination and certification protocol evaluates the three areas of learning. The written examination tests cognitive learning, although perhaps at its more simple levels. Psychomotor and affective learning is evaluated in an ongoing manner by anesthesiology faculty of residency training programs and is attested to by the faculty granting a certificate of clinical competence to the successful learners. The oral examination evaluates cognitive learning, one hopes at its more complex levels. In addition, the oral examination may assess affective learning, although this is accomplished in an unsystematic approach.

/das/book/view/29494766/875/892.html

THE METHODS

When faculty members talk about education, one of their first considerations is how to teach. Although this is obviously an important aspect of instruction, it is of relatively minor importance when viewed in the entire context of education. Before one can decide if a lecture is a better method to teach a specific topic than a group discussion, or whether slides, a chalk board, or computer-assisted instructional software should be used to facilitate making a concept clear, it is essential to understand the student, the student's needs, the purpose of the education, and the content to be taught.

Too often, the instructional methodology, which is easy to consider, receives the major emphasis, while the difficult questions about education, such as what is its rationale, are glanced over or never even considered. After the fundamental questions about educational philosophy are answered, the selection of a particular instructional technique becomes critical. The specific teaching method selected is intended to be the one best suited to the specific educational goal desired.

Use of simulation games is a good example of how the method satisfies the educational goal. In cardiopulmonary resuscitation training, the simulated cardiac arrest is an exercise in which students play the resuscitator roles using all of the real-life equipment in a real-time setting. The involved students as well as other students and the teacher or teachers who observe the simulation review and critique the resuscitation to point out correct actions and those that could have been performed better. The goal of the exercise is to teach the students to coordinate the entire cardiopulmonary resuscitation effort, bringing together the facts and skills in an atmosphere in which reasonable attitudes are exhibited despite the tense nature of the emergency situation, all without jeopardizing any patient. A lecture, a slide show, or even a small group discussion could not achieve this goal.

Simulation is becoming an integral teaching methodology in anesthesia education. [39] Borrowed from flight simulation, which is an essential part of the training and certification of commercial and military pilots, anesthesia patient simulators have been developed and utilized to educate individuals in the discipline of anesthesiology in two major ways: (1) for specific recognition and management of critical events and (2) in the general comprehensive education about all aspects of anesthesia patient care. By coupling a mannequin with a computer and anesthesia patient care equipment, a simulation setting is created that so closely mimics real life that it is a virtual reality. Physiology, pharmacology, pathophysiology, and crisis management are a few of the curricular areas that can be most effectively taught via the anesthesia simulator approach, that is, modeling a real patient scenario for students to manage with zero risk to the simulated patient and with no real risk to the student (except for the trainee's self-imposed stress to achieve). Use of this technology is limited only by the ability of the educators and students to create and "live" the scenarios. [40] Additional advantages of the human patient simulators include their use in teaching all types of students (e.g., medical students, student nurse anesthetists, allied health professionals in a wide variety of disciplines, practitioners in continuing education programs) and the ability to conduct educational research and to collect "simulated" patient management outcome data. Undoubtedly, the field of human simulator education and research will continue to grow exponentially in the next few years.

An in-depth study of the individual teaching techniques is appropriate after the links between the questions about educational

philosophy and rationale and the methods of teaching have been established. Lectures, small group discussions, use of questions, clinical problem solving at the bedside or in the classroom, psychomotor skill learning at the bedside or in the classroom, and use of adjunc-tive educational media, such as slides, chalk board, videotape, audiotape, overhead projector, computer, and teaching models, are all at the teacher's disposal for effective use in the proper situation. Each of these can be used more effectively and efficiently when the method is studied and understood.

Effective use of questioning, for example, occurs when the teacher understands the difference between closed and open questions. [41] The teacher uses *closed questions* when he or she is interested in having the student remember facts. Because the range of responses to closed questions is limited, students answer with facts and have a limited opportunity to delve into more complex cognitive learning, that is, problem solving. The teacher who wishes to direct the teaching/learning activity toward application of knowledge to new settings or analysis of information for conceptual learning, rather than mere regurgitation of facts, employs *open questions* as the teaching device. There is a considerable difference in learning that might occur when a question such as "What might explain postanesthetic stupor in a patient operated on for head trauma?" is asked of a student as compared with asking a question such as "What are the signs and symptoms of increased intracranial pressure?"

Developing a psychomotor skill lesson is another example of how understanding instructional methodology can lead to effective teaching and learning. The old adage about teaching psychomotor skills in medicine is "see one, do one, teach one." The absurd nature of this approach has been highlighted in the following way: "This is akin to a piano instructor playing 'The Minute Waltz' for a beginner and then saying, 'Now, try it yourself.' " [41] Rather than employing the repetitive trial and error approach to teaching/learning psychomotor skills, a systemic methodology can be employed. [41]

1. Analyze and separate the skill into its component parts and determine which aspects of the skill are most difficult to perform.
2. Provide students with a model of the skill they are expected to perform, demonstrated effectively in its entirety.
3. Make provisions for students to practice until the expected behavior is mastered.
4. Provide adequate supervision and an evaluation of the final performance.

Anesthesiology instructors need only think of the protocol they are using to teach, for example, pulmonary artery catheterization via the internal jugular venous route, to assess whether they are expecting their students to perform (learn) with the type of plan outlined above or rather to "learn as they go" on each successive patient as they probe in the neck.

A final example of an answer to the question of how to teach comes from review of the effective use of audiovisual aids. Although it is true that "a picture is worth a thousand words," the anesthesiology teacher must be sure that this image is the "text" the teacher wishes the students to read. Slides, for example, focus the viewer's attention on an idea(s) that the lecturer wishes to amplify in some manner. By definition, the entire lecture cannot be put on slides. Only a few important portions of the presentation are conveyed by slides, and these are emphasized in some specific way by the visual image(s), which add to the verbal presentation. Slides are not the TelePrompTer, although they are often used this way.

Even more basic is the need to understand the proper production formatting of slides so that the message on a 35-mm transparency can be clearly seen when projected onto a 12-foot-high screen in a large 800-seat lecture hall. If format is not considered, the slide is not visible and undoubtedly detracts from, rather than enhances, the lecture. Finally, even the best-produced slide is useless if nobody, including the lecturer, knows how to troubleshoot the nonfunctional projector. Surely, the thousands of hours that have been devoted to slide lectures about anesthesiology could have benefitted from the teachers' taking more responsibility in the preparation of effective visual aids.

/das/book/view/29494766/875/893.html

SUMMARY

What is the anesthesiologist's responsibility in teaching colleagues and other health care professionals? The answer lies in the answers to the many aspects of the following question:

> How shall who teach what to whom for what purpose now and in the future"?!

For many, however, this type of review of education is "soft" material that lacks the "hard" research data to prove its validity. Perhaps this is true. Perhaps by its very nature (i.e., psychosocial) the science of education has its limits. On the other hand, however, enough experimental studies of education may not have been performed. A model to conduct

Figure 81-2 (Figure Not Available) Diagrammatic representation of a model to conduct educational outcome analysis. The six components are joined in "chain-link" fashion to signify that the outcome analysis is as strong as its weakest link. Essential to the model, therefore, is sound development and implementation of the educational plan and process. This includes definition of the educational objectives, understanding of both the teaching faculty and student participants, and execution of the instructional activity. Having established the educational experience, its outcome can be assessed by applying an appropriate evaluation design [42] and employing the measurement techniques to collect the data for analysis. The final step in the analysis is to apply the results to the program objectives and instructional activities to enhance future desired learner outcomes. *(From Hutchins [44])*

---

such studies might view the preceding question in terms of educational outcome analysis (Fig. 81-2) (Figure Not Available) . Although the educational setting is not a pure, controlled laboratory environment, accepted quasi-experimental design techniques exist for this naturalistic research setting. [42]

What then is the anesthesiologist's responsibility in teaching? It is 2-fold: to understand all aspects of education and then to scientifically study educational outcome so the future students of anesthesiology will be more effectively taught and better prepared as experts in the field.

ACKNOWLEDGMENT

I wish to thank George E. Miller, M.D., for the insight on Socrates, and Denise Distefano for her expert preparation of this manuscript.

References

1. Schwartz AJ, Ellison N, Ominsky AJ et al: Advanced CPR: Student, teacher, administrator, researcher. Anesth Analg 61:629, 1982.
2. U.S. Department of Labor: Dictionary of Occupational Titles. 4th ed. Washington, DC, U.S. Government Printing Office, 1977.
3. U.S. Department of Labor: Dictionary of Occupational Titles. 4th ed. Suppl. Washington, DC, U.S. Government Printing Office, 1986.
4. Knowles M: The Adult Learner: A Neglected Species. Houston, Gulf Publishing, 1978.
5. Booklet of Information. American Board of Anesthesiology: Raleigh, NC, December 1998.
6. Annual Report and Reference Handbook: 1992. Evanston, Illinois, American Board of Medical Specialties, 1992.
7. Accreditation Council for Graduate Medical Education: 1998-1999 Graduate Medical Education Directory. Chicago, American Medical Association, 1998.
8. Rockoff MA, Hall SC: Subspecialty training in pediatric anesthesiology: What does it mean? Anesth Analg 85:1185, 1997.
9. Donini-Lenhoff F (ed): Health Professions Education Directory 1997-1998. 25th ed. Chicago, American Medical Association, 1997.
10. Appendix II, Graduate Medical Education. JAMA 280:836, 1998.
11. Martini CJM: Evaluating the competence of health professionals. JAMA 260:1057, 1988.
12. Langsley DG: Medical competence and performance assessment: A new era. JAMA 266:977, 1991.
13. Singer I (ed): Physician Competence: Whose Responsibility? Conference Proceedings. Chicago, American Medical Association, 1989.
14. Epstein RM: The American Board of Anesthesiology: Thoughts on the occasion of its fiftieth anniversary. J Clin Anesth 2:3, 1990.
15. American Board of Anesthesiology: Continued demonstration of qualifications for board-certified anesthesiologists. Anesthesiology 73:770, 1990.
16. Glass DD: Time-limited Certification: American Board of Anesthesiology. Anesthesiology 83:413, 1995.
17. Clark AJM: Continuing medical education is as important as patient care [editorial]. Can J Anaesth 39:637, 1992.
18. CMA Policy Summary: Maintenance of competence. Can Med Assoc J 46:264A, 1992.
19. Silber JH, Williams SV, Krakauer H et al: Hospital and patient characteristics associated with death after surgery. Med Care 30:615, 1992.
20. Dubin SA, Jense HG, Yodlowski E et al: Continuous quality improvement in an anesthesia residency training program. Int Anesthesiol Clin 30:29, 1992.
21. Schisler JQ: Implementing continuous, quality improvement: A private practice's experience. Int Anesthesiol Clin 30:45, 1992.
22. Barzansky B, Jonas HS, Etzel SI: Educational programs in U.S. medical schools, 1997-1998. JAMA 280:803, 1998.
23. Ratzan RM: On teachers. N Engl J Med 306:1420, 1982.
24. Jason H, Westberg J: Teachers and Teaching in U.S. Medical Schools. East Norwalk, CT, Appleton & Lange, 1982.
25. Mattern WD, Weinholtz D, Friedman CP: The attending physician as teacher. N Engl J Med 308:1129, 1983.
26. Tyler RW: Basic Principles of Curriculum and Instruction. Chicago, University of Chicago Press, 1949.
27. Dewey J: Democracy and Education. New York, Macmillan, 1916.
28. ABA-ASA: Content Outline. Joint Council On In-Training Examinations. Park Ridge, IL, American Board of Anesthesiology-American Society of Anesthesiologists, 1996.
29. Bloom BS (ed): Taxonomy of Educational Objectives. Handbook I: Cognitive Domain. New York, David McKay, 1956.
30. Woolf SH: Practice guidelines: A new reality in medicine. I. Recent developments. Arch Intern Med 150:1811, 1990.
31. Woolf SH: Practice guidelines: A new reality in medicine. II. Methods of developing guidelines. Arch Intern Med 152:946, 1992.
32. Arens JF: A practice parameters overview [editorial]. Anesthesiology 78:229, 1993.
33. American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization: Practice guidelines for pulmonary artery catheterization. Anesthesiology 78:380, 1993.
34. American Society of Anesthesiologists Task Force on Management of the Difficult Airway: Practice guidelines for management of the difficult airway. Anesthesiology 78:597, 1993.
35. American Society of Anesthesiologists Task Force on Pain Management: Practice guidelines for acute pain management in the perioperative setting. Anesthesiology 82:1071, 1995.
36. American Society of Anesthesiologists Task Force on Blood Component Therapy: Practice guidelines for blood component therapy. Anesthesiology 84:732, 1996.

37. Krathwohl DR, Bloom BS, Masia BB: Taxonomy of Educational Objectives. Handbook. II: Affective Domain. New York, David McKay, 1964.

38. Schwartz AJ, Blank LL, Horrow JC et al: Are anesthesiology residents educated to be professionals? Anesthesiology 87:A950, 1997.

39. Good ML, Gravenstein JS: Training for safety in an anesthesia simulator. Semin Anesth XII:235, 1993.

40. Euliano T, Good ML: Simulator training in anesthesia growing rapidly. J Clin Monit 13:53, 1997.

41. Foley RP, Smilansky: Teaching Techniques. A Handbook For Health Professionals. New York, McGraw-Hill, 1980.

42. Campbell DT, Stanley JC: Experimental and Quasi-Experimental Designs For Research. Boston, Houghton Mifflin, 1963.

43. Atkins E: Curriculum theorizing as a scientific pursuit: A framework for analysis. Unpublished doctoral dissertation, University of Pennsylvania, 1982.

44. Hutchins EB: Unpublished lecture notes: Evaluation methods in professional education. Course ED668, Graduate School of Education. University of Pennsylvania, 1981.

Selected Readings

Barrows HS: Simulated (Standardized) Patients and Other Human Simulations. Chapel Hill, NC, Health Sciences Consortium, 1987.

Bunker JP (ed): Education in Anesthesiology. New York, Columbia University Press, 1967.

Dick W, Reiser RA: Planning Effective Instruction. Englewood Cliffs, NJ, Prentice-Hall, 1989.

Epstein J (ed): Masters: Portraits Of Great Teachers. New York, Basic Books, 1981.

Gagne RM, Briggs LJ: Principles Of Instructional Design. 2nd ed. New York, Holt, Rinehart & Winston, 1979.

Greenberg LW, Jewett LS: Commitment to teaching: Myth or reality? South Med J 76:910, 1983.

Greene NM: Anesthesiology and the University. Philadelphia, JB Lippincott, 1975.

Jason H, Westberg J: Instructional Decision-Making Self-Study Modules for Teachers in the Health Professions (Preview Package). National Center for Faculty Development, Miami, University of Miami School of Medicine, 1980.

Joyce B, Weil M: Models of Teaching. Englewood Cliffs, NJ, Prentice-Hall, 1980.

Knowles MS: Andragogy in Action. San Francisco, Jossey-Bass, 1984.

Lear E (ed): Virtual Reality in Patient Simulators. American Society of Anesthesiologists Newsletter 61(October), 1997.

Lyman RA: Disaster in pedagogy. N Engl J Med 257:504, 1957.

McGaghie WC, Frey JJ (eds): Handbook for the Academic Physician. New York, Springer-Verlag, 1986.

McGuire CH, Foley RP, Gorr A et al: Handbook of Health Professions Education. San Francisco, Jossey-Bass, 1983.

McKeachie WJ: Teaching Tips: A Guidebook for the Beginning College Teacher. 7th ed. Lexington, MA, DC Heath, 1978.

Miller GE: Adventure in pedagogy. JAMA 162:1448, 1956.

Miller GE (ed): Teaching and Learning in Medical School. Cambridge, MA, Harvard University Press, 1961.

Miller GE: Educating Medical Teachers. Cambridge, MA, Harvard University Press, 1980.

Popham WJ, Baker EL: Establishing Instructional Goals. Planning an Instructional Sequence. Englewood Cliffs, NJ, Prentice-Hall, 1970.

Schwenk TL, Whitman NA: Residents as Teachers: A Guide to Educational Practice. Salt Lake City, University of Utah, 1984.

Schwenk TL, Whitman NA: The Physician as Teacher. Baltimore, Williams & Wilkins, 1987.

Segall AJ, Vanderschmidt H, Burglass R et al: Systemic Course Design for the Health Fields. New York, John Wiley & Sons, 1975.

Whitman NA: There Is no Gene for Good Teaching: A Handbook on Lecturing for Medical Teachers. Salt Lake City, University of Utah, 1982.

Whitman NA, Schwenk TL: A Handbook for Group Discussion Leaders: Alternative to Lecturing Medical Students to Death. Salt Lake City, University of Utah, 1983.

Whitman NA, Schwenk TL: Preceptors as Teachers: A Guide to Clinical Teaching. Salt Lake City, University of Utah, 1984.

Appendix - Joint Council on In-Training Examinations Content Outline (Abridged)

I. Physiological sciences
   A. Physiology
      1. Respiration: lung functions and cellular processes
      2. Cardiovascular
      3. Central and peripheral nervous systems
      4. Hepatic function
      5. Renal function
      6. Endocrine function
      7. Temperature regulation
      8. Aging: physiologic and pharmacologic implications
   B. Pharmacology
      1. General concepts
      2. Anesthetics: gases and vapors
      3. Anesthetics: intravenous
      4. Anesthetics: local
      5. Muscle relaxants
      6. Autonomic drugs
      7. Cardiovascular drugs
      8. Central nervous system drugs
      9. Diuretics
      10. Immunosuppressive and antirejection drugs
      11. Drug interactions
      12. Pharmacogenetics
      13. Drug reactions
II. Physical sciences
   A. Anatomy
      1. Topographic anatomy as landmarks
      2. Radiologic anatomy
      3. Respiratory system
      4. Cardiovascular system
      5. Nervous system
      6. Regional anesthesia, main nerve blocks
   B. Biochemistry
      1. Normal body metabolism
      2. Acid-base regulation
      3. Water and electrolytes
      4. Hyperalimentation
   C. Physics
      1. Mechanics
      2. Flow velocity
      3. Properties of liquids, gases, and vapors
      4. Gas laws
      5. Vaporizers
      6. Uptake and distribution of inhalation agents
      7. Design of anesthesia machines
      8. Physics of breathing system
      9. Monitoring methods
      10. Instrumentation
      11. Ventilators
      12. Alarms
      13. Defibrillators
      14. Pacemakers
      15. Electrical; fire, and explosion hazards
      16. Basic electronics
   D. Mathematics
      1. Simple mathematics
      2. Statistics
      3. Computer
III. Clinical sciences
   A. Anesthesia procedures, methods, and techniques
      1. Evaluation of the patient and preoperative preparation
      2. Regional anesthesia
      3. General anesthesia
      4. Intravenous fluid therapy during anesthesia
      5. Complications (etiology, prevention, treatment)
      6. Special techniques
      7. Postoperative period
      8. Anesthesia recordkeeping and quality assurance
   B. Disease states: clinical problems and their management
      1. Painful disease states
      2. Respiratory system
      3. Cardiovascular
      4. Central nervous system
      5. Other entities

6. Special problems

/das/book/view/29494766/875/897.html

Chapter 82 - Operating Room Management

William Mazzei

INTRODUCTION

An excellent example of the maxim that "not all progress is forward" is the evolution of operating room (OR) management. The typical structure for administrative leadership of this crucial area of health care often seems more suited for creating disorder and waste rather than providing efficient, effective, and seamless care. This chapter describes the history that produced this common organizational structure, the forces that are prompting changes in this structure, and most importantly, the ideal arrangement for the management of the OR.

HISTORY OF OPERATING ROOM MANAGEMENT

Up to the 1960s, surgical procedures delivered revenues so far in excess of expenses that little thought was given regarding how to efficiently structure either management or service. Hospital builders calculated how many ORs should be constructed by use of empirically determined ratios of number of ORs per number of inpatient beds. [1] Once these ORs were built, enough nurses and support staff were hired to staff all of the operating rooms every day. Equipment to satisfy almost all surgical requests was rapidly purchased as fee-for-service medicine and indemnity insurance gave confidence to administrators that all new costs could be counterbalanced with charges that would surely be collected. In fact, the acceptable charges (i.e., those reimbursed by insurance companies) often exceeded five times the actual costs, a rate of return that made the ORs a significant revenue center for hospitals and encouraged ever greater expansion of surgical services.

Before the duration of elective surgery exceeded the normal daytime hours of facility availability, surgery was scheduled on a first-come, first-served basis with a large degree of acceptance. As surgical specialties developed, the various services were granted specific rooms and blocks of OR time in order to provide specialty care. As long as all of the surgeons perceived that they had adequate access to the operating room, very few rules or structures were put in place to deal with scheduling and other management concerns, such as cost containment.

As the volume of elective surgery grew beyond the daytime capacity of the existing ORs, the medical staff of a hospital generally formed OR committees to establish rules for the distribution of OR time and the function of the OR. Although policy was created by these OR committees, multiple lines of authority still remained for operational decisions. [2] In private institutions, rules were generally enforced by the OR nurses. In academic institutions, some of the departments of anesthesia were also involved in their enforcement. Typically, high-level administrators, who were not working in, or knowledgeable of, the OR, were responsible for capital equipment and other budgetary decisions for the OR; OR nurses, working for the department of nursing, were in charge of preparing patients and handling the equipment; housekeepers and technicians, reporting to a different administrative structure, kept the supplies and ORs clean; anesthesiologists, working individually or as part of a specialty group, had only unofficial authority in the OR; and surgeons sought service for their individual patients or specialty group, but not for the OR as a whole. These multiple lines of authority caused a lack of continuity for daily operations and also prevented any long-term planning. Few people had any vested interest in the overall performance of the OR, and certainly the modern idea of customer responsiveness was not contained in such a structure. Utilization was also grossly inefficient, although this did not become a major issue in most institutions until the 1980s, when government-mandated limitations on the number of hospital beds and OR suites forced medical staffs to use only those ORs that were present rather than build more ORs as access became limited. [3] As surgeons attempted to perform more procedures within the same number of operating rooms, the OR day grew longer, elective cases on Saturday became commonplace, and scheduling "games" began. [4] The

combination of a limited supply of ORs, ineffective administration, and demanding users prompted a chorus of complaints about how ORs function.

The management problems produced by this history of development are common to most hospitals. [5] Generally, no one person is in charge of the daily functions of the ORs, and operational authority is shared (or declined, depending on the problem) among the highest-ranking OR nurse, the anesthesiologist in charge for that day (typically, the one who created the daily anesthesia assignments), the clerk answering the central phone, and the surgeon. Because usually no one has vested authority for management decisions, the rules that do exist are variably enforced. Rules, in fact, vary, depending on the institutional memory of the person making an operational decision. Even when carefully crafted policy and procedures have been created by OR committees and medical staff, shrewd physician-users of the OR can effectively lobby to higher authorities (high-ranking administrators, department of anesthesiology or surgery chairs, even deans) to have rules temporarily overturned in their favor. These "end-arounds" discourage existing leaders from making correct but unpopular decisions. Absent an established leader, long-term planning for the operating rooms is difficult to create.

FORCES PROMPTING CHANGE

In spite of these administrative and organizational problems, poor management structures continue to exist unless significant institutional pressure arises to force changes. Occasionally, such pressure is brought to bear by visionary leaders of anesthesiology, hospital administration, or surgery. For example, the president of the Johns Hopkins Hospital, faced with dramatic monetary losses and poor utilization of the hospital, created the first physician-led OR directorship by appointing the acting chair of the department of anesthesiology as the administrative leader for the OR. At times, external regulatory bodies, such as the Joint Commission on Accreditation of Healthcare Organizations, force changes. [6] Impending inspections prompt full-scale evaluations of administrative structure so as to correctly divide areas of responsibility (or allow assignment of blame). These evaluations may produce permanent changes in the organization of the OR. Trends in management, such as continuous quality improvement or re-engineering, may also provoke alterations in practice. [7]

In the 1990s, the overwhelming concerns over health-care costs and competition for patients have provided the major impetus for improving OR performance. Hospitals and health-care systems wish to simultaneously reduce the cost of surgical care while providing service that is viewed by patients and physicians as efficient and accommodating. This desire is prompting creation of new OR management structures in multiple hospitals throughout the United States, in both private practice and academic institutions.

IDEAL MANAGEMENT

Centralization of Authority: The Director of the Operating Room

The most important step to improving OR management is to centralize authority over the critical personnel and processes involved in OR services under one individual (Fig. 82-1) . Several consulting firms have labeled this position the "OR czar," although the official title often used is director of the OR or perioperative services. [2] The extent of control granted for this position reflects the local politics and the extent and the urgency of problems, but reasonable effectiveness requires supervision of the areas of scheduling; preoperative clinic (or its equivalent); day-in-progress decision-making; postanesthesia care and sometimes acute pain management; and perioperative information services. If the person chosen to fill this post is a physician, debate usually arises over whether the OR nursing director should report to the OR director or to a higher-level nursing administrator. Although medical supervision of nursing practice is probably not warranted, it is very important that the OR director have control over nursing deployment and practice patterns to address both efficiency and service issues. Similarly, a reasonable degree of authority over anesthesia services is necessary.

To whom this position should report is controversial, as is the source of the director's salary. In this author's opinion

Figure 82-1 Organizational chart for director of the operating room (OR). Solid vertical lines imply direct reporting relationships, dashed lines imply important informal relationships, and horizontal lines imply important collaborative relationships.

the greatest perceived neutrality is created if the OR director works for hospital administration rather than a specific clinical department. To achieve the greatest level of authority, the OR director should report to as senior a level of administrator as is practical in a given hospital. In medical centers where a sense of urgency exists, this is often the hospital director. Clearly, the OR director must work closely with the chairperson of anesthesiology, surgery, and other departments that provide operating or procedural room care. From a practical standpoint, however, it is easier if the OR director reports to only one direct superior.

If problems in OR finances are to be addressed, then the director of the OR should be given control over the OR budget. If this is not possible, then, at the very least, the immediate supervisor must have budgetary authority over perioperative services. In order to maintain a clinical practice, the OR director may continue with a clinical appointment in an appropriate department. For a physician, the time required away from direct patient care responsibilities requires a sacrifice of clinical income that few would accept. Thus, as a practical matter, an administrative stipend is usually required to secure a physician to fill the post.

Several personal characteristics are vital for success of the OR director. A vested interest in overall performance of the OR, as opposed to one department or an individual service, is crucial for objective decision-making. Strong interpersonal skills and the ability to plan and perform long-term projects involving multiple personnel are necessary. Because of the need to lead groups that are extremely diversified along socioeconomic, ethnic, and educational lines, sensitivity to human relation issues is important. Likewise, leadership by consensus gathering, rather than single-minded determination, is more likely to produce long-term success. Although personality and human management skills are most important, strong clinical skills and frequent presence in the OR are a tremendous advantage. Respect from surgical colleagues is most often gained through the clinical arena, and the person who is perceived to be an excellent and omnipresent clinician is more likely to be listened to than the distant, nonclinical administrator. Knowledge of the internal history of an institution is also an asset, although the problems in providing perioperative service are so universal that experience in one hospital will certainly aid in improving performance in another.

Why should an anesthesiologist be interested in serving as an OR director? There certainly is a shared interest between hospital administration and departments of anesthesia, because an efficiently run OR is economically advantageous for both parties. Anesthesiologists are intimately familiar with the medical aspects of the perioperative process and have already established themselves as leaders in the areas of preoperative evaluation, intraoperative management, and postoperative care. Anesthesiologists' working familiarity with all of the surgical specialties makes them cognizant of different service needs but permits an overall perspective to be maintained. Further, application of clinical judgment in day-to-day issues by "front-line" personnel permits more effective problem solving than is possible through a distant administrator and is consistent with the current useful trend of physician management of medical processes. Of course, other scientific skills commonly possessed by anesthesiologists, such as knowledge of data processing and modern communication systems, provide invaluable assistance in addressing OR concerns.

There are disadvantages for anesthesiologists involved in OR management. Anesthetists are accustomed to a high degree of personal control over the service they provide in the OR and may find the lobbying necessary for personnel management slow and frustrating. In distinction to the singlepatient focus of OR care, productive managers must deal with multiple patients and issues on a daily basis. Absent an administrative stipend, personal income decreases if clinical time is sacrificed for administrative duties; conversely, personal time may disappear if one chooses to maintain a full clinical responsibility while serving as manager as well. The need to occasionally make unpopular decisions that affect surgeons who are providing one's customer base creates conflicts of interest that may be difficult to bear. Lack of formal business training may also be a disadvantage.

To make the responsibilities of the OR director clear to all interested parties, a well-defined job description is invaluable. One developed by the Association of Anesthesia Clinical Directors (see the appendix to this chapter) is an excellent guide if an anesthesiologist is chosen as OR director. Modifications to accommodate local conditions and other health-care professionals are clearly appropriate. Relationships to other OR personnel and governing bodies are as important as are the supervisor and job description (see Fig. 82-1) . To assist in gathering support of key players (powerful physicians and leading OR administrators) but still allow rapid decision-making, the OR director would be wise to create an executive committee to meet with on a regular (weekly) basis. An ideal group is the lead hospital administrator for the OR, the OR nursing director, the chairperson of anesthesiology and surgery, and a rotating group of two or three clinically active physician users of the OR. An OR committee made up of a much broader representation of surgical and procedural specialties is essential for examination of large issues. The OR committee should serve as an opinion-gathering and consensus-creating body and is an excellent forum for dissemination of information back to the medical staff.

Scheduling: Definitions and Guidelines

On the practical level, allocation of resources in perioperative services occurs via creation of the OR schedule; the effective OR director thus focuses much of his or her attention on this process. Whether done by hand or sophisticated computer systems, creation of the OR and out-of-OR schedule represents the implementation of all of the openly acceptable rules and regulations and the hidden biases and behind-the-scenes agreements, for perioperative service at a given institution. Frequently, arguments over scheduling arise from perceptual differences over the meanings of certain times, time periods, and utilization indices. The use of common definitions reduces such misunderstandings. Well-accepted definitions can be found in the procedural times glossary, a lexicon for scheduling and monitoring of

diagnostic and therapeutic procedures. [8] A few critical definitions from this glossary are repeated here, along with an explanation of their use, to aid in subsequent discussion.

Case time = time from room setup start to room cleanup finished.

This definition includes all of the time for which a given procedure requires an OR. It allows for the different duration of room setup and room cleanup times that occur because of the varying supply and equipment needs for a particular procedure. For purposes of scheduling and efficiency analysis, this definition is ideal because it includes all of the time that an OR must be reserved for a given procedure.

Resource hours = total number of hours scheduled to be available for performance of procedures (i.e., the sum of all available block time and open time).

For a given institution, this is the time during which the appropriate personnel are expected to be available to work on cases. This may include more than one shift of personnel, or personnel working extended shifts (e.g., >8 hours) in order to gain vertical expansion of OR hours. It may also include electively scheduled time on weekends to gain horizontal expansion of OR hours. Resource hours do not include time gained through overtime or use of on-call personnel, even though this time may be routinely accrued at a given institution.

Raw utilization = for the system as a whole, this is the percent of time that patients are in the room during resource hours.

For an individual service, this is the percent of time in which a service has a patient in the OR during its block time.

Adjusted-percent service utilization = (in-own block hours + outside-own block hours) × 100/block time.

This measures the percentage of time a service utilizes their block time during resource hours. It is adjusted, compared with raw utilization, in that it gives a service "credit" for the time necessary to set up and clean up a room, during which time a patient cannot be in the room. It may exceed 100 percent because of the inclusion of cases performed during resource hours that are outside a service's .

Adjusted-percent utilized resource hours = (total hours - evening/weekend/holiday hours)/resource hours × 100.

This calculation provides the percentage of time that the ORs are being prepared for a patient, are occupied by a patient, or are being cleaned after a patient is taken care of during resource hours. It is adjusted, compared with raw utilization, in that it includes the time necessary to set up and clean up a room, during which time a patient cannot be in the room.

Frequently, institutions attempt to assess the extent to which a service uses its allotted block time by calculating a utilization percentage. Such a calculation should be performed for the system as a whole to measure the extent to which the normal hours of operation are actually used for patient care. If one considers only the time that a patient is in the OR (raw utilization), then the percentage of time that a service uses their block time is artificially decreased because the time necessary to set up and clean up a room, during which time a patient cannot be in the room, is not analyzed. Similarly, the calculation of percentage utilization of resource hours is artificially reduced if only patient in room time is used. The larger the number of procedures done in a given room during resource hours, the greater the error.

Cost-effective utilization requires highly effective scheduling and optimum utilization of the resource hours, with minimal overtime and/or use of more highly paid on-call personnel. For proper assessment of the extent to which a service or system utilizes its block or resource hours, respectively, the utilization calculations should be adjusted as defined earlier. For the individual service, this provides a fairer determination of how much of their block time is truly used. For the system as a whole, it provides the actual percentage of time that the ORs are being used for patient care. Perhaps as important, it provides an accurate percentage of time that is not used and therefore available for efficiency improvements.

Room ready = time when room is cleaned and supplies and equipment necessary for beginning of next case are present.

To maximize efficiency, the patient should be brought into the OR as early as possible. Although some wish to have all the supplies and equipment necessary for the entire case present and open before the patient enters the OR, institutions that have minimized turnover times move patients into the OR as soon as it is clean with only the minimum supplies and equipment (i.e., those needed to start the case) present, but not necessarily open. In those institutions, room preparation continues as anesthesia is induced, allowing an overlap of processes (anesthesia induction and room preparation) that saves time.

Start time = patient in room time

Significant debate, indeed, even argument, exists over the proper definition of start time. This author has listened to this debate at many national meetings. Often, nurses, anesthesiologists, and surgeons define the "start time" differently. Operating and procedural room nurses often feel that they have properly accomplished their preparatory tasks if the room is ready at the scheduled start time, regardless of where the patient is at that time. Anesthesiologists often feel that they are "on time" if anesthesia induction has been completed by the scheduled start time. Surgeons generally believe start time should be the time at which the skin incision is made. Because room setup time is procedure-specific and therefore generally known at the time of scheduling, one can reasonably predict room ready time. Anesthesia preparation time, however, depends on both the procedure and the patient's needs. It is thus more variable and is not known at the time a procedure is scheduled, making accurate prediction of anesthesia ready time impossible. This variability in anesthesia preparation time also makes prediction of surgery start time inaccurate. Variability in case times, resulting from varying lengths of surgery, makes prediction of start times after the first scheduled case of the day even more inaccurate.

Much of the concern over start time is for the first case of the day, particularly if a service or a surgeon follows himself or herself in the same OR throughout the day. Prediction, then, of accurate start times for the first case of the day is most critical. Once the procedure is known, it is almost always possible to have the room ready at any time that is desired for the start of the day. It should also be possible, and desirable for maximizing efficiency, to have the patient in the room for the first case of the day as soon as the room is ready. For maximizing scheduling accuracy and attempting to encourage the most efficient patient flow, it is optimal to define start time as patient in room time.

Turnover time = time from prior patient outof room to succeeding patient in room time.

Strong perceptual differences exist over the definition of turnover time. Anesthesiologists and OR nurses usually consider turnover time to be the time between cases when the room is not occupied by a patient. Surgeons consider any time when they are unable to operate as "downtime" and thus more often consider turnover time to be the time between the end of surgery on one case and the beginning of surgery on the next case. The latter may appear to be particularly long to an academic surgeon who leaves an OR before the wound is closed (allowing the residents to close and dress the incision) and does not re-enter the OR until the next patient is ready for incision.

As with start time, the variability of anesthesia preparation time makes prediction of turnover times inaccurate if anesthesia preparation time were to be included. Thus, to maximize scheduling accuracy and to encourage distinction of time spent preparing the OR from time spent preparing the patient, it is preferable to define turnover time as time from prior patient out of room to succeeding patient in room for sequentially scheduled cases. Because this definition attempts to include the time spent cleaning and preparing the OR for the next case, it should be calculated only if a subsequent case is scheduled to immediately follow.

Before the era of surgical specialization, the long-term schedule could be created by granting individual surgeons OR time on a first-come, first-served basis, a

completely "open" schedule. As surgical care advanced, each specialty developed its own equipment needs that were not interchangeable with the needs of other specialties. Configuring an OR for a single specialty became a practical necessity for those services whose equipment was large and relatively immobile (e.g., cardiac surgery, with its cardiopulmonary bypass machine, or ophthalmology, with its ceiling-mounted microscope). Also, regardless of specialty, it was more convenient for individual physician users of the OR to schedule several cases in a row in the same OR. This sequential scheduling became increasingly difficult in a completely open schedule as competition for OR time increased. In order to reserve either space or time for a surgeon or a service (a group of surgeons performing the same specialty operations), portions of the available OR time were divided into blocks into which only one service could schedule. In the ideal system, enough ORs existed to grant each service that needed specialty equipment its own OR, while enough generic ORs remained to fulfill the needs of those who preferred to schedule as needed, and sufficient surgery was performed to occupy all of the ORs for an entire business day. This ideal was never attained. Invariably, surgical demand for OR time exceeded the available daytime hours of both block and open time. Services responded by requesting more block time so as to guarantee reasonable time availability. If additional block time was not granted, some services scheduled first into open time before utilizing their block time. Once this practice was recognized by surgeons who used only open time, it led either to new rules to outlaw this practice or to requests by the surgeons now crowded out for their own block time. In many institutions, this pattern has led to schedules that are 100 percent blocked. Of course, such systems effectively eliminate access to new users.

When using block time in long-term scheduling, one must decide which services will be granted it and how much use of a service's block time is required in order to maintain it. The former is most often historically determined (i.e., which services were granted it first), and the latter is often fruitlessly argued over. No studies have been conducted to determine what rate of utilization is most cost-effective or efficient for an institution. In the author's experience, adjusted utilization rates that average less than 70 percent are not associated with full use of available block time and lead to significant waste of personnel time, whereas rates above 90 percent are frequently accompanied by the need for overtime hours. Reducing block time for services that do not maintain at least 70 percent adjusted utilization and granting more block time to services who consistently use more than 90 percent of their available time are reasonable guidelines. The situation at a given hospital must be considered when local set points are established. A hospital with sufficient resources but local competition may wish to encourage surgical use through granting of more block time and lower rate of utilization requirements, whereas a financially challenged center may be forced to require higher rates of utilization in order to reserve a block.

Adjustments in availability of block time can also be made though setting of the "hold" time, that is, the time before the procedure date that a given block is held for a service before it is released for open scheduling. Services prefer short hold times because this maintains their OR access for as long as possible. Of course, OR time that is reserved and not used results in wasted resources and may deny another physician the opportunity to schedule a case. A single hold time for all blocks rarely pleases the majority of users. Improved satisfaction may be realized by using service-specific hold times. Services that are able to schedule electively and far in advance may be comfortable with blocks that are held only up until 2 weeks before the day of surgery, whereas specialties that frequently must provide services to patients admitted the evening before may do best with blocks held up until the day of surgery. Special circumstances arise for surgeons treating patients with suspected malignancies. Although waiting for even a few weeks may not change the course of medical therapy in such patients, the anxiety associated with the suspected diagnosis creates a great deal of psychological urgency. Similarly, acute personal needs may arise for patients or surgeons that produce an unanticipated nonmedical urgency. In systems in which OR time is usually fully booked within a few days of surgery, the use of an "urgent" room may assist in expeditiously handling these needs. An

urgent room is an OR that is held open for any service but into which no case can be booked until a few days before surgery and whose availability is held until a day before surgery. Such rooms permit access for an important subset of patients that would normally be crowded out of a busy OR system.

In creating the long-term schedule for a single medical center, the location of different operative and procedural sites may have to be considered. During the 1980s and 1990s, most medical centers established outpatient surgery suites because of the belief that surgical care could be provided more cheaply if it were performed on an outpatient basis [9] (Ch. 65) . Opening of such suites increased the complexity of scheduling because surgeons needed to choose between two locations within the same system. They were forced to consider whether it would be better to schedule all of one's outpatients on one day and inpatients on another, in order to maintain block time in both sites, or whether to use only open time and schedule both inpatients and outpatients on the same day, at the risk of needing to be two places at the same time. How should the system monitor the latter? Centralization of scheduling for all sites into one office, and preferably on one computerized system, is the most important step for handling multisite problems. Review of the schedule for personnel conflicts, either manually or automatically, can prevent duplicate scheduling of one physician. In certain situations, however, scheduling of simultaneous procedures by a single physician is warranted. The use of residents or surgical assistants may permit concurrent scheduling of procedures in a staggered fashion, as in cardiac surgery in which the primary surgeon only performs the maneuvers required on bypass. This is acceptable as long as the two procedures are performed within close enough geographic proximity to permit rapid availability to both sites (rapid availability implying within accessible walking distance).

Another arena of burgeoning growth that must be accommodated is the out-of-OR sites where therapeutic or diagnostic procedures are performed that require anesthesia care (Table 82-1) (Ch. 66) . Although OR committees may wish to ignore these sites as simply a problem for the department of anesthesiology to solve, the same issues of access and prioritization arise as with OR procedures. In order to apportion the hospital-based resource of anesthesia care

TABLE 82-1 -- Out-of-OR Locations Where Elective Anesthesia Care May Be Required

Angiography suites
Bronchoscopy suites
Burn unit (e.g., dressing changes)
CT scanner
Catheterization laboratories
Endoscopy offices
Evoked potential laboratories
Interventional radiology
ICU
MRI scanner
PACU (for brief nonsurgical procedures, e.g., electroconvulsive therapy)
Radiation therapy center

CT, computed tomographic; ICU, intensive care unit; MRI, magnetic resonance imaging; PACU, postanesthesia care unit

in a manner that is consistent with overall institutional goals, it is better to include the scheduling of out-of-OR sites with the same guidelines and processes as for the ORs. In most commercially available computerized scheduling systems, this can be accomplished by designating one or more OR numbers above the actual number of ORs for these outside sites (e.g., a hospital with 20 ORs could assign ORs 21 and 22 for out-of-OR procedures).

Setting the resource hours, which requires deciding the number and the duration of OR and out-of-OR sites to staff, is perhaps an even more contentious issue than allocation of block time. The ideal arrangement depends on one's vantage point. To the hospital administrator counting salary costs, OR and procedural rooms that are completely filled during straight time hours but empty just before overtime pay accrues is the optimal solution. Salaried employees generally prefer the same solution, as long as adequate resources exist to provide the union-mandated breaks and lunch time. Salaried anesthesiologists may feel similarly, whereas fee-for-service anesthesiologists prefer to work constantly without interruption until their desired quitting time and could happily exist without any evening and weekend hours. Surgeons with afternoon clinics seek OR time that runs from 7 AM until their clinic opens and then additional OR time after the clinic closes to complete urgent cases. Of course, patients would prefer to schedule elective surgery at their convenience and wish to be transported immediately to the OR for any urgent or emergent care that they require.

As with block time utilization, no study has been completed that defines the optimal amount and arrangement of resource hours. Indeed, tradeoffs between access, convenience, and cost preclude a solution that will satisfy everyone. Patient needs certainly mandate around-the-clock availability of emergency care. Beyond that,

the amount of OR time required is primarily driven by the service needs of the various surgical and nonsurgical specialties, needs that may vary over time and are relatively unpredictable. This author's experience suggests the following guidelines:

1. Enough resource hours should be available to permit scheduling of elective cases within a reasonable waiting period. In competitive markets, an acceptable wait period is between 1 and 2 weeks (i.e., one can schedule an elective case within 1 to 2 weeks).
2. Hours for electively scheduled surgery are best confined to the normal working shift of OR personnel (generally, 7 AM-3 PM). Routinely performing surgery that exceeds these hours leads to expensive use of overtime pay and leads to strife among nonsalaried OR personnel.
3. To accommodate urgent procedures that arise during the day, sufficient hours should be available to permit these cases to start within 2 to 4 hours of the request for OR time. First priority should be given to placing these cases into gaps that occur because of case cancellations, thereby minimizing wasted personnel time. Likewise, these "add-on" cases should be placed into any available OR that has the equipment to perform the necessary surgery.
4. Sufficient staffing should be provided to accommodate the average emergency load, based on historical data (6 months). Although this suggestion may appear obvious, it is striking how many hospitals routinely interrupt elective

cases for emergencies that could have been reasonably anticipated.
5. After providing these suggested hours, if the adjusted percent utilization of the ORs is greater than 80 percent, additional OR hours are warranted. Options for increasing these hours include staffing for longer days, staffing for elective evening or weekend hours, or opening new ORs. If new ORs are already available, they represent the best path for providing more service. Commonly, however, all of the ORs are already in service, and one must choose to expand hours in the existing ORs. It is often suggested that improvements in OR efficiency will permit more cases to be performed within the same number of hours at existing sites. Although significant improvement in start times and turnover times is possible, such improvements rarely provide enough time to schedule even one additional case during the electively scheduled day. [10] [11]

Although appropriate creation of the long-term schedule is critical, proper Management of Day-in-Progress schedule is equally important. Multiple medical, social, and environmental events produce changes in the anticipated cases that cannot be foreseen before the day of surgery. One should thus expect that a few to many changes will have to be made in the daily schedule. To efficiently deal with these changes, a single person working in the OR should have the authority to adjust the schedule as the day progresses. Although the guidelines and the policies for schedule adjustments can be established in larger forums, enforcing these rules is best left to a single OR manager each day. This person is often referred to as the floor runner, or the person running the floor. In large academic centers, this person is usually an anesthesiologist, but in private centers, a senior OR nurse may perform this function. Ideally, however, the director of the OR performs this function on the overwhelming majority of days, sharing the responsibility with a very limited number of others.

The most common day-in-progress problem is scheduling of add-on cases. Procedures that are booked to be performed on the same day as they are scheduled can produce tremendous conflict. Both the patient and the scheduling physician may wish to proceed to the OR as soon as possible, but frequently, no time is immediately available. When is an add-on case of sufficient urgency that the electively scheduled cases should be interrupted and delayed? Further, if there is more than one add-on case, who should go first? The most common and medically reasonable approach is to separate add-on cases into three categories: elective, urgent, and emergent. Elective cases are those that can be performed at any time without risk of medical harm to the patient. Examples include cosmetic and joint replacement surgery. Add-on cases that are truly elective should be scheduled to follow after the days that electively scheduled cases are completed. Depending on resource hours available, it may be acceptable to ask the scheduling physician to defer the procedure until the following day. Emergent cases are those that must be performed immediately in order to prevent loss of life or limb, such as penetrating trauma with hypotension and fractured extremity that has lost its vascular supply. Organ transplants may be placed in this category if the donated organ cannot be preserved. Emergent cases must proceed in the next available OR. If emergency cases routinely interrupt regularly scheduled procedures, it is wise to maintain an unoccupied emergency OR during the electively scheduled hours. Enough anesthesia and nursing staff should be available to immediately provide care if an emergency case arrives.

Urgent cases are the most difficult to define, although many types are proposed to be in this category. To many, a procedure is urgent if it must be performed within 24 hours to avoid significant morbidity. This establishes the need to complete the procedure on the day it is scheduled. Several strategies exist to accommodate these cases. If, as suggested earlier, sufficient openings in the schedule exist, because of either cancellations or flexible staffing, to accommodate all urgent requests within 2 to 4 hours, then further clarification of need is rarely required. If such flexibility is not available, it is wise to determine whether the scheduling physician has any cases already scheduled that he or she may delay in order to accommodate the urgent case. Similarly, such "bumping" of cases may be the rule within service lines (i.e., if the urgent case is being performed by general surgery, then one of the general surgery cases should be bumped to accommodate it).

In questionable cases, a formal anesthesia evaluation may provide valuable information for determining priority. Occasionally, suggesting that the case will be performed, but not until the late evening, may lead to a voluntary deferment on the part of the surgeon to the next or another day. Absent any clear priority, the OR manager running the floor should have discretion to settle the final order of cases.

A Rational Approach to Solving Problems

Because of the ineffective manner in which OR management systems have developed in the United States, problems in the delivery of perioperative services are similar and commonplace in American hospitals. However, even though these problems are universal, it is the local milieu that determines which problems are most important for a single institution to solve. A financially struggling hospital may need to stress cost reduction, whereas a more economically advantaged site facing local competition may wish to concentrate on improving service. The concerns of all parties may not deserve equal attention. A few powerful physicians may require careful consideration, whereas union presence may instead demand accommodation of a much larger number of rank and file personnel. It is important to remember the perspective of the patient, who may be completely unaware of the departmentalized structure of the hospital and wishes seamless travel through the health-care system. Finally, the interests of the insurers demand that one demonstrate the value of services provided. Given this variation in priorities, how does one decide which issues to address first?

The local political situation may dictate the answer, or regulatory requirements may demand certain corrections. Overwhelming financial constraints may similarly demand draconian solutions. For the medical center not faced with such restrictive requirements, a consensus-building approach is preferable. This should start with a generalized survey of all operating room staff and physician users, asking,

TABLE 82-2 -- Typical Structural Problems

Locker room is too small.
Too many scheduling sites.
Too many numbers to call to schedule.
No waiting room for families.
Time clocks are inaccurate.
Insufficient scrub suits are available.
OR hallways are too crowded with equipment.
Surgical lights are poor in some ORs.
OR climate control does not work adequately.
Insufficient anesthesia specialty coverage.

for example, for the top ten problems faced in the delivery of perioperative care. Once a list of problems is accumulated, it is helpful to separate them into structural versus process problems because the approach to solving these problems differs. Structural problems are those requiring a change in the physical environment or

alterations of the function of a single job (Table 82-2) . Problems that affect only one service, such as anesthesiology and nursing, may also be placed in the structural category if alteration in practice for a single group can produce improvements. Process problems are those involving multiple services and/or sites (Table 82-3) . To solve process problems, changes in the way several personnel do their jobs may be required.

After creating a separate structural and process problem list, prioritization of which problems should be addressed should take place. Depending on where the pressure for change comes from, one may want to give more weight to the concerns of the surgeons, the administrators, or the OR staff. A way to effectively try to please all parties is to use a multiattribute decision model, in which problems are judged on the basis of their affect on desirable goals (Appendix). A committee of key players, representing all services involved in OR care, ranks each of the problems according to how likely solving that problem will achieve these goals, and then a summated score for each problem is generated. The advantage of this technique is that it allows all parties to express their opinion and generally produces a list of prioritized problems that has several of each group's "pet peeves" in the top ten of the list. Once this prioritized list is formulated, it is wise to share them with as large an audience as possible, partly to engender a feeling of universal input and also to ensure that no glaring errors were made in the process.

Structural problems are solved most quickly if they are assigned to a single individual. The OR director should assess

TABLE 82-3 -- Common Process Problems

First cases start late.
Turnovers are too long.
Surgery takes too long.
Incorrect or missing surgical supplies.
Low morale among staff.
Patients arrive to OR too late.
Too much suture is wasted.
Surgical preference cards are inaccurate.
Surgeons/anesthesiologists are not available on time.
Records and x-ray studies are not available at time of surgery.

the problem, decide which individual can most likely address the entire issue, and then enlist that person. An initial meeting with this person should clarify the goal desired and then establish the resources necessary to achieve that goal, including personnel, money, and space. From a practical standpoint, if the problem requires the input of more than five people, then it should be broken down into smaller components before proceeding.

Process problems require greater effort and a different approach than structural problems. Because process problems involve multiple services, each service has its own particular view on what the real cause of the problem is. Attempting to solve process problems by appointing a single individual or service to determine and dictate a solution leads, at best, to a solution that considers only one service's viewpoint, or, at worse, a deepening of the problem and an alienation of all the other parties. In almost all instances, process problems require a total quality management (TQM) approach in order to achieve an effective and long-lasting solution.

Total quality management, also referred to as continuous quality improvement, is the management method originally developed by Deming and others in Japan to improve their automobile industry. It requires that an independent team be created for each problem. This team must follow a rigorous path for forming, installing, and monitoring a solution (Table 82-4) . Details of team function are beyond the scope of this chapter but are provided in the references. [12] [13] [14] [15] Practical points in the use of continuous quality improvement teams for improving OR performance are as follows.

To properly address the concerns of all parties involved in a problem, it is critical to form a team that is composed of a member of each group or service that has an interest in solving the problem. Generally, effective team sizes range from six to 12 people (if >12 individuals are needed, the problem is too large and should be broken down). Choosing members of the team is an important task. It is necessary that the members chosen have firsthand knowledge of the problem assigned and that they have no previously existing personality conflicts. Equally important is that the entire team receive adequate training in TQM so that they have the tools to address their given problem. Ideally, this happens by having all team members attend an institutionally provided training course. If this is not feasible, it may be sufficient for the leader of the team to be expertly trained. It is extremely helpful if this leader has previously served on a TQM team. In addition to the regular team members, a person familiar with TQM, whose usual job is not involved with the team's problem, should be chosen to be the facilitator, a person who is responsible for keeping the team focused and moving. The facilitator serves as an objective moderator when

TABLE 82-4 -- Total Quality Management Approach to Solving Process Problems

Stage 1	Define the problem
Stage 2	Understand and measure the process
Stage 3	Eliminate errors and implement solutions
Stage 4	Remeasure the process
Stage 5	Identify and reduce variation in the process
Stage 6	Plan for continuous improvement

TABLE 82-5 -- Prioritization of Problems Using a Multiattribute Decision Model

PROBLEMS	GOALS							GOAL-WEIGHTED PRIORITY SCORE
	IMPROVED SURGEON SATISFACTION 25%	*IMPROVED ANESTHETIST SATISFACTION 25%*	*IMPROVED NURSING SATISFACTION 25%*	*IMPROVED EFFICIENCY OR PRODUCTIVITY 10%*	*IMPROVED PATIENT SATISFACTION 5%*	*IMPROVED QUALITY OF CARE 5%*	*IMPROVED FINANCES 5%*	
First cases start late	5	4	3	4	1	1	3	3.65
Turnovers are too long	5	3	3	4	1	1	3	3.40
Surgery takes too long	2	5	5	4	2	3	4	3.85
Incorrect/missing supplies	5	2	4	3	1	2	3	3.35
Patients arrive to OR too late	3	4	3	3	3	2	3	3.20
Locker room is too small	2	2	5	2	1	1	1	2.60
Too many scheduling sites	3	1	1	4	1	1	3	1.90

No family waiting room	4	1	2	1	5	1	1	2.20
Time clocks are inaccurate	1	3	4	3	1	1	3	2.55
Insufficient scrub suits	3	2	5	2	1	1	1	2.85

Each problem is graded on whether its solution will achieve the designated goal, using a scale of 1 (extremely unlikely to achieve goal) to 5 (extremely likely to achieve goal) if the problem is solved. The goal-weighted priority score is the sum of the products of the percent priority assigned each goal times the grade assigned to a problem for that goal.

disagreements arise. The OR director should meet with the team leader and the facilitator on a regular basis, but compared with the structural problem teams, it is extremely important that the OR director allow the process problem team to set its own time line. A critical aspect for success is the development of team spirit, or buy-in, for the problem. The best-functioning teams are those that feel the problem is theirs to solve. Overriding external input can negate this feeling and thus should be avoided. Just as it is important for the team to deal with the problem on its own terms, it is important for them to make regular announcements about progress and results. This forces the team to clarify what it is doing and to defend its approach so as to mollify outside criticism. Although at times it may seem counterproductive, when individual members of the team hear criticism and relay this to the rest of the team, it forces re-examination of ideas and allows the team to become more secure in its actions.

How many problems should be addressed and how many teams should be formed are dependent on the urgency of the issues and the resources available to the OR director. To establish momentum and to demonstrate progress early, it is wise to initially address a few high-priority problems that can be solved quickly. Frequent and wide promulgation of actions and results also promotes an atmosphere of continuous improvement. Once a significant number of structural and process problems have been solved, a resurvey of interested parties is helpful to ensure recognition of progress and to reassess the extent of remaining problems (Table 82-5) . Although it is true that there will always be a top ten problems list, priorities change. [16] The continuously successful OR director will want to approach problems with an eye toward the most current general concerns.

SUMMARY

The usual evolution of OR management has typically produced an administrative structure that is not well suited to provide efficient perioperative services or to address the multiservice problems that are indigenous to this area of health care. Changes in the medical marketplace, which demand both reductions in cost and improvement in service, are pressuring medical centers to improve the way OR services are provided. This can be accomplished by centralizing authority over the essential personnel and processes involved in OR services and then systematically addressing the issues that are most important at a given institution. Establishing the appropriate hours of OR availability via datadriven selection of resource hours, block times, and hold times leads to a fair and equitable distribution of OR access for the various physician and service users. Careful assignment of cases according to locally determined priorities and policies should ease accommodation of add-on cases. Limiting day-in-progress administration to a small, select group of floor managers permits consistent interpretation and application of these policies, which then encourages collegial and efficient use of OR time.

References

1. Goldman J, Knappenberger HA: How to determine the optimum number of operating rooms. Mod Hosp III:114, Sept 1968.

2. Clockwork Surgery: Perfecting Service for Physicians. Washington, DC, The Advisory Board Company, 1992.

3. American Hospital Association: Annual Survey of Hospitals. Chicago, American Hospital Association, 1998.

4. American Hospital Association: Operating Room Utilizations. Technical Bulletin. Chicago, American Hospital Association, 1983.

5. Wilhite WC: Operating Room Management: The Anesthesiologist as a Leader and Director. In Mazzei WJ (ed): Operating Room Management. San Diego, Association of Anesthesia Clinical Directors, 1994, p 5.

6. Joint Committee on Accreditation of Health Organizations: Accreditation Manual for Hospitals (Surgical and Anesthesia Services). Chicago, 1995.

7. Dufek S, Gaucher E, Gialanella J et al: The total quality process applied to the operating rooms and other clinical processes. Surgery 113:255, 1993.

8. Donham RT, Mazzei WM, Jones RL: Glossary of times used for scheduling and monitoring of diagnostic and therapeutic procedures. Am J Anesth 23:4, 1996.

9. Freestanding Outpatient Surgicenters. Chicago, SMG Marketing, 1987.

10. Mazzei WJ: Operating room start times and turnover times in a university hospital. J Clin Anesth 22:183, 1994.

11. Dexter F, Coffin S, Tinker JH: Decreases in anesthesia-controlled time cannot permit one additional surgical operation to be reliably scheduled during the workday. Anesth Analg 81:1263, 1995.

12. Deming WE: Out of the Crisis. Cambridge, Massachusetts Institute of Technology Center for Advanced Engineering Study, 1986.

13. Juran JM: Managerial Breakthrough. New York, McGraw-Hill, 1964.

14. Ishikawa K: What Is Total Quality Control? The Japanese Way. Englewood Cliffs, New Jersey, Prentice-Hall, 1987.

15. Scholtes PR: The Team Handbook: How to Use Teams to Improve Quality. Madison, Wisconsin, Joiner Associates Consulting Group, 1988.

16. Kissick WL: Medicine's Dilemmas. New Haven, Connecticut, Yale University Press, 1994.

Appendix-Guidelines for the Role of the Clinical Director of Anesthesiology and Director of the Operating Rooms

CRNA, certified registered nurse anesthetist; OR, operating room; PACU, postanesthetic care unit

I. Responsibilities to the department of anesthesiology
   A. Personnel management
      1. Long-term faculty schedule
      2. Daily faculty/resident/CRNA assignments; assurance of comprehensive resident case exposures/coordination with program director
      3. Manpower calculations and planning; recommendations to chairman
      4. Creation of management team representing all clinical aspects of the department
   B. Subspecialty coverage
      1. Develop appropriate faculty daily and on-call coverage
      2. Participate in resident subspecialty rotation development
   C. Daily operations
      1. Early morning review of schedule
      2. Morning clinical/manpower conference
      3. Assignment changes during the day
      4. Chief arbiter of clinical and interstaff problems
   D. Participative roles (with significant institutional variations)
      1. Preoperative evaluation clinic/preadmission testing procedure
      2. Anesthesia equipment/monitoring
      3. Quality assurance/quality management process
      4. Disaster planning
   E. Evaluation and promotion of the clinical director
      1. Clinical management-oriented job may require special criteria
      2. Clinical tract appointment most likely
      3. Teaching time may be limited
      4. Research areas may exist in management, statistical, and clinical studies

II. Responsibilities to the OR/hospital/medical staff
   A. Scheduling and data gathering
      1. Daily reviewer/final arbiter of OR scheduling
      2. Supervisor of scheduling/data processing personnel
      3. Enforce scheduling policy
      4. Management of OR utilization data and submission of reports to appropriate governing body
   B. Communications center (OR front desk)
      1. Establish practices that provide expeditious service
      2. Supervise front desk personnel
   C. Clinical director's role with OR nurses, PACU nurses, and support staff (with significant institutional variation)
      1. Leadership and supervisory role for OR personnel
      2. Strong working relationship with nursing hierarchy and hospital administration
      3. May function as OR manager with budgetary, materials management, and quality assurance functions
   D. Chief liaison to:
      1. Hospital administration (formal position)
      2. Nursing administration
      3. OR committee (may serve as chairman of the committee). Authority must be delegated from surgical and anesthesiology departments and hospital administration
   E. Basic support from hospital administration
      1. Office, secretary, scheduler, and other personnel as necessary
      2. Financial subsidy may be appropriate
      3. Administrative authority

III. General qualifications
   1. Seniority, appropriate academic rank--associate or professor level may facilitate the role
   2. Clinical proficiency/commitment--being respected for clinical abilities is a significant attribute
   3. Educational qualifications--formal training or experience in negotiation and interpersonal relations and business administration may be desirable

Chapter 83 - Electrical Safety in the Operating Room

Lawrence Litt

INTRODUCTION

Despite modern safeguards and alarm systems, unsafe electrical configurations still cause injury during surgery and anesthesia. Although surgical equipment by itself can be the culprit, anesthesia and physiologic monitoring equipment are also often involved.

Tragic events reported in the medical literature show the serious consequences of inattention to electrical safety. Patient electrocution, once a well-recognized hazard of surgery and the operating room, [1] is now uncommon. Even so, during the past 20 years, electrocution has still occurred four times outside the operating room: in 1975, from connections to a dialysis machine [2] ; in 1976, from a faulty endoscope [3] ; and in 1987 and 1993, from electrocardiographic leads that were mistakenly plugged into a power cord. [4] [5] More usual, however, have been severe burns caused by inadequate grounding, faulty equipment, and induced currents from radiofrequency fields. One neonate had third-degree burns after application of an external cardiac pacing device for a prolonged period. [6] Serious burns have also occurred from direct currents; in one instance, the source was a battery-powered neuromuscular stimulator. [7]

Although much modern equipment appears different from its ancestral counterparts, injuries now caused by electricity are similar, if not identical, to those occurring generations ago. Electrical malfunctions in the operating room continue to cause fires and explosions, central and peripheral nerve stimulation and damage, muscle stimulation and contracture, tissue burns, pacemaker interference, and sudden loss of power to important equipment. Because safety standards for medical equipment have been improving, most complications can be avoided by preventive maintenance of equipment, careful attention to the electrical contacts used on patients, and appropriate responses to alarm signals. Understanding electrical safety is an especially important responsibility for anesthesiolo-gists because perioperative electrical dangers can often be identified before they lead to disruption of patient care or to injury. [8] [9] [10] [11] [12]

Before the important issues affecting electrical safety and the guidelines for safe clinical practice can be discussed, some basic concepts must be reviewed.

ELECTRICAL GROUND

Discussions of electrical safety often center on whether circuits are grounded. To the clinician, an electrical ground is the wire connected to the third prong on plugs that are inserted into electrical wall outlets. With regard to a circuit, an electrical ground is any object connected to the circuit that is capable of instantaneously supplying or receiving arbitrarily large amounts of electrical charge. The National Electrical Code (National Fire Protection Association [NFPA] *) defines "ground" as a conducting connection, intentional 0or accidental, between an electrical circuit or equipment, and earth, or a connection to some conducting body that serves in place of the earth. Because the earth is an infinite reservoir of electrical charges, having a limitless ability to give up or receive electrons, any charged object connected to earth loses its charge and assumes the same potential as the earth. [8] Relative to earth and to each other, the voltage between two grounded objects is zero.

When a circuit is intentionally grounded, the actual physical objects chosen to serve as the electrical ground can vary. In a remotely located Mobile Army Surgical Hospital unit, equipment might be grounded by connections to a spike that goes into the earth. In a large urban medical center, ground might consist of a subterranean network of pipes. For a very small hand-held radio, a human being might serve as the connection to ground.

In hospital settings, it is generally not necessary for the clinician to understand the details regarding the choice of ground. However, clinicians must often know whether they, their patients, or their pieces of equipment are grounded.

* National Fire Protection Association, 1 Batterymarch Park, P.O. Box 9146, Quincy, Mass 02269-9959.

Living organisms tolerate only small amounts of electric current. Contacts with electrical ground are dangerous when they enable large electric currents to travel through the body--or when they render circuits one step away from the establishment of large currents. Human protection from large currents can be ensured if connections to ground always occur through a sizable resistance. An unrealistic but vivid hypothetical example illustrating the danger of electrical grounding is that of a person standing at the center of a giant copper cylinder that extends to the molten core of the earth. This situation would be quite unsafe because the person would essentially be a fuse, poised to suffer whatever large electrical current is applied. The need for additional electrical resistance between the person and the copper cylinder explains a requirement that was established in the days when explosive anesthetic gases, such as cyclopropane, were used. Operating rooms were then required to have conductive floors made of specific resistive materials. Such substances had high carbon content, so that they were not as conductive as metal. The high carbon content imparted a dark black color, one that can commonly be found today in operating room tables and cushions made of resistive materials.

In the United States, electrical plugs have three prongs: two that provide voltage (or, equivalently, power) and a special third prong that serves only as a connection to ground (i.e., to an object that makes an electrical connection with the earth). Travelers to Europe and elsewhere will recall seeing electrical outlets for plugs that have only two prongs and no separate ground wire. A two-wire system becomes especially unsafe if three-pronged equipment is plugged into it, leaving the third prong unattached to anything.

A *ground fault current interruption* (GFCI) electrical outlet allows one to test that the third connection in the outlet is indeed connected to a functional ground. More significantly, GFCI outlets enhance electrical safety by serving as emergency circuit breakers that shut off power when one of the two power lines in the outlet is accidentally connected to ground. GFCI outlets, found in hospitals (and homes), have two buttons: "test" and "reset." Pushing "test" causes a special resistor to be connected across the power and ground terminals in the receptacle. If the ground connection (the third wire) is in place and connected to the system ground, as it should be, current flows through the resistor and causes a circuit breaker in the outlet to open. No electricity can then be delivered by the outlet. Pushing the "reset" button resets the circuit breaker and restores electrical power. Pushing "test" would not cause the circuit breaker to open if, for example, a contractor accidentally forgot to install the ground wire or if an earthquake or other mishap caused a break in an installed ground wire. Protection against accidental grounding of one power line in an outlet is required by the NFPA for "wet environments," such as operating rooms. The installation of GFCI electrical outlets is one way to satisfy NFPA protection requirements. As is discussed further on, a second way (the traditional but more expensive way) is to have power come from an isolation transformer equipped with a line isolation monitor. [13] [14]

Electrical engineers commonly choose ground as the place where the electrical potential (voltage) is defined to be zero. Therefore, the voltage at any point in a circuit is the difference between the voltage at that point and the voltage at the electrical ground. Because of this, ground connections in commercial circuits help professional personnel check for proper functioning. A technician connects one voltmeter probe to ground while touching different circuit elements with the other voltmeter probe. The manufacturer's table can be used to compare readings and, in this way, identify problems in the circuit. Specifying the location of ground helps people communicate standards for circuit performance.

THE ISOLATION OF ELECTRICAL POWER FROM GROUND

Electrical contacts with ground can cause injury when they complete a circuit that permits a large flow of current. One strategy for ensuring safety is to isolate all electrical power sources from ground, making it impossible for ground to be used as a path for injurious or damaging currents.

Traditionally, implementation of this strategy in the operating room has been accomplished by means of isolation transformers, which usually take the form of large wall panels having outlets and meters. The term "isolation transformer" comes from the fact that power outputs are isolated from ground.

Electrical power for an operating room comes from a primary hospital source that usually originates from a connection to an alternating-current (AC) station of the local power company. (Sometimes an emergency gasoline-powered electrical generator is the primary source.) After arriving at an operating room, electrical power is modulated, isolated, and dispensed to electrical outlets in the room by the secondary coils of one or more large isolation transformers. Connections in three-hole power outlets in operating rooms, therefore, are somewhat different from connections in standard outlets found elsewhere in the hospital. [12] In operating rooms, a circuit cannot be completed by connecting one of the two power contacts to the ground contact.

The panel of each isolation transformer is required to have a *line isolation monitor* (LIM), which is simply an electrical current meter that demonstrates the isolation of the transformer's output power from ground. The large isolation transformers seen in operating rooms are somewhat anachronistic because the NFPA requires their presence only for environments in which inflammable anesthetics are used. [14] This does not mean that basic notions of safety have changed with respect to the need to isolate circuits from ground. However, isolation of electrical power is now accomplished with advanced technology that was unavailable when large isolation transformers were initially required. In principle, manufacturers are capable of incorporating good electrical isolation into the design of each piece of electrical equipment used in the operating room. Indeed, it is possible to argue that the obsolescence of central isolation and LIMs has already been demonstrated by the absence of these items in the intensive care unit (ICU) and the postanesthesia care unit (PACU). All electrical instruments that are permitted in the operating room are also used in ICUs and PACUs, yet one does not see isolation transformers and LIMs in ICUs and PACUs. Should one then assume that isolation transformers and LIMs should be eliminated from operating rooms or not installed in new operating rooms? The answer is neither yes nor no, [13] [14] as suggested earlier.

Figure 83-1 Schematic diagrams of (A) an isolation transformer and (B) electrical grounding for an ECG in the operating room (outlet to equipment).

The issue of safety for surgical patients who are wet with fluids that conduct electricity is better understood after a review of some fundamentals of electrical isolation.

Figure 83-1 A shows a schematic diagram of an isolation transformer. For each power outlet, two hot-wire contacts come from the secondary coil of the transformer. The primary circuit of the transformer is attached to ground, but the secondary circuit of the transformer is not. The third contact, which is at the end of the ground wire in the plug, is connected to the standard hospital ground and not to the isolation transformer.

When an ECG monitor is plugged into a power outlet in the operating room (Fig. 83-1 B), neither of the two "hot wires" from the secondary coil of the transformer is connected to ground by the ECG circuitry. This demonstrates the general principle that electrical circuits within an apparatus need not be grounded, although the metal case that houses the circuits is always grounded. Indeed, for many circuits, proper functioning depends on good isolation. Thus the statement "all operating room equipment must be grounded" is always true regarding connections between ground and the external case but is not always true regarding powered circuits within the apparatus.

In the example given in Figure 83-1 B, the ECG case is connected to the hospital's electrical ground, and the internal circuitry is connected to the output of the isolation transformer. This safe system is worthy of further discussion.

Let us suppose that mechanical or electrical damage causes us to worry about the electrical safety of an ECG monitor. Could a failure occur inside the ECG monitor that would place the patient or the anesthesiologist in contact with the internal circuitry? If so, would electric current travel through the person from the ECG circuitry to ground, causing injury or distress? Thanks to isolation of the ECG circuitry, the answer is no.

Figure 83-2 A shows how isolation provides safety. In Figure 83-2 A, a grounded person is touching the internal circuitry at point B. The isolation transformer supplies current to pathways that connect the two "hot" leads in the outlet, indicated by points A and D. However, the only way for electric current to get from point A to D is through impedance Z. Because each of the hot points in the wall outlet is not grounded, the person in Figure 83-2 A is safe from shock.

Figure 83-2 B, however, shows that two inadvertent ground contacts could produce a dangerous situation, especially if one of those contacts is a human being. Suppose that a fault occurs near point D, causing the internal circuitry to come in contact with the external metal case. A dangerous shock would result from touching the circuit at point B. Because of the fault, current could complete a pathway through the person and ground (i.e., from point A to D). Thus, it is useful to isolate power lines from ground and to know when isolation is compromised by a fault.

As mentioned, every isolation transformer has a LIM that monitors the isolation of the transformer's two power output lines from ground. Figure 83-2 C shows how the LIM (an ammeter) replaces the smiling and frowning people in Figures 83-2 A and B. When very low amperage is indicated, the LIM verifies that the power output lines of the transformer are indeed isolated from ground, as in Figure 83-2 A. The reality of the LIM connections is actually different because either of the hot wires could become grounded accidentally. Therefore, the LIM is actually connected to both sides of the isolated power output (Fig. 83-3) and is set to sound an alarm when either side has an impedance to ground that is less than 25,000 ohms, or when the maximum current that a short circuit could cause exceeds 2 mA. Note that the LIM is insensitive to currents below 2 mA. As is discussed later, the LIM provides no protection against microamp currents and microshock.

One event that occurs commonly in the operating room could produce a short circuit between power and ground, causing the LIM to go off. This event is the dripping of saline, blood, or other conducting liquid into the receptacles of an electrical extension cord that is on the floor near the operating table. For this reason, electrical extension cords in operating rooms frequently have watertight covers that flip into place over unused outlets. If wet receptacles on an extension cord appear to set off an LIM, the extension cord should be changed. If, on the other hand, the LIM rings suddenly and unexpectedly or immediately after a new piece of equipment is plugged in, that equipment should be unplugged immediately. If plugging in a piece of equipment repeatedly causes the LIM to sound an alarm, the equipment should not be used until it is checked. Similarly, if use of a particular power outlet repeatedly causes an alarm, it, too, should not be used until it has been checked. When an

LIM alarm indicates a "first fault," that is, that one power line is grounded, large, potentially damaging currents may subsequently occur through ground connections if there is a second ground fault. The path of damage might include the anesthesiologist, the patient, or an essential piece of equipment. Thus, an alarming LIM warns that someone in the operating room might receive an electrical shock or burn when touching connections to electrical equipment.

As mentioned earlier, detection of a first fault in grounding is possible without the use of isolation transformers and LIMs. The direct-installation GFCI outlets provide protection against a first fault. However, it provides protection, as described earlier, by suddenly shutting off all power from

Figure 83-2 Diagrams showing that (A) no electric shock occurs if an isolated power line is touched, (B) an electric shock *does* occur if a faulted secondary power line is touched, and (C) a line isolation monitor can watch for a fault.

the outlet. An advantage of the LIM is that one learns about a first fault without losing electrical power. A disadvantage of the LIM is its susceptibility to newly developed artifactual causes of alarm. Certain new devices used in operating rooms emit electrical radiation, intentionally or incidentally, that falsely cause LIMs to sound an alarm. These include instruments that generate ultrasonic sound waves for tumor disintegration and aspiration and stereotaxic monitors that use radio waves to track sensors attached to patients.

Figure 83-3 Schematic showing complete connections of the line isolation monitor (LIM). The alarm sounds that there is a "first fault" if either isolated power line has less than 25,000 ohms impedence, corresponding to 2 mA or more being drawn through the LIM.

CAPACITIVE COUPLING

Resistive coupling, the direct connection of two circuit elements by a wire or resistor, is the easiest kind of coupling for an anesthesiologist to recognize and understand. The connection is visible, and the effects of the connection are apparent for circuits carrying either direct current (DC) or AC at all frequencies. More subtle and abstract is the concept of capacitive coupling, which applies only to AC current. This concept is relevant to the anesthesiologist because it can account for electrical connections being present at high but not low electrical frequencies. If the alarm of an LIM goes off only when the electrosurgical electrode delivers high-frequency current to the patient, the dangerous pathway to ground might be caused by capacitive coupling. The power outlets might be safe for low-frequency currents but not high-frequency currents. Grounding pads, connections to electrical plugs, and equipment might need to be separated even farther from each other before the problem is remedied. The rationale will become more apparent after a review of the basic principles governing capacitive coupling.

The parallel-plate capacitor (Fig. 83-4) is a circuit element that permits the temporary storage of electrical charge and the passage of alternating electric current. However, the parallel-plate capacitor does not permit the passage of direct electric current. The electrical impedance of an object is the

Figure 83-4 Schematic diagram of a parallel-plate capacitor. f, frequency of alternating current; C, capacitance in farads.

total number of ohms that obstruct the flow of current. This term is a generalization of the term "electrical resistance." Electrical impedance includes contributions from capacitive, resistive, and inductive elements and is dependent on frequency. Using a simple formula, however, permits one to quantitate the impedance (Z) of a pure parallel-plate capacitor (of C farads) as a function of the AC frequency (f):

$$Z\ (\text{ohms}) = 1/(2\pi f C)$$

In this instance, capacitance (C) is directly proportional to the area of the capacitor plates and is inversely proportional to the space between the plates. As frequency (f) increases, impedance to the flow of current decreases.

At very high frequencies, the coupling to ground occurs through fewer ohms of impedance than would occur at low frequencies. Because any two conducting objects in a room have surface area and an average distance of separation, they form a kind of capacitor. Thus, any two objects have a capacitive coupling. This means that each of the two output lines of an isolation transformer is always coupled to ground at AC frequencies.

Although such capacitive coupling is usually insignificant, it can sometimes be significant at frequencies of 60 cycles/s (or 60 Hz) and is more commonly a problem during electrosurgery, which occurs at higher frequencies, typically hundreds to thousands of kilocycles/s. Capacitive coupling, which lets high-frequency currents pass easily, is commonly used by manufacturers in the connection between the electrosurgical unit and the electrosurgical pencil (cutting/coagulation tip) and in the connection between the electrosurgical unit and the large-area "grounding pad" that attaches to the patient. (The proper term for this conducting pad is "dispersive electrode.") Therefore, high-frequency currents used during electrosurgery have a low impedance path to and from the patient. At the same time, capacitive coupling prevents the electrosurgical pencil and the large-area conducting pad from participating in dangerous low-frequency grounding of the patient.

Capacitive coupling, which is not present in the connection of an older electrosurgical unit to its ground pad, might have prevented a serious DC burn caused by a 9.5-volt battery within a damaged nerve stimulator used by an anesthesiologist. [7] In laparoscopic and endoscopic surgery, it is important for surgeons to avoid unwanted capacitive coupling between the unipolar cautery tool and neighboring metal conductors, such as trocar cannulas. Stray currents from unwanted capacitive coupling can involve and injure organs such as the bile duct and bowel. [15] [16]

Anesthesiologists should be aware of such potential surgical complications, which might be erroneously attributed to anesthesia.

Capacitive coupling may have been responsible for severe patient burns from pulse oximetry in patients anesthetized for magnetic resonance imaging (MRI). [17] [18] [19] However, the possibility of being burned by a faulty pulse oximeter probe exists independently of capacitive coupling or radiofrequency currents induced by the MRI environment. [20] [21] In such a burn, the patient is external to a malfunctioning electrical circuit that causes the probe (i.e., the unit that contains the photodiode and attaches to the patient) to overheat and burn tissue. Such a catastrophe can be caused by connecting the wrong kind of probe (e.g., one from another type of unit) to an oximeter console.

Surprisingly, the MRI environment can transform a perfectly safe pulse oximeter setup (probe and console) into a dangerous, burn-causing device when attached to a patient lying in an MRI magnet. The problem arises from changing magnetic and electric fields that occur both at megahertz frequencies (in radiofrequency coils) and at kilohertz frequencies (in gradient coils) during taking of MRI data. Capacitive coupling can connect the patient to wires in a pulse oximeter cable and to metal in a pulse oximeter probe. In such an instance, the patient can become part of a high-frequency loop circuit, with currents entering and exiting at the points of capacitive coupling--particularly at the site of probe attachment. [22] [23] [24] [25] Fortunately, newer pulse oximeter cables have long, nonconducting fiberoptic attachments between the photogenerating and photodetecting parts. These attachments stay outside the magnet, so that only nonconducting components are connected to the patient, who is inside the magnet. The absence of metal or conducting components to the cable or probe attachment eliminates the possibility of patient burns from induced currents during MRI.

Anesthesiologists monitoring patients with pulse oximetry in MRI magnets should use such units, which have a long fiberoptic cable. These are generally available in radiology departments. Severe burns might result if one simply takes a pulse oximeter setup from an operating room and innocently attaches it to a patient in an MRI magnet.

/das/book/view/29494766/875/910.html

ELECTRIC SHOCK

The passage of even small amounts of electric current through the body can interfere with normal functioning of muscles and nerves.

Figure 83-5 Frequency dependence of the "let-go" and pain-threshold currents. RMS, root-mean-square average.

Macroshock

Macroshock, which refers to the application of large voltages or currents to the skin or tissue, can cause injury when contact is made at locations remote from the heart. For example, macroshock was responsible for the death of a patient when ECG leads were accidentally attached to a power cord. [4]

The response to electric current flowing through a person's arm depends on the amplitude and the frequency of the current. Sensation of a 60-cycle current occurs at approximately 300 muA, and pain occurs at approximately 1 mA. After a certain current (the "let-go" current) has been exceeded, the person is unable to release objects. [26] The value for the let-go current varies with frequency and also among individuals. Figure 83-5 shows the range of average values as a function of AC frequency. The 50- and 60-cycles/s currents have the lowest values and are therefore the most dangerous. The response of cardiac muscle to electroshock is also dependent on frequency. Electric current is more important than voltage when issues of safety arise. Table 83-1 (Table Not Available) indicates physiologic responses to increasing total body currents.

Continuous total body currents that reach 0.1 to 2.5 A (approximately 10 times the let-go value) can cause ventricular fibrillation. The electric current generated in one pulse by an implanted cardiac pacemaker ranges from 0.1 to 10 mA. Only a small part of the total body current needs to pass through the heart to affect cardiac function. An electrosurgical unit generates so much power that it can induce microshock currents when it is used near implanted pacemaker wires. However, thanks to compliance with the safe grounding practices described earlier, the last convincing report of ventricular fibrillation induced by electrosurgery occurred in 1968. [27]

Defibrillation is often based on the same principle: that the skin is a good electrical insulator requiring large electrical fields at its surface in order to produce small electrical fields internally. A jolt of 400 watt-seconds (or joules) during closed-chest cardiopulmonary resuscitation delivers the same amount of energy to the body as that produced by a large-caliber handgun. (A 0.45-caliber bullet weighs 250 grains and has a muzzle velocity of 860 ft/s when fired. This corresponds to an energy of approximately 540 watt-seconds.) Only a very small portion of the energy dose of a defibrillator is needed to depolarize the heart.

Microshock

Microshock refers to the direct application of very small voltages or currents to the heart, often intentionally, by means of external or internal cardiac pacemaker electrodes. Inadvertent microshock, however, is dangerous because it can produce ventricular fibrillation. Arterial and central venous pressure transducers were once a potential source of microshock because they brought electrodes very close to heparinized saline that is in contact with the intravascular compartment. [28] [29] However, in recent years, pressure transducers have decreased in size and are now connected to monitors by means of low-voltage telephone cables. That they are generally safe is shown by their frequent use without reported complications. Nevertheless, microshock delivered by a faulty endoscope and faulty dialysis equipment has caused deaths. [2] [3]

TABLE 83-1 -- Average Effects on Humans of 60-Hz Currents Applied at Body Surface and Passing Through the Trunk

(Not Available)

Modified from Bruner [8]

Electric current is the variable most convenient to address when setting safety limits. Because investigators have reported that electric current passing through the human heart needs to be at least 50 muA before ventricular fibrillation occurs, [26] [30] [31] the American National Standards Institute (February 5, 1990) or the NFPA code sets 10 muA as the maximum leakage of current allowable through electrodes or catheters contacting the heart. This amount of current is considerably smaller than the peak electric current generated by an implanted pacemaker during a single pulse (0.1-10 mA). Recalling that 2 mA is the LIM warning level, one can see that the LIM does not provide protection against microshock hazards.

Electrocardiogram (ECG) monitoring electrodes are electrically isolated from the power circuits in the monitor by an isolation transformer in the main unit (a second level of isolation). However, an anesthesiologist who wishes to perform intravenous or intracardiac ECG monitoring, as occurs during the placement of a central venous pressure catheter, should have qualified personnel check the ECG monitor for leakages of current. In some ECG and electroencephalogram (EEG) systems, the electrode signals from the patient are translated into light by a battery-powered amplifier having a photodiode output and are then optically coupled to the main ECG or EEG unit (an even more thorough second level of isolation).

Endovascular procedures performed by interventional neuroradiologists now include the placement and activation of electrical coagulation coils inside certain types of intracranial aneurysms. Electricity in such coils causes coagulation more slowly than occurs in conventional electrosurgery. So far, currents in these unipolar devices have not caused macroshock or microshock. Nevertheless, despite the good safety record for such equipment, anesthesiologists monitoring the care of patients in an interventional neuroradiology suite should be aware of potential electrical hazards that come with new techniques. [32]

/das/book/view/29494766/875/911.html

ELECTROSURGERY

Most of our concerns with electrical safety in the operating room come from the need to use electrosurgical units, which can cause electric shock, burns, explosions, arrhythmias, and disturbances in pacemaker functioning. [33] Electrosurgical units operate at frequencies of approximately 300,000 to 2,000,000 cycles/s (300 kHz-2 MHz), so as to minimize the likelihood of ventricular fibrillation (see Fig. 83-5). During electrosurgery, high currents enter the patient through the small area on the surface where the tip of the electrode is applied. The combination of high resistance (R), which is attributable to the small area, and high current (I) causes local tissues heating proportional to $I^2 R$, which in turn produces cutting or coagulation. The tip of the electrode is also designed to produce lower current densities (low $I^2 R$) at points farther than a few millimeters from the electrode tip. Figure 83-6 shows the fanning out of the electric current. Electrosurgery is therefore a form of highly controlled localized burning of tissue.

Because there is often smoke where there is fire, concerns have been expressed regarding the safety of inhaling the smoke from the electrocautery. One group, assisted by the National Institute of Occupational Safety and Health, used the Ames test to examine the potential mutagenicity of electrocautery smoke collected during breast surgery. [34] Although the compounds collected were mutagenic, it is not known whether electrocautery smoke represents a serious health risk to operating room personnel. Nevertheless, the study recommended that surgeons minimize not only the production of electrocautery smoke but also the exposure of human beings to the smoke.

Because there is fire where there is smoke, it is also important that nonflammable materials be used during electrosurgery. Fires have occurred in operating rooms because highly combustible surgical boundary drapes were placed close to electrosurgical units. [35] The smoke from such fires can contain toxic substances.

From the preceding discussion, it is not surprising to find that electrosurgical units are powerful enough to provide excess electric current that is sufficient to cause extensive tissue burns. Surgical patients who become wet with blood, saline, urine, or other conducting fluids can form electrical contacts with the operating table, ground, or other conductors (e.g., monitoring electrodes and surgical retractors). Such contacts become potentially dangerous pathways for current. For example, current from an electrosurgical unit might enter a patient through the grounding pad and return to the unit via one or more ECG electrodes. In this situation, the electrosurgical unit could provide current that burns the patient but never passes through the tip of the electrosurgical pencil used in the operative procedure.

The dangers of electrosurgery in a "wet" environment, especially the possibility of establishing ground faults through wet connections, once accounted for the presence of an isolation

Figure 83-6 The flow of electric current through the body when small-area versus large-area grounding pads are used.

transformer (and LIM) in every operating room. As mentioned earlier, compared with GFCI outlets, which cause sudden power deprivation, isolation transformers, by turning on an LIM alarm, permit less disruptive detections of ground faults. For example, loss of electrical power during cardiac surgery can be a serious concern, and anesthesiologists must know how to hand-crank cardiopulmonary bypass pumps. [36] Sevoflurane vaporizers, of course, require electricity for operation. The NFPA requires first ground fault detectors in the wet environments of operating rooms. However, anesthesiologists, surgical colleagues, and hospital administrators are free to choose either GFCIs or isolation transformers with LIMs, whichever best suits local conditions and practices. [13] [14]

Unipolar Electrosurgery

It is important to understand the difference between unipolar and bipolar electrosurgery. In unipolar electrosurgery, the more common of the two, the surgeon applies current from the tip of a cutting/coagulation electrode to the relevant tissue location. The second electrode of the electrosurgical unit is connected to a large ground pad attached to a wide area of skin outside the surgical field. Skin burns can occur if the grounding pad is dry (most of the conducting gel is gone) or otherwise in poor contact with the patient. In both situations, electric current is again required to traverse a small surface area. The skin would then present high electrical resistance (R) to the returning current. Because $I^2 R$ can increase substantially, such increases in resistance can cause electrical burns of the skin. [37] Electrical burns have also occurred at the site of ECG leads when the grounding pad was defective and the leads became an alternate path for the returning high-frequency electrosurgery current. [38] [39]

A new, more powerful unipolar electrosurgical tool, the argon beam coagulator (ABC), has become available to surgeons. [40] Operating room personnel unfamiliar with its design and use can easily mistake the ABC for an argon laser because a well-collimated brightly colored beam of argon light glows at the tip of the electrosurgical pencil. The glow, which has the same color as light emitted from an argon laser, represents a continuous electrical discharge in a small, flowing column of argon gas having a density that supports electric current.

One problem with metal coagulation/cutting tips is that during electrical surgery, sticky, burnt tissue often adheres to and coats the tip, electrically insulating the tip and making it impossible to use for surgery. Surgery must then stop while the tip is scraped clean. When large areas of vascular tissue must be traversed (e.g., as in hepatic resection or repair of traumatic lacerations of the liver), conventional metal tips become difficult surgical tools. With the ABC, no metal surface is present to attract sticky, burnt tissue. The tip of the pencil is a cushion of argon gas that can transmit current as long as it touches tissue.

The anesthesiologist must understand that use of the ABC means that a lot of electrosurgery is taking place and that safety measures are more important than ever. As in conventional electrosurgery, surgical cutting and coagulation with the ABC come from local $I^2 R$ heating losses at the point where the electrosurgical pencil is applied--in this case, where the argon gas meets the tissue. ABC operation therefore resembles conventional arc welding. Because the ABC is perhaps the ultimate spark generator, its use illustrates the extent to which we have abandoned one safety concern that was prominent in the days of inflammable anesthetic gases.

Bipolar Electrosurgery

Some locations of the body are never safe for unipolar electrosurgery. For such locations, which are encountered frequently during neurosurgery, one employs bipolar electrosurgery. In bipolar electrosurgery, two pencil-point electrodes are applied to the area of surgery, and the electric current flowing through the tissue is confined to the few millimeters between the two electrodes. Bipolar devices are required when electrosurgery is performed on an ovary or a fallopian tube. Several cases of

fatal bowel injury have been reported after female sterilizations with unipolar devices. [41] [42]

Patients with implanted pacemakers frequently come to the operating room for procedures entailing electrosurgery. Even though bipolar devices are used whenever possible for these types of patients, pacemaker interference does sometimes occur. The avoidance of pacemaker interference depends on the type of pacing electrodes (unipolar or bipolar) in the patient, how well the pacemaker circuitry is shielded, and the strength and the proximity of the discharge from the electrosurgical unit. The grounding pad should be placed as far away as possible from the pacemaker and its wires. Additionally, the path from the grounding pad to the electrosurgical tip should not traverse the pacemaker circuit. Because of capacitive coupling, it is possible for electrosurgical noise to inhibit or turn off any pacemaker or to disrupt the pacing program in a programmable pacemaker. Such interference can result in complete heart block and no pacing, or in severe tachycardia. Anesthesiologists should always be prepared to reset a pacemaker to the asynchronous mode (i.e., regular, uninhibited pacing). Isoproterenol, a pharmacologic pacer, should be available to the anesthesiologist when the patient has a cardiac pacemaker.

SAFE PRACTICE

Because explosive anesthetic agents are no longer used, [43] hospitals are no longer required to regulate the conductivity of operating room floors and tables. Therefore, problems resulting from poor electrical grounding might occur more frequently in the future. The following general guidelines describe safe electrical practice.

1. All electrical equipment used in the operating room should be grounded (such equipment will contain ungrounded circuits). If the power plug for the electrical outlet has only two prongs, the equipment should not be in the operating room.
2. Do not connect patients to the operating room electrical ground.
3. When electrosurgery is in use, do use a grounding pad

to connect the patient to the ground connection provided on the electrosurgery machine. Be sure that the grounding pad is in contact with the patient across a large area and that the pad is well gelled. Inspect the pad during long cases and re-gel or replace the pad if necessary. Place the electrosurgical ground plate as near the operative site as possible and as far from pacemaker wires and ECG wires as possible.

4. If increasing levels of current are required for electrosurgery, beware of faulty connection of the electrosurgical grounding pad. Beware also of errant current paths that include the grounding pad and another electrical contact (e.g., an ECG electrode) but not the electrosurgical pencil.
5. If the line isolation monitor alarms after someone activates equipment, immediately unplug the piece of equipment that caused the LIM to sound. This piece of equipment has allowed the secondary side of the main isolation transformer to be coupled to ground. It is also possible that so many items were plugged in simultaneously that their combined capacitance coupled the secondary side to ground. You could therefore unplug another piece of equipment and then plug in the item, causing the LIM alarm to sound. If, however, the LIM alarm goes on after the other piece of equipment has been unplugged, remove the offending item from the operating room. It has an unwanted connection to ground somewhere.
6. Use a bipolar unit when a patient with an implanted cardiac pacemaker needs electrosurgery. Understand the type of pacemaker your patient has and have the appropriate magnets and equipment available for immediate use in case of pacemaker interference or dysfunction. For patients with complex, programmable pacemakers, this might require preoperative consultations with cardiologists and cardiac electrophysiologic personnel. Understand how you would initiate pharmacologic treatment of complete heart block for any of your pacemaker-dependent patients.
7. Make sure that all electrical equipment is tested periodically by experienced personnel, that the equipment is maintained properly to ensure that standards of performance are met, and that the entire electrical environment also meets NFPA standards. [14] [44] [45] [46] [47] [48] [49]
8. When using a pulse oximeter to monitor oxygen saturation in an MRI magnet, make sure that the connection between the oximeter console and the patient occurs through a long fiberoptic cable having no wires or conducting segments.
9. If the cause of an electrical burn is uncertain, have experienced biomedical personnel participate in a thorough investigation that might include simulation of patient conditions. [7]

References

1. Hull CJ: Electrocution hazards in the operating theatre. Br J Anaesth 50:647, 1978.

2. Gotloib L, Servadio C: Microampere electrocution during haemodialysis: An unrecognised cause of sudden death. Proc Eur Dial Transplant Assoc 11:210, 1975.

3. Switz DM, Clarke AM, Longacher JW Jr: Electrical malfunction at endoscopy: Possible cause of arrhythmia and death. JAMA 235:273, 1976.

4. Katcher ML, Shapiro MM: Severe burns and death associated with electronic monitors [letter]. N Engl J Med 317:56, 1987.

5. Newborn is electrocuted. (Chicago, IL, hospital accident). The New York Times August 27 Sect A (Col 6):18, 1993.

6. Pride HB, McKinley DF: Third-degree burns from the use of an external cardiac pacing device. Crit Care Med 18:572, 1990.

7. Cooper JB, DeCesare R, D'Ambra MN: An engineering critical incident: Direct current burn from a neuromuscular stimulator. Anesthesiology 73:168, 1990.

8. Bruner JMR: Hazards of electrical apparatus. Anesthesiology 28:396, 1967.

9. Bruner JMR: Common abuses and failures of electrical equipment. Anesth Analg 51:810, 1972.

10. Bruner JMR: Fundamental concepts of electrical safety. Refresher Courses Anesthesiol 2:11, 1974.

11. Ward CS: On electrical safety. Anaesthesia 35:921, 1980.

12. Buczko GB, McKay WPS: Electrical safety in the operating room. Can J Anaesth 34:315, 1987.

13. Day FJ: Electrical safety revisited: A new wrinkle. Anesthesiology 80:220, 1994.

14. Early MW, Murray RH, Caloggero JM (eds): National Electrical Code Handbook. 6th ed. Quincy, Mass, National Fire Protection Association, 1993, p 637.

15. Tucker RD, Voyles CR, Silvis SE: Capacitive coupled stray currents during laparoscopic and endoscopic electrosurgical procedures. Biomed Instrum Technol 26:303, 1992.

16. Odell RC: Electrosurgery: Principles and safety issues. Clin Obstet Gynecol 38:610, 1995.

17. Shellock FG, Slimp GL: Severe burn of the finger caused by using a pulse oximeter during MR imaging [letter]. AJR Am J Roentgenol 153:1105, 1989.

18. Kanal E, Shellock FG: Burns associated with clinical MR examinations [letter]. Radiology 175:585, 1990.

19. Bashein G, Syrovy G: Burns associated with pulse oximetry during magnetic resonance imaging [letter]. Anesthesiology 75:382, 1991.

20. Sobel DB: Burning of a neonate due to pulse oximeter: Arterial saturation monitoring [letter]. Pediatrics 89:154, 1992.

21. Murphy KG, Secunda JA, Rockoff MA: Severe burns from a pulse oximeter. Anesthesiology 73:350, 1990.

22. Shellock FG: Monitoring sedated pediatric patients during MR imaging [letter]. Radiology 177:586, 1990.

23. Kanal E, Shellock FG, Talagala L: Safety considerations in MR imaging. Radiology 1976:593, 1990.

24. Salvo I, Colombo S, Capocasa T et al: Pulse oximetry in MRI units [letter]. J Clin Anesth 2:65, 1990.

25. Wagle WA: Technique for RF isolation of a pulse oximeter in a 1.5-T MR unit [letter]. Am J Neuroradiol 10:208, 1989.

26. Dalziel CF, Lee WR: Lethal electrical currents. IEEE Spectrum 6:44, 1969.

27. Titel JH, El Etr AA: Fibrillation resulting from pacemaker electrodes and electrocautery during surgery. Anesthesiology 29:845, 1968.

28. Atkin DH, Orkin LR: Electrocution in the operating room. Anesthesiology 38:181, 1973.

29. Chambers JJ, Saha AK: Electrocution during anaesthesia. Anaesthesia 34:173, 1979.

30. Geddes LA, Cabler P, Moore AG et al: Threshold 60-Hz current required for ventricular fibrillation in subjects of various body weights. IEEE Trans Biomed Eng 20:465, 1973.

31. Roy OZ: 60 Hz ventricular fibrillation and rhythm thresholds and the nonpacing intracardiac catheter. Med Biol Eng 13:228, 1975.

32. Litt L, Ehrenwerth J: Electrical safety in the operating room: Important old wine, disguised new bottles. Anesth Analg 78:417, 1994.

33. Aronow S, Bruner JMR: Electrosurgery [editorial]. Anesthesiology 42:525, 1975.

34. Gatti JE, Bryant CJ, Noone RB et al: The mutagenicity of electrocautery smoke. Plast Reconstr Surg 89:781, 1992.

35. Stouffer DJ: Fires during surgery: Two fatal incidents in Los Angeles. J Burn Care Rehabil 13:114, 1992.

36. Troianos CA: Complete electrical failure during cardiopulmonary bypass. Anesthesiology 82:298, 1995.

37. Battig CG: Electrosurgical burn injuries and their prevention. JAMA 204:1025, 1968.

38. Chandra P: Severe skin damage from EKG electrodes [letter]. Anesthesiology 56:157, 1982.

39. Parker EO III: Electrosurgical burn at the site of an esophageal temperature probe [letter]. Anesthesiology 61:93, 1984.

40. Go PMNYH, Goodman GR, Bruhn EW et al: The argon beam coagulator provides rapid hemostasis of experimental hepatic and splenic hemorrhage in anticoagulated dogs. J Trauma 31:1294, 1991.

---

41. Deaths following female sterilization with unipolar electrocoagulating devices. MMWR Morb Mortal Wkly Rep 30:149, 1981.

42. Deaths attributable to tubal sterilization: United States, 1977-1981. MMWR Morb Mortal Wkly Rep 32:249, 1983.

43. Fineberg HV, Pearlman LA, Gabel RA: The case for abandonment of explosive anesthetic agents. N Engl J Med 303:613, 1980.

44. Whelpton D: Safety of electrical equipment [comment]. J Med Eng Technol 3:62, 1979.

45. Whelpton D: Acceptance testing of medical electrical equipment. J Med Eng Technol 8:19, 1984.

46. Rubenstein ML: Electrical safety standards for electrocardiographic apparatus. Circulation 62:1392, 1980.

47. Geselowitz DB, Arzbaecher RC, Barr RC et al and the American Heart Association Committee on Electrocardiography: Electrical safety standards for electrocardiographic apparatus. Circulation 61:669, 1980.

48. NFPA 76C: High Frequency Electricity in Health Care Facilities, 1975. Quincy, Mass, National Fire Protection Association, 1975.

49. NFPA 56A: Standard for the Use of Inhalation Anesthetics, 1973. Quincy, Mass, National Fire Protection Association, 1973.

Chapter 84 - Environmental Safety Including Chemical Dependency

William P. Arnold III

INTRODUCTION

In the past, perhaps the greatest threat both to patients and to anesthesiologists was the potential for fires and explosions. With the advent of nonexplosive anesthetics, these hazards gradually vanished. Newer anesthetics, modern intravenous drugs, state-of-the-art electronic equipment, and patients with transmissible diseases are now part of our everyday practice and consequently have introduced another generation of hazards. The purpose of this chapter is to discuss these contemporary risks and appropriate preventive measures. This review includes many of the well-known sources of apprehension, such as waste gases, radiation hazards, and infections; emphasis is placed on infection and chemical dependence.

For the past 30 or more years, interest in the hazards presented by the operating room environment has been directed at several issues. Figure 84-1 shows the distribution of the National Library of Medicine (NLM) database of references from 1966 through late 1997, indexed by both "occupational diseases" and "anesthesiology." One hundred forty-nine publications were identified, not including letters. Although the search was influenced by the NLM's method of indexing and obviously did not identify all the relevant work, it provides some indication of the general concerns as reflected in the literature. From 1966 to 1972 , waste anesthetic gases dominated the publications. More recently, infection has become the predominant topic.

WASTE GASES

The central points concerning waste gases (Ch. 6) are that (1) anesthetic vapors do enter the operating room atmosphere, (2) their concentrations may be well controlled with proper scavenging, and (3) although there are data to suggest that chronic inhalation of trace concentrations of anesthetics may be harmful, these studies are inconclusive. At this writing, a task force composed of internationally recognized experts on waste anesthetic gases, working by direction of the American Society of Anesthesiologists, is preparing an up-to-date document on the issue. Publication in mid-1999 was anticipated.

Concentrations of waste gases are usually reported on a volume per volume basis in parts per million (ppm). Thus, 100 percent halothane, such as in the saturated vapor above the liquid in a bottle or vaporizer, has a concentration of 1 million ppm. Similarly, 1 percent halothane represents 10,000 ppm. Waste nitrous oxide and halogenated agents in the absence of scavenging may approach concentrations of 3,000 and 50 ppm, respectively. [1] The National Institute for Occupational Safety and Health (NIOSH) has recommended that the upper limits in the atmosphere of operating rooms be 25 ppm for nitrous oxide and 2 ppm for halogenated agents (or 0.5 ppm for halogenated agents used in combination with nitrous oxide). [2] To put these figures in perspective, assuming that 1 mL of a volatile liquid anesthetic produces 200 mL of vapor, that volume of liquid spilled in a closed room measuring 20 by 20 by 9 feet results in a concentration of vapor of nearly 2 ppm. In practice, the NIOSH recommendations are nearly impossible to achieve,

Figure 84-1 Relative interest in occupational diseases. One hundred forty-nine publications, excluding letters, were identified in a MEDLINE search from January 1966 to late 1997 using the strategy *explore occupational diseases* and *anesthesiology.* In the 1970s, operating room pollution was of significant interest. Over the past 15 years, the number of publications relating to infection has increased. The apparent paucity of citations on addiction reflects the methods by which these articles are indexed.

although proper scavenging methods decrease concentrations by about 90 percent. [1] The maximal concentration of halothane recommended by NIOSH is several-fold lower than the lowest concentration that humans can recognize. Fifty percent of volunteers are able to detect halothane at concentrations as low as 33 ppm. The threshold of perception ranges from less than 3 to more than 100 ppm. [3] Thus, if one smells the anesthetic, its concentration is well above the maximum recommended level.

Health Risks

Until the late 1960s, there was little concern about the potential for adverse effects on operating room personnel from inhaling trace concentrations of anesthetic gases and vapors. For the decade that followed there was a flourish of interest that more recently has apparently declined in intensity (see Fig. 84-1). The inaugural report suggesting that there was a problem appeared in 1967 in the Russian literature. [4] A multitude of retrospective reports followed, each suggesting that trace concentrations of anesthetics presented considerable risk to operating room personnel. Of these, three large studies conducted during the mid-1970s in the United States and in the United Kingdom all concluded that the prevalence of abortion was substantially higher in female anesthesiologists than in female physicians working outside the operating room. Furthermore, the incidence of congenital anomalies seen in children of both male and female anesthesiologists was higher than in the control groups of physicians. Although the prevalence of malignancy was similar in both anesthesiologists and controls, liver disease was reported more often by male anesthesiologists. [5] The authors of each of the reports recognized that problems were associated with reporting retrospective data; nevertheless, their observations provoked significant concern among anesthesiologists. Some readers may have discounted the possibility that other environmental factors in the operating room, such as radiation, stress, and contact with organic chemicals, might also be culpable.

In addition to fear, the reports also stimulated the appearance of numerous review articles, many of which critiqued the original data and reinterpreted them. Methodologic concerns, including the retrospective cohort design based on questionnaires completed by each respondent, were prominent in these critiques. Biases may have arisen for many reasons, including (1) inadequate response rates; (2) lack of control for confounding variables, such as age, nutrition, obstetric history, drinking, smoking, exposure to methylmethacrylate, and radiation; (3) lack of quantification of the exposure to anesthetic vapors; (4) losses to follow-up; (5) inappropriate comparison groups; and (6) lack of independent verification of the reported data. [6] [7] Even the titles of some questionnaires, for example, "Effects of Waste Anesthetics on Health" and "Anesthetic Practice and Pregnancy," may have introduced bias by stimulating respondents who work with anesthetics to overreport their past experiences. [8] [9] In any study of this type, self-reported historical information and disease outcomes are certain to be biased if the respondents have a preconceived idea of its goals. To summarize, all the data may be inconclusive.

Rather than continuing to reexamine the data already obtained, what is needed is a well-planned long-term prospective assessment of the health of appropriately selected cohorts and controls. [6] [7] These groups will require close monitoring to eliminate bias. Such a study involving 11,000 women in Great Britain was completed in the mid-1980s, but at this writing, the long-awaited results remain unavailable. [10]

Even though no firm evidence suggests that trace concentrations of anesthetic agents present a health hazard, there is no definite proof to the contrary. Perhaps for this reason, the Occupational Health and Safety Administration (OSHA) requires compliance with its Hazard Communication Standard on toxic and hazardous substances (29 CFR Part 1910.1200). This includes required courses for operating

room and recovery room personnel on the potential for harm from these agents. In any case, it makes sense to minimize our exposure to waste gases by exercising care when filling vaporizers with volatile anesthetics and preventing gases from venting into the operating room. [11]

Effect on Performance

The possibility that waste anesthetic gases could adversely affect the intellectual and motor skills of anesthesiologists was also addressed during the 1970s. In a laboratory setting using male volunteers, Bruce and Bach [12] demonstrated that concentrations of nitrous oxide as low as 50 ppm, either alone or in combination with 1 ppm of halothane, resulted in decreased behavioral performance; however, 25 ppm of nitrous oxide combined with 0.5 ppm of halothane had no effect. It was from these data that the NIOSH recommendations arose. [2] Subsequently, three other groups of researchers studying volunteers in laboratories have been unable to confirm the findings of Bruce and Bach. [12] The lack of agreement between investigators has led some to conclude that "it is reasonable to state that there is no convincing evidence that anesthetic agents in concentrations equal to those found in unscavenged operating theatres have any effect on the psychomotor performance of healthy subjects in the laboratory." [13] A study conducted on volunteers in an operating room during normal clinical activities in which trace

concentrations of nitrous oxide and halothane ranged from zero to 2,300 and zero to 37 ppm, respectively, also failed to detect impairments in psychomotor performance. [14] Although there is no incontestable proof that inhaling trace concentrations of anesthetics alters higher mental functions, common sense dictates that care should be exercised to keep levels as low as possible.

RADIATION

During the course of patient management, the anesthesiologist is almost routinely exposed to both ionizing and nonionizing electromagnetic radiation. The former is primarily from x-rays and occasionally from radioactive isotopes that release gamma rays, and the latter is from lasers. Less common is contact with ionizing radiation from radioactive isotopes that release either alpha or beta particles. Ionizing radiation has enough energy to create both free radicals and ionized molecules in tissues by driving electrons completely out of their stable orbitals. If the radiation exposure is severe enough, tissues may be destroyed or chromosomal changes may cause malignant growth. Nonionizing radiation may excite electrons to move from ground state to higher orbitals in molecules, but the electrons remain in the molecule. In this case, damage to tissues may result from the heat produced by the absorbed radiation.

Ionizing Radiation: X-Rays

The increasing use of x-rays during the past 2 decades in the operating room and in remote locations has revolutionized the practices of several surgical specialties (Ch. 66) . Fluoroscopy coupled with image intensifiers and video displays has significantly improved the surgical care of patients by providing immediate information to the neurosurgeon, orthopedic surgeon, urologist, gastroenterologist, and others. It may also have decreased operating time by preventing delays inherent in waiting for films to be processed. The disadvantage of this increased use of fluoroscopy is the exposure of operating room personnel to ionizing radiation. Because this type of radiation is undetectable with our normal senses, it occasionally creates undue fear, termed *radiation mystique* by some. A basic understanding of its features may reduce some of the unwarranted concerns, while permitting one to keep personal exposure to a minimum. Film badges, although not protective, provide a means of monitoring exposure.

Exposure is commonly reported in units of rem *(roentgen equivalents man).* The rem is essentially a measure of the biologic damage from radiation adjusted to apply to all tissues. [15] Estimates of radiation exposure from natural sources vary, depending on geographic location. The average in the United States ranges from 80 to 200 millirems (mrem) per year. Natural radiation comes primarily from cosmic rays (about 40 mrem at sea level, with an increase of 10 mrem/1,000 ft) and also from radioactive compounds found in soil, brick, and concrete. An isotope of potassium contained in body fluids is an internal source of beta particles. For most physicians, the additional radiation from occupational exposure is no greater than that from natural sources. Although the maximum yearly occupational exposure is mandated to be no more than 5 rem, radiology personnel rarely absorb more than 10 percent of this dose. Their greatest source of exposure is fluoroscopy. [16] During pregnancy, radiograph personnel are advised to limit their exposure to a maximum of 500 mrem.

Occupational exposure to radiation comes primarily from x-rays scattered by both the patient and the surrounding equipment. One chest radiograph results in about 25 mrem of exposure to the patient; procedures requiring multiple films occasionally involve more than 1 rem. The amount of radiation generated during fluoroscopy depends on how long the x-ray beam is on. Although radiograph machines are designed to minimize stray radiation, some radiation scatters and is absorbed by personnel who are near the patient. Just as light is reflected from surfaces, x-rays are reflected from surfaces on which they impinge (Fig. 84-2) . This scattering accounts for most occupational exposure. Because the intensity of scattered radiation is inversely proportional to the square of the distance from the source, the best protection is physical separation. A distance of at least 3 feet from the patient is recommended. Six feet of air provides protection the equivalent of 9 inches of concrete or 2.5 mm of lead. [17] Although they are uncomfortable, aprons containing the equivalent of 0.25 to 0.5 mm of lead sheet are effective in blocking most scattered radiation, and such devices are recommended to be worn whenever there is an exposure risk. [18] Uncovered areas, such as the lens of the eye, still bear risk of injury. Intraoperative radiation measurements have shown that exposure is inversely related to the experience of the surgeon and also that the amount of radiation received by the anesthesiologist during orthopedic procedures is unmeasurable. [19]

Radiation physicists recommend adhering to the ALARA

Figure 84-2 Scattering of radiation. Most of the radiation striking the target and table is reflected upward; some of it passes through and strikes the detector. Personnel adjacent to the table are struck by scattered radiation.

program: radiation exposure should be kept *as low as reasonably achievable.* The staff of departments of radiology have been extensively schooled in the physics of radiation as applied both to its diagnostic use and to the safety of occupational exposure. Attention to their methods of protection will limit exposure to minimal levels for all. As questions of radiation safety arise, they should be directed to health physicists at your hospital.

Nonionizing Radiation: Lasers

Laser (Ch. 64) is an acronym for *light amplification by stimulated emission of radiation.* Lasers produce infrared, visible, or ultraviolet light. Although the radiation from lasers is nonionizing, it is potentially unsafe both because of its intensity and because of the matter released from tissues during treatment.

Lasers are used in many surgical specialties, including ophthalmology, plastic surgery, gynecology, neurosurgery, urology, head and neck surgery, and gastrointestinal surgery. The surgical laser produces intense focused electromagnetic radiation to cut or destroy tissues. The radiation is usually infrared or visible light and is created in a "laser medium" that is stimulated by high-intensity energy to release photons of identical wavelengths (coherent or monochromatic light) from a laser chamber. The material in the medium (e.g., carbon dioxide, argon) is responsible for the wavelength produced by the laser. Of those in common clinical use, carbon dioxide and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers emit light in the far-infrared and near-infrared wavelengths, respectively; the argon and tunable dye lasers produce visible light. [20] The choice of laser used is based on the surgical goal.

Eye injuries are the greatest risk to personnel working near lasers. Strict standards for protection have been developed on the basis of current understanding but are subject to periodic revision as more experience is gained with these instruments. Either direct exposure or reflected radiation may cause eye damage. Injuries include burns to the cornea and retina, destruction of the macula or optic nerve, and cataract formation. Protective eyewear is designed to filter out the radiation produced by a specific type of laser, while still permitting vision. For example, clear plastic lenses block the far infrared (10.6 mum) radiation from carbon dioxide lasers but provide no protection against the nearinfrared (1,060-nm) radiation emitted by Nd:YAG lasers. The type of protection provided by a given filter is marked on the frame of the goggles and should be checked before use. Filters that are scratched or crazed should not be used. Because certain filters block portions of the visible spectrum, it is prudent to confirm preoperatively that patient monitors can be seen and interpreted correctly with goggles in place. Protective eyewear is recommended for all personnel because reflected radiation can be as hazardous as direct radiation, and the intensities are not diminished significantly in the distances traveled in the average operating room. [20]

Although the *plume,* the vapor and cellular debris produced during laser surgery, is commonly malodorous, until recently, it was not considered to be other than unpleasant. Now, there is concern that the plume may present a significant risk. The median size of particles in plume samples obtained intraoperatively is 0.31 mum in diameter and ranges from 0.1 to 0.8 mum. Most surgical masks do not trap such small particles. [21] Even after filtration of particles greater than 0.5 mum in diameter, exhaust smoke from tissues treated with a carbon dioxide laser causes pulmonary lesions in laboratory animals. If all particles larger than 0.1 mum are scavenged, no lung damage occurs, pointing out the importance of scrupulous removal of the plume. [22] Under experimental

---

conditions, viable bacteria have been recovered from the plume emanating from laser irradiation. [23] In addition, intact DNA from human papillomavirus (HPV) has been detected in the vapor from both laser-treated plantar warts and genital condylomata. [24] [25] More frightening is that human immunodeficiency virus (HIV) proviral DNA has been found in laser smoke produced by vaporizing cultures of HIVpositive cells. Although these experiments, which used tissue cultures, do not replicate the clinical situation, they stress the importance of strict attention to smoke removal. [26] With adequate evacuation and filtration using equipment specifically designed to scavenge such vapors, it is unlikely that operating room personnel will be contaminated by laser-dispersed HPV DNA. [25] However, a case report documents the appearance of laryngeal papillomata in a laser surgeon who, without the benefit of a laser smoke evacuator, had previously treated several patients infected with anal condylomata. Tissue from the surgeon's laryngeal tumors contained HPV DNA types 6 and 11, the same viral types that are commonly harbored by anogenital condylomata. Although not conclusive, these findings suggest that the laryngeal papillomata may have been caused by inhaled virus particles. [27] It therefore seems prudent to ensure that utmost care is taken to scavenge all vaporized debris.

INFECTION

While managing patients, the anesthesiologist is exposed to a multitude of communicable diseases, most of which present no significant threat to healthy people. [28] For example, infection with herpes simplex virus, particularly herpetic whitlow (infection of the digits), a self-limited disease, may result from contact with contaminated secretions from the airway. The recommended use of appropriate precautions usually prevents this and other types of viral infection, including cytomegalovirus (see *Standard Precautions*). However, some still recommend that pregnant health care workers avoid patients with cytomegalovirus because of its teratogenic effects. Although the potential of infection is low, it is important to consider the possibility and take the necessary precautions.

The greatest concerns stem from contact with patients infected with viruses causing HIV, hepatitis C, or hepatitis B. As a rule, the probabilities of becoming infected from a needle contaminated with one of these viruses are 0.3, 3, and 30 percent, respectively. This section concentrates on these three catastrophic diseases while also addressing tuberculosis, the incidence of which has declined appreciably in the United States during the past few years, although it remains unabated in many parts of the world.

In March 1992, OSHA issued comprehensive, enforceable standards designed to minimize occupational exposure to blood-borne pathogens. The employer is responsible for maintaining an exposure control plan that protects all health care workers who have the potential for contact with blood or blood products. Protective equipment, including gloves, gowns, and eye shields, must be supplied by the employer at no cost to the employee. The standard also provides for hand-washing facilities, proper receptacles for contaminated materials, methods for handling contaminated laundry, and management of waste, among many other things. [29]

Acquired Immunodeficiency Syndrome

Since the early 1980s, the word AIDS (acquired immunodeficiency syndrome) has come to instill fear in many health-care workers. [30] The possibility of a slow demise resulting from contact with an unseen but deadly virus that gradually destroys the immune system, that promotes a multitude of opportunistic infections, and that may result in progressive dementia is frightening. HIV, which is responsible for the syndrome, is a relatively fragile virus. With proper attention to cleanliness and care in performing invasive procedures, the likelihood that an anesthesiologist will develop the disease in the course of patient management is exceedingly low.

Two human immunodeficiency viruses, HIV-1 and HIV-2, are responsible for infections in humans. The former is found worldwide, and the latter occurs principally in northwest Africa, although it is now spreading into Europe. [31] Both are retroviruses that attach to cells having CD4 surface antigen (predominantly T-helper lymphocytes) and ultimately replicate by integrating virally produced DNA into the nucleus of the host cell. [32]

Initial infection with HIV follows within 2 to 10 weeks of inoculation. It is usually a self-limited, nonspecific, febrile viral syndrome lasting 1 or 2 weeks. An individual is considered to be both infected with HIV and infective if the results of both a serologic screening test, the enzyme-linked immunosorbent assay (ELISA), also called enzyme immunoassay (EIA), and a supplemental, more sensitive test, either Western blot or indirect fluorescent antibody, are repeatedly positive. ELISA tests are relatively easy to perform in a clinical laboratory but may be subject to false-positive results. Supplemental tests are time consuming but are necessary for confirmation. Results of the tests become positive within weeks of inoculation, but the median latency for the first opportunistic disease may be as long as 11 years. [32]

Epidemiology of AIDS

The apparent incidence, death rates, and other epidemiologic features of AIDS are influenced by methods used to obtain these values. Although AIDS is a reportable disease in the United States, infection with HIV is not. Because the incidence of HIV is derived from studies of population cohorts rather than from individual cases, its numerical significance is less precise than are data concerning AIDS. [33]

On January 1, 1993, the criteria for defining AIDS were expanded from those of 1987 to include objective laboratory data and illnesses not previously used in confirming the diagnosis. With these changes, all HIV-infected patients with CD4 T-lymphocyte counts of less than 200/muL, and also those with opportunistic infections, including pulmonary tuberculosis, recurrent pneumonia, and cervical cancer, were defined as having AIDS. The result was an apparent 200 percent increase in cases of the disease reported in early 1993. [34] At that time, nearly 900,000 persons in the United States were estimated to be infected with HIV. In spite of these methodologic changes, the proportional rate of the annual increase in cases of HIV has declined in recent years, and the downward trend in both incidence and deaths that

began in the mid-1990s is apparently continuing. [35] [36] These encouraging observations can perhaps be attributed to an expanding body of information concerning the virology, biology, and treatment of HIV. In spite of these overall declines, the incidence of AIDS appears to be increasing certain subpopulations, including black men and women and persons born after 1960. [35] [36] Since 1993, infection with HIV/AIDS has been the leading cause of death in persons aged 25 to 44 years. [37] At present, more than one in five of those with AIDS is female, a significant increase from the one in seven reported less than 5 years ago. A consequence may be an increased incidence in children, because perinatal transmission of HIV-1 occurs in as many as 25 percent of the offspring of infected mothers. Transplacental infection and possible transmission via breast milk have been implicated. [32]

AIDS and Health-Care Workers

Health-care workers comprise about 5 percent of the cases of AIDS in the United States. Although there are some reports of occupationally related infections, most of the cases have been attributed to nonvocational contact. [38] However, epidemiologic data, coupled with the observation that more than 4 percent of 2,300 patients presenting to an urban emergency department had unrecognized HIV infections, [39] suggest that the potential for health-care workers to have contact with an unidentified carrier of the disease is significant. By mid-1998, the Centers for Disease Control and Prevention (CDC) had documented 54 cases of occupationally acquired HIV infection in the United States, 88 percent of which were the result of an injury from a sharp object. [40]

Injury from a needle is the most likely route of infection for anesthesiologists. Of 493 anesthesia personnel surveyed in a multicenter study, 32 percent reported having been stuck with a contaminated needle at least once in the preceding 12 months. Of those, only half sought treatment. [41] The risk of infection is greater with hollow-core than with solid needles and is further increased with large-bore needles and deep intramuscular injection. [32] In a study evaluating percutaneous injuries in anesthesia personnel, nearly 90 percent were from hollow-bore needles, were self-inflicted, most commonly involved the nondominant hand, and were deemed preventable. A significant number of the injuries occurred during disposal of contaminated needles. [42] The minimal dose of contaminated blood needed to infect humans is unknown, although one patient became HIV positive after the accidental intravenous injection of 100 to 200 muL of infected blood. [43] The likelihood of developing antibodies to HIV is related to the volume of the inoculum and the concentration of viral particles. [44] Consequently, most seroconversions have been associated with deep intramuscular injection of contaminated blood through large-bore needles. The theoretical risk for occupational infection in anesthesiologists

over a 30-year exposure period has been calculated to range from 0.05 to 4.5 percent, depending on infectivity of the patient population; however, these estimates are based on incomplete data. [45] The overall risk to health-care workers of seroconversion after documented percutaneous exposure to HIV-infected body fluids is usually said to be about 0.3 percent. Although seroconversion has been documented after nonintact skin has been in contact with infected blood, the incidence from this route is far lower than from needle injuries. [44] [46]

The risk of transmission of HIV from health-care workers to patients, with the exception of errors in technique, is extremely small. No infections were identified in more than 19,000 patients who had been treated by 57 infected health-care workers comprising 29 dentists, 12 surgeons, and 16 physicians in nonsurgical specialties. The only documented infections have been in 6 of 1,100 patients treated by a dentist in Florida. [47]

With proper attention to routine methods of disinfection, sterilization, and housekeeping, the AIDS virus on instruments, surfaces, and laundry can be destroyed. When at concentrations of five orders of magnitude greater than normally found clinically, HIV may survive for several days after being dried. This represents an extreme. Several hours of drying usually inactivates 90 to 99 percent of viable virus. The amount of HIV usually found on contaminated surgical instruments and equipment used in anesthetic management can be killed with "high-level disinfection." This involves careful cleaning, followed by exposure either to one of the commercially available germicides or to a 1:10 to 1:100 dilution of sodium hypochlorite (household bleach). These methods annihilate bacteria and viruses but may not be effective against bacterial spores. If the instruments are to be sterilized, they should first be thoroughly cleaned. Contaminated hospital linen should not be washed or rinsed in the operating room or another patient care area; instead, it should be placed directly in sealed, water-impenetrable bags. It can be safely laundered by normal methods. Infective waste, including secretions, blood, and other body fluids, should be incinerated or autoclaved. Alternatively, large volumes of fluids may be discarded in a sanitary sewer. [48] Personal protection and protection of patients is afforded through standard precautions.

Hepatitis

Viral hepatitis may result from infection with any of several different pathogens. Of greatest interest to the anesthesiologist are the viruses responsible for hepatitis B virus (HBV), and hepatitis C virus (HCV), the major cause of non-A, non-B (NANB) hepatitis. In contrast to these hazardous pathogens, hepatitis A is an insignificant occupational threat. It is normally transmitted by the fecal-oral route and almost never by contact with blood. It is usually self-limiting, and although it may produce jaundice, it has few long-term sequelae. The appearance of antibodies to the virus several weeks after exposure confirms the diagnosis. Treatment is limited to one dose of gamma globulin. [49]

Hepatitis B

Hepatitis B is a serious disease that may be life threatening, but it can be prevented. In the 1980s, it was estimated that 200 to 300 health-care workers would die annually from the effects of HBV. Fortunately, the introduction of an effective vaccine for hepatitis B has dramatically decreased the incidence, morbidity, and mortality of the disease. [44] Infection

may be documented serologically by the appearance of HBV surface antigen (HBsAg), HBV surface antibody (anti-HBs), or HBV core antibody (anti-HBc) in serum. Before routine vaccination, the development of covert seropositivity for hepatitis B during residency was common. In a multicenter study involving hospitals in both rural and metropolitan areas, the overall prevalence of serologic indicators for hepatitis B in anesthesiology residents who had received neither hepatitis vaccine nor hepatitis B immune globulin (HBIG) was 17.8 percent of 267 tested. Most seropositive residents were unaware of having been exposed to hepatitis. There was no correlation between incidence and geographic location, but the incidence of seropositivity increased in parallel with clinical experience. Thirty percent of residents with more than 11 total years of experience, including their current residency and previous work in other specialties, were seropositive for hepatitis B. The routine use of gloves and attention to obtaining detailed histories from patients did not appear to decrease the incidence of infection. [50]

An estimated 200,000 new cases of HBV infection occur each year. Of these cases, 50,000 will develop jaundice, and 10,000 will require hospitalization. As many as 12,000 to 20,000 annually become asymptomatic carriers of HBsAg, with the total number of carriers in the United States estimated to be nearly 800,000. [51] It is this group that threatens the nonimmunized anesthesiologist. The epidemiologic features of HBV and AIDS have much in common, although intravenous drug abuse has surpassed homosexual activity as the most common risk factor associated with HBV infection. [52] The likelihood of nonimmunized health-care workers developing hepatitis from contact with infected body fluids is much higher than that for AIDS. The incidence of seroconversion after parenteral inoculation with HBV can be as high as 40 percent, depending on the infectivity of the host and the magnitude of contact with the blood. [53] In comparison to HIV, HBV is much more robust. Neither treatment at 60°C for 4 hours nor use of disinfectants containing phenol or chlorine is sufficient to inactivate the hepatitis B particle with certainty. It remains viable on needles, environmental surfaces, and gloves for longer than 14 days. [26] Because gloves do not guarantee protection from accidental needle sticks, and because HBV is relatively resistant, accidental contact with live virus may occur in the course of patient management and also during the cleaning of equipment.

Active immunization of seronegative health-care workers with hepatitis B vaccine is imperative for prophylaxis against infection. The first vaccine was composed of inactivated particles of surface antigen prepared from sera of HBsAg carriers. Ninety percent of recipients of the vaccine became seropositive and are thus were protected against infection. [51] In spite of the efficacy and the safety of the early vaccine, in the mid-1980s, substantial numbers of anesthesia personnel refused to be immunized for unspecified reasons. [50] Some were concerned that because the vaccine for hepatitis B was prepared from sera obtained from patients at high risk for developing HIV infection, it might also transmit HIV. In the late 1980s, a vaccine was developed in yeast by use of recombinant DNA methods. Although there is no possibility that HIV could be present in this vaccine, it is less effective in producing antibodies to HBV than is vaccine prepared from plasma. [54] The OSHA standard on blood-borne pathogens mandates that employers must make vaccine against HBV available at no cost to all employees who have a reasonable chance of exposure to the virus. [29] In spite of its proven safety and economic appeal, a substantial number of health-care workers have continued to refuse the immunity conferred by this vaccine. [55]

Anesthesiologists in whom no antibodies are present in serum who suspect that contact with HBV has occurred should be passively immunized with HBIG and should also receive a series of three injections of hepatitis B vaccine. [44] Prior vaccination and seroconversion eliminate the need for HBIG, whose acronym is an appropriate description of the discomfort it produces after injection.

Hepatitis C

Hepatitis C virus is now recognized as one of the major causes of NANB hepatitis. This disease, whose symptoms and signs are nonspecific, is the predominant source of hepatitis from transfusion. Chronic hepatitis develops in more than 85 percent of hepatitis C infections, with 20 percent progressing to cirrhosis and 3 percent to hepatocellular carcinoma. It may also result in the development of a chronic carrier state. [56]

Important discoveries in the diagnosis of HCV were reported in 1989 when (1) a segment of the genome of an NANB virus was isolated, cloned, and designated "hepatitis C virus," and (2) an assay for circulating anti-HCV antibodies was developed. [57] [58] Like HBV, HCV appears to be transmitted principally by infected blood. Studies with the anti-HCV assay have shown that HCV is responsible for up to 90 percent of transfusion-related NANB hepatitis. [59] With this assay, some have reported only a 1 to 2 percent incidence of antibody to HCV in health-care workers (similar to that seen in volunteer donors), suggesting that HCV is not easily transmitted. [59] [60] Reports based on the same assay indicate that transmission of HCV by contaminated needles occurs in less than 4 percent of these injuries. [61] More sensitive assays for HCV are currently under investigation. One of these, the detection of HCV RNA by polymerase chain reaction, documented an incidence of HCV infection of 10 percent in health-care workers. [62] This method is limited to laboratory investigation, it is not licensed for clinical use, and its accuracy is widely variable. [63] However, with further refinement, it may become an important method for determining precisely the incidence of occupationally acquired HCV infection.

Unfortunately, at present, there is no treatment for HCV infection. Even so, health-care workers who are exposed percutaneously to HCV should have liver function tests and baseline testing for antibody to the virus as soon as possible after the injury and should be retested 3 and 6 months after exposure. [63] Some institutions offer immune serum globulin to these persons as prophylaxis against infection. However, this is of little value because anti-HCV antibodies are not consistently found in production lots of immune globulin. [44]

Tuberculosis

Tuberculosis, the leading cause of death in the early 20th century, appeared to be steadily decreasing in incidence

with the advent of streptomycin in 1946, isoniazid in 1952, and rifampin in 1970. However, in 1985, the incidence in the United States began to climb significantly. Between then and 1990, reported cases increased by 16 percent, with a 10 percent increase in 1990 alone. This was the largest increase since national reporting began in 1953. [64] Most cases were from reactivation of old infections in immigrants or in patients whose immune system had been compromised, and many involved multidrug-resistant strains of *Mycobacterium tuberculosis.* Epidemic transmission between hospitalized patients and from patients to health-care workers also occurred. [65] [66] Common to most of these cases was a low index of suspicion for tuberculosis, occasionally not confirmed prior to postmortem examination. [67]

In response, in 1990, the CDC issued new guidelines for preventing the transmission of tuberculosis in hospitals, and in 1992, the CDC published recommendations for managing multidrug-resistant tuberculosis. [68] [69] Since then, there has been a steady decline in the number of new cases of tuberculosis, resulting in the lowest number of reported cases since 1953, the first year of reporting in the United States. [70] In 1994, the CDC replaced all previous guidelines with a comprehensive new program for the prevention of multidrug-resistant tuberculosis in health-care facilities. [71] The program places the responsibility for managing tuberculosis prevention on individual health-care facilities rather than requiring identical standards for all hospitals. Paramount are the identification and treatment of patients with tuberculosis; the development of engineering controls, including isolation rooms, filters, and ventilation; the use of personal protective equipment; and the implementation of educational programs for health-care workers. Anesthesiologists should be aware of the applicability of these guidelines to the specialty. [64]

In 1996, the overall incidence of tuberculosis in the United States was 8 cases per 100,000 population. The incidence was highest in the District of Columbia (26/100,000), followed by Hawaii (17/100,000) and California (14/100,000). The rate was highest in foreign-born persons (31/100,000), most of whom were from Asia and the Caribbean. The goal of the CDC is to decrease the rate to 3.5 cases per 100,000 population by the year 2000 and to less than 1 per million by 2010. Close attention will be paid to these cohorts. [70]

Tuberculosis spreads by small (1- to 5-mum) airborne droplets released when an infected person speaks, coughs, sneezes, or sings. Transmission of the bacillus is more likely in small, poorly ventilated areas and during coughproducing procedures, including bronchoscopy and laryngoscopy. The probability or transmission is also directly related to the concentration of infectious droplets and the duration of exposure. In healthy persons who have inhaled contaminated droplets, the resulting systemic infection is usually limited by the immune system within 2 to 10 weeks. In these individuals, the risk of developing active tuberculosis after infection is about 10 percent. The likelihood is higher in patients with HIV. [71]

All health-care workers who are at high risk for exposure to *M. tuberculosis* should be skin tested at the time of employment. Those whose test results are negative should be retested annually. The appearance of a positive tuberculin skin test (purified protein derivative) in an individual who has never had such a reaction suggests that a new infection has developed. Subsequent progression to active tuberculosis can usually be prevented by 6 to 12 months of preventive therapy, which should be considered for all persons who are newly infected. Nosocomial transmission of tuberculosis is a significant threat to health-care workers. Prevention should include (1) increased awareness of the disease, (2) appropriate isolation and treatment of infected patients, and (3) a national program of education [71] similar to that already mandated for blood-borne pathogens. [29]

Isolation Precautions

In the late 1980s, the CDC prepared a series of guidelines for health-care workers who have contact with patients or body fluids. [48] [72] They were subsequently incorporated into the OSHA standard on occupational exposure to blood-borne pathogens. [29] The recommendations can be best summarized by stating that because there are no symptoms or signs that conclusively reflect the presence of blood-borne pathogens, all patients, blood, and body fluids should be considered potentially infective. The same safeguards should be used for all, hence the guidelines were given the title *universal precautions.*

In 1996, the CDC published an all-encompassing guideline on nosocomial transmission of diseases. The new guideline, termed *isolation precautions,* addresses the potential that contact with any bodily emission may be hazardous to health-care workers. In addition to direct contact, the hazards include all body fluids, secretions, and excretions, and airborne droplets. The guideline includes methods of hand washing and gloving, patient placement, transport of infected patients, design and use of protective gear for medical personnel, equipment used in patient care, linen, laundry, and cleaning of spaces inhabited by infected patients. [73]

The guideline is composed of two tiers, *standard precautions* and *transmission-based precautions. Standard precautions* merges the principles of *universal precautions* and *body substance isolation,* which was proposed in 1987 to reduce the risk of transmission of pathogens from moist body substances through the use of gloves. Standard precautions should be used during *all* encounters with patients. *Transmission-based precautions* are necessary in the management of patients known to be or suspected of being infected or colonized with epidemiologically important pathogens. The isolation methods employed depend on the pathogen involved. [73]

Standard Precautions

Standard precautions should be practiced at all times. The following are taken almost verbatim from CDC publications. [29] [72] [73] Barrier precautions appropriate for the procedure being performed, including gloves, gowns, masks, and eye shields, should be worn when the potential for contact with blood or body fluids is present. Precautions apply to (1) blood; (2) all body fluids, secretions, and excretions except sweat, regardless of whether or not they contain visible blood; (3) nonintact skin; and, (4) mucous membranes. Strict attention should be given to hand washing after gloves

are removed, even if there has been no direct contact with blood or fluid. Needles should not be recapped, bent, or broken by hand but should instead be discarded in a puncture-resistant container. Resuscitation equipment that prevents the need for mouth-to-mouth contact should be available. All specimens sent to laboratories should be handled as if they are infected.

Transmission-Based Precautions

Transmission-based precautions should be followed when patients are known to be or are suspected of being infected with highly transmissible or epidemiologically important pathogens. They are based on the properties of specific pathogens and are to be used in addition to standard precautions.

1. *Airborne precautions* are to be used when transmission of small particles or droplets (<5 mum) is likely. Because these particles can be carried for long distances, special filtration and air handling are necessary. Diseases in this category include measles, varicella, and tuberculosis.
2. *Droplet precautions* apply to diseases transmitted by large particles (>5 mum). Because of their size and because the droplets do not remain suspended in air, transmission is limited to short distances; a meter or less is the norm. Examples include invasive *Haemophilus influenzae* type b (meningitis, epiglottitis), mycoplasma pneumonia, streptococcal pharyngitis, and rubella.
3. *Contact precautions* apply to direct skin-to-skin contact, including hands. Indirect contact may also occur if surfaces in an infected patient's environment are contaminated. Included are colonies of antibiotic-resistant organisms, hepatitis A, herpes simplex, viral conjunctivitis, and major abscesses. [73]

Latex Allergy

Since 1992, health-care workers who come in contact with infectious materials have been required to use barrier precautions, including protective gloves. [29] Coincidental with this mandate has been a progressively increasing number of allergic reactions to latex-containing products, especially in health-care workers. Components used in making gloves, including latex, accelerators (used to shorten the manufacturing process), and glove powder, have been implicated as causes. Responses may be limited to irritant contact dermatitis, a delayed type IV reaction mediated by T cells, or may be manifested by more serious IgE-mediated type I

reactions. The latter include contact urticaria, rhinitis, conjunctivitis, asthma, and occasionally full-blown anaphylactic shock. [74]

Prevalence appears to be higher in persons who have regular contact with latex-containing products. One report indicated that nearly 16 percent of the staff of a single anesthesia department had positive skin test results to latex, although of those tested, far fewer developed respiratory changes during work hours. [75] Allergic responses to latex are also associated with a history of atopy and with allergies to certain foods such as avacado, potato, banana, tomato, chestnuts, kiwi fruit, and papaya. Some individuals have developed such a severe sensitivity that they are no longer able to work in areas containing airborne latex particles or to eat food that has come in contact with latex.

NIOSH has developed recommendations for the prevention of latex allergies as they currently exist. These include protection of workers from undue exposure to latex, hand washing after removing gloves, and educational programs for hospital workers. [76] Modifications of manufacturing processes for latex products, more accurate methods to assess allergies to latex, and perhaps development of substitutes are additional goals of the recommendations. Up-to-date information concerning this dynamic area of interest is available on several Internet Web sites.

STRESS

Stresses in the practice of medicine and in one's personal life are inevitable. Sources of stress come from the job--dealing with suffering and death; uncertainty; selfperceptions of inadequacy; recurring academic deadlines, including recertification; and recent changes in the health- care system, including loss of autonomy that stems from managed care--and also from outside pressures, including family and finances. Some physicians seem to thrive in a stressful environment; others are unable to cope. [77] Stress has been implicated as a cause of drug abuse among physicians, but this is disputed by some (see *Chemical Dependence*).

Some sources of job-related stress are unavoidable, but others may be controlled. The former include the moral pressure placed on physicians by society for successful outcomes in all cases, uncertainty of the future in the era of managed care, and aging. In the latter category, at least two warrant discussion: the relationships between job performance and fatigue and between job performance and noise.

Unavoidable Stress

Management of stress is rarely addressed in medical school or in continuing medical education seminars for anesthesiologists, but it should be. Rather than being a sign of weakness, stress is a universal phenomenon to which *no one* is immune. Vital to our interactions with others is the ability to recognize stressed behavior, not only in them but also in ourselves. Healthy means of coping with stress include ability to communicate, appropriate assertiveness, interactive management of conflicts, adequate time with family, and time for recreational pastimes totally unrelated to professional activities. Irritability, anger, and aggressive behavior are common signs of improperly managed stress. A willing ear from a friend may be all that a stressed colleague needs to deal with the situation, although professional counseling may be indicated.

In a study conducted in Great Britain, the most significant source of stress for those beyond their training years was lack of control of circumstances at work. [78] Specific causes included professional relationships (especially with surgeons), work overload, threats of litigation, peer review, and increasing administrative responsibilities. Added to these were conflicts between professional pressures and personal

life. Although moderate levels of stress serve as healthy stimuli for productivity, excessive levels may impair clinical skills, resulting in potential risks to patients.

Professional dissatisfaction with medicine, an additional source of stress, is becoming an international phenomenon. It has been attributed by some to increasing health problems in the expanding elderly population, to the rapidly rising cost of health care, and to advancing technology. [79] Managed care, an evolving force in the practice of medicine in the United States, has become a source of stress that has stimulated a significant number of physicians to leave medicine (*The Washington Post,* February 16, 1998). To date, these responses to change have not been documented in anesthesiologists. [79]

Avoidable Stress

Altered Sleep Patterns

Regulation of physiologic functions, such as body temperature, sleep, alertness, and hormone release, is indexed to the 24-hour day by environmental cues that include light and temperature. These cues, termed zeitgebers by sleep physiologists, interact adversely with variable work schedules. The interactions may contribute to the higher rates of job stress, heavy drinking, and emotional problems seen in shift workers and in those working irregular hours. [80]

Well-defined periods of vulnerability to sleep have been identified in humans. The major peak occurs between 2 and 7 AM, and a smaller peak occurs in the midafternoon. These peaks appear to be enhanced by irregular work schedules and sleep disruption, and they may also contribute to diurnal variations in the frequency of mishaps. For example, single-occupant motor vehicle accidents occur with alarming regularity in the early morning. Their timing is attributed in part to this cycle. Similar relationships have been observed in the timing of catastrophic industrial accidents. The nuclear reactor accidents at Three Mile Island, Chernobyl, and two other sites in the United States all began between 1 and 5 AM. Human error was a significant factor in each mishap. Critical errors in judgment involving both the Challenger space shuttle accident and another near-disaster in the shuttle program were made in the early morning by personnel working irregular hours. Again, human error was a contributing element. Although none of these accidents can be conclusively attributed to sleep-related processes, all involved a lack of proper response by well-trained personnel working to the best of their abilities at the time of the accident. [81] On the basis of these observations, the Committee on Catastrophes, Sleep, and Public Policy of the Association of Professional Sleep Societies has made the following recommendations: (1) management should be made aware that performance errors are more common between 1 and 8 AM, (2) programs should be developed to identify signs of sleep-related error, and (3) because inadequate sleep or irregular sleep patterns enhance the tendency for error, work hours should be limited in order to permit adequate sleep. [81]

Altered patterns of sleep are a way of life for anesthesiologists. [82] As in industry, sleep deprivation may have subtle effects on vigilance in the operating room and may contribute to critical incidents. [83] Some published abstracts have documented subtle performance deficits and an increased likelihood of automobile accidents in sleep-deprived anesthesiologists. [84] [85] Considering the observations in industry and these new reports, further investigation of these relationships in anesthesiology is warranted. Changes in practice patterns may be warranted.

Noise

The effects of noise on people depend primarily on the duration and the timing of the sounds. The intensity of sound, also called sound pressure level, is displayed on a logarithmic scale and is reported in decibels (dB). A measured increase of 10 dB implies that the intensity of a sound has increased 10-fold. Sound-level meters are commonly biased to the A-weighted scale (dBA), which is thought to give a reasonably accurate measure of the response of humans to sound, although other scales are preferred by some. Conversational speech, lecture level speech, and nearby shouted speech have intensities of about 55, 65, and 75 dBA, respectively. These levels are far below OSHA standards that mandate the use of protective devices in environments where continuous sound intensities and duration of exposure are at least 90 dB and 8 hours, respectively. In addition to disrupting communication, unpleasant or unexpected noises may hinder concentration, contributing to physiologic stress. [86]

The flat, water-impermeable walls of the modern operating room are outstanding reflecting surfaces for sounds. Noise levels in operating rooms can easily approach those from a diesel engine. Particularly loud are such actions as opening packages of gloves (86 dBA), striking instruments together (80 dBA), moving equipment (60-80 dBA), conversing (66-72 dBA), power drills, and various objects striking floors. [87] The intensities of most of these sounds are greater than the intensity of normal conversation. Nonspecific tones from monitors and surgical equipment, especially when several are alarming at once, although perhaps not loud enough to impair communication, may also add to confusion. Simultaneous conversations and other distracting sounds are frequently louder than tones produced by monitors

such as electrocardiography machines, pulse oximeters, and equipment alarms. If these unnecessary auditory diversions hamper communication between anesthesiologists during stressful events in patient management, they should be stopped. Loud sounds have been shown to contribute to stress, as measured by responses of the pituitary-adrenal axis. In addition to affecting health-care workers, the din of the operating room and other acute care areas can be disconcerting to conscious patients. [88] Although noise is not known to cause problems other than hearing loss, it appears prudent to limit unnecessary sources in the operating room.

CHEMICAL DEPENDENCE

The morbidity from self-administration of drugs is far more common among anesthesiologists than are adverse effects from other potential threats in the operating room. For example, with the exception of the rare anesthesiologist who has contracted hepatitis after administering halothane to patients, no serious effects have been reported from waste

gases. By contrast, although unexplained, the suicide rate of anesthesiologists has been reported to be three times higher than that of an appropriate control group. [89] Although one may only speculate that substance abuse may play a role in this frightening figure, it is unequivocally involved in the four to eight deaths of residents by overdose that are reported each year (Arnold WP: personal observation).

The signs and symptoms of chemical dependence are so subtle that the disease is usually not obvious until it has reached its late stages. However, it occurs frequently enough in our profession to be of concern. Even those who understand the disease find it hard to imagine that a friend could be addicted to drugs and may feel powerless or hostile when it occurs. This section provides information about chemical dependence in anesthesiologists and guidance with the initial steps required to help a colleague or yourself. However, it is no substitute for the invaluable help available from experts.

The terminology in the section is based on recommendations of experts in the field of substance abuse. [90] *Addiction* is the compulsive continued use of a substance in spite of adverse consequences. Drug *dependence* is either physical or psychologic dependence on a drug. It is the result of an inability to control drug use. Drug or substance *abuse* is use of drugs in a detrimental way, but not to the point of addiction. Put simply, the drug abuser can quit without help; the addict cannot. *Recovery* is the process of conquering the disease. People who have previously been chemically dependent are referred to as *recovering,* rather than as recovered. This terminology emphasizes that chemical dependence is an incurable disease; chemical dependence, like other chronic diseases, such as diabetes and hypertension, can be controlled but not cured.

Disease

A growing body of scientific advances has proved that addiction is a chronic, relapsing disease resulting from long-term effects of drugs on the brain. [91] Acceptance of this incontrovertible fact is crucial for those dealing with chemically dependent physicians and other addicts. By considering an impaired colleague to be ill rather than an object of disdain, one will be better equipped to provide the initial guidance that the impaired physician so desperately needs.

During the 1980s, independent genetic, neurophysiologic, and biochemical observations demonstrated the complex etiology of addiction to drugs. For example, alcoholism is four times more common in the offspring of alcoholics than in appropriate controls and is related more to genetic than to environmental influences. [92] [93] Familial transmission of drug addiction has also been documented. [94] Alcoholics metabolize their drug of choice differently from nonalcoholics. [95] In inbred strains of alcoholic rats, condensation products that form between alcohol metabolites and catecholamine precursors fit opiate receptors. Similar compounds in humans may be responsible for the opiate-like euphoria that some alcoholics report. [96]

It has been discovered that essentially all drugs of abuse work through a single pathway in the brain. The mesolimbic reward system, extending from the ventral tegmentum to the nucleus accumbens with projections to other areas of the brain, is not only activated by drugs of abuse but is also irreparably altered by chronic exposure to these drugs. The molecular, structural, cellular, and functional changes that result from continued drug abuse are felt to be responsible for relapses that frequently follow periods of abstinence. At the outset, drug abuse is a voluntary event. However, once these neural changes have begun to develop, it becomes an addiction that is characterized by compulsive, irrational, drug-seeking behavior. Treatment should be directed at these changes through pharmacologic and behavioral approaches based on an understanding of the pathologic effects that the drugs have produced. A detailed presentation of these fascinating neurologic responses to chronic drug use, including upregulation of central cyclic adenosine monophosphate pathways in the locus caeruleus and the nucleus accumbens, alterations in drug receptor-G protein coupling, changes in gene expression, and modification of central neurotransmission, is beyond the scope of this chapter. The interested reader is encouraged to read several informative review articles, all of which appear in a single issue of *Science*. [90] [97] [98] [99]

The Problem in Anesthesiologists

The true prevalence of substance abuse and chemical dependence in physicians is unknown. [100] However, a national survey estimates a 2.1 percent annual and a 7.9 percent lifetime prevalence among physicians, substantially lower than the corresponding rate of 16 percent reported for the general population. [101] In the 1980s, the disease was believed to be more common in some specialties, especially anesthesiology and family medicine. [102] Estimates of the scope of chemical dependence in anesthesiologists have come primarily from two sources: questionnaires and treatment centers. Three retrospective surveys suggest that the prevalence of the disease in the specialty ranges from 1 to 2 percent. [103] [104] [105] These studies either are based on cases that have come to the attention of a superior or have relied on the honesty of those responding to the surveys. A prospective survey evaluating the incidence of the disease in training programs confirms these figures (Arnold WP, manuscript in preparation). It is unlikely that the extent to which substances are *abused* without the development of addiction will ever be known.

Treatment programs provide another source of data. Twelve to 14 percent of physicians treated in three well-known programs were anesthesiologists, although only 4 percent of physicians in the United States practice the specialty. [106] [107] [108] Anesthesiologists made up 146 of 1,225 physicians treated in one of these centers. [106] Although all of these anesthesiologists were chemically dependent, about 10 percent of the remaining physicians had other forms of impairment, such as depression. Of the anesthesiologists, nearly 50 percent were younger than 35 years of age, and one-third were residents. One-half of anesthesiologists used both drugs and alcohol, 40 percent used drugs alone, and a minority used only alcohol. Narcotics were more frequently preferred by younger anesthesiologists. Fentanyl was the most commonly abused narcotic, followed by sufentanil, meperidine, morphine, and oral agents. Some use of benzodiazepines, cocaine, and marijuana was also reported.

These data imply that the incidence of chemical dependence

is significantly greater among anesthesiologists than among physicians practicing other specialties. They also suggest that anesthesiology residents are particularly vulnerable to opiate addiction. Some believe that this apparently high incidence is indicative of the diligence of anesthesiologists in recognizing the disease in colleagues. [106] However, referral patterns may also have influenced the observations of these programs because anesthesiologists may have been sent to the programs preferentially. Other successful programs report a lower percentage of anesthesiologists in their series. [109]

Causes

Chemical dependence is a complex disease with multiple factors modifying the genetic predisposition. Although it is tempting to point to a single factor, such as stress and availability, as the cause in anesthesiologists, this approach overlooks many possibilities. Other elements to be considered are the addictive potential of the drug of choice, the prior use of drugs, and a family history of drug abuse.

Stress

Exposure to stress is a universal feature of medical school, residency, and the practice of medicine. Most physicians are able to manage these stresses through the use of acceptable outlets, such as athletics, exercise programs, social interaction, and occasional drinking of alcoholic beverages in moderation. A few do not have these abilities and instead withdraw from others. Roughly 10 percent of medical students are not graduated, and of those who are, nearly one-half need counseling. [77] Residency is particularly difficult for some. The working environment is usually highly competitive. Long hours preclude much time for true relaxation, and certain patients may evoke negative emotions. In addition, there are nonprofessional pressures, such as separation from parents, marriage, raising of children, and financial matters, to contend with during time spent away from work. A sense of professional inadequacy is nearly universal. [110] Perhaps the death of a patient after an outstanding resident has provided hours of high-quality medical care in a hopeless situation may cause these feelings to surface for the first time. Residency may breed a form of social isolation, resulting in withdrawal from friends and family and avoidance of contacts except with other physicians. The withdrawal itself may contribute to further stress because the physician senses social failure. The reluctance of physicians to acknowledge such feelings to themselves or to others contributes to a self-imposed isolation that may extend well beyond the resident years. [77] All these elements may prompt certain physicians to seek unhealthy escapes, such as the inappropriate use of alcohol and the abuse of drugs.

Availability

Anesthesiologists are unique among physicians in that they administer drugs directly, rather than order their administration by others. Thus, drugs are immediately available. This is perhaps the most important cause of addiction in the specialty. To quote many recovering anesthesiologists: "We work in the candy store." One report indicated that 85 percent of anesthesiology residents treated in one large program stated that having drugs within reach influenced their career choice. [106] Some institutions have developed elaborate control measures to combat drug pilferage. However, all such measures can be rendered inadequate by an addict who is desperate for drugs.

Drug Potency

Abuse of drugs by physicians is much more common than addiction. Some physicians abuse drugs "recreationally" to get high; others "self-medicate" to treat either a perceived illness or stress. Casual abuse of alcohol obviously does not always lead to addiction, and although exceedingly risky, neither does abuse of morphine, meperidine, or codeine. [111] In contrast, the addictive potential of fentanyl and other potent opioids is so great that anyone who experiments with these drugs is at enormous risk of becoming chemically dependent (Fig. 84-3) . [106] Some have said that a single experience with sufentanil is so overwhelming that it is impossible to stop using the drug. The doses needed to sustain a habit or to prevent the symptoms of withdrawal skyrocket once abuse begins. Rapidly developing tolerance stimulates the ever-increasing doses needed to attain the desired sensation. The use of 50 to 100 mL of fentanyl or 10 to 20 mL of sufentanil per day is common in the addicted physician. These doses are easily reached within a few months for fentanyl and a few weeks for sufentanil.

Other Factors

Some other factors predispose to the development of chemical dependence. A history of experimental use of drugs increases the risk of future addiction. [111] Genetic predisposition to chemical dependence may contribute to the progression from abuse to addiction. Lack of self-respect, denial that one's pattern of drug abuse can lead to addiction,

Figure 84-3 Time course of addiction, illustrating the relative addictive potential of several drugs. Its intent is to display a concept visually rather than to present data; thus, no numerical values appear. Dependence on alcohol typically requires years to become apparent, whereas addiction to sufentanil develops almost instantaneously. The slopes are roughly proportional to the addictive potential for each drug.

and the false assumption that an understanding of pharmacology prevents one from becoming addicted are all involved.

Management

Management of physicians who are chemically dependent includes identification, intervention, referral for treatment, and help with reentry. Having established mechanisms facilitates dealing with an impaired colleague. [112]

Identification

Identification of the chemically dependent physician usually does not occur until the disease is in its late phases, when performance at work becomes significantly impaired. Although none of its signs and symptoms is diagnostic, an awareness of the usual sequence of events may help one identify an ill colleague in the earlier stages of the disease (Table 84-1) .

Normally, withdrawal from outside interests is the first sign. Examples include giving up athletics, community activities, church, and getting together with friends. Next comes increased turmoil at home. Domestic arguments, sexual problems, and lack of interest in family matters are common. Third is the appearance of frequent unexplained illnesses, personality changes, multiple jobs, and frequent moves between cities. This progression, which may take years to become apparent, is common with addictions that develop slowly. It is uncommon in addictions to fentanyl and sufentanil because of their rapidity of onset (see Fig. 84-3) .

The last activity to be affected usually is job performance (Table 84-2) . Page operators and nurses may be the first to recognize behavioral changes. Record-keeping may become sloppy. Excessive use of certain drugs becomes apparent, perhaps accompanied by an unusual compulsion to explain the need for these drugs in patient management. Colleagues may note similar changes. Direct observation of selfadministration confirms the diagnosis, but it is not common. [113]

Denial is a keystone of the disease. Impaired physicians disclaim their illness by using superficially logical reasons to

TABLE 84-1 -- Signs and Symptoms of Chemical Dependence Seen Outside of the Workplace

1. Withdrawal from family, friends, and leisure activities
2. Changes in behavior (e.g., wide mood swings)
3. Fights and arguments at home
4. Frequent unexplained illness (common in alcoholism)
5. Gambling
6. Extramarital affairs
7. Legal problems (e.g., arrests for driving while intoxicated)
8. Decrease in sexual drive

9. Drugs and syringes found in the home
10. Seclusive behavior at home
11. Odor of alcohol on breath
12. Weight loss
13. Pinpoint pupils (in persons addicted to opioids)
14. Symptoms of withdrawal (e.g., diaphoresis, tremulousness)
15. Denial of drug or alcohol use if confronted

TABLE 84-2 -- Signs and Symptoms of Chemical Dependence Seen in the Hospital

1. Unusual changes in behavior (e.g., wide mood swings, depression, anger, euphoria)
2. Gossip by others
3. Progressive increase in apparent narcotic use for anesthetic management
4. Careless charting
5. Preference for working alone
6. Frequent requests for bathroom breaks
7. Unusual willingness to provide relief for others
8. Inappropriate willingness to take call
9. Often appears in the hospital when not on call
10. Frequent unexplained absences
11. Difficult to find when on call
12. Excessive postoperative pain in patients cared for by an individual
13. Commonly wears long sleeved gowns (to prevent chills often seen in early withdrawal and to hide needle tracks)
14. Pinpoint pupils
15. Weight loss
16. Found comatose
17. Found dead
18. Witnessed self-administration (the only pathognomonic sign)

explain their bizarre patterns of behavior. Colleagues, too, use denial. Typically, they would rather accept these explanations than consider that a friend is a drug addict. For these reasons, the diagnosis is usually not made until its manifestations are clear. Only when the pieces of puzzle have been assembled is the picture obvious.

Intervention

Although contempt for a chemically dependent physician may be felt by some, the appropriate initial response is to seek help. A call to a person experienced in managing chemically dependent physicians initiates the next steps. [108] [114] In the United States, all state medical societies have committees on impaired physicians to act as advocates for sick physicians. Advocacy continues as long as the physician cooperates with the committee's recommendations. These committees serve as a buffer between the physician and the medical board or licensing agency. They also provide advisers to aid in confirmation of the diagnosis and to intervene and refer impaired physicians to appropriate treatment centers. Although laws vary, the committees are usually required to notify the board of a physician's recalcitrance at any stage of treatment. In many states, the board does not censure impaired physicians who comply with the committee's recommendations.

Intervention is the process of demonstrating to a chemically dependent person that he or she is ill and needs treatment. [115] (Although both the masculine and the feminine pronouns are used here, statistically, most addicted anesthesiologists are male.) Interventions should *never* be attempted with less than two concerned persons and ideally should be directed by a person with prior experience, frequently a member of a state committee. The key is to be caring and compassionate, in spite of the patient's arguments, but to be persistent. The addicted physician is a superb con artist. He or she is able to counter all ploys attempted by a single individual and usually gives a group of people a good

workout. Hours of preparation are needed to collect information, to assemble appropriate participants (including coworkers, family, friends, and a recovering physician, if one is available), and to rehearse. Pertinent pharmacy records, anesthetic records, and other documentation of the illness should be gathered. All involved must be prepared to present their nonjudgmental observations in as much detail as possible. Many suggest that each participant prepare written notes to be used for reference during the intervention. The objectives are to present irrefutable proof of the addict's symptoms, to describe the disease, and to get him or her to an appropriate treatment facility. It is not a kangaroo court but rather a caring act of compassion for an ill colleague who is unable to recognize his or her illness. A recovering physician at the intervention is invaluable as a role model for the patient. Arrangements for treatment and travel, should they be required, must be made before the intervention.

In spite of meticulous planning, it is important to realize that an intervention may be like a football play in a downpour--although it may sound great in the huddle, once the ball is snapped, the play may go awry. Just as in football, the intervenors must anticipate the "broken play." They may need to improvise during the intervention, but they must keep the goal of referral for evaluation and treatment (if needed) continually in sight.

When all is in order, the patient is invited into a room in which the other participants are already seated. Each in turn should express concern for the colleague's well-being and, without passing judgment, should describe the aberrant behavior that he or she has seen. If necessary, the documents at hand can be shown. The basics of the disease and its treatment should be explained, and the patient should be urged to accept the proposed plan. If the patient refuses, as many do initially for fear of losing control, he or she should be told that the ultimate decision regarding therapy will not be made until the patient has been thoroughly evaluated by a group of specialists at the facility. [114] If the evaluation does not confirm the diagnosis, the patient will be discharged. Otherwise, formal treatment perhaps lasting several months will start. If the patient is still reluctant, he or she should be advised that the intervenors must, by law, report him or her to both the medical board and the controlled substance authorities. The patient has diverted narcotics, a felony subject to prosecution. Although acceptance of treatment does not provide legal immunity, it is looked on favorably by many courts.

After the intervention, someone should stay with the patient continuously, not only to prevent the possibility of self-inflicted injury but also to provide friendship. With adequate preparation, most interventions are successful.

Principles of Treatment

Treatment consists of an in-depth evaluation, which is usually followed by both inpatient and outpatient therapy. Formal therapy may last for as long as several months, [107] [114] but on the basis of the initial work-up, some programs permit the recovering physician to continue practicing medicine during what may be several years of outpatient care. [108] Although debated by some, physicians often fare better if treated at a facility experienced in managing physicians. On admission, many feel guilty, ashamed, and totally alone. Just seeing that other physicians share their disease is therapeutic. Philosophies of treatment vary between programs, but the

common goal is to provide the recovering physician with the ability to remain sober. The physician is assisted in developing a strong relationship with peer support groups, such as *Alcoholics Anonymous* and *Narcotics Anonymous.* In the last stage, the physician may become involved in evaluating new patients. This permits personal reflection on his or her own course, referred to by some as "mirror imaging." As understanding of the biology of addiction expands, specific pharmacologic treatment may become more common. [99]

Return

Return from treatment is a difficult process for the recovering physician. The comprehensive treatment program has provided a structured environment that is much different from the work place. During treatment each person has learned a great deal about his or her disease but those with whom the person interacts after discharge are far less knowledgeable and perhaps fearful of both the individual and the disease. For this reason, reentry is greatly facilitated by understanding, compassionate peers who are willing to provide emotional support to the recovering physician. Gradual return to work, perhaps with others initially managing narcotic administration, is important. Without this support, the likelihood of relapse may be much greater.

In many states, the committee on impaired physicians plays a vital role in recovery. At discharge from formal treatment, the committee prepares an "aftercare contract" with the physician, who agrees to be bound by the committee's recommendations. The contract usually stipulates the number and the type of meetings the physician must attend, the name of a "monitoring physician," the requirement for random urine samples on demand, and the procedures to be used in the event of a relapse. [107] [109] [116] Many recovery programs insist on the use of naltrexone or disulfiram, or both, for 6 months or more after returning. Novel treatments with drugs such as acamprosate, bromocriptine, selective serotonin reuptake inhibitors, and buspirone are under investigation. [117] As long as the physician adheres to the contract, the committee continues to serve as his or her advocate.

Federal law in the United States (the *Americans with Disabilities Ac*[ADA]) provides limited protection against employment discrimination for recovering individuals. [118] Although persons who are currently using drugs are not protected by this law, those who have been successfully treated and are otherwise capable of working are considered to be "qualified individuals with a disability." The ADA thus defines a history of chemical dependence as a disability. Although it does not require an employer to provide for treatment, the ADA may require that "reasonable accommodation" be made for a qualified individual who wants to return to practice. For a recovering physician, this might include a modified work schedule, such as no call for several months and assistance with administration of narcotics. An employer is not required to make accommodation if "undue hardship" for the employer would result. For example, it could be argued

in court that accommodations needed to permit a recovering physician to return might have a negative impact on other employees or could result in prohibitive costs for the employer. Whether or not the ADA can be used also depends on the type of employer-employee relationship between an individual and a hospital or group practice. Clearly, any person or entity who seeks the support of the ADA needs competent legal guidance.

Prognosis

As indicated by reports from treatment programs, most recovering physicians are able to return to a productive professional life. [109] [119] Successful outcomes are dependent on lifelong participation in aftercare programs, total abstinence from drugs and alcohol, and continual acknowledgment of one's disease. Unfortunately, these data include all physicians treated rather than indexing rates of recovery by medical specialty. Although no data are yet in print, some now believe that the prognosis for long-term sobriety in anesthesiologists depends on the age and the status of the physician at the time of identification. Residents who have been dependent on fentanyl appear to have a significant rate of relapse. [105] Although each case must be handled separately, strong consideration should be given to a change in specialty for junior residents who become addicted to potent opioids.

The American Board of Anesthesiology permits a physician recovering from alcoholism or other drug dependence, who is otherwise qualified, to take both the written and the oral examinations. After a candidate with this history has satisfied the requirements for certification, "the [board] will determine whether it should defer awarding its certification to the candidate for a period of time in order to avoid certification of a candidate who poses a direct threat to the health and safety of others." [120] If the American Board of Anesthesiologists deems that such deferral is appropriate "the [Board] will determine the length of time the candidate's certification is deferred following an individual assessment of the specific circumstances of the candidate's history of alcoholism or illegal use of drugs." This is in keeping with the intent of the ADA. [120]

Addiction is a lifelong disease. Its acute effects can be overcome, but its sequelae leave an indelible mark on each victim. Recovering physicians have a disease that makes them guilty in the eyes of others, forcing them to prove their innocence whenever they are challenged. Because there is no way to ensure that substance abuse will not lead to addiction, the only absolute protection is to avoid the illicit use of drugs entirely.

SUMMARY

There are many aspects of environmental safety in the operating room involving waste gases, radiation, infection, stress, and chemical dependence. Because anesthesiologists are the physicians who are most consistently in the operating room, they are expected not only to be knowledgeable in these areas but also to provide leadership in developing policies to protect operating room personnel and patients.

References

1. Dorsch JA, Dorsch SE: Controlling trace gas levels. In Dorsch JA, Dorsch SE (eds): Understanding Anesthesia Equipment: Construction, Care and Complications. 3rd ed. Baltimore, Williams & Wilkins, 1994, p 281.

2. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard: Occupational Exposure to Waste Anesthetic Gases and Vapors. DHEW (NIOSH) Publication no. 77-140, 1977.

3. Flemming DC, Johnstone RE: Recognition thresholds for diethyl ether and halothane. Anesthesiology 46:68, 1977.

4. Vaisman AI: Working conditions in the operating room and their effect on the health of anesthetists [Russian]. Eksp Khir Anesteziol 12:44, 1967.

5. Spence AA, Cohen EN, Brown BW Jr et al: Occupational hazards for operating room-based physicians: Analysis of data from the United States and the United Kingdom. JAMA 238:955, 1977.

6. Buring JE, Hennekens CH, Mayrent SL et al: Health experiences of operating room personnel. Anesthesiology 62:325, 1985.

7. Tannenbaum TN, Goldberg RJ: Exposure to anesthetic gases and reproductive outcome: A review of the epidemiologic literature. J Occup Med 27:659, 1985.

8. Vessey MP: Epidemiological studies of the occupational hazards of anaesthesia: A review. Anaesthesia 33:430, 1978.

9. Spence AA, Knill-Jones RP: Is there a health hazard in anaesthetic practice? Br J Anaesth 50:713, 1978.

10. Spence AA: Environmental pollution by inhalation anaesthetics. Br J Anaesth 59:96, 1987.

11. Mazze RI, Lecky JH: The health of operating room personnel. Anesthesiology 62:226, 1985.

12. Bruce DL, Bach MJ: Effects of trace anaesthetic gases on behavioral performance of volunteers. Br J Anaesth 48:871, 1976.

13. Smith G, Shirley AW: A review of the effects of trace concentrations of anaesthetics on performance. Br J Anaesth 50:701, 1978.

14. Gambill AF, McCallum RN, Henrichs TF: Psychomotor performance following exposure to trace concentrations of inhalation anesthetics. Anesth Analg 58:475, 1979.

15. Voelz GL: Ionizing radiation. In Zenz C (ed): Occupational Medicine: Principles and Practical Applications. 2nd ed. Chicago, Year Book, 1988, p 426.

16. Bushong SC: Radiologic Science for Technologists: Physics, Biology, and Protection. 4th ed. St Louis, CV Mosby, 1988.

17. Barker D: Protection and safety in the x-ray department. Radiography 44:45, 1978.

18. Mohr H: The design of x-ray equipment for use in operating rooms. Med Biol Eng 11:396, 1973.

19. Kiviniitty K, Lahti R, Lahde S et al: Radiation doses from x-ray units used outside radiology departments. Health Phys 38:419, 1980.

20. Holmes JA: A summary of safety considerations for the medical and surgical practitioner. In Apfelberg DB (ed): Evaluation and Installation of Laser Systems. New York, Springer-Verlag, 1987, p 69.

21. Nezhat C, Winer WK, Nezhat F et al: Smoke from laser surgery: Is there a health hazard? Lasers Surg Med 7:376, 1987.

22. Baggish MS, Baltoyannis P, Sze E: Protection of the rat lung from the harmful effects of laser smoke. Lasers Surg Med 8:248, 1988.

23. Byrne PO, Sisson PR, Oliver PD et al: Carbon dioxide laser irradiation of bacterial targets in vitro. J Hosp Infect 9:265, 1987.

24. Garden JM, O'Banion K, Shelnitz LS et al: Papillomavirus in the vapor of carbon dioxide laser-treated verrucae. JAMA 259:1199, 1988.

25. Ferenczy A, Bergeron C, Richart RM: Human papillomavirus DNA in CO 2 laser-generated plume of smoke and its consequences to the surgeon. Obstet Gynecol 75:114, 1990.

26. Baggish MS, Poiesz BJ, Joret D et al: Presence of human immunodeficiency virus DNA in laser smoke. Lasers Surg Med 11:197, 1991.

27. Hallmo P, Naess O: Laryngeal papillomatosis with human papillomavirus DNA contracted by a laser surgeon. Eur Arch Otorhinolaryngol 248:425, 1991.

28. du Moulin GC, Hedley-Whyte J: Hospital-associated viral infection and the anesthesiologist. Anesthesiology 59:51, 1983.

29. Department of Labor, Occupational Health and Safety Administration: Occupational exposure to bloodborne pathogens: Final rule (29 CFR Part 1910.1030). Fed Register 56:64004, 1991.

30. Gerbert B, Maguire B, Badner V et al: Why fear persists: Health care professionals and AIDS. JAMA 260:3481, 1988.

31. Berkelman RL, Heyward WL, Stehr-Green JK et al: Epidemiology of human immunodeficiency virus infection and acquired immunodeficiency syndrome. Am J Med 86:761, 1989.

32. Kessler HA, Bick JA, Pottage JC Jr et al: AIDS. Part I. Dis Mon 38:633, 1992.

33. Gourevitch MN: The epidemiology of HIV and AIDS: Current trends. Med Clin North Am 80:1223, 1996.

34. Centers for Disease Control: Impact of the expanded AIDS surveillance case definition on AIDS case reporting--United States, first quarter, 1993. MMWR Morb Mortal Wkly Rep 42:308, 1993.

35. Rosenberg PS: Scope of the AIDS Epidemic in the United States. Science 270:1372, 1995.

36. Update: Trends in AIDS incidence--United States, 1996. MMWR Morb Mortal Wkly Rep 46:861, 1997.

37. Update: Trends in AIDS incidence, deaths and prevalence--United States, 1996. MMWR Morb Mortal Wkly Rep 46:165, 1997.

38. Weiss SH: Risks and issues for the health care worker in the human immunodeficiency virus era. Med Clin North Am 81:555, 1997.

39. Kelen GD, Fritz S, Qaqish B et al: Unrecognized human immunodeficiency virus infection in emergency department patients. N Engl J Med 318:1645, 1988.

40. Centers for Disease Control and Prevention: HIV/AIDS surveillance report 10(no 1):24, 1998.

41. Tait AR, Tuttle DB: Prevention of occupational transmission of human immunodeficiency virus and hepatitis B among anesthesiologists: A survey of anesthesiology practice. Anesth Analg 79:623, 1994.

42. Greene ES, Berry AJ, Arnold WP III et al: Percutaneous injuries in anesthesia personnel. Anesth Analg 83:273, 1996.

43. Centers for Disease Control: Patient exposures to HIV during nuclear medicine procedures. MMWR Morb Mortal Wkly Rep 41:575, 1992.

44. Lanphear BP: Trends and patterns in the transmission of bloodborne pathogens to health care workers. Epidemiol Rev 16:437, 1994.

45. Buergler JM, Kim R, Thisted RA et al: Risk of human immunodeficiency virus in surgeons, anesthesiologists, and medical students. Anesth Analg 75:118, 1992.

46. Centers for Disease Control: Update: Acquired immunodeficiency virus infection among health-care workers. MMWR Morb Mortal Wkly Rep 37:229, 1988.

47. Centers for Disease Control: Update: Investigations of persons treated by HIV-infected health-care workers--United States. MMWR Morb Mortal Wkly Rep 42:329, 1993.

48. Centers for Disease Control: Recommendations for prevention of HIV transmission in health-care settings. MMWR Morb Mortal Wkly Rep 36:1S, 1987.

49. Browne RA, Chernesky MA: Viral hepatitis and the anesthetist. Can Anaesth Soc J 31:279, 1984.

50. Berry AJ, Issacson IJ, Kane MA et al: A multicenter study of the epidemiology of hepatitis B in anesthesia residents. Anesth Analg 64:672, 1985.

51. Centers for Disease Control: Inactivated hepatitis B virus vaccine. MMWR Morb Mortal Wkly Rep 31:317, 1982.

52. Centers for Disease Control: Changing patterns of groups at high risk for hepatitis B in the United States. MMWR Morb Mortal Wkly Rep 37:429, 1988.

53. Gerberding JL: Drug therapy: Management of occupational exposures to blood-borne viruses. N Engl J Med 332:444, 1995.

54. Odaka N, Eldred L, Cohen S et al: Comparative immunogenicity of plasma and recombinant hepatitis B virus vaccines in homosexual men. JAMA 260:3635, 1988.

55. Gerberding JL: Risks to health care workers from occupational exposure to hepatitis B virus, human immunodeficiency virus and cytomegalovirus. Infect Dis Clin North Am 3:735, 1989.

56. Alter MJ: Epidemiology of hepatitis C in the west. Semin Liver Dis 15:5, 1995.

57. Choo QL, Kuo G, Weiner AJ et al: Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 244:359, 1989.

58. Kuo G, Choo QL, Alter HJ et al: An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 244:362, 1989.

59. Cooper BW, Krusell A, Tilton RC et al: Seroprevalence of antibodies to hepatitis C virus in high-risk hospital personnel. Infect Control Hosp Epidemiol 13:82, 1992.

60. Hofmann H, Kunz C: Low risk of health care workers for infection with hepatitis C virus. Infection 18:286, 1990.

61. Wormser GP, Forseter G, Joline C et al: Hepatitis C infection in the health care setting. I. Low risk from parenteral exposure to blood of human immunodeficiency virus-infected patients. Am J Infect Control 19:237, 1991.

62. Mitsui T, Iwano K, Yamakazi C et al: Hepatitis C virus in medical personnel after needlestick accident. Hepatology 16,1300, 1992.

63. Centers for Disease Control and Prevention: Recommendations for follow-up of health-care workers after occupational exposure to hepatitis C virus. MMWR Morb Mortal Wkly Rep 46:603, 1966.

64. Tait AR: Occupational transmission of tuberculosis: Implications for anesthesiologists. Anesth Analg 85:444, 1997.

65. Edlin BR, Tokars JI, Grieco MH et al: An outbreak of multidrugresistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. N Engl J Med 326:1514, 1992.

66. Beck-Sague C, Dooley SW, Hutton M et al: Hospital outbreak of multidrug-resistant *Mycobacterium tuberculosis* infections: Factors in transmission to staff and HIV-infected patients. JAMA 268:1280, 1992.

67. Gordin F: Tuberculosis control: Back to the future? JAMA 267:2649, 1992.

68. Centers for Disease Control: Guidelines for preventing transmission of tuberculosis in health-care settings, with special focus on HIVrelated issues. MMWR Morb Mortal Wkly Rep 39 (RR-17):1, 1990.

69. Centers for Disease Control: Management of persons exposed to multidrug-resistant tuberculosis. MMWR Morb Mortal Wkly Rep 41(RR-11):61, 1992.

70. Centers for Disease Control and Prevention: Tuberculosis morbidity-- United States, 1996. MMWR Morb Mortal Wkly Rep 46,695, 1997.

71. TB Infection-Control Guidelines Work Group: Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. MMWR Morb Mortal Wkly Rep 43(RR-13):1, 1994.

72. Centers for Disease Control: Update: Universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep 37:377, 1988.

73. Garner JS: Guideline for isolation precautions in hospitals. Infect Control Hosp Epidemiol 17:54, 1996.

74. Kam PC, Lee MS, Thompson JF: Latex allergy: An emerging clinical and occupational health problem. Anaesthesia 52:570, 1997.

75. Konrad C, Fieber T, Gerber H et al: The prevalence of latex sensitivity among anesthesiology staff. Anesth Analg 84:629, 1997.

76. NIOSH Alert: Preventing allergic reactions to natural rubber latex in the workplace. DHHS (NIOSH) Publication no. 97-135, 1997.

77. McCue JD: The effects of stress on physicians and their medical practice. N Engl J Med 306:458, 1982.

78. Dickson DE: Stress. Anaesthesia 51:523, 1966.

79. Seeley HF: The practice of anesthesia: A stressor for the middle-aged? Anaesthesia 51:571, 1996.

80. Gordon NP, Cleary PD, Parker CE et al: The prevalence and health impact of shiftwork. Am J Public Health 76:1225, 1986.

81. Mitler MM, Carskadon MA, Czeisler CA et al: Catastrophes, sleep, and public policy: Consensus report. Sleep 11:100, 1988.

82. Howard SK, Healzer JM, Gaba DM: Sleep and work schedules of anesthesia residents: A national study. Anesthesiology 87:A932, 1997.

83. Cooper JB, Newbower RS, Kitz RJ: An analysis of major errors and equipment failures in anesthesia management: Considerations for prevention and detection. Anesthesiology 60:34, 1984.

84. Howard SK, Smith BE, Gaba DM et al: Performance of well-rested vs. highly fatigued residents: A simulator study. Anesthesiology 87:A980, 1997.

85. Geer RT, Jobes DR, Tew JD Jr et al: Incidence of automobile accidents involving anesthesia residents after on-call duty cycles. Anesthesiology 87:A938, 1997.

86. Kryter KD: The Effects of Noise on Man. 2nd ed. San Diego, Academic Press, 1985.

87. Shapiro RA, Berland T: Noise in the operating room. N Engl J Med 287:1236, 1972.

88. Falk SA, Woods NF: Hospital noise: Levels and potential health hazards. N Engl J Med 289:774, 1973.

89. Bruce DL, Eide A, Smith NJ et al: A prospective survey of anesthesiologist mortality, 1967-1971. Anesthesiology 41:71, 1974.

90. Rinaldi RC, Steindler EM, Wilford BB et al: Clarification and standardization of substance abuse terminology. JAMA 259:555, 1988.

91. Leshner AI: Addiction is a brain disease, and it matters. Science 278:45, 1997.

92. Cloninger CR: Neurogenetic adaptive mechanisms in alcoholism. Science 236:410, 1987.

93. Ingraham LJ, Wender PH: Risk for affective disorder and alcohol and other drug abuse in the relatives of affectively ill adoptees. J Affect Disord 26:45, 1992.

94. Cadoret R, Troughton E, O'Gorman TW et al: An adoption study of genetic and environmental factors in drug abuse. Arch Gen Psychiatry 43:1131, 1986.

95. Thacker SB, Veech RL, Vernon AA et al: Genetic and biochemical factors relevant to alcoholism. Clin Exp Res 8:375, 1984.

96. Myers RD: Multiple metabolite theory, alcohol drinking and the alcogene. Prog Clin Biol Res 183:201, 1985.

97. Koob GF, LeMoal M: Drug abuse: Hedonic, homeostatic dysregulation. Science 278:52, 1997.

98. Nestler EJ, Aghajanian GK: Molecular and cellular basis of addiction. Science 278:58, 1997.

99. O'Brien CP: A range of research-based pharmacotherapies for addiction. Science 278:66, 1997.

100. Brewster JM: Prevalence of alcohol and other drug problems among physicians. JAMA 255:1913, 1986.

101. Hughes PH, Brandenburg N, Baldwin DC Jr et al: Prevalence of substance use among US physicians. JAMA 267:2333, 1992.

102. Talbott GD, Gallegos KV, Wilson PO et al: The Medical Association of Georgia's impaired physicians program: Review of the first 1000 physicians: Analysis of specialty. JAMA 257:2927, 1987.

103. Ward CF, Ward GC, Saidman LJ: Drug abuse in anesthesia training programs, a survey: 1970 through 1980. JAMA 250:922, 1983.

104. Gravenstein JS, Kory WP, Marks RG: Drug abuse by anesthesia personnel. Anesth Analg 62:467, 1983.

105. Menk EJ, Baumgarten RK, Kingsley CP et al: Success of reentry into anesthesiology training programs of residents with a history of substance abuse. JAMA 263:3060, 1990.

106. Gallegos KV, Browne CH, Veit FW et al: Addiction in anesthesiologists: Drug access and patterns of substance abuse. QRB 14:116, 1988.

107. Herrington RE, Benzer DG, Jacobson GR et al: Treating substance-use disorders among physicians. JAMA 247:2253, 1982.

108. Gualtieri AC, Cosentino JP, Becker JS: The California experience with a diversion program for impaired physicians. JAMA 249:226, 1983.

109. Shore JH: The Oregon experience with impaired physicians on probation: An eight-year follow-up. JAMA 257:2931, 1987.

110. McCall TB: The impact of long working hours on resident physicians. N Engl J Med 318:775, 1988.

111. McAuliffe WE, Rohman M, Santangello S et al: Psychoactive drug use among practicing physicians and medical students. N Engl J Med 315:805, 1986.

112. Lecky JH, Aukberg SJ, Conahan T III et al: A departmental policy addressing chemical substance abuse. Anesthesiology 65:414, 1986.

113. Spiegelman WG, Saunders L, Mazze RI: Addiction and anesthesiology. Anesthesiology 60:335, 1984.

114. Talbott GD: Elements of the impaired physicians program. J Med Assoc Ga 73:749, 1984.

115. Johnson VE: Intervention: How to Help Someone Who Doesn't Want Help. Minneapolis, Johnson Institute Books, 1986.

116. Talbott GD, Martin CA: Relapse and recovery: Special issues for chemically dependent physicians. J Med Assoc Ga 73:763, 1984.

117. Moncrieff J, Drummond DC: New drug treatments for alcohol problems: A critical appraisal. Addiction 92:939, 1997.

118. Equal Employment Opportunity Commission: A Technical Assistance Manual on the Employment Provisions (Title 1) of the Americans with Disabilities Act. Washington, DC, U.S. Government Printing Office, 1992.

119. Morse RM, Martin MA, Swenson WM et al: Prognosis of physicians treated for alcoholism and drug dependence. JAMA 251:743, 1984.

120. Booklet of Information: Hartford, Conn, The American Board of Anesthesiology, 1993.

/das/book/view/29494766/875/923.html

Chapter 85 - Ethical and Legal Aspects

Jerome H. Modell
A. Joseph Layon
Charles S. Modell

INTRODUCTION: ETHICAL ASPECTS OF ANESTHESIA

The practice of medicine, in general, and to no lesser extent, anesthesiology, has been altered and continues to undergo changes that significantly affect our practice and the social and biomedical context in which we live. If legal behavior is the "minimal" accepted standard and ethical behavior is the standard that we strive to achieve, then study of medical ethics becomes critical, given the moral issues that these changes encompass. This chapter discusses some ethical issues significant to the practice of anesthesiology. Several topics are presented to show how medical ethics influence both clinical practice and research. First, however, we review the nature of moral philosophy.

Values Versus Facts

In the Platonic dialogues, Socrates asks his students the questions "What is virtue?" "What is justice?" The response to the question, which the young student thinks is obvious, is then criticized by Socrates. For example, the student may have responded that virtue is doing one's duty or listed roles taught by parents or leaders. Socrates tried to convince his students that such answers are inadequate because it is the rationality of the good that we must try to understand. A behavior is good not *because* it is taught, rather, it *is* good and that is *why* it is taught.

In moral philosophy, the problem is similar. A person first exposed to the subject may think that an issue can be solved by repeating the dictates of religious or political authorities. Indeed, it is precisely the tendency to rely on authorities that is the central question of moral philosophy: Are conflicts about values settled in the same way as conflicts about facts? Attempting an answer shows that invoking a higher authority can lead to ultimate incoherence. For example, if torture is wrong, then it remains so even if ordered by authority of God or political leaders. Wrong is wrong, independent of authorities. Furthermore, our obedience to an authority is mandated only as long as that authority commands actions that we, after careful consideration, agree are good.

Once the infallibility of authority is eliminated, we must answer the question "What is good?" in the same manner that we answer other questions about our world. Yet, factual problems are normally settled by the collection of observable data. For the question, "How many chairs are in the room in which you sit as you read this?" collecting observable data may be simple, but for the question, "What is a virus?" the data are relatively abstract and difficult to understand. Further, when we say, "It is wrong to kill," "It is wrong to have an abortion," "It is wrong to eat the flesh of animals," we are evaluating human actions *rather* than describing *facts.* Evaluative, as opposed to factual, judgments are resolved differently. We can know, from observable data, that prolonged deprivation of oxygen results in death, that a woman is pregnant, and that some humans do eat meat. We frequently agree on matters of fact, but we may disagree profoundly on the judgment or evaluation of actions.

How then do we decide whether an action is good or bad? In the premise of any moral argument, there is always a principle defended; by doing so, we also defend our ethical standards. Historically, a moral principle has been defended by using either *consequentialist* or *nonconsequentialist* models. When defending a principle, the consequentialist, sometimes called utilitarian, tries to evaluate the outcome (consequences) of a given action, whereas the nonconsequentialist considers the future effects of an action either irrelevant or impossible to determine and, thus, defends a moral principle on its merits alone. *Goodness* to the consequentialist is that which is best for the greatest number of people. This method of analysis, in which all relevant members of a group affected by a moral issue are taken as equals, is called *utilitarianism.* We can see that there are problems with this method of analysis, however. How can we be sure we agree with a consequentialist on what is best for the majority or who comprises the majority? How do we know when a consequentialist is simply acting on personal, cultural, or social biases?

The view of the nonconsequentialist, an ethicist who emphasizes rules and principles, seems to be stronger. However, would an ethicist uphold rules that made things worse for everyone? Further, what do we do when moral and ethical principles conflict?

To answer such questions, we must probe more deeply into the reasoning behind morals. For example, because the consequentialist determines *good* or *bad* by the effect an action has on the greatest number of people, to say that killing is wrong simply means that most frequently, but not always, killing produces great harm to those involved. Thus, within this moral framework, there are situations in which killing would be beneficial, and in such a case, killing would be morally right. For example, it is normally considered wrong for physicians to harm a patient; the consequentialist would defend this view on the grounds that the greatest good is served when the physician considers the patient's welfare as primary. However, what if a patient is mortally ill, coherent, and suffering and wishes a rapid, painless death? The consequentialist would then reject as hopelessly dogmatic the assertion that it is wrong to kill under these conditions. Thus, killing is not wrong in itself; rather, it is the consequence of killing (in this case mercy killing) that is right or wrong. It is not necessary to accept this line of reasoning to recognize that it is one approach to moral dilemma. Those who support physician-assisted suicide utilize such consequentialist logic.

There are several problems with the consequentialist framework. The first is that, depending on the problem being considered, morality changes. The general rule, killing is wrong, exists but is subject to modification. A second problem has been termed the " *slippery slope*" *phenomenon:* if we make an exception to a moral rule for one difficult case, the next time we are faced with a similar conflict, further exceptions will be easier to make. This position was forcefully argued by Alexander in his landmark article on Nazi medicine. [1]

For the nonconsequentialist, principles always supercede consequences. Thus, it is never justifiable to kill, even to ease the suffering of a terminally ill patient whose imminent death causes great pain. The nonconsequentialist warns that there can always be some justification devised for killing. The slippery slope argument suggests that, if we start justifying euthanasia or physician-assisted suicide in some cases, we will soon be killing with impunity. As with consequentialism, there also are problems with nonconsequentialism, or fixed moral principles. First of all, although we can identify a moral principle--for example, do not kill--it is relatively difficult to be clear about what we mean by this phrase. For example, is it wrong to kill in self-defense or during war?

A different problem arises when two or more principles contradict each other. To take an extreme case, what is to be done with the principles do not lie and do not kill when the Gestapo asks us in 1940, "Do you have a Jewish family in your cellar?" If we make an exception and lie, we are exhibiting the behavior of a consequentialist, with all the potential dilemmas that that entails. On the other hand, could we do anything *but* lie to preserve the lives of the family in our cellar?

The reason for discussing moral philosophy is to show that moral decisions must be based on more than just opinions or fleeting emotion. We must know the facts of the moral dilemma and how the dilemma occurred, but we must also be able to reason about our moral principles in order to make sound decisions.

Conflicting Values

People of goodwill and conscience may disagree. Perhaps the classic example of value conflict is the physician asked to care for a Jehovah's Witness (Chs. 25 , 46 , and 47). This religion prohibits its followers from receiving banked blood products. The belief stems from scriptural passages suggesting that "life" or the "life force" is found in blood and, thus, must be treated respectfully. [2] [3] This belief generally precludes receipt of banked blood products, but it may not, at the patient's discretion,

preclude receipt of albumin, plasmanate, or clotting factors or even bone marrow transplantation. [4] Jehovah's Witnesses consider their time on Earth as a temporary period followed by eternal life after death and resurrection. [5] Witnesses who voluntarily allow the transfusion of blood, unless repentant, may be "cut off" from the deity they believe in, eliminating the possibility of "eternal life," which constitutes damnation on Earth. [5] Receipt of blood by a Jehovah's Witness without the person's permission causes "loss of innocence," a serious transgression, but with no negative religious consequences for the Witness. However, loss of innocence is considered serious enough that the believer may bring a charge of assault against the health worker. Conversely, although there have been suits against physicians for withholding blood or blood products when requested to do so by the patient, no negative legal decisions have been found when this is done under clearly defined preoperative conditions. [5]

Many ideologic systems serve as a framework for living. No person's belief system, even if it seems to us extremely unusual, should be denigrated. Under medically elective conditions, if one cannot consent to the patient's requests, the only moral solution is for the physician to withdraw from that patient's care and to make a serious attempt to locate a colleague who does not feel morally compromised by the request. In an immediately life-threatening situation, as may happen with Jehovah's Witnesses, there is often no time to

determine whether the patient would sacrifice his or her life for a religious belief and even less time to find a colleague who would agree to provide the necessary care under the apparent religious constraints. In this situation, we think that it is better to err such that life is preserved rather than lost. This is even more true when a child is involved. If we accept that there are many valid ways to live a life, it must also be recognized that the world views of a child and a parent do not always agree once the child reaches the age of reason. In our experience, Jehovah's Witness parents are very easy to work with when their children require surgical intervention. They wish their child to receive optimal therapy while blood is, under all circumstances, withheld. Although we respect the parent's central moral beliefs and attempt to be faithful to them, we inform the parents that, in the event of an unexpected or uncontrollable hemorrhage that jeopardizes the child's life, blood will be transfused if deemed absolutely lifesaving. A court order allowing transfusion may be obtained if time allows, but this will clearly not be the case in an emergency unless procedures that predate the emergency and a relationship between the court and hospital to implement these procedures exist. Such legal intervention is required very rarely when communication, as noted earlier, is maintained.

When a competent patient has received our promise not to transfuse blood, that promise should be rescinded only in the most extreme situation. Some clinicians view that significant hemorrhage while the patient is anesthetized justifies breaking faith with the patient. [6] Others may believe that consideration of whether the patient was competent or the consent was freely given preoperatively should be overriding. [6] Finally, transfusion need not be performed simply because blood is being or will be lost. In an otherwise healthy individual, the hematocrit level may be diluted to as low as 15 to 20 volumes percent with crystalloid or colloid and still provide adequate reserve for tissue oxygen extraction.

Rationing Care

Expensive Health Care and Not-So-Expensive Health Care

Many third-party carriers ration expensive types of health care by excluding certain conditions, therapies, or both in their coverage policies. In such situations, health-care providers are frequently placed in the position of denying such care to patients unless the cost can be funded by private sources. In other cases, the care is provided, but, because of the large unreimbursed expense, the cost is shifted to other patients. The managed care organizations (MCO) go even further. [7] [8] Emergency department physicians are obligated under federal law to determine, for each person presenting to the emergency department, whether or not an emergency medical condition exists. This must be done irrespective of the patient's payer class. Denial of authorization of payment for these federally required services by MCOs reached such proportions that some states have passed legislation requiring MCOs to pay the cost of such evaluations. Clearly, abuses of these situations must be resolved via social policy rather than by physicians on a case-by-case basis.

Intensive Care

When are resources allocated to health care sufficient? At some point, does the consumption of a specific portion of the national economic output for health care become excessive? Health care consumed $511 billion (11.4% of the gross domestic product [GDP]) in 1987 [9] ; in constant dollars, this is a 133 percent increase in expenditures for health care since 1960 (Ch. 71) . Each year, the amount spent has increased further: $666 billion in 1990 (12% of GDP), $736 billion in 1991 (13% of GDP), and an estimated $820 billion in 1992 (13.9% of GDP). [10] Yearly, approximately 15 percent of this amount is used for intensive-care services. [11] Despite this outlay of funds, at present, 30 to 37 million people in the United States are without any access to health-care services. [12] Thus, at a minimum, the allocation of resources is inadequate. Nonetheless, many insist that society must decrease the cost of health care or at least stem its steady climb. [9] [11] [12] [13] Because physicians are responsible for directing the use of approximately 70 percent of health-care expenditures, [9] it comes as no surprise that physicians are asked to assist in conserving these funds. There are, however, potential problems and even conflicts of interest that arise once physicians take on the role of advocate of *both* society and patients. This is a prototypic ethical issue. We have neither laws nor collective experience clearly showing us the way to decrease health expenditures, to limit health-care services, or to continue on the present course. In any case, the role of the health-care team, and particularly physicians and nurses, in this debate is exceptionally important.

When consulting a physician, the patient expects that the decisions and choices made by that professional are competent, respectful, disinterested, and uncolored by social judgments. [14] Therefore, in a debate with politicians, economists, health-care planners, and our patients, physicians must argue forcefully for those whom they serve, which is no more than an extension of the "ethic of agency," which states that the physician's role is to help the person under his or her care to obtain every possible resource necessary. In general, it is potentially dangerous, from an ethical viewpoint, for the active clinician (as distinguished from the physicianadministrator) to make rationing judgments that may affect the patient under his or her care. The peril is even greater if the physician receives some form of financial incentive to limit resources used on the patient, especially if there is no serious evaluation of how alterations in the resources used will affect the patient's outcome.

The basic conflict surrounding the concept of rationing care in the intensive care unit (ICU) is that of casting the physician in a role as gatekeeper. If physicians accept the ethic of agency, it would be difficult to rationalize keeping certain types of necessary care from their patients. A key concept here is the word *necessary.* There is no conflict when physicians do not arrange for an ICU bed for a healthy outpatient who undergoes a tonsillectomy and is discharged hours after the procedure. However, the situation is not always so clear. For example, it had been suggested that, among patients with acquired immunodeficiency syndrome (AIDS) and *Pneumocystis carinii* pneumonia (PCP) who require tracheal intubation and mechanical ventilation, mortality was approximately 85 percent, [15] but several reported

series showed that, with aggressive therapy, mortality could be decreased to approximately 50 percent. [16] [17] [18] In spite of this improvement in short-term survival, until recently, the mortality from the human immunodeficiency virus (HIV) after an AIDS-defining illness was nearly 100 percent over a period of approximately 2 years. [19] The introduction of protease inhibitors, in conjunction with dual nucleoside analogues, has led to a decrease in HIV-related mortality. Unfortunately, however, these medications are very expensive. What is the appropriate response of the physician in charge of such a patient? Being an agent of the patient justifies, indeed mandates, the physician's obtaining every *necessary* resource for that patient. Would this be possible if, at the same time, the physician were in some way forced, as an agent of society, to conserve scarce resources? The answer is, we think, self-evident.

As a patient's agent, the physician is not required to use every available resource but must use those that the patient *and* the physician deem necessary. Aggressive treatment, however, does not mean unintelligent or uncompassionate care. In the recent past, outpatient men with AIDS questioned about their desire for life-sustaining treatment in the face of PCP opted for hospitalization and antibiotic therapy 95 percent of the time, 55 percent would accept aggressive care, and 46 percent would agree to cardiopulmonary resuscitation (CPR), were it required. [20] In the presence of PCP and concomitant severe memory loss, only 19 and 17 percent, respectively, wanted ICU therapy including mechanical ventilation and CPR. Although 73 percent wanted to discuss the matter with their primary physician, only 33 percent had done so; the reasons for this discrepancy are unclear, but they could relate to discomfort in discussing such matters on the part of either the physician or the patient. Other data suggest that, in general, these discussions occur infrequently (4-19%), [21] [22] even though patients want the opportunity to discuss such options with their physician. [22]

When considering the case for rationing any health service, we must consider the moral implications of attempting to salvage a health-care system in which equity plays such a small role. Economic and political decisions that work to maintain a fair health-care system must meet two general criteria: (1) the health-care system must be closed, meaning that saying no to one therapy (e.g., heart transplants) allows us to say yes to another (e.g., prenatal care for all mothers); (2) the system must be governed by the principle of equity in decisions about technologic advances. The present health-care system in the United States fulfills neither of these criteria. [14] [23] There is some evidence that rationing imposed by the Oregon Health Plan has resulted in a system that comes much closer to fulfilling these two criteria than the present market-driven system. [24]

Under present circumstances, the function of the physician in cost containment and rationing of services must be to maintain the ethic of agency. As with all moral principles, this one is not infallible. However, it may be the most morally appropriate decision. Additionally, we physicians can argue for decreased waste in our system, [25] [26] and we can educate ourselves, our colleagues, our political leaders, and our fellow citizens about problems, modifications, or alternatives to the current system. [27] [28] [29] This has always been important, but it is even more critical now.

Life as the Ultimate Value

When, if ever, is it appropriate to cease attempting to salvage the life of a patient? How far do we physicians go and how hard do we try to maintain life when survival is unwanted by the patient, unlikely to result from any therapeutic regimen, or unlikely to be attended by normal function?

From the moral point of view, there are limits to our obligation to save or prolong life. Decisions about limitation of treatment or about nontreatment are frequently made when a patient appears to have a rapidly progressing, terminal illness for which no curative or adequate palliative therapy is available. With regard to palliative therapy, a key term is *adequate.* Although therapeutic modalities often prolong existence, frequently it is not simply the length of life, but its quality, that concerns patients and their families. When this quality can no longer be maintained, it is professionally and socially acceptable to let the dying process take its course. Clinically, this process usually involves do-not-resuscitate (DNR) orders.

Do-Not-Resuscitate Orders

Are we not, as physicians, always required to preserve life? Is a DNR order simply euthanasia disguised? If by euthanasia we mean an intervention that anticipates a terminal pathophysiologic process and purposefully speeds that process to minimize suffering, a DNR order is clearly not euthanasia. The DNR order allows the natural process of dying to take its course without interference. Although some call this *passive euthanasia,* we reject such formulations, which would make all therapy, short of extraordinary care, passive euthanasia. Further, the assertion that physicians *must always* strive to save life is uninformed. As one moral philosopher states [30] :

> The success of intensive care is not, therefore, to be measured only
> by the statistics of survival, as though each death were a medical failure. It
> is to be measured by the quality of lives preserved or restored; and by the
> quality of the dying of those in whose interest it is to die; and by the
> quality of human relationships involved in each death.

Although some may disapprove, most physicians accept and use DNR orders. In these cases, there are several points to be made [31] [32] :

1. The medical order to withhold resuscitation in the event of a cardiopulmonary arrest must be documented on the patient's chart. A physician does not become less liable in a legal or moral sense by making DNR orders verbal rather than written formally on the medical record.
2. The order should specify exactly what should be withheld. Is it just CPR that will not be administered, or are pharmacologic agents to be withheld as well?
3. Decisions regarding DNR status must be made in conjunction with the patient, if possible, with the patient's family, or both, and must be documented in the chart. This is both moral and strengthens the relationship between physician and patient. [33]
4. Considerations regarding DNR status should be discussed with the other members of the health-care team involved in the care of a patient. Frequently, nurses first identify

patients who are considering rejecting life-sustaining treatments. Encouraging the participation of fellow health workers, in ICU rounds, for example, enhances patient care and, by allowing varied input, decreases reactionary and emotional responses to limitation of care orders.
5. The DNR status of a patient should be reviewed regularly, because a patient with a DNR order may recover. Indeed, up to 38 percent of hospitalized patients with DNR orders do not suffer a cardiac arrest and are discharged from the hospital. [34] There should be a clear mechanism for revoking a DNR order when and if this is deemed appropriate.
6. Patients and their families must be made to understand that DNR status is not cryptic terminology for abandonment, either medically or psychologically, nor is it the same as withdrawal of therapy.

These considerations would seem to pertain more to ICU patients than to routine surgical patients. However, DNR orders when patients must undergo surgical intervention have become an issue. Patients with a DNR order on their medical record may require one of several operative interventions, depending on the underlying pathophysiology. Exploratory laparotomy for lysis of adhesions resulting in a small bowel obstruction in a patient with cancer, and tracheostomy, gastrostomy, and jejunostomy for a patient in a persistent vegetative state are but two possible situations. Several groups have noted that the requirement for an operative intervention in these patients places both surgeon and anesthesiologist in some difficulty. [35] [36] [37] [38] [39] [40] The reason is an apparent contradiction in our actions if we physicians are faithful to the central principles of medical ethics. The principle of autonomy would lead us to accept a patient's choice to undergo operation with a DNR order. In case of an untoward event, we would not resuscitate the patient. The principles of beneficence and nonmaleficence, however, would lead us to intervene in case of some untoward event.

The resolution of this apparent quandary lies in focusing on the specific patient in each case and ensuring that channels of communication are both open and well used. When obtaining informed consent and explaining what will occur in the operating room, including the potential for complications, we physicians must also point out therapeutic options if problems occur. Once again, it is only through careful and responsive discussion that we can resolve our dilemma. As best as possible, the patient or surrogate must understand the nature of the physiologic insult entailed by the anticipated surgical procedure, as well as the possible surgical and anesthetic complications involved and their consequences. These complications range from hypotension on induction of anesthesia to cardiac arrest. If appropriate, the surgeon and anesthesiologist could request that the DNR order be rescinded for 24 to 48 hours. This would allow the surgical team to intervene with any mode of therapy for that period of time, after which the DNR order would be reestablished. It should be clear that any therapy would be discontinued when no longer necessary or no longer effective in reversing the acute physiologic abnormalities induced by surgery. Thus, the patient or surrogate could consent to the procedure with one of three options: with the DNR order rescinded, with some stipulations of what therapies could be administered, or with the DNR order intact. [35]

After weighing the moral risk of proceeding with the intervention, if the second or third aforementioned option is chosen by the patient or surrogate and the surgical team decides not to proceed, the team is obliged to refer the patient to others who could be inclined to perform the operation. This assumes an elective situation in which there is time to discuss options rationally. In an emergency, especially when the patient has come from a medical ward to the operating room, all therapies should be used to preserve life; these may be withdrawn at a later time, if appropriate. Finally, when the patient or surrogate agrees to the procedure with any therapy deemed necessary intraoperatively and for the first 24 to 48 hours postoperatively, what is to be done if the patient does not improve and cannot be tracheally extubated or weaned from vasoactive agents after 48 hours? Because this possibility would have been discussed prior to the operative intervention, consideration of withdrawal of life support would be appropriate. [35] [36] [38] [39] [41]

In difficult cases, and when disagreements arise, the hospital ethics committee can be extremely useful. [26] [29] [32] [42] At our institution, the hospital ethics advisory committee is multidisciplinary, composed of representatives from pastoral, social, nursing, medical, and surgical services, as well as from administration. The committee functions include education of hospital personnel on ethics, advisory consultations performed at the request of a primary service, and advisement and review of hospital policy matters involving ethical concerns.

Withdrawal or Withholding of Therapy

Withdrawal-of-therapy decisions, although not fundamentally different from a DNR order, are usually made in a different clinical setting. The decision to withdraw or withhold a specific therapy or therapies is almost always made in the setting of terminal care. *Terminal* must be defined. Although one may glibly state that we are all terminal, in as much as to be alive is to progress toward death, we define *terminal* as the imminence of death despite aggressive intervention. Precision in predicting the date of a patient's death is difficult, if not impossible, and, in addition to necessitating complete knowledge of the natural course of the disease process, it requires honed clinical judgment.

Having concluded that death is imminent, the next consideration is the competency of the patient. A competent person may request further heroic measures or may request that supportive therapy be withdrawn. Either of these options is entirely within the legal and moral rights of a patient. Although a physician may have moral reservations about a competent patient's requests to reject terminal care, the patient's choice should be preeminent over the physician's moral stance. If the physician strongly opposes withdrawing or withholding therapy, care of the patient should be turned over to a colleague not so constrained.

All these considerations are affected when a patient is incompetent. Incompetent patients fall into one of three subgroups. [43] The first is a patient currently incompetent but who, while competent, expressed a choice regarding terminal care. Such a choice is usually considered to be valid when a patient becomes incompetent. An example of this is the case of Brother Fox. [44] A member of the Society of Mary,

a Roman Catholic religious order, for more than 66 years, this man had expressed his wish at least twice, the final time being shortly before he became incompetent, that nothing extraordinary be done if his medical condition were hopeless. In 1979, while undergoing a herniorrhaphy, Brother Fox suffered an intraoperative cerebral ischemic event that left him in a persistent vegetative state. Despite a request by family and friends to discontinue mechanical ventilation, the hospital refused to do so without a court order. The New York State Supreme Court ruled that, because Brother Fox had made clear his opposition to use of a ventilator to maintain him in a vegetative state, he had the right to decline treatment. Although not without controversy, [45] [46] [47] [48] cases like that of Brother Fox helped to stimulate the movement for "living will" or "natural death" legislation.

The second group of incompetent patients comprises those who have either never been competent or who have never expressed themselves while competent regarding their wishes about terminal care and who are without family members or friends who could take on the role of guardian. An exemplary legal case is that of *Superintendent of Belchertown State School v Saikewicz.*[49] The patient, Joseph Saikewicz, was a 67-year-old mentally retarded man, with a mental age of 2 to 3 years. He had previously enjoyed reasonably good health and had been ambulatory, but he was unable to communicate aside from gestures and grunts. During the course of medical treatments for conditions arising during his stay at the Belchertown State School, Mr. Saikewicz had been unable to respond intelligibly to inquiries as to whether or not he was in pain. In April 1976, Mr. Saikewicz was diagnosed with acute myelomonocytic leukemia. The legal case revolved around the issue of the appropriateness of chemotherapy. Mr. Saikewicz had, of course, never been competent, and the only two members of his family who could be found preferred not to become involved. The court determined that chemotherapy would cause the patient significant suffering with very little chance of changing the ultimate outcome of the disease. Thus, chemotherapy was withheld, and the patient died in September of 1976 from an infectious complication. In making this decision, the court invoked the doctrine of substituted judgment, which states "that the decision in cases such as this should be that which would be made by the incompetent person, if that person were competent, but taking into account the present and future incompetency of the individual as one of the factors that would necessarily enter into the decision-making process of the competent person." [49]

Veatch [43] expressed his displeasure with some of the wording of this decision. In substituted judgment, the decision maker takes into account the idiosyncratic factors that the patient has expressed, even if they are not in the "best interest" of the now-incompetent patient. With a person such as Mr. Saikewicz, this was not possible because he never had the ability to express himself intelligibly. Thus, the "best interest" rule should have been invoked, rather than substituted judgment. For this group of patients, it is reasonable to turn to the courts for help in decisions of withholding and withdrawing therapy.

The final group of patients comprises those who are incompetent or who have never addressed the question of terminal care while competent but have family members available to act as guardians, as in the Dinnerstein case. [50] Shirley Dinnerstein was admitted to a nursing home in 1975 for intensive nursing care secondary to Alzheimer disease. Three years later, she suffered a massive stroke. Her physician wished to write a DNR order but thought the Saikewicz case had made it impossible to do so, even though the patient's family agreed to it, without seeking the permission of the court. Although the court in the Saikewicz case did not set out a complicated set of rules that had to be followed before denying treatment to a ward of the state, [49] the Massachusetts Appeals Court stated clearly that the Saikewicz decision did not mandate the resuscitation of dying patients. Because CPR would not change the outcome of Dinnerstein's illness, the court ruled that the attending physician could take "what measures are appropriate to ease the imminent passing of an irreversibly, terminally ill patient in light of the patient's history and condition and the wishes of her family." [50] The implication here is that the patient's family, along with the patient's physicians, should choose the best course for the patient; the courts should be involved only if family and physician disagree.

Thus, with regard to incompetent patients, the following conclusions may be drawn [43] :

1. Incompetency must be proved, not assumed, especially if the patient appears to make decisions in ways that seem unusual to the physician.
2. With incompetency, priority should be given to following instructions that predate the patient's incompetence.
3. If no written instructions exist, the family should be relied on as the guardian. This should hold unless and until the family makes judgments that seem unreasonable, at which point judicial review should be requested.
4. If written instructions conflict with the family's position, the safest course is to seek an opinion from the court.
5. In rare cases, the courts may intervene from the outset, as when no guardian can be found.
6. Decisions about which therapies are appropriate to withhold or withdraw must be individualized. It is unlikely that a single list of criteria will hold for all persons.

Euthanasia

Euthanasia, from the Greek "an easy or happy death," is defined as the act of putting to death painlessly one who is suffering from an incurable condition (Table 85-1) (Table Not Available) . [51] Only because we now have the technical ability to delay imminent death indefinitely do the problems of active and passive euthanasia, or withdrawal of therapy, arise. Withdrawal of therapy is now considered, *under the appropriate circumstances,* reasonable, humane, and legal. [52] [53] [54] [55] [56] [57] [58] [59] Several courts have addressed circumstances from which we may derive an idea of the appropriate circumstances.

```
1976, Quinlan/New Jersey Supreme Court. The court stated that if
family and physician agreed there is no hope of the patient's ever
emerging from a coma, and the hospital ethics committee consented, ventilator
therapy could be withdrawn. The court acknowledged that this action would
likely result in the patient's death.
```

[55]

```
1980,
Severns/Delaware Supreme Court. The court ruled that it would consider a
request to withdraw therapy from a 55-year-old comatose woman after an
evidentiary hearing to clarify the patient's medical status. The court
stated its preference, however, for action by the General Assembly of Delaware
because of the "community values at stake."
```

[56]

TABLE 85-1 -- Definitions Related to Active Life-Ending Interventions

(Not Available)

Modified from Emanuel [51]

1980, Spring/Massachusetts Supreme Court. The court ruled it was permissible to invoke substituted judgment to withdraw therapy from a severely ill, profoundly demented patient. In addition, while supporting the concept of substituted judgment, the court added that if the judge hearing the case was not persuaded that the incompetent patient's choice, as determined by the substituted judgment standard, would have been to forego potentially lifeprolonging treatment, or if the interests of the state required it, therapy would not be withdrawn. The court further stated that it wanted judicial review of withdrawal before action was taken because it "disapproved the delegation of the ultimate decision-making responsibility to any committee, panel or group, ad hoc or permanent."

[57] [57]

1985, Conroy/New Jersey Supreme Court. When the patient is an elderly demented person with a clearly limited life expectancy, the court determined the following: withdrawal of therapy is not suicide; a living will is significant, whether legally binding or not; what the patient, not some theoretical "reasonable" person, would have desired under the circumstances is significant; the Office of the Ombudsman for the Institutionalized Elderly must be involved in a contemplated action to withdraw therapy and must appoint two physicians to confirm the patient's medical condition and prognosis; and the court has to determine incompetency and appoint a guardian whose approval, along with that of ombudsman, physician, and in some cases the family, is required for therapy to be withheld or withdrawn. This ruling has been criticized as too complicated to be workable, bureaucratizing death, not being in the patient's best interest because it could lead to widespread disregard of the law or to continuation of futile therapy.

[58] [59] [60] [61]

No legal cases have supported active euthanasia. The case for this form of euthanasia is based on two central claims [62] : relieving unbearable pain, which is a medically straightforward rationale, and respecting individual autonomy, which is generally interpreted as a patient's right to take part in treatment-related decisions, even to reject therapy. This does not mean a health-care worker must do everything a patient asks. Indeed, we physicians are obliged to abridge autonomy when it would result in harm. In the case of a patient dying in pain, however, it is difficult to conceive of the harm that would result from a physician's granting a patient's request and making a patient's death less prolonged and agonizing. The cases of active euthanasia we are most familiar with are those of Dr. Kevorkian and "Debbie," both of which gained great national attention. [63] [64]

The uproar created in both the medical literature and the lay literature by these cases must be addressed thoughtfully. Even while criticizing the Kevorkian "series" and the Debbie case, clinician-ethicists have been careful to point out the real fears and concerns that many patients have with regard to their deaths. [65] Dying patients are afraid that their terminal suffering may be prolonged by technology over which they have no control, that they will be "held hostage to our inability or unwillingness to be responsible for knowing right from wrong in each specific situation." [65] Although arguments against euthanasia raise the point that there are no procedural safeguards to prevent abuse, this issue appears to be a lesser consideration to the dying. The concern of one man with a terminal malignancy makes most vivid the fear and anger that coexist in the hearts of many: "If a patient opts for either active or passive euthanasia, it is a craven abdication for the physicians to hide behind moral or religious dogma and deny that person the right to die a pain-free and dignified death." [66] One ethicist holds that, although he is opposed to killing generally, physicians must on occasion actively help to speed death to stop a patient's suffering. [67] That abuses could accrue if active euthanasia were allowed is noted by many investigators, [62] [65] [67] [68] even those generally supportive of the action.

The extreme positions taken by Kevorkian and the Debbie resident are the result of clinicians avoiding the issues of terminality and pain and of granting patients control over their deaths. An explicit and open approach to euthanasia, however, would likely lead to fewer, rather than more, mistakes and abuses. In Holland, for example, four criteria are used in euthanasia cases to determine its legitimacy:

1. The patient must be under severe mental and/or physical anguish, with no prospect of relief.
2. The patient must make the request freely, frequently, consistently, and without coercion; the physician may not solicit the patient.
3. Assisted death may not be an answer to pain, fear, failing care, or loneliness; further, alternatives to euthanasia must be offered by the physician.
4. A colleague must be consulted by the primary physician to confirm the diagnosis and prognosis and the lack of other treatment options and to ensure that all legal requirements for euthanasia have been met.

In spite of the possible benefits of euthanasia, it may be both perilous as public policy and corrosive as medical practice. [62] The public policy concern is centered around the issue of potential involuntary euthanasia. Marginalized and disempowered persons could face discriminatory euthanasia.

Moreover, euthanasia could be used, in our present environment of cost-containment and social-injustice, as a means of "rationing" care. Euthanasia could have a corrosive effect on the practice of medicine by detracting attention from other issues such as the need to improve pain control, patient-physician communication, and care for the dying. Finally, euthanasia could strike a lethal blow at the heart of what it means to be a physician--the social and professional role of physicians as healers would be destroyed. [62]

Data [69] [70] evaluating the Dutch experience with euthanasia and physician-assisted suicide, during the period 1990 to 1995, suggest no decrement in the care given when making decisions that result in the patient's death. Other investigators, [71] however, note that the "slippery slope" border may have been broached. Indeed, a worrisome and disturbing trend, noted in physician interviews, was that 16 of 84 unreported euthanasia deaths were not voluntary; that is, informed consent was not obtained. [69] Fifty percent of these patients were judged incompetent, and 95 percent of the time, discussion took place with the family and/or colleagues prior to the act of euthanasia. [70] Nevertheless, the patients were killed without their consent. In the patient groups studied, the frequency of euthanasia/physician-assisted suicide was approximately 2 percent. In another Dutch study of homosexual men with AIDS, the frequency of euthanasia/ physician-assisted suicide was approximately 24 percent, a 12-fold difference. [72]

How then do we as physicians handle cases in which a competent patient makes an informed request for assisted death? There are several possibilities. One is to use a variation of the Dutch system, in which strict criteria would have to be met prior to euthanasia; the cases would be carefully scrutinized after the act by state or county judicial officials. This system would clearly require some changes in the penal code as well as in the ethical codes of the medical profession. Our opinion, and that of others, [73] is that legalization of euthanasia would multiply the problems we now face; in attempting to protect patient autonomy and to prevent abuse, the rights of patients and physicians would suffer. Another possibility is to handle euthanasia as is currently the case, without any clear criteria but by implicit agreement. Euthanasia is performed in the United States today, but without any checks or balances. This approach is simply an adaptation to legal constraints. The ideal system

for voluntary euthanasia should be a hybrid. Patients, physicians, nurses, and families would discuss and choose (or reject) the option of euthanasia. As in the Dutch system, a hospital ethics committee (or other appointed board) would ensure that the four criteria determining legitimacy were met; if these were fulfilled, euthanasia could be performed. The committee would ensure that the potential for abuse was minimized; this safeguard, in turn, would provide a rationale to keep our legal colleagues out of the clinical decision-making arena, except in cases of abuse. Indeed, this system would likely ensure that abuse would be kept to a minimum. [74] [75] Whether the Patient Self-Determination Act and emphasis on advanced directives has made it less difficult for health workers to take part in either active or passive euthanasia is unclear. In our institution, however, querying patients on admission as to whether they have an advanced directive and ensuring, whenever possible, that the issues involved with terminal care are discussed before patients become critically ill have made end-of-life conflicts less common. One study suggests that advanced directives are frequently difficult to interpret and that a surrogate decision maker be appointed at the time the advanced directive is drafted. [76]

Finally, physician-assisted suicide has, as a concept, moved into our collective consciousness. This variation on the theme of life-ending interventions involves the prescription of, usually, a lethal quantity of a drug by request to a terminally ill patient (see Table 85-1 (Table Not Available)). Although the Oregon physician-assisted suicide law was invalidated by the United States Supreme Court, a more narrowly crafted law could possibly meet with the Court's approval. Thus, the concerns raised earlier with regard to active euthanasia will be of no less concern with regard to physician-assisted suicide. [77] The ultimate role that physician-assisted suicide will play in our society, and whether it may be rendered irrelevant by appropriate use of hospice care, [78] remains to be seen.

We have reviewed some of the major medical-moral questions of our time. Moral decision making is an area in which people of goodwill can disagree and in which ambiguities persist. Because of the ambiguity, moral decisions require wide discussion and debate; this may be frustrating to the practicing physician, but it is a necessity from a moral point of view. Moral questions cannot be answered in private or by monologue because they are social as well as personal.

Ethics and Research

Are there special problems created when human subjects are used in medical research? In 1966, Beecher [79] reported that 12 of 100 consecutive human studies published in a well-referenced medical journal appeared to be ethically questionable. In another part of this protocol, he found 50 examples of studies that appeared to contain ethical violations. Some of the categories of research that raised ethical questions included evaluations of physiologic effects of known toxic drugs, pathophysiology of disease states, new drugs, new invasive techniques, new treatments for a disease that had accepted therapy, and studies that appeared to have no basis in science. Beecher concluded that three things were necessary to ensure that ethically sound research would be carried out in the future: (1) true informed consent; (2) intelligent, compassionate, informed, and responsible principal investigators; and (3) an unmistakably clear message from journal editors that no data are so important that they may be obtained unethically and that data thus obtained will not be published.

Although true informed consent may be difficult to attain, its importance as a legal and moral principle is unquestioned. [80] [81] In fact, based on the difficulty of attaining true informed consent, some investigators have suggested that a surrogate system be used as an adjunct to institutional review of proposed projects. [81] The technique involves having persons who are not candidates for a protocol listen to the investigator give the rationale and risks of the project. The surrogate may ask questions or make comments at any point in the process. It was thought that such surrogacy, although not substituting for the research subject's personal decision making, would provide comments, questions, and criticisms that may not normally arise during the institutional review

process. A further aspect of the problem of informed consent is whether certain captive populations can give informed consent because of their coercive environment. [82] [83] For example, if consent is to be free and informed, the subject must be able to withdraw from the project without adverse consequences. For example, short-term studies involving small numbers of prison inmates may be ethically appropriate if the investigator is not a prison authority and if informed consent is given several times over the course of the study. [82]

Even in noncaptive populations, significant barriers impede true informed consent. [84] One of these barriers is that, rather than being a series of discrete events, medical decision making usually evolves, and, although patients may want to be informed, they may not want to be involved in the decision making. In addition, physicians may view informed consent as a legal obstruction, rather than as an integral part of excellent care. Obtaining informed consent from any patient considered a candidate for a research protocol merits special emphasis. Equally important, a patient's physician has the responsibility of the "ethic of agency" and therefore cannot hesitate to encourage a patient to withdraw from a protocol if it appears to be against that person's best interests.

Finally, a very disturbing aspect of research that increasingly has come to the attention of both the scientific community and the public at large is scientific fraud, an extreme form of misrepresentation. There are three ways an investigator can make inaccurate statements: (1) justifiable mistake, by which the scientist misunderstands a phenomenon and, thus, misrepresents it; (2) negligence or carelessness, by which data that would prove or disprove a hypothesis are overlooked; and (3) fraud, by which facts are deliberately misrepresented or data are forged. [85] Although any scientist can, and most do, make mistakes, some have deliberately sought to mislead their colleagues. Whether this is a result of "bad" persons or a "bad" scientific system cannot be resolved here. [85] Research directors, department chairpersons, and the entire scientific community as well as coauthors, editors, and reviewers have a responsibility to be vigilant and rigorously honest to help prevent misrepresentation. [85] [86]

One editorial suggested that guidelines now in place will allow editors of biomedical journals to deal with allegations of research fraud better. [87] Furthermore, the authors commented favorably on criteria devised by the Harvard Medical School [87] (Table 85-2) (Table Not Available) , which may begin to deal not with the results of fraud, but with its prevention. For instance,

TABLE 85-2 -- Guidelines for Prevention of Research Fraud

(Not Available)

From Angell [87]

the Harvard criteria address the issue that, to improve chances of promotion or tenure, some people may be prone to take shortcuts to increase their numbers of publications. Unfortunately, the jump from shortcut to outright fraud may be small.

MEDICAL MALPRACTICE

One of the most frightening experiences in the life of an anesthesiologist may be receiving a subpoena for alleged malpractice. A conscientious anesthesiologist can be devastated by such an experience; indeed, suicide as a consequence of this experience is not unknown. Although representatives of the plaintiff's bar may proclaim that the malpractice crisis is the result of bad doctors, [89] and although physicians frequently attribute the spiraling number of alleged malpractice cases to greedy attorneys, [89] the truth is certainly somewhere in between. There clearly are patients who suffer harm because standards of care are not followed. Likewise, there are other patients who suffer an untoward event despite excellent care by the anesthesiologist. This chapter does not settle this debate but, rather, addresses factors that determine the outcome of such litigation.

The Process

Although untoward events during anesthesia can lead to dramatic adverse outcomes, in other situations, the severity of the alleged damage is in the eyes of the beholder. In either case, when an adverse or unexpected outcome occurs, the onus is on the plaintiff to prove that the outcome resulted from substandard care. [89] The defendant must demonstrate that the level of care administered to the patient was acceptable, based on the standards of that specialty and subject only to the surrounding circumstances (which may allow for a lesser standard of medical care in rural communities, where sophisticated equipment and subspecialty care are not available). Otherwise, the national standards of the board-certified specialist, especially in anesthesiology, apply. [89] In many situations, standards as such do not exist. Furthermore, adverse events occur in medicine without an obvious cause, in which case the cause is determined by exclusion or, in some cases, speculation. In this situation, a jury, virtually always composed of nonphysicians, is left to decide what caused the untoward event and whether it was due to the negligence of the physician.

It is curious to us that, even though a physician may go through a detailed medical history and physical examination of the patient, appropriate laboratory tests, and a differential diagnosis and still not pinpoint the cause of the medical problem, a jury of nonphysicians is expected to determine, by "a preponderance of the evidence," the cause of an alleged adverse outcome. The jury's decision is based on information gleaned from direct and indirect questioning of medical experts for both the plaintiff and the defendant. Persons who testify as medical experts may not necessarily be considered expert by their peers, and yet the expert's testimony, for what it is worth, may be admitted as such by the courts. Although the legal system in the United States professes that a defendant is innocent until proven guilty, in the

case of alleged malpractice, if the defendant cannot prove an alternative cause of the adverse outcome, the physician may be judged guilty of malpractice. Although an identifiable cause of death at autopsy may assist in a physician's defense, many juries are led to believe that the physician has erred if the autopsy does not conclusively demonstrate an alternative cause of death. This logic precludes the possibility that an adverse outcome or death may occur without obvious anatomic cause. It further, for lack of a specific, established cause of the outcome, assumes that the defendant must be guilty of negligence, although the care delivered to the patient may have been completely consistent with accepted standards of practice. The legal process of identifying a diagnosis, evaluating whether the therapy was appropriate, and judging the competence of the physician in the courts is an environment completely foreign to a person whose entire life has been spent practicing medicine. This chapter deals with some of the elements that contribute to this process.

Patient Rapport

Perhaps the single most important factor in whether or not a lawsuit is filed is the rapport the physician has with the patient. The practice of anesthesiology is such that the anesthesiologist can spend a significant amount of time in the preoperative and postoperative periods establishing rapport with the patient or, conversely, can limit time with the patient, who then thinks of the anesthesiologist as "that doctor behind the mask in the operating room." Clearly, a patient will be far more reluctant to initiate a lawsuit if there is confidence in the physician and if the physician has demonstrated compassion, welcomes the opportunity to answer the patient's questions, is attentive to the patient's psychologic as well as medical requirements, and is ever present. The preoperative and postoperative visits, therefore, become extremely important, not only in determining the appropriate choice of anesthesia and whether postanesthetic complications occurred, but also in cementing a mutually satisfactory relationship.

During the preoperative visit, the anesthesiologist should give patient and family ample opportunity to ask questions and to receive answers. At no time should questions be evaded, nor should the patient be given answers that only reflect what the physician thinks the patient wants to hear when that differs from the appropriate answer. When options exist in anesthetic management, these options should be explained to the patient, but the anesthesiologist has a responsibility to recommend the method that he or she believes is indicated and to explain the reasons for the selection. Potential complications should be explained; however, the physician must use some discretion. There is no question that some patients really do not want to hear all the potentially terrible things that can happen to them under anesthesia. It is possible to frighten patients to the point that they refuse operations. In this situation, if an adverse result occurs, the anesthesiologist may be sued for dissuading the patient from obtaining the appropriate care. However, we are unaware of any physician who has been held liable by the courts for such action. Therefore, in making it clear to the patient that, although anesthesia is safe from a statistical standpoint, it is not innocuous, and severe complications can occur, even to the point of death, the patient should receive as detailed a description as wanted. If the patient does not want to hear all the complications or the "gory details" and tells this to the anesthesiologist, we personally believe that the patient should be spared this detailed information. In this case, a note should be written, dated, and signed in the patient's medical record.

Many institutions use a common-consent form for both surgery and anesthesia. Although this is acceptable, a separate consent form for anesthesia is preferred; it can be tailored more directly to the anesthetic management. The contents of this consent form should either be read by the patient or read to the patient, as appropriate, before it is signed, and certainly any questions that arise should be addressed. A brief narrative note, either on the consent form, or a separate preanesthetic form, or in the progress note section of the patient's record, should record any pertinent events that occurred during this process, any discussion of importance, and the anesthetic plan, if a specific plan was agreed on at that time. When a specific anesthetic plan is presented to the patient and agreed on, the patient must be informed that the plan may have to be modified as conditions dictate intraoperatively. Because patients, not infrequently, are moved from one operating room to another to facilitate efficient operating room scheduling, if the anesthesiologist practices in a group setting where the actual anesthesiologist or anesthetist may differ from the one who conducts the preoperative visits, the patient should be so informed, particularly if the patient requests such information.

Policies and Procedures

Each department of anesthesiology should have a policy and procedure manual (Chs. 79 and 82). All too often, preparation of these manuals is delegated to administrative personnel who may have little knowledge of the practice of anesthesiology. In other circumstances, a manual may be adopted verbatim from another institution. When this occurs, it is not uncommon that the manual guiding practice procedures conflicts with the actual practice in that institution. This creates an intolerable situation for the defense attorney, who then has the responsibility of defending both the institution and the physician when the standards of practice differ

between them. Although there may be common policies and procedures among institutions, many are applicable to one institution but are not appropriate for another. Therefore, it is essential that policies and procedures manuals be individualized. Responsibility for development of these manuals should rest with the chief or chair of anesthesiology within the institution. It is the responsibility of each anesthesiologist who practices within the institution to be familiar with the policies and procedures of that institution. Revision of these manuals on a regular basis ensures that the policies and procedures specified are appropriate and enforceable and that outdated methods or methods impossible to follow in that specific institution are eliminated. We recommend that these manuals should be reviewed and updated by the chief of anesthesiology at least annually.

Preoperative Preparation

During the preanesthetic visit, it is essential that an adequate history and physical examination be available (Chs. 23 and 25). Furthermore, supplemental information must be gathered as appropriate. For example, frequently the patient's other physicians do not elicit or record information important to the anesthesiologist, such as airway anatomy, drug allergy, previous anesthetic history, and familial disease with anesthetic implications. The anesthesiologist should know the intricacies of the patient's medical problems and treatment. For elective surgery, patients should be in optimal health whenever possible. Anesthesiologists frequently are caught between the surgeon and the patient in regard to the timing of the procedure. This conflict may occur because the surgeon influences the patient's choice of anesthesiologist and because "cooperative" anesthesiologists may be preferentially assigned to more profitable patients. It is all too easy to overlook, or to minimize, severe but treatable medical problems to meet an operating room schedule. Fortunately, for the majority of patients, this seldom results in a severe, irreversible adverse occurrence, yet it is not a practice that should be condoned. Furthermore, if an adverse event does occur, the onus is on the anesthesiologist to justify why anesthesia was administered for an elective procedure when further work-up or treatment would possibly have made it safer. To state that the surgeon insisted on proceeding even though it was an elective procedure is not an adequate defense.

In the legal climate of joint and several liability, a physician who is found even 1 percent at blame may end up funding virtually the entire settlement if the other physician is uninsured and does not have sufficient assets to cover the judgment. [89] Therefore, if the surgeon is shown to have exerted undue pressure on the anesthesiologist to proceed with a case when the latter thought it should be postponed pending further testing or therapy, it may be very costly financially for the surgeon. It is in the best interest of both parties not to subject a patient to elective anesthesia and surgery when additional time for evaluation and treatment will improve the patient's physical status.

Importance of Records

The medical record is the cornerstone of defense in a malpractice suit. If information is missing from the medical record, the plaintiff's attorney will argue to the jury, "If it is not on the record, it did not occur" or will question the anesthesiologist's motive for not recording the data. It is imperative, therefore, that the anesthesiologist record all pertinent events on the record in a timely fashion. Should an emergency event occur that necessitates the anesthesiologist's undivided attention, someone else should be enlisted to serve as a scribe, if possible, to continue recording events. The routine elements of an anesthetic record, such as gas flow rates, drug dosages, timing of events, and frequent vital sign recording, must be performed diligently.

With emerging technology, the anesthetic record can be prepared electronically via automatic processing. [90] Such records can be extremely helpful, but when erroneous data are entered on such a record, they must be noted immediately. These recorders not only can note the patient's vital signs but also can be used to monitor aspects of the case such as equipment, gas flows, and neuromuscular transmission. When a monitoring tool is deliberately interrupted, such as interrupting capnographic monitoring of end-tidal carbon dioxide tension when an endotracheal tube is inserted, it should be noted on the automatic record so that it does not appear as if it were an adverse event, such as a ventilator disconnection.

Detailed attention to the record should not stop the moment the anesthetic agents are discontinued. All events that occur up to the time that the patient is left in the care of the nurse in the postanesthesia care unit (PACU) should be appropriately recorded. Before leaving the patient in the care of the PACU nurse, the anesthesiologist should note and record the status of the patient. A PACU or Aldrete score [91] should be recorded and initialed by both the PACU nurse and the anesthesiologist. This method minimizes the potential for subsequent disagreement between nurse and physician if both are named in a lawsuit. If the patient is not stable on arrival to the PACU, it is the anesthesiologist's responsibility to remain with the patient, or, before leaving the patient's bedside, to ensure that adequate personnel are available to care for the patient appropriately. To leave an unstable patient to press on with an elective operating room schedule is unacceptable.

Monitoring

We have heard anesthesiologists claim that they do not want to monitor the patient extensively with capnography, pulse oximetry, automatic record keepers, and the like, because this would only provide additional material for a plaintiff's attorney (Chs. 28 - 38). We personally believe that we are obligated to monitor all appropriate systems for each patient when we have the capability to do so. Furthermore, we believe that recording the data gives a clearer picture of the cause of adverse events and, thus, facilitates the defense of an anesthesiologist who has practiced appropriately. At a minimum, the Harvard standards should be followed. [92] In addition, monitoring by pulse oximetry and capnography is now considered the standard of care in most, if not all, parts of the United States. [93]

Risk Management

Physicians should be aware of the incident-reporting requirements of the hospitals where they practice and their duty to report adverse incidents to the insurer as delineated in the insurance contract (Ch. 79) . When an unexpected event occurs, the appropriate individuals must immediately be informed, notwithstanding that, when two or more health-care professionals are involved in the same incident, there is the possibility for conflicts of interest, which can be exacerbated by financial considerations when different insurance companies or self-insurers are involved. It is often required by law and/or hospital bylaws and is in the physician's best interest to contact the hospital risk-management office to review the case with the risk manager, with the concurrence and full participation of all interested parties.

When the cause of the untoward event is not readily apparent, convening a meeting of a medical review committee, which should consist of all persons involved in the care of the patient at that particular time, such as the anesthesiologist, surgeon, circulating nurse, and scrub nurse, is frequently helpful.

Such committee meetings called to evaluate and improve the quality of health care must be structured to protect them from discovery and subpoena. [94] Many states have passed laws to encourage the open and candid review of incidents by protecting peer review reports from discovery or from use as evidence; therefore, it is very important that the proceeding be deemed a peer review. In states where such laws do not exist, counsel representing the involved parties should be present, so that the attorney-client privilege will apply. A senior member of the staff who was not directly involved in the care of the patient should chair the meeting and play devil's advocate, to ensure that all pertinent material is brought forth, whether or not it is a matter of record in the patient's chart. Areas of disagreement among participants in the care of the patient should be aired at that time to help uncover the facts of the case and to put the puzzle together.

Recordings of these meetings should be kept by the risk manager, insurers, and legal representatives, so that, if a claim or suit were filed in the future, the defendant could review the material collected at the time of the event and would not have to reconstruct the facts from memory several months or years after the event. Needless to say, it is extremely difficult, if not impossible, to reconstruct events accurately subsequent to the filing of a lawsuit and notification thereof years after the event, which can happen. Moreover, insurance carriers require that they be promptly notified of an adverse outcome that could result in a liability claim. Failure of timely notification of the carrier may compromise coverage and may result in denial of responsibility on the part of the insurance company for the case in question, if the carrier can establish that a delayed notice prejudiced its ability to settle or defend the suit.

Expert Witness

Frequently, the outcome of a suit does not depend as much on exactly what was or was not done by the physician in the care of the patient as on the opinion of "expert witnesses" for both plaintiff and defense. For some time, many physicians were reluctant to serve as expert witnesses, particularly on behalf of the plaintiff.

This resulted in the plaintiff's attorney's frequent use of physicians who proclaimed to be expert in many fields, but whose credentials were at times unimpressive, to say the least. If the patient clearly has been harmed by inappropriate care from a physician, it is the responsibility of the medical community to facilitate the process and to deal with the physician's lack of competence. On the other hand, if the patient suffered an untoward event despite appropriate therapy, it is inappropriate for a physician, no matter what the compensation, to distort the facts or to give questionable professional opinions that could aid the attorney in convincing a jury that malpractice has been committed. Some states have passed legislation that defines "physician expert witness" according to specialty or percentage of time devoted to clinical practice, teaching, or both. One such state is Ohio, where legislation passed in 1991 states:

> No person shall be deemed competent to give expert testimony on the liability issues ... unless: (1) The person is licensed to practice medicine and surgery, osteopathic medicine and surgery, or podiatric medicine and surgery by the state medical board or by the licensing authority of any state; (2) the person devotes three-fourths of his professional time to the active clinical practice of medicine and surgery, osteopathic medicine and surgery, and podiatric medicine and surgery, or its instruction in an accredited university.

[95]

Legislation of this type limits the use of "professional experts," who may testify on virtually any medical subject, although they may never have been trained in or practiced the specialty in question in recent years. The Supreme Court of the United States signaled in 1993 that it was ready to tackle the subject of the quality of science acceptable in court or, at least, to set some standards for expert scientific testimony in court. [96] To date, this has not occurred. Any resultant ruling by the Supreme Court will have an enormous impact on medical liability, not only for alleged malpractice, but also for product liability. Absent such legislation, the jury is left to weigh the credentials of the expert in determining the level of credibility to give to the expert's testimony.

Unfortunately, a lawsuit frequently seems to be played in the courtroom as a sporting event, and the players seem more engrossed in winning or losing than in determining justice. This results from the adversary system, by which "justice" is done by the jury or judge, who decides between two advocates. In addition, the influence of television has had a dramatic effect on the way many lawsuits are tried. In part, this happens when jurors, and even attorneys and judges, watch too many legal dramas and try to emulate the actors and actresses in those shows. Even more important, lawyers who know they are being televised may have a tendency to "act" more than "practice law." The legal field of malpractice has become a very specific subspecialty, and many attorneys trying such cases frequently have acquired a great deal of medical knowledge applicable to the specific case. It is in the best interest of both plaintiff and defendant to have attorneys of the highest quality in this field represent them. Anything less than this places them at a distinct disadvantage in the legal process and in the courtroom.

Establishing Standards of Care

Establishing the standard of care is frequently based on the testimony of expert witnesses rather than on published authoritative documents. Many physicians have resisted attempts to develop and accept strict standards, which could dictate specifically what care patients should receive. These physicians argue that medicine is not a precise science, and a physician's judgment should be exercised in determining what is best for each individual patient. However, there has been increasing interest in the development of practice parameters, which may serve as a guide to acceptable practice. Some clinicians think that, if a physician adheres to such practice parameters but an adverse outcome nevertheless results, simply following such parameters may prove helpful in the defense against an alleged malpractice suit. The

---

American Society of Anesthesiologists (ASA) has been quite active in developing a series of parameters related to the specialty of anesthesiology. These parameters, as well as standards, guidelines, and statements related to practice and patient care issues, have been published by the Society. [93]

Assigning Responsibility

Not infrequently, when an adverse reaction occurs during anesthesia, the question of who is legally responsible arises. A lawyer for the plaintiff frequently sues everyone who has come in contact with the patient. Anesthesiologists, certified registered nurse anesthetists (CRNA), surgeons, operating room nurses, postanesthesia care nurses, and hospitals have all been sued individually as well as collectively. [97] One person may be liable for the acts of another under the doctrine of *respondeat superior* or on a "right to control" theory. The law must not be clear on this point, however, because courts have not applied respondeat superior consistently. In the past, a Colorado court, holding a surgeon liable for the acts of an independent licensed anesthesiologist, stated that "once the operating surgeon assumes control in the operating room, the surgeon is liable for the negligence of all personnel working under the surgeon's supervision." [98] The question must be raised, however, whether the surgeon has the necessary level of expertise to "supervise" the anesthesiologist. We maintain that he or she does not. The Supreme Court of Kansas ruled that the surgeon is generally not liable for the negligence of an anesthesiologist but is liable for the negligence of a nurse anesthetist under the doctrine of "captain of the ship." [99] The Supreme Court of West Virginia in 1987 rejected the "captain of the ship" doctrine and concluded that the surgeon was not responsible for the alleged negligent acts of a nurse anesthetist who was working under the medical direction of an anesthesiologist. [100]

Attempting to clarify responsibility in this area often has led to debate. [101] [102] Our position is that the practice of anesthesiology by an anesthesiologist is a specialty unto itself, just as the practice of surgery is a medical specialty of the surgeon. An anesthesiologist who personally administers anesthesia to a patient is alone responsible for the outcome. If a CRNA administers anesthesia, the picture becomes clouded by the employment relationships of the CRNA. Most state laws that govern the practice of CRNAs license them to practice under the medical direction or supervision of a licensed physician. In that situation, if the CRNA is both employed and medically directed by an anesthesiologist, clearly both the anesthesiologist and the CRNA should be held liable. If the CRNA is employed by the hospital and is medically directed by an anesthesiologist, all three should be held liable. If the CRNA is self-employed and is performing anesthesia under the medical direction of the surgeon, then both the CRNA and the surgeon should be held liable, whereas if the CRNA is employed by the hospital and is medically directed by the surgeon, in our opinion, the hospital, the CRNA, and the surgeon all should be held liable. In this situation, if the surgeon takes the position of knowing little about anesthesia and states that the CRNA is more expert than the surgeon in this area, we think that this is not an adequate defense, because, unless one is prepared to diagnose and treat the medical problems that occur, one cannot medically direct the services of others. Several state legislatures have considered legislative proposals to establish CRNA as independent practitioners not requiring medical direction or supervision by a licensed physician. One would think that such laws, if passed, would make the CRNA solely responsible for his or her actions. However, we are not aware at this time of any cases tried in which claiming that the CRNA was an independent practitioner released the physician from liability.

Preparing for the Defense

We believe that the most important single item in the defense of an anesthesiologist whose practice is appropriate and who has been sued for alleged malpractice is the quality of the defense attorney. It is in the anesthesiologist's best interest to have the most knowledgeable individual available, even if this means hiring counsel separate from that hired by the anesthesiologist's insurer. It is then imperative that the attorney be provided with all the facts of the case, whether they are perceived to be beneficial or detrimental to the defendant. It is very difficult for an attorney to deal with surprises in court. Furthermore, the selection of expert witnesses should be a decision made in concert by the attorney and the defendant anesthesiologist. It is important to obtain experts who are knowledgeable in the field and who also will make a good court appearance before lay jurors.

During the process of working through the defense, there will be a period when the defense attorney essentially conducts an independent investigation. The defendant anesthesiologist, the risk manager, and anyone else involved in the suit must be open and frank in providing all the details about the care of the patient, again, whether or not they are perceived to be important or beneficial. The expert witness should be asked for a frank opinion about the case and, even if this person believes in the defendant's cause, should be asked to play the devil's advocate to ensure that all pertinent information is accounted for during the preparation. The expert should also be asked to predict the strategy of the plaintiff's expert, even if it must be purely speculative. Such speculation may provide information that will help the defense attorney to prepare for dealing with the testimony of the plaintiff's expert.

Statements regarding the case should be given only to the risk manager and to the defendant's attorney. Whether it is appropriate to share information with others is a decision that should be made by counsel. Anything said in deposition may be read verbatim before the jury in court. Therefore, before giving any deposition, the

defendant should review the patient's record and also should study the standard of care, as well as appropriate pharmacologic, physiologic, and clinical-care decisions, that may be addressed by the opposing attorney. Giving a deposition without prior review of the record and then reviewing the record before a court appearance and giving different answers at that time can be disastrous. In fact, some attorneys use this technique to impeach or frustrate the witness or to cause the witness to decompensate before the jury. The medical defendant should always retain composure and should answer questions in a forthright and professional manner. After all, it is the appearance that the defendant projects to the jury that frequently

---

makes the difference in whether the defendant is perceived as the type of doctor they would want to treat them. This perception has a strong psychologic impact on the jury's final decision.

In short, it is the attentive, compassionate, meticulously vigilant physician who strives to maintain currency in the field who is least likely to be judged negligent in the care of a specific patient. Anything short of this type of practice increases the exposure to lawsuits and the potential for financial loss.

Financial Impact of Malpractice Claims

It is well recognized, even in the legal literature, that the dramatic growth of medical malpractice litigation in recent years has contributed significantly to an overall increase in health-care costs in this country. [103] Although lawmakers, physicians, and others have proposed numerous solutions to curb the crisis, these proposals generally have been ineffective. Some states have legislated reforms such as arbitration panels, a cap on recovery for noneconomic damages, and a briefer statute of limitation. Each alternative has weaknesses and strengths. For example, whether an alleged claim for malpractice is heard by an arbitration panel frequently is at the discretion of the plaintiff, not the defendant. Placing a cap on recovery for noneconomic damages is a rational approach, particularly because pain and suffering are subjective, not objective, factors, and tolerance to discomfort varies widely among people. Although some states have passed legislation regarding these issues, on the appeal of plaintiff's bar, some have overturned it as unconstitutional. Still other states have not addressed these issues at all. We believe the ultimate answer to this costly problem is rational tort reform that is uniform among the 50 states, rather than sporadic and independent action by each state.

The legal literature refers to the finding that "nuisance suits" are frequently filed by attorneys who are confident that the suit will never go to court because the defense costs of such suits may well exceed what would be acceptable in settlement. [103] Indeed, in many cases, insurance companies settle such suits out of court even though that is not the wish of the physician, who is the client. In such situations, the physician has little or no recourse and must accept the implication that some may infer--that he or she performed in a manner that was below standard, even though there may be no evidence of that. Nevertheless, the insurance company can make such a decision based on finances, rather than on whether the physician was innocent or guilty. Any such settlements should contain statements that the physician admits no guilt and is held harmless from further action in this matter.

In some situations, physicians have countersued the plaintiff's attorney, the claimant, or both and have been successful. [103] This process is very difficult and potentially very costly, however. Not only does a physician have to have been tried already and to have received a defense verdict in court, but he or she may then have to prove that "malicious prosecution" has occurred. For an action against alleged malicious prosecution to succeed, the plaintiff, in this case, the physician, must prove that the suit was instituted without probable cause, that the suit was decided in favor of the physician because the suit was instituted maliciously, and that the physician sustained special damages. [103] Even the last point can be difficult to prove. In one case, the court held that litigation expenses, increase in insurance premiums, and injury to professional reputation did not constitute special damages. The rule in Georgia is even more extreme, where the court concluded that a "cause of action ... will not lie absent a showing that the defendant was arrested or his property attached." [103] Thus, in some states, a patient who alleges out-of-pocket expenses or inability to function in his or her chosen field of employment as a result of injury from the alleged action of a physician can be reimbursed for economic damages based on past and future expenses and earning potential for a lifetime and can obtain hundreds of thousands, if not millions, of dollars. When a physician who is harmed brings forth an action, however, the same elements of determining economic damages do not apply. Such an inequity results in a double standard and should not be permitted to stand unchallenged.

LEGAL CONTRACTS IN MEDICAL PRACTICE

Contractual Agreements Restricting the Right to Practice Medicine

Apart from state licensing requirements, a contractual agreement can limit the right to practice when and where an anesthesiologist chooses. An anesthesiologist encounters noncompete agreements in a number of situations. As a condition of employment with a hospital, an anesthesiologist may be asked to sign a noncompete agreement, which prevents the applicant from seeking employment or privileges at a competing hospital during and after termination of employment with the contracting hospital. An anesthesiologist may be required to sign a similar agreement on joining a group practice, in large part because the new anesthesiologist will have access to the group's existing patients. Moreover, when an anesthesiologist in private practice sells that practice, the buyer will seek to acquire the goodwill of the practice and therefore may require a noncompete agreement. Finally, an indirect form of agreement can also restrict competition; for example, hospitals sometimes enter into an exclusive contract with a physician, which gives that physician access to the hospital and excludes the physician's competitors.

The legal system has reacted with mixed views toward contracts that limit the ability of one party to conduct its trade or business freely. On the one hand, the capitalistic system on which our legal system is based is premised on the ability of private parties to contract freely among themselves. The civil legal system exists to uphold such contracts. On the other hand, the Sherman Anti-Trust Act [104] was enacted to make contracts that restrain trade unlawful.

Almost any business contract literally restrains trade simply because the contract binds two parties to conduct business in a prescribed manner. The United States Supreme Court, therefore, established a "rule of reason," by which a court looks at a contract in light of all the facts, circumstances, and the advantages gained by the contract, as a

whole, to determine whether the restraint on trade is reasonable. [105] However, some restraints are considered so egregious that they are held to be per se unlawful regardless of any legitimate business reasons for the restraints; for example, those that involve fixing prices, [106] those that enable one party to establish or maintain a monopoly on a market, [107] those that enable a group of competitors to boycott another competitor, [108] and those that involve an illegal "tying" arrangement, that is, a contract by which one party having market power to control a product "ties" the purchase of that product (the "tying" product) to the purchase of a second product (the "tied" product) (discussed in detail later). [109]

Covenants Not to Compete

When a covenant not to compete is challenged as a restraint on trade, the challenge is almost always initiated by one of the parties to the contract itself, namely, the physician who agreed to the covenant. This is contrary to per se violations, which usually involve a claim by a third party that the contracting parties' actions were designed to injure the third party; for example, entering into an agreement to fix prices or to exclude the injured party from a market. Therefore, covenants not to compete are judged by the rule of reason, and courts will strike down a covenant only if the restraint on trade and resultant injury are greater than the reasonable interest of the party seeking to enforce the covenant.

Noncompete Agreements in the Sale of a Practice

Generally, noncompete agreements ancillary to the sale of a medical practice are enforced if the agreement is supported by consideration, is reasonable in scope, is protective of the buyer's legitimate business interests, and is not unduly harmful to the public. Every contract must be supported by consideration to be enforceable, regardless of whether the consideration is adequate. Generally, a noncompete agreement given in exchange for a practice's goodwill is supported by adequate consideration, because the noncompete agreement is intended to preserve the goodwill being acquired. [110] However, a noncompete agreement ancillary to the sale of a practice may be void for lack of consideration, if separate consideration is not paid and the practice's goodwill is not purchased (when only tangible assets are transferred). Likewise, a noncompete agreement entered into subsequent to the sale of a practice is not supported by consideration, absent separate, specific consideration given in exchange for the noncompete agreement.

Most of the cases that have enforced noncompete agreements against a physician turn on the question of the reasonableness of the restriction. Cases look to whether a particular restriction is necessary to secure the benefits and goodwill purchased and whether the restriction unnecessarily injures the rights of the seller or the public. The very nature of the service rendered by a physician to a patient is personal; when a physician contracts away the right to serve a particular patient, the patient, not the physician, may suffer the greater loss. Therefore, before enforcing a noncompete agreement involving physicians, the courts look carefully at the public interest, the benefits gained from the agreement, and the harm caused by it.

If the sole purpose of the covenant is to ensure that the seller is excluded from competing with the buyer (as opposed to protecting the goodwill purchased by the buyer), then the exclusion bears no relation to the tangible benefits of the purchase, and the noncompete agreement is unenforceable. For example, a noncompete agreement is unenforceable if it bars an anesthesiologist from practicing not only in the town where the practice is located but also in another county not served by the practice. [111] The issue here is not the geographic scope of the noncompete agreement but the tangible benefits bargained for in connection with the acquisition of the practice. Thus, if the practice serves several communities, the noncompete agreement may extend to all those communities, but not to additional communities into which the buyer merely seeks to expand. Similarly, an agreement that excludes a seller from competing with another practice owned by the same buyer in another community is not enforceable. [111]

Whether a covenant not to compete injures the rights of the seller depends on the reasonableness of the covenant's time and territory restrictions. Therefore, a covenant not to compete should specify a definite duration and a definite geographic area. Covenants that are unlimited in both time and area are not likely to be enforced. [112]

In looking at the time period specified by a covenant, courts are more liberal when the covenant is connected with the sale of a business, as opposed to an employment contract. Because the goodwill of a business is usually built over an extended period of time, contracts not to compete within a limited area for an unlimited duration have been enforced in some courts, [113] but it is more likely that the court will apply a time limit to a contract of unlimited duration. [114] Time restrictions of up to 10 years in connection with the sale of a business have routinely been held to be reasonable.

Courts scrutinize the territory covered by a covenant not to compete more carefully than the time limits. Covenants not to compete in a particular community or county served by a practice are routinely considered reasonable. The larger the territory, the more carefully the court scrutinizes whether the practice serves a sufficient number of patients in the outer reaches of the restricted territory to justify imposing a greater restraint on the seller. As early as 1946, one court acknowledged "the reduction of barriers of space and time made possible by modern transportation and communication," in enforcing a covenant not to compete covering more than one

county. [115] Thus, it is possible for a court to find a covenant overly broad if it covers all of Los Angeles County, but valid if it covers several sparsely populated counties in Alaska. However, a restricted territory's reasonableness also depends on the service provided. A covenant not to compete against an anesthesiologist who, with a particular sophisticated specialty, serves patients from a broad area is more likely to be enforced over a larger territory than one sought to be enforced against a general practitioner who serves patients from a particular neighborhood.

A covenant that is found to interfere unduly with the interest of the public will not be enforced. Thus, the court must be satisfied that, if the agreement is enforced, other

physicians in the area can serve the community. Although early courts considered only the number of practitioners in an area, without regard to specialties, an anesthesiologist seeking to avoid a noncompete agreement would be permitted to introduce evidence that other anesthesiologists are lacking in the community. A Nebraska court, more than 70 years ago, in a case involving a proctologist, considered not only whether there were other proctologists in the area but also whether the other physicians were qualified to practice "the seller's method of proctology." [116]

If the physician's recognized methods of treatment are unique in the community, a court could carve out an exception to the covenant and allow the physician to offer the unique services but not the readily available services. For example, a Texas court enforced a covenant not to compete against a radiologist, but it permitted the radiologist to perform certain subspecialties of radiology that were not generally available from other radiologists in the community. [117]

Perhaps the most difficult issue in these cases involves the rights of patients. Should a physician have a right to contract away a patient's right to the physician's services? If a patient had no other options, the court would void the noncompete agreement as contrary to public policy. However, when other physicians are available, a patient does not have specific rights to the services of a particular physician, because the desire of the patient is outweighed by the rights of a physician to acquire the goodwill of a practice and to secure the value purchased with a noncompete agreement. In fact, some courts have rationalized that patients outside the restricted area profit from the services of the physician who, because of the noncompete agreement, can no longer practice in the restricted territory. [118]

Noncompete Agreements in an Employment Setting

Although the rules for enforcing a noncompete agreement between an employer and an employee are similar to those between seller and buyer, there are important differences. Some state legislatures have specifically outlawed noncompete agreements between employers and employees. [119] When such a statute is unavailable, courts generally note that an employee lacks the bargaining power that a seller of a business has and therefore may sign an employment contract containing a noncompete provision without any ability to negotiate such a provision.

Courts are concerned that employers may take undue advantage of the employee in requiring a noncompete agreement. [120] The position of an employee differs from that of a seller of a business, who receives payment for the goodwill of the business in return for an agreement not to compete. If there is no fraud on the part of the employer, these cases usually turn on the question of consideration. To be enforced, such an agreement must be supported by valid consideration, must be reasonable in scope, must protect a legitimate business interest of the employer, and must not unduly harm the public. A court will not find consideration to exist if the only consideration is the employer's decision to continue employing the physician. [121] Therefore, a noncompete agreement cannot be imposed as an afterthought by an employer once employment has commenced without specific consideration for the subsequent noncompete agreement. An increase in compensation that would otherwise have been due to such employees would not represent new consideration, [122] but a promotion could. [123]

Compared with decisions in past decades, courts are now tending to disfavor noncompete agreements within the employment context and therefore are scrutinizing these agreements more closely. More than 70 years ago, courts enforced noncompete agreements covering an entire city for 10 years after the termination of employment, [124] but more recent courts have found a 35-mile radius from the employer clinic for 2 years after termination, [125] and a 50-mile radius for 3 years after termination, [126] to be unreasonable.

One factor sometimes considered is whether the physician has reasonable alternatives available to practice his or her profession. Thus, a Georgia court upheld a covenant that prevented a surgeon from practicing in ten populous counties in and around Atlanta because the covenant left the surgeon free to practice in at least three other heavily populated counties in the metropolitan area. [127]

These cases turn on the facts of each situation, and decisions vary from state to state. In 1986, an Arkansas court struck down a noncompete agreement that covered a radius of 30 miles for only 1 year after termination. [128] Apparently, the size of the restricted area was not even an issue, because the physician, an orthopedic surgeon, had joined a clinic practicing in the same building as his former employer. The court noted, however, that there was no evidence that the surgeon either attempted, or succeeded in, enticing any of his former employer's patients to continue to see him (even though he did perform "normal medical follow-ups" on patients on whom he had operated while employed by the former employer). The doctor had received his training and skills before employment, he acquired no special skills during the employment, and he even performed some procedures the employer did not. Based on these factors, the restrictions were an unreasonable restraint of trade and unduly interfered with the public's interest in the availability of this orthopedic surgeon.

As in the case of noncompete agreements ancillary to the sale of a business, a noncompete agreement given by an employee will be stricken if it imposes an undue hardship on the public that results from the unavailability of physicians performing similar services in the area. Indeed, the trend is to look more carefully to find undue hardship in cases arising out of employment relationships.

Noncompete Agreements Among Members of a Group Practice

Another time physicians may be asked to enter into a noncompete agreement is when they join a medical group. A noncompete agreement among members of a group practice is a hybrid: the contract is one of employment, but, when a physician leaves a group practice, the physician's share in the partnership property, including its goodwill, is transferred, as in the sale of a practice. Courts have held that covenants in an employer-employee relationship require "a stricter scrutiny in determining the reasonableness of the restrictions" than one given among partners. [129]

Courts frequently use the sale of goodwill to justify enforcement

of noncompete agreements against former members of a group practice, [130] even though a state statute may prohibit employers from requiring employees to agree to noncompete agreements. [131] Noncompete agreements, given by physicians on joining a group practice, have been enforced in the following contexts: a covenant covering a 25-mile radius for 3 years after a physician leaves the partnership, [132] a covenant not to practice in a 5-mile radius for 5 years, [133] and a 5-year noncompete agreement covering a radius of 30 miles, for a physician who had repeatedly changed professional associations within a range of thousands of miles. [134]

As with any noncompete agreement, the covenant must be found to protect a legitimate interest of the group practice, and if the court finds that competition from the terminating partner will not affect the group, the covenant will not be enforced. [135] The court also must find that enforcing the covenant would not cause undue hardship in the general public.

Exclusive Agreements Between Hospitals and Physicians

Hospitals may enter into an agreement with a physician or a medical group that gives a few physicians exclusive hospital privileges. Although such agreements are not noncompete agreements because the right to practice in a given area has not been contracted away, they have the same effect of restraining competition because other physicians are deprived of access to that hospital for the treatment of patients. In recent years, exclusive agreements have been executed in which the physicians must give up their right of due process, because their hospital privileges remain in effect only so long as the exclusive agreement is in effect. This, in

essence, results in economic credentialing.

Exclusive Contract as an Unlawful Tying Agreement

Because a third party may claim injury from the agreement, these contracts are examined carefully to determine whether they are illegal. Such contracts have been attacked under a number of theories, the most prominent being that the contract violates federal antitrust laws because it constitutes an unlawful tying arrangement. As related to physicians and hospitals, a patient can only obtain the tying product or service (access to the operating room) by purchasing from the seller another product or service, the tied product (the services of a particular physician).

For a court to hold that a contract is a tying agreement under federal antitrust laws, there must be two separate products. Once this is established, a tying agreement will be considered unreasonable per se if a party has sufficient economic power over the tying product (the operating room) to restrain free competition for it. [136] (An additional requirement, that interstate commerce be affected substantially, is addressed separately.)

In a 1984 decision that has had a significant impact on how the courts view tying arrangements, the United States Supreme Court addressed a claim involving a hospital's exclusive contract with a group of anesthesiologists. In *Jefferson Parish Hospital District No. 2 v Hyde,*[137] an anesthesiologist who was excluded from the hospital because of an agreement between the hospital and another group of anesthesiologists sought to have the agreement set aside as an unlawful tying arrangement under federal antitrust laws. The Court decided that a hospital's services and the services of an anesthesiologist are two separate products, separately priced and purchased, from the perspective of the patient. Anesthesiologists may be treated differently from radiologists, pathologists, and other hospital-based physicians in this regard. The demand for anesthesia services was considered separate from the demand for hospital services, as evidenced by the unique phenomenon of patients' and physicians' requesting a specific anesthesiologist. [138] Therefore, the hospital's services and those of the anesthesiologist are considered two separate products, whereas the services provided by some hospital-based physicians may not be considered separate from other services provided by the hospital.

The next question to be determined by the Court was whether the hospital had sufficient "market power" to force a purchaser to do something the purchaser would not do in a competitive market, namely, purchase the tied product (the services of the chosen anesthesiology group) to obtain the tying product (access to the operating room). The hospital need not have an absolute monopoly in the area to have sufficient market power to enforce a tying arrangement. Generally, if a business seeking to enforce a tying arrangement had a significant presence in the market, the business was found to have sufficient market power to enforce a tying arrangement. However, in *Jefferson Parish,* the Supreme Court declared that a significant market share, even when teamed with market imperfections such as minimal price and quality competition, is not sufficient to establish market power in the relevant market, absent some significant restraint on trade other than a tying of two services.

On the question of market power, the individual Justices of the Supreme Court differed. Five Justices held that, absent a significant restraint on trade other than the tying of these two products, the hospital did not have sufficient market power to enforce the tying arrangement because 70 percent of the patients residing in the parish entered different hospitals. Although concurring in the judgment, four other Justices disagreed with the majority's reasoning and instead decided that, based on prior precedent, a 30 percent market share was sufficient to give the hospital market power, but, more important, they determined that the Court should apply the rule of reason rather than per se illegality in judging tying arrangements. In applying a reasonableness test to the agreement, the concurring Justices found valid business reasons for the agreement and found that it foreclosed "only a small fraction of the markets in which anesthesiologists may sell their services, and a still smaller fraction of the market in which hospitals may secure anesthesiology services." [139] The concurring Justices implied that a hospital with an even greater market share could be able to enforce an exclusive agreement if there were valid reasons for the agreement.

The majority and concurring opinions used different reasoning, but both clearly signaled the Court's intent to constrict

the scope of the antitrust laws, at least as they apply to tying agreements. Since *Jefferson Parish,* the Supreme Court has expressly counseled against extending per se analysis to rules adopted by professional associations and to restraints imposed in the context of business relationships in which an anticompetitive economic impact is not immediately obvious. [140] Thus, many lower courts have expressed a reluctance to apply the per se rules and instead apply the rule of reason, which, in turn, requires proof of economic impact on competition and an extensive examination of the challenged conduct. [141] This is significant because most contracts considered under a rule of reason analysis are upheld. Even in a rule of reason case, at least one court has stated that "substantial" market power must be proven in order to sustain a claim. [142]

Other Antitrust Grounds for Voiding Exclusive Contracts

Following *Jefferson Parish,*[143] exclusive contracts between hospitals and non-hospital-based physicians are likely to be upheld unless an ulterior motive for the agreement is shown. Those seeking to uphold such an agreement will argue they have valid business reasons for signing an exclusive contract, such as maintaining or improving the quality of medical care or increasing efficiency. Persons excluded by these contracts must show that other, impermissible reasons are behind the agreement.

There are several possible means by which to attack such a contract. If an exclusive agreement (or any agreement) is found to be an attempt to fix prices for the services offered by hospitals or physicians, the contract will likely be stricken because such practices are per se unlawful under federal antitrust laws. [144] If the challenging party can show that the exclusive contract has a substantially harmful effect on competition, such as by "a reduction of output," or by proof of increased prices, the contract may be held to be unlawful. [145] Likewise, an exclusive contract found to be nothing more than a conspiracy to boycott certain physicians from obtaining hospital privileges will be set aside as an unlawful group boycott. [146] However, the plaintiffs must show the exclusive contract has "predominately anticompetitive effects" and essentially has no other valid purpose. [147] An exclusive contract that is an attempt to monopolize a market is also unlawful, because all contracts designed to monopolize a market are per se violative of federal antitrust laws. [148] In making such a claim, a competing physician must prove that one of the defendants possesses monopoly power in the relevant market and that this defendant willfully acquired or maintained that power through the exclusive contract, as opposed to having acquired a monopoly through ordinary growth or development as a consequence of superior service, business acumen, or historic accident. [149]

A competitor seeking to challenge an exclusive agreement as creating or furthering a monopoly is required to show the relevant market involved, the monopoly power of the defendant, and proof that the purpose of the exclusive agreement was to drive others from the market. [150] Once this threshold is satisfied, the defendant can establish a prima facie case of lawful conduct if valid business reasons justify the agreement. Therefore, the plaintiff must also prove that any proffered justifications are merely pretextual. [151] As a result of these many requirements, competing parties, medical or otherwise, have had difficulty proving that an exclusive contract constitutes a monopoly or an attempt to monopolize.

Defenses Against an Antitrust Claim

Even if an exclusive contract does violate federal antitrust laws, there are two defenses by which a hospital may prevent a challenge to the contract. First, federal antitrust laws apply only when interstate commerce is affected, although the courts have disagreed about whether the challenged conduct, itself, must be a form of interstate commerce or whether it must only have more than a de minimis effect on interstate commerce. [152] Thus, the size and drawing power of a hospital may have an influence on this decision. It should be noted, however, that even if interstate commerce is not affected, most states have their own antitrust laws, which do not require that interstate commerce be affected. Therefore, not affecting interstate commerce provides a complete defense to a claim under federal antitrust laws, but not to a claim under state antitrust laws. The individual states generally follow the federal courts in interpreting their own antitrust laws, but they are not obligated to do so.

The second defense against antitrust liability, and one that may apply more often in a hospital setting, is referred to as the "state action exemption doctrine." Under this doctrine, a hospital will be exempt if it can demonstrate that its anticompetitive activities were authorized by the state "pursuant to state policy to displace competition with regulation or monopoly public service." [153] This doctrine applies directly only to state hospitals, but county and municipal hospitals can also use the state action doctrine if they show they acted "pursuant to clearly articulated and affirmatively expressed state policy." [154] For a private hospital, such a defense would be available only if it could be shown that the state is actively supervising the hospital's activity and that the activity is in compliance with state regulatory policy. A federal appellate court, however, has ruled that when a state statute gives private hospitals the power to determine which physicians may practice in those hospitals, then all hospitals in that state are authorized to restrict those who are allowed to practice at the hospital, and the hospitals are immune from claims by competing

practitioners under the state action exemption. [155]

The state action exemption doctrine is a powerful exemption, as evidenced by the 11th Circuit's declaration that, with the possible exception of actual market participation, any action that qualifies as state action is ipso facto exempt from the operation of the antitrust laws, even if the state action takes the form of an unauthorized conspiracy to restrain competition. [156] Therefore, under the state action exemption, conduct that is the result of state regulations is not actionable even though it may otherwise be improper under federal antitrust laws. Once again, although state antitrust laws vary, most states recognize the state action exemption doctrine, and some even specifically include this exemption in their antitrust laws. [157]

Use of Anesthesiologists or Nurse Anesthetists: Antitrust Considerations

Numerous legal challenges have been made to actions taken by hospitals to exclude or to limit the practice of nurse anesthetists in their hospitals. The hospital practices that have come under attack are those requiring nurse anesthetists to be supervised by physicians or those dealing exclusively with anesthesiologists and not using the services of nurse anesthetists.

A hospital policy will be judged by the rule of reason, unless a plaintiff can show a policy was adopted as a means of imposing a restraint that is per se unlawful under federal antitrust laws (see the earlier section on *Exclusive Contract as an Unlawful Tying Agreement*). Pursuant to that analysis, it is likely a hospital will be able to show that its procedures were adopted as a reasonable means of ensuring efficiency and quality of anesthesia services. Thus, most attempts by nurse anesthetists to set aside hospital policies that exclude or limit the practice of nurse anesthetists have been unsuccessful. This is true even in spite of cases acknowledging that anesthesia services may affect interstate commerce in more than a de minimis way and that actions affecting these services are therefore covered by federal antitrust laws, [158] that nurse anesthetists and anesthesiologists do compete in a single market that can be monopolized, [159] and that it is possible for a hospital to conspire with its staff physicians in violation of federal antitrust laws. [160] Most nurse anesthetist- plaintiffs have failed because they could not prove that an exclusive contract between a hospital and a group of anesthesiologists unreasonably restrained competition or that the defendants were not pursuing permissible independent business (medical) interests. [161]

If a plaintiff successfully shows there was a reason other than a unilateral effort to provide quality care most efficiently to the patient for a hospital to exclude nurse anesthetists or to require their work to be supervised by an anesthesiologist, then the policy may be successfully challenged. In *Oltz v St. Peter*' *s Community Hospital,*[162] the plaintiff anesthetist, in bringing an action against both the hospital and a group of anesthesiologists, alleged that the hospital's granting an exclusive right to the anesthesiologists to furnish anesthesia services in that hospital and subsequently terminating the plaintiff's contract constituted an unlawful conspiracy to grant a monopoly to the anesthesiologists. In that case, the defendant hospital was the only hospital equipped to do general surgery in Helena, Montana, and had a market share of 84 percent. The trial court acknowledged that the hospital had a monopoly, but the mere fact that one has a monopoly does not make all of one's contracts unlawful. If the hospital had acted unilaterally, its actions would have been upheld. The evidence, however, showed that statements made by the anesthesiologists and exchanges of letters among the anesthesiologists and between the anesthesiologists and members of the hospital's Board of Trustees urged that the policy be adopted. Under these facts, the court held that the hospital had conspired with the anesthesiologists to exclude the plaintiff from the market and therefore had violated federal antitrust laws.

The *St. Peter*' *s Community Hospital*[162] [163] example should be noted by all medical practitioners. Its principles apply in every contract: conduct that has a valid business (or medical) purpose will generally be upheld under scrutiny of federal antitrust laws as long as the agreement and the resulting restriction are reasonably necessary to advance such legitimate business (or medical) purposes. When that conduct goes further and involves an attempt by one party, or a conspiracy among several, to exceed these legitimate purposes, the contract may not withstand antitrust scrutiny.

Publication of Relative Value Guides, Scales, and Studies for Medical Services

On several occasions, medical associations have sought to establish guidelines for fees charged for specialized medical services. Such concerted action, whether through mere communication of relative values for services or through the imposition of maximum fees for services rendered, has been viewed by courts and the U.S. Federal Trade Commission (FTC) as disruptive to a competitive market. [164] The distribution of price information has been attacked under two of this nation's broadest legal prohibitions. As noted previously, price fixing in general is prohibited by Section 1 of the Sherman Act. [165] The FTC also has attacked price guidelines under Section 5 of the FTC Act, which prohibits "unfair methods of competition in or among commerce, and unfair or deceptive acts or practices in or affecting commerce." [166]

In *State of Arizona v Maricopa County Medical Society,*[167] the United States Supreme Court reviewed the effect of the publication by the Maricopa County Medical Society (MCMS) of relative values for services and establishing maximum fees for such services in the Phoenix market. The MCMS was formed in 1969 to promote fee-for-service medicine and to provide the community with a competitive alternate to existing health insurance plans. Approximately 70 percent of all practitioners in the county were members. The MCMS published a relative value schedule for each medical service and a conversion factor to multiply by the relative value to establish maximum fees, which participating doctors agreed to accept as payment for services performed for patients insured under MCMS-approved plans. Doctors were permitted to charge higher fees to uninsured patients.

The Supreme Court determined that this concerted action constituted an agreement to fix prices in restraint of trade--a per se violation of the Sherman Act. The Court's application of the per se rule precluded examination of possible procompetitive justifications. In refusing to examine such possible procompetitive justifications, the Court stated, "The anticompetitive potential inherent in all price fixing agreements justified their facial invalidation even if procompetitive justifications are offered for some." [148] The fact that it established maximum rather than minimum fees was considered irrelevant by the Court. The issue whether the fixing of maximum prices or maximum fees should constitute a per se violation of the antitrust laws is expected to be heard by the United States Supreme Court. [168]

In 1962, the American Academy of Orthopaedic Surgeons (AAOS) published a booklet entitled *Relative Value Systems*

for Orthopaedic Procedures.[169] In the book, numeric values were assigned to medical procedures and were convertible into a monetary fee. The AAOS did not, however, impose a maximum schedule for fees to be charged for services based on such values. The FTC alleged that, notwithstanding the absence of a direct price-fixing scheme in violation of the Sherman Act, the publication of such information distorted the competitive balance in the market in violation of Section 5 of the FTC Act. [170] The AAOS eventually entered into a consent decree whereby it was required to cease publication and circulation of relative values that established and maintained fees for orthopedic services.

Although the FTC has been unwavering in its attacks against publication of any type of relative value study, the ASA successfully fought an attack against publication of a relative value study in 1979 in *United States v the American Society of Anesthesiologists, Inc.*[171] In contrast to the schedules published by the MCMS a few years later, the ASA had not ascribed any conversion factor to their guides but merely set forth a list of medical procedures, individually described in medical terminology and referenced by an abstract number known as a "unit of value." The District Court in *American Society of Anesthesiologists* pointed out that the mere adoption, publication, and dissemination of a relative value guide did not constitute a restraint on trade. The critical question was whether there was an agreement, express or implied, that the guide would be used to price anesthesia services, which the court did not find in this case.

Notwithstanding the success of the ASA in overcoming the FTC's objection to publication of relative value guides, it remains the official position of the FTC that publication of such studies is improper. [172] State attorneys general have likewise taken the position that any discussion leading to an understanding, whether tacit or explicit, about prices to be charged to consumers is considered a violation of Section 5 of the FTC Act and of comparable state statutes. Relative value studies and minimum or maximum price guidelines, discussed or distributed among competitors, whether among members of the medical profession or in other industries, will continue to be viewed with suspicion regardless of the stated purpose, because such practices can lead to an express or implied understanding among competitors as to the prices that can be charged. This presents an interesting dilemma because the U.S. Health Care Finance Administration (HCFA) has adopted a uniform relative value method to calculate physician payment for services rendered to Medicare recipients. [173] This method resulted from an extensive study conducted by Professor Hsaio and his colleagues [174] [175] [176] [177] and is now known as the Resource-Based Relative Value Study (RB/RVS). [173] Thus, it appears that two separate agencies of

the United States government, the FTC and HCFA, have completely opposite positions on the issue of relative value publications. When this chapter was written, that conflict had not been formally addressed, but it is clear that the RB/RVS published by HCFA will be used to calculate Medicare reimbursement for physicians' professional services.

Of interest to anesthesiologists is that the anesthetic section of the RB/RVS is basically the same as the ASA relative value guide. [178] The HCFA, however, has not accepted the section on modifiers and has published its intent to eliminate time units. This decision will destroy the time-tested appropriateness of considering concurrent disease, duration of effort, and complexity in determining the relative value of anesthetic care for one patient compared with another. Clearly, concurrent disease and time frequently play a larger role in the relative value of anesthetic care than simply the surgical procedure alone. This concept was understood by both houses of Congress when they passed legislation mandating the use of time in calculating relative value for anesthesia. This was signed into law by President Bill Clinton as part of the Omnibus Budget Reconciliation Act (OBRA) of 1993. [179]

Physician Self-Referral Issues

The practice of self-referral has been traced back at least as far as the 1920s, and the rules controlling such practices have seldom, if ever, been enforced. However, in the 1980s, the U.S. Department of Health and Human Services (HHS) began enforcing Section 1128B of the Social Security Act, [180] otherwise known as the Medicare and Medicaid AntiKickback Statute. This statute is broadly worded and is intended to restrict the corrupting influence of money on a physician's decision of when and where to refer patients. The statute is violated "whenever an individual or entity knowingly and willfully offers or pays anything of value, in any manner or form, with the intent of exercising influence over a physician's reason or judgment in an effort to cause the referral of a program-related [Medicare and Medicaid] business." [181] The statute was enacted in 1972, but dramatic increases in competition and in interrelationships among health-care providers since then have caused the HHS to take a more aggressive position in enforcing the statute.

In 1991, two events dramatically changed the legal and ethical landscape for physicians referring Medicare and Medicaid patients to health-care facilities or joint ventures in which the physician has an ownership (financial) interest. First, the HHS issued its "safe harbor" regulation. [182] This was followed by the landmark decision of the HHS Appellate Board in *The Inspector General v The Hanlester Network et al.* [180] The safe harbors were Congress' way of narrowing the scope of the overbroad Anti-Kickback Statute, so as to protect legitimate or innocuous business arrangements. Two investment-interest safe harbors were created. The first applies to physicians who may own less than a controlling interest in a publicly traded entity. The statute does not prohibit referral to that entity if the entity has assets of $50 million or more and the physicians' stock was purchased through public trading. [182]

The second safe harbor is for smaller entities, such as joint venture limited partnerships. [182] This safe harbor provision requires that all eight of its standards be met before protection is granted. [182] These requirements include, among others, that no more than 40 percent of the entity's ownership interests be held by persons who can make referrals to the entity. It is also required that at least 60 percent of the entity's revenue must come from noninvestor referrals. Furthermore, the entity cannot require investors to refer patients to it or to base profit distributions on the amount of referrals made or expected to be made by each physician. Therefore, the safe harbor provision narrows the scope of the Anti-Kickback Statute by creating a well-defined, albeit limited, safe harbor.

The *Hanlester* case is important because the Departmental Appeals Board declared that no agreement to refer is required in order to find a violation of the Anti-Kickback Statute. A violation now exists any time an inducement exists, which creates the potential for a conflict between the physician's self-interest and the patient's interests. A physician has a fiduciary duty to act in the patient's best interest, which means that a referral should be based on the cost, quality, and necessity of the relevant services. A physician's self-interests, such as investment and self-referral, are inconsistent with the fiduciary duty owed to the patient. [183]

Although these developments have dramatically altered the self-referral issue, the changes are not complete. Therefore, when referring patients to health-care facilities in which the physician has an ownership interest, the physician must be careful to comply with the safe harbor provisions or will risk prosecution under the Anti-Kickback Statute. In addition, the Council on Ethical and Judicial Affairs of the American Medical Association (AMA) developed recommendations for determining when self-referrals are appropriate. [183] * Under the AMA recommendations, physicians generally should not refer patients to a health-care facility outside their office practice if they have an investment in the facility but do not directly provide care or services at the facility (recommendation 1). [182] An exception to this general principle exists when the physician's investment is made in a facility for which there is a demonstrated need in the community, and alternative financing for the facility was not available. In these instances, however, certain other conditions must be met. The conditions require disclosure of the investment to patients and third-party payers and are otherwise designed to prevent preferential treatment to patients of the referring physician or any requirement or inducement for referrals to be made to the facility (AMA recommendation 2). [183]

LAWS AND REGULATIONS AFFECTING THE PRACTICE OF ANESTHESIA

Before the implementation of the Medicare program in 1965, the U.S. Government rarely passed laws or implemented regulations dealing with the practice of medicine. Since that time, however, legislators have been more interested in describing appropriate methods of medical practice and financial reimbursement for same. Regulations finalized in 1983 to implement the Tax Equity and Fiscal Responsibility Act for the first time specified requirements for the practice of anesthesiology that anesthesiologists would have to meet to be paid for their services under the Medicare program. [184] This was the first description in law of specific requirements for the practice of a medical specialty. Since that time, in an effort to contain costs, additional laws have been passed that mandate lower levels of financial reimbursement for certain services rendered to Medicare recipients, [185] as well as reductions based on the level of supervision or medical direction by an anesthesiologist. [186]

In 1992 and 1993, there was considerable effort to enact a diagnosis-related group mechanism for reimbursing anesthesiologists and to eliminate actual time as a method of calculating anesthesiology fees. Neither of these initiatives survived the legislative process, and, at least as of 1999, the diagnosis-related group mechanism for reimbursement does not apply to anesthesia, and actual time units are now, by law, part of the method for determining the appropriate value for professional anesthesia services. [179] Also passed in 1993 was a method for reimbursing for anesthesia services provided by an anesthesia care team, when an anesthesiologist medically directs the anesthetic care of up to four patients simultaneously with the assistance of CRNAs.

On January 1, 1994, the HCFA changed its policy on reimbursement of physicians in the teaching environment, so that the supervising or teaching anesthesiologist is compensated as though he or she were administering anesthesia as part of an anesthesia care team. The HCFA policy for reimbursement of an anesthesia care team permits the attending anesthesiologist to supervise, or medically direct, four cases concurrently. The essentials for accreditation of residency programs in anesthesiology, however, suggest that an attending anesthesiologist supervise no more than two concurrent cases. As a result, reimbursement is more restrictive when an anesthesiologist medically directs resident physicians than when CRNAs are medically directed. The teaching anesthesiologist will receive 50 percent of the fee from each of the two patients whose care he or she so supervises. However, the HCFA will not pay the other 50 percent to the resident or to the sponsoring institution, because the HCFA claims that reimbursement for the resident is already covered under part A of Medicare. Thus, in essence, there is a negative financial incentive to administering anesthesia while teaching residents as opposed to administering anesthesia while supervising nurse anesthetists.

The HCFA published in the Federal Register [187] its intent to discontinue the requirement that CRNA-administered anesthesia be supervised by the operating surgeon or an anesthesiologist who is immediately available in order to qualify for reimbursement by Medicare. The conference report language of the FY99 Omnibus Appropriations Bill [188] suggests that the secretary request the Agency for Health Care Policy and Research to work with HCFA in the design and implementation of an outcome approach that would examine, utilizing existing Medicare operating room anesthesia data, mortality and adverse outcome rates by different anesthesia providers, adjusted to patient acuity, and other relevant scientific variables. A bill, HR 632 Safe Seniors Assurance Study Act of 1999, was introduced in the House of Representatives on February 10, 1999. This bill requires the Secretary of Health and Human Services to conduct a study of mortality and adverse outcome rates of Medicare patients by providers of anesthesia services. A report containing the results of this study is to be submitted to Congress not later than June 30, 2000. If the secretary determines that the lack of physician supervision of providers of anesthesia services results in an adverse impact on outcome rates of Medicare patients, then providers of anesthesia services furnished under the Medicare or Medicaid program

* The AMA recommendations obviously do not have the same legal effect as the Social Security Act. However, whereas the Social Security Act applies only to referrals of Medicare and Medicaid patients, the AMA recommendations apply to all referrals of patients to facilities in which the physician has a financial interest.

shall be supervised by a physician in the same manner as such providers are supervised under regulations of the Department of Health and Human Services in effect on January 1, 1999.

At the time this chapter is submitted for publication, proposals for health care reform continue to be heavily debated both in Congress and by the public. Although the details of any plan that may be adopted by Congress are not available, it appears that such a plan will further reduce reimbursement for anesthesia services and may affect the methods of practice of anesthesiologists. The reader is encouraged to follow such legislation and any rules and regulations that may result from it, to evaluate their impact on the practice of anesthesiology.

ACKNOWLEDGMENT

Special thanks go to professor Robert D'Amico, Department of Philosophy, University of Florida, for his help with the section on ethics, and to Ms. Lynn Dirk and Ms. Anita Yeager, editors, Department of Anesthesiology, University of Florida, for their editorial assistance.

References

1. Alexander L: Medical science under dictatorship. N Engl J Med 241:39, 1949.

2. Acts 15:29. Revised Standard Version.

3. Jehovah's Witnesses and the Question of Blood. Brooklyn, NY, Watchtower Bible and Tract Society, 1977, p 1.

4. Dixon JL, Smalley MG: Jehovah's Witnesses: The surgical/ethical challenge. JAMA 246:2471, 1981.

5. Kambouris AA: Major abdominal operations on Jehovah's Witnesses. Am Surg 53:350, 1987.

6. Lichtenstein A, Eckhart WF, Swanson KJ et al: Unplanned intraoperative and postoperative hemodilution: Oxygen transport and consumption during severe anemia. Anesthesiology 69:119, 1988.

7. Kassirer JP: Managing managed care's tarnished image (editorial). N Engl J Med 337:338, 1997.

8. Annas GJ: Patients' rights in managed care: Exit, voice, and choice. N Engl J Med 337:210, 1997.

9. Ginzberg E: A hard look at cost containment. N Engl J Med 316:1151, 1987.

10. Burner ST, Waldo DR, McKusick DR: National health expenditures projections through 2030. Health Care Financing Rev 14:1, 1992.

11. Birnbaum ML: Cost-containment in critical care. Crit Care Med 14:1068, 1986.

12. Reagan MD: Physicians as gatekeepers: A complex challenge. N Engl J Med 317:1731, 1987.

13. Callahan D: Ethics and health care: The next 20 years. Am J Hosp Pharm 42:1053, 1985.

14. Leeder SR: All for one or one for all? The ethics of resource allocation for health care. Med J Aust 147:68, 1987.

15. Wachter MW, Luce JM, Turner J et al: Intensive care of patients with acquired immunodeficiency syndrome. Am Rev Respir Dis 134:891, 1986.

16. Friedman Y, Franklin C, Rackow EC et al: Improved survival in patients with AIDS, *Pneumocystis carinii* pneumonia, and severe respiratory failure. Chest 96:862, 1989.

17. Friedman Y, Franklin C, Freels S et al: Long-term survival of patients with AIDS, *Pneumocystis carinii* pneumonia, and respiratory failure. JAMA 266:89, 1991.

18. LaRocco A Jr, Amundson DE, Wallace MR et al: Corticosteroids for *Pneumocystis carinii* pneumonia with acute respiratory failure. Chest 102:892, 1992.

19. Greco D, Stazi MA, Rezza G: Length of survival of patients with AIDS. BMJ 293:451, 1986.

20. Steinbrook R, Lo B, Moulton J et al: Preferences of homosexual men with AIDS for life-sustaining treatment. N Engl J Med 314:457, 1986.

21. Murphy DJ, Murray AM, Robinson BE et al: Outcomes of cardiopulmonary resuscitation in the elderly. Ann Intern Med 111:199, 1989.

22. Bedell SE, Delbanco TL: Choices about cardiopulmonary resuscitation in the hospital: When do physicians talk to patients? N Engl J Med 310:1089, 1984.

23. Daniels N: Why saying no to patients in the United States is so hard: Cost containment, justice, and provider autonomy. N Engl J Med 314:1380, 1986.

24. Iglehart JK: Managed competition. N Engl J Med 328:1208, 1993.

25. Himmelstein DU, Woolhandler S: Cost without benefit: Administrative waste in U.S. health care. N Engl J Med 314:441, 1986.

26. Fuchs VR: The counterrevolution in health care financing. N Engl J Med 316:1154, 1987.

27. Miller FH, Miller GAH: The painful prescription: A procrustean perspective? N Engl J Med 314:1383, 1986.

28. Soffer A: Cost effective or quality care: Which shall it be? (editorial) Chest 88:806, 1985.

29. Nutter DO: Medical indigency and the public health care crisis: The need for a definitive solution. N Engl J Med 316:1156, 1987.

30. Dunstan GR: Hard questions in intensive care: A moralist answers questions put to him at a meeting of the Intensive Care Society, Autumn, 1984. Anaesthesia 40:479, 1985.

31. Youngner SJ: Do-not-resuscitate orders: No longer secret, but still a problem. Hastings Cent Rep 17:24, 1987.

32. Chernow B, Seeland AD, Snyder R: Orders not to resuscitate: The DNR patient (editorial). Crit Care Med 12:922, 1984.

33. Bedell SE, Delbanco TL: Choices about cardiopulmonary resuscitation in the hospital: When do physicians talk with patients? N Engl J Med 310:1089, 1984.

34. Bedell SE, Pelle D, Mahan PL et al: Do-not-resuscitate orders for critically ill patients in the hospital: How are they used and what is their import? JAMA 256:233, 1986.

35. Keffer MJ, Keffer HL: Do-not-resuscitate in the operating room: Moral obligations of anesthesiologists. Anesth Analg 74:901, 1992.

36. Franklin CM, Rothenberg DM: Do-not-resuscitate orders in the presurgical patient. J Clin Anesth 4:181, 1992.

37. Cohen CB, Cohen PJ: Do-not-resuscitate orders in the operating room. N Engl J Med 325:1879, 1991.

38. Walker RM: DNR in the OR: Resuscitation as an operative risk. JAMA 266:2407, 1991.

39. Truog RD: "Do-not-resuscitate" orders during anesthesia and surgery. Anesthesiology 74:606, 1991.

40. Reeder JM: Do-not-resuscitate orders in the operating room. AORN J 57:947, 1993.

41. Martin RL, Soifer BE, Stevens WC: Ethical issues in anesthesia: Management of the do-not-resuscitate patient. Anesth Analg 73:221, 1991.

42. Doudera AE: Developing issues in medical decision making: The durable power of attorney and institutional ethics committees. Primary Care 13:315, 1986.

43. Veatch RM: An ethical framework for terminal care decisions: A new classification of patients. J Am Geriatr Soc 32:665, 1984.

44. *Eichner v Dillon,* 52 NY2d 363, 420 NE2d, 64 (1981).

45. Eisendrath SJ, Jonsen AR: The living will: Help or hindrance? JAMA 249:2054, 1983.

46. Haber JG: The living will and the directive to provide maximum care: The scope of autonomy. Chest 90:442, 1986.

47. Rosner F: The living will. Chest 90:441, 1986.

48. Rafflin TA: Value of the living will. Chest 90:444, 1986.

49. *Superintendent of Belchertown State School v. Saikewicz,* 373 NE2d 728 (1977).

50. *In the Matter of Shirley Dinnerstein,* Mass App, 380 NE2d 134 (App C Mass, 1978.2).

51. Emanuel EJ: Pain and symptom control: Patient rights and physician responsibilities. Hematol Oncol Clin North Am 10:41, 1996.

52. Lo B, Rouse F, Dornbrand L: Family decision making on trial: Who decides for incompetent patients? N Engl J Med 322:1228, 1990.

53. Angell M: Prisoners of technology: The case of Nancy Cruzan (editorial). N Engl J Med 322:1226, 1990.

54. Annas GJ: Nancy Cruzan and the right to die. N Engl J Med 323:670, 1990.

55. *In the Matter of Karen Quinlan,* 70 NJ 10, 355 A2d 647 (1976).

56. *Severns v Wilmington Medical Center, Inc.,* Del. Supr., 421 A.2d 1334, (1980).

57.

In the Matter of Earle N. Spring, Mass., 405 NE2d 115 (1980).

58. *In the Matter of Claire C. Conroy,* 486 A2d 1209 (NJ 1985).

59. Lo B, Dornbrand L: The Case of Claire Conroy: Will administrative review safeguard incompetent patients? Ann Intern Med 104:869, 1986.

60. Schneiderman LJ, Jecker NS, Jonsen AR: Medical futility: Its meaning and ethical implications. Ann Intern Med 112:949, 1990.

61. Tomlinson T, Brody J: Futility and the ethics of resuscitation. JAMA 264:1276, 1990.

62. Singer PA, Siegler M: Euthanasia: A critique. N Engl J Med 322:1881, 1990.

63. Kevorkian J: Prescription: Medicide: The Goodness of Planned Death. New York, Prometheus Books, 1991, p 221.

64. Anonymous: It's over, Debbie. JAMA 259:272, 1988.

65. Cassel CK, Meier DE: Morals and moralism in the debate over euthanasia and assisted suicide. N Engl J Med 323:750, 1990.

66. Hardy A: It's almost over: More letters on Debbie (letter). JAMA 260:787, 1988.

67. Miller PJ: Death with dignity and the right to die: Sometimes doctors have a duty to hasten death. Med Ethics 13:81, 1987.

68. de Wachter MAM: Active euthanasia in the Netherlands. JAMA 262:3316, 1989.

69. van der Wal G, van der Maas PJ, Bosma JM et al: Evaluation of the notification procedure for physician-assisted death in the Netherlands. N Engl J Med 335:1706, 1996.

70. van der Maas PJ, van der Wal G, Haverkate I et al: Euthanasia, physician-assisted suicide, and other medical practices involving the end of life in the Netherlands, 1990-1995. N Engl J Med 335:1699, 1996.

71. Hendin H, Rutenfrans C, Zylicz Z: Physician-assisted suicide and euthanasia in the Netherlands: Lessons from the Dutch (commentary). JAMA 277:1720, 1997.

72. Bindels PJE, Krol A, van Ameigden E et al: Euthanasia and physician-assisted suicide in homosexual men with AIDS. Lancet 347:499, 1996.

73. Misbin RI: Physicians' aid in dying. N Engl J Med 325:1307, 1991.

74. Brody H: Assisted death: A compassionate response to a medical failure. N Engl J Med 327:1384, 1992.

75. Quill TE, Cassell CK, Meier DE: Care of the hopelessly ill: Proposed clinical criteria for physician-assisted suicide. N Engl J Med 327:1380, 1992.

76. Silverman HJ, Vinicky JK, Gasner MR: Advance directives: Implications for critical care. Crit Care Med 20:1027, 1992.

77. Sobel RM, Layon AJ: Physician-assisted suicide: Compassionate care or brave new world (editorial)? Arch Intern Med 157:1638, 1997.

78. Bartholome WG: Physician-assisted suicide, hospice, and rituals of withdrawal. J Law Med Ethics 24:233, 1996.

79. Beecher HK: Ethics and clinical research. N Engl J Med 274:1354, 1966.

80. Committee on Ethics of the American Heart Association: Ethical implications of investigations in seriously and critically ill patients. Circulation 50:1063, 1974.

81. Frost NC: A surrogate system for informed consent. JAMA 233:800, 1975.

82. Marini JL, Sheard MH, Bridges CI: An evaluation of "informed consent" with volunteer prisoner subjects. Yale J Biol Med 49:427, 1976.

83. Klerman G, Dworrkin G: Can convicts consent to castration? Hastings Cent Rep, October 17, 1975.

84. Lidz CW, Meisel A, Osterweis M et al: Barriers to informed consent. Ann Intern Med 99:539, 1983.

85. Engler RL, Covell JW, Friedman PJ et al: Misrepresentation and responsibility in medical research. N Engl J Med 317:1383, 1987.

86. Schiedermayer DL, Siegler M: Believing what you read: Responsibilities of medical authors and editors. Arch Intern Med 146:2043, 1986.

87. Angell M, Relman AS: Fraud in biomedical research: A time for congressional restraint, editorial. N Engl J Med 318:1462, 1988.

88. Spence JB: A walk on the wild side: Malpractice 1982. Presented at Critical Care Update 1982, Lake Buena Vista, Fla, November 23, 1982.

89. Rinamin JC Jr: The tort liability system: Overview for the anesthesiologist. In Gravenstein JS, Holzer JF (eds): Safety and Cost Containment in Anesthesia. Boston, Butterworths, 1988, p 57.

90. Gravenstein JS, Newbower RS, Ream AK et al (eds): The Automated Anesthesia Record and Alarm Systems. Boston, Butterworths, 1987.

91. Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 49:924, 1970.

92. Eichhorn JH: Standards for patient monitoring during anesthesia at Harvard Medical School. JAMA 256:1017, 1986.

93. American Society of Anesthesiologists: ASA Standards, Guidelines, and Statements. Park Ridge, Ill, American Society of Anesthesiologists, 1998.

94. *Medical Review Committees, Immunity from Liability,* Fla Stat §768.40.

95. 119th General Assembly of Ohio, House Bill 576, 1991, §2305.11 of the Revised Code.

96. Marshall E: Supreme Court to weigh science. Science 259:588, 1993.

97. Modell JH: Who is captain of the anesthesia ship? (editorial) Arch Surg 121:753, 1986.

98. *Krane v Saint Anthony Hospital Systems,* 738 P2d 75 (Col. 1987).

99. *McCullough v Bethany Medical Center,* 235 Kan 732; 683 P2d 1258 (Kan 1984).

100. *Thomas v Raleigh General Hospital et al,* 358 SE2d 222 (WVa 1987).

101. Blumenreich GA: "Captain of the anesthesia ship": Does it make a difference? (letter) Arch Surg 122:1088, 1987.

102. Modell JH: "Captain of the anesthesia ship": Does it make a difference? (letter) Arch Surg 122:1089, 1987.

103. Sokol DJ: The current status of medical malpractice countersuits. Am J Law Med 10:439, 1985.

104. 15 USC §1 et seq (1890).

105. *United States v American Tobacco Co,* 221 US 106, 31 S Ct 632, 55 L Ed 663 (1911).

106. *United States v Trenton Potteries Co,* 273 US 392, 47 S Ct 377, 71 L Ed 700 (1927).

107. *Standard Oil Co v United States,* 221 US 1, 31 S Ct 502, 55 L Ed 619 (1911).

108. *Christianson v Colt Industries Operating Corp.,* 766 F Supp 670, 676-680 (C.D. Ill. 1991) (citing *Kling v St. Paul Fire and Marine Insurance Co.,* 626 F. Supp. 1285 (C.D. Ill. 1986) and *Business Electronics v Sharp Electronics,* 485 US 717, 108 S Ct 1515, 99 L Ed 2d 808 (1988).

109. *Times-Picayune Publishing Co v United States,* 345 US 594, 73 S Ct 872, 97 L Ed 1277 (1953).

110. *McCurry v Gibson,* 108 Ala 451, 18 So 806 (1895).

111. *Newman v Sablosky,* 268 Pa Super 851, 407 A2d 448 (1979).

112. *Randolph v Graham,* 254 SW 402 (Tex Civ App 1923).

113. *Martin v Murphy,* 129 Ind 464, 28 NE 1118 (Ind 1891).

114. *Burdine v Brooks,* 206 Ga 12, 55 SE2d 605 (1949).

115. *Hanlon v Morrissey,* 30 Northampton Co R 282 (Pa 1946).

116. *Tarry v Johnston,* 114 Neb 496, 208 NW 615 (1926).

117. *Isuari v Manske-Sheffield Radiology,* 798 SW 2d 346 (Tex 1990).

118. *Canfield v Spear,* 114 Ill 2d 49, 254 NE2d 433 (1969).

119. Ala Code §8-11 (1984); Cal Bus & Prof Code §§16600-16602 (West 1987); Fla Stat Ann §542.33 (West 1988); La Rev Stat Ann §23.921 (West 1985); Mont Code Ann. §§28-2-703-28-2-705 (1991); NC Gen Stat §75-2 (1985); ND Cent Code §9-08-06 (1987); Okla Stat CC 15 §§217-219 (West 1993); SD Codified Laws Ann §§53-9-8-53-9-11 (1990).

120. *Styles v Lyon,* 87 Conn. 23, 86 A. 564 (1913); *Turner v Abbot,* 116 Tenn 718, 94 SW 64 (1906).

121. *Insurance Agents, Inc v Abel,* 338 NW2d 531 (Iowa Ct App 1983).

122. *Freeman v Duluth Clinic, Ltd.* 334 NW2d 626 (Minn 1983).

123. *Amex Distributing Co., Inc. v Mascari,* 150 Ariz 510, 724 P2d 596 (Ariz Ct App 1986).

124. *Erikson v Hawley,* 12 F2d 491 (DC Cir 1926).

125. *Freeman v Duluth Clinic, Ltd,* 334 NW2d 626 (Minn 1983).

126. *Hospital Consultants Inc v Potyka,* 531 SW2d 657 (Tex Civ App 1975).

127. *McAlpin v Cowetta Fayette Surgical Associates PC,* 428 SE 2d 499 (Ga 1995).

128. *Duffner v Alberty,* 19 Ark App 137, 718 SW2d 111 (1986).

129. *McAlpin v Cowetta Fayette Surgical Associates PC,* 458 SE 2d 499, 502 (Ga 1995).

130. *Brown v Stough,* 292 P2d 176 (Okla 1956).

131. *McCray v Blackburn,* 236 So 2d 859, (La Ct App 1970); cert denied, 256 La 845, 239 So 2d 355 (1970).

132. *Rash v Toccoa Clinic Medical Associates,* 253 Ga 322, 320 SE2d 170 (1984).

133. *Field Surgical Associates, Ltd v Shadah,* 59 Ill App 3d 991, 376 NE2d 660 (1978).

134. *Gelder Medical Group v Webber,* 41 NY2d 680, 363 NE2d 573 (1977).

135. *Droba v Berry,* 139 NE2d 124 (Ohio Ct Comm Pleas 1955).

136. *Fortner Enterprises, Inc v United States Steel Corp,* 394 US 495, 89 S Ct 1252, 22 L Ed 2d 495 (1969).

137.

Jefferson Parish Hospital District No. 2 v Hyde, 466 US 2, 104 S Ct 1551, 80 L Ed 2d 2 (1984).

138. *Collins v Associated Pathologists, Ltd,* 844 F2d 473, 477 (7th Cir) (citing *Jefferson Parish,* 466 US at 23 n. 36, 104 S Ct at 1564 n. 36), cert denied, 488 US 852, 109 S Ct 137, 102 L Ed 2d 110 (1988).

139. *Jefferson Parish,* 466 US at 46-47, 104 S Ct at 1576.

140. *Federal Trade Commission v Indiana Federation of Dentists,* 476 US 447, 458-59, 106 S Ct 2009, 2018, 90 L Ed 2d 445 (1986).

141. *Oltz v St. Peter' s Community Hosp.,* 861 F2d 1440, 1445 (9th Cir. 1988) (citing *Harkins Amusement Enters., Inc. v General Cinema Corp.,* 850 F2d 477, 486 (9th Cir. 1988) and *Federal Trade Comm' n v Indiana Fed' n of Dentists,* 476 US 447, 458-59, 106 S Ct 2009, 2017-18, 90 L Ed 2d 445 (1986)); See also, e.g., *Anesthesia Advantage, Inc. v the Metz Group,* 759 F Supp 638, 644 (D Colo 1991) (citing *F.T.C. v Indiana Fed' n of Dentists,* 476 US at 458-59).

142. *Sanjuan v American Board of Psychiatry and Neurology,* 40 F3d 247 (7th Cir 1994).

143. *Jefferson Parish,* 466 US 2, 104 S Ct 1551, 80 L Ed 2d 2 (1984).

144. *Federal Trade Commission v Superior Ct. Trial Lawyers Assoc.,* 493 US 411, 432-36, 110 S Ct 768, 780-81, 107 L Ed 2d 851 (1990).

145. *Capital Imaging v Mohawk Valley Medical Assoc.,* 596 F2d 537 (2d Cir 1993).

146. *Weiss v York Hospital,* 745 F2d 786 (3rd Cir 1994).

147. *Flegel v Christian Hospital Northeast-Northwest,* 804 F Supp 1165 (Ed Mo 1992).

148. *Standard Oil Co. v United States,* 221 US 1, 31, S Ct 502, 55 L Ed 619 (1911).

149. *White v Rockingham Radiologists, Ltd,* 820 F2d 98, 104 (4th Cir 1987) (citing *U.S. v Grinnell,* 384 US 563, 570-71, 86 S Ct 1698, 1703-04, 16 L Ed 2d 778 (1966).

150. *Aspen Skiing Co. v Aspen Highlands Skiing, Corp.,* 472 US 585, 602-05, 105 S Ct 2847, 2857-58, 86 L Ed 2d 467 (1985).

151. *Trans Sport, Inc. v Starter Sportswear, Inc.,* 964 F2d 186, 190 (2d Cir 1992).

152. *Shahawy v Harrison,* 778 F2d 636, 639 (11th Cir 1985); see also *Furlong v Long Island College Hospital,* 710 F2d 922 (2d Cir 1983).

153. *Bolt,* 980 F2d 1381, 1385 (11th Cir 1993) (citing *Town of Hallie v City of Eau Claire,* 471 US 34, 38-39, 105 S Ct 1713, 1716, 85 L Ed 2d 24 (1985)), rehearing denied 988 F2d 1220 (11th Cir. 1993).

154. *Crosby v Hospital Authority of Valdosta and Lowndes County,* 93 F3d 1515 (11th Cir 1996).

155. *Coastal Neuro-Psychiatric Associates, P.A. v Onsolow Memorial Hosp., Inc.,* 795 F2d 340 (4th Cir 1986).

156. *Bolt,* 980 F2d at 1388 (citing *City of Columbia v Omni Outdoor Advertising, Inc.,* 499 US 365, 111 S Ct 1344, 113 L Ed 2d 382 (1991).

157. *Minn Stat* §325.D55, subd 2 (1992).

158. *Anesthesia Advantage,* 759 F Supp 638 (D Colo 1991).

159. *Bahn v NME Hospitals, Inc.,* 929 F2d 1404 (9th Cir 1991), cert denied, -- US -- , 112 S Ct 617, 116 L Ed 2d 639 (1991).

160. *Bolt,* 980 F2d 1381 (11th Cir 1993); see also *Oltz v St. Peter' s Community Hosp.,* 861 F2d 1440 (9th Cir 1988).

161. *Jefferson Parish,* 466 US 2; *Bahn,* 929 F2d 1404; *Balaklaw v Lovell,* 1993-1 Trade Cases p. 70, 261 (NDNY); *Anesthesia Advantage,* 759 F. Supp. 638.

162. *Oltz v St. Peter' s Community Hospital,* 861 F2d 1440 (9th Cir 1988).

163. *Trans Sport,* 964 F2d 186 (2d Cir 1992).

164. *United States v Healthcare Partners, Inc,* 1996 WL 193753 (D. Conn).

165. 15 USC §1 (1985).

166. 15 USC §45(a) (1) (1991).

167. *State of Arizona v Maricopa County Medical Society et al,* 457 US 332, 351, 102 S Ct 2466, 73 L Ed 2d 48 (1982).

168. *State Oil v Khan* (Supp Ct.DKT.96-871).

169. Relative Value Systems for Orthopaedic Procedures. Park Ridge, Ill, American Academy of Orthopaedic Surgeons, 1962.

170. *In re The American Academy of Orthopaedic Surgeons,* 88 FTC 968 (1976).

171. *United States v the American Society of Anesthesiologists, Inc,* 1979-2 Trade Cases §62,739 (SDNY 1979).

172. *In re The American Academy of Orthopaedic Surgeons,* 105 FTC 248 (1985). See also, *In re Michigan State Medical Society,* 101 FTC 191 (1983).

173. Hsiao W, Braun P, Becker E et al: A National Study of Resource-Based Relative-Value Scale for Physician Services: Final Report. Boston, Harvard University School of Public Health, 1988.

174. Hsiao W, Braun P, Yntema D et al: Estimating physician's work for a resource-based relative-value scale. N Engl J Med 319:835, 1988.

175. Hsiao W, Braun P, Dunn D et al: Results and policy implications of the resource-based relative-value study. N Engl J Med 319:981, 1988.

176. Hsiao W, Braun P, Kelly N et al: Results, potential effects, and implementation issues of the resource-based relative-value scale. JAMA 260:2429, 1988.

177. Hsiao W, Braun P, Dunn D et al: Resource-based relative values: An overview. JAMA 260:2347, 1988.

178. American Society of Anesthesiologists: Relative Value Guide, 1989. Park Ridge, Ill, American Society of Anesthesiologists, 1989.

179. Omnibus Budget Reconciliation Act of 1993, 103 PL 66; 1993 HR 2264; 107 Stat 312, §13516.

180. 42 USC §1320a-7b (b).

181. *The Inspector General v Hanlester Network, Department of Health and Human Services; Departmental Appeals Board; Appellate Division;* Dec No 1275 (Sept 1991) (CCH Medicare and Medicaid Guide, para 39,556).

182. 42 CFR §1001.952 (a) (1), (2), (2) i-viii (July 1992).

183. *Code of Medical Ethics Report of the American Medical Association Council on Ethical and Judicial Affairs,* vol III, no 1. Chicago, American Medical Association, 1992, report 37.

184. Tax Equity and Fiscal Responsibility Act of 1982, Public Law 97-248, 96 Stat 324, 26 USC §1 et seq.

185. Omnibus Budget Reconciliation Act of 1986, Public Law 99-509, 100 Stat 1874, 7 USC §1929 (a) et seq.

186. Omnibus Budget Reconciliation Act of 1987, Public Law 100-203, 101 Stat 1330, 7 USC §1421 et seq.

187. 62 Federal Register 66726 et seq (12/19/97).

188. FY99 Omnibus Appropriations Bill. HR 4328 (Public Law 105-277).

APPENDIX: Practice Guidelines for Pulmonary Artery Catheterization[D]

A Report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization

I. Introduction

The balloon-flotation pulmonary artery (PA) catheter was introduced in 1970. [1] It has become an important tool for the evaluation and treatment of critically ill patients. PA catheter monitoring has expanded rapidly and broadly in clinical practice since the late 1970s. An estimated 2 million catheters are sold annually in the United States. [2]

The appropriate indications for PA catheter monitoring have been debated for over a decade. The potential benefits of using the device are well known. Its ability to measure important hemodynamic indices (*e.g.,* PA occlusion pressure, cardiac output, mixed venous oxygen saturation) allows more accurate determination of the hemodynamic status of critically ill patients than is possible by clinical assessment alone. The additional information can be important in caring for patients with confusing clinical pictures, in whom errors in fluid management and drug therapy can have important consequences. In surgical patients, PA catheter data often help to evaluate serious perioperative complications from hemodynamic changes. Preoperative PA catheter data are purported to be helpful in determining whether it is safe for high-risk patients to proceed with surgery.

PA catheterization can also have important adverse effects. Catheter insertion can result in unintended arteriotomy, pneumothorax, and arrhythmias. The catheter can be associated with potentially fatal pulmonary artery hemorrhage, thromboembolism, sepsis, and endocardial damage. The widespread use of PA catheters in the United States is also costly. Precise figures are lacking, but some authors have estimated that as much as two billion dollars may be spent each year in the United States on PA catheter use. [3] [4]

Several groups have issued statements on the appropriate indications for PA catheterization and on competency requirements for hemodynamic monitoring. These groups include the American College of Physicians/ American College of Cardiology/American Heart Association Task Force on Clinical Privileges in Cardiology, [5] a panel established by the Ontario Ministry of Health, [6] and an expert panel of the European Society of Intensive Care Medicine. [7] Few groups have performed a comprehensive review of evidence regarding the benefits, harms, and costs of PA catheterization.

The American Society of Anesthesiologists established the Task Force on Pulmonary Artery Catheterization in 1991 to examine the evidence for benefits and risks from PA catheter use in settings encountered by anesthesiologists. This report summarizes the task force's recommendations on PA catheterization and its rationale, based on scientific evidence and expert opinion. A complete description of the evidence reviewed by the task force is available in the full-length report.

Developed by the Task Force on Guidelines for Pulmonary Artery Catheterization: Michael F. Roizen, M.D. (Chairman), Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois; David L. Berger, M.D., (Private Practice) Piedmont; California; Ronald A. Gabel, M.D., Department of Anesthesiology, University of Rochester, Rochester, New York; John Gerson, M.D., (Private Practice) Syracuse, New York; Jonathan B. Mark, M.D., Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina; Robert I. Parks, Jr., M.D., (Private Practice) Dallas, Texas; David A. Paulus, M.D., Department of Anesthesiology, University of Florida, Gainesville, Florida; John S. Smith, M.D., (Private Practice) Las Vegas, Nevada; and Steven H. Woolf, M.D., M.P.H., (Methodology Consultant) Washington, D.C.

II. Methodology

Task force documents and primary evidence are available at the Wood Library, American Society of Anesthesiologists, Park Ridge, Illinois.

A. Task Force Composition

Members were selected by the American Society of Anesthesiologists Committee on Practice Parameters and by the task force chairman. The task force included four university-based anesthesiologists, four private-practice anesthesiologists, and a methodologist. Mean experience with PA catheter use was 14 yr (range of 7-28 yr). Task force members used an average of 11 PA catheters per month (range of 0-18 per month), primarily for cardiovascular surgery cases. Additional details about panel composition are in the full-length report.

B. Purpose and Focus

The objectives of the task force were to develop guidelines on the appropriate indications for PA catheter use. The purpose was not to describe how to perform the procedure or to interpret results. The task force sought to develop guidelines based on scientific evidence, supplemented by expert opinion, and to follow a systematic methodology for reviewing evidence and developing recommendations. The guidelines were intended for situations encountered by anesthesiologists and the perioperative care team. They do not address the use of PA catheters in non-surgical settings or by other medical specialties.

C. Process

The task force developed its recommendations following a systematic review of the clinical benefits and harms of PA catheterization. Benefits and harms were evaluated by reviewing relevant scientific evidence and expert opinion about effectiveness. The review was guided by an evidence model developed by the task force (fig. 1) . In addition to clinical effects, the panel also considered public policy issues, such as costs and implementation issues.

D. Review of Scientific Evidence

The review of scientific evidence included a detailed literature search, a critical appraisal of individual studies to assess methodologic quality, and a synthesis of the results.

1. Literature Search

The computerized and manual literature search was conducted in November 1991 and was updated in May 1992. It sought all relevant English-language literature published after 1972. A total of 860 clinical trials, controlled observational studies, uncontrolled case series reports, and individual case reports were considered.

2. Exclusion Criteria

Detailed exclusion criteria are described in the full-length report. The task force focused its review on evidence of effectiveness based on clinical outcomes. The task force did not directly examine the accuracy of PA catheter monitoring, the value of PA catheter data as predictors of morbidity and mortality, or evidence of

Figure 1 Evidence model for literature review. The outcomes (benefits, harms, costs) listed in this model represent the potential effects of PA catheterization that were identified by the task force before performing its literature review. The literature review was organized around this model to determine whether evidence existed to validate the potential benefits and harms that it had identified. Supporting evidence was found only for those linkages identified by an asterisk (*). Linkages not identified by an asterisk, which represent potential benefits that have not been studied, define important priorities for future research. [1] Decreased incidence of myocardial infarction, arrhythmias, congestive heart failure; [2] Length of surgery, duration of stay in post-anesthesia care unit and intensive care unit, and total hospital stay; [3] *E.g.* , trauma, infection, dysrhythmias due to catheterization.

the effectiveness of treatment for PA catheter-detectable conditions. Issues related to the performance of PA catheterization, such as rates of utilization, practitioner skill, resource constraints imposed by staff and equipment availability, medicolegal concerns, and reimbursement were not a specific focus of the literature review.

3. Evaluation of Individual Studies

The methodologic quality of individual studies was assessed in a systematic manner by considering study design category (*e.g.,* observational *vs.* experimental design) and the quality of the research methods (*e.g.,* statistical power, selection bias, measurement error, confounding variables, internal and external validity).

4. Synthesis of Results

The synthesis was narrative and utilized traditional evidence tables. Evidence of effectiveness was not suitable for formal meta-analysis. [*]

E. Assessment of Expert Opinion

The expert opinion of the task force was assessed by informal consensus development. Opinions of outside experts were obtained through critical peer review. Consensus within the task force was unanimous except where noted. All conclusions and recommendations that were based on expert opinion are documented explicitly.

F. Assessment of Public Policy Issues

Costs and implementation issues were considered by the task force only after the clinical benefits and harms of PA catheterization were studied. The task force's recommendations were based on perceived clinical benefits and harms and not on the cost-effectiveness of PA catheterization. Cost information provided in published clinical research was reviewed, but the task force did not seek out cost data from other sources (*e.g.,* payers, manufacturers). The panel's consideration of public policy issues was informed by a widely publicized open forum on the proposed guidelines, which was held in San Francisco in March 1992 at a large meeting of anesthesiologists.

G. Peer Review

The guideline underwent peer review by experts in PA catheterization and by relevant specialty societies and organizations. Reviewers are listed in table 1 .

TABLE 1 -- Outside Reviewers

Content Experts
Thomas J. Iberti, M.D., F.C.C.M., F.C.C.P.
Director, Critical Care
Associate Professor of Surgery, Medicine, and Anesthesiology
Mount Sinai Medical Center
New York, New York
Nathan L. Pace, M.D.
Professor of Anesthesiology
Adjunct Professor of Bioengineering
University of Utah
Salt Lake City, Utah
Jeffery S. Vender, M.D., F.C.C.M.
Chief, Division of Anesthesia
Director, Medical/Surgical Intensive Care Unit
Associate professor of Clinical Anesthesia
Northwestern University Medical School
Evanston, Illinois
Organizational Reviewers
American College of Cardiology
American College of Physicians
American College of Surgeons
Organizations that Received but Did Not Review the Document
Agency for Health Care Policy and Research
American College of Obstetricians and Gynecologists
American College of Pediatricians

III. Clinical Effectiveness of Pulmonary Artery Catheterization

Clinical effectiveness was judged by considering the benefits and harms of PA catheterization. Clinical benefits and harms were evaluated by reviewing relevant scientific evidence and expert opinion of effectiveness.

A. Scientific Evidence of Effectiveness

The results and design of individual studies are reviewed in detail in the full report. The following provides an overview of the findings. The results of controlled studies are summarized in table 2 .

1. Benefits

a. Effect on Treatment Decisions:

Survey studies in postoperative and intensive care units have demonstrated that PA catheter data appear to change therapy in 30-62% of cases. [8] [9] [10] [11] [12] [13] The clinical significance of these changes is uncertain. Treatment modifications were judged important in 25% of adults [11] and in 10% of children [14] monitored by PA catheter. Studies have found no effect on mortality among patients whose therapy is altered based on PA catheter data. [12] [13]

The quality of this evidence is poor. The conclusions are based largely on self-reported data in questionnaires,

* The task force recommends consideration of a meta-analysis of data on the adverse effects of PA catheterization.

which are subject to measurement and recall biases. Most studies were unblinded and, in many cases, judgments about whether treatment was altered based on PA catheter data were made subjectively. Sample sizes were inadequate to conclude that alterations in treatment had no effect on mortality, and clinical outcomes beside mortality were not examined.

b. Preoperative Catheterization:

Uncontrolled case series reports have shown that preoperative PA catheterization is associated with cancellation or modification of surgical procedures, and investigators have concluded that it therefore prevents mortality. [15] Post-hoc data analysis in one trial demonstrated a lower mortality rate in patients who were monitored preoperatively than in patients who were first monitored after surgery. [4] Another trial suggested that preoperative catheterization reduced intraoperative complications and graft thrombosis in patients undergoing peripheral vascular surgery. [16] Catheterization 12 h before surgery did not produce better outcomes than catheterization 3 h before surgery. An observational study found no difference in outcomes between elderly patients who did not undergo preoperative catheterization and unmatched patients who were admitted to the hospital during the same time period for other reasons. [17] The similar outcomes may have been due to selection biases.

c. Perioperative Monitoring:

A randomized controlled trial involving 146 patients found no difference in intraoperative mortality, length of hospital stay, length of intensive care unit (ICU) stay, ventilator usage, or postoperative mortality when surgical patients monitored by PA catheter were compared with central venous catheter (CVC)-monitored patients. [18] However, sample size may have been inadequate to reveal a true benefit. Patients monitored by PA catheter who were managed with the goal of achieving supranormal metabolic goals appeared to have significantly lower postoperative mortality, length of ICU stay, and ventilator usage. Due to uncertain methodology and inconsistent data reporting, it is unclear whether this group of patients differed in case mix from other patients monitored by PA catheter.

An observational study of 733 patients found that patients with previous myocardial infarction who underwent noncardiac surgery during a period when invasive hemodynamic monitoring was common had lower reinfarction and mortality rates than patients in previous years during which invasive monitoring was less common. [19] It is unclear from this study whether hemodynamic monitoring or other temporal factors were responsible for the improved outcomes and whether the two groups of nonrandomly selected patients were comparable in terms of case mix and severity of illness.

i. Cardiac Surgery:

Uncontrolled observational studies that examined outcomes in cardiac surgery patients who were monitored by PA catheter [20] [21] [22] [23] [24] [25] have been limited by the lack of comparison data from unmonitored patients. A small study that included historical controls found that patients who underwent PA catheterization for repair of left main coronary artery stenosis had lower rates of perioperative myocardial infarction, ventricular fibrillation, and deaths than patients from the previous year who were monitored by CVC. [26] However, the historical design leaves unanswered questions about whether the results were due to temporal factors or differences in case mix.

Studies that included internal controls found little difference in outcomes. A controlled retrospective observational study of 1094 patients found no difference in measured outcomes (*e.g.,* mortality, cardiac ischemia, postoperative myocardial infarction) among coronary artery bypass graft patients who were monitored by CVC, elective PA catheterization, or emergency PA catheterization. [27] High-risk patients who underwent elective PA catheterization had longer ICU stays and were more likely to receive vasopressor agents. These differences and the lack of observed differences in other outcomes may have been due to case mix, since patient assignment to groups was made selectively.

A randomized controlled trial involving 226 patients found no difference in measured outcomes (deaths, length of ICU stay, use of vasopressors) between coronary artery bypass graft patients monitored by PA catheter and CVC, but this may have been due to small sample size and selection biases. Patients were removed selectively from the control group after randomization if the anesthesiologist thought that they required PA catheterization. [28]

ii. Peripheral Vascular Surgery:

A randomized controlled trial found that patients undergoing peripheral vascular surgery were less likely to experience intraoperative disorders (tachycardia, hypotension, arrhythmia) if PA catheters were placed preoperatively and if hemodynamic status was optimized. [16] The overall incidence of postoperative complications (renal failure, congestive heart failure, myocardial infarction, graft thrombosis, death) appeared to be lower in the patients monitored by PA catheter. This was due mainly to a higher incidence of postoperative graft thrombosis

TABLE 2 -- Controlled Studies of Pulmonary Artery Catheterization with Clinical Outcomes *

Study	Location	N	Clinical Setting	Study Design	Significant Clinical Outcomes	Comments
General Surgery						
Shoemaker *et al.* (1988)	Los Angeles, California	146	General surgery in high-risk patients	RCT; groups = CVC, PAC-normal,PAC-supranormal	Post-operative mortality, mean ICU stay, ventilator use lower in PAC-supranormal group	Small sample size, poor control for confounding, uncertain case mix
Rao *et al.* (1983)	Maywood, Illinois	733/364	Noncardiac surgery in patients with prior myocardial infarction	Obs-historical controls; 1977-1982 cohort vs. 1973-76 cohort	Lower perioperative reinfarction and mortality rates in study cohort	Historical controls, nonrandom selection, uncertain case mix, role of hemodynamic monitoring unclear
Cardiac Surgery						
Pearson *et al.* (1989)	Iowa City, Iowa	226	Elective cardiac surgery	RCT; groups = CVC, PAC, PAC With mixed venous oxygen	None	Small sample size, significant crossover between groups
Tuman *et al.* (1989)	Chicago, Illinois	1094	Elective coronary artery bypass graft surgery	Controlled prospective cohort	Mean ICU stay greater in PAC high-risk group than CVC group	Nonrandom selection, uncertain case mix
Moore *et al.* (1978)	Beaumont, Texas	28/20	Surgery for left main coronary artery stenosis	Obs-historical controls; study cohort vs. previous year	Lower rates of perioperative myocardial infarction, ventricular fibrillation, deaths in PAC vs. CVC	Historical controls, nonrandom selection, statistical significance not reported
Peripheral Vascular Surgery						

Berlauk *et al.* (1991)	Minneapolis, Minnesota	89	Vein graft arterial bypass for limb salvage	RCT; groups = PAC 12 and 3 hrs before surgery, no preoperative PAC	Fewer intraoperative hemodynamic disorders and postoperative graft thromboses	Uncertain group assignment methods, discrepancies in data reporting regarding cardiac morbidity
Aortic Reconstruction						
Isaacson *et al.* (1990)	Atlanta, Georgia	102	Abdominal aortic reconstruction	RCT; groups = CVC, PAC	No difference in morbidity, mortality, ICU or hospital stay	Possible type II error
Joyce *et al.* (1990)	Toronto, Canada	40	Abdominal aortic aneursym repair	RCT; groups = CVC, PAC. Comparison group of 11 high-risk patients	ICU stay longer in CVC and high-risk patients (combined) then PA catheter	Small sample size, comparison of CVC and PAC ICU stay not reported
Headorffer *et al.* (1987)	Johannesburg, South Africa	61/87	Abdominal aortic aneurysm repair	Obs-historical controls; 1983-1984 cohort vs. 1980-1982 cohort	Lower perioperative hypotensive episodes and mortality in study cohort than historical controls	Historical controls, nonrandom selection, does not compare PA catheter use, inconsistent data, uncertain attrition, statistical significance not reported

RCT=randomized controlled trial (composition of randomized groups described); Obs-historical=observational study with historical controls; PAC=patients monitored by pulmonary artery catheter; CVP=patients monitored by central venous pressure measurements.

* See text for results of uncontrolled studies and case series.

In observational studies with historical controls, sample size of study group and historical cohort reported.

Does not include outcomes for which no significant benefit observed.

in the control group, which was attributed to poor cardiac output. Postoperative morbidity and mortality otherwise did not differ between groups. The reported data do not support the authors' conclusion that postoperative morbidity was reduced. The study was limited by discrepancies in data reporting and by uncertain methods for group assignment.

iii. Abdominal Aortic Reconstruction:

Although some case series reports have noted that outcomes in patients monitored by PA catheter were better than adjusted rates for the general population, [29] the absence of control groups limits the value of the data. A study with historical controls found that mortality, perioperative hypotensive episodes, and renal failure were less common in patients who received an aggressive fluid management protocol that included PA catheterization than in previous patients who did not receive the protocol. [30] The study was limited by its historical design, inconsistent data reporting, unexplained attrition, and the fact that PA catheterization was only one component of the protocol. Two randomized controlled trials of patients undergoing abdominal aortic reconstruction found no difference in outcomes between patients monitored by PA catheter and CVC. [31] [32]

iv. Neurosurgery:

An uncontrolled case series and an observational study with a comparison group have examined the effectiveness of PA catheterization in patients undergoing neurosurgical procedures. [33] [34] The studies only addressed the ability of PA catheters to detect air embolism and did not measure clinical outcomes. An uncontrolled observational study of pediatric head trauma patients who underwent monitoring that included PA catheterization reported lower mortality rates than published rates for patients with similar trauma scores. [35] The study lacked internal controls, and PA catheterization was only one of multiple interventions that were offered.

d. Obstetric-Gynecologic Procedures:

Evidence regarding the effectiveness of PA catheterization in obstetrics and gynecology is lacking. It has been recommended for severe preeclampsia [36] and case reports have supported its value, [37] but controlled clinical outcome studies have not been reported. Case reports have also described PA catheter use in uncommon obstetric settings. [38] [39] Uncontrolled case series have examined mortality and other outcomes in series of obstetric and gynecologic surgical patients that underwent PA catheterization, but they did not include control groups for comparison. [40] [41]

e. Pediatric Catheterization:

PA catheterization is performed in critically ill new-borns, infants, and children, [14] but few studies have evaluated its effect on clinical outcomes. Uncontrolled case series reports have shown that it is useful in clarifying diagnoses, but these studies have not examined clinical outcomes or included unmonitored controls. [42] [43]

f. Hemodynamic Disorders:

Numerous studies have examined the benefits of PA catheterization in critically ill patients with severe hemodynamic disorders. Although the subjects in the studies were usually medical patients who did not undergo surgery, the studies were reviewed because the hemodynamic disorders that prompted PA catheter use

(*e.g.,* myocardial infarction, sepsis, pulmonary edema) include the principal risk factors for which surgical patients often undergo PA catheterization.

Uncontrolled studies have produced inconsistent findings. [44] [45] Studies with control groups have generally found that patients with myocardial infarction and other hemodynamic disorders who are monitored by PA catheters have higher in-hospital mortality, longer hospital stay, and shorter long-term survival than patients who do not undergo PA catheterization. [46] [47] [48] Although these studies have included large samples (300-6,000 patients), their designs were retrospective and failed to control adequately for differences in severity of illness, selection bias, and variation in catheter use. The data therefore do not clarify whether patients who underwent PA catheterization were sicker than unmonitored patients. A study with historical controls reported that mortality in patients with septic shock decreased during a period in which PA catheterization had increased, but the study design provided weak evidence that PA catheters had a causal role. [49]

2. Harms

Evidence regarding the adverse effects of PA catheterization comes from studies that examined multiple complications [50] [51] [52] [53] [54] [55] [56] [57] [58] [59] and from studies of specific complications. Only potentially life-threatening complications were considered by the task force. The reported incidence of complications is summarized in table 3 . The designs and complications rate of individual studies are provided in the full-length report.

In summary, complications from PA catheterization can occur with the establishment of central venous access, the catheterization procedure, and catheter residence. Complications of establishing central venous access include unintentional puncture of nearby arteries, (*e.g.,* carotid or subclavian artery), [60] bleeding, neuropathy, air embolism, and pneumothorax. [61]

Dysrhythmias are the primary complication of the catheterization procedure. Minor dysrhythmias, such as premature ventricular and atrial contractions, occur commonly with catheter insertion but usually resolve spontaneously after the catheter is advanced or withdrawn through the right ventricle. [62] [63] [64] Ventricular tachycardia or fibrillation occur occasionally and can usually be cardioverted with antiarrhythmic agents or electrical defibrillation. [65] [66] Catheter advancement can produce right bundle-branch block and, in patients with preexisting left bundle-branch block, can precipitate complete heart block. [67] [68] [69]

TABLE 3 -- Reported Incidence of Adverse Effects

Complication	Reported Incidence (%)
Central Venous Access	
Arterial puncture	1.1-13
Bleeding at cut down site (children)	5.3
Postoperative neuropathy	0.3-1.1
Pneumothorax	0.3-4.5
Air embolism	0.5
Catheterization	
Minor dysrhythmias *	4.7-68.9
Severe dysrhythmias (ventricular tachycardia or fibrillation) *	0.3-62.7
Right bundle-branch block *	0.1-4.3
Complete heart block (in patients with prior LBBB) *	0-8.5
Catheter Residence	
Pulmonary artery rupture *	0.1-1.5
Positive catheter-tip cultures	1.4-34.8
Catheter-related sepsis	0.7-11.4
Thrombophlebitis	6.5
Venous thrombosis	0.5-66.7
Pulmonary infarction *	0.1-5.6
Mural thrombus *	28-61
Valvular/endocardial vegetations or endocarditis *	2.2-100
Deaths (attributed to PA catheter) *	0.02-1.5

* Complications thought to be more common (or exclusively associated) with PA catherizaion than with central venous catheterization.

Complications of catheter residence include venous thrombosis, [70] thrombophlebitis, and pulmonary embolism and infarction. [71] Autopsy studies have revealed evidence of mural thrombi, endocarditis, and valvular injury in patients with indwelling PA catheters. [72] [73] [74] [75] [76] A serious complication of PA catheters is pulmonary artery rupture. [77] [78] [79] Mortality from this complication has been estimated to be 53%, [80] a rate that can be influenced by a variety of factors (*e.g.,* age, pulmonary hypertension, coagulopathy, heparinization).

Sepsis is a potential complication of PA catheter residence but its exact incidence is uncertain. Cultures of indwelling PA catheter tips are often positive, [81] [82] [83] [84] [85] but it is unclear whether these represent contamination, colonization from another source, or the primary nidus of infection. Incidence rates for culture-positive catheters, positive blood cultures, and catheter-related sepsis therefore vary considerably in the literature.

The rate of iatrogenic deaths from PA catheterization is uncertain. Patients who are monitored by PA catheter have high mortality rates, but in few cases is it possible to attribute their deaths specifically to PA catheterization and not the underlying illness.

B. Expert Opinion of Effectiveness

Currently available evidence from published research provides incomplete information about the effectiveness of PA catheter monitoring and the incidence of complications. Gaps in the evidence occur at several levels. First, surgical procedures that have been examined in studies of PA catheterization (*e.g.,* cardiac surgery, abdominal aortic reconstruction, neurosurgery) represent only a subset of clinical settings for which PA catheters are used. Second, available studies generally suffer from poor design and lack statistical power to demonstrate benefit. Third, available data generally do not control for differences in case mix and practitioner skill and therefore may not be generalizable to typical practice conditions.

Due to deficiencies in the evidence, it is difficult to draw meaningful conclusions about the effectiveness and safety of PA catheterization based on currently available data. There is a great need for additional research to provide this information (see "Research Agenda" below). In the meantime, important insights about the benefits and harms of PA catheterization can be obtained from clinical experience. The task force acknowledges the limitations of expert opinion, which include subjectivity, recall bias, nonuniformity of measures, and confounding.
With these caveats in mind, the following observations about the benefits and harms of PA catheterization are offered:

Clinical experience suggests that PA catheter monitoring of selected surgical patients can reduce the incidence of perioperative complications, primarily by providing immediate access to critical hemodynamic data. The expert opinion of the task force is that access to these data, coupled with accurate interpretation and appropriate treatment tailored to hemodynamic status, can reduce perioperative mortality and morbidity through reduced cardiac complications (*e.g.,* myocardial ischemia, congestive heart failure, arrhythmias), renal insufficiency, brain injury, and pulmonary complications. The task force also believes that PA catheter use may reduce length of stay in the hospital and intensive care unit, enhance postoperative functional status, and reduce the need for transfused blood products through optimization of fluid therapy. The task force believes the use of PA catheters in selected obstetric patients may reduce maternal and neonatal morbidity and mortality.

Although these benefits may not be realized in every surgical patient who is catheterized, the task force believes that having immediate access to PA catheter data allows important preemptive measures for that subset of patients who encounter hemodynamic disturbances that require immediate and precise decisions about fluid management and drug treatment. The exact proportion of patients for whom this applies and the magnitude of benefit from PA catheterization are uncertain. However, the task force believes that reliance on clinical assessment or alternative devices (*e.g.,* CVC monitoring) and the delay associated with PA catheter placement after complications have developed may endanger the patient and may increase the risk of complications from insertion. Emergency catheterization under hastily prepared sterile conditions may increase the risk of vascular injury and catheter-related sepsis. Prospective studies have found that the relative risk for catheter-related sepsis is 2.1 when PA catheters are inserted in the operating room under less stringent sterile technique. [86]

Numerous studies have shown that PA catheter data are more accurate than clinical assessment in evaluating the hemodynamic status of complicated patients. [8] [9] For postoperative patients, who have less immediate access to physicians after leaving the operating room, PA catheter data and trained nurses provide an important means of rapidly communicating precise information about hemodynamic status to physicians not at the bedside. This enables immediate execution of treatment decisions that are tailored to the patient's physiologic state.

The task force believes that these benefits have not been demonstrated in currently available research because most of these outcomes have not been properly evaluated. It is suggested that a properly designed randomized controlled trial with adequate sample size, well trained physicians and nurses, and meaningful outcome measures would reveal the benefits observed in practice. Meaningful outcome measures would include perioperative mortality and the incidence of cardiac, renal, and neurologic end-organ damage due to perioperative complications from hemodynamic changes. It is recognized that the performance of such a study might be difficult due to logistical and ethical considerations.

"Nonuniformity of measures" refers to lack of standardization and inconsistencies among experts in defining interventions and outcomes. "Confounding" refers to factors that may have a causal role in affecting outcomes that may not be consciously considered by experts in assessing effectiveness.

The generalizability of research findings to practice conditions is often limited. For example, the task force believes that outcomes for experienced clinicians may differ significantly from published rates, because catheterizations in clinical studies were often performed by less experienced physicians (*e.g.,* house staff) or in early years, when outmoded techniques and materials were used. The task force believes that experience and understanding are major determinants of PA catheter effectiveness. Experienced PA catheter users can achieve better outcomes and encounter fewer complications because of their enhanced skill in the interpretation of PA catheter data, in the prompt design of rational treatment strategies, and in the use of safe techniques of catheter insertion and balloon management. Characteristics of the practice setting, such as the skill of nurses and their attentiveness to PA catheter tracings, also influence significantly the outcome of PA catheter use.

There is compelling evidence that PA catheterization can result in serious and potentially fatal complications. Catheterization is therefore inappropriate as a routine practice in surgical patients and should be limited to cases in which the anticipated benefits of catheterization outweigh the potential risks. The actual complication rate is uncertain, in part because of variability in the designs and results of studies of complications and in part because only a subset of reported complications is attributable uniquely to PA catheters. Unintentional arteriotomy, pneumothorax, line sepsis, and similar complications also occur with the principal alternatives to PA catheterization (*ie.,* CVC monitoring). Published rates for certain complications are based on old studies that may not reflect recent advances. For example, venous thrombosis has been reduced by the use of heparin-bonded catheters. [87] The opinion of the task force based on clinical experience is that serious complications due specifically to PA catheterization (pulmonary artery rupture, serious ventricular dysrhythmias, endocardial lesions) occur in 0.1-0.5% of monitored surgical patients.

The task force believes that this risk is acceptable in selected surgical patients undergoing procedures associated with complications from hemodynamic changes (*e.g.,* cardiac surgery, aortic reconstruction) or entering surgery with preexisting risk factors for hemodynamic disturbances (*e.g.,* advanced cardiopulmonary disease). The role of PA catheterization in lowrisk patients is less certain, and there is less consensus within the panel as to whether the potential benefits outweigh the risks. Routine catheterization in low-risk surgical patients is often inappropriate. The decision to use PA catheters in this population should be based on individual circumstances and a careful assessment of the patient's risk factors and personal preferences.

/das/book/view/29494766/875/946.html

IV. Public Policy Issues

Although the recommendations in this report are based primarily on clinical benefits and harms, the following resource and implementation issues were considered by the task force in structuring its recommendations:

A. Costs

The costs of PA catheterization include the costs of equipment (*e.g.* PA catheters, pressure transducers, electronic monitoring devices, solutions) and personnel (*e.g.,* physician costs for insertion and interpretation, nurses, technicians). There is limited information from published literature about the actual costs of PA catheterization. It has been estimated that the procedure costs $ 300-500 per catheterization. [88] One study reported that mean total charges (monitoring catheter, physician charges for catheter insertion, hemodynamic measurements) were $ 855 per patient monitored by PA catheter and $ 1128 per patient for those who also received mixed venous O_2 measurements. [28] Another study found that the anesthesiologist's fee was an average of $ 188 higher for PA catheterization than for CVC monitoring. [32] On a national scale, it has been estimated that two billion dollars are spent each year on PA catheter use. [3] [4] There are no published cost-benefit or cost-effectiveness analyses of PA catheter monitoring.

B. Implementation Issues

In addition to clinical benefits, harms, and costs, the task force also considered patient and provider concerns that could influence implementation of the guideline:

1. Patient Concerns

1. *a. Access to Care:*
   Some disadvantaged patients who meet criteria for PA catheterization may lack access to hospitals with facilities and qualified personnel to perform the procedure.
2. *b. Personal Preferences:*
   Patients may have different preferences about the desirability of PA catheterization, depending on the relative importance they place on potential benefits and

   harms. Patients with the ability and desire to participate in the decision require information about the probability of potential outcomes and the potential impact on morbidity and mortality.
3. *c. Comfort:*
   Insertion of the PA catheter in the operating room may be more comfortable, less anxiety-provoking, and induce less physiologic stress than preoperative catheterization.

2. Provider Concerns

1. *a. Independent Decision-making:*
   Due to uncertainties in the scientific evidence, providers require flexible guidelines that do not interfere with the ability to make independent assessments in individual cases.
2. *b. Ease of Use:*
   Recommendations should be clear, specific, and rapidly interpretable to be useful in patient care. Conversely, recommendations that are too rigid in the absence of adequate evidence or that introduce restrictive administrative rules may interfere with the proper delivery of care.
3. *c. Competency and Training:*
   The appropriateness of PA catheterization and the determination of whether benefits exceed risks hinge on the competence of physicians and nurses in catheter use. This competence encompasses both technical and cognitive skills, which are first acquired in residency or post-residency training. Maintenance of skills following training often requires regular catheter use. Because PA catheterization by persons who have not maintained these skills is potentially harmful to patients and could threaten the acceptability of the procedure, it is important for the profession to periodically assess technical and cognitive performance. The best measure of competence is clinical outcome, but long periods of observation and careful data analysis may be necessary to obtain meaningful information. Surrogate measures such as the frequency of catheter use or the results of proficiency examinations may be the best alternative, but they are imperfect measures of competence.
4. *d. Reimbursement:*
   Although reimbursement for PA catheterization is important to providers, this document is not intended and should not be used as a basis for determining coverage policy. The task force is specifically opposed to the use of guidelines to require precertification for reimbursement for PA catheterization.
5. *e. Utilization Review and Medicolegal Liability:*
   Due to limitations in scientific evidence about the limits of appropriateness for PA catheterization, guidelines based on expert opinion should not be used as standards of care or to define cases of unnecessary catheterization.

V. Recommendations

The following recommendations are based on expert opinion, informed by scientific evidence.

Indications

A. Perioperative PA catheterization should be considered in surgical settings associated with an increased risk because of complications from hemodynamic changes. The risk of hemodynamic disturbance should be assessed as a function of three interrelated variables: the health status of the patient, the type of surgical procedure, and the characteristics of the practice setting. Consideration of the interrelationships between these three variables (fig. 2) aids in the accurate assessment of hemodynamic risk.

Patient

Patients at increased risk for hemodynamic disturbances are those with clinical evidence of significant cardiovascular disease, pulmonary dysfunction, hypoxia, renal insufficiency, or other conditions associated with hemodynamic instability (*e.g.,* advanced age, endocrine disorders, sepsis, trauma, burns). The assessment of risk should be based on a thorough analysis of the medical history and physical examination findings, rather than exclusive consideration of specific laboratory results or other quantitative criteria.

Procedure

Surgical procedures associated with an increased risk of complications from hemodynamic changes, including damage to the heart, kidneys, lungs, or brain, increase the chance of benefitting from PA catheterization. This report does not provide a list of indicated procedures and disease states for catheterization because the task force believes that catheterization decisions should be based on the hemodynamic risk characteristics of the individual case rather than on the type of procedure. Patients undergoing procedures that usually lack hemodynamic complications may need PA catheterization if circumstances pose a special risk. The clinician should therefore assess hemodynamic risks based on the case at hand and not on generic criteria.

Figure 2 Factors affecting risk of complications from hemodynamic changes.

/das/book/view/29494766/875/949.html

Practice Setting

The setting for the procedure may increase the risk of complications from hemodynamic changes. Factors that should be considered in assessing preoperative risk include physician skills, duration of procedure, and technical support. Factors affecting postoperative risk include the level of training and experience of nursing staff in the recovery room and intensive care unit, technical support for ancillary services, and the availability of specialists and equipment to manage potential complications detected by the PA catheter.

B. PA catheterization is not recommended when the patient, procedure, and practice setting each pose a low risk for hemodynamic complications, as defined above. The triangle in figure 2 defines the appropriate settings for PA catheterization. In certain cases, the alternative to PA catheterization should be CVC or noninvasive monitoring, rather than no hemodynamic monitoring.

Preoperative Catheterization

C. There is insufficient evidence to support preoperative PA catheter monitoring (*e.g.,* the evening before surgery) in patients who are hemodynamically stable. The risk of catheter-related sepsis and other complications appears to increase significantly if catheterization extends beyond 72 h in duration. [81] [82] [86] It is recognized that preoperative PA catheterization is often under the control of other medical specialists, such as cardiologists, pulmonologists, and surgeons.

Competency

D. Due to the risk of complications from PA catheterization, the procedure should not be performed by clinicians who lack competence in safe insertion or in the accurate interpretation of results. Competence in catheter placement is related to experience and is a function of the quality of the initial training and regular performance of the procedure after training.

1. All persons who use PA catheters should undergo high-quality, supervised training to establish competency.
2. A quality improvement program must be in place at all sites where PA catheters are used. Maintenance of knowledge and skills should be evaluated based on clinical outcomes. Proficiency examinations, simulation testing, and frequency of recent catheterizations may also aid in the evaluation process.
3. Competence in the interpretation of catheter data should be based on cognitive requirements, such as those outlined by the American College of Physicians/American College of Cardiology/American Heart Association Task Force on Clinical Privileges in Cardiology (table 4) (Table Not Available)
4. Nurses who provide care to patients who are monitored by PA catheter should be required to meet minimum training requirements for catheter maintenance and for the interpretation and communication of PA catheter data.

Note: These recommendations are intended as general guidelines. Departure from these guidelines should not necessarily be viewed as inappropriate care. The recommendations are intended for practitioners in the United States; elements of the recommendations and the principles on which they are based may also apply to practice settings in other countries. The recommendations are based on currently available evidence and should be updated as relevant new data become available.

VI. Research Agenda

Additional research is needed to demonstrate the effectiveness of PA catheterization. Deficiencies in current

TABLE 4 -- Cognitive Skills for Hemodynamic Monitoring
Reprinted from American College of Physicians/American College of Cardiology/ American Heart Association Task Force on Clinical Privileges in Cardiology: Clinical competence in hemodynamic monitoring. J Am Coll Cardiol 15:1463, 1990.

(Not Available)

evidence suggest that future studies should emphasize certain design features to provide more meaningful evidence. Future studies should use relevant clinical outcome measures to judge effectiveness, including measures of morbidity (*e.g.,* Cardiac, pulmonary, renal, and neurologic disease; patient functional status after discharge) and mortality (*e.g.,* in-hospital fatality rates, 5-yr survival, quality-adjusted life years). Intermediate physiologic outcomes should not be used as measures of effectiveness.

Future studies should include adequate sample sizes to demonstrate statistically significant effects. Investigators should perform power calculations before initiating studies to confirm the adequacy of the sample size. Researchers should collect adequate information about severity of illness and comorbid variables to help separate the influence of these factors from the effects of PA catheterization on observed clinical outcomes. Studies must be clear about the endpoints of treatment, specifying the hemodynamic indices that clinicians use to make decisions based on PA catheter data. Published reports from studies should provide complete information about methodology and complete data reporting to minimize confusion about statistical calculations. Many authors have emphasized the need for well designed randomized controlled trials to test the effectiveness of PA catheterization. [89] The task force supports the need for such research but is concerned about logistical and ethical problems with randomizing the allocation of PA catheters in critically ill patients. Of particular concern is the potential contamination of control groups. This crossover effect has occurred frequently in past research when patients assigned to receive no monitoring or CVC monitoring were subsequently reassigned by their physicians to undergo PA catheterization because of clinical deterioration or because the physicians were uncomfortable with the group assignment.

The task force therefore recommends that future randomized controlled trials should use low-risk patients (*e.g.,* no renal or pulmonary disorders, ejection fraction greater than 50%) to minimize the potential for crossover and should restrict the analysis to a specific type of surgery (*e.g.,* coronary artery bypass graft surgery). Physicians participating in such studies should adhere closely to the protocol and should not violate the design by reassigning patients following randomization. Studies that use low-risk patients may require large sample sizes to demonstrate statistically significant results, depending on power calculations, and therefore multicenter involvement may be necessary. The study should be performed in a setting attuned to the management of postoperative hemodynamic status, and the control groups should be monitored by CVC or other appropriate alternate methods (*e.g.,* transesophageal echocardiography).

The optimal randomized controlled trial will provide evidence from only one class of patients and one type of surgery. To provide more comprehensive data about the effects of PA catheterization, the task force recommends the performance of a large-scale multicenter

observational study that (1) includes adequate numbers of patients for each indication; (2) collects adequate data to generate a comprehensive database regarding past medical history, comorbidity, severity of illness, hospital course, and immediate and long-term clinical outcomes; and (3) provides details about catheter insertion techniques, practitioner skills, and data interpretation. For example, rather than stating that PA catheter monitoring was performed for 48 h, the investigators should document the type of device, the specific hemodynamic variables that were measured, and the manner in which PA catheter data were used to make treatment decisions.

If properly designed randomized studies in low-risk patients do not demonstrate a potential benefit from PA catheter monitoring, the task force recommends the performance of similar studies in high-risk patients and would urge adherence to randomization (*e.g.,* not providing PA catheterization to patients in the control group). Ultimately, the state of knowledge will need to move beyond expert opinion to provide objective evidence about the benefits and harms of PA catheterization.

References

1. Swan HJC, Ganz W, Forrester JS, et al: Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med 283:447-451, 1970

2. Swan HJ: The pulmonary artery catheter. Dis Mon 37:473-543, 1991

3. Califano JA Jr: America's Health Care Revolution: Who Lives? Who Dies? Who Pays? New York, Random House, 1986

4. Shoemaker WC: The efficacy of central venous and pulmonary artery catheters and therapy based upon them in reducing mortality and morbidity. Arch Surg 125:1332-1338, 1990

5. American College of Physicians/American College of Cardiology/American Heart Association Task Force on Clinical Privileges in Cardiology: Clinical competence in hemodynamic monitoring. J Am Coll Cardiol 15:1460-1464, 1990

6. Technology Subcommit TEE of the Working Group on Critical Care, Ontario Ministry of Health: Hemodynamic monitoring: A technology assessment. Can Med Assoc J 145:114-121, 1991

7. European Society of Intensive Care Medicine: Expert panel: The use of the pulmonary artery catheter. Intensive Care Med 17:I-VIII, 1991

8. Connors AF Jr, Dawson NV, McCaffree DR, Gray BA, Siciliano CJ: Assessing hemodynamic status in critically ill patients: Do physicians use clinical information optimally? J Crit Care 2:174-180, 1987

9. Eisenberg PR, Jaffe AS, Schuster DP: Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. Crit Care Med 12:549-553, 1984

10. Quinn K, Quebbeman EJ: Pulmonary artery pressure monitoring in the surgical intensive care unit: Benefits vs difficulties. Arch Surg 116:872-876, 1981

11. Rekik N, Brochard L, Rauss A, Brun-Buisson C, Teboul JL, Andrivet P, Besbes M, Messadi AA, Lemaire F: Prospective assessment of the benefit and risk of Swan Ganz catheter in critically ill patients (abstr). Am Rev Respir Dis 139:A17, 1989

12. Tuchschmidt J, Sharma OP: Impact of hemodynamic monitoring in a medical intensive care unit. Crit Care Med 15:840-843, 1987

13. Steingrub JS, Celoria G, Vickers-Lahti M, Teres D, Bria W: Therapeutic impact of pulmonary artery catheterization in a medical/surgical ICU. Chest 99:1451-1455, 1991

14. Katz RW, Pollack MM, Weibley RE: Pulmonary artery catheterization in pediatric intensive care. Adv Pediatr 30:169-190, 1983

15. Del Guercio LRM, Cohn JD: Monitoring operative risk in the elderly. JAMA 243:1350-1355, 1980

16. Berlauk JF, Abrams JH, Gilmour IJ, O'Connor SR, Knighton DR, Cerra FB: Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: A prospective, randomized clinical trial. Ann Surg 214:289-299, 1991

17. Schrader LL, McMillen MA, Watson CB, MacArthur JD: Is routine preoperative hemodynamic evaluation of nonagenarians necessary? J Am Geriatr Soc 39:1-5, 1991

18. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS: Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94:1176-1186, 1988

19. Rao TLK, Jacobs KH, El-Etr AA: Reinfarction following anesthesia in patients with myocardial infarction. ANESTHESIOLOGY 59:499-505, 1983

20. Pierson MG, Funk M: Technology versus clinical evaluation for fluid management decisions in CABG patients. Image J Nurs Sch 21:192-195, 1989

21. Bashein G, Johnson PW, Davis KB, Ivey TD: Elective coronary bypass surgery without pulmonary artery catheter monitoring. ANESTHESIOLOGY 63:451-454, 1985

22. Prakash O, Meij SH, van der Borden SG, Clementi G, Mak J: Cardiovascular monitoring with special emphasis on mixed venous oxygen measurements. Acta Anaesthesiol Beig 29:253-258, 1978

23. Lehot JJ, Carre R, Cottet-Emard JM, Guidollet J, Estavove S: Does Swan-Ganz catheter help weaning from mechanical ventilation after mitral valve replacement? Presse Med 17:2121-2124, 1988

24. Kaplan JA, Wells PH: Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 60:789-793, 1981

25. Sanchez R, Wee M: Perioperative myocardial ischemia: Early diagnosis using the pulmonary artery catheter. J Cardiothorac Vasc Anesth 5:604-607, 1991

26. Moore CH, Lombardo R, Allums JA, Gordon FT: Left main coronary artery stenosis: Hemodynamic monitoring to reduce mortality. Ann Thor Surg 26:445-451, 1978

27. Tuman KJ, McCarthy RJ, Spless BD, DaValle M, Hompland SJ, Dabir R, Ivankovich AD: Effect of pulmonary artery catheterization on outcome in patients undergoing coronary artery surgery. ANESTHESIOLOGY 70:199-206, 1989

28. Pearson KS, Gomez MN, Moyers JR, Carter JG, Tinker JH: A cost/benefit analysis of randomized invasive monitoring for patients undergoing cardiac surgery. Anesth Analg 69:336-341, 1989

29. Whittemore AD, Clowes AW, Hechtman HB, Mannick JA: Aortic aneurysm repair: Reduced operative mortality associated with

maintenance of optimal cardiac performance. Ann Surg 192:414-421, 1980

30. Hesdorffer CS, Milne JF, Meyers AM, Clinton C, Botha R: The value of Swan-Ganz catheterization and volume loading in preventing renal failure in patients undergoing abdominal aneurysmectomy. Clin Nephrol 28:272-276, 1987

31. Joyce WP, Provan JL, Ameli FM, McEwan P, Jelenich S, Jones DP: The role of central haemodynamic monitoring in abdominal aortic surgery: A prospective randomised study. Eur J Vasc Surg 4:633-636, 1990

32. Isaacson IJ, Lowdon JD, Berry AJ, Smith RB, Knos GB, Weitz FI, Ryan KL: The value of pulmonary artery and central venous monitoring in patients undergoing abdominal aortic reconstructive surgery: A comparative study of two selected, randomized groups. J Vasc Surg 12:754-760, 1990

33. Bedford RF, Marshall WK, Butler A, Welsh JE: Cardiac catheters for diagnosis and treatment of venous air embolism: A prospective study in man. J Neurosurg 55:610-614, 1981

34. Marshall WK, Bedford RF: Use of a pulmonary-artery catheter for detection and treatment of venous air embolism: A prospective study in man. ANESTHESIOLOGY 52:131-134, 1980

35. Kasoff SS, Lansen TA, Holder D, San Filippo J: Aggressive physiologic monitoring of pediatric head trauma patients with elevated intracranial pressure. Pediatr Neurosci 14:241-249, 1988

36. Clark SL, Cotton DB: Clinical indications for pulmonary artery catheterization in the patient with severe preeclampsia. Am J Obstet Gynecol 158:453-458, 1988

37. Hjertberg R, Belfrage P, Hagnevik K: Hemodynamic measurements with Swan-Ganz catheter in women with severe proteinuric gestational hypertension (preeclampsia). Acta Obstet Gynecol Scand 70:193-198, 1991

38. Berkowitz RL, Rafferty TD: Pulmonary artery flow-directed catheter use in the obstetric patient. Obstet Gynecol 55:507-511, 1980

39. Spapen HD, Umbrain V, Braekmans P, Huyghens L: Use of the Swan-Ganz catheter in amniotic fluid embolism (letter). Intensive Care Med 14:678, 1988

40. Clark SL, Horenstein JM, Phelan JP, Montag TW, Paul RH: Experience with the pulmonary artery catheter in obstetrics and gynecology. Am J Obstet Gynecol 152:374-378, 1985

41. Orr JW Jr, Shingleton HM, Soong SJ, Hatch KD, Bryant JW, Partridge EE, Austin JM, Taylor PT, Pearce SC: Hemodynamic parameters following pelvic exenteration. Am J Obstet Gynecol 146:882-892, 1983

42. Todres ID, Crone RK, Rogers MC, Shannon DC: Swan-Ganz catheterization in the critically ill newborn. Crit Care Med 7:330-334, 1979

43. Neches WH, Park SC, Lenox CC, Zuberbuhler JR, Mullins CE, McNamara DG: Pulmonary artery wedge pressures in congenital heart disease. Cathet Cardiovasc Diagn 3:11-19, 1977

44. Bayliss J, Norell M, Ryan A, Thurston M, Sutton GC: Bedside hemodynamic monitoring: Experience in a general hospital. Br Med J 287:187-190, 1983

45. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: An evaluation of outcome from intensive care in major medical centers. Ann Intern Med 104:410-418, 1986

46. Gore JM, Goldberg RJ, Spodick DH, Alpert JS, Dalen JE: A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. Chest 92:721-727, 1987

47. Zion MM, Balkin J, Rosenmann D, Goldbourt U, Reicher-Reiss H, Kaplinsky E, Behar S: Use of pulmonary artery catheters in patients with acute myocardial infarction: Analysis of experience in 5,841 patients in the SPRINT Registry. Chest 98:1331-1335, 1990

48. Bush HS, Taylor RW, Thoi L, Deppe SA, Dellinger RP: Does invasive hemodynamic monitoring improve survival in a medical intensive care unit (abstr)? Crit Care Med 17:S137, 1989

49. Reynolds NH, Haupt MT, Thill-Baharozian MC, Carlson RW: Impact of critical care physician staffing on patients with septic shock in a university hospital medical intensive care unit. JAMA 260:3446-3450, 1988

50. Katz JD, Cronau LH, Barash PG, Mandel SD: Pulmonary artery flow-guided catheters in the perioperative period: Indications and complications. JAMA 237:2832-2834, 1977

51. Elliott CG, Zimmerman GA, Clemmer TP: Complications of pulmonary artery catheterization in the care of critically ill patients: A prospective study. Chest 76:647-652, 1979

52. Nehme AE: Swan-Ganz catheter: Comparison of insertion techniques. Arch Surg 115:1194-1196, 1980

53. Sise MJ, Hollingsworth P, Brimm JE, Peters RM, Virgilio RW, Shackford SR: Complications of the flow-directed pulmonary artery catheter: A prospective analysis in 219 patients. Crit Care Med 9: 315-318, 1981

54. De Lange JJ: Pulmonary circulation pressures in surgical patients: The use of the Swan-Ganz catheter. Arch Chir Neerl 31:17-27, 1981

55. Boyd KD, Thomas SJ, Gold J, Boyd AD: A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. Chest 84:245-249, 1983

56. Davies MJ, Cronin KD, Domaingue CM: Pulmonary artery catheterization: An assessment of risks and benefits in 220 surgical patients. Anaesth Intensive Care 10:9-14, 1982

57. Shah KB, Rao TLK, Laughlin S, El-Etr AA: A review of pulmonary artery catheterization in 6,245 patients. ANESTHESIOLOGY 61:271-275, 1984

58. Horst HM, Obeid FN, Vij D, Bivins BA: The risks of pulmonary arterial catheterization. Surg Gynecol Obstet 159:229-232, 1984

59. Gill JB, Cairns JA: Prospective study of pulmonary artery balloon flotation catheter insertions. J Intensive Care Med 3:121-128, 1988

60. McNabb TG, Green LH, Parker FL: A potentially serious complication with Swan-Ganz catheter placement by the percutaneous internal jugular route. Br J Anaesth 47:895-897, 1975

61. Culpepper JA, Setter M, Rinaldo JE: Massive hemoptysis and tension pneumothorax following pulmonary artery catheterization. Chest 82:380-382, 1982

62. Shaw TJI: The Swan-Ganz pulmonary artery catheter: Incidence of complications, with particular reference to ventricular dysrhythmias, and their prevention. Anaesthesia 34:651-656, 1979

63. Sprung CL, Marcial EH, Garcia AA, Sequeira RF, Pozen RG: Prophylactic use of lidocaine to prevent advanced ventricular arrhythmias during pulmonary artery catheterization: Prospective double-blind study. Am J Med 75:906-910, 1983

64. Iberti TJ, Benjamin E, Gruppi L, Raskin JM: Ventricular arrhythmias during pulmonary artery catheterization in the intensive care unit: Prospective study. Am J Med 78:451-454, 1985

65. Sprung CL, Jacobs LJ, Caralis PV, Karpf M: Ventricular arrhythmias during Swan-Ganz catheterization of the critically ill. Chest 79:413-415, 1981

66. Lopez-Sendon J, Maqueda IG, Coma-Canella I, Dominguez F, Jadraque LM: Right ventricular infarction as a risk factor for ventricular fibrillation during pulmonary artery catheterization using Swan-Ganz catheters. Am Heart J 119:207-209, 1990

67. Thomson IR, Dalton BC, Lappas DG, Lowenstein E: Right bundle-branch block and complete heart block caused by the Swan-Ganz catheter. ANESTHESIOLOGY 51:359-362, 1979

68. Morris D, Mulvihill D, Lew WYW: Risk of developing complete heart block during bedside pulmonary artery catheterization in patients with left bundle-branch block. Arch Intern Med 147:2005-2010, 1987

69. Sprung CL, Elser B, Schein MH, Marcial EH, Shrager BR: Risk of right bundle-branch block and complete heart block during pulmonary artery catheterization. Crit Care Med 17:1-3, 1989

70. Chastre J, Cornud F, Bouchama A, Viau F, Benacerraf R, Gibert C: Thrombosis as a complication of pulmonary-artery catheterization via the internal jugular vein: Prospective evaluation by phlebography. N Engl J Med 306:278-281, 1982

71. Foote GA, Schabel SI, Hodges M: Pulmonary complications of the flow-directed balloon-tipped catheter. N Engl J Med 290:927-931, 1974

72. Ducatman BS, McMihan JC, Edwards WD: Catheter-induced lesions of the right side of the heart: A one-year prospective study of 141 autopsies. JAMA 253:791-795, 1985

73. Greene JF Jr, Fitzwater JE, Clemmer TP: Septic endocarditis and indwelling pulmonary artery catheters. JAMA 233:891-892, 1975

74. Pace NL, Horton W: Indwelling pulmonary artery catheters: Their relationship to aseptic thrombotic endocardial vegetations. JAMA 233:893-894, 1975

75. Rowley KM, Clubb KS, Smith GJW, Cabin HS: Right-sided infective endocarditis as a consequence of flow-directed pulmonaryartery catheterization: A clinicopathological study of 55 autopsied patients. N Engl J Med 311:1152-1156, 1984

76. Sasaki TM, Panke TW, Dorethy JF, Lindberg RB, Pruitt BA: The relationship of central venous and pulmonary artery catheter position to acute right-sided endocarditis in severe thermal injury. J Trauma 19:740-743, 1979

77. Hardy JF, Morissette M, Taillefer J, Vauclair R: Pathophysiology of rupture of the pulmonary artery by pulmonary artery balloontipped catheters. Anesth Analg 62:925-930, 1983

78. Carlson TA: Catheter-induced delayed recurrent pulmonary artery hemorrhage: Intervention with therapeutic embolism of the pulmonary artery. JAMA 261:1943-1945, 1989

79. Pellegrini RV, Marcelli G, Di Marco RF, Bekoe S, Grant K, Marrangoni AG: Swan-Ganz catheter induced pulmonary hemorrhage. J Cardiovasc Surg (Torino) 28:646-649, 1987

80. Kelly TF Jr, Morris GC, Crawford ES, Espada R, Howell JF: Perforation of the pulmonary artery with Swan-Ganz catheters: Diagnosis and surgical management. Ann Surg 193:686-692, 1981

81. Applefeld JJ, Caruthers TE, Reno DJ, Civetta JM: Assessment of the sterility of long-term cardiac catheterization using the thermodilution Swan-Ganz catheter. Chest 74:377-380, 1978

82. Aikawa N, Martyn JAJ, Burke JF: Pulmonary artery catheterization and thermodilution cardiac output determination in the management of critically burned patients. Am J Surg 135:811-817, 1978

83. Prachar H, Dittel M, Jobst C, Kiss E, Machacek E, Nobis H, Spiel R: Bacterial contamination of pulmonary artery catheters. Intensive Care Med 4:79-82, 1978

84. Michel L, Marsh M, McMichan JC, Southorn PA, Brewer NS: Infection of pulmonary artery catheters in critically ill patients. JAMA 245:1032-1036, 1981

85. Singh S, Nelson N, Acosta I, Check FE, Puri VK: Catheter colonization and bacteremia with pulmonary and arterial catheters. Crit Care Med 10:736-739, 1982

86. Mermel LA, McCormick RD, Springman SR, Maki DG: The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: A prospective study utilizing molecular subtyping. Am J Med 91 (3B):197S-205S, 1991

87. Hoar PF, Wilson RM, Mangano DT, et al: Heparin-bonding reduces thrombogenesis of pulmonary artery catheters. N Engl J Med 305:993-995, 1981

88. Bonchek LI: Severe endobronchial hemorrhage (letter). Ann Thorac Surg 53:739-740, 1992

89. Robin ED: Death by pulmonary artery flow-directed catheter: Time for a moratorium? Chest 92:727-731, 1987

APPENDIX: Practice Guidelines for Perioperative Transesophageal Echocardiography[D]

A Report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography

Echocardiography was introduced in the operating room in the 1970s, with its initial applications involving epicardial echocardiography (EE). The use of transesophageal echocardiography (TEE) during surgery was first described in 1980 and did not become commonplace until high-frequency transducers and color Doppler imaging became available in the mid1980s. The improved quality of the acoustic image enabled anesthesiologists and surgeons to use TEE intraoperatively to diagnose myocardial ischemia, confirm the adequacy of valve reconstruction and other surgical repairs, determine the cause of hemodynamic disorders and other intraoperative complications, and provide diagnostic information that could not be obtained preoperatively. Real-time access to this information has enabled surgeons to correct inadequate repairs before patients leave the operating room, has reduced the need for reoperation, and has facilitated the prevention and early treatment of perioperative complications.

Although other intraoperative monitoring devices can provide some of this information, TEE offers important advantages over other diagnostic monitoring techniques. For example, intraoperative echocardiograms can be obtained by transthoracic echocardiography (TTE) or, if the chest is open, by EE. However, the acoustic images of TTE are generally poorer than those of TEE, and monitoring must be discontinued if the chest is opened or if surgical equipment, drapes, or monitors block access to the chest. Epicardial echocardiographic images are equivalent and sometimes superior to TEE, but the probe must be placed in a sterile field, can disrupt surgical procedures, and must be removed once the chest is closed. In contrast, TEE can facilitate diagnosis, allow the institution of specific treatments, and monitor interventions throughout the operative course without disrupting surgical technique. Other devices, such as electrocardiography (ECG) and pulmonary artery catheters, can provide continuous monitoring of cardiac performance, but are often unable to provide important information (*e.g.,* wall motion abnormalities, perivalvular leakage) that can be provided readily and rapidly by TEE.

Anesthesiologists also have used TEE outside the operating room. Typical applications in this setting include the emergency assessment of patients preoperatively to determine whether surgery is indicated (*e.g.,* thoracic aortic disruption after blunt chest trauma), as well as the postoperative assessment and treatment of patients in the hours and days after surgery. Even in nonoperative settings, anesthesiologists engaged in critical care medicine increasingly use TEE to evaluate and treat unstable patients in the intensive care unit (ICU).

There are important limitations to TEE. Some regions of the heart and great vessels cannot be well visualized (although some of these limitations may be overcome by more advanced technology and new imaging planes). The procedure is generally safe, but insertion and manipulation of the TEE probe can produce pharyngeal and/or laryngeal trauma, dental injuries, esophageal trauma or bleeding, arrhythmias, respiratory

Developed by the Task Force on Perioperative Transesophageal Ecocardiography: Daniel M. Thys, M.D. (Chair), New York, New York; Martin Abel, M.B.B.Ch., Rochester, Minnesota; Bruce A. Bollen, M.D., Missoula, Montana; Michael K. Cahalan, M.D., San Francisco, California; Patrick Curling, M.D., Houston, Texas; Robert J. Dean, D.O., Grand Rapids, Michigan; David Paulus, M.D., Gainesville, Florida; Alan S. Pearlman, M.D., Seattle, Washington (American Society of Echocardiography); Michael F. Roizen, M.D., Chicago, Illinois; John Smith, M.D., Las Vegas, Nevada; William J. Stewart, M.D., Cleveland, Ohio (American College of Cardiology); and Steven H. Woolf, M.D., M.P.H. (Methodologist), Fairfax, Virginia.

distress, and hemodynamic effects. Case reports have attributed some perioperative deaths to TEE. The inaccurate interpretation of TEE images by inexperienced examiners can generate incorrect information, potentially resulting in improper clinical decisions by the anesthesiologist and surgeon and, hence, unnecessary perioperative complications. The performance of TEE can consume anesthesiologists' time and attention that they need to attend to other intraoperative responsibilities.

In recent years, the publication of practice guidelines has become a useful, and often necessary, means of establishing the scientific support for clinical procedures and for justifying their use in patient care. Although practice guidelines on TEE have been issued by the American College of Cardiology, American Society of Echocardiography, and Society of Pediatric Echocardiography, they include only brief comments on the use of TEE in the operating room. In 1993, the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists established the Ad Hoc Task Force on Practice Parameters for Transesophageal Echocardiography to develop evidence-based guidelines on the proper indications for performing TEE in the operative setting. The 12-member task force included 9 anesthesiologists (6 of whom hold academic appointments and 3 of whom are private practitioners), 2 cardiologists, and 1 methodologist.

Before developing its recommendations, the task force reviewed all evidence regarding the effectiveness of TEE in the perioperative setting. A computerized and manual literature search retrieved 1,844 studies, of which 558 were considered relevant to the perioperative setting. Evidence was considered relevant if it addressed the accuracy and reliability of perioperative TEE, its yield and predictive value, or the effect of perioperative TEE on therapeutic decisions or clinical outcomes. The role of TEE in the emergent preoperative assessment of potential surgical emergencies also was considered. Studies investigating TEE in nonoperative critical care patients were examined, but studies of TEE in the cardiac catheterization or echocardiography laboratory were not reviewed. Thus, a large body of indirect evidence of potential relevance to critical care and surgical patients is omitted from this report but is examined elsewhere. [1] [2] Further details about the literature review process are available on request.

A detailed summary of the studies examined by the task force is published in a separate monograph. This Executive Summary provides an overview of the evidence for each of the topic categories examined by the task force. Each section includes a summary discussing the evidence obtained directly from studies of perioperative TEE, and an "Expert Opinion" section, in which the task force cites other relevant data and documents its opinions regarding the benefits and harms of perioperative TEE. The recommendations of the task force address *indications,* the clinical settings in which TEE should be considered, and *proficiency,* the cognitive and technical skills expected of anesthesiologists who perform perioperative TEE. Guidelines on how to perform TEE examinations were considered beyond the scope of this report.

Recommendations for performing TEE in this report are intended for those anesthesiologists who use TEE, rather than for all anesthesiologists. The recommendations are divided into three categories based on the strength of supporting evidence or expert opinion that the technology improves clinical outcomes (table 1). *Category I* indications are supported by the strongest evidence or expert opinion; TEE frequently is useful in improving clinical outcomes in these settings and often is indicated, depending on individual circumstances (*e.g.,* patient risk and practice setting; fig. 1). *Category II* indications are supported by weaker evidence and expert consensus; TEE may be useful in improving clinical outcomes in these settings, depending on individual circumstances, but appropriate indications are less certain. *Category III* indications have little current scientific or expert support; TEE infrequently is useful in improving clinical outcomes in these settings, and appropriate indications are uncertain. The lack of supporting evidence for category III indications is often owing to the absence of relevant studies rather than to existing evidence of ineffectiveness. Thus, many category III indications are currently investigational, and future research and technological developments

may enhance their role in routine practice.

Recommendations in this report refer to clinical problems rather than to individual patients, who often have more than one potential reason for performing TEE. Thus, although patients may not necessarily require perioperative TEE because of a cardiomyopathy (category III), the same patients may need TEE because of coexisting hemodynamic problems (category I). Similarly, physicians must integrate multiple variables in assessing a patient's need for TEE. As illustrated in figure 1 , factors associated with the patient, procedure,

TABLE 1 -- Quick Reference Guide: Indications for Perioperative Transesophageal Echocardiography

Category I indications: Supported by the strongest evidence or expert opinion; TEE is frequently useful in improving clinical outcomes in these settings and is often indicated, depending on individual circumstances (*e.g.,* patient risk and practice setting; see fig. 1).
Intraoperative evaluation of acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and have not responded to treatment
Intraoperative use in valve repair
Intraoperative use in congential heart surgery for most lesions requiring cardiopulmonary bypass
Intraoperative use in repair of hypertrophic obstructive cardiomyopathy
Intraoperative use for endocarditis when preoperative testing was inadequate or extension of infection to perivalvular tissue is suspected
Preoperative use in unstable patients with suspected thoracic aortic aneurysms, dissection, or disruption who need to be evaluated quickly
Intraoperative assessment of aortic valve function in repair of aortic dissections with possible aortic valve involvement
Intraoperative evaluation of pericardial window procedures
Use in intensive care unit for unstable patients with unexplained hemodynamic disturbances, suspected valve disease, or thromboembolic problems (if other tests or monitoring techniques have not confirmed the diagnosis or patients are too unstable to undergo other tests)
Category II indications: Supported by weaker evidence and expert consensus; TEE may be useful in improving clinical outcomes in these settings, depending on individual circumstances, but appropriate indications are less certain.
Perioperative use in patients with increased risk of myocardial ischemia or infarction
Perioperative use in patients with increased risk of hemodynamic disturbances
Intraoperative assessment of valve replacement
Intraoperative assessment of repair of cardiac aneurysms
Intraoperative evaluation of removal of cardiac tumors
Intraoperative detection of foreign bodies
Intraoperative detection of air emboli during cardiotomy, heart transplant operations, and upright neurosurgical procedures
Intraoperative use during intracardiac thrombectomy
Intraoperative use during pulmonary embolectomy
Intraoperative use for suspected cardiac trauma
Preoperative assessment of patients with suspected acute thoracic aortic dissections, aneurysms, or disruption
Intraoperative use during repair of thoracic aortic dissections without suspected aortic valve involvement
Intraoperative detection of aortic atheromatous disease or other sources of aortic emboli
Intraoperative evaluation of pericardiectomy, pericardial effusions or evaluation of pericardial surgery
Intraoperative evaluation of anastomotic sites during heart and/or lung transplantation
Monitoring placement and function of assist devices
Category III indications: Little current scientific or expert support; TEE is infrequently useful in improving clinical outcomes in these settings, and appropriate indications are uncertain.
Intraoperative evaluation of myocardial perfusion, coronary artery anatomy, or graft patency
Intraoperative use during repair of cardiomyopathies other than hypertrophic obstructive cardiomyopathy
Intraoperative use for uncomplicated endocarditis during noncardiac surgery
Intraoperative monitoring for emboli during orthopedic procedures
Intraoperative assessment of repair of thoracic aortic injuries
Intraoperative use for uncomplicated pericarditis
Intraoperative evaluation of pleuropulmonary diseases
Monitoring placement of intraaortic balloon pumps, automatic implantable cardiac defibrillators, or pulmonary artery catheters
Intraoperative monitoring of cardioplegia administration
TEE = tranesophageal Echocardiography.

and clinical setting each contribute to the overall risk of perioperative complications and cumulatively alter the benefit-harm ratio of using TEE. Physicians should consider each of these variables when calculating the appropriateness of using TEE.

The recommendations in this report are intended as general guidelines. Guidelines differ from *standards,* which prohibit departure from recommended practices except under special circumstances. [3] Guidelines are intended to provide practitioners with sufficient flexibility to alter their practices based on important clinical considerations or differing interpretations of the evidence. Accordingly, deviation from the guidelines in this report is expected and should not necessarily be viewed as inappropriate care. Recommendations to perform TEE are not applicable when the procedure cannot be performed properly or safely, neither do they apply when TEE equipment or skilled examiners are

Figure 1 The three domains of risk in assessing the appropriateness of transesophageal echocardiography (TEE). Risk factors for perioperative complications associated with the *patient* include age, sex, coexisting medical disorders, and past medical history, which influence the risk of perioperative complications. Factors associated with the *procedure* include characteristics of the operation that increase the likelihood of complications. Factors associated with the clinical setting include hospital-specific variables (*e.g.,* complication rates, availability and skills of personnel, and access to equipment) and other special circumstances. A thoughtful examination of each of these variables is necessary to accurately assess a patient's risk of perioperative complications and to gauge whether the potential benefits of TEE in reducing these risks outweigh potential harms associated with TEE itself. The complex interactions among these variables makes it inappropriate to specify surgical procedures or clinical problems that uniformly do or do not require TEE. For example, a healthy

patient undergoing a simple procedure may require TEE if it occurs in a high-risk clinical setting; the overall risk of complications may exceed that of a high-risk patient undergoing surgery with skilled providers and excellent equipment. Only the overall magnitude of risk is useful in determining the potential utility and benefit-harm ratio of performing TEE.

unavailable. The recommendations in this report are based on consideration of clinical benefits and harms. The economic implications of providing TEE, although important, were not explicitly examined by the task force because available data are inadequate to properly evaluate cost-effectiveness. The recommendations are intended for practitioners in the United States; elements of the recommendations and the principles on which they are based also may apply to practice settings in other countries. The recommendations are based on currently available evidence and should be updated as relevant new data become available.

Recommendations regarding training, certification, credentialing, and quality assurance were based on the aforementioned scientific evidence, as well as on legal, regulatory, and scientific literature and expert opinion. The task force refers to two levels of training in perioperative TEE, basic and advanced. Both basic and advanced TEE training refer to specialized training that extends beyond the minimum exposure to TEE that occurs during normal anesthesia residency training. Anesthesiologists with basic training are considered able to use TEE for indications that lie within the customary practice of anesthesiology. Anesthesiologists with advanced training are considered, in addition to the above, to be able to exploit the full diagnostic potential of perioperative TEE. Further details about requirements for each level of training are discussed later.

In this report, evidence of effectiveness, recommendations, and proficiency levels are discussed relative to the specific conditions that TEE can detect (*e.g.,* hemodynamic disturbances, congenital heart disease, emboli). This reductionist approach to examining the evidence often understates the important ability of TEE to detect multiple problems at once. For example, although the ability of TEE to evaluate myocardial ischemia, ventricular dysfunction, valvular insufficiency, thrombi, and air emboli is discussed in separate sections of this report, these problems often occur together during surgery and can be detected simultaneously by TEE. The capacity to study the physiologic and anatomic interrelationships of these problems and to monitor response to treatment is one of the unique advantages that TEE offers over other methods of intraoperative monitoring or diagnosis, as discussed later.

Wall Motion, Myocardial Ischemia, and Coronary Artery Disease

Hemodynamic and other physiologic stresses during the perioperative period increase the risk of perioperative myocardial ischemia, especially among patients with coronary artery disease, multiple risk factors for coronary artery disease, and peripheral vascular disease. Traditional methods for monitoring myocardial ischemia during surgery, such as continuous ECG, have limited sensitivity in the early detection of tissue injury. A growing body of evidence therefore has examined the role of TEE in detecting ischemia during both cardiac and noncardiac surgery.

Summary of the Evidence.

There is good evidence that the development of regional ventricular dysfunction during surgery increases a patient's risk of developing perioperative myocardial infarction (MI) and sudden death. Transesophageal echocardiography can detect regional ventricular dysfunction, but there is

little evidence about its accuracy, because neither a reliable reference standard is available, nor is it certain that the wall motion abnormalities reflect true myocardial ischemia. Most studies have examined the accuracy of TEE relative to intraoperative ECG tracings, an imperfect reference standard, and find weak concordance. Intraoperative TEE evidence of regional ventricular dysfunction is reported to occur in 27-100% of cases in which there is ECG evidence of ischemia and in 56-85% of cases in which ECG evidence of ischemia is lacking. The reportedly high incidence of intraoperative regional ventricular dysfunction (21-30% of cardiac surgery cases, 10-52% of vascular cases, and 20-60% of noncardiovascular cases) and postoperative dysfunction (47-60% of cardiac surgery patients) raises important questions about the frequency of false-positive findings.

Moreover, there is little direct evidence that the detection of regional ventricular dysfunction or other TEE evidence of ischemia results in improved perioperative clinical outcomes or long-term survival. This lack of evidence is mainly due to the absence of studies examining these outcomes. Studies of cardiac surgery patients report that TEE findings were "valuable or essential" or resulted in a change in therapy (graft revision, hemodynamic support) in 2-12% of patients, but there is no direct evidence that patients experience better outcomes as a result of these changes. Intraoperative TEE also is capable of evaluating myocardial perfusion patterns, coronary artery anatomy, and graft patency, but few studies have examined whether this information improves clinical outcomes.

Expert Opinion.

Evidence from animal experiments and angioplasty studies suggests that wall motion abnormalities generally precede ECG changes during myocardial ischemia. [4] [5] [6] [7] The task force believes that TEE provides a more meaningful reference standard for ischemia than ECG. The limitations of TEE also are recognized, however. Interpretations of wall motion and thickening often are more subjective than quantifiable ECG changes (*e.g.,* ST-segment depression). Transesophageal echocardiography interpretations can be influenced by translational motion of the heart, bundle branch block, and ventricular pacing. A marked worsening of segmental wall motion and thickening is required (in the absence of similar global changes) to strongly suggest the diagnosis of ischemia; less pronounced changes are interpreted inconsistently, even by experts. Moreover, all segmental wall motion abnormalities are not indicative of myocardial ischemia. Segmental wall motion abnormalities not caused by ischemia can occur because of preexisting disease (*e.g.,* prior MI, myocarditis) or confounding intraoperative events (*e.g.,* myocardial stunning after cardiopulmonary bypass [CPB]). Protocols have recently been suggested for distinguishing intraoperatively between stunned and infarcted myocardium, but they require further evaluation to be validated. Because an automated system for analyzing wall motion and thickness is currently unavailable for TEE, only qualitative wall motion assessment is available in real time. Moreover, real-time assessment of segmental wall motion may be less accurate than off-line (laboratory) assessment. When TEE is used to evaluate wall motion, the yield will increase with the use of multiple planes and methods that facilitate temporal comparisons (*e.g.,* side-by- side cine loops).

Although there is little direct evidence that TEE detection of myocardial ischemia improves clinical outcome, the task force believes that indirect evidence can be extrapolated from non-TEE studies showing that early treatment of myocardial ischemia and MI improves survival. Intraoperative TEE detection of ischemia permits corrective interventions, including alterations in surgery, anesthetic management, and postoperative triage, which can prevent perioperative complications. For example, TEE detection of post-CPB myocardial ischemia during coronary artery bypass graft surgery permits, if indicated, immediate revascularization before the patient leaves the operating room, thereby reducing the risk of perioperative MI. Both indirect evidence and expert opinion suggest that these measures improve clinical outcomes.

Recommendations

Indications. An increased risk of myocardial ischemia or infarction during the perioperative period is a category II indication for perioperative TEE. An increased risk may occur when conditions associated with the *patient* (*e.g.,* history of prior MI or coronary artery disease, left ventricular dysfunction, dysrhythmias), *procedure* (*e.g.,* coronary artery bypass graft, operations on the great vessels or that involve aortic cross clamping, noncardiac intrathoracic surgery, upper abdominal procedures), or *clinical setting* (*e.g.,* anticipated duration of surgery, hospital-specific factors) predispose to myocardial ischemia or MI (fig. 1). Use of perioperative TEE to evaluate myocardial perfusion, coronary artery anatomy, or graft patency are category III indications. The argument for using TEE is strengthened

when ECG monitoring cannot provide accurate information, such as in patients with conduction disorders or in procedures that interfere with ECG lead placement. The argument for using TEE is weakened when clinical factors (*e.g.,* preexisting regional ventricular dysfunction) limit the accuracy of wall motion interpretations.

Proficiency. Anesthesiologists with basic TEE training should be able to use TEE to detect unequivocal changes in segmental wall thickening and motion (*e.g.,* from normal wall motion to akinesis) and should be able to distinguish these changes from artifacts (*e.g.,* translational motion of the heart, changing cross section, image dropout, abnormal ventricular activation). Subtle changes in segmental wall motion and thickening, however, are difficult to detect, even for experts. The ability to evaluate or quantify such changes in association with myocardial ischemia and MI requires advanced training.

Hemodynamic Function

Transesophageal echocardiography has been used extensively for the evaluation (monitoring of presence, followed by determination of etiology) of hemodynamic and global ventricular function. Some have used TEE to estimate standard hemodynamic variables (*e.g.,* filling pressures, cardiac output) that are normally obtained by other invasive techniques, such as pulmonary artery catheterization, whereas others have used it to quantify cardiac dimensions, intracardiac flow rates, and overall cardiac performance. Such measurements were previously not readily obtainable in the operating room or ICU.

Summary of the Evidence.

Current studies provide conflicting information about the correlation between TEE estimates of hemodynamic indexes (*e.g.,* cardiac output, filling pressure) and measurements obtained by more conventional tests (*e.g.,* thermodilution). Studies comparing TEE and thermodilution measurements of cardiac output report wide ranges in correlation coefficients (R = 0.72-0.97), bias estimates (0.03-1.01 1/min), and limits of agreement. The frequency with which TEE detects hemodynamic disturbances has not been studied. Moreover, there is little evidence beyond case reports to confirm that hemodynamic monitoring by TEE results in improved clinical outcomes.

Expert Opinion.

Quantitative analysis of TEE information may increase its sensitivity in detecting small changes in ventricular dimensions or ejection, a capacity that would dramatically enhance conventional hemodynamic monitoring, but it is time consuming and requires considerable skills. Until automated analysis systems overcome these limitations, intraoperative TEE will remain a largely qualitative tool for assessing hemodynamic function. Even with these limitations, however, the task force believes that TEE provides more accurate estimates of preload (end-diastolic volume) than the pulmonary artery catheter. Preload is physiologically determined by sarcomere length, a variable more accurately estimated by volume than by pressure measurements. When compared with the pulmonary artery catheter, TEE may be more expedient, because it can be inserted more quickly and without sterile technique; safer, because it does not enter the great vessels and heart; and more comprehensive, because it provides more global hemodynamic information about the performance and structure of the heart.

Although direct evidence is lacking, the task force believes that detecting acute hemodynamic disturbances during surgery improves clinical outcomes. These benefits are realized by using TEE to diagnose the hemodynamic problem (*e.g.,* hypovolemia, myocardial depression) and to suggest appropriate therapy (*e.g.,* volume expansion, inotropic therapy). The task force believes that failing to take action to correct or prevent hemodynamic disturbances increases the risk of end-organ damage and perioperative mortality.

Recommendations

Indications. An increased risk of hemodynamic disturbances during the perioperative period is a category II indication for perioperative TEE. Increased risk may occur when conditions associated with the *patient* (*e.g.,* congestive heart failure, valvular heart disease, abdominal aortic aneurysm, preeclampsia, trauma, burn injuries), *procedure* (*e.g.,* vascular surgery, CPB, extensive tumor resection, liver transplantation, total hip replacement), or *clinical setting* (*e.g.,* difficulties in inserting central venous pressure catheters, inability to estimate blood loss, poor hospital-specific conditions, such as complication rates for a specific procedure) predispose to hemodynamic disturbances (fig. 1.) The emergent use of perioperative TEE to determine the cause of acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and have not responded to treatment is a category I indication.

Proficiency. Anesthesiologists with basic TEE training should be able to make qualitative assessments of hemodynamic status and should have a cognitive understanding of more sophisticated TEE techniques for quantifying hemodynamic function.

Valvular Surgery

For patients requiring valve surgery, because of the potential for suboptimal results, it is preferable to recognize the need for further surgery in the operating room rather than waiting for postoperative complications to develop that necessitate a second operation. The unique ability of TEE to make these assessments during valve surgery accounts for its widespread application in this setting.

Summary of the Evidence.

Perioperative TEE can characterize valvular insufficiency and morphology. Studies report a fair correlation between intraoperative TEE estimates of valvular insufficiency and preoperative angiographic data (R = 0.83-0.88). Access to this information before and after valve repair appears to be useful. Pre-CPB TEE provides new information or prompts changes in valve surgery in 9-13% of cases. Its ability to reveal unanticipated valvular disease (*e.g.,* endocarditis, aortic valve tumor) is described in case reports. Post-CPB TEE identifies significant valve dysfunction in 6-11% of cases, prompting second pump runs in 3-10% of patients undergoing mitral valve repair. However, although there is evidence that post-CPB valve dysfunction is associated with increased postoperative complications and poorer survival, there is little evidence beyond case reports that perioperative interventions prompted by TEE improve clinical outcomes.

Expert Opinion.

Although direct evidence of benefit is lacking, the task force believes that indirect evidence can be extrapolated to infer effectiveness. Observational data from patients undergoing surgery for ischemic heart disease suggest that mitral regurgitation on post-CPB TEE is the most important predictor of postoperative mortality. Based in part on these data and on expert opinion, the task force believes that patients who are not evaluated by TEE during valve surgery may have longer ICU stays and a higher incidence of congestive heart failure, reoperation, and mortality than patients monitored by TEE. Transesophageal echocardiography evaluation appears to decrease the need for valve replacement, and observational data suggest that the latter increases the risk of mechanical dysfunction, perivalvular leakage, thromboembolic events, and anticoagulation therapy. Although observational data cannot prove effectiveness conclusively, the findings are consistent with the expert opinion of the task force. While most available evidence comes from patients undergoing valve repair, the task force believes that similar benefits (lower incidence of reoperation, congestive heart failure, and mortality) are also realized for patients undergoing valve replacement, albeit less frequently than for valve repair. After valve replacement, significant periprosthetic leaks are uncommon but may require immediate correction. At centers experienced with valve replacement, the yield of intraoperative TEE is likely to be low.

The task force recognizes that the effectiveness of TEE during valve surgery may be limited by inaccurate interpretation: "false-positive" or "false-negative" findings. Moreover, TEE evaluation of post-CPB valvular regurgitation can be confounded by the presence of abnormal loading conditions or myocardial ischemia. These conditions must be normalized or resolved before valvular insufficiency can be confirmed. Hemodynamic changes associated with the induction of anesthesia can alter valvular function and render comparisons between pre-CPB TEE and preoperative echocardiography problematic. Patients with evidence of tricuspid regurgitation on preoperative echocardiography, for example, may have normal examinations on pre-CPB TEE, prompting inappropriate revision of the surgical plan. The absence of regurgitation on post-CPB TEE also can be falsely negative when the patient is volume underloaded.

The potential benefits of TEE evaluation during valve surgery are not limited to valve assessment. Hemodynamic disturbances are common (see Hemodynamic Function), and TEE may be especially helpful in weaning the patient from CPB. Transesophageal echocardiography can detect entrapped air and facilitate venting procedures (see Air Emboli). Other potential benefits are discussed in separate sections.

Recommendations

Indications. Valve repair is a category I indication, and valve replacement is a category II indication, for the use of intraoperative TEE.

Proficiency. When valve surgery will be dictated by TEE assessment of valve function, TEE should be performed by, or in timely consultation with, a physician with advanced TEE training. Anesthesiologists with basic TEE training should have an understanding of the

anatomy and function of native and prosthetic valves, the hemodynamic changes that occur in valvular disease, and the echocardiographic tools (*e.g.,* continuous-wave Doppler) that are available for valve assessment. They should be able to obtain multiple views of all valves, recognize gross valvular dysfunction on two dimensional echocardiography, and appreciate the color patterns of antegrade and retrograde flow on color Doppler examinations. Quantitative echocardiographic measurements of valve function (*e.g.,* jet area, flow-velocity pattern, effective valve orifice area) require advanced training. Utilization of TEE to detect and diagnose the causes of hemodynamic disturbances and to detect the presence of air emboli during valve surgery can be performed by anesthesiologists with basic TEE training.

Congenital Heart Surgery

Although the acoustic window provided by TEE gives access to a variety of congenital heart lesions, especially in the atria and atrioventricular junction, its use in children was limited for many years because available probes were too large. As recently as 1989, available probe sizes limited the use of TEE to children older than 7 yr. Smaller probes that are now available measure 5.9 mm in diameter and enable examination of children as small as 2,400 g. Transesophageal echocardiography has special application in evaluating the adequacy of surgical repair of congenital heart lesions. New technologies (*e.g.,* biplane pediatric probes) and imaging techniques (*e.g.,* longitudinal planes) have enhanced further the information obtainable from TEE examinations of children.

Summary of the Evidence.

Intraoperative TEE has a reported sensitivity of 86-94% in detecting congenital heart lesions. Especially when performed with biplane probes, TEE can detect lesions not seen on preoperative TTE in as many as 30% of patients. The sensitivities of intraoperative TEE and EE are comparable, although each test may lack sensitivity in evaluating certain cardiac structures. In patients undergoing congenital heart surgery, pre-CPB findings prompt changes in treatment in 1-16% of patients, post-CPB TEE findings result in second pump runs or altered medical therapy in 3-45% of cases, and postoperative TEE detects information not available by TTE in 15-48% of patients. However, there is little direct evidence beyond case reports as to whether this information or the treatment changes that they prompt (*e.g.,* returning to CPB to correct residual defects) improve clinical outcomes.

Expert Opinion.

Most studies of TEE during congenital heart surgery, including those reporting poor visualization of the right ventricular outflow tract, pulmonary valve, and interventricular septum, lacked access to the enhanced imaging capabilities of recently introduced pediatric TEE technology (*e.g.,* biplane probes, continuous-wave Doppler) and techniques (*e.g.,* transgastric view of right ventricular outflow tract). When compared with EE, TEE offers the advantages of uninterrupted operation, decreased potential violation of the sterile field, and continuous hemodynamic evaluation. An important role of perioperative TEE during congenital heart surgery is the ability to detect previously unrecognized congenital anomalies.

The task force believes on the basis of indirect evidence [8] that the detection of residual defects improves outcomes by reducing the residual hemodynamic burden of these lesions and by decreasing the patient's risk of pulmonary hypertension and endocarditis. Despite these potential benefits, TEE may be inappropriate or infeasible in certain circumstances. Pre-CPB and post-CPB TEE examinations frequently are useful for patients undergoing repair of complex congenital heart lesions. In the repair of other defects (*e.g.,* patent ductus arteriosus, patent foramen ovale) where TEE may be useful, the physician must be especially careful in weighing the potential benefits of TEE against its potential risks. In addition to the usual potential adverse effects of TEE, small children may face the added risks of hemodynamic or respiratory compromise, which is more common among patients weighing less than 3 kg or when an appropriately sized probe is unavailable. For patients in whom esophageal intubation is difficult, repeated attempts at probe insertion may result in more harm than good. When TEE is not appropriate or small probes are not available, EE can be used to assess the repair of congenital heart defects.

Practical constraints related to the recent introduction of pediatric TEE technology also may limit the feasibility of its routine use during congenital heart surgery. Because pediatric TEE probes of appropriate size and imaging quality (*e.g.,* biplane) have become available only recently, practitioners currently face a temporary transition period during which some centers may lack access to appropriate equipment and expertise.

Recommendations

Indications. Congenital heart surgery for most lesions requiring CPB is a category I indication for intraoperative TEE, including pre-CPB and post-CPB imaging. Use of TEE is not recommended when available probes are too large for the child. Epicardial echocardiography can provide a useful alternative when TEE is inappropriate or small probes are unavailable.

Proficiency. When repair of congenital heart defects will be dictated by the results of intraoperative TEE assessment, TEE should be performed by, or in timely consultation with, a physician with advanced pediatric TEE training in complex congenital heart disease. Anesthesiologists with basic TEE training should have an understanding of how TEE is used during congenital heart surgery.

Cardiomyopathy

Hypertrophic, dilated, and restrictive cardiomyopathies are diagnosed accurately by echocardiography. The use of intraoperative TEE in patients with cardiomyopathy has centered on the detection and treatment of hypertrophic obstructive cardiomyopathy.

Summary of the Evidence.

There is little evidence regarding the accuracy or yield of intraoperative TEE relative to cardiomyopathy. One study reported that the detection of persistent outflow tract gradients aided surgical revision in 20% of patients undergoing hypertrophic obstructive cardiomyopathy repair, but otherwise there is little evidence that TEE alters therapy or improves outcome.

Expert Opinion.

Epicardial echocardiography may offer important advantages over TEE in evaluating hypertrophic cardiomyopathies. In addition to increased accuracy, EE can obtain outflow gradient measurements without the need for cardiac needle punctures. By either means, however, the task force believes that echocardiographic confirmation of the adequacy of hypertrophic obstructive cardiomyopathy repair improves clinical outcomes, based in part on natural history data suggesting poorer outcomes for patients with persistent hemodynamic compromise from hypertrophic obstructive cardiomyopathy. [9] Echocardiographic assessment also facilitates weaning from CPB, may offer improved myocardial protection during the procedure, and enables intraoperative detection of iatrogenic septal defects or systolic anterior motion resulting from the repair. The task force believes that these benefits improve clinical outcomes.

Recommendations

Indications. Hypertrophic obstructive cardiomyopathy repair is a category I indication for either EE or TEE assessments, but use of intraoperative TEE for other cardiomyopathies is a category III indication.

Proficiency. When hypertrophic obstructive cardiomyopathy repair will be dictated by intraoperative TEE assessment, TEE should be performed by, or in timely consultation with, a physician with advanced TEE training.

Cardiac Aneurysms

Summary of the Evidence.

Beyond case reports, there is little evidence that intraoperative TEE is accurate in detecting cardiac aneurysms or results in improved outcomes for patients undergoing aneurysmectomy.

Expert Opinion.

The task force believes that intraoperative TEE during aneurysmectomy can play an important role in evaluating the adequacy of repair and, occasionally, in detecting previously unsuspected abnormalities (*e.g.,* pseudoaneurysms). Patients with cardiac aneurysms typically have advanced ischemic heart disease and associated hemodynamic complications, and TEE often is useful in evaluating these problems (see "Wall Motion, Myocardial Ischemia, and Coronary Heart Disease" and "Hemodynamic Function"). Patients with cardiac aneurysms who undergo cardiac surgery often have difficulty weaning from CPB, and TEE monitoring of hemodynamic function often is helpful in withdrawing extracorporeal circulatory support.

Recommendations

Indications. Assessing surgical repair of cardiac aneurysms is a category II indication for intraoperative TEE.

Proficiency. When surgical repair of cardiac aneurysms will be dictated by the results of intraoperative TEE assessment, TEE should be performed by, or in timely consultation with, a physician with advanced TEE training.

Endocarditis

Summary of the Evidence.

Although its accuracy in detecting endocarditis outside the operating room is well established, there is little evidence beyond case

reports that the use of TEE during surgery is accurate in detecting endocarditis or achieves improved clinical outcomes.

Expert Opinion.

Beyond the accepted applications of intraoperative TEE during valve surgery (see "Valvular Heart Disease"), there is little role for TEE in evaluating endocarditis during surgery, unless preoperative testing was inadequate or the patient required urgent surgery. There are limitations to the sensitivity and specificity of TEE in detecting endocarditis. A negative TEE does not rule out endocarditis, and studies suggest that TEE evidence of vegetations may persist long after bacteriologic cure.

Recommendations

Indications. Noncardiac surgery involving patients with uncomplicated endocarditis is a category III indication for intraoperative TEE. A category I indication exists, however, when preoperative testing has been inadequate or extension of infection to perivalvular tissue is suspected.

Proficiency. When surgical exploration of endocarditic disease will be dictated by the results of intraoperative TEE assessment, TEE should be performed by, or in timely consultation with, a physician with advanced TEE training.

Cardiac Tumors

Summary of the Evidence.

There is some evidence that intraoperative TEE may be more accurate than preoperative testing in characterizing the anatomy of some cardiac tumors and intracardiac extensions of pulmonary or renal tumors, but there is little evidence beyond case reports that this information or the use of TEE during resection results in improved clinical outcomes.

Expert Opinion.

In many cases, the information that intraoperative TEE provides about the location and anatomy of intracardiac tumors to plan incision and excision techniques can be obtained before surgery by careful preoperative testing (including preoperative TEE). If preoperative testing is adequate, the most important role for intraoperative TEE is determining whether a mass has embolized and the new location of the mass, often preempting the need for further exploration or a change in surgical planning.

Recommendations

Indications. The removal of cardiac masses is a category II indication for intraoperative TEE.

Proficiency. Physicians with basic TEE training should be able to detect large, unequivocal cardiac masses. The use of TEE to accurately detect smaller or ill-defined masses, especially to distinguish potential masses from normal intracardiac structures, identify associated lesions, inspect the inferior vena cava, and rule out iatrogenic valve injury during resection of intracardiac masses, should be performed by, or in timely consultation with, a physician with advanced TEE training.

Foreign Bodies

Summary of the Evidence.

The ability of intraoperative TEE to locate bullet fragments and medical devices (*e.g.,* catheter fragments) is reported, but there is no evidence regarding its impact on clinical outcomes.

Expert Opinion.

The yield of intraoperative TEE in detecting foreign bodies is likely to be low in most settings, but it may have greater utility at centers with a high incidence of gunshot injuries.

Recommendations

Indications. The detection of foreign bodies is a category II indication for intraoperative TEE.

Proficiency. To accurately detect foreign bodies, TEE should be performed by, or in timely consultation with, a physician with advanced TEE training.

Air Emboli

Summary of the Evidence.

Intraoperative TEE can detect air bubbles in 8-60% of patients undergoing neurosurgery and 11-79% of patients undergoing cardiac surgery. Current evidence is inadequate, however, to determine whether these emboli increase the risk of neurologic complications or whether intraoperative TEE monitoring for air emboli improves clinical outcomes.

Expert Opinion.

Transesophageal echocardiography is an extremely sensitive test for air (emboli as small as 2 mum usually can be detected) but the clinical significance of these bubbles is unclear. Animal studies suggest that air entrainment greater than 1 cc/kg increase the risk of neurologic complications, but the threshold value for safe air volumes in humans is uncertain. The task force believes that patients benefit when TEE detects air during cardiotomy and neurosurgical

procedures. During cardiotomy, venting procedures before cessation of CPB can eliminate retained air, and the task force believes that such measures decrease the patient's risk of embolic neurologic events, right ventricular failure due to right coronary artery air embolism, and MI. [10] Transesophageal echocardiography offers similar benefits during sitting craniotomies, especially if the patient has not been screened preoperatively for patent foramen ovale. Patent foramen ovale appears to be a risk factor for stroke, and intraoperative maneuvers can induce intracardiac pressure changes that open probe-patent defects to permit paradoxical emboli. Transesophageal echocardiography is the only intraoperative tool for detecting these abnormalities; few other tests can detect air and sources of right-to-left shunts as accurately. The task force recognizes that the use of TEE during upright neurosurgical procedures may increase the risk of vocal cord injury, although these risks may be reduced by using proper technique and equipment.

Recommendations

Indications. The detection of air emboli during cardiotomy and heart transplant operations is a category II indication for using intraoperative TEE. It also should be considered on an individual basis for patients undergoing upright neurosurgical procedures (category II).

Proficiency. Anesthesiologists with basic TEE training should have an understanding of the physiologic effects of air emboli and should be technically capable of detecting air emboli intraoperatively, especially during upright neurosurgical procedures. The use of intraoperative TEE to accurately detect patent foramen ovale should be performed by, or in timely consultation with, a physician with advanced TEE training.

Intracardiac Thrombi

Summary of the Evidence.

Intraoperative TEE can detect intracardiac thrombi in 2-10% of patients undergoing cardiac surgery, often exposing thrombi that were inapparent on preoperative TTE, but there is little evidence beyond case reports that the detection or evacuation of these clots results in improved clinical outcomes.

Expert Opinion.

In patients undergoing thrombectomy, a preoperative echocardiographic examination can prevent an unnecessary operation if it determines that the thrombus has already embolized. If TTE was not performed in the immediate preoperative period, a pre-CPB TEE examination therefore is essential.

Recommendations

Indications. Intracardiac thrombectomy is a category II indication for pre-CPB TEE.

Proficiency. The use of intraoperative TEE to accurately detect intracardiac thrombi and to distinguish between true thrombi and artifacts should be performed by, or in timely consultation with, a physician with advanced TEE training.

Pulmonary Emboli

Summary of the Evidence.

Case reports describe the use of perioperative TEE to detect and evaluate treatment of pulmonary emboli, but there is little evidence regarding its impact on clinical outcomes.

Expert Opinion.

The task force believes that perioperative TEE is especially useful during pulmonary embolectomy to evaluate hemodynamic status and to detect residual emboli. The expert opinion of the task force, based on perioperative TEE monitoring, is that about 30% of embolectomy procedures fail to completely remove all emboli. The task force believes that these residual emboli are potentially harmful to the patient and that the use of TEE to detect them intraoperatively is therefore beneficial.

Recommendations

Indications. Transesophageal echocardiography may be useful to determine the cause of acute hemodynamic disturbances, such as those resulting from pulmonary emboli (see "Hemodynamic Function"), but it is not necessary for all patients with known or suspected pulmonary emboli. Pulmonary embolectomy is a category II indication for using TEE.

Proficiency. The use of perioperative TEE to accurately diagnose pulmonary emboli or to monitor embolectomy or thrombolysis should be performed by, or in timely consultation with, a physician with advanced TEE training.

Emboli during Orthopedic Procedures

Summary of the Evidence.

Intraoperative TEE can detect embolized air or medullary contents in as many as 30-62% of patients undergoing total hip replacement

and, after tourniquet deflation, in 27-100% of patients undergoing knee arthroplasty. There is little evidence, however, that this information results in improved clinical outcomes.

Expert Opinion.

In clinical practice, TEE detection of emboli during orthopedic procedures often prompts clinical interventions (*e.g.,* replacing tourniquets) but the ultimate benefit to the patient of these maneuvers is uncertain.

Recommendations

Indications. Monitoring for emboli during orthopedic procedures is a category III indication for intraoperative TEE.

Traumatic Cardiac Injuries

Summary of the Evidence.

Case reports describe the role of intraoperative TEE in detecting unrecognized traumatic injuries to the heart and of postoperative TEE in detecting injuries not seen on TTE, but there is otherwise little evidence that TEE improves the clinical outcome of cardiac trauma patients (see "Traumatic Aortic Disruption" and "Nonoperative Critical Care Medicine" later).

Expert Opinion.

Routine use of TEE for evaluating cardiac trauma is predicated on the availability of TEE equipment and qualified staff at trauma units. Although there have been no studies beyond case reports to determine whether intraoperative TEE inspections during trauma surgery improve outcomes, cohort studies of postoperative trauma patients have shown that TEE in this setting often discloses injuries that went undetected during surgery. This evidence suggests that unsuspected injuries could be detected during surgery if TEE was performed intraoperatively. The need to return for further surgery and the risk of complications might thereby be reduced by intraoperative TEE, but this hypothesis needs to be confirmed through further research.

Recommendations

Indications. Suspected cardiac trauma is a category II indication for perioperative TEE.

Proficiency. The use of TEE to accurately detect traumatic cardiac injuries should be performed by, or in timely consultation with, a physician with advanced TEE training.

Thoracic Aortic Aneurysms and Dissections

The mortality rate in the first 48 h of aortic dissection is about 1% per hour, and prompt diagnosis and surgical intervention therefore are critical. Angiography and other imaging studies are often impractical because of the patient's rapidly worsening hemodynamic instability. The ability of TEE to detect aortic dissection was first described in 1986 and its ease of application has expanded its role in both the emergent evaluation of suspected dissection and in the recognition of dissections that occur during surgery.

Summary of the Evidence.

With aortography, surgical findings, or necropsy as the reference standard, the use of TEE in the emergent preoperative assessment of aortic dissections has a reported sensitivity and specificity of 88-100% and 77-100%, respectively. Most of these studies, however, were unable to collect enough data to assess the true sensitivity and specificity of TEE. Transesophageal echocardiography in this setting appears to be more sensitive than TTE. However, beyond case reports and suggestive retrospective series, there is little direct evidence that the use of TEE for the emergent preoperative assessment of suspected aortic dissection results in improved clinical outcomes. In one series, its use during the repair of aortic dissections prompted a change in therapy in 14% of patients, but there is no direct evidence that the patients had better outcomes as a result of such interventions.

Expert Opinion.

Although direct evidence of improved clinical outcomes is lacking, there is evidence that delayed detection of acute aortic dissection increases mortality. The task force therefore believes that any method that enhances prompt detection of acute dissections is potentially beneficial. The principal benefits of perioperative TEE during aortic reconstruction are to assess hemodynamic status (*e.g.,* after cross-clamping), document entry and exit sites, confirm decompression of the false lumen, and determine whether valve surgery is needed.

Recommendations

Indications. The preoperative assessment of patients with suspected acute thoracic aortic dissections or aneurysms is a category II indication for TEE. Transesophageal echocardiography is among several accurate diagnostic tests, including angiography, computerized tomography, and magnetic resonance imaging. In unstable patients who should be evaluated quickly, there is a category I indication for TEE because it allows a

more expedient examination than other preoperative imaging procedures.

The intraoperative use of TEE for assessing aortic valve function when patients undergo repair of aortic dissections with possible aortic valve involvement is a category I indication. The repair of other types of thoracic aortic dissections is a category II indication for intraoperative TEE.

Proficiency. The use of TEE to diagnose thoracic aortic dissection or aortic aneurysms should be performed by, or in timely consultation with, a physician with advanced TEE training. See "Hemodynamic Function" for proficiency recommendations in assessing intraoperative hemodynamic status.

Traumatic Thoracic Aortic Disruption

In trauma patients with suspected aortic injuries, hemodynamic shock often precludes the performance of diagnostic tests before the patient is taken to surgery. Preoperative or intraoperative TEE therefore can play an important role in the early detection of aortic injuries.

Summary of the Evidence.

In most studies, the reported sensitivity and specificity of TEE in the emergent preoperative assessment of suspected aortic trauma is 100% and 94-100%, respectively, but limitations in study design make it difficult to determine the true sensitivity and specificity. There is little direct evidence that the use of TEE in this setting results in improved clinical outcomes.

Expert Opinion.

Although scientific evidence may currently be lacking, the task force believes that early detection of undiagnosed traumatic aortic disruption improves clinical outcomes, because of the life-threatening nature of such injuries, and that TEE is an important method for diagnosing aortic trauma.

Recommendations

Indications. The preoperative assessment of suspected thoracic aortic trauma is a category II indication for TEE. It is among several accurate diagnostic tests, including angiography, computerized tomography, and magnetic resonance imaging. In unstable patients who need to be evaluated quickly, there is a category I indication for preoperative TEE because it allows a more expedient examination than other preoperative imaging procedures. Assessing the repair of thoracic aortic injuries is a category III indication for intraoperative TEE.

Proficiency. The use of TEE to accurately diagnose traumatic thoracic aortic disruption should be performed by, or in timely consultation with, a physician with advanced TEE training. See "Hemodynamic Function" for proficiency recommendations in diagnosing the cause of intraoperative hemodynamic dysfunction.

Sources of Aortic Emboli

About 1-5% of patients suffer strokes during CPB, and embolization of atheromatous ulcers on the aorta is considered a major risk factor. Palpation of the aorta, the standard method for detecting atherosclerotic aortic disease, is known to be insensitive. Transesophageal echocardiography, which has been shown outside the operating room to be capable of detecting aortic atheromas, has been used intraoperatively to complement palpation.

Summary of the Evidence.

Intraoperative TEE may be less accurate than epivascular echocardiography in evaluating atheromatous disease in the ascending aorta. Atheromatous disease is noted on intraoperative TEE in 9% of elderly patients and result in a change in therapy in 8-17% of patients. However, although some studies suggest an association between TEE evidence of aortic atheroma and subsequent strokes, there is little direct evidence that the detection and treatment of such findings results in improved clinical outcomes.

Expert Opinion.

Intraoperative TEE and epivascular echocardiography are capable of detecting aortic atheromatous disease, but it is currently unclear whether its detection improves clinical outcomes. Some studies suggest that the risk of embolism and stroke may be reduced by altering patient treatment.

Recommendations

Indications. The detection of aortic artheromatous disease or other sources of aortic emboli is a category II indication for intraoperative TEE. Transesophageal echocardiography infrequently is useful when compared with epivascular echocardiography.

Pericarditis

Summary of the Evidence.

No studies have been performed to determine whether intraoperative TEE is accurate in detecting pericarditis or results in improved clinical outcomes.

Expert Opinion.

In clinical practice, TEE may be helpful in evaluating constrictive pericarditis and pericardiectomy procedures.

Recommendations

Indications. Evaluating the effectiveness of pericardiectomy is a category II indication for intraoperative TEE. Uncomplicated pericarditis is a category III indication.

Proficiency. Use of TEE to guide diagnosis or surgical treatment of pericarditis should be performed by, or in timely consultation with, a physician with advanced TEE training.

Pericardial Effusions and Tamponade

Summary of the Evidence.

There is some evidence suggesting that perioperative TEE is more sensitive than TTE in detecting pericardial effusions, but there is little evidence beyond case reports that such findings during or after surgery result in improved clinical outcomes.

Expert Opinion.

Although supporting scientific evidence is limited, the task force believes that perioperative TEE is clinically beneficial if it detects pericardial tamponade and avoids serious hemodynamic sequelae. This application is especially important when effusions cannot be detected easily by other means. For example, clinical experience suggests that posterior or loculated pericardial effusions that are easily missed by the surgeon may develop in patients receiving pericardial windows.

Recommendations

Indications. The detection of pericardial effusions or evaluation of pericardial surgery is a category II indication for intraoperative TEE. In patients undergoing pericardial window procedures, there is a category I indication for using TEE to evaluate the adequacy of treatment.

Proficiency. Anesthesiologists with basic TEE training should be able to detect large, pericardial effusions. Physicians with advanced TEE training should be able to detect and assess the hemodynamic significance of effusions. Transesophageal echocardiography that is used to guide pericardial surgery should be performed by, or in timely consultation with, a physician with advanced TEE training.

Pleuropulmonary Diseases

Summary of the Evidence.

There is no direct evidence that intraoperative TEE is accurate in detecting pleural or pulmonary parenchymal disease, or that such monitoring results in improved clinical outcomes.

Recommendations

Indications. The evaluation of pleuropulmonary diseases is a category III indication for perioperative TEE.

Transplant Surgery

Summary of the Evidence.

Some studies suggest that TEE is more sensitive than TTE in screening cardiac donor patients and more accurate than pulmonary capillary wedge pressure measurements in detecting hemodynamic disturbances during transplant surgery. Postoperative studies have demonstrated its ability to evaluate cardiac allograft function and detect thrombotic obstruction and stenoses in patients with lung transplants. However, its effect on clinical outcomes has not been evaluated systematically.

Expert Opinion.

Anastomotic integrity may be accurately assessed by TEE. The task force also believes that the hemodynamic benefits of TEE during major organ transplant surgery are especially important. In these patients, TEE is believed to be more accurate in diagnosing the cause of hemodynamic disturbances than is central venous pressure or pulmonary artery catheter monitoring.

Recommendations

Indications. Evaluating anastomotic sites during heart and/or lung transplantation is a category II indication for intraoperative TEE.

Proficiency. Perioperative TEE to evaluate the surgical results of transplant surgery, such as the integrity of anastomoses, should be performed by, or in timely consultation with, a physician with advanced TEE training. Anesthesiologists with basic training should be able to evaluate hemodynamic disturbances (see "Hemodynamic Function") and to detect entrapped air (see "Air Emboli") during transplant operations.

Mechanical Circulatory Support, Defibrillators, and Catheter Placement

Summary of the Evidence.

Case reports and small series have described the use of intraoperative TEE to aid placement and monitor function of intraaortic balloon pumps, ventricular assist devices, automatic implantable

cardiac defibrillators, pulmonary artery catheters, coronary sinus catheters, and ventriculoatrial shunts. There is little direct evidence, however, that TEE is necessary to insert and operate these devices safely or that its use results in improved clinical outcomes.

Expert Opinion.

Although there is no direct evidence regarding the clinical effectiveness of TEE monitoring of mechanical circulatory assist devices, patients receiving such devices usually are experiencing hemodynamic disturbances for which TEE is considered beneficial (see "Hemodynamic Function" earlier). The task force also believes that its use to confirm placement of such devices reduces the need for intraoperative radiography, thereby decreasing radiation exposure and operating room time.

Recommendations

Indications. Monitoring placement and function of assist devices is a category II indication for TEE. Monitoring placement of intraaortic balloon pumps, automatic implantable cardiac defibrillators, or pulmonary artery catheters is a category III indication.

Proficiency. The specific use of TEE to monitor placement and function of mechanical circulatory assistance devices should be performed by, or in timely consultation with, a physician with advanced TEE training. Anesthesiologists with basic training should be capable of evaluating accurately the mechanism of hemodynamic disturbances in patients receiving mechanical circulatory assistance (see "Hemodynamic Function").

Cardioplegia

Summary of the Evidence.

Studies have described the use of intraoperative TEE to evaluate the distribution of cardioplegia solution and to aid placement of cannulas for cardioplegia infusions, but there is little direct evidence that using TEE for this purpose results in improved clinical outcomes.

Expert Opinion.

The use of TEE for achieving cardioplegia is an emerging technology, and future research findings may warrant a more routine role for aiding cannula placement and confirming adequate distribution of the solution.

Recommendations

Indications. Monitoring the administration of cardioplegia solution is a category III indication for intraoperative TEE.

Nonoperative Critical Care Medicine

The increasing availability of TEE, along with recent technological advances, has resulted in its increased use in nonsurgical ICU patients. Many anesthesiologists engaged in critical care medicine encounter potential applications of TEE when caring for unstable ICU patients, and supporting scientific evidence is briefly reviewed below. As noted earlier, the methodology of the task force required it to limit its literature review to studies of TEE conducted specifically in the critical care or perioperative setting. Thus, evidence from echocardiographic and cardiac catheterization laboratories regarding the accuracy and effectiveness of TEE in evaluating valvular heart disease, hemodynamic disturbances, embolic sources, and a variety of other common problems in the ICU could not be included. Although an examination of this large body of indirect evidence was beyond the scope of the task force project and is omitted from this report, information about these studies is available in other reviews. [1] [2]

Summary of the Evidence.

Some studies report that TEE detects information not detected by TTE in 44-59% of ICU patients, but the studies did not compare both tests systematically. Information provided by TEE examinations is reported to change therapy in 17-48% of critical care patients. There is little direct evidence of clinical benefit, however, beyond case reports of the use of TEE to detect the cause of hemodynamic disturbances; to diagnose endocarditis, aortic disease, valvular insufficiency, embolic sources; or to aid ventilator management, thrombolytic therapy, and resuscitation. These studies provide little direct evidence that the diagnoses could not be made by other means or that patients diagnosed or monitored by TEE experience better clinical outcomes than those without it.

Expert Opinion.

Although there is little direct evidence that TEE affects clinical outcomes in the ICU, its effectiveness in correcting life-threatening problems can be inferred from its proven accuracy in detecting these problems and from evidence that early detection and treatment improves outcomes (*e.g.,* see earlier sections on acute aortic dissection, myocardial ischemia, and hemodynamic function). For those conditions that can be evaluated accurately by TEE, the task force believes its use in the ICU is appropriate when TTE or other tests are unable to make the diagnosis or when patients are too unstable to consider other tests. Transesophageal echocardiography may be the first choice in diagnosing certain problems. Its superiority

over other tests in detecting valve disease, hemodynamic disturbances, unsuspected traumatic cardiac injuries, embolic sources, and other problems has been reviewed already. The task force notes that, although the evidence reviewed in this section is limited to the nonoperative critical care patient, transophageal echocardiography has similar, if not greater, utility in the unstable postoperative patient being cared for in the postanesthesia care unit or ICU.

Recommendations

Indications. Unexplained hemodynamic disturbances, suspected valve disease, or thromboembolic problems in unstable ICU patients are category I indications for TEE if other tests or monitoring techniques have failed to confirm the diagnosis or if patients are too unstable to undergo other tests. Other reviews provide more detailed recommendations on the role of echocardiography and other diagnostic procedures in the critical care setting.

Proficiency. Transesophageal echocardiography examinations of nonoperative critical care patients for indications other than determining the cause of hemodynamic disturbances should be performed by, or in consultation with, a physician with advanced transophageal echocardiography training.

Adverse Effects

Summary of the Evidence.

In most studies, serious complications (*e.g.,* esophageal injury or bleeding, vocal cord paralysis, dysrhythmias, hypotension, seizures, cardiac arrest) occur in less than 3% of TEE examinations. Studies reporting a higher incidence of serious complications (8-13%) generally involve select study populations, outdated TEE techniques, or broader case definitions (e.g.,including atrial ectopy among dysrhythmias). The reported mortality rate associated with TEE is 0.01-0.03%, but in most cases a causal link with TEE has not been established. Minor complications from TEE (and their reported incidence) include lip injuries (13%), hoarseness (12%), dysphagia (1.8%), endotracheal intubation (0.3%), bradycardia (0.2%), and dental injuries (0.1%). The reported incidence of bacteremia in most studies is 0-4%, but there is little direct evidence that patients experience clinical consequences. Respiratory complications occur more frequently in awake examinations (0.1-4%) or in small children (2%), whose membranous trachea is easily compressed by the probe. Hemodynamic compromise also may be more common in small children. There is no scientific evidence that anticoagulation increases significantly the risk of bleeding during transophageal echocardiography examinations.

Expert Opinion.

Reported complication rates for TEE, although low, may overestimate true complication rates in the operating room, for several reasons. First, operator skill is an important determinant of complication rates, and reported rates from TEE studies involving inexperienced examiners may not be applicable to rates observed by experienced practitioners. (Conversely, rates reported by seasoned TEE examiners may underestimate the risk of complications among other practitioners). Second, reported incidence rates for adverse effects often originate from examinations of awake patients, in whom some complications are more common than in anesthetized surgical patients. For example, the task force believes that dysrhythmias may be less common in anesthetized than in awake patients. Inadvertent endotracheal insertion of the TEE probe is uncommon in the operating room, in part because endotracheal intubation precedes placement of the transophageal echocardiography probe. Third, confounding variables may have a more direct effect on observed complications than TEE. For example, endotracheal intubation, rather than TEE, may account for the high reported incidence (12-13%) of hoarseness and lip injuries. Comorbidity (*e.g.,* coronary artery disease, neoplasms), rather than TEE, may account for such observed outcomes as myocardial ischemia, dysrhythmias, and gastroesophageal bleeding.

Recommendations

Contraindications. The risk of esophageal injury can be minimized by avoiding TEE examination of patients with extensive esophageal or gastric disease. Relative contraindications include esophageal varices, Barrett's esophagus, Zenker's diverticulum, and postradiation therapy of the esophageal area. Attempts should be made to minimize the pressure exerted on the esophageal mucosa by the TEE probe, including avoiding the practice of keeping the probe in a locked, flexed position. An appropriate probe size should be selected for small children, and airway pressure monitoring should be emphasized during examinations. Most importantly, anesthesiologists performing TEE examinations should be careful that the procedure does not distract them from other intraoperative responsibilities.

Routine safety procedures also can reduce complication rates. Infectious complications can be reduced

by adhering to proper probe sterilization practices. Universal precautions to reduce transmission of infectious diseases should be followed. In patients with valve disease or congenital heart malformations, preoperative antibiotic prophylaxis should be prescribed according to current guidelines. Manufacturers' recommendations for ensuring electrical safety should also be followed.

Proficiency. All anesthesiologists who perform TEE should be familiar with the full range of potential complications of the procedure and with methods for minimizing their risk.

Certification, Credentialing, Quality Assurance, and Training

The incorporation of TEE in the practice of anesthesia has led to a number of challenging issues related to certification, credentialing, quality assurance and training. Using the available legal, regulatory, and scientific literatures, the task force has attempted to address some of these issues. In many instances, however, the task force has needed to rely on expert opinion in its efforts to formulate recommendations.

Certification

Certification of proficiency is not currently available for practitioners of TEE. While the authority and responsibility for certification of consultants in anesthesiology lies with the American Board of Anesthesiology, it has no precedent for certifying proficiency in technical procedures. The task force recommends that certification of special qualification in perioperative TEE be pursued through multispecialty collaboration.

Credentialing

Credentialing of health-care professionals is a volatile arena for physician-hospital and physician-physician relations, because the stakes for practitioners and institutions are so high. Physicians are credentialed for two reasons: first, to ensure that, at a given hospital, an even standard of care is delivered to patients; and second, to fulfill the legal responsibility of the hospital for the patient. Although these reasons are similar, the difference is crucial. Hospitals usually are corporations, legal entities established under state law, with authority and responsibilities provided by those laws. The law recognizes a corporate duty on the part of a hospital's board of directors (or trustees) that is much more specific than is the case for their broader responsibility for the provision of quality medical care. In the fulfillment of these duties, hospital boards rely on state-specific directives from statutory law as well as common law and Joint Commission for the Accreditation of Health Care Organizations guidelines. Although the hospital board passes the responsibility on to the medical staff for the specifics of appointment, reappointment and granting of privileges, which the medical staff codifies in the medical staff bylaws, the final authority for credentialing rests with the hospital board.

The Joint Commission for the Accreditation of Health Care Organizations requires that the medical staff be responsible to the hospital board for the quality of care provided to patients. This quality of care responsibility begins with the granting of clinical privileges and is hospital-specific. Thus, the hospital must have adequate facilities and support staff to provide the services for which privileges are granted. Furthermore, "Professional criteria specified in the medical staff bylaws and *uniformly* applied to all applicants for delineated clinical privileges constitute the basis for granting initial or continuing privileges." Each clinical department develops its own criteria for determining an applicant's ability to provide services within the scope of privileges requested. However, these department-specific criteria are in addition to the general medical staff criteria for clinical privileges.

These criteria must include evidence of relevant training and experience, and evidence of current competence. This evidence ideally includes at least proof of skill in performing invasive procedures and information on appropriateness and outcomes as well as the application of appropriate clinical judgment. Reappointment also must include information regarding the person's clinical and technical skills, as indicated in part by the results of quality assurance and improvement activities. The process should be most thorough when privileges are for complicated treatment or procedures.

Although many organizations, most notably the American College of Physicians, are attempting to develop guidelines to assist hospitals in the granting of clinical privileges, they are primarily based on the recommendations of postgraduate training programs with little supporting evidence. This problem is recognized by the Joint Commission for the Accreditation of Health Care Organizations, which requires that the granting of privileges take into account hospital-specific factors and, by inference, the local pool of specifically trained

---

professionals. In view of these considerations, the task force cannot justify the imposition of nationwide recommendations for the granting of initial clinical privileges in perioperative TEE. However, it strongly supports requirements of continuous assessment of an individual's clinical performance using objective evidence as the basis for the renewal of privileges.

Quality Assurance

Quality assurance programs employing total quality management concepts are used widely to improve medical services. [11] [12] [13] [14] [15] [16] [17] Quality management employs three basic, closely related activities: quality planning, quality control, and quality improvement. Quality planning involves developing definitions of quality as applied to the customer, designing products and services to meet customer needs, and designing processes capable of producing these products and services. Quality control involves developing and applying methods for ensuring that processes work as they are designed. Quality improvement focuses on improving the level of performance of key processes. Continuous quality improvement maintains periodic reviews of the quality assurance program to meet changing customer needs and improve the organization's efficiency. When applying total quality management concepts to perioperative TEE, the terms "products" and "customers" need to be employed in their broadest meaning. The major product of perioperative TEE is information,which is provided to customers. These customers can include other anesthesiologists, surgeons, cardiologists, other physicians, the patient, or the manufacturers of echocardiographic equipment.

Which process of a TEE program is the current "key process" that may benefit from improvement will vary from program to program. The following outline of "processes" was developed to assist in focusing on possible key processes within echocardiography programs.

1. Indications for performing TEE
2. Technical aspects of performing and recording the examination
3. Application of examination findings to physiologic condition
4. Documentation
5. Equipment
6. Professional Communications
7. Education
8. Billing

The application of quality management to an echocardiographic service need not be restricted to the areas mentioned earlier. Periodic updating of the quality assurance program as the TEE service evolves will facilitate meeting the goals originally set forth and defining new goals to meet clinical needs.

Training

General Principles.

While several guidelines for the training of physicians who wish to practice TEE have been developed, few have focused on the specifics of a perioperative TEE practice. [18] [19] [20] [21] The task force recommends that two levels of training in perioperative TEE, basic and advanced, be recognized for the anesthesiologist. Advanced training should be pursued only after basic training has been completed.

Anesthesiologists with basic training in perioperative TEE should be able to use TEE for indications that lie within the customary practice of anesthesiology. Examples of such indications include: the perioperative diagnosis of myocardial ischemia, the perioperative assessment of hemodynamics and ventricular function, the perioperative management of cardiovascular collapse, and others. The task force realizes, however, that anesthesiologists with basic training occasionally will encounter unanticipated diagnostic issues that require the assistance of a physician with advanced TEE training. Anesthesiologists with basic training must be able to recognize their limitations in this setting and request assistance, in a timely manner, from a physician with advanced training. Anesthesiologists with advanced training in perioperative TEE should,in addition to the above, be able to exploit the full diagnostic potential of TEE in the perioperative period. The task force recognizes that, once basic training has been completed, advanced training may occur along a continuum and in a gradual manner. Learning curves will vary from person to person, but are likely to be substantial for some of the TEE applications requiring advanced training. Because it is essential for many intraoperative applications to obtain a definitive interpretation of the TEE examination at the time of surgery, the task force strongly recommends that anesthesiologists actively pursue collaboration with surgeons, cardiologists, or other physicians involved in a patient's care. Specific objectives for basic and advanced training are defined in table 2.

TABLE 2 -- Specific Training Objectives

Basic training
Cognitive skills
1. Knowledge of the physical principles of echocardiographic image formation and blood flow velocity measurement
2. Understanding the operation of the ultrasonographic instrument, including the function of all controls affecting the quality of data displayed
3. Knowledge of the equipment handling, infection control, and electrical safety recommendations associated with the use of TEE
4. Knowledge of the indications and the absolute and relative contraindications to the use of TEE
5. General knowledge of appropriate alternative diagnostic modalities, especially transthoracic and epicardial echocardiography
6. Knowledge of the normal cardiovascular anatomy as visualized tomographically by TEE
7. Knowledge of commonly encountered blood flow velocity profiles as measured by Doppler echocardiography
8. Detailed knowledge of the echocardiographic presentations of myocardial ischemia and infarction
9. Detailed knowledge of the echocardiographic presentations of normal and abnormal ventricular function
10. Detailed knowledge of the physiology and TEE presentation of air embolization
11. Knowledge of native valvular anatomy and function as displayed by TEE knowledge of the major TEE manifestations of valve lesions and dysfunction and of the TEE techniques available for valve assessment
12. Knowledge of the principal TEE manifestations of cardiac masses, thrombi, and emboli; cardiomyopathies; pericardial effusions; and lesions of the great vessels
Technical skills
1. Ability to operate the ultrasonograph, including controls affecting the quality of the displayed data
2. Ability to perform safely a TEE-probe insertion in the anesthetized, tracheally intubated patient
3. Ability to perform a basic TEE examination
4. Ability to recognize major echocardiographic changes associated with myocardial ischemia and infarction
5. Ability to detect qualitative changes in ventricular function and hemodynamic status
6. Ability to recognize echocardiographic manifestations of air embolization
7. Ability to visualize cardiac valves in multiple views, ability to recognize gross valvular lesions and dysfunction
8. Ability to recognize large intracardiac masses and thrombi
9. Ability to detect large pericardial effusions
10. Ability to recognize common artifacts and pitfalls in TEE examination
11. Ability to communicate the results of a TEE examination to the patient and to other health care professionals and to summarize these results cogently in the medical record
Advanced training
Cognitive skills
1. All the cognitive skills defined under basic proficiency
2. Knowledge of the principles and methodology of quantitative echocardiography
3. Detailed knowledge of native valvular anatomy and function; knowledge of prosthetic valvular structure and function; detailed knowledge of the echocardiographic manifestations of valve lesions and dysfunction
4. Knowledge of the echocardiographic manifestations of congenital heart disease.

5. Detailed knowledge of echocardiographic manifestations of pathologic conditions of the heart and great vessels (such as cardiac aneurysms, HOCM, endocarditis, intracardiac masses, cardioembolic sources, aortic aneurysms and dissections, pericardial disorders, and postsurgical changes)

6. Detailed knowledge of other cardiovascular diagnostic methods for correlation with TEE findings

Technical skills

1. All the technical skills defined under basic proficiency

2. Ability to perform a complete TEE examination

3. Ability to quantify subtle echocardiographic changes associated with myocardial ischemia and infarction

4. Ability to utilize TEE to quantify ventricular function and hemodynamics

5. Ability to utilize TEE to evaluate and quantify the function of all cardiac valves (*e.g.,* measurement of gradient, regurgitant jet area, flow-velocity pattern, valve orifice area); ability to assess surgical intervention on cardiac valvular function

* 6. Ability to utilize TEE to evaluate congenital heart lesions; ability to assess surgical intervention in congenital heart disease

* 7. Ability to detect and assess the functional consequences of pathologic conditions of the heart and great vessels (such as cardiac aneurysms, HOCM, endocarditis, intracardiac masses, cardioembolic sources, aortic aneurysms and dissections, and pericardial disorders); ability to evaluate surgical intervention in these conditions if applicable

8. Ability to monitor placement and function of mechanical circulatory assistance devices

TEE = transesophageal echocardiography; HOCM = hypertrophic obstructive cardiomyopathy.

*Some of the technical skills may not apply, depending on practice setting.

Training Pathways

Anesthesiologists.

The anesthesiologist who wishes to attain basic or advanced training in perioperative TEE must undertake certain steps in the process. First, the anesthesiologist should begin to master the cognitive and some of the technical skills outlined in table 2 by studying standard texts and commercially available videotapes and by attending TEE workshops and training sessions. Second, the anesthesiologist should establish a collaborative relationship with a physician who is proficient in TEE to assist the anesthesiologist in acquiring additional technical skills in TEE. The nature of the collaborative relationship should be such that the anesthesiologist refers to the other physician in a timely manner when his/her expertise is exceeded. The collaboration should be an ongoing relationship rather than a brief period of assistance. Third, as with other clinical procedures, mastery of TEE requires time, practice, and repetition on the part of the anesthesiologist to achieve adequate proficiency. While training in perioperative echocardiography need not be restricted to a specific training pathway or protocol (*e.g.,* specified duration of echocardiography laboratory rotations, mandatory TTE training, videotape reviews, required number of examinations to be performed), the task force recommends that anesthesiologist training in TEE be one of the essential processes that are assessed objectively in a quality assurance program for perioperative TEE. Recognizing the importance of maintaining proficiency, the task force recommends that another essential quality assurance process should evaluate an anesthesiologist's ability to maintain skills after training is complete.

Residents in Anesthesiology.

Introductory Knowledge. The task force recommends that all residents in anesthesiology acquire introductory knowledge in perioperative TEE.Every resident who completes the continuum of education in anesthesiology should understand how TEE can be safely and effectively used in essential perioperative applications. The training should include knowledge on the physical principles of echocardiographic imaging and blood flow measurements, two-dimensional echocardiographic anatomy of the heart and great vessels, and the perioperative indications, limitations, diagnostic capabilities, and risks of TEE.

Basic Proficiency. Residents in anesthesiology who wish to pursue basic training in perioperative TEE should acquire the cognitive and technical skills outlined in table 2 for basic training. The training program should have an active perioperative TEE program. Although basic TEE skills can be taught by a physician with basic proficiency, the training program should be under the guidance of, or in close collaboration with, a physician with advanced training in perioperative TEE.

Advanced Proficiency. Residents in anesthesiology who wish to attain an advanced level of training in perioperative TEE should acquire the cognitive and technical skills defined in table 2 for advanced training. The training should occur in cooperation with an established echocardiography service and under the direct guidance of a physician with advanced proficiency in perioperative TEE.

The members of the task force thank all the reviewers for their constructive comments, without which the completion of the practice guidelines would not have been possible.

References

1. Khanderia BK, Seward JB, Tajik AJ: Transesophageal echocardiography. Mayo Clin Proc 1994; 69:856-63

2. Foster E. Schiller NB: Transesophageal echocardiography in the critical care patient. Cardiol Clin 1993; 11:489-503

3. Eddy DM. A Manual for Assessing Health Practices and Designing Practice Policies: The Explicit Approach. Philadelphia, American College of Physicians, 1992

4. Tennant R, Wiggers CJ: The effect of coronary occlusion on myocardial contraction. Am J Physiol 1935; 112:351-61

5. Battler A, Froelicher VF, Gallagher KP, Kemper WS, Ross J: Dissociation between regional myocardial dysfunction and ECG changes during ischemia in the conscious dog. Circulation 1980; 62:735-44

6. Hauser Am, Gangadharan V, Ramos RG, Gordon S, Timmis GC: Sequence of mechanical electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: Echocardiographic observations during coronary angioplasty. J Am Coll Cardiol 1985; 5:193-7

7. Wohlgelernter D, Jaffe CC, Cabin HS, Yeatman LA Jr, Cleman M: Silent ischemia during coronary occlusion produced by balloon and inflation: Relation to regional myocardial dysfunction. J Am Coll Cardiol 1987; 10:491-8

8. Ungerleider RM, Greeley WJ, Sheikh KH, Philips J, Pearce FB, Kern FH, Kisslo JA:. Routine use of intraoperative epicardial echocardiography and Doppler color flow imaging to guide and evaluate repair of congenital heart lesions: A prospective study. J Thorac Cardiovasc Surg 1990; 100:297-309

9. Romeo F, Pelliccia F, Cristofani R, Martuscelli E, Reale A: Hypertrophic cardiomyopathy: Is a left ventricular outflow tract gradient a major prognostic determinant? Eur Heart J 1990; 11: 233-40

10. Obarski TP, Loop FD, Cosgrove DM, Lytle BW, Stewart WJ: Frequency of acute myocardial infarction in valve repairs versus valve

replacement for pure mitral regurgitation. Am J Cardiol 1990; 65:887-90

11. Berwick DM, Godfrey AB, Roessner J: Curing Health Care: New Strategies for Quality Improvement. A Report on the National Demonstration Project on Quality Improvement in Health Care. San Francisco, Josie-Bass, 1990

12. Berwick DM: Continuous improvement as an ideal in health care. N Engl J Med 1989; 320:53-6

13. Deming WE: Out of the Crisis. Cambridge, Massachusetts Institute of Technology, 1986

14. Feigenbaum AV: Total Quality Control. New York, McGraw Hill, 1983

15. 15. Kritchevsky SB, Simmons BP: Continuous quality improvement, concepts and applications for physician care. JAMA 1991; 266: 1817-23

16. Laffel G, Blumenthal D: The case for using industrial quality management science in health care organizations. JAMA 1989; 272: 2869-73

17. Wenzel RP: Beyond total quality management. Clinical performance and quality health care. 1993; 1:43-8

18. Pearlman AS, Gardin JM, Martin RP, Parisi AP, Popp RL, Quinones MA, Stevenson JG. Guidelines for optimal physician training in echocardiography: Recommendations of the American Society of Echocardiography Committee for Physician Training in Echocardiography. Am J Cardiol 1987; 60:158-63.

19. Pearlman AS, Gardin JM, Martin RP, Parisi AF, Popp RL, Quinones MA, Stevenson JG, Schiller NB, Seward JB, Stewart WJ: Guidelines for physician training in transesophageal echocardiography: Recommendations of the American Society of Echocardiography Committee for Physician Training in Echocardiography. J Am Soc Echocardiogr. 1992; 5;187-94

20. Ewy GA, Appleton CP, Demaria AN, Feigenbaum H, Rogers EW, Ronan JA, Skorton DJ, Tajik AJ, Williams RG, Fisch C, Beller GA, DeSanctis RW, Dodge HT, Kennedy JW, Reeves TJ, Weinberg SL: ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures. J Am Coll Cardiol 1990; 16;1505-28

21. Fyfe DA, Ritter SB, Snider AR, Silverman NH, Stevenson JG, Sorensen G, Ensing G, Ludomirsky A, Sahn DJ, Murphy D, Hagler D, Marx GR: Guidelines for transesophageal echocardiography in children: Report of the Committee on Standard for Pediatric Transesophageal Echocardiography of the Society of Pediatric Echocardiography. J Am Soc Echocardiogr 1992; 5:640-4

APPENDIX: Practice Guidelines for Management of the Difficult Airway[D]

A Report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway

Introduction

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to revision from time to time, as warranted by the evolution of medical knowledge, technology, and practice.

A. Purpose of Guidelines for Difficult Airway Management

The purpose of these guidelines is to facilitate the management of the difficult airway and to reduce the likelihood of adverse outcomes. The principal adverse outcomes associated with the difficult airway include (but are not limited to): death, brain injury, myocardial injury, and airway trauma.

B. Focus

The primary focus of the guidelines is the management of the difficult airway encountered during tracheal intubation. * Some aspects of the guidelines may be relevant in other clinical contexts. The guidelines do not represent an exhaustive consideration of all manifestations of the difficult airway or all possible approaches to management.

c. Application

The guidelines are intended for use by anesthesiologists and by individuals who deliver anesthetic care under the direct supervision of an anesthesiologist.

The guidelines apply to all types of anesthetic care delivered in anesthetizing locations.

The guidelines are intended for patients of all ages.

Guidelines

I. Evaluation of the Airway

History.

The literature and consultant opinion strongly support the conduct of an airway history. This support is based upon recognized associations between the difficult airway and a variety of congenital, acquired, and traumatic disease states. The predictive value of the airway history and its effect on outcome have not been clearly defined in the literature.

Recommendations: A. An airway history should be conducted, whenever feasible, prior to the initiation of anesthetic care in all patients. The intent of the airway history is to detect medical, surgical, and anesthetic factors that may indicate the presence of a difficult airway. Examination of previous anesthetic records, if available, may provide useful information.

Physical Examination.

The literature and consultant opinion strongly support the conduct of an airway

Developed by the Task Force on Guidelines for Management of the Difficult Airway: Robert A. Caplan, M.D. (Chairman); Jonathan L. Benumof, M.D.; Frederick A. Berry, M.D.; Casey D. Blitt, M.D.; Robert H. Bode, M.D.; Frederick W. Cheney, M.D.; Richard T. Connis, Ph.D. (Health Services Research Methodologist); Orin F. Guidry, M.D.; and Andranik Ovassapian, M.D. Approved by the House of Delegates, October 21, 1992. To become effective July 1, 1993.

physical examination. This support is based upon recognized associations between the difficult airway and physical findings. Specific features of the airway physical examination have been incorporated into rating systems that predict the likelihood of a difficult airway. These rating systems exhibit modest sensitivity and specificity. No current rating system is fail-safe. The specific effect of the airway physical examination on outcome has not been clearly defined in the literature.

Recommendations: B. An airway physical examination should be conducted, whenever feasible, prior to the initiation of anesthetic care in all patients. The intent of this examination is to detect physical characteristics that may indicate the presence of a difficult airway.

Additional Evaluation.

The airway history or physical examination may provide indications for additional diagnostic testing in some patients. The literature does not provide a basis for using specific diagnostic tests as routine screening tools in the evaluation of the difficult airway.

Recommendations: C. Additional evaluation may be indicated in some patients to characterize the likelihood or nature of the anticipated airway difficulty. The findings of the airway history and physical examination may be useful in guiding the selection of specific diagnostic tests and consultation.

II Basic Preparation for Difficult Airway Management

The literature has not rigorously addressed the effects of patient preparation and equipment preparation on outcome. However, there is strong agreement among consultants that preparatory efforts enhance success and minimize risk. The Task Force has identified several fundamental features of preparation that merit consideration.

Recommendations: A. At least one portable storage unit that contains specialized equipment for difficult airway management should be readily available. Specialized equipment suggested by the Task Force is listed in table 1.

B. If a difficult airway is known or suspected, the anesthesiologist should:

TABLE 1 -- Suggested Contents of the Portable Storage Unit for Difficult Airway Management

IMPORTANT: The items listed in this table represent suggestions. The contents of the portable storage unit should be customized to meet the specific needs, preferences, and skills of the practitioner and health-care facility.
1. Rigid laryngoscope blades of alternate design and size from those routinely used.
2. Endotracheal tubes of assorted size.
3. Endotracheal tube guides. Examples include (but are not limited to) semirigid stylets with or without a hollow core for jet ventilation, light wands, and forceps designed to manipulate the distal portion of the endotracheal tube.
4. Fiberoptic intubation equipment.
5. Retrograde intubation equipment.
6. At least one device suitable for emergency nonsurgical airway ventilation. Examples include (but are not limited to) a transtracheal jet ventilator, a hollow jet ventilation stylet, the laryngeal mask, and the esophageal-tracheal combitube.
7. Equipment suitable for emergency surgical airway access (e.g., cricothyrotomy).
8. An exhaled CO^2 detector.

1. Inform the patient (or responsible person) of the special risks and procedures pertaining to management of the difficult airway.
2. Ascertain that there is at least one additional individual who is immediately available to serve as an assistant in difficult airway management.
3. Consider the feasibility of supplemental oxygen administration during the process of difficult airway management. Opportunities for supplemental oxygen administration include (but are not limited to) mask preoxygenation before induction of anesthesia; oxygen delivery by mask, insufflation, or jet ventilation during intubation attempts; and oxygen delivery by mask, blow-by, or nasal cannulae after extubation of the trachea. The uncooperative patient may restrict the opportunities for supplemental oxygen administration, particularly options that involve the application of a mask.

Strategy for Intubation of the Difficult Airway

The literature provides strong evidence that specific strategies facilitate the management of the difficult airway. Although the degree of benefit cannot be determined from the literature, there is strong agreement among consultants that specific strategies lead to improved outcome. Specific strategies can be linked together to form more comprehensive treatment plans or *algorithms.* The cardiopulmonary resuscitation literature provides evidence for the beneficial effects of algorithms in the management of life-threatening cardiac events. The Task Force considers the technical and physiologic complexity of life-threatening airway events to be sufficiently similar to life-threatening cardiac events to

---

encourage the use of algorithms in difficult airway management.

Recommendations: A. The anesthesiologist should have a preformulated strategy for intubation of the difficult airway. This strategy will depend in part upon the anticipated surgery, the condition of the patient, and the skills and preferences of the anesthesiologist. An algorithm recommended by the Task Force is shown in figure 1.

B. The strategy for intubation of the difficult airway should include:

1. An assessment of the likelihood and anticipated clinical impact of three basic problems that may occur alone or in combination:
   a. Difficult intubation.
   b. Difficult ventilation.
   c. Difficulty with patient cooperation or consent.
2. A consideration of the relative clinical merits and feasibility of three basic management choices:
   a. Use of nonsurgical techniques for the initial approach to intubation *versus* use of surgical techniques for the initial approach to intubation.
   b. Preservation of spontaneous ventilation during intubation attempts *versus* ablation of spontaneous ventilation during intubation attempts.
   c. Awake intubation *versus* intubation attempts after induction of general anesthesia.
3. The identification of a primary or preferred approach to:
   a. Awake intubation.
   b. The patient who can be adequately ventilated but is difficult to intubate.
   c. The life-threatening situation in which the patient cannot be ventilated or intubated.
4. The identification of alternative approaches that can be employed if the primary approach fails or is not feasible:
   a. table 2 displays options for difficult airway management.
   b. The uncooperative patient may restrict the options for difficult airway management, particularly options that involve awake intubation. Airway management in the uncooperative patient may require an approach (*e.g.,* intubation attempts after induction of general anesthesia) that might not be regarded as a primary approach in a cooperative patient.
   c. The conduct of surgery using local anesthetic infiltration or regional nerve blockade may provide an alternative to the direct management of the difficult airway, but this approach does *not* represent a definitive solution to the presence of a difficult airway, *nor* does it obviate the need for a preformulated strategy for intubation of the difficult airway.
5. The use of exhaled CO2 to confirm tracheal intubation.

IV.Strategy for Extubation of the Difficult Airway

Although the literature does not provide a sufficient basis for evaluating the merits of an extubation strategy, the Task Force regards the concept of an extubation strategy as a logical extension of the intubation strategy. Consultant opinion strongly supports the use of an extubation strategy.

Recommendations: A. The anesthesiologist should have a preformulated strategy for extubation of the difficult airway. This strategy will depend in part upon the surgery, the condition of the patient, and the skills and preferences of the anesthesiologist.

B. The preformulated extubation strategy should include:

1. A consideration of the relative merits of awake extubation *versus* extubation before the return of consciousness.
2. An evaluation for general clinical factors that may produce an adverse impact on ventilation after the patient has been extubated.
3. The formulation of an airway management plan that can be implemented if the patient is not able to maintain adequate ventilation after extubation.
4. A consideration of the short-term use of a device that can serve as a guide for expedited reintubation. This type of device is usually inserted through the lumen of the endotracheal tube and into the trachea *before* the endotracheal tube is removed. The device may be rigid to facilitate intubation and/or hollow to facilitate ventilation.

Follow-Up Care

Although the literature does not provide a sufficient basis for evaluating the benefits of follow-up care, this

Figure 1

TABLE 2 -- Techniques for Difficult Airway Management

IMPORTANT: This table displays commonly cited techniques. It is not a comprehensive list. The order of presentation is alphabetical and does not imply preference for a given technique or sequence of use. Combinations of techniques may be employed. The techniques chosen by the practitioner in a particular case will depend upon specific needs, preferences, skills, and clinical constraints.

I Techniques for difficult intubation
Alternative laryngoscope blades
Awake intubation
Blind intubation (oral or nasal)
Fiberoptic intubation
Intubating stylet/tube changer
Light wand
Retrograde intubation
Surgical airway access
II Techniques for difficult ventilation
Esophageal-tracheal combitube
Intratracheal jet stylet
Laryngeal mask
Oral and nasopharyngeal airways
Rigid ventilating bronchoscope
Surgical airway access
Transtracheal jet ventilation
Two-person mask ventilation

activity is strongly supported by consultant opinion. The Task Force has identified several fundamental concepts that merit consideration.

Recommendations: A. The anesthesiologist should document the presence and nature of the airway difficulty in the medical record. The intent of this documentation is to guide and facilitate the delivery of future care. Aspects of documentation that may prove helpful include (but are not limited to):

1. A description of the airway difficulties that were encountered. If possible, the description should distinguish between difficulties encountered in mask ventilation and difficulties encountered in tracheal intubation.
2. A description of the various airway management techniques that were employed. The description should indicate the extent to which each of the techniques served a beneficial or detrimental role in management of the difficult airway.

B. The anesthesiologist should inform the patient (or responsible person) of the airway difficulty that was encountered. The intent of this communication is to provide the patient (or responsible person) with a role in guiding and facilitating the delivery of future care. The information conveyed may include (but is not limited to): the presence of a difficult airway, the apparent reasons for difficulty, and the implications for future care.

C. The anesthesiologist should evaluate and follow the patient for potential complications of difficult airway management. These complications include (but are not limited to): edema, bleeding, tracheal and esophageal perforation, pneumothorax, and aspiration.

Appendix

A. Definition of the Difficult Airway

A standard definition of the difficult airway cannot be identified in the available literature. The Task Force has not given preference to literature based upon any particular system of definition or classification. For these guidelines, *a difficult airway is defined as the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with mask ventilation, difficulty with tracheal intubation, or both.*

The difficult airway represents a complex interaction between patient factors, the clinical setting, and the skills and preferences of the practitioner. Analysis of this interaction requires precise collection and communication of data. The Task Force urges clinicians and investigators to use explicit descriptions of the difficult airway. Descriptions that can be categorized or expressed as numerical values are particularly desirable, as this type of information lends itself to aggregate analysis and cross-study comparisons. Suggested descriptions include (but are not limited to):

1. Difficult Mask Ventilation.

1. It is *not* possible for the unassisted anesthesiologist to maintain the Sp_{o2} >90% using 100% oxygen and positive pressure mask ventilation in a patient whose Sp_{o2} was >90% before anesthetic intervention.
2. It is *not* possible for the unassisted anesthesiologist to prevent or reverse signs of inadequate ventilation during positive pressure mask ventilation.

Signs of inadequate mask ventilation include (but are not limited to): cyanosis, absence of exhaled CO_2, absence of spirometric measures of exhaled gas flow, absence of breath sounds, absence of chest movement, auscultatory signs of severe airway obstruction, gastric air entry or dilatation, and hemodynamic changes associated with hypoxemia or hypercarbia (*e.g.,* hypertension, tachycardia, arrhythmia).

2. Difficult Laryngoscopy.

It is *not* possible to visualize any portion of the vocal cords with conventional laryngoscopy.

3. Difficult Endotracheal Intubation.

1. Proper insertion of the tracheal tube with conventional laryngoscopy requires *more than three attempts.*
2. Proper insertion of the tracheal tube with conventional laryngoscopy requires *more than 10 min.*

B. Assessment of Scientific Evidence and Consultant Opinion

The assessment of scientific evidence focused on the following 10 statements or *linkages.* These linkages represent hypotheses about the relationships between clinical care and clinical outcome
in difficult airway management.

1. Preanesthetic evaluation predicts a difficult airway.
2. Preanesthetic evaluation leads to fewer adverse outcomes.
3. Preparation of the patient and equipment facilitates successful airway management.
4. Preparation of the patient and equipment leads to fewer adverse outcomes.
5. Use of a strategy or algorithm facilitates successful airway management.
6. Use of a strategy or algorithm leads to fewer adverse outcomes.
7. Confirmatory tests of endotracheal intubation facilitate successful management.
8. Confirmatory tests of endotracheal intubation lead to fewer adverse outcomes.
9. Use of an extubation strategy or algorithm leads to fewer adverse outcomes.
10. Follow-up care leads to fewer adverse outcomes.

Scientific support for the linkages was assessed by a structured literature search and meta-analysis. The bibliographic files of the National Library of Medicine and other large reference sources were searched for citations containing key words, subject headings, and text entries related to the 10 linkages. Task Force members provided supplemental citations. Several thousand citations were initially identified, of which 537 were associated with the specified linkages. Literature that could not be analyzed was eliminated. A total of 273 articles, published in the interval from 1973 to 1991, were available for consideration. Each article was reviewed, summarized, and coded by the research methodologist using a standardized rating instrument. Agreement between the Task Force members and the methodologist was established by interrater reliability testing.

Two approaches to meta-analysis were employed. First, the directional result of each study was classified as either 1) supporting a linkage, 2) refuting a linkage, or 3) neutral. These results were averaged to obtain an aggregate directional measure of support for each linkage. Second, the literature relating to linkages 1,5, and 6 contained enough studies with well defined experimental designs and statistical information to calculate significance levels for the direction of support. Using the Fisher combined test, the following results were obtained: linkage 1, $P < 0.001$; linkage 5, $P < 0.001$; linkage 6, $P < 0.01$. For this type of metaanalysis, $P < 0.01$ was considered significant. There were not enough data to assess the relative strength of the directional measures of support.

The findings of the literature analysis were supplemented by opinion from Task Force members and 50 consultant anesthesiologists with recognized interest in airway management and guidelines. The kappa statistic (k) was used to obtain a quantitative measure of agreement among consultants. Consultants exhibited strong agreement ($_k$
0.75) on the potential beneficial effects of the following activities: conduct of the airway history and physical examination, advance preparation of the patient and equipment, formulation of strategies for intubation and extubation of the difficult airway, and provision of follow-up care.

C. References

A list of the articles used to develop these guidelines is available by writing to the American Society of Anesthesiologists, 520 North Northwest Highway, Park Ridge, Illinois 60068-2573.

The process of guideline development was conducted according to the technique described by S.H. Woolf in the *Manual for Clinical Practice Guideline Development,* U.S. Department of Health and Human Services, March 1991, Agency for Health Care Policy and Research, publication number 91-0007.

See Introduction, Section A, for the principal adverse outcomes associated with difficult airway management.

The Task Force gratefully acknowledges the contributions of the members of the American Society of Anesthesiologists who responded to surveys on difficult airway management, reviewed guideline drafts, contributed oral and written testimony to the Open Forum, and participated in tests of clinical feasibility.

APPENDIX: Practice Guidelines for Blood Component Therapy[D]

A Report by the American Society of Anesthesiologists Task Force on Blood Component Therapy

In 1994, the American Society of Anesthesiologists established the Task Force on Blood Component Therapy to develop evidence-based indications for transfusing red blood cells, platelets, fresh-frozen plasma, and cryoprecipitate in perioperative and peripartum settings. The guidelines were developed according to an explicit methodology. The principal conclusions of the task force are that red blood cell transfusions should not be dictated by a single hemoglobin "trigger"but instead should be based on the patient's risks of developing complications of inadequate oxygenation. Red blood cell transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL. The indications for autologous transfusion may be more liberal than for allogeneic (homologous) transfusion. The risks of bleeding in surgical and obstetric patients are determined by the extent and type of surgery, the ability to control bleeding, the actual and anticipated rate of bleeding, and the consequences of uncontrolled bleeding. Prophylactic platelet transfusion is ineffective when thrombocytopenia is due to increased platelet destruction. Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50 × 109/1 and rarely require therapy if it is greater than 100 × 109/1. Fresh-frozen plasma is indicated for urgent reversal of warfarin therapy, correction of known coagulation factor deficiencies for which specific concentrates are unavailable, and correction of microvascular bleeding when prothrombin and partial thromboplastin times are >1.5 times normal. It is contraindicated for augmentation of plasma volume or albumin concentration. Cryoprecipitate should be considered for patients with von Willebrand's disease unresponsive to desmopressin, bleeding patients with fibrinogen levels below 80‐100 mg/dL. The task force recommends careful adherence to proper indications for blood component therapy to reduce the risks of transfusion. (Key words: Practice guidelines: anemia; blood component therapy; coagulopathy; cryoprecipitate; fresh-frozen plasma; red blood cells; transfusion.)

MORE than 22 million blood components are transfused each year in the United States [1] Many of these transfusions are administered to surgical and obstetric patients. The transfusion of red blood cells (RBCs), platelets, fresh-frozen plasma (FFP), and cryoprecipitate has the potential of improving clinical outcomes in perioperative and peripartum settings. These benefits include improved tissue oxygenation and decreased bleeding. However, transfusions are not without risks or costs. The transmission of infectious diseases (*e.g.,* hepatitis, human immunodeficiency virus (HIV) infection), hemolytic and nonhemolytic transfusion reactions, immunosuppression, alloimmunization, and other complications are potential sequelae of blood component therapy.

A number of groups have issued clinical practice guidelines for blood component therapy in an effort to improve transfusion practices, minimize the incidence of adverse transfusion reactions, and decrease costs. In the 1980s, the National Institutes of Health convened consensus conferences and published recommendations for RBC transfusion, platelet therapy, and the administration of FFP. [2] [3] [4] In 1984, the American College of Obstetricians and Gynecologists (ACOG) issued recommendations

Developed by the Task Force on Blood Component Therapy: Linda C. Stehling, M.D., (Chair), Scottsdale, Arizona; Dennis C. Doherty, D.O., Atlanta, Georgia; Ronald J. Faust, M.D., Rochester, Minnesota; A. Gerson Greenburg, M.D., Ph.D. (Representative, American College of Surgeons), Providence, Rhode Island; Chantal R. Harrison, M.D. (Representative, College of American Pathologists), San Antonio, Texas; Dennis F. Landers, M.D., Dallas, Texas; Russell K. Laros, Jr., M.D. (Representative, American College of Obstetricians and Gynecologists), San Francisco, California; Ellison C. Pierce, Jr., M.D., Boston, Massachusetts; Randall S. Prust, M.D., Tucson, Arizona; Andrew D. Rosenberg, M.D., New York, New York; Richard B. Weiskopf, M.D., San Francisco, California; Steven H. Woolf, M.D., M.P.H. (Methodologist), Fairfax, Virginia; and John F. Zeiger, M.D., Ft. Wayne, Indiana.

on blood component therapy. [5] In 1990, the Transfusion Practices Committee of the American Association of Blood Banks issued guidelines for transfusion of patients undergoing coronary artery bypass surgery. [6] In 1992, the American College of Physicians (ACP) issued recommendations for RBC transfusion. [7] In 1994, the College of American Pathologists (CAP) published a practice parameter for FFP, cryoprecipitate, and platelet transfusion. [8] Guidelines for blood utilization review were published in the same year by the American Association of Blood Banks. [9] Although these documents include sections on the use of blood components in the surgical setting, no group has issued current and comprehensive recommendations on perioperative and peripartum blood component therapy.

In 1994, the American Society of Anesthesiologists convened the Task Force on Blood Component Therapy to develop evidence-based guidelines on the proper indications for perioperative and peripartum administration of RBCs, platelets, FFP, and cryoprecipitate. The task force included nine anesthesiologists (in private and university-based practice); one physician representative from the American Pathologists, and ACOG; and a methodologist.

Before the guidelines were developed, the task force reviewed published evidence regarding the clinical effectiveness of perioperative and peripartum blood component therapy. A total of 1,417 articles were retrieved in a computerized and manual literature search conducted in mid-1994. The computerized search sought all English-language literature published in any country on the use of RBCs, platelets, FFP, or cryoprecipitate in the perioperative or peripartum setting. A total of 160 articles were considered relevant. Published evidence was considered relevant if it addressed the perioperative or peripartum use tof the above blood components and measured effectiveness in terms of clinical outcomes. The strength of evidence was classified by study design category, using the scale in table 1 (Table Not Available) . Further details about the literature review methodology are available on request. Input from practicing anesthesiologists was obtained at an open forum held in October 1994. The document was sent to members of the American Society of Anesthesiologists House of Delegates, Board of Directors, and Component Society Presidents for review. The overall guideline development process is reviewed elsewhere. [10] [11]

This article summarizes the results of the literature review and the recommendations of the task force. Recommendations apply to typical surgical and obstetric patients. Infants, children, and special clinical settings (*e.g.,* liver transplantation, sickle cell anemia) are beyond the scope of the report. Thus, the task force has not considered the transfusion of neonatal, infant, or pediatric patients or the recommendations on this topic that have been published by other groups. [12] [13] The recommended indications are based on scientific evidence and expert opinion regarding the effectiveness of the intervention. Effectiveness was judged by considering the potential clinical benefits, adverse effects, and costs of blood component therapy.

TABLE 2 -- Grading of Evidence

From U.S. Preventive Services Task Force: Guide to Clinical Preventive Services: An Assessment of the Effectiveness of 169 Interventions. Baltimore, Williams and Wilkins, 1989.

(Not Available)

Adverse Effects

Transfusion Reactions

Nonhemolytic transfusion reactions, often manifested in awake patients by fever, chills, or urticaria, are the most common adverse effects of RBC transfusion, but these signs may not be detectable during anesthesia. Nonhemolytic transfusion reactions occur in approximately 1-5% of all transfusions. [4] Hemolytic reactions due to administration of incompatible blood can be life-threatening. The estimated risk of ABO-incompatible transfusion is 1:33,000 RBC transfusions. [14] [15] As with nonhemolytic reactions, general anesthesia may mask the symptoms of hemolytic reactions, and many of the signs (hypotension, tachycardia, hemoglobinuria and microvascular bleeding) may be attributed erroneously to other causes. The probability of a fatal hemolytic transfusion reaction is uncertain with estimates ranging from 1:500,000 to 1:800,000. [15] Between 1976 and 1985, the U.S. Food and Drug Administration was notified of 131 fatal ABO-incompatible transfusions. [16]

Infectious Diseases

The incidence of post-transfusion hepatitis, more than 90% of which is due to hepatitis C virus, has decreased

since the introduction of testing for the virus in 1990. [17] The reported incidence of hepatitis C virus seroconversion is 0.03% per unit transfused. [18] However, the actual incidence is believed to be lower because of improved testing introduced in 1992. [19] The risk of transmission of hepatitis B is estimated to be 1:200,000 units. [20]

The risk of exposure to HIV through blood transfusion is uncertain. Although a range of incidence rates has been reported, [21] [22] [23] recent estimates suggest that the mean infectious window period (the period between viral infection and its detection by tests for the presence of antibodies) is approximately 22 days [24] and that the current risk of HIV infection in the United States is 1:450,000-1:660,000 per transfused unit of blood. [25] Implementation of donor screening tests for HIV-1 antigen is expected to prevent up to 25% of the window period cases, or five to ten cases per year. [25] Higher rates may occur in areas with increased HIV prevalence. [26] Perhaps the most common viral agent transmitted by blood transfusion is cytomegalovirus. Most infections are subclinical, although immunocompromised patients may develop severe morbidity. Parasitic and bacterial agents can be transmitted by blood components, but the incidence of clinically significant disease in the United States is low, possibly 1:1,000,000 units of blood. [27] Twenty-six deaths due to bacterial contamination of blood components were reported to the Food and Drug Administration between 1976 and 1985. [16]

Immunosuppression and Blood Transfusion

Some studies suggest that patients with colorectal, breast, prostate, and certain other cancers may experience earlier recurrence and lower survival rates if they receive allogeneic (homologous) blood transfusions in the perioperative period, [28] [29] but other data challenge the association [30] Higher rates of postoperative infections have been reported in patients who received perioperative allogeneic transfusions than in those who were not transfused or who received only autologous blood. [31] [32] [33] [34] Other studies, however, have not confirmed this relationship. [35] [36]

Costs

Although the costs of blood component therapy are substantial, exact figures are lacking. A study at one medical center estimated that the base cost for providing one unit of allogeneic RBCs was $114 and that the direct and indirect services involved in transfusing the unit increased the cost to $151. [37] A study at 18 hospitals estimated that average hospital costs were $155 per transfused unit of whole blood or RBCs, or $397 per patient for all blood components. [38] [39] With an estimated 12 million units transfused each year in the United States, this amounts to an annual cost of at least 2 billion dollars, with some estimating costs as high as 5-7 billion dollars for all transfused components. [40] Such estimates are of limited validity, because they do not include the cost of all blood components, administrative expenses, and indirect transfusion costs, [40] and they do not reflect the economic benefits of transfusion therapy. Nonetheless, the resource implications of blood component therapy must be recognized, and the role of improved transfusion practices in reducing costs must be considered. Almost 25% of the costs of RBC transfusions may be attributable to inappropriate transfusions. [39] These costs can be reduced through the adoption of more appropriate transfusion practices. For example, one large teaching hospital was able to reduce transfusion costs by $1.6 million over 3 yr by adopting new transfusion guidelines. [41]

Red blood cells

Approximately 12,000,000 units of RBCs are transfused each year in the United States. [1] Although most of these transfusions are performed for appropriate reasons, studies have documented substantial rates of unnecessary transfusions. Inappropriate rates of 18-57% have been reported. [42] [43] [44] [45] [46] [47] [48] [49] [50] . The proper objective of RBC transfusion is the improvement of inadequate oxygen delivery. The scientific argument for perioperative RBC transfusion therefore rests on two principal assumptions: (1) surgical patients experience adverse outcomes as a result of diminished oxygen-carrying capacity, and (2) RBC transfusions, by enhancing oxygen-carrying capacity, can prevent these adverse outcomes. Evidence to support these assumptions is reviewed below.

Adverse Effects of Diminished Oxygen-carrying Capacity

Diminished oxygenation due to inadequate oxygen-carrying capacity can have serious clinical implications, primarily because of ischemic effects on the myocardium and brain. Oxygen delivery (Do2) is defined as

---

the product of cardiac output (Qt) and arterial oxygen content (Ca_{o2}). The latter is a function of hemoglobin saturation (Sa_{o2}), hemoglobin concentration (Hb), and the amount of oxygen physically dissolved in arterial blood:

DO2 =; (CaO2).(Qt),

CaO2 =; (SaO2/100).(1.39.Hb) + (0.003.PaO2).

Although an increase in cardiac output is the primary compensation for reduced oxygen-carrying capacity, changes in the microcirculation can affect oxygen transport at the tissue level. For example, during periods of blood loss, the autonomic nervous system can restrict blood flow and oxygen delivery to skin, muscle, and the abdominal viscera to preserve oxygen delivery to the central nervous system and heart.

The effects of anemia must be separated from those of hypovolemia, although both can interfere with oxygen transport. The clinical manifestations of hypovolemia are well known, and a classification based on blood loss has been established by the American College of Surgeons. [51] A loss of up to 15% of total blood volume (class I hemorrhage) usually has little hemodynamic effect other than vasoconstriction and mild tachycardia. A loss of 15-30% of blood volume (class II hemorrhage) produces tachycardia and decreased pulse pressure; unanesthetized patients may also exhibit anxiety or restlessness. A loss of 30-40% (class III hemorrhage) produces increasing signs of hypovolemia, including marked tachycardia, tachypnea, and systolic hypotension; unanesthetized patients demonstrate altered mental status. Experience has shown that, in young healthy patients, losses of up to 30-40% of blood volume usually can be treated adequately with crystalloid therapy. Loss of more than 40% of total blood volume (class IV hemorrhage) is life-threatening and accompanied by marked tachycardia and hypotension, very narrow pulse pressure, and low urine output; mental status is markedly depressed.

The lower limit of human tolerance to acute normovolemic anemia has not been established. It is believed that oxygen delivery is adequate in most individuals at hemoglobin concentrations as low as 7 g/dL. [4] In healthy, normovolemic individuals, tissue oxygenation is maintained and anemia tolerated at hematocrit values as low as 18-25%. [52] [53] The heart does not begin producing lactic acid until a hematocrit of 15-20% is reached. [54] [55] Myocardial lactate flux does not appear to be affected at hemoglobin concentrations as low as 6 g/dL. [56] Heart failure usually does not occur until the hematocrit reaches 10%. [57] [58]

Chronic anemia is better tolerated than acute anemia. Oxygen delivery is facilitated through increases in 2,3-diphosphoglycerate levels in RBCs. In patients with chronic anemia, cardiac output usually does not change until the hemoglobin concentration falls below 7 g/dL. Significant symptoms are unusual unless the RBC mass is decreased by approximately 50%. [58] Chronic anemia has special implications for pregnant women. Obstetric patients usually tolerate chronic anemia without significant adverse maternal or fetal effects. A review of 17 studies of obstetric patients revealed no effect of hemoglobin concentration on the incidence of stillbirth or intrauterine growth retardation, [59] whereas another found increased complications of pregnancy associated with both low (<10.4 g/dL) and high (>13.2 g/dL) hemoglobin concentrations. [60] Studies of acute isovolemic anemia in animals suggest that fetal oxygen extraction is maintained until the maternal hematocrit is reduced by more than 50%. [61] In a study of pregnant sheep with chronic anemia (hematocrit less than 14% for 6 days), decreased oxygen delivery to the placenta did not reduce fetal oxygen consumption. [62]

In acute anemia, reductions in arterial oxygen content usually are well tolerated because of compensatory increases in cardiac output. This compensatory mechanism may be affected by several factors, however, such as left ventricular, dysfunction and vasoactive pharmacologic agents (*e.g.,* beta adrenergic or calcium channel blockade), necessitating a higher hemoglobin concentration for adequate oxygen delivery. Human tolerance of acute anemia is further affected by certain pharmacologic agents, such as anesthetics, hypnotics, and neuromuscular blocking drugs, and by intraoperative conditions (*e.g.,* hypothermia). Anesthetics have important cardiovascular and endocrine actions that influence oxygen transport and consumption and the physiologic response to acute anemia. Most anesthetics cause myocardial depression and decrease arterial blood pressure, cardiac output, stroke volume, peripheral vascular resistance, total-body oxygen consumption, and cerebral and myocardial oxygen demands. [63] The magnitude of these effects varies among anesthetics and as a function of anesthetic depth. In addition, anesthetics differ in their effects on hepatic blood flow, and thus they may differ in how they influence the development of systemic lactic acidosis and base-deficit in patients with anemia or impaired oxygen transport.

The physiologic limit of oxygen transport is not known in either awake humans or those under general anesthesia. Case reports suggest that humans may tolerate lower hemoglobin concentration and oxygen transport during anesthesia than when awake. [64] This may be due to an anesthetic-and neuromuscular block-ade-induced reduction of oxygen consumption. However, there are no controlled prospective studies addressing this important issue. The impact of regional anesthesia on oxygen transport is also unclear.

These physiologic principles have been reinforced by clinical studies demonstrating inconsistent associations between anemia and adverse perioperative or peripartum outcomes. Case series reports of Jehovah's Witnesses indicate that some patients tolerate very low hemoglobin concentrations (less than 6-8 g/dL) in the perioperative period without an increase in mortality. [65] [66] [67] A review of 16 series published between 1983 and 1990, involving 1,404 operations on Jehovah's Witnesses, found that lack of blood was implicated as the primary cause of death in only 8 (0.6%) patients and as a contributor to death in an additional 12 (0.9%) patients. [68] Another review of 61 reports of 4,722 Jehovah's Witnesses identified 23 deaths due to anemia, all but 2 of which occurred at hemoglobin concentrations

less than 5 g/dL. [64] A stastistical analysis of one series of Jehovah's Witnesses found that hemoglobin alone was not a statistically significant predictor of outcome unless it was less than 3 g/dL. [69] Both hemoglobin and intraoperative blood loss must be taken into consideration. [65] This body of literature represents self-selected reports, however, in which clinicians are more likely to report survivors than nonsurvivors. The information provided in most reports is insufficient to allow for independent conclusions regarding the degree to which profound anemia contributed to morbidity or mortality.

Decisions regarding perioperative transfusion are often difficult, necessitating clinical judgment. There is little scientific support for relying on a specific hemoglobin or hematocrit value as a "transfusion trigger," such as the outdated "10/30 rule" that transfusion is necessary in patients with a hemoglobin concentration less than 10 g/dL or an hematocrit less than 30%. [70] Estimates of blood volume are also unreliable, because of inaccuracies of intraoperative blood loss measurement, intercompartmental fluid shifts during surgery, and the dilutional effects of crystalloid therapy. Although often useful, intraoperative hemoglobin determinations can be misleading. Alterations of intravascular volume due to the concomitant administration of colloids and crystalloids can produce artificially lowered or elevated hemoglobin concentrations.

Intraoperative estimates of blood volume are indirect, being inferred from pressure measurements obtained at various locations (arterial, central venous, or pulmonary capillary wedge pressures). Whole-body oxygen consumption, oxygen extraction ratio, and oxygen delivery have been used to estimate the need for RBC transfusion. [71] [72] [73] These measurements require invasive monitoring (*e.g.,* arterial, pulmonary artery), have not been independently verified, and are global (not organ-specific) measures of oxygen utilization. In the clinical setting, it is not possible to directly measure the adequacy of oxygen transport to specific organs or to regions within these organs.

The perioperative decision-making process regarding transfusion is complicated by knowledge that myocardial ischemia is often silent and most frequent in the postoperative period, when monitoring is less intense. [74] [75] A patient's oxygen transport needs can increase at any time during the postoperative period because of pain, fever, shivering, or physical activity.

Aside from the more obvious potential benefits of RBC transfusion in improving oxygen-carrying capacity, other unsubstantiated claims of benefit have been made, including effects on wound-healing. However, in healing tissue, collagen deposition is dependent on oxygen tension and perfusion and not on blood hemoglobin concentration. [76]

Effectiveness of Red Blood Cell Transfusion

The transfusion of one unit of whole blood or RBCs increases the hematocrit by approximately 3%, or the hemoglobin concentration by 1 g/dL, in a 70-kg nonbleeding adult. [77] Controlled studies have not been performed to determine the hemoglobin concentration at which RBC transfusion improves clinical outcome. Indirect evidence suggests that many RBC transfusions are unnecessary, because mild to moderate blood loss does not appear to be associated with increased perioperative morbidity or mortality. [78] [79] [80] [81] [82] [83] [84] and reduced transfusions brought about by concerns over transfusion-related infections have not been associated with poorer perioperative outcomes. [85] [86] [87] However, most of these studies were uncontrolled and lacked long-term follow-up.

A relationship between perioperative anemia and myocardial ischemia or infarction has been proposed. A controlled observational study of 27 high-risk patients

undergoing infrainguinal arterial bypass surgery found that the incidence of postoperative myocardial ischemia and morbid cardiac events was significantly higher among the 14 patients with hematocrits less than 28% than among patients with higher hematocrits. [88] However, the anemic group was significantly older and underwent longer procedures, the results were not adjusted for confounding variables that increase ischemic risk, and the study did not examine the effectiveness of RBC transfusions. A study of 30 postoperative critical care patients with hemoglobin concentrations less than 10 g/dL found that RBC transfusions had little impact on oxygen consumption, [89] a finding consistent with other studies of critical care patients. [90] [91] [92] [93]

Strength of Evidence: Category II-2 and II-3 (Controlled and Uncontrolled Observational Studies)

Expert Opinion.

Recommendations of Other Groups. In 1988, the National Institutes of Health Consensus Conference on Perioperative Red Blood Cell Transfusion concluded that evidence did not support the use of a single criterion for transfusion, such as a hemoglobin concentration less than 10 g/dL, nor was there evidence that mild to moderate anemia contributed to perioperative morbidity. [64] In 1992, the ACP recommended distinguishing between stable and unstable vital signs in determining whether to transfuse anesthetized patients. The ACP concluded that patients with stable vital signs and no risk of myocardial or cerebral ischemia do not require RBC transfusion, independent of hemoglobin level, and recommended transfusing patients with unstable vital signs only if risks of myocardial or cerebral ischemia were present. [67] A consensus conference convened by the Royal College of Physicians of Edinburgh concluded that RBC transfusion is indicated only to increase oxygen-carrying capacity, the transfusion decision should be made by a qualified practitioner as part of the overall management of the illness, patients should be offered information about RBC transfusion and available alternatives, and the indication for transfusion should be documented in the medical record. [94]

Expert Opinion of Task Force. The task force believes that any uniform "transfusion trigger" (*e.g.,* an absolute hemoglobin or hematocrit value) provides an inappropriate basis for determining the need for perioperative or peripartum RBC transfusion. Hemoglobin concentration alone is an inadequate measure of oxygen delivery. The ACP recommendation to rely solely on vital signs [67] is inappropriate for anesthetized patients. The decision to transfuse often is affected by the dynamic nature of surgical hemorrhage. [95] Patients with hypovolemia and anemia may be transfused more aggressively when rapid blood loss is anticipated (*e.g.,* aortic unclamping). Changes in vital signs often are masked by anesthetics and other drugs and are frequently a late sign of cardiovascular decompensation. Moreover, silent ischemia of the myocardium, cerebrum, liver, kidney, and other tissues can occur in the presence of stable vital signs. Intraoperative myocardial ischemia, a predictor of cardiac morbidity and mortality, [74] is associated with tachycardia in only 26% of patients and with blood pressure changes in less than 10% of patients. [75]

Factors affecting the surgical patient's response to decreased hemoglobin concentration, and thus the factors that should influence the physician's decision to transfuse, include the patient's cardiopulmonary reserve (determined by the presence or absence of cardiac and/or pulmonary disease and hemodynamic indexes, and affected by drugs and anesthetics), the rate and magnitude of blood loss (actual and anticipated), oxygen consumption (affected by body temperature, drugs/anesthetics, sepsis, muscular activity), and atherosclerotic disease (cerebrovascular, cardiovascular, peripheral, renal).

Recommendations. The task force bases its recommendations on available category II-2 and II-3 evidence and expert opinion. The task force concludes that (1) transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute; (2) the determination of whether intermediate hemoglobin concentrations (6-10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation; (3) the use of a single hemoglobin "trigger" for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation are not recommended; (4) when appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacologic agents) may be beneficial; and (5) the indications for transfusion of autologous RBCs may be more liberal than for allogenic RBCs because of the lower (but still significant) risks associated with the former.

Platelets

More than 7,000,000 units of platelets are transfused each year in the United States. [1] Platelets are used in the perioperative and peripartum setting when a quantitative or qualitative platelet defect is the suspected cause of bleeding. The scientific rationale rests on two principal arguments: (1) surgical patients experience adverse outcomes as a result of thrombocytopenia and/or platelet dysfunction, and (2) platelet transfusion can correct platelet defects and thereby reduce, minimize, or prevent bleeding. Evidence to support these arguments follows.

Adverse Effects of Thrombocytopenia and Platelet Dysfunction

Patients with thrombocytopenia or platelet dysfunction may experience morbidity and mortality from severe surgical hemorrhage. The platelet count at which surgical and obstetric patients are likely to experience increased bleeding is unknown. In nonsurgical patients, spontaneous bleeding is uncommon with platelet counts greater than 20 × 109/1, [96] and some studies suggest low complication rates in surgical patients with thrombocytopenia. [97] Performance of paracentesis and thoracentesis was not associated with increased bleeding in patients with platelet counts of 50-99 × 109/1. [98]

Coexisting clinical conditions influence the value of platelet counts in predicting the occurrence of bleeding in surgical and obstetric patients, but the probability of clinically significant thrombocytopenia increases in proportion to the number of units of blood transfused. [99] [100] [101] [102] In a study of 39 massively transfused patients, platelet counts less than 50 × 109/1 were found in 75% of patients who received 20 or more units of RBCs and in no patients who received less than 20 units. [103] Consumption of platelets, as well as simple dilution, can lead to microvascular bleeding (*e.g.,* diffuse bleeding from wound edges, mucous membranes, insertion sites of vascular cannulae). [102]

Gestational thrombocytopenia is usually a benign phenomenon during pregnancy. [104] There is little evidence of bleeding complications from anesthetic procedures (*e.g.,* epidural placement) performed in pregnant women with thrombocytopenia. [105] Because hemostasis after placental separation is largely mechanical, thrombocytopenia has virtually no effect on the incidence of postpartum uterine bleeding. [106] Mild thrombocytopenia is detected in approximately 15% of women with preeclampsia. [107] With the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome associated with preeclampsia, the thrombocytopenia is more severe, but spontaneous resolution usually occurs by the 4th postpartum day. [108] [109]

In some circumstances, platelet dysfunction (*e.g.,* secondary to preoperative aspirin therapy) may be more important than platelet count in explaining a bleeding disorder. Although preoperative platelet aggregation studies may be helpful in predicting bleeding in some surgical patients, [110] the bleeding time is a poor predictor. [111] [112] [113] Neither test is useful in the operating room. The bleeding time, which assesses both platelet function and the vascular component of hemostasis, lacks specificity, is affected by technique and body temperature, and is subject to individual interpretation.

Effectiveness of Platelet Transfusion

It is well established that platelet transfusion can increase platelet counts. The magnitude of effect is variable and is influenced by the release of stored platelets from the spleen and peripheral platelet destruction. Transfusion of one platelet concentrate will increase the platelet count by approximately 5-10 × 109/1 in the average adult. The usual therapeutic dose is one platelet concentrate per 10 kg body weight. Singledonor platelets obtained by apheresis are the equivalent of approximately six platelet concentrates. Patients repeatedly transfused over a prolonged period may become alloimmunized and refractory to platelet transfusion. In such patients, human leukocyte antigenmatched or crossmatched platelets may be required. [114]

There is indirect evidence from nonsurgical settings regarding the effectiveness of platelets in controlling bleeding. Studies of leukemic patients with platelet counts of 30 × 109/1 or less have suggested that the incidence of spontaneous bleeding can be decreased by platelet transfusions. [115] [116] However, similar studies in surgical patients are lacking. Controlled trials of prophylactic platelet transfusion have not demonstrated benefit for patients undergoing cardiopulmonary bypass [117] or massive transfusion. [101]

Strength of Evidence: Category II-2 and II-3 (Controlled and Uncontrolled Observational Studies)

Expert Opinion.

Recommendations of Other Groups. In 1987, the National Institutes of Health Consensus Conference on

Platelet Transfusion Therapy recommended prophylactic platelet transfusion for patients with platelet counts less than 10-20 × 109/1, noting that patients with platelet counts above 50 × 109/1 were unlikely to benefit. It added that platelet transfusions at higher platelet counts may be indicated for patients with systemic bleeding or those at increased risk of bleeding because of coagulation defects, sepsis, or platelet dysfunction. [3] In 1994, the CAP recommended platelet transfusion in patients with decreased platelet production and platelet counts below 5 × 109/1. The CAP also recommended considering prophylactic platelet transfusions in patients with platelet counts between 5 × 109/1 and 30 × 109/1. For major surgery with life-threatening bleeding, they concluded that transfusions may be indicated at higher platelet counts to maintain a concentration greater than 50 × 109/1. The CAP recommended transfusing patients with enhanced platelet destruction and platelet counts below 50 × 109/1 in the presence of microvascular bleeding. [8] It indicated that some experts recommend platelet transfusion after cardiopulmonary bypass in patients with normal coagulation values and platelet counts below 100 × 109/1 I when major unexplained bleeding occurs. Similar guidelines may be appropriate for patients undergoing neurosurgical procedures, in part because of concerns about local tissue damage from extravasation. The ACOG recommends platelet transfusion in certain patients with hereditary or acquired thrombocytopenia. [5] A 1992 survey of 630 hospitals caring for hematology and oncology patients reported that prophylactic platelets transfusions usually were ordered for patients with platelet counts of 20 × 109/1 or less; for patients undergoing minor invasive procedures (*e.g.,* biopsy, central line placement, lumbar puncture), the most commonly cited criteria was 50 × 109/1 or less. [18]

Expert Opinion of Task Force. The task force believes that the need for platelet transfusion is dependent on multiple risk factors and not a single laboratory value (*e.g.,* platelet count, bleeding time). The risk in surgical and obstetric patients is defined by the type and extent of surgery, the ability to control bleeding, the consequences of uncontrolled bleeding, the actual and anticipated rate of bleeding, and the presence of factors that adversely affect platelet function (*e.g.,* extracorporeal circulation, renal failure, medications).

There is inadequate scientific evidence to determine the platelet count below which the risk of surgical bleeding is increased. Some recommendations of other groups (*e.g.,* CAP) regarding safe platelet counts are based on evidence that may not be applicable to all surgical patients. In the absence of evidence, the opinion of the task force is that platelet transfusion is justified in bleeding patients at higher platelet counts than recommended for nonbleeding patients because of the increased risk of complications due to bleeding in the surgical patient. The task force believes that intraoperative platelet counts are beneficial in bleeding patients who are massively transfused. Under normal circumstances, platelet counts should be obtained to determine the need for platelet transfusion. In unusual situations, massively transfused patients with microvascular bleeding suspected to be secondary to platelet deficiency may benefit from empirical platelet therapy.

Recommendations. The task force bases its recommendations on available category II-2 and II-3 evidence and expert opinion. The task force concludes that (1) prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction (*e.g.,* idiopathic thrombocytopenic purpura); (2) prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia due to decreased platelet production when the platelet count is greater than 100 × 109/1 and is usually indicated when the count is below 50 × 109/1. The determination of whether patients with intermediate platelet counts (50-100 × 109/1) require therapy should be based on the risk of bleeding; (3) surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50 × 109/1 and rarely require therapy if it is greater than 100 × 109/1. With intermediate platelet counts (50-100 × 109/1), the determination should be based on the patient's risk for more significant bleeding; (4) vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50 × 109/1; and (5) platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

Fresh-frozen Plasma

Approximately 2,000,000 units of FFP are transfused each year in the United States. [1] A significant portion of FFP is transfused inappropriately. [119] [120] The scientific rationale for administering FFP rests on the assumptions that (1) patients are at risk of adverse effects from inadequate coagulation factors, and (2) FFP transfusions

can decrease those risks. Evidence to support these assumptions is reviewed below.

Adverse Effects of Inadequate Plasma Coagulation Factors

Evidence that coagulation factors can be depleted sufficiently to produce perioperative bleeding due to dilutional coagulopathy is limited. Blood usually coagulates appropriately when coagulation factor concentrations are at least 20-30% of normal and when fibrinogen levels are greater than 75 mg/dL. [101] [102] [121] Replacement of an entire blood volume leaves the patient with approximately one-third of the original concentration of coagulation factors. [122] [123] Although laboratory values such as prothrombin time (PT) and partial thromboplastin time (PTT) may be abnormal, clinical coagulopathy from dilution does not usually occur until replacement exceeds one blood volume or when the PT and PTT exceed 1.5-1.8 times control values. [99] [100] [101] [102] [121] [124] [125] [126] [127] In a study of 39 massively transfused patients, Leslie and Toy reported PT values greater than 1.5 times normal in all patients who received 12 or more units of RBCs and in 36% of patients who received less than 12 units. [103] In a series of 12 patients who received RBCs for massive blood loss, Murray *et al.* reported that PT and PTT were increased in nine patients before replacement of one blood volume but that there was no clinical evidence of abnormal bleeding. Abnormal bleeding occurred primarily in patients with PT or PTT values greater than 1.5 times normal. [121] In a subsequent study of 32 patients who lost more than 50% of their blood volume during elective spinal surgery, Murray *et al.* found once again that patients with PT or PTT values greater than 1.5 times normal were more likely to have evidence of abnormal hemostasis during surgery. Abnormal PT or PTT, which occurred in 30 of the 32 patients, was not predictive of intraoperative bleeding due to inadequate hemostasis, which occurred in only 17 patients. [127]

Shock, independent of blood loss, may be associated with a consumptive coagulopathy, leading to microvascular bleeding. A study of 36 massively transfused patients found that approximately 150 min of shock was required before significant prolongation of PTT or decreases in factor V activity were noted. [128] A retrospective review of 64 massively transfused patients found that prolongation of PTT during the first 3-4 hcorrelated with the volume of electrolyte solution administered. Thereafter, the prolongation of PTT corresponded with the duration of the preceding hypotension. [129] A retrospective study of 44 trauma patients found that 33% of those with blunt trauma and brain injuries and 55% of those with penetrating trauma and no brain injuries had a PT greater than 18 s and a PTT greater than 55 s on arrival in the emergency department, after having received only electrolyte solution as prehospital therapy. [130]

In the preoperative patient with no history of bleeding, retrospective studies show that abnormal PT and PTT are poor predictors of surgical bleeding. [131] [132] Friedman and Sussman reported no cases of significant bleeding in 71 invasive procedures performed on patients with chronic liver disease and a PT greater than 15 s. [133] McVay and Toy reported that paracentesis and thoracentesis were not associated with increased bleeding in patients with a PT or PTT of up to 2 times control values, [98] Ewe found no association between clotting indexes and bleeding in 200 patients undergoing percutaneous liver biopsy, [134] and Foster *et al.* reported no complications from coagulopathies in 259 central venous catheterizations. [135] However, outcomes from these noninvasive procedures may not be relevant to the surgical setting.

Prolongation of the PT and/or PTT rarely is seen in association with preeclampsia. However, evidence of increased fibrinolysis without clinically significant hypofibrinogenemia is found in approximately one-third of patients when a D-dimer assay is used. [136] ; these abnormalities generally do not require treatment.

Effectiveness of Fresh-frozen Plasma Transfusions

Few Studies have been performed to determine whether perioperative administration of FFP improves clinical outcome. Although Miller *et al.* reported correction of PT and PTT with FFP administration in patients massively transfused with whole blood, no change in bleeding occurred until thrombocytopenia was corrected. [124] Spector *et al.* reported that 600-1,800 ml of FFP was required to reduce the PT to within 3 s of control values in patients with liver disease and that the responses were generally transient (a finding possibly related to hepatic dysfunction and not to normal surgical conditions). [137] A retrospective review of 100 sequential patients having coronary artery bypass surgery and given either albumin or an average of six units of FFP did not demonstrate any differences in blood loss or transfusion requirements. [138] In 17 patients with abnormal intraoperative bleeding due to dilutional coagulopathy, Murray *et al.* reported that hemostasis improved after FFP administration in 14 patients.

Coagulation studies in this group were comparable after FFP transfusion to those of massively transfused patients undergoing the same procedure with no evidence of abnormal hemostasis. [127]

Strength of Evidence: Category II-2 and II-3 (Controlled and Uncontrolled Observational Studies)

Expert Opinion.

Recommendations of Other Groups. In 1985, the National Institutes of Health Consensus Conference on Fresh-Frozen Plasma concluded that FFP is indicated for the following conditions that may occur in the perioperative or peripartum setting: certain coagulation factor deficiencies, selected cases of massive transfusion, and multiple coagulation defects (*e.g.,* liver disease). [2] In 1994, the CAP recommended FFP transfusions for the following indications: massive blood transfusion (more than one blood volume) with active bleeding, urgent reversal of warfarin therapy, and a history or clinical course suggestive of an inherited or acquired coagulopathy (with active bleeding or before an operative procedure). The CAP indicated that the use of FFP as a volume expander or for wound healing was contraindicated. [8] Similar guidelines for FFP transfusion have been issued by the ACOG [5] and the British Committee for Standards in Hematology; the Committee noted that at least four units of FFP usually will promote coagulation in adults. [139]

Expert Opinion of Task Force. The task force believes that few clinical circumstances in the perioperative or peripartum setting result in coagulopathies that require replacement of coagulation factors with FFP. The special clinical circumstances that might warrant FFP in the nonbleeding patient include the urgent reversal of warfarin therapy and the treatment of known coagulation factor deficiencies for which specific factor concentrates are unavailable.

In the patient with microvascular bleeding, there is adequate scientific evidence to suggest that coagulation studies (PT/PTT) obtained in the operating room are useful in detecting a coagulopathy that may respond to FFP transfusion. Although massive blood replacement can produce prolongation of PT and/or PTT, the task force believes that a true dilutional coagulopathy does not ordinarily occur until more than 100% of the patient's blood volume has been replaced. The task force believes that FFP is beneficial in patients with microvascular bleeding or hemorrhage who are massively transfused if the PT/PTT values exceed 1.5 times the laboratory's normal values. If PT and PTT cannot be obtained in a timely fashion, the task force believes that massively transfused patients with microvascular bleeding that is believed to be secondary to coagulation factor deficiency may benefit from empirical FFP therapy.

Recommendations. The task force bases its recommendations on available category II-2 and II-3 evidence and expert opinion. The task force recommends the administration of FFP with the following guidelines: (1) for urgent reversal of warfarin therapy; (2) for correction of known coagulation factor deficiencies for which specific concentrates are unavailable; (3) for correction of microvascular bleeding in the presence of elevated (>1.5 times normal) PT or PTT; (4) for correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when PT and PTT cannot be obtained in a timely fashion; (5) FFP should be given in does calculated to achieve a minimum of 30% of plasma factor concentration (usually achieved with administration of 10-15 m1/kg of FFP), except for urgent reversal of warfarin anticoagulation, for which 5-8 m1/kg of FFP usually will suffice. Four to five platelet concentrates, one unit of single-donor apheresis platelets, or one unit of whole blood provide a quantity of coagulation factors similar to that contained in one unit of FFP (except for decreased, but still hemostatic, concentrations of factors V and VIII in whole blood); and (6) FFP is contraindicated for augmentation of plasma volume or albumin concentration.

Cryoprecipitate

Almost 1,000,000 units of cryoprecipitate are transfused each year in the United States. [1] Cryoprecipitate, which contains factor VIII, fibrinogen, fibronectin, von Willebrand's factor, and factor XIII, is used for the correction of inherited and acquired coagulopathies. Its use in the operative setting is based on the assumptions that (1) patients with these coagulation factor deficiencies are at increased risk of hemorrhagic complications, and (2) replacement of coagulation factors is effective in decreasing these risks. Evidence to support these assumptions is reviewed below.

Adverse Effects of Coagulation Factor Deficiencies

There is limited evidence from observational studies that patients with certain inherited or acquired coagulopathies

---

(*e.g.,* hemophilia A, von Willebrand's disease, hypofibrinogenemia, disseminated intravascular coagulation, hepatic insufficiency) are at increased risk of perioperative or peripartum bleeding. [95] [140]

Effectiveness of Cryoprecipitate Transfusion

One unit of cryoprecipitate per 10 kg body weight raises plasma fibrinogen concentration by approximately 50 mg/dL in the absence of continued consumption or massive bleeding. No studies have been performed to determine whether perioperative or peripartum administration of cryoprecipitate improves clinical outcome. Indirect observational evidence suggests a beneficial effect for patients with factor VIII deficiency and certain subtypes of von Willebrand's disease. [141] [142] However, most patients with factor VIII deficiency are treated with factor VIII concentrates, and patients with some subtypes of von Willebrand's disease respond to administration of desmopressin acetate (DDAVP). [143] [144] [145] [146] Similarly, coagulopathy associated with uremia can be treated with cryoprecipitate, but DDAVP is usually the first-line therapy.

Severe placental abruption frequently is associated with disseminated intravascular coagulation, in which thrombocytopenia, hypofibrinogenemia, and increased fibrinolytic activity are the most consistent findings. Indirect evidence suggests that administration of cryoprecipitate in these settings increases the plasma fibrinogen concentration. The hypofibrinogenemia responds well to treatment with cryoprecipitate once delivery has been accomplished. [140] [147]

Strength of Evidence: Category II-3 and III (uncontrolled Observational and Descriptive Studies)

Expert Opinion.

Recommendations of Other Groups. In 1994, the CAP recommended cryoprecipitate transfusions in bleeding patients with hypofibrinogenemia, von Willebrand's disease, and patients with hemophilia A (When factor VIII concentrate is not available) [8] Similar recommendations have been issued by the ACOG. [5] The British Committee for Standards in Haematology recommended the administration of cryoprecipitate for massively transfused patients with microvascular bleeding when the fibrinogen level is less than 80 mg/dL. [114]

Expert Opinion of Task Force. There is little scientific evidence regarding the effectiveness of cryoprecipitate in improving clinical outcomes, and therefore, the task force believes that its perioperative and peripartum use should be limited to selected indications. Based on clinical experience, the task force believes that cryoprecipitate is likely to be effective in patients with von Willebrand's disease unresponsive to DDAVP, congenital fibrinogen deficiencies, and consumptive coagulopathies when fibrinogen levels are below 80-100 mg/dL.

Recommendations. The task force bases its recommendations on available category II-3 evidence and expert opinion. The task force recommends considering the administration of cryoprecipitate for (1) prophylaxis in nonbleeding perioperative or peripartum patients with congenital fibrinogen deficiencies or von Willebrand's disease unresponsive to DDAVP (whenever possible, these decisions should be made in consultation with the patient's hematologist), (2) bleeding patients with von Willebrand's disease, and (3) correction of microvascular bleeding in massively transfused patients with fibrinogen concentrations less than 80-100 mg/dL (or when fibrinogen concentrations cannot be measured in a timely fashion).

Conclusions

Adherence to proper indications for blood component therapy is essential because of the potential adverse effects and costs of transfusion. These risks can be reduced further by other effective measures, the most important being efforts to minimize exposure to allogeneic blood through use of autologous transfusion and other blood conservation techniques, but the costeffectiveness of these practices requires further study. [148] The unnecessary complications of incompatible blood transfusions can be minimized by careful specimen, unit, and patient identification before blood sampling and transfusion and by maintaining a high index of suspicion for transfusion reactions. Most importantly, transfusion decisions should be based on sound physiologic principles and a comprehensive assessment of the patient's risk factors.

A variety of comprehensive intervention strategies and transfusion algorithms have been associated with reductions in inappropriate blood component therapy. [9] [41] [87] [149] [150] [151] [152] [153] Inappropriate RBC use has been decreased by audits, discussions with ordering physicians, ward rounds, computer-based decision-support systems, and comprehensive educational outreach programs. [47] [154] [155] [156] Studies have suggested that FFP transfusions can be reduced by programs that include chart

audits and the review of results with ordering physicians, dissemination of practice guidelines, case presentations, house staff education and review by pathologists of transfusion orders. [157] [158] [159] [160] Similar results have been achieved for platelet use. [161] [162]

All available evidence regarding the effectiveness of blood component therapy qualifies as category II-2, II-3, or III evidence. The lack of data from prospective, randomized studies with adequate sample size, control groups, clinical outcome measurements, and other features of well designed clinical effectiveness research impedes development of evidence-based clinical practice guidelines for blood component therapy. To establish a stronger scientific basis for transfusion practice, future research is essential to provide meaningful evidence regarding the indications and effectiveness of blood component therapy. As these data become available, guidelines for blood component therapy are likely to change.

References

1. Wallace EL, Surgenor DM, Hao HS, An J, Chapman RH, Churchill WH: Collection and transfusion of blood and blood components in the United States, 1989. Transfusion 1993; 33:139-44

2. Office of Medical Applications of Research, National Institutes of Health: Fresh-frozen plasma: Indications and risks. JAMA 1985; 253:551-3

3. Office of Medical Applications of Research, National Institutes of Health: Platelet transfusion therapy. JAMA 1987; 257:1777-80

4. Office of Medical Applications of Research, National Institutes of Health: Perioperative red blood cell transfusion. JAMA 1988; 260: 2700-3

5. American College of Obstetricians and Gynecologists: Blood component therapy, Technical Bulletin no. 78. Washington, DC: American College of Obstetricians and Gynecologists, 1984

6. Goodnough LT, Johnston MF, Ramsey G, Sayers MH, Eisenstadt RS, Anderson KC, Rutman RC, Silberstein LE: Guidelines for transfusion support in patients undergoing coronary artery bypass grafting. Ann Thorac Surg 1990; 50:675-83

7. American College of Physicians: Practice strategies for elective red blood cell transfusion. Ann Intern Med 1992; 116:403-6

8. College of American Pathologists: Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. JAMA 1994; 271:777-81

9. Stehling L, Luban NL, Anderson KC, Sayers MH, Long A, Attar S, Leitman SF, Gould SA, Kruskall MS, Goodnough LT, Hines DM: Guidelines for blood utilization review. Transfusion 1994; 34:438-48

10. Woolf SH: Practice guidelines: A new reality in medicine: II. Methods of developing guidelines. Arch Intern Med 1992; 152:946-52

11. Arens JF: A practice parameters overview. ANESTHESIOLOGY 1993; 78:380-94

12. DePalma L, Luban NL: Blood component therapy in the perinatal period: Guidelines and recommendations. Semin Perinatol 1990; 14:403-15

13. Voak D, Cann R, Finney RD, Fraser ID, Mitchell R, Murphy MF, Napier JA, Phillips P, Rejman AJ, Waters AH, Wood JK: Guidelines for the administration of blood products: Transfusion of infants and neonates, British Committee for Standards in Hematology Blood Transfusion Task Force. Transfus Med 1994; 4:63-9

14. Linden JV, Paul B, Dressler KP: A report of 104 transfusion errors in New York State. Transfusion 1992;32:601-6

15. Linden JV, Kaplan HS: Transfusion errors: Causes and effects. Transfus Med Rev 1994; 8:169-83

16. Sazama K: Reports of 355 transfusion-associated deaths: 1976 through 1985. Transfusion 1990; 30:583-90

17. Alter MJ: Review of serologic testing for hepatitis C virus infection and risk of posttransfusion hepatitis C. Arch Pathol Lab Med 1994; 118:342-5

18. Donahue JG, Munoz A, Ness PM, Brown DE Jr, Yawn DH, McAllister HA Jr, Reitz BA, Nelson KE: The declining risk of post-transfusion hepatitis C virus infection. N Engl J Med 1992; 327:369-73

19. Alter HJ: To C or not to C: These are the questions. Blood 1995; 85:1681-95

20. Centers for Disease Control and Prevention: Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues, and semen for evidence of hepatitis B and hepatitis C. MMWR 1991; 40(RR-4):1-17

21. Cumming PD, Wallace EL, Schorr JB, Dodd RY: Exposure of patients to human immunodeficiency virus through the transfusion of blood components that test antibody negative. N Engl J Med 1989; 32:941-6

22. Busch MP, Eble BE, Khayam-Bashi H, Heilbron D, Murphy EL, Kwok S, Sninsky J, Perkins HA, Vyas GN: Evaluation of screened blood donations for human immunodeficiency virus type I infection by culture and DNA amplification of pooled cells. N Engl J Med 1991; 325:1-5

23. Petersen LR, Satten GA, Dodd R, Busch M, Kleinman S, Grindon A, Lenes B, HIV Seroconversion Study Group: Duration of time from onset of human immunodeficiency virus type 1 infectiousness to development of detectable antibody. Transfusion 1994; 34:283-9

24. Busch MP, Lee LLL, Satten GA, Henrard DR, Farzadegan HH, Nelson KE, Read S, Dodd RY, Petersen LR: Time course of detection of viral and serologic markers preceding human immunodeficiency virus type 1 seroconversion: Implications for screening of blood and tissue donors. Transfusion 1995; 35:91-7

25. Lacritz EM, Satten GA, Aberle-Grasse J, Dodd RY, Raimondi VP, Janssen RS, Lewis WF, Notari EP, Petersen LR: Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. N Engl J Med 1995; 333:1721-5

26. Selik RM, Ward JW, Buehler JW: Demographic differences in cumulative incidence rates of transfusion-associated acquired immunodeficiency syndrome. AM J Epidemiol 1994; 140:105-12

27. Dodd RY: The risk of transfusion-transmitted infection. N Engl J Med 1992; 327:419-20

28. Blumberg N, Chuang-Stein C, Heal JM: The relationship of blood transfusion, tumor staging, and cancer recurrence. Transfusion 1990; 30:291-4

29. Vamvakas E, Moore SB: Perioperative blood transfusion and colorectal cancer recurrence: A qualitative statistical overview and meta-analysis. Transfusion 1993; 33:754-65

30. Busch OR, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J: Blood transfusion and prognosis in colorectal cancer. N Engl J Med 1993; 328: 1372-6

31. Triulzi DJ, Vanek K, Ryan DH, Blumberg N: A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. Transfusion 1992; 32:517-24

32. Mezrow CK, Bergstein I, Tartter PI: Postoperative infections following autologous and homologous blood transfusions. Transfusion 1992; 32:27-30

33. Murphy P, Heal JM, Blumberg N: Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. Transfusion 1991; 31:212-7

34. Edna TH, Bjerkeset T: Association between blood transfusion and infection in injured patients. J Trauma 1992; 33:659-61

35. Vamvakas EC, Moore SB: Blood transfusion and postoperative septic complications. Transfusion 1994; 34:714-27

36. Vamvakas EC, Moore SB, Cabanela M: Blood transfusion and septic complications after hip replacement surgery. Transfusion 1995; 35:150-6

37. Lubarsky DA, Hahn C, Bennett DH, Smith LR, Bredehoeft SJ, Klein HG, Reves JG: The hospital cost (fiscal year 1991/1992) of a simple perioperative allogeneic red blood cell transfusion during elective surgery at Duke University. Anesth Analg 1994; 79:629-37

38. Forbes JM, Anderson MD, Anderson GF, Bleecker GC, Rossi EC, Moss GS: Blood transfusion costs: A multicenter study. Transfusion 1991; 31:318-23

39. Goodnough LT, Soegiarso RW, Birkmeyer JD, Welch HG: Economic impact of inappropriate blood transfusions in coronary artery bypass graft surgery. Am J Med 1993; 94:509-14

40. Lawrence VA, Birch S, Gafni A: The impact of new clinical guidelines on the North American blood economy. Transfus Med Rev 1994; 8:232-41

41. Rosen NR, Bates LH, Herod G: Transfusion therapy: Improved patient care and resource utilization. Transfusion 1993; 33:341-7

42. Clarke AM, Dorman T, Bell MJ: Blood loss and transfusion requirements in total joint arthroplasty. Ann R Coll Surg Engl 1992; 74:360-3

43. Goodnough LT, Verbrugge D, Vizmeg K, Riddell J IV: Identifying elective orthopedic surgical patients transfused with amounts of blood in excess of need: The transfusion trigger revisited [published erratum appears in Transfusion 1992; 32:838] Transfusion 1992; 32:648-53

44. Gianoutsos MP, Thompson JF, Storey DW, Kronenberg H: The rational use of homologous blood in elective surgery. Aust NZJ Surg 1992; 62:266-9

45. Hallissey MT, Crowson MC, Kiff RS, Kingston RD, Fielding JW: Blood transfusion: An overused resource in colorectal cancer surgery. Ann R Coll Surg Engl 1992; 74:59-62

46. Thompson A, Contreras M, Knowles S: Blood component treatment: A retrospective audit in five major hospitals. J Clin Pathol 1991; 44:734-7

47. Morrison JC, Sumrall DD, Chevalier SP, Robinson SV, Morrison FS, Wiser WL: The effect of provider education on blood utilization practices. Am J Obstet Gynecol 1993; 169:1240-5

48. Brandis K, Richards B, Ghent A, Weinstein S: A strategy to reduce inappropriate red blood cell transfusion. Med J Aust 1994; 160:721-2

49. Hasley PB, Lave JR, Kapoor WN: The necessary and the unnecessary transfusion: A critical review of reported appropriateness rates and criteria for red cell transfusions. Transfusion 1994; 34:110-5

50. Ghali WA, Palepu A, Paterson WG: Evaluation of red blood cell transfusion practices with the use of preset criteria. Can Med Assoc J 1994; 150:1449-54

51. American College of Surgeons, Committee on Trauma: Advanced Trauma Life Support Course Manual. Chicago, American College of Surgeons, 1989

52. Messmer K, Sunder-Plassmann L, Jesch F, Gornandt L, Sinagowitz E, Kessler M: Oxygen supply to the tissues during limited normovolemic hemodilution. Res Exp Med 1973; 159:152-66

53. Czer LSC, Shoemaker WC: Optimal hematocrit value in critically ill postoperative patients. Surg Gynecol Obstet 1978; 147: 363-8

54. Delano BG, Nacht R, Friedman EA, Krasnow N: Myocardial anerobiosis in anemia in man. Circulation 1970; 42(suppl 3):148

55. Jan KM, Heldman J, Chien S: Coronary hemodynamics and oxygen utilization after hematocrit variations in hemorrhage. Am J Physiol 1980; 239:H326-32

56. Doak GJ, Hall RI: Does hemoglobin concentration affect perioperative myocardial lactate flux in patients undergoing coronary artery bypass surgery? Anesth Analg 1995; 80:910-16

57. Johansen SH, Laver MB: Cardiovascular effects of severe anemic hypoxia. Acta Anaesth Scand 1966; 24(suppl):63-8

58. Varat MA, Adolph RJ, Fowler NO: Cardiovascular effects of anemia. Am Heart J 1972; 83:415-26

59. Hemminki E, Starfield B: Prevention of low birth weight and pre-term birth: Literature review and suggestions. Milbank Mem Fund Q Health Soc 1978; 56:339-61

60. Murphy JF, O'Riordan J, Newcombe RG, Coles EC, Pearson JF: Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. Lancet 1986; 1:992-4

61. Paulone ME, Edelstone DI, Shedd A: Effects of maternal anemia on uteroplacental and fetal oxidative metabolism in sheep. Am J Obstet Gynecol 1987; 156:230-7

62. Delpapa EH, Edelstone DI, Milley JR, Balsan M: Effects of chronic maternal anemia on systemic and uteroplacental oxygenation in near-term pregnant sheep. Am J Obstet Gynecol 1992; 166:1007-12

63. Spahn DR, Leone BJ, Reves JG, Pasch T: Cardiovascular and coronary physiology of acute isovolemic hemodilution: A review of nonoxygen-carrying and oxygen-carrying solutions. Anesth Analg 1994; 78:1000-21

64. Viele MK, Weiskopf RB: What can we learn about the need for transfusion from patients who refuse blood?: The experience with Jehovah's Witnesses. Transfusion 1994; 34:396-401

65. Carson JL, Spence RK, Poses RM, Bonavita G: Severity of anaemia and operative mortality and morbidity. Lancet 1988; 1:727-9

66. Spence RK, Carson JA, Poses R, McCoy S, Pello M, Alexander J, Popovic J, Norcross E, Camishion RC: Elective surgery without transfusion: Influence of preoperative hemoglobin level and blood loss on mortality. Am J Surg 1990; 159:320-4

67. Spence RK, Alexander JB, DelRossi AJ, Cernaianu AD, Cilley J Jr. Pello MJ, Atabek U, Camishion RC, Vertrees RA: Transfusion guidelines for cardiovascular surgery: Lessons learned from operations in Jehovah's Witnesses. J Vasc Surg 1992; 16:825-31

68. Kitchens CS: Are transfusions overrated?: Surgical outcome of Jehovah's Witnesses. Am J Med 1993; 94:117-9

69. Spence RK, Costabile JP, Young GS, Norcross ED, Alexander JB, Pello MJ, Atabek UM, Camishion RC: Is hemoglobin level alone

a reliable predictor of outcome in the severely anemic surgical patient? Am Surg 1992; 58:92-5

70. Stehling L, Simon TL: The red blood cell transfusion trigger: Physiology and clinical studies. Arch Pathol Lab Med 1994; 118:429-34

71. Gould SA, Sehgal LR, Sehgal HL, Moss GS: Hypovolemic shock. Crit Care Clin 1993; 9:239-59

72. Levy PS, Chavez RP, Crystal GJ, Kim SJ, Eckel PK, Sehgal LR, Sehgal HL, Salem MR, Gould SA: Oxygen extraction ratio: A valid indicator of transfusion need in limited coronary vascular reserve? J Trauma 1992; 32:769-73

73. van Woerkens ECSM, Trouwborst A, van Lanschot JJB: Profound hemodilution: What is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? Anesth Analg 1992; 75:818-21

74. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990; 323:1781-8

75. Mangano DT, Hollenberg M, Fegert G, Meyer ML, London MJ, Tubau JF, Krupski WC: Perioperative myocardial ischemia in patients undergoing noncardiac surgery: I. Incidence and severity during the 4 day perioperative period. J Am Coll Cardiol 1991; 17:843-50

76. Jonsson K, Jensen JA, Goodson WH III, Scheuenstuhl H, West J, Hopf HW, Hunt TK: Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. Ann Surg 1991; 214:605-13

77. Wiesen AR, Hospenthal DR, Byrd JC, Glass KL, Howard RS, Diehl LF: Equilibration of hemoglobin concentration after transfusion in medical inpatients not actively bleeding. Ann Intern Med 1994; 121:278-80

78. Cooley DA, Bloodwell RD, Beall AC Jr, Hallman GL: Cardiac valve replacement without blood transfusion. Am J Surg 1966; 112:743-51

79. Finlayson DC, Suri RK: Management of open heart surgery without the use of blood: The function of blood volume determinations. Can Anaesth Soc J 1972; 19:335-8

80. Aris A, Padro JM, Bonnin JO, Caralps JM: Prediction of hematocrit changes in open-heart surgery without blood transfusion. J Cardiovasc Surg (Torino) 1984; 25:545-8

81. Makuuchi M, Takayama T, Gunven P, Kosuge T, Yamazaki S, Hasegawa H: Restrictive versus liberal blood transfusion policy for hepatectomies in cirrhotic patients. World J Surg 1989; 13:644-8

82. Jamieson GG, Corbel L, Campion JP, Launois B: Major liver resection without a blood transfusion: Is it a realistic objective? Surgery 1992; 112:32-6

83. Wittmann PH, Wittmann FW: Total hip replacement surgery without blood transfusion in Jehovah's Witnesses. Br J Anaesth 1992; 68:306-7

84. Kim DM, Brecher ME, Estes TJ, Morrey BF: Relationship of hemoglobin level and duration of hospitalization after total hip arthroplasty: Implications for the transfusion target. Mayo Clin Proc 1993; 68:37-41

85. Benjamin I, Barakat RR, Curtin JP, Jones WB, Lewis JL Jr, Hoskins WJ: Blood transfusion for radical hysterectomy before and after the discovery of transfusion-related human immunodeficiency virus infection. Obstet Gynecol 1994; 84:974-8

86. Mann R, Heimbach DM, Engrav LH, Foy H: Changes in transfusion practices in burn patients. J Trauma 1994; 37:220-2

87. Sitting KM, Deitch EA: Blood transfusions: For the thermally injured or for the doctor? J Trauma 1994; 36:369-72

88. Nelson AH, Fleisher LA, Rosenbaum SH: Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. Crit Care Med 1993; 21:860-6

89. Babineau TJ, Dzik WH, Borlase BC, Baxter JK, Bistrian BR: Reevaluation of current transfusion practices in patients in surgical intensive care units. Am J Surg 1992; 164:22-5

90. Dietrich KA, Conrad SA, Hebert CA, Levy GL, Romero MD: Cardiovascular and metabolic response to red blood cell transfusion in critically ill volume-resuscitated nonsurgical patients. Crit Care Med 1990; 18:940-4

91. Lorente JA, Landin L, De Pablo R, Renes E, Rodriguez-Diaz R, Liste D: Effects of blood transfusion on oxygen transport variables in severe sepsis. Crit Care Med 1993; 21:1312-8

92. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 1993; 269:3024-9

93. Hebert PC, Wells G, Marshall J, Martin C, Tweeddale M, Pagliarello G, Blajchman M: Transfusion requirements in critical care: A pilot study. JAMA 1995; 273:1439-44

94. Royal College of Physicians of Edinburgh: Consensus statement on red cell transfusion. Transfus Med 1994; 4:177-8

95. Faust RJ: Perioperative indications for red blood cell transfusion: Has the pendulum swung too far? Mayo Clin Proc 1993; 68:512-4

96. Gmur J, Burger J, Schanz U, Fehr J, Schaffner A: Safety of stringent prophylactic platelet transfusion policy for patients with acute leukaemia. Lancet 1991; 338:1223-6

97. Bishop JF, Schiffer CA, Aisner J, Matthews JP, Wiernik PH: Surgery in acute leukemia: A review of 167 operations in thrombocytopenic patients. Am J Hematol 1987; 26:147-55

98. McVay PA, Toy PTCY: Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. Transfusion 1991; 31:164-71

99. Counts RB, Haisch C, Simon TL, Maxwell NG, Heimbach DM, Carrico CJ: Hemostasis in massively transfused trauma patients. Ann Surg 1979; 190:91-9

100. Miller RD: Complications of massive blood transfusions. ANESTHESIOLOGY 1973; 39:82-93

101. Reed RL, Heimbach DM, Counts RB, Ciavarella D, Baron L, Carrico CJ, Pavlin E: Prophylactic platelet administration during massive transfusion. Ann Surg 1986; 203:40-8

102. Ciaverella D, Reed RL, Counts RB, Baron L, Pavlin E, Heimbach DM, Carrico CJ: Clotting factor levels and the risk of diffuse microvascular bleeding in the massively transfused patient. Br J Haematol 1987; 67:365-8

103. Leslie SD, Toy PTCY: Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. Am J Clin Pathol 1991; 96:770-3

104. Anteby E, Shalev O: Clinical relevance of gestational thrombocytopenia of <100,000/ul. Am J Hematol 1994; 47:118-22

105. Rasmus KT, Rottman RL, Kotelko DM, Wright WC, Stone JJ, Rosenblatt RM: Unrecognized thrombocytopenia and regional anesthesia in parturients: A retrospective review. Obstet Gynecol 1989; 73:943-6

106. Laros RK Jr, Kagan R: Route of delivery for patients with immune thrombocytopenic purpura. Am J Obstet Gynecol 1984; 148:901-8

107. Katz VL, Thorp JM Jr, Rozas L, Bowes WA Jr: The natural history of thrombocytopenia associated with preeclampsia. Am J Obstet Gynecol 1990; 163:1142-3

108. Martin JN, Blake PG, Perry KG, McCaul JF, Hess LW, Martin RW: The natural history of HELLP syndrome: Patterns of disease progression and regression. Am J Obstet Gynecol 1991; 164:1500-13

109. Neiger R, Contag SA, Coustan DR: The resolution of preeclampsia-related thrombocytopenia. Obstet Gynecol 1991; 77:692-5

110. Ray MJ, Hawson GAT, Just SJE, McLachlan G, O'Brien M: Relationship of platelet aggregation to bleeding after cardiopulmonary bypass. Ann Thorac Surg 1994; 57:981-6

111. Burns ER, Lawrence C: Bleeding time: A guide to its diagnostic and clinical utility. Arch Pathol Lab Med 1989; 113:1219-24

112. Rodgers RP, Levin J: A critical appraisal of the bleeding time. Semin Thromb Hemost 1990; 16:1-20

113. Lind SE: The bleeding time does not predict surgical bleeding. Blood 1991; 77:2547-52

114. British Committee for Standards in Haematology: Guidelines for platelet transfusions. Transfus Med 1992; 2:311-8

115. Higby DJ, Cohen E, Holland JF, Sinks L: The prophylactic treatment of thrombocytopenic leukemic patients with platelets: A double blind study. Transfusion 1974; 14:440-6

116. Murphy S, Litwin S, Herring LM, Koch P, Remischovsky J, Donaldson MH, Evans AE, Gardner FH: Indications for platelet transfusion in children with acute leukemia. Am J Hematol 1982; 12:347-56

117. Simon TL, Abel BF, Murphy W: Controlled trial of routine administration of platelet concentrates in cardiopulmonary bypass surgery. Ann Thorac Surg 1984; 37:359-64

118. Pisciotto PT, Benson K, Hume H, Glassman AB, Oberman H, Popovsky M, Hines D, Anderson K: Prophylactic versus therapeutic platelet transfusion practices in hematology and/or oncology patients. Transfusion 1995; 35:498-502

119. Blumberg N, Laczin J, McMican A, Heal J, Arvan D: A critical survey of fresh-frozen plasma use. Transfusion 1986; 26:511-3

120. Shanberge JN, Quattrociocchi-Longe T: Analysis of fresh frozen plasma administration with suggestions for ways to reduce usage. Transfus Med 1992; 2:189-94

121. Murray DJ, Olson J, Strauss R, Tinker JH: Coagulation changes during packed red cell replacement of major blood loss. ANESTHESIOLOGY 1988; 69:839-45

122. Flaum MA, Cuneo RA, Applebaum FR, Deisseroth AB, Ensel WK, Gralnick HR: The hemostatic imbalance of plasma-exchange transfusion. Blood 1979; 54:694-702

123. Domen RE, Kennedy MS, Jones LL, Senhauser DA: Hemostatic imbalances produced by plasma exchange. Transfusion 1984; 24:336-9

124. Miller RD, Robbins TO, Tong MJ, Barton SL: Coagulation defects associated with massive blood transfusions. Ann Surg 1971; 174:794-801

125. Lucas CE, Ledgerwood AM: Clinical significance of altered coagulation tests after massive transfusion for trauma. Ann Surg 1981; 47:125-30

126. Mannucci PM, Federici AB, Sirchia G: Hemostasis testing during massive blood replacement: A study of 172 cases. Vox Sang 1982; 42:113-23

127. Murray DJ, Pennell BJ, Weinstein SL, Olson JD: Packed red cells in acute blood loss: Dilutional coagulopathy as a cause of surgical bleeding. Anesth Analg 1995; 80:336-42

128. Harke H, Rahman S: Haemostatic disorders in massive transfusion. Biblthca Haematol 1980; 46:179-88

129. Hewson JR, Neame PB, Kumar N, Ayrton A, Gregor, Davis C, Shragge BW: Coagulopathy related to dilution and hypotension during massive transfusion. Crit Care Med 1985; 13:387-91

130. Faringer PD, Mullins RJ, Johnson RL, Trunkey DD: Blood component supplementation during massive transfusion of AS-1 red cells in trauma patients. J Trauma 1993; 34:481-7

131. Eika C, Havie O, Godal HC: The value of preoperative haemostatic screening. Scand J Haematol 1978; 21:349-54

132. Robbins JA, Rose SD: Partial thromboplastin time as a screening test. Ann Intern Med 1979; 90:796

133. Friedman EW, Sussman II: Safety of invasive procedures in patients with the coagulopathy of liver disease. Clin Lab Haematol 1989; 11:199-204

134. Ewe K: Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. Dig Dis Sci 1981; 26:388-93

135. Foster PF, Moore LR, Sankary HN, Hart ME, Ashmann MK, Williams JW: Central venous catheterization in patients with coagulopathy. Arch Surg 1992; 127:273-5

136. Proietti AB, Johnson MJ, Proietti FA, Repke JT, Bell WR: Assessment of fibrin (ogen) degradation products in preeclampsia using immunoblot, enzyme-linked immunosorbent assay, and latex-based agglutination. Obstet Gynecol 1991; 77:696-700

137. Spector I, Corn M, Ticktin HE: Effect of plasma transfusions on the prothrombin time and clotting factors in liver disease. N Engl J Med 1966; 275:1032-7

138. Roy RC, Stafford MA, Hudspeth AS, Meredith JW: Failure of prophylaxis with fresh frozen plasma after cardiopulmonary bypass. ANESTHESIOLOGY 1988; 69:254-7

139. British Committee for Standards in Haematology: Guidelines for the use of fresh frozen plasma. Transfus Med 1992; 2:57-63

140. Gilabert J, Estelles A, Aznar J, Galbis M: Abruptio placentae and disseminated intravascular coagulation. Acta Obstet Gynecol Scand 1985; 64:35-9

141. Green D, Potter EV: Failure of AHV concentrate to control bleeding in von Willebrand's disease. Am J Med 1976; 60:357-60

142. Holmberg L. Nilsson IM: Von Willebrand's disease. Eur J Haematol 1992; 48:127-41

143. Aledort LM: Treatment of von Willebrand's disease. Mayo Clin Proc 1991; 66:841-6

144. Schulman S: DDAVP--the multipotent drug in patients with coagulopathies. Transfus Med Rev 1991; 5:132-44

145. Rodeghiero F, Castaman G, Meyer D, Mannucci PM: Replacement therapy with virus-inactivated plasma concentrates in von Willebrand disease. Vox Sang 1992; 62:193-9

146. Hoyer LW: Hemophilia A. N Engl J Med 1994; 330:38-47

147. Sutton DM, Hauser R, Kulapongs P, Bachmann F: Intravascular coagulation in abruptio placentae. Am J Obstet Gynecol 1971; 109:604-14

148. Etchason J, Petz L, Keeler E, Calhoun L, Kleinman S, Snider C, Fink A, Brook R: The cost effectiveness of preoperative autologous blood donations. N Engl J Med 1995; 332:719-24

149. Lichtiger B, Fischer HE, Huh YO: Screening of transfusion service requests by the blood bank pathologist: Impact on cost containment. Lab Med 1988; 19:228-30

150. Blanchette VS, Hume HA, Levy GJ, Luban NL, Strauss RG: Guidelines for auditing pediatric blood transfusion practices. Am J Dis Child 1991; 145:787-96

151. Toy PTCY: Effectiveness of transfusion audits and practice, guidelines. Arch Pathol Lab Med 1994; 118:435-7

152. Despotis GJ, Grishaber JE, Goodnough LT: The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. Transfusion 1994; 34:290-6

153. Paone G, Spencer T, Silverman NA: Blood conversation in coronary artery surgery. Surgery 1994; 116:672-8

154. Renner SW, Howanitz JH, Fishkin BG: Toward meaningful blood usage review: Comprehensive monitoring of physician practice. QRB 1987; 13:76-80

155. Lepage EF, Gardner RM, Laub RM, Golubjatnikov OK: Improving blood transfusion practice: Role of a computerized hospital information system. Transfusion 1992; 32:253-9

156. Soumerai SB, Salem-Schatz S, Avorn J, Casteris CS, Ross-Degnan D, Popovsky MA: A controlled trial of educational outreach to improve blood transfusion practice. JAMA 1993; 270:961-6

157. Shanberge JN: Reduction of fresh frozen plasma use through a daily survey and education program. Transfusion 1987; 27:226-7

158. Solomon RR, Clifford JS, Gutman SI: The use of laboratory intervention to stem the flow of fresh-frozen plasma. Am J Clin Pathol 1988; 89:518-21

159. Ayoub MM, Clark JA: Reduction of fresh frozen plasma use with a simple education program. Am Surg 1989; 55:563-5

160. Barnette RE, Fish DJ, Eisenstaedt RS: Modification of fresh-frozen plasma transfusion practices through educational intervention. Transfusion 1990; 30:253-7

161. Simpson MB: Prospective-concurrent audits and medical consultation for platelet transfusions. Transfusion 1987; 27:192-5

162. McCullough J, Steeper TA, Connelly DP, Jackson B, Huntington S, Scott EP: Platelet utilization in a university hospital. JAMA 1988; 259:2414-8

APPENDIX: Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists[D]

A Report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists

ANESTHESIOLOGISTS possess specific expertise in the pharmacology, physiology, and clinical management of patients receiving sedation and analgesia. For this reason, they are frequently called on to participate in the development of institutional policies and procedures for sedation and analgesia in nonoperating-room settings. To assist in this process, the American Society of Anesthesiologists developed these Guidelines for Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines are systematically developed recommendations that assist practitioners in making decisions about health care. These recommendations may be adopted, modified, exceeded, or rejected according to clinical needs and constraints, and they are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. Practice guidelines are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome.

The practice guidelines enumerated below have been developed using systematic literature summarization techniques. Results of the literature analyses have been supplemented by the opinions of the Task Force members and a panel of more than 60 consultants, drawn from a variety of medical specialties in which sedation and analgesia are commonly provided. In those instances when the literature does not provide conclusive data, there is an explicit statement that the guidelines are based on the opinion of the consultants or the consensus of the Task Force members. A detailed description of the analytic methods is included in appendix 1.

A. Definition

"Sedation and analgesia" describes a state that allows patients to tolerate unpleasant procedures while maintaining adequate cardiorespiratory function and the ability to respond purposefully to verbal command and/or tactile stimulation. The Task Force decided that the term "sedation and analgesia" (sedation/analgesia) more accurately defines this therapeutic goal than does the commonly used but imprecise term "conscious sedation." Note that patients whose only response is reflex withdrawal from a painful stimulus are sedated to a greater degree than encompassed by "sedation/analgesia."

B. Purpose

The purpose of these guidelines is to allow clinicians to provide their patients with the benefits of sedation/analgesia while minimizing the associated risks. Sedation/analgesia provides two general types of benefit: First, sedation/analgesia allows patients to tolerate unpleasant procedures by relieving anxiety, discomfort, or pain. Second, in children and uncooperative adults, sedation/analgesia may expedite the conduct of procedures that are not particularly uncomfortable but require that the patient not move. Excessive sedation/analgesia may result in cardiac or respiratory depression that must be rapidly recognized and appropriately

Developed by the Task Force on Sedation and Analgesia by Non-Anesthesiologists: Jeffrey B. Gross, M.D. (Chair), Farmington, Connecticut; Peter L. Bailey, M.D., Salt Lake City, Utah; Robert A. Caplan, M.D., Seattle, Washington; Richard T. Connis, Ph.D. (Methodologist), Woodinville, Washington; Charles J. Cote, M.D., Chicago, Illinois; Fred G. Davis, M.D., Burlington, Massachusetts; Burton S. Epstein, M.D., Washington, D.C.; Patricia A. Kapur, M.D., Los Angeles, California; John M. Zerwas, M.D., Houston, Texas; and Gregory Zuccaro, Jr., M.D., Cleveland, Ohio.

managed to avoid the risk of hypoxic brain damage, cardiac arrest, or death. Conversely, inadequate sedation/analgesia may result in undue patient discomfort or patient injury because of lack of cooperation or adverse physiologic response to stress.

C. Focus

These guidelines have been designed to be applicable to procedures performed in a variety of settings (*e.g.,* hospitals, free-standing clinics, physicians' offices) by practitioners who are not specialists in anesthesiology. The guidelines specifically exclude the following: (1) patients who are not undergoing a diagnostic or therapeutic procedure (*e.g.,* postoperative analgesia, sedation for treatment of insomnia); (2) otherwise healthy patients receiving peripheral nerve blocks, local or topical anesthesia, and/or no more than 50% N_2O with oxygen and no other sedative or analgesic agents administered by any route; (3) situations when it is anticipated that the required sedation will eradicate the purposeful response to verbal commands or tactile stimulation (as distinct from reflex withdrawal from a painful stimulus); such patients require a greater level of care than recommended by these guidelines; and (4) perioperative management of patients undergoing general anesthesia or major conduction anesthesia (spinal or epidural/caudal blockade).

D. Application

These guidelines are intended to be general in their application and broad in scope. The appropriate choice of agents and techniques for sedation/analgesia is dependent on the experience and preference of the individual practitioner, requirements or constraints imposed by the patient or procedure, and the likelihood of producing unintended loss of consciousness. Templates are provided as examples to illustrate principles; clinicians and their institutions have ultimate responsibility for selecting patients, procedures, medications, and equipment.

Guidelines

I. Patient Evaluation

Published data suggest and consultant opinion strongly supports the contention that appropriate preprocedure evaluation of patients' histories and physical findings reduces the risk of adverse outcomes. Additionally, consultant opinion supports the contention that an appropriate history, physical examination, and laboratory evaluation leads to improved patient satisfaction.

Recommendations: Clinicians administering sedation/analgesia should be familiar with relevant aspects of the patient's medical history including: (1) abnormalities of the major organ systems, (2) previous adverse experience with sedation/analgesia, as well as regional and general anesthesia, (3) current medications and drug allergies, (4) time and nature of last oral intake, and (5) history of tobacco, alcohol, or substance use or abuse. Patients presenting for sedation/analgesia should undergo a focused physical examination including auscultation of the heart and lungs and evaluation of the airway (template 1). Preprocedure laboratory testing should be guided by the patient's underlying medical condition and the likelihood that the results will affect the management of sedation/analgesia.

Preprocedure Preparation

Patient Counseling: There is insufficient evidence in the literature to establish the benefit of providing the patient (or her/his guardian, in the case of a child or impaired adult) with preprocedure information about sedation/analgesia. However, the consultants strongly support the contention that appropriate preprocedure counseling improves patient satisfaction and reduces risks; they also support the view that costs may be reduced. The Task Force members concur that patients undergoing sedation/analgesia should be informed of the benefits, risks, and limitations associated with this therapy, as well as possible alternatives.

Preprocedure Fasting: Because sedatives and analgesics tend to impair airway reflexes in proportion to the degree of sedation/analgesia achieved, members of the Task Force support the concept of preprocedure fasting before sedation/analgesia for elective procedures. However, the literature provides insufficient data to test the hypothesis that preprocedure fasting results in a decreased incidence of adverse outcomes in patients undergoing sedation/analgesia (as distinct from patients undergoing general anesthesia).

Recommendations: Patients (or their legal guardians in the case of minors or legally incompetent adults) should be informed of and agree to the administration of sedation/analgesia before the procedure begins. Patients undergoing sedation/analgesia for elective procedures should not drink fluids or eat solid foods for a sufficient period of time to allow for gastric emptying

---

Template 1. Example of Airway Assessment Procedures for Sedation and Analgesia

Positive pressure ventilation, with or without endotracheal intubation, may be necessary if respiratory compromise develops during sedation/analgesia. This may be more difficult in patients with atypical airway anatomy. Also, some airway abnormalities may increase the likelihood of airway obstruction during spontaneous ventilation. Factors that may be associated with difficulty in airway management are:
History
Previous problems with anesthesia or sedation
Stridor, snoring, or sleep apnea
Dysmorphic facial features (e.g., Pierre-Robin syndrome, trisomy 21)
Advanced rheumatoid arthritis
Physical examination
Habitus
Significant obesity (especially involving the neck and facial structures)
Head and neck
Short neck, limited neck extension, decreased hyoid-mental distance (<3 cm in an adult), neck mass, cervical spine disease or trauma, tracheal deviation
Mouth
Small opening (<3 cm in an adult); edentulous; protruding incisors; loose or capped teeth; high arched palate; macroglossia; tonsillar hypertrophy; nonvisible uvula
Jaw
Micrognathia, retrognathia, trismus, significant malocclusion

before their procedure (template 2). In urgent, emergent, or other situations when gastric emptying is impaired, the potential for pulmonary aspiration of gastric contents must be considered in determining the timing of the intervention and the degree of sedation/analgesia.

III. Monitoring

Level of Consciousness: The response of patients to commands during procedures performed with sedation

Template 2. Example of Fasting Protocol for Sedation and Analgesia for Elective Procedures

Gastric emptying may be influenced by many factors, including anxiety, pain, abnormal autonomicfunction (e.g., diabetes), pregnancy, and mechanical obstruction. Therefore, the suggestions listeddo not guarantee that complete gastric emptying has occurred. Unless contraindicated, pediatricpatients should be offered clear liquids until 2-3 h before sedation to minimize the risk ofdehydration.

	Solids and Nonclear Liquids *	Clear Liquids
Adults	6-8 h or none after midnight	2-3 h
Children older than 36 months	6-8 h	2-3 h
Children aged 6-36 months	6 h	2-3 h
Children younger than 6 months	4-6 h	2 h

* This includes milk, formula, and breast milk (high fat content maydelay gastric emptying).

There are no data to establish whether a 6-8 hfast is equivalent to an overnight fast before sedation/analgesia.

/analgesia serves as a guide to their level of consciousness. Spoken responses also provide an indication that the patients are breathing. Patients whose only response is reflex withdrawal from painful stimuli are likely to be deeply sedated, approaching a state of general anesthesia, and should be treated accordingly. The consultants strongly support the contention that monitoring level of consciousness reduces risks and support the concept that overall costs may be reduced. The members of the Task Force believe that many of the complications associated with sedation/analgesia can be avoided if adverse drug responses are detected and treated in a timely manner (*i.e.,* before the development of cardiovascular decompensation or cerebral hypoxia); this may pose a special risk to patients given sedatives/analgesics in unmonitored settings in anticipation of a subsequent procedure.

Pulmonary Ventilation: It is the opinion of the Task Force that a primary cause of morbidity associated with sedation/analgesia is drug-induced respiratory depression. The literature suggests and consultant opinion strongly supports the observation that monitoring of ventilatory function reduces the risk of adverse outcomes associated with sedation/analgesia. Ventilatory function usually can be effectively monitored by observation of spontaneous respiratory activity or auscultation of breath sounds. In circumstances where patients are physically separated from the caregiver, the consultants support and the Task Force members concur

that automated apnea monitoring (by detection of exhaled carbon dioxide or other means) may decrease risks; the consultants suggest that such monitoring will not reduce overall costs. The Task Force cautions practitioners that impedance plethysmography may fail to detect airway obstruction.

Oxygenation: Published data suggest and the consultants strongly support the view that early detection of hypoxemia through the use of oximetry during sedation/analgesia decreases the likelihood of adverse outcomes, such as cardiac arrest and death. The literature suggests, the consultants strongly support, and Task Force members agree that hypoxemia during sedation and analgesia is more likely to be detected by oximetry than by clinical assessment alone. The Task Force emphasizes that oximetry is not a substitute for monitoring ventilatory function.

Hemodynamics: Although there is insufficient published data to reach a conclusion, it is the opinion of the Task Force that sedative and analgesic agents may blunt the appropriate autonomic compensation for hypovolemia and procedure-related stresses. Early detection of changes in patients' heart rate and blood pressure may enable practitioners to detect problems and intervene in a timely fashion, reducing the risk of cardiovascular collapse. The consultants support the concept that regular monitoring of vital signs reduces risks and suggest that it decreases costs. Although the literature provides no guidance, the consultants suggest the use of continuous electrocardiographic monitoring in patients with hypertension and strongly support its use in patients with significant cardiovascular disease or dysrhythmias; the consultants suggest that electrocardiographic monitoring is not required in patients without cardiovascular disease.

Recommendations: Monitoring of patient response to verbal commands should be routine, except in patients who are unable to respond appropriately (*e.g.,* young children, mentally impaired or uncooperative patients) or during procedures in which facial movement could be detrimental. During procedures in which a verbal response is not possible (*e.g.,* oral surgery, upper endoscopy), the ability to give a "thumbs up" or other indication of consciousness in response to verbal or tactile (light tap) stimulation suggests that the patient will be able to control his airway and take deep breaths if necessary. Note that a response limited to reflex withdrawal from a painful stimulus represents a greater degree of sedation/analgesia than addressed by this document.

Ventilatory function should be continually monitored by observation and/or auscultation. When ventilation cannot be directly observed, exhaled carbon dioxide detection is a useful adjunct to these modalities. All patients undergoing sedation/analgesia should be monitored by pulse oximetry with appropriate alarms. If available, the variable pitch "beep," which gives a continuous audible indication of the oxygen saturation reading, may be helpful. When possible, blood pressure should be determined before sedation/analgesia is initiated. Once sedation/analgesia is established, blood pressure should be measured at regular intervals during the procedure, as well as during the recovery period. Electrocardiographic monitoring should be used in patients with significant cardiovascular disease as well as during procedures in which dysrhythmias are anticipated.

/das/book/view/29494766/875/1043.html

IV. Recording of Monitored Parameters

Both the literature and consultant opinion suggest that contemporaneous recording of patients' level of consciousness, respiratory function, and hemodynamics reduces the risk of adverse outcomes.Although consultant opinion suggests that recording of this information may not improve patient comfort or satisfaction, the consultants suggest that it may reduce costs resulting from adverse events. The consultants strongly support recording of vital signs and respiratory variables before initiating sedation/analgesia, after administration of sedative/analgesic medications, at regular intervals during the procedure, on initiation of recovery, and immediately before discharge. It is the opinion of the Task Force that contemporaneous recording (either automatic or manual) of patient data provides information that could prove critical in determining the cause of any adverse events that might occur. Additionally, manual recording ensures that an individual caring for the patient is aware of changes in patient status in a timely fashion.

Recommendations: Patients' ventilatory and oxygenation status and hemodynamic variables should be recorded at a frequency to be determined by the type and amount of medication administered as well as the length of the procedure and the general condition of the patient. At a minimum, this should be: (1) before the beginning of the procedure, (2) after administration of sedative/analgesic agents, (3) on completion of the procedure, (4) during initial recovery, and (5) at the time of discharge. If recording is performed automatically,

device alarms should be set to alert the care team to critical changes in patient status.

V. Availability of a Staff Person Dedicated Solely to Patient Monitoring and Safety

Although there are insufficient data in the literature to provide guidance on this issue, the Task Force recognizes that it is difficult for the individual performing a procedure to be fully cognizant of the patient's condition during sedation/analgesia. The consultants support the contention that the availability of an individual other than the person performing the procedure to monitor the patient's status improves patient comfort and satisfaction; they also strongly support the view that risks are reduced. The consultants support the observation that this would not decrease overall costs. It is the consensus of the Task Force members that the individual monitoring the patient may assist the practitioner with interruptible ancillary tasks of short duration once the patient's level of sedation/analgesia and vital signs have stabilized, provided that adequate monitoring is maintained.

Recommendations: A designated individual, other than the practitioner performing the procedure, should be present to monitor the patient throughout procedures performed with sedation/analgesia. This individual may assist with minor, interruptible tasks.

VI. Training of Personnel

Although there is insufficient literature to determine the effectiveness of training on patient outcomes, the consultants strongly support the observation that providing appropriate training in clinical pharmacology for individuals administering sedative/analgesic medications reduces the risk of adverse outcomes; they also support the views that patient comfort is improved and overall costs are reduced. Specific concerns include: (1) potentiation of sedative-induced respiratory depression by concomitantly administered opioids; (2) inadequate time intervals between doses of sedative or analgesic agents, resulting in a cumulative overdose; and (3) inadequate familiarity with the role of pharmacologic antagonists for sedative and analgesic agents.

Because the primary complications of sedation/analgesia are related to respiratory or cardiovascular depression, it is the consensus of the Task Force that the individual responsible for monitoring the patient should be trained in the recognition of complications associated with sedation/analgesia. In addition, at least one qualified individual, capable of establishing a patent airway and maintaining ventilation and oxygenation, should be present during the procedure.

Recommendations: Individuals responsible for patients receiving sedation/analgesia should understand the pharmacology of the agents that are administered, as well as the role of pharmacologic antagonists for opioids and benzodiazepines. Individuals monitoring patients receiving sedation/analgesia should be able to recognize the associated complications. At least one individual capable of establishing a patent airway and positive pressure ventilation, as well as a means for summoning additional assistance, should be present whenever sedation/analgesia is administered. It is recommended that an individual with advanced life-support skills be immediately available.

VII. Availability of Emergency Equipment

The literature suggests and the consultants strongly support the view that the ready availability of appropriately sized emergency equipment reduces the risk of sedation and analgesia. The consultants also support the contention that overall costs, including those associated with adverse outcomes, may be reduced. The literature does not address the need for cardiac defibrillators during sedation/analgesia. The consultants strongly support the availability of a defibrillator whenever sedation/analgesia is administered.

Recommendations: Pharmacologic antagonists as well as appropriately sized equipment for establishing a patent airway and providing positive pressure ventilation with supplemental oxygen should be present whenever sedation/analgesia is administered. Advanced airway equipment and resuscitation medications should be immediately available (template 3). A defibrillator should be immediately available when sedation/analgesia is administered to patients with significant cardiovascular disease.

VIII. Use of Supplemental Oxygen

The literature supports the use of supplemental oxygen during sedation/analgesia: There is a decreased incidence and severity of hypoxemia among sedation/analgesia patients given oxygen as compared to those breathing room air. However, it must be appreciated that, by delaying the onset of hypoxemia, supplemental oxygen will delay the detection of apnea by pulse oximetry, emphasizing the importance of monitoring pulmonary ventilation by other means (see above). Consultant opinion supports the view that supplemental oxygen decreases patient

Template 3. Example of Emergency Equipment for Sedation and Analgesia

Appropriate emergency equipment should be available whenever sedative or analgesic drugscapable of causing cardiorespiratory depression are administered. The table below should be used as a guide, which should be modified depending on the individual practice circumstances. Items inbrackets are recommended when infants or children are sedated.

- Intravenous equipment
  - Gloves
  - Tourniquets
  - Alcohol wipes
  - Sterile gauze pads
  - Intravenous catheters [24- or 22-G]
  - Intravenous tubing [pediatric "microdrip" (60 drops/ml)]
  - Intravenous fluid
  - Three-way stopcocks
  - Assorted needles for drug aspiration, intramuscular injection [intraosseous bone marrow needle]
  - Appropriately sized syringes
  - Tape
- Basic airway management equipment
  - Source of compressed oxygen (tank with regulator or pipeline supply with flowmeter)
  - Source of suction
  - Suction catheters [pediatric suction catheters]
  - Yankauer-type suction
  - Face masks [infant/child]
  - Self-inflating breathing bag-valve set [pediatric]
  - Oral and nasal airways [infant/child-sized airways]
  - Lubricant
- Advanced airway management equipment (for practitioners with intubation skills)
  - Laryngoscope handles (tested)
  - Laryngoscope blades [pediatric]
  - Endotracheal tubes
    - Cuffed; 6.0, 7.0, or 8.0 mm ID [Uncuffed; 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, or 6.0 mm ID]
  - Stylet (appropriately sized for endotracheal tubes)
- Pharmacologic antagonists
  - Naloxone
  - Flumazenil
- Emergency medications
  - Epinephrine
  - Ephedrine
  - Atropine
  - Lidocaine
  - Glucose, 50% [10% or 25%]
  - Diphenhydramine
  - Hydrocortisone, methylprednisolone, or dexamethasone
  - Diazepam or midazolam
  - Ammonia pirits

risk, while suggesting that routine use of supplemental oxygen may increase costs.

Recommendations: Equipment to administer supplemental oxygen should be present when sedation/analgesia is administered. If hypoxemia is anticipated or develops during sedation/analgesia, supplemental oxygen should be administered.

IX. Use of Multiple Sedative/Analgesic Agents

The literature supports the observation that combinations of agents may be more effective than single agents in certain circumstances. However, the published data also suggest and consultant opinion supports the observation that combinations of sedatives and opioids may increase the likelihood of adverse outcomes,

including ventilatory depression and hypoxemia. Although not evaluated in the literature, it is the consensus of the Task Force that fixed combinations of sedative and analgesic agents may not allow the individual components of sedation/analgesia to be appropriately titrated to meet the individual requirements of the patient and procedure.

Recommendations: Combinations of sedative and analgesic agents should be administered as appropriate for the procedure being performed and the condition of the patient. Ideally, each component should be administered individually to achieve the desired effect (*e.g.,* additional analgesic medication to relieve pain, additional sedative medication to decrease awareness or anxiety). The propensity for combinations of sedative and analgesic agents to potentiate respiratory depression emphasizes the need to appropriately reduce the dose of each component as well as the need to continually monitor respiratory function.

X. Titration of Sedative/Analgesic Medications to Achieve the Desired Effect

The literature suggests that the administration of small, incremental doses of intravenous sedative/analgesic drugs until the desired level of sedation and/or analgesia is achieved is preferable to a single dose based on patient size, weight, or age. The consultants support the concept that incremental drug administration improves patient comfort and decreases costs; they strongly support the contention that the potential risks associated with excessive doses are reduced.

Recommendations: Intravenous sedative/analgesic drugs should be given in small, incremental doses that are titrated to the desired endpoints of analgesia and sedation. Sufficient time must elapse between doses to allow the effect of each dose to be assessed before subsequent drug administration. When drugs are administered by nonintravenous routes (*e.g.,* oral, rectal, intramuscular), allowance should be made for the time required for drug absorption before supplementation is considered.

XI. Intravenous Access

Published data suggest that, in cooperative patients, administration of sedative/analgesic agents by the intravenous route improves patient comfort and satisfaction. The consultants strongly support the importance of intravenous access in reducing patient risks. In situations when sedative/analgesic medications are to be administered intravenously, it is the consensus of the Task Force that maintaining intravenous access until the patient is no longer at risk for cardiorespiratory depression improves patient safety. In those situations when sedation is begun by nonintravenous routes (*e.g.,* oral, rectal, intramuscular), the need for intravenous access is not sufficiently addressed in the literature. However, initiation of intravenous access after the initial sedation takes effect allows additional sedative/analgesic and resuscitation drugs to be administered if necessary.

Recommendations: In patients receiving intravenous medications for sedation/analgesia, vascular access should be maintained throughout the procedure and until the patient is no longer at risk for cardiorespiratory depression. In patients who have received sedation/analgesia by nonintravenous routes or whose intravenous line has become dislodged or blocked, practitioners should determine the advisability of establishing or reestablishing intravenous access on a case-by-case basis. In all instances, an individual with the skills to establish intravenous access should be immediately available.

XII. Reversal Agents

Specific antagonist agents are available for the opioids (*e.g.,* naloxone) and benzodiazepines (*e.g.,* flumazenil). The literature supports the ability of naloxone to reverse opioid-induced sedation and ventilatory depression during sedation/analgesia. However, the Task Force reminds practitioners that acute reversal of opioid-induced analgesia may result in pain, hypertension, tachycardia, or pulmonary edema. The literature supports the ability of flumazenil to reverse benzodiazepine-induced sedation and its effectiveness in reversing ventilatory depression in patients who have received benzodiazepines alone. In patients who have received both benzodiazepines and opioids, published data support the ability of flumazenil to reverse sedation; however, there are insufficient data to establish the effectiveness of flumazenil in reversing ventilatory depression under these circumstances. The consultants strongly support the contention that the availability of reversal agents is associated with decreased risk. It is the consensus of the Task Force that respiratory depression should be initially treated with supplemental oxygen and, if necessary, positive pressure ventilation by mask.

Recommendations: Specific antagonists should be available whenever opioid analgesics or benzodiazepines are administered for sedation/analgesia. Naloxone and/or flumazenil may be administered to improve

Template 4. Example of Recovery and Discharge Criteria after Sedation and Analgesia

Each patient-care facility in which sedation/analgesia is administered should develop recovery and discharge criteria that are suitable for its specific patients and procedures. Some of the basic principles that might be incorporated in these criteria are enumerated.

General principles

1. All patients receiving sedation/analgesia should be monitored until appropriate discharge criteria are satisfied. The duration of monitoring must be individualized depending on the level of sedation achieved, overall condition of the patient, and nature of the intervention for which sedation/analgesia was administered.

2. The recovery area should be equipped with appropriate monitoring and resuscitation equipment.

3. A nurse or other trained individual should be in attendance until discharge criteria are fulfilled. An individual capable of establishing a patent airway and providing positive pressure ventilation should be immediately available.

4. Level of consciousness and vital signs (including frequency and depth of respiration in the absence of stimulation) should be recorded at regular intervals during recovery. The responsible practitioner should be notified if vital signs fall outside of the limits previously established for each patient.

Guidelines for discharge

1. Patients should be alert and oriented; infants and patients whose mental status was initially abnormal should have returned to their baseline. Practitioners must be aware that pediatric patients are at risk for airway obstruction should the head fall forward while the child is secured in a car seat.

2. Vital signs should be stable and within acceptable limits.

3. Sufficient time (up to 2 h) should have elapsed after the last administration of reversal agents (naloxone, flumazenil) to ensure that patients do not become resedated after reversal effects have abated.

4. Outpatients should be discharged in the presence of a responsible adult who will accompany them home and be able to report any post-procedure complications.

5. Outpatients should be provided with written instructions regarding post-procedure diet, medications, and activities and a phone number to use in case of emergency.

spontaneous ventilatory efforts in patients who have received opioids or benzodiazepines, respectively. This may be especially helpful in cases in which airway control and positive pressure ventilation are difficult. Before or concomitantly with pharmacologic reversal, patients who become hypoxemic or apneic during sedation/analgesia should: (1) be encouraged or stimulated to breathe deeply, (2) receive positive pressure ventilation if spontaneous ventilation is inadequate, and (3) receive supplemental oxygen. After pharmacologic reversal, patients should be observed long enough to ensure that cardiorespiratory depression does not recur.

XIII. Recovery Care

Patients may continue to be at significant risk for complications after their procedure is completed. Decreased procedural stimulation, prolonged drug absorption after oral or rectal administration, and postprocedure hemorrhage may contribute to cardiorespiratory depression. When sedation/analgesia is administered to outpatients, one must assume there will be no medical supervision once the patient leaves the medical facility. Although there is not sufficient literature to examine the effects of post-procedure monitoring on patient outcomes, the consultants suggest that appropriate monitoring of patients during the recovery period will improve patient comfort and strongly support the view that adverse outcomes may be reduced. It is the consensus of the Task Force that discharge criteria should be established that minimize the risk for cardiorespiratory depression after patients are released from observation by trained personnel.

Recommendations: After sedation/analgesia, patients should be observed until they are no longer at increased risk for cardiorespiratory depression. Vital signs and respiratory function should be monitored at regular intervals until patients are suitable for discharge. Discharge criteria should be designed to minimize the risk of central nervous system or cardiorespiratory depression after discharge from observation by trained personnel (template 4.)

XIV. Special Situations

The literature suggests, the consultants strongly support, and the Task Force members concur that certain classes of patients (*e.g.,* uncooperative patients; extremes of age; severe cardiac, pulmonary, hepatic, renal, or central nervous system disease; morbid obesity; sleep apnea; pregnancy; drug or alcohol abuse) are at increased risk for developing complications related to sedation/analgesia unless special precautions are taken. However, the consultants support the view

that risks may be reduced by preprocedure consultation with appropriate specialists (*e.g.,* cardiologist, pulmonologist, nephrologist, obstetrician, pediatrician, anesthesiologist) before administration of sedation/analgesia to these individuals. The consultants support the concept that patient comfort is improved and risks are reduced by consultation with an anesthesiologist before administering sedation/analgesia to patients who are likely to develop complications (*e.g.,* inadequate spontaneous ventilation, loss of airway control, cardiovascular compromise) or in whom sedation/analgesia alone is not expected to provide adequate conditions (*e.g.,* young children, uncooperative patients). However, the consultants also support the contention that such consultation will not reduce costs.

Recommendations: Whenever possible, appropriate medical specialists should be consulted before administration of sedation/analgesia to patients with significant underlying conditions. The choice of specialists depends on the nature of the underlying condition and the urgency of the situation. For significantly compromised patients (*e.g.,* severe obstructive pulmonary disease, coronary artery disease, congestive heart failure) or if it appears likely that sedation to the point of unresponsiveness or general anesthesia will be necessary to obtain adequate conditions, practitioners who are not specifically qualified to provide these modalities should consult an anesthesiologist.

Appendix 1: Methods and Analyses

The scientific assessment of these guidelines was based on the following statements or evidence linkages. These linkages represent directional hypotheses about relationships between sedation/analgesia by non-anesthesiologists and clinical outcomes.

1. A preprocedure patient evaluation (*i.e.,* history, physical examination, laboratory evaluation) improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
2. Preprocedure preparation of the patient (*e.g.,* counseling, fasting) improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
3. Patient monitoring (*i.e.,* level of consciousness, pulmonary ventilation, oxygenation, hemodynamics) improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
4. Contemporaneous recording of monitored parameters (*e.g.,* level of consciousness, respiratory function, hemodynamics) improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
5. Availability of a staff person dedicated solely to patient monitoring and safety improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
6. Education and training of (sedation/analgesia) providers improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
7. Availability of appropriately sized emergency and airway equipment, including trained staff, improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
8. Use of supplemental oxygen improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
9. Use of multiple sedative/analgesic agents improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
10. Titration of sedative/analgesic medications to achieve the desired effect improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
11. Administration of sedative/analgesic agents by the intravenous route improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
12. Availability of reversal agents (*e.g.,* naloxone, flumazenil) improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
13. Post-procedure monitoring (*e.g.,* during duration of recovery stay, postdischarge) improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.
14. Special regimens for patients with special problems (*e.g.,* uncooperative patients; extremes of age; severe cardiac, pulmonary, hepatic, renal, or central nervous system disease; morbid obesity; sleep apnea; pregnancy; drug or alcohol abuse; emergency/unprepared patients; metabolic and airway difficulties) improves patient satisfaction, increases clinical benefits, and reduces adverse outcomes.

Scientific evidence was derived from multiple sources, including aggregated research literature (with metaanalyses when appropriate), surveys, open presentations, and other consensus-oriented activities. For purposes of literature aggregation, potentially relevant clinical studies were identified *via* electronic and manual searches of the literature. The electronic search covered a 29 yr, from 1966 through 1994. Manual searches covered 48 yr, from 1947 through 1994. More than 3,000 citations were initially identified, yielding 1,315 nonoverlapping articles that addressed topics related to the 14 evidence linkages. After review of the articles, 1,046 studies did not provide direct evidence and were subsequently eliminated, yielding 269 articles containing direct linkage-related evidence. Journals represented by the 269 articles included the following disciplines: anesthesiology, 59; oncology, 5; cardiology, 12; oral/maxillofacial/dental, 71; emergency medicine, 19; gastroenterology, 50; lithotripsy, 4; obstetrics/gynecology, 5; pediatrics, 4; pharmacology, 7; pulmonary medicine, 4; radiology, 17; surgery, 8; and urology, 4.

A directional result for each study was initially determined by classifying the outcome as: (1) supporting a linkage, (2) refuting a linkage, or (3) neutral. The results were averaged to obtain a directional assessment of support for each linkage. The literature relating to linkages 8 (supplemental oxygen); 9 (multiple agents); and 12a, 12b, and 12c (naloxone to reverse opioids, flumazenil to reverse benzodiazepines, and flumazenil to reverse benzodiazepines combined with opioids, respectively) contained enough studies with well defined experimental designs and statistical information to conduct formal metaanalyses. Combined probability tests were applied when studies reported continuous data, and an odds-ratio procedure was applied to dichotomous study results.

Two combined probability tests were employed as follows: (1) the Fisher combined test, producing chi-square values based on logarithmic transformations of the reported *P* values from the independent studies, and (2) the Stouffer combined test, providing representation of the studies by weighting each of the standard normal deviates by the size of the sample. A procedure based on the Mantel-Haenszel method for combining study results using 2 × 2 tables was used when sufficient outcome frequency information was available. An acceptable significance level was set at $P < 0.01$ (one-tailed), and effect size estimates were calculated. Interobserver agreement was established through assessment of interrater reliability testing. Tests for heterogeneity of the independent samples were conducted to ensure consistency among the study results. To control for potential publishing bias, a "failsafe" N value was calculated for each combined probability test. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Results of the combined probability tests are reported in table 1. Significance levels from the weighted Stouffer combined tests for clinical efficacy were $P < 0.001$ for four linkages: 9 (multiple agents), 12a (naloxone for opioid reversal), 12b (flumazenil for benzodiazepine reversal), and 12c (flumazenil for benzodiazepine-opioid combinations). Weighted effect size estimates ranged from r = 0.20 to r = 0.42, demonstrating small-to-moderate effect size estimates. Significance levels from the weighted Stouffer combined tests for beneficial outcomes were $P < 0.001$ for two linkages, 8 (supplemental oxygen) and 12a (naloxone). Significance levels for adverse outcomes ($P < 0.001$) were found for linkage 9 (multiple agents). Linkage 12b was not significant. Weighted effect size estimates ranged from r = 0.30 to r = 0.36. Sufficient data were available to conduct Mantel-Haenszel analyses for linkages 8 (supplemental oxygen) and 9 (multiple agents). Significant differences in the odds of hypoxemia (assessed by Spo2 levels) were found between patients breathing supplemental oxygen versus those breathing room air (odds ratio 4.68, 99% confidence limits 4.13-5.23, Z = 6.51, $P < 0.001$). The odds of an adverse outcome for multiple agents were found to be nonsignificant.

Tests for heterogeneity of statistical tests and effect size were nonsignificant in all cases ($P > 0.01$) except linkage 9 (multiple agents) and 12c (flumazenil to reverse benzodiazepines combined with opioids), indicating that the majority of pooled studies provided common estimates of significance and population effect sizes for the linkages. The two significant effect size estimates for heterogencity may be due to a variety of factors (*e.g.,* methodologic differences among the various studies), dissimilar outcome measures, or other mediating effects.

Agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a kappa statistic for two-rater agreement pairs were as follows: (1) type of study design, $k = 0.69\text{-}0.95$; (2) type of analysis, $k = 0.48\text{-}0.81$; (3) evidence linkage assignment, $k = 0.65\text{-}0.90$; and (4) literature inclusion for database, $k = 0.35\text{-}1.00$. Three-rater chance-corrected agreement values were: (1) design, $S_{a\backslash} = 0.79$, Var (S_{av}) = 0.06; (2) analysis, $S_{a\backslash} = 0.61$, Var ($S_{a\backslash}$) = 0.06; (3) linkage identification, $S_{av} = 0.74$, Var ($S_{a\backslash}$) = 0.01; and (4) literature inclusion, $S_{av} = 0.53$, Var ($S_{a\backslash}$) = 0.02. These values represent moderate to high levels of agreement.

The findings of the literature analyses were supplemented by the opinions of Task Force members and surveys of the opinions of a panel of consultants drawn from the following specialties in which sedation/analgesia are commonly administered: anesthesiology, 9; cardiology, 5; dental anesthesiology, 3; dermatology, 1; emergency medicine, 3; gastroenterology, 6; hematology/oncology; 2; intensive care, 2; oral and maxillofacial surgery, 5; pediatric dentistry, 2; pediatric oncology, 1; pharmacology, 2; plastic surgery, 1; pulmonary medicine, 5; radiology, 8; surgery, 4; and urology, 2. Consultants, in general, were highly supportive of the linkage(*i.e.,* agreed that they resulted in improvement of patient comfort/satisfaction, reduced risk of adverse outcomes, reduced overall costs, and were important issues for the guidelines to address). Responses were given on a 5-point scale, ranging from 1, strongly disagree, to 5, strongly agree; support for a linkage was defined as the fraction of consultants responding "4" or "5" to a given linkage. The percentage of consultants reporting support for each linkage is reported in table 2. Additional responses from consultants are listed as follows: (1) percentage of consultants supporting continuous electrocardiographic monitoring of different classes of patients was, for all patients, 23%; patients with hypertension, 51%; patients with cardiovascular disease, 91%; and patients with cardiac dysrhythmias, 94%; (2) percentage of consultants supporting the immediate availability of a defibrillator for different classes of patients was: for all patients, 64%; patients with hypertension, 68%; patients with cardiovascular disease, 83%; and patients with dysrhythmias, 85%; and (3) percentage of consultants supporting determination of vital signs and respiratory variables at the following times was: before sedation, 91%; immediately after sedation initiated, 79%; at regular intervals during procedure, 83%; at beginning of recovery, 89%; at intervals during recovery, 81%; and just before discharge, 87%.

The feasibility of implementing these guidelines into clinical practice was assessed by an opinion survey of those respondents from the consultant panel who were non-anesthesiologists (N = 37). Responses for feasibility of implementation of the guidelines were as follows: Seventy-five percent of these consultants indicated that implementation of the guidelines would not result in the need to purchase new equipment, supplies, or pharmaceuticals. Among the 25% who stated that purchases would be required, the median anticipated cost was $ 3,750 (mean $ 6,167; range $ 1,500-$ 20,000). Anticipated new costs included: hiring and training (*e.g.,* ACLS) personnel, the presence of a nurse during procedures, establishing intravenous access as a routine procedure, exhaled carbon dioxide monitoring equipment, defibrillator, more attention to preprocedure needs (*e.g.,* NPO status), and additional personnel time during recovery.

The non-anesthesiologist consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the guidelines were instituted. Percentages of consultants expecting no change associated with each linkage were as follows: preprocedure history, 81%; preparation of the patient, 76%; direct monitoring of respiration, 89%; automated ventilatory monitoring, 38%; pulse oximetry, 95%; cardiovascular monitoring, 95%; patient-dedicated staff, 89%; education and training, 95%; emergency equipment, 95%; supplemental oxygen, 95%; multiple classes of agents, 95%; titration, 92%; i.v. access, 89%; reversal agents, 92%; post-procedure monitoring, 89%; and preprocedure consultation with an anesthesiologist, 84%.

Sixty-six percent of the respondents indicated that the guidelines would have no effect on the amount of time spent on a typical case. None reported that the guidelines would reduce the amount of time spent per case. For all respondents, the mean increase in the amount of time spent on a typical case was 4.8 min. Of the 32% of respondents who reported an anticipated increase in time spent on a typical case, the mean was 14.0 min (range 5.0-30.0 min).

TABLE 1 -- Statistical Summary

Combined Test Results		*P*	df
Sedation efficacy			
Linkage 9: Multiple agents			
Fisher's combined test	chi^2 = 92.54	<0.001	38
Stouffer combined test	Zc (weighted) = 5.270	<0.001	
Effect size estimate	r (weighted) = 0.20		
Failsafe n value	Nfs 0.01 = 117.9		
Reversal efficacy			
Linkage 12a: Naloxone to reverse opioids			
Fisher's combined test	chi^2 = 50.66	<0.001	10
Stouffer combined test	Zc (weighted) = 3.894	<0.001	
Effect size estimate	r (weighted) = 0.36		
Failsafe n value	Nfs 0.01 = 24.6		
Linkage 12b: Flumazenil to reverse benzodiazepines			
Fisher's combined test	chi^2 = 220.54	<0.001	46
Stouffer combined test	Zc (weighted) = 6.450	<0.001	
Effect size estimate	r (weighted) = 0.32		
Failsafe n value	Nfs 0.01 =628.4		
Linkage 12c: Flumazenil to reverse benzodiazepines + opioids			
Fisher's combined test	chi^2 = 80.39	<0.001	12
Stouffer combined test	Zc (weighted) = 3.183	<0.001	
Effect size estimate	r (weighted) = 0.42		
Failsafe n value	Nfs 0.01 = 79.4		
Adverse outcomes			
Linkage 9: Multiple agents			
Fisher's combined test	chi^2 = 86.17	<0.001	28
Stouffer combined test	Zc (weighted) = 3.716	<0.001	
Effect size estimate	r (weighted) = 0.32		
Failsafe n value	Nfs 0.01 = 127.9		
Beneficial respiratory outcomes			
Linkage 8: Supplemental oxygen			
Fisher's combined test	chi^2 = 73.95	<0.001	14
Stouffer combined test	Zc (weighted) = 7.227	<0.001	
Effect size estimate	r (weighted) = 0.30		
Failsafe n value	Nfs 0.01 = 61.3		
Linkage 12a: Naloxone to reverse opioids			
Fisher's combined test	chi^2 = 45.94	<0.001	10
Stouffer combined test	Zc (weighted) = 4.487	<0.001	

Effect size estimate	r (weighted) = 0.36		
Failsafe n value	Nfs 0.01 = 24.7		
Linkage 12b: Flumazenil to reverse benzodiazepines			
Fisher's combined test	chi^2 = 29.07	<0.001	10
Stouffer combined test	Zc (weighted) = 0.740	>0.010	NS
Effect size estimate	r (weighted) = 0.35		
Failsafe n value	Nfs 0.01 = 9.8		

Readers with special interest in the statistical analyses used in establishing these guidelines can receive further information by writing to: Jeffrey B. Gross, M.D., Department of Anesthesiology (M/C 2015), University of Connecticut School of Medicine, Farmington, Connecticut 06030-2015.

Appendix 2: Definition of Terms

In these guidelines, the following terms are used to express the strength of the evidence relating various interventions and the associated outcomes.

TABLE 2 -- Proportion of Consultants Indicating Support for Linkages (%)

Linkage	Patient Comfort/Satisfaction	Reduced Risk	Reduced Costs	Important Topic
1. Patient evaluation	57	92	63	62
2. Preprocedure preparation	92	85	63	65
3a. Level of consciousness	70	87	52	71
3b. Ventilation monitoring, observation/auscultation	45	85	43	70
3c. Automated apnea monitoring	32	74	30	72
3d. Pulse oximetry	77	96	56	81
3e. Heart rate, blood pressure	55	83	45	66
4. Contemporaneous recording of monitored parameters	23	67	38	67
5. Staff availability	58	65	31	75
6. Training of personnel	69	94	67	77
7. Availability of emergency equipment	42	96	54	63
8. Supplemental oxygen	35	50	19	67
9. Multiple agents	48	13	7	71
10. Titration	87	81	55	70
11. Intravenous access	42	85	33	67
12. Reversal agents	35	85	29	71
13. Post-procedure monitoring	67	92	52	81
14a. Special regimens	71	88	37	67
14b. Anesthesia consultation	70	74	34	68

Literature review

Insufficient data: There are insufficient published data to provide an indication of the relationship between intervention and outcome.

Suggests: There is qualitative evidence in the form of case reports or descriptive studies, but there is insufficient quantitative evidence to establish a statistical relationship between intervention and outcome.

Supports: Quantitative data indicate a significant relationship between intervention and outcome ($P < 0.01$), and qualitative data are supportive.

Consultant opinion

The consultants' questionnaire was based on a 5-point scale ranging from "1" (strongly disagree) to "5" (strongly agree), with a score of "3" being neutral.

Suggests: The number of individuals responding "4" or "5" exceeds the number responding "1" or "2".

Supports: 50% or more of the responses were "4" or "5".

Strongly supports: 50% or more of the responses were "5".

Appendix 3: Summary of Guidelines*

- Preprocedure evaluation
  - Relevant history
    - Focused physical examination (to include heart, lungs, airway)
    - Laboratory testing when indicated
  - Patient counseling
    - Risks, benefits, limitations, and alternatives
  - Preprocedure fasting
    - Elective procedures
      - Sufficient time for gastric emptying
    - Urgent or emergent situations
      - Benefits of sedation/analgesia must be weighed against the potential risk of regurgitation and aspiration of gastric contents
  - Monitoring
    - Data to be recorded at appropriate intervals before, during, and after procedure
    - Pulse oximetry
    - Response to verbal commands when practical
    - Pulmonary ventilation (observation, auscultation, other means)
    - Blood pressure and heart rate at appropriate intervals
    - Electrocardiograph for patients with significant cardiovascular disease
- Personnel
  - Designated individual, other than the practitioner performing the procedure, present to monitor the patient throughout the procedure
- Training
  - Pharmacology of sedative and analgesic agents
  - Pharmacology of available antagonists
  - Basic life support skills present
  - Advanced life support skills immediately available
- Emergency equipment
  - Suction, appropriately sized airway equipment, means of positive-pressure ventilation
  - Intravenous equipment, pharmacologic antagonists, and basic resuscitative medications
  - Supplemental oxygen
    - Oxygen delivery equipment available
    - Oxygen administered if hypoxemia occurs
- Choice of agents
  - Sedatives to decrease anxiety, promote somnolence
  - Analgesics to relieve pain
- Dose titration
  - Medications given incrementally with sufficient time between doses to assess effects
  - Appropriate does reduction if both sedatives and analgesics are used

Intravenous access

Sedatives administered ntravenously, maintain intravenous access

Sedatives administered by other routes, case-by-case decision

Recovery

Observation until patients are no longer at risk for cardiorespiratory depression

Appropriate discharge criteria

Special situations

Severe underlying medical problems, consult with appropriate specialist

Risk of severe cardiovascular or respiratory compromise or need for deep sedation/general anesthesia to obtain adequate operating conditions, consult anesthesiologist

*This is a summary of the guidelines. The body of the document should be consulted for complete details.

GUIDELINES FOR AMBULATORY SURGICAL FACILITIES
(Approved by House of Delegates on October 11, 1973 and last amended on October 12, 1988)

ASA endorses and supports the concept of Ambulatory Surgery and Anesthesia and encourages the anesthesiologist to play a role of leadership in both the hospital and freestanding setting.

I. An ambulatory surgical facility may be hospital-affiliated or freestanding. The facility is established, equipped and operated primarily for the purpose of performing outpatient surgical procedures.
II. ASA Standards, Guidelines and Policies should be adhered to in all areas except where they are not applicable to outpatient care.
III. A licensed physician, preferably an anesthesiologist, must be in attendance in the facility at all times during patient treatment, recovery and until medically discharged.
IV. The facility must be established, equipped, constructed and operated in accordance with applicable local, state and federal laws.
V. Staff shall be adequate to meet patient and facility needs, and consist of:
    A. Professional Staff
        1. Physicians and other practitioners who are duly licensed and qualified.
        2. Nurses who are duly licensed and qualified.
    B. Administration Staff
    C. Housekeeping and Maintenance Staff
VI. Physicians providing medical care in the facility should be organized into a Medical Staff which assumes responsibility for credentials review, delineation of privileges, quality assurance and peer review.
VII. Personnel and equipment shall be on hand to manage emergencies. The facility must have an established policy and procedure concerning unanticipated patient transfer to an acute care hospital.
VIII. Minimal patient care shall include:
    A. Preoperative instructions and preparation.
    B. An appropriate history and physical exam by a physician prior to anesthesia and surgery.
    C. Preoperative studies as medically indicated.
    D. Anesthesia shall be administered by anesthesiologists, other qualified physicians or medically directed nonphysician anesthetists.
    E. Discharge of the patient is a physician responsibility.
    F. Patients who receive other than unsupplemented local anesthesia must be discharged to the company of a responsible adult.
    G. Written postoperative and follow-up care instructions.
    H. Accurate, confidential and current medical records.

APPENDIX: Practice Guidelines for Acute Pain Management in the Perioperative Setting

A Report by the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section

Introduction

Developed by the Task Force on Pain Management, Acute Pain Section: L. Brain Ready, M.D. (Chair), Seattle, Washington; Michael Ashburn, M.D., Salt Lake City, Utah; Robert A. Caplan, M.D., Seattle, Washington; Daniel B. Carr, M.D., Boston, Massachusetts; Richard T. Connis, Ph.D., Woodinville, Washington; Cheryl L. Dixon, M.D., Jacksonville, Florida; Lex Hubbard, M.D., Shreveport, Louisiana; and Linda Jo Rice, M.D., Hartford, Connecticut.

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to revision from time to time, as warranted by the evolution of medical knowledge, technology, and practice. The guidelines provide basic recommendations that are supported by analysis of the current literature and by a synthesis of expert opinion, open forum commentary, and clinical feasibility data (Appendix).

A. Definition of Acute Pain in the Perioperative Setting

Acute pain in the perioperative setting has not been specifically defined in the available literature. The Task Force has not given preference to literature based on any particular system of definition or classification. For these guidelines, acute pain in the perioperative setting is defined as pain that is present in a surgical patient because of preexisting disease, the surgical procedure (*e.g.,* associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.

B. Purpose of Guidelines for Acute Pain Management in the Perioperative Setting

The purpose of these guidelines is to facilitate the efficacy and safety of acute pain management in the perioperative setting and to reduce the risk of adverse outcomes. A number of adverse outcomes can result from undertreatment of postoperative pain. These include (but are not limited to) thromboembolic and pulmonary complications, extension of time spent in an intensive care unit and/or in a hospital, and reduced patient satisfaction. The principal adverse outcomes associated with management of perioperative pain include (but are not limited to) respiratory depression, brain injury, other neurologic injury, sedation, circulatory depression, nausea and/or vomiting, impairment of bowel function, pruritus, and urinary retention.

C. Focus

These guidelines focus on modalities of perioperative pain management that require a higher level of expertise and organizational structure than "as needed" intramuscular or intravenous injections of opioids and that generally provide more effective relief of pain. Examples include (but are not limited to) epidural (and intrathecal) analgesia (EA), intravenous patient-controlled analgesia (Patient-controlled analgesia), and a number of regional analgesic (RA) techniques. The guidelines are not intended as an exhaustive or detailed consideration of specific techniques or all possible approaches.

The specialty of anesthesiology brings an exceptional level of interest and expertise to the area of perioperative

---

pain management. As a consequence, the anesthesiologist is in a unique position to provide leadership in integrating pain management into other aspects of perioperative care and thus improve this area of practice. In this leadership role, the anesthesiologist can contribute further to quality of care by developing and directing institution-wide perioperative analgesia programs that include collaboration with and participation by others, when appropriate.

The role of anesthesiologists in managing acute pain extends beyond the perioperative setting. Patients with severe or concurrent medical illness such as sickle cell crisis, pancreatitis, or acute pain related to cancer or cancer treatment also benefit from aggressive pain control. Labor pain is another condition of interest to anesthesiologists. However, the complex interactions of concurrent medical therapies and physiologic alterations make it impractical to address pain management for these populations within the context of this document.

D. Application

These guidelines focus on management of acute pain in the perioperative setting for adult (including geriatric) and pediatric patients. The guidelines apply to inpatient and outpatient surgery. These guidelines are intended for use by anesthesiologists or by individuals who deliver care under the supervision of anesthesiologists.

Evidence to support each guideline was carefully sought. The search included a comprehensive review of the published literature, surveys of the opinions of a large panel of consultants with expertise in acute pain management, and the opinions of the members of the Task Force. An indication of the strength of the evidence supporting each guideline is provided.

Guidelines

1. Proactive Planning

The Task Force defines proactive planning as a process of integrating pain management into the perioperative care of patients. The literature, the panel of consultants, and the Task Force members strongly support the use of proactive planning for postoperative pain management. This support is based on recognized associations between preoperative and intraoperative analgesic techniques for the reduction of pain in the postoperative period.

Recommendations: An individualized proactive plan (*e.g.,* a predetermined strategy for postoperative analgesia) should be considered for all surgical patients. Factors that may influence the formulation of a proactive plan include (but are not limited to) type of surgery and expected severity of postoperative pain, underlying medical conditions (*e.g.,* presence of respiratory or cardiac disease, allergies), the risk-benefit ratio of the techniques available, and patients' preferences and/or previous experience with pain. Proactive planning of perioperative pain should be part of the preoperative evaluation by the anesthesiologist and, in collaboration with others (*e.g.,* nurses, surgeons, pharmacists), should be part of an institution's general plan for patient care.

Activities that are commonly encompassed by proactive planning include (but are not limited to) (1) obtaining a pain history based on patients' experiences, (2) preoperative pain therapy when appropriate and feasible, (3) intraoperative procedures (*e.g.,* wound infiltration) when appropriate and feasible, and (4) intraoperative or postincisional preparation of patients for postoperative pain management (*e.g.,* initiating EA administration before the completion of surgery). Any treatment plan requires regular assessment and refinement based on the changing responses of individual patients.

II. Education and Training of Hospital Personnel

The available literature suggests that training and experience of hospital personnel (*e.g.,* nurses, house-officers, pharmacists, psychologists) may be helpful in reduction of risk. There is strong agreement among the panel of consultants and the Task Force members that such education, training, and experience also contribute to improved quality of care.

Recommendations: Anesthesiologists offering perioperative analgesia services should provide, in collaboration with others as appropriate, ongoing education and training to ensure that hospital personnel are knowledgeable and skilled with regard to the effective and safe use of the available treatment options within the institution. The scope of education should include topics ranging from basic bedside skills for evaluation of acute pain to an understanding of sophisticated pharmacologic techniques (*e.g.,* PCA, EA, and various RA techniques) and nonpharmacologic techniques (*e.g.,* relaxation, imagery, hypnotic methods). The need for education and training is ongoing as new personnel enter an institution and as modifications in therapeutic approaches are made.

TABLE 1 -- Template 1. Information Recorded on a Bedside Pain Management Flow Sheet

1. Patient assessment at regular intervals
According to institutional protocols (*e.g* ., pain levels, respiratory evaluation, sedation) *
2. Medication administration
Intravenous PCA
Incremental dose
Lockout interval
1 or 4 h limit
Rate of continuous infusion (if applicable)
Supplemental doses for breakthrough pain
Total drug use per unit of time (*e.g* ., nursing shift end total)
Epidural analgesia
Bolus dose and time (if applicable)
Infusion rate (if applicable)
Supplemental doses for breakthrough pain

PCA = patient-controlled analgesia.

*These and other observations may be documented on a separate Vital Signs Flow Sheet.

TABLE 2 -- Template 2. Important Elements of Intravenous PCA Preprinted Orders

1. Drug(s), concentration(s)
2. Pump settings
Incremental dose
Lockout interval
Other limits (*e.g* ., 4 h, 1 h)
3. Mode of use
PCA only
Continuous infusion
4. Initial drug loading instructions
5. Instructions for treating breakthrough pain
6. A statement to eliminate the ordering of CNS depressants by others
7. Monitoring instructions
8. Availability of drugs to treat side effects
9. Instructions for treatment of side effects
Respiratory depression
Nausea and/or vomiting
Pruritus
Urinary retention
10. Instructions about concurrent use of other CNS depressants
11. Instructions for whom to contact if problems occur
12. Date, time, signature

PCA = patient-controlled analgesia; CNS = central nervous system.

TABLE 3 -- Template 3. Important Elements of Epidural Analgesia Preprinted Orders

1. Drug(s), concentration(s)
2. Instructions for administration
   - If boluses
     - Drug dose
     - Interval between injections
   - If infusion
     - Loading dose
     - Infusion rate
3. Instructions for treating breakthrough pain
4. Maintain iv route and access to drugs for immediate use
5. A statement to eliminate the ordering of CNS depressants by others
6. Monitoring instruction
   - For effects of opioids
   - For effects of local anesthetics
     - Bradycardia
     - Hypotension
     - Extensive sensory or motor block
7. Observations that should be communicated to the anesthesiologist (*e.g* ., systolic blood pressure less than --mmHg)
8. Instructions for treatment of side effects
   - Respiratory depression
   - Nausea and/or vomiting
   - Pruritus
   - Urinary retention
9. Instructions about concurrent use of other CNS depressants
10. Instructions for whom to contact if problems occur
11. Date, time, signature

CNS = central nervous system.

III. Education and Participation of Patients and Families in Perioperative Pain Control

The panel of consultants and the Task Force members regard the concept of education of patients and families in planning and participation in perioperative pain control as being important to their comfort and wellbeing.

Recommendations: Anesthesiologists offering perioperative analgesia services should provide, in collaboration with others as appropriate, education to patients and families regarding their roles in achieving comfort, reporting pain, and using the recommended analgesic methods to optimal benefit. Common misconceptions about the risk of side effects and addiction should be dispelled. Educational methods that facilitate optimal care of patients using PCA and other sophisticated methods might include (but are not limited to) discussion of analgesic methods at the time of the preanesthetic evaluation, brochures and video tapes to educate

TABLE 4 -- Template 4. Elements of Intravenous PCA Care by Anesthesiologists

The following items should be included during a bedside evaluation at least once a day while iv PCA is administered.

1. Note the dose of analgesic medication given in the past 24 h, and parameters of PCA settings (PCA bolus dose, lockout interval, basal infusion [if applicable], hourly or other interval limit).
2. Evaluate pain intensity both at rest and with operation-specific convalescent activity (*e.g.,* passive continuous movement for knee replacement or chest physical therapy for thoracotomy). If pain is out of proportion to the surgical procedure, the number of days elapsed postoperatively, and analgesic therapy given, consider whether another cause is present (*e.g.,* surgical complication, personality disorder, opioid tolerance) and initiate appropriate evaluation, including communication with the surgeon and/or other consultant physicians.
3. Determine whether side effects are present. Assess each side effect in the context of the type of operation and days elapsed since the operation. Decide whether the side effect is in proportion to the operation, the number of days postoperatively, and the amount of opioid and other medications given. For sedation, as an example, note other concurrent drug therapy and decide whether to undertake additional workup (*e.g.,* glucose, electrolytes, arterial blood gas, calcium, magnesium, electrocardiogram).
4. Perform a problem-oriented physical examination (*e.g.,* surgical site, presence of rales, venous thrombosis). Note the current vital signs (HR, RR, BP) and compare them with the last evaluation. If these are unstable or unsatisfactory (*e.g.,* low BP or irregular pulse), consider suitable diagnostic workup (*e.g.,* hematocrit, electrocardiogram).
5. Consider whether the patient would benefit from changing the PCA pump settings or the PCA opioid.
6. Note concurrent medications and consider whether the patient would benefit from changing the overall regimen (*e.g.,* simplifying to avert drug interactions), or employing adjuvant analgesic medication or nonpharmacologic therapies, and if so, order these.
7. Evaluate overall patient satisfaction with current care.
8. Evaluate patient's response(s) to prior adjustments of pain therapy or addition of adjuvants (*e.g.,* for nausea or anxiety).
9. Evaluate patient's suitability for making the transition to simpler alternatives (*e.g.,* oral analgesics). *
10. Discuss the assessment and plan with the patient and the patient's nurse and/or surgeon, when appropriate.
11. Document findings, impression, and plan in the hospital chart.
12. Ensure availability of personnel with appropriate expertise to deal with questions or problems at any time.

PCA = patient-controlled analgesia; HR = heart rate; RR = respiratory rate; BP = blood pressure.

*See template 7 on transition from sophisticated techniques to simpler analgesic methods.

See template 6 for an example of a preprinted daily clinical note form.

patients about therapeutic options, and discussion at the bedside during postoperative visits.

IV. Assessment and Documentation of Perioperative Pain Management

The panel of consultants and the Task Force members strongly support the concept of assessment and documentation of response to perioperative pain therapy as important to effective care. Unless the response to pain therapy is regularly evaluated, there is no basis for rational, individualized therapy.

Recommendations: Anesthesiologists offering perioperative analgesia services should use, in collaboration with others as appropriate, pain assessment instruments to facilitate the regular evaluation and documentation of pain, the effects of pain therapy, and side effects caused by the therapy (templates 1 and 6) .

V. 24-Hour Availability of Anesthesiologists

The panel of consultants and the Task Force members support the concept of 24-hour availability of anesthesiologists providing perioperative pain management as being important for maximizing patient comfort and safety. The condition of patients after surgery is frequently dynamic, and analgesic needs may change at any time.

Recommendations: Most analgesic techniques place patients at some risk for side effects or complications that require prompt medical evaluation. Anesthesiologists responsible for perioperative analgesia, in collaboration with others as appropriate, should be available at all times to consult with ward nurses, surgeons, or other involved physicians and assist in evaluating patients who are experiencing problems with any aspect of postoperative pain relief.

VI. Use of Standardized Institutional Policies and Procedures for Ordering, Administering, Discontinuing, and Transferring Responsibility for Perioperative Pain Management

The available literature suggests that institutional protocols and procedures for ordering, administering, discontinuing, and transferring responsibility for pain management are helpful in providing effective and

TABLE 5 -- Template 5. Elements of Epidural Analgesia Daily Care by Anesthesiologists

The following items should be included during a bedside evaluation at least once a day while epidural analgesia is administered.

1. Note the dose of analgesic medication given in the past 24 h, and present parameters of bolus administration or infusion pump settings (if used).
2. Evaluate pain intensity both at rest and with operation-specific convalescent activity (*e.g.,* passive continuous movement for knee replacement or chest physical therapy for thoracotomy). If pain is out of proportion to the surgical procedure, the number of days elapsed postoperatively, and analgesic therapy given, consider whether another cause is present (*e.g.,* surgical complication, personality disorder, opioid tolerance) and initiate appropriate evaluation, including communication with the surgeon and/or consultant physicians.
3. Determine whether side effects are present. Assess each side effect in the context of the type of operation and days elapsed since the operation. Decide whether the side effect is in proportion to the operation, the number of days postoperatively, and amount of opioid and other medications given. For sedation, as an example, note other concurrent drug therapy, as well as the patient's physical status, and decide whether to undertake other workup (*e.g.,* glucose, electrolytes, arterial blood gas, calcium, magnesium, electrocardiogram).
4. Perform a problem-oriented physical examination (*e.g.,* surgical site, presence of rales, venous thrombosis, sensory/motor function). Included in the physical examination should be an examination of the catheter site and brief neurologic evaluation for evidence of catheter-related complications (*e.g.,* change in position, infection, hematoma), as well as an evaluation for cardiovascular stability (especially in patients receiving local anesthetics). Note the current vital signs (HR, RR, BP) and compare them with the last evaluation. If these are unstable or unsatisfactory, consider suitable diagnostic workup (*e.g.,* hematocrit, electrocardiogram).
5. Adjust drug doses, administration interval, infusion pump settings, or change to a different analgesic, as appropriate.
6. Note concurrent medications and consider whether the patient would benefit from changing the overall regimen (*e.g.,* simplifying to avert drug interactions), or employing adjuvant analgesic medications or nonpharmacologic therapies, and if so, order these.
7. Evaluate overall patient satisfaction with current care.
8. Evaluate the patient's response(s) to prior adjustments of pain therapy or addition of adjuvants (*e.g.,* for nausea or anxiety). Make changes in pain and adjuvant therapy as indicated.
9. Evaluate the patient's suitability for making the transition to simpler alternatives (*e.g.,* oral analgesics). *
10. Discuss the assessment and plan with the patient's nurse and/or surgeon, when appropriate.
11. Document findings, impression, and plan in the hospital chart.
12. Ensure availability of personnel with appropriate expertise to deal with questions or problems at any time.

HR = heart rate; RR = respiratory rate; BP = blood pressure.

*See template 7 on transition from sophisticated techniques to simpler analgesic methods.

See template 6 for an example of a preprinted daily clinical note form.

continuous pain control. The Task Force regards the use of institutional policies and procedures as a logical part of interdisciplinary management of perioperative pain, and there is strong agreement from the panel of consultants that this approach is beneficial. The development of hospital-wide policies and procedures helps standardize clinical practice using techniques such as PCA, EA, and various RA techniques (templates 2 and 3). Standardization promotes safety and creates a framework for customization of care. Routine use of bedside documentation encourages caregivers to continually reevaluate pain treatment and respond to inadequate therapy in a timely manner. Daily evaluation, planning, and written documentation by those who are medically responsible for pain relief help establish the importance of a formal and structured approach to pain management (templates 4 - 7).

Recommendations: Anesthesiologists offering perioperative analgesia services should participate in developing, in collaboration with others as appropriate (especially nurses), standardized institutional policies and procedures for ordering, administering, discontinuing, and transferring responsibility for postoperative pain management. Policies (the foundation or "ground rules" for practice) and procedures (outlining the "how to" aspects of applying policies to patient care) should be readily available on each patient care unit. The polices and procedures also serve as ongoing educational and informational references.

VII. Use of Three Specific Techniques for Perioperative Pain Management

The literature strongly supports the efficacy and safety of three techniques used by anesthesiologists for the control of pain in the perioperative setting: (1) PCA with systemic opioids, (2) EA with opioids or opioid/local anesthetic mixtures (or intrathecal opioids), and (3) RA techniques, including (but not limited to) intercostal blocks, plexus infusions, and local anesthetic infiltration of incisions. The literature

TABLE 6 -- Template 6. Preprinted Daily Clinical Note Form

TECHNIQUE

PCA

Opioid:
morphine
meperidine
hydromorphone
other

Concentration: mg/ml

Incremental dose mg Lockout min

Infusion mg/h
Continuous
Night only

Total opioid use mg/8 h

Epidural

Bolus mg/ h
Infusion ml/h

Opioid

Morphine(1 mg/ml)
Meperidine(2 mg/ml)
Fentanyl (4 mug/ml)
Other

Local anesthetic

Bupivacaine 0.0625%
Bupivacaine 0.125%
Other

Other care

Problem-oriented history and physical examination

Pain levels (0-10 scale)

At rest With activity
Patient unable to report

Patient satisfied with current pain management
Yes
No

Epidural catheter Vital signs

Site clean and nontender
Yes
No Satisfactory
Yes
No

Removed intact

Neurologic function

Sensory or motor block is limiting function
Yes
No

Side effects: (0 = absent; 1 = present, no treatment needed; 2 = present, treatment effective; 3 = present, treatment not effective)

Respiratory depression N & V Pruritus

Urinary retention Sedation

Treatment plan

Continue present therapy to maintain control of severe pain.

Modify present therapy to improve control of severe pain.

Discontinue present therapy; analgesia to be provided by primary care team.

Comments

Patient seen and examined.

Date Time Signature M.D.

---

indicates that these three techniques used by anesthesiologists have no higher incidence of side effects than less effective techniques for perioperative pain management. The panel of consultants and the Task Force members strongly support the use of PCA, EA, and RA by anesthesiologists when appropriate and feasible.

Recommendations: To meet the diverse needs of individual patients, anesthesiologists who manage perioperative pain should make available as appropriate a variety of effective therapeutic options such as PCA, EA, and RA.

VIII. A Multimodality Approach to Perioperative Pain Management

During the administration of anesthetics for surgery, the needs of many patients may best be met by taking advantage of the combined effects of a number of

TABLE 7 -- Template 7. Considerations in Making the Transition of Pain Therapy from More Sophisticated Techniques (*e.g.,* PCA, EA, RA) to Less Sophisticated Techniques (*e.g.,* oral analgesics)

1. Review the efficacy and dose requirement of the sophisticated technique.
2. Consider the pain expected following the transition: type of procedure, level of activity (including physical therapy), and other sources of discomfort (*e.g.,* nasogastric tube).
3. Review the patient's past experience with oral analgesics. What has been effective? What has caused side effects?
4. Based on the above information, use the simple technique with an analgesic drug and dose calculated to provide adequate analgesia. Adjust the dose as needed based on regular assessment.
5. Overlap therapy during the transition, *i.e.*, do not discontinue the original therapy until the replacement has reached a therapeutic effect.
6. Provide for treatment of "breakthrough" pain during use of the simpler method.
7. If there is to be a change in responsibility for prescribing an analgesic (*e.g.,* the surgeon assumes responsibility for an oral analgesic), be sure the change is clearly understood and that orders are available from the new therapist.
PCA = patient-controlled analgesia; EA = epidural analgesia; RA = regional analgesic techniques.

agents. Similarly, there is growing conviction that a multimodality approach (*i.e.,* two or more analgesic agents or techniques used in combination) to providing postoperative analgesia has advantages over the use of a single modality.

The literature supports the efficacy of two or more analgesic techniques (including nonpharmacologic methods) used in combination for the control of perioperative pain, especially when different sites and/or mechanisms of action are involved and/or when synergy of effect is achieved. In addition, the literature indicates that multimodality approaches are associated with side effects no greater than those resulting from single analgesic techniques for perioperative pain management. The panel of consultants and the Task Force members support the use of multimodality techniques when appropriate and feasible.

Recommendations: Anesthesiologists managing perioperative pain should make available as appropriate a variety of analgesic techniques and should consider their use in combination under appropriate circumstances.

IX. An Organized Interdisciplinary Approach to Perioperative Pain Management

Although dedicated individuals can improve perioperative pain control for the individual patients they treat, comprehensive programs provide optimal analgesia throughout an institution. Such programs have been advocated by national and international pain specialty societies [1] [2] and the Federal government. * The Task Force strongly believes that, based on training, knowledge, skills, interest, and historical innovation, anesthesiologists are uniquely qualified to provide leadership within their institutions in developing and managing perioperative pain management programs.

TABLE 8 -- Template 8. Organizational Aspects of an Anesthesiology-based Postoperative Pain Program.

1. Education (initial, updates)
Anesthesiologists
Surgeons
Nurses
Pharmacists
Patients and families
Hospital administrators
Health insurance carriers
2. Areas of regular administrative activity
Maintenance of clear lines of communication
Human resources: 24-hour a day availability of pain service personnel.
Evaluation (including safety) of equipment (*e.g.,* pumps)
Secretarial support
Economic issues
Continuing quality improvement (CQI)
Resident physician teaching (if applicable)
Pain management-related research (if applicable)
3. Collaboration with nursing services
Job description for pain service nurse (if applicable)
Nursing policies and procedures
Nurses' in-service and continuing education
Definition of roles in patient care
Institutional administrative activities
Continuing quality improvement (CQI)
Research activities (if applicable)
4. Elements of documentation
Preprinted orders
Policies
Procedures
Bedside pain management flow sheet
Daily consultation notes
Educational packages

*Clinical Practice Guideline--Acute Pain Management: Operative or Medical Procedures and Trauma, Agency for Health Care Policy and Research. Co-chairs Carr DB. Jacox AK. Washington, D.C., U.S. Department of Health and Human Services, 1992. Available by calling 1-800-358-9295.

The panel of consultants and the Task Force members regard organized interdisciplinary activities (*e.g.,* anesthesiologists in collaboration with nurses, surgeons, and pharmacists) as important and optimal in providing effective, safe, and continuous perioperative pain control (template 8) . An essential feature of such an approach should be an ongoing strong working relationship between anesthesiologists and nurses.

Recommendations: Anesthesiologists who manage perioperative pain should develop (in collaboration with nurses, surgeons, pharmacists, and others) an organized, interdisciplinary approach to perioperative pain management within their institutions.

/das/book/view/29494766/875/1071.html

X. Recognition and Management of Special Features of Pediatric Perioperative Pain Management.

Pediatric patients (infants and children) present unique problems regarding perioperative pain management for reasons that include differences in the perception of care-givers regarding the need for analgesia, differences in the pharmacology of analgesic medications when used in this group, and the strong emotional components of pain in children. In the past, safe methods for providing analgesia have been underused in pediatric patients because of fear of opioid-induced respiratory depression.

The emotional component of pain is very strong in children. Absence of parents, security objects, and familiar surroundings may be perceived by the child to be as painful as the surgical incision. When clear evidence of physical pain is not seen, the tendency of health-care providers is to assume pain is not present and therefore defer treatment. In addition, young childrens' fear of injections makes intramuscular opioids or other methods, which themselves cause discomfort, less acceptable to this group than to adults. Many children will choose to suffer in silence knowing that an expression of pain will result in a dreaded injection.

Pain assessment is more difficult in children because, as they grow and develop, cognitive and emotional responses are different from adults and are constantly changing. Special instruments are available to assist young children in self-reporting of pain, and behavioral and physiologic parameters can be employed to assess preverbal children or in those who cannot self-report.

The literature strongly supports the effectiveness of a variety of techniques in providing analgesia in pediatric patients. Many of these are the same techniques used in adults, although some techniques (*e.g.,* caudal analgesia) are more commonly used in children. There is strong agreement among the panel of consultants and the Task Force members that it is important to recognize that pediatric patients represent a unique population with special features when planning and providing perioperative analgesia.

Recommendations: Anesthesiologists who treat perioperative pain in pediatric patients should be familiar with the special features of this group. Based on that knowledge, pharmacologic and nonpharmacologic strategies for perioperative analgesia appropriate for the age of the child should be offered in a manner that promotes efficacy and safety.

XI. Recognition and Management of Special Features of Geriatric Perioperative Pain Management

Elderly patients are a unique population facing surgery. They may experience physical and mental limitation and may have different attitudes than younger patients with regard to expressing pain and appropriate therapy for it. Altered physiology with aging changes the way analgesic drugs and local anesthetics are distributed and metabolized, frequently necessitating alterations in dosing. There is strong agreement from the panel of consultants and the Task Force members on the importance of recognizing the unique features of geriatric patients in planning and providing perioperative analgesia.

The literature indicates that single and multimodality techniques that have been shown to be effective in younger adult patients are also effective (often with reduced drug dose requirements) in geriatric patients without increasing side effects.

Recommendations: Anesthesiologists who treat perioperative pain in geriatric patients should be familiar with the special features of this group. In particular, dose reduction for drugs that may cause central nervous system depression should be considered.

XII. Recognition of Special Features of Perioperative Pain Management in Ambulatory Surgery Patients

The increasing trend toward ambulatory surgery poses special problems in perioperative pain management. One of the most common reasons for unanticipated hospital admission in this population is inadequate pain control. Analgesic techniques must provide safe, ade-quate

pain relief for patients who quickly leave the supervised hospital environment. Techniques such as EA and intravenous PCA, which require special nursing and monitoring, are not suitable for such patients, but others such as local anesthetic wound infiltration and oral nonsteroidal antiinflammatory drugs may be very effective.

The panel of consultants and the Task Force members strongly agree that the provision of effective analgesia to ambulatory surgery patients is important and beneficial. A limited search of this evolving literature suggests that planning of perioperative analgesia for ambulatory patients including the use of certain procedures (*e.g.,* local anesthetic wound infiltration and certain RA techniques) may improve analgesia without increasing the risk of side effects.

Recommendations: Anesthesiologists who care for ambulatory surgery patients should proactively plan therapeutic strategies appropriate for them, recognizing that they are expected to leave the surgical facility within a few hours after the completion of surgery.

The Task Force thanks those who responded to surveys on acute pain in the perioperative setting, reviewed guideline drafts, contributed oral and written testimony to the Open Forum, and participated in tests of clinical feasibility.

The development of these guidelines included methods recommended in the following publications: (1) Clinical Practice Guidelines--Directions for a New Program, Committee to Advise the Public Health Service on Clinical Practice Guidelines, Division of Health Care Services, Institute of Medicine. Edited by Field MJ, Lohr KN. Washington, D.C., National Academy Press, original document 1990, summary document 1992; and (2) Woolf SH: Manual for Clinical Practice Guideline Development. Washington, D.C., U.S. Department of Health and Human Services, Agency for Health Care Policy and Research, publication number 91-0007, March 1991.

Appendix: Assessment of Scientific Evidence and Consultant Opinion

The scientific assessment was based on the following statements or evidence linkages. These linkages represent directional hypotheses about relationships between perioperative pain management and clinical outcomes.

1. Proactive planning for perioperative pain management improves pain control and reduces adverse outcomes.
2. Education and training of hospital personnel improve pain control and reduce adverse outcomes.
3. Education and participation of patients and families improve pain control and reduce adverse outcomes.
4. Monitoring and documentation activities improve pain control and reduces adverse outcomes.
5. Availability of anesthesiologists providing perioperative pain management improves pain control and reduces adverse outcomes.
6. Standardized institutional policies and procedures for perioperative pain management improve pain control and reduce adverse outcomes.
7. Use of PCA, EA, or RA techniques improves pain control and reduces adverse outcomes.
8. Use of multimodality techniques improves pain control and reduces adverse outcomes.
9. Organizational characteristics related to perioperative pain management improve pain control and reduce adverse outcomes.
10. Pediatric perioperative pain management techniques improve pain control and reduce adverse outcomes.
11. Geriatric perioperative management techniques improve pain control and reduce adverse outcomes.
12. Ambulatory surgery acute pain management techniques improve pain control and reduce adverse outcomes.

Scientific evidence was derived from aggregated research findings, including metaanalyses, and from surveys, open forum presentations, and other consensusoriented activities. For purposes of literature aggregation, potentially relevant clinical studies were identified *via* electronic and manual searches of the literature. The search covered a 27-yr period from 1966 through 1993. More than 4,000 articles were identified initially, yielding 465 nonoverlapping articles that addressed the 12 evidence linkages. Studies that could not be analyzed statistically were reviewed and eliminated, yielding 233 articles used in the formal metaanalyses.

A directional result for each study was determined initially by classifying the outcome as (1) supporting a linkage, (2) refuting a linkage, or (3) neutral. The results were averaged to obtain a directional assessment of support for each linkage. The literature relating to linkages 1, 7 (PCA, EA, and RA as separate assessments), 8, 10, and 11 contained enough studies with well defined experimental designs and statistical information for formal metaanalysis. Combined probability tests were applied to continuous data, and an odds-ratio procedure was applied to dichotomous study results.

Two combined probability tests were employed as follows: (1) the Fisher combined test, producing chisquare values based on logarithmic transformations of the reported *P* values from the independent studies, and (2) the Stouffer combined test, providing representation of the studies by weighting each of the standard normal deviates by the sample size. A procedure based on the Mantel-Haenszel method for combining study results using 2 × 2 tables was used when sufficient outcome frequency information was available. An acceptable significance level was set at $P < 0.01$ (onetailed), and effect-size estimates were calculated. Interobserver agreement was established through assessment of interrater reliability testing. Tests for heterogeneity of the independent samples were conducted to ensure consistency among the study results. To control for potential publishing bias, a "fail-safe N" value was calculated for each combined probability test. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Significance levels from the weighted Stouffer combined tests for pain reduction were as follows: linkage 1 ($P < 0.001$, linkage 7 (PCA $P < 0.001$), EA ($P < 0.001$), and RA ($P < 0.001$)), and linkage 8 ($P < 0.003$), linkage 10 ($P < 0.004$), and linkage 11 ($P < 0.001$). Weighted effect size estimates ranged from r = 0.14 to r = 0.35, demonstrating small-to-moderate effect size estimates. Significance levels for all beneficial/adverse outcomes were $P > 0.01$ (*i.e.,* not significant). Tests for heterogeneity/homogeneity of statistical tests and of effect size estimates were nonsignificant in all cases ($P > 0.01$), indicating that the various studies provided common estimates of the population effect sizes for the linkages. Agreement among the Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a Kappa statistic for two-rater agreement pairs were as follows: (1) type of study design, kappa = 0.61-0.65; (2) type of analysis, kappa = 0.65-0.87; (3) evidence linkage assignment, kappa = 0.60-0.74; and (4) literature inclusion for database, kappa = 0.22-0.64. Three-rater chance-corrected agreement values were: (1) design, $S_{av} = 0.62$, Var (S_{av}) = 0.16; (2) analysis, $S_{av} = 0.76$, Var (S_{av}) = 0.15; and (3) linkage, $S_{av} = 0.65$, Var (S_{av}) = 0.12. These values represent moderate to high levels of agreement.

The findings of the literature analyses were supplemented by survey of opinions from a panel of 65 consultant anesthesiologists with expertise in acute pain in the perioperative setting and from the opinions of the Task Force members. Consultants were highly supportive of the linkages (*i.e.,* agreed that they resulted in improvement in pain control, reduced adverse side effects, and were important issues for the guidelines to address). The percentage of consultants supporting each linkage based on these criteria were 1 (86%), 2 (98%), 3 (71%), 4 (78%), 5 (79%), 6 (75%), 7 (74%), 8 (60%), 9 (78%), 10 (86%), and 11 (81%). Linkage 12 was added to the guidelines after completion of the consultant survey.

The feasibility of implementing these guidelines into clinical practice was assessed using a survey of opinions from a panel of 61 consultant anesthesiologists with expertise in acute pain in the perioperative setting. Analysis of the responses indicated that these guidelines can be implemented in a large majority of institutions with minimal additional cost.

Eighty-nine percent of the consultant anesthesiologists indicated that implementation of the guidelines would not result in the need to purchase new equipment, supplies, or pharmaceuticals. Mean estimate of guideline implementation costs for all respondents was $ 3,705 (range 0 to $ 100,000). Among the 11% who stated that purchases would be required, the median anticipated cost was $ 15,000 (mean $ 32,286, range = $ 6,000-100,000). Anticipated new equipment consisted of PCA pumps, epidural pumps, and PCA/epidural disposable equipment.

The consultant anesthesiologists were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the guidelines were instituted. The percent of consultants expecting no change associated with each linkage were as follows: proactive planning 82%; education and training 89%; education and participation of patients and families 80%; monitoring and documentation 77%; availability

---

of anesthesiologist 90%; institutional policies and procedures 87%; use of PCA, EA, and RA techniques 90%; use of multimodality techniques 89%; organizational characteristics 90%; pediatric techniques 95%; geriatric techniques 92%; and ambulatory surgery techniques 85%.

Sixty-four percent of the respondents indicated that the guidelines would have no effect on the amount of time spent on a typical case. None reported that the guidelines would reduce the amount of time spent per case. For all respondents, the mean increase in the amount of time spent on a typical case was 3.4 min. Of the 36% of respondents who reported an anticipated increase in time spent on a typical case, the mean was 9.7 min (range 3.0-30.0 min).

References

1. Max MB, Donovan M, Portenoy RK: American Pain Society Quality Assurance Standards for Relief of Acute Pain and Cancer Pain, Committee on Quality Assurance Standards, American Pain Society, Proceedings of the VIth World Congress on Pain. Edited by Bond MR, Charlton JE, Woolf GJ. New York, Elsevier, 1991, pp 185-189

2. Management of Acute Pain: A Practical Guide, Task Force on Acute Pain, International Associate for the Study of Pain. Edited by Ready LB, Edwards WT. Seattle, IASP, 1992

Readers with special interest in the statistical analyses used in establishing these guidelines can receive further information by writing to: L. Brian Ready, M.D., F.R.C.P.(C), Professor, Department of Anesthesiology, RN-10, Director, UWMC Acute Pain Service, University of Washington School of Medicine, Seattle, Washington 98195.

APPENDIX: Practice Guidelines for Chronic Pain Management[D]

A Report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section

PRACTICE guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. The Guidelines provide basic recommendations that are supported by analysis of the current literature and by a synthesis of expert opinion, open forum commentary, and clinical feasibility data (appendix).

A. Definition of Chronic Pain

For these Guidelines, *chronic pain* is defined as persistent or episodic pain of a duration or intensity that adversely affects the function or well-being of the patient, attributable to any nonmalignant etiology. The Task Force has not given preference to literature based on any particular system of definition or classification of chronic pain.

B. Purpose of Guidelines for Chronic Pain Management

The purpose of these Guidelines is to 1) optimize pain control, recognizing that a pain-free state may not be achievable, 2) minimize adverse outcomes and costs, 3) enhance functional abilities and physical and psychological well-being, and 4) enhance the quality of life for patients with chronic pain.

C. Focus

These Guidelines focus on the knowledge base, skills, and range of interventions that are the essential elements of effective management of chronic pain and pain-related problems. The Guidelines recognize that the management of chronic pain occurs within the broader context of health care, including psychosocial function and quality of life.

The Guidelines recognize that all anesthesiologists may not have access to the same knowledge base, skills, or range of modalities. However, aspects of these Guidelines may be helpful to anesthesiologists who manage patients with chronic pain in a variety of practice settings.

The decision to implement a particular management approach should be based on a comprehensive assessment of the patient's overall health. The Guidelines recognize that accurate diagnosis and appropriate therapies used to modify the underlying causes of pain may improve analgesia and outcome. The risks and benefits of therapies designed to modify or correct the underlying cause(s) of pain is outside the scope of these Guidelines. Although headache is included in the definition of chronic pain, these Guidelines are not specifically intended for the management of headache. The literature search was not comprehensive with respect to headache, but the general principles of these Guidelines may be applied to the management of headache.

D. Application

These Guidelines are intended for use by anesthesiologists and health care personnel who deliver care under the direct supervision of anesthesiologists. The Guidelines

Developed by the Task Force on Pain Management, Chronic Pain Section: Peter R. Wilson, M.B.B.S., Ph.D. (Chair), Rochester, Minnesota; Robert A. Caplan, M.D., Seattle, Washington; Richard T. Connis, Ph.D., Woodinville, Washington; Hugh C. Gilbert, M.D., Chicago, Illinois; Eric J. Grigsby, M.D., Napa, California; J. David Haddox, D.D.S., M.D., Atlanta, Georgia; Alan M. Harvey, M.D., M.B.A., Springfield, Massachusetts; Wilhelmina C. Korevaar, M.D., Bala Cynwyd, Pennsylvania; Timothy R. Lubenow, M.D., Chicago, Illinois; and Dana L. Simon, M.D., West Des Moines, Iowa.

do not compare the relative effectiveness of different interventions. They are not intended to provide treatment algorithms for specific pain syndromes. Complementary therapies are beyond the scope of these Guidelines.

Guidelines

I. A Comprehensive History and Physical Examination of the Patient with Chronic Pain

The literature suggests that a comprehensive history and physical examination be conducted. The Task Force and panel of consultants support the conduct of a comprehensive pain-related history and physical examination.

Recommendations: General Constructs. The Task Force identifies four fundamental issues that should guide a comprehensive history and physical examination of the patient with chronic pain.

1. The patient's general medical condition and extent of concurrent medical and surgical diagnoses.
2. Knowledge of chronic pain syndromes is a necessary prerequisite for conducting a chronic pain evaluation. Chronic pain syndromes may be related to pathology or dysfunction in one or more organ systems or to psychological conditions. In addition, knowledge of other medical or surgical conditions that may present with pain and may mimic chronic pain syndromes also is necessary.
3. Knowledge of the diagnosis and management of painful crises.
4. Knowledge of the diagnosis and management of medical emergencies and complications arising from the underlying cause or treatment.

Elements. The Task Force identifies five essential features of a comprehensive evaluation and treatment plan (template 1).

Figure Template 1. Algorithm for Comprehensive Evaluation and Longitudinal Assessment of Chronic Pain.

1. History. A complete pain history includes a general medical history with emphasis on the chronology and symptomatology of the presenting complaint. The data should include information about the onset, quality, intensity, distribution, duration, course and affective components of the pain, and details about exacerbating and relieving factors. Additional symptoms (*e.g.,* motor, sensory, and autonomic changes) should be noted. Information regarding previous diagnostic tests, results of previous therapies, and current therapies should be reviewed by the anesthesiologist (template 2).
2. Physical examination. The physical examination should include an appropriate, directed neurologic and musculoskeletal evaluation, with attention to other systems as indicated. Not only the cause(s) of the pain, but also the effects of the pain, such as physical deconditioning, should be evaluated and recorded.
3. Psychosocial evaluation. The psychosocial evaluation should include information about the presence of psychological symptoms (*e.g.,* anxiety, depression, or ranger), psychiatric disorders, personality traits or states, coping mechanisms, and the meaning of the pain. Evidence of family, vocational, or legal issues and involvement of rehabilitation agencies should be noted. The expectations of the patient, significant others, employer, attorney, and other agencies (*e.g.,* Workers' compensation, Social Security Administration) also should be determined.
4. Impression and differential diagnosis. The previous findings should be used to determine the possible etiologies and effects of the pain (template 3 (Table Not Available)).
5. Treatment plan. Once a working diagnosis has been determined, a treatment plan is formulated with input from the patient, other involved professionals, and other involved persons (e.g., significant others

or qualified rehabilitation counselors). Treatment and outcome goals should be discussed with the patient.

Template 2. History Review--Sample Form

Patient:		Physician:	
Date:	Referred:	Time in:	Time out:
Chief complaint:			
History of present illness	Pain from onset to present:		
	Location	Past medical history	
	Quality	Illnesses	
	Severity	Operations	
	Duration	Injuries	
	Timing	Treatments	
	Context	Medications	
	Modifying factors	Family history	
	Associated signs/symptoms	Social history	
Review of symptoms			
	Constitutional symptoms	Integumentary	
	Eyes	Neurologic	
	Ear, nose, mouth, throat	Psychiatric	
	Cardiovascular	Endocrine	
	Respiratory	Hematologic/Lymphatic	
	Gastrointestinal	Allergic/Immunologic	
	Genitourinary		
	Musculoskeletal	Drug reactions	

/das/book/view/29494766/875/1081.html

II. Diagnostic Evaluation

The literature is supportive of the conduct of a diagnostic evaluation for chronic pain. The panel of consultants and Task Force members also support diagnostic evaluation for purposes of determining potential etiologies of chronic pain and for identification of pain sites for treatment. The use of diagnostic local anesthetic blockade is suggested by the literature and supported by the Task Force.

Recommendations: Anesthesiologists treating chronic pain should have a working knowledge of the utility and interpretation of diagnostic evaluations, including diagnostic neural blockade, imaging modalities, pharmacodiagnosis, electrodiagnosis, and laboratory studies. Diagnostic evaluation is an essential addition to the history and physical examination in the evaluation of patients with chronic pain. The treatment plan, contingencies, and plan for reassessment should be formulated based on these sources of clinical data.

Neural blockade with local anesthetic, including somatic and autonomic blocks, may be useful in determining the site and etiology of chronic pain. Anesthesiologists have unique skills in this area that may benefit carefully selected patients. Anesthesiologists should personally review and interpret diagnostic data when clinically indicated.

III. Counseling and Coordination of Care

There is insufficient literature to suggest that the anesthesiologist's role in counseling and coordination of care is associated with improved analgesia or other health effects. The Task Force and consultants are supportive of the effectiveness of counseling and appropriate coordination of care in improving analgesia and quality of life.

Recommendations: Anesthesiologists should provide appropriate counseling of the patient regarding the pain syndrome diagnosis, treatment options, rehabilitation, and follow-up goals. In addition, the anesthesiologist should coordinate care with other health professionals, rehabilitation and vocational agencies, and social and legal entities. Longitudinal assessments of outcome should be maintained.

IV. Periodic Monitoring and Measurement of Clinical Outcomes

There is insufficient literature to evaluate the effectiveness of periodic pain assessment in chronic pain management. Multiple times of measurements, fluctuating patient and disease status, and variable interventions over time are confounding factors that make useful analysis difficult. The Task Force and consultants support the contention that periodic monitoring of the effects of therapy and patient status will result in improved

Template 3. Elements of Medical Decision-making for Treatment of Chronic Pain*

(Not Available)

* *Adapted from the Physician's Current Procedural Terminology (CPT), American Medical Association, 1996 Edition.*

pain management and reduced adverse health effects from therapy.

Recommendations: Accurate and complete records of pain therapies should be maintained. Reports of pain made by the patient should be the primary source of pain assessment (template 4) and should be obtained at periodic intervals. Periodic monitoring may include, but is not limited to, a patient's verbal report of treatment efficacy, other pain records (*e.g.,* pain diaries), and reports of side effects associated with pain management. Analyses of aggregate outcomes are essential to continuous quality improvement of chronic pain management in the clinical setting.

V. Multidisciplinary Pain Management

For these Guidelines, multidisciplinary care includes, but is not limited to 1) contributions to patient pain care by more than one health care discipline, 2) a process or program of pain care by more than one health care discipline, or 3) a combination of 1 and 2.

The literature does not provide a standard definition for multidisciplinary care. The available literature was only sufficient to address multidisciplinary care on a programmatic basis. This literature is supportive of the efficacy of multidisciplinary programs in providing analgesia and improvement of health status (*e.g.,* functional status, quality of life). The panel of consultants and Task Force members endorse multidisciplinary chronic pain management.

The literature, Task Force, and consultants also support programs that emphasize the reduction or elimination of pain medications as a primary objective of therapy (*i.e.,* through use of physical therapy, biofeedback, behavior modification, or other psychosocial techniques).

Recommendations: Anesthesiologists offer a unique contribution to patient care in the context of multidisciplinary chronic pain management. Anesthesiologists should be involved in patient evaluation, provision and interpretation of diagnostic procedures, clinical pharmacology, provision of alternative drug delivery methods, provision of temporary or long-term neural blockade, and provision of neuromodulatory techniques.

Figure Template 4. Pain Intensity Scales.

VI. Multimodality Pain Management

For these Guidelines, *multimodal therapy* is defined as concomitant use of separate therapeutic interventions under the direction of a single practitioner to obtain additive beneficial effects or reduction of adverse effects. Examples include, but are not limited to 1) the use of neural blockade with medications, 2) rehabilitative therapies (*e.g.,* physical therapy) with neural blockade or medications, and 3) medications of different categories (template 5).The literature suggests that concomitant application of separate therapeutic interventions in chronic pain management provides effective analgesia. The literature on other health effects is equivocal. The panel of consultants and Task Force members also are supportive of the efficacy of multimodality techniques for the management of chronic pain.

Recommendations: Multiple modalities, such as the combined use of neural blockade, medications, or rehabilitative therapies should be considered when analgesia with acceptable adverse effects is no longer attained with single modalities. Ideally, each modality should be administered as appropriate to achieve the desired therapeutic effect. A multimodal approach may reduce the potential for adverse effects arising from either escalating frequency or dosage levels of a single modality.

VII. Adjuvant Analgesics: Antidepressants, Membrane Stabilizing Agents, and Nonsteroidal Antiinflammatory Drugs (NSAIDs)

The literature supports the use of antidepressants for reducing chronic pain without notable adverse effects. The literature also supports the use of antidepressants for providing overall health benefits and for improving mood. The literature supports the benefits of membrane

Template 5. Elements of Multimodality Pain Management and Therapeutic Options for Treatment

Elements
1. Comprehensive speciality pain history and physical examination.
2. Personal review of previous consultations, examinations, and diagnostic studies (e.g., radiographs, scans, laboratory data).
3. Discussion or communication with patient's other physicians and allied health care professionals (e.g., rehabilitation counselor).
4. Indicated laboratory or radiologic diagnostic testing procedures (e.g., radiograph, CT scan, MRI, three-phase bone scan, sedimentation rate, ANA).
5. Indicated diagnostic, clinical interventions, procedures, surgical consultation, psychosocial evaluation.
6. Formulation of an appropriate and specific diagnosis.
Options
Physical therapies
Active and passive range of motion
Tone and strengthening
Desensitization
Other
Medications
NSAIDs
Antidepressants
alpha-adrenergic antagonist
Membrane stabilizing drugs
Opioids
Neural blockade
Somatic, sympathetic, neuraxial
Local single injection technique
Continuous infusion-catheter techniques
Local anesthetic, opioid, steroid, other
Neuroablation (chemical, thermal)
Neuroaugmentation
Transcutaneous electrical nerve stimulation (TENS)
Peripheral nerve stimulation (PNS)
Spinal cord stimulation (SCS)
Biofeedback-relaxation technique

stabilizing agents (*i.e.,* anticonvulsants) and NSAIDs for providing analgesia but is equivocal regarding other health effects. The Task Force and consultants are supportive of the use of antidepressants, membrane stabilizing agents, and NSAIDs for providing analgesic and health benefits.

Recommendations: Antidepressants are useful medications for the reduction of pain and improvement of sleep. The specific agent and the dosage should be optimized for each patient. The beneficial and adverse effects should be monitored. NSAIDS and membrane stabilizing agents (*e.g.,* anticonvulsants) also may be used for the reduction of pain. As with antidepressants, the specific agent and dosage should be optimized for each patient, with periodic monitoring of beneficial and undersirable health effects.

VIII. Regional Sympathetic Blockade

The literature suggests that regional sympathetic blockade (*e.g.,* lumbar sympathetic block, stellate ganglion block, intravenous regional block) is effective in providing analgesia and is equivocal regarding beneficial or adverse health effects. The Task Force and panel of consultants are supportive of the analgesic benefits of regional sympathetic blockade. The Task Force and panel of consultants are equivocal regarding potentially beneficial or adverse health effects (*e.g.,* hypotension, hyperalgesia, sensory and motor deficit).

Recommendations: The adequacy of sympathetic blockade should be objectively assessed and recorded. Appropriate sympathetic blockade by the anesthesiologist should be provided within the context of the patient's overall treatment plan. To ensure the judicious use of sympathetic blockade, periodic monitoring should be conducted to assess analgesic benefit and adverse effects (*e.g.,* sensory or motor block; failed blockade of sympathetic outflow, especially to the upper extremity; local anesthetic toxicity; site infections).

IX. Corticosteroid Injection Therapy

The literature suggests that locally injected corticosteroids are effective in providing analgesia. The literature is equivocal regarding other health effects. The panel of consultants support the importance of locally injected corticosteroids in improving analgesia and enhancing patient functioning and quality of life. The consultants are equivocal regarding the adverse effects of corticosteroids.

Recommendations: Local injection of corticosteroids by the anesthesiologist should be provided within the context of the patient's overall treatment plan. A directed neurologic evaluation should precede the local injection of corticosteroids. Appropriate follow-up evaluation is necessary to monitor health effects, including analgesia, function, and adverse effects on local tissues and the hypothalamic-pituitary-adrenal axis.

X. Neurostimulation Therapy

The literature is supportive of transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS) techniques in providing analgesia and is suggestive of the analgesic benefit of peripheral nerve stimulation (PNS) techniques. The literature is equivocal regarding the beneficial or adverse health effects of TENS, PNS, and SCS. The Task Force and panel of consultants are supportive of neurostimulation therapy for analgesia.

Recommendations: An office or home trial of TENS should be considered as an early management option because of its low complexity and low risk. TENS also may be considered as adjunctive therapy.

Peripheral nerve stimulation should be reserved for patients with a peripheral monoeuropathy who have responded to a diagnostic sequence of local neural blockade and a stimulation trial.

Spinal cord stimulation should not be a first-line treatment but may be considered after failure of oral medications. SCS may be effective in the management of patients with peripheral neuropathic pain or with pain arising from the spinal cord (*e.g.,* arachnoiditis, syringomyelia, spinal cord injury, multiple sclerosis). It should be preceded by a trial with a percutaneous electrode system.

XI. Opioid Therapy

Opioid therapy for chronic pain management may be administered by several routes, the most common being systemic delivery (*e.g.,* oral, transdermal, or intravenous). Opioids also may be delivered directly to the neuraxis (*e.g.,* epidural, intrathecal). The relative merit of systemic versus neuraxial opioid administration for chronic pain management was not addressed in the these guidelines.

The literature supports the analgesic efficacy of systemic opioids. However, the literature suggests that systemic use of opioids may be associated with increased risk of adverse sequelae (*e.g.,* tolerance, dependence, pruritus, nausea, and respiratory depression).

The literature suggests that neuraxial delivery of opioids for chronic pain is associated with effective analgesia

---

and is equivocal regarding adverse effects. The consultants are supportive of the analgesic benefits of opioid therapies and are equivocal regarding adverse effects.

Recommendations: Opioid therapy may be considered when analgesia provided by other modalities (*e.g.,* NSAIDs, TENS) is no longer adequate to manage chronic pain. Systemic or neuraxial opioids should be administered on the basis of patient need. Delivery of opioids should occur within the context of a logistic system that provides the resources and availability of personnel to respond to patient needs and according to applicable local, state, and federal regulations. The analgesic benefits of opioids should be balanced against the potential adverse sequelae of long-term opioid use. Patients treated with opioids for chronic pain may require frequent follow-up evaluation. A controlled substance agreement or a second opinion from another provider with expertise in pain management may be considered.

XII. Neuroablative Techniques

Neuroablative techniques destroy neural tissue using chemicals (e.g., alcohol or phenol) or thermal lesions (e.g., radiofrequency or cryoneurolysis). The literature suggests that chemical and thermal neuroablative techniques can provide some control of chronic pain and reduction in regional sympathetic overactivity. Severe adverse health effects from treatment are possible but reported rarely. There is insufficient literature regarding the value of prognostic neural blockade before neuroablative techniques. The Task Force and consultants are supportive of the value of neurolytic techniques in symptom management and are neutral regarding other health effects.

Recommendations: Neuroblation should be preceded by confirmation of needle placement using local anesthetic, imaging, or electrical stimulation. Successful temporary blockade does not guarantee the success of subsequent neuroablation. Although the reported incidence of adverse effects of neuroblative techniques is very low, the impact on the patient may be catastrophic. Reported adverse effects include motor, sensory, and autonomic dysfunction (*e.g.,* paralysis, deafferentation pain, loss of sphincter control, or impotence), regeneration pain, and neuralgias. Neuroablative techniques should be used as part of a comprehensive approach to managing pain and applied only as a last resort after failure of other therapies. Follow-up assessments of pain and other health effects should be conducted periodically.

Appendix: Methods and Analyses

The scientific assessment of these Guidelines was based on the following statements, or *evidence linkages.* These linkages represent directional hypotheses about relationships between chronic pain, symptom management, and clinical outcomes.

1. A comprehensive history and physical examination: a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
2. Diagnostic evaluation (*e.g.,* neural blockade, imaging, pharmacodiagnosis, epiduroscopy, electrodiagnostics) a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
3. Counseling and coordination of care (*i.e.,* within-practice) a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
4. Monitoring and measurement of clinical outcomes a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
5. Multidisciplinary pain management a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
6. Multimodality pain management a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
7. Adjuvant analgesics (*e.g.,* antidepressants, membrane stabilizing agents, and nonsteroidal antiinflammatory drugs [NSAIDs]) a) reduce pain or suffering, b) reduce adverse effects from pain therapy, c) improve function and quality of life, d) provide optimal utilization and cost of services.
8. Regional sympathetic blockade (*e.g.,* lumbar sympathetic block, stellate ganglion block, intravenous regional block) a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provide optimal utilization and cost of services.
9. Corticosteroid injection therapy a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
10. Neurostimulation therapy (*i.e.,* transcutaneous electrical nerve stimulation [TENS], peripheral nerve stimulation [PNS], spinal cord stimulation [SCS]) a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
11. Opioid therapy (*i.e.,* systemic drug delivery and neuraxial drug delivery) a) reduces pain or suffering, b) reduces adverse effects from pain therapy, c) improves function and quality of life, d) provides optimal utilization and cost of services.
12. Neuroablative techniques (*i.e.,* chemical and thermal) a) reduce pain or suffering, b) reduce adverse effects from pain therapy, c) improve function and quality of life, d) provide optimal utilization and cost of services.

Scientific evidence was derived from aggregated research literature,

with meta-analyses used when appropriate, and from surveys, open presentations, and other consensus-oriented activities. For purposes of literature aggregation, potentially relevant clinical studies were identified via electronic and manual searches of the literature. The electronic search covered a 30-yr period from 1966 through 1995. The manual search covered a 52-yr period from 1944 through 1995. More than 3,000 citations were initially identified, yielding 1,450 nonoverlapping articles that addressed topics related to the 12 evidence linkages. After review of the articles, 1,074 studies did not provide direct evidence and were subsequently eliminated. A total of 376 articles (from 153 journals) contained direct linkage-related evidence.

A directional result for each study was initially determined by classifying the outcome as either supporting a linkage, refuting a linkage, or neutral. The results were then summarized to obtain a directional assessment of support for each linkage. The literature relating to five evidence linkages contained enough studies with well-defined experimental designs and statistical information to conduct formal meta-analyses. These five linkages were linkage 2 (diagnostic evaluation), 5a (multidisciplinary pain management programs), 5b (multidisciplinary pain management programs that emphasize the reduction or elimination of pain medications as a primary objective of therapy), 7a (antidepressants), and 7b (anticonvulsants and NSAIDS), 10a (TENS), 10b (SCS), and 11b (opioid therapy, systemic drug delivery).

The following terms were used in the Guidelines to express the strength of the evidence relating to various interventions and their associated outcomes.

1. *Insufficient data* : there are insufficient published data to provide an indication of the relationship between the intervention and outcome.
2. *Suggestive data* : there is qualitative evidence in the form of case reports or descriptive studies, but there is insufficient quantitative evidence to establish a statistical relationship between intervention and outcome.
3. *Supportive data* : quantitative data indicate a significant relationship between intervention and outcome ($P < 0.01$), and qualitative data are supportive.

Combined probability tests were applied to continuous data, and an odds-ratio procedure was applied to dichotomous study results. Two combined probability tests were used as follows: 1) The Fisher Combined Test, producing chi-square, values based on logarithmic transformations of the reported P values from the independent studies, and 2) the Stouffer Combined Test, providing weighted representation of the studies by weighting each of the standard normal deviates by the size of the sample. A procedure based on the MantelHaenszel method for combining study results using 2 × 2 tables was available for use with outcome frequency information. An acceptable significance level was set at $P < 0.01$ (one-tailed), and effect size estimates were calculated. Interobserver agreement was established through assessment of interrater reliability testing. Tests for heterogeneity of the independent samples were conducted to assure consistency among the study results. To control for potential publishing bias, a "fail-safe N" value was calculated for each combined probability test. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Results of the combined probability tests are reported in Table 1 . Significance levels from the weighted Stouffer combined tests for analgesic efficacy were significant for linkages 2 (diagnostic evaluation), 5a (multidisciplinary pain management programs), 5b (multidisciplinary pain management programs with emphasis on pain medication reduction or elimination), 7a (antidepressants), 7b (anticonvulsants and NSAIDs), 10a (TENS), 10b (SCS), and 11a (systemic opioid therapy. Weighted effect size estimates ranged from r = 0.10 to r = 0.28, demonstrating small-to-moderate effect size estimates. Significance levels from the weighted Stouffer combined tests for beneficial effects were significant for linkages 5a (multidisciplinary pain management programs), 5b (multidisciplinary pain management programs, pain medication reduction), and 7a (antidepressants). Weighted effect size estimates for beneficial effects ranged from r = 0.19 to r = 0.22. For linkage 7a, a separate analysis was conducted excluding mood state findings to determine if there were any nonmood state effects associated with the use of these medications. Significance levels for this linkage were not significant ($Z_c = 0.113$, $P > 0.10$). Sufficient data were not available in the literature to conduct Mantel-Haenszel analyses on these linkages.

Tests for heterogeneity of statistical tests and effect size were non-significant for linkages 2, 10a, and 10b, indicating that the pooled studies provided common

estimates of significance and population effect sizes. Tests for heterogeneity of statistical tests were significant for linkages 5a (health effects) and 5b (analgesia and health effects). Tests for heterogeneity of effect size were significant for linkages 5a (health effects), 5b (analgesia and health effects), 7a (analgesia), 7b (analgesia), and 11b (analgesia). Significant findings for analgesic efficacy for linkage 11b may reflect the small number of studies used in the pooled analysis (N = 5). Significant findings for analgesic efficacy of 7a and 7b may reflect either the differential influence of the various adjuvant medications or that the pooled analysis used adjuvant medications whose primary purpose was not specifically intended for pain management. Significant findings for linkages 5a and 5b suggest that the findings be further examined for commonalities in therapeutic approaches, medications, personnel, or targeted patient populations in multidisciplinary pain programs.

Agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a kappa statistic for two-rater agreement pairs were 1) type of study design, kappa = 0.77-0.89;2) type of analysis, kappa = 0.41-0.88; 3) evidence linkage assignment, kappa = 0.65-0.80; and 4) literature inclusion for database, kappa = 0.30-0.71. Three-rater chance-corrected agreement values were 1) design, Sav = 0.85, Var (Sav) = 0.005; 2) analysis, Sav = 0.59, Var (Sav) = 0.008; 3) linkage identification, Sav = 0.74, Var (Sav) = 0.006; and 4) literature database inclusion, Sav = 0.46, Var (Sav) = 0.043. These values represent moderate levels of agreement.

The findings of the literature analyses were supplemented by the opinions of Task Force members and by surveys of the opinions of a panel of consultants with expertise in chronic pain management (N = 96). The rate of return was 60% (N = 58 of 96). The percentage of consultants supporting each linkage is reported in Table 2 (Table Not Available) . Consultants, in general, were highly supportive of the linkages (*i.e.,* a] agreed that they provided analgesic benefit, b] reduced risk of adverse outcomes, c] improved function and quality of life, and d] were important issues for the Guidelines to address).

The feasibility of implementing these Guidelines into clinical practice was assessed by an opinion survey of the chronic pain consultant panel. The rate of return was 54% (N = 51). The mean number of patients treated annually by the consultants was reported to be 1,636 (min/max = 10--9,000). Responses for feasibility of implementation of the Guidelines were as follows: 96% (N = 50) of these consultants indicated that implementation of the Guidelines would not result in the need to purchase new equipment, supplies, or pharmaceuticals.

TABLE 1 -- Statistical Summary: Combined Test Results

Analgesic Efficacy			
Linkage #2: Diagnostic evaluation			
Fisher Combined Test	X^2 = 69.23	$P < 0.001$	df = 12
Stouffer Combined Test	Z_c (weighted) = 3.886	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.28		
Fail-Safe N Value	Nfs 0.01 = 51		
Linkage #5a: Multidisciplinary Programs			
Fisher Combined Test	X^2 = 94.78	$P < 0.001$	df = 24
Stouffer Combined Test	Z_c (weighted) = 2.863	$P < 0.010$	
Effect Size Estimate	r (weighted) = 0.19		
Fail-Safe N Value	Nfs 0.01 = 112		
Linkage #5b: Multidisciplinary Programs (Emphasis on Reduction of Medications)			
Fisher Combined Test	X^2 = 258.91	$P < 0.001$	df = 50
Stouffer Combined Test	Z_c (weighted) = 10.755	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.25		
Fail-Safe N Value	Nfs 0.01 = 1070		
Linkage #7a: Adjuvant Analgesics (Antidepressants)			
Fisher Combined Test	X^2 = 149.33	$P < 0.001$	df = 40
Stouffer Combined Test	Z_c (weighted) = 5.592	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.20		
Fail-Safe N Value	Nfs 0.01 = 248		
Linkage #7b: Adjuvant Analgesics (Anticonvulsants and NSAIDs)			
Fisher Combined Test	X^2 = 70.59	$P < 0.001$	df = 18
Stouffer Combined Test	Z_c (weighted) = 3.515	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.18		
Fail-Safe N Value	Nfs 0.01 = 69		
Linkage #10a: Neurostimulation Therapy (TENS)			
Fisher Combined Test	X^2 = 22.05	$P < 0.001$	df = 14
Stouffer Combined Test	Z_c (weighted) = 3.343	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.10		
Fail-Safe N Value	Nfs 0.01 < 1		
Linkage #10b: Neurostimulation Therapy (SCS)			
Fisher Combined Test	X^2 = 58.86	$P < 0.001$	df = 12
Stouffer Combined Test	Z_c (weighted) = 3.817	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.24		
Fail-Safe N Value	Nfs 0.01 = 40		
Linkage #11b: Opioid Therapy (Systemic Drug Delivery)			
Fisher Combined Test	X^2 = 53.10	$P < 0.001$	df = 10
Stouffer Combined Test	Z_c (weighted) = 4.857	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.19		
Fail-Safe N Value	Nfs 0.01 = 18		
Beneficial Health Outcomes			
Linkage #5a: Multidisciplinary Programs			
Fisher Combined Test	X^2 = 77.24	$P < 0.001$	df = 20

Stouffer Combined Test	Z_c (weighted) = 7.180	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.22		
Fail-Safe N Value	Nfs 0.01 = 94		
Linkage #5b: Multidisciplinary Programs (Emphasis on Reduction of Medications)			
Fisher Combined Test	X^2 = 253.00	$P < 0.001$	df = 56
Stouffer Combined Test	Z_c (weighted) = 7.772	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.20		
Fail-Safe N Value	Nfs 0.01 = 969		
Linkage #7a: Adjuvant Analgesics (Antidepressants)			
Fisher Combined Test	X^2 = 56.72	$P < 0.001$	df = 24
Stouffer Combined Test	Z_c (weighted) = 4.042	$P < 0.001$	
Effect Size Estimate	r (weighted) = 0.19		
Fail-Safe N Value	Nfs 0.01 = 35		
Adverse Effects			
Linkage #7a: Adjuvant Analgesics (Antidepressants)			
Fisher Combined Test	X^2 = 24.53	$P < 0.010$	df = 10
Stouffer Combined Test	Z_c (weighted) = 0.113	$P > 0.100$	
Effect Size Estimate	r (weighted) = 0.20		
Fail-Safe N Value	Nfs 0.01 = 6		

TABLE 2 -- Consultant Survey of Evidence Linkages: Percentage Agreement (N = 58)

(Not Available)

The two respondents who stated that purchases would be required estimated cost of initial implementation of the Guidelines to be $ 20,000-30,000 for the purchase of improved nerve stimulators, cryotherapy, and radiofrequency equipment.

The consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the Guidelines were instituted. The percentage of consultants expecting no change associated with each linkage was as follows: comprehensive history and physical examination, 92%; diagnostic evaluation, 98%; counseling and coordination of care, 92%; monitoring and measurement of outcomes, 83%; multidisciplinary pain management, 96%; multimodality pain management, 100%; adjuvant analgesics, 100%; regional sympathetic blockade, 100%; corticosteroid therapy, 100%; neurostimulation therapy, 96%; opioid therapy, 98%; and neuroablative techniques, 94%.

Ninety-two percent of the respondents indicated that the Guidelines would have no effect on the time spent on a typical case. None reported that the Guidelines would reduce the amount of time spent per case. For all respondents, the mean increase in the amount of time spent on a typical case was 2.1 min. Of the 8% of respondents who reported an anticipated increase in time spent on a typical case, the mean was 18.0 min (range, 4-60 min). [*] ["]

*Readers with special interest in the statistical analyses used in establishing these Guidelines can receive further information by writing to: Peter R. Wilson, MBBS, PhD, Anesthesia Department, Mayo Clinic, 200 First Street, Rochester, Minnesota 55905.

APPENDIX: Practice Guidelines for Cancer Pain Management[D]

A Report by the American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to revision from time to time as warranted by the evolution of medical knowledge, technology, and practice. The guidelines provide basic recommendations that are supported by analysis of the current literature and by a synthesis of expert opinion, open forum commentary, and clinical feasibility data (Appendix 1).

A. Definition of Cancer Pain.

For these guidelines, cancer pain is defined as pain that is attributable to cancer or its therapy. The Task Force has not given preference to literature based on any particular system of definition or classification of cancer pain.

B. Purpose of Guidelines for Cancer Pain Management.

The purpose of these guidelines is to: (1) optimize pain control; (2) minimize side effects, adverse outcomes, and costs; (3) enhance functional abilities and physical and psychological well-being; and (4) enhance the quality of life for cancer patients.

C. Focus.

These guidelines focus on the knowledge base, skills, and range of interventions that are the essential elements of effective management of pain and pain-related problems in patients with cancer. The guidelines recognize that the management of cancer pain occurs within the broader context of supportive care which also encompasses other quality of life concerns (*e.g.,* functional status, psychosocial well-being).

The guidelines recognize that comprehensive pain management by anesthesiologists may not be feasible in every clinical setting. However, aspects of these guidelines may be useful when comprehensive pain management cannot be offered.

The Task Force recognizes that therapies used to modify the underlying cause of pain may improve analgesia and outcome. Commonly used approaches include radiotherapy, surgery, and chemotherapy. The decision to implement primary therapy should be based on a comprehensive assessment of risks and benefits and are outside the scope of these guidelines.

D. Application.

The guidelines are intended for use by anesthesiologists and individuals who deliver care under the direct supervision of anesthesiologists. The guidelines apply to patients of all ages and with all types of cancer.

I. Comprehensive Evaluation and Assessment of the Patient with Cancer Pain

The literature suggests that a comprehensive cancer pain evaluation is associated with improved analgesia. The Task Force and panel of consultants support the conduct of a comprehensive pain evaluation. In the opinion of the Task Force and consultants, effective cancer pain management requires a clear understanding of the etiology and pathophysiology of the pain.

Developed by the Task Force on Pain Management, Cancer Pain Section: F. Michael Ferrante, M.D., F.A.B.P.M. (Chair), Philadelphia, Pennsylvania; Marshall Bedder, M.D., F.R.C.P.(C), Portland, Oregon; Robert A. Caplan, M.D., Seattle, Washington; Hui-Ming Chang, M.D. Houston, Texas; Richard T. Connis, Ph.D. (Methodologist), Woodinville, Washington; Patricia Harrison, M.D., Buffalo, New York; Robert N. Jamison, Ph.D, Boston, Massachusetts; Elliot J. Krane, M.D., Stanford, California; Srdjan Nedeljkovic, M.D., Boston, Massachusetts; Richard Patt, M.D., Houston, Texas; and Russell K. Portenoy, M.D., New York, New York.

Recommendations:

1. General Constructs.

The Task Force identifies four fundamental features that should guide the comprehensive evaluation of the patient with cancer pain.

a. The patient's general medical condition and the extent of disease must be assessed.
b. A knowledge of common pain syndromes is a prerequisite for conducting a cancer pain evaluation. Common pain syndromes include but are not limited to bone metastases, abdominal (visceral) pain, neuropathic pain (*e.g.,* peripheral neuropathies, acute herpes zoster and postherpetic neuralgia, plexopathies), and mucositis.
c. A knowledge of oncologic emergencies (*e.g.,* hypercalcemia, spinal cord compression, cardiac tamponade, superior vena cava syndrome) is also required to conduct a comprehensive cancer pain evaluation.
d. A thorough knowledge of the modalities that car be employed in the treatment of painful crisis (*i.e.* pain emergency) is also necessary.

2. Elements.

The Task Force identifies six essentia features of a comprehensive evaluation and treatment plan. These features are outlined below (template 1)

a. History: A complete history includes a general medical and oncologic history with a description of the extent of disease and prognosis. A pain history should include: (1) the quality of the pain *e.g.,* "burning", "aching"), (2) pain intensity (*i.e.,* numeric, categorical, or visual analog scales), (3) spatial relationships of the pain (*i.e.,* location, areas of radiation), (4) factors that palliate or provoke pain, (5) temporal characteristics of the pain (*i.e.,* continuous, episodic), (6) duration of the pain, (7) course of the pain (*e.g.,* stable, progressive, "crescendo"), and (8) associated features of the pain (*e.g.,* numbness, weakness, vasomotor changes).
b. Psychosocial evaluation: A psychosocial evaluation should include: (1) the presence of psychological symptoms (*e.g.,* anxiety, depression), (2) indicators of psychiatric disorder (*e.g.,* delirium, major depression), (3) investigation of the "meaning" of the pain to the patient and his or her significant others, (4) changes in mood state, (5) premorbid and current coping mechanisms, (6) family function, (7) the availability of psychosocial support systems, and (8) assessment of the patient's expectations and preconceptions regarding pain management (*e.g.,* fear of addiction surrounding opioids, psychostimulants).
c. Physical examination: A physical examination should include general medical and neurologic examinations and a specific examination of the site of pain and surrounding anatomic regions.
d. Impression and differential diagnosis: The findings of the history and physical examination should be used to determine the probable etiology and pathophysiology of the pain.
e. Diagnostic evaluations: Additional diagnostic tests may be required to ascertain or confirm the etiology of the pain and its relationships to underlying disease processes.
f. Treatment plan: Once a definitive diagnosis has been made, a treatment plan should be formulated and discussed with the patient. The treatment plan should characterize the expected outcome, define contingencies, and outline a plan for reassessment.

Figure Template 1. Algorithm for comprehensive evaluation and longitudinal assessment of cancer pain.

II. Longitudinal Monitoring of Pain

There is insufficient literature to evaluate the efficacy of the longitudinal monitoring of pain. The Task Force

and consultants support the contention that the longitudinal monitoring of pain will result in improved pain management and reduced adverse effects from therapy (template 1) .

Recommendations:

The Task Force identifies three fundamental concepts in the longitudinal monitoring of pain.

1. Patient Self-report.

Reports of pain made by the patient should be the primary source of pain assessment and should take precedence, whenever possible, over inferences and observations made by others. Continuous assessment over time (*e.g.,* pain diaries) is appropriate for outpatients. For some age groups and populations (*e.g.,* the cognitively or developmentally impaired), external observation may be preferable. Age-appropriate instruments should be used in children.

2. Rating Scale.

The longitudinal monitoring of pain intensity should be based on rating scales that are easy to use and interpret. Typical examples of rating scales include discrete numeric scales (*e.g.,* 0-10), categorical scales (none, mild, moderate, severe, worst possible), and continuous visual analog scales of pain or pain relief (template 2) .

3. Frequency of Pain Ratings.

Self-report should be obtained at regular intervals. Increased frequency and evaluation of self-reports may be indicated: (1) at the onset of new pain, (2) when established pain exhibits changes in pattern and/or intensity, or (3) when a major therapeutic intervention is performed.

III. Involvement of Specialists from Multiple Disciplines

The literature supports the concept that involvement of specialists from multiple disciplines results in effective analgesia and suggests that such involvement improves other health outcomes. The panel of consultants and Task Force members endorse the importance of collaboration between anesthesiologists and other health-care providers in the management of cancer pain.

Recommendations:

Anesthesiologists who engage in cancer pain management should avail themselves of interdisciplinary expertise in their clinical environments. It is important to note that the patient's primary physician must be a part of the coordination of pain management. The Task Force recognizes that full interdisciplinary coordination of cancer pain treatment is not feasible in every clinical setting.

Figure Template 2. Pain intensity scales.

IV. Paradigm for the Management of Cancer Pain

The guidelines conceptualize the--pharmacologic management of cancer pain as a continuum from indirect drug delivery (*i.e.,* systemic analgesia) to direct drug delivery (*i.e.,* neuraxial drug administration and neuroablation; template 3) . *Indirect* drug delivery systems rely on blood-borne carriage of analgesic to receptors after (1) systemic absorption, (2) formation of a depot for sustained and continuous release, or (3) administration into the blood stream. *Direct* drug delivery systems involve administration of an agent to the neuraxis or in the vicinity of "target" neural tissue.

Recommendations for the oral administration of analgesics are provided by the World Health Organization (WHO) analgesic ladder (template 4) . These American Society of Anesthesiologists guidelines provide evidence and recommendations for cancer pain management involving the oral and other routes of administration. The literature provides supportive evidence for specific elements of the paradigm (template 5) .

A. Indirect Delivery Systems: Systemic Analgesia

a. Oral pharmacologic interventions: The literature suggests and consultant opinion supports the view that oral pharmacologic interventions applied according to the WHO analgesic ladder are associated with adequate analgesia. The literature indicates an

increased risk of adverse sequelae with the use of oral opioids (Appendix 2).
b. Rectal and transdermal analgesia: The literature suggests that rectal and transdermal modes of analgesia are effective alternatives to oral analgesics. The Task Force supports the use of these analgesic modalities, when appropriate, before employment of more invasive systemic therapies.
c. Subcutaneous and intravenous drug delivery: The literature suggests that subcutaneous or intravenous administration of opioids is effective for patients requiring continuous infusions and does not increase the risk of adverse effects. Subcutaneous administration provides blood levels similar to intravenous infusion, and the comparative risks and benefits of the continuous parenteral techniques have not been evaluated.

Template 3. Drug Delivery Systems

Method of Access to the "Receptor" *	
Indirect (*via* blood-borne carriage, *i.e* ., systemic analgesia)	**Direct**
Via systemic absorption	Neuraxial drug delivery
Oral, bucchal	Epidural
Sublingual, intranasal	Subarachnoid
Rectal	Intraventricular
Via depot formation	Neuroablation
Transdermal	Chemical
Intramuscular	Thermal
Subcutaneous	Surgical
Intravenous administration	

*Neural tissue.

Indirect (systemic) delivery systems rely on the transport of an analgesic to the receptor site in neural tissue by the blood. Access to the blood may be achieved by systemic absorption, formation of a depot with sustained release, and instillation into the blood.

Direct drug delivery systems involve administration of an agent to the neuraxis (*i.e.,* in proximity to the receptor) or in the vicinity of "target" neural tissue.

Recommendations:

1. General Recommendations.

Oral medications should be used as the first line approach in most patients when initiating analgesic therapy. Because it is not effective in all patients and may not be optimal therapy in painful crisis (*i.e.,* the pain emergency), the indications, risks, and potential benefits of alternative interventions must be understood and assessed.

Any proposed systemic regimen must be individualized for the patient, and inflexible reliance should not be placed on any "standard" mixture of medications and/or dosing regimens. For patients with moderate or severe pain, opioid therapy is recommended. Once an opioid and a route of administration are chosen, the dose should be increased until a favorable response occurs or when unmanageable or intolerable adverse effects ensue. There is no predetermined maximum dose of an opioid. Dose titration may be required periodically because of the natural history of the primary

Figure Template 4. The World Health Organization (WHO) analgesic ladder consists of a hierarchy of oral pharmacologic interventions designed to effectively treat pain of increasing magnitude. The ladder presents a framework for the rational use of oral medication before application of other techniques of drug administration. Opioid therapy is considered the mainstay approach for patients with moderate or severe pain. The type of medication administered is sequentially escalated from nonopioids (*e.g.,* nonsteroidal antiinflammatory drugs (NSAIDs) ± adjuvants to opioids used for mild to moderate pain (codeine, dihydrocodeine, oxycodone (compounded with a coanalgesic), hydrocodone, dihydrocodone) ± adjuvants to opioids commonly used for severe pain (morphine, hydromorphone, methadone, oxycodone (without compounding), fentanyl or levorphanol). Adjuvant medications are listed in template 7 . *(Modified with permission from WHO: Cancer pain relief and palliative care: Report of a WHO expert committee. Geneva, World Health Organization, 1990 (technical report series, no. 804).)*

Figure Template 5. Paradigm for the management of cancer pain.

disease or the development of tolerance. When pain is continuous or occurs frequently, medication generally should be administered around-the-clock with additional "rescue" doses available for breakthrough pain. The practitioner should be aware of the potential adverse sequelae of opioids and their appropriate treatment.

When considering changing opioids or routes of administration, dose adjustments should be made to correct for differences in potency. Apparent differences in potency among opioids are the result of physicochemical and pharmacokinetic differences rather than pharmacodynamic distinctions (template 6) . When tolerance to a particular opioid develops, another opioid may be substituted at approximately 50-75% of the equianalgesic dose, because cross-tolerance is incomplete. The size of the reduction should be based on the severity of pain, the presence of adverse effects, and the medical status of the patient. Based on clinical observation, a switch to methadone should be done with a reduction of 75% of the equianalgesic dose.

Adjuvant agents should be used as coanalgesics (*e.g.,* corticosteroids, antidepressants) or to treat adverse drug effects. These agents may be added at any stage (template 7) .

2. Specific Recommendations.

Template 6. Opioid Analgesics Commonly Used to Manage Cancer Pain*

Generic Name	Proprietary Name	Route	Dose Equivalence (mg)	Comments
Opioids conventionally used to manage mild to moderate pain				
Codeine	Various	Oral	200	With the exception of codeine, these opioids are compounded with aspirin or acetaminophen, which imposes a dosage ceiling.
Dihydrocodeine	Various	Oral		
Hydrocodone	Vicodin, Lortab, various	Oral		
Oxycodone	Various	Oral		
Opioids conventionally used to manage moderate to severe pain				
"Immediate release" morphine	MSIR	Oral	30	Especially useful for initial dose titration and prn supplementation with long-acting opioids
Controlled release morphine	MS Contin, Oramorph	Oral	30	Used around-the-clock for basal pain (Do not break, crush, or chew.)
Morphine	Various	Parenteral	10	Usual standard for comparison
Hydromorphone	Dilaudid	Oral	7.5	Especially useful for initial dose titration and prn supplementation with long-acting opioids
Hydromorphone	Dilaudid	Parenteral	1.5	Often used subcutaneously

Oxycodone	Various	Oral	20-30	Often compounded with adjuvants for moderate pain Used as single entity for severe pain Sustained release form is available
Fentanyl	Sublimaze	Intravenous	0.1	Minimal experience outside the hospital setting
Fentanyl	Duragesic	Transdermal	45-134 mg oral morphine ~25 mug/h fentanyl	Used around-the-clock for stable pain, especially with GI dysfunction
Methadone	Dolophine	Oral	20	Inexpensive, but long, variable half-life may complicate titration and predispose to toxicity
Methadone	Dolophine	Parenteral	10	Inexpensive, but long, variable half-life may complicate titration and predispose to toxicity
Levorphanol	Levodromoran	Oral	4	Long half-life with much shorter dosing interval
Levorphanol	Levodromoran	Parenteral	2	Long half-life with much shorter dosing interval

*This list is partial and based on commonly used U.S. formulations. Meperidine and the agonist-antagonist opioids are not included in the table. Meperidine may produce seizures because of accumulation of the normeperidine breakdown product during chronic administration. This is of particular importance in the elderly and in patients with abnormal renal function. The agonist-antagonist opioids have ceiling and dysphoric effects and may precipitate withdrawal in patients chronically receiving pure agonist opioids.

Dose equivalencies are approximate.

When converting between drugs or routes of administration, it is recommended to reduce the calculated dose by 25-50% to account for incomplete cross-tolerance. (Based on clinical observation, methadone dose should be reduced by 75%.) Appropriate titration of dosage should then be performed as clinically indicated.

a. Oral medications: Oral medications such as acetaminophen, acetylsalicylic acid or other nonsteroidal antiinflammatory drugs (NSAIDs) should be employed first for mild to moderate pain. (Note: the simultaneous use of more than one NSAID or the concomitant use of an NSAID with a glucocorticoid is not recommended because the risk of toxicity is increased, and additional analgesia is not achieved.) If pain is not relieved or increases or if moderate pain is present at presentation, an opioid conventionally used for moderate pain (*e.g.,* codeine, dihydrocodeine, oxycodone (compounded with a coanalgesic), or hydrocodone) should be used, usually combined with a nonopioid analgesic. When increasing opioid dose, an increment of 25-50% is usually the minimum required to observe effect. If pain is not relieved, increases, or is severe at presentation, an opioid conventionally used for severe pain (*e.g.,* morphine, hydromorphone, methadone, oxycodone (not compounded with a coanalgesic), fentanyl, or levorphanol) should be selected. (Note: Besides consideration of a change in opioid, an increase in pain intensity should prompt a reevaluation of the cause of pain.)
b. When analgesia with acceptable adverse effects is no longer attained with the oral route of administration or when oral administration is no longer viable (inability to swallow and/or absorb medication), an alternate systemic route of administration should be chosen. (Note: The enteral route should be used in patients with percutaneous feeding tubes and inability to swallow, as long as absorption still

occurs.) If dose-limiting toxicity precludes effective therapy, a trial of a different opioid, a reduction of adverse effects by optimization of adjuvants, neuraxial drug delivery, or neuroablative therapy should be considered.
c. Rectal and transdermal: Use of an alternative route of administration, specifically rectal or transdermal, should be chosen before use of invasive therapies. Rectal administration usually is considered when oral therapy is temporarily unavailable (*e.g.,* nausea and vomiting refractory to therapy), although long-term use is effective in some patients. Transdermal

fentanyl should be used in patients with stable pain states who are (1) noncompliant with oral medication, (2) unable to swallow or absorb, or (3) may benefit from a trial of fentanyl.
d. Subcutaneous and intravenous administration: The subcutaneous route of administration should be used in (1) patients unable to swallow or absorb opioids who may benefit from a continuous infusion of opioid and (2) similar patients with dynamic pain states requiring frequent "rescue" doses for break-through pain. Subcutaneous administration of opioids may be used in the home setting. The recommendations for intravenous administration are the same as for subcutaneous administration. Intravenous administration may be preferred when the patient has permanent venous access. (Note: Intramuscular injection is not recommended as either short- or long-term therapy for cancer pain management because of the attendant discomfort, variable blood concentrations, and fluctuating levels of analgesia.)

Template 7. Commonly Used Adjuvant Analgesics

Class (examples)	Usual Indications
Anticonvulsants	
Phenytoin	Neuropathic pain, particularly lancinating or paroxysmal pain
Carbamazepine	
Clonazepam	
Valproate	
Antidepressants	
Amitriptyline	Neuropathic pain
Nortriptyline	
Imipramine	
Desipramine	
Trazodone	
Local anesthetics	
Lidocaine	Neuropathic pain
Mexiletine	
Corticosteroids	
Dexamethasone	Tumor invasion of neural tissue, elevated intracranial pressure, spinal cord compression, additional effects (mood elevation, antiemesis, appetite stimulation)
Antihistaminics	
Hydroxyzine	Coanalgesic, antiemetic
Muscle relaxants	
Orphenadrine	Occasionally useful for musculoskeletal pain
Carisoprodol	

Methocarbamol	
Chlorzoxazone	
Cyclobenzaprine	
Neuroleptics	
Methotrimeprazine	Neuropathic pain
Fluphenazine	
Other drugs for neuropathic pain	
Baclofen	Neuropathic pain
Clonidine	
Calcitonin	
Capsaicin, topical	
Drug action on bone	
Biphosphonates (pamidronate)	Bone pain
Calcitonin	
Radiopharmaceuticals (Strontium 89)	
Anticholinergics	
Scopalamine	Visceral pain due to bowel obstruction
Glycopyrrolate	
Psychostimulants	
Caffeine	Decrease sedation due to opioid analgesia
Methylphenidate	
Dextroamphetamine	

B. Direct Delivery Systems: Neuraxial Drug Delivery and Neuroablation

Opioids and local anesthetics can be delivered directly to the vicinity of neural tissue, obviating the need for systemic absorption as a means to reach receptor sites. Other potential agents for neuraxial drug delivery are under development. Neuroablation refers to the chemical, thermal, or surgical destruction of neural tissue.

Neuroablation is preceded by diagnostic neural blockade. Regional analgesic techniques are referred to in these guidelines as neural blockade (*e.g.,* intercostal blocks, celiac plexus blocks) and are distinct from neurolytic blocks. Neural blockade is used alone for short-term pain management with specific indications (see below). The Task Force is supportive of the efficacy of neural blockade for prognostic purposes. (Note: Sufficient literature is not available to assess the effectiveness of neural blockade as either a prognostic procedure or a long-term analgesic modality for the treatment of cancer pain.)

a. Neuraxial drug delivery: The literature is supportive of the efficacy of neuraxial analgesic delivery (*i.e.,* epidural, subarachnoid, intraventricular). Epidural or subarachnoid drug administration may be performed by either percutaneous catheterization, reservoir, or implantation of a catheter and pump. Although

the literature suggests that neuraxial techniques are not associated with an increased incidence of adverse effects, the Task Force and consultants suggest that adverse effects may be possible (*e.g.,* catheter-site infections).

b. Neuroablation: The literature suggests and consultants and Task Force members support the view that neuroablation by chemical and thermal neurolysis or surgery can provide long-term control of severe cancer pain without a substantial incidence of adverse effects. Examples of chemical neuroablative procedures include but are not limited to intercostal neurolysis, neurolytic celiac plexus block, neurolytic superior hypogastric plexus block, neurolytic ganglion impar (ganglion of Walther) block, craniofacial neurolytic techniques, and subarachnoid rhizolysis. Examples of thermal neuroablative techniques include radiofrequency ablation (heat) and cryoanalgesia (cold).

Recommendations:

1. General Recommendations.

When adequate analgesia cannot be achieved or intolerable side effects occur with indirect methods of drug delivery, direct drug delivery systems should be considered. In certain specific circumstances, neuraxial drug delivery or neuroablative therapies should be considered at the initiation of therapy or early in the natural history of the pain (see below). Neuraxial drug delivery and neuroablative therapies should not be used: (1) in individuals who are unmotivated or noncompliant or do not possess the cognitive functioning necessary to understand the risks and benefits and (2) when an appropriate logistical system does not exist. Patients must have access to a logistical system that provides the resources and availability of personnel to respond to patient needs on an around-the-clock basis. The establishment of an office or network with professional support may be necessary. For long-term therapies, appropriate home care must be available and functionally integrated into the office, hospital, and community.

2. Specific Recommendations.

a. Neuraxial drug delivery: Neuraxial drug delivery should be used: (1) when severe pain cannot be controlled with systemic drugs because of doselimiting toxicity, (2) when there is immediate need for local anesthetic (some neuropathic pains), (3) after failed neuroablation, or (4) patient preference indicates its use. The choice between epidural or subarachnoid catheterization is determined in part by patient life expectancy. When extended life expectancy is anticipated, subarachnoid catheter placement should be considered because epidural catheters may become obstructed. The presence of epidural metastases necessitates subarachnoid catheterization.
   Before insertion of an indwelling neuraxial drug delivery system, efficacy and appropriate dose range should be ascertained by trial injection or use of a temporary delivery system. Patients should have access to "rescue" doses for breakthrough pain. "Rescue" doses may be given by any route of administration as deemed appropriate by the practitioner.
   Intraventricular administration of opioids may be considered in patients with head and neck cancer and Ommaya reservoirs. (Note: Neural blockade should be used before neuraxial drug delivery because of (1) the presence of pain therapeutically amenable to neural blockade (*e.g.,* myofascial pain, sympathetically-maintained pain, pain of acute herpes zoster); or (2) patient preference, when appropriate.)
b. Neuroablation: Neuroablative techniques should be initiated (1) when systemic therapies have failed to provide adequate pain control or when adverse side effects from systemic therapies are unacceptable; (2) after failure of neuraxial drug administration; (3) early in the natural history of the cancer pain in the presence of selected focal somatic lesions (*e.g.,* rib metastases), visceral (*e.g.,* cancer of the pancreas), or neuropathic (*e.g.,* craniofacial) pain that is believed to be highly responsive to neuroablation with limited risk; or (4) patient preference indicates use of neuroablative techniques, if appropriate. Except for the aforementioned specific indications, chemical, radiofrequency (thermal), and surgical neuroablation should be deferred until anticipated life expectancy is short-term, thereby minimizing the potential for deafferentation pain. On the other hand, consideration of life expectancy is moot with cryoanalgesia because of the potential for nerve regeneration associated with the technique. The cryoanalgesia procedure often must be repeated because the endoneurium is spared, allowing regrowth over time. After performance of successful chemical, thermal, or surgical neurolysis, opioid administration should not be immediately curtailed to avoid precipitation of withdrawal. Dosage

---

should be immediately reduced, and opioids should be weaned to avoid respiratory depression, which may occur in the setting of abrupt pain relief.
c. Neural blockade should be used prognostically to determine the possible efficacy of neuroablation. However, even with proper needle placement under fluoroscopic guidance, successful neural blockade does not ensure the subsequent success of a neurodestructive procedure. Neural blockade should be performed at the time of potential neuroablation and should not be performed as a separate procedure. If analgesia is not achieved with neural blockade or significant adverse sequelae result, neuroablation should be reconsidered.
   Definitive neuroablation should be performed with the aid of imaging techniques when feasible or with direct visualization of the intended neural target in the case of open surgical ablation.

V. Management of Cancer-related Symptoms and Adverse Effects of Pain Therapy

The literature supports the efficacy of interventions designed to manage symptoms related to primary disease and its treatment. In addition, the literature suggests that specific interventions used to treat the adverse effects of pain therapy are efficacious. Adverse drug effects directly resulting from cancer pain therapies include but are not limited to sedation, nausea and vomiting, pruritus, constipation, urinary retention, and respiratory depression. (Note: Respiratory depression is rare in the cancer patient receiving chronic opioid therapy (Appendix 2)).

The literature does not suggest that management of symptoms or adverse effects has an effect on analgesia.

The Task Force and consultants are supportive of the value of managing cancer-related symptoms and adverse drug effects as part of the comprehensive management of cancer pain.

Recommendations:

1. General Recommendations.

Adverse effects should be promptly identified and assessed, and appropriate remedies should be offered. Opioids should not be withheld from cancer patients for fear of producing respiratory depression, tolerance, physical dependence, or addiction.

2. Specific Recommendations.

a. Constipation: All patients with an increased risk for constipation should receive prophylaxis (Appendix 2). Prophylactic or symptomatic therapy should involve the use of bulk agents, osmotic laxatives (*e.g.,* magnesium or sodium salts, lactulose or sorbitol), and/or stimulant cathartics (*e.g.,* senna or bisacody1). A stool softener may be concomitantly used with the aforementioned agents. Occasionally, patients require enemas.
b. Sedation: Sedation should be treated by (1) eliminating contributory factors such as nonessential drugs and metabolic disturbances, (2) reducing the dose of an opioid by 25-50% if analgesia is satisfactory, (3) lowering the requirement for opioids by the addition of a nonopioid analgesic or adjuvant analgesic, (4) switching to another opioid, (5) the use of psychostimulants, or (6) considering more invasive modalities if sedation is refractory to therapy.
c. Nausea and vomiting: Persistent nausea is rare, and prophylactic therapy is not indicated. Transitory nausea and vomiting should be treated initially with standard antiemetics, such as promethazine, prochlorperazine, haloperidol, metoclopramide, or hydroxyzine. In some cases, ondansetron or meclizine can be helpful. Some patients may benefit from the use of low-dose corticosteroid, alternative treatment for gastroparesis (*i.e.,* cisapride), or a benzodiazepine (*i.e.,* lorazepam). Treatment of factors contributing to nausea (*e.g.,* constipation) should be considered when appropriate.
d. Mental clouding: The treatment of cognitive impairment should mirror the management of sedation. The addition of low-dose haloperidol occasionally may be necessary for confusional states induced by opioids. Psychostimulants can be administered to reverse mental clouding in the absence of sedation but should not be administered to agitated patients.
e. Myoclonus: Myoclonus is not usually a clinical problem, and reassurance should be given to patients regarding its benign nature. However, if myoclonus impairs function, prevents sleep, or increases pain, clonazepam or valproate should be administered. A reduction in opioid dose or a switch to a different opioid should be considered in the face of refractory or severe myoclonus.

f. Pruritus: Pruritus is rarely a problem with chronic opioid administration, and consideration should be given to an initial trial of diphenhydramine if it occurs.
g. Urinary retention: Urinary retention is also rare with chronic opioid administration and should be treated by administration of a direct cholinomimetic agent, such as bethanecol.
h. Respiratory depression: The least amount of naloxone should be administered to preserve analgesia and avoid withdrawal (Appendix 2). Because of the short half-life of naloxone, a continuous infusion may be necessary.

VI. Recognition, Assessment, and Management of Psychosocial Factors

The literature suggests that psychosocial interventions are effective in improving analgesia and the quality of life for cancer pain patients. The Task Force and panel of consultants offer similar support. Psychosocial interventions for the management of cancer pain include pain diaries, hypnosis, biofeedback, relaxation training, psychotherapy, and behavior management. Recognition is given to the nonspecific effects of listening and showing concern for the welfare of the patient. Management of the psychosocial consequences of cancer pain includes the use of nonpharmacologic interventions (*e.g.,* psychotherapy and pastoral counseling), psychotropic medications, and antidepressants.

Recommendations:

A psychosocial assessment should be conducted initially as an integral part of the comprehensive pain evaluation. Results of the psychosocial assessment should be considered when formulating a pain treatment plan. Pain diaries and counseling should be considered to enhance medication compliance, if needed. The anesthesiologist should recognize that pharmacologic and neurolytic techniques may not be fully effective in controlling pain and that relaxation training, hypnosis, biofeedback, and behavior therapy are important adjuncts. The anesthesiologist should collaborate with psychologists and other health professionals when psychosocial interventions are indicated. The anesthesiologist should recognize that psychosocial manifestations related to cancer (but not to cancer pain) may require referral to appropriate mental health professionals.

VII. Home Parenteral Therapy

The literature suggests that home parenteral therapy is effective for analgesia without notable risk of adverse effects. The panel of consultants and Task Force members support the importance of home parenteral therapy in increasing analgesia and enhancing patient quality of life. Home parenteral therapy provides an infrastructure for the logistical support and clinical management of complex drug delivery systems in a nonhospital setting. Home parenteral therapy includes subcutaneous, intravenous, and neuraxial drug delivery techniques, either on an outpatient basis or with the assistance of a home health-care provider. The coordination of home parenteral therapy may be accomplished by various providers (*e.g.,* hospitals, clinics, or home health-care professionals).

Recommendations:

Before changing from the oral route of administration, the anesthesiologist should ascertain the availability of family and professional support systems. The patient and family must be educated in the use of the home therapy system. The anesthesiologist should determine whether the patient and/or significant others are motivated and competent to care for sophisticated delivery systems. An assessment must be made as to whether appropriate professional services and supplies are obtainable in specific locales, because special planning may be required in rural areas. Communication among the patient, the home health-care professional, and the prescribing physician must be maintained at all times.

VII. End-of-Life Care

The need for supportive care intensifies for patients and their families at the end of life. The literature, Task Force members, and consultants are supportive of the efficacy of palliative therapies for cancer patients approaching the end of life. End-of-life care is intended to improve patient comfort and quality of life by means of palliative therapies, including but not limited to anxiolytics, skin care, mouth care, massage, and appetite stimulants. Palliative therapies may be provided in the form of comprehensive programs, such as hospice or nursing-care outreach programs.

Recommendations:

The management of cancer pain must be integrated into a comprehensive care system that may include hospice and psychosocial support for patients and their families. Assessing and monitoring a patient's palliative care needs are essential parts of the

evaluative/therapeutic process. When cancer patients are approaching the end of life, the anesthesiologist should integrate pain management with palliative care needs. Collaboration with palliative care providers is recommended to maximize patient comfort and improve patient and family quality of life.

IX. Recognition and Management of Special Features of Pediatric Cancer Pain Management

The literature suggests that child-specific interventions are associated with improved analgesia and health outcomes. The Task Force and consultants are supportive of the effectiveness of pediatric cancer pain therapies in improving analgesia and quality of life. Age-appropriate assessment includes behavioral observation (*e.g.,* facial expressions, crying) and self-reports using age-appropriate scales (*e.g.,* visual analog scale, facial pain scale). Pharmacologic interventions designed for children's use include but are not limited to (1) adjustment of dosage to those levels specific for children and (2) interventions designed to be less invasive or to alleviate patient fears or anxieties about their pain therapy (*e.g.,* topical anesthetics as premedication). Psychological and other nonpharmacologic interventions include those designed specifically for children or adult interventions modified to be applicable to children.

Recommendations:

The anesthesiologist should give special attention to the assessment of pain in pediatric patients. For children unable to communicate verbally, observation of patient behavior should be the primary assessment tool. For children who can communicate verbally, age-appropriate pain scales are the recommended self-report instruments when evaluating the efficacy of pain therapy. Observation should be used as an adjunct to self-report.

Administration of oral medications to children should follow the schema of the WHO analgesic ladder, with particular attention paid to age-appropriate dosing regimens. Liquids or suspensions should be employed whenever possible, because many children find them more palatable than pills. (Note: Continuous-release morphine preparations cannot be crushed and still maintain their continuous release properties.) Every attempt should be made to minimize repetitive exposure to needles, if possible. Patient-controlled analgesia (intravenous or subcutaneous) is a viable alternative when children are of sufficient cognitive age. Invasive systemic therapies and direct delivery systems should be used when oral and noninvasive analgesic deliveries do not achieve sufficient analgesia, or side effects make their continued use untenable. Psychological and other nonpharmacologic methods of pain management should be considered as adjuvants.

The Task Force thanks those who responded to surveys on cancer pain management, reviewed guideline drafts, contributed oral and written testimony to the Open Forum, and participated in tests of clinical feasibility.

The development of these guidelines included methods recommended in the following publications: (1) Committee to Advise the Public Health Service on Clinical Practice Guidelines, Division of Health Care Services, Institute of Medicine: Clinical Practice Guidelines: Directions for a New Program. Edited by Field MJ, Lohr KN. Washington, DC, National Academy, 1990, 1992; and (2) Woolf SH: Manual for Clinical Practice Guidelines Development. Washington, DC, US Department of Health and Human Services, Agency for Health Care Policy and Research, publication number 91-0007, March 1991.

Appendix 1. Assessment of Scientific Evidence and Consultant Opinion

The scientific assessment of these guidelines was based on the following statements or evidence linkages. These linkages represent directional hypotheses about relationships between cancer pain, symptom management, and clinical outcomes.

1. Comprehensive evaluation and assessment of pain (*i.e.,* history, physical examination, laboratory evaluation) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.
2. Longitudinal monitoring of pain (*e.g.,* patient self-report, rating scales, and frequency of pain ratings) improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
3. Involvement of specialists in multiple disciplines improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
4. Indirect drug delivery systems (*i.e.,* systemic analgesia: oral medications administered by application of the WHO pain ladder, rectal and transdermal analgesia, subcutaneous drug delivery, and intravenous drug delivery) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.
5. Direct drug delivery systems (*i.e.,* neuraxial drug delivery (epidural, subarachnoid, intraventricular), neural blockade (diagnostic blockade, neural blockade for pain management), and neuroablation

(chemical, thermal, and surgical neurolysis)) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.
6. Management of cancer-related symptoms, side effects of cancer treatment, and adverse effects from pain therapy (*e.g.,* use of antiemetics and laxatives) improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
7. Psychosocial interventions for pain management and interventions to treat psychosocial consequences from cancer pain and pain management improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.
8. Home parenteral therapy improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
9. End-of-life care improves analgesia, reduces adverse effects of pain therapy, and improves quality of life.
10. Special features of pediatric cancer pain management (*i.e.,* age-appropriate assessments and dosage levels, interventions to alleviate fears and anxieties about pain therapy, less invasive routes of pharmacologic administration) improve analgesia, reduce adverse effects of pain therapy, and improve quality of life.

Scientific evidence was derived from aggregated research literature with metaanalyses when appropriate, surveys, open presentations, and other consensus-oriented activities. For purposes of literature aggregation, potentially relevant clinical studies were identified *via* electronic and manual searches of the literature. The electronic search covered a 30-yr period from 1966 through 1995. The manual search covered a 48-yr period from 1948 through 1995. More than 3,000 citations were identified initially, yielding 953 non-overlapping articles that addressed topics related to the 10 evidence linkages. After review of the articles, 603 studies did not provide direct evidence and were subsequently eliminated, yielding 350 articles containing direct evidence. Journals (n = 116) represented by the 350 articles included the following disciplines: anesthesiology, 205; oncology, 36; internal medicine, 3; neurology, 4; neurosurgery, 34; nursing, 8; palliative care, 27; pediatrics, 6; pharmacology, 9; psychology, 14; and radiology, 4.

A directional result for each study was determined initially by classifying the outcome as either supporting a linkage, refuting a linkage, or neutral. The results were summarized to obtain a directional assessment of support for each linkage. The literature relating to linkages 3 (involvement of specialists from multiple disciplines), 5a (neuraxial, *i.e.,* epidural and subarachnoid drug delivery), 6 (management of symptoms or adverse effects), and 9 (end-of-life care) contained enough studies with well defined experimental designs and statistical information to conduct formal metaanalyses.

The following terms were used in the guidelines to express the strength of the evidence relating to various interventions and their associated outcomes: (1) *insufficient* data: There is insufficient published data to provide an indication of the relationship between intervention and outcome; (2) *suggestive* data: There is qualitative evidence in the form of case reports or descriptive studies, but there is insufficient quantitative evidence to establish a statistical relationship between intervention and outcome; (3) *supportive* data: Quantitative data indicate a significant relationship between intervention and outcome ($P < 0.01$), and qualitative data are suggestive.

Combined probability tests were applied to continuous data, and an odds-ratio procedure was applied to dichotomous study results. Two combined probability tests were employed as follows: (1) Fisher's combined test, producing chi-square values based on logarithmic transformations of the reported P values from the independent studies, and (2) the Stouffer combined test, providing representation of the studies by weighting each of the standard normal deviates by the size of the sample. A procedure based on the Mantel-Haenszel method for combining study results using 2 × 2 tables was used when sufficient outcome frequency information was available. An acceptable significance level was set at $P < 0.01$ (one-tailed), and effect-size estimates were calculated. Interobserver agreement was established through assessment of interrater reliability testing. Tests for heterogeneity of the independent samples were conducted to assure consistency among the study results. To control for potential publishing bias, a "fail-safe n" value was calculated for each combined probability test. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Results of the combined probability tests are reported in table A1 . Significance levels from the weighted Stouffer combined test for clinical efficacy were significant for linkages 3 (multiple disciplines) and 5a (neuraxial drug delivery). The weighted Stouffer test for linkage

TABLE 1 -- Staistical Summary: Combined Test Results

Analgesic efficacy			
Linkage 3. Involvement of specialists in multiple disciplines			
Fisher combined test:	Chi-square = 35.83	$P < 0.001$	$df = 12$
Stouffer combined test:	Z_c (weighted) = 3.025	$P < 0.010$	
Effect size estimate:	r (weighted) = 0.13		
Fail-safe N value:	Nfs .01 = 15.7		
Linkage 5a. Epidural and subarachnoid drug delivery			
Fisher combined test:	Chi-square = 34.45	$P < 0.001$	$df = 12$

Stouffer combined test:	Z_c (weighted) = 3.742	*P* = 0.001	
Effect size estimate:	r (weighted) = 0.34		
Fail-safe N value:	Nfs .01 = 20.2		
Linkage 9. End-of-life care			
Fisher combined test:	Chi-square = 48.39	*P* < 0.001	*df* = 10
Stouffer combined test:	Z_c (weighted) = 2.286	*P* < 0.011 (NS)	
Effect size estimate:	*r* (weighted) = 0.20		
Fail-safe N value:	Nfs .01 = 23.1		
Beneficial outcomes			
Linkage 3. Involvement of specialists from multiple disciplines			
Fisher combined test:	Chi-square = 40.06	*P* < 0.001	*df* = 10
Stouffer combined test:	Z_c (weighted) = 3.442	*P* < 0.010	
Effect size estimate:	*r* (weighted) = 0.17		
Fail-safe N value:	Nfs .01 = 19.1		
Linkage 6. Management of side effects (primary disease and treatment)			
Fisher combined test:	Chi-square = 80.21	*P* < 0.001	*df* = 16
Stouffer combined test:	Z_c (weighted) = 3.650	*P* < 0.001	
Effect size estimate:	*r* (weighted) = 0.34		
Fail-safe N value:	Nfs .01 = 83.7		
Linkage 9. End-of-life care			
Fisher combined test:	Chi-square = 47.34	*P* < 0.001	*df* = 14
Stouffer combined test:	Z_c (weighted) = 4.147	*P* < 0.001	
Effect size estimate:	*r* (weighted) = 0.18		
Fail-safe N value:	Nfs .01 = 28.8		

9 (end-of-life care) was not significant. Weighted effect size estimates ranged from r = 0.13 to r = 0.34, demonstrating small-to-moderate effect size estimates. Significance levels from the weighted Stouffer combined tests for beneficial outcomes were significant for linkages 3 (multiple disciplines), 6 (symptoms or adverse effects), and 9 (end-of-life care). Weighted effect size estimates for beneficial outcomes ranged from r = 0.17 to r = 0.34. Tests for heterogeneity of statistical tests and effect size were nonsignificant in all cases, indicating that the pooled studies provided common estimates of significance and population effect sizes. Sufficient data were not available in the literature to conduct Mantel-Haenszel analyses on these linkages.

Metaanalysis was not performed on linkage 4 (indirect drug delivery systems) for either efficacy or outcomes because literature was not conducive to an appropriate assessment. The literature did not consistently report analgesic requirements of the patients studied, which may vary over time as a function of the natural history of the disease. Lack of concurrent analytical control for time-of-measurement and cohort effects preclude valid comparisons. However, subgroup analyses indicated that mild adverse outcomes were associated with the use of weak opioids in comparison to NSAID administration. Weighted Stouffer combined test results were: Zc = 4.69, *P* < 0.001; the weighted effect size estimate (r = 0.32) indicated a moderate effect size. The odds of adverse effects (*e.g.,* sedation, nausea, vomiting) were greater for weak opioids *versus* NSAID groups (odds ratio 1.95, 99% confidence limits 1.45-2.46, Z = 3.10, *P* < 0.001).

Agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a Kappa statistic for two-rater agreement pairs were as follows: (1) type of study design, k = 0.37-0.67; (2) type of analysis, k = 0.47-0.72; (3) evidence linkage assignment, k =

0.47-0.96; and (4) literature inclusion for database, k = 0.35-1.00. Three-rater chance-corrected agreement values were: (1) design, Sav = 0.46, Var (Sav) = 0.008; (2) analysis, Sav = 0.63, Var (Sav) = 0.006; (3) linkage identification, Sav = 0.64, Var (Sav) = 0.005; and (4) literature database inclusion, Sav = 0.53, Var (Sav) = 0.030. These values represent moderate to high levels of agreement.

The findings of the literature analyses were supplemented by the opinions of Task Force members as well as by surveys of the opinions of a panel of consultants with expertise in cancer pain management (n = 72). The rate of return of the surveys was 81% (n = 58 of 72). The percentage of consultants supporting each linkage is reported in table A2 . Consultants, in general, were highly supportive of the linkages (*i.e.,* agreed that they provided analgesic benefit, reduced risk of adverse outcomes, improved other cancer-related symptoms, improved quality of life, and were important issues for the guidelines to address).

The feasibility of implementing these guidelines into clinical practice was assessed by an opinion survey of the cancer pain consultant panel (n = 71). Rate of return of the survey was 65% (n = 46 of 71). The mean number of patients treated annually by the consultants was reported to be 557.5 (min/max = 10/5,000). Responses for feasibility of implementation of the guidelines were as follows: (1) Ninety-one percent (n = 42 of 46) of these consultants indicated that implementation of the guidelines would not result in the need to purchase new equipment, supplies, or pharmaceuticals. (2) Among the four respondents who stated that purchases would be required, the median anticipated cost was $ 25,000 (mean $ 24,625; range $ 13,500-35,000).

The consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the guidelines were instituted. The percent of consultants expecting no change associated with each linkage were as follows: comprehensive evaluation, 76%; longitudinal monitoring, 78%; multiple disciplines, 89%; administration of systemic opioids, 100%; neuraxial drug delivery, 87%; neurolytic techniques, 87%; management of symptoms/adverse effects, 89%; psychosocial factors, 89%, use of parenteral therapy, 94%, end-of-life care, 80%, and pediatric pain management, 83%.

Eighty percent of the respondents indicated that the guidelines would have no effect on the amount of time spent on a typical case. None reported that the guidelines would reduce the amount of time spent per case. For all respondents, the mean increase in the amount of time spent on a typical case was 7.1 min (range 0-120 min). Of the 20% of respondents who reported an anticipated increase in time spent on a typical case, the mean was 36.1 min (range 10-120 min).

Readers with special interest in the statistical analyses used in establishing these guidelines can receive further information by writing to the American Society of Anesthesiologists: 520 North Northwest Highway, Park Ridge, Illinois 60068-2573.

TABLE 2 -- Consultant Responses to Evidence Linkages Survey (n = 58)

Linkages	Analgesic Benefit (% Supportive)	Reduced Risk (% Supportive)	Improved Symptoms (% Supportive)	Improved Quality of Life (% Supportive)	Important Topic (% Supportive)
1. Comprehensive evaluation	98	93	90	91	98
2. Longitudinal monitoring	98	100	85	100	100
3. Involvement of specialists in multiple disciplines	83	64	90	83	79

4. Administration of systemic opioids	71	66	38	74	91
5. Neuraxial drug administration	83	64	41	69	91
6a. Management of cancer-related symptoms or side effects of cancer	81	91	--	98	93
6b. Management of side effects from pain therapy	85	--	79	100	100
7. Psychosocial interventions	83	71	79	95	98
8. Parenteral therapy	81	62	53	81	41
9. End-of-life care	85	86	97	97	95
10. Pediatric cancer pain management	93	83	67	91	98

Appendix 2. Adverse Drug Effects from Opioid Therapies

Tolerance, physical dependence, and addiction are concerns expressed by patients and physicians and must be understood to optimize therapy.

1. Tolerance refers to the progressive decline in the potency of an opioid with continued use, such that increasingly greater doses are needed to achieve the same degree of analgesia. The phenomenon is characteristic of opioids as a class of analgesics and is receptor-mediated. Clinical observations confirm that most patients with stable pain do not require dose escalation to maintain relief. Hence, tolerance is seldom the "driving force" for dose escalation.
   When tolerance to an opioid develops, incomplete cross-tolerance to other opioids concomitantly develops. In such cases, another opioid can be substituted to provide better analgesia.
2. Physical dependence does not imply addiction. Physical dependence is a physiologic state characterized by withdrawal (abstinence syndrome) after abrupt discontinuation of an opioid.
3. Addiction is a psychological and behavioral syndrome characterized by compulsive drug-seeking behavior (among other behaviors), loss of control over drug use, and continued use despite harm. Addiction implies compulsive behavior and psychological dependence. This is exceedingly rare among cancer patients who are given opioids. Tolerance (a pharmacologic property of a class of drugs) and physical dependence (a physiologic effect characteristic of this class of drugs) are conceptually and phenomenologically distinct from addiction.
4. Constipation is highly prevalent among patients receiving chronic treatment with opioids. All patients with an increased risk for constipation should receive prophylactic therapy. Clinical scenarios or syndromes with an increased risk for the development of constipation include: (1) cachexia and/or debilitation, (2) poor performance status (especially the bedridden patient), (3) intraabdominal neoplasm, (4) a history of prior abdominal radiation, (5) autonomic neuropathy, (6) poor fluid intake, and (7) the concurrent use of constipating agents. A stool softener (*e.g.,* docusate) often is used in combination with bulk, osmotic, or stimulant cathartics.
5. Sedation is a common adverse effect associated with the analgesic therapy of cancer pain.
6. Nausea and vomiting are usually uncommon and transitory in patients undergoing opioid titration. Persistent nausea is rare, and prophylaxis is not indicated.
7. Mental clouding or cognitive impairment can vary from mild mental clouding to frank delirium. Mental clouding may occur without sedation.
8. Myoclonus, pruritus, and urinary retention occur infrequently in patients receiving chronic opioid therapy.
9. Respiratory depression is rare in the cancer patient receiving chronic opioid therapy and occurs in association with obtundation and bradypnea. Respiratory depression can occur with abrupt resolution of pain and inadequate reduction of opioid dosage after successful neuroablation. If respiratory depression occurs in a patient taking stable opioid doses without abrupt resolution of pain due to a major therapeutic maneuver, an explanation other than opioid toxicity should be sought (*e.g.,* pulmonary embolism). Reversal of respiratory problems with naloxone only signifies that an opioid was contributing to the respiratory problem. Reversal of respiratory depression with naloxone does not obviate the need to consider other possible etiologies or pursue further evaluation.

APPENDIX: Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures[D]

A Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting

PRACTICE guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. The guidelines provide basic recommendations that are supported by analysis of the current literature and by a synthesis of expert opinion, open forum commentary, and clinical feasibility data (Appendix).

A. Purposes of the Guidelines for Preoperative Fasting

The purposes of these Guidelines are to enhance the quality and efficiency of anesthesia care, stimulate evaluation of individual practices, and reduce the severity of complications related to pulmonary aspiration of gastric contents, should it occur. Enhancements in the quality and efficiency of anesthesia care include, but are not limited to, the cost-effective utilization of perioperative preventive medication, increased patient satisfaction, avoidance of delays and cancellations, decreased risk of dehydration or hypoglycemia from prolonged fasting, and the minimization of perioperative morbidity. Complications of aspiration include, but are not limited to, aspiration pneumonia, respiratory disabilities, and related morbidities.

B. Focus

Prevention of pulmonary aspiration is part of the larger process of preoperative evaluation and preparation of the patient. The Guidelines specifically focus on preoperative fasting recommendations, as well as recommendations regarding the administration of pharmacologic agents to modify the volume and acidity of gastric contents during procedures in which upper airway protective reflexes may be impaired.

Airway management techniques that are intended to reduce the occurrence of pulmonary aspiration are not the focus of these Guidelines. For example, a rapid-sequence induction/endotracheal intubation technique or awake endotracheal intubation technique may be useful to prevent this problem during the delivery of

Developed by the Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Mark A. Warner, M.D. (Chair), Rochester, Minnesota; Robert A. Caplan, M.D., Seattle, Washington; Burton S. Epstein, M.D., Washington, DC; Charles P. Gibbs, M.D., Denver, Colorado; Candace E. Keller, M.D., M.P.H., Hattiesburg, Mississippi; Jessie A. Leak, M.D., Fayetteville, North Carolina; Roger Maltby, M.B.B.S., Calgary, Alberta, Canada; David G. Nickinovich, Ph.D., Bellevue, Washington; Mark S. Schreiner, M.D., Philadelphia, Pennsylvania; Chris M.Weinlander, M.D., Appleton, Wisconsin.

anesthesia care. The Guidelines do not address the selection of anesthetic technique.

The intended patient population is limited to healthy patients of all ages undergoing elective procedures. The Guidelines do not apply to patients who undergo procedures with no anesthesia or only local anesthesia when upper airway protective reflexes are not impaired, and no risk factors for pulmonary aspiration are apparent. The Guidelines are not intended for women in labor.

The Guidelines may not apply to or may need to be modified for patients with co-existing diseases or conditions that might affect gastric emptying or fluid volume (*e.g.,* pregnancy, obesity, diabetes, hiatal hernia, gastroesophageal reflux disease, ileus or bowel obstruction, emergency care, or enteral tube feeding) and patients in whom airway management might be difficult. Anesthesiologists and other anesthesia providers should recognize these conditions and minimize the opportunity for regurgitation and pulmonary aspiration.

C. Application

The Guidelines are intended for use by anesthesiologists and other anesthesia providers. They also may serve as a resource for other health care professionals who advise or care for patients who will receive anesthesia care during procedures. Anesthesia care during procedures is defined as general anesthesia, regional anesthesia, or sedation/analgesia (*i.e.,* monitored anesthesia care). Throughout these Guidelines, the term "preoperative" should be considered synonymous with "preprocedural", as the latter term relates to procedures commonly not considered to be operations.

D. Task Force Members and Consultants

The ASA appointed a Task Force of 10 members to (a) review the published evidence; (b) obtain consultant opinion from a representative body of anesthesiologists, nurse anesthetists, anesthesiology assistants, perioperative nurses, surgeons, gastroenterologists and other internists, dentists and oral surgeons, ophthalmologists, psychiatrists, emergency medicine physicians, and practice management staff personnel; and (c) build consensus within the Task Force. The Task Force members consisted of anesthesiologists in both private and academic practices from various geographic areas of the United States and Canada and methodologists from the ASA Ad-Hoc Committee on Practice Parameters.

The Task Force met its objective in a five-step process. First, original published research studies relevant to these issues were reviewed and analyzed. Second, Consultants from around the world who practice or work in various settings (*e.g.,* academic and private practice) were asked to (a) participate in a survey of their impressions of the effectiveness of various fasting and pharmacologic interventions to decrease the risks of perioperative pulmonary aspiration, and (b) review and comment on the initial draft report of the Task Force. Third, the Task Force held an open forum at a major national anesthesia meeting to solicit input on its draft recommendations from attendees of the meeting. Fourth, all available information was used to build consensus within the Task Force on the recommended guidelines that follow. Finally, the Consultants were surveyed to assess their opinions on the feasibility of implementing the Guidelines.

E. Availability and Strength of Evidence

Evidence-based guidelines are developed by a rigorous analytic process. To assist the reader, the Guidelines make use of several descriptive terms that are easier to understand than the technical terms and data that are used in the actual analyses. These descriptive terms are defined below: The following terms describe the availability of scientific evidence in the literature.

Insufficient:

There are too few published studies to investigate a relationship between a clinical intervention and clinical outcome.

Inconclusive:

Published studies are available, but they cannot be used to assess the relationship between a clinical intervention and a clinical outcome because the studies either do not meet predefined criteria for content as defined in the "Focus of the Guidelines," or do not meet research design or analytic standards.

Silent:

There are no available studies in the literature that address a relationship of interest.

The following terms describe the strength of scientific data when sufficient literature is available.

Supportive:

There is sufficient quantitative information from adequately designed studies to describe a statistically significant relationship (P<0.01) between a clinical intervention and a clinical outcome, using the technique of meta-analysis.

Suggestive:

There is enough information from case reports

and descriptive studies to provide a directional assessment of the relationship between a clinical intervention and a clinical outcome. This type of qualitative information does not permit a statistical assessment of significance.

Equivocal: Qualitative data have not provided a clear direction for clinical outcomes related to a clinical intervention and (1) there is insufficient quantitative information or (2) aggregated comparative studies have found no quantitatively significant differences among groups or conditions.

The following terms describe survey responses from Consultants for any specified issue. Responses are weighted as agree = +1, undecided = 0 or disagree = -1.

Agree: The average weighted responses must be equal to or greater than +0.30 (on a scale of -1 to 1) to indicate agreement.

Equivocal: The average weighted responses must be between -0.30 and
0.30 (on a scale of -1 to 1) to indicate an equivocal response.

Disagree: The average weighted responses must be equal to or less than -0.30 (on a scale of -1 to 1) to indicate disagreement.

Guidelines

I. Preoperative Assessment

There is insufficient published evidence to evaluate the effect of a preoperative assessment (e.g., history, physical examination, survey/interview) on the frequency or severity of pulmonary aspiration of gastric contents during the perioperative period. The Consultants and the Task Force agree that a preoperative assessment may be associated with improved outcome related to the prevention of perioperative pulmonary aspiration of gastric contents.

Recommendations:

A review of pertinent medical records, a physical examination, and patient survey or interview should be performed as part of the preoperative evaluation. The history, examination, and interview should include pertinent assessment of gastroesophageal reflux disease, dysphagia symptoms, or other gastrointestinal motility disorders, potential for difficult airway management, and metabolic disorders (e.g., diabetes mellitus) that may increase the risk of regurgitation and pulmonary aspiration. Patients should be informed of fasting requirements and the reasons for them sufficiently in advance of their procedures. Verification of their compliance with the fasting requirements should be assessed at the time of their procedures. When the following fasting guidelines are not followed, the practitioner should compare the risks and benefits of proceeding, with consideration given to the amount and type of liquids or solids ingested.

II. Preoperative Fasting Status (Clear Liquids)

Published evidence is silent on the relationship between fasting times, gastric volume, or gastric acidity and the risk of emesis/reflux or pulmonary aspiration in humans. Studies comparing fasting times of between 2 and 4 hours versus more than 4 hours found smaller gastric volumes in adult patients who fasted 2 to 4 hours, although the effect size was small. No differences in gastric volume were found for children who fasted 2 to 4 hours versus more than four hours. In studies that examine the ingestion of clear liquids between 2 and 4 hours before procedures and in which ingested liquid volumes were recorded, participants received volumes of clear liquids ranging widely from 2 ml/kg to unrestricted amounts. Published evidence is equivocal regarding the effect of clear liquid ingestion on gastric acidity for both adults and children.

The Consultants are equivocal regarding a fasting period for clear liquids of between 2 and 4 hours for adults, but they support a fasting period of 2 hours for infants and children. The Task Force supports a fasting period for clear liquids of 2 hours for all patients.

Recommendations:

It is appropriate to fast from intake of clear liquids for 2 or more hours before procedures requiring general anesthesia, regional anesthesia, or sedation/analgesia (i.e., monitored anesthesia care) [*Table 1*]. Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee. These liquids should not include alcohol. The volume of liquid ingested is less important than the type of liquid ingested.

III. Preoperative Fasting Status (Breast Milk)

There is insufficient published evidence to evaluate the relationship of the timing of breast milk intake before procedures to the incidence of emesis/reflux or pulmonary aspiration. The Consultants and Task Force support a fasting period for breast milk of 4 hours for both neonates and infants.

Recommendations:

It is appropriate to fast from intake of breast milk for 4 or more hours before procedures requiring general anesthesia, regional anesthesia,

TABLE 1 -- Summary of Fasting Recommendations to Reduce the Risk of Pulmonary Aspiration*

Ingested Material	Minimum Fasting Period (h)
Clear liquids	2
Breast milk	4
Infant formula	6
Non-human milk	6
Light meal	6

*These recommendations apply to healthy patients who are undergoing elective procedures. They are not intended for women in labor. Following the Guidelines does not guarantee complete gastric emptying.
The fasting periods noted above apply to all ages.
Examples of clear liquids include water, fruit juices without pulp, carbonatedbeverages, clear tea, and black coffee.
Since non-human milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.
A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period.

or sedation/analgesia (i.e., monitored anesthesia care) *[Table 1].*

IV. Preoperative Fasting Status (Infant Formula)

There is insufficient published evidence to address the safety of any preoperative fasting period for infant formula. For infants and children, the Consultants and Task Force support a fasting period of 6 hours. For neonates, the Consultants support a fasting period of 4 hours, and the Task Force supports a fasting period of 6 hours.

Recommendations:

It is appropriate to fast from intake of infant formula for 6 or more hours before elective procedures requiring general anesthesia, regional anesthesia, or sedation/analgesia (i.e., monitored anesthesia care) *[Table 1]* .

V. Preoperative Fasting Status (Solids and Non-human Milk)

There is insufficient published evidence to address the safety of any preoperative fasting period for solids or non-human milk. For patients of all ages, the Consultants and Task Force support a fasting period for a light meal (e.g., toast and a clear liquid) of 6 hours before elective procedures requiring general anesthesia, regional anesthesia, or sedation/analgesia (i.e., monitored anesthesia care). They also support a fasting period for a meal that includes fried or fatty foods or meat of 8 or more hours before elective procedures. For infants and children, the Consultants and Task Force support a fasting period of 6 hours for non-human milk.

Recommendations:

It is appropriate to fast from intake of a light meal or non-human milk for 6 or more hours before elective procedures requiring general anesthesia, regional anesthesia, or sedation/analgesia (i.e., monitored anesthesia care) *[Table 1]* .The Task Force notes that intake of fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period. Since non-human milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.

VI. Preoperative Gastrointestinal Stimulants

Published evidence supports the efficacy of gastroin-testinal stimulants (e.g., metoclopramide) for reducing gastric volume during the perioperative period. It is equivocal regarding the relationship between gastroin-testinal stimulants and gastric acidity. There is insufficient published evidence to examine the relationship between gastrointestinal stimulants and the frequency of pulmonary aspiration. The Consultants and Task Force are equivocal regarding the preoperative use of gastrointestinal stimulants to reduce the risks of pulmonary aspiration.

Recommendations:

The routine preoperative use of gastrointestinal stimulants to decrease the risks of pulmonary aspiration in patients who have no apparent increased risk for pulmonary aspiration is not recommended *(Table 2).*

VII. Preoperative Pharmacologic Blockade of Gastric Acid Secretion

Published evidence supports the efficacy of histamine-2 receptor antagonist agents (e.g., cimetidine, famotidine, or ranitidine) to reduce gastric acidity and volume during the perioperative period and also suggests that proton pump inhibitors (e.g., omeprazole or lansoprazole) are effective for these same purposes. However, it does not sufficiently examine the relationship between reduced gastric acid secretion and the frequency of pulmonary aspiration in humans, and it is silent on the relationship between agents that block gastric acid secretion and the frequency of pulmonary aspiration. There is not sufficient published evidence to evaluate whether reduced gastric acid secretion is associated with decreased morbidity or mortality in patients who have aspirated gastric contents. The Consultants

TABLE 2 -- Summary of Pharmacologic Recommendations to Reduce the Risk of Pulmonary Aspiration

Medication Type and Common Examples	Recommendation
Gastrointestinal stimulants	No routine use
Metoclopramide	
Gastric acid secretion blockers	No routine use
Cimetidine	
Famotidine	
Ranitidine	
Omeprazole	
Lansoprazole	
Antacids	No routine use
Sodium citrate	
Sodium bicarbonate	
Magnesium trisilicate	
Antiemetics	No routine use
Droperidol	
Ondansetron	
Anticholinergics	No use
Atropine	
Scopolamine	
Glycopyrrolate	
Combinations of the medications above	No routine use

and Task Force are equivocal regarding the use of agents that block preoperative gastric acid secretion to reduce the risks of pulmonary aspiration.

Recommendations:

The routine preoperative use of medications that block gastric acid secretion to decrease the risks of pulmonary aspiration in patients who have no apparent increased risk for pulmonary aspiration is not recommended.

VIII. Preoperative Antacids

Published evidence supports the efficacy of preoperative antacids (e.g., sodium citrate, sodium bicarbonate; or magnesium trisilicate) for decreasing gastric acidity during the perioperative period, but it does not support their efficacy in reducing gastric volume. It does not sufficiently examine the relationship between reduced gastric acidity and the frequency of pulmonary aspiration in humans. It also does not examine the relationship between the preoperative use of antacids and the frequency of emesis. There is insufficient published evidence to evaluate whether reduced gastric acidity or volume is associated with decreased morbidity or mortality in patients who have aspirated gastric contents. The Task Force agrees that the pulmonary aspiration of antacids that contain particulates, compared with those that do not, may increase the risk of pulmonary damage. The Consultants and Task Force are equivocal regarding the preoperative use of antacids.

Recommendations:

The routine preoperative use of antacids to decrease the risks of pulmonary aspiration in patients who have no apparent increased risk for pulmonary aspiration is not recommended. Only nonparticulate antacids should be used when antacids are indicated for selected patients for purposes other than reducing the risk of pulmonary aspiration.

IX. Preoperative Antiemetics

Published evidence suggests that preoperative antiemetics (e.g., droperidol, ondansetron) reduce nausea and vomiting during the perioperative period, but statistical significance was not obtained. The literature does not sufficiently examine the relationship between nausea or vomiting and the frequency of pulmonary aspiration in humans during the perioperative period, nor does it sufficiently examine the relationship between preoperative antiemetics and the frequency of pulmonary aspiration. The Consultants and Task Force are equivocal regarding the preoperative use of antiemetics. These Guidelines do not address the use of antiemetics during the extended postoperative period after upper airway protective reflexes are no longer impaired.

Recommendations:

The routine preoperative use of antiemetics to reduce the risks of pulmonary aspiration in patients who have no apparent increased risk for pulmonary aspiration is not recommended.

X. Preoperative Anticholinergics

Published evidence is equivocal regarding the use of anticholinergics (e.g., atropine, scopolamine, or glycopyrrolate) to decrease gastric volume or acidity. The Consultants and Task Force agree that the preoperative use of anticholinergics is not associated with improved outcomes related to pulmonary aspiration.

Recommendations:

The use of anticholinergics to decrease the risks of pulmonary aspiration is not recommended.

XI. Preoperative Multiple Agents

Published evidence supports the preoperative effectiveness of multiple agents, such as histamine-2 receptor antagonists, gastrointestinal stimulants, and antacids, to decrease gastric volume and acidity. However, it is equivocal regarding the added benefit of multiple agents when compared with single agents. It also does not sufficiently examine the relationship between reduced gastric volume or acidity and the frequency of pulmonary aspiration in humans, and it is silent on the relationship between multiple pharmacologic agents and the

frequency of pulmonary aspiration. There is not sufficient published evidence to evaluate whether reduced gastric volume or acidity is associated with decreased morbidity or mortality in patients who have aspirated gastric contents. The Consultants and Task Force are equivocal regarding the use of multiple pharmacologic agents to reduce the frequency or severity of complications associated with pulmonary aspiration.

Recommendations:

The routine preoperative use of multiple agents in patients who have no apparent increased risk for pulmonary aspiration is not recommended.

Appendix: Methods and Analyses*

The scientific assessment of these Guidelines was based on the following statements, or evidence linkages. These linkages represent directional statements about relationships between preoperative fasting and pharmacologic prophylaxis of pulmonary aspiration and clinical outcomes.

1. A preoperative assessment (e.g.,history, physical exam, survey/interview): a) increases patient comfort, b) reduces adverse outcomes, c) improves patient satisfaction, and d) improves cost/utilization of services.
2. For adults, preoperative fasting status of solids between 4 and 8 hours: a) increases patient comfort, b) reduces adverse outcomes, c) improves patient satisfaction, and d) improves cost/utilization of services.
3. For adults, preoperative fasting status of liquids between 2 and 4 hours: a) increases patient comfort, b) reduces adverse outcomes, c) improves patient satisfaction, and d) improves cost/utilization of services.
4. For children, infants and neonates, preoperative fasting status of milk, breast milk or formula between 2 and 4 hours: a) increases patient comfort, b) reduces adverse outcomes, c) improves patient satisfaction, and d) improves cost/utilization of services.
5. Preoperative gastrointestinal stimulants: a) increases patient comfort, b) reduces adverse outcomes, c) improves patient satisfaction, and d) improves cost/utilization of services.
6. Preoperative pharmacologic blockage of gastric acid secretion (i.e., histamine-2 receptor antagonists and proton pump inhibitors): a) increases patient comfort, b) reduces adverse outcomes, c) improves patient satisfaction, and d) improves cost/utilization of services.
7. Preoperative antacids: a) increase patient comfort, b) reduce adverse outcomes, c) improve patient satisfaction, and d) improve cost/utilization of services.
8. Preoperative antiemetics: a) increase patient comfort, b) reduce adverse outcomes, c) improve patient satisfaction, and d) improve cost/utilization of services.
9. Preoperative anticholinergics: a) increase patient comfort, b) reduce adverse outcomes, c) improve patient satisfaction, and d) improve cost/utilization of services.
10. Preoperative multiple agents (e.g., triple prophylaxis): a) increase patient comfort, b) reduce adverse outcomes, c) improve patient satisfaction, and d) improve cost/utilization of services.

TABLE 3 -- Summary of First-, Second-, Third- and Fourth-order Comparisons of Outcomes Related to Fasting and Pharmaceutical Interventions

Fasting of Pharmaceutical Intervention	Number of Studies
First-order comparison	
Intervention--gastric outcomes	194
Gastric volume or *p* H--emesis/reflux	2
Emesis/reflux--pulmonary aspiration	0
Pulmonary aspiration--adverse outcomes	5
Second-order comparisons	
Intervention--emesis/reflux	7
Gastric volume or *p* H--pulmonary aspiration	2
Emesis/reflux--adverse outcomes	0
Third-order comparisons	
Intervention--pulmonary aspiration	4
Gastric volume or *p* H--adverse outcomes	0
Fourth-order comparisons	
Intervention--adverse outcomes	0

Scientific evidence was derived from aggregated human research literature, with meta-analyses utilized when appropriate, and from surveys, open presentations and other consensus-oriented activities. For purposes of literature aggregation, potentially relevant clinical studies were identified via electronic and manual searches of the literature. The electronic search covered a 31-year period from 1966 through 1996. The manual search covered a 57-year period of time from 1940 through 1996. Over 3000 citations were initially identified, yielding a total of 1156 non-overlapping articles that addressed topics related to the 10 evidence linkages. Following review of the articles, 924 studies did not provide direct evidence, and were subsequently eliminated. A total of 232 articles (from 48 journals) contained direct linkage-related evidence.

The literature was first categorized according to the proximity or directness of the outcome to the intervention. Generally, a study should either evaluate a direct comparison or institute methodologic controls (e.g., control for intervening variables) in order to appropriately evaluate an outcome. For these Guidelines, the primary outcome of interest was either pulmonary aspiration or the adverse consequences from aspiration. Therefore, comparison of an intervention with pulmonary aspiration or comparison of an intervention with an adverse consequence from aspiration (e.g.,pneumonitis) was the focus of these Guidelines. However, the literature was generally not sufficient to evaluate such relationships. The literature revealed four types of analytic relationships between interventions and outcomes of interest. These types of relationships are referred to as first, second, third, or fourth-order comparisons (Table 3)

A first-order comparison represents a direct comparison either between an intervention (e.g., antacid administration) and a clinical outcome, or between two

outcomes. In the studies reviewed with first-order comparisons, the relationship between one of the identified

*Readers with special interest in the statistical analyses used in establishing these Guidelines can receive further information by writing to the American Society of Anesthesiologists: 520 North Northwest Highway, Park Ridge, Illinois 60068-2573.

TABLE 4 -- Statistical Summary: Combined Test Results

Gastric volume			
Linkage 3a: Preoperative fasting status of liquids between 2 and 4 h for adults			
Fisher combined test:	Chi-square = 43.92	*P* <0.001	*df* = 18
Stouffer combined test:	Z_c (weighted) = 2.914	*P* <0.010	
Effect size estimate:	r (weighted) = 0.11		
Fail-safe N value:	Nfs 0.01 = 22		
Linkage 3b: Preoperative fasting status of liquids between 2 and 4 h for children			
Fisher combined test:	Chi-square = 10.07	*P*> 0.100 (NS)	*df* = 18
Stouffer combined test:	Z_c (weighted) = 0.028	*P* > 0.100 (NS)	
Effect size estimate:	r (weighted) = 0.13		
Linkage 5: Preoperative gastrointestinal stimulants			
Fisher combined test:	Chi-square = 79.00	*P* < 0.001	*df* = 20
Stouffer combined test:	Z_c (weighted) = 1.823	*P* > 0.010 (NS)	
Effect size estimate:	r (weighted) = 0.30		
Linkage 6: Preoperative histamine-2 receptor antagonists			
Fisher combined test:	Chi-square = 252.97	*P*< 0.001	*df* = 96
Stouffer combined test:	Z_c (weighted) = 5.768	*P* < 0.001	
Effect size estimate:	r (weighted) = 0.24		
Fail-safe N value:	Nfs 0.01 = 856		
Linkage 7: Preoperative antacids			
Fisher combined test:	Chi-square = 11.98	*P* > 0.100 (NS)	*df* = 14
Stouffer combined test:	Z_c (weighted) = 0.326	*P*> 0.100 (NS)	
Effect size estimate:	r (weighted) = 0.05		
Linkage 10: Preoperative multiple agents			
Fisher combined test:	Chi-square = 30.40	*P* > 0.100 (NS)	*df* = 24
Stouffer combined test:	Z_c (weighted) = 3.532	*P*< 0.010	
Effect size estimate:	r (weighted) = 0.07		
Gastric volume, airway/salivary secretions			
Linkage 9: Preoperative anticholinergics			
Fisher combined test:	Chi-square = 49.76	*P*<0.001	*df* = 18
Stouffer combined test:	Z_c (weighted) = 3.416	*P*<0.001	
Effect size estimate:	r (weighted) = 0.17		
Fail-safe N value:	Nfs 0.01 = 22		
Gastric *p*H			
Linkage 3a: Preoperative fasting status of liquids between 2 and 4 h for adults			
Fisher combined test:	Chi-square = 11.98	*P*> 0.100 (NS)	*df* = 18
Stouffer combined test:	Z_c (weighted) = 1.521	*P*> 0.50 (NS)	
Effect size estimate:	r (weighted) = 0.04		
Linkage 3b: Preoperative fasting status of liquids between 2 and 4 h for children			
Fisher combined test:	Chi-square = 17.89	*P*> 0.100 (NS)	*df* = 22
Stouffer combined test:	Z_c (weighted) = 0.019	*P*> 0.100 (NS)	
Effect size estimate:	r (weighted) = 0.03		
Linkage 5: Preoperative gastrointestinal stimulants			
Fisher combined test:	Chi-square = 24.13	*P*> 0.025 (NS)	*df* = 14
Stouffer combined test:	Z_c (weighted) = 0.151	*P*> 0.100 (NS)	
Effect size estimate:	r (weighted) = 0.12		
Linkage 6: Preoperative histamine-2 receptor antagonists			
Fisher combined test:	Chi-square = 595.24	*P*<0.001	*df* = 110
Stouffer combined test:	Z_c (weighted) = 10.572	*P*< 0.001	
Effect size estimate:	r (weighted) = 0.39		
Fail-safe N value:	Nfs 0.01 = 3915		
Linkage 7: Preoperative Antacids			
Fisher combined test:	Chi-square = 66.80	*P*< 0.001	*df* = 22
Stouffer combined test:	Z_c (weighted) = 4.245	*P*<0.001	
Effect size estimate:	r (weighted) = 0.22		
Fail-safe N value:	Nfs 0.01 = 55		
Linkage 9: Preoperative Anticholinergics			

Fisher combined test:	Chi-square = 15.20	*P*> 0.100 (NS)	*df* = 10
Stouffer combined test:	Z_c (weighted) = 1.991	*P*> 0.010 (NS)	
Effect size estimate:	r (weighted) = 0.09		
Linkage 10: Preoperative Multiple Agents			
Fisher combined test:	Chi-square = 28.38	*P*> 0.100 (NS)	*df* = 28
Stouffer combined test:	Z_c (weighted) = 3.261	*P*< 0.010	
Effect size estimate:	r (weighted) = 0.05		
Nausea and vomiting			
Linkage 8: Preoperative Antiemetics			
Fisher combined test:	Chi-square = 64.38	*P*< 0.001	*df* = 28
Stouffer combined test:	Z_c (weighted) = 1.957	*P*> 0.010 (NS)	
Effect size estimate:	r (weighted) = 0.14		

interventions in the Guidelines and the incidence of pulmonary aspiration (i.e., the primary outcome) was not assessed. Therefore, cause-and-effect relationships between the intervention of interest and pulmonary aspiration cannot be shown. Although some outcomes (e.g., gastric volume or pH) were considered by the authors to be representative of a predicted "risk" of pulmonary aspiration, results of such comparisons were not sufficient to provide methodologically acceptable evidence.

Levels 2 through 4 represent comparisons that must first control for an intermediate outcome. For example, in order to examine the effectiveness of a histamine-2 receptor antagonist on pulmonary aspiration, the effect of the histamine-2 receptor antagonist on gastric content as well as the occurrence of emesis must be methodologically controlled. The gastric content and emesis "outcomes" are intervening steps between the intervention and pulmonary aspiration. This example would be considered a "third-order" comparison.

Level 2 represents a comparison in which one step, or intermediate outcome, exists between the intervention and the outcome of interest. However, level 2 relationships do not examine the association between an intervention of interest and the occurrence of pulmonary aspiration.

Level 3 contains one relationship of interest to the Guidelines (i.e., intervention/pulmonary aspiration), and Level 4 contains the other relationship of interest to the Guidelines (i.e., the association between an intervention and clinical consequences from pulmonary aspiration).

Table 3 indicates that outcomes related to preoperative fasting and the administration of pharmacologic agents were insufficient to evaluate cause-and-effect relationships that link the interventions of interest in these Guidelines with the occurrence of pulmonary aspiration or the clinical consequences from pulmonary aspiration.

Although the literature was not sufficient for casual assessment related to pulmonary aspiration, the efficacy of the interventions of interest regarding intermediate outcomes are reported below. For these purposes, a directional result for each study was initially determined by classifying the outcome as either supporting a linkage, refuting a linkage, or neutral. The results were then summarized to obtain a directional assessment of support for each linkage. The literature relating to eight evidence linkages contained enough studies with well-defined experimental designs and statistical information to conduct formal meta-analyses. These eight linkages were: linkage 3a [preoperative fasting status of liquids between 2 and 4 hours for adults], 3b [preoperative fasting status of liquids between 2 and 4 hours for children], 5 [preoperative gastrointestinal stimulants], 6 [preoperative histamine-2 receptor antagonists], 7 [preoperative antacids], 8 [preoperative antiemetics], 9 [preoperative anticholinergics], and 10 [preoperative multiple agents versus single agents]. Outcomes for all of the above linkages consisted of gastric volume, pH, gastric secretions, or nausea and vomiting.

Combined probability tests were applied to continuous data, and an odds-ratio procedure was applied to dichotomous study results. Two combined probability tests were employed as follows: (1) The Fisher Combined Test, producing chi-square values based on logarithmic transformations of the reported p-values from the independent studies, and (2) the Stouffer Combined Test, providing weighted representation of the studies by weighting each of the standard normal deviates by the size of the sample. A procedure based on the Mantel-Haenszel method for combining study results using 2 × 2 tables was available for use with outcome frequency information. An acceptable significance level was set at $p < 0.01$ (one-tailed) and effect size estimates were calculated. Interobserver agreement was established through assessment of interrater reliability testing. Tests for heterogeneity of the independent samples were conducted to assure consistency among the study results. To control for potential publishing bias, a "fail-safe N" value was calculated for each combined probability test. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Results of the combined probability tests are reported in Table 4. Significance levels from the Fisher and weighted Stouffer Combined Tests for gastric volume were significant for linkages 3a (preoperative fasting status of liquids between 2 and 4 hours for adults), and 6 (preoperative histamine-2 receptor antagonists). Significance levels for gastric pH were significant for linkages 6 (preoperative histamine-2 receptor antagonists) and 7 (preoperative antacids). Significance levels for gastric volume and airway/salivary secretions were significant for linkage 9 (preoperative anticholinergics). Weighted effect size estimates for these linkages ranged from r = 0.17 to r = 0.40, demonstrating moderate effect size estimates.

Tests for heterogeneity of statistical tests and effect size were non-significant for: a) gastric volume outcomes; linkages 3a, 3b, 5, 7, and 10; b) gastric pH outcomes, linkages 3a, 3b, 5, 6, 7, 9, and 10; for gastric volume and airway/salivary secretions; linkage 9; for nausea and vomiting: linkage 8. These findings indicate that the pooled studies provided common estimates of significance and population effect sizes. Tests for heterogeneity of statistical tests and for effect size were

TABLE 5 -- Consultant Survey of Evidence Linkages: Weighted Responses (N = 77)

Linkages	Reduces Adverse Outcomes	Increases Patient Comfort	Improves Patient Satisfaction	Improves Cost/Utilization
1. A preoperative assessment	0.83	0.92	0.97	0.66
2. 4-8 h fasting of solids for adults	-0.49	0.42	0.45	-0.43
3a. 2-4 h fasting of liquids for adults	0.16	0.92	0.89	0.15
3b. 2-4 h fasting of clear liquids for children	0.55	1.00	0.99	0.22
4. 2-4 h fasting of milk for infants	-0.12	0.88	0.73	-0.07
5. Preoperative gastrointestinal stimulants	-0.03	-0.32	-0.27	-0.27
6. Preoperative gastric acid secretion blockage	0.26	-0.19	-0.22	-0.19
7. Preoperative antacids	0.12	-0.53	-0.54	-0.22
8. Preoperative antiemetics	0.29	0.14	0.34	-0.11
9. Preoperative anticholinergics	-0.45	-0.89	-0.84	-0.57
10. Preoperative multiple drugs	-0.07	-0.14	-0.14	-0.29

significant for linkage 6 (gastric volume). These findings may reflect the differential influence of the various types of histamine-2 receptor antagonists (e.g.,

cimetidine,ranitidine, famotidine), and further analysis may need to separate the distinct influence on gastric volume of each agent.

Agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a Kappa statistic for two-rater agreement pairs were as follows: (1) type of study design, k = 0.75 to 0.95; (2) type of analysis, k = 0.54 to 0.85; (3) evidence linkage assignment, k = 0.68 to 0.82; and (4) literature inclusion for database, k = 0.64 to 0.78. Three-rater chance-corrected agreement values were: (1) design, Sav = 0.81, Var (Sav) = 0.006; (2) analysis, Sav = 0.66, Var (Sav) = 0.014; (3) linkage identification, Sav = 0.75, Var (Sav) = 0.005; (4) literature database inclusion, Sav = 0.67, Var (Sav) = 0.050. These values represent moderate to high levels of agreement.

The findings of the literature analyses were supplemented by the opinions of Task Force members as well as by surveys of the opinions of a panel of Consultants as described in the text of the Guidelines (N = 92). The rate of return was 84% (N = 77/92). The percentage of Consultants supporting each linkage is reported in Table 5. Consultants, in general, were highly supportive (i.e., they agreed that the specified linkage reduced the risk of adverse outcomes) of linkage 1 (preoperative assessment) and linkage 3b (2-4 hour fasting of clear liquids for children). Consultants believed that each of the 10 linkages were important issues for the Guidelines to address. Consultants generally did not agree with linkage 2 (4-8 hour fasting of solids for adults), linkage 4 (2-4 hour fasting of milk for infants), and linkage 9 (preoperative anticholinergics).

A second survey addressing fasting periods for liquids, breast milk, infant formula, non-human milk and solids was conducted. The rate of return was 76% (N = 84/110). The percentage of Consultants indicating a specific number of fasting hours is reported in Table 6. For clear liquids, the Consultants indicated support for a 2-hour fasting period for both infants and children. For breast milk, the Consultants indicated support for a 4-hour fasting period for both neonates and infants. For infant formula, the Consultants indicated support for a 4-hour fasting period for neonates, and a 6-hour fasting period for infants. For non-human milk, a 6-hour fasting period was supported for both infants and children. For solids, a 6-hour fasting period was supported for infants and children. For a light meal, the Consultants indicated

TABLE 6 -- Consultant Fasting Survey: Percentage Agreement (N = 84)

	Number of Hours								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**>8**
Clear liquids--infants	11%	83%	3%	3%	0%	0%	0%	0%	0%
Clear liquids--children	12%	78%	5%	5%	0%	0%	0%	0%	0%
Breast milk--neonates	0%	22%	20%	54%	0%	4%	0%	0%	0%
Breast milk--infants	0%	19%	12%	56%	0%	13%	0%	0%	0%
Formula--neonates	0%	4%	9%	48%	1%	38%	0%	0%	0%
Formula--infants	0%	1%	9%	39%	1%	48%	0%	1%	0%
Non-human milk--infants	0%	1%	7%	36%	1%	49%	0%	6%	0%
Non-human milk--children	0%	0%	3%	38%	0%	50%	0%	9%	0%
Solids--infants	0%	0%	0%	8%	1%	71%	0%	19%	0%
Solids--children	0%	0%	0%	8%	0%	64%	0%	28%	0%
Light meal--adults	1%	8%	1%	14%	1%	65%	0%	10%	0%
Meat, milk, fried food--adults	0%	1%	0%	3%	1%	15%	1%	75%	4%

support for a 6-hour fasting period for adults. For a meal of meat, milk, or fried foods, an 8-hour fasting period was supported for adults.

The Consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the Guidelines were instituted. The percent of Consultants expecting no change associated with each linkage were as follows: preoperative assessment--95%; preoperative fasting of solids--75%; preoperative fasting of liquids--67%; preoperative fasting of breast milk--78%; gastrointestinal stimulants--95%; pharmacologic blockage of gastric secretion--91%; antacids--100%; antiemetics--98%, anticholinergics--100%, and multiple agents--98%.

Ninety-six percent of the respondents indicated that the Guidelines would have no effect on the amount of time spent on a typical case. For all respondents, the mean increase in the amount of time spent on a typical case was 2.4 minutes. Two respondents reported that the Guidelines would increase the amount of time spent per case. The anticipated increase for these two respondents was 5 and 120 minutes.

APPENDIX: Practice Guidelines for Obstetrical Anesthesia[D]

A Report by the American Society of Anesthesiologists Task Force on Obstetrical Anesthesia

PRACTICE guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints.

Practice guidelines are not intended as standards or absolute requirements. The use of practice guidelines cannot guarantee any specific outcome. Practice guidelines are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. The guidelines provide basic recommendations that are supported by analysis of the current literature and by a synthesis of expert opinion, open forum commentary, and clinical feasibility data (Appendix).

A. Purposes of the Guidelines for Obstetrical Anesthesia

The purposes of these Guidelines are to enhance the quality of anesthesia care for obstetric patients, reduce the incidence and severity of anesthesia-related complications, and increase patient satisfaction.

B. Focus

The Guidelines focus on the anesthetic management of pregnant patients during labor, non-operative delivery, operative delivery, and selected aspects of postpartum care. The intended patient population includes, but is not limited to intrapartum and postpartum patients with uncomplicated pregnancies or with common obstetric problems. The Guidelines do not apply to patients undergoing surgery during pregnancy, gynecological patients or parturients with chronic medical disease (*e.g.,* severe heart, renal or neurological disease).

C. Application

The Guidelines are intended for use by anesthesiologists. They also may serve as a resource for other anesthesia providers and health care professionals who advise or care for patients who will receive anesthesia care during labor, delivery and the immediate postpartum period.

D. Task Force Members and Consultants

The ASA appointed a Task Force of 11 members to review the published evidence and obtain consultant opinion from a representative body of anesthesiologists and obstetricians. The Task Force members consisted of anesthesiologists in both private and academic practices from various geographic areas of the United States.

The Task Force met its objective in a five-step process. First, original published research studies relevant to these issues were reviewed and analyzed. Second, Consultants from various geographic areas of the United States who practice or work in various settings (*e.g.,* academic and private practice) were asked to participate

Developed by the Task Force on Obstetrical: Anesthesia: Joy L. Hawkins, M.D. (Chair), Denver, Colorado; James F. Arens, M.D., Galveston, Texas; Brenda A. Bucklin, M.D., Omaha, Nebraska; Robert A. Caplan, M.D., Seattle, Washington; David H. Chestnut, M.D., Birmingham, Alabama; Richard T. Connis, Ph.D., Woodinville, Washington: Patricia A. Dailey, M.D., Hillsborough, California; Larry C. Gilstrap, M.D., Houston, Texas; Stephen C. Grice, M.D., Alpharetta, Georgia; Nancy E. Oriol, M.D., Boston, Massachusetts; Kathryn J. Zuspan, M.D., Edina, Minnesota.

in opinion surveys and review and comment on drafts of the Guidelines. Third, the Task Force held two open forums at major national meetings to solicit input from attendees on its draft recommendations. Fourth, all available information was used by the Task Force in developing the Guideline recommendations. Finally, the Consultants were surveyed to assess their opinions on the feasibility of implementing the Guidelines.

E. Availability and Strength of Evidence

Evidence-based guidelines are developed by a rigorous analytic process. To assist the reader, the Guidelines make use of several descriptive terms that are easier to understand that the technical terms and data that are used in the actual analyses. These descriptive terms are defined below:

The following terms describe the availability of scientific evidence in the literature.

Insufficient: There are too few published studies to investigate a relationship between a clinical intervention and clinical outcome.

Inconclusive: Published studies are available, but they cannot be used to assess the relationship between a clinical intervention and a clinical outcome because the studies either do not meet predefined criteria for content as defined in the "Focus of the Guidelines," or do not meet research design or analytic standards.

Silent: There are no available studies in the literature that address a relationship of interest.

The following terms describe the strength of scientific data.

Supportive: There is sufficient quantitative information from adequately designed studies to describe a statistically significant relationship ($p < 0.01$) between a clinical intervention and a clinical outcome, using the technique of meta-analysis.

Suggestive: There is enough information from case reports and descriptive studies to provide a directional assessment of the relationship between a clinical intervention and a clinical outcome. This type of qualitative information does not permit a statistical assessment of significance.

Equivocal: Qualitative data have not provided a clear direction for clinical outcomes related to a clinical intervention and (1) there is insufficient quantitative information or (2) aggregated comparative studies have found no quantitatively significant differences among groups or conditions.

The following terms describe survey responses from Consultants for any specified issue. Responses are weighted as agree = +1, undecided = 0 or disagree = -1.

Agree: The average weighted responses must be equal to or greater than +0.30 (on a scale of -1 to 1) to indicate agreement.

Equivocal: The average weighted responses must be between -0.30 and +0.30 (on a scale of -1 to 1) to indicate an equivocal response.

Disagree: The average weighted responses must be equal to or less than -0.30 (on a scale of -1 to 1) to indicate disagreement.

Guidelines

I. Perianesthetic Evaluation.

History and Physical Examination.

The literature is silent regarding the relationship between anesthesia-related obstetric outcomes and the performance of a focused history and physical examination. However, there is suggestive data that a patient's medical history and/or findings from a physical exam may be related to anesthetic outcomes. The Consultants and Task Force agree that a focused history and physical examination may be associated with reduced maternal, fetal and neonatal complications. The Task Force agrees that the obstetric patient benefits from communication between the anesthesiologist and the obstetrician.

Recommendations: The anesthesiologist should do a focused history and physical examination when consulted to deliver anesthesia care. This should include a maternal health history, an anesthesia-related obstetric history, an airway examination, and a baseline blood pressure measurement. When a regional anesthetic is planned, the back should be examined. Recognition of significant anesthetic risk factors should encourage consultation with the obstetrician.

Intrapartum Platelet Count.

A platelet count may indicate the severity of a patient's pregnancy-induced hypertension. However, the literature is insufficient to assess the predictive value of a platelet count for anesthesia-related complications in either uncomplicated parturients or those with pregnancy-induced hypertension. The Consultants and Task Force both agree that a routine platelet count in the healthy parturient is not

---

necessary. However, in the patient with pregnancy-induced hypertension, the Consultants and Task Force both agree that the use of a platelet count may reduce the risk of anesthesia-related complications.

Recommendations: A specific platelet count predictive of regional anesthetic complications has not been determined. The anesthesiologist's decision to order or require a platelet count should be individualized and based upon a patient's history, physical examination and clinical signs of a coagulopathy.

3. Blood Type and Screen.

The literature is silent regarding whether obtaining a blood type and screen is associated with fewer maternal anesthetic complications. The Consultants and Task Force are equivocal regarding the routine use of a blood type and screen to reduce the risk of anesthesia-related complications.

Recommendations: The anesthesiologist's decision to order or require a blood type and screen or cross-match should be individualized and based on anticipated hemorrhagic complications (e.g., placenta previa in a patient with previous uterine surgery).

4. Perianesthetic Recording of the Fetal Heart Rate.

The literature suggests that analgesic/anesthetic agents may influence the fetal heart rate pattern. There is insufficient literature to demonstrate that perianesthetic recording of the fetal heart rate prevents fetal complications. However, both the Task Force and Consultants agree that perianesthetic recording of the fetal heart rate reduces fetal and neonatal complications.

Recommendations: The fetal heart rate should be monitored by a qualified individual before and after administration of regional analgesia for labor. The Task Force recognizes that continuous electronic recording of the fetal heart rate may not be necessary in every clinical setting [1] and may not be possible during placement of a regional anesthetic.

Fasting in the Obstetric Patient.

Clear Liquids.

Published evidence is insufficient regarding the relationship between fasting times for clear liquids and the risk of emesis/reflux or pulmonary aspiration during labor. The Task Force and Consultants agree that oral intake of clear liquids during labor improves maternal comfort and satisfaction. The Task Force and Consultants are equivocal whether oral intake of clear liquids increases maternal risk of pulmonary aspiration.

Recommendations: The oral intake of modest amounts of clear liquids may be allowed for uncomplicated laboring patients. Examples of clear liquids include, but are not limited to, water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee. The volume of liquid ingested is less important than the type of liquid ingested. However, patients with additional risk factors of aspiration (e.g., morbid obesity, diabetes, difficult airway), or patients at increased risk for operative delivery (e.g., nonreassuring fetal heart rate pattern) may have further restrictions of oral intake, determined on a case-by-case basis.

2. Solids.

A specific fasting time for solids that is predictive of maternal anesthetic complications has not been determined. There is insufficient published evidence to address the safety of *any* particular fasting period for solids for obstetric patients. The Consultants agree that a fasting period for solids of 8 hours or more is preferable for uncomplicated parturients undergoing *elective* cesarean delivery. The Task Force recognizes that in laboring patients the timing of delivery is uncertain; therefore compliance with a predetermined fasting period is not always possible. The Task Force supports a fasting period of at least 6 hours before elective cesarean delivery.

Recommendations: Solid foods should be avoided in laboring patients. The patient undergoing elective cesarean delivery should undergo a fasting period for solids consistent with the hospital's policy for nonobstetric patients undergoing elective surgery. Both the amount and type of food ingested must be considered when determining the timing of surgery.

III. Anesthesia Care for Labor and Vaginal Delivery

A. Overview of Recommendations.

Anesthesia care is not necessary for all women for labor and/or delivery. For women who request pain relief for labor and/or delivery, there are many effective analgesic techniques available. Maternal request represents sufficient justification for pain relief, but the selected analgesia technique depends on the medical status of the patient, the progress of the labor, and the resources of the facility. When sufficient resources (e.g., anesthesia and nursing staff) are available, epidural catheter techniques should be one of the analgesic options offered. The primary goal is to provide adequate maternal analgesia with as little motor block as possible when regional analgesia is used for uncomplicated labor and/or vaginal delivery. This can be achieved by the administration of local anesthetic at low concentrations. The concentration of the local anesthetic may be further reduced by the addition of narcotics and still provide adequate analgesia.

B. Specific Recommendations.

1. Epidural anesthetics:

a. Epidural local anesthetics.

The literature supports the use of single-bolus epidural local anesthetics for providing greater quality of analgesia compared to *parenteral opioids.* However, the literature indicates a reduced incidence of spontaneous vaginal delivery associated with single-bolus epidural local anesthetics. The literature is insufficient to indicate causation. Compared to *single-injection spinal opioids* the literature is equivocal regarding the analgesic efficacy of single-bolus epidural local anesthetics. The literature suggests that epidural local anesthetics compared to spinal opioids are associated with a lower incidence of pruritus. The literature is insufficient to compare the incidence of other side-effects.

b. Addition of opioids to epidural local anesthetics. The literature supports the use of epidural local anesthetics with opioids, when compared with equal concentrations of epidural local anesthetics without opioids for providing greater quality and duration of analgesia. The former is associated with reduced motor block and an increased likelihood of spontaneous delivery, possibly as a result of a reduced total dose of local anesthetic administered over time. [N]

The literature is equivocal regarding the analgesic efficacy of *low* concentrations of epidural local anesthetics with opioids compared to *higher* concentrations of epidural local anesthetics without opioids. The literature indicates that low concentrations of epidural local anesthetics with opioids compared to higher concentrations of epidural local anesthetics are associated with reduced motor block.

No differences in the incidence of nausea, hypotension, duration of labor, or neonatal outcomes are found when epidural local anesthetics with opioids were compared to epidural local anesthetics without opioids. However, the literature indicates that the addition of opioids to epidural local anesthetics results in a higher incidence of pruritus. The literature is insufficient to determine the effects of epidural local anesthetics with opioids on other maternal outcomes (e.g., respiratory depression, urinary retention).

The Task Force and majority of Consultants are supportive of the case-by-case selection of an analgesic technique for labor. The subgroup of Consultants reporting a preferred technique, when all choices are available, selected an epidural local anesthetic technique. When a low concentration of epidural local anesthetic is used, the Consultants and Task Force agree that the addition of an opioid(s) improves analgesia and maternal satisfaction without increasing maternal, fetal or neonatal complications.

Recommendations: The selected analgesic/anesthetic technique should reflect patient needs and preferences, practitioner preferences or skills, and available resources. When an epidural local anesthetic is selected for labor and delivery, the addition of an opioid may allow the use of a lower concentration of local anesthetic and prolong the duration of analgesia. Appropriate resources for the treatment of complications related to epidural local anesthetics (e.g., hypotension, systemic toxicity, high spinal anesthesia) should be available. If opioids are added, treatments for related complications (e.g., pruritus, nausea, respiratory depression) should be available.

c. Continuous infusion epidural techniques (CIE) The literature indicates that effective analgesia can be maintained with a low concentration of local anesthetic with an epidural infusion technique. In addition, when an opioid is added to a local anesthetic infusion, an even lower concentration of local anesthetic provides effective analgesia. For example, comparable analgesia is found, with a reduced incidence of motor block, using bupivacaine infusion concentrations of *less than* 0.125% with an opioid compared to bupivacaine concentrations *equal to* 0.125% without an opioid. [R] No comparative differences are noted for incidence of instrumental delivery.

The literature is equivocal regarding the relationship between different local anesthetic infusion regimens and the incidence of nausea or neonatal outcome. However, the literature suggests that local anesthetic infusions with opioids are associated with a higher incidence of pruritus.

The Task Force and Consultants agree that infusions using low concentrations of local anesthetics with or without opioids provide equivalent analgesia, reduced motor block, and improved maternal satisfaction when compared to higher concentrations of local anesthetic.

No meta-analytic differences in the likelihood of spontaneous delivery were found when studies using morphine or meperidine were added to studies using only fentanyl or sufentanil.
References to bupivacaine are included for illustrative purposes only, and because bupivacaine is the most extensively studied local anesthetic for CIE. The Task Force recognizes that other local anesthetic agents are equally appropriate for CIE.

Recommendations: Adequate analgesia for uncomplicated labor and delivery should be provided with the secondary goal of producing as little motor block as possible. The lowest concentration of local anesthetic infusion that provides adequate maternal analgesia and satisfaction should be used. For example, an infusion concentration of bupivacaine equal to or greater than 0.25% is unnecessary for labor analgesia for most patients. The addition of an opioid(s) to a low concentration of local anesthetic may improve analgesia and minimize motor block. Resources for the treatment of potential complications should be available.

2. Spinal Opioids with or without Local Anesthetics.

The literature suggests that spinal opioids with or without local anesthetics provide effective labor analgesia without significantly altering the incidence of neonatal complications. There is insufficient literature to compare spinal opioids with parenteral opioids. However, the Consultants and Task Force agree that spinal opioids provide improved maternal analgesia compared to parenteral opioids.

The literature is equivocal regarding analgesic efficacy of spinal opioids compared to epidural local anesthetics. The Consultants and Task Force agree that spinal opioids provide equivalent analgesia compared to epidural local anesthetics. The Task Force agrees that the rapid onset of analgesia provided by single-injection spinal techniques may be advantageous for selected patients (e.g., those in advanced labor).

Recommendations: Spinal opioids with or without local anesthetics may be used to provide effective, although time-limited, analgesia for labor. Resources for the treatment of potential complications (e.g., pruritus, nausea, hypotension, respiratory depression) should be available.

3. Combined spinal-epidural techniques.

Although the literature suggests that combined spinal-epidural techniques (CSE) provide effective analgesia, the literature is insufficient to evaluate the analgesic efficacy of CSE compared to epidural local anesthetics. The literature indicates that use of CSE techniques with opioids when compared to epidural local anesthetics with or without opioids results in a higher incidence of pruritus and nausea. The Task Force and Consultants are equivocal regarding improved analgesia or maternal benefit of CSE versus epidural techniques. Although the literature is insufficient to evaluate fetal and neonatal outcomes of CSE techniques, the Task Force and Consultants agree that CSE does not increase the risk of fetal or neonatal complications.

Recommendations: Combined spinal-epidural techniques may be used to provide rapid and effective analgesia for labor. Resources for the treatment of potential complications (e.g., pruritus, nausea, hypotension, respiratory depression) should be available.

4. Regional Analgesia and Progress of Labor.

There is insufficient literature to indicate whether timing of analgesia related to cervical dilation affects labor and delivery outcomes. Both the Task Force and Consultants agree that cervical dilation at the time of epidural analgesia administration does not impact the outcome of labor.

The literature indicates that epidural analgesia may be used in a trial of labor for previous cesarean section patients without adversely affecting the incidence of vaginal delivery. However, randomized comparisons of epidural versus other specific anesthetic techniques were not found, and comparison groups were often confounded.

Recommendations: Cervical dilation is not a reliable means of determining when regional analgesia should be initiated. Regional analgesia should be administered on an individualized basis.

5. Monitored or Stand-by Anesthesia Care for Complicated Vaginal Delivery.

Monitored anesthesia care refers to instances in which an anesthesiologist has been called upon to provide specific anesthesia services to a particular patient undergoing a planned procedure. [2] For these Guidelines, stand-by anesthesia care refers to the availability of the anesthesiologist in the facility, in the event of obstetric complications. The literature is silent regarding the subject of monitored or stand-by anesthesia care in obstetrics. However, the Task Force and Consultants agree that monitored or stand-by anesthesia care for complicated vaginal delivery reduces maternal, fetal, and neonatal complications.

Recommendations: Either monitored or stand-by anesthesia care, determined on a case-by-case basis for complicated vaginal delivery (e.g., breech presentation, twins, and trial of instrumental delivery), should be made available when requested by the obstetrician.

IV. Removal of Retained Placenta

1. Anesthetic Choices.

The literature is insufficient to indicate whether a particular type of anesthetic is more effective than another for removal of retained placenta. The literature is also insufficient to assess the relationship between a particular type of anesthetic and maternal complications. The Task Force and Consultants agree that spinal or epidural anesthesia (i.e., regional anesthesia)

---

is associated with reduced maternal complications and improved satisfaction when compared to general anesthesia or sedation/analgesia. The Task Force recognizes that circumstances may occur when general anesthesia or sedation/analgesia may be the more appropriate anesthetic choice (e.g., significant hemorrhage).

Recommendations: Regional anesthesia, general endotracheal anesthesia, or sedation/analgesia may be used for removal of retained placenta. Hemodynamic status should be assessed before giving regional anesthesia to a parturient who has experienced significant bleeding. In cases involving significant maternal hemorrhage, a general anesthetic may be preferable to initiating regional anesthesia. Sedation/analgesia should be titrated carefully due to the potential risk of pulmonary aspiration in the recently delivered parturient with an unprotected airway.

2. Nitroglycerin for Uterine Relaxation.

The literature suggests and the Task Force and Consultants agree that the administration of nitroglycerin is effective for uterine relaxation during removal of retained placental tissue.

Recommendations: Nitroglycerin is an alternative to terbutaline sulfate or general endotracheal anesthesia with halogenated agents for uterine relaxation during removal of retained placental tissue. Initiating treatment with a low dose of nitroglycerin may relax the uterus sufficiently while minimizing potential complications (e.g., hypotension).

V. Anesthetic Choices for Cesarean Delivery

The literature suggests that spinal, epidural or CSE anesthetic techniques can be used effectively for cesarean delivery. When compared to regional techniques, the literature indicates that general anesthetics can be administered with shorter induction-to-delivery times. The literature is insufficient to determine the relative risk of maternal death associated with general anesthesia compared to other anesthetic techniques. However, the literature suggests that a greater number of maternal deaths occur when general anesthesia is administered. The literature indicates that a larger proportion of neonates in the general anesthesia groups, compared to those in the regional anesthesia groups, are assigned Apgar scores of less than 7 at one and five minutes. However, few studies have utilized randomized comparisons of general versus regional anesthesia, resulting in potential selection bias in the reporting of outcomes.

The literature suggests that maternal side effects associated with regional techniques may include hypotension, nausea, vomiting, pruritus and postdural puncture headache. The literature is insufficient to examine the comparative merits of various regional anesthetic techniques.

The Consultants agree that regional anesthesia can be administered with fewer maternal and neonatal complications and improved maternal satisfaction when compared to general anesthesia. The consultants are equivocal about the possibility of increased maternal complications when comparing spinal or epidural anesthesia with CSE techniques. They agree that neonatal complications are not increased with CSE techniques.

Recommendations: The decision to use a particular anesthetic technique should be individualized based on several factors. These include anesthetic, obstetric and/or fetal risk factors (e.g., elective versus emergency) and the preferences of the patient and anesthesiologist. Resources for the treatment of potential complications (e.g., airway management, inadequate analgesia, hypotension, pruritus, nausea) should be available.

VI. Postpartum Tubal Ligation

There is insufficient literature to evaluate the comparative benefits of local, spinal, epidural or general anesthesia for postpartum tubal ligation. Both the Task Force and Consultants agree that epidural, spinal and general anesthesia can be effectively provided without affecting maternal complications. Neither the Task Force nor the Consultants agree that local anesthetic techniques provide effective anesthesia, and they are equivocal regarding the impact of local anesthesia on maternal complications. Although the literature is insufficient, the Task Force and Consultants agree that a postpartum tubal ligation can be performed safely within eight hours of delivery in many patients.

Recommendations. Evaluation of the patient for postpartum tubal ligation should include assessment of hemodynamic status (e.g., blood loss) and consideration of anesthetic risks. The patient planning to have an elective postpartum tubal ligation within 8 hours of delivery should have no oral intake of solid foods during labor, and postpartum until the time of surgery. Both the timing of the procedure and the decision to use a particular anesthetic technique (i.e., regional versus general) should be individualized, based on anesthetic and/or obstetric risk factors and patient preferences. The anesthesiologist should be aware that an epidural catheter placed for labor may be more likely to fail with longer postdelivery time intervals. If a postpartum tubal ligation is to be done before the patient is discharged

TABLE 1 -- Suggested Resources for Obstetric Hemorrhagic Emergencies*

1. Large bore iv catheters
2. Fluid warmer
3. Forced air body warmer
4. Availability of blood bank resources
5. Equipment for infusing iv fluids and/or blood products rapidly. Examples include (but are not limited to) hand squeezed fluid chambers, hand inflated pressure bags, and automatic infusion devices.

* The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and health-care facility.

from the hospital, the procedure should not be attempted at a time when it might compromise other aspects of patient care in the labor and delivery area.

VII. Management of Complications

1. Resources for Management of Hemorrhagic Emergencies.

The literature suggests that the availability of resources for hemorrhagic emergencies is associated with reduced maternal complications. The Task Force and Consultants agree that the availability of resources for managing hemorrhagic emergencies is associated with reduced maternal, fetal and neonatal complications.

Recommendations: Institutions providing obstetric care should have resources available to manage hemorrhagic emergencies *(Table 1).* In an emergency, the use of type-specific or O negative blood is acceptable in the parturient.

2. Equipment for Management of Airway Emergencies.

The literature suggests, and the Task Force and Consultants agree that the availability of equipment for the management of airway emergencies is associated with reduced maternal complications.

Recommendations: Labor and delivery units should have equipment and personnel readily available to manage airway emergencies. Basic airway management equipment should be immediately available during the initial provision of regional analgesia (Table 2) In addition, portable equipment for difficult airway management should be readily available in the operative area of labor and delivery units (Table 3) (Table Not Available) .

3. Central Invasive Hemodynamic Monitoring.

There is insufficient literature to indicate whether pulmonary artery catheterization is associated with improved maternal, fetal or neonatal outcomes in patients with pregnancy-related hypertensive disorders. The literature is silent regarding the management of obstetric

TABLE 2 -- Suggested Resources for Airway Management During Initial Provision of Regional Anesthesia *

1. Laryngoscope and assorted blades
2. Endotracheal tubes, with stylets
3. Oxygen source
4. Suction source with tubing and catheters
5. Self-inflating bag and mask for positive pressure ventilation
6. Medications for blood pressure support, muscle relaxation, and hypnosis

*The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and health-care facility.

Recommendations: The decision to perform invasive hemodynamic monitoring should be individualized and based on clinical indications that include the patient's medical history and cardiovascular risk factors. The Task Force recognizes that not all practitioners have access to resources for utilization of central venous or pulmonary artery catheters in obstetric units.

TABLE 3 -- Suggested Contents of a Portable Unit for Difficult Airway Management for Cesarean Section Rooms *

(Not Available)

* The items listed represent suggestions. The items should be customized to meet the specific needs, preferences, and skills of the practitioner and health-care facility.

patients with central venous catheterization alone. The literature suggests that pulmonary artery catheterization has been used safely in obstetric patients; however, the literature is insufficient to examine specific obstetric outcomes. The Task Force and Consultants agree that it is not necessary to use central invasive hemodynamic monitoring routinely for parturients with severe preeclampsia.

4. Cardiopulmonary Resuscitation.

The literature is insufficient to evaluate the efficacy of CPR in the obstetric patient during labor and delivery. The Task Force is supportive of the immediate availability of basic and advanced life-support equipment in the operative area of labor and delivery units.

Recommendations: Basic and advanced life-support equipment should be immediately available in the operative area of labor and delivery units. If cardiac arrest occurs during labor and delivery, standard resuscitative measures and procedures, including left uterine displacement, should be taken. In cases of cardiac arrest, the American Heart Association has stated the following: "Several authors now recommend that the decision to perform a perimortem cesarean section should be made rapidly, with delivery effected within 4 to 5 minutes of the arrest." [3]

/das/book/view/29494766/875/1145.html

Appendix: Methods and Analyses.

The scientific assessment of these Guidelines was based on the following statements, or evidence linkages. These linkages represent directional statements about relationships between obstetrical anesthetic interventions and clinical outcomes.

I. Perianesthetic Evaluation

1. A directed history and physical examination reduces maternal, fetal & neonatal complications.

2a. A routine intrapartum platelet count reduces maternal anesthetic complications.

2b. For pregnancy-induced hypertension, an intrapartum platelet count reduces maternal anesthetic complications.

3. For all parturients, an intrapartum blood type & screen reduces maternal, fetal & neonatal complications.

4. Perianesthetic recording of the fetal heart rate reduces fetal & neonatal complications.

II. Fasting for Labor and Delivery

5a. Oral intake of clear liquids during labor improves patient comfort and satisfaction, and does not increase maternal complications.

5b. Oral intake of solids during labor increases maternal complications.

III. Anesthetic Choices for Labor and Delivery

6a. Epidural techniques versus parenteral opioids: (a) improve maternal analgesia, (b) decrease maternal anesthetic complications, and (c) decrease fetal and neonatal complications.

6b. Epidural techniques versus spinal techniques: (a) improve maternal analgesia and (b) decrease maternal anesthetic complications.

6c. Epidural local anesthetics with opioids versus equal concentrations of epidural local anesthetics without opioids: (a) improve maternal analgesia, but (b) increase maternal, fetal & neonatal anesthetic complications.

6d. Epidural local anesthetics with opioids versus higher concentrations of epidural local anesthetics without opioids: (a) improve maternal analgesia, and (b) reduce maternal, fetal & neonatal anesthetic complications.

6e. Epidural infusion of lower concentrations of local anesthetics with opioids (i.e., bupivacaine concentrations less than 0.125% with opioids versus concentrations equal to 0.125%): (a) provides equivalent maternal analgesia, (b) reduces maternal motor block, but (c) increases opioid-related maternal anesthetic complications.

6f. Epidural infusion of lower concentrations of local anesthetics with opioids (i.e., bupivacaine concentrations less than 0.25% with opioids versus bupivacaine equal to or greater than 0.25%): (a) provides equivalent maternal analgesia, (b) reduces maternal motor block, but (c) increases opioid-related maternal anesthetic complications.

6g. Spinal opioids (with or without local anesthetic) versus parenteral opioids: (a) improve maternal analgesia, (b) reduce maternal, fetal & neonatal anesthetic complications, and (c) improve maternal satisfaction.

6h. Combined spinal-epidural techniques versus epidural local anesthetics: (a) improve maternal analgesia, but (b) increase maternal, fetal & neonatal anesthetic complications.

6i. Administering epidural analgesia at cervical dilatations of 3 to 5 centimeters (versus <3 cm) (a) improves maternal analgesia, (b) reduces maternal, fetal & neonatal obstetric complications, and (c) improves maternal satisfaction.

6j. Administering epidural analgesia at cervical dilatations of 3 to 5 centimeters (versus >5 cm) (a) improves maternal analgesia, (b) reduces maternal, fetal & neonatal anesthetic complications, and (c) improves maternal satisfaction.

6k. Epidural techniques for trial of labor patients: (a) reduces the incidence of cesarean delivery, (b) reduces maternal, fetal & neonatal obstetric complications, and (c) improves maternal satisfaction.

6l. Monitored or stand-by anesthesia care for complicated vaginal delivery reduces maternal, fetal & neonatal complications.

IV. Removal of Retained Placenta

7. Regional anesthesia [versus general anesthesia or sedation] for pain management during removal of retained placenta reduces maternal anesthetic complications and improves patient satisfaction.

8. Administration of nitroglycerin for uterine relaxation improves success at removing retained placenta.

V. Anesthetic Choices for Cesarean Delivery

9a. Spinal anesthesia for cesarean section provides maternal comfort & satisfaction without clinically significant maternal, fetal & neonatal anesthetic

complications.

9b. Epidural anesthesia for cesarean section provides maternal comfort & satisfaction without clinically significant maternal, fetal & neonatal anesthetic complications.

9c. General anesthesia for cesarean section provides maternal comfort & satisfaction without clinically significant maternal, fetal & neonatal anesthetic complications.

9d. Combined spinal-epidural techniques versus epidural or spinal techniques alone for cesarean section provide maternal comfort & satisfaction without clinically significant maternal, fetal & neonatal anesthetic complications.

VI. Postpartum Tubal Ligation

10a. Local anesthesia for postpartum tubal ligation without preexisting anesthesia (a) improves maternal analgesia, (b) reduces maternal anesthetic complications, and (c) improves maternal satisfaction.

10b. Spinal anesthesia for postpartum tubal ligation without preexisting anesthesia (a) improves maternal analgesia, (b) reduces maternal anesthetic complications, and (c) improves maternal satisfaction.

10c. Epidural anesthesia for postpartum tubal ligation without preexisting anesthesia (a) improves maternal analgesia, (b) reduces maternal anesthetic complications, and (c) improves maternal satisfaction.

10d. General anesthesia for postpartum tubal ligation without preexisting anesthesia (a) improves maternal analgesia, (b) reduces maternal anesthetic complications, and (c) improves maternal satisfaction.

11. A postpartum tubal ligation [i.e., within 8 hours of delivery]: (a) does not increase maternal anesthetic complications, (b) improves patient satisfaction, and (c) improves cost/efficiency.

VII. Management of Complications

12. Availability of resources for management of hemorrhagic emergencies reduces maternal, fetal & neonatal anesthetic complications.

13. Availability of equipment for management of airway emergencies reduces maternal, fetal & neonatal anesthetic complications.

14. Peripartum invasive hemodynamic monitoring for preeclamptic patients reduces maternal, fetal & neonatal anesthetic and obstetric complications.

15. Immediate availability of basic and advanced life-support equipment in the operative area of labor and delivery units reduces maternal, fetal & neonatal complications.

.

Scientific evidence was derived from aggregated research literature with meta-analyses utilized when appropriate, and from surveys, open presentations and other consensus-oriented activities. For purposes of literature aggregation, potentially relevant clinical studies were identified via electronic and manual searches of the literature. The electronic search covered a 33-year period from 1966 through 1998. The manual search covered a 59-year period of time from 1940 through 1998. Over 4000 citations were initially identified, yielding a total of 2347 nonoverlapping articles that addressed topics related to the 33 evidence linkage. Following review of the articles, 1819 studies did not provide direct evidence, and were subsequently eliminated. A total of 528 articles (from 57 journals) contained direct linkage-related evidence.

A directional result for each study was initially determined by classifying the outcome as either supporting a linkage, refuting a linkage, or neutral. The results were then summarized to obtain a directional assessment of support for each linkage. The literature relating to 8 evidence linkages contained enough studies with well-defined experimental designs and statistical information to conduct formal meta-analyses. These eight linkages were: linkage 6a [epidural versus parenteral techniques for labor], 6b [epidural versus single-shot spinal techniques for labor], 6c [epidural local anesthetics with opioids versus equal dosages of local anesthetics without opioids], 6d [epidural local anesthetics with opioids versus higher concentrations of local anesthetics without opioids], 6e [epidural infusion of local anesthetic (bupivacaine) concentrations of less than 0.125% versus concentrations equal to 0.125%], 6h [combined spinal-epidural techniques versus epidural local anesthetics for labor], 6k [epidural anesthesia for trial of labor], and 9c [general anesthesia versus epidural or spinal anesthesia for cesarean delivery].

Combined probability tests were applied to continuous data, and an odds-ratio procedure was applied to dichotomous study results. Two combined probability tests were employed as follows: (1) The Fisher Combined Test, producing chi-square values based on logarithmic transformations of the reported p-values from the independent studies, and (2) the Stouffer Combined Test, providing weighted representation of the studies by weighting each of the standard normal deviates by the size of the sample. An odds-ratio procedure based on the Mantel-Haenszel method for combining study results using 2 × 2 tables was used with outcome frequency information. An acceptable significance level was set at $p < 0.01$ (one-tailed) and effect size estimates were calculated. Interobserver agreement was established through assessment of interrater reliability testing. Tests for heterogeneity of the independent samples were conducted to ensure consistency among the study results. To control for potential publishing bias, a "fail-safe N" value was calculated for each combined probability test. No search for unpublished studies was conducted, and no reliability tests for locating research results were done.

Meta-analytic results are reported in Table 4 . To be considered acceptable evidence, both the Fisher and weighted Stouffer combined test results must agree. Significant combined test values were found for: (1) *analgesic efficacy* linkages 6a (epidural versus parenteral techniques for labor) and 6c (epidural local anesthetics with opioids versus equal dosages of local anesthetics without opioids); (2) *duration of analgesia* -linkage 6c (epidural local anesthetics with versus without opioids), and (3) *incision-to-delivery time* -linkage 9c (general anesthesia versus epidural or spinal anesthesia for cesarean delivery). Weighted effect size values for these linkages ranged from $r = 0.13$ to $r = 0.41$, representing small-to-moderate effect size estimates.

To be considered acceptable evidence, combined test results must agree with Mantel-Haenszel odds-ratios when both types of data are assessed. Odds ratios were significant for the following outcomes: (1) *analgesic efficacy* -linkage 6c (epidural local anesthetics with opioids versus equal dosages of local anesthetics without opioids); (2) *mode of delivery* - linkage 6a (epidural versus parenteral techniques for labor); (3) *motor block;* linkage 6c (epidural local anesthetics with opioids versus equal dosages of local anesthetics without opioids), 6d (epidural local anesthetics with opioids versus higher concentration of local anesthetics without opioids), and 6e (epidural infusion of local anesthetic concentrations of less than 0.125% versus concentrations equal to 0.125%); (4) *pruritus* - linkage 6c (epidural local anesthetics with opioids versus equal dosages of local anesthetics without opioids), 6d (epidural local anesthetics with opioids versus higher concentrations of local anesthetics without opioids) and 6h (combined spinal-epidural techniques versus epidural local anesthetics for labor); (5) *nausea* - 6h

TABLE 4 -- Meta-analysis Summary

Linkages	No. Studies	Fisher X2	*P*	Weighted Stouffer Zc	*P*	Effect Size	Mantel-Haenszel X2	*P*	Odds Ratio	Heterogeneity	
										Significance	Effect Size
6a. Epidural vs. parenteral techniques											
Analgesic efficacy *	8	92.85	<0.001	2.95	<0.01	0.25				<0.001	<0.001
Mode of delivery *	9						41.80	<0.001	0.47		>0.05 (NS)
Cesarean delivery *	6						9.16	<0.01	0.57		>0.01 (NS)
Duration of labor *	6	12.85	>0.10 (NS)	0.47	>0.10 (NS)	0.02				>0.10 (NS)	>0.10 (NS)
APGAR at 1 min	7						7.07	<0.01	0.61		>0.10 (NS)
APGAR at 5 min	7						5.42	>0.01 (NS)	0.44		>0.10 (NS)
6b. Epidural vs. spinal techniques											
Analgesic efficacy *	5	17.03	>0.01 (NS)	-0.92	>0.10 (NS)	0.22				>0.10 (NS)	>0.10 (NS)
6c. Epidural local anesthetics with opioids vs. equal LA dosages											
Analgesic efficacy *	11	78.72	<0.001	2.75	<0.01	0.20	39.12	<0.001	4.25	>0.10 (NS)	>0.10 (NS)
Duration of analgesia *	10	46.00	<0.001	2.55	<0.01	0.13				>0.10 (NS)	<0.001
Mode of delivery *	13						5.12	>0.01 (NS)	1.32		>0.01 (NS)
Mode of delivery *	8						7.17	>0.01 (NS)	1.45		>0.10 (NS)
Mode of delivery *	6						11.45	<0.01	1.65		>0.10 (NS)
Duration of labor *	8	10.55	>0.10 (NS)	1.32	>0.10 (NS)	0.06				>0.10 (NS)	>0.10 (NS)
Motor block *	10						18.79	<0.001	0.44		>0.10 (NS)
Dense motor block *	8						18.53	<0.001	0.29		>0.10 (NS)
Motor block *	7						14.37	<0.001	0.46		>0.10 (NS)
Pruritus *	13						155.14	<0.001	7.23		>0.10 (NS)
Pruritus *	12						153.32	<0.001	7.36		>0.10 (NS)
Nausea *	13						1.004	>0.10 (NS)	0.84		>0.10 (NS)
Nausea *	11						1.27	>0.10 (NS)	0.81		>0.10 (NS)
Hypotension *	5						0.003	>0.10 (NS)	0.98		>0.10 (NS)
APGAR at 1 min *	11						0.52	>0.10 (NS)	1.16		>0.10 (NS)
APGAR at 1 min *	9						0.15	>0.10 (NS)	1.09		>0.10 (NS)
APGAR at 5 min *	6						0.07	>0.10 (NS)	1.11		>0.10 (NS)
APGAR at 5 min *	6						0.01	>0.10 (NS)	0.97		>0.10 (NS)
6d. Epidural local anesthetics with opioids vs. higher LA dosages											
Analgesic efficacy *	9	15.39	>0.10 (NS)	-0.03	>0.10 (NS)	-0.03	0.24	>0.10 (NS)	>1.10 (NS)	>0.10 (NS)	>0.10 (NS)
Analgesic efficacy *	8	15.39	>0.10 (NS)	-0.003	>0.10 (NS)	-0.04				>0.10 (NS)	>0.10 (NS)
Mode of delivery *	8						0.003	>0.10 (NS)	1.01		>0.10 (NS)
Mode of delivery *	7						2.20	>0.10 (NS)	1.25		>0.10 (NS)
Mode of delivery *	6						0.67	>0.10 (NS)	1.14		>0.10 (NS)
Mode of delivery *	5						1.17	>0.10 (NS)	1.19		>0.10 (NS)
Duration of labor *	5	2.23	>0.10 (NS)	0.17	>0.10 (NS)	0.01				>0.10 (NS)	>0.10 (NS)

Motor block *	6						93.58	<0.001	0.20		>0.01 (NS)
Motor block *	5						91.16	<0.001	0.20		>0.01 (NS)
Pruritus *	7						62.63	<0.001	6.16		>0.10 (NS)
Nausea *	5						0.11	>0.10 (NS)	1.07	>0.10 (NS)	
Hypotension *	7						0.08	>0.10 (NS)	0.90		>0.10 (NS)
Hypotension *	6						0.01	>0.10 (NS)	1.03		>0.10 (NS)
APGAR at 1 min *	5						0.03	>0.10 (NS)	0.96		>0.10 (NS)
6e. Epidural <0.125% vs. 0.125%											
Analgesic efficacy *	5	26.55	<0.01	-1.82	>0.01 (NS)	0.06	2.10	>0.10 (NS)	0.76	<0.01	<0.001
Mode of delivery *	6						0.54	>0.10 (NS)	1.11		>0.01 (NS)
Mode of delivery *	5						0.29	>0.10 (NS)	1.09		>0.10 (NS)
Motor of block *	5						26.24	<0.001	0.36		>0.10 (NS)
APGAR at 1 min *	5						0.05	>0.10 (NS)	1.05		>0.10 (NS)
6h CSE for labor											
Pruritus *	6						186.21	<0.001	6.14		<0.01
Nausea	6						11.14	<0.001	2.56		>0.10 (NS)
6k Epidural for VBAC											
Mode of delivery	8						0.0002	>0.10 (NS)	1.00		<0.01
9c. General anesthesia for cesarean											
Incision delivery time	15	109.54	<0.001	4.41	<0.001	0.41			<0.001	<0.001	
APGAR <7 at 1 min	18	149.25	<0.001	9.09	<0.001	0.23	161.64	<0.001	3.28	<0.001	<0.001
APGAR <7 at 5 min	14	107.02	<0.001	6.33	<0.001	0.16	70.25	<0.001	3.45	<0.001	>0.01 (NS)

* All studies in series were randomized comparative studies.

All studies in series were comparisons using bupivacaine as the local anesthetic and fentanyl or sufentanil as the opioid.

Only studies reporting both motor block and mode of delivery values were compared.

TABLE 5 -- Consultant Survey Summary: Weighted Responses

Evidence Linkages	N *	Improves Maternal Analgesia	Reduces Maternal Complications	Reduces Fetal Complications	Reduces Neonatal Complications	Improves Patient Satisfaction	Improves Cost/Efficiency	Important To Evaluate
1. Directed history and physical exam	111		0.97	0.81	0.67	0.76	0.52	0.91
2a. Routine platelet count	114		-0.66					0.02
2b. Platelet count for PIH	111	0.46						0.66
3. Blood type and screen	111	0.14						0.30
4. Recording of fetal heart rate	114				0.32			0.86
5a. Intake of clear liquids	114		-0.35			0.79		0.74
5b. Intake of solids	114							0.91
6b. Epidural local anesth vs spinal opioids	114	0.43	0.15	-0.59		0.32		
6c/6d. Epidural local with vs without opioids	114	0.79	0.61		0.84	0.80		
6e. <0.125% local + opioid infusion *vs* 0.125%	114	-0.30	-0.12		0.37	0.30		
6g. Spinal vs parenteral opioids	114	0.90	0.21		0.63	0.81		

6h. CSE Techniques vs epidural local anesth	114	-0.05	-0.10		0.50	0.06		
6l. MAC/standby anesth care	111		0.77		0.73			0.80
7. Regional anesthesia for retained placenta	114	0.55	0.54			0.56	0.14	0.71
8. Nitroglycerine for uterine relaxation	114		0.50 §					0.51
9a. Spinal anesthesia for cesarean section	111		0.75	0.35	0.31	0.80	0.42	0.87
9b1. Epidural anesthesia for cesarean section	111		0.84	0.42	0.37	0.71	-0.53	0.86
9b2. Epidural vs spinal anesthesia for cesarean	114		0.64		0.86	-0.57		
9c1. General anesthesia for cesarean section	111		-0.93	-0.78	-0.86	-0.64	-0.77	0.80
9c2. General vs regional for cesarean	114		-0.87		-0.24	-0.92		
9d. CSE for cesarean	114		0.16		0.66	-0.40		
10a. Local anesthesia for PPTL	111	-0.59	-0.30			-0.84	-0.57	0.01
10b. Spinal anesthesia for PPTL	111	0.86	0.48			0.66	0.26	0.80
10c. Epidural anesthesia for PPTL	111	0.82	0.51			0.59	-0.60	0.68
10d. General anesthesia for PPTL	111		-0.87			-0.33	-0.60	0.64
11. Immediate postpartum tubal ligation	114		0.75 ¶			0.59	0.85	0.65
12. Hemorrhagic resources	111		1.00		0.79			0.99
13. Airway resources	111		1.00		0.96			1.00
14. Routine invasive hemodynamic monitoring	114		-0.42		-0.52			0.39

* Two surveys were administered at different times.

Some responses are centered because the question referred to fetal/neonatal complications combined.

38% agreed that clear liquid intake increases aspiration risk.
§Refers to success in removing retained placenta.
¶Refers to the safety of performing a postpartum tubal ligation (PPTL) less than 8 h after delivery.

(combined spinal-epidural techniques versus epidural local anesthetics for labor; (6) *Apgar scores at 1-minute* - linkage 6a (epidural versus parenteral techniques for labor), and linkage 9c (general anesthesia versus epidural or spinal anesthesia for cesarean delivery), and (7) *Apgar scores at 5-minutes* - linkage 9c (general anesthesia versus epidural or spinal anesthesia for cesarean delivery).

For the findings noted above, tests for heterogeneity of statistical tests and effect size were *nonsignificant* for the following outcomes and linkages: (1) *analgesic efficacy - linkage* 6c; (2) mode of delivery - linkage 6a; (3) motor block - linkages 6c, 6d, and 6e; (4) pruritus - linkages 6c and 6d; (5) *nausea* - linkage 6h; (6) *Apgar scores at 1-minute - linkage* 6a; and (7) *Apgar scores at 5-minutes - linkage 9c.*

These findings indicate that the pooled studies provided common estimates of significance and population effect sizes.

For the findings noted above, tests for heterogeneity of statistical tests were significant for the following outcomes and linkages: (1) analgesic efficacy - linkage 6a; (2) Apgar scores at 1-minute - linkage 9c; (3) Apgar scores at 5-minutes - linkage 9c, and (4) incision-to-delivery time - linkage 9c. Tests for heterogeneity of effect size were significant for the following outcomes and linkages:

(1) analgesic efficacy - linkage 6a; (2) duration of analgesia - linkage 6c; (3) pruritus - linkage 6h; (3) Apgar scores at 1-minute - linkage 9c; and (4) incision-to-delivery time - linkage 9c. For analgesic efficacy, the heterogeneous findings for linkage 6a may reflect the differential influence of the various statistical tests combined with a small number of studies used in the analysis. For pruritus, variability in the reported odds ratios may reflect the varying use of opioids in the epidural local anesthetic groups, in contrast with consistent opioid use in the CSE groups, and further analysis may need to control for opioid use in both groups. For incision-to-delivery times and Apgar scores at 1-minute, variability in statistical tests and effect sizes may be the result of nonrandomized comparisons in these meta-analyses. Due to the small number of studies included in these meta-analyses, examination of the analyses for moderator variables could not be conducted.

Agreement among Task Force members and two methodologists was established by interrater reliability testing. Agreement levels using a Kappa statistic for two-rater agreement pairs were as follows: (1) type of study design, k = 0.79 to 0.83; (2) type of analysis, k = 0.57 to 0.73; (3) evidence linkage assignment, k = 0.65 to 0.93; and (4) literature inclusion for database, k = 0.54 to 1.00. Three-rater chance-corrected agreement values were: (1) design, Sav = 0.80, Var (Sav) = 0.004; (2) analysis, Sav = 0.64, Var (Sav) = 0.008; (3) linkage identification, Sav = 0.76, Var (Sav) = 0.040. (4) literature database inclusion, Sav = 0.65, Var (Sav) = 0.040. These values represent moderate to high levels of agreement.

The findings of the literature analyses were supplemented by the opinions of Task Force members as well as by surveys of the opinions of a panel of Consultants as described in the text of the Guidelines. The rate of return was 78% (N = 114/147). The percentage of Consultants supporting each linkage is reported in Table 5 . Consultants were supportive (i.e., they agreed that the specified linkage improved analgesia, reduced the risk of adverse outcomes or improved maternal satisfaction) of the following linkages: linkage 1 (history and physical exam), linkage 4 (recording of fetal heart rate), linkage 6c/d (epidural local anesthetics with versus without

opioids), linkage 61 (monitored/stand-by anesthesia care), linkage 7 (regional anesthesia for retained placenta), linkage 8 (nitroglycerin for retained placenta), linkage 9a (spinal anesthesia for cesarean delivery), linkage 9b (epidural anesthesia for cesarean delivery), linkage 10b (spinal anesthesia for PPTL), linkage 10c (epidural anesthesia for PPTL), linkage 11 (immediate postpartum tubal ligation), linkage 12 (availability of hemorrhagic resources), and linkage 13 (availability of airway resources). Consultants were not supportive of linkage 9c (general anesthesia for cesarean delivery), linkage 10a (local anesthesia for PPTL), 10d (general anesthesia for PPTL), and linkage 14 (invasive hemodynamic monitoring). Consultants believed that all of the linkages were important issues for the Guidelines to address.

Seventy-six percent of the responding Consultants indicated that fasting times for solids should be determined either on a case-by-case basis or by institutional protocol. Fifty-five percent reported a safe fasting time (for solids) for uncomplicated vaginal delivery of no less than 8 hours. Seventy-six percent indicated a safe fasting time (for solids) for elective cesarean delivery of no less than 8 hours.

The Consultants were asked to indicate which, if any, of the evidence linkages would change their clinical practices if the Guidelines were instituted. The rate of return was 59% (N = 86/147). The percent of responding Consultants expecting no change associated with each linkage were as follows: history and physical exam - 98%; routine platelet count - 96%; blood type and screen - 96%; fetal heart rate recording - 98%; oral intake of liquids - 92%; oral intake of solids - 95%; epidural local anesthetics for labor - 100%; epidural infusion for labor - 100%, spinal opioids for labor - 98%, CSE for labor - 98%, cervical dilation - 98%, monitored/stand-by anesthesia care - 100%, retained placenta analgesia - 99%, nitroglycerin for retained placenta - 94%, cesarean anesthetic choices - 100%, tubal ligation - 96%, hemorrhagic emergencies - 99%, airway emergencies - 96%, hemodynamic monitoring - 99%, and CPR - 99%. Ninety-eight percent of the respondents indicated that the Guidelines would have no effect on the amount of time spent on a typical case. Readers with special interest in the statistical analyses used in establishing these Guidelines can receive further information by writing to the American Society of Anesthesiologists: 520 North Northwest Highway, Park Ridge, Illinois 60068-2573.

References

1. Guidelines for Perinatal Care, 4th ed. American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 1997, p 100-102

2. American Society of Anesthesiologists: Position on monitored anesthesia care, ASA Standards, Guidelines and Statements. Park Ridge, IL, American Society of Anesthesiologists, October 1997, pp 20-21

3. Guidelines for cardiopulmonary resuscitation and emergency cardiac care: recommendations of the 1992 national conference. JAMA 1992; 268:2249

APPENDIX: Systeme International

SYSTEME INTERNATIONAL

The following information on Systeme International (SI) units and factors for conversion between SI and older conventional units is provided for the convenience of readers and authors. Reprints of these tables are available on request from. The Canadian Anaesthetists' Society Journal, 178 St. George Street, Toronto, Canada, M5R 2M7. [R]

Basic SI Units

Physical Quantity	Name	Symbol
Length	Metre	m
Mass	Kilogram	kg
Time	Second [*]	s
Electric current	Ampere	A
Thermodynamic temperature	Kelvin	K
Luminous intensity	Candela	cd
Amount of substance	Mole	mol

*Minute (min), hour (h) and day (d) will remain in use although they are not official SI units.

Prefixes for SI Units

Factor	Name	Symbol	Factor	Name	Symbol
10^{18}	Exa-	E	10^{-18}	Atto-	a
10^{15}	Peta-	P	10^{-15}	Femto-	f
10^{12}	Tera-	T	10^{-12}	Pico-	p
10^{9}	Giga-	G	10^{-9}	Nano-	n
10^{6}	Mega-	M	10^{-6}	Micro-	mu
10^{3}	Kilo-	k	10^{-3}	Milli-	m
10^{2}	Hecto-	h	10^{-2}	Centi-	c
10^{1}	Deca-	da	10^{-1}	Deci-	d

Derived SI Units

Quantity	SI Unit	Symbol	Expression in Terms of SI Base Units or Derived Units
Frequency	Hertz	Hz	1 Hz = 1 cycle/s (1 s^{-1})
Force	Newton	N	1 N = 1 kg · m/s^2 (1 kg · mps^{-2})
Work, energy, quantity of heat	Joute	J	1 J = 1 N · m
Power	Watt	W	1 W = 1 J/s (1 J · s^{-1})
Quantity of electricity	Coulomb	C	1 C = 1 A · s
Electric potential, potential difference, tension, electromotive force	Volt	V	1 V = 1 W/A (1 W · A^{-1})
Electric capacitance	Farad	F	1 F = 1 A · s/V (1 A · s · V^{-1})
Electric resistance	Ohm	Omega	1 Omega = 1 V/A (1 V · A^{-1})
Flux of magnetic induction, magnetic flux	Weber	Wb	1 Wb = 1 V · s
Magnetic flux density, magnetic induction	Tesla	T	1 T = 1 Wb/m^2 (1 Wb · m^{-2})
Inductance	Henry	H	1 H = 1 V · s/A (1 V · s · A^{-1})
Pressure	Pascal	Pa	1 Pa = 1 N/m^2 (1 N · m^{-2})
			= 1 kg/m · s^2 (1 kg · m-1 · s^{-2})

The litre (10^{-3} m^3 = dm^3), though not official, will remain in use as a unit of volume as also will the dyne (dyn) as a unit of force (1 dyn = 10^{-5} N).

Reprinted from The Canadian Anaesthetists' Society Journal.

SI Unit	Old Unit	Conversion Factors	
		Old to SI (Exact)	SI to Old (Approx.)
kPa	mm Hg*	0.133	7.5
kPa	1 standard atmosphere (approx. 1 Bar)	101.3	0.01
kPa	cmH_2O	0.0981	10
kPa	lbs/sq in	6.89	0.145

*e.g., systolic BP of 120 mm Hg = 16 kpa and diastolic BP of 80 mm Hg = 11 kPa.

= 760 mm Hg.

Blood Chemistry, Units and Conversion Factors

Measurement	SI Unit	Old Unit	Conversion Factors	
			Old to SI (Exact)	SI to Old (Approx.)
Blood				
Acid-Base				
Pco_2	kPa	mg Hg	0.133	7.5
Po_2	kPa	mm Hg	0.133	7.5
Standard bicarbonate	mmol/litre	mEq/litre	Numerically equivalent	
Base excess	mmol/litre	mEq/litre	Numerically equivalent	
Glucose	mmol/litre	mg/100 ml	0.0555	18
Plasma				
Sodium	mmol/litre	mEq/litre	Numerically equivalent	
Potassium	mmol/litre	mEq/litre	Numerically equivalent	
Magnesium	mmol/litre	mEq/litre	0.5	2
Chloride	mmol/litre	mEq/litre	Numerically equivalent	
Phosphate (inorganic)	mmol/litre	mEq/litre	0.323	3.0
Creatinine	mumol/litre	mg/100 ml	88.4	0.01
Urea	mmol/litre	mg/100 ml	0.166	6.0
Serum				
Calcium	mmol/litre	mg/100 ml	0.25	4.0
Iron	mumol/litre	mug/100 mol	0.179	5.6
Bilirubin	mumol/litre	mg/100 mol	17.1	0.06
Cholesterol	mmol/litre	mg/100 ml	0.0259	39
Total proteins	g/litre	g/100 ml	10.0	0.1
Albumin	g/litre	g/100 ml	10.0	0.1
Globulin	g/litre	g/100 ml	10.0	0.1

Biochemical Content of Other Body Fluids

Measurement	SI Unit	Old Unit	Conversion Factors	
			Old to SI (Exact)	SI to Old (Approx.)
Urine				
Calcium	mmol/24 h	mg/24 h	0.025	40
Creatinine	mmol/24 h	mg/24 h	0.00884	113
Potassium	mmol/litre	mEq/litre	Numerically equivalent	
Sodium	mmol/litre	mEq/litre	Numerically equivalent	
Cerebro-spinal fluid				
Protein	g/litre	mg/100 ml	0.01	100
Glucose	mmol/litre	mg/100 ml	0.0555	18

Haematology

Measurement	SI Unit	Old Unit	Conversion Factors	
			Old to SI	SI to Old
Haemoglobin (Hb)	g/dl	g/100 ml	Numerically equivalent	
Packed cell volume	No unit*	Per cent	0.01	100
Mean cell Hb conc.	g/dl	Per cent	Numerically equivalent	

Mean cell Hb	pg	mumug	Numerically equivalent			
Red cell count	Cells/litre	Cells/mm^3	10^6		10^{-6}	
White cell count	Cells/litre	Cells/mm^3	10^6		10^{-6}	
Reticulocytes	Per cent	Per cent	Numerically equivalent			
Platelets	Cells/litre	Cells/mm^3	10^6		10^{-6}	

*Expressed as decimal fraction, e.g., normal adult male value 0.40 to 0.54.

pH and nmol/litre of H* Activity

pH	nmol/litre
6.80	158
6.90	126
7.00	100
7.10	79
7.20	63
7.25	56
7.30	50
7.35	45
7.40	40
7.45	36
7.50	32
7.55	28
7.60	25
7.70	20

MDConsult
What makes doctors click™

Member Log On

Please enter your User Name and Password to log on to MD Consult. (Remember, your User Name and Password are case sensitive)

User Name Password

Athens User: Click here to login

Forget your user name or password? Contact Customer Service for assistance at (800) 401-9962, Monday - Friday, 7:30 AM to 7:00 PM, Central Time, or email: mdc.customerservice@elsevier.com .

Membership
If you've already tried MD Consult and now want to become a regular member, click here to learn more.

Subscribe now

Or sign up for a free trial membership
Start a **FREE Trial** of any edition now! Select an edition: MD Consult Core Collection MD Consult Respiratory and Critical Care MD Consult Pain Medicine MD Consult Infectious Disease PDxMD

You can also learn more about MD Consult.

Information for users without passwords

By logging on you indicate your acceptance of the terms and conditions of the subscriber agreement. (last updated January 2, 2003)